

Long-acting injectable cabotegravir for HIV Pre-Exposure Prophylaxis

HPTN 083

**Raphael J. Landovitz MD MSc
Professor of Medicine
UCLA Center for Clinical AIDS Research & Education
AIDS Institute Grand Rounds
May 14, 2021**

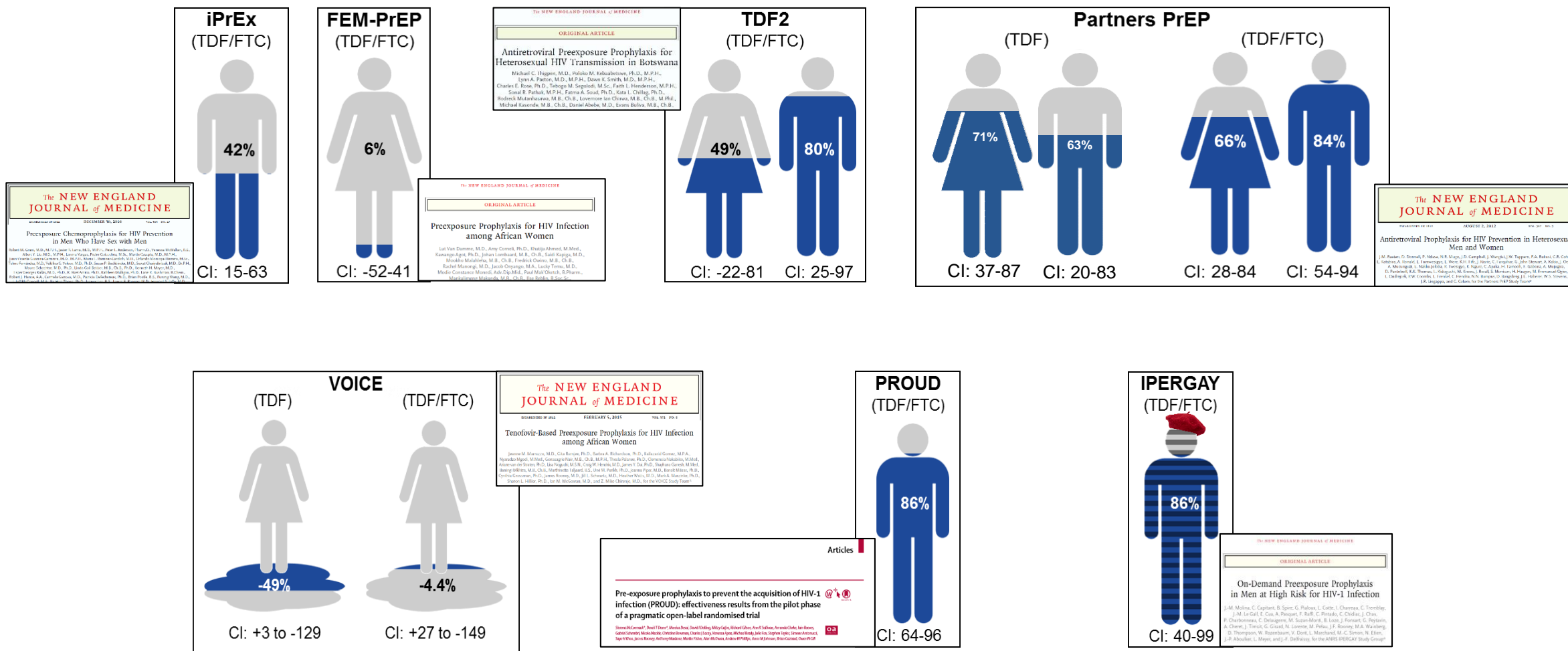
Disclosures

Raphael J. Landovitz has served as on scientific advisory boards for Gilead Sciences and Merck Inc, and has received honoraria from Roche, Inc and Janssen.

Today's Agenda

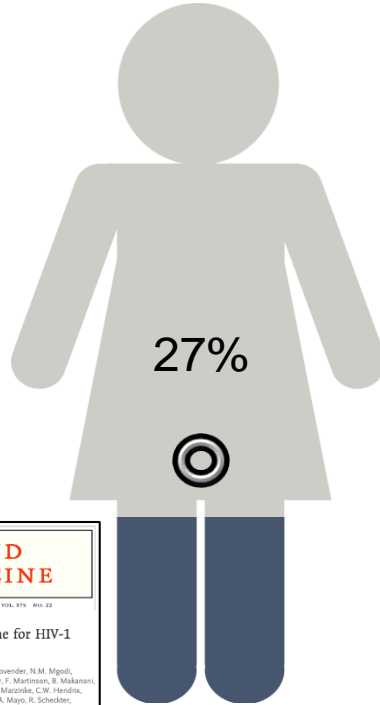
- **PrEP Background and Context**
- **HPTN 083 Study Design**
- **Statistical Methods**
- **Results**
 - **Population**
 - **HIV Incidence**
 - **Safety**
 - **Seroconversion events**
 - **Additional outcomes of interest**
 - **Update and PK, resistance in seroconversion**
- **Conclusions**

Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials



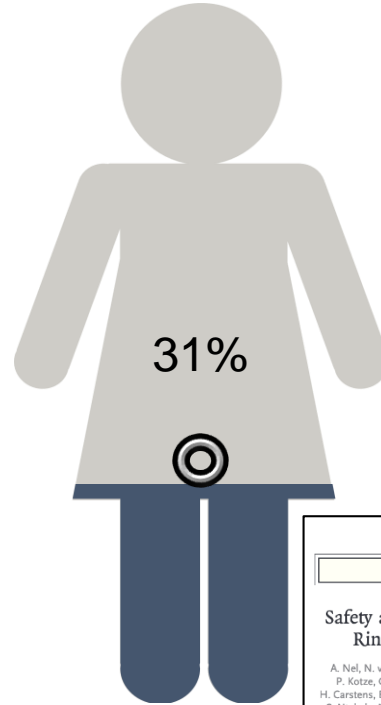
“PrEP 2.0”: Trials of Novel PrEP Agents

ASPIRE (Dapivirine)



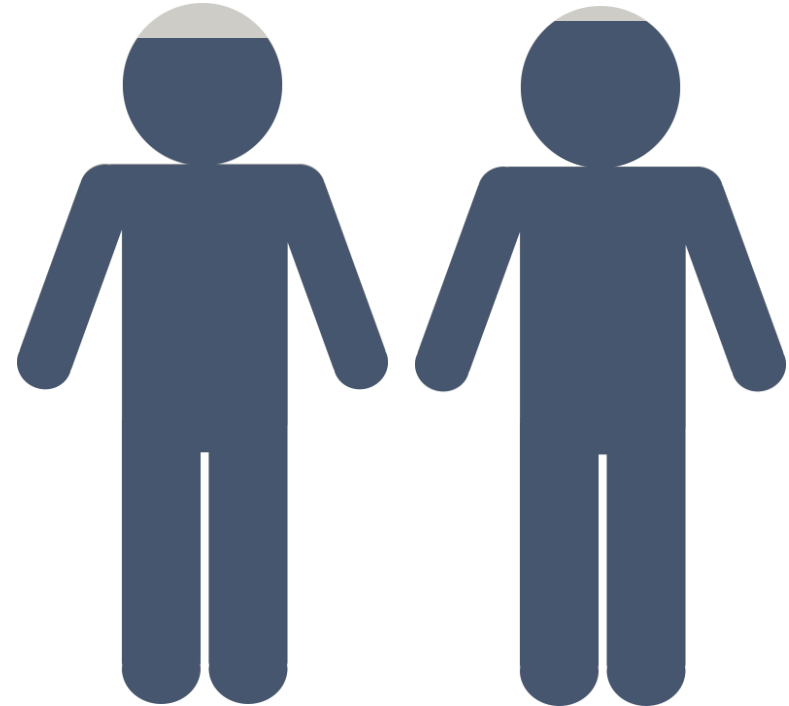
CI: 1 – 46

Ring (Dapivirine)



CI: 1 – 51

DISCOVER (TDF/FTC) (TAF/FTC)



Incidence rate
0.30%

Incidence rate
0.16%

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

J.M. Baeten, T. Palanee-Phillips, E.R. Brown, K. Schwartz, L.E. Soto-Torres, V. Govender, N.M. Mgedi, F. Maitwa Khweza, G. Nair, F. Mhlanga, S. Siva, L.-G. Bekker, N. Jeenaarain, Z. Gaffoor, F. Martinson, B. Mukanani, A. Pather, L. Naidoo, M. Hapink, B.A. Richardson, L.M. Parikh, J.W. Mellors, M.A. Marston, C.W. Hendrix, A. van der Straten, G. Ramjee, Z.M. Chirreje, C. Nakabito, T.E. Taha, J. Jones, A. Mayo, R. Schechter, J. Berthiaume, E. Luvizi, C. Jacobson, P. Nkase, R. White, K. Patterson, O. Gernaga, B. Galaska, K. Rungu, D. Singh, D.W. Zepeda, E.T. Montgomery, E.S. Messich, K. Torjesen, C.I. Gijssels, N. Chakravana, A. Nel, Z. Rosenberg, I. McGowan, and S. Hillier, for the MTN-020-ASPIRE Study Team*

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

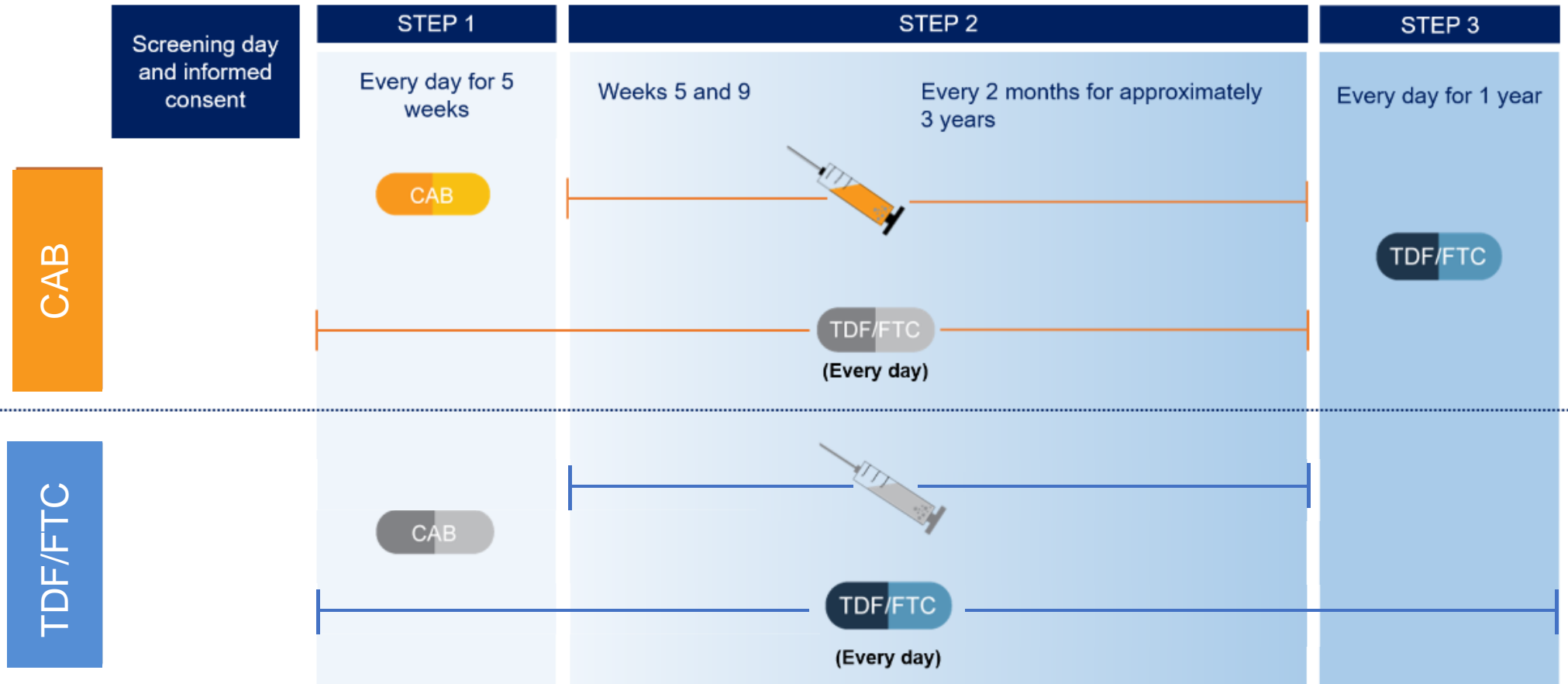
A. Nel, N. van Niekerk, S. Kapiga, L.-G. Bekker, C. Gama, K. Gill, A. Kamali, P. Kotze, C. Louw, Z. Mabude, N. Miti, S. Kusemererwa, H. Tempelman, H. Carstens, B. Devlin, M. Isaacs, M. Malherbe, W. Mans, J. Nuttall, M. Russell, S. Ntshhele, M. Smit, L. Solai, P. Spence, J. Steytler, K. Windle, M. Boremans, S. Ressler, J. Van Rooy, W. Parys, T. Vangeneugden, B. Van Baelen, and Z. Rosenberg, for the Ring Study Team*

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**
 - **$\geq 50\%$ under age 30**
 - **$\geq 10\%$ TGW**
 - **$\geq 50\%$ of US enrollment Black**
- **Primary efficacy endpoint: Incident HIV infections during blinded comparison**
- **Primary safety endpoint: G2 or higher clinical and laboratory AEs**



HPTN 083 Study Design



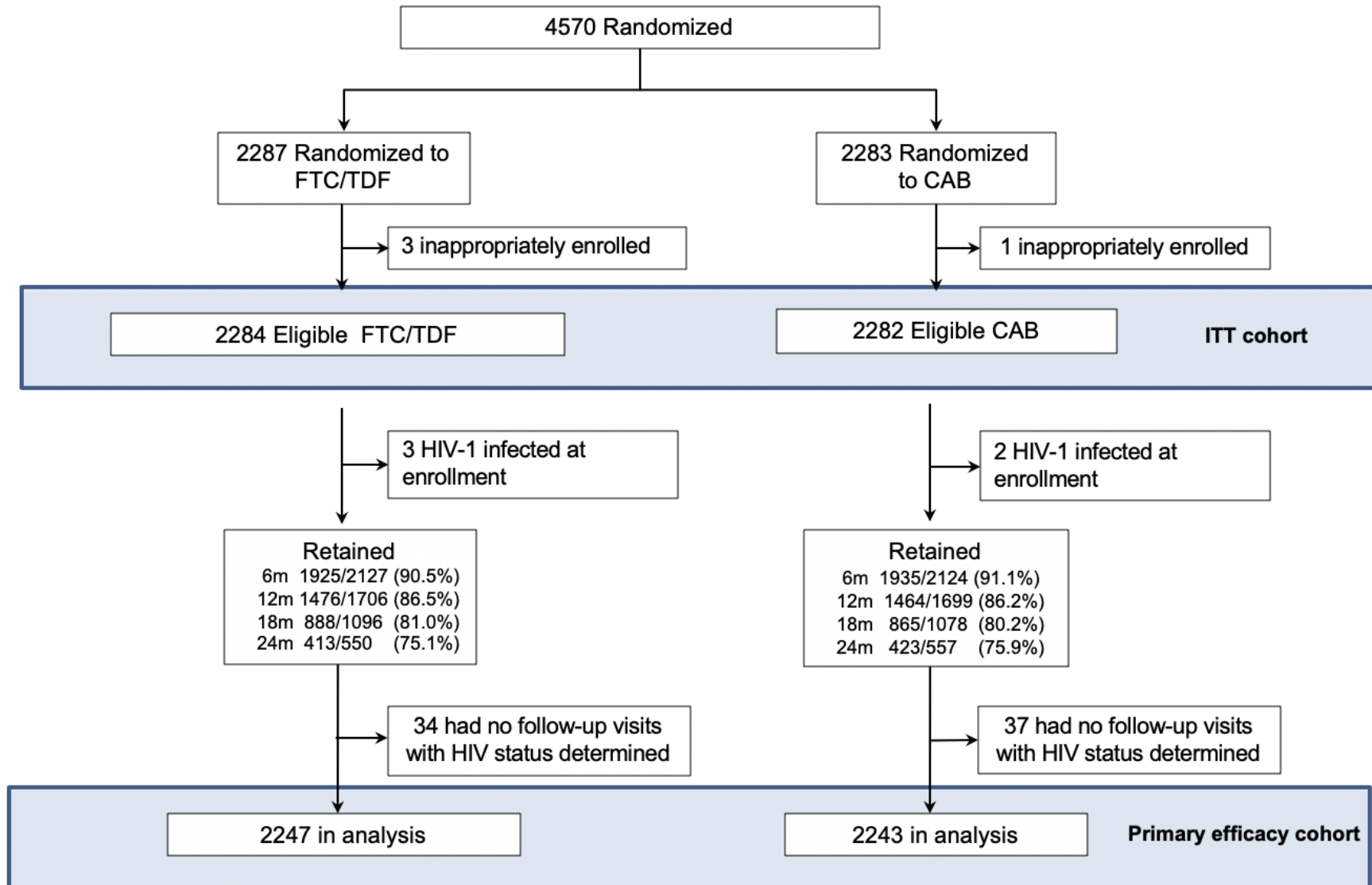
 TDF/FTC pill
  Cabotegravir (CAB) injection
  Placebo for TDF/FTC pill
  Placebo for cabotegravir (CAB) injection (20% Intralipid solution)

 Cabotegravir (CAB) pill
  Placebo for cabotegravir (CAB) pill

Statistical Design: Efficacy

- **Non-inferiority design**
 - **Non-inferiority margin 1.23**
 - **Alternative hypothesis of HR 0.75**
 - **Target background HIV Incidence ~4.5%**
 - **Anticipated TDF/FTC adherence by TFV plasma detectable ~57%**
- **Endpoint-driven (172 events) with pre-specified interim analyses at 25%, 50%, and 75% of endpoints**
 - **O'Brien-Fleming stopping boundaries for interim data analysis used to determine early stopping metrics**
- **DSMB recommended termination of blinded study after interim analysis on May 14, 2020 (25% endpoints accrued) for crossing pre-specified stopping bound**
- **Results include events occurring through May 14, 2020; participants unblinded, continuing on study**
 - **All to be offered CAB as soon as available at sites**

Participant Disposition

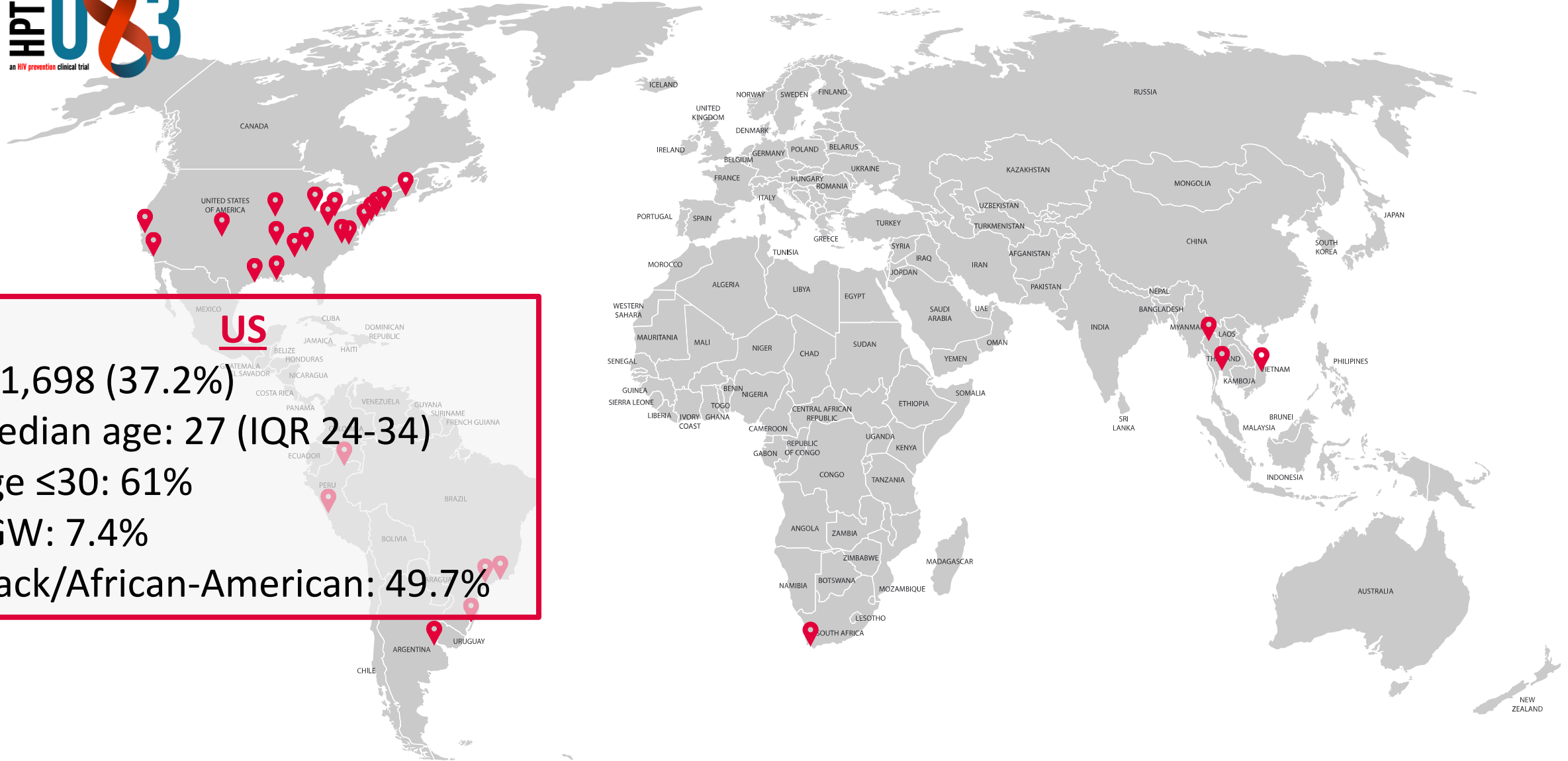


Study Population

	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)

Study Population

	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)



US

N:1,698 (37.2%)

Median age: 27 (IQR 24-34)

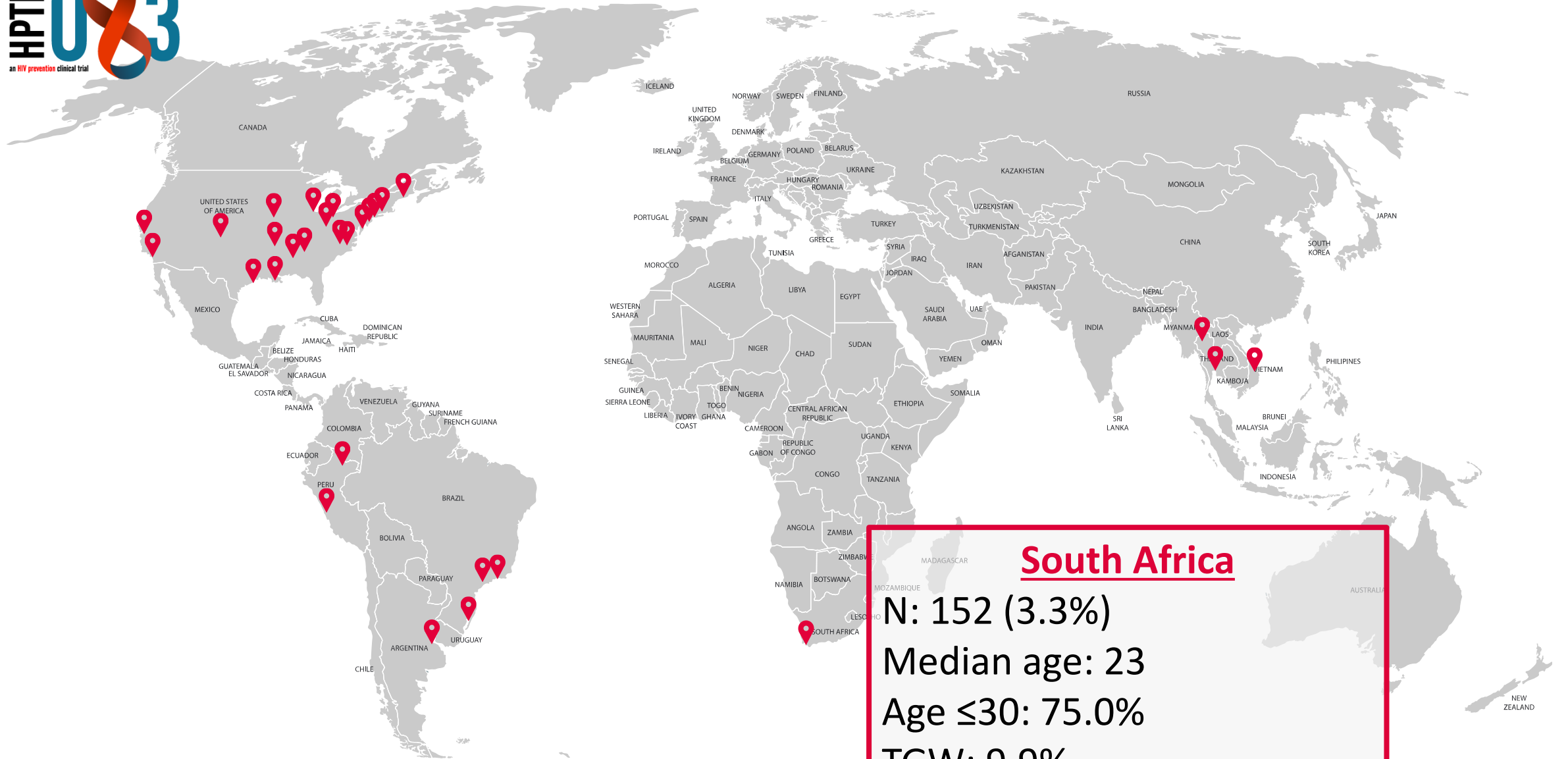
Age \leq 30: 61%

TGW: 7.4%

Black/African-American: 49.7%



LA
N: 1,964 (43.0%)
Median age: 26
Age ≤30: 67.7%
TGW: 10.3%



South Africa

N: 152 (3.3%)

Median age: 23

Age ≤30: 75.0%

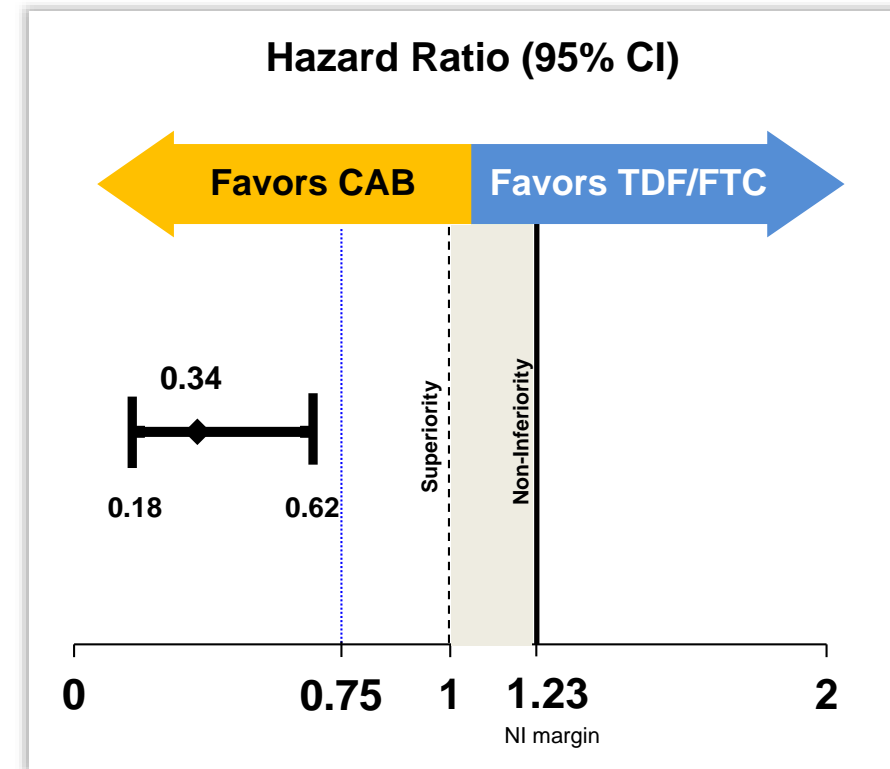
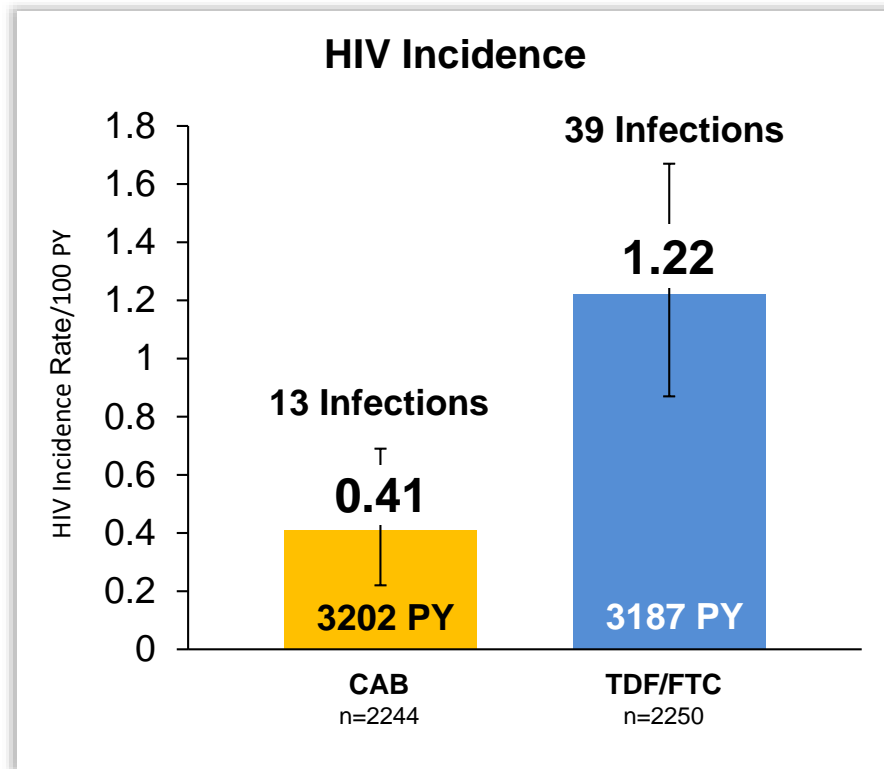
TGW: 9.9%



HIV Incidence

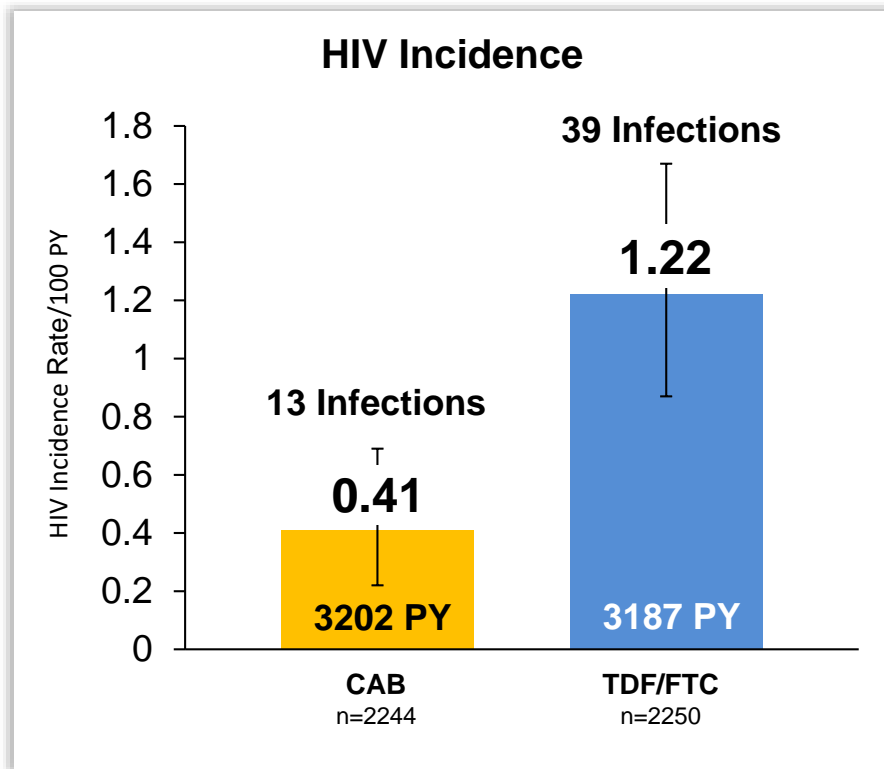
CAB vs. TDF/FTC

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

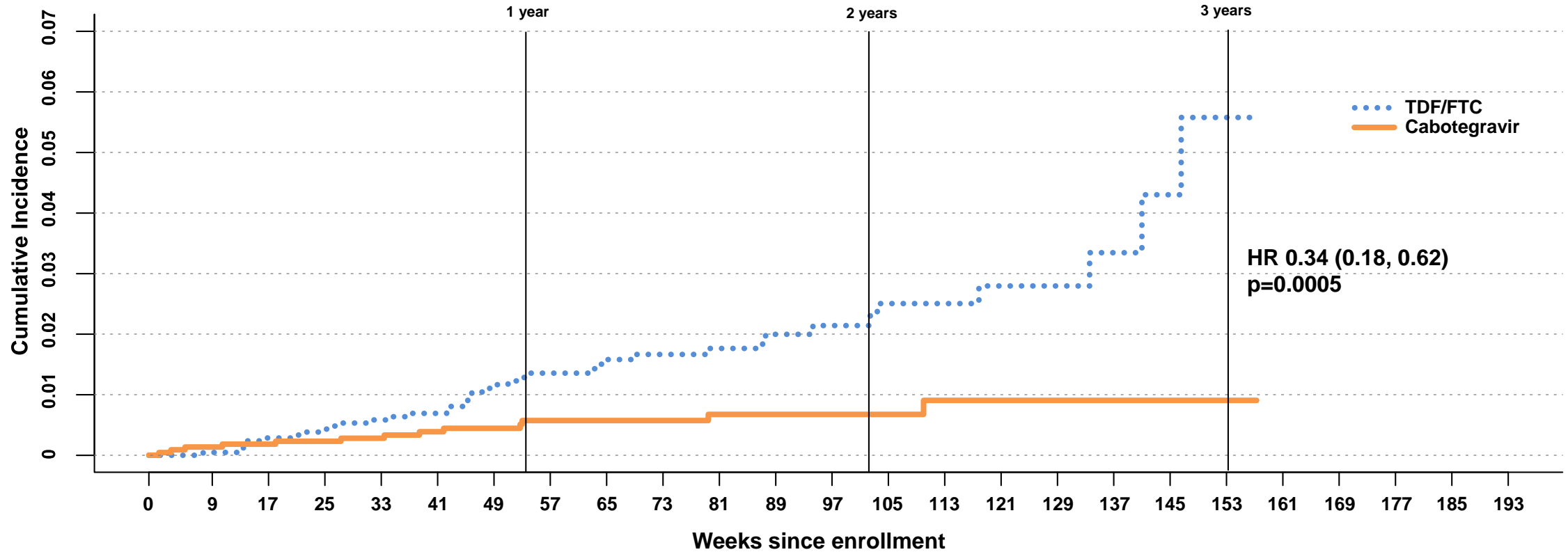
Number Needed to Treat CAB vs. TDF/FTC



CI, confidence interval

**NNT is 123 (95% CI 100-215)
to prevent one additional HIV
infection using CAB vs.
TDF/FTC with adherence seen
in HPTN 083**

HIV Incidence – ITT



Number at risk

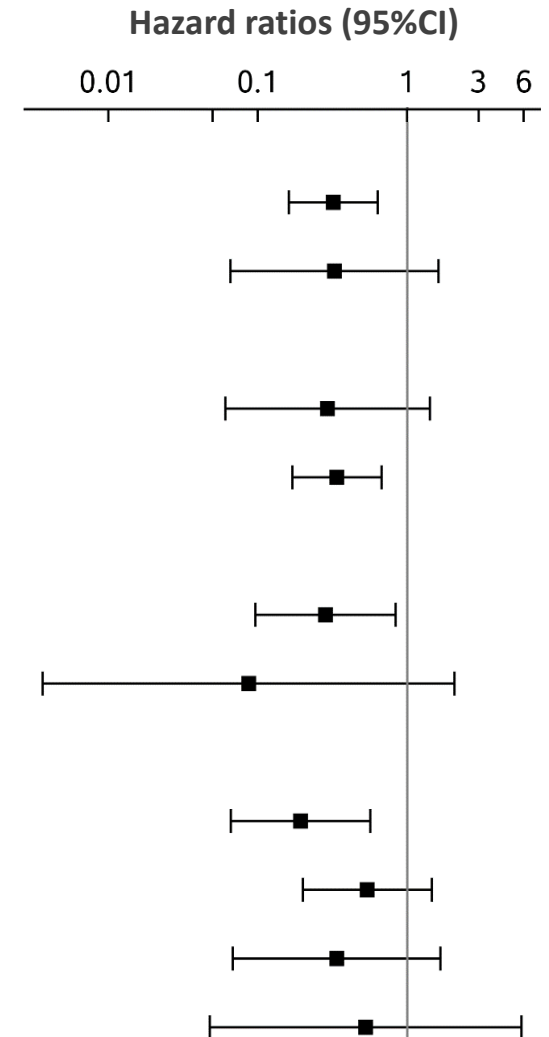
TDF/FTC	2247	2133	2081	2019	1913	1764	1624	1494	1294	1132	965	816	643	516	400	310	230	149	85	33	0	0	0	0	0
Cabotegravir	2243	2138	2092	2032	1921	1776	1632	1488	1312	1119	957	795	644	503	401	318	243	172	111	42	0	0	0	0	0

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

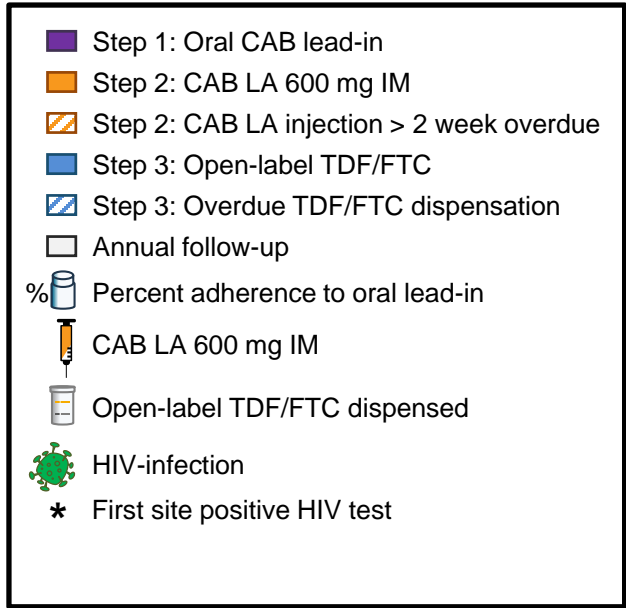
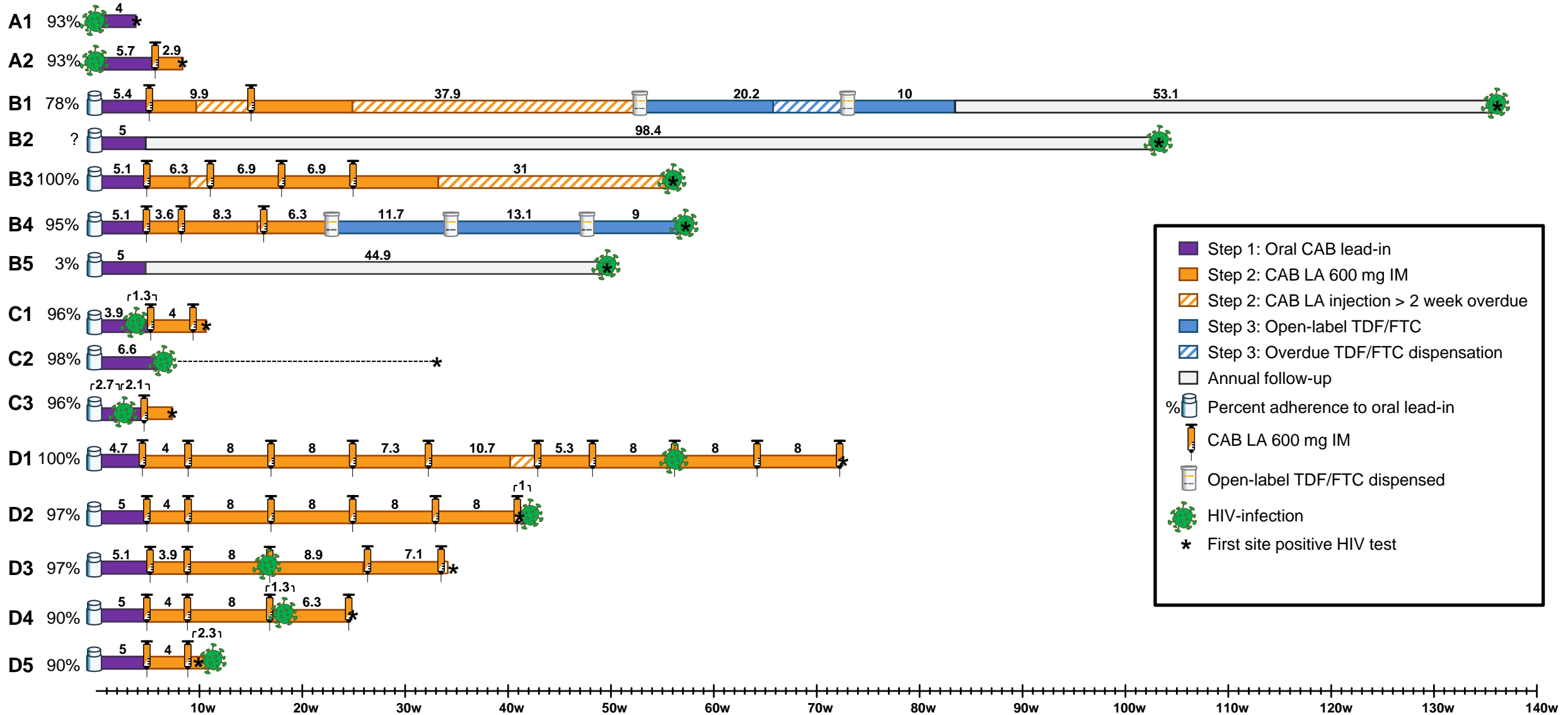
Results: HIV incidence in key populations

Subgroup	CAB Events/PY (IR%)	TDF/FTC Events/PY (IR%)	HR (95%CI)
Age			
≤30	11/2185 (0.50)	33/2114 (1.56)	0.32 (0.16, 0.63)
>30	2/1016 (0.20)	6/1071 (0.56)	0.33(0.07, 1.61)
Cohort			
TGW	2/368 (0.54)	7/383 (1.83)	0.29 (0.06, 1.41)
MSM	11/2829 (0.39)	32/2800 (1.14)	0.34 (0.17, 0.67)
Race			
Black/African-American	4/686 (0.58)	15/711 (2.11)	0.28 (0.10, 0.83)
Non-Black/African-American	0/837 (0.00)	5/790 (0.63)	0.09 (0.00, 2.06)
Region			
US	4/1523 (0.26)	20/1501 (1.33)	0.19 (0.07, 0.56)
Latin America	6/1016 (0.59)	11/1007 (1.09)	0.54 (0.20, 1.46)
Asia	2/569 (0.35)	6/580 (1.03)	0.34 (0.07, 1.66)
Africa	1/92 (1.08)	2/96 (2.08)	0.52 (0.05, 5.77)



13 Incident HIV Infections

Cabotegravir

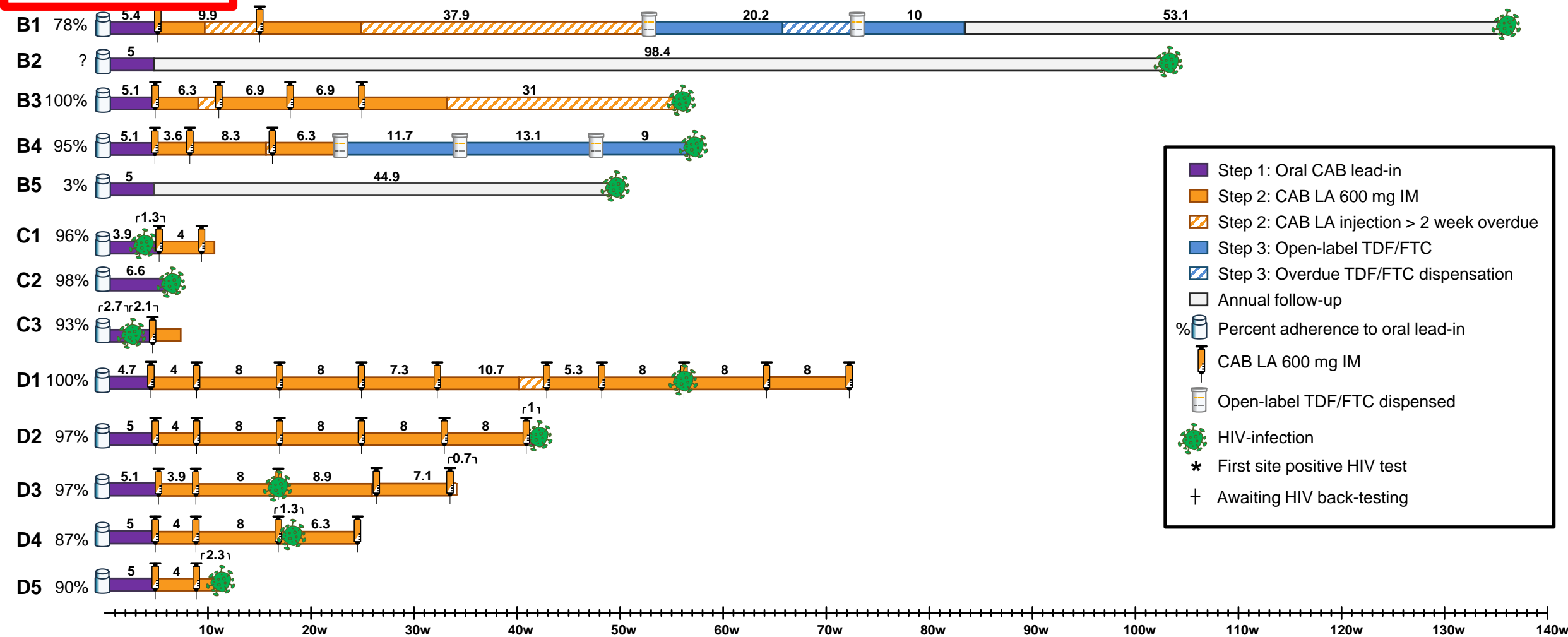


13 Incident HIV Infections

Cabotegravir

Infection prior to administration of study product

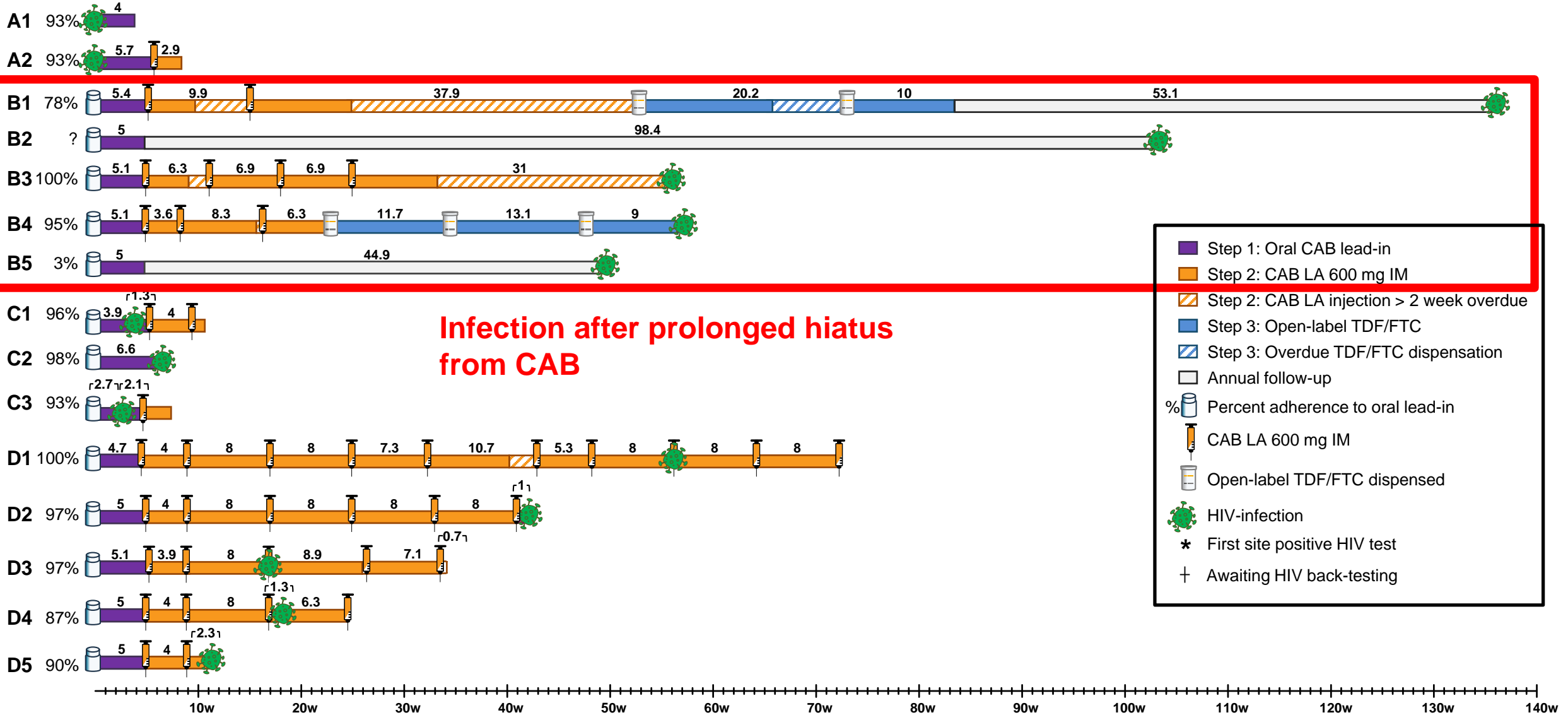
A1 93%
A2 93%



- 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

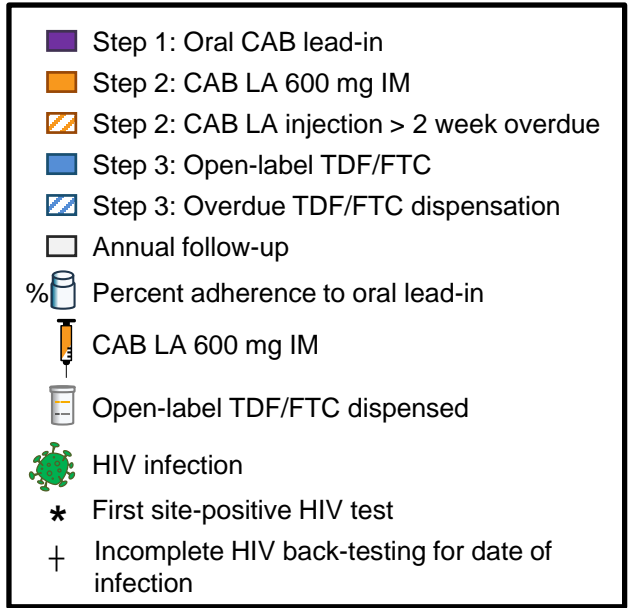
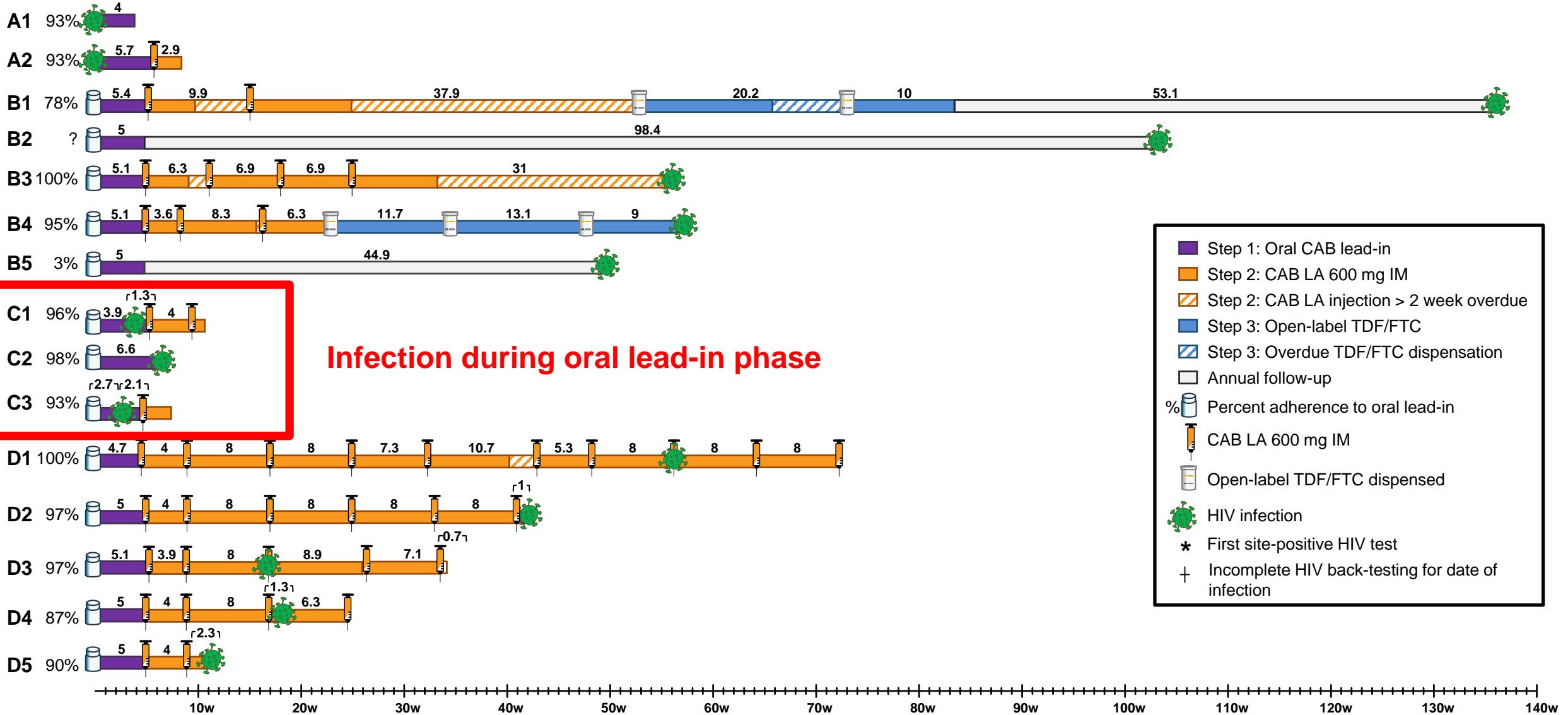
13 Incident HIV Infections

Cabotegravir



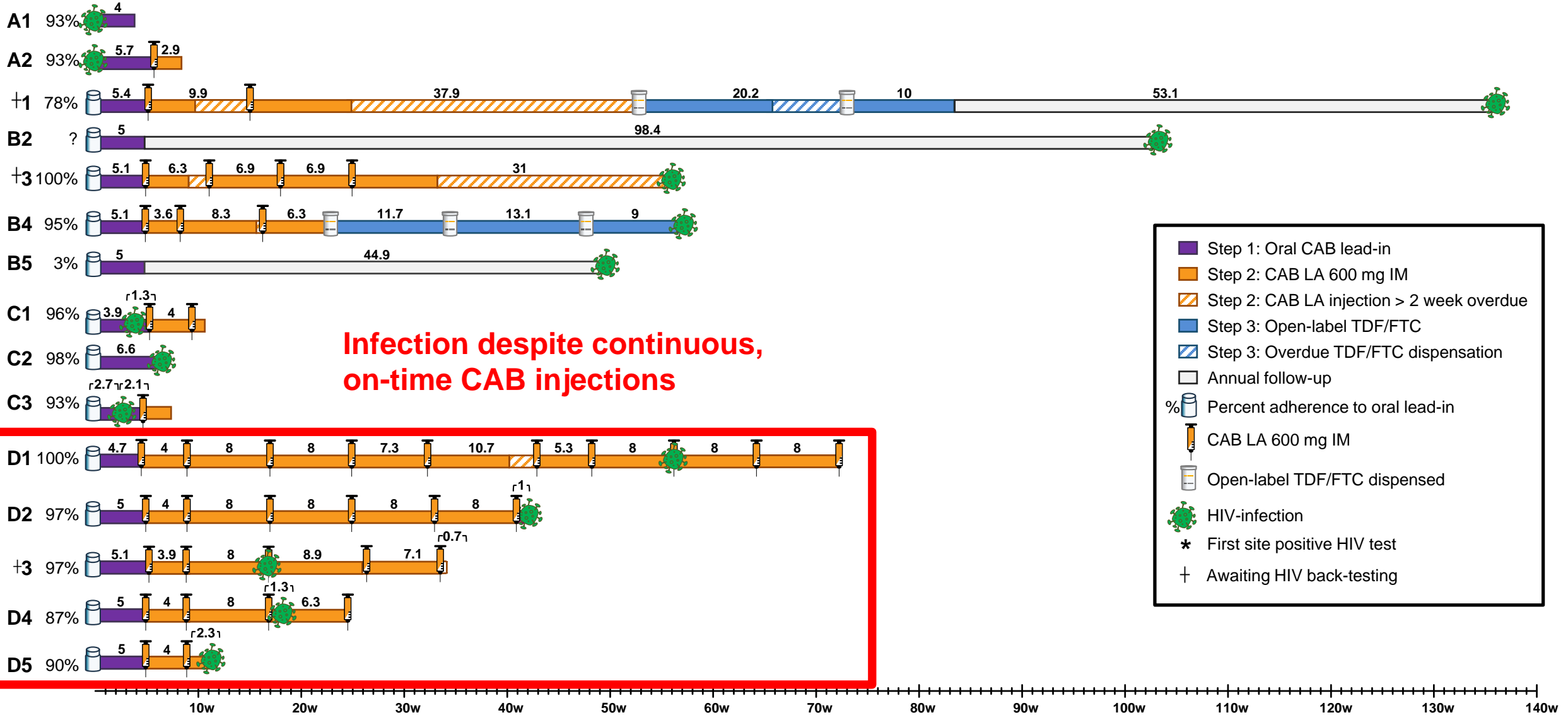
13 Incident HIV Infections

Cabotegravir



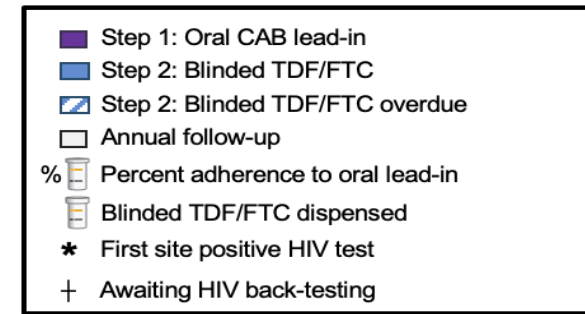
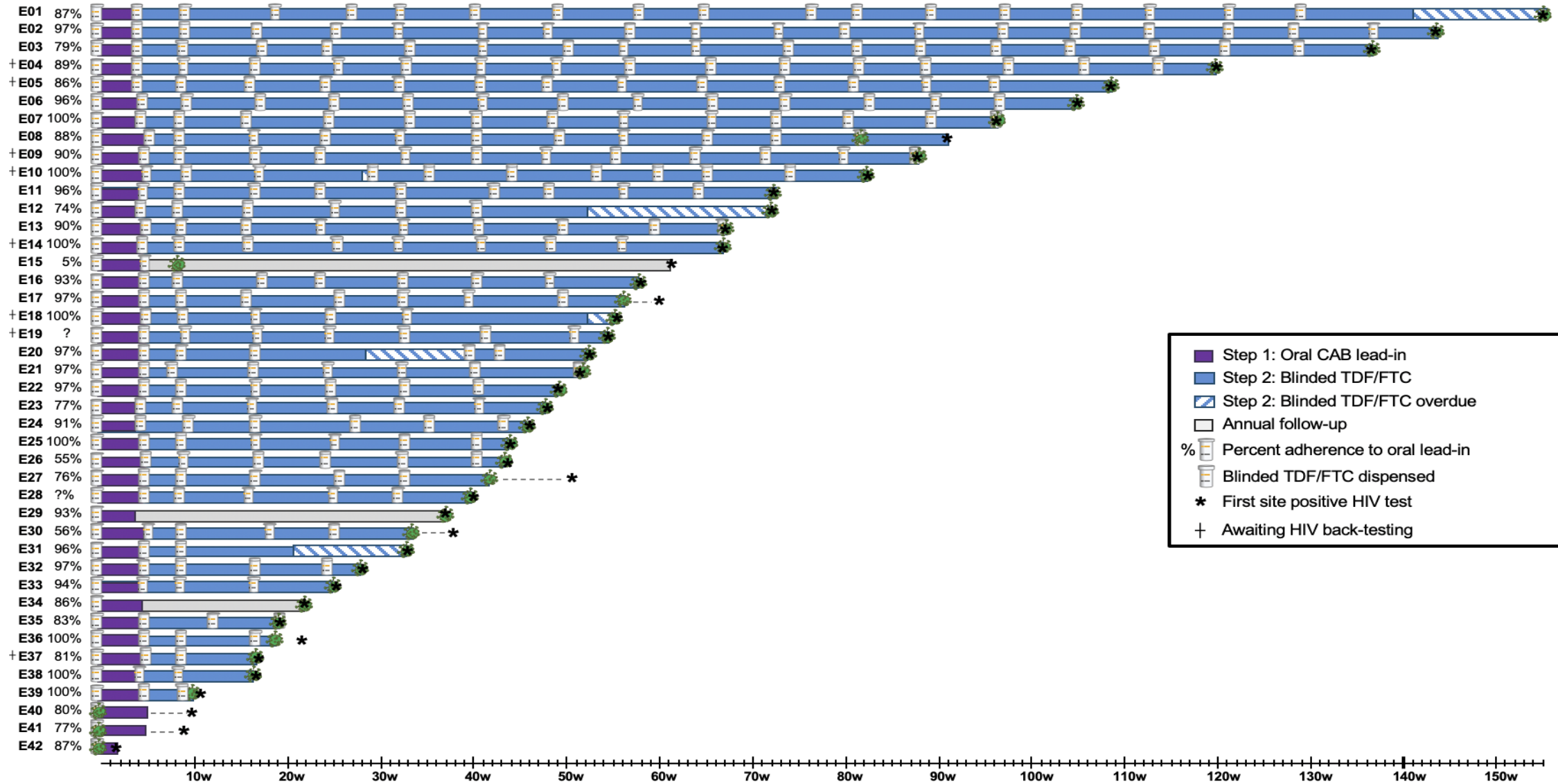
13 Incident HIV Infections

Cabotegravir

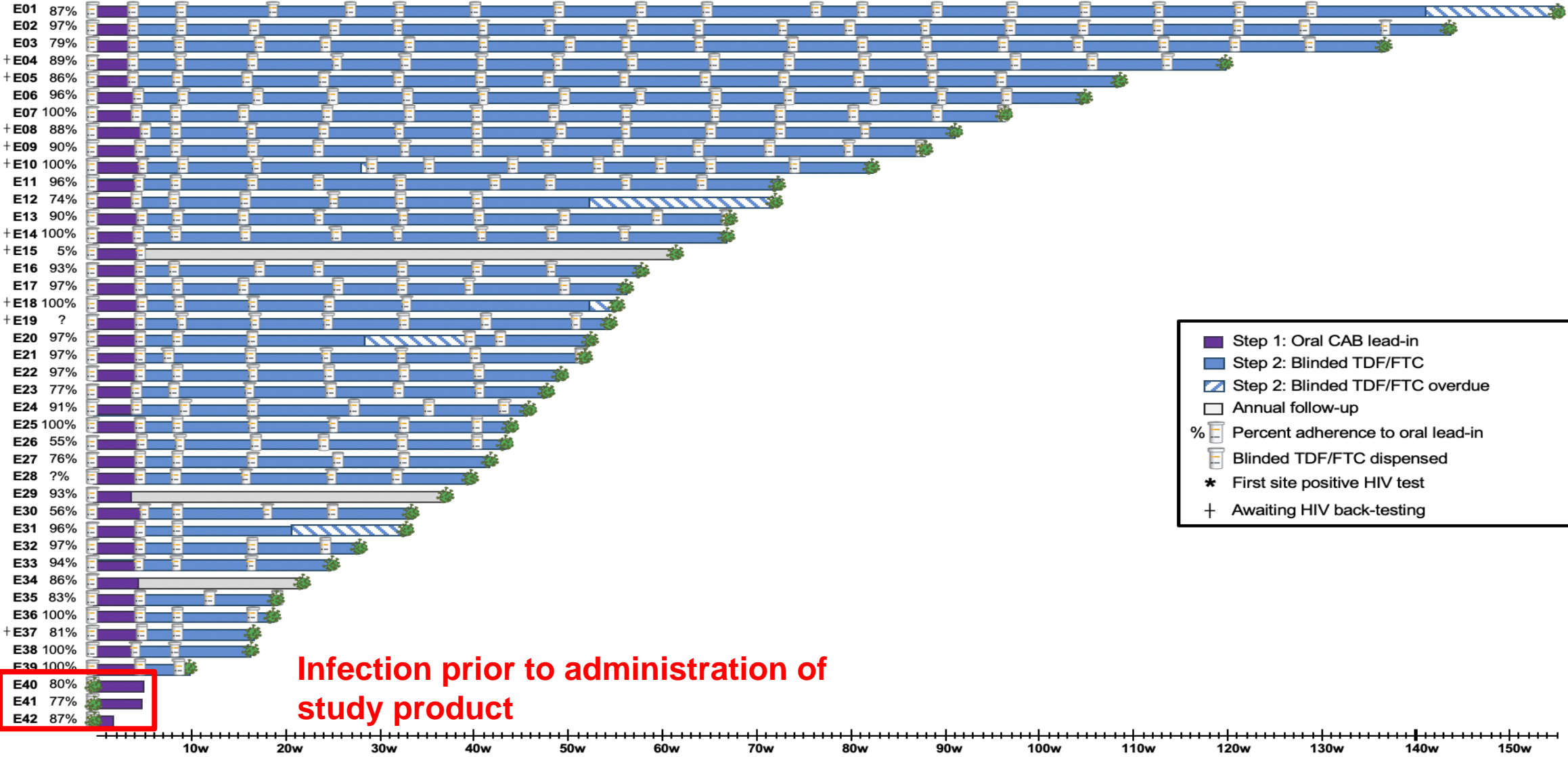


- Step 1: Oral CAB lead-in
- Step 2: CAB LA 600 mg IM
- Step 2: CAB LA injection > 2 week overdue
- Step 3: Open-label TDF/FTC
- Step 3: Overdue TDF/FTC dispensation
- Annual follow-up
- % Percent adherence to oral lead-in
- CAB LA 600 mg IM
- Open-label TDF/FTC dispensed
- 🦠 HIV-infection
- ★ First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

39 Incident HIV Infections TDF/FTC



39 Incident HIV Infections TDF/FTC

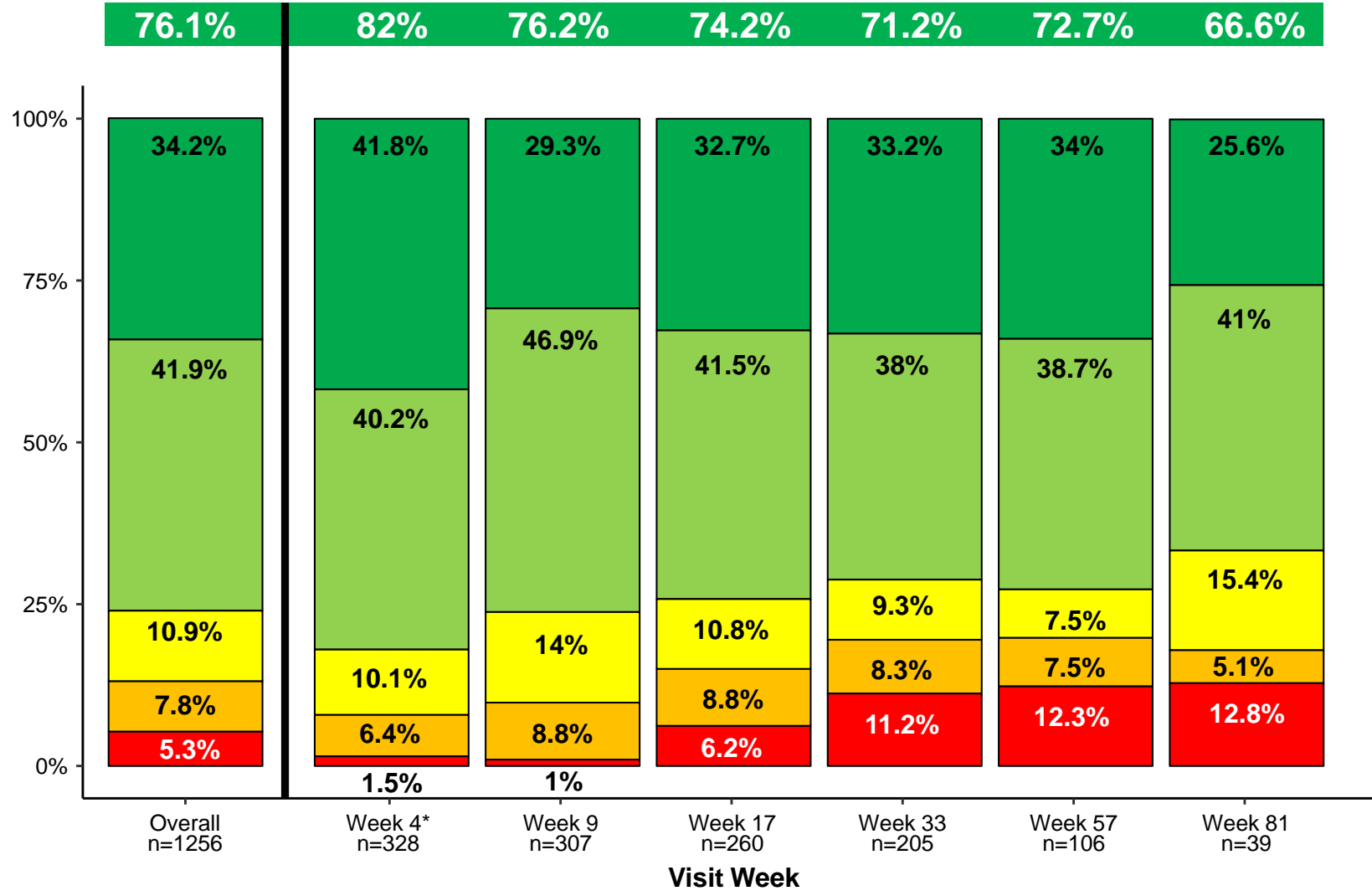


- Step 1: Oral CAB lead-in
- Step 2: Blinded TDF/FTC
- Step 2: Blinded TDF/FTC overdue
- Annual follow-up
- % Percent adherence to oral lead-in
- Blinded TDF/FTC dispensed
- * First site positive HIV test
- + Awaiting HIV back-testing

Infection prior to administration of study product

DBS TFV-DP

Randomly selected “adherence” subset



Number of participants: 372
Number of samples assayed: 1256

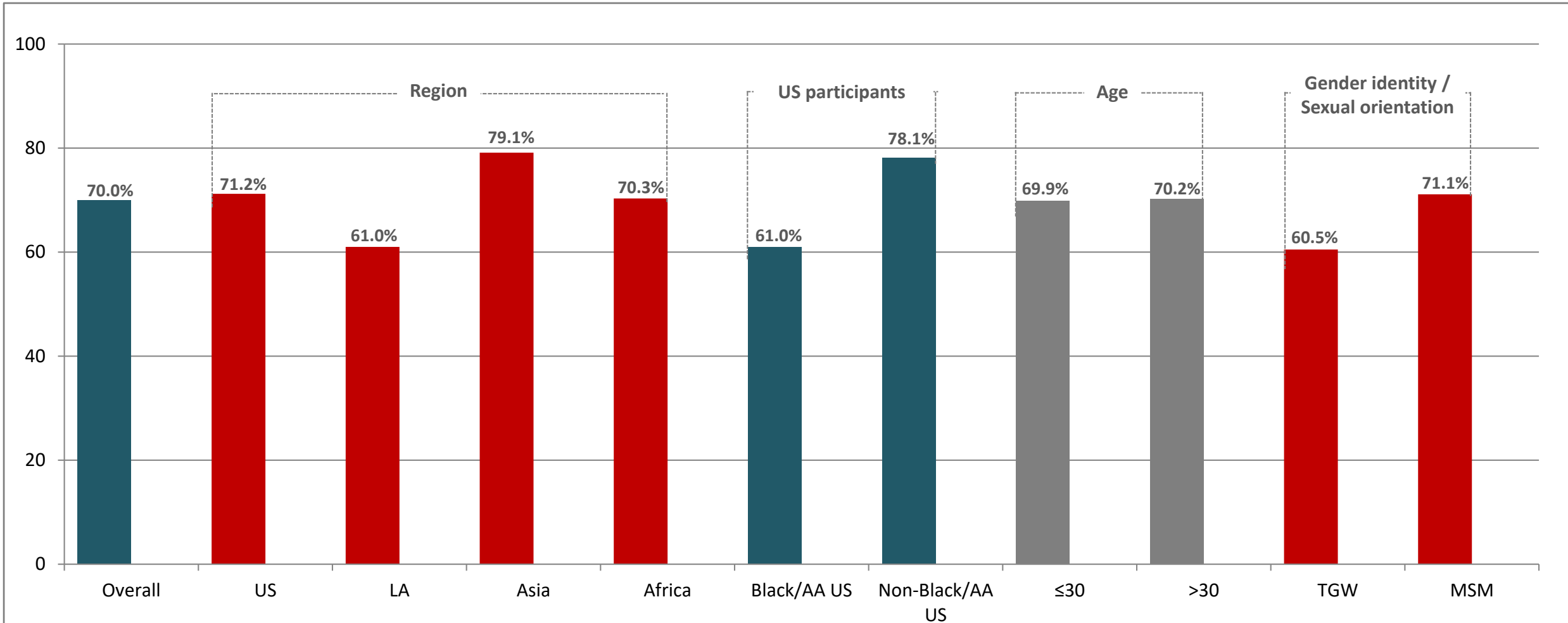
- 7 doses/week (≥1250 fmol/punch)
- 4 – 7 doses/week (700 - <1250 fmol/punch)
- 2 – 4 doses/week (350 - <700 fmol/punch)
- <2 doses/week (LLOQ - <350 fmol/punch)
- No detectable drug (BLQ)

Plasma TFV
87% >0.3 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

Results: TDF/FTC Adherence

TFV-DP \geq 700fmol/punch in DBS^{1,2}



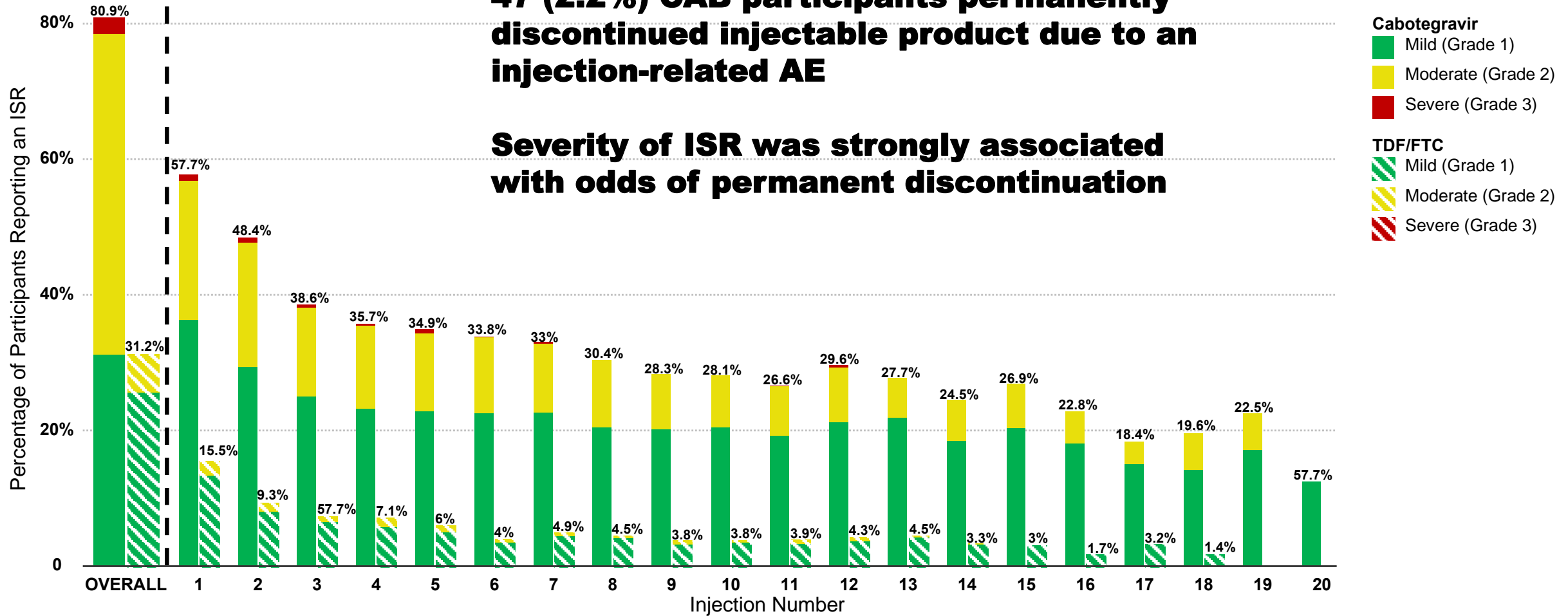
1 \geq 700fmol/punch consistent with 4+ TDF/FTC doses per week.

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

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



Cabotegravir, n	2117	2117	2037	1938	1872	1761	1620	1464	1360	1200	1034	877	744	604	465	372	298	234	168	111	8
TDF/FTC, n	2081	2081	2014	1940	1869	1760	1606	1463	1355	1193	1037	903	760	596	482	370	288	220	146	89	6

Grade 2+ Adverse Events Reported in $\geq 5\%$

	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

*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%)

Adverse Events: Grade 3+

Reported in $\geq 2\%$

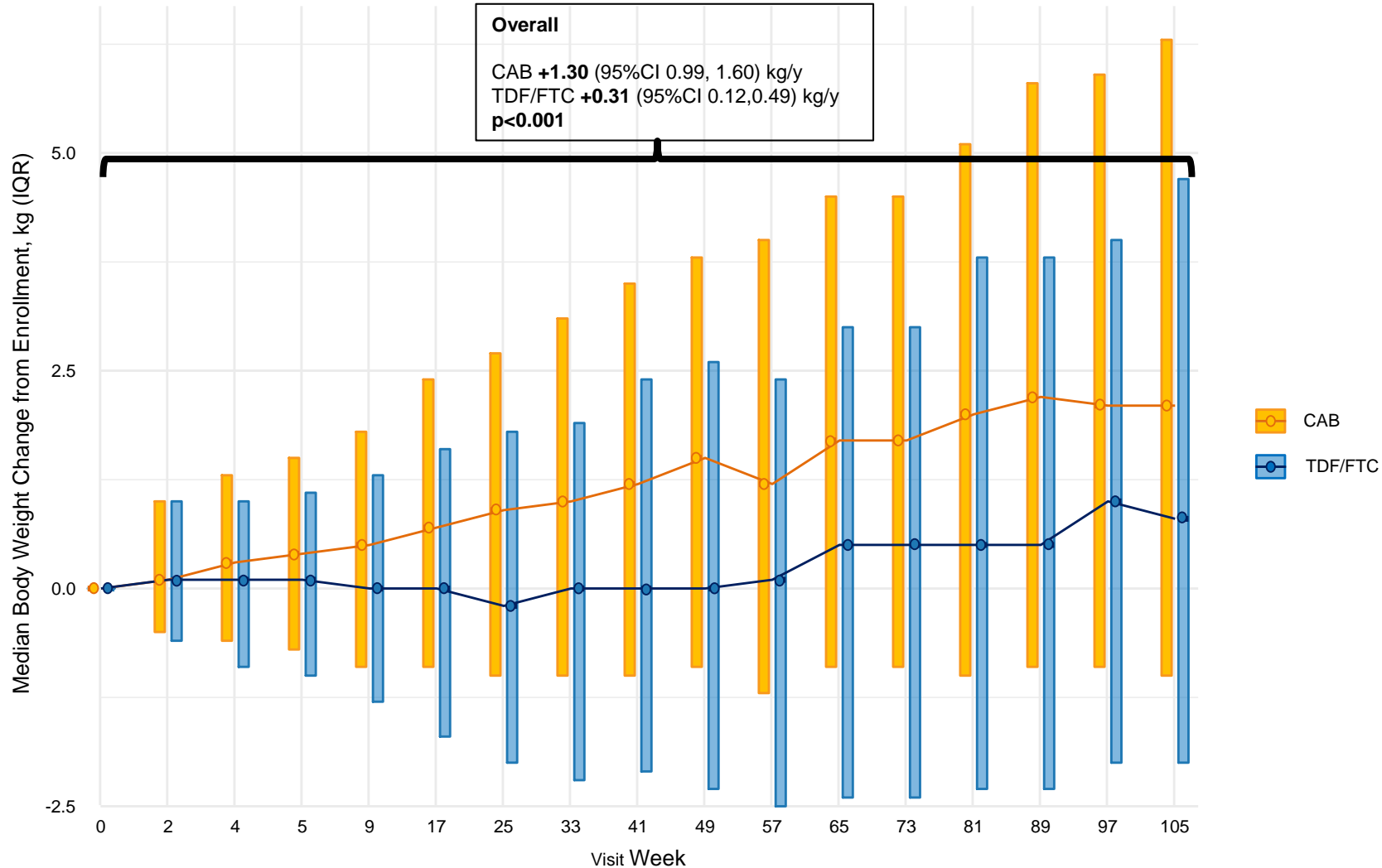
	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)	p-value
Participants with grade 3+ AEs, n (%)	1490 (32.7%)	766/2282 (33.6%)	724/2280 (31.8%)	
CPK increased	633 (13.9%)	309 (13.5%)	324 (14.2%)	0.51
Creatinine clearance decreased	348 (7.6%)	190 (8.3%)	158 (6.9%)	0.08
Lipase increased	152 (3.3%)	76 (3.3%)	76 (3.3%)	0.99
Creatinine increased	152 (3.3%)	75 (3.3%)	77 (3.4%)	0.87
AST/SGOT increased	122 (2.7%)	69 (3.0%)	53 (2.3%)	0.14
Participants with EAEs and SAEs, n (%)	240 (5.3%)	122 (5.4%)	118 (5.2%)	
Participant deaths, n (%)	11 (0.24%)	7 (0.3%)	4 (0.2%)	

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)

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 Landovitz¹, Sahar Z Zangeneh², Gordon Chau², Beatriz Grinsztejn³, Joseph J Eron⁴, Halima Dawood⁵, Manya Magnus⁶, Albert Y Liu⁷, Ravindre Panchia⁸, Mina C Hosseinipour⁹, Ryan Kofron¹, David A Margolis¹⁰, Alex Rinehart¹⁰, Adeola Adeyeye¹¹, David Burns¹¹, Marybeth McCauley¹², Myron S Cohen⁴, Judith S Currier¹

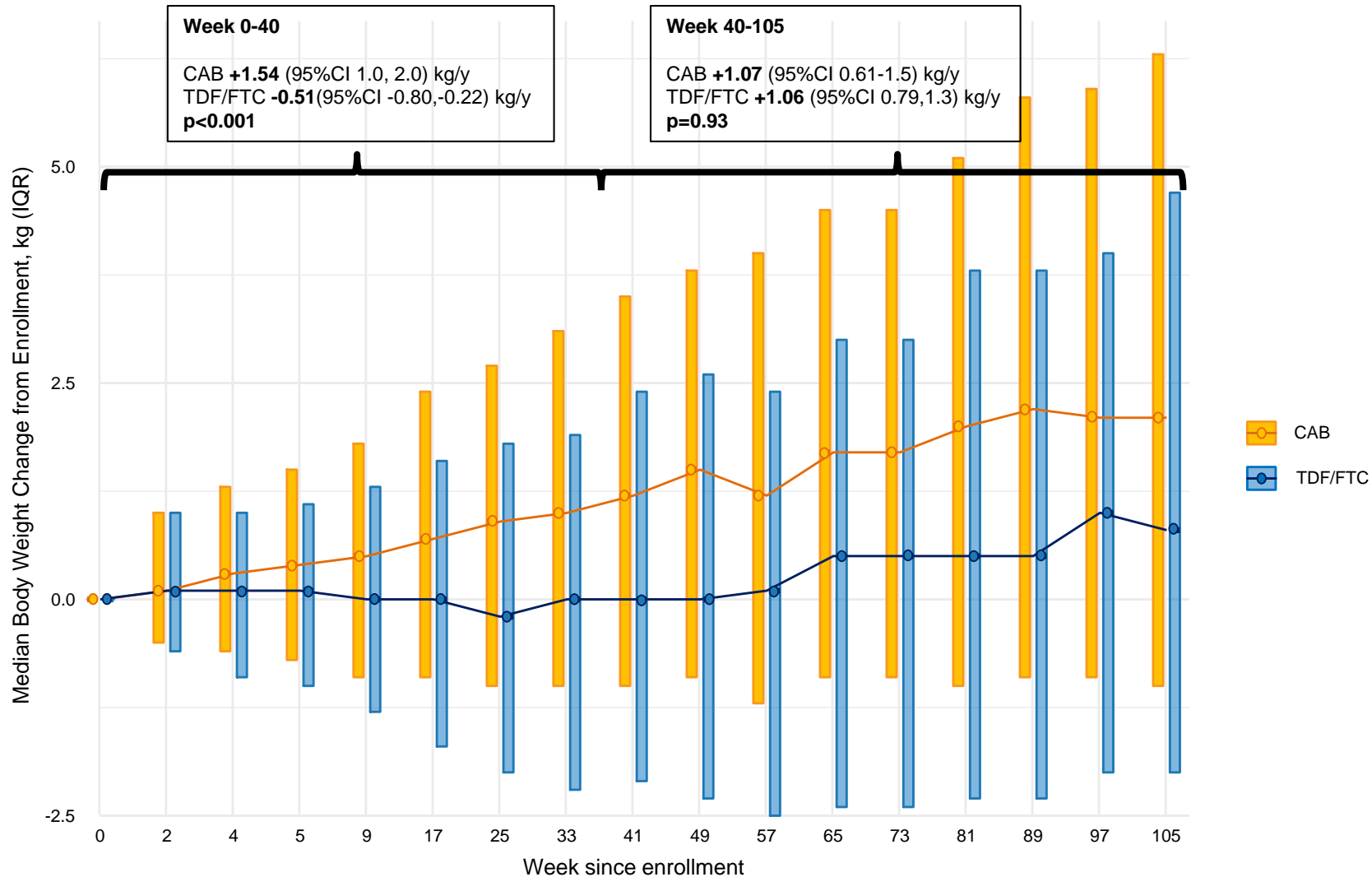
HPTN 077: Over 41 weeks

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.

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 Landovitz¹, Sahar Z Zangeneh², Gordon Chau², Beatriz Grinsztejn³, Joseph J Eron⁴, Halima Dawood⁵, Manya Magnus⁶, Albert Y Liu⁷, Ravindre Panchia⁸, Mina C Hosseinipour⁹, Ryan Kofron¹, David A Margolis¹⁰, Alex Rinehart¹⁰, Adeola Adeyeye¹¹, David Burns¹¹, Marybeth McCauley¹², Myron S Cohen⁴, Judith S Currier¹

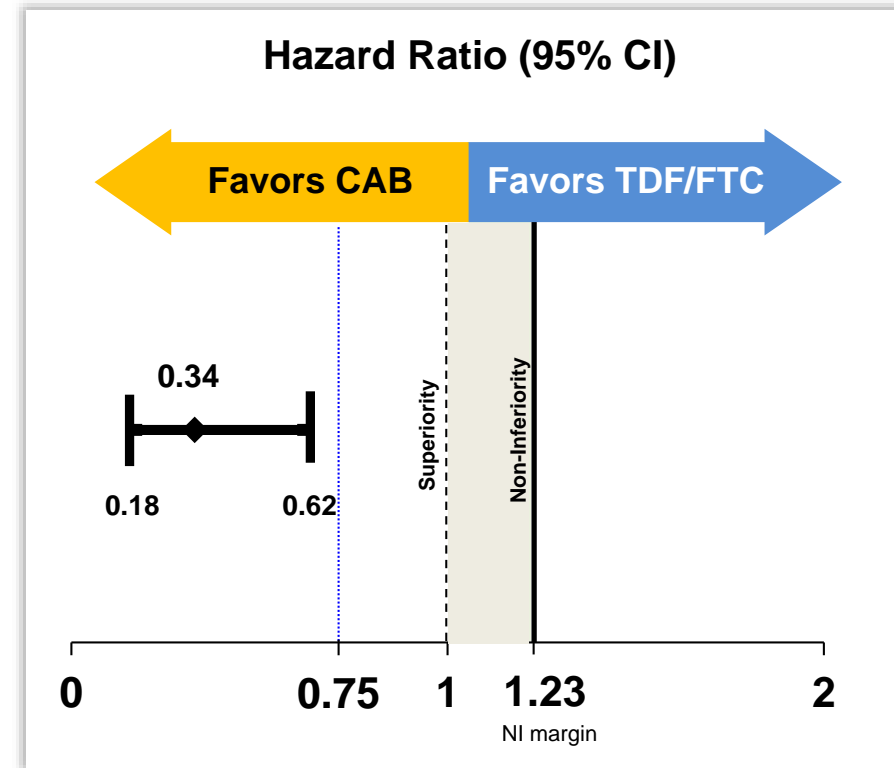
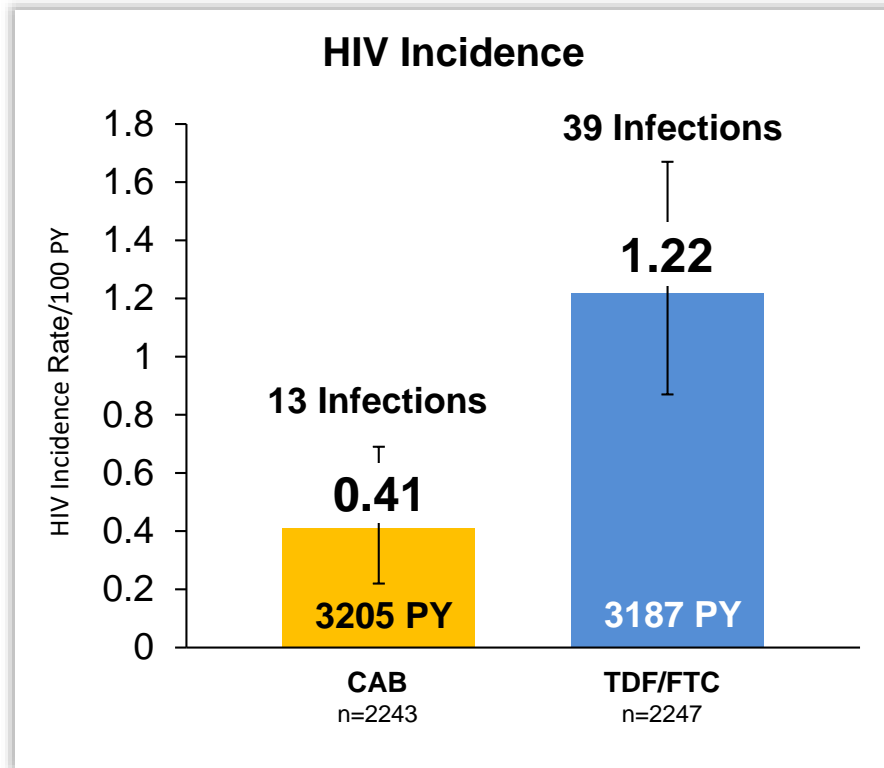
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p=0.95

Landovitz RJ et al. CID 2019.

**And then we observed
something unexpected...**

HIV Incidence: CAB vs. TDF/FTC



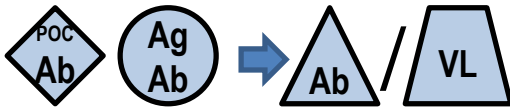
Pre-specified HIV Testing

Real-time site testing

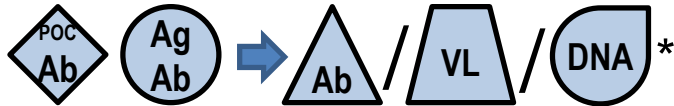
Screening



Enrollment*



Follow-up visits

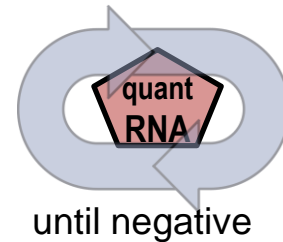


HPTN Laboratory Center testing (retrospective)

Visits with reactive/positive site tests



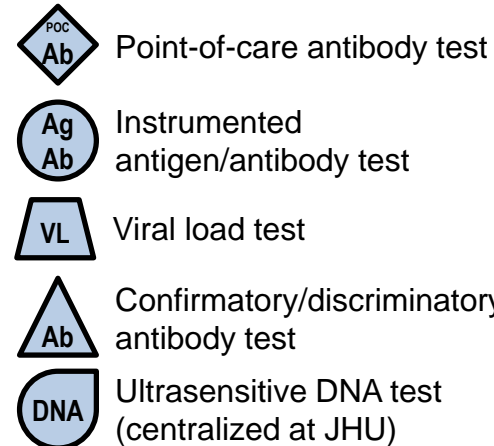
Back-testing



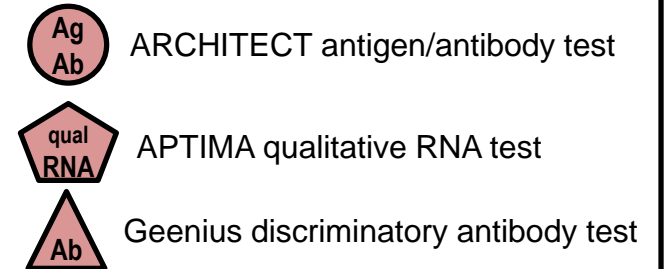
Blinded adjudication of study endpoints



Site testing



HPTN LC testing



*Selected cases

Extended HPTN LC Testing

HIV testing

Back-testing



CAB arm: All visits
TDF/FTC arm: Enrollment, weeks 2, 4, 5



CAB arm: Enrollment plus three visits prior to the first RNA pos visit
TDF/FTC arm: Enrollment plus one visit prior to the first RNA pos visit



If Ag/Ab test reactive



If qualitative RNA test reactive



Selected cases/visits

HIV genotyping (VL >500 c/mL)

CAB arm

- All study visits

TDF/FTC arm

- First HIV positive visit
- First site positive visit

Pharmacology testing

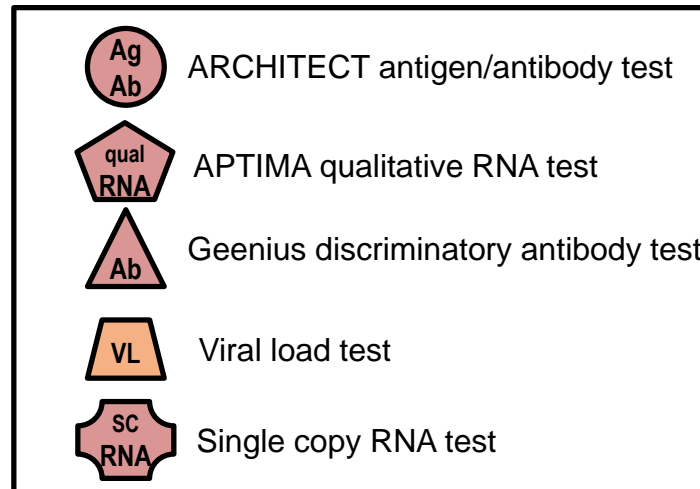
CAB concentrations

CAB arm

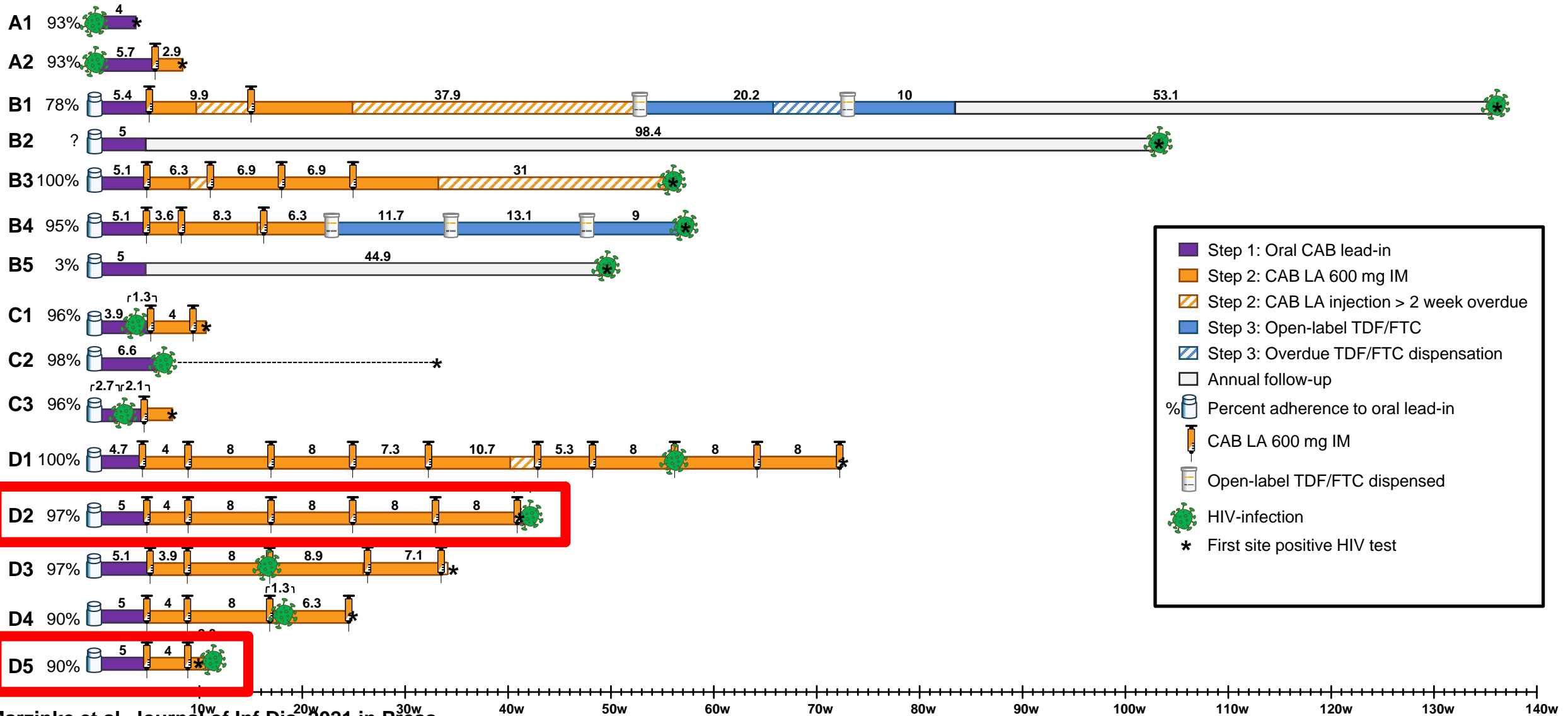
Plasma [CAB]: all study visits
Plasma [TFV]: baseline infections, step 3 infections
DBS [TFV-DP]: step 3 infections

TDF/FTC concentrations

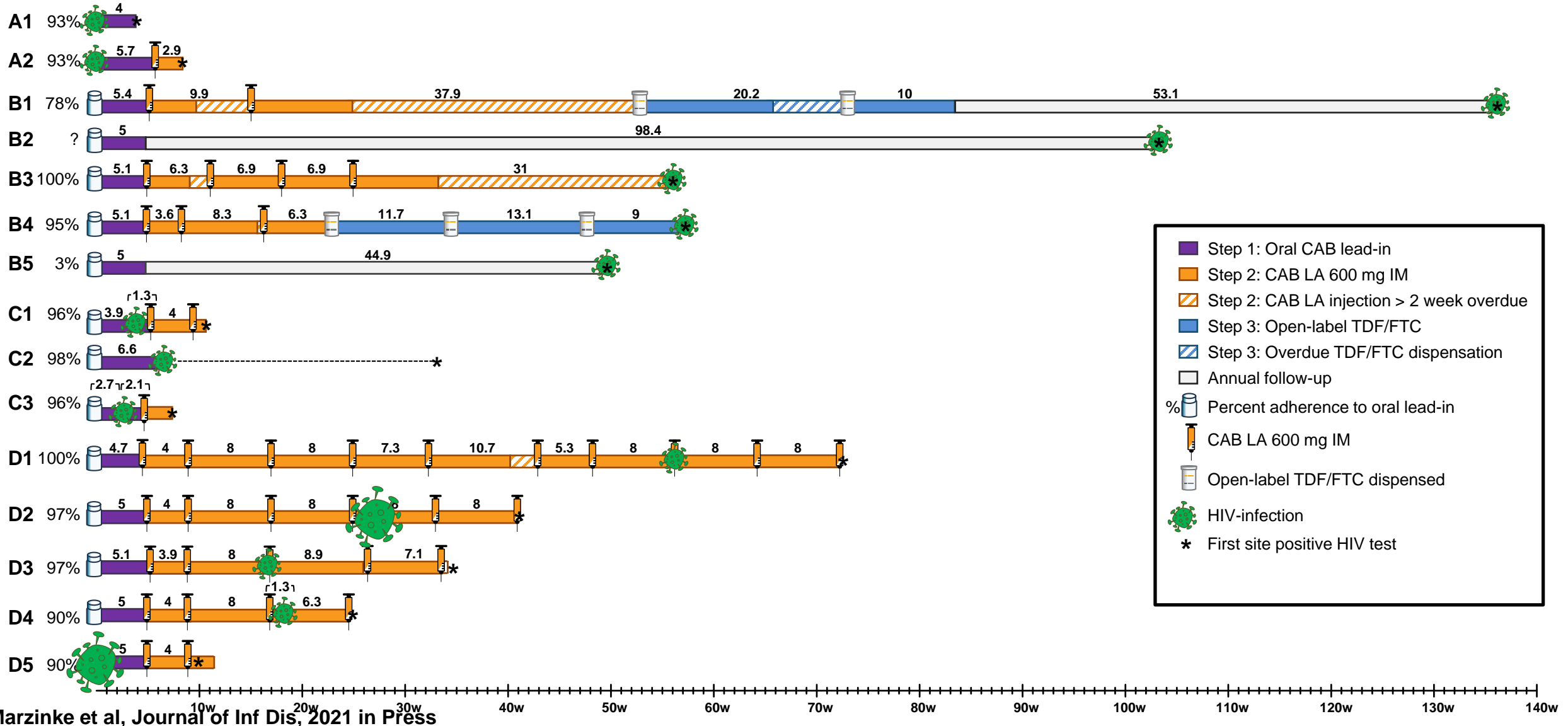
Plasma [TFV]: first site pos, first HIV pos, 3 prior visits
DBS [TFV-DP]: first site pos, 1 prior visit



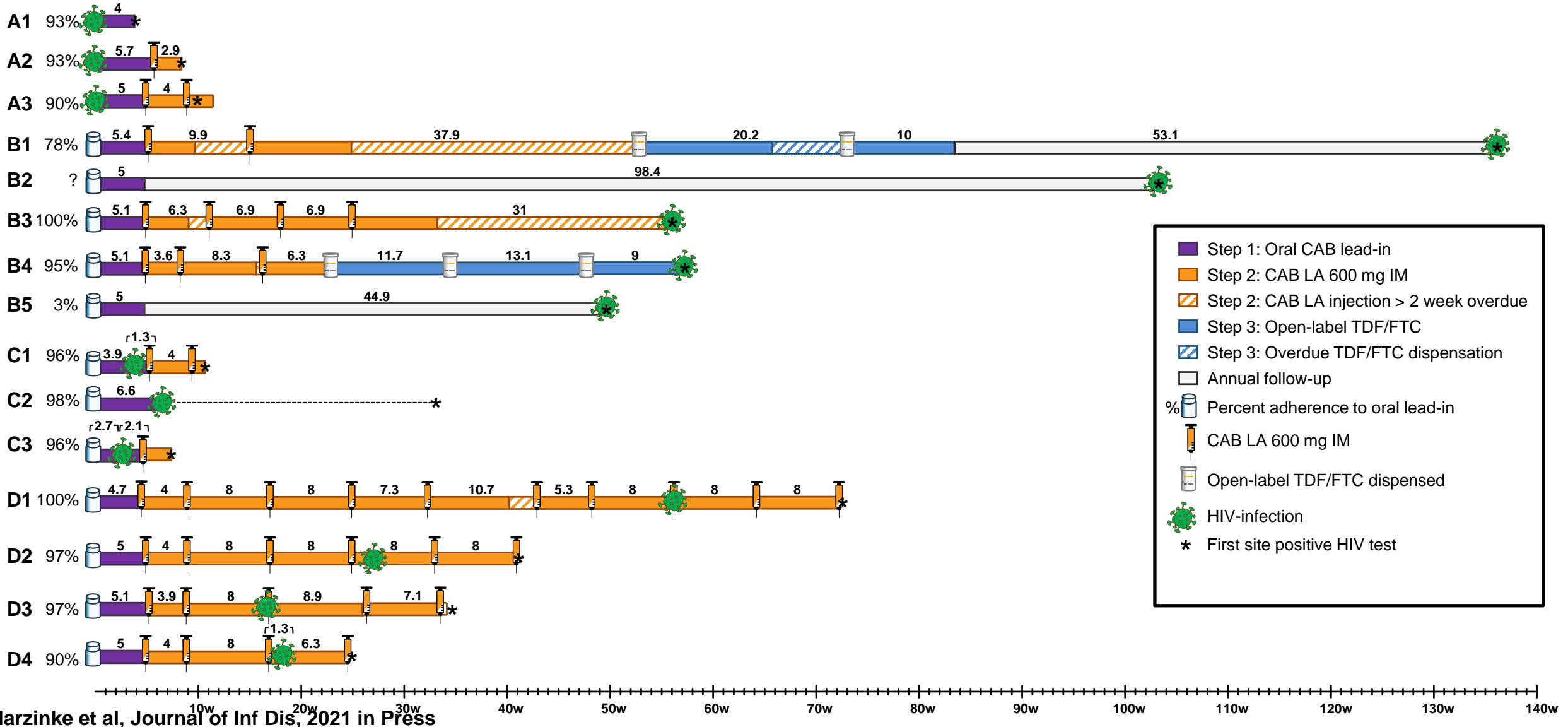
13 Incident, 2 baseline Infections: Cabotegravir



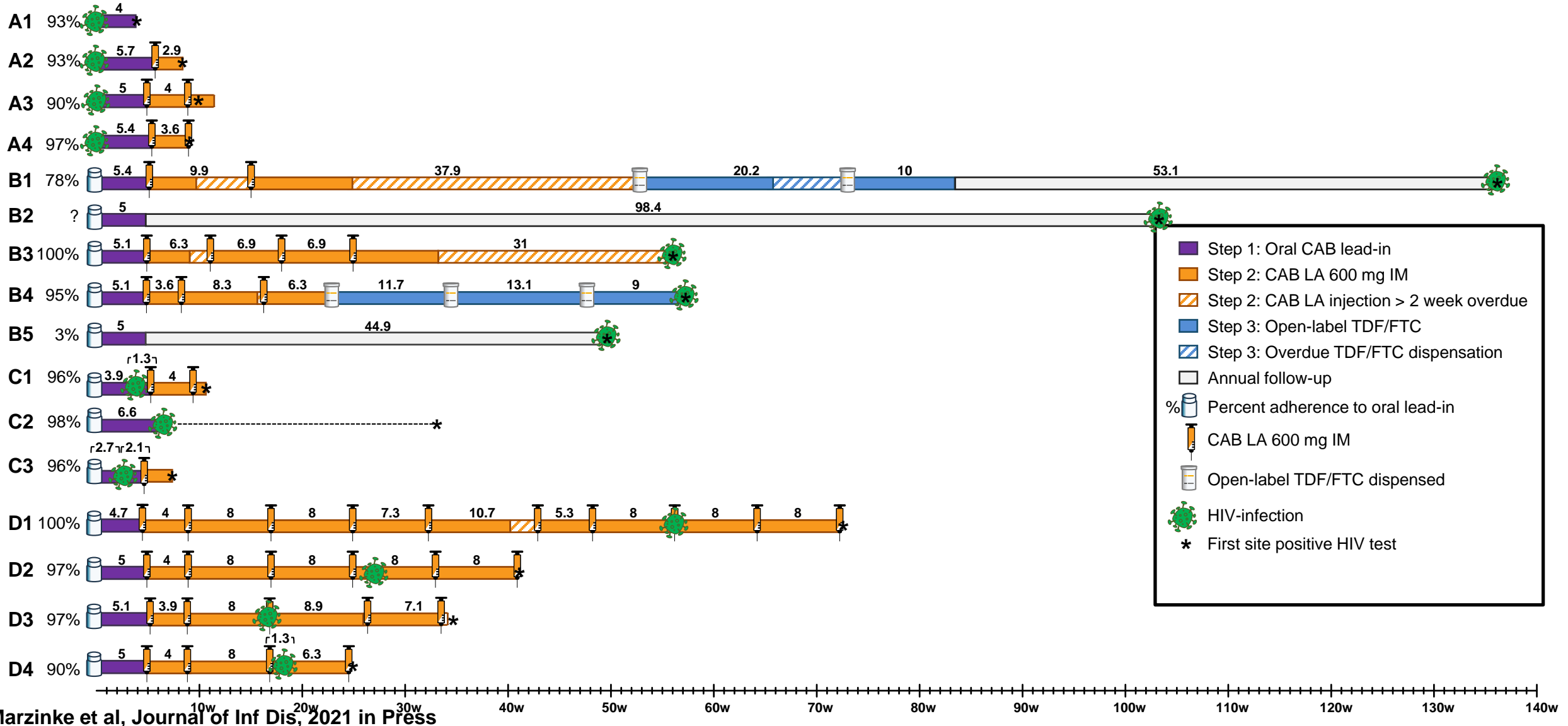
13 Incident, 2 baseline Infections: Cabotegravir



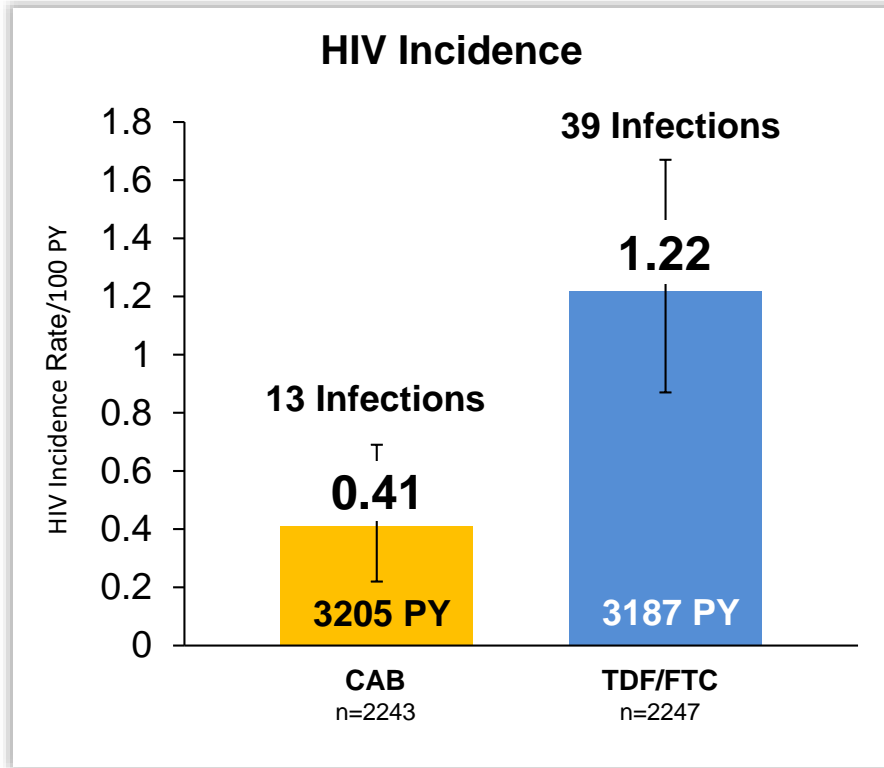
13 Incident, 3 baseline Infections: Cabotegravir



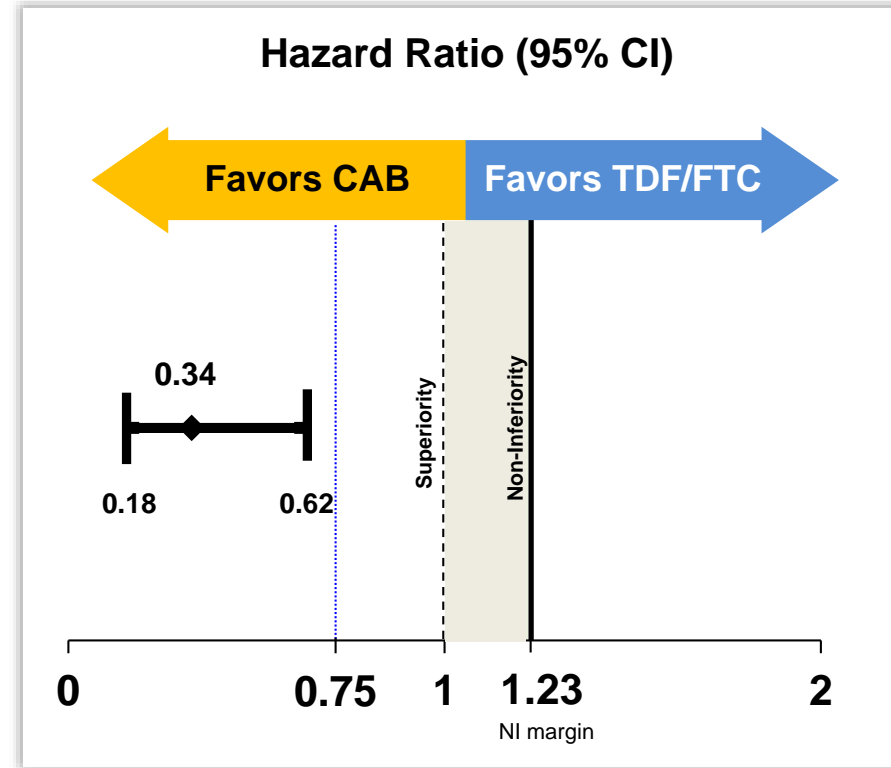
12 Incident, 4 baseline Infections: Cabotegravir



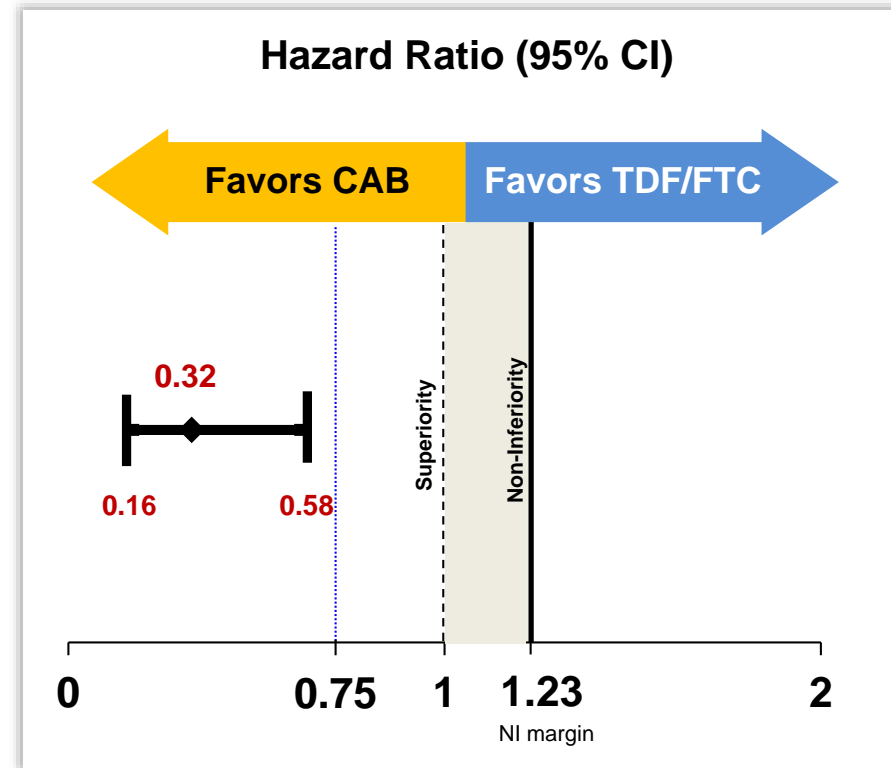
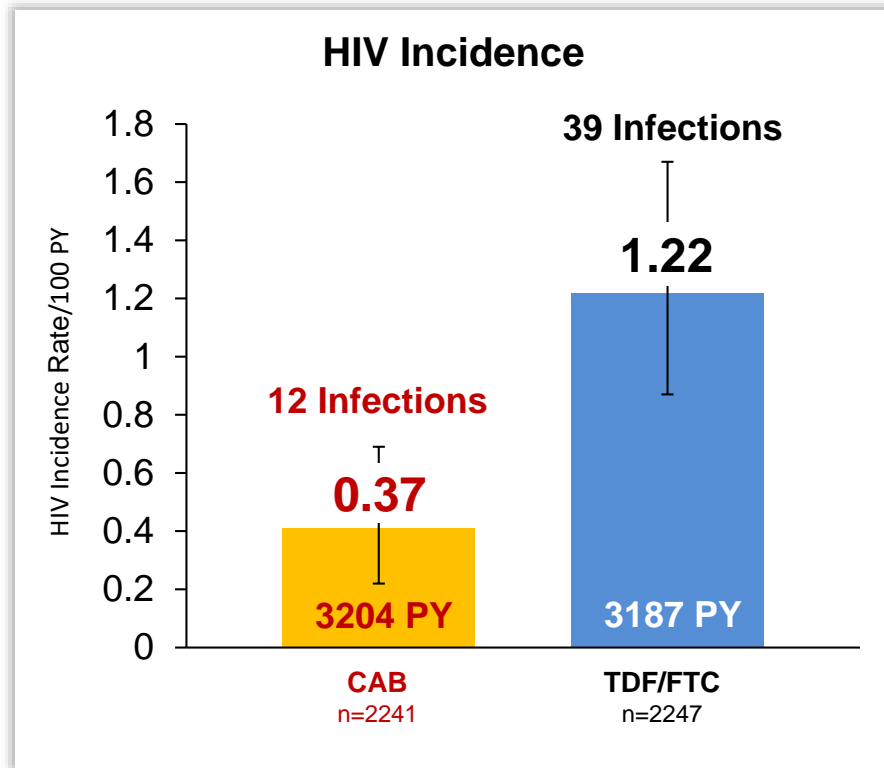
HIV Incidence: CAB vs. TDF/FTC



CI, confidence interval

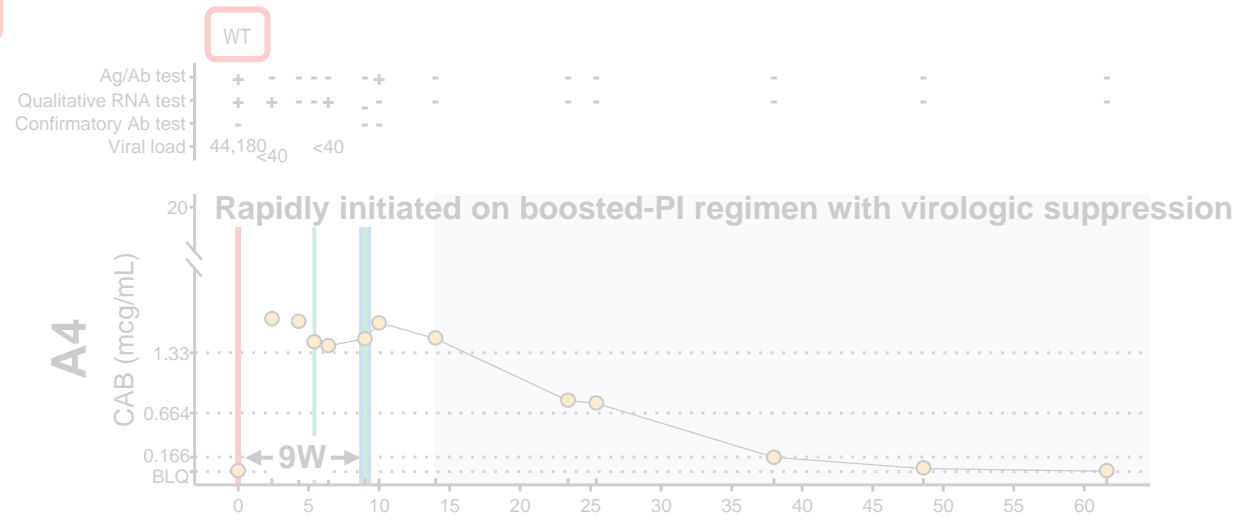
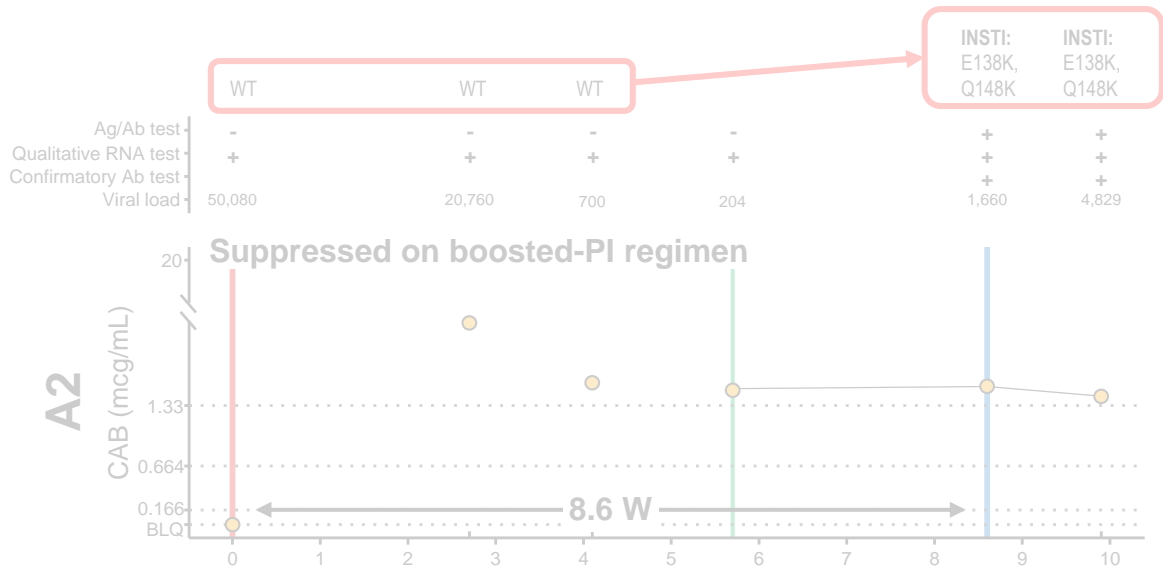
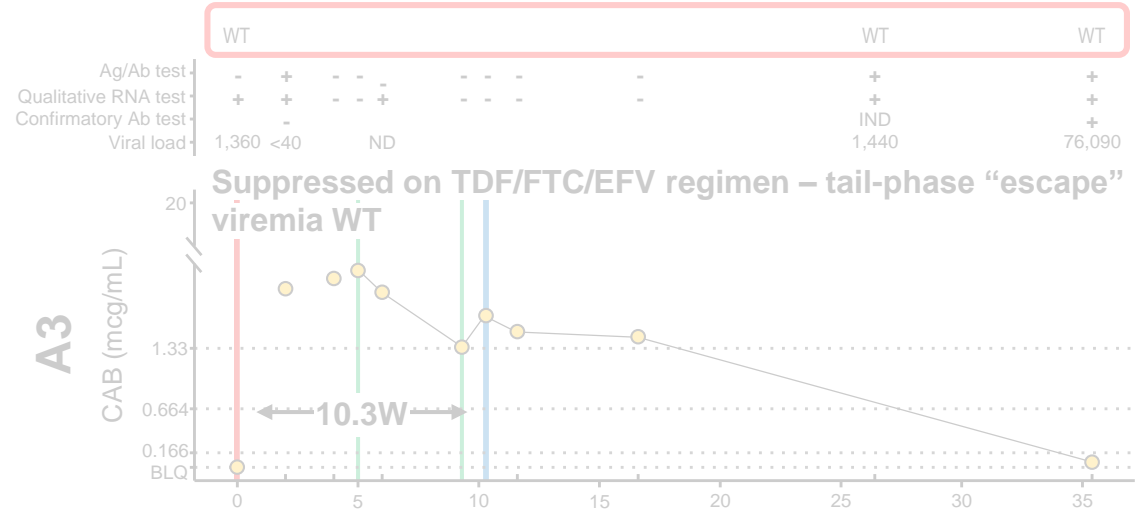
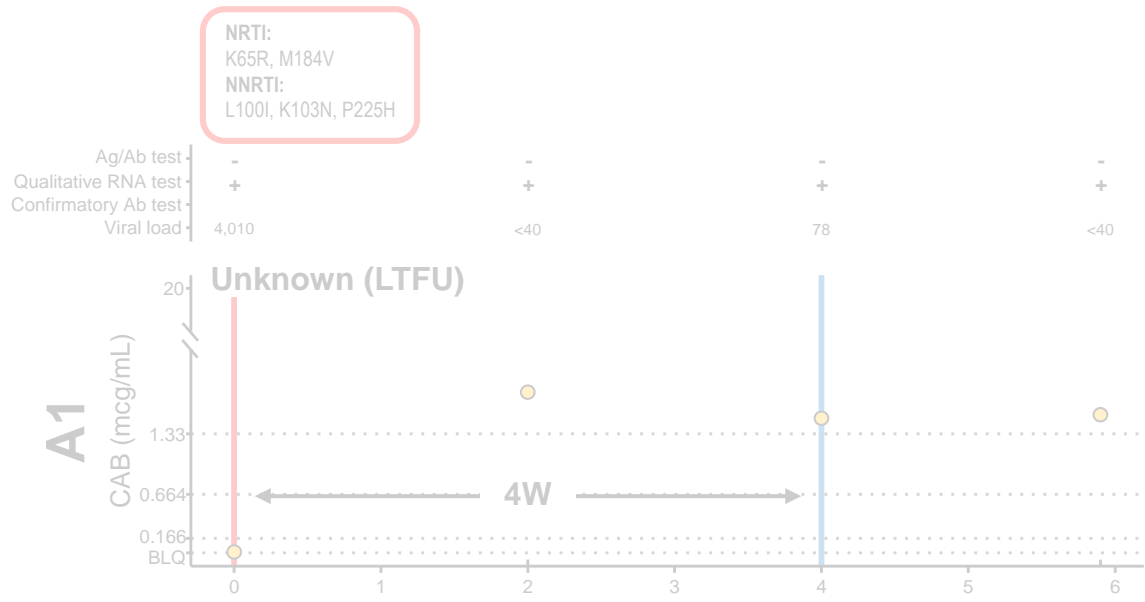


HIV Incidence: CAB vs. TDF/FTC



CI, confidence interval

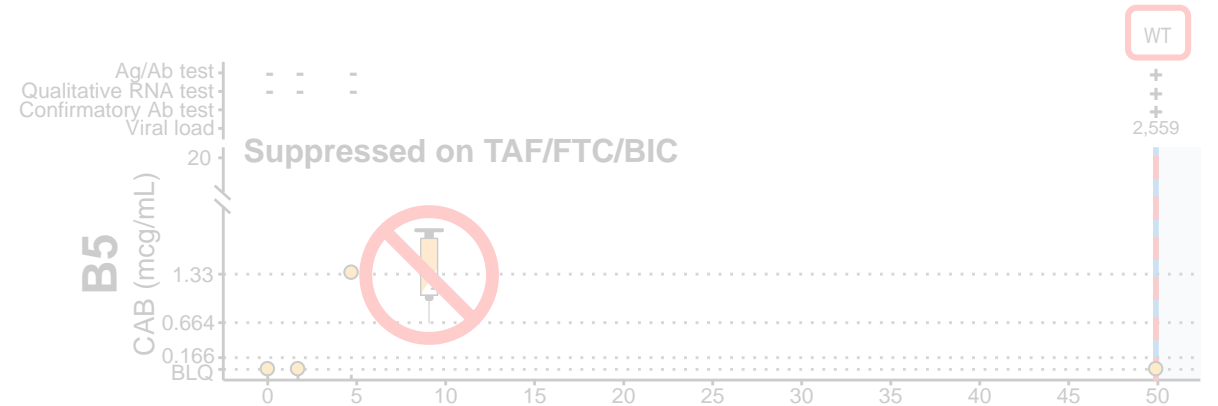
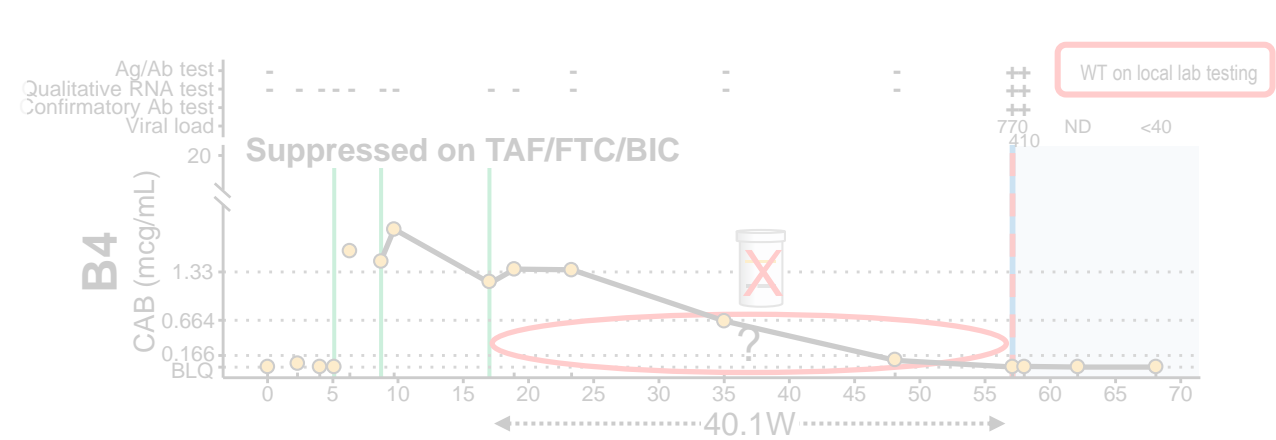
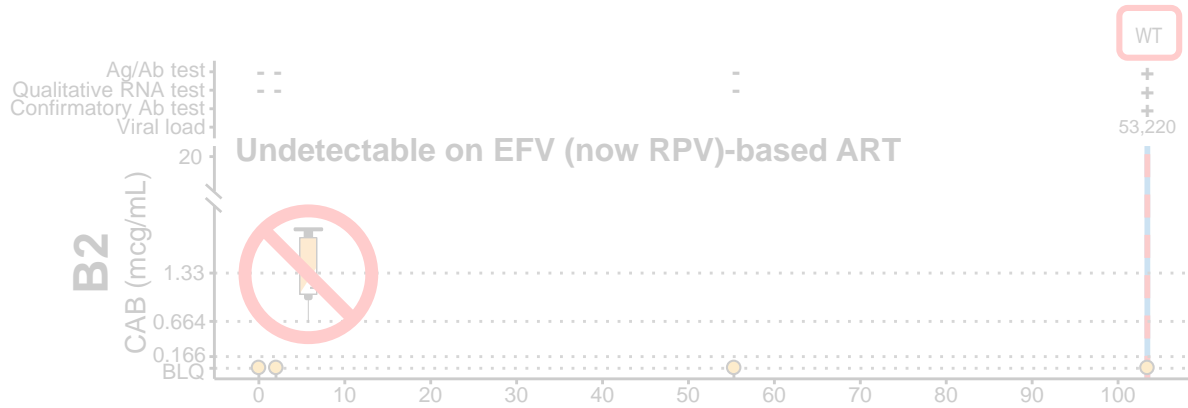
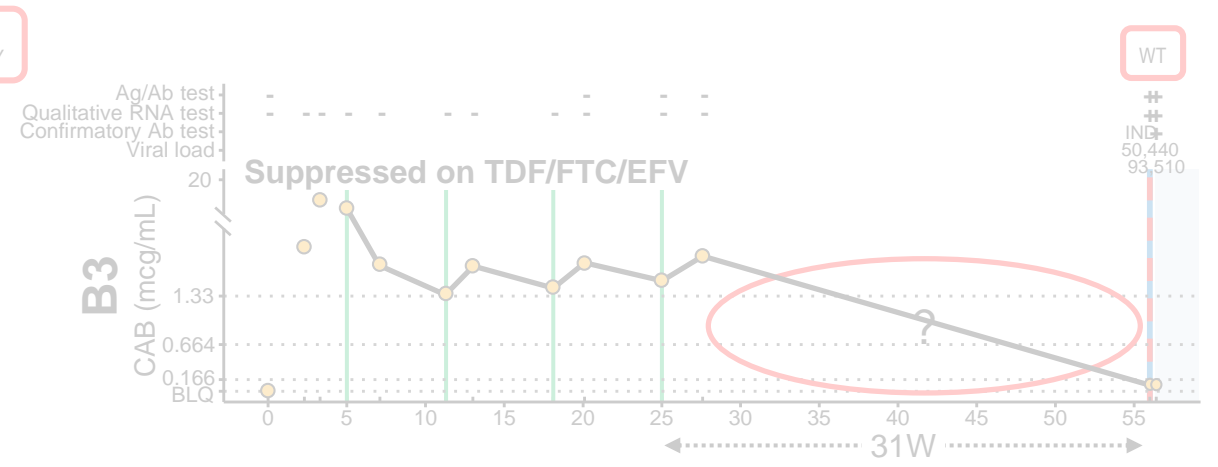
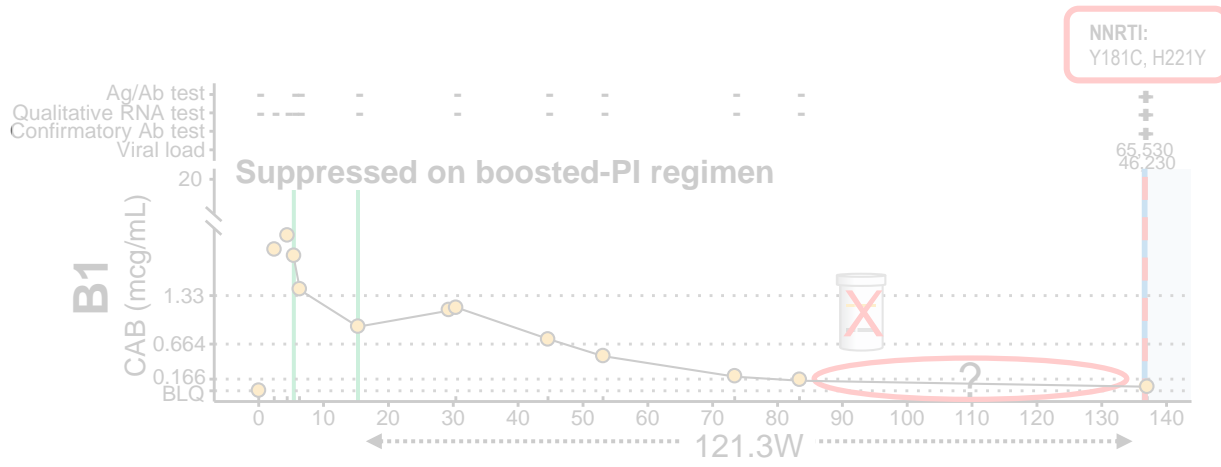
CAB arm, Group A
HIV positive at study enrollment



● CAB concentration ■ CAB injection ■ First HIV positive visit ■ First site positive visit ■ First HIV positive visit and first site positive visit
 ← # → Weeks between first HIV positive visit and the first site positive test

The x-axis represents weeks since enrollment. The shaded area represents time on ART.

CAB arm, Group B
No recent CAB exposure



- CAB concentration
- CAB injection
- First HIV positive visit
- First site positive visit
- First HIV positive visit and first site positive visit
- ←.....#.....→ Weeks between last injection and the first HIV positive test

The x-axis represents weeks since enrollment. The shaded area represents time on ART.

CAB arm, Group C
Infected during the CAB oral
lead-in period

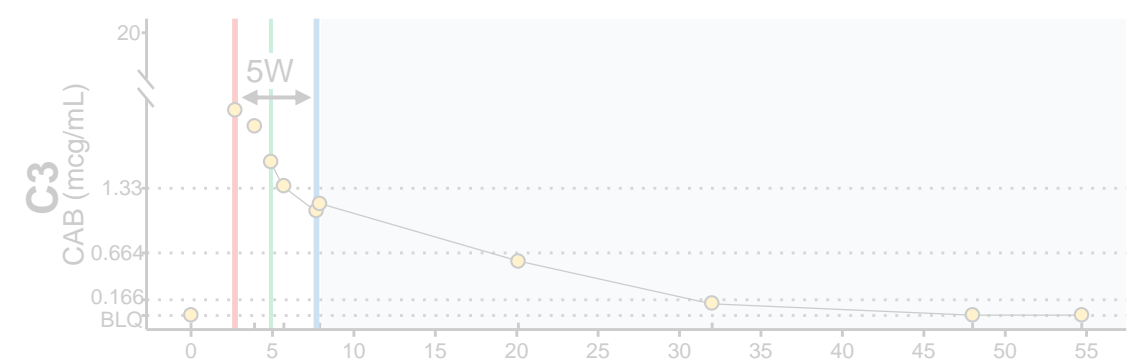
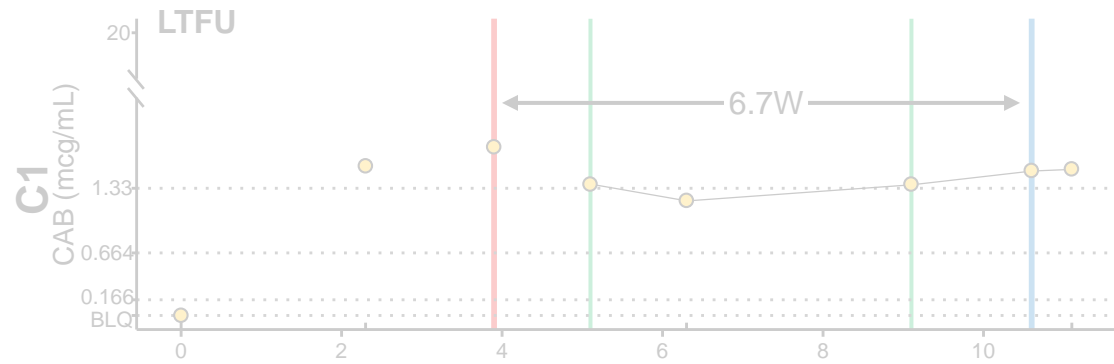
Ag/Ab test	-	-	-	-	-	-	+	-
Qualitative RNA test	-	-	+	+	+	+	+	+
Confirmatory Ab test	-	-	-	-	-	-	-	-
Viral load	ND		120	161	137	2,174	1,373	2,549

INSTI:
L74I,
Q148R

INSTI:
L74I,E138E/K,
G140G/S, Q148R

Ag/Ab test	-	-	-	-	+			
Qualitative RNA test	-	+	+	+	+			
Confirmatory Ab test	-	-	-	-	IND			
Viral load	ND	ND	102,329	375	<40	99,218,776	ND	ND

INSTI:
E138A, Q148R



Ag/Ab test	-	-	-	+
Qualitative RNA test	-	-	+	+
Confirmatory Ab test	-	-	-	+
Viral load			494	229,810 207,810

WT

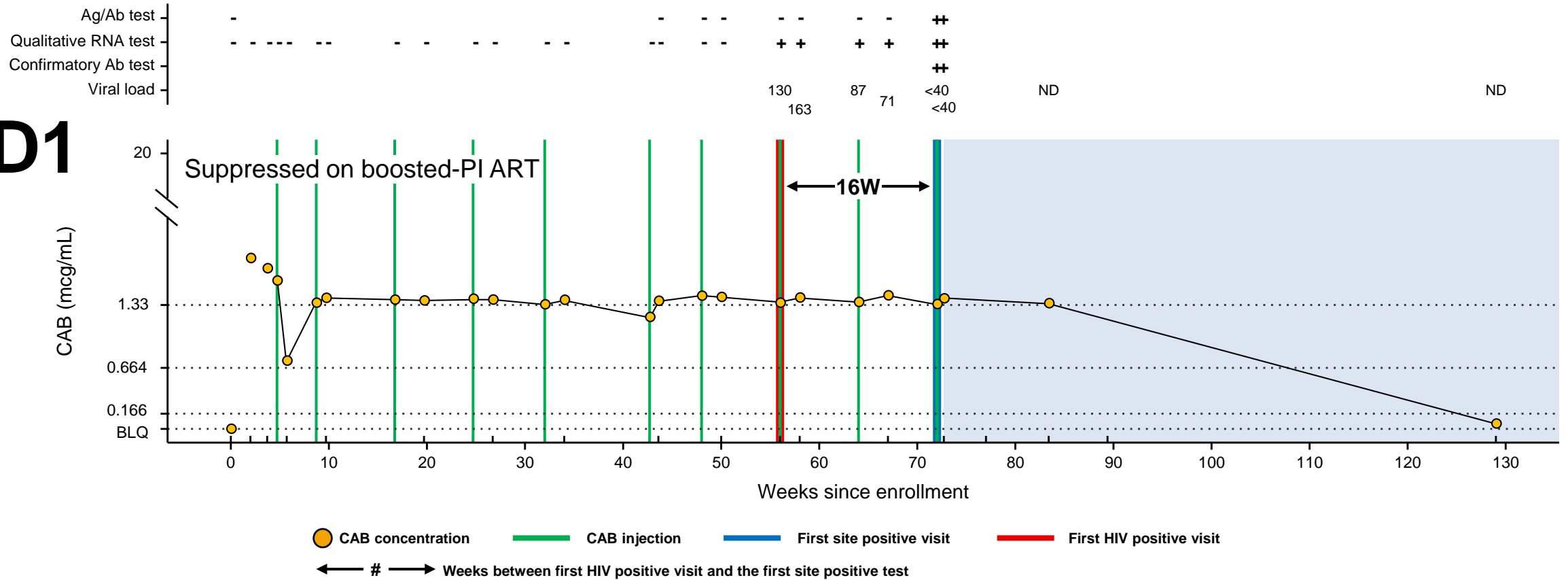


- CAB concentration
- CAB injection
- First HIV positive visit
- First site positive visit
- First HIV positive visit and first site positive visit
- ← # → Weeks between first HIV positive visit and the first site positive test

The x-axis represents weeks since enrollment. The shaded area represents time on ART.

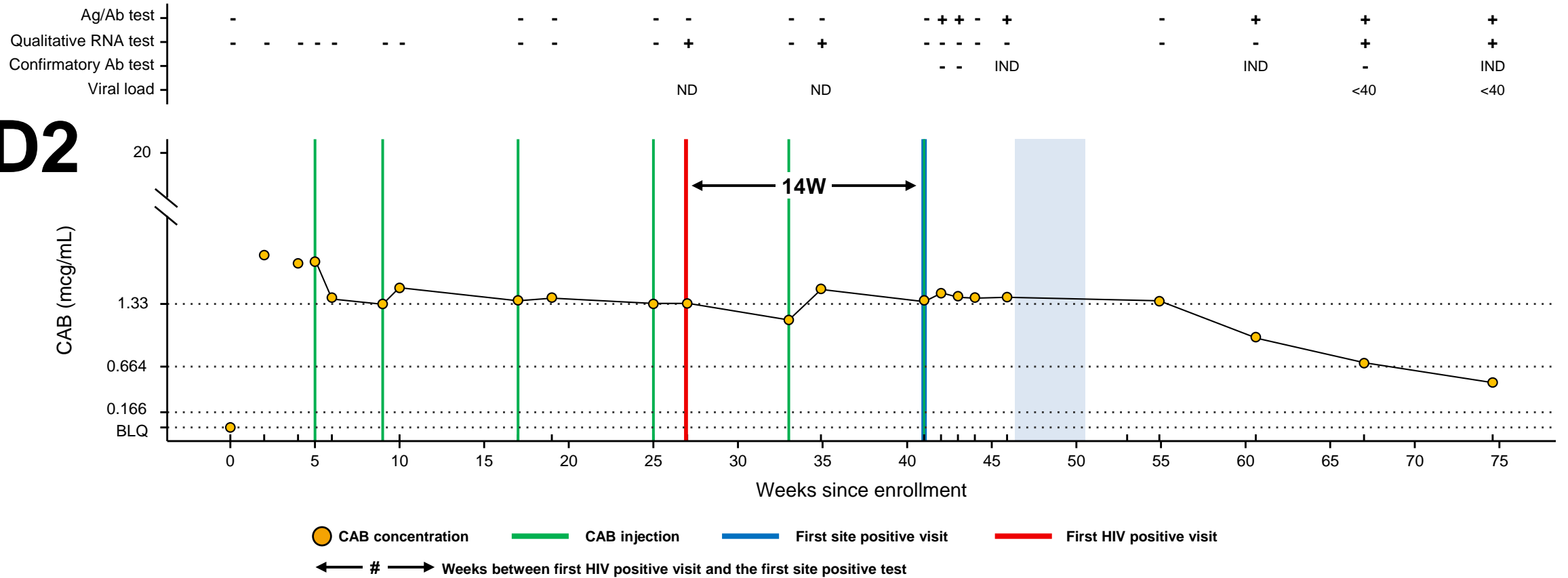
CAB arm, Group D
Infected in the setting of on-time
CAB injections

D1



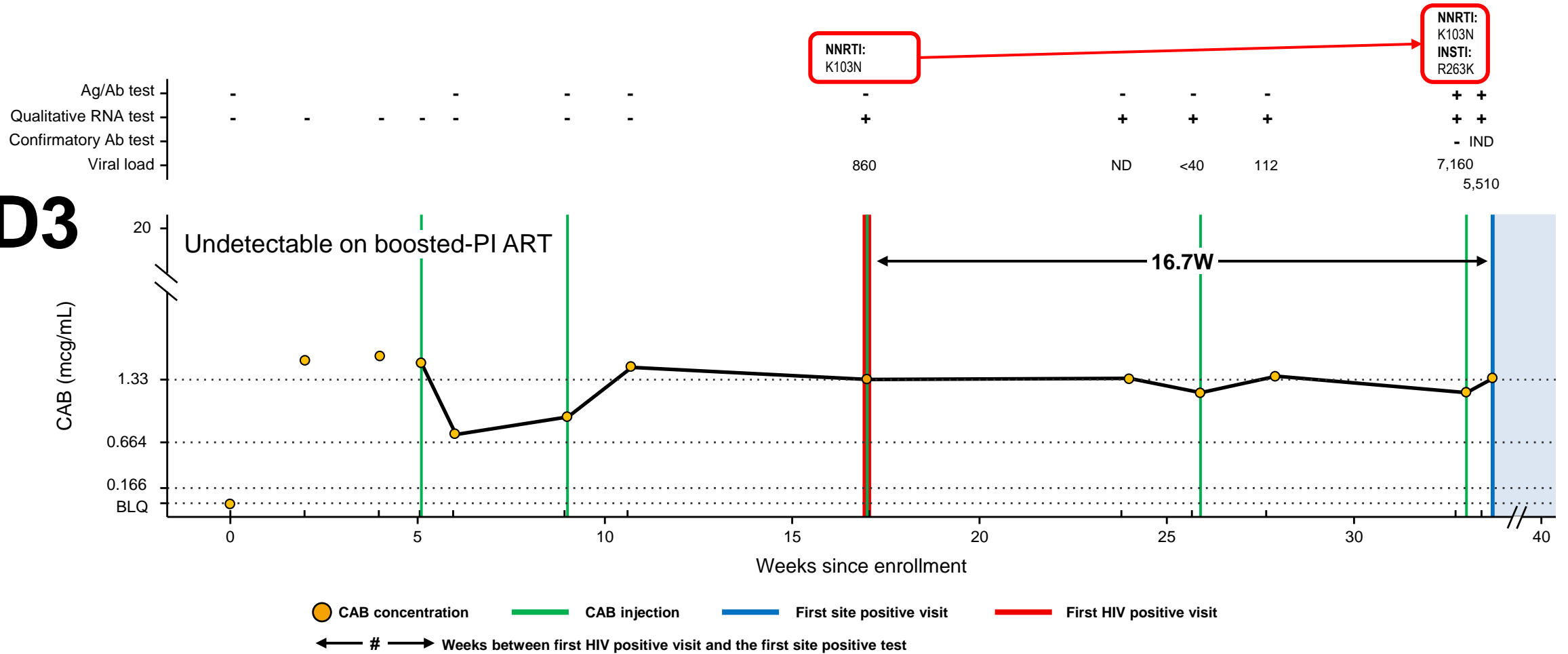
The shaded area represents time on ART.

D2



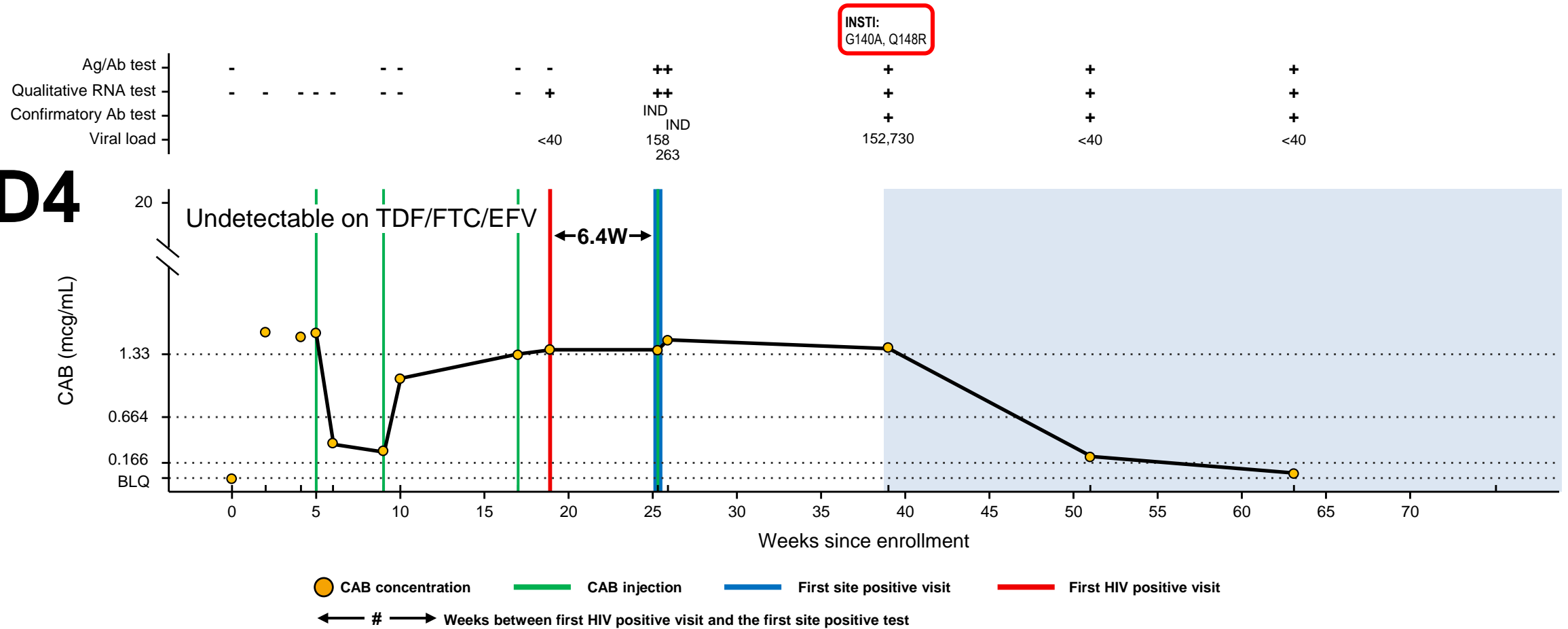
The shaded area represents time on ART.

D3



The shaded area represents time on ART.

A Cautionary Tale



The shaded area represents time on ART.

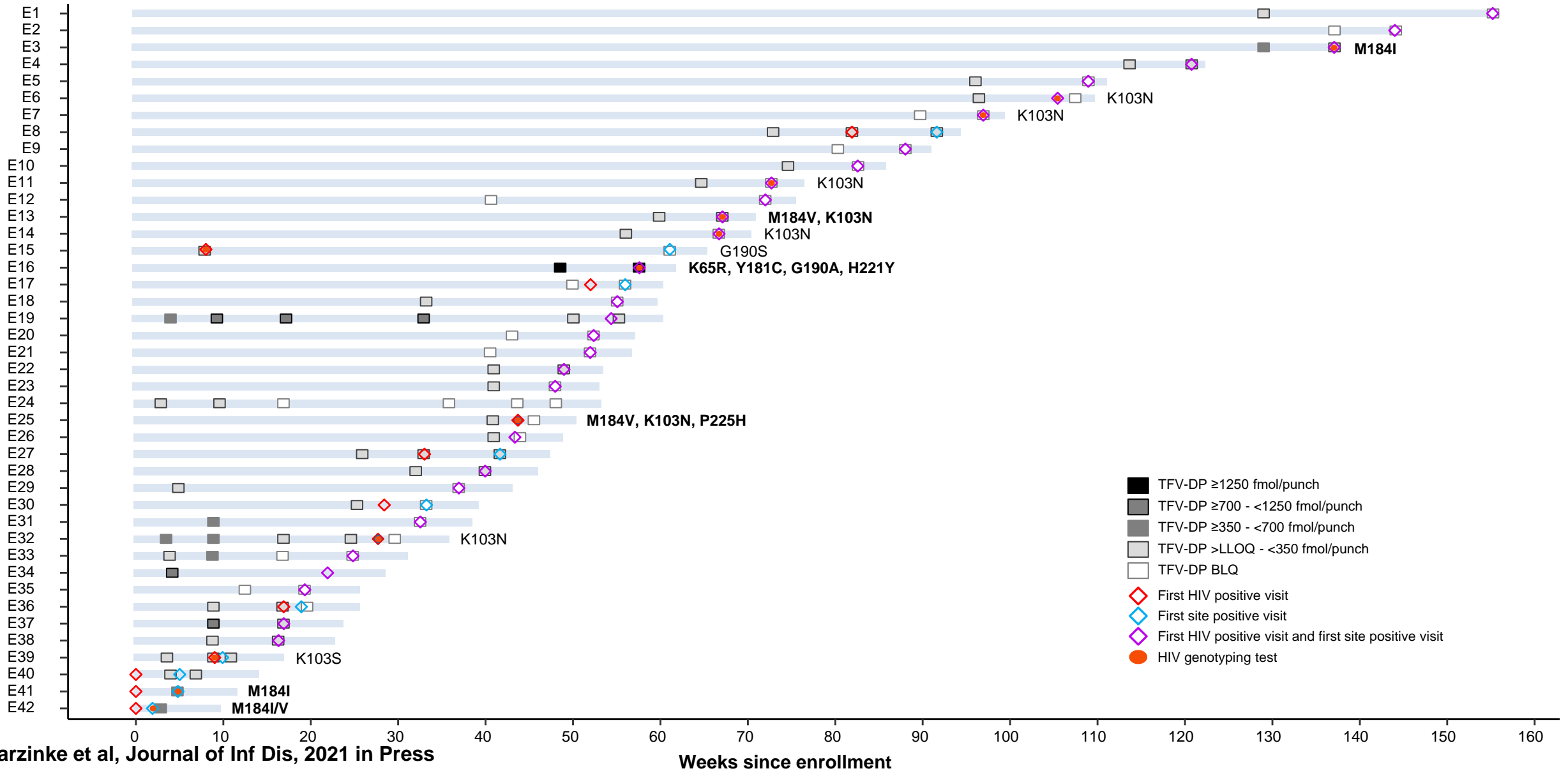
Case	Sample type	Visit type	Subtype	Drug resistance mutations ^a				INSTI Phenotype ^b (Fold change)
				NRTI	NNRTI	PI	INSTI	
A1	1 st viremic	Enrollment	B	K65R, M184V	L100I, K103N, I135T, P225H	L10V, I62V		N/A (assay failure)
A2	1 st viremic	Enrollment	C		I135T, Q207E	I13V, M36I, L89M		Sensitive to all INSTIs RC: 101% (95% CI: 64-160%)
	Follow-up (60 days later)	Week 6			I135T, Q207E	I13V, M36I, L89M	E138K, Q148K	N/A (assay failure)
	Follow-up (69 days later)	Week 6			I135T, Q207E	I13V, M36I, L89M	E138K, Q148K	N/A (assay failure)
B1	1 st viremic	Yearly 1	B		I135T, V179T, Y181C, H221Y	I62V		N/A (assay failure)
C1	1 st viremic	Week 9	B			L10I, I13V, M36I	L74I, Q148R	N/A (assay failure)
	Follow-up (10 days later)	Week 10				L10I, I13V, M36I	L74I, E138E/K, G140G/S, Q148R	N/A (assay failure)
	Follow-up (14 days later)	Week 10				L10I, I13V, M36I	L74I, E138E/K, G140G/S, Q148R	N/A (assay failure)
C3	1 st viremic	Week 9	B	V118I		M36I, I62V, A71T	E138A, Q148R	CAB (5.92), EVG (>max), RAL (17), DTG (1.69), BIC (1.2); RC: 1.3% (95% CI: 0.82-2.1%)
	Follow-up (1 day later)	Interim visit		V118I		M36I, I62V, A71T	E138A, Q148R	CAB (7.42), EVG (>max), RAL (35), DTG (2.39), BIC (1.48); RC: 5.2% (95% CI: 3.3-8.3%)
D3	1 st viremic	Week 17	BF		K103N, I135T	L10V, M36I		Sensitive to all INSTIs; RC: 47% (95% CI: 30-47%)
	Follow-up (112 days later)	Week 33			K103N, I135T	L10V, M36I	R263K	N/A (assay failure)
	Follow-up (117 days later)	Week 33			K103N, I135T	L10V, M36I	R263K	CAB (2.32), EVG (4.14), RAL (1.38), DTG (2.29), BIC* (2.89); RC: 24% (95% CI: 15-38%)
D4	1 st viremic	F/U Week 12	C			K20R, E35D, M36I, L89M	G140A, Q148R	CAB (13), EVG (107), RAL (43), DTG (2.09), BIC* (2.77); RC: 25% (95% CI: 16-40%)

Key virology findings - CAB arm

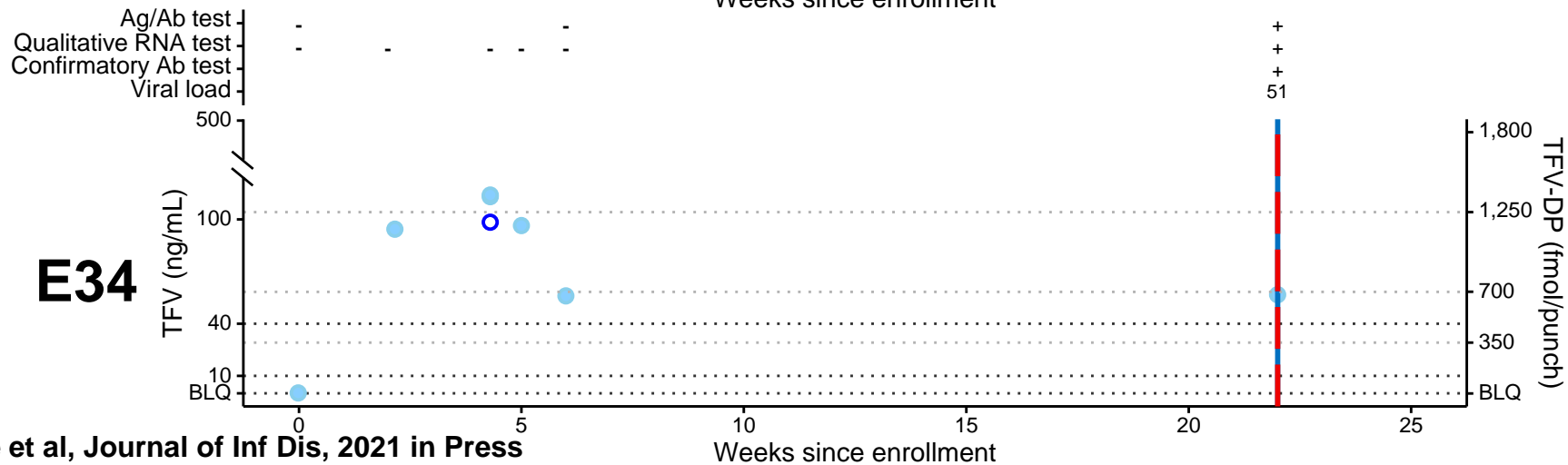
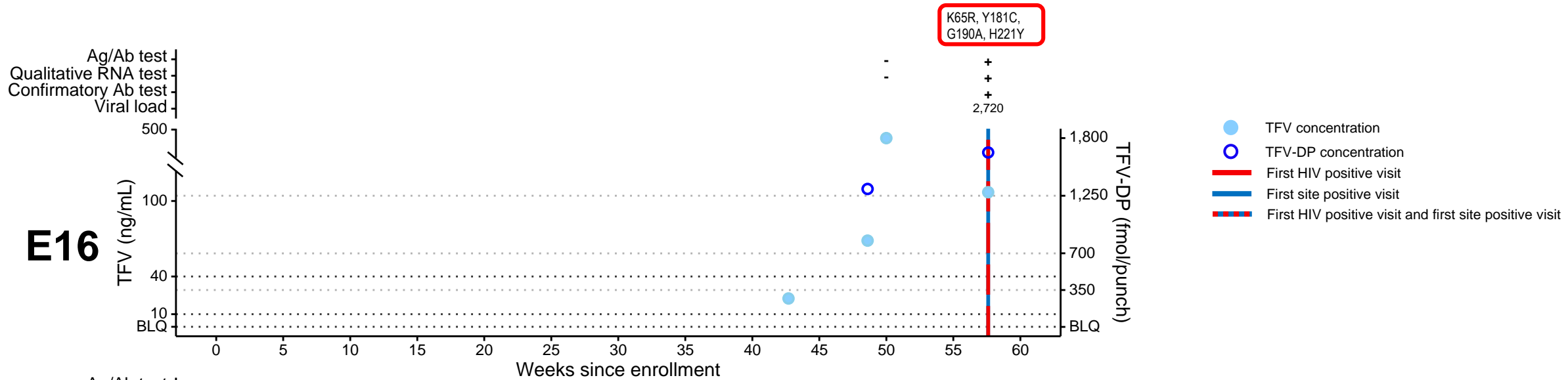
- **Extended testing identified earlier infection dates in many cases**
- **Virus loads were often low at the first HIV positive visit**
- **There was often a prolonged period of viral suppression after infection**
- **Antibody expression was diminished / delayed in many cases**
- **In some cases, RNA and Ab tests reverted to negative/non-reactive early in infection**

TDF/FTC arm

39 Incident, 3 Baseline Infections: TDF/FTC



TDF/FTC arm – infected despite good adherence





Key Observations & Conclusions

Key observations:

- **4 incident infections in the CAB arm occurred despite target plasma CAB concentrations; evaluation of correlates of protection is ongoing**
- **CAB-LA can delay detection of infection using standard HIV testing algorithms**
- **INI resistance seen when viremic “escape” occurs at higher CAB concentrations**
- **INI resistance was not seen in 3 tail-phase infections or 1 tail “escape” case**
- **37/39 in the TDF/FTC arm with incident infection had suboptimal or non-adherence**

Conclusions:

- **Oral lead-in will be optional in 083 OLE**
- **Use of VL testing as a primary screen for HIV infection will be assessed in 083 OLE**
- **In the setting of CAB-LA, prompt diagnosis and ART initiation are needed to avoid resistance**

**In HPTN 083, CAB-LA and TDF/FTC were both highly effective for HIV prevention
CAB-LA was superior to daily oral TDF/FTC for HIV PrEP in HPTN 083**

HIV Incidence

Counterfactual Placebo Incidence

Adherence subset: TFV plasma detectable 86.5%

Meta-regression of PBO-controlled TDF/FTC PrEP trials anticipates 74.7% risk reduction for adherence based 86.5% plasma TFV > 0.3 ng/mL

Caveat: If higher risk associated with higher adherence

TDF/FTC arm 1.22% HIV incidence

Risk reduced by 74.7% based on TDF/FTC use

Background HIV incidence is estimated to be 4.82% (95% CI 2.32-10.50%)

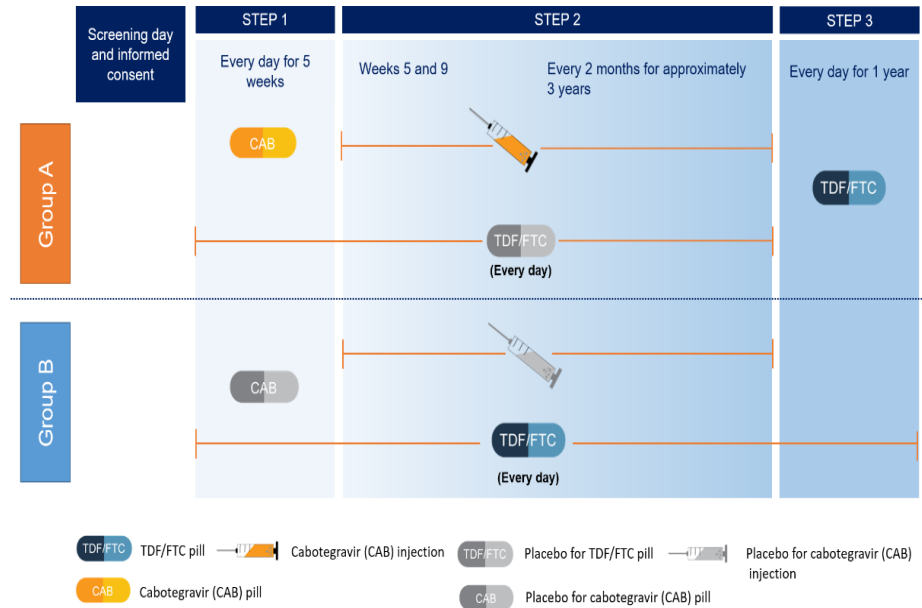
CAB risk reduction (incidence 0.41%) compared to a counterfactual placebo would be estimated to be 91.5% (95% CI 82-96%)

CAB-LA vs. daily oral TDF/FTC for Women in Sub-Saharan Africa



- **Primary Objective: Reduce HIV Incidence** (superiority, double blind, double dummy design)
- Endpoint-driven trial (HIV infection) – monitored by NIAID DSMB every 6 months
- Est. study duration: enrollment 24 months; follow-up up to 4.5 years
- N=3200 at 20 sites in Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe

Sinead Delaney-Moretlwe and Mina Hosseinipour, *Protocol Chairs*



*Start Nov 2017
Blinded Study halted by DSMB November 2020*

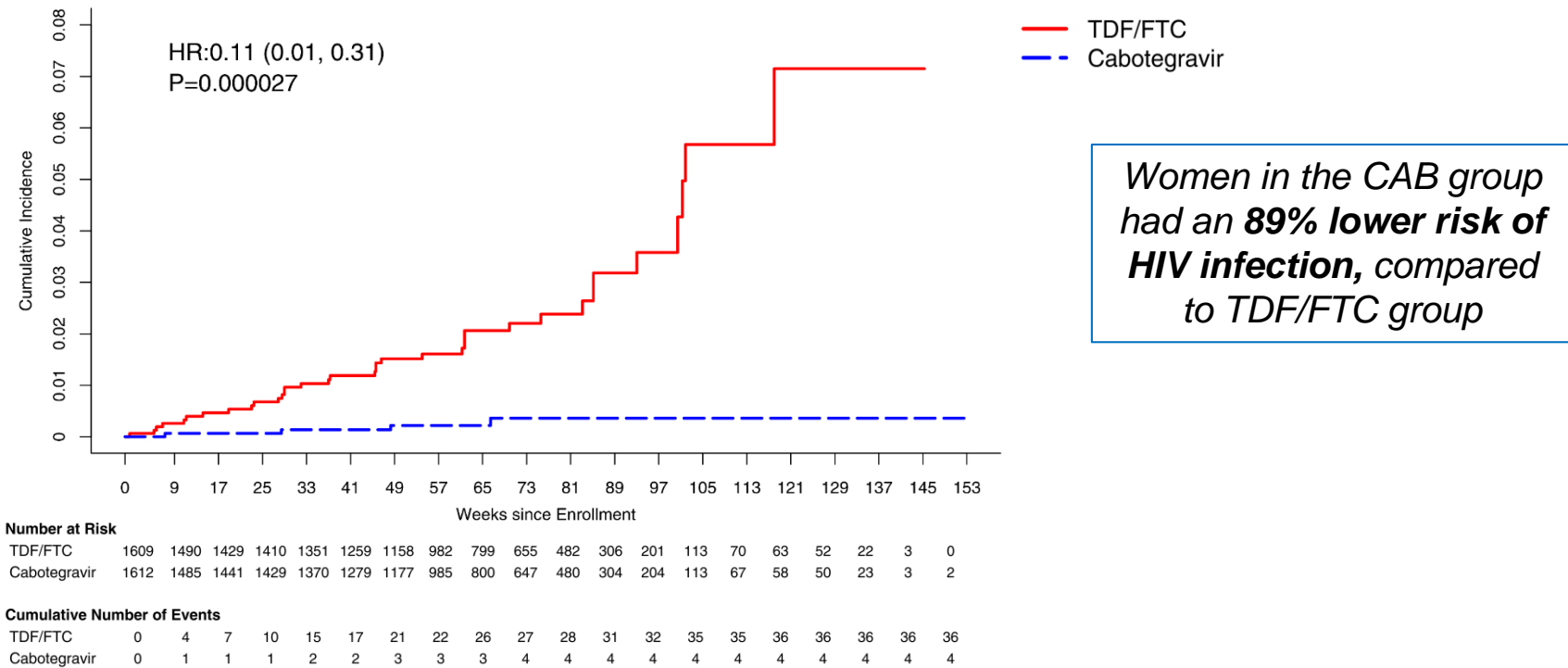
Primary outcome: HIV incidence

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

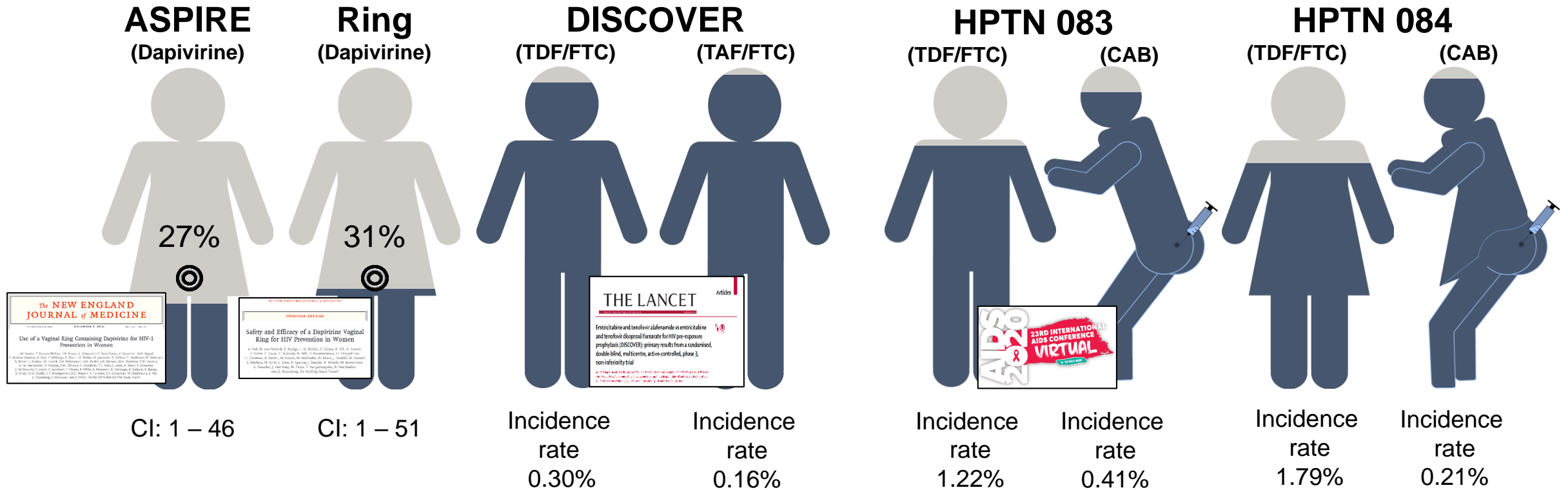
	CAB	TDF/FTC
HIV infections	4	36
Person-years	1,953	1,939
HIV incidence (95% CI)	0.2 (0.06, 0.52)	1.86 (1.3, 2.57)

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

Cumulative HIV incidence – ITT



“PrEP 3.0”: Trials of Novel PrEP Agents



Conclusions

- **Both CAB and TDF/FTC highly effective for HIV prevention**
- **The PrEP regimen containing CAB-LA was superior to a daily oral regimen of TDF/FTC in HPTN 083 and HPTN 084**
- **CAB-LA was generally well tolerated despite injection site reactions**
- **1/4, 0/5, 2/3, and 2/4 Acute (Prevalent), Distant from CAB, Oral-lead-in, and On-time injection participants developed INSTI resistance**
 - **Tail phase seroconversion did not result in INSTI resistance**
 - **Breakthrough at high and expected CAB concentrations resulted in INSTI resistance**
- **CAB is the first long-acting injectable agent to demonstrate robust HIV prevention efficacy**

Acknowledgements

Sponsor

- U.S. National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), and the National Institute of Child Health and Human Development (NICHD) all components of the U.S. National Institutes of Health (NIH)
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HIV Prevention Trials Network (HPTN)

- Laboratory Center (Johns Hopkins University)
- Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Fred Hutchinson Cancer Research Center
- Leadership and Operations Center, FHI 360
- HPTN Leadership

Pharmaceutical Support

- ViiV Healthcare
- Gilead Sciences, Inc.

HPTN 083 Study Team

Community Program Managers Community Educators & Recruiters, CAB Members

Our 43 Sites in 7 countries

...and our Study Participants!

Questions? Email rlandovitz@mednet.ucla.edu or



@doc_in_a_box

