PrEP & Other HIV Prevention Methods in Women

Jeanne Marrazzo, MD, MPH
UAB Division of Infectious Diseases

Women and HIV Inter-CFAR Symposium on HIV Research in Women

December 7, 2016
Preventing HIV among Women — A Step Forward, but Much Farther to Go

Adaora A. Adimora, M.D., M.P.H.

NEJM Dec 1, 2016
Discussion

- The PrEP experience with TDF-FTC in women
  - Untangling the efficacy conundrum: adherence? Drug delivery?

- Testing new interventions
  - Addressing challenges with adherence & user preferences
  - The end of the placebo arm

- Evolving evidence
  - New products & potential indications
  - Long acting delivery platforms
  - Combination prevention
What We Learned from Placebo-Controlled RCTs of Daily TDF-FTC PrEP: Percent of Samples with Detectable TFV & Efficacy

- **FEM PREP**: 6% Protection of PrEP vs Placebo, 26% % with detected TDF
- **iPrEx**: 44% Protection of PrEP vs Placebo, 51% % with detected TDF
- **TDF2**: 62% Protection of PrEP vs Placebo, 79% % with detected TDF
- **PARTNERS PrEP**: 75% Protection of PrEP vs Placebo, 81% % with detected TDF

Legend:
- Red: Protection of PrEP vs Placebo
- Blue: % with detected TDF
Lack of Efficacy in the VOICE Study

Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women

Was it all due to non-adherence?
Does suboptimal drug delivery to tissues (pharmacokinetics) play a role?

‘Nonadherence’: A bitter pill for drug trials
Drug developers seek new ways to ensure that subjects take their medicine

Science, October 17, 2014
Cottrell, J Clin Pharm 2014
Evidence of non-adherence by route of administration and different measures in VOICE participants

Van der Straten, J IAS 2016
Combined in vitro efficacy target with mucosal tissue PK data and mathematical modeling to determine number of doses required for effective PrEP

Measured endogenous nucleotides that compete with TFVdp (dATP, dCTP)
Dose proportionality in blood plasma, PBMCs, & mucosal tissues


Female genital tract tissue
Colorectal tissue
Plasma / PBMCs

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Endogenous nucleotides compete with NRTIs for binding sites as viral ssRNA is translated into dsDNA strand, thus reducing efficacy


iPerGay: On-Demand PrEP

- Randomized double-blind trial of event-driven oral TDF/FTC* (n = 199) vs placebo (n = 201) in MSM
  - 2 tablets taken 2-24 hrs before sex
  - 1 tablet 24 hrs after sex
  - 1 tablet 48 hrs after first event-driven dose

86% reduction in risk in PrEP arm (95% CI: 40% to 99%, P = .002)
- No. needed to treat for 1 yr to prevent 1 infection: 18
- Median of 16 pills taken per month in each arm

Time to protection and minimally effective preexposure prophylaxis (PrEP) dosing.


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Time to protection and minimally effective preexposure prophylaxis (PrEP) dosing.

- Most achieved EC$_{90}$ ratios by 3$^{rd}$ daily dose of TDF / FTC in colorectal and FGT tissues after beginning PrEP
- 7 doses/week: all achieve EC$_{90}$ ratios in FGT and colorectal tissues
- 2 doses/week: only 65% achieve target exposure in FGT, but ≥95% do in colorectal tissue

TFV-PrEP: Other Issues for Women

- PrEP safe during pregnancy (Mugo JAMA 2014)
- No reduction in contraceptive efficacy (Murnane AIDS 2014)
- TAF should not be used for PrEP…yet
  - Low tissue levels of TFVdp after oral dosing
  - RCT of TDF/FTC vs. TAF underway in MSM (NCT02842086)
Should We Go Beyond Oral PrEP?

<table>
<thead>
<tr>
<th>No—Why Bother?</th>
<th>Yes!</th>
</tr>
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<tbody>
<tr>
<td>Stabilization of the epidemic likely attainable with combination of ART &amp; oral PrEP (TDF-FTC, TDF)</td>
<td>Bridge to critical threshold of ART/PrEP coverage</td>
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<tr>
<td>Sustained delivery systems for ARV PrEP advancing in investigative pipeline</td>
<td>Need on-demand protection</td>
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<tr>
<td>Rilpivirine, cabotegravir</td>
<td>Expand choice for personalized protection</td>
</tr>
<tr>
<td>Low adherence in clinical trials suggests limited marketability &amp; uptake for some products (gel)</td>
<td>Aim for low / minimal systemic absorption, low systemic toxicity</td>
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<tr>
<td></td>
<td>Different PK for cervix vs. rectum</td>
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<td></td>
<td>Possibility for co-protection (HSV)</td>
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<td>Multi-purpose prevention (contraception)</td>
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Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women


Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women

ASPIRE & RING Studies

• Randomized, double-blind, placebo-controlled phase III trials of a vaginal matrix ring containing NNRTI dapivirine

• Primary objectives: determine effectiveness and safety of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active women
HIV-1 Protection

RING Study

No. at Risk
Dapivirine: 1300 1248 1208 1176 1150 1121 993 872 755 671 622 587 133
Placebo: 650 617 591 570 555 530 477 428 367 324 302 291 69

No. at risk: 2395 2352 2275 2218 2020 1739 1459 1235 1108 748 428 223

Months since randomization

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use
Age and HIV-1 Protection

- HIV-1 protection effectiveness was explored in additional age-stratified categories, and lack of HIV-1 protection was limited to those ≤21 years of age:

<table>
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<tr>
<th>Age Range</th>
<th>Protection Effectiveness</th>
<th>Placebo Incidence</th>
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<td>Age 18-21</td>
<td>27% (-133,31)</td>
<td>5.4%/yr</td>
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<td>Age 22-26</td>
<td>56% (19,76)</td>
<td>6.1%/yr</td>
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<tr>
<td>Age 27-45</td>
<td>51% (8,74)</td>
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Age and HIV-1 Protection

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Among women >21 years of age, HIV-1 protection effectiveness was 56% (95% CI 31-71%, p<0.001)
MTN-020/ASPIRE Subcohort: Adherence by Residual DAP Levels in Vaginal Ring

- A lower level of residual DAP in the returned ring is indicative of higher adherence.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Nonadherent (≥ 23.5 mg*)</th>
<th>Low-High Adherence (&lt; 23.5 mg*)</th>
<th>Med-High Adherence (&lt; 22 mg*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections, n</td>
<td>50</td>
<td>13</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>HIV incidence/100 PY</td>
<td>4.6</td>
<td>3.6</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Risk reduction vs PBO, %</td>
<td>--</td>
<td>31</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td>(95% CI; P value)</td>
<td>(28 to 63; .24)</td>
<td>(20 to 76; .007)</td>
<td>(22 to 84; .01)</td>
<td></td>
</tr>
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</table>

*Residual levels of DAP remaining in returned rings.

MTN-020/ASPIRE Subcohort: Adherence vs HIV Protection 3 Mos Before Detection

- Sustained adherence associated with 92% reduction in risk of HIV infection

*For seroconversions, adherence level taken from visit with lowest adherence of 3 months (3 visits) before HIV detection.

Renewed Interest in Vaginal Ring Delivery for ARV, hormones

- These data have revitalized discussion of ARV delivery by rings
- Numerous products under evaluation
  - TDF; TFV; Vicriviroc (MK-4176) & MK-2048 (II)
  - Combo rings have varying progestin (HC) component
  - Different progestins may have varying effects on menses; estrogen needed to suppress menses
Long-Acting Injectable PrEP

- Cabotegravir: integrase inhibitor (dolutegravir analogue) formulated as a nanosuspension for IM injection
- ÉCLAIR study established safety, tolerability, dosing schedule

Good for PrEP:
- High genetic barrier to resistance
- PK profile: half life of 21-50 days allows once-daily oral or 1-3 month injectable dosing

Testing a New PrEP Agent with an Active Comparator Arm (TDF-FTC)

- Non-inferiority: is CAB-LA not unacceptably less effective than TDF-FTC? Double blind design preferred: Men/TGW
- Superiority: is CAB-LA more effective than TDF-FTC? Adherence to pills may not be “real” if participant is blinded: Women
Cabotegravir: HPTN 083

- Phase 2B/3 safety / efficacy study of quarterly injectable CAB compared to daily oral TDF/FTC for PrEP in 4500 MSM / TGW

- Step 1: Oral TDF/FTC or oral CAB 30 mg daily x 5 weeks

- Step 2: Oral TDF/FTC daily or injectable CAB 800 mg every 3 mos
  - Continues until 286 seroconversions reached

- Step 3: Open label TDF/FTC daily to cover PK “tail” / post-trial access
Cabotegravir: HPTN 084

- 3600 women in an open-label Phase 3 trial testing hypothesis that CAB-LA is superior to daily oral TDF/FTC
- Sub-Saharan Africa
- Protocol in development
# Sustained Release Devices: MPT IVRs

<table>
<thead>
<tr>
<th>90-day MIV-150 + ZA + C + LNG (Pop Council)</th>
<th>90-day Dapivirine + LNG (IPM)</th>
<th>90-day TFV + LNG (CONRAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- EVA matrix with reservoir core</td>
<td>- Silicone matrix ring</td>
<td>- Segmented PU ring</td>
</tr>
<tr>
<td>- Pre-clinical stages</td>
<td>- Advanced pre-clinical stages</td>
<td>- Phase I clinical study</td>
</tr>
<tr>
<td>- Pregnancy, HIV, HSV-2, HPV</td>
<td>- Pregnancy, HIV</td>
<td>- Pregnancy, HIV, HSV-2</td>
</tr>
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</table>

MPTs: a promising response to current challenges around hormonal contraceptive methods and HIV
2016 International Conference on Family Planning - 27 January 2016 – Nusa Dua, Indonesia
Thoughts & Next Steps

- PrEP works, when taken consistently, and is the most effective tool for preventing sexual HIV transmission we have so far
  - Only one ARV (TFV) available; data for women still limited
- Critically dependent results coming up:
  - HPTN studies of long-acting ARV (cabotegravir, rilpivirine)
  - Rectal microbicide development
- Combination product development
  - Antiretroviral + hormonal contraceptive
KEEP CALM AND Make Good Choices
Protection with pericoital preexposure prophylaxis (PrEP) dosing.


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Protection with pericoital preexposure prophylaxis (PrEP) dosing.

The maximal percentage of the population achieving EC$_{90}$ ratios in colorectal tissue over a 240-hour postcoital window is achieved by initiating the Ipergay dosing 24 hours before coitus. Dosing at 24 hours or 2 hours before coitus did not appear to alter the percentage of the population achieving target exposure in the FGT tissue over a 72-hour postcoital window.