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Changes in Sexual Behaviors in Men Who Have Sex with Men: A Comparison Between the Double-Blind and Open-Label Extension Phases of the ANRS-IPERGAY Trial

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AIDS and Behavior

Changes in sexual behaviors in men who have sex with men: a comparison between the double-blind and open-label extension phases of the ANRS-IPERGAY trial --Manuscript Draft--

Manuscript Number:	AIBE-D-19-00398R2	
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Abstract:	Pre-Exposure Prophylaxis (PrEP) is changing the landscape of HIV prevention, and	

	<p>may bring changes in sexual behaviors. The double-blind phase (DBP) and open-label extension (OLE) study of the ANRS-IPERGAY trial allowed us to assess changes in sexual behavior of men who have sex with men (MSM) taking sexual activity-based (i.e., on-demand) PrEP. Generalized Estimating Equation (GEE) models found a significant decrease in the number of sexual partners (Coefficient [CI95%], p-value; -0.37[-0.70 – -0.04], p=0.03) between the DBP and OLE as well as in the number of sexual relations (-0.25 [-0.49 – 0.00], 0.04). GEE estimates also showed that respondents' most recent sexual relation was less likely to have been with an unknown casual partner during the OLE than during the DBP (Odds Ratio [CI95%], p-value: 0.75[0.62–0.92], 0.005). Furthermore, they showed an increase in the proportion of condomless anal sex in the OLE (1.32[1.04–1.67], 0.02), a decrease in the proportion of 'suboptimal PrEP adherence' over time (0.75[0.58–0.97], p=0.03), a decrease in PrEP only use (0.73[0.55–0.96], 0.03) and in both PrEP and condom use over time (0.70[0.51–0.95], 0.02) and finally, a decrease in alcohol consumption between the DBP and OLE (0.74[0.61–0.90], 0.002).</p> <p>We observed both protective and risky behaviors in terms of HIV and STI risk after on-demand PrEP uptake in the OLE phase. Our findings are consistent with results from previous PrEP trials.</p>
<p>Response to Reviewers:</p>	<p>Dear Editor,</p> <p>We would like to resubmit our manuscript entitled "Changes in sexual behaviors in men who have sex with men: a comparison between the double-blind and open-label extension phases of the ANRS-IPERGAY trial" for publication in AIDS and Behavior. We have taken into account all the comments made by the reviewers. A separate document explains the changes made to the manuscript in greater detail.</p> <p>Neither this manuscript nor the data therein have been previously published, nor are they under consideration for publication elsewhere. All authors have read and approved the content of the submitted manuscript and have no conflict of interest to declare.</p> <p>We hope that this manuscript will be suitable for publication in AIDS and Behavior and we look forward to receiving recommendations and suggestions from your Editorial Board.</p> <p>Yours faithfully,</p> <p>Marion Di Ciaccio</p>

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Marseille, 07 April 2020

Dear Editor,

We would like to resubmit our manuscript entitled “Changes in sexual behaviors in men who have sex with men: a comparison between the double-blind and open-label extension phases of the ANRS-IPERGAY trial” for publication in AIDS and Behavior. We have taken into account all the comments made by the reviewers. A separate document explains the changes made to the manuscript in greater detail.

Neither this manuscript nor the data therein have been previously published, nor are they under consideration for publication elsewhere. All authors have read and approved the content of the submitted manuscript and have no conflict of interest to declare.

We hope that this manuscript will be suitable for publication in AIDS and Behavior and we look forward to receiving recommendations and suggestions from your Editorial Board.

Yours faithfully,

Marion Di Ciaccio

Dear Dr. Di Ciaccio,

The review of your revised manuscript (AIBE-D-19-00398R1) resubmitted for publication in AIDS and Behavior. I sent your paper back to the original reviewers. The response to your revision was mostly favorable. The reviewers had additional suggestions. From my own reading of your revision, I agree with the reviewers and I believe that your paper is much closer to publishable form. I also believe that your paper will benefit from additional careful edit.

I can therefore offer provisional acceptance of your paper based on its current form. However, your paper will not be publishable unless it addresses the most recent comments and is formatted correctly for the journal. Authors once more and be sure that your text, references, and tables/figures are properly formatted. Please provide a point-by-point response to remaining comments and submit your next version as a clean copy, without any tracked changes.

AIDS and Behavior now offers the opportunity to publish abstracts for articles in English and Spanish. Although not required, I am hoping that you will take advantage of this chance to broaden access of your work. If you would like to include your Abstract in Spanish, please be sure that your Abstract is in the proper format and finalized. Be sure to remove all subheadings from the Abstract so that it reads as a continuous narrative of no more than 150 words in English. Then translate your final Abstract into Spanish. Upload the English version in the Editorial Manager System step for Abstracts and include both the English and Spanish versions in your Manuscript file that you upload into the system. The two abstracts should be placed together, first the English followed by the Spanish on a separate pages. Label the Spanish version "Resumen".

Please carefully proof read your paper before resubmitting. You might also take this one more opportunity to be sure that the data are all reported correctly in your paper.

Please resubmit your revision within 2 months of receipt of this correspondence.

Reviewer #1: Overall, the revised manuscript is significantly improved, and the writing is easier to follow. The topic remains important, and the findings have potential impact on PrEP implementation strategies. However, there are a number of issues that still need to be addressed.

1. The introduction could be further strengthened by a more detailed description of the social context specially applied to PrEP use such as risk compensation. The addition of references is great, but it still needs to be more explicitly stated what you mean by social context, For example, risk compensation has been a major issue identified by critics of PrEP, and your manuscript really addresses this and provides important information that PrEP does not increase risk. This is worthwhile of a discussion that is currently absent in the introduction.

We added information about risk compensation in terms of PrEP use in the introduction section (p3 l 34-51) to better explain what we mean by social context.

2. In the methods, can you briefly describe the OLE phase? Was it the same procedures as DBP or were there more provisions for a "real-world context?" Why were new participants added? Also, you should state that you only included participants that were in both studies- it is confusing that the analysis numbers don't match the numbers described in the methods.

We added more information concerning the OLE phase in the method section (p 8 l166-172). The only difference between the DBP and the OLE was the suppression of the placebo arm following the proof of on-demand PrEP effectiveness. New inclusions were permitted for the OLE phase in order to increase the reliability of the study. It is worth pointing out that PrEP was not yet authorized for MSM in France at the time of this study, so extending the study's reach to include new participants

also brought PrEP to a larger number of people. We also specified in the statistical analysis section (p12 1266-268) that analyses were conducted only on participants enrolled in both phases.

3. Were questions about drug and alcohol use specifically related to sexual activity (e.g. used during sexual intercourse)? This is not stated in the description of the outcomes in the methods, although in the discussion it states (line 356): "decrease in alcohol consumption during sexual intercourse." Please clarify in the methods.

Yes, drug and alcohol use were specifically related to sexual activity. We now specify this in the outcome section (p10 1209 and 212).

4. What is the justification for the comparison between DBP & OLE and DBP only? Is there something particularly compelling about the 67 participants that did not continue on to DBP that is relevant to the present study? I would consider removing it, since the primary outcomes focus only on those that were in both studies, and the DBP only data in Tables I add confusion. If it is important to note differences between these groups 1) state why this is important in the methods, and 2) maybe just mention it in the text rather than include in the table.

We compared the 67 participants who left the trial before the OLE with the 332 participants who completed both phases in order to verify that the former did not have a greater number of HIV risky sexual behaviors than the latter, as such a situation could have biased our results.

To take into account your comment, we removed data about these 67 participants from Table 1 and added the statistical analysis used for the comparison in the methods section, as well as a sentence indicating why this was important to compare these samples (p12 1269-272).

5. It is a bit misleading to say "We observed no obvious increase of HIV risky behaviors after onset of on-demand PrEP initiation," (lines 366-369), and this is inconsistent with the findings in the results and the previous paragraph (lines 357-360) that state that you did find increases in risky behavior. This paragraph needs to be revised to be consistent and accurate with the study findings. The data the authors highlight in the discussion seem a bit cherry-picked. That is, there seems to be a focus on decreases in risky behavior (alcohol consumption, casual partners) and less focus on behaviors that did not change or increased (CAS, drug use, multiple partners). The discrepancies between the non-longitudinal results (Table II) and the longitudinal results are still not fully explained, and the statement in line 424 "...globally our results confirmed the absence of additional risk taking" implies the non-longitudinal comparisons (Table II) that did find differences in risky behavior between DBP and OLE. This discrepancy needs to be addressed, and perhaps the discussion needs to include a fuller interpretation of the results.

We deleted the sentence "We observed no obvious increase of HIV risky behaviors after onset of on-demand PrEP initiation" and now provide a more in-depth discussion of our results. More specifically, we now discuss the evolution of PrEP adherence from GEE results in light of PrEP persistence issues. We also discuss the difference in results between non-longitudinal and GEE models, given that the latter took into account time trends during both phases, while the former only focused on changes between both phases (p17 1387-399 and p 18 1400-408).

We added a paragraph about the sexual factors which did not change with the use of PrEP (specifically, drug use in the sexual context and sexual intercourse with multiple or known casual partners) (p18 1409-411).

Furthermore, we deleted "...globally our results confirmed the absence of additional risk taking" and now present protective and risky sexual behaviors regarding HIV and STI after PrEP initiation in the study (p19 1432-443).

6. There is a fairly substantial section of the discussion focused on STIs, but this is not a result that is provided and seems out of context and is really just reporting results from a previous paper. It would be a stronger discussion to focus on the findings from the present study.

We shortened the section focused on STIs (p18-19 l417-431) in order to develop discussion about other results, especially regarding risk compensation (p20 l461-467).

7. There remains a lack of discussion on how these data might inform future roll-outs of PrEP cohort studies, and the implications of the findings in successful implementation strategies for PrEP. **Based on our results, we now develop recommendations which should be taken into account for future PrEP cohort studies, mainly concerning STI prevention and PrEP persistence (p21 l479-495).**

Minor edits

1. Overall, the writing is much more clear, but it could still benefit from careful proofreading.
2. Write out OLS and OLE the first time they are used in the manuscript (line 62). Also, it is not clear what the difference between OLE and OLS studies are in the introduction.

We have written out what OLS and OLE mean in the manuscript (p4 l79 and p 5 l80) and we now explain the difference between both (p5 l80-82). The main difference is that OLE refers to an open-label phase in a clinical trial which follows a double-blind phase, while OLS is an open-label study (cohort) in a context outside a clinical trial.

3. The statements starting after the colon in line 279 all end in periods even though they are part of the same sentence. This makes it look like sentences that have been cut off. Please revise the format.

We changed the periods for semi-colons.

4. Define "IST risk" line 359

We modified the term for "STI incidence"

5. The term sexual intercourses is not typically plural, and the use of sexual intercourses is awkward in multiple places.

We have decided to use the terms "sexual relation" and "sexual relations" almost exclusively throughout the manuscript.

Changes in sexual behaviors in men who have sex with men: a comparison between the double-blind and open-label extension phases of the ANRS-IPERGAY trial

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Competing interests

JMM reports receiving support as an adviser for Gilead Sciences, Merck, Janssen, Bristol–Myers Squib (BMS), and ViiV Healthcare, as well as research grants from Gilead Sciences and Merck. BS reports receiving support as an adviser for Gilead Sciences, Merck, Janssen, and BMS, as well as research grants from Gilead Sciences and Merck. CCh reports receiving support as an adviser for Gilead, Pfizer, Janssen, and Astellas. CT reports receiving support from Gilead Sciences and Pfizer. All other authors declare no competing interests.

Authors' contributions

MDC implemented this work under the supervision of LST and BS. MDC, MM and LST led the analysis. The manuscript was written collaboratively between MDC, LST, MSM, CP and BS, with input from DRC, LM, MP and JMM. CT, CCh and CC provided ongoing support to design and perform data collection throughout the cohort study. All authors approved the final manuscript.

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1 Abstract

2 Pre-Exposure Prophylaxis (PrEP) is changing the landscape of
3 HIV prevention, and may bring changes in sexual behaviors. The
4 double-blind phase (DBP) and open-label extension (OLE)
5 study of the ANRS-IPERGAY trial allowed us to assess changes
6 in sexual behavior of men who have sex with men (MSM) taking
7 sexual activity-based (i.e., on-demand) PrEP. Generalized
8 Estimating Equation (GEE) models found a significant decrease
9 in the number of sexual partners (Coefficient [CI95%], p-value;
10 -0.37[-0.70 – -0.04], p=0.03) between the DBP and OLE as well
11 as in the number of sexual relations (-0.25 [-0.49 – 0.00], 0.04).
12 GEE estimates also showed that respondents' most recent sexual
13 relation was less likely to have been with an unknown casual
14 partner during the OLE than during the DBP (Odds Ratio
15 [CI95%], p-value: 0.75[0.62–0.92], 0.005). Furthermore, they
16 showed an increase in the proportion of condomless anal sex in
17 the OLE (1.32[1.04–1.67], 0.02), a decrease in the proportion of
18 'suboptimal PrEP adherence' over time (0.75[0.58–0.97],
19 p=0.03), a decrease in PrEP only use (0.73[0.55–0.96], 0.03) and
20 in both PrEP and condom use over time (0.70[0.51–0.95], 0.02)
21 and finally, a decrease in alcohol consumption between the DBP
22 and OLE (0.74[0.61–0.90], 0.002).
23 We observed both protective and risky behaviors in terms of
24 HIV and STI risk after on-demand PrEP uptake in the OLE
25 phase. Our findings are consistent with results from previous

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26 PrEP trials.

27 **Keywords:** HIV risk management, PrEP, behaviors, MSM,

28 ANRS-IPERGAY trial.

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30 Introduction

31 In recent years, Pre-Exposure Prophylaxis (PrEP) has emerged
32 as one of the most important innovations in HIV prevention for
33 high-risk HIV-negative people, especially men who have sex
34 with men (MSM) (1–3). HIV prevention innovation is regularly
35 associated with the question of “risk compensation” (RC),
36 whereby individuals may take more risks based on the belief that
37 they are protected from infection (e.g., because of condom use,
38 voluntary male circumcision, etc.) (4–6). In the context of PrEP,
39 this translates into a possible increase in condomless sex or in
40 the number of partners, which in turn could negatively impact
41 sexually transmitted infections (STI) incidence. Social norms,
42 moral judgment and the sexuality of people at high risk of HIV
43 infection are all factors in RC and in reticence to provide PrEP
44 access (7,8). Indeed, the editorial, “PrEP why we are waiting”,
45 published in *The Lancet HIV*, illustrates the moral debate
46 surrounding PrEP use and the interaction of social norms with
47 decision-making regarding health (22). More specifically, the
48 authors explained that the first studies on PrEP were focused on
49 its effectiveness and cost, not on normative aspects such as MSM
50 responsibility to use condoms or the important effect of no
51 longer being afraid of HIV infection during sex (22). The very
52 different stances taken by MSM and medical communities
53 regarding PrEP initiation underline that it is not simply a
54 biomedical preventive tool but can also be considered a social

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object (9–11) whose adoption is influenced by social and environmental factors (12,13). The psychosocial approach to health hypothesizes that health behaviors (e.g., preventive and sexual behaviors) are influenced by context at the micro/meso (e.g., attitudes and social norms related to sexuality and prevention strategies in social groups which people belong to) and macro (e.g., a culture’s attitudes and ideologies toward health and sexuality; the availability of and access to prevention tools) levels (14).

In this context, we hypothesized that making PrEP available leads to a change in the field of HIV prevention, which in turn may bring about a change in sexual and preventive behaviors. Accordingly, it is important to study whether sexual behaviors are modified by PrEP initiation and whether they change over time.

In the double-blind phase (DBP) of the US CDC Safety Study (a randomized clinical PrEP trial with quarterly follow-up over 2 years), participants reported fewer partners and less condomless anal sex (CAS) (15). The DBP of the ANRS-IPERGAY trial showed no increase in risky sexual practices (16). During the DBP of the iPrEx trial (quarterly follow-up over 3 years), no increase in receptive CAS or syphilis incidence was observed (17,18). The absence of reported changes in double-blind studies may be due to participants not modifying their behavior because they know they may be taking a placebo (18). As open-label

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80 extension (OLE) and open-label (OLS) studies (the former
81 following DBP in clinical trials, while the latter are performed
82 in non-clinical contexts) both reflect near real-world situations,
83 they constitute excellent research opportunities to determine
84 whether changes in sexual behaviors occur over time in
85 participants who initiate PrEP. Results from the OLE study of
86 the iPrEx trial (quarterly follow-up over 3 years) showed no
87 increase in receptive CAS or syphilis incidence (17,18), while
88 mixed results were found in the OLS PROUD trial, which
89 compared participants randomized into an ‘immediate PrEP’
90 arm with those randomized into a ‘one-year deferred PrEP’ arm.
91 More specifically, a larger proportion of respondents in the
92 former reported CAS, yet no difference was observed between
93 both arms concerning the number of sexual partners (2).
94 Furthermore, objective indicators of CAS, including the
95 incidence of rectal gonorrhea and chlamydia infections, were not
96 different between both arms. Despite the longitudinal dimension
97 of the PROUD trial, the changes in sexual behaviors were only
98 analyzed for one time-point (12 months). The OLS US PrEP
99 Demonstration Project showed a decrease in the mean number
100 of anal intercourse partners and no change in the proportion of
101 CAS during follow-up (quarterly follow-up over one year) (19).
102 STI incidence also remained stable (19). To summarize, results
103 from OLE and OLS studies to date have not shown any clear
104 changes in MSM risky sexual behaviors after PrEP initiation.

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105 With regards to real-world settings, results are mixed. A clinical
106 PrEP program in Rhode Island showed an increase in the number
107 of CAS partners 6 months after PrEP initiation compared with
108 baseline data (20) while findings from a different clinical setting
109 indicated no increase in either STI incidence or the number of
110 sexual partners after PrEP initiation (bi-annual follow-up over
111 one year) (21).

112 Apart from the iPrEx trial, no study to date has collected
113 longitudinal data about changes in sexual behaviors before and
114 after PrEP initiation. Moreover, no OLE or OLS study has
115 evaluated changes in sexual behaviors in MSM who take sexual
116 activity-based PrEP (i.e., on-demand PrEP). The efficacy of
117 sexual activity-based PrEP in MSM was shown in the ANRS-
118 IPERGAY trial which involved a longitudinal follow-up of
119 participants in both the DBP and OLE phases (3,22). Unlike
120 daily PrEP, sexual activity-based PrEP requires individuals to
121 assess risks before sexual relations. This may prompt MSM to
122 reappraise their preconceptions of the risks involved over time
123 (i.e., a change in risk perception), leading in turn to changes in
124 their sexual behaviors.

125 The present paper aimed to assess changes in sexual behaviors
126 of MSM between the DBP and OLE phases of the ANRS-
127 IPERGAY trial. Although previous studies of sexual behaviors
128 in PrEP trials primarily used only two indicators (the proportion
129 of CAS and the number of partners), in order to guarantee a more

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130 holistic approach, we chose to study changes for a much wider
131 set of behavioral factors, described in detail in the methods
132 section below.

133 **Methods**

134 **ANRS-IPERGAY trial design**

135 The ANRS-IPERGAY trial, conducted in France (Paris, Nantes,
136 Lyon, Lille and Nice) and Canada (Montreal), consisted in
137 providing sexual activity-based PrEP to high-risk MSM (3).
138 Inclusion criteria were HIV-negative status, being at least 18
139 years old, being a male or transgender female who had sex with
140 men, and being at high risk of HIV infection (defined as a history
141 of CAS with at least two partners during the previous 6 months)
142 (3). At baseline, participants completed a questionnaire covering
143 socio-demographic characteristics and sexual behaviors. The
144 trial was conducted in partnership with the community-based
145 association AIDES, which identified and enrolled participants,
146 thanks to its members' proximity to the MSM community. At
147 follow-up visits (two-monthly), participants benefited from one-
148 to-one, tailored, risk-reduction counselling provided by a peer
149 counsellor. As part of the trial, they were provided condoms and
150 lubricants, and were regularly tested for HIV and other sexually
151 transmitted infections free of charge (STI) (3). During
152 counselling visits, peer counsellors encouraged PrEP uptake as
153 part of combined prevention (e.g., PrEP in conjunction with
154 condom use). The PrEP treatment schedule was as follows: two

1 155 pills (TDF-FTC or placebo) 2 to 24 hours before sexual relations,
2 156 followed by a third and fourth pill 24 and 48 hours after the first
3
4 157 dose, respectively. For participants who had very frequent sexual
5
6 158 relations, the schedule was one pill per day for each day when
7
8 159 sexual relations occurred, then one pill 24 and 48 hours after
9
10 160 their most recent sexual relation (3,22). The randomized DBP
11
12 161 started in February 2012, and thanks to the reduction observed
13
14 162 in HIV incidence between the two arms, the placebo arm was
15
16 163 discontinued in November 2014 (3,22). The trial then continued
17
18 164 as an OLE study until June 2016. MSM who had not participated
19
20 165 in but were eligible for the DBP could be included in the OLE
21
22 166 sample, depending on eligibility. The OLE phase included 29
23
24 167 new participants. The only difference between the DBP and the
25
26 168 OLE was the suppression of the placebo arm following the proof
27
28 169 of on-demand PrEP effectiveness. New inclusions were
29
30 170 permitted for the OLE phase in order to provide PrEP access to
31
32 171 a larger sample of MSM in France (a sub-population for which
33
34 172 PrEP was not yet authorized in France at the time of this study).
35
36 173 During the DBP and OLE phases, online questionnaires were
37
38 174 completed every 2 months covering socio-demographic
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40 175 characteristics, alcohol and recreational drug use, sexual
41
42 176 behaviors, and PrEP adherence during participants' most recent
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44 177 sexual relation. Questionnaires were sent through an online link
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46 178 10 days before the scheduled follow-up visit. Participants had
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48 179 one month to complete them before the online link expired.
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180 When a delay in filling in a questionnaire was detected, two
181 reminders were sent by email, the first 5 days before the
182 scheduled follow-up visit and the second before the online link
183 expired. Participants could fill in the questionnaires together
184 with the peer counsellor during the follow-up visit if they
185 wished. PrEP delivery was guaranteed irrespective of whether
186 the questionnaire was filled in or not.

187 The protocol (amended for the OLE study) was approved by
188 public health authorities and ethics committees in France
189 (Comité de Protection des Personnes, Paris, Ile de France IV)
190 and Canada (Comité d'éthique de la recherche, Montreal, QC).
191 All participants provided written informed consent to participate
192 in the DBP. All 361 participants of the OLE study provided oral
193 informed consent, with 353 (98%) of them also providing
194 written consent.

195 **Outcomes**

196 At each bi-monthly visit (from M0 to M24 in the DBP, and from
197 M0 to M18 in the OLE), sexual behavior and prevention
198 strategies were assessed at each follow-up visit using the
199 following eight outcomes, two of which were continuous (i and
200 ii) and six of which concerned the most recent sexual relation (iii
201 to viii): (i) number of sexual relations during the previous 4
202 weeks; (ii) number of sexual partners during the previous 2
203 months; (iii) a 4-category outcome for the type of partner: main,
204 unknown casual, known casual or multiple; (iv) a dichotomous

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205 indicator for insertive/receptive CAS (yes= 1 and no = 0); (v) a
206 4-category outcome for combined prevention: PrEP only,
207 condom use only, PrEP and condom use, and no PrEP or condom
208 use; (vi) a 6-category outcome for the use of the following
209 recreational drugs (in the context of sexual relations): ecstasy,
210 cocaine, poppers, GHB/GBL, Ketamine, Viagra; (vii) a
211 dichotomous indicator for alcohol consumption (in the context
212 of sexual relations) (yes=1/no=0) ; and (viii) a 3-category
213 outcome for PrEP adherence: correct use, no PrEP use, and
214 suboptimal use. ‘Correct’ use was defined as taking at least one
215 pill within 24 hours before sexual relations and one pill within
216 24 hours after relations, ‘no PrEP use’ was defined as not taking
217 any pills within 48 hours either before or after the most recent
218 sexual relation, while ‘suboptimal use’ was defined as any other
219 use (3).

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220 We hypothesized that investigating several behavioral factors
221 would provide a more holistic overview of the changes in sexual
222 behaviors and prevention strategies in the study population.

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223 Although measures of plasma drug levels show whether
224 participants have been exposed to TDF-FTC, it is not clear if this
225 occurs before and after PrEP pill intake (22). Accordingly, we
226 were not able to use this variable to assess on-demand PrEP
227 schedule adherence. The iPrEx study showed that self-reporting
228 PrEP use was a strong predictor of concentration in plasma (23).

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229 Therefore, we used self-reported adherence to measure on-

230 demand PrEP adherence during the most recent sexual relation.

231 We were able to observe how PrEP uptake influenced study

232 participants' sexual behaviors by evaluating the following: CAS,

233 the number of partners, number of sexual relations, type of

234 sexual partner, and alcohol and recreational drug use before and

235 during sex.

236 **Statistical analysis**

237 Chi-square tests (dichotomous and categorical outcomes) and t-

238 tests (continuous outcomes) were performed to describe the

239 sociodemographic characteristics and sexual behaviors of

240 participants at inclusion in the DBP. The same tests were also

241 performed to compare outcomes between the DBP and OLE

242 phases.

243 We also implemented generalized estimating equation (GEE)

244 models to study changes over time over time in the study

245 population's sexual behaviors after PrEP initiation. The main

246 advantage of GEE models is that they take account of intra-

247 individual correlation in longitudinal settings, which allows

248 robust estimations of outcomes and associated variances (24,25).

249 We used a negative binomial function for continuous outcomes,

250 a binary logistic function for dichotomous outcomes, and a

251 multinomial logistic function for outcomes with more than 2

252 categories.

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253 In line with our study's objectives, the GEE models were
254 adjusted according to the three following explanatory variables:
255 i) a dichotomous variable to investigate whether the outcomes
256 changed significantly between DBP and OLE phases, ii) time as
257 a continuous variable, to measure the overall changes in
258 outcomes over time and iii) a variable measuring the interaction
259 between time and the DBP/OLE indicator, which enabled us to
260 investigate whether changes over time occurred more during the
261 DBP or more during the OLE. Three GEE models were tested
262 for each outcome by adding the explicative variables one by one.
263 We used the Independence model Criterion (QIC) for the
264 goodness-of-fit in order to choose the model with the best
265 specification.

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266 In line with our study's objectives, analyses were performed
267 only for the 332 participants who participated in both the DBP
268 and OLE.

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269 To compare whether participants who left the trial after the DBP
270 phase (n=67) were not at greater risk than those participating in
271 both phases (n=332) a comparison was performed using chi-
272 square/T test.

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273 All analyses were performed using SAS 9.4 statistical software.

51 **Results**

52 **Results**

53 Sample characteristics

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276 The present analyses were performed on the 332 participants
277 enrolled in both the DBP and OLE phases (Table 1),
278 corresponding to 4978 analyzable questionnaires.
279 Mean age was 35.8 years (sd=14.0) (Table 1). Most participants
280 self-defined as gay (n=305, 91.9%), and only 10 as bisexual
281 (3.0%). A majority (73.9%) reported having an education level
282 equal to or higher than high-school diploma, while 84.6%
283 reported being in active employment.
284 With regard to sex life, at DBP baseline, 41.9% reported having
285 a main partner. Of these, 61.3% had an HIV-negative main
286 partner. The mean number of sexual relations (in the previous 4
287 weeks) and of sexual partners (in the previous 2 months) was,
288 13(sd=11.7) and 13.5(sd=16.1), respectively. At baseline, 60.7%
289 and 58.6% reported CAS and PrEP use, respectively. A majority
290 (78.8%) reported sexual relations with partners other than a main
291 partner. Use of recreational drugs and alcohol consumption
292 before/during sex were reported by 36.7% and 12.6% of the
293 participants, respectively. No significant difference was
294 estimated between the 332 respondents who participated in both
295 the DBP and OLE phases, and those who left the trial after the
296 DBP phase (n=67).

51 Comparative description of sexual behaviors and prevention
52 strategies between the DBP and OLE phases
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299 No significant difference was reported between the DBP and
300 OLE in terms of the mean number of sexual relations during the

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301 previous 4 weeks (13.2(sd=15.9) vs 12.5(sd=14.7); p=0.11) or
302 the mean number of sexual partners during the previous 2
303 months (13(sd=16.1) vs 12.3(sd=19.3), p=0.20) (Table 2; Fig.1).
304 With respect to the most recent sexual relation, the following
305 results were found regarding changes in sexual behaviors
306 between the DBP and the OLE study:
307 i) a significant increase in the proportions of most recent sexual
308 relation with unknown casual partners (48.0% in the DBP vs.
309 52.0% in the OLE, p<0.005) and most recent sexual relation
310 with main partners (41.1% in the DBP vs. 58.9% in the OLE,
311 p<0.001) (Table 2; Fig.2);
312 ii) a significant increase in the proportion of CAS (Table 2;
313 Fig.3) (42.2% vs. 57.8%, p<0.001);
314 iii) an increase in the proportions of reported 'correct' PrEP
315 adherence (39.9% in DBP vs. 60.1% in OLE, p<0.005) and
316 'suboptimal' PrEP adherence (48.1% vs 51.9%, p<0.001) (Table
317 2; Fig.4);
318 iv) a significant increase in the proportions of most recent sexual
319 relations with 'PrEP only' (39.6% vs. 60.4%, p<0.005) and with
320 'both PrEP and condom use' (48.3% vs. 51.7%, p<0.001) (Table
321 2, Fig.5);
322 v) no change for the use of recreational drugs (44.6% in DBP vs.
323 55.4% in OLE, p=0.3), but a significant decrease for alcohol
324 consumption (51.6% in DBP vs. 48.4% in OLE, p<0.001) (Table
325 2, Fig.6).

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326 It is important to underline that all the descriptive statistics listed
327 in (i) to (v) above are based on comparisons of averages between
328 DBP and OLE, and none suggested a trend.

329 Multivariate analysis of sexual behaviors and prevention
330 strategies

331 The GEE model estimates (Table 3a) showed a significant
332 decrease both in the number of sexual partners and in the number
333 of sexual relations between the DBP and OLE study phases. On
334 average, participants in the OLE had 0.37 fewer sexual partners
335 during the previous 2 months than those in the DBP (Coefficient
336 [CI95%], p-value; -0.37[-0.70 – -0.04], p=0.03) and 0.25 fewer
337 sexual relations during the previous 4 weeks (-0.25 [-0.49 –
338 0.00], 0.04).

339 With regard to the type of partner, the GEE model estimates
340 (Table 3b) showed that the proportion of sexual relations with an
341 unknown casual partner was significantly lower (on average
342 25%) during OLE than DBP (Odds Ratio [CI95%], p-value:
343 0.75[0.62–0.92], 0.005). As the GEE model accounted for time
344 trends, we were able to estimate that, all things being equal, the
345 proportion of sexual relations with unknown casual partners
346 decreased between the DBP and OLE.

347 With respect to prevention strategies, the GEE model estimates
348 (Table 3b) confirmed that the proportion of CAS during the most
349 recent sexual relation increased significantly (on average 32%
350 per year), but only during the OLE (1.32[1.04–1.67], 0.02, Table

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351 3b). The proportion of ‘suboptimal PrEP use’ (Table 3b) during
352 the most recent sexual relation, decreased over time during the
353 whole follow-up (i.e., the DBP and OLE combined as one long
354 period) (0.75[0.58–0.97], p=0.03, Table 3b). Figure 4 shows that
355 the proportion of suboptimal PrEP use decreased from 33.5% to
356 14.3% during the whole follow-up. Again, the fact that the GEE
357 model took into account time trends resulted in a significant
358 decrease of 25% per year being highlighted, something which
359 the Chi-square test was not able to observe.

360 With regard to combined prevention, the GEE model (Table 3b)
361 showed, all things being equal, a significant decrease in ‘PrEP
362 use only’ (on average 27% per year) (0.73[0.55–0.96], 0.03) and
363 in ‘PrEP and condom use’ (on average 30% per year)
364 (0.70[0.51–0.95], 0.02). As for the use of recreational drugs
365 (Table 3b), no changes were observed in the GEE models
366 concerning, but estimates did show a significant decrease in
367 alcohol consumption between the DBP and OLE phases
368 (0.74[0.61–0.90], 0.002).

369 From these results we see that our decision to account for intra-
370 individual correlations of repeated measures over time with GEE
371 models offered a better overview of sexual behavior changes
372 than just describing the dataset.

373 **Discussion**

374 Our analysis provided estimates for the changes in sexual
375 behaviors after PrEP initiation in the ANRS-IPERGAY trial in

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376 high-risk HIV-negative MSM taking on-demand PrEP.

377 Results from GEE models showed an increase in several

378 protective behaviors regarding HIV risk between DBP and OLE,

379 including a significant decrease in the number of sexual relations

380 and sexual partners, a decrease in the proportion of sexual

381 relations with unknown causal partners, and a decrease in

382 alcohol consumption during sexual relations. However, results

383 also showed an increase in risky sexual behaviors, including a

384 significant increase in CAS in the OLE phase. The increase in

385 CAS is of major concern in terms of IST incidence.

386 Non-longitudinal results showed a high level of ‘correct’ and

387 ‘suboptimal’ PrEP use during DBP and OLE, which is consistent

388 with findings from a previous study on the same cohort (22). An

389 increase in the proportions of sexual encounters where PrEP-

390 only and combined PrEP-condom prevention was used was also

391 observed between the DBP and OLE. However, GEE results

392 provided a more precise measure of the evolution of PrEP use in

393 the trial. Indeed, the proportions of suboptimal PrEP, PrEP-only

394 and combined PrEP-condom prevention all decreased

395 significantly over time, not only after the placebo arm was

396 suppressed. These results were not seen by the non-longitudinal

397 analysis, which focused only on changes between the DBP and

398 OLE (i.e., it did not take trends over time into account). Results

399 from our GEE models might reflect the issue of lack of PrEP

400 persistence which has been highlighted elsewhere (26,27). A

1 401 recent qualitative study showed that the barriers to PrEP
2 402 persistence are strongly linked to issues regarding insurance
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4 403 costs and to scheduled medical appointments which are
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7 404 mandatory in PrEP programs (28). In our study, PrEP was free
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10 405 of charge for participants. Accordingly, the trial's scheduled
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12 406 two-monthly medical appointments may have led to a lack of
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14 407 PrEP persistence (i.e., temporary treatment interruptions).
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17 408 PrEP use did not seem to impact recreational drug use in the
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19 409 sexual context or the proportion of sexual relations with multiple
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21 410 partners or with known casual partners.
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24 411 Our study took into account a larger set of sexual behavioral
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26 412 factors than in the majority of previous studies. Accordingly, our
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28 413 results may provide more detailed information on the impact of
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30 414 PrEP use on sexual behaviors and prevention strategy dynamics
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33 415 in MSM.
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36 416 The increase in CAS during the OLE is a major concern for the
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38 417 risk of STI infection. However, while previous results from the
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40 418 ANRS-IPERGAY trial showed that the rate of STI was high
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42 419 among participants, it did not differ between the DBP and OLE
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44 420 study phases (22). Different studies have shown similar results
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46 421 (i.e., increase in CAS without an increase in STI among MSM
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48 422 PrEP users) (2) (29) . This suggests that PrEP uptake is not the
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51 423 only predictive factor of STI. While a study in Germany showed
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53 424 that PrEP uptake did not lead to an increase in of STI (30), a
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55 425 recent retrospective cohort study of PrEP users in Canada found
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1 426 the opposite at 12 months after PrEP initiation (31).
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3 427 Therefore, the relationship between PrEP uptake, CAS and
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5 428 increase in STI is not clear. In any case, STI do not undermine
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7 429 PrEP efficacy and if anything, PrEP monitoring is an opportunity
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9 430 to increase testing and treatment for STI (22).
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11 431 With regard to risk compensation (RC), our results highlighted
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13 432 changes in behavior after PrEP initiation which reflected greater
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15 433 protection but also greater risk. More specifically, the number
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17 434 of sexual relations and number of sexual partners both
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19 435 decreased, as did sexual relations with unknown casual partners
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21 436 and alcohol consumption during sex. Risky behaviors included
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23 437 an increase in CAS - despite the STI rate remaining stable
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25 438 between the DBP and OLE (20) - and issues associated with
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27 439 PrEP persistence over time. Therefore, our results were unable
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29 440 to conclude whether a risk compensation mechanism was
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31 441 present or not with on-demand PrEP in the ANRS-IPERGAY
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33 442 trial.
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35 443 However, a recent publication suggested that RC is not a valid
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37 444 framework to study PrEP use (7). Some studies, including a
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39 445 qualitative study previously conducted among participants
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41 446 during the OLE phase of the ANRS-IPERGAY trial, have
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43 447 highlighted that PrEP has the potential to reduce fear of HIV
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45 448 infection and can lead to a more satisfying sex life (32,33,34). In
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47 449 that ANRS-IPERGAY study, participants perceived condoms as
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49 450 a barrier (materially and symbolically) to pleasure and desire,
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451 whereas PrEP was seen as a means to freely choose sexual
452 positions and to better enjoy intimacy (34). Participants also
453 reported improved sexual quality of life thanks to PrEP use (34).
454 These results reflect the World Health Organization’s policy that
455 everyone has the right to a good quality of sexual life (35).
456 Therefore, one of the most important benefits of PrEP use is an
457 improvement in sexual life, something which not considered in
458 the RC concept (7).
459 Moreover, the concept of RC was originally established for the
460 road injury prevention context, and subsequently applied to that
461 of sexual behaviors (36) without considering that psychosocial
462 factors may differ between contexts.
463 Therefore, sexual behavior changes linked to PrEP initiation
464 should not be studied only in light of RC but also in terms of
465 quality of sexual life and sexual health.
466 Our results showed that HIV risk taking in MSM depends on the
467 prevention tools available to them. The MSM recruited in
468 ANRS-IPERGAY were recruited on the basis of their high-risk
469 practices. After PrEP initiation, this risk was largely removed
470 with only one HIV infection occurring during the OLE (22). In
471 addition, a previous study on “chemsexers” in the ANRS-
472 IPERGAY trial showed that they were more likely to report
473 high-risk sexual practices but also had a higher perception of risk
474 (37). Chemsexers were also more likely to use PrEP correctly
475 (37). These results would therefore suggest that PrEP may also

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476 be a suitable tool to reduce HIV transmission in high-risk
477 populations, such as chemsexers.
478 Our results provide recommendations which should be taken
479 into account for future PrEP cohort studies. The increase in CAS
480 in ANRS-IPERGAY and the resulting potential increase of STI
481 are serious public health concerns for MSM PrEP users. In order
482 to reduce them, it may be useful to increase the focus on STI
483 prevention during PrEP counseling and move to a global sexual
484 health support. Establishing protocols for partner notification
485 may also accelerate treatment for STI in MSM, in turn reducing
486 the potential STI rate in this population. Furthermore, PrEP
487 persistence is a major issue in PrEP success. PrEP adherence
488 slowly decreased over time in our trial. It would be useful in
489 future studies on other cohorts to provide qualitative data
490 concerning PrEP persistence and its associated factors in order
491 to adapt PrEP protocols. Access to PrEP needs to be investigated
492 in greater detail, especially regarding the issue of mandatory
493 medical appointments and more globally, the various steps
494 which to be followed in order to obtain it.
495 Our study has limitations. First, the data we analyzed were
496 collected in a clinical trial with a strict follow-up and with highly
497 motivated participants. Therefore, our results cannot be
498 generalized to all PrEP users. Second, we do not have specific
499 qualitative data for all the elements investigated in our study,
500 which could have helped us to understand the reasons for the

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501 different prevention choices, specifically for sexual relations
502 without PrEP or condoms (i.e., an individual choice, unavailable
503 PrEP at the time and location of sexual relations, etc.). Third, the
504 participant-peer counsellor relationship may have led to social
505 desirability bias. Fourth, we had no control group with the same
506 characteristics as our participants to compare changes in sexual
507 behaviors, and to confirm that the changes observed were indeed
508 related to participation in the PrEP trial and not due to trends in
509 sexual practices in the MSM community.

510 **Conclusion**

511 The move from the DBP to the OLE study in high-risk HIV-
512 negative MSM enrolled in the ANRS-IPERGAY trial was
513 associated with several protective changes in sexual behaviors.
514 Reductions in the numbers of sexual partners and number of
515 sexual relations were observed, as were reductions in sexual
516 relations with unknown casual partners and alcohol consumption
517 during sex. However, an increase in condomless sex was also
518 observed, which highlights the increased potential risk of STI
519 associated with PrEP use.

520 Further in-depth studies need to explore the characteristics
521 associated with condomless anal sex without PrEP, the
522 introduction of PrEP in real-world contexts and the PrEP
523 persistence dynamic.

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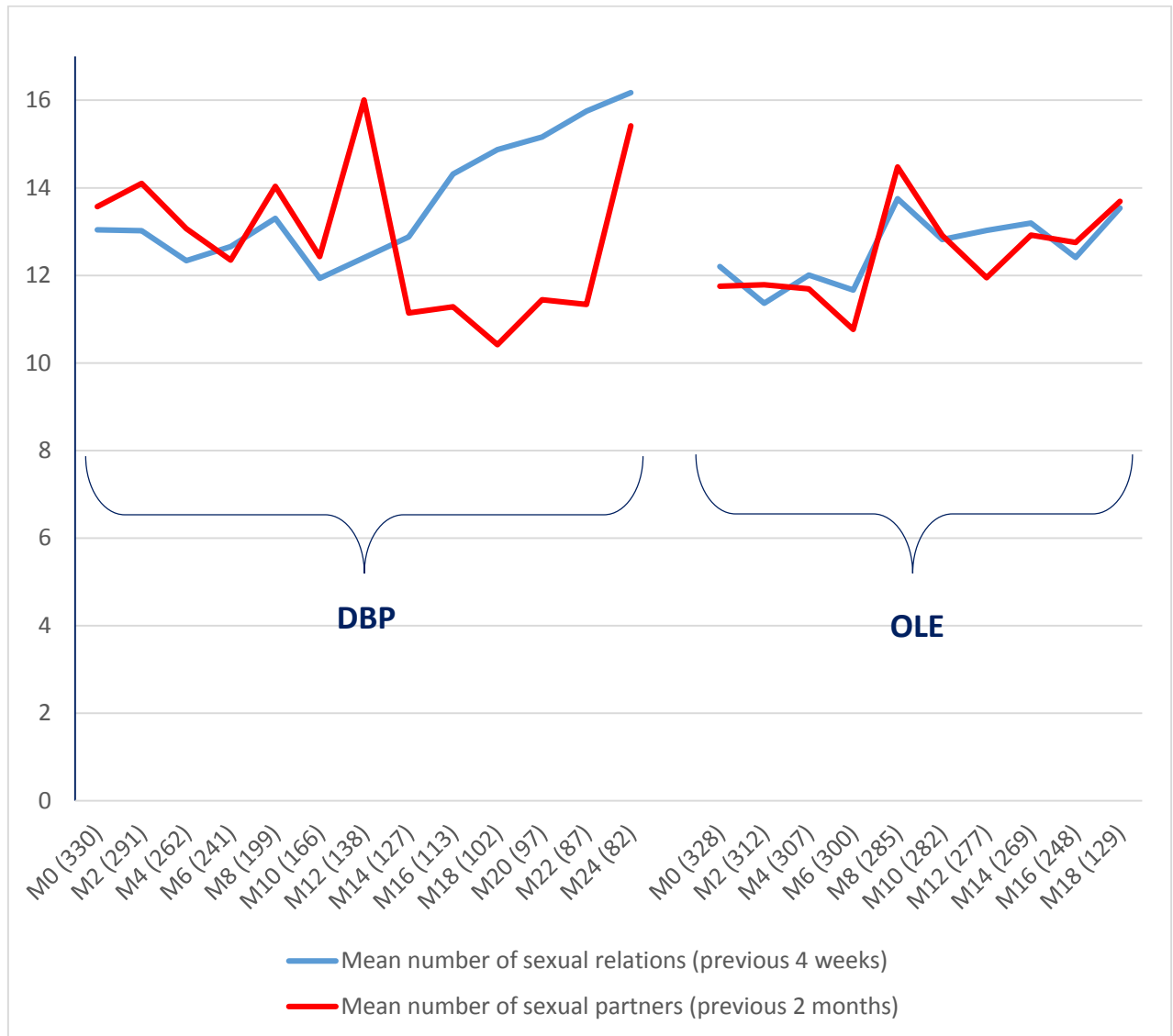


Fig.1 Evolution of the mean number of sexual relations and number of partners (n=332)

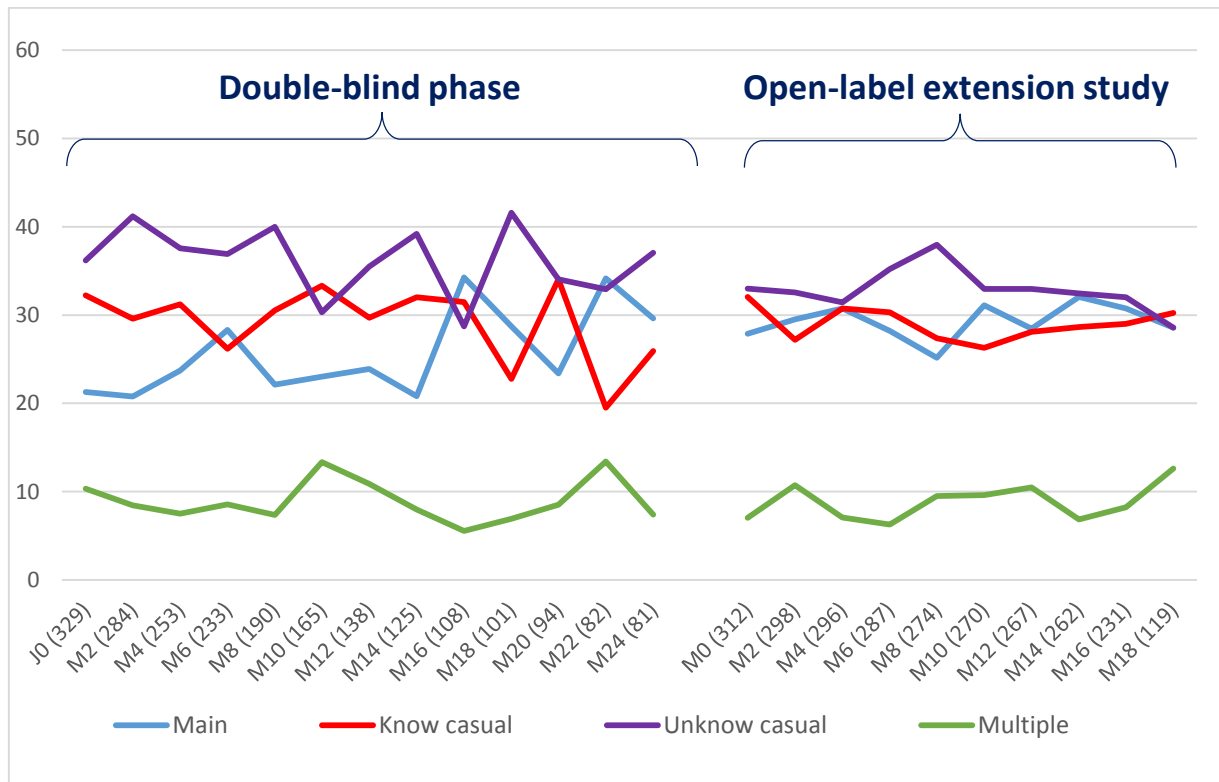


Fig.2 Evolution of the type of partner at most recent sexual encounter (n=332)

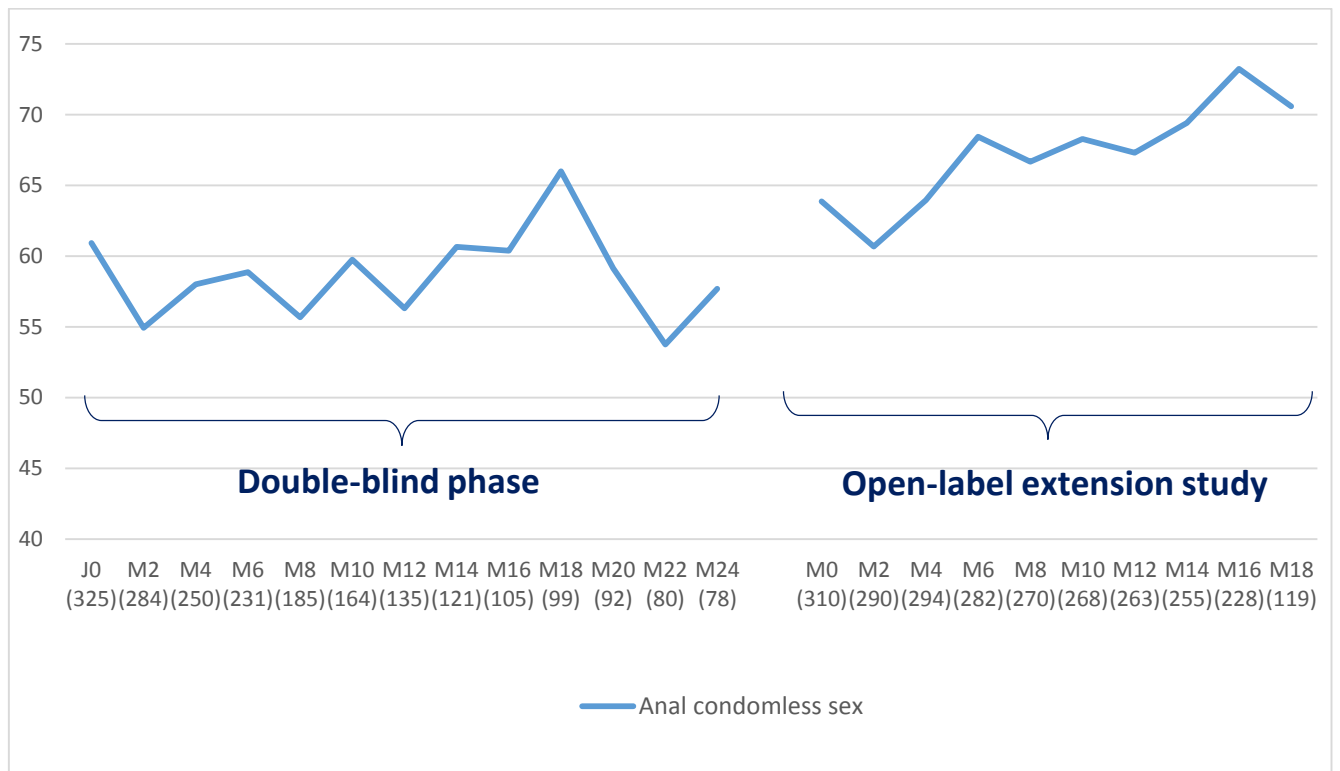


Fig.3 Evolution of anal condomless sex (n=332)



Fig.4 Evolution of PrEP adherence (n=332)

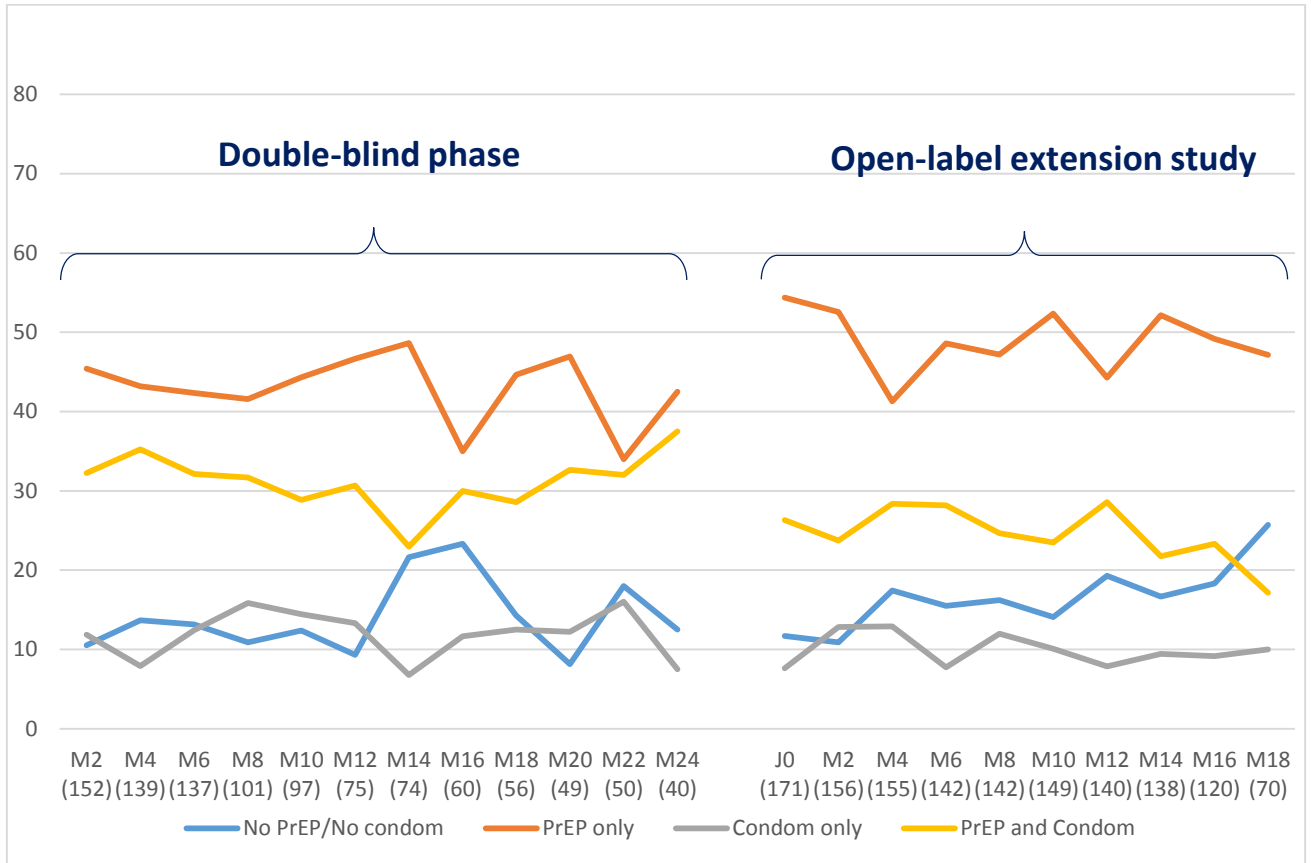


Fig.5 Evolution of combined prevention (n=332)

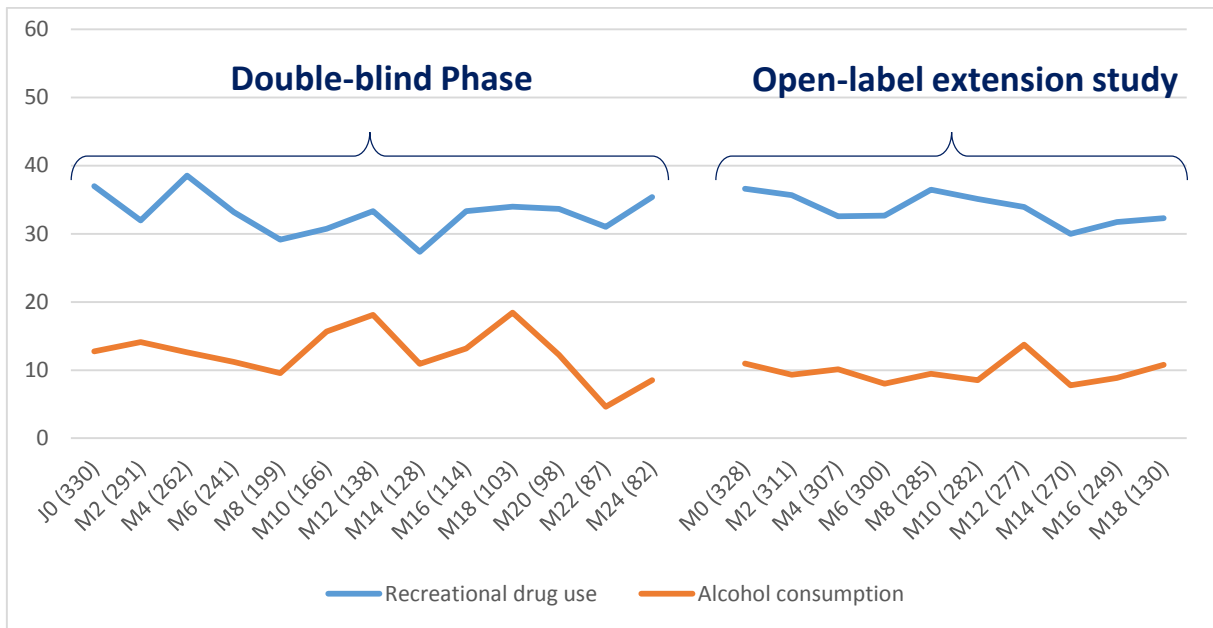


Fig.6 Evolution of recreational drug and alcohol use (n=332)

Table 1 Main Characteristics at DBP baseline of those who participated in both the DBP and OLE phases (ANRS IPERGAY, n=332)

	Number of those who participated in both phases (N=332)
Age, mean (Standard Deviation, SD)	35.8 (14.0)
Sexual orientation, n (%)	
Gay	305 (96.5) ^a
Bisexual	10 (3.2)
Trans / transsexual / transgender	1 (0,3)
Education level, n (%)	
< High-school diploma	86 (26.1) ^b
≥ High-school diploma	243 (73.9)
Active employment, n (%)	
No	51 (15.4) ^c
Yes	279 (84.6)
Main male partner, n (%)	
No	191 (58.1) ^b
Yes	138 (41.9)
Main male partner HIV status, n (%)	
HIV negative	84 (61.3) ^d
HIV positive	43 (31.4)
Do not know	10 (7.3)
Number of sexual relations (previous 4 weeks), mean (SD)	13 (11.7) ^e
Number of sexual partners (previous 2 months), mean (SD)	13.5 (16.1)
Condomless anal sex during most recent sexual relation, n (%)	
No	128 (39.3) ^e
Yes	198 (60.7)
PrEP adherence (M2) during most recent sexual relation, n (%)	
No PrEP	34 (22.2) ^f
Suboptimal	51 (33.3)
Correct	67 (44.5)
Type of partner during most recent sexual relation, n (%)	
Multiple partners	34 (10.3) ^c
Unknown casual partner	119 (36.0)
Known casual partner	107 (32.6)
Main partner	70 (21.2)

**Number of those who
participated in both phases
(N=332)**

Recreational drug use during most recent sexual
relation, n (%)

No	210 (63.3)
Yes	122 (36.7)

Alcohol consumption during most recent sexual
relation, n (%)

No	290 (87.4)
Yes	42 (12.6)

- ^a 16 missing values
^b 3 missing values
^c 2 missing values
^d 195 missing values
^e 6 missing values
^f 180 missing values
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Table 2 Comparison of sexual behaviors and prevention strategy variables between the DBP and OLE phases (n=332; 4978 questionnaires)

	DBP (n=2239, 45.0%)	OLE (n=2739, 55.0%)	p-value ^a
Number of sexual relations (previous 4 weeks), mean (Standard Deviation, SD)	13.2 (15.9) ^b	12.5 (14.7) ^c	0.11
Number of sexual partners (previous 2 months), mean (SD)	13 (16.1) ^d	12.3 (19.3) ^e	0.20
Condomless anal sex at most recent sexual relation, n (%)			
Yes	1259 (42.2) ^f	1723 (57.8) ^g	<0.001
No	894 (51.1)	856 (48.9)	<0.001
PrEP adherence at most recent sexual relation, n (%)			
No PrEP	261 (42.2) ^h	358 (57.8) ⁱ	0.38
Suboptimal	309 (48.1)	333 (51.9)	<0.001
Correct	460 (39.9)	692 (60.1)	<0.005
PrEP-condom use at most recent sexual relation, n (%)			
No PrEP - No condom	139 (38.7) ^h	220 (61.3) ⁱ	0.05
PrEP only	446 (39.6)	679 (60.4)	<0.005
Condom only	122 (46.9)	138 (53.1)	0.07
PrEP and condom	323 (48.3)	346 (51.7)	<0.001
Type of partner at most recent sexual relation, n (%)			
Multiple partners	196 (46.6) ^j	225 (53.4) ^k	0.32
Unknown casual partner	803 (48.0)	869 (52.0)	<0.005
Known casual partner	650 (46.1)	760 (53.9)	0.28
Main partner	534 (41.1)	766 (58.9)	<0.001
Recreational drug use at most recent sexual relation, n (%)			
Yes	748 (44.6)	928 (55.4)	0.36
No	1491 (45.2)	1811 (54.9)	0.36
Alcohol consumption at most recent sexual relation, n (%)			
Yes	284 (51.6)	266 (48.4)	<0.001
No	1955 (44.2)	2473 (55.8)	<0.001
a Chi-Square Test/ T-Test	i 1356 missing data		
b 75 missing data	j 56 missing data		
c 128 missing data	k 119 missing data		
d 16 missing data			
e 19 missing data			
f 86 missing data			
g 160 missing data			
h 1209 missing data			

Table 3a Evolution of sexual behaviors between the DBP and OLE phases (GEE, continuous variables)

	Evolution in the number of sexual relation (previous 4 weeks)¹	Evolution of the number of sexual partners (previous 2 months)²
	Coefficient [CI95%], p-value*	Coefficient [CI95%], p-value*
Phase: DBP (ref) vs OLE	-0.25 [-0.49 – 0.00], 0.04	-0.37 [-0.70 – - 0.04], 0.03
Evolution over time	0.09 [0.00 – 0.18], 0.05	-0.07 [-0.19 – 0.06], 0.30
Evolution over time X phase(OLE)	–	0.16 [0.00 – 0.33], 0.05
QIC**	-136995.0515	-133604.7802

* Results from the GEE model

** Quasi-likelihood under the Independence model Criterion

¹ QIC model with study phases as explicative variables: -134142.4725; model with time, study phases and the interaction of time with study phases as explicative variables: -136975.3351

² QIC model with study phases as explicative variables: -133100.2591; model with time and study phases as explicative variables: -133076.6388

Table 3b Evolution of sexual behaviors and prevention strategies between the DBP and OLE phases (GEE, categorical variables)

	Condomless sex (ref No) ¹	PrEP adherence (ref No PrEP) ²		Combined PrEP-condom use (ref. No PrEP or condom use) ³		
	Yes * OddsRatio [CI95%], p-value	Suboptimal* OddsRatio [CI95%], p-value	Correct* OddsRatio [CI95%], p-value	Condom only* OddsRatio [CI95%], p-value	PrEP only* OddsRatio [CI95%], p-value	PrEP and condom* OddsRatio [CI95%], p-value
Phase: DBP (ref) vs OLE	0.63 [0.38–1.03], 0.06	1.41[0.76–2.62], 0.27	1.50[0.90–2.52], 0.12	1.30[0.63–2.70], 0.48	1.80[0.98–3.32], 0.05	1.39[0.70–2.77], 0.34
Evolution over time	1.02 [0.86–1.22], 0.82	0.75[0.58–0.97], 0.03	0.85[0.69–1.06], 0.15	0.74[0.52–1.05], 0.09	0.73[0.55–0.96], 0.03	0.70[0.51–0.95], 0.02
Evolution over time X Phase (OLE)	1.32[1.04–1.67], 0.02	–	–	–	–	–
QIC**	6205.7717	5094.7733	5094.7733	5969.9733	5969.9733	5969.9733

*Results from the GEE model

** Quasi-likelihood under the Independence model Criterion

¹ QIC model with study phases as explicative variables: 6211.369; model with time and study phases as explicative variables: 6209.0642

² QIC model with study phases as explicative variables: 5096.5498; model with time, study phases and the interaction of time with study phases as explicative variables: 5094.8083

³ QIC model with study phases as explicative variables: 5971.0632; model with time, study phases and the interaction of time with study phases as explicative variables: 5975.5118

(Continued)

	Type of partner (ref Main partner) ¹			Recreational drug use(ref No) ²	Alcohol consumption(ref No) ³
	Multiple partners* OddsRatio [CI95%], p-value	Unknown casual partner* OddsRatio [CI95%], p-value	Known casual partner * OddsRatio [CI95%], p-value	Yes * OddsRatio [CI95%], p-value	Yes * OddsRatio [CI95%], p-value
Phase: DBP (ref) vs OLE	0.80[0.62–1.03], 0.08	0.75[0.62–0.92], 0.005	0.82[0.66–1.00], 0.05	1.27[0.90–1.79], 0.17	0.74[0.61–0.90], 0.002
Evolution over time	–	–	–	0.90[0.79–1.03], 0.13	–
Evolution over time X Phase(OLE)	–	–	–	–	–
QIC**	12451.6282	12451.6282	12451.6282	6378.1142	3461.5202

* Results from the GEE model

** Quasi-likelihood under the Independence model Criterion

¹ QIC model with time and study phases as explicative variables: 12451.8187; model with time, study phases and the interaction of time with study phases as explicative variables: 12457.9333

² QIC model with study phases as explicative variables: 6378.565; model with time, study phases and the interaction of time with study phases as explicative variables: 6380.2935

³ QIC model with time and study phases as explicative variables: 3463.473; model with time, study phases and the interaction of time with study phases as explicative variables: 3465.5496

