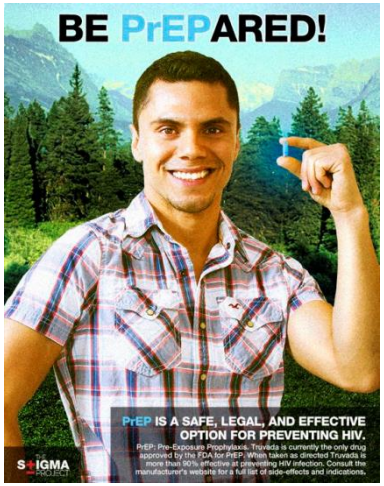
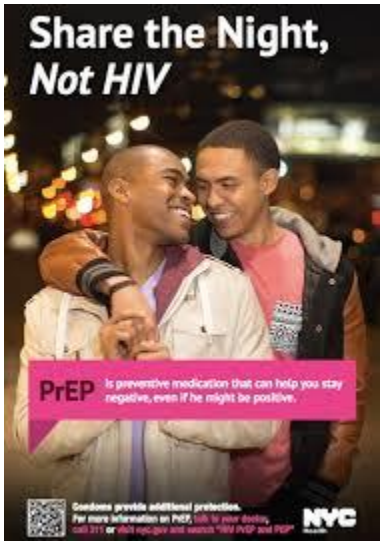
HIV PRE-EXPOSURE PROPHYLAXIS (PREP) UNDER RESEARCH - WHAT IS COMING DOWN THE PIKE

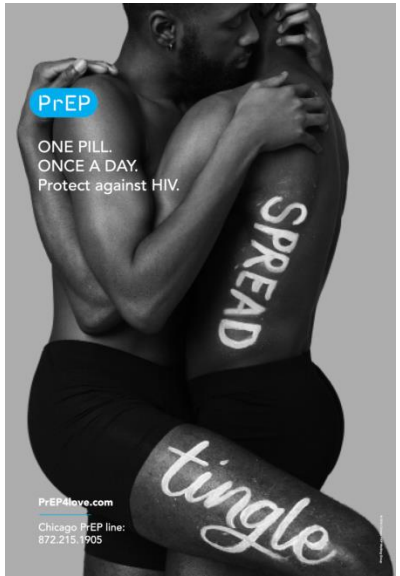
Aditya H. Gaur

Department of Infectious Diseases

St. Jude Children's Research Hospital







Disclosure

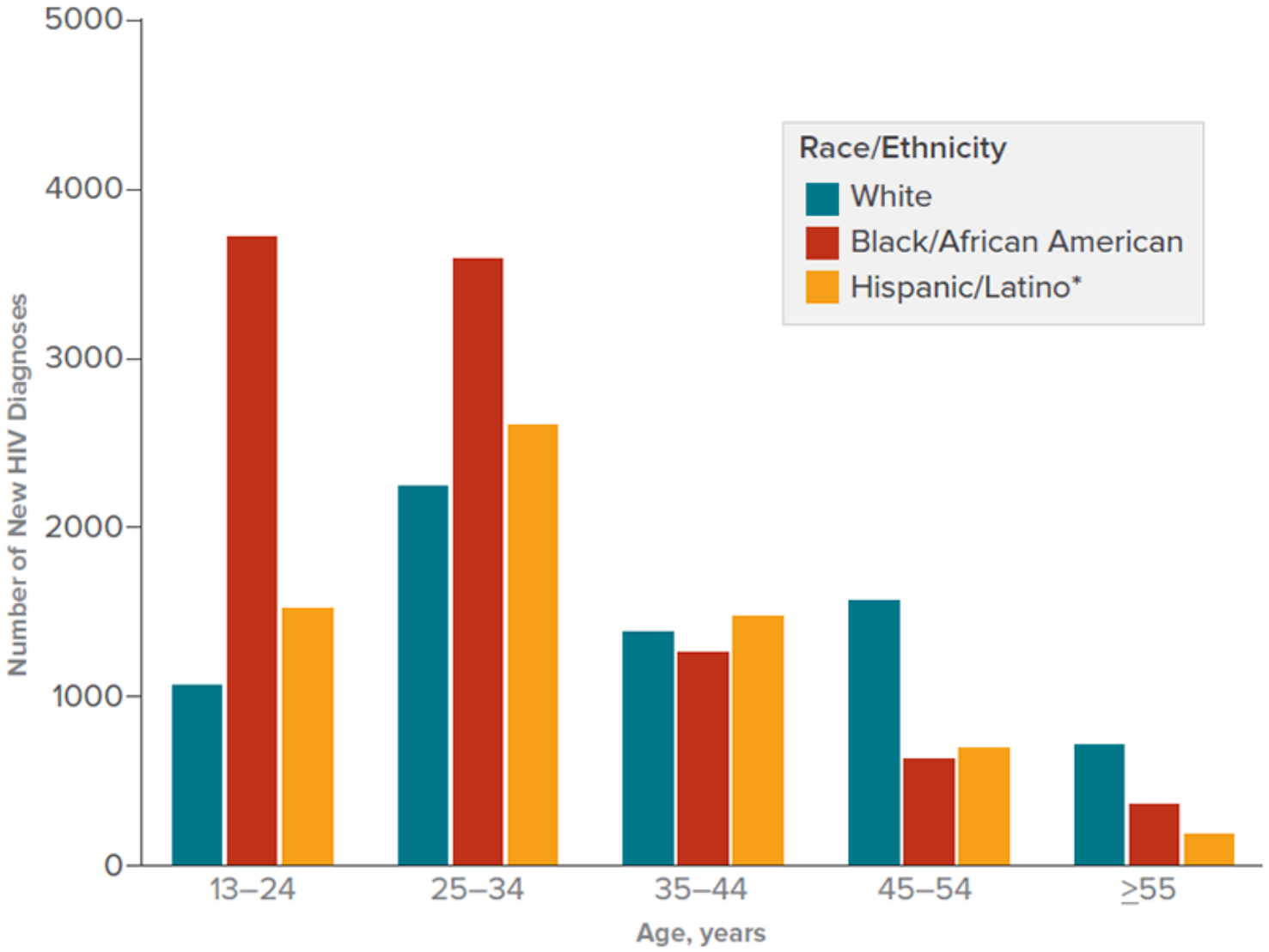
- St. Jude has a Clinical Trial agreement with Gilead Sciences, Inc. for participating in Gilead sponsored multi-center clinical trials
- Gilead manufactures tenofovoir-emtricitiabine which is FDA approved for HIV Preexposure prophylaxis since 2012

Objectives

- Provide a brief overview of standard of care HIV Pre-exposure Prophylaxis (PrEP)
- Review what HIV PrEP approaches are currently being researched

PREP AS STANDARD OF CARE

The ongoing need for HIV Prevention



https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2015-vol-27.pdf

What we know about **PrEP**

- PrEP stands for Pre-exposure Prophylaxis; giving medications to prevent a person from getting HIV-infected
- Different from PEP which is Post-exposure prophylaxis; giving medications to prevent someone exposed to HIV from getting an established infection
- A combination of two oral HIV medicines (tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC]), sold under the name Truvada® (pronounced tru vá duh) approved by the FDA in July 2012 for PrEP
- Truvada currently approved for daily use as PrEP to help prevent an HIV-negative person from getting HIV from a sexual or injection-drug-using partner who's positive
- Truvada taken one pill a day prevents HIV infection in:
  - Up to 92% of Men who have sex with Men
  - Up to 90% of the uninfected partner in HIV discordant couples

http://www.cdc.gov/hiv/prevention/research/prep/

Table 2: Evidence Summary—Overall Evidence Quality (per GRADE Criteria[28])

Study	Design[a]	Participants		Limitations	Quality of Evidence (See Table 14, Appendix 2)
		Agent	Control		
Among Men Who have Sex with Men					
iPrEx Trial	Phase 3	TDF/FTC (n = 1251)	Placebo (n = 1248)	Adherence	High
US MSM Safety Trial	Phase 2	TDF (n = 201)	Placebo (n = 199)	Minimal	High
Among Heterosexual Men and Women					
Partners PrEP	Phase 3	TDF (n = 1589) TDF/FTC (n = 1583)	Placebo (n = 1586)	Minimal	High
TDF2	Phase 2	TDF/FTC (n = 611)	Placebo (n = 608)	High loss to follow-up; modest sample size	Moderate
Among Heterosexual Women					
FEM-PrEP	Phase 3	TDF/FTC (n = 1062)	Placebo (n = 1058)	Stopped at interim analysis, limited follow-up time; very low adherence to drug regimen	Low
West African Trial	Phase 2	TDF (n = 469)	Placebo (n = 467)	Stopped early for operational concerns; small sample size; limited follow-up time on assigned drug	Low
VOICE	Phase 2B	TDF (n = 1007) TDF/FTC (n = 1003)	Placebo (n = 1009)	TDF arm stopped at interim analysis (futility); very low adherence to drug regimen in both TDF and TDF/FTC arms	Low
Among Injection Drug Users					
BTS	Phase 3	TDF (n = 1204)	Placebo (n = 1207)	Minimal	High

Clinical Trial Evidence for HIV Prevention Options (February 2016)

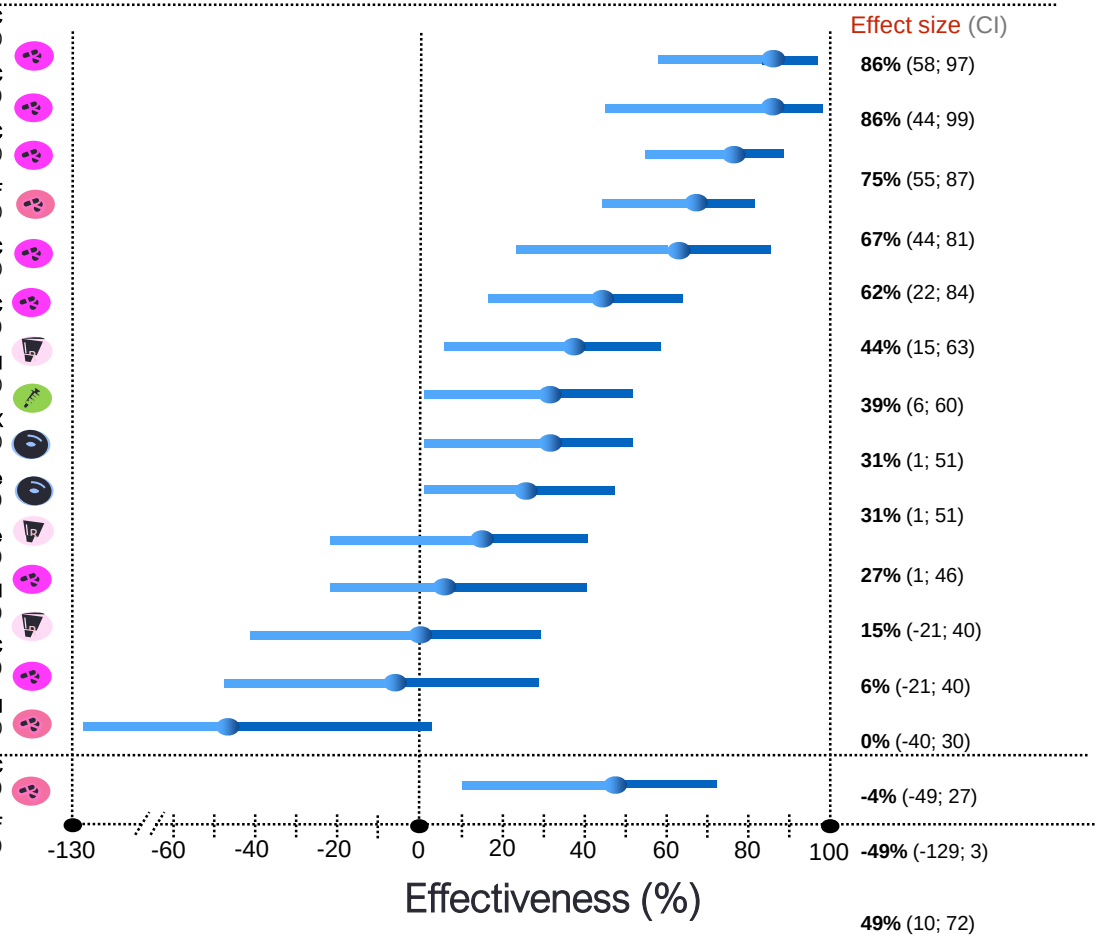
AVAC
Global Advocacy for HIV Prevention

Prevention of sexual transmission

DELIVERY SYSTEM
- Vaccine
- Oral pills
- Vaginal gel
- Vaginal ring

ACTIVE DRUG
- ALVAC/AIDSVAX
- Dapivirin
- Tenofovir
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir/ emtricitabine (TDF/FTC)

Prevention in people who inject drugs



From JM Marrazzo, MD, MPH, at Washington, DC: April 15, 2016, IAS-USA.

Adapted from: Salim S. Abdool Karim, CAPRISA

PrEP Efficacy linked to adherence to PrEP medication

	% of blood samples with TFV detected	HIV protection efficacy in randomized comparison
Partners PrEP **FTC/TDF arm**	81%	75%
TDF2	79%	62%
iPrEx	51%	44%
FEM-PrEP	26%	NS
VOICE	28%	NS

Baeten et al N Engl J Med 2012
Grant et al N Engl J Med 2010
Van Damme et al N Engl J Med 2012
Thigpen et al N Engl J Med 2012

Clear dose-response relationship between evidence of PrEP use & efficacy

Described cases of PrEP failure

- Two cases of PrEP failure have been reported under adequate tenofovir-diphosphate (TFV-DP) levels in dried blood spots. Both these individuals were infected with a multiclass resistant virus
- First case of infection with wild type HIV-1 in a person with documented supposedly protective intracellular levels of TFV-DP described at CROI 2017

Fox J et al. Infect Dis Ther. 2016 Mar; 5(1):65-71
Hoornenborg E et al CROI 2017 Abstract # 953

PREP UNDER RESEARCH

PrEP Research – an overview

- Oral PrEP:
  - Oral TDF-FTC – used different ways
  - Tenofovir alafenamide (TAF) instead of TDF
  - Other oral PrEP agents: maraviroc
- Injectable PrEP – cabotegravir, rilpivirine, VRC01
- Microbicides – dapivirine vaginal ring

ON DEMAND PREP

Cell-PrEP: A prospective, observational pharmacokinetic study of 21 HIV-uninfected volunteers.

	Proportion with levels above EC_{90}	Estimated HIV risk reduction (95% CI)
One	17%	77% (40–93)
Two	44%	89% (51–98)
Three	71%	96% (60–100)
Four	84%	98% (67–100)
Seven	90%	99% (70–100)

PrEP=pre-exposure prophylaxis with tenofovir disoproxil fumarate with emtricitabine. EC_{90}=drug concentration associated with 90% risk reduction.

Table: Proportion protected and average efficacy of different pill doses of PrEP for men who have sex with men

Pharmacology supports on-demand PrEP

www.thelancet.com/hiv Vol 3 September 2016

How little of PreP is enough?

Original Article

On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection

Jean-Michel Molina, M.D., Catherine Capitant, M.D., Bruno Spire, M.D., Ph.D., Gilles Pialoux, M.D., Laurent Cotte, M.D., Isabelle Charreau, M.D., Cecile Tremblay, M.D., Jean-Marie Le Gall, Ph.D., Eric Cua, M.D., Armelle Pasquet, M.D., François Raffi, M.D., Claire Pintado, M.D., Christian Chidiac, M.D., Julie Chas, M.D., Pierre Charbonneau, M.D., Constance Delaugerre, Pharm.D., Ph.D., Marie Suzan-Monti, Ph.D., Benedicte Loze, B.S., Julien Fonsart, Pharm.D., Gilles Peytavin, Pharm.D., Antoine Cheret, M.D., Ph.D., Julie Timsit, M.D., Gabriel Girard, Ph.D., Nicolas Lorente, Ph.D., Marie Préau, Ph.D., James F. Rooney, M.D., Mark A. Wainberg, Ph.D., David Thompson, B.C.L., LL.B., Willy Rozenbaum, M.D., Veronique Doré, Ph.D., Lucie Marchand, B.S., Marie-Christine Simon, B.S., Nicolas Etien, B.S., Jean-Pierre Aboulker, M.D., Laurence Meyer, M.D., Ph.D., Jean-François Delfraissy, M.D., for the ANRS IPERGAY Study Group

N Engl J Med
Volume 373(23):2237-2246
December 3, 2015

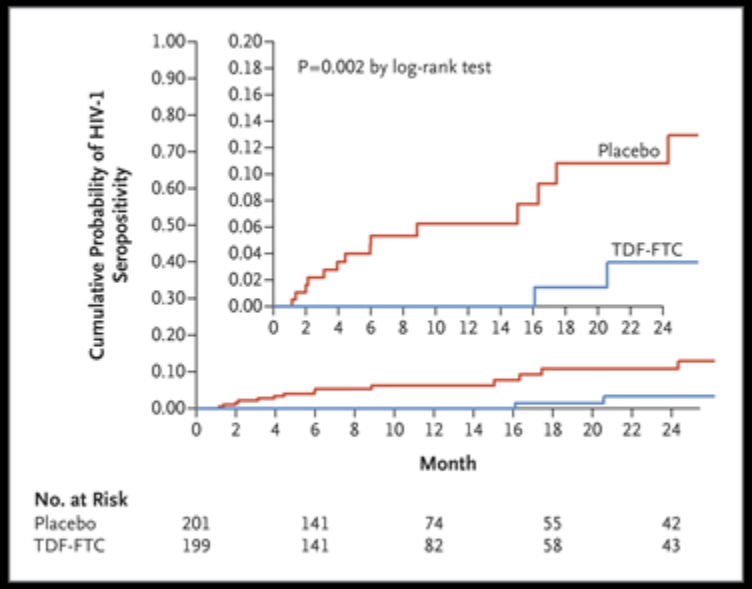
The NEW ENGLAND JOURNAL of MEDICINE

IPERGAY evaluated an on-demand PrEP regimen consisting of a loading double tablet dose of tenofovir disoproxil fumarate and emtricitabine 2–24 h before sex, with single tablets at 24 h and 48 h after.

The intent-to-treat efficacy was 86% (95% CI 40–98)

Participants reported using a median of 15 tablets per month (IQR 9–21), which is nearly four tablets per week.

Kaplan–Meier Estimates of the Probability of HIV-1 Infection.



Molina J-M et al. N Engl J Med 2015;373:2237-2246

The NEW ENGLAND JOURNAL of MEDICINE

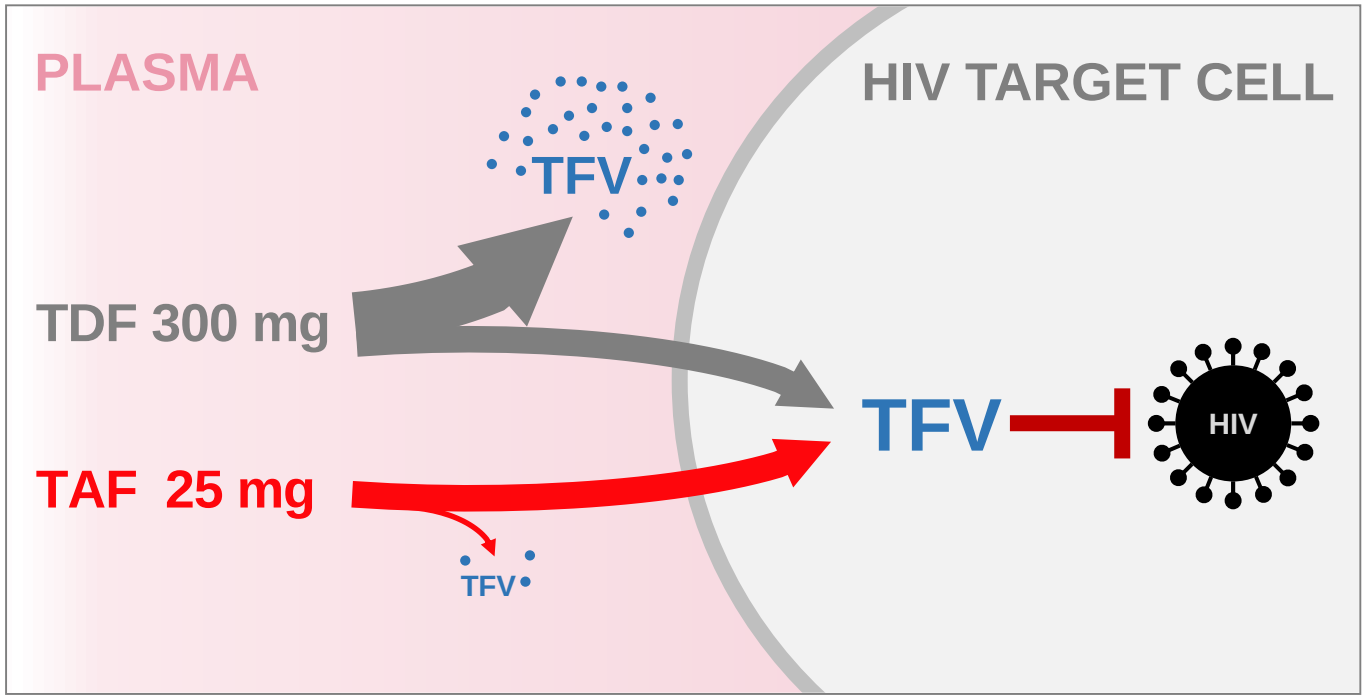
On-demand PrEP works in the open label extension of IPERGAY

- Men and transgender women who have sex with men, previously enrolled in the ANRS IPERGAY trial at seven sites (six in France and one in Canada) invited in an open-label extension with on-demand PrEP
- 361 participants with a median follow-up of 18·4 months
- HIV incidence was 0·19 per 100 person-years (95% CI 0·01-1·08), compared with 6·60 per 100 person-years (3·60-11·05) in the placebo group of the randomised study, indicating a relative reduction of 97% (95% CI 81-100) in the incidence of HIV with on-demand PrEP.
- The proportion of participants reporting condom less sex at their last receptive anal intercourse significantly increased from 77% (136 of 176 participants) at baseline to 86% (66 of 77 participants) at 18 months' follow-up (p for trend=0·0004). The incidence of a first bacterial STI during this open-label phase did not change significantly compared with the randomised phase (59·0 vs 49·1 per 100 person-years, respectively; p=0·11).

Molina JM et al Lancet HIV. 2017 Sep;4(9):e402-e410

OTHER ORAL PREP MEDICATIONS

Tenofovir Alafenamide (TAF)
Prodrug of Tenofovir

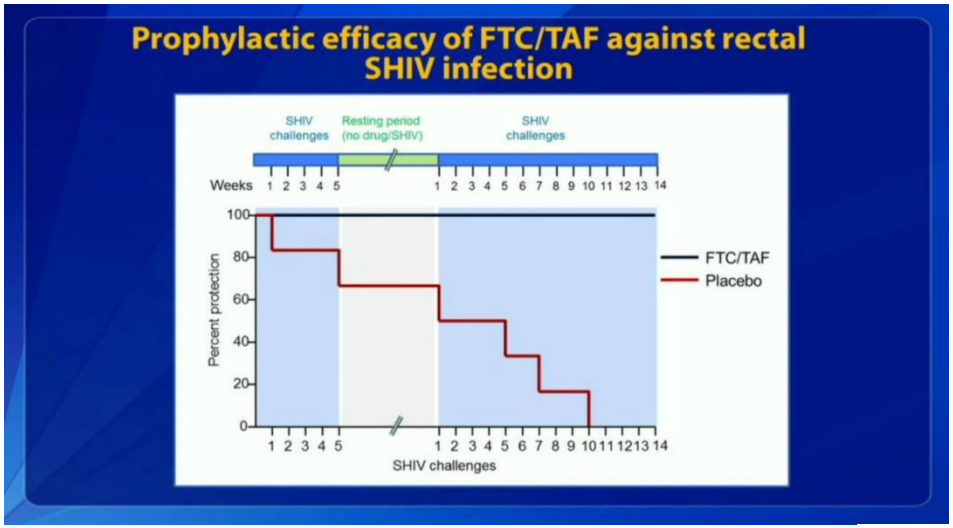


- 90% lower TFV levels minimizes renal and bone effects while maintaining high potency for suppressing HIV

1. Lee W et. Antimicr Agents Chemo 2005;49:1898-906; 2. Birkus G et al. Antimicr Agents Chemo 2007;51:543-50; 3. Babusis D, et al. Mol Pharm 2013;10:459-66; 4. Ruane P, et al. J Acquir Immune Defic Syndr 2013;63:449-55; 5. Sax P, et al. JAIDS 2014;2014;67:52-8. 6. Sax P, et al. Lancet 2015;385:2606-15.

Gaur AH et al; Abstract #MOAB0104; IAS 2015

Can Tenoforvir Alafenamide (TAF) be used instead of Tenofovir Disoproxil Fumarate (TDF) for PrEP?

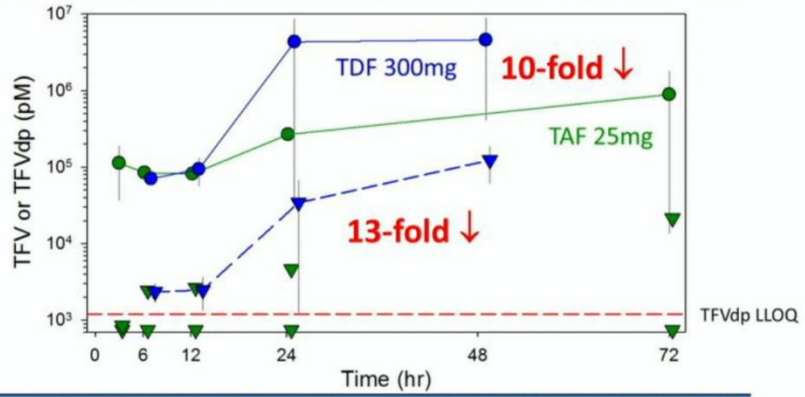


Chemoprophylaxis With Oral FTC/TAF Protects Macaques From Rectal SHIV Infection
Gerardo Garcia-Lerma; Centers for Disease Control and Prevention, Atlanta, GA, United States

HIV-uninfected women

Garrett KL et al. TFV and TFVdp in female mucosal tissues after a single dose of TAF. Oral late breaker abstract 102LB CROI 2016.

Pharmacokinetic Results: Rectal Tissue



	TAF 25mg	TDF 300mg*		TAF 25mg	TDF 300mg*
TFV	n=8; 0% BLQ	n=8; 0% BLQ	TFVdp	n=8; 63% BLQ	n=8; 0% BLQ
$AUC_{0\text{-}48hrs}$ (ng*h/g)	3,790	38,493	$AUC_{0\text{-}48hrs}$ (fmol*h/g)	153,767	2,046,546

* Cottrell ML, et al. *J Infect Dis.* 2016.

Ongoing study comparing FTC/TAF to FTC/TDF

- A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection – The DISCOVER Trial
- Study ongoing but not recruiting participants
- ClinicalTrials.gov Identifier: NCT02842086

Maraviroc as an alternate PrEP agent

- TDF drug concentrations are > 100-fold lower in the female genital tract compared to the colorectal mucosa
- Conflicting efficacy results of oral TDF containing PrEP from clinical trials in women and at least in part the difference attributed to differences in adherence
- Maraviroc (MVC) is a CCR5 antagonist HIV entry inhibitor approved for treatment of HIV infection and with attributes that favor consideration for PrEP
- MVC containing PrEP regimens shown as safe and tolerable compared to TDF-FTC for PrEP in MSM, trans female and women.

Gulick RM J Infect Dis. 2017; 215:238-246
Gulick RM Ann Intern Med. 2017;167:384-393

What else is being investigated for PrEP

dapivirine IVR (MTN 020/ASPIRE clinical trial)
vicriviroc/MK2048 IVR (MTN 027/MTN 028 clinical trials)
tenofovir IVR (Albert Einstein College of Medicine)
Truvada IVR (Oak Crest Institute of Science)

cabotegravir (SLAP-HIV project)
tenofovir alafenamide (Oak Crest Institute of Science)
tenofovir alafenamide (SLAP-HIV project)

injectable rilpivirine (HPTN 076 clinical trial)
cabotegravir (HPTN 077 clinical trial)
tenofovir alafenamide (SLAP-HIV project)

PreP and contraception …….there are so many similarities

INJECTABLE PREP

Background

- CAB is an HIV-1 integrase inhibitor
  - Oral 30 mg tablet ($t_{1/2}$, ~40 hours)
  - LA nanosuspension 200 mg/mL ($t_{1/2}$, ~20-40 days)
- RPV is an HIV-1 NNRTI
  - Oral 25 mg tablet ($t_{1/2}$, ~50 hours)
  - LA nanosuspension 300 mg/mL ($t_{1/2}$, ~30-90 days)
- Oral 2-drug CAB + RPV proof of efficacy through Week 96 in LATTE-1

BL, baseline; CAB, cabotegravir; CI, confidence interval; EFV, efavirenz; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; $t_{1/2}$, half-life.

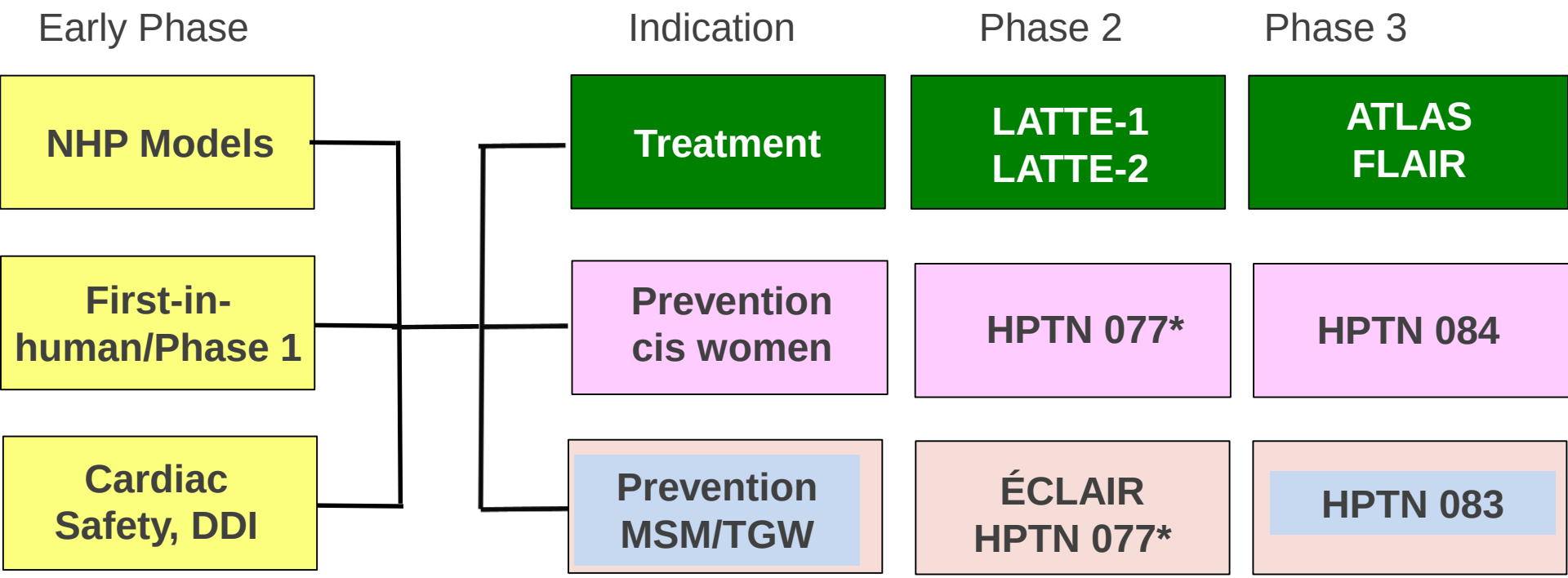
HPTN 076

- A phase 2 safety study designed to answer: Could injectable rilpivirine, a FDA-approved NNRTI in its oral formulation, be a useful sustained-release PrEP agent in women?
- ClinicalTrials.gov Identifier: NCT02165202
- Study ongoing; not recruiting
- Safety results to date:
  - Safe and well-tolerated
  - Acceptable to women
  - old chain required

Information courtesy Raphael J. Landovitz, MD from the HIV Prevention Trials Network

HPTN
HIV Prevention
Trials Network

Cabotegravir development



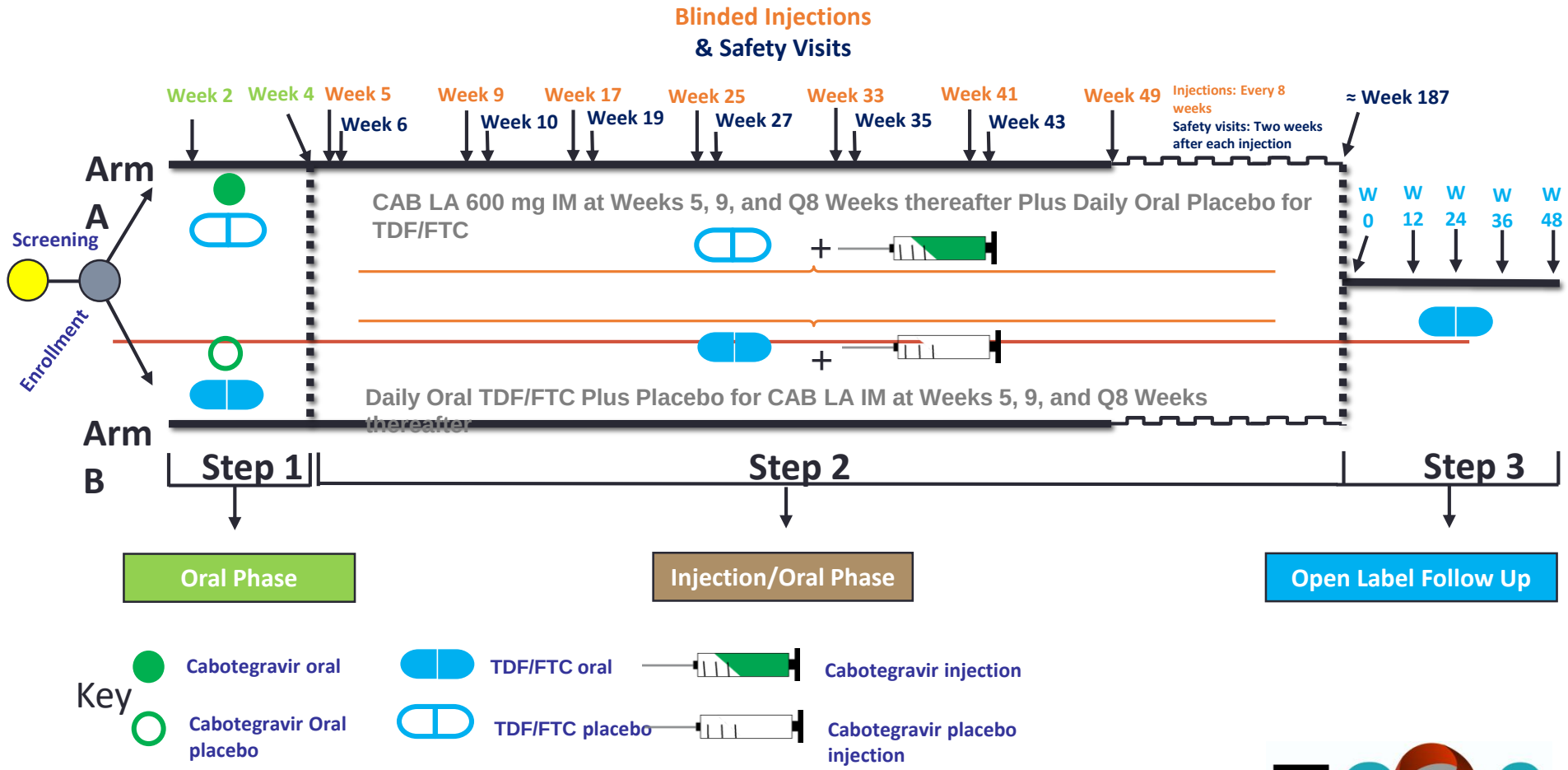
***INCLUDES BOTH MEN AND WOMEN**

Information courtesy Raphael J. Landovitz, MD from the HIV Prevention Trials Network

HPTN 083

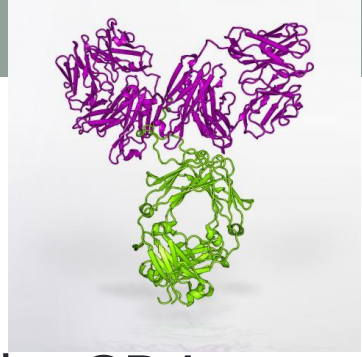
- Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) for PrEP in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men
- ClinicalTrials.gov Identifier: NCT02720094
- Anticipated Study population:
  - 4500 HIV-uninfected MSM in Asia, North & South America Randomized 1:1 - Group A or B
  - Study open for enrollment
  - St. Jude Memphis site currently enrolling

HPTN 083: Study Visit Schema



HPTN 083
an HIV prevention clinical trial

VRC01:Human monoclonal antibody infusion



- VRC01 is a broadly neutralizing antibody that targets the CD4-binding site of the HIV envelope glycoprotein
- The AMP Studies: To Evaluate the Safety and Efficacy of VRC01 Broadly Neutralizing Monoclonal Antibody in Reducing Acquisition of HIV-1 Infection Among Men and Transgender Persons Who Have Sex With Men (HVTN 704/HPTN 085) and sexually active women (HVTN 703/HPTN 081)
- ClinicalTrials.gov Identifiers: NCT02716675 & NCT02568215
- Currently enrolling
- Three study arms – low dose infusion q 8 weeks, high-dose infusion q 8 weeks and placebo infusions every 8 weeks
- Note: All study participants can receive standard of care for HIV prevention including approved PrEP in their respective countries.

PREP IMPLANTS

Subcutaneous PrEP Implants

Modeled After Implanon/Nexplanon Contraception

- Simple insertion AND removal
- Long-acting (months to years)
- PrEP + contraception?
- Current development:
  - TAF, CAB, EFdA (MK-8591)

Schlesinger, et al, Pharm Res 2016
Gunawardana, et al., AAC 2015

MICROBICIDES

ASPIRE STUDY

MTN-020/ASPIRE

- MTN-020/ASPIRE was a multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine.
- The primary objectives were to determine the ***effectiveness*** and ***safety*** of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-1 uninfected women.

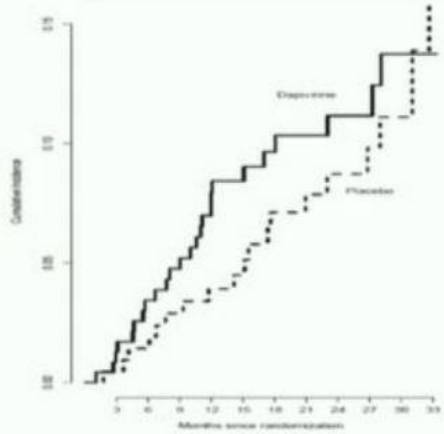
Study result details:

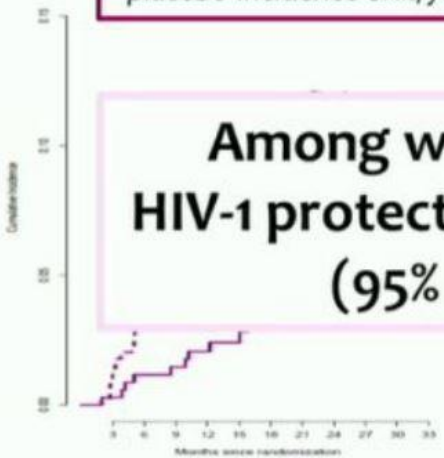
ASPIRE STUDY

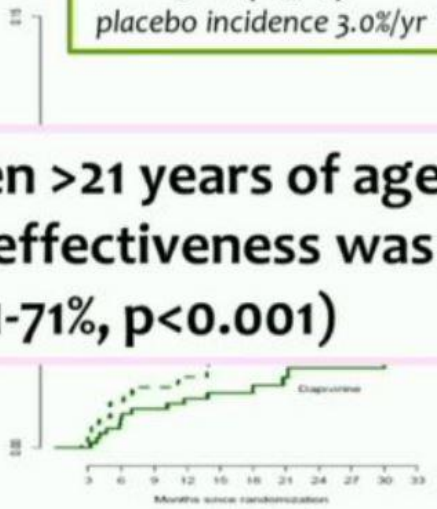
Age and HIV-1 Protection

- HIV-1 protection effectiveness was explored in additional age-stratified categories, and lack of HIV-1 protection was limited to those ≤21 years of age:

Age 18-21	Age 22-26	Age 27-45
-27% (-133,31)	56% (19,76)	51% (8,74)
placebo incidence 5.4%/yr	*placebo incidence 6.1%/yr*	*placebo incidence 3.0%/yr*







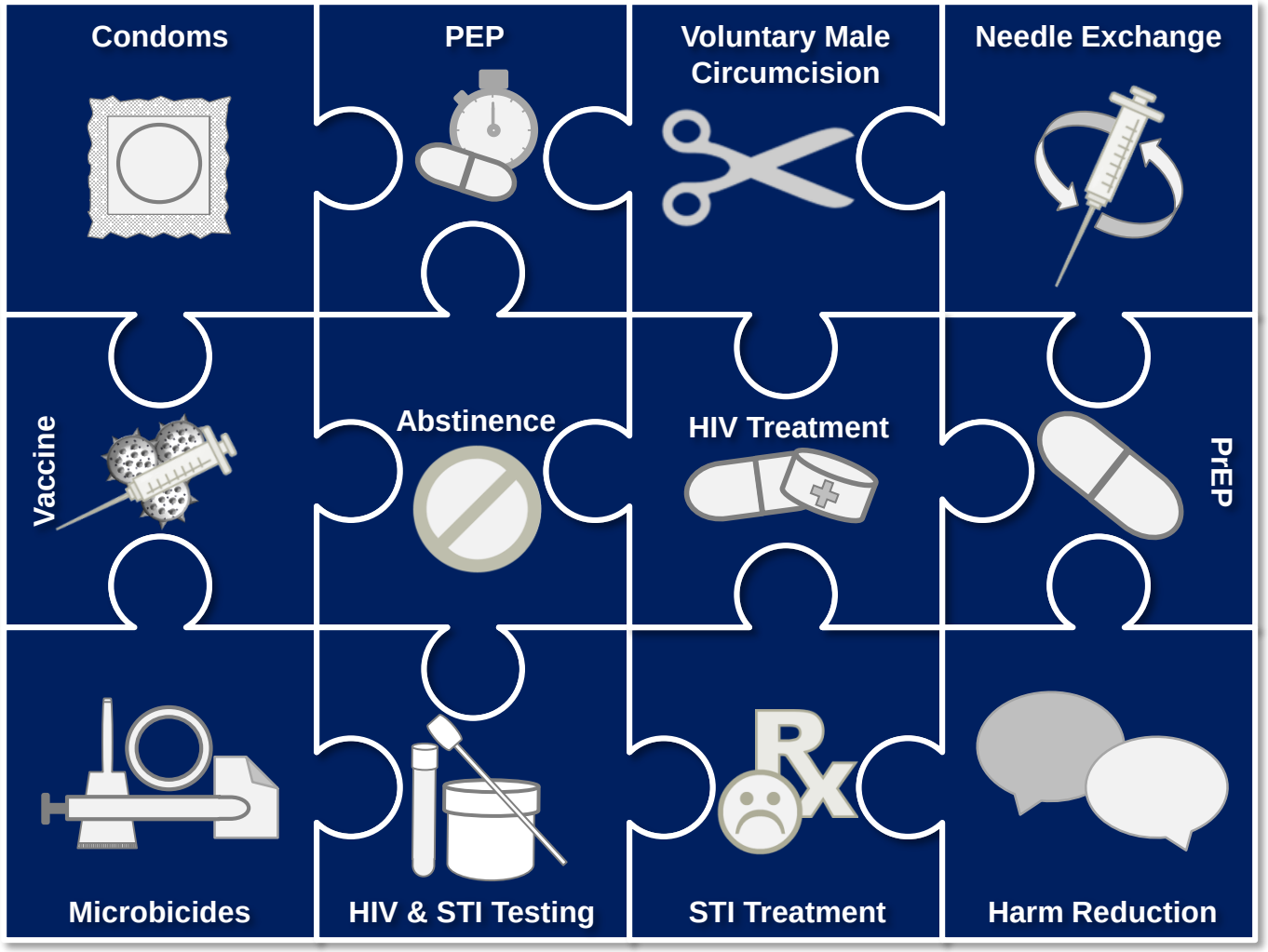
Among women >21 years of age, HIV-1 protection effectiveness was 56% (95% CI 31-71%, p<0.001)

MTN microbicide trials network

ASPIRE A Study to Prevent Infection with a Ring for Extended Use

IN SUMMARY

Prevention Modalities



Landovitz RJ, CROI 2015.

- HIV Pre-exposure prophylaxis (PrEP) works
- PrEP efficacy tied to adherence to PrEP
- Similar to what is available with contraceptives, options for PrEP are being researched that ultimately should allow a person to choose and tailor the PrEP option that fits her or his life
- While a number of PrEP studies have focused on MSM and trans females, given gender differences in PrEP efficacy from a global perspective concerted efforts to specifically research PrEP in women remain important
- Layering of protection interventions and not relying on any one will remain critical

aditya.gaur@stjude.org