HIV Prevention Strategies

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Summary of the global HIV epidemic (2017)

	People living with HIV in 2017	People newly infected with HIV in 2017	HIV-related deaths 2017
Total	36.9 million [31.1 million – 43.9 million]	1.8 million [1.4 million – 2.4 million]	940 000 [670 000 – 1.3 million]
Adults	35.1 million [29.6 million – 41.7 million]	1.6 million [1.3 million – 2.1 million]	830 000 [590 000 – 1.2 million]
Women	18.2 million [15.6 million – 21.4 million]	–	–
Men	16.8 million [13.9 million – 20.4 million]	–	–
Children (<15 years)	1.8 million [1.3 million – 2.4 million]	180 000 [110 000 – 260 000]	110 000 [63 000 – 160 000]

Source: UNAIDS/WHO estimates

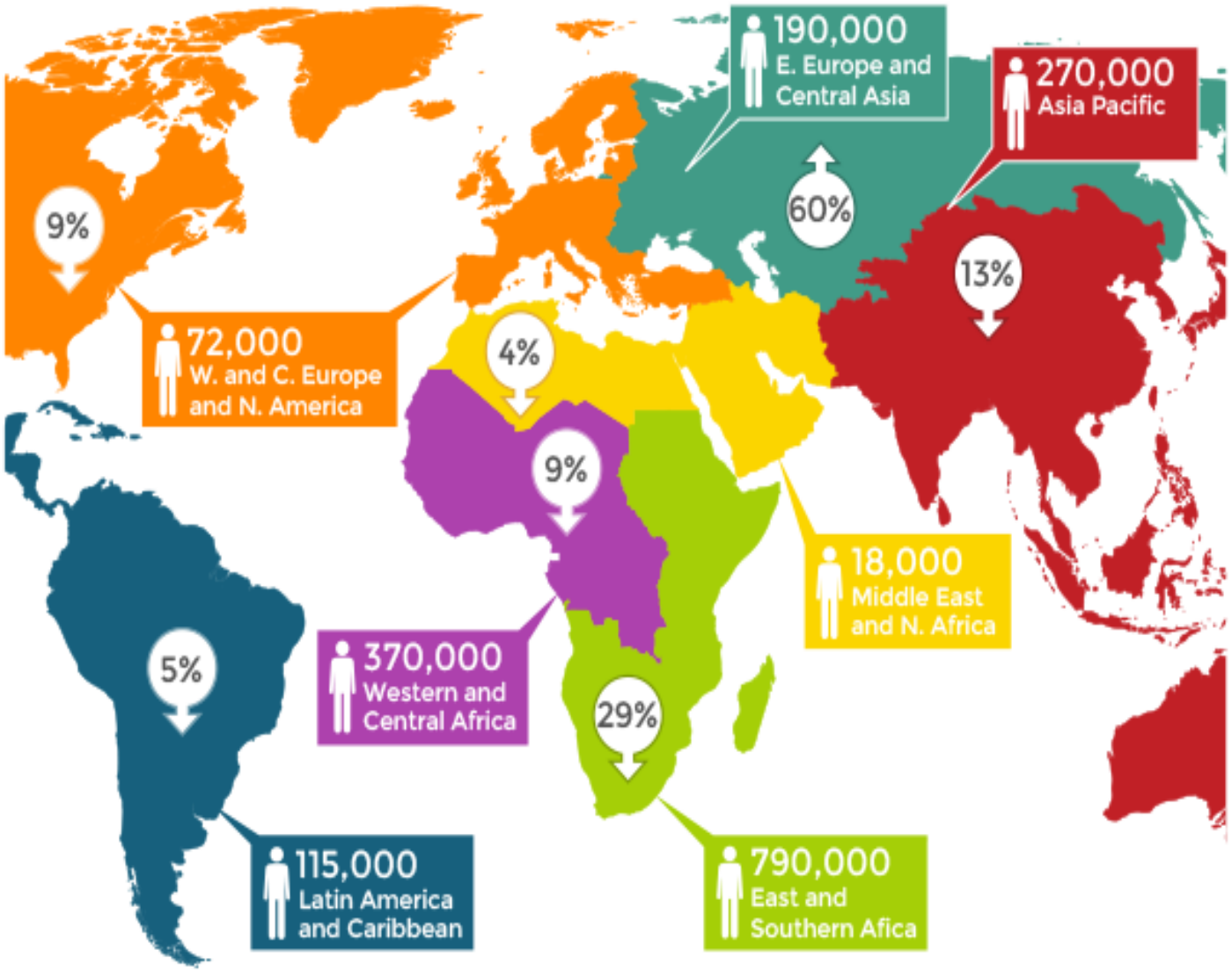
World Health Organization

Number of new HIV infections in 2016 and change since 2010

1.8 million people newly infected in 2016 globally

Decrease in number of new infections across the global population each year since 2010

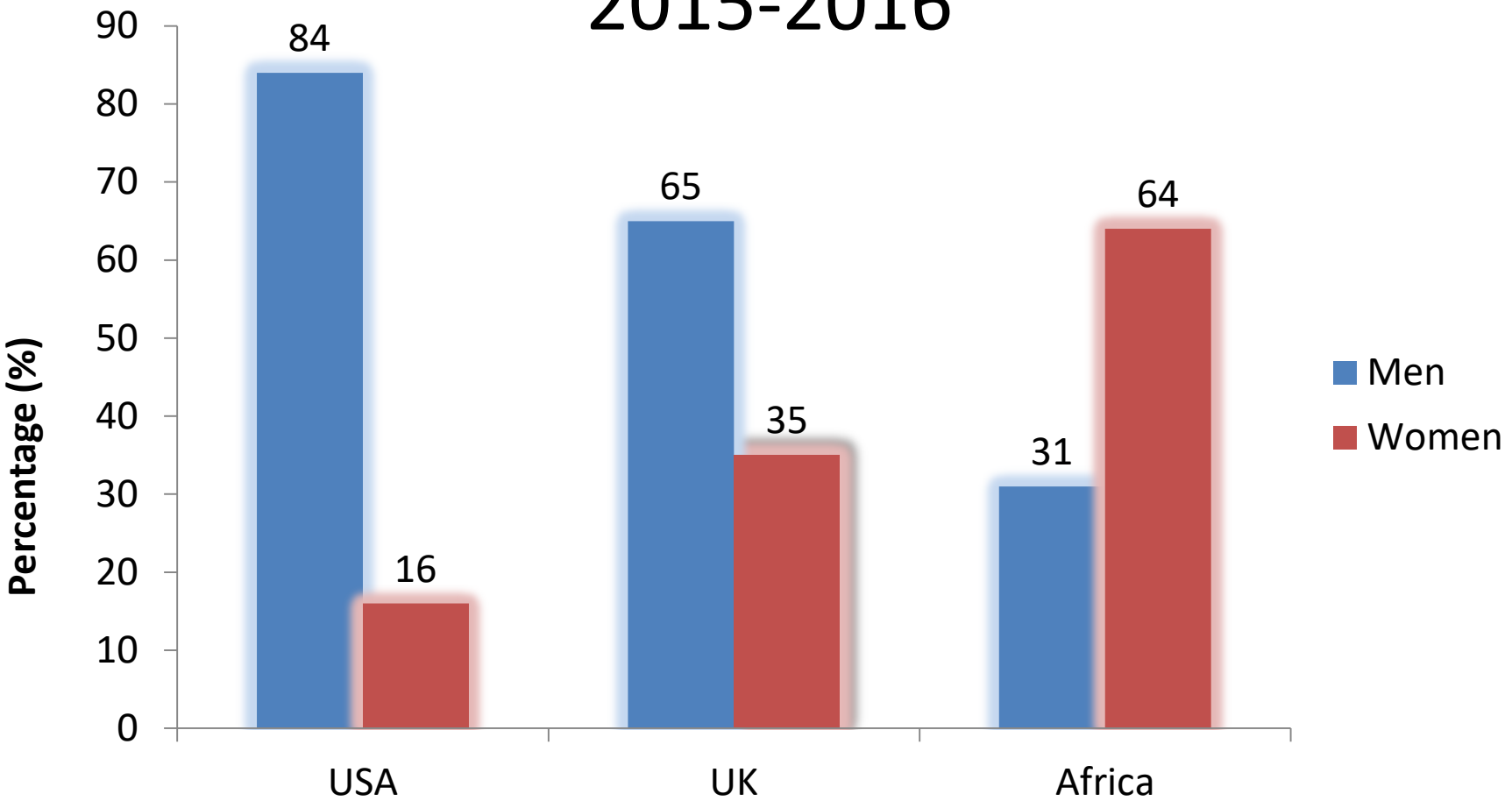
16%



AVERT.org

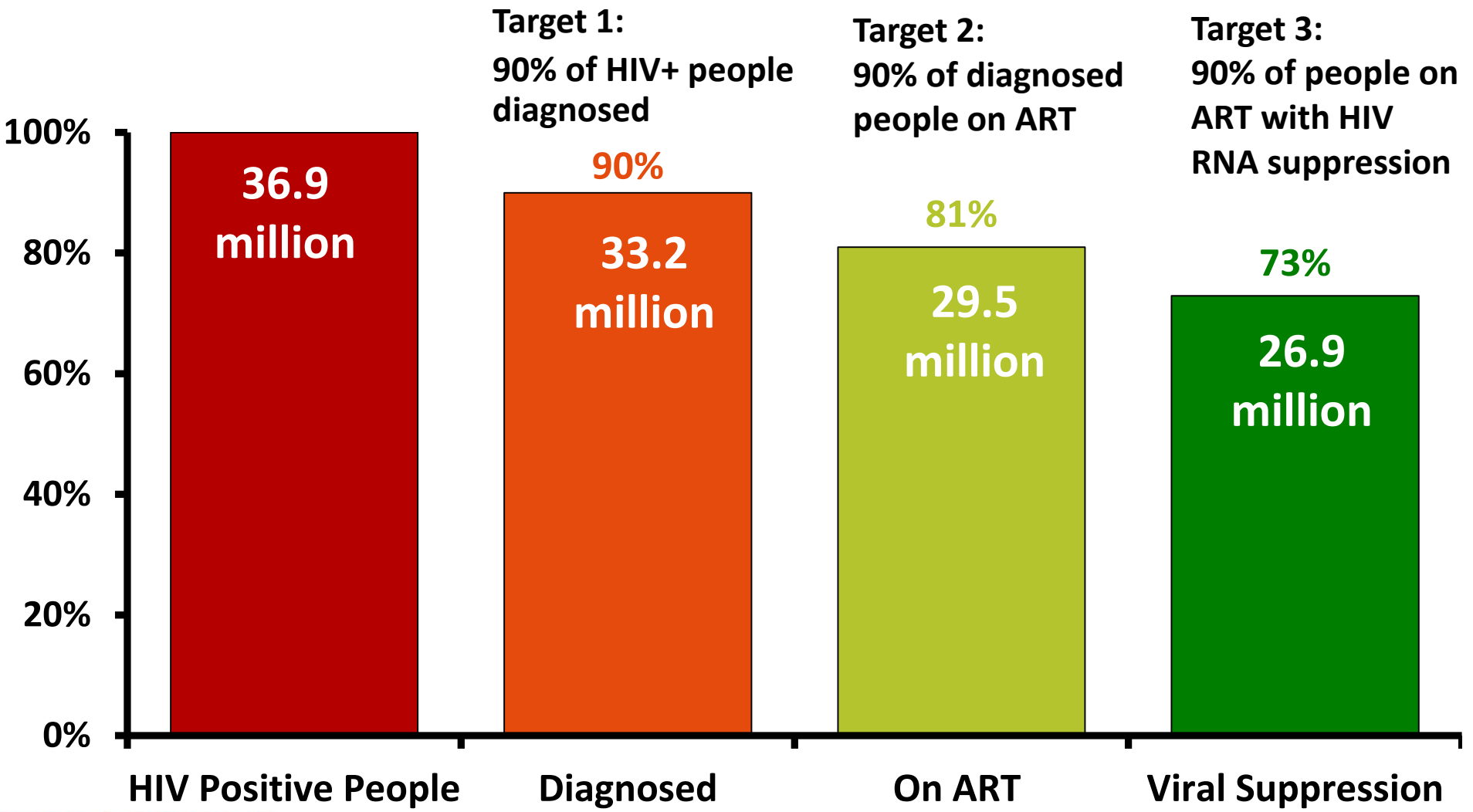
Source: UNAIDS Data 2017

New HIV Diagnoses by Gender 2015-2016



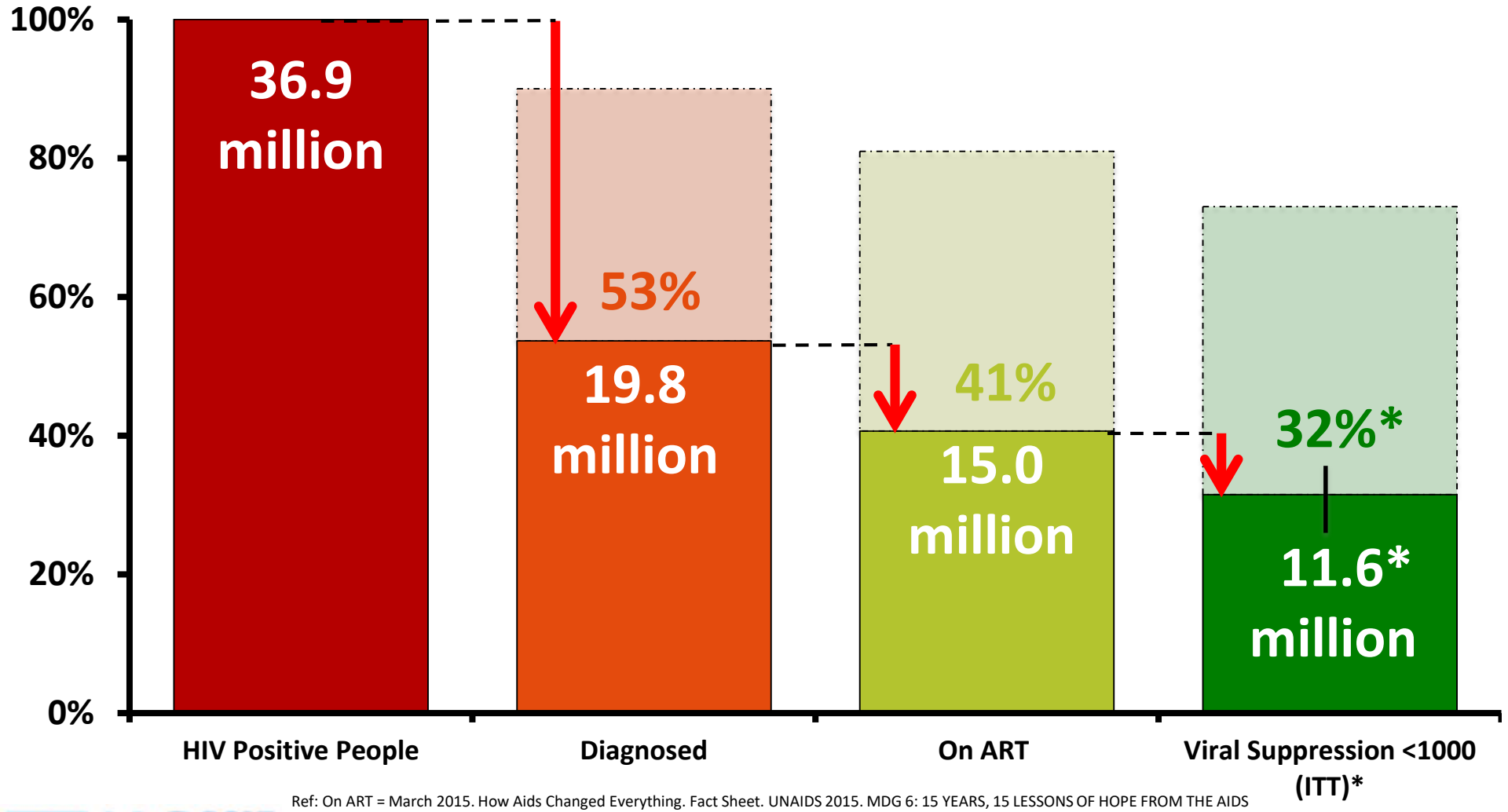
- Young African women are especially at risk, with 59% of new infections among young people aged 15-24 occurring among this group
- There is much more that needs to be done to improve knowledge of HIV and HIV testing among adolescents and young adults

UNAIDS 90-90-90:
HIV Treatment Targets for 2020 with Global Estimates (2014)



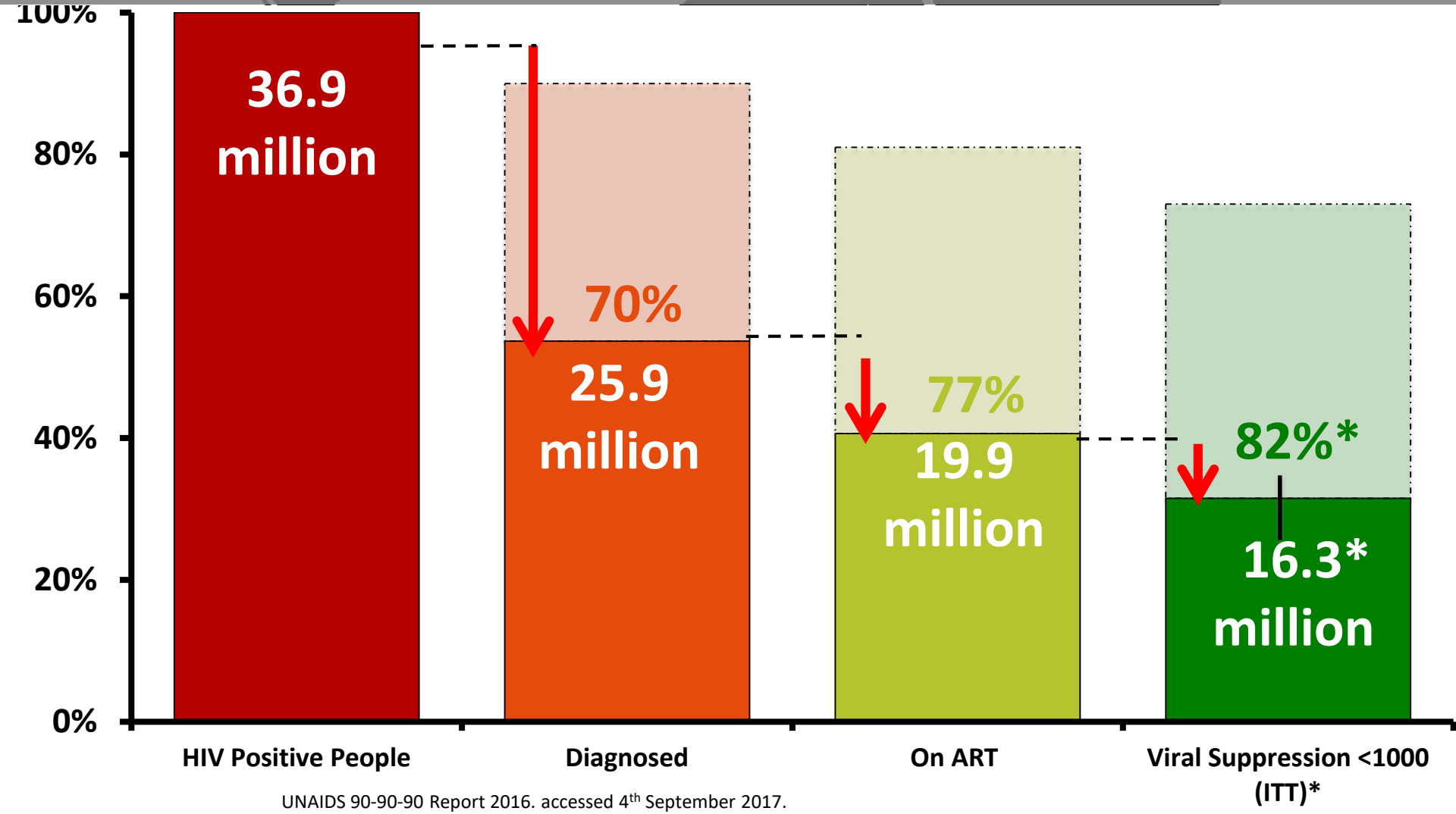
Ref: The Joint United Nations Programme on HIV/AIDS. 90-90-90 An ambitious treatment target to help end the AIDS epidemic. 2014; JC2684 (Numbers as of March 2015) How Aids Changed Everything. Fact Sheet. UNAIDS 2015. MDG 6: 15 YEARS, 15 LESSONS OF HOPE FROM THE AIDS RESPONSE July 2015.

Global Estimates (2014-15) vs the Gap to reach 90-90-90 Targets



Ref: On ART = March 2015. How Aids Changed Everything. Fact Sheet. UNAIDS 2015. MDG 6: 15 YEARS, 15 LESSONS OF HOPE FROM THE AIDS RESPONSE July 2015. * Average viral suppression% Intention to Treat LMIC rate from a Systematic Review by McMahon J. et al. Viral suppression after 12 months of antiretroviral therapy in low-and middle-income countries: a systematic review." *Bulletin of the World Health Organization* 91.5 (2013): 377-385.

Global Estimates (2017) vs the Gap to reach 90-90-90 Targets



UNAIDS 90-90-90 Report 2016. accessed 4th September 2017.

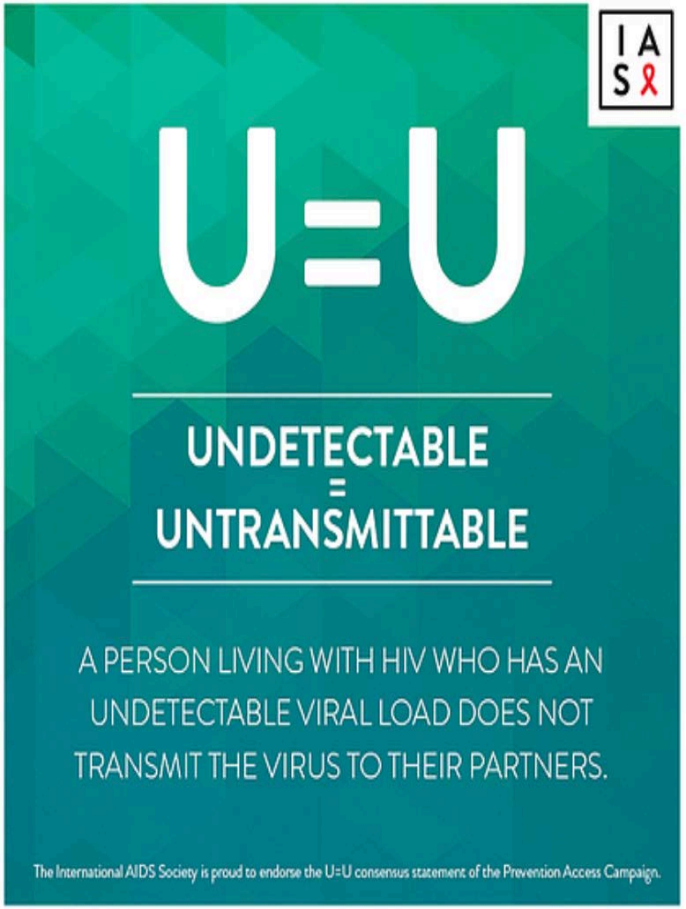
2008

HPTN 052 study – treatment reduced risk of transmission by 96%

2017

Partner study - zero transmissions after >58,000 episodes sex without condoms when viral load was undetectable <200

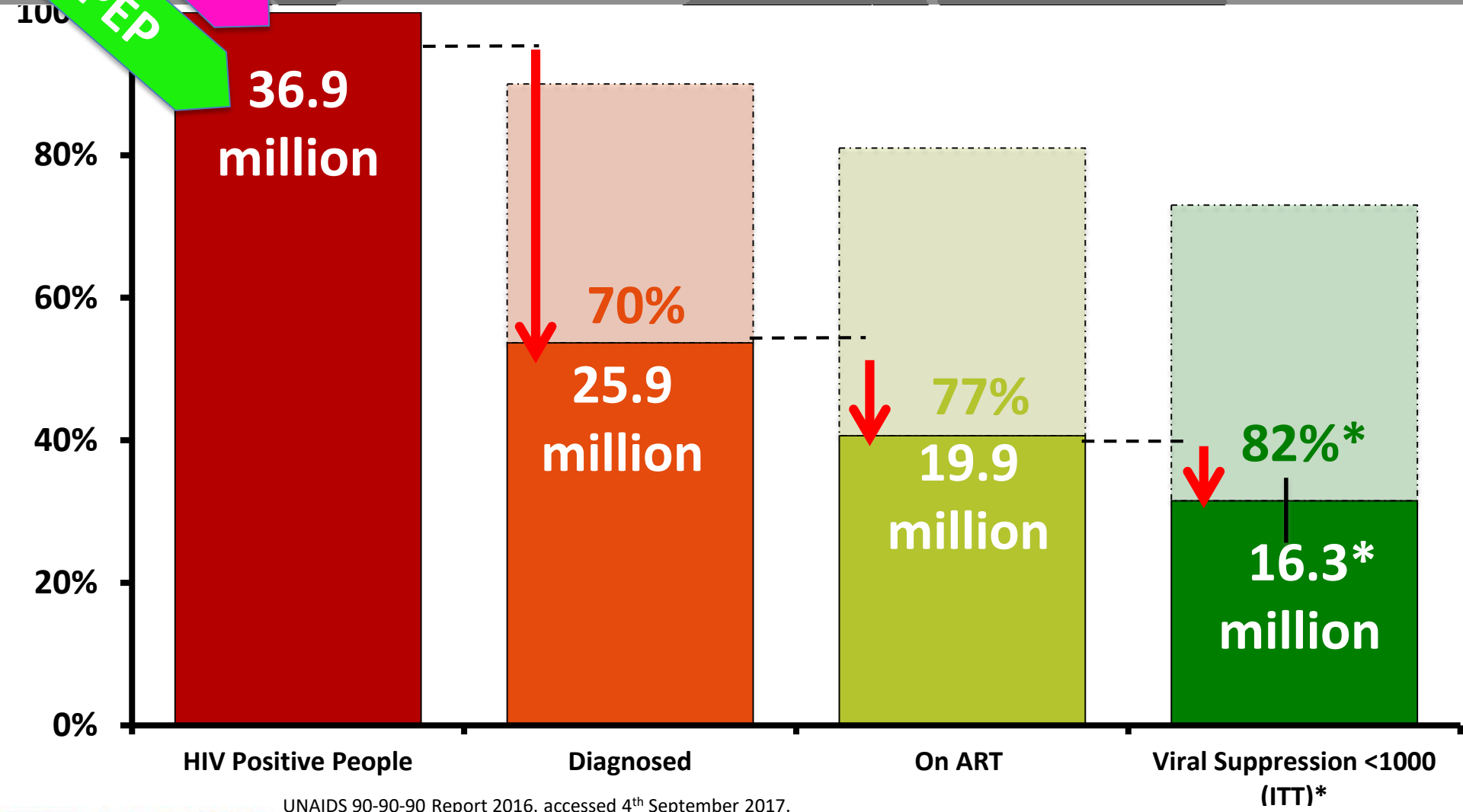
‘I don’t feel like I’m a threat anymore.’ New HIV guidelines are changing lives.



Global Estimates (2017) vs the Gap to reach 90-90-90 Targets

PrEP

PEP



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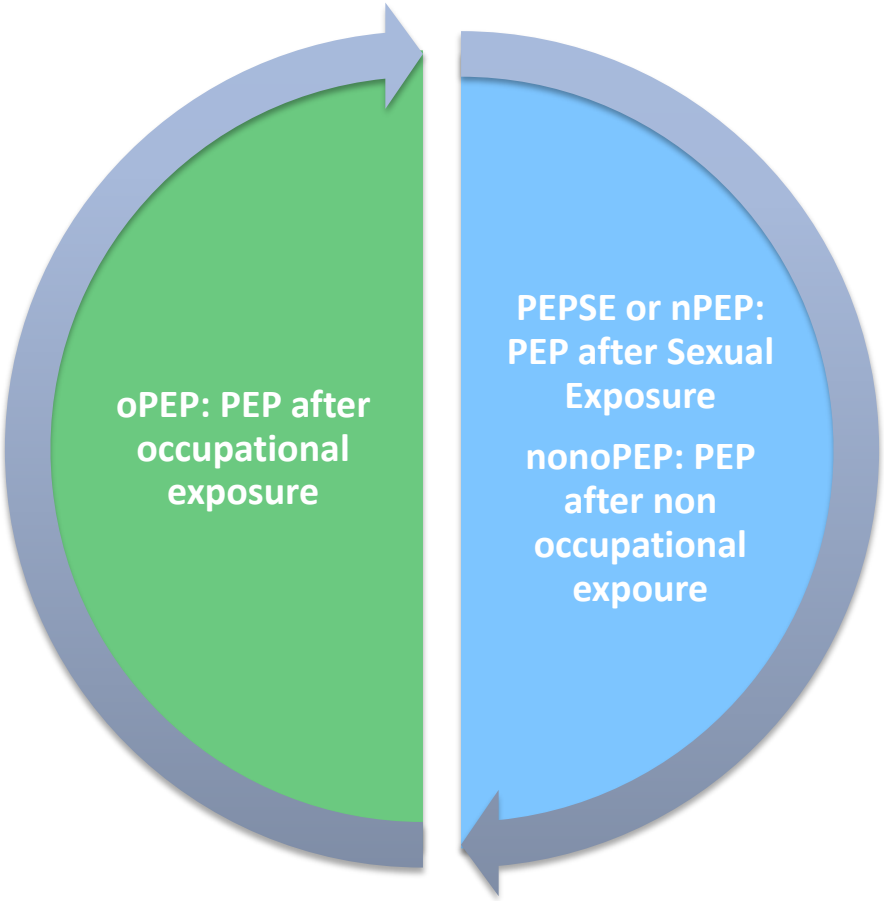
Post Exposure Prophylaxis
PEP

PEP


oPEP: PEP after occupational exposure
PEPSE or nPEP: PEP after Sexual Exposure
nonoPEP: PEP after non occupational expoure

What is considered substantial risk?

Substantial risk

• Exposure of

- Vagina, rectum, eye, mouth or other mucous membrane, non intact skin, or percutaneous

contact

• With

- Blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid

that is visibly contaminated with

blood

• When

- The source is known to be HIV positive and not on treatment or HIV status unknown

Negligible risk

• Exposure of

- Vagina, rectum, eye, mouth or other mucous membrane, intact or non intact skin, or percutaneous contact

• With

- Urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood

• Regardless

- Of the known or suspected HIV status of the source

Risk of exposure

Type of exposure	Estimated risk of HIV transmission
Receptive anal intercourse	1.1 (0.042– 3%)
Receptive vaginal intercourse	0.1 (0.004– 0.32%)
Insertive vaginal intercourse	0.082 (0.011– 0.38%)
Insertive anal intercourse	0.06 (0.06-0.065%)
Receptive oral sex	0.02 (0– 0.04%)
Insertive oral sex	0
Needle-stick injury	0.3 (0.2-0.5%)
Sharing injecting equipment	0.67%
Mucous membrane exposure	0.63 (0.018-3.47%)

In addition to PEP

Education about risk

Hepatitis and HPV vaccinations

Occupational Exposure	Sexual Exposure
Washing of wound with soap and water	Identification of high risk individuals
No squeezing of wound	Use of condoms

Considerations of PEP

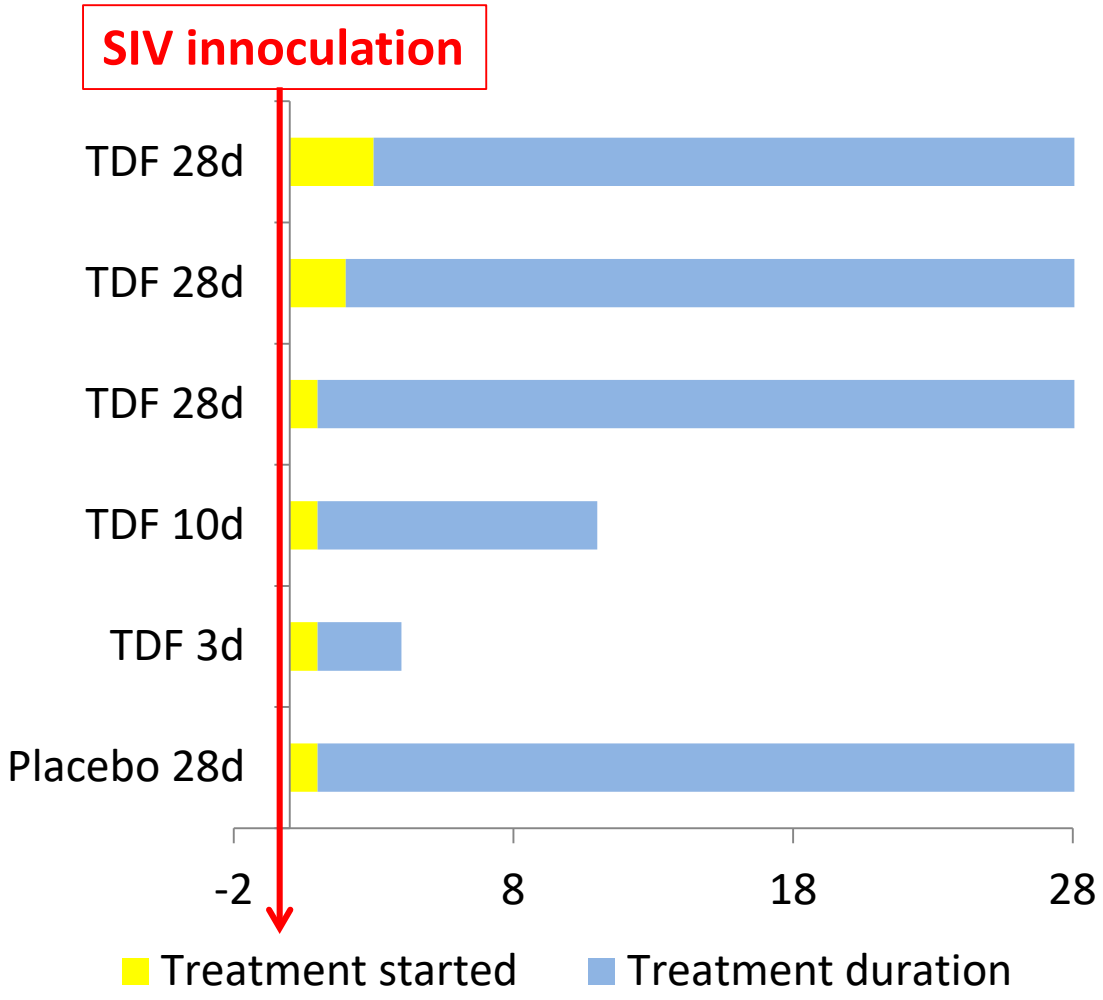
- Adherence
- Side effects
- Missed doses
- Prescribed medication
- Toxicity
- Cost
- Impact on sexual behaviour

PEP

- No randomized, placebo-controlled clinical trial of PEPSE has been conducted
- Data relevant to PEPSE guidelines are available from
  - animal transmission models
  - perinatal clinical trials
  - observational studies of health care workers receiving prophylaxis after occupational exposures
  - observational and case studies of PEPSE use

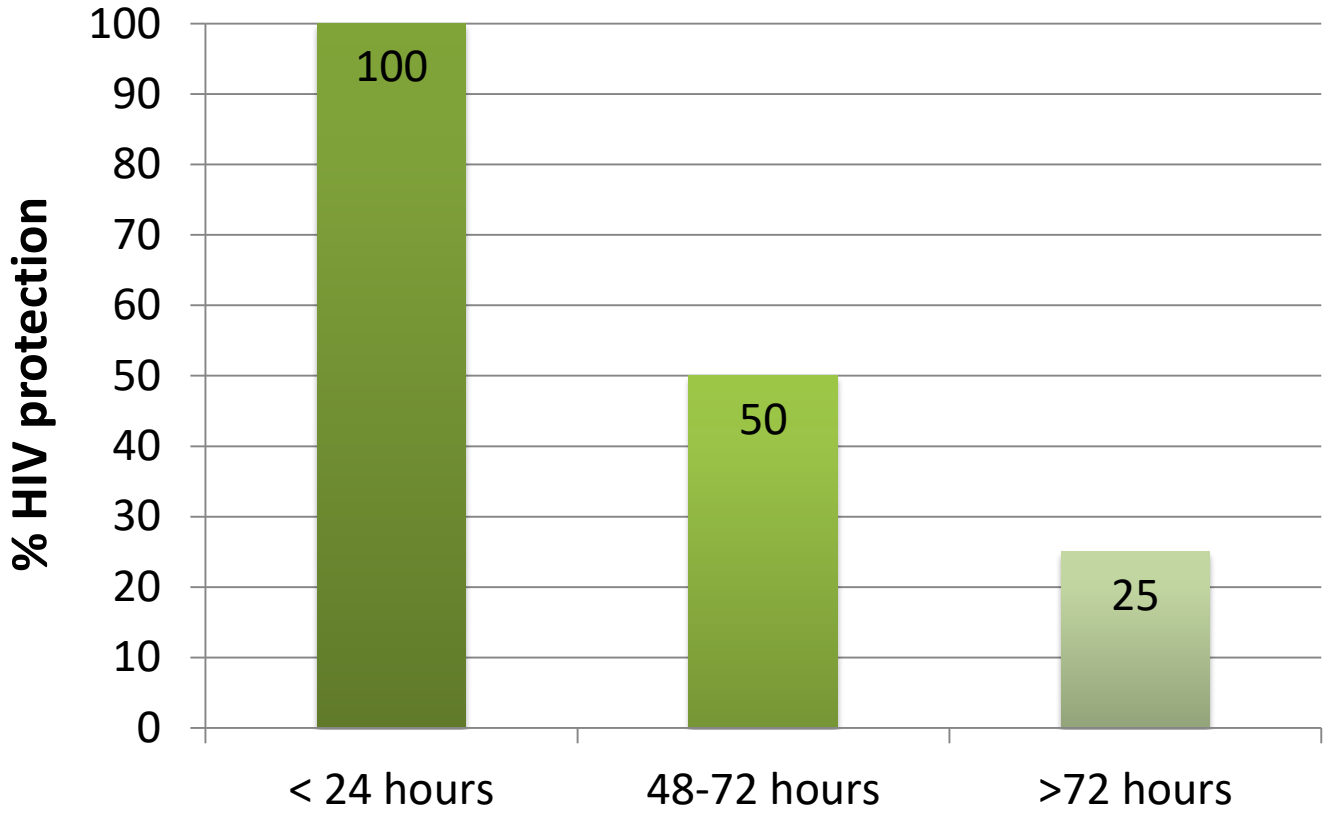
Effectiveness of Tenofovir-DF PEP in Macaques

- Study Features
- N = 24 macaques
- Randomized to 6 treatment arms
- SIV inoculated intravenously
- SIV dose 10x 50% infective dose
- PEP started at 24, 48, or 72 hours
- PEP duration: 3, 10, or 28 days
- PEP regimen: tenofovir-DF SQ
- Analyzed for antibody and viremia



Tsai CC, Fransen K, Diallo MO et al. J Virol 1998;72:4265–73

Macaque animal models – timing of PEP



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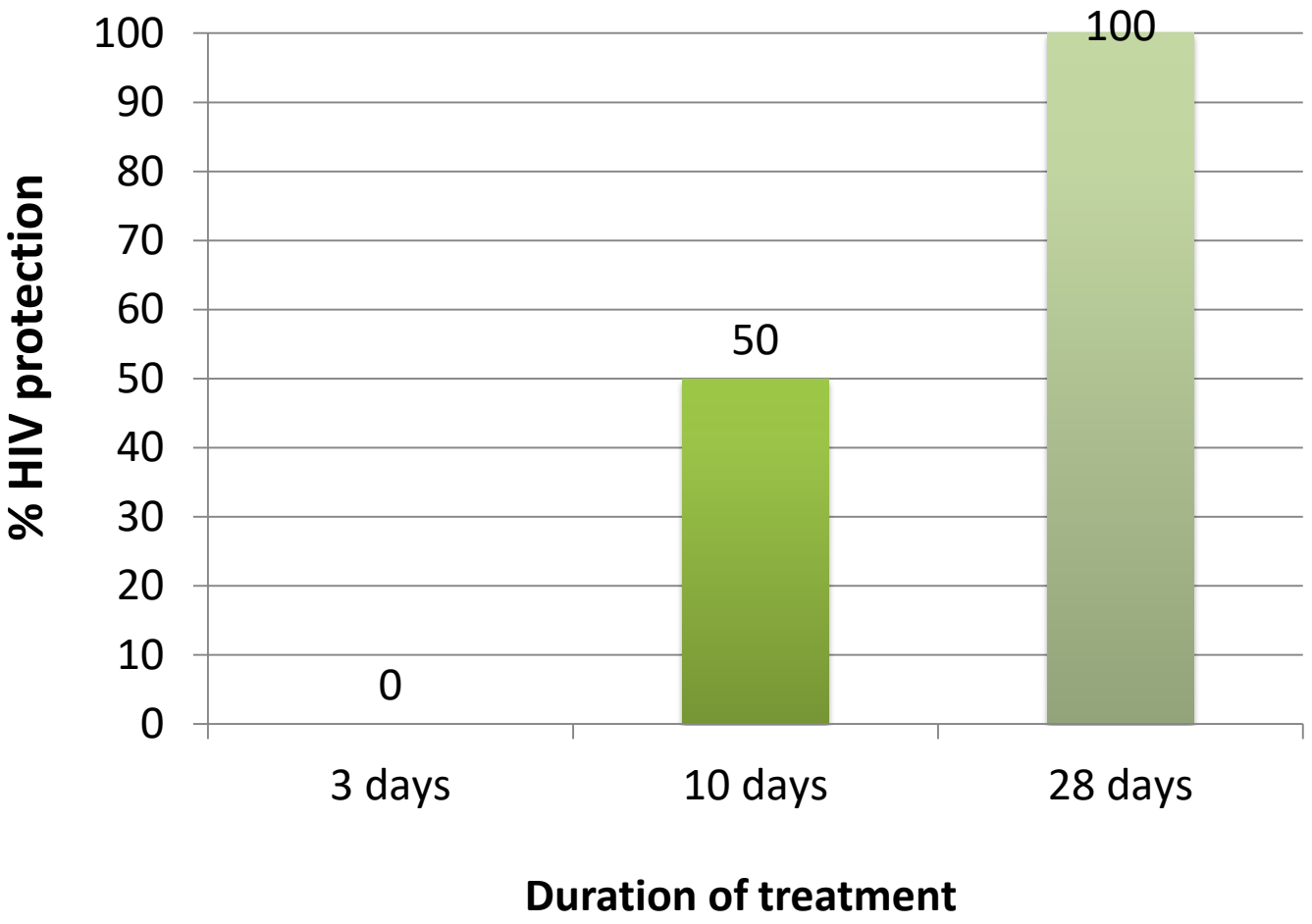
Macaque animal models – duration of PEP



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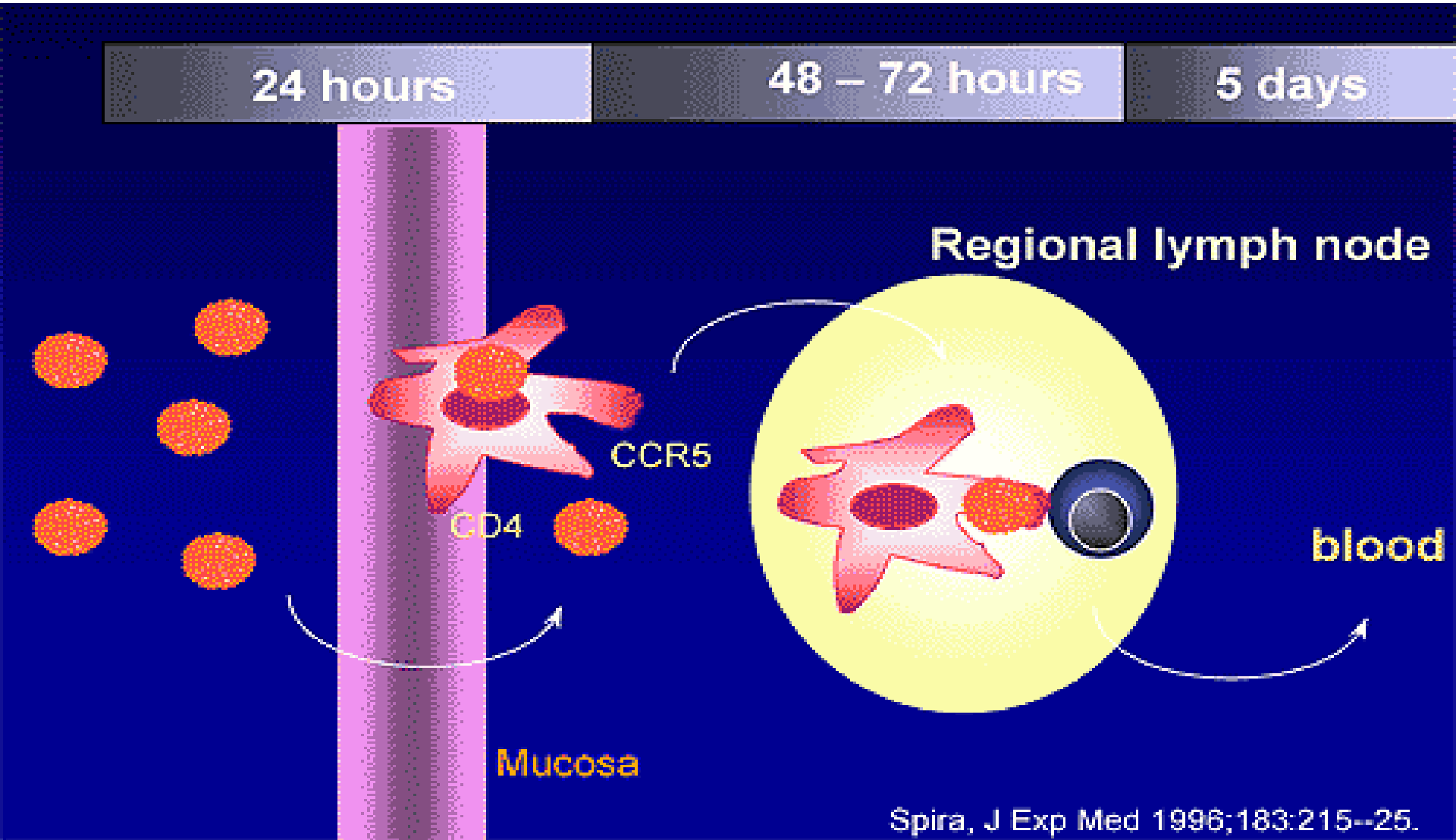
Dynamics following exposure to HIV



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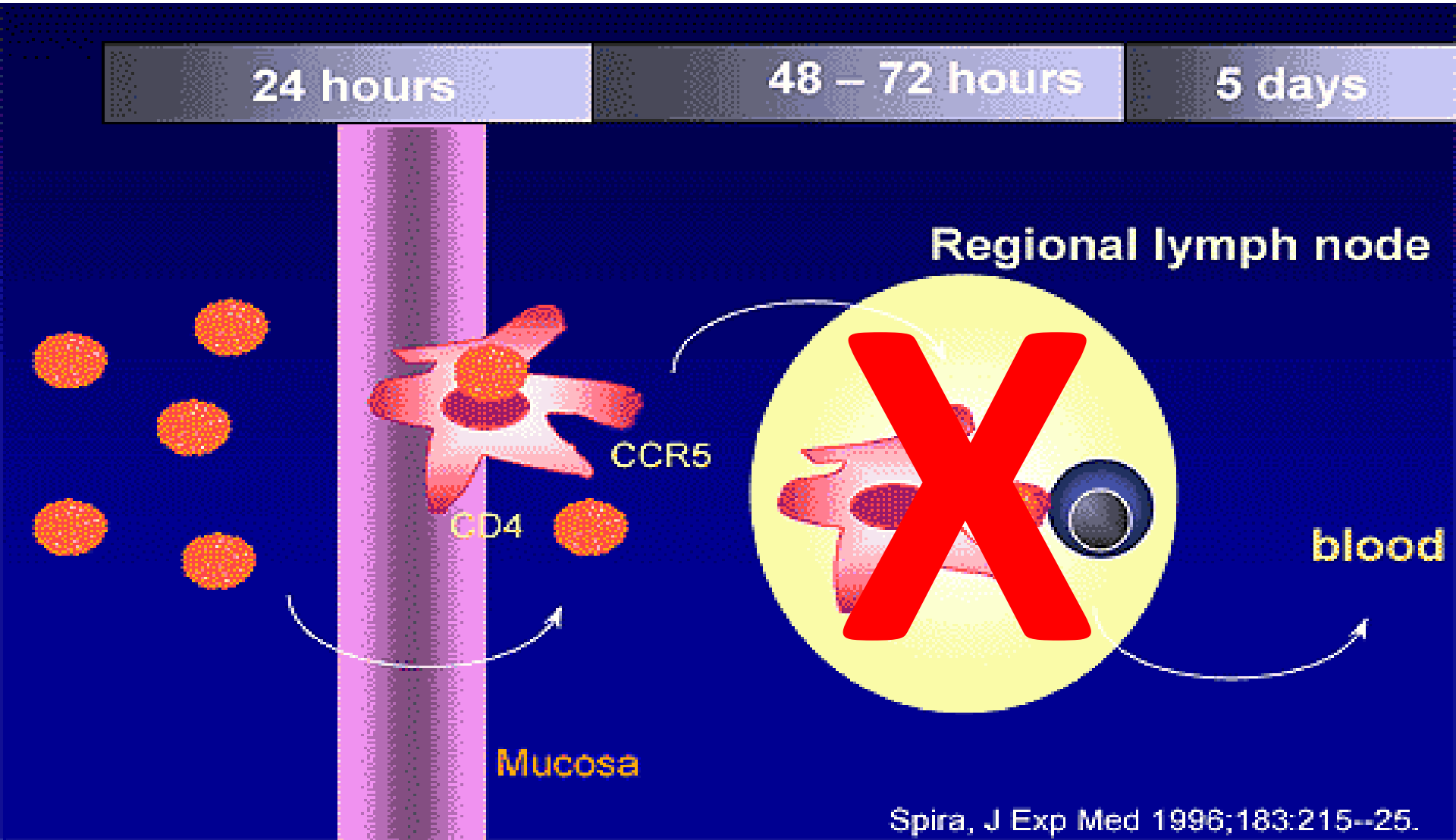
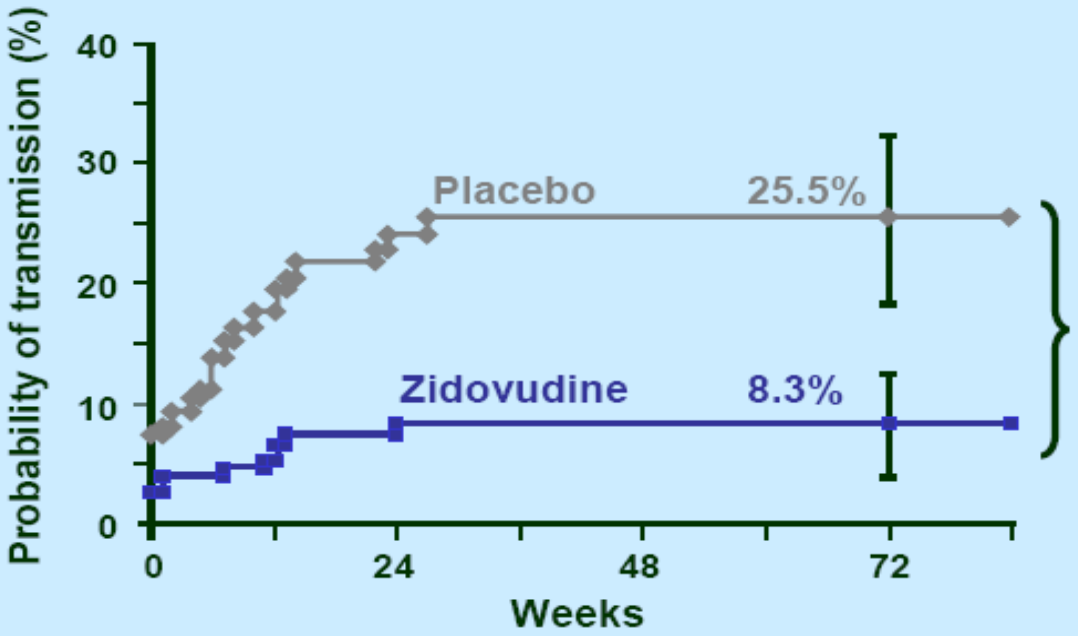


Zidovudine significantly reduces MTCT

PACTG 076 Study



Placebo (n)	183	84	42	37
Zidovudine (n)	180	105	51	43

Connor EM *et al. NEJM* 1994;331:1173–1180

Occupational PEP (oPEP)

- A retrospective case-control study
- Zidovudine (ZDV) prophylaxis vs nothing for health care workers with percutaneous exposure to HIV
- Demonstrated an 81% (95% CI = 48%–94%) reduction in the odds of HIV transmission among who received oPEP
- The first study to describe the efficacy of oPEP

Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *New Engl J Med.* 1997;337(21):1485-1490.

MSM PEPSE study Brazil

- 2-year prospective study in Brazil
- 200 seronegative MSM at high risk of HIV were provided with
  - education regarding PEPSE
  - a 4-day starter pack with instructions to initiate its use for a suspected eligible exposure
  - a follow-up 24-day pack (to complete a 28-day course) but only for those men with eligible exposures
  - 68/200 MSM initiated PEPSE
  - Adherence to PEPSE medications was estimated on the basis of questions at the 28-day visit and remaining pill counts
  - The entire 28-day PEPSE regimen was completed by 89% of men with eligible exposures including 1 participant who seroconverted
  - Ten of 11 seroconversions occurred among men who did not initiate PEPSE despite risk exposure

Schechter M, do Lago RF, Mendelsohn AB, et al. Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV.
J Acquir Immune Defic Syndr. 2004;35(5

Tenofovir-Emtricitabine (TDF-FTC) plus Raltegravir BD for PEPSE

- 100 participants enrolled at Fenway Health
- 98% male, 83% MSM, mean age 33 yrs
- Prescribed TDF-FTC plus raltegravir for PEPSE
- 85/100 had 3-months follow-up
- None were HIV infected
- 57% finished the regimen as prescribed
- Comparable to historic controls (AZT-3TC or TDF-FTC + PI/r)
- Biggest limitation = missed second dose of raltegravir by 27%
- Well tolerated and fewer side effects than historic controls

Mayer K, et al. J Acquir Immune Defic Syndr. 2012;59(4):354-359.

PEPSE and sexual behaviour

- UK nonoPEP Study:
  - 77% reported reduced high-risk activity with casual partners
- Brazil:
  - Baseline: 57% reported high-risk behaviour; 24 months: 40%
- San Francisco:
  - 74% reported reduction in high-risk behaviour; 10% reported an increase

Benn et al, BHIVA 2006; Schecter et al, JAIDS 2004; Roland et al, CID 2005

PEPSE failure in Men who have Sex with Men (MSM)

- 49 seroconversions were reported after PEPSE use based on case reports and 6 studies of 1535 MSM

- Common findings
  - Ongoing sexual risk
  - Seroconversion occurred long after PEPSE was completed: 91-168 days and >180 days
  - Already HIV positive at presentation

Terzi R, Niero F, Iemoli E, Capetti A, Coen M, Rizzardini G. Late HIV seroconversion after non-occupational postexposure prophylaxis against HIV with concomitant hepatitis C virus seroconversion. *AIDS.* 2007;21(2):262-263.
Donnell D, Mimiaga MJ, Mayer K, Chesney M, Koblin B, Coates T. Use of non-occupational post-exposure prophylaxis does not lead to an increase in high risk sex behaviors in men who have sex with men participating in the EXPLORE trial. *AIDS Behav.* 2010;14(5):1182-1189..
Sonder GJB, Prins JM, Regez RM, et al. Comparison of two HIV postexposure prophylaxis regimens among men who have sex with men in Amsterdam: adverse effects do not influence compliance. *Sex Transm Dis.* 2010;37(11):681-686.
16.):519-525.

EACS PEP Guidelines

- Rapid testing of the source person for HCV and HIV (if HIV-status unknown) recommended
- If source person HIV-positive on ART, order resistance testing if HIV-VL detectable
- Individualise PEP according to the source's treatment history and previous resistance tests
- For sexual exposure, if HIV-positive source has documented undetectable HIV-VL, PEP is no longer recommended
- PEP to be started ideally < 4 hours after the exposure and no later than 48/72 hours
- Duration of PEP: 4 weeks
- PEP regimens: TDF/FTC (alternative: ZDV/3TC) + RAL bid, or + DRV/r qd or + LPV/r bid. TDF/FTC + DTG qd may be also considered as an alternative.

- Full sexual health screen in case of sexual exposure
- Follow-up: HIV serology + HBV and HCV, pregnancy test (women) within 48 hours of exposure
- Re-evaluation of PEP indication by HIV expert within 48-72 hours
- Assess tolerability of PEP regimen
- Transaminases, HCV-PCR and HCV serology at month 1 if source person HCV-positive (observed or suspected)
- Repeat HIV serology after 2 and 4 months, syphilis serology after 1 month if sexual exposure

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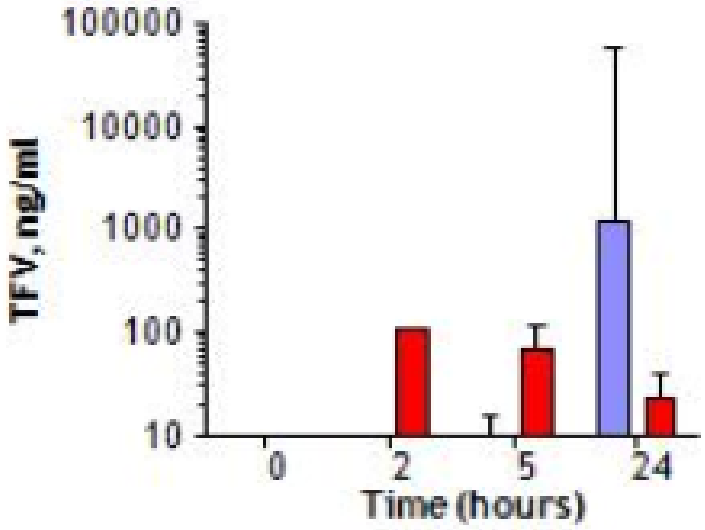
Assess need for PrEP

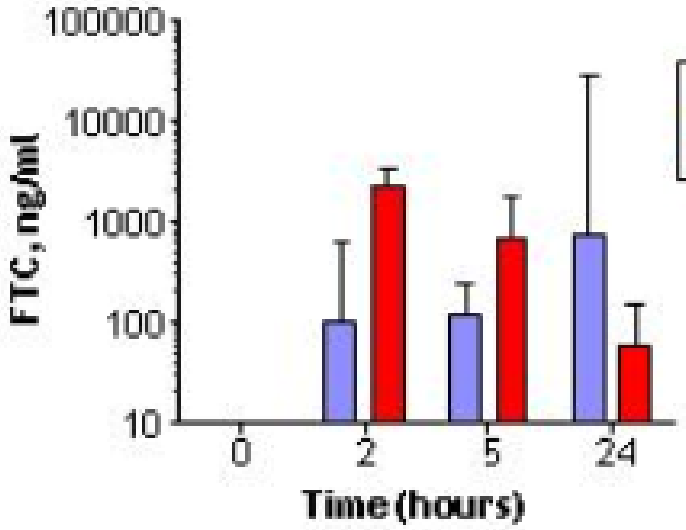
Pre Exposure Prophylaxis
PrEP

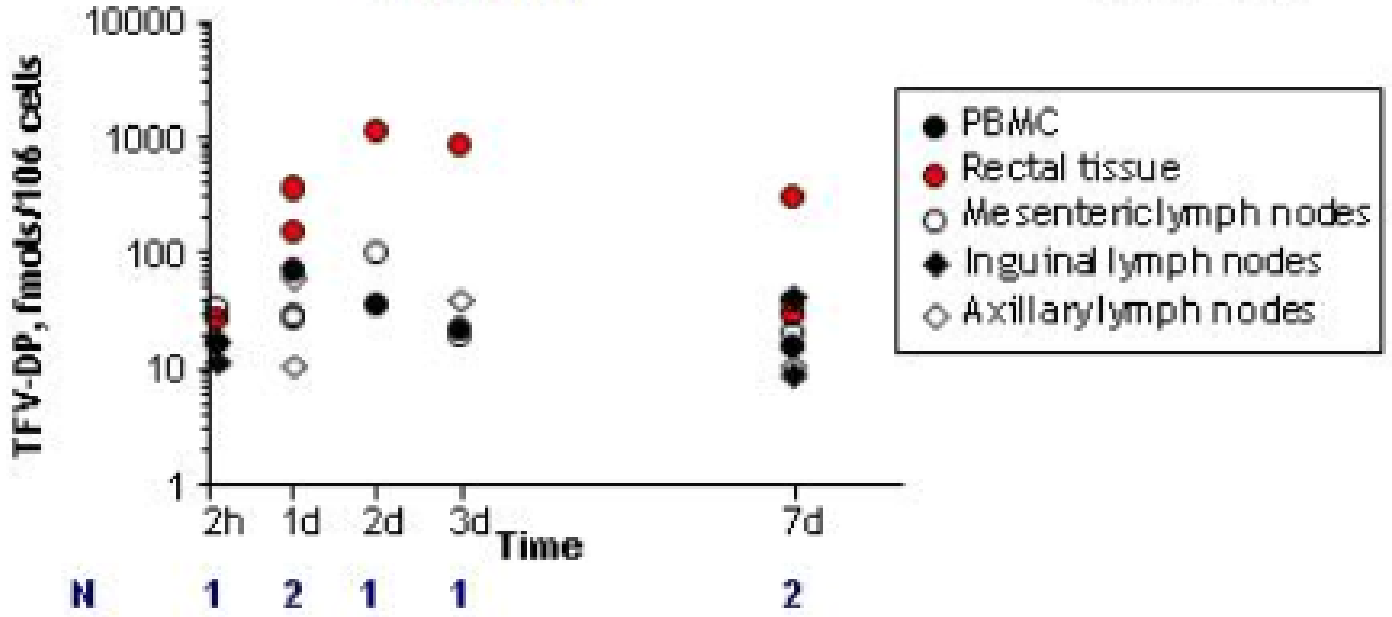
How do we know oral PrEP is effective?

- Animal studies
- Major PrEP trials
  - PROUD
  - Ipergay
  - iPREX OLE

Local and systemic drug concentrations after oral administration of Truvada







Efficacy of intermittent PrEP with Truvada in the repeat low-dose macaque model: design

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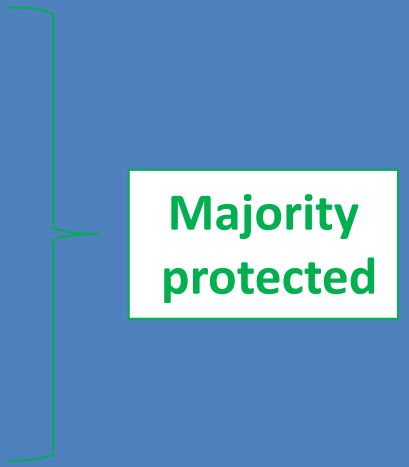

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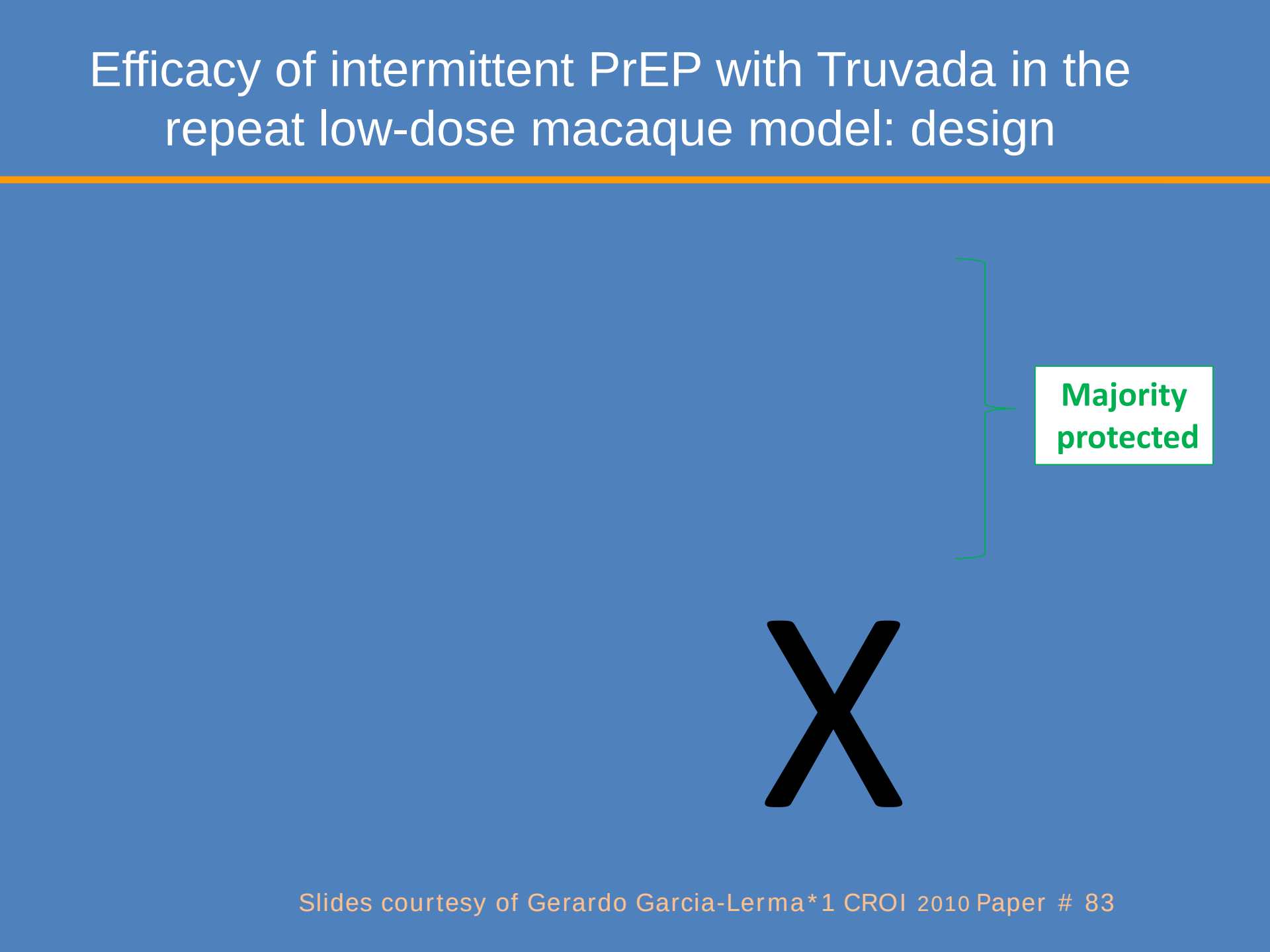
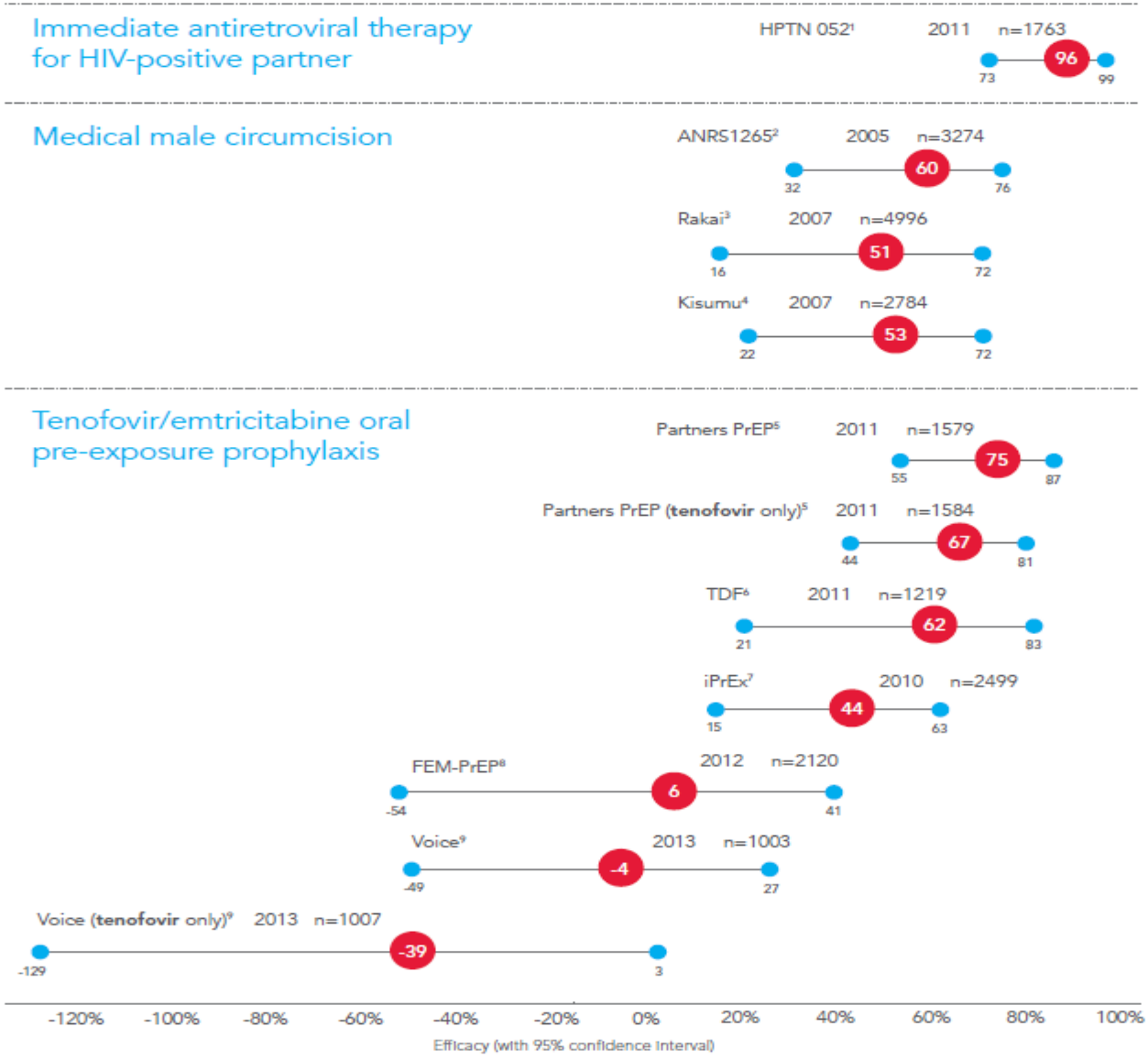


EFFICACY OF AVAILABLE BIO-MEDICAL PREVENTION INTERVENTIONS DERIVED FROM RANDOMIZED CLINICAL TRIALS. MODIFIED WITH PERMISSION FROM MARRAZZO ET AL, JAMA, IN PRESS, 2014.*



Sources: 1. Cohen M, Chen Y, McCauley M, Gamble T, Hosseinipour MC, et al. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med, 2011;365:493–505. DOI:10.1056/NEJMoa1105243 2. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. (2005)

Pragmatic Open-Label Randomised Trial of Pre-Exposure Prophylaxis: the PROUD study

PROUD

Public Health England

MRC Clinical Trials Unit

MSM reporting UAI last/next 90 days

Truvada **NOW**

N= 267

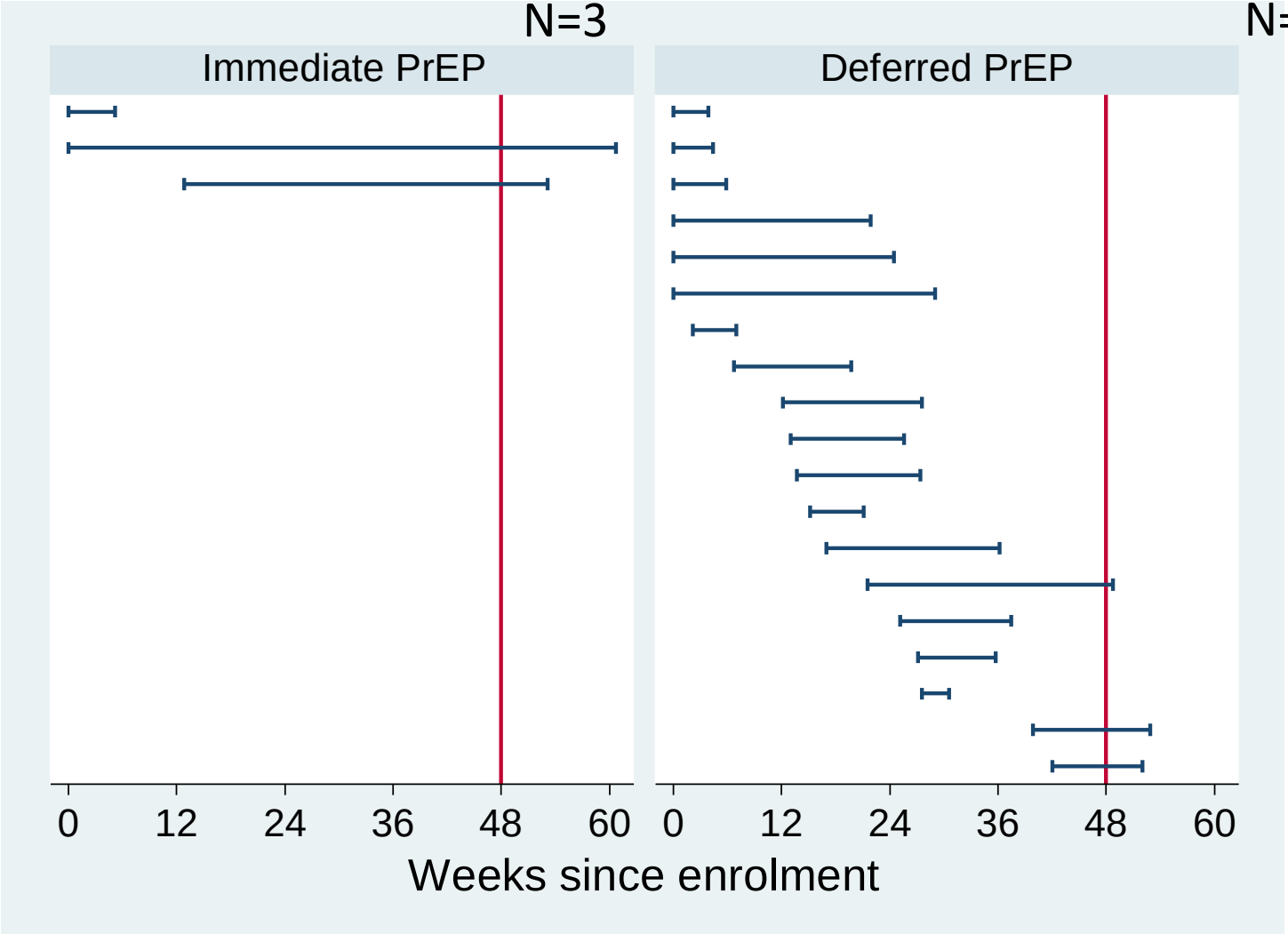
Truvada **AFTER 12M**

N=256

Follow **3 monthly** for up to 24 months

Main endpoints in Pilot: HIV infection in first 12 months

PROUD: new HIV infections

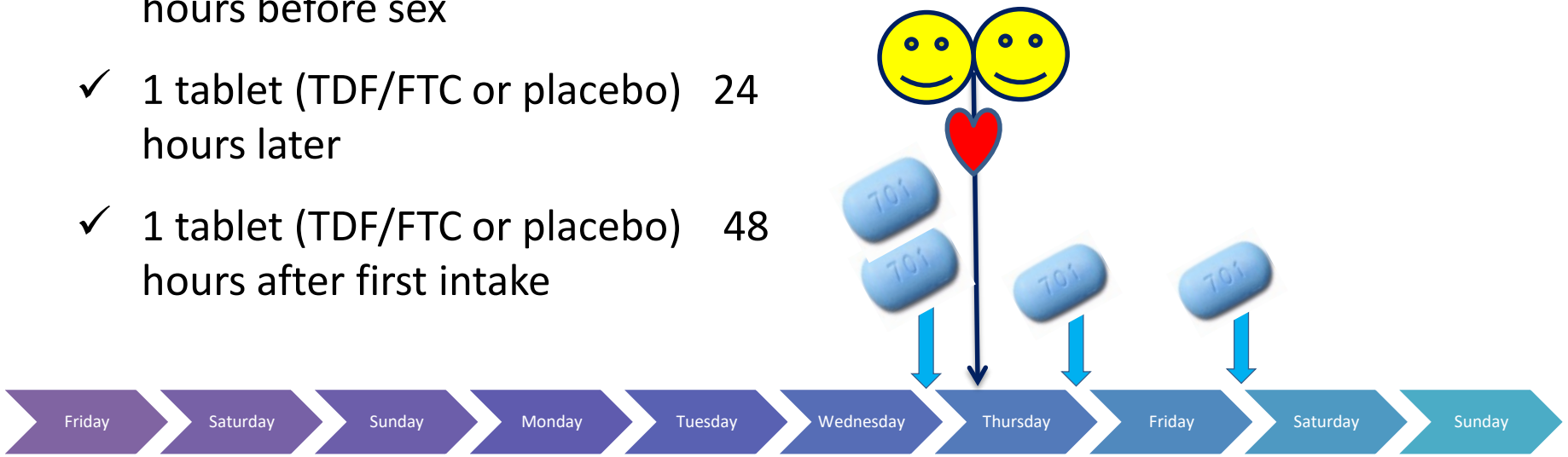


86% reduction in HIV Transmission

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

Ipergay : Event-Driven iPrEP

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake



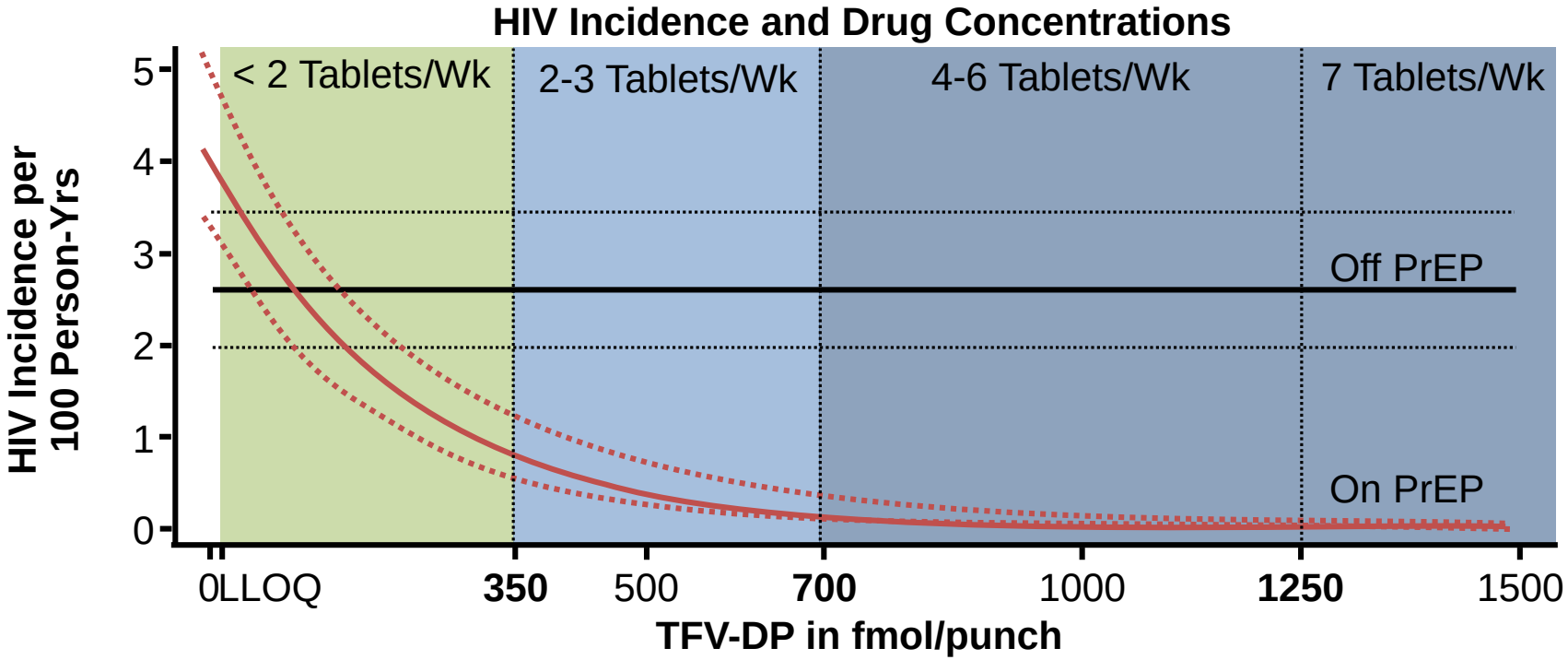
86% reduction in HIV infections in PrEP arm

Drug Detection in Patients Assigned to Daily TDF/FTC and Efficacy

Study	% Adherence *	Efficacy (mITT)	Adherence-Adjusted Efficacy
Partners PrEP	81%	75%	90% (58-98)
CDC TDF2	80%	62%	84% (NS)
Bangkok TDF study	66%	49%	70% (2-91)
iPrEx	51%	42%	92% (40-99)
FEM-PrEP	26%	6%	NA
VOICE	29%	- 4%	NA

* proportion of participants with drugs detectable in plasma and who remained free of infection in the active PrEP arms

iPrEX OLE: 100% Adherence With Daily PrEP Not Required to Attain Full Benefit

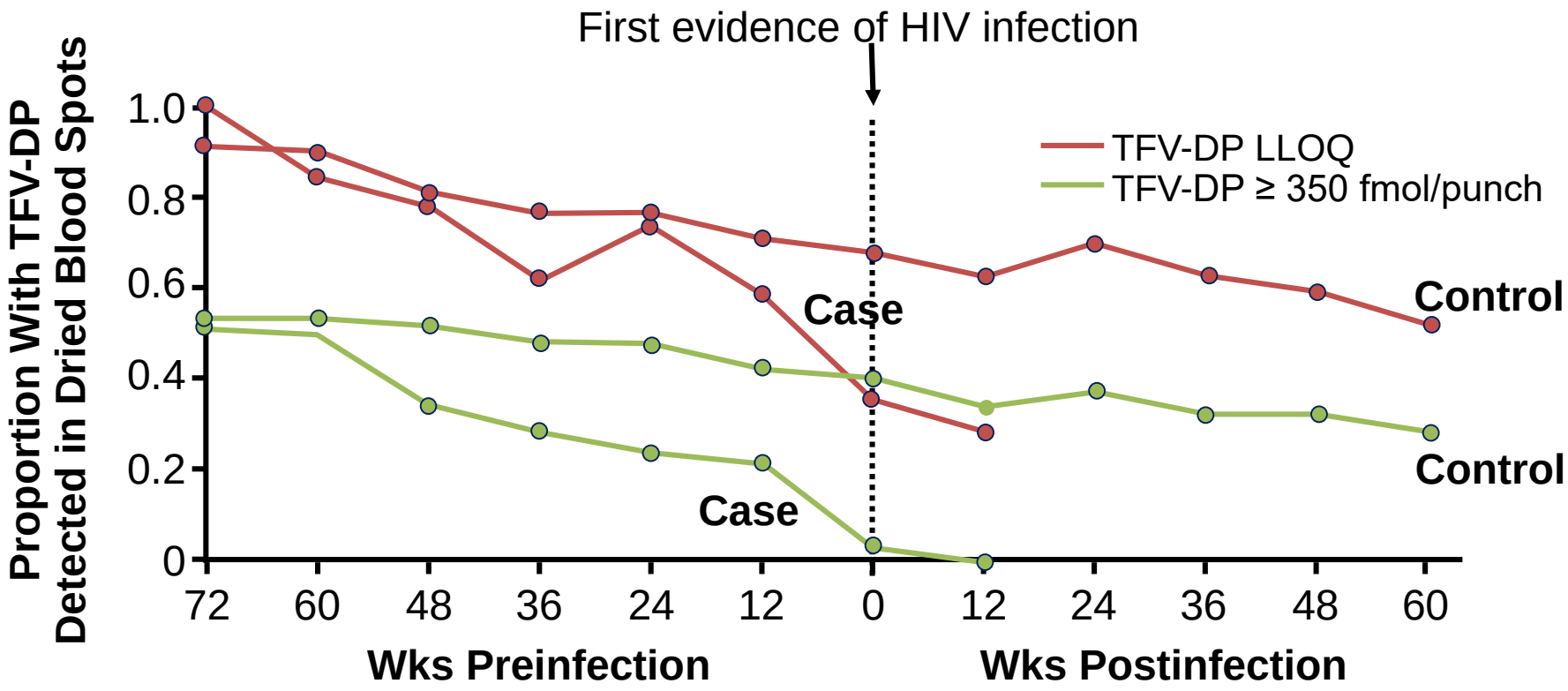


Follow-up,%	26	12	21	12
Risk Reduction,%	**44**	**84**	**100**	**100**
95% CI, %	-31 to 77	21 to 99	86 to 100 (combined)	

- TFV-DP: tenofovir diphosphate (measurable tenofovir in dried blood spots)

Grant R, et al. AIDS 2014. Abstract TUAC0105LB. Graphic used with permission.

iPrEX OLE: HIV Infection Occurred During Periods of Nonadherence



Grant R, et al. AIDS 2014. Abstract TUAC0105LB. Graphic used with permission.

ANRS Prevenir: Daily vs On-Demand PrEP With FTC/TDF

- Multicenter, open-label, prospective cohort study mainly in MSM (98.6%) from Paris

HIV-negative adults at high risk of HIV infection with inconsistent condom use; eGFR ≥ 50 mL/min; HBsAg negative in on-demand arm (N = 3045)*

Beginning of Study
May 3, 2017

Current Analysis
May 2, 2019

End of Study
May 31, 2020

Daily FTC/TDF PrEP†
(n = 1546)

On-Demand FTC/TDF PrEP†
(n = 1499)

Primary end point: ≥ 15% reduction in new HIV diagnoses among MSM in Paris vs rate reported by National Surveillance network in 2016

Secondary endpoints: PrEP adherence, sexual behavior, safety

*Participants enrolled on arm of their choice with ability to switch. †Plus condoms, gels, risk reduction and adherence counseling, questionnaire on sexual behavior. Follow-up every 3 mos with STI and/or HIV testing, plasma creatinine measurement.

ANRS Prevenir: HIV Incidence

mITT Analysis	Daily PrEP (1072.9 PYFU)	On-Demand PrEP* (1132.7 PYFU)	*P* Value
HIV incidence/100 PY (95% CI)	0 (0-0.3)	0.2 (0-0.6)	.132

- Global HIV incidence: 0.09/100 PY (n = 2)
  - PrEP stopped 7-10 wks before infection in both cases
- Mean follow-up: 8.7 mos
- Overall HIV infections averted: n = 143
  - Assuming incidence of 6.6/100 PY as reported for placebo arm in ANRS IPERGAY study
- Rate of study discontinuation: 8.9/100 PY (n = 196)

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

Molina. IAS 2019. Abstr TUAC0202.

ANRS Prevenir: PrEP Adherence, Sexual Behavior, Safety

At Last Sexual Encounter, n (%)	Daily PrEP (3806 Acts)	On-Demand PrEP (3879 Acts)
PrEP use	3705 (97.3)	3188 (82.2)
▪ Correct*	3613 (97.5)	3072 (96.4)
Condom use	716 (18.8)	851 (21.9)

Participants with adherence data, n = 2134.
*Per protocol, or at least 1 pill before and after within 24 hrs.

- Daily PrEP users had:
  - More sexual partners
  - More frequent condomless sex
  - Higher incidence of bacterial STIs

Molina. IAS 2019. Abstr TUAC0202.

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▪ Correct*	3613 (97.5)	3072 (96.4)
Condom use	716 (18.8)	851 (21.9)

Participants with adherence data, n = 2134.
*Per protocol, or at least 1 pill before and after within 24 hrs.

- Daily PrEP users had:
  - More sexual partners
  - More frequent condomless sex
  - Higher incidence of bacterial STIs

Incidence/100 PY (95% CI)	Daily PrEP (1072.9 PYFU)	On-Demand PrEP (1132.7 PYFU)
Drug-related AEs†	11.4 (9.4-13.6)	13.2 (11.2-15.5)
▪ Leading to d/c	0 (0-0.3)	0.3 (0-0.8)‡
Grade 3/4 AEs	5.3 (4.0-6.9)	4.4 (3.3-5.8)
Viral hepatitis	0.9 (0.5-1.7)	1.2 (0.6-2.0)
ALT abnormality	13.0 (10.9-15.3)	10.3 (8.5-12.4)
▪ Grade 3/4	0.8 (0.4-1.6)	0.6 (0.3-1.3)
Grade 1 creatinine	15.4 (13.1-17.9)	15.6 (13.4-18.1)

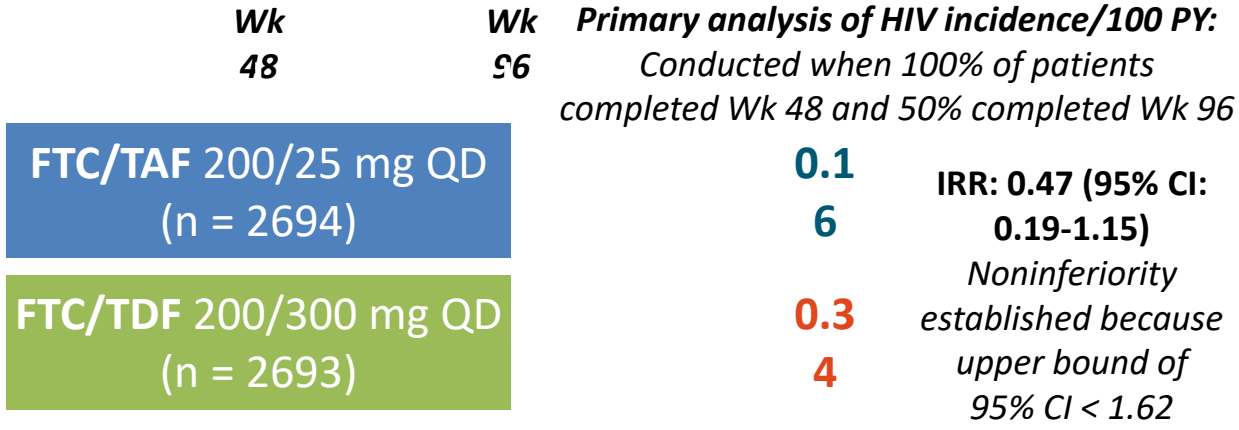
†Most were gastrointestinal. ‡Grade 3 vomiting, grade 1 diarrhea, grade 1 nausea/headache/dizziness; each n = 1.

Molina. IAS 2019. Abstr TUAC0202.

DISCOVER: FTC/TAF vs FTC/TDF as PrEP in MSM, TGW

- International, randomized, double-blind, active-controlled phase III trial

Adult cis-MSM or TGW at high risk of HIV infection,* no HBV infection, previous PrEP use permitted (N = 5387)



Adherence comparable between arms by self-report over time, pill count (median adherence: 98% in each arm), and TFV-DP levels in DBS

Steady-state PBMC TFV-DP levels were 6.3-fold higher with FTC/TAF vs FTC/TDF

Modeling found that concentrations > EC_{90} would last for 16 days after final dose of FTC/TAF vs 10 days after FTC/TDF

Spinner. IAS 2019. Abstr TUAC0403LB. Hare. CROI 2019. Abstr 104LB.

DISCOVER: FTC/TAF vs FTC/TDF as PrEP in MSM, TGW

- International, randomized, double-blind, active-controlled phase III trial

Adult cis-MSM or TGW a… HIV i… no HB… previo… pe… (N…

Wk 48 ***Wk 96***

Primary analysis of HIV incidence/100 PY: *Conducted when 100% of patients …ted Wk 96*

…(95% CI: …15)

…riority …l because …ound of …< 1.62

STI incidence could account for observed differences in HIV infection rates

Adhe… …dian adherence: 98% in each arm), and TFV-DP levels in DBS

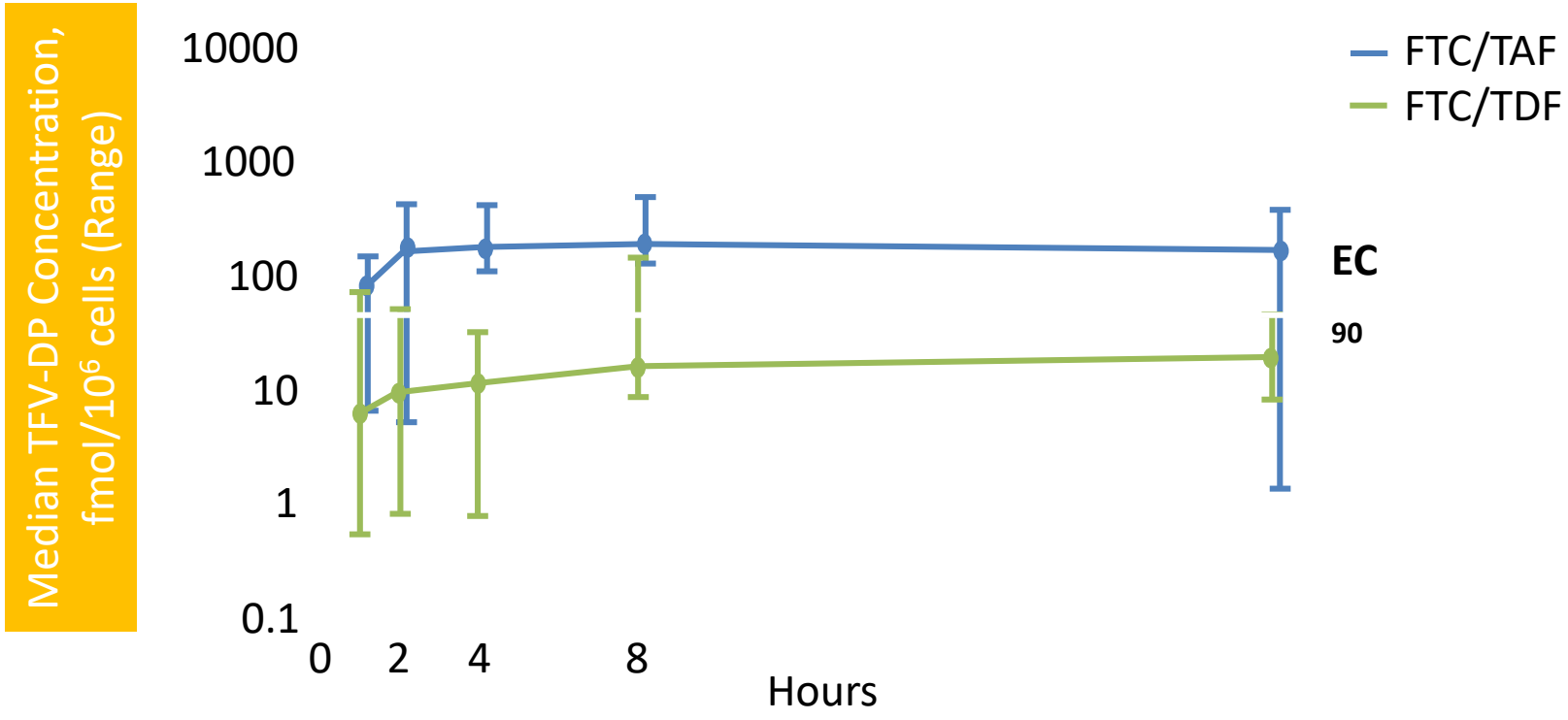
Steady-state PBMC TFV-DP levels were 6.3-fold higher with FTC/TAF vs FTC/TDF

Modeling found that concentrations > EC_{90} would last for 16 days after final dose of FTC/TAF vs 10 days after FTC/TDF

Spinner. IAS 2019. Abstr TUAC0403LB. Hare. CROI 2019. Abstr 104LB.

DISCOVER: Rapidity in Achieving EC_{90}

- In a phase I study in healthy volunteers, median PBMC TFV-DP concentration > EC_{90} reached within **1-2 hrs (all within 4 hrs) of dosing with FTC/TAF** vs **3 days of dosing with FTC/TDF**



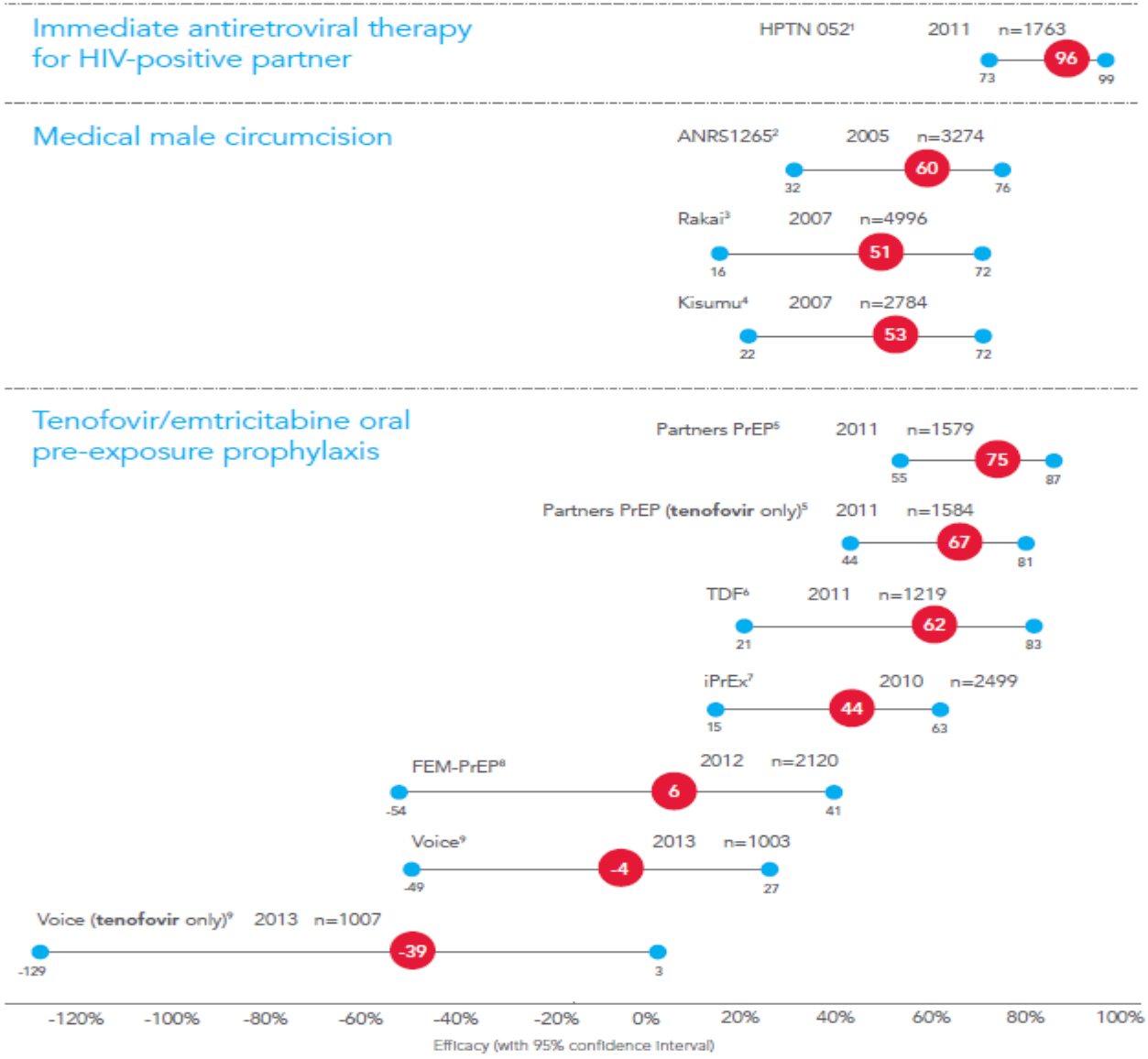
Spinner. IAS 2019. Abstr TUAC0403LB. Reproduced with permission.

Select Agents Under Early Investigation For the Prevention of HIV

Agent	MOA	Phase	n	Key Findings
Ad26.Mos4.HIV and either clade C gp140 or bivalent gp140[1]	Vaccine	I/IIa	126	▪ Both regimens induced immune responses against a broad range of HIV-1 subtypes in healthy adults; well tolerated
Islatravir (ISL; MK-8591)[2]	NRTTI	I	12	▪ Drug-eluting implants projected to provide HIV prophylaxis for ≥ 1 yr; well tolerated. ISL + DOR tx regimen in phase IIb[3]
2-hydroxypropyl-β-cyclodextrin cabotegravir nanochannel delivery implant[4]	INSTI	PK	6 (rats)	▪ Clinically-relevant plasma CAB concentrations and drug penetration into relevant tissues; no AEs observed

1. Stieh. IAS 2019. Abstr TUAC0402LB. 2. Matthews. IAS 2019. Abstr TUAC0401LB. 3. Molina. IAS 2019. Abstr WEAB0402LB. 4. Pons-Faudoa. IAS 2019. Abstr TUPEA106. 5. Daar. IAS 2019. Abstr LBPEB13. 6. Chen. IAS 2019. Abstr WEAA0305LB. 7. Riddler. IAS 2019. Abstr WEAA0304.

EFFICACY OF AVAILABLE BIO-MEDICAL PREVENTION INTERVENTIONS DERIVED FROM RANDOMIZED CLINICAL TRIALS. MODIFIED WITH PERMISSION FROM MARRAZZO ET AL, JAMA, IN PRESS, 2014.*



Sources: 1. Cohen M, Chen Y, McCauley M, Gamble T, Hosseinipour MC, et al. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med, 2011;365:493–505. DOI:10.1056/NEJMoa1105243 2. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. (2005)

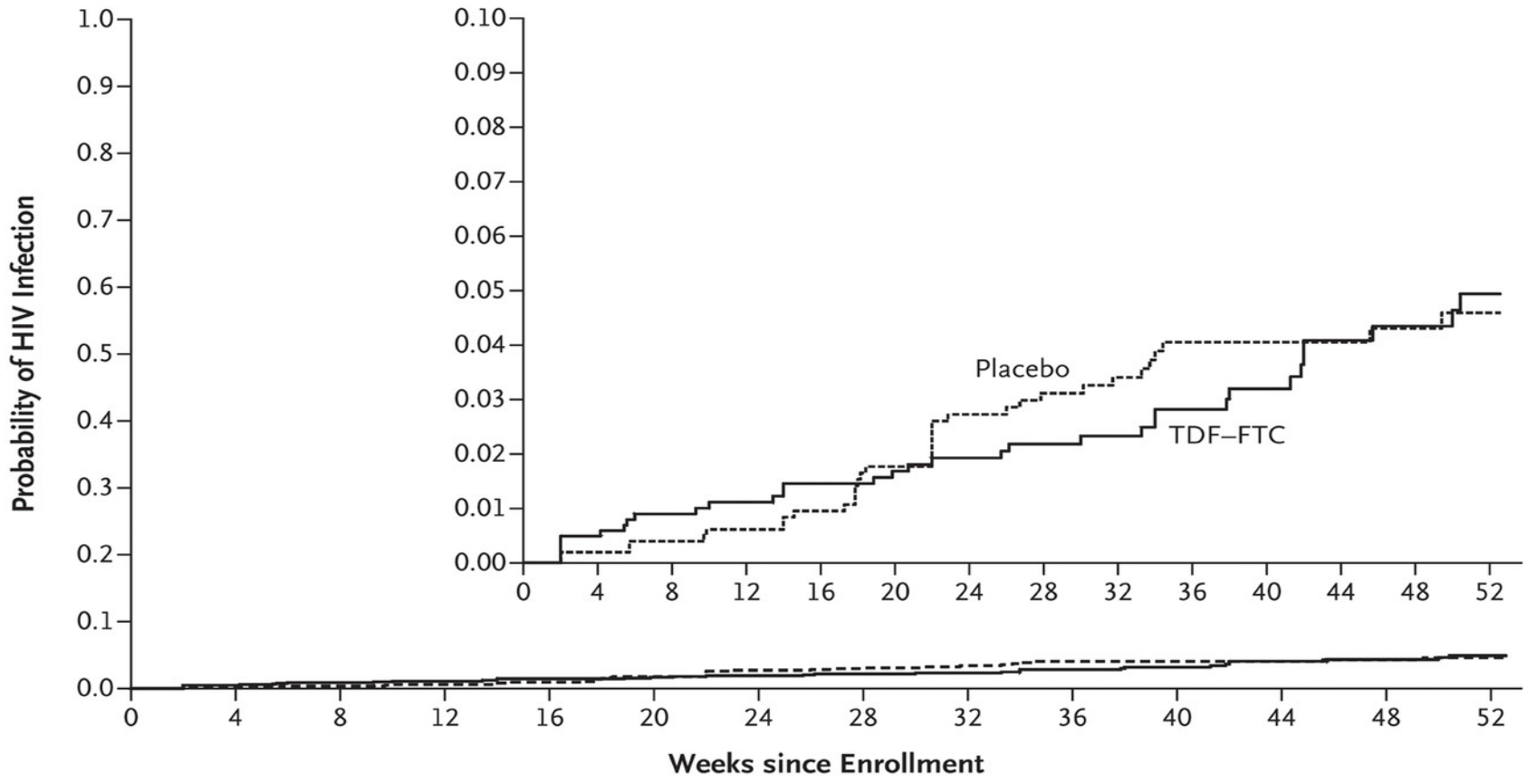
Has PrEP Been Shown to Be Effective?

Other studies have found PrEP ***not to be effective***

- ***FemPrEP*** study
  - Tested Truvada in Kenyan, Tanzanian, South African women at high risk for HIV
  - Stopped early – did not seem to help in preventing HIV transmission
- ***VOICE*** study
  - >5,000 women in South Africa, Zimbabwe, Uganda
  - Tested:

FemPrEP

Preexposure Prophylaxis for HIV Infection among African Women, randomised, double blind, placebo controlled trial, n= 2120 in Kenya, S Africa and Tanzania



No. at Risk

Placebo	1032	1019	963	917	864	841	799	736	659	565	491	420	360	229
TDF–FTC	1024	1008	953	904	860	844	811	733	663	569	486	418	356	212

Van Damme, et al. N Engl J Med 2012; 367:411-422

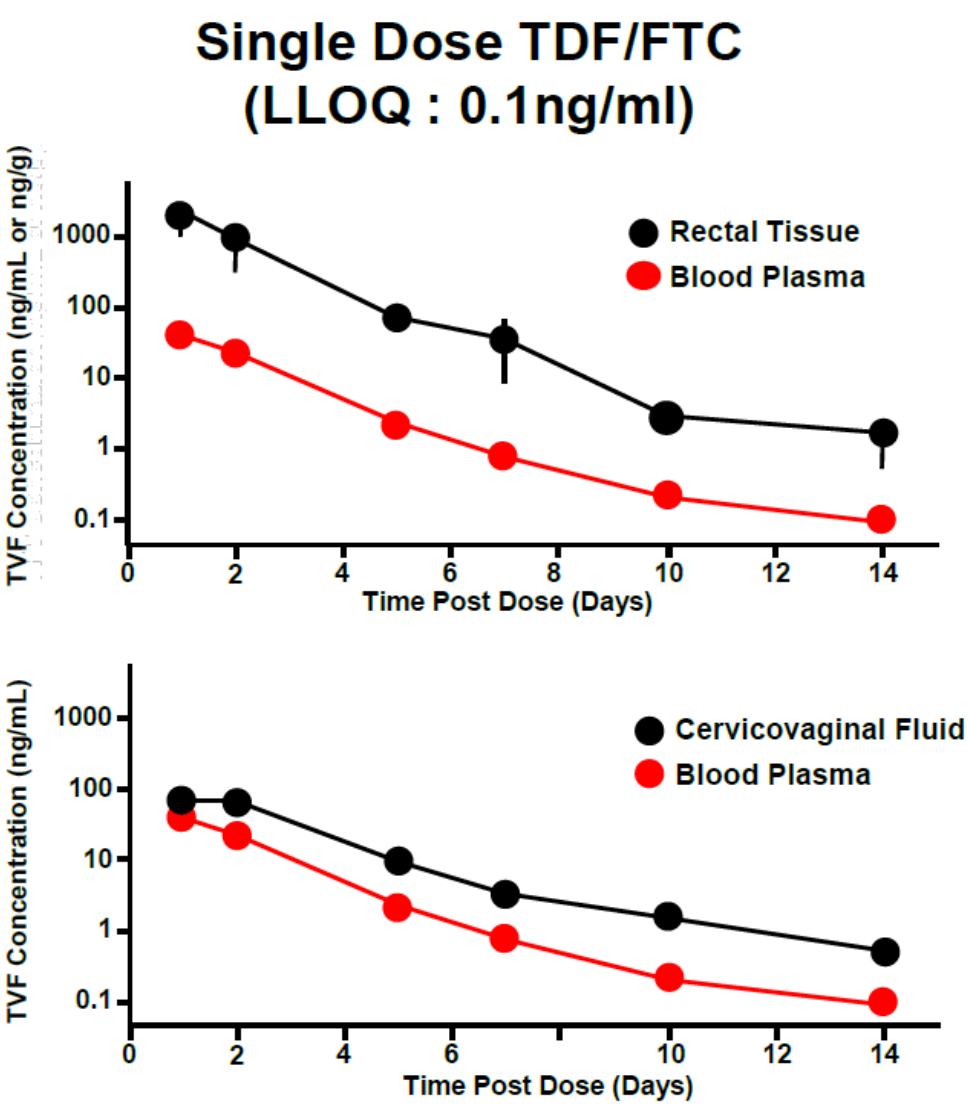
Adherence in women is the major limitation of oral PrEP

	VOICE	FemPrEP
Self-report	88-90%	95%
Product count	86%	88%
PK drug level*	25-30%	15-37%

*Tested at end of trial due to blinded trial

- VOICE: no detectable drug at any quarterly visit in approximately half of women tested (41-58%)

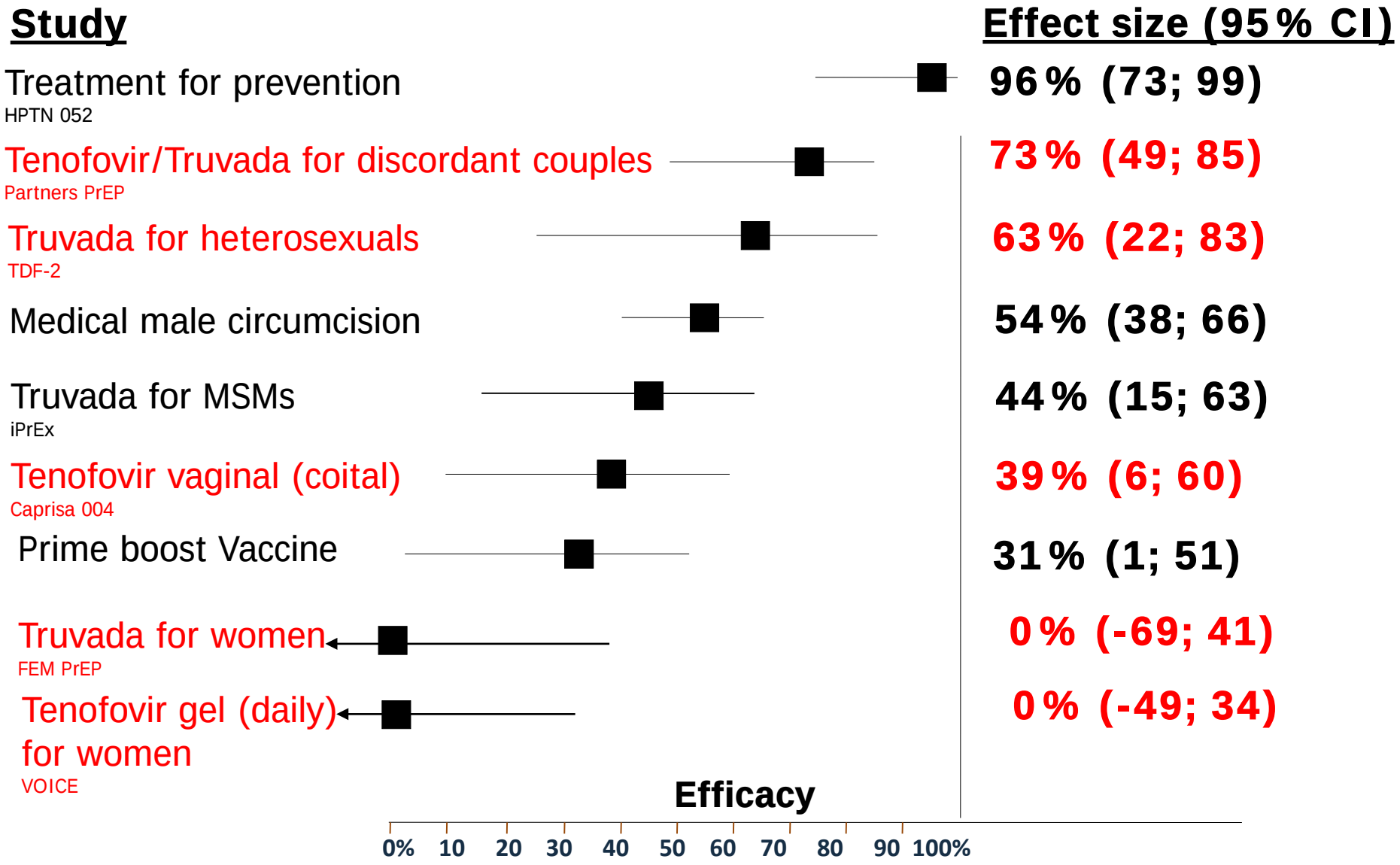
TDF/FTC PK in Blood and Mucosal Tissue



- 8 healthy men and 7 women
- Blood and tissue concentrations of TDF and FTC quantified up to 14 days
- Long half-lives : 47-49 hours
- Cumulative exposure of rectal tissue to TDF > 30-fold higher vs. blood, only 4-fold higher for FTC
- Cumulative exposure of cervical tissue to TDF 6-fold higher vs. blood, but > 40-fold higher for FTC

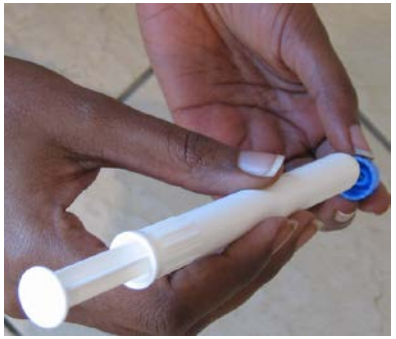
Patterson K, et al. Sci Transl Med 3, 2011, 112re4

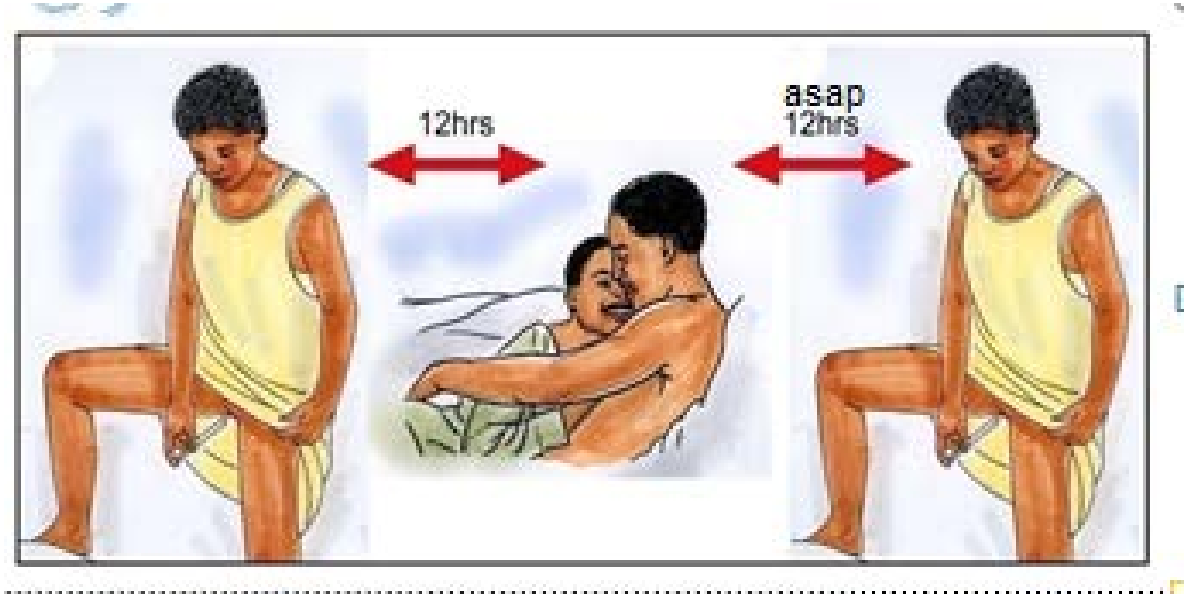
Examples of Prevention Trials



CAPRISA & FACTS: **on-demand** topical PrEP

- BAT 24 on-demand topical PrEP
  - Insert 1 gel up to 12 hours **B**efore sex,
  - Insert 1 gel as soon as possible within 12 hours **A**fter sex,
  - No more than **T**wo doses in **24** hours





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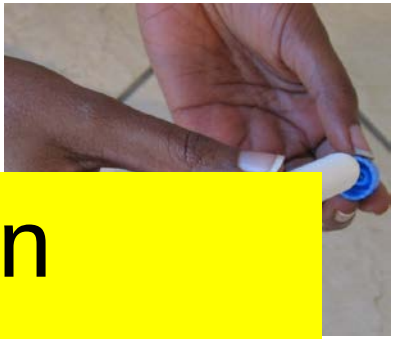
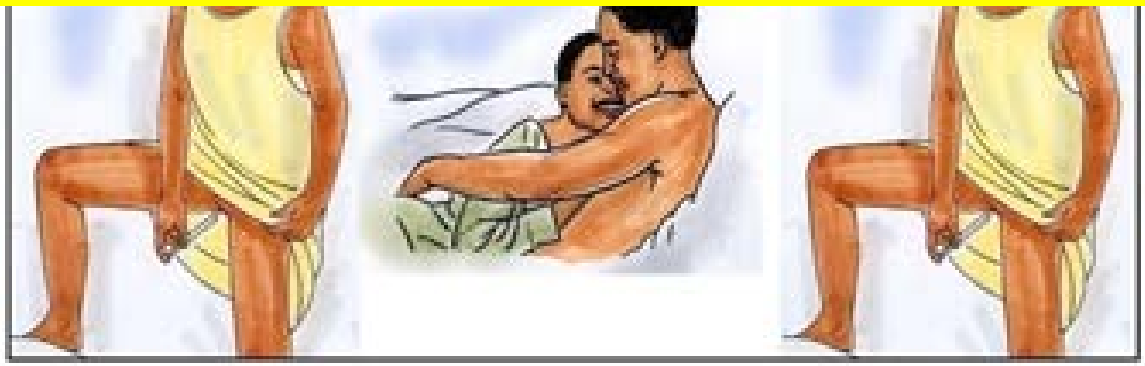


FACTS: no gel used in approximately half of all sex acts (40-50%)



Vaginal bacteria do affect blood and tissue concentrations of tenofovir in microbicide use

RESULTS:

- In vaginal fluid there was a significant correlation between higher levels of non-*Lactobacillus* bacteria and lower tenofovir levels, minor correlation blood
- Much stronger positive correlation between *Lactobacillus* bacteria and tenofovir levels in both vaginal fluid and blood samples.
- Women with no *Lactobacillus* were more likely to have undetectable levels of tenofovir
- Similarly strong relationships were found after a single dose in the laboratory
- Possible mechanism: the inflammation caused by BV bacteria may be turning tenofovir into adenine, the non-active 'base' compound it is designed to imitate

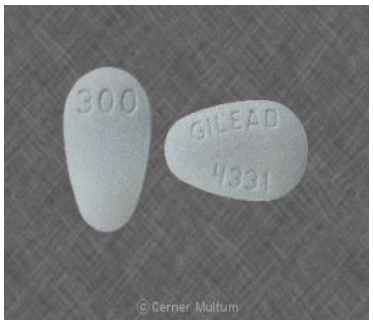
- BUT it does not directly prove that these impact on the efficacy of topical PrEP

MDP 401 Program

A pragmatic randomized open-label wait-listed trial to evaluate the effectiveness of tenofovir (PrEP) to reduce the risk of HIV acquisition among women at high risk of HIV in Mozambique, Rwanda, Tanzania and Uganda

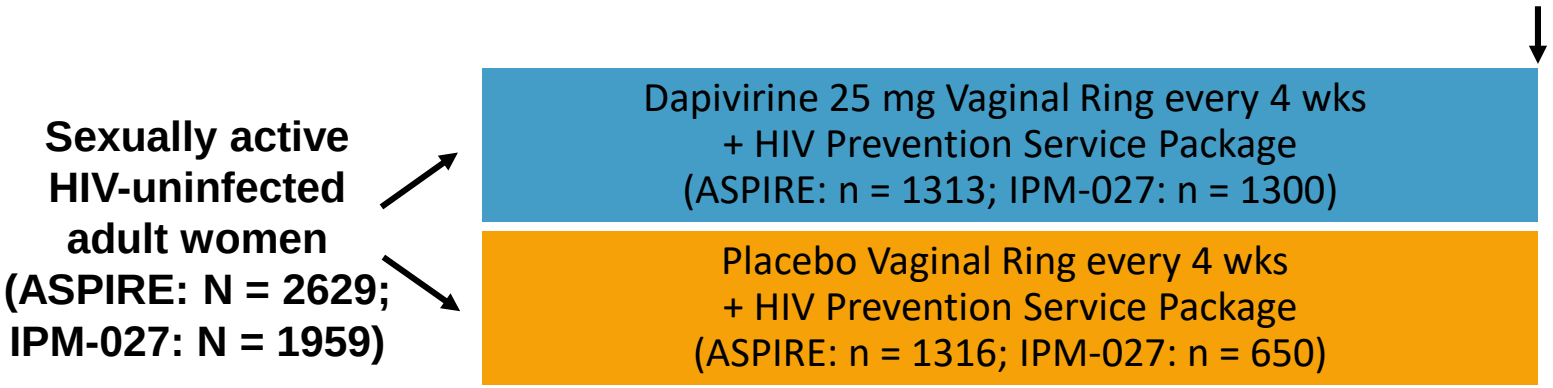
- Conduct an intensive **PREPARATORY STUDY** to inform which of three tenofovir products to test in the clinical trial.
- Followed by an open-label wait-listed randomised **CLINICAL TRIAL** designed to evaluate the preferred tenofovir product whereby women are randomised to receive the product immediately or after a deferred period of 12 months.

1. Tenofovir on-demand gel
   - Efficacy, acceptability, HSV2 protection
2. Tenofovir on-demand oral tablet
   - Cheaper, less drug, less resistance
3. Tenofovir vaginal ring
   - Three-monthly, longer half-life than Dapivirine



MTN-020/ASPIRE & IPM-027: Dapivirine Vaginal Ring for HIV Prevention in Women

- Silicone elastomer vaginal matrix ring containing NNRTI dapivirine 25 mg; ring replaced every 4 wks
- Randomized, double-blind phase III trials
  - MTN-020/ASPIRE[1,2]: Malawi, South Africa, Uganda, Zimbabwe
  - IPM-027 (The Ring Study)[3]: South Africa, Uganda
  - Primary endpoints: efficacy and safety



1. Baeten JM, et al. CROI 2016. Abstract 109LB.
2. Baeten JM, et al. N Engl J Med. 2016;[Epub ahead of print].
3. Nel A, et al. CROI 2016. Abstract 110LB.

MTN-020/ASPIRE & IPM-027: Efficacy and Safety of Dapivirine Vaginal Ring (4 weekly)

- Efficacy for HIV prevention similar in both studies
- No clinically relevant safety differences between arms

Outcome	ASPIRE[1,2]: 15 Sites		ASPIRE[1,2]: 13 Sites*		The Ring Study[3]	
	Dapivirine (n = 1308)	Placebo (n = 1306)	Dapivirine (n = 1198)	Placebo (n = 1197)	Dapivirine (n = 1300)	Placebo (n = 650)
HIV infections, n	71	97	54	85	77	56
HIV incidence (per 100 PYs)	3.3	4.5	2.8	4.4	4.1	6.1
HIV protection efficacy, %	**27 (*P* = .046)**		**37 (*P* = .007)**		**31 (*P* = .040)**	
▪ **Among women older than 21 yrs**	-		**56 (*P* < .001)**		**37 (*P* = .10)**	

*Excludes 2 sites with low adherence.

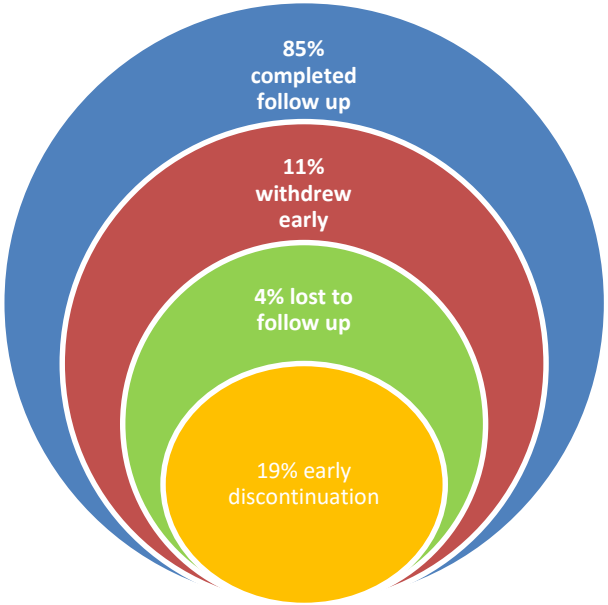
1. Baeten JM, et al. CROI 2016. Abstract 109LB.
2. Baeten JM, et al. N Engl J Med. 2016;[Epub ahead of print].
3. Nel A, et al. CROI 2016. Abstract 110LB.

Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Women: A Phase 2 Randomized Trial, n= 188

- To assess the safety and tolerability of MVC-containing PrEP over 48 weeks in U.S. women at risk for HIV infection.
- Phase 2 randomized, controlled, double-blinded study of 4 antiretroviral regimens used as PrEP
- 12 clinical research sites of the HIV Prevention Trials Network and AIDS Clinical Trials Group.
- HIV-uninfected women reporting condomless vaginal or anal intercourse with at least 1 man with HIV infection or unknown serostatus within 90 days

MVC only	MVC-emtricitabine (FTC)	MVC-tenofovir disoproxil fumarate (TDF)	TDF-FTC (control)

- Grade 3 or 4 adverse events occurred in 5 (MVC), 13 (MVC-FTC), 9 (MVC-TDF), and 8 (TDF-FTC) participants; rates did not differ among regimens. Of available plasma samples at week 48 (n = 126), 60% showed detectable drug concentrations. No new HIV infections occurred
- **Limitations:**
- Participants were not necessarily at high risk for HIV infection. The regimen comprised 3 pills taken daily. The study was not powered for efficacy



Gulick RM, et al. Ann Intern Med 2017 Sep 19;167(6):384-393

HPTN-069/A5305: Safety, Tolerability, and Efficacy

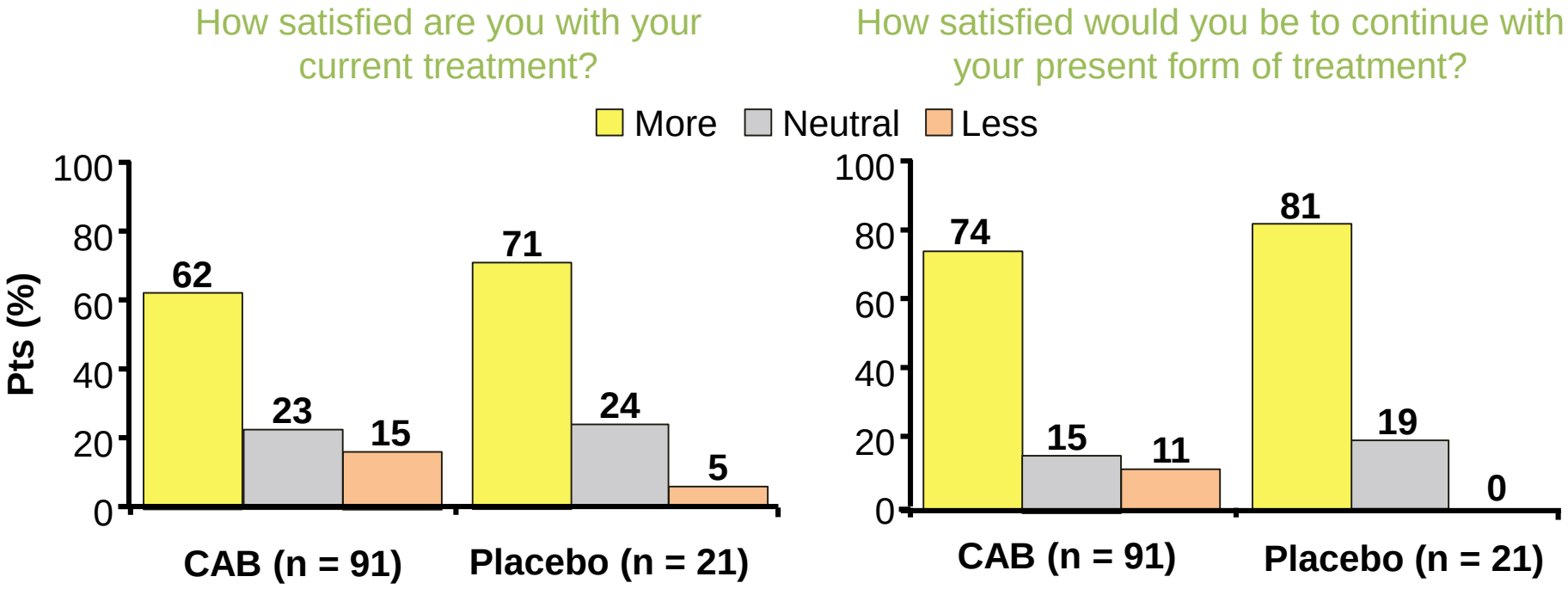
- 67 grade 3/4 AEs; rates similar across arms
- 9% discontinued study drug early
  - Rates of study drug discontinuation (*P* = .6) and time to permanent discontinuation (*P* = .6) similar across arms
- 5 new HIV infections occurred during study for annual incidence rate of 1.4% (95% CI: 0.8-2.3); all R5 tropic; no transmitted drug resistance

Age (Yrs), Race of Newly Infected Pt	Study Arm	First HIV+ Test, Wk	HIV-1 RNA, c/mL	Plasma Drug Conc. at Seroconv. Visit (ng/mL)*
20, black	MVC + TDF	4	122,150	MVC: 0† TDF: 0
61, Asian	MVC alone	16	981	MVC: 145
21, mixed race	MVC alone	24	106,240	MVC: 0†
35, white	MVC alone	32	13,626	MVC: 6.7
36, black	MVC alone	48	52,191	MVC: 0.7

*Anticipated predose steady-state MVC concentration: 32 ng/mL. †Undetectable plasma drug concentrations at every study visit.

ÉCLAIR: Patient Satisfaction With IM Therapy vs Oral Phase

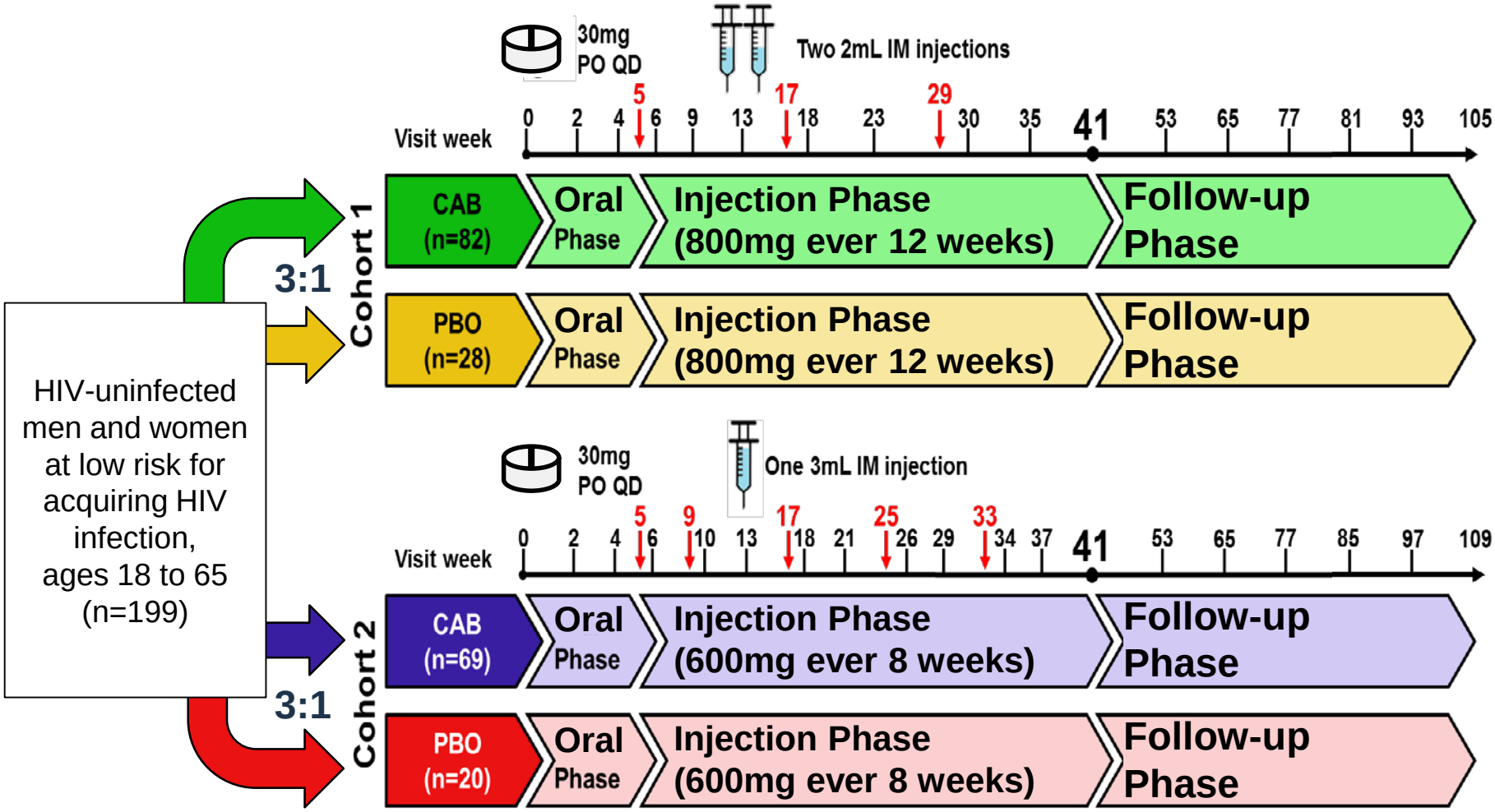
- Pt satisfaction assessed by questionnaire at Wk 18 of IM treatment; asked pts to compare satisfaction of current IM vs past oral therapy[1]



- In separate macaque study, CAB LA conferred 88% protection (21/24 animals) against IV exposure to SIVmac251; results may be relevant to humans who inject drugs[2]

1. Markowitz M, et al. CROI 2016. Abstract 106. 2. Andrews CD, et al. CROI 2016. Abstract 105.

HPTN 077 Study Design



HPTN 084: CAB LA 600mg

To Prevent HIV Acquisition in Women

Delaney-Moretlwe and Hosseinipour, *Protocol Chairs*

Step 1	**Daily oral CAB and TDF/FTC placebo**	**Oral TDF/FTC and oral CAB placebo**
Step 2	**CAB LA and oral TDF/FTC placebo at two time points 4 weeks apart and every 8 weeks thereafter**	**Oral TDF/FTC and injectable placebo at two time points 4 weeks apart and every 8 weeks thereafter**
Step 3	**Open-label oral TDF/FTC to cover the PK tail**	**Open-label oral TDF/FTC to cover the PK tail**

HPTN 084
Long-acting Injectable For the Epidemic

Primary Objective: Reduce HIV Incidence (superiority, double blind, double dummy design)

Study duration: Enrollment 24 months; follow-up up to 4.5 years

N=3200

ImPREP: Same-Day PrEP With TDF/FTC for High-Risk 5019 MSM (94%) and TGW 335 TGW (6%)in Brazil, Mexico, and Peru 30-day supply of TDF/FTC

- Primary outcomes
  - **PrEP early continuation:** attendance to the first 2 follow-up visits within 120 days of PrEP initiation
  - **PrEP adherence:** ≥ 16 days of PrEP medication filled per 30-day period (medication possession ratio ≥ 0.53)

Population	Early Continuation, %	Medication Possession Ratio ≥ 0.53, %	Follow-up, PY	HIV Incidence per 100 PY (95% CI)
Brazil	85.4	98.7	1438.6	0.2 (0.1-0.6)
Mexico	84.0	98.0	344.0	0.6 (0.2-2.3)
Peru	52.7	91.0	286.4	2.4 (1.2-5.1)
Overall ▪ TGW	79.6 55.7	97.2 88.7	2069.0 --	0.6 (0.3-1.0) --

Veloso. IAS 2019. Abstr TUAC0404LB.

PrEP is acceptable

- PrEP publications 2016/17 mainly on willingness to take PrEP
  - Transgender women Argentina
  - Black MSM Chicago
    - Apart from a small group who believe in a conspiracy theory
  - MSM China
    - On demand but not daily
  - ChemSex MSM US
    - On demand prior to chems use, but not daily
  - Long Acting Injectible PrEP
    - Acceptable if efficacious

Limited awareness of pre-exposure prophylaxis among black men who have sex with men and transgender women in New York city

- STAR Study, which recruited black MSM/TGW in New York City for HIV testing and linked HIV-infected individuals into care from July 2012 to April 2015
- 1673 participants
  - median age was 43 years
  - 25% were under age 30
  - 85.8% reported having insufficient income for basic necessities at least occasionally
  - 54.8% were homeless
  - 71.3% were unemployed

Garnett M[1], Hirsch-Moverman Y[1,2], Franks J[1], Hayes-Larson E[1,2], El-Sadr WM[1,2], Mannheimer S[1,2,3]. AIDS Care. 2017 Aug 9:1-9

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  - 25% were under age 30
  - 85.8% reported having insufficient income for basic necessities at least occasionally
  - 54.8% were homeless
  - 71.3% were unemployed

- Awareness of PrEP was reported among **18.2%** of participants
- PrEP awareness was associated with
  - younger age (adjusted odds ratio [aOR] 0.87, per 5 years)
  - gay identity (aOR 2.46)
  - higher education (aOR 1.70)
  - more frequent past HIV testing (aOR 3.18)
  - less HIV stigma (aOR 0.61)
  - less hazardous/harmful alcohol use (aOR 0.61)
  - more sexual partners (aOR 1.04, per additional partner in past 30 days)

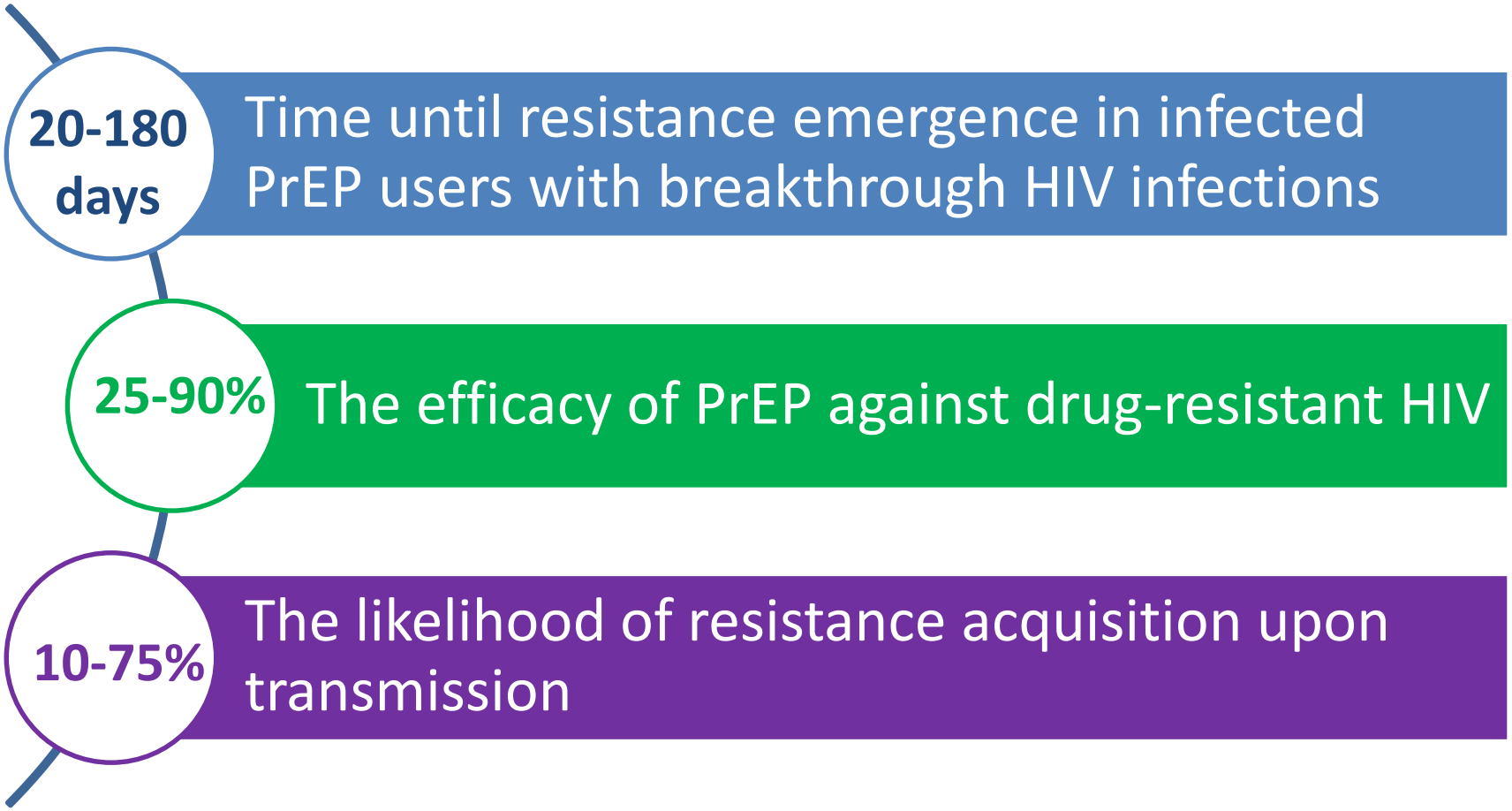
Garnett M[1], Hirsch-Moverman Y[1,2], Franks J[1], Hayes-Larson E[1,2], El-Sadr WM[1,2], Mannheimer S[1,2,3]. AIDS Care. 2017 Aug 9:1-9

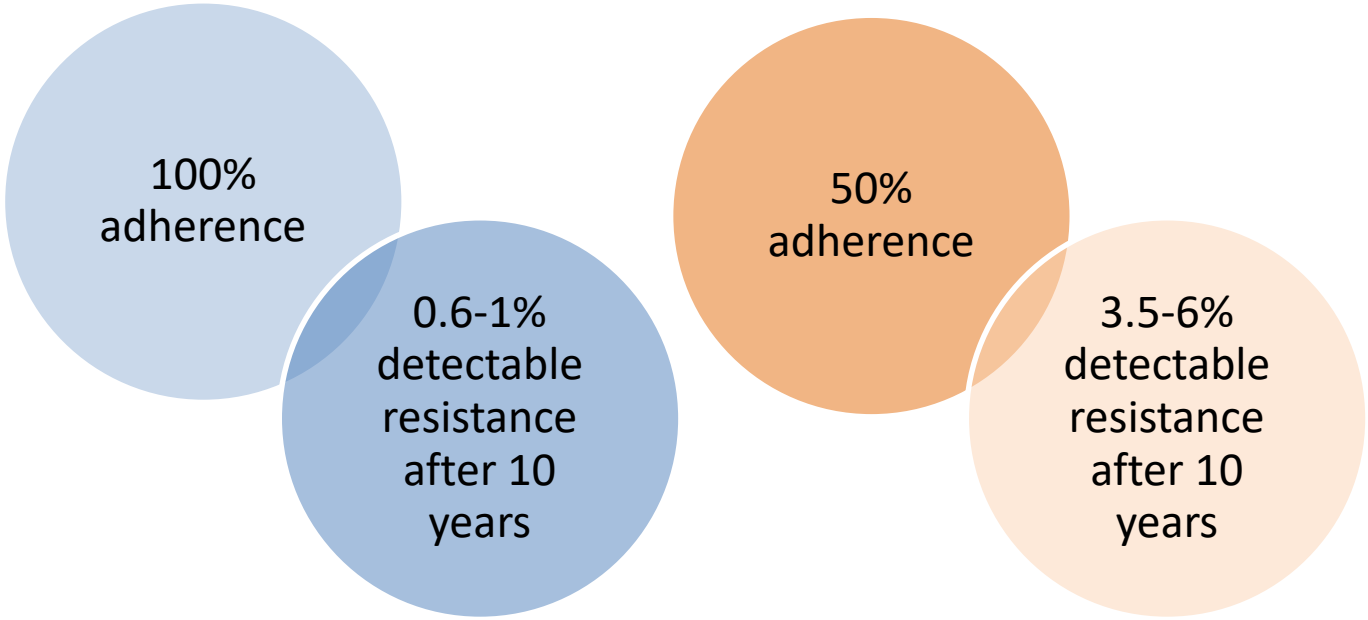
How Much Do We Know about Drug Resistance Due to PrEP Use?

- Will widespread use of PrEP outside well controlled trial conditions result in increased drug resistance?
- A survey of expert virologists with questions about biological assumptions regarding drug resistance due to PrEP use
- For comparability, 50% PrEP-coverage of and 90% per-act efficacy of PrEP in preventing HIV acquisition are assumed in all simulation

Dimitrov DT, Boily MC, Hallett TB, Albert J, Boucher C, Mellors JW, Pillay D, van de Vijver DAMC. PLoS One 2016;11(7):e0158620

Virologists disagreed!





KEY POINT

- 17–23% infected individuals could virologically fail treatment as a result of past PrEP use or transmitted resistance to PrEP with moderate adherence

PrEP is Recommended in

- HIV neg patients with rectal STIs or syphilis in preceding year
- HIV neg patients taking 2x PEP in year
- HIV neg who report condomless sex in context of chem-sex
- HIV neg who report multiple episodes of condomless sex with unknown HIV status who request PrEP
- Patients vaccinated for hepatitis B

EACS PrEP Guidelines

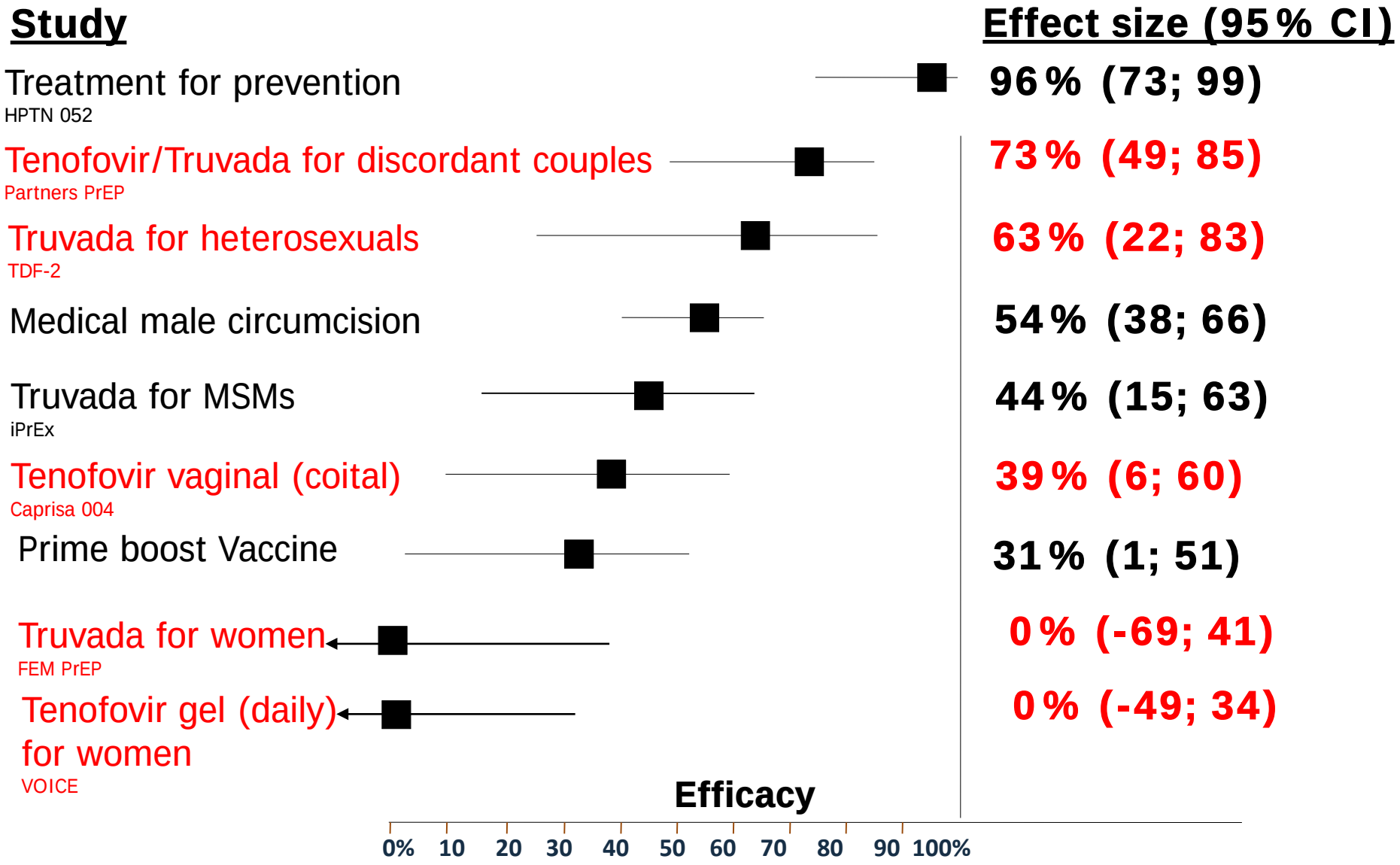
- PrEP can be used in adults at high-risk of acquiring HIV infection.
- Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment
- A recent STD or use of post-exposure prophylaxis may be markers of increased risk for HIV acquisition.
- May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and likely to have HIV positive partners who are not on treatment
- PrEP is a medical intervention that may not provide full protection against acquiring HIV, does not protect against other STDs and should be used in combination with other preventive interventions, including the use of condoms.
- PrEP should be supervised by a doctor, experienced with sexual health and use of HIV medicines, possibly as part of a shared care arrangement.
- The following procedures are recommended:
- Documented negative fourth generation HIV test prior to starting PrEP.
- During PrEP, this test should be repeated every 3 months, and PrEP should be stopped immediately in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test and the person referred for evaluation to an HIV unit.

EACS PrEP Guidelines

- Before PrEP is initiated, HBV serology status should be documented.
- If HBsAg positive see Clinlical Management and Treatment of HBV and HCV Co-infection in HIV-positive Persons.
- Counsel that PrEP does not prevent other types of STD; screen for STD (including HCV) when starting PrEP and regularly during use of PrEP.
- Counsel that PrEP may impact renal and bone health
- Check renal function and bone mineral density according to guidelines on TDF use.
- Counsel that PrEP, like other prevention methods, only works when it is taken. Adherence counselling is recommended.
- Counsel that PrEP can be prescribed long term but that each consecutive PrEP prescription should be for a period of maximum 3 months (90 tablets) to ensure appropriate monitoring.
- 3. PrEP regimen
- TDF/FTC 300*/200 mg 1 tablet qd. For MSM with high-risk sexual behavior PrEP may be dosed ‘on demand’ (double dose of drug 2-24 hours before each sexual intercourse, followed by two single doses of drug, 24 and 48 hours after the first drug intake). If dosed ‘on demand’, the total dose per week should not exceed 7 tablets.
- In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate).

NEW! EACS online PrEP course

Examples of Prevention Trials



APPROACH study, Lancet July 2018

- APPROACH was an international study in low risk individuals in the US (38%), Rwanda or Uganda (33%), South Africa (14%) and Thailand (15%)
- 3 components
- The env and gag/pol gene sequences were enclosed inside ‘vectors’ – the outer shells of two quite different viruses called Ad26 (adenovirus 26) and MVA (modified vaccinia ankara).
  - Can get inside human cells and mimic an infection stimulating an immune response.
  - Cannot replicate and cause ongoing infection
  - Can create immune memory in event of real HIV infection
- The third vaccine component was pure gp140 with the mineral aluminium phosphate added to it as an adjuvant to further stimulate the humoral immunity

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- Various doses given at different timings
- N = 349 by week 52 a year later, a 10% discontinuation rate.
- Vaccine produced an antibody response to HIV in **100%** of recipients by week 12
- ADCP (antibody-dependent cellular phagocytosis) response in **80%** of recipients by week 52
- CD4/CD8 responses in **83%** of recipients responsive to a broad panel of HIV viruses taken from different people at different stages of infection,.
- Vaccine did *not* generate a strong neutralising-antibody response - that the so-called broadly neutralising antibodies (bNAbs)

Imbokodo (HVTN 705/HPX2008) vaccine trial

HIV VACCINE
TRIALS NETWORK

- Mosaic technology combines immune-stimulating proteins from different HIV strains, representing different types of virus from around the world aiming for a global HIV vaccine for use in any geographic region
- Collaboration between Pharma and HIV organisations
- “Imbokodo” is the Zulu word for “rock” which is part of a well-known proverb in South Africa that refers to the strength of women and their importance in the community
- Aims to enroll 2,600 sexually-active women aged 18-35 in five southern African countries, starting in South Africa, then Malawi, Mozambique, Zambia and Zimbabwe
- Ad26 will be combined with a protein, Clade C gp140, which is similar to a protein found on the surface of HIV, and also helps to develop an immune response to the virus, and mixed with booster Aluminum Phosphate

Summary HIV Prevention Strategies

- Assessment of risk inc STIs and Hepatitis
- Part of risk reduction strategy
- Treatment as Prevention (TasP) is key
- PEP and certain PrEP are highly effective
- Regimens well tolerated
- Newer agents/methodologies/populations being assessed for PrEP
- Vaccine research moving forward finally– may be the solution for women
- Clear guidelines on management and follow-up
- Essential part of HIV and Sexual Health Care