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Preventing HIV with One Pill a Day: Evidence for PrEP

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Continuing Medical Education Disclosure

- Program Faculty: Kevin Ard, MD, MPH
- Current Position: Medical Director, The National LGBT Health Education Center, Fenway Health and Massachusetts General Hospital
- Disclosure: No relevant financial relationships. Presentation does not include discussion of off-label products.

This Live activity, Preventing HIV with One Pill a Day: Using PrEP in Clinical Practice, with a beginning date of 04/15/2016, has been reviewed and is acceptable for up to 3.75 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Objectives

1. Summarize PrEP efficacy and safety data
2. Understand the impact of adherence on PrEP effectiveness
3. Review new PrEP formulations that are currently being developed



Antiretrovirals play a central role in HIV treatment and prevention.

HIV-positive persons

- Individual health benefit (START, TEMPRANO)
- Prevention of transmission to others (HPTN 052)

HIV-negative persons

- PrEP for those at highest risk

Pre-exposure prophylaxis (PrEP)



- Oral or topical antiretrovirals taken in a continuous or episodic manner
- Once-daily oral tenofovir-emtricitabine approved for PrEP by the FDA
- Does not require the knowledge or cooperation of one's partners



RCTs have demonstrated the efficacy of oral PrEP in several groups.

Men who have sex with men (iPrEX, N Engl J Med 2010)

- **Population:** 2,499 MSM and transgender women in 6 countries
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** Reduced HIV acquisition by 44%

Serodiscordant heterosexual couples (Partners PrEP, N Engl J Med 2012)

- **Population:** 4,747 serodiscordant couples in Kenya and Uganda
- **Intervention:** Oral tenofovir-emtricitabine or tenofovir alone
- **Results:** Reduced HIV acquisition by 67-75%

Heterosexual adults (TDF2 Botswana, N Engl J Med 2012)

- **Population:** 1,219 heterosexual men and women in Botswana
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** Reduced HIV acquisition by 62%

2 RCTs in African women have not shown a benefit to oral PrEP.

FEM-PrEP (N Engl J Med 2012)

- **Population:** 2,120 women in sub-Saharan Africa
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** No HIV risk reduction with PrEP

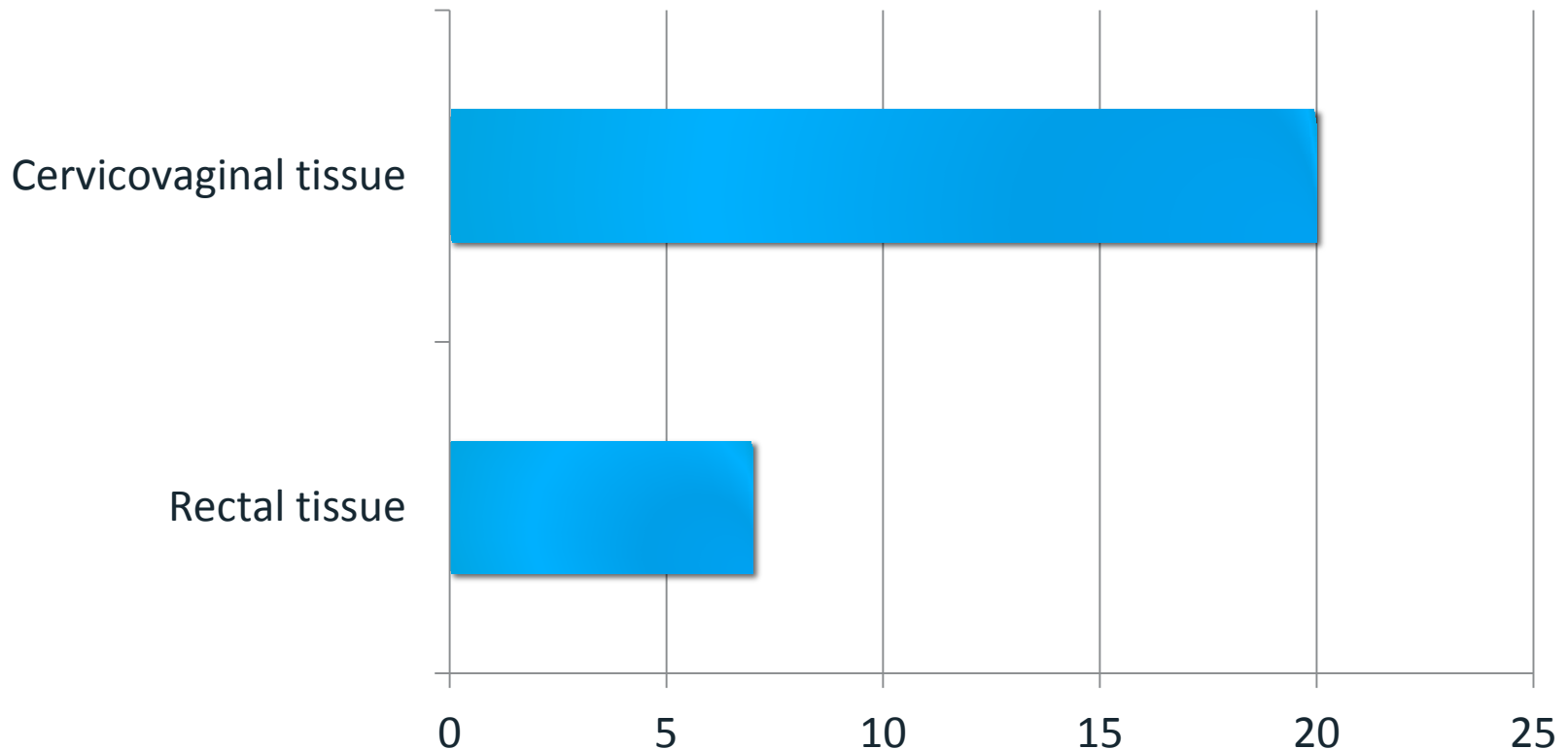
VOICE (N Engl J Med 2015)

- **Population:** 5,029 women in sub-Saharan Africa
- **Intervention:** Oral tenofovir-emtricitabine, oral/vaginal tenofovir
- **Results:** No HIV risk reduction with PrEP

In VOICE and FEM PrEP, fewer than 50% of participants ever took the study drug.

Imperfect adherence may be less forgiving for women.

Time to maximal tissue tenofovir levels with daily use



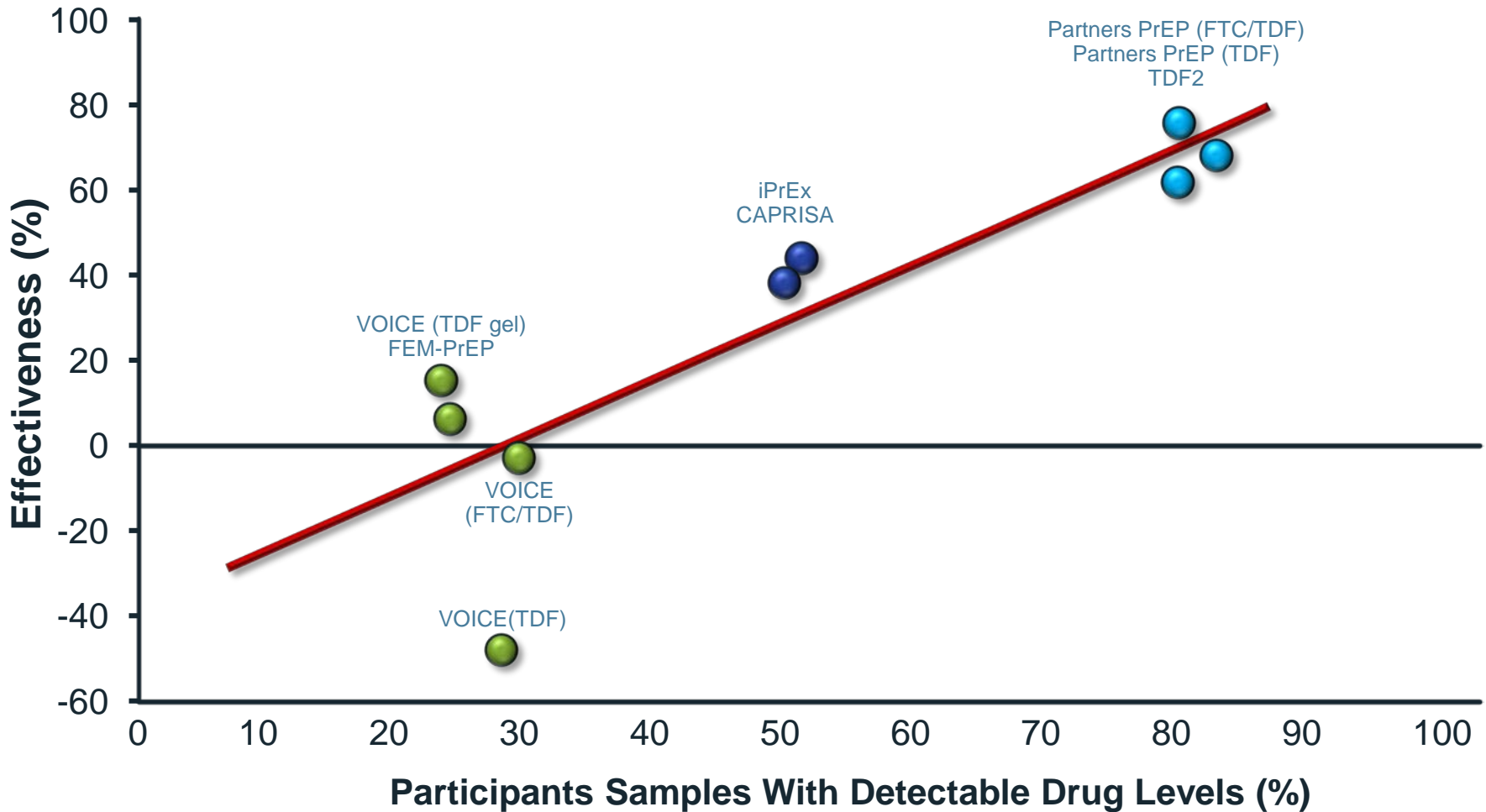
Preexposure prophylaxis for the prevention of HIV infection in the United States – 2014. CDC. Available from:
<http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf>

Does PrEP work in transgender women?

- No benefit in 339 transgender women in a post-hoc analysis of iPrEX
- 18% of transgender women had protective drug levels, compared to 36% of MSM.
- No transgender women who contracted HIV had detectable drug levels at the time of diagnosis.
- 0 infections occurred in transgender women taking 4 or more doses of PrEP per week.
- **Bottom line:** PrEP can work, but adherence is crucial.

Deutsch MB, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. *Lancet HIV*. 2015;2:e512.

PrEP Is Effective: Adherence Is Critical



Pearson correlation: 0.86 ($P=0.003$).

AVAC Report 2013. http://www.avac.org/sites/default/files/resource-files/AVAC%20Report%202013_0.pdf.



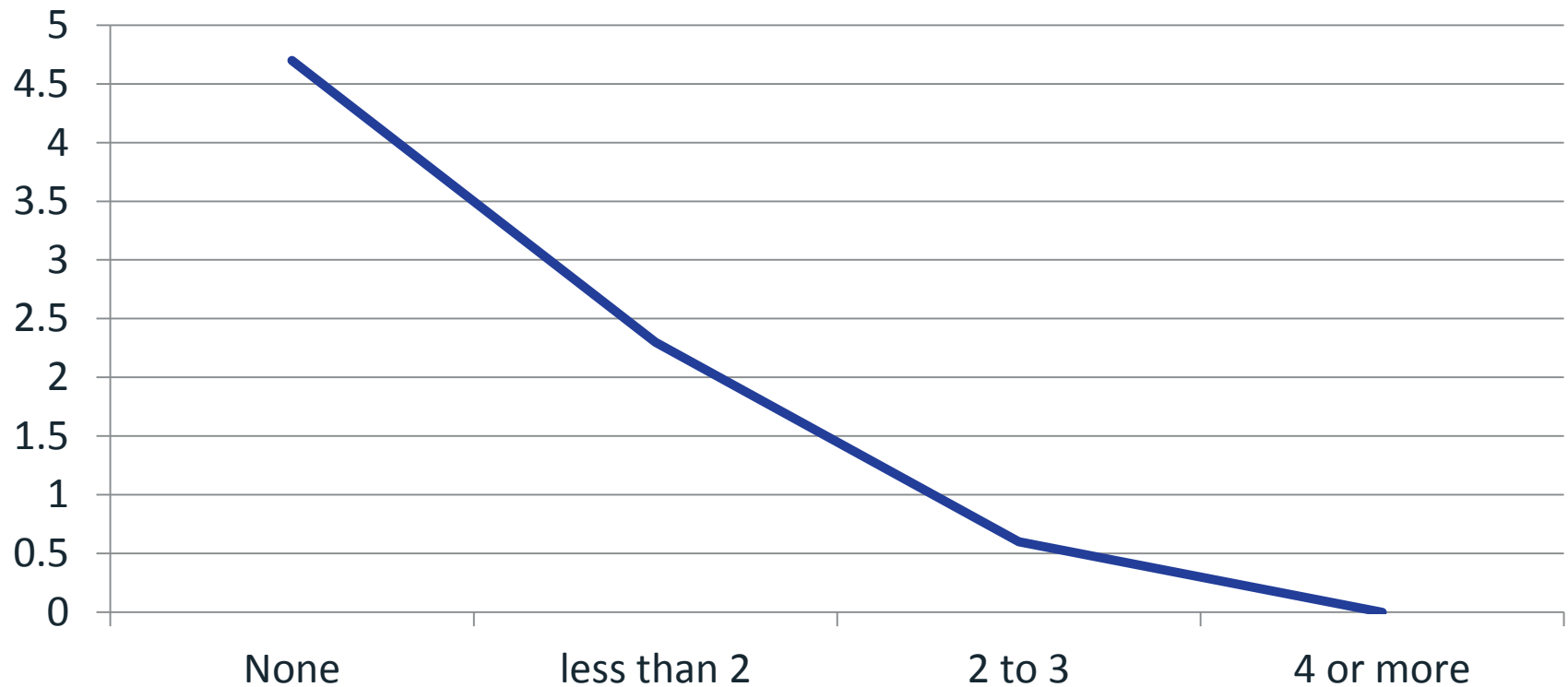
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HIV acquisition is rare in MSM taking ≥ 4 doses of PrEP per week.

HIV incidence (cases per 100 person-years) by PrEP doses per week in iPrEx OLE



Grant RM, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis.* 2014;14(9):820-829.



In the real world, PrEP may work at least as well as in RCTs.

PROUD (Lancet 2015)

- **Population:** 545 high-risk MSM in the United Kingdom
- **Intervention:** Immediate or deferred oral tenofovir-emtricitabine
- **Results:** Reduced HIV acquisition by 86%

TDF2 OLE (IAS 2015)

- **Population:** 229 men and women in Botswana
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** 0 HIV infections; 5-6 expected

Kaiser (Clin Infect Dis 2015)

- **Population:** 657 people in San Francisco, predominantly MSM
- **Intervention:** Oral tenofovir-emtricitabine
- **Results:** 0 HIV infections; ~9% incidence expected

More lessons from “real-world” studies.

- Concerns about risk compensation have not been borne out.
- MSM at highest risk preferentially access and adhere to PrEP.
 - **PrEP Brasil (IAS 2015):** RR 1.65 for PrEP uptake with a history of multiple condomless anal sex partners
 - **ATN 110 (IAS 2015):** Participants reporting condomless sex had higher TDF blood levels



PrEP is safe.

Adverse Event	PrEP	Placebo	P value
Any adverse event	69%	70%	0.50
Any serious event	5%	5%	0.57
Grade 3 or 4 events	12%	13%	0.51
Discontinuation of study drug	6%	6%	0.49

Grant RM, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363:2587.

PrEP is not foolproof, even with optimal adherence.

- 43-year-old man who developed HIV infection after 24 months on PrEP
- Clinical, pharmacy, and pharmacokinetic data indicated adherence to tenofovir-emtricitabine.
- HIV infection featured multi-class resistance (NRTI, NNRTI, INSTI)
- Failure of PrEP was likely due to exposure to a drug-resistant virus.

Knox DC, et al. HIV-1 infection with multiclass resistance despite preexposure prophylaxis (PrEP). Conference on Retroviruses and Opportunistic Infections. Boston, 2016. Abstract 169aLB.

What will PrEP look like in the future?

Injections of long-acting PrEP (e.g., cabotegravir?)



Other oral agents (e.g., TAF, maraviroc?)



Rectal microbicides



PrEP-impregnated vaginal rings (e.g., dapivirine)



A vaginal dapivirine ring provided modest HIV protection in African women.

- Study: MTN-020 ASPIRE
- Population: 2629 African women
- Intervention: Dapivirine-impregnated vaginal ring or placebo ring
- Results: 27% HIV risk reduction (56% in women older than 21 years)

Baeten JM, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med. 2016;DOI 10.1056/NEJMoa1506110.

Take-home points

- Oral tenofovir-emtricitabine substantially reduces the risk of HIV infection if taken regularly.
- Serious adverse events were not more common with PrEP than with placebo in clinical trials.
- Injectable formulations, alternative oral drugs, and vaginal rings for PrEP are under development.