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On-demand pre-exposure prophylaxis with tenofovir disoproxil fumarate plus emtricitabine among men who have sex with men with less frequent sexual intercourse: a post-hoc analysis of the ANRS IPERGAY trial

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1 **On-demand PrEP with TDF/FTC remains effective among men who have sex with men with**
2 **infrequent sexual intercourses. A sub-study of the ANRS IPERGAY trial.**

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27 **Keywords**

28 On-demand PrEP, Efficacy, MSM, Infrequent sexual intercourse

29 **Research in context**

30 **Evidence before study**

31 Pre-exposure prophylaxis (PrEP) of HIV infection with oral tenofovir/emtricitabine (TDF/FTC) is highly
32 effective among high-risk men who have sex with men (MSM) with daily (Iprex [1], Proud [2]) or on-
33 demand regimen (Ipergay [3]). The open-label extension of the Iprex trial reported no incident HIV-
34 infection in individuals taking at least 4 pills per week [7]. The on-demand dosing regimen in the ANRS
35 Ipergay trial requested the intake of 4 pills to cover one sexual intercourse. Participants reported a
36 median of 10 sexual acts per month (i.e. 2.5 /week) and a median intake of 15 pills per month (i.e.
37 nearly 4 pills/week) [3]. Therefore, it was unclear whether the efficacy reported during the ANRS
38 Ipergay trial was not merely due to the repeated use of 4 pills per week with enough accumulation of
39 active drugs. However, monkeys and pharmacokinetics studies argue in favour of efficacy of event-
40 driven PrEP [14, 16]. We searched on PubMed until April 31, 2019 with the terms ((PrEP) OR (Pre-
41 exposure prophylaxis)) AND ((on-demand) OR (event driven)). We identified 65 studies: none of them
42 evaluated the efficacy of on-demand PrEP in case of infrequent sexual intercourse. We therefore
43 investigated whether on-demand PrEP remained effective among MSM having infrequent sexual
44 intercourses with high PrEP adherence during the randomized double-blind placebo-controlled ANRS-
45 IPERGAY trial.

46 **Added value of this study**

47 Based on data collected in the double-blind phase of the IPERGAY trial, we identified periods of follow-
48 up between visits during which participants took 15 pills or less per month but used them
49 systematically or often during sexual intercourses, as a proxy of infrequent sexual intercourses covered
50 by PrEP. During these 134 person-years of follow-up, the participants used a median of 9.5 pills per
51 month and had a median of 5 sexual intercourses per month, i.e. around 2.2 pills and less than 1.2
52 intercourses per week, on average. Six infections occurred in the placebo arm (HIV incidence: 9.2
53 infections per 100 person-years; 95% CI: 3.4-20.1) versus 0 in the TDF/FTC arm (HIV incidence: 0; 95%
54 CI: 0.0-5.4), $p=0.013$, leading to a relative reduction of HIV incidence of 100% (95% CI: 39-100).

55 **Implications of all the available evidence**

56 This study provides evidence that sex-driven PrEP is an adequate alternative to daily PrEP for high-risk
57 MSM even during periods of infrequent sexual intercourses. The choice of the regimen (daily or sex-
58 driven) should be offered to all MSM subjects, who could therefore adapt their uptake according to

59 their evolving sexual lives and their lives context. The efficacy of on-demand PrEP in persons with very
60 low sexual activity such as once per month could not be stated here given the size of the sample and
61 should be confirmed in current open studies of on-demand PrEP.

62 **Abstract**

63 **Background:** The randomized double-blind ANRS-IPERGAY trial demonstrated among high-risk men
64 who have sex with men (MSM) a major reduction of HIV-1 incidence with on-demand PrEP with
65 TDF/FTC as compared to placebo. During the trial participants used a median of 15 pills of TDF/FTC per
66 month and had a median of 10 sexual intercourses per month. We wished to investigate whether on-
67 demand PrEP remained effective among MSM having less frequent sexual intercourses and using
68 therefore fewer pills.

69 **Methods:** We focused our analysis on periods during which participants took 15 pills or less per month
70 but used them “systematically or often during sexual intercourses” as a proxy of infrequent sexual
71 intercourses covered by PrEP. We then cumulated in each arm follow-up time spent with this pattern
72 of PrEP use. To estimate a window time of HIV acquisition during the study, results of 4th generation
73 HIV-1/2 ELISA assays and plasma HIV-1 RNA levels from frozen samples, Western Blot and Fiebig
74 staging were reviewed blindly. Incidence rates of HIV-infection per 100 person-years (py) were
75 compared between the two arms by using mid-p exact test.

76 **Findings:** Two hundred and seventy participants have used 15 pills/month or less between two visits
77 at least once during the study, with PrEP being used systematically or often during sexual intercourses,
78 representing 134 py of follow-up and 31% of the total study follow-up. During these periods,
79 participants reported a median of 5 (IQR: 2-10) sexual intercourses/month and used a median of 9.5
80 (IQR: 6-13) pills/month. Six HIV-1 infections were diagnosed: 6 in the placebo arm (HIV incidence: 9.2
81 infections per 100 py; 95% CI: 3.4-20.1) and 0 in the TDF/FTC arm (HIV incidence: 0; 95% CI: 0.0-5.4),
82 $p=0.013$, with a relative reduction of HIV incidence of 100% (95% CI: 39-100).

83 **Interpretation:** On-demand PrEP with TDF/FTC remained highly effective in MSM having infrequent
84 sexual intercourses.

85 **Introduction**

86 Pre-exposure prophylaxis (PrEP) of HIV infection with oral tenofovir/emtricitabine (TDF/FTC) is highly
87 effective among high-risk men who have sex with men (MSM). Relative reduction in incidence rates
88 conferred by daily PrEP was 44% in the iPrex trial¹ and reached 86% in the Proud study². The ANRS
89 Ipergay trial which evaluated the efficacy of on-demand PrEP with TDF/FTC, i.e. driven by sex events
90 (two pills 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a
91 fourth pill 24 hours later), found an 86% relative reduction of HIV incidence compared to placebo³.
92 Based on these data, both daily and on-demand PrEP regimens are proposed to MSM in Europe⁴ but
93 the on-demand dosing regimen is not yet endorsed by CDC or WHO because of uncertain efficacy
94 among participants having infrequent sexual intercourses^{5,6}. Indeed, since the on-demand dosing
95 regimen in the ANRS Ipergay trial requested the intake of 4 pills to cover one sexual intercourse, and
96 since the open-label extension of the Iprex trial⁷ reported no incident HIV-infection in individuals taking
97 at least 4 pills per week, it was unclear whether the efficacy reported during the ANRS Ipergay trial
98 was not merely due to the repeated use of 4 pills per week with enough accumulation of active drugs.
99 Participants reported indeed a median of 10 sexual acts per month (i.e. 2.5 /week) and a median intake
100 of 15 pills per month (i.e. nearly 4 pills/week) during the ANRS Ipergay trial.

101 We therefore wished to investigate whether on-demand PrEP remained effective among MSM having
102 less frequent sexual intercourses with high PrEP adherence and using therefore fewer pills during the
103 ANRS Ipergay trial.

104 **Methods**

105 ***The ANRS IPERGAY trial***

106 The ANRS IPERGAY trial has already been reported³. Briefly, this double-blind, randomized trial of on-
107 demand PrEP enrolled HIV-negative adult MSM or transgender women who had condomless anal sex
108 with at least two partners during the past six months³. Participants were assigned in a 1:1 ratio to

109 receive either TDF/FTC or placebo. TDF/FTC was given as a fixed-dose combination of 300 mg of TDF
110 and 200 mg of FTC per pill. Participants were instructed to take a loading dose of two pills of TDF/FTC
111 or placebo 2 to 24 hours before sex, unless the last drug intake was less than 1 week earlier in which
112 case they were instructed to take only one pill, followed by a third pill 24 hours after the first drug
113 intake and a fourth pill 24 hours later. In case of multiple consecutive sexual intercourses, participants
114 were instructed to take one pill per day until the last sexual intercourses and then to take the two post
115 exposure pills.

116 The protocol was approved by public health authorities and ethics committees in France (Comité de
117 Protection des Personnes Ile de France IV) and Canada (Comité d’Ethique de la Recherche de
118 Montreal). All participants provided written informed consent.

119 Participants had a screening visit followed by the inclusion visit (D0) one month later; next visits were
120 scheduled at month one (M1), two (M2), and every two months thereafter. The protocol required
121 serum and plasma storage at -80°C at each study visit. Drugs were dispensed at each visit with enough
122 pills to cover the daily use of TDF/FTC or placebo between visits. Participants were asked to return
123 their bottles at each visit. A pill count of unused medication was performed, allowing assessment of
124 the number of pills used per month. Pills uptake was also estimated by tenofovir concentration from
125 frozen plasma at each visit, with a limit of quantification of $1\ \mu\text{g}/\text{L}$ ⁸. At each visit during a face-to-face
126 interview with the physician, participants were asked if they had used PrEP since last visit:
127 “systematically, respecting the dosing recommendation”, “for each sexual period, but not fully
128 respecting dosing recommendations”, “often, respecting dosing recommendations”, “often, not fully
129 respecting dosing recommendations”, “from time to time, respecting dosing recommendations”,
130 “from time to time, not fully respecting dosing recommendations”, or “not at all”. At each visit, the
131 number of sexual acts during the previous month as well as the number of sexual partners since the
132 previous visit were recorded in a computer-assisted structured interview completed online by the
133 participants.

134 The primary end point was the diagnosis of HIV-1 infection. During the trial, a fourth-generation
135 enzyme linked immunosorbent assay (ELISA-4G) for HIV-1 and HIV-2 combined was performed at each
136 scheduled visit and anytime in case of suspicion of primary HIV infection, using the ARCHITECT HIV
137 Ag/Ab Combo[®] (Abbott, Rungis, France) or the LIAISON[®] XL Murex HIV Ab/Ag HT (Diasorin, Antony,
138 France). Furthermore, when primary HIV infection was suspected, concomitant plasma HIV-1 RNA was
139 measured using a HIV1-RNA PCR with a RealTime[®] HIV-1 assay (limit of quantification 40 copies/ml)
140 (Abbott) or AmpliPrep/COBAS[®] TaqMan[®] HIV-1 test v2.0 (limit of quantification 20 copies/ml) (Roche,
141 Meylan, France). In case of a positive ELISA-4G result, HIV-1 RNA was retrospectively measured from
142 frozen plasma stored at previous visit. The date of HIV diagnosis in the trial was the earliest date of the
143 first positive test, HIV-1 RNA or EIA-4G.

144 Furthermore, frozen samples obtained at the date of HIV diagnosis were centralized at Saint Louis
145 hospital and retested with the ARCHITECT ELISA-4G assay, the BioPlex[®] 2200 HIV Ag-Ab assay (Biorad,
146 Marnes-La-Coquette, France) with the p24 result separately from HIV antibodies and HIV-1 Western
147 Blot[®] (WB, Biorad, Marnes-La-Coquette, France). This allowed to define six stages, according to Fiebig
148 ⁹.

149 ***Study Oversight***

150 The conduct of the trial at each study site was monitored by the Service Commun 10–Unité de Service
151 19 (a Clinical Trial Unit) of INSERM. Gilead Sciences donated the study medications and provided
152 funding for the pharmacokinetics analysis but had no role in data collection, data analysis, or
153 manuscript preparation. All the authors vouch for the completeness and accuracy of the data reported
154 and adherence to the study protocol.

155 ***Study population***

156 All subjects enrolled in the modified-intent to treat population of the double-blind phase of the ANRS
157 IPERGAY trial were eligible for this analysis. Follow-up was censored in case of HIV infection acquired
158 during the blind phase, and for all other participants at their last visit of the blind phase.

159 Because of the highly variable sexual activity and therefore pill intake within and between participants
160 over time, we grouped for the analysis the periods between visits during which participants had a
161 similar behaviour, categorised in the three following patterns.

162 Periods during which participants took 15 pills or less per month but used them “systematically or
163 often during sexual intercourses”, a proxy for infrequent sexual intercourses covered by PrEP, were
164 categorized in the pattern “high PrEP adherence with infrequent sexual intercourses”. Two other
165 behaviour patterns were defined: “low adherence to PrEP”, defined by an uptake of 15 pills or less per
166 month, taken from time to time or never during sexual intercourses; “high PrEP use”, defined by an
167 uptake of more than 15 pills per month. We then cumulated in each arm follow-up (FU) time spent
168 with each behaviour pattern.

169 Our main analysis focused on periods of “high PrEP adherence with infrequent sexual intercourses”.

170 ***Estimation of timing of HIV infection***

171 For each HIV infection occurring during the trial, we blindly estimated the time of HIV acquisition
172 without knowing the treatment arm and the pattern of PrEP use, using dates of positive plasma HIV-
173 RNA, ELISA-4G tests, results of Western blots and Fiebig staging. HIV-1 RNA becomes detectable in
174 plasma on average 11 days following infection^{10,11}; therefore, HIV infection was estimated to have
175 occurred within 11 to 19.1 days prior to a Fiebig I diagnosis, 14.1 to 24.5 days prior to a Fiebig II, 18.1
176 to 28.0 days prior to a Fiebig III, 21.0 to 33.9 days for Fiebig IV, 26.3 to 140.8 days for Fiebig V, and
177 more than 58.4 days before for a Fiebig VI diagnosis¹¹ (Figure 1).

178 In some cases, the infection window period could even be shortened due to a tight sequence of a
179 negative followed by a positive ELISA-4G or HIV-1 RNA: since HIV-1 RNA becomes detectable after
180 around eleven days following infection and ELISA-4G becomes positive after around 16 days following
181 infection^{10,11}, we considered that HIV infection could not have occurred more than 11 or 16 days
182 respectively before the last negative HIV-1 RNA or ELISA-4G, nor less than 11 or 16 days respectively
183 before the first positive HIV-1 RNA or ELISA-4G (figure 1).

184 **Statistical analysis**

185 In the main analysis, HIV incidence rate was estimated as the ratio of the number of HIV-1 infections
186 occurring during a period of high adherence to PrEP with infrequent sexual intercourses, to the total
187 of person-years cumulated with this pattern of PrEP use. Incidence rates in the TDF/FTC and placebo
188 arm were compared to assess the efficacy of the PrEP. The efficacy of the PrEP was also assessed for
189 the two other patterns of PrEP use.

190 When the estimated time window of HIV infection spread over two different periods of pattern of PrEP
191 use, the longest period was considered to be the one during which HIV infection occurred. A sensitivity
192 analysis was performed, where infection was considered to have occurred during the alternative
193 period.

194 Other analyses were performed, lowering the threshold from 15 pills to 10 pills per month in order to
195 explore the efficacy of PrEP with an even more restrictive definition of infrequent sexual intercourses.

196 All analyses were conducted with R version 3.5.2. Exact confidence intervals and tests to compare HIV
197 incidence rates between the two arms were obtained by the mid-p method, which avoids over-
198 conservative estimation of confidence intervals and p-values¹². Relative risks (RR), relative reductions
199 of risk (RRR), 95% confidence intervals (CI) and p-values were obtained using the package {epitools},
200 the function epitab(), and the following parameters: method="rateratio", rateratio="midp".

201 **Results**

202 Four hundred participants were included in the blind phase of the Ipergay trial, 201 in the placebo arm
203 and 199 in the Truvada arm, for a total follow-up of 431 Person-Years (PY). The number of pills used
204 per month was above 15 pills for 188 PY ("high PrEP use"), 15 pills or less for 180 PY, unknown for 63
205 PY. When the number of pills used per month was 15 pills or less, PrEP was reported to be used
206 "systematically or often" during sexual intercourses for 134 PY ("high adherence to PrEP with
207 infrequent sexual intercourses"), as opposed to "from time to time" or "not at all" ("low adherence",

208 45 PY). Our main analysis focused on these 134 PY of high adherence to PrEP with infrequent sexual
209 intercourses, representing 31% of the total follow-up of the Ipergay trial, and provided by 270
210 participants, 134 from the placebo arm and 136 from the TDF/FTC arm. Compared to the other 130
211 participants of the Ipergay trial who never experienced this pattern of PrEP use during follow-up, they
212 had a higher level of education (77% of post-secondary education vs. 65%, $p=0.02$) and reported at
213 enrolment a lower number of sexual partners over the past 2 months (median 8 vs. 10, respectively,
214 $p=0.002$) and of sexual intercourses over the past 4 weeks (median 10 vs. 12, $p=0.03$). They did not
215 differ for age or for bacterial sexually transmitted infection diagnosed at screening (supplementary
216 table 1). The baseline characteristics of these 270 participants did not significantly differ between the
217 two study arms, TDF/FTC *versus* Placebo (table 1).

218 During the periods of infrequent sexual intercourses with high adherence to PrEP, the median number
219 of sexual intercourses per month was 5 [IQR: 2; 10] (range from 0 to >100), and the median number of
220 pills used per month was 9.5 [IQR: 6; 13] (table 2). In the TDF/FTC arm, the percentage of plasma
221 samples with unquantifiable TDF was 38%; the median dosage when quantifiable was 41 $\mu\text{g/L}$ [IQR:
222 11-92]. The corresponding figures during periods when the participants had a “low adherence” to PrEP
223 were 8.5 [4.0; 18.5] sexual intercourses/month, 0 [0; 4] pills/month and 87% of unquantifiable TDF. In
224 contrast, during periods when participants were using more than 15 pills per month (“high PrEP use”),
225 they had a median of 12 [8-20] sexual intercourses per month and an intake of 23.5 [19-27] pills per
226 month; 11% had unquantifiable TDF in plasma (median dosage [IQR] when quantifiable: 84 $\mu\text{g/L}$ [39-
227 146]).

228 Among the 16 HIV-1 infections which occurred during the blind phase of the Ipergay trial (14 in the
229 placebo arm and 2 in the TDF/FTC arm), 6 infections occurred during periods when pill use was 15 or
230 less per month and PrEP was systematically or often taken during sexual intercourses (figure 2). These
231 6 participants had all been randomized in the placebo arm. The HIV-1 incidence rate was 9.2 per 100

232 PY (95% CI: 3.4 - 20.1) in the placebo arm versus 0.0 (0.0 – 5.4) per 100 PY in the TDF/FTC arm, p=0.013
233 (table 2); the relative reduction of incidence rate was 100% (95% CI: 39-100).

234 In one case (#3), the infection window period slightly overlapped with the following period when he
235 used more than 15 pills per month, actually 16/month. A sensitivity analysis considering that this
236 infection occurred when the number of pills used per month was more than 15 led to similar
237 conclusions, with five infections with placebo and an incidence rate of 7.7 per 100 PY (95% CI: 2.5 - 18)
238 versus 0.0 with TDF/FTC arm, p=0.027.

239 Other analyses assessing the efficacy of PrEP with lower thresholds of pill intake showed similar trends,
240 although the difference was not always statistically significant, due to a lower number of events. For
241 instance, when the analysis was restricted to periods when participants used 10 pills or less per month,
242 taken systematically or often during sexual intercourses, HIV incidence was 7.86 per 100 PY [1.6; 23]
243 in the placebo arm (3 infections during 38.2 PY of FU) and 0.0 per 100 py in the TDF/FTC arm (0 infection
244 during 38.8 PY of FU), p=0.12.

245 No efficacy of TDF/FTC was observed when participants used 15 pills or less per month taken from
246 time to time or not at all (table 2). The 2 cases of HIV-1 infections diagnosed in the TDF/FTC arm during
247 the blind phase of the trial occurred in periods when the participants declared to have used PrEP not
248 at all or from time to time: they had used 2.5 and 1 pills/month and had 6 and 12 sexual
249 intercourses/month, respectively.

250 **Discussion**

251 This study showed that on-demand PrEP with TDF/FTC remains highly effective among MSM enrolled
252 in the ANRS IPERGAY trial during periods when they reported systematic or frequent PrEP use and
253 infrequent sexual intercourses, leading to an uptake of 15 pills or less per month. The chosen threshold
254 of 15 pills per month led to consider periods of follow-up when the participants actually used a median
255 of 9.5 pills per month and had a median of 5 sexual intercourses per month, i.e. around 2.2 pills and

256 less than 1.2 intercourses per week, on average. During these periods of low pill intake due to
257 infrequent sexual exposure, the HIV-1 incidence rate with placebo was 9.2 per 100 PY (95%CI: 3.4 -
258 20.1), versus 0 (0.0 – 5.4) with TDF/FTC, p=0.013.

259 Modelling studies from the iPrEx and STRAND studies indicated that TFD-dp concentration
260 corresponding to a use of 4 pills/week gave a relative reduction of risk (RRR) of 96% [95% CI: 90%-
261 >99%]. The RRR was 76% [95% CI: 56%-96%] for 2 pills per week¹³. In addition, modelling from iPrEx
262 OLE found that the TFV-dp concentration associated with 90% reduction risk was consistent with use
263 of 2 to 3 tablets per week⁷. Here, we observed a RRR of 100% [95% CI: 39%-100%] with an average
264 uptake of 2.2 pills/week, provided that adherence to the on-demand PrEP regimen was good. Our
265 results provide evidence of high efficacy of on-demand PrEP in case of infrequent periods of sexual
266 intercourses, whatever the number of sexual acts during these periods.

267 The efficacy of the event-driven PrEP, even with an infrequent use, is consistent with both monkey
268 studies and pharmacokinetic studies. Studies including groups of six rhesus macaques receiving
269 different PrEP regimen showed that significant protection is achieved by event-driven PrEP of TDF/FTC
270 22 hours before and 2 hours before the exposure (4/6 uninfected macaques after 14 weekly virus
271 challenge *versus* 0/6 control receiving no PrEP)¹⁴. Of note, in another study with daily oral TDF/FTC, 4
272 out of 6 macaques were also still uninfected after 14 weekly challenges¹⁵ suggesting that in macaques,
273 intermittent oral preexposure prophylaxis with TDF/FTC was as effective as daily prophylaxis.

274 Pharmacokinetic/pharmacodynamic studies in healthy women reinforce this conclusion. The
275 proportion of the population that achieved the target of 90% effective concentration ratios of TFV-dp
276 to dATP (EC90 TFVdp:dATP) in the colorectal tissue was 100% after 3 TDF/FTC daily doses and >95%
277 with a regimen of 2 doses/week¹⁶. Using an intermittent regimen based on the Ipergay protocol, 81%
278 and 98% of the population achieved EC90 TFVdp:dATP at the time of the coitus when 2 TDF/FTC doses
279 were administered 2 hours and 24 hours before coitus, respectively. Since no difference in colorectal

280 drug concentration and risk of transmission during anal intercourses has been identified by sex, we
281 can reasonably extrapolate these results to the MSM population.

282 This study is not strictly speaking a randomized comparison since the periods of infrequent PrEP uptake
283 occurred after randomization; however, since the trial was double-blind, neither adherence to
284 treatment nor sexual behaviour were dependent on the arm. We are therefore confident that the
285 comparison between the arms is not biased.

286 We want to underline that the results are based on a large sample of the IPERGAY blind phase: two-
287 thirds of the Ipergay participants were at least once in the case of infrequent use due to infrequent
288 sexual intercourses. Noteworthy, when 15 pills or less per month were taken, PrEP was systematically
289 or often used during intercourses in 75% of the participation time. It appears therefore that an
290 infrequent use of pills corresponded in the vast majority of participants to a reasoned choice based on
291 the frequency of their sexual activity.

292 Among the strengths of this study is the precise estimation of the window period when HIV infection
293 occurred. This was made possible through the high frequency of HIV testing during the Ipergay trial, at
294 each study-visit, month 1, month 2 and every 2 months thereafter, and the possibility to perform
295 additional assays from frozen samples drawn at previous visits in order to date the infection more
296 precisely.

297 Of note, the 2 cases of HIV-1 infections diagnosed in the TDF/FTC arm during the blind phase of the
298 trial occurred in periods when the participants reported having used PrEP not at all or from time to
299 time. Our results therefore confirm that among strongest determinants of on-demand PrEP efficacy is
300 compliance to the regimen.

301 We acknowledge that due to a low number of person-years, the efficacy of on-demand PrEP with very
302 low levels of PrEP uptake, such as once a month, could not be studied. Future open studies of on-
303 demand PrEP will help to clarify this issue.

304 In conclusion, these data provide evidence that sex-driven PrEP is an adequate alternative to daily PrEP
305 for high-risk MSM even during periods of less frequent sexual intercourses. The choice of the regimen
306 (daily or sex-driven) should be offered to all MSM subjects, who could therefore adapt their uptake
307 according to their evolving sexual lives and more broadly to their lives context.

308 **Contributors**

309 L.M, J-M.M, G.A and C.T designed the study. G.A wrote the first draft of the report. GA, LM and IC
310 designed the analysis. G.A, C.D, L.M, I.C, C.C, and J-M.M analysed the data. C.C coordinated data
311 management. C.D, E.C, F.R, T.H, L.C, J.C, C.T and J-M.M did the study at their sites. B.S and D.R
312 organized the community support of the participants. All authors critically reviewed and approved the
313 manuscript.

314 **Declaration of interests**

315 J-MM reports receiving support as an adviser for Gilead Sciences, Merck, ViiV Healthcare and Teva,
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Table 1: Baseline characteristics of the 270 participants who had at least once during follow-up periods of infrequent sexual intercourses with high adherence to on-demand PrEP regimen: : the ANRS Ipergay trial

Baseline characteristics	Placebo (N=134)	TDF/FTC (N=136)	P value
Median age [IQR]	34 [28-42]	35 [29-43]	0.88
White Race			0.08
No -no.(%)	15 (11%)	7 (5%)	
Yes -no.(%)	119 (89%)	129 (95%)	
Relationship status			0.80
Does not live with his partner -no.(%)	100 (81%)	98 (78%)	
Lives with a HIV positive partner -no.(%)	8 (7%)	11 (9%)	
Lives with a HIV negative partner -no.(%)	15 (12%)	16 (13%)	
Missing -no.	11	11	
Post-secondary education			0.47
No -no.(%)	34 (25%)	29 (21%)	
Yes -no.(%)	100 (75%)	106 (79%)	
Missing -no.	0	1	
Use of recreational drugs(2)			0.62
No -no.(%)	69 (53%)	76 (56%)	
Yes -no.(%)	62 (47%)	59 (44%)	
Missing -no.	3	1	
At least 5 glasses a typical day of drinking			0.15
No -no.(%)	109 (81%)	100 (74%)	
Yes -no.(%)	25 (19%)	36 (26%)	
Site of enrolment			0.82
Paris -no.(%)	72 (54%)	70 (51%)	
Lyon -no.(%)	28 (21%)	34 (25%)	
Nice -no.(%)	11 (8%)	7 (5%)	
Tourcoing -no.(%)	9 (7%)	7 (5%)	
Nantes -no.(%)	5 (4%)	6 (4%)	
Montreal -no.(%)	9 (7%)	12 (9%)	
Median no. of sexual partners in past 2 months [IQR]	8 [4-15]	8 [4-15]	0.84
Median no. of episodes of sexual intercourses in past 4 weeks [IQR] (Missing)	10 [4-15] (1)	10 [5-15] (2)	0.62
Circumcision			0.65
No -no.(%)	105 (78%)	110 (81%)	
Yes -no.(%)	29 (22%)	26 (19%)	
Bacterial sexually transmitted infection diagnosed at screening(3)			0.22
No -no.(%)	93 (69%)	104 (76%)	
Yes -no.(%)	41 (31%)	32 (24%)	

(1) Non parametric Wilcoxon and Fisher tests for continuous and qualitative characteristics, respectively.

(2) Recreational drugs in past 12 months including ecstasy, crack, cocaine, crystal, speed, GHB/GBL

(3) Infections included Syphilis (as detected on serologic testing by means of rapid plasma reagin confirmed with the use of a treponema-specific assay), N. gonorrhoeae and C. trachomatis (as detected on PCR on urine samples, throat or anal swabs)

Periods of infrequent sexual intercourses with high adherence to PrEP were defined as a PrEP intake of 15 pills or less per month with a systematic or frequent use during sexual intercourses.

Table 2: Efficacy of on-demand PrEP according to the pattern of use: : the ANRS Ipergay trial

	Number of sexual intercourses/month (median [IQR])	Number of pills/month (median [IQR])	TFV concentration (ng/mL, median [IQR])	Person- Years	Number of HIV1 infections	HIV1 Incidence Rate	p
High PrEP adherence with infrequent sexual intercourses (1)	5 [2-10]	9.5 [6-13]		133.8	6		
Placebo				64.9	6	9.2 [3.4;20.1]	
TDF/FTC			7[0-63]	68.9	0	0.0 [0;5.4]	0.013
High PrEP use (2)	12 [8-20]	23.5 [19-27]		187.8	7		
Placebo				86.4	7	8.1 [3.3;16.7]	
TDF/FTC			72[20-133]	101.4	0	0.0 [0;3.6]	0.0044
Low PrEP adherence (3)	8.5 [4-18.5]	0 [0-4]		45.3	2		
Placebo				25.6	0	0.0 [0;14.4]	
TDF/FTC			0[0-0]	19.6	2	10.2 [1.2;36.8]	0.19
Unknown (4)	10 [5-16]	9 [6.5-12]		64.4	1 (5)		
Placebo				35.3	1	2.8 [0.1;15.8]	
TDF/FTC			0[0-18]	29.1	0	0.0 [0;12.7]	0.55

(1) ≤15 pills/month taken systematically or often during sexual intercourses

(2) >15 pills/month

(3) ≤15 pills/month taken from time to time or never during sexual intercourses

(4) Bottles not returned or question about compliance not answered with 15 pills or less/month.

(5) One infected participant from the placebo arm could not be categorized because he did not return the bottles. He reported 20 sexual acts in the previous period and a systematic use of PrEP during sexual intercourses.

Supplementary table 1: Comparison of baseline characteristics of infrequent PrEP users with other Ipergay participants: : the ANRS Ipergay trial

Baseline characteristics	infrequent PrEP users ⁽¹⁾ N=270	other participants N=130	p value ⁽²⁾
Median age [IQR] - years	34 [28-42]	36 [30-43]	0.34
White - no. (%)	248 (92%)	118 (91%)	0.71
Post-secondary education - no. (%)	206 (77%)	81 (65%)	0.02
Relationship status – no (%)			0.51
Not in a couple	198 (73%)	95 (73%)	
In a couple with HIV-1-positive partner	19 (7%)	13 (10%)	
Other	53(20%)	22(17%)	
> 5 alcoholic drinks per day at least once in past month - no. (%)	61 (24%)	30 (26%)	0.70
Use of recreational drugs⁽³⁾ - no. (%)	121 (45%)	56 (47%)	0.91
Site of enrolment- no. (%)			0.04
Lyon	62 (23%)	21 (16%)	
Montreal	21 (8%)	22 (17%)	
Nantes	11 (4%)	4 (3%)	
Nice	18 (7%)	13 (10%)	
Paris	142 (53%)	59 (45%)	
Tourcoing	16 (6%)	11 (8%)	
Median no. of sexual partners in past 2 months [IQR]	8 [4-15]	10 [6-20]	0.002
Median no. of episodes of sexual intercourses in past 4 weeks [IQR]	10 [5-15]	12 [6-20]	0.03
Circumcision- no. (%)	55 (20%)	24 (18%)	0.69
Bacterial sexually transmitted infection diagnosed at screening⁽⁴⁾ - no. (%)	73 (27%)	38 (29%)	0.72

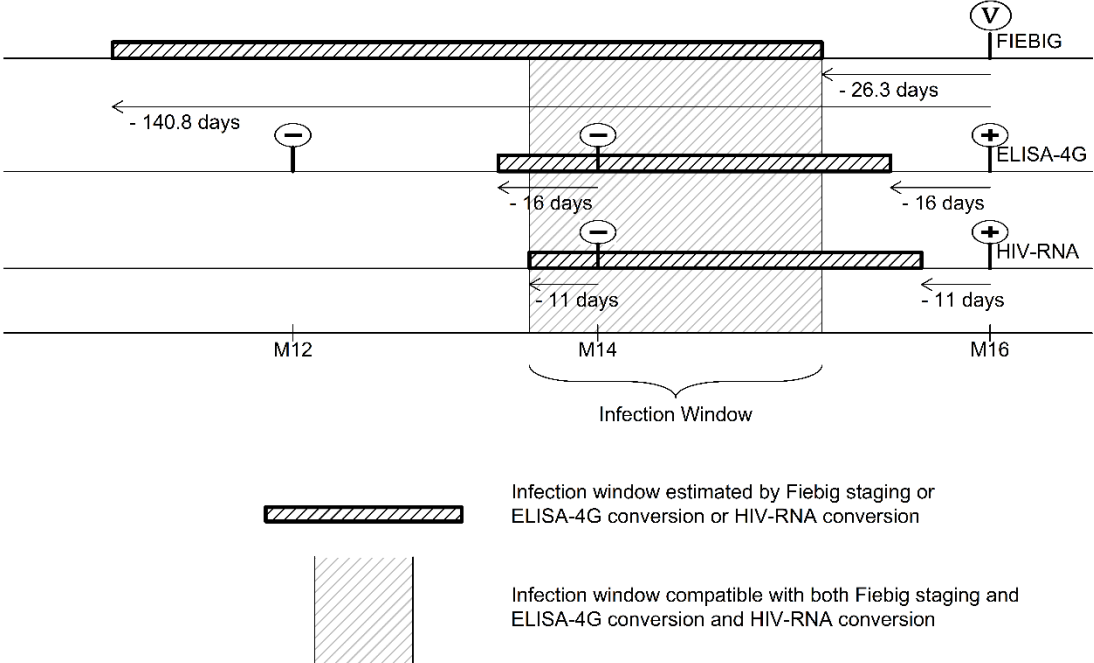
(1) Defined by at least once an uptake of 15 pills or less per month with a systematic or often use during intercourses

(2) Non parametric tests: Wilcoxon and Fisher test for continuous and qualitative characteristics, respectively.

(3) Recreational drugs in past 12 months including ecstasy, crack, cocaine, crystal, speed, GHB/GBL

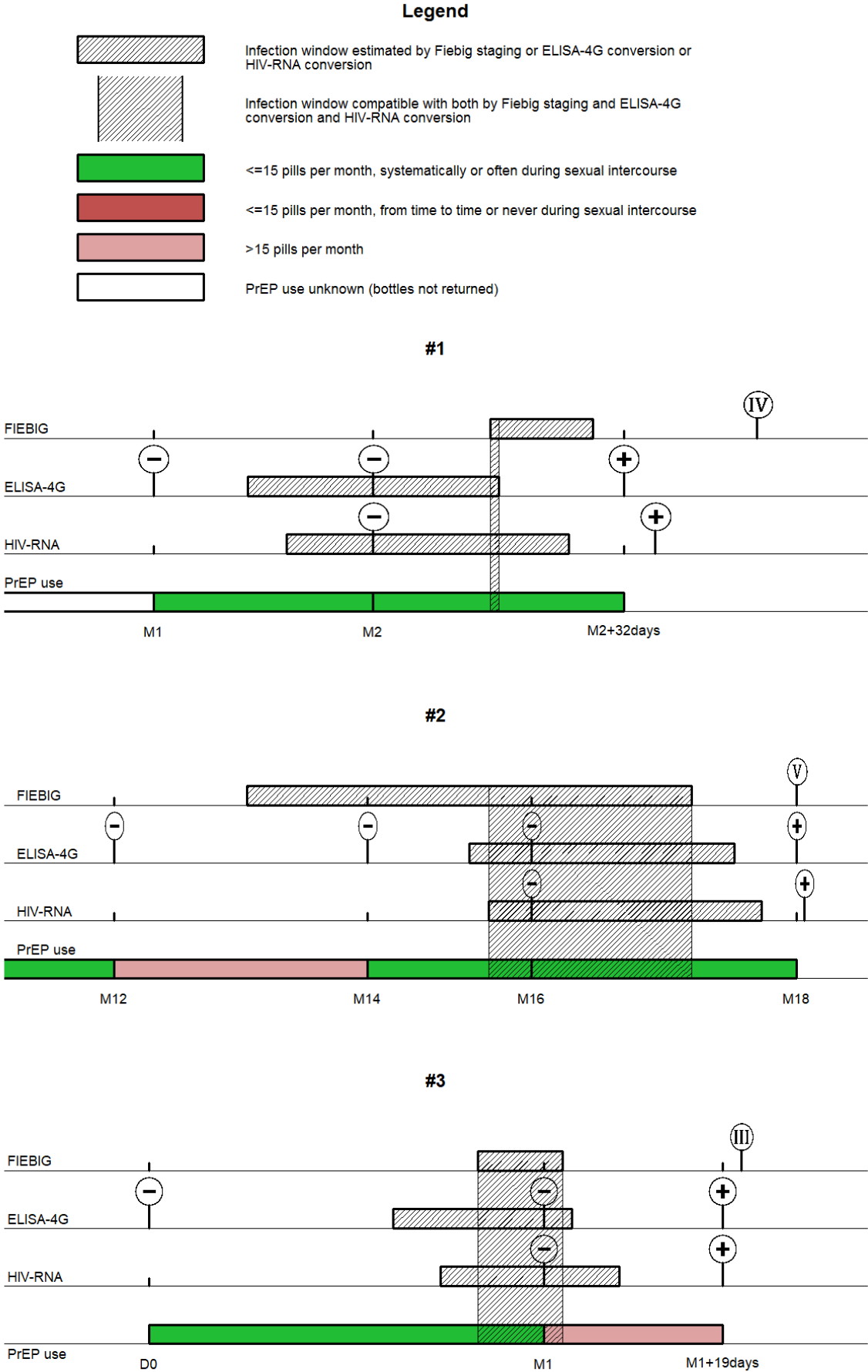
(4) Infections included Syphilis (as detected on serologic testing by means of rapid plasma reagin confirmed with the use of a treponema-specific assay), N. gonorrhoeae and C. trachomatis (as detected on PCR on urine samples, throat and anal swabs)

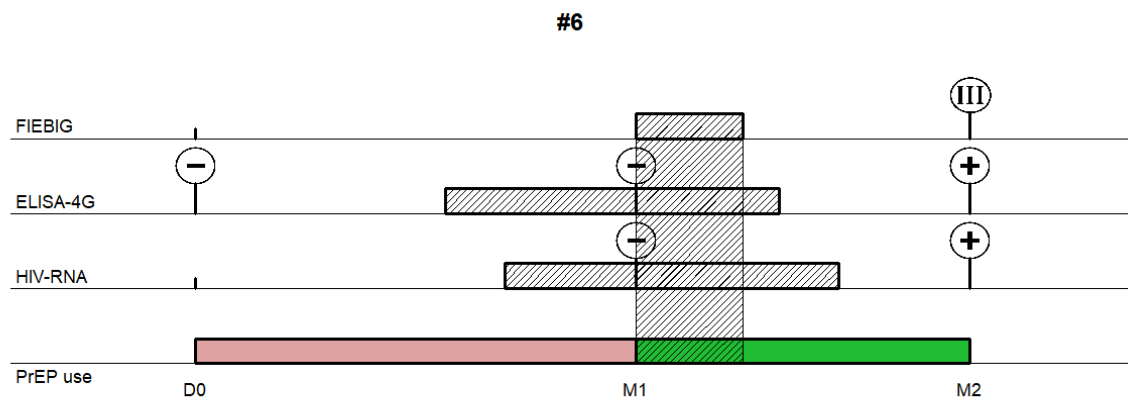
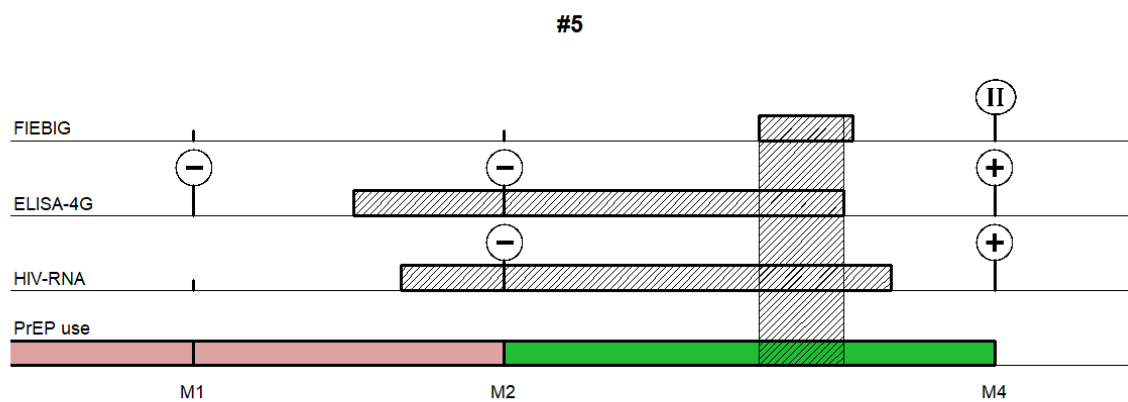
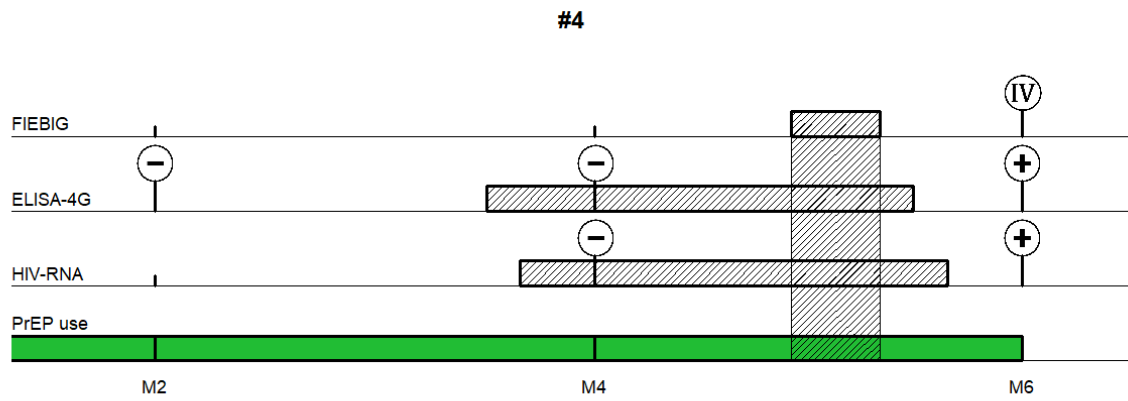
Figure 1. Estimation of the time interval during which the infection occurred using dates of HIV-RNA conversion, of ELISA-4G conversion, and results of Western blot and Fiebig staging



HIV infection was estimated to have occurred within 11 to 19.1 days prior to a Fiebig I diagnosis, 14.1 to 24.5 days prior to a Fiebig II, 18.1 to 28.0 days prior to a Fiebig III, 21.0 to 33.9 days for Fiebig IV, 26.3 to 140.8 days for Fiebig V, and more than 58.4 days before for a Fiebig VI diagnosis¹⁰. Furthermore, HIV infection could not have occurred more than 11 or 16 days respectively before the last negative HIV-1 RNA or ELISA-4G, nor less than 11 or 16 days respectively before the first positive HIV-1 RNA or ELISA-4G⁹. In this example, the diagnosis was made in M16 at the Fiebig V stage with an infection period ranging from -140.8 days to -26.3 days before M16. This period of contamination could be shortened by the knowledge of an undetectable viral load at M14. Thus, the period of infection compatible with both Fiebig staging and ELISA-4G conversion and HIV-RNA conversion ranges from -11 days before M14 to -26.3 days before M16.

Figure 2. Infection windows for the six participants infected during a period between two visits when 15 pills or less per month systematically or often during sexual intercourse were used (all in Placebo arm)





#1 : HIV-RNA 5529 cp, EIA-4G Agp24- Ab+, undetermined Western-Blot (Fiebig IV); **#2** : HIV-RNA 9198 cp, EIA-4G Agp24- Ab+, Positive Western-Blot without p34 Ab (Fiebig V); **#3** : HIV-RNA 9346500 cp, EIA-4G Agp24+ Ab+, Negative Western-Blot (Fiebig III); **#4** : HIV-RNA 20672 cp, EIA-4G Agp24- Ab+, undetermined Western-Blot (Fiebig IV); **#5** : HIV-RNA 4774294 cp, EIA-4G Agp24+ Ab-, Negative Western-Blot (Fiebig II); **#6** : HIV-RNA 8985536 cp, EIA-4G Agp24+ Ab+, Negative Western-Blot (Fiebig III).