

Challenges and Opportunities for Preexposure Prophylaxis

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Financial Relationships With Ineligible Companies*

Dr Buchbinder has no relevant financial relationships with ineligible companies to declare. (Updated 04/28/2021)

Slide 2 of 39

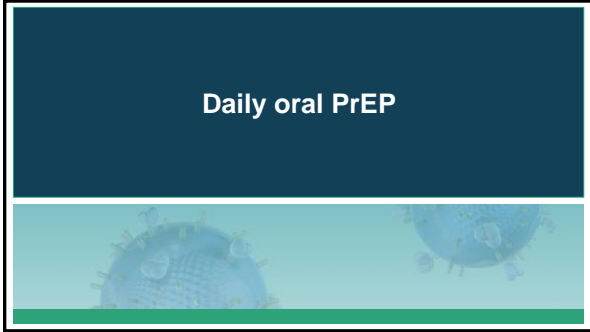
*The ACCME recently updated the term from commercial interests to ineligible companies.

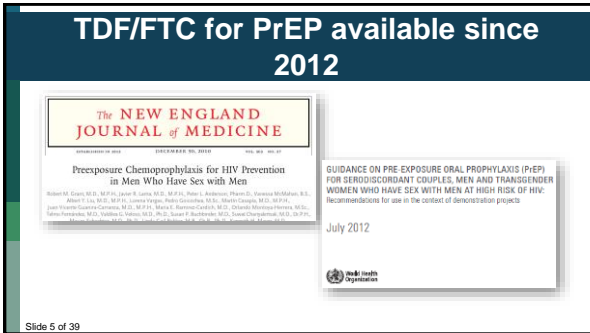
Learning Objectives

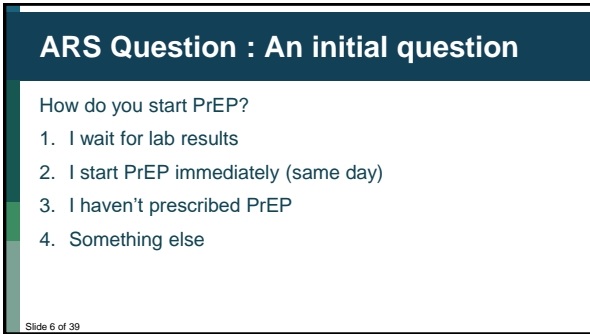
After attending this presentation, learners will be able to:

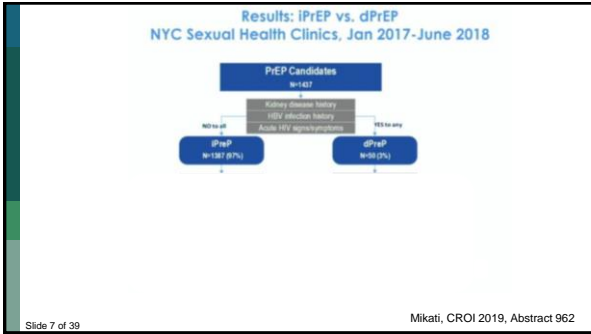
- Safely start and stop preexposure prophylaxis (PrEP)
- Counsel patients about 2-1-1 PrEP
- Describe new PrEP modalities

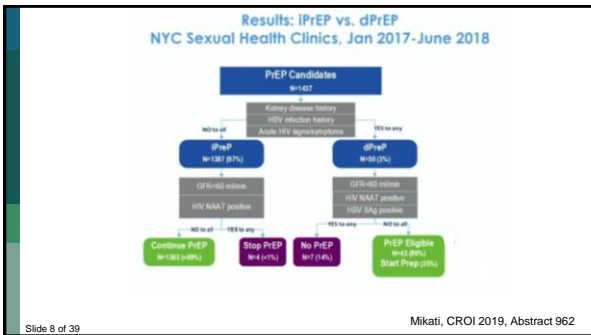
Slide 3 of 39

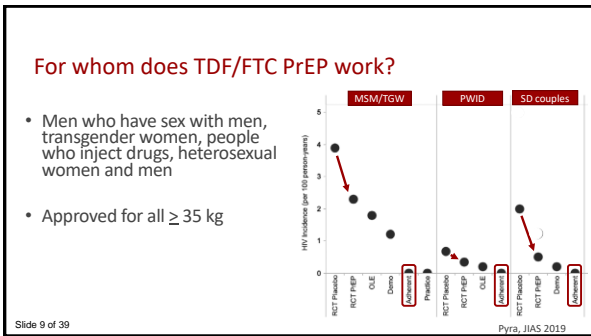


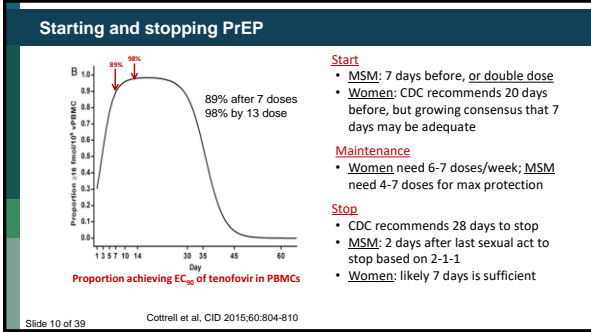


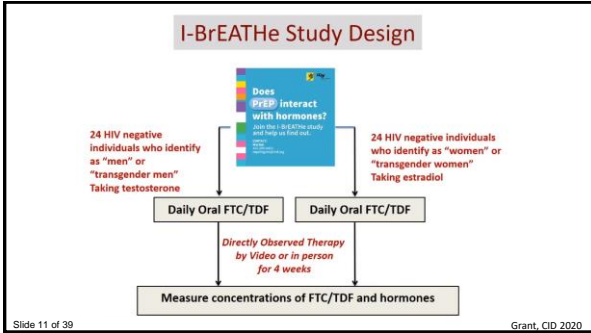


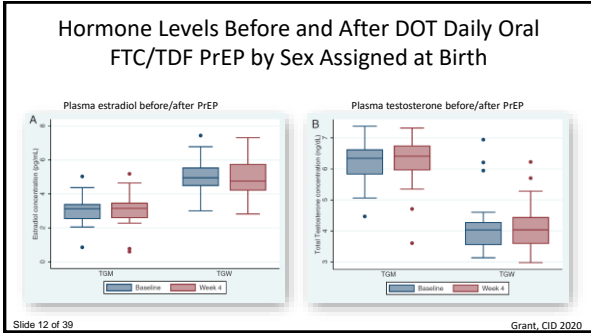




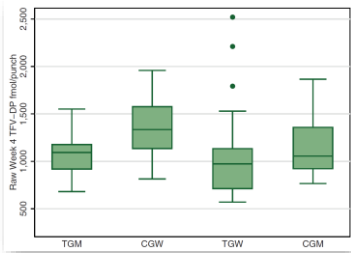








TFV-DP Concentrations in DBS after 4 Weeks of Directly Observed Daily Dosing



Slide 13 of 39

Grant, CID 2020

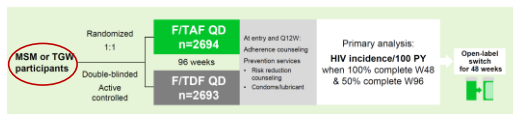
Modest renal effects in older persons and those with low baseline GFR

- Studies in multiple populations suggest risk for eGFR < 70 ml/min if:
 - Baseline eGFR < 90
 - > 40-50 years old
 - Weight < 55 kg
 - Higher adherence
- But:
 - Creatinine bump often unconfirmed on repeat testing
 - Creatinine reverts to near baseline after trial
 - Re-challenge has been used successfully

Slide 14 of 39

Marcus JAIDS 2016; Mugwanya JAIDS 2016; Martin CID 2014

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

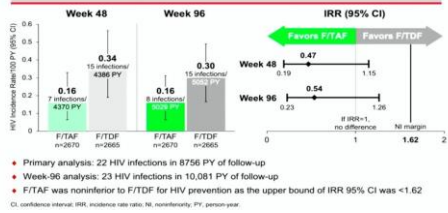


Demographics		F/TAF n=2694	F/TDF n=2693
Median age, y (range)		34 (18-76)	34 (18-72)
Race, n (%)			
White		2264 (84)	2247 (84)
Black*		240 (9)	234 (9)
Asian		113 (4)	120 (5)
Hispanic or Latinx ethnicity, n (%)		635 (24)	683 (25)
Proportion TGW, n (%)		45 (2)	28 (1)

Slide 15 of 39

DISCOVER Trial: HIV incidence

Primary Endpoint Analysis: HIV Incidence



Slide 16 of 39

Ogbuagu, Abstract 92, CROI 2020

DISCOVER: Differences in safety at 96 weeks

Favors F/TAF

- **Bone mineral density:** 1-2% difference in BMD at spine and hip; no difference in fractures
- **Renal function:** 4 ml/min difference in eGFR at 96 weeks

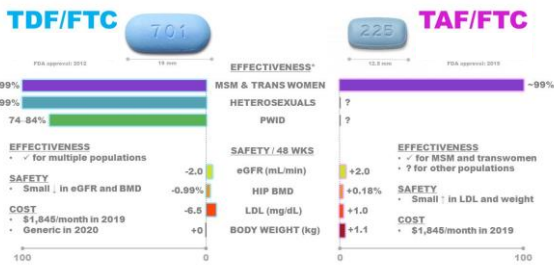
Favors F/TDF

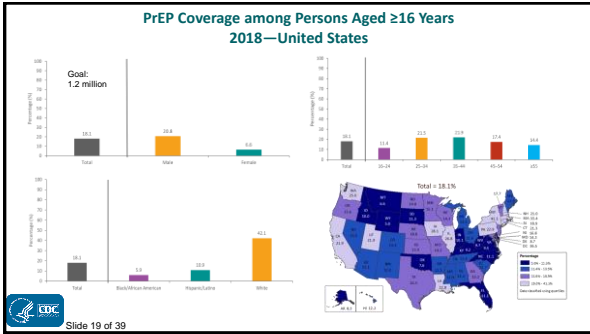
- **Lipids:** 11 mg/dl lower total cholesterol; no difference in TC: HDL
- **Body weight:** 1 kg difference in body weight

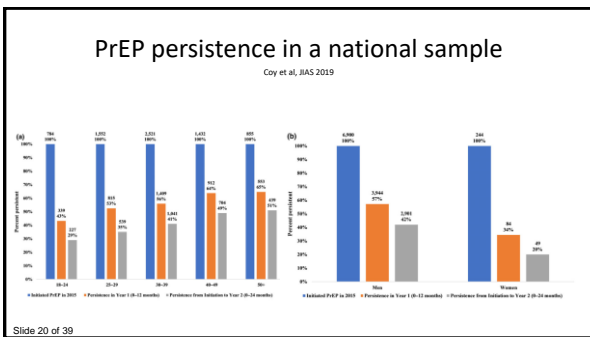
Ogbuagu, Abstract 92, CROI 2020

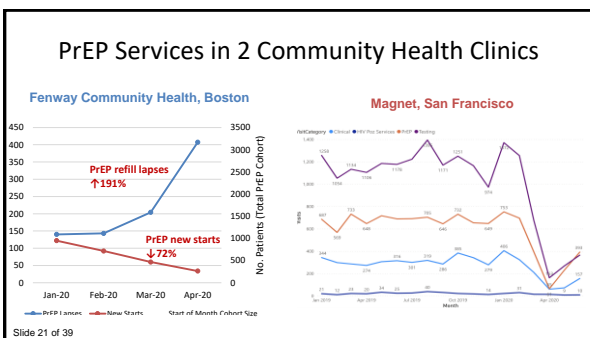
Slide 17 of 39

Which medication should I prescribe for daily PrEP?









Top reasons why people who may benefit from PrEP don't take or stop PrEP

Consistent problem	Problem alleviated by different PrEP modality
Sexual risk	
Access	
Concerns about medication	
Stigma	
Life events	

Whitefield AIDS and Behavior 2018; Morgan AIDS and Behavior 2018; Chan JIAS 2016; Holloway JAIDS 2017; Zucker JAIDS 2019; Brooks AIDS and Behavior 2019; Dubov AMH 2018; Linkowski AIDS and Behavior 2018; Hevey AIDS Education and Prevention 2018; Arnold PLOS One 2017; Krakower JIAS 2019; Laborde AIDS and Behavior 2020.

Slide 22 of 39

Top reasons why people who may benefit from PrEP don't take or stop PrEP

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Slide 23 of 39

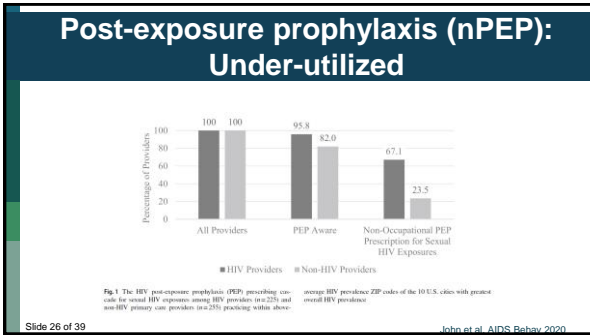
Top reasons why people who may benefit from PrEP don't take or stop PrEP

Consistent problem	Problem alleviated by different PrEP modality
Sexual risk	
Low self-perceived risk	Infrequent sexual contact
Access	
Lack of providers	Difficulty adhering to visit/lab schedule
Cost, insurance coverage	
Concerns about medication	
Medical mistrust	Specific side effects
	Don't want to take a daily pill
Stigma	
Concern about being labeled "high risk"	Privacy
Life events	

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Slide 24 of 39





- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake

"2-1-1"

ipergay **ipergay : Event-Driven iPrEP**

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake

“2-1-1-1-1....”

- ✓ Daily pills until 48 hours after last sex
- ✓ If last pill within 7 days, take single pill to start

Slide 28 of 39

ipergay Results

HIV Incidence (mITT Analysis)

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
Placebo (double-blind)	212	6.60 (3.60-11.1)
TDF/FTC (double-blind)	219	0.91 (0.11-3.30)
TDF/FTC (open-label)	515	0.19 (0.01-1.08)

Median Follow-up in Open-Label Phase 18.4 months

86% efficacy in RCT

97% relative reduction vs. Placebo in OLE

Slide 29 of 39

Molina et al. Lancet HIV 2017;4:e402-10

Considerations of 2-1-1 vs Daily PrEP

	2-1-1 PrEP	Daily PrEP
Who can use it?	Only studied in MSM	Anyone
What can be used?	TDF/FTC only	TDF/FTC or TAF/FTC
Chronic HBV	Can trigger a flair	Can be safety used
Planning	Need to plan sex at least 2 hrs in advance	No planning needed
"Forgiveness"	Not forgiving of missed doses	Forgiving of missed doses during the week

Slide 30 of 39

World Health Organization

TECHNICAL BRIEF

WHAT'S THE 2+1+1?

EVENT-DRIVEN ORAL PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV FOR MEN WHO HAVE SEX WITH MEN: UPDATE TO WHO'S RECOMMENDATION ON ORAL PREP

JULY 2019

Slide 31 of 39

Rectal douche can achieve high tissue concentrations and are highly protective in animal studies

DREAM Program: Tenofovir Douche

Human PK: Colon Cell TFV-DP

MIMC TFV-DP fmol/10⁶ cells

DREAM-03

Daily Oral: 2/1wk, 4/1wk, 2/1wk

15h 24h 15h 24h 15h 24h

Douche A Douche B Douche C

Macaque PD: SHIV Challenge

Daily Oral PrEP / Enema 1 hr Exp

Percent uninfected

Number of challenges

P = 0.004

Douche C

Oral TDF/FTC

Oral TDF

Douche B

Vehicle control

R4P: OA20.03 Weld; P29.13LB Villinger; P24.20 Hoang

Slide 32 of 39

Long-acting PrEP

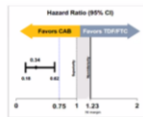
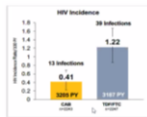
Two Efficacy Trials of CAB-LA for PrEP

- Cabotegravir: INSTI (analog of dolutegravir)
 - Long-acting injectable $t_{1/2}$: 21-50 days
- HPTN 083** for MSM/TGW globally
- HPTN 084** for women in sub-Saharan Africa
- Both had 3 steps:
 - Oral lead-in
 - IM loading at 0 and 4 weeks, q 8 week injections
 - Oral to cover the PK tail for 1 year
- Both trials were double-blind, double-dummy with TDF/FTC as comparator group



Slide 34 of 39

Efficacy Results



Risk reduction: 66%



	CAB	TDF/FTC
Infections	4	36
Person-years	1,953	1,939
Incidence	0.2 (0.06-0.52)	1.86 (1.3-2.57)

Risk reduction: 89%

Slide 35 of 39

Remaining Questions

- How best to diagnose infections on CAB-LA?
 - Delays in diagnosis because of delayed seroconversion; open label extension study will use VL testing for diagnostics
- Why did breakthrough infections with CAB-LA occur?
 - In HPTN 083: Of 16 breakthroughs, 4 were infected at baseline, 5 during hiatus from CAB, 3 during oral lead-in, 4 with on-time injections of CAB-LA
- How common will INSTI resistance be?
 - 5/16 (31%) had INSTI resistance, but responded to non-INSTI treatment
 - Did not see INSTI resistance in tail, but more data needed
- Can we use "direct-to-inject" without oral lead in?
- How will we administer q2 month injections in streamlined way?

Slide 36 of 39

Long-acting investigational drugs - 2

Islatravir

- NRTTI
- Being evaluated as a monthly pill for MSM, transgender persons, cisgender women
- Will be evaluated as a yearly implant, possible with contraception

Lenacapavir

- Capsid inhibitor
- Being evaluated as a semi-annual subcutaneous injection for MSM, transgender persons, cisgender women
- Studies will also evaluate TAF/FTC as daily pill for cisgender women

Slide 37 of 39

Long-acting investigational drugs - 3

Dapivirine vaginal rings

- NNRTI
- Found to have approximately 30% efficacy in RCTs, approximately 50% efficacy in open-label extension studies
- Recently approved by EMA and WHO
- Next generation products will include new agents, combinations with contraception, less frequent replacement

Slide 38 of 39

Conclusions

- We already have highly effective PrEP and PEP options, with more under development
 - CAB-LA IM is latest product, but robust pipeline of monthly pills, semi-annual SQ injections, annual implants, possibly vaginal rings
- Challenges with uptake and persistence in all populations, but particularly for youth, people of color, women, PWID
 - Long-acting agents will solve some, but not all of the problems associated with daily pills
- Need to offer choice and provide support tools to keep people on PrEP during periods of risk

Slide 39 of 39