PrEP 2013

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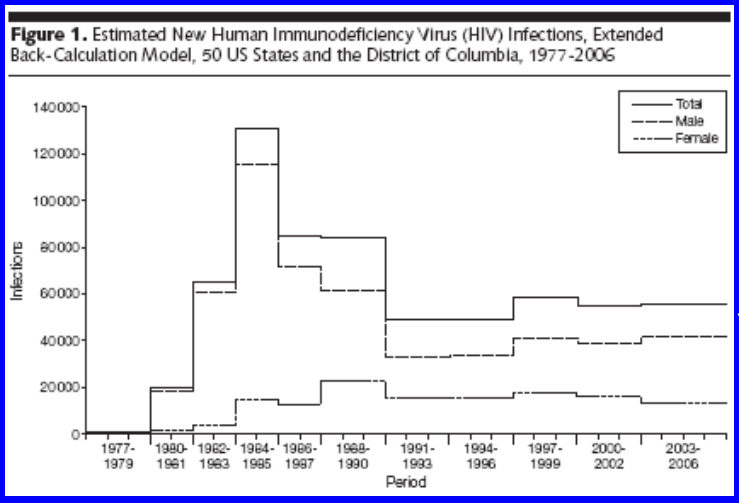
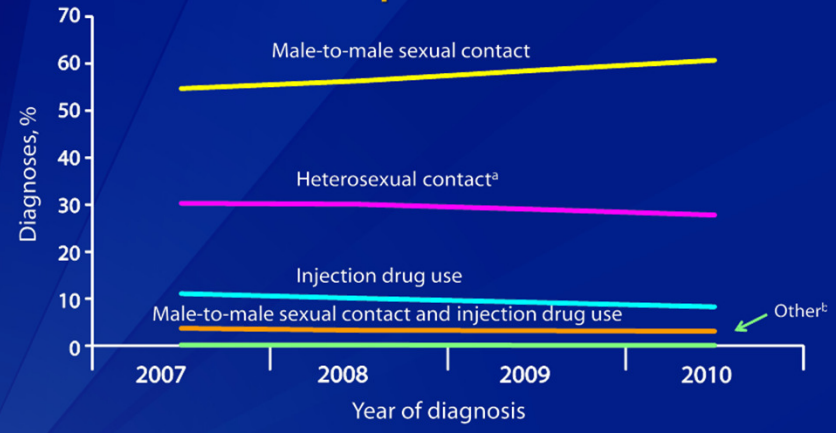
U.S.: New HIV Infections Per Year



~50,000 a year

Hall JAMA 2008;300:520
Prejean PLoS One 2011;6:e17502

Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2007–2010—46 States and 5 U.S. Dependent Areas

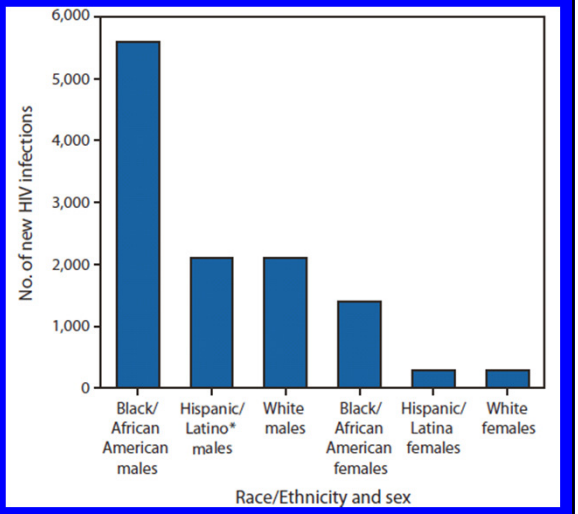


Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing risk-factor information, but not for incomplete reporting.
[a] Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
[b] Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

Slide #4

New HIV infections among 13–24 year olds — U.S., 2010

- Of all new HIV infections in 2010, 26% occurred in 13-24 year olds
- 60% are not aware they are infected
- 72% were MSM
- 20% were heterosexuals
- 13% were IDU



MMWR 2012;61:971-976

Slide #5

PrEP = Pre-Exposure Prophylaxis

- **PrEP = an HIV uninfected at-risk individual takes ART.**
- **By having ART in the bloodstream & genital tract, HIV may be unable to establish infection.**
- **ART = HIV prevention**

Slide #6

Tenofovir (TDF) + Emtricitabine (FTC) for PrEP

Optimal PrEP candidates:
potency, safety, tolerability, and convenience

 = TDF (tenofovir)

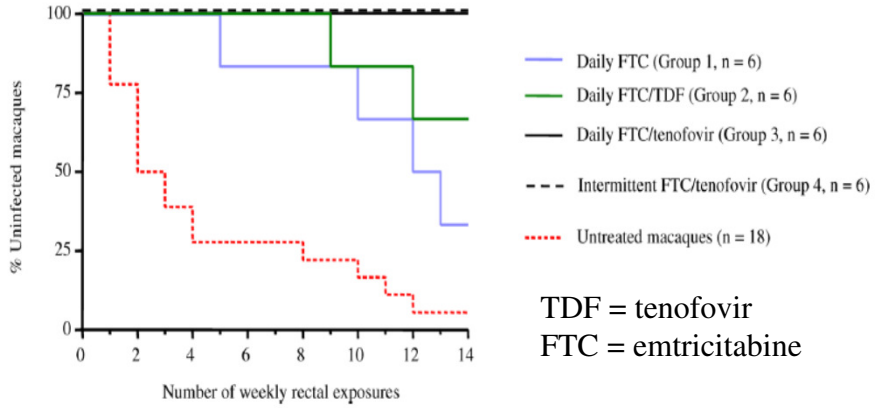
 = FTC/TDF (co-formulated emtricitabine + tenofovir)

Potential concerns:

- Used widely; preferred first-line treatment
- Drug resistance
- Toxicities: renal, bone
- Cost >$10,000/year

PrEP: Animal Model

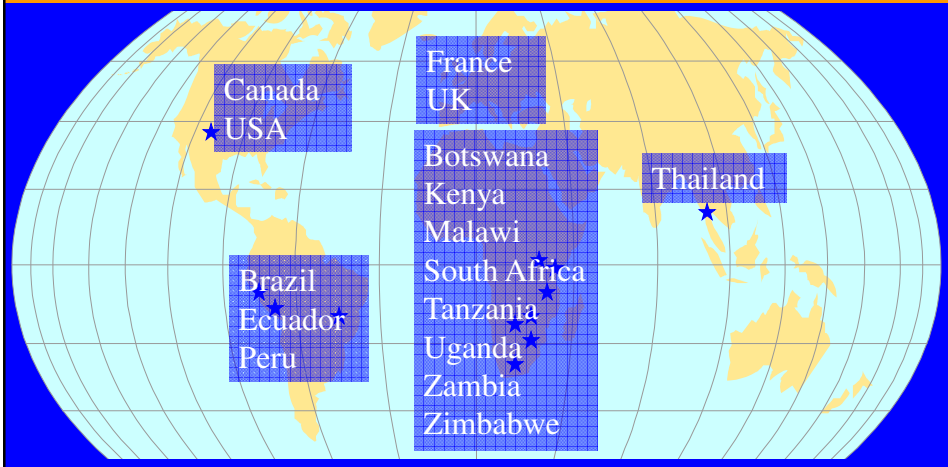
Effect of daily and intermittent PrEP in monkeys: SHIV rectal challenge model



TDF = tenofovir
FTC = emtricitabine

Garcia-Lerma, PLoS Med 2008

Completed and Current Studies of Oral PrEP



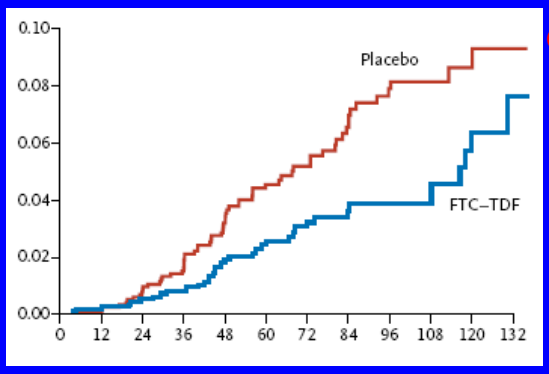
14 studies and projects, up to 16 countries

32,000+ participants

Slide #9

IPREX: PrEP in MSM

Phase III study of PREP with TDF/FTC or placebo
Study population: HIV uninfected MSM or transgendered women from South America, South Africa, Thailand and U.S. (N=2499)
Ten were HIV-infected at enrollment



64 new infections

36 new infections

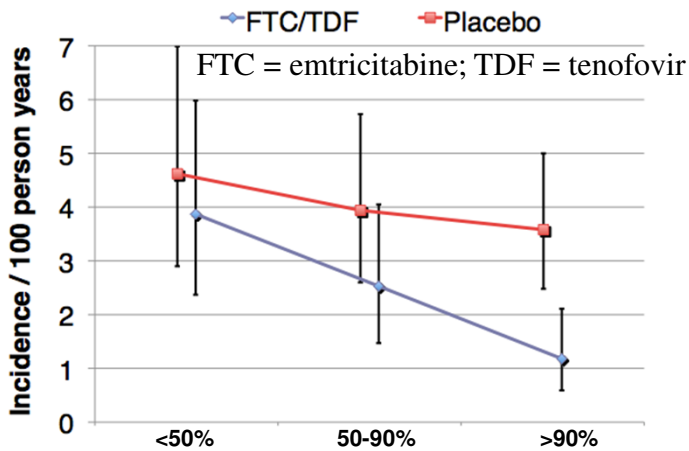
44% reduction (95% CI, 15%-63%, p=0.005)

92% effective if drug level detectable

Grant NEJM 2010;363:2587

Slide #10

IPREX: Recorded Adherence and Efficacy



	<50%	50-90%	>90%
% of Visits	18%	33%	49%
Efficacy	**16%**	**34%**	**68%**
95% CI	-54 - 54	-20 - 64	36 - 84

Grant et al, CROI 2010

Slide #11

Adverse events

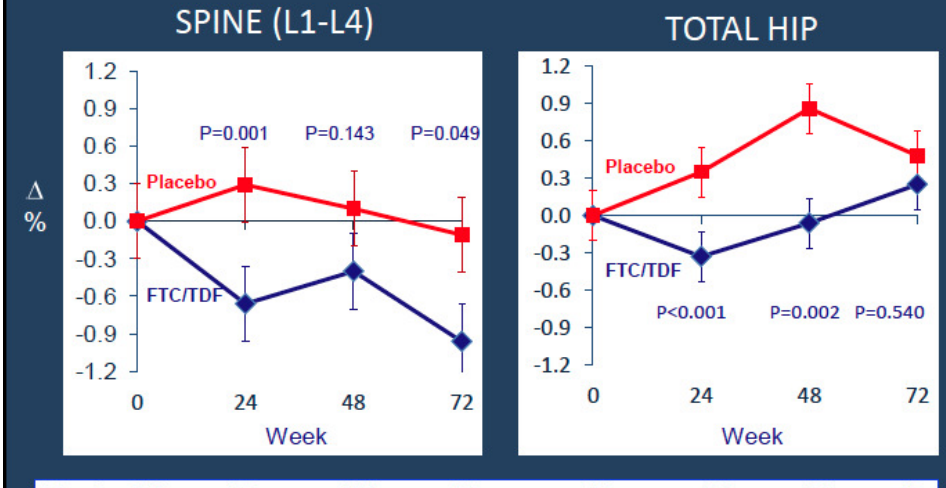
Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Creatinine Elevated	25 (2%)	28	14 (1%)	15	p=0.08
Headache	56 (4%)	66	41 (3%)	55	p=0.10
Nausea	20 (2%)	22	9 (<1%)	10	p=0.04
Weight Decreased	27 (2%)	34	14 (1%)	19	p=0.04

TDF = tenofovir; FTC = emtricitabine

Grant NEJM 2010;363:2587

Slide #12

PERCENT CHANGES FROM BASELINE IN BMD BY RANDOMIZATION GROUP



Mean, SE and P-values by linear mixed model

Liu PLoS One 2011;6:e23688

Slide #13

Drug Resistance

Genotypic Resistance	HIV Status at Enrollment			
	Infected (N=10)		Uninfected (N=100)	
	Placebo N=8	FTC/TDF N=2	Placebo N=83	FTC/TDF N=48
65R	0 (0%)	0 (0%)	0 (0%)	0 (0%)
70E	0 (0%)	0 (0%)	0 (0%)	0 (0%)
184I	0 (0%)	1 (50%)	0 (0%)	0 (0%)
184V	1 (13%)	1 (50%)	0 (0%)	0 (0%)
TDF Resistance	0 (0%)	0 (0%)	0 (0%)	0 (0%)
FTC Resistance	1 (13%)	2 (100%)	0 (0%)	0 (0%)

Grant NEJM 2010;363:2587

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CDC Guidance for PrEP for MSM: (Interim; 1/27/11)

- Before starting:
  - document HIV Ab- and r/o acute infection
  - CrCl ≥60, screen for STIs and HBV
- Rx tenofovir/emtricitabine 1 po qd X 90 days
  - provide risk reduction, adherence counseling, condoms
- On treatment:
  - check HIV Ab every 2-3 months
  - check BUN/creat at 3 months and yearly
  - risk reduction, condoms, STI assessments/rx

http://www.cdc.gov/hiv/prep/index.htm

Slide #15

PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
Partners PREP Baeten NEJM 2012;367:399	4758 discordant Kenya and Uganda couples	tenofovir vs. tenofovir/ emtricitabine vs. placebo	tenofovir: **67%** tenofovir/ emtricitabine: **75%** (**86-90%** if tenofovir detected)
CDC – TDF-2 Thigpen NEJM 2012;367:423	1200 Botswana adults (45% women)	tenofovir/ emtricitabine vs. placebo	tenofovir/ emtricitabine: **63%**

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U.S. Food and Drug Administration (FDA) Approval of PrEP (7/16/12)

- **U.S. FDA approves tenofovir/emtricitabine (Truvada) for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk.**

Slide #17

PrEP -- REMS

- **REMS = Risk Evaluation and Mitigation Strategy**
- **FDA mandated**
- **Purpose: to educate and inform healthcare providers and uninfected individuals at high risk for acquiring HIV-1**
- **Provider training; resources for providers and patients; 1-page agreement form**

https://www.truvadapreprems.com/

Slide #18

PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
FEM-PREP Van Damme NEJM 2012;367:411	2120 women in Kenya, South Africa, Tanzania	tenofovir/ emtricitabine vs. placebo	tenofovir/ emtricitabine: **6%** (adherence <40%)
VOICE Marrazzo CROI 2013 #26LB	5029 women in South Africa, Uganda, Zimbabwe	1% tenofovir gel vs. placebo gel; oral tenofovir vs. oral tenofovir/ emtricitabine vs. oral placebo	no study drugs effective (adherence <30%)

PrEP: Adherence and Efficacy

	Blood Samples With Tenofovir Detected, %	HIV Protection Efficacy in Randomized Comparison,%
Partners PrEP*[1]	81	75
TDF2[2]	79	62
iPrEx[3]	51	44
FEM-PrEP[4]	26	6

*TDF/FTC arm

Dose-response between evidence of PrEP use and efficacy

1. Baeten JM, et al. N Engl J Med. 2012. 2. Thigpen MC, et al N Engl J Med. 2012; 3. Grant RM, et al. N Engl J Med. 2010; 4. Van Damme L, et al N Engl J Med. 2012 .

CDC Guidance for PrEP for heterosexuals (8/9/12)

- Targeted to high-risk individuals, such as those with an HIV+ sex partner.
- It is critical to take PrEP consistently.
- Discuss risks/benefits with pregnant women or those trying to conceive; data are incomplete and mostly from HIV+ women.
- PrEP is not a stand-alone solution.
- Individuals must be confirmed HIV- prior to PrEP; monitor HIV status, side effects, adherence, and risk behaviors.

Slide #21

IPREX F/U: Modeling PK

- Using data from a separate PK study:
  - 2 doses/week: 76% risk reduction
  - 4 doses /week: 97% risk reduction
  - 7 doses/week: 99% risk reduction

Anderson Sci Transl Med 2012;4:151ra125.

Slide #22

HPTN 069: NEXT-PrEP

- Design: Phase II, 4-arm, multisite, study
- Study population
  - N=400 at-risk HIV-negative gay men; currently 232/58%; N=200 at risk HIV-negative women; currently 10/5%
- Study Treatment:
  - maraviroc monotherapy
  - maraviroc + emtricitabine
  - maraviroc + tenofovir
  - tenofovir + emtricitabine (control arm)

- Duration: 48 weeks
- Primary endpoint: Grade ≥3 toxicities; time to study treatment discontinuation

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Newer PrEP Agents

	mechanism	dosing route	dosing frequency	PrEP stage
rilpivirine-LA	NNRTI	injectable, SC	once monthly	Phase 1 pilot
S/GSK 1265744 ('744)	integrase inhibitor	injectable, SC	once monthly (or less)	Phase 1 pilot
ibalizumab	CD4 attachment inhibitor	injectable, SC	once every 1-4 weeks	Phase 1 pilot

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PrEP: Pros and Cons

PROS

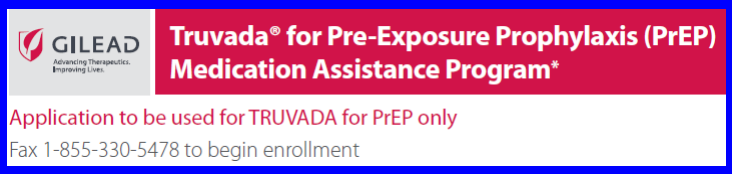
- **Proven efficacy**
- **FDA-approved**
- **Can be highly effective**
- **Generally well-tolerated**
- **Drug resistance not seen**
- **No risk compensation**

CONS

- **Short-term data**
- **Daily adherence required**
- **Side effects**
- **Drug resistance in acute infection**
- **Risk compensation could lead to ↓ condoms**
- **Cost**
- **Logistics**

PrEP: Logistics (1)

- By prescription
  - NY Medicaid: TDF/FTC for PrEP approved 1/13
  - Requires prior authorization 1-877-309-9493
  - Private insurance: prior authorization
  - Gilead Patient Assistance Program: http://start.truvada.com/hcp



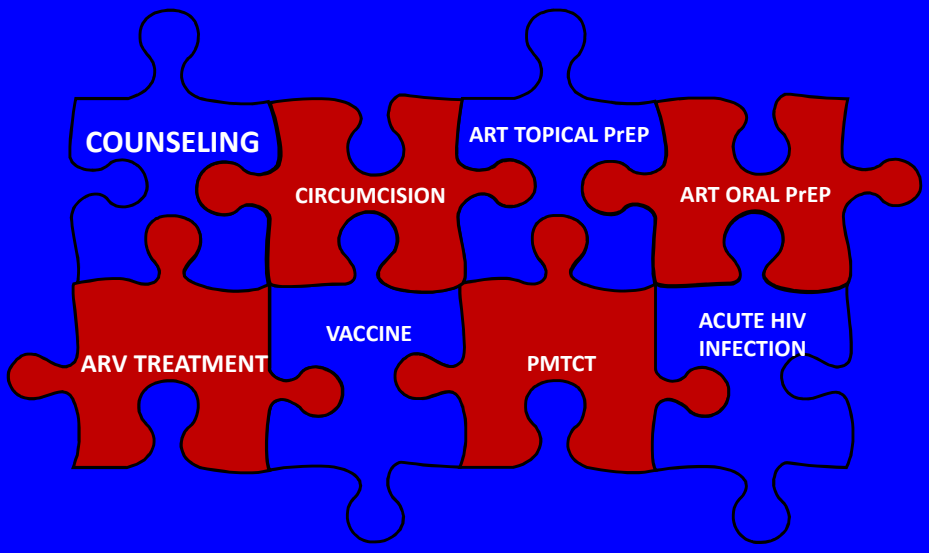
  - Up to 500% of the federal poverty level in NYC ($57,450 for an individual in 2013)

PrEP: Logistics (2)

- Demonstration project
  - Callen-Lorde (coming soon)
- Research studies
  - NEXT PrEP (maraviroc-based regimens)
    - Cornell 212-746-4177
  - HPTN 067 (intermittent dosing)
    - Harlem 212-939-2928

Slide #27

HIV Prevention 2013



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Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
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- Division of AIDS, NIAID, NIH
- The patient volunteers!