The Data-Free Zone: Tough Cases in HIV Prevention

Raphael J. Landovitz, MD, MSc
Professor of Medicine
University of California Los Angeles
Los Angeles, California

Financial Relationships With Commercial Entities

Dr Landovitz has served as a consultant to Gilead Sciences, Inc, Merck & Co, Inc, and Roche. (Updated 08/05/20)

Learning Objectives

After attending this presentation, learners will be able to describe:

▪ Options for preexposure prophylaxis (PrEP) in patients with decreased kidney function and low bone mineral density
▪ The state of the science on sexually transmitted infection (STI) prevention strategies
▪ Recent data on the safety and efficacy on injectable PrEP options
Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials

Effectiveness of Daily TDF/FTC in Clinical Trials

“PrEP 2.0”: Trials of Novel PrEP Agents

Landovitz RJ et al. AIDS 2020, #OAXLB0101

SS Abdool Karim, personal communication
PrEP is straightforward when...

- Cr Cl ≥ 60
- No history of osteopenia/osteoporosis/non-traumatic fractures
- HBsAg negative
- Patients come in every 3 months for safety labs, STI testing, and adherence checks prior to refills
- Limited medical co-morbidities

Case 1: Beans, beans and nothing but beans

- A 50-year-old man with type 2 DM, CKD 3, and hypertension recently started a new relationship with an HIV-infected man and is seeking advice on how best to avoid HIV infection
- His partner admits to struggling with taking ART regularly, but says he is “mostly adherent” and does not like to use condoms
- One month after initiating PrEP, Cr Cl dropped to 55 mL/min
- UA is normal and safety labs are rechecked and show Cr Cl is further decreased to 50 mL/min

ARS Question #1

Your best advice regarding his PrEP is:

1. Continue daily oral TDF/FTC, recheck in 1 month
2. Switch to event-based (“2-1-1”) dosing of TDF/FTC
3. Dose reduce TDF/FTC to 3 x week
4. Switch to TAF/FTC daily
5. Something else
Impact of Long-Term PrEP Use and Renal Function

  - PrEP users (n=172 over 689 visits)
  - Baseline creatinine <1 year before PrEP initiation and ≥1 follow-up creatinine
- Mean Cr Cl change: -6 mL/min at month 24
  - No cases of elevated creatinine with Cr Cl <60 mL/min
  - No discontinuations of PrEP due to decline in eGFR
  - Cr Cl <70 mL/min after baseline Cr Cl ≥70 mL/min (n=8)
    - Recovered (n=3); remained ≥60 mL/min (n=5)
  - Significantly associated with age ≥50 years and baseline Cr Cl <90 mL/min (both P<0.0001)

↑ Age, ↓ Baseline Cr Cl, and Adherence Associated with Declining Renal Function

- iPrEx-Ole (n=1224) found a greater decline in renal function with older age
  - 40–50 years: -4.2% [-2.8, -5.5]
  - 50+ years: -4.2% [-2.8, -5.5]
- The likelihood of Cr Cl falling below 60 mL/min were higher in participants with a baseline Cr Cl of 90 mL/min or less.

↑ Age, ↓ Baseline Cr Cl, and Adherence Associated with Declining Renal Function

- The EPIC Hair study enrolled and collected hair samples for 280 PrEP Demo participants
  - Drug level concentrations in hair were highly correlated with DBS concentrations
  - Decline in renal function associated with higher drug level concentrations.
**CCTG 595: PrEP Associated with Fanconi Syndrome**

- 49-year-old white man, Hx kidney stones, HBV/HCV negative, no ongoing medical problems or medication use
- Mild renal impairment detected at baseline (Cr Cl: 79.9 mL/min).
- Initiated daily oral TDF/FTC-based PrEP
- 12 weeks after PrEP initiation
  - 25% decrease in Cr Cl.
  - Hypophosphatemia with renal phosphate wasting

**DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP**

- **Intervention**
  - F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg.
  - Study conducted in NA, EU in cities/sites with high HIV incidence.
  - 94 sites in 11 countries.
  - Participants: US, 60%; EU, 34%; Canada, 7%.
- **Eligibility**
  - High sexual risk of HIV.
  - 2+ episodes condomless anal sex in past 12W or rectal gonorrhea/chlamydia in past 24W.
  - HIV & HBV negative, eGFR ≥60 mL/min.
  - Prior use of PrEP allowed.
- **Primary efficacy endpoint:** HIV incidence
  - Evaluated by rate ratio with noninferiority (NI) margin ≤1.62.
  - Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY.
- **Randomization**
  - 1:1.
  - Double-blind, active controlled.
- **Primary analysis:** HIV incidence/100 PY when 100% complete W48 & 50% complete W96.
- **Study conduct:** MSM or TGW participants.
- **Open-label switch for 48 weeks** at entry and Q12W:
  - Adherence counseling.
  - Prevention services.
  - Risk reduction counseling.
  - Condoms/lubricant.

**DISCOVER: HIV Incidence**

- **Primary Endpoint Analysis: HIV Incidence**
  - CI, confidence interval; RR, rate ratio.
IPERGAY: eGFR changes not different TDF/FTC v. PBO

<table>
<thead>
<tr>
<th>Blinded phase</th>
<th>TDF/FTC (n=201)</th>
<th>PBO (n=199)</th>
<th>P value</th>
<th>All participants on TDF/FTC (N=399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median of follow-up months (QIR)</td>
<td>9.4 (5.1-26.9)</td>
<td>9.4 (5.1-26.9)</td>
<td>-1.55</td>
<td>-0.88</td>
</tr>
<tr>
<td>Mean slope of eGFR decline per year* (ml/min/1.73m²)</td>
<td>-0.84</td>
<td>0.04</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>At least one eGFR &lt;60ml/min/1.73m² - n</td>
<td>20</td>
<td>9</td>
<td>0.04</td>
<td>45</td>
</tr>
<tr>
<td>At least one eGFR &lt;50ml/min/1.73m² - n</td>
<td>4</td>
<td>3</td>
<td>0.24</td>
<td>14</td>
</tr>
<tr>
<td>Treatment discontinuation for kidney adverse event - n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The slope of eGFR decline was not statistically different between TDF/FTC and placebo group.

Case 2: Broken Dreams

- A 35-year-old man reports having receptive anal sex with 2-3 different partners each month, and he is eager to start PrEP
- He was diagnosed with early osteoporosis in 2015 and has a history of non-traumatic fractures.
ARS Question #2

Your best advice is:

1. Proceed with daily oral TDF/FTC alone
2. Initiate PrEP with TAF/FTC
3. Proceed with daily oral TDF/FTC but recommend Vitamin D and Calcium supplementation
4. Something else

iPrEx: Bone Mineral Density Loss and Recovery

- iPrEx DXA substudy (n=498) found spine BMD decreases in the TDF/FTC group compared to the PBO group.
- Hip BMD initially decreased TDF/FTC group, but rebounded before decreasing again at Week 96
- Decreases in BMD were statistically significant in those with detectable drug levels when compared to the PBO group
iPrEx: Bone Mineral Density Loss and Recovery

1. Mulligan K et al., CID, 2015
2. Glidden D V et al., JAIDS, 2017

• iPrEx DXA substudy (n=498) found spine BMD decreases in the TDF/FTC group compared to the PBO group
• Hip BMD initially decreased TDF/FTC group, but rebounded before decreasing again at Week 96
• Decreases in BMD were statistically significant in those with detectable drug levels when compared to the PBO group
• Recovery of BMD realized between 48 and 79 weeks after discontinuing TDF/FTC.
• Similar results were noted in young African women in the VOICE substudy (MTN-003B)

BMD Loss Attenuated by Vitamin D and Calcium

1. 167 HIV-infected patients initiating ART were randomized to receive vitamin D3 plus calcium (n=81) or PBO (n=86).
2. Percentage of BMD change from baseline to week 48:
   - Hip: -1.5 (IQR -3.2, -0.4) vs. -3.2 (IQR -5.1 to -1)
   - Spine: -1.4 (IQR 2.8) vs. -2.9 (IQR -4.8 to -1.1)
3. Percentage of changes in BTM and PTH levels at weeks 24 and 48:
   - Increases were attenuated in the vitamin D3 plus calcium group compared with the placebo group at 24 weeks

BMD Loss Attenuated by Vitamin D and Calcium

1. Baseline
2. Visit
3. Vitamin D Supplementation
4. Case
5. Control
Case 3: A kiss is a terrible thing to waste

- 28-year-old man is referred for PrEP
- He was diagnosed with obesity, hypertension and sleep apnea and underwent gastric bypass surgery 6 months ago
- Since the surgery, he insists on “eating clean” and takes several vitamin supplements daily, including Vitamin A, B3, B6, E, gingko biloba, and milk thistle

ARS Question #3

How do you instruct him to optimally implement PrEP?

1. Daily oral TDF/FTC
2. Double dose daily oral TDF/FTC
3. On-demand “2-1-1” TDF/FTC
4. Daily oral TAF/FTC
5. Something else
Gastric Bypass and Gastric Sleeve

TDF PK After Sleeve-Gastrectomy in 4 HIV-infected individuals

- Decrease in absorption of tenofovir at 1 month as assessed by AUC0–24h and Cmax
- Decrease in absorption of tenofovir at 6 months as assessed by AUC0–24h
- Cmax comparable to pre-operative levels
- At 12 months, AUC0–24h and Cmax return to post-operative levels
- No available data on absorption of tenofovir in HIV-uninfected individual after Sleeve-Gastrectomy.

Muzzardi et al., Obesity Research & Clinical Practice, 2017

TDF Double-Dose in Treatment-Experienced HIV-Infected Patients (n=10)

- TDF 600 mg QD added to background ART
- Patients were seen at baseline, W2, and W4 for clinical exam, plasma HIV-1 RNA load, liver and kidney function tests, tenofovir plasma and urine concentrations, and AE assessments
- One patient (male, 50 years old) experienced Fanconi syndrome
  - W2 decline in Cr Cl from 96 mL/min to 43 mL/min
  - Proteinuria 12g/24h
  - Hypophosphatemia, glycosuria

Case 4: It's a dangerous world out there

- A 55-year-old man comes regularly for PrEP follow-up and all indications suggest he is adherent to PrEP
- 4-5 male sexual partners per month; condom use inconsistent
- He has a history of recurrent rectal chlamydia, with interim documentation of clearance with appropriate treatment (you confirm dates and treatment provided)

ARS Question #4

You tell him:

1. If he has one more STI you will stop his PrEP
2. This is an "Occupational Hazard" of Condomless Sex
3. "Grow Up America, Use a Condom"*
4. Daily doxycycline with his daily TDF/FTC
5. Doxycycline 200 mg post-coitally up to 3 doses per week
6. Have his partners gargle with listerine before oral sex or oral-anal contact

IPERGAY OLE: PEP with Doxycycline and STIs

- 232 ANRS IPERGAY OLE participants were randomly assigned to a doxycycline PEP group (n=116) no-PEP group (n=116)
- 73 participants presented with a new STI infection during follow-up, 28 (22% [15–32]) in the PEP group 45 (42% [33–53])
- Doxycycline PEP reduced the occurrence of a first episode of bacterial STI in high-risk men who have sex with man, but NOT gonorrhea
- Larger prospective studies needed
- Bacterial resistance
- Lowered gut bacterial diversity/Gut Microbiota Modification

Molina J et al., Lancet, 2017

<table>
<thead>
<tr>
<th></th>
<th>Cumulative Probability</th>
<th>Cumulative Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No PEP</td>
<td>PEP</td>
</tr>
<tr>
<td>HR 0.53</td>
<td>95% CI: 0.33–0.8</td>
<td>p=0.008</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.007</td>
<td></td>
</tr>
<tr>
<td>HR 0.83</td>
<td>95% CI: 0.47–1.47</td>
<td>p=0.52</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.527</td>
<td></td>
</tr>
<tr>
<td>HR 0.30</td>
<td>95% CI: 0.13–0.7</td>
<td>p=0.006</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.003</td>
<td></td>
</tr>
<tr>
<td>HR 0.27</td>
<td>95% CI: 0.07–0.98</td>
<td>p=0.047</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.04</td>
<td></td>
</tr>
</tbody>
</table>
**Antiseptic Mouthwash Against Pharyngeal N gonorrhoeae**

**In Vitro**

- Listerine Total Care and Cool Mint were found to significantly inhibit the growth of the tested strain of N. gonorrhoeae at dilutions of 1:2 and 1:4.
- The PBS control displayed no inhibitory effect against N. gonorrhoeae.

**Antiseptic Mouthwash Against Pharyngeal N gonorrhoeae**

**Randomized Control Trial**

- Men in the saline group had a higher gonorrhoea culture positivity at the tonsillar fossae.
- Men in the Listerine group had a lower odds of testing positive for gonorrhoea at the tonsillar fossae.

**Case 5: Shot through the heart (And you’re to blame)**

- 19-year-old man with a history of bulimia returned for PrEP follow-up.
  - He thinks maybe he takes TDF/FTC doses twice during the week, and regularly on weekends.
- 7 male sexual partners in the past month; engages in oral and insertive anal sex; does not use condoms.
- HIV (4th gen) and STI testing three months ago negative.
- He says he heard there is a “shot” that he can take every two months rather than taking a pill - can he get “that”?
- He is very concerned about weight gain.
ARS Question #5

Your best advice is:

1. He must strive for 100% adherence to daily oral TDF/FTC
2. Try TAF/FTC daily
3. “T’s and S’s” is just fine with TDF/FTC
4. Drive to Canada to acquire CAB LA + RPV LA for treatment, split it apart and use the CAB LA for prevention
5. I have a headache stop asking me hard questions
Injection Site Reactions

47 (5.2%) CAB participants permanently discontinued injectable product due to an injection-related AE.

Severity of ISR was strongly associated with odds of permanent discontinuation.

Grade 2+ Adverse Events Reported in ≥5%

<table>
<thead>
<tr>
<th>Event</th>
<th>TOTAL (n=4566)</th>
<th>TDF/FTC (n=2284)</th>
<th>CAB (n=2282)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose increased</td>
<td>323 (7.1%)</td>
<td>117 (5.1%)</td>
<td>206 (9.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rash</td>
<td>253 (5.5%)</td>
<td>139 (6.1%)</td>
<td>114 (5.0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>181 (4.0%)</td>
<td>60 (2.6%)</td>
<td>121 (5.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*70% of pyrexia events in CAB were within 7 days of an injection (event probability 0.65%).
16% of pyrexia events in TDF/FTC were within 7 days of an injection (event probability 0.05%).

Landovitz RJ et al. AIDS 2020, #OAXLB0101

Changes in Weight

Median of changes from baseline (IQR)

HPTN 077: Over 41 weeks
CAB: +1.48 kg (95%CI 0.15, 2.8) kg/y
PBO: +1.57 kg (95%CI -1.35, 4.49) kg/y
p=0.95

Landovitz RJ et al. CID 2019.
Changes in Weight
Median of changes from baseline

<table>
<thead>
<tr>
<th>Week Since Enrollment</th>
<th>Median Body Weight Change from Enrollment, kg (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAB</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
</tr>
<tr>
<td>Week 0</td>
<td>-40</td>
</tr>
<tr>
<td></td>
<td>+1.54 (95%CI 1.0, 2.0) kg/y</td>
</tr>
<tr>
<td>Week 40</td>
<td>-105</td>
</tr>
<tr>
<td></td>
<td>+1.07 (95%CI 0.61, 1.5) kg/y</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
</tr>
<tr>
<td>Week 0</td>
<td>-0.51 (95%CI -0.80, -0.22) kg/y</td>
</tr>
<tr>
<td>Week 40</td>
<td>+1.06 (95%CI 0.79, 1.3) kg/y</td>
</tr>
</tbody>
</table>

HPTN 077: Over 41 weeks

CAB +1.48 (95%CI 0.15, 2.8) kg/y
PBO +1.57 (95%CI -1.35, 4.49) kg/y

p=0.95

Landovitz RJ et al. CID 2019.

Suggested Further Reading


Nanayakkara D et al., Effect of Vitamin D Supplementation on Bone Turnover Markers during HIV Pre-exposure Prophylaxis using Tenofovir Disoproxil Fumarate-Emtricitabine in Men who have Sex with Men. AIDS research and human retroviruses. 2019 Mar 23(ja).


Molina JM et al., Efficacy, safety, and effect on sexual behaviour of on‐demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. The lancet HIV. 2017 Sep 1;4(9):e402-10.

