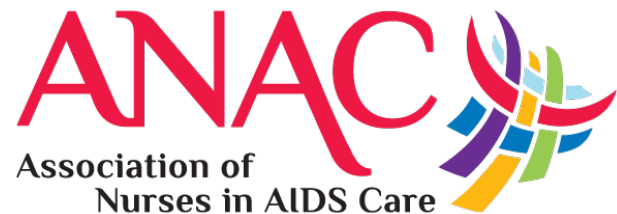


# Making Science Work: Current and Future PrEP Use

Association of Nurses in AIDS Care  
Thursday March 23, 2017

Charlene Flash, MD MPH

Carole Treston, RN MPH ACRN FAAN



# Continuing Nursing Education

Upon full participation in this webinar & completion of an evaluation, participants will be awarded 1.0 contact hours.



The Association of Nurses in AIDS Care (ANAC) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.



# Disclosures

## Faculty Conflict of Interest Disclosures

Charlene Flash serves on the Scientific Advisory Board for Gilead Sciences and is a recipient of Gilead investigator-initiated research funding.

Carole Treston has no actual or perceived conflicts of interest related to the content of this program.

## Commercial Support Disclosures

This program is part of a project supported by funding from Gilead Sciences, Inc. awarded to ANAC.

# Learning Objectives

At the end of this session participants will be able to:

1. List the clinical research that demonstrates the efficacy & safety of PrEP
2. Discuss issues related to adherence monitoring
3. Describe PrEPception and PrEP for Breastfeeding
4. Discuss Future formulations and use

# Housekeeping

- Participant lines muted during the webinar
- Type questions in the “Question” pane of your Dashboard
- Q & A session at the end of the webinar.



# Agenda

- Highlights of the Clinical Science Related to PrEP
- Current Usage
- Future Considerations
- PrEP Resources for Clinicians
- Q&A

# Making Science Work: Current and Future PrEP Use

Charlene A. Flash MD MPH

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# Overview

- Highlights of the clinical science related to PrEP
  - Efficacy
  - Adherence monitoring
  - Safety
  - PrEPception and Breastfeeding
  - Future formulations and use



# Pre-exposure prophylaxis (PrEP)

- Vulnerable people take antiretrovirals to prevent HIV.
- Only one FDA approved drug
  - Once daily co-formulated tenofovir disoproxil fumarate 300 mg (TDF) and emtricitabine (FTC) 200 mg
- 44 to 67% effective in clinical trials
- ...If taken perfectly 92% effective



# Clinical Trial Evidence for Tenofovir and Dapivirine-Based Prevention (February 2016)

Prevention of sexual transmission

**PROUD – daily oral TDF/FTC**  
(MSM – United Kingdom)

**IPERGAY – event-driven TDF/FTC**  
(MSM – Canada, France)

**Partners PrEP – daily oral TDF/FTC**  
(Serodiscordant couples – Kenya, Uganda)

**Partners PrEP – daily oral TDF**  
(Serodiscordant couples – Kenya, Uganda)

**TDF2 – daily TDF/FTC**  
(Heterosexual men and women – Botswana)

**iPrEx – daily oral TDF/FTC**  
(MSM – North and South America, South Africa, Thailand)

**CAPRISA 004 – BAT-24 dosing vaginal tenofovir gel**  
(Women – South Africa)

**The Ring Study – monthly vaginal ring containing dapivirine**  
(Women – South Africa, Uganda)

**ASPIRE – monthly vaginal ring containing dapivirine**  
(Women – Malawi, South Africa, Uganda, Zimbabwe)

**MTN 003/VOICE – daily dosing vaginal tenofovir gel**  
(Women – South Africa, Uganda, Zimbabwe)

**FEM-PrEP – daily oral TDF/FTC**  
(Women – Kenya, South Africa, Tanzania)

**MTN 003/VOICE – daily oral TDF/FTC**  
(Women – South Africa, Uganda, Zimbabwe)

**MTN 003/VOICE – daily oral TDF**  
(Women – South Africa, Uganda, Zimbabwe)

Effect size (CI)

86% (64; 96)

86% (44; 99)

75% (55; 87)

67% (44; 81)

62% (22; 84)

44% (15; 63)

39% (6; 60)

31% (1; 51)

27% (1; 46)

15% (-21; 40)

6% (-21; 40)

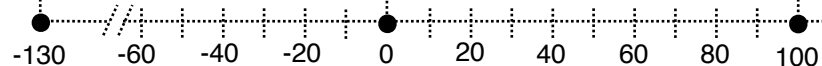
-4% (-49; 27)

-49% (-129; 3)

49% (10; 72)

Prevention in people who inject drugs

**Bangkok Tenofovir Study – daily oral TDF**  
(IDUs – Thailand)

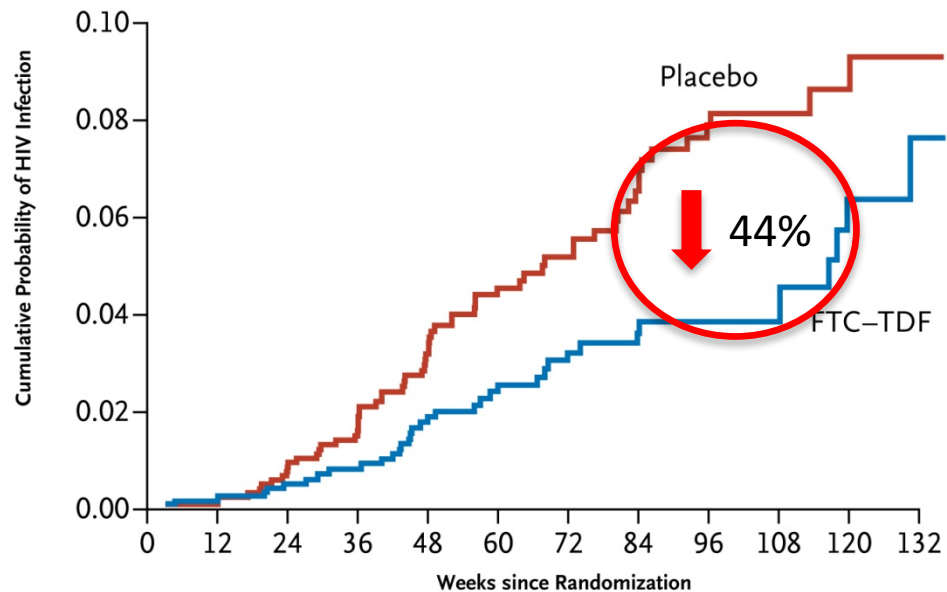


Effectiveness (%)

# Pre-exposure Prophylaxis Initiative Trial (iPrEx)

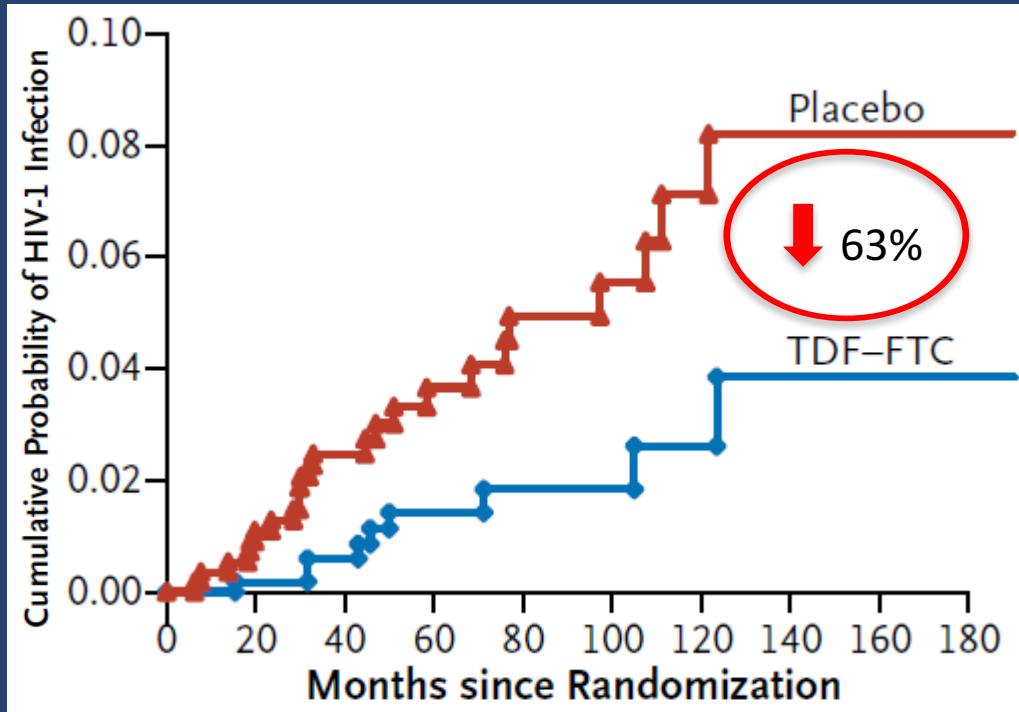
- RCT of 2500 gay or bisexual men and transgender women
- Once-daily oral FTC-TDF or Placebo
- 44% reduction in HIV incidence in the intervention group

Figure 2. Kaplan–Meier Estimates of Time to HIV Infection (Modified Intention-to-Treat Population).



# Oral PrEP - heterosexuals

## TDF2-CDC

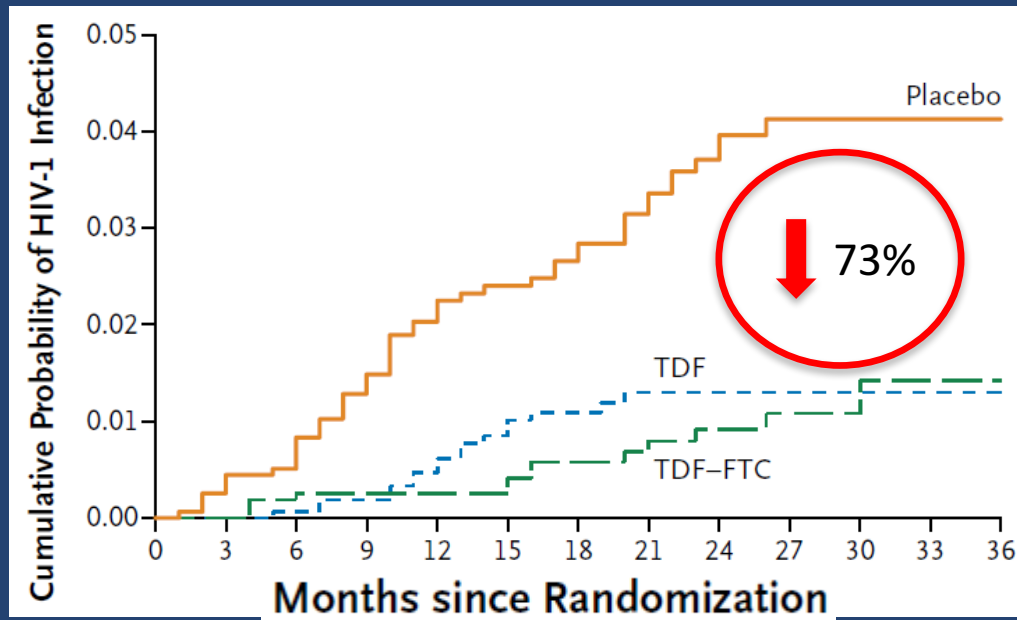


- 63% reduction in the risk of HIV acquisition

- Randomized Control Trial
- 1200 men and women
  - Botswana
  - Daily oral
  - FTC-TDF vs. placebo

# Oral PrEP - couples

## Partners PrEP



- TDF → 62% fewer infections
- FTC-TDF → 73% fewer infections

- 4758 HIV sero-discordant heterosexual couples
  - Kenya & Uganda
  - TDF vs. FTC-TDF vs. placebo

# Oral PrEP – IDU

## Bangkok Tenofovir Study

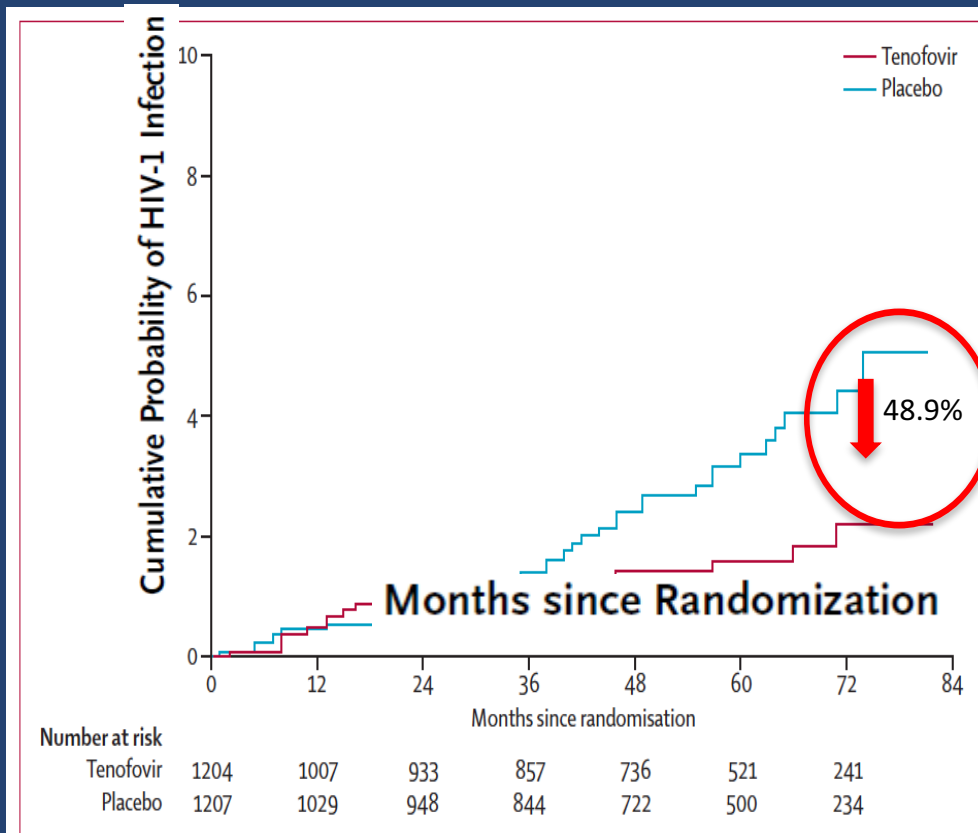


Figure 2: Kaplan-Meier estimates of time to HIV infection in the modified intention-to-treat population

- 2413 IDU
  - Thailand
  - TDF vs. placebo
  - DOT vs. non-DOT
- TDF → 48.9% fewer infections

Choopanya, Lancet 2013

Charlene A. Flash MD MPH

# PrEP works, if taken consistently

Study	Overall Efficacy	Efficacy if TFV detected (%)
iPrEx	44%	<b>92%</b>
Partners PrEP	75	<b>90</b>
TDF2	62	<b>85</b>
Bangkok IDU	49	<b>74</b>

# Adherence monitoring

- Indirect:
  - Self-report
    - Social desirability
    - SMS/text survey
  - Pill counts
  - Refill records
  - Medication event monitoring systems (MEMS)
- Direct:
  - Dried blood spots
  - Hair samples
  - Stored samples



# How long until it takes effect?

- Oral PrEP maximum intracellular concentration
  - Rectal tissue - 7 days
  - Cervicovaginal tissue – 20 days
  - Blood – 20 days

# Drug safety considerations

- GI side effects
- Dizziness/headache
- Rare renal toxicity (<1%) amongst predisposed patients
- 1% BMD loss at the total hip and femoral neck
  - Rate of bone fractures was no different

# CDC Guidelines - 2014

**Table 1: Summary of Guidance for PrEP Use**

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work  In high-prevalence area or network	HIV-positive injecting partner Sharing injection equipment Recent drug treatment (but currently injecting)
Clinically eligible	Documented negative HIV test result before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function; no contraindicated medications Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply		
Other services	Follow-up visits at least every 3 months to provide the following: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment At 3 months and every 6 months thereafter, assess renal function Every 6 months, test for bacterial STIs		
	Do oral/rectal STI testing	Assess pregnancy intent Pregnancy test every 3 months	Access to clean needles/syringes and drug treatment services

STI: sexually transmitted infection

# PrEP Failure/Drug Resistance

- **Randomized trials:** Participants already HIV-infected at the time of enrollment
  - Window period of acute HIV
- **Real world:** rare PrEP users with multiple mutations upon seroconversion.

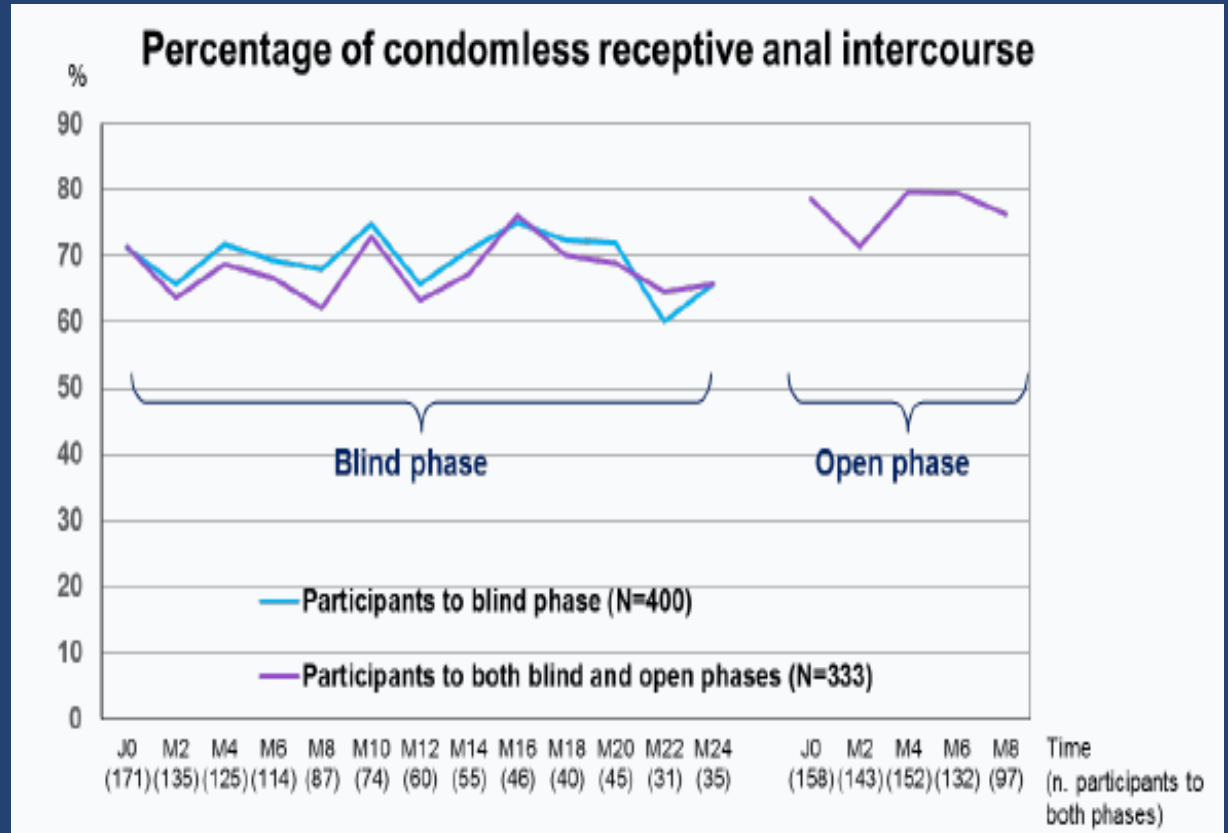
Grossman, *HIVR4P* Chicago, 2016  
Knox DC, *CROI* Boston, 2016

# Risk compensation

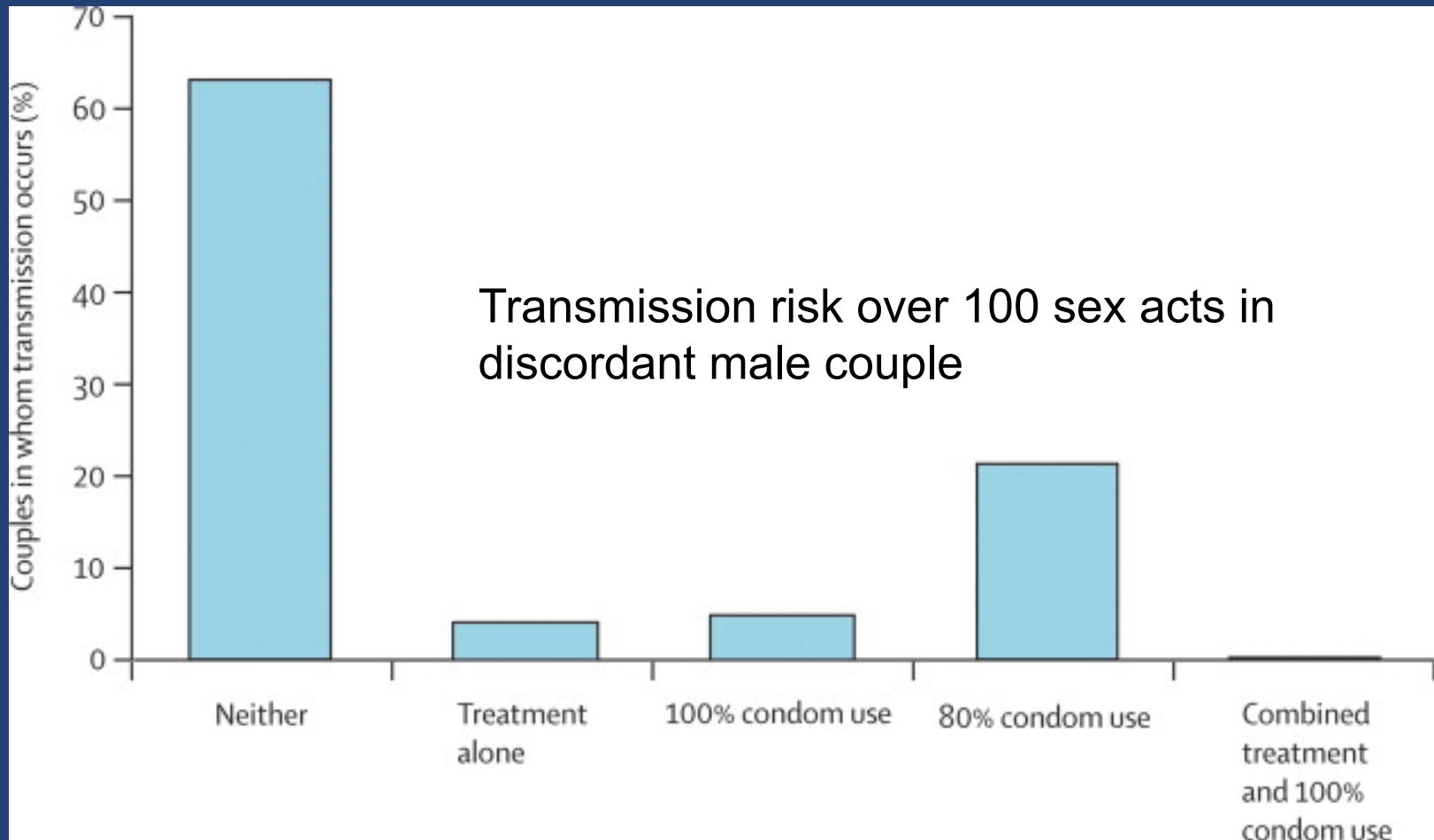
- Sexual disinhibition and reduction in use of condoms as an adjunct safety measure
- In many clinical trials trend toward **decreased** sexual risk behavior
  - Self-report, clinical trial setting, coupled with behavioral interventions
- In non-trial settings, risk-taking behavior varies by personal, psychosocial and health-related features.

# Risk Compensation Ipergay (Open Label)

- No change in median number of sexual partners or episodes of anal sex
- Increase in % of receptive anal sex episodes that were condomless



# Treatment as Prevention and Condoms



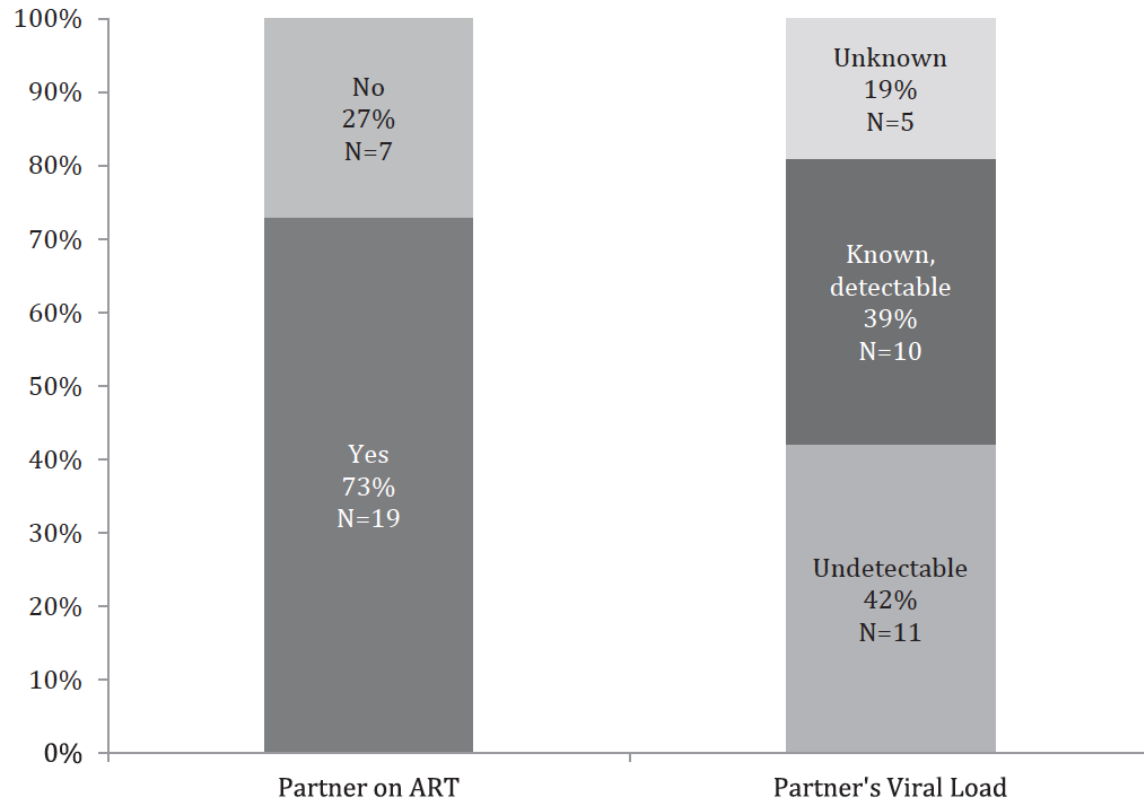
Geoffrey P Garnett, Brian Gazzard. **Risk of HIV transmission in discordant couples** null, Volume 372, Issue 9635, 2008, 270–271

# PrEPception

- Discuss with heterosexual women and men whose partners have HIV infection (IIB)
  - One of several options
  - Begin one month before conception
  - Continue one month after conception
- Antiretroviral Pregnancy Registry  
<http://www.apregistry.com/>

FIGURE 1

Partner's treatment status and viral load (n = 26)

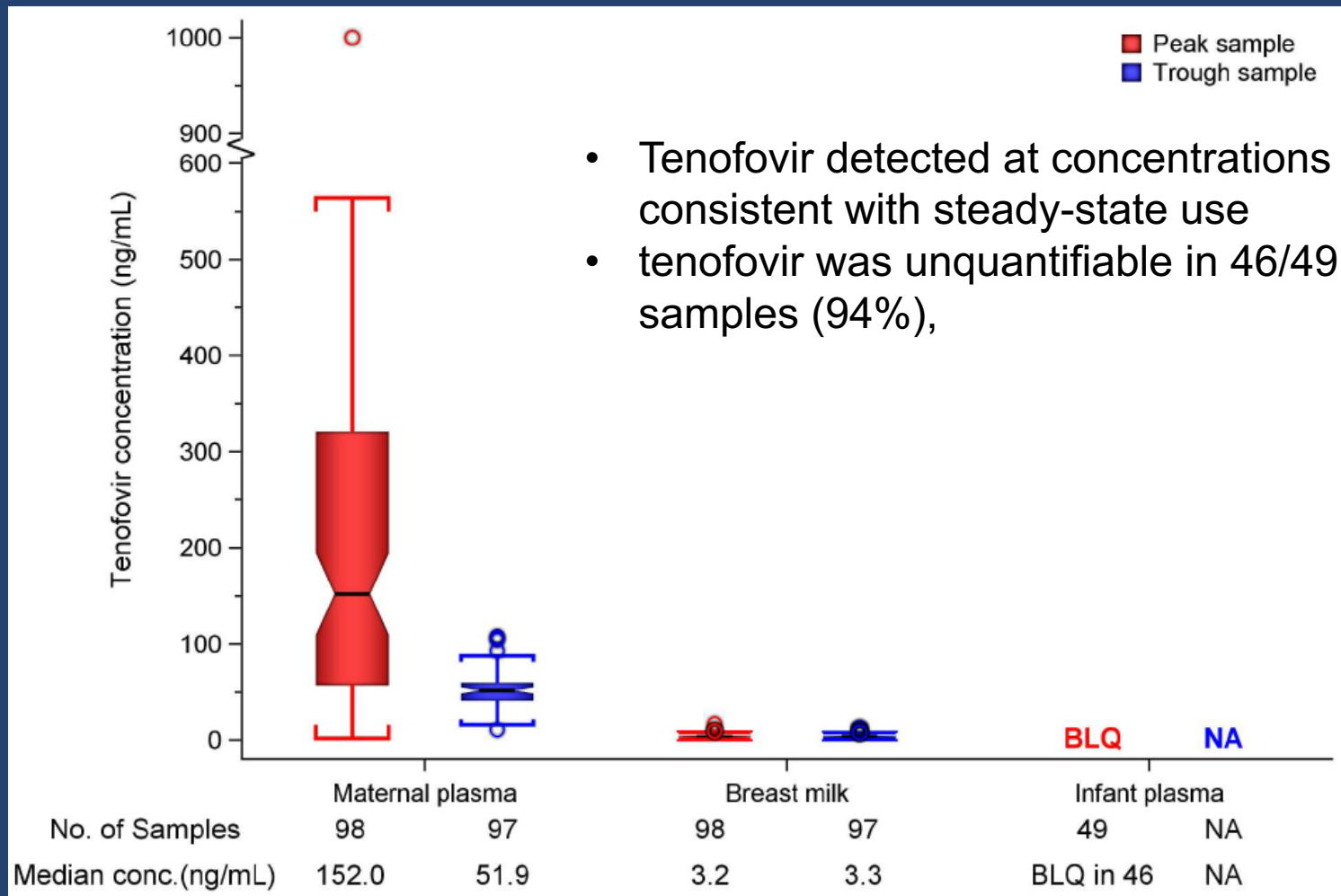


Twenty-six women reported having partners living with HIV, of whom 27% were not on antiretroviral therapy and 58% had known detectable or unknown viral loads.

*ART*, antiretroviral therapy.



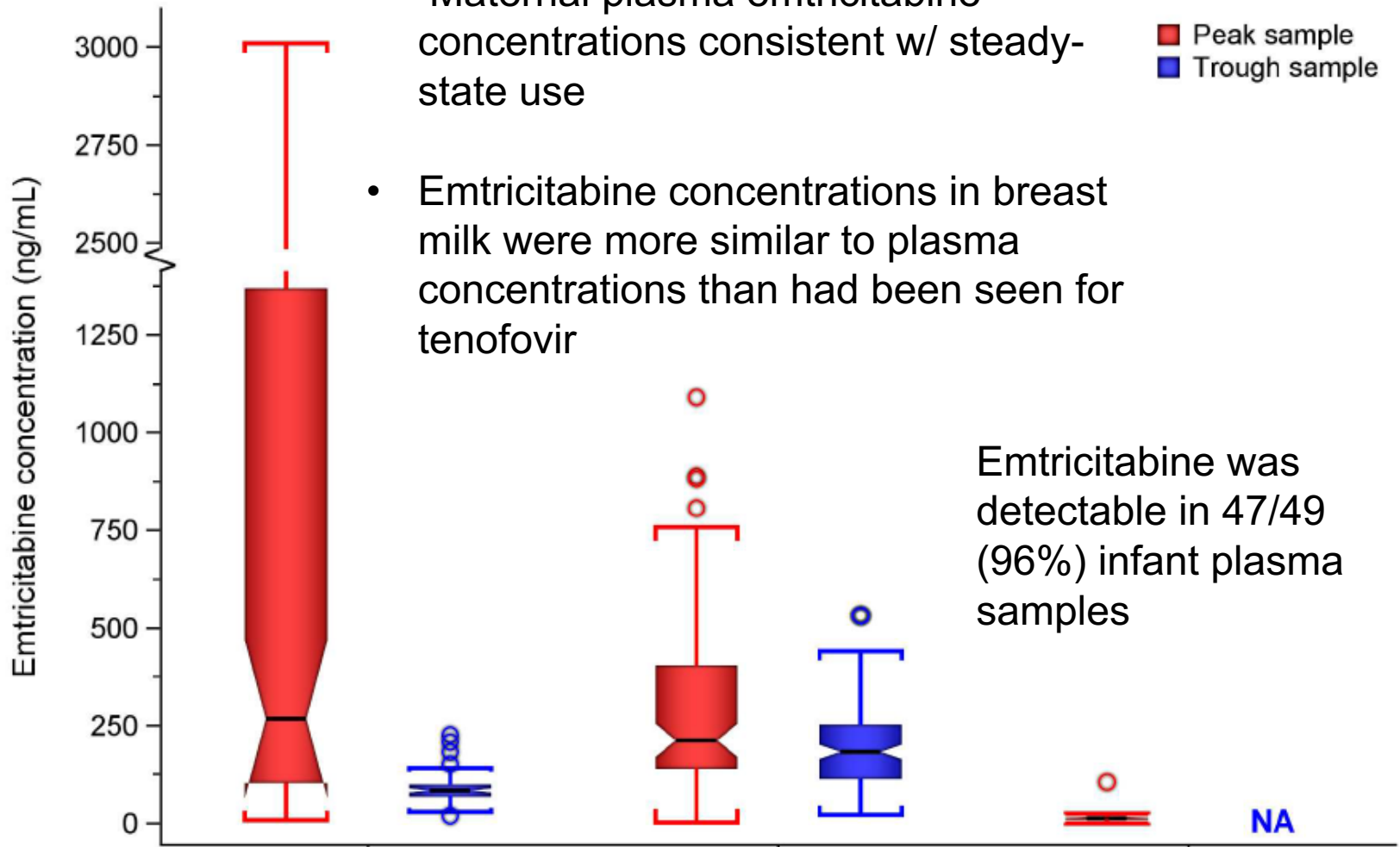
# Breastfeeding and PrEP



- Maternal plasma emtricitabine concentrations consistent w/ steady-state use

- Emtricitabine concentrations in breast milk were more similar to plasma concentrations than had been seen for tenofovir

■ Peak sample  
■ Trough sample



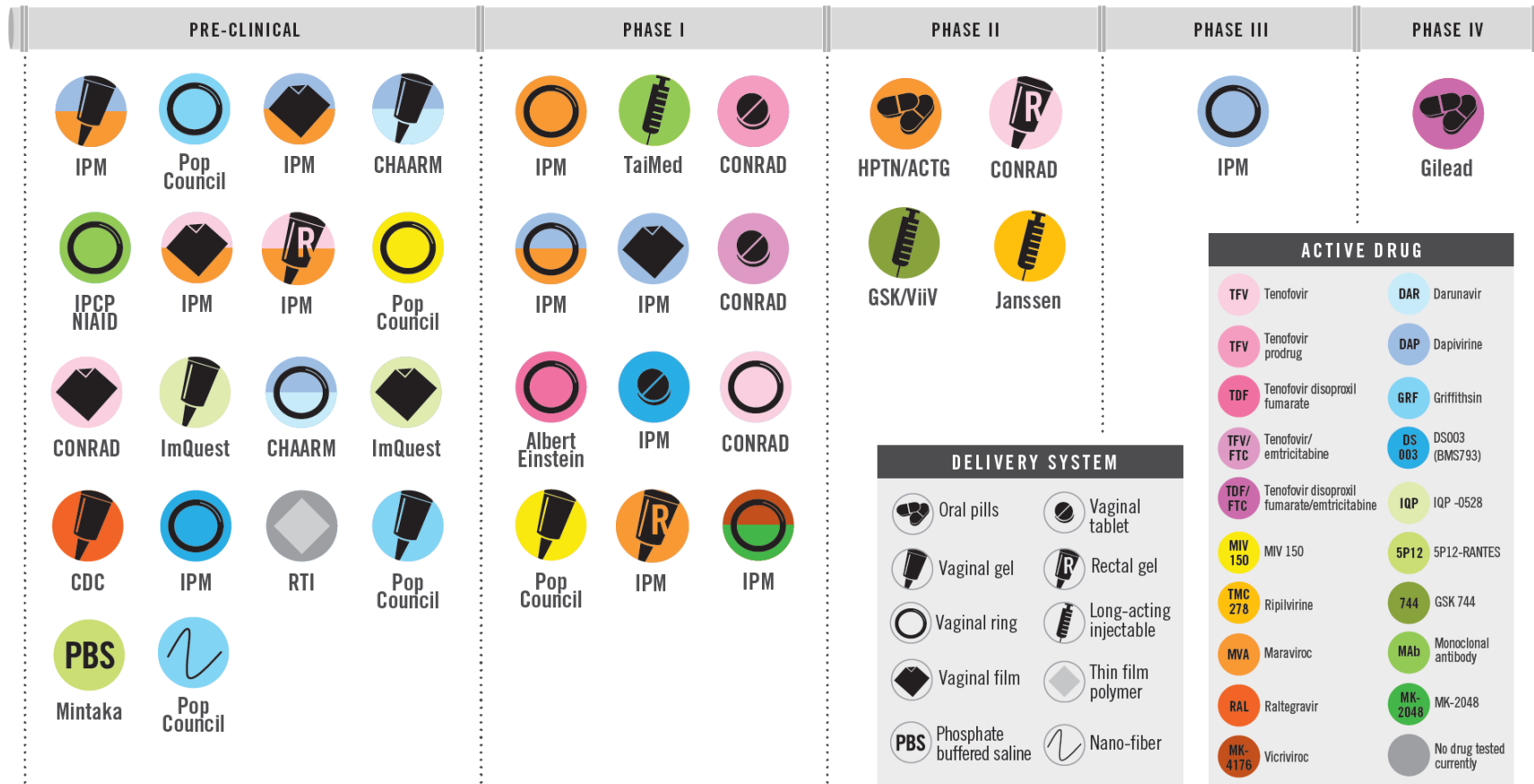
Emtricitabine was detectable in 47/49 (96%) infant plasma samples

	Maternal plasma		Breast milk		Infant plasma	
No. of samples	98	97	98	97	49	NA
Median conc.(ng/mL)	267.5	84.4	212.5	183.0	13.2	NA

# What is the future of PrEP?

- Alternative agents
  - Long-acting agents
  - Alternative delivery systems
- Multi-purpose prevention technology
- Alternative dosing strategies

# ARV-Based Prevention Pipeline



# Potential Alternative Active Drug

- Cabotegravir
- Rilpivirine
- Dapivirine
- Maraviroc
- TAF

TFV	Tenofovir	DAR	Darunavir
TFV	Tenofovir prodrug	DAP	Dapivirine
TDF	Tenofovir disoproxil fumarate	GRF	Griffithsin
TFV/FTC	Tenofovir/emtricitabine	DS003	DS003 (BMS793)
TDF/FTC	Tenofovir disoproxil fumarate/emtricitabine	IQP	IQP -0528
MIV 150	MIV 150	5P12	5P12-RANTES
TMC 278	Rilpivirine	744	GSK 744
MVA	Maraviroc	MAb	Monoclonal antibody
RAL	Raltegravir	MK-2048	MK-2048
MK-4176	Vicriviroc		No drug tested currently

# Tenofovir alafenamide (TAF)

- Oral prodrug of tenofovir (TFV)
- At low doses achieves ~90% lower plasma TFV exposure and increased intracellular TFV-diphosphate (TFV-DP) levels
- FTC/TAF prevented rectal SHIV infection in 6 macaques.

# Inadequate tissue levels after oral tenofovir alafenamide (TAF)

- TFV in mucosal tissues and genital fluids (as opposed to lymphoid cells) MAY contribute to preventive efficacy of PrEP.
- Despite comparable plasma TFV PK and PBMC TFVdp levels; TFVdp was **undetectable** in 83% tissues after TAF dosing.
- Phase III trial enrolling F/TAF vs TDF/FTC
- Pending further study, TAF/FTC should not be prescribed for PrEP outside of a clinical trial setting.

Garrett KL et al, CROI 2016;. Abstract 102LB.

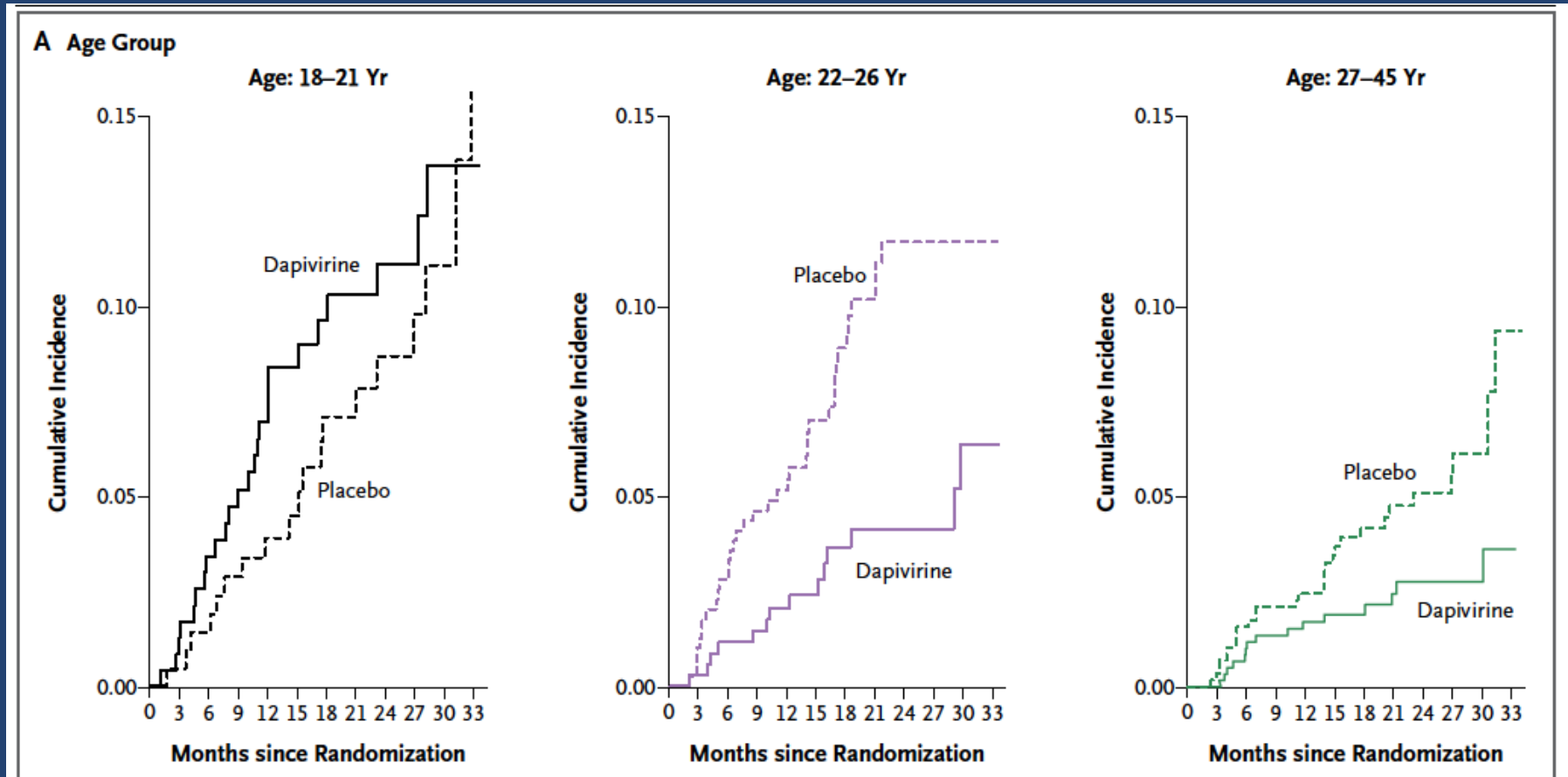
# Alternative Delivery Systems

- Creams, gels, films, vaginal and rectal suppositories
- Intra-vaginal rings – ASPIRE, Ring Study
  - Dapivirine release over a few weeks or months
  - Open label extension and licensure data collection
- Rectal microbicides: TDF applicator, dapivirine lube





# Dapivirine Ring – ASPIRE



- $\leq 21$  y/o : No evidence of protection
- $>21$  y/o: **56%** rate HIV-1 protection; 95% CI, 31 to 71;  $P < 0.001$ )

# Cabotegravir LA

- Dolutegravir analogue
- half life of 21-50 days
  - allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation
- Demonstrates efficacy in Macaques
- HPTN 083 - Randomised non-inferiority study compared to oral TDF/FTC in early stages

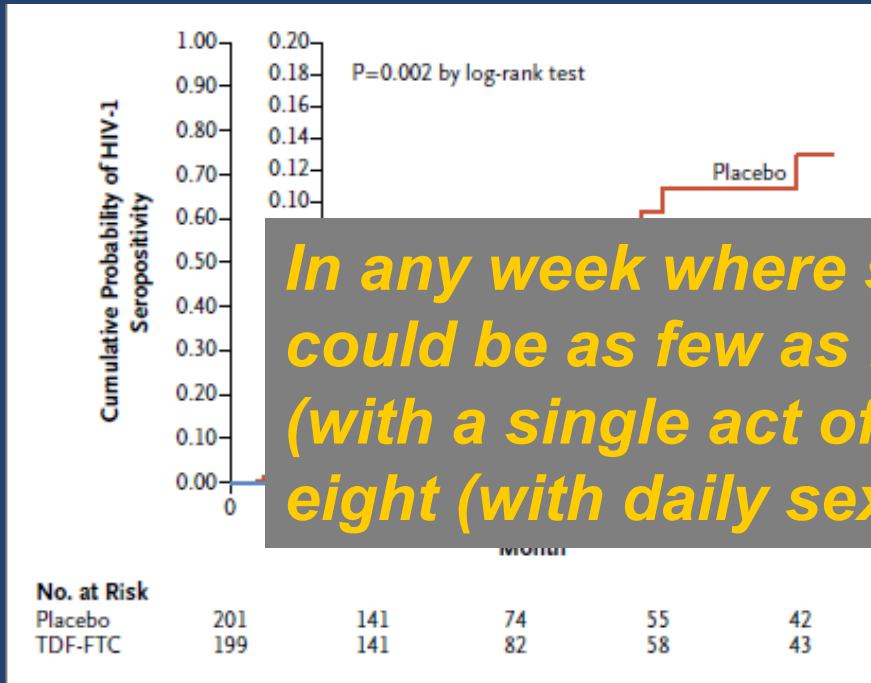
# Multipurpose Prevention Technologies

## HIV/STIs/pregnancy

MPT Product Development: Many possibilities for MPT development

Indications	Delivery Modes	Mechanisms of Action	Dosage & Administration
BV*	Diaphragm*	Anti-microbial*	Oral daily*
Candida	Film*	Anti-fungal	Oral on-demand Gel*
Chlamydia*		Anti-viral*	Systemic sustained*
Gonorrhea*	Implant	Barrier*	Topical daily*
HIV*	Injection*	HC *	Topical on-demand*
HPV*	Intrauterine Device	Non-HC*	Topical sustained
HSV*	Oral pill*	Probiotic	
Pregnancy*	Ring (Non-IVR)		
Syphilis	Ring (IVR)*	<i>*Currently being tested in human clinical trials.</i>	
Trichomoniasis	Tablet*		

# Intermittent dosing -Ipergay



- 2 pills 2 to 24 hours before sex (or one pill, if the most recent dose was taken between 1 and 6 days ago)

*In any week where sex occurred, there could be as few as four PrEP pills used (with a single act of sex) or as many as eight (with daily sex).*

...e-pill doses  
...the last  
...daily if  
additional sex events before  
above regimen completed

- RCT Feb 2012 - Oct 2014
- Stopped early
- 400 MSM

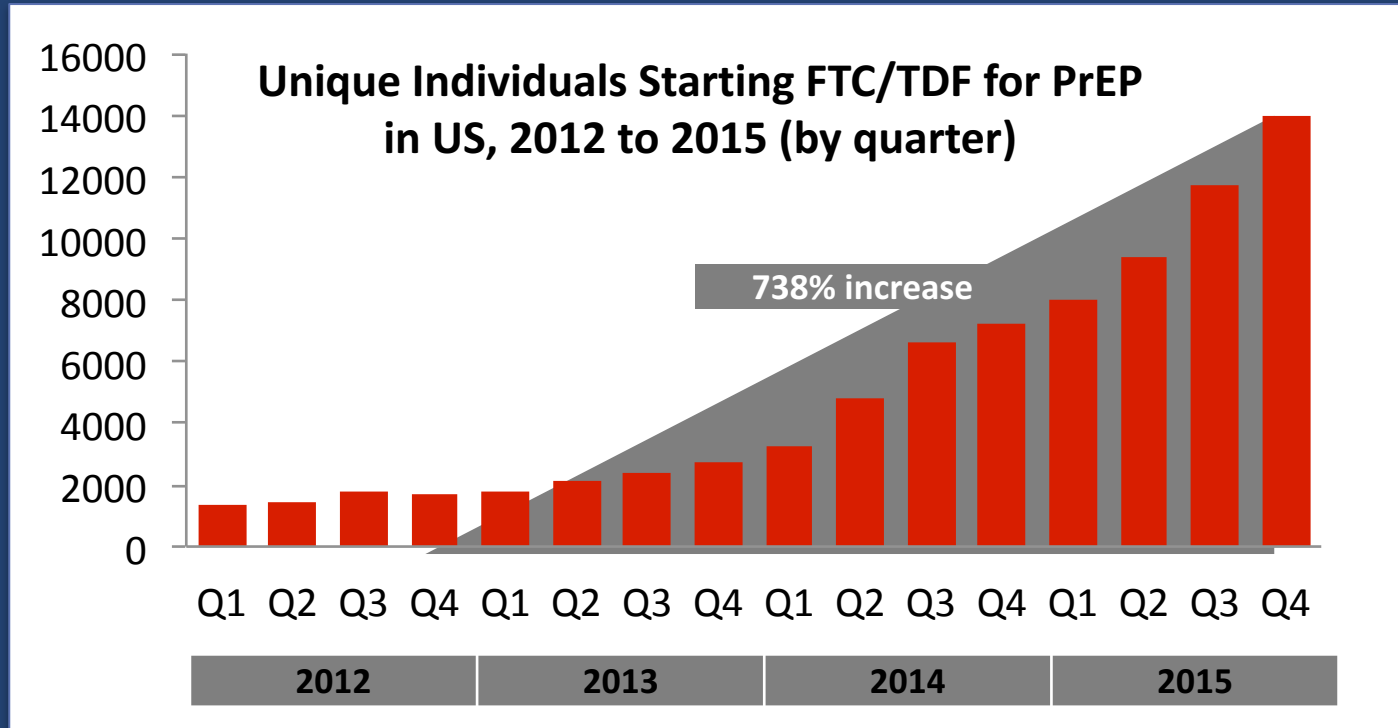
Molina J.M. et al. NEJM, 2015.

# Intermittent PrEP

## IPIRGAY

- Complex dosing strategy ....real world adherence
- ?Time to optimal level of active metabolites
- ? Efficacy among heterosexual men and women and injection drug users
- CDC recommends daily use of PrEP, as approved by the FDA.

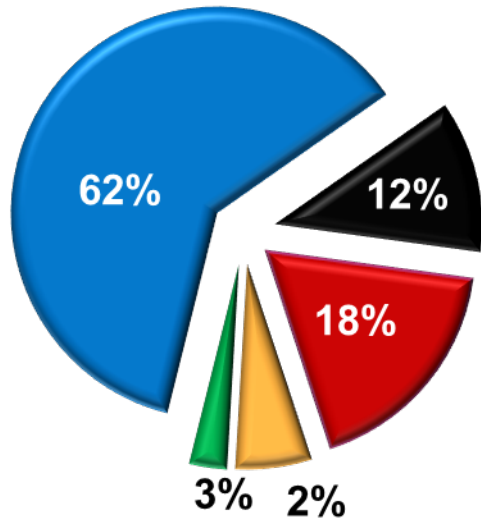
# PrEP Utilization in the US: 2012-2015



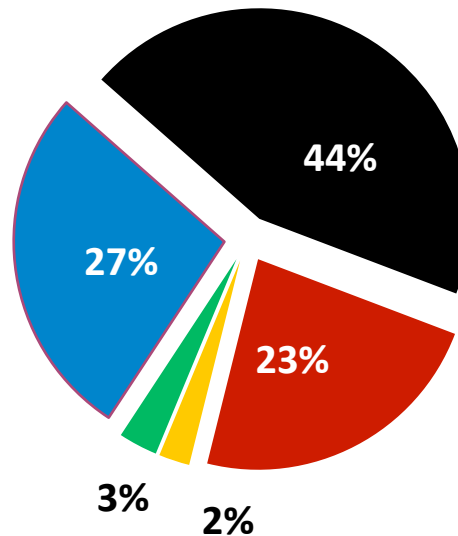
- National electronic patient-level data from 80% of US retail pharmacies
- 79,684 individuals started FTC/TDF for PrEP.
- 1,671 in Q4 2012 → 14,000 in Q4 2015

# Disparities in PrEP Utilization

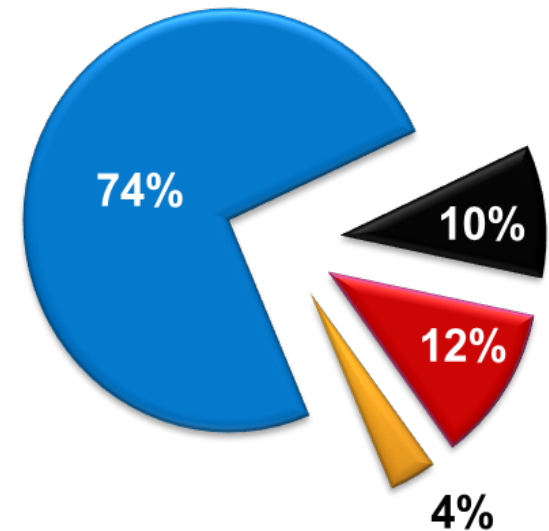
- Estimated Population Distribution by Race/Ethnicity, 2014, US<sup>a</sup>



- Estimated New HIV Infections, 2014, US<sup>b</sup>



- Total FTC/TDF for PrEP Utilization by Race/Ethnicity, Sept 2015, US<sup>c</sup>



AA
  White
  Hispanics
  Asians
  Multiracial/Other

**PrEP use among AA and Hispanics is low relative to the rate of new HIV infections**

Bush S, et al. ASM/ICAAC 2016; Boston, MA. #2651

a. <https://www.census.gov/quickfacts/table/PST045215/00>

b. Other: American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander. CDC. *HIV Surveillance Report, 2014*

c. These data represent 43.7% (n=21,463) of unique individuals who have started TVD for PrEP from 2012-3Q2015.

# Summary

- Highlights of the clinical science related to PrEP
  - Efficacy
  - Adherence monitoring
  - Safety
  - PrEPception and Breastfeeding
  - Future formulations
  - Current Uptake



# Acknowledgements

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- Research Grant support from
  - NIMH
  - Gilead Sciences
  - Thomas Street Health Center and the HIV Prevention Program staff and patients

# PrEP Resources

- **ANAC website**: Resources & Tools: PrEP Information for Clinicians [www.nursesinaidscare.com](http://www.nursesinaidscare.com)
- **CDC Resources**: [www.cdc.gov/hiv/risk/prep](http://www.cdc.gov/hiv/risk/prep)
- **PrEPline**: Peer to Peer Consultation:  
[www.nccc.ucsf.edu](http://www.nccc.ucsf.edu). Clinician Consultation Center  
UCSF, HRSA/HAB, AETC  
Mon-Fri 11 a.m. – 6 p.m. EST 855-448-7737
- **PrEP Locator: Find Your Provider**  
[www.preplocator.org](http://www.preplocator.org)
- **UPCOMING ANAC PREP WEBINARS**

# Questions



# Continuing Nursing Education

**After the webinar an email will be sent to you with a link to the slides and evaluation form. To be awarded contact hours for this webinar, complete the evaluation at that link or it can be found at**

<https://www.nursesinaidscare.org/i4a/forms/index.cfm?id=175>

**Additional questions?  
Email Erin at [erin@anacnet.org](mailto:erin@anacnet.org)**

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