Azienda Ospedaliera
SAN PAOLO
POLO UNIVERSITARIO

HIV Prevention

PrEP: nuovi dati dai trials

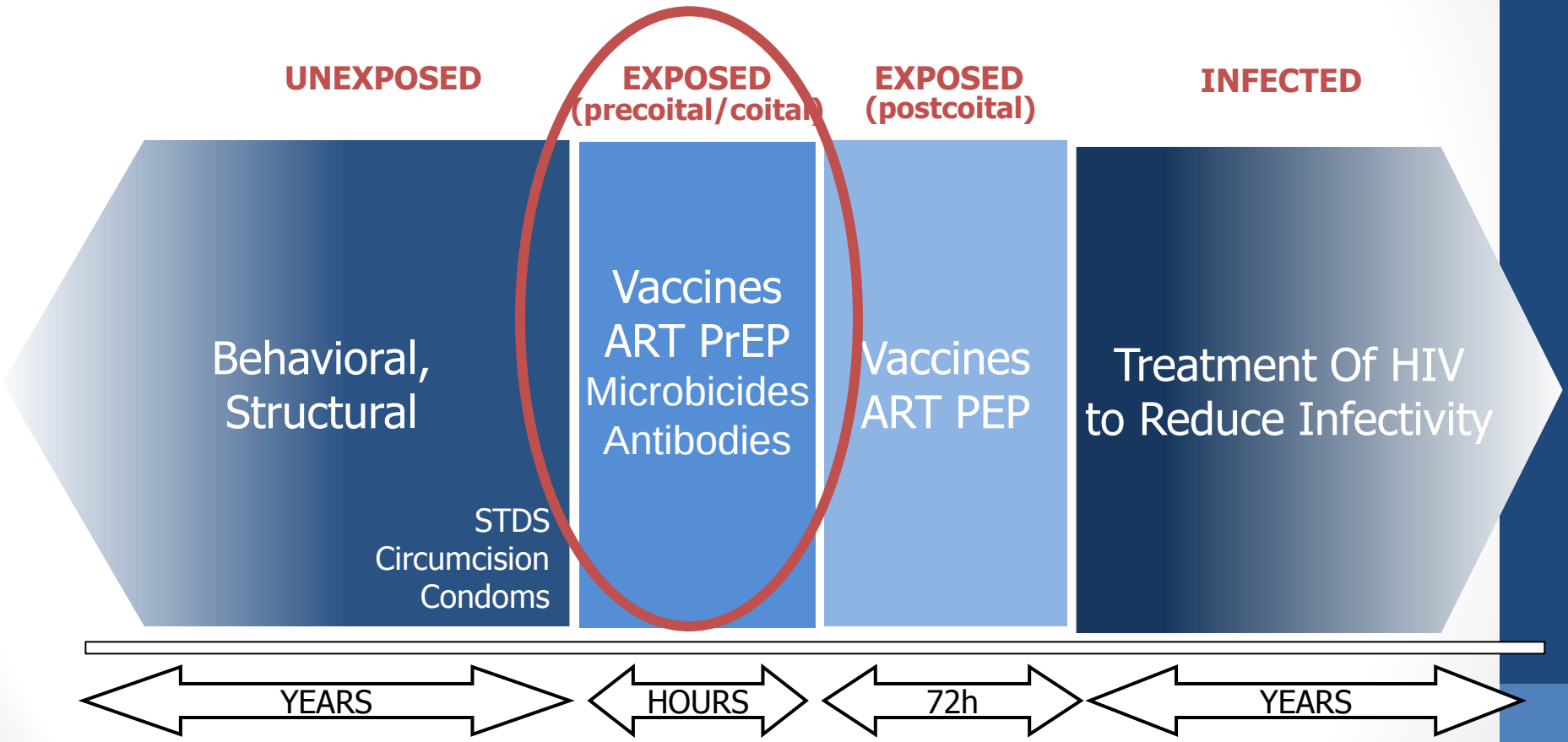
Dr.ssa Teresa Bini
AO San Paolo - Milano
Università degli studi di Milano

Combination HIV Prevention:

- Biomedical Interventions
- Behavioral Interventions
- Structural Interventions

http://www.cdc.gov/hiv/basics/prevention.html (2015)
Pettifor A et al. Tailored combination prevention package and PrEP for young key population, JAIDS 2015

Four Prevention Opportunities



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

Combination HIV Prevention:

- **Biomedical Interventions**
- Behavioral Interventions
- Structural Interventions

http://www.cdc.gov/hiv/basics/prevention.html *(2015)*
Pettifor A et al. Tailored combination prevention package and PrEP for young key population, JAIDS 2015

Biomedical Intervention:

ART based strategies to prevent HIV transmission:

- Pre-exposure prophylaxis (PrEP)
- Treatment as prevention
- Post-exposure prophylaxis (PEP)
- Mother to Child Transmission

Biomedical Intervention:

ART based strategies to prevent HIV transmission:

- Pre-exposure prophylaxis (PrEP)
- Treatment as prevention
- Post-exposure prophylaxis (PEP)
- Pregnancy

PrEP: Pre-exposure Prophylaxis

- **How does it work?**
- HIV-uninfected individuals take **antiretrovirals**
- May prevent replication of virus & infection

- Approved studies for oral use
- On-going studies:
  - slow release delivery mechanism (vaginal ring)
  - long acting injectable

PrEP: Pre-exposure Prophylaxis

- **Who? (PrEP Candidates)**

- Men who have sex with men (**MSM**)
  - HIV-positive sexual partner
  - Recent bacterial STI
  - High number of sex partners
  - History of inconsistent/no condom use
  - Commercial sex work

- Transgender individuals
  - Engaging in high-risk sexual behaviors

PrEP: Pre-exposure Prophylaxis

- **Who? (PrEP Candidates)**

- Heterosexual women and men
  - HIV-positive sexual partner
  - Recent bacterial STI
  - High number of sex partners
  - History of inconsistent/no condom use
  - Commercial sex work

- Injection Drug Users (IDU)
  - HIV-positive injecting partner
  - Sharing injection equipment

www.hivguidelines.org

PrEP: Pre-exposure Prophylaxis

- **Which antiretroviral therapy?**

The **ideal candidate** drug or drugs for PrEP would have the following characteristics:

- Excellent tolerability
- Low toxicity
- Pharmacokinetics allowing once-daily dosing
- A high genetic barrier of resistance
- Adequate drug concentrations in blood, rectal mucosa, and genital fluids
- Demonstration of safety, tolerability, and efficacy in clinical trials
- Low cost

PrEP: Pre-exposure Prophylaxis

- **Which antiretroviral therapy?**

- The only medication regimen approved by the FDA (2012) and recommended for PrEP with all the populations is **daily oral TDF 300 mg** co-formulated with **FTC 200 mg** (Truvada) **(IA)**

- **TDF alone** has shown substantial efficacy and safety in trials with IDUs and heterosexually active adults and can be considered as an alternative regimen for these populations, but **not for MSM**, among whom its efficacy has not been studied. **(IC)**

US Public Health Service, Preexposure Prophylaxis For The Prevention Of Hiv Infection In The United States - 2014 A Clinical Practice Guideline

PrEP: Pre-exposure Prophylaxis

- **Which antiretroviral therapy?**

- The use of other antiretroviral medications for PrEP, either in place of or in addition to TDF/FTC (or TDF) is **not recommended.** **(IIIA)**

- The prescription of oral PrEP for coitally-timed or other noncontinuous daily use is not recommended. **(IIIA)**

US Public Health Service, Preexposure Prophylaxis For The Prevention Of Hiv Infection In The United States - 2014 A Clinical Practice Guideline

PrEP: Pre-exposure Prophylaxis

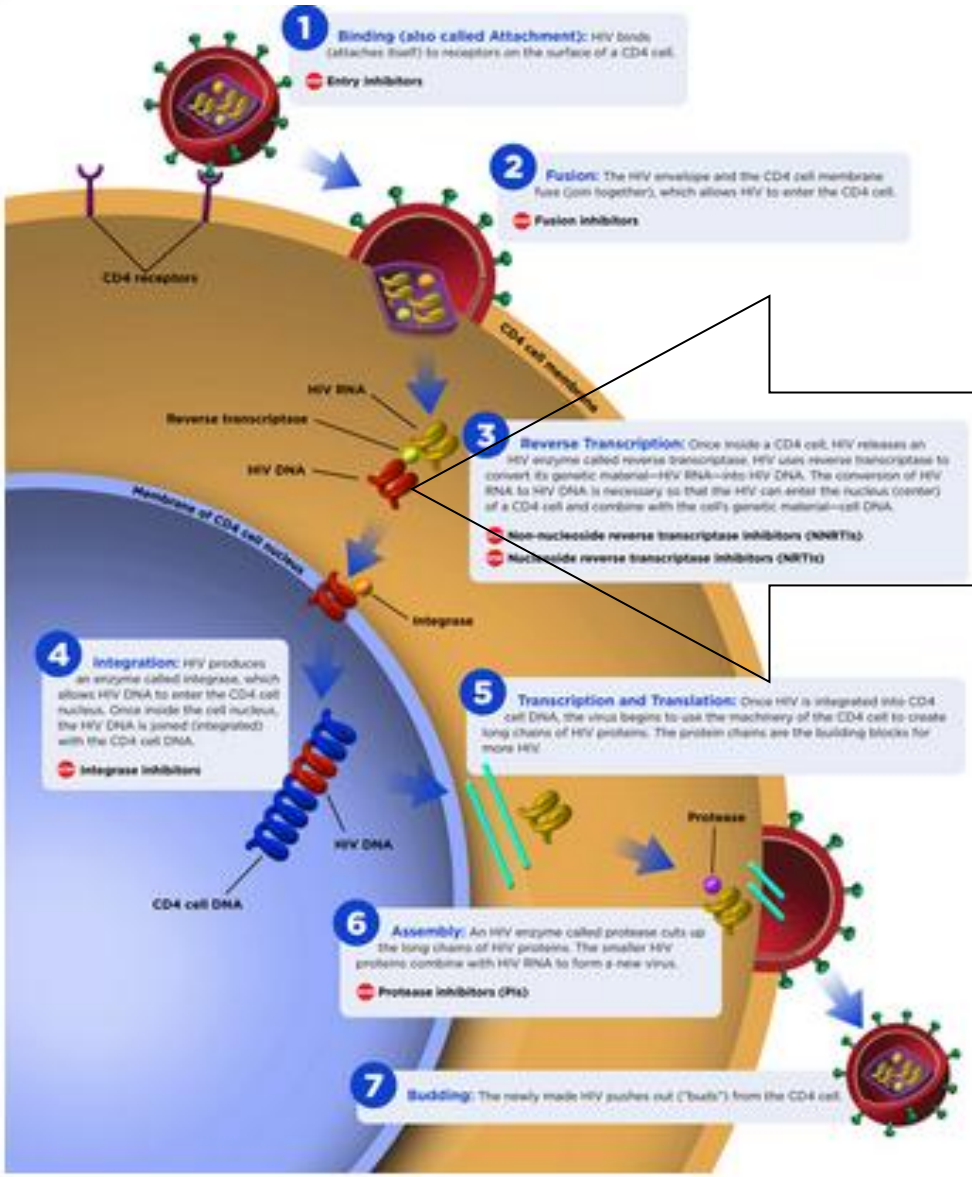
- **TENOFOVIR (TDF):**

- Achieve high concentrations in genital compartments, particularly high in rectal mucosa
- High genetic barrier to resistance
- Rapid antiretroviral activity
- Long intracellular and plasma half-lives

- **EMTRICITABINE (FTC)**

- Excellent safety profile and achieves high concentrations in the female genital tract
- Long intracellular and plasma half-lives

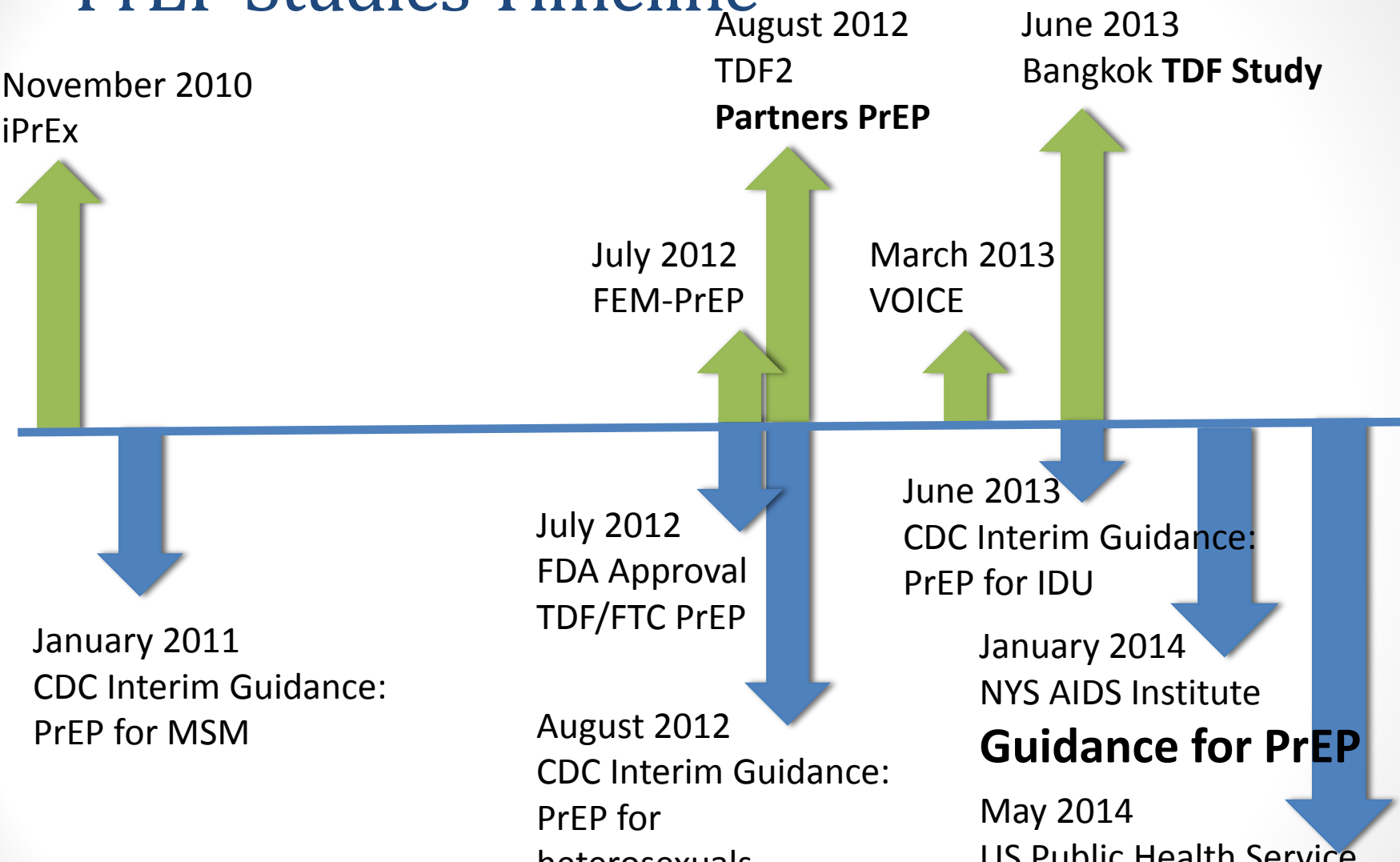
Krakowe SD et al. *Pre-Exposure Prophylaxis to Prevent HIV Infection: Current Status, Future Opportunities and Challenges, Drugs (2015)*



NRTI's and NNRTI's work here

http://www.aidsinfo.nih.gov/education-materials/fact-sheets/19/73/the-hiv-life-cycle

PrEP Studies Timeline



PrEP Studies who validated this strategy

HIV transmission risk lowest when participants took PrEP consistently

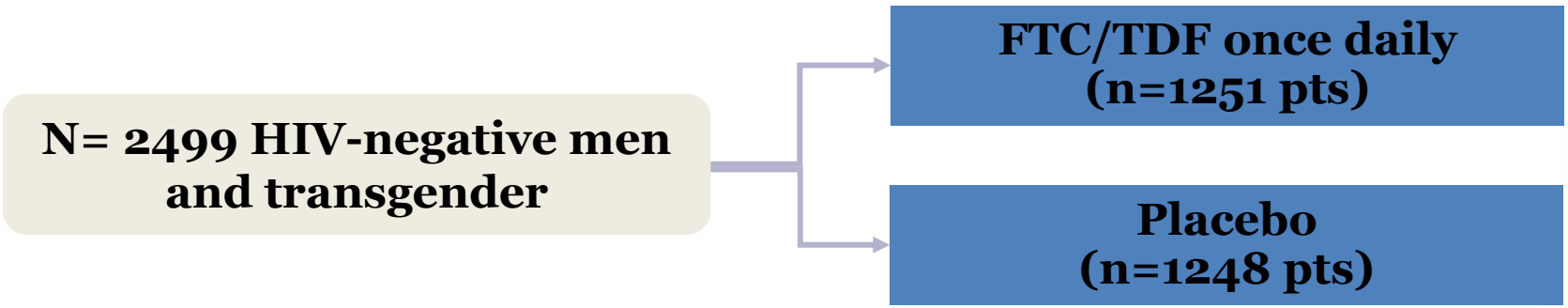
STUDY	**OVERALL** Reduction in risk of HIV infection	**Detectable level of medication in the blood** Reduction in risk of HIV infection
iPrEx	44%	>90%
TDF2	62%	---
Partners PrEP	75%	90%
BTS (Bankog Tenofovir Study)	49%	74%

Adapted from summary of research at http://www.cdc.gov/hiv/prevention/research/prep/

Pre-exposure Prophylaxis Initiative (iPrEX)

Study Design

Randomised, double-blind, placebo-controlled trial conducted in 6 countries (Brazil, Ecuador, Peru, South Africa, Thailand and United States) on 4 continents.

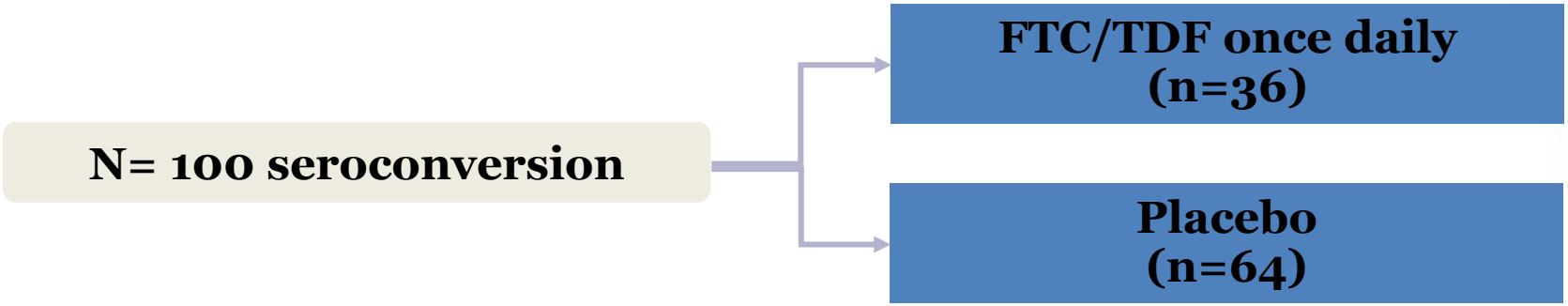


Primary Outcome: HIV infection (new seroconversion)

Robert M. Grant et al, Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men, N Engl J Med Volume 363(27):2587-2599 December 30, 2010

Pre-exposure Prophylaxis Initiative (iPrEX)

Results



Indicating a 44% reduction in the incidence of HIV (95%CI 15 to 63; P=0.005) in the FTC/TDF group.

In the FTC–TDF group, the study drug was detected in 22 of 43 of seronegative subjects (51%) and in 3 of 34 HIV-infected subjects (9%) (P<0.001)

Detectable blood levels strongly correlated with the prophylactic effect.

Robert M. Grant et al, Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men, N Engl J Med Volume 363(27):2587-2599 December 30, 2010

Partners PrEP

Study Design

Randomised, double-blind, placebo-controlled efficacy and safety study for HIV-negative partner (Kenya, Uganda)

Serodiscordant couples (HIV-positive partner not medically eligible for ART)
N=4747* couples
Randomised 1:1:1

- **FTC/TDF once daily (n=1579 couples)**
- **TDF once daily (n=1584 couples)**
- **Placebo once daily (n=1584 couples)**

*11 couples found after randomization to be ineligible and exited study

Primary Outcome: HIV infection in HIV-1 negative partner

Secondary Outcomes: Safety, risk behavior, adherence

DSMB recommended placebo arm be discontinued on 10th July 2011

All participants received safer sex counseling (individually and as a couple), HIV testing, free condoms, testing and treatment for STIs, and monitoring and care for HIV.

Baeten JM and Partners PrEP Study Team. *Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial.* Lancet Infect Dis. 2014 Nov

Partners PrEP

Primary Endpoint: HIV Seroconversion in Partner

Updated Analysis with Data Through November 20, 2014[1]

Modified Intention-to-Treat Analysis	TDF	FTC/TDF	Placebo
Number of HIV infections	17	13	52
HIV protection efficacy vs. placebo (95% CI)	67% (44-81%)	75% (55-87%)	n/a
P-value	<0.0001	<0.0001	
Relative risk reduction associated with detectable study drug* (95%CI)	86% (57%, 95%)	90% (56%, 98%)	
P-value	< 0.001	0.002	

*Adjusting for demographic and risk factors does not substantively change estimates

- HIV-1 protective effects were not significantly different for TDF and FTC/TDF (67% vs. 75%; *P*=0.23)[1]
- Both TDF and FTC/TDF **significantly reduced HIV-1 risk** in both genders

"Among persons taking TDF or FTC/TDF PrEP, detection of TDF in plasma was strongly predictive of high protection from HIV-1 acquisition"

[1]Baeten JM and Partners PrEP Study Team. *Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial.* Lancet Infect Dis. 2014 Nov

FEM PrEP

Study Design

Randomised, placebo-controlled efficacy and safety study
(Kenya, South Africa, Tanzania)
Endpoint-driven trial: 72 seroconversions

HIV-negative women at high risk for HIV acquisition
18-35 years old
Not planning to become pregnant
N = 2,120[2] (Planned N=3900)

→ **FTC/TDF once daily**

→ **Placebo once daily**

Outcomes measured:

- HIV seroconversion, sexual behavior, adherence, drug resistance
- VL / viral set point, CD4 count (if infected)

DSMB recommended study be stopped early on 18th April 2011

Unlikely to be able to demonstrate the effectiveness of Truvada in preventing HIV infection in the study population, even if it continued to its originally planned conclusion

"Adherence was too low to adequately assess the efficacy of PrEP in FEM-PrEP"[2]

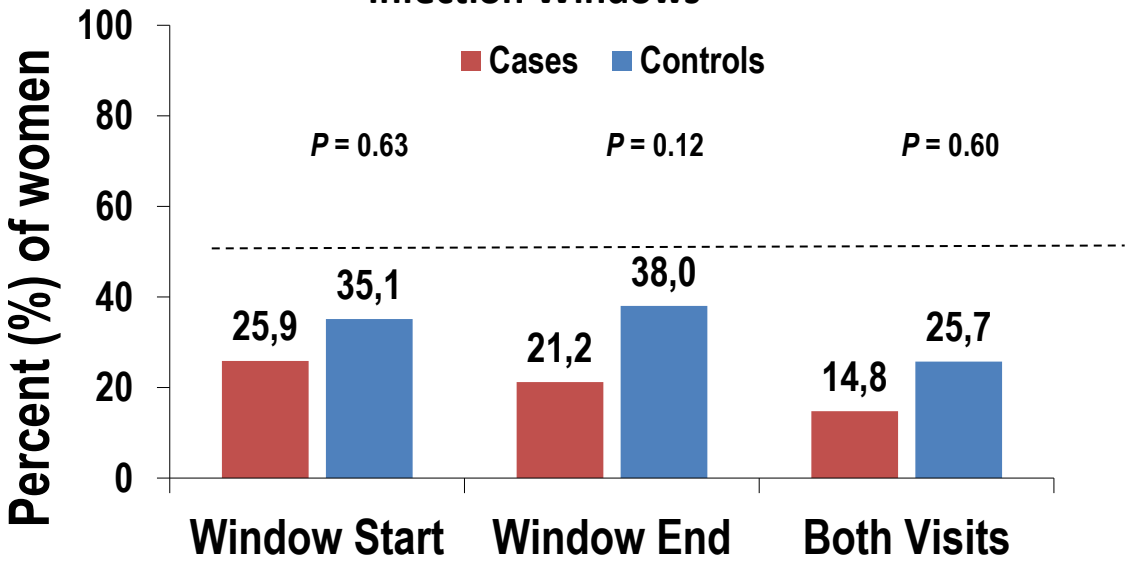
1. FHI; Press Release: April 18, 2011
2. Van Damme L, et al. CROI 2012. Seattle. #32LB

FEM PrEP

Results

	FTC/TDF	Placebo
Number of HIV infections	33	35
HIV incidence rate	4.7/100 PY	5.0/100 PY
HR for HIV protection (vs. placebo)	0.94 (0.59 - 1.52) p = 0.81	n/a

Infected Cases and Matched Controls with ≥ 10 ng/mL TDF in Plasma at Visits Defining Infection Windows



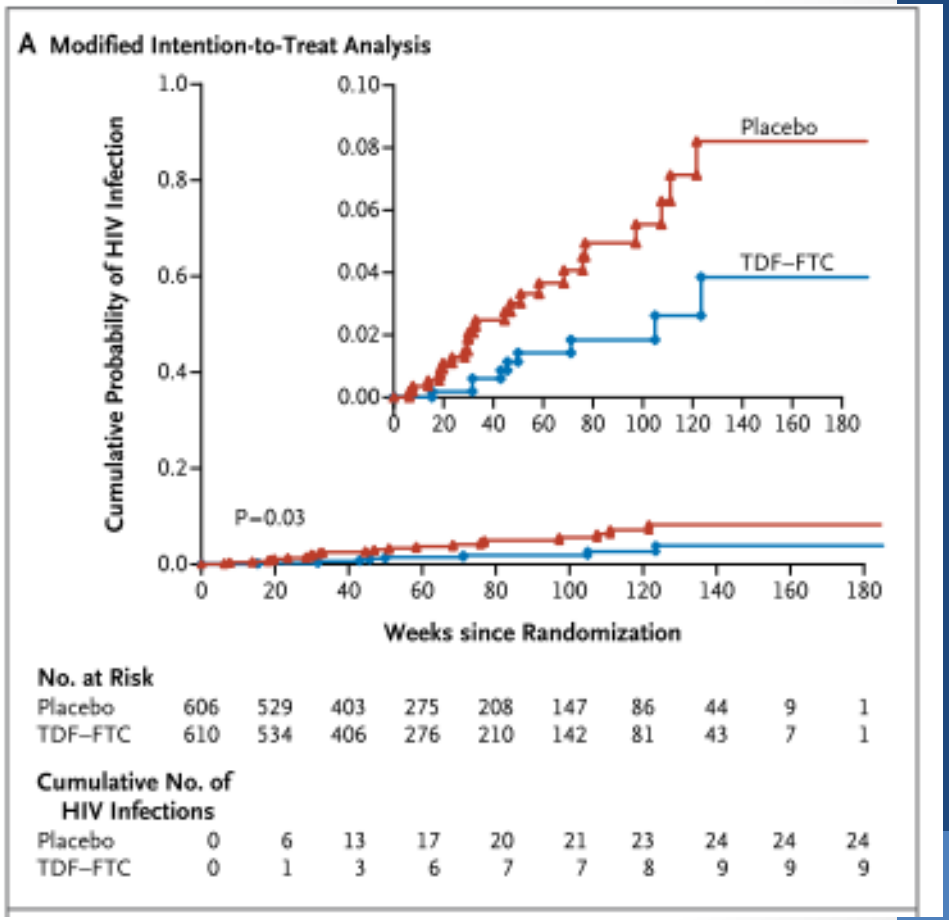
Less than 15% of cases had >10 ng/mL of tenofovir in plasma

Van Damme L, et al. CROI 2012; Seattle. #32LB

TDF 2 Study

1219 heterosexual men and women

- TDF/FTC daily
- Placebo daily



- In the TDF/FTC group higher rate of side effects (nausea, vomiting and dizziness) than placebo group; but similar rates of serious adverse events

- In the TDF/FTC group patients had a significant decline in bone density

➢ **Efficacy of TDF/FTC → 62.2%**

What's new about PrEP?

CROI and IAS 2015 updates

Alternative to Daily Truvada:

- Event- driven
- Local delivery drug

PROUD: Immediate vs Deferred PrEP in High-Risk MSM in "Real World" Trial

Study Design

- Randomized, open-label trial of **daily oral TDF/FTC** PrEP in HIV- MSM in 13 clinics in London
  - Immediate (n = 267) **vs**
  - Deferred for 12 mos (n = 256)
- **Primary endpoint**: HIV infection in first 12 mos
- **86%** reduction in risk seen over 60 wks with **immediate PrEP** (90% CI: 58% to 96%, *P* = .0002)
  - Rate difference: 7.6 (90% CI: 4.1-11.2)
  - Number needed to treat to prevent 1 infection: 13 (90% CI: 9-25)

McCormack S, et al. CROI 2015. Abstract 22LB.
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PROUD: Immediate vs Deferred PrEP in High-Risk MSM in "Real World" Trial

Results

HIV Incidence		
Group	Infected, n	Incidence/100 PY (90% CI)
Immediate	3	1.3 (0.4-3.0)
Deferred	19	8.9 (6.0-12.7)

- All 3 infected persons in immediate group seroconverting at study entry or shortly after first dose of PrEP
- M184V/I observed in 3/6 patients who seroconverted
  - No K65R observed
- High rate of STIs seen in both groups
- **DMSB interrupted trial**; recommended that all participants be offered PrEP

McCormack S, et al. CROI 2015. Abstract 22LB.
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ANRS IPERGAY: On-Demand Oral PrEP in High-Risk MSM

Study Design

- Randomized double-blind trial of event-driven oral TDF/FTC* (n = 199) vs placebo (n = 201) (both with prevention services) in France
  - 2 tablets taken 2-24 hrs before sex
  - 1 tablet 24 hrs after sex
  - 1 tablet 48 hrs after first event-driven dose
- Primary endpoint: HIV seroconversion
- **86%** reduction in risk seen in PrEP arm (95% CI: 40% to 99%, *P* = .002)
  - Number needed to treat for 1 yr to prevent 1 infection: **18**
  - on average 4 pills/week (15 pills/month)

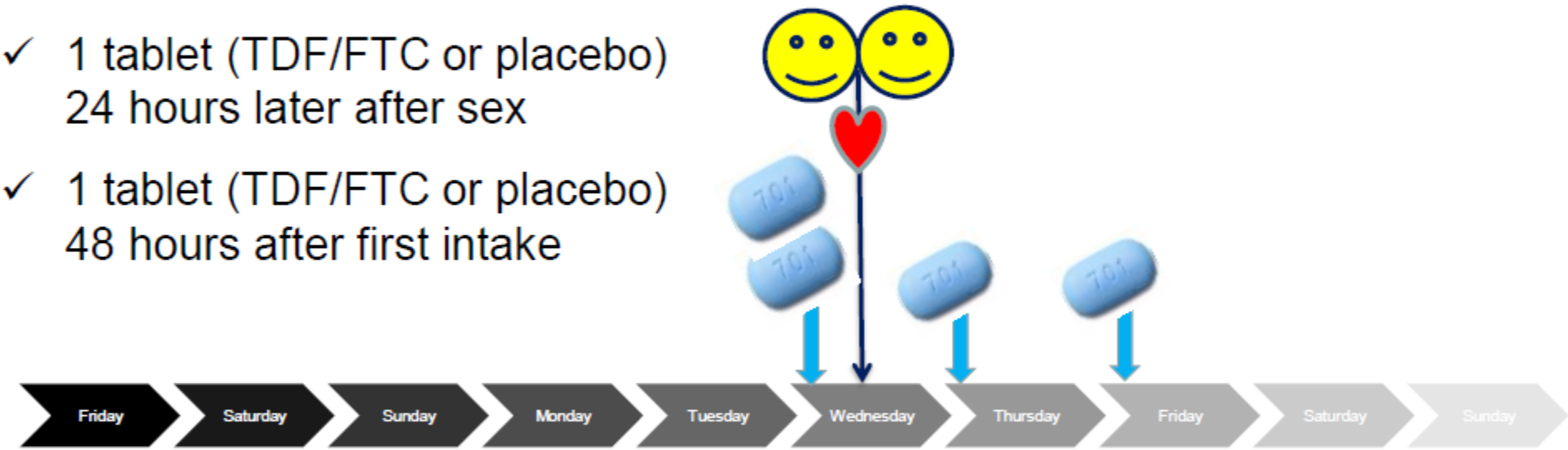
***On-demand PrEP strategy not FDA approved.**

Molina JM, et al. CROI 2015. Abstract 23LB.
Reproduced with permission.

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

Ipergay : Event-Driven iPrEP

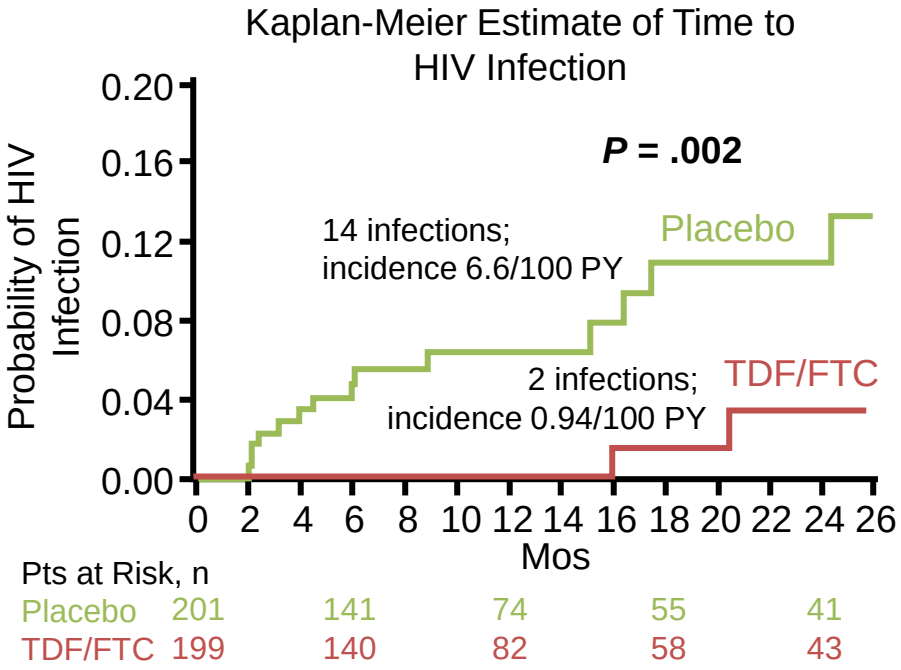
- ✓ 2 tablets (TDF/FTC or placebo)
  2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo)
  24 hours later after sex
- ✓ 1 tablet (TDF/FTC or placebo)
  48 hours after first intake



4 pills over 3 days for one sexual intercourse
two pills before and two pills after

ANRS IPERGAY: On-Demand Oral PrEP in High-Risk MSM

Results



- In pts with infection (2 in TDF/FTC arm)**, no TFV found in serum in last 2 visits**
- 4 cases of acute HCV infection noted among lab abnormalities
- **DSMB stopped trial early** and recommended all participants start PrEP

Molina JM, et al. CROI 2015. Abstract 23LB.
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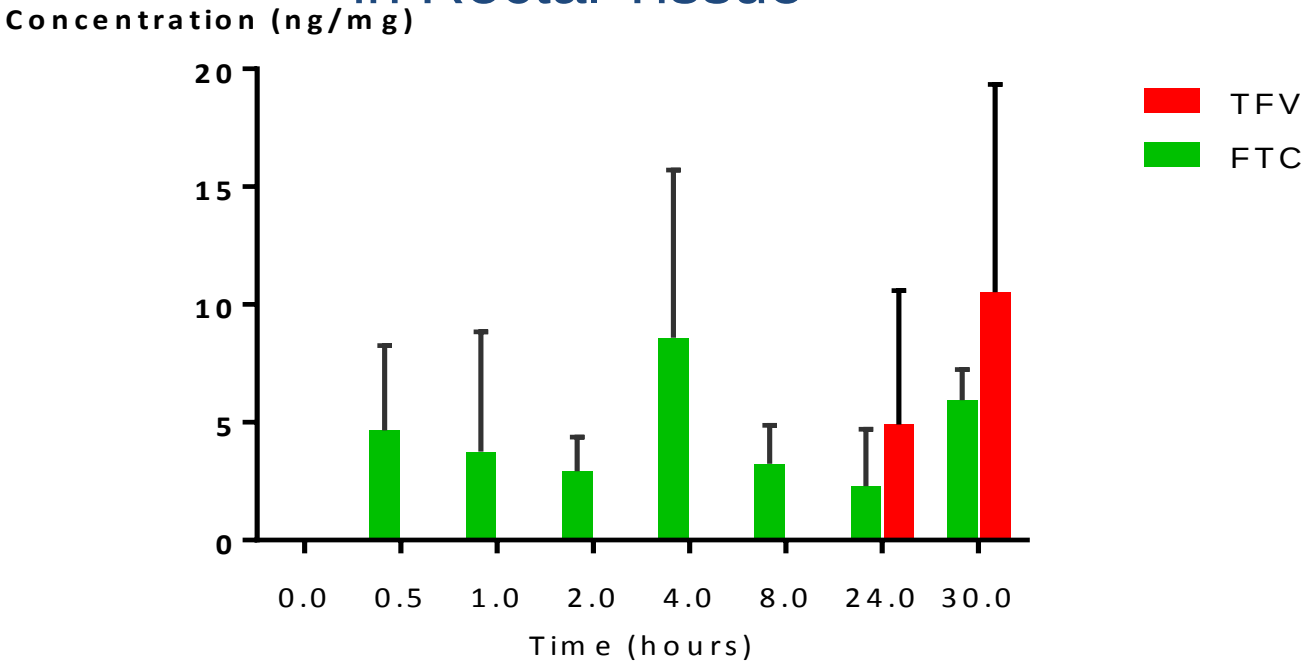
ANRS IPERGAY: On-Demand Oral PrEP in High-Risk MSM

TFV and FTC Concentration in Rectal Tissue



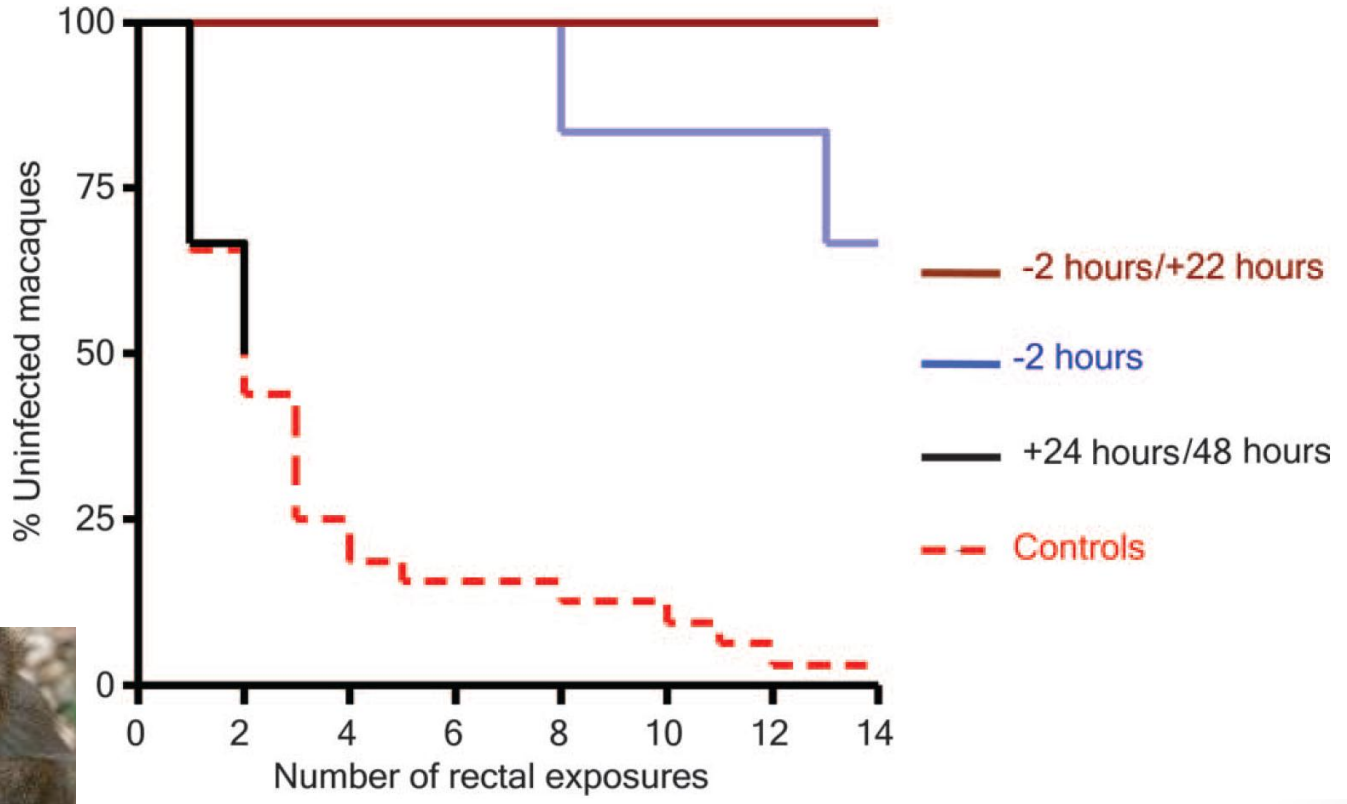
- Early detection of FTC in rectal tissue at high concentrations similar to HIV-infected patients on ART
- TFV is only detectable at 24h post drug intake at high concentrations

Jean-Michel Molina
and the ANRS Ipergay Study Group, IAS 2015

ANRS IPERGAY: On-Demand Oral PrEP in High-Risk MSM

Are post-exposure doses needed?

Protection by SC TDF/FTC Given Before and/or After SHIV Exposure



Garcia-Lerma , Science Trans Med 2010, 14,14ra4

ANRS IPERGAY: On-Demand Oral PrEP in High-Risk MSM

Conclusions

- A double-dose of TDF/FTC is associated with rapid and high concentrations of TVF and FTC in plasma
- FTC can achieve rapid and high concentrations in rectal tissue and saliva
- Pre- and Post-exposure doses both appear to be critical for providing full protection against HIV acquisition
- **The effectiveness of coitally-dependent PrEP in people with less frequent sex has yet to be demonstrated**
- The IPERGAY study is ongoing open-label and will hopefully provide additional information

Oral PrEP + ART as Prevention in High-Risk Serodiscordant Couples

- **Partners Demonstration Project in Africa**
  - Oral daily TDF/FTC PrEP for HIV-uninfected partner in serodiscordant couple continued 6 mos beyond initiation of ART for infected partner (bridge solution)
  - High-risk couples defined as younger age, fewer children, uncircumcised HIV-negative male, cohabitating, unprotected sex in past mo, high HIV-1 RNA in HIV-positive partner

- Interim analysis
  - > 95% of HIV-negative partners using PrEP
  - 80% of HIV-positive partners have initiated ART;

  of these, > 90% with suppression

Baeten J, et al. CROI 2015. Abstract 24. Reproduced with permission.

Oral PrEP + ART as Prevention in High-Risk Serodiscordant Couples

- **96%** reduction in expected infections
  - IRR, expected vs observed: 0.04 (95% CI: 0.01-0.19; *P* < .0001)

HIV Incidence, Actual vs Expected		
Group	Infected, n	Incidence/100 PY (95% CI)
Expected	39.7	5.2 (3.7-6.9)
Actual	2	0.2 (0-0.9)

- In pts with seroconversion, **no TFV detectable in plasma** at time of seroconversion
  - HIV-positive partner in 1 couple not on ART (high CD4+ count)
  - Other couple dissolved and HIV-negative partner in new relationship

Observed HIV incidence <0.5% per year compared to an expected incidence >5% per year

Baeten J, et al. CROI 2015. Abstract 24. Reproduced with permission.

Concerns about PrEP:

- Efficacy dependent on adherence (daily regimen)
- Long-term safety (bone and kidney)
- Side Effects
- Cost
- Drug resistance in acute infection

In study solutions:

- Topical administration
- Less-than-daily regimen
- Other ARV classes

VOICE STUDY: Vaginal and Oral Intervention to Control the Epidemic

Study Design

- 15 trial sites in Uganda, South Africa and Zimbabwe enrolled **5,029** sexually active HIV-negative **women**
- 5 study groups (each of~ 1000 pts):
  - tenofovir gel
  - inactive placebo gel
  - oral tenofovir
  - oral tenofovir/emtricitabine
  - inactive placebo tablet

Primary Objectives:

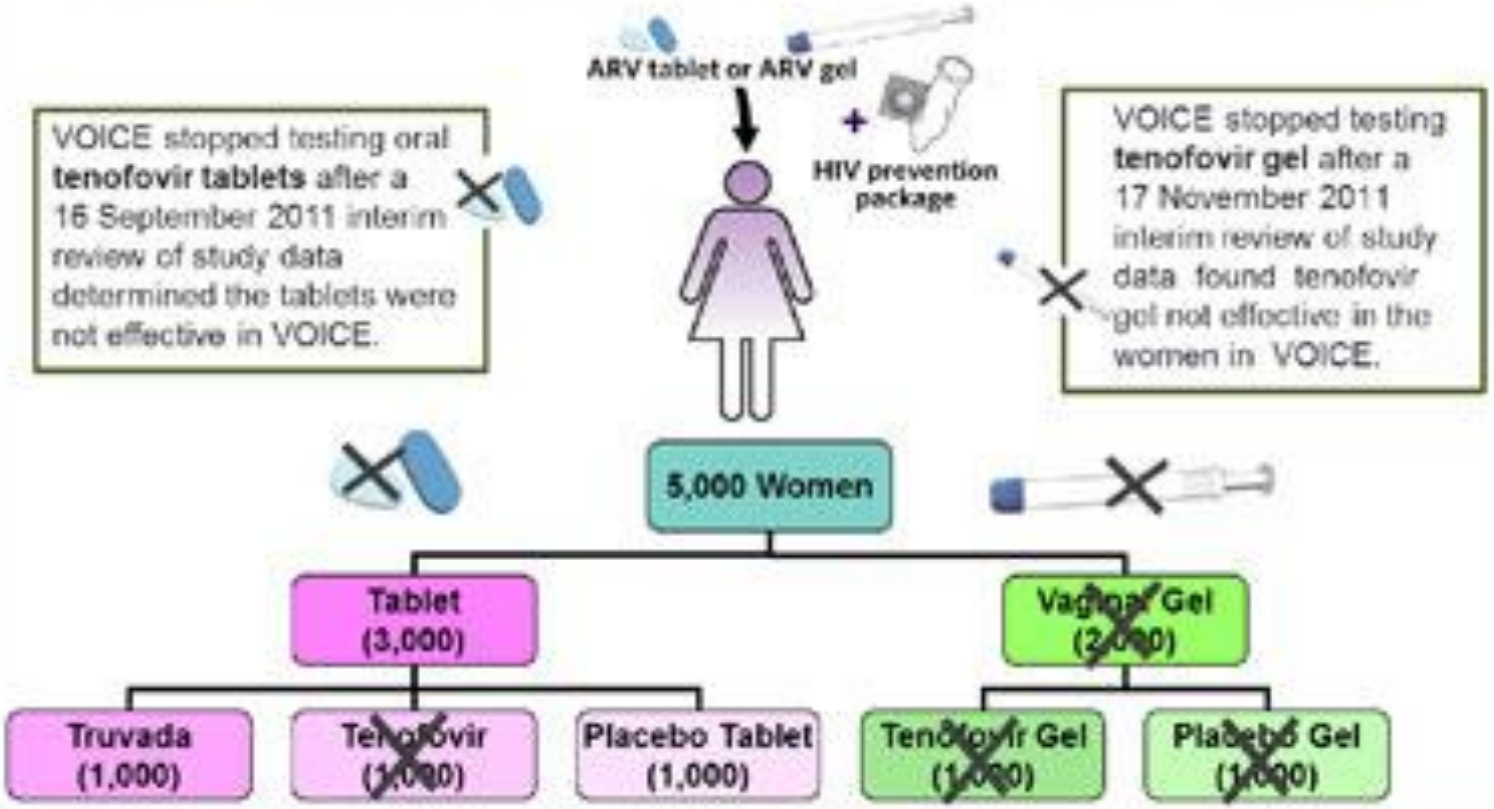
- To estimate the effectiveness of daily tenofovir 1% gel compared to a vaginal placebo gel, and the effectiveness of oral TDF and oral FTC/TDF compared to an oral placebo in preventing HIV infection among women at risk for sexually transmitted infection (STI)
- To evaluate the extended safety of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection

VOICE STUDY:Vaginal and Oral Intervention to Control the Epidemic

Results

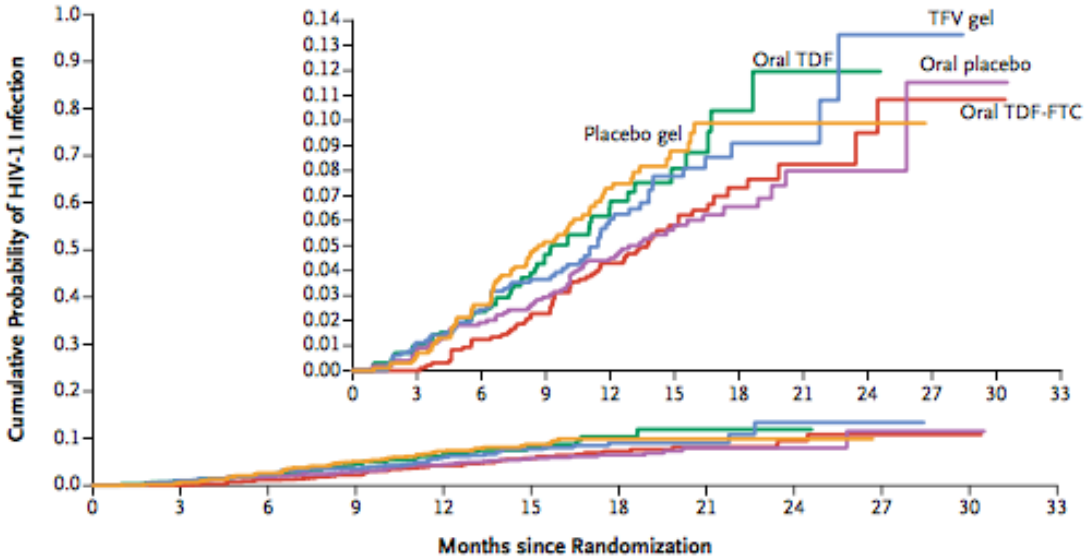
VOICE already found oral tenofovir tablets and tenofovir gel were safe but not effective in preventing HIV but continued to test oral Truvada until the scheduled end of the study in August 2012.

Results of VOICE will determine whether daily use of Truvada was safe and effective in preventing HIV among the women in the study and provide insight into *why* oral tenofovir and tenofovir gel were not effective.



VOICE STUDY:Vaginal and Oral Intervention to Control the Epidemic

Results



No. at Risk

Oral TDF	1002	966	752	504	309	155	72	23	2	0	0
Oral TDF-FTC	994	971	953	931	802	467	271	143	71	22	2
Oral placebo	1008	982	966	943	818	485	281	152	72	22	1
TFV gel	1003	973	944	702	486	288	154	64	14	1	0
Placebo gel	1000	985	952	699	493	278	145	64	16	0	0

Figure 2. Cumulative Probability of HIV-1 Infection, According to Study Group.

The numbers shown below the graph are the numbers of participants who were at risk at the start of each quarterly interval. The inset shows the same data on an enlarged y axis.

Marrazzo JM et VOICE study team. *Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women*, NEJM Feb 2015

VOICE STUDY:Vaginal and Oral Intervention to Control the Epidemic

Results

Table 3. Primary Efficacy Results.

Result	Oral TDF*		Oral TDF-FTC	Oral Placebo	TFV Gel	Placebo Gel
	Active Agent	Placebo				
Person-years	823	838	1284	1308	1024	1030
Number of HIV-1 infections	52	35	61	60	61	70
HIV-1 incidence — cases per 100 person-years (95% CI)	6.3 (4.7–8.3)	4.2 (2.9–5.8)	4.7 (3.6–6.1)	4.6 (3.5–5.9)	6.0 (4.6–7.6)	6.8 (5.3–8.6)
Hazard ratio (95% CI)	1.49 (0.97–2.29)	—	1.04 (0.73–1.49)	—	0.85 (0.61–1.21)	—
P value	0.07	—	0.81	—	0.37	—

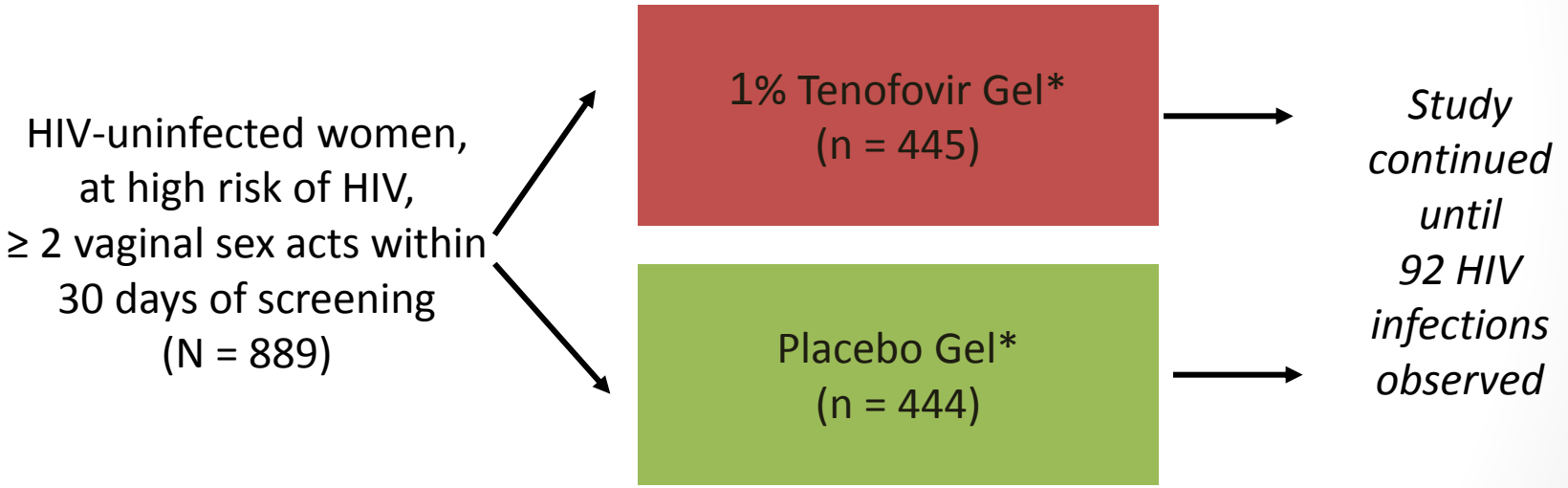
* Data were censored on the date when sites were asked to discontinue treatment in the oral TDF group.

- Adherence was very low
- Importance of education and motivation
- **Only oral PrEP showed effective protection**
- Among women in the tenofovir gel group whose blood tests indicated use of the gel, **HIV risk appeared to be reduced significantly.**

Marrazzo JM et VOICE study team. *Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women*, NEJM Feb 2015

CAPRISA 004
Study design

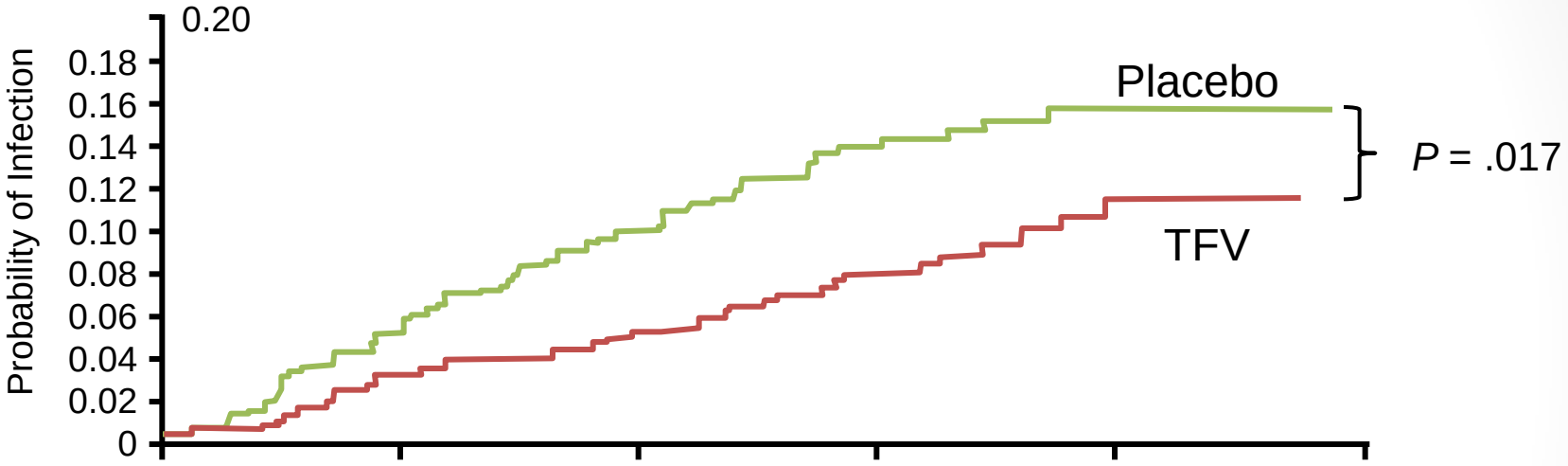
- Randomized, placebo-controlled, double-blind, proof-of-concept study conducted at 2 sites in South Africa



*Gel applied using "BAT 24" regimen: 1 gel dose up to 12 hrs before sex; 1 gel dose as soon after sex as possible, within 12 hrs after sex; maximum of 2 doses to be used within 24-hr period.

Abdool Karim, Q, et al. Science. 2010;329:1168-1174.
Sokal D, et al. AIDS 2010. Abstract TUSS0503.

CAPRISA 004
HIV incidence

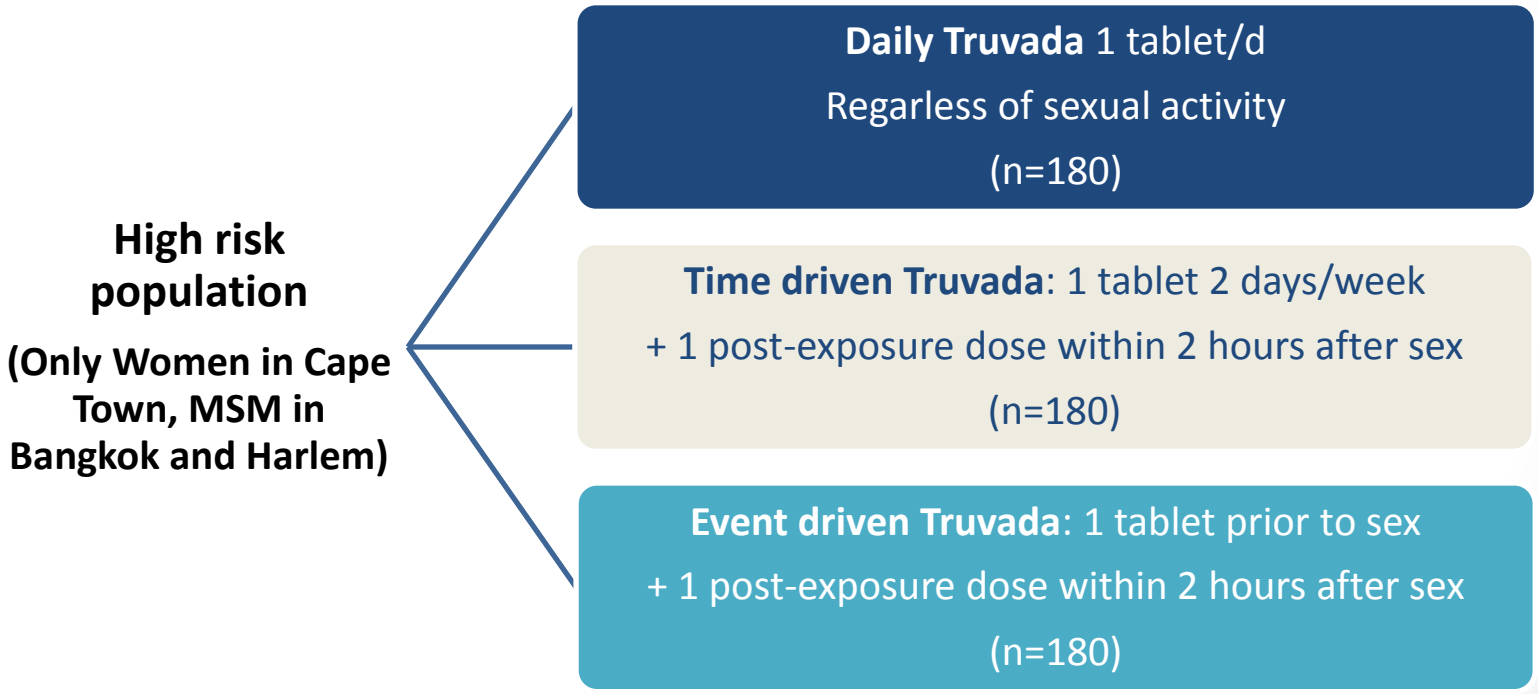


Mos of Follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-yrs	432	833	1143	1305	1341
HIV incidence rates (TFV vs placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness, % (*P* value)	**47 (.064)**	**50 (.007)**	**47 (.004)**	**40 (.013)**	**39 (.017)**

Abdool Karim, Q, et al. Science. 2010;329:1168-1174.

HPT 067/**ADAPT**
Study Design

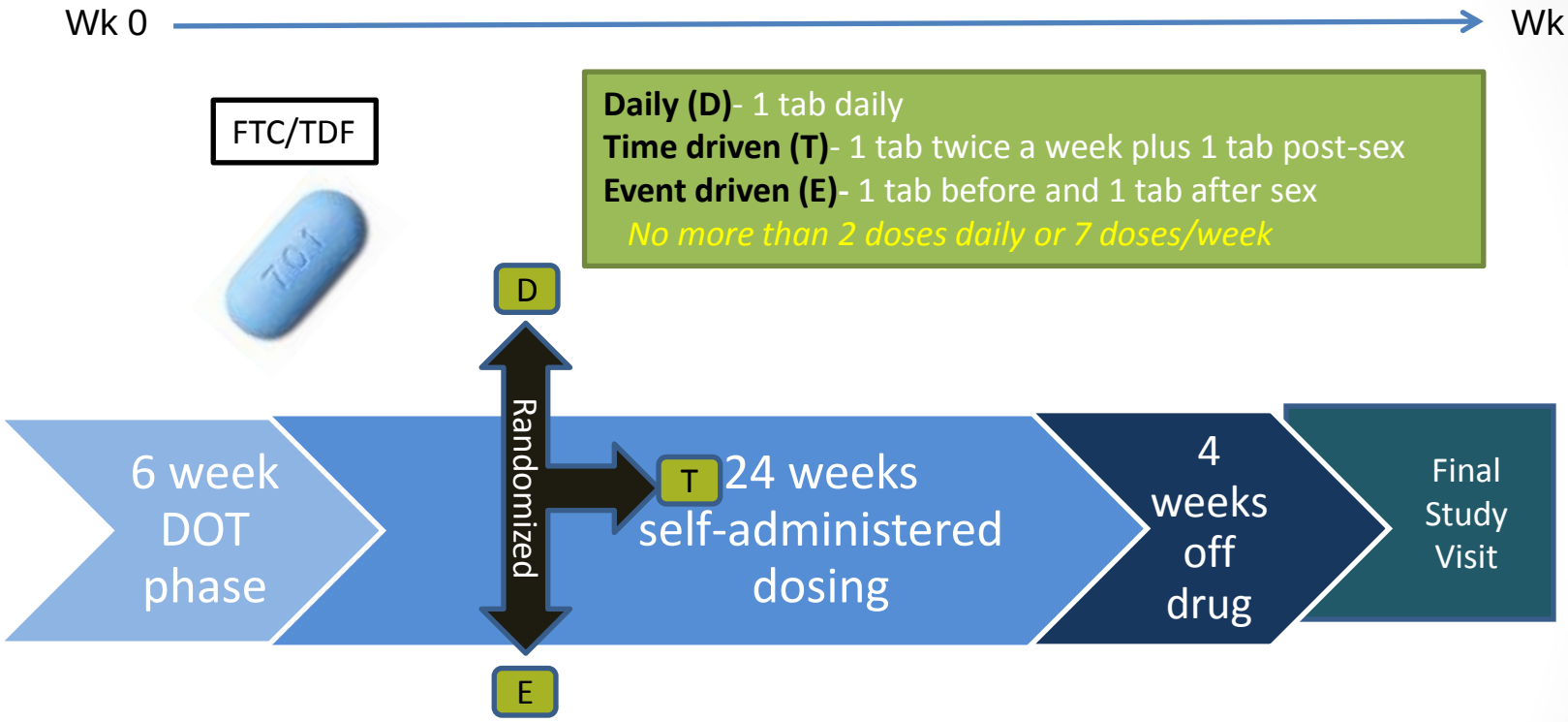
- Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of **Intermittent Oral PrEP with TDF/FTC**



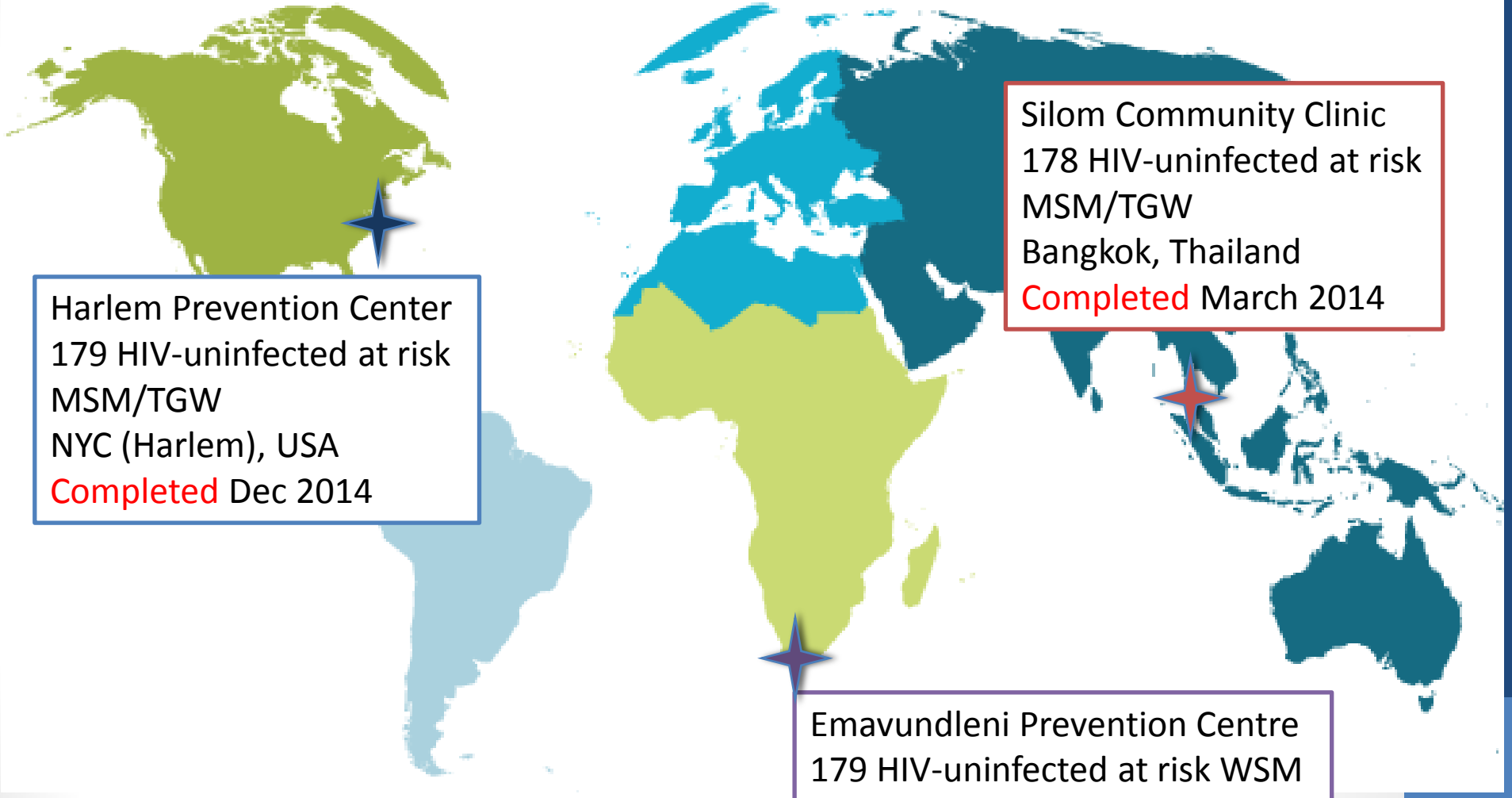
- **Primary Objective**: intermittent vs daily dosing associated with equivalent coverage of sex events, lower number of pills used and decreased side effects

http://www.hptn.org/web%20documents/HPTN067/HPTN067_SAresults_Fact%20Sheet_V1.0.pdf

HPT 067/**ADAPT**
Study Design

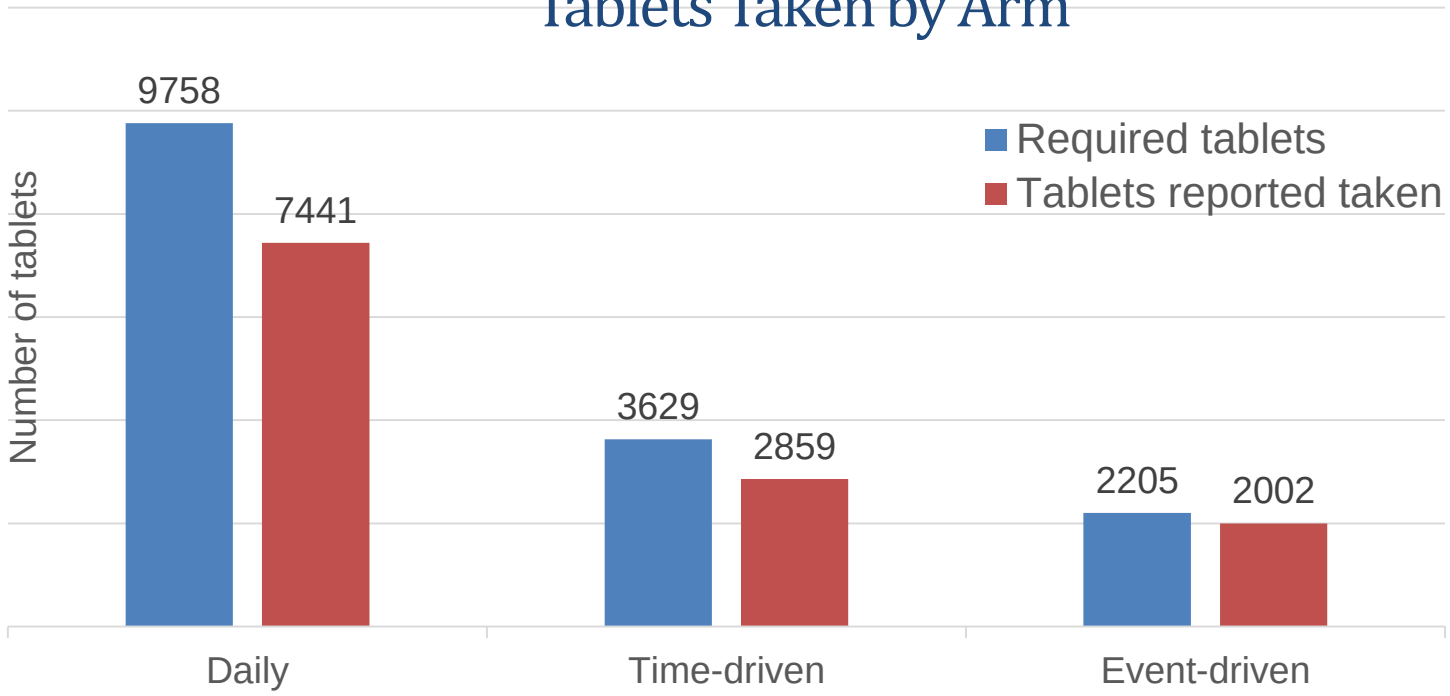


Mannheimer S, Feasibility of Intermittent PrEP Among US MSM: Data from the Harlem Site, HPTN 067: ADAPT Study, IAS 2015


Harlem Prevention Center
179 HIV-uninfected at risk
MSM/TGW
NYC (Harlem), USA
Completed Dec 2014
Silom Community Clinic
178 HIV-uninfected at risk
MSM/TGW
Bangkok, Thailand
Completed March 2014
Emavundleni Prevention Centre
179 HIV-uninfected at risk WSM
Cape Town, South Africa
Completed June 2013

HPT 067/**ADAPT** (Cape Town) Results

Adherence: FTC/TDF Tablets Required and Tablets Taken by Arm



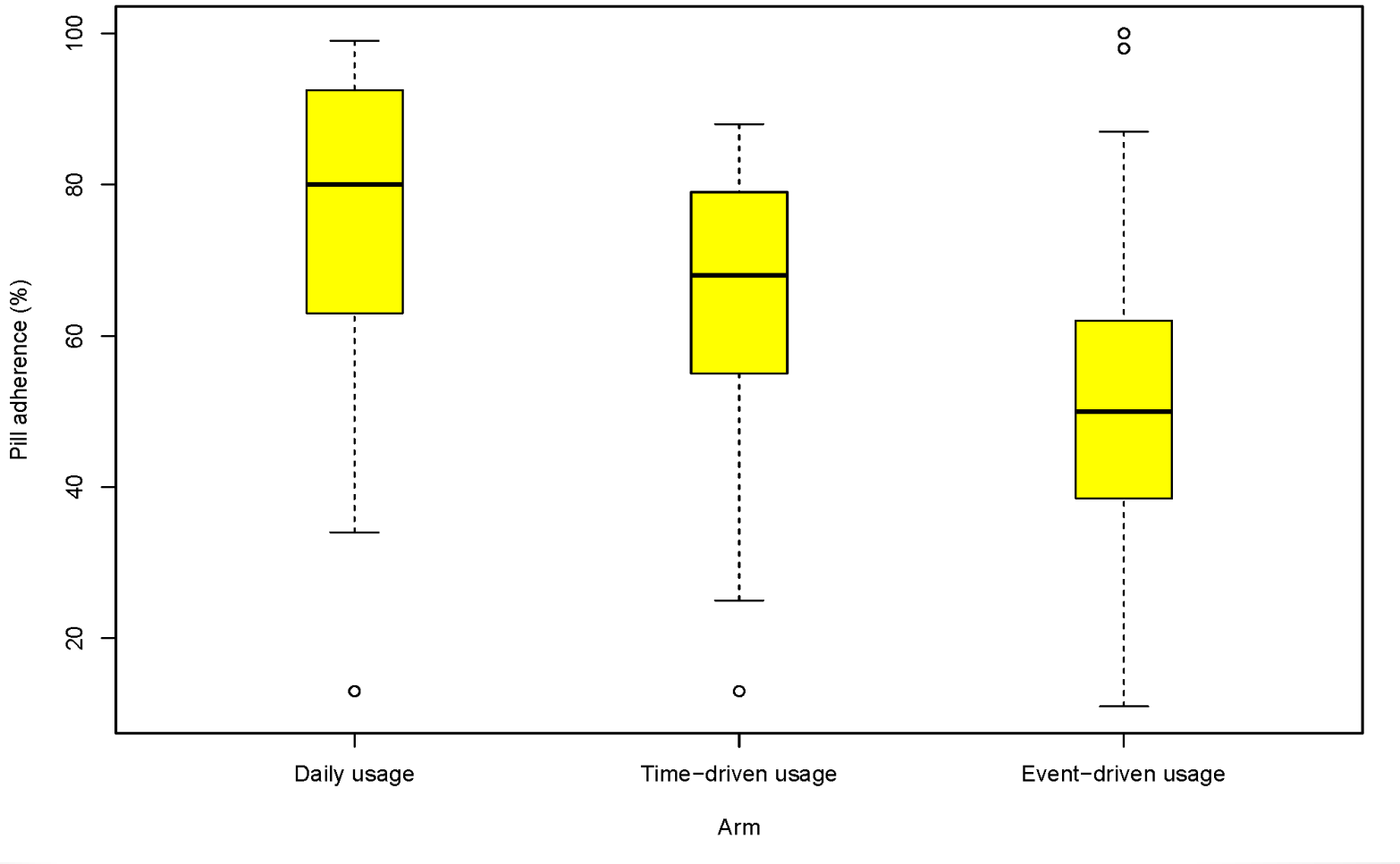
Required tablets: p<0.0001 for all comparisons (D/T, D/E, and T/E)
Tablets actually taken: p<0.0001 for all comparisons (D/T, D/E, and T/E)

Weekly telephone contact may have served as reminders.

HPT 067/**ADAPT** (Cape Town)

Results

Adherence



Time *vs.* Daily p = 0.002, Event *vs.* Daily p < 0.0001, Time *vs.* Event p < 0.0001.

HPT 067/**ADAPT** (Cape Town) Results

Dosing Regimen	Drug in Plasma at Week 10	Drug in Plasma at Week 30
Daily	93%	79%
Time-driven	87%	63%
Event-driven	78%	53%

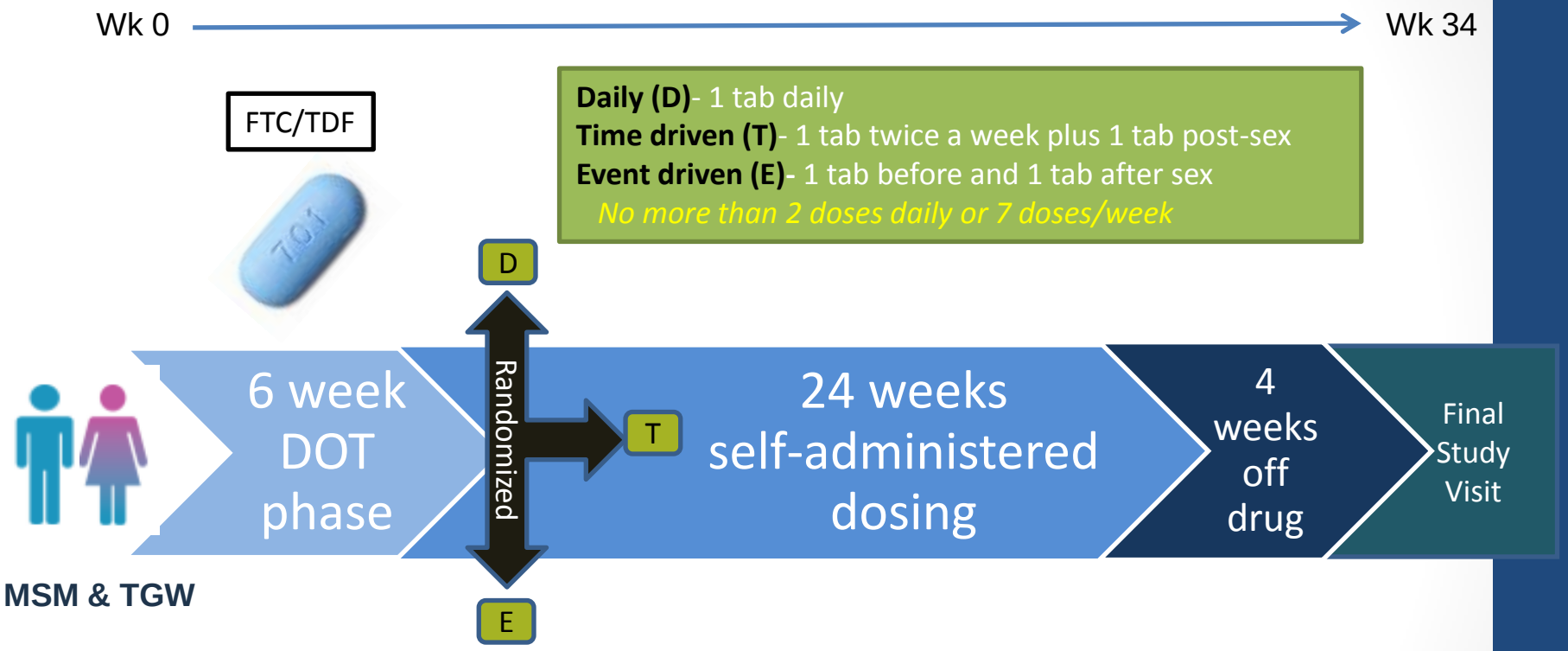
- There was **no significant difference** in the number of women who became HIV-positive between the three dosing arms, with two identified HIV infections during the directly observed therapy (DOT) phase and five HIV infections after randomization into the three dosing arms.

- Women assigned to a daily dosing regimen led to better adherence of PrEP and coverage of sexual acts, when compared to those assigned to non-daily dosing regimens. Daily dosing appeared to foster better adherence, better coverage of potential sexual exposure, and more sustained use of PrEP.

These findings support current recommendations for daily use of oral PrEP in women.

http://www.hptn.org/web%20documents/HPTN067/HPTN067_SAresults_Fact%20Sheet_V1.0.pdf

HPT 067/**ADAPT** (Harlem)
Study Design



179 participants randomized

Mostly young (one third ≤ 25, median age 30 y)

MSM (98%)

TGW (2%)

Black (70%)

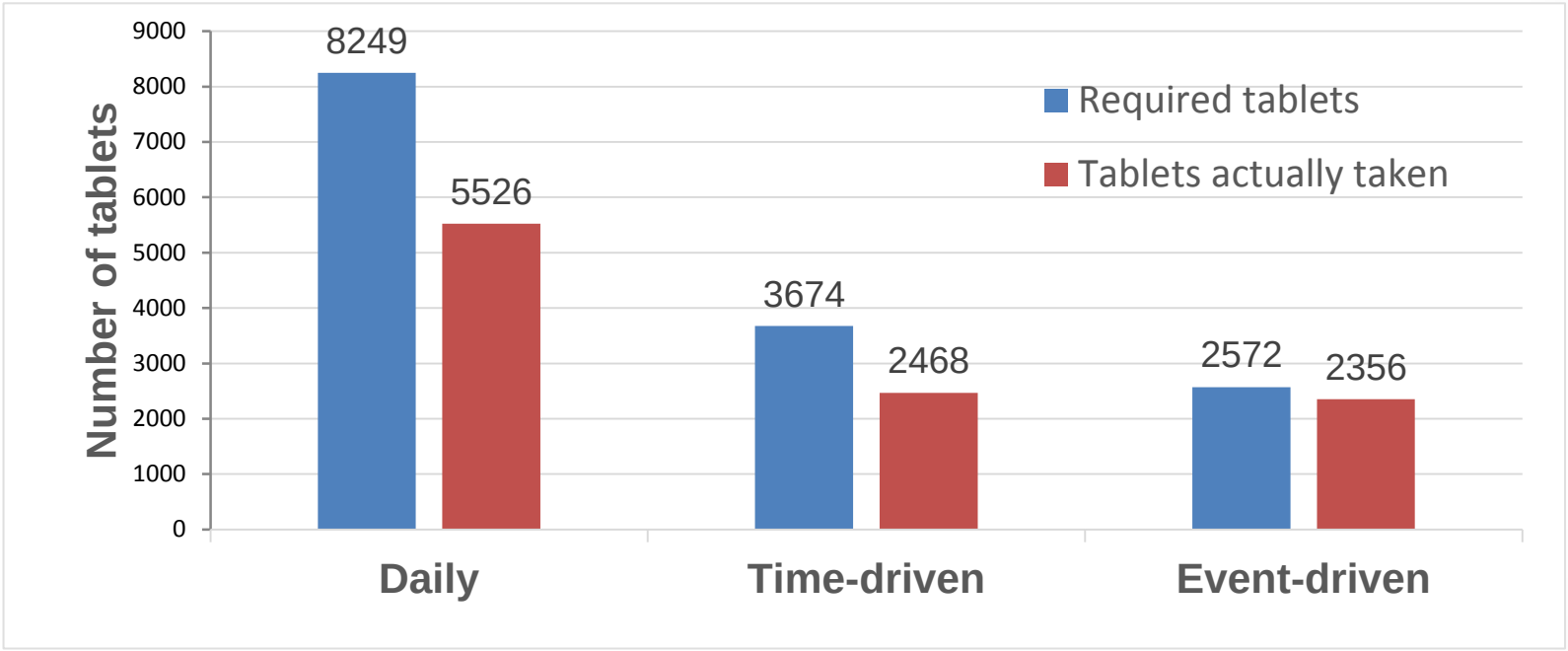
Latino (25%)

Unemployed (69%)

Mannheimer S, Feasibility of Intermittent PrEP Among US MSM: Data from the Harlem Site, HPTN 067: ADAPT Study, IAS 2015

HPT 067/**ADAPT** (Harlem) Results

Adherence: FTC/TDF Tablets Required and Tablets Taken by Arm



Required tablets: p<0.0001 for all comparisons (D/T, D/E, and T/E)
Tablets actually taken: D/T and D/E p<0.0001; T/E p=0.33

The number of tablets actually taken were significantly lower in both non-daily arms compared to Daily (no diff btwn Time & event)

Mannheimer S, Feasibility of Intermittent PrEP Among US MSM: Data from the Harlem Site, HPTN 067: ADAPT Study, IAS 2015

HPT 067/**ADAPT** (Harlem) Results

2 Seroconversions occurred at the Harlem site:

- 1 seroconversion during 6-week pre-randomization weekly DOT study phase
  - **No detectable drug at visits preceding or at seroconversion visit**
  - 1 of 238 participants over 22.6 person-years
  - Incidence 4.4%
- 1 seroconversion during 24-week post-randomization self administered PrEP phase
  - Occurred at Week 18 (Daily arm), 12 weeks post-randomization
  - No detectable drug at visit preceding seroconversion
  - very low level of TDF was detected only in dried blood spot (not in plasma) at the seroconversion visit
  - 1 of 179 participants over 83.1 person years
  - Incidence 1.2%

Mannheimer S, Feasibility of Intermittent PrEP Among US MSM: Data from the Harlem Site, HPTN 067: ADAPT Study, IAS 2015

HPT 067/**ADAPT** (Bangkok) Study and Results

- 178 randomized participants (MSM and TGW)
- 2 seroconversion during the 6-week pre-randomization weekly DOT study phase:
  - Both occurred at week 4
  - Both had low levels of FTC detected and no detectable TVF in plasma
  - Both had low detectable levels of both FTC and TVF in PBMC

Holtz TH, A Comparison of Daily and Non-daily Pre-exposure Prophylaxis Dosing in Thai Men Who Have Sex With Men, Bangkok, HPTN 067 / ADAPT Study, IAS 2015

Alternative Strategies On going Studies

MTN-020/**ASPIRE**

- Phase III, **dapivirine vaginal ring** worn for a month at a time
- With or without levonorgestrel: provides also lasting but reversible contraception.

- 2,629 women ages 18 to 45, who are randomly assigned in equal numbers to use either the dapivirine ring or a placebo ring. Women use their assigned ring for at least one year, some for more than two years

- from 15 clinical research sites in Malawi,

South Africa, Uganda and Zimbabwe.

- **Primary endpoint**: HIV seroconversion
- **Secondary endpoint**: long-term safety of the ring and acceptability


Andrew Loxely

Results are expected to be reported early 2016

http://www.mtnstopshiv.org/news/studies/mtn020

HPTN 076
Study Design

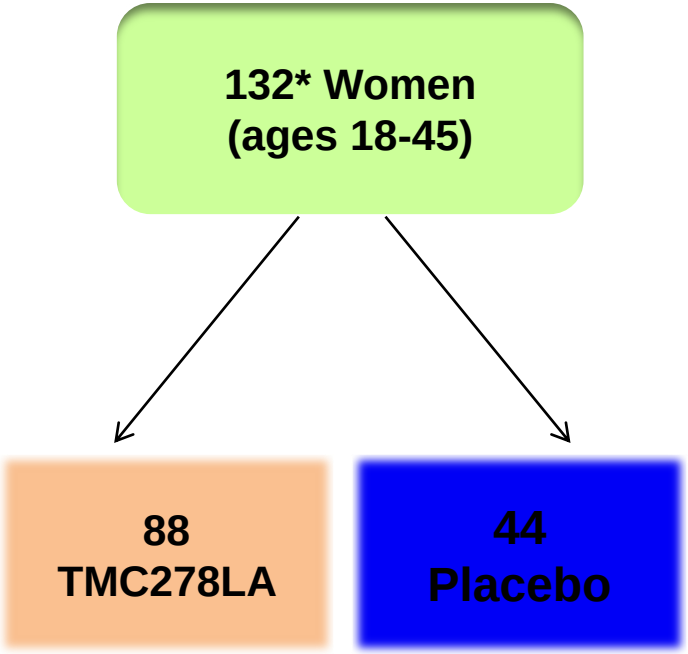
- Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for Pre Exposure Prophylaxis (PrEP)

- **Study Purpose:** To evaluate the safety and acceptability of the injectable product, **TMC278 LA** in healthy, HIV-uninfected women.

- **Study Design:** multi-site, double-blinded, two-arm, two:one, randomized, trial comparing the safety of an intramuscular (IM) injection of TMC278 LA to a placebo given once every eight weeks over a 40 week period among sexually active, HIV-uninfected women. Approximately 132 women will be randomized.

- **Study Population:** HIV-uninfected women, ages 18-45.

HPTN 076
Study Design



2:1 randomization
active:placebo

Treatment:

- Oral TMC278 (rilpivirine) 25 mg cp or placebo once daily for 4 ws
- IM injections of active TMC278 LA, 1200 mg or placebo at 8 ws intervals (until w 44)

HPTN 077
Study Design

- A Phase IIa Safety, Tolerability and Acceptability Study of an Investigational Injectable **HIV Integrase Inhibitor**, GSK1265744, for PrEP in HIV Uninfected Men and Women

- **Study Purpose:** To evaluate the safety, tolerability, pharmacokinetics and acceptability of the injectable agent, GSK1265744 long-acting injectable (744LA), in healthy, HIV-uninfected men and women.

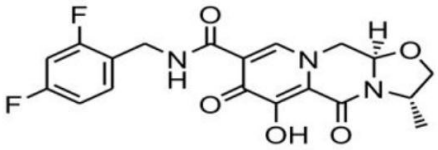
- **Study Design:** Multi-site, double-blind, two-arm, randomized, placebo-controlled trial of the safety, tolerability, and acceptability of 744LA.

- **Study Population:** HIV-uninfected men and women at low to minimal risk for acquiring HIV infection, ages 18 to 65.

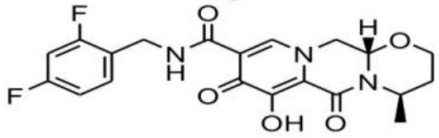
HPTN 077

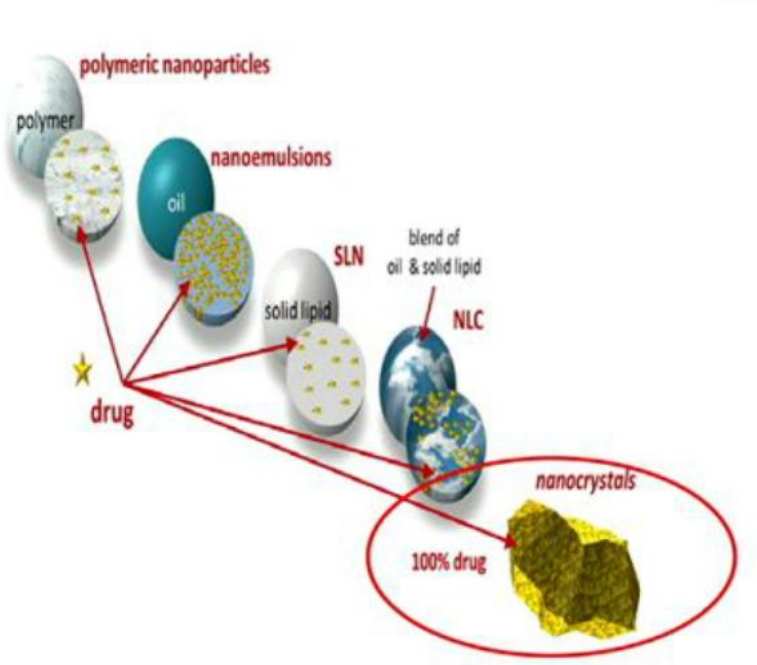
CABOTEGRAVIR: GSK126744 Long Acting (744LA)

GSK1265744 (GSK744)



Dolutegravir



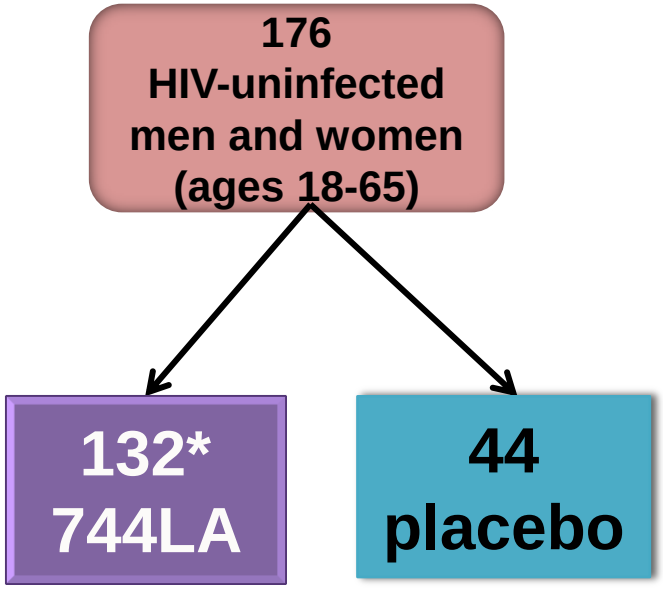


Favorable attributes for PrEP:

- High genetic barrier to resistance
- PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation

Muller *et al*, European Journal of Pharmaceutics and Biopharaceutics,2011
Spreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012

HPTN 077
Study Design



3:1 randomization
active:placebo

Treatment:

- Oral Cabotegravir (30 mg tablets) or daily oral placebo for 4 weeks
- one-week washout
- IM gluteal injections of 744LA (800 mg, administered as two 400 mg injections) or placebo at three study visits performed at 12-week intervals until 41 weeks.

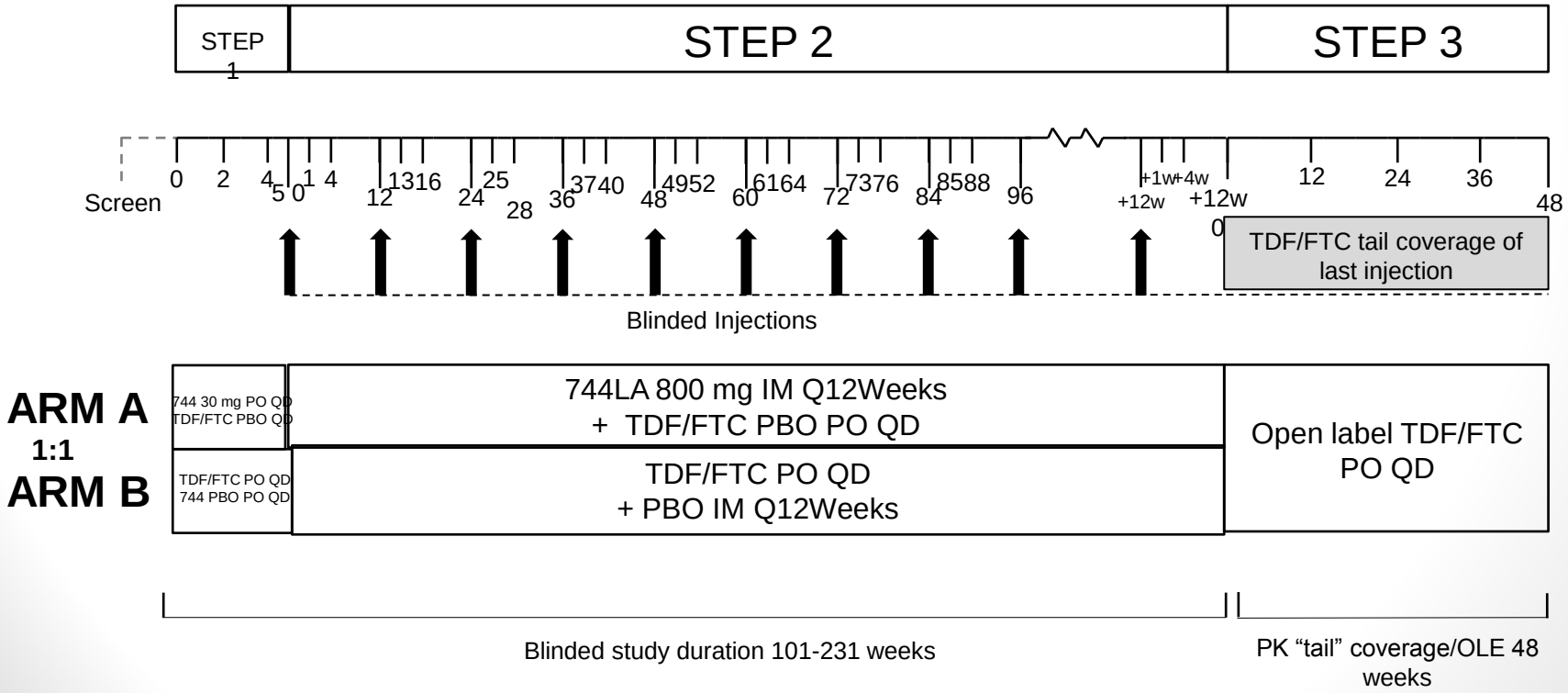
HPTN 083
Study Design

A Phase 2b/3 Double Blind Efficacy Study Of Quarterly Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (Truvada), For Pre-Exposure Prophylaxis in HIV-Uninfected Men and Transgender Women who have Sex With Men

HPTN 083
Study Design

4500 HIV-uninfected MSM in North & South America, Asia will be randomized 1:1 to:

Step 1: Oral TDF/FTC or Oral 744 30 mg daily x 5 weeks (DB)
Step 2: Oral TDF/FTC daily or Injectable 744 800 mg every 3 months (DB)
Continues until **286** seroconversions reached (mean 3.5 py)
Step 3: Open label TDF/FTC daily to cover PK "tail" / post-trial access if locally unavailable



PrEP Today: a clinical experience

Kaiser Permanente San Francisco Medical Center

- Study population: 657 PrEP initators:
  - mean age 37 years (range, 20–68 years)
  - 99% were MSM

- 12 months follow-up:
  - 187 (28%) were diagnosed with **1** STI, 78 (12%) **multiple** STIs
  - 41% reported decrease in condom use, 56% unchanged frequency
  - There were **no HIV diagnoses** during the 388 person-years of follow-up

- Limits:
  - lack of a control group
  - results may not be generalizable to other settings

Volk JE et al., **No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting** Clinical Infectious Diseases 2015 : civ778v2-civ778.

PrEP Today: a clinical experience

Kaiser Permanente San Francisco Medical Center

- Conclusions:
  - Dramatic increase in PrEP referrals and intakes
  - **No new HIV infection** despite high STIs rate

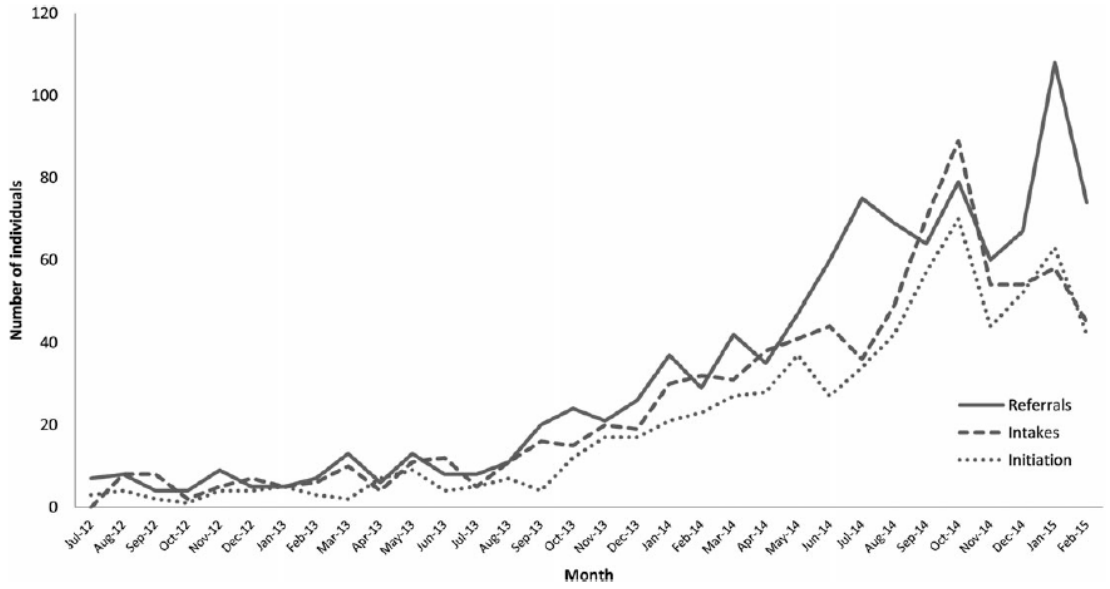
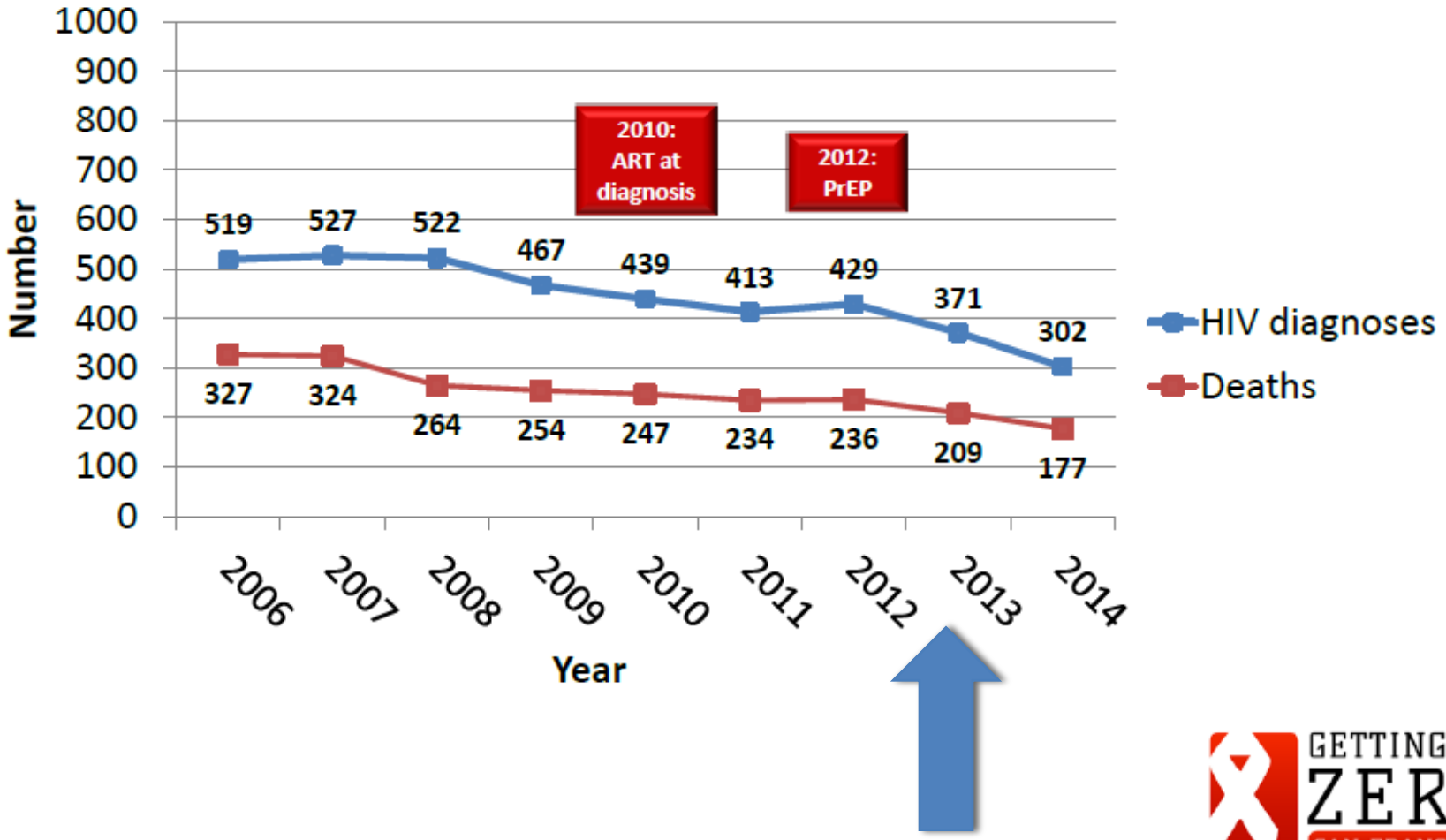


Figure 1. Human immunodeficiency virus preexposure prophylaxis (PrEP) referrals, intakes, and initiation by month at Kaiser Permanente San Francisco, July 2012–February 2015. The graph includes a total of 1045 referrals, 835 intakes, and 677 initiations, including 20 individuals who restarted PrEP after discontinuing during the study period.

Volk JE et al., **No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting** Clinical Infectious Diseases 2015 : civ778v2-civ778.

HIV diagnoses in San Francisco



GETTING TO ZERO SAN FRANCISCO
www.GettingToZeroSF.org

Medical Cost Savings Associated With HIV Prevention in the United States

- Cost modeling analysis of the Medical Expenditure Panel Survey
- Investigators used Cost-Effectiveness of Preventing AIDS Complications Model to project discounted lifetime medical costs, assuming HIV infection at 35 yrs of age
- **The medical cost savings of averting 1 HIV infection was found to be $229,800**
- Cost savings are higher if taking secondary infections into account and lower if infection is delayed vs totally averted

Schackmann R, et al. CROI 2015. Abstract 1104.

Biomedical Intervention:

ART based strategies to prevent HIV transmission:

- Pre-exposure prophylaxis (PrEP)
- Treatment as prevention
- Post-exposure prophylaxis (PEP)
- Pregnancy

TREATMENT IS PREVENTION

HIV treatment can reduce HIV transmission by up to...

Treatment as prevention (TasP) refers to HIV prevention methods that use antiretroviral treatment (ART) to decrease the risk of HIV transmission. ART reduces the HIV viral load in the blood, semen, vaginal fluid and rectal fluid to very low levels ('undetectable'), reducing an individual's risk of HIV transmission.[1]

For a number of years now, there has been growing evidence of the benefits of HIV treatment as a prevention method. In 2011, a landmark study, HPTN 052, showed early initiation of antiretroviral treatment (in people with a CD4 count between 350 and 550) for the HIV-positive partner in a serodifferent couple reduced HIV transmission to the HIV-negative partner by 96 percent.[2]

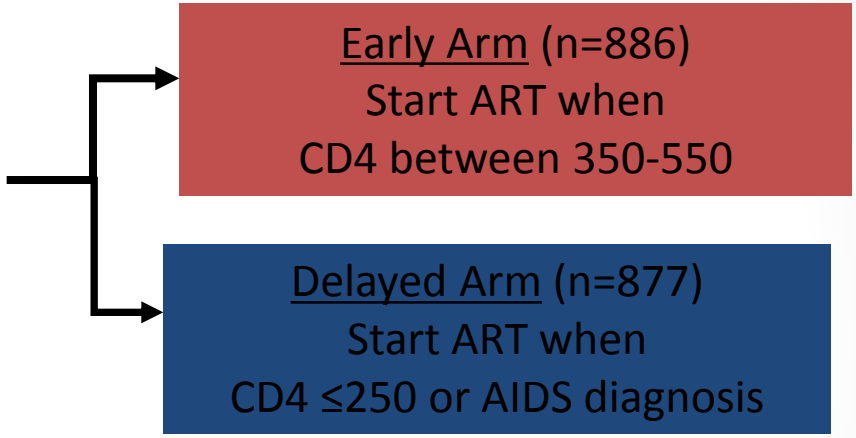
HPTN 052

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Multicenter, international, randomized, NIH-funded Phase III study

HIV serodiscordant adult couples
ART-naïve, HIV-infected partner
CD4 between 350-550

N=1,763 couples



HIV infected partner: 50% male

Primary Clinical Endpoint (in HIV-positive partner)

- Clinical Event: Pulmonary tuberculosis, severe bacterial infection, a World Health Organization stage 4 event, or death
  - 41% relative risk reduction in clinical events with early vs. delayed treatment

Primary Prevention Endpoint (in HIV-negative partner)

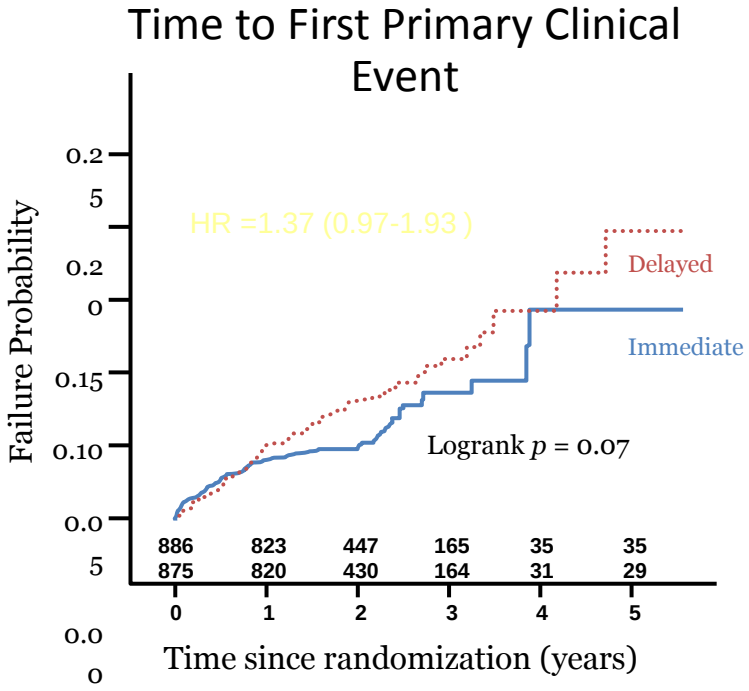
- Linked HIV transmission to HIV-1 negative partners

DSMB recommended study be stopped early on 28th April 2011

DSMB = Data and Safety Monitoring Board
Adapted from Cohen MS, et al. N Engl J Med 2011;365:493-505

HPTN 052

Effect of Early versus Delayed Initiation of Antiretroviral Therapy[1] and Cost-Effectiveness[2]



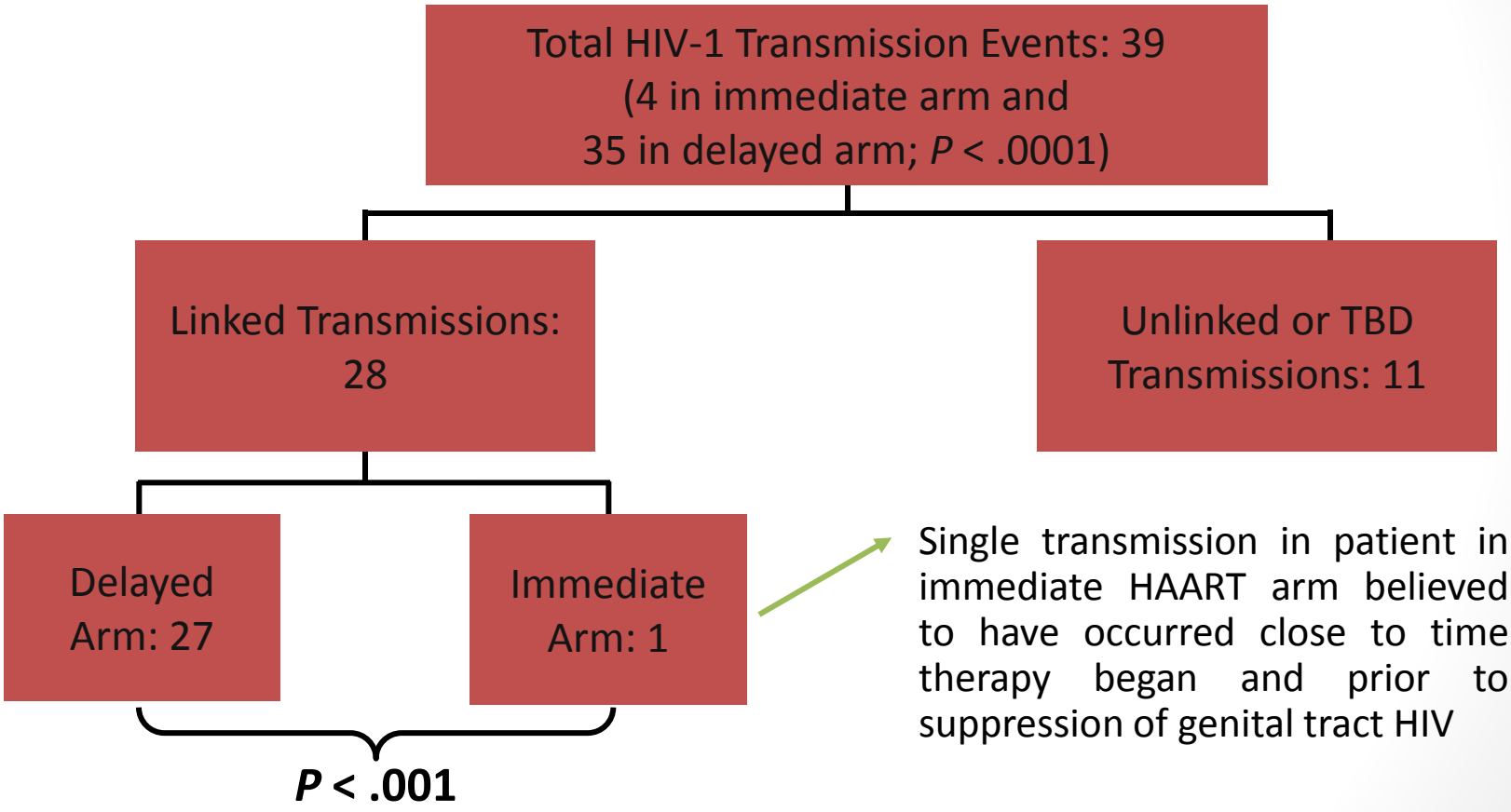
- Delayed compared to Immediate ART was associated with[1]
  - 37% higher risk of primary clinical event indicating a strong trend favoring immediate ART
  - Significantly shorter time to AIDS-defining disease (p=0.03) & tuberculosis (p=0.02)
  - Significant risk factors for primary events included age (>40yrs), Grade ≥2 haemoglobin deficiency, HBV co-infection and HIV-1 log10 RNA (per 1log higher)

- In serodiscordant couples, with ART efficacy and behavior data modelled from HPTN 052, early ART is very cost-effective[2]
  - As expected, cost-effectiveness analysis is sensitive to country-specific costs inputted into the model

[1]Grinsztejn B, et al. IAC 2012; Washington, DC. THLBB05
[2]Freedberg K, et al. IAC 2012; Washington, DC. FRLBC01

HPTN 052

HIV Transmission Reduced by 96% in Serodiscordant Couples



Cohen MS, et al. N Engl J Med. 2011;365:493-505.

The Partner Study: Partners of people on ART: a New Evaluation of the Risks

A study in HIV serodifferent partnerships to investigate factors associated with consistent condom use adoption and to estimate the rate of transmission of HIV .

PARTNER 1: MSM and Eterosexual Couples. COMPLETED.

PARTNER 2: Only MSM, on-going

PARTNER

The Partner Study: Partners of people on ART: a New Evaluation of the Risks

Enrolment

Inclusion criteria for the HIV positive partner:

- Confirmed HIV positive
- On ART (regardless of viral load)
- Age > 18
- Expected to remain under care at the clinic for as long as they participate in the study
- Has a partner not known to be HIV infected

The Partner Study: Partners of people on ART: a New Evaluation of the Risks
Results

- **No case of trasmission**, either by anal or vaginal sex, with HIV-RNA< 200 copies

- Statistical analysis shows that the maximum chance of trasmission **is 1% per year for anal sex and 4% per year for anal sex with eiaculation** where the negative partner is receptive

Rodger A et al. *HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER study.* 21st CROI, Boston, abstract 153LB, 2014.

Grazie per l'attenzione

Thanks