Pre-Exposure Prophylaxis (PrEP)
Daily medication to reduce HIV

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March 24, 2017

Disclosures

- None declared

Agenda

- What is PrEP?
- How effective is it?
- Why do we need it?
- Who benefits from PrEP?
- What are drawbacks?
- Who can prescribe?
- How to prescribe?
- The future of PrEP

But first, a case

62-year-old man presents to discuss primary prevention to reduce his risk of MI and stoke. He has a 30-pack-year smoking history (quit 2 years ago), is moderately overweight, and has well-controlled hypertension on HCTZ. What do you do?

Case 1

A: Encourage weight loss only

B: Recommend daily aspirin 81mg

C: Congratulate him on his smoking cessation

D: Refer him to a cardiologist

(you can only do only do one thing)

Case 2.10

62-year-old man presents to discuss primary prevention to reduce his risk of MI and stroke. He has a 20 pack-year smoking history (quit 2 years ago), is moderately overweight, and has well-controlled hypertension on HCTZ.

What do you do?

22-year-old man presents to discuss primary prevention to reduce his risk of HIV infection. He has a 20 pack-year smoking history (quit 2 years ago), is moderately overweight, and has well-controlled hypertension on HCTZ.

What do you do?

Case 2.0

A: Encourage abstinence only

B: Recommend daily Truvada PrEP

C: Congratulate him on his smoking cessation

D: Refer him to an Infectious Disease specialist

What is 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

Also approved in Australia, Canada, France, Peru, Israel, Kenya, and South Africa

This is different from PEP

- PrEP = Pre-Exposure Prophylaxis
  - HIV exposure has not yet ocurred
- PEP = Post-Exposure Prophylaxis
  - HIV exposure HAS occurred
  - Goal is to reduce incidence of established infection
  - THREE drugs required: Truvada (TDF/FTC) + raltegravir

How well does PrEP work?

iPrEX

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ORIGINAL ARTICLE

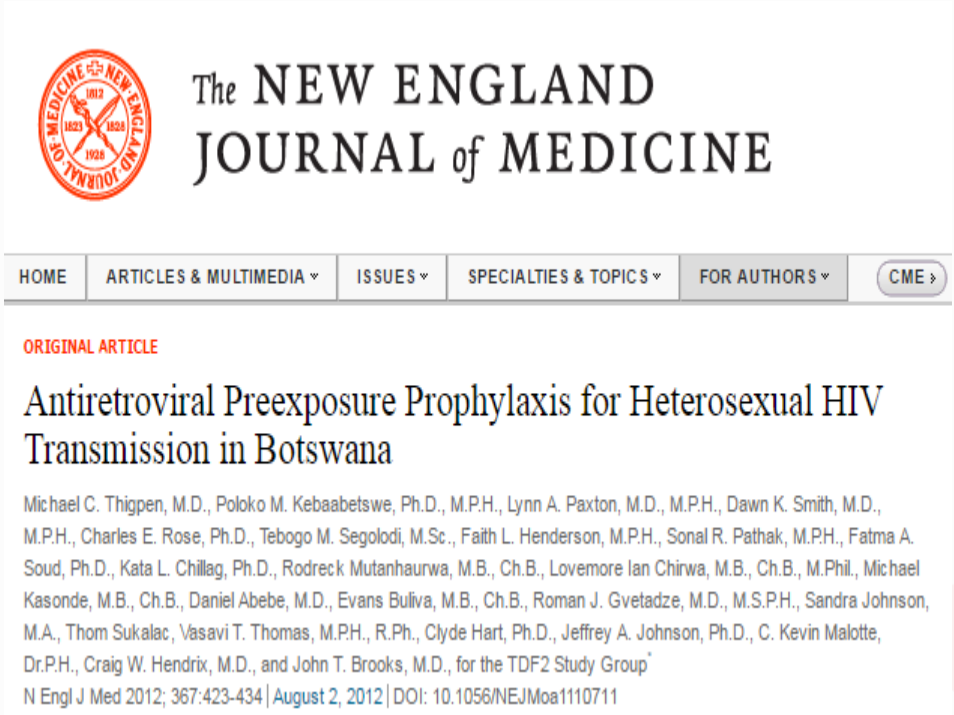
Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

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., Valdilea 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

TDF2 Study Group



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ORIGINAL ARTICLE

Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana

Michael C. Thigpen, M.D., Poloko M. Kebaabetswe, Ph.D., M.P.H., Lynn A. Paxton, M.D., M.P.H., Dawn K. Smith, M.D., M.P.H., Charles E. Rose, Ph.D., Tebogo M. Segolodi, M.Sc., Faith L. Henderson, M.P.H., Sonal R. Pathak, M.P.H., Fatma A. Soud, Ph.D., Kata L. Chillag, Ph.D., Rodreck Mutanhaurwa, M.B., Ch.B., Lovemore Ian Chirwa, M.B., Ch.B., M.Phil., Michael Kasonde, M.B., Ch.B., Daniel Abebe, M.D., Evans Buliva, M.B., Ch.B., Roman J. Gvetadze, M.D., M.S.P.H., Sandra Johnson, M.A., Thom Sukalac, Vasavi T. Thomas, M.P.H., R.Ph., Clyde Hart, Ph.D., Jeffrey A. Johnson, Ph.D., C. Kevin Malotte, Dr.P.H., Craig W. Hendrix, M.D., and John T. Brooks, M.D., for the TDF2 Study Group*

N Engl J Med 2012; 367:423-434 | August 2, 2012 | DOI: 10.1056/NEJMoa1110711

62.2% HIV risk reduction among heterosexual men and women

Partners PrEP Study Team

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ORIGINAL ARTICLE

Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

Jared M. Baeten, M.D., Ph.D., Deborah Donnell, Ph.D., Patrick Ndase, M.B., Ch.B., M.P.H., Nelly R. Mugo, M.B., Ch.B., M.P.H., James D. Campbell, M.D., Jonathan Wangisi, M.B., Ch.B., Jordan W. Tappero, M.D., M.P.H., Elizabeth A. Bukusi, M.B., Ch.B., Ph.D., Craig R. Cohen, M.D., M.P.H., Elly Katabira, M.B., Ch.B., Allan Ronald, M.D., Elioda Tumwesigye, M.B., Ch.B., Edwin Were, M.B., Ch.B., M.P.H., Kenneth H. Fife, M.D., Ph.D., James Kiarie, M.B., Ch.B., M.P.H., Carey Farquhar, M.D., M.P.H., Grace John-Stewart, M.D., Ph.D., Aloysious Kakia, M.B., Ch.B., Josephine Odoyo, M.P.H., Akasiima Mucunguzi, M.B., Ch.B., Edith Nakku-Joloba, M.B., Ch.B., Ph.D., Rogers Twesigye, M.B., Ch.B., M.P.H., Kenneth Ngure, Ph.D., Cosmas Apaka, B.Sc., Harrison Tamooh, M.B., Ch.B., Fridah Gabona, M.B., Ch.B., Andrew Mujugira, M.B., Ch.B., Dana Panteleeff, B.S., Katherine K. Thomas, M.S., Lara Kidoguchi, M.P.H., Meighan Krows, B.A., Jennifer Revall, B.A., Susan Morrison, M.D., M.P.H., Harald Haugen, M.S., Mira Emmanuel-Ogier, B.A., Lisa Ondrejcek, M.A., Robert W. Coombs, M.D., Ph.D., Lisa Frenkel, M.D., Craig Hendrix, M.D., Namandjé N. Bumpus, Ph.D., David Bangsberg, M.D., M.P.H., Jessica E. Haberer, M.D., M.P.H., Wendy S. Stevens, M.D., F.C.Path., Jairam R. Lingappa, M.D., Ph.D., and Connie Celum, M.D., M.P.H., for the Partners PrEP Study Team*

N Engl J Med 2012; 367:399-410 | August 2, 2012 | DOI: 10.1056/NEJMoa1108524

75% HIV risk reduction among heterosexual sero-discordant couples, 90% among those with detectable drug levels

Bangkok Tenofovir Study Group

THE LANCET

Volume 381, Issue 9883, 15–21 June 2013, Pages 2083–2090

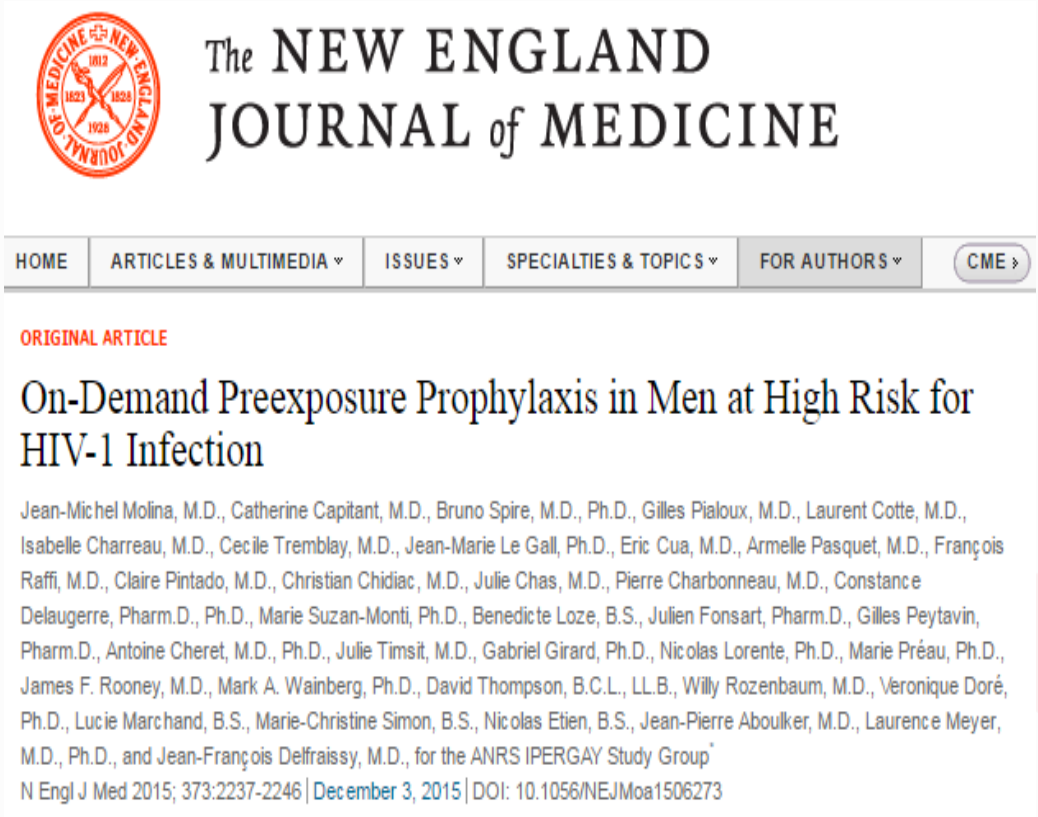
Articles

Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial

Kachit Choopanya, MD[a], Dr Michael Martin, MD[b, c], Pravan Suntharasamai, MD[a], Udomsak Sangkum, MD[a], Philip A Mock, MAppStats[b], Manoj Leethochawalit, MD[d], Sithisat Chiamwongpaet, MD[d], Praphan Kitisin, MD[d], Pitinan Natrujirote, MD[d], Somyot Kittimunkong, MD[e], Rutt Chuachoowong, MD[b], Roman J Gvetadze, MD[c], Janet M McNicholl, MD[b, c], Lynn A Paxton, MD[c], Marcel E Curlin, MD[b, c], Craig W Hendrix, MD[f], Suphak Vanichseni, MD[a], for the Bangkok Tenofovir Study Group

48.9% risk reduction, but 74% HIV risk reduction when taken consistently, among IDUs (TDF only)

IPERGAY



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ORIGINAL ARTICLE

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

Jean-Michel Molina, M.D., Catherine Capitant, M.D., Bruno Spire, M.D., Ph.D., Gilles Pialoux, M.D., Laurent Cotte, M.D., Isabelle Charreau, M.D., Cecile Tremblay, M.D., Jean-Marie Le Gall, Ph.D., Eric Cua, M.D., Armelle Pasquet, M.D., François Raffi, M.D., Claire Pintado, M.D., Christian Chidiac, M.D., Julie Chas, M.D., Pierre Charbonneau, M.D., Constance Delaugerre, Pharm.D., Ph.D., Marie Suzan-Monti, Ph.D., Benedicte Loze, B.S., Julien Fonsart, Pharm.D., Gilles Peytavin, Pharm.D., Antoine Cheret, M.D., Ph.D., Julie Timsit, M.D., Gabriel Girard, Ph.D., Nicolas Lorente, Ph.D., Marie Préau, Ph.D., James F. Rooney, M.D., Mark A. Wainberg, Ph.D., David Thompson, B.C.L., LL.B., Willy Rozenbaum, M.D., Veronique Doré, Ph.D., Lucie Marchand, B.S., Marie-Christine Simon, B.S., Nicolas Etien, B.S., Jean-Pierre Aboulker, M.D., Laurence Meyer, M.D., Ph.D., and Jean-François Delfraissy, M.D., for the ANRS IPERGAY Study Group*

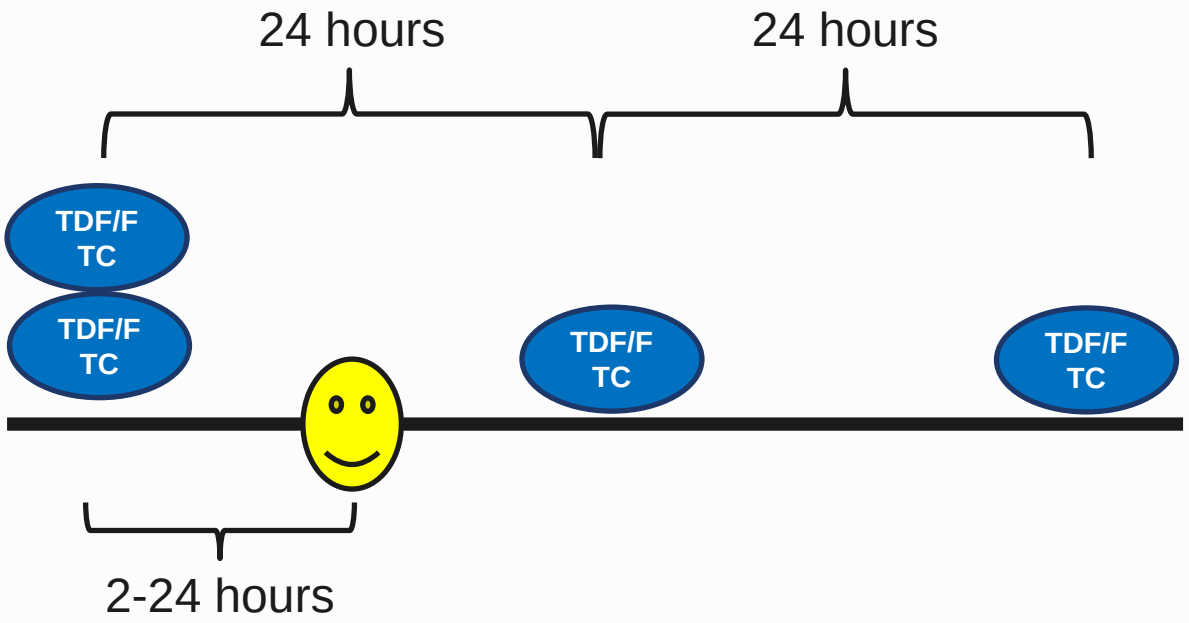
N Engl J Med 2015; 373:2237-2246 | December 3, 2015 | DOI: 10.1056/NEJMoa1506273

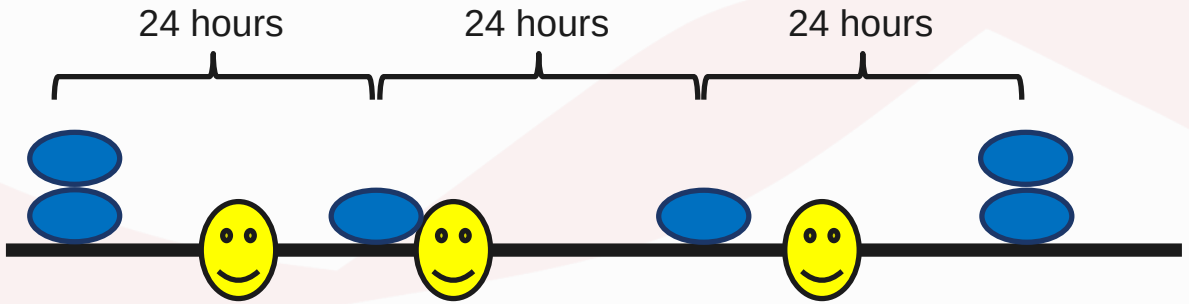
86% HIV risk reduction in MSM using on-demand PrEP

IPERGAY

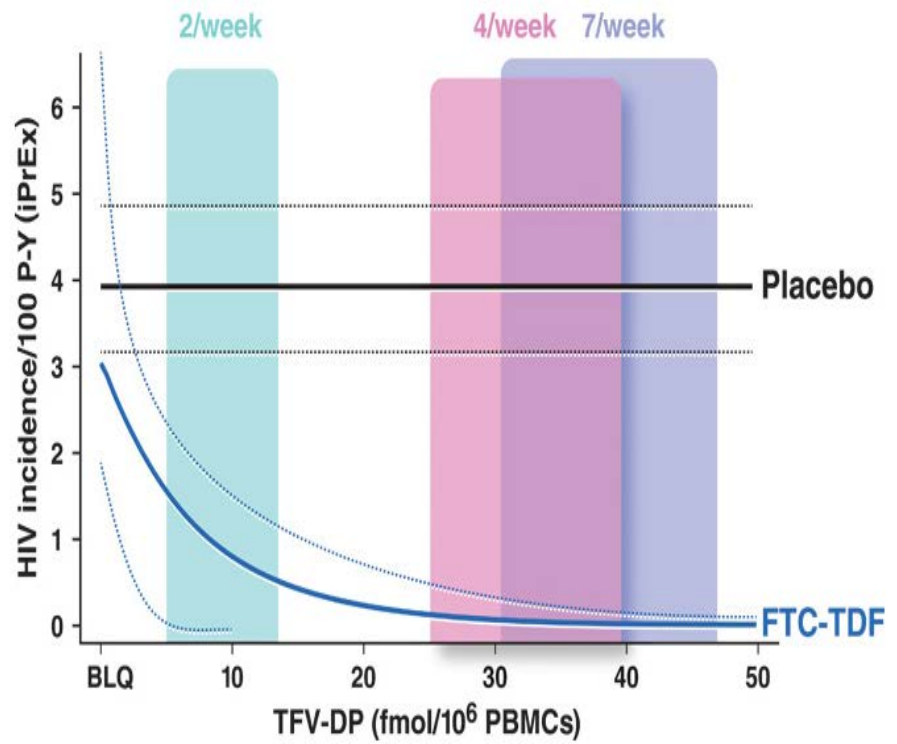
- Study was discontinued early, all offered on-demand PrEP in open-label phase and more enrolled.
- Mean pill use: 18 pills/month
- 97% reduction in relative risk of HIV in this extended arm versus the discontinued placebo arm

On-Demand Dosing





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.

Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012;4: 151ra125. doi: 10.1126/scitranslmed.3004006. pmid:22972843

Studies Summary

Study	Population	Dosing	Risk Reduction
iPrEX	MSM	Daily	44% (92% with ideal adherence)
TDF2	Heterosexual men and women	Daily	62.2%
Partners	Sero-discordant heterosexual couples	Daily	75% (90% with ideal adherence)
Bangkok Tenofovir Study Group	Intravenous drug users	Daily	48.9% (74% with ideal adherence)
IPERGAY	MSM	On-demand	86%

Why PrEP matters

90 90 90

Joint United Nations Program on HIV/AIDS (UNAIDS) goal to have **90%** of those living with HIV to know their status, **90%** of those to be on ART, and **90%** of those on ART to be virologically suppressed by 2020

60

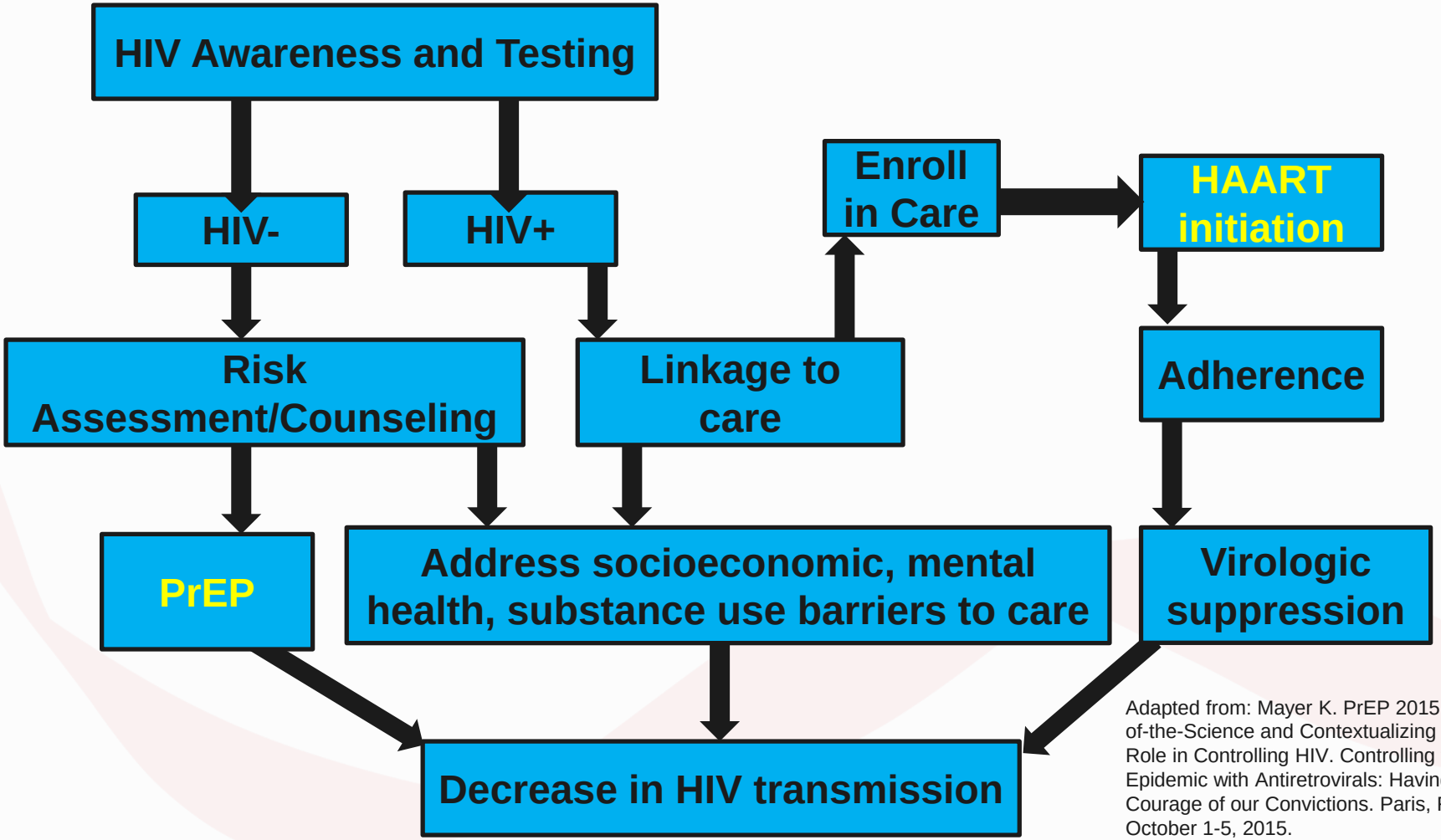
46

38

As of 2015, **60%** of those living with HIV know their status,
46% of those are on ART, and
38% of those on ART are virologically suppressed.

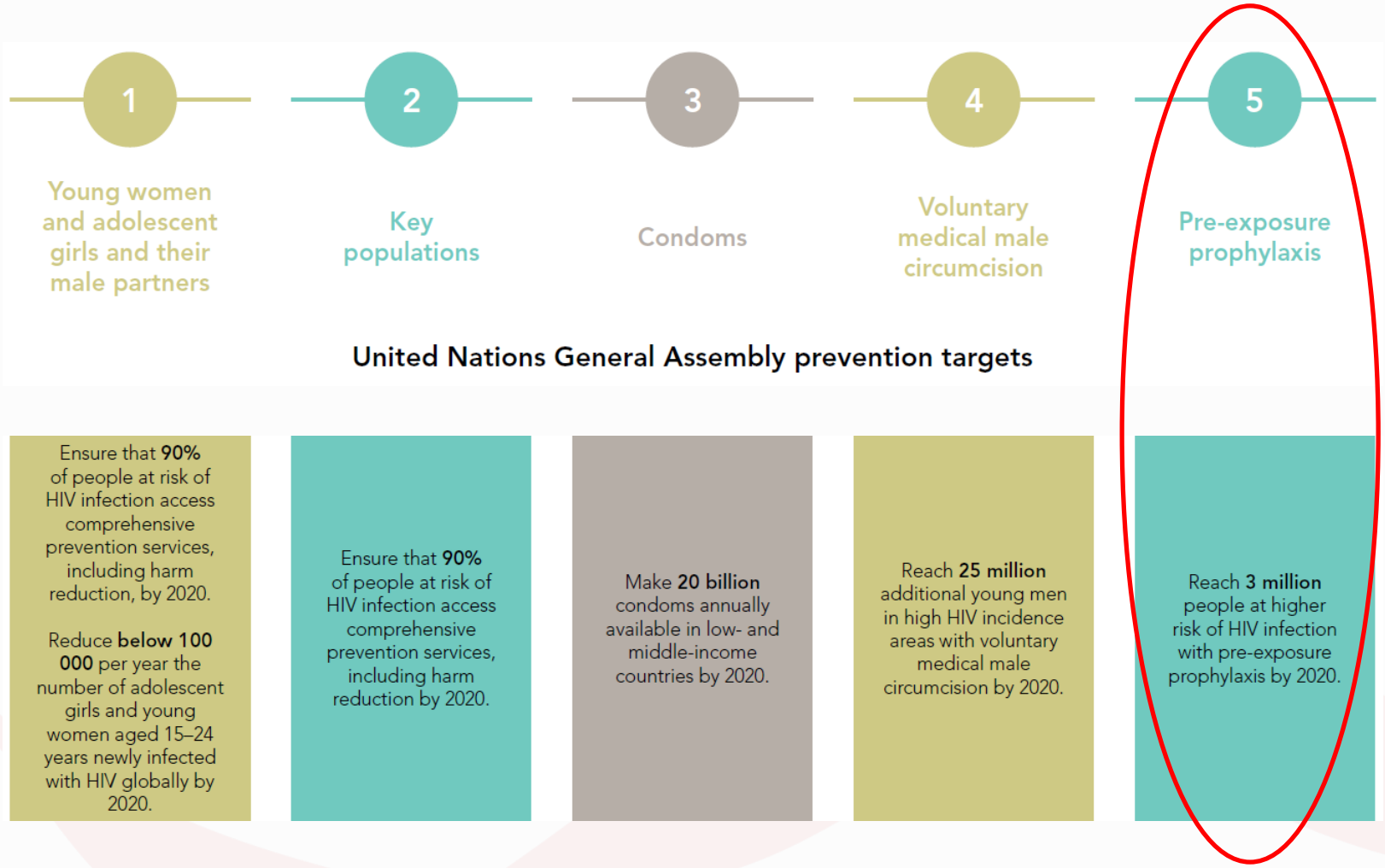
http://www.unaids.org/en/resources/documents/2016/prevention-gap

HAART alone is not the only key



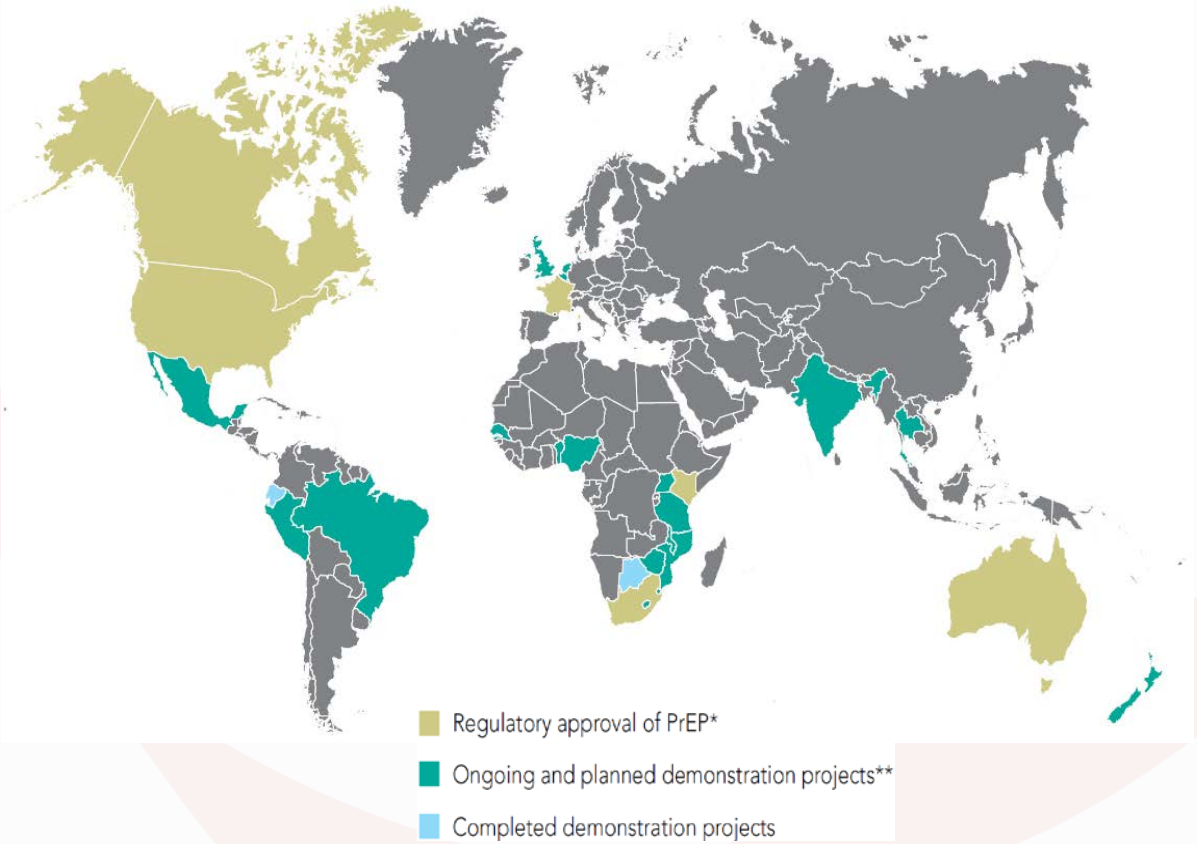
Adapted from: Mayer K. PrEP 2015: State-of-the-Science and Contextualizing PrEP's Role in Controlling HIV. Controlling the HIV Epidemic with Antiretrovirals: Having the Courage of our Convictions. Paris, France. October 1-5, 2015.

FIVE PREVENTION PILLARS



http://www.unaids.org/en/resources/documents/2016/prevention-gap

COUNTRIES THAT HAVE DEMONSTRATION PROJECTS OR HAVE APPROVED TENOFOVIR DISOPROXYL FUMARATE/EMTRICITABINE FOR PRE-EXPOSURE PROPHYLAXIS, AS OF JUNE 2016



***These countries also have completed, ongoing and/or planned demonstration projects.**

**** These projects investigate different aspects of PrEP provision and impact including acceptability, safety, adherence, effect, appropriate service delivery, integration in combination prevention services, costing and associated behavioural aspects. Their aim is to increase access to PrEP for those people who could benefit most from it, especially in situations of stigma, marginalization and criminalization.**

AVAC, U.S. FDAood and Drug Administration, Department of Health, Republic of South Africa, ANSM, MCC, Health Canada, AVERT, and Therapeutic Goods Administration, Department of Health, Australia. (See Notes section for details.) http://www.unaids.org/en/resources/documents/2016/prevention-gap

How are we doing?

- By the end of 2015, 79,684 individuals had prescriptions for PrEP (TDF/FTC) in the US
  - Out of an estimated 415,000 eligible
  - 19.2% of those eligible

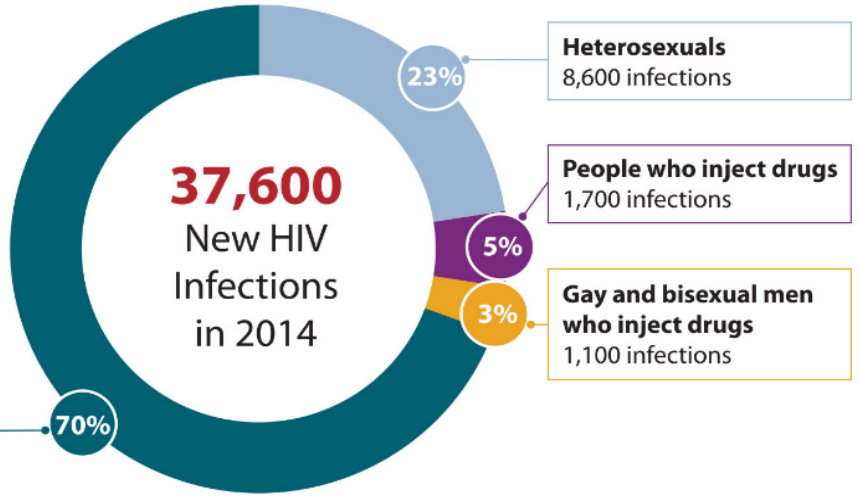
Mera R, et al. Truvada (TVD) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States (2013-2015). Presented at: AIDS 2016. Durban, South Africa. July 18-22. 2016.

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

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

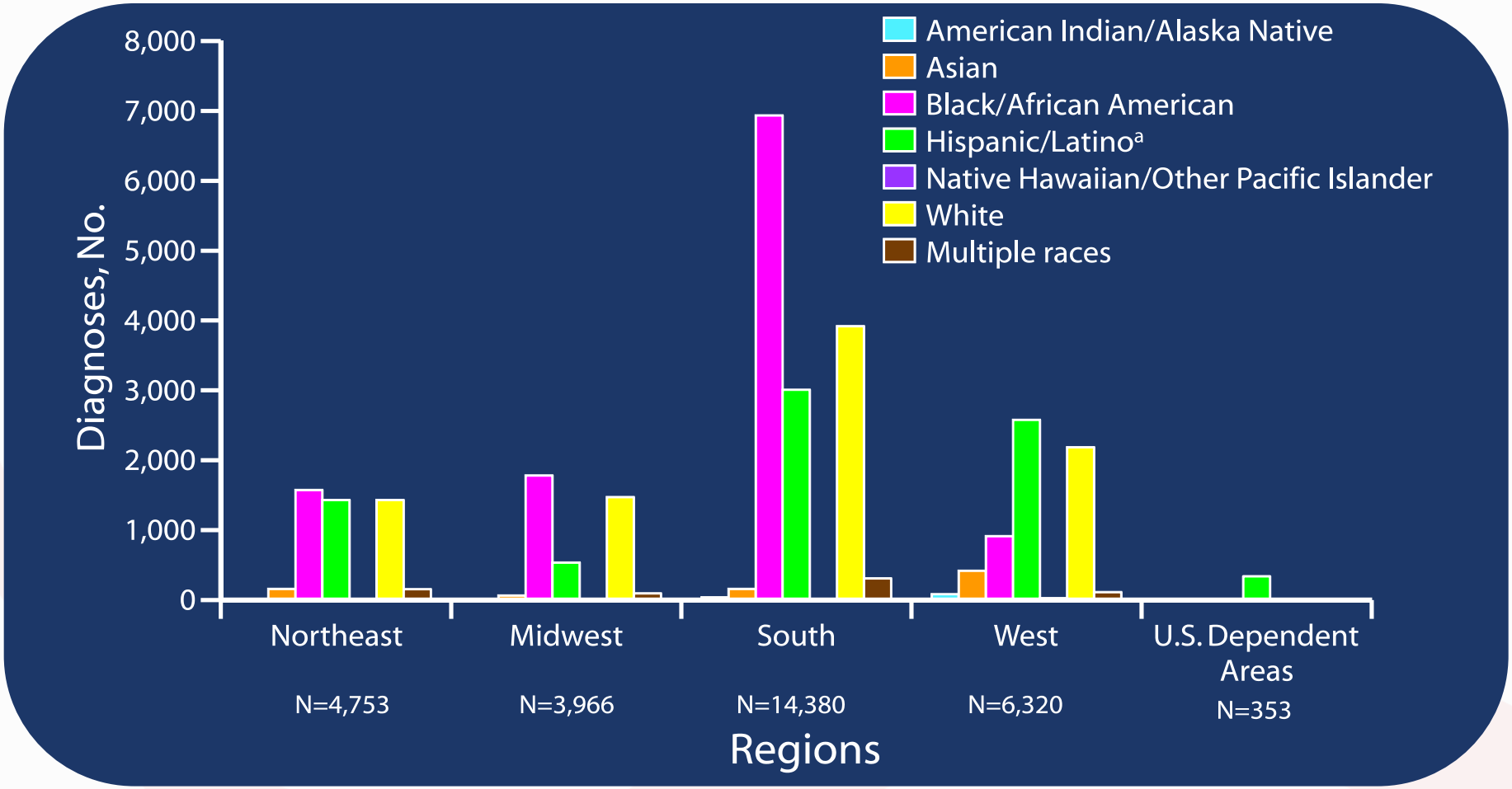
56% decline	36% decline	26% decline	18% decline
among **people who inject drugs**	among **heterosexuals**	among **gay and bisexual men aged 35-44 years**	among **gay and bisexual men aged 13-24 years**

Gay and bisexual men remain most affected



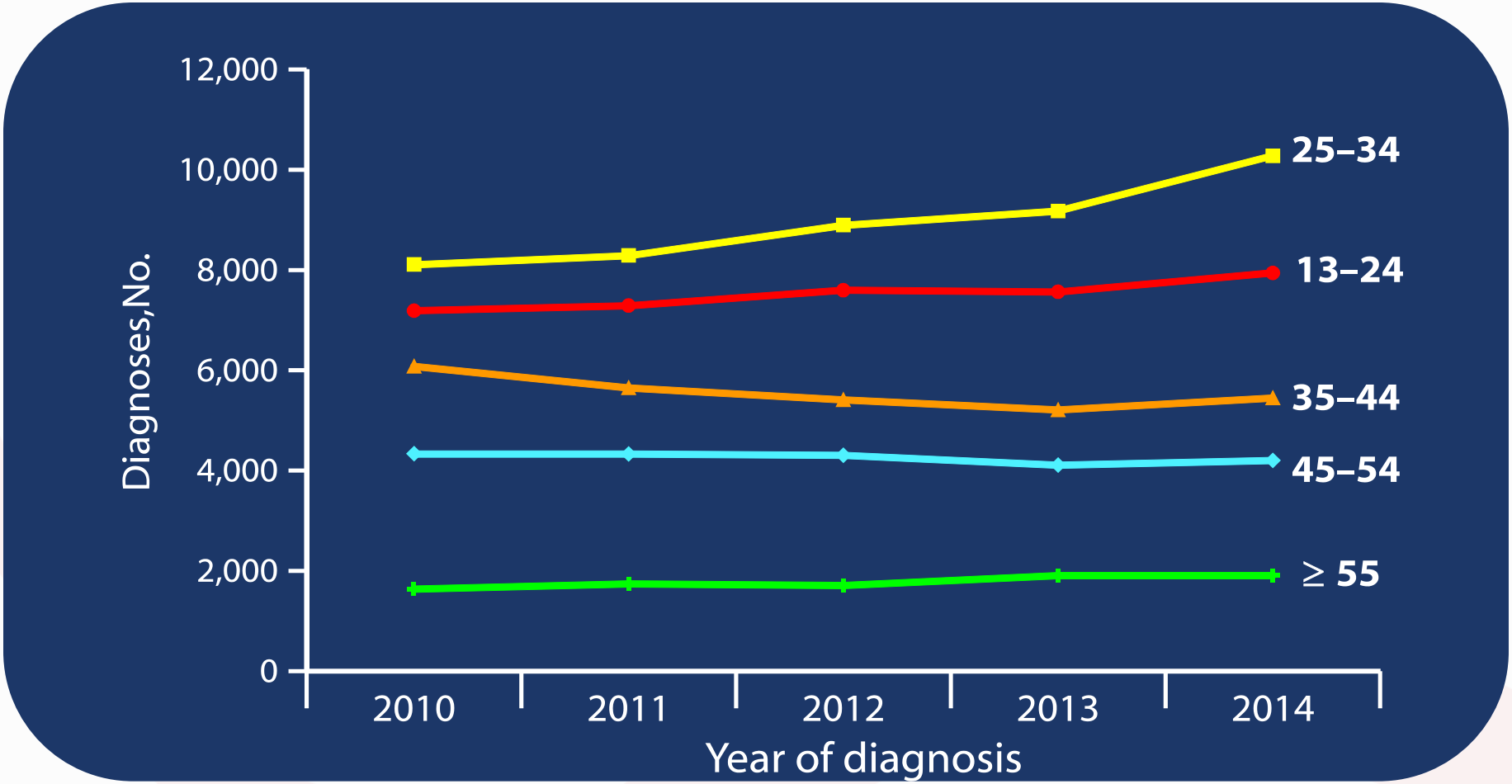
https://www.cdc.gov/nchhstp/newsroom/2017/croi-2017.html#Graphics

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



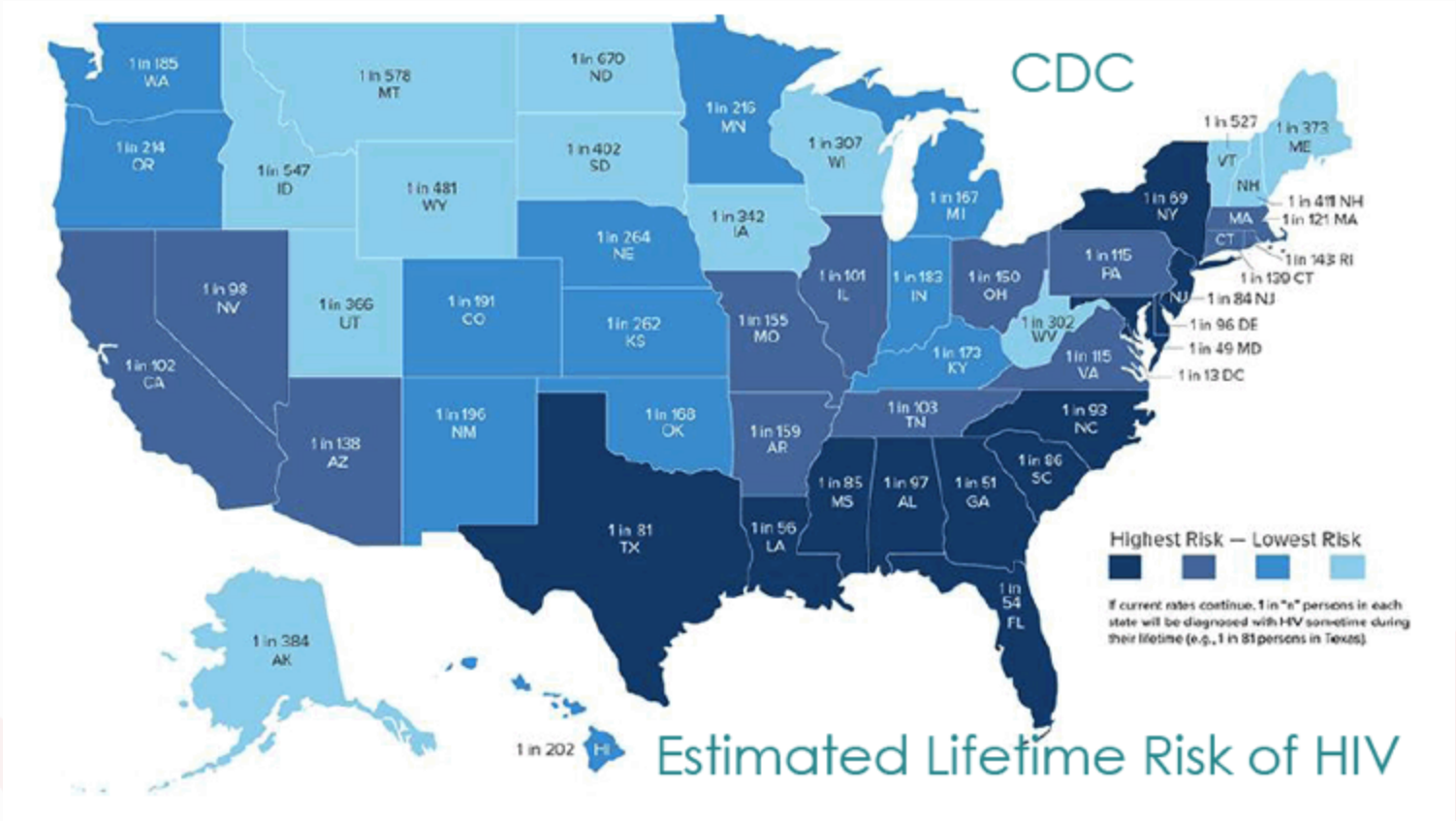
Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include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

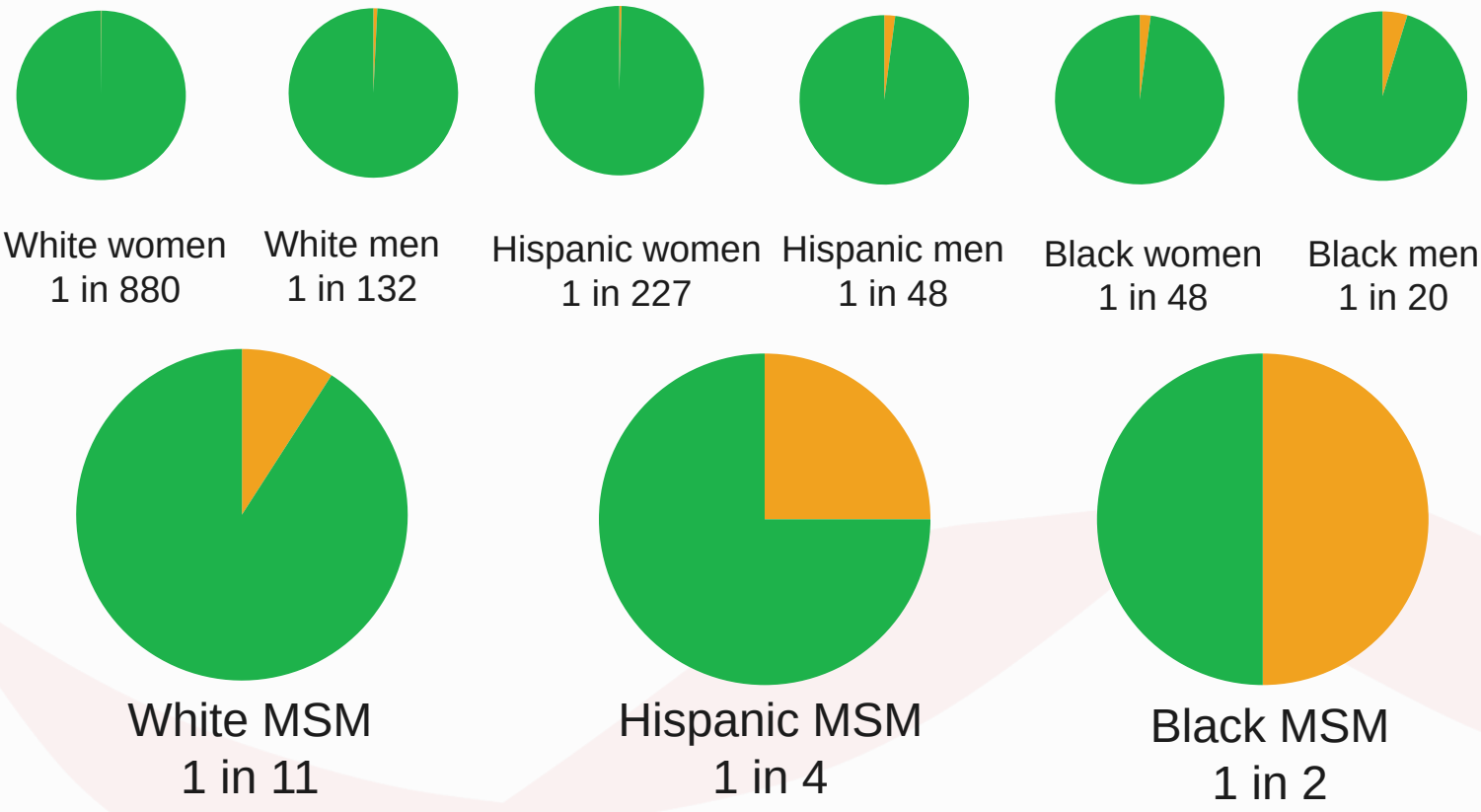


Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include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



CDC, 23 Feb 2016: http://www.cdc.gov/nchhstp/newsroom/2016/croi-press-release-risk.html

Who benefits from PrEP?

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

https://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf

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

https://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf

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

https://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf

Who benefits from PrEP?

- Sero-discordant sexual activity (couples)
- Multiple sex partners (especially sex partners with unknown HIV status or at risk for HIV) with inconsistent or no condom use
- History of sexually transmitted infections
- Exchange of sex for money or commodities
- Injection drug use

Who doesn't benefit?

- HIV infection
- Those at risk for adverse effects due to pre-existing comorbid conditions (chronic kidney disease)
- Unwilling to take daily medication
- Not engaging in activity with increased HIV risk

HIV risk is behavioral

The only way to know is to ask

Taking a sexual history

- Survey of 85 HIV-infected MSM
  - 77of MSM had a sexual history documented
  - 75 of those who were sexually active had STI screens offered, and 68 of those accepted screening
  - Of these, **16 had an STI**
  - 63 had a recreational drug use history taken
  - **17 of these reported active drug use, 3 used drugs for sex (“chemsex”)**

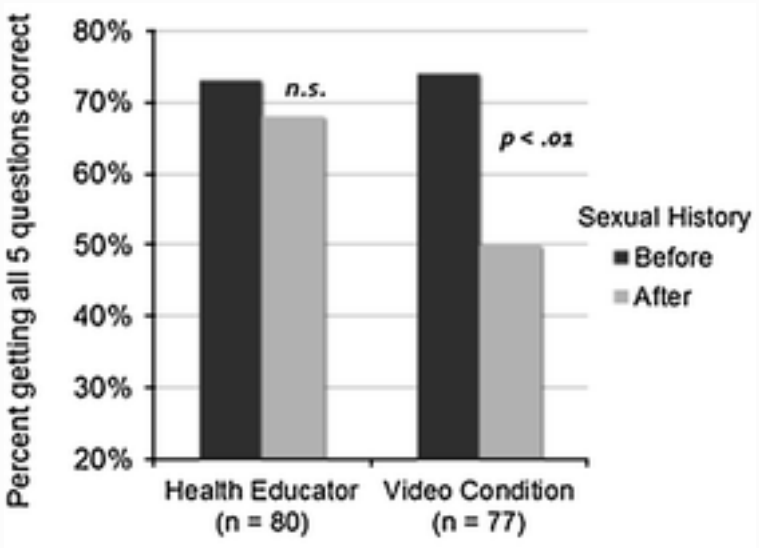
MacRae A, et al. Int J STD AIDS. 2017 Mar;28(3):294-296.

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



Golub SA, et al. AIDS Behav. 2016 Jul 30. [Epub ahead of print]

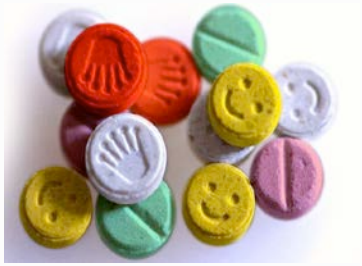
STI Epidemic

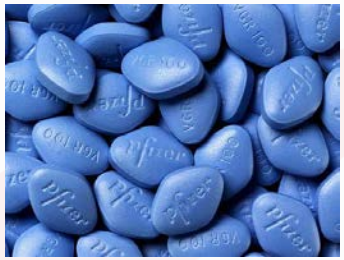
- Between 2014 and 2015
  - Chlamydia cases increased 5.9% (to 1.5 million cases)
  - Gonorrhea cases increased 12.8% (to 400,000 cases)
  - Syphilis cases increased 19% (to 24,000 cases)
  - Adolescents/young adults age 15-24 account for half of these
- Screening in MSM
  - Syphilis, chlamydia, gonorrhea, and HIV screen annually if sexually active
  - More frequent (every 3 or 6 months) if multiple or anonymous partners
- Screening in women
  - Gonorrhea, chlamydia annually if ≤25 years, or annually if >25 and multiple partners
  - Syphilis, HIV, chlamydia, gonorrhea, and HBV in all pregnant women

https://www.cdc.gov/nchhstp/newsroom/2016/std-surveillance-report-2015-press-release.html

Chemsex

- Use of recreational substances to augment the sexual experience
- Among MSM, associated with:
  - Having HIV or HCV-infected partners
  - Higher risk-taking behaviors (i.e. condomless sex, multiple partners)
  - Acute bacterial STIs
  - Rectal STIs
  - Hepatitis C incidence
  - HIV incidence





Hegazi A, et al. Int J STD AIDS. 2017 Mar;28(4):362-366.

How often do you discuss sexual behavior with your patients?

A. Every single encounter

B. Initial encounter only

C. Occasionally

D. Very seldom

E. Almost Never

What are your barriers to the discussion?

*Wordcloud

Stigma

A preventative measure against the consequences of sexual activity

… *condones* sexual activity

… *promotes* sexual activity

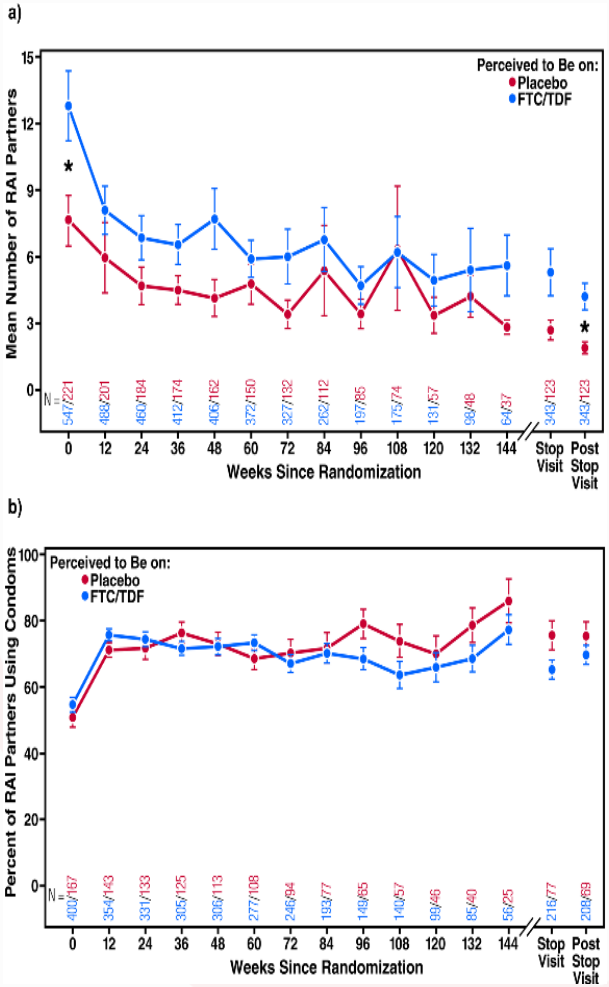
… *causes* sexual activity

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 preexposure 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

Julia L. Marcus, David V. Glidden, Kenneth H. Mayer, Albert Y. Liu, Susan P. Buchbinder, K. Rivet Amico, Vanessa McMahan, Esper Georges Kallas, Orlando Montoya-Herrera, Jose Pilotto, Robert M. Grant. PLoS One. 2013 Dec 18;8(12):e81997

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

Biello KB, et al. The "Safe Sex" Conundrum: Anticipated Stigma From Sexual Partners as a Barrier to PrEP Use Among Substance Using MSM Engaging in Transactional Sex. AIDS Behav. 2016 Jun 28.

…and Missed Opportunities

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

Patel R, et al. Missed Opportunities to Prescribe PrEP by Primary Care Physicians in Saint Louis. Presented at: CROI, February 22–25, 2016, Boston, Massachusetts

The drawbacks of PrEP

Cost

- $13,000 for one year in USA
- Covered by most private insurance companies
  - Variable co-pays, deductibles, etc.
- Medicaid coverage varies by state
- Co-pay and cost assistance available
  - Up to $3,600/year in co-pay assistance
  - Medication assistance if <500% federal poverty level

Adverse Events

Table 2. Adverse Events.*

Adverse Event	FTC–TDF (N=1251)		Placebo (N=1248)		P Value†
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*	
Any adverse event	867 (69)	2630	877 (70)	2611	0.50
Any serious adverse event	60 (5)	76	67 (5)	87	0.57
Any grade 3 or 4 event	151 (12)	248	164 (13)	285	0.51
Grade 3 event	110 (9)	197	117 (9)	225	0.65
Grade 4 event	41 (3)	51	47 (4)	60	0.57
Elevated creatinine level	25 (2)	28	14 (1)	15	0.08
Headache	56 (4)	66	41 (3)	55	0.10
Nausea	20 (2)	22	9 (<1)	10	0.04
Unintentional weight loss (≥5%)	27 (2)	34	14 (1)	19	0.04
Death	1 (<1)‡	1	4 (<1)	4	0.18
Discontinuation of study drug					
Permanently	25 (2)	26	27 (2)	33	0.82
Permanently or temporarily	79 (6)	99	72 (6)	92	0.49

* A listing of all laboratory abnormalities and clinical adverse events of grade 2 or higher that were reported in 25 or more subjects (1%) is provided in Tables S9 and S10 in the Supplementary Appendix. FTC–TDF denotes emtricitabine and tenofovir disoproxil fumarate.
† P values were calculated by the log-rank test.
‡ This death was due to a motorcycle accident.

iPrEX, 2010

Adverse Events

Table 2. Adverse Events, According to Treatment Group.*

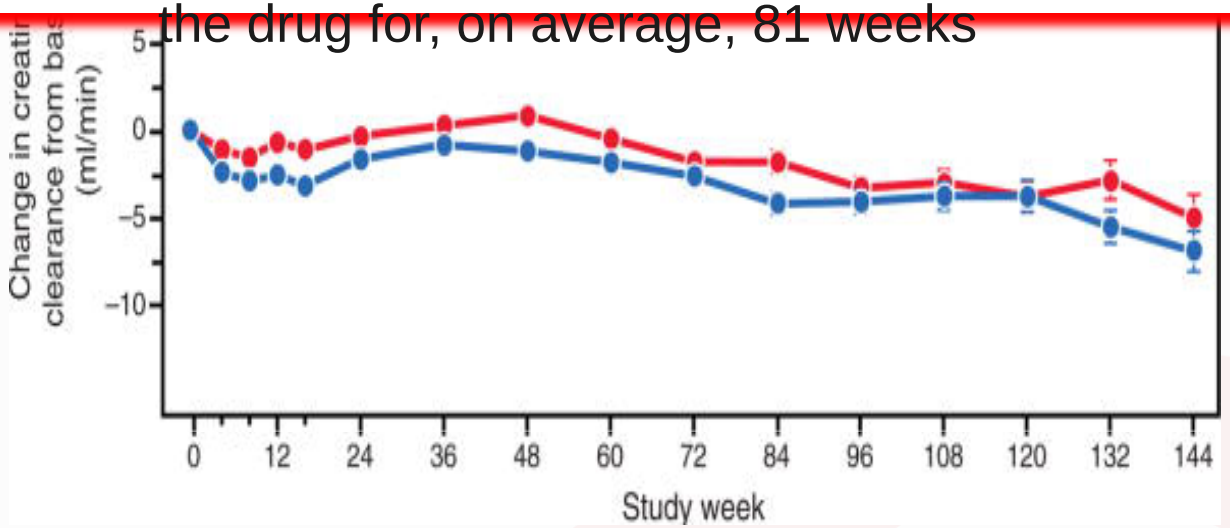
Adverse Event	TDF–FTC (N=611)		Placebo (N=608)		P Value†
	no. of participants (%)	*no. of events*	*no. of participants (%)*	*no. of events*	
Any	557 (91.2)	4357	536 (88.2)	4390	0.003
Any serious	63 (10.3)	68	66 (10.9)	79	0.90
Grade 3 or 4 only	19 (3.1)	21	29 (4.8)	32	0.17
At least possibly related to study drug	20 (3.3)	21	27 (4.4)	29	0.35
Upper respiratory tract infection	231 (37.8)	385	241 (39.6)	439	0.84
Headache	227 (37.2)	390	226 (37.2)	411	0.73
Dizziness	92 (15.1)	109	67 (11.0)	82	0.03
Nausea	113 (18.5)	132	43 (7.1)	48	<0.001
Vomiting	69 (11.3)	87	43 (7.1)	47	0.008
Fracture	7 (1.1)	7	6 (1.0)	8	0.74
Elevated creatinine	1 (0.2)	1	0	0	1.00
Hypophosphatemia	142 (23.2)	219	159 (26.2)	245	0.65
Hyperamylasemia	315 (51.6)	997	302 (49.7)	1017	0.45
Elevated AST	36 (5.9)	43	38 (6.2)	42	0.90
Elevated ALT	38 (6.2)	48	43 (7.1)	66	0.57
Death‡	2 (0.3)	2	4 (0.7)	4	0.45

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† All P values were calculated with the use of a time-to-first-event analysis (regression analysis of survival data on the basis of the Cox proportional-hazards model), with the exception of the P values for weight loss of 5% or more and death, which were calculated with the use of Fisher's exact test.
‡ The causes of death in the TDF–FTC group were motor vehicle accident (one participant) and suicide (one); the causes of death in the placebo group were motor vehicle accident (two), homicide (one), and cerebrovascular accident (one).

TDF2 Study Group, 2012

Adverse Events

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



iPrEX, 2013

Adverse Events

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
24 mo	−0.87	−0.13		0.20	0.76		−1.09	−0.28	

* 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.

BUT THIS CAN RECOVER!

Bone mineral density recovered after 6 months of stopping TDF/FTC in both young and older adults.

TDF2 Study Group, 2012

Grant RM, et al. Recovery of bone mineral density after stopping oral HIV pre-exposure prophylaxis. CROI 2016 Feb 20-24 Boston

How to provide PrEP

- Complete Risk Evaluation and Mitigation Strategies (REMS) training and registration
- Identify patient who will benefit (they may not ask)
- Engage in discussion
  - If unable or unwilling to offer, refer
- Advise patient to contact their insurance
  - May need co-pay assistance, prior-authorization

How to provide PrEP

- Follow CDC Guidelines
  http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf
  - Make sure the patient is HIV-negative!
    - Screen for HIV prior to starting PrEP
    - Assess for symptoms of acute HIV
    - Document HIV-negative status
  - Make sure they have normal renal function
    - Check serum creatinine
  - Obtain and document hepatitis B and C status
    - Check HBV serologies to evaluate immunity or infection
    - Check HCV screen
  - Screen for other STIs
  - Assess pregnancy intention

How to provide PrEP

- Prescribe PrEP
  - No more than 3 months at a time
- At 3 months
  - Repeat HIV screen, repeat serum creatinine
  - Assess adherence
  - Reassess eligibility
  - Assess for side effects
  - Provide behavioral risk reduction support
  - Assess pregnancy intention (test if could be pregnant)
  - If HIV-negative and eligible, refill PrEP

How to provide PrEP

- Every 3 months
  - HIV screen
  - Assess adherence
  - Reassess eligibility
  - Assess for side effects
  - Provide behavioral risk reduction support
  - Assess pregnancy intention (test if could be pregnant)
  - If HIV-negative and eligible, refill PrEP

How to provide PrEP

- Every 6 months
  - Screen for other STIs
  - Repeat serum creatinine

How to provide PrEP

- At any time, stop PrEP if:
  - The patient doesn't want it
  - Behavior or life situations have changed that lower risk for HIV infection
  - Intolerable adverse events/toxicities
  - Nonadherence despite attempted interventions to improve
  - HIV-infection

How to provide PrEP

Encounter	To do
Month 0	• Screen for HIV • Confirm HBV and HCV status • Check serum creatinine • Screen for STIs • Counseling • Prescribe
Month 3	• Screen for HIV • Check serum creatinine • Counseling • Prescribe
Month 6	• Screen for HIV • Screen for STIs • Counseling • Prescribe
Month 9	• Screen for HIV • Check serum creatinine • Counseling • Prescribe
Month 12	• 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)

Healthcare Provider's Signature _____ Date _____

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

HIV-Negative Person's Signature _____ Date _____

Truvada®
(emtricitabine-tenofovir disoproxil fumarate)

GILEAD

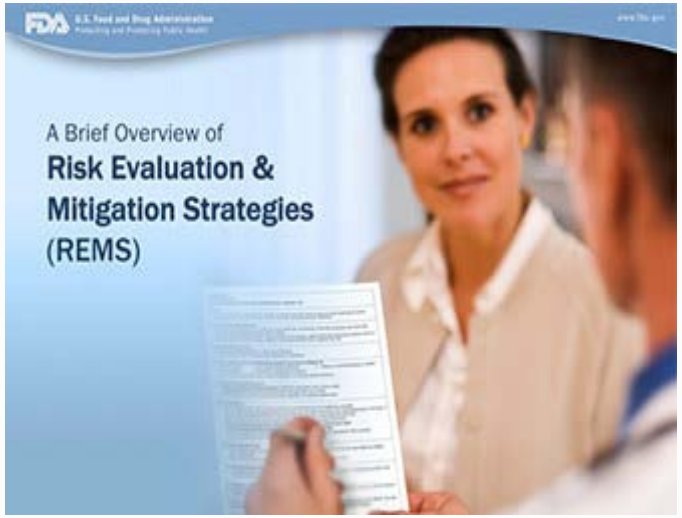
Special considerations

- **Pregnant or breastfeeding women**
  - Pregnancy Category B (No known risk)
  - Minimally secreted in breastmilk, not contraindicated in breastfeeding
- **Chronic HBV**
  - TDF and FTC are active against HBV
  - If TDF/FTC no longer used for PrEP, consider continuing with chronic HBV as the indication
- **Chronic Renal Failure (eGFR <60ml/min)**
  - Don’t use TDF/FTC; safety has not been adequately determined
- **Adolescent Minors**
  - Careful consideration, no subjects <18 years were included in trials

Adolescent Trials Network for HIV/AIDS Interventions (ATN) study

- 78 HIV-negative MSM, ages 15-17, who reported HIV risk behavior during the previous 6 months received daily PrEP
- Follow-up monthly for 12 weeks, then quarterly for the remainder of 48-week study
- Adherence was high during monthly follow-up, then dropped dramatically (by more than half)
- 32 discontinued before the end of the study
- HIV acquisition rate: 6.4%

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.

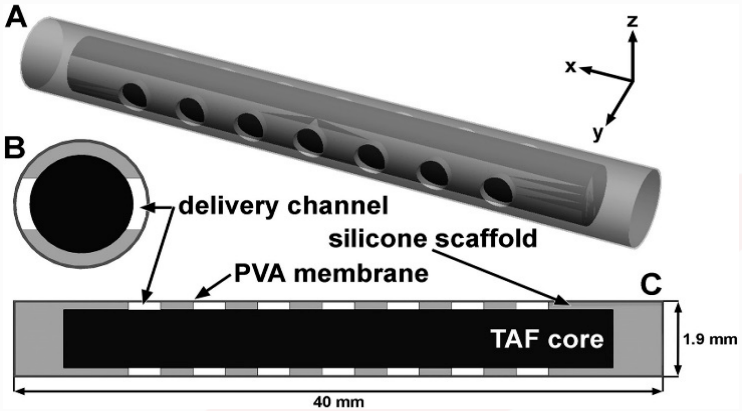
REMS for TDF/FTC

- 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

Future of PrEP

Tenofovir Alafenamide (TAF)

- More potent than TDF
- No known side effects of bone loss or reduced renal function
- Formulation as subdermal implant in development



Gunawardana M, Remedios-Chan M, Miller CS, Fanter R, Yang F, Marzinke MA, *et al.* Pharmacokinetics of long-acting tenofovir alafenamide (GS-7340) subdermal implant for HIV prophylaxis. *Antimicrob Agents Chemother* 2015,**59**:3913-3919.

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

Markovitz M, et al. ÉCLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men. Presented at: CROI, February 22–25, 2016, Boston, Massachusetts

Rilpiverine

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

Maraviroc

- CCR5-antagonist currently used in some ART regimens
- A recent phase 2 trial demonstrated it's as safe and well-tolerated as TDF/FTC
- Efficacy remains under investigation

Gulick R, et al. HPTN 069/ACTG 5305: Phase II Study of Maraviroc-Based Regimens for HIV PrEP in MSM. Presented at: CROI, February 22–25, 2016, Boston, Massachusetts

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

Cranston R, et al. MTN-017: Rectal Phase 2 Extended Safety and Acceptability Study of 1% Tenofovir Gel. Presented at: CROI, February 22–25, 2016, Boston, Massachusetts

Dapivirine vaginal ring

- Non-nucleoside reverse-transcriptase inhibitor
- Empowering women in HIV-endemic countries
- A recent phase III trial demonstrated disappointing HIV risk reduction (only up to 37%)

Where to start, learn more

- Review prescribing guidelines
- Start asking your patients
- Use reliable sources:
  - www.cdc.gov/hiv/prep
  - www.truvada.com

Thank you!

Questions?