Descovy® for PrEP

Antimicrobial Drugs Advisory Committee Meeting

August 7, 2019

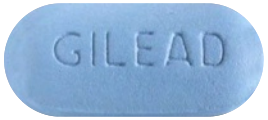
NDA 208215/S-012

Introduction

Diana Brainard, MD

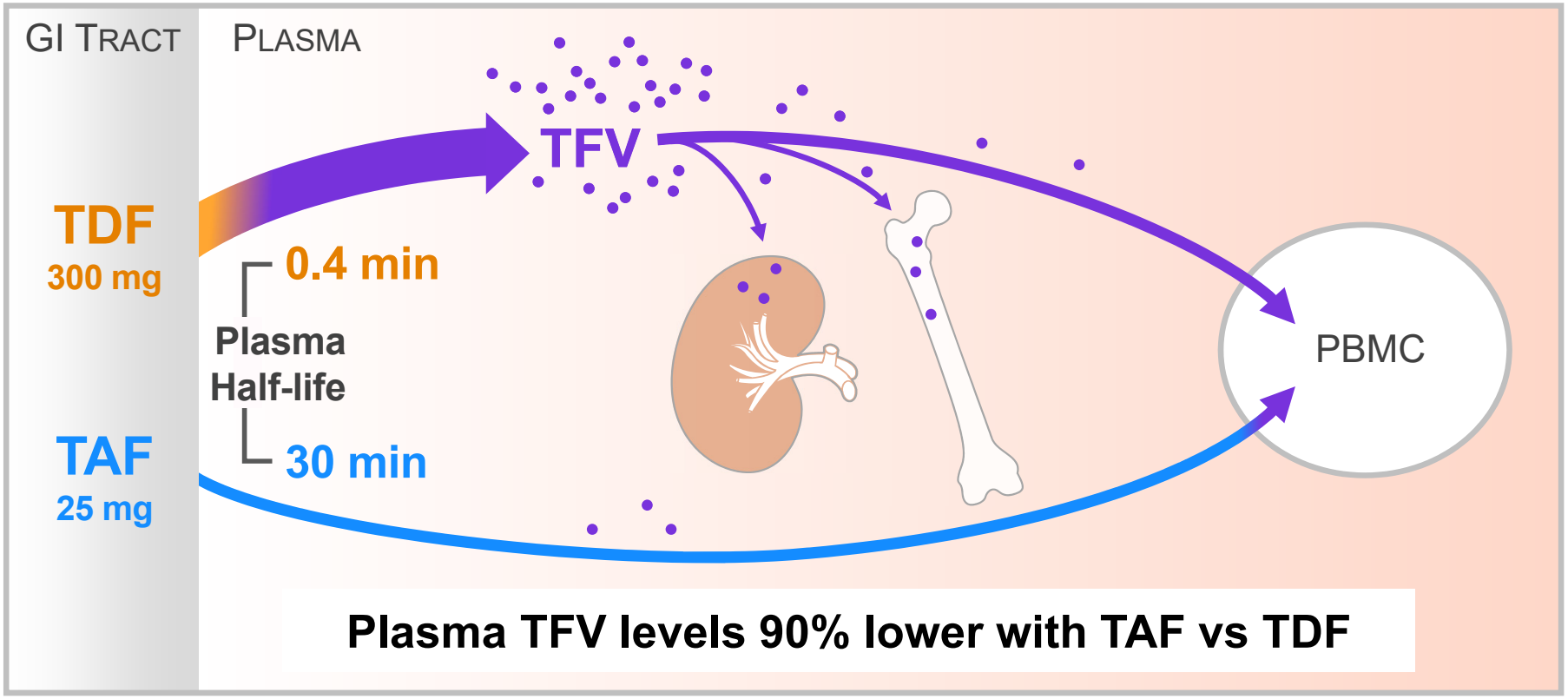
Senior Vice President
HIV & Emerging Viruses

Truvada® and Descovy®

	Truvada	Descovy
		
Components	Emtricitabine (FTC) + Tenofovir disoproxil fumarate (TDF)	Emtricitabine (FTC) + Tenofovir alafenamide (TAF)
Indications	HIV treatment (as part of a complete regimen) in adults and adolescents HBV treatment (TDF alone) PrEP in adults and adolescents	HIV treatment (as part of a complete regimen) in adults and adolescents HBV treatment (TAF alone) PrEP in adults and adolescents

HBV=hepatitis B virus.

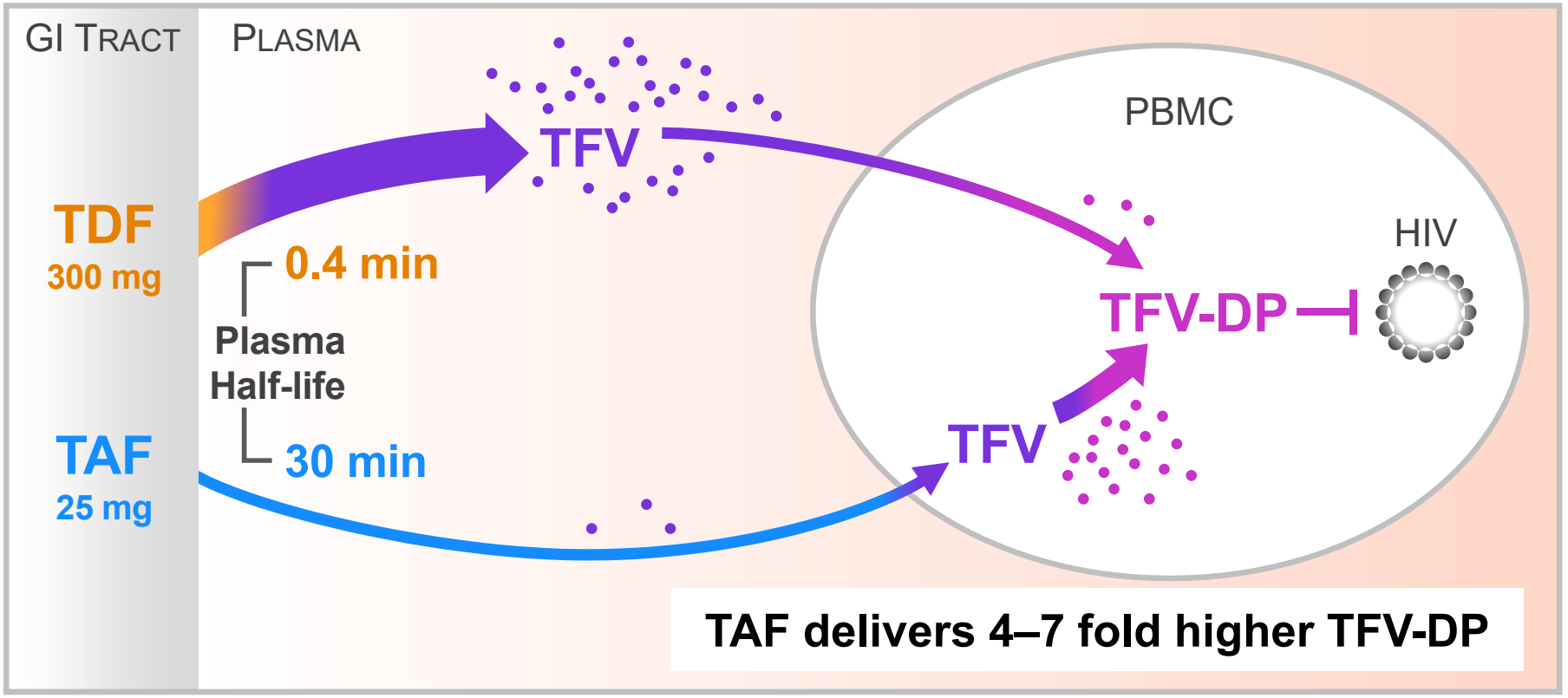
Tenofovir Alafenamide: Longer Half-Life Allows for Lower Dose



GI=gastrointestinal; PBMC=peripheral blood mononuclear cell; TFV=tenofovir.

Lee W, et al. Antimicr Agents Chemo 2005;49:1898-1906; Birkus G, et al. Antimicr Agents Chemo 2007;51:543-50; Babusis D, et al. Mol Pharm 2013;10:459-66; Ruane P, et al. J Acquir Immune Defic Syndr 2013; Sax P, et al. JAIDS 2014;67:52-8.

Tenofovir Alafenamide: Higher Diphosphate Levels in PBMCs

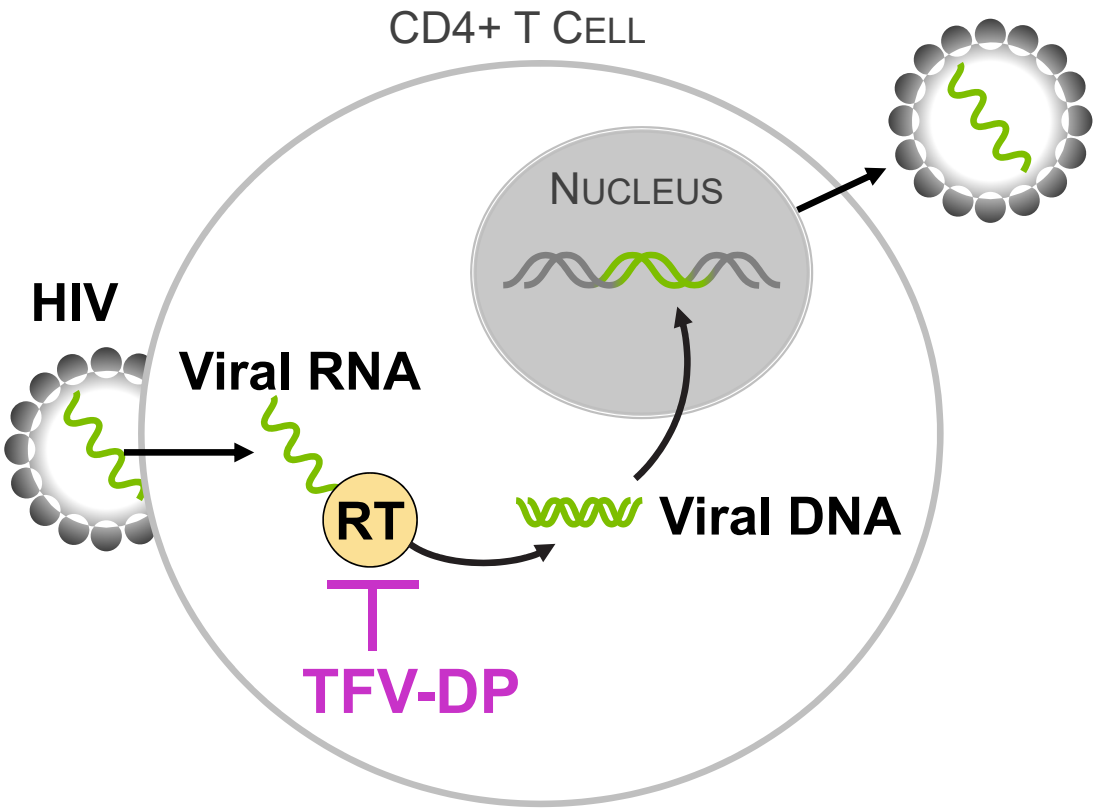


TFV-DP=tenofovir diphosphate.

Lee W, et al. Antimicr Agents Chemo 2005;49:1898-1906; Birkus G, et al. Antimicr Agents Chemo 2007;51:543-50;
Babusis D, et al. Mol Pharm 2013;10:459-66; Ruane P, et al. J Acquir Immune Defic Syndr 2013; Sax P, et al. JAIDS 2014;67:52-8.

Mechanism of Action for Tenofovir Disphosphate (TFV-DP)

Active Metabolite of TDF and TAF



A=adenosine; C=cytosine; DNA=deoxyribonucleic acid; G=guanine; RT=reverse transcriptase; U=uridine.

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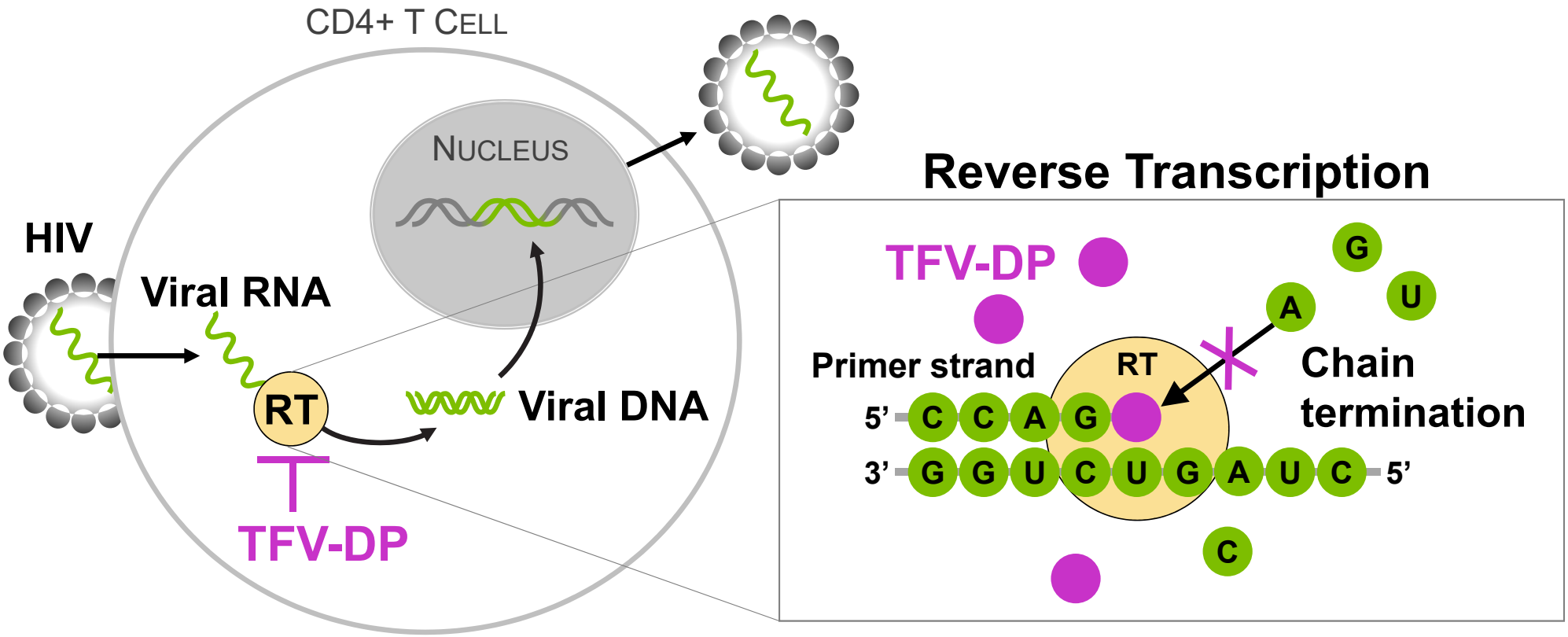
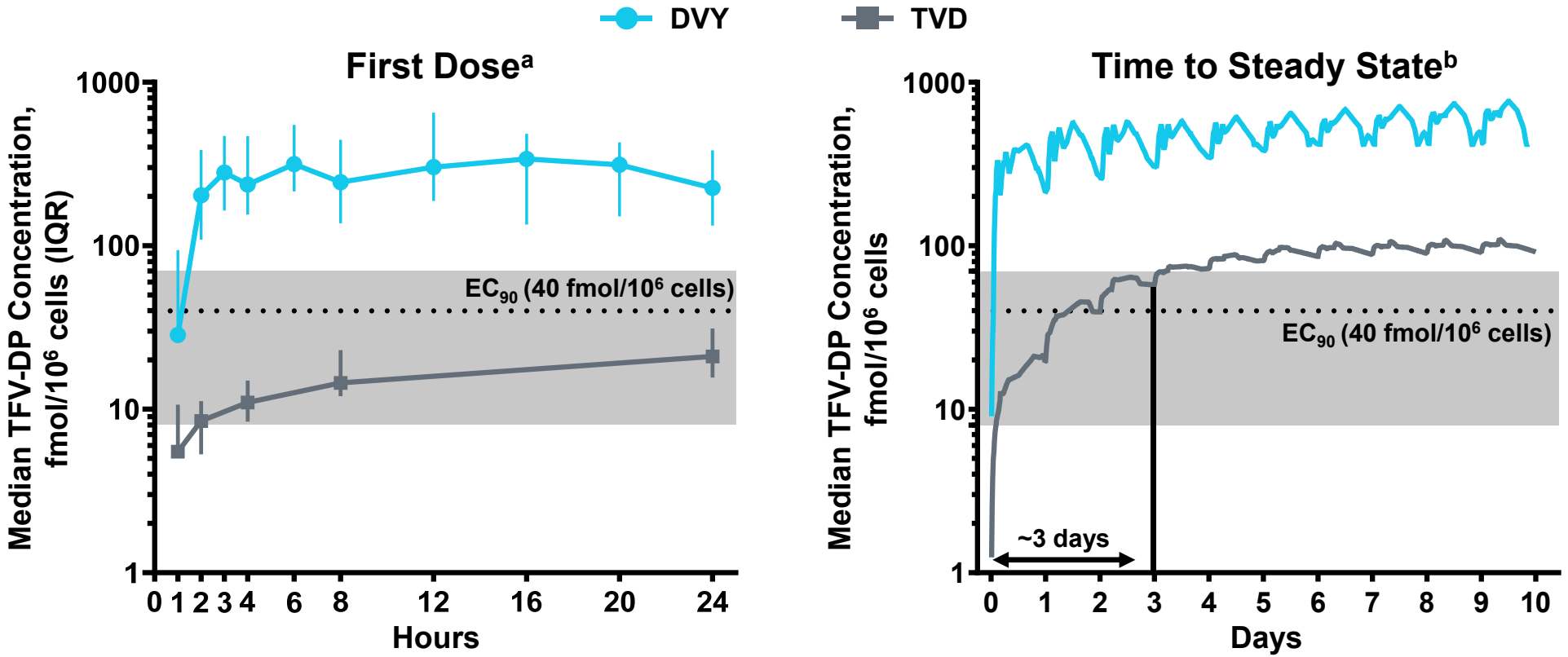


A=adenosine; C=cytosine; G=guanine; RT=reverse transcriptase; U=uridine.

Descovy and Truvada TFV-DP Levels in PBMCs

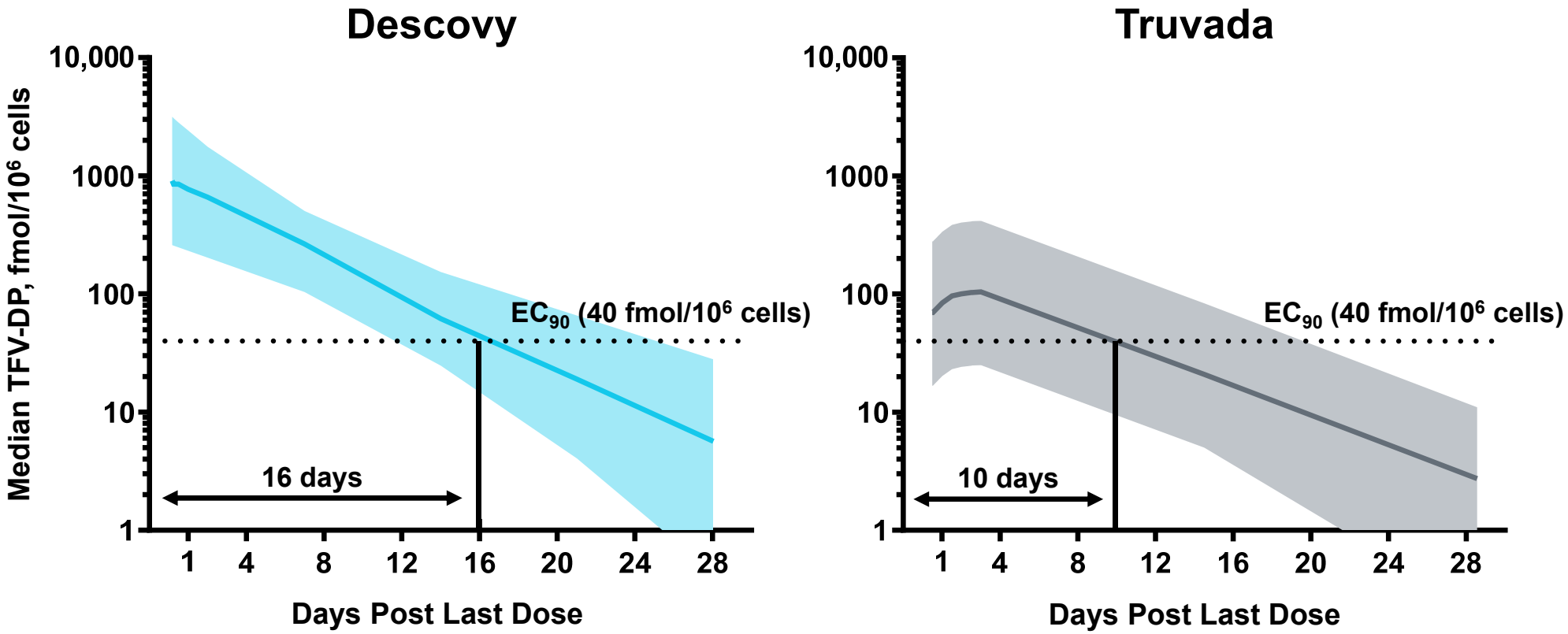
Phase 1 Study in Healthy Volunteers



EC_{90}=90% effective concentration (40 fmol/10^6 cells, Anderson PL, et al. CROI 2012); IQR=interquartile range.
a. DVY data from bictegravir/F/TAF 50/200/25 mg in volunteers (N=26) and TVD data from Schwartz JL, et al. HIV Research for Prevention 2018 (n=25), Cottrell 2017; b. Mean simulated time to steady state.

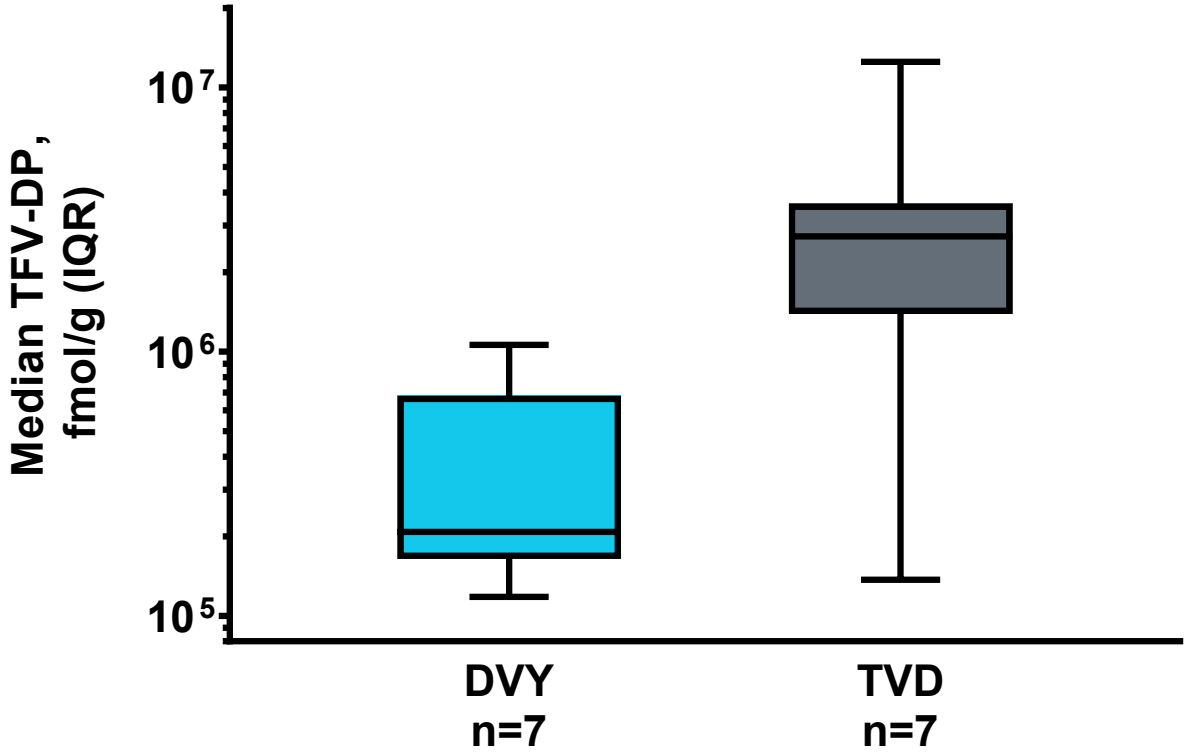
TFV-DP Levels Over Time Once Dosing Stops

Simulation of Descovy vs Truvada Based on Observed TFV-DP at Steady State



Shading represents 5th–95th percentiles. 1. Anderson PL, et al. CROI 2012; 2. Custodio J, et al. EACS 2017; 3. Custodio J, et al. ASM 2016, poster SUNDAY-410; 4. Hawkins J Acquir Immune Defic Syndr 2005;39:406-11.

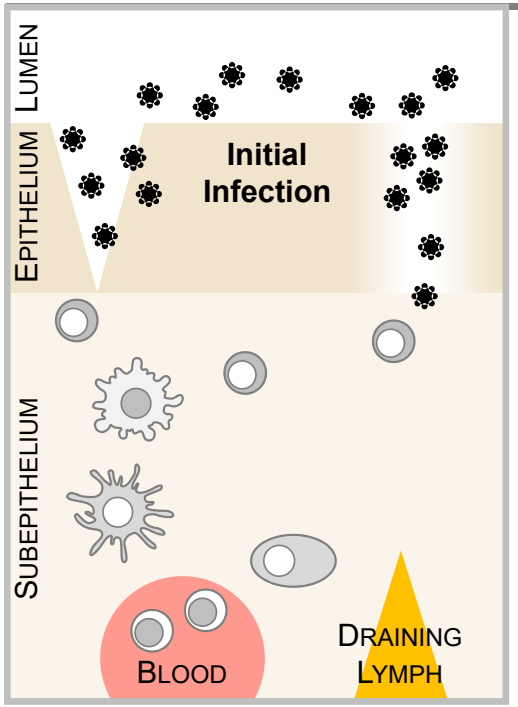
TFV-DP Levels in Rectal Tissue



BLQ=below limit of quantification.
4 different rectal samples were collected for each participant at 4h postdose. 8/28 DVY samples BLQ; 1/28 TVD samples BLQ.
Schwartz JL, et al. HIV Research for Prevention 2018, updated unpublished data.

Mechanism of Sexually Acquired HIV Infection

Virus Breaches the Epithelium



Dendritic/Langerhans cell

Macrophage

Plasmacytoid dendritic cell

PBMC

HIV virus

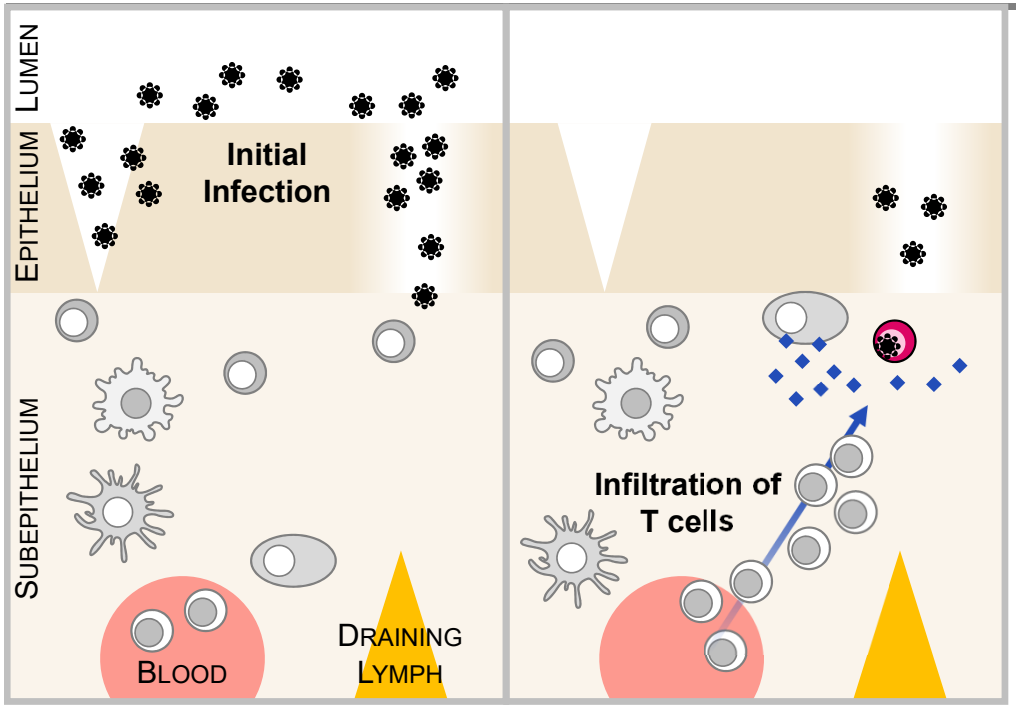
CD4+ T cell

Infected CD4+ T cell

Martins E, et al. Swiss Med Wkly 2018;148:w14580; Haase AT, Nature 2010;464:217-23; Li Q, et al. Nature 2009;458:1034-8.

Mechanism of Sexually Acquired HIV Infection

Infiltration of T Cells



Dendritic/Langerhans cell

Macrophage

Plasmacytoid dendritic cell

PBMC

Chemokines

HIV virus

CD4+ T cell

Infected CD4+ T cell

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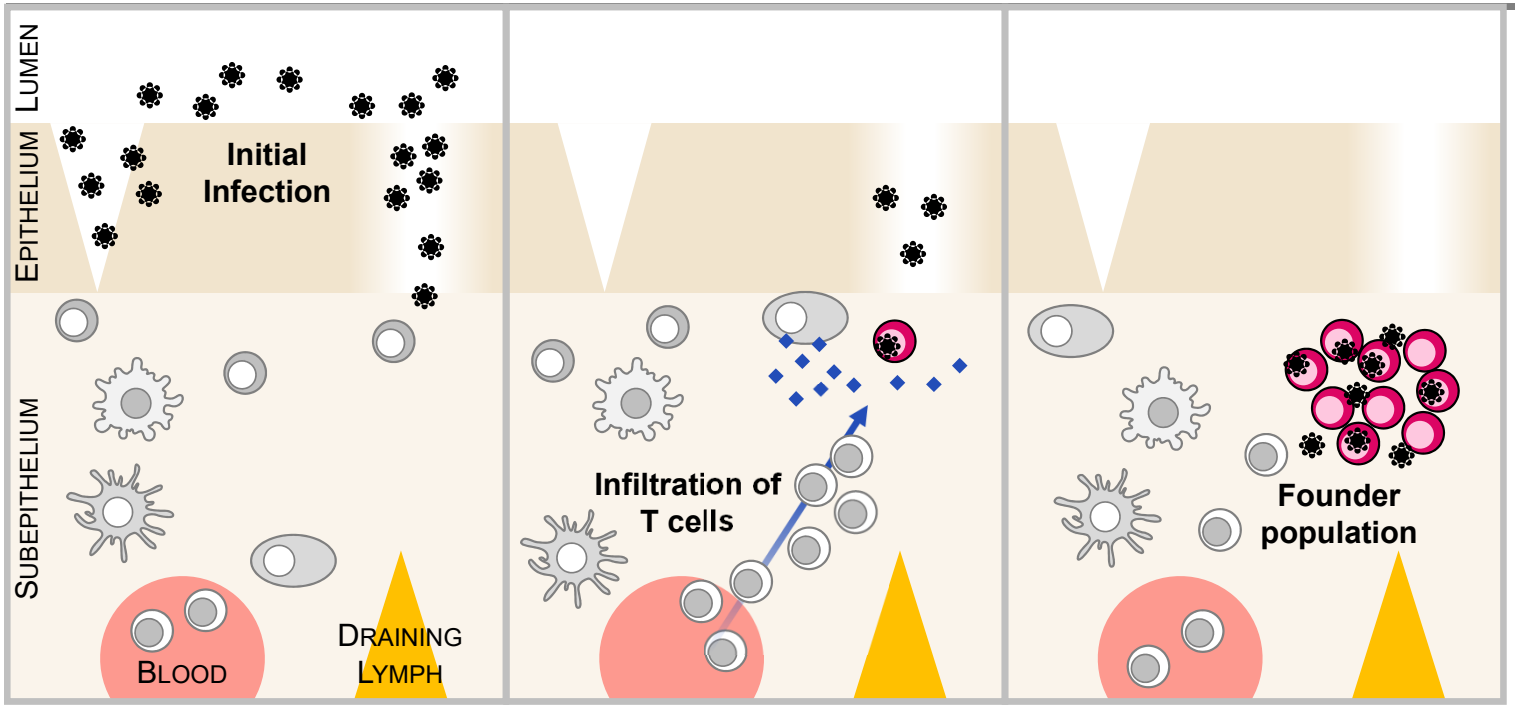
Mechanism of Sexually Acquired HIV Infection

Focus of Infection



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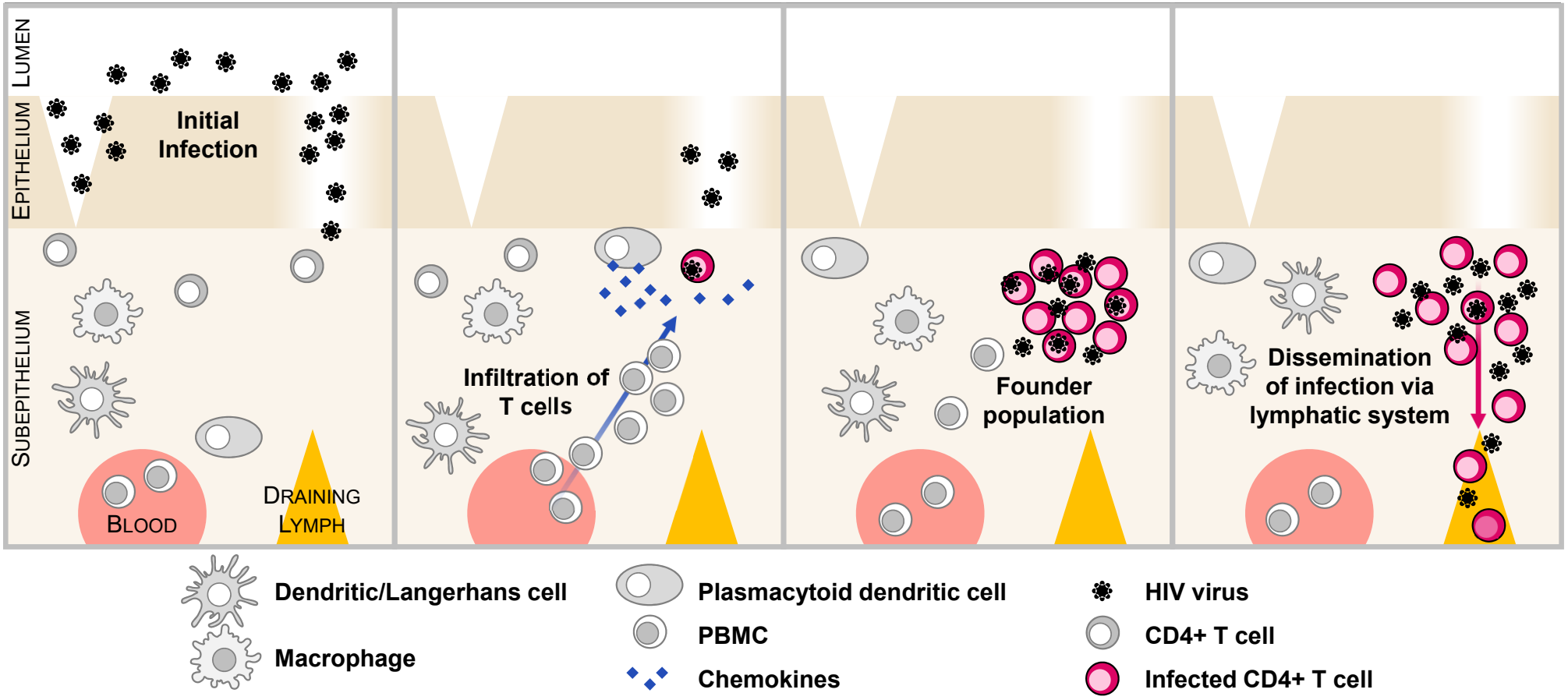
Mechanism of Sexually Acquired HIV Infection

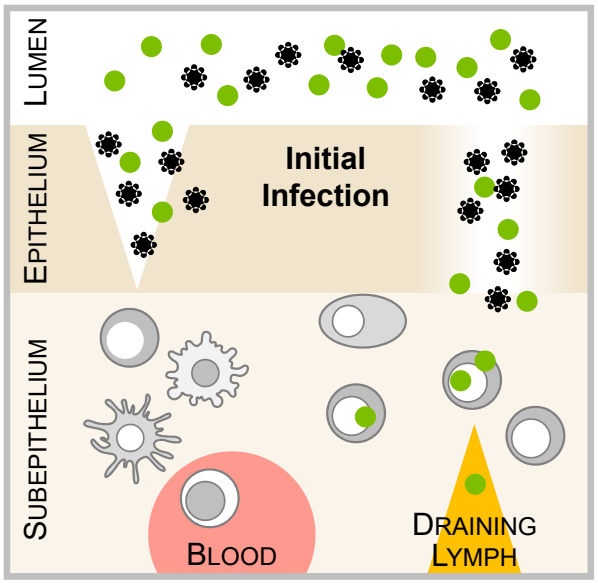
Dissemination to Lymph Nodes



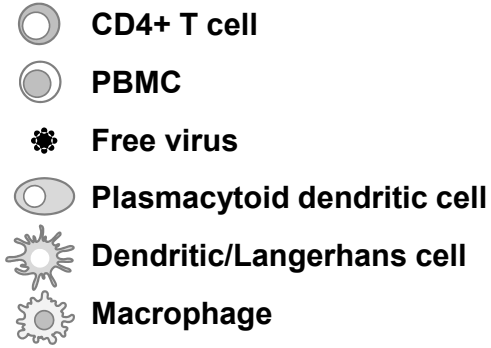
Martins E, et al. Swiss Med Wkly 2018;148:w14580; Haase AT, Nature 2010;464:217-23; Li Q, et al. Nature 2009;458:1034-8.

Mechanism of Topical vs Systemic Prevention Intervention

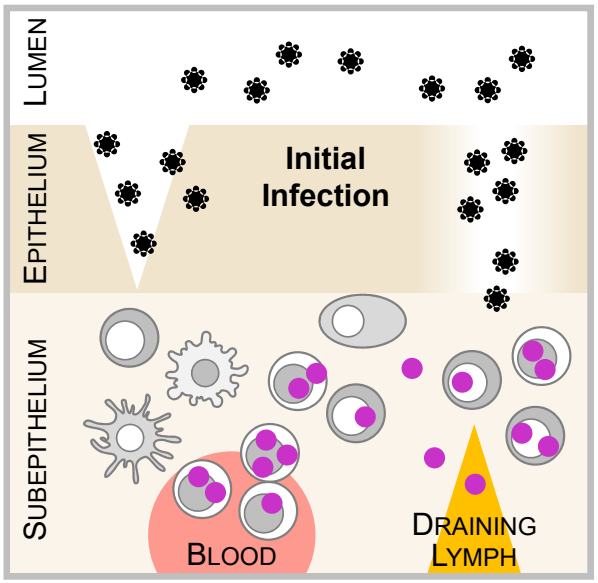
Topical Agents



- Drug absorbed into local tissues/cells
- Efficacy among high adherers 54%[1]



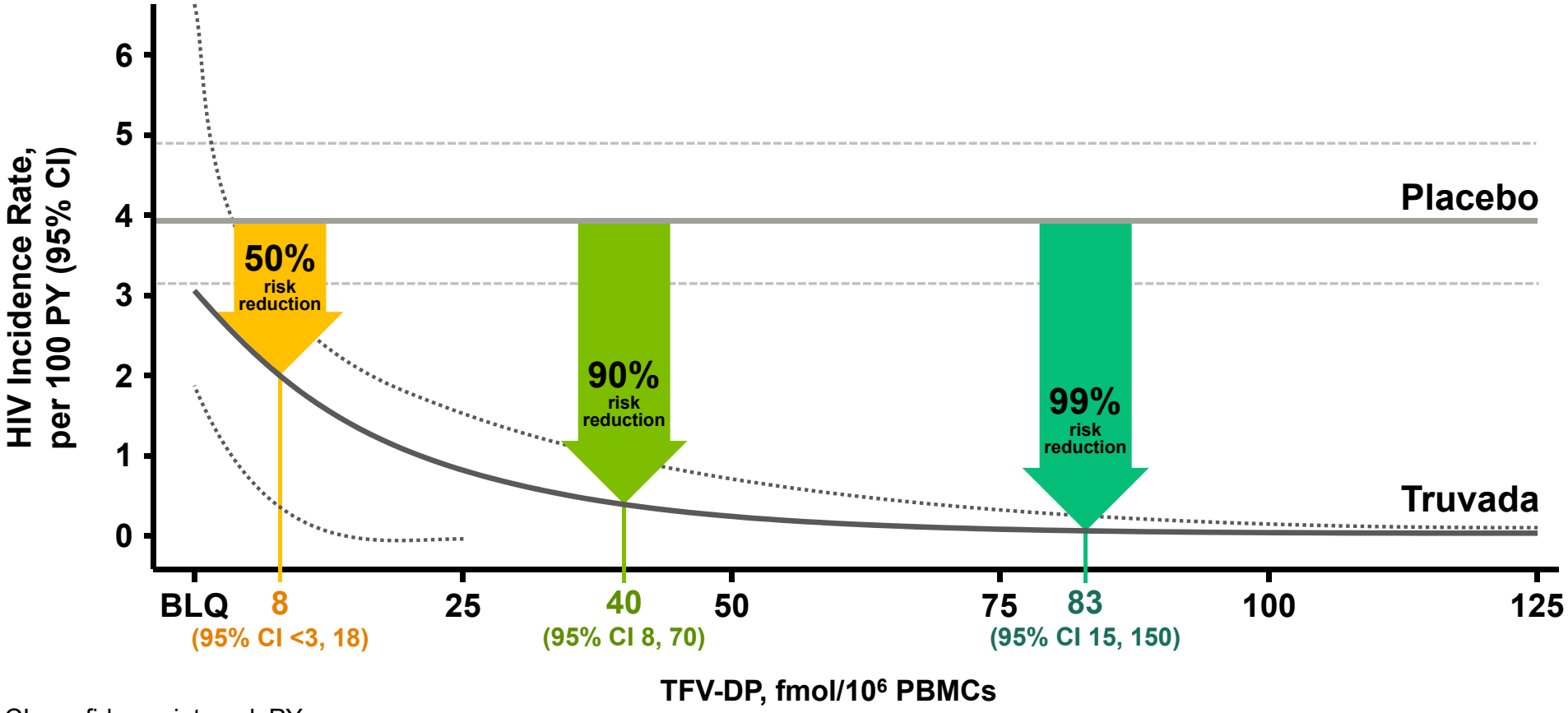
Systemic Agents



- Drug diffuses into local tissues/cells; PBMCs with drug reach tissues
- Efficacy among high adherers 99%[2]

1. Karim QA, et al. Science 2010;329:1168-74.
2. CDC HIV Prevention Strategies. https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html. Accessed July 18, 2019.

PBMC TFV-DP Levels and HIV Risk Reduction



CI=confidence interval; PY=person-year.

Figure adapted from Anderson PL, et al. Sci Transl Med 2012; 2. Anderson PL, et al. CROI 2012.

Truvada vs Descovy for PrEP in 2015

Context

1. Truvada for PrEP was approved in adults only
2. Descovy was undergoing FDA review for approval for HIV treatment
3. Data suggested low rectal tissue levels;
ongoing debate regarding which compartment correlated with protection

Purpose

Conduct a statistically rigorous Phase 3 study to definitively establish the safety and efficacy of Descovy for PrEP in MSM and transwomen

MSM=men who have sex with men.

Phase 3 DISCOVER Trial Design

- International, double-blind, randomized, active-controlled, noninferiority study comparing Descovy with Truvada for PrEP
- Enrolled 5387 cismen and transgender women who have sex with men and are at high risk of HIV
- Designed in close collaboration with FDA and the community

DISCOVER Trial: Key Findings

- Primary endpoint met: Descovy was noninferior to Truvada
  - 7 infections (0.16 per 100 PY) with Descovy
  - 15 infections (0.34 per 100 PY) with Truvada
- The incidence rate ratio was 0.47 and the upper bound of the confidence interval was 1.15, less than the prespecified noninferiority margin of 1.62
- Descovy was superior to Truvada on 6 prespecified, alpha controlled secondary safety endpoints, including markers of bone and renal toxicity

Truvada vs Descovy for PrEP in 2019

Context

1. For both Truvada and Descovy, adherence is the key determinant of efficacy
2. Correlate of protection established for PBMC TFV-DP levels
3. Truvada rectal tissue levels 10-fold higher than Descovy;
   Descovy PBMC TFV-DP levels 7-fold higher than Truvada
4. DISCOVER point estimate suggests possible efficacy advantage for Descovy

Implication PBMC drug levels drive efficacy for Truvada and Descovy

Efficacy of Truvada for PrEP in Women

- Clinical trials of Truvada for PrEP have shown heterogeneous efficacy related to highly variable rates of adherence
- Controlling for adherence, Truvada is equally and highly effective in men and women[1]
- Biology of HIV transmission is independent of gender
  - Virus only replicates in mononuclear cells
  - Systemic transmission requires recruitment of target cells from the periphery to the site of initial infection
- Adequate drug levels within mononuclear cells are necessary and sufficient to mediate protection against HIV infection

1. https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html.

DISCOVER Results Are Relevant for Ciswomen

- Efficacy and safety for HIV treatment well established in >2,000 women and similar to men in clinical trials
- HIV behaves similarly in men and women
- Descovy and Truvada inhibit HIV in CD4+ T cells through the same active metabolites in men and women
- Pharmacokinetics similar irrespective of HIV status, sex
- Data support Descovy for PrEP in ciswomen

DISCOVER Results Are Relevant for Adolescents

- Descovy and 3 Descovy-based single tablet regimens approved in adolescents for HIV treatment based on established safety and efficacy in this group
- HIV behaves similarly in adolescents and adults
- Similar Descovy pharmacokinetics and pharmacodynamics in DISCOVER participants and adolescents with HIV
- Data support Descovy for PrEP in adolescents

Proposed Indication

Descovy is indicated:

- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg
- **for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg**

Agenda

Introduction	Diana Brainard, MD Senior Vice President HIV and Emerging Viruses Gilead Sciences, Inc.
DISCOVER Study Design, Treatment Population, and Efficacy Results	Scott McCallister, MD Executive Director HIV and Emerging Viruses Gilead Sciences, Inc.
DISCOVER Safety and Descovy for PrEP for Women and Adolescents	Moupali Das, MD, MPH Executive Director HIV and Emerging Viruses Gilead Sciences, Inc.
Clinical Context	Richard Elion, MD Director of Research Washington Health Institute Clinical Professor of Medicine George Washington University

DISCOVER Response Team

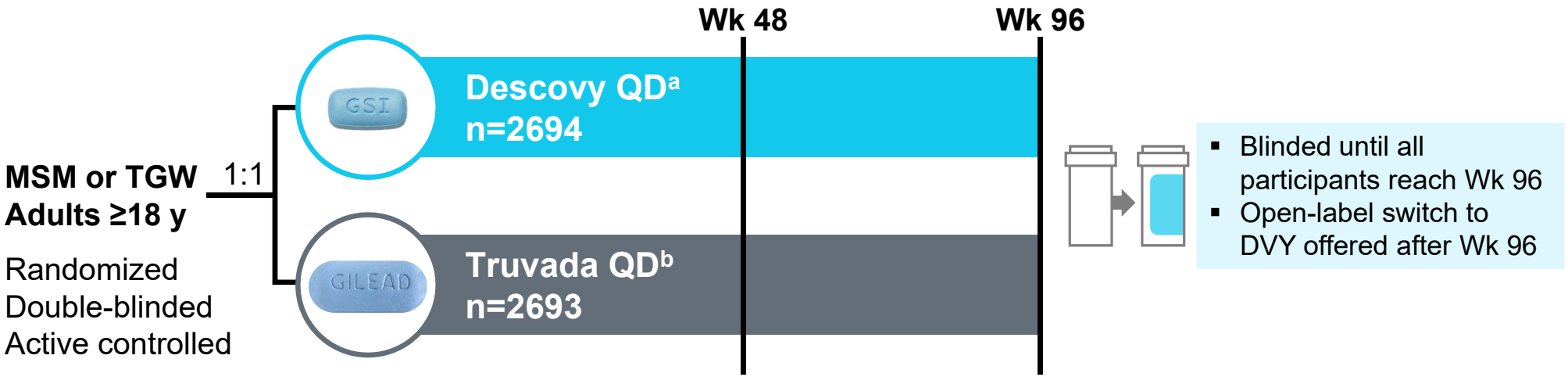
Clinical Pharmacology	Anita Mathias, PhD
Nonclinical Safety	Anne Chester, PhD
Risk Management	Terry Farrow, MD
Statistics	Michael Wulfsohn, MD, ScD
Virology	Christian Callebaut, PhD
External Pharmacoadherence Specialist	Peter Anderson, PharmD Professor, Department of Pharmaceutical Sciences Skaggs School of Pharmacy and Pharmaceutical Sciences University of Colorado Anschutz Medical Campus

Study Design, Treatment Population, and Efficacy Results

Scott McCallister, MD

Executive Director, Clinical Research
HIV & Emerging Viruses

Study Design



Primary analysis is HIV incidence per 100 person years when

- **100% complete Week 48**
- **50% complete Week 96**

QD=once daily; TGW=transgender women.
a. F/TAF dose: 200/25 mg; pill size 12 x 6 mm; b. F/TDF dose: 200/300 mg; pill size 19 x 8 mm.

Eligibility Criteria

- High sexual risk of HIV
  - ≥2 episodes of condomless anal sex (>1 unique partner), in the 12 weeks prior to enrollment

    OR
  - Diagnosis of rectal gonorrhea, rectal chlamydia, or syphilis, in the 24 weeks prior to enrollment
- HIV negative (prior PrEP use allowed), HBV negative
- Creatinine clearance ≥60 mL/min

Site Selection

Criteria

- High community incidence of HIV
- Cultural competency with populations at risk for HIV, ability to enroll and retain persons of color and transgender women

Conducted in cities with high HIV incidence

- 94 sites in 11 countries
- Participants:
  - 60% in US
  - 34% in EU
  - 7% in Canada

Study Protocol Development

- Study design discussed with: lead investigators, DISCOVER investigators, community, and FDA

GCP=good clinical practice; GLP=good laboratory practice; GMP=good manufacturing practice.

Primary Efficacy Endpoint

- HIV incidence rate (events per 100 PY) = $\frac{\text{Number of HIV Infections}}{\text{Person Years Exposure}} \times (100)$

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- $\frac{\text{HIV incidence rate, DVY arm}}{\text{HIV incidence rate, TVD arm}}$ = Incidence Rate Ratio (IRR)

Primary Efficacy Endpoint

- HIV incidence rate (events per 100 PY) = $\frac{\text{Number of HIV Infections}}{\text{Person Years Exposure}} \times (100)$
- $\frac{\text{HIV incidence rate, DVY arm}}{\text{HIV incidence rate, TVD arm}}$ = Incidence Rate Ratio (IRR)
- Noninferiority margin = 1.62, preserves 50% of TVD effect in 3 prior RCTs in MSM
- DVY noninferiority to TVD established if the upper bound of the IRR 95% CI is less than 1.62

RCT=randomized controlled trial.

On Study Safety Testing

Safety assessments

General safety evaluation (each visit)

Renal labs, urine proteins (each visit)

BMD tests of hip & spine (every 48 weeks)

STI testing (each visit)

BMD=bone mineral density; STI=sexually transmitted infection.

On Study Safety Testing, Secondary Endpoint Analysis

Safety assessments

General safety evaluation (each visit)

Renal labs, urine proteins (each visit)

BMD tests of hip & spine (every 48 weeks)

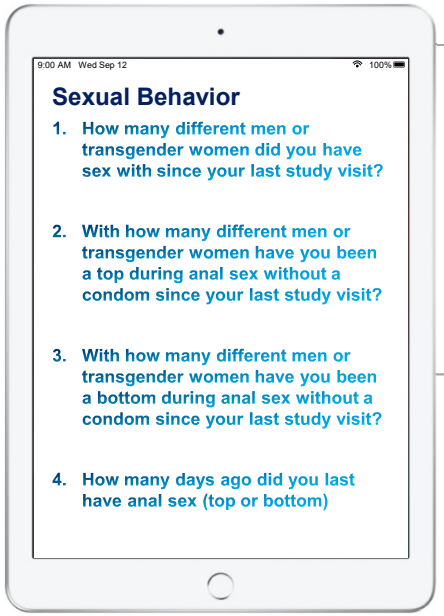
STI testing (each visit)

Prespecified Secondary Safety Endpoints (α-controlled)

1. Hip BMD % change from baseline
2. Spine BMD % change from baseline
3. Urine β2M:Cr % change from baseline
4. Urine RBP:Cr % change from baseline
5. Distribution of UPCR categories
6. Serum Cr ($eGFR_{CG}$) change from baseline

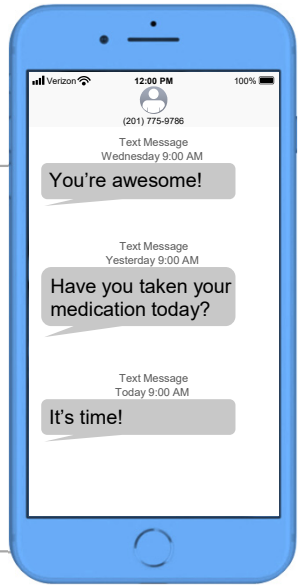
β2M:Cr=β2-microglobulin:creatinine ratio; Cr=creatinine; $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault method; RBP:Cr=retinol-binding protein:creatinine ratio; UPCR=urine protein:creatinine ratio.

On Study Evaluation of Sexual Behavior and Adherence



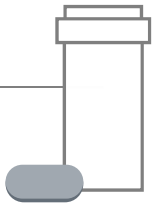
- Confidential questionnaires completed at screening and at each on study visit
  - Type and frequency of sexual events, condom use and drug adherence
- Site staff unaware of responses

- Support from site staff at each on study visit
  - Prevention education, risk reduction counseling
  - Condoms, lubricant provided
- Drug adherence support at each on study visit
  - Could also receive daily text reminders, and opt in/opt out at any time



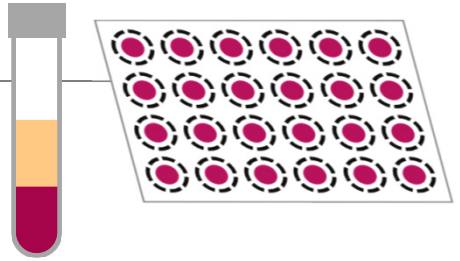
On Study Adherence Evaluations

Subjective Testing



- All study participants: confidential questionnaire, and pill counts from returned bottles at all on-study visits

Objective Testing

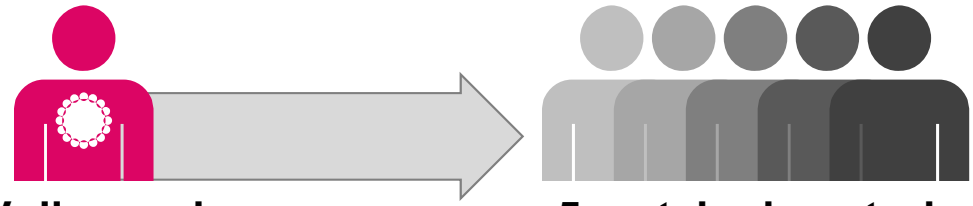


- Dried blood spot substudy: randomly selected subset (n=540), collected at all on study visits
  - TFV-DP levels in RBCs
  - These levels provide information on adherence in the past 8 weeks before collection[1]

RBC=red blood cell.

1. Anderson et al. Antimicrob Agents Chemo 2017.

On Study Case-Control Analysis

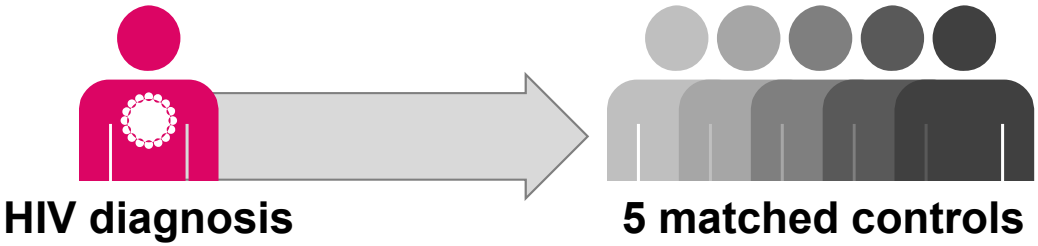


HIV diagnosis

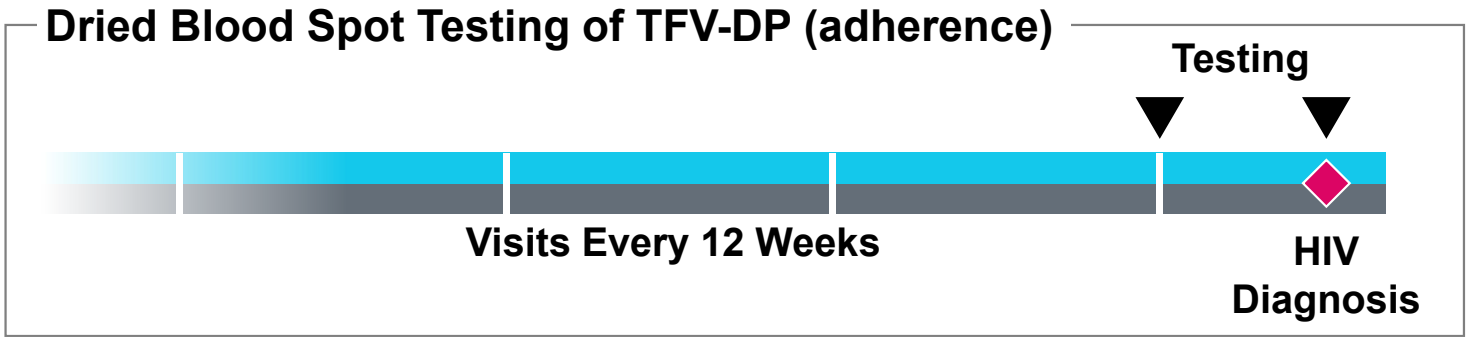
5 matched controls

Matched on geography, timing of HIV diagnosis, and diagnosis of a rectal STI

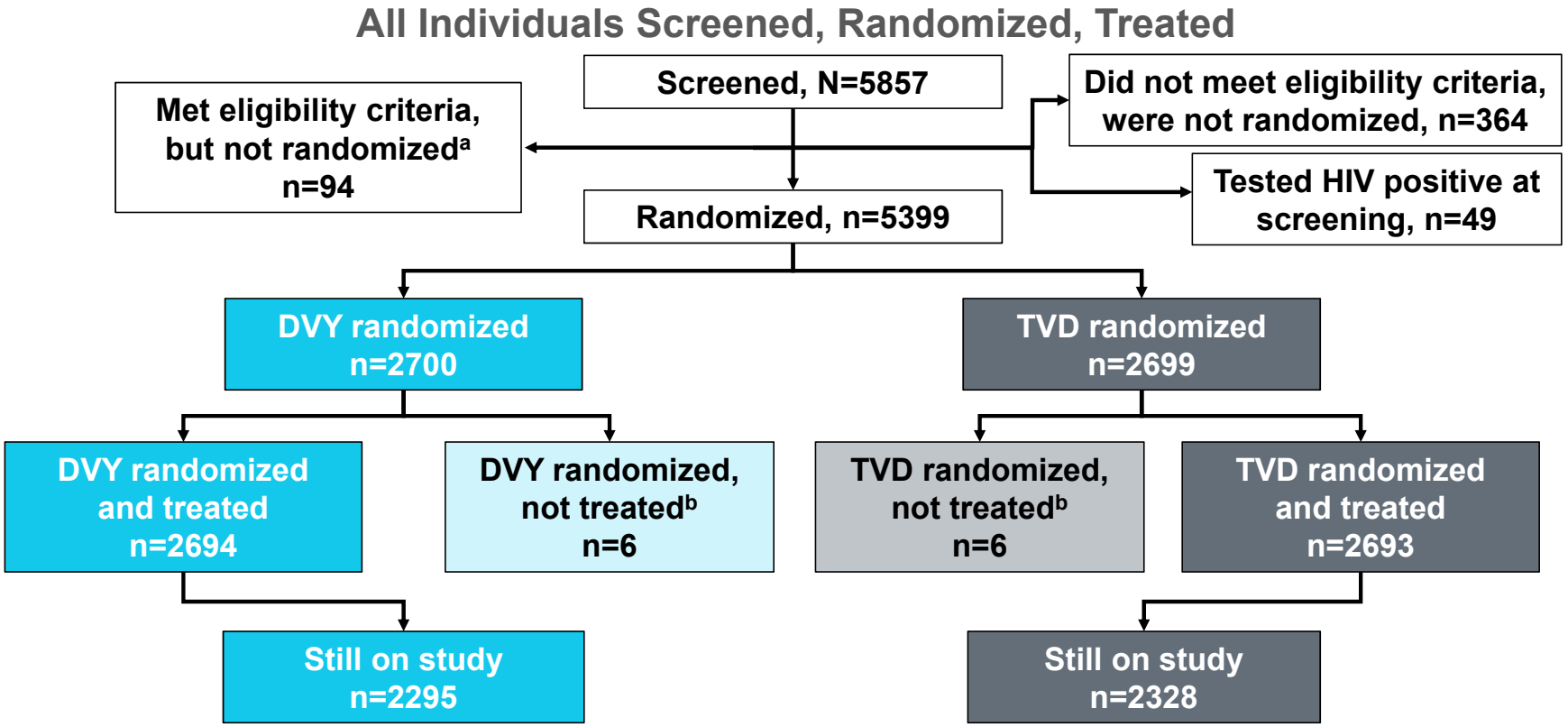
On Study Case-Control Analysis



Matched on geography, timing of HIV diagnosis, and diagnosis of a rectal STI



Participant Disposition: Screening to Data Analysis



a. Reasons (n) were: lost to follow-up (32); withdrew consent (51); investigator's discretion (3); outside of visit window (6); enrollment closed (1); participant death (1).

b. Reasons (n) were: protocol violation (1); withdrew consent (8); HIV-1 infection (2); investigator's discretion (1).

Baseline Demographics

		DVY n=2694	TVD n=2693
Age	**Median, y (range)**	34 (18–76)	34 (18–72)
	<25 y, n (%)	336 (12)	293 (11)
Race, n (%)	**White**	2264 (84)	2247 (84)
	Black[a]	240 (9)	234 (9)
Ethnicity, n (%)	**Hispanic or Latinx**	635 (24)	683 (25)
Gender, n (%)	**Transgender women**	45 (2)	29 (1)
Sexual orientation, n (%)	**Gay**	2461 (92)	2434 (91)
	Bisexual	171 (6)	214 (8)
	Heterosexual	25 (1)	16 (1)

a. includes mixed black race.

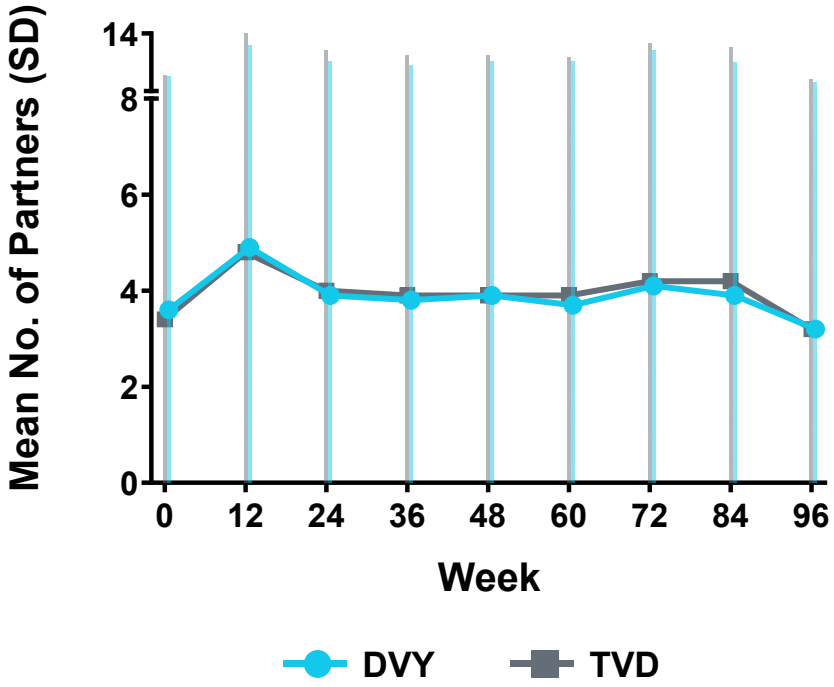
Baseline Sexual Behavior

Participants, %	DVY n=2694	TVD n=2693
≥2 receptive condomless anal sex partners, past 12 weeks	60	58
Rectal gonorrhea, past 24 weeks	10	10
Rectal chlamydia, past 24 weeks	13	12
Syphilis, past 24 weeks	9	10
Recreational drug use, past 12 weeks	67	67
Binge drinking[a]	23	22
Any prior use of TVD for PrEP	23	23
Using TVD for PrEP at baseline	17	16

a. ≥6 drinks on ≥1 occasion, at least monthly.

On Study Sexual Behavior

Condomless Receptive Anal Sex Partners (Number Since Last Visit)



Sexually Transmitted Infection Results

- Consistently high sexual behavior rate in study participants led to high rates of STIs
- 57% had gonorrhea or chlamydia diagnosed from any anatomic site (lab test) on study
- STI rates of gonorrhea, chlamydia or syphilis (AE report) on study:
  - DVY arm, 145 per 100 PY
  - TVD arm, 139 per 100 PY

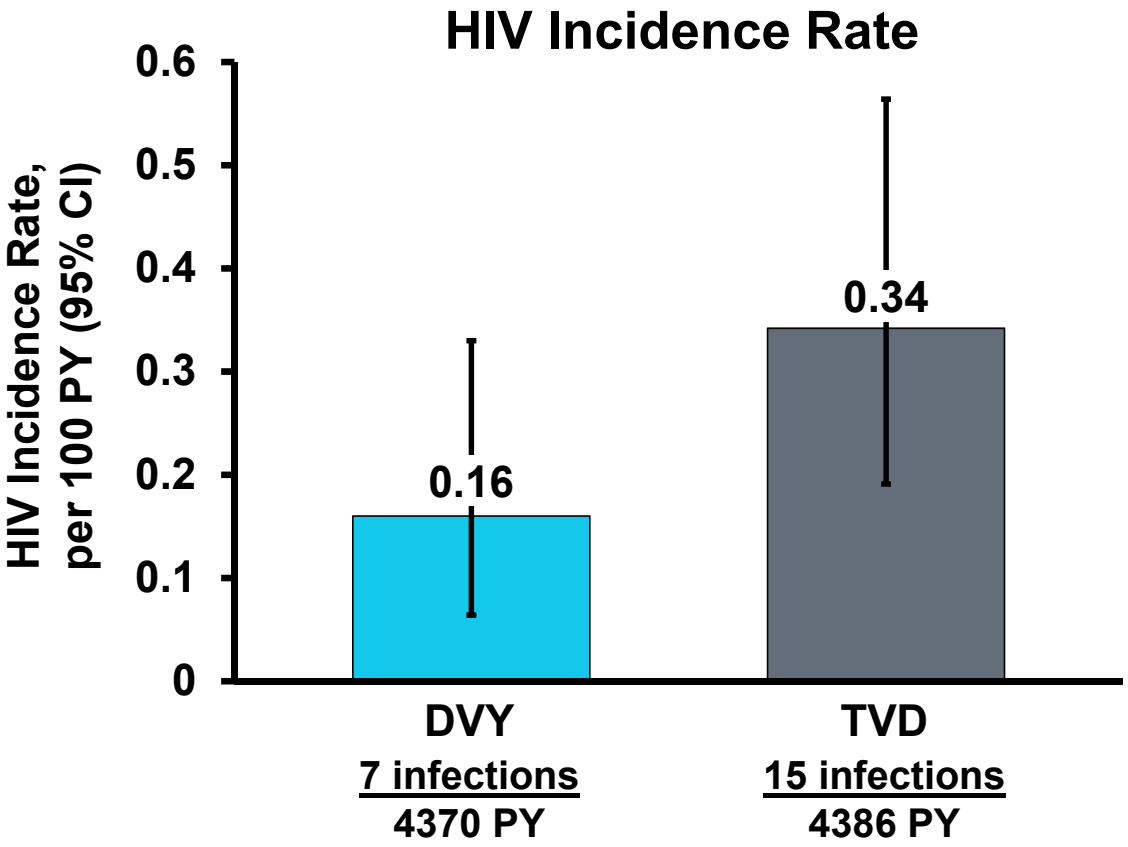
SD=standard deviation.

Disposition at Time of Primary Endpoint Evaluation

Participants, n (%)	DVY n=2694	TVD n=2693
Still on study drug	2242 (83)	2263 (84)
Premature discontinuation	452 (17)	430 (16)
Lost to follow up	201 (7)	170 (6)
Participant decision	193 (7)	175 (6)
Adverse event	36 (1)	49 (2)
Nonadherence	8 (<1)	12 (<1)
Investigator discretion	5 (<1)	10 (<1)
Protocol violation	4 (<1)	3 (<1)
Death[a]	1 (<1)	2 (<1)

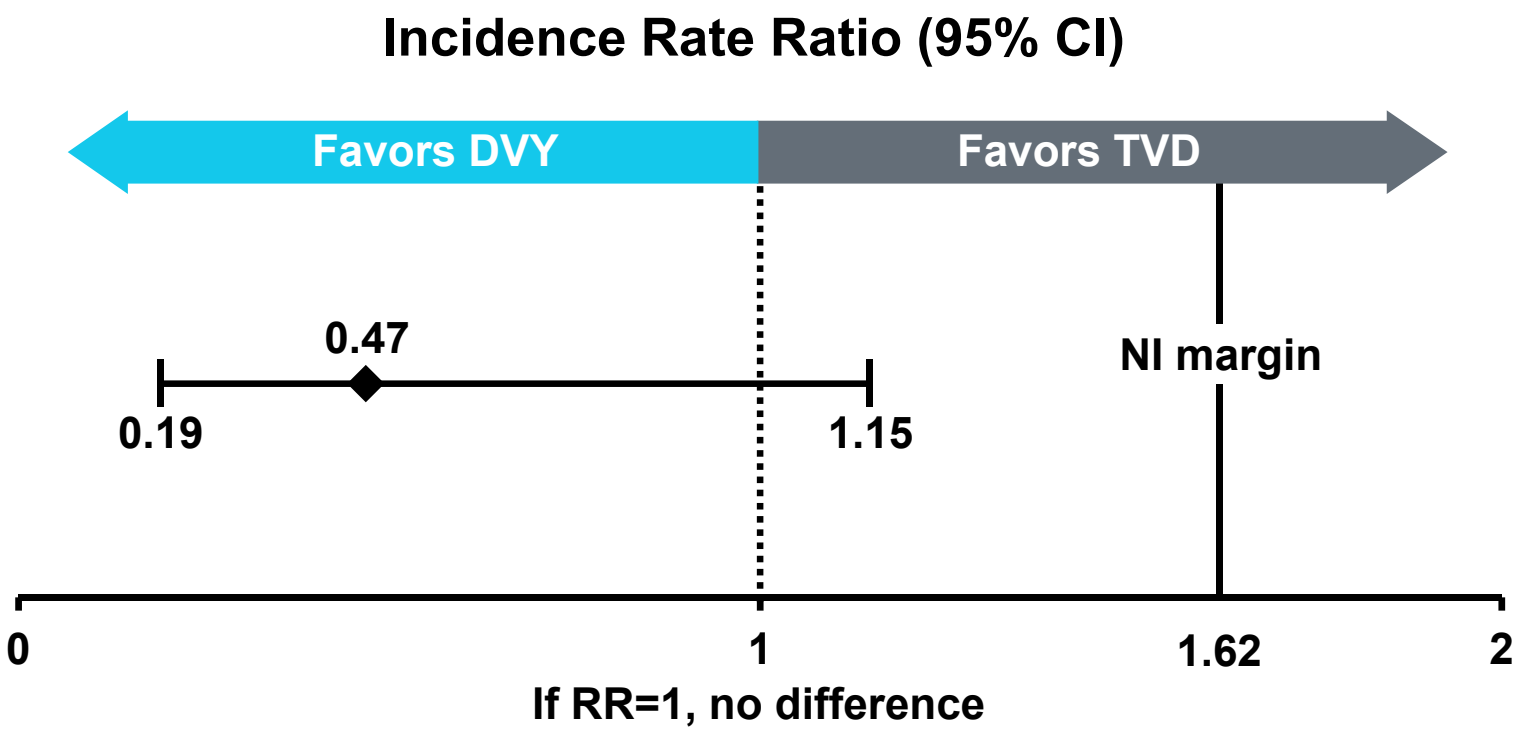
a. 1 of 3 deaths occurred after study drug discontinuation.

Primary Efficacy Endpoint: Noninferiority Achieved



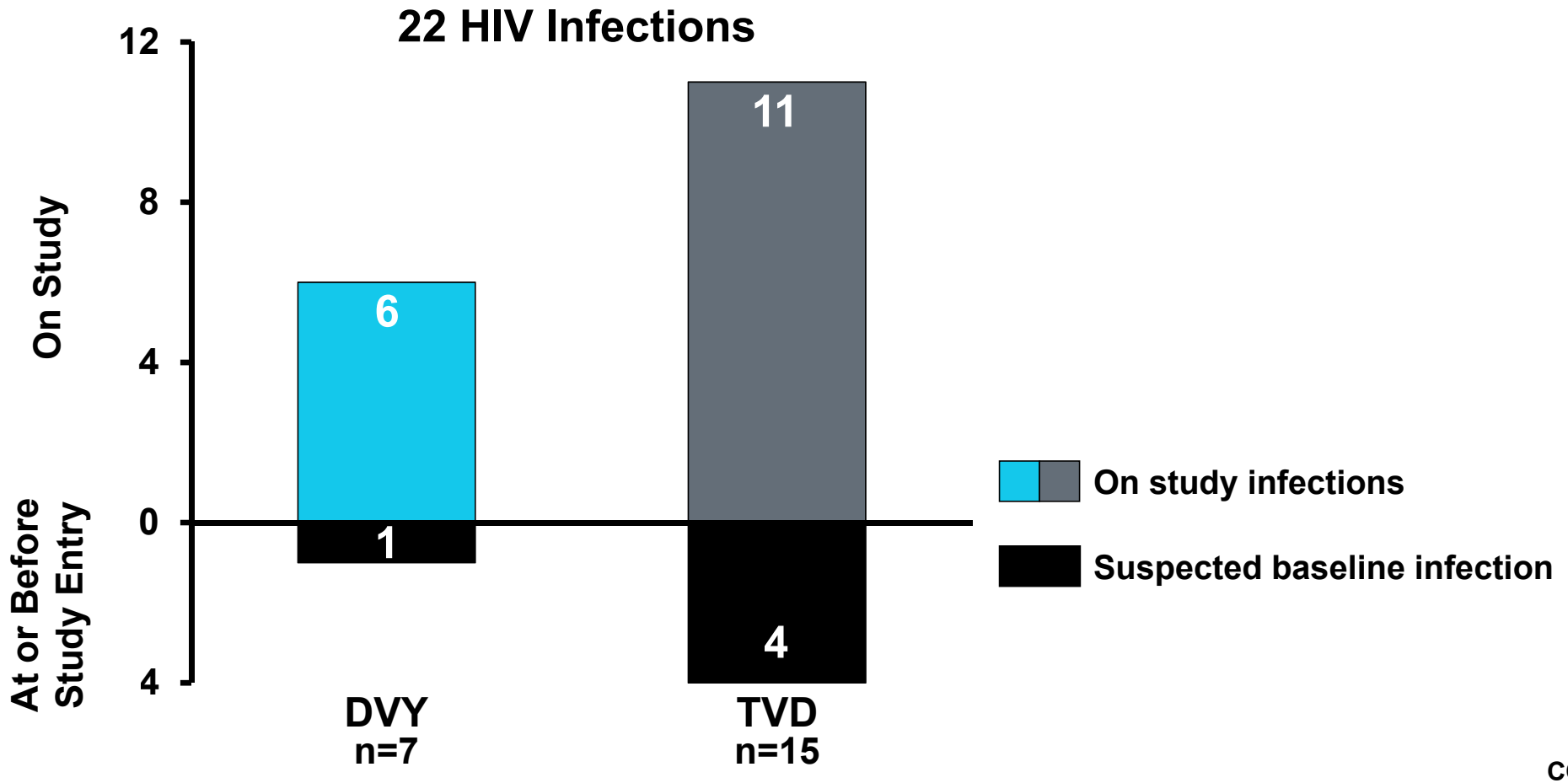
- 22 HIV infections diagnosed in 8756 PY of follow-up
- Rate ratio: 0.47 (95% CI: 0.19, 1.15)

Primary Efficacy Endpoint: Noninferiority Achieved



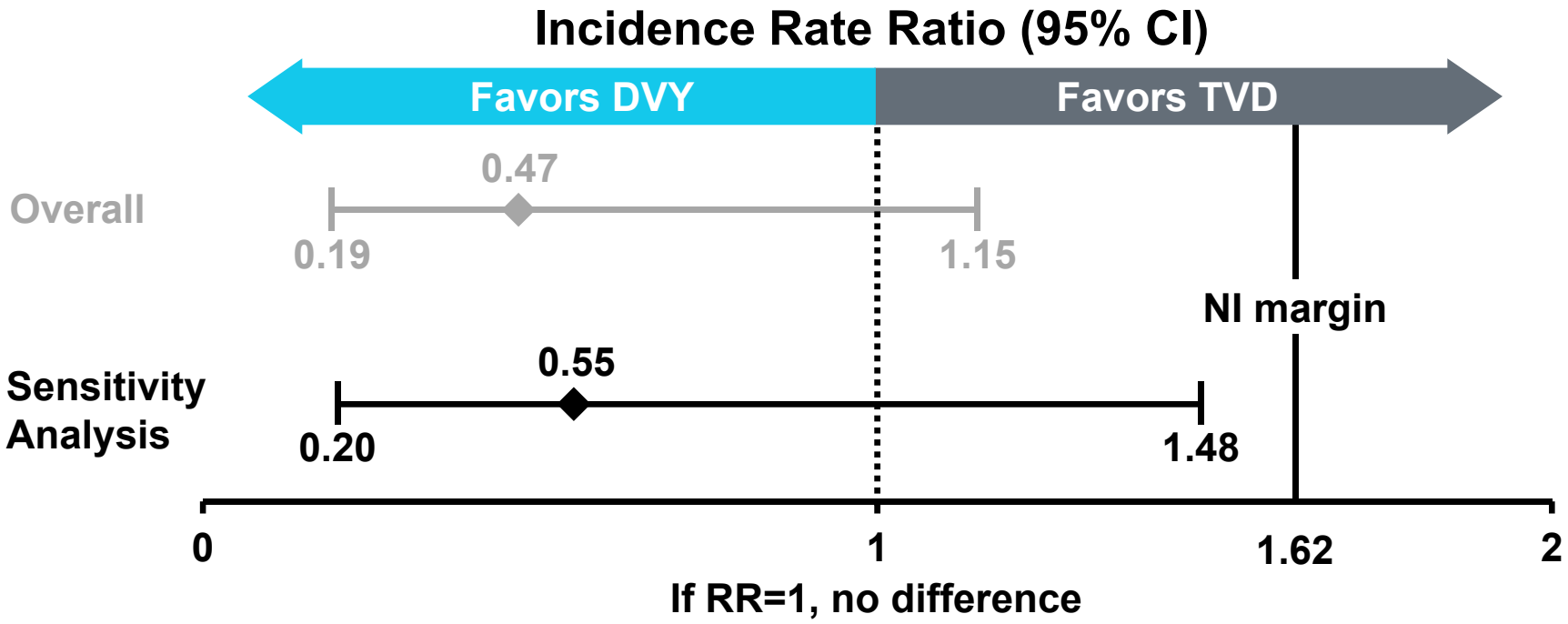
NI=noninferiority; RR=rate ratio.

Primary Efficacy Endpoint Details



Primary Efficacy Endpoint Sensitivity Analysis

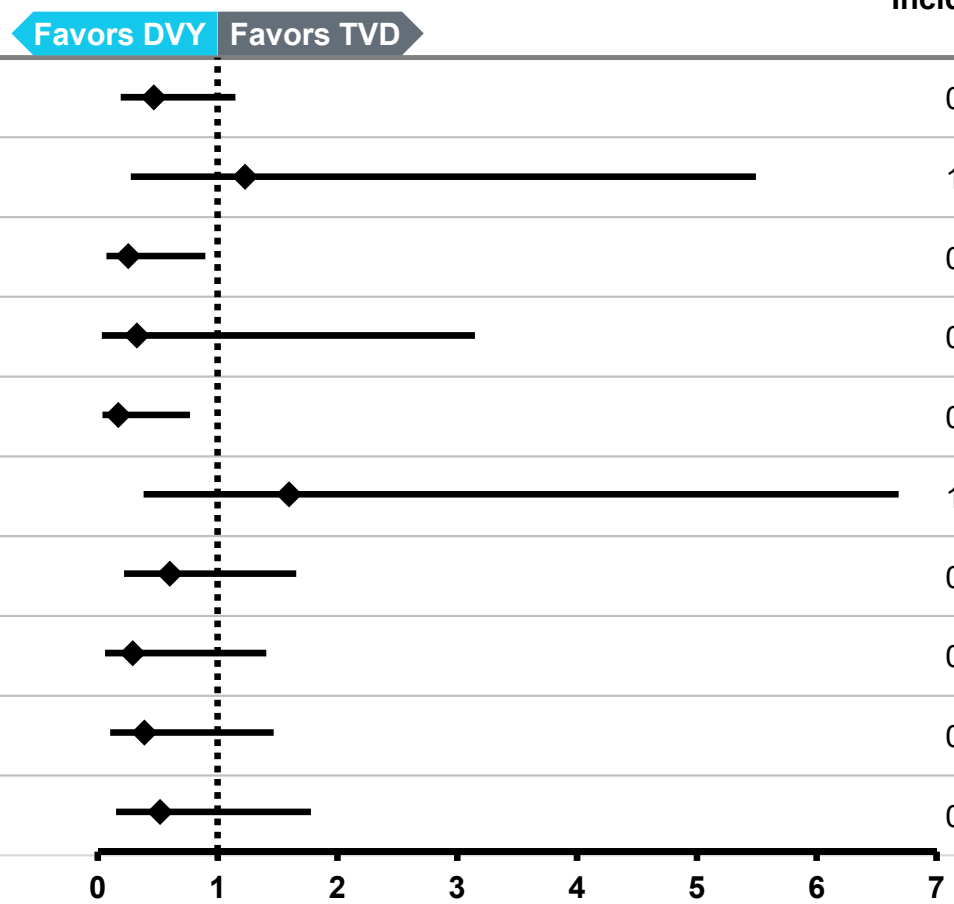
Excluding Baseline Infections



- Excluding 5 baseline infections (DVY=1, TVD=4):
  DVY incidence rate, 0.14 per 100 PY; TVD incidence rate, 0.25 per 100 PY
- Rate ratio=0.55 (95% CI: 0.20, 1.48)

HIV Incidence Rate Ratios: Subgroups

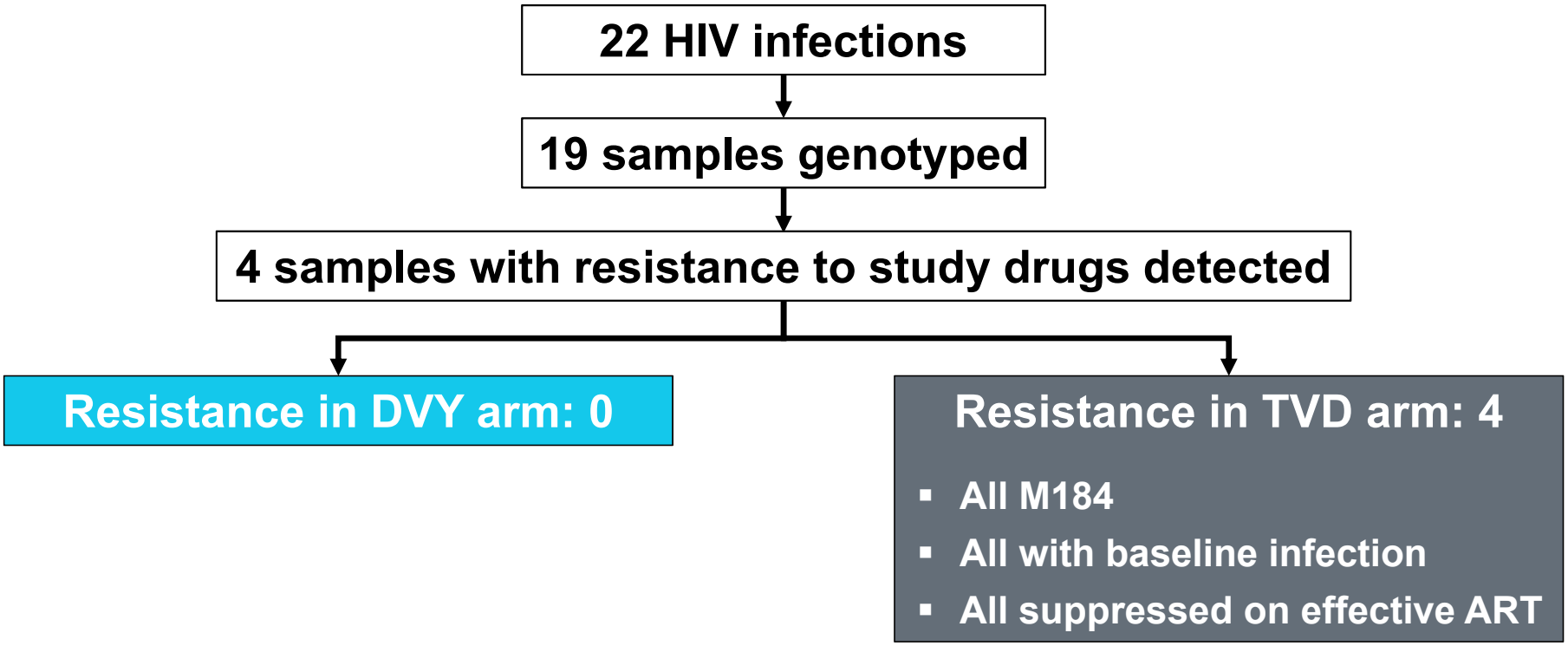
		Incidence Rate, Per 100 PY (95% CI)	Incidence Rate Ratio (95% CI)
Overall	DVY: n=2670 TVD: n=2665	0.16 (0.1, 0.3) 0.34 (0.2, 0.6)	0.47 (0.19, 1.15)
Age <25 y	DVY: n=329 TVD: n=289	0.82 (0.2, 2.1) 0.66 (0.1, 1.9)	1.23 (0.28, 5.49)
Age ≥25 y	DVY: n=2341 TVD: n=2376	0.08 (0.0, 0.2) 0.31 (0.2, 0.5)	0.25 (0.07, 0.90)
Black race	DVY: n=234 TVD: n=225	0.27 (0.0, 1.5) 0.82 (0.2, 2.4)	0.33 (0.03, 3.15)
US	DVY: n=1573 TVD: n=1604	0.08 (0.0, 0.3) 0.45 (0.2, 0.8)	0.17 (0.04, 0.77)
Ex-US	DVY: n=1097 TVD: n=1061	0.28 (0.1, 0.7) 0.18 (0.0, 0.5)	1.60 (0.38, 6.68)
Recreational drug use	DVY: n=1771 TVD: n=1768	0.21 (0.1, 0.5) 0.35 (0.2, 0.6)	0.60 (0.22, 1.66)
Binge alcohol use	DVY: n=1466 TVD: n=1495	0.08 (0.0, 0.3) 0.29 (0.1, 0.6)	0.29 (0.06, 1.41)
≤3 URAI partners	DVY: n=1843 TVD: n=1891	0.10 (0.0, 0.3) 0.26 (0.1, 0.5)	0.39 (0.10, 1.47)
>3 URAI partners	DVY: n=735 TVD: n=678	0.33 (0.1, 0.9) 0.64 (0.3, 1.3)	0.52 (0.15, 1.78)



URAI=unprotected receptive anal intercourse.

CC-50

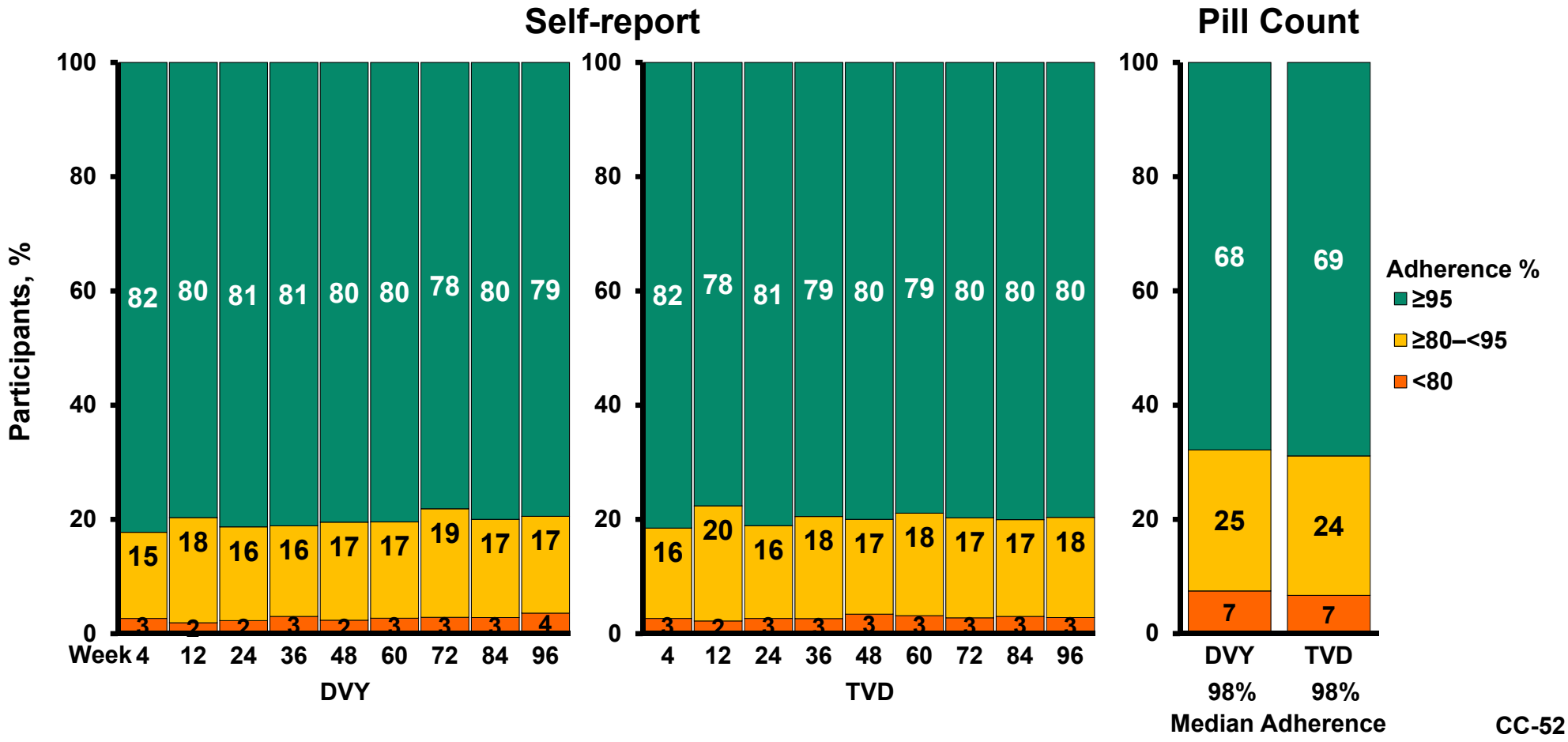
Primary Efficacy Endpoint Details, Resistance



ART=antiretroviral therapy.

Adherence Results: Self Reports, Pill Counts

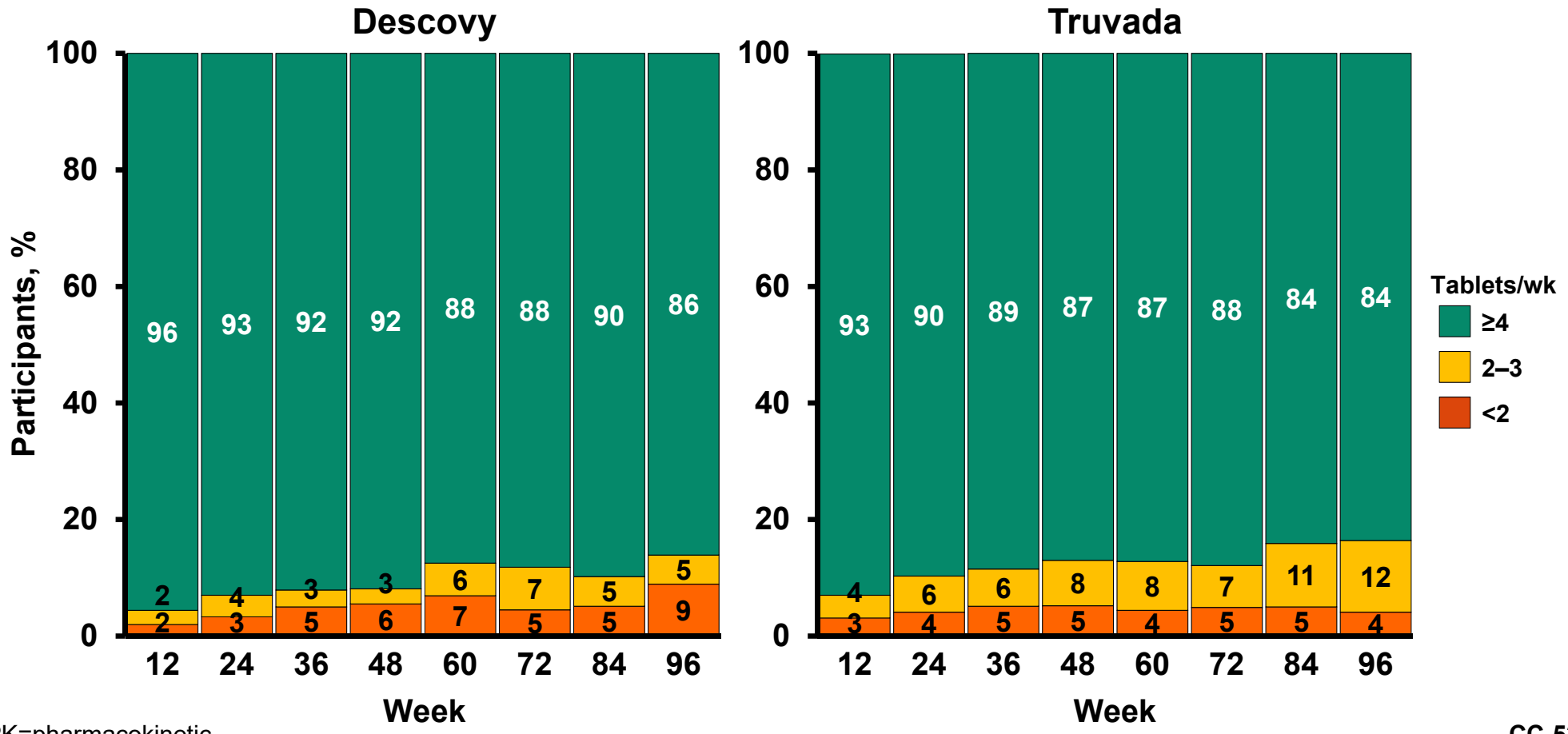
Full Analysis Set



CC-52

Adherence by TFV-DP Levels in Dried Blood Spots

PK Cohort Analysis Set (n=536)



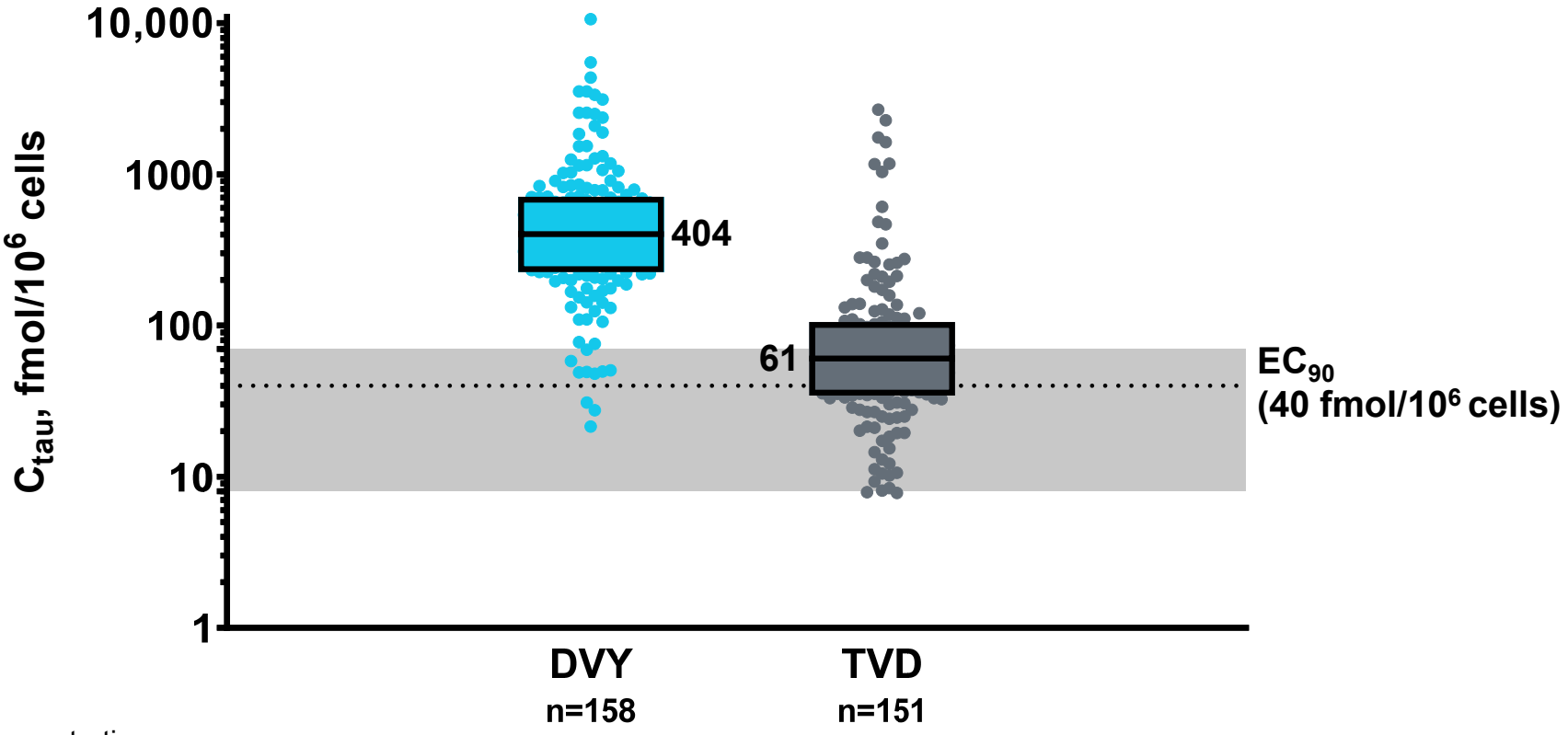
PK=pharmacokinetic.

Case Control: Adherence by TFV-DP Levels in Dried Blood Spots

- Median TFV-DP levels significantly lower in participants diagnosed with HIV (cases) than uninfected matched controls (p=0.001)
  - DVY: cases, 277 fmol/punches (IQR: 13, 474); controls, 1736 (1382, 2358)
  - TVD: cases, 133 fmol/punch (13, 755); controls, 1075 (735, 1612)

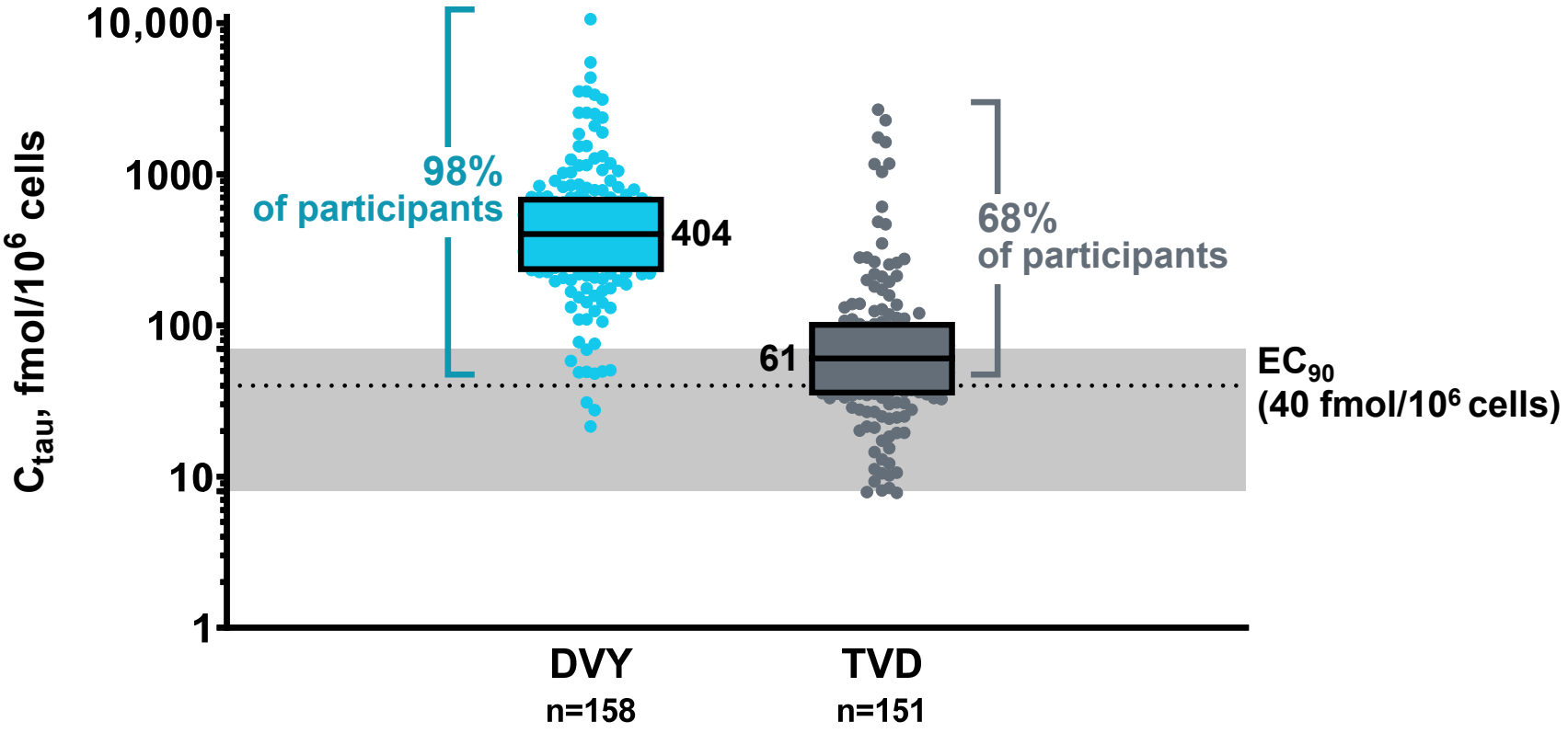
	DVY		TVD	
	Cases n=7	**Controls n=34**	**Cases n=15**	**Controls n=75**
Proportion with TFV-DP levels at <2 doses/week	71%	3%	67%	9%

Pharmacokinetic Data: Week 4 TFV-DP Levels in PBMCs



C_{tau}=trough concentration.
Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.
1. Anderson P, et al, 2015 J Clin Pharm: EC_{90} for TFV-DP in PBMCs is 40 fmol/10^6 cells.

Pharmacokinetic Data: Week 4 TFV-DP Levels in PBMCs



Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.

1. Anderson P, et al, 2015 J Clin Pharm: EC_{90} for TFV-DP in PBMCs is 40 fmol/10^6 cells.

Efficacy Conclusions

- Descovy was noninferior to Truvada for HIV prevention
  - DISCOVER population at high risk of HIV infection
  - Low HIV incidence rates in both arms
- Low adherence was the most significant risk factor for HIV infection
- There was no resistance observed in the Descovy arm, 4 cases of M184 reported in the Truvada arm
- Significantly more participants in the Descovy arm reached the EC_{90} in PBMCs than in Truvada arm

DISCOVER Safety

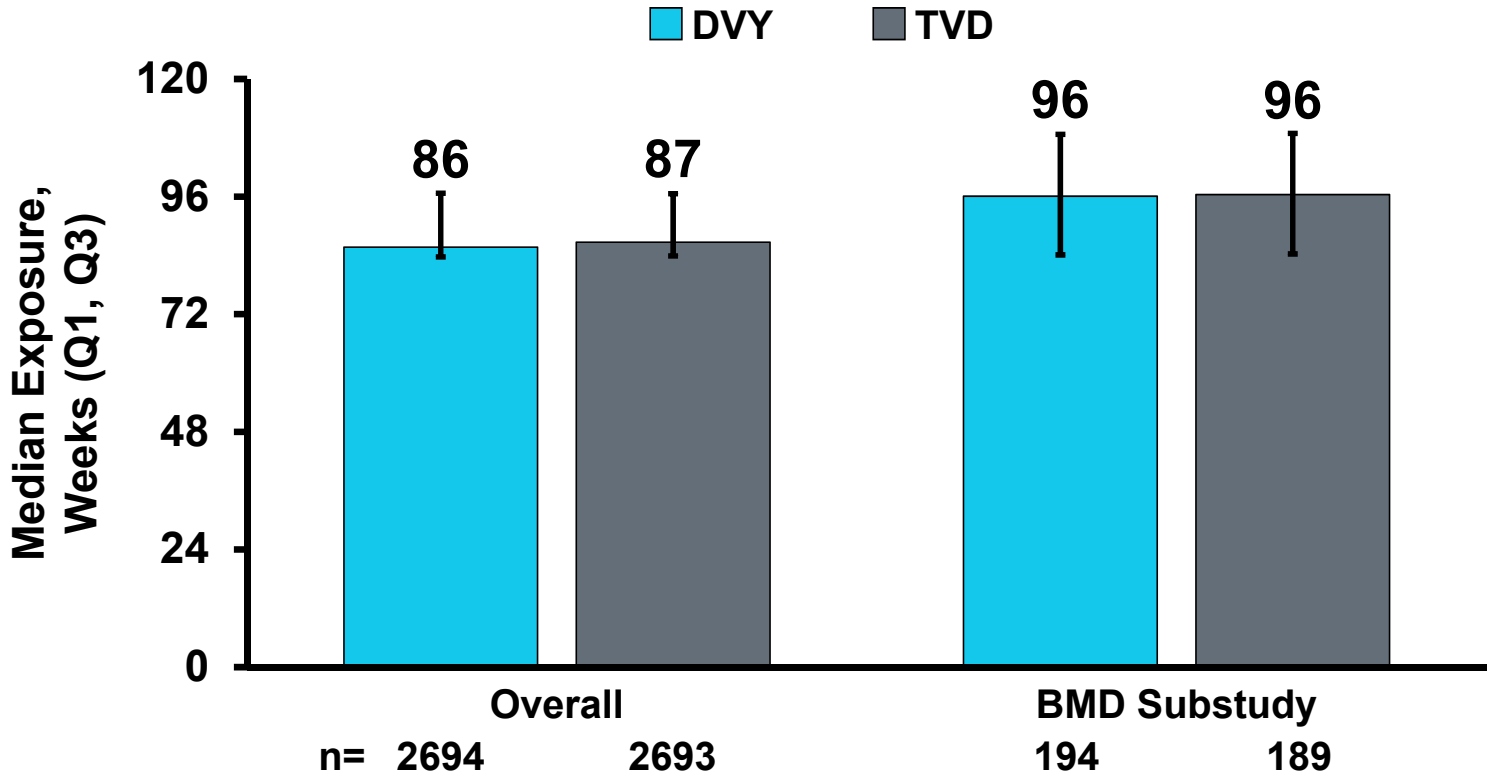
Moupali Das, MD, MPH

Executive Director
HIV and Emerging Viruses

Descovy: Safety Profile

- Safety and tolerability thoroughly established in HIV and HBV treatment
  - >26,000 PY in clinical trials
  - >1.6 million PY in clinical experience
- Improved renal and bone safety profile compared with Truvada
  - Favorable renal and bone biomarkers correlate with fewer clinical events
- DISCOVER confirms similar safety benefits in HIV-uninfected people

Descovy and Truvada Exposure



- At the primary endpoint, the total drug exposure was 8658 PY

Overall Summary of Safety

Participants, %	DVY n=2694	TVD n=2693
Any AEs	93	93
Grade ≥3 AEs	6	6
Study-drug related AEs	20	23
Grade ≥3 AEs	<1	<1
SAE	6	5
Study-drug related SAEs	<1	<1
AEs leading to study drug discontinuation	1	2
Death[a]	<1	<1

AE=adverse event; SAE=serious adverse event.
a. 1 death due to traffic accident on DVY, 1 due to unknown reason in 26-year-old on TVD.

DISCOVER

Most Common Adverse Events

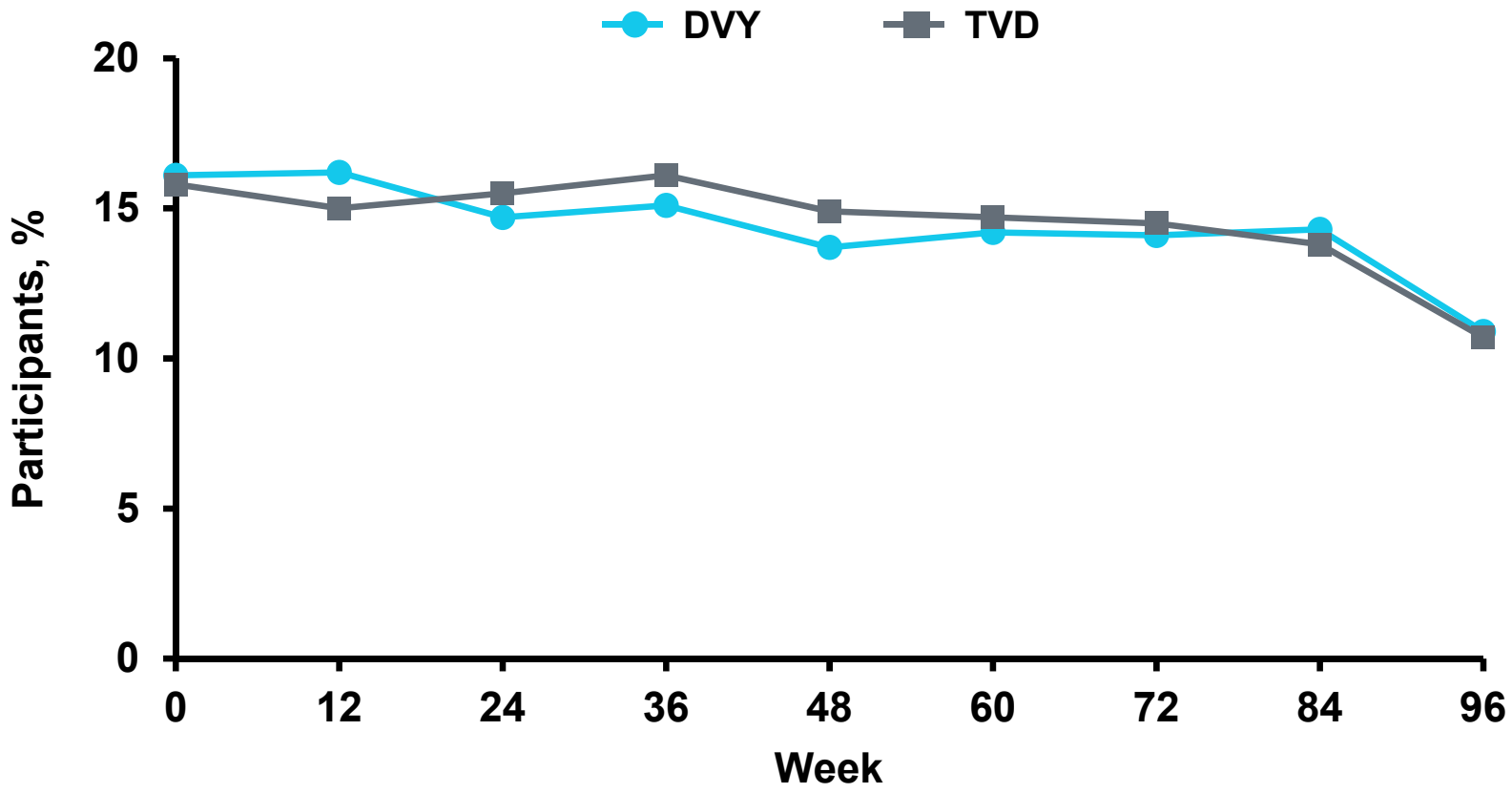
≥10% in Either Arm

Participants, %	DVY n=2694	TVD n=2693
Rectal chlamydia	29	29
Oropharyngeal gonorrhea	27	27
Rectal gonorrhea	26	25
Exposure to communicable disease	17	16
Diarrhea	16	16
Nasopharyngitis	13	13
Upper respiratory tract infection	13	12
Syphilis	13	12
Urethral chlamydia	10	10

DISCOVER

Gonorrhea and Chlamydia

3 Anatomic Site NAAT Testing by Study Visit

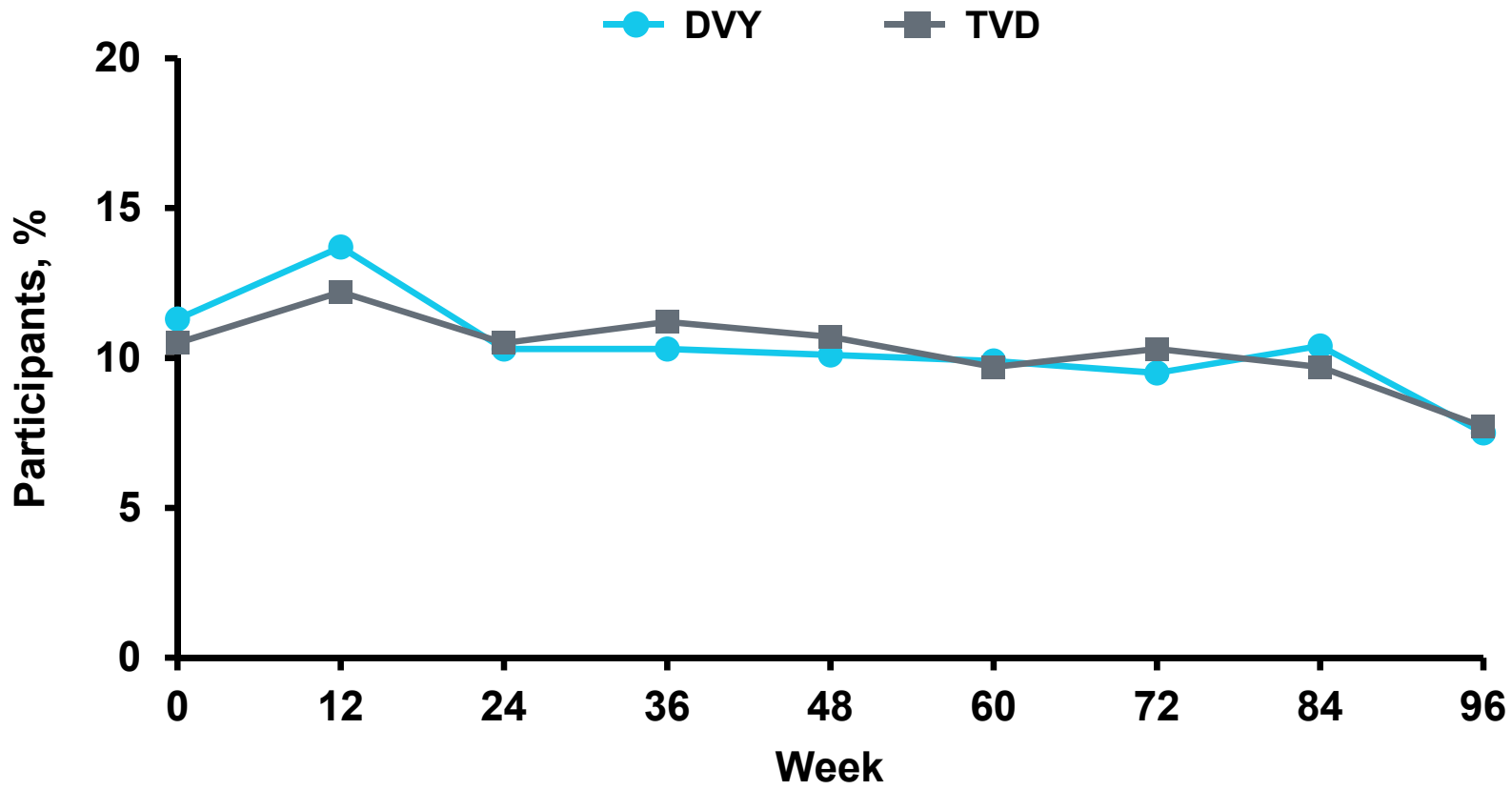


NAAT=nucleic acid amplification test.

DISCOVER

Rectal Gonorrhea and Chlamydia

Rectal NAAT Testing by Study Visit



Concomitant Medications Used by >10% of Participants

Drug, %	DVY n=2694	TVD n=2693
Azithromycin	60	57
Ceftriaxone	53	52
Doxycycline	29	28
Ibuprofen	19	19
Vitamins	18	17
Benzathine benzylpenicillin	14	14
Acetaminophen	14	12

Common Study Drug-Related Adverse Events

≥1% in Either Arm

Participants, %	DVY n=2694	TVD n=2693
Study drug-related AEs	20	23
Diarrhea	5	6
Nausea	4	5
Headache	2	2
Fatigue	2	3
Abdominal pain	1	1
Flatulence	<1	1
Abdominal discomfort	<1	1

DISCOVER

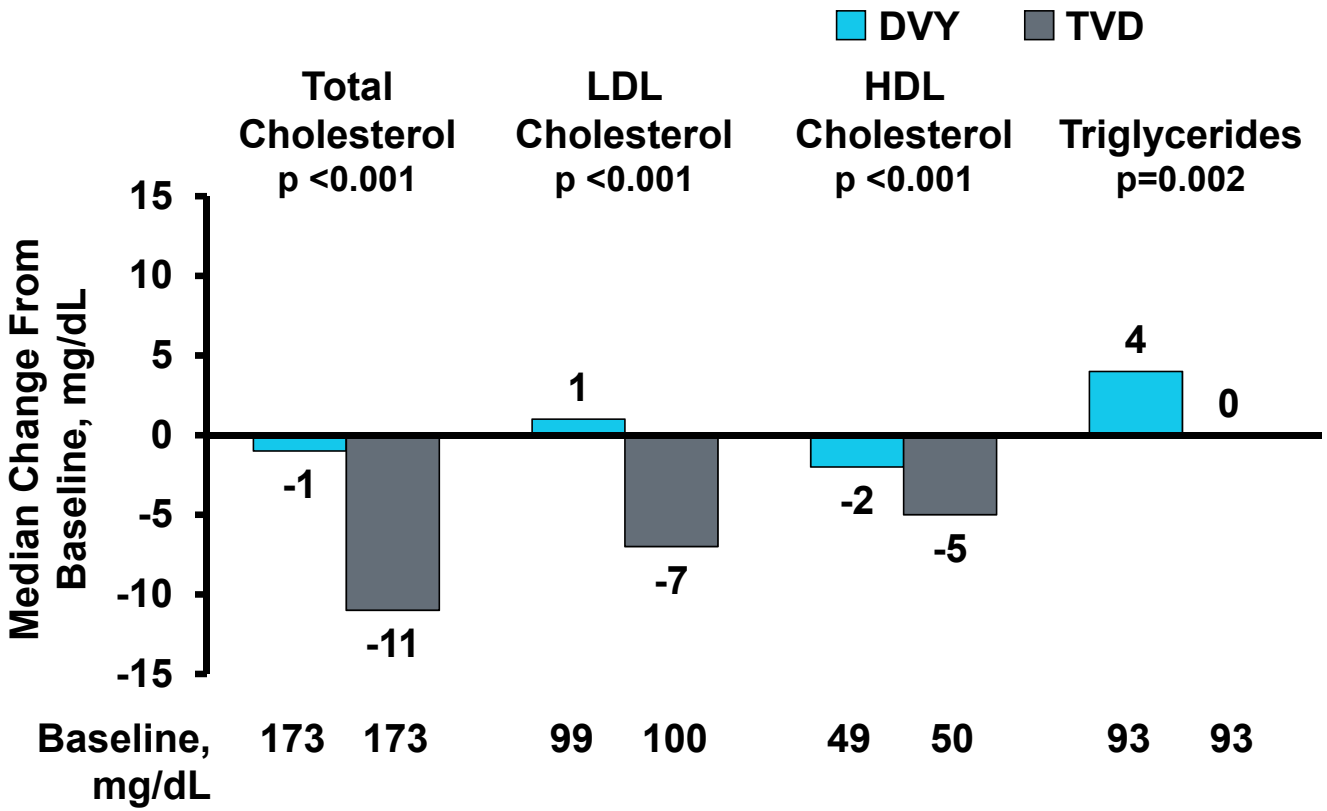
Select Grade ≥3 Laboratory Abnormalities

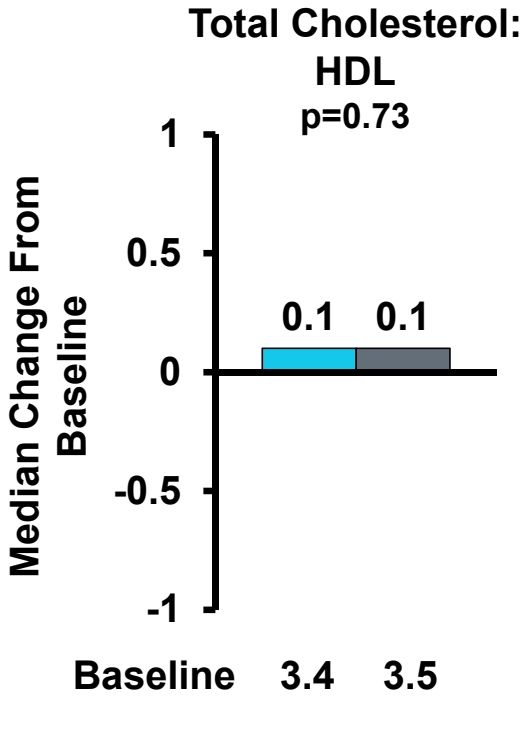
≥1% in Either Arm

Participants, %	DVY n=2694	TVD n=2693
AST	2	2
ALT	1	1
Amylase	1	2
Serum glucose (nonfasting)	<1	1
LDL (fasting)	2	<1
Urine glucose	<1	1

ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDL=low-density lipoprotein.

Fasting Lipid Changes From Baseline at Week 48



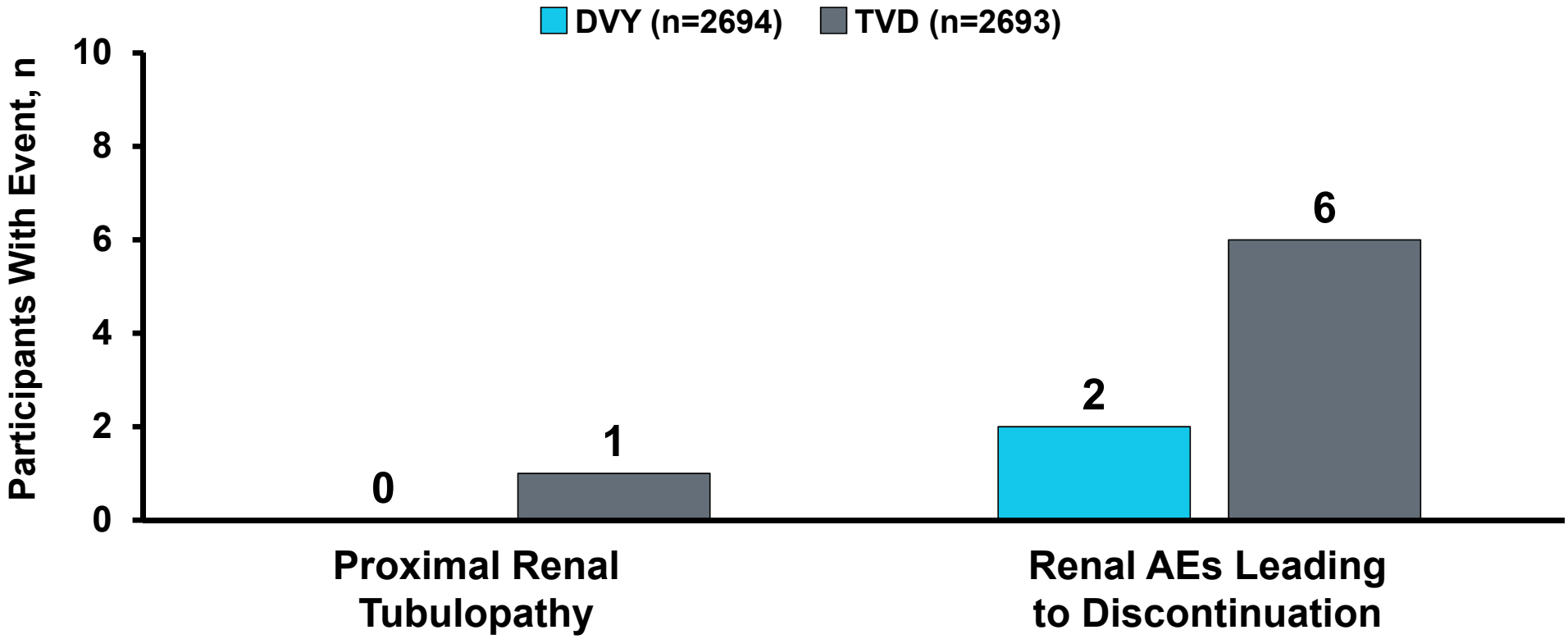


HDL=high-density lipoprotein.
p-values from 2-sided Wilcoxon rank sum test to compare treatment groups.

Renal Safety Assessment

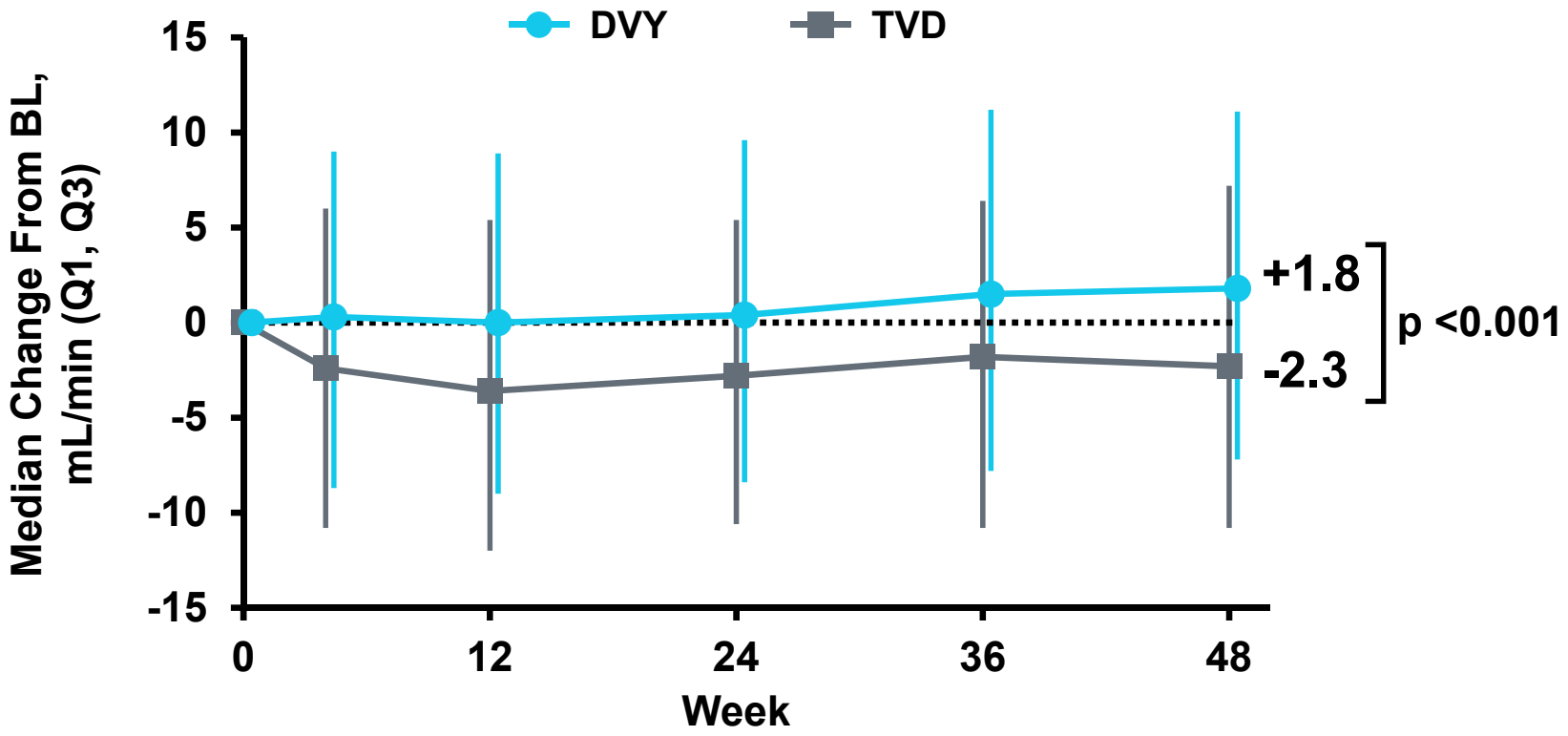
- Clinical events
  - Proximal tubulopathy including Fanconi Syndrome
  - Renal AEs leading to discontinuation
- Glomerular function endpoints
  - Serum creatinine and estimated glomerular filtration rate$_{\text{Cockcroft-Gault}}$
  - Total proteinuria (dipstick and UPCR)
- Proximal tubular function endpoints
  - Urine RBP:Cr
  - Urine β2M:Cr

Clinical Renal Events



- No cases of proximal tubulopathy in Descovy; one case of Fanconi syndrome in Truvada

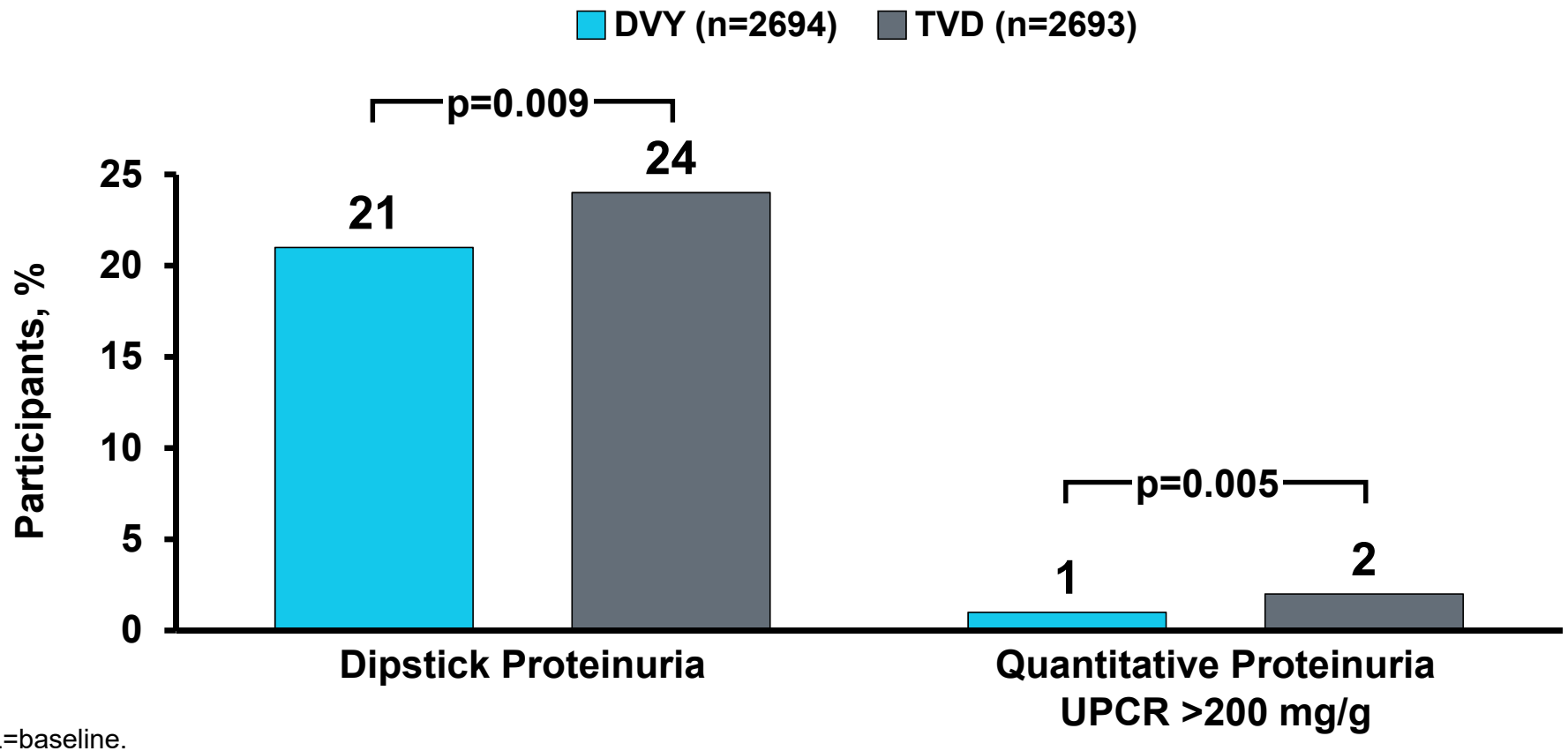
Glomerular Function: $eGFR_{CG}$



- DVY significantly improved median change from baseline in SCr compared with TVD (p <0.001)

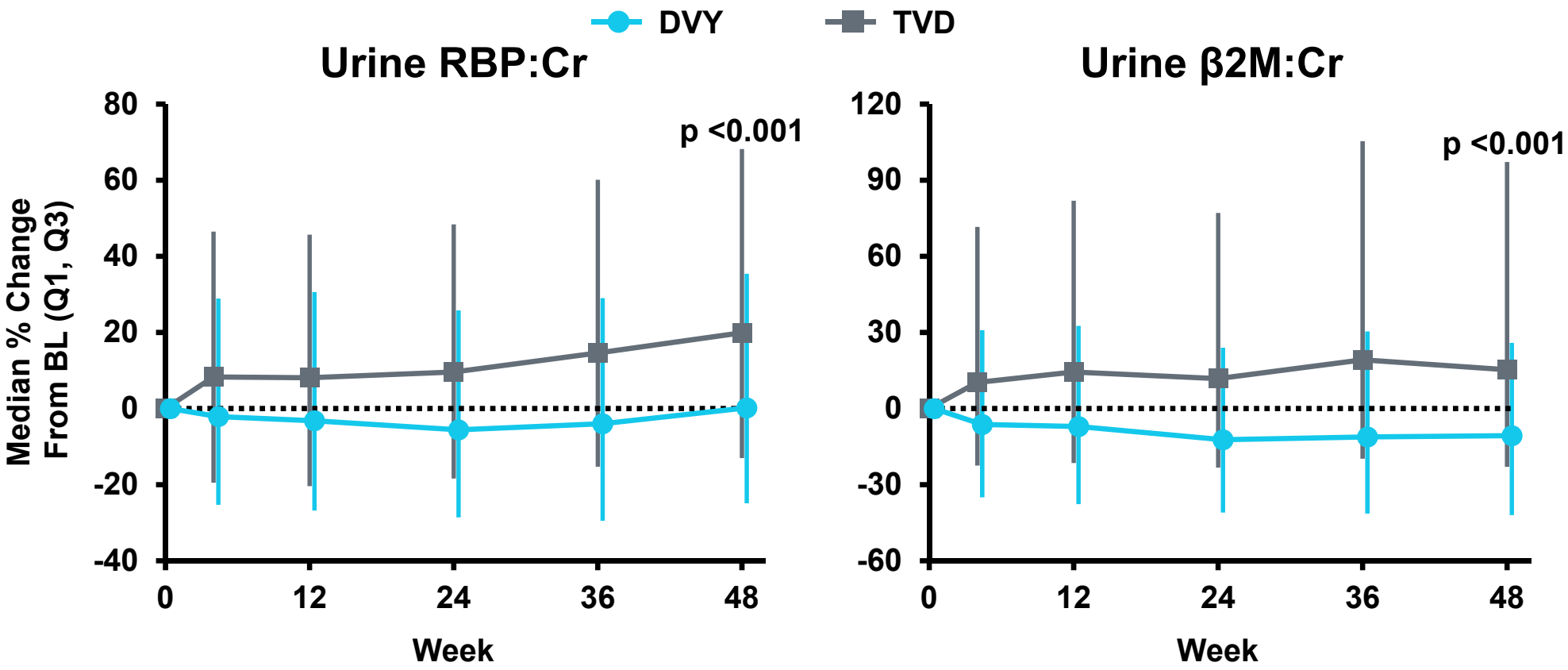
SCr=serum creatinine. p-values from Van Elteren test stratified by BL Truvada for PrEP to compare treatment groups.

Dipstick and Quantitative Proteinuria



BL=baseline.
p-values from rank analysis of covariance adjusting for BL category and BL Truvada for PrEP.
NKF KDOQI. Am J Kidney Dis 2002;39:S1-266.

Proximal Tubular Proteinuria: RBP:Cr and β2M:Cr



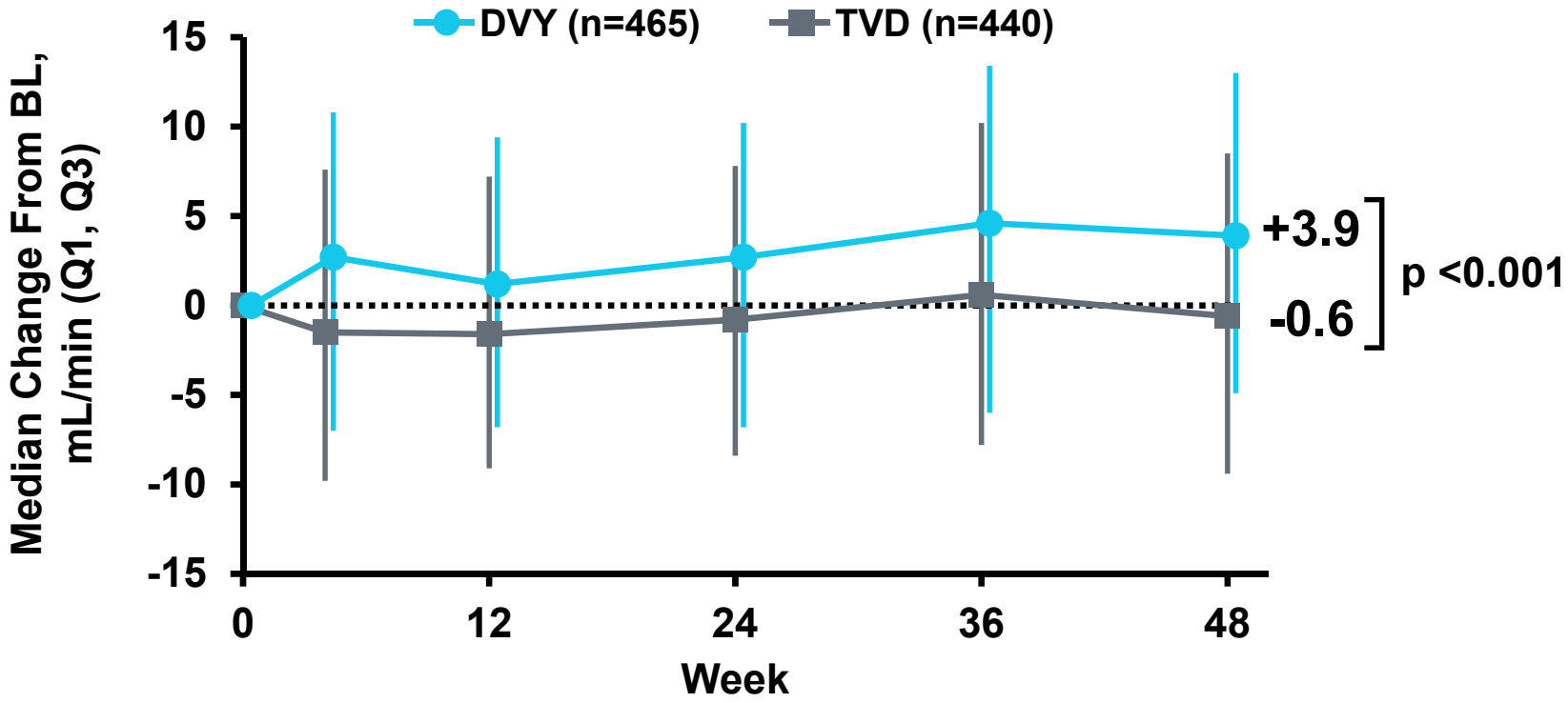
p-values from Van Elteren test stratified by baseline Truvada for PrEP to compare treatment groups.

Renal Safety Endpoints in Participants on Baseline Truvada

- DISCOVER trial included individuals using Truvada for PrEP and did not require washout prior to randomization (n=905)
- Prespecified safety analysis of current Truvada users who were randomized to Descovy
  - Significant improvements in glomerular and proximal tubular function observed

Glomerular Function: $eGFR_{CG}$

Participants on Baseline Truvada



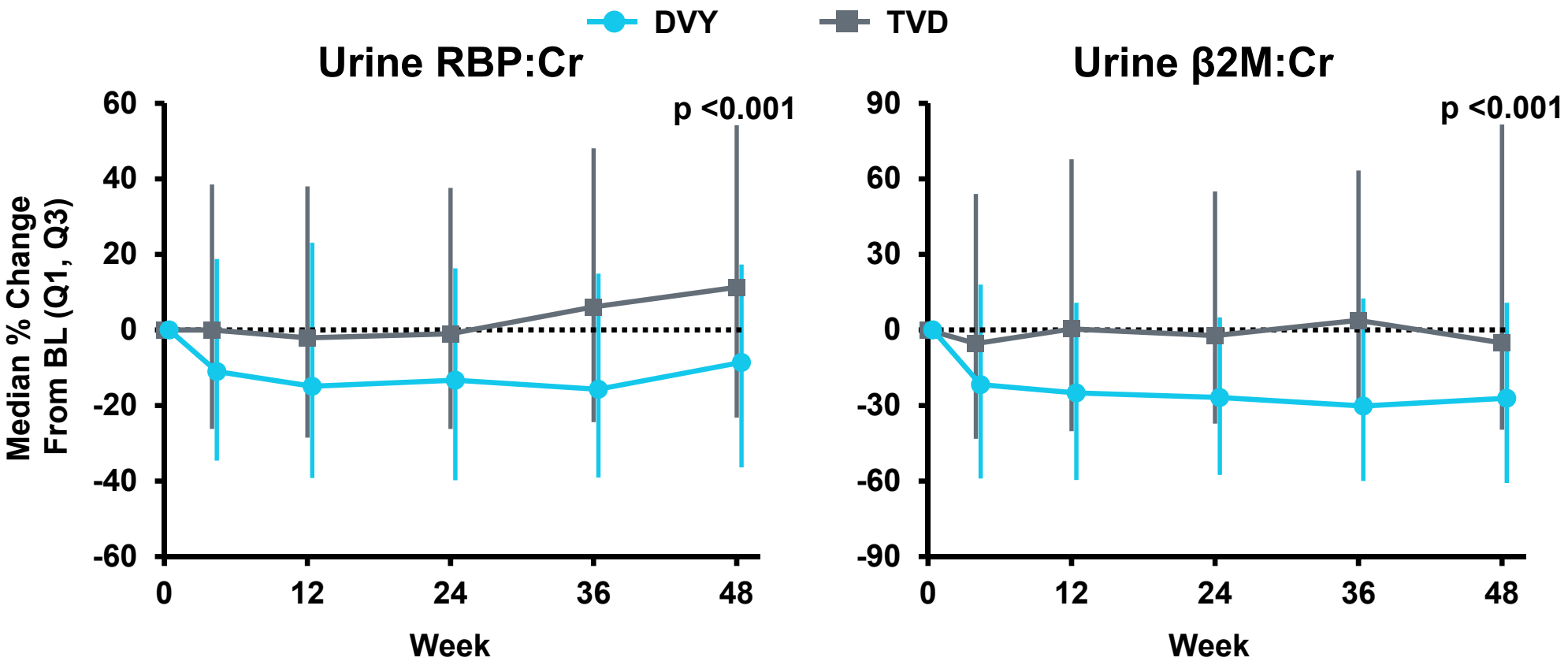
- Baseline $eGFR_{CG}$: DVY 119 mL/min, TVD 117 mL/min

p-value from 2-sided Wilcoxon rank sum test to compare treatment groups at Week 48.
Within participants on baseline TVD for PrEP, p <0.001 for all timepoints compared to baseline.

DISCOVER

Proximal Tubular Function: RBP:Cr and β2M:Cr

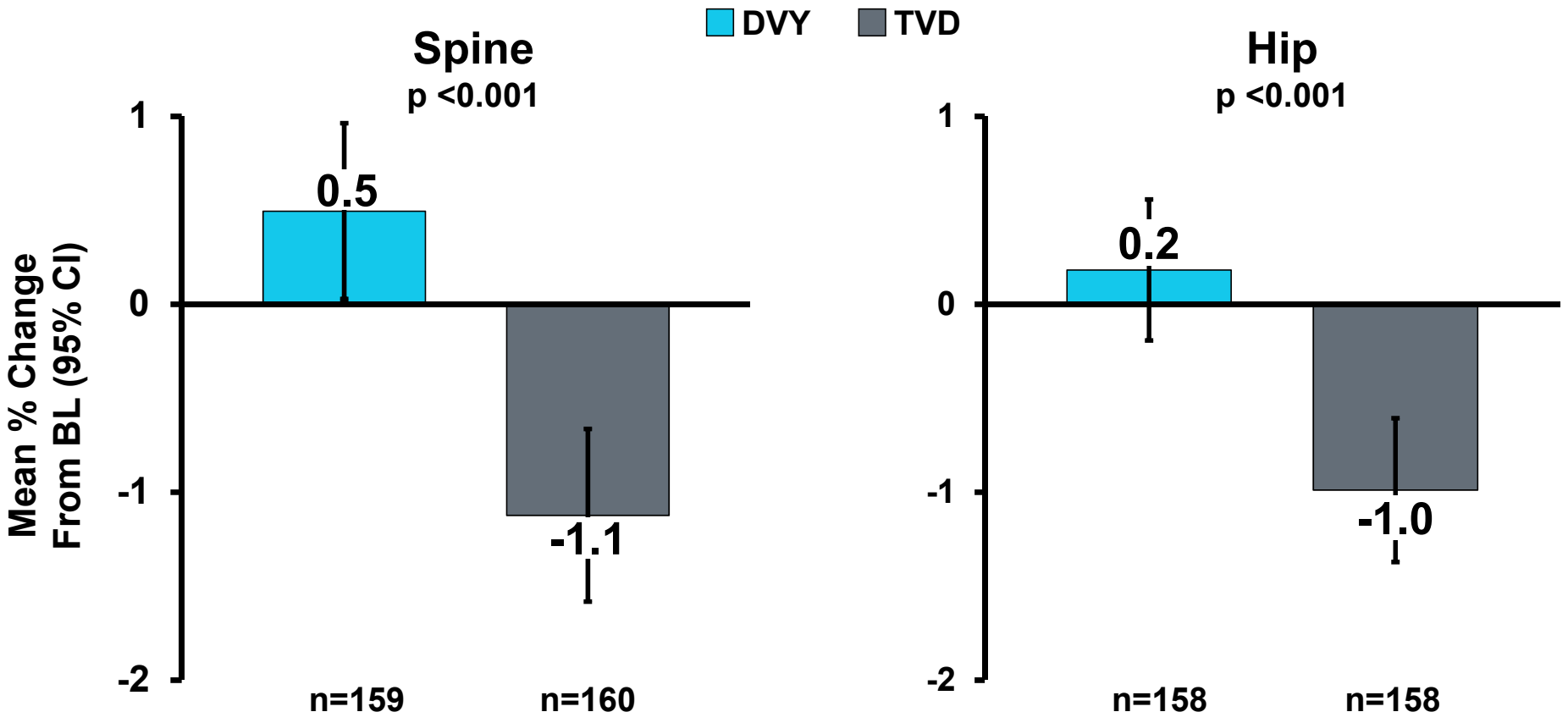
Participants on Baseline Truvada



p-values from Van Elteren test stratified by baseline Truvada for PrEP to compare treatment groups.

Bone Safety at Week 48

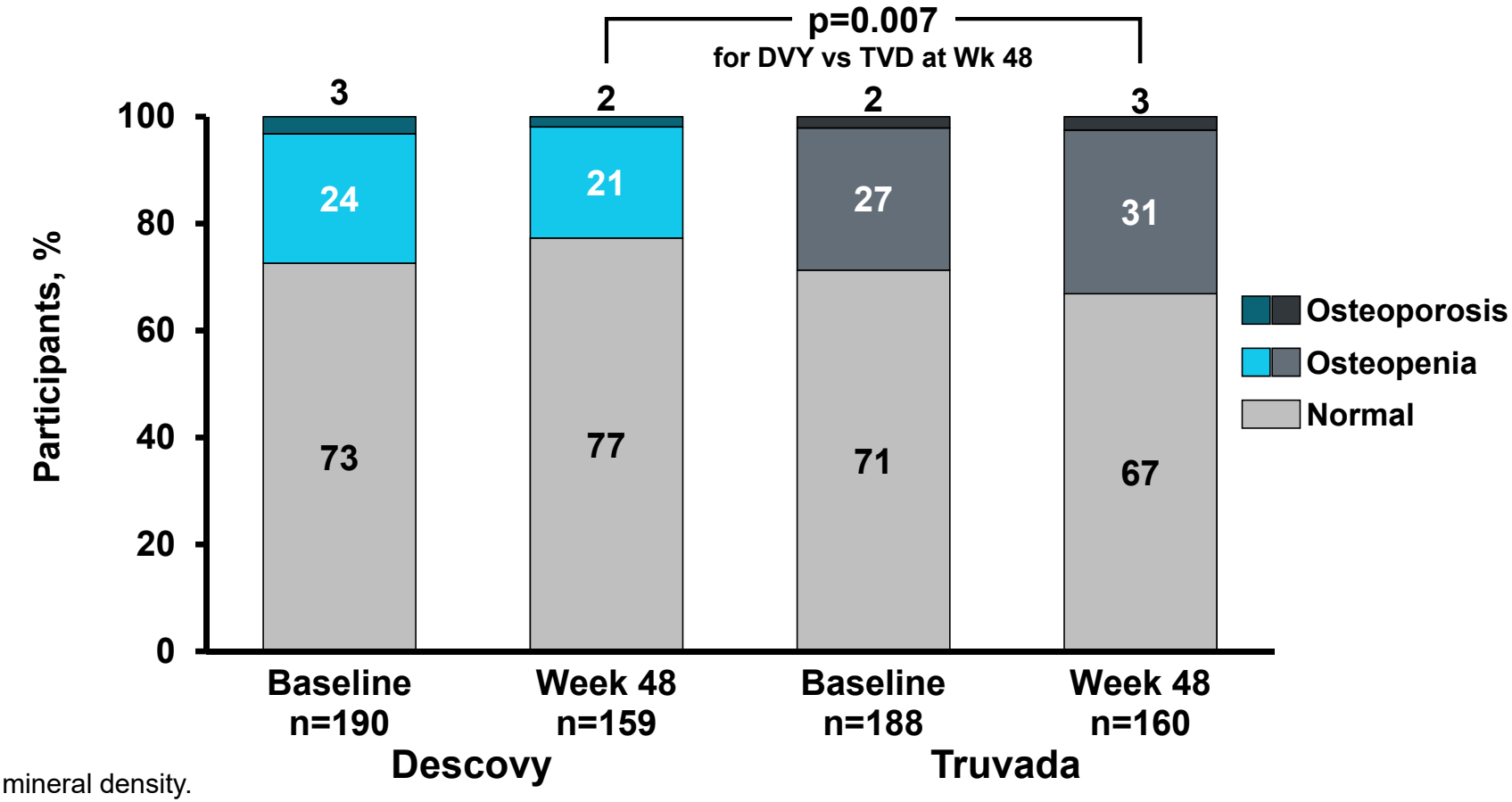
Bone Mineral Density Substudy (n=383)



p-values from analysis of variance model with BL TVD for PrEP and treatment as fixed effects.

Spine Osteopenia and Osteoporosis

Bone Mineral Substudy (n=383)



BMD=bone mineral density.
p-value from rank analysis of covariance adjusting for BL BMD clinical status and BL TVD for PrEP to compare treatments.

Prespecified Secondary Safety Endpoints

	Superior	
	DVY	TVD
1 % Change from baseline in hip BMD	✓	
2 % Change from baseline in spine BMD	✓	
3 % Change from baseline in urine β2M:Cr	✓	
4 % Change from baseline in urine RBP:Cr	✓	
5 Distribution of UP and UPCR categories	✓	
6 Change from baseline in serum creatinine	✓	

Descovy Safety Conclusions

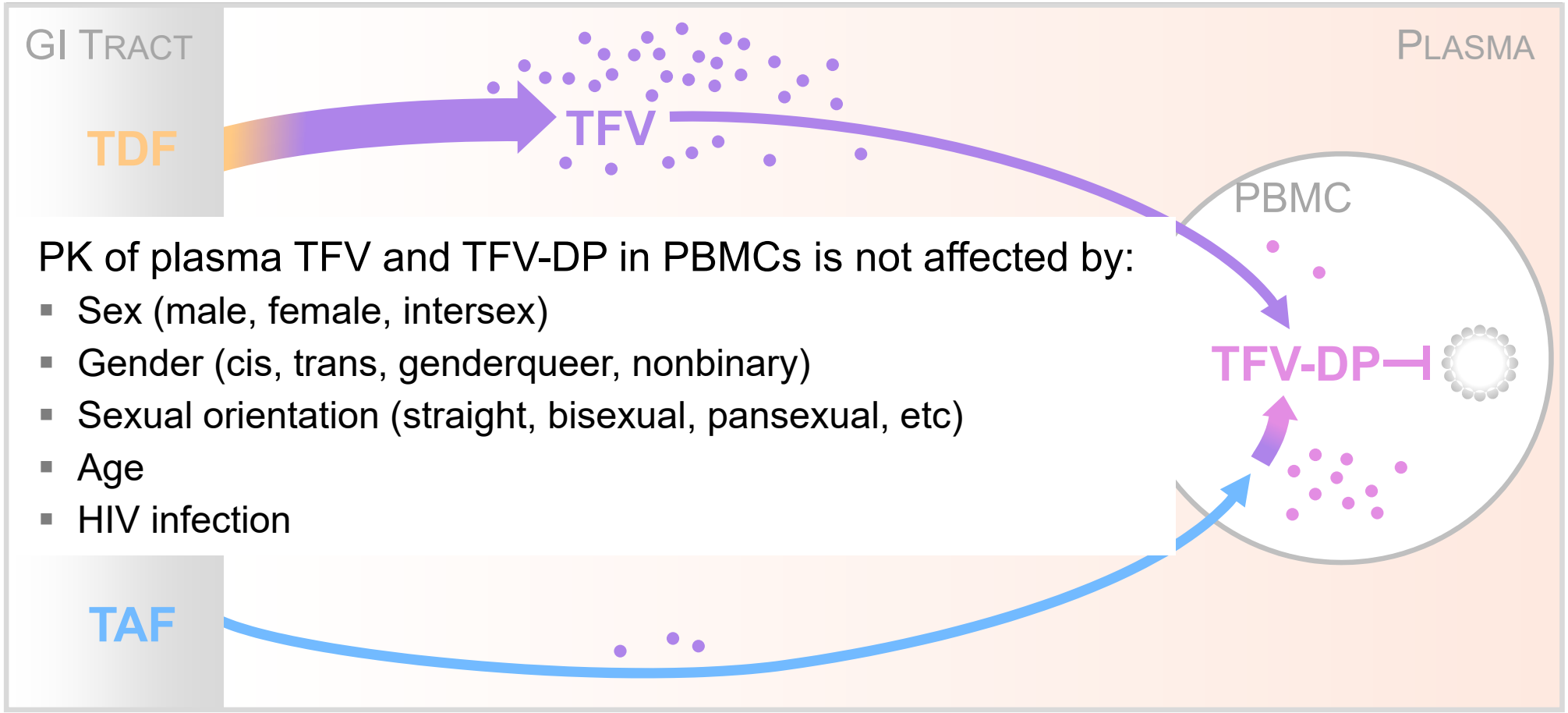
- Low rates of SAEs and AEs leading to discontinuation
- DISCOVER results consistent with trials in HIV and HBV treatment
- DISCOVER confirmed Descovy's superior safety
  - PrEP-naïve
  - Truvada switchers

Descovy for PrEP in Ciswomen and Adolescents

Efficacy and Safety in HIV Treatment and Prevention

Treatment		Prevention	
TVD-based 15 m PY	**DVY-based 1.6 m PY**	**TVD for PrEP 108,000 PY**	**DVY for PrEP 6,500 PY**
Efficacy driven by tenofovir diphosphate in PBMCs			
High virologic suppression	**High virologic suppression**	Low HIV incidence	**Low HIV incidence**
Safety driven by plasma tenofovir			
Bone and renal adverse effects	**No bone and renal adverse effects**	Bone and renal adverse effects	**No bone and renal adverse effects**

PK is Independent of Intrinsic and Extrinsic Factors



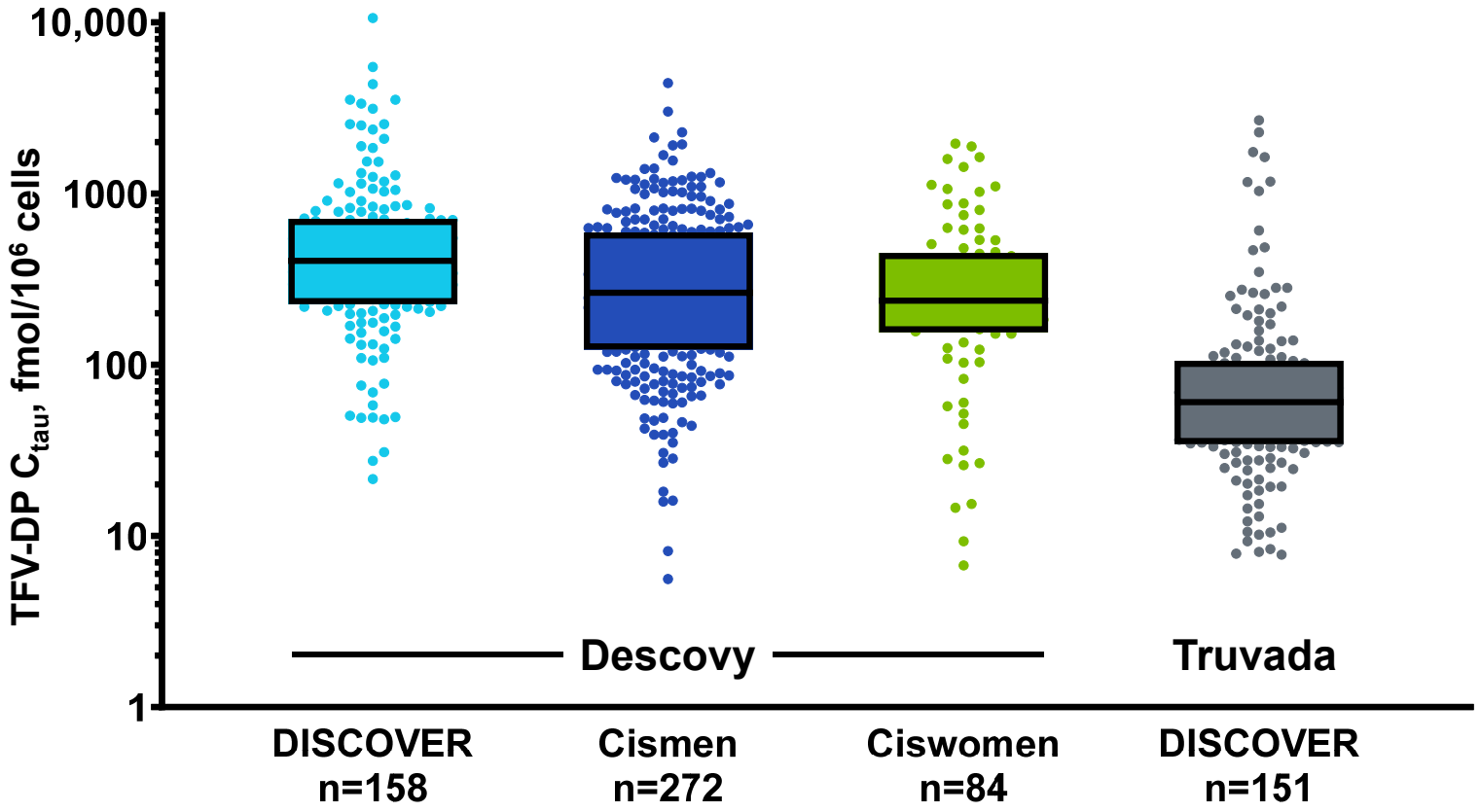
PK of plasma TFV and TFV-DP in PBMCs is not affected by:

- Sex (male, female, intersex)
- Gender (cis, trans, genderqueer, nonbinary)
- Sexual orientation (straight, bisexual, pansexual, etc)
- Age
- HIV infection

PK=pharmacokinetics.

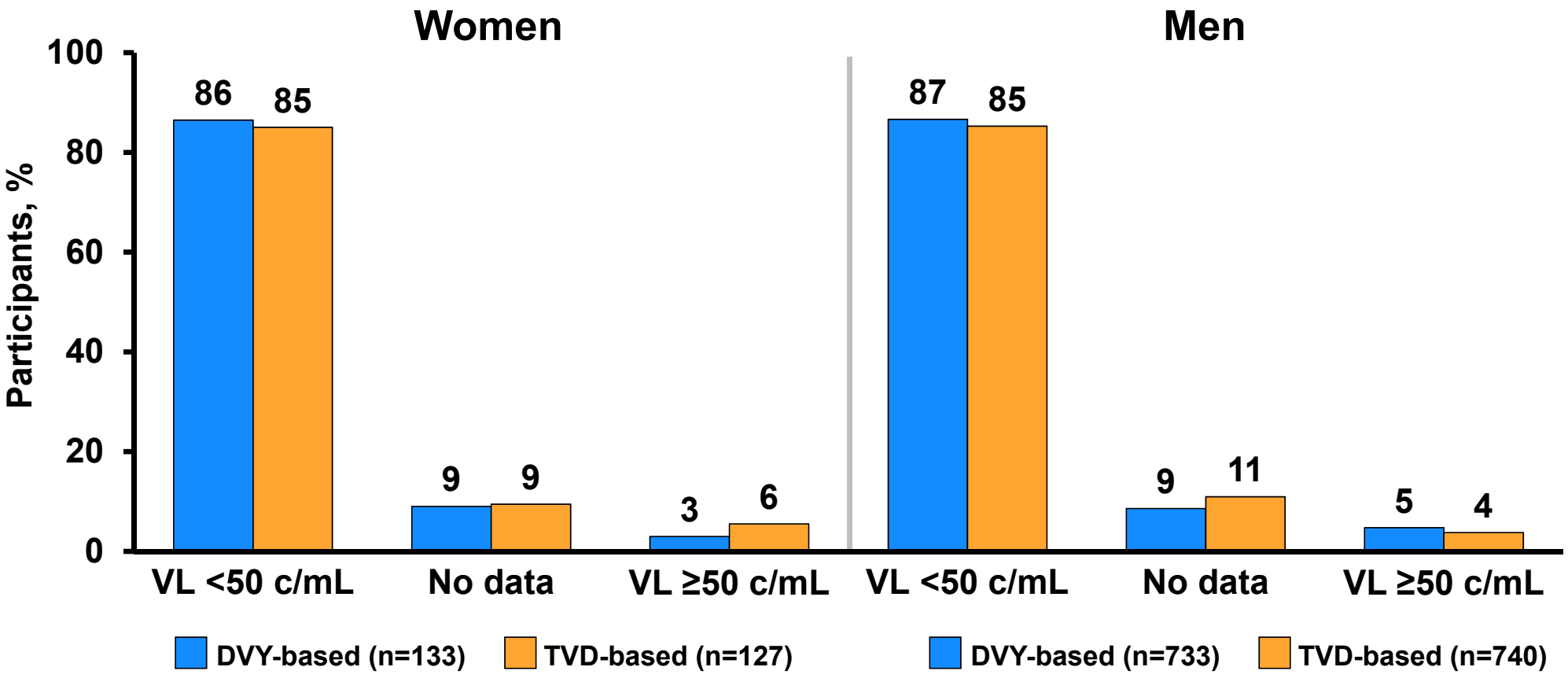
TFV-DP in PBMCs in DISCOVER, Cismen, and Ciswomen

Descovy and Truvada



Boxes show median (Q1, Q3); dots represent individual data in Q1, Q4. Data from cismen and ciswomen living with HIV.

HIV Treatment Efficacy in Women and Men

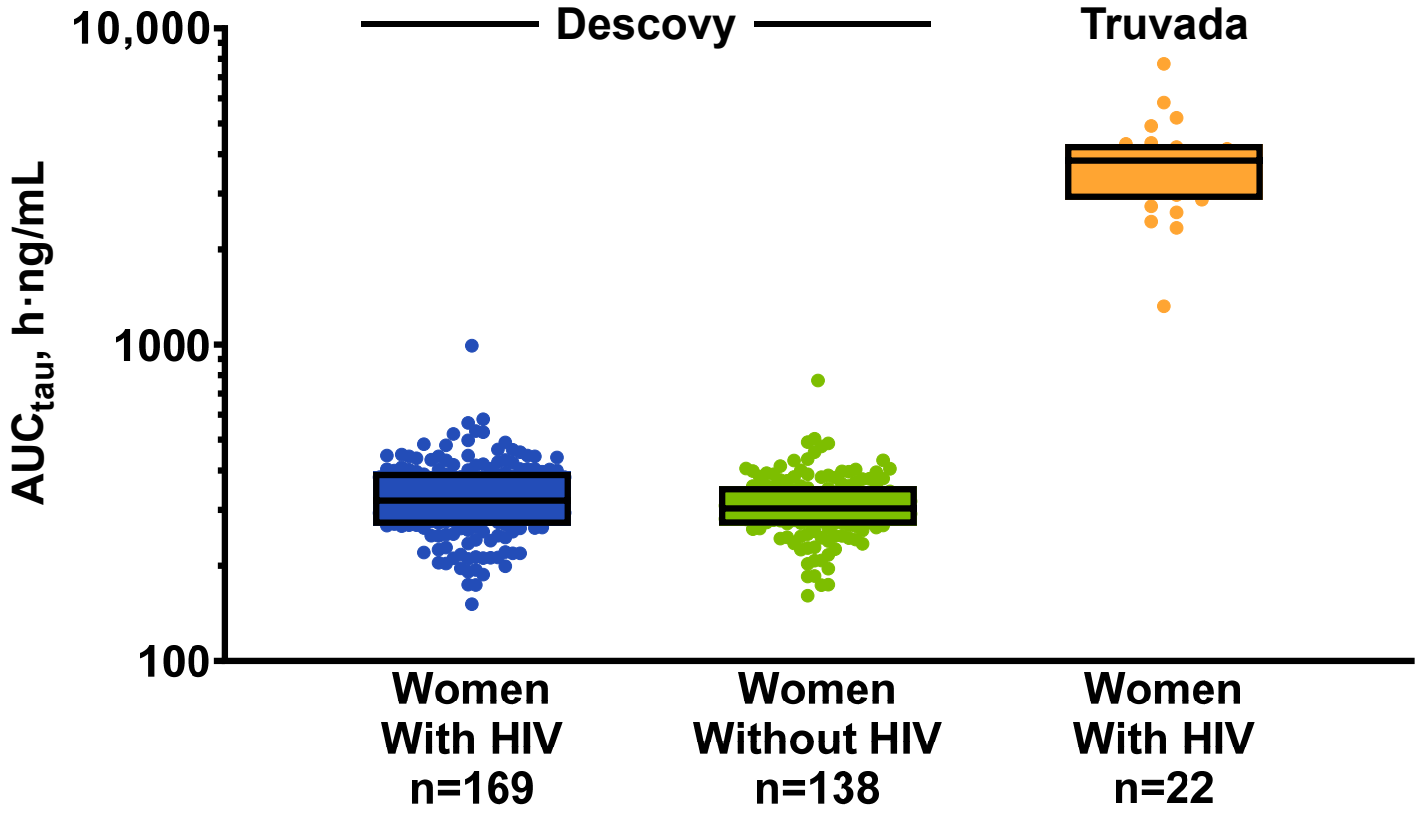


ARV=antiretroviral; VL=viral load.

CC-85

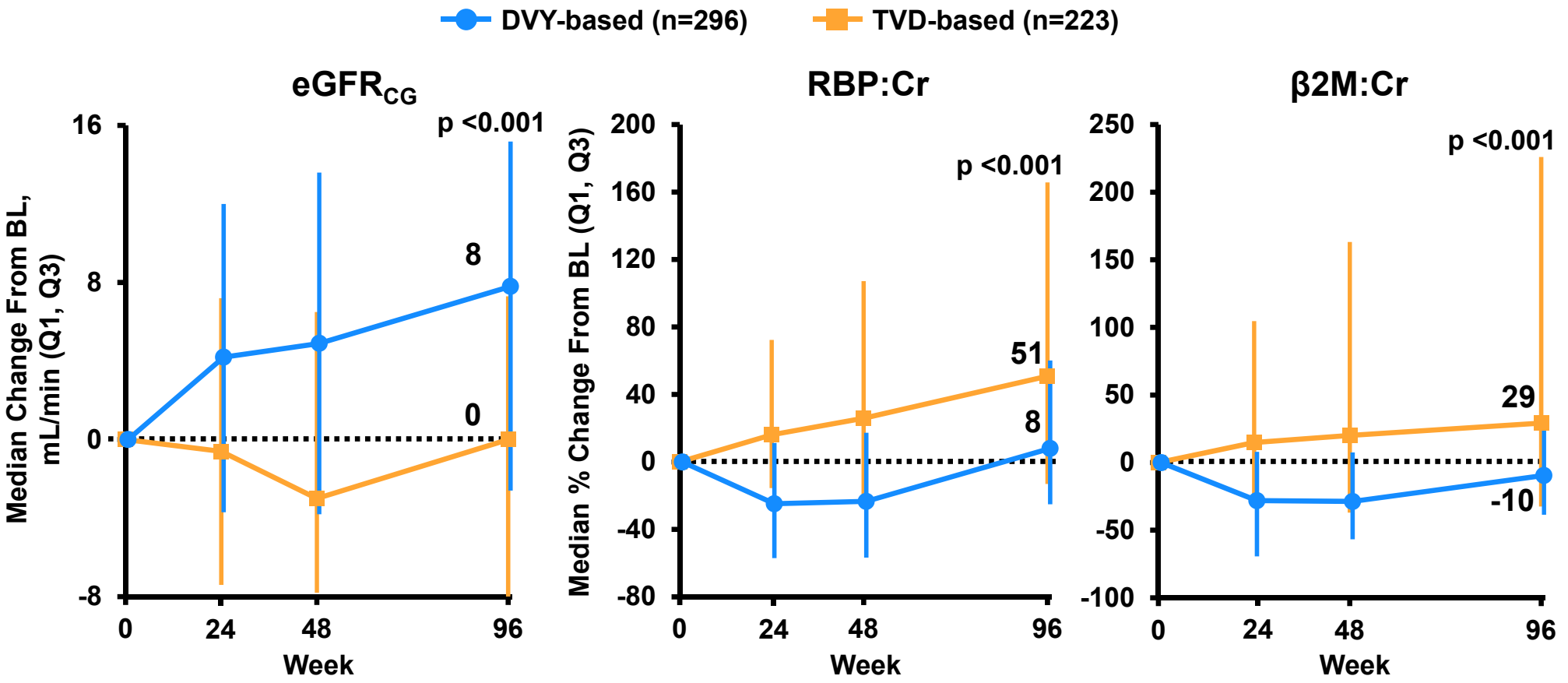
Plasma TFV PK in Women With and Without HIV: AUC_{tau}

Descovy and Truvada



Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.

Renal Safety in Women With HIV Through Week 96



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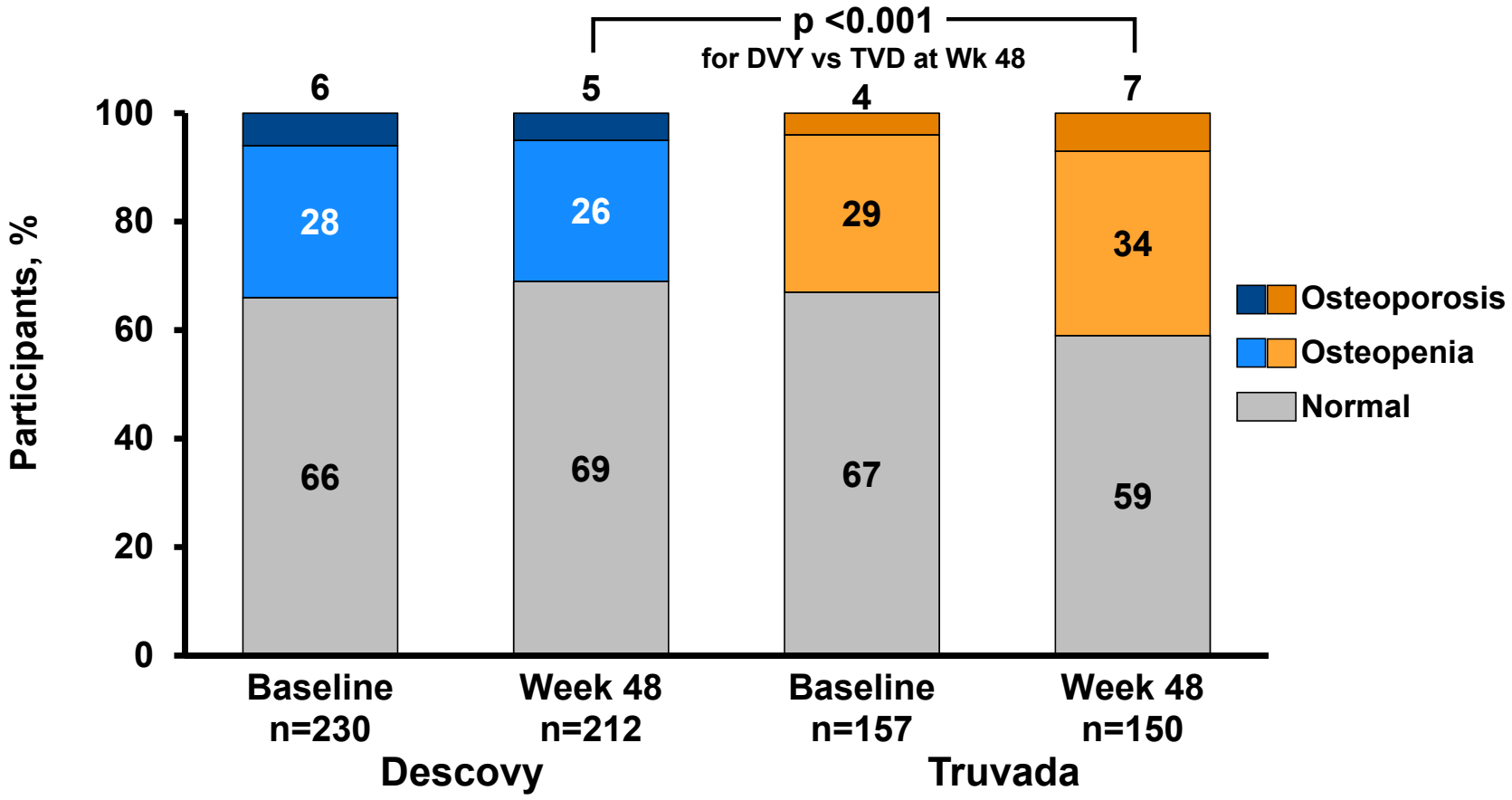
Spine Osteopenia and Osteoporosis in Women With HIV Through Week 48



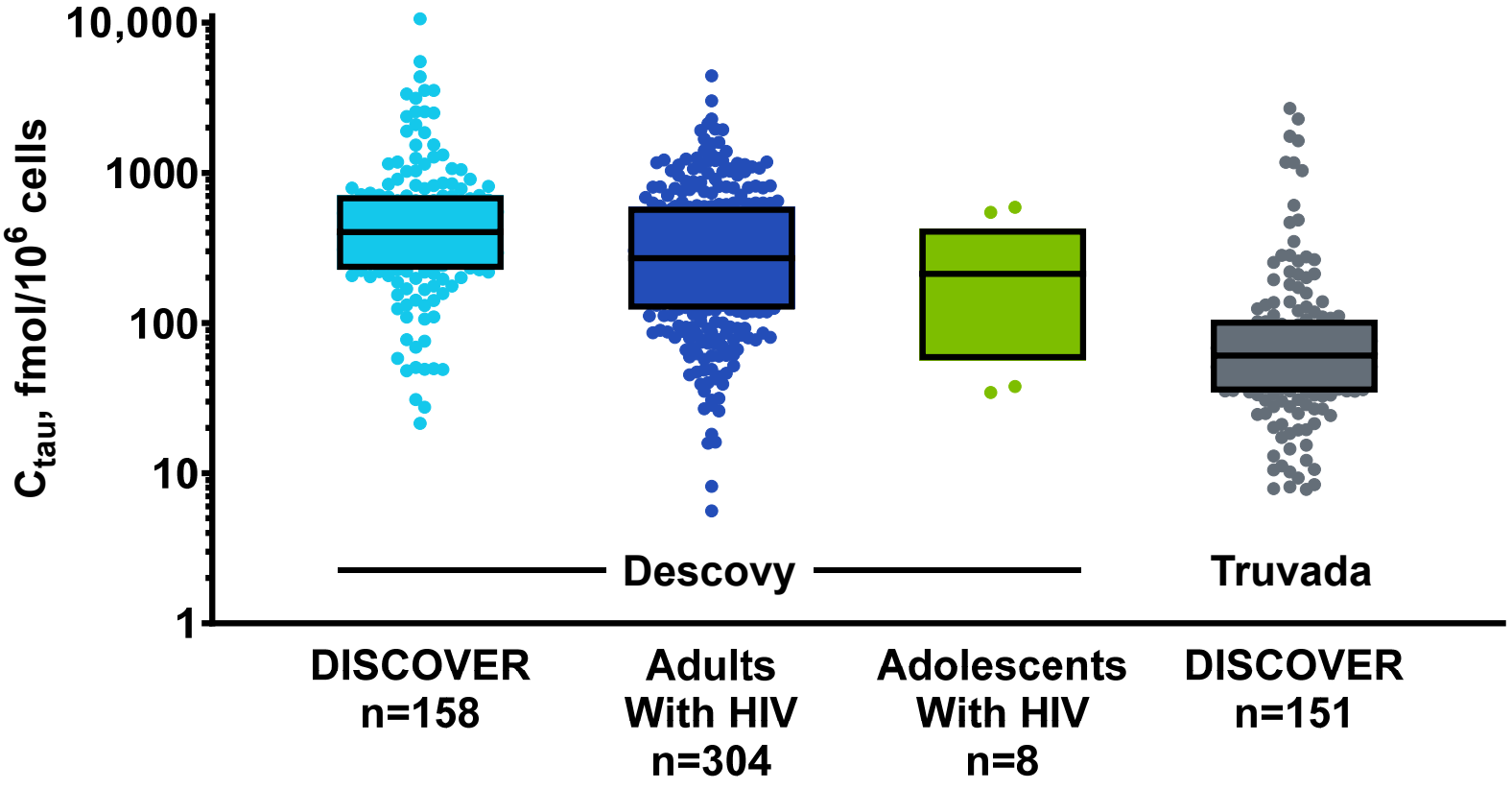
p-value by rank analysis of covariance adjusting for baseline clinical status to compare treatments.

Descovy in Adolescents

- Descovy and three Descovy-containing single tablet regimens are approved for the treatment of HIV in adolescents weighing ≥35 kg
- Descovy has similar bone and renal safety benefits in adolescents with HIV
- Truvada was approved for PrEP in adolescents weighing ≥35 kg in 2018

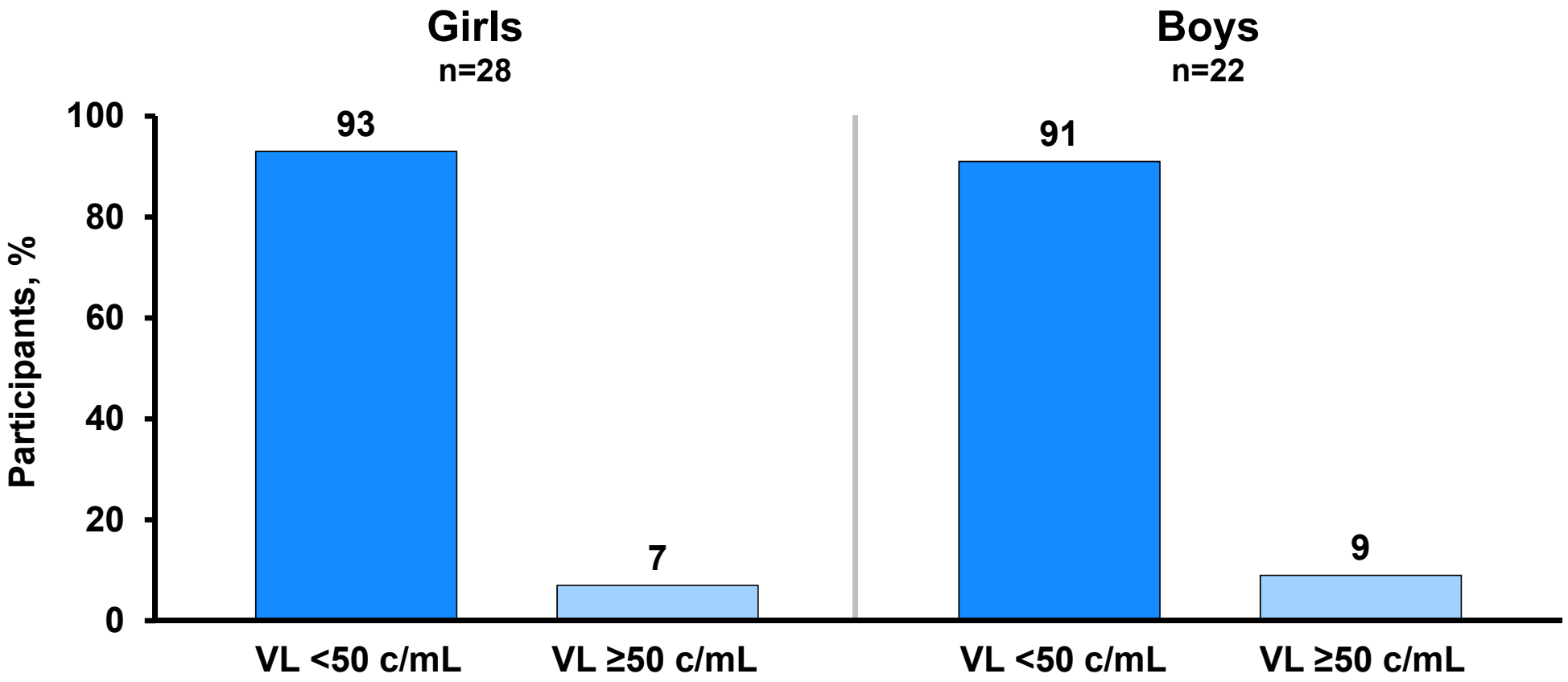
TFV-DP in PBMCs in DISCOVER, Adults, and Adolescents: C_{tau}

Descovy and Truvada



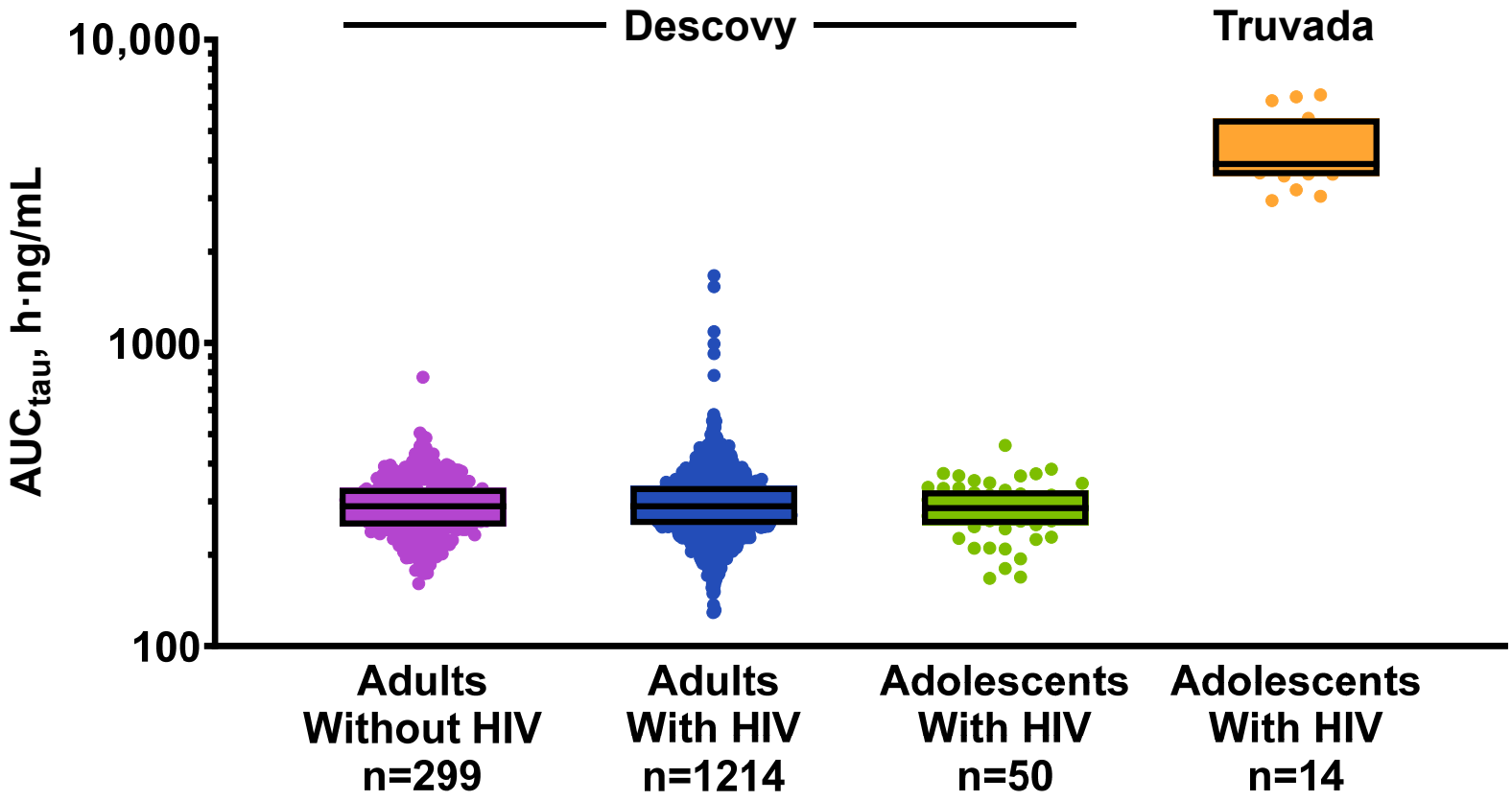
Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.

HIV Treatment Efficacy in Adolescents



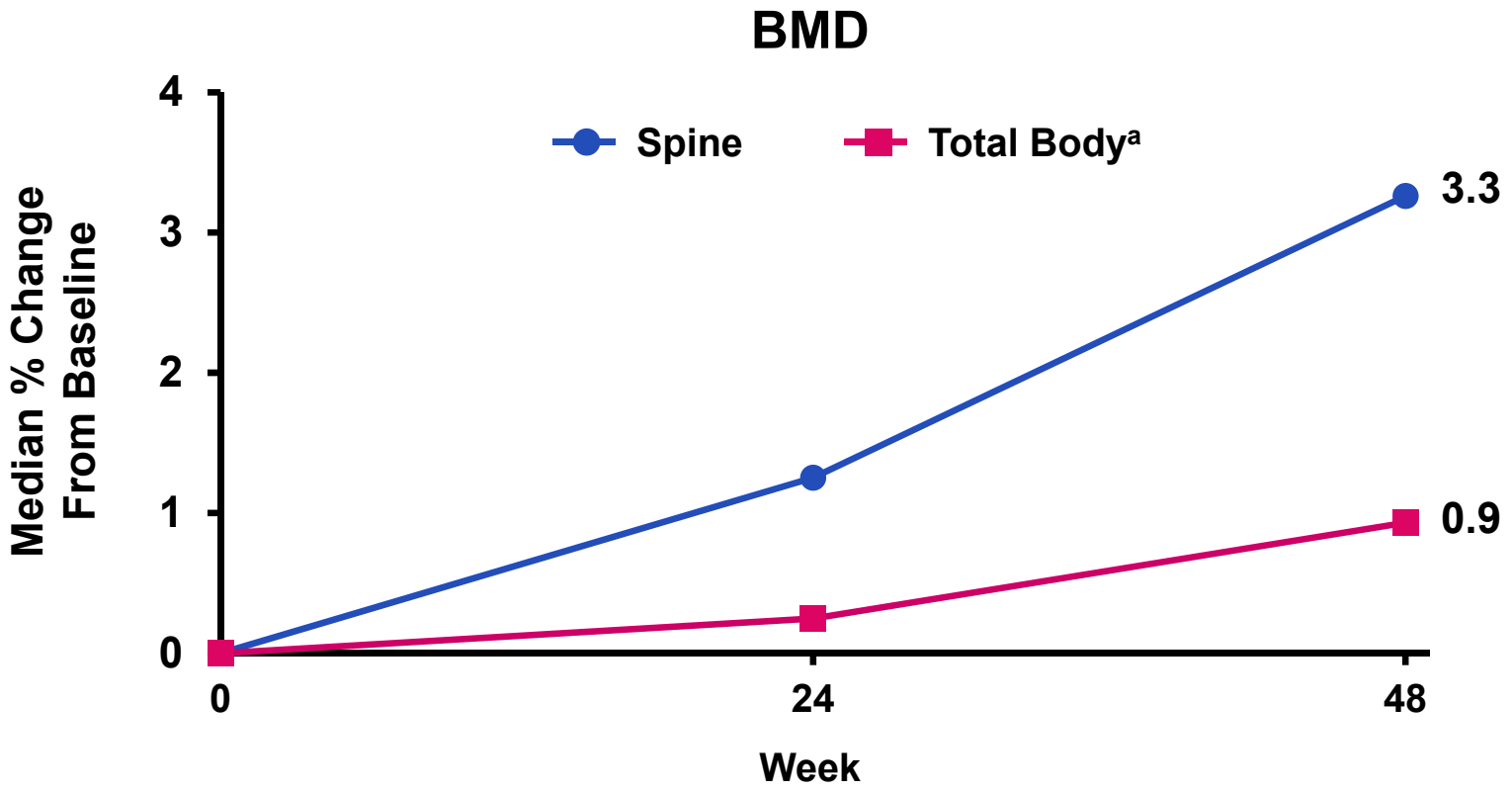
Plasma TFV PK in Adults and Adolescents: AUC_{tau}

Descovy and Truvada



Boxes show median (Q1, Q3); dots represent individual data in Q1, Q4.

Bone Safety in Adolescents With HIV Through Week 48



a. Total body less head.

Conclusions for Descovy in Ciswomen and Adolescents

- Descovy is noninferior to Truvada in HIV treatment and prevention efficacy
  - Tenofovir diphosphate levels in PBMCs are comparable in the men and transwomen in DISCOVER, in ciswomen, and in adolescents
- Descovy is superior to Truvada in renal and bone safety—relevant for women and adolescents
  - Plasma tenofovir is 90% lower with Descovy than Truvada and comparably low in DISCOVER, ciswomen, and adolescents
- Data support the inclusive indication

Future Studies

Studying Descovy for PrEP in Ciswomen and Adolescents

- Ciswomen not included in DISCOVER
  - HIV incidence is 13-fold lower for US women vs MSM at high risk for HIV
- Placebo-controlled trial not ethical
  - Truvada efficacy established in adherent women
- Superiority to Truvada trial not appropriate
  - Oral daily pills differentiated primarily on safety
- Dedicated NI trial in women has considerable statistical design challenges: N=22,000, ~8–10 years to conduct
- DISCOVER design not optimized for adolescents

Selected PrEP Effectiveness Studies for Descovy

PrEP Vacc
N~1688
Women & men
South Africa

Descovy for PrEP
N~525
Women & men
US & Sub-Saharan Africa

Descovy for PrEP
N=500
Adolescents, women & men
>15 y
Rural Kenya and Uganda

DVY for PrEP in Pregnancy
N~360
Pregnant & breastfeeding women
Kampala, Uganda

YW Telehealth
N=100
Black cis- & transwomen
>15 y
Birmingham, AL

Rapid PrEP
N=290
Black adolescent MSM
16–24 y
Southern US

Clinical Context

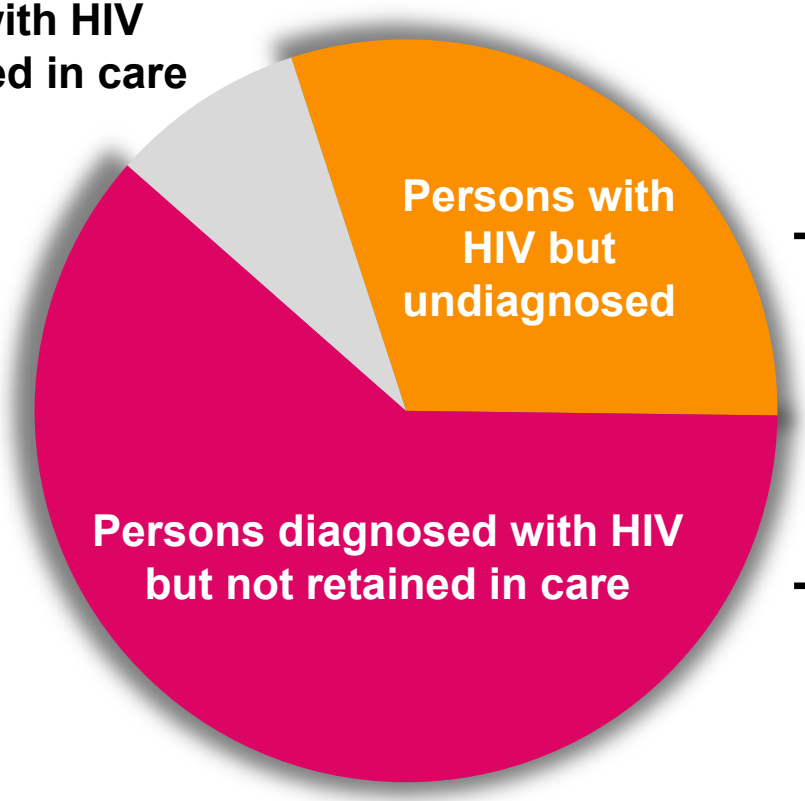
Richard Elion, MD

Director of Research
Washington Health Institute

Clinical Professor of Medicine
George Washington University

Current HIV Treatment Coverage Is Not Enough to Prevent New HIV Transmission

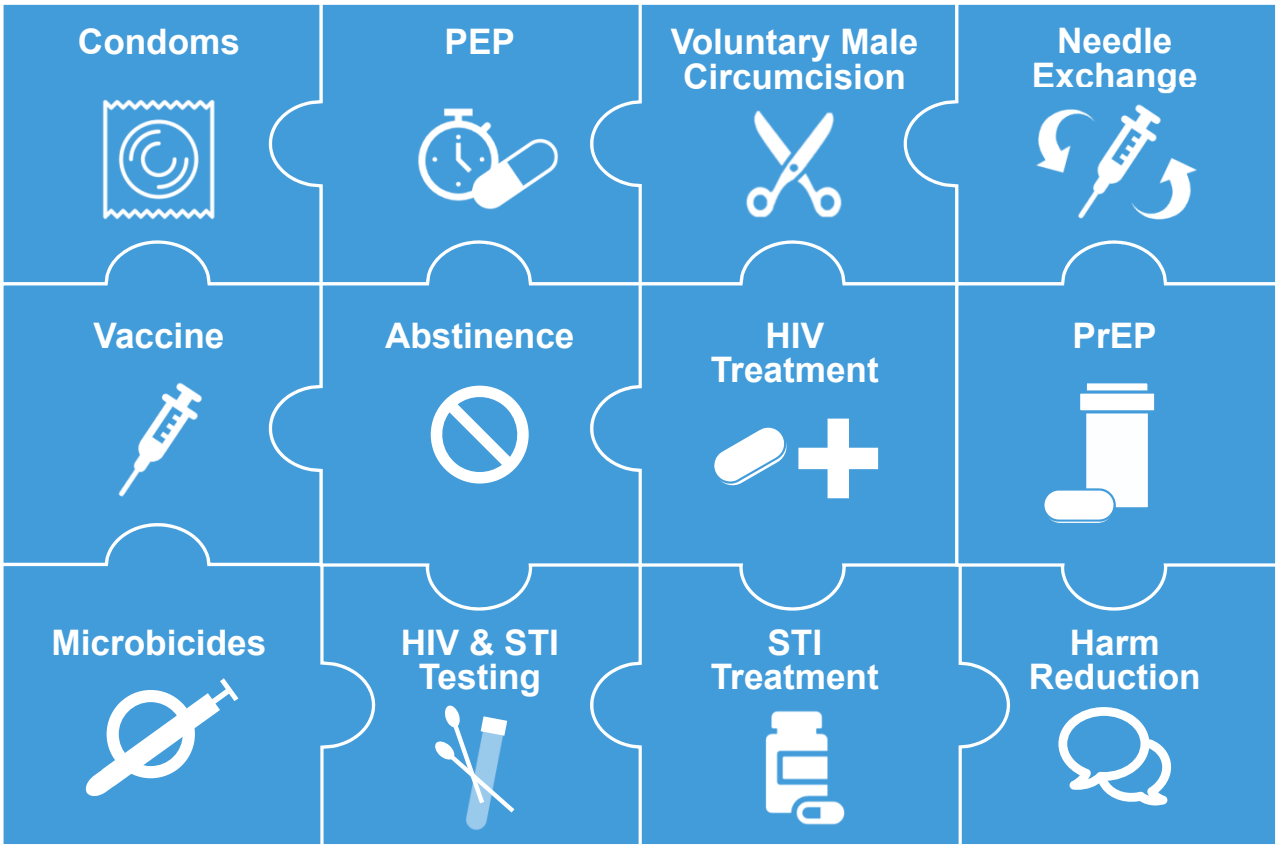
8.5% persons with HIV who are engaged in care



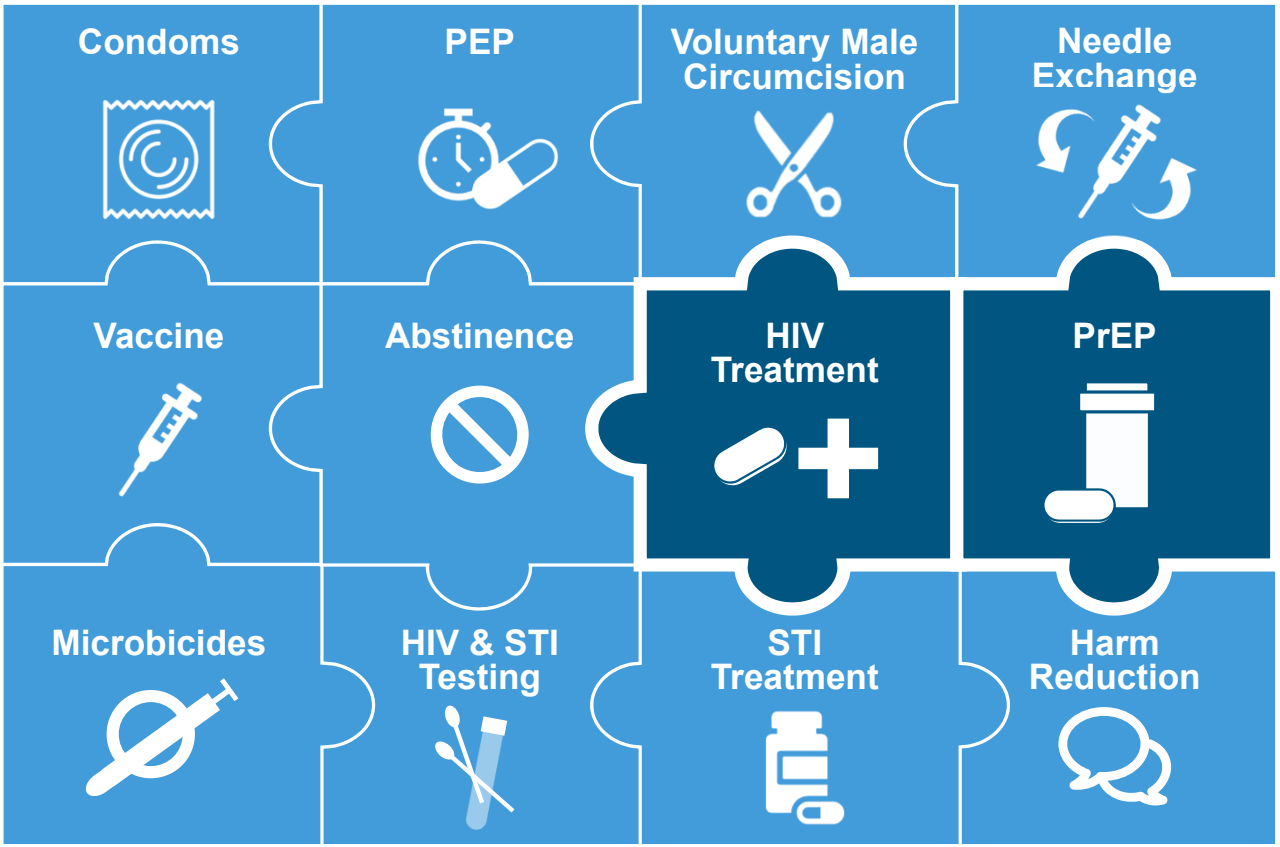
Unmet Need: 91.5%

Based on chronic HIV in the US (2009): estimated 45,000 new HIV infections and awareness of HIV serostatus.
Skarbinski J, et al. JAMA Intern Med. 2015;175:588-596.

HIV Prevention Strategies

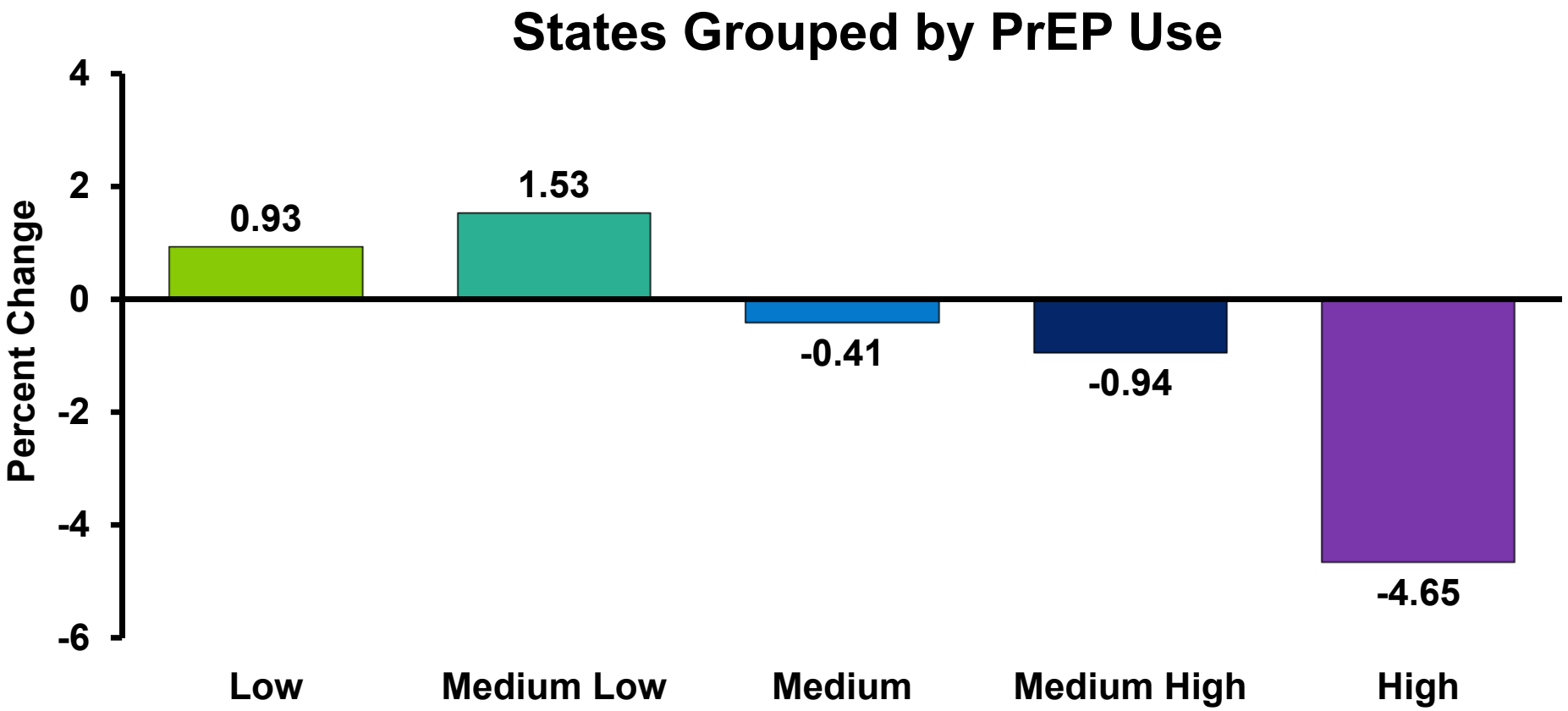


HIV Prevention Strategies



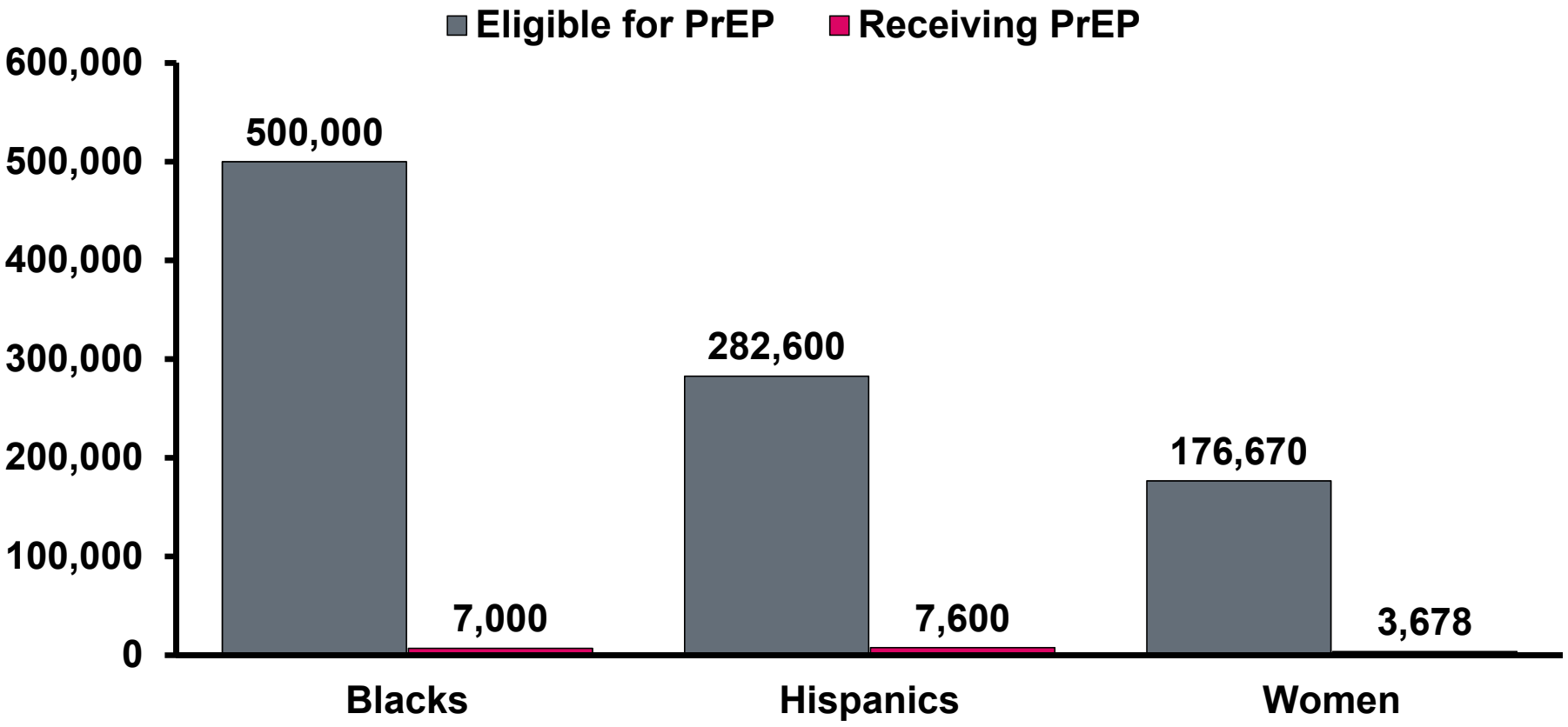
- Biomedical interventions, including TasP and PrEP, are among the most useful

Effect of PrEP Uptake on HIV Diagnoses
2012–2016



Low: 13–42/100K; Medium low: 42–53/100K; Medium: 53–61/100K; Medium high: 62–78/100K; High: 81–178/100K.
Sullivan PS, et al. International AIDS Conference 2018, abstr LBPEC036.

PrEP Use in Communities in Need



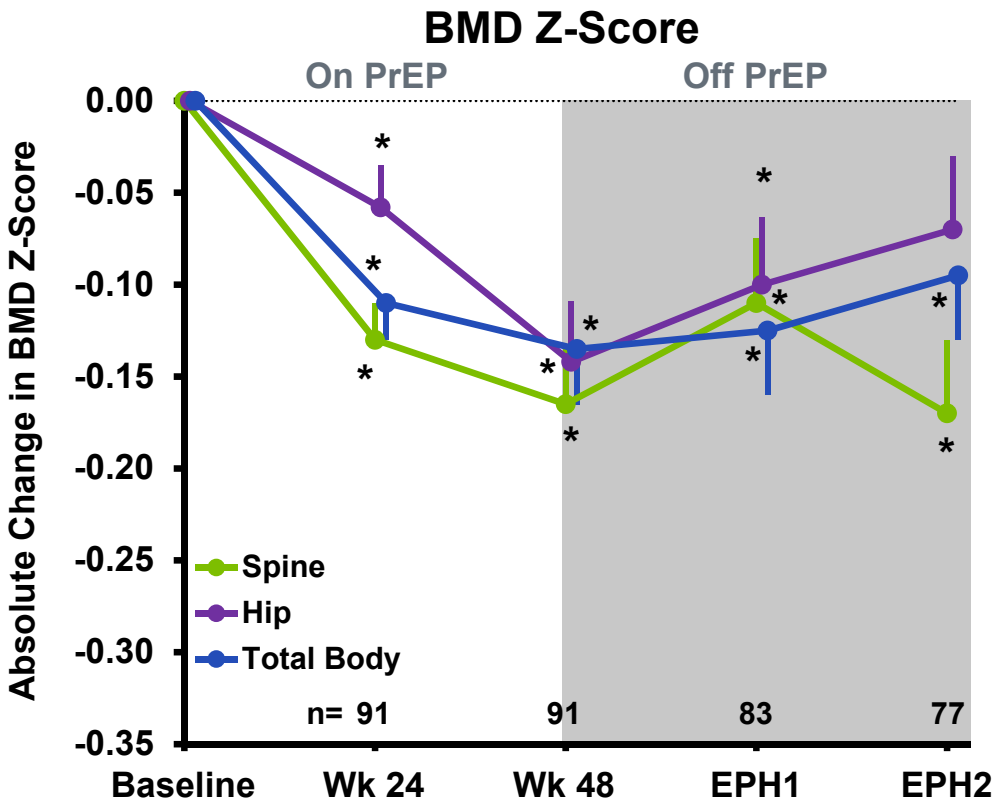
1. Smith DK, et al. J. Ann Epidemiol 2018;S1047-2797(17)31069-4; 2. Huang YA et al. 2014–2016 MMWR October 19, 2018;67:1147-50;
3. CDC, Press Release, March 2019; 4. Mera Giler R, et al. J Int AIDS Soc 2017;20(suppl 5);WEPEC 0919.

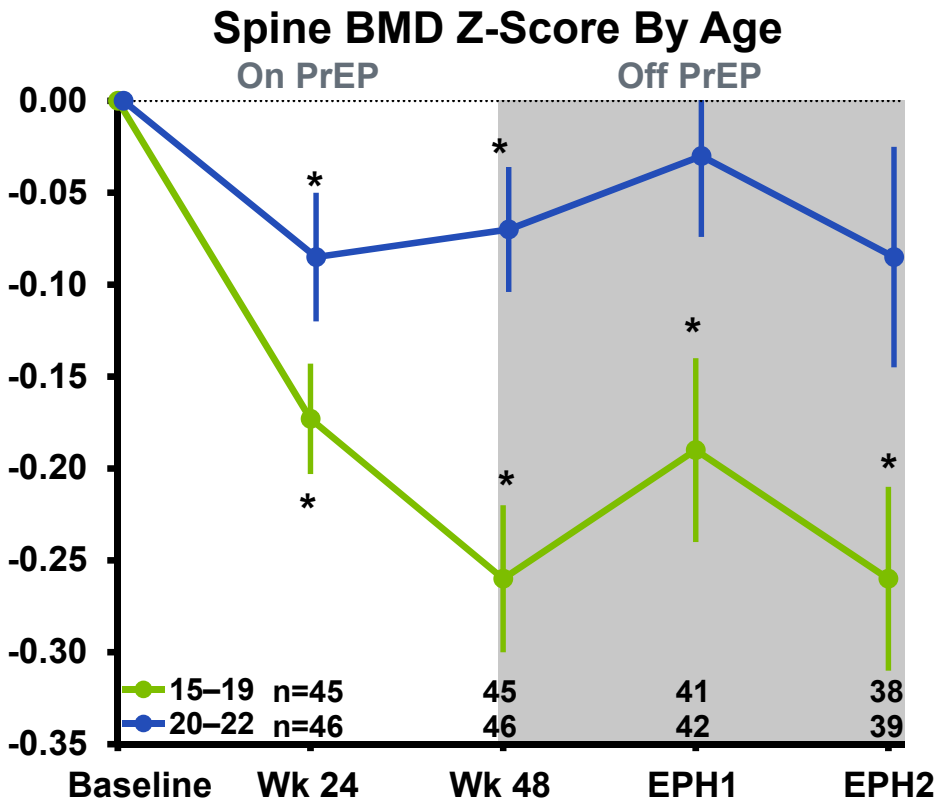
Descovy for PrEP for Adolescents

- Truvada for PrEP efficacious in adolescents
- HIV infection and prevention biology consistent across ages
- Descovy data support use with adolescents
  - Descovy for treatment efficacious in adolescents
  - Descovy for PrEP efficacious in cismen and transgender women
  - Descovy pharmacology consistent across ages
- Important option for adolescents
  - Deposit bone through mid-thirties

Adolescents: Value of Z scores (Age-adjusted)

On and off Truvada for PrEP





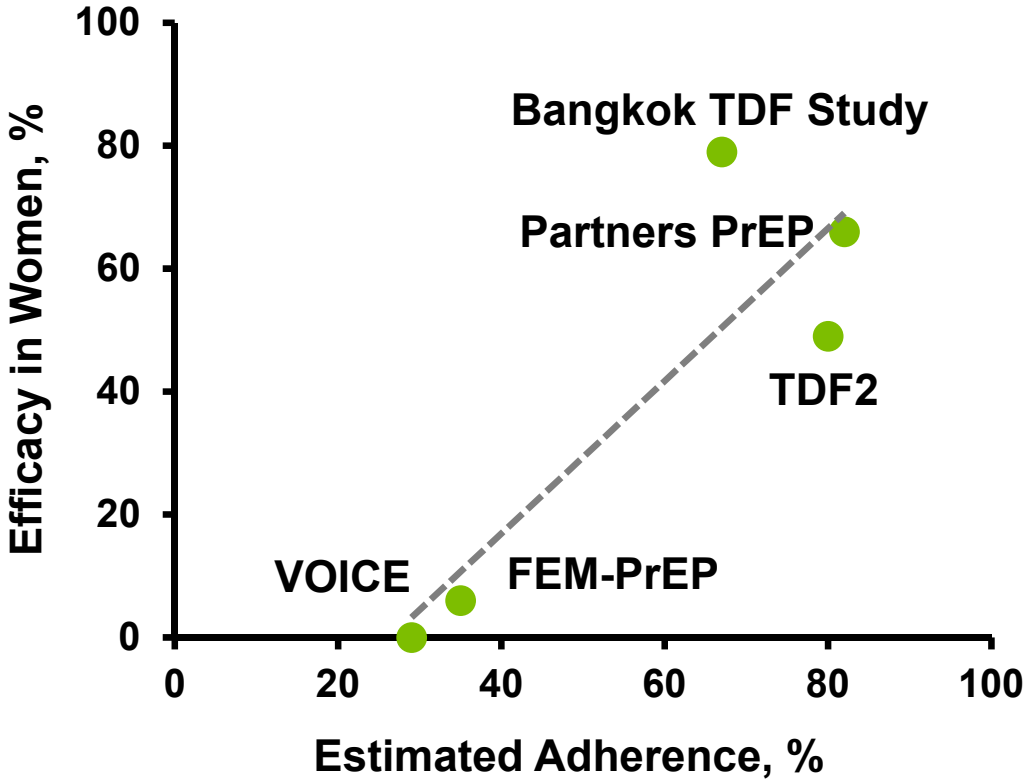
*p ≤0.05 for change from baseline by paired t-test; Havens PL. Clin Infect Dis 2019 [in press]. EPH=extension phase out through 96 additional weeks of follow from either Week 48 or a positive HIV diagnosis.

CC-105

Potential PK Advantages

- TAF leads to lower plasma TFV levels resulting in reduced off target side effects
- TAF rapidly leads to higher TFV-DP in PBMCs resulting in increased antiviral effect and potential efficacy advantage
  - The TFV-DP PK advantages represent a potential forgiveness advantage if adherence is imperfect
- These PK advantages may be beneficial for prevention

Efficacy of Truvada for PrEP in Women



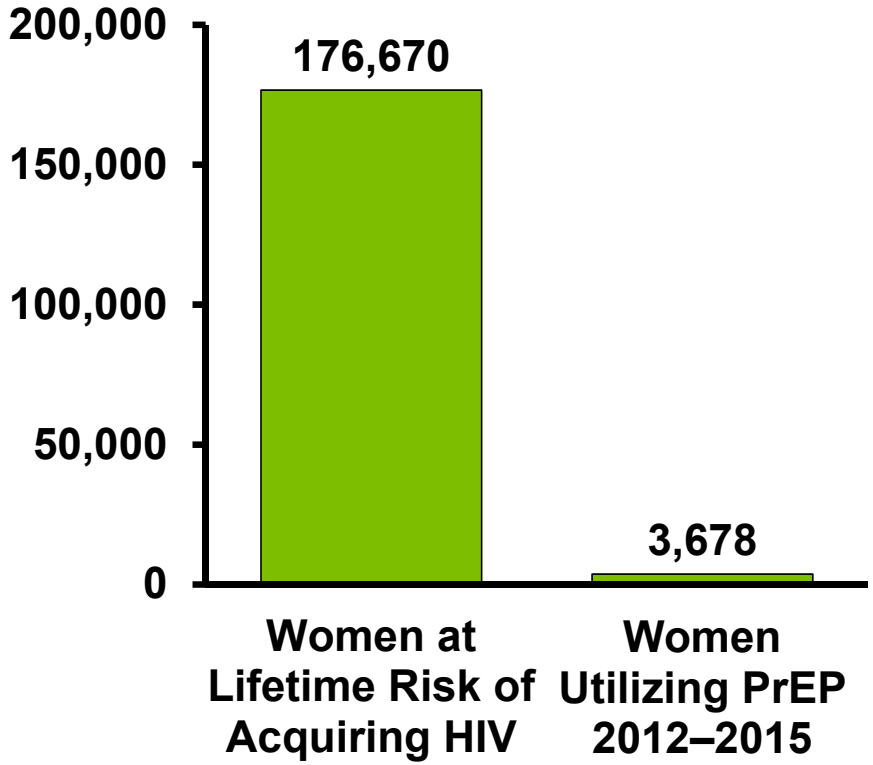
- Partners PrEP and TDF2 reflected efficacy in women when adherence was comparable to other studies
- VOICE and FEM-PrEP showed poor efficacy when adherence was equally deficient

Baeten J et al. HIV Research for Prevention Conference, Madrid, October 2018.

Women and PrEP

- 93% of HIV-negative women reported having vaginal sex without a condom in the previous year
- 26% reported having anal sex without a condom

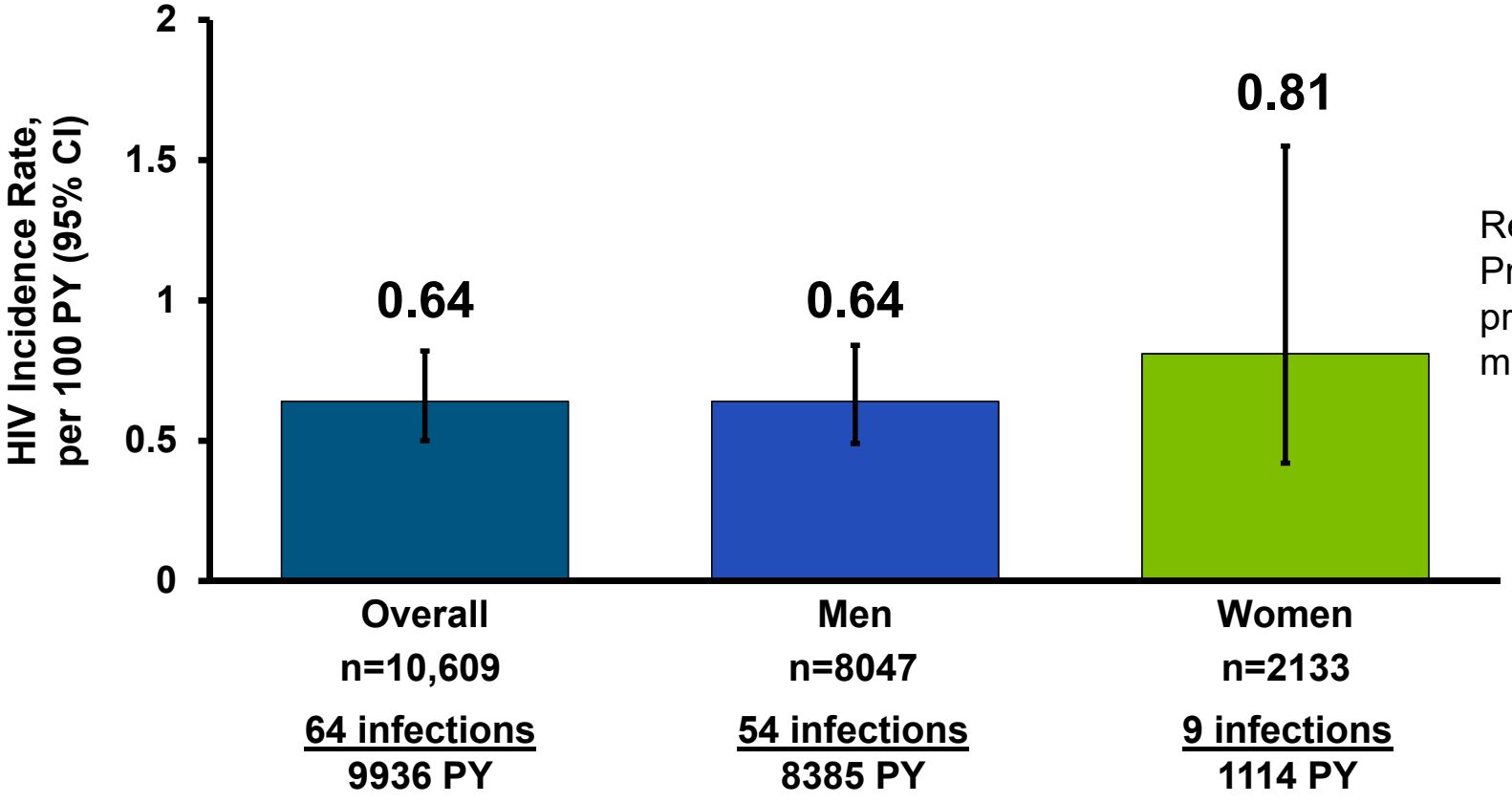
Of the >170,000 women at risk, only 2% have started Truvada for PrEP



Huang YA et al. MMWR October 19, 2018 / 67(41);1147–1150. Smith D, et al. MMWR Morb Mortal Wkly Rep 2015;64:1-6; Mera, R. et al. AIDS 2016. Durban, South Africa. Oral #TUAX0105LB.

HIV Incidence

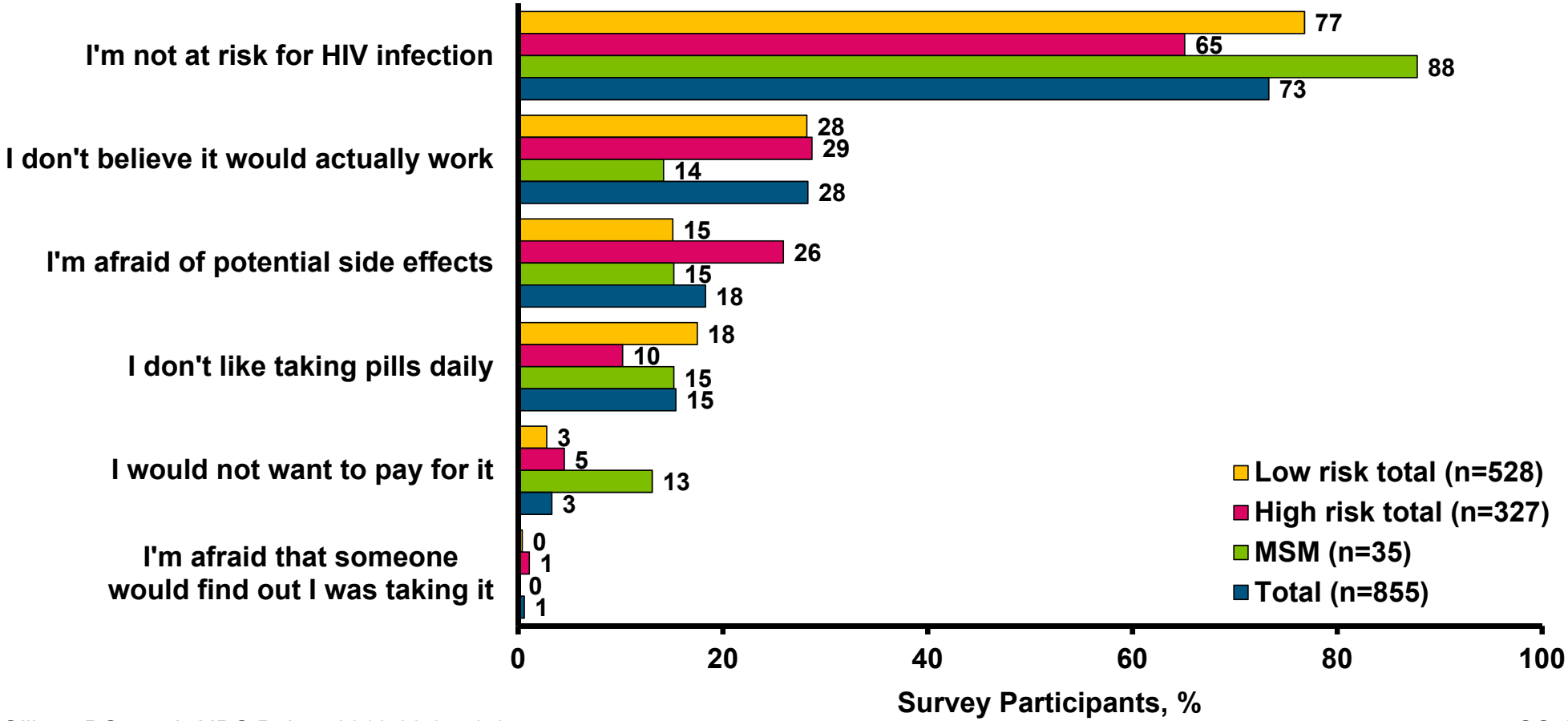
HIV Seroconversion Across 46 TVD for PrEP Demonstration Projects



Real world data on TVD PrEP use from 46 demo projects in nearly 10,000 men and women

Baeten J, et al. AIDS Res Hum Retroviruses. 2018;34(suppl 1):121. Abstract OA23.01.

Reasons for Lack of Willingness to Use PrEP



Ojikutu BO, et al. AIDS Behav 2018;22:3576-87.

CC-110

Women: Descovy Bone Safety Data

- Truvada-based regimens are associated with declines in bone mineral density[1]
- Increased risk of fracture in people living with HIV who have taken Truvada-based regimens[2]
- Descovy-based regimens are not associated with declines in bone mineral density

1. Grigsby IF, et al. Ther Clin Risk Manag 2010:6 41-7; 2. Borges AH, et al. CID 2017;64:1413–21; 3. Wohl D, et al. J Acquir Immune Defic Syndr 2016;72:58-64; 4. Hare CB, et al. CROI March 2019; 5. Wohl DA, et al. Lancet HIV, May 2019.

Descovy for PrEP for Cis Women

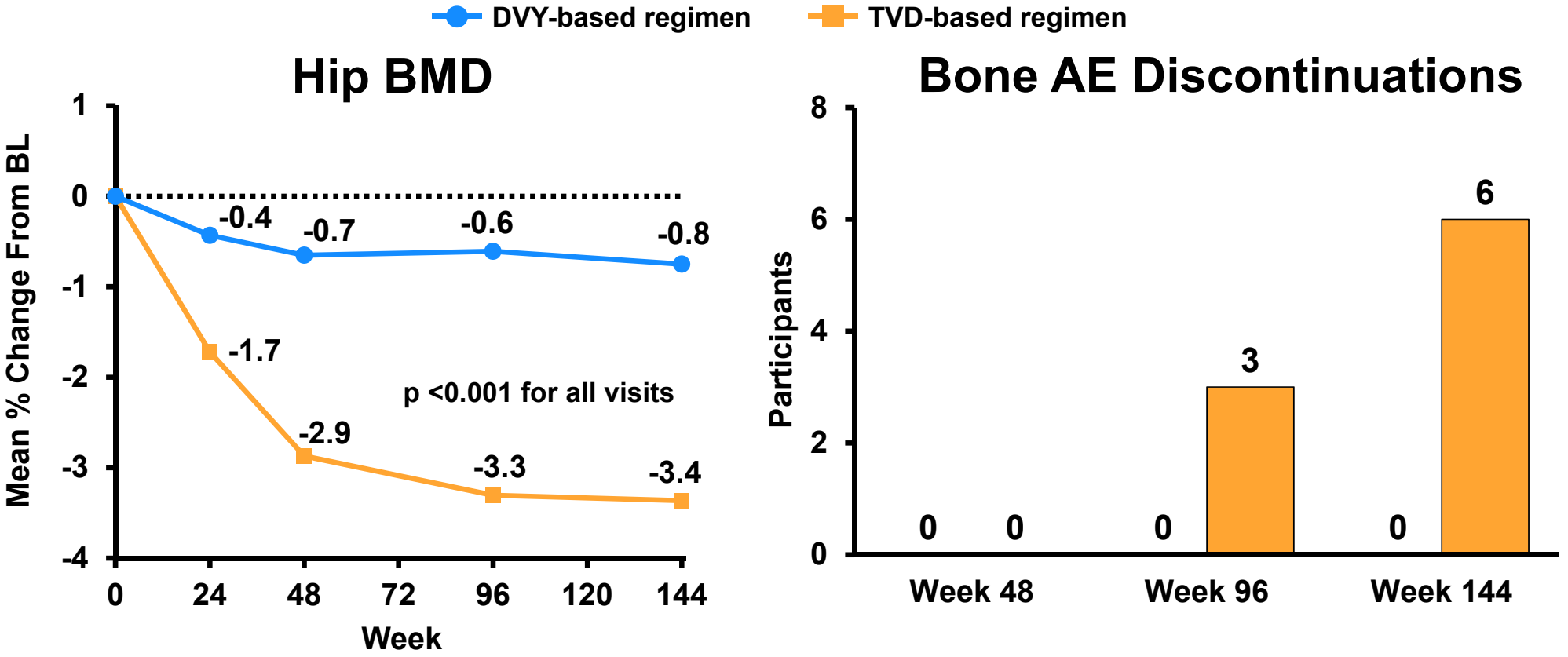
- Truvada for PrEP is equally effective in men and women when controlling for adherence as seen in clinical trials (Partner's PrEP, TDF2, and Bangkok, as well as demonstration projects)
- PBMC drug levels are associated with efficacy for HIV prevention
  - HIV is a systemic disease
  - Drug levels in PBMCs correlate with efficacy in treatment and prevention
- PBMC drug levels for Descovy are similar between men and women
  - Higher than with Truvada
- Descovy will be effective for PrEP in cis-women

Conclusions

- PrEP is a key tool in the ongoing fight to end the HIV epidemic
- Descovy is a safer, well tolerated and effective treatment for PrEP
  - Improved bone and renal safety
  - At least as effective as Truvada
- Evidence supports extrapolation to ciswomen and adolescents
- The benefit:risk profile of Descovy for HIV prevention supports making this drug available to all those in need

Backup Slides Shown

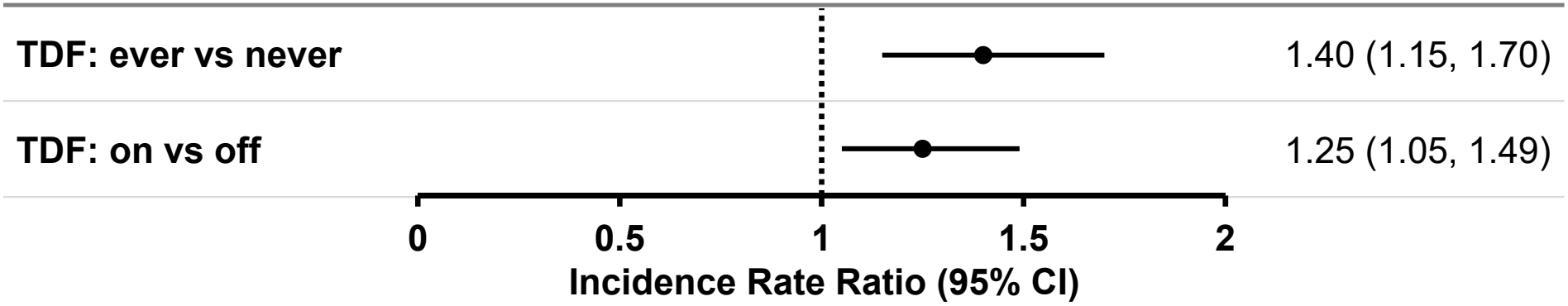
Bone Mineral Density and Bone Adverse Events



AE=adverse event; BMD=bone mineral density.

TDF Use and Fracture Risk

- Analysis from the EuroSIDA cohort, with 619 fractures in 86,118 PY of follow-up[1]
- Multivariate analysis of fracture risk adjusted for demographics, HIV-specific variables, and comorbidities

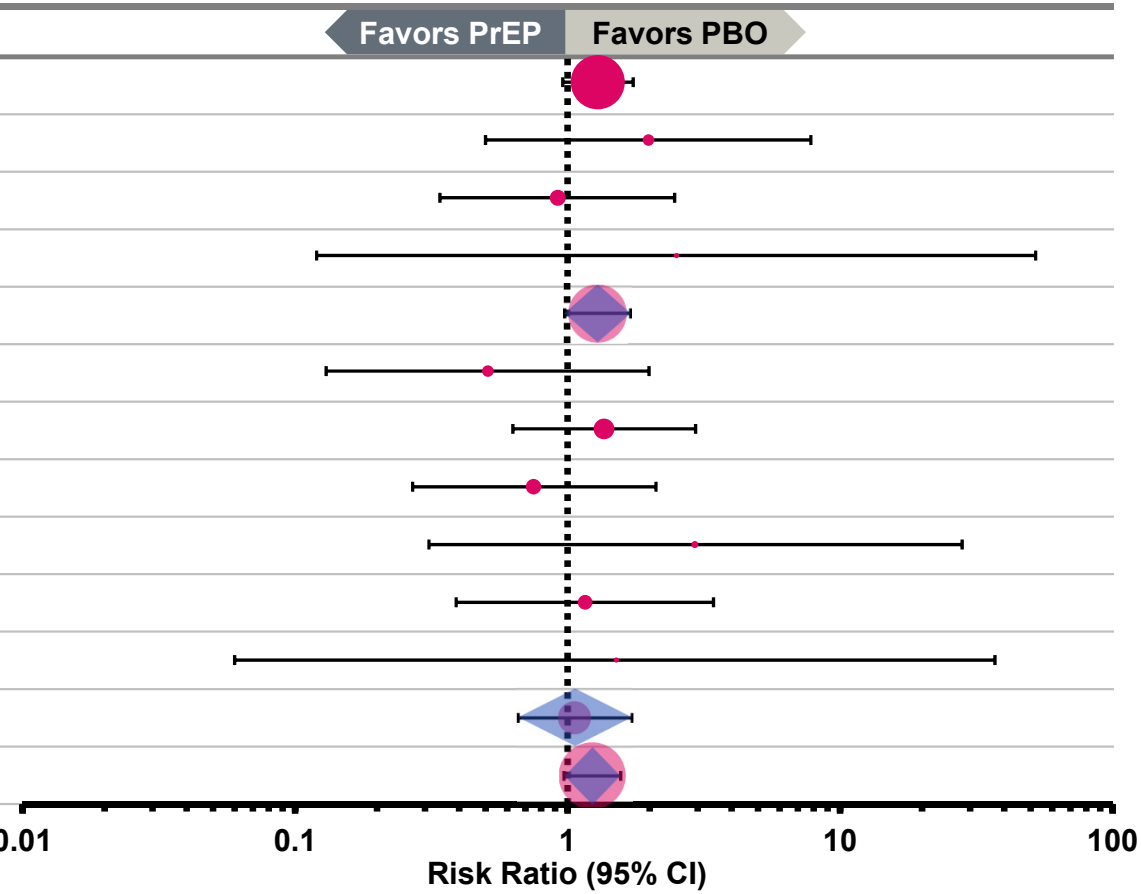


CI=confidence interval; PY=person-year; TDF=tenofovir disoproxil fumarate.

1. Borges et al. Clin Infect Dis. 2017;64:1413-21.

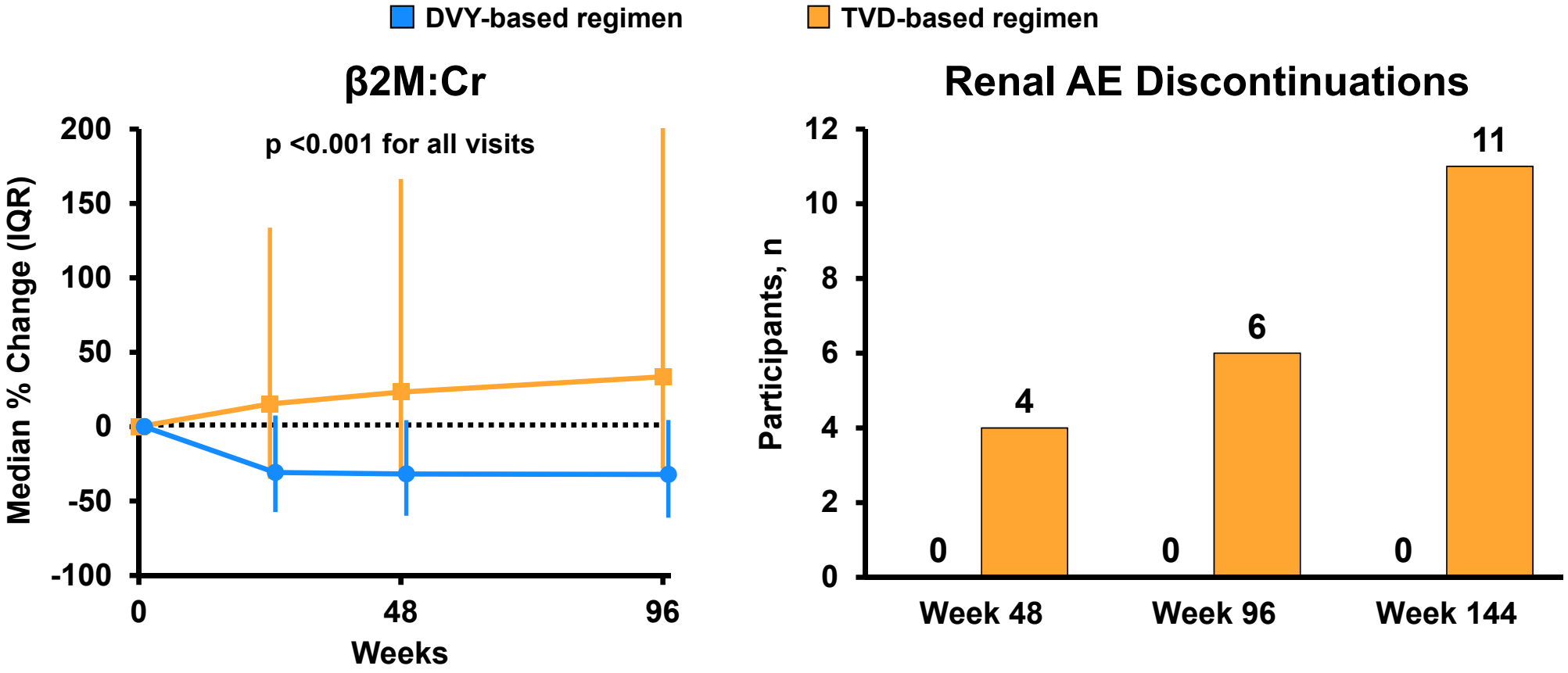
TDF and Truvada PrEP With Trend Towards Increased Fractures

Treatment	Study or subgroup	Risk Ratio (95% CI)
TDF	Bangkok TFV Study	1.29 (0.96, 1.74)
	CDC Safety Study[a]	1.98 (0.50, 7.81)
	Partners PrEP: TDF arm	0.92 (0.34, 2.47)
	VOICE: TDF arm	2.51 (0.12, 52.18)
	Subtotal	1.29 (0.98, 1.70)
TVD	IPERGAY[a]	0.51 (0.13, 1.99)
	iPrEx	1.36 (0.63, 2.95)
	Partners PrEP: TVD arm	0.75 (0.27, 2.11)
	PROUD[a]	2.93 (0.31, 28.04)
	TDF2	1.16 (0.39, 3.43)
	VOICE: TVD arm[b]	1.51 (0.06, 36.98)
	Subtotal	1.06 (0.66, 1.72)
Total		1.23 (0.97, 1.56)



CI=confidence interval; TDF=tenofovir disoproxil fumarate; TFV=tenofovir.
a. US, Canada, or Europe; b. Lower limb fracture. Area of each circle represents weight given to study in meta-analysis. Area of diamond represents sample size for pooled estimate; width of diamond represents CI for pooled estimate. Chou R, JAMA 2019;321:2214-30.

Renal Discontinuation and Renal Tubular Biomarkers

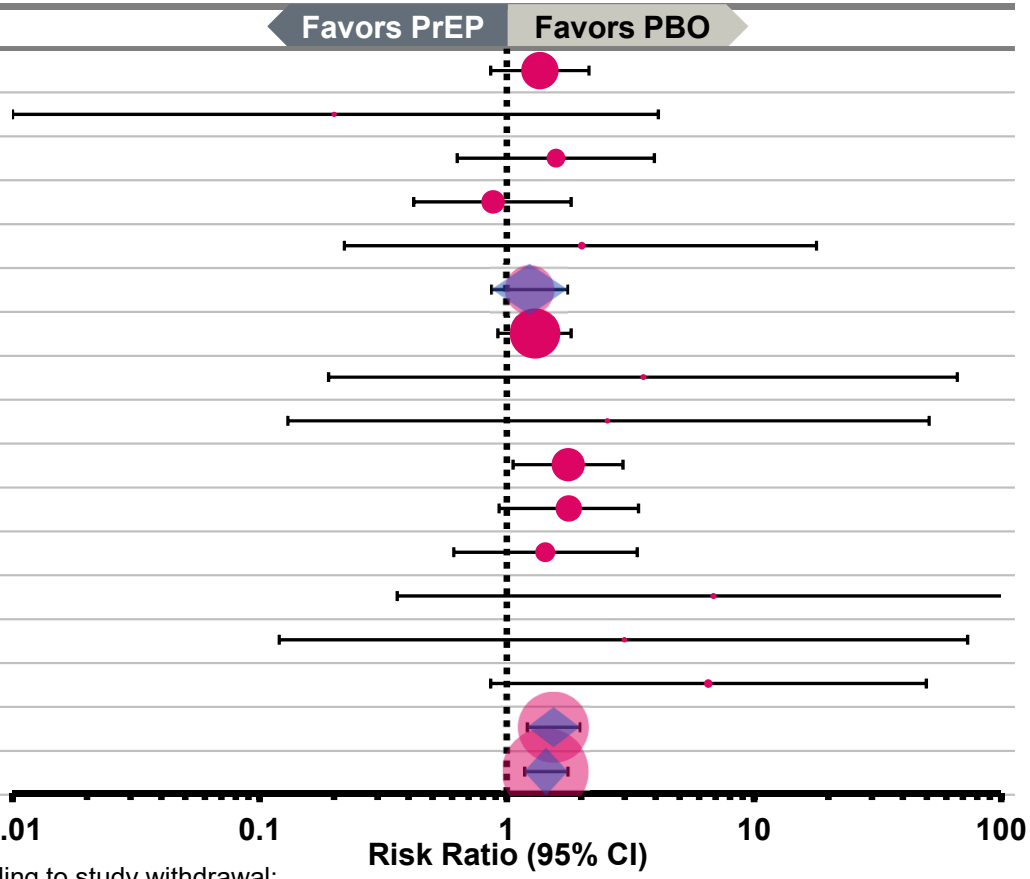


AE=adverse event; β2M:Cr=β2-microglubulin:creatinine; IQR=interquartile range.

BU-594

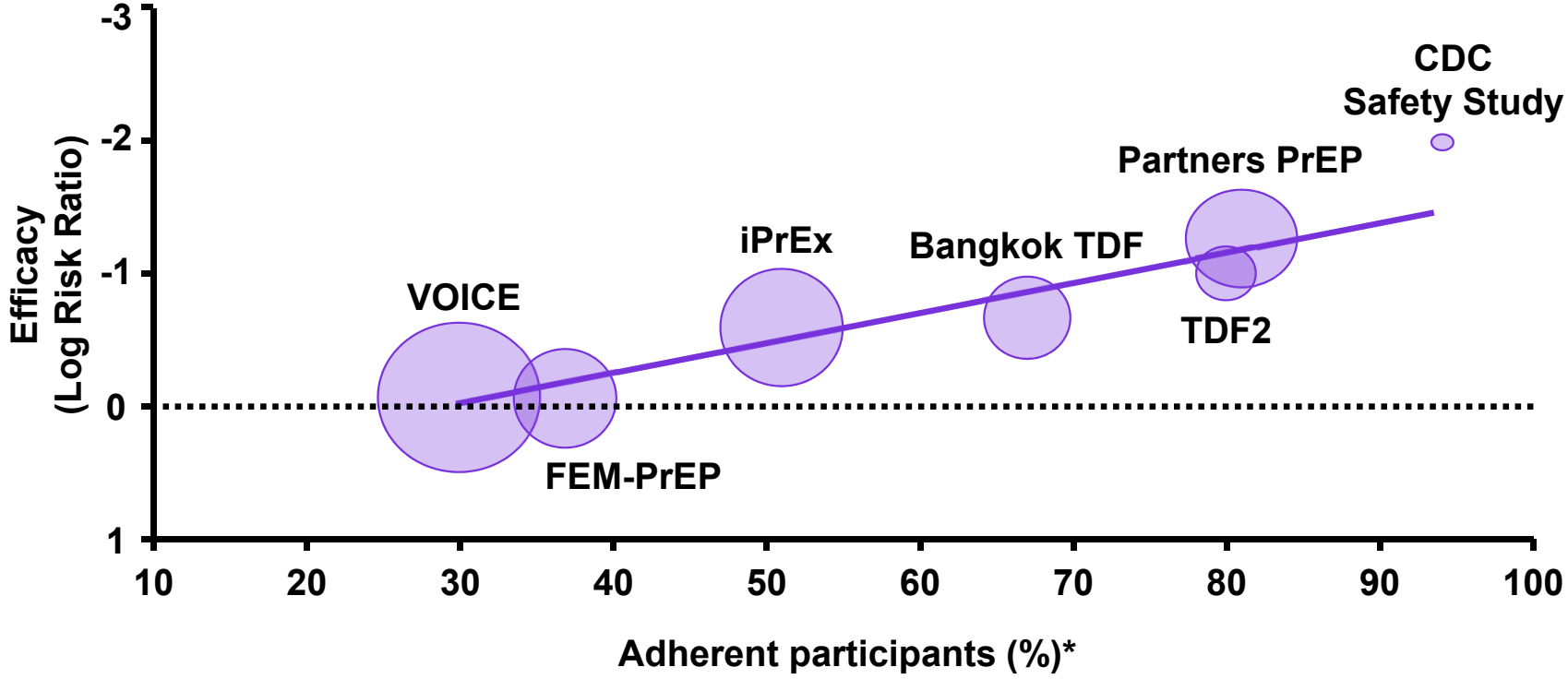
Truvada PrEP associated with Increased Risk of Renal AEs

Treatment	Study or subgroup	Risk Ratio (95% CI)
TDF	Bangkok TFV Study	1.36 (0.86, 2.15)
	CDC Safety Study[a,b]	0.20 (0.01, 4.10)
	Partners PrEP: TDF arm	1.58 (0.63, 3.95)
	Study of TDF	0.88 (0.42, 1.82)
	VOICE: TDF arm[c]	2.01 (0.22, 17.90)
	Subtotal	1.24 (0.87, 1.76)
TVD	FEM-PrEP	1.30 (0.92, 1.82)
	IAVI Kenya Study	3.57 (0.19, 66.47)
	IAVI Uganda Study	2.55 (0.13, 51.13)
	IPERGAY[a]	1.77 (1.06, 2.95)
	iPrEx	1.78 (0.93, 3.41)
	Partners PrEP: TVD arm	1.43 (0.61, 3.37)
	PROUD[a,d]	6.85 (0.36, 131.92)
	TDF2	2.99 (0.12, 73.14)
	VOICE: TVD arm[e]	6.53 (0.86, 49.79)
	Subtotal	1.54 (1.21, 1.96)
Total (95% CI)		1.43 (1.18, 1.75)



AE=adverse event; CI=confidence interval; Cr=creatinine; TDF=tenofovir disoproxil fumarate; TFV=tenofovir. a. U.S, Canada, or Europe; b. Cr elevation leading to study withdrawal; c. Any Cr event; d. Study drug interruption due to high Cr concentration; e. Any Cr event. Area of each circle represents weight given to study in meta-analysis. Area of diamond represents sample size for pooled estimate; width of diamond represents CI for pooled estimate. Chou R, JAMA 2019;321:2214-30.

PrEP Adherence Correlates with Efficacy in Previous Trials



TFV=tenofovir.
* TFV "Detected" in Plasma Samples in Active Arm or >90% by Self-report/pill Count/refill Records
Fonner VA, et al. AIDS. 2016;30:1973-83.

BU-1232

PrEP is Highly Effective in MSM, Heterosexual Men and Women

CDC PrEP Guidance[1]

Oral Daily Pre-Exposure Prophylaxis (PrEP)† for HIV-Negative Persons

Population	Effectiveness Estimate	Source	Interpretation
"Optimal or Consistent Use"[a] (Taking PrEP daily or at least 4 times per week)			
Men who have sex with men (MSM)	~99%	Grant, 2014 Liu, 2015 McCormack, 2015 Volk, 2015 Marcus, 2017	When taking PrEP daily or consistently (*at least 4 times per week*), the risk of acquiring HIV is reduced by about 99% among MSM. While daily use is recommended in the U.S., taking PrEP consistently (*at least 4 times per week*) appears to provide similar levels of protection among MSM. The effectiveness of oral PrEP is highly dependent on PrEP adherence. When taking oral PrEP daily or consistently, HIV acquisition is extremely rare and has not been observed in any of the studies described below. In clinical practice, a few cases of new HIV infections have been confirmed while HIV-negative individuals were on PrEP with verified adherence.
Heterosexual Men and Women	~99%	*N/A*	There is evidence for the effectiveness of PrEP when used recently[b] (based on detecting TFV in plasma), which is estimated to be 88 – 90% as described below. There is no effectiveness estimate of PrEP when taken daily or consistently among heterosexuals; however, it is likely to be greater than the estimates corresponding to recent use and similar to what has been observed for MSM. The effectiveness of oral daily PrEP is highly dependent on PrEP adherence, with maximum effectiveness when taking PrEP daily and lower effectiveness when not taken consistently.

1. https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html

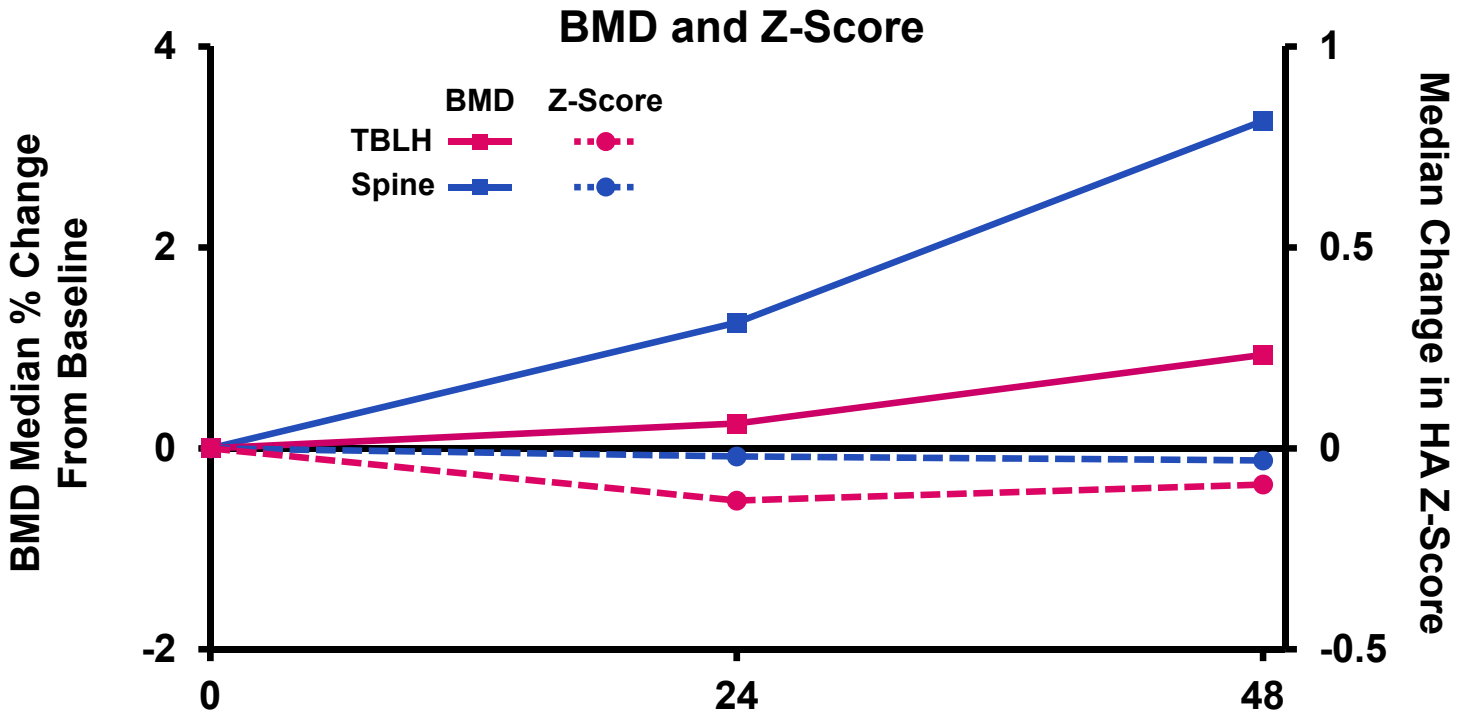
† The guidelines for PrEP use in the U.S. recommends daily oral PrEP and daily dosing is the only FDA-approved schedule for taking PrEP to prevent HIV.

[a] "Optimal use" is defined as taking PrEP daily, "Consistent use" is defined as taking PrEP at least 4 pills/week

[b] "Recent use" of oral PrEP is determined by detecting any amount of TFV in plasma.

NON-DISCOVER: ARV-Naïve Adolescents Who Initiated DVY-based Treatment (N=50)

Bone Safety in Adolescents With HIV



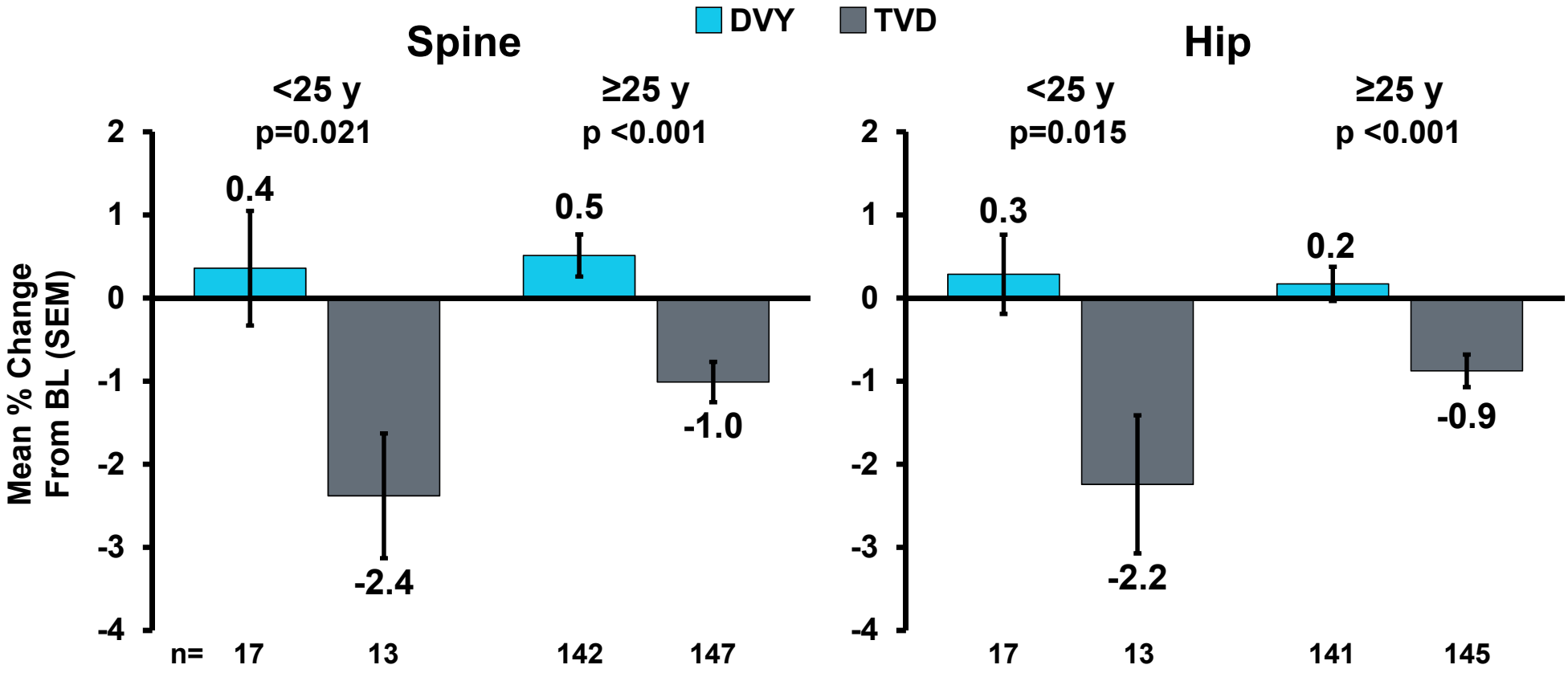
HA=height-adjusted; Q=quartile; TBLH=total body less head.

BU-1198

DISCOVER

Spine and Hip BMD at Week 48

Age <25 and ≥25 y



BMD=bone mineral density; SEM=standard error of the mean.
p-values from analysis of variance model including baseline TVD for PrEP and treatment as fixed effects.

BU-542

PrEP is Highly Effective in MSM, Heterosexual Men and Women

Evidence supporting CDC PrEP Guidance[1]

- Case-control study of Partners PrEP[2]
  - Risk reduction in participants with detectable plasma TFV for the visit at which HIV was diagnosed was 90%
- Gender-specific case-control study of Partners PrEP[3]
  - Risk reduction for participants taking Truvada with detectable TFV levels:

    All: 92%

    Men: 89%

    Women: 94%
- Both the original analysis and the gender-specific sub-analysis concluded that PrEP was similarly effective in men and women

1. https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html
2. Baeten et al. N Engl J Med. 2012 Aug 2;367(5):399-410
3. Donnell et al. J Acquir Immune Defic Syndr. 2014 Jul 1;66(3):340-8

PrEP Efficacy in Women: HPTN 082

400 women aged 16–25 years

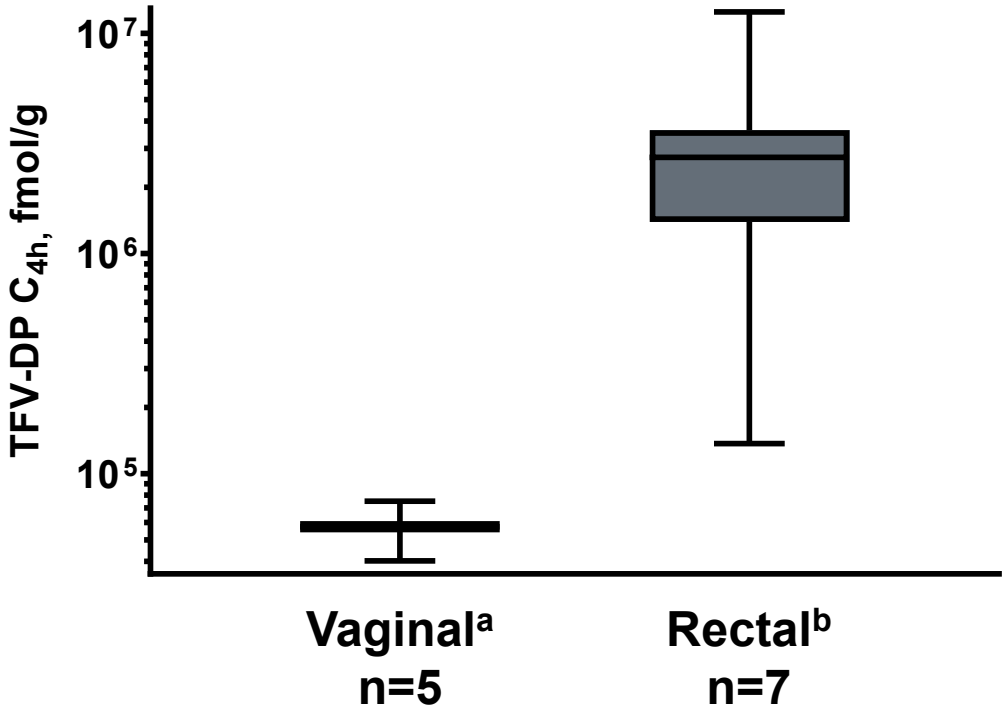
- South Africa and Zimbabwe
- HIV incidence = 1.0 per 100 PY (95% CI 0.3, 2.5)

Adherence, DBS	HIV Infections n=4
≥4 doses/wk	0
2–3 doses/wk	0
<2 doses/wk	2
BLQ TFV-DP	2

BLQ=below the level of quantitation; CI=confidence interval; DBS=dried blood spot; PY=person-years; TFV-DP=tenofovir diphosphate.

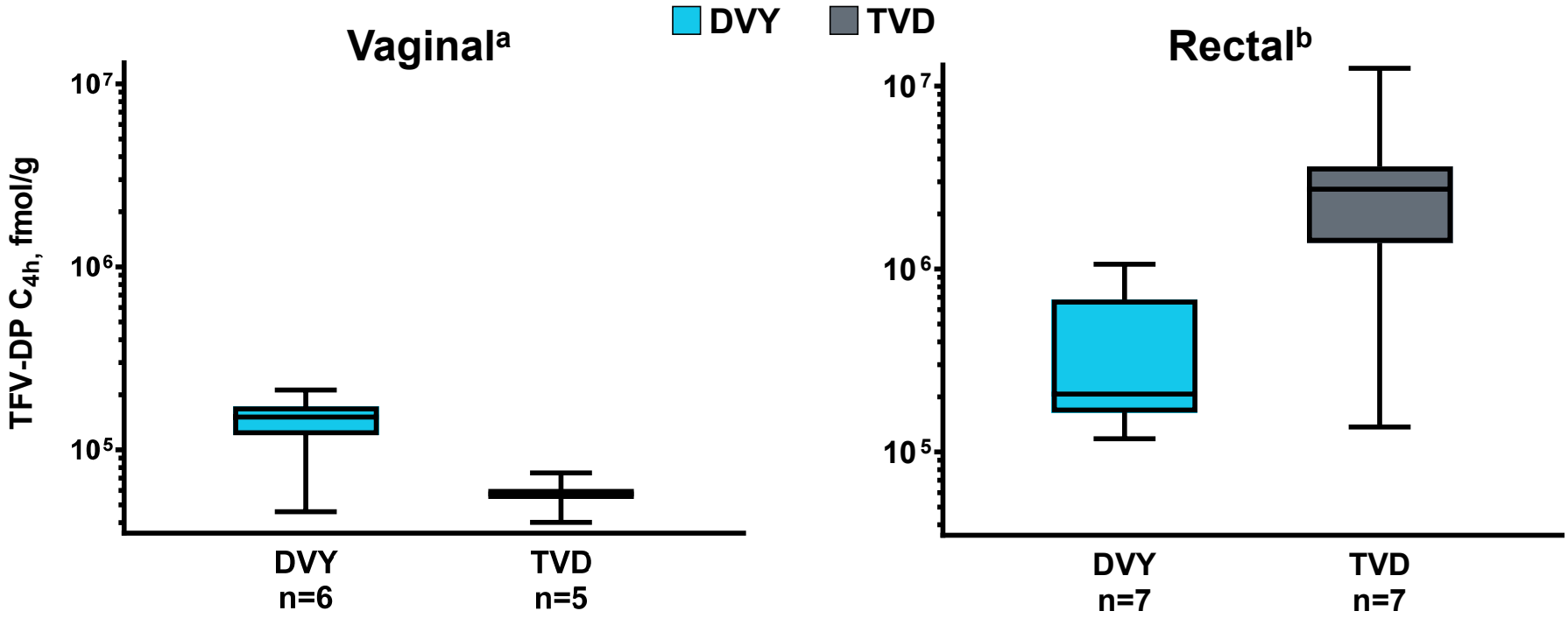
1. Celum C et al. IAS 2019; 21-24 July 2019, Mexico City, Mexico.

TFV-DP in Vaginal and Rectal Tissue With Truvada



C_{4h}=concentration at 4 h; IQR=interquartile range; TFV-DP=tenofovir diphosphate. Boxes depict median (IQR); whiskers depict min, max.
a. 1 vaginal sample collected 4h postdose; 40% TVD samples quantifiable in vaginal tissues.
b. 4 different rectal samples collected for each participant 4h postdose; 96% TVD samples quantifiable in rectal tissues.
Schwartz JL, et al. HIV Research for Prevention 2018, updated unpublished data.

TFV-DP in Vaginal and Rectal Tissue: C_{4h}



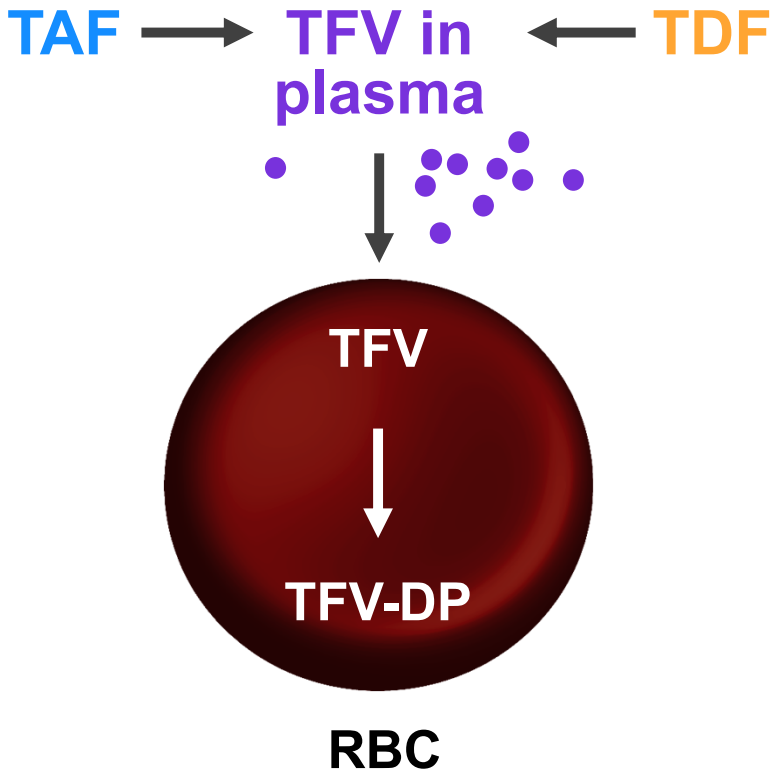
C_{4h}=concentration at 4 h; IQR=interquartile range; TFV-DP=tenofovir diphosphate. Boxes depict median (IQR); whiskers depict min, max.

a. 1 vaginal sample collected 4h postdose; 100% DVY samples quantifiable; 40% TVD samples quantifiable in vaginal tissues.

b. 4 different rectal samples collected for each participant 4h postdose; 71% DVY samples quantifiable; 96% TVD samples quantifiable in rectal tissues.

Schwartz JL, et al. HIV Research for Prevention 2018, updated unpublished data

TFV-DP is an Adherence Biomarker in DBS



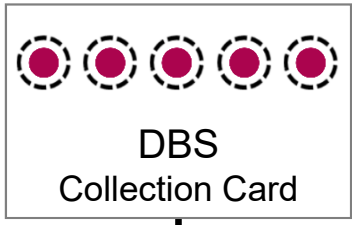
TFV-DP Half Life in RBC ~17–20 days

- DBS provides an objective measure of average adherence during the prior ~8 weeks

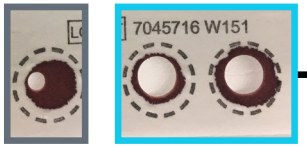
DBS=dried blood spot; RBC=red blood cell; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; TFV-DP=tenofovir diphosphate.

Bushman LR, et al. J Pharm Biomed Anal. 2011;56:390-401; Durand-Gasselin L, et al. AAC 2007;51:2105-11; Castillo-Mancilla, J. 2012 AHRH.

Determination of TFV-DP Level and Adherence by DBS



Sample punches



TVD 3 mm

DVY 2 x 7 mm

Analysis LC-MS/MS

TFV-DP level fmol/punches

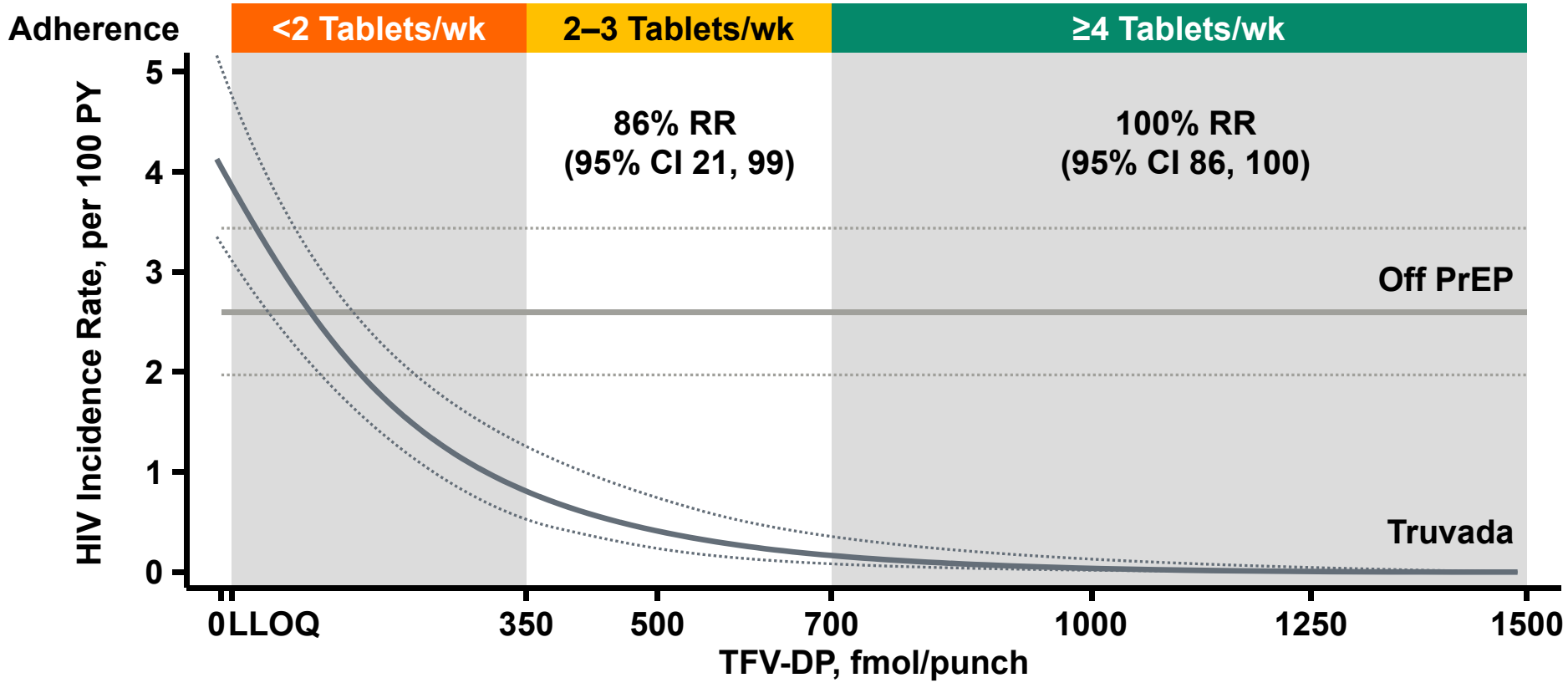
Directly observed dosing studies

Interpretation	DBS TFV-DP, fmol/punch(es) DVY	TVD
≥4 doses/wk	900	700
2–3 doses/wk	450–899	350–699
<2 doses/wk	<450	<350

DBS=dried blood spot; LC-MS/MS=liquid chromatography–tandem mass spectrometry; RBC=red blood cell; TFV-DP=tenofovir-diphosphate.

Zheng JH, et al. J Pharm Biomed Anal 2016;122:16-20. Castillo-Mancilla JR. AIDS Res Hum Retroviruses. 2013 Feb;29(2):384-90. Anderson PL. Antimicrob Agents Chemother. 2018.; Yager J. Abstract 0463. 2019 CROI.

iPrEx OLE: DBS Thresholds and HIV Risk Reduction With Truvada



CI=confidence interval; DBS=dried blood spot; LLOQ=lower limit of quantitation; PY=person-year; RR=risk reduction; TFV-DP=tenofovir diphosphate.

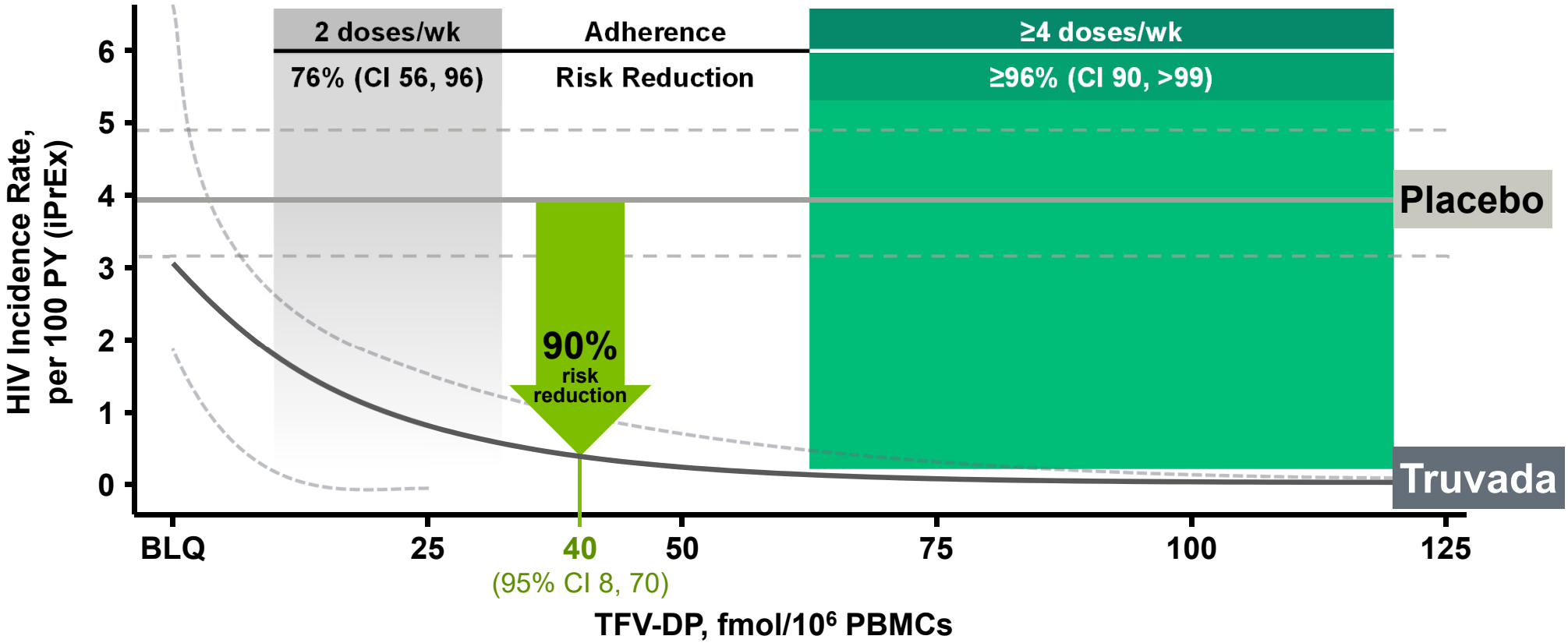
Grant RM, et al. Lancet Infect Dis. 2014;14:820–9.

BU-461

NON-DISCOVER

PBMC TFV-DP Levels and Protection From HIV With Truvada

EC_{90} Established From iPrEx Case-Control; Dosing from STRAND



CI=confidence interval; EC_{90}=90% effective concentration; PBMC=peripheral blood mononuclear cell; PY=person-year; TFV-DP=tenofovir-diphosphate.

1. Figure adapted from Anderson PL, et al. Sci Transl Med 2012;4:151ra125; 2. Anderson PL, et al. CROI 2012.

BU-727

Vaginal TFV-DP Tissue Levels With Descovy and Truvada

- Descovy and Truvada achieve comparable TFV-DP levels in vaginal tissue:
  - Single dose Descovy and Truvada cross-study comparison
  - Single dose Descovy and Truvada within-study comparison
  - Multiple dose Descovy and Truvada within-study comparison

TFV-DP=tenofovir-diphosphate.

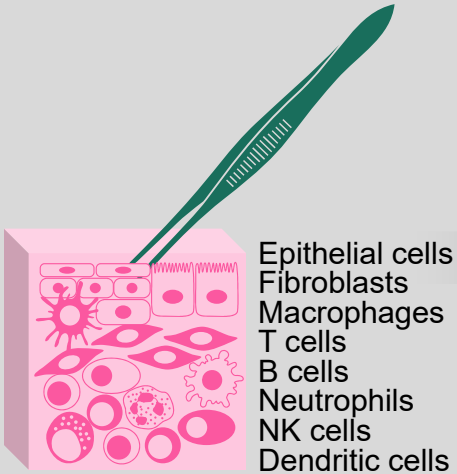
Vaginal TFV-DP Tissue Levels With Descovy and Truvada

	PK Parameter	TVD	DVY	Interpretation
Single dose[1]	$AUC_{0\text{-}48h}$[a]	170,674	132,098	1.3[1] to 1.8-fold[2] lower with DVY
Single dose[3]	C_{4h}[b]	100% BLQ	69% BLQ	Multiple dose data needed
Multiple dose[3]	C_{4h}[b]	57,450	151,000	2.6-fold higher with DVY
	C_{24h}[b]	69% BLQ	80% BLQ	Comparable and low levels with DVY and TVD
	C_{48h}[b]	75% BLQ	80% BLQ	

$AUC_{0\text{-}48h}$=area under curve from time 0 to 48 h; C_{Xh}=concentration at X h; BLQ=below limit of quantification; TFV-DP=tenofovir-diphosphate.
a. h·fmol/g; b. fmol/g.
1. n=8; Cottrell M, et al. HIVR4P 2014, abstr OA22.06 LB; 2. Cottrell M, et al. J Infect Dis 2016;214:55-64; Cottrell M, et al. J Antimicrob Chemother 2017;72:1731-40; 3. n=11–13 per group for single dose; n=5–7 per group for multiple dose; Schwartz JL, et al. HIVR4P 2018, updated unpublished data.

Methods to Measure TFV-DP Levels in Tissue

Tissue Sampling

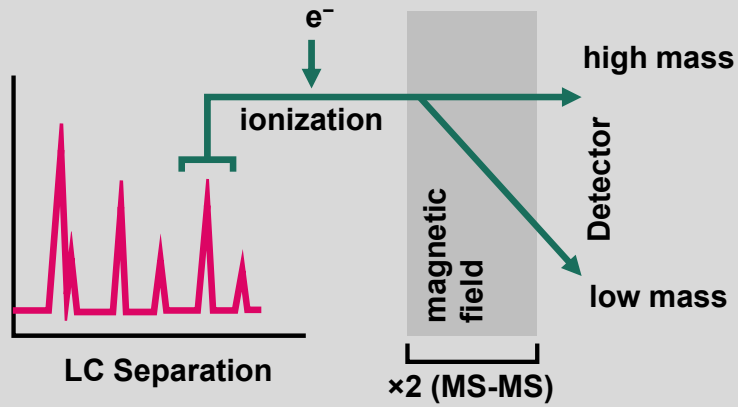


Colonic or vaginal tissue collected using pinch biopsy forceps

Homogenization of Tissue

Biopsies incubated with enzymes to break up cells and tissue

TFV-DP Analysis



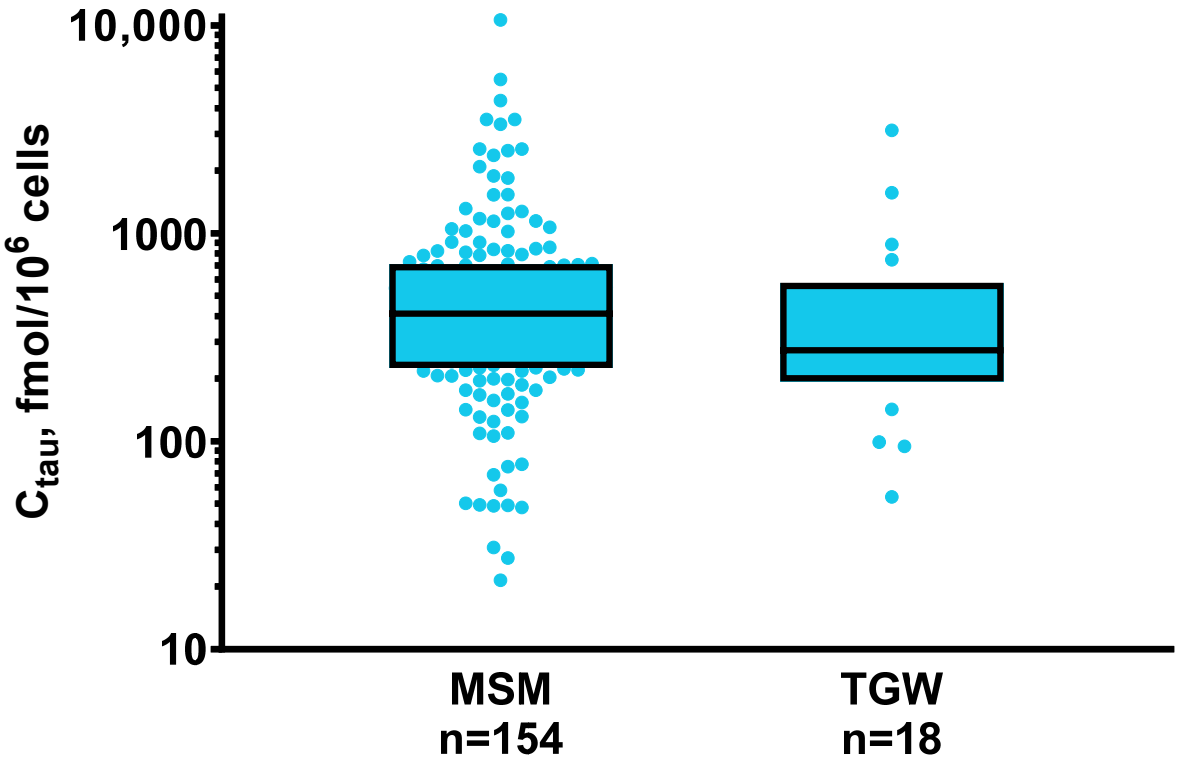
TFV-DP, TFV-MP and TFV present in cell lysates analyzed with a LC-MS/MS mass spectrometer

LC-MS/MS=liquid chromatography-tandem mass spectrometry; NK=natural killer; TFV-D/MP=tenofovir di/monophosphate.

Louissaint NA, et al. AIDS Res Hum Retroviruses 2013;29:1443-50.

TFV-DP in PBMCs in MSM and TGW on High-dose Hormones

Descovy



C_{tau}=trough concentration; MSM=men who have sex with men; PBMC=peripheral blood mononuclear cell; Q=quartile; TFV-DP=tenofovir-diphosphate; TGW=transgender women.
Boxes depict median (Q2, Q3); circles depict individual data in Q1, Q4.

DISCOVER

Condomless Insertive Anal Intercourse Partners

Number in the 90 Days Prior to Screening

	DVY n=2602	TVD n=2597	Total n=5199
Mean (SD)	4 (6.8)	4 (7.3)	4 (7.0)
Median (Q1, Q3)	2 (1, 5)	2 (1, 4)	2 (1, 5)
Partners, n (%)			
0	495 (19)	534 (21)	1029 (20)
1	455 (17)	453 (17)	908 (17)
2	490 (19)	489 (19)	979 (19)
3	325 (12)	315 (12)	640 (12)
4–5	305 (12)	315 (12)	620 (12)
6–10	320 (12)	294 (11)	614 (12)
≥11	212 (8)	197 (8)	409 (8)
Missing	92	96	188

Q=quartile; SD=standard deviation.
Missing categories were excluded from % calculation; CASI questionnaires from screening visit.

NON-DISCOVER

Women's Study Sample Size Calculations in US and High-Incidence Settings

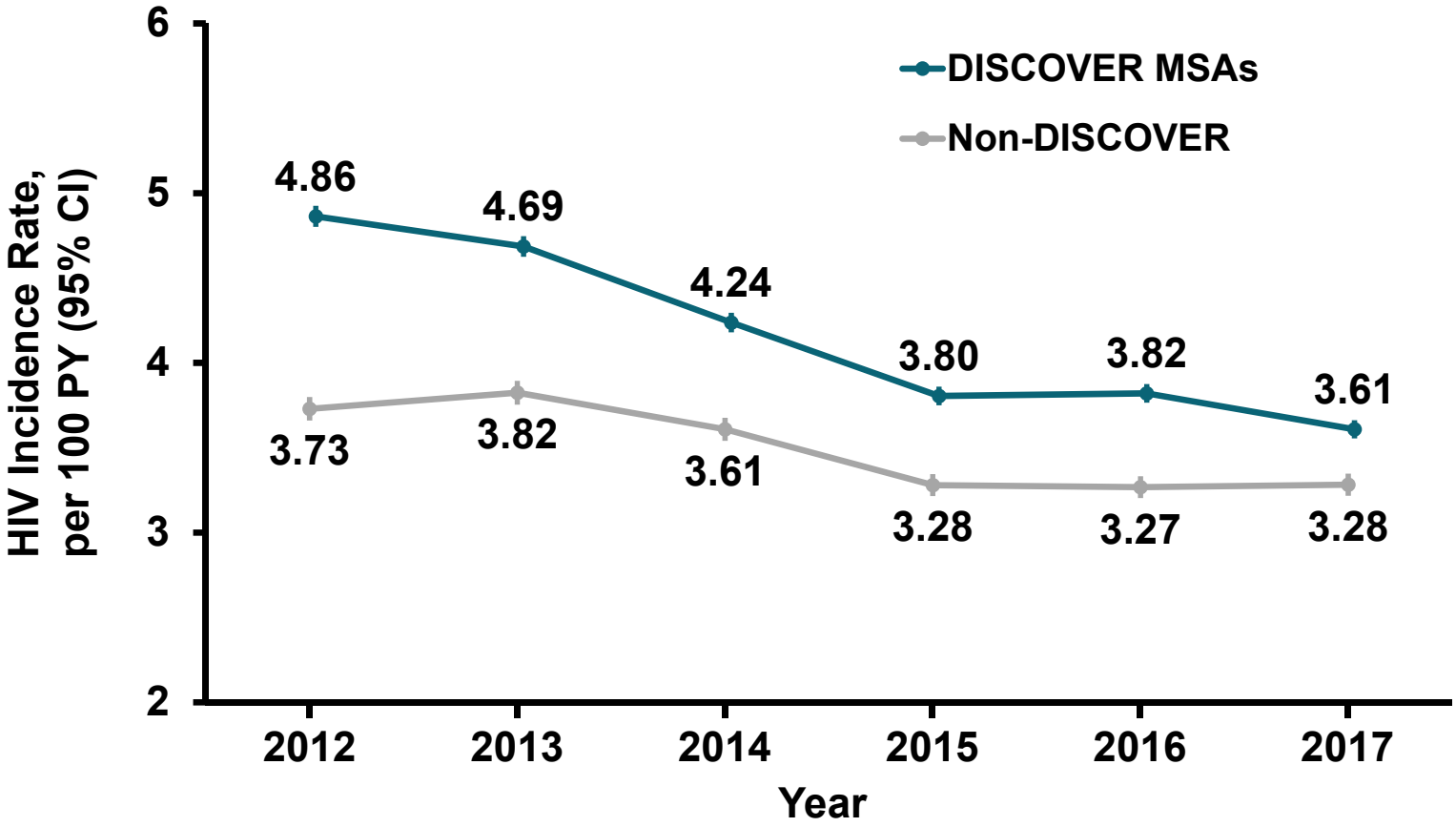
	Randomized, Placebo-Controlled Studies in Women				
Study	**VOICE**	**Fem-PrEP**	**TDF2**	**Partners PrEP**	**Bangkok Tenofovir Study**
HR (TVD/PBO)	1.04	0.94	0.506	0.34	0.214

- US: incidence in high risk women =0.32/100 PY
- Africa: incidence in high risk women in 2019= 4/100 PY
- Based on Partners PrEP and Bangkok Tenofovir Study, NI margin=1.27 (to preserve 50% effect)

	TVD Incidence rate, per 100 PY	**IRR, DVY to TVD**	**Test**	**Power**	**N**
US women	0.10	1	Noninferiority test, margin 1.27	80%	275,000
African women High-incidence	1.25	1	Noninferiority test, margin 1.27	80%	22,000

IDU=injecting drug users; IRR=incidence rate ratio; MSM=men who have sex with men; PY=person-year; RR=rate ratio.

Estimated Placebo Rate for New HIV Cases by Site

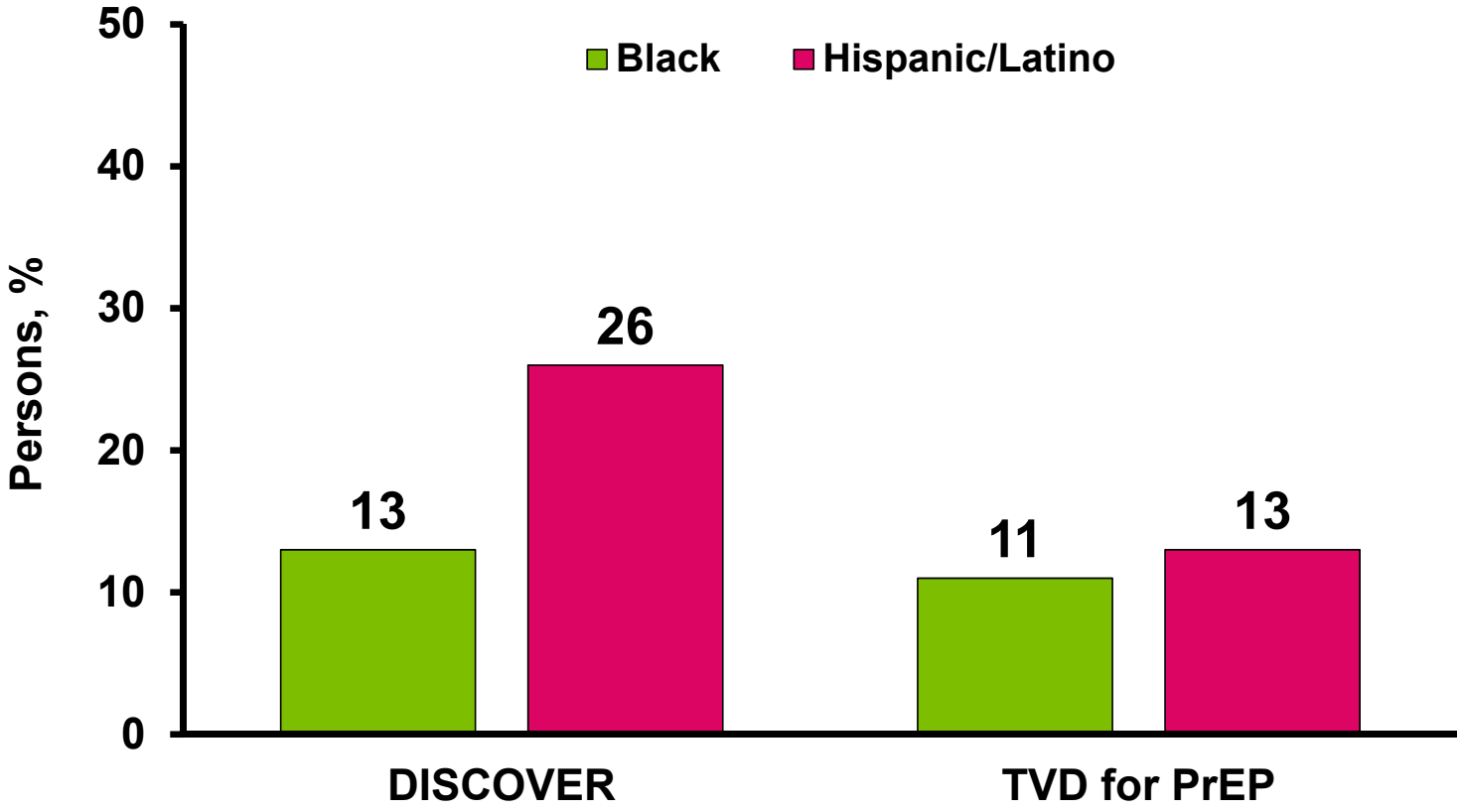


CI=confidence interval; MSA=metropolitan statistical area; PY=person-years.
CDC-defined persons with an indication for PrEP use (Smith Ann Epidemiol 2018); Mera JIAS 2019, under review.

BU-581

DISCOVER Study and Truvada for PrEP Use

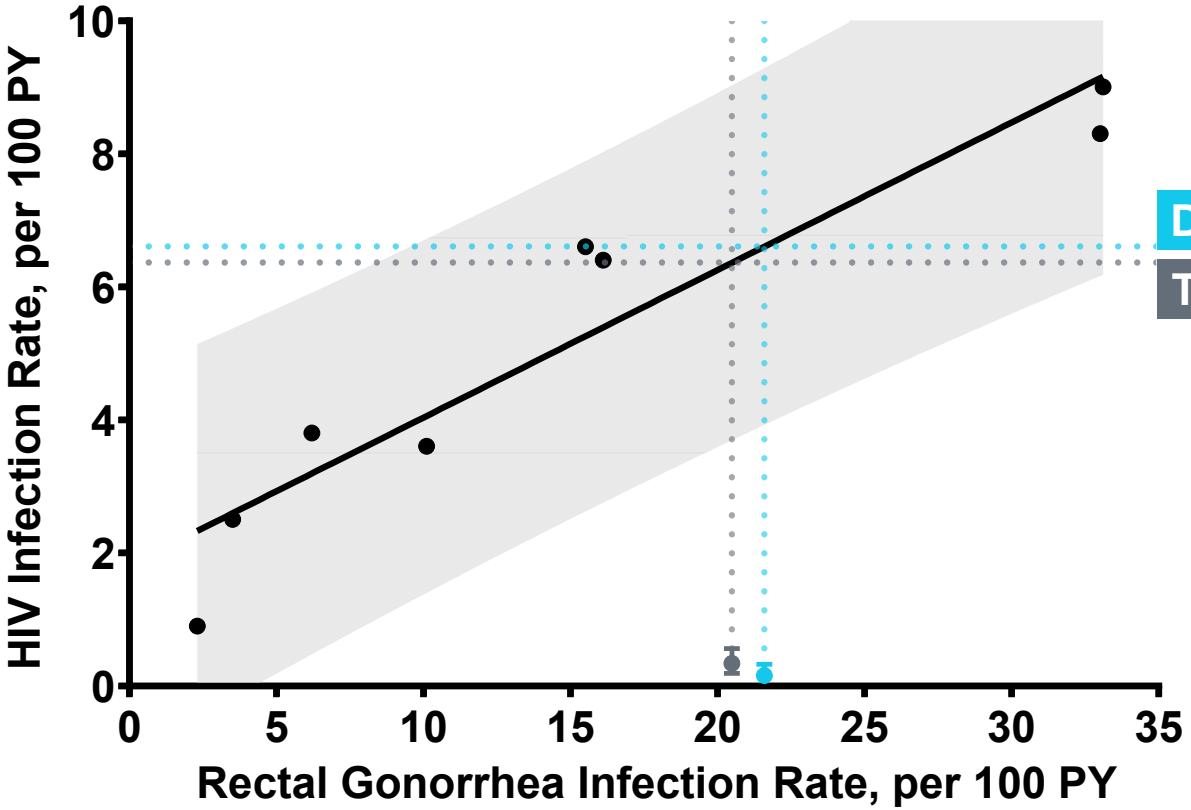
US Race and Ethnicity



CDC 2014-2016, Huang YA, et al. MMWR 2018;67:1147-50.

BU-1205

HIV Incidence Predicted by Rectal Gonorrhea Rate



DVY=6.61 **HIV infection rate**
TVD=6.36 **predicted by RG rate**

- Mullick and Murray[1] analyzed MSM RG incidence and HIV incidence in several cohort studies (not on PrEP), concluded that the observed RG rate could be used to predict the expected HIV incidence rate in PrEP studies

MSM=men who have sex with men; PY=person-year; RG=rectal gonorrhea.

1. Mullick C and Murray J. J Infect Dis 2019 Jan 3.

Observed Rates Compared to Historic Rates

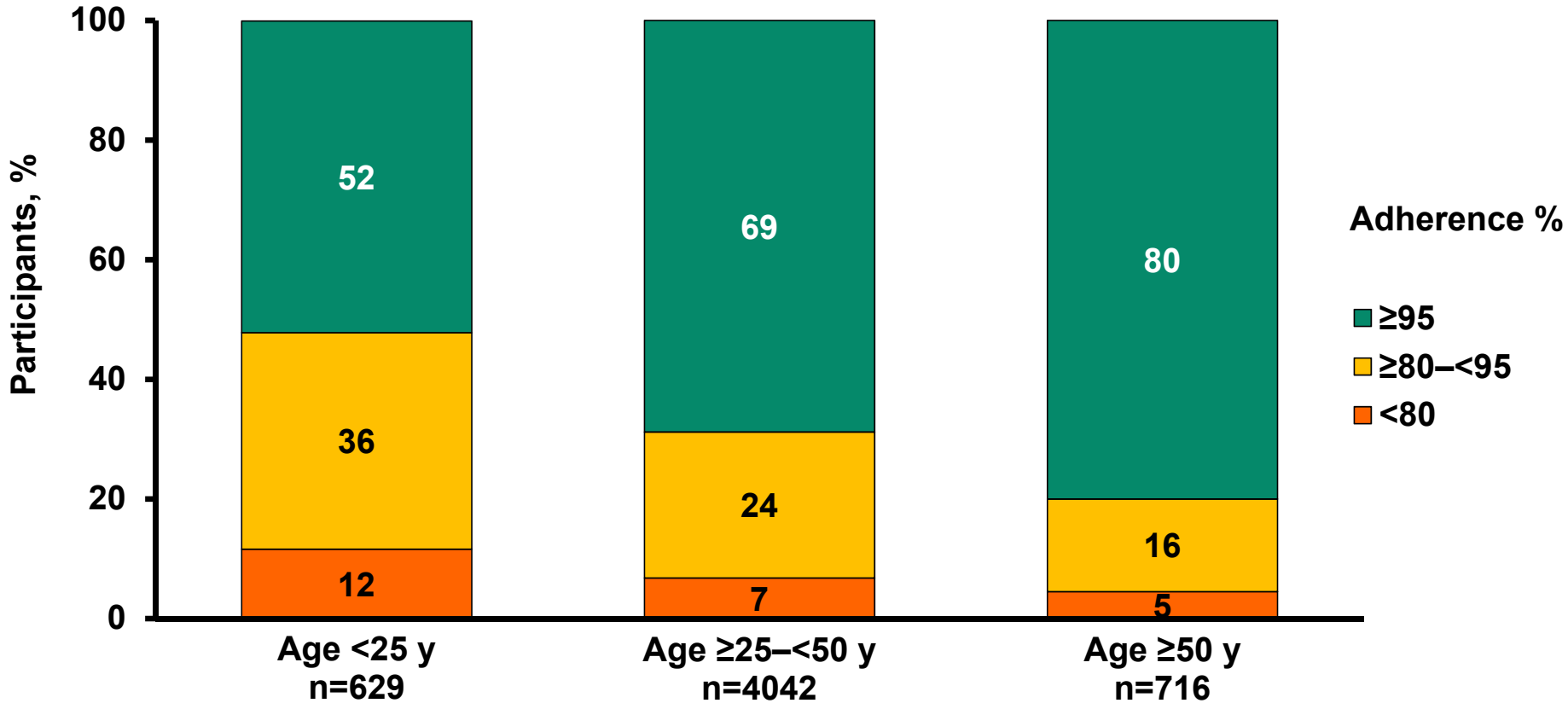
- Primary analysis: the observed incidence rate ratio=0.47 (95% CI 0.19, 1.15)

Setting	Source	HIV Incidence Rate, per 100 PY	Incidence Rate Ratio
Protocol (2016)	3 reference CTs: iPrEX (URAI)[1], PROUD[2], IPERGAY[3]	PBO=6.96	5.1
		TVD=1.44	
Epi (CDC) & DISCOVER	Mera et al (2019)[4]	PBO=3.83	8.6
	DISCOVER study (US)	TVD=0.446	
rGC Correlate & DISCOVER	Mullick & Murray (2019)[5]	PBO=6.36	19.0
	DISCOVER study	TVD=0.342	

CI=confidence interval; MSM=men who have sex with men; URAI=Unprotected Receptive Anal Intercourse; rGC=rectal gonorrhea.

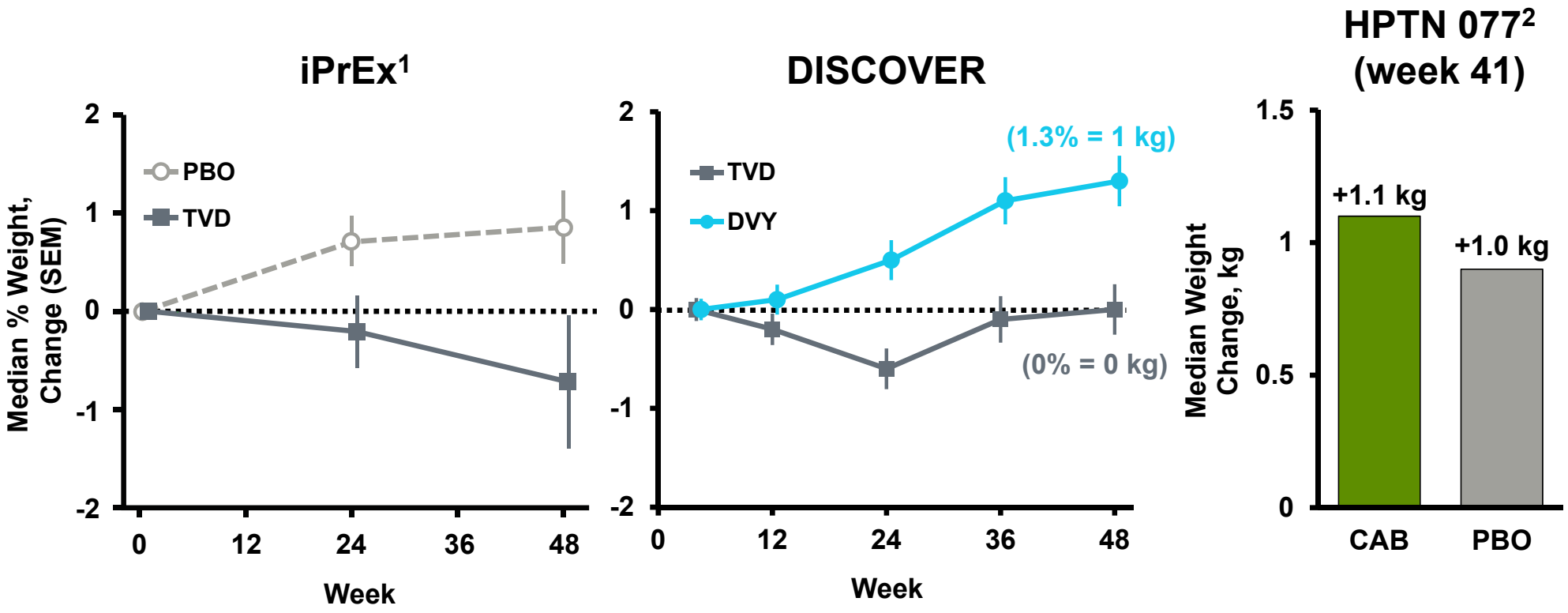
1. Grant RM, et al. N Engl J Med 2010;363:2587-99; 2. McCormack S, et al. Lancet 2016;387:53-60;
3. Molina JM, et al. N Engl J Med 2015;373:2237-46; 4. Mera et al J IAS 2019; 5. Mullick C, Murray J. J Infect Dis 2019.

Adherence by Pill Counts: Age Subgroups



BU-636

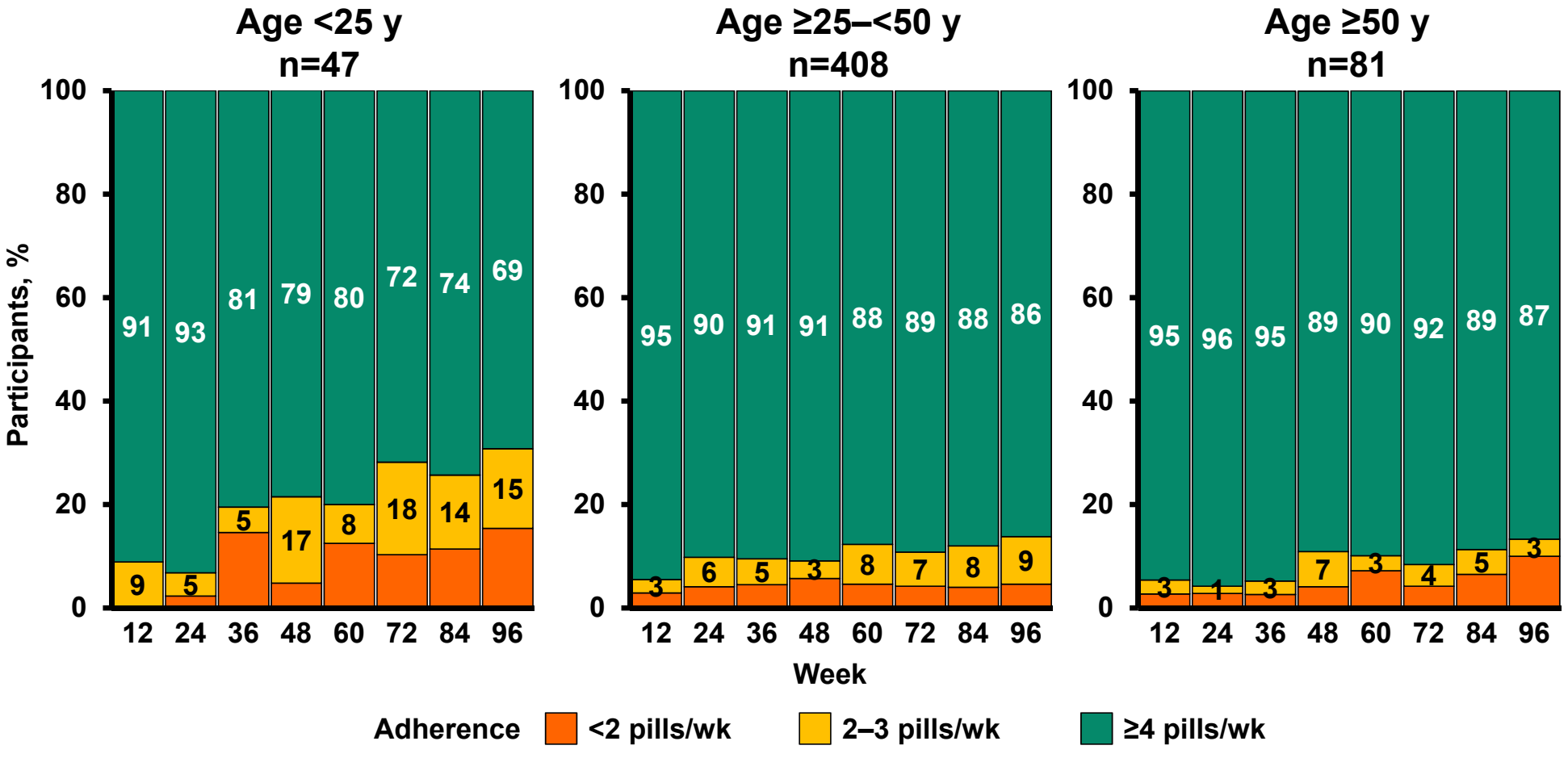
Weight Gain in PrEP Trials



1. Adapted from Glidden DV, et al. Clin Infect Dis 2018;67:411-9. 2. Landovitz RJ, et al. Clin Infect Dis 2019 May 24.

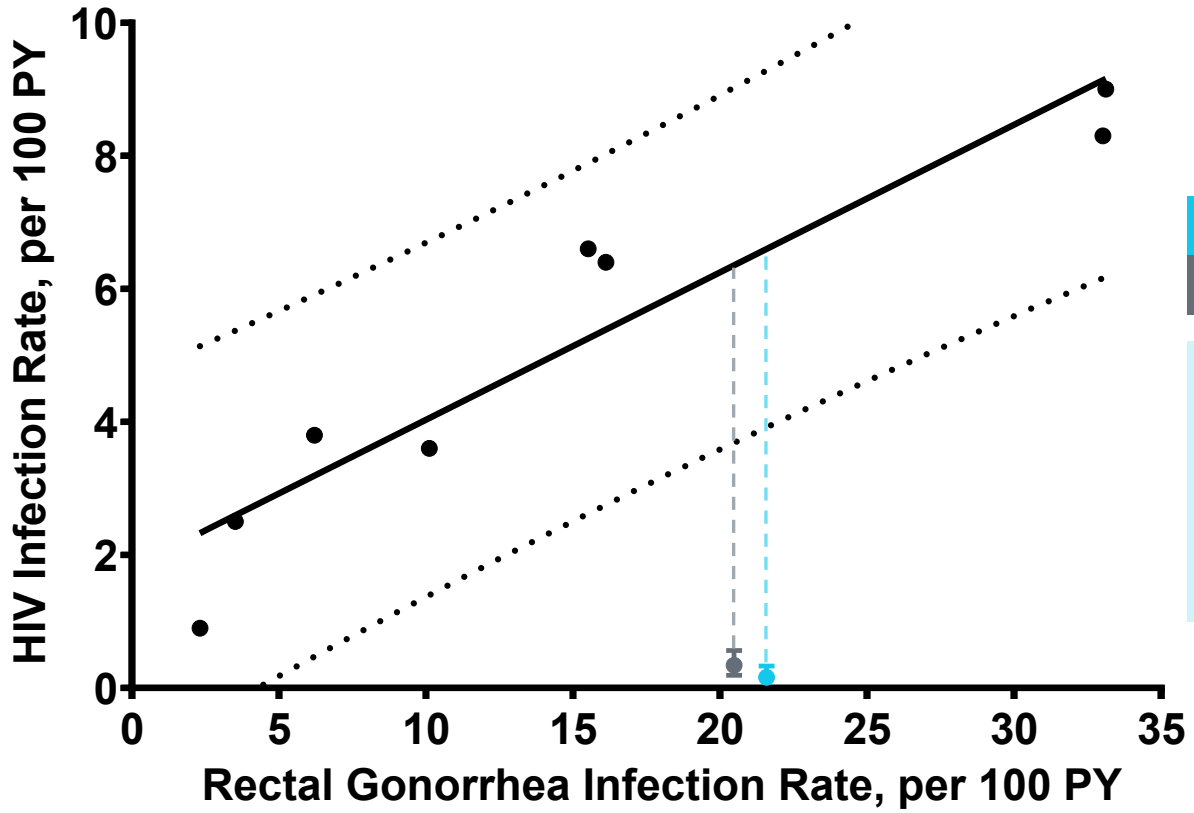
BU-888

Adherence by DBS: Age Subgroups



BU-644

HIV Incidence Predicted by Rectal Gonorrhea Rate



DVY=6.61 **HIV incidence rate predicted by rectal gonorrhea rate**

TVD=6.36

- Mullick and Murray[1] analyzed MSM rectal GC incidence and HIV incidence in 8 cohort studies (not on PrEP)
- Concluded that observed rectal GC rate could be used to predict the expected HIV incidence rate in PrEP studies

CI=confidence interval; GC=gonococcal proctitis; MSM=men who have sex with men; PY=person-years.

1. Mullick C, Murray J. J Infect Dis 2019 Jan 3.