# PrEP: State of the Science

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# Why Chemoprophylaxis Post-HPTN 052?

- Only 37 MSM couples, 2 unlinked cases, so generalization warrants further study
- ¼ PLHIV globally are now on treatment; full access will take years
- Not all PLHIV want to start meds with high CD4 counts, and virologic suppression rates vary
- Serostatus awareness is limited among many at risk
- HIV stigma limits willingness to disclose
- Not either/or; models suggest some synergy

# PrEP can prevent HIV infection

| TRIAL | POPULATION | LOCATION | Active arm(s) | EFFICACY (mITT-analysis) |
|---|---|---|---|---|
| **iPrEx** | 2499 MSM and TGF | South America, USA, Thailand, South Africa | FTC/TDF | **42%** (95% CI 18-60) |
| **TDF-2** | 1219 heterosexual men and women | Botswana | FTC/TDF | **63%** (95% CI 22-83) |
| **Partners PrEP** | 4758 serodiscordant heterosexual couples | Kenya and Uganda | FTC/TDF<br>TDF | **75%** (95% 55-87)<br>**67%** (95% CI 44-81) |

# …but didn't always work

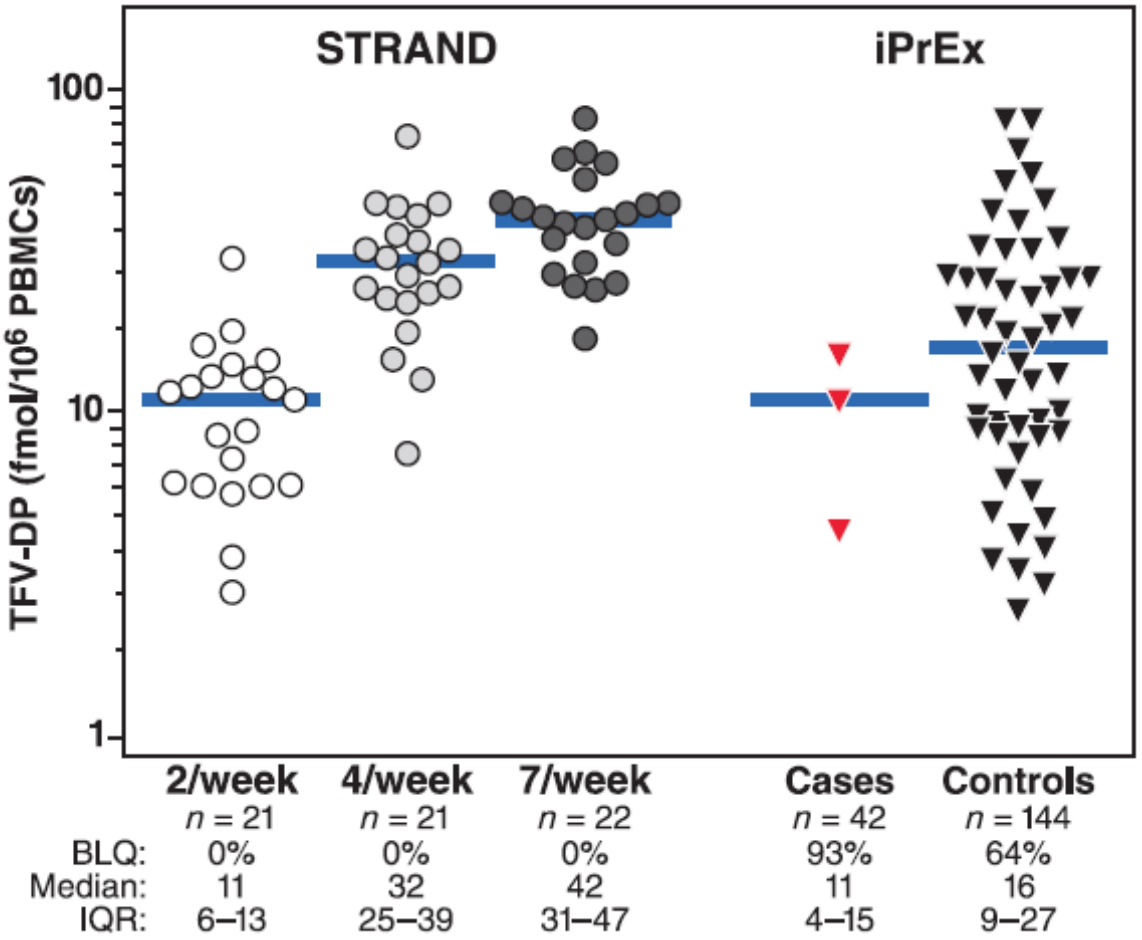
| TRIAL | POPULATION | LOCATION | Active arm(s) | EFFICACY (mITT-analysis) |
|---|---|---|---|---|
| **FEM-PrEP** | 2120 heterosexual women | Kenya, Tanzania, Zimbabwe, South Africa | FTC/TDF | **6%** (p=0.8)<br><br>***Stopped early due to lack of efficacy*** |
| **VOICE** | 5000 heterosexual women | Uganda, Zimbabwe, South Africa | FTC/TDF<br>TDF | -4% (p>0.2)<br>-49% (p=0.07) |

- Low adherence
- Other issues?
  - Drug concentration at exposure site: Rectal vs. vaginal sex
  - Integrity of epithelium: Other STDs, trauma, other products (douching, soaps, drying product)
  - Intensity of exposure: # partners, frequency of sex
  - Stage of infection in index partner (acute vs. chronic)

# Adherence is critical for PrEP efficacy

| Study | Efficacy overall | Drug detected overall | Estimated Risk reduction with drug detection |
|---|---|---|---|
| iPrEx | 42% | ~50% | 92% |
| Partners PrEP | 67-75% | 82% | 86% (TDF)<br>90% (FTC/TDF) |
| TDF-2 | 62% | 80% | 78% |
| Fem-PrEP | No efficacy | 26% | "adherence too low to assess efficacy" |
| VOICE | No efficacy | 29% | "adherence too low to assess efficacy" |

# Adherence, drug levels, and efficacy




| Dosing | Estimated PrEP Efficacy |
|---|---|
| 2x/week | 76% |
| 4x/week | 90% |
| Daily | 99% |

Anderson PL. Sci Transl Med 2012;4:1-8.

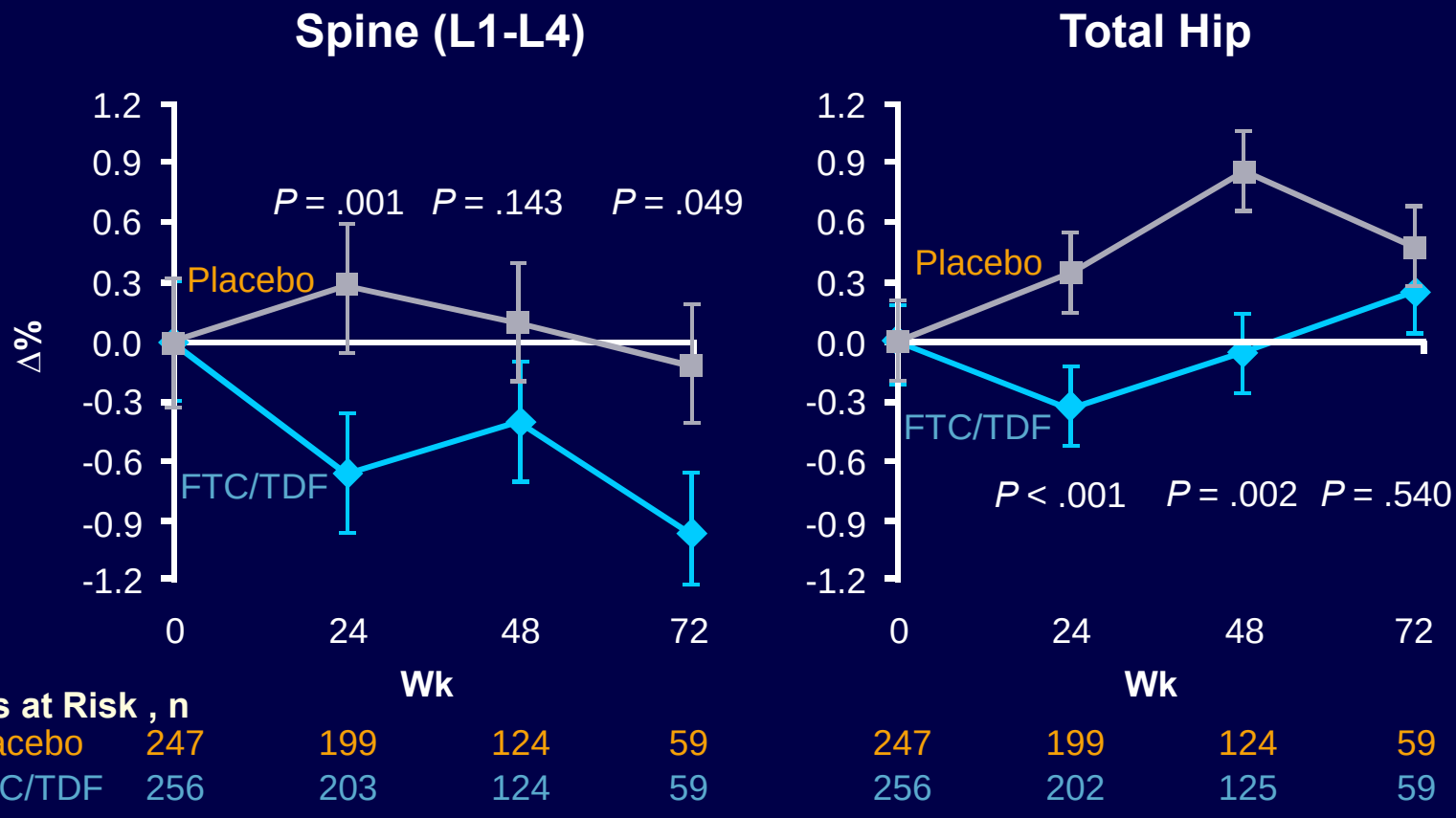
# PrEP generally safe and well tolerated, but requires monitoring

- Adverse events well balanced between active and placebo arms

| Adverse Event | FTC/TDF (n = 1251) | | Placebo (n = 1248) | | *P* Value |
|---|---|---|---|---|---|
| | % | Events | % | Events | |
| Any grade 3/4 event | 12 | 248 | 13 | 285 | .51 |
| Death | < 1 | 1 | < 1 | 4 | .18 |
| Serious adverse event | 5 | 76 | 5 | 87 | .57 |
| Elevated creatinine | 2 | 28 | 1 | 15 | .08 |
| Creatinine elevation confirmed on next visit | 0.4 | 7.0 | 0 | 0 | .06 |

- Start up syndrome seen in minority of individuals

# iPrEx: Percent BMD Change From Baseline




| Pts at Risk , n | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 247 | 199 | 124 | 59 | 247 | 199 | 124 | 59 |
| FTC/TDF | 256 | 203 | 124 | 59 | 256 | 202 | 125 | 59 |

Mean, SE, and *P* values by linear mixed model.

Mulligan K, et al. CROI 2011. Abstract 94LB. Graphics used with permission.

# Summary of the data

- Adherence is critical
- FTC/TDF in HIV-negatives appears safe and well-tolerated across a number of PrEP studies
- Resistance: crucial to rule out acute HIV at initiation; not seen with high or low adherence
- No increase in risk behavior, in context of blinded use

*CDC. MMWR Morb Mortal Wkly Rep. 2011;60:65-68. Grant RM. N Engl J Med. 2010;363:2587-2599. Baeten J. Annu. Rev. Med. 2013. 64:3.1–3.14*

# Why Tenofovir-Emtricitabine?

- Limited side effects
- Strong safety profile as therapy among HIV positive people
- Relatively long duration of action in the body (product ñhalf-lifeò)
- Less likelihood of promoting drug resistance compared to other ARVs
- First of many ARVs that may be used for PrEP


**HPTN 069 RECRUITMENT WEBSITE**

# Strategies to improve PrEP delivery and adherence

## New PrEP drugs and dosing strategies

NEXT PrEP
AN HPTN/ACTG STUDY

HPTN 067 ADAPT


## Novel adherence strategies

## Alternative delivery systems and formulations

**Rectal Microbicides: MTN-017 (TFV rectal gel)**

**Intra-vaginal rings: ASPIRE (Dapivirine)**

**Injectable PrEP: HPTN 076 (TMC278LA)**

# What about intermittant PrEP?

- IAVI studies in East Africa: MSM and FSW, small size, but many missed post-coital doses
- HPTN 066: dose proportionality study of weekly TDF/FTC, twice weekly, and double dose twice weekly. Tissue PK
- HPTN 067: MSM in Bangkok and NYC, and high risk women in Cape Town, comparing coitally dependent vs. fixed intermittent PrEP.
- iPERGAY: (France, Canada) pericoital

# New Antiretrovirals for Prevention

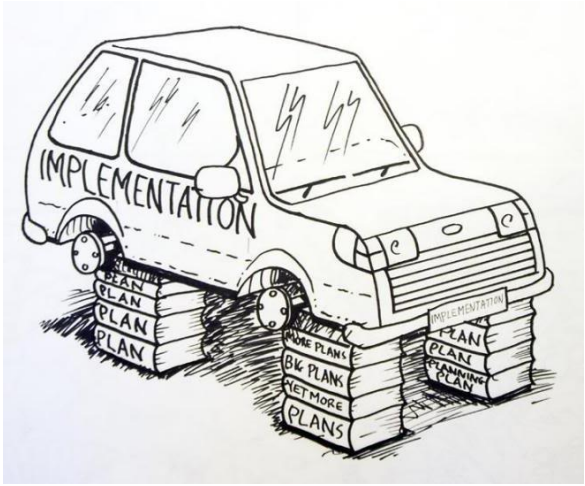
| Agent | Mechanism | Status | Developers/ Sponsors |
|---|---|---|---|
| Dapivirine (gel and ring) | NNRTI | Phase 2/3 (ring) | Tibotec/IPM MTN |
| Maraviroc (oral and ring) | CCR5 inhibitor | Phase 1 | ViiV/IPM HPTN/MTN |
| Rilpivirine/TMC278 (injectable) | NNRTI | Phase 1 | Tibotec |
| GSK744 | Integrase Inhibitor | Preclinical | Shinogi/GSK |

# What about Topical Microbicides?

- Vaginal Gel: waiting for the tie breaker: the FACTS study
- Vaginal gel not tolerated rectally b/c glycerin (MTN 006)
- MTN 007: Phase 1 study of reformulated tenofovir 1% gel
- Reduced glycerin tenofovir 1% gel
  - Reduced incidence and severity of GI adverse events
  - No significant changes in histology, inflammatory markers, and epithelial sloughing
  - Improved acceptability
- New studies focusing on younger MSM and MSW, and expanded safety, adherence (MTN 017; Project Gel)

McGowan I, et al. 19th CROI. Seattle, 2012. Abstract 34LB.

# Why do we need PrEP demonstration projects?




- Will at risk people want PrEP?
- How will at risk people use PrEP?
- How will sexual practices change?
- Where are PrEP delivery systems best located?
- Will PrEP be safe in the “real world”?

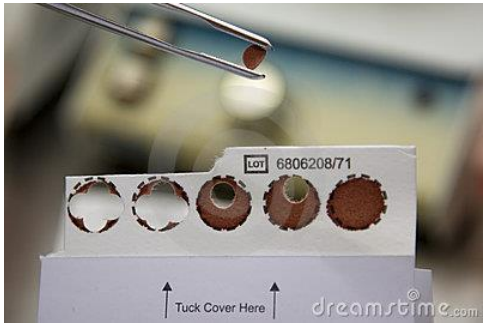
**Efficacy -> Effectiveness?  What will be PrEP’s public health impact?**

| Study | Population (N) | Locations | Timeline |
|---|---|---|---|
| **iPrEx Open Label Extension** | MSM and transgender women (n=2499) | Brazil, Ecuador, Peru, South Africa, Thailand, US | Enrollment began: June 2011<br>Results expected: 2014 |
| **Partners PrEP Study (post-placebo phase)** | Heterosexual men and women with known HIV infected partners (HIV serodiscordant couples) (N=4747 couples) | Kenya, Uganda | Enrollment began: July 2011<br>Results expected: 2013 |
| **CDC 494 / TDF2 Open Label Extension** | Heterosexual men and women (N=1219) | Botswana | Enrollment began: February 2013<br>Results expected: 2014 |
| **US PrEP Demonstration Project (Demo Project)** | MSM and transgender women in STD clinic setting (n=500) | US (San Francisco, Miami, DC) | Enrollment began: September 2012<br>Results expected: 2014 |
| **Partners Demonstration Project** | Heterosexual men and women with known HIV infected partners (HIV serodiscordant couples) (N=1000 couples) | Kenya, Uganda | Enrollment began: November 2012<br>Results expected: 2014/2015 |
| **ATN 110 and 113** | Young MSM, ages 15-22 (N=300) | 14 US sites | Enrollment began: December 2012<br>Results expected: Q4 2014 |
| **PROUD** | Gay men in genito-urinary medicine clinics (N=500) | United Kingdom | Enrollment began: November 2012<br>Results expected: November 2015 |
| **CCTG 595** | MSM and transgender women (N=400) | US (Long Beach, Los Angeles, San Diego, Torrance) | Enrollment planned: Q1-2 2013<br>Results expected: 2016 |
| **PATH - PrEP** | 375 MSM and transgender women (N=375) | US (Los Angeles) | Enrollment planned: April 2013<br>Results expected: 2017 |
| **HPTN 073** | Black MSM (N=225) | US (Los Angeles, Washington DC, Chapel Hill) | Enrollment planned: June 2013<br>Results expected: December 2015 |
| **SCOPE** | Female sex workers (N=500) | Kenya | Enrollment planned: June 2013<br>Results expected: 2014 |

# Measuring adherence

Self report

Pill counts




Dried blood spots (DBS)

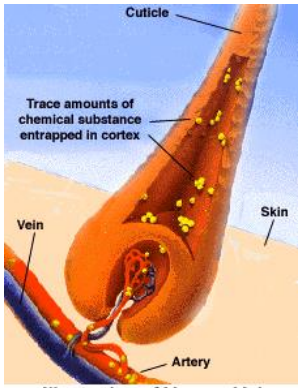



Illustration of Human Hair

Hair (opt-in)

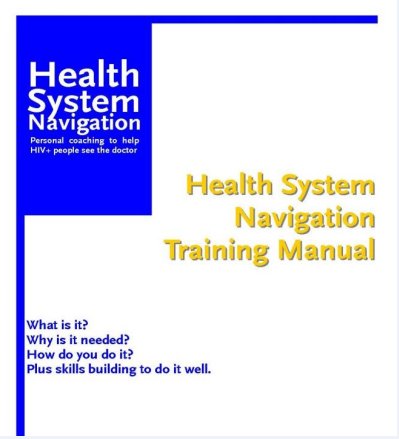
# Strategies to Improve PrEP Adherence

- Weekly SMS messaging vs. SOC
- F/U call by nurse if not response received (Lester, Lancet 2010)

| | SMS | SOC | RR (95% CI) | P value |
|---|---|---|---|---|
| **Adherence (>95%)** | **168 (62%)** | **132 (50%)** | **0.81 (0.69-0.94)** | **0.006** |
| **HIV RNA (<400 copies/ml)** | **156 (57%)** | **128 (48%)** | **0.85 (0.72-0.99)** | **0.04** |

- NIMH R34 (Mayer/Safren) CBT intervention, text messaging and Wisepill to enhance PrEP adherence among MSM
- NIMH R01 (Liu): Building on Next Step Counseling (Amico) from iPrEX and text messaging to enhance PrEP adherence among MSM
- PATH-PrEP (Landovitz/Amico): Pills counts/drug levels
- NIDA R21 (Mimiaga/Mitty): MSM substance users
- Health system navigation: HPTN 073

  (Bradford, AIDS Pt Care &STDs, 2007)



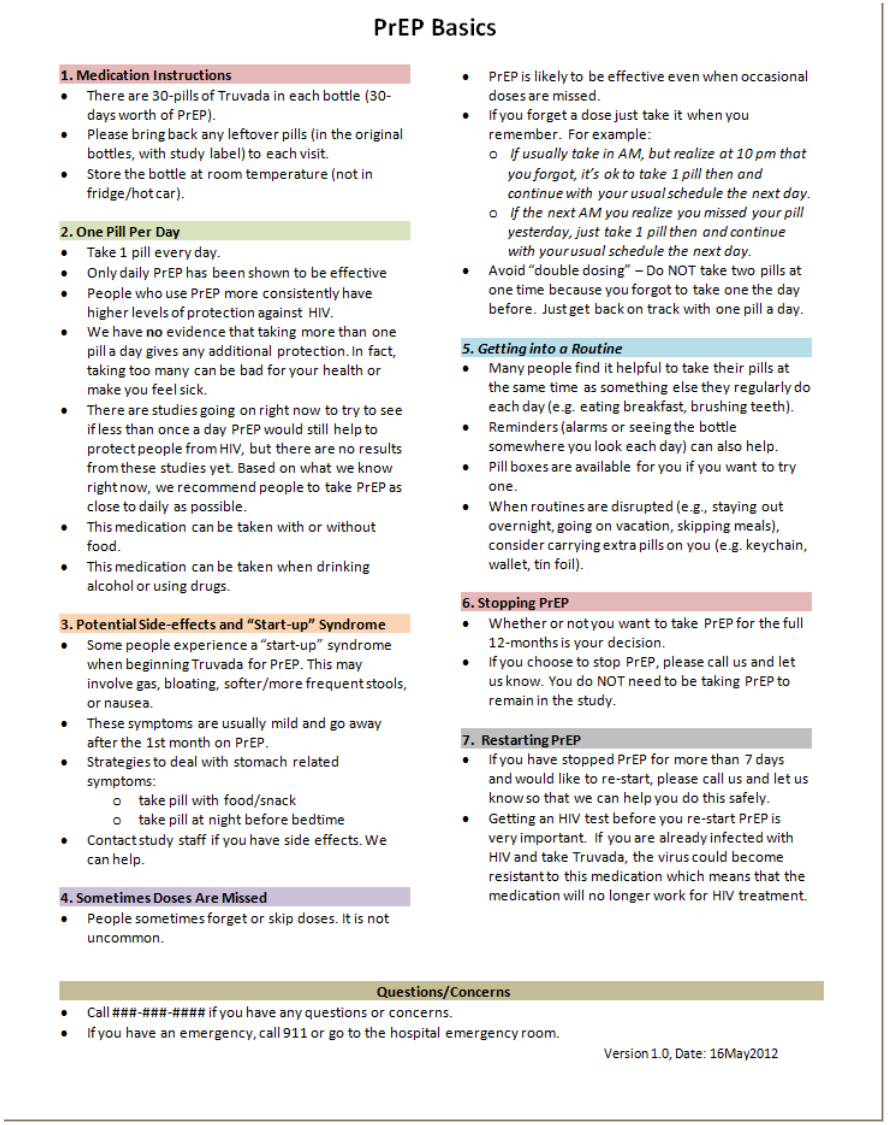
# Project Prepare

- Modeled after "Life-Steps," (Safren et al) ART adherence intervention
- Modular intervention: 4 weekly visits and 2 booster sessions.
- Intervention content:
  - CBT-oriented adherence problem-solving skills
  - brief motivational interviewing
  - sexual risk-reduction strategies
- Optional modules:
  - mental health and substance-use barriers to adherence.

**Adherence to PrEP was measured daily via Wisepill, and sexual risk taking was assessed by text messages**

# SF Demo: Integrated Counseling

- Only one pill per day
- People who use PrEP more consistently have higher levels of protection against HIV
- Potential side-effects
  - Bloating, soft/more frequent stools, nausea
- Missed Doses
- Developing a routine
- Discussing PrEP with others
- Stopping and restarting PrEP



PrEP Basics

**1. Medication Instructions**

- There are 30-pills of Truvada in each bottle (30-days worth of PrEP).
- Please bring back any leftover pills (in the original bottles, with study label) to each visit.
- Store the bottle at room temperature (not in fridge/hot car).

**2. One Pill Per Day**

- Take 1 pill every day.
- Only daily PrEP has been shown to be effective
- People who use PrEP more consistently have higher levels of protection against HIV.
- We have **no** evidence that taking more than one pill a day gives any additional protection. In fact, taking too many can be bad for your health or make you feel sick.
- There are studies going on right now to try to see if less than once a day PrEP would still help to protect people from HIV, but there are no results from these studies yet. Based on what we know right now, we recommend people to take PrEP as close to daily as possible.
- This medication can be taken with or without food.
- This medication can be taken when drinking alcohol or using drugs.

**3. Potential Side-effects and "Start-up" Syndrome**

- Some people experience a "start-up" syndrome when beginning Truvada for PrEP. This may involve gas, bloating, softer/more frequent stools, or nausea.
- These symptoms are usually mild and go away after the 1st month on PrEP.
- Strategies to deal with stomach related symptoms:
  - take pill with food/snack
  - take pill at night before bedtime
- Contact study staff if you have side effects. We can help.

**4. Sometimes Doses Are Missed**

- People sometimes forget or skip doses. It is not uncommon.
- PrEP is likely to be effective even when occasional doses are missed.
- If you forget a dose just take it when you remember. For example:
  - *If usually take in AM, but realize at 10 pm that you forgot, it's ok to take 1 pill then and continue with your usual schedule the next day.*
  - *If the next AM you realize you missed your pill yesterday, just take 1 pill then and continue with your usual schedule the next day.*
- Avoid "double dosing" – Do NOT take two pills at one time because you forgot to take one the day before. Just get back on track with one pill a day.

***5. Getting into a Routine***

- Many people find it helpful to take their pills at the same time as something else they regularly do each day (e.g. eating breakfast, brushing teeth).
- Reminders (alarms or seeing the bottle somewhere you look each day) can also help.
- Pill boxes are available for you if you want to try one.
- When routines are disrupted (e.g., staying out overnight, going on vacation, skipping meals), consider carrying extra pills on you (e.g. keychain, wallet, tin foil).

**6. Stopping PrEP**

- Whether or not you want to take PrEP for the full 12-months is your decision.
- If you choose to stop PrEP, please call us and let us know. You do NOT need to be taking PrEP to remain in the study.

**7. Restarting PrEP**

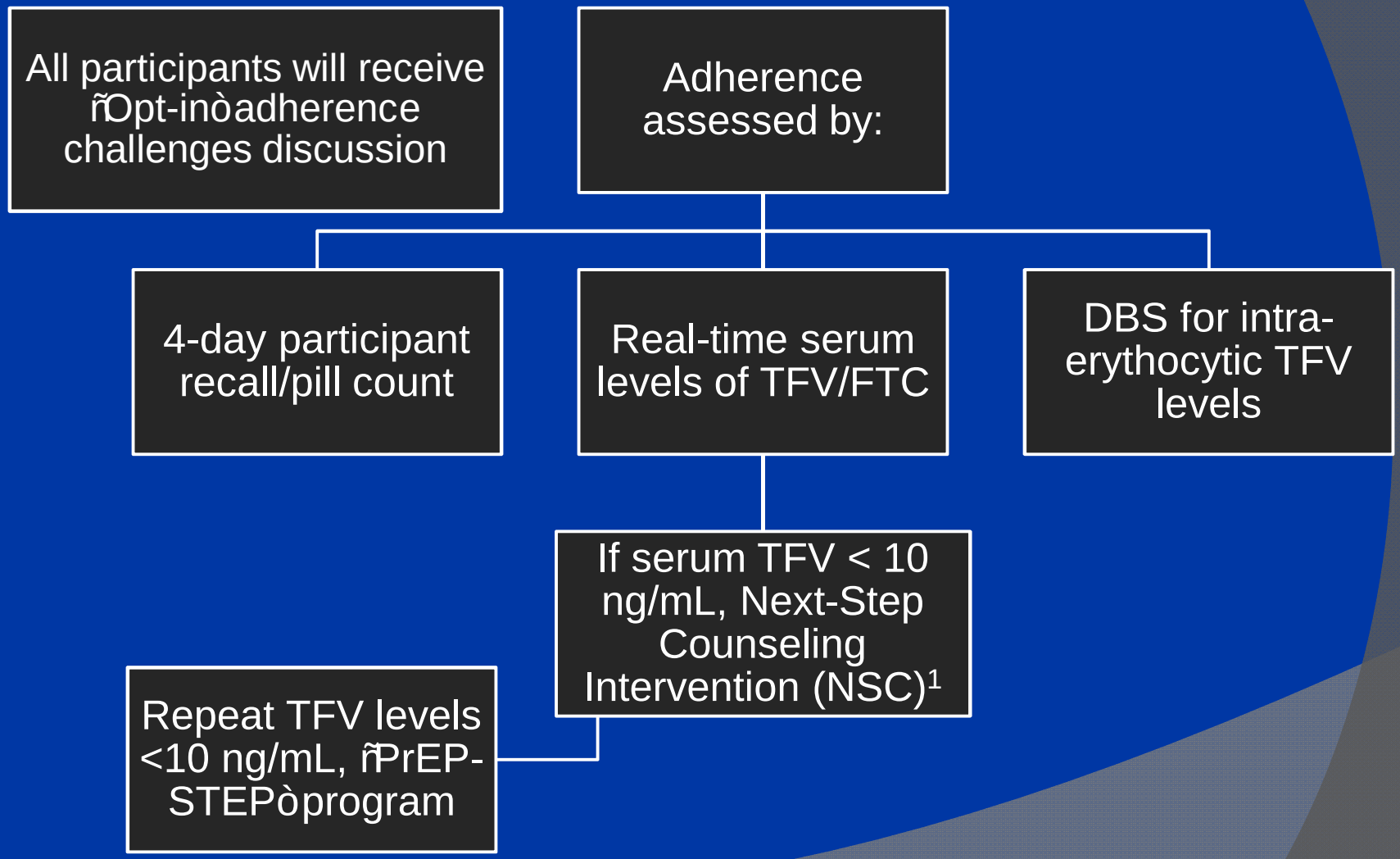
- If you have stopped PrEP for more than 7 days and would like to re-start, please call us and let us know so that we can help you do this safely.
- Getting an HIV test before you re-start PrEP is very important. If you are already infected with HIV and take Truvada, the virus could become resistant to this medication which means that the medication will no longer work for HIV treatment.

**Questions/Concerns**

- Call ###-###-#### if you have any questions or concerns.
- If you have an emergency, call 911 or go to the hospital emergency room.

Version 1.0, Date: 16May2012

# Path-PrEP: Staged Adherence




1. Amico *et al.* AIDS Behavior. 2012.

# HPTN 061: HIV Prevention for Black MSM

- 1,553 Black MSM enrolled in 6 U.S. cities
- Annual HIV incidence 3.0% (CI: 2.0-4.4%)
- 5.9% in men ≤30 years old (CI: 3.6-9.1%)
- Men ≤30 y.o. ŷ sexual risk and STI;  less likely to have a usual place for health care, and to have unmet health care needs.
- Lessons: If prevention is going to be effective, need to address social and structural issues, as well as behavioral concerns

# HPTN 073 Study Design

- Demonstration project
- A total of 225 participants, 75 participants to enroll in DC, LA, NC
- Once daily oral emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (FTC/TDF) combined with Comprehensive Clinical Care Coordination (C4).

# HPTN 073 Main Study Questions

- Will BMSM use PrEP?
- Is it safe for BMSM to use PrEP?
- Is it acceptable for local health care facilities to administer client-centered care coordination (C4) along with PrEP to BMSM?

# Adolescent PrEP

- ATN 082 enrolled 68 young MSM
- 70% agreed to take PrEP
- Of PrEP users, blood levels indicate about 50% adherence, comparable to self-report
- Lots of psychosocial issues reported
- ATN 110 and 113: open label TDF-FTC plus either group (Many Men, Many Voices) or individual intervention (Personal Cognitive Counseling)
- ATN 110: 18-12 yo; ATN 113: 15-17 yo

# REMS Materials
# Available at www.truvadapreprems.com

- Dear Healthcare Provider Letter
- Training Guide for Healthcare Providers
- Important Safety Information for Healthcare Providers
- Safety Information Fact Sheet
- Agreement Form
- Checklist for Prescribers
- Medication Guide
- Important Safety Information for Uninfected Individuals
- Full Prescribing Information

# PrEP Attitudes and Uptake

- Manhunt survey pre/post iPrEX
  - -4,825 MSM:46 states and 5 Canadian provinces
  - -Less than 20% heard of PrEP
  - -Less than 1% had used PrEP
  - -Majority were interested, dependingé ..
- Massachusetts MD survey post-CAPRISA
  - -Most had heard of CAPRISA 004
  - -Some knew that PrEP studies were underway
  - -Many concerns about risk compensation, resistance, cost

Krakower et al, PLoS ONE, 2012; White et al, AIDS Pt Care and STDs, 2012

REVIEW | Annals of Internal Medicine

# What Primary Care Providers Need to Know About Preexposure Prophylaxis for HIV Prevention

## A Narrative Review

Douglas Krakower, MD, and Kenneth H. Mayer, MD

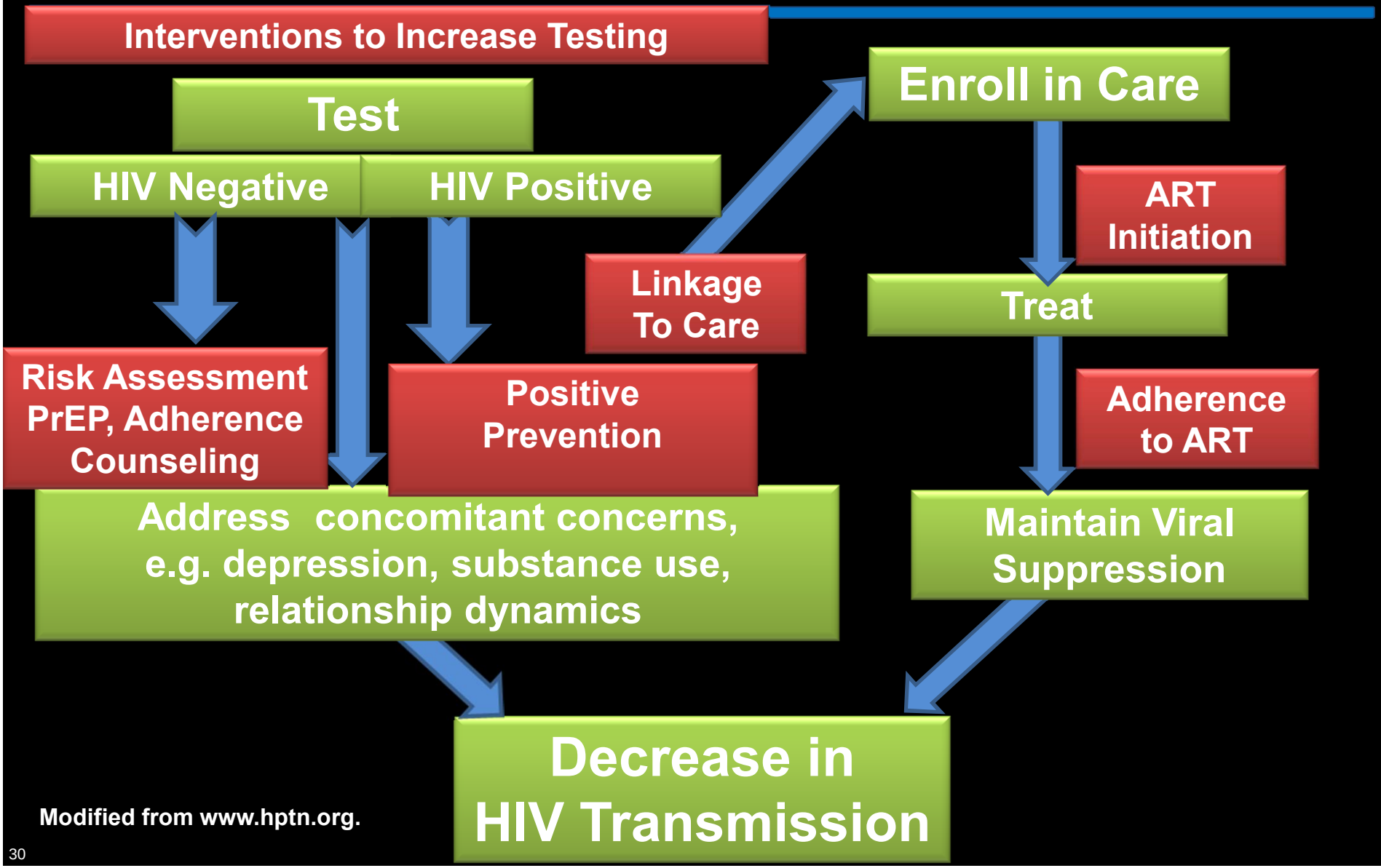
As HIV prevalence climbs globally, including more than 50 000 new infections per year in the United States, we need more effective HIV prevention strategies. The use of antiretrovirals for preexposure prophylaxis (PrEP) among high-risk persons without HIV is emerging as one such strategy. Randomized, controlled trials have demonstrated that once-daily oral PrEP decreased HIV incidence among at-risk men who have sex with men and African heterosexuals, including serodiscordant couples. An additional randomized, controlled trial of a topical pericoital antiretroviral microbicide gel decreased HIV incidence among at-risk heterosexual South African women. Two other studies in African women did not demonstrate the efficacy of oral or topical PrEP, raising concerns about adherence patterns and efficacy in this population.

The U.S. Food and Drug Administration (FDA) Antiviral Drugs Advisory Committee reviewed these studies and additional data in May 2012 and voted to advise the approval of oral tenofovir–emtricitabine for PrEP in high-risk populations. On 16 July 2012, the FDA recommended that this combination medication be approved for use as PrEP in high-risk persons without HIV. Patients may seek PrEP from their primary care providers, and those receiving PrEP require monitoring. Thus, primary care providers should become familiar with PrEP. This review outlines current knowledge about PrEP as it pertains to primary care, including identifying persons likely to benefit from PrEP; counseling to maximize adherence and reduce potential increases in risky behavior; and monitoring for potential drug toxicities, HIV acquisition, and antiretroviral drug resistance. Issues related to cost and insurance coverage are also discussed. Recent data suggest that PrEP, combined with other prevention strategies, holds promise in helping to curtail the HIV epidemic.

*Ann Intern Med.* 2012;157:490-497. www.annals.org
For author affiliations, see end of text.
This article was published on www.annals.org on 22 July 2012.

ñPurview paradoxò(Krakower et al)

# Combination Antiretroviral Prevention




Modified from www.hptn.org.

# Thank You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