

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

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Professor of Medicine  
University of California Los Angeles  
Los Angeles, California



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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)

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**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

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**PrEP is straightforward when...**

- Cr Cl  $\geq$  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

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**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

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**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

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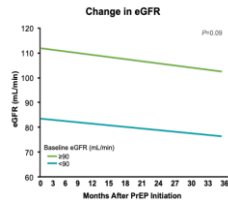
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## Impact of Long-Term PrEP Use and Renal Function

- Longitudinal clinical cohort study (2014-2017)
  - 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)



Harvey M et al. AIDS Res Hum Retroviruses, 2018

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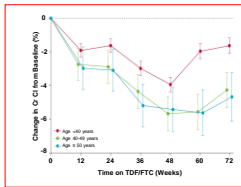
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## ↑ Age, ↓ Baseline Cr Cl, and Adherence Associated with Declining Renal Function



- 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.

Gandhi M et al. Lancet, 2016

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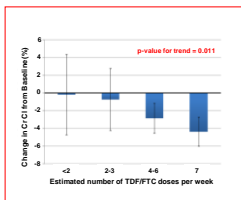
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## ↑ Age, ↓ Baseline Cr Cl, and Adherence Associated with Declining Renal Function



- 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.

Gandhi M et al. AIDS, 2017

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## CCTG 595: PrEP Associated with Fanconi Syndrome

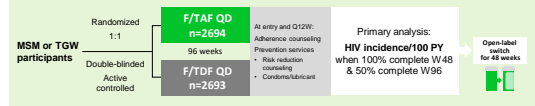
- 49-year-old white man, Hx kidney stones, HBV/HCV negative, no ongoing medical problems or medication use
- Mild renal impairment detected at baseline (Cr Cl: 79.9 mL/min).
- Initiated daily oral TDF/FTC-based PrEP
- 12 weeks after PrEP initiation
  - 25% decrease in Cr Cl.
  - Hypophosphatemia with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

Test	Screen	Week 4	Week 12	Week 16	Week 18	Week 21	Week 24	
Estimated creatinine clearance <sup>a</sup> , mL/min	79.9	68.7	68.9	68.1	66.6	71.0	74.8	
Serum creatinine, mg/dL	1.15	1.32	1.68	1.28	1.92	1.27	1.20	
Serum phosphorus, mg/dL, normal 2.7-4.5b	---	---	1.8	Stop TDF-FTC	2.7	3.2	2.6	2.8
Fractional excretion of Phosphate, % (normal 10-25)	---	---	26.6	---	---	---	---	

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.  
<sup>a</sup>Estimated creatinine clearance by Cockcroft-Gault formula.

Khan S et al., OFID, 2017

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



**Eligibility required high sexual risk of HIV**

- 2+ episodes condomless anal sex in past 12W or rectal gonorrhea/chlamydia, syphilis in past 24W
- HIV & HBV negative, eGFR ≥60 mL/min
- Prior use of PrEP allowed



**Study conducted in NA, EU in cities/sites with high HIV incidence**

- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%



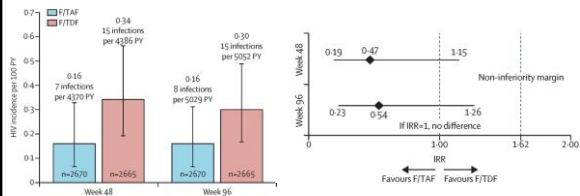
**Primary efficacy endpoint: HIV incidence**

- Evaluated by rate ratio with noninferiority (NI) margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg; eGFR, estimated glomerular filtration rate.

Slide courtesy of Gilead Sciences

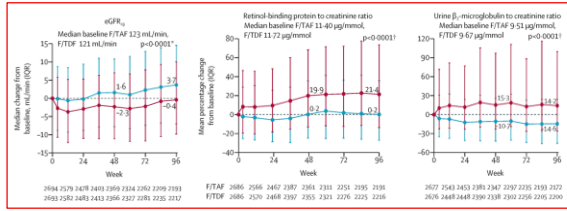
## DISCOVER: HIV Incidence



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% CI.  
 F/TAF-tenofovir alafenamide; F/TDF-tenofovir disoproxil fumarate. IRR-incidence rate ratio; PY-person year.

Ogugu O et al. Lancet HIV. 2021

## DISCOVER: Renal Safety



Ogumsoy O et al. *Lancet HIV*. 2021

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

	Blind phase			All participants on TDF/FTC (N=389)
	TDF/FTC (n=201)	Placebo (n=199)	p value	
Median of follow-up - months (IQR)	9.4 (5.1-20.6)	9.4 (5.1-20.6)		19.2 (18-26.9)
Mean slope of eGFR decline per year <sup>a</sup> (mL/min/1.73m <sup>2</sup> )	- 1.53	- 0.88	0.27	- 1.20
At least one eGFR <70mL/min/1.73m <sup>2</sup> - n	20	9	0.04 <sup>b</sup>	45
At least one eGFR <60mL/min/1.73m <sup>2</sup> - n	4	3	0.74 <sup>b</sup>	14
Treatment discontinuation for kidney adverse event - n (%)	0	0		3 <sup>c</sup> (1%)

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

Liegeon B et al. *CROI* 2019

## 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

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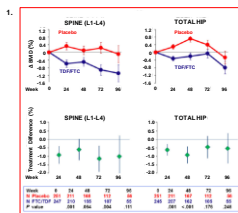
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### iPrEx: Bone Mineral Density Loss and Recovery



- 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

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

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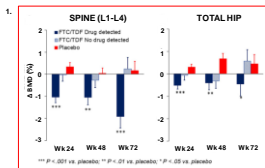
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### iPrEx: Bone Mineral Density Loss and Recovery



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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

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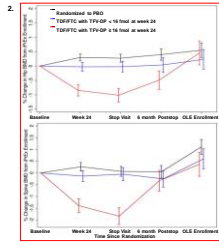
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## iPrEx: Bone Mineral Density Loss and Recovery



- 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
- 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)

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

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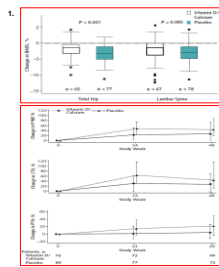
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## BMD Loss Attenuated by Vitamin D and Calcium



- 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

1. Overton TE et al., Ann. Intern. Med., 2015  
2. Nanayakkara D et al., AIDS Res Hum Retroviruses, 2019

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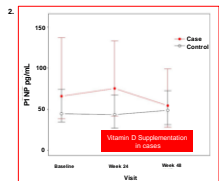
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    - Spine: -1.4 (IQR -3.8; 0) VS -2.9 (IQR -4.8 to -1.1)
  - Percentage of changes in BTM and PTH levels at weeks 24 and 48.
    - Increases were attenuated in the vitamin D3 plus calcium group compared with the placebo group at 24 weeks
- A subset of 48 HIV-uninfected men enrolled in CCTG 595 were selected to receive VitD 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

1. Overton TE et al., Ann. Intern. Med., 2015  
2. Nanayakkara D et al., AIDS Res Hum Retroviruses, 2019

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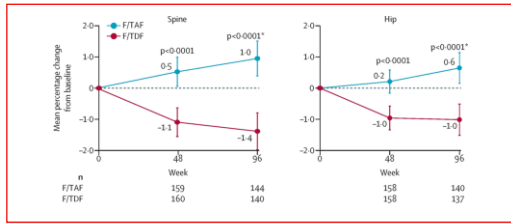
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## DISCOVER: Bone Safety



Ogumsoy O et al. *Lancet HIV*. 2021

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## Which medication should I prescribe for daily PrEP?




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## 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, ginkgo biloba, and milk thistle

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## 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

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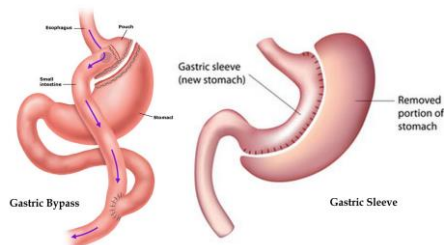
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## Gastric Bypass and Gastric Sleeve




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

Time	Patient	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)	AUC <sub>0-24h</sub> (ng·h/mL)	Steady-state (h)	Elimination half-life (h)
Pre-operative	Mean ± SD	1.25	263 ± 79	47 ± 15	2348 ± 643	13 ± 3	113 ± 37
	Patient #1	1	275	50	2364	27	104
	Patient #2	1	311	57	2538	12	97
	Patient #4	1	383	56	3017	14	81
1 month after SG	Mean ± SD	1.5	162 ± 44	34 ± 13	1575 ± 415	19 ± 3	171 ± 54
	Patient #1	1	158	48	1827	22	136
	Patient #2	1	225	46	1906	15	139
	Patient #4	1	142	22	1425	19	174
3 months after SG	Mean ± SD	1.5	252 ± 93	40 ± 10	2174 ± 547	14 ± 3	119 ± 34
	Patient #1	1	150	30	1479	16	166
	Patient #2	1	240	49	2766	13	89
	Patient #4	1	322	32	2055	15	119
6 months after SG	Mean ± SD	1.25	239 ± 148	32 ± 6	1997 ± 355	15 ± 4	141 ± 45
	Patient #1	1	479	31	1878	16	151
	Patient #2	1	183	35	1776	12	138
	Patient #4	1	210	38	1641	21	148
12 months after SG	Mean ± SD	1	325 ± 43	47 ± 17	2344 ± 949	16 ± 2	114 ± 46
	Patient #1	1	294	20	1639	17	146
	Patient #2	1	355	39	3009	14	81

Muzzard L et al. Obesity Research & Clinical Practice, 2017

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

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**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

Dominguez S et al., J. Med. Virol., 2007

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**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)

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**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

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**You thought I was joking**

**I wasn't**

**West Hollywood, California 2012**

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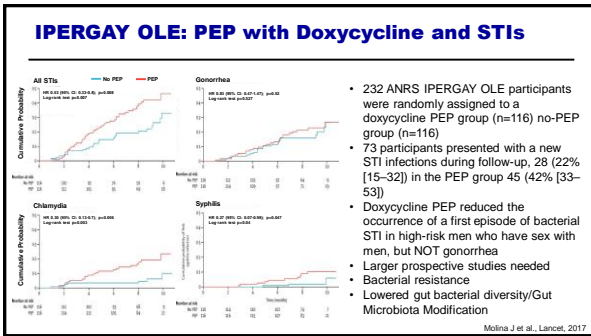
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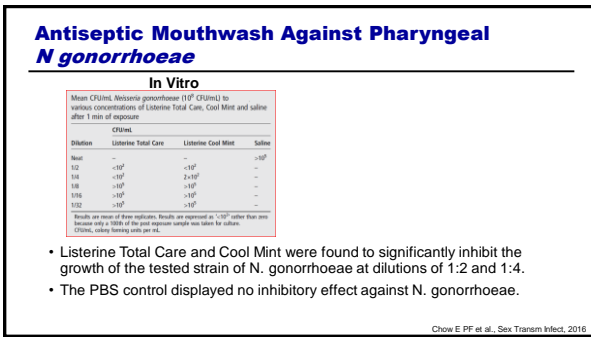
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## Antiseptic Mouthwash Against Pharyngeal *N gonorrhoeae*

### In Vitro

Mean CFU/mL Neisseria gonorrhoeae ( $10^6$  CFU/mL) to various concentrations of Listerine Total Care, Cool Mint and saline after 1 min of exposure

Dilution	CFU/mL		
	Listerine Total Care	Listerine Cool Mint	Saline
None	-	-	$\approx 10^6$
1:2	$< 10^4$	$< 10^4$	-
1:4	$< 10^4$	$2 \times 10^2$	-
1:8	$< 10^4$	$> 10^4$	-
1:16	$> 10^4$	$> 10^4$	-
1:32	$> 10^4$	$> 10^4$	-

\*Results are mean of three replicates. Results are reported as  $< 10^4$  rather than zero because only a 10% of the post exposure sample was taken for culture. CFU/mL values ranging from 0-10.

### Randomized Controlled Trial

	Listerine group (n=33)	Saline group (n=25)	p Value*
Gonorrhoea positivity by culture after rinsing and gargling			
Pharyngeal surface (posterior oropharynx and/or tonsillar fossae)			
Positive	17 (52%)	21 (84%)	0.013
Negative	16 (48%)	4 (16%)	
Tonsillar fossae†			
Positive	13 (37%)	18 (69%)	0.016
Negative	10 (42%)	2 (15%)	
Posterior oropharynx‡			
Positive	13 (37%)	14 (56%)	0.277
Negative	10 (42%)	6 (20%)	

- 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

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## 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

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## ARS Question #5

Your best advice is:

- Rechallenge with daily oral TDF/FTC with MVI supplementation
- Rechallenge with TAF/FTC daily using Vitamin B6 supplementation
- Prescribe CAB LA + RPV LA for treatment, split it apart and use the CAB LA for prevention
- Complete compassionate use CAB LA application until commercially available
- I have a headache stop asking me hard questions

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## Case 5: Who knew?

International Medical Case Reports Journal

Dovepress

CASE REPORT

Neurological syndrome in an HIV-prevention trial participant randomized to daily tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) in Bondo, Kenya

Frederick Obong'o  
Justin Mwangi  
John Mwangi  
Katherine Apol  
Lucy Chelimo

**Abstract** The effects of antiretroviral therapy (ART) on HIV-positive patients have been extensively studied. However, there are limited data on the effects of antiretroviral therapy on HIV-negative patients living with HIV. This report describes the case of a 37-year-old participant in the HPTN 083 trial. This case is discussed in relation to the effects of ART on HIV-negative patients. The patient presented with acute trigeminal neuralgia (ATN) and was treated with gabapentin. The patient's symptoms improved after treatment with gabapentin. This case highlights the need for further research on the effects of ART on HIV-negative patients.

Case Report

**Acute Trigeminal Neuralgia Associated with Initiation of Emtricitabine/Tenofovir for HIV Pre-Exposure Prophylaxis**

Loraine Van Slyke, MPhC<sup>1</sup>, and Mia Scott, DO<sup>2</sup>

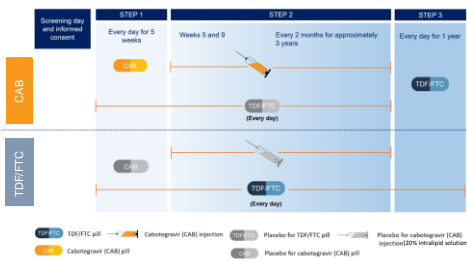
**Abstract** HIV pre-exposure prophylaxis (PrEP) with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) has been shown to reduce the risk of HIV acquisition. However, there are limited data on the effects of PrEP on HIV-negative patients. This report describes the case of a 37-year-old participant in the HPTN 083 trial. This case is discussed in relation to the effects of PrEP on HIV-negative patients. The patient presented with acute trigeminal neuralgia (ATN) and was treated with gabapentin. The patient's symptoms improved after treatment with gabapentin. This case highlights the need for further research on the effects of PrEP on HIV-negative patients.

**Keywords**  
neurology, trigeminal neuralgia, PrEP

Journal of the International  
Medical Case Reports Journal  
Volume 12 | 2021  
https://doi.org/10.21956/ijmcr.v12i12.11111

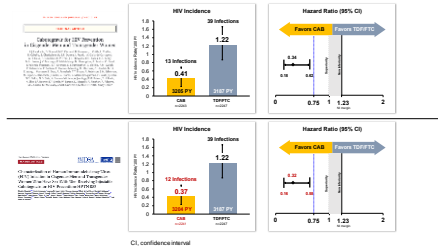
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Mia Scott, DO<sup>2</sup>. All rights reserved.  
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original author(s) and source are credited.

## HPTN 083 Study Design



Landovitz RJ et al. NEJM. 2021.

## HIV Incidence: CAB vs. TDF/FTC











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