What is the Future of PrEP?

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Disclosures

Raphael J. Landovitz has served as a consultant to Gilead Sciences, Merck Inc., and Roche.
1.7 Million New Infections in 2018
5000 New Infections per Day
~160,000 persons were diagnosed with HIV in the WHO European Region 2017

- West: 16% = 22,400 cases, Rate = 6.4/100,000
- Centre: 4% = 6,200 cases, Rate = 3.2/100,000
- East: 80% = 130,000 cases, Rate = 51.1/100,000

Prevention Modalities

- Condoms
- PEP
- Voluntary Male Circumcision
- Needle Exchange
- Vaccine
- Abstinence
- HIV Treatment
- PrEP
- Microbicides
- HIV & STI Testing
- STI Treatment
- Harm Reduction
Effectiveness of TDF/FTC in Clinical Trials

- iPrEx (TDF/FTC): 42% CI: 15-63
- FEM-PrEP (TDF/FTC): 6% CI: -52-41
- TDF2 (TDF/FTC): 49% CI: -22-81, 80% CI: 25-97
- Partners PrEP (TDF/FTC): 63% CI: 20-83, 71% CI: 37-87, 66% CI: 28-84, 84% CI: 54-94
- VOICE (TDF): -49% CI: +3 to -129
- -4.4% CI: +27 to -149
- PROUD (TDF/FTC): 86% CI: 64-96
- IPERGAY (TDF/FTC): 86% CI: 40-99
Status of formal PrEP implementation in Europe: October, 2019

The Power of Targeted PrEP Implementation


- **San Francisco**: 51% Reduction (2012-2016)
- **Seattle**: 42% Reduction (2010-2017)
- **London**: 42% Reduction (2016)
- **Sydney**: 32% Reduction (2017)

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Seattle & King County and the Infectious Disease Assessment Unit. HIV/AIDS Epidemiology Report 2017, Volume 86.
The Future of PrEP?

Maraviroc
Riplivirine
TAF/FTC
Cabotegravir
bNAbs
Implants
Rings
Microneedles/Patches
**Maraviroc**

**CD4 Binding** → **Coreceptor Binding** → **Virus-Cell Fusion**

- **CCRS Inhibitors**
  - maraviroc
  - PRO 140
  - TAK 652
  - vicriviroc
- **CXCR4 Inhibitors**
  - AMD-070
  - KRH-cpds
  - enfuvirtide
  - TRI-999
  - TRI-1144

- **Cell Membrane**
- **V3 loop**
- **gp120**
- **gp41**
- **BMS-cpds**
- **TNX-355**
- **PRO 542**
- **CD4**

**GeSIDA 2019**
**Objective:** To evaluate the safety and tolerability of four ARV regimens for PrEP in MSM and Women

**Maraviroc: HPTN 069/ACTG 5305**

- **Screening**
- **Enrollment and Randomization**
  - N = 600
  - (400 MSM/TGW; 200 ciswomen)

- **Arm 1, N=150**
  - MVC
  - 100/50

- **Arm 2, N=150**
  - MVC FTC
  - 100/50

- **Arm 3, N=150**
  - MVC TDF
  - 100/50

- **Arm 4, N=150**
  - FTC TDF
  - 100/50

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Gulick RM, JID, 2016
Gulick RM, Annals, 2017
## Maraviroc: HPTN 069/ACTG 5305

### Results

<table>
<thead>
<tr>
<th>Arm</th>
<th>Demographics</th>
<th>First reactive HIV+ test</th>
<th>HIV RNA (cps/mL)</th>
<th>CD4 cells (/mm³)</th>
<th>Plasma drug conc. at seroconversion visit (ng/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC TDF</td>
<td>20, black MSM</td>
<td>4W</td>
<td>122,150</td>
<td>357</td>
<td>MVC=0, TFV=0</td>
</tr>
<tr>
<td>MVC</td>
<td>61, Asian MSM</td>
<td>16W</td>
<td>981</td>
<td>294</td>
<td>MVC=145</td>
</tr>
<tr>
<td>MVC</td>
<td>21, mixed MSM</td>
<td>24W</td>
<td>106,240</td>
<td>325</td>
<td>MVC=0†</td>
</tr>
<tr>
<td>MVC</td>
<td>35, white MSM</td>
<td>32W</td>
<td>13,626</td>
<td>828</td>
<td>MVC=6.7</td>
</tr>
<tr>
<td>MVC</td>
<td>36, black MSM</td>
<td>48W</td>
<td>52,191</td>
<td>804</td>
<td>MVC=0.7</td>
</tr>
</tbody>
</table>

* expected pre-dose steady state MVC = 32 ng/ml

† undetectable plasma drug concentrations at every study visit

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Gulick RM, JID, 2016
Gulick RM, Annals, 2017
TAF/FTC: Works for Treatment—How about PrEP?

TAF 25 mg results in >90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP

Eligibility required high sexual risk of HIV
- 2+ episodes condomless anal sex in past 12W or rectal gonorrhea/chlamydia, syphilis in past 24W
- HIV & HBV negative, eGFR ≥60 mL/min
- Prior use of PrEP allowed

Study conducted in NA, EU in cities/sites with high HIV incidence
- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%

Primary efficacy endpoint:
HIV incidence
- Evaluated by rate ratio with noninferiority (NI) margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg. eGFR, estimated glomerular filtration rate.

MSM or TGW participants
Randomized 1:1
Double-blinded
Active controlled

F/TAF QD n=2694
At entry and Q12W:
Adherence counseling
Prevention services
- Risk reduction counseling
- Condoms/lubricant

96 weeks

F/TDF QD n=2693

Primary analysis:
HIV incidence/100 PY when 100% complete W48 & 50% complete W96

Open-label switch for 48 weeks

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CI, confidence interval; RR, rate ratio.

DISCOVER: HIV Incidence

Primary Endpoint Analysis: HIV Incidence

Week 48
- F/TAF: 0.16, 7 infections 4370 PY (n=2670)
- F/TDF: 0.16, 8 infections 5029 PY (n=2665)

Week 96
- F/TAF: 0.30, 15 infections 5052 PY (n=2670)
- F/TDF: 0.34, 15 infections 4386 PY (n=2665)

IRR (95% CI)
- Week 48: 0.47 (0.19, 1.15)
- Week 96: 0.54 (0.23, 1.26)

If IRR=1, no difference. NI margin 1.62, 2.

Ruane PJ. EACS 2019, Abstract PS3/1
DISCOVER: Bone Safety

Bone Safety: BMD Substudy (n=375)*

Week 48
Spine
- F/TAF
-1.1
- F/TDF
-1.4

Week 96
- F/TAF
1.0
- F/TDF
-1.0

Week 48
Hip
- F/TAF
0.2
- F/TDF
0.6

Week 96
- F/TAF
0.6
- F/TDF
-1.0

*p-values from analysis of variance model with baseline F/TDF for PrEP and treatment as fixed effects.

Ruane PJ. EACS 2019, Abstract PS3/1
DISCOVER: Renal Safety

**Renal Safety**

eGFR_{CG}

<table>
<thead>
<tr>
<th>Proximal Tubular Protein:Cr Ratios</th>
<th>Baseline</th>
<th>F/TAF: 101 μg/g</th>
<th>F/TDF: 104 μg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBP:Cr</td>
<td>Baseline</td>
<td>F/TAF: 84 μg/g</td>
<td>F/TDF: 86 μg/g</td>
</tr>
<tr>
<td>β2M:Cr</td>
<td>Baseline</td>
<td>F/TAF: 84 μg/g</td>
<td>F/TDF: 86 μg/g</td>
</tr>
</tbody>
</table>

* p-values from Van Elteren test stratified by baseline F/TDF for PrEP to compare 2 treatment groups. β2M, β2-microglobulin; Cr, creatinine; Q, quartile; RBP, retinol-binding protein.

- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1

Ruane PJ. EACS 2019, Abstract PS3/1
When administering agents with long $t_{1/2}$ in non-removable method

- May require oral lead-in to assess toxicity before administering LA formulation
- May have prolonged sub-therapeutic tail; great concern for poorly adherent

Theoretical Infection-Exposure-Resistance Relationships

- HIV infection
- Resistant infection

Fraction infected or resistant

Low | High

Drug Exposure

- No Drug
- No Resistance
- Infection

Zone of Resistance Risk

- No Infection
- No Resistance

J. Mellors FDA Hearing 2012
Markowitz et al, Lancet HIV 2017;4:e331-40
Residual RPV Led to Resistance Selection

![Graph showing viral load over time with ART initiation](Penrose, et al JID 2016)
Long-Acting Injectables: Cabotegravir

- Cabotegravir LA is a long-acting suspension for delivery via IM injection (Currently in advanced development for Maintenance of virologic suppression [with RPV LA] and PrEP-monotherapy)
- **Agent class:** Strand-transfer integrase inhibitor
- **Half-life:** Oral: 40 hours Injectable: 40-65 days
CAB LA: Pharmacokinetic Tail

Median time to LLOQ, weeks (range)

Male 43.7 (20.4, 152.5)
Female 67.3 (17.7, 225.5)

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084).

In Steps 1 and 2, the tablets and the injections will look alike, so staff and participants will not know if they are getting the active or placebo products. In step 3, everyone will be given active TDF/FTC.
+In step 2 the first two injections are four weeks apart and 8 weeks apart thereafter.
## Antibodies Used in Vaccination Efforts: Pharmacokinetic Tail

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>PRODUCT DESCRIPTION</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Polio</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus Immune Globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Immune serum globulin (ISG)</td>
<td>Prevention (travel)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>RSV</td>
<td>mAb (palivizumab) for prophylaxis of high risk infants</td>
<td>Prevention in High Risk Infants</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella Zoster Immune Globulin</td>
<td>Post Exposure</td>
</tr>
</tbody>
</table>

Mascola, CROI 2016, Boston, MA
Schematic of an HIV-1 gp120/gp41 trimer interacting with bNAbs
Comparison of Breadth and Potency of bNabs vs 208 Diverse Isolates

- CD4 binding site
- MPER
- High mannose V3 loop
- V1/V2 loop
- gp41/gp120 interface

Implantable Devices

- Reversible with removal
- Long-acting (months to years)
- Potential for Multi-purpose
- Current development
  - TAF, CAB, EFdA
  - Others

Gunawardana, et al., AAC 2015
Monthly Dapivirine Ring

- Flexible silicone vaginal ring developed by IPM
- Woman-initiated
  - Self-inserted monthly
  - Discreet
- Slowly releases ARV dapivirine
- Reduced women’s HIV-1 risk by ~30% in two Phase III trials
- Interim data from open-label studies show greater use and suggest ~50% risk reduction
  - New interim data presented at R4P
- Under regulatory review
Microneedles

Donnelly R. Queens Univ, Belfast.
DeMuth, Retrovirology, 2012.
Microneedles

Donnelly R. Queens Univ, Belfast.
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Microneedles

- Plasmids expressing SIV-Gag + poly(I:C) in mice
- Adenoviral vectors expressing SIV-gag Adjuvanted recombinant HIV-1 CN54gp140
- Queens University (Belfast)/PATH/ViiV/Pop Council/LTS/USAID - CAB
Conclusions

• TDF/FTC PrEP has set a high bar for preventive effectiveness
  – Daily and on-demand (“2-1-1”) both work
• What will it take for a new agent to be “game changing”?
  – Long-acting preparations will solve some challenges, not all – but will be available imminently
  – Future is ripe with possibility in implants, antibody mediated protection, and microneedles
  – Study designs will need to be adaptive, and negotiations with regulators likely complex
  – MPT may increase use for cisgender women
  – More nuanced understanding of DDI/transgender populations
• More on-demand options, and better diagnostics are needed
• Need a more sophisticated understanding and better partnership with most-affected communities
• More options are better
Thank You!

Any Questions
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Thank you, Colleagues

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