

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

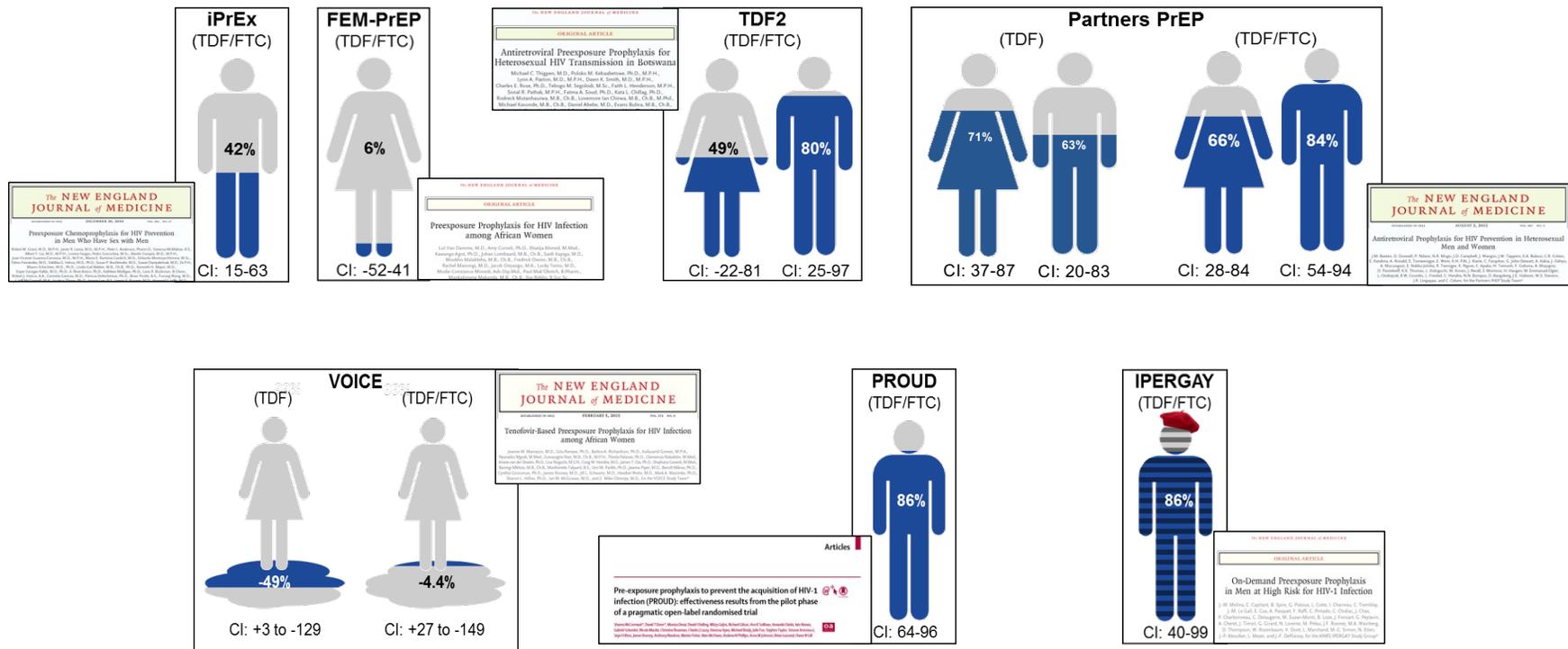
Dr Landovitz has served on scientific advisory boards for Gilead Sciences, Inc, and Merck & Co, Inc. (Updated 9/20/21)

Learning Objectives

After attending this presentation, learners will be able to:

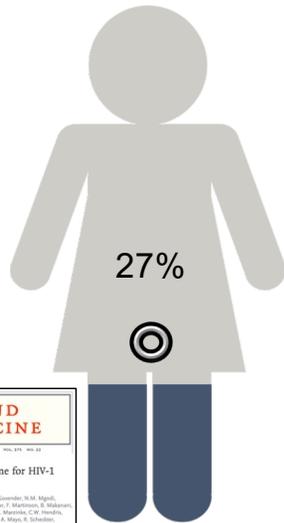
- Describe options for PrEP in patients with decreased kidney function and low bone mineral density
- Describe the state of the science on STI prevention strategies
- Describe recent data on the safety and efficacy on injectable PrEP options

Effectiveness of TDF/FTC in Randomized Clinical Trials



“PrEP 2.0”: Trials of Novel PrEP Agents

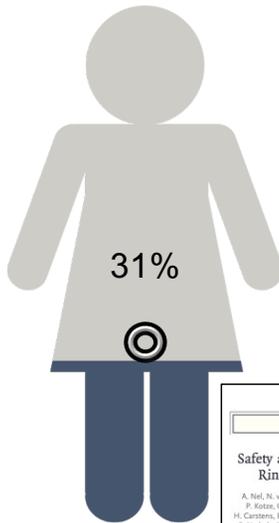
ASPIRE
(Dapivirine)



The NEW ENGLAND
JOURNAL of MEDICINE
DECEMBER 3, 2015 VOL 373 NO 24
Use of a Vaginal Ring Containing Dapivirine for HIV-1
Prevention in Women
J.M. Baeten, F. Fuzess-Phillips, E.B. Brown, K. Schwartz, L.J. Soto-Torres, V. Gooneratne, N.M. Mugo, F. Mwanza, G. Nzi, J. Mwingi, S. Shis, G. Bollen, N. Kamukama, C. Gifford, J. Mwanza, R. Mwakima, A. Juma, L. Njiru, M. Njiru, B.B. Bwambale, L.H. Purdy, J.M. Njiru, M.A. Mwanza, C.W. Hendricks, A. van der Straten, C. Farizo, Z.M. Ching'ola, C. Nalubula, F.E. Jaki, J. Jones, A. Moyo, R. Schuler, J. Bwambale, E. Lwiza, C. Chikanda, F. Njiru, R. Mwa, K. Mwa, C. Gifford, G. Gooneratne, N. Mwakima, A. Nzi, D. Singh, D. de Souza, B.T. Mangum, B.S. Maman, A. Tzipori, C.J. Grossman, N. Chakrabarti, A. Nzi, Z. Rosenberg, J. Mwanza, and S. Hillier for the ATHENA-ASPIRE Study Team

CI: 1 – 46

Ring
(Dapivirine)



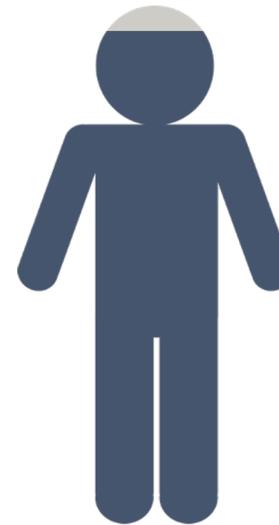
THE NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Safety and Efficacy of a Dapivirine Vaginal
Ring for HIV Prevention in Women
A. Nzi, N. van Nieuwen, S. Kijaga, L.C. Bekker, C. Gama, K. Gill, A. Kamali, P. Kotze, C. Low, Z. Mahade, N. Misi, S. Kusumera, H. Tempelman, H. Carstens, B. Devlin, M. Isaacs, M. Malherbe, W. Muna, J. Ntshali, M. Russell, S. Nshaha, M. Smit, L. Solis, P. Spence, J. Steyler, N. Wisse, M. Burenzana, S. Ressel, J. Van Rooy, W. Papis, T. Vangeneugden, B. Van Baalen, and Z. Rosenberg, for the Ring Study Team

CI: 1 – 51

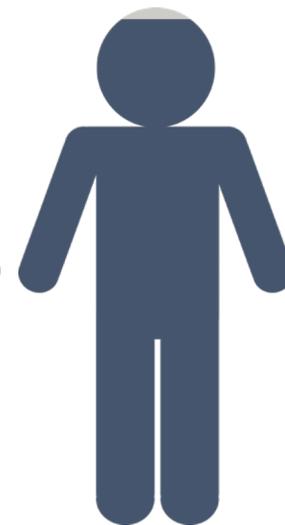
DISCOVER

(TDF/FTC)

(TAF/FTC)

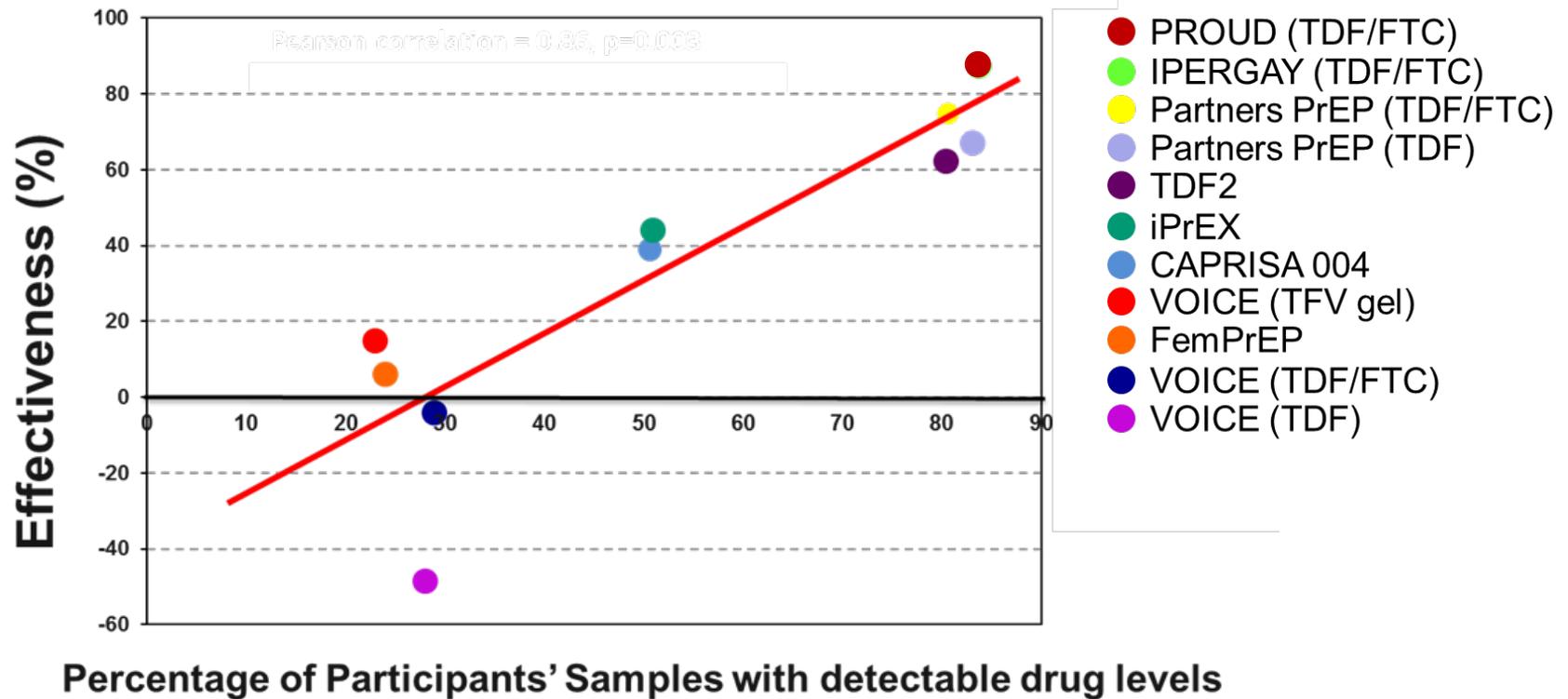


Incidence rate
0.30%



Incidence rate
0.16%

Effectiveness of Daily TDF/FTC in Clinical Trials



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

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

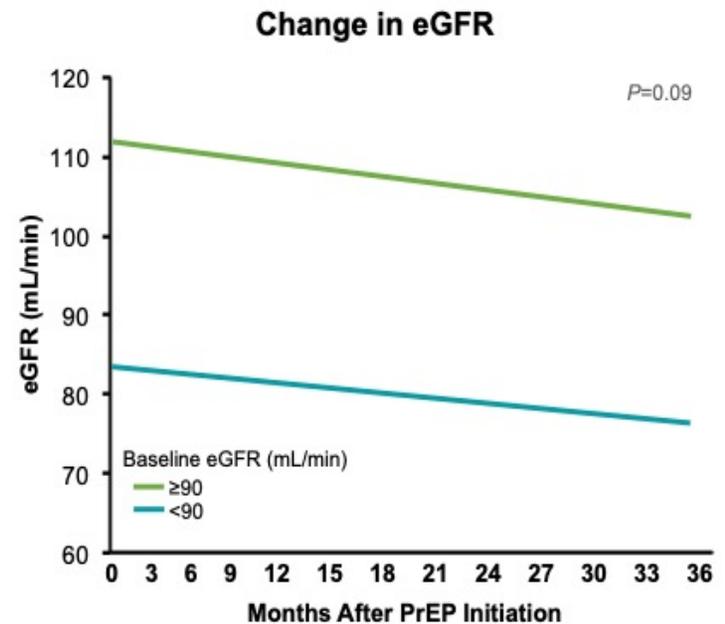
ARS Question #1

Your best advice regarding his PrEP is:

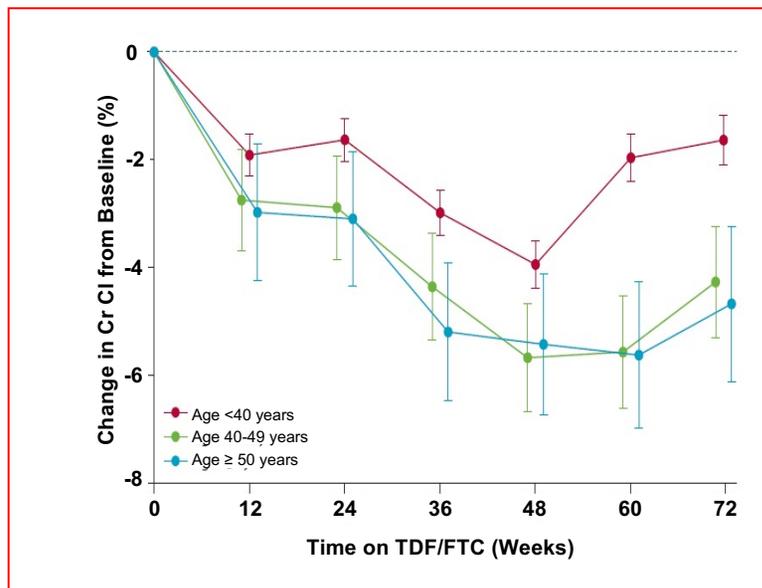
1. Continue daily oral TDF/FTC, recheck in 1 month
2. Switch to event-based (“2-1-1”) dosing of TDF/FTC
3. Dose reduce TDF/FTC to 3 x week
4. Switch to TAF/FTC daily
5. Something else

Impact of Long-Term PrEP Use and Renal Function

- 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)

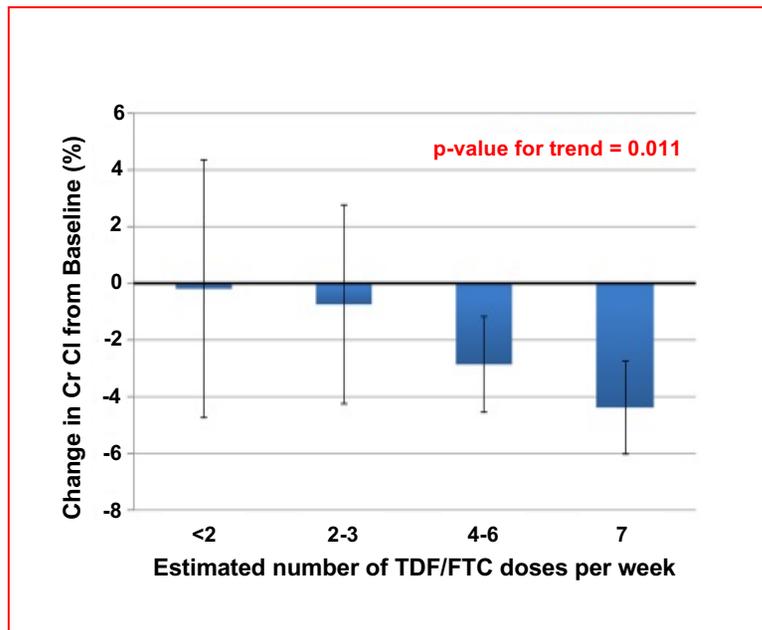


↑ Age, ↓ Baseline Cr Cl , and Adherence Associated with Declining Renal Function



- 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

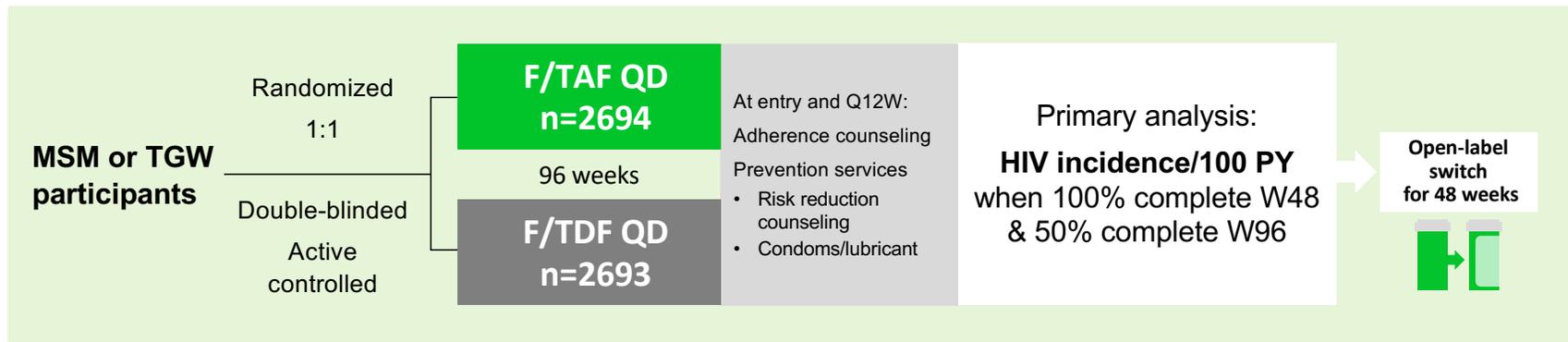
- 49-year-old white man, Hx kidney stones, HBV/HCV negative, no ongoing medical problems or medication use
- Mild renal impairment detected at baseline (Cr Cl: 79.9 mL/min).
- Initiated daily oral TDF/FTC-based PrEP
- 12 weeks after PrEP initiation
 - 25% decrease in Cr Cl,
 - Hypophosphatemia with renal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

Test	Screen	Week 4	Week 12		Week 16	Week 18	Week 21	Week 24
Estimated creatinine clearance ^a , mL/min	79.9	68.7	58.9		69.1	66.6	71.0	74.0
Serum creatinine, mg/dL	1.15	1.33	1.58		1.28	1.32	1.27	1.20
Serum phosphorus, mg/dL (normal 2.7–4.5)	—	—	1.8	Stop TDF-FTC	2.7	3.2	2.6	2.8
Fractional excretion of Phosphate, % (normal 10–20)	—	—	26.6		12.2	—	—	—

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

^aEstimated creatinine clearance by Cockcroft-Gault formula.

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

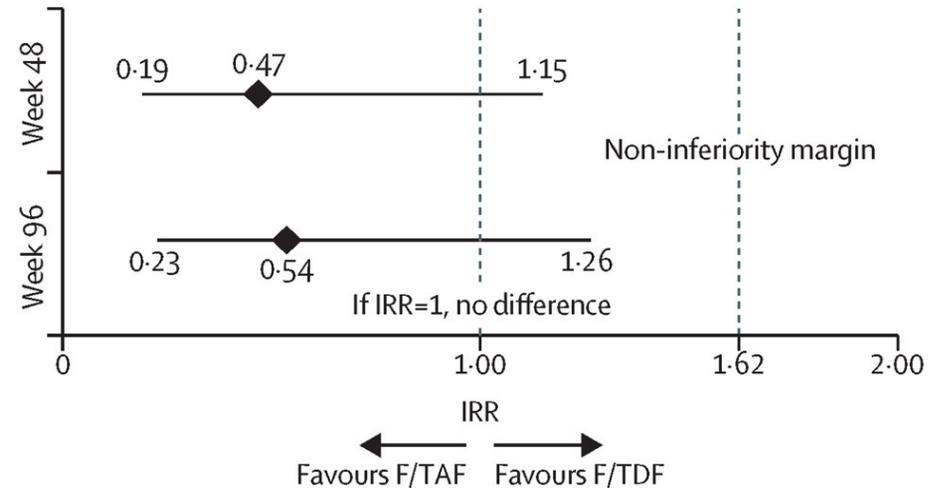
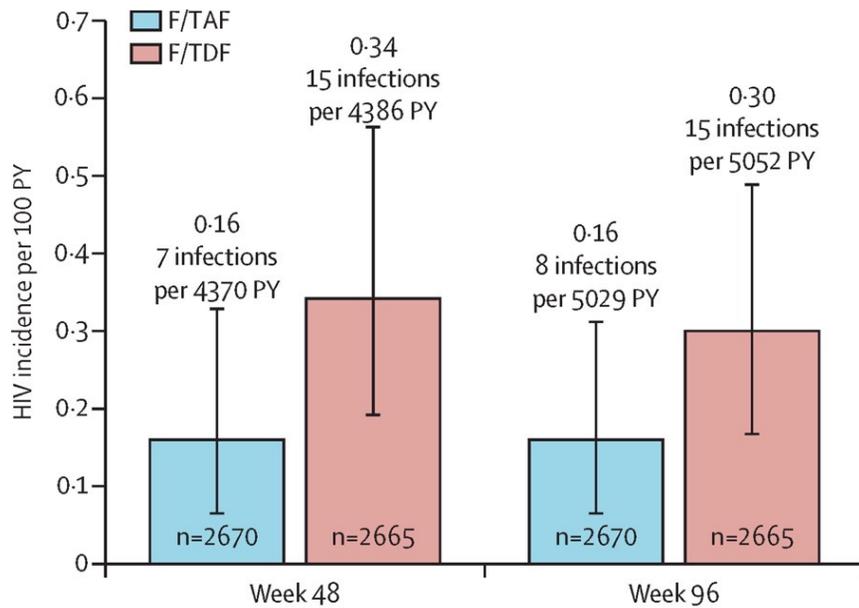
- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%



Primary efficacy endpoint: HIV incidence

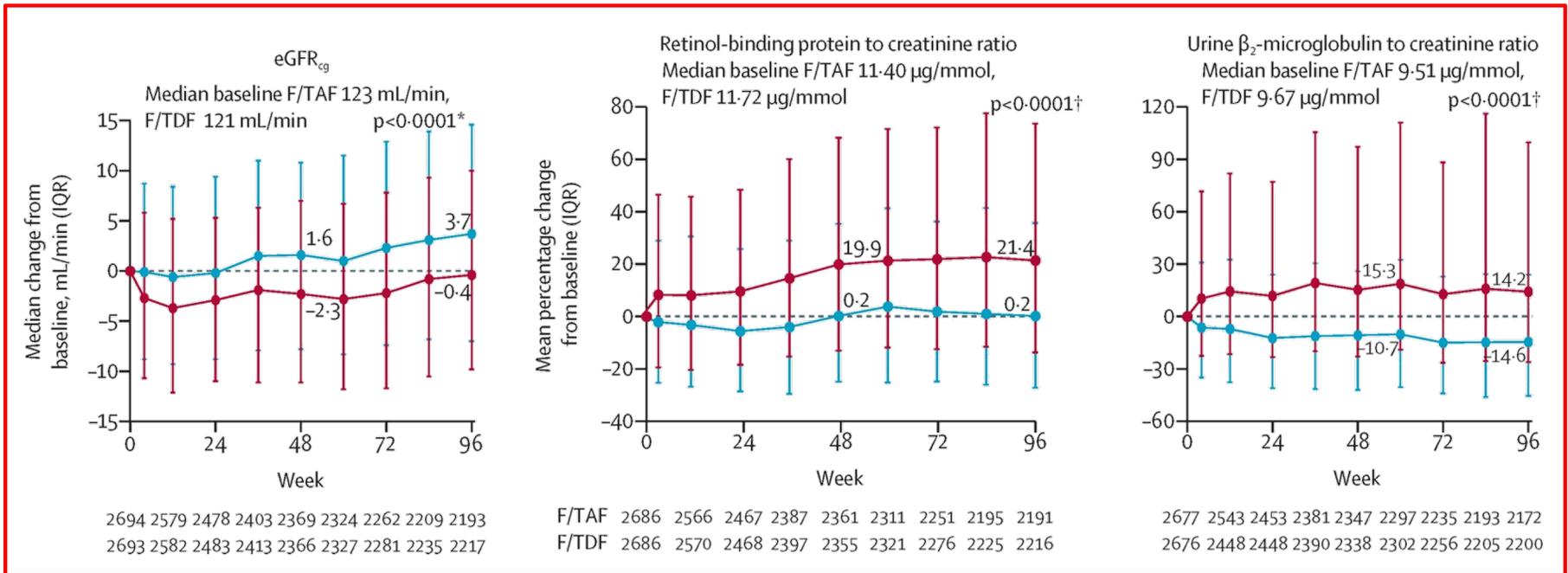
- Evaluated by rate ratio with noninferiority (NI) margin < 1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

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: Renal Safety



● F/TDF ● F/TAF

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 ^a (mL/min/1.73m ²)	- 1.53	- 0.88	0.27	- 1.20
At least one eGFR <70mL/min/1,73m ² - n	20	9	0.04 ^b	45
At least one eGFR <60mL/min/1,73m ² - n	4	3	0.74 ^b	14
Treatment discontinuation for kidney adverse event - n (%)	0	0		3 ^c (1%)

- 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.

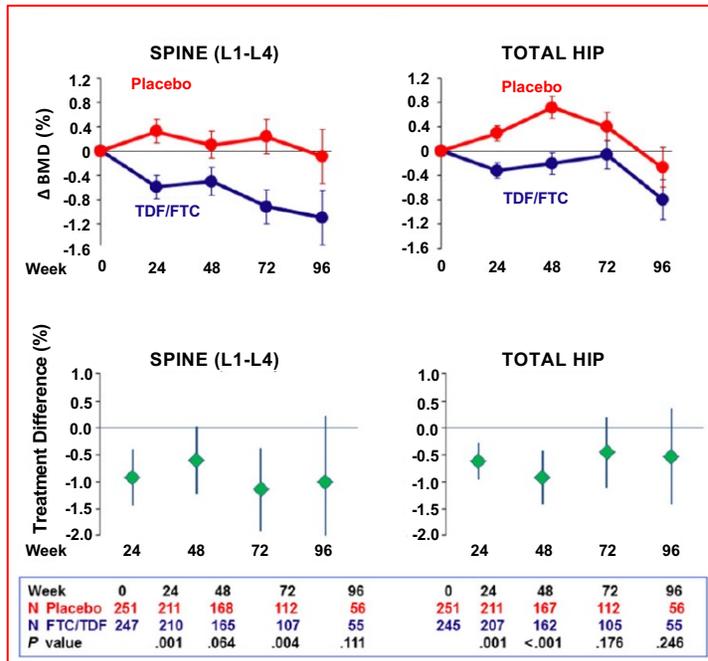
ARS Question #2

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

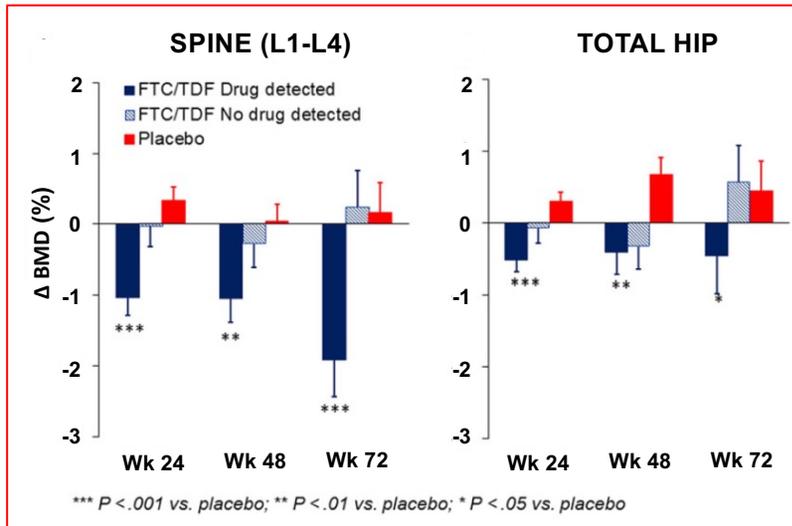
1.



- 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

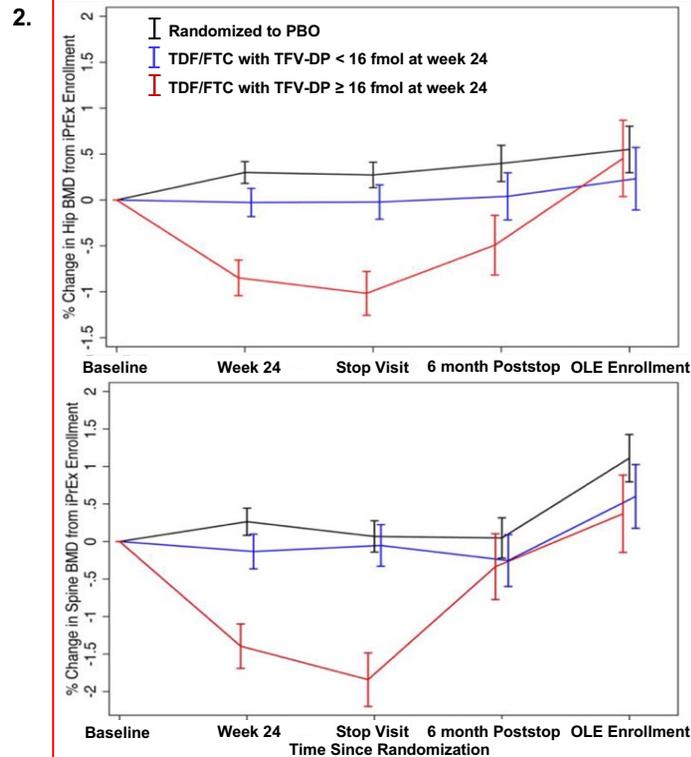
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- Decreases in BMD were statistically significant in those with detectable drug levels when compared to the PBO group

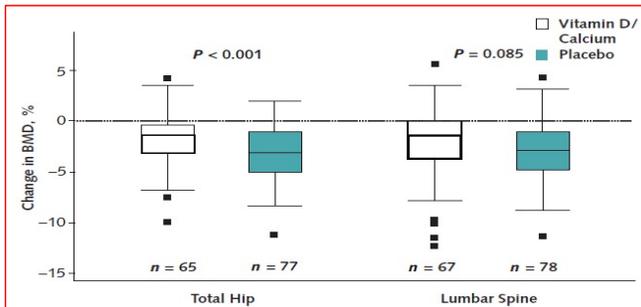
iPrEx: Bone Mineral Density Loss and Recovery



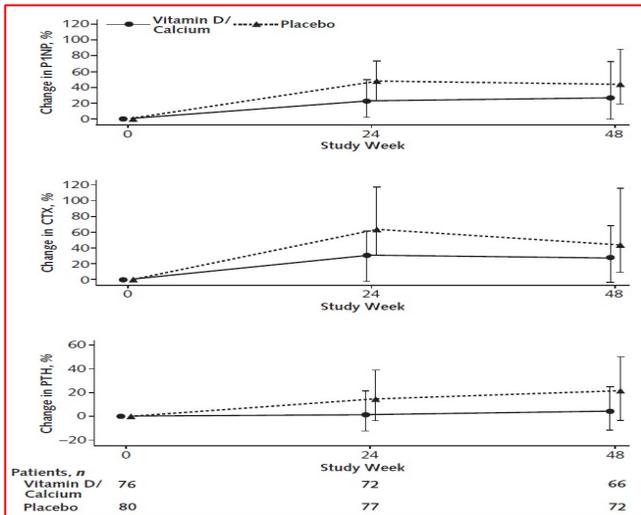
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- Hip BMD initially decreased TDF/FTC group, but rebounded before decreasing again at Week 96
- Decreases in BMD were statistically significant in those with detectable drug levels when compared to the PBO group
- Recovery of BMD realized between 48 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

1.



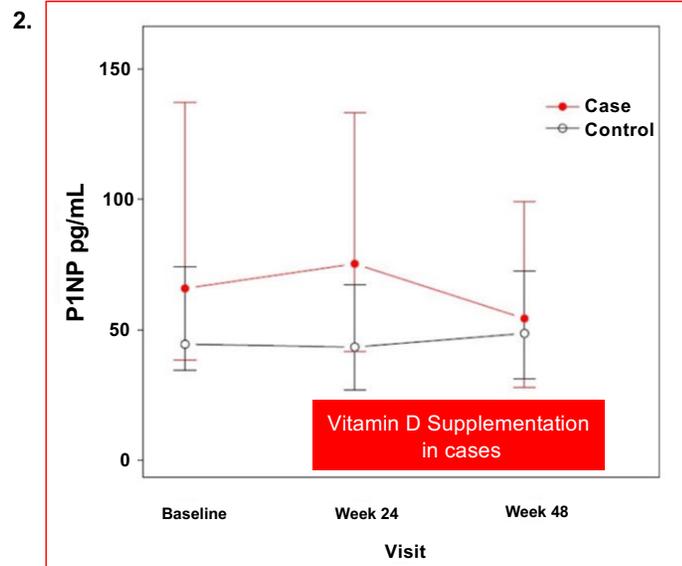
- 167 HIV-infected patients initiating ART were randomized to receive vitamin D3 plus calcium (n=81) or PBO (n=86).
 - Percentage of BMD change from baseline to week 48:
 - Hip: -1.5 (IQR -3.2, -0.4) VS -3.2 (IQR -5.1 to -1)
 - Spine: -1.4 (IQR -3.8; 0) VS -2.9 (IQR -4.8 to -1.1)
 - Percentage of changes 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



Slide 23 of 49

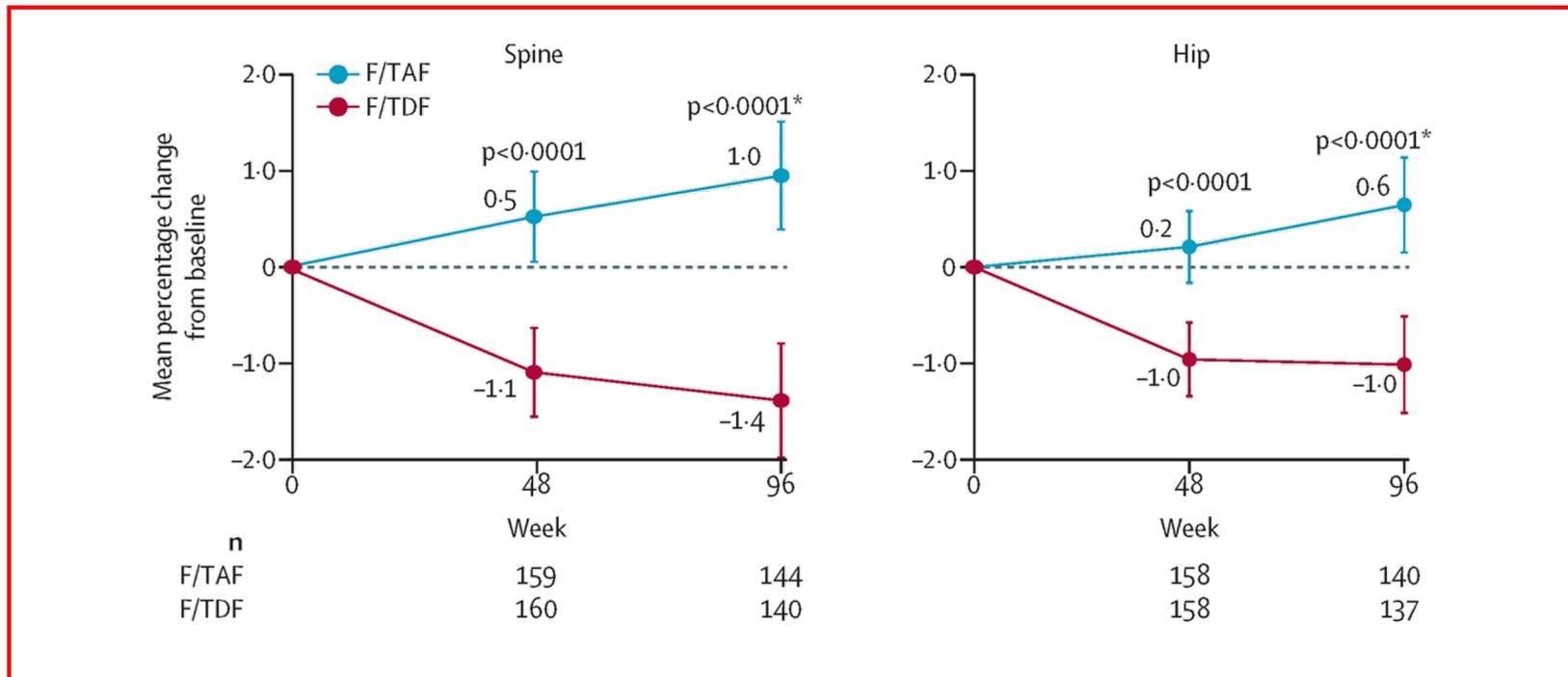
1. Overton TE et al., Ann. Intern. Med., 2015
 2. Nanayakkara D et al., AIDS Res Hum Retroviruses, 2019

BMD Loss Attenuated by Vitamin D and Calcium

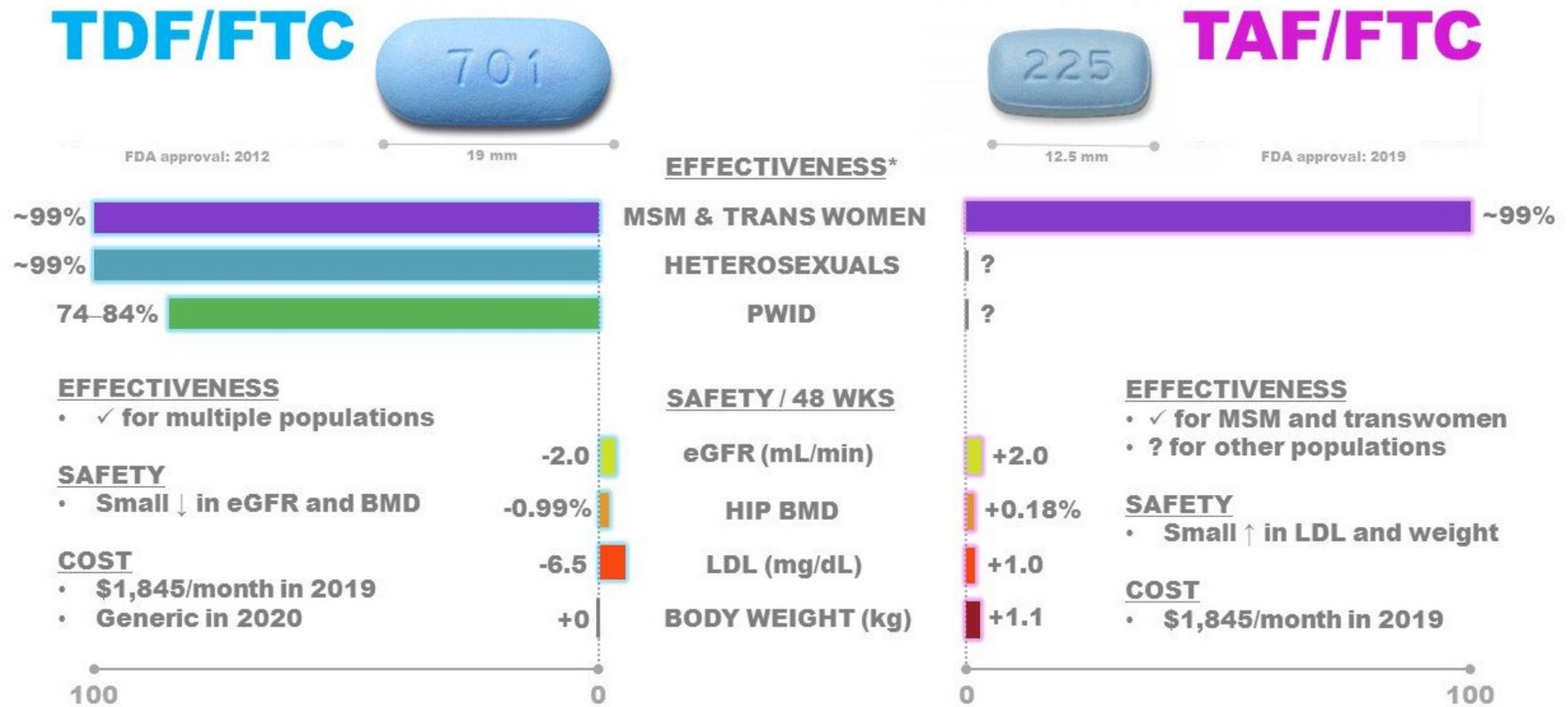


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 - Percentage of changes in BTM and PTH levels at weeks 24 and 48.
 - Increases were attenuated in the vitamin D3 plus calcium group compared with the placebo group at 24 weeks
- A subset of 48 HIV-uninfected men enrolled in CCTG 595 were selected 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

DISCOVER: Bone Safety



Which medication should I prescribe for daily PrEP?



*No data available for trans men. Sources: [fda.gov/media/129607/download](https://www.fda.gov/media/129607/download); [fda.gov/media/129609/download](https://www.fda.gov/media/129609/download); [cdc.gov/hiv/risk/estimates/preventionstrategies.html](https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html) Created by: @JuliaLMarcus

Case 3:

A kiss is a terrible thing to waste

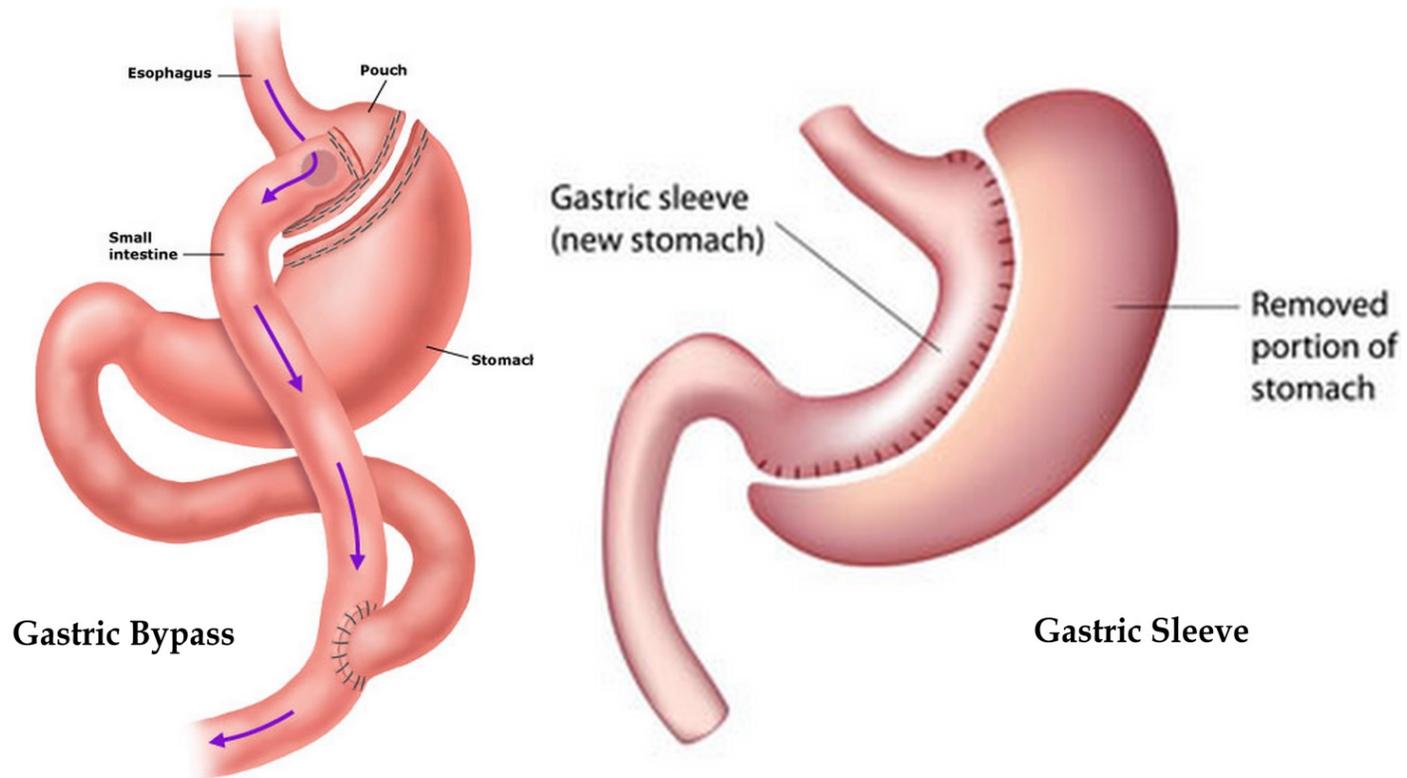
- 28-year-old cisgender woman is referred for PrEP
- She was diagnosed with obesity, hypertension and sleep apnea and underwent gastric bypass surgery 6 months ago
- Since the surgery, she insists on “eating clean” and takes several vitamin supplements daily, including Vitamin A, B3, B6, E, ginkgo biloba,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

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



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

Time	Patient	T_{max} (h)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC (h ng/mL)	Terminal half-life (h)	Clearance (L/h)
Pre-operative	Mean \pm SD	1.25	263 \pm 79	47 \pm 15	2346 \pm 643	13 \pm 3	112 \pm 37
	Patient #1	1	272	50	2364	17	104
	Patient #2	1	311	57	2528	12	97
	Patient #3	2	320	56	3017	14	81
	Patient #4	1	148	24	1476	10	166
1 month after SG	Mean \pm SD	1.5	162 \pm 44	34 \pm 13	1529 \pm 415	19 \pm 3	171 \pm 54
	Patient #1	2	158	48	1807	22	136
	Patient #2	1	225	41	1906	15	129
	Patient #3	2	142	22	1405	19	174
	Patient #4	1	124	23	997	19	246
3 months after SG	Mean \pm SD	1.5	252 \pm 93	40 \pm 10	2174 \pm 547	14 \pm 3	119 \pm 34
	Patient #1	1	150	30	1479	16	166
	Patient #2	1	340	49	2766	13	89
	Patient #3	1	322	32	2055	15	119
	Patient #4	3	197	48	2394	10	102
6 months after SG	Mean \pm SD	1.25	259 \pm 148	32 \pm 6	1597 \pm 355	15 \pm 4	161 \pm 45
	Patient #1	1	479	31	1870	16	131
	Patient #2	2	183	35	1776	12	138
	Patient #3	1	210	38	1661	21	148
	Patient #4	1	162	24	1079	12	227
12 months after SG	Mean \pm SD	1	325 \pm 43	47 \pm 17	2344 \pm 941	16 \pm 2	114 \pm 46
	Patient #1	1	294	35	1678	17	146
	Patient #2	1	355	59	3009	14	81

- 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.

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 deceline 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

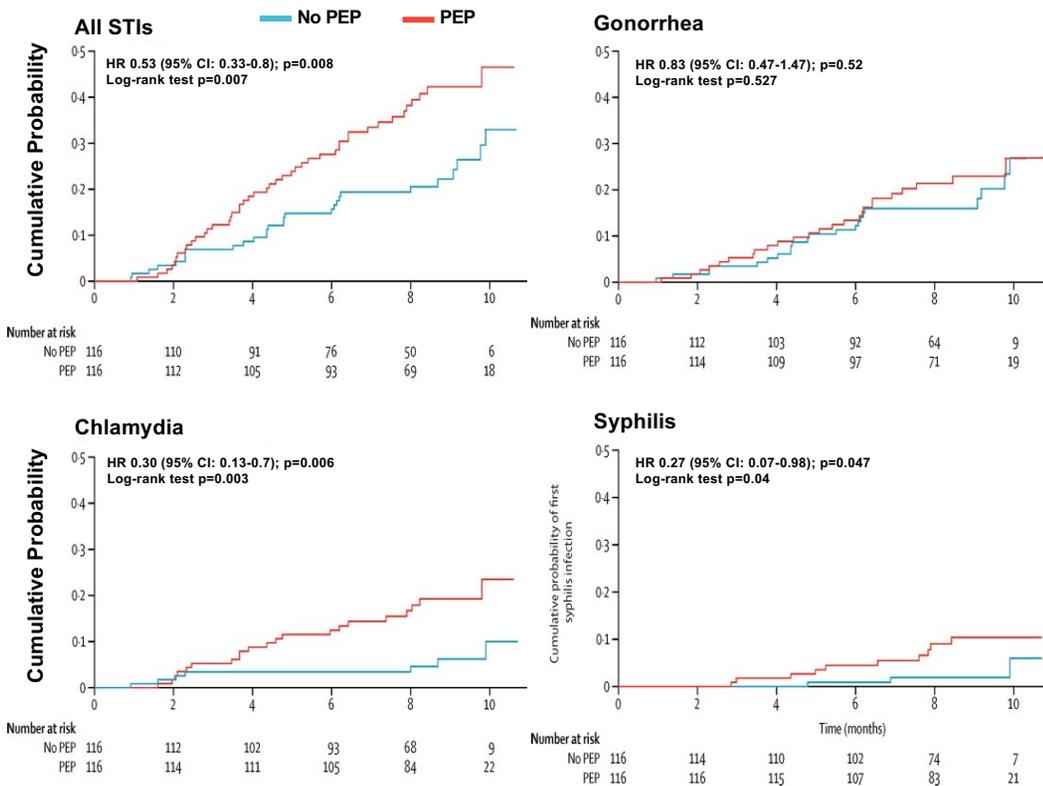


**You thought I was
joking**

I wasn't

**West Hollywood,
California
2012**

IPEGAY OLE: PEP with Doxycycline and STIs



- 232 ANRS IPEGAY 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*

In Vitro

Mean CFU/mL *Neisseria gonorrhoeae* (10^8 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
Neat	–	–	$>10^5$
1/2	$<10^2$	$<10^2$	–
1/4	$<10^2$	2×10^2	–
1/8	$>10^5$	$>10^5$	–
1/16	$>10^5$	$>10^5$	–
1/32	$>10^5$	$>10^5$	–

Results are mean of three replicates. Results are expressed as ' $<10^2$ ' rather than zero because only a 100th of the post exposure sample was taken for culture. CFU/mL, colony forming units per mL

- 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*.

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1/8	$>10^5$	$>10^5$	–
1/16	$>10^5$	$>10^5$	–
1/32	$>10^5$	$>10^5$	–

Results are mean of three replicates. Results are expressed as ' $<10^2$ ' rather than zero because only a 100th of the post exposure sample was taken for culture. CFU/mL, colony forming units per mL

Randomized Controlled Trial

	Listerine group (n=33)	Saline group (n=25)	p Value*
<i>Gonorrhoea positivity by culture after rinsing and gargling</i>			
Pharyngeal surface (posterior oropharynx and/or tonsillar fossae)			0.013
Positive	17 (52%)	21 (84%)	
Negative	16 (48%)	4 (16%)	
Tonsillar fossaet			0.016
Positive	13 (57%)	18 (90%)	
Negative	10 (43%)	2 (10%)	
Posterior oropharynx†			0.277
Positive	13 (57%)	14 (70%)	
Negative	10 (43%)	6 (30%)	

- 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)

- 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?

International Medical Case Reports Journal

 Open Access Full Text Article

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

This article was published in the following Dove Press journal:
International Medical Case Reports Journal
28 November 2013
[Number of times this article has been viewed](#)

Fredrick Owino¹
Justin Mandala²
Julie Ambia³
Kawango Agot¹
Lut Van Damme²

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Abstract: Side effects of antiretroviral drug use by HIV-positive patients have been extensively studied; however, there are limited data on the side effects of antiretroviral drugs used as an HIV prophylaxis among healthy, HIV-negative individuals. Here we report on an unusual neuropathy in a 24-year-old participant in the FEM-PrEP trial. This was a Phase III randomized, double blind, placebo-controlled trial to test the safety and effectiveness of tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) (TDF-FTC) to prevent HIV. At the eighth week of taking TDF-FTC with moderate adherence, the participant complained of mild paresthesiae, numbness, and a tingling sensation in her upper limbs that was associated with pain and cold. After an additional 4 days, she developed a disabling weakness of her upper limbs and tremors in her hands. The study product was discontinued, and within 2 weeks she was free of all symptoms. One month after restarting the drug, she complained of posture-dependent numbness of her upper limbs. Results of clinical and neurological exams, laboratory tests, and magnetic resonance imaging are described here.

Keywords: pre-exposure prophylaxis, toxic neuropathy, NRTI

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CASE REPORT

Case Report

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

Loraine Van Slyke, FNP-C¹, and Mia Scott, DO¹

Abstract

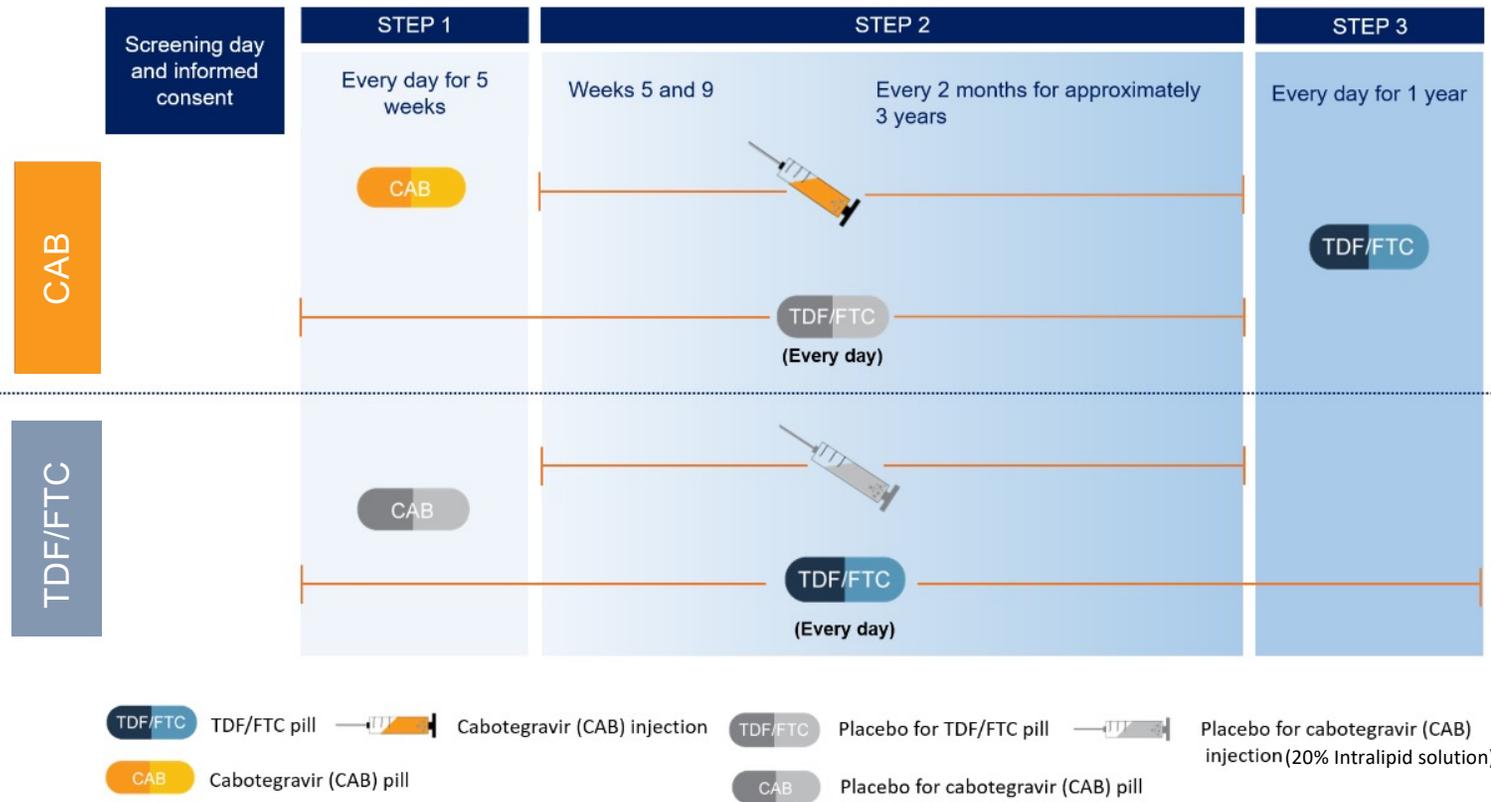
HIV pre-exposure prophylaxis (PrEP) with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) fixed-dose combination (FTC/TDF) is undergoing rapid scale-up in the United States. While FTC/TDF is typically well tolerated, to our knowledge, cranial nerve pathology associated with FTC/TDF has not been previously described. We report the case of a 35-year-old patient who began FTC/TDF PrEP and developed acute trigeminal neuralgia. The neurologic symptoms resolved after treatment discontinuation and recurred upon rechallenge, resulting in permanent discontinuation of PrEP treatment.

Keywords

neuralgia, tenofovir/emtricitabine, PrEP

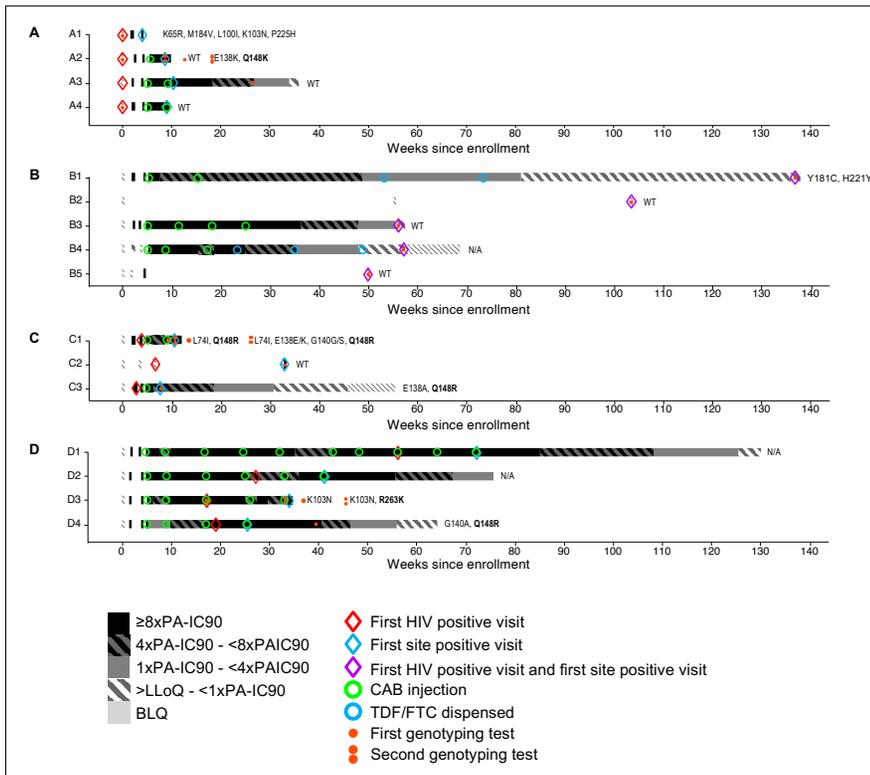
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HPTN 083 Study Design

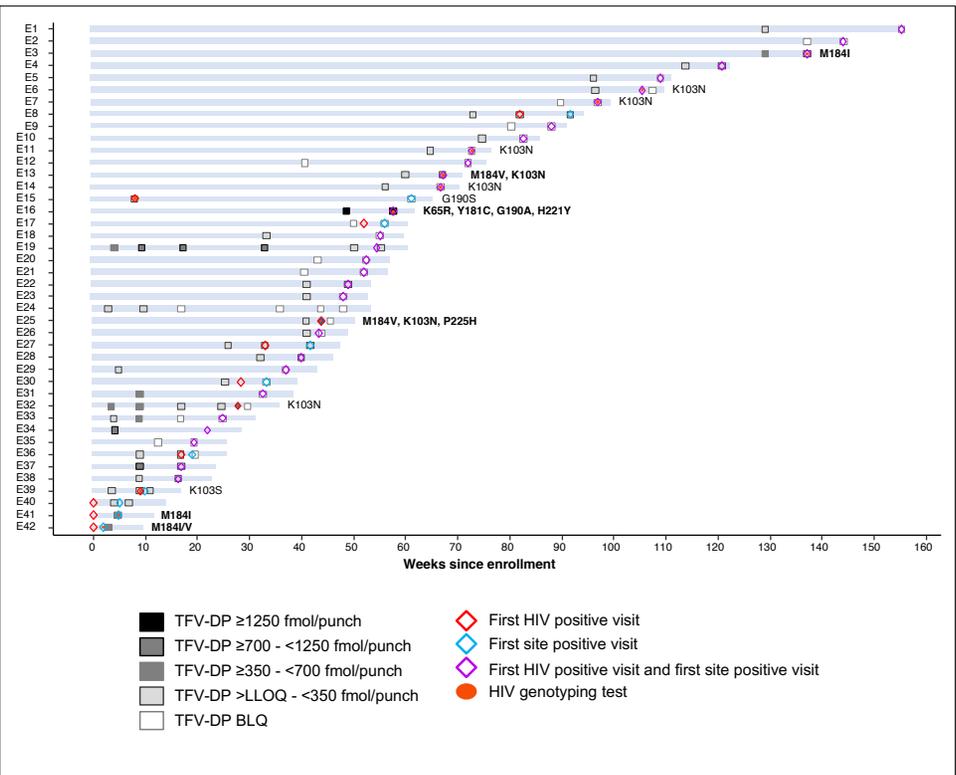




Pharmacology and Virology of HPTN 083 Seroconversion Events



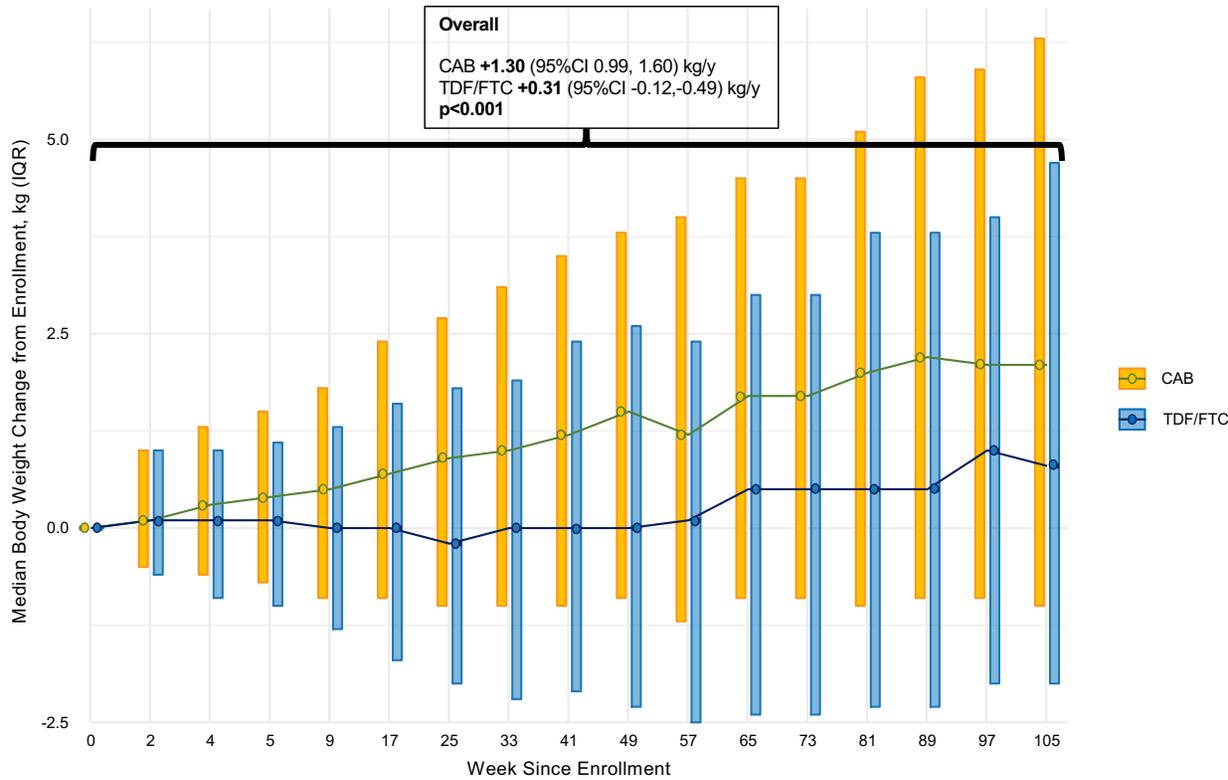
Slide 43 of 49 Landovitz RJ et al. NEJM 2021



Marzinke MA et al JID 2021

Changes in Weight

Median of changes from baseline (IQR)



Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus-uninfected Individuals in HPTN 077

Raphael J Landovitz ¹, Sahar Z Zangeneh ², Gordon Chau ², Beatriz Grinsztejn ³, Joseph J Eron ⁴, Halima Dawood ⁵, Manyá Magnus ⁶, Albert Y Liu ⁷, Ravindre Panchia ⁸, Mina C Hosseini ⁹, Ryan Kofron ¹, David A Margolis ¹⁰, Alex Rinehart ¹⁰, Adeola Adeyeye ¹¹, David Burns ¹¹, Marybeth McCauley ¹², Myron S Cohen ⁴, Judith S Currier ¹

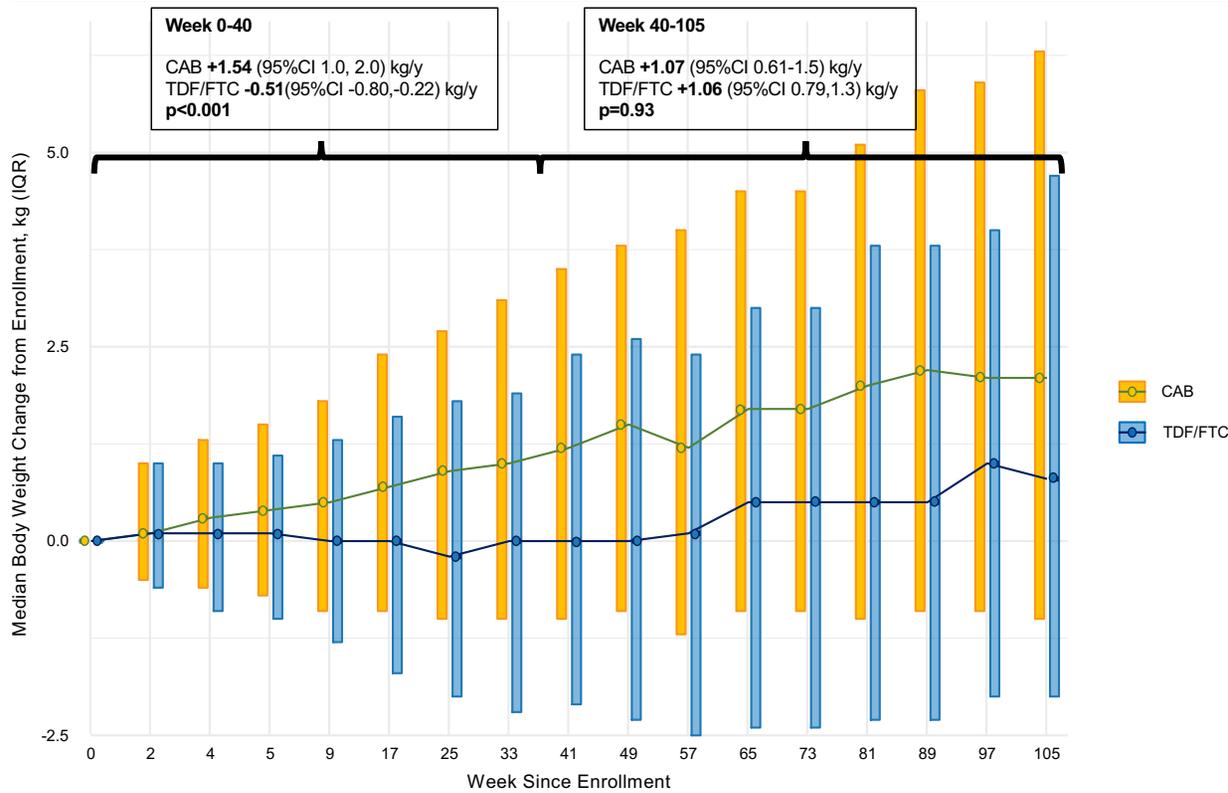
HPTN 077: Over 41 weeks

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.

Changes in Weight

Median of changes from baseline



Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus-uninfected Individuals in HPTN 077

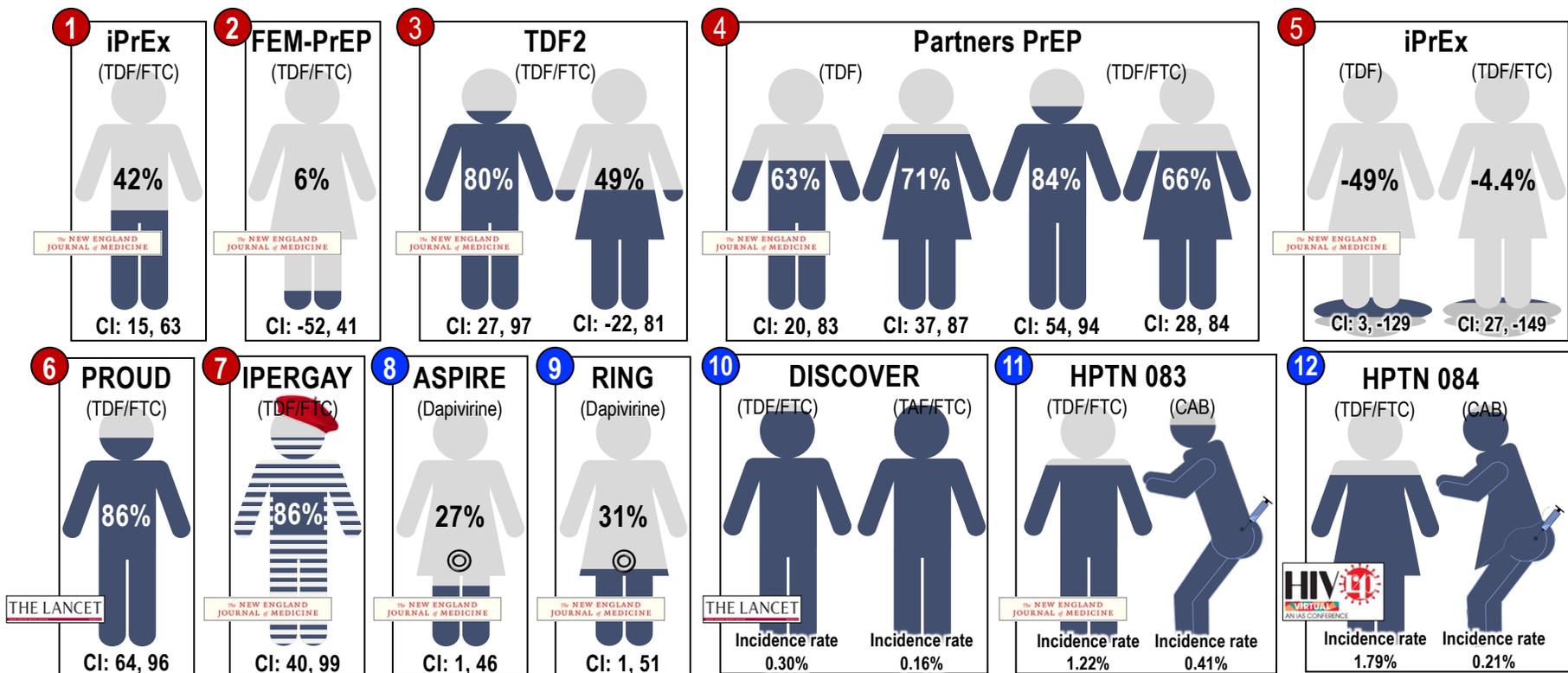
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Landovitz RJ et al. CID 2019.

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Thank you!

Suggested Further Reading

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Question-and-Answer Session

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