Pre-Exposure Prophylaxis for HIV Prevention

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2 Million New Infections in 2014
5,600 New Infections per Day

Prevention Modalities

- Condoms
- PEP
- Voluntary Male Circumcision
- Needle Exchange
- Vaccine
- Abstinence
- HIV Treatment
- PrEP
- Microbicides
- HIV & STI Testing
- STI Treatment
- Harm Reduction
Prevention Modalities

- Condoms
- PEP
- Voluntary Male Circumcision
- Needle Exchange
- Vaccine
- Abstinence
- HIV Treatment
- PEP
- Microbicides
- HIV & STI Testing
- STI Treatment
- Harm Reduction
- PrEP
- Harm Reduction
Today’s Agenda

- What is PrEP?
- Origins of PrEP
- Effectiveness Trials and Aspirational Modeling
- Implementation Considerations and Debate
- Progress and Challenges to Scale-up
- Looking Forward
Pre-Exposure Prophylaxis (PrEP)

- **PrEP (Pre-exposure prophylaxis)**
  - Strategy of administering ART to uninfected, at-risk individuals
  - Think of: Malaria prevention, birth control pill
- **Tenofovir Disoproxil Fumarate (TDF) +/- Emtricitabine (FTC)**
  - Safe and well-tolerated
  - Daily dosing of co-formulated tablet supported by PK/PD
  - Relatively high barrier to resistance
  - Rapid concentration in genital/rectal tissues
- **Nonhuman Primate Models**
  - Suggest TDF + FTC offers better protection than TDF alone
  - Effective protection from IV, rectal, and vaginal challenges
  - Lower concentrations in CV vs. rectal compartments with oral
  - Intermittent dosing may be possible

TDF/FTC Mechanism of Action

Entry/Fusion Inhibitors
Nucleos(t)ide RTI’s
Non-Nucleoside RTI’s
Integrase Inhibitors
Protease Inhibitors

How did we get here?

Time

HIV Exposure-To-Dose Time

Efficacy

How did we get here?

Efficacy

HIV Exposure-To-Dose Time

Time

How did we get here?

### Effectiveness of Daily TDF/FTC in Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>TDF/FTC (TDF/FTC)</th>
<th>CI:</th>
<th>Percent</th>
<th>CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROUD</td>
<td></td>
<td></td>
<td>86%</td>
<td>-22 - 81 CI:</td>
</tr>
<tr>
<td>TDF2</td>
<td></td>
<td></td>
<td>49%</td>
<td>25 - 97 CI:</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td></td>
<td></td>
<td>6%</td>
<td>52 - 41 CI:</td>
</tr>
<tr>
<td>iPrEx</td>
<td></td>
<td></td>
<td>99%</td>
<td>15 - 63 CI:</td>
</tr>
<tr>
<td>VOICE</td>
<td></td>
<td></td>
<td>49%</td>
<td>+3 to 129 CI:</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td></td>
<td></td>
<td>63%</td>
<td>+27 to 149 CI:</td>
</tr>
</tbody>
</table>

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### Preexposure Prophylaxis for HIV Infection among African Women

Relationship Between Effectiveness and Adherence in Microbicide & PrEP Trials

Pearson correlation = 0.86, p=0.003

Percentage of Participants’ Samples with detectable drug levels

SS Abdool Karim, personal communication
TDF Concentrates 10-100x More in Rectal Tissue than in Cervico-vaginal Tissues

Patterson KB et al. Sci Transl Med. 2011.
Maximizing the Potential Effectiveness

TDF/FTC (7x/week)

- CI: 96 - 99
- 99%
- Some adherence forgiveness with retained protection


TDF/FTC (~1x/24°)

- CI: -17 - 100
- 94%
- 6-7 doses per week likely required

Cottrell ML et al, JID, 2016.
Modeled Adherence Required for Protection

Cottrell ML et al, JID 2016.
The Issues Holding us Back

- **What** is the effect of PrEP on risk behavior?
- **What** are the resistance implications of seroconversion “on” PrEP?
- **What** is the “onset” of protection? **How** quickly does protection wane?
- **Long Term Safety** in diverse populations?
- **Optimal** deployment?
- **How** do we best support adherence?
- **Are** less-than-daily dosing regimens protective? **Is** something better coming?
- **Can we** make PrEP available to, and will people most at risk use it and adhere to it?
Safety: Youth Bone Health

**Spine**

- TFV-DP>700
- BLQ

- Wk 24: P=0.03
- Wk 48: P<0.001

**Hip**

- TFV-DP>700
- BLQ

- Wk 24: P=0.25
- Wk 48: P=0.001

*Significance of change vs. baseline: * P≤0.05; ** P<0.001 (Wilcoxon signed rank)*

Mulligan, K et al. Comorbidities and Adverse Drug Reactions. 2015.
How Do We Best Support PrEP Adherence?

- Next Step Counseling\(^1\)
- CDC Guidance\(^2\)
- Text messaging\(^3,4\)
- “Smart” devices\(^5,6\)

2. CDC 2014 Clinical Practice Guideline
5. Grant RM, et al. HPTN 067
6. Gulick RM, et al. HPTN 069
“What about iPERGAY?” or Does less-than-daily dosing work?
Mean follow-up of 13 months: 16 subjects infected
14 in placebo arm (incidence: 6.6 per 100 PY), 2 in TDF/FTC arm (incidence: 0.94 per 100 PY)

86% relative reduction in the incidence of HIV-1 (95% CI: 40-99, p=0.002)
NNT for one year to prevent one infection : 18

Molina JM, NEJM 2015
- **Median number of pills/month (IQR):** 16 pills (10-23) in the placebo arm and 16 pills (12-24) in the TDF/FTC arm (p=0.84)

- **48 participants (12%)** received PEP
  - 25 (13%) in the TDF/FTC arm and 23 (11%) in the placebo arm (p=0.73)

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Molina JM, NEJM 2015
### iPERGAY Adherence: CASI

**PrEP use during the last sexual intercourse**

1212 sexual intercourses assessed in 319 participants

<table>
<thead>
<tr>
<th>% PrEP Use (min-max)</th>
<th>TDF/FTC n = 649 acts</th>
<th>Placebo n = 563 acts</th>
<th>Total % (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct use*</td>
<td>45 (36-57)</td>
<td>40 (22-49)</td>
<td>43 (35-51)</td>
</tr>
<tr>
<td>Suboptimal use</td>
<td>27 (14-35)</td>
<td>31 (18-44)</td>
<td>29 (20-38)</td>
</tr>
<tr>
<td>No PrEP</td>
<td>27 (15-37)</td>
<td>29 (24-44)</td>
<td>28 (20-38)</td>
</tr>
</tbody>
</table>

* According to the protocol, or at least one pill before and one pill after sex

*Molina JM, NEJM 2015*
TFV and FTC Concentration in Rectal Tissue

Molina JM, IAS 2015, Abstract MOSY0102
HPTN 067

HIV-uninfected MSM and Women
N=540

6 weeks of DOT Weekly Therapy

Week 7-30

Daily TDF/FTC

2 Times/week + post-boost

24-48h pre-Event, + 24h post

Bekker LG. CROI 2015, Abstract 978LB.
Adherence was higher for the daily rather than non-daily doses.
Open-label data suggest that Perfect Adherence Not Required for High levels of protection

iPrEx OLE

- Open label extension study of daily oral PrEP (TDF/FTC) in MSM and transgender women (N = 1,603)
- PrEP provides protection even when adherence is < 100%:
  - Efficacy of 4–6 tablets/wk similar to 7 tablets/wk (100% risk reduction)
  - 2–3 tablets/wk also associated with significant risk reduction (84%)
- Participants at highest risk had the greatest levels of adherence

Demo Projects

Kaiser-Permanente Clinical Cohort

- Enrolled 801 MSM/TG/Women
  - 657 (82%) Initiated PrEP
- No seroconversions
- High rates of STIs at follow-up
  - 30% of PrEP users were diagnosed with any STI at 6 month follow-up
  - 50% of PrEP users were diagnosed with any STI at 12 month follow-up

Volk, JE et al, CID. 2015. Figure 1. Human immunodeficiency virus preexposure prophylaxis (PrEP) referrals, intakes, and initiation by month at Kaiser Permanente San Francisco, July 2012–February 2015. The graph includes a total of 1045 referrals, 835 intakes, and 677 initiations, including 20 individuals who restarted PrEP after discontinuing during the study period.
Demonstration project – Clinicaltrials.gov NCT01989611

Main Objectives – Assess uptake, safety and feasibility of PrEP implementation provided at no cost for high risk MSM and TGW in the context of the Brazilian public health system

Secondary objectives – PrEP awareness – Adherence pattern TDF levels in DBS – Social harm – Risk compensation – Adherence patterns
Uptake

Approached
N=986

Potentially eligible
N=798

Screened
N=490

Enrolled
N=409

% uptake = # Enrolled * 100 / # Potentially eligible

51.25%

Grinsztejn B, IAS 2015.
## Predictors of uptake

<table>
<thead>
<tr>
<th>Predictor</th>
<th>aOR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year increase)</td>
<td>1.01</td>
<td>1.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Schooling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 years vs. &gt; 12 years</td>
<td>0.95</td>
<td>0.70</td>
<td>1.29</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-SP vs. FIOCRUZ</td>
<td>1.22</td>
<td>1.04</td>
<td>1.44</td>
</tr>
<tr>
<td>USP-SP vs. FIOCRUZ</td>
<td>1.69</td>
<td>1.45</td>
<td>1.98</td>
</tr>
<tr>
<td>Steady partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>1.21</td>
<td>1.05</td>
<td>1.39</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGW vs. Male</td>
<td>1.64</td>
<td>1.30</td>
<td>2.08</td>
</tr>
<tr>
<td>Perceived likelihood of getting HIV on the next year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-100% vs. 0-25%</td>
<td>1.17</td>
<td>1.03</td>
<td>1.33</td>
</tr>
<tr>
<td>Previous HIV test (last 12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>1.23</td>
<td>1.02</td>
<td>1.49</td>
</tr>
<tr>
<td>Prior PrEP awareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>1.30</td>
<td>1.11</td>
<td>1.52</td>
</tr>
<tr>
<td># Male condomless anal sex partners (last 12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or more vs. &lt; 2</td>
<td>1.77</td>
<td>1.53</td>
<td>2.04</td>
</tr>
<tr>
<td>Anal sex with HIV-positive partners (12 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. No</td>
<td>1.40</td>
<td>1.10</td>
<td>1.78</td>
</tr>
<tr>
<td>I do not know vs. No</td>
<td>0.89</td>
<td>0.70</td>
<td>1.12</td>
</tr>
</tbody>
</table>

Grinsztejn B, IAS 2015.
Are there PrEP Failures?

Two MSM in UK taking TDF (alone) for HBV rx

- One suppressed viremia but had significant reservoir seeding by DNA PCR
- One had VL 158,899, also with reservoir seeding (GT WT)
- Both had plasma levels consistent with regular dosing

One Canadian MSM taking TDF/FTC

- HIV test 2 months prior to PrEP initiation
- DBS levels c/w daily dosing
- Seroconversion with R5, Clade B
  - INI 51Y, 92Q
  - 1.3 fold change in TDF phenotypic susceptibility
- Rx TDF/FTC/RAL/r/DRV -> DTG/COB/DRV/RPV

Fox J, Inf Dis Ther. 2016.  
Knox DC, CROI 2016.
Finding a PrEP Provider/
Building Infrastructure for PrEP Delivery

- Provider lists
- Crowd Sourcing
- Leadership from CBO’s
- Clinician hotlines/warmlines
- CDC and WHO Guidance
- Academic Detailing - NYC
What Does the Future Hold?

- Maraviroc – HPTN 069/ACTG A5305¹
- TAF – Macaque protection (?) but low tissue levels²
- Long Acting Therapies
  - Rilpivirine (TMC278) – HPTN 076
  - Čabotegravir (GSK1265744) – HPTN 077/HPTN 083/ECLAIR³
  - Immunotherapies – VRC01
  - Implantable devices
- More on Intermittent (i)PrEP
- Special populations
  - ATN 110/113 – Youth⁵,⁶
- Combinations of interventions

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2. Garrett K, CROI 2016
Maraviroc – HPTN 069/ACTG A5305
HPTN 069

Screening

Enrollment and Randomization
N = 600
(400 men; 200 women)

Arm 1, N=150
100 men; 50 women
MVC (active)
+ FTC (placebo)
+ TDF (placebo)

Tissue Subset
N = 30
15m; 15w
Drug Interaction Subset
N = 18

Arm 2, N=150
100 men; 50 women
MVC (active)
+ FTC (active)
+ TDF (placebo)

Tissue Subset
N = 30
15m; 15w
Drug Interaction Subset
N = 18

Arm 3, N=150
100 men; 50 women
MVC (active)
+ FTC (placebo)
+ TDF (active)

Tissue Subset
N = 30
15m; 15w
Drug Interaction Subset
N = 18

Arm 4, N=150
100 men; 50 women
MVC (placebo)
+ FTC (active)
+ TDF (active)

Tissue Subset
N = 30
15m; 15w
Drug Interaction Subset
N = 18
Long Acting Rilpivirine (TMC278)  
HPTN 076: Phase 2 Safety

- TMC278 LA is a novel poloxamer 338-containing formulation of TMC278. TMC278 LA is long-acting suspension and well-suited for delivery via IM injection.
- HPTN 076 enrolling at 4 sites, low-risk HIV-uninfected women (NY, NJ, Zim, SA)
- Fully enrolled, Data available 2017
Randomize (2:1) a total of 132 seronegative female volunteers

- Week 0
- Oral RPV 25 mg
- Oral placebo

- Week 4
- Six IM injections of RPV LA 1200 mg
- Six IM injections of saline

- Week 20
- Washout
- Washout

- Week 44

Primary endpoints: safety/acceptability of ‘maximum feasible dose’

Williams, P. HIV DART 2014
SSAT040: Seroconversion Event During Washout of 300 mg

Summary: Drug Levels, Viraemia, Resistance

HIV RNA (copies/mL) vs. Days post RPV injection

- Green: Viral load
- Blue: Plasma [RPV]
- Red: K101E (%)

ART = antiretroviral therapy

Penrose K, et al. HIVR4P 2014. Abstract OA27.01

Williams, P. HIV DART 2014
Cabotegravir (GSK 1265744) development

Early Phase

- NHP Models
- First-in-human/Phase 1
- Cardiac Safety, DDI

Indication

- Treatment
- Prevention cis women
- Prevention MSM/TGW

Phase 2a

- LATTE-1
- HPTN 077*
- ECLAIR

Phase 2b ± 3

- LATTE-2 Pivotal Phase 3
- HPTN 084
- HPTN 083

*INCLUDES BOTH MEN AND WOMEN
Long Acting Cabotegravir
HPTN 077 – Phase 2a

- Cabotegravir is a novel strand-transfer integrase inhibitor
  - Nanomolar activity against clinical HIV strains
  - Chemical congener of dolutegravir
- Pure nanosuspension, suitable for IM injection
- HPTN 077 low-risk HIV-uninfected women and men
  - Planned >60% women
### Long Acting Cabotegravir
**HPTN 077 – Phase 2a**

A Phase 2a Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, Cabotegravir, in HIV-uninfected Men and Women

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>41</th>
<th>81</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM 1</td>
<td>Daily Oral 744 30mg</td>
<td>Injections of 744LA 800 mg every 12 weeks at three time points</td>
<td>Follow-up Phase (Tail Phase)</td>
</tr>
<tr>
<td>N = 79</td>
<td></td>
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<tr>
<td>ARM 2</td>
<td>Daily Oral Placebo</td>
<td>Injections of 744LA placebo every 12 weeks at three time points</td>
<td></td>
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<tr>
<td>N = 27</td>
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<td></td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
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</tr>
<tr>
<td>ARM 1</td>
<td>Daily Oral 744 30mg</td>
<td>Injections of 744LA 600 mg every 8 weeks after monthly load at five time points</td>
<td>Follow-up Phase (Tail Phase)</td>
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<tr>
<td>N = 66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM 2</td>
<td>Daily Oral Placebo</td>
<td>Injections of 744LA placebo every 8 weeks after monthly load at five time points</td>
<td></td>
</tr>
<tr>
<td>N = 22</td>
<td></td>
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</tbody>
</table>
Long Acting Cabotegravir  
HPTN 077 – Phase 2a

Enrollment as of April 7. 2015: 152
HPTN 083 – Cabotegravir Ph 2b/3

4500 HIV-uninfected MSM in Asia, South Africa, North & South America

**ARM A**
- Oral CAB 30 mg PO QD
- TDF/FTC PBO QD

**ARM B**
- Oral CAB PRO PO QD
- TDF/FTC PO QD

**CAB LA 600 mg IM at Weeks 5, 9, and Q8 Weeks thereafter Plus**
- Daily Oral Placebo for TDF/FTC
- Daily Oral TDF/FTC Plus
  - Placebo for CAB LA IM at Weeks 5, 9, and Q8 Weeks thereafter

Open label TDF/FTC PO QD

**Blinded study duration 113-233 weeks**
Arm A participants will begin Step 3 approximately 4-8 weeks after final injection

PK “tail” coverage for Arm A, Ongoing access for Arm B
# Dapivirine Rings

| Study | **The Ring Study (IPM 027)** International Partnership for Microbicides | **ASPIRE (MTN 020)** Microbicide Trials Network |
|-------|==========================================================================|==================================================================|
| **Study design and enrollment** | | |
| **Objectives** | Long term safety and effectiveness | Safety and effectiveness |
| **Study design** | Double blind randomized placebo controlled with 2:1 randomization (active: placebo) | Double blind randomized placebo controlled with 1:1 randomization (active: placebo) |
| **Enrollment** | Total: 1959 women, ages 18-45 Active arm: ~1300 | Total: 2629 women, ages 18-45 Active arm: ~1325 |
| **Regulatory requirement** | 3000 women on dapivirine ring for at least 1 year follow-up 1500 women on dapivirine ring for 2 year follow-up | |
| **Participant follow-up** | 2 years + 6 weeks following ring discontinuation | Minimum 1 year + 4 weeks following ring discontinuation |
| **Research sites** | 7 IPM research center partners in South Africa and Uganda | 15 MTN research centers in Malawi, South Africa, Uganda, Zimbabwe |
| **Results** | | |
| **Overall results** | 31% effective, confidence interval 1-51 | 27% effective, confidence interval 1-46 |
| **Secondary analysis that excluded data from 2 sites with lower retention and adherence** | 37% effective, confidence interval 12-56 | |
| **Results by age stratification (post hoc analysis)** | | |
| **Women over 21 years of age** | 37% effective, confidence interval 3.5-59 | 56% effective, confidence interval 31-71 |
| **Women 18-21 years of age** | No statistically significant effect | No statistically significant effect |
| **HIV incidence** | 4.1% among women in active arm 6.1% among women in placebo arm | 3.3% among women in active arm 4.5% among women in placebo arm |
Conclusions

- PrEP is highly effective when taken as prescribed
- We need to target most at-risk populations
  - We need more data in transgender populations and women at risk, including peri-conception
  - In partnership with communities
- TDF-based PrEP is the first example of successful PrEP – we await generational improvements
- PrEP scale-up is a global health imperative as part of combination prevention efforts
Thank you!