Risk compensation in PrEP

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- Participation to the scientific boards of RACING (MSD) and SToRy studies (GILEAD)
- Support from MSD to go to AIDS 2014
What is risk compensation?

- Some times called “behavioral disinhibition”
- Often seen as the Achilles' heel of innovations in HIV prevention
- The idea is that the level behavior changes could overtake the gains brought by a new prevention intervention
- Scientific evidence is weak:
  - perception reports: ex concerns in HIV vaccine trials
  - modeling studies
- PreP is the ideal topic for such debate though the issue is not new
Circumcision

- A concern of anti-circumcision researchers
  - Van Howe, J Public Health Afr 2011

- No impact on STI incidence and behavioral outcomes in circumcision RCT in Kenya

- No association of behavioral outcome and circumcision in Kenya during circumcision scale-up programs between 2008 and 2013
  - Westercamp, JAIDS 2017

- No clear evidence of risk compensation in a long-term cohort study in Dominican Republic
  - Brito, J Sex Med 2017
Antiretroviral therapy and impact on epidemic decline in resource-limited settings: models were modified according to the level of potential risky sexual behaviors

TEMPRANO data analyses suggest that important reduction of HIV transmission may be expected from the scale-up of early ART, even in the context of behavioral change: only cumulative dramatic changes could impact the protective effect of ART

Abbas, JAIDS 2006
Jean, Am J Epidemiol 2016
Risk compensation in PrEP studies

- In the first (inconclusive) tenofovir trial in high-risk women, no differences were found in number of sexual partners and condomless sexual intercourse (CSI) between placebo and tenofovir arm. Guest, Sex Transm Dis, 2008

- In the IPREX trial (44% efficacy): diminution of STI in placebo and TDF/FTC arms overtime. No increase of CSI among participants believing they were receiving TDF/FTC. Marcus, PLoS One, 2013

- No evidence of risk compensation among heterosexual participants of the TDF2 trial (62% efficacy) in Botswana. Gust, JAIDS, 2016

- Limitations: selection of participants, blinded randomization.
Risk compensation in the PROUD trial

- Daily MSM PrEP trial where participants were randomly immediately or one year later to PrEP: design more adequate to observe risk compensation
- Efficacy on prevention of HIV acquisition = 86%
- Measured through bacterial sexually transmitted infections diagnosed during deferral phase of follow-up

McCormack, Lancet 2016
## Table 3

Bacterial sexually transmitted infections

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Deferred</th>
<th>Unadjusted odds ratio</th>
<th>Adjusted odds ratio (90% CI)(^*)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>152/265 (57%)</td>
<td>124/247 (50%)</td>
<td>1.33</td>
<td>1.07 (0.78–1.46)</td>
<td>0.74</td>
</tr>
<tr>
<td>Gonorrhoea(^†)</td>
<td>103/261 (39%)</td>
<td>89/242 (37%)</td>
<td>1.12</td>
<td>0.86 (0.62–1.20)</td>
<td>0.46</td>
</tr>
<tr>
<td>Chlamydia(^†)</td>
<td>77/261 (30%)</td>
<td>54/242 (22%)</td>
<td>1.46</td>
<td>1.27 (0.89–1.80)</td>
<td>0.27</td>
</tr>
<tr>
<td>Syphilis</td>
<td>30/263 (11%)</td>
<td>22/247 (9%)</td>
<td>1.32</td>
<td>1.29 (0.79–2.10)</td>
<td>0.39</td>
</tr>
<tr>
<td>Rectal gonorrhoea or chlamydia</td>
<td>93/258 (36%)</td>
<td>77/238 (32%)</td>
<td>1.18</td>
<td>1.00 (0.72–1.38)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Infections diagnosed during deferral phase of follow-up. Analysis based on participants with at least one screen.

\(^*\) Adjusted for the number of screens for specific infection.

\(^†\) Detected in throat, urethra, or rectum.

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McCormack, Lancet 2016
What about real life?

- More studies to come
- More willingness to take PrEP for high risk MSM  
  - Grov, Aids Behav 2015
- In the IPREX-OLE study, PrEP drug concentrations were higher among older MSM/Trans, with more schooling, who reported non-condom receptive anal intercourse, who had more sexual partners, and who had a history of syphilis or herpes.  
  - Grant, Lancet Inf Dis 2014
- PrEP uptake is influenced by the context and perceived risk, with few impact on other adopted prevention strategies  
  - Carlo Hojilla, Aids Behav 2016
- PrEP prescription is influenced by race in the US  
  - Calabrese, Aids Behav 2014
The IPERGAY study

Randomized Double-Blinded vs. Placebo then Open-Label Extension

- HIV-negative MSM
- Condomless anal sex with $\geq 2$ partners in prior 6 months
- Creatinine clearance $> 60$ mL/mn
- HbS Ag negative

Condoms, gels, tests for HIV (using 4th generation assays) and STIs, vaccinations for Hepatitis A and B, and peer counseling on risk reduction and adherence

Follow-up every two months
Risk compensation studies

Study sample

- MSM participating to both the double-blinded and the open-label extension phases excluding 1 participant who never had anal sex (n=332)
- 2397 analyzable questionnaires with longitudinal data about PrEP/condom use during their last sexual intercourse

Analyses:

- Description of sexual behavior, condom use and PrEP use during the follow-up
- Longitudinal latent multi-trajectory model over two outcomes:
  - On demand PrEP uptake (yes/no)
  - Condom use for anal sex (yes/no)
Sex & PrEP use

Double-blinded  
\text{diff:}(p=0.002)  
Open-label extension

Follow up time (participants)

- High exposure: without PrEP
- High exposure: with PrEP
- Low exposure: without PrEP
- Low exposure: with PrEP

Low exposure: anal sex with condom or oral sex; High exposure: condomless anal sex
Anal sex & PrEP use

Double-blinded  diff: (p<0.001)  Open-label extension

% of last anal sexual intercourses according to PrEP use

Follow up time (participants)

Suboptimal use  Correct use

Sexual intercourses

Double-blind vs. Open-label extension

No significant trend, p=0.14
No significant trend, p=0.12

Follow up time (participants)

Median number of sexual intercourses (previous 4 weeks)

Number of partners

Double-blinded  diff:(p=0.001) Open-label extension

Median number of sexual partners (previous 2 months)

Significant trend, p=0.02

No significant trend, p=0.7

Follow up time (participants)
Condomless anal sex

Double-blinded \text{\textasciitilde} \text{diff}(p<0.001) \text{\textasciitilde} \text{Open-label extension}

Percentage of condomless last anal intercourse

No significant trend, \text{p}=0.38

Significant trend, \text{p}<0.001

Follow up time (participants)
Receptive condomless anal sex

Follow up time (participants)

Percentage of condomless last receptive anal intercourse

Significant trend, $p = 0.49$

Significant trend, $p = 0.002$

Double-blinded

Open-label extension

Follow up time (participants)
Multi-trajectories analyses

PrEP use (n=318)

Double blind phase (DBP)  Open-label extension study (OLE)

Probability of PrEP use

- PrEP-LLU (11.9%)
- PrEP-HLU (34.4%)
- PrEP-DU (5.8%)
- PrEP-SU (48%)

Time

Condom use (n=332)

Double blind phase (DBP)  Open-label extension study (OLE)

Probability of condom use

- C-LLU (33.6%)
- C-MLU (49.9%)
- C-HLU (16.4%)

Time
Condom use among Prep adopters

- 2 condom use trajectories were identified among systematic or frequent PrEP users.

- A small significant condom use decrease was observed among the 40% who were more incline to use PrEP.
PrEP uptake among non-condom users

- 2 PrEP uptake trajectories were identified among low/medium condom users.
- A majority (60%) compensate low/medium condom use by PrEP uptake.
- A minority (a third of the total sample) does not compensate and this trend is worse with time.
Summary of findings in the IPERGAY study

- A majority of high-risk MSM protected their sexual intercourses using either prevention tools provided in the ANRS Ipergay trial.
- Some sexual behavior changes were observed during the OLE.
- The decrease in condom use was compensated by high PrEP use.
- Special attention must be paid to the remaining subgroup of MSM with low condom use that did not compensate by using PrEP.
- On demand PrEP included into comprehensive HIV services for MSM could improve prevention in this population.
Conclusion

- PrEP related modifications of sexual behavior are small.
- Risk compensation, if any, has no impact in terms of HIV incidence.
- The issue is to enroll and to maintain in PrEP programs.
- Risk compensation should not be an argument for health policies makers to deny access to PrEP.
• **The Study Staff and Peer-Counselors**
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  - Nantes: C. Bernaud, M. Besnier, B. Bonnet, N. Hall, M. Cavellec, H. Hue, L. Larmet, M. Colas, R. Choquet, F. Raffi


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• **The Community Advisory Board:** S. Karon, D. Villard (Action Santé Alternative), JM Astor (Boucle Rouge), D. Ganay (Federation LGBT), T. Craig (Act-Up), B. Brive (J’y suis j’y reste), R. Orioli (les flamands roses), M. Vanhede (Solidarite SIDA), H. Baudoin (Sida info service), H. Fisher (TRT-5)


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