

CDC PUBLIC HEALTH GRAND ROUNDS

Pre-exposure Prophylaxis (PrEP) for Prevention of HIV Infection



May 20, 2014



**U.S. Department of
Health and Human Services**
Centers for Disease
Control and Prevention

HIV Pre-exposure Prophylaxis: Preclinical Research in Animal Models



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NCHHSTP



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Importance of Animal Models to Assess PrEP Efficacy

- ❑ **Provide first *in vivo* evidence of protection from infection**

- ❑ **Assess relationship between efficacy and pharmacologic parameters**
 - How well the drug prevents infection
 - How drugs are distributed systemically
 - How drugs are distributed at mucosal sites of HIV entry (e.g. vaginal, rectal tissue)

Importance of Animal Models to Assess PrEP Efficacy

- ❑ **Help inform clinical trial designs in humans**
 - Prioritization of PrEP regimens
 - Dose selection
- ❑ **Identify most promising PrEP candidates for clinical trials in humans**
 - ~\$20-80 million
 - ~3-5 years to provide answers

CDC Repeat Exposure Macaque Models

❑ Repeat Exposure Macaque Model

- Macaques – preferred animal model for HIV infection
- Virus used - simian HIV (SIV or SHIV)
- Weekly rectal or vaginal exposure to SHIV
- SHIV dose within upper range of HIV infectious dose in humans

❑ Exposures to virus repeated to mimic high-risk human exposures to HIV

- Better simulate HIV exposures in humans than do previous models with single high-dose virus challenge
- Protection evaluated against multiple exposure events

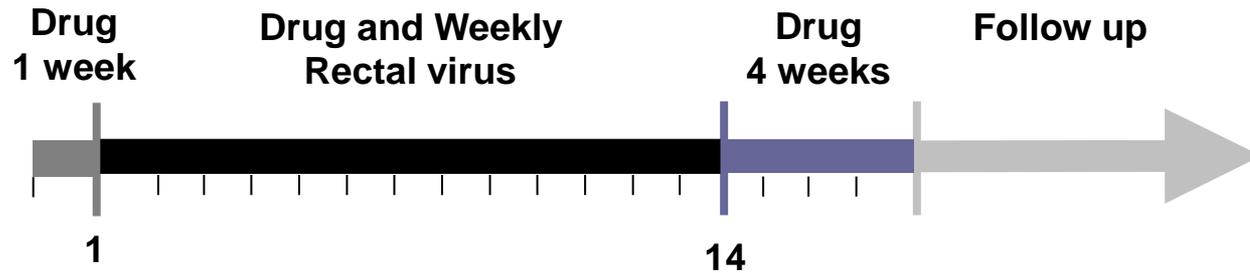
CDC Repeat Exposure Macaque Models (cont.)

- ❑ **Protection measured over multiple exposures per animal**
 - Power to detect protective effect using smaller numbers of study animals
- ❑ **PrEP regimens that are equivalent to clinical drug exposures in humans**
- ❑ **Inform potential PrEP efficacy trials in humans**

Drug Selection for PrEP

- ❑ **Among marketed antiretroviral drugs for treatment of HIV-1 infected persons, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) considered because:**
 - Safe, well tolerated, and potent
 - Reverse transcriptase inhibitors
 - Co-formulated as single once-daily pill marketed as Truvada®
 - Have long plasma (10 to 17 hours) and intracellular (40 to ≥ 60 hours) half-lives
 - Long half-life allows forgiveness for imperfect daily use
 - Have even higher penetration in vaginal and rectal tissues

Design of PrEP Efficacy Study in Animals



Group 1 (n = 18)
Untreated controls

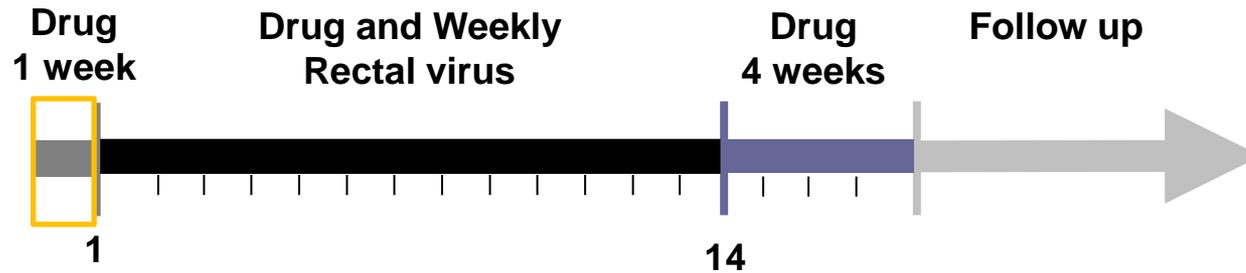
Group 2 (n = 6)
Daily oral TDF and FTC

Group 3 (n = 6)
Daily subcutaneous FTC and high-dose tenofovir

Group 4 (n = 6)
Daily subcutaneous FTC



Design of PrEP Efficacy Study in Animals



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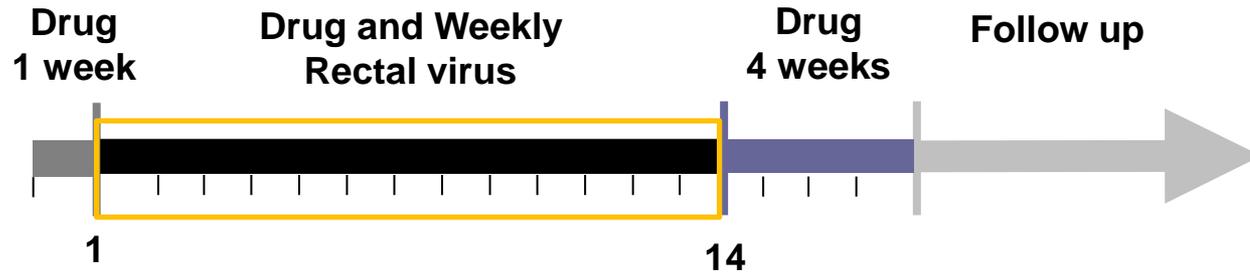
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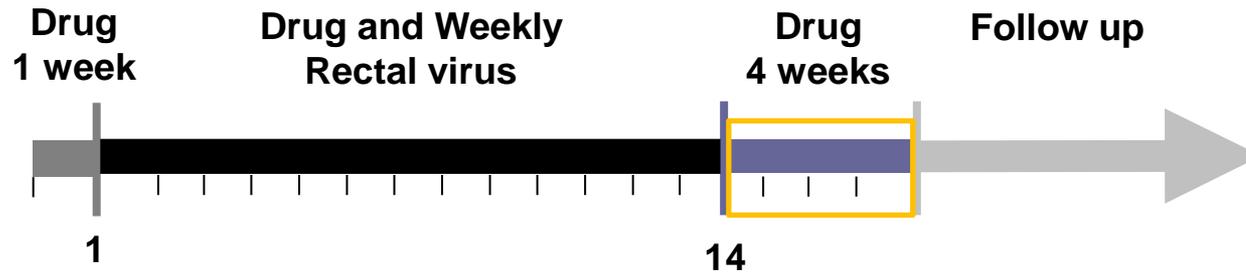
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Design of PrEP Efficacy Study in Animals



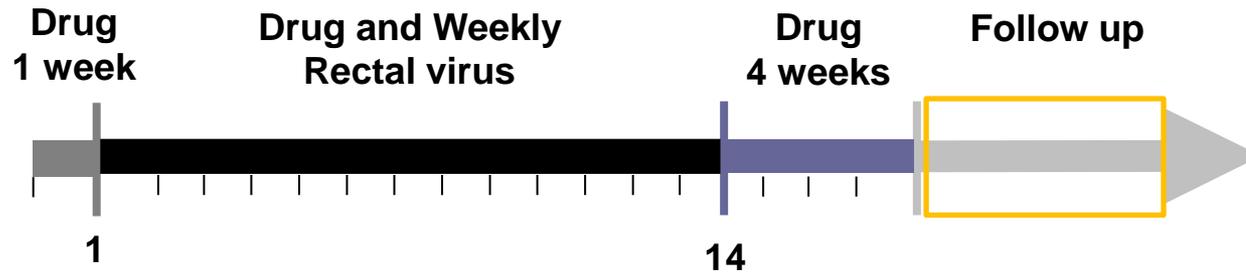
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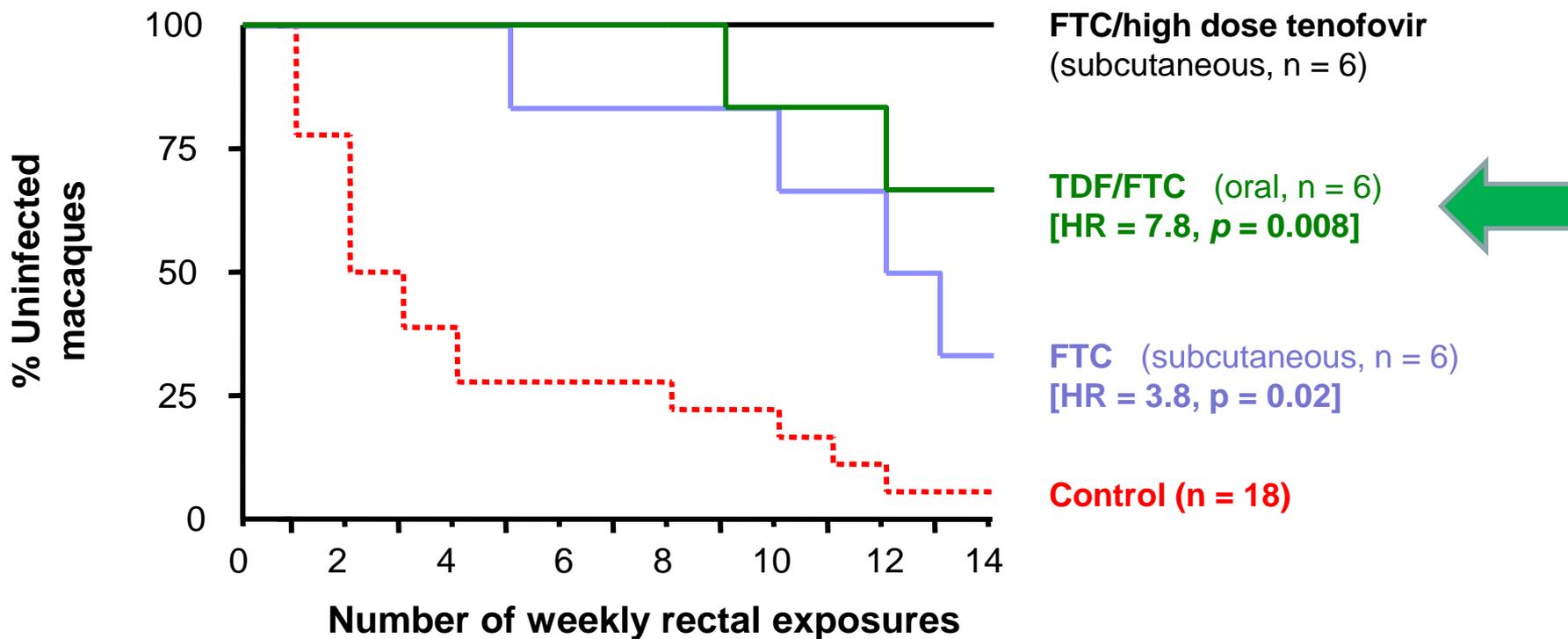
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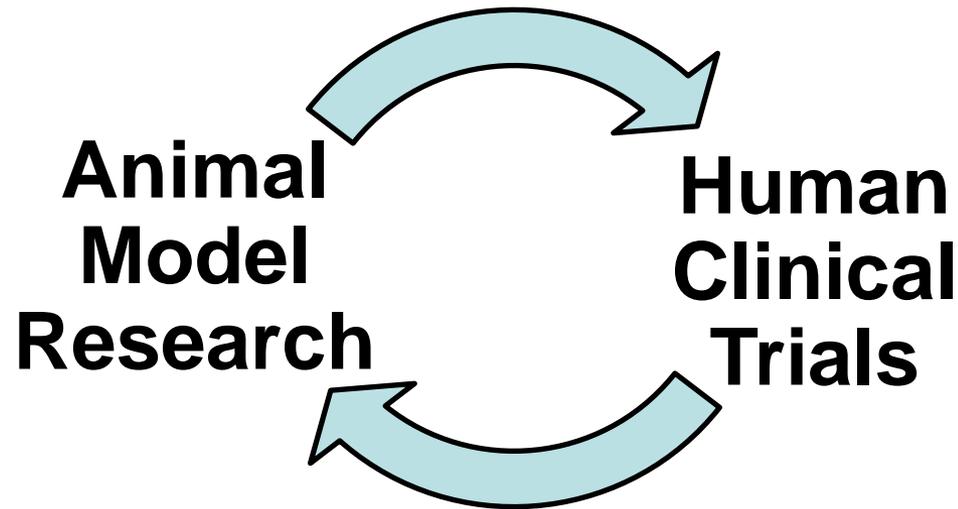
Daily PrEP Regimens Against Rectal SHIV in Macaques



Interpretation and Implications of Animal PrEP Efficacy Study

- ❑ **Daily oral TDF/FTC provided substantial protection against rectal infection**
 - Substantial reduction among oral TDF/FTC-treated compared to control animals
- ❑ **Data informed advancement of oral PrEP into clinical trials in humans**

Animal and Human PrEP Research



- ❑ **Rectal and vaginal protection**
- ❑ **Drug dose and delivery modality**
- ❑ **Single drug and drug combinations**

Evolving Evidence from Clinical Trials of HIV Pre-exposure Prophylaxis



Melanie Thompson, MD
Principal Investigator
AIDS Research Consortium of Atlanta



ARCA

AIDS Research Consortium of Atlanta
Working Together For a Cure



U.S. Department of
Health and Human Services
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Control and Prevention

Disclosures

- ❑ **All research funding is for clinical trials through AIDS Research Consortium of Atlanta; no funding paid directly to Dr. Thompson**
- ❑ **Site Principal Investigator for clinical trials from the following sponsors:**
 - Bristol Myers Squibb, Inc., Cepheid, Inc., Gilead Sciences, GeoVax, Inc., Kowa Research Institute, Pharmasset, Inc., Pfizer Inc., Janssen/Tibotec Therapeutics, Merck & Co., Tobira Therapeutics, ViiV Healthcare
- ❑ **Data Safety Monitoring Boards:**
 - Janssen/Tibotec Therapeutics and ViiV Healthcare

Common Design Elements of Oral PrEP Trials

- **Community consultation**
 - To assess trial feasibility, acceptability and implementation
- **Random assignment to placebo or intervention groups receiving either TDF/FTC or TDF**
- **Daily dosing of study medication in oral arms of all studies**
- **Data and safety monitoring board**
 - Periodic expert panel reviews to ensure data quality and participant safety

Common Design Elements of Oral PrEP Trials

- **Symptom assessment and laboratory tests for safety monitoring (e.g. liver enzymes and renal function)**
- **HIV testing, risk reduction and adherence counseling, adherence assessments at every visit**
- **Additional follow-up, viral resistance testing, and linkage to HIV care for participants who seroconvert during trial**
- **Efficacy determined by modified intention-to-treat (mITT)**
 - mITT - analysis based on the initial treatment assignment
 - Modified to exclude persons found to be acutely infected with HIV at the time of enrollment in the study

Randomized, Controlled PrEP Efficacy Trials

Trial (Sponsor) Sample Size	Intervention vs. Placebo	Population	Location
iPrEx (NIH; Gates) <i>n=2499</i>	Oral TDF/FTC	MSM, transgender women	Peru, Ecuador, S Africa, Brazil, Thailand, US
Partners PrEP (Gates) <i>n=4747 couples</i>	Oral TDF/FTC Oral TDF	Heterosexual serodiscordant couples	Kenya, Uganda
TDF2 (CDC) <i>n=1200</i>	Oral TDF/FTC	Sexually active adults	Botswana
Bangkok Tenofovir (CDC) <i>n=2413</i>	Oral TDF	Injection drug users	Thailand
FEM-PrEP (USAID, Gates, FHI 360) <i>n=1951</i>	Oral TDF/FTC	Heterosexual women	Kenya, S Africa, Tanzania
VOICE (MTN-003) <i>n=5029</i>	Oral TDF/FTC Oral TDF Vag 1% tenofovir gel	Heterosexual women	Uganda, S Africa, Zimbabwe

Grant et al. NEJM 2010; 363 :2587- 2599
 Baeten et al NEJM 2012;367:399-410;CROI 2014: Abstract 43
 Thigpen, et al. NEJM 2012;367:423-34

Choopanya et al. Lancet 2013 Jun 15;381(9883):2083-90
 Van Damme, et al. NEJM. 2012;367:411-22
 Marazzo et al. CROI 2013: Abstract 26LB

Results of PrEP Efficacy Trials

Detection of Tenofovir Levels in Blood Associated with Greater Efficacy

Study	Oral Regimen Dosed Daily	Relative Risk Reduction (95% CI)	
		All Subjects	Drug Detectable
iPrEx	TDF/FTC	0.44 (0.15 – 0.63)	0.92 (0.40 – 0.99)



Study drug:
Enrollment:
Sites:

Oral TDF/FTC
2,499 MSM and transgender women
Peru, Ecuador, South Africa,
Brazil, Thailand, USA

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61
TDF/FTC: tenofovir/emtricitabine
MSM: Men who have sex with men

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Partners PrEP	TDF	0.67 (0.44 – 0.81)	0.86 (0.67 – 0.94)
	TDF/FTC	0.75 (0.55 – 0.87) <i>TDF vs TDF/FTC not significantly different</i>	0.90 (0.58 - 0.98)



PARTNERS PrEP STUDY

Study drug:
Enrollment:
Sites:

Oral TDF/FTC, Oral TDF
4,747 heterosexual serodiscordant couples
Kenya, Uganda

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61
Baeten et al. CROI 2014: Abstract 43

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Bangkok Tenofovir	TDF	0.49 (0.10 – 0.72)	0.74 (0.17– 0.94)

Bangkok Tenofovir Study

Study drug:

Oral TDF

Enrollment:

2,413 Injection drug users

Sites:

Thailand

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		<i>TDF vs TDF/FTC not significantly different</i>	
Bangkok Tenofovir	TDF	0.49 (0.10 – 0.72)	0.74 (0.17–0.94)
		% Pts with Detectable Drug	
TDF2	TDF/FTC	0.62 (0.22 – 0.83)	50% among HIV infected 80% among not infected

TDF2

Study drug:
Enrollment:
Sites:

Oral TDF/FTC
1,200 sexually active adults
Botswana

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61
Baeten et al. CROI 2014: Abstract 43
Hendrix C. Cell 2013;155: 515-518.

Study	Oral Regimen Dosed Daily	Relative Risk Reduction (95% CI)	
		All Subjects	Drug Detectible
FEM-PrEP	TDF/FTC	Stopped due to futility	< 40% among all participants
VOICE	TDF TDF/FTC	Stopped due to futility Showed no efficacy	< 30% among all participants

- Poor adherence, as measured by detectable drug levels, was a major factor in lack of efficacy in both studies
- Self reported adherence was very high and was not predictive of outcome except when patients said that they did not take drug
- In VOICE, no behavioral measures correctly predicted adherence as measured by drug concentration in the blood

Futility: stopping clinical trial when interim results suggest that it is unlikely to achieve statistically significant differences between treatment arm and placebo/control arm

Table adapted from Hendrix, C. HIV Pre-Exposure Prophylaxis: Clinical Pharmacology Insights. CROI 2014, Oral Abstract 61
 Baeten et al. CROI 2014: Abstract 43
 Hendrix C. Cell 2013;155: 515-518.
 van der Straten, et al. CROI 2014: Abstract 44
 Snapinn S, Chen Mg, Jiang Q et al. Pharm Stat. 2006 Oct-Dec;5(4):273-81.

Safety of Tenofovir-based PrEP in Clinical Trials

- ❑ **No significant differences in serious adverse events, renal function markers or deaths among patients taking study drug compared to those taking placebo**
- ❑ **Adverse events more common on TDF or TDF/FTC than placebo in any study included**
 - Short-duration nausea, vomiting; dizziness
 - Back pain; decreased weight
 - Mild elevation in liver enzymes; mild neutropenia (more with TDF/FTC than TDF)
 - Small but statistically significant decreases in bone mineral density; no difference in atraumatic fractures
- ❑ **Among women who became pregnant, study drug was not associated with increased pregnancy complications**

HIV Resistance and PrEP

- ❑ **Viral resistance occurs when mutations arise in genetic material of HIV that help it to survive in presence of an antiretroviral drug**
- ❑ **Resistance means that a drug no longer works optimally, or at all, to suppress HIV**
- ❑ **Resistance to one antiretroviral drug can result in cross-resistance to others that have never been taken**
- ❑ **Persons who acquire HIV while taking TDF/FTC, or who have HIV before taking TDF/FTC for PrEP, are at risk for viral resistance that may limit treatment options**

HIV Resistance in PrEP Trial Participants

- ❑ **Among persons with undetected acute infections before starting medication, resistance mutations found in**
 - 8 of 30 persons randomized to TDF/FTC or TDF
- ❑ **Among persons infected after enrollment**
 - None randomized to TDF/FTC or TDF had TDF-resistant viruses (0 out of 263)
 - 5 had FTC-resistant viruses (1 in VOICE, 4 in FEM PrEP)
- ❑ **In IPrEx and Partners PrEP, among persons infected after enrollment**
 - 6 out of 99 randomized to TDF/FTC or TDF had low levels of minor resistance mutations, found using more sensitive research assays
 - Clinical implications unknown
- ❑ **Viral resistance risk is highest if starting PrEP when already HIV infected, especially those recently infected**
- ❑ **HIV testing before and during use is critical**

No Evidence of Increased Risk Behavior Seen in Clinical Trials

Trial	Risk Behavior Assessed
iPrEx	<ul style="list-style-type: none"> • Episodes of receptive anal sex declined • Condom use during receptive anal sex increased • No difference in condom use by perceived treatment group
US MSM Safety Study	<ul style="list-style-type: none"> • Number of partners and percent reporting anal sex without condom declined • Episodes of anal sex without condom remained stable
Partners PrEP	<ul style="list-style-type: none"> • HIV uninfected participants reported declines in sex without condom use
TDF2	<ul style="list-style-type: none"> • Reported number of sex partners declined • Percent reporting sex without condom remained stable
Bangkok Tenofovir	<ul style="list-style-type: none"> • Reports of injecting drugs, sharing needles, and sex with more than 1 partner in preceding 3 months declined

Implementation Insights from PrEP Trials

- ❑ **TDF-based PrEP can be highly effective in reducing HIV acquisition risk- up to 92% in these studies - *if* medication adherence is high**
- ❑ **Risk of viral resistance highest if beginning PrEP with unrecognized HIV infection**
 - Need to test for HIV infection, ideally both acute and established, before and during use
- ❑ **Risk of acquiring HIV is not completely eliminated:**
 - Combine PrEP with other prevention methods for optimal results
 - Consistent and correct condom use
 - Substance use treatment programs, use of injection equipment that has not been used by other persons
 - Antiretroviral treatment for HIV-infected partner in HIV-discordant couples

Implementation Insight from PrEP Trials

- ❑ **Safety monitoring will be important in real-world setting**
- ❑ **Health care providers who are not HIV specialists need comprehensive education about PrEP**
 - How to talk with patients about benefits and risks of PrEP
 - How to initiate and monitor PrEP to minimize toxicity and maximize effectiveness
 - How to discuss and support adherence
 - How to support other risk reduction strategies
 - How to manage HIV infection if it occurs

Program and Policy Challenges for Delivery of PrEP



Dawn K. Smith, MD, MS, MPH

Biomedical Interventions Activity Lead

Prevention with Negatives Team

Epidemiology Branch, Division of HIV/AIDS Prevention

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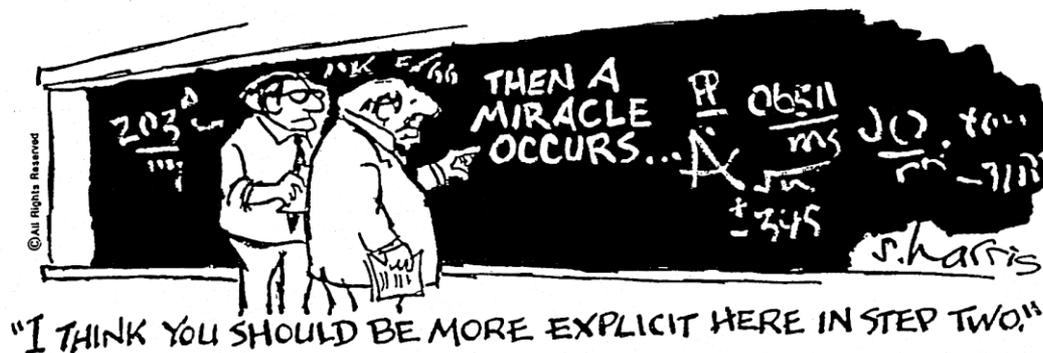
FDA Approval and Plans for Mitigating Health Risks for PrEP Use

□ July 2012 approval of Truvada®

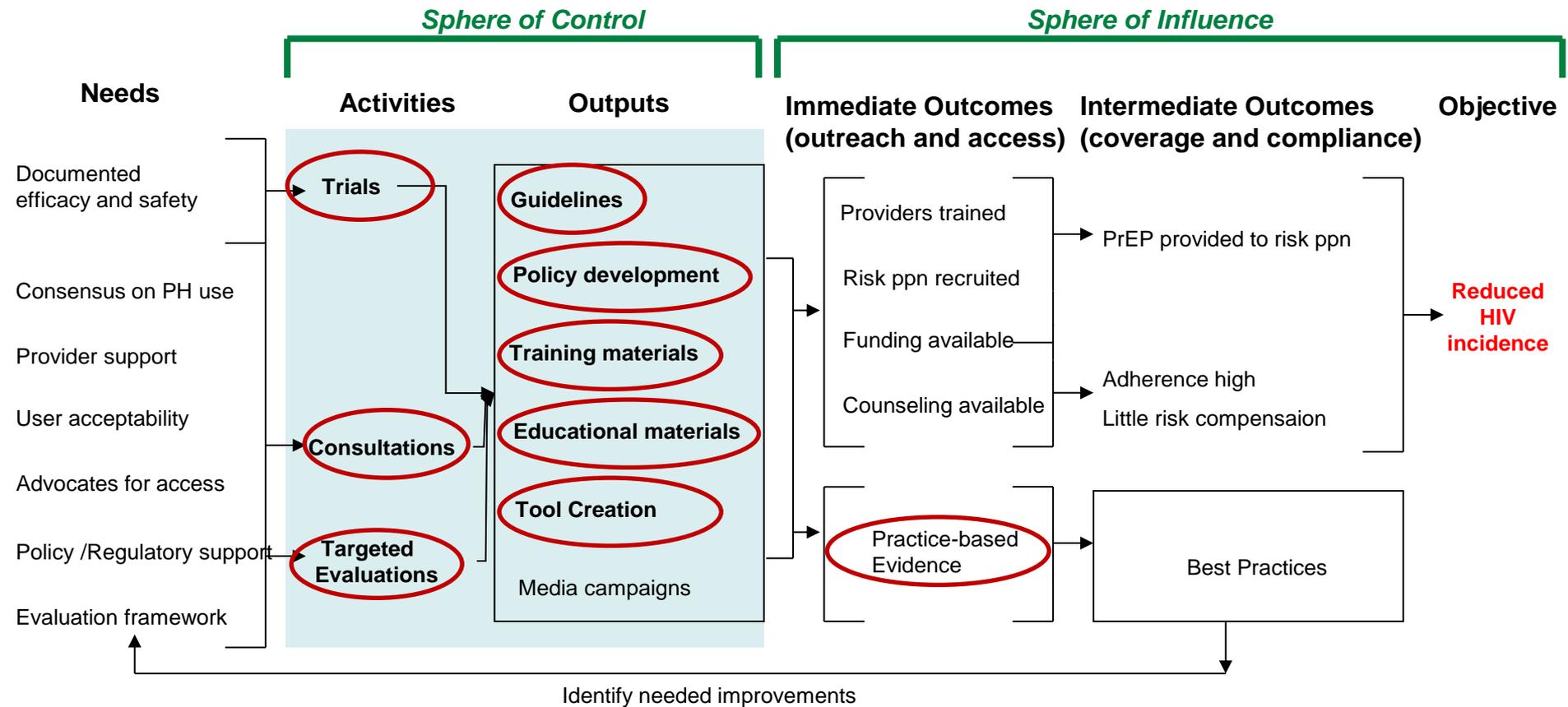
- Indication for PrEP with sexually-active adults
- Risk Evaluation and Mitigation Strategy (REMS)
 - No restriction to specific providers or dispensing sites
 - Required medication guide and provider training
 - Required educational materials for HIV-negative persons
 - Annual assessment of effectiveness of REMS
- Elements to Assure Safe and Effective Use
 - Added language to package insert
 - Required HIV testing (boxed warning)
 - Indications/contraindications for prescribing PrEP
 - Strict adherence to daily dosing
 - Use in combination with other prevention methods

Implementation in Context of Rapidly Evolving Evidence Base

- ❑ **Need to understand how to support PrEP when delivered as clinical HIV prevention in communities**
 - Solicited lessons learned from implementation and evaluation science
 - Learn what providers and potential users know about PrEP
 - Focus group with young adults in Atlanta
 - Questions added to an existing clinician survey (DocStyles)



“Roadmap” for PrEP Implementation in the US



External Stakeholder and Expert Engagement

Guidelines Work Groups

- ❑ Clinical Care
- ❑ Clinic-based Counseling
- ❑ PrEP integration with other prevention services
- ❑ IDU
- ❑ MSM
- ❑ Heterosexual men
- ❑ Women
- ❑ Adolescents

Technical Expert Meetings

- ❑ Public Health Ethics
- ❑ Monitoring and Evaluation
- ❑ Financing/Reimbursement
- ❑ HIV discordant couples and conception/pregnancy
- ❑ Network Science
- ❑ Public Health Law
- ❑ Insurers

Supporting Introduction and Scale Up for Public Health Impact

- ❑ **Adapting interim guidance as the evidence evolved**
 - Men who have sex with men, 2011
 - Heterosexually active adults, 2012-2013
 - Injection drug users, 2013

- ❑ **Public Health Service Clinical Practice Guidelines for PrEP Use in the US (May 14, 2014)**
 - These Clinical Practice Guidelines replace the previous interim guidance documents

Public Health Service Clinical Practice Guidelines: Key Messages

❑ **Daily, oral PrEP with Truvada®**

- Is recommended as one prevention option for persons at substantial risk of HIV infection including:
 - Sexually-active MSM
 - Heterosexually active men and women
 - Injection drug users
- Should be discussed with HIV discordant couples for use during conception and pregnancy
- Use should be weighed carefully for adolescent minors

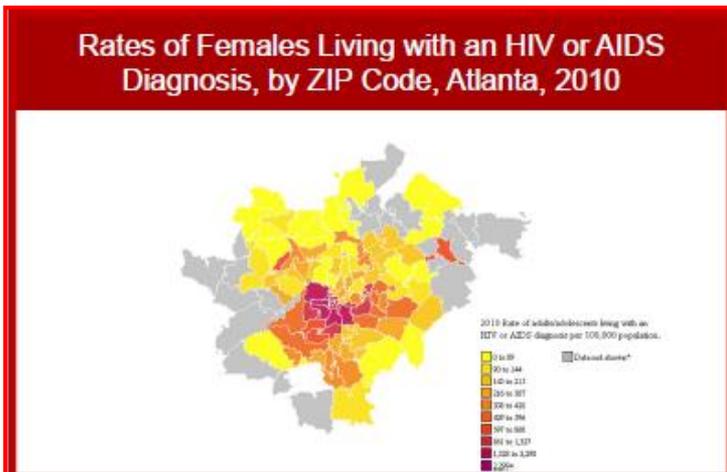
❑ **Support medication adherence and risk reduction practices**

Indications for PrEP Use by Subpopulation

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	<ul style="list-style-type: none"> • HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work 	<ul style="list-style-type: none"> • HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • In high-prevalence area or network 	<ul style="list-style-type: none"> • HIV-positive injecting partner • Sharing injection equipment • Recent drug treatment (but currently injecting)

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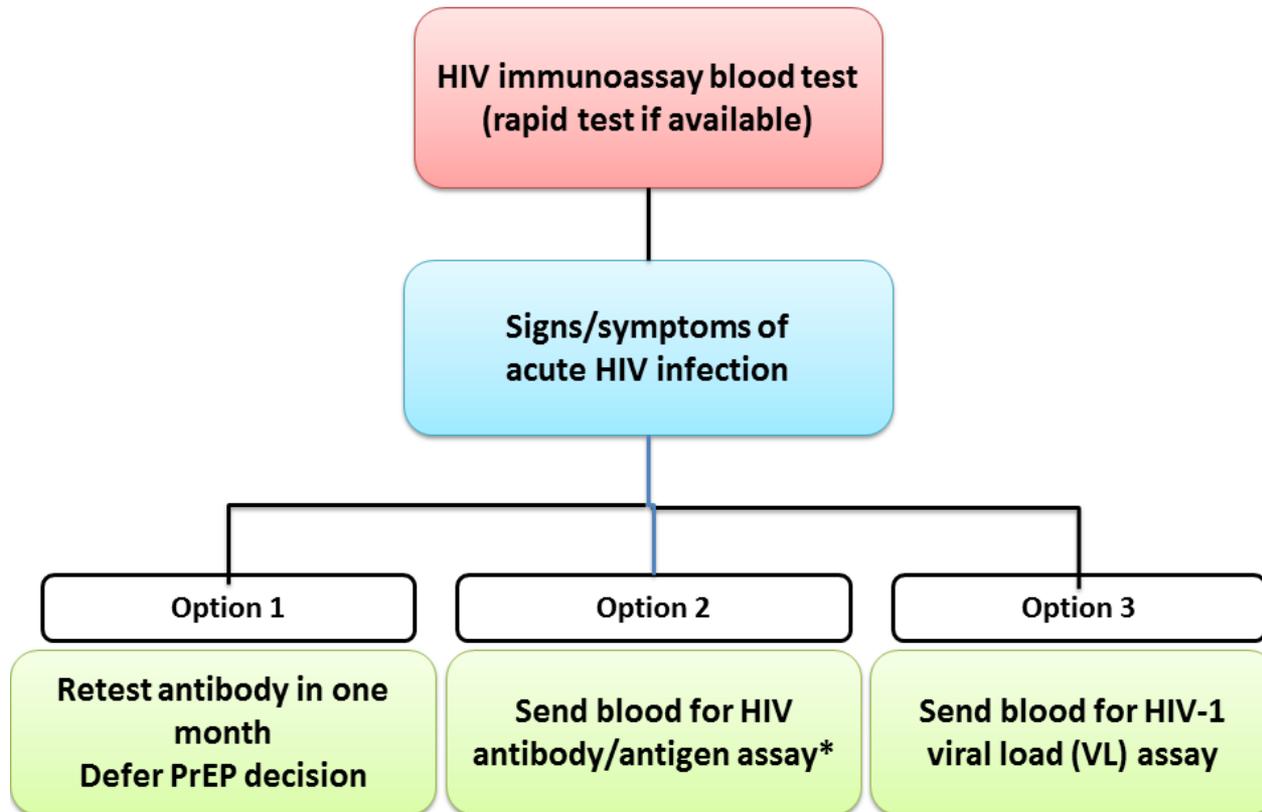
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Assessing for Contraindications and Prescribing PrEP

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Clinically eligible	<ul style="list-style-type: none"> • Documented negative HIV test result before prescribing PrEP • No signs/symptoms of acute HIV infection • Normal renal function; no contraindicated medications • Documented hepatitis B virus infection and vaccination status 		
Prescription	<ul style="list-style-type: none"> • Daily, continuing, oral doses of TDF/FTC (Truvada®), ≤90-day supply 		

Excluding Acute or Established HIV Infection



* Use only HIV antigen/antibody tests that are approved by FDA for diagnostic purposes

Follow-up Visits While Prescribing PrEP

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Other services	<p>Follow-up visits at least every 3 months to provide the following:</p> <ul style="list-style-type: none"> • HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment • At 3 months and every 6 months thereafter, assess renal function • Every 6 months, test for bacterial STIs 		
	<ul style="list-style-type: none"> • Do oral/rectal STI testing 	<ul style="list-style-type: none"> • Assess pregnancy intent • Pregnancy test every 3 months 	<ul style="list-style-type: none"> • Access to clean needles/syringes and drug treatment services

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Clinical Providers Supplement to Guidelines: Educational and Training Materials

□ Patient factsheets

- PrEP
- Truvada®
- Acute HIV infection

□ Provider materials

- Patient/Provider checklist
- Information on PrEP during conception, pregnancy, and breastfeeding
- HIV incidence risk index for MSM
- Potential PrEP practice quality measures
- Supplemental counseling information

Tools for Implementation of PrEP in Clinical Practice

- ❑ Materials for persons considering PrEP
- ❑ Guide for billing codes
- ❑ Risk screening tools
 - Published for MSM
 - Under development for HIV-discordant couples, injection drug users

Choose an ARCH tool



HOW TO TALK TO YOUR DOCTOR ABOUT PrEP

Before Your Visit

Make an appointment with your health care provider. Your doctor can help you to decide if PrEP would be a good choice for you.

Do research. Make a list of reasons that you think that PrEP would be a good choice for you.

Think about your routine, especially things that might make it easy or hard to take a daily medication.

Make a health history list for your doctor. That includes any past illnesses or concerns you have, as well as a list of your current medications (including supplements, herbs, etc.).

Make sure a translator is available or bring someone who can translate if you would prefer to speak a language other than English during your appointment.

During Your Visit

Be clear. Take out your notes and tell your doctor that you are interested in PrEP right away.

Do not be shy. Give your doctor all the details about your life that could be important to your health. Don't worry about being judged.

If your sex life is a hard topic to talk about, say that to your doctor. It will help to start the conversation.

Ask questions. You want to be sure that you understand what your doctor is telling you.

Take notes during your visit so that you can remember what your doctor said.

After Your Visit

Review your notes or any information provided by your doctor.

Consider your options. Your doctor gave you a lot of information. Now it is up to you to make the right decision for you.
<http://www.cdc.gov/hiv/risk/behavior/index.html>

Call your doctor if you have more questions. Ask to speak to a nurse if your doctor is unavailable.

Schedule tests or follow-up appointments your doctor requested.

Get your results if you had tests done at your appointment.

If you feel comfortable, you may want to discuss this choice with your partners, family, or friends.

www.cdc.gov/hiv/pdf/risk_PrEP_TalkingtoDr_FINALcleared.pdf

Smith DK, Pals SL, Herbst JH et al. J Acquir Immune Defic Syndr. 2012 Aug 1;60(4):421-7.

MSM: men who have sex with men

ARCH: Assessing the risk for contracting HIV

Policy Development to Mitigate PrEP Costs

❑ Average retail pharmacy price for a one month supply of Truvada® is \$1400

- Negotiated drug price reductions
- Most private employer, school-based and public insurers (e.g. Medicaid) provide coverage for PrEP medications and care

❑ PrEP drug and co-pay assistance programs available

- Free medication for those with low income and no insurance coverage
 - Gilead Sciences
 - Free condoms and HIV testing can be provided
 - Free hepatitis B screening, and HIV resistance testing for those who seroconvert while on PrEP
 - Washington State

Cost-effectiveness of PrEP

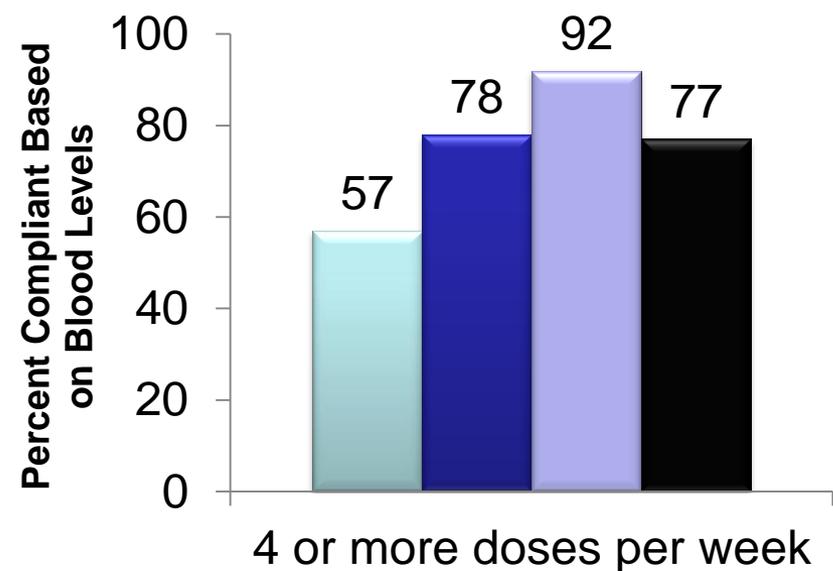
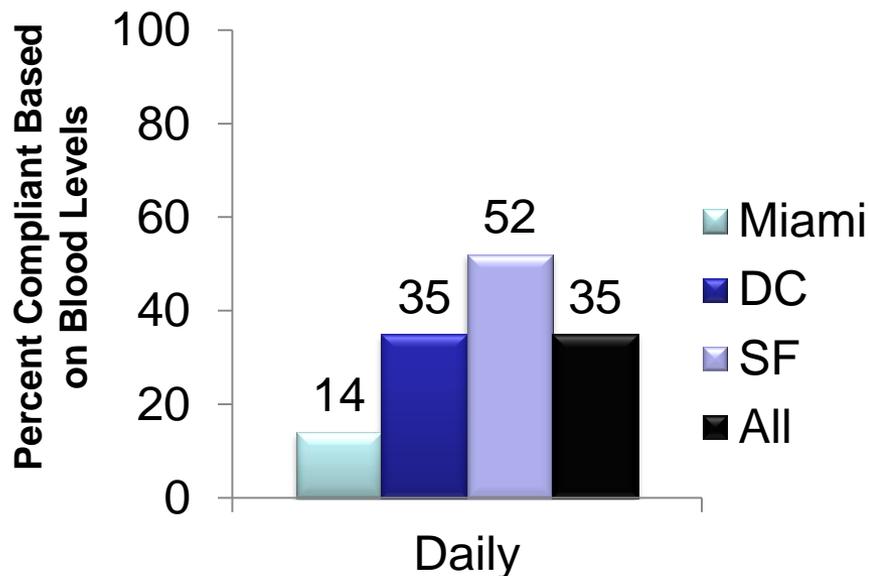
- ❑ **4 cost-effectiveness studies in MSM in the US**
- ❑ **Delivery of PrEP is most cost-effective when:**
 - **Targeted to populations with high HIV incidence**
 - **High coverage is achieved in targeted populations**
 - **Medication adherence is high**
 - **Cost of medication and clinical services are minimized**

Estimating Early PrEP Uptake Using US Retail Pharmacy Claims Data

- ❑ **Analysis of a commercial pharmacy database**
 - Includes 55% of U.S. prescriptions
- ❑ **PrEP prescribers in ~700 US cities, 49 states**
 - 31% family practice and internal medicine
 - 17% non-physician prescribers (NP and PA)
 - 14% emergency medicine
 - 12% infectious disease
- ❑ **Prescriptions rose 8.5-fold**
 - 150 in 2011 to 1274 in 2012
 - 48% of prescribing for women
 - 14% for persons under age 25 years

An Early Study to Evaluate PrEP Uptake and Adherence

- ❑ MSM recruited in STD clinics; 60% of eligible patients enrolled
- ❑ Medication adherence assessed at 4 weeks by blood drug level
 - Daily adherence suboptimal; ≥ 4 doses/week adherence higher
- ❑ Other modeled data* suggest high efficacy may be achieved at ≥ 4 doses/wk



Study of PrEP as Implemented in Community Health Centers



❑ Health Services Observational Cohort (SHIPP Study)

- Collects de-identified data from medical records
- Evaluate prescribing practices, patient outcomes, and service costs for all clinic patients receiving PrEP

❑ Medication Adherence Substudy (SHIPP Study)

- Offers participation with informed consent
- Collects dried blood spots to measure drug levels
- Provides adherence aids to those with suboptimal adherence

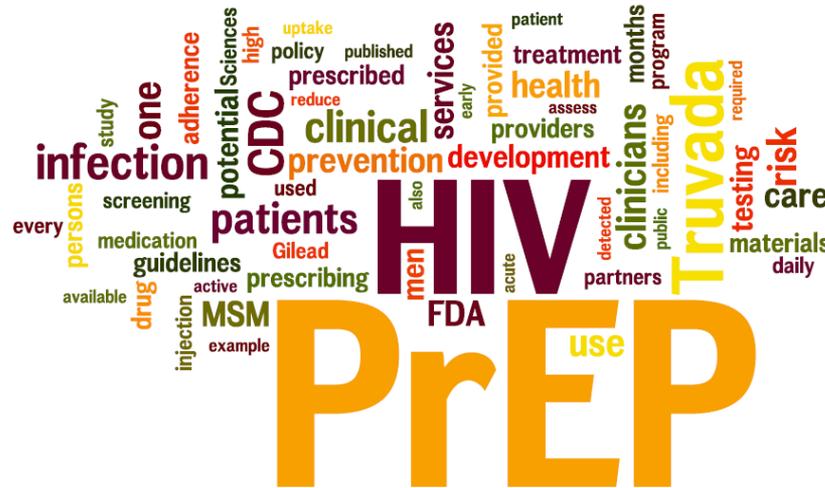
❑ Community Surveys (Context Matters Study)

- Clinician attitudes about PrEP and its provision in each clinic
- Knowledge and attitudes about PrEP among lay persons and key stakeholders in communities served by each clinic

Role of PrEP in HIV Prevention

The United States will become a place where new HIV infections are rare...

-National HIV/AIDS Strategy Vision Statement



Clinician Resources

Public Health Service Guidelines	www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf
Providers' Supplement	www.cdc.gov/hiv/pdf/guidelines/PrEPProviderSupplement2014.pdf
REMS clinician materials	www.truvadapreprems.com/truvadaprep-resources
Medication Assistance Programs	www.nastad.org/docs/PrEP%20and%20PEP%20PAP%20fact%20sheet.pdf
Co-Pay Assistance Program	www.gileadcopay.com/
Free condoms for patients	https://start.truvada.com/individual/truvadaprep-patient-resources
Free HIV testing for patients	https://start.truvada.com/hcp#
Adolescent Law Analysis	www.sciencedirect.com/science/article/pii/S0749379712007118
<u>Online HIV Data maps:</u> CDC NCHHSTP Atlas	www.cdc.gov/nchhstp/atlas
AIDSVu	aidsvu.org/