

PrEP Cases

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Diseases

9/13/17

Case 1

- A 24-year-old African American man presents to Internal Medicine clinic as an urgent visit. He reports mild dysuria and requests STI screening. He is MSM, has had 5 partners in the past 6 months, uses condoms inconsistently, and has anal insertive, receptive and oral sex. He has never had a known STI, but has only been screened once before (2 years ago).

Case 1

Let's talk about PrEP

PrEP is primary prevention

It is intended to PREVENT
the onset of a disease in
those who are AT RISK

It is a concept, fulfilled by medication
that has been FDA-approved for this
purpose

But what is PrEP, really?

- Right now, PrEP is Truvada®
 - Fixed dose combination of tenofovir disoproxil fumarate (TDF) 300mg/emtracitabine (FTC) 200mg
 - Developed by Gilead
 - FDA-approved for use as PrEP on June 6, 2012
- Generic TDF/FTC approved 6/2017



Also approved in Australia, Canada, France,
Norway, Belgium, Netherlands, Peru, Israel,
Kenya, Botswana, Zimbabwe and South
Africa

*Coming soon in: Brazil, Nigeria, Zambia, Malawi, Uganda, India,
Thailand, United Kingdom, Italy*

Case 1

- Your patient says he has heard of PrEP, but doesn't know anyone taking it. He asks if it really works.

If taken daily, how effective is TDF/FTC
at reducing HIV risk?

- A. 60%
- B. 70%
- C. 85%
- D. >90%

iPrEX



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ORIGINAL ARTICLE

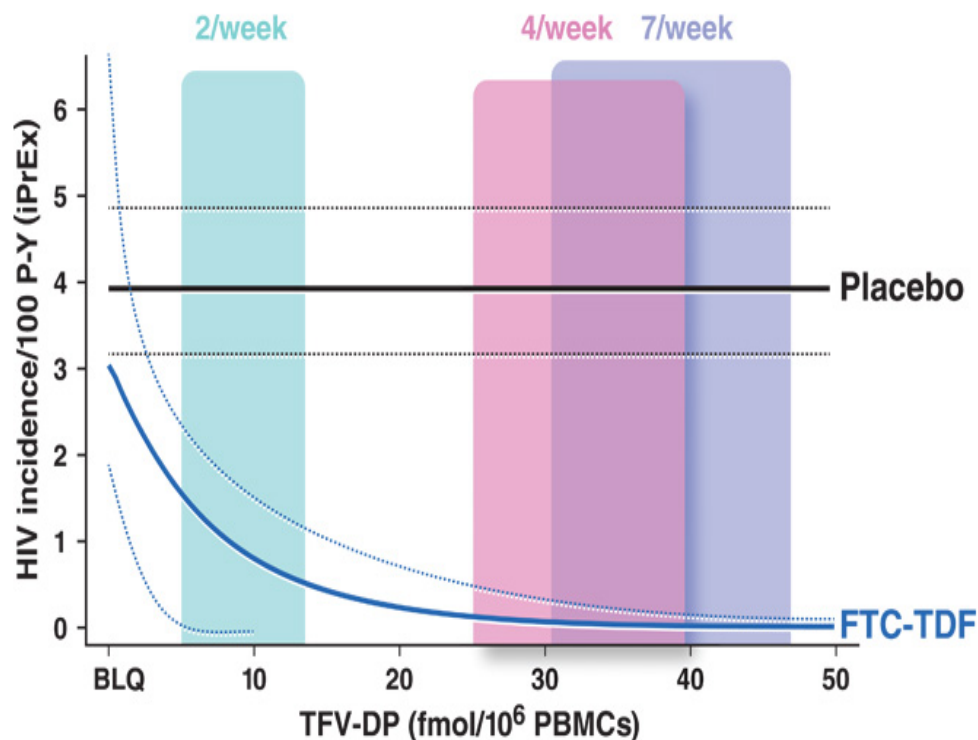
Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D., Valdílea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D., Suwat Chariyalertsak, M.D., Dr.P.H., Mauro Schechter, M.D., Ph.D., Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D., Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D., Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D., J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D., Ana I. Martinez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

N Engl J Med 2010; 363:2587-2599 | [December 30, 2010](#) | DOI: 10.1056/NEJMoa1011205

44% HIV risk reduction, but 92% risk reduction when taken consistently among MSM and transgender women

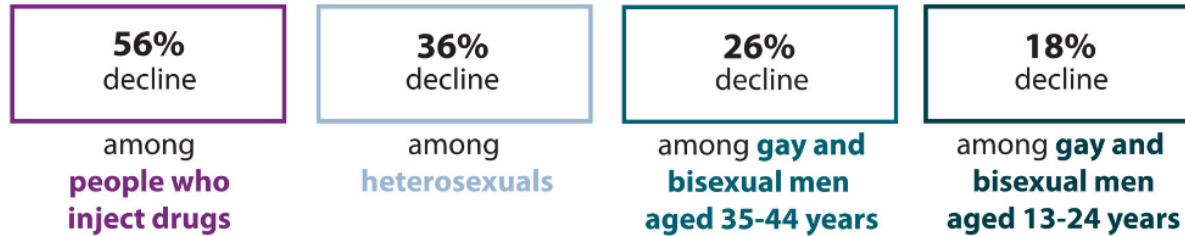
Dosing matters



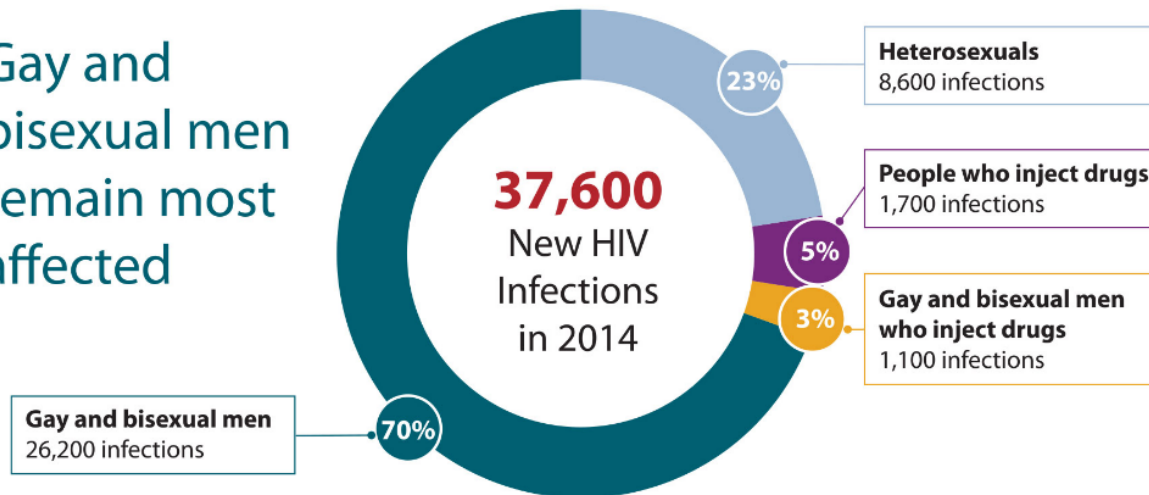
Using drug concentrations in iPrEX and STRAND, pharmacokinetic models predict **76%** risk reduction with 2 doses/week, **96%** with 4 doses/week, and **99%** with 7 doses/week.

Estimated annual HIV infections in the U.S. declined **18%**

Between 2008 - 2014 infections fell from 45,700 to 37,600



Gay and
bisexual men
remain most
affected



CDC Recommendations (for MSM)

- Adult man
- Without acute or established HIV infection
- Any male sex partners in past 6 months
- Not in a monogamous partnership with a recently tested, HIV-negative man

AND at least one of the following

- Any anal sex without condoms (receptive or insertive) in past 6 months
- Any STI diagnosed or reported in past 6 months
- Is in an ongoing sexual relationship with an HIV-positive male partner

CDC Recommendations (for heterosexual men and women)

- Adult person
- Without acute or established HIV infection
- Any sex with opposite sex partners in past 6 months
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual)
- Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner

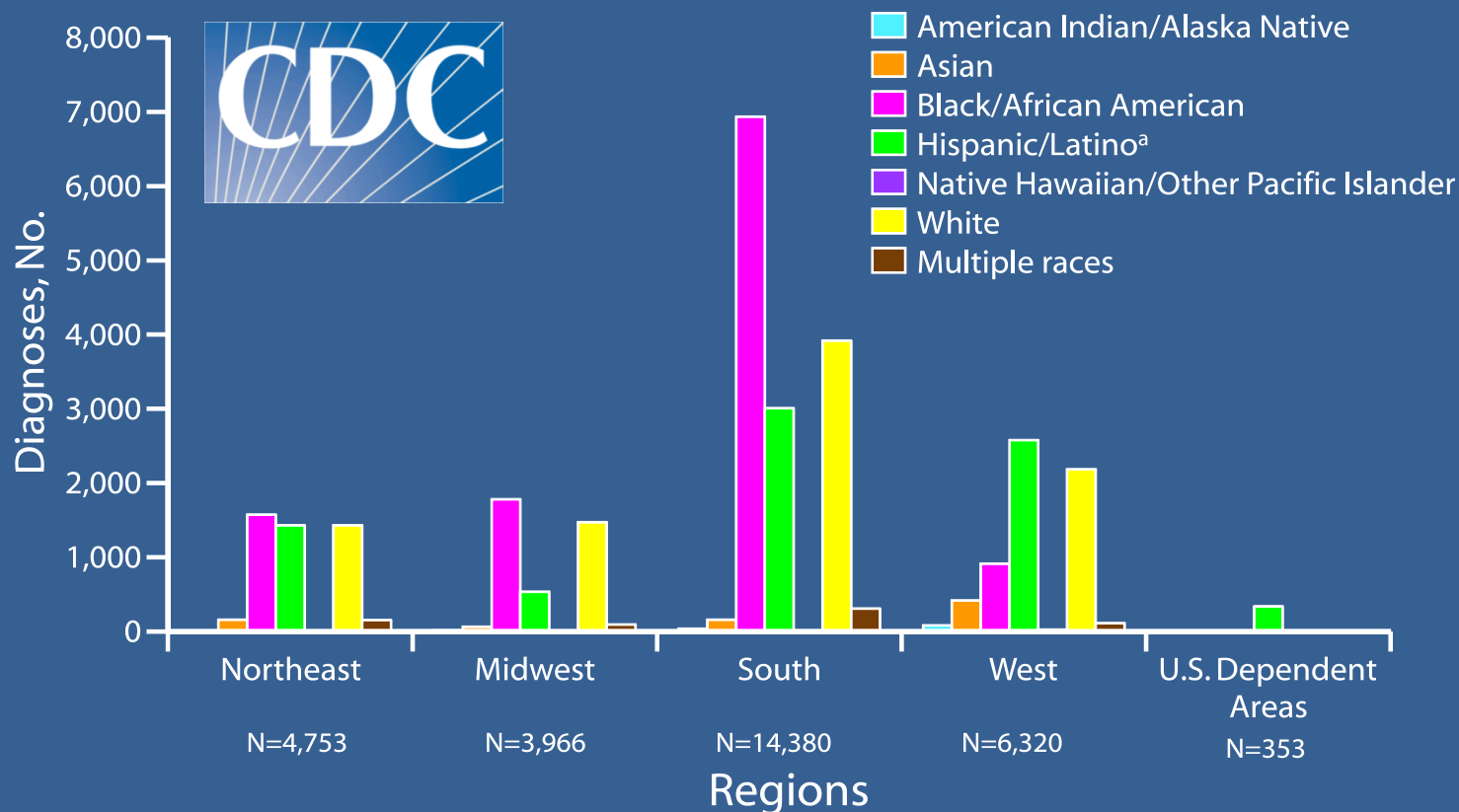
CDC Recommendations (for IDU)

- Adult person
- Without acute or established HIV infection
- Any injection of drugs not prescribed by a clinician in past 6 months

AND at least one of the following

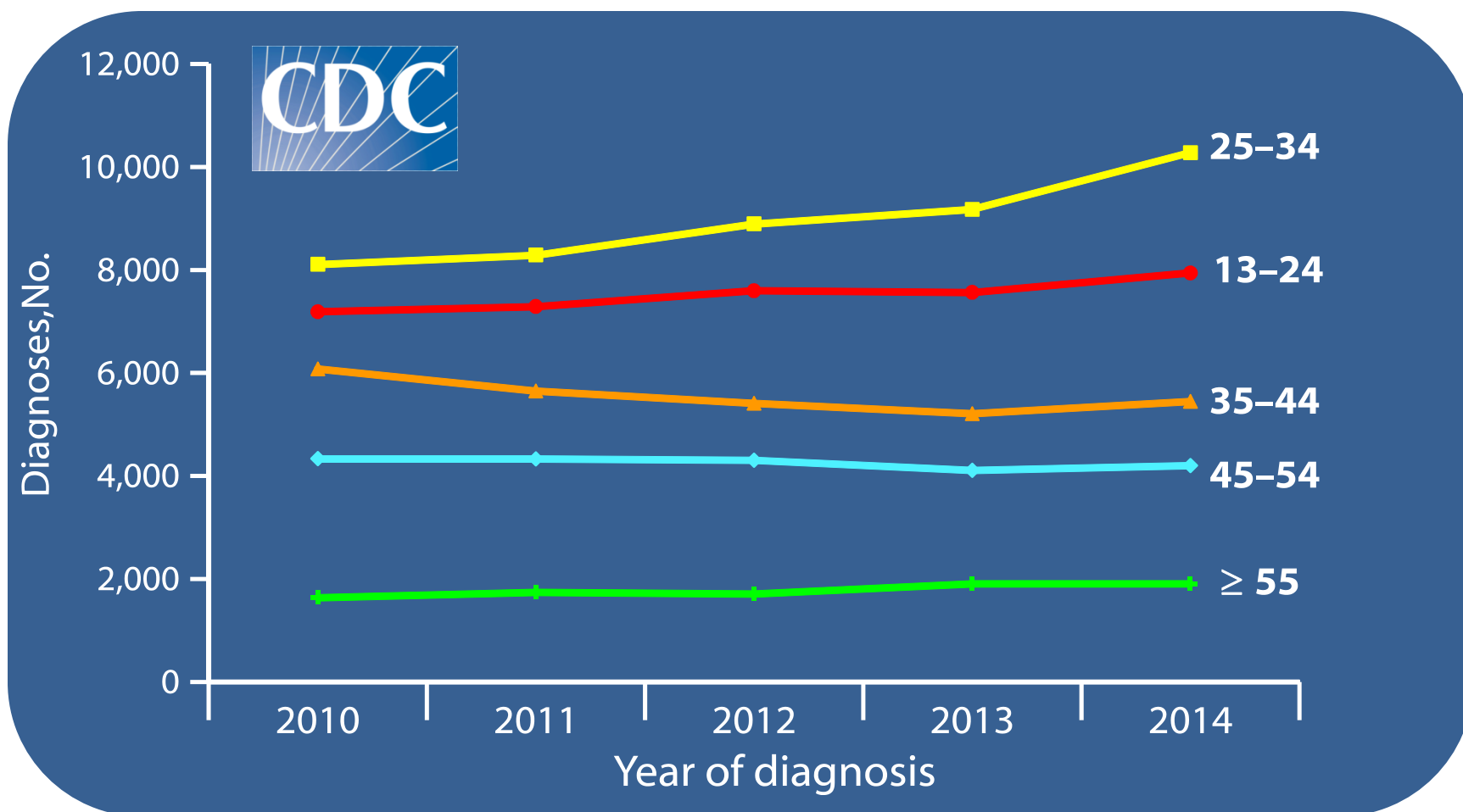
- Any sharing of injection or drug preparation equipment in past 6 months
- Been in a methadone, buprenorphine, or suboxone treatment program in past 6 months
- Risk of sexual acquisition

Diagnoses of HIV Infection among Men Who Have Sex with Men, by Region of Residence and Race/Ethnicity 2014 - United States and 6 Dependent Areas



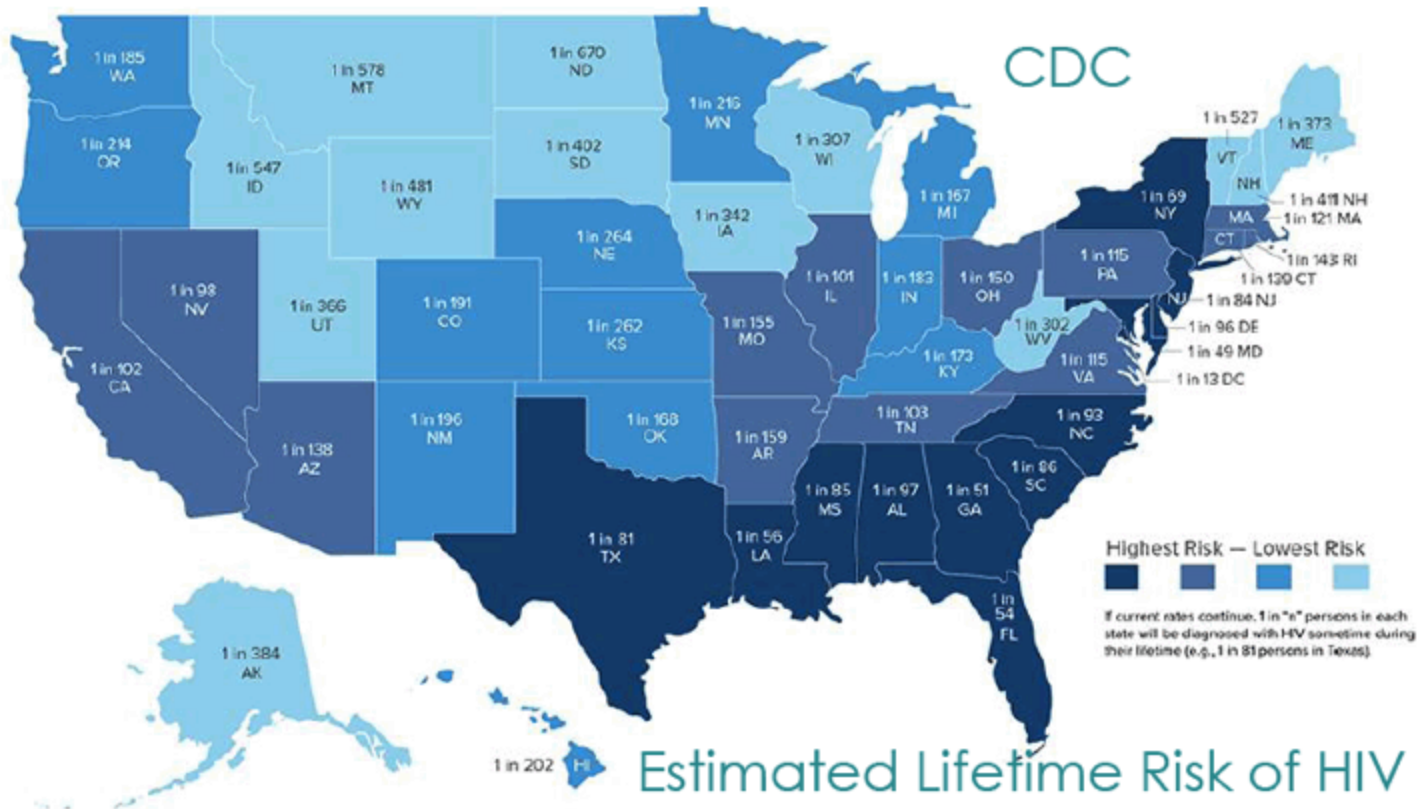
Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include men with HIV infection attributed to male-to-male sexual contact *and* injection drug use. ^a Hispanics/Latinos can be of any race.

Diagnoses of HIV Infection among Men Who Have Sex with Men, by Age Group, 2010–2014—United States and 6 Dependent Areas

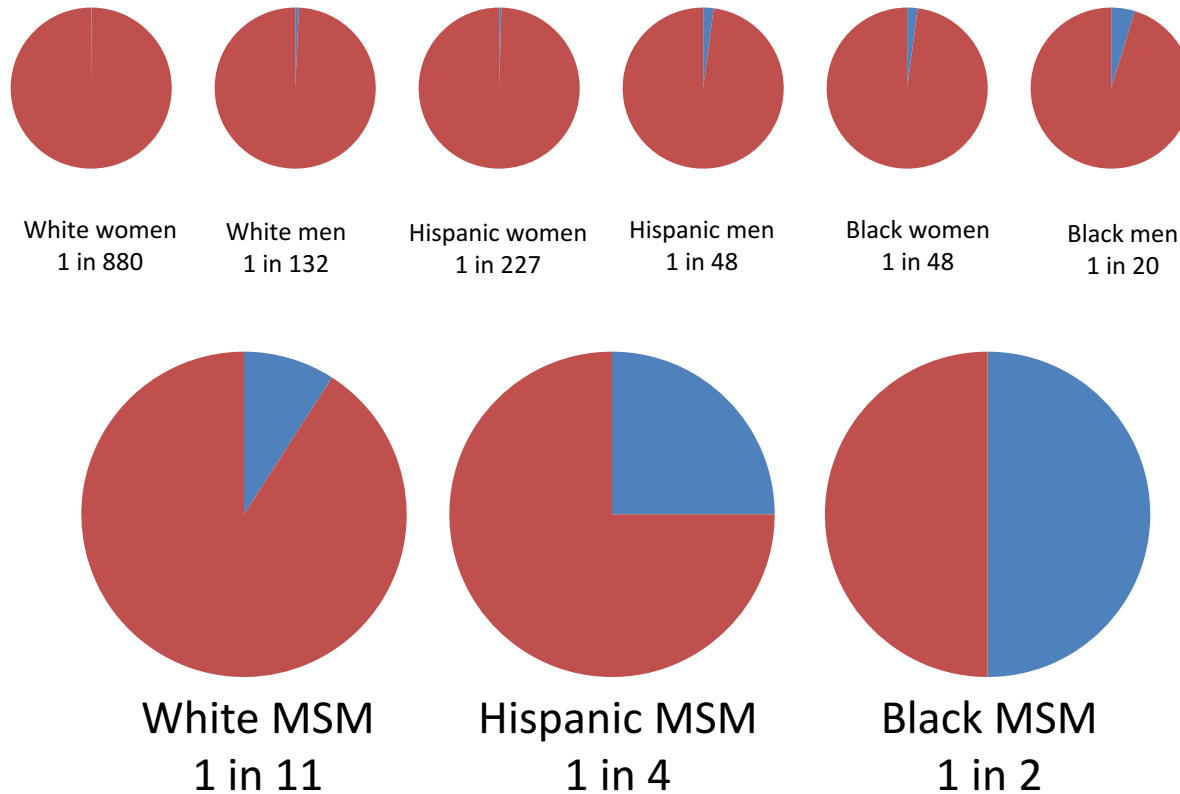


Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include men with HIV infection attributed to male-to-male sexual contact *and* injection drug use.

HIV Risk by State



HIV Risk by Race/Ethnicity and MSM



Case 1

- After discussing PrEP, your patient is interested.

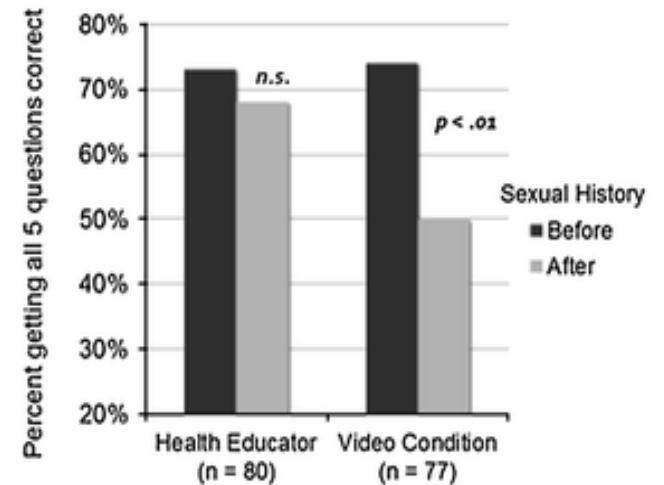
What just happened?

Taking a sexual history promotes comprehensive STI risk reduction counseling

Condom use
Knowing HIV status
Knowing partner's HIV status
PrEP

Sexual history and comprehension of PrEP

- Counseling on PrEP after a sexual history discussion significantly **increases comprehension** of HIV-prevention strategies
- Engagement in a sexual history discussion may heighten the **self-relevance** of information, increasing memory and cognitive processing during PrEP education



How often do you discuss sexual history with your patients?

- A. Every. Single. Visit.
- B. Almost always
- C. Occasionally
- D. Not often at all

What are your barriers to discussing
your patients' sexual histories?

Case 1

- You're excited to be writing your first prescription for TDF/FTC for Pre-exposure Prophylaxis. Now what?

How to provide PrEP

Encounter	To do
Month 0	<ul style="list-style-type: none">• Screen for HIV• Confirm HBV and HCV status• Check serum creatinine• Screen for STIs• Counseling• Prescribe
Month 3	<ul style="list-style-type: none">• Screen for HIV• Check serum creatinine• Counseling• Prescribe
Month 6	<ul style="list-style-type: none">• Screen for HIV• Screen for STIs• Counseling• Prescribe
Month 9	<ul style="list-style-type: none">• Screen for HIV• Check serum creatinine• Counseling• Prescribe
Month 12	<ul style="list-style-type: none">• Screen for HIV• Screen for STIs• Counseling• Prescribe

Labs:

- HIV screen: 5
- Serum creatinine: 3
- STI screen: 3

Prescriptions/Refill
authorizations: 5

Discussions: 5+

Agreement Form

for Initiating TRUVADA® for Pre-exposure Prophylaxis (PrEP)

Individual Label

Instructions: Review form with an HIV-negative person who is about to start or is taking TRUVADA for a PrEP indication at each visit. File form in the person's medical record.

TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. The following factors may help to identify individuals at high risk:

- Has partner(s) known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and one or more of the following:
 - Inconsistent or no condom use
 - Diagnosis of sexually transmitted infections
 - Exchange of sex for commodities (such as money, shelter, food, or drugs)
 - Use of illicit drugs, alcohol dependence
 - Incarceration
 - Partner(s) of unknown HIV-1 status with any of the factors listed above

Healthcare Provider Agreement

By signing below, I signify my understanding of the risks and benefits of TRUVADA for a PrEP indication and my obligation as a prescriber to educate the HIV-negative person about these risks, counsel the person on risk reduction, monitor the person appropriately, and report adverse events. Specifically, I attest to having done the following:

- Confirmed the negative HIV-1 status of this person prior to starting TRUVADA for a PrEP indication
- Read the Prescribing Information, including the BOXED WARNING
- Discussed with the HIV-negative person the known safety risks with use of TRUVADA for a PrEP indication
- Reviewed the importance of adherence with a comprehensive prevention strategy, including practicing safer sex
- Discussed the importance of regular HIV-1 testing (at least every 3 months) while taking TRUVADA for a PrEP indication
- Reviewed the TRUVADA Medication Guide with the HIV-negative person at high risk prior to prescribing TRUVADA for a PrEP indication
- Completed the items on the Checklist for Prescribers: Initiation of TRUVADA for Pre-exposure Prophylaxis (PrEP)

HIV-Negative Person Agreement

By signing below, I acknowledge that I have talked with my healthcare provider about the risks and benefits of TRUVADA to reduce the risk of getting HIV-1 infection, and I understand them clearly. Specifically, I attest to the following:

- My healthcare provider talked with me about the importance of follow-up HIV-1 testing, and I agree to have repeat HIV-1 screening tests (at least every 3 months) as scheduled by my healthcare provider
- My healthcare provider talked with me about the safety risks involved with using TRUVADA to reduce the risk of getting HIV-1 infection
- My healthcare provider talked with me about a complete prevention strategy and always practicing safer sex by using condoms correctly
- I will talk with my healthcare provider if I have any questions
- I have read the TRUVADA Medication Guide

Healthcare Provider's
Signature

Date

HIV-Negative Person's
Signature

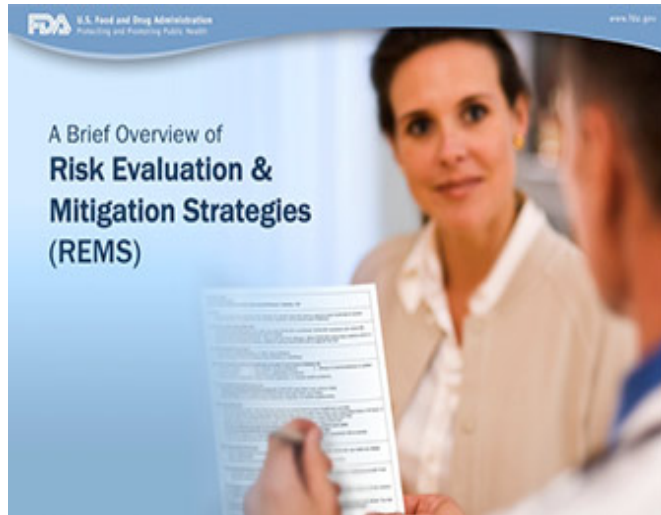
Date

Truvada
emtricitabine, tenofovir disoproxil fumarate



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REMS



<http://www.truvadapreprems.com>

- REMS is a safety strategy to manage risks associated with a drug and to enable continued access to the drug by managing its safe use.
- REMS is a safety measure beyond the professional labeling to ensure the drug's benefits outweigh its risks.
- REMS requirements are different for different drugs.

REMS for TDF/FTC

- Required for TDF/FTC for use in PrEP because
 - The benefit is different than for its use in HIV infection
 - The risk/benefit scale changes, depending on patient behavior



Billing and Coding

- ICD-10 did not take into account medical prevention of HIV
- Suggested codes:
 - Z71.7 - Human immunodeficiency virus [HIV] counseling
 - Z20.6 - Contact with and (suspected) exposure to human immunodeficiency virus [HIV]
 - Z11.3 - Encounter for screening for infections with a predominantly sexual mode of transmission
 - Z79.899 - Other long term (current) drug therapy
 - Z51.81 – Encounter for therapeutic drug level monitoring
- Not suggested
 - Z72.52 – High risk homosexual behavior

Case 2

A 27-year-old man presents for a routine health maintenance exam. You notice he was seen by another provider 3 months ago and diagnosed with gonorrhea by rectal swab. He also has a history of syphilis, treated 2 years ago. He is MSM, has anal receptive sex and uses condoms “80 percent” of the time. He has had 10-15 partners in the past 6 months and gets HIV screens consistently every 6 months. You initiate a conversation about PrEP...

Case 2



Case 2

Your patient has heard about PrEP and tells you he is absolutely not interested. You ask him why not.

“You know what they say about PrEP, it will make me have more sex and get STDs,” he responds.

PrEP Stigma



Stigma

A preventative measure against the consequences of sexual activity

... *condones* sexual activity

... *promotes* sexual activity

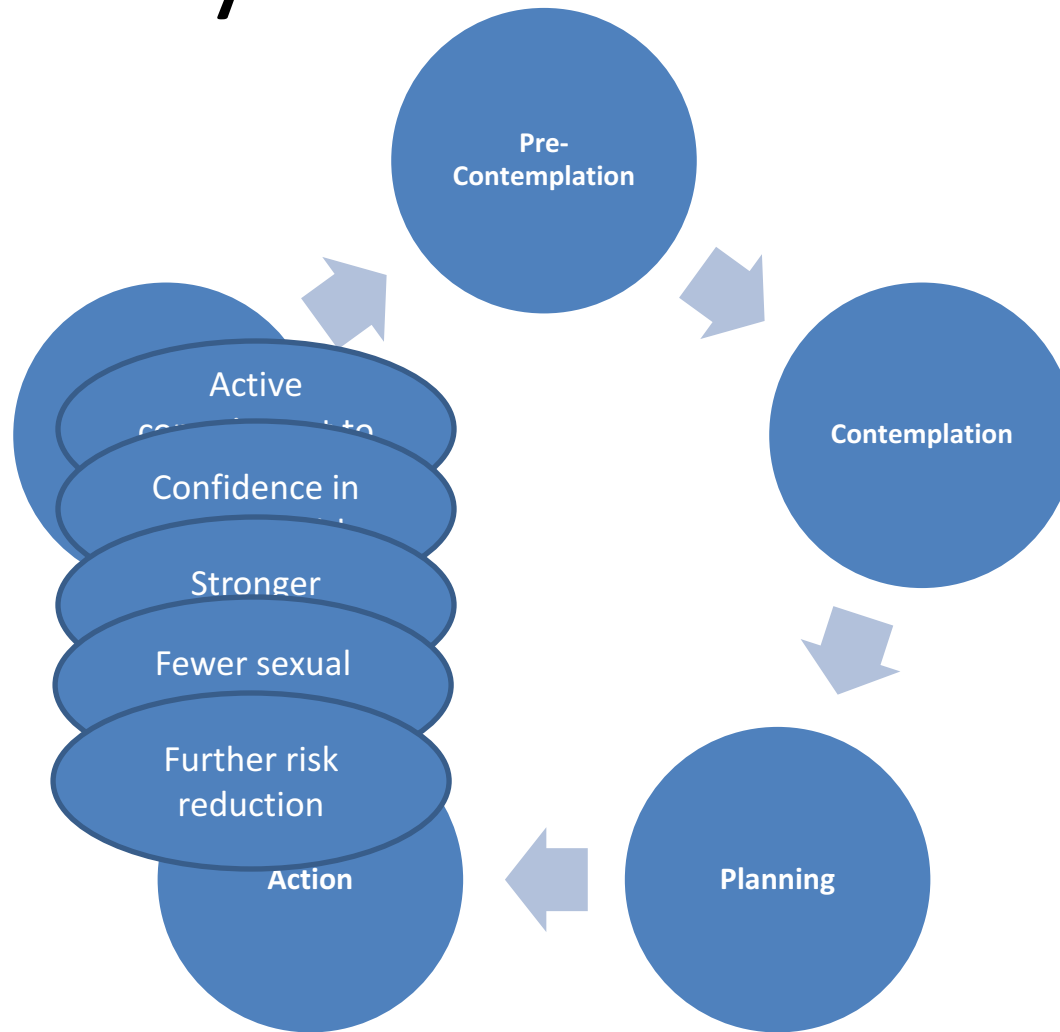
... *causes* sexual activity



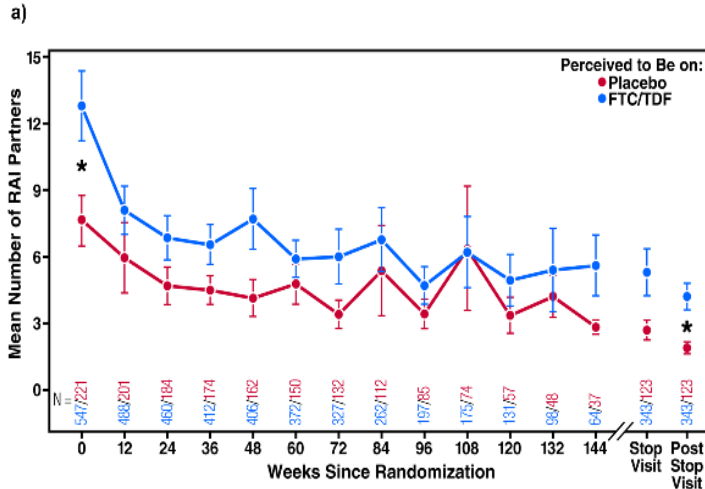
Stigma

- PrEP is a “party drug”
- PrEP promotes “bareback sex”
- PrEP users will stop using condoms
- PrEP users will acquire more STIs

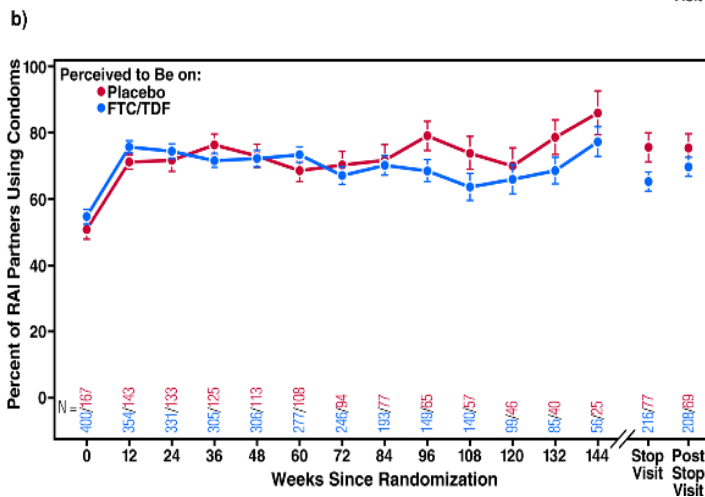
But actually...



No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV Pre-exposure Prophylaxis.



For patients believing they were on PrEP, the number of receptive anal intercourse partners decreased.



For patients believing they were on PrEP, condom use increased.

Syphilis incidence also decreased in both study arms

Real questions, real barriers

- Cost
- Judgment from providers
- Judgment from partners
- Partner could find out about sex outside of the relationship
- Partner would misinterpret taking PrEP as having HIV

...and Missed Opportunities

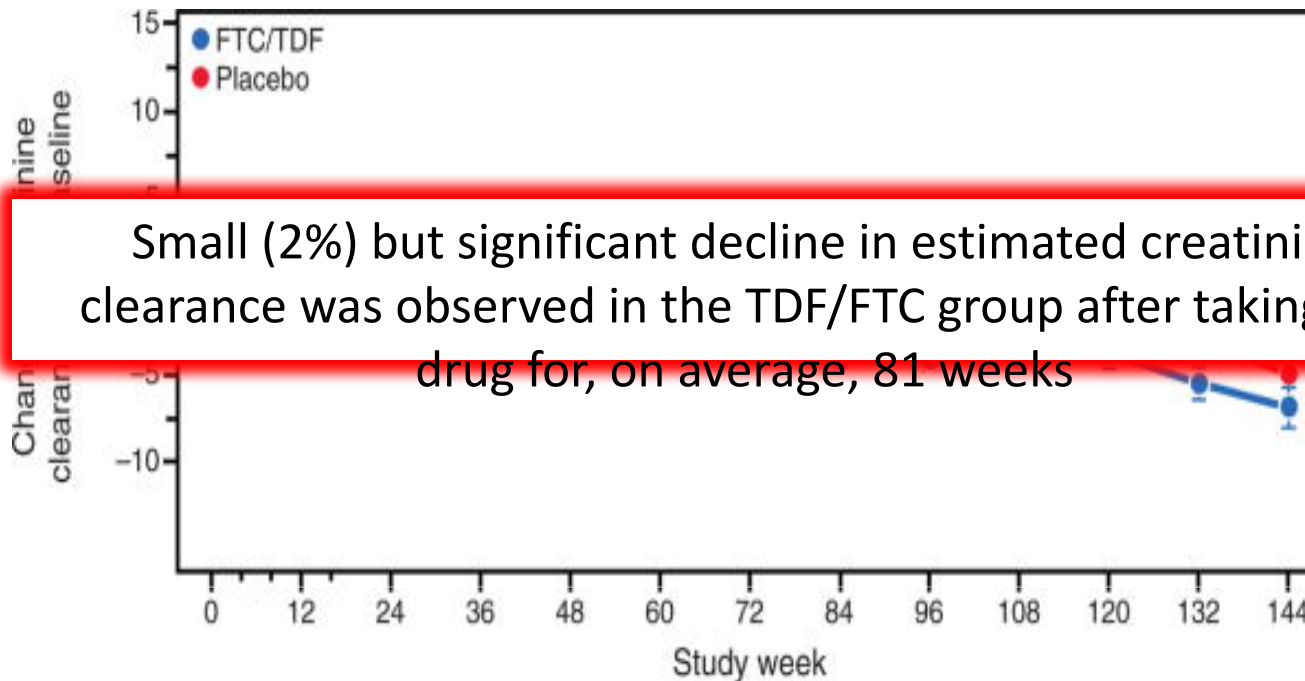
- PrEP is experimental
- PrEP is too expensive
- PrEP is not a primary care activity
- Recommending condom use is enough
- Uncomfortable prescribing PrEP
- Unaware of PrEP



Case 3

32-year-old white man taking TDF/FTC for the past year presents for routine follow-up. He is MSM, has one long-term partner and 4 other partners over the past 3 months. He remains HIV-negative, but his renal function has declined (serum creatinine 0.9 mg/dL three months ago, now is 2.3 mg/dL with eGFR mL/min).

Nephrotoxicity



Small (2%) but significant decline in estimated creatinine clearance was observed in the TDF/FTC group after taking the drug for, on average, 81 weeks

Nephrotoxicity

- Tenofovir disoproxil fumarate (TDF)
 - Proximal tubulopathy due to mitochondrial toxicity
 - May occur with or without decline in eGFR
 - Fanconi syndrome
 - Generalized proximal tubulopathy
 - » renal tubular acidosis
 - » glycosuria
 - » hypophosphatemia
 - » hypouricemia
 - » Proteinuria
 - Tubular dysfunction may precede loss of renal function
 - Underlying CKD increases risk

Case 3

Your patient reveals that his partner, a physician, has been providing him with IM testosterone. The patient subsequently developed hypertension, for which his partner provided lisinopril. The patient has also been taking daily ibuprofen for headaches.

Case 3

You stopped TDF/FTC and counseled extensively on HIV risk reduction strategies. The patient stopped taking testosterone, ibuprofen and, eventually, lisinopril. Three months later, his serum creatinine was 1.5 mg/dL, eGFR 82 mL/min.

Nephrotoxicity

- Tenofovir disoproxil fumarate (TDF) is contraindicated if CrCl <60 mL/min
- In the absence of HIV infection, renal toxicity due to tenofovir disoproxil fumarate (TDF) is generally reversible after TDF discontinuation.

Case 4

82-year-old white man presents to discuss PrEP initiation. He has a new partner, a 78-year-old woman with HIV-infection, undetectable for many years. Your patient has a history of prostate cancer s/p TURP, coronary artery disease, and well-controlled hypertension. He reports falling once in the past year while raking his yard, denies any injuries.

Bone Mineral Density Loss

Table 3. Bone Mineral Density Scores.*

Assessment	Forearm			Hip			Lumbar Spine		
	TDF-FTC (N=109)	Placebo (N=112)	P Value	TDF-FTC (N=109)	Placebo (N=112)	P Value	TDF-FTC (N=109)	Placebo (N=112)	P Value
T score			0.004			<0.001			<0.001
Enrollment	-0.75	-0.58		0.44	0.53		-0.72	-0.59	
6 mo	-0.77	-0.50		0.33	0.57		-0.84	-0.45	
12 mo	-0.76	-0.48		0.33	0.54		-0.77	-0.56	
18 mo	-0.88	-0.21		0.18	0.78		-0.88	-0.41	
24 mo	-0.87	-0.13		0.20	0.76		-1.09	-0.28	

Significant decline in T scores and z scores for BMD at the forearm, hip, and lumbar spine in participants who received TDF/FTC, as compared with those who received placebo

* In the TDF-FTC group, 58 participants completed bone mineral density testing at the 6-month visit, 45 at the 12-month visit, 36 at the 18-month visit, and 23 at the 24-month visit. In the placebo group, 66 participants completed bone mineral density testing at the 6-month visit, 44 at the 12-month visit, 33 at the 18-month visit, and 35 at the 24-month visit.

Sero-discordant partners

- Effective ART use by the HIV+ partner can significantly reduce, if not eliminate, transmission risk
 - 1238 sero-discordant couples, representing 58,000+ condomless sex acts over ~2 years
 - No transmissions observed
 - 343 gay sero-discordant couples, representing 12,000+ condomless sex acts over ~1.5 years
 - No transmissions observed
- Long-term follow-up studies are needed to precisely determine risk reduction by effective ART

Rodger AJ, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA, July 2017

Bavinton B, Grinsztejn B, Phanuphak N, et al. HIV treatment prevents HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. 9th IAS Conference on HIV Science (IAS 2017), July 23-26, 2017, Paris. Abstract TUAC0506LB.

Case 4

BENEFIT

- Further reduction in HIV risk (which is already very low)



RISK

- Bone mineral density loss
- Increased fracture risk
- Nephrotoxicity
- Medication interactions

Case 5

19-year-old white male patient presents to request PrEP. He is MSM, 6 partners over the past 6 months, uses condoms inconsistently, gets STI screening at the local health department.

You discuss that he is a great candidate for PrEP. He states, “yeah but I don’t think I can afford it.”

Truvada Cost

- \$13,000 out-of-pocket for one year in USA
 - (But nobody pays this)
- Covered by private insurance companies
 - Variable co-pays, deductibles, etc.
- Medicaid covers Truvada, but varies state-by-state
- Co-pay and cost assistance available

Truvada Access: Insured

- Prescribe as usual
- Complete prior authorization if required
- Copay card
 - Annual benefit for \$3,600, no income restrictions
 - Gilead copay card usually brings patient cost to \$0
 - <https://www.gileadadvancingaccess.com/copay-coupon-card>
 - Federal beneficiaries not eligible (Medicaid, Medicare, VA, etc)

Truvada Access: Uninsured

- If income <500% federal poverty level (\$60,300 in 2017)
 - Gilead patient assistance program
 - www.truvada.com/truvada-patient-assistance
 - For drug cost only
- For laboratory tests and doctor visits, consider community health center, federally qualified health center

Case 6

45-year-old white man taking TDF/FTC for HIV risk reduction, but struggles with pill aversion. He also dislikes the quarterly doctor visits. He manages to take his daily medication but inquires about alternative, less-frequently dosed medications for HIV risk reduction.

Future of PrEP



Tenofovir Alafenamide (TAF)

- Achieves high intracellular concentrations, but lower plasma and tissue concentrations than TDF
 - 13-fold lower than TDF in rectal tissues
 - 11-fold lower than TDF in cervicovaginal fluid

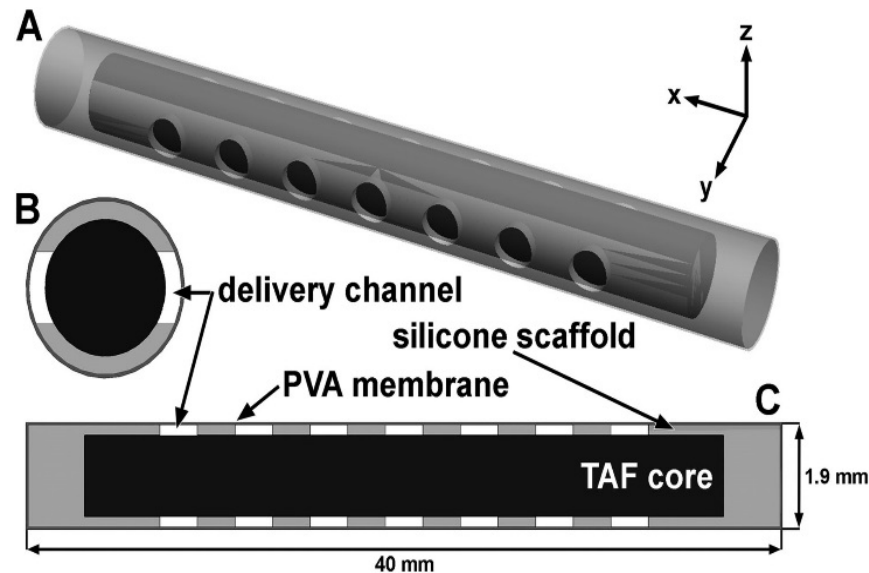
Due to low plasma and tissue concentrations, TAF's use in PrEP is uncertain

Tenofovir Alafenamide (TAF)

- However...
 - An animal study suggests efficacy
 - 6 macaques received TAF/FTC before and after rectal weekly exposure of SHIV or up to 19 weeks
 - 6 macaques received placebo
 - None of the 6 receiving TAF/FTC acquired SHIV, while all 6 receiving placebo did

Tenofovir Alafenamide (TAF)

- Formulation as subdermal implant in development



Cabotegravir

- Integrase inhibitor with long half-life
- Long acting, depot-controlled nanosuspension has an even longer half-life (25-54 days)
- Use as PrEP in phase 2 trials:
 - Oral lead-in
 - Will likely need every 2 months (6 injections/year)
 - Injection site reactions common
 - Most patients still preferred this over daily oral PrEP

Rilpiverine

- Non-nucleoside reverse-transcriptase inhibitor
- Long-acting, depot-controlled nanosuspension has a long half life (44-62 days)
- Use in PrEP remains undetermined

Rectal tenofovir gel

- On-demand use, vs. every day dosing
- Integrated into lubricant
- In a recent phase 2 study, there was no difference in adherence, or preference, compared to daily oral PrEP
- Efficacy remains under investigation
- A tenofovir vaginal film and gel is also under investigation

MK-8591

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- High, long-lasting (>7 days) concentrations in rat lymphoid tissue, macaque rectal/vaginal tissue
- Weekly dosing with MK-8591 (N=8) vs placebo (N=8) in macaques
 - All subjected to repeated intra-anal exposure to SHIV
 - After 12 weeks, all in control group were infected with SHIV, 0 in MK-8591 group were infected

Grobler J et al. *MK-8591 concentrations at sites of HIV transmission and replication*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 435, 2017.

Markowitz M. Weekly Oral MK-8591 Protects Male Rhesus Macaques against Repeated Low Dose Intrarectal Challenge with SHIV109CP3 . 9th IAS Conference on HIV Science (IAS 2017), July 23-26, 2017, Paris

Pharmacy-Driven PrEP Initiatives

- “One-Step PrEP” in Seattle, WA
 - Pharmacist provides screening, counseling and provision of PrEP under the remote oversight of physician
 - Between 2015-2016, initiated PrEP in 245 patients, 43% without a PCP
 - Retention was 75%
 - Financially sustainable for pharmacy

ONE-STEP PrEP®

Pharmacy-Driven PrEP Initiatives

Walgreens

- As of 7/2017, select sites offer PrEP counseling, STI screening, and Truvada provision
- Sites are those with existing Walgreens Healthcare Clinics with APNs, PAs
- Sites include:
 - Cincinnati, Cleveland, Columbus, Dallas, Denver, Kansas City, Knoxville, Las Vegas, Louisville, Memphis, Nashville, Orlando, Philadelphia, Phoenix, Tucson, Washington D.C., and Wichita.
- <https://www.walgreens.com/topic/scheduler/hiv-prep.jsp>

Thank you!

- Questions?