PrEP in cis-gender women

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Outline

• What did we know about PrEP effectiveness for cis-gender women on TDF/FTC before it was approved?
• How sex differences in PK led to idea that 7 doses/week TDF/FTC in women necessary
• But what did the demonstration projects in women tell us?
• What do we know about TAF/FTC for PrEP in cis-gender women
  • Nothing from clinical trials yet
  • PK modeling
# Placebo-controlled PrEP trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population/Setting</th>
<th>Intervention</th>
<th>Reduction in HIV Infection Rate, %</th>
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</thead>
<tbody>
<tr>
<td>iPrEx[^1] (N = 2499)</td>
<td>MSM, 11 sites in US, S. America, Africa, Thailand</td>
<td>▪ Daily oral TDF/FTC</td>
<td>44% (95% CI 15-63, p 0.005)</td>
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<tr>
<td></td>
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<td>▪ Women: 66%; men: 84%</td>
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<tr>
<td>Bangkok TFV Study[^6]</td>
<td>IDU (use in last year) in Bangkok (men, women)</td>
<td>▪ Daily oral TDF</td>
<td>49% (95% CI 9.6-72.2, p 0.01)</td>
</tr>
<tr>
<td>VOICE[^5] (N = 5029)</td>
<td>High-risk women, Africa</td>
<td>▪ Daily oral TDF ▪ Daily oral TDF/FTC ▪ 1% TFV gel</td>
<td>1% TDF gel &amp; daily oral TDF arm both stopped early, futile ▪ Daily TDF/FTC arm – no efficacy (adherence)</td>
</tr>
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FEM-PrEP and VOICE: Pharmacologic monitoring indicated adherence was issue

<table>
<thead>
<tr>
<th>Adherence Measure</th>
<th>VOICE</th>
<th>FEM-PrEP</th>
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<tbody>
<tr>
<td>Self-report</td>
<td>91%</td>
<td>95%</td>
</tr>
<tr>
<td>Returned pill counts</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Plasma TFV detection</td>
<td>29%</td>
<td>24%</td>
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Marrazzo et al. NEJM 2015; Van Damme et al. NEJM 2012
Idea that adherence to TDF/FTC may need to be higher in women on PrEP came from PK modeling and surprising results of FEM-PrEP/VOICE

- TFV concentrations are higher in rectal than vaginal tissue\(^1\)
- Cumulative exposure of rectal tissue to TFV and TFV-DP 30x and 120x higher, respectively, vs vaginal tissue in same women\(^2\)
- Modeling of 4 doses/wk okay for men may not apply for women\(^3\)

What did PrEP demonstration projects in women tell us?
HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women

**Target Enrollment**
- 400 women who accept PrEP at enrollment
- ≤ 200 women who decline PrEP at enrollment

**Eligibility criteria**: Sexually active in past month; VOICE risk score >5; interest in PrEP; normal creatinine clearance; hepatitis B seronegative; access to mobile phone

**Study Population**
- Uninfected women
  - Ages 16-25 yrs
  - Johannesburg & Cape Town, South Africa
  - Harare, Zimbabwe

**Standard adherence support**
- **plus** drug level feedback

Slide courtesy C. Celum
HPTN 082: PrEP uptake

Figure 1: PrEP uptake overall and by site

- **Overall**: 95%
- **Harare**: 97%
- **Cape Town**: 99%
- **Johannesburg**: 88%

PrEP accepted

PrEP not accepted

Slide courtesy C. Celum
<table>
<thead>
<tr>
<th></th>
<th>3 months (N=371)</th>
<th>6 months (N=363)</th>
<th>12 months (N=347)</th>
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<tbody>
<tr>
<td><strong>Tenofovir diphosphate (TFV-DP), DBS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Detectable</td>
<td>83.6%</td>
<td>56.5%</td>
<td>31.4%</td>
</tr>
<tr>
<td>( \geq 700 \text{ fmol/punch} ) (4 doses/week; among those with detectable TFV-DP)</td>
<td>24.8%</td>
<td>20.9%</td>
<td>8.6%</td>
</tr>
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</table>

* TFV-DP \( \geq 700 \text{ fmol/punch} \) was associated with 100% efficacy among MSM in the iPrEX OLE study & the 25th percentile of 4 doses/week on average (Grant Lancet HIV 2014)

Slide courtesy C. Celum
HIV seroconversions

- Four HIV seroconverters observed in 404 person-years of follow-up (at months 3, 6, and two at 9)

- HIV incidence of 1.0/100 person-years (95% CI 0.3-2.5)

- 2 had undetectable DBS TFV-DP concentrations and 2 detectable but low concentrations (74 and 243 fmol/punch) in the visit at or prior to when they were first detected HIV seropositive

- Three had no resistance mutations & one had D67N (NRTI mutation) and four NNRTI mutations (K101E, K103N, E138A, and G109A)
  - No resistance mutations associated with TDF or FTC

Slide courtesy C. Celum
HPTN 082: Summary

- Very high PrEP uptake (95%) among young women at risk for HIV, a majority of whom took PrEP in the first 6 months

- Women who perceived themselves to be at risk of HIV and were motivated to use PrEP had higher adherence at 6 months

- Low HIV incidence (1%) given risk profile of this cohort
  - 4 doses a week seemed to be enough

Slide courtesy C. Celum
The 3P study: Social marketing & conditional incentives to increase PrEP adherence

3P cohort characteristics
N=200

- Young (median age 19)
- Most had a primary partner; 71% of whom reported suspecting he had other partners
- 30% had CT, GC or trichomonas at baseline
- 19% reported IPV in the past year
- All but one had detectable TFV-DP in first 3 months
Incentives conditioned on tenofovir levels to increase adherence among young women on PrEP in Cape Town

Table 1: PrEP adherence, as assessed by TFV-DP levels at 3 months by study arm

<table>
<thead>
<tr>
<th>Tenofovir diphosphate in DBS at months</th>
<th>Total</th>
<th>Incentive Arm</th>
<th>Control Arm</th>
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<tbody>
<tr>
<td>Concentration in ng/ml</td>
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<tr>
<td>Median (IQR)</td>
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<tr>
<td>N Undetectable (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Detectable</td>
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NO HIV seroconversions in 3P so 4 doses a week may be enough...argues for pharmacodynamic rather than pharmacokinetic evaluations for efficacy (e.g. trials in women)

- All but 1 of the women had at least 1 detectable TFV-DP level.
- At 3 months, 80% had medium or greater adherence at 2 and 3 months.

Slide courtesy C. Celum
What do we know about PK for TAF?
Early Events in HIV Infection

- Where should infection be aborted?
- What is the ARV target conc’n needed to abort HIV infection?

We don’t know; we know that TAF has TFV-DP levels that are higher and TFV levels lower than TDF; but what does that mean?
Pharmacokinetic Results

Plasma

TFV AUC<sub>0-48hrs</sub> (ng*hr/ml)

- TAF 25mg: 92 (59-126)
- TDF 300mg: 1,778 (1,402-3,381)

TFVdp AUC<sub>0-48hrs</sub> (hr*fmol/10<sup>6</sup> cells)

- TAF 25mg: 3,978 (2,551-6,979)
- TDF 300mg*: 438 (265-675)

PBMC

TFV 19-fold ↓

TDF 300mg 9-fold ↑

TAF 25mg

TDF 300mg

Half of all HIV infections globally are in women yet...

- Women still underrepresented in clinical trials of new HIV medications
  - Elvitegravir\(^1\) and Bictegravir\(^2\) (latter published 2017) both with \(<15\%\) women in pivotal start studies
- Only 8.3\% of participants enrolled in cure studies are women\(^3\)
- When women are at the table to plan trials (e.g. important GRACE study\(^4\)), women are enrolled

\(^1\)Sax PE. Lancet 2012; \(^2\)Sax PE. Lancet 2017; \(^3\)Johnston RE. ARHR 2015; \(^4\)Currier J. Ann Intern Med 2010
Overall conclusion

• Much being said about TAF going to be more effective (so should work for women) due to TFV-DP in PMBCs, but we not know the PK correlate of efficacy
• The PK versus pharmacodynamic data for TDF/FTC showed us maybe 7 doses a week is not needed for women – maybe 4 is enough (PK modeling versus demonstration project data from HPTN082/3P)
• Not having original data in women is frustrating and one option could have been for FDA to NOT approve this drug at all, awaiting this data
• Now need to figure out best approach for women (likely demonstration projects; more work on best correlates of efficacy)