Pre-exposure Prophylaxis (PrEP) a Potent Tool for the Prevention of HIV Infection

François Clavel, M.D., Infectious Diseases Department, Hôpital Saint Louis, Paris
1.8 M Newly Diagnosed HIV-Infection in 2017
6,000 New Infections each Day

UNAIDS. Report 2018
HIV in Georgia

People living with HIV (all ages)

New HIV infections (all ages)

Source: UNAIDS Estimates 2018
Prevention of HIV/AIDS

- **Abstain**
- **Be Faithful**
- **Condoms**: 70-80% risk reduction of HIV sexual transmission (observational studies)
- **Circumcision in males**: 60% risk reduction of HIV transmission from women to men (2005 ANRS 12126 randomized trial)
- **Drugs (Antiretrovirals) for HIV Prevention**
  - Prevention of mother to child transmission: 67.5% reduction with AZT monotherapy (1994 ACTG 076 randomized trial)
  - Post-Exposure Prophylaxis: 80% risk reduction with 4 weeks of AZT in health care workers (1997 case-control study USA/France)
  - Treatment of HIV-infected individuals: 93% risk reduction of HIV transmission to HIV-uninfected partner (2011 RCT HPTN 052 trial)
  - Pre-Exposure Prophylaxis (PrEP)
What is PrEP?

Use of antiretroviral drugs started before sexual exposure and continued after exposure to reduce the risk of HIV acquisition in high-risk individuals.
iPrEx Study Design

Double-blinded, randomized, placebo-controlled trial

- HIV uninfected MSM at high risk of sexual acquisition of HIV
  - TDF/FTC 1 pill/day (n=1251)
  - Placebo 1 pill/day (n=1248)

- High risk: in the 6 months prior to screening: anal sex with > 4 partners, STI, transactional sex, condomless anal sex
- HIV prevalence at screening: 8%
- Events driven trial: 85 events yield a power of 80% to reject the null hypothesis of efficacy of < 30% if the true efficacy is > 60%
- Rapid HIV testing at every 4 weeks visit, with drug dispensation and adherence counseling

After a median follow-up of 14 months, 100 subjects became infected, 36 in the TDF/FTC arm and 64 in the placebo arm:

44% reduction in the incidence of HIV (95% CI: 15-63, p=0.005)

Partners PrEP Design

4758 HIV-1 serodiscordant couples
(HIV-1 seropositive partner not yet medically eligible for ART)

Randomize HIV-1 seronegative partners
(normal liver, renal, & hematologic function and no HBV-infection)

Placebo once daily  FTC/TDF once daily  TDF once daily

All receiving comprehensive HIV-1 prevention services

Follow couples monthly for up to 36 months

1° endpoint: HIV-1 infection in the HIV-1 seronegative partner
Co-1° endpoint: Safety

Primary efficacy results

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>FTC/TDF</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HIV- infections</td>
<td>17</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>HIV-1 incidence, per 100 person-years</td>
<td>0.65</td>
<td>0.50</td>
<td>1.99</td>
</tr>
<tr>
<td>HIV-1 protection efficacy, men &amp; women</td>
<td>67%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(44-81%)</td>
<td>(55-87%)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HIV-1 protection efficacy, men</td>
<td>63%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(20-83%)</td>
<td>(54-94%)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HIV-1 protection efficacy, women</td>
<td>71%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(37-87%)</td>
<td>(28-84%)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0002</td>
<td>0.005</td>
<td></td>
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</tbody>
</table>

PrEP is Effective: Adherence is Critical

Pearson correlation: 0.86 (P=0.003).

Potential Benefits of On Demand PrEP

- Convenient dosing regimen which could improve adherence and overall effectiveness
- Clear guidance on how to start and stop PrEP
- Better safety due to lower drug exposure (kidneys, bones)
- Improved cost-effectiveness
- Easier diagnosis of breakthrough HIV-infection
- Lower risk of selecting drug resistance in case of HIV-infection
« On Demand » or Event-Driven PrEP

How fast can it work?

How long should it work?
Timing of HIV Infection

Drug concentration needed to prevent infection at the entry site yet unknown
TDF/FTC PK in Blood and Rectal Tissue

- Drugs concentrations measured in blood, rectal, vaginal and cervical tissues in 15 healthy volunteers following a single dose of TDF/FTC
- TVF long half-life: 47-49 hours
- Cumulative exposure of rectal tissue to TVF > 30-fold higher vs. blood,

Patterson K B et al. Sci Transl Med 2011;3:112re4
Effect of a Double Dose of oral TDF/FTC (-2h, + 24h)

% Uninfected Macaques

Untreated Controls (n = 32)

Double dose oral TDF/FTC (n = 6) HR : 16.7 p = 0.006

83% Efficacy

Garcia-Lerma et al. Science Trans Med 2010, 14,14ra4
Study Design

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

- HIV-negative MSM
- Condomless anal sex with ≥ 2 partners in prior 6 months
- Creat. 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

Feb 2012

TDF/FTC On Demand

Placebo On Demand

Nov 2014

TDF/FTC On Demand

Jun 2016

Molina JM et al NEJM 2015
IPERGAY: Sex-Driven PrEP

- 2 tablets 2-24 hours before sex
- 1 tablet 24 hours later
- 1 tablet 48 hours after first intake

4 pills of TDF/FTC taken over 3 days to cover one sexual intercourse
## HIV Incidence (mITT Analysis)

**Median Follow-up in Open-Label Phase**: 18.4 months (17.5-19.1)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>212</td>
<td>6.60 (3.60-11.1)</td>
</tr>
<tr>
<td>TDF/FTC (double-blind)</td>
<td>219</td>
<td>0.91 (0.11-3.30)</td>
</tr>
<tr>
<td>TDF/FTC (open-label)</td>
<td>515</td>
<td>0.19 (0.01-1.08)</td>
</tr>
</tbody>
</table>

97% relative reduction vs. placebo

Molina et al Lancet HIV 2017
IPERGAY Summary

- High incidence of HIV infection among MSM in France
- On Demand PrEP with oral TDF/FTC highly effective in high risk MSM
- Low condom use did not undermine efficacy
- Safety of PrEP was good
- PrEP improved satisfaction and removed fear during sexual activit
Study Design

Open-Label Prospective Cohort Study in the Paris Region

- HIV-negative high risk adults
- Inconsistent Condom use
- Creat. Clearance ≥ 50 mL/mn
- HbS Ag negative if On Demand

Participants opted for either Daily or On Demand PrEP and could switch regimens

Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine

STI screening at physicians’ discretion (Guidelines recommend every 3 months in MSM)

Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

http://prevenir.anrs.fr/

Show 15% reduction in new HIV diagnoses among MSM in the Paris Region

n = 3,000

May 3rd 2017

TDF/FTC Daily

TDF/FTC On Demand

May 31st 2020
# HIV Incidence (mITT Analysis)

**Mean Follow-up in this Open-Label Cohort:** 7 months (SD: 4)

**Incidence of study discontinuation:**
3.3/100 PY including 1.5/100 PY who discontinued PrEP

<table>
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<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC (Daily)</td>
<td>443</td>
<td>0 (0-0.8)</td>
</tr>
<tr>
<td>TDF/FTC (On Demand)</td>
<td>506</td>
<td>0 (0-0.7)</td>
</tr>
</tbody>
</table>

85 HIV-infections averted*  

* assuming an incidence of 9.17/100 PY as observed in the ANRS Ipergay study in Paris
Summary

• High incidence of HIV infection in MSM
• Daily and On Demand PrEP with oral TDF/FTC both highly effective in high risk MSM
• On demand oral PrEP gives information on how to start and stop PrEP
• Safety of PrEP is good
• PrEP improved satisfaction and removed fear during sexual activity
• PrEP combined with up-scaled testing and rapid treatment of HIV-infection may reverse the epidemic
Acknowledgments