LONG –ACTING DRUG and PRE-EXPOSURE PROPHYLAXIS FOR HIV

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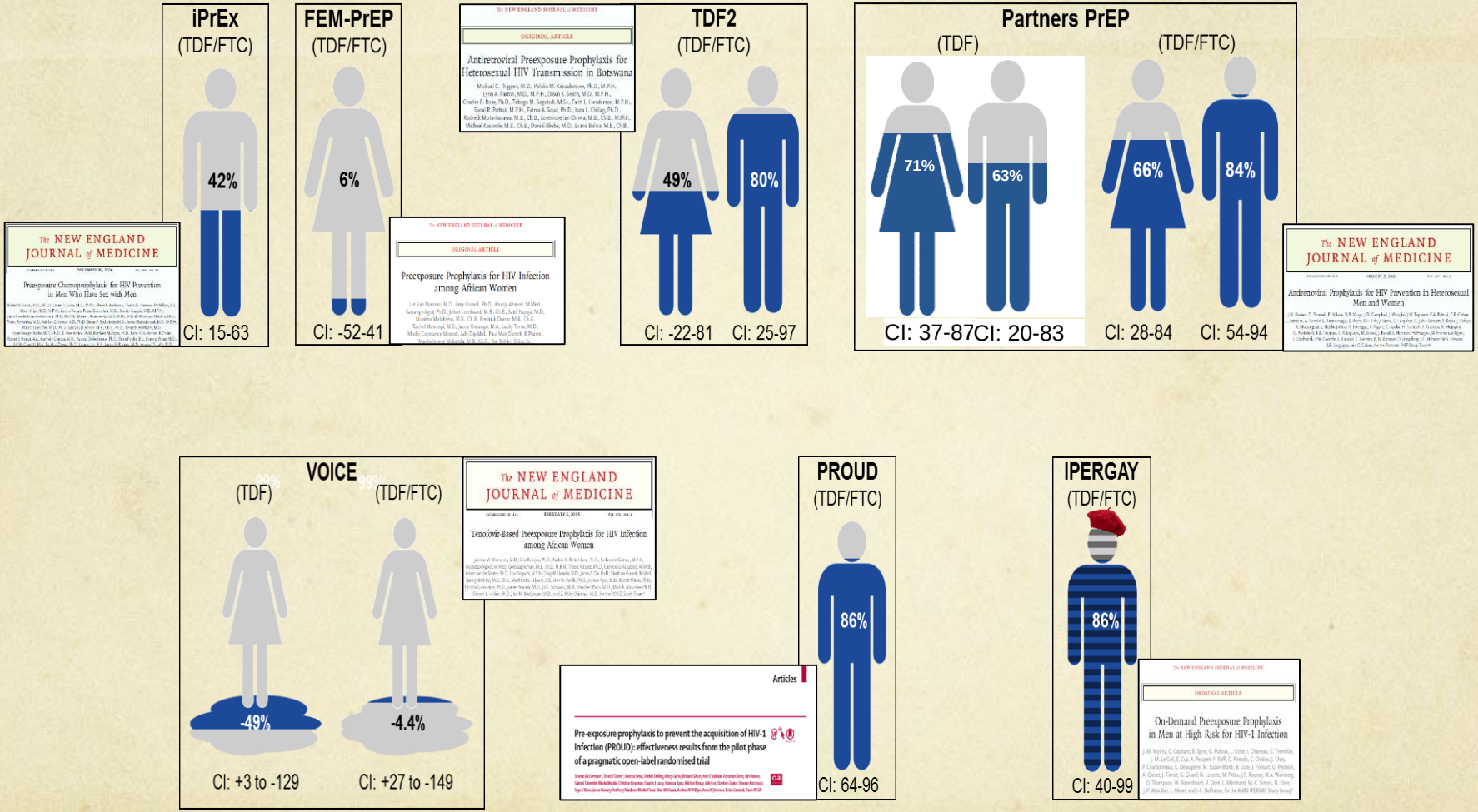
HPTN 083 Final Results: Pre-exposure Prophylaxis Containing Long-Acting Injectable Cabotegravir Is Safe and Highly Effective for Cisgender Men and Transgender Women Who Have Sex With Men

R.J. Landovitz et AL
for the HPTN 083 Study Team

Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials

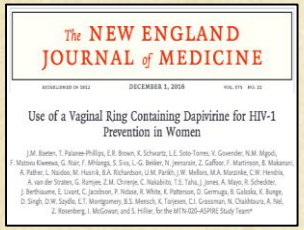


Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

“PrEP 2.0”: Trials of Novel PrEP Agents

ASPIRE
(Dapivirine)

27%


The NEW ENGLAND JOURNAL of MEDICINE

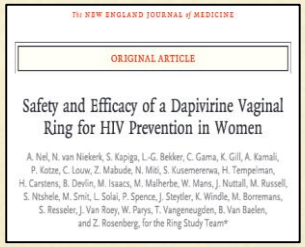
DECEMBER 1, 2016

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

CI: 1 – 46

Ring
(Dapivirine)

31%


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women

CI: 1 – 51

DISCOVER

(TDF/FTC)

Incidence rate
0.30%

(TAF/FTC)

Incidence rate
0.16%

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

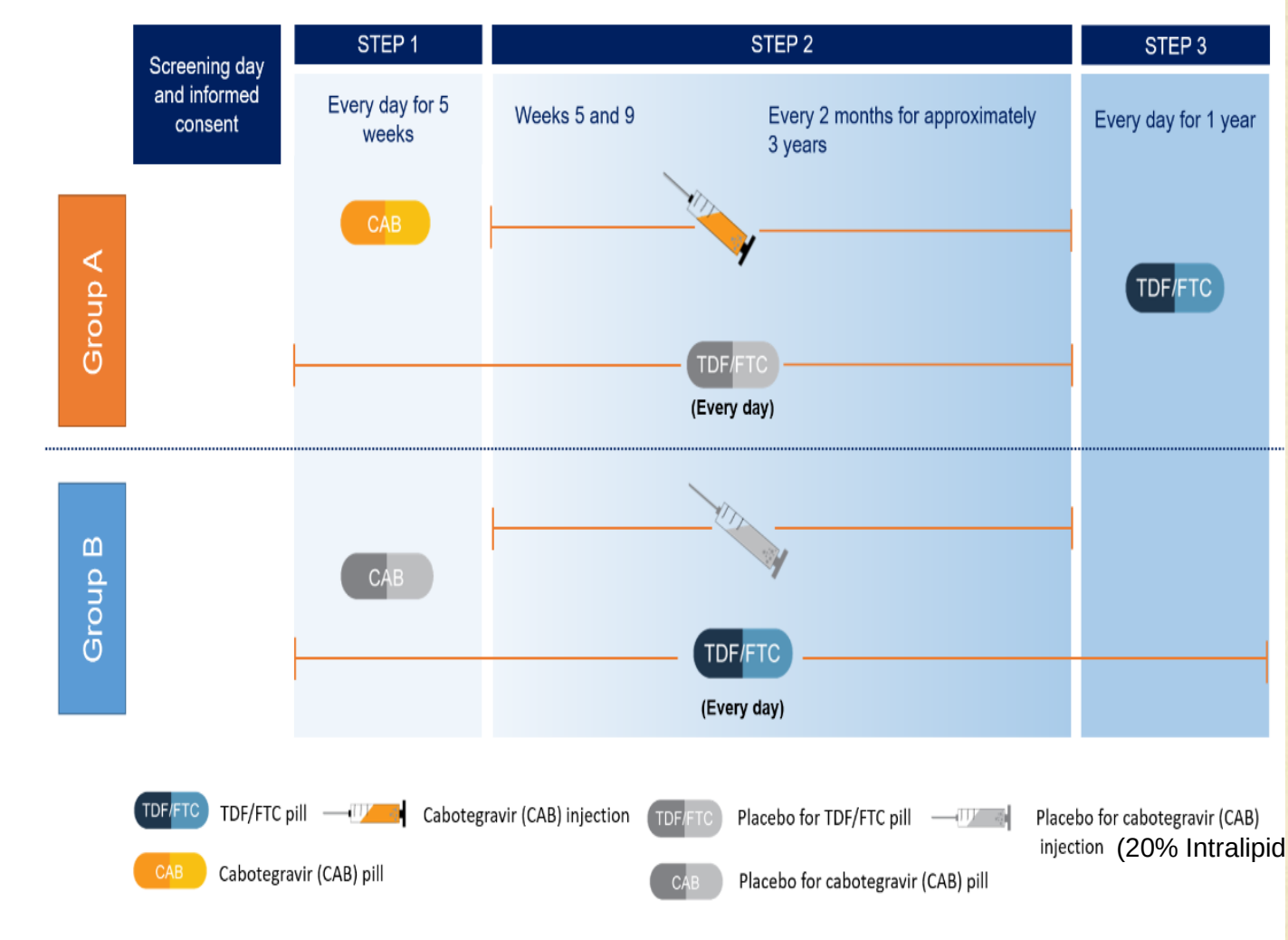
HPTN 083 Study Design

- Phase 2b/3 randomized, double-blind, double-dummy @ 43 sites globally
  - MSM/TGW age 18+
  - Risk: any nCRAI, >5 partners, stimulant drug use, incident rectal or urethral STI (or incident syphilis) in past 6 months; or SexPro Score ≤16 (US only)
  - Generally good health
  - No HBV or HCV
  - No contraindication to gluteal injections, seizures, gluteal tattoos/skin conditions
- Planned enrollment 5000
  - ≥ 50% under age 30
  - ≥ 10% TGW
  - ≥ 50% of US enrollment Black
- Primary efficacy endpoint: Incident HIV infections during blinded comparison
- Primary safety endpoint: G2 or higher clinical and laboratory AEs

Please see Grinsztejn B. et al, Abstract #OAXLB0104.

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

HPTN 083 Study Design (cont)



(20% Intralipid solution)

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

Study Population

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Gender Identity, n (%)			
MSM	3995 (87.5	1981 (86.7)	2014 (88.3)
TGW	567 (12.4)	302 (13.2)	265 (11.6)
Age, median (IQR)	26 (22, 32)	26 (22, 32)	26 (22, 32)
Age, n (%)			
18-29	3079 (67.4)	1508 (66.0)	1571 (68.8)
30-39	1049 (23)	550 (24.1)	499 (21.9)
40-49	315 (6.9)	170 (7.4)	145 (6.4)
50-59	110 (2.4)	50 (2.2)	60 (2.6)
≥60	13 (0.3)	6 (0.3)	7 (0.3)
Region, n (%)			
United States	1698 (37.2%)	849 (37.2%)	849 (37.2%)
Latin America	1964 (43.0%)	984 (43.2%)	980 (42.9%)
Asia	752 (16.5%)	377 (16.5%)	375 (16.5%)
Africa	152 (3.3%)	74 (3.2%)	78 (3.4%)
Education, n (%)			
Post-Secondary (YES)	3477 (76.1)	1715 (75.1)	1762 (77.2)
Relationship Status, n (%)			
Single (YES)	3750 (82.1)	1863 (81.6)	1887 (82.7)

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

Study Population (cont)

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Race, n (%)			
United States			
Black/African American	844 (49.7)	433 (51.0)	411 (48.9)
White/Asian/Native/Other	854 (50.4)	416 (49.0)	438 (51.1)
Latin America			
Black/Afro-Caribbean	395 (20.1)	196 (19.9)	199 (20.3)
Native	858 (43.7)	425 (43.2)	433 (44.2)
White/Asian/Other	711 (59.6)	363 (36.8)	348 (35.5)
Asia			
Asian	749 (99.6)	375 (99.5)	374 (99.7)
Other	3 (0.4)	2 (0.5)	1 (0.3)
Africa			
Black	119 (78.3)	57 (77.0)	62 (79.5)
Other	5 (3.3)	3 (4.1)	2 (2.6)
Ethnicity, n (%)			
United States: Latinx	303 (17.8)	154 (18.1)	149 (17.6)
Latin America: Latinx	1805 (91.9)	912 (92.7)	893 (91.1)

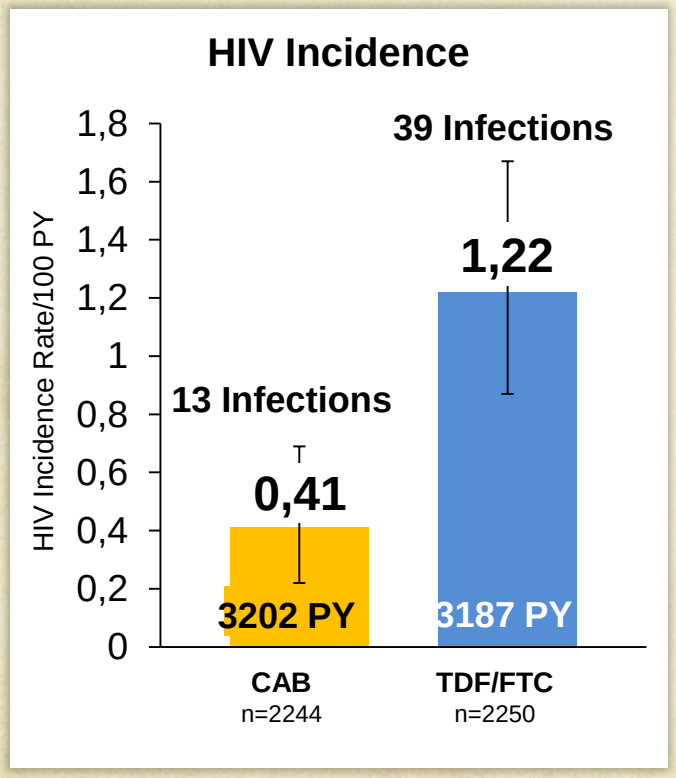
Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

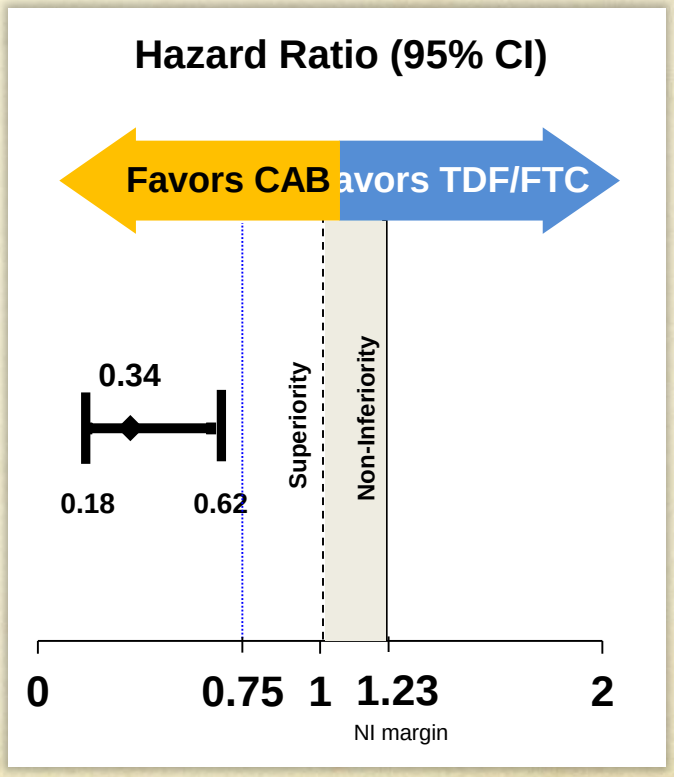
HIV Incidence
CAB vs. TDF/FTC

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

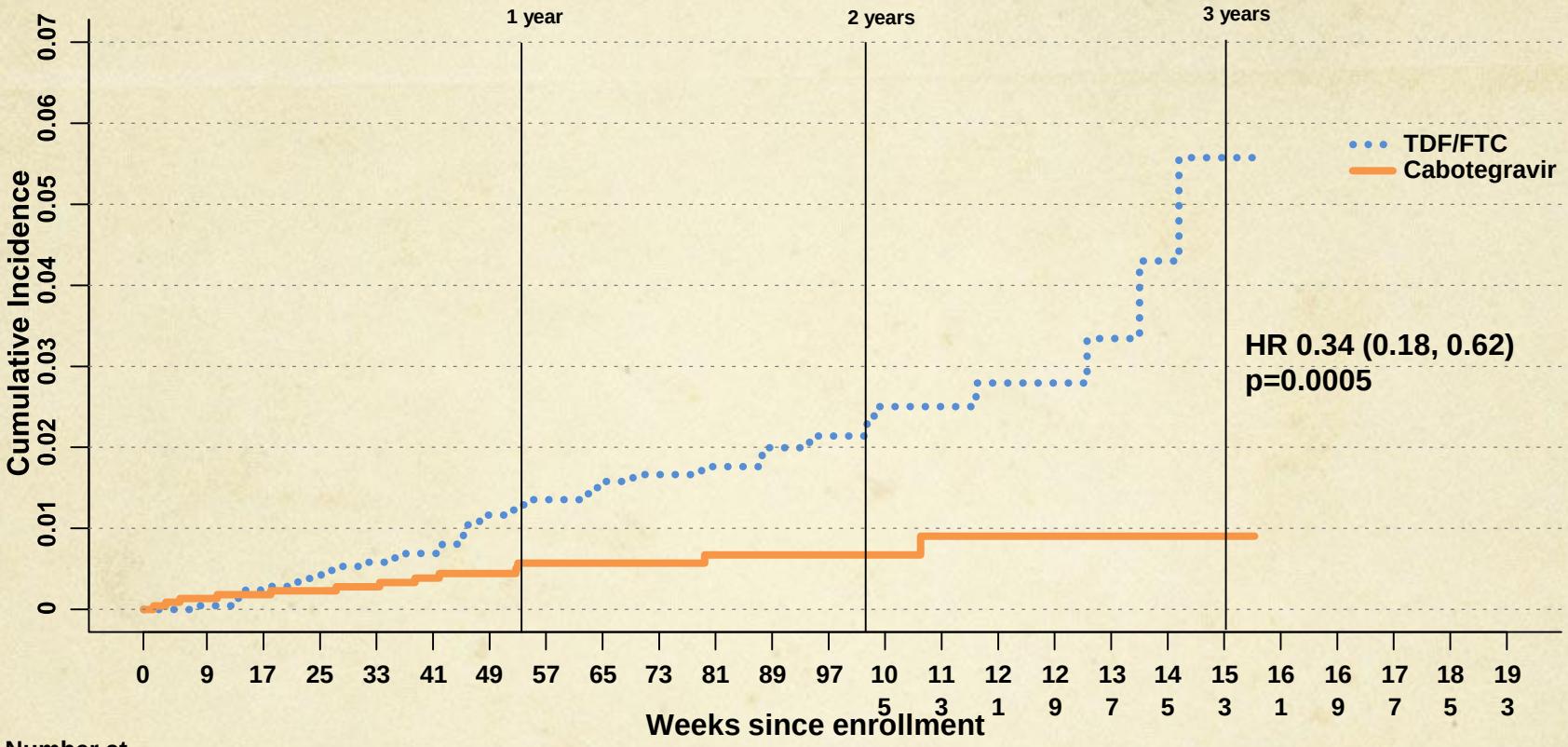




CI, confidence interval.

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

HIV Incidence – ITT



Number at risk

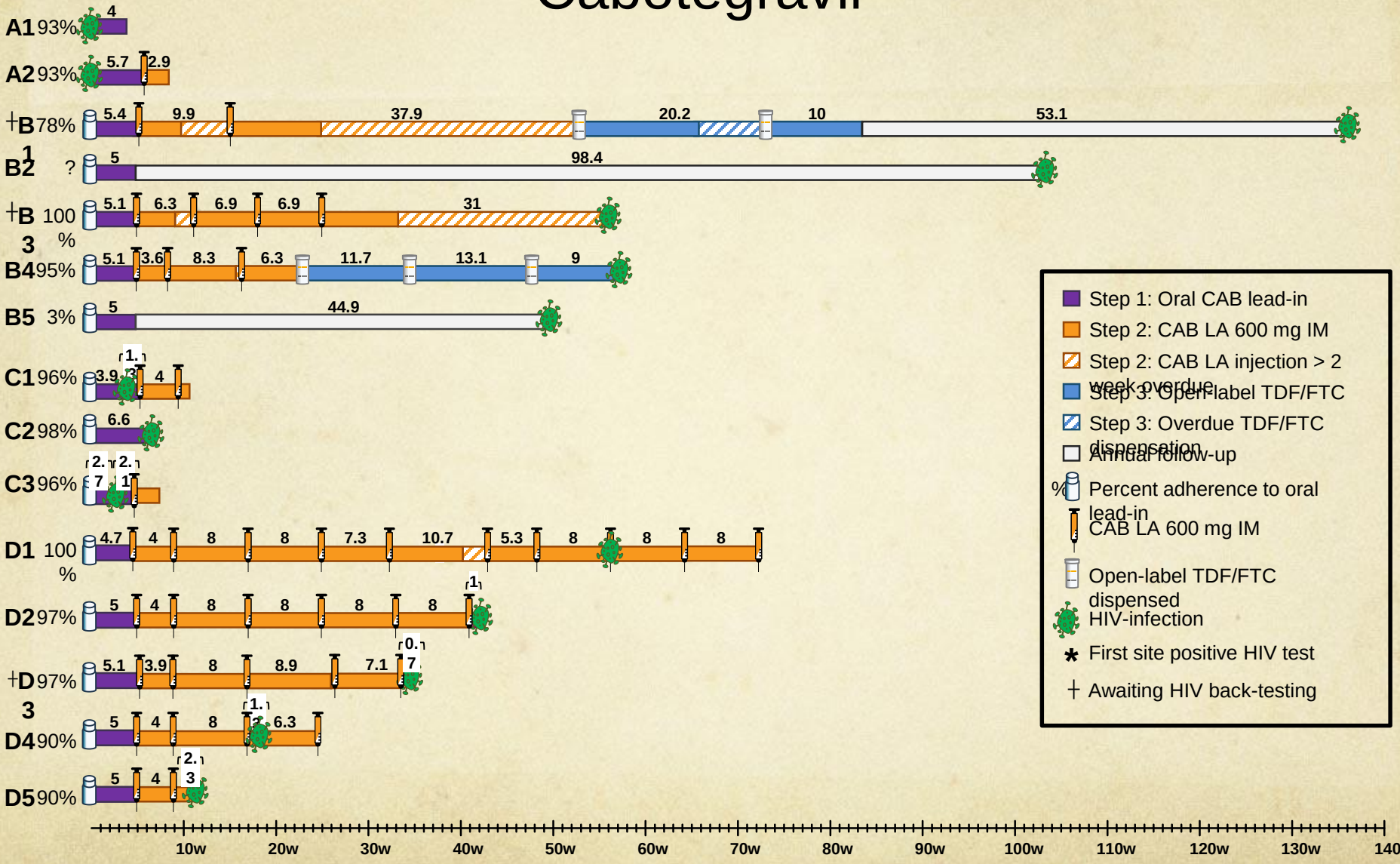
TDF/FTC	2247	2133	2081	2019	1913	1764	1624	1494	1294	1132	965	816	643	516	400	310	230	149	85	33	0	0	0	0	0
Cabotegravir	2243	2138	2092	2032	1921	1776	1632	1488	1312	1119	957	795	644	503	401	318	243	172	111	42	0	0	0	0	0

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

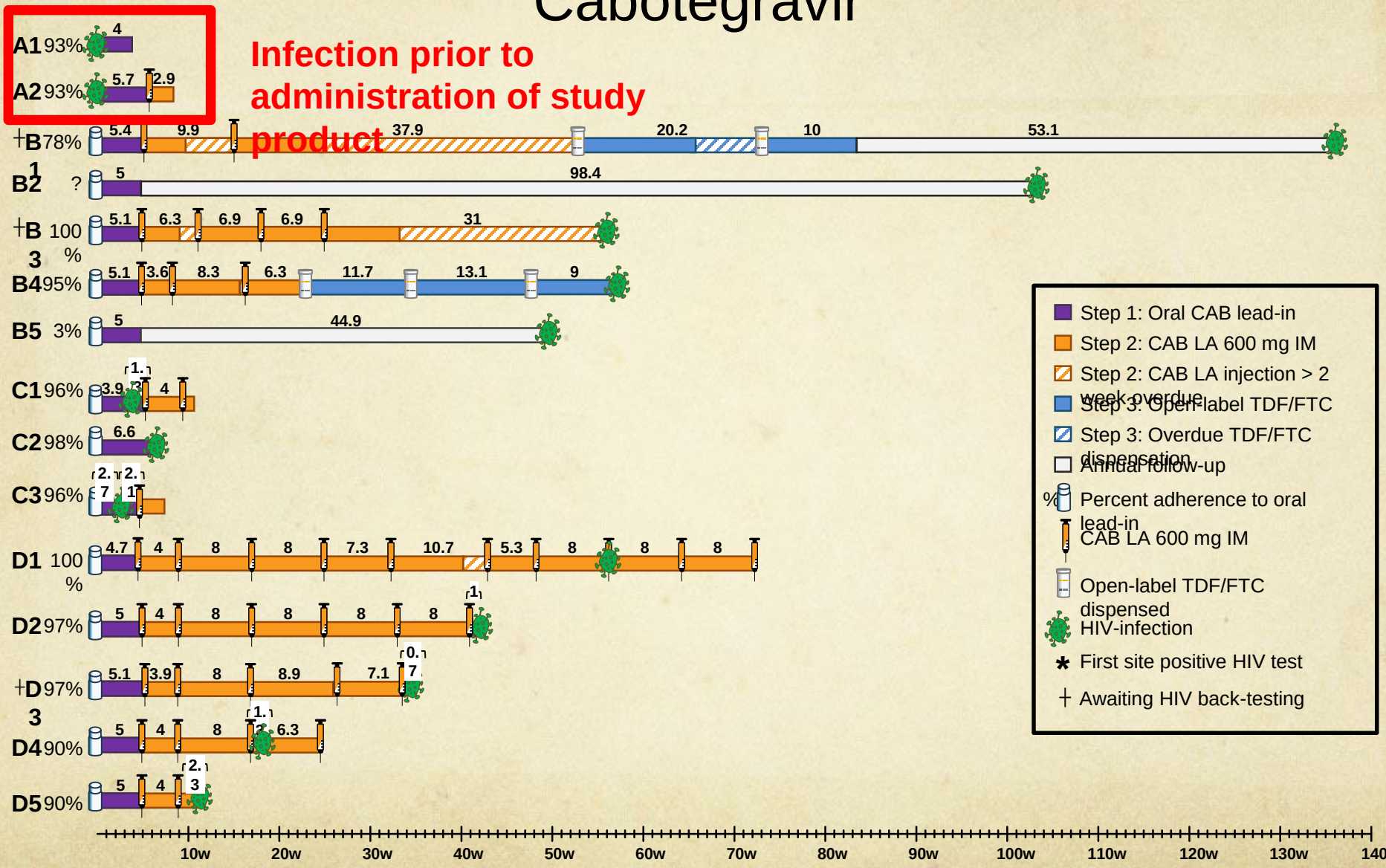
Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

13 Incident HIV Infections
Cabotegravir



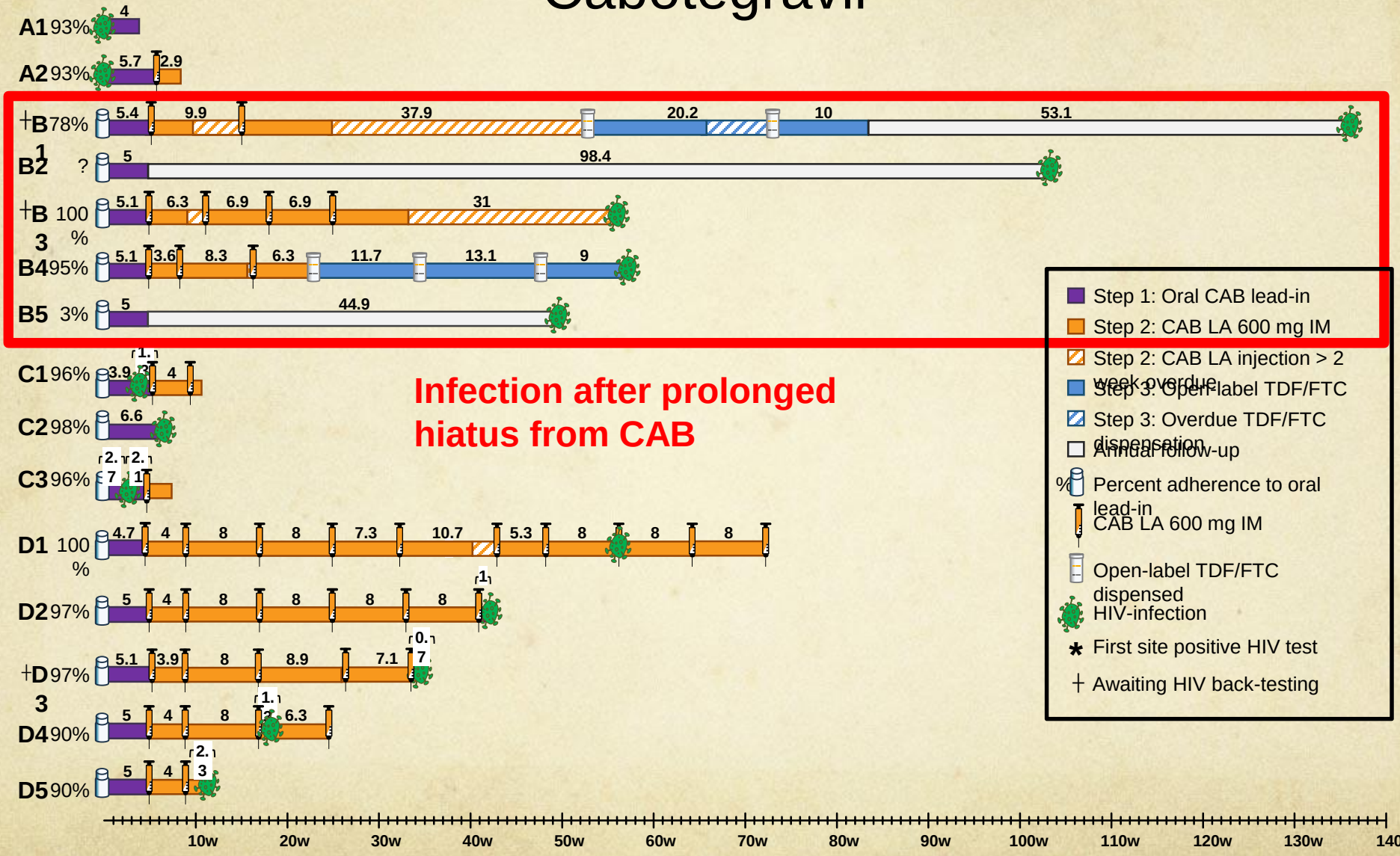
Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

13 Incident HIV Infections
Cabotegravir



Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

13 Incident HIV Infections
Cabotegravir

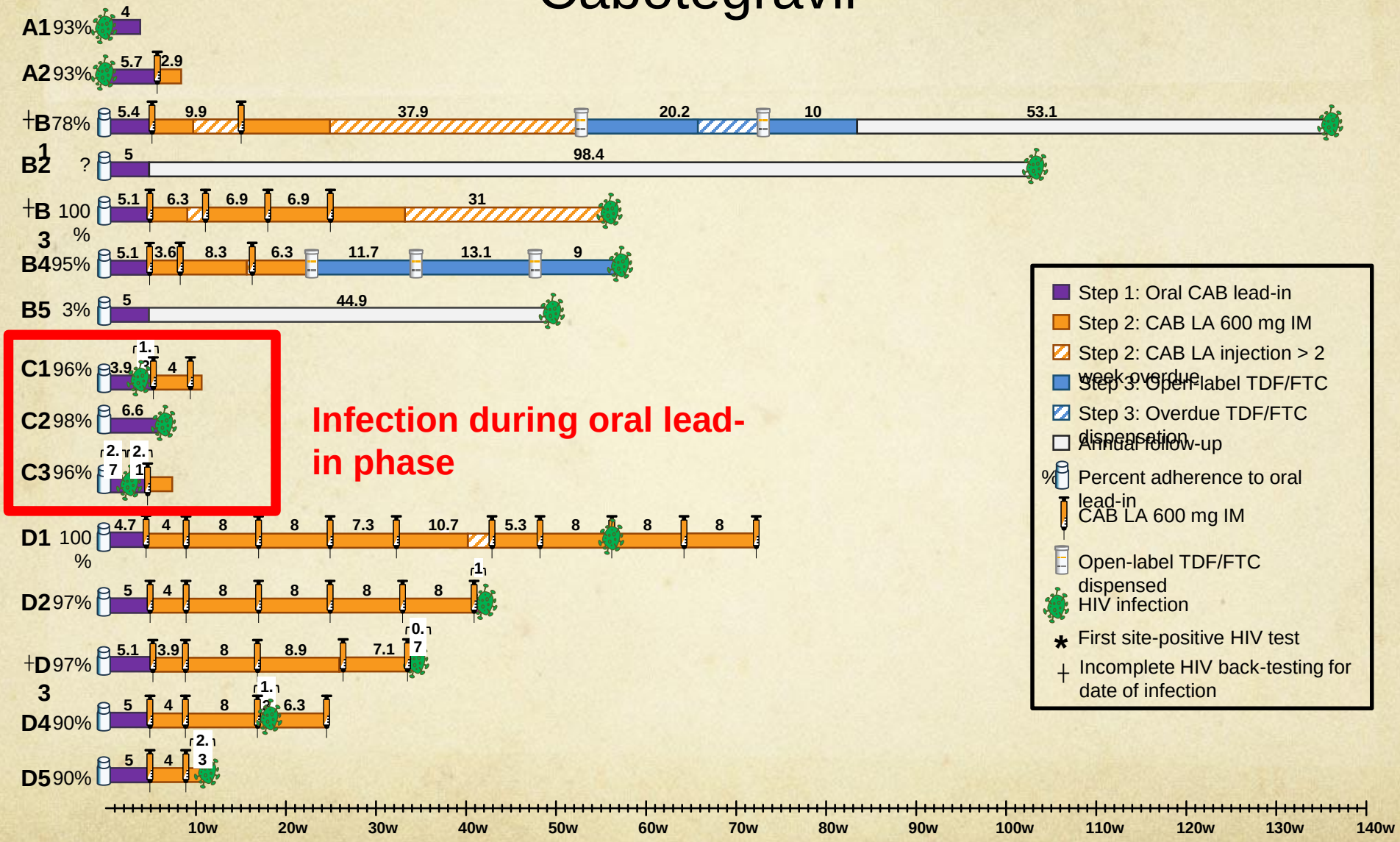


Infection after prolonged hiatus from CAB

- Step 1: Oral CAB lead-in
- Step 2: CAB LA 600 mg IM
- Step 2: CAB LA injection > 2 week overdue
- Step 3: Open-label TDF/FTC dispensation
- Step 3: Overdue TDF/FTC
- Annual follow-up
- % Percent adherence to oral lead-in
- CAB LA 600 mg IM
- Open-label TDF/FTC dispensed
- HIV-infection
- * First site positive HIV test
- † Awaiting HIV back-testing

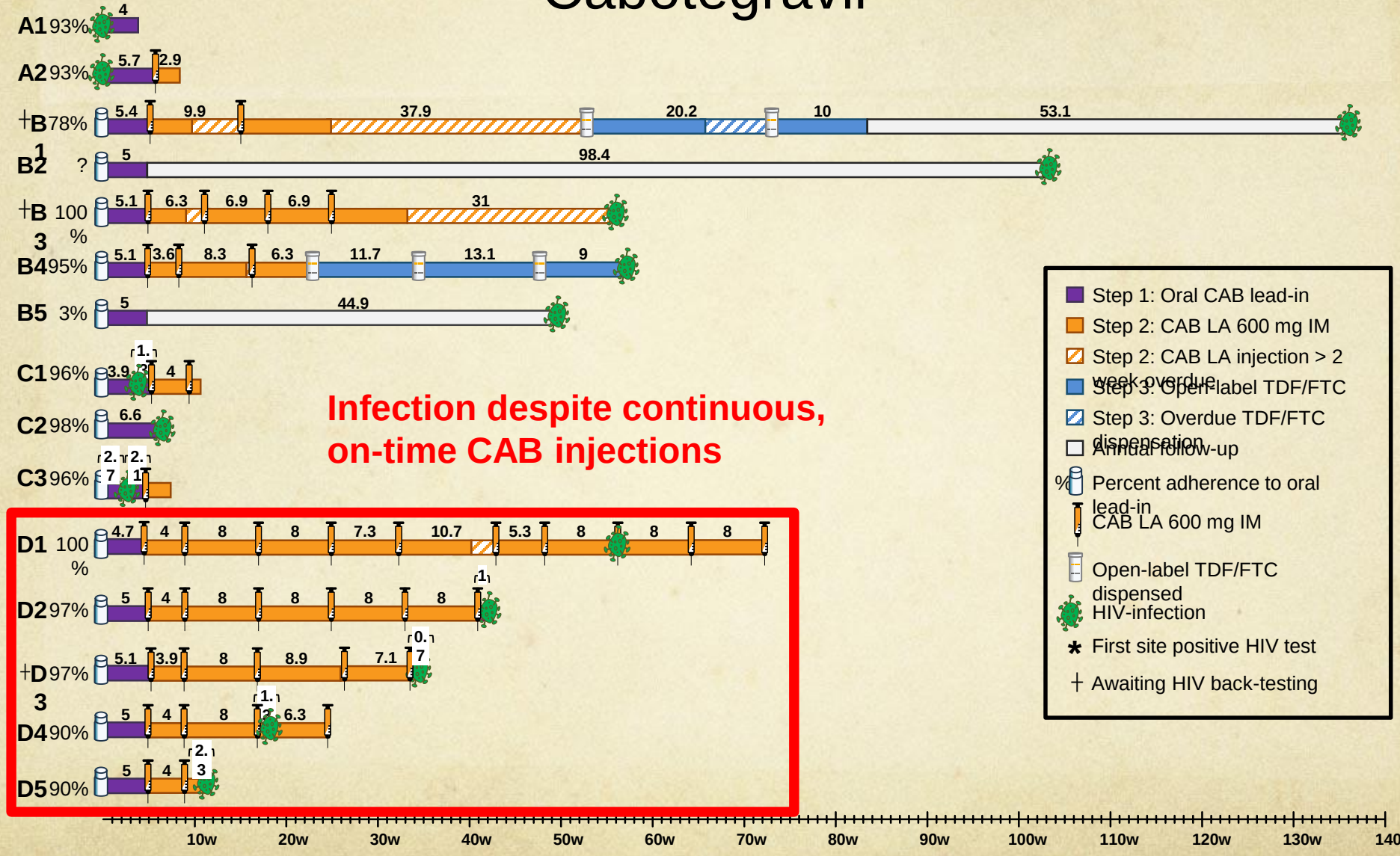
Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

13 Incident HIV Infections
Cabotegravir



Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

13 Incident HIV Infections
Cabotegravir

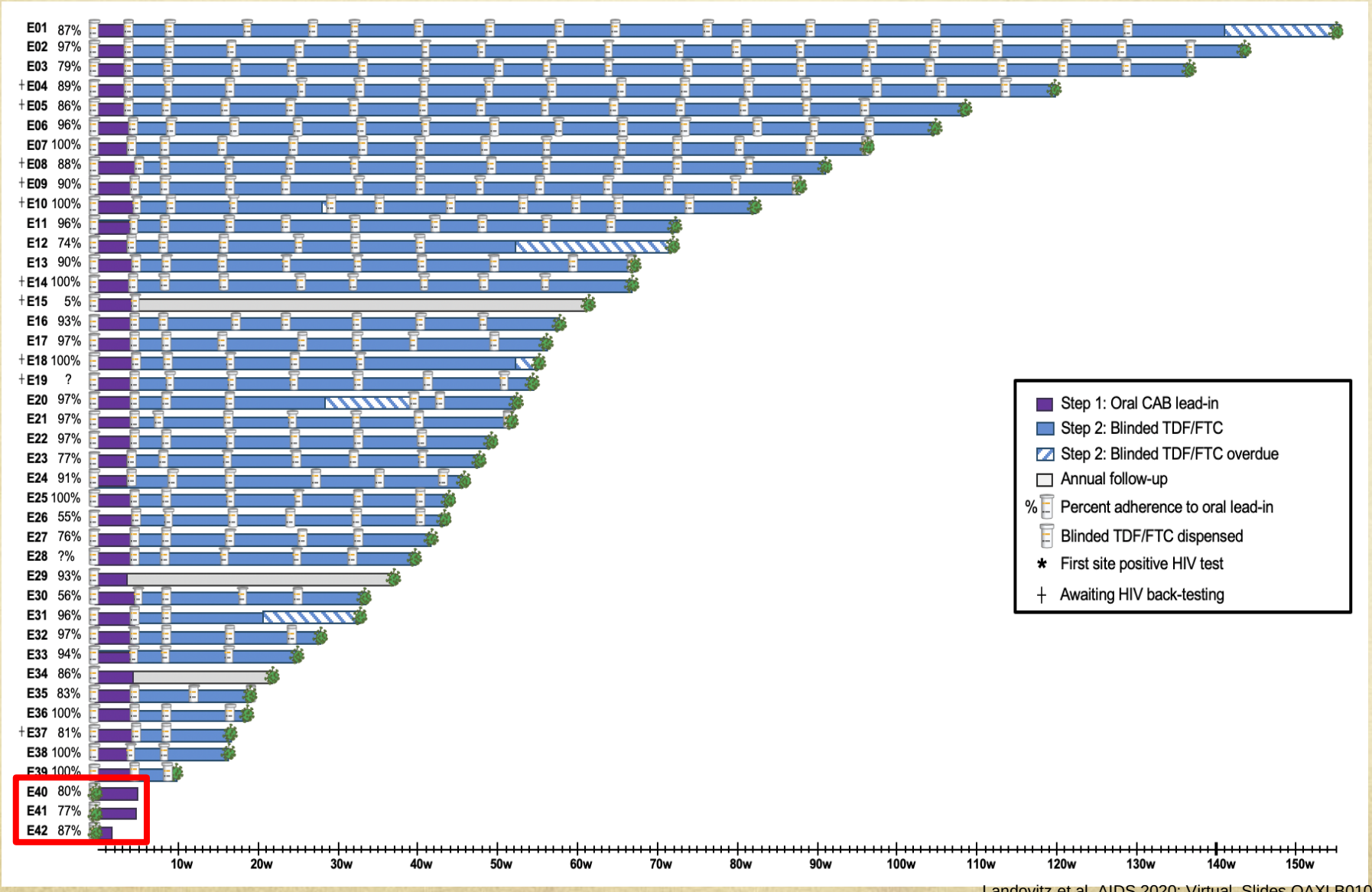


Infection despite continuous, on-time CAB injections

- Step 1: Oral CAB lead-in
- Step 2: CAB LA 600 mg IM
- Step 2: CAB LA injection > 2 week overdue
- Step 3: Open-label TDF/FTC
- Step 3: Overdue TDF/FTC dispensation
- Annual follow-up
- % Percent adherence to oral lead-in
- CAB LA 600 mg IM
- Open-label TDF/FTC dispensed
- HIV-infection
- * First site positive HIV test
- † Awaiting HIV back-testing

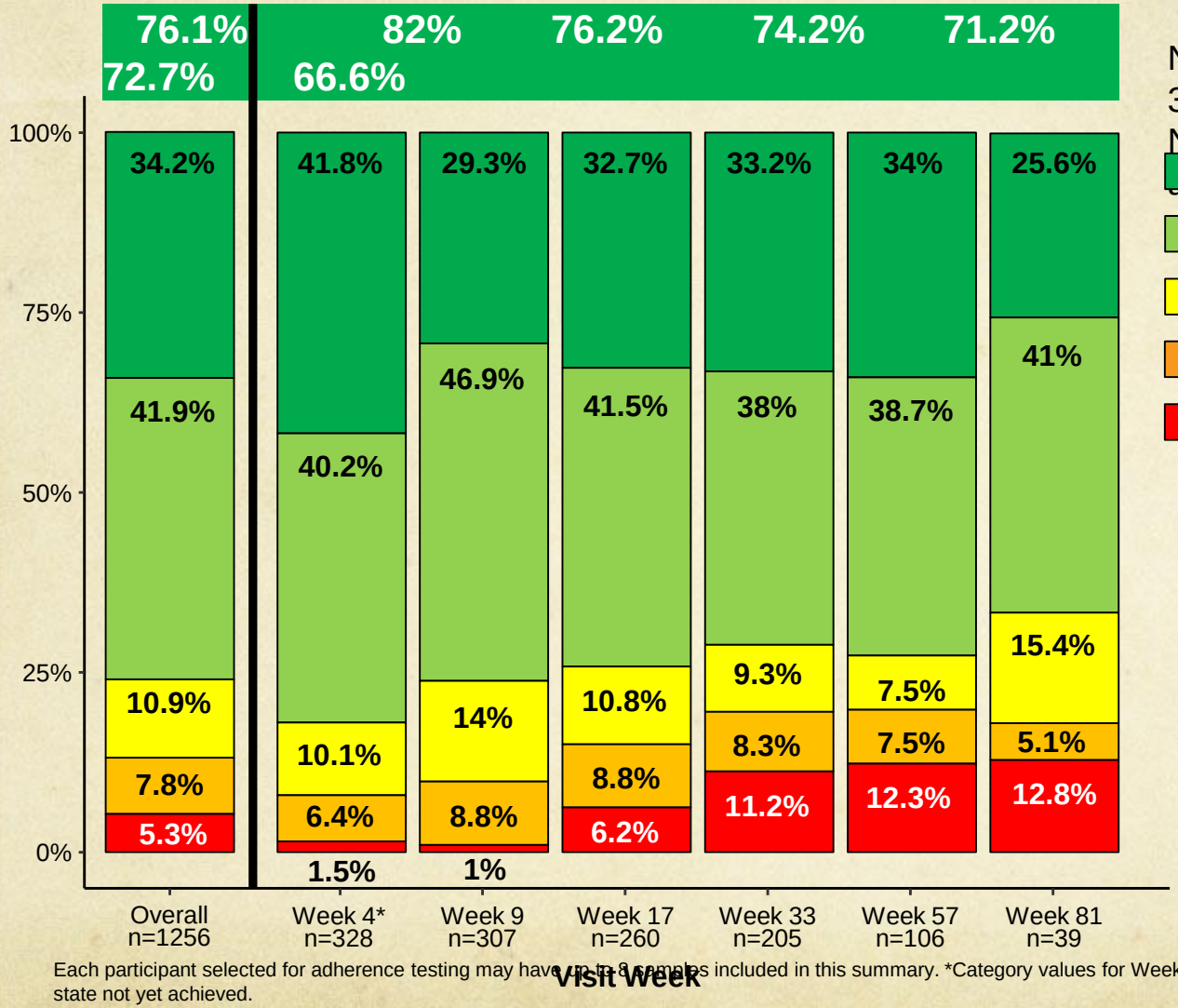
Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

39 Incident HIV Infections
TDF/FTC



Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

DBS TFV-DP
Randomly Selected “Adherence” Subset



Number of participants: 372

Number of samples assayed: 1256

- 7 doses/week (≥1250 fmol/punch)
- 4 – 7 doses/week 700 - <1250 fmol/punch)
- 2 – 4 doses/week (350 - <700 fmol/punch)
- <2 doses/week (LLOQ - <350 fmol/punch)
- No detectable drug (BLQ)

Plasma TFV

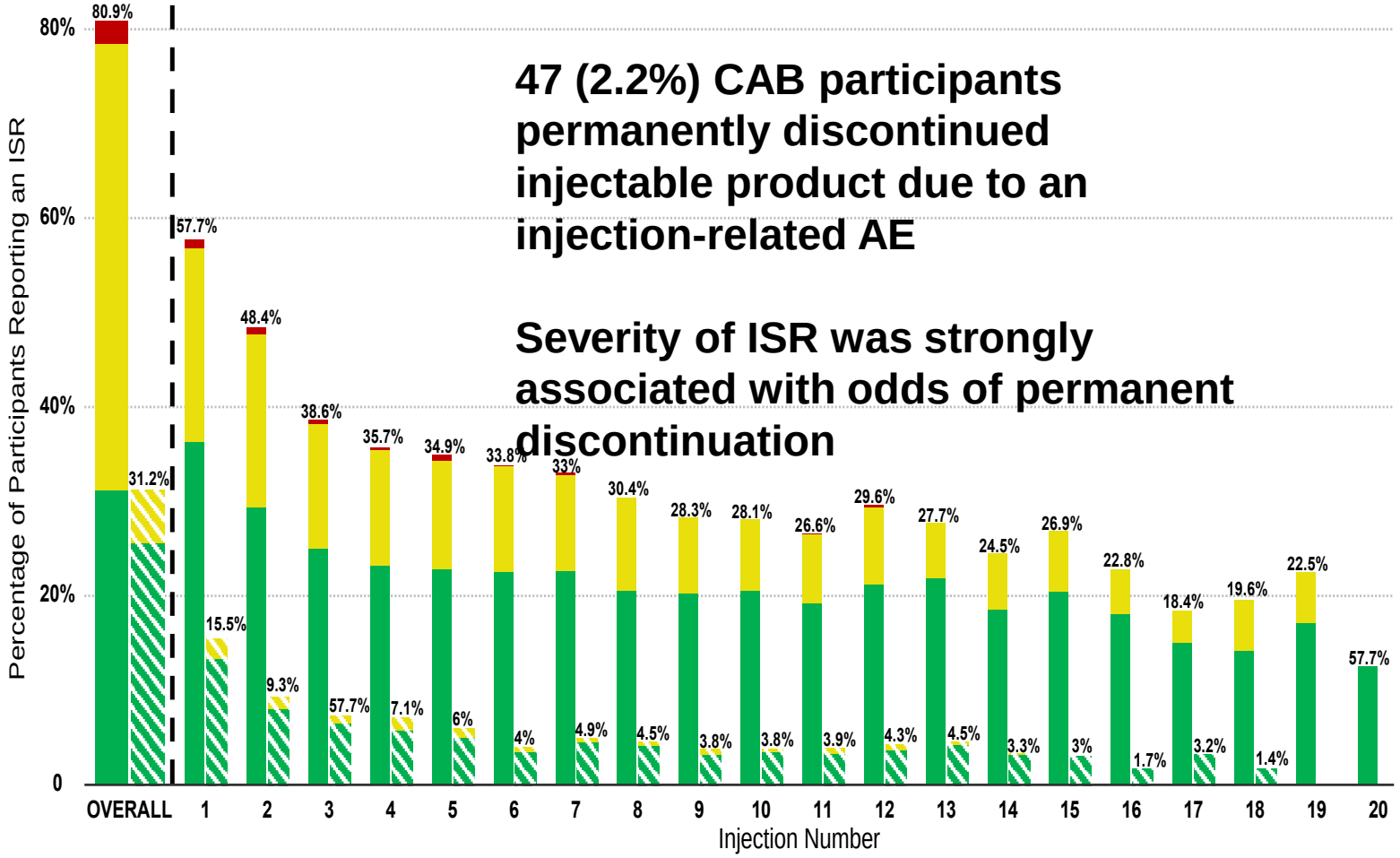
87% >10 ng/mL

75% >40 ng/mL

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.

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

Injection Site Reactions

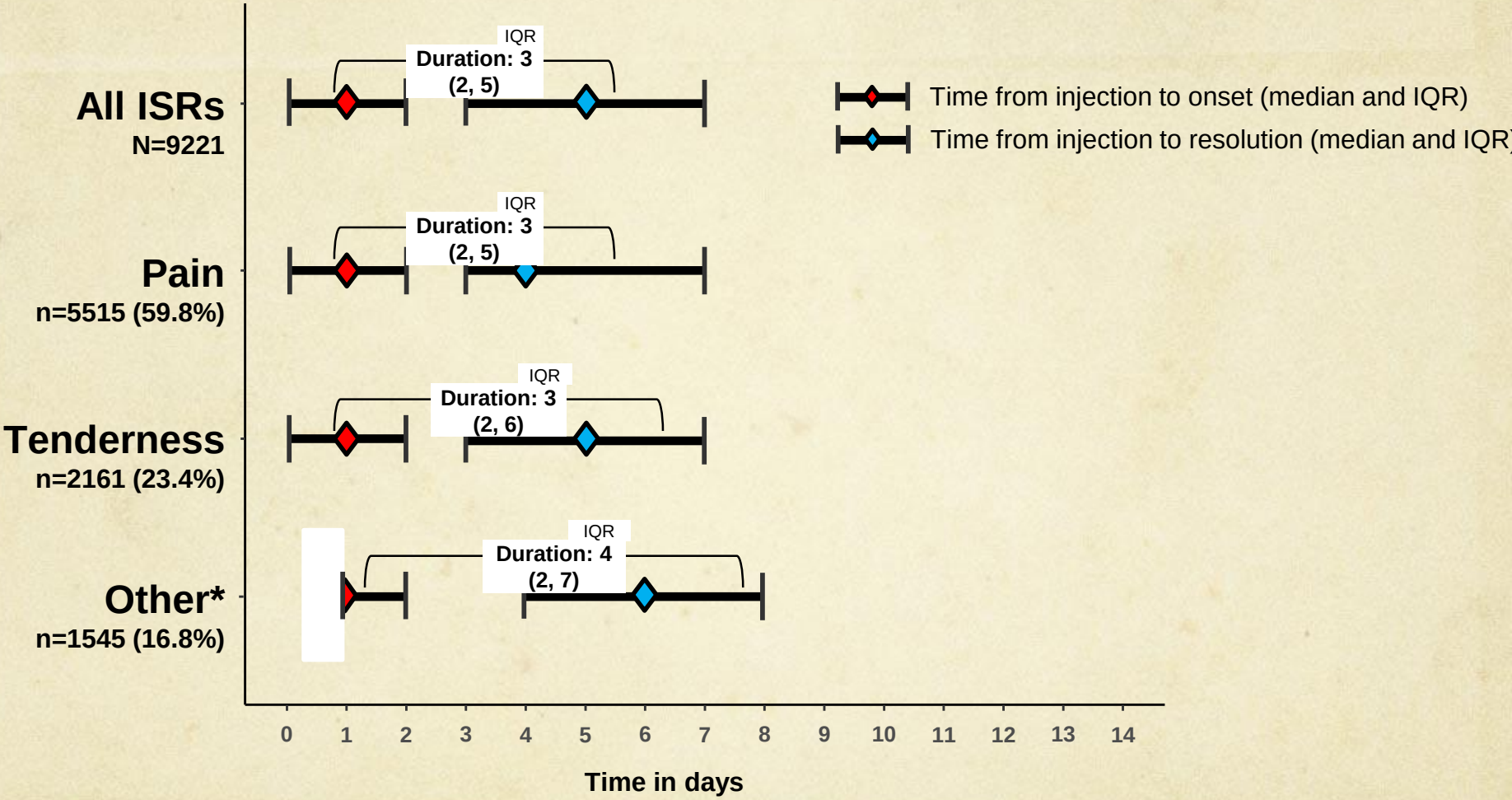


47 (2.2%) CAB participants permanently discontinued injectable product due to an injection-related AE

Severity of ISR was strongly associated with odds of permanent discontinuation

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

ISR Timing/Duration



*Other injection site reactions include induration, nodule, hematoma, bruising, discoloration, swelling, erythema, itching, warmth, anesthesia, hemorrhage, and abscess.

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

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
Creatinine increased	775 (17.0%)	412 (18.1%)	363 (15.9%)	0.06
Upper Respiratory Infection	510 (11.2%)	255 (11.2%)	255 (11.2%)	0.99
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

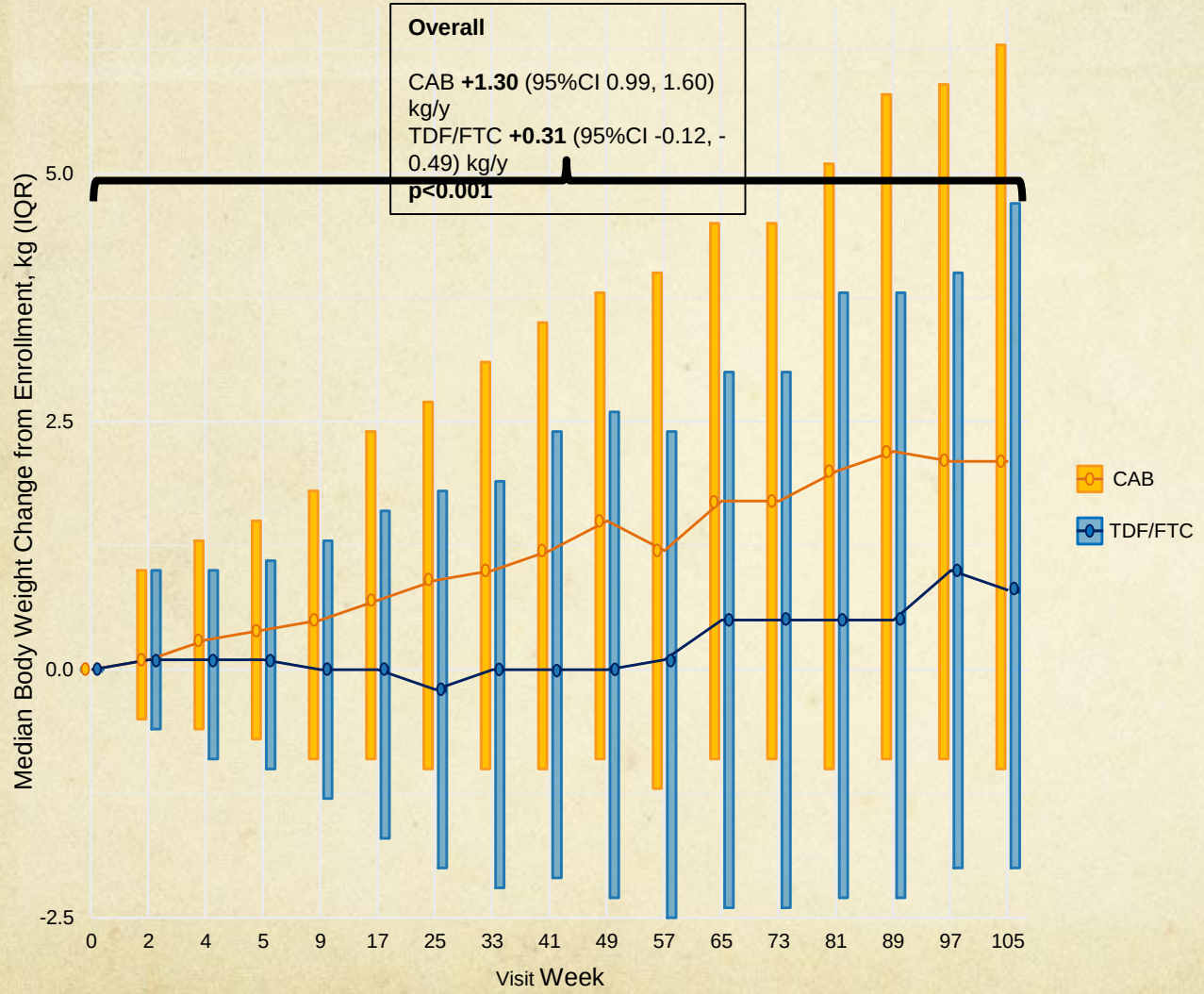
Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

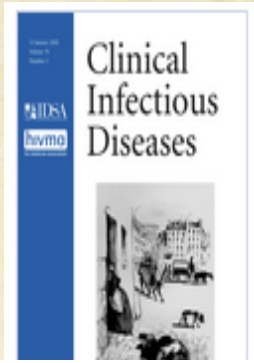
Prevalent and Incident STIs

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
Prevalent at baseline, n (%)			
Syphilis	241 (5.3)	115 (5.1)	126 (5.5)
$Gonorrhea_{urine}$	29 (0.6)	17 (5.1)	12 (0.5)
$Gonorrhea_{rectal}$	297 (6.5)	150 (6.6)	147 (6.5)
$Chlamydia_{urine}$	122 (2.7)	57 (2.5)	65 (2.9)
$Chlamydia_{rectal}$	502 (11)	255 (11.2)	247 (10.9)
Incidence, n (rate per 100 py)			
Syphilis	908 (16.5)	451 (16.4)	457 (16.5)
$Gonorrhea_{urine}$	128 (2.4)	57 (2.1)	71 (2.6)
$Gonorrhea_{rectal}$	592 (10.9)	295 (10.9)	297 (11)
$Chlamydia_{urine}$	241 (4.4)	124 (4.6)	117 (4.3)
$Chlamydia_{rectal}$	906 (16.7)	481 (17.8)	425 (15.7)

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

Changes in Weight
Median of Changes From Baseline (IQR)





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

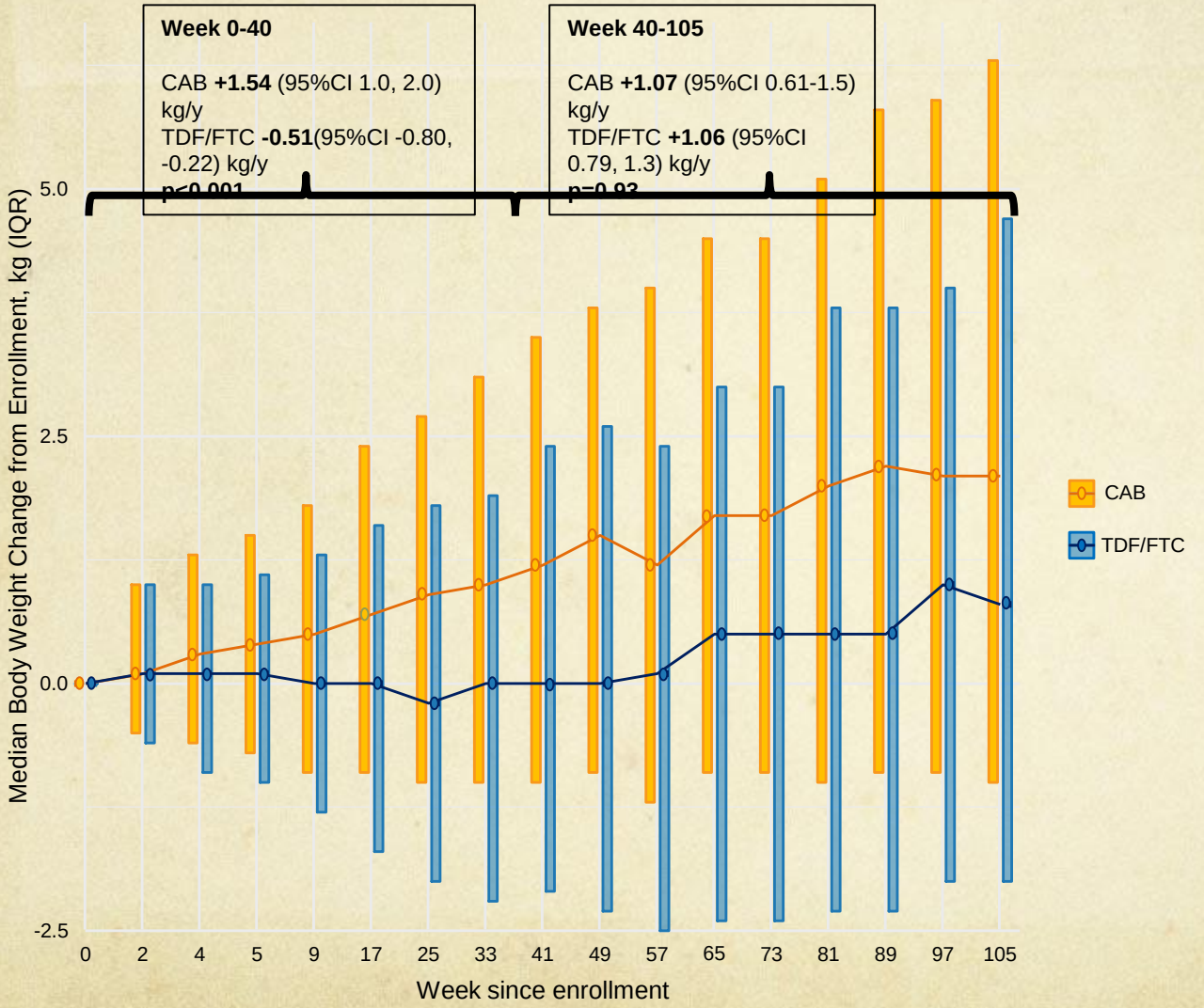
Raphael J Landovitz [1], Sahar Z Zangeneh [2], Gordon Chau [2], Beatriz Grinsztejn [3], Joseph J Eron [4], Halima Dawood [5], Manya Magnus [6], Albert Y Liu [7], Ravindre Panchia [8], Mina C Hosseinipour [9], Ryan Kofron [1], David A Margolis [10], Alex Rinehart [10], Adeola Adeyeye [11], David Burns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

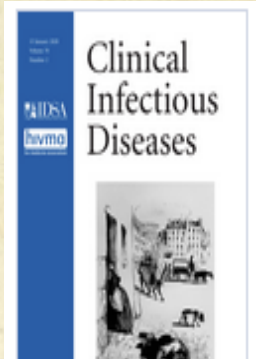
HPTN 077: Over 41 weeks

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 et al. AIDS 2020; Virtual. Slides OAXLB0101.

Changes in Weight
Median of Changes From Baseline





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p=0.95

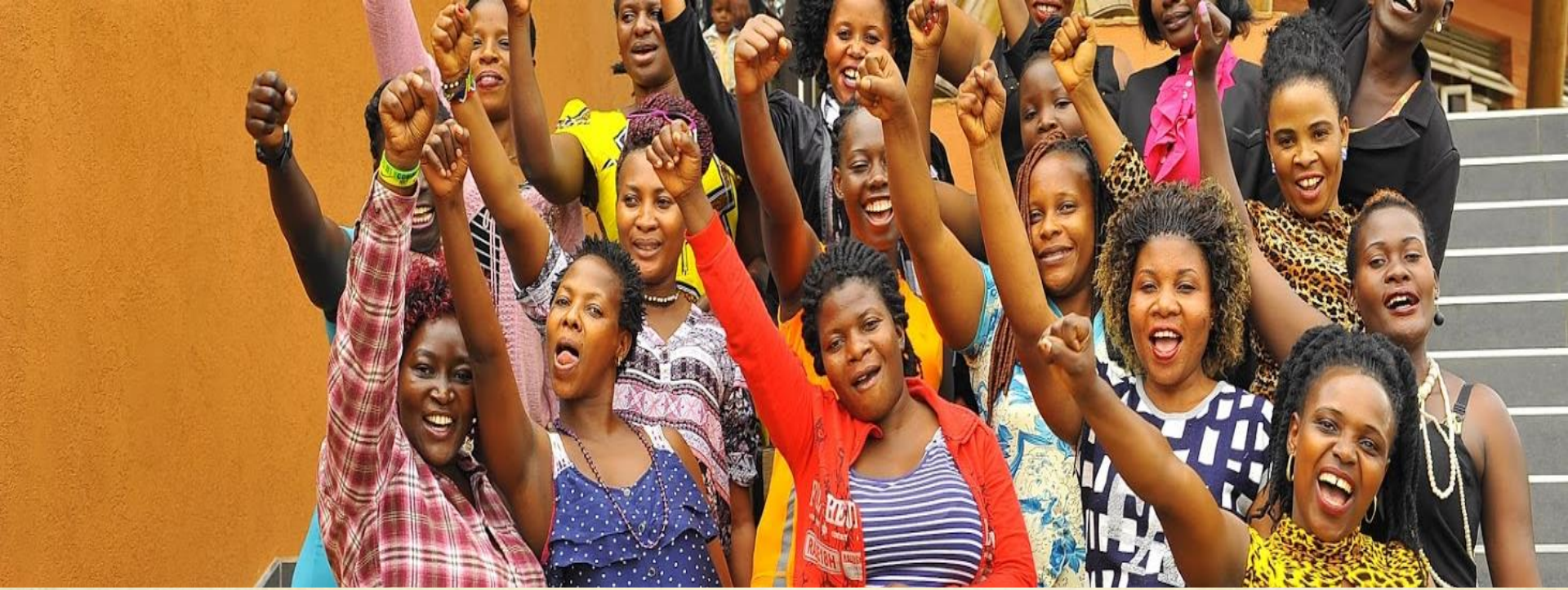
Landovitz RJ et al. CID 2019.

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.

Conclusions

- Both agents were highly effective for HIV prevention
- The PrEP regimen containing CAB-LA was superior to a daily oral regimen of TDF/FTC in HPTN 083, with a 66% reduction in risk of HIV infection observed in participants receiving CAB compared to TDF/FTC
- CAB-LA was well tolerated despite injection site reactions
- Peri-infection drug concentrations and detailed resistance profiles are needed to fully understand and contextualize results
- CAB is the first long-acting injectable agent to demonstrate robust HIV prevention efficacy in MSM/TGW
- Awaiting results for cisgender women (HPTN 084)

Landovitz et al. AIDS 2020; Virtual. Slides OAXLB0101.



HPTN 084
Long-acting Injectable For the Epidemic

Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: results from HPTN 084

Sinead Delany-Moretlwe, MBBCh PhD
on behalf of the HPTN 084 study team

HPTN
HIV Prevention Trials Network

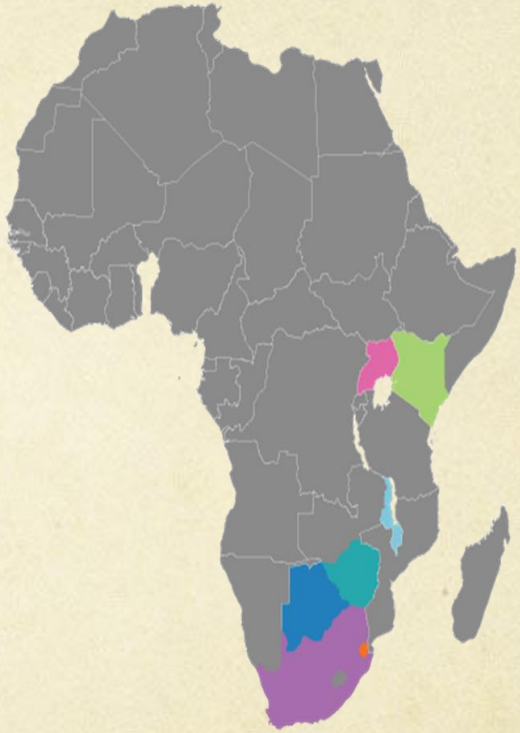
Primary Objectives

- To evaluate the relative efficacy of oral CAB/CAB LA vs. daily oral TDF/FTC for HIV prevention.

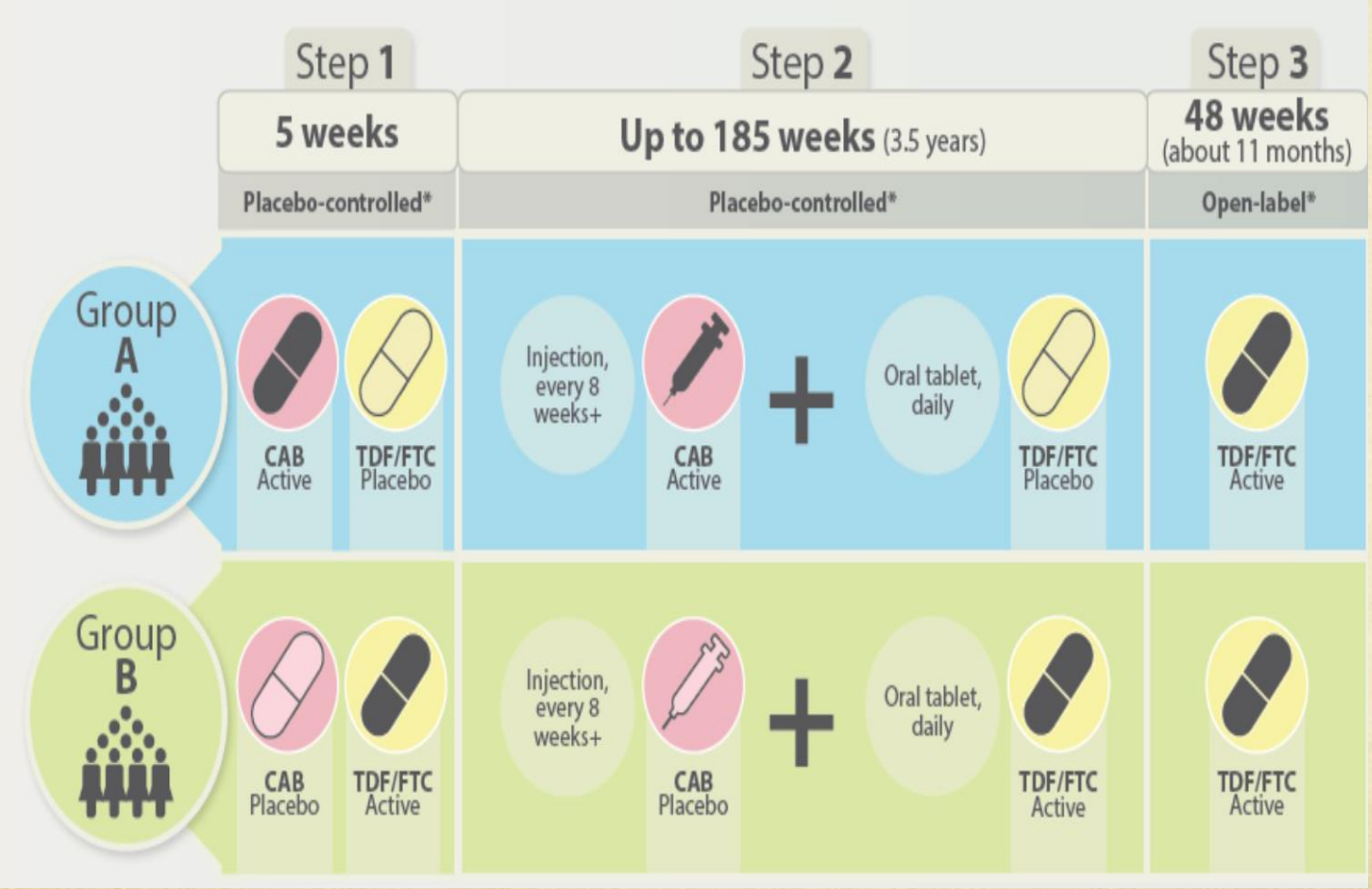
- To evaluate the relative safety of oral CAB/CAB LA vs. daily oral TDF/FTC for HIV prevention.

Study population

- Planned enrolment n=3200 at 20 sites
- Cisgender women aged 18-45 years
- HIV negative
- Sexually active
- Modified VOICE Risk Score ≥3*
  - Age, partner characteristics, alcohol use
  - Increased to ≥ 5
- No contraindications to either agent
  - No hepatic or renal insufficiency, seizures
- Not pregnant or breastfeeding
- Use reliable form of modern contraception



Study design



HPTN
HIV Prevention
Trials Network

Primary outcome: HIV incidence

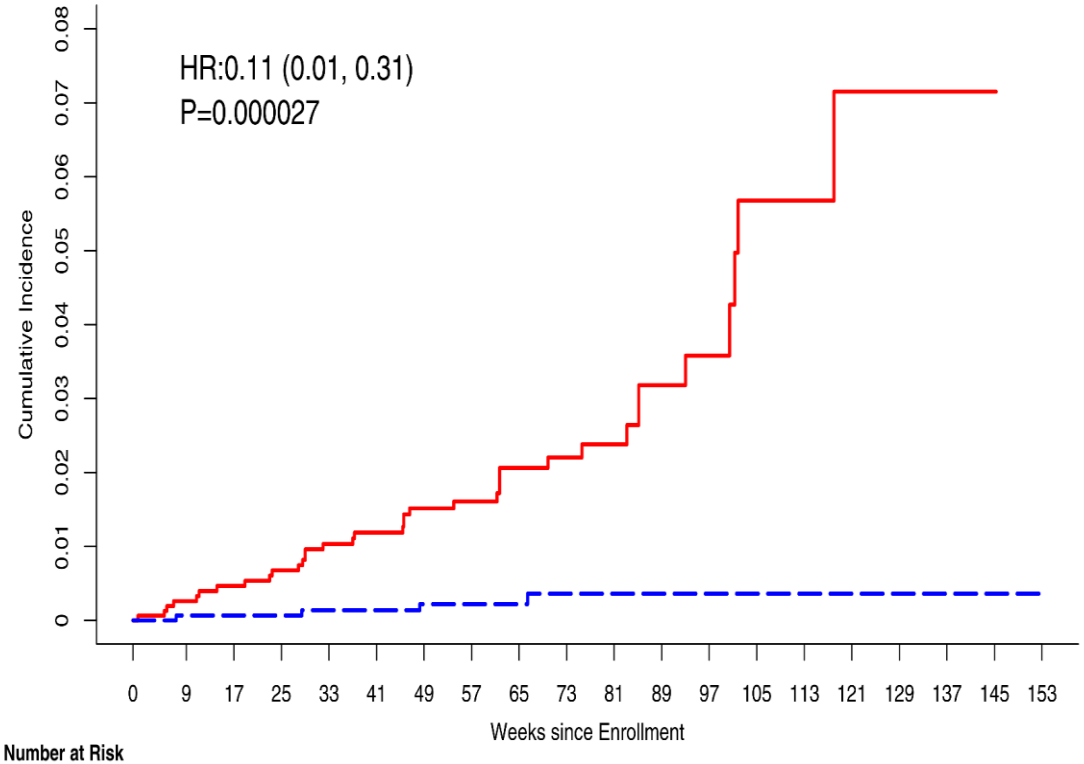
40 infections over 3892 person-years
Pooled HIV incidence 1.03 (0.73, 1.4) per 100 person-years

	CAB	TDF/FTC
HIV infections	4	36
Person-years	1,953	1,939
HIV incidence (95% CI)	0.2 (0.06, 0.52)	1.86 (1.3, 2.57)

Wald test z statistic - 4.20, efficacy stopping bound (z scale) - 3.61

Cumulative HIV incidence

ITT



Number at Risk

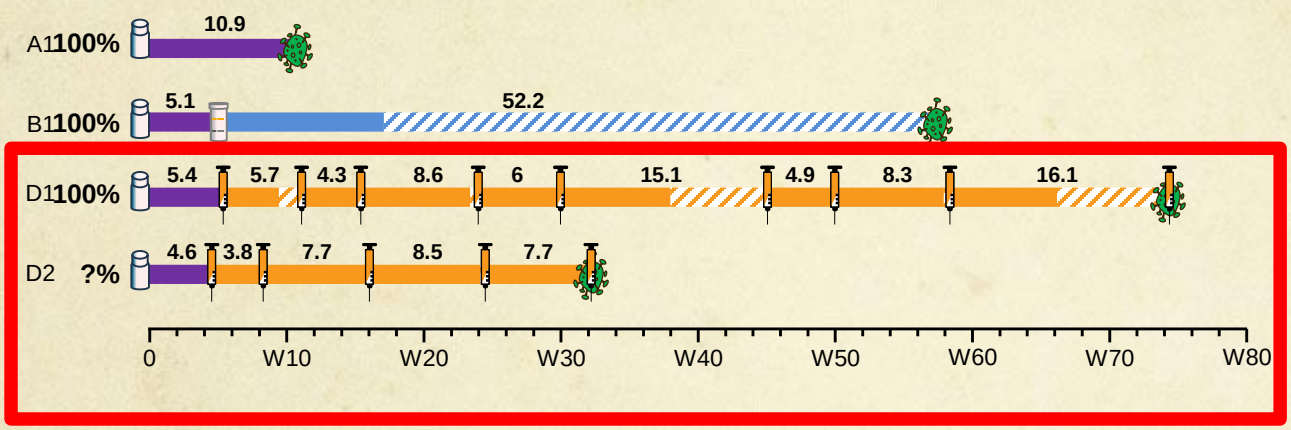
TDF/FTC	1609	1490	1429	1410	1351	1259	1158	982	799	655	482	306	201	113	70	63	52	22	3	0
Cabotegravir	1612	1485	1441	1429	1370	1279	1177	985	800	647	480	304	204	113	67	58	50	23	3	2

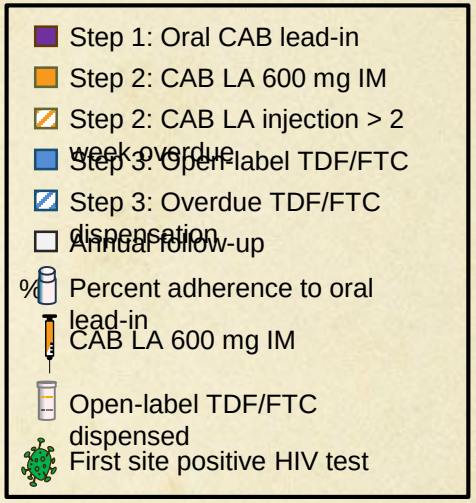
Cumulative Number of Events

TDF/FTC	0	4	7	10	15	17	21	22	26	27	28	31	32	35	35	36	36	36	36	36
Cabotegravir	0	1	1	1	2	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4

*Women in the CAB group had an **89% lower risk of HIV infection,** compared to TDF/FTC group*

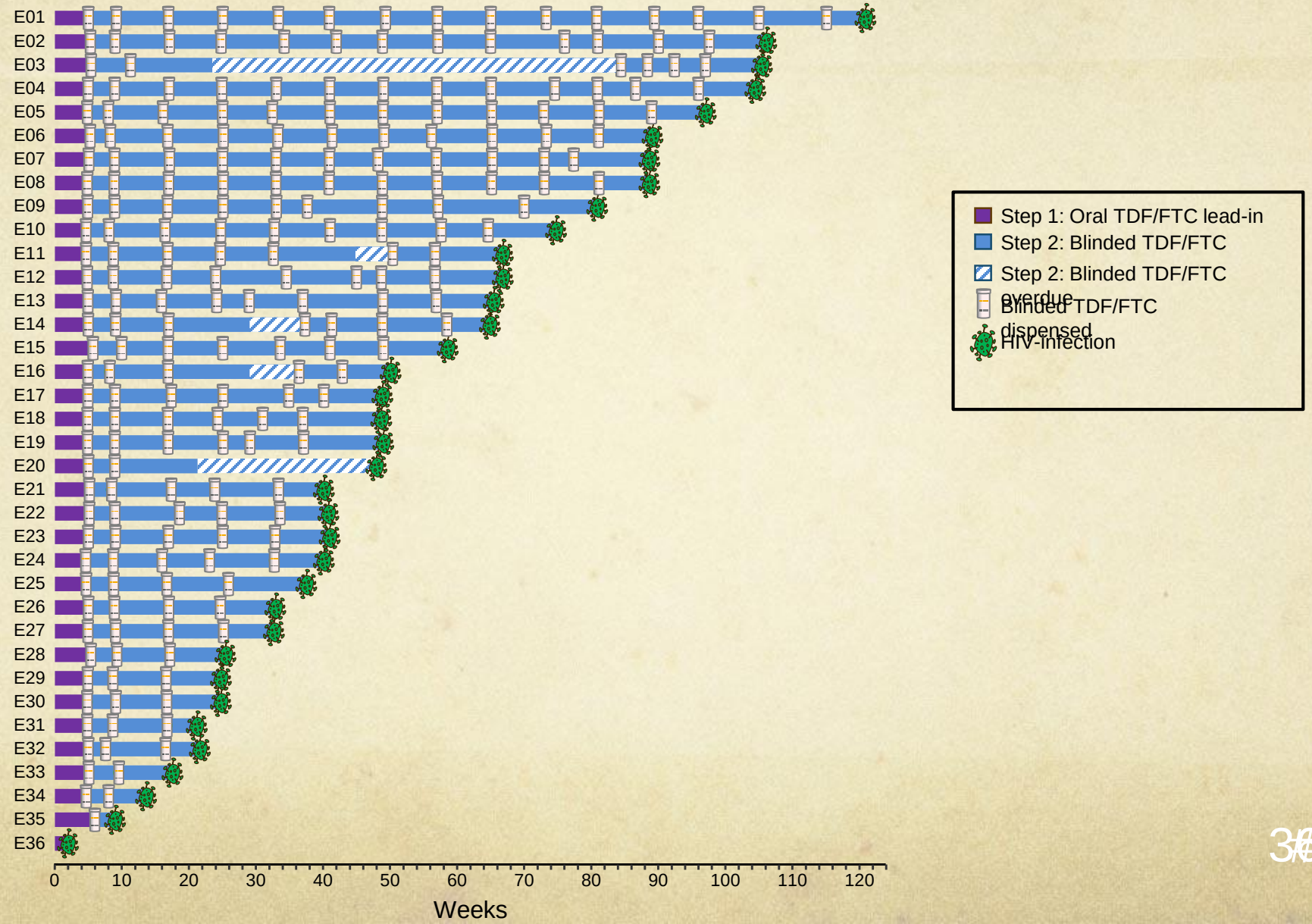
Cabotegravir - 4 incident HIV Infections



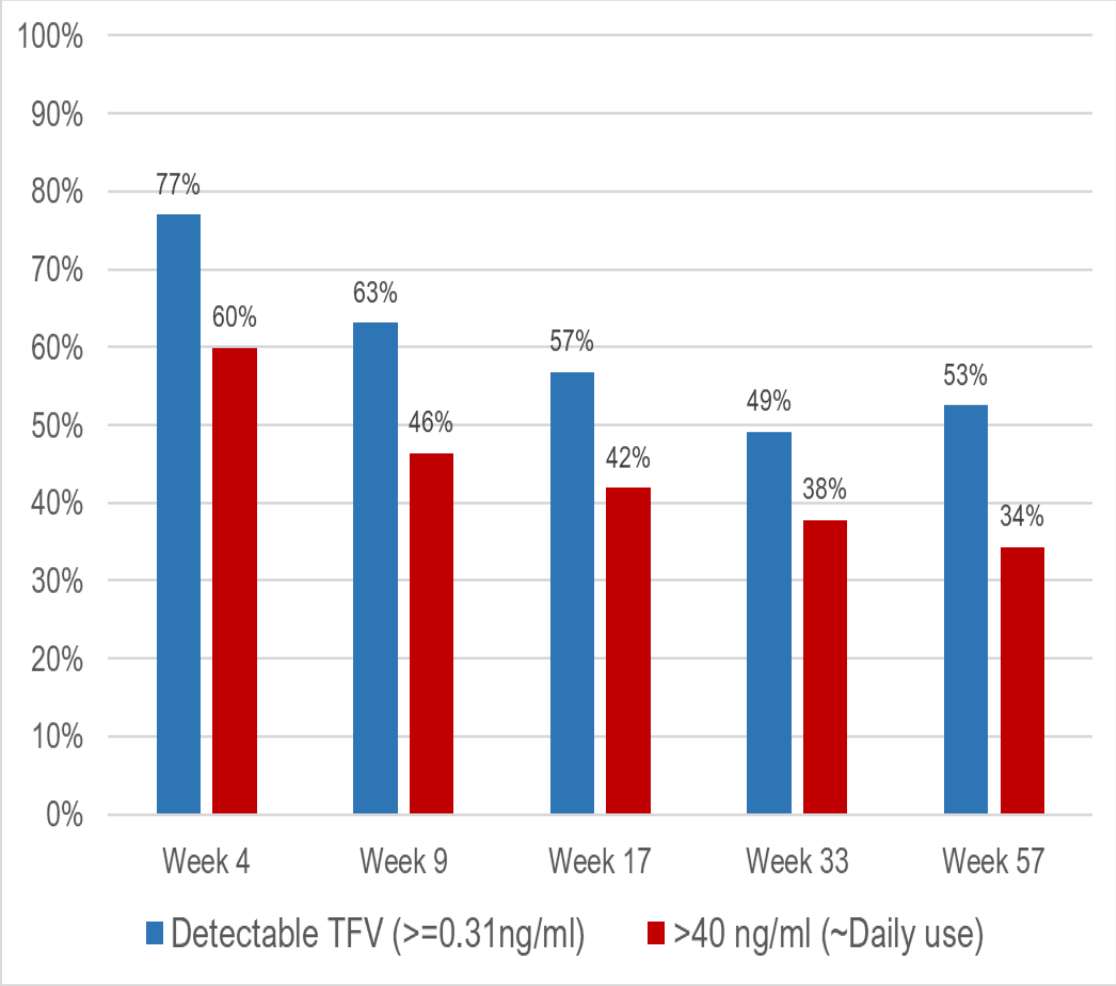


Infection despite CAB injections

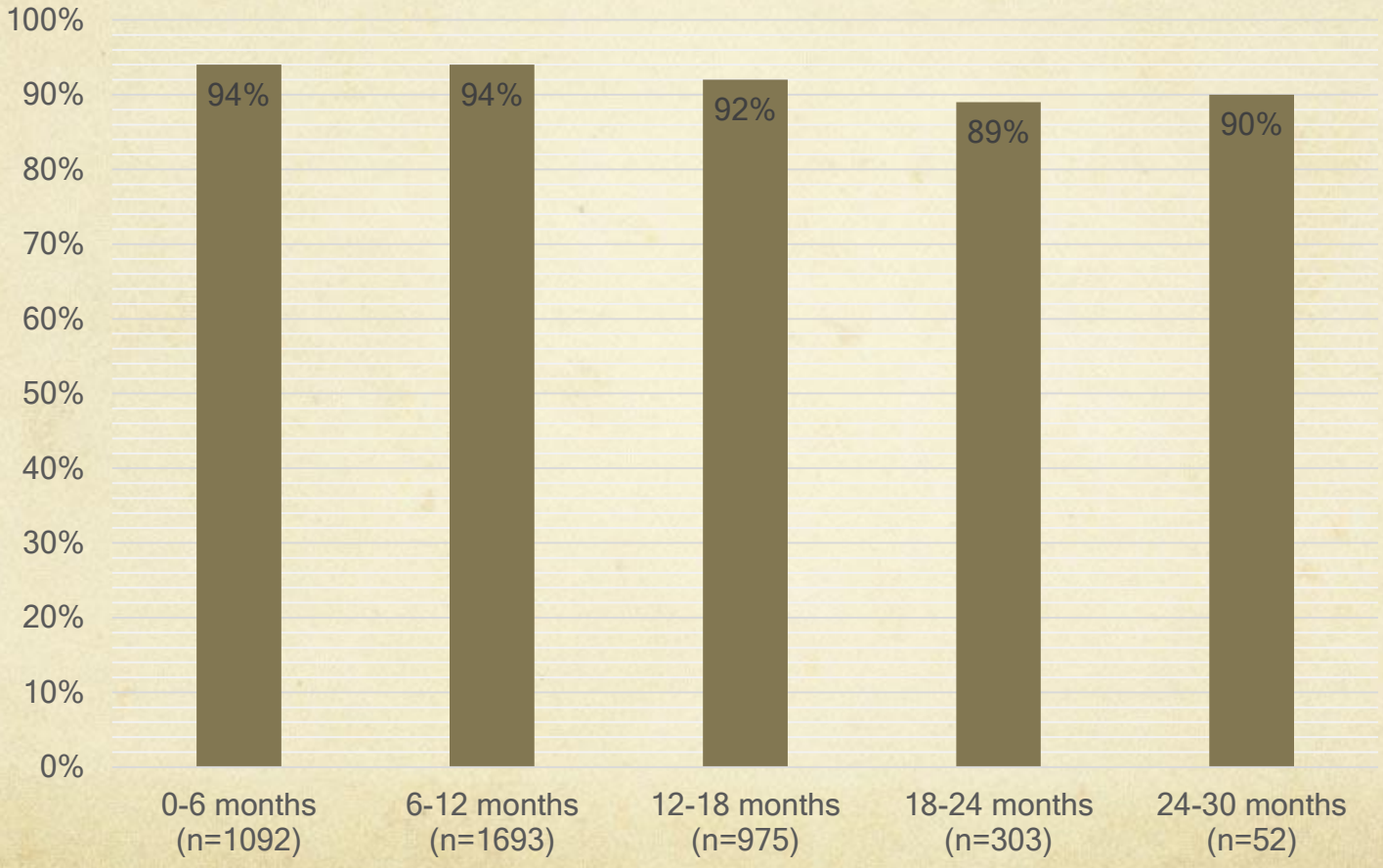
TDF/FTC - 36 Incident HIV Infections



TDF/FTC plasma concentrations – adherence subset (n=375)

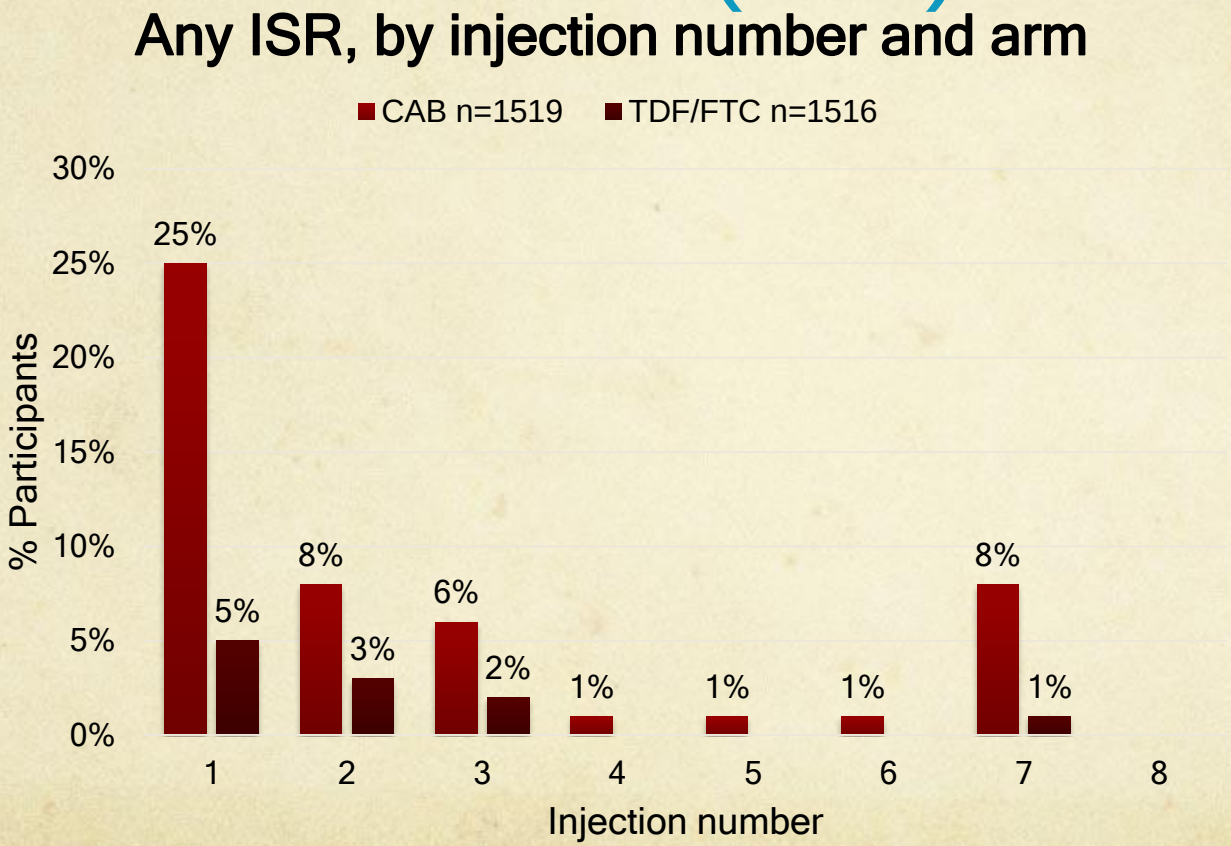


Injection coverage, 6-month intervals - all



Injection coverage: injections administered as a proportion of total expected injection visits

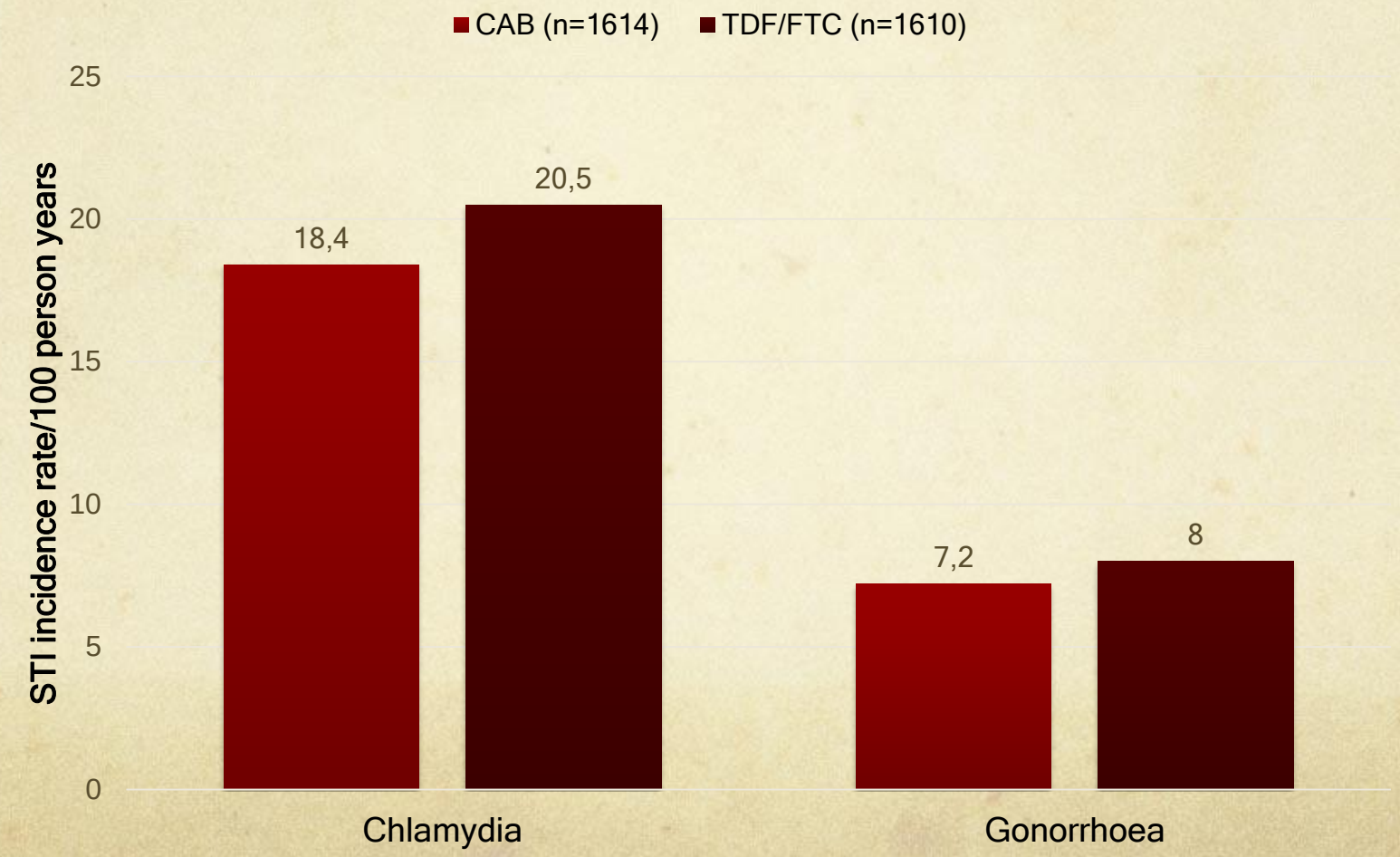
Safety: Injection site reactions (ISR)



- 21% participants any ISR
  - 32% CAB vs. 9% TDF/FTC
- 4% participants Grade 2+ ISR
  - 7% CAB vs. 1% TDF/FTC
- Zero discontinuations d/t ISR

HPTN
HIV Prevention Trials Network

CT/GC incidence - ITT (n=3,224)

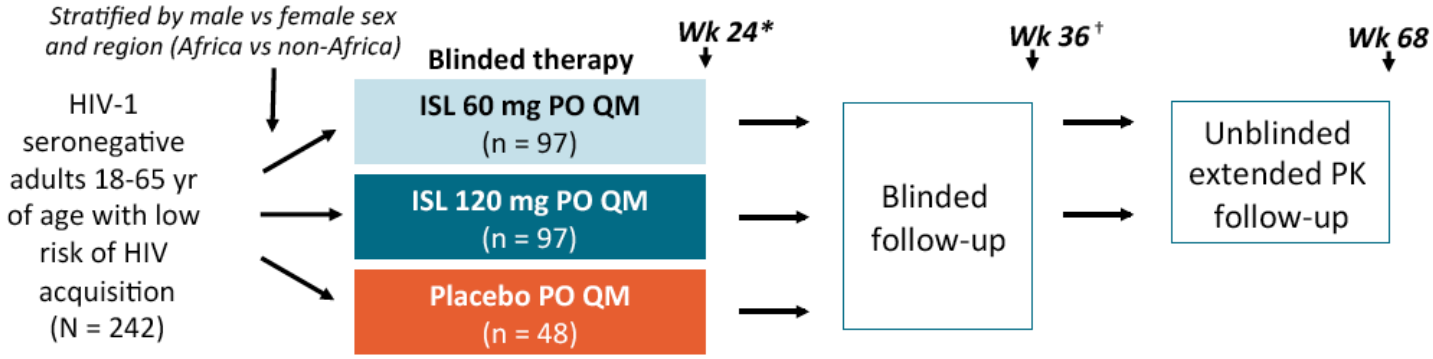


Conclusions

- Both agents highly effective in preventing HIV
  - Pooled incidence 1.03 (0.73, 1.4) per 100 py
- CAB was superior to daily oral TDF/FTC in preventing HIV in cisgender women
  - 89% lower risk of HIV infection in participants receiving CAB compared to TDF/FTC
  - Ongoing testing to fully understand reasons for breakthrough infections
  - CAB LA 8-weekly likely provided an adherence advantage over daily oral TDF/FTC
- Both products were safe and well tolerated with few differences in Grade 2+ adverse events by arm, apart from ISR
  - ISR were generally mild, associated with pain, and generally occurred at 1st injection
  - No discontinuations due to ISR
- Results complement data from HPTN 083, and confirm CAB as first safe and effective injectable HIV prevention agent for cisgender women

Protocol 016 Oral Islatravir Once Monthly for PrEP: Wk 24 Safety and Pharmacokinetics Analysis

- Multicenter, randomized, double-blind, placebo-controlled phase IIa trial: 67% female, 53% White, 42% Black, median age 31 yr



*Sponsor unblinded at Wk 24 to allow for interim evaluation of safety. Participants and investigators remain blinded to Wk 36.
†After Wk 36, participants in PBMC/PK Bridging Subset randomized to receive ISL have an additional 32-wk unblinded PK follow-up.

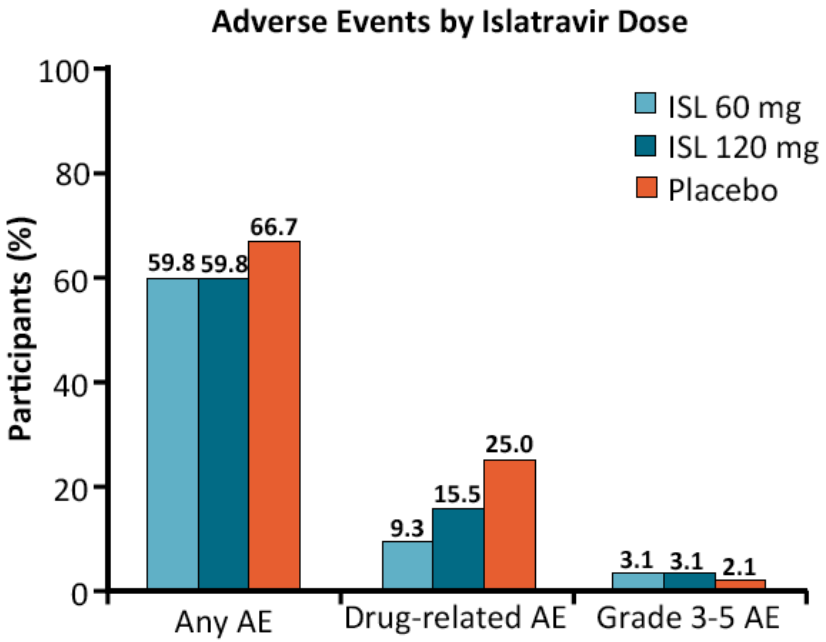
- Primary endpoints: safety/tolerability, pharmacokinetics of ISL-TP (active form of ISL)
- Exploratory endpoints: pharmacokinetics in PBMCs, pharmacokinetics in tissue, hormonal drug-drug interactions

Hillier. IAS 2021. Abstr OALC01LB03.

Slide credit: clinicaloptions.com

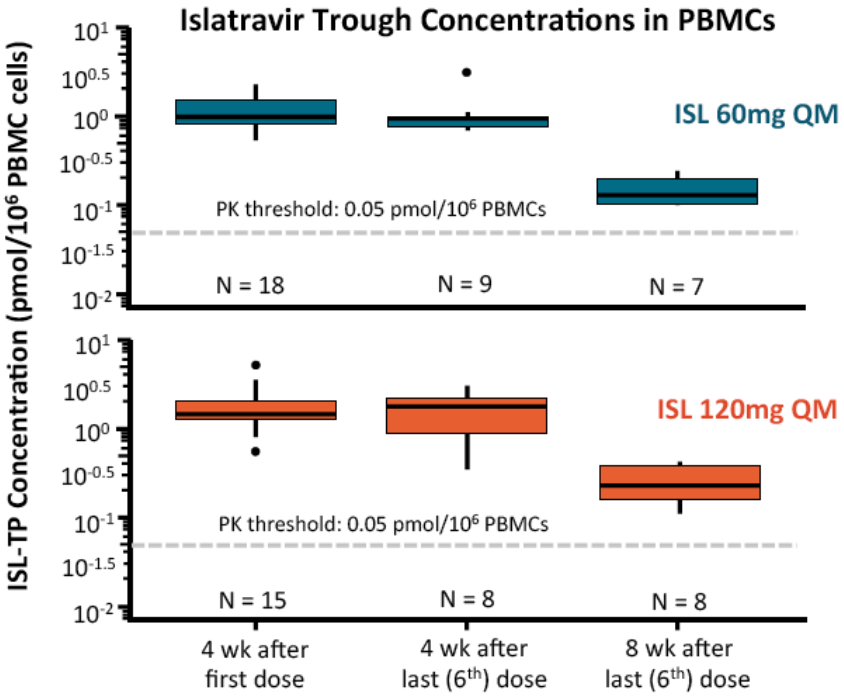
Protocol 016: Wk 24 Adverse Events

- 73.5% of AEs were mild
  - 2 discontinuations* due to AEs considered drug-related
    - Mild foreign body sensation in throat
    - Moderate rash and pruritis
  - 1 participant* had 2 serious AEs; neither considered drug-related



*Treatment assignment not identified to avoid unblinding individual participants.

Protocol 016: Wk 24 Islatravir Pharmacokinetics



- Trough concentrations of ISL-TP (active form of ISL) remained above prespecified PK threshold for HIV-1 prevention for at least 8 wk following last dose

Hillier. IAS 2021. Abstr OALC01LB03.

Slide credit: clinicaloptions.com

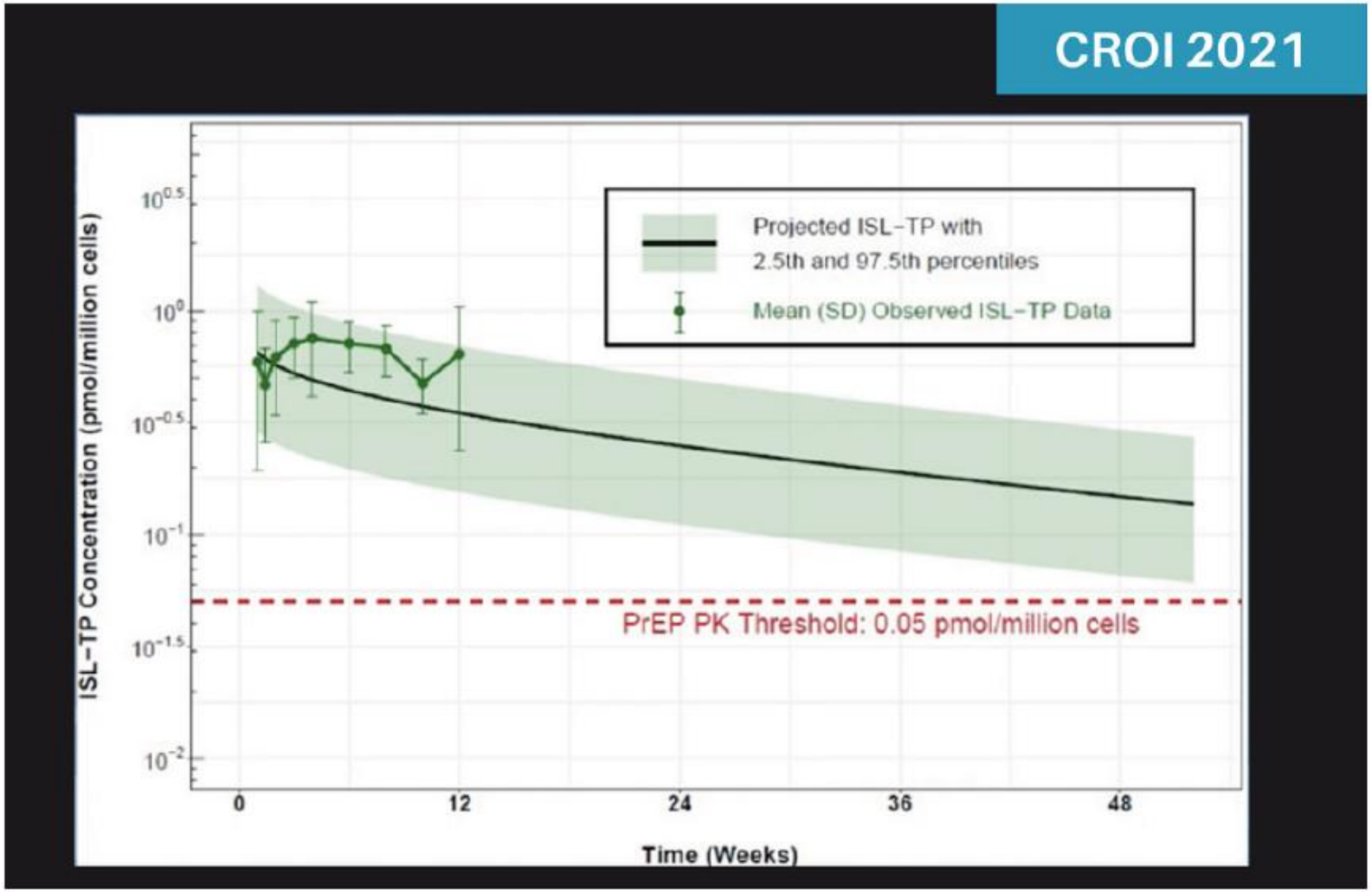
PHASE 3 ISLATRAVIR IN PREP

- IMPOWER 22: Cisgender and girl at high risk in SSA (ISL vs Truvada ou Descovy every one month)

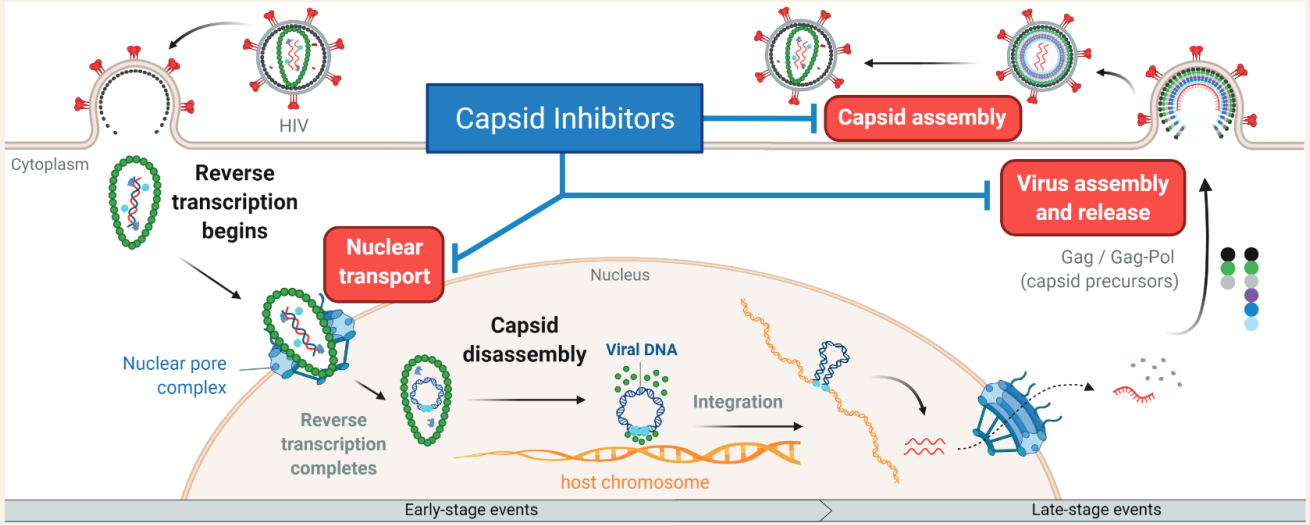
- IMPOWER 24: Cisgender and transgender Who have sex with men around the world ((ISL vs Truvada ou Descovy every one month)

Reformulated islatravir implant should provide PrEP for over a year

9 March 2021



Novel Capsid Inhibitors With Long-acting Potential



- Lenacapavir (LEN) and GS-CA1 inhibit multiple capsid-dependent functions essential for HIV replication

Gag, group antigens; Pol, DNA polymerase.

LEN and GS-CA1 Are Effective Against HIV/SHIV In Vitro and In Vivo

Gilead Capsid Inhibitors

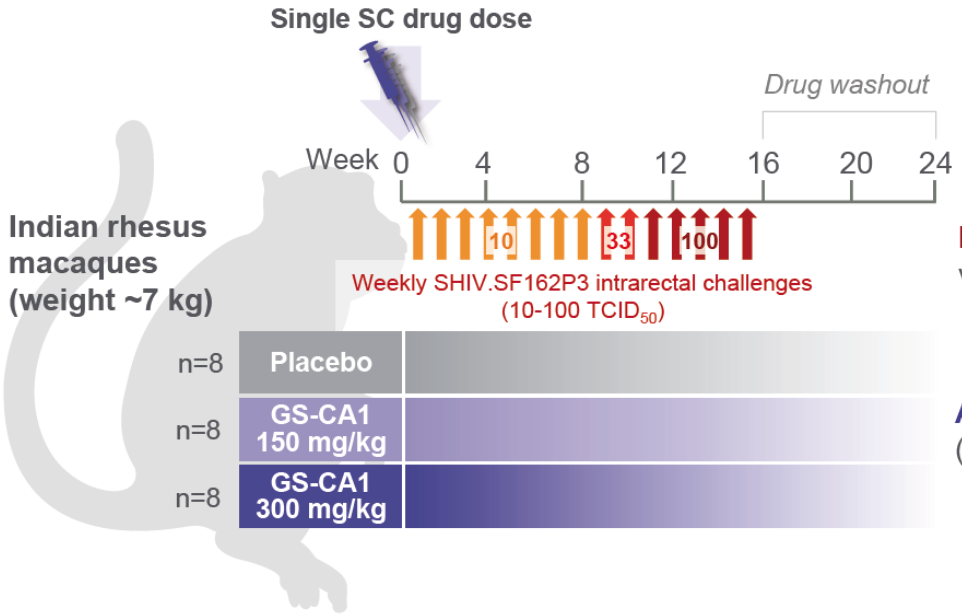
- Multistage capsid-specific MOA
- High metabolic stability, low clearance, and low solubility
- Long-acting potential

	Status	PBMC EC_{50}, nM
LEN (GS-6207)[2]	▪ Favorable safety and tolerability profile in clinical trials* ▪ 2.3-log_{10} HIV-1 RNA decline after 9 d of monotherapy* ▪ q6mo formulation in Phase 2/3 for people with HIV	HIV† 0.050 SHIV‡ 0.569
GS-CA1 (LEN analog)[3]	▪ Preclinical efficacy in humanized mice ▪ Tool compound for preclinical research studies	HIV† 0.130 SHIV‡ 0.748

*GS-US-200-4538, GS-US-200-4071, and GS-US-200-4072; †Tested in human peripheral blood mononuclear cells (PBMCs); ‡Tested in rhesus macaque PBMCs. EC_{50}, half-maximal effective concentration; MOA, mechanism of action; q6mo, every 6 months; SHIV, chimeric simian immunodeficiency virus (SIV)/HIV.

Study Design: Repeat Mucosal Challenge Macaque Model[1-4]

Study objective: To determine the efficacy of **GS-CA1** long-acting formulation at preventing infection after repeat SHIV exposure in rhesus macaques

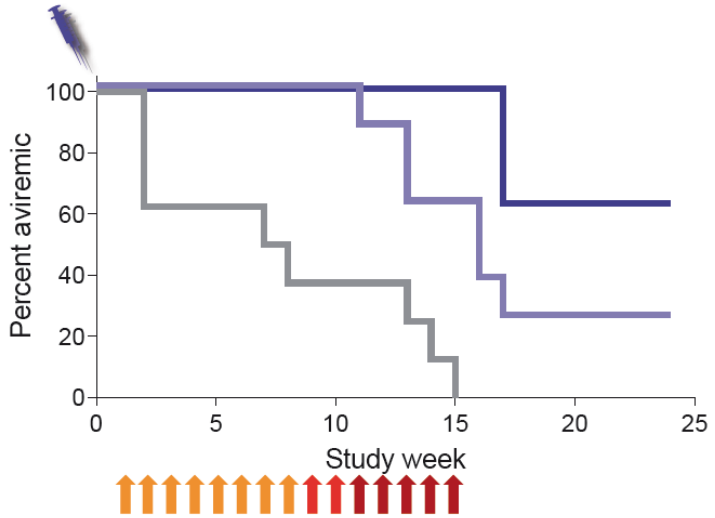


Infection monitoring: weekly plasma viral load (qRT-PCR) & serology

Analysis: per-exposure risk reduction (Cox proportional hazard model)

qRT-PCR, quantitative reverse transcription polymerase chain reaction; SC, subcutaneous; $TCID_{50}$,median tissue culture infectious dose. 1. Subbarao S, et al. J Infect Dis 2006; 2. Garcia-Lerma JG, et al. PLoS Med 2008; 3. Andrews CD, et al. Sci Transl Med 2015; 4. Bekerman E, et al. J Antimicrob Chemother 2020.

GS-CA1 Protects from Repeat Intrarectal SHIV Challenges



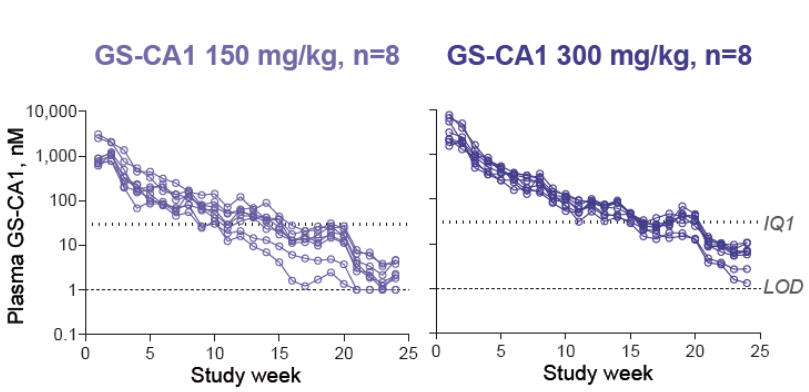
	No. Protected	Median Weeks to Infection (95% CIs)	Hazard Ratio	p-value
GS-CA1 300 mg/kg	5 / 8	Not reached (17, –)	0.038	**0.0002**
GS-CA1 150 mg/kg	2 / 8	16 (11, –)	0.141	**0.0061**
Placebo	0 / 8	7.5 (2,14)	1	

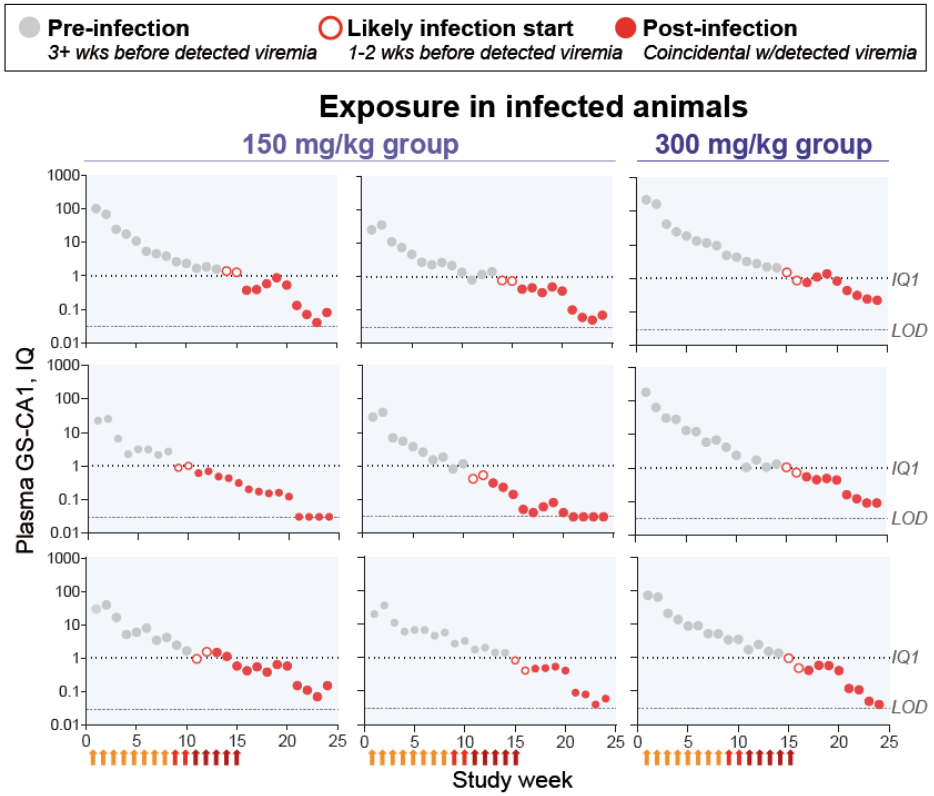
Hazard ratios, p-values calculated using Cox regression model.

- 100% infection of placebo controls within 15 challenges
- Significant infection risk reduction with GS-CA1 vs placebo (86% and 96% for low- and high-dose groups, respectively)
- Infections in GS-CA1-dosed groups occurred only after marked compound washout (9+ weeks post dose*)

CI, confidence interval. *Assumes 2-week infection-detection window.

Protection Correlates with GS-CA1 Exposure





Main conclusions:

- Single GS-CA1 dose achieved long-acting exposure (>IQ1 for 2-4 months) in macaques
- Mean IQ at time of infection was 1* (0.41-1.5 range)
- Complete protection from infection observed with GS-CA1 exposures above IQ1.5 (1.5x paEC95)
- GS-CA1 preclinical data support clinical evaluation of capsid inhibitors for HIV prevention

IQ, inhibitory quotient (protein-adjusted 95% effective concentration). LOD, limit of detection. *Assumes 2-week infection-detection window.

THXXXX