2020 Ryan White HIV/AIDS Program
CLINICAL CONFERENCE

The Data-Free Zone: Tough Cases in HIV Prevention

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Financial Relationships With Commercial Entities

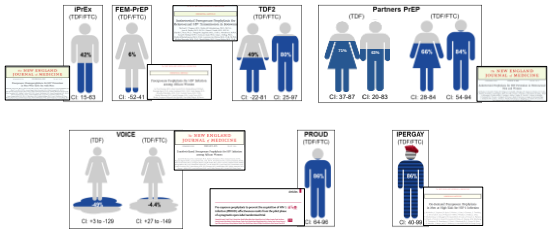
Dr Landovitz has served as a consultant to Gilead Sciences, Inc, Merck & Co, Inc, and Roche. (Updated 08/05/20)

Learning Objectives

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

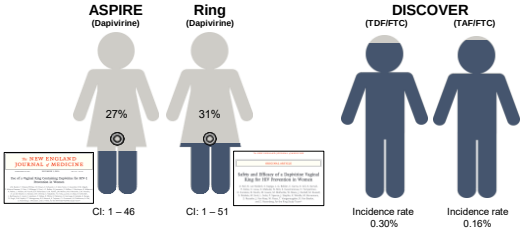
- Options for preexposure prophylaxis (PrEP) in patients with decreased kidney function and low bone mineral density
- The state of the science on sexually transmitted infection (STI) prevention strategies
- Recent data on the safety and efficacy on injectable PrEP options

Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials



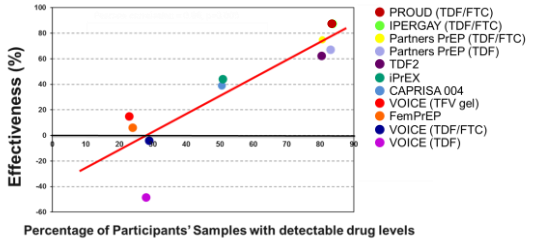
Landovitz RJ et al. AIDS 2020, #OAXLB0101

"PrEP 2.0": Trials of Novel PrEP Agents



Landovitz RJ et al. AIDS 2020, #OAXLB0101

Effectiveness of Daily TDF/FTC in Clinical Trials



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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

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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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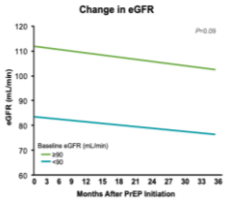
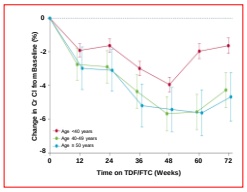
Impact of Long-Term PrEP Use and Renal Function

- 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 eGRF
- 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

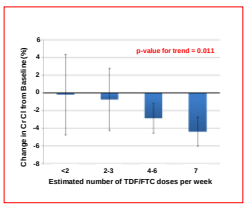
↑ Age, ↓ Baseline Cr Cl , and Adherence Associated with Declining Renal Function



- 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

↑ 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

CCTG 595: PrEP Associated with Fanconi Syndrome

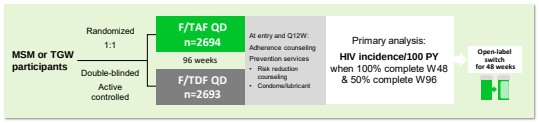
- 49-year-old white man, Hx kidney stones, HBV/HCV negative, no ongoing medical problems or medication use
- Mild renal impairment detected at baseline (Cr Cl: 79.9 mL/min).
- Initiated daily oral TDF/FTC-based PrEP
- 12 weeks after PrEP initiation
  - 25% decrease in Cr Cl,
  - Hypophosphatemia with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

Test	Screen	Week 4	Week 12		Week 16	Week 18	Week 21	Week 24
Estimated creatinine clearance*, 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.
*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

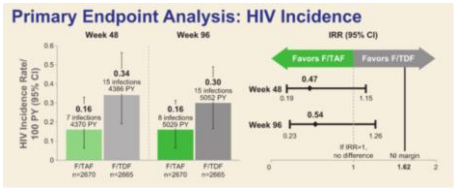
Study conducted in NA, EU in cities/sites with high HIV incidence
- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%

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

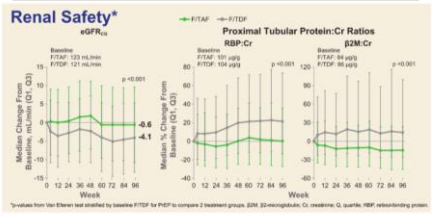
DISCOVER: HIV Incidence



CI, confidence interval; RR, rate ratio.

Ruane PJ. EACS 2019, Abstract PS3/1

DISCOVER: Renal Safety



- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1

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Ruane PJ. EACS 2019. Abstract PS3/1

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/1.73m²)	- 1.53	- 0.88	0.27	- 1.20
At least one eGFR <70mL/min/1,73m² - n	20	9	0.04[b]	45
At least one eGFR <60mL/min/1,73m² - 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.

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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.

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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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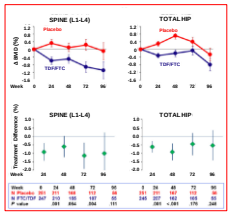
iPrEx: Bone Mineral Density Loss and Recovery

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

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

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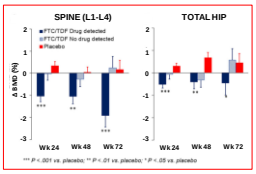
iPrEx: Bone Mineral Density Loss and Recovery

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

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

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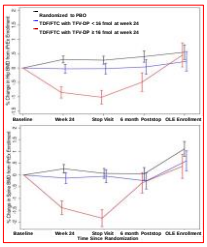
iPrEx: Bone Mineral Density Loss and Recovery

2.



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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)

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

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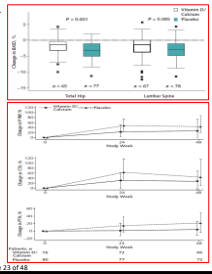
BMD Loss Attenuated by Vitamin D and Calcium

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

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

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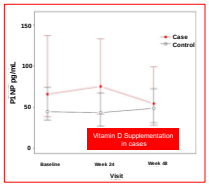
BMD Loss Attenuated by Vitamin D and Calcium

2.



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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

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

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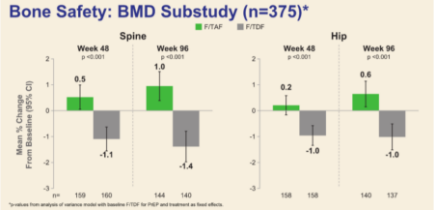
DISCOVER: Bone Safety



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Rsane PJ. EACS 2019. Abstract PS3/1

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

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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

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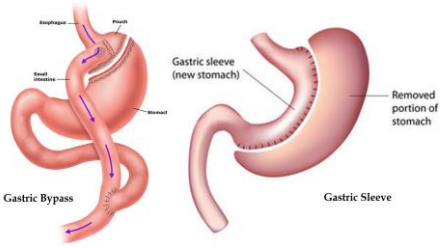
Gastric Bypass and Gastric Sleeve



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

Time	Patient	T_{max} (h)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC (h·ng/mL)	Terminal half-life (h)	Clearance (L/h)
Pre-operative	Mean ± SD	1.25	263 ± 79	47 ± 15	2346 ± 643	13 ± 3	112 ± 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 ± SD	1.5	162 ± 44	34 ± 13	1529 ± 415	19 ± 3	171 ± 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 ± SD	1.5	252 ± 93	40 ± 10	2174 ± 547	14 ± 3	119 ± 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 ± SD	1.25	259 ± 148	32 ± 6	1597 ± 355	15 ± 4	161 ± 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 ± SD	1	325 ± 43	47 ± 17	2344 ± 941	16 ± 2	114 ± 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-unfected individual after Sleeve-Gastrectomy.

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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 deceline in Cr Cl from 96 mL/min to 43 mL/min
  - Proteinuria 12g/24h
  - Hypophosphatemia, glycosuria

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

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)

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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

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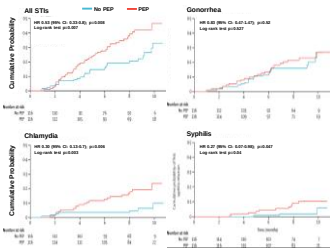
IPERGAY OLE: PEP with Doxycycline and STIs



- 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

Molina J et al., Lancet, 2017

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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

	CFU/mL		
Dilution	Listerine Total Care	Listerine Cool Mint	Saline
Neat	–	–	$>10^8$
1/2	$<10^2$	$<10^2$	–
1/4	$<10^2$	2×10^2	–
1/8	$>10^8$	$>10^8$	–
1/16	$>10^8$	$>10^8$	–
1/32	$>10^8$	$>10^8$	–

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

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

	CFU/mL		
Dilution	Listerine Total Care	Listerine Cool Mint	Saline
Neat	–	–	$>10^8$
1/2	$<10^2$	$<10^2$	–
1/4	$<10^2$	2×10^2	–
1/8	$>10^8$	$>10^8$	–
1/16	$>10^8$	$>10^8$	–
1/32	$>10^8$	$>10^8$	–

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 Control 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)			0.013
Positive	17 (52%)	21 (84%)	
Negative	16 (48%)	4 (16%)	
Tonsillar fossae†			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

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

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

- 19-year-old man with a history of bulemia 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

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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

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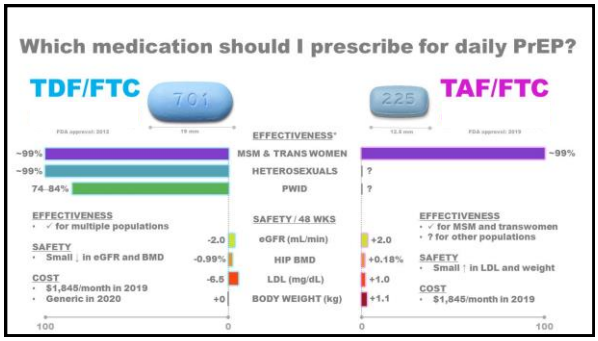

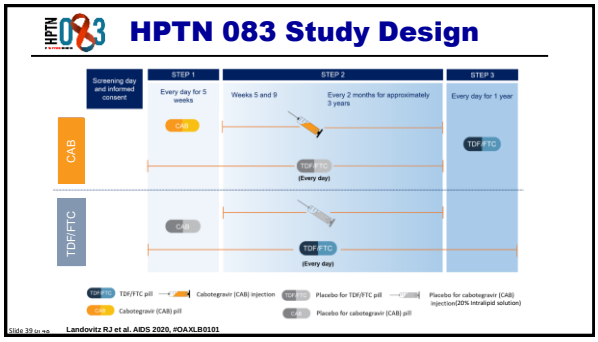

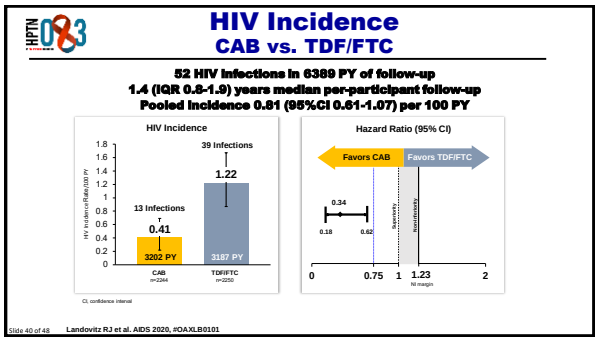
HPTN 083
HIV Incidence
CAB vs. TDF/FTC
52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY
HIV Incidence
39 Infections
1.22
13 Infections
0.41
3202 PY
3187 PY
CAB
TDF/FTC
Hazard Ratio (95% CI)
Favors CAB
Favors TDF/FTC
0.34
0.18
0.62
Superiority
Inconclusive
0
0.75
1
1.23
2
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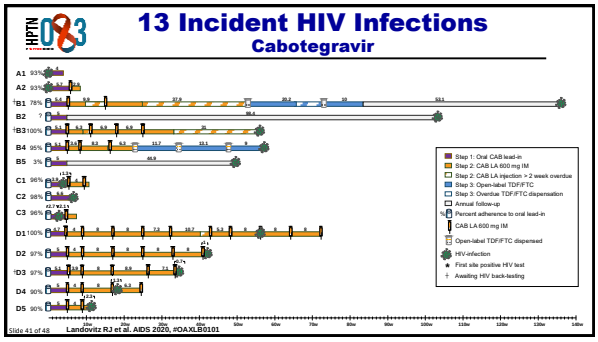
Landovitz RJ et al. AIDS 2020, #OAXLB0101


HPTN 083
13 Incident HIV Infections
Cabotegravir
Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 2: CAB LA injection > 2 week overdue
Step 3: Open-label TDF/FTC
Step 3: Overdue TDF/FTC dispensation
Annual follow-up
Percent adherence to oral lead-in
CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
First site positive HIV test
Awaiting HIV back-testing
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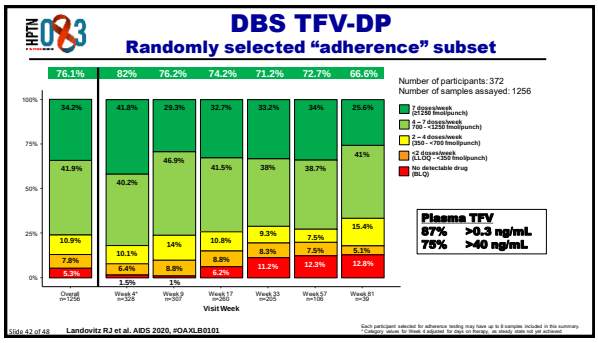
Landovitz RJ et al. AIDS 2020, #OAXLB0101


HPTN 083
DBS TFV-DP
Randomly selected "adherence" subset
76.1%
82%
76.2%
74.2%
71.2%
72.7%
66.6%
Number of participants: 372
Number of samples assayed: 1256
Plasma TFV
67% >0.3 ng/mL
75% >40 ng/mL
Visit Week
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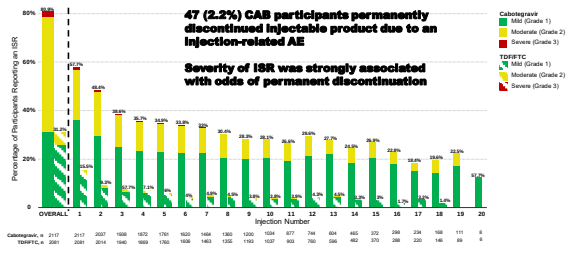
Landovitz RJ et al. AIDS 2020, #OAXLB0101

Injection Site Reactions



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Grade 2+ Adverse Events
Reported in ≥5%

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)	p-value
Participants with grade 2+ AEs, n (%)	4202 (92.1%)	2106 (92.3%)	2096 (91.9%)	
Creatinine clearance decreased	3204 (70.2%)	1642 (72.0%)	1562 (68.5%)	0.01
CPK increased	937 (20.5%)	460 (20.2%)	477 (20.9%)	0.52
Nasopharyngitis	828 (18.1%)	388 (17.0%)	440 (19.3%)	0.04
Creatinine increased	775 (17.0%)	412 (18.1%)	363 (15.9%)	0.06
Upper Respiratory Infection	510 (11.2%)	255 (11.2%)	255 (11.2%)	0.99
Musculoskeletal discomfort	507 (11.1%)	253 (11.1%)	254 (11.1%)	0.95
Lipase increased	495 (10.9%)	252 (11.0%)	243 (10.7%)	0.68
Headache	448 (9.8%)	216 (9.5%)	232 (10.2%)	0.42
AST/SGOT increased	382 (8.4%)	197 (8.6%)	185 (8.1%)	0.53
ALT/SGPT increased	347 (7.6%)	191 (8.4%)	156 (6.8%)	0.05
Blood glucose increased	323 (7.1%)	117 (5.1%)	206 (9.0%)	<0.001
Amylase increased	316 (6.9%)	166 (7.3%)	150 (6.6%)	0.36
Diarrhoea	306 (6.7%)	158 (6.9%)	148 (6.5%)	0.56
Rash	253 (5.5%)	139 (6.1%)	114 (5.0%)	0.11
Hypoglycaemia	241 (5.3%)	123 (5.4%)	118 (5.2%)	0.75
Pyrexia*	181 (4.0%)	60 (2.6%)	121 (5.4%)	<0.001

*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%)

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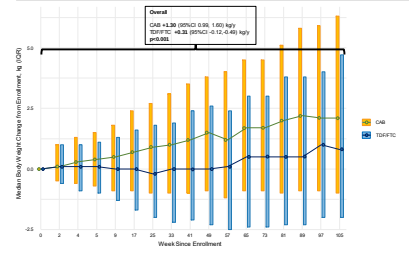
Changes in Weight
Median of changes from baseline (IQR)



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

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.

Landovitz RJ et al. AIDS 2020, #OAXLB0101

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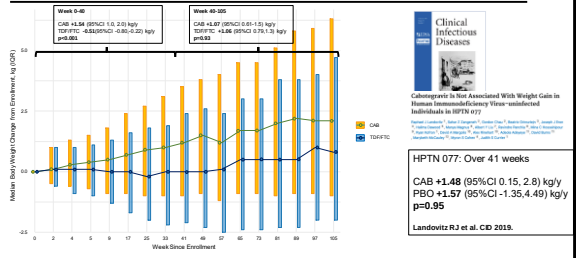
Changes in Weight
Median of changes from baseline



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Landovitz RJ et al. CID 2019.

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Thank you!

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Suggested Further Reading

Pilkington V et al.,
How safe is TDF/FTC as PrEP? A systematic review and meta-analysis of the risk of adverse events in 13 randomised trials of PrEP. Journal of Virus Eradication. 2018 Oct;4(4):215.

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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. 2019Mar 23(ja).

Mulligan K et al.,
Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. Clinical infectious diseases. 2015 Apr 23;61(4):572-80.

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Overton ET et al.,
Vitamin D and calcium attenuate bone loss with antiretroviral therapy initiation: a randomized trial. Annals of internal medicine. 2015 Jun 16;162(12):815-24.

Dominguez S et al.,
Efficacy and safety of tenofovir double-dose in treatment-experienced HIV-infected patients: The tenoplus study. Journal of medical virology. 2007 Feb;79(2):105-10.

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2020 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Question-and-Answer Session

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