
Raphael J. Landovitz, MD MSc
Associate Professor of Medicine
UCLA Center for Clinical AIDS Research & Education
January 19, 2018
Raphael J. Landovitz has received research grants awarded to his institution from Gilead Sciences, has served as a consultant to Gilead Sciences.
1.8 Million New Infections in 2016
5,000 New Infections per Day
Prevention Modalities

- Condoms
- PEP
- Voluntary Male Circumcision
- Needle Exchange
- Vaccine
- Abstinence
- HIV Treatment
- PrEP
- Microbicides
- HIV & STI Testing
- STI Treatment
- Harm Reduction
# Effectiveness of Daily TDF/FTC in Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>CI (%)</th>
<th>HIV-1 incidence reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROUD</td>
<td>TDF/FTC</td>
<td>58-96</td>
<td>86%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>TDF/FTC</td>
<td>-22-81</td>
<td>49%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>TDF/FTC</td>
<td>25-97</td>
<td>80%</td>
</tr>
<tr>
<td>TDF2</td>
<td>TDF/FTC</td>
<td>-52-41</td>
<td>6%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>TDF/FTC</td>
<td>15-63</td>
<td>42%</td>
</tr>
<tr>
<td>VOICE</td>
<td>TDF/FTC</td>
<td>-49%</td>
<td>99%</td>
</tr>
<tr>
<td>Partners</td>
<td>TDF/FTC</td>
<td>-4.4%</td>
<td>99%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>TDF</td>
<td>+3 to -129</td>
<td>63%</td>
</tr>
</tbody>
</table>

---

**Preexposure Prophylaxis for HIV Infection among African Women**


---

*The NEW ENGLAND JOURNAL of MEDICINE

---

Pre-infected by a...
Relationship Between Effectiveness and Adherence in Microbicide & PrEP Trials

Pearson correlation = 0.86, p=0.003

-60 -40 -20 0 20 40 60 80 100
0 10 20 30 40 50 60 70 80 90

Effectiveness (%)

Percentage of Participants’ Samples with detectable drug levels

SS Abdool Karim, personal communication
Maximizing the Potential Effectiveness

TDF/FTC (7x/week)  
CI: 96 - 99  
99%  
Some adherence forgiveness with retained protection  

TDF/FTC (~1x/24°)  
CI: -17 - 100  
94%  
6-7 doses per week likely required  
Cottrell ML et al, JID, 2016.
PrEP Demonstration: High Adherence in STD/Community-Based Clinics

A

PrEP Engagement, % of Participants (N=296)

Visit Week

0% 20% 40% 60% 80% 100%

1250+ fmol/punch (7 tablets/week)

700–<1250 fmol/punch (4-6 tablets/week)

350–<700 fmol/punch (2-3 tablets/week)

LLQ – <350 fmol/punch (<2 tablets/week)

BLQ (No detectable drug)

Missed Visit

700+ fmol/punch (4-7 tablets/week)

B

Visit Week

0% 20% 40% 60% 80% 100%

Non-Hispanic White n=150

Non-Hispanic Black n=32

Hispanic/Latino n=82

Mixed Race/Other n=32

Landovitz RJ, et al, JAIDS. 2017
HPTN 069 / ACTG A5305

A phase 2 safety study designed to answer: Could daily oral maraviroc, a CCR5 receptor antagonist, be a next-gen PrEP agent for men and/or women?
Maraviroc – HPTN 069/ACTG A5305
**HPTN 069 / ACTG A5305**

**Screening**

**Enrollment and Randomization**

*N = 600*

(400 MSM/TGW; 200 ciswomen)

**Arm 1, N=150**

100/50

- MVC (active)
- FTC (placebo)
- TDF (placebo)

**Arm 2, N=150**

100/50

- MVC (active)
- FTC (active)
- TDF (placebo)

**Arm 3, N=150**

100/50

- MVC (active)
- FTC (placebo)
- TDF (active)

**Arm 4, N=150**

100/50

- MVC (placebo)
- FTC (active)
- TDF (active)

Gulick RM, JID 2016, Gulick RM, Annals 2017
**HPTN 069 / A5305: HIV Infections**

- In MSM/TGW Cohort: 5 new HIV infections during the study
- Annual incidence rate 1.4% [95% CI: 0.8%, 2.3%]

<table>
<thead>
<tr>
<th>#</th>
<th>Demos. (age, race/ethnicity, HIV risk)</th>
<th>Study arm</th>
<th>First reactive HIV+ test (week)</th>
<th>HIV RNA (cps/mL)</th>
<th>CD4 cells (/mm³)</th>
<th>HIV tropism</th>
<th>Genotypic drug resistance</th>
<th>Plasma drug conc. at seroconversion visit (ng/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20, black MSM</td>
<td>MVC+ TDF</td>
<td>4</td>
<td>122,150</td>
<td>357</td>
<td>R5</td>
<td>none</td>
<td>MVC=0† TFV=0</td>
</tr>
<tr>
<td>2</td>
<td>61, Asian MSM</td>
<td>MVC alone</td>
<td>16</td>
<td>981</td>
<td>294</td>
<td>R5</td>
<td>none</td>
<td>MVC=145</td>
</tr>
<tr>
<td>3</td>
<td>21, mixed MSM</td>
<td>MVC alone</td>
<td>24</td>
<td>106,240</td>
<td>325</td>
<td>R5</td>
<td>none</td>
<td>MVC=0†</td>
</tr>
<tr>
<td>4</td>
<td>35, white MSM</td>
<td>MVC alone</td>
<td>32</td>
<td>13,626</td>
<td>828</td>
<td>R5</td>
<td>none</td>
<td>MVC=6.7</td>
</tr>
<tr>
<td>5</td>
<td>36, black MSM</td>
<td>MVC alone</td>
<td>48</td>
<td>52,191</td>
<td>804</td>
<td>R5</td>
<td>none</td>
<td>MVC=0.7</td>
</tr>
</tbody>
</table>

* expected pre-dose steady state MVC = 32 ng/ml
† undetectable plasma drug concentrations at every study visit
Pre-Clinical and Animal Models of TAF for PrEP

Will it be equi-efficacious as TDF-based PrEP?

Perhaps
Perhaps not
Prodrug Pharmacology of TDF and TAF

TAF 25 mg results in >90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Concentrations of TFV and TFV-DP in Female Mucosal Tissues After Single Dose of TAF

<table>
<thead>
<tr>
<th>Tissue Samples</th>
<th>TAF 25mg, BLQ, %</th>
<th>TDF 300mg, BLQ, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVF</td>
<td>TFV 58, TFV-DP n/a</td>
<td>TFV 23, TFV-DP n/a</td>
</tr>
<tr>
<td>Genital Tissue</td>
<td>TFV 6, TFV-DP 75</td>
<td>TFV 0, TFV-DP 25</td>
</tr>
<tr>
<td>Rectal Tissue</td>
<td>TFV 0, TFV-DP 63</td>
<td>TFV 0, TFV-DP 0</td>
</tr>
</tbody>
</table>

BLQ=below the level of quantification. 0=all the samples had detectable TFV (none were BLQ)

TAF/FTC for PrEP in SHIV-Challenged Macaques

- TAF/FTC prevents rectal SHIV infection in macaques to a degree similar to that previously found with TDF/FTC but with a substantially reduced TFV dose\(^1\)
  - TAF/FTC protected 100% of macaques (N=6) challenged with SHIV in a similar, preclinical trial\(^2\)

\(^1\) Massud I, et al. CROI 2016. Boston, MA. #107
HPTN 076

A phase 2 safety study designed to answer: Could injectable rilpivirine, a FDA-approved NNRTI in its oral formulation, be a useful sustained-release PrEP agent?
**HPTN 076: Safety and acceptability of injectable rilpivirine (TMC278 LA) for PrEP**

136 HIV-uninfected, women ages 18-45 years

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>52</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1</td>
<td>Daily oral TMC278</td>
<td>Six injections of TMC278 LA 1200 mg every 8 weeks</td>
<td>Follow-up phase (tail phase)</td>
</tr>
<tr>
<td>N = 91</td>
<td>Daily oral placebo</td>
<td>Six injections of TMC278 LA placebo every 8 weeks</td>
<td></td>
</tr>
</tbody>
</table>
HPTN 076: Phase 2 Safety Results

- Safe and well-tolerated
- Acceptable to women
- Cold chain required
- Unclear interest of sponsor in pursuing PrEP indications
- Concern about cross-resistance to agents used as first line in LMIC

Bekker LG, CROI 2017. Abstract 421 LB.
CABOTEGRAVIR

Formerly known as GSK1265744
Or “744”
HPTN 083
A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral TDF/FTC, for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Target enrollment: 4,500 HIV-uninfected cisgender men and transgender women who have sex with men and who are at risk of HIV acquisition

Primary outcome: HIV Prevention effectiveness of cabotegravir compared to daily oral TDF/FTC

ClinicalTrials.gov Identifier: NCT02720094
Cabotegravir
Cabotegravir and Intralipid
### Study Schema for The Study

#### REGIMEN

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2700</strong></td>
<td><strong>1500</strong></td>
<td><strong>4200</strong></td>
</tr>
</tbody>
</table>

- 10 infusions total & Infusions every 8 weeks
- Study duration: ~22 months
Subcutaneous PrEP Implants Modeled After Implanon/Nexplanon Contraception

- Simple insertion AND removal
- Long-acting (months to years)
- PrEP + contraception?
- Current development:
  - TAF, CAB, EFdA (MK-8591)

Gunawardana, et al., AAC 2015
Topical agents for PrEP: As Good as Systemic PrEP?

Commentary

HIV Prevention: The Need for Methods Women Can Use

Zena A. Stein, MA, MB, BCH

“…a less efficacious barrier (one that fails more often than another on each sexual encounter), if frequently used, might serve the public health as well or better than a more efficacious but less frequently used barrier, and could in the end play an important role in preventing transmission at the population level.”

(Am J Pub Health, 1990)
Thank you!