# HIV Pre-Exposure Prophylaxis (PrEP)

**Carlos Malvestutto, MD, MPH**
**Assistant Professor, Internal Medicine**
**Division of Infectious Diseases**
**The Ohio State University College of Medicine**

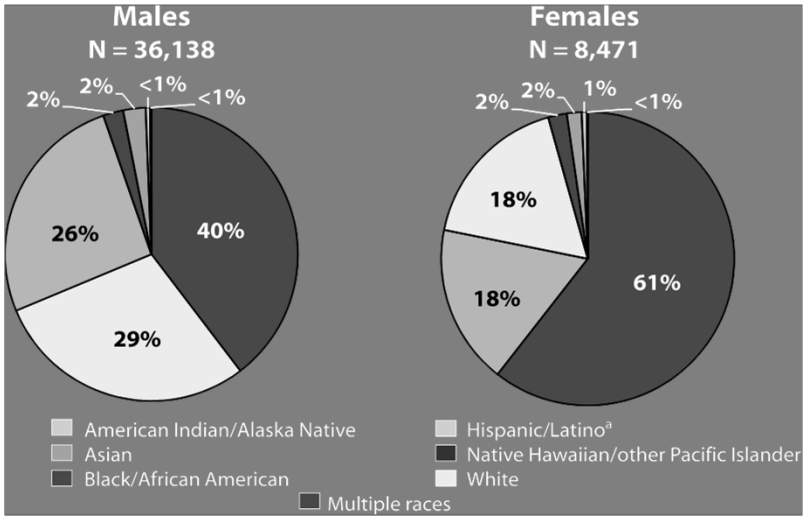
# Disclosures

- **No disclosures to report**

# Objectives

- Define PrEP in the context of the current AIDS Epidemic
- Review the scientific evidence supporting PrEP use
- Share data on the awareness and uptake of PrEP in high risk populations
- Discuss Guidelines for PrEP Implementation
- Discuss future PrEP modalities

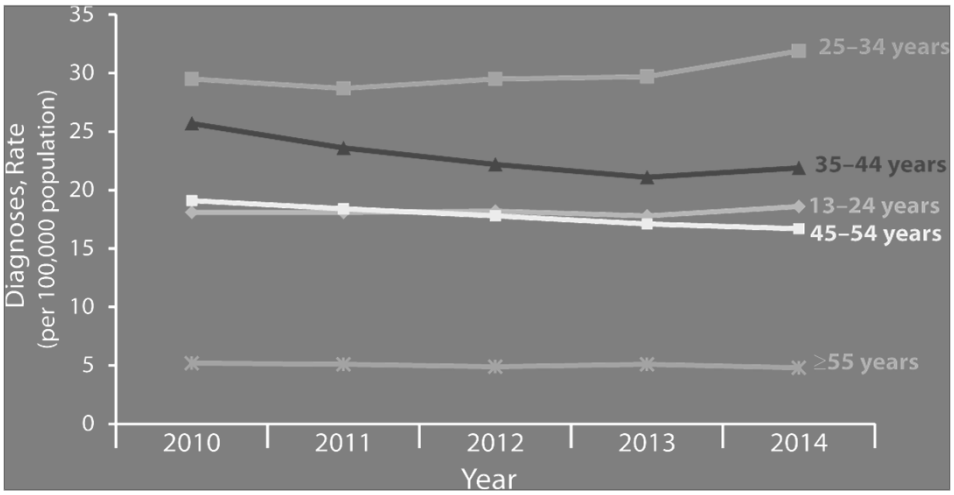
**Diagnoses of HIV Infection among Adults and Adolescents, by Sex and Race/Ethnicity, 2014—United States and 6 Dependent Areas**




*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, but not for incomplete reporting.

[a] Hispanics/Latinos can be of any race.

## Rates of Diagnoses of HIV Infection among Adults and Adolescents, by Age at Diagnosis, 2010–2014—United States




*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, but not for incomplete reporting.

# Lifetime Risk of HIV Diagnosis in the U.S.

**Mortality Data from National Center for Health Statistics (2009-2013, US census data)**

**Methods:**

- **Lifetime risk = cumulative probability of HIV diagnosis from birth (results presented as 1 in N)**

**Results: Lifetime Risk of Acquiring HIV**

- **Overall in USA: 1 in 99**
- **Black MSM: 1 in 2**
- **Hispanic MSM: 1 in 4**
- **White MSM: 1 in 11**

| HIV Risk Group | Relative Risk | Lifetime Risk |
|---|---|---|
| Male vs female | 4X for male | 1 in 62 (2%) vs 1 in 221 (0.5%) |
| Male: black vs white | 7X for black male | 1 in 20 (5%) vs 1 in 132 (1%) |
| **Female: black vs white** | **19X for black female** | **1 in 48 (2%) vs 1 in 880 (0.1%)** |
| Male: IDU vs heterosexual | 13X for PWID | 1 in 36 (3%) vs 1 in 473 (0.2%) |
| MSM vs heterosexual male | 79X for MSM | 1 in 6 (17%) vs 1 in 473 (0.2%) |

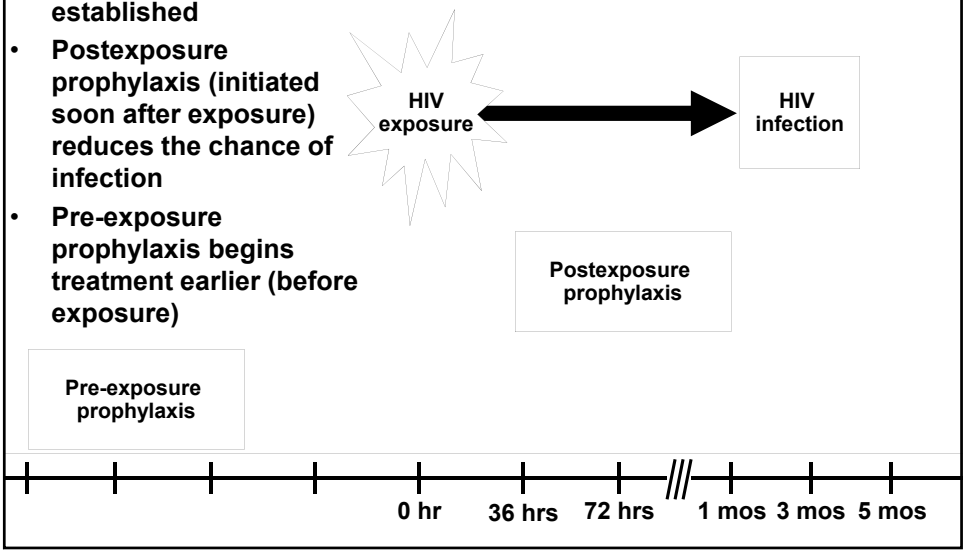
Hess K. et al. CROI 2016. Boston, MA. Oral 52

# What Is PrEP?

- **Pre-exposure Prophylaxis: A pharmacologic HIV prevention intervention for persons at high risk of becoming infected with HIV.**
- **An HIV-uninfected individual takes antiretroviral medication(s) *before* potential HIV exposure**
- **The use of medication for prophylaxis is well established:**
  - **Use of contraceptive methods to prevent pregnancy**
  - **Use of antimalaria medications before traveling to endemic areas**

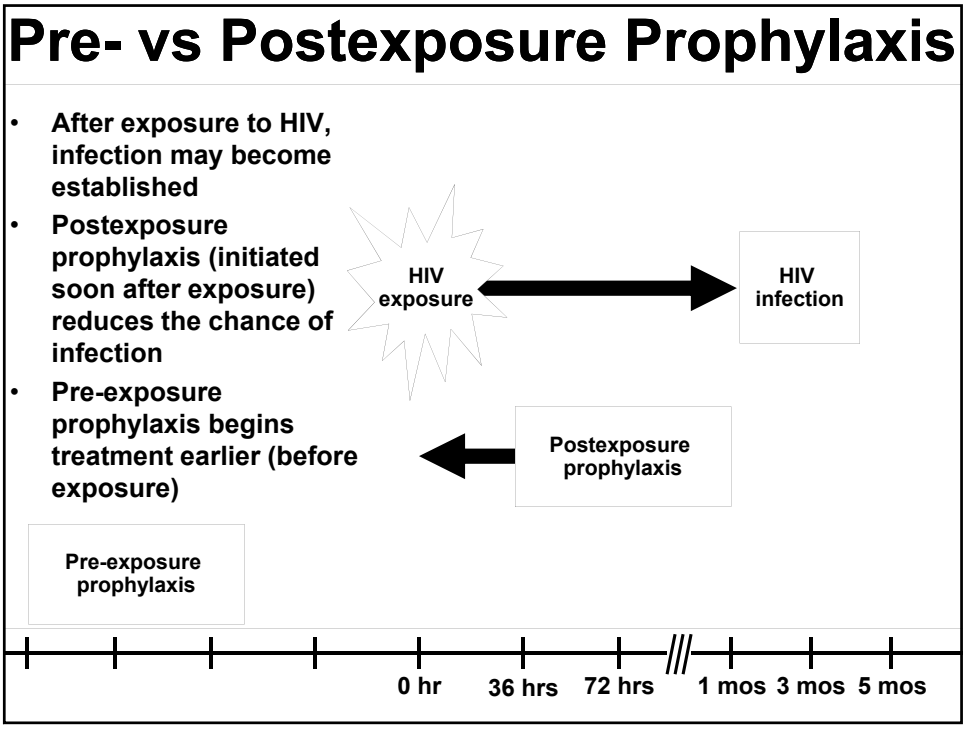
# Pre- vs Postexposure Prophylaxis

- **After exposure to HIV, infection may become established**
- **Postexposure prophylaxis (initiated soon after exposure) reduces the chance of infection**
- **Pre-exposure prophylaxis begins treatment earlier (before exposure)**



# Pre- vs Postexposure Prophylaxis

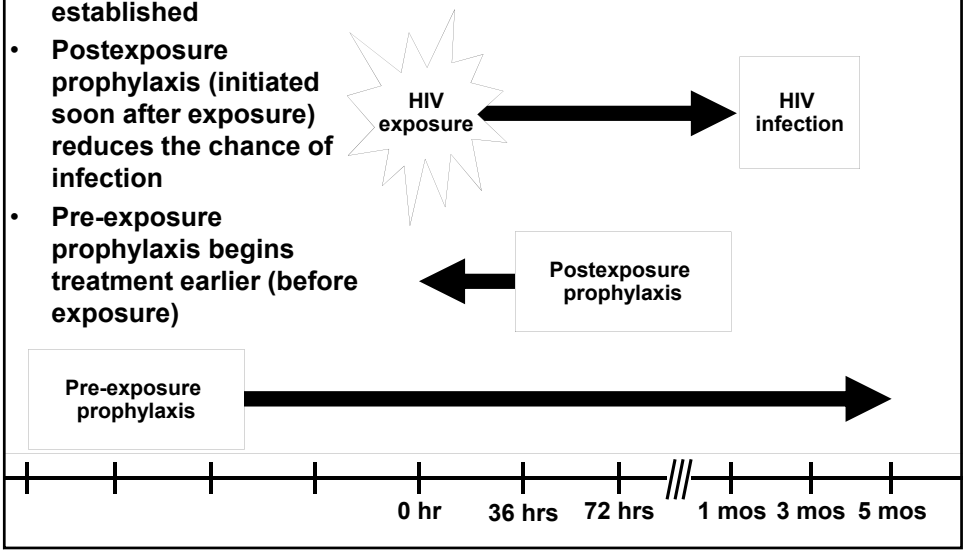
- After exposure to HIV, infection may become established
- Postexposure prophylaxis (initiated soon after exposure) reduces the chance of infection
- Pre-exposure prophylaxis begins treatment earlier (before exposure)





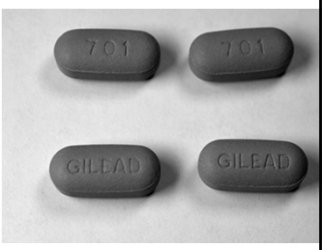
# Pre- vs Postexposure Prophylaxis

- After exposure to HIV, infection may become established
- Postexposure prophylaxis (initiated soon after exposure) reduces the chance of infection
- Pre-exposure prophylaxis begins treatment earlier (before exposure)

# What medication is used for PrEP?

- Truvada®
  - Tenofovir (TDF) + Emtricitabine (FTC)
  - Used for the *treatment* of HIV (~10 years)
  - Favorable characteristics for PrEP use:
    - Once daily dosing
    - Good drug levels at sites where infection occurs (vaginal and rectal tissue)
    - Relatively low toxicity and good tolerability
    - Tenofovir has a high genetic barrier for resistance
  - Approved for PrEP use in 2012 by the FDA






http://www.cdc.gov/hiv/pdf/PrEP_fact_sheet_final.pdf; Duwal et al, PLoS One 2012;7(7):e40382; Jackson et al, JAIDS 2013;62(3):275-281

# How were the drugs used in PrEP selected?

- Tenofovir disiproxil fumarate (TDF) and emtricitabine (FTC) well established nucleoside reverse transcriptase inhibitors already used for treatment of HIV-1
- Clinical trials have evaluated oral TDF, oral TDF/FTC combination and TDF vaginal gel
  - Safe, potent and well tolerated
  - Available co-formulated in single pill (Truvada)
  - Both FTC and TDF have long plasma (10 to 17 hours) and intracellular ($39^1$ and $150^2$ hours) half-lives
  - Have high penetration in vaginal and rectal tissues

1. Duwal et al, PLoS One 2012;7(7):e40382
2. Jackson et al, JAIDS 2013;62(3):275-281

# PrEP Safety

- TDF/FTC is well tolerated
- Start-up syndrome
  - 1-18.5% with nausea, vomiting ± dizziness
- Renal safety
  - 0.2% Grade 2-4 elevations in creatine among 5469 participants randomized to TDF/FTC
- Bone safety
  - 0.4 to 1.5% loss of BMD across total hip, spine
  - Return to baseline after discontinuation
  - Not associated with increased fracture risk


1. Grant RM, et al. N Engl J Med. 2010;363:2587-2599.
2. Van Damme. N Engl J Med 2012; 367:411-422
3. Thigpen MC, et al. N Engl J Med 2012; 367:423-434
4. Grant, et al. Abstract 48 LB. CROI 2016. Boston, MA
5. Baeten JM, et al. N Engl J Med. 2012;367:399-410.


# What is the scientific evidence supporting PrEP?

# Efficacy of PrEP in High-Risk MSM, Heterosexual Men & Women, and IDUs

| Trial | Population/Setting | Intervention | HIV Infections, n | | Reduction in HIV Infection Rate, % (95% CI) |
|---|---|---|---|---|---|
| | | | PrEP | Placebo | |
| iPrEX[1] (N = 2499) | MSM and transgender women, 11 sites in US, South America, Africa, Thailand | TDF/FTC | 36 | 64 | 44 (15 – 63) |
| Partners PrEP[2] (N = 4747) | Serodiscordant couples in Africa | TDF | 17 | 52 | 67 (44 – 81) |
| | | TDF/FTC | 13 | | 75 (55 – 87) |
| TDF2[3] (N = 1219) | Heterosexual males and females in Botswana | TDF/FTC | 9 | 24 | 62 (21 – 83) |
| Thai IDU[4] (N = 2413) | Volunteers from 17 drug Thai treatment centers | TDF | 17 | 33 | 49 (10 – 72) |

- 2 additional trials of PrEP (FEM-PrEP[5] and VOICE[6]), both conducted among high-risk African women, did not demonstrate protection against HIV; In both trials, PrEP adherence was very low

1. Grant RM, et al. N Engl J Med. 2010;363:2587-2599. 2. Baeten JM, et al. N Engl J Med. 2012;367:399-410. 3. Thigpen MC, et al. N Engl J Med. 2012;367:423-434. 4. Choopanya K, et al. Lancet. 2013;381:2083-2090. 5. Van Damme L, et al. N Engl J Med. 2012;367:411-422. 6. Marrazzo J, et al. CROI 2013. Abstract 26LB

# Efficacy of PrEP in High-Risk MSM, Heterosexual Men & Women, and IDUs

| Trial | Population/Setting | Intervention | HIV Infections, n | | Reduction in HIV Infection Rate, % (95% CI) |
|---|---|---|---|---|---|
| | | | PrEP | Placebo | |
| iPrEX[1] (N = 2499) | MSM and transgender women, 11 sites in US, South America, Africa, Thailand | TDF/FTC | 36 | 64 | 44 (15 – 63) |
| Partners PrEP[2] (N = 4747) | Serodiscordant couples in Africa | TDF | 17 | 52 | 67 (44 – 81) |
| | | TDF/FTC | 13 | | 75 (55 – 87) |
| TDF2[3] (N = 1219) | Heterosexual males and females in Botswana | TDF/FTC | 9 | 24 | 62 (21 – 83) |
| Thai IDU[4] (N = 2413) | Volunteers from 17 drug Thai treatment centers | TDF | 17 | 33 | 49 (10 – 72) |

- 2 additional trials of PrEP (FEM-PrEP[5] and VOICE[6]), both conducted among high-risk African women, did not demonstrate protection against HIV; In both trials, PrEP adherence was very low

1. Grant RM, et al. N Engl J Med. 2010;363:2587-2599. 2. Baeten JM, et al. N Engl J Med. 2012;367:399-410. 3. Thigpen MC, et al. N Engl J Med. 2012;367:423-434. 4. Choopanya K, et al. Lancet. 2013;381:2083-2090. 5. Van Damme L, et al. N Engl J Med. 2012;367:411-422. 6. Marrazzo J, et al. CROI 2013. Abstract 26LB

# Adherence is Critical for PrEP

| Study | Efficacy Overall, % | Blood Samples With TFV Detected, % | Efficacy By Blood Detection of TFV, % |
|---|---|---|---|
| iPrEx[1] | 44 | 51 | 92 |
| iPrEx OLE[2] | 49 | 71 | NR |
| Partners PrEP[3] | 67 (TDF)<br>75 (TDF/FTC) | 81 | 86 (TDF)<br>90 (TDF/FTC) |
| TDF2[4] | 62 | 80 | 85 |
| Thai IDU[5] | 49 | 67 | 74 |
| Fem-PrEP[6] | No efficacy | < 30 | NR |
| VOICE[7] | No efficacy | < 30 | NR |

**Efficacy among those who took PrEP (confirmed by TFV detection in blood) was 74 – 92%!**

1. Grant RM, et al. N Engl J Med. 2010;363:2587-2599. 2. Grant RM, et al. Lancet Infect Dis. 2014; 14:820-829. 3. Baeten JM, et al. N Engl J Med. 2012;367:399-410. 4. Thigpen MC, et al. N Engl J Med. 2012;367:423-434. 5. Choopanya K, et al. Lancet. 2013;381:2083-2090. 6. Van Damme L, et al. N Engl J Med. 2012;367:411-422. 7. Marrazzo J, et al. CROI 2013. Abstract 26LB

# Adherence is Critical for PrEP

| Study | Efficacy Overall, % | Blood Samples With TFV Detected, % | Efficacy By Blood Detection of TFV, % |
|---|---|---|---|
| iPrEx[1] | 44 | 51 | 92 |
| iPrEx OLE[2] | 49 | 71 | NR |
| Partners PrEP[3] | 67 (TDF)<br>75 (TDF/FTC) | 81 | 86 (TDF)<br>90 (TDF/FTC) |
| TDF2[4] | 62 | 80 | 85 |
| Thai IDU[5] | 49 | 67 | 74 |
| Fem-PrEP[6] | No efficacy | < 30 | NR |
| VOICE[7] | No efficacy | < 30 | NR |

**Efficacy among those who took PrEP (confirmed by TFV detection in blood) was 74 – 92%!**

1. Grant RM, et al. N Engl J Med. 2010;363:2587-2599. 2. Grant RM, et al. Lancet Infect Dis. 2014; 14:820-829. 3. Baeten JM, et al. N Engl J Med. 2012;367:399-410. 4. Thigpen MC, et al. N Engl J Med. 2012;367:423-434. 5. Choopanya K, et al. Lancet. 2013;381:2083-2090. 6. Van Damme L, et al. N Engl J Med. 2012;367:411-422. 7. Marrazzo J, et al. CROI 2013. Abstract 26LB

# PrEP in Women: FEM-PrEP and VOICE Trials

- **FEM-PrEP: Study of oral TDF/FTC for 3900 high-risk women in Africa (2120 randomized)[1]**
  - **Study ended early by DSMB due to lack of efficacy**
  - **35 vs 33 new HIV infections in the placebo and TDF/FTC arms**
  - **TDF blood levels show that adherence was very low (< 30%)**
  - **Risk Perception problems: 52% of women who acquired HIV felt they had no chance of becoming HIV infected**


1. Van Damme L, et al N Engl J Med. 2012 Jul 11. [Epub ahead of print].
2. Marrazzo J, et al. CROI 2013. Abstract 26LB.



# PrEP in Women: FEM-PrEP and VOICE Trials

- **FEM-PrEP: Study of oral TDF/FTC for 3900 high-risk women in Africa (2120 randomized)[1]**
  - **Study ended early by DSMB due to lack of efficacy**
  - **35 vs 33 new HIV infections in the placebo and TDF/FTC arms**
  - **TDF blood levels show that adherence was very low (< 30%)**
  - **Risk Perception problems: 52% of women who acquired HIV felt they had no chance of becoming HIV infected**

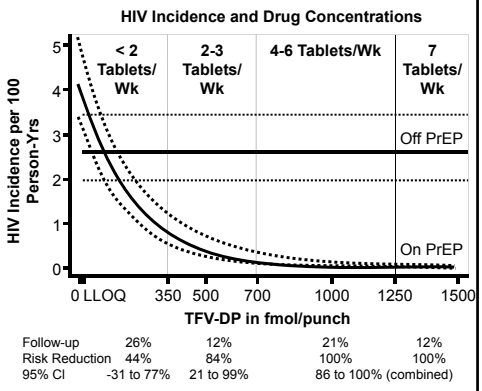

- **VOICE: Placebo-controlled trial of > 5000 women in South Africa, Uganda, and Zimbabwe[2]**
  - **Daily oral TDF; daily oral TDF/FTC; daily vaginal TFV 1% gel**
  - **DSMB stopped the daily oral TDF arm and daily vaginal gel arm for lack of efficacy**
  - **Daily oral TDF/FTC arm continued but shown to have low efficacy due to poor treatment adherence**


1. Van Damme L, et al N Engl J Med. 2012 Jul 11. [Epub ahead of print].
2. Marrazzo J, et al. CROI 2013. Abstract 26LB.

# Oral PrEP Reduces HIV Incidence in MSM, Even With Incomplete Adherence

- **iPreX OLE: open-label extension of iPrEX trial of daily TDF/FTC oral PrEP in MSM and transgender women (N = 1603)**
- **100% adherence was not required to attain full benefit from PrEP**
  - **Benefit of 4-6 tablets/wk similar to 7 tablets/wk**
  - **2-3 tablets/wk also associated with significant risk reduction**

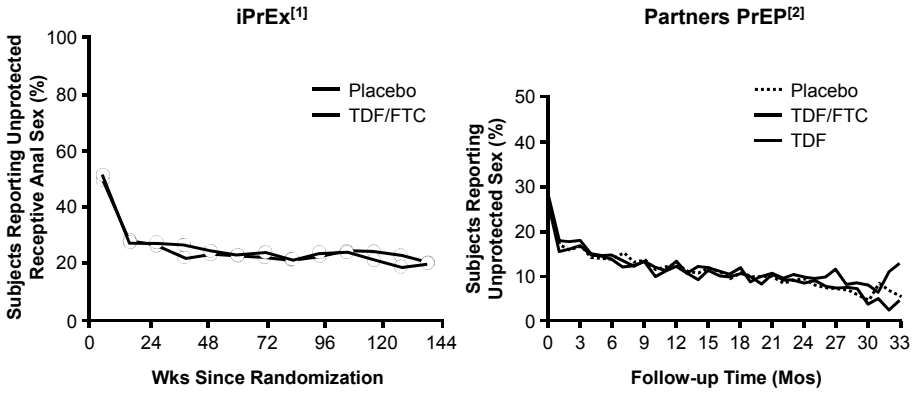
Higher levels of sexual risk taking at baseline associated with *increased* adherence to PrEP




1. Grant R, et al. IAC 2014. Abstract TUAC0105LB. 2. Grant R, et al. Lancet Infect Dis. 2014;14:820-829.

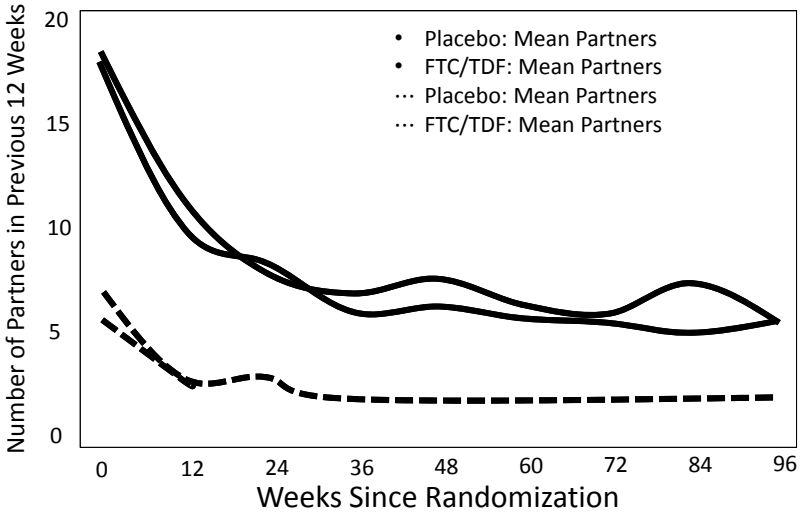
# Safety and Tolerability

# PrEP Trials Found No Risk Compensation



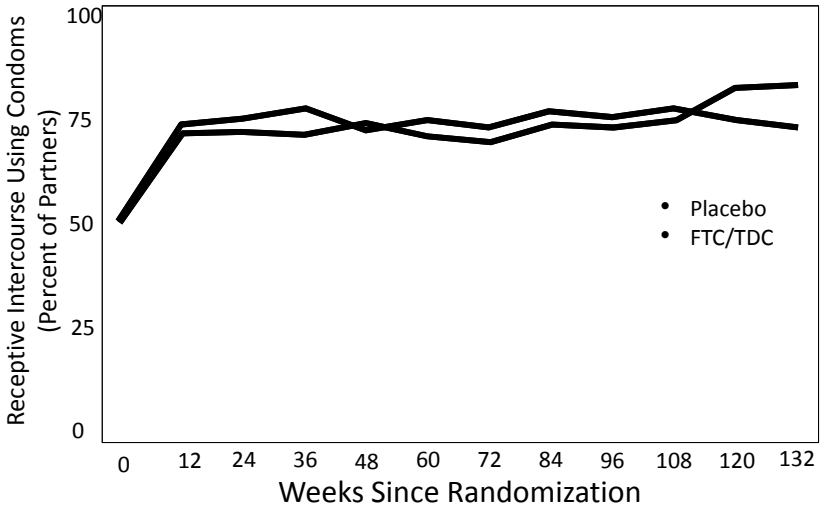

1. Grant RM, et al. N Engl J Med. 2010;363: 2587-2599.
2. Baeten JM, et al. N Engl J Med. 2012;367:399-410.

# Risk Behavior: Partners Decreased




N Engl J Med Nov 23, 2010

## Risk Behavior: Condom Use Increased




N Engl J Med Nov 23, 2010

# Drug Resistance

# PrEP and HIV Resistance

- **Resistance was rare in PrEP clinical trials, except for those with acute infection at baseline**
- **Resistance mutations seen: K65R (TDF) or M184V/I (FTC)**
- **Although M184V one of most commonly transmitted mutations, TDF in TDF/FTC remains protective**

**Number of HIV Seroconverters on *Active PrEP Arms* With HIV Resistance**

| Trial | HIV Infected After Enrollment, n/N | Seronegative Acute HIV Infection at Enrollment, n/N | HIV Infections Averted, n |
|---|---|---|---|
| iPrEx[1,2] | 0/36 | 2/2 | 28 |
| Partners PrEP[3] | 0/30 | 2/8 | 74 |
| TDF2[4] | 0/10 | 1/1 | 16 |

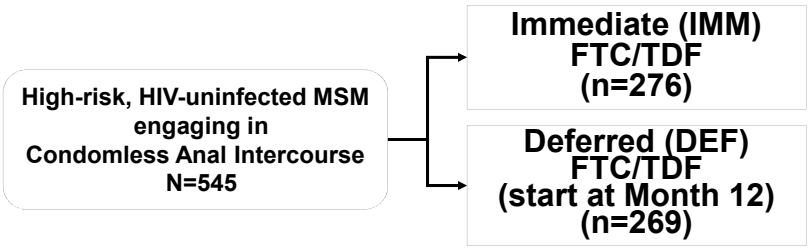
1. Liegler T, et al. CROI 2011. Abstract 97LB. 2. Grant RM, et al. N Engl J Med. 2010;363:2587-2599.
3. Baeten JM, et al. N Engl J Med. 2012;[Epub ahead of print] (supplementary appendix).
4. Thigpen MC, et al. N Engl J Med. 2012;[Epub ahead of print] (supplementary appendix).

# "Real World" Experience

## PROUD: Pragmatic Open-Label Randomized Trial of Pre-Exposure Prophylaxis

**Randomized, multi-center, open-label pilot study in London**

**Study Design**




**Primary endpoint:** HIV seroconversion rates at Month 12

**Secondary endpoints:** Safety, adherence, sexual behavior, new resistance

All subjects received HIV prevention services, including condoms, risk-reduction counseling, PEP, STI testing/treatment, HIV pre- and post-test counseling

**Oct 2014: PROUD DSMB announced deferred arm subjects, who had not yet started PrEP, would be offered opportunity to start PrEP**

McCormack S, et al. CROI 2015; Seattle, WA. #22LB

## PROUD: "Real World" Use of PrEP was highly effective.

- **86% reduction in risk seen over 60 wks with immediate PrEP (90% CI: 58% to 96%, *P* = .0002)**
  - **Rate difference: 7.6 (90% CI: 4.1-11.2)**
  - **Number needed to treat to prevent 1 infection: 13 (90% CI: 9-25)**
- **2 of 3 infected persons in immediate group seroconverting at study entry or shortly after first dose of PrEP**
  - **High rate of STIs seen in both groups (suggests no risk compensation!)**
  - **DSMB stopped trial; recommended that all participants be offered PrEP**

McCormack S, et al. CROI 2015. Abstract 22LB.

# PrEP + ART as Prevention in Serodiscordant Couples

- **Partners Demonstration Project in Uganda**
  - **Oral daily TDF/FTC PrEP for HIV-uninfected partner in 1013 serodiscordant couples continued for 6 mos beyond initiation of ART for infected partner**

**HIV Incidence, Actual vs Expected**

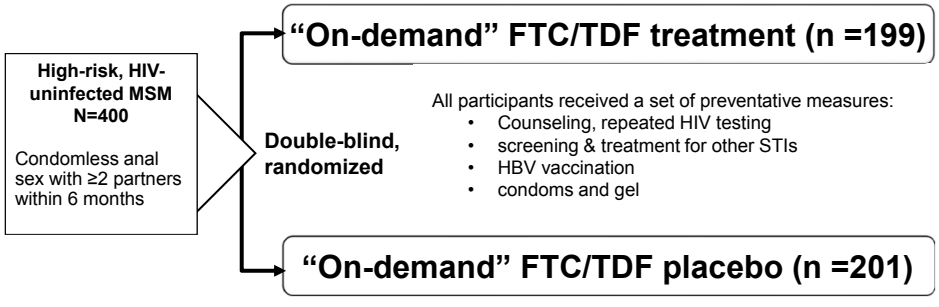
| Group | Infected, n | Incidence/100 PY (95% CI) |
|---|---|---|
| Expected | 39.7 | 5.2 (3.7-6.9) |
| Actual | 2 | 0.2 (0-0.9) |

- **Results**
  - **97% of HIV-negative partners used PrEP**
  - **78% of HIV-positive partners initiated ART; of these, > 90% with suppression**
- **96% reduction in expected infections**
  - **IRR, expected vs observed: 0.04 (95% CI: 0.01-0.19; *P* < .0001**
- **In pts with seroconversion, no tenofovir detectable in plasma at time of seroconversion**
  - **HIV-positive partner in 1 couple not on ART (high CD4+ count)**
  - **Other couple dissolved and HIV-negative partner in new relationship**

**Baeten J, et al. PLoS Medicine. 2016 Aug 23;13(8):e1002099. eCollection 2016.**

# ANRS IPERGAY: "On-Demand" PrEP

## Study Design




**"On-demand" regimen constitutes:**

**2 FTC/TDF or 2 placebo 2 - 24 hrs prior to sexual intercourse exposure**
**+**
**1 FTC/TDF or placebo 24 hrs after sex and then 48 hrs after first dose**

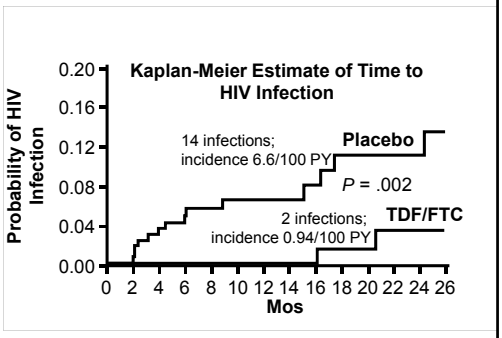
**Primary endpoint:** HIV seroconversion

Secondary endpoints: Sexual behavior, safety events, adherence

**Molina J, et al. CROI 2015; Seattle, WA. #23LB**

# Ipergay: "On-Demand" Oral PrEP in High-Risk MSM

- **Primary endpoint: HIV seroconversion**
- **86% reduction in risk seen in PrEP arm (95% CI: 40% to 99%, *P* = .002)**
  - **Number needed to treat for 1 yr to prevent 1 infection: 18**
  - **Median of 16 pills taken per mo in each arm**




- **In pts with infection, no tenofovir found in serum in last 2 visits**
- **4 cases of acute HCV infection noted among lab abnormalities**
- **DSMB stopped trial early and recommended all participants start PrEP**

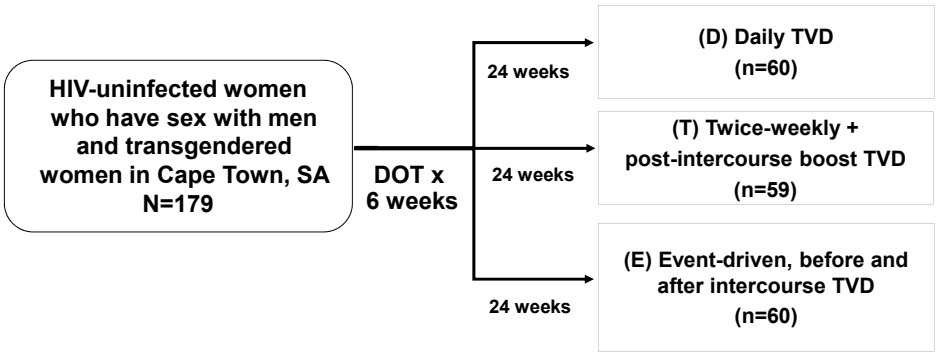
***On-demand PrEP strategy not FDA approved.**

Molina JM, et al. CROI 2015. Abstract 23LB.

**HPTN 067 / ADAPT (Cape Town)**

## Daily vs Nondaily PrEP Dosing in African Women

**Phase 2, randomized, open-label trial of PrEP**




**Primary Endpoints:** **PK steady state after DOT X 6 weeks**
**Feasibility of intermittent dosing of PrEP regimen in women**

**Bekker L, et al. CROI 2015; Seattle, WA. #978LB**

## HPTN 067 / ADAPT (Cape Town)
## Daily PrEP Offers Better Coverage and Enhances Adherence Compared With Nondaily PrEP in African Women

| Randomization at 6 weeks* | Daily (D) | Time-Driven | Event-Driven | *P* |
|---|---|---|---|---|
| Subjects, n | 60 | 59 | 60 | |
| HIV seroconversions, n | 1 | 2 | 2 | NS |
| Pills used, n | 7441 | 2850 | 2002 | <0.001 |
| Adherence, % | 76 | 65 | 53 | <0.001 |
| % with detectable drug levels when reporting sex in last 7 days: Wk 10; Wk 30 | 93; 80 | 87; 63 | 78; 53 | 0.018 |
| % with ≥9.1 fmol/$10^6$ cells in PBMC when reporting sex in last 7 days: Wk 10, Wk 30 | 81; 66 | 52; 46 | 54; 32 | 0.003 |
| Sex events fully covered, % | 75 | 58 | 52 | <0.001 |

*Time-Driven = 2x/wk + a post-intercourse boost; Event-Driven = before & after intercourse

Daily dosing compared to Time-Driven or Event-Driven resulted in:

- Better adherence
- Higher drug levels
- Better coverage of sex acts

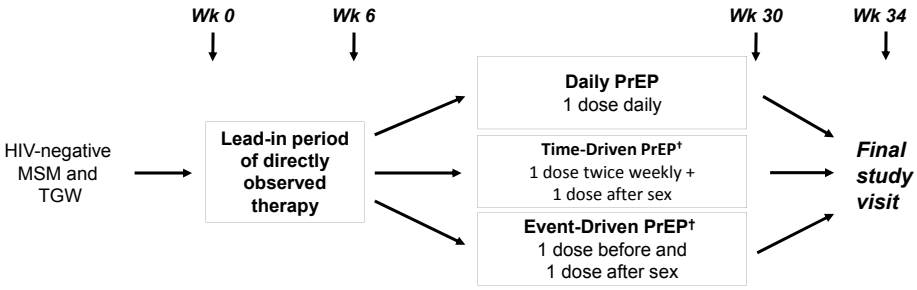
Bekker L, et al. CROI 2015; Seattle, WA. #978LB

# US PrEP Demo Project for MSM and TG Women

- 557 MSM and TG women
- Municipal STI/community health clinics in San Francisco, Miami, & Washington DC
- 63% participants had protective TFV DBS levels at all study visits
- STI rates high but did not increase
- Retention rates higher among those with self-reported condomless anal sex at baseline
- Adherence and engagement rates lower for African-Americans

# HPTN 067/ADAPT: PrEP for MSM/TGW

- International, randomized, open-label phase II trial; results reported from Harlem and Bangkok cohorts

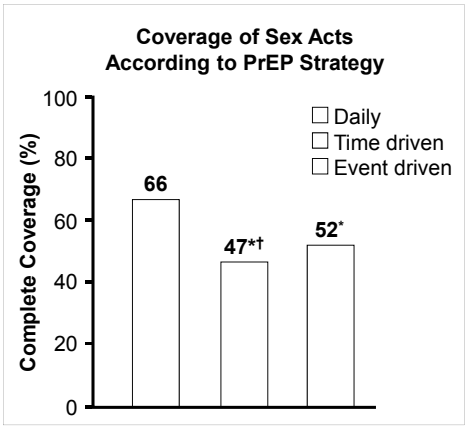



TDF/FTC PrEP given at standard dose and dispensed using an electronic monitoring device.
Adherence and sexual risk behavior assessed by weekly interview conducted by phone or in person.
*†Participants instructed to take no more than 2 doses daily or 7 doses/wk.

Mannheimer S, et al. IAS 2015. Abstract MOAC0305LB.

# HPTN 067/ADAPT: Harlem Cohort Comparison of PrEP Strategies

- **179 MSM or TGW randomized**
  - **Daily PrEP, n = 59**
  - **Time-driven PrEP, n = 60**
  - **Event-driven PrEP, n = 60**
- **Baseline characteristics: median age 30 yrs, 98% MSM, 70% black**
- **HIV seroconversion seen in 2 pts**
  - **Both pts had low or undetectable TDF in dried blood spots/plasma at study visits**



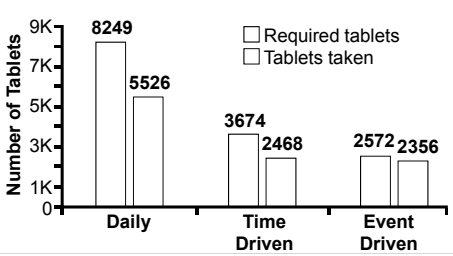

***P* = .001 vs daily. †*P* = .47 vs event driven.**
**Complete coverage: taking ≥ 1 PrEP dose within 4 days before sex and ≥ 1 dose within 24 hrs after sex.**

**Mannheimer S, et al. IAS 2015. Abstract MOAC0305LB. Reproduced with permission.**

# HPTN 067/ADAPT: Adherence to PrEP Strategies in Harlem Cohort

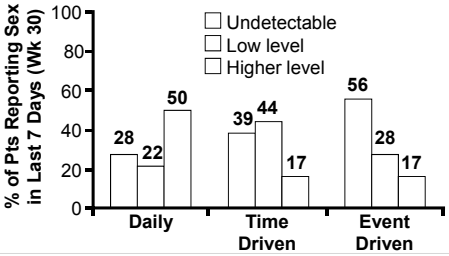
- **Adherence significantly higher in daily dosing arm vs time-driven or event-driven arms (65% vs 46% vs 41%, respectively; *P* < .0001 for both comparisons)**
- **Adherence did not differ significantly between the 2 nondaily dosing arms (*P* = .16)**

**Doses Required vs Taken**




**Doses required: *P* < .0001 for all strategy-type comparisons**
**Doses taken: *P* < .0001 for daily vs time-driven PrEP and event-driven vs daily PrEP; *P* = .33 when comparing nondaily dosing arms**

**TFV in Dried Blood Spots**




**Low level: detectable to ≤ 350 fmol**
**High level: > 350 fmol**
***P* = .07 for daily vs time-driven PrEP**
***P* = .01 for daily vs event-driven PrEP**
***P* = .36 for time-driven vs event-driven PrEP**

**Mannheimer S, et al. IAS 2015. Abstract MOAC0305LB. Reproduced with permission.**

# PrEP Implementation

# CDC PrEP Guideline: For Which Patients Is PrEP Recommended?

- **PrEP is recommended as one prevention option for the following adults at substantial risk of HIV acquisition**
  - **Sexually active MSM**
  - **Heterosexually active men and women at high risk**
  - **Injection drug users**

| | MSM | Heterosexual Women and Men | Injection Drug Users |
|---|---|---|---|
| **Potential indicators of substantial risk of acquiring HIV infection** | ▪ HIV-positive sexual partner<br>▪ Recent bacterial STI<br>▪ High number of sex partners<br>▪ History of inconsistent or no condom use<br>▪ Commercial sex work | ▪ HIV-positive sexual partner<br>▪ Recent bacterial STI<br>▪ High number of sex partners<br>▪ History of inconsistent or no condom use<br>▪ Commercial sex work<br>▪ In high-prevalence area or network | ▪ HIV-positive injecting partner<br>▪ Sharing injection equipment<br>▪ Recent drug treatment (but currently injecting) |

CDC. PrEP Guideline. 2014.

# Risk Assessment

- **Ask the right questions**
  - **Do you have sex with men, women, or both?**
  - **Have you had a sexually transmitted infection?**
  - **For women: Have you had a male partner who may be at risk of HIV?**
  - **For MSM: Are you ever a "bottom" (receptive anal intercourse) without a condom?**

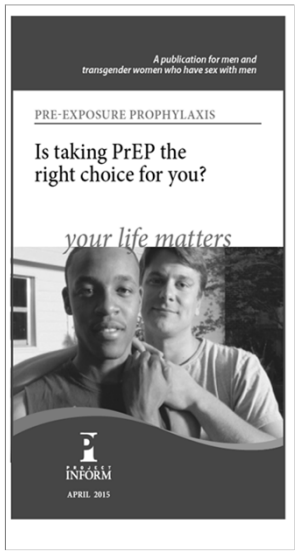
CDC. PrEP Guideline. 2014.

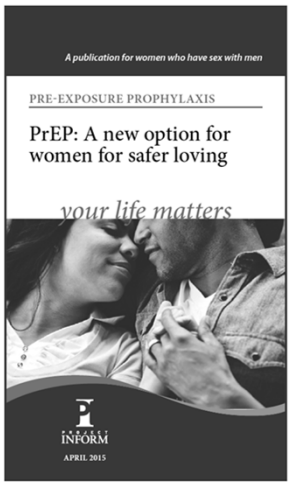
# CDC Guideline: Clinical Eligibility for PrEP

- **The following are required before prescribing PrEP to identify patients for whom PrEP would be harmful or may present risks to health:**
  - **Documented negative HIV test result**
  - **No signs or symptoms of acute HIV infection**
  - **Normal renal function; no use of contraindicated medications**
  - **Documented HBV infection status and vaccination status**

**CDC. PrEP Guideline. 2014.**

# Educational Materials: Pamphlets




**Projectinform.org**

# Patient Counseling

- Safety/adverse effects
  - Nausea and diarrhea usually resolve in 1 month
  - Do not use PrEP with eGFR< 60 ml/min
  - TDF can cause lactic acidosis and hepatomegaly with steatosis
  - In patients at risk, check bone density
- Adherence
  - PrEP for those who take it every day, but it may not be 100% effective
  - Do not refill medication without retesting

# HIV Screening

- Exclude acute and chronic HIV infection[1,2]
  - Use 4th-generation HIV Ag/Ab or HIV-1 RNA using nucleic acid–based tests if acute infection is suspected
  - Document negative antibody test within the week before starting PrEP
  - Do not accept patient-reported results
  - Avoid use of oral rapid HIV testing due to lower sensitivity

1. CDC. PrEP Guideline. 2014.
2. Daar ES, et al. Curr Opin HIV AIDS. 2008;3:10-15.

# Acute HIV Infection

- **Patients who are candidates for PrEP are at substantial risk of HIV infection**
- **Acute HIV infection should be suspected in patients with recent HIV exposure[1]**
  - **Signs and symptoms include fever, rash, pharyngitis, lymphadenopathy, myalgia, headache, diarrhea, arthralgia[2]**
- **All PrEP candidates with a negative or indeterminate HIV antibody test MUST be asked about symptoms of viral illness in the previous month or on the day of evaluation**
  - **Additional confirmatory testing is needed in patients reporting recent signs or symptoms suggestive of acute HIV**

1. CDC. PrEP Guideline. 2014.
2. Daar ES, et al. Curr Opin HIV AIDS. 2008;3:10-15.

# CDC Guideline: Follow-up and Monitoring

| Follow-up | At Least Every 3 Mos | After 3 Mos and at Least Every 6 Mos Thereafter | At Least Every 6 Mos | At Least Every 12 Mos |
|---|---|---|---|---|
| **All patients** | ▪ HIV test<br>▪ Medication adherence counseling<br>▪ Behavioral risk reduction support<br>▪ Adverse event assessment<br>▪ STI symptom assessment | ▪ Assess renal function | ▪ Test for bacterial STIs | ▪ Evaluate need to continue PrEP |
| **Women** | ▪ Pregnancy test (where appropriate) | | | |
| **HBsAg+** | | | ▪ HBV DNA by quantitative assay* | |

***Every 6-12 mos.**

CDC. PrEP Guideline. 2014.

# Stopping PrEP

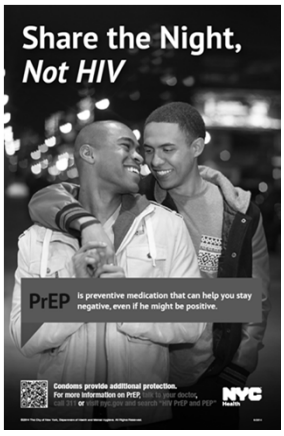
- PrEP is not meant to be a "permanent" intervention. PrEP should be used during periods of high risk.
- Reasons to stop PrEP:
  - Evidence of HIV infection
  - Adverse events
  - Chronic nonadherence
  - Change in level of risk
  - Patient choice
- If restarting PrEP after stopping, repeat standard pre-PrEP evaluation

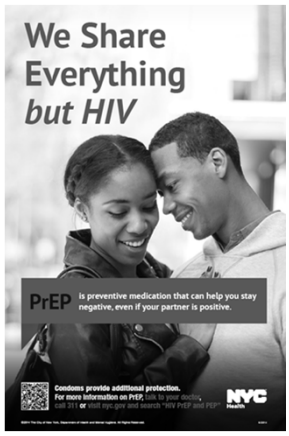
CDC. PrEP Guideline. 2014.

# Recommendations for PrEP Implementation

- Coordinated effort to educate potential users
- Offering PrEP to highest risk individuals will yield best adherence and effectiveness
- Adherence support is essential
- Visible marketing campaign needed
- Need to engage and educate local primary care providers

# NYC DOH PrEP Posters





**Author: New York City Department of Health and Mental Hygiene (DOHMH)**

# PrEP Awareness and Uptake of in U.S.

## Awareness of PrEP Among Young MSM

- 759 MSM 18-29 y/o in Atlanta, Chicago, NYC, or online surveyed.
- 67.5 % aware of PrEP
- Only 8.7 % overall used PrEP.
  - In NYC, 13.4 %
  - In Chicago, 6.7 %
  - In Atlanta, 4.3%
  - Nationwide, 8.3 %

Strauss, et al. AIDS Behav. 2016 Jul 11. [Epub ahead of print]

## PrEP Uptake

- Uptake of PrEP in the U.S. has increased by 500% between 2013 and 2015.
- 75% of all PrEP prescriptions filled by Whites (only 10% and 12% filled by Blacks and Hispanics)
- 64.1% of HIV-negative MSM in San Francisco meet PrEP criteria
- 9.2% of MSM overall and 14.5% of eligible MSM using PrEP in San Francisco in 2014.
- PrEP LESS likely to be used by MSM of color, particularly black and Hispanic, and by younger MSM in San Francisco

Bush S, et al. Characteristics of FTC/TDF for pre-exposure prophylaxis users in the US. ASM Microbe 2016; June 16-20, 2016, 2016; Boston, MA

Snowden JM, et al. Sex Transm Infect 2016;0:1–4

## Barriers and Facilitators to PrEP Uptake for Blacks and Latino MSM

- **Black and Latino MSM more likely than White MSM**
  - **to regard talking to provider about sex as a barrier**
  - **to report PrEP stigma**
  - **to report concerns regarding PrEP efficacy**
  - **to consider free sexual health care and additional supportive services, e.g., counseling or text-based support, to be significant facilitators of PrEP.**

J Acquir Immune Defic Syndr. 2016 Jul 21. [Epub ahead of print]

# PrEP Impact

- **Assuming 61% adherence (>4 doses/week) and 40% coverage of eligible MSM over the next 10 years would avert 33% of expected infections**
- **Predicted NNT = 25**

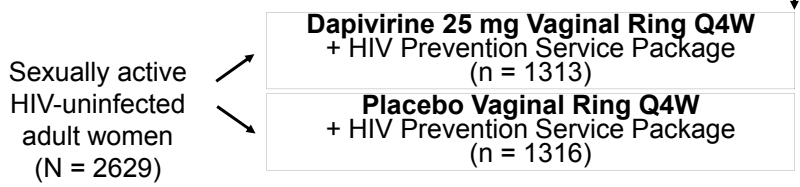
**Jenness, et al. J Infect Dis 2016 July 14. pii: jiw223. [Epub ahead of print]**

# New PrEP Modalities

## MTN-020/ASPIRE: Dapivirine Vaginal Ring for HIV Prevention in Women

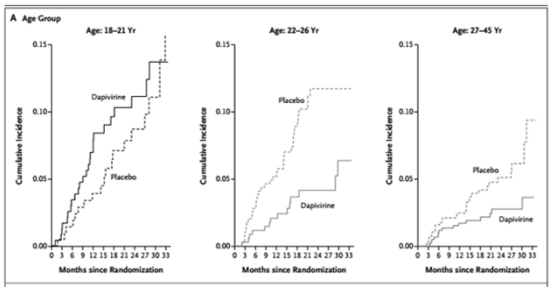
- **Multicenter, double-blind, placebo-controlled, randomized phase III trial in Malawi, South Africa, Uganda, and Zimbabwe**
- **Silicone elastomer vaginal matrix ring containing NNRTI dapivirine**
  **25 mg; ring replaced every 4 wks**
- **Primary endpoints: efficacy and safety**
- **HIV protection efficacy vs placebo: 27% (*P* = .046)**

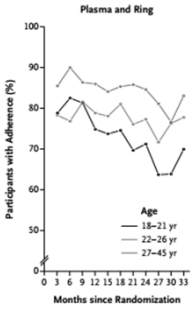
***≥ 1 yr; endpoint-driven duration***




**Brown E, et al. AIDS 2016. Abstract TUAC0105LB.**
**Baeten JM, et al. N Engl J Med. 2016;[Epub ahead of print].**

# MTN-20/ASPIRE Results



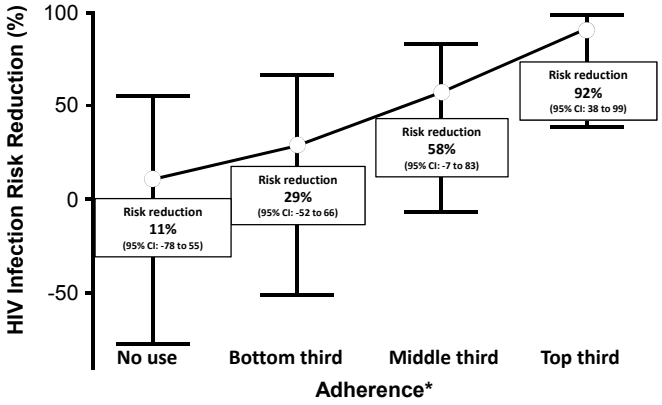

- Efficacy of dapivirine vs placebo:
  - - 27% (95% CI, −133 to 31) for 18-21 y/o
  - 56% (95% CI, 19 to 76) for 22-26 y/o
  - 51% (95% CI, 8 to 74) for 27-45 y/o
  - 56% (95% CI, 31 to 71; P<0.001) for > 21 y/o combined

Adherence decreased over time and lowest among 18-21 y/o

**Images courtesy of Microbicide Trials Network**

# MTN-020/ASPIRE Subcohort: Adherence vs HIV Protection 3 Mos Before Detection

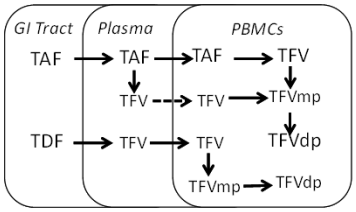
- Sustained adherence associated with 92% reduction in risk of HIV infection




*For seroconversions, adherence level taken from visit with lowest adherence of 3 months (3 visits) before HIV detection.

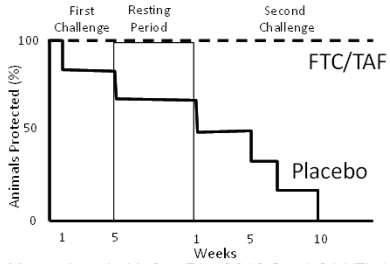
Brown E, et al. AIDS 2016. Abstract TUAC0105LB.
Reproduced with permission.

## Tenofovir alafenamide



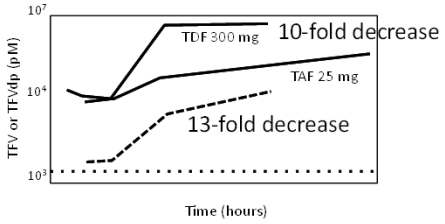

- 9-fold higher TFVdp in PBMCs with TAF than TDF
- 19--fold lower TFV concentration in plasma with TAF than with TDF
- TFV exposure in mucosal tissues 2-10 fold lower after TAF than TDF
- TFVdp exposure was 13-fold lower in rectal tissue and 1-fold lower in the female genital tract

Adapted from Liu Y. Poster H-664. ICAAC 2013




Massud et al, J Infect Dis 2016 Oct 1;214(7):1058-62

Pharmacokinetic Results: Rectal Tissue



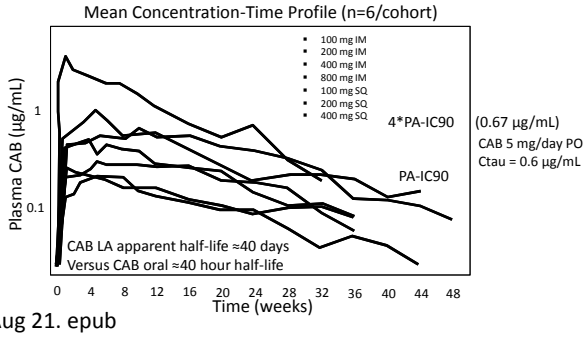

Garrett, et al. 102LB. CROI 2016, Boston, MA

# The Future of PrEP

- **Long Acting Injectable Drugs for PrEP**

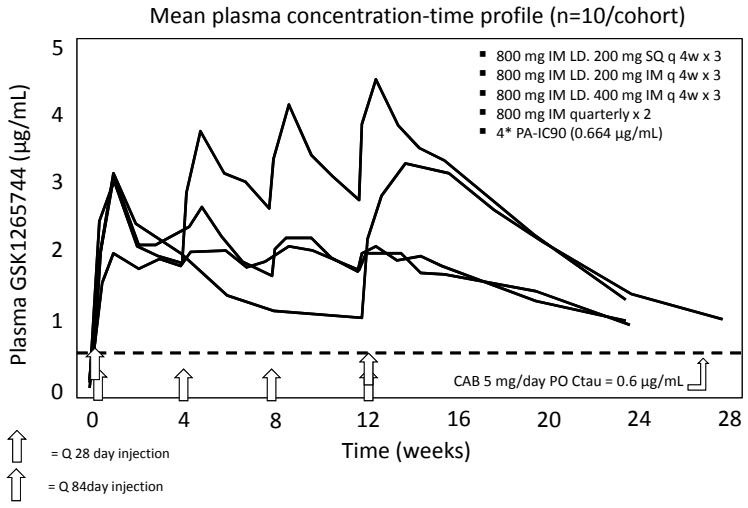
# Cabotegravir

- Investigational HIV integrase inhibitor
- High genetic barrier to resistance
- Well suited for formulation as a LA injection
- Cabotegravir LA provides detectable drug in plasma for 48 weeks




Spreen, et al. JAIDS 2014 Aug 21. epub

# Cabotegravir LA Monthly or Quarterly Doses Exceed Minimum Target Plasma Levels




Trezza, et al. Curr Opin HIV AIDS 2015, 10:239-245

# HPTN 083: Cabotegravir LA vs TDF/FTC

- Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral TDF/FTC
- Study Population: 4500 HIV-uninfected MSM and TGW at risk for acquiring HIV infection, ages 18 or older at sites in the Americas, Asia and South Africa.
- Study Design
  - Step 1:
    - Arm A – Daily oral CAB and oral TDF/FTC placebo x 5 weeks
    - Arm B – Daily oral TDF/FTC and oral CAB placebo x 5 weeks
  - Step 2:
    - Arm A – CAB LA (600 mg as a single intramuscular [IM] injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral TDF/FTC placebo.
    - Arm B – Daily oral TDF/FTC and IM placebo at two time points 4 weeks apart and every 8 weeks thereafter

https://www.hptn.org

# HPTN 083: Cabotegravir LA vs TDF/FTC

  - Step 3:
    - Both arms: Open-label daily oral TDF/FTC no later than 8 weeks after the last injection (in order to cover the PK tail for Arm A participants, for up to 48 weeks.
  - Participants will then transition to locally-available HIV prevention services, including services for PrEP
- Study Duration: 3-5 years
- Primary Objective: To compare the HIV incidence among participants receiving oral CAB/CAB LA (oral lead in and quarterly injections) vs. oral TDF/FTC

https://www.hptn.org

# HPTN 083: Cabotegravir LA vs TDF/FTC

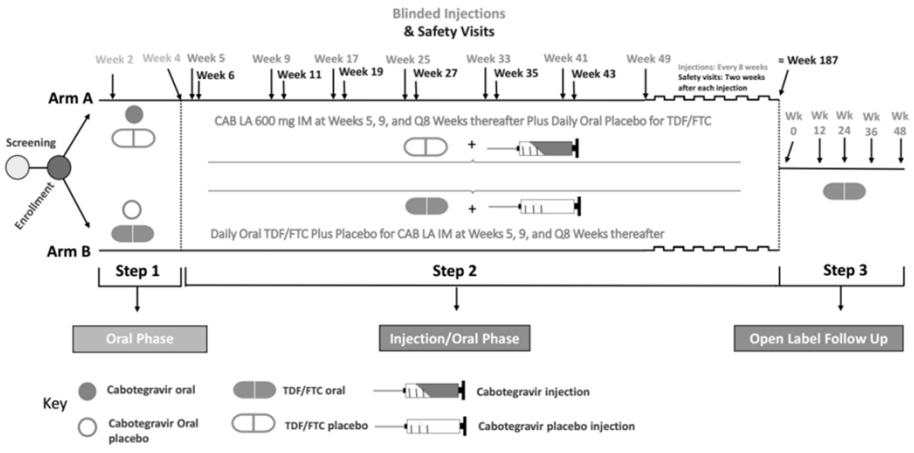



Image permission provided by Dr. Raphael Landovitz

# Conclusions

- PrEP is safe and effective in reducing transmission of HIV in high risk individuals.
- PrEP does not protect against other STIs and is not meant to replace condom use
- Adherence is essential for PrEP success and may be more critical in women than in MSM because TFV levels are higher in rectal tissue than in vaginal tissue
- New PrEP modalities are currently in development.

# Conclusions

- We must increase awareness and uptake of PrEP among individuals at highest risk, particularly in young, Black and Latino MSM.
- Do not forget the 4 pillars of HIV prevention:
  - HIV Testing that adheres to CDC/USPTF guidelines
  - HIV Treatment as Prevention
  - Post-Exposure Prophylaxis
  - PrEP
- No single intervention will end the HIV epidemic but a comprehensive prevention and treatment strategy will get us a lot closer to achieving an AIDS Free Generation.


# Acknowledgements

- Dr. Susan Koletar
- Dr. Jose Bazan
- Dr. Raphael Landovitz
- Ohio State University AIDS Clinical Trials Unit Staff
- Our patients and clinical trial participants