Pitfalls of PrEP

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Disclosures

Advisory boards: Gilead, Merck, ViiV, Sanofi

Research grants: Gilead
Number of New HIV Diagnoses in Paris from 2010 to 2018

Decrease by 16% from 2015 to 2018 and by 28% among MSM born in France
Demonstration Projects
EPIC Study among MSM in NSW

3700 recruited from 03/01/2016 to 10/31/2016 and dispensed PrEP at baseline

62 No HIV follow-up test (1.7%)

49 Withdrawal from study
- 20 no longer at risk of HIV infection
- 8 side effects
- 4 moved out of jurisdiction
- 6 can no longer attend
- 2 tired of taking pills every day
- 3 eGFR dropped below 60 ml/mn
- 6 others

3069 (83%) with visit M12 or later

2 new HIV infections:
1 was dispensed but never commenced PrEP
1 took no PrEP for months prior to infection

Incidence rate:
0.048/100 person-years (95% CI 0.012-0.195)

Grulich A. et al. Lancet HIV 2018
Multiple Causes of “PrEP Failures”

« PrEP failures could be defined more broadly as HIV infections that occur at any point along the PrEP continuum of care »

- Users
- System
- Health Care Providers
- Assays
- Drugs
PrEP Failures in BMSM

EleMENt study: 300 young BMSM in Atlanta (16-29 years) to understand role of substances on HIV/STIs were offered PrEP free of charge
52.5% attended a PrEP initiation visit and were given a prescription
- 14 incident HIV diagnoses (6.2% annually)
  - 4 who started PrEP became infected:
    ✓ 1 biomedical failure may have had acute HIV-infection at PrEP initiation
    ✓ 1 with low PrEP adherence
    ✓ 2 discontinued PrEP
  - 5 expressed no interest in PrEP
  - 5 expressed interest but failed to start PrEP
PrEP Failures in BMSM

EleMENt study: 300 young BMSM in Atlanta (16-29 years) to understand role of substances on HIV/STIs were offered PrEP free of charge
52.5% attended a PrEP initiation visit and were given a prescription
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    - 1 biomedical failure may have had acute HIV-infection at PrEP initiation
    - 1 with low PrEP adherence
    - 2 discontinued PrEP

It is critical to monitor PrEP users every 3 months to reinforce PrEP adherence and detect early HIV-infection
KPNC members with referrals for PrEP 2012-2017: 7124 persons

- 26 (0.4%) diagnosed with HIV during PrEP eligibility
- 30% did not start PrEP: 22 diagnosed with HIV: incidence 1.1/100PY
- 70% started PrEP: No HIV-infection during PrEP use (5104 PY of FU)
- 26% discontinued PrEP: 11 HIV-infection with incidence: 1.3/100PY
System Failures

- Lack or limited access to PrEP
  - Not approved
  - Slow implementation
  - Supply chain issues
  - Cost: not subsidized

- Lack of awareness among people at risk and health care providers

- IQVIA database on prescriptions: **98,599 PrEP users in 2016**, 93.4% males, 470% increase from 2014, 7% of people in need

- Women accounted for 6.6% of PrEP users but only 2% of those in need

- PrEP in the US: Mostly white Gay men get it

Huang YA et al. MMWR 2018, 67: 1147
HCP Failures

✓ Missed opportunities to prescribe PrEP:
  - 885 persons newly diagnosed with HIV in South Carolina (2013-2016)
  - 66% had of 6.9 visits to a health care facility prior to HIV diagnosis
  - Being female, black and <30 years: predictors of prior visits.
  - Visits by emergency medicine (61%) and primary care doctors (10%).

✓ Increase knowledge and improve training

✓ Address reluctance to prescribe PrEP (moral issues)

✓ PrEP to be integrated in health care services

✓ Organize community-based PrEP delivery

Smith DK et al. OFID 2019
Challenges with HIV Diagnostic Tests

- Rule-out acute HIV-infection
- Diagnose HIV-infection
- Manage false-positive tests
Sequential Appearance of Viral Markers and Antibodies during Acute HIV Infection

Performance of HIV Screening Tests in a PrEP Trial

Retrospective analysis of stored sera from 28 HIV-infections during the trial

<table>
<thead>
<tr>
<th>WB Assay</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; G Ag/Ab Architect°</th>
<th>Rapid POC Vikia°</th>
<th>Autotest° AAZ</th>
<th>Ag/Ab POC Alere°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete (n=7) (&gt; 6 bands)</td>
<td>7 (100%)</td>
<td>7 (100%)</td>
<td>7 (100%)</td>
<td>6/6 (100%)</td>
</tr>
<tr>
<td>Incomplete (n=8) (1-6 bands)</td>
<td>8 (100%)</td>
<td>6 (75%)</td>
<td>7 (88%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Negative (n=13) (No antibodies)</td>
<td>11 (85%)</td>
<td>2 (15%)</td>
<td>0 (0%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Overall (n=28)</td>
<td>26* (83%)</td>
<td>15 (54%)</td>
<td>(50%)</td>
<td>21 (78%)</td>
</tr>
</tbody>
</table>

- Two patients with negative 4G had HIV RNA of 110 and 450 c/ml at time of diagnosis
- 18% non reactivity of 4G assay in acute infection in Thailand (42/234)

Delaugerre C. et al JID 2017; De Souza et al. CID 2016
Screened for Acute HIV Infection
HIV Ag/Ag Combination Assay

74,334 pts screened for HIV

HIV Prevalence: 10.9%

Screened for Acute HIV Infection
HIV Ag/Ag Combination Assay

81 Reactive Ag/Ab Combined assays

89 reactive Ag/Ab 2-5 days later

Pooled HIV RNA: 31 positive detected

Median viral load: 2482 c/ml (82-84,545)

72% acute HIV infections detected

De Souza et al. AIDS 2015
Determination of HIV Status for PrEP Provision

- **HIV immunoassay blood test (rapid test if available)**
  - Negative
  - Indeterminate
  - Positive: Consider HIV+ (pending confirmatory testing)

  - Signs/symptoms of acute HIV infection anytime in prior 4 weeks
    - HIV-:
      - No
      - Yes
    - **Option 1 (Preferred)**: Send blood for HIV antibody/antigen assay
      - Positive: HIV+
      - Negative: HIV-
    - HIV-
      - Eligible for PrEP
      - HIV +: Not Eligible for PrEP
      - HIV Status Unclear: Defer PrEP decision

  - **Option 2**: Send blood for HIV-1 viral load (VL) assay
    - VL ≥ 3,000 copies/ml: HIV+
    - VL < 3,000 copies/ml: Retest VL, Defer PrEP decision

  - **Option 3**: Retest antibody in one month, Defer PrEP decision

  - HIV-
    - VL < level of detection, no signs/symptoms on day of blood draw
    - VL < level of detection with signs/symptoms on day of blood draw
      - Retest in one month, Defer PrEP decision
Very Low Number of Signs and Symptoms During Acute HIV-Infection

71% participants no symptoms
Median 1 symptom and/or sign

Prospective Study of Acute HIV-1 Infection in Adults in East Africa and Thailand

Robb et al, NEJM 2016
**Determination of HIV Status: IAS-USA Guidelines**

- **HIV immunoassay blood test** (rapid test if available)
  - **Negative**
  - **Indeterminate**
  - **Positive**
    - **Consider HIV + (pending confirmatory testing)**

**Signs/symptoms of acute HIV infection anytime in prior 4 weeks**

- **HIV -**
  - No
  - Yes

**Option 1 (Preferred)**
- Send blood for HIV antibody/antigen assay
  - **Positive**
    - HIV +
  - **Negative**
    - HIV -

**Option 2**
- Send blood for HIV-1 viral load (VL) assay
  - **VL ≥3,000 copies/ml**
    - HIV +
  - **VL <3,000 copies/ml**
    - **Defer PrEP decision**

**Option 3**
- Retest antibody in one month
- **Defer PrEP decision**

**HIV -**
- **Eligible for PrEP**
- **Not Eligible for PrEP**
- **HIV Status Unclear**
- **Defer PrEP decision**

Effect of Oral PrEP with TDF/FTC on Detection of HIV Infection

Retrospective testing of timing to HIV seroconversion and plasma viral load in the Partners PrEP study

102 seroconverters: 31 PrEP (with detectable TDF) and 71 placebo

- Significant increased in delayed site detection of infection with PrEP (OR: 3.49, p=0.04),

- Plasma HIV RNA was $0.64 \log$ lower with PrEP ($p<0.001$) with 11% PrEP vs 3% placebo samples with undetectable HIV RNA (OR: 3.9, $p=0.02$)

- No differences found in the Architect signal to cut-off ratio at any stage

Adapted from Donnel D. et al AIDS 2017
### Positive HIV Test Results in a PrEP User

- 34-y man, PrEP > 1y, tested neg. with GS HIV Combo Ag/Ab EIA (Bio-Rad), excellent adherence
- Enters a study to evaluate performance of POC tests while remaining on PrEP
- Determine HIV-1/2 Combo (Alere): p24 Ag pos., Ab neg., acute HIV-infection?

<table>
<thead>
<tr>
<th>Days from first pos. test</th>
<th>Determine HIV1/2 Ag/Ab Combo</th>
<th>Instrumented Ag/Ab test (Architect, Bio-Rad GS)</th>
<th>HIV Ab POC Tests</th>
<th>Geenius HIV1/2 suppl. assay</th>
<th>HIV-1 Viral Load c/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ag pos., Ab neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>TND*</td>
</tr>
<tr>
<td>16</td>
<td>Ag pos., Ab neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>TND</td>
</tr>
<tr>
<td>29</td>
<td>Ag pos., Ab neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>TND</td>
</tr>
<tr>
<td>70</td>
<td>Ag pos., Ab neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Neg.</td>
<td>TND</td>
</tr>
</tbody>
</table>

* Target not detected

Stekler JD et al. OFID 2018
How to Manage Ambiguous HIV Test Results during PrEP

Subject on PrEP
Quarterly screening

More experience needed to manage ambiguous tests results

To resolve false-positive results:
Repeat testing, discussion between clinicians and virologists
Seek expert opinion

PrEPline toll-free 855-448-7737 (11 am – 6 pm EST)

Continue PrEP if PrEP adherence
Maintains protection
Risk for resistance

Stop PrEP
Reassess HIV status
Facilitate diagnosis
Risk of infection

Initiate ART if no PrEP adherence
Drug-related AEs
Confirm diagnosis

Smith DK et al OFID 2018; Stekler JD et al. OFID 2018; Saag M et al. IAS-USA 2018 guidelines JAMA 2018
False-Positive HIV 4G-EIA in a PrEP User?

- Participant used on demand PrEP with TDF/FTC since January 2016, high adherence
- Always HIV negative by 4G-EIA, last negative test in March 2018 (Liaison XL Murex)
- June 2\textsuperscript{nd} 2018, tested at another lab: 4G EIA Elecsys® HIV Duo positive, WB negative

<table>
<thead>
<tr>
<th>Dates</th>
<th>PreP</th>
<th>TFV ng/mL</th>
<th>4G-EIA Index</th>
<th>4G-EIA Bioplex</th>
<th>WB Ab</th>
<th>HIV RNA Roche</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/05/18</td>
<td>ON</td>
<td>52.8</td>
<td>1.58</td>
<td>NEG</td>
<td>p24</td>
<td>&lt; 20 c/mL</td>
</tr>
<tr>
<td>Supervised Interruption of PrEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>06/11/18</td>
<td>OFF d6</td>
<td>1.36</td>
<td>1.49</td>
<td>NEG</td>
<td>p24</td>
<td>&lt; 20 c/mL</td>
</tr>
<tr>
<td>06/15/18</td>
<td>OFF d10</td>
<td>&lt; 1</td>
<td>1.56</td>
<td>NEG</td>
<td>p24</td>
<td>&lt; 20 c/mL</td>
</tr>
<tr>
<td>07/04/18</td>
<td>OFF d30</td>
<td>&lt; 1</td>
<td>1.76</td>
<td>NEG</td>
<td>p24</td>
<td>&lt; 20 c/mL</td>
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False reactivity of ARCHITECT test, PrEP could be re-introduced

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<th>PreP</th>
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<tbody>
<tr>
<td>10/18/18</td>
<td>OFF M4</td>
<td>&lt; 1</td>
<td>1.38</td>
<td>NEG</td>
<td>p24</td>
<td>&lt; 20 c/mL</td>
</tr>
<tr>
<td>01/23/19</td>
<td>OFF M7</td>
<td>&lt; 1</td>
<td>1.82</td>
<td>NEG</td>
<td>p24</td>
<td>&lt; 20 c/mL</td>
</tr>
<tr>
<td>Date</td>
<td>Drug</td>
<td>p24</td>
<td>Index</td>
<td>Architect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
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<td>1.56</td>
<td>NEG</td>
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<td>1.76</td>
<td>NEG</td>
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<td>NEG</td>
<td></td>
<td></td>
</tr>
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</table>

- Participant used on demand PrEP with TDF/FTC since January 2016, high adherence
- Always HIV negative by 4G-EIA, last negative test in March 2018 (Liaison XL Murex)
- June 5th, tested at another lab: 4G EIA Elecsys® HIV Duo positive, WB negative
Time to Virologic Rebound after ART Interruption in Persons Treated during Fiebig I Acute HIV Infection

- 8 Pts (7 men, 1 woman)
- Treated during Fiebig 1
- Median ART: 2.8 years
- All rebounded > 20 c/ml
- Median time: 26 days
- Range: 13 to 48 days

Colby DJ et al RV411 study group Nat Medicine 2018
# Acquisition of TDF/FTC Resistant HIV Despite High PrEP Adherence

<table>
<thead>
<tr>
<th>Cases</th>
<th>Time since PrEP Initiation</th>
<th>NRTI RAMs</th>
<th>Drug Concentration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knox et al. NEJM 2017</td>
<td>24 months</td>
<td>M184V, K70R, Y215E, M41L</td>
<td>DBS, plasma</td>
</tr>
<tr>
<td>Markowitz et al. JAIDS 2017</td>
<td>5 months</td>
<td>M184V, K65R</td>
<td>Hair, DBS</td>
</tr>
<tr>
<td>Thaden et al. AIDS 2018</td>
<td>14 months</td>
<td>M184V, K65R, K70T</td>
<td>Hair, plasma</td>
</tr>
<tr>
<td>Colby et al. CID 2018</td>
<td>8 weeks</td>
<td>M184V</td>
<td>Hair, plasma</td>
</tr>
<tr>
<td>Cohen et al. Lancet HIV 2019</td>
<td>13 months</td>
<td>M184V, L74V</td>
<td>Hair, DBS, plasma</td>
</tr>
</tbody>
</table>

* DBS and hair levels consistent with daily dosing in prior 6 weeks

Adapted from Cohen S. et al Lancet HIV 2019
Effect of TDF/FTC against Rectal Challenges with R-SHIV and M184V

% Uninfected Macaques

Untreated Controls (n = 5)

Oral TDF/FTC (-72h, +2h) (n = 5)

100% Efficacy

Cong ME. et al. J. Virol 2011
Effect of TDF/FTC against Rectal Challenges with R-SHIV and K65R

% Uninfected Macaques

Oral TDF/FTC (-72h, +2h)
(n = 6)

33% Efficacy

Untreated Controls (n = 6)

Cong ME. et al. JID 2013
# Rates of Transmitted HIV-1 Resistance to TDF/FTC among Treatment Naïve Patients

<table>
<thead>
<tr>
<th>References</th>
<th>Nb Pts</th>
<th>Years</th>
<th>M184V/I (Nb, %)</th>
<th>K65R (Nb, %)</th>
<th>K70E (Nb, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhee et al. CID 2019</td>
<td>4,253</td>
<td>2003-2016</td>
<td>20 (0.5%)</td>
<td>2 (0.05%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Banez Ocfemia CROI 2014</td>
<td>10,894</td>
<td>2008-2011</td>
<td>44 (0.4%)</td>
<td>3 (0.03%)</td>
<td>4 (0.04%)</td>
</tr>
<tr>
<td>Gupta et al. Lancet ID 2017</td>
<td>56,044</td>
<td>2014-2016</td>
<td>292 (0.5%)</td>
<td>(0.1%)</td>
<td>NA</td>
</tr>
<tr>
<td>Chan et al. JIAS 2012</td>
<td>19,823</td>
<td>1999-2008</td>
<td>NA</td>
<td>20 (0.1%)</td>
<td>3 (0.015%)</td>
</tr>
<tr>
<td>Olson et al. AIDS 2018</td>
<td>4,717</td>
<td>1996-2012</td>
<td>34 (0.7%)</td>
<td>8 (0.2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

NA: not available
Acquisition of TDF/FTC Susceptible HIV Despite High PrEP Adherence

✓ 50-year old MSM, started daily PrEP, condomless sex with 12-75 partners per month, use chemsex, multiple STIs

✓ HIV Ab/Ag tests negative at months 1, 3 and 6

✓ Month 8: fever, *E. coli* UTI, anal LGV and positive 4G HIV test

✓ High adherence to 7 pills/week (pill count and daily diary) and TVF-DP in DBS consistent with daily dosing in prior 6 weeks

✓ Positivity of 4G test confirmed D+6 (May 24) with negative Ag but positive for Ab with only gp160 on WB, no HIV RNA in plasma and PBMC, no DNA in PBMC and sigmoid biopsies

Hoornenborg E. et al Lancet HIV 2017
Acquisition of TDF/FTC Susceptible HIV Despite High PrEP Adherence

**Diagram A**
- Plasma HIV RNA viral load (copies per mL)
- PrEP Stopped

**Diagram B**
- Dates: May 24, 2016, June 23, 2016, July 18, 2016
- Positive control

Hoornenborg E. et al Lancet HIV 2017
Acquisition of TDF/FTC Susceptible HIV Despite High PrEP Adherence

✓ High inoculum effect?
✓ Concomitant LGV infection with inflammation?
✓ Brief period of nonadherence not detected in these cumulative adherence markers?
✓ Variable PK of TDF/FTC in blood or rectal mucosa?
✓ Combination of all the above?
✓ HIV-infection after PrEP discontinuation despite reported condom use with a false positive WB?
Selection of Drug Resistance in Clinical Trials with TDF/FTC for PrEP

- Resistance rare in clinical trials of PrEP
- RAMs assessed: K65R (TDF, FTC), K70E (TDF) or M184V/I (FTC)
- Resistance when seroconverting in the TDF/FTC arm: M184V/I (1 K65R)

<table>
<thead>
<tr>
<th>Trial</th>
<th>N (TDF/FTC)</th>
<th>Seroconverted after enrollment Nb resistance / total</th>
<th>Acute Infection At enrollment Nb resistance / total</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>1224</td>
<td>0/48</td>
<td>2/2</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>1579</td>
<td>0/21</td>
<td>2/4</td>
</tr>
<tr>
<td>TDF2</td>
<td>611</td>
<td>0/9</td>
<td>1/1</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>1062</td>
<td>4/33</td>
<td>0/1</td>
</tr>
<tr>
<td>VOICE</td>
<td>1003</td>
<td>1/61</td>
<td>2/9</td>
</tr>
<tr>
<td>PROUD</td>
<td>275</td>
<td>0/2</td>
<td>2/3</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>199</td>
<td>0/2</td>
<td>0/2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>5953</strong></td>
<td><strong>5/176 (&lt; 3%)</strong></td>
<td><strong>9/22 (41%)</strong></td>
</tr>
</tbody>
</table>

Adapted from Parikh and Mellors, Curr Opin HIV AIDS 2016
Treatment of HIV Infection on PrEP

- Difficult situation to handle

- Expert opinion
  - Start ART immediately with a regimen with high barrier to resistance
  - TDF or TAF/FTC (or AZT/3TC) as the backbone
  - Boosted Darunavir/Lopinavir or Dolutegravir/Bictegravir (unless pregnancy of childbearing potential)
  - Simplify regimen when resistance genotype available
  - Reinforce adherence to ART

DHHS 2018 guidelines
Summary

- PrEP with oral TDF/FTC is very effective when taken
- Failures are rare and have multiple causes
- Rule out acute HIV-infection before starting PrEP
- Repeat HIV tests at 1 month and every 3 months
- Rare true biomedical failures but most feared
- Thorough investigation of biomedical failures
Acknowledgments

Constance Delaugerre
Marie-Laure Chaix
Claire Pintado
Determination of HIV Status with a Positive Screen Test on PrEP

Any Positive HIV Serology Screen Test in a Subject on PrEP

1. Stop PrEP (measure drug concentration)
2. Confirmation Tests
   - 4G HIV Ag/Ab Combination Assay
   - HIV RNA testing with Resistance Genotype
3. Condoms until HIV Excluded or Confirmed

Both Tests Negative
- Resume PrEP

Indeterminate
- Repeat HIV Serologic and RNA Tests

HIV-Infection Confirmed
- Start Suppressive ART

Saag M et al. IAS-USA 2018 guidelines JAMA 2018