Long-Acting Drugs for PrEP

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HIV Prevention: The promise of injections

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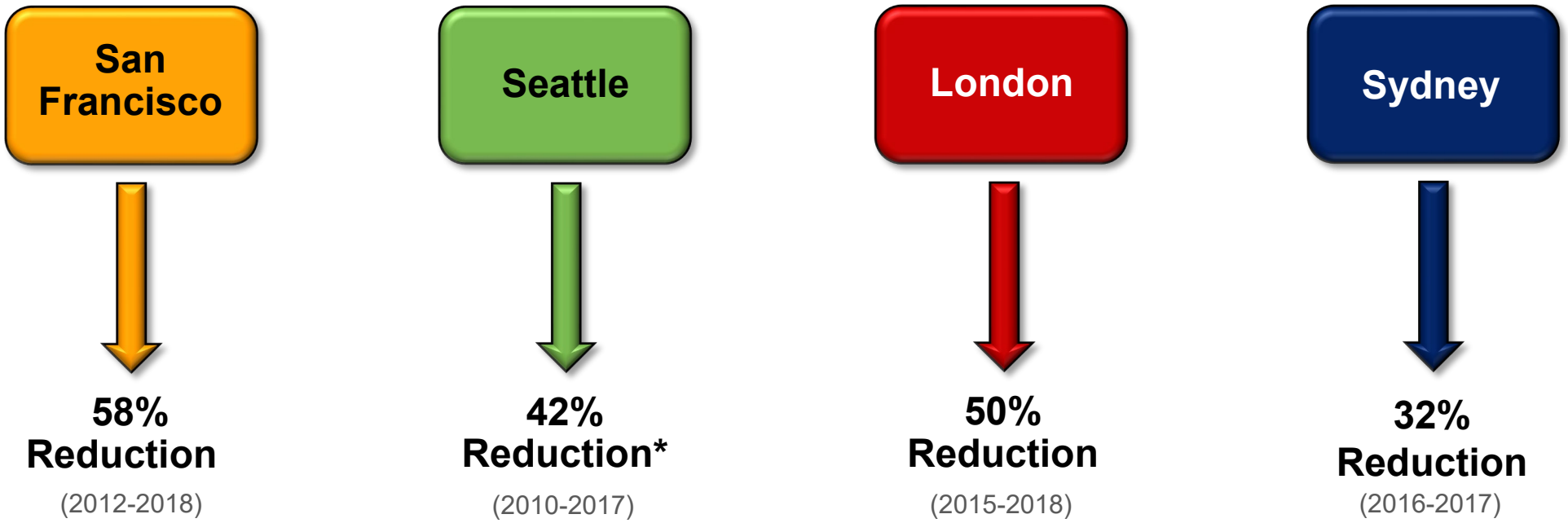
Disclosures

- Gilead Sciences
  - Research grant, honoraria and speakers bureau

- ViiV Healthcare
  - Research grants, honoraria and speakers bureau

The Power of Targeted PrEP Implementation

Scaling Up PrEP Access in Major Cities Has Resulted in Population-Level Reductions in HIV Risk, among PrEP Users and Non-Users Combined

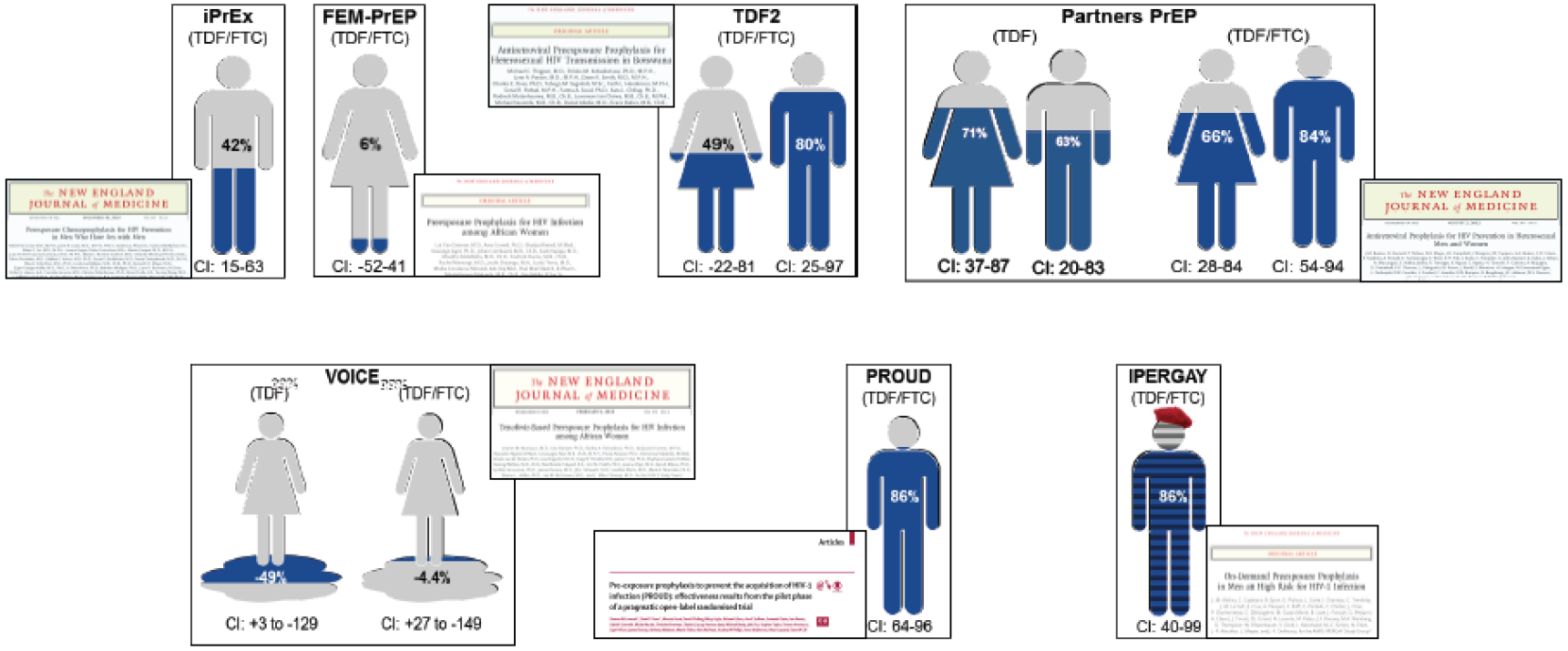


*In 2018, King County experienced its largest 1-year increase in the number of new HIV diagnoses since 2002 (218 cases in 2018 versus 162 in 2017). This increase was driven by a 400% increase in the number of new HIV diagnoses among PWIDs, while the number of new diagnoses in persons with other risks (MSM, non-PWID) remained stable.

Buchbinder SP, et al. *J Acquir Immune Defic Syndr*. 2019;82(suppl 3):S176-S182.
Seattle & King County and the Infectious Disease Assessment Unit. HIV/AIDS Epidemiology Report 2019, Volume 88.
Public Health England. Health Protection Report. 2019;13(31).
Grulich A, et al. *Lancet HIV*. 2018;5:e629-e637.

Previous data on prevention by gender

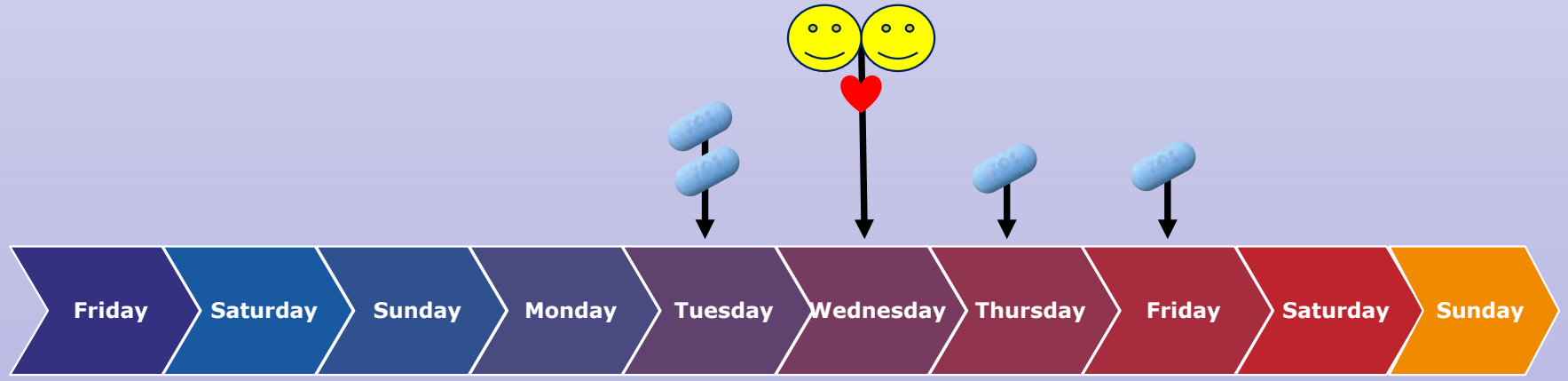
Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials



Landovitz RJ et al. AIDS 2020, #OAXLB01

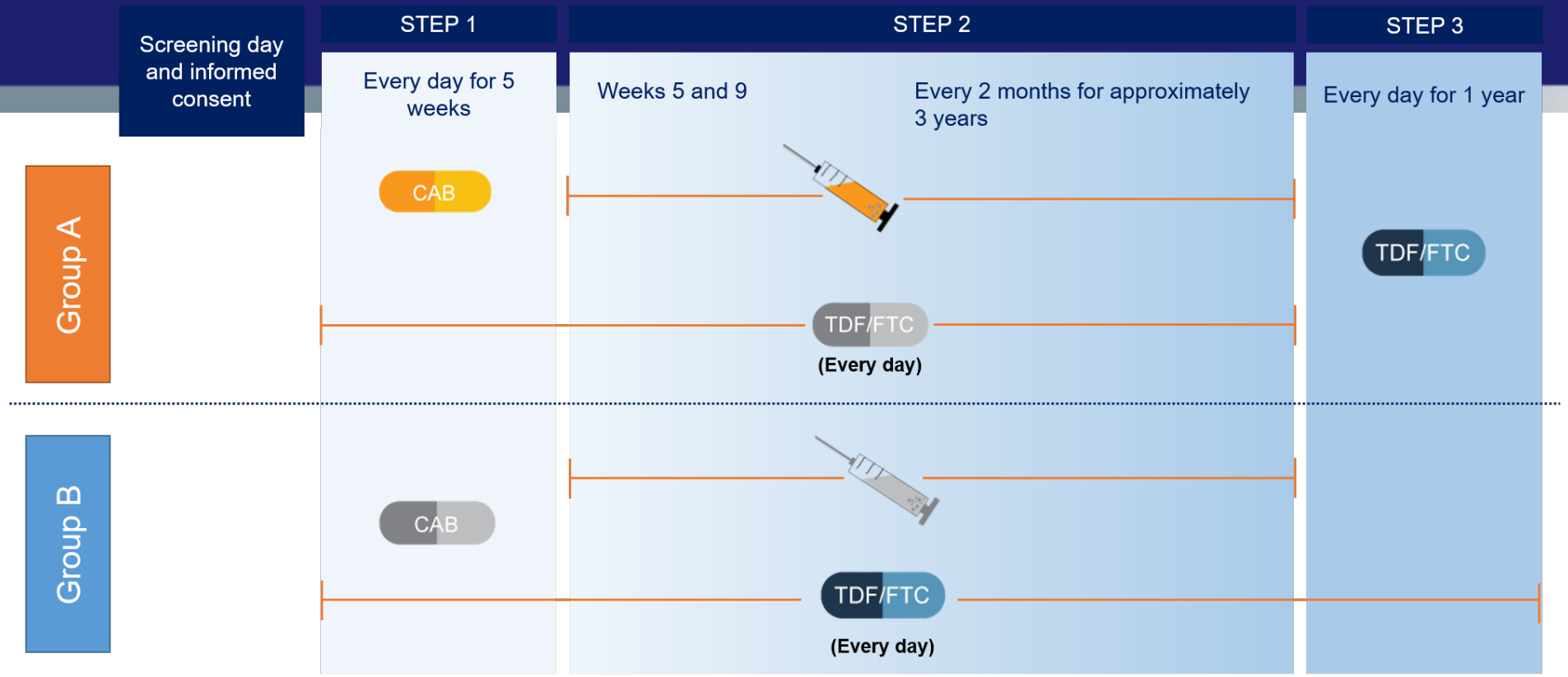
IPERGAY: Sex-Driven iPrEP

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



4 pills of TDF/FTC taken over 3 days to cover one sexual encounter

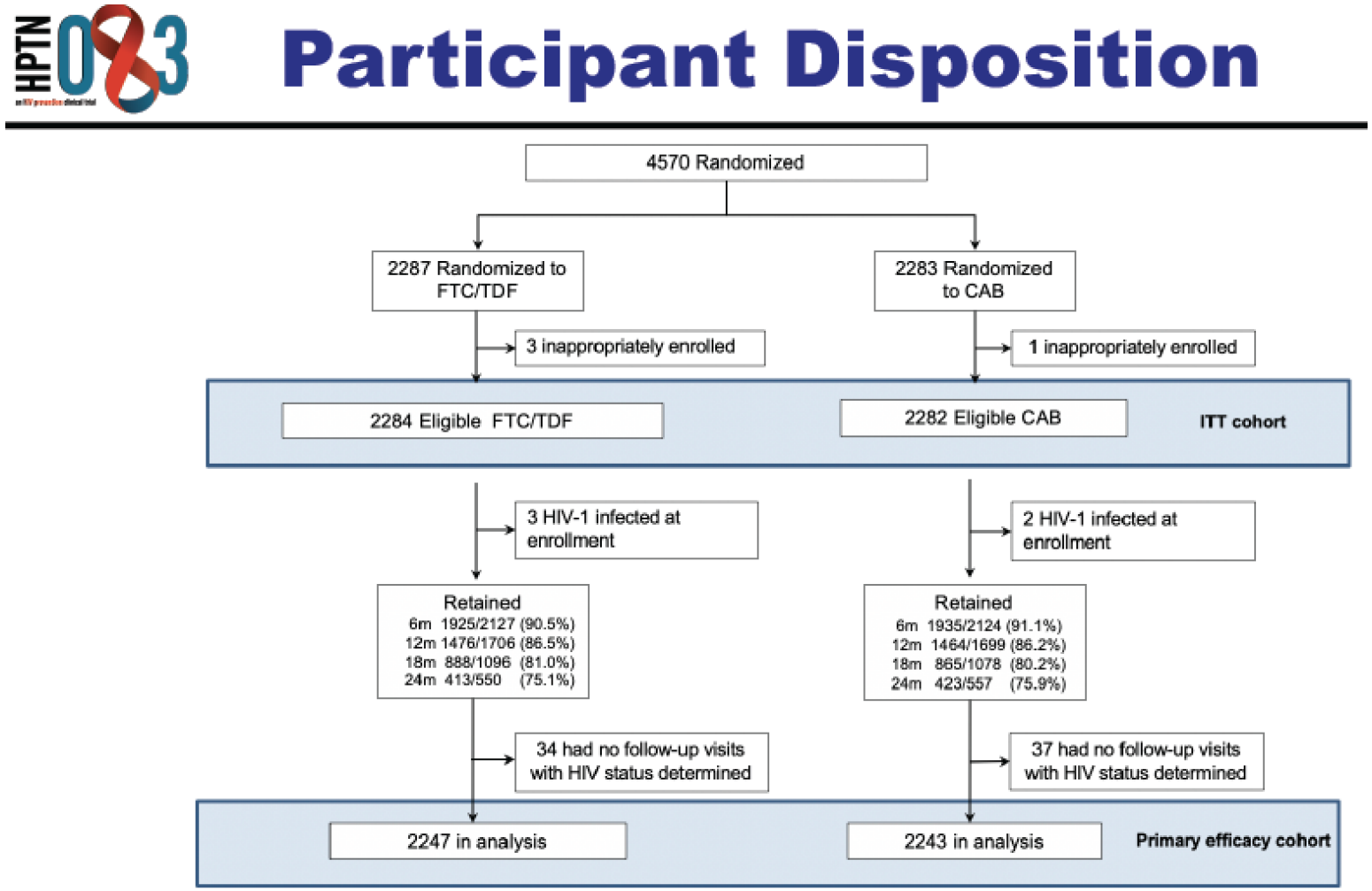
HPTN 083 Study Design



HPTN
HIV Prevention Trials Network

083

Participants Flow Diagram



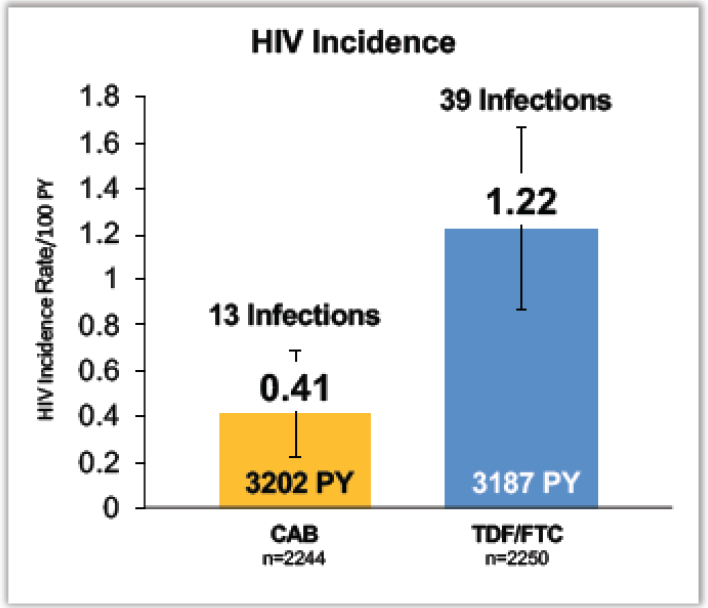
Study Population

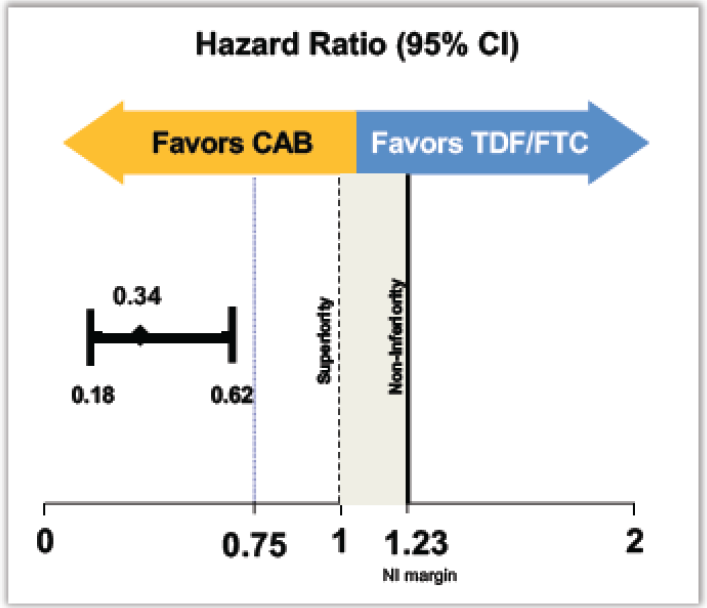
- 4565 cisgender-MSM and TGW who have sex with men were included in the analysis
  - Average age 28 years
  - 66% under the age of 30
  - 40% under the age of 25
  - 12% TGW enrollment
  - 50% African American or Black enrolled in the US

HIV Incidence: CAB vs TDF/FTC

HIV Incidence
CAB vs. TDF/FTC

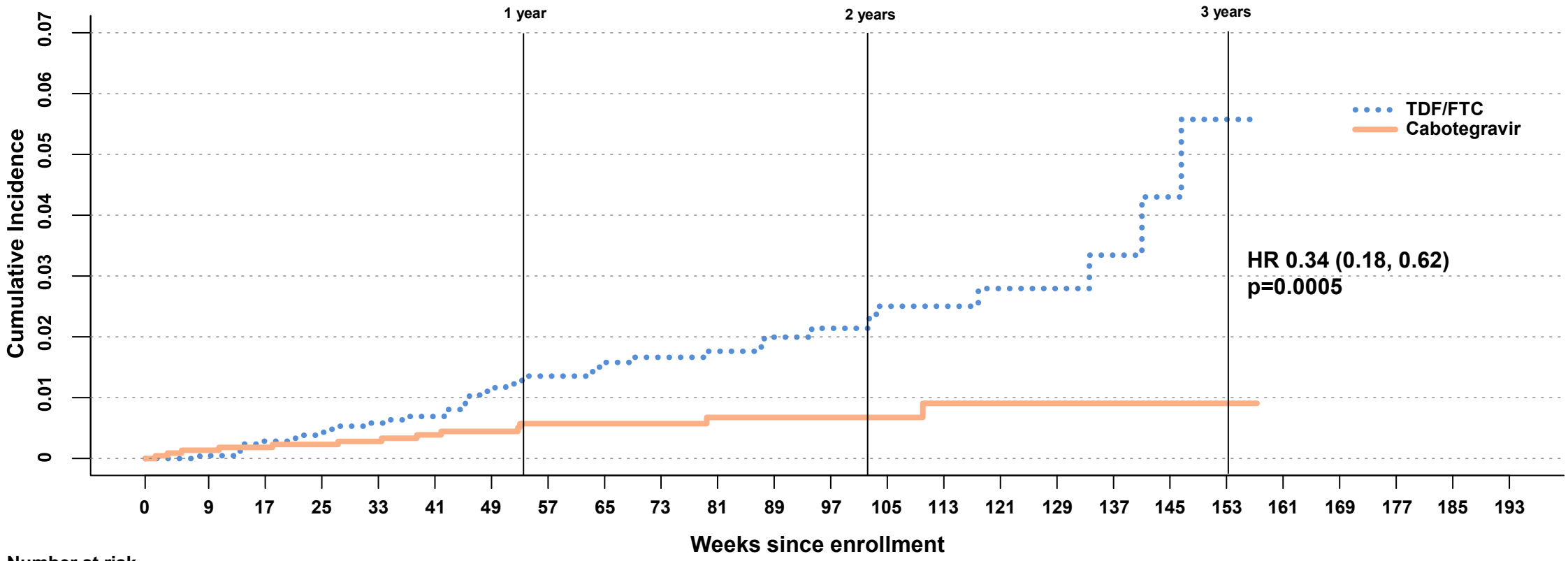
52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY





CI, confidence interval

HIV Incidence – ITT



Number at risk

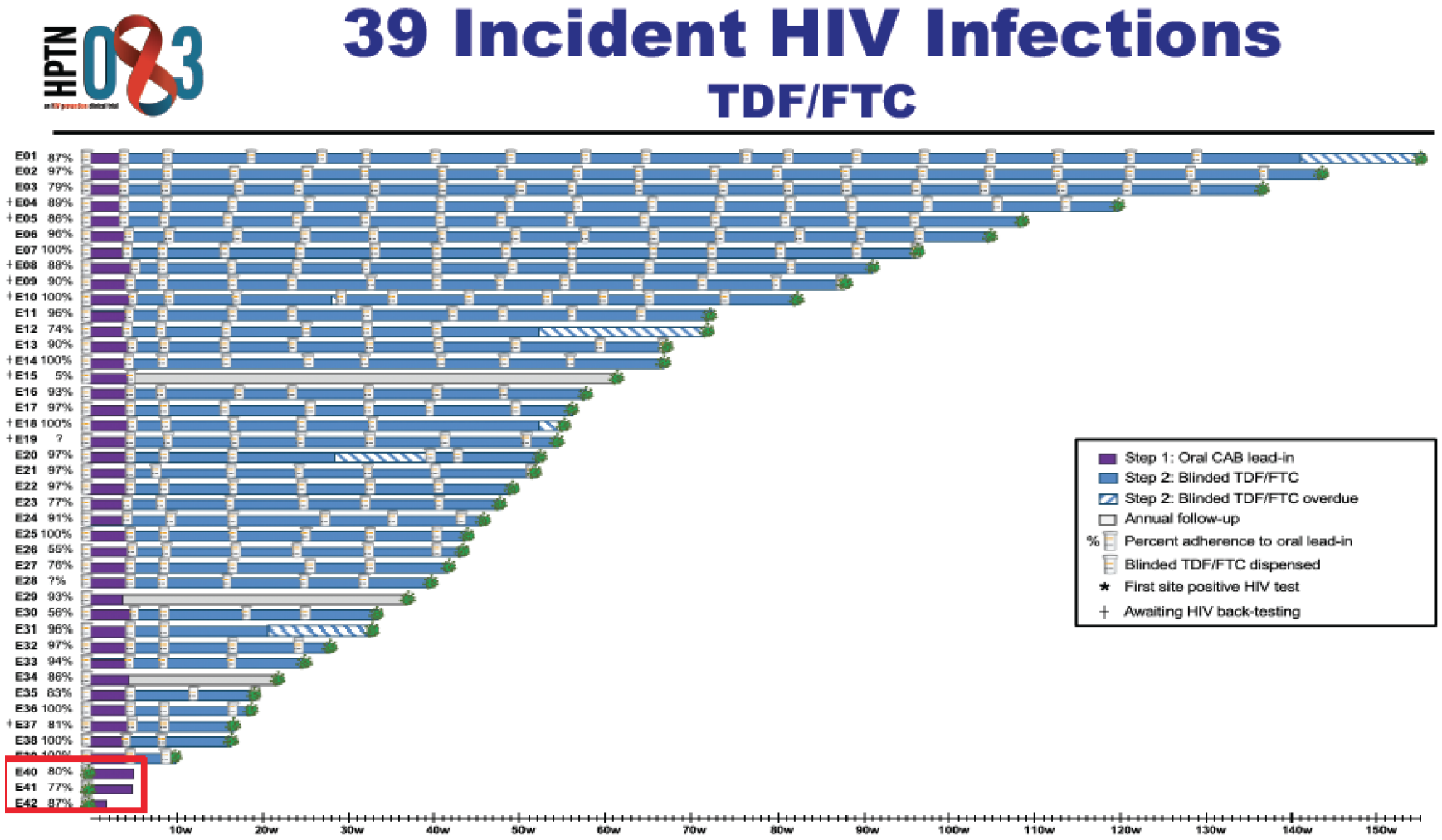
TDF/FTC	2247	2133	2081	2019	1913	1764	1624	1494	1294	1132	965	816	643	516	400	310	230	149	85	33	0	0	0	0	0
Cabotegravir	2243	2138	2092	2032	1921	1776	1632	1488	1312	1119	957	795	644	503	401	318	243	172	111	42	0	0	0	0	0

Cumulative number of events

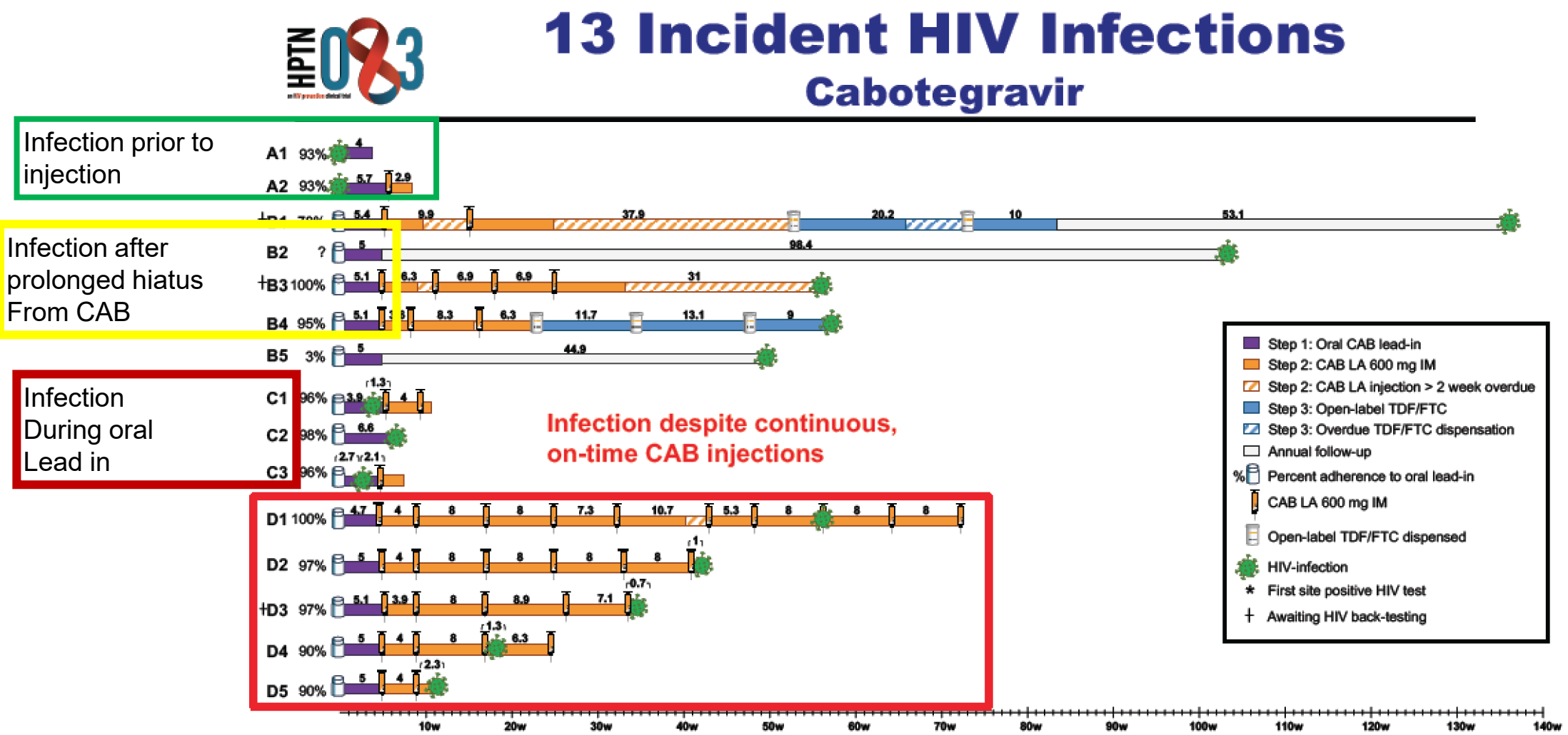
TDF/FTC	0	1	6	8	12	14	22	25	27	29	30	32	33	35	35	36	36	37	38	39	0	0	0	0	0
Cabotegravir	0	3	4	5	6	8	9	11	11	11	12	12	12	12	13	13	13	13	13	13	0	0	0	0	0

Landovitz RJ et al. AIDS 2020, #OAXLB01

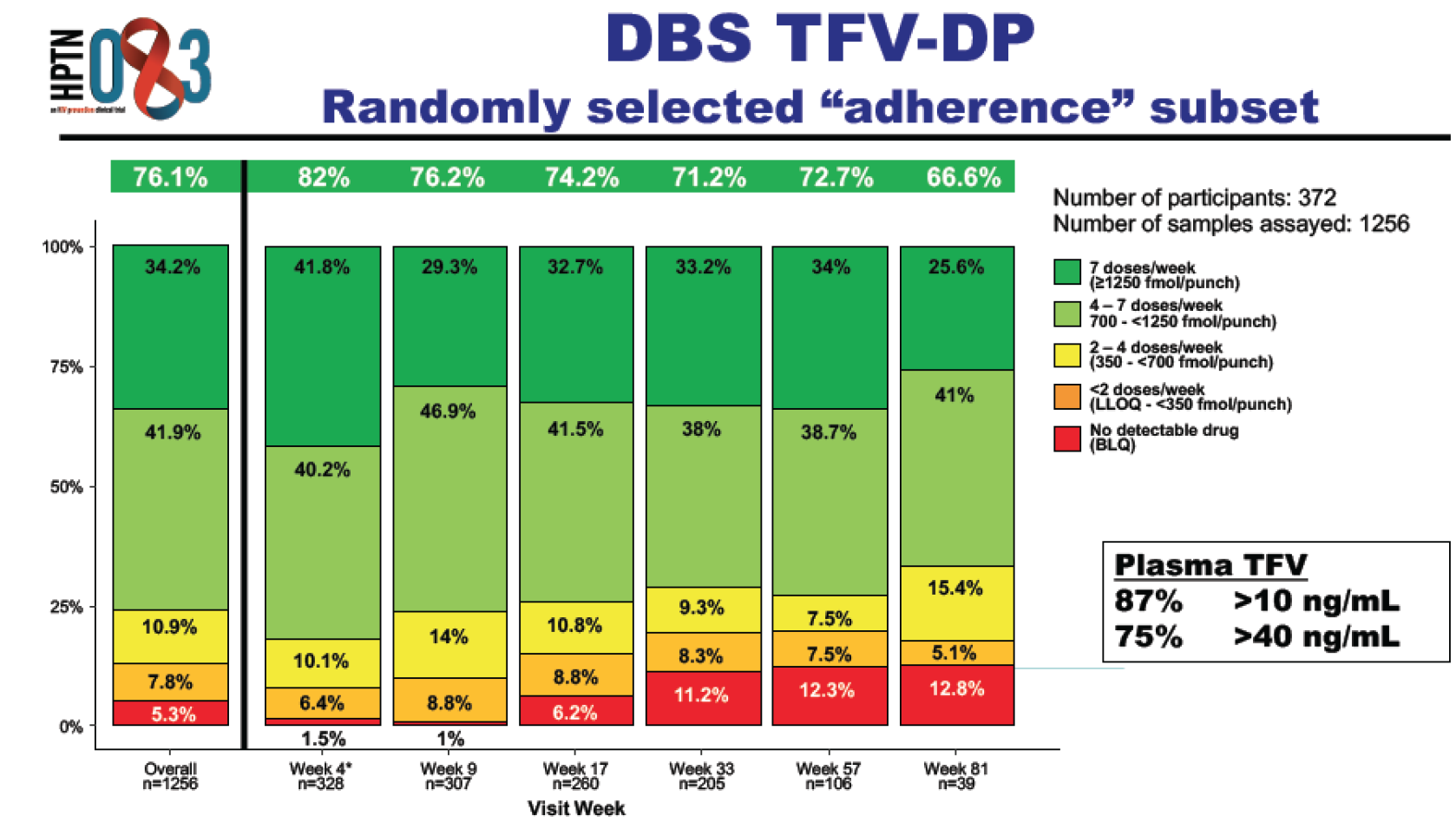
HIV infections on TDF/FTC



Analysis of HIV prevention failures



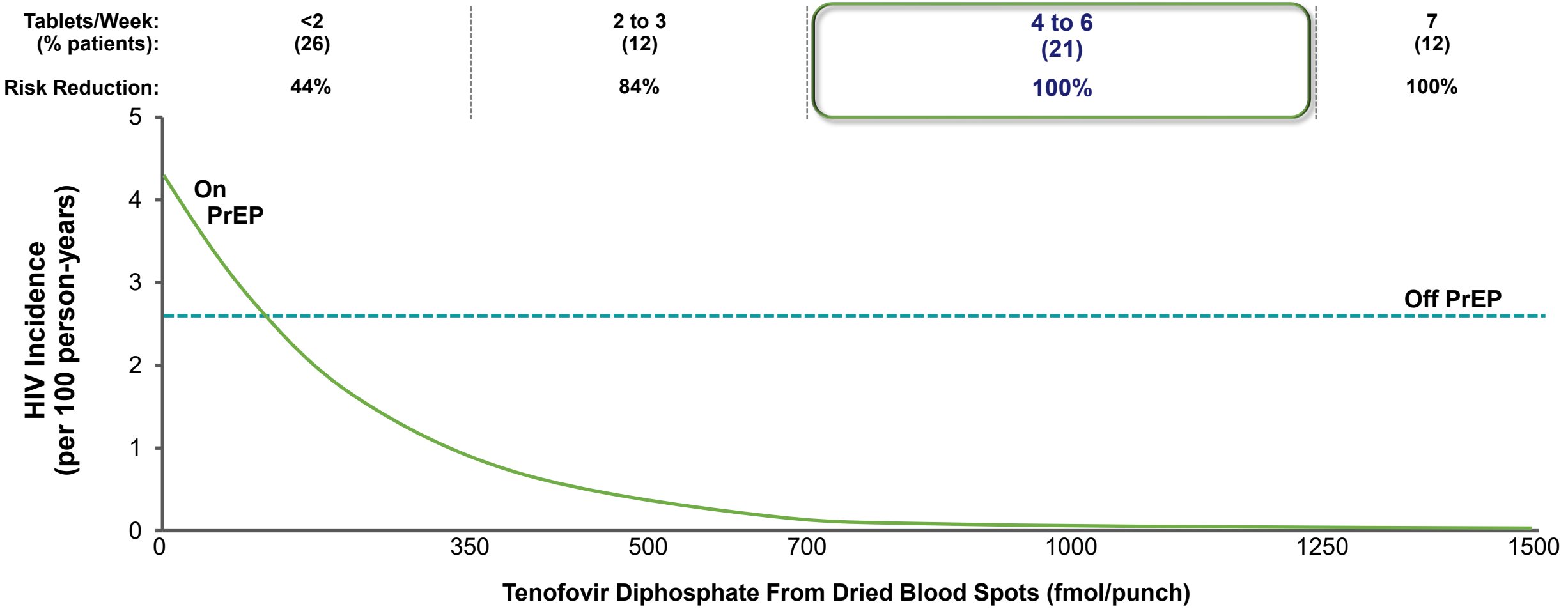
DBS Levels for TFV-DP



Landovitz RJ et al. AIDS 2020, #OAXLB01

Each participant selected for adherence testing may have up to 8 samples included in this summary.
* Category values for Week 4 adjusted for days on therapy, as steady state not yet achieved

iPrEx Open-Label Extension (OLE): PrEP Appears to be Forgiving to Occasional Missed Doses

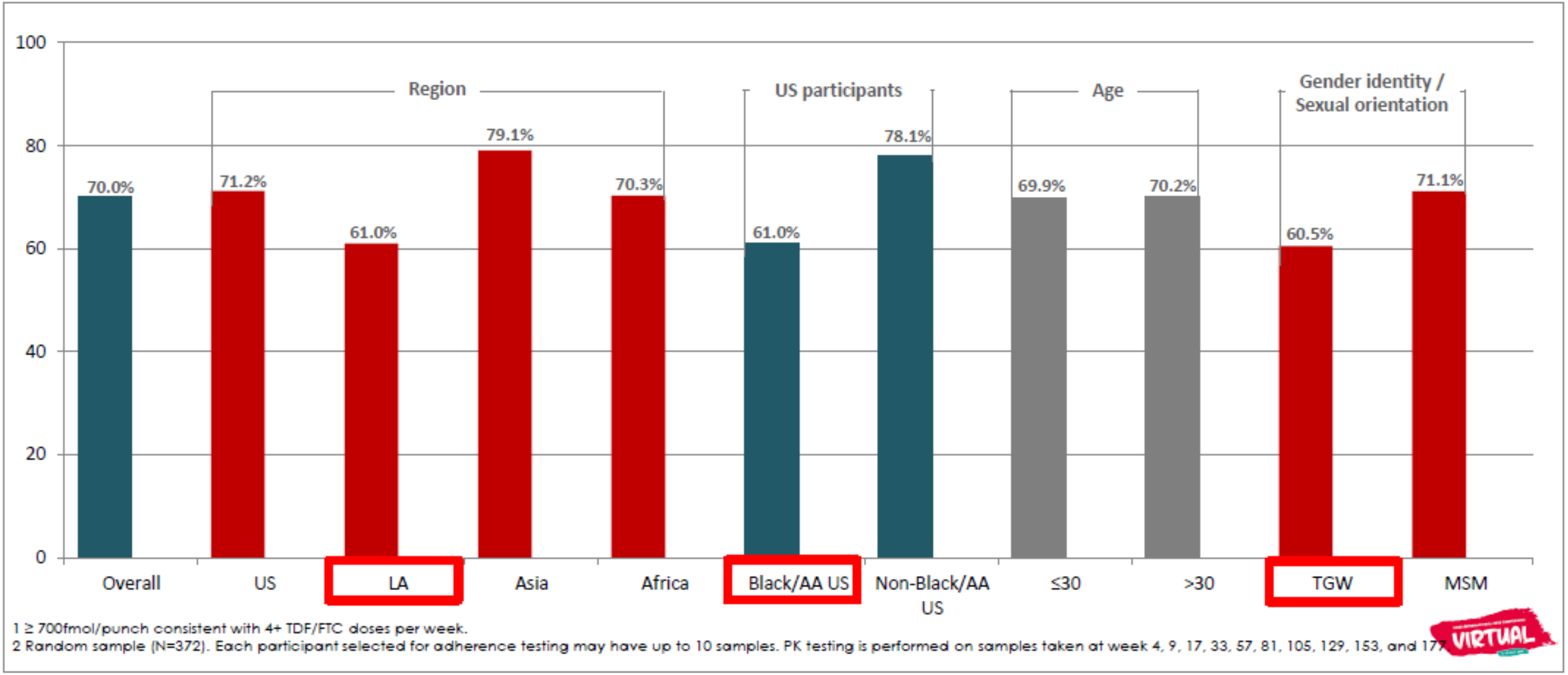


iPrEx OLE included MSM and transgender women.

Grant RM, et al. *Lancet Infect Dis.* 2014;14:820-829.

Results: TDF/FTC Adherence

TFV-DP ≥ 700fmol/punch in DBS[1,2]

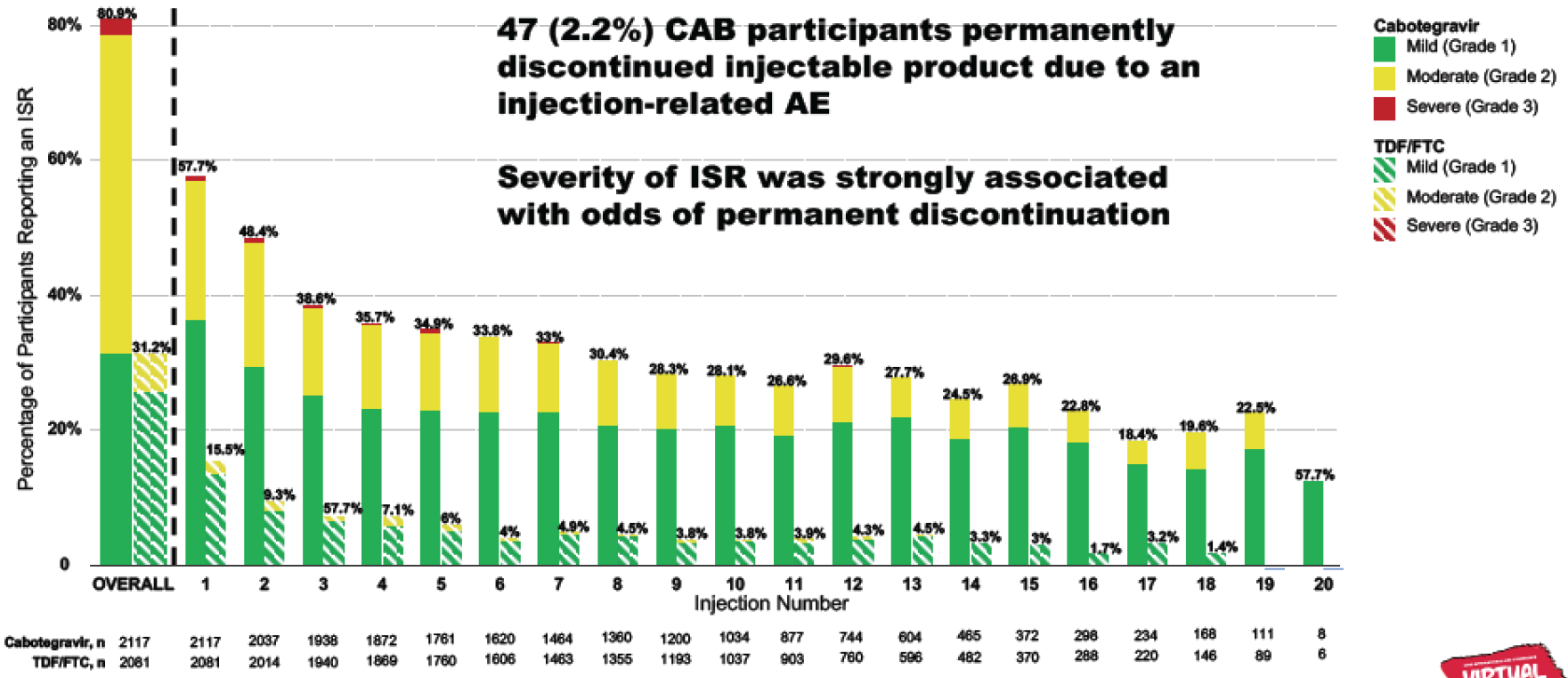


1 ≥ 700fmol/punch consistent with 4+ TDF/FTC doses per week.

2 Random sample (N=372). Each participant selected for adherence testing may have up to 10 samples. PK testing is performed on samples taken at week 4, 9, 17, 33, 57, 81, 105, 129, 153, and 177

Injection site reactions

Injection Site Reactions



Landovitz RJ et al. AIDS 2020, #OAXLB01

Grade 2+ Adverse Events

Grade 2+ Adverse Events
Reported in ≥5%

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)	p-value
Participants with grade 2+ AEs, n (%)	4202 (92.1%)	2106 (92.3%)	2096 (91.9%)	
Creatinine clearance decreased	3204 (70.2%)	1642 (72.0%)	1562 (68.5%)	0.01
CPK increased	937 (20.5%)	460 (20.2%)	477 (20.9%)	0.52
Nasopharyngitis	828 (18.1%)	388 (17.0%)	440 (19.3%)	0.04
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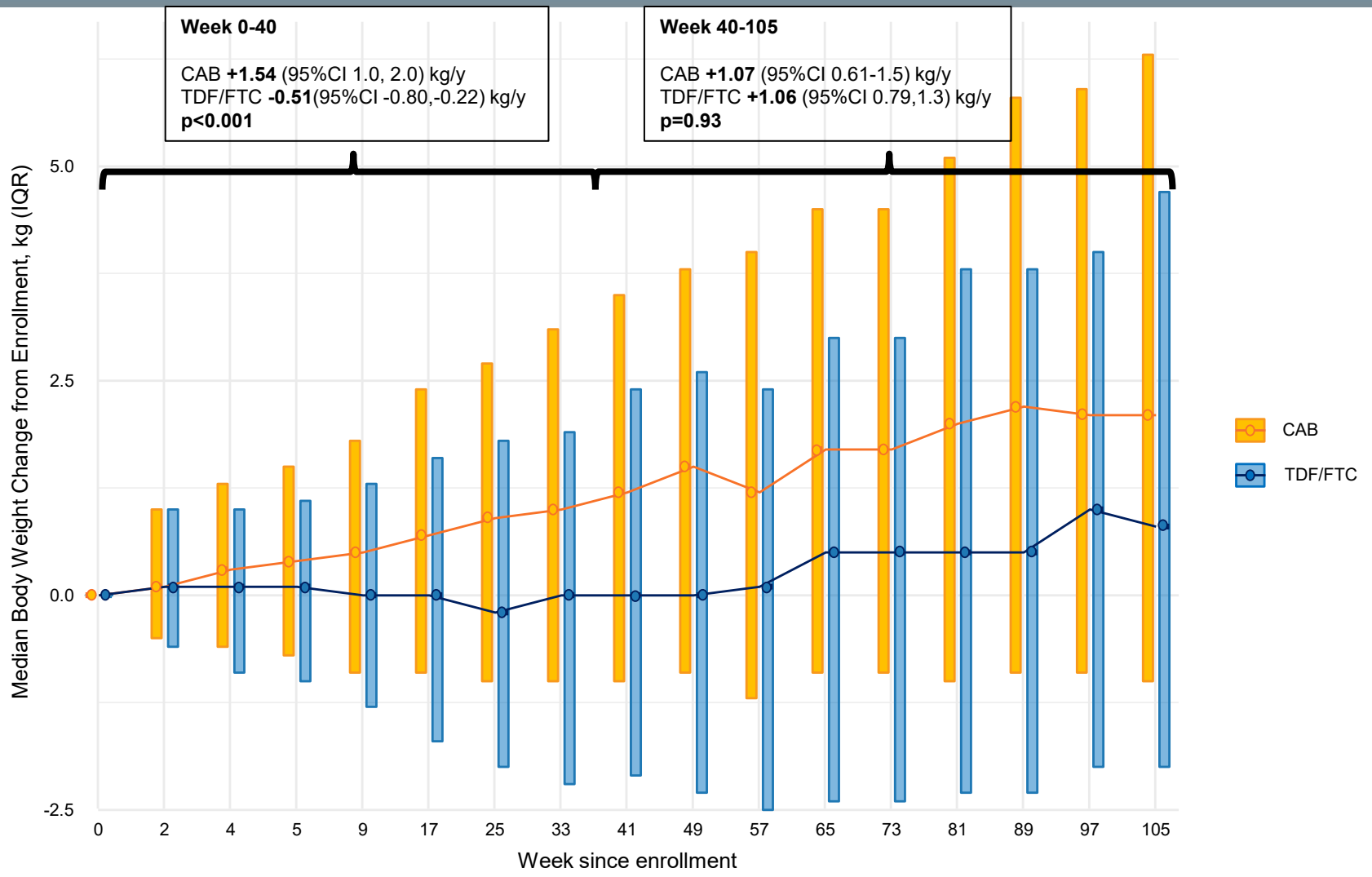
Musculoskeletal discomfort	507 (11.1%)	253 (11.1%)	254 (11.1%)	0.95
Lipase increased	495 (10.9%)	252 (11.0%)	243 (10.7%)	0.68
Headache	448 (9.8%)	216 (9.5%)	232 (10.2%)	0.42
AST/SGOT increased	382 (8.4%)	197 (8.6%)	185 (8.1%)	0.53
ALT/SGPT increased	347 (7.6%)	191 (8.4%)	156 (6.8%)	0.05
Blood glucose increased	323 (7.1%)	117 (5.1%)	206 (9.0%)	<0.001
Amylase increased	316 (6.9%)	166 (7.3%)	150 (6.6%)	0.36
Diarrhoea	306 (6.7%)	158 (6.9%)	148 (6.5%)	0.56
Rash	253 (5.5%)	139 (6.1%)	114 (5.0%)	0.11
Hypoglycaemia	241 (5.3%)	123 (5.4%)	118 (5.2%)	0.75
Pyrexia*	181 (4.0%)	60 (2.6%)	121 (5.4%)	<0.001

*70% of pyrexia events in CAB were within 7 days of an injection (event probability 0.65%)
16% of pyrexia events in TDF/FTC were within 7 days of an injection (event probability 0.05%)

Changes in Weight
Median of changes from baseline



Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus–uninfected Individuals in HPTN 077

Raphael J Landovitz [1], Sahar Z Zangeneh [2], Gordon Chau [2], Beatriz Grinsztejn [3], Joseph J Eron [4], Halima Dawood [5], Manya Magnus [6], Albert Y Liu [7], Ravindre Panchia [8], Mina C Hosseinipour [9], Ryan Kofron [1], David A Margolis [10], Alex Rinehart [10], Adeola Adeyeye [11], David Burns [11], Marybeth McCauley [12], Myron S Cohen [4], Judith S Currier [1]

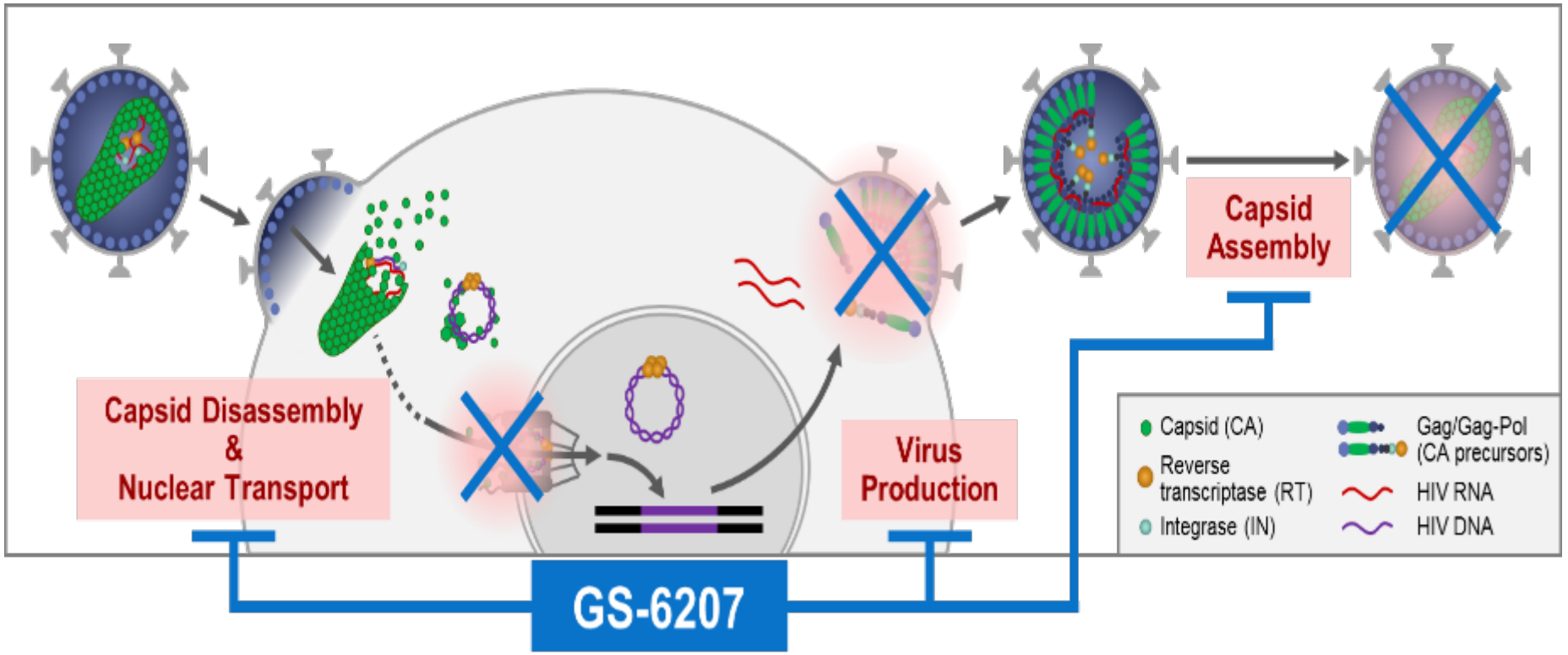
HPTN 077: Over 41 weeks

CAB **+1.48** (95%CI 0.15, 2.8) kg/y
PBO **+1.57** (95%CI -1.35,4.49) kg/y
p=0.95

Landovitz RJ et al. CID 2019.

Landovitz RJ et al. AIDS 2020, #OAXLB01

Lenacapavir: First-in-Class HIV Capsid Inhibitor

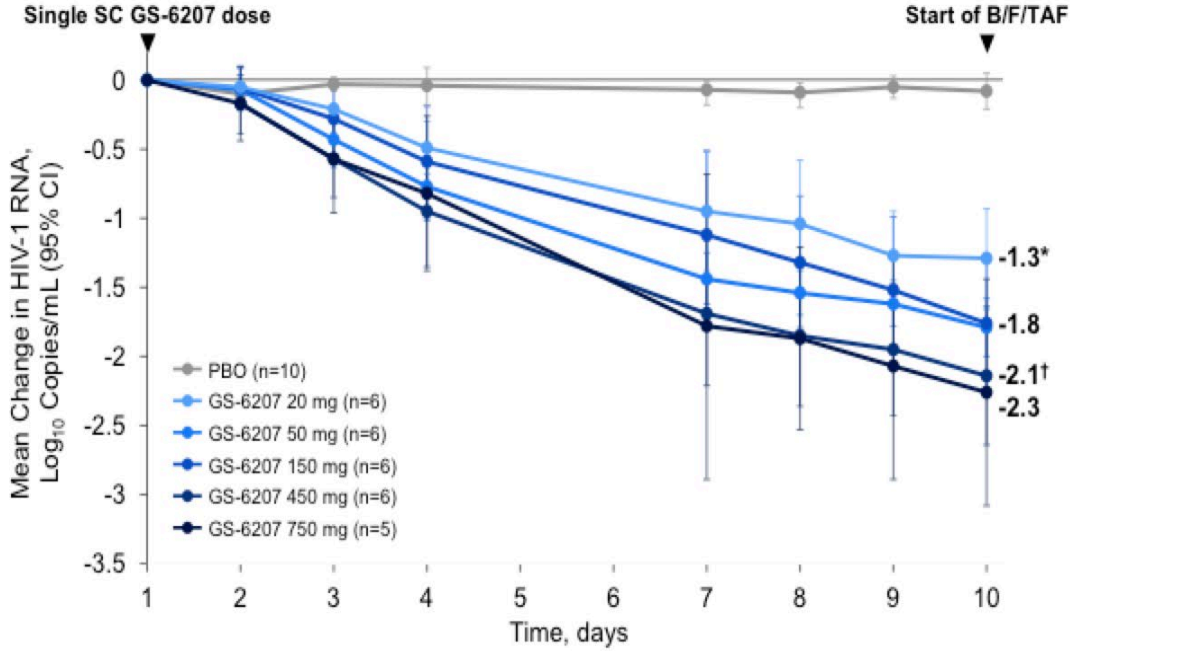


- inhibits multiple processes essential for viral replication
- modulates the stability and/or transport of capsid complexes

Yant SR, et al. CROI 2019. Seattle, WA; Abstract 480; Yant SR, et al. CROI 2019. Seattle, WA; Abstract 141

DOSE-RESPONSE RELATIONSHIP OF SUBCUTANEOUS LONG-ACTING HIV CAPSID INHIBITOR GS-6207

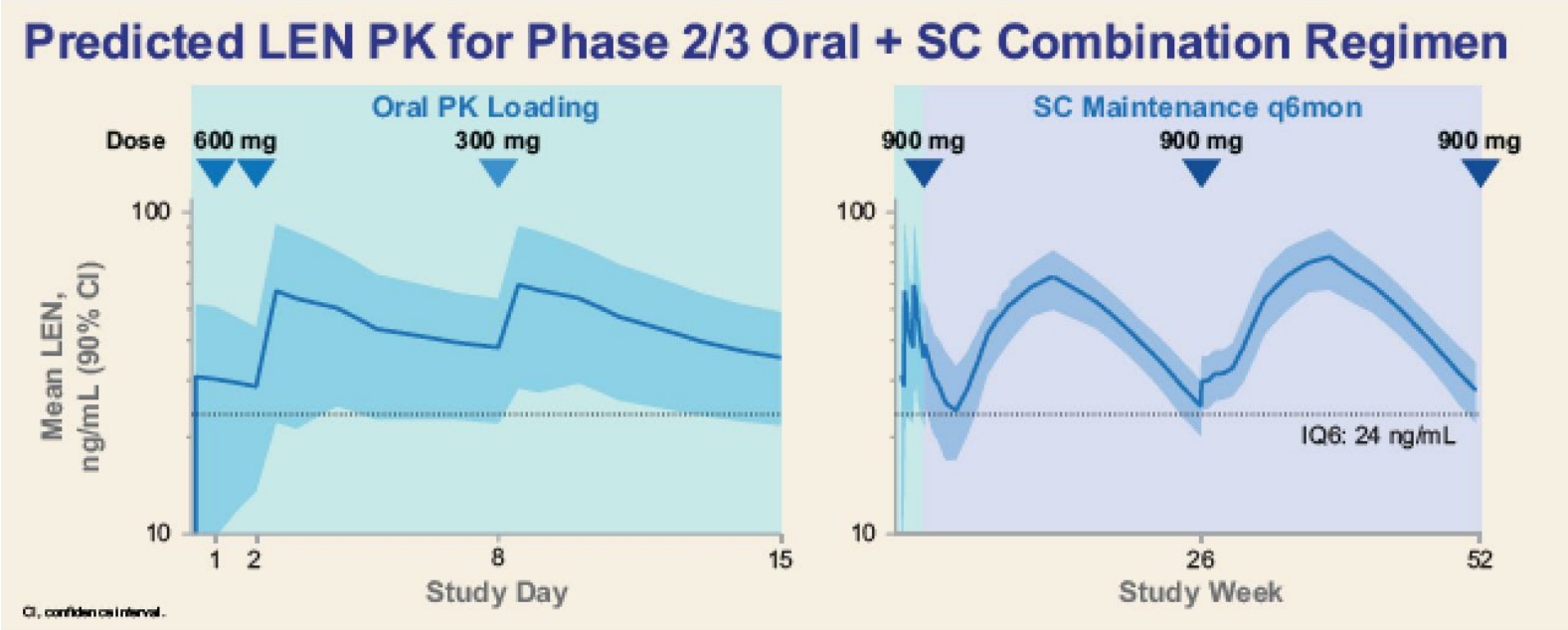
Subcutaneous GS-6207: Antiviral Activity



*Change (mean) on Day 10 in 20-mg cohort was -1.3 log_{10} copies/mL while maximal change (mean) through Day 10 was -1.4 log_{10} copies/mL; †Change (mean) on Day 10 in 450-mg cohort was -2.1 log_{10} copies/mL while maximal change (mean) through Day 10 was -2.2 log_{10} copies/mL.
CI, confidence interval.

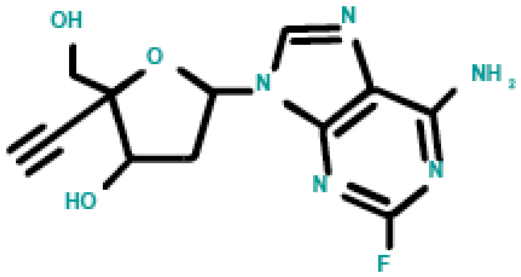
Daar et al CROI 2020 (also IAS 2019)

PK dynamics for lenacapavir



Islatravir: Novel NRTTI has two different mechanisms of action

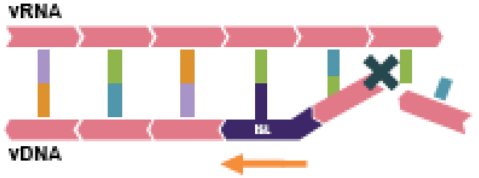
Islatravir, a First-in-Class NRTTI with Multiple Mechanisms of Action



Translocation Inhibition

- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination



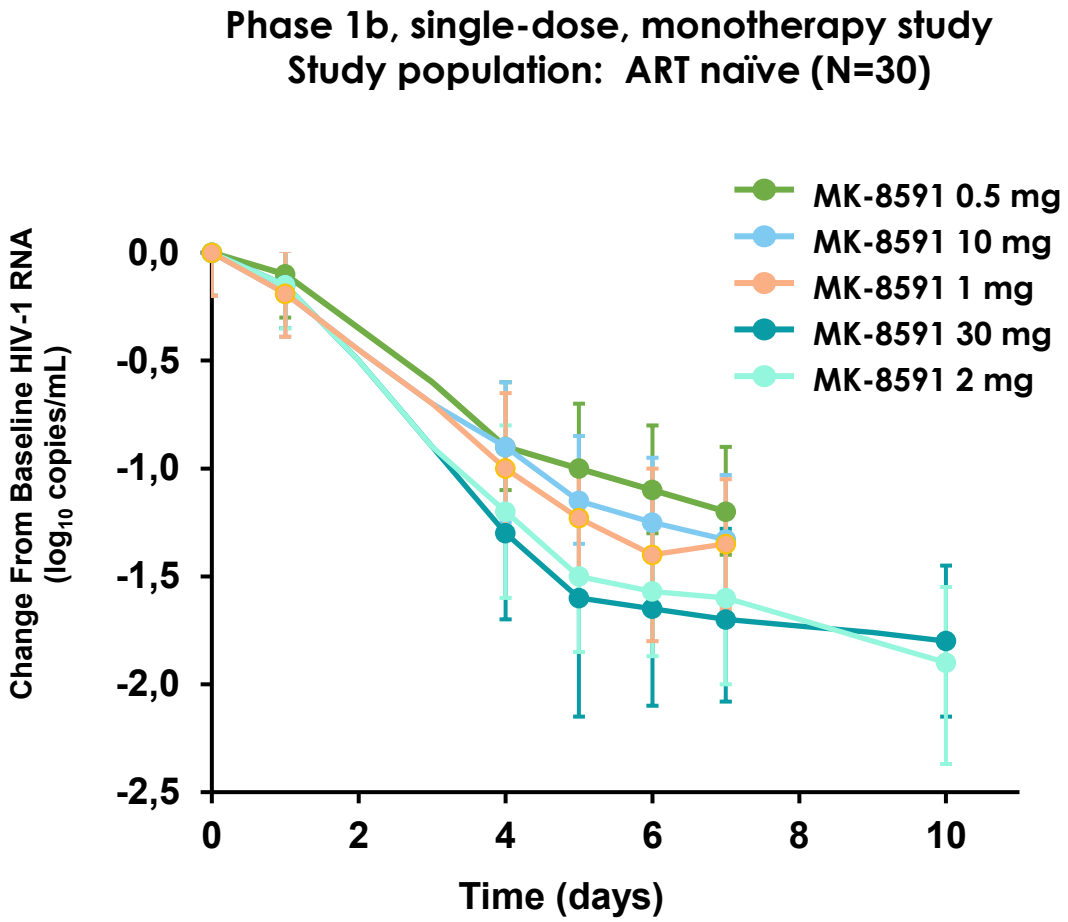
- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to RT-associated resistance-conferring mutations
- **Viral replication is inhibited**

Multiple mechanisms contribute to the high potency of ISL against HIV-1 (including drug-resistant variants) and its high barrier to resistance

ISL, islatravir; NRTTI, nucleoside reverse transcriptase translocation inhibitor; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA.

Long-acting NRTTI: Islatravir

- Nucleoside RT translocation inhibitor (NRTTI)
- Half life of active anabolite: ≈80-130 hr
- Humans: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days



Grobler et al CROI 2017 #435
Matthews et al IAS 2017 #TUPDB0202LB

Islatravir: Adverse event profile

Most Common AEs, Week 0-48 (Incidence >10% in Any Group)

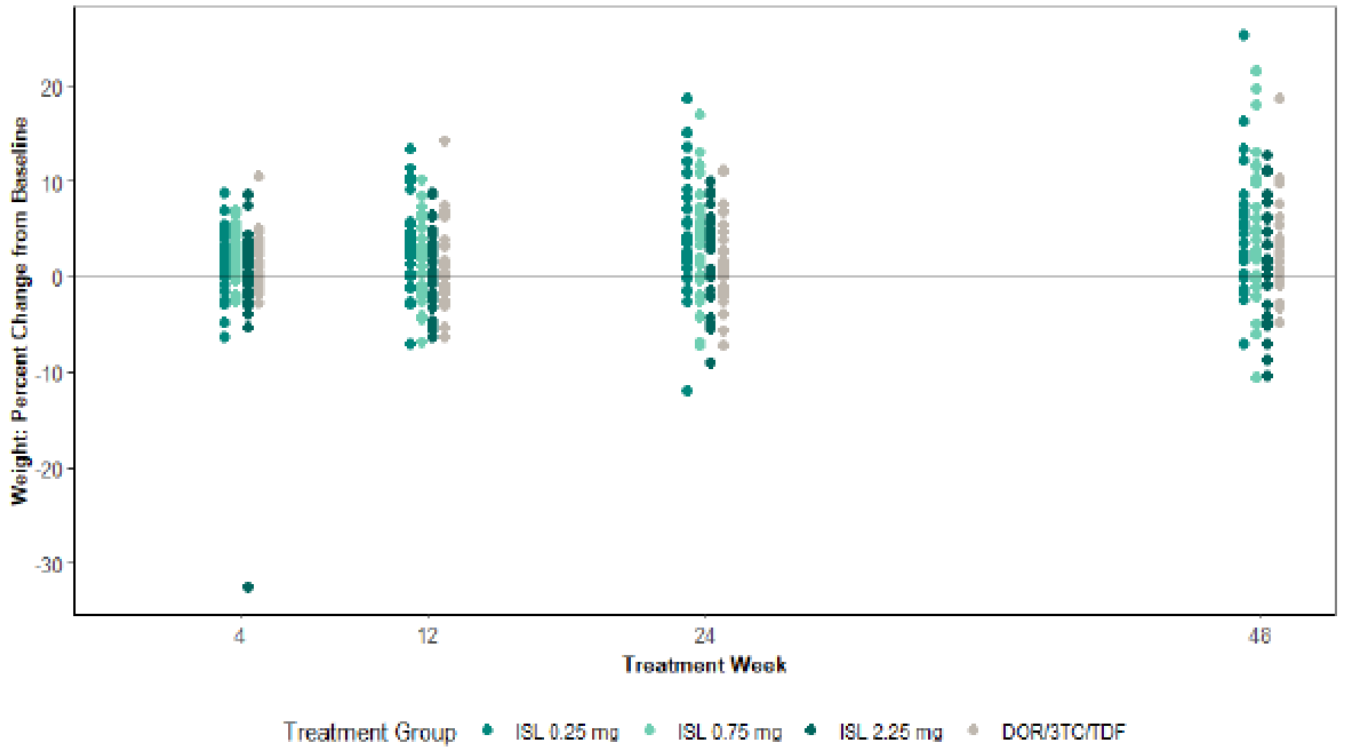
	ISL (0.25 mg) + DOR* QD	ISL (0.75 mg) + DOR* QD	ISL (2.25 mg) + DOR* QD	Combined ISL Groups	DOR/3TC/TDF QD
Number (%) of participants with	N=29	N=30	N=31	N=90	N=31
Headache	4 (13.8)	2 (6.7)	4 (12.9)	10 (11.1)	2 (6.5)
Diarrhea	0 (0.0)	4 (13.3)	2 (6.5)	6 (6.7)	5 (16.1)
Nausea	1 (3.4)	4 (13.3)	3 (9.7)	8 (8.9)	3 (9.7)
Syphilis	2 (6.9)	3 (10.0)	2 (6.5)	7 (7.8)	4 (12.9)
Arthralgia	1 (3.4)	2 (6.7)	4 (12.9)	7 (7.8)	1 (3.2)
Bronchitis	2 (6.9)	4 (13.3)	0 (0.0)	6 (6.7)	4 (12.9)
Nasopharyngitis	1 (3.4)	4 (13.3)	1 (3.2)	6 (6.7)	3 (9.7)
Vitamin D deficiency	0 (0.0)	4 (13.3)	2 (6.5)	6 (6.7)	1 (3.2)
Sinusitis	3 (10.3)	0 (0.0)	0 (0.0)	3 (3.3)	1 (3.2)
Pain in extremity	3 (10.3)	0 (0.0)	0 (0.0)	3 (3.3)	0 (0.0)

*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.

- The most common AEs across all treatment groups were headache, diarrhea, and nausea.
- Headache was more common in the ISL groups; diarrhea was more common in the DOR/3TC/TDF group.

Islatravir: Changes in weight

Weight: Percent Change from Baseline



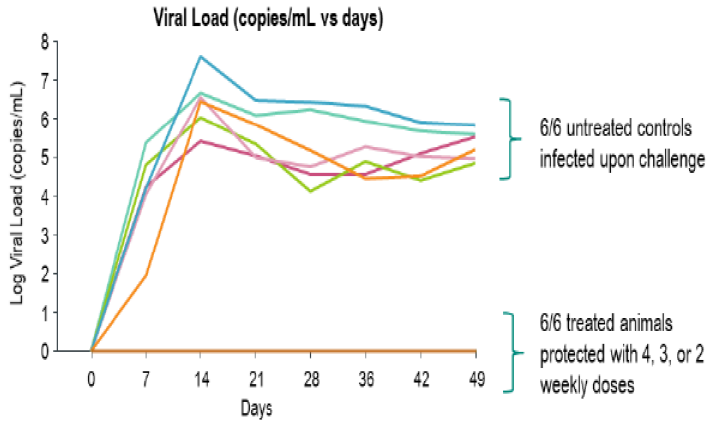
Number (%) with >5% Increase		
	Week 24	Week 48
ISL 0.25 mg	11/29 (37.9)	15/29 (51.7)
ISL 0.75 mg	12/30 (40.0)	11/30 (36.7)
ISL 2.25 mg	7/31 (22.6)	8/31 (25.8)
ISL combined	30/90 (33.3)	34/90 (37.8)
DOR/3TC/TDF	5/31 (16.1)	7/31 (22.6)

- Weight gain occurred primarily during Weeks 0-24 and may reflect a return-to-health effect.

Islatravir May also be considered for PEP

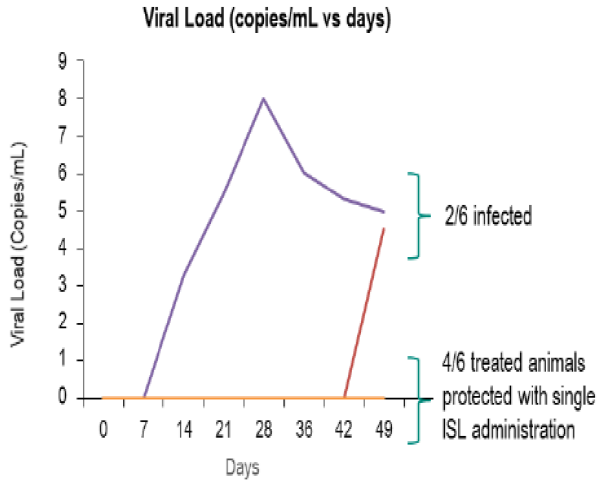
- IV Challenge of macaques with pathogenic SIV
- Two experiments 24 hours post challenge
  - Multiple doses of weekly islatravir
  - Single dose of islatravir

ISL Provides Complete Protection Against Infection When Administered 24 Hours After Challenge With Two or More Weekly Doses



ISL Administered Once 24 Hours After Challenge Is Effective in Reducing Infection

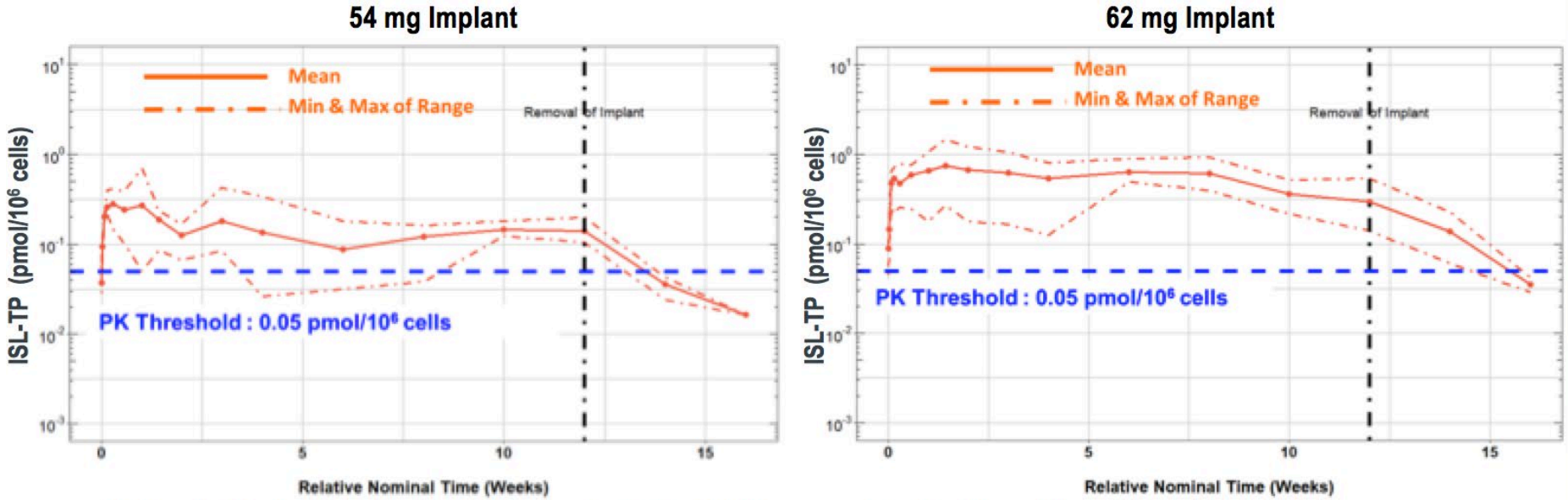
- When ISL was administered only once 24 hours after challenge, two of six animals became viremic with M184M $SIVmac_{251}$ (viremia detected at Day 14 and Day 49)



WEEKLY ORAL ISLATRAVIR PROVIDES EFFECTIVE PEP AGAINSTIV CHALLENGE WITH SIVMAC251
Markowitz et al

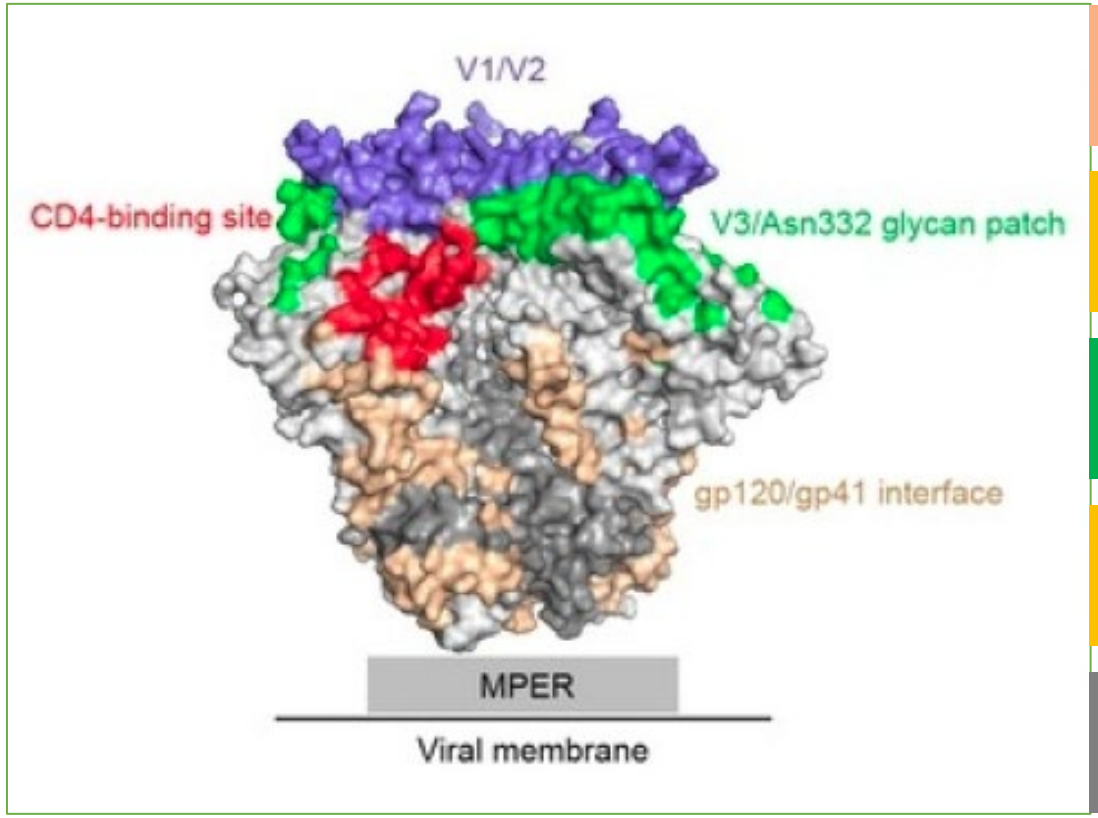
Islatravir – Implant PK data in Healthy Volunteers

Intracellular ISL-TP PK Threshold of 0.05 pmol/10^6 Cells Maintained Throughout Placement for Both Doses



- Ratio of TP/plasma remains fairly constant at ~1000:1 – consistent with oral dosing
- Half-life after removal of implant similar to half-life of orally dosed ISL

Broadly Neutralizing Antibodies



CD4-binding site
B12, VRC01, VRC07, NIH45-46, 3BNC117, VRC-PG04

V1/V2
PG9, PG16, CH01-04, PGT141-145, PGDM1400

V3/Asn332 glycan patch
PGT121-123, PGT125-131, PGT135, 10-1074, 2G12

Gp120/gp41-interface
PGT151, 35022, 8ANC195

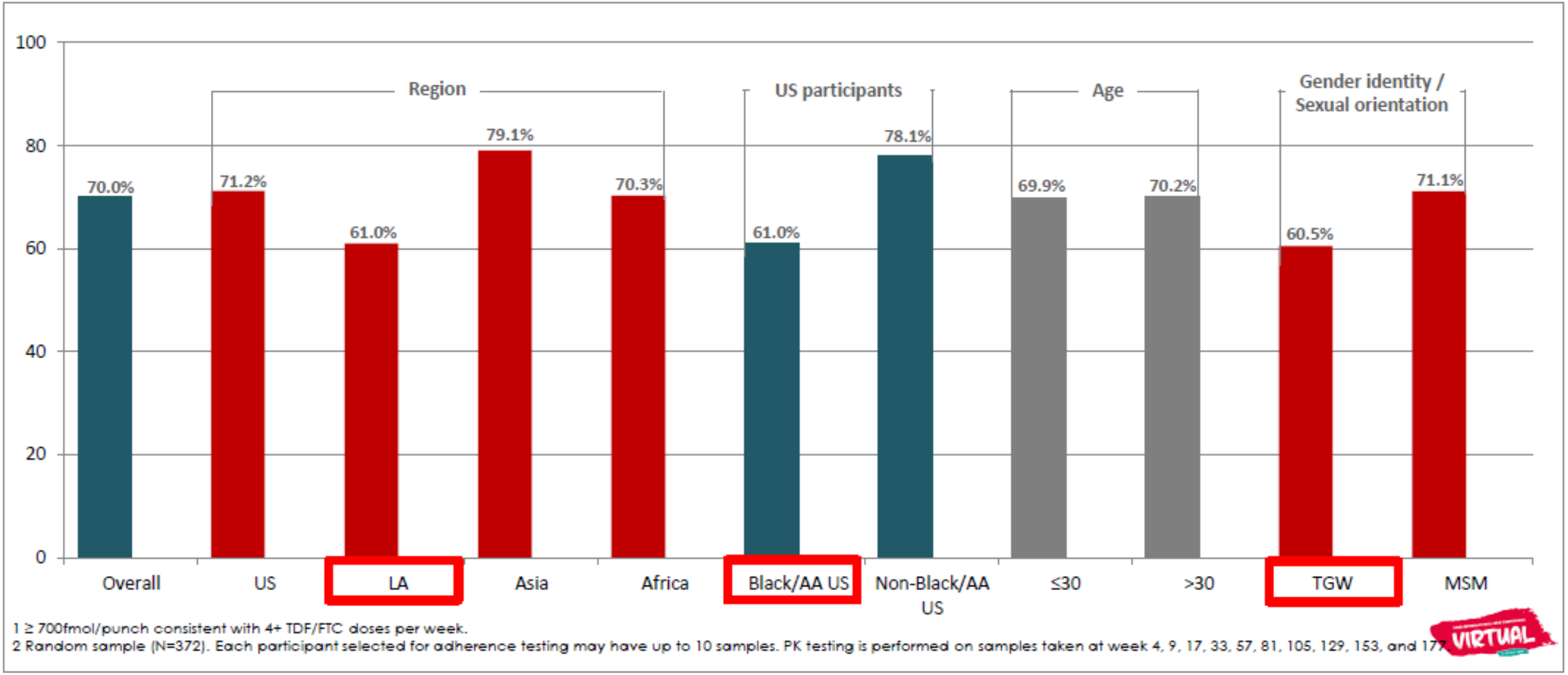
MPER
2F5, 4E10, 10EB

Conclusions

- More choices for consumers
- Injections will provide longer acting protection with different susceptibility to adherence
- High user acceptability despite some local reactions
- Evolving landscape as oral agents may become once weekly, SC injections or implantation technology may provide more options

Results: TDF/FTC Adherence

TFV-DP ≥ 700fmol/punch in DBS[1,2]



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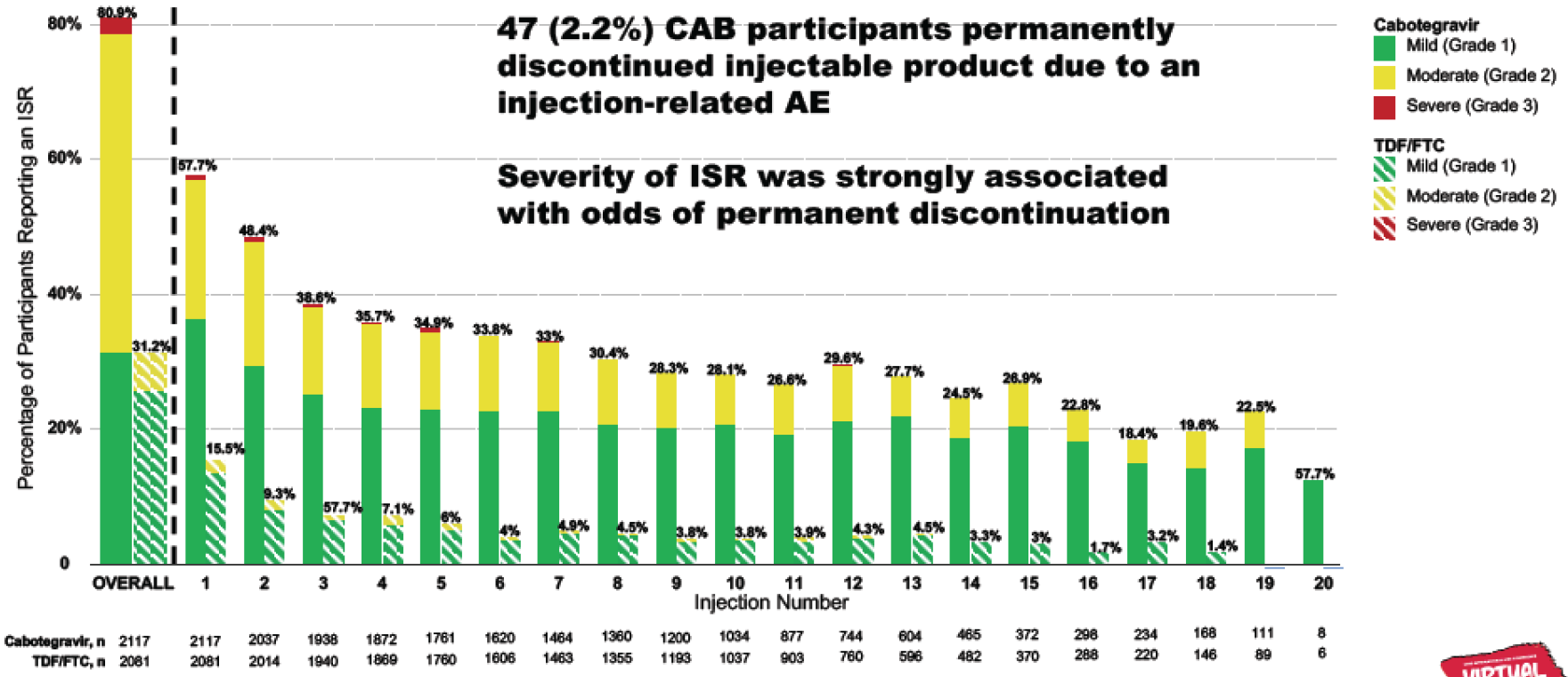

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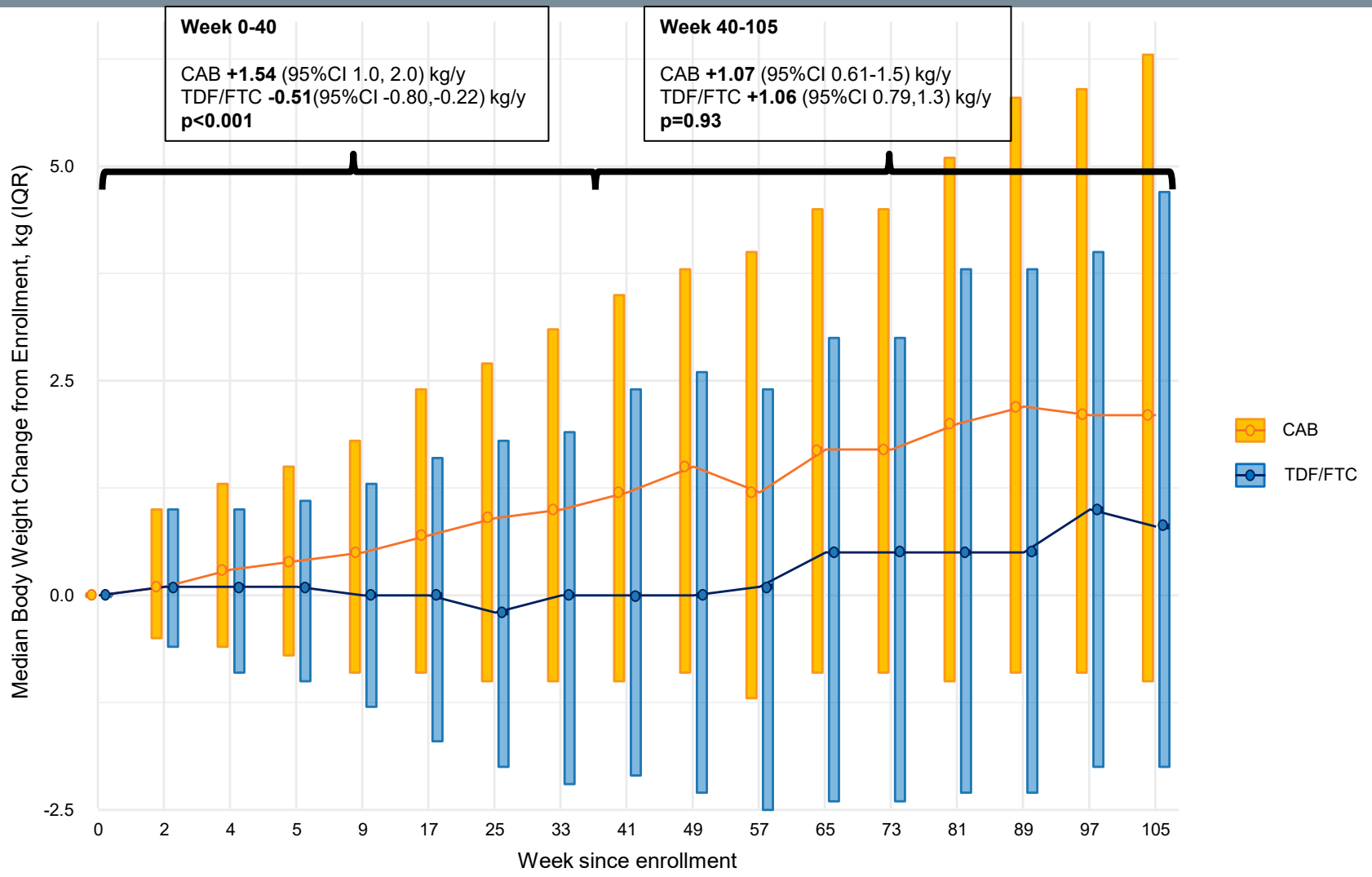
Lipase increased	495 (10.9%)	252 (11.0%)	243 (10.7%)	0.68
Headache	448 (9.8%)	216 (9.5%)	232 (10.2%)	0.42
AST/SGOT increased	382 (8.4%)	197 (8.6%)	185 (8.1%)	0.53
ALT/SGPT increased	347 (7.6%)	191 (8.4%)	156 (6.8%)	0.05
Blood glucose increased	323 (7.1%)	117 (5.1%)	206 (9.0%)	<0.001
Amylase increased	316 (6.9%)	166 (7.3%)	150 (6.6%)	0.36
Diarrhoea	306 (6.7%)	158 (6.9%)	148 (6.5%)	0.56
Rash	253 (5.5%)	139 (6.1%)	114 (5.0%)	0.11
Hypoglycaemia	241 (5.3%)	123 (5.4%)	118 (5.2%)	0.75
Pyrexia*	181 (4.0%)	60 (2.6%)	121 (5.4%)	<0.001

*70% of pyrexia events in CAB were within 7 days of an injection (event probability 0.65%)
16% of pyrexia events in TDF/FTC were within 7 days of an injection (event probability 0.05%)

Changes in Weight
Median of changes from baseline



Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus–uninfected Individuals in HPTN 077

Raphael J Landovitz [1], Sahar Z Zangeneh [2], Gordon Chau [2], Beatriz Grinsztejn [3], Joseph J Eron [4], Halima Dawood [5], Manya Magnus [6], Albert Y Liu [7], Ravindre Panchia [8], Mina C Hosseinipour [9], Ryan Kofron [1], David A Margolis [10], Alex Rinehart [10], Adeola Adeyeye [11], David Burns [11], Marybeth McCauley [12], Myron S Cohen [4], Judith S Currier [1]

HPTN 077: Over 41 weeks

CAB **+1.48** (95%CI 0.15, 2.8) kg/y
PBO **+1.57** (95%CI -1.35,4.49) kg/y
p=0.95

Landovitz RJ et al. CID 2019.

Landovitz RJ et al. AIDS 2020, #OAXLB01