Making Science Work: Current and Future PrEP Use

Association of Nurses in AIDS Care
Thursday March 23, 2017

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Carole Treston, RN MPH ACRN FAAN
Continuing Nursing Education

Upon full participation in this webinar & completion of an evaluation, participants will be awarded 1.0 contact hours.

The Association of Nurses in AIDS Care (ANAC) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
Disclosures

**Faculty Conflict of Interest Disclosures**

Charlene Flash serves on the Scientific Advisory Board for Gilead Sciences and is a recipient of Gilead investigator-initiated research funding.

Carole Treston has no actual or perceived conflicts of interest related to the content of this program.

**Commercial Support Disclosures**

This program is part of a project supported by funding from Gilead Sciences, Inc. awarded to ANAC.
Learning Objectives

At the end of this session participants will be able to:

1. List the clinical research that demonstrates the efficacy & safety of PrEP
2. Discuss issues related to adherence monitoring
3. Describe PrEPception and PrEP for Breastfeeding
4. Discuss Future formulations and use
Housekeeping

- Participant lines muted during the webinar
- Type questions in the “Question” pane of your Dashboard
- Q & A session at the end of the webinar.
Agenda

• Highlights of the Clinical Science Related to PrEP
• Current Usage
• Future Considerations
• PrEP Resources for Clinicians
• Q&A
Making Science Work: Current and Future PrEP Use

Charlene A. Flash MD MPH
Assistant Professor of Medicine
Division of Infectious Diseases
Baylor College of Medicine
Overview

• Highlights of the clinical science related to PrEP
  • Efficacy
  • Adherence monitoring
  • Safety
  • PrEPception and Breastfeeding
  • Future formulations and use
Pre-exposure prophylaxis (PrEP)

- Vulnerable people take antiretrovirals to prevent HIV.
- Only one FDA approved drug
  - Once daily co-formulated tenofovir disoproxil fumarate 300 mg (TDF) and emtricitabine (FTC) 200 mg
- 44 to 67% effective in clinical trials
- ....If taken perfectly 92% effective
Clinical Trial Evidence for Tenofovir and Dapivirine-Based Prevention (February 2016)

Prevention of sexual transmission

- PROUD – daily oral TDF/FTC
  (MSM – United Kingdom)
- IPERGAY – event-driven TDF/FTC
  (MSM – Canada, France)
- Partners PrEP – daily oral TDF
  (Serodiscordant couples – Kenya, Uganda)
- Partners PrEP – daily oral TDF
  (Serodiscordant couples – Kenya, Uganda)
- TDF2 – daily TDF/FTC
  (Heterosexual men and women – Botswana)
- iPrEx – daily oral TDF/FTC
  (MSM – North and South America, South Africa, Thailand)
- CAPRISA 004 – BAT-24 dosing vaginal tenofovir gel
  (Women – South Africa)
- The Ring Study – monthly vaginal ring containing dapivirine
  (Women – South Africa, Uganda)
- ASPIRE – monthly vaginal ring containing dapivirine
  (Women – Malawi, South Africa, Uganda, Zimbabwe)
- MTN 003/VOICE – daily dosing vaginal tenofovir gel
  (Women – South Africa, Uganda, Zimbabwe)
- FEM-PrEP – daily oral TDF/FTC
  (Women – Kenya, South Africa, Tanzania)
- MTN 003/VOICE – daily oral TDF/FTC
  (Women – South Africa, Uganda, Zimbabwe)
- MTN 003/VOICE – daily oral TDF
  (Women – South Africa, Uganda, Zimbabwe)

Prevention in people who inject drugs

- Bangkok Tenofovir Study – daily oral TDF
  (IDUs – Thailand)

Effect size (CI)

- 86% (64; 96)
- 86% (44; 99)
- 75% (55; 87)
- 67% (44; 81)
- 62% (22; 84)
- 44% (15; 63)
- 39% (6; 60)
- 31% (1; 51)
- 27% (1; 46)
- 15% (-21; 40)
- 6% (-21; 40)
- -4% (-49; 27)
- -49% (-129; 3)
- 49% (10; 72)

Adapted from: Salim S. Abdool Karim, CAPRISA
Pre-exposure Prophylaxis Initiative Trial (iPrEx)

- RCT of 2500 gay or bisexual men and transgender women
- Once-daily oral FTC-TDF or Placebo
- 44% reduction in HIV incidence in the intervention group

*Grant, RM, NEJM 2010*
**Oral PrEP - heterosexuals**

**TDF2-CDC**

- Randomized Control Trial
- 1200 men and women
  - Botswana
  - Daily oral
  - FTC-TDF vs. placebo

- **63%** reduction in the risk of HIV acquisition

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Thigpen, NEJM 2012

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Oral PrEP - couples
Partners PrEP

• 4758 HIV sero-discordant heterosexual couples
  • Kenya & Uganda
  • TDF vs. FTC-TDF vs. placebo

- TDF → 62% fewer infections
- FTC-TDF → 73% fewer infections

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Baeten, NEJM 2012
Oral PrEP – IDU
Bangkok Tenofovir Study

- 2413 IDU
- Thailand
- TDF vs. placebo
- DOT vs. non-DOT
- TDF → 48.9% fewer infections

Choopanya, Lancet 2013

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PrEP works, if taken consistently

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall Efficacy</th>
<th>Efficacy if TFV detected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>44%</td>
<td>92%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>TDF2</td>
<td>62</td>
<td>85</td>
</tr>
<tr>
<td>Bangkok IDU</td>
<td>49</td>
<td>74</td>
</tr>
</tbody>
</table>

Grant RM, NEJM. 2010.
Thigpen MC, NEJM 2012.
Baeten JM, NEJM 2012.
Adherence monitoring

• **Indirect:**
  - Self-report
    - Social desireability
    - SMS/text survey
  - Pill counts
  - Refill records
  - Medication event monitoring systems (MEMS)

• **Direct:**
  - Dried blood spots
  - Hair samples
  - Stored samples

Haberer, AIDS, 2015; Ghandi, JID 2015;
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How long until it takes effect?

- Oral PrEP maximum intracellular concentration
  - Rectal tissue - 7 days
  - Cervicovaginal tissue – 20 days
  - Blood – 20 days
Drug safety considerations

- GI side effects
- Dizziness/headache
- Rare renal toxicity (<1%) amongst predisposed patients
- 1% BMD loss at the total hip and femoral neck
  - Rate of bone fractures was no different

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Table 1: Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th>Detecting substantial risk of acquiring HIV infection</th>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive injecting partner</td>
<td></td>
</tr>
<tr>
<td>Recent bacterial STI</td>
<td>Recent bacterial STI</td>
<td>Sharing injection equipment</td>
<td></td>
</tr>
<tr>
<td>High number of sex partners</td>
<td>High number of sex partners</td>
<td>Recent drug treatment (but currently injecting)</td>
<td></td>
</tr>
<tr>
<td>History of inconsistent or no condom use</td>
<td>History of inconsistent or no condom use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial sex work</td>
<td>Commercial sex work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In high-prevalence area or network</td>
<td>In high-prevalence area or network</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinically eligible</th>
<th>Documented negative HIV test result before prescribing PrEP</th>
<th>Documented negative HIV test result before prescribing PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No signs/symptoms of acute HIV infection</td>
<td>No signs/symptoms of acute HIV infection</td>
</tr>
<tr>
<td></td>
<td>Normal renal function; no contraindicated medications</td>
<td>Normal renal function; no contraindicated medications</td>
</tr>
<tr>
<td></td>
<td>Documented hepatitis B virus infection and vaccination status</td>
<td>Documented hepatitis B virus infection and vaccination status</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescription</th>
<th>Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Other services</th>
<th>Follow-up visits at least every 3 months to provide the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV test, medication adherence counseling, behavioral risk reduction support,</td>
</tr>
<tr>
<td></td>
<td>side effect assessment, STI symptom assessment</td>
</tr>
<tr>
<td></td>
<td>At 3 months and every 6 months thereafter, assess renal function</td>
</tr>
<tr>
<td></td>
<td>Every 6 months, test for bacterial STIs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do oral/rectal STI testing</th>
<th>Assess pregnancy intent</th>
<th>Access to clean needles/syringes and drug treatment services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy test every 3 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STI: sexually transmitted infection
PrEP Failure/Drug Resistance

• **Randomized trials:** Participants already HIV-infected at the time of enrollment
  - Window period of acute HIV

• **Real world:** rare PrEP users with multiple mutations upon seroconversion.

Knox DC, *CROI* Boston, 2016

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Risk compensation

• Sexual disinhibition and reduction in use of condoms as an adjunct safety measure

• In many clinical trials trend toward decreased sexual risk behavior
  • Self-report, clinical trial setting, coupled with behavioral interventions

• In non-trial settings, risk-taking behavior varies by personal, psychosocial and health-related features.
Risk Compensation Ipergay (Open Label)

- No change in median number of sexual partners or episodes of anal sex
- Increase in % of receptive anal sex episodes that were condomless
Transmission risk over 100 sex acts in discordant male couple
PrEPception

- Discuss with heterosexual women and men whose partners have HIV infection (IIB)
  - One of several options
  - Begin one month before conception
  - Continue one month after conception
  - Antiretroviral Pregnancy Registry
    http://www.apregistry.com/

![Figure 1](FIGURE_1_Partner’s_treatment_status_and_viral_load_(n=26).png)

Twenty-six women reported having partners living with HIV, of whom 27% were not on antiretroviral therapy and 58% had known detectable or unknown viral loads.

ART, antiretroviral therapy.


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Breastfeeding and PrEP

- Tenofovir detected at concentrations consistent with steady-state use
- tenofovir was unquantifiable in 46/49 samples (94%),

- Maternal plasma emtricitabine concentrations consistent with steady-state use

- Emtricitabine concentrations in breast milk were more similar to plasma concentrations than had been seen for tenofovir

Emtricitabine was detectable in 47/49 (96%) infant plasma samples

<table>
<thead>
<tr>
<th></th>
<th>Maternal plasma</th>
<th>Breast milk</th>
<th>Infant plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of samples</td>
<td>98</td>
<td>97</td>
<td>49</td>
</tr>
<tr>
<td>Median conc. (ng/mL)</td>
<td>267.5</td>
<td>84.4</td>
<td>13.2</td>
</tr>
</tbody>
</table>

What is the future of PrEP?

- Alternative agents
  - Long-acting agents
  - Alternative delivery systems
- Multi-purpose prevention technology
- Alternative dosing strategies
# ARV-Based Prevention Pipeline

<table>
<thead>
<tr>
<th>PRE-CLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
<th>PHASE IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPM</td>
<td>IPM</td>
<td>IPM</td>
<td>HPTN/ACTG</td>
<td>IPM</td>
</tr>
<tr>
<td>Pop Council</td>
<td>IPM</td>
<td>TaiMed</td>
<td>CONRAD</td>
<td>Gilead</td>
</tr>
<tr>
<td>CHAARM</td>
<td>IPM</td>
<td>IPM</td>
<td>GSK/ViiV</td>
<td></td>
</tr>
<tr>
<td>IPM</td>
<td>IPM</td>
<td>IPM</td>
<td>Janssen</td>
<td></td>
</tr>
</tbody>
</table>

**ACTIVE DRUG**
- TFV: Tenofovir
- TFV prodrug: D4T
- TDF: Tenofovir disoproxil fumarate
- FTC: Emtricitabine
- TFV/FTC: Tenofovir disoproxil fumarate/Emtricitabine

**DELIVERY SYSTEM**
- Oral pills
- Vaginal gel
- Vaginal ring
- Vaginal film
- Phosphate buffered saline
- Rectal gel
- Long-acting injectable
- Thin film
- Nano-fiber

**AVAC**
February 2016

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Potential Alternative Active Drug

- Cabotegravir
- Rilpivirine
- Dapivirine
- Maraviroc
- TAF
Tenofovir alafenamide (TAF)

- Oral prodrug of tenofovir (TFV)
- At low doses achieves ~90% lower plasma TFV exposure and increased intracellular TFV-diphosphate (TFV-DP) levels
- FTC/TAF prevented rectal SHIV infection in 6 macaques.

Garcia-Lerma G. et al, CROI, 2016
Inadequate tissue levels after oral tenofovir alafenamide (TAF)

- TFV in mucosal tissues and genital fluids (as opposed to lymphoid cells) MAY contribute to preventive efficacy of PrEP.
- Despite comparable plasma TFV PK and PBMC TFVdp levels; TFVdp was undetectable in 83% tissues after TAF dosing.
- Phase III trial enrolling F/TAF vs TDF/FTC
- Pending further study, TAF/FTC should not be prescribed for PrEP outside of a clinical trial setting.

Garrett KL et al, CROI 2016; Abstract 102LB.
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Alternative Delivery Systems

• Creams, gels, films, vaginal and rectal suppositories

• Intra-vaginal rings – ASPIRE, Ring Study
  • Dapivirine release over a few weeks or months
  • Open label extension and licensure data collection

• Rectal microbicides: TDF applicator, dapivirine lube
Dapivirine Ring – ASPIRE

- ≤ 21 y/o: No evidence of protection
- >21 y/o: 56% rate HIV-1 protection; 95% CI, 31 to 71; P<0.001)

Baeten JM., NEJM, 2016
Cabotegravir LA

- Dolutegravir analogue
- half life of 21-50 days
  - allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation
- Demonstrates efficacy in Macaques
- HPTN 083 - Randomised non-inferiority study compared to oral TDF/FTC in early stages
Multipurpose Prevention Technologies
HIV/STIs/pregnancy

<table>
<thead>
<tr>
<th>Indications</th>
<th>Delivery Modes</th>
<th>Mechanisms of Action</th>
<th>Dosage &amp; Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV*</td>
<td>Diaphragm*</td>
<td>Anti-microbial*</td>
<td>Oral daily*</td>
</tr>
<tr>
<td>Candida</td>
<td>Film*</td>
<td>Anti-fungal</td>
<td>Oral on-demand Gel*</td>
</tr>
<tr>
<td>Chlamydia*</td>
<td>Implant</td>
<td>Anti-viral*</td>
<td>Systemic sustained*</td>
</tr>
<tr>
<td>Gonorrhea*</td>
<td>Injection*</td>
<td>Barrier*</td>
<td>Topical daily*</td>
</tr>
<tr>
<td>HIV*</td>
<td>Intrauterine Device</td>
<td>HC*</td>
<td>Topical on-demand*</td>
</tr>
<tr>
<td>HPV*</td>
<td>Oral pill*</td>
<td>Non-HC*</td>
<td>Topical sustained</td>
</tr>
<tr>
<td>HSV*</td>
<td>Ring (Non-IVR)</td>
<td>Probiotic</td>
<td></td>
</tr>
<tr>
<td>Pregnancy*</td>
<td>Ring (IVR)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>Tablet*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td></td>
<td></td>
<td>*Currently being tested in human clinical trials.</td>
</tr>
</tbody>
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Intermittent dosing - Ipergay

- 2 pills 2 to 24 hours before sex (or one pill, if the most recent dose was taken between 1 and 6 days ago)
- Two additional single-pill doses 24 and 48 hours after the last pre-sex dose
- Continue one pill daily if additional sex events before above regimen completed

In any week where sex occurred, there could be as few as four PrEP pills used (with a single act of sex) or as many as eight (with daily sex).

- RCT Feb 2012 - Oct 2014
- Stopped early
- 400 MSM

Intermittent PrEP
IPERGAY

• Complex dosing strategy ....real world adherence
• ?Time to optimal level of active metabolites
• ? Efficacy among heterosexual men and women and injection drug users
• CDC recommends daily use of PrEP, as approved by the FDA.

- National electronic patient-level data from 80% of US retail pharmacies
- 79,684 individuals started FTC/TDF for PrEP.
- 1,671 in Q4 2012 → 14,000 in Q4 2015

Disparities in PrEP Utilization

PrEP use among AA and Hispanics is low relative to the rate of new HIV infections

Bush S, et al. ASM/ICAAC 2016; Boston, MA. #2651

  - AA: 62%
  - White: 12%
  - Hispanics: 18%
  - Asians: 3%
  - Multiracial/Other: 2%

  - AA: 44%
  - White: 27%
  - Hispanics: 23%
  - Asians: 3%
  - Multiracial/Other: 2%

- Total FTC/TDF for PrEP Utilization by Race/Ethnicity, Sept 2015, US
  - AA: 74%
  - White: 10%
  - Hispanics: 12%
  - Asians: 4%
  - Multiracial/Other: 4%

a. https://www.census.gov/quickfacts/table/PST045215/00
b. Other: American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander. CDC. *HIV Surveillance Report, 2014*
c. These data represent 43.7% (n=21,463) of unique individuals who have started TVD for PrEP from 2012-3Q2015.
Summary

- Highlights of the clinical science related to PrEP
  - Efficacy
  - Adherence monitoring
  - Safety
  - PrEPception and Breastfeeding
  - Future formulations
  - Current Uptake
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• Gilead Sciences
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PrEP Resources

- **ANAC website**: Resources & Tools: PrEP Information for Clinicians [www.nursesinaidscare.com](http://www.nursesinaidscare.com)
- **CDC Resources**: [www.cdc.gov/hiv/risk/prep](http://www.cdc.gov/hiv/risk/prep)
- **PrEPline**: Peer to Peer Consultation: [www.nccc.ucsf.edu](http://www.nccc.ucsf.edu). Clinician Consultation Center UCSF, HRSA/HAB, AETC
  
  Mon-Fri 11 a.m. – 6 p.m. EST  855-448-7737

- **PrEP Locator**: Find Your Provider [www.preplocator.org](http://www.preplocator.org)

- **UPCOMING ANAC PREP WEBINARS**
Questions
Continuing Nursing Education

After the webinar an email will be sent to you with a link to the slides and evaluation form. To be awarded contact hours for this webinar, complete the evaluation at that link or it can be found at

https://www.nursesinaidscare.org/i4a/forms/index.cfm?id=175

Additional questions?
Email Erin at erin@anacnet.org

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