Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School

PrEP: Update and Controversies

Douglas Krakower, MD

HOPE Conference Series

November 12, 2019

Potential Competing Interests

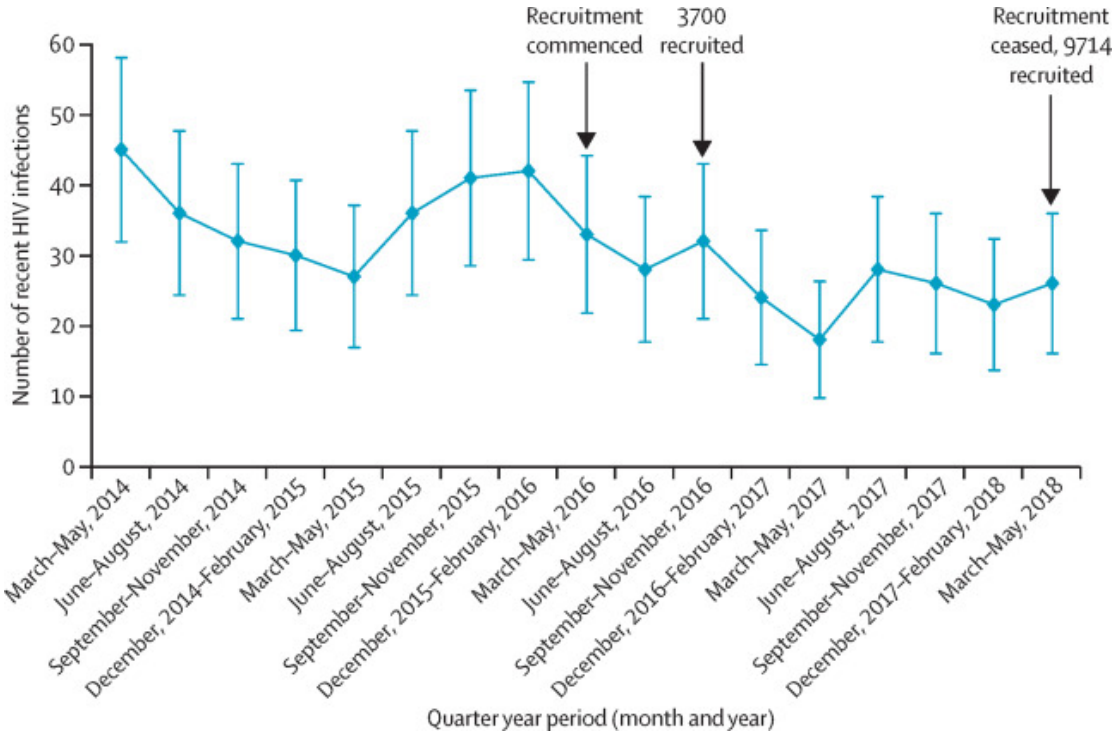
- Dr. Krakower: investigator-initiated research regarding HIV prevention
  - National Institutes of Health
  - Harvard Center for AIDS Research P30 AI060354
  - Consultant to Fenway Health on research funded by grant from Gilead Sciences
- CME content for Medscape, MED-IQ, DKBmed, UptoDate, Inc.

Has PrEP been shown to have a population-level impact on HIV incidence?

1. Not yet, hopefully in the future
2. Modest impact in some settings
3. Major impact in some settings

Community roll-out of PrEP for MSM is associated with population-level decrease in HIV incidence

- EPIC-NSW, Australia (3700 MSM)
- 4100 person-years of PrEP use
  - 2 new infections
  - Both non-adherent
- HIV diagnoses in MSM in NSW
  - 295 in 12m before roll-out
  - 221 in 12m after
  - Relative risk reduction 25%
- 20% coverage of MSM in NSW



Grulich Lancet HIV 2018

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Persons at high risk of HIV acquisition	The USPSTF recommends that clinicians offer preexposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high risk of HIV acquisition.	A

USPSTF, *JAMA* 2019

33y cisgender MSM has had 12 partners, rectal GC in the past 12m. Wants PrEP. No renal disease, hep B, symptoms. You order HIV Ab/Ag, hep B/C serologies, Cr. What next?

1. Schedule visit in 1 month to review labs. If all wnl, prescribe PrEP
2. Schedule visit in 1 week to review labs. If all wnl, prescribe PrEP
3. Plan to call him back when labs return. If all wnl, prescribe PrEP
4. Start PrEP now (and call to d/c if labs abnormal)
5. Other

Figure 1. Follow-Up PrEP Care Cascade After Same-Day Initiation

Denver STI clinic

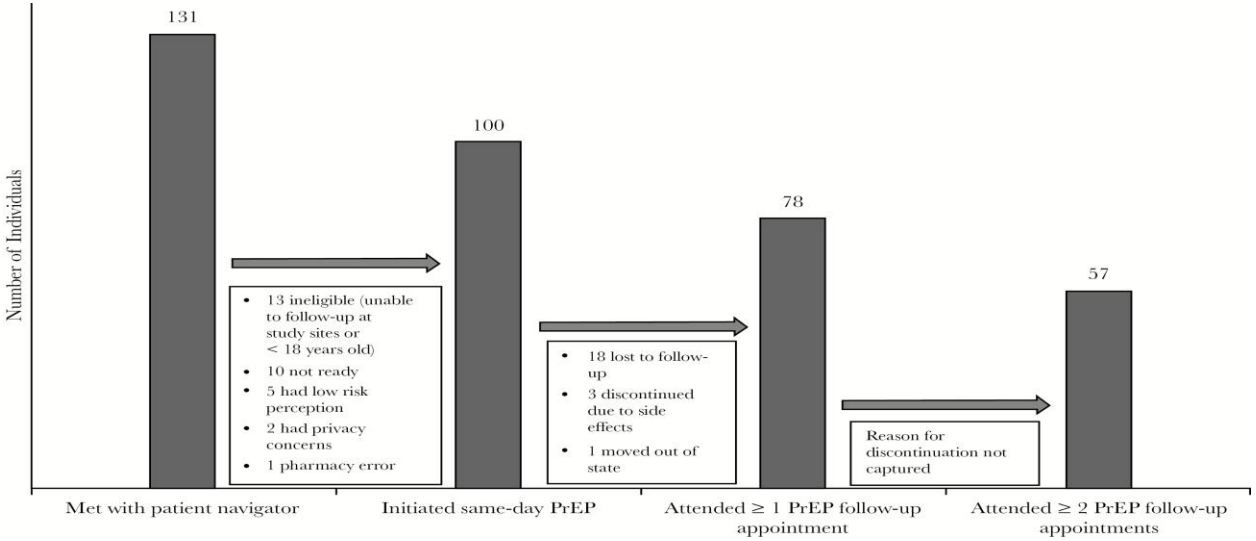
N=100 attendees

Testing: SCr, HbsAg, uHCG, point-of-care HIV antigen/antibody test

Assessed for history of HBV or renal disease

30d starter pack, PrEP navigation to community clinic

57% attended ≥2 clinic visits



Open Forum Infectious Diseases, Volume 6, Issue 7, July 2019, ofz310, https://doi.org/10.1093/ofid/ofz310

Do you check HCV Ab prior to PrEP initiation?

1. Not routinely
2. Only in people who inject drugs
3. Only in MSM
4. Only in MSM or people who inject drugs
5. All people

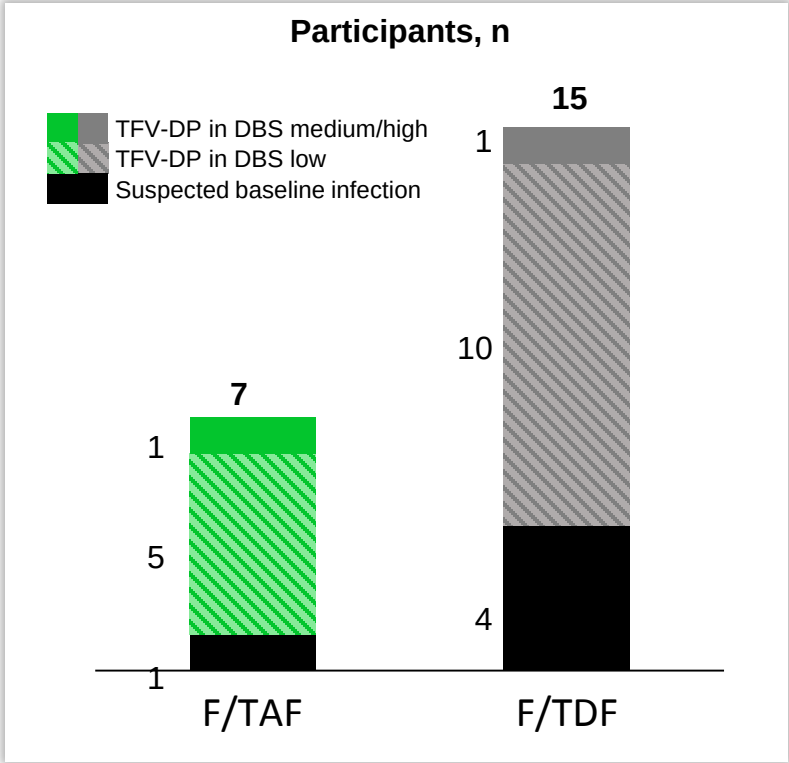
USPHS/CDC Guidelines on Prescribing PrEP: Updates 2018

- Baseline HCV Ab for PWID, MSM, and probably everybody
- STI screen q3 mo. for MSM at risk for recurrent bacterial STI
- No need to delay PEP to PrEP transition

52y cisgender MSM with 3 partners in past 12m. He has DM2, HTN, OA with NSAID use. Baseline CrCl 65 mL/min. Wants PrEP. What do you recommend?

1. No PrEP due to risk of renal harms
2. TDF/FTC daily
3. TAF/FTC daily
4. TDF/FTC event-driven (i.e. only before and after sex)
5. Other

DISCOVER Adherence and Resistance Analyses of HIV Infections



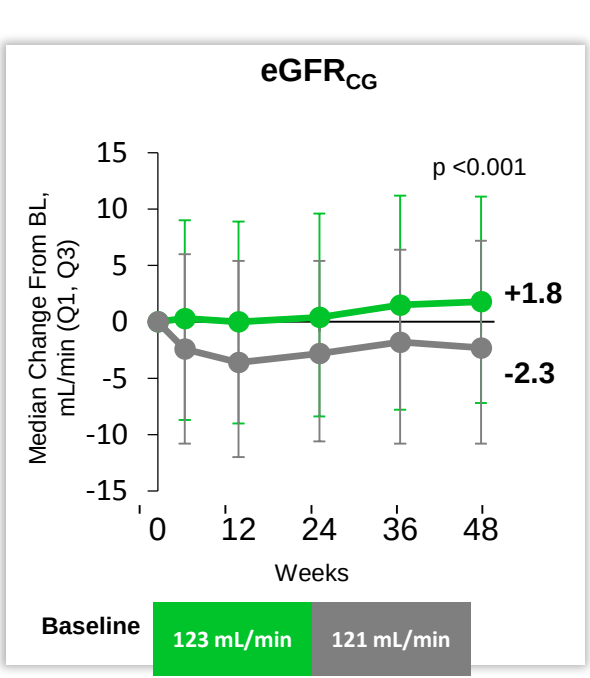
- 7 F/TAF infections: 1 suspected baseline infection, 5 low levels of TFV-DP in DBS,1 medium level
- 15 F/TDF infections: 4 suspected baseline infections, 10 low levels of TFV-DP in DBS, 1 high level
- In a sensitivity analysis that excluded suspected baseline infections, noninferiority was maintained (0.55 [0.20, 1.48])

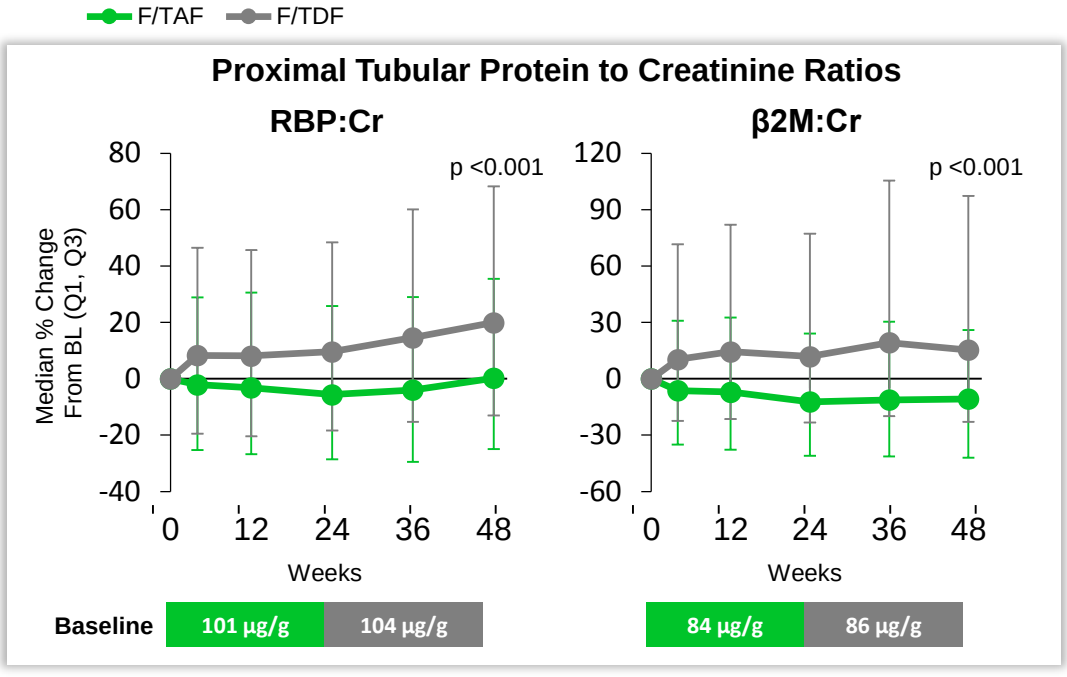
n	F/TAF n=7	F/TDF n=15
Resistance genotyped*	6	13
Resistance to study drugs		
FTC	0	4†
TFV	0	0

*3 samples could not be amplified; †All 4 participants with resistance were suspected baseline infections.

Renal Safety Through Week 48

Secondary Endpoint



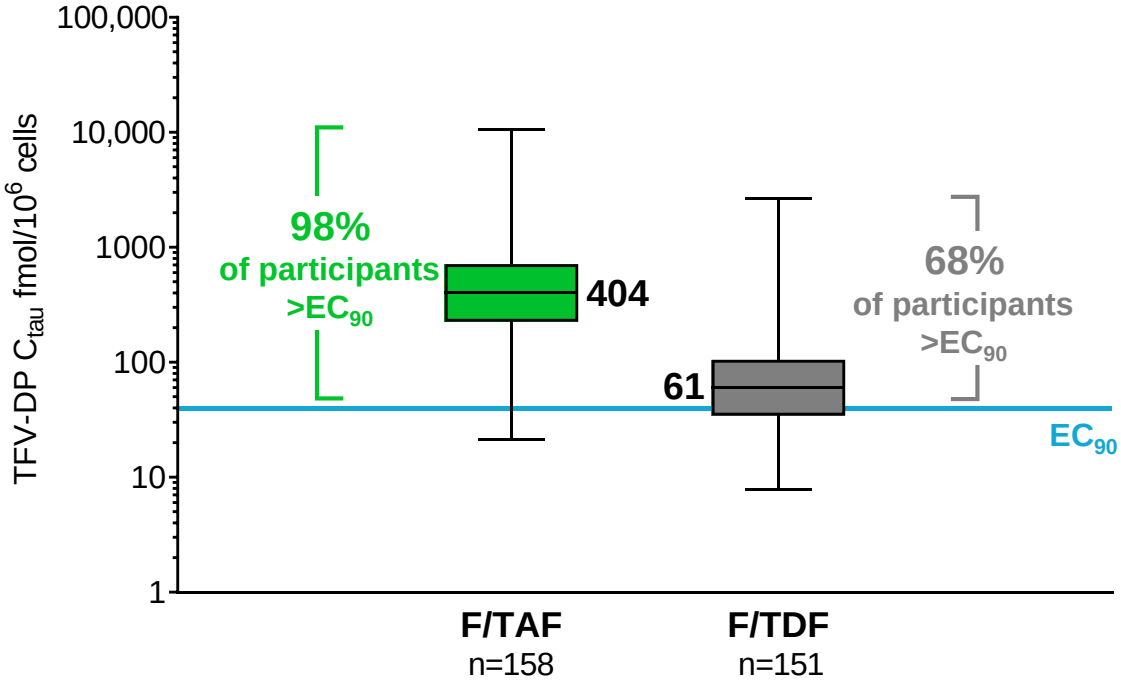


- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1

β2M, β2-microglobulin; Cr, creatinine; eGFR$_{CG}$, eGFR by Cockcroft Gault; Q, quartile; RBP, retinol-binding protein.
p-values were from the Van Elteren test stratified by baseline F/TDF for PrEP to compare the 2 treatment groups.

DISCOVER: F/TAF Has Higher PBMC TFV-DP Levels vs F/TDF

Week 4, n=324

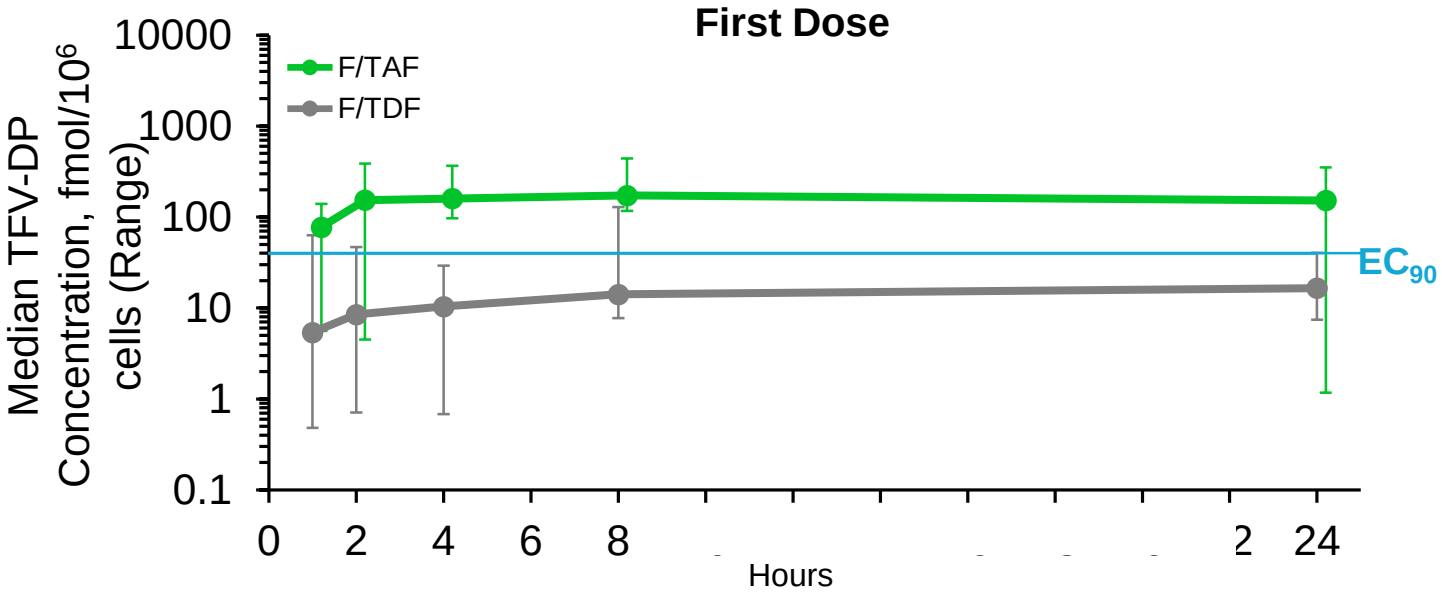


- Steady-state TFV-DP levels in PBMCs were 6.3-fold higher with F/TAF vs F/TDF

C_{tau}, concentration 20–28 h postdose. Box median, IQR, whiskers min, max

F/TAF Achieves EC90 More Rapidly than F/TDF

Phase 1 Study in Healthy Volunteers



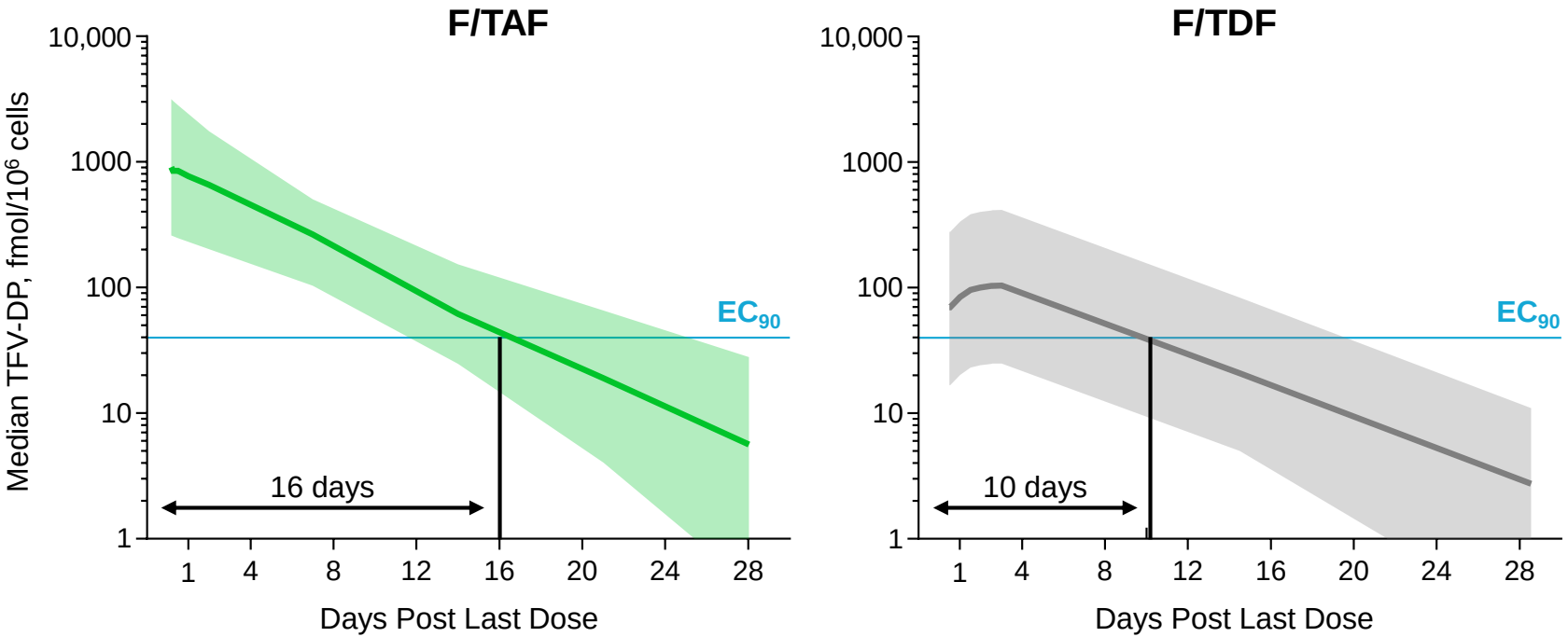
- With F/TAF, median TFV-DP concentrations exceeded EC_{90} within 1-2 h, all within 4 h, consistent with 2 prior studies[1-3]
- In contrast, 3 daily doses of F/TDF are needed to achieve EC_{90} in PBMCs[4]

EC_{90}, 90% effective concentration.

1. Schwartz JL, et al. R4P 2018.; 2. data on file; 3. Cottrell ML, et al. J Antimicrob Chemother 2017; 4. Anderson PL, et al. CROI 2012

F/TAF has a Longer Duration > EC_{90} After Last Dose

Simulation Based on Observed TFV-DP at Steady State



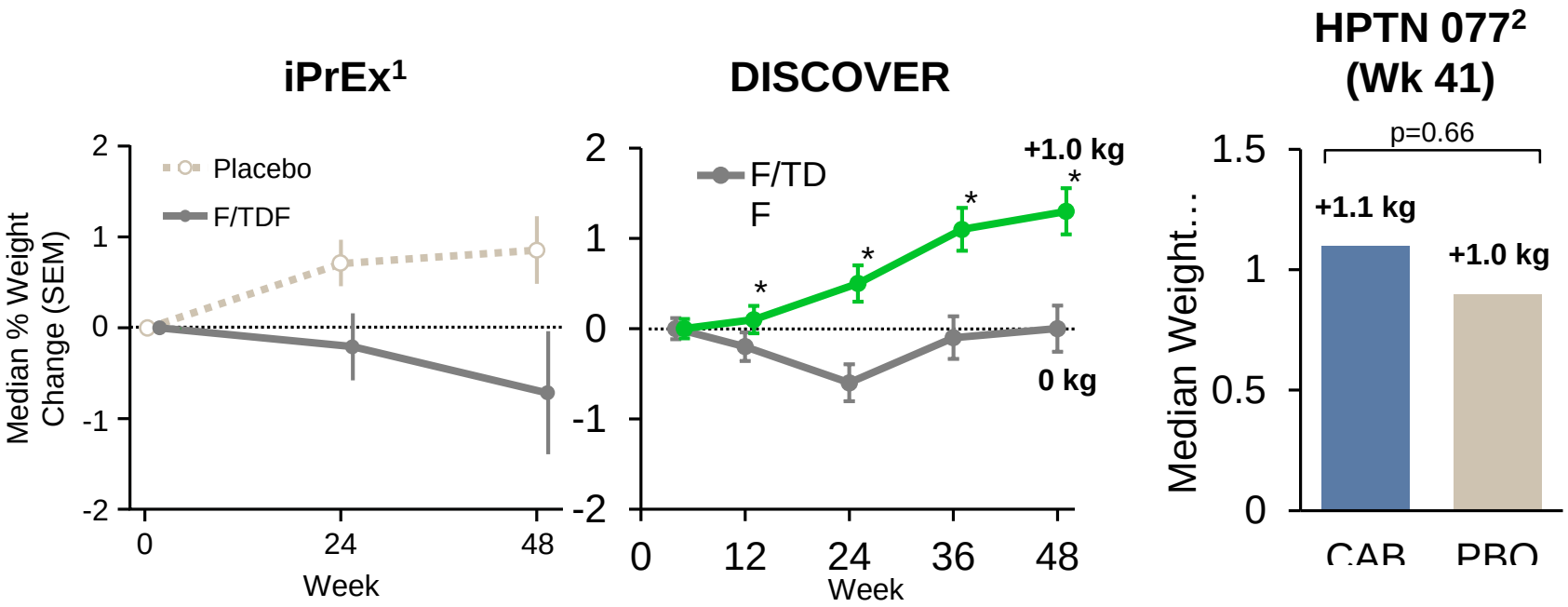
- At steady state, after the last dose, F/TAF would provide TFV-DP levels in PBMCs above EC_{90} for 16 days compared to 10 days with F/TDF

Shading represents 5th–95th percentiles. 1. Anderson PL, et al. CROI 2012; 2. Custodio J, et al. EACS 2017; 3. Custodio J, et al. ASM 2016; 4. Hawkins J Acquir Immune Defic Syndr 2005;39:406-11.

Conclusions: F/TAF Has a More Rapid Onset and Longer Sustained Duration of Protection than F/TDF

- Noninferiority of F/TAF to F/TDF was established by the lower HIV incidence of F/TAF compared with F/TDF
  - Risk behavior, STIs, and Adherence were similar between arms
- HIV prevention efficacy PK parameters differed between F/TAF vs F/TDF:
  - TFV-DP levels in PBMCS were 6.3 fold higher with F/TAF vs F/TDF
  - 98% in the F/TAF arm are above EC_{90} compared with 68% in F/TDF arm
  - F/TAF achieved EC_{90} within 1–2 hrs of first dose vs 3 days of daily doses of F/TDF
  - F/TAF expected to remain above EC_{90} for 16 days vs 10 days for F/TDF
- The more rapid onset and longer duration of protection may be the most probable explanation for the higher prevention efficacy of F/TAF
- F/TAF is a safer, potentially more efficacious option than F/TDF for prevention of HIV

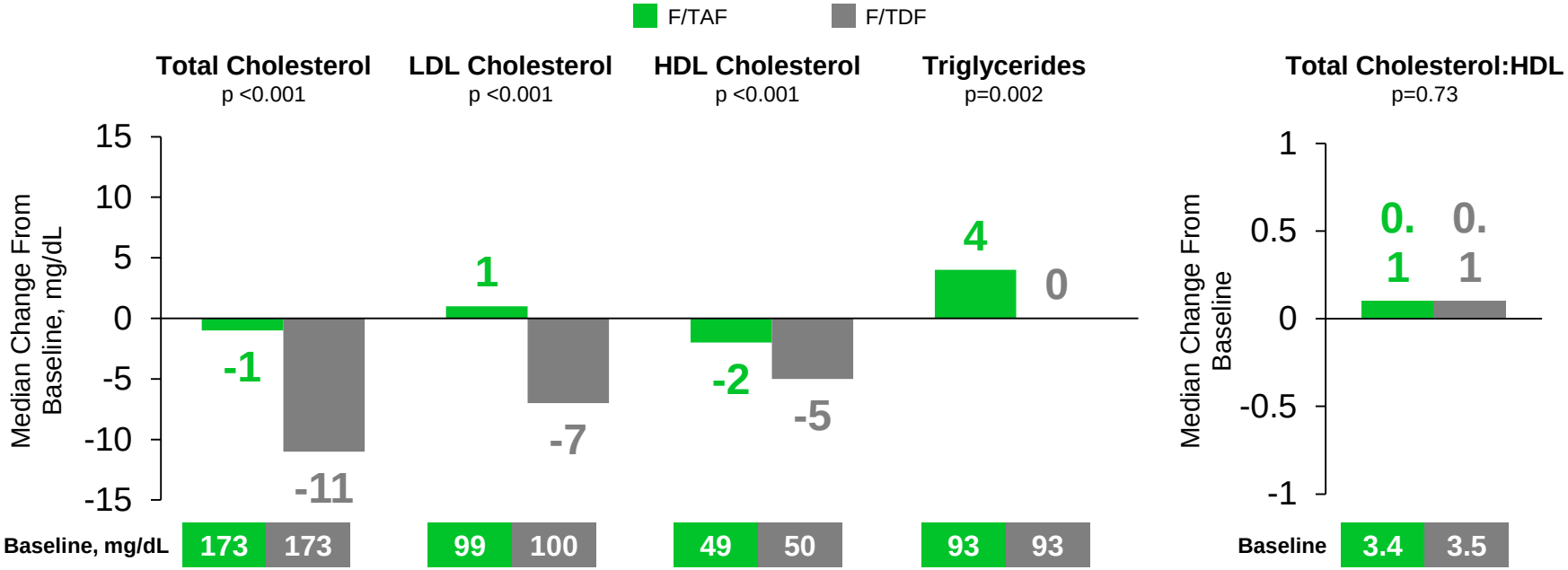
Weight Gain in PrEP Trials



*p <0.05 analysis of covariance (ANCOVA) model including baseline F/TDF for PrEP and treatment as fixed effects and baseline weight as a covariate.
CAB, cabotegravir; SEM, standard error of mean.

1. Adapted from Glidden DV, et al. Clin Infect Dis 2018;67:411-9. 2. Landovitz RJ, et al. Clin Infect Dis 2019 May 24.

Fasting Lipid Changes From Baseline at Week 48



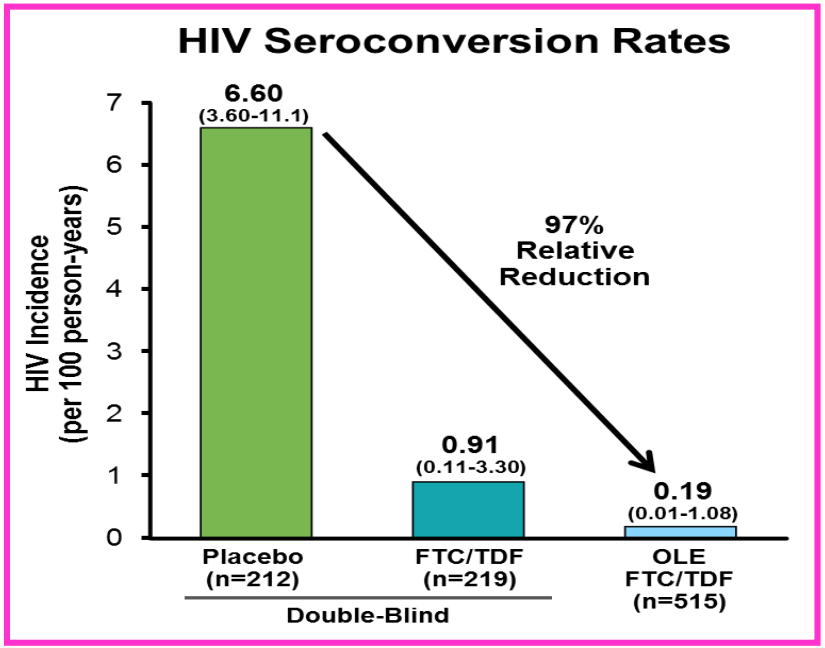
- There were minimal clinically significant changes in lipids in the F/TAF arm, with some small decreases in the F/TDF arm
- There was no change in the TC: HDL ratio

Spinner IAS 2019

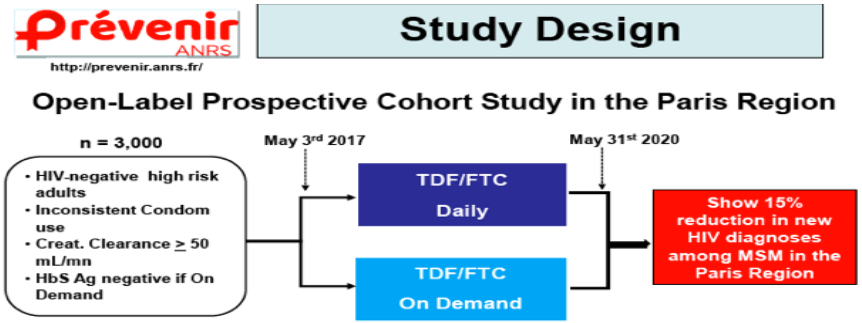
p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

On Demand PrEP: *Prêt à Prescrire?*

Ipergay RCT and OLE



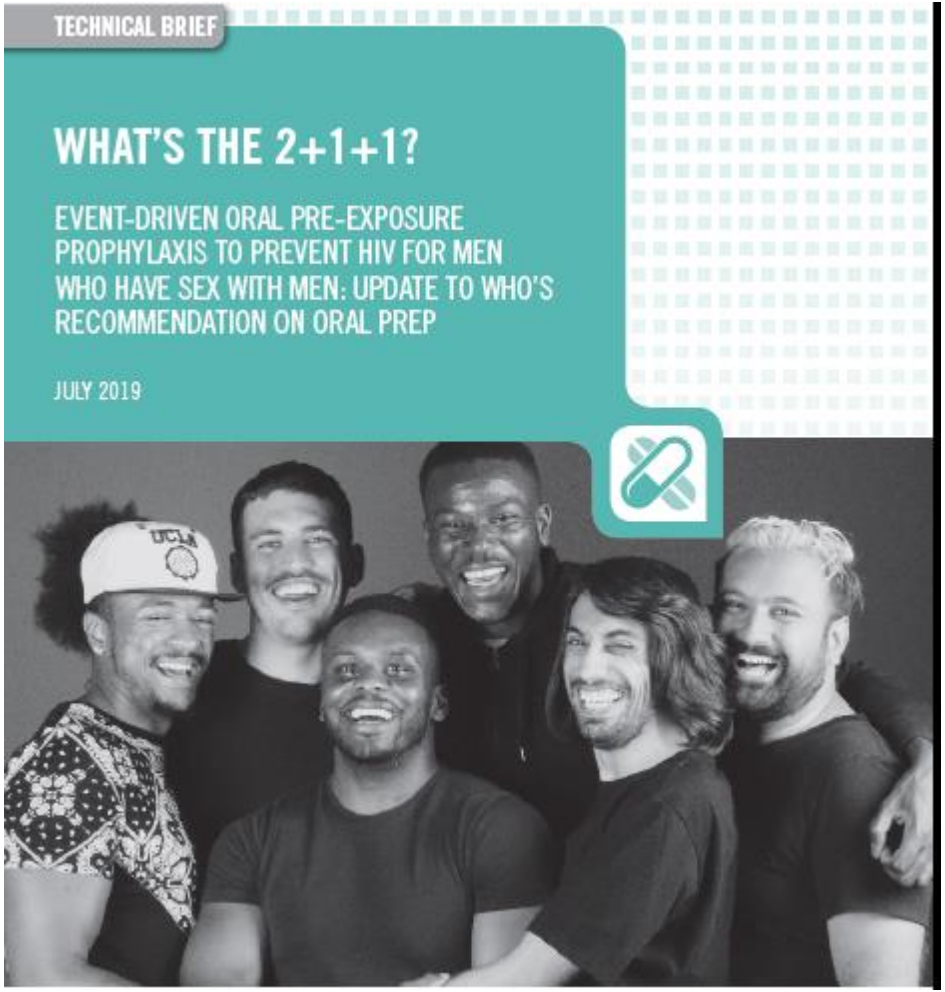
PREVENIR Open Label



- 2143 pts, interim analysis
- Half on-demand regimen
- 0 infx in daily, 2 infx in on-demand
- Estimated 143 infx averted

Molina NEJM 2015, Lancet HIV 2017, IAS 2019

WHO endorses 2-1-1



WHO, July 2019

28y cisgender woman has an HIV+ cisgender male partner. He uses ART with undetectable VL. Have sex 2x/wk. Do not want to use condoms.

Your counseling about HIV transmission is…

1. “Studies suggest that the risk of HIV transmission is still substantial.”
2. “Studies suggest that the risk of HIV transmission is low.”
3. “Studies suggest that the risk of HIV transmission is extremely low.”
4. “Studies suggest that the risk of HIV transmission is zero.”
5. Other

PARTNER1, PARTNER2 studies

888 HIV serodiscordant couples (extended to 972 gay couples)

- 36,000 condomless sex acts (extended to 76,000 for gay couples)
- **0** linked transmissions when VL undetectable

Opposites Attract

- 358 HIV serodiscordant MSM couples
- 12,477 condomless anal acts with PVL BLD and no PrEP
- **0** transmissions when VL undetectable
- 3 pts infected by outside partner

Rodger JAMA 2016, Rodger Lancet 2019; Bavinton Lancet HIV 2018

VIEWPOINT

HIV Viral Load and Transmissibility of HIV Infection

Undetectable Equals Untransmittable

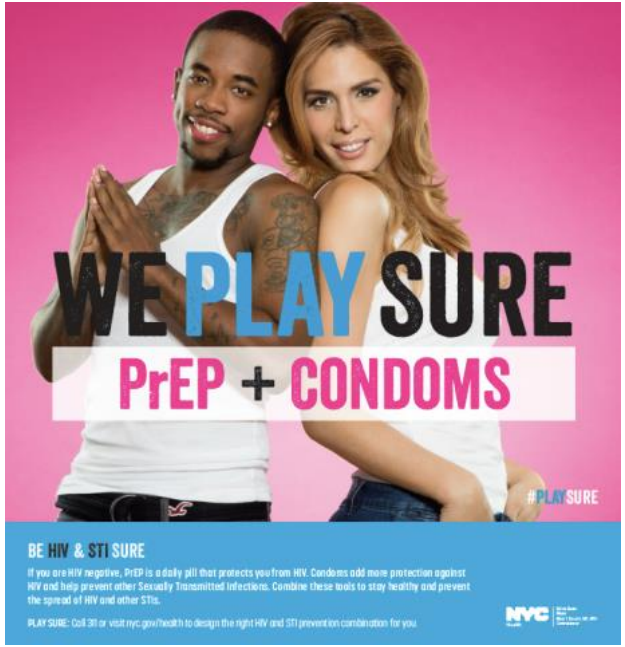
“U = U signifies that individuals with HIV who receive antiretroviral therapy (ART) and have achieved and maintained an undetectable viral load cannot sexually transmit the virus to others.

This concept, based on strong scientific evidence, has broad implications for treatment of HIV infection from a scientific and public health standpoint, for the self-esteem of individuals by reducing the stigma associated with HIV, and for certain legal aspects of HIV criminalization.”

Robert W. Eisinger, PhD; Carl W. Dieffenbach, PhD; Anthony S. Fauci, MD

JAMA 2018

CDC estimates there are 1.1 million Americans who are likely to benefit from using PrEP



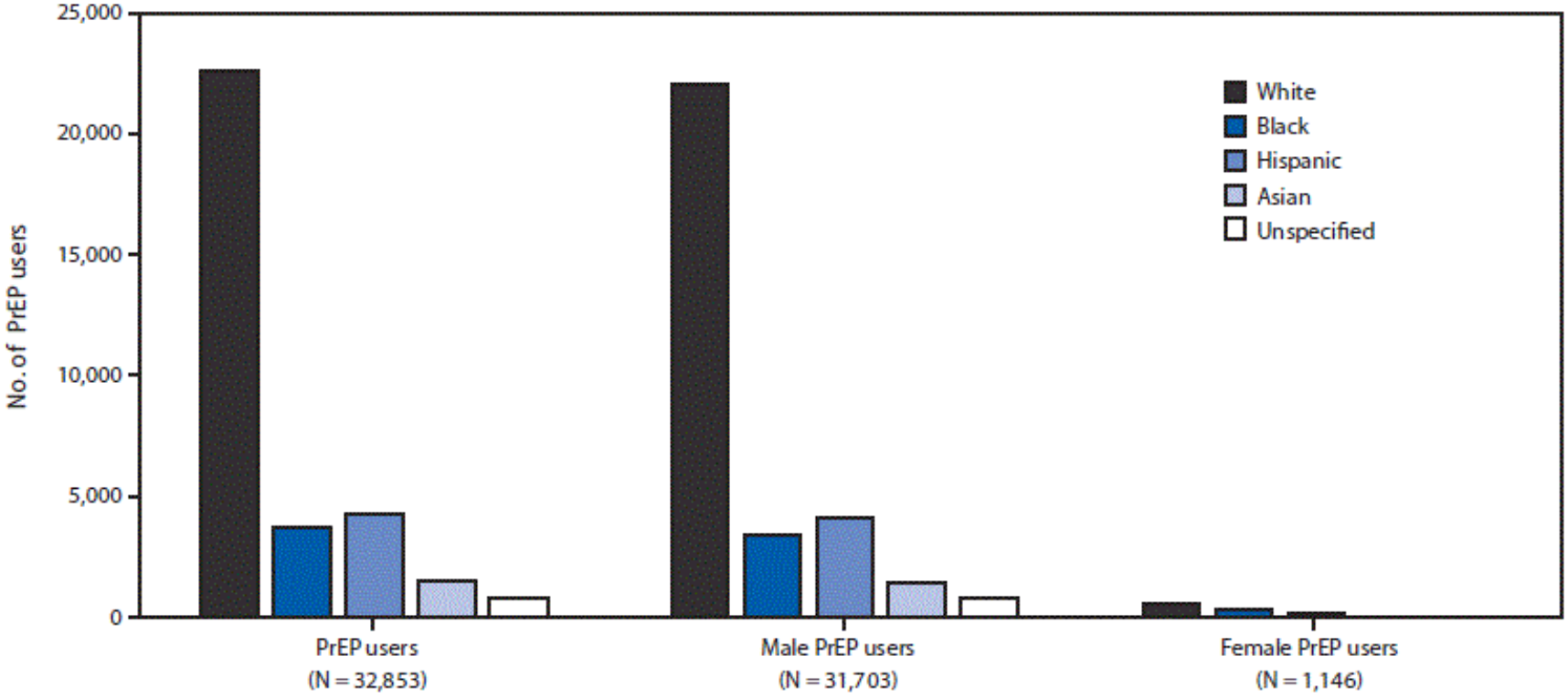
MSM…….813,000 (38% Black, 27% Latino)

Persons who inject drugs…….72,000 (37% Black, 21% Latino)

Heterosexual adults……258,000 (64% Black, 18% Latino)

<250,000 have been prescribed PrEP

Number of PrEP users by sex and race/ethnicity*— IQVIA Longitudinal Prescription Database, United States, 2016



April 2018: Increase in new HIV infections among PWID in Lowell, MA

PRESS RELEASE

CDC joins Department of Public Health in investigating HIV cluster among people who inject drugs

FOR IMMEDIATE RELEASE:
4/05/2018

Department of Public Health

BOSTON — The US Centers for Disease Control and Prevention has agreed to assist the Massachusetts Department of Public Health (DPH) with investigating a large cluster of new HIV infections in the northeast region of the state among people who inject drugs and/or experience homelessness. After seeing the increase in new HIV cases last year in Lawrence and Lowell among people who inject drugs, DPH requested formal assistance from the CDC.

MEDIA CONTACT

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TELL US WHAT YOU TH

Any experiences prescribing PrEP to people who inject drugs?

Please share!

How should we identify PrEP candidates in generalized epidemics?

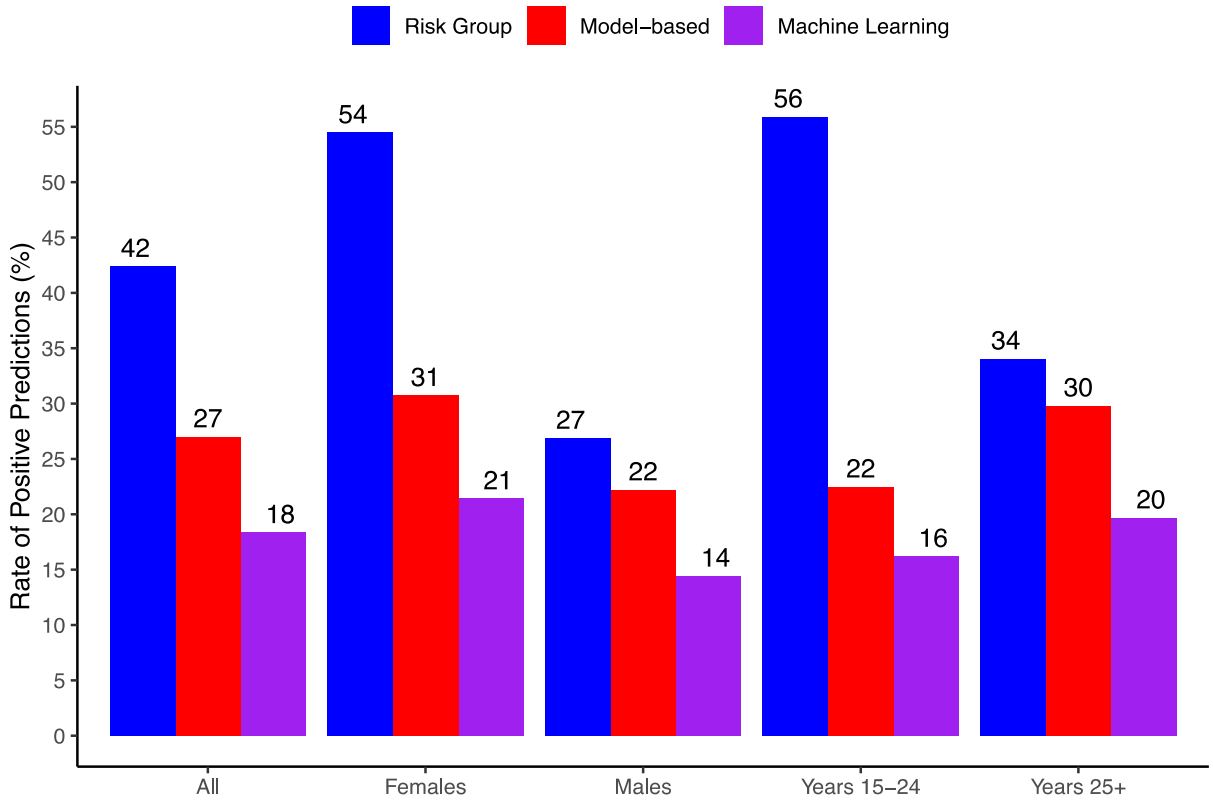
1. Offer to all people with HIV+ partner(s)
2. Offer to all people in major risk groups (e.g. people with HIV+ partners, young women, men who have sex with men)
3. Offer to all people who self-identify as being at increased risk for HIV infection
4. Offer to all people identified as high-risk by machine learning algorithms using sociodemographic and health data
5. All of the above

Machine learning to identify PrEP candidates in rural Kenya and Uganda

- Using population-based testing data on 75,558 adults followed over 166,723 person-years in rural Kenya and Uganda
  - 16 communities in intervention arm of SEARCH trial (2013-2017)
  - Varying HIV prevalence by region: 4% – 19%
- Evaluated 3 strategies for using demographic factors to predict the one-year risk of HIV seroconversion
  1. Membership in ≥1 known risk group (e.g. young woman or HIV+ spouse)
  2. Model-based risk score constructed with logistic regression
  3. Machine Learning risk score constructed with the Super Learner algorithm

(Balzer et al. CID,

Machine learning was more efficient: Fewer PrEP candidates to achieve a fixed sensitivity



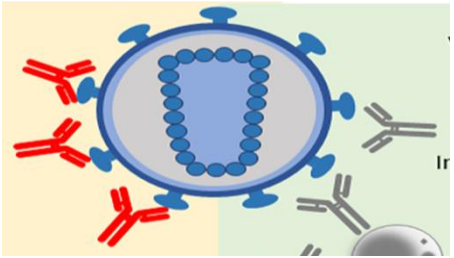
(Balzer et al. CID,

Conclusion & Ongoing work

- In generalized epidemic settings, machine learning can improve the identification of candidates for PrEP
- Open questions remain: generalizability, feasibility, and acceptability
- Preliminary data:
  - During population-based testing in SEARCH (2016-2017), 69,121 HIV-negative persons screened
  - 12,935 assessed to be at elevated HIV-risk: 10% serodifferent partnership; 54% point-of-contact Super Learner risk score; 36% otherwise self-identified
  - 3,489 (27%) initiated PrEP within 90 days

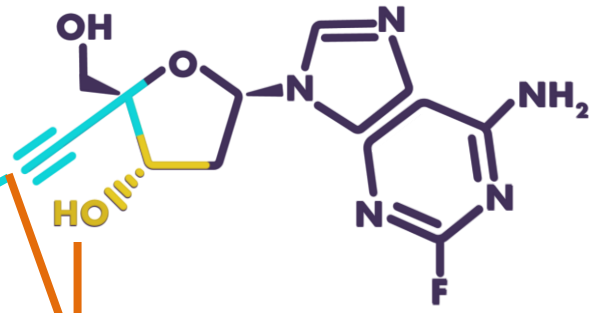
(Balzer et al. CID, 2019; Koss et al. IAS,

Future options?



https://www.youtube.com/watch?v=Dr7werW5Or4

Islatravir (MK-8591): A First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI) With Multiple Mechanisms of Action



Translocation Inhibition

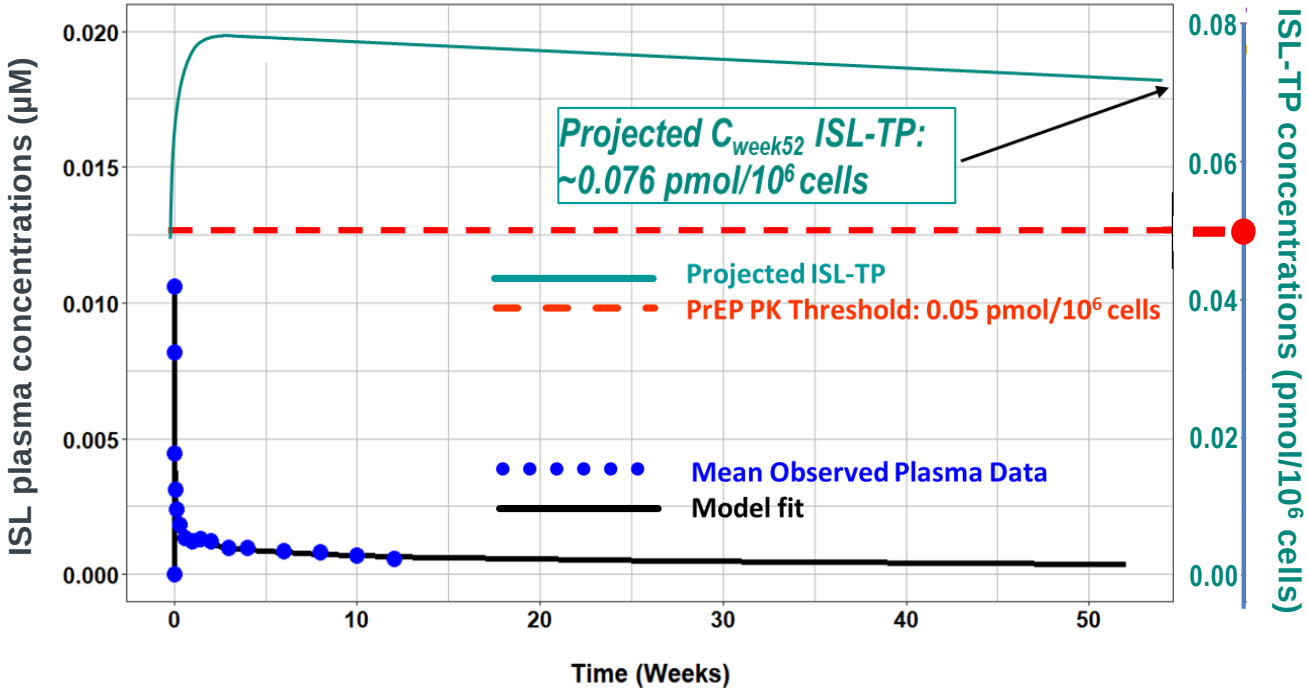
Due to the 4’-ethynyl Group

Delayed Chain Termination

Due to the 4’-ethynyl and 3’-hydroxyl Groups

Multiple mechanisms contribute to the high potency of islatravir against HIV-1 and drug-resistant variants and its high barrier to resistance.

62 mg Implant Projected to Lead to Concentrations Above Threshold for at Least 12 Months



- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10^6 cells) for >12 months
  - Projected concentration at 12 months: **0.076 pmol/10^6 cells**
  - Projected time at which concentration falls below 0.05 pmol/10^6 cells: 68-70 weeks (~**16 months**)

Matthews IAS 2019

GOAL:

Our goal is ambitious and the pathway is clear –
employ strategic practices in the *places* focused on the right *people* to:

75% reduction in new HIV infections in 5 years and at least **90%** reduction in 10 years.

- **Diagnose** all people with HIV as early as possible after infection.
- **Treat** the infection rapidly and effectively to achieve sustained viral suppression.
- **Protect** people at risk for HIV using potent and proven prevention interventions, including PrEP, a medication that can prevent HIV infections.
- **Respond** rapidly to detect and respond to growing HIV clusters and prevent new HIV infections.
- **HIV HealthForce** will establish local teams committed to the success of the Initiative in each jurisdiction.

Resources targeted to 48 highest burden counties; Washington, D.C.; San Juan, Puerto Rico; 7 states with substantial rural HIV burden.

THANK YOU!