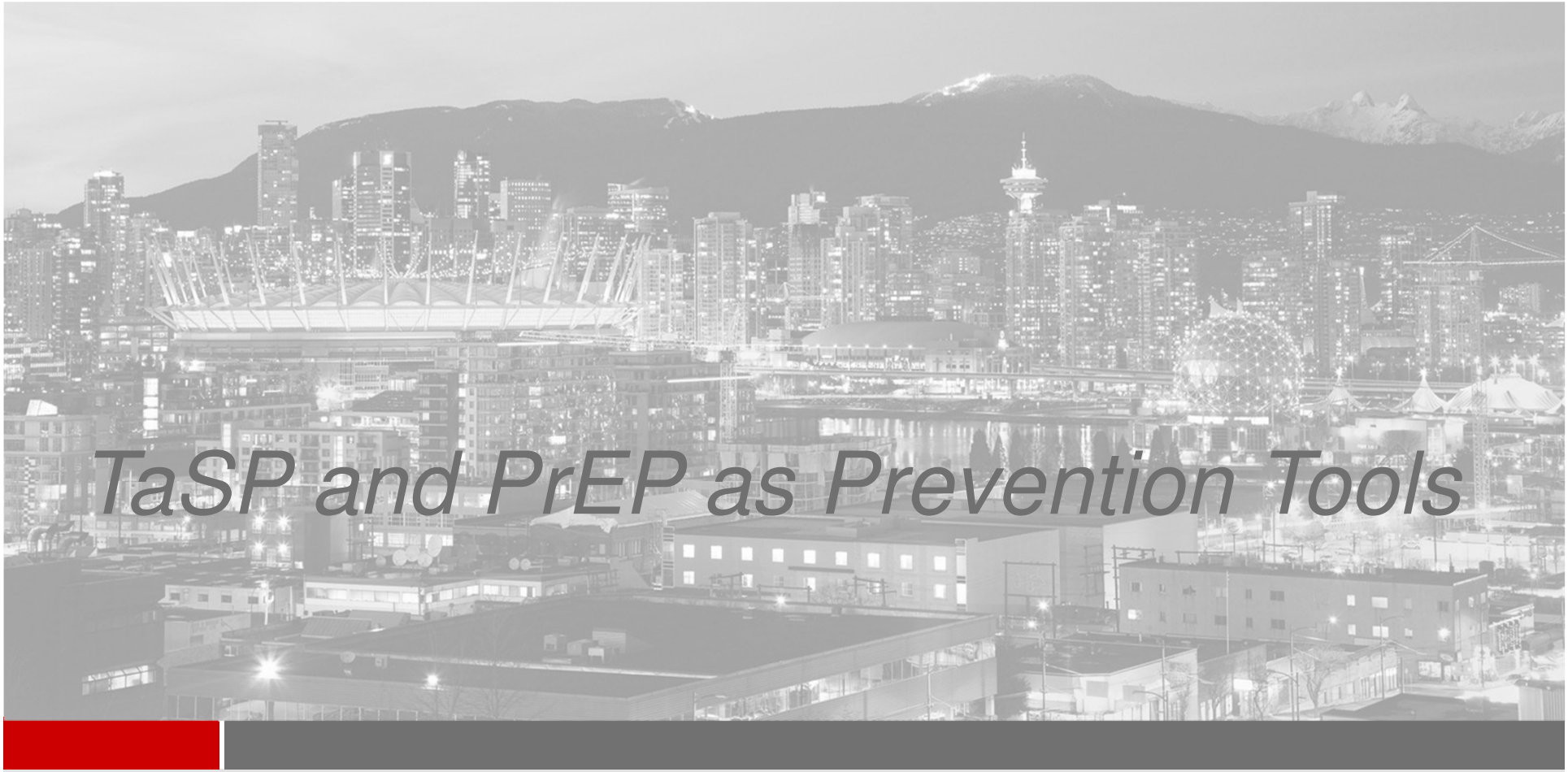

TaSP and PrEP as Prevention Tools

Dr Muhangwi Ben Mulaudzi (MBChB)

SA HIV Clinician Society
02 February 2017, Glenhove Conference Centre

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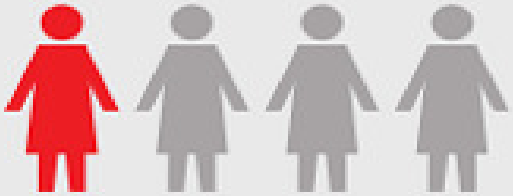
A good head and a good heart are always a formidable combination

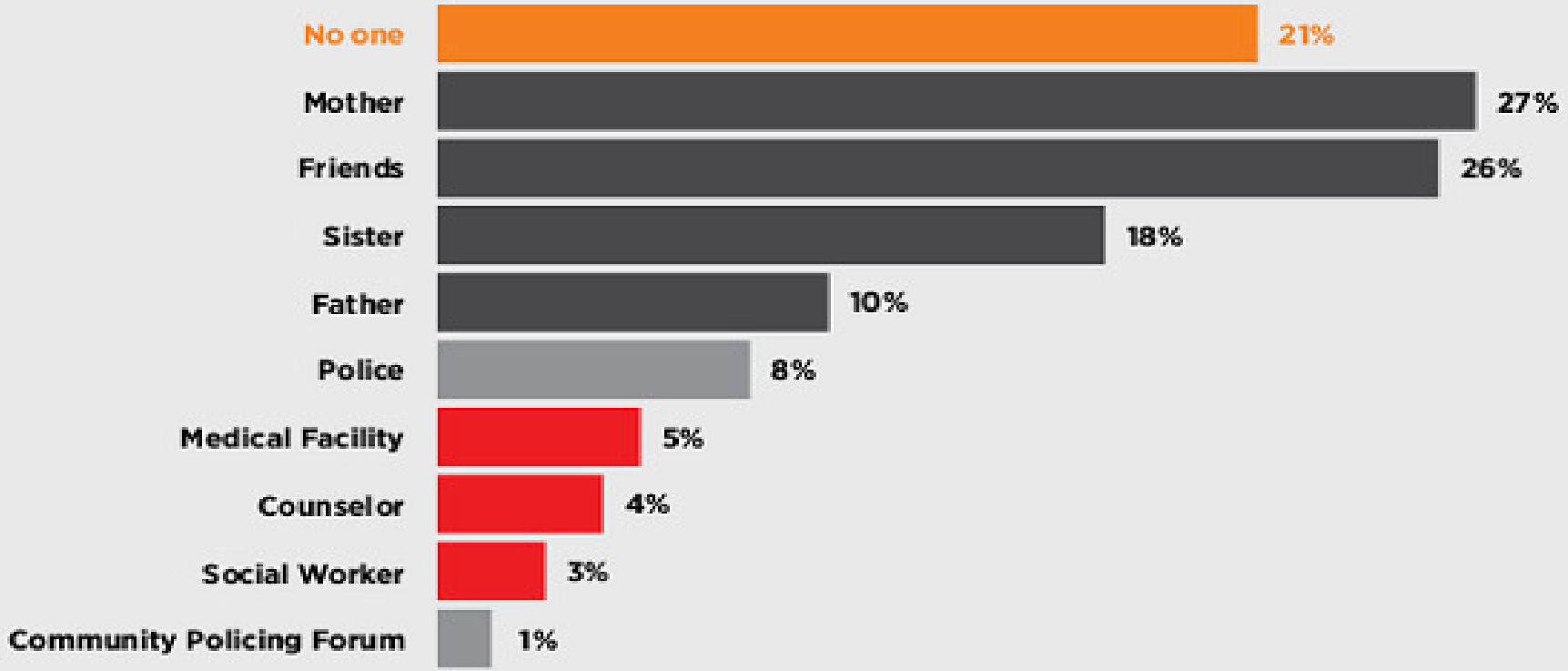
– Nelson Mandela,

Founder of The Elders (www.theelders.org)



ONE IN FOUR WOMEN LIVING IN RUSTENBURG HAS BEEN RAPED IN HER LIFETIME

Who women told about their experience of rape*

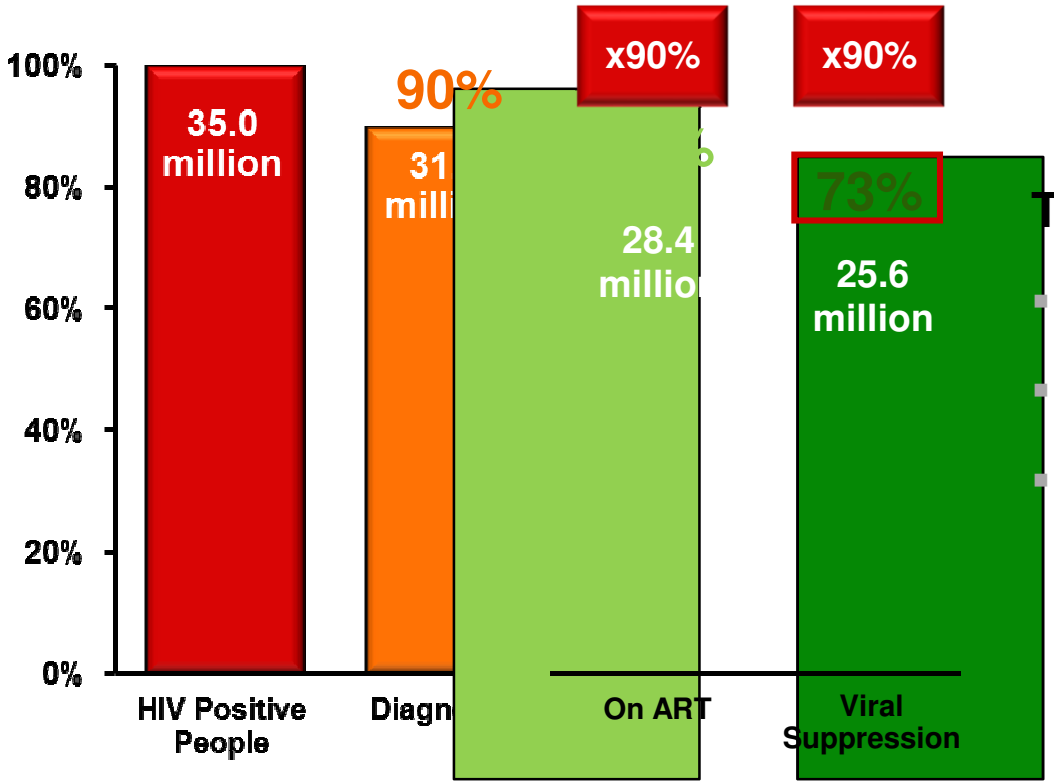


*If women told someone about their experience, options were not mutually exclusive

‡

HIV Treatment Targets for 2020 with Global 2013 Estimates

Global HIV treatment cascades from 12 countries/regions: Switzerland, Australia, UK, Denmark, Netherlands, France, Brazil, Canada (BC), USA, Sub-Saharan Africa, Georgia, Estonia, Russia



Treatment Target Goals by 2020

- 90% of HIV+ people diagnosed
- 90% of those diagnosed on ART
- 90% of those on ART with undetectable HIV RNA

- **No country or region analysed so far met the UNAIDS 90-90-90 coverage target of 73% of HIV positive people achieving undetectable HIV RNA**

Levi J, et al. IAS 2015. Vancouver, Canada. Oral # MOAD0102

UNAIDS: 90-90-90

*Adapted from: UNAIDS. 90-90-90: an ambitious treatment target to help end the AIDS epidemic. 2014. Available at http://unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. Accessed on 25 April 2016

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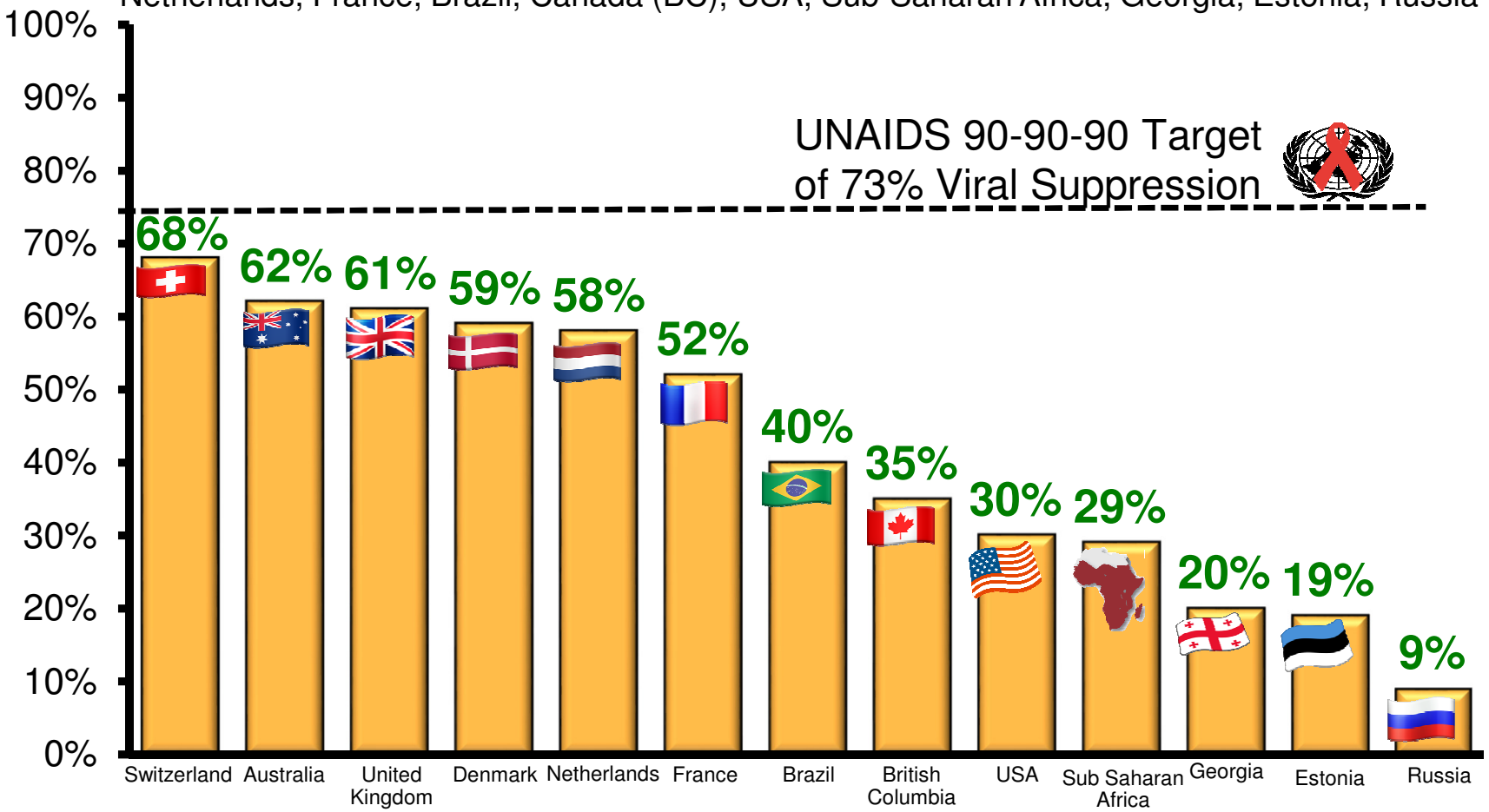


- **No country or region analysed so far met the UNAIDS 90-90-90 coverage target of 73% of HIV positive people achieving undetectable HIV RNA.**

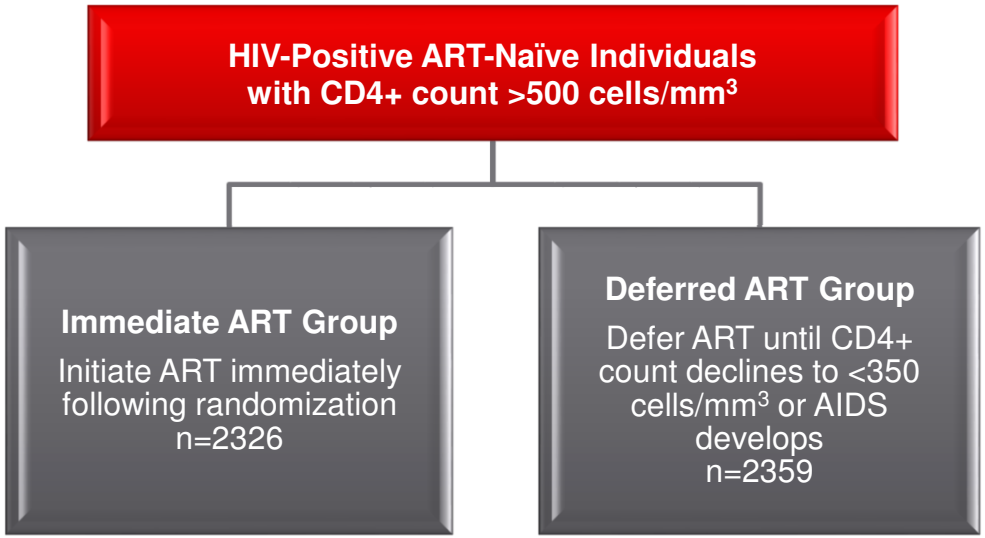
Levi J, et al. IAS 2015. Vancouver, Canada. Oral # MOAD0102

‡

Study Design and Baseline Characteristics

START is an international randomized trial comparing immediate ART (CD4 >500cells/µL) versus deferred ART (CD4 <350 cells/µL)

•Primary endpoint is the development of a serious AIDS event, a serious non-AIDS event, or death from any cause



Characteristic	N=4685
Age (yr)*	36 (29, 44)
Female, n (%)	1257 (27)
Race, n (%)	
White	2086 (45)
Black	1410 (30)
Time since HIV diagnosis (yr)*	1.0 (0.4, 3.1)
CD4 cell count (cells/mm^3)*	651 (584-765)
Baseline HIV-RNA (copies/mL)*	12,759 (3019-43,391)
TDF Usage	89% in both groups

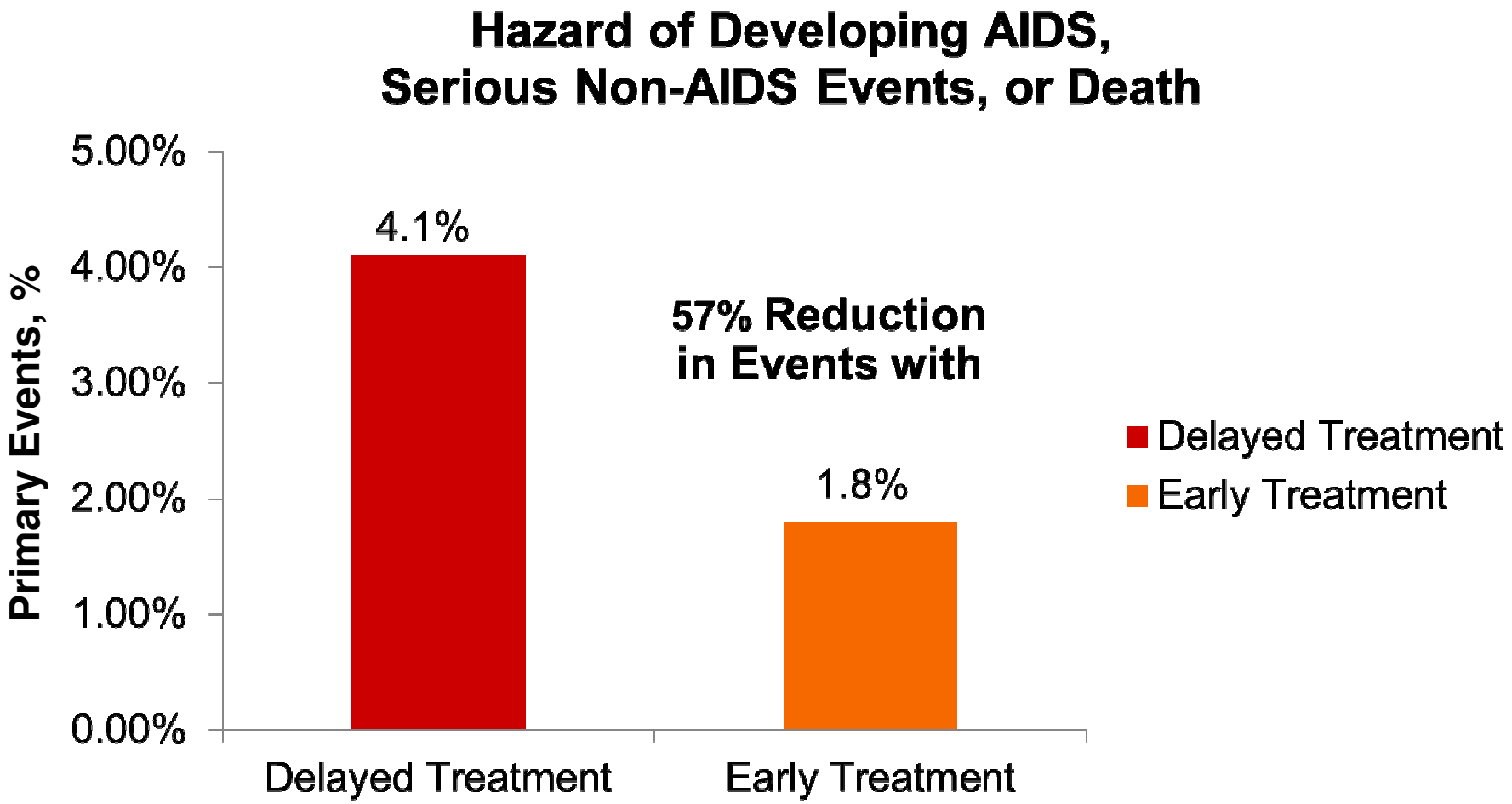
* Median (IQR)

- On May 15, 2015 at a planned interim review, the international Data & Safety Monitoring Board recommended that participants in the deferred arm who were not already on ART should be offered ART and follow-up should continue with all subjects on therapy

Lundgren D, et al. IAS 2015. Vancouver, CAN. Oral # MOSY03
Lundgren D, et al. NEJM 2015 Published Epub ahead of print July 20, 2015 DOI: 10.1056/NEJMoa1506816

‡

Primary Results

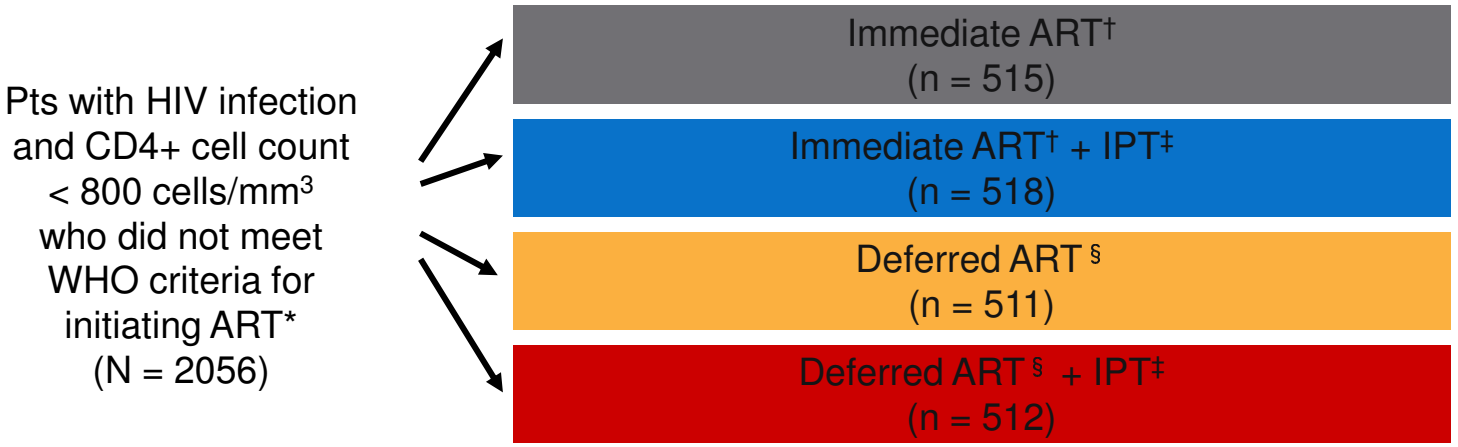


"Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4+ count."

Lundgren D, et al. IAS 2015. Vancouver, CAN. Oral # MOSY03
Lundgren D, et al. NEJM 2015 Published Epub ahead of print July 20, 2015 DOI: 10.1056/NEJMoa1506816

TEMPRANO: Immediate or Deferred ART Initiation ± IPT for African Pts

- Randomized, controlled, unblinded, multicenter (Ivory Coast), 2 x 2 factorial



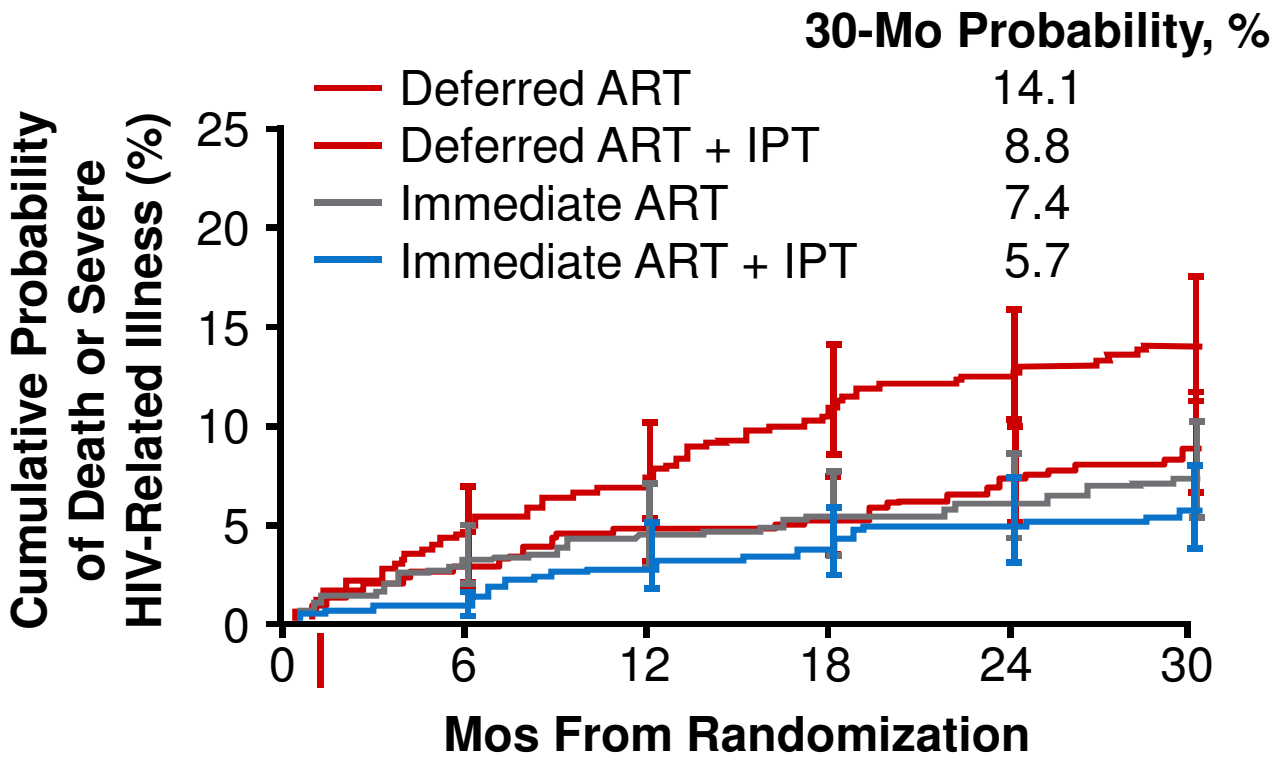
*WHO criteria evolved during the study (updates 2006, 2010, 2013). †ART initiated immediately following randomization. ‡IPT = 300 mg daily isoniazid initiated 1 mo after enrollment and terminated 7 mos after enrollment. § Deferred until meeting WHO criteria for initiating ART.

- Pts in the treatment arms well matched at baseline
  - First-line ART primarily EFV + TDF/FTC (68% to 71%) or LPV/RTV + TDF/FTC (22% to 24%)
- Median duration of follow-up: 29.9 mos

TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015;[Epub ahead of print].

‡

TEMPRANO: Immediate vs Deferred ART Initiation and IPT Delivery for African Pts



TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015;[Epub ahead of print].

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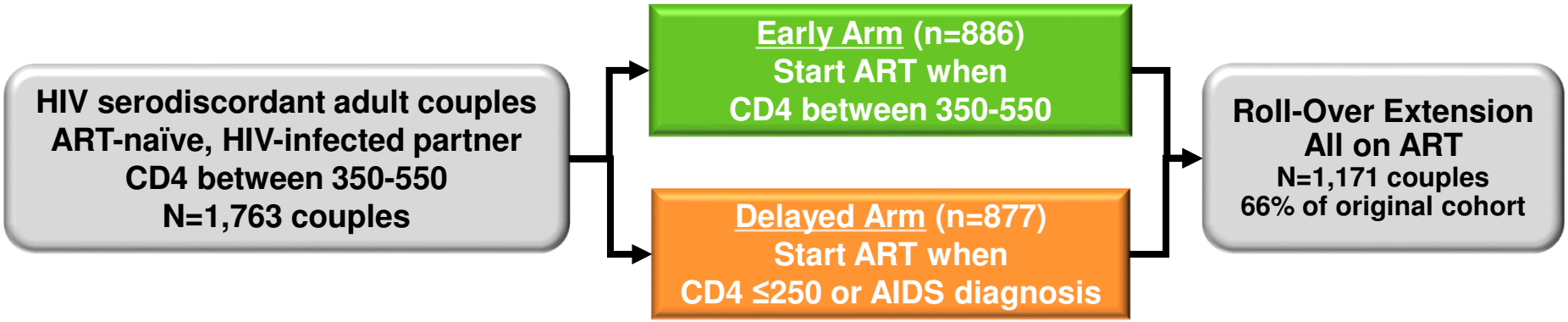
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

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



Primary Clinical Endpoint (in HIV-positive partner)

- Clinical Event: Pulmonary tuberculosis, severe bacterial infection, a World Health Organization stage 4 event, or death

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 after showing a 96% reduction of HIV transmission

- **An updated analysis through 2011 showed a 97% risk reduction of HIV transmission by early treatment: 1 linked infection in the early arm vs. 36 linked infections in the delayed arm**
- **Here reporting results during the Roll-Over Extension period and overall**

Adapted from Cohen MS, et al. *N Engl J Med* 2011;10.1056
Adapted from Cohen MS, et al. IAS 2015, Vancouver, Canada. Oral# MOAC0101LB

‡

HPTN 052: Partner Infections With Early vs Delayed ART

- No linked HIV transmissions observed when index participant stably suppressed on ART

Partner Infections, n (rate/100 PY)	April 2005 - May 2011		May 2011 - May 2015		Overall (April 2005 - May 2015)	
	Early (1751 PY F/U)	Delayed (1731 PY F/U)	Early (2563 PY F/U)	Delayed (2449 PY F/U)	Early (4314 PY F/U)	Delayed (4180 PY F/U)
All	4 (0.23)	42 (2.43)	15 (0.59)	17 (0.69)	19 (0.44)	59 (1.41)
Linked	1 (0.06)	36 (2.08)	2 (0.08)	7 (0.29)	3 (0.07)	43 (1.03)
Risk Reduction With Early ART, %						
All infections	91	--	14	--	69	--
Linked infections	97	--	72	--	93	--

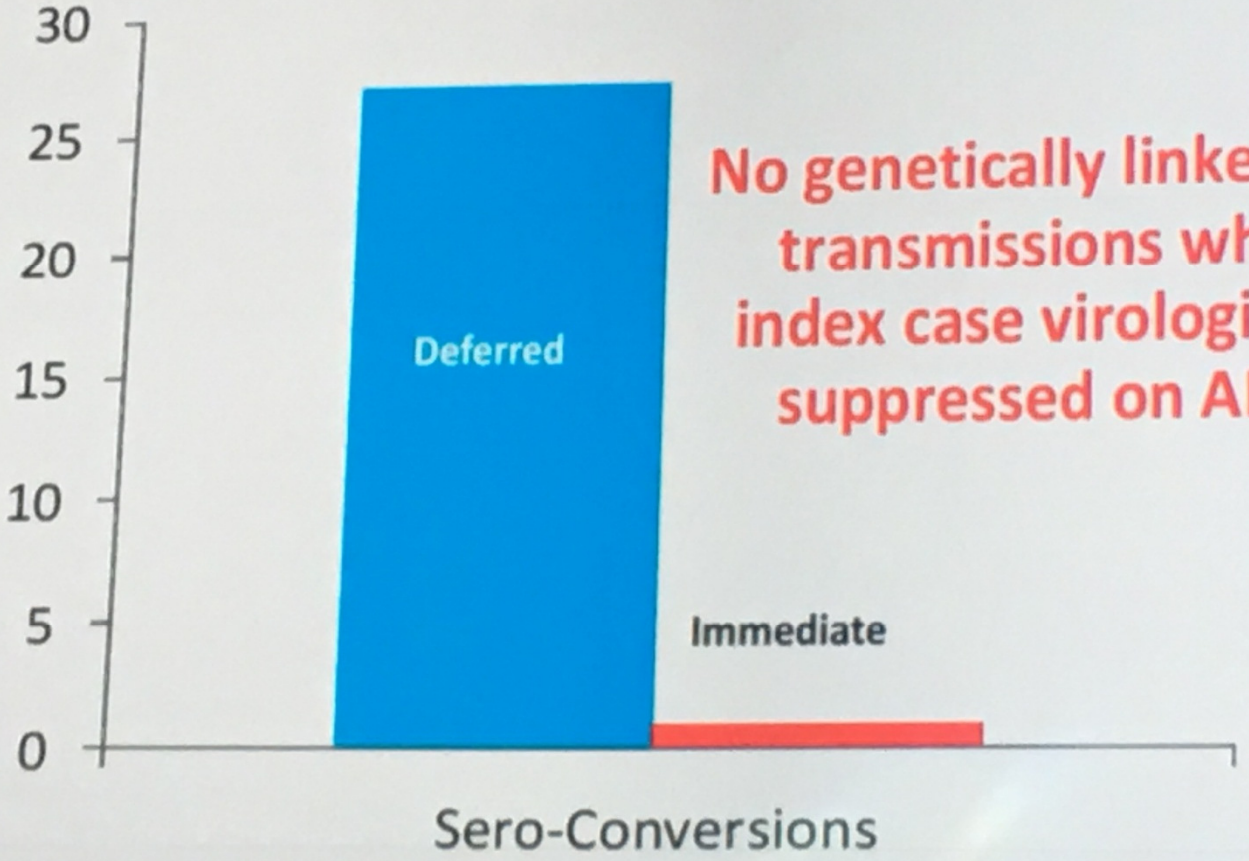
- 8 linked HIV infections diagnosed after seropositive pt started ART
  - 4 infections likely occurred before, or soon after, ART initiation, and 4 infections occurred after ART failure in seropositive pt
- Unlinked partner infection rates similar between study arms

Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.

BRITISH COLUMBIA CENTRE for EXCELLENCE in HIV/AIDS

HPTN 052: Effectiveness of Treatment as Prevention

RCT of Immediate vs. Delayed ART in Sero-Discordant Couples[1,2]



No genetically linked HIV transmissions when index case virologically suppressed on ART[3]

1 Cohen et al. IAS 2011. Abst MOAX0102; 2 Cohen et al. N Engl J Med. 2011; 3 Cohen et al. IAS 2015. Abst MOAC0101LB.

HPTN 052: Treatment as Prevention

‡

Final Results: Early ART in Serodiscordant Couples is Highly Effective in Prevention of Sexually-Acquired HIV

Overall Results Partner Infections: April 2005 – May 2015 (N=1171)			
	PYFU	**All partner Infections # (rate)**	**Linked partner Infections # (rate)**
Total	8494	78 (0.92)	46 (0.54)
Early Arm	4314	19 (0.44)	3 (0.07)
Delayed Arm	4180	59 (1.41)	43 (1.03)
Rate Ratio		0.31	0.07
Risk Reduction		69%	**93%**

Roll-Over Extension Results Linked Partner Infections: May 2011– May 2015: (N=8)	
Status of HIV-Infected Partner	**Linked Partner Infections #**
Before or soon after ART Initiation	4*
Post ART Failure	4
Virologically-Suppressed	**0**

*For three of these cases the index partner was virologically suppressed at time of partner diagnosis

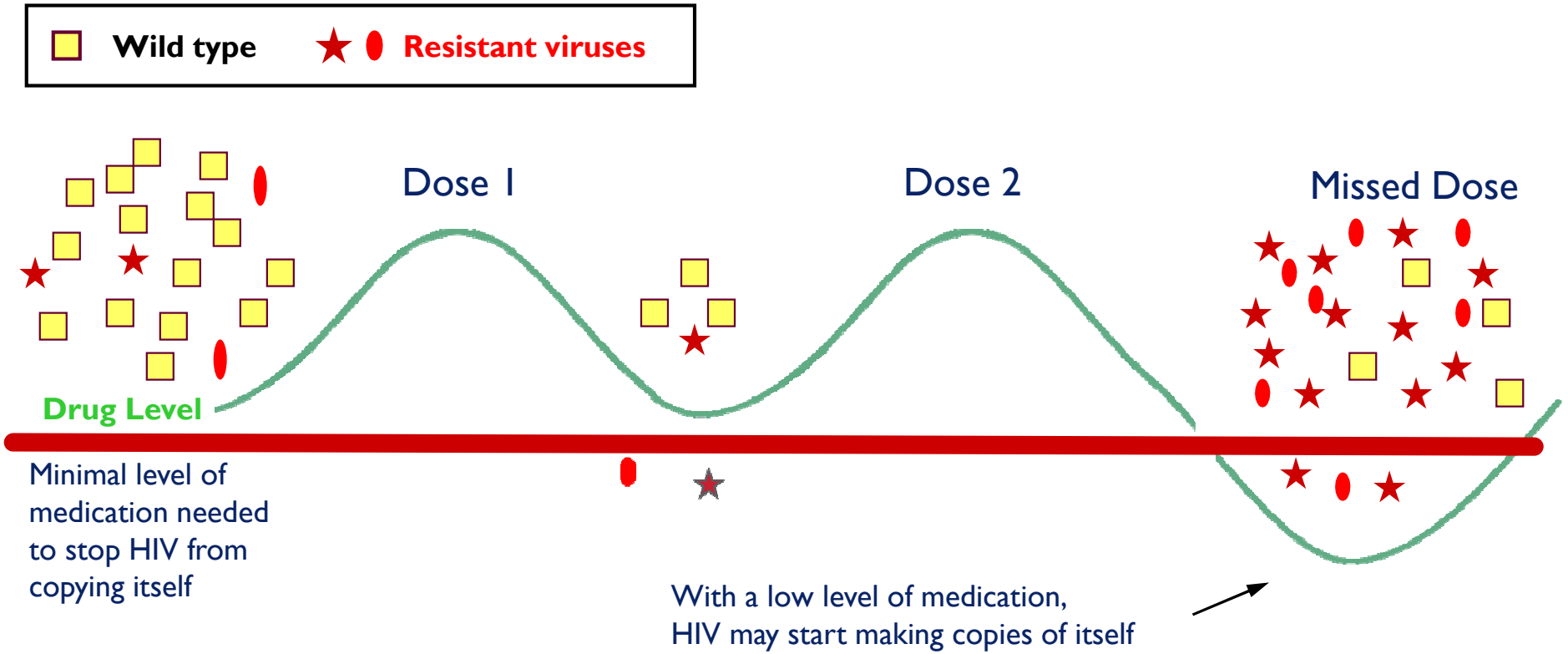
- **By the end of the study, risk reduction of HIV transmission in linked partners was 93% with 3 linked infections (early arm) vs. 43 linked infections (delayed arm)**
  - 8 linked partner infections diagnosed AFTER the index partner started ART, but no linked HIV transmissions were observed when the index participant was virologically suppressed.
  - Ten year results show that the benefit of TasP is durable

1. Cohen MS, et al. IAS 2015, Vancouver, Canada. Oral # MOAC0101LB
2. Eshleman S, et al. IAS 2015, Vancouver, Canada. Poster # MOLBPE18

PrEP Safety Data

Michelle Moorhouse

Potential Effects of Sub-therapeutic Doses of Medication on HIV Replication



Available at: http://www.aidsinfo.nih.gov/contentfiles/HIVandItsTreatment_cbrochure_en.pdf. Accessed October 8, 2010.

‡

Drug Resistance

	Individuals Uninfected at Baseline Who Acquired HIV-1 on Study, n		Unrecognised Baseline Infections, n	
Study	**HIV Infections**	**Resistant to FTC or TDF**	**HIV Infections**	**Resistant to FTC or TDF**
iPrEx	131 (48 on TDF/FTC, 83 on placebo)	0	10 (2 on TDF/FTC, 8 on placebo)	2 on TDF/FTC (M184V/I); 1 on placebo (M184V/I)
Partners PrEP	63 (12 on TDF/FTC, 51 on placebo)	0	9 (3 on TDF/FTC, 6 on placebo)	1 on TDF/FTC (M184V)

Resistance development to FTC or TDF was more likely to occur when TDF/FTC for PrEP was given during unrecognised/acute infection.

US Public Health Services. Preexposure Prophylaxis For The Prevention Of HIV Infection In The United States, 2014. http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf. Accessed June 13, 2014.

‡

Infection with Multidrug Resistant HIV Despite Use of TDF/FTC for PrEP

43 y/o MSM (no IDU) on PrEP (TDF/FTC) X 2 years, with high adherence by self report

- Multiple, condomless, anal sexual exposures in 2-4 weeks prior to HIV diagnosis
- Day 0: 4th Gen+, p24+, Western blot-

- TDF/FTC levels:
  - FTC and TDF detected at Day 0 (by LC-MS)
  - Based on DBS data, TFV-DP level were consistent with being adherent to PrEP > 8 weeks
- Transmission of multidrug, class-resistant HIV
  - 4 TAMs, M184V, phenotypic resistance to INSTI EVG (FC >100x)
  - Clade B, CCR5-tropic

Resistance Testing Results

Class	Mutation	Resistance Analysis (est. IC50 FC)
NRTI	41L, 67G, 69D, 70R, 184V, 215E	ABC ↓ 1.9x 3TC resistant FTC resistant TDF ↓ 1.3x
NNRTI	181C	NVP resistant
PI	10I	
INSTI	51Y, 92Q	RAL ↓ 2.7x EVG resistant DTG ↓ 9.6x

First reported case of breakthrough HIV infection with a virus carrying TFV and FTC resistance, in a patient with evidence of long-term adherence to TDF/FTC for PrEP

LC-MS - Liquid Chromatography-Mass Spectroscopy
DBS – Dried Blood Spot

Knox D, et al. CROI 2016. Boston, MA. #169aLB

Creatinine Clearance Measurements

- 2 mechanisms which falsely ↑ s-creatinine without renal impairment.
- 1. Barbeque or lots of meat: anhydrous creatine
- 2. Egogermic supplements: phosphorus creatine

Creatinine Clearance Measurements

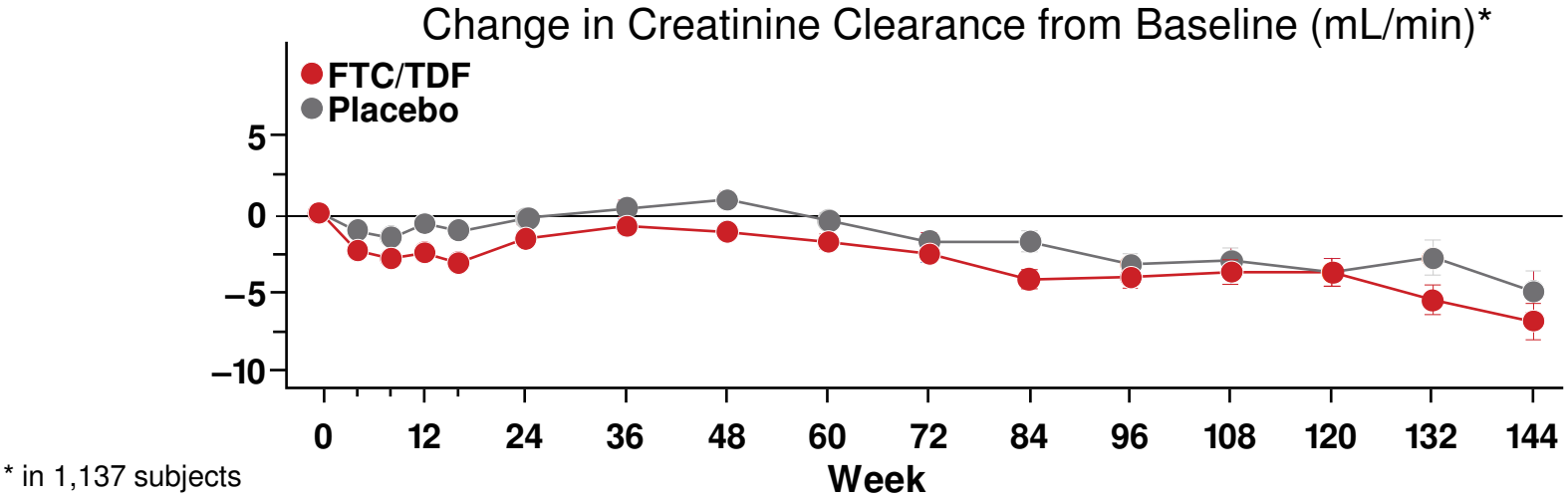
- Two methods of measuring creatinine at the lab
- 1. Jaffey method: cheaper
- -suffers interference (i).glucose
  - (ii) ketones
  - (iii) some drug metabolites
- 2. Enzymatic creatine measurements: expensive
- -doesn't suffer from interference

Renal Safety

Renal safety assessment of 2499 HIV-negative subjects in iPrEx study

- A mild, non-progressive decrease in creatinine clearance (Cockcroft-Gault), that was reversible and readily managed with routine monitoring
  - Did not vary by race, age, or HTN history
  - Affected by NSAID use
    - -3.4 mL/min (+NSAID) vs. -0.3 mL/min (no NSAID), *P* = 0.04

Mean Change in CrCL (mL/min)			
	TDF/FTC	**Placebo**	**P-value**
Wk 4	-2.4	-1.1	0.02
At Stop	+0.3	+1.8	0.02
Post-stop	-0.1	0.0	0.83

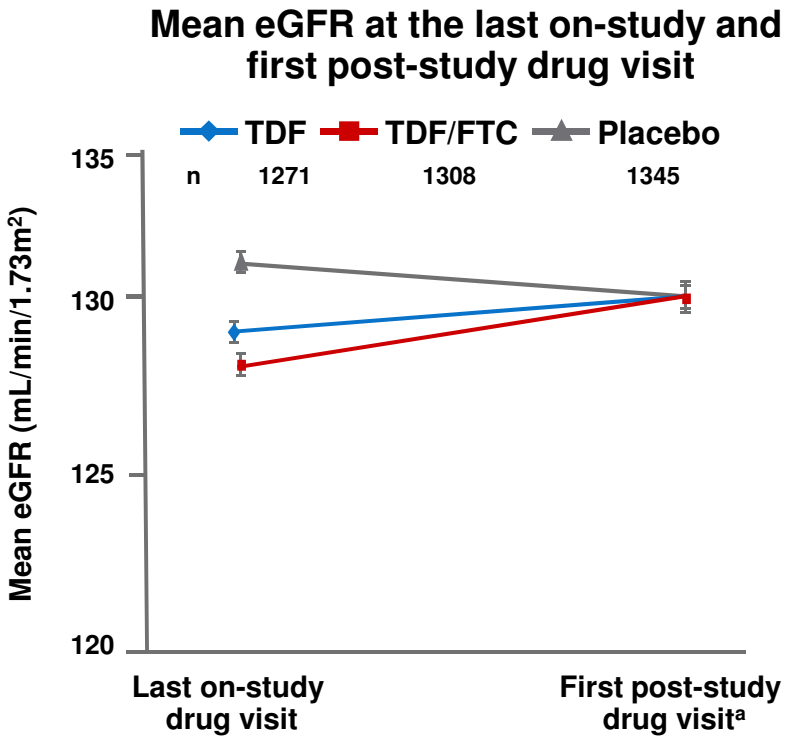


* in 1,137 subjects

Solomon M, et al. AIDS 2014;28(6):851-9

Decline in eGFR Resolves Within Weeks of Discontinuing TDF or TDF/FTC for PrEP

- Partners PrEP: Phase 3, randomised trial of daily oral TDF PrEP vs. TDF/FTC PrEP vs. placebo among African HIV-negative men and women (N=4747) with normal baseline renal parameters
  - SCr was assessed quarterly while on study medication, and at 2 monthly visits after d/c
  - eGFR was calculated using CKD-EPI[a]
- **Mean eGFR was 2-3 mL/min lower on PrEP vs. PBO (*P* < 0.01) at first post-study drug visit**
- > 96% of participants had > 75% eGFR reversion to baseline levels by 8 weeks of study drug discontinuation

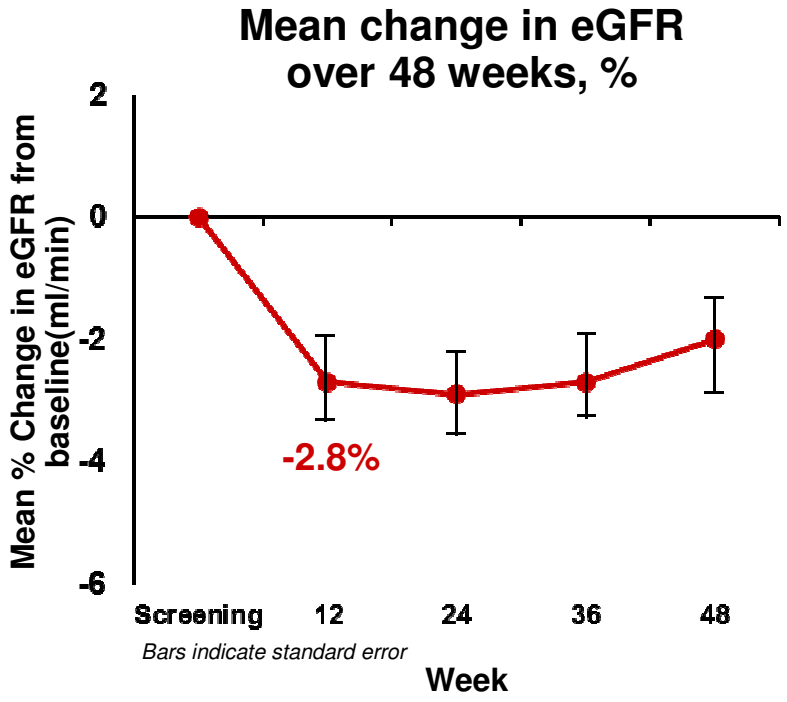


[a] Chronic Kidney Disease Epidemiology Collaboration Equation.
[b] Median time from the last on-study drug visit to the first post-study drug visit was 4 weeks (IQR: 3 - 5), which was similar across treatment groups.

Changes in Renal Function Associated with TDF/FTC for PrEP Use

Open-label US PrEP Demo Project of 557 MSM and transgender women (TGW)
Median age 33; baseline median Cr 0.92 / median eGFR 97 mL/min
Objective: evaluate changes in renal function over 48 weeks

- 3 patients required interruption of TDF/FTC for PrEP due to elevated Cr; all 3 patients re-started TDF/FTC for PrEP
- 34 (7%) of patients had > 25% eGFR loss from baseline; only 4 (0.8%) confirmed on repeat testing
- TFV-DP levels ≥ 4 doses/week were associated with declines of ~4 mL/min in eGFR, compared with those with lower adherence
- New onset eGFR < 70 mL/min (n=59; 13%) was more common with baseline eGFR < 90 mL/min, particularly in older adults; may warrant additional monitoring



TDF/FTC PrEP was associated with modest decline in eGFR and was non-progressive through Week 48. Older patients with baseline eGFR < 90 mL/min more commonly experienced eGFR < 70 mL/min

Liu A, et al. CROI 2016. Boston, MA. #867

‡

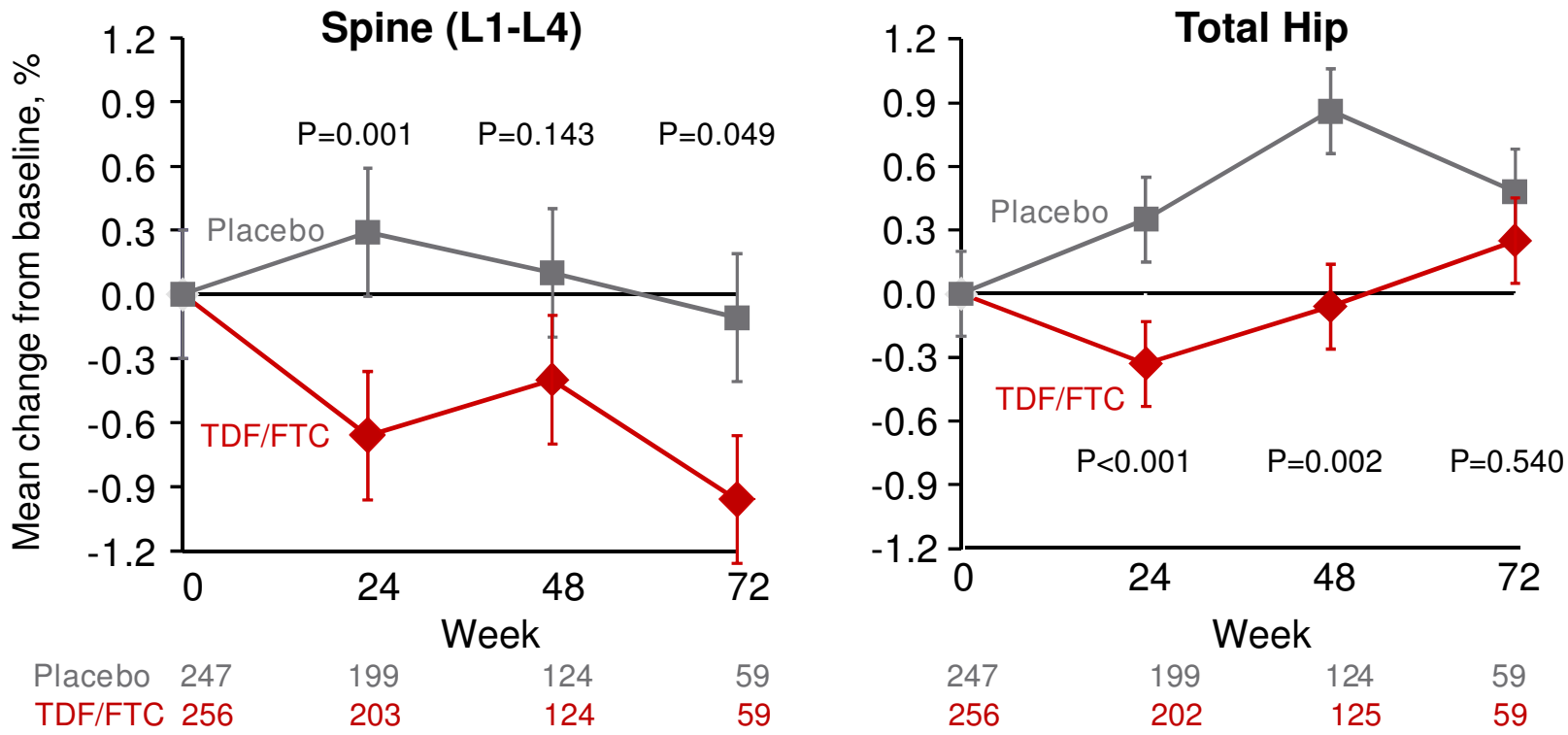
Renal Monitoring for PrEP

- Do not use TDF/FTC in HIV-uninfected individuals for PrEP if CrCl is below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using TDF/FTC for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of TDF
- It is recommended that estimated creatinine clearance be assessed in all individuals prior to initiating therapy and as clinically appropriate during therapy with TDF/FTC
- If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TDF/FTC for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.
- TDF/FTC should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs)

TRUVADA Prescribing Information. Gilead Sciences, Inc. 2013.

‡

Change from Baseline in Bone Mineral Density (BMD)



Mean, SE and P-values by linear mixed model

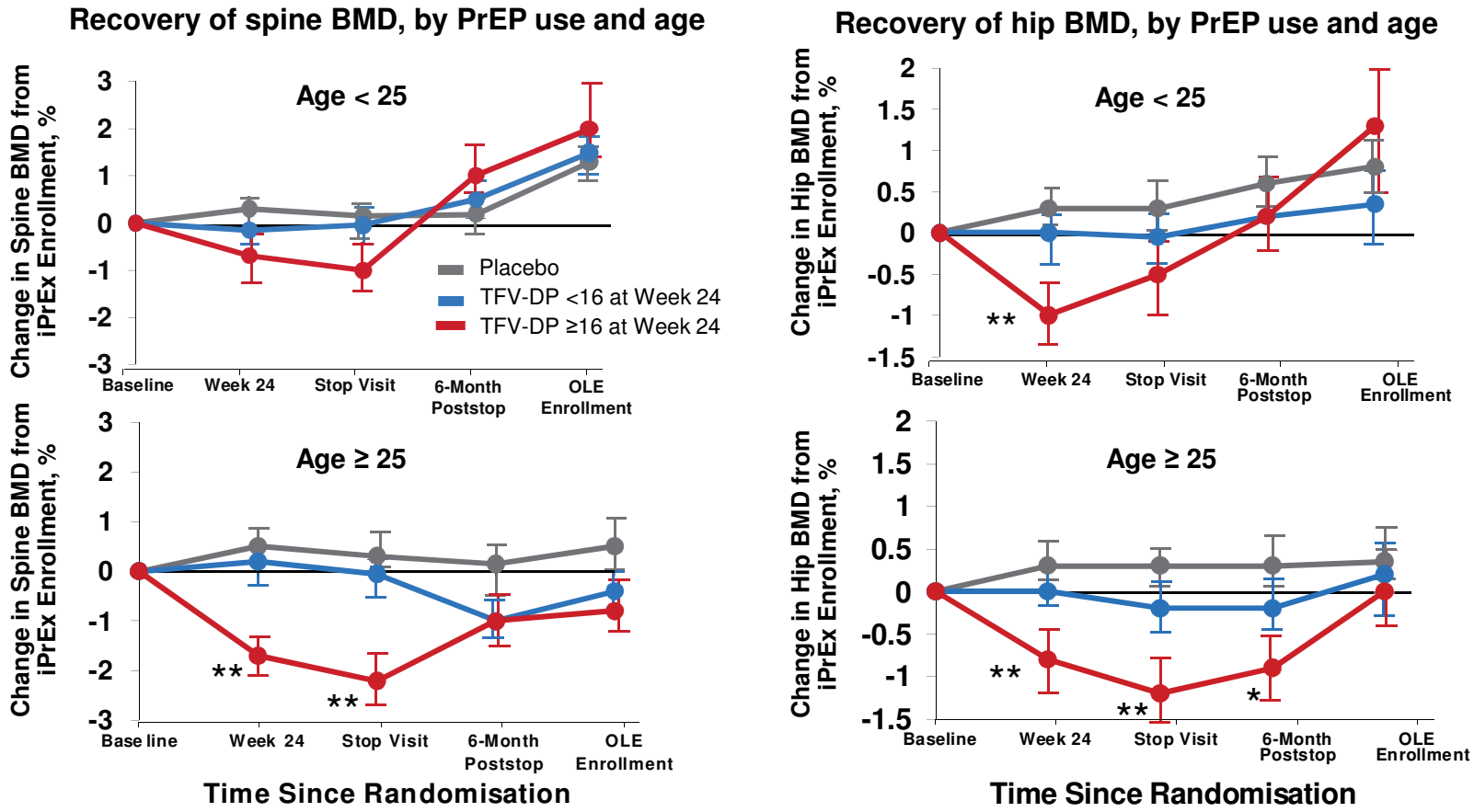
- **Small but significant decreases in BMD at the spine, but not the hip, were observed in HIV-negative men randomised to TDF/FTC relative to placebo**
- **There were no differences in bone fractures between the groups (P=0.41)**

Mulligan K, et al. CROI 2011; Boston, MA. #94LB

‡

BMD Recovers Completely After Cessation of Oral TDF/FTC for PrEP

DXA substudy of 498 subjects (median age 25; 446 MSM, 52 transgender women)



*P<0.05; **P<0.001

- BMD recovered completely in BOTH hip and spine in young adults (< 25yrs)
- BMD recovered completely by enrollment in iPrEx OLE (median 73 weeks) in both spine and hip
- **Though BMD declined in HIV-negative MSM/trans women with therapeutic levels of TDF/FTC on PrEP, BMD recovered completely in both older (≥ 25) and younger patients within 6 months of discontinuation**

Grant R et al, CROI 2016. Boston, MA, Oral #48LB

ATN 110 Study Extension Phase (EPH)

BMD Changes in 18-24 Year Old MSM After Discontinuing TDF/FTC PrEP

‡

Extension Phase

- DXA scans at 48 weeks after discontinuing PrEP study, i.e. 48 weeks on TDF/FTC followed by 48 weeks off TDF/FTC
- N=72 individuals followed-up through the EPH

BMD change (mean)	From BL to Wk 48 (on TDF/FTC)	From Wk 48 to end of EPH (off TDF/FTC)	Overall change from BL to end of EPH
Hip	**-1.43%***	**+1.02%***	-0.35%
Whole Body	**-0.63%***	**+0.64%***	-0.11%
Lumbar Spine 1-4	-0.25%	**+1.15%***	**+0.87%***

***p<0.05**

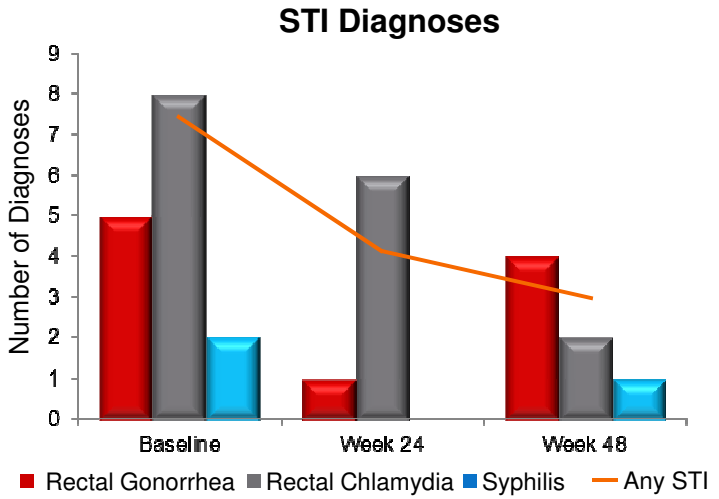
- **There is evidence of impact on bone density caused by exposure to TDF/FTC used as PrEP over 48 weeks in 18-22 year old males**
- **Discontinuation of exposure to TDF/FTC leads to a trend to recovery of bone density changes over a 48 week follow-up period**

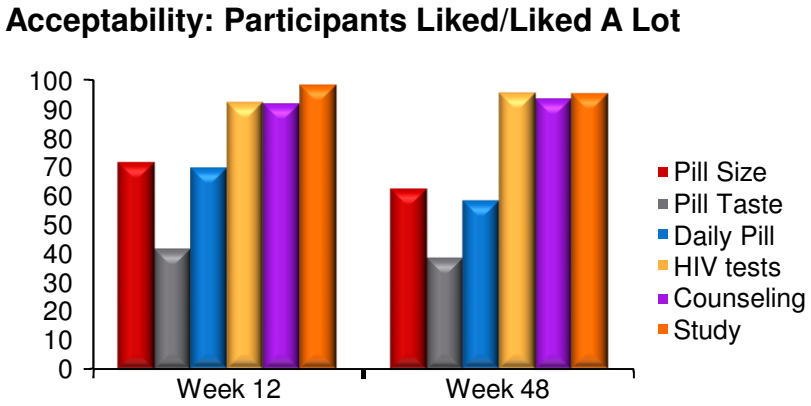
Mulligan K, et al. AIDS 2016, Durban, South Africa. Oral #WEAC0305LB

Safety and Efficacy of TVD for PrEP in US MSM Aged 15-17*

- Safety:
  - No d/c due to side effects
  - Three Grade 3 AEs (weight loss) in 2 participants deemed related to study drug by investigator
  - No abnormal laboratory results
- 15.4% of participants had STIs on screening
  - STI incidence decreased while on TDF/FTC for PrEP
- Participants liked the engagement aspects of the study more than the medication aspects

TDF/FTC for PrEP was well tolerated in these younger MSM and adherence may be improved by addressing barriers of frequent monitoring and stigma

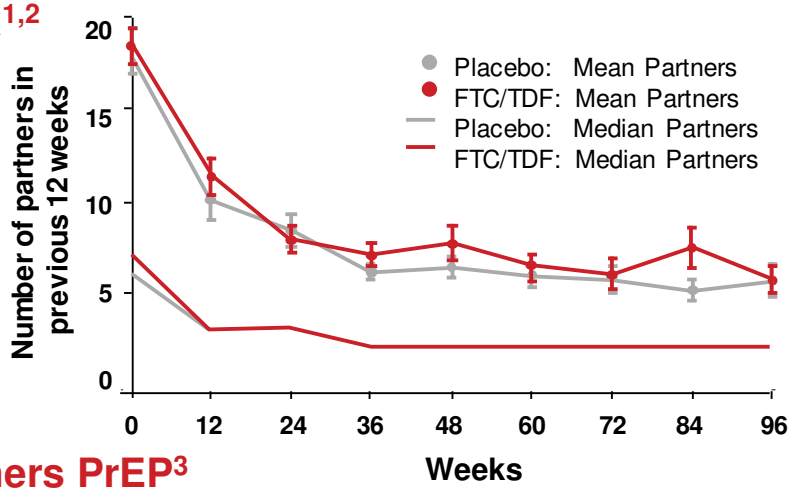


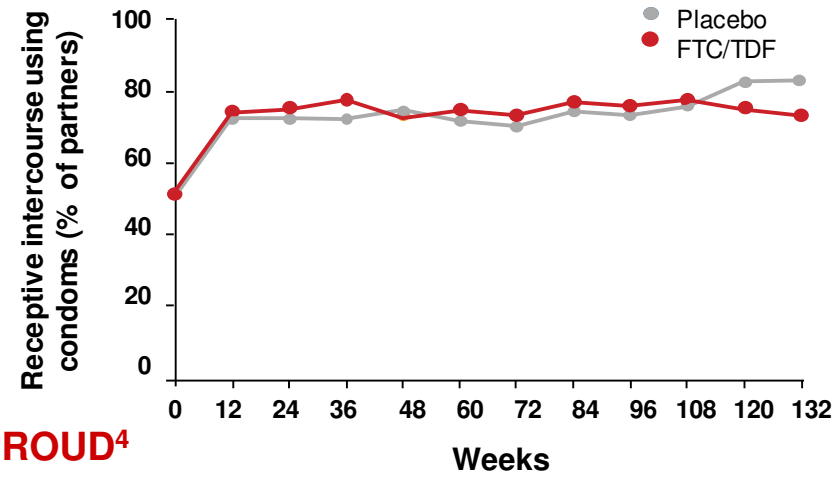


Hosek S, et al. AIDS 2016. Durban, South Africa. Oral# TUAX0104LB ***TDF/FTC is not FDA approved for use in those <18 years old**

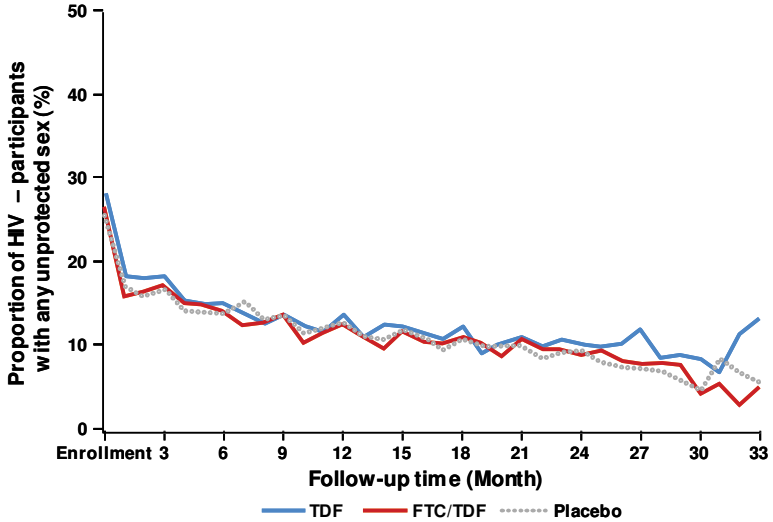
Risk Compensation in PrEP Clinical Trials

iPrEx[1,2]

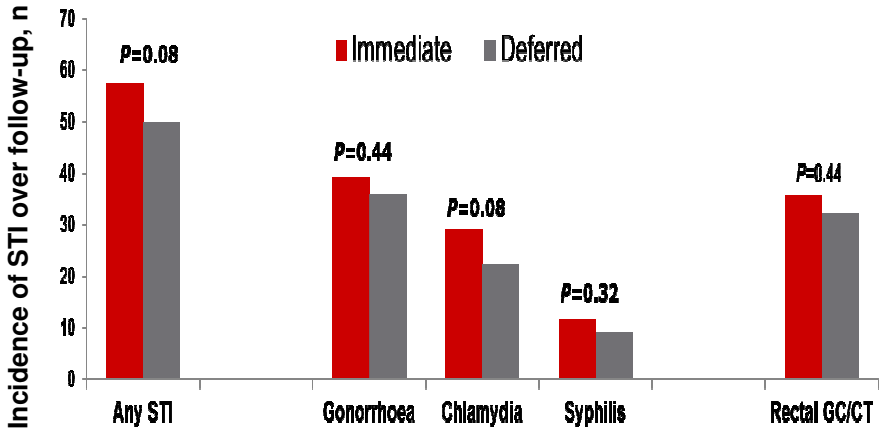




Partners PrEP[3]



PROUD[4]



There was no risk compensation seen in iPrEX, Partners PrEP, or PROUD

1. Grant R, et al. CROI 2011. Boston #92
2. Grant R, et al. N Engl J Med 2010;30:2587-9
3. Baeten J, et al. IAS 2011; Rome. #MOAX0106
4. McCormack S, et al. CROI 2015; Seattle, WA. #22LB

IPERGAY Open-Label Extension (OLE)

HIV Incidence (mITT analysis), Adherence and Sexual Behaviour

‡

	Open-label	Double-blind	
		TDF/FTC	PBO
HIV Incidence per 100py (95%CI)	**0.19** (0.01-1.08)	**0.91** (0.11-3.30)	**6.60** (3.60-11.1)
Total Follow-up (py)	515	219	212
Median follow-up (months)	18.4	9.3	
Adherence Measures:			
Median pills/month (no.)	18	15	
Participants with plasma TFV > 40 ng/mL (%)	55	46	
Correct* PrEP use at last sexual intercourse (%)	50	42	
Sexual Behaviour:			
Change in no. reporting condomless AI (%)	77→86% (p=0.0003)	No significant change	
Incidence rate of first STI (/100py)	40.6	35.2	
Participants with any STI (%)	58	37	

*At least one pill before and one pill after

On Demand PrEP with oral TDF/FTC remained highly effective in at-risk MSM
97% relative reduction in HIV incidence vs. placebo

Molina JM, et al. AIDS 2016. Durban, South Africa. Oral #WEAC0102
Molina JM. N Engl J Med 2015; 373:2237-2246.

mITT, Modified Intention-to-Treat Population
py, patient years
STI, sexually transmitted infection

STI Data from Community-Based PrEP Implementation

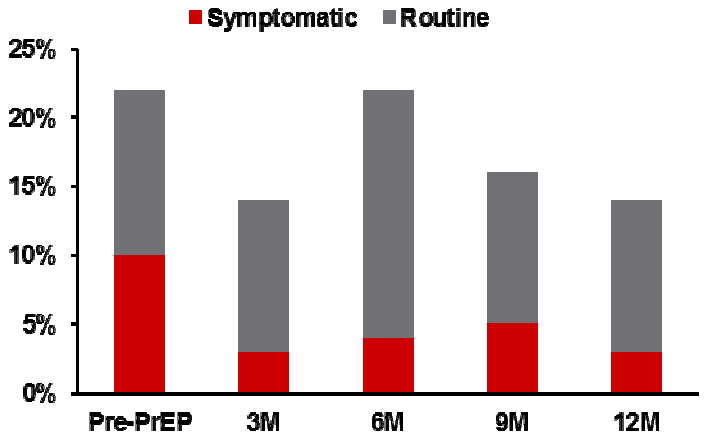
**Retrospective record review in SPARK (NYC);
prospective cohort analysis in The Demo Project (SF, DC, Miami)**

	NYC SPARK (n=280)[1]	The Demo Project (n=557)[2]
STIs pre-PrEP	21%	> 25%
STIs on PrEP	13-21% quarterly	18-25% quarterly
STIs that CDC guidelines* would have missed (asymptomatic at 3M and 9M)	77% at 3M; 68% at 9M	34% GC; 40% CT; 20% syphilis
Extragenital STIs	71-100% quarterly	83% GC; 76% CT

*Current CDC guidelines recommend STI screening q6mo and asking about symptoms quarterly

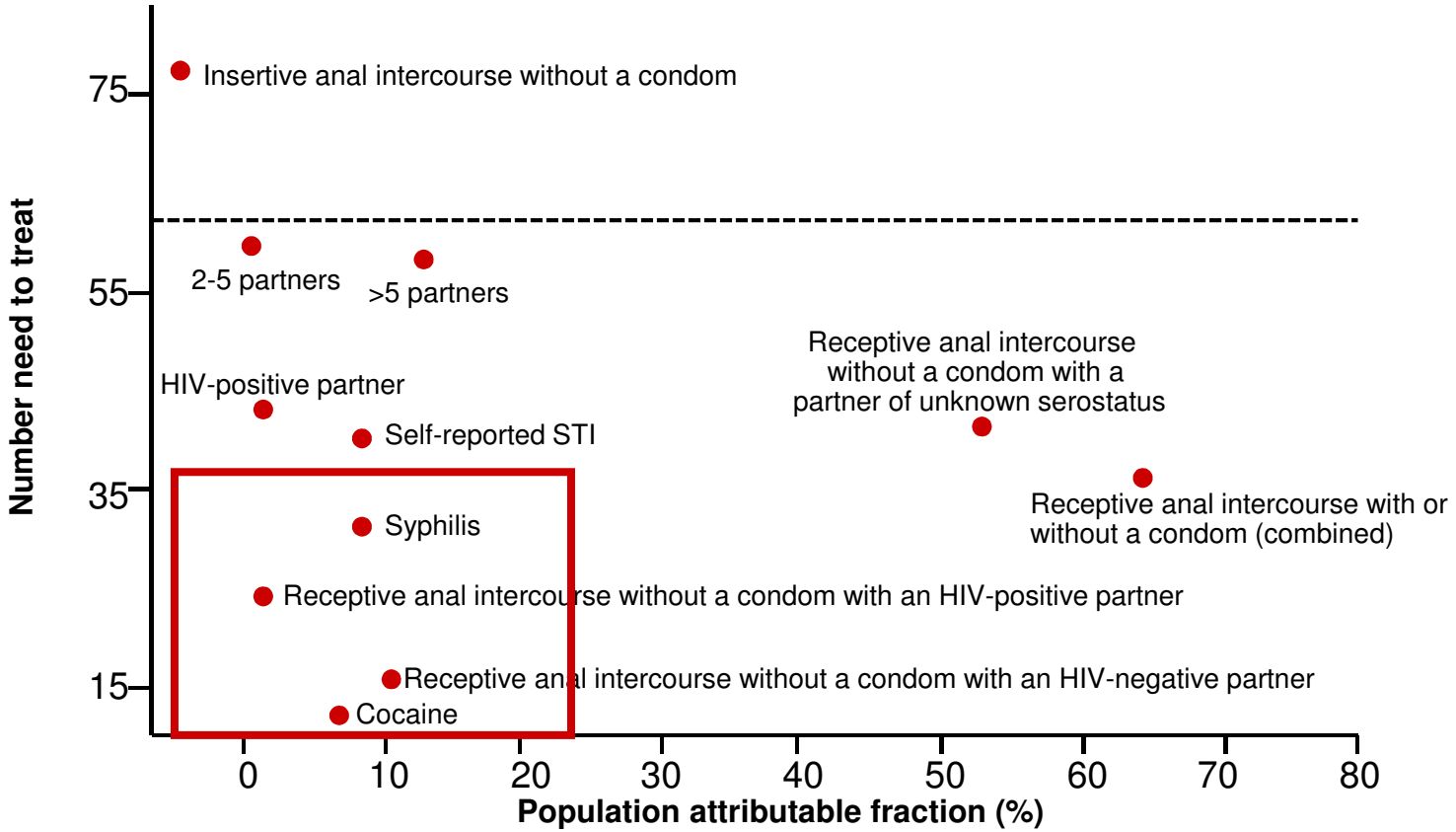
- In The Demo Project, transmission modeling suggested that q3mo screening prevented a median of 3 partners from being exposed to an STI via condomless anal sex
- **Data from both projects indicate that not screening extra-genital sites and only following the CDC's current STI screening guidelines would miss or delay many STI diagnoses**

NYC SPARK STI diagnoses by time point[1]



1. Golub S, et al. CROI 2016. Boston, MA. #869
2. Cohen S, et al. CROI 2016. Boston, MA #870

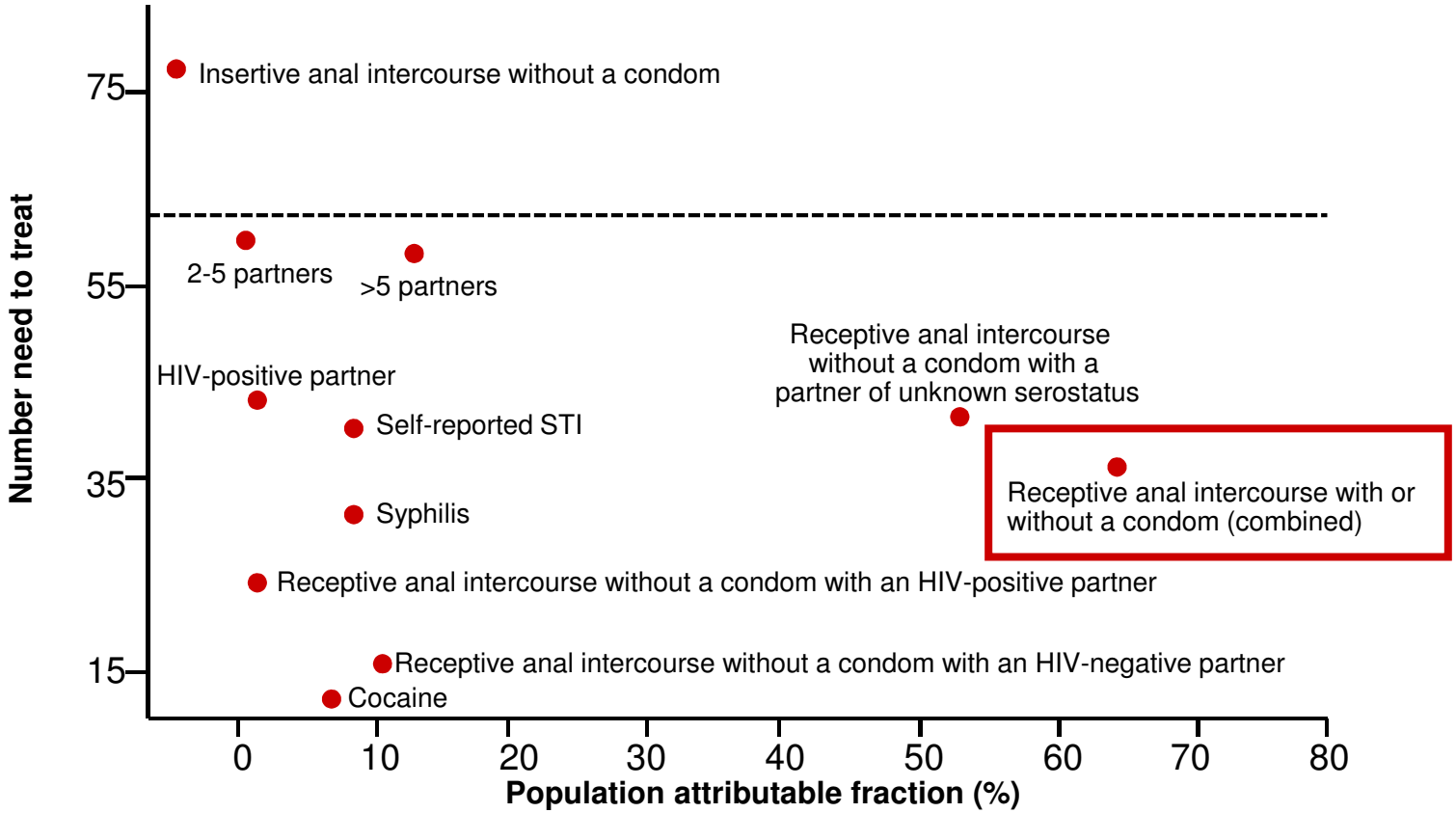
Quantifying Individual and Public Health Benefits of PrEP



In iPrEx, subgroups with strong risk factors for HIV (new syphilis, drug use, sex with known HIV+ partner) had very low number needed to treat (NNT), suggesting individual benefit from PrEP

Buchbinder S, et al. Lancet ID 2014;14(6):468–475

Quantifying Individual and Public Health Benefits of PrEP



The largest PAF was for men who had RAI without a condom, regardless of HIV status of partners (HIV+, "HIV-", or HIV-unknown). Even in this group, the number needed to treat was only 36

Buchbinder S, et al. Lancet ID 2014;14(6):468–475

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Can TDF/FTC for PrEP Be Used During Pregnancy?

- There are no adequate and well-controlled studies of TDF/FTC for PrEP in pregnant women
- Use TDF/FTC for PrEP during pregnancy only if clearly needed
  - In uninfected women who become pregnant while taking TDF/FTC for PrEP, careful consideration to continuing TDF/FTC should be given, taking into account the potential increased risk of HIV-1 infection during pregnancy
- To monitor foetal outcomes of pregnant women exposed to antiretroviral regimens, an **Antiretroviral Pregnancy Registry (APR)** has been established. Healthcare providers are encouraged to register patients by calling 800-258-4263
- **http://www.apregistry.com/** .

TRUVADA US Prescribing Information. Gilead Sciences, Inc. 2013.

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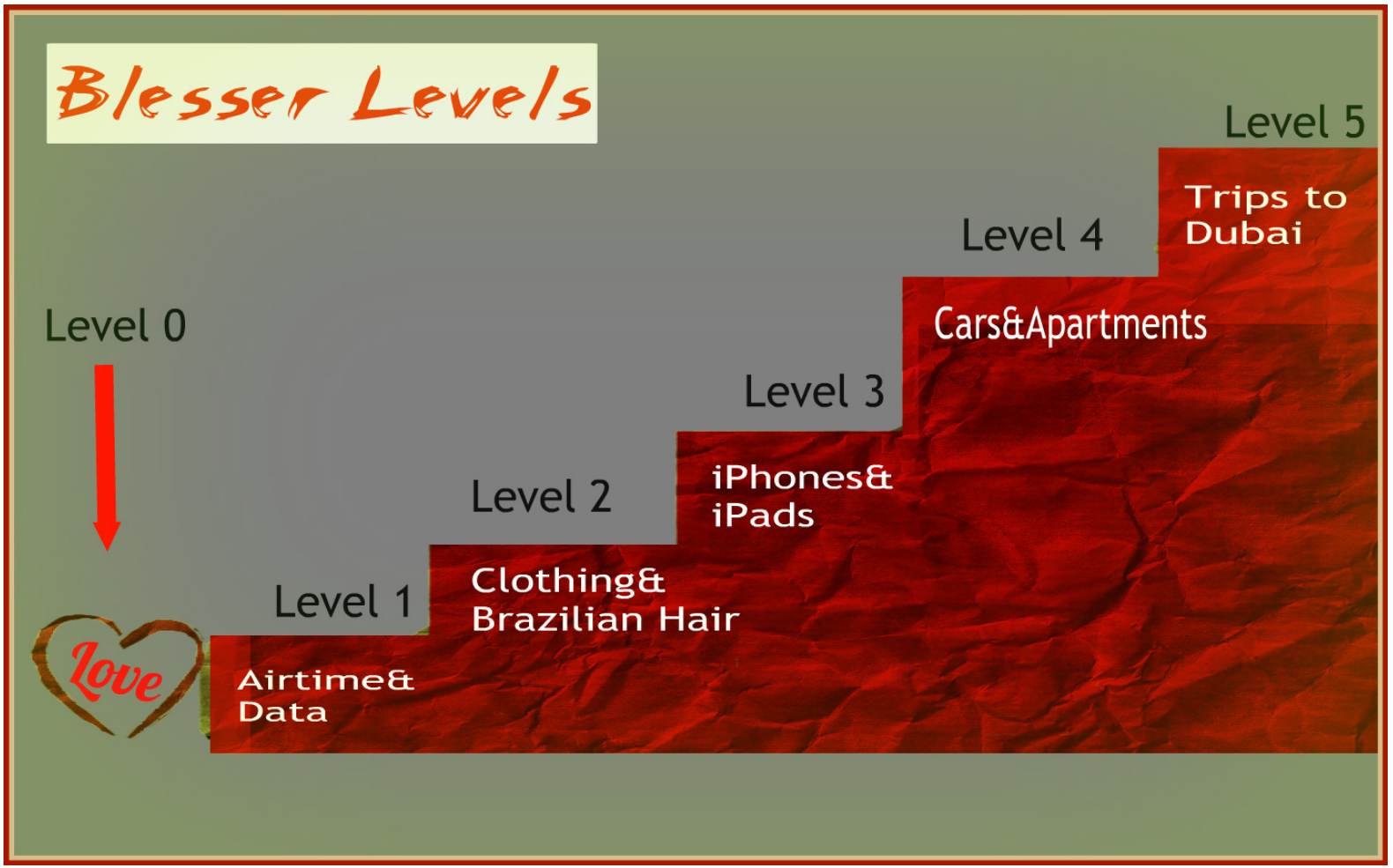
No Association Found Between the Components of TDF/FTC and Birth Defects in ART-Treated, HIV+ Women

HIV+ Women on ART	Any FTC-Containing Regimen[1]	Any TDF-Containing Regimen[1]
Pregnancies enrolled, n		
First trimester	1728	2478
Second trimester	525	670
Third trimester	206	351
Defects/live births, n/N (%)		
First trimester exposure	35/1543 (2.3%)	47/2141 (2.2%)
Second/third trimester exposure	15/729 (2.1%)	21/1021 (2.1%)

- Among pregnant women in the US reference population, the background rate of birth defects is 2.7%. There was no association between FTC or TDF and overall birth defects observed in the APR[1,2]

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2014. Wilmington, NC: Registry Coordinating Center; 2014. http://www.APRegistry.com
2. TRUVADA US Prescribing Information. Gilead Sciences, Inc. 2013.


Blesser Levels
Level 0
Level 1
Airtime&
Data
Level 2
Clothing&
Brazilian Hair
Level 3
iPhones&
iPads
Level 4
Cars&Apartments
Level 5
Trips to
Dubai
Love

Additional insights on why the high HIV rates in young women

Why such high risk of HIV acquisition following exposure?

LPS released by Prevotella bivia

Why such high variability in the efficacy of PrEP?

Tenofovir absorption by Gardnerella

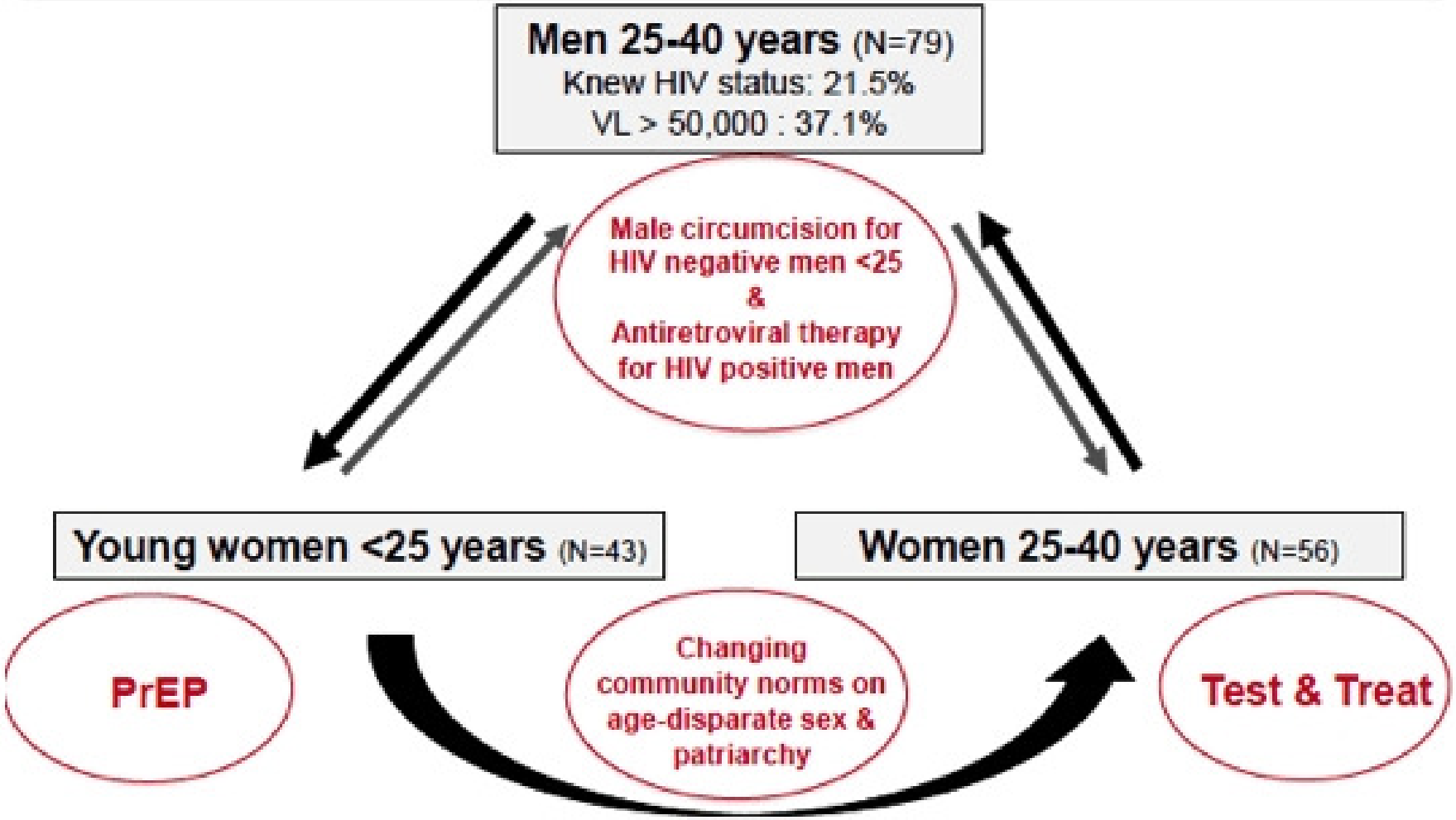
Who is exposing young women to HIV?

Men with high viral loads in their thirties

Young women at high HIV risk

Technologies to empower women to protect themselves from HIV infection

Combination prevention to break the Cycle of HIV transmission



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'Nothing will ever be attempted if all possible objections must first be overcome' – Samuel Johnson (1709-1784)