PrEP Dosing Strategies
Outline

- Background
  - PrEP absorption and tissue penetration
- Oral versus topical
- Lead in and lead out dosing
  - Time to protection
- Cycling on and off PrEP
- Balancing toxicity and adherence
**ART-Based PrEP**

| How are antiretrovirals used? | • Oral pill  
|                              |   • Topical gel (microbicide)  
|                              |     • Rectal  
|                              |     • Vaginal  
|                              |     • Injection  
|                              |     • Intravaginal ring  
| How often are the antiretrovirals used? | • Daily  
| How many antiretrovirals are used? | • Combination  
| | • Monotherapy  
| What antiretrovirals are used? | • Truvada  
| | • Tenofovir  
| | • (Cabotegravir/miravirroc)  

**Post Exposure prophylaxis (PEP)**

**Treatment as Prevention (TasP)**

**Combination Prevention with existing and new technologies**
## Four Early Trials Demonstrating PrEP Efficacy in Diverse Geographic and Risk Populations

<table>
<thead>
<tr>
<th>Study, population</th>
<th>PrEP agent</th>
<th># of HIV infections</th>
<th>PrEP efficacy (95% CI) publication</th>
</tr>
</thead>
</table>
| **Partners PrEP Study**  
Heterosexual couples  
Kenya, Uganda (n=4758) | TDF/FTC | 13 | 75% (55-87%)  
| | TDF | 17 | 67% (44-81%)  
| **TDF2 Study**  
Heterosexuals  
Botswana (n=1219) | TDF/FTC | 10 | 62% (16-83%)  
| **Bangkok Tenofovir Study (BTS)**  
IDUs  
Thailand (n=2413) | TDF | 17 | 49% (10-72%)  
Choopanya et al. Lancet 2013 |
| **iPrEx**  
MSM  
Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499) | TDF/FTC | 36 | 44% (15-63%)  
Grant et al. N Engl J Med 2010 |
Penetration of TDF in Mucosal Tissues

- Exposure to TFV, TFV-DP, FTC, FTC-TP varied widely in different mucosal tissues
- Women may need to be more adherent to PrEP than MSM

Concentrations of TFV (A) and TFV-DP (B) in Rectal, Vaginal, and Cervical Tissues After a Single Dose of TDF/FTC

Days After Single TDF/FTC dose


Slide credit: clinicaloptions.com
Lead In and Out Doses

…Or Time to Protection

7 days for anal tissue levels to reach high level steady state
  ➔ Protects against anal acquisition of HIV

20-30 days for vaginal tissue levels to reach high level steady state
  ➔ Protection against vaginal acquisition of HIV
  ➔ May need higher adherence levels for women

28 day lead out time (cf. PEP)
Cycling On or Off PrEP

- PrEP is not a lifelong drug-taking intervention
- PrEP should be used only if there is possible exposure to HIV
  - Risk levels expected to change
  - People will use PrEP for variety of reasons
  - Case example e.g. student / CSW
- People can cycle off PrEP
- This is NOT non-adherence
- Remember lead in and lead out times
Getting The Right Balance

Convenience Adherence

Toxicity Efficacy
Partners PrEP: Efficacy and Resistance Results

- Both PrEP arms significantly reduced HIV acquisition risk; similar efficacy in men and women\(^1\)
  - TDF levels correlated with HIV protection

- No differences in serious AEs, creatinine abnormalities across arms

- No evidence of risk compensation

- Ultradeep sequencing in 121 HIV seroconverters (25 TDF/FTC, 38 TDF, 58 placebo)\(^2\)
  - Overall resistance: 7.4% (9/121)
  - In 26 pts, drug levels suggested PrEP use during or after HIV acquisition; in 5/26, resistance detected

Highly anticipated results were reported today from the VOICE trial, which looked at the safety and efficacy of daily oral PrEP and drug-containing vaginal microbicide gel in more than 5,000 women in South Africa, Uganda, and Zimbabwe.

Jeanne Marrazzo, MD, MPH, explained to a packed auditorium at the 20th Retrovirus Conference that these approaches did not prevent new HIV infections in this particular study because most participants didn’t actually use them.

When VOICE—short for Vaginal and Oral Interventions to Control the Epidemic—began enrolling women in September 2009, it had five study groups. Participants were randomized to use one of the following products daily:

- tenofovir gel
- placebo gel
- oral tenofovir tablet
- oral Truvada (the tenofovir/emtricitabine combination)
- oral placebo pill

March 4, 2013, by Reilly O'Neal
Preexposure Prophylaxis for HIV Infection among African Women

RCT of 2120 HIV negative women in Kenya and Tanzania
- TDF/FTC PrEP versus placebo
- Objectives: effectiveness and safety

Results
- HIV incidence 4.7% PrEP and 5.0% placebo → no difference
- Significantly higher side effects in intervention arm (GIT)

CONCLUSIONS
Prophylaxis with TDF–FTC did not significantly reduce the rate of HIV infection and was associated with increased rates of side effects, as compared with placebo. Despite substantial counseling efforts, drug adherence appeared to be low. (Supported by the U.S. Agency for International Development and others; FEM-PrEP ClinicalTrials.gov number, NCT00625404.)
iPrEX: Daily Oral TDF/FTC PrEP for MSM

- Double-blinded, randomised trial of oral TDF/FTC QD PrEP vs PBO for HIV-negative MSM/TGW at high risk for HIV infection (N = 2499)

- Relative reduction in cumulative risk of HIV infection: 44% with TDF/FTC vs PBO \((P = .005)\)\[^{[1]}\]

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Slide credit: clinicaloptions.com
## Summary

### Efficacy of Oral FTC/TDF PrEP

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to Treat</td>
<td>47%</td>
<td>22-64</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Modified Intention to Treat</td>
<td>44%</td>
<td>15-63</td>
<td>P=0.005</td>
</tr>
<tr>
<td>As Treated (50%)</td>
<td>50%</td>
<td>18-70</td>
<td>P=0.006</td>
</tr>
<tr>
<td>As Treated (90%)</td>
<td>73%</td>
<td>41-88</td>
<td>P&lt;0.0006</td>
</tr>
<tr>
<td>Unprotected RAI at Baseline</td>
<td>58%</td>
<td>32-74</td>
<td>P&lt;0.0006</td>
</tr>
</tbody>
</table>
iPrEX: Adherence and Efficacy

FTC = emtricitabine; TDF = tenofovir

Incidence / 100 person years

% of Visits | FTC/TDF | Placebo
--- | --- | ---
<50% | 18% | 33% | 49%
50-90% | 34% | 68%
>90% | 68% | 95% CI

Grant, R et al. CROI, 2010
Perfect adherence is not required: iPrEx OLE

100% HIV protection was seen with adherence consistent with ≥4 tablets per week

Grant et al. Lancet ID 2014
PROUD Study
UK

- 545 MSM recruited to take Truvada PrEP
- Immediate or delayed initiation with 24 months follow up
- Study stopped early by DSMB as efficacy dictates that continuing would be unethical
- Efficacy =86% (90% CI: 58 – 96%) P-value =0.0002
- Number Needed to Treat =13 (90% CI: 9 – 25)
- HIV incidence amongst gay men in England is much higher than what was thought
- There was no difference in the rate of STIs other than HIV
- The use of Truvada for PrEP was safe and concerns about resistance are minimal
- PrEP can be delivered as part as routine HIV reduction package
- RCT of Truvada versus placebo in 400 recruited high risk MSM
- Sex-based dosing (4 or more doses)
- Relative RR of HIV incidence was 86% (95% CI 40% to 99%, P = 0.002)
- Number needed to treat for 1 year to prevent 1 infection was 18
- Also stopped early by DSMB because of high efficacy
- Very sexually active
- Self-reported adherence: 43% took tablets correctly; 29% took tablets sub-optimally
- Did they not get almost daily dosing by default?
On-Demand PrEP: Points for Discussion

- Risk if patient not adherent (poor coverage)?
- Risk if patient infrequently having sex?
- Does median monthly number of pills in IPERGAY translate to “on demand”?
- Do pharmacokinetics affect whether results can be extrapolated to women?

Current evidence supports daily dosing
iPrEX: Bone Mineral Density Substudy

- iPrEX substudy: dual-energy x-ray absorptiometry assessment (N = 498)
- Small net decrease in spine and total hip BMD with TDF/FTC vs PBO at Wk 24 (-0.91% and -0.61%, respectively; P = .001 for both)
- No difference in fracture rate between groups (P = .62)

iPrEx BMD Sub study: BMD Recovery After Discontinuation of TDF/FTC PrEP

- Data compared for TFV-DP < or ≥ 16 fmol/M

![Graph showing changes in BMD from iPrEx enrollment](image)

- *P < .001; †P < .05

Cumulative Decline in Renal Function on TFV/FTC PrEP

- Higher TFV exposure associated with greater eGFR decreases in 2 studies
  - iPrEx OLE[1] (n = 220): hair sampling for exposure
- In both studies, eGFR decrease to < 70 mL/min more frequent among those with BL eGFR < 90 mL/min and older persons (older than 40-45 yrs)

Change in eGFR From BL vs Concentration of TFV or FTC in Hair[1]

<table>
<thead>
<tr>
<th>Quartile of Hair Drug Concentrations</th>
<th>% Change in Mean eGFR From Baseline (95% CI)</th>
<th>Trend</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>-8</td>
<td>P</td>
<td>.008</td>
</tr>
<tr>
<td>Second</td>
<td>-6</td>
<td></td>
<td>.006</td>
</tr>
<tr>
<td>Third</td>
<td>-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
## Adherence and HIV protection

<table>
<thead>
<tr>
<th>Study</th>
<th>% of blood samples with tenofovir detected</th>
<th>HIV protection efficacy in randomized comparison</th>
<th>HIV protection estimate with high adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP TDF/FTC arm</td>
<td>81%</td>
<td>75%</td>
<td>90% (tenofovir in blood)</td>
</tr>
<tr>
<td>TDF2</td>
<td>79%</td>
<td>62%</td>
<td>78% (prescription refill)</td>
</tr>
<tr>
<td>BTS</td>
<td>67%</td>
<td>49%</td>
<td>70% - 84% (tenofovir in blood / pill count)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>44%</td>
<td>92% (tenofovir in blood)</td>
</tr>
<tr>
<td>FEM-PrEP &amp; VOICE</td>
<td>&lt;30%</td>
<td>No HIV protection</td>
<td>N/A</td>
</tr>
</tbody>
</table>

When adherence was high HIV protection is consistent and high.

Oral PrEP Adherence

Longitudinal analysis of tenofovir detection in blood samples from persons on PrEP has shown that, for those who were taking PrEP, adherence was frequently consistent over time:
US PrEP Demonstration Project

- Launched in Sep 2012
- Fully enrolled Mar 2014
- Eligible: At risk, HIV and HBV negative

Fuchs, J et al. Lessons learned from the US PrEP Demonstration Project: Moving from the "real world" to the "real, real world".

PrEP and ARV Resistance

Resistance from PrEP was very rare; with only a small number who had acute infection at the time they were started on PrEP.

<table>
<thead>
<tr>
<th></th>
<th># of HIV seroconverters assigned PrEP with HIV resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV infected after enrollment</td>
</tr>
<tr>
<td><strong>Partners PrEP</strong></td>
<td>0 / 48</td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>0 / 36</td>
</tr>
<tr>
<td><strong>TDF2</strong></td>
<td>0 / 10</td>
</tr>
</tbody>
</table>

Resistance = K65R (TDF) or M184V/I (FTC) mutations
PrEP in Pregnancy

- PrEP use at conception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition[1]

- Data directly related to the safety of PrEP use for a developing fetus are limited

- Potential risks and limited information should be discussed

- TDF and FTC are classified as FDA Pregnancy Category B medications[2]

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# Future PrEP Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dosing Route</th>
<th>Dosing Frequency</th>
<th>Research Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine LA</td>
<td>NNRTI</td>
<td>SC Injection</td>
<td>1 Monthly</td>
<td>Phase 1</td>
</tr>
<tr>
<td>GSH 1265744</td>
<td>Integrase inhibitor</td>
<td>SC Injection</td>
<td>1 Monthly</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>CD4 attachment inhibitor</td>
<td>SC Injection</td>
<td>1-4 Weekly</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

Alternate drug mechanisms
Alternate delivery methods
Alternate dosing frequencies
Thank You
SA Clinicians Society
PEPFAR / USAID
Elton John Foundation
Anova Health Institute

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