Antiretrovirals for HIV Prevention: Optimizing the Use of PrEP and PEP in 2018

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the current evidence for the efficacy of TDF/FTC PrEP
- List the range of PrEP agents currently in development
- Describe the pros and cons of seamless PEP to PrEP transition

Effectiveness of Daily TDF/FTC in Clinical Trials
Audience Question #1...
Differences in clinical trial efficacy for TDF/FTC PrEP are attributable to

1. Intrinsic efficacy differential between females and males (sex at birth)
2. Differences in tissue/compartmental pharmacokinetics
3. Adherence
4. Absorption differences
5. 2 and 3
6. 3 and 4

Effectiveness of Daily TDF/FTC in Clinical Trials

PrEP Utilization

* Other indicates American Indian or Alaska Native, Native Hawaiian or Pacific Islander

National Harbor, Maryland, December 9-11, 2018
PEP to PrEP Transition

- PEP is a response to an acute exposure
- Some pts who present for PEP may be at recurrent risk for HIV
- When monitoring PEP, ascertain if the pt would benefit from PrEP
- It is important to confirm if the pt is HIV infected prior to transitioning from PEP to PrEP
- PEP entails taking up to 3 medications daily for 28 days; PrEP entails 1 pill/day while risk persists
  - Counseling about the importance of adherence is indicated

NY nPEP Guideline. 2014.
Slide credit: clinicaloptions.com

PEP to PrEP Transition – But HOW?

- No data (“Data Free Zone”)
- The concern: Could PEP “fail” – that is – patient is actually HIV infected, suppressed and antibody response attenuated due to 3-drug PEP – and now transition to PrEP (2 drugs) will lead to viral resistance
- Any hiatus in PrEP/PEP in a high-risk individual is a window for HIV acquisition.
- No perfect way to rule out HIV acquisition between test acquisition and resulting IN ANY CIRCUMSTANCE
- Best Practice: Perform Ag/Ab test at Week 4 of PEP (while still on PEP) and then seamlessly de-escalate to 2-drug PrEP.

Maraviroc

CD4 Binding → Coreceptor Binding → Virus-Cell Fusion

- Maraviroc
- CD4 Binding
- Coreceptor Binding
- Virus-Cell Fusion
- CCR5 inhibitors
  - PRO 140
  - PRO 542
  - TAK 652
  - Vicriviroc
- CCR5 antagonists
  - Maraviroc
  - BMS-663068
  - TNX-355
- CXCR4 inhibitors
  - AMD-070
  - KRH-004
  - enfuvirtide
  - TRI-999
  - TRI-1144
- CCR5/CXCR4 (R5/X4)
- CD4 Binding
- Coreceptor Binding
- Virus-Cell Fusion

National Harbor, Maryland, December 9-11, 2018
**Objective:** To evaluate the safety and tolerability of four ARV regimens for PrEP in MSM and Women

**Maraviroc: HPTN 069/ACTG 5305 Results**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Demographics</th>
<th>First reactive HIV+ test (W)</th>
<th>HIV RNA (cps/mL)</th>
<th>CD4 cells (/mm$^3$)</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

**Audience Question #2...**

Which is FALSE about TAF:

1. TAF is cleared more quickly from the plasma of women than men
2. TAF is metabolized to TFV less in blood plasma than TDF
3. TAF is known to concentrate in rectal/cervical tissues better than TDF
4. TAF/FTC has been shown to work equally well to TDF/FTC for HIV Prevention
TAF/FTC: Works for Treatment - - How about PrEP?

![Diagram showing TAF and FTC](image)

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


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

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

Rates of Detectable TFV/TFV-metabolite detection in Female mucosal tissues – single dose

![Graph showing rates of detectable TFV/TFV-metabolite detection](image)

TAF 25mg
TDF 300mg

Efficacy of TAF/FTC Against Vaginal and Rectal SHIV Infection

![Graph showing efficacy of TAF/FTC against vaginal and rectal SHIV infection](image)

Adapted from Massud, CROI 2018, Abstract 85
Adapted from Massud, JID, 2016
**TAF/FTC for PrEP: DISCOVER**

**Objective:** To assess HIV incidence in MSM and TGW who have sex with men and who are administered daily TAF/FTC or TDF/FTC

<table>
<thead>
<tr>
<th>Primary Endpoint: Seroconversion rate/100 p-y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
</tr>
<tr>
<td>96</td>
</tr>
<tr>
<td>48</td>
</tr>
</tbody>
</table>

**Switch option**

- FTC/TAF (200/25 mg) QD
- FTC/TDF (200/300 mg) QD

Slide courtesy of Gilead Sciences

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**Long-Acting Agents: Good, Bad, or Ugly?**

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; concern for poorly adherent

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**Long-Acting Injectables: Rilpivirine**

- Rilpivirine LA is a long-acting nanosuspension for delivery via IM injection (regulatory approvals for HIV treatment in combination with other ART agents – in development with CAB LA)
- **Agent class:** Non-nucleoside reverse transcriptase inhibitor
- **Half-life:**
  - Oral: 45 hours
  - Injectable: 90 days

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Markowitz et al, Lancet HIV 2017;4:e331-40
**HPTN 076:** RPV LA in low-risk HIV-uninfected women

**Objective:** To evaluate the safety and acceptability of rilpivirine LA in healthy, HIV-uninfected females.

<table>
<thead>
<tr>
<th>WEEKS</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1</td>
<td>N = 91</td>
<td>Daily oral RPV</td>
<td>Six injections of RPV LA 1200 mg every 8 weeks</td>
</tr>
<tr>
<td>ARM 2</td>
<td>N = 45</td>
<td>Daily oral placebo</td>
<td>Six injections of placebo every 8 weeks</td>
</tr>
</tbody>
</table>

**HPTN 076: Phase 2 Safety Results**

- Two 2mL IM injections every 8 weeks were safe, well-tolerated, and acceptable to women
- Lower quartile RPV concentrations were consistently above the PA-IC$_{90}$ 8 weeks post injection at all time points
- Cold chain required

**Seroconversion during pharmacokinetic tail after 300 mg IM dose**

National Harbor, Maryland, December 9-11, 2018
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

CABOTEGRAVIR

DOLUTEGRAVIR

CAB LA: Phase 2 #1 – ECLAIR Study

Objective: To evaluate the safety and tolerability of the injectable agent in HIV uninfected US men.

ECLAIR: Predicted vs Observed CAB LA PKs

ECLAIR: CAB C, Following Each Injection and PK tail

Modified from Markowitz et al, Lancet HIV 2017

<table>
<thead>
<tr>
<th>Injection number</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Participants</td>
<td>24%</td>
<td>45%</td>
<td>32%</td>
</tr>
<tr>
<td>Percent of Participants</td>
<td>61%</td>
<td>31%</td>
<td>30%</td>
</tr>
</tbody>
</table>

CAB LA in Development: HPTN 077

Objective: To evaluate the safety, tolerability, and pharmacokinetics of CAB LA in healthy, HIV-uninfected males and females.


HPTN077: CAB C, Following Each Injection

Adapted from Landovitz, R. IAS. 2017
**Audience Question #3...**

The Pharmacokinetic Tail of Long-Acting Injectable ARVs:

1. Is of no concern
2. Can be overcome by hemodialysis
3. Can be overcome by surgical excision of the muscular depot
4. Requires clinical study to determine if it is an advantage or a liability

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**CAB LA pharmacokinetic tail by sex at birth**

![Diagram showing pharmacokinetic tail by sex at birth]

**Ka, terminal half life, and estimated Time to LLOQ**

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_a$, μg/mL·day (95% CI)</td>
<td>0.02 (0.01, 0.05)</td>
<td>0.01 (0, 0.04)</td>
</tr>
<tr>
<td>$t_{1/2,app}$ days (95% CI)</td>
<td>42.5 (13.5, 133.9)</td>
<td>64.6 (19.2, 217.1)</td>
</tr>
<tr>
<td>Median time to LLOQ, weeks (range)</td>
<td>42.7 (20.4, 134)</td>
<td>66.3 (17.7, 182)</td>
</tr>
</tbody>
</table>

*17% of the $t_{1/2,app}$ variability was explained by sex and BMI*
HPTN 083 and 084: Phase 3 for CAB LA PrEP

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)

Antibodies Used in Vaccination Efforts

<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>

Audience Question #4...
The best broadly neutralizing antibody for HIV treatment and prevention is:

1. VRC07-523LS
2. 10e8
3. The “Tri-specific” Antibody
4. The antibody your cousin brewed in their basement
5. No one knows the answer at this time
Schematic of an HIV-1 gp120/gp41 trimer interacting with bNAb

Comparison of Breadth and Potency of bNAb vs 208 Diverse Isolates

Study Schema for The AMP Studies

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in SSA</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1500</td>
<td>4200</td>
</tr>
</tbody>
</table>

VRC01 10 mg/kg: 10 infusions total & Infusions every 8 weeks

VRC01 30 mg/kg: Study duration: ~22 months
Implantable Devices

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


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

Nel A et al. NEJM 2016
Baeten J et al. NEJM 2016
Baeten J et al. CROI 2018, #143LB
Nel A et al. CROI 2018, #144LB

Microneedles

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

- Plasmids expressing SIV-Gag + poly(I:C) in mice
- Adenoviral vectors expressing SIV-gag
  Adjuvanted recombinant HIV-1 CNS4gp140
- Queens University (Belfast)/PATH/ViIV/Pop Council/LTS/USAID - CAB
Conclusions

• TDF/FTC PrEP has set a high bar for preventive effectiveness
• 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
• On-demand options are needed
• More options are better

Thank you

• Ryan Kofron
• Quarraisha Abdul-Karim
• Trip Gulick
• Ian McGowan
• Marybeth McCauley
• Zeda Rosenberg
• Mike Cohen
• Wafaa El-Sadr
• Susan Buchbinder
• John Mascola
• Ryan Donnelly
• Charlie Flexner/LEAP
• Sybil Hosek
• Sheryl Zwerski
• Ninupama Sista
• Leslie Cottle
• Lucio Gama
• Trevor Hawkins
Question-and-Answer
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SUGGESTED READINGS


