

## HIV Pre-Exposure Prophylaxis (PrEP)

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

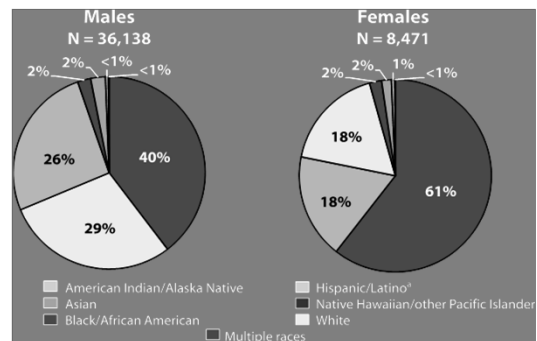
## Disclosures

- No disclosures to report

## Objectives

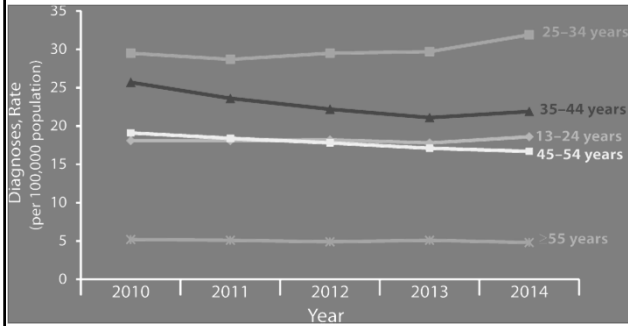
- Define PrEP in the context of the current AIDS Epidemic
- Review the scientific evidence supporting PrEP use
- Share data on the awareness and uptake of PrEP in high risk populations
- Discuss Guidelines for PrEP Implementation
- Discuss future PrEP modalities

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.  
<sup>a</sup>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

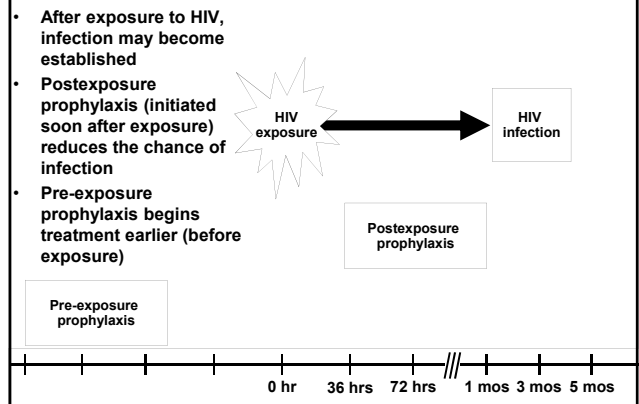
HIV Risk Group	Relative Risk	Lifetime Risk
Male vs female	4X for male	1 in 62 (2%) vs 1 in 221 (0.5%)
Male: black vs white	7X for black male	1 in 20 (5%) vs 1 in 132 (1%)
Female: black vs white	19X for black female	1 in 48 (2%) vs 1 in 880 (0.1%)
Male: IDU vs heterosexual	13X for PWID	1 in 36 (3%) vs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

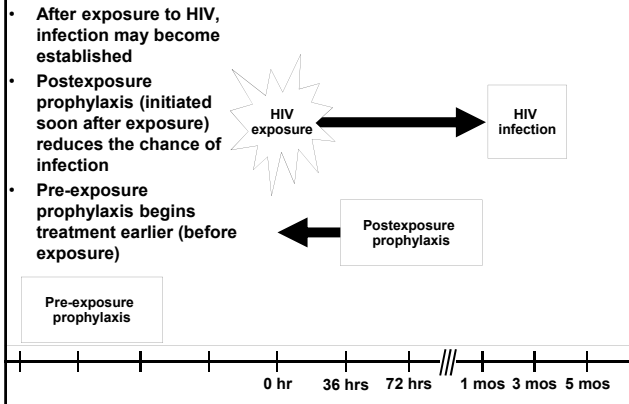
## What Is PrEP?

- **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

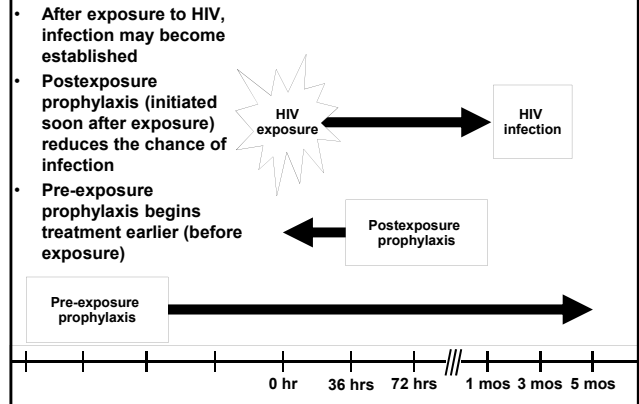
## Pre- vs Postexposure Prophylaxis



## Pre- vs Postexposure Prophylaxis



## Pre- vs Postexposure Prophylaxis



## 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



Author: Jeffrey Beall  
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[http://www.cdc.gov/hiv/pdf/PrEP\\_fact\\_sheet\\_final.pdf](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 disoproxil 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<sup>1</sup> and 150<sup>2</sup> 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  $\pm$  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 <sup>[1]</sup> (N = 2499)	MSM and transgender women, 11 sites in US, South America, Africa, Thailand	TDF/FTC	36	64	44 (15 – 63)
Partners PrEP <sup>[2]</sup> (N = 4747)	Serodiscordant couples in Africa	TDF	17	52	67 (44 – 81)
		TDF/FTC	13	52	75 (55 – 87)
TDF2 <sup>[3]</sup> (N = 1219)	Heterosexual males and females in Botswana	TDF/FTC	9	24	62 (21 – 83)
Thai IDU <sup>[4]</sup> (N = 2413)	Volunteers from 17 drug Thai treatment centers	TDF	17	33	49 (10 – 72)

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

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### Adherence is Critical for PrEP

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

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

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### PrEP in Women: FEM-PrEP and VOICE Trials

- FEM-PrEP: Study of oral TDF/FTC for 3900 high-risk women in Africa (2120 randomized)<sup>1</sup>
  - 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

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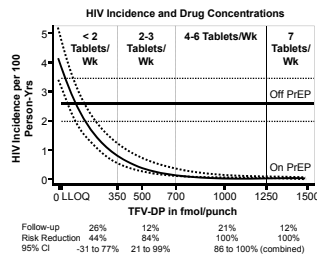
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  - TDF blood levels show that adherence was very low (< 30%)
  - Risk Perception problems: 52% of women who acquired HIV felt they had no chance of becoming HIV infected
- VOICE: Placebo-controlled trial of > 5000 women in South Africa, Uganda, and Zimbabwe<sup>2</sup>
  - 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

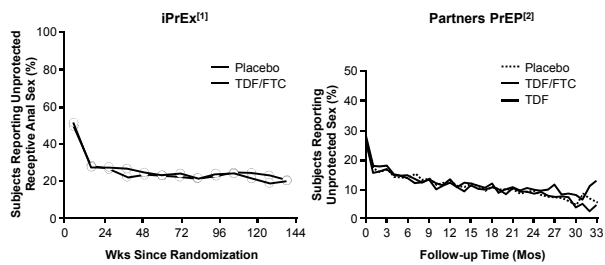


Higher levels of sexual risk taking at baseline associated with *increased* adherence to PrEP

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

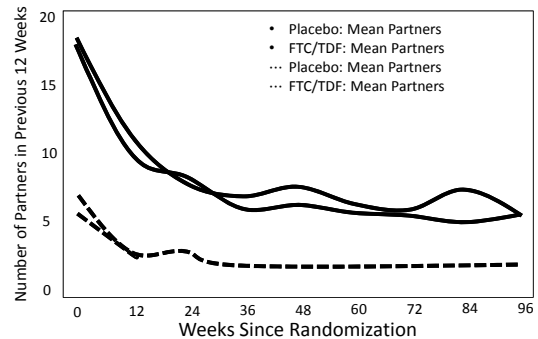
## Safety and Tolerability

## PrEP Trials Found No Risk Compensation



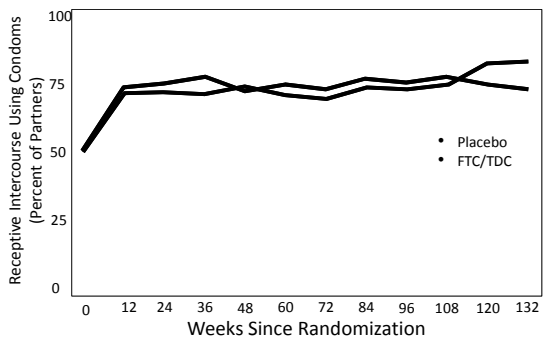
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## Risk Behavior: Partners Decreased



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 <sup>1,2</sup>	0/36	2/2	28
Partners PrEP <sup>3</sup>	0/30	2/8	74
TDF2 <sup>4</sup>	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
- 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

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)

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

### ANRS IPERGAY: “On-Demand” PrEP

#### Study Design

All participants received a set of preventative measures:
 

- Counseling, repeated HIV testing
- screening & treatment for other STIs
- HBV vaccination
- condoms and gel

“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

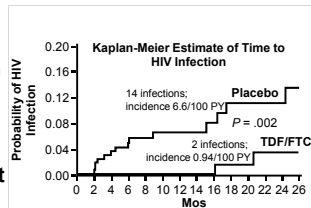
**Primary endpoint:** HIV seroconversion  
**Secondary endpoints:** Sexual behavior, safety events, adherence

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



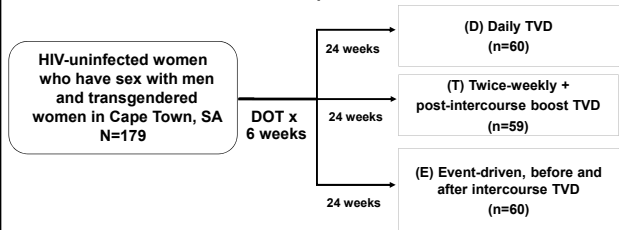
- In pts with infection, no tenofovir found in serum in last 2 visits
  - 4 cases of acute HCV infection noted among lab abnormalities
- DSMB stopped trial early and recommended all participants start PrEP

\*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 $\geq 9.1$ 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

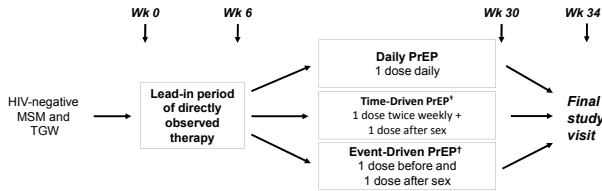
Bekker L, et al. CROI 2015; Seattle, WA. #978LB

## 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

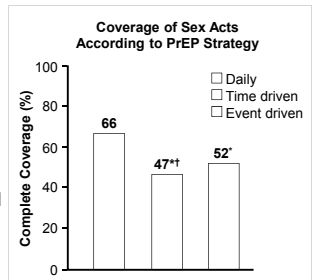


TDF/FTC PrEP given at standard dose and dispensed using an electronic monitoring device. Adherence and sexual risk behavior assessed by weekly interview conducted by phone or in person. \*Participants instructed to take no more than 2 doses daily or 7 doses/wk.

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



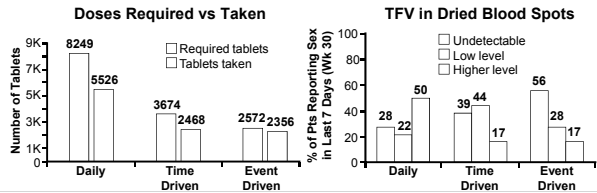
\*P = .001 vs daily. †P = .47 vs event driven.

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: 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  
 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

### Potential indicators of substantial risk of acquiring HIV infection

MSM	Heterosexual Women and Men	Injection Drug Users
<ul style="list-style-type: none"> <li>▪ HIV-positive sexual partner</li> <li>▪ Recent bacterial STI</li> <li>▪ High number of sex partners</li> <li>▪ History of inconsistent or no condom use</li> <li>▪ Commercial sex work</li> </ul>	<ul style="list-style-type: none"> <li>▪ HIV-positive sexual partner</li> <li>▪ Recent bacterial STI</li> <li>▪ High number of sex partners</li> <li>▪ History of inconsistent or no condom use</li> <li>▪ Commercial sex work</li> <li>▪ In high-prevalence area or network</li> </ul>	<ul style="list-style-type: none"> <li>▪ HIV-positive injecting partner</li> <li>▪ Sharing injection equipment</li> <li>▪ Recent drug treatment (but currently injecting)</li> </ul>

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?

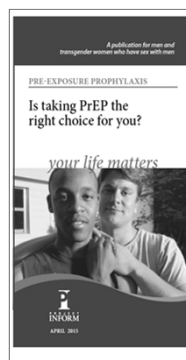
CDC. PrEP Guideline. 2014.

## 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<sup>1,2</sup>**
  - 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<sup>1</sup>
  - Signs and symptoms include fever, rash, pharyngitis, lymphadenopathy, myalgia, headache, diarrhea, arthralgia<sup>2</sup>
- 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
<b>All patients</b>	<ul style="list-style-type: none"> <li>▪ HIV test</li> <li>▪ Medication adherence counseling</li> <li>▪ Behavioral risk reduction support</li> <li>▪ Adverse event assessment</li> <li>▪ STI symptom assessment</li> </ul>	<ul style="list-style-type: none"> <li>▪ Assess renal function</li> </ul>	<ul style="list-style-type: none"> <li>▪ Test for bacterial STIs</li> </ul>	<ul style="list-style-type: none"> <li>▪ Evaluate need to continue PrEP</li> </ul>
<b>Women</b>	<ul style="list-style-type: none"> <li>▪ Pregnancy test (where appropriate)</li> </ul>			
<b>HBsAg+</b>			<ul style="list-style-type: none"> <li>▪ HBV DNA by quantitative assay*</li> </ul>	
<b>*Every 6-12 mos.</b>				
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

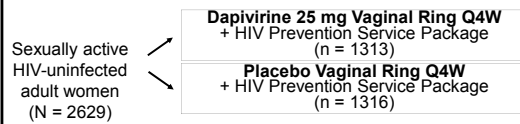
- Assuming 61% adherence (>4 doses/week) and 40% coverage of eligible MSM over the next 10 years would avert 33% of expected infections
- Predicted NNT = 25

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

# New PrEP Modalities

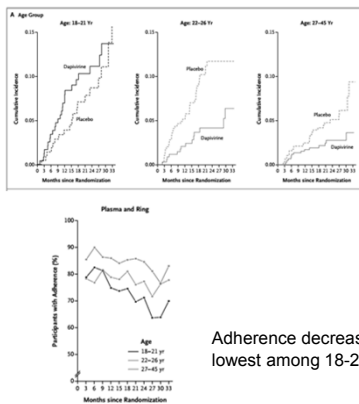
## MTN-020/ASPIRE: Dapivirine Vaginal Ring for HIV Prevention in Women

- 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% ( $P = .046$ )  $\geq 1$  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



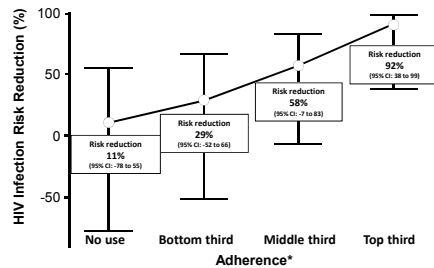
- Efficacy of dapivirine vs placebo:
  - 27% (95% CI, -133 to 31) for 18-21 y/o
  - 56% (95% CI, 19 to 76) for 22-26 y/o
  - 51% (95% CI, 8 to 74) for 27-45 y/o
  - 56% (95% CI, 31 to 71;  $P < 0.001$ ) for  $> 21$  y/o combined

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

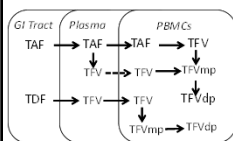
- Sustained adherence associated with 92% reduction in risk of HIV infection



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

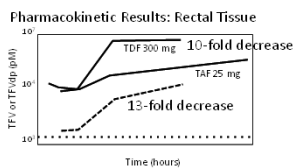
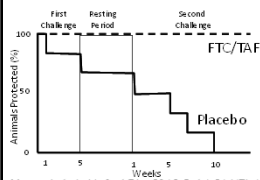
Brown E, et al. AIDS 2016. Abstract TUAC0105LB.  
Reproduced with permission.

## 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

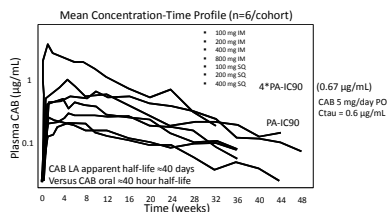
Garrett, et al. 102LB. CROI 2016, Boston, MA

## The Future of PrEP

- Long Acting Injectable Drugs for PrEP

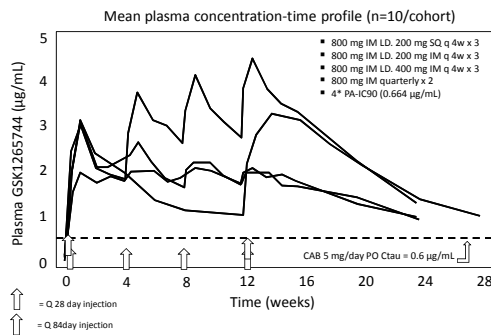
## Cabotegravir

- 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

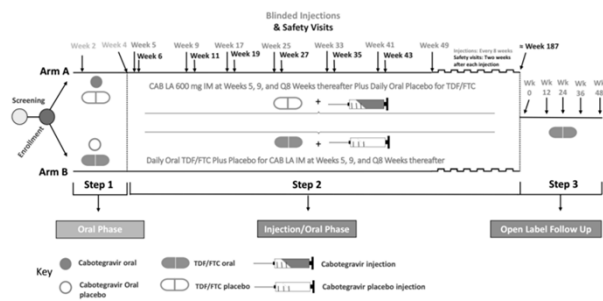


Image permission provided by Dr. Raphael Landovitz

## 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**

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