The Role of TAF in PrEP

KATY GARRETT, PHARMD
UNIVERSITY OF NORTH CAROLINA

Dr. Garrett has nothing to disclose
Outline

PrEP Efficacy
- Adherence among populations
- Pharmacokinetic and pharmacodynamics relationship to adherence

TAF pharmacology

TAF’s role in PrEP by risk group
- Receptive vaginal intercourse
- Receptive anal intercourse
- Injection drug use
## PrEP Clinical Efficacy

<table>
<thead>
<tr>
<th>Population</th>
<th>Drug</th>
<th>Overall Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PrEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,785 heterosexual women in serodiscordant relationships</td>
<td>TDF</td>
<td>71% (37-87)</td>
</tr>
<tr>
<td></td>
<td>FTC/TDF</td>
<td>66% (28-84)</td>
</tr>
<tr>
<td><strong>FEM-PrEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,120 heterosexual women</td>
<td>FTC/TDF</td>
<td>6% (-52 - 41)</td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,029 heterosexual women</td>
<td>TDF</td>
<td>-49% (-129-3)</td>
</tr>
<tr>
<td></td>
<td>FTC/TDF</td>
<td>-4% (-49-27)</td>
</tr>
</tbody>
</table>

References:
## PrEP Clinical Efficacy

<table>
<thead>
<tr>
<th>Population</th>
<th>Drug</th>
<th>Overall Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PrEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,785 heterosexual women in serodiscordant relationships</td>
<td>TDF</td>
<td>71% (37-87)</td>
</tr>
<tr>
<td></td>
<td>FTC/TDF</td>
<td>66% (28-84)</td>
</tr>
<tr>
<td><strong>FEM-PrEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,120 heterosexual women</td>
<td>FTC/TDF</td>
<td>6% (-52 - 41)</td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,029 heterosexual women</td>
<td>TDF</td>
<td>-49% (-129-3)</td>
</tr>
<tr>
<td></td>
<td>FTC/TDF</td>
<td>-4% (-49-27)</td>
</tr>
<tr>
<td><strong>Partners PrEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,962 heterosexual men in serodiscordant relationships</td>
<td>TDF</td>
<td>63% (20-83)</td>
</tr>
<tr>
<td></td>
<td>FTC/TDF</td>
<td>84% (54-94)</td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,499 MSM/TGW (59% unprotected receptive anal intercourse)</td>
<td>FTC/TDF</td>
<td>44% (15-63)</td>
</tr>
<tr>
<td><strong>IPERGAY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 MSM/TGW</td>
<td>FTC/TDF</td>
<td>86% (40-98)</td>
</tr>
</tbody>
</table>

---

## PrEP Clinical Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Drug</th>
<th>Overall Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP</td>
<td>1,785 heterosexual women in serodiscordant relationships</td>
<td>TDF</td>
<td>71% (37-87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FTC/TDF</td>
<td>66% (28-84)</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>2,120 heterosexual women</td>
<td>FTC/TDF</td>
<td>6% (-52 - 41)</td>
</tr>
<tr>
<td>VOICE</td>
<td>5,029 heterosexual women</td>
<td>TDF</td>
<td>-49% (-129-3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FTC/TDF</td>
<td>-4% (-49-27)</td>
</tr>
<tr>
<td>Partners PrEP (men)</td>
<td>2,962 heterosexual men in serodiscordant relationships</td>
<td>TDF</td>
<td>63% (20-83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FTC/TDF</td>
<td>84% (54-94)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>2,499 MSM/TGW (59% unprotected receptive anal intercourse)</td>
<td>FTC/TDF</td>
<td>44% (15-63)</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>400 MSM/TGW</td>
<td>FTC/TDF On-Demand</td>
<td>86% (40-98)</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>2,413 PWID</td>
<td>TDF</td>
<td>49% (9.6-72)</td>
</tr>
</tbody>
</table>

References:
Modified AVAC Infographic “PrEP Works If you Take It –Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention”
Pharmacokinetics (PK) & Pharmacodynamics (PD)

**Concentration vs Time**
- $C_{\text{max}}$
- $T_{1/2}$
- $C_{\text{min}}$
- AUC

**Effect vs Concentration**
- Effective Concentration
- $EC_{90} = 0.3$
Plasma TFV PD of PrEP Clinical Trials

No relationship between plasma concentration and efficacy
Surrogates for Systemic PrEP Efficacy

EC$_{90}$ rectal tissue equivalent $\approx 700$ fmol/10$^6$ rectal mononuclear cells
EC$_{90}$ rectal tissue equivalent $\approx$ 700 fmol/10$^6$ rectal mononuclear cells
Surrogates for Systemic PrEP Efficacy

Possible Surrogates

- TFVdp PBMC EC<sub>90</sub> (iPrEx)
- Freshly lysed PBMCs ≈ 37 (23-50) fmol/10<sup>6</sup> cells

- TFVdp rectal mononuclear cells EC<sub>90</sub> (iPrEx)
- 700 fmol/10<sup>6</sup> cells

- TFVdp:dATP EC<sub>50</sub> & EC<sub>90</sub> (in vitro)
- Molar Ratio = 0.09-0.29
TAF Pharmacology
Optimizing the PK Profile

4-7-fold higher TFVdp concentrations in PBMCs
4-7-fold lower TFV concentrations in plasma

Adapted from Liu Y. Poster Number H-664, ICAAC 2013.
TAF’s Pharmacokinetic Utility

MINIMIZE ADVERSE REACTIONS

PLASMA

MAXIMIZE EFFICACY

PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCS)

Protecting the Target Population

RECEPTIVE VAGINAL INTERCOURSE
TFV exposure 2-fold lower in FGT after 25mg TAF
TFVdp exposure 1.3-fold lower in FGT after 25mg TAF
TFVdp 75% BLQ in FGT after TAF 25mg (25% for TDF)
Female Genital Tract Tissue - Simulations

Only ~15-39% of population are protected with daily TDF dosing

Unable to simulate with TAF due to minimally quantifiable TFVdp

Expect less protection conferred by TAF secondary to tissue penetration

Data represent 5, 50, and 95 percentiles of simulated ratios

Cottrell ML et al. J Infect Dis. 2016 Feb 24
Protecting the Target Population

RECEPTIVE ANAL INTERCOURSE
TFV exposure 10-fold lower following TAF 25mg

TFVdp exposure 13-fold lower following TAF 25mg

TFVdp 63% BLQ in rectal tissue with TAF 25mg (0% for TDF)
~100% of population are protected with daily dosing of TDF

Unable to simulate with TAF due to minimally quantifiable TFVdp

Cannot extrapolate PBMC TFVdp to rectal tissue

Data represent 5, 50, and 95 percentiles of simulated ratios

TAF Macaque Models- Rectal Transmission

13.7 mg/kg TAF 3 days prior to weekly SHIV exposure up to 14 weeks

No difference in Protection Rate

TAF Macaque Models - Rectal Transmission

13.7 mg/kg TAF 3 days prior to weekly SHIV exposure up to 14 weeks

No difference in Protection Rate

EC_{90} = 50
TAF Macaque Models-Rectal Transmission

13.7 mg/kg TAF 3 days prior to weekly SHIV exposure up to 14 weeks

No difference in Protection Rate

![Graph showing no difference in protection rate between controls and GS7340 groups.](image)

EC\textsubscript{90} = 50

EC\textsubscript{90} = 700

TAF Macaque Models-Rectal Transmission

Ratio in PBMCs above threshold

Ratio in rectal mononuclear cells below threshold—cause for futility?

TAF Macaque Models—Rectal Transmission

TAF 1.5 mg/kg (with FTC) 24h prior and 2h after weekly SHIV challenge

Same dosing strategy demonstrated 94% efficacy with FTC/TDF

100% Protection

TAF Macaque Models-Rectal Transmission

TAF 1.5 mg/kg (with FTC) 24h prior and 2h after weekly SHIV challenge

Same dosing strategy demonstrated 94% efficacy with FTC/TDF

100% Protection

TAF Macaque Models - Rectal Transmission

TAF 1.5 mg/kg (with FTC) 24h prior and 2h after weekly SHIV challenge

Same dosing strategy demonstrated 94% efficacy with FTC/TDF

100% Protection

>10-fold lower than TDF study

Protecting the Target Population

INJECTION DRUG USE
9-fold **higher** AUC over 48 hours with 25mg TAF than 300mg TDF

TAF 25mg doses result in TFVdp >50 fmol/10^6 cells from 3-24h

50% of concentrations at 72h after 25mg TAF drop below 50 fmol/10^6 cells

300mg TDF remains below target concentration over 48h
TAF-PWID Simulations

TDF alone maximally protects ~90% of population with daily dosing-after one week.


TAF Model in development

Expect much higher percentage of population protected with TAF alone compared to TDF.

Data represent 5, 50, and 95 percentiles of simulated ratios.
Conclusions

Pharmacodynamic targets for PrEP still require validation
- Tissue ratio of TFVdp:dATP correlates with clinical trials and macaque model data

TAF has potential for use in PrEP
- Vaginal - due to low TFVdp concentrations in tissue may require combination therapy
- Rectal - TAF’s role alone uncertain, likely in combination with FTC based on macaque data
- Injection drug use - promising results for single-agent use

TAF is not recommended for PrEP until more data are known
Current/Future Studies

CDC Macaque Studies
- Vaginal SHIV challenge
- Rectal SHIV challenge with only TAF

CONRAD human phase 1 multiple-dose PK study (NCT02904369)
- PK and PD Study of Oral F/TAF for HIV Prevention

Gilead Sciences Phase 3 Clinical Trial (NCT02842086)
- A Phase 3, Randomized, double-blind study to evaluate the safety and efficacy of emtricitabine and tenofovir alafenamide (F/TAF) fixed-dose combination once daily for pre-exposure prophylaxis in men and transgender women who have sex with men and are at risk of HIV-1 infection

Other formulations
Acknowledgements

Virology Education organizers

Kashuba Lab
  ◦ Angela Kashuba
  ◦ Mackenzie Cottrell
  ◦ Heather Prince
  ◦ Craig Sykes
  ◦ Amanda Schauer

Funding Sources
  ◦ UNC Center for AIDS Research
  ◦ P30AI050410
  ◦ Clinical Trials Research Center
  ◦ UL1TR001111
  ◦ Gilead Sciences, Inc.