Biomedical Prevention Update

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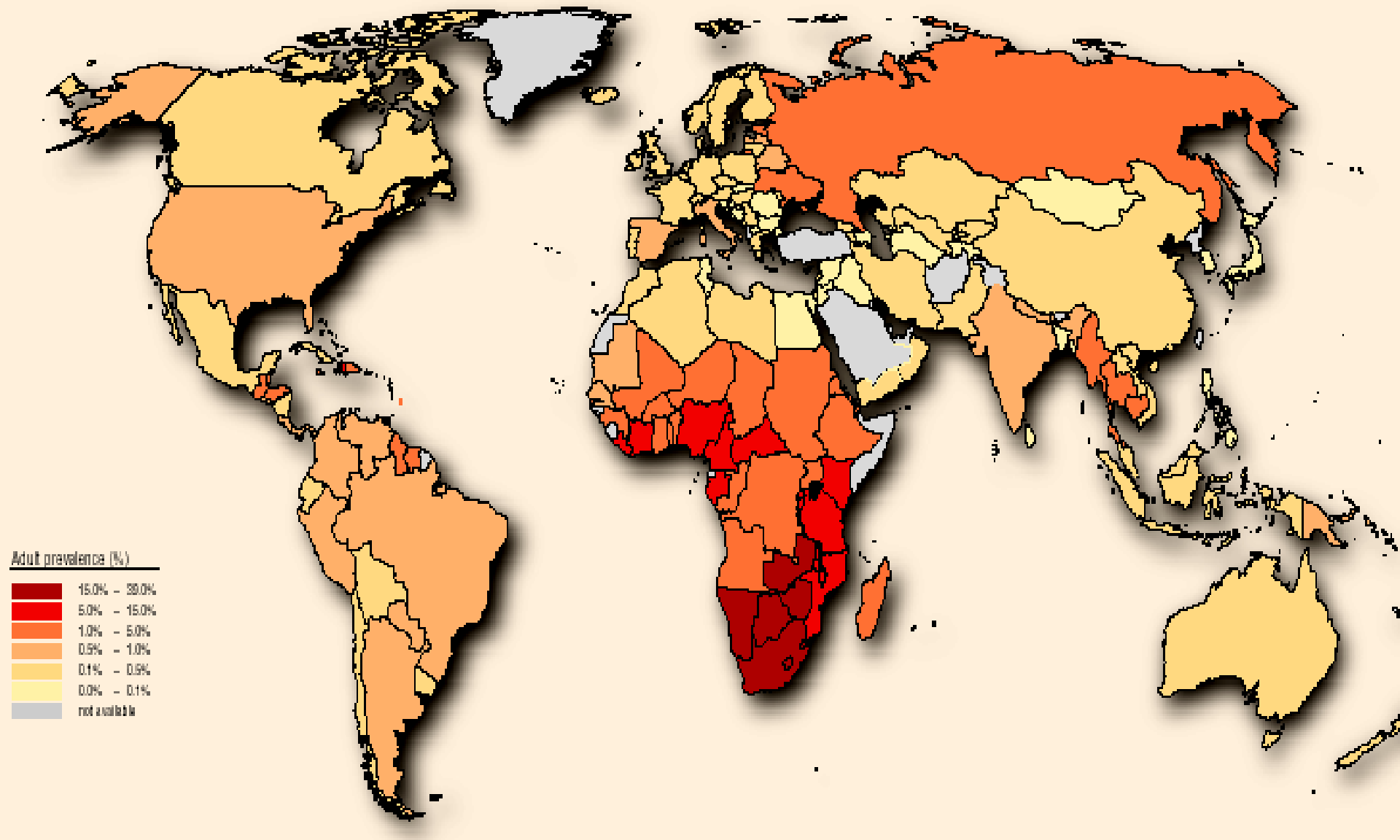
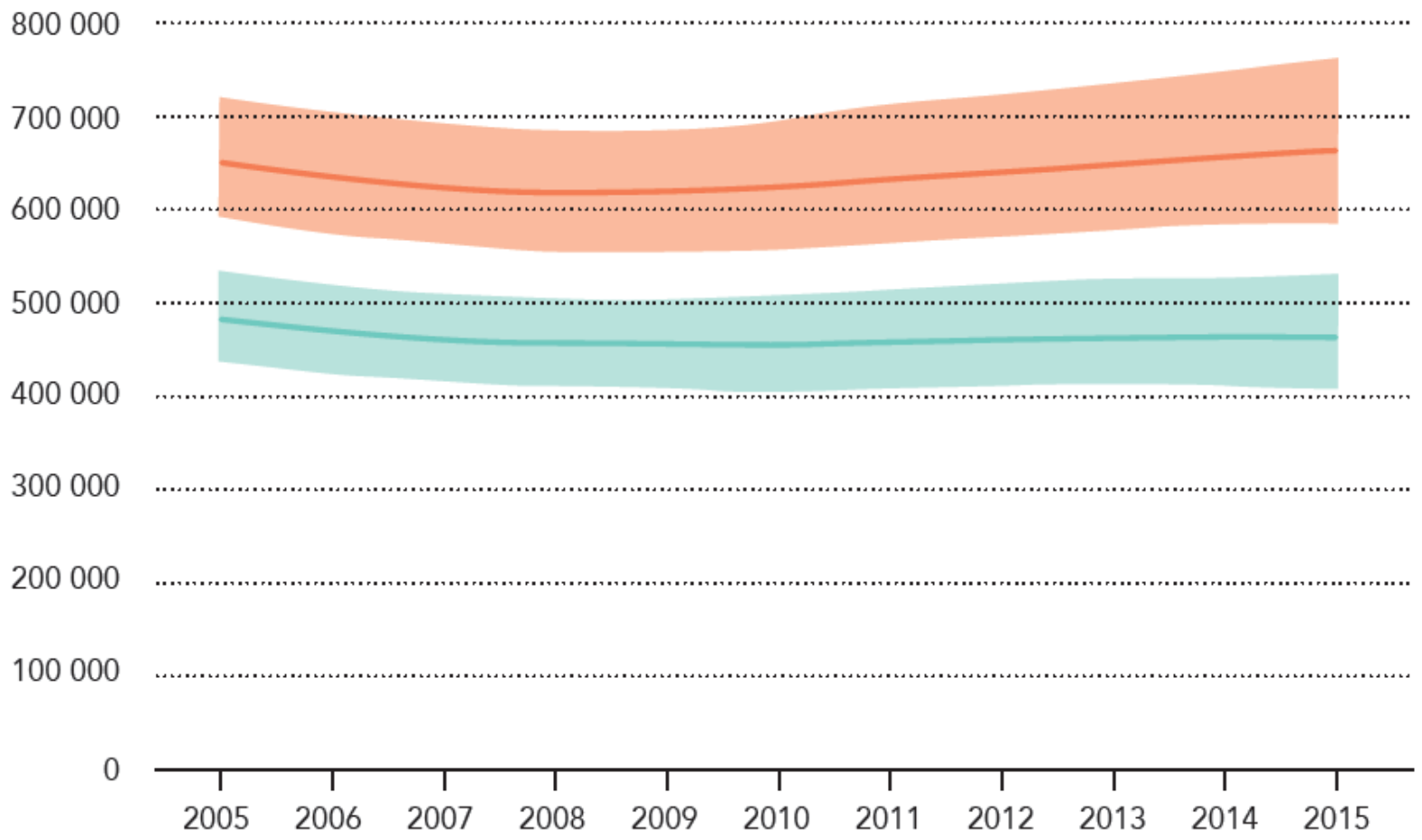
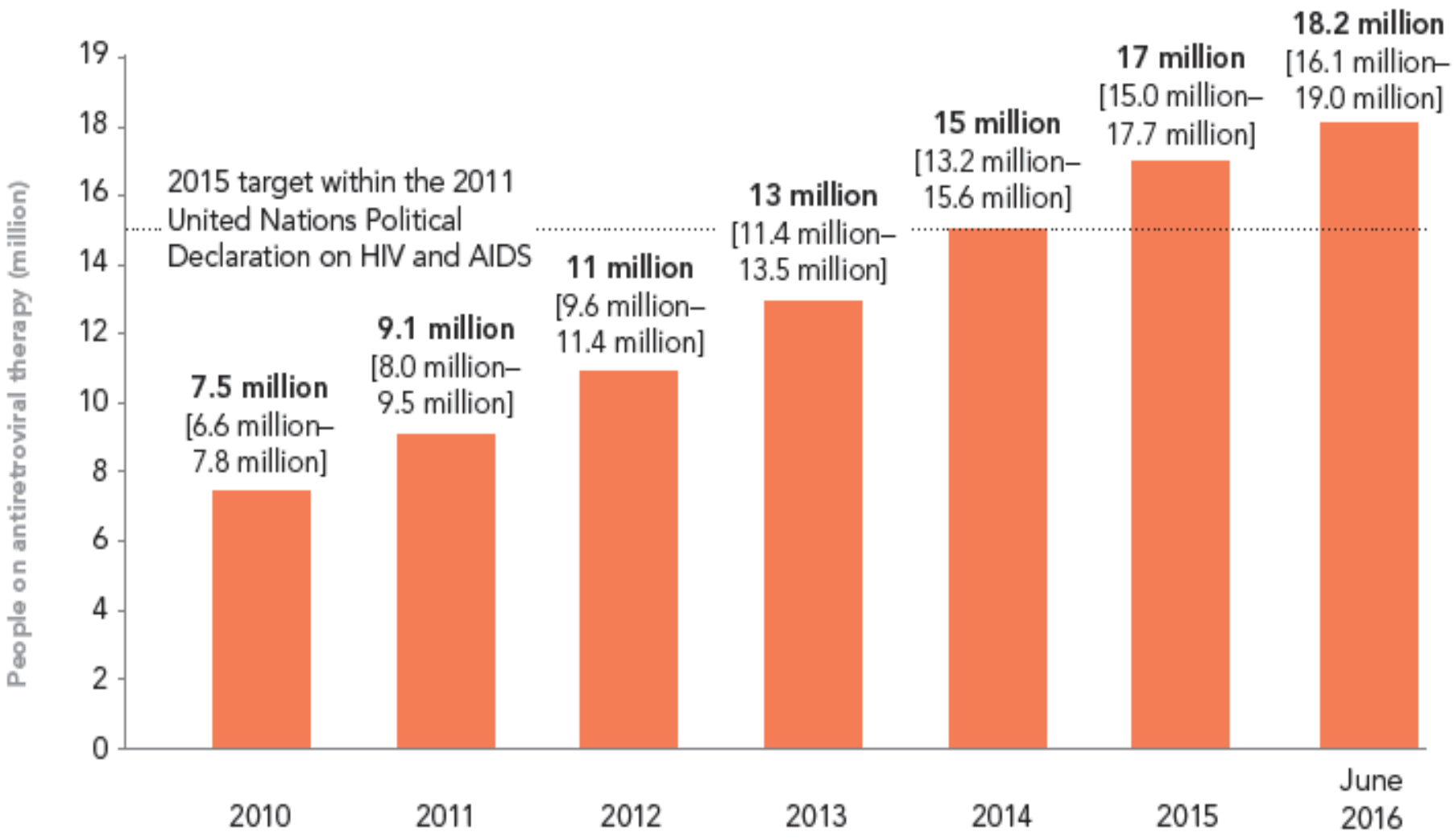
Global Prevalence of HIV infection: 36.7 Million Incidence 2.1 Million; 1.1 Million Deaths



New HIV infections among men and women (aged 25–49 years), global, 2005–2015

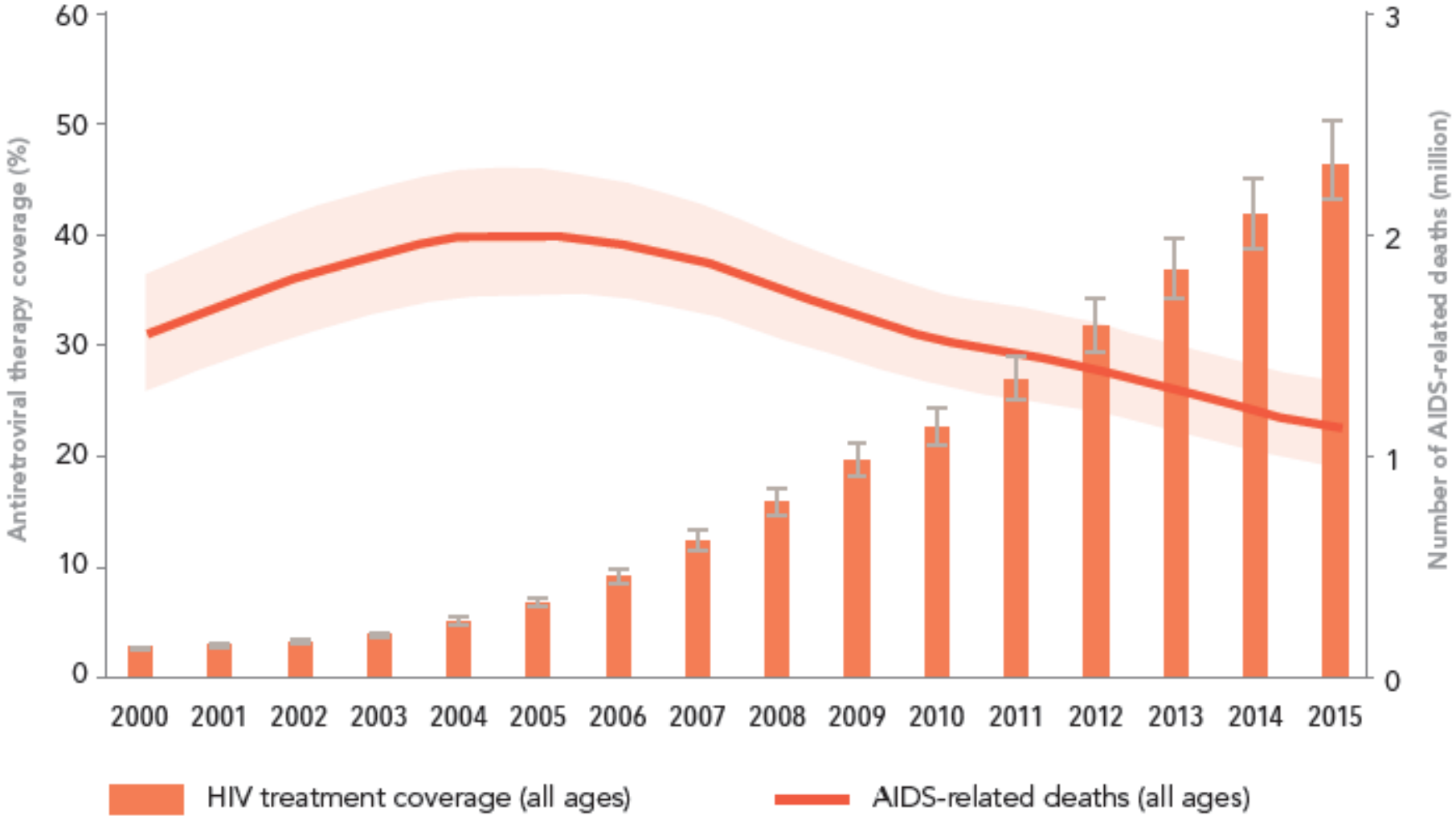


Number of people living with HIV on antiretroviral therapy, global, 2010–2016



Sources: Global AIDS Response Progress Reporting (GARPR) 2016; UNAIDS 2016 estimates.

Antiretroviral therapy coverage and number of AIDS-related deaths, global, 2000–2015

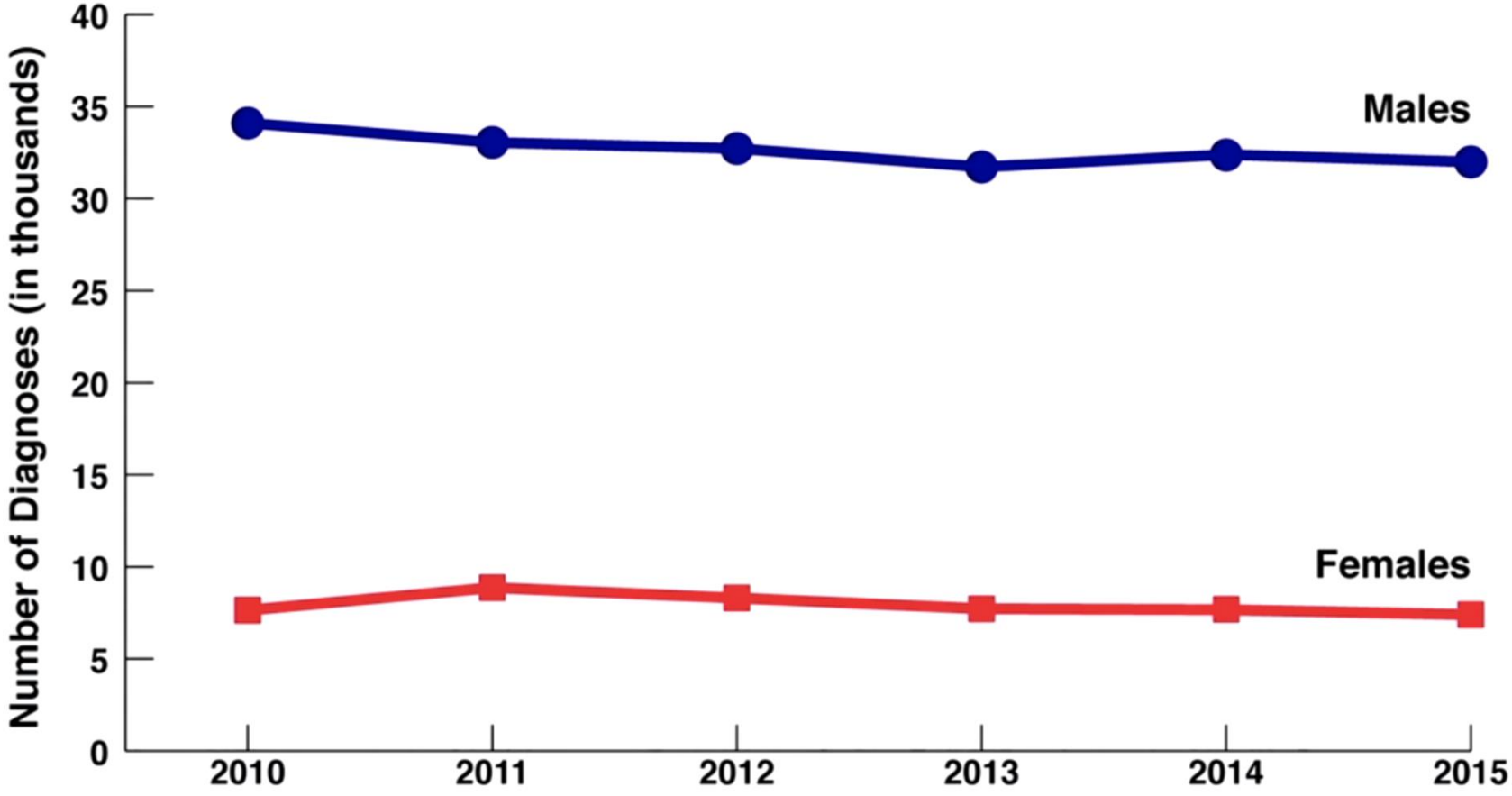


Sources: GARPR 2016; UNAIDS 2016 estimates.

HIV in the United States

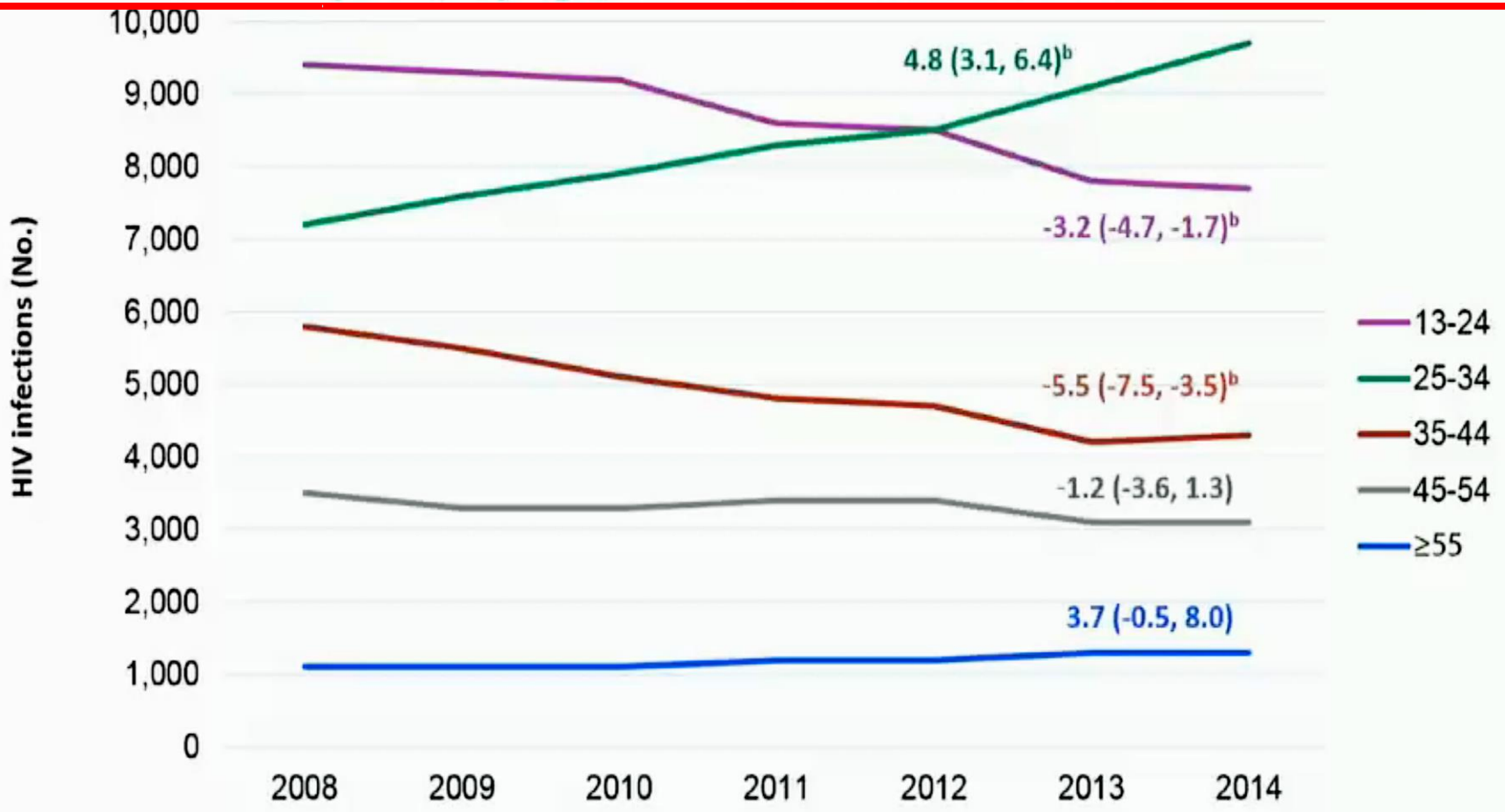
- 1.2 million people living with HIV infection, of whom 14% are unaware of their infection
- 648,000 people have died of AIDS
- Approximately 50,000 new infections/yr. for past two decades
- MSM, Blacks/African Americans face the most severe burden of HIV
- Youths aged 13-24 years account for >25% of new infections

Diagnoses of HIV Infection among Adults and Adolescents, by Sex, 2010–2015 — United States



Source: CDC, 11/2016

Estimated HIV incidence among men who have sex with men[a], aged ≥13 years, by age, United States, 2008–2014

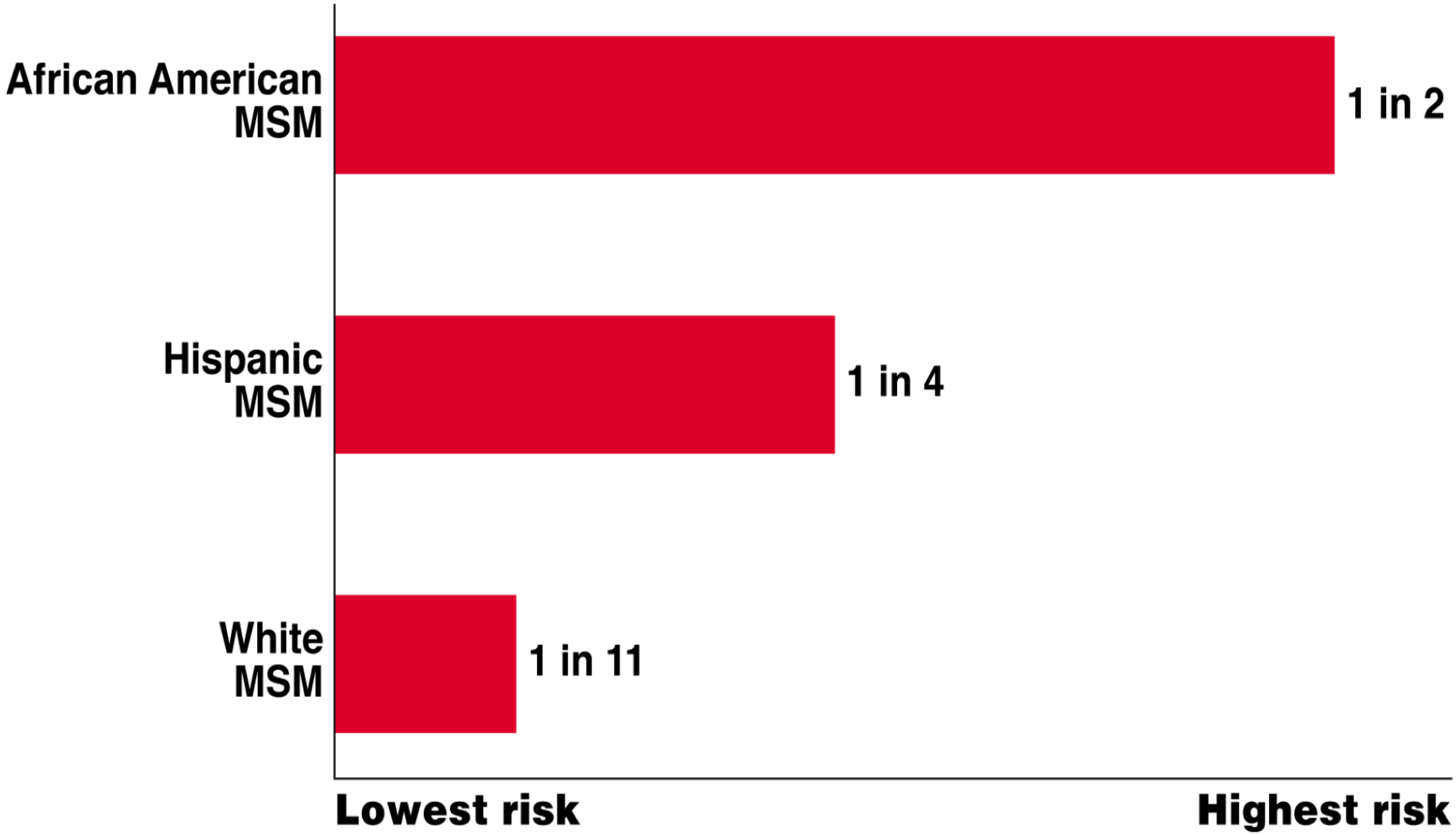


Note: Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Age is in years.

[a]Adjusted for missing risk factor information.

[b]Estimated annual percentage change is different from zero at the 5% significance level.

Lifetime Risk of HIV Diagnosis among MSM by Race/Ethnicity



AS Fauci/NIAID

Source: CDC, 2016

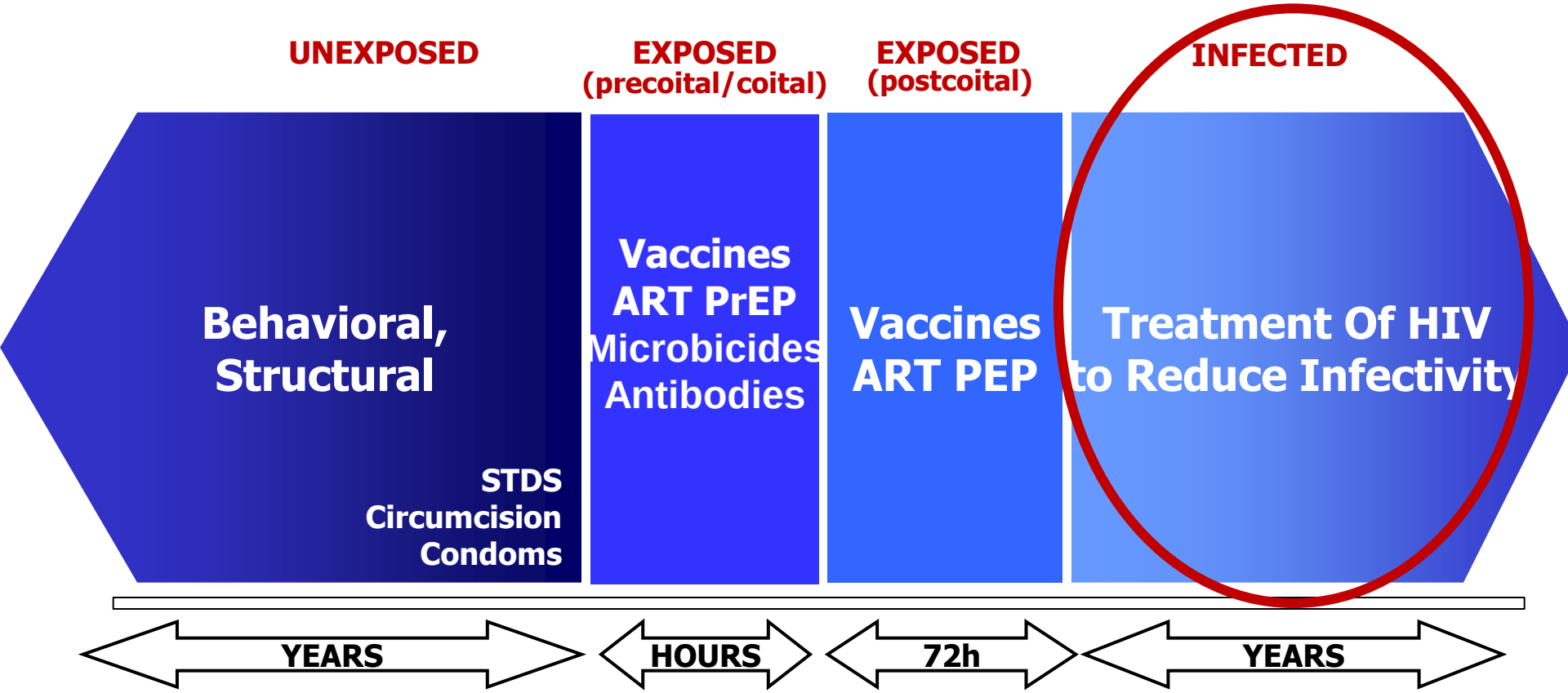
HIV Prevention Strategies

Advances in 4 key areas are of critical focus for the next 5 years:

- **Widespread testing and linkage to care**, enabling people living with HIV to access treatment early.
- **Broad support for people living with HIV to remain engaged in comprehensive care**, including support for treatment adherence.
- **Universal viral suppression** among people living with HIV.
- **Full access to comprehensive PrEP services** for those for whom it is appropriate and desired, with support for medication adherence for those using PrEP.

Four Prevention Opportunities

Cohen et al., JCI, 2008
Cohen et al., JIAS ,2008



ART for Prevention of HIV Transmission in Serodiscordant Couples

- **HPTN 052**: HIV-infected partner in healthy serodiscordant couples randomized to early or delayed ART (N = 1,763 couples)
  - Overall **93% reduction in risk** of transmission with early therapy
  - **No linked HIV transmissions where index partner suppressed on ART**

- **PARTNER**: observational study in serodiscordant couples where HIV-infected partner on suppressive ART and condoms not used (N = 888 couples)[2]
  - **No linked transmissions recorded in any couple**
  - Median follow-up: 1.3 yrs; ~ **58,000 sex acts**

1. Cohen MS, et al. N Engl J Med. 2016;375:830-839.
2. Rodger A, et al. JAMA. 2016;316:171-181.

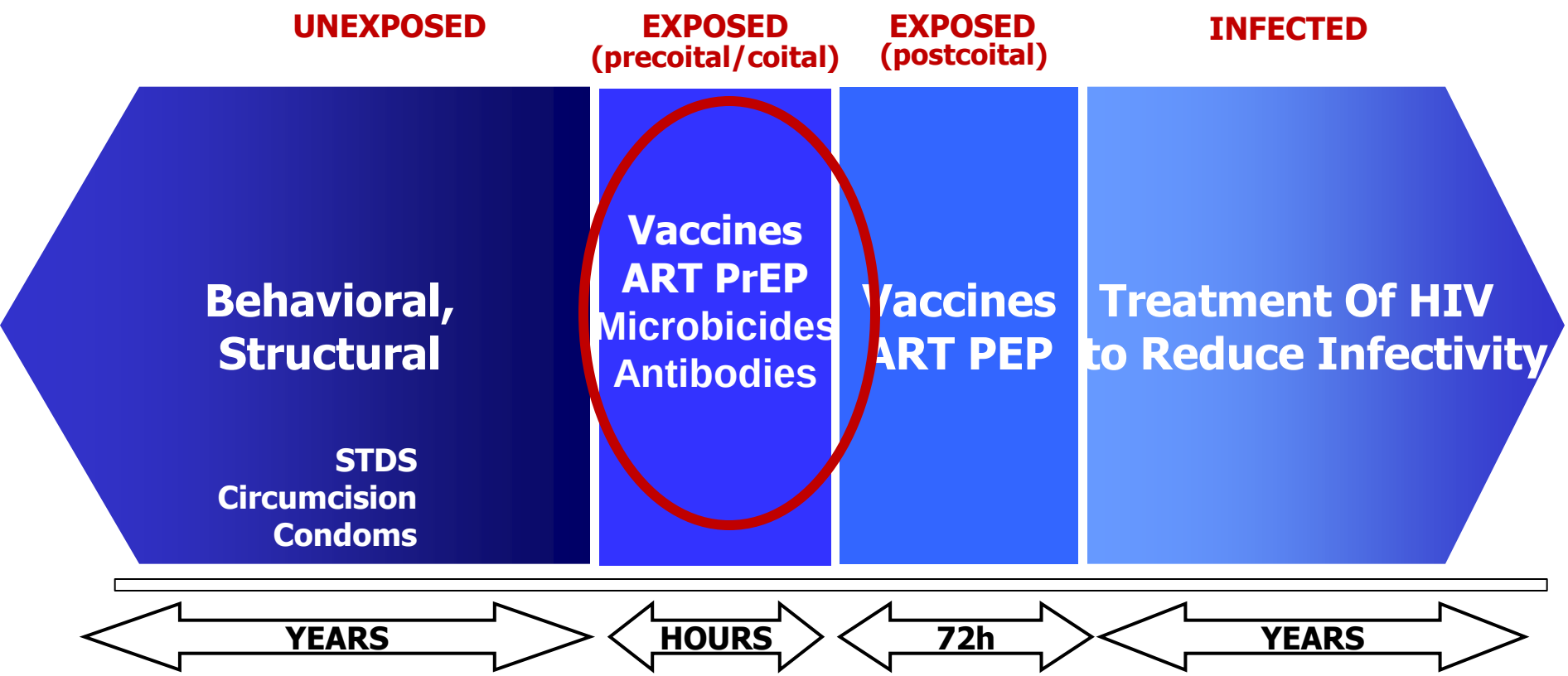
World Health Organization

30 September 2015

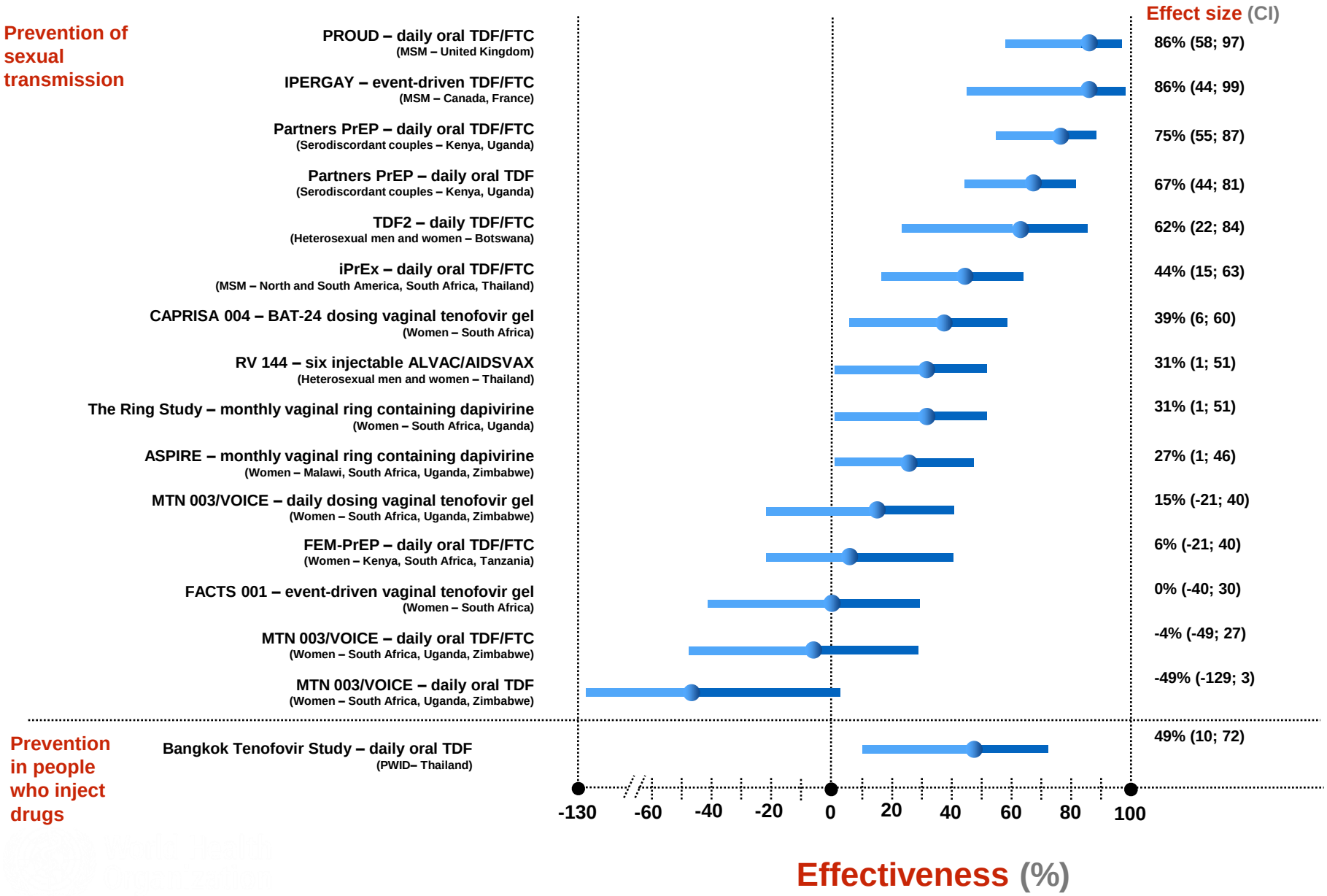
Treat All People Living with HIV, Offer Antiretrovirals as Additional Prevention Choice for People at Substantial Risk

Four Prevention Opportunities

Cohen et al., JCI, 2008
Cohen et al., JIAS ,2008



Clinical Trial Evidence for HIV Prevention Options (Feb. 2016)



TDF/FTC Was FDA Approved for use for Prevention on July 16, 2012

- Success depends entirely on adherence
- Alternatives to daily dosing are possible
- Tenofovir/emtricitabine PrEP uptake has been limited to date
- Perhaps longer-acting agents will prove more attractive?

WHO Guidelines 2015

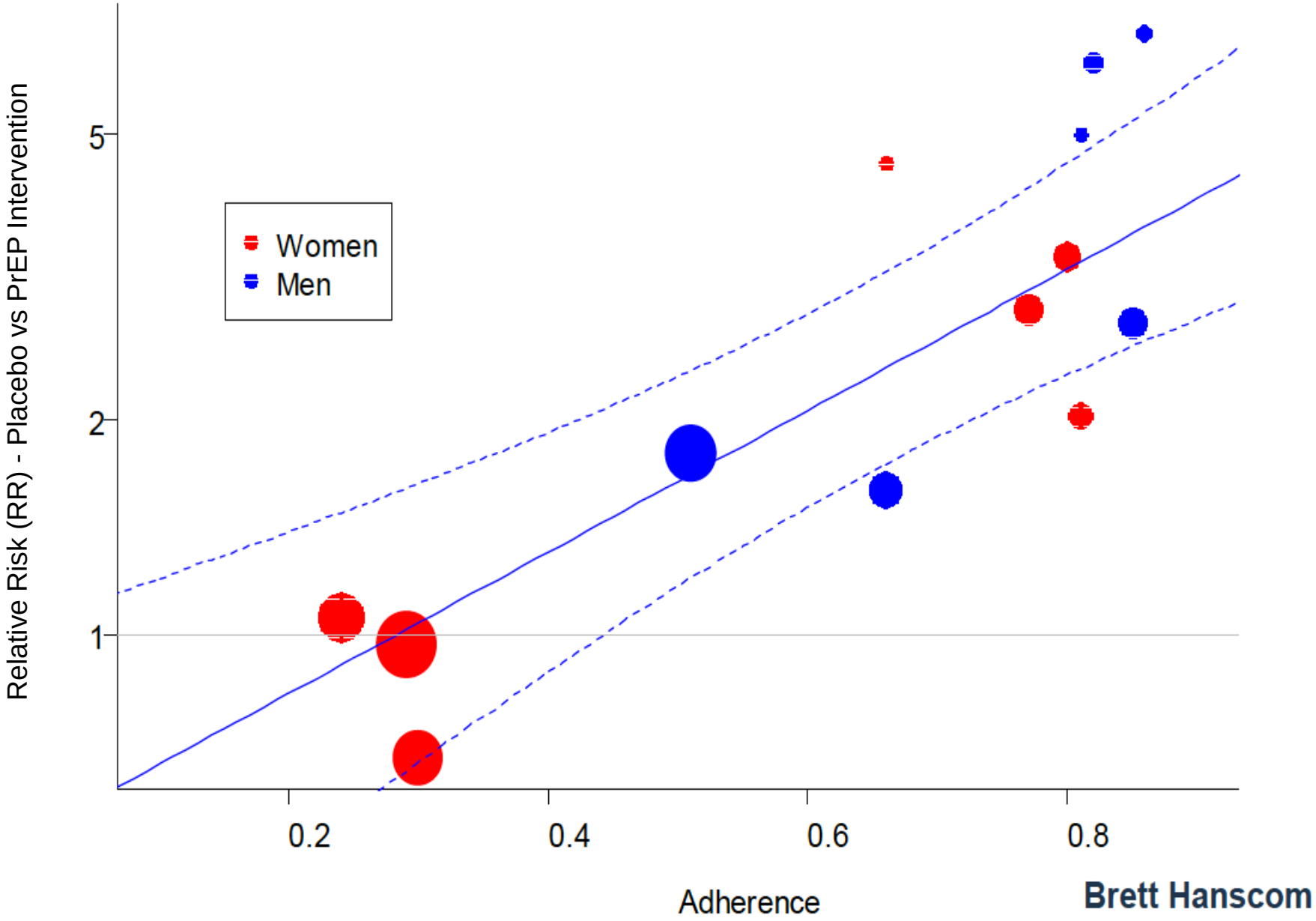
Recommendation 2: Oral pre-exposure prophylaxis to prevent HIV acquisition			
Target population	**Specific recommendation**	**Strength of the recommendation**	**Quality of the evidence**
HIV-negative individuals at substantial risk of HIV infection[b]	Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches	*Strong*	*High* NEW

Recommendation

NEW

Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches *(strong recommendation, high-quality evidence)*.

Association between Adherence and Effectiveness



THE LANCET Infectious Diseases
Volume 14 September 2014

Uptake of Pre-Exposure Prophylaxis, Sexual Practices, and HIV Incidence in Men and Transgender Women Who Have Sex With Men: A Cohort Study

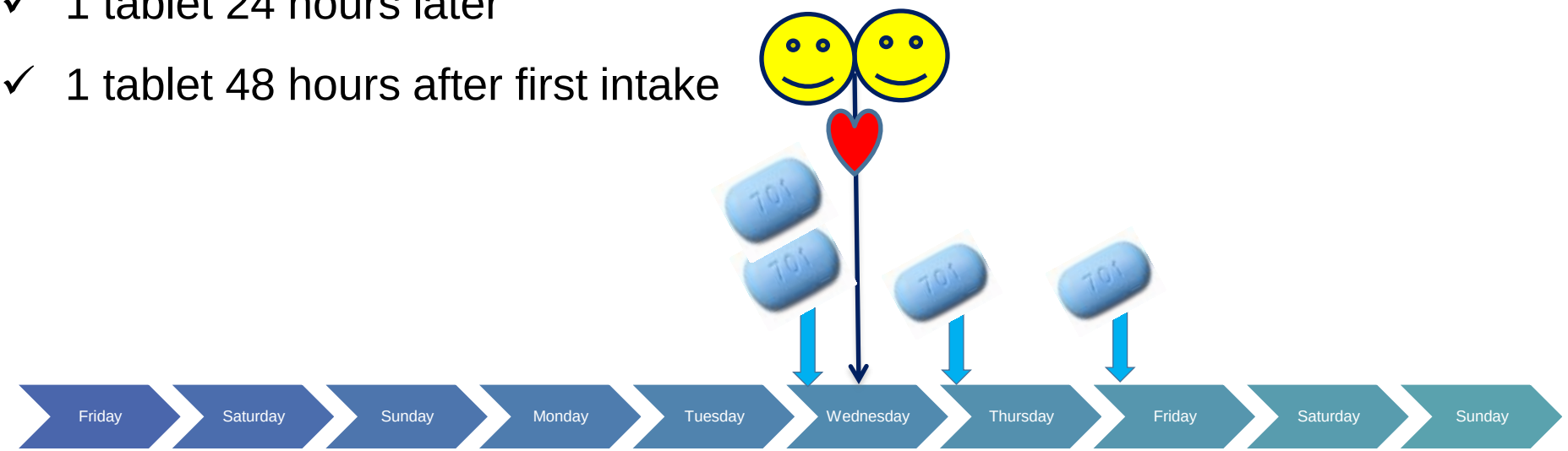
RM Grant, DV Glidden et al. for the iPrEx Study Team

- Open-label study of 1,603 HIV-negative individuals
- Any PrEP use reduced risk of HIV acquisition by ~50%
- 100% effective in those taking 4+ doses/week

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

IPERGAY: Sex-Driven iPrEP

- ✓ 2 tablets 2-24 hours before sex
- ✓ 1 tablet 24 hours later
- ✓ 1 tablet 48 hours after first intake



4 pills of TDF/FTC taken over 3 days to cover 1sexual intercourse

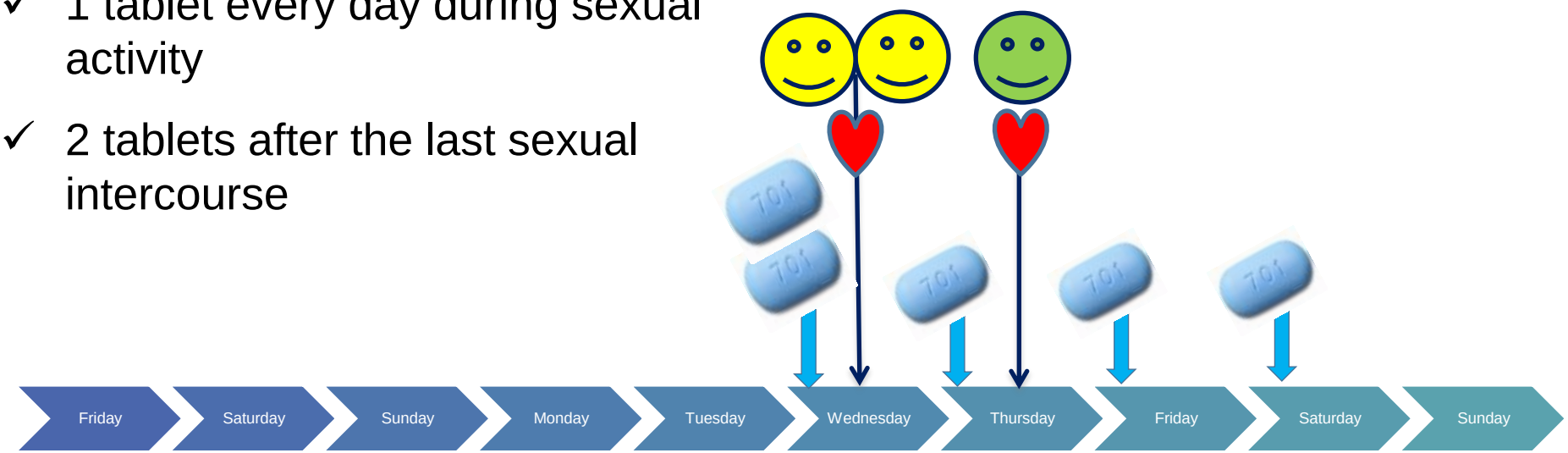
World Health Organization
Europe

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

IPERGAY: Sex-Driven iPrEP

- ✓ 2 tablets 2-24 hours before sex
- ✓ 1 tablet every day during sexual activity
- ✓ 2 tablets after the last sexual intercourse



On demand PrEP tells you **How to Start and How to Stop PrEP**

World Health Organization

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ANRS
Intervention Préventive
de l'Exposition aux Risques
avec et pour les Gays

HIV Incidence (mITT Analysis)

Treatment	Follow-Up Pt-years	HIV Incidence per 100 Pt-years (95% CI)
Placebo (double-blind)	212	**6.60** (3.60-11.1)
TDF/FTC (double-blind)	219	**0.91** (0.11-3.30)
TDF/FTC (open-label)	515	**0.19** (0.01-1.08)

Median Follow-up in Open-Label Phase: 18.4 months (IQR:17.5-19.1)

97% relative reduction vs placebo

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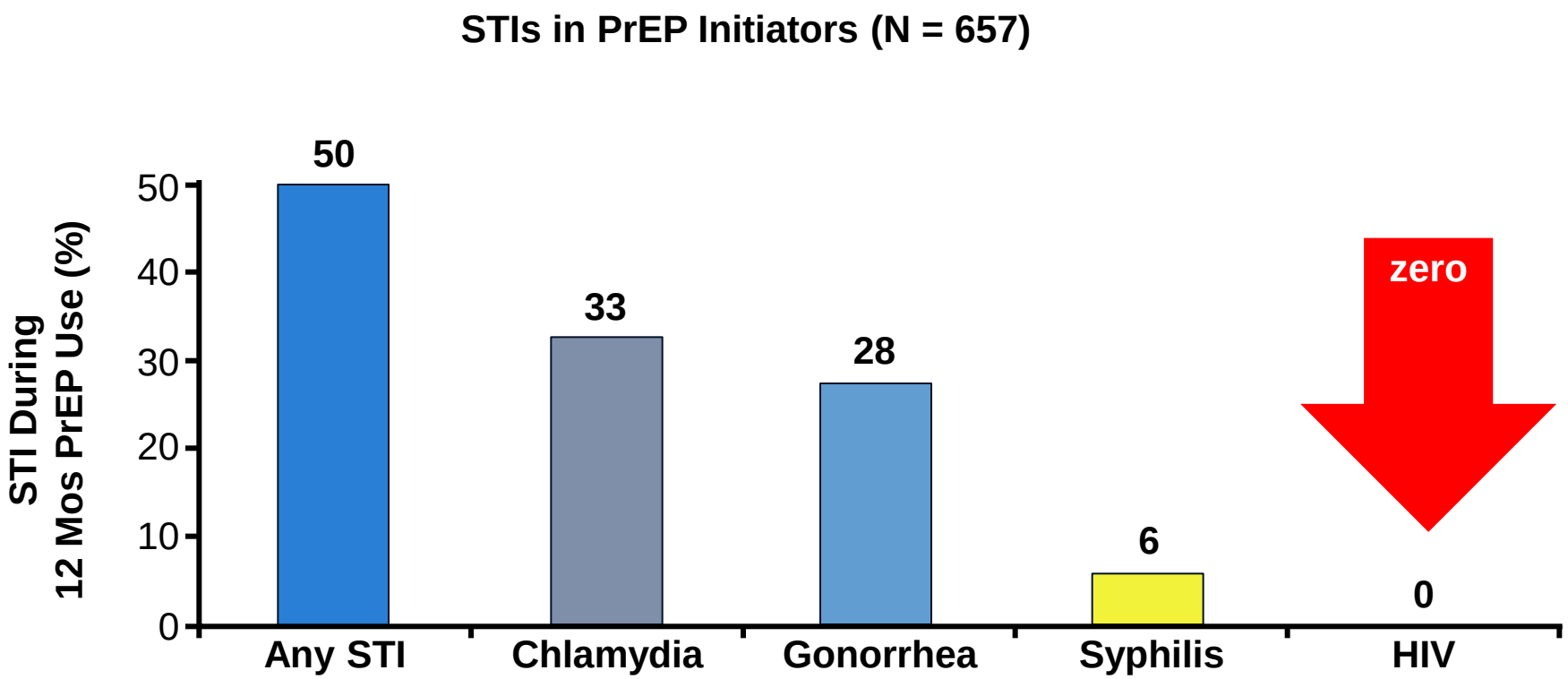
Agence autonome de l'Inserm

STIs Will Occur for Persons Using PrEP

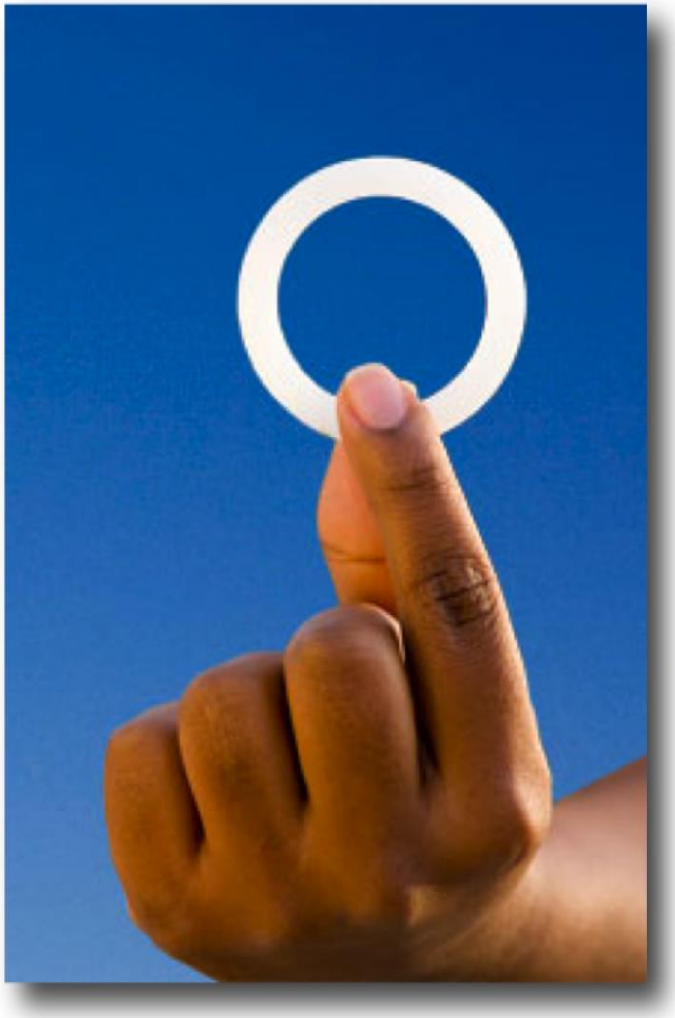
- **Analysis of HIV/STI incidence in PrEP users in large healthcare system (Kaiser Permanente San Francisco) from 2012 to 2015**



- PROUD: similar rates of any STI in 12 mos before starting PrEP (63%) vs during 12 months of PrEP (57%)[2]

1. Volk JE, et al. Clin Infect Dis. 2015;61:1601-1603.
2. McCormack S, et al. Lancet. 2016;387:53-60.

Dapivirine Microbicide Rings

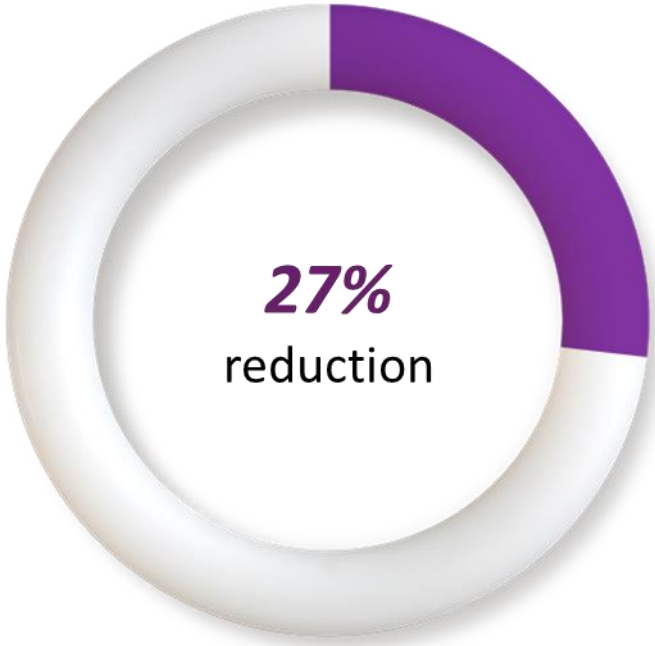


- Monthly use
- Two large-scale trials in 2012
  - **ASPIRE** ~3500 women in Malawi, South Africa, Uganda, Zambia, and Zimbabwe
  - **The Ring Study (IPM 027)** ~1,650 women in South Africa, Rwanda, and Malawi

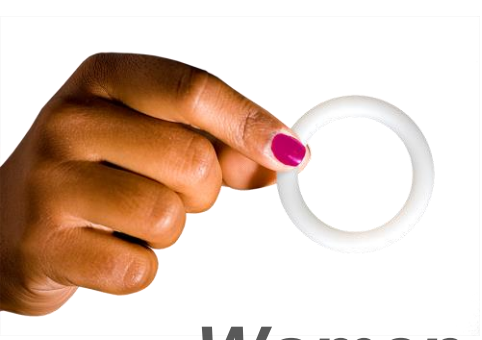
Efficacy

Approximately 30% reduction in HIV-1 infection among women ages 18-45 overall

The Ring Study

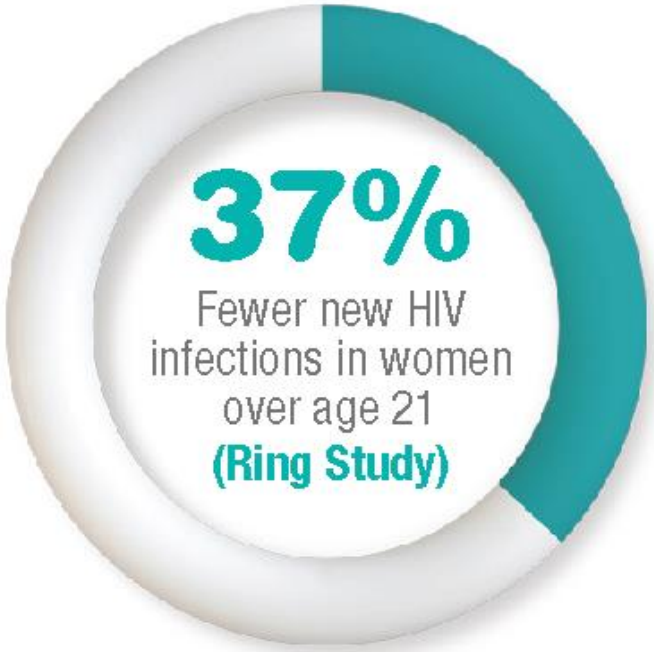


ASPIRE

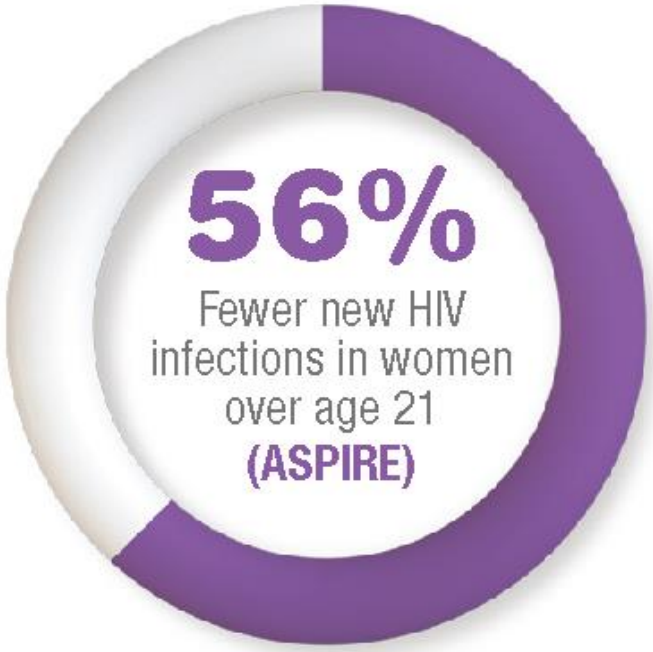


Efficacy

Women older than 21 years tended to be more adherent with a greater protection from HIV-1

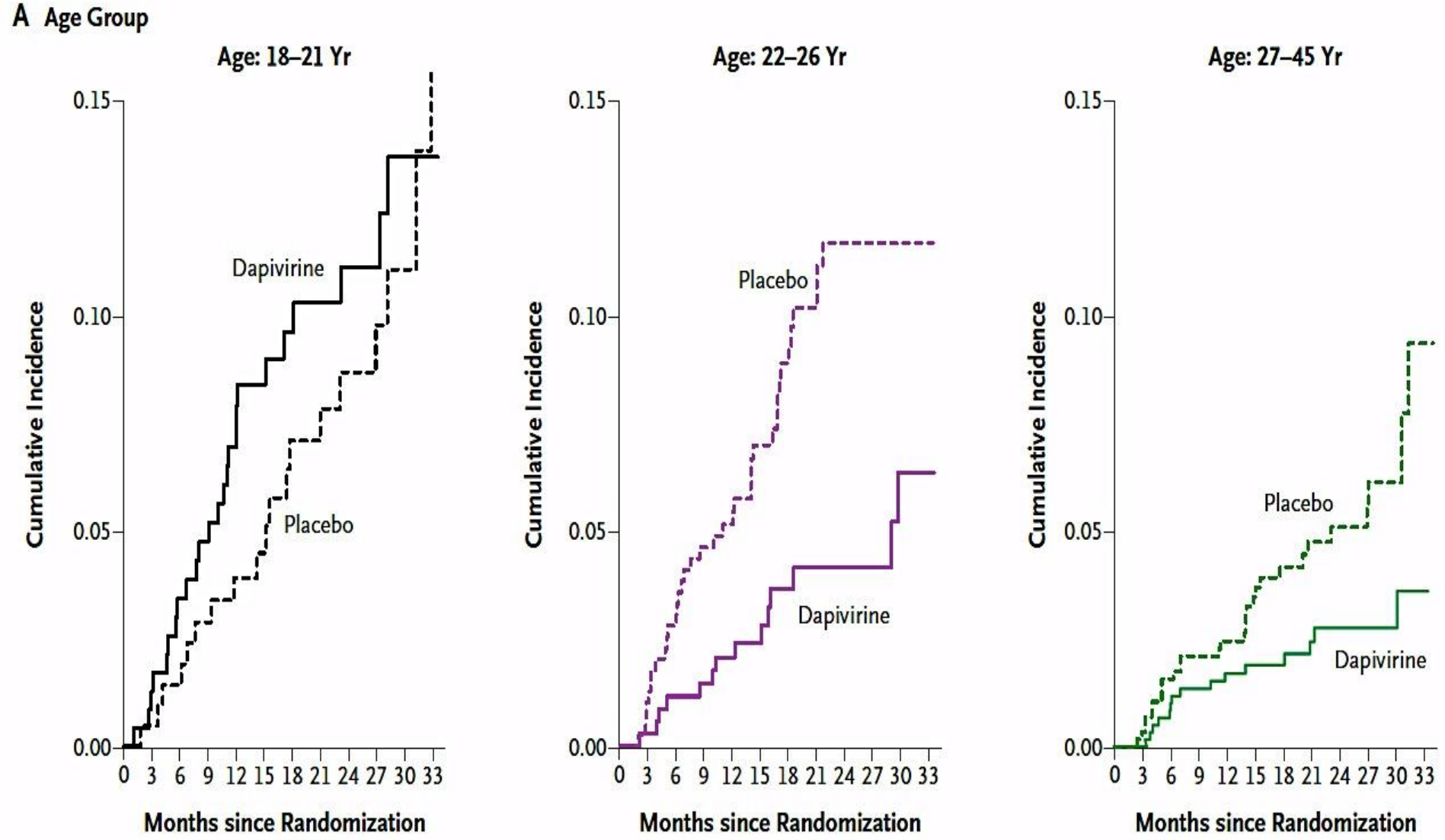


The Ring Study



ASPIRE

ASPIRE Dapivirine Ring Study



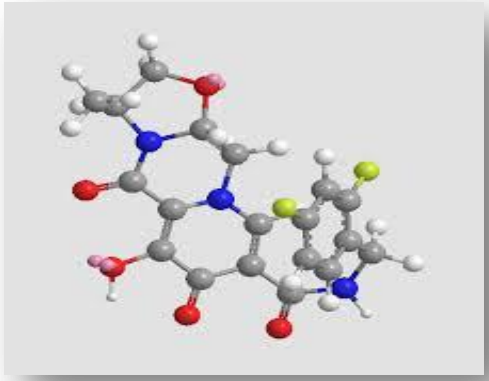
Baeten JM et al. N Engl J Med 2016.

Long-Acting Injectable Nano-Suspensions

TMC278LA (rilpivirine; PATH)

- NNRTI (rilpivirine)
- Oral coformulation as rilpivirine/TDF/FTC
- Long-acting: up to 3 months?
- Multiple trials:
  - Dose-ranging PK; PK/PD
  - Phase-2: HPTN 076

Cabotegravir (GSK ‘744; ViiV)



- Integrase inhibitor
- Similar to dolutegravir
- Safe in humans with oral run-in
- Activity up to 3 months
- NHP model efficacy
- Phase 2: Éclair and HPTN 077

HPTN 083: Phase 2B/3 Study of Efficacy of injectable cabotegravir for PrEP in MSM and transgender women

N = 4500 (10% TGW overall; 50% of US BMSM; 50% overall < 30 year old

	CAB	TDF/FTC
Step 1	Daily oral CAB and oral TDF/FTC placebo	Daily oral TDF/FTC and oral CAB placebo
Step 2	Injectable CAB and daily oral TDF/FTC placebo	Daily oral TDF/FTC and injectable placebo
Step 3	Open-label daily oral TDF/FTC for up to 48 weeks	Open-label daily oral TDF/FTC for up to 48 weeks

Primary objective: HIV Incidence

40+ sites chosen in the Americas (Argentina, Brazil, Peru, US) and Asia (Thailand, Vietnam; India pending)

HPTN 084: Phase 2B/3 Study of efficacy of injectable cabotegravir for PrEP in women (*under development*)

On the Horizon: Long-Acting ARV Implants

July 2015 Vol 59 No 7

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY

Pharmacokinetics of Long-Acting Tenofovir Alafenamide (GS-7340) Subdermal Implant for HIV Prophylaxis

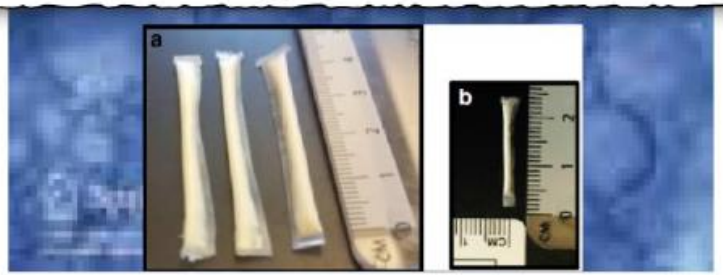
M Gunawardana, M Baum et al.

PHARMACEUTICAL RESEARCH

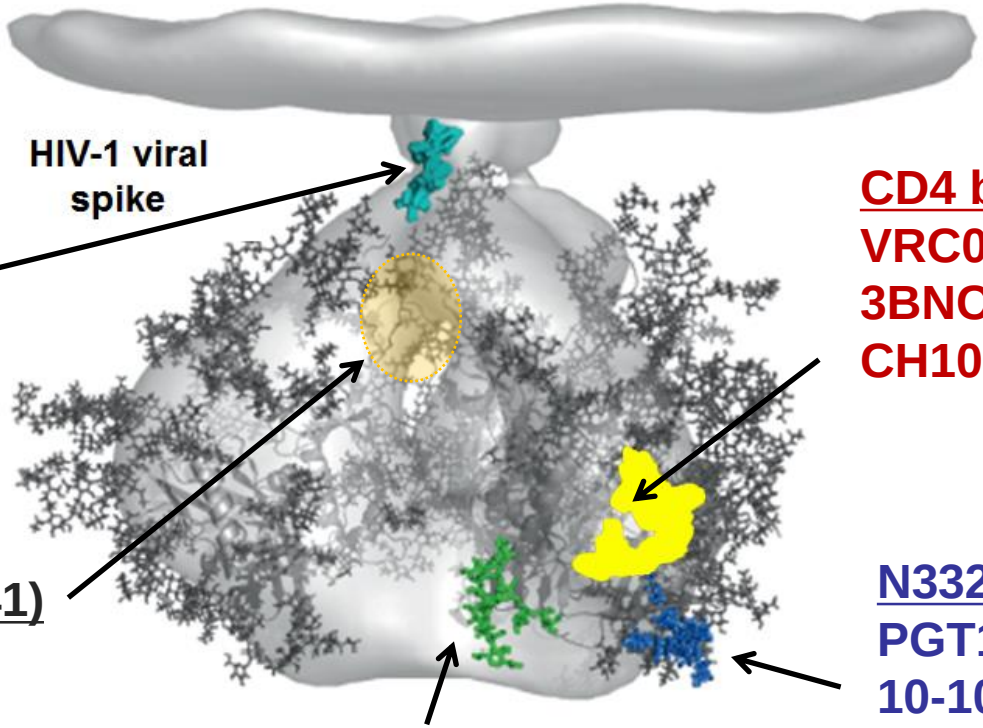
July 2016

A Tunable, Biodegradable, Thin-Film Polymer Device as a Long-Acting Implant Delivering Tenofovir Alafenamide Fumarate for HIV Pre-exposure Prophylaxis

E Schlesinger, T Desai et al.



Neutralizing Antibody Epitopes on Native Trimer (since 2009)



gp41 MPER:
2F5, 4E10
10e8

CD4 binding site:
VRC01, PG04, CH31
3BNC117, 12A12
CH103, VRC07

Trimer (gp120/41)
8ANC195
PGT151
35022

N332 glycan supersite:
PGT121, PGT128
10-1074

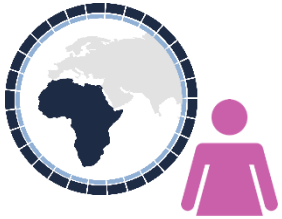
V1V2 Glycan:
PG6, PG16, CH01-04
PGT141-45
CAP256-VRC26

Highly selected donors

Cryo-EM of viral spike by Subramaniam group. Fit with atomic-level structures from Kwong and Wilson groups

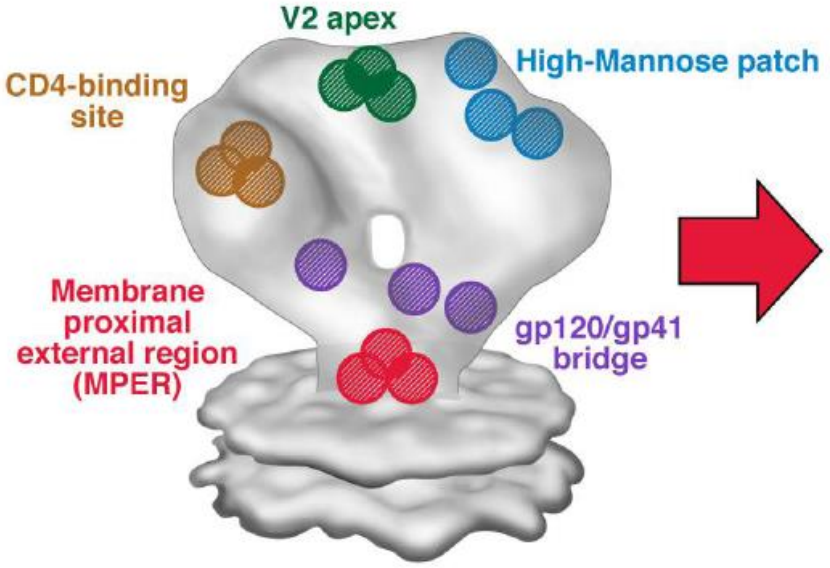
Enrolled participants
2400 MSM and TG + 1500 women 18 to 50 yo
Study duration
92 weeks (infusions given through Week 72)

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection

Regimen			Total	Note
VRC01 10 mg/kg	800	500	2,600	Infusions every 8 weeks through Week 72 (10 total infusions per participant)
VRC01 30 mg/kg	800	500		
Control*	800	500	1,300	
Total	**2,400**	**1,500**	**3,900**	
	MSM and transgender persons	**Sub-Saharan African women**		

Primary objective: HIV incidence, safety and tolerability

Fundamental Challenge in HIV Vaccinology: Convert Neutralizing Epitopes to Immunogens Inducing bNAbs



Neutralizing epitopes

Immunogen

Induction of bNAbs

Disappointing Trials of HIV Vaccines

B-Cell Approach

T-Cell Approach

1987

First trial of an HIV vaccine – MicroGeneSys gp160 subunit

2003

Vax003 – VaxGen AIDSVAX (B/B)

Vax004 – VaxGen AIDSVAX (B/E)

2007

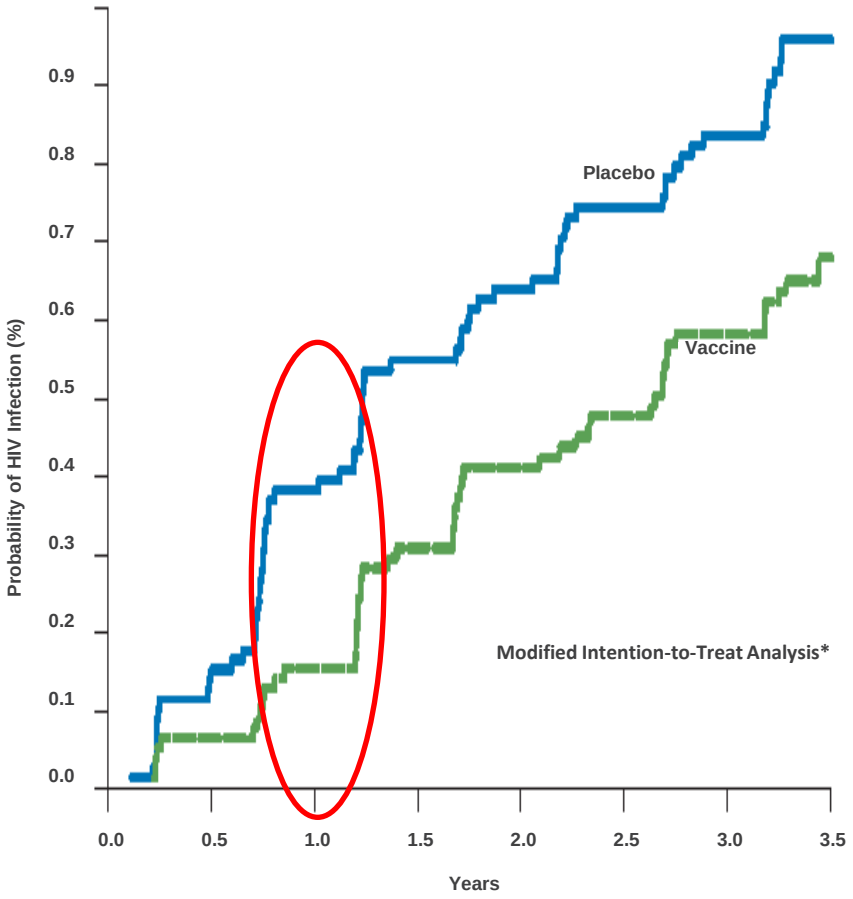
STEP – Merck V520

Phambili – Merck V520

2013

HVTN 505 – VRC DNA prime/Ad5 boost

Thai Trial (RV144) Primary Results



Vaccine efficacy decreases over time

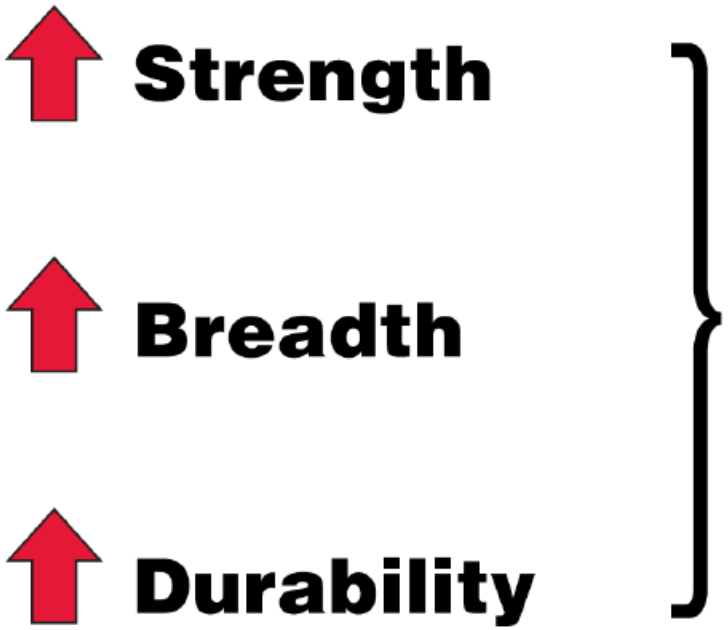
	Vaccine		Placebo		
Time (mo)	Cumulative Infections	% HIV-1 infection rate (95% CI)	Cumulative Infections	% HIV-1 infection rate (95% CI)	Vaccine Efficacy (%)
12	12	0.15 (0.07,0.24)	30	0.38 (0.24,0.52)	61
24	32	0.41 (0.27,0.55)	50	0.64 (0.46,0.82)	36
36	45	0.58 (0.41,0.75)	65	0.84 (0.63,1.04)	31
42	51	0.68 (0.49,0.87)	74	0.96 (0.74,1.18)	31

Perks-Ngarm et al: NEJM 2009

Immune Correlates Analysis from RV144

- IgG antibodies against the V1V2 region of the HIV-1 envelope protein associated with reduced infection
- Non-neutralizing antibodies mediate ADCC activity
- IgA antibodies correlated with increased infection

Strategies to Amplify RV144 Response



Potential approaches:

- Multiple boosts
- Modified vectors
- Adjuvants

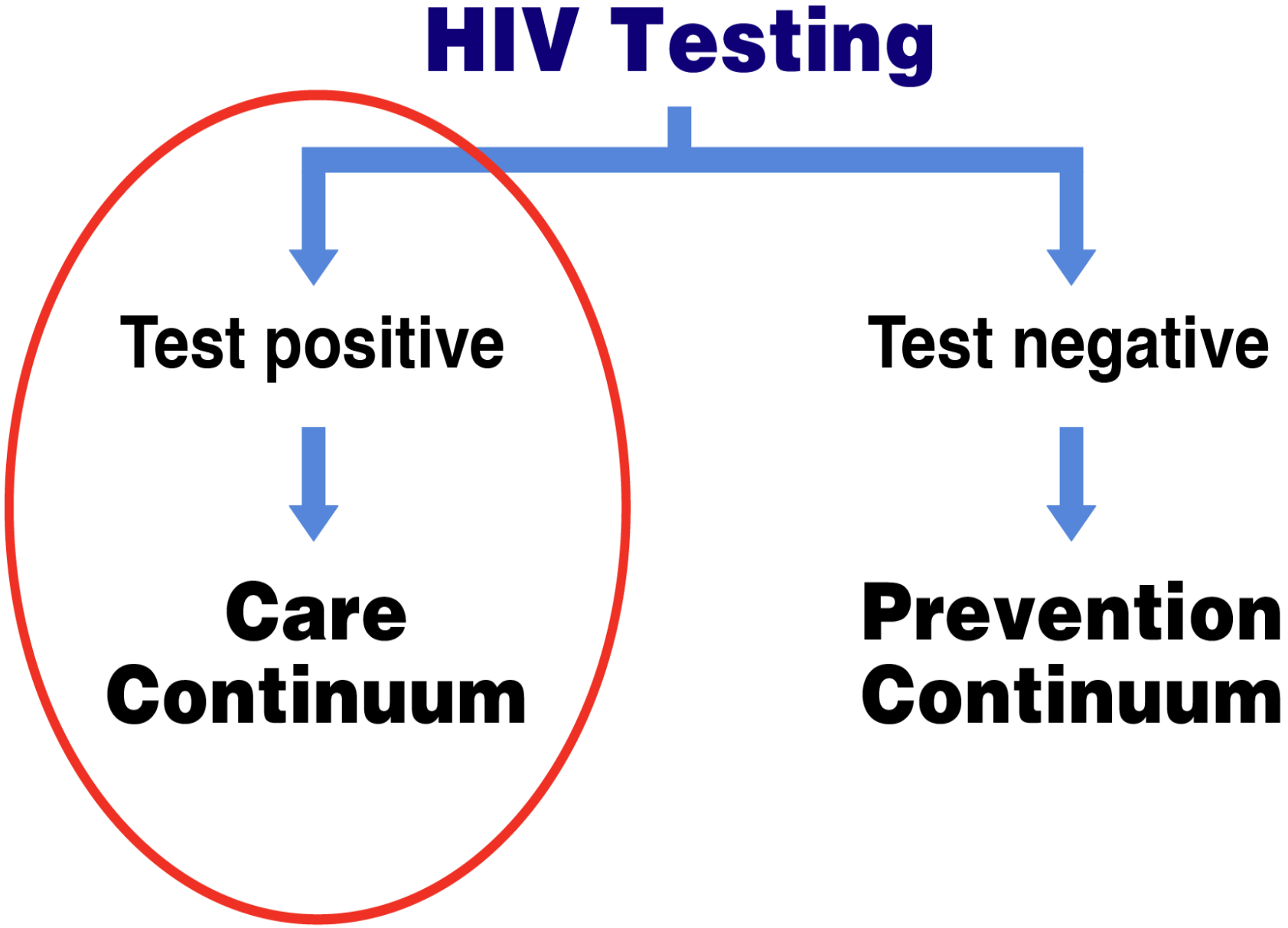
National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

FOR IMMEDIATE RELEASE
November 27, 2016

First New HIV Vaccine Efficacy Study in Seven Years Has Begun

South Africa Hosts Historic NIH-Supported Clinical Trial

- HVTN 702, modified RV144 prime-boost regimen
  - HIV Clade C; ALVAC-HIV + gp120 protein subunit vaccine with MF59 adjuvant
- Target n = 5,400 men and women aged 18-35 years


HIV Testing
Test positive
Test negative
Care Continuum
Prevention Continuum

“90-90-90” Targets for 2020

Diagnosed

On Treatment

Virally Suppressed

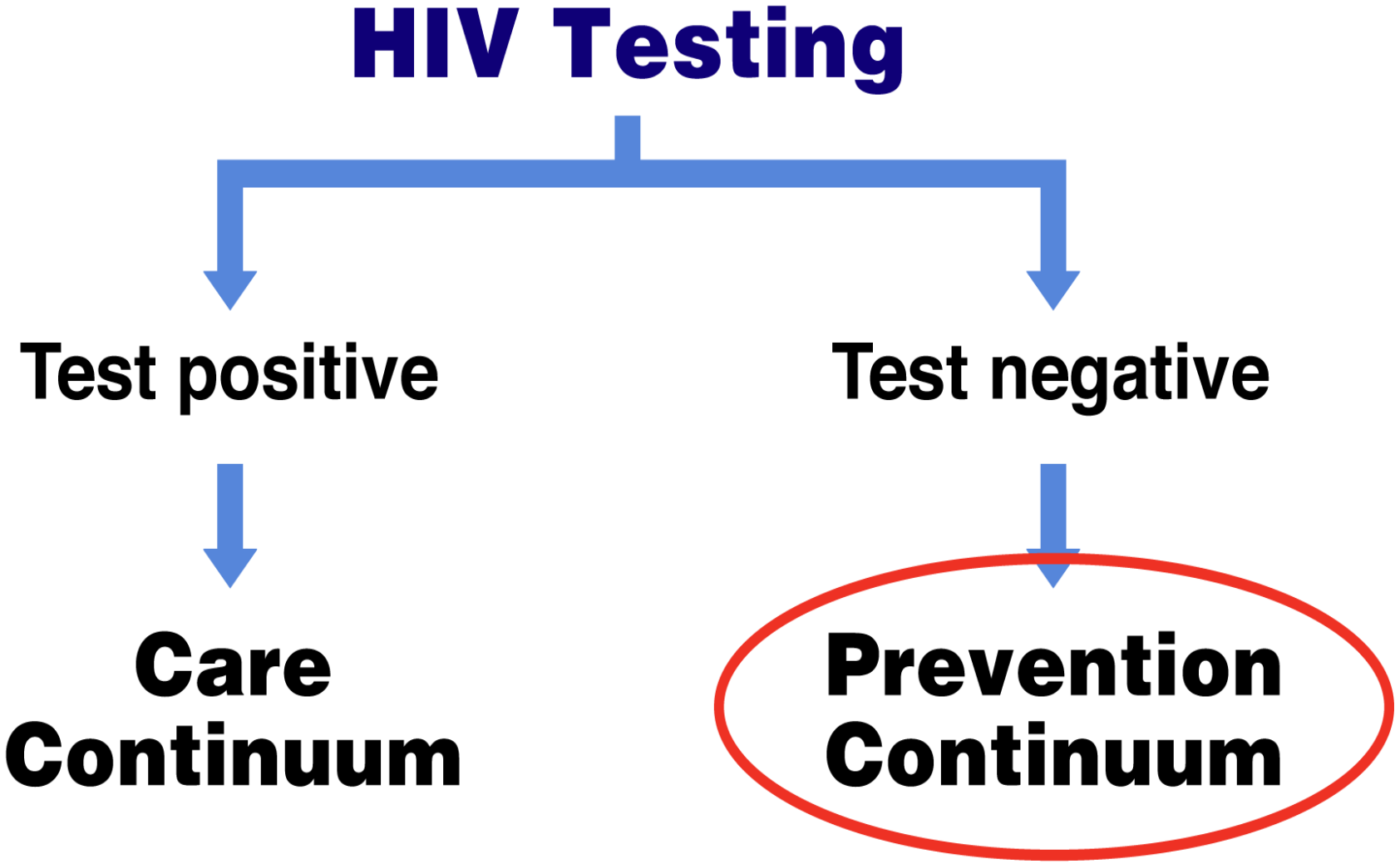
Source: UNAIDS, 2014

Selected Outcomes on the HIV Care Continuum -- United States

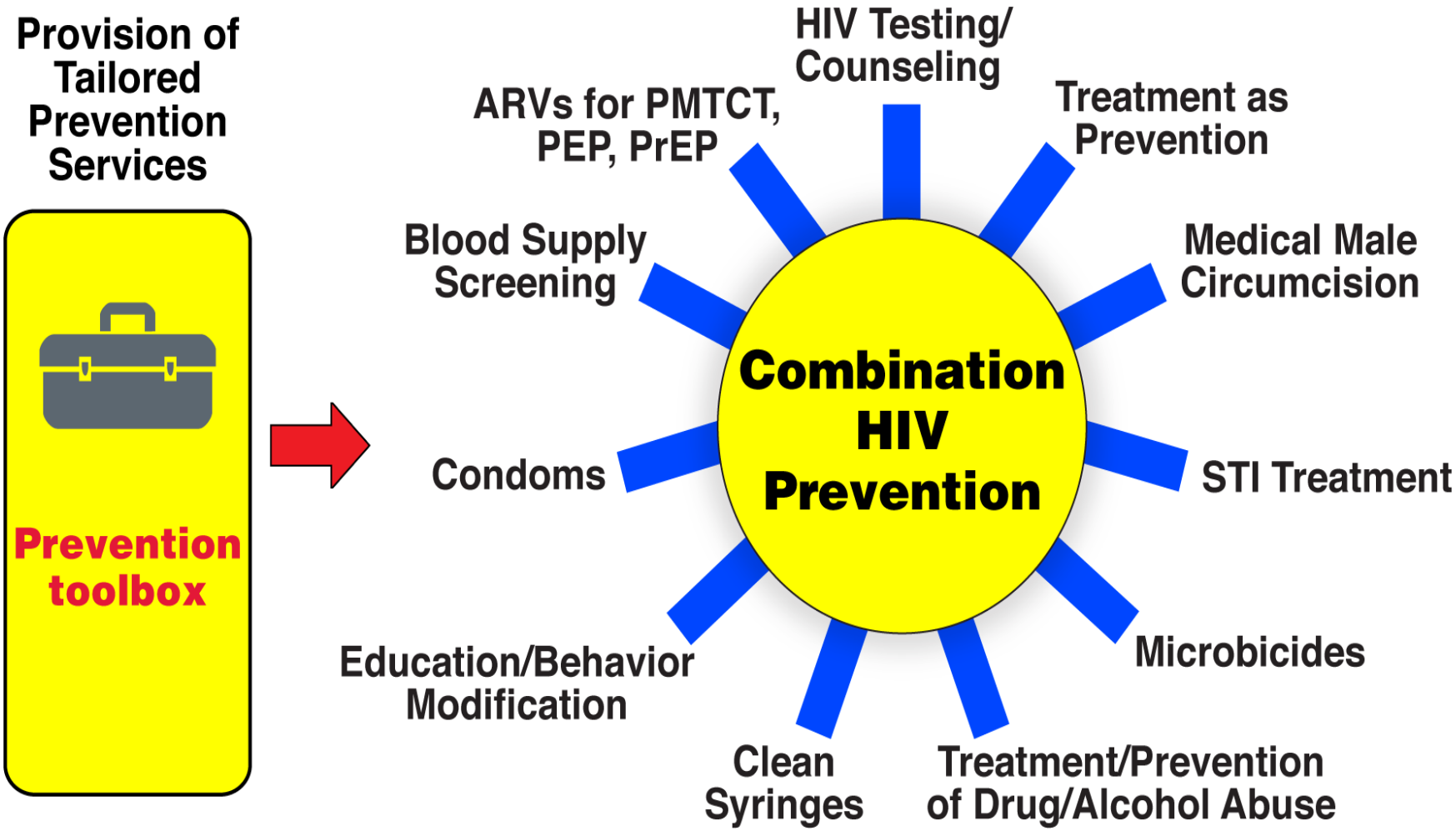
- **Diagnosed** with HIV infection (end-2013) — **87%**
- **Linked** to HIV medical care (2014)* — **75%**
  - ≥1 CD4 or VL test within 1 month of diagnosis
- **Retained** in care (2013)* — **57%**
  - ≥2 CD4 or VL tests ≥3 months apart
- **Virally suppressed** (2013)* — **55%**
  - <200 HIV RNA copies/mL on most recent VL test

*32 states and D.C.

Source: CDC, 2016. Data for people ≥13 years.


HIV Testing
Test positive
Test negative
Care Continuum
Prevention Continuum

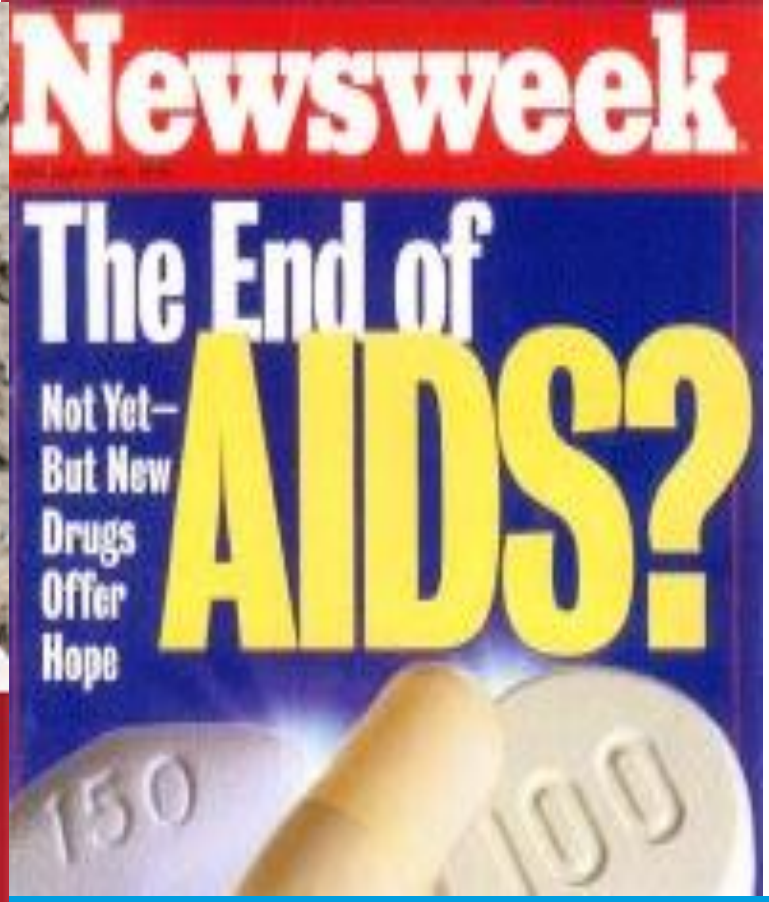
Tailored Prevention Using HIV Prevention Toolkit



Fast-Tracking the End of AIDS

- More **HIV testing** with prompt linkage to care or prevention services
- **Immediate antiretroviral therapy (ART)** for all HIV-infected people for their health and to help prevent ongoing transmission
- **Pre-exposure prophylaxis (PrEP)** and **other HIV prevention services** for individuals at high risk of infection

CAN YOU IMAGINE
THE END OF AIDS?



PEPFAR BLUEPRINT:
CREATING AN AIDS-*free* GENERATION

TOGETHER
WE WILL
END AIDS.

HIV Management
Hepatitis Management

THE NEW YORK COURSE