The Data-Free Zone: Tough Cases in HIV Prevention, 2021 Edition

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Landovitz has served on scientific advisory boards for Gilead Sciences, Inc, and Merck & Co, Inc. (Updated 9/20/21)

Learning Objectives

After attending this presentation, learners will be able to:

- Describe options for PrEP in patients with decreased kidney function and low bone mineral density
- Describe the state of the science on STI prevention strategies
- Describe recent data on the safety and efficacy on injectable PrEP options
**Effectiveness of TDF/FTC in Randomized Clinical Trials**

- TDF/FTC
- TAF/FTC
- TAF
- TDF
- PrEP

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**PrEP 2.0: Trials of Novel PrEP Agents**

- ASPIRE (Dapivirine): 27%
- Ring (Dapivirine): 31%
- DISCOVER (TDF/FTC): 27%
- DISCOVER (TAF/FTC): 31%

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**Effectiveness of Daily TDF/FTC in Clinical Trials**

- Effectiveness (%)
- Percentage of Participants’ Samples with detectable drug levels

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Landovitz RJ et al. AIDS 2020, #OAXLB0101

"PrEP 2.0": Trials of Novel PrEP Agents

Incidence rate 0.33%
Incidence rate 0.16%
CI: 1 – 46
CI: 1 – 51
**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 CI change: -6 mL/min at month 24
  - No cases of elevated creatinine with Cr CI >90 mL/min
  - No discontinuations of PrEP due to decline in eGFR
- Cr CI <70 mL/min after baseline Cr CI ≥70 mL/min (n=8)
  - Recovered (n=3); remained ≥60 mL/min (n=5)
  - Significantly associated with age ≥50 years and baseline Cr CI <90 mL/min (both P<0.0001)

↑ Age, ↓ Baseline Cr CI, 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 CI falling below 60 mL/min were higher in participants with a baseline Cr CI of 90 mL/min or less.

The virtual 2021 Ryan White HIV/AIDS Program (RWHAP) CLINICAL CONFERENCE, October 3-6, 2021
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

<table>
<thead>
<tr>
<th>Week</th>
<th>Screen</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum creatinine (mg/dL)</td>
<td>1.15</td>
<td>0.98</td>
<td>0.97</td>
<td>0.96</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Serum phosphorus (mg/dL)</td>
<td>—</td>
<td>2.34</td>
<td>2.38</td>
<td>2.37</td>
<td>2.38</td>
<td>2.39</td>
</tr>
<tr>
<td>Note</td>
<td>Renal phosphate wasting end point</td>
<td>End of study</td>
<td>24.04</td>
<td>24.07</td>
<td>24.11</td>
<td>24.14</td>
<td>24.17</td>
</tr>
</tbody>
</table>

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

- MSM or TGW participants
  - Randomized: 1:1
- Active controlled
  - F/TAF QD (200/25 mg): n=2694
  - F/TDF QD (200/300 mg): n=2693

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

Primary analysis:
- HIV incidence/100 PY when 100% complete W48 & 50% complete W96

Eligibility required 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

DISCOVER: HIV Incidence

- Incidence of HIV per 100 PY in the F/TAF and F/TDF groups and IRR (F/TAF divided by F/TDF). Error bars represent 95% CIs.
- F/TAF=emtricitabine and tenofovir alafenamide. F/TDF=emtricitabine and tenofovir disoproxil fumarate. IRR=incidence rate ratio. PY=person-year.

DISCOVER: HIV Incidence

Ogbuagu O et al. Lancet HIV. 2021
**DISCOVER: Renal Safety**

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

**IPERGAY: eGFR changes not different TDF/FTC v. PBO**

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
<th>Placebo</th>
<th>P value</th>
<th>All participants on TDF/FTC (N=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median of follow-up - months (IQR)</td>
<td>9.4 (5.1-26.6)</td>
<td>9.4 (5.1-26.6)</td>
<td>19.2 (18-26.9)</td>
<td></td>
</tr>
<tr>
<td>Mean slope of eGFR decline per year* (ml/min/1.73m²)</td>
<td>-1.55</td>
<td>-0.88</td>
<td>0.27</td>
<td>-1.20</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;45ml/min/1.73m² - n</td>
<td>4</td>
<td>3</td>
<td>0.74</td>
<td>14</td>
</tr>
<tr>
<td>Treatment discontinuation for kidney adverse event - n (%)</td>
<td>0</td>
<td>0</td>
<td>3 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

**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**

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- 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**

- 167 HIV-infected patients initiating ART were randomized to receive vitamin D3 plus calcium (n=81) or PBO (n=86).
- 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: -3.8, 0) VS -2.9 (IQR: -4.8 to -1.1)
- 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.

<table>
<thead>
<tr>
<th>Case</th>
<th>Control</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1NP</td>
<td>pg/mL</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
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- A subset of 48 HIV-uninfected men enrolled in CCTG 595 were selected to receive VID 4000 IU/day.
- Matched 1:1 with controls based on age, race, and BMI.
- Vitamin D3 supplementation with 4000 IU/day resulted in a significant reduction in the BTM P1NP compared to controls.

2. Nanayakkara D et al., AIDS Res Hum Retroviruses, 2019
Case 3: A kiss is a terrible thing to waste

- 28-year-old cisgender woman is referred for PrEP
- She was diagnosed with obesity, hypertension and sleep apnea and underwent gastric bypass surgery 6 months ago
- Since the surgery, she 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 her 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

- Decrease in absorption of tenofovir at 1 month as assessed by AUC_{0-24h} and C_{max}
- Decrease in absorption of tenofovir at 6 months as assessed by AUC_{0-24h}
- C_{max} comparable to pre-operative levels
- At 12 months, AUC_{0-24h} and C_{max} return to post-operative levels
- No available data on absorption of tenofovir in HIV-uninfected individual after Sleeve-Gastrectomy.

Muzzard L 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 decelined 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 transgender woman comes regularly for PrEP follow-up and all indications suggest she is adherent to PrEP
- 4-5 male sexual partners per month; condom use inconsistent
- She 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 her:
1. If she has one more STI you will stop her PrEP
2. This is an “Occupational Hazard” of Condomless Sex
3. “America, Grow up! Use a Condom”*
4. Daily doxycycline with her daily TDF/FTC
5. Doxycycline 200 mg post-coitally up to 3 doses per week
6. Have her partners gargle with listerine before oral sex or oral-anal contact
You thought I was joking
I wasn’t
West Hollywood, California 2012

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 infections 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 men, but NOT gonorrhea
- Larger prospective studies needed
- Bacterial resistance
- Lowered gut bacterial diversity/Gut Microbiota Modification

Antiseptic Mouthwash Against Pharyngeal N gonorrhoeae

- 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

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

Chow E PF et al., Sex Transm Infect, 2016

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

24-year-old man with a history of a severe trigeminal-neuralgia syndrome provoked by TDF/FTC PrEP on two occasions (immediately after initial dosing, and on rechallenge 1 month later)

- Identical syndrome upon immediate dosing with TAF/FTC
- Extensive neurologic work-up otherwise unrevealing

7 male sexual partners in the past month; engages in oral and insertive anal sex; does not use condoms

ARS Question #5

Your best advice is:

1. Rechallenge with daily oral TDF/FTC with MVI supplementation
2. Rechallenge with TAF/FTC daily using Vitamin B6 supplementation
3. Prescribe CAB LA + RPV LA for treatment, split it apart and use the CAB LA for prevention
4. Complete compassionate use CAB LA application until commercially available
5. I have a headache stop asking me hard questions
Case 5: Who knew?

HPTN 083 Study Design

HIV Incidence: CAB vs. TDF/FTC
Effectiveness of PrEP in Randomized Clinical Trials

Thank you!

Suggested Further Reading


Grant ET et al., The impact of dose on adherence to daily tenofovir/emtricitabine in treatment-naive patients receiving tenofovir/emtricitabine in the DISCOVER trial. The Lancet. 2015 Oct 3;386(10002):1242-7.


Cohen MS et al., Risk of HIV infection associated with the use of injectable antiretroviral prophylaxis for HIV prevention. The Lancet. 2015 Sep 19;386(10001):1293-301.


