

# **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**

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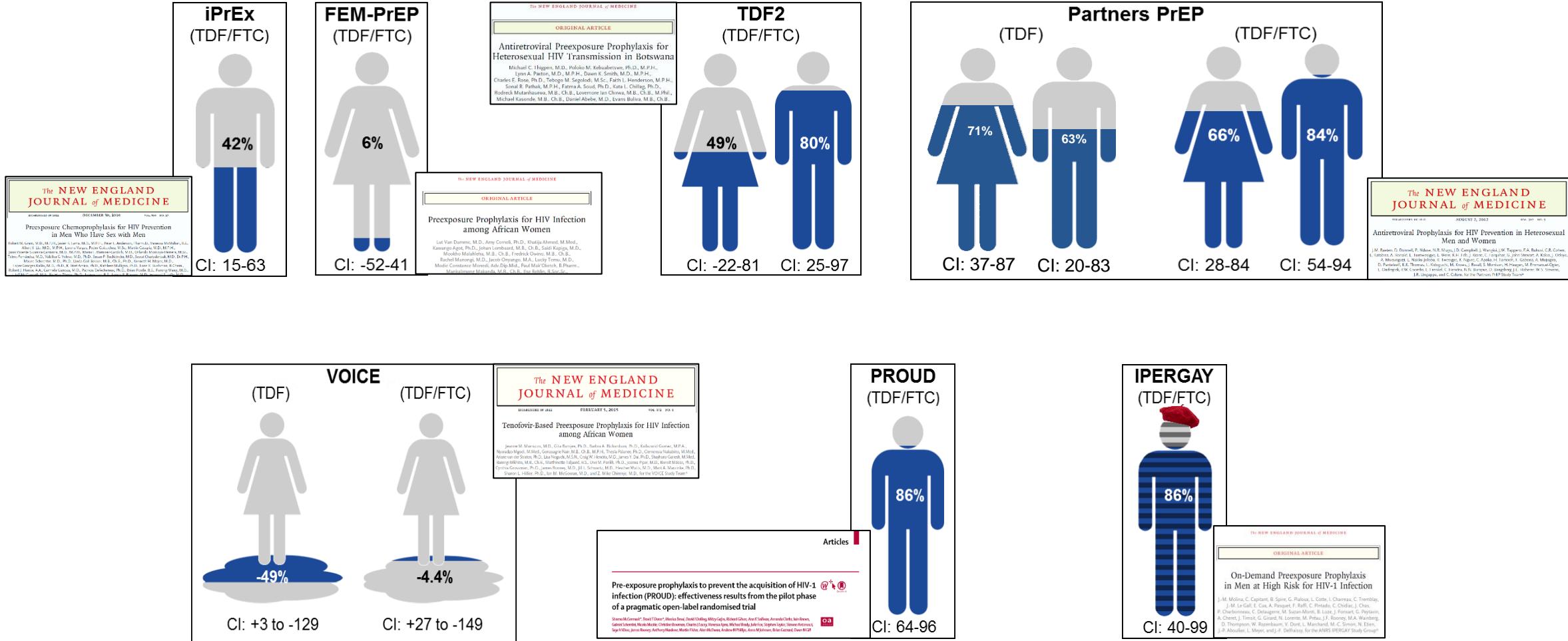
**Raphael J. Landovitz has served as on scientific advisory boards for Gilead Sciences and Merck Inc, and has received honoraria from Roche, Inc and Janssen.**

# **Today's Agenda**

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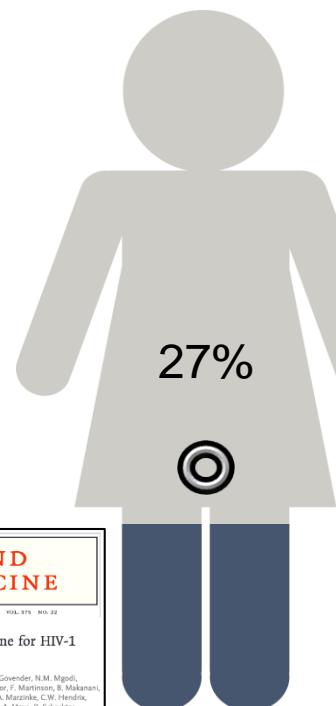
- **PrEP Background and Context**
- **HPTN 083 Study Design**
- **Statistical Methods**
- **Results**
  - **Population**
  - **HIV Incidence**
  - **Safety**
  - **Seroconversion events**
  - **Additional outcomes of interest**
  - **Update and PK, resistance in seroconversion**
- **Conclusions**

# Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials



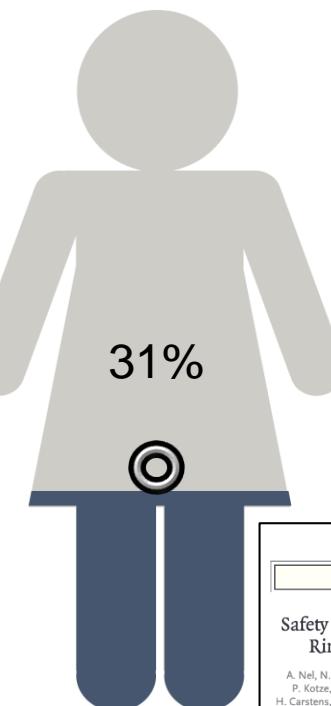
# “PrEP 2.0”: Trials of Novel PrEP Agents

**ASPIRE**  
(Dapivirine)



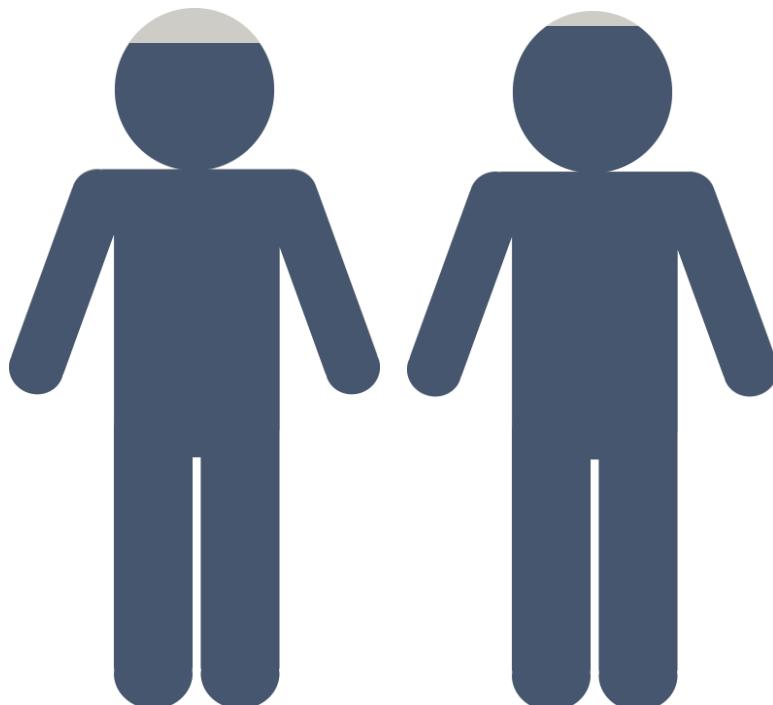
CI: 1 – 46

**Ring**  
(Dapivirine)



CI: 1 – 51

**DISCOVER**  
(TDF/FTC)  
(TAF/FTC)



Incidence rate  
0.30%

Incidence rate  
0.16%

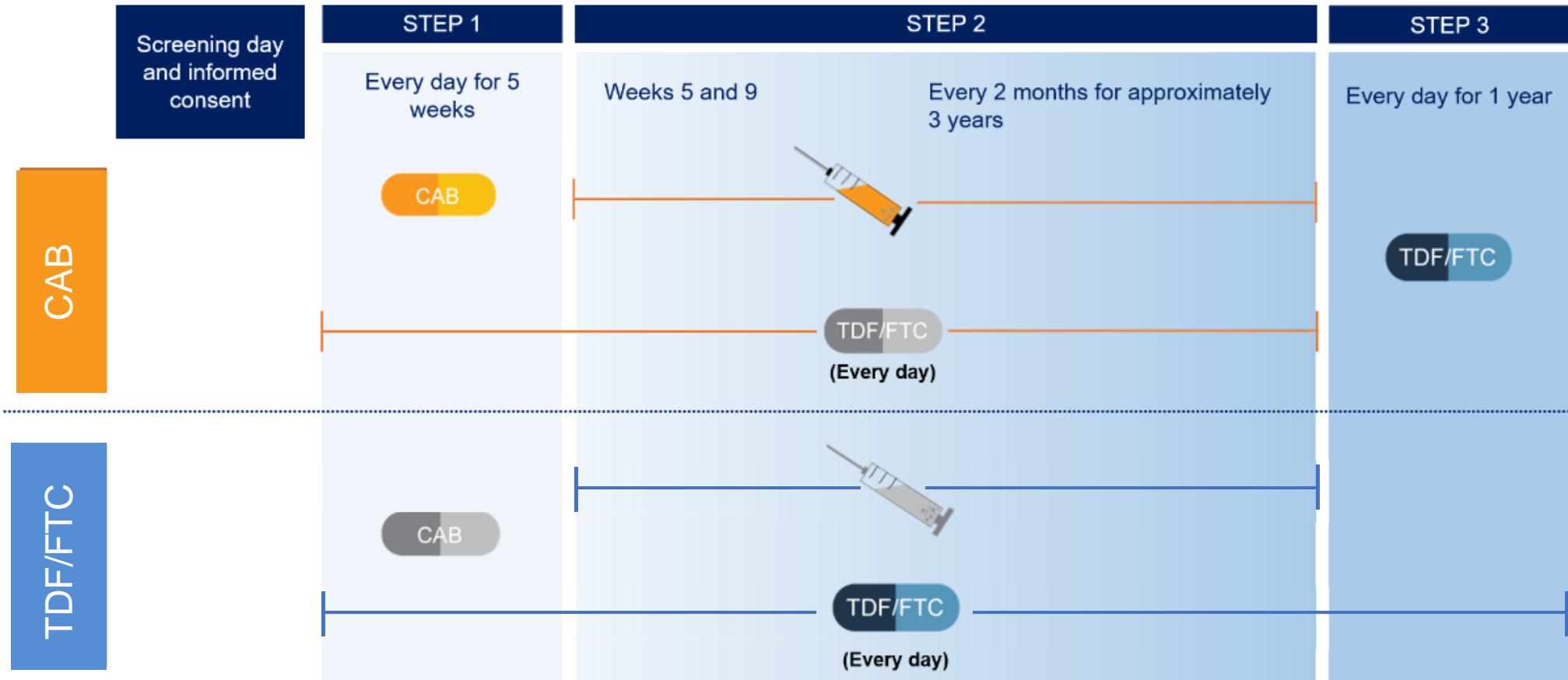


# HPTN 083 Study Design

- **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**



# HPTN 083 Study Design



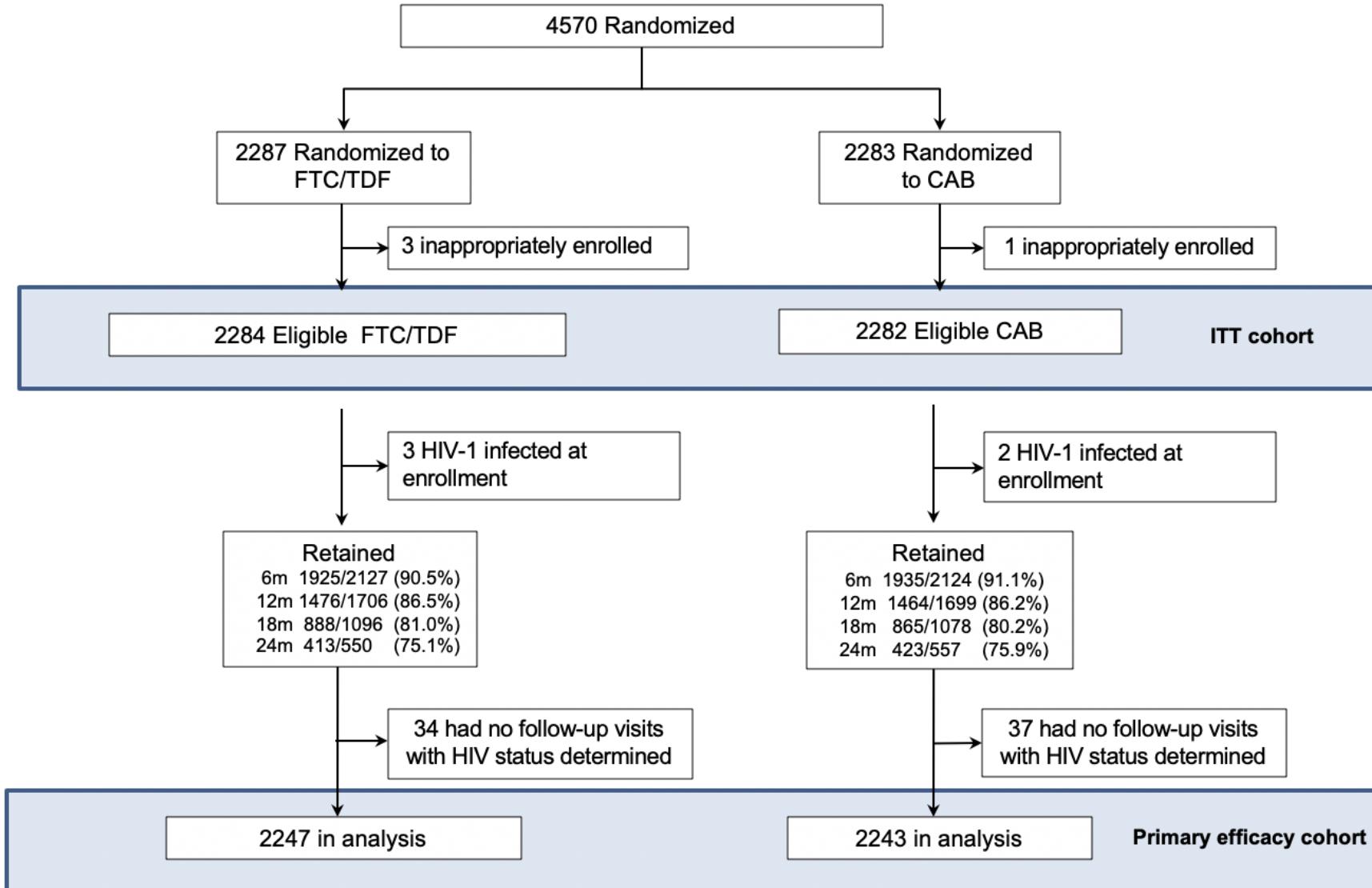
TDF/FTC pill	Cabotegravir (CAB) injection	Placebo for TDF/FTC pill	Placebo for cabotegravir (CAB) injection(20% Intralipid solution)
CAB	Cabotegravir (CAB) pill	CAB	Placebo for cabotegravir (CAB) pill

# Statistical Design: Efficacy

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- **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

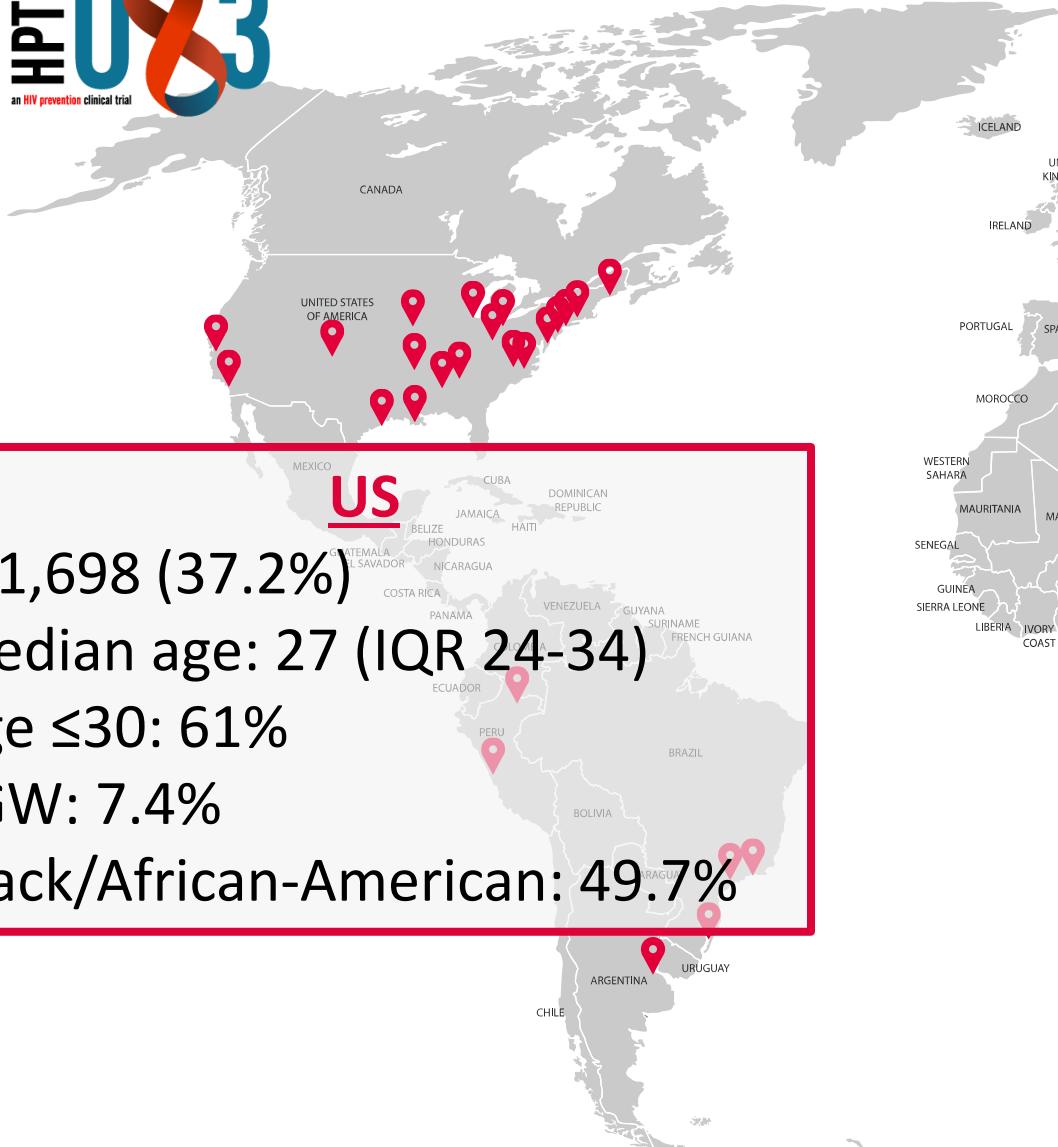


# Study Population

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
<b>Gender Identity, n (%)</b>			
MSM	3995 (87.5)	1981 (86.7)	2014 (88.3)
TGW	567 (12.4)	302 (13.2)	265 (11.6)
<b>Age, median (IQR)</b>	26 (22, 32)	26 (22, 32)	26 (22, 32)
<b>Age, n (%)</b>			
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)
<b>Region, n (%)</b>			
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%)
<b>Education, n (%)</b>			
Post-Secondary (YES)	3477 (76.1)	1715 (75.1)	1762 (77.2)
<b>Relationship Status, n (%)</b>			
Single (YES)	3750 (82.1)	1863 (81.6)	1887 (82.7)

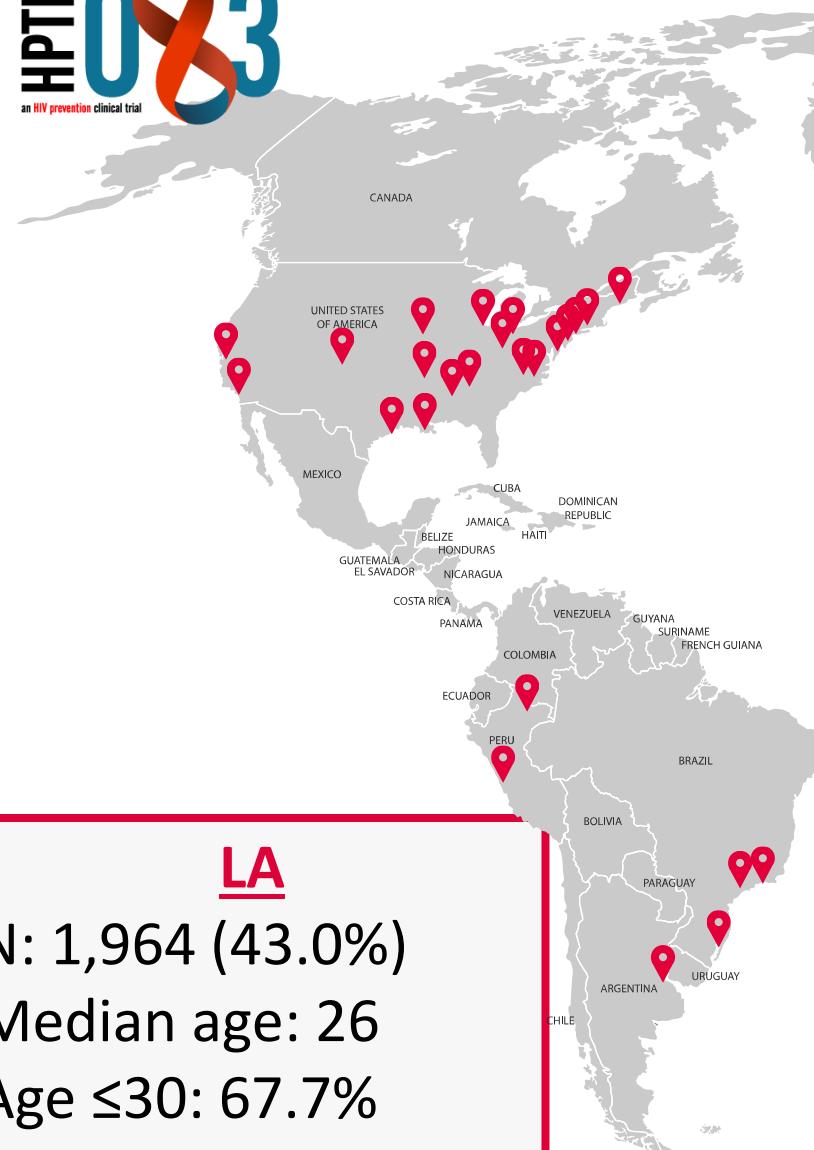
# Study Population

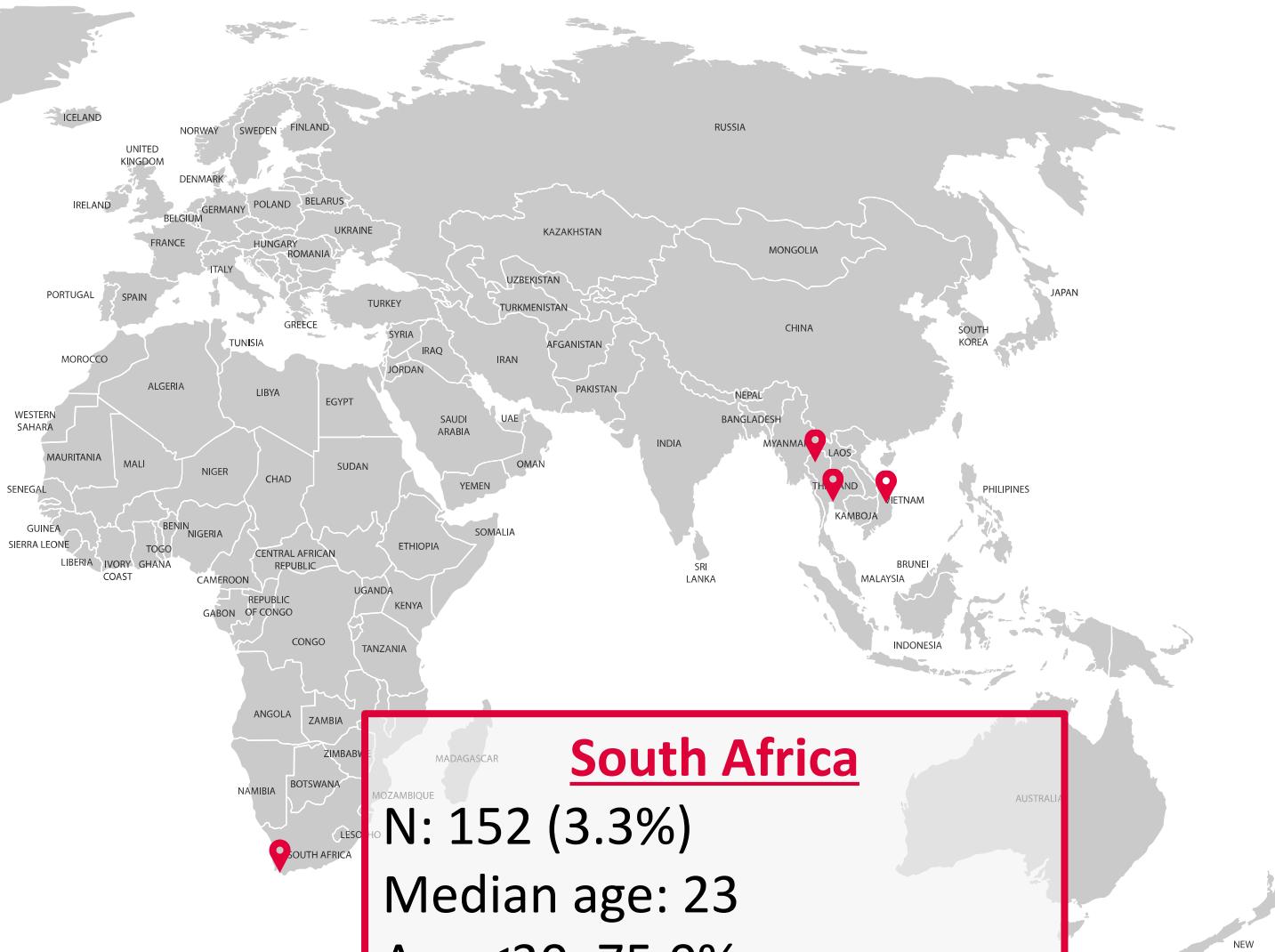
	<b>TOTAL (n=4566)</b>	<b>TDF-FTC (n=2284)</b>	<b>CAB (n=2282)</b>
<b>Race, n (%)</b>			
<b>United States</b>			
Black/African American	844 (49.7)	433 (51.0)	411 (48.9)
White/Asian/Native/Other	854 (50.4)	416 (49.0)	438 (51.1)
<b>Latin America</b>			
Black/Afro-Caribbean	395 (20.1)	196 (19.9)	199 (20.3)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



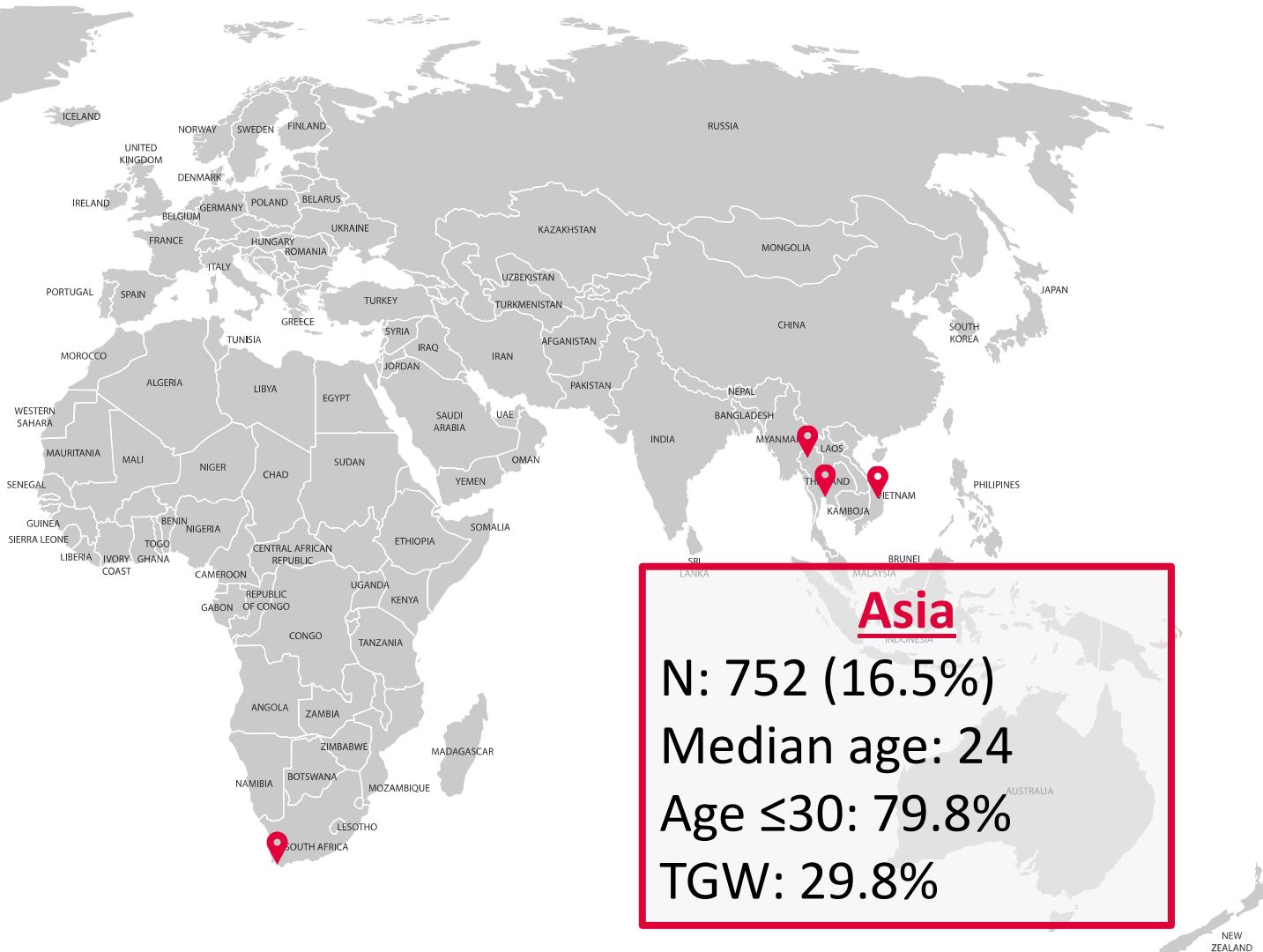


an HIV prevention clinical trial





**South Africa**  
**N: 152 (3.3%)**  
**Median age: 23**  
**Age  $\leq$ 30: 75.0%**  
**TGW: 9.9%**



## Asia

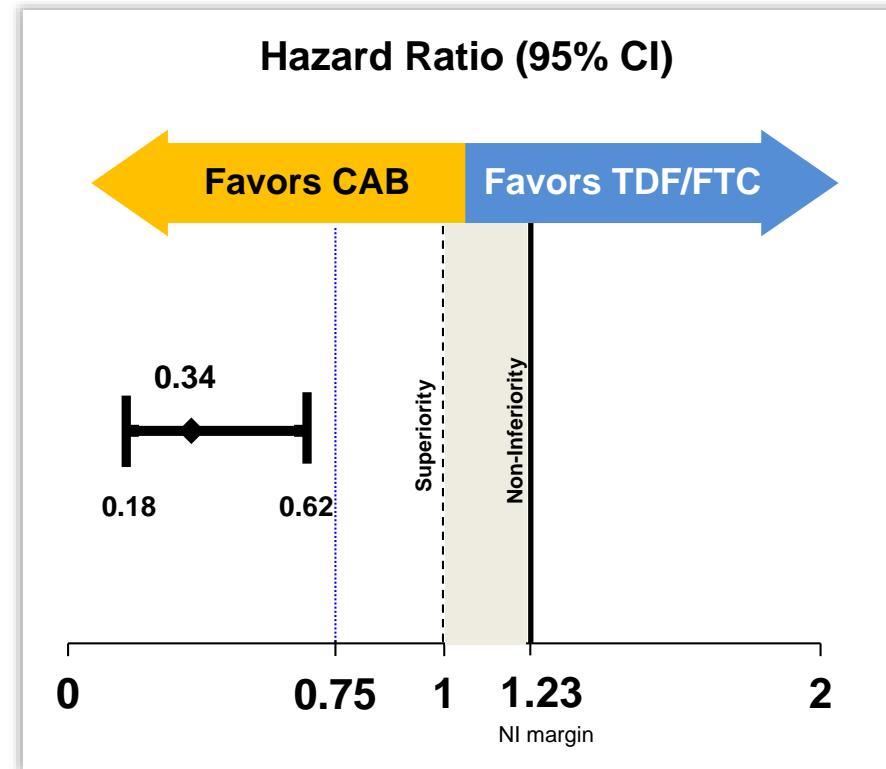
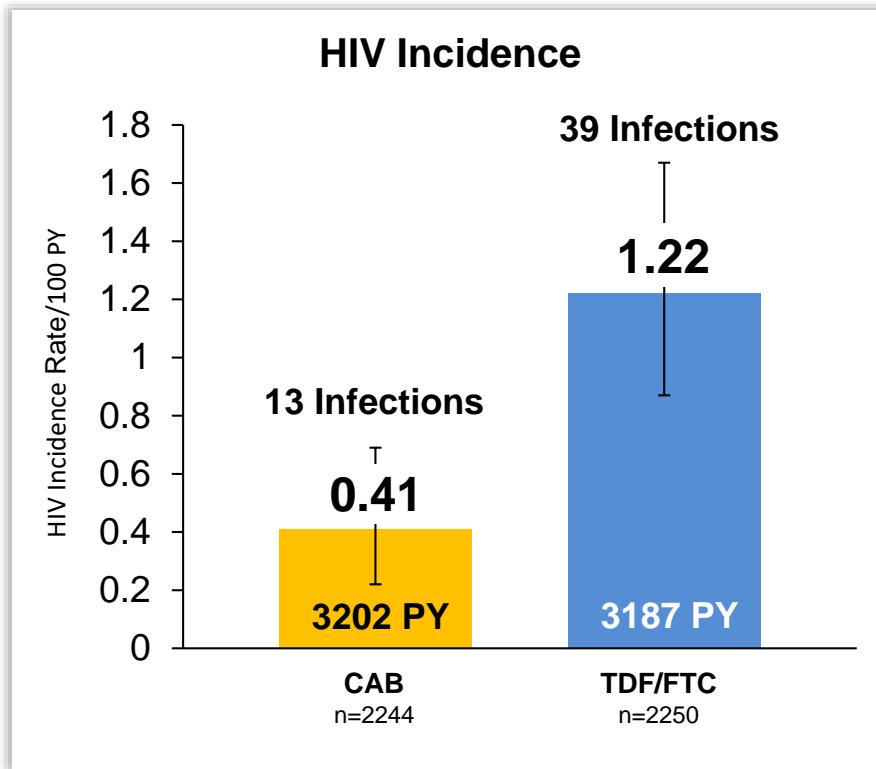
N: 752 (16.5%)  
Median age: 24  
Age  $\leq$ 30: 79.8%  
TGW: 29.8%

# HIV Incidence CAB vs. TDF/FTC

**52 HIV infections in 6389 PY of follow-up**

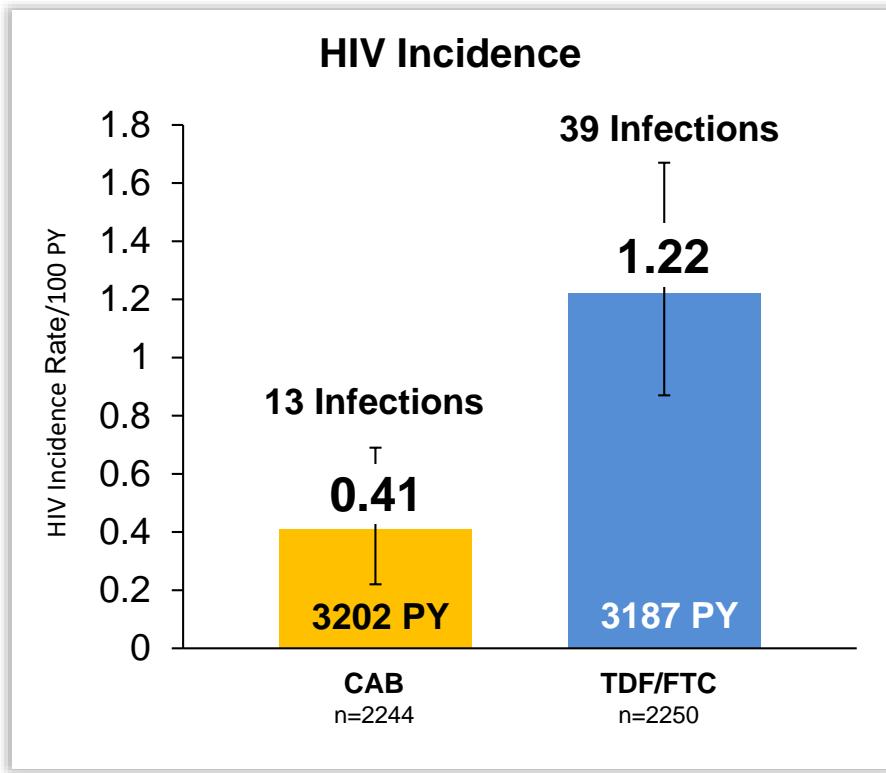
**1.4 (IQR 0.8-1.9) years median per-participant follow-up**

**Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY**



CI, confidence interval

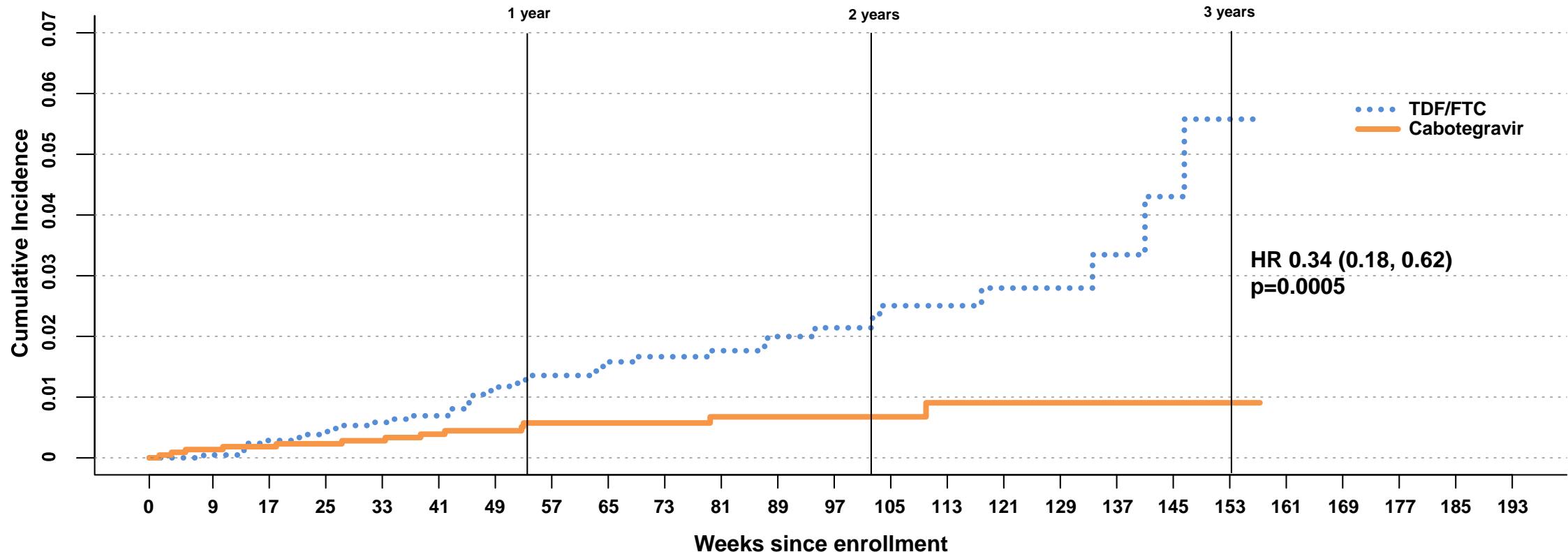
# Number Needed to Treat CAB vs. TDF/FTC



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



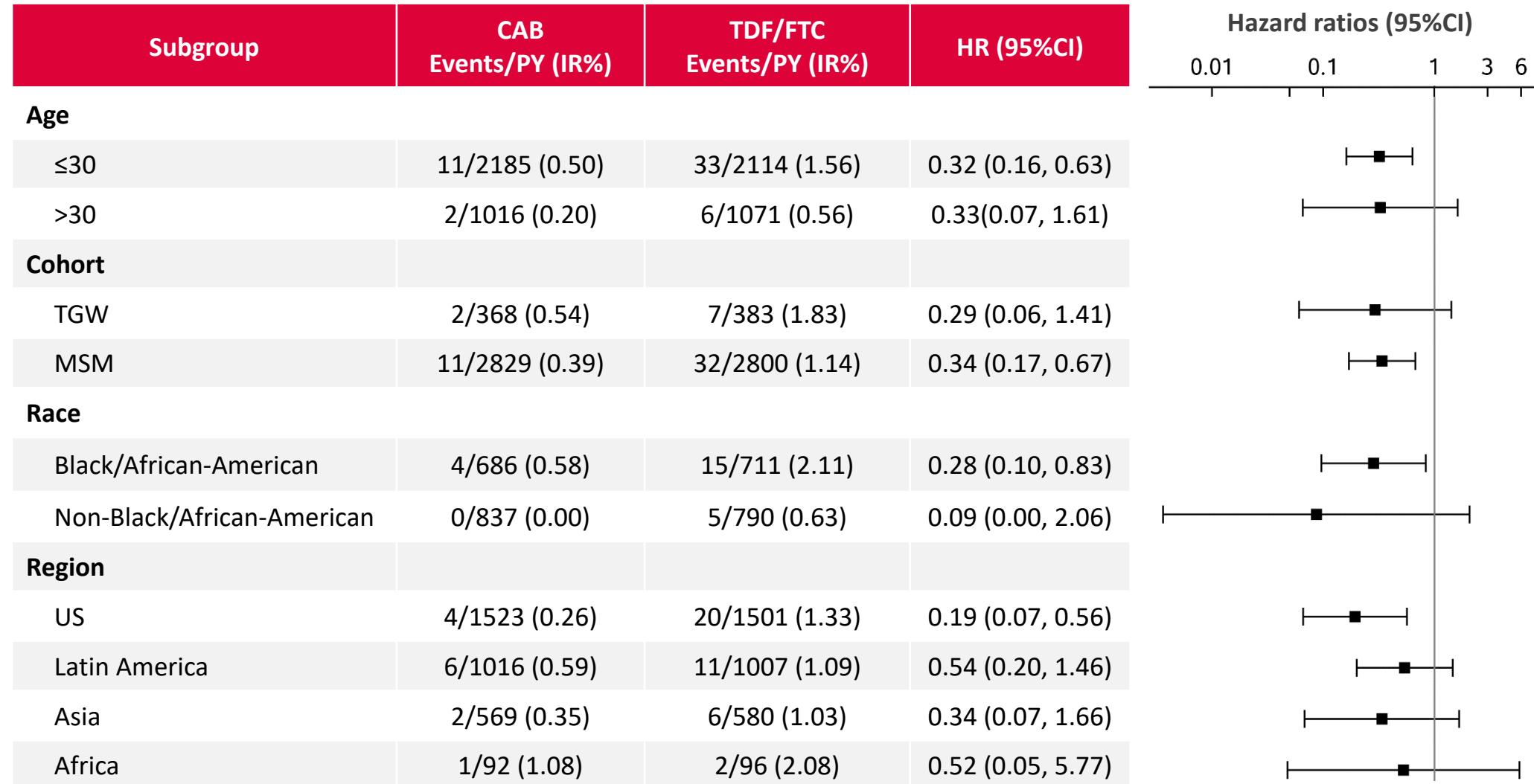
#### Number at risk

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
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

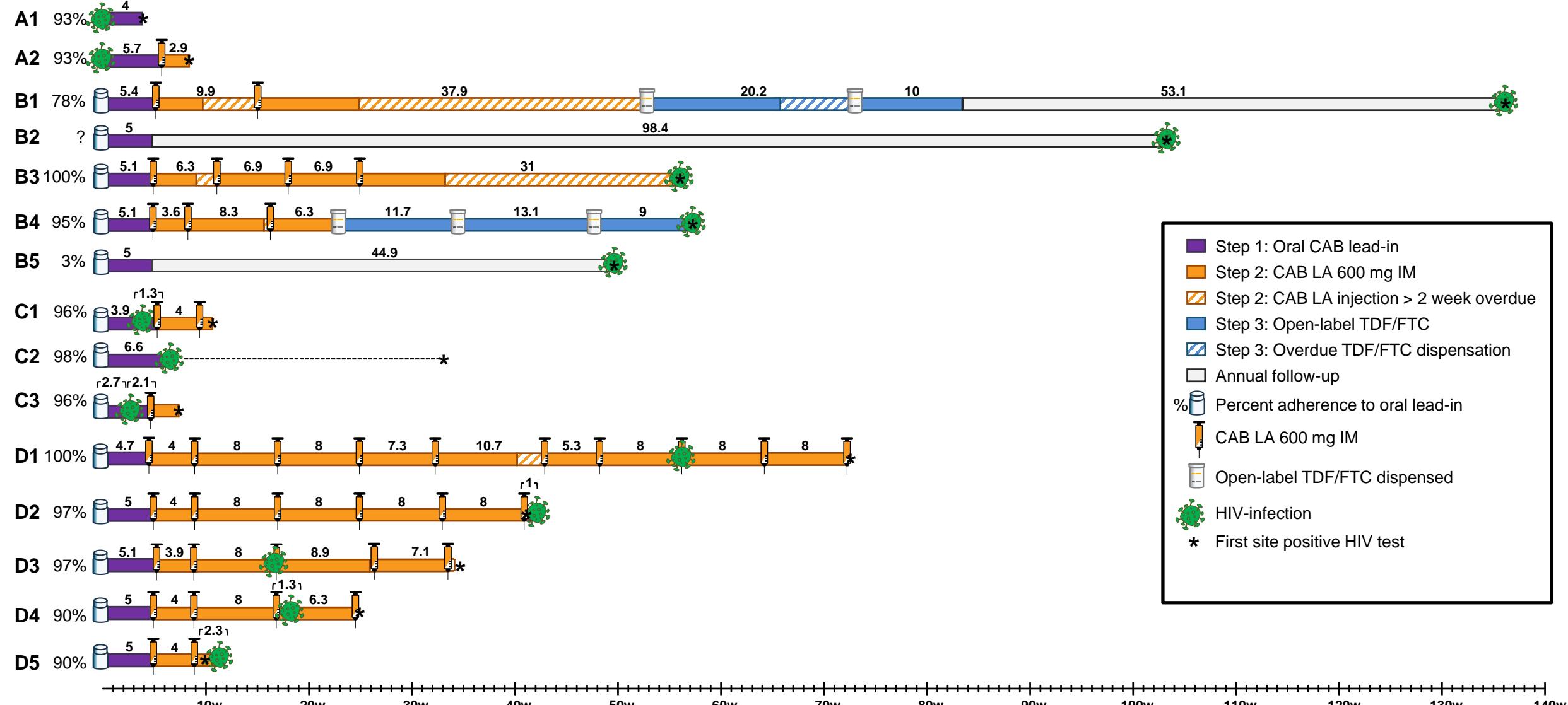
#### Cumulative number of events

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
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

**HPTN 083** Results: HIV incidence in key populations

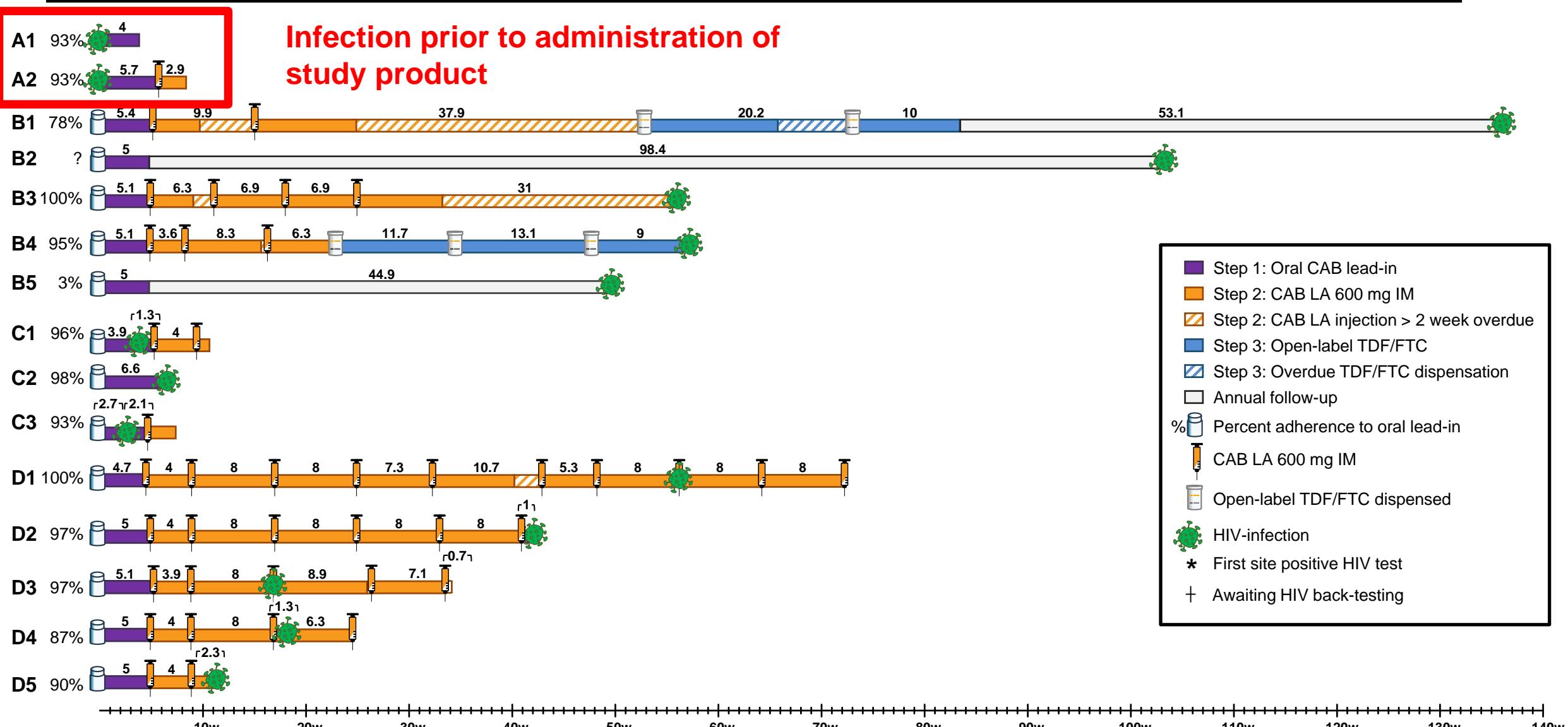


# 13 Incident HIV Infections Cabotegravir

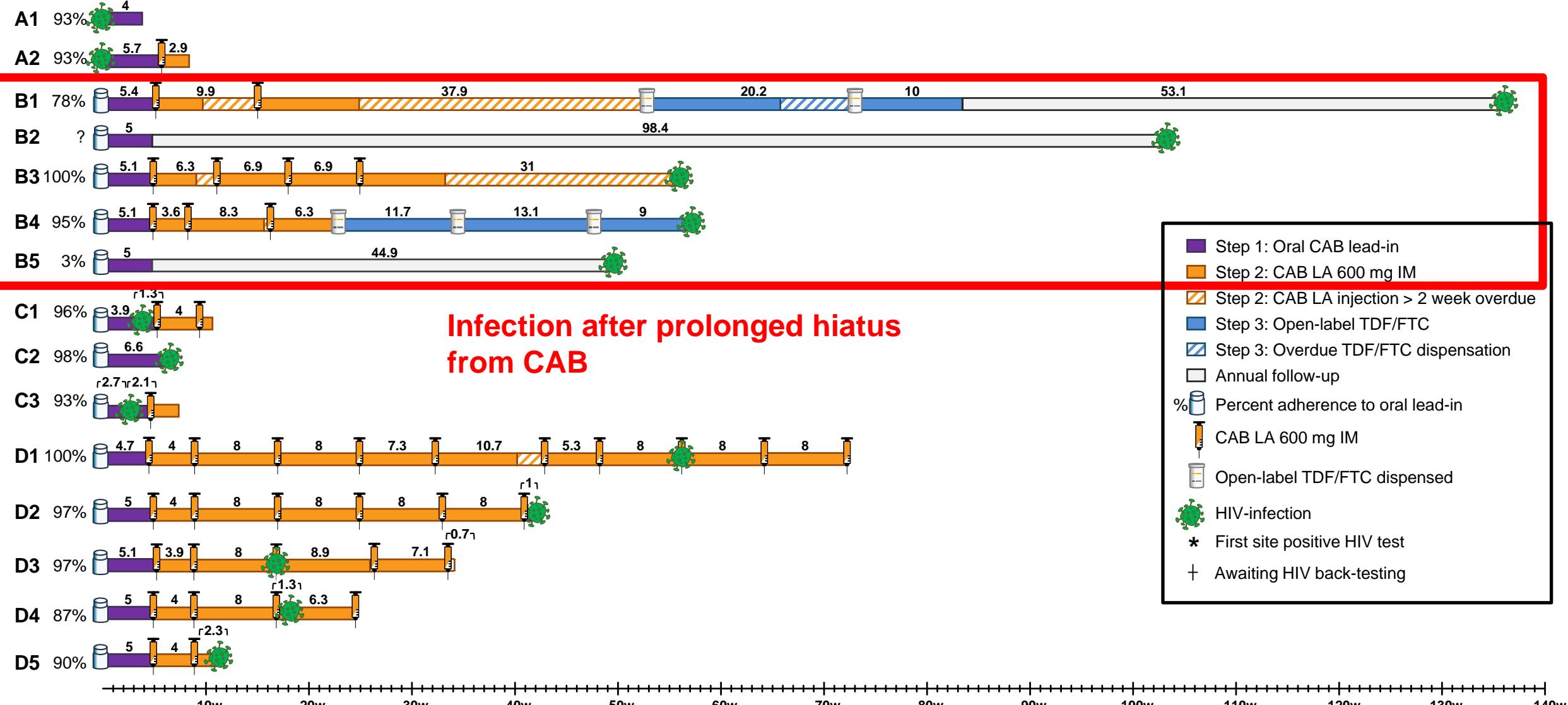


# 13 Incident HIV Infections Cabotegravir

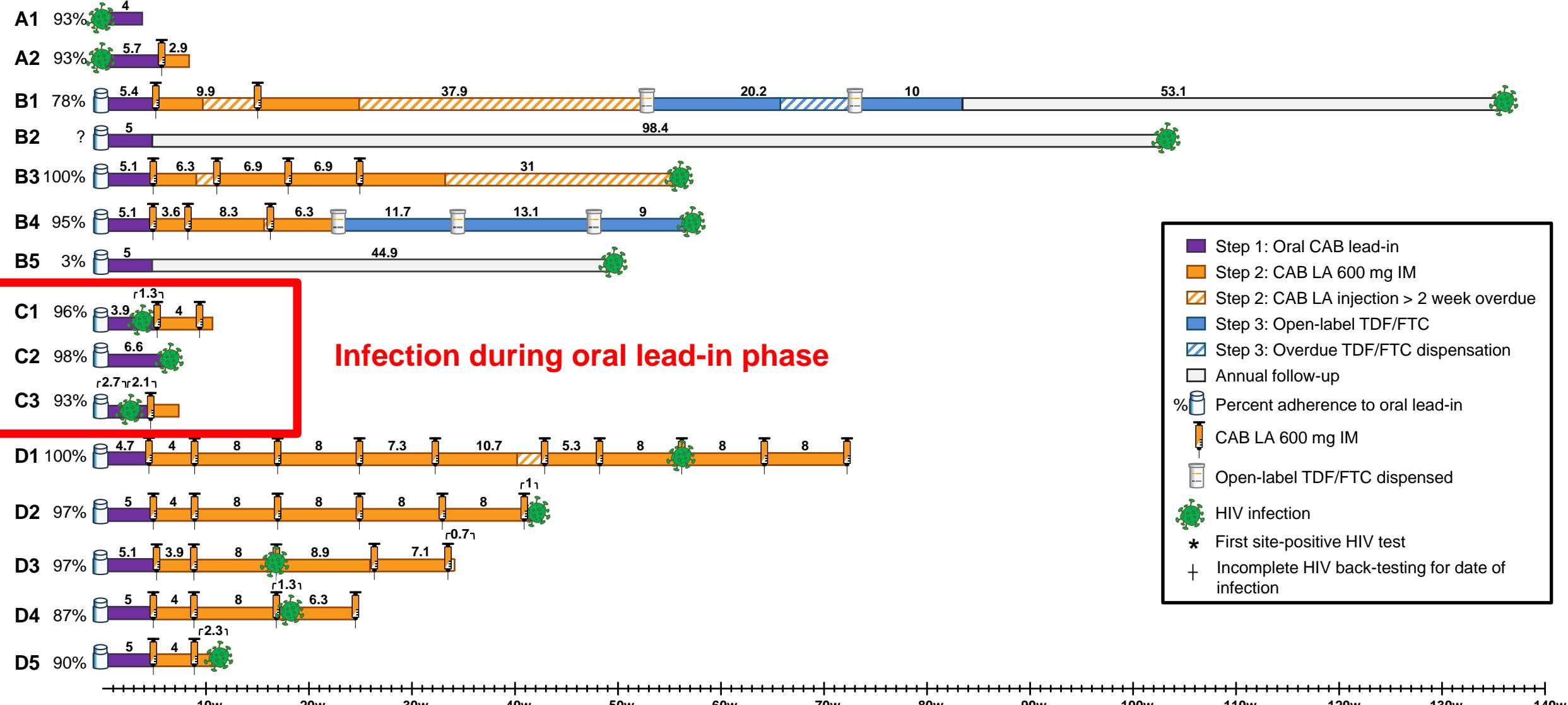
Infection prior to administration of study product



# 13 Incident HIV Infections Cabotegravir

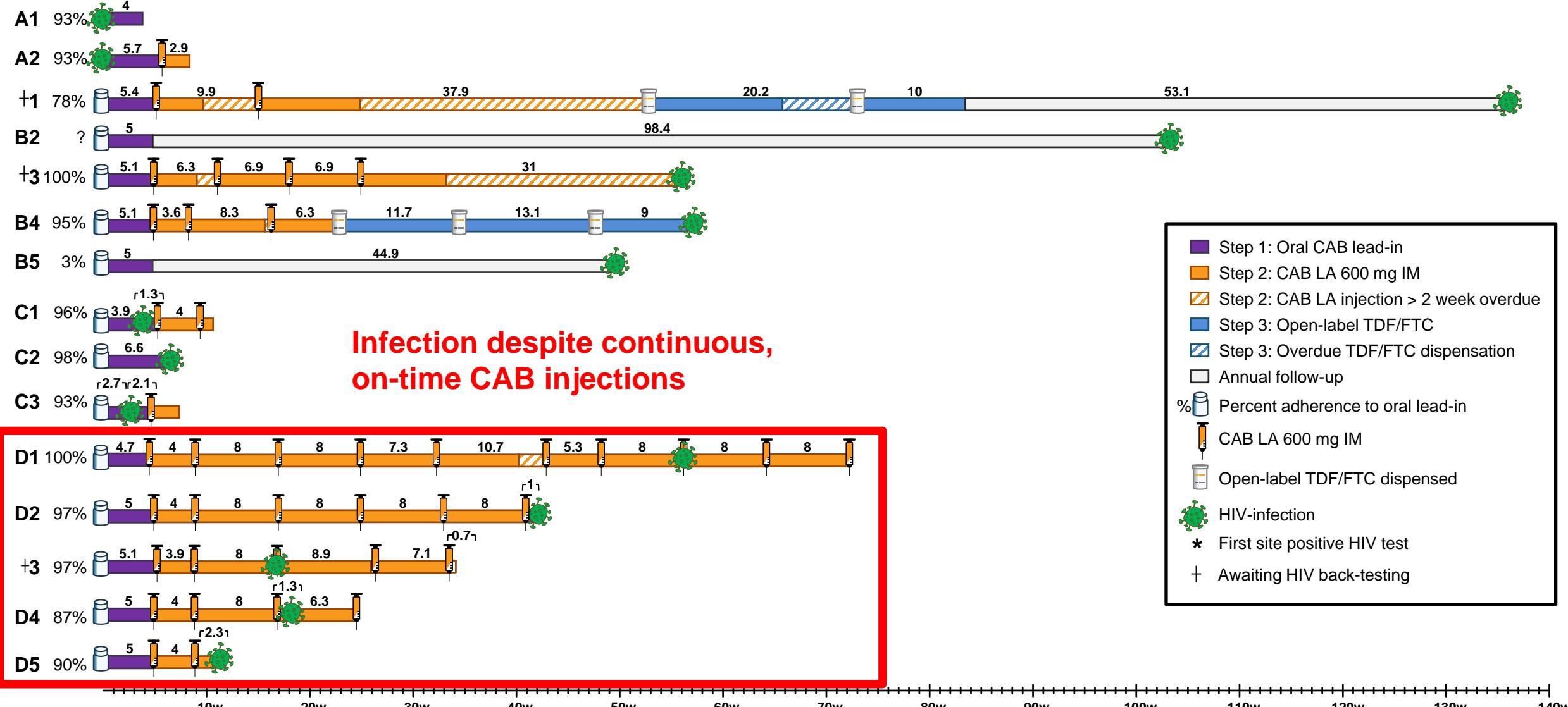


# 13 Incident HIV Infections Cabotegravir

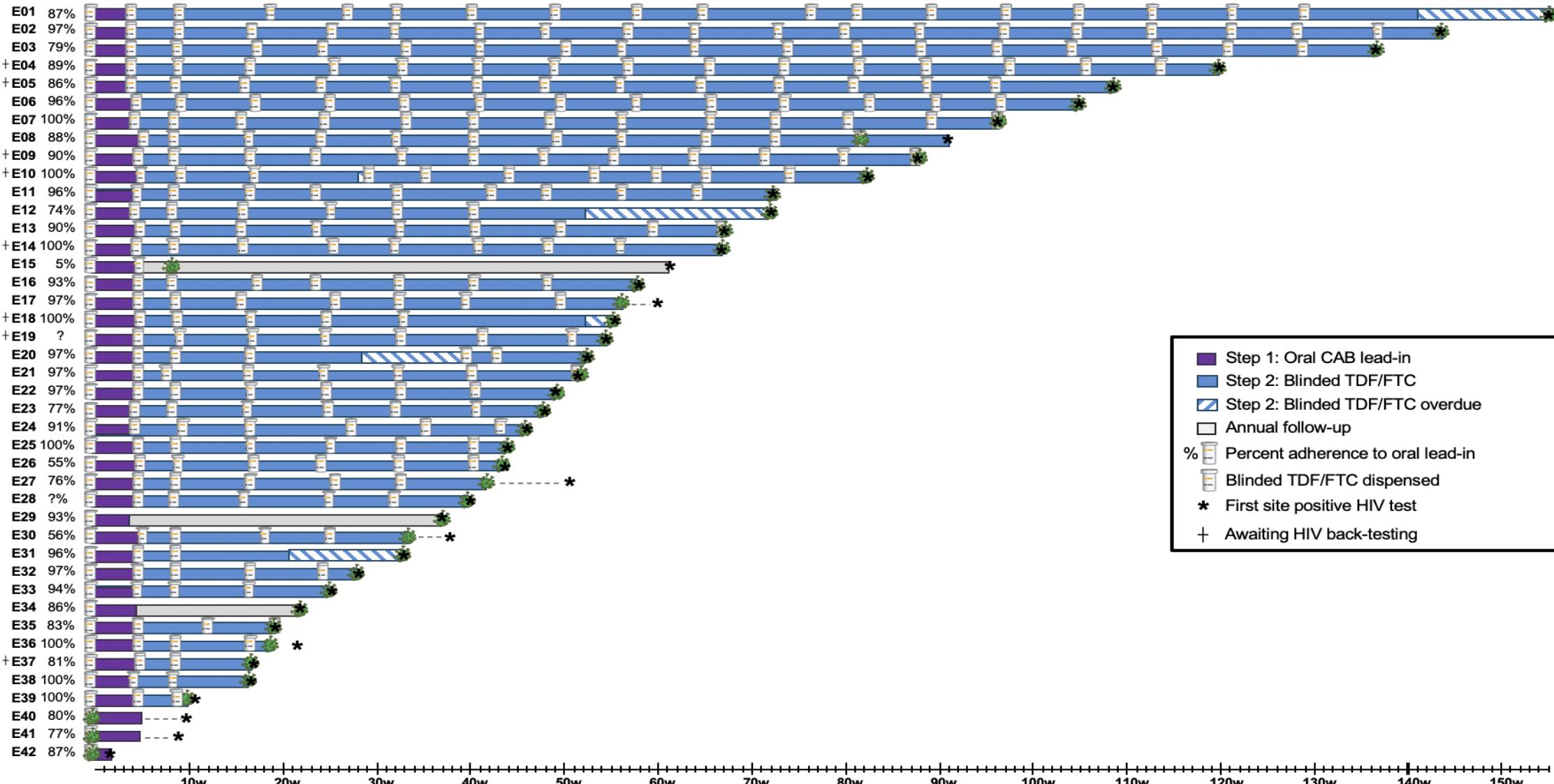


Infection during oral lead-in phase

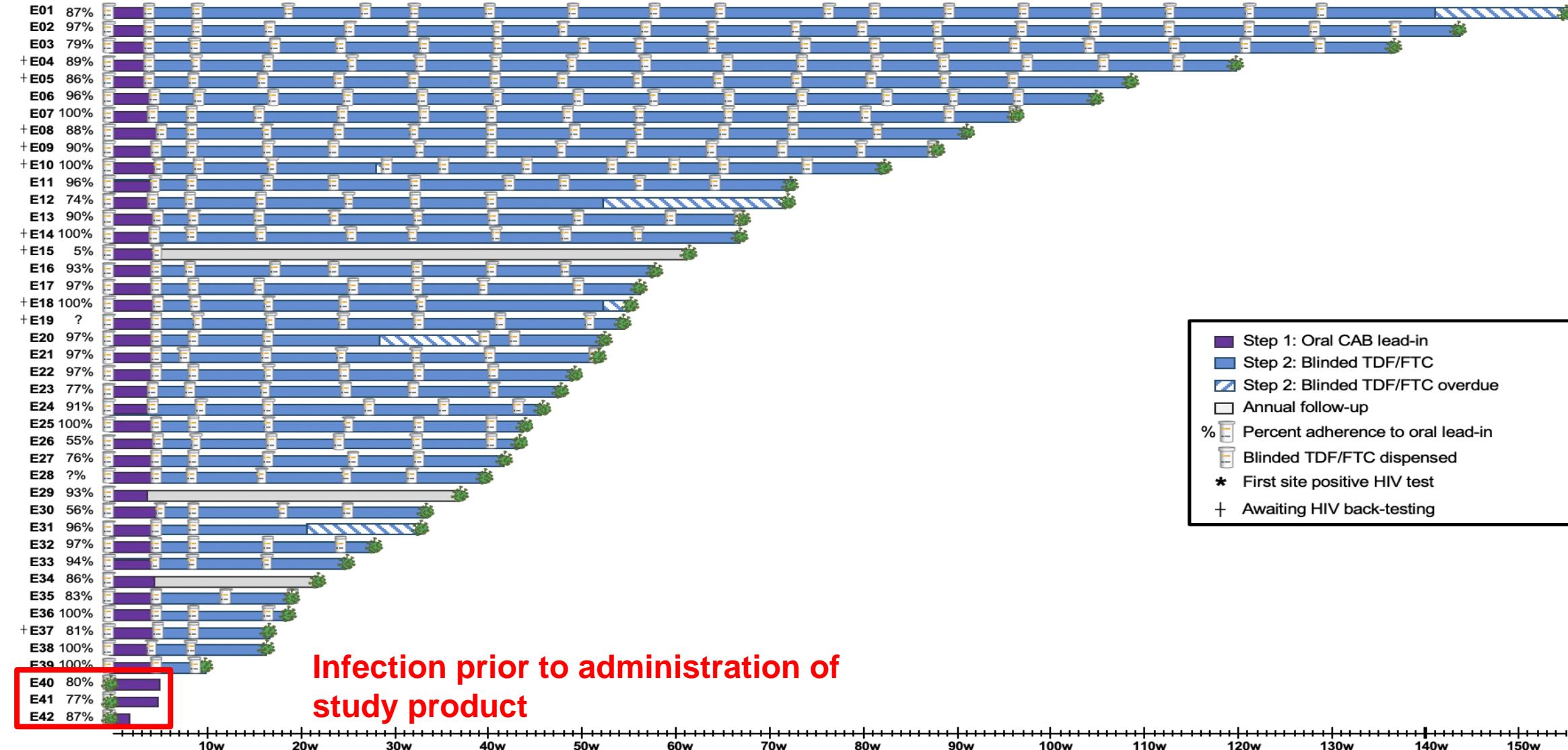
# 13 Incident HIV Infections Cabotegravir



# 39 Incident HIV Infections TDF/FTC

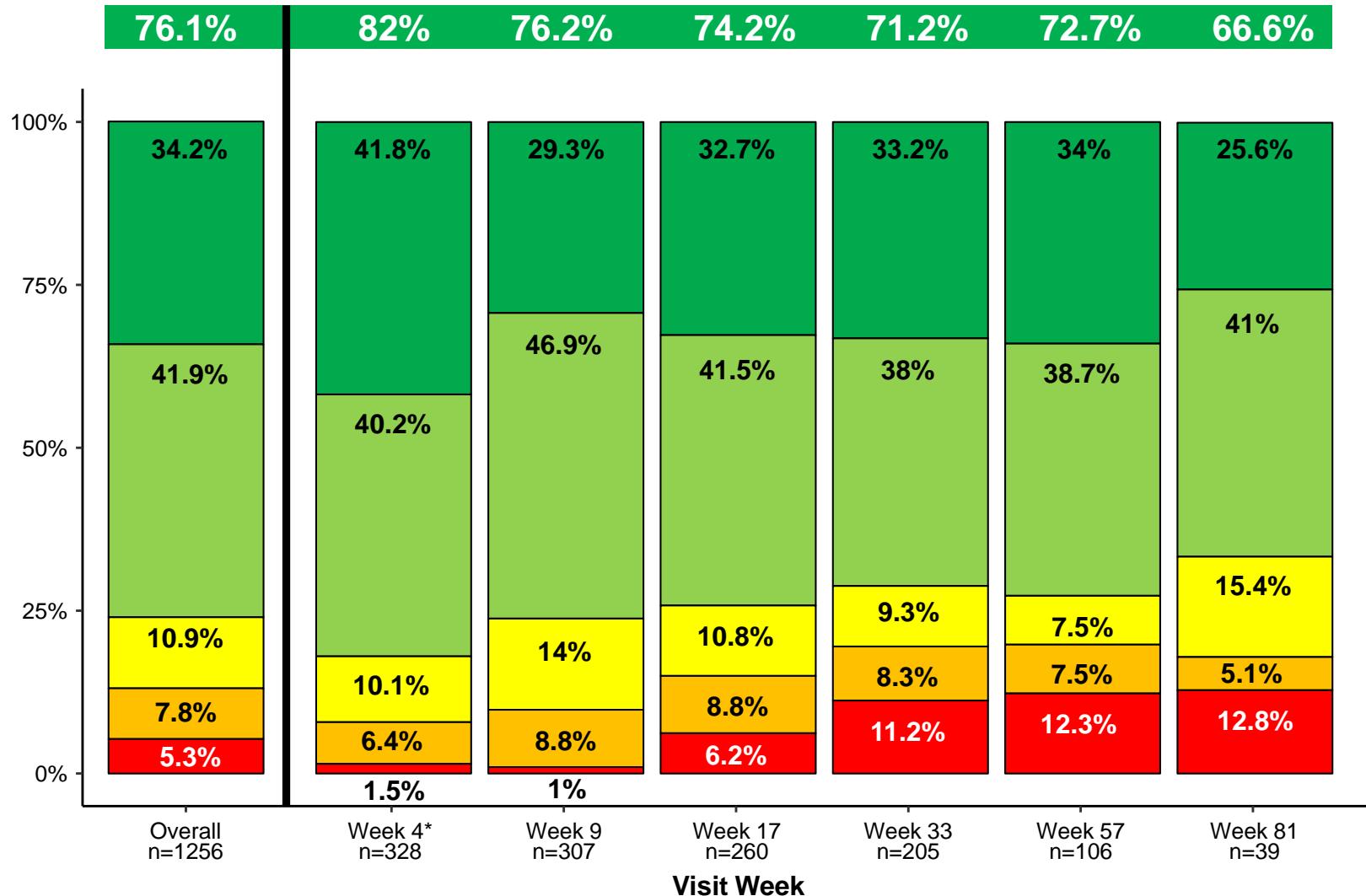


# 39 Incident HIV Infections TDF/FTC



# DBS TFV-DP

## Randomly selected “adherence” subset



Number of participants: 372

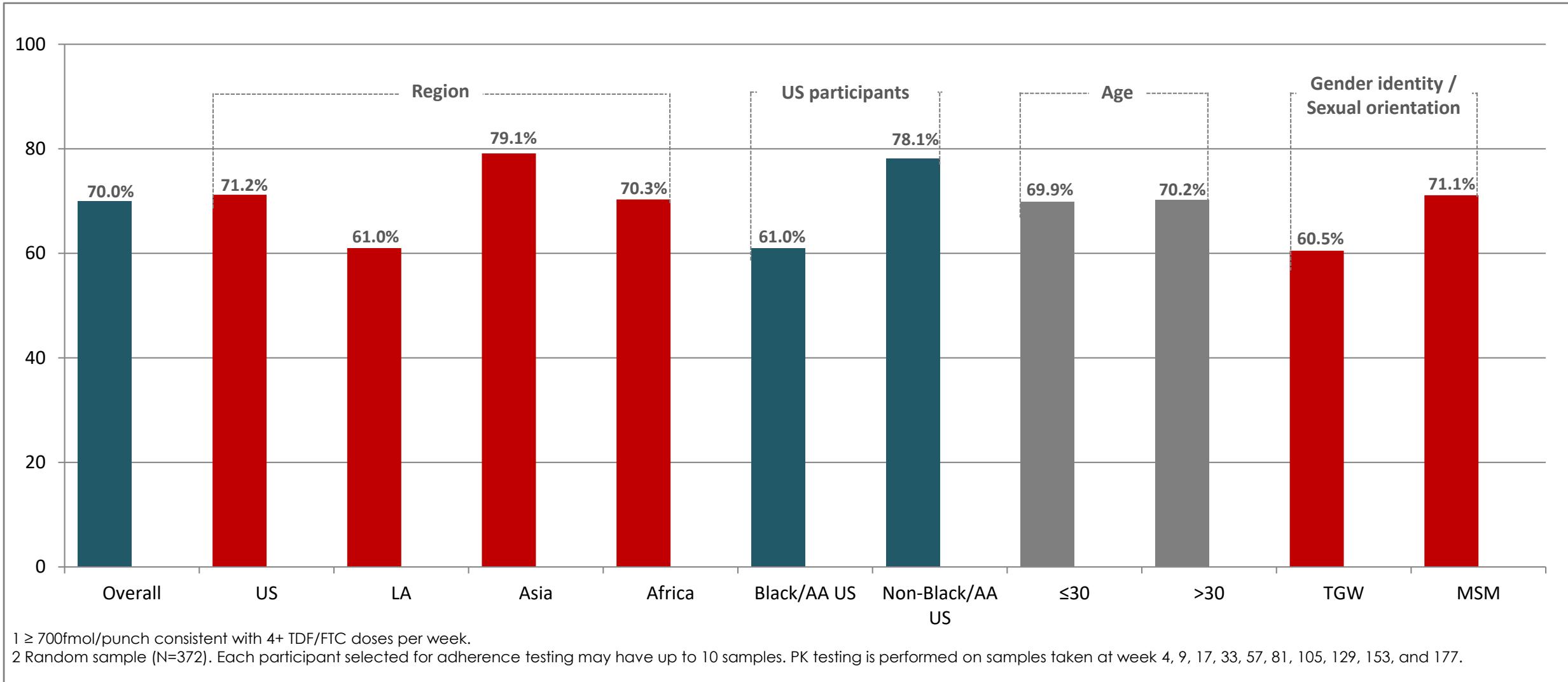
Number of samples assayed: 1256

- █ 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**

# Results: TDF/FTC Adherence

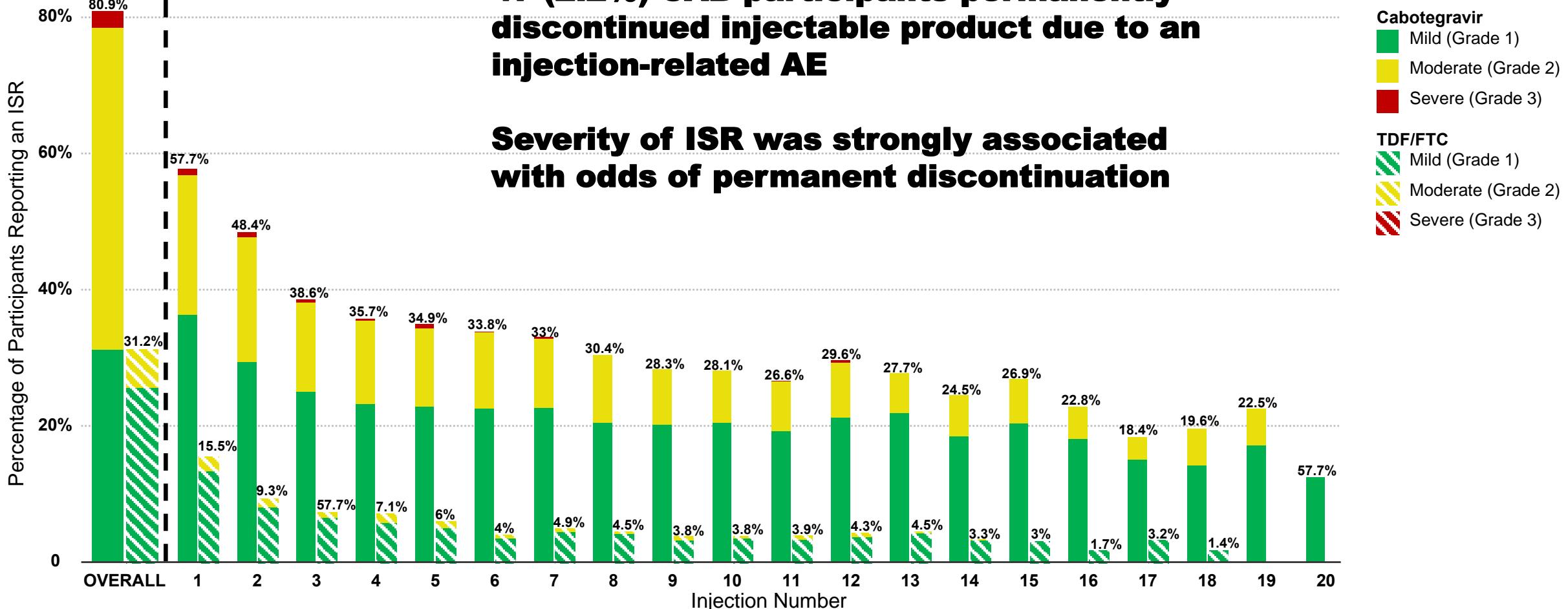
**TFV-DP  $\geq$  700fmol/punch in DBS<sup>1,2</sup>**



# 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 ≥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 ≥2%

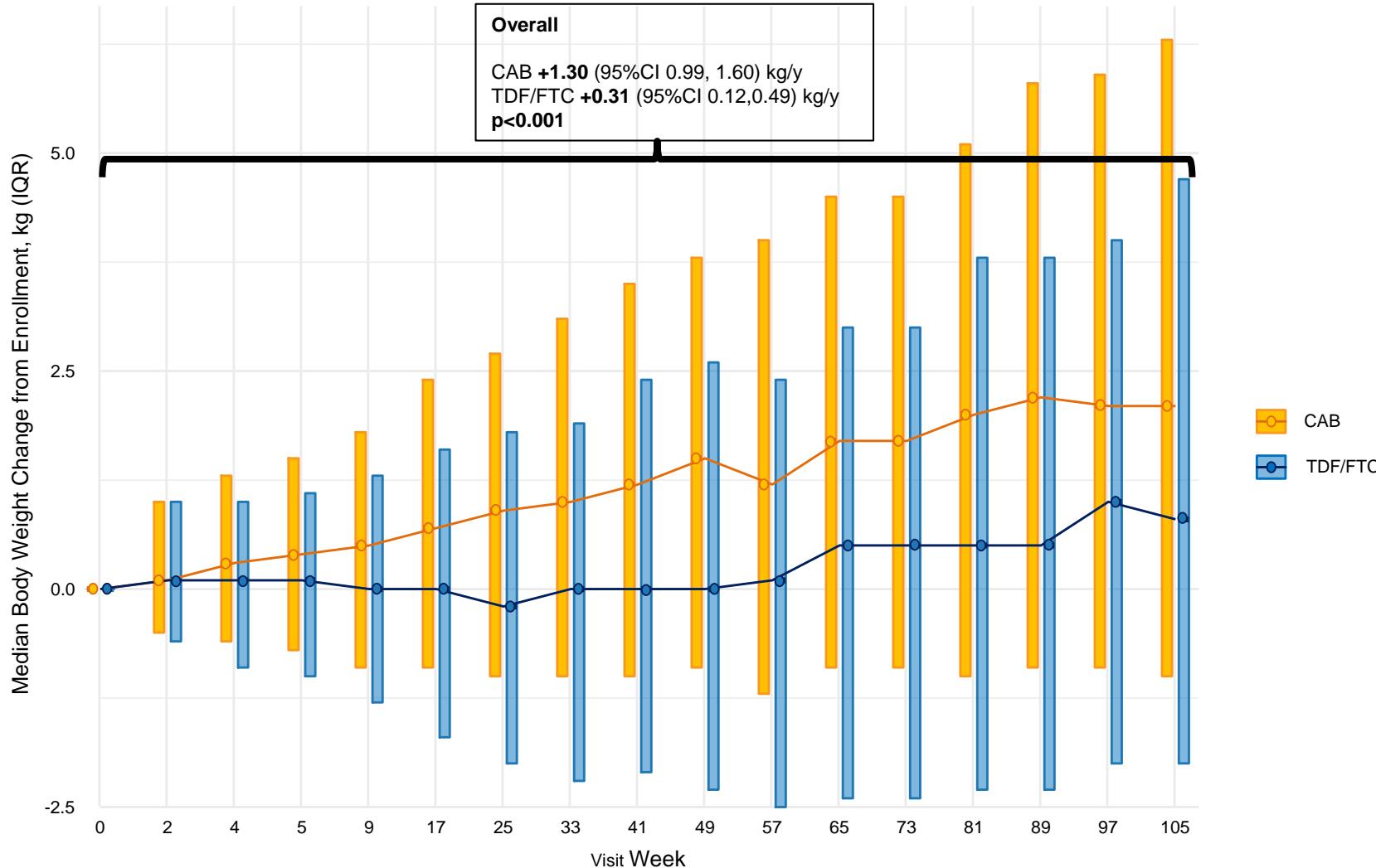
	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)	p-value
<b>Participants with grade 3+ AEs, n (%)</b>	1490 (32.7%)	766/2282 (33.6%)	724/2280 (31.8%)	
CPK increased	633 (13.9%)	309 (13.5%)	324 (14.2%)	0.51
Creatinine clearance decreased	348 (7.6%)	190 (8.3%)	158 (6.9%)	0.08
Lipase increased	152 (3.3%)	76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

# Prevalent and Incident STIs

	TOTAL (n=4566)	TDF-FTC (n=2284)	CAB (n=2282)
<b>Prevalent at baseline, n (%)</b>			
Syphilis	241 (5.3)	115 (5.1)	126 (5.5)
Gonorrhea <sub>urine</sub>	29 (0.6)	17 (5.1)	12 (0.5)
Gonorrhea <sub>rectal</sub>	297 (6.5)	150 (6.6)	147 (6.5)
Chlamydia <sub>urine</sub>	122 (2.7)	57 (2.5)	65 (2.9)
Chlamydia <sub>rectal</sub>	502 (11)	255 (11.2)	247 (10.9)
<b>Incidence, n (rate per 100 py)</b>			
Syphilis	908 (16.5)	451 (16.4)	457 (16.5)
Gonorrhea <sub>urine</sub>	128 (2.4)	57 (2.1)	71 (2.6)
Gonorrhea <sub>rectal</sub>	592 (10.9)	295 (10.9)	297 (11)
Chlamydia <sub>urine</sub>	241(4.4)	124 (4.6)	117 (4.3)
Chlamydia <sub>rectal</sub>	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 Landovitz <sup>1</sup>, Sahar Z Zangeneh <sup>2</sup>, Gordon Chau <sup>2</sup>, Beatriz Grinsztejn <sup>3</sup>, Joseph J Eron <sup>4</sup>, Halima Dawood <sup>5</sup>, Manya Magnus <sup>6</sup>, Albert Y Liu <sup>7</sup>, Ravindre Panchia <sup>8</sup>, Mina C Hosseiniour <sup>9</sup>, Ryan Kofron <sup>1</sup>, David A Margolis <sup>10</sup>, Alex Rinehart <sup>10</sup>, Adeola Adeyeye <sup>11</sup>, David Burns <sup>11</sup>, Marybeth McCauley <sup>12</sup>, Myron S Cohen <sup>4</sup>, Judith S Currier <sup>1</sup>

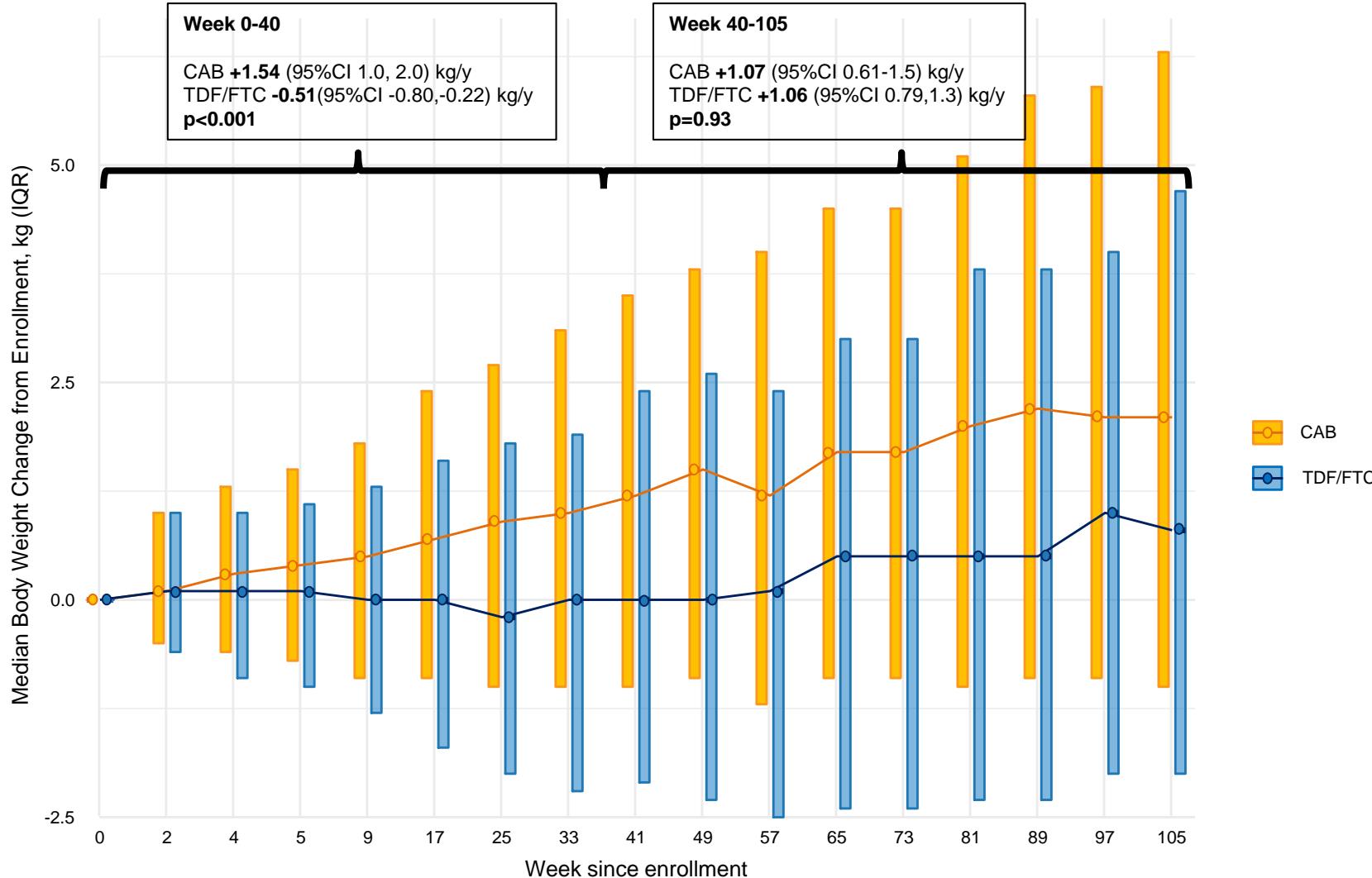
HPTN 077: Over 41 weeks

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

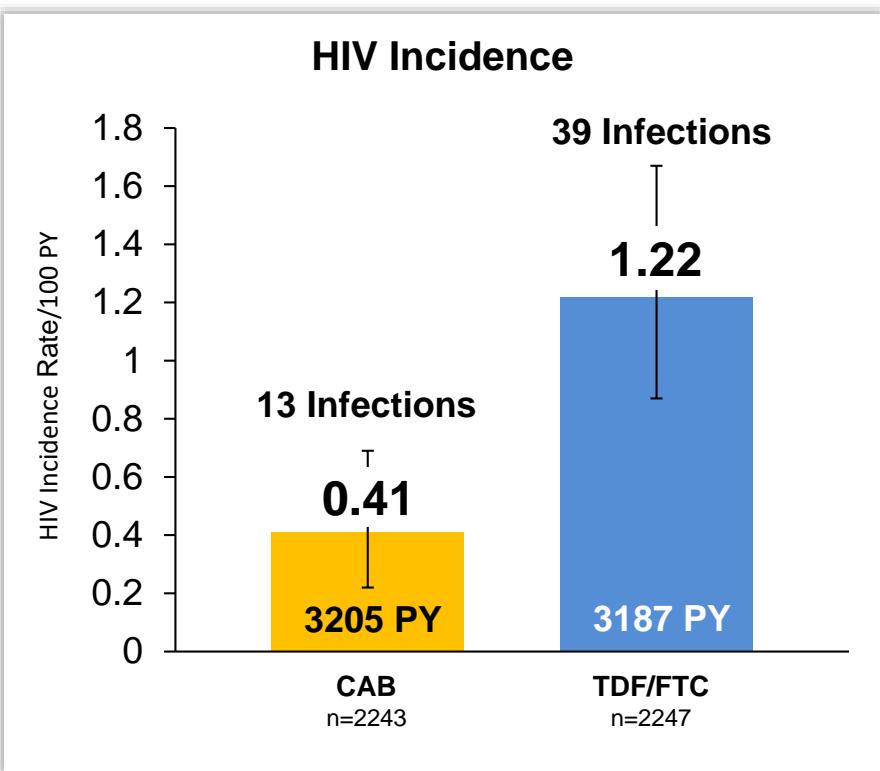
**HPTN 077: Over 41 weeks**

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

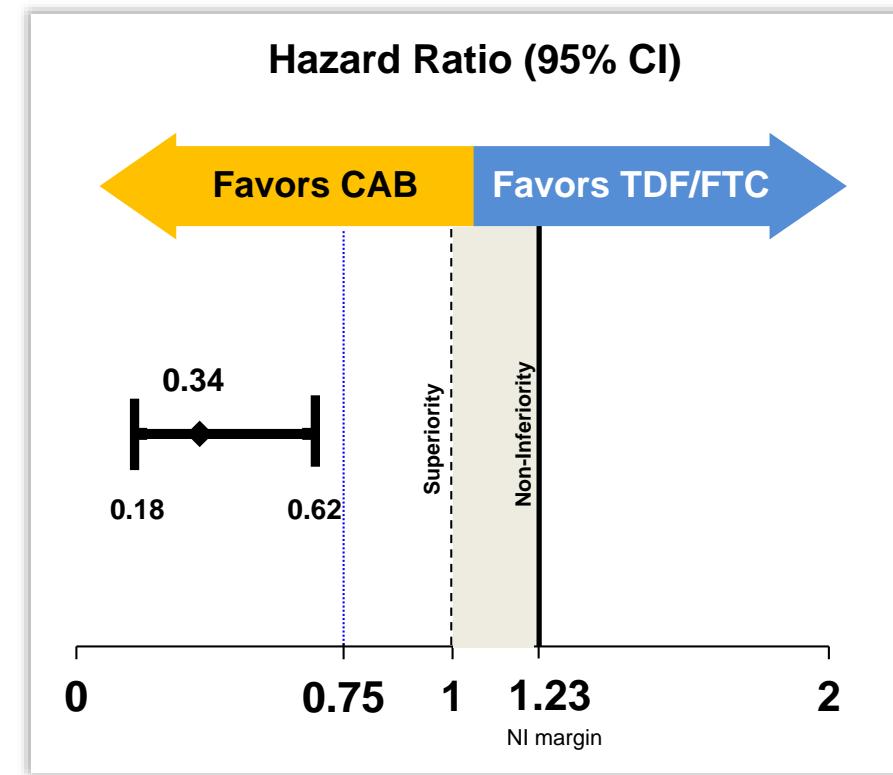
**Landovitz RJ et al. CID 2019.**

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

# HIV Incidence: CAB vs. TDF/FTC



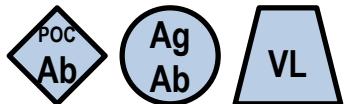
CI, confidence interval



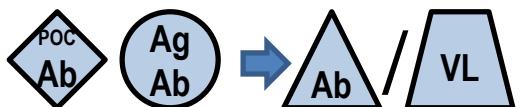
# Pre-specified HIV Testing

## Real-time site testing

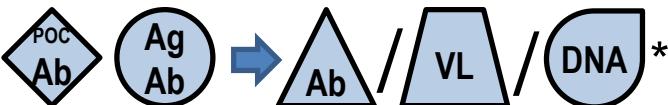
### Screening



### Enrollment\*



### Follow-up visits



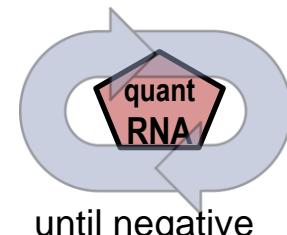
\*Selected cases

## HPTN Laboratory Center testing (retrospective)

### Visits with reactive/positive site tests



### Back-testing



## Blinded adjudication of study endpoints



## Site testing

- Point-of-care antibody test
- Instrumented antigen/antibody test
- Viral load test
- Confirmatory/discriminatory antibody test
- Ultrasensitive DNA test (centralized at JHU)

## HPTN LC testing

- ARCHITECT antigen/antibody test
- APTIMA qualitative RNA test
- Geenius discriminatory antibody test

# Extended HPTN LC Testing

## HIV testing

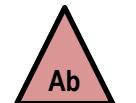
### Back-testing



**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

	ARCHITECT antigen/antibody test
	APTIMA qualitative RNA test
	Geenius discriminatory antibody test
	Viral load test
	Single copy RNA test

## Pharmacology testing

### CAB concentrations

#### CAB arm

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

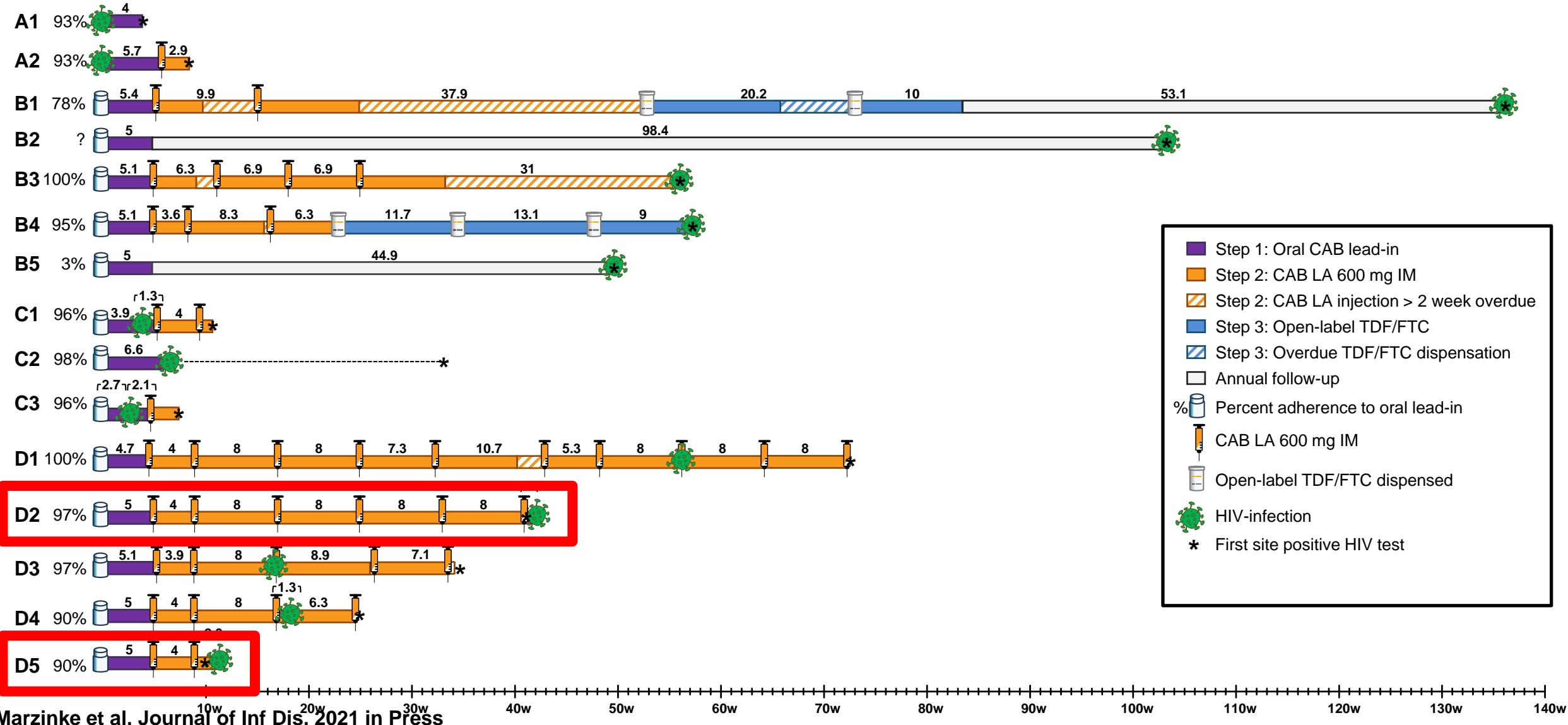
DBS [TFV-DP]: step 3 infections

### TDF/FTC concentrations

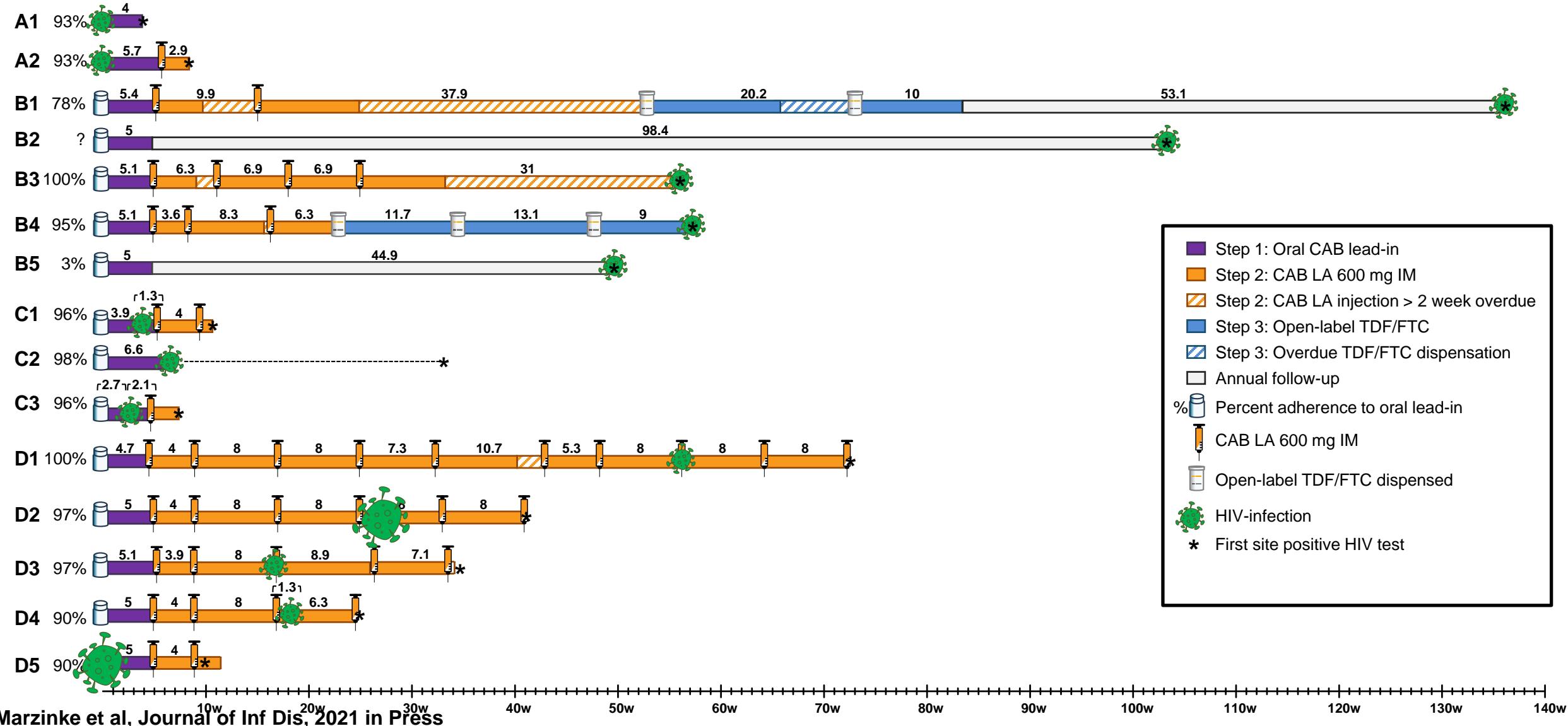
Plasma [TFV]: first site pos, first HIV pos, 3 prior visits

DBS [TFV-DP]: first site pos, 1 prior visit

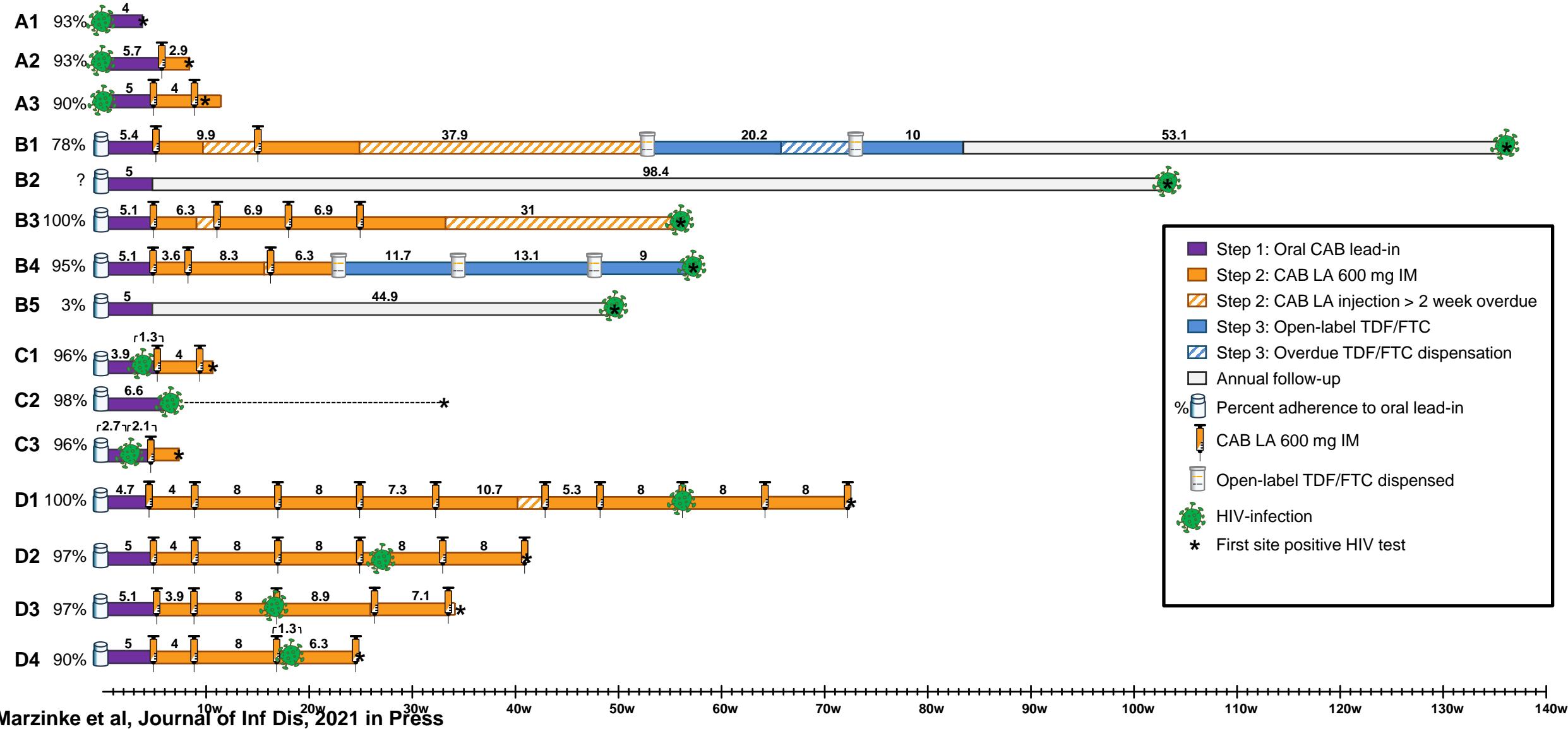
# 13 Incident, 2 baseline Infections: Cabotegravir



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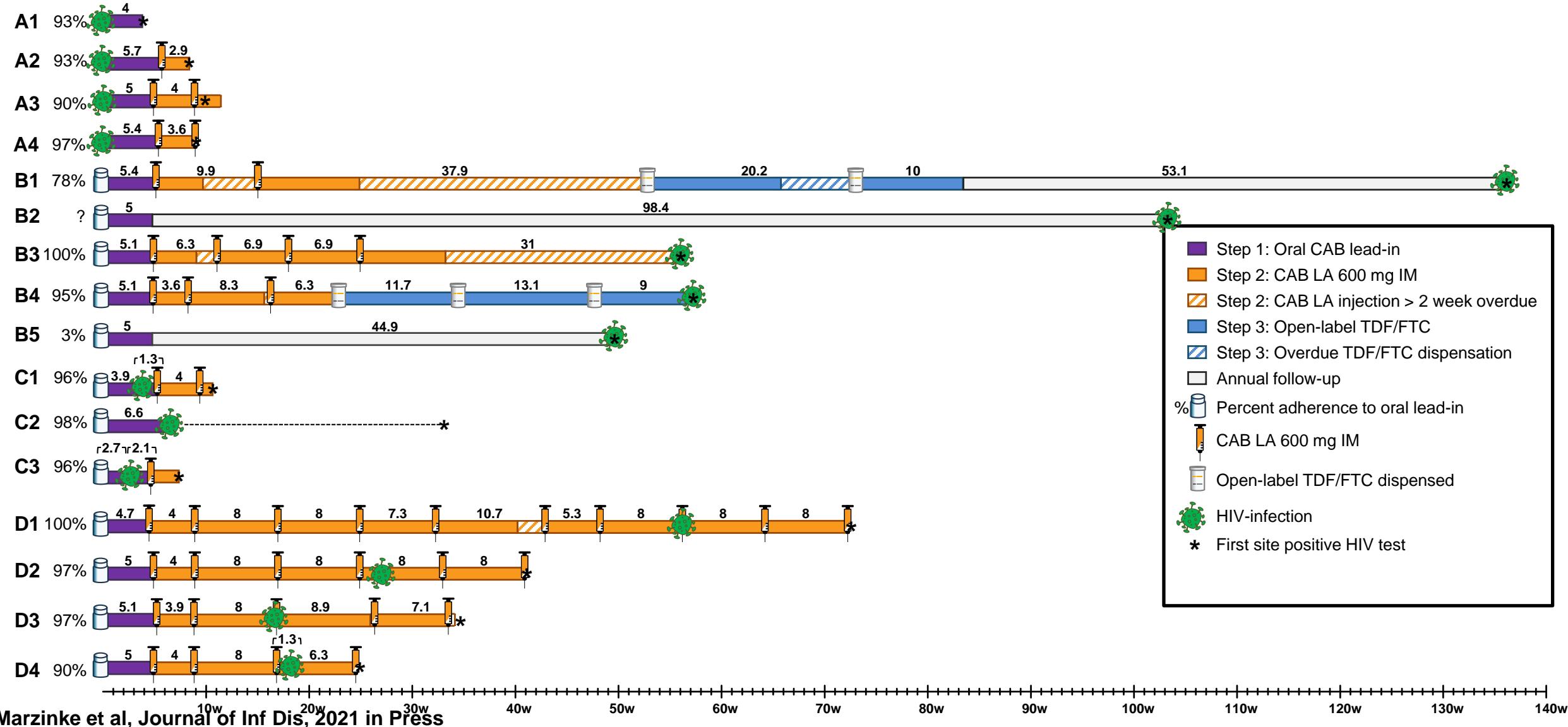


# 13 Incident, 3 baseline Infections: Cabotegravir

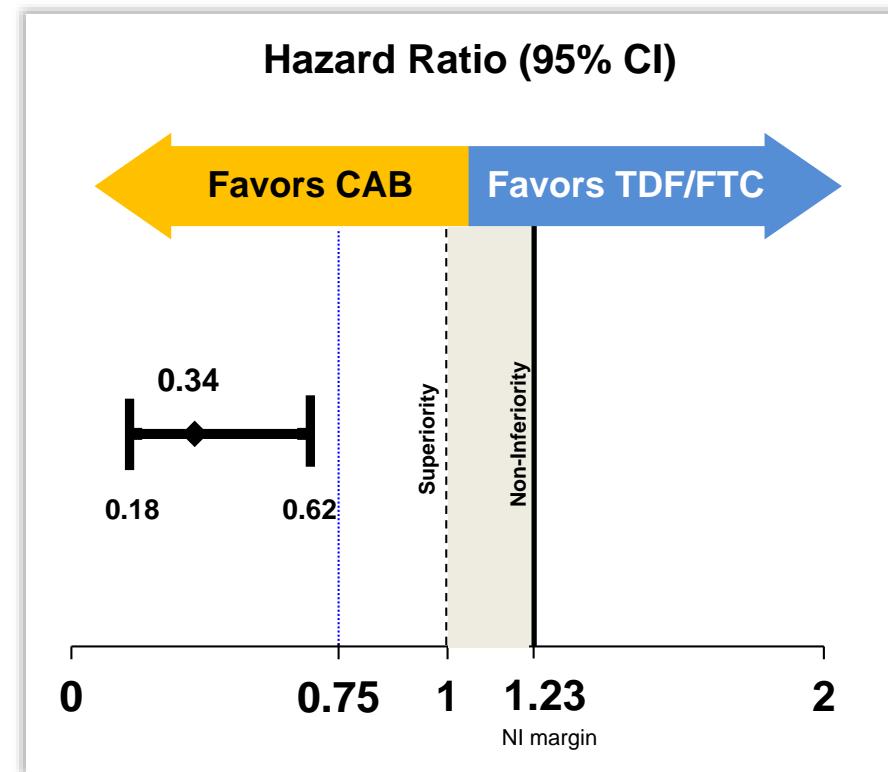
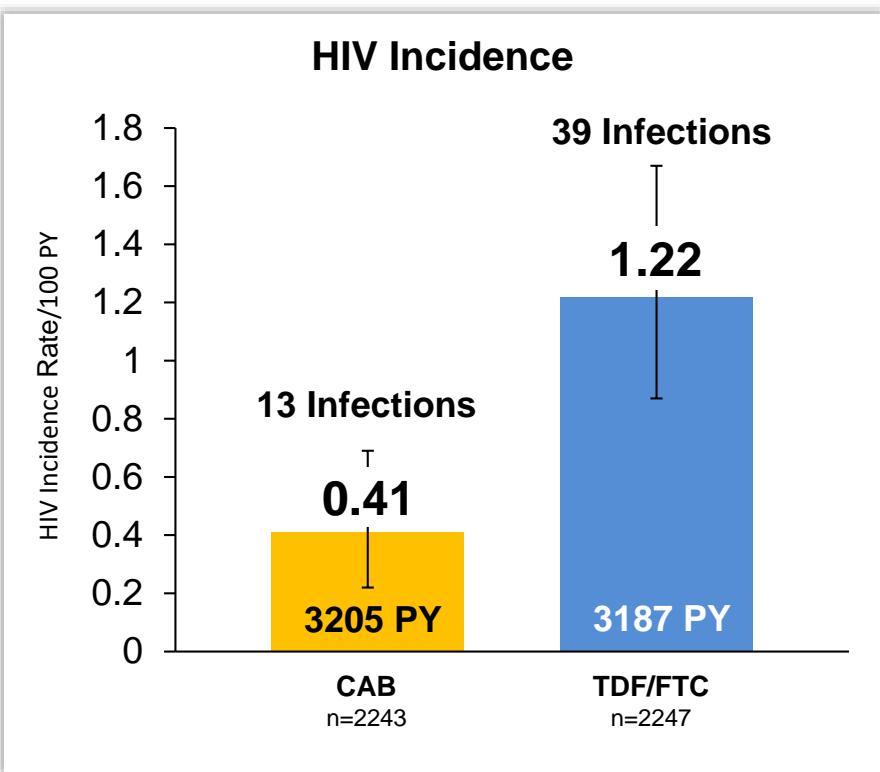




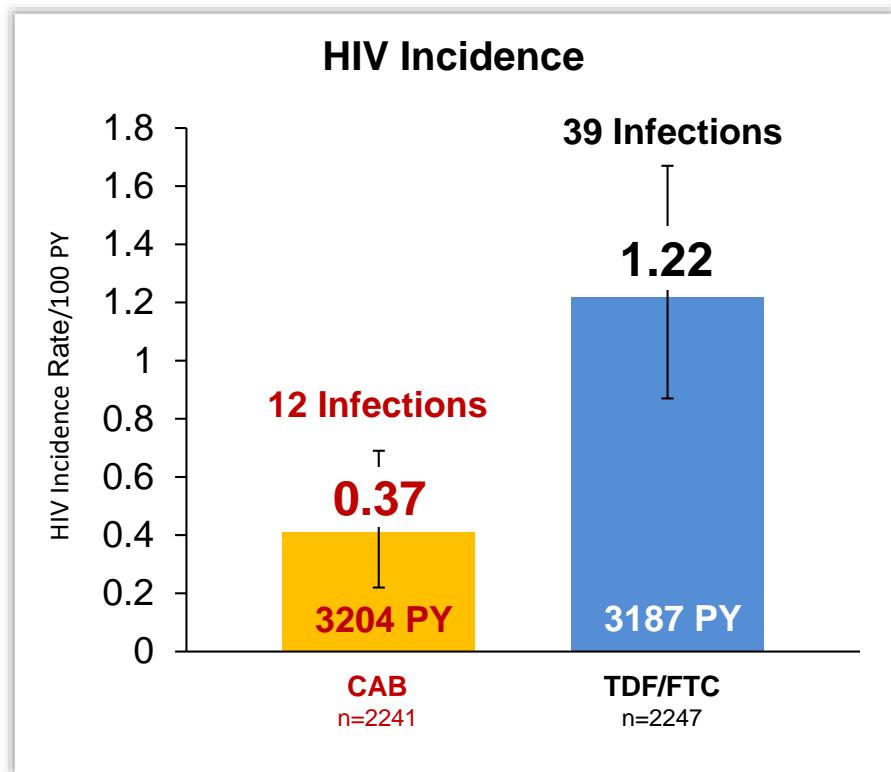
# **12 Incident, 4 baseline Infections: Cabotegravir**



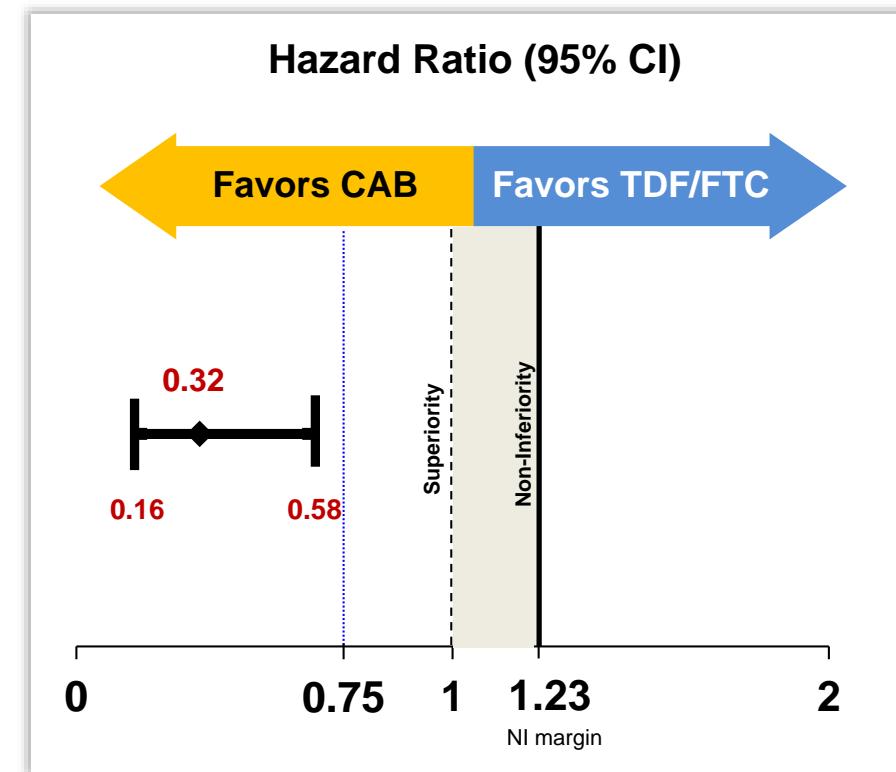
# HIV Incidence: CAB vs. TDF/FTC



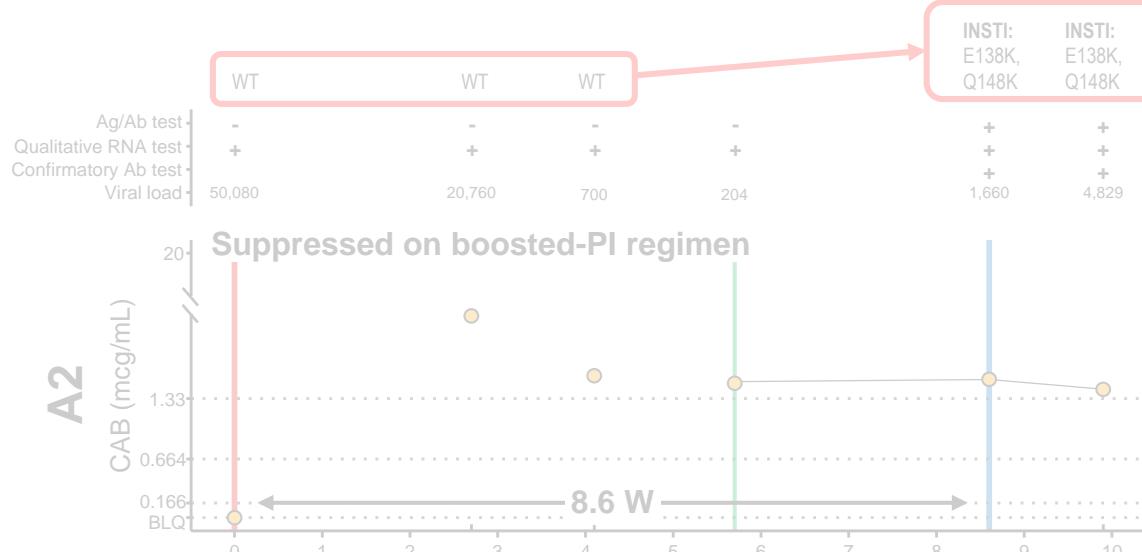
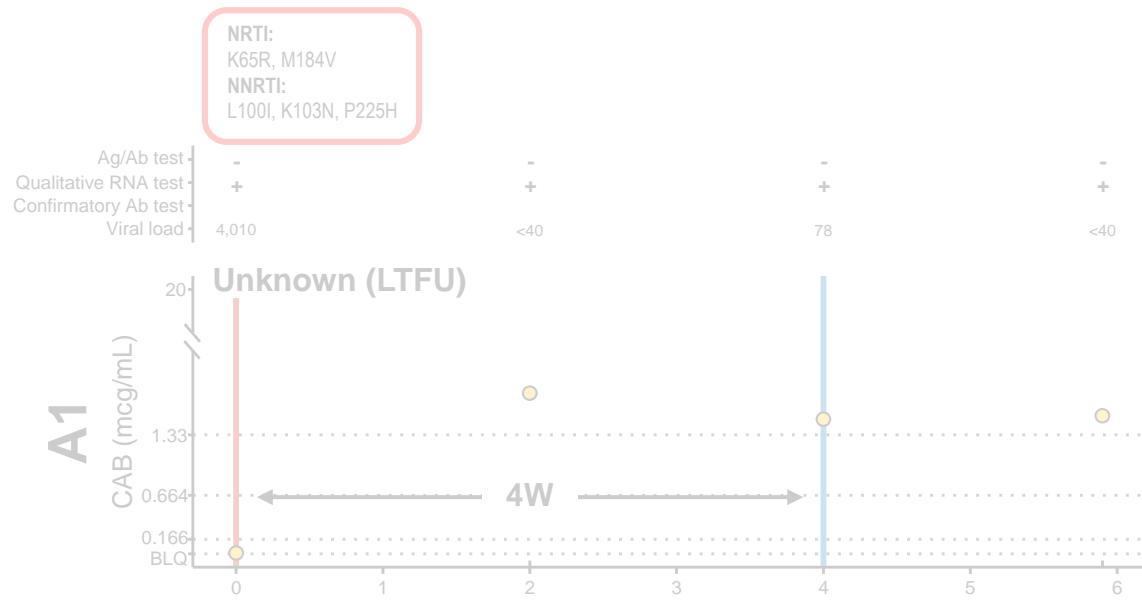
# HIV Incidence: CAB vs. TDF/FTC



CI, confidence interval



**CAB arm, Group A**  
**HIV positive at study enrollment**



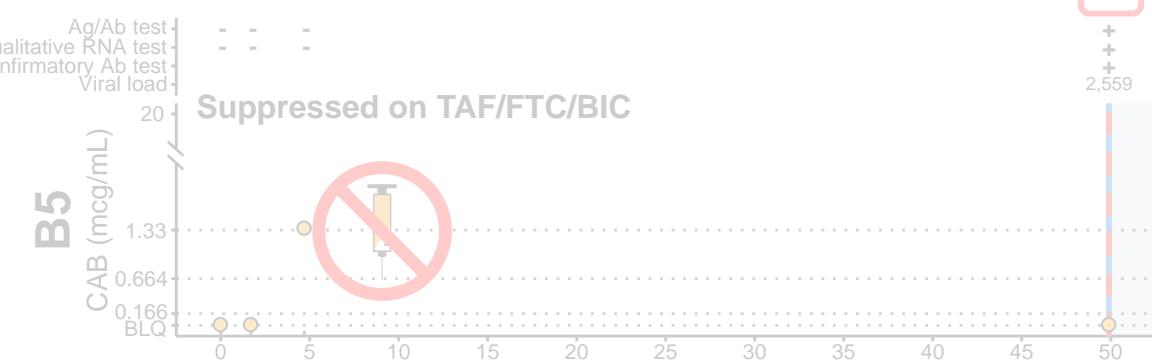
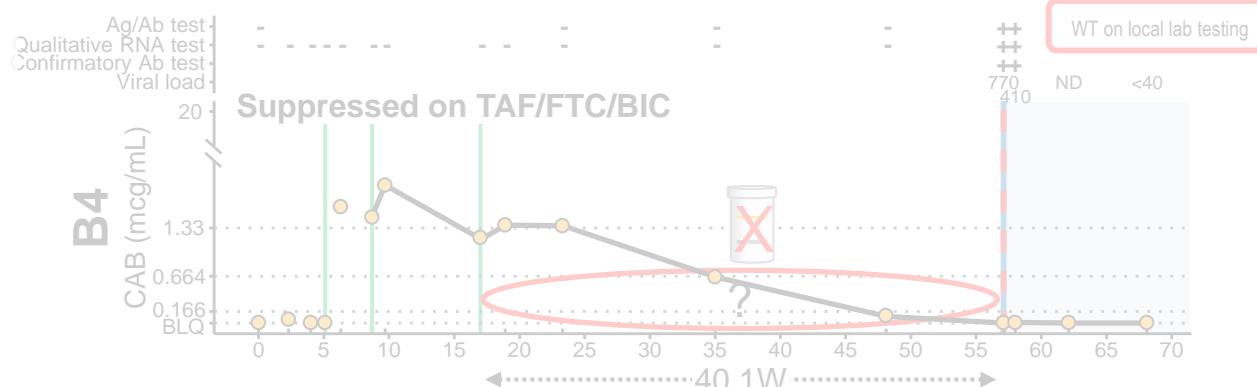
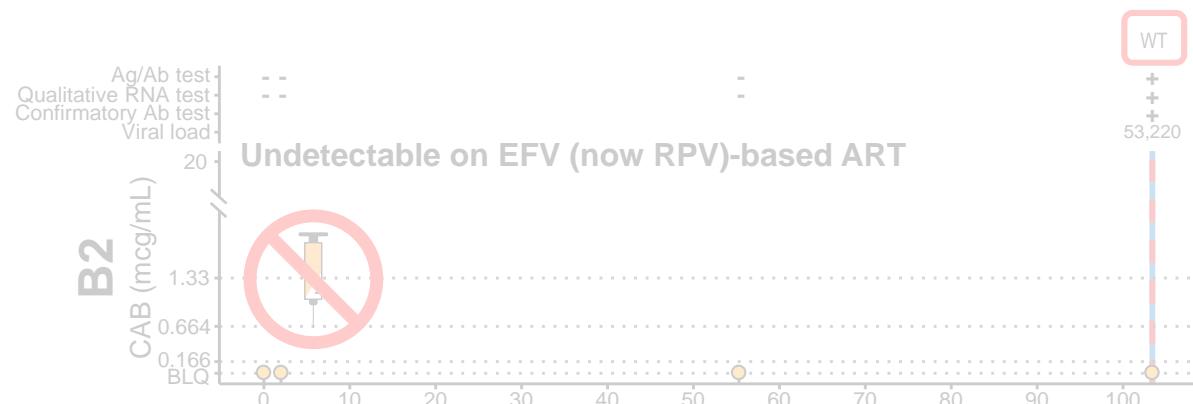
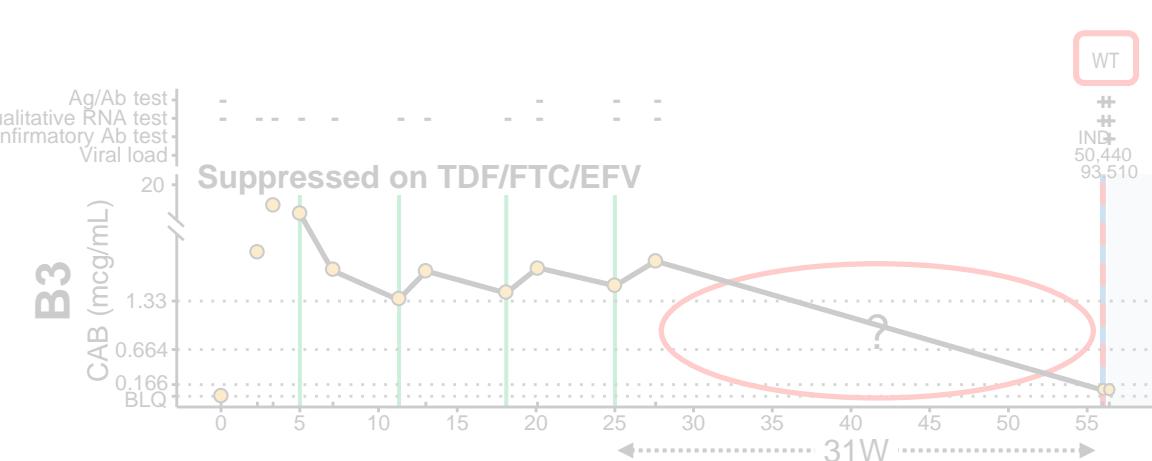
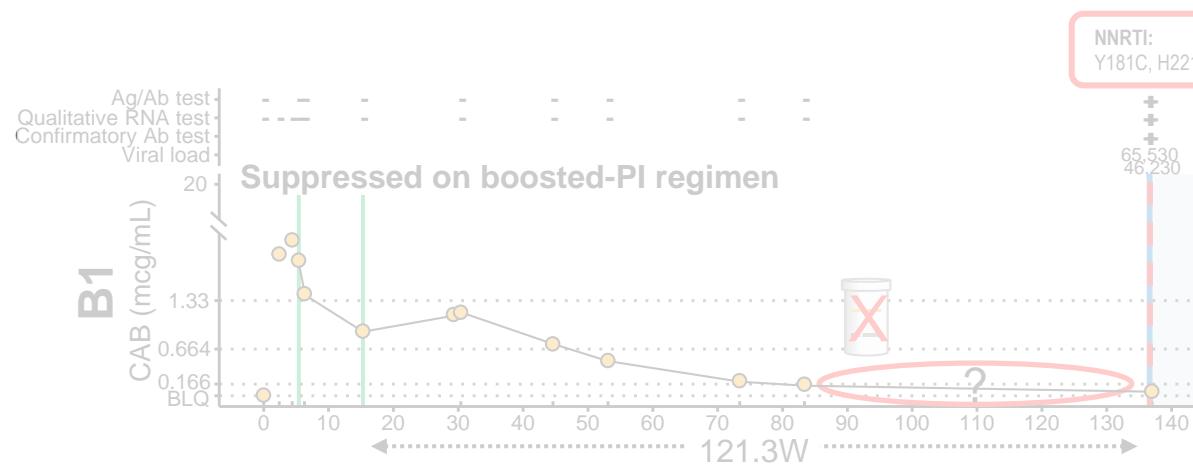
● CAB concentration    — CAB injection    — First HIV positive visit    — First site positive visit    — First HIV positive visit and first site positive visit

← # → 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.

Marzinke et al, Journal of Inf Dis, 2021 in Press

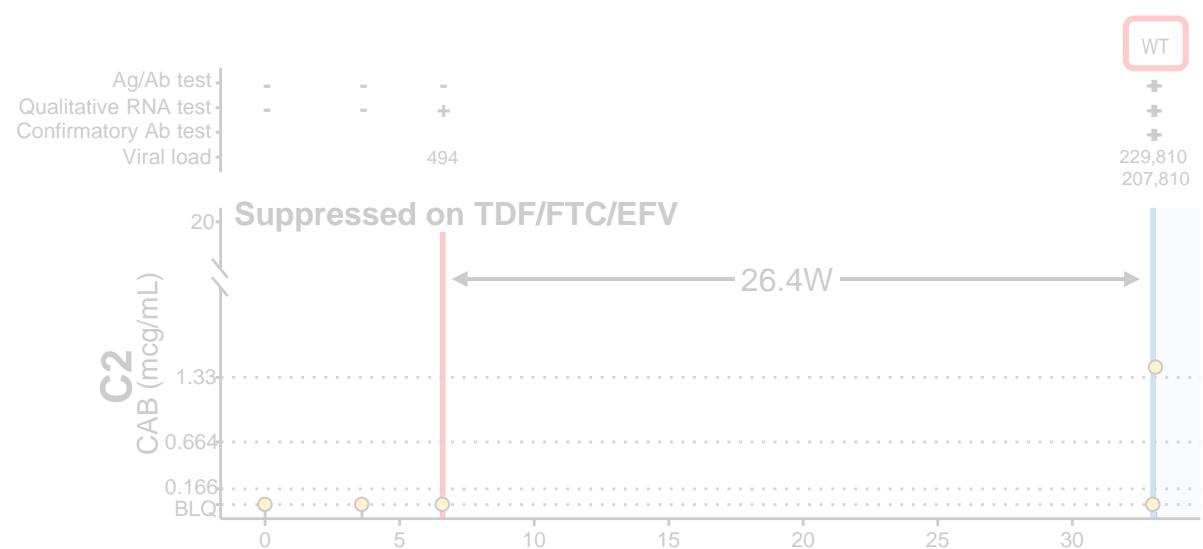
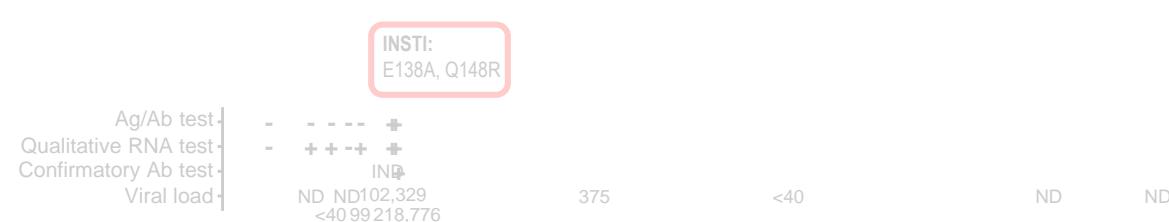
**CAB arm, Group B**  
**No recent CAB exposure**



- 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.

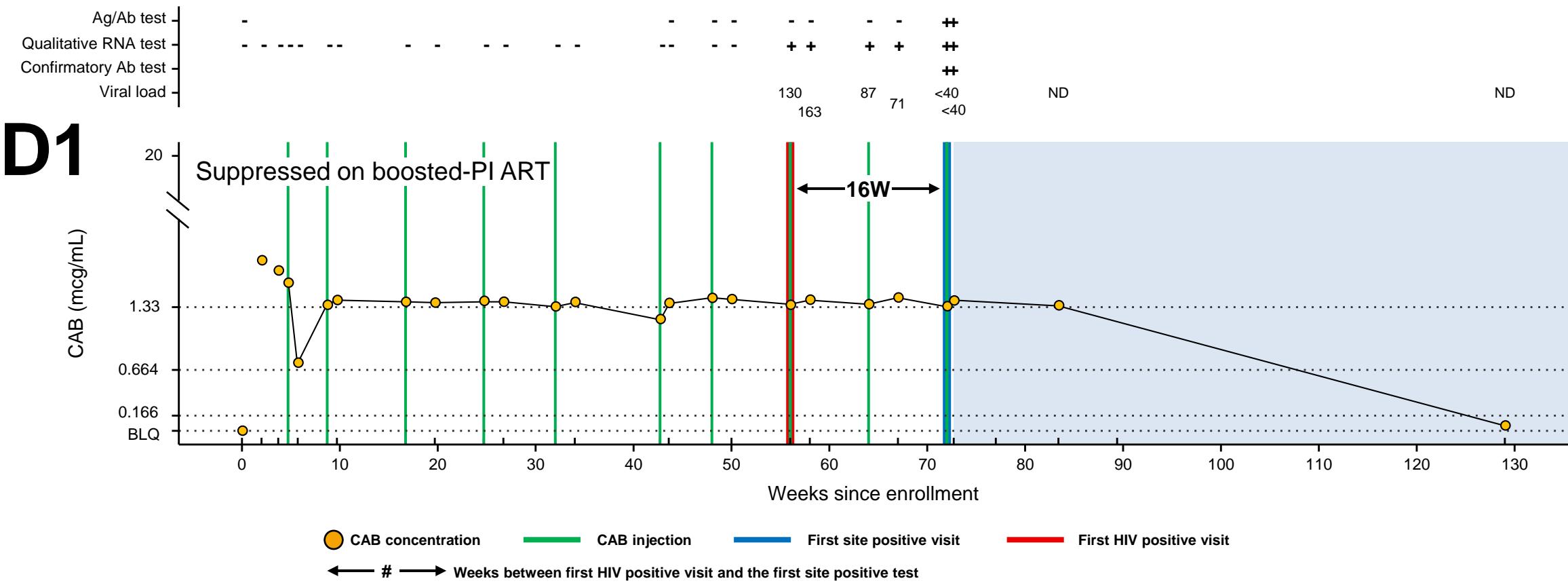
**CAB arm, Group C  
Infected during the CAB oral  
lead-in period**



● 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**

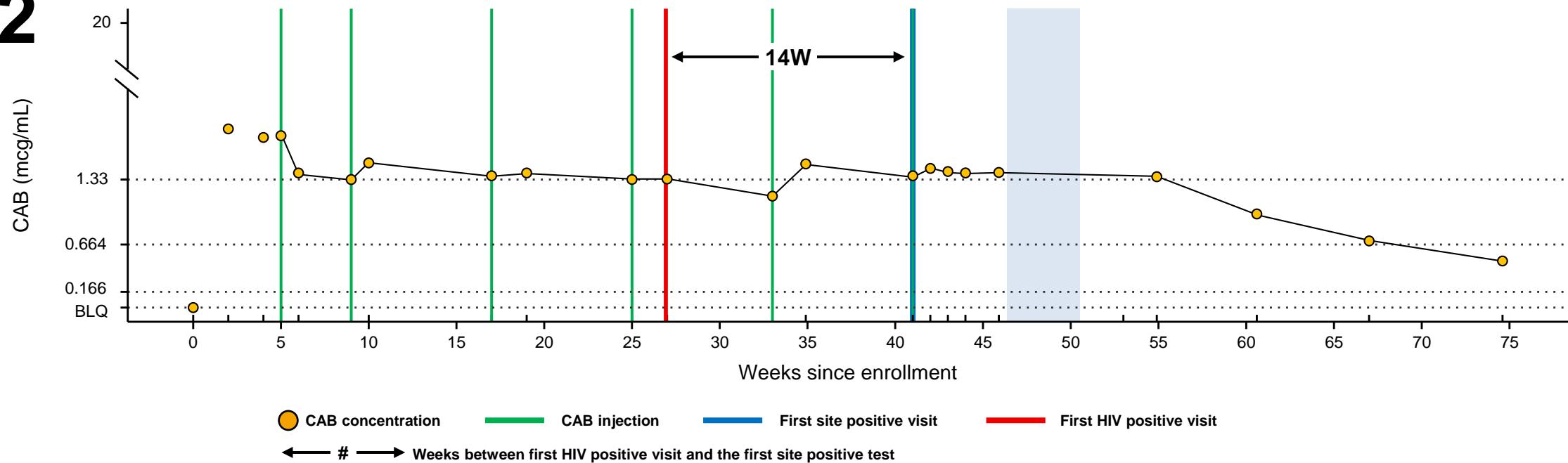


The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press

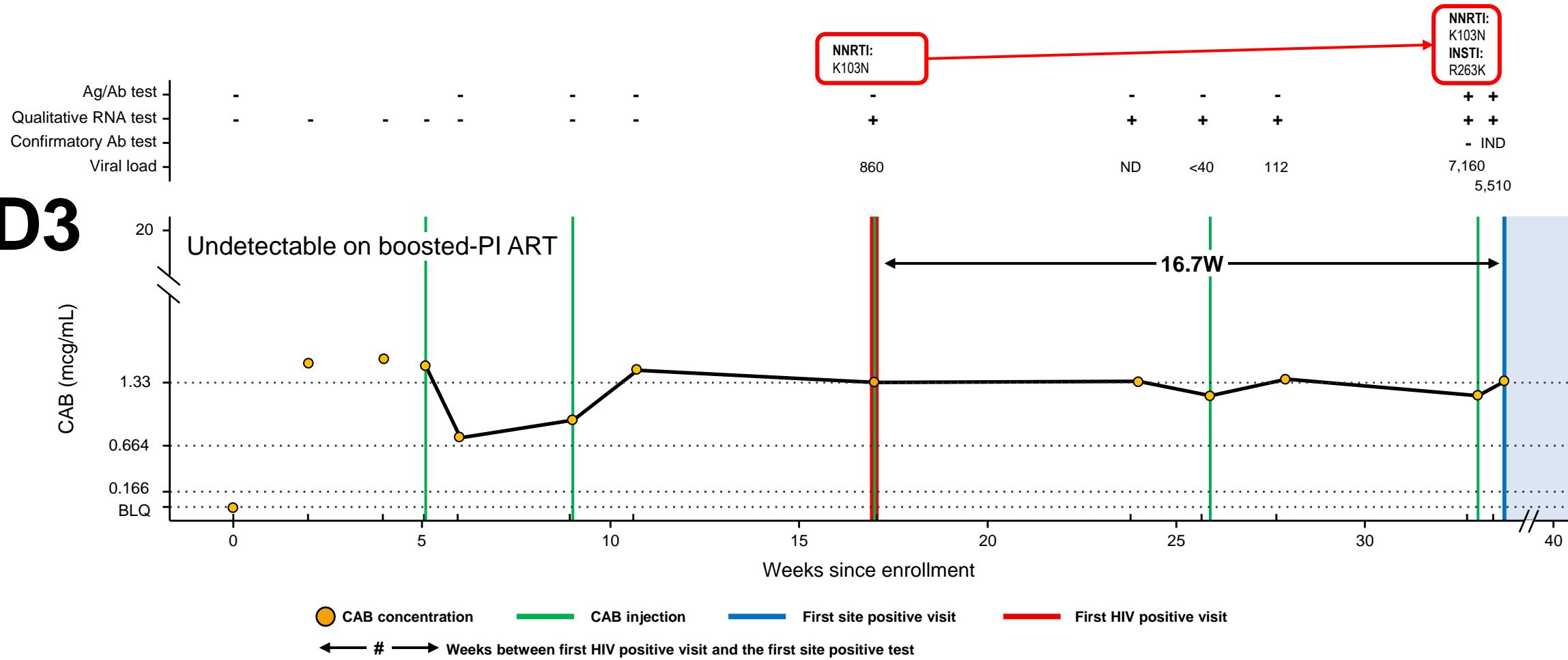
Ag/Ab test	-	-	-	-	-	-	-	-	-	-	-	-	-
Qualitative RNA test	-	-	-	-	-	-	-	-	-	-	-	-	-
Confirmatory Ab test	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral load	ND	ND	IND	IND	IND	<40	<40						

D2



The shaded area represents time on ART.

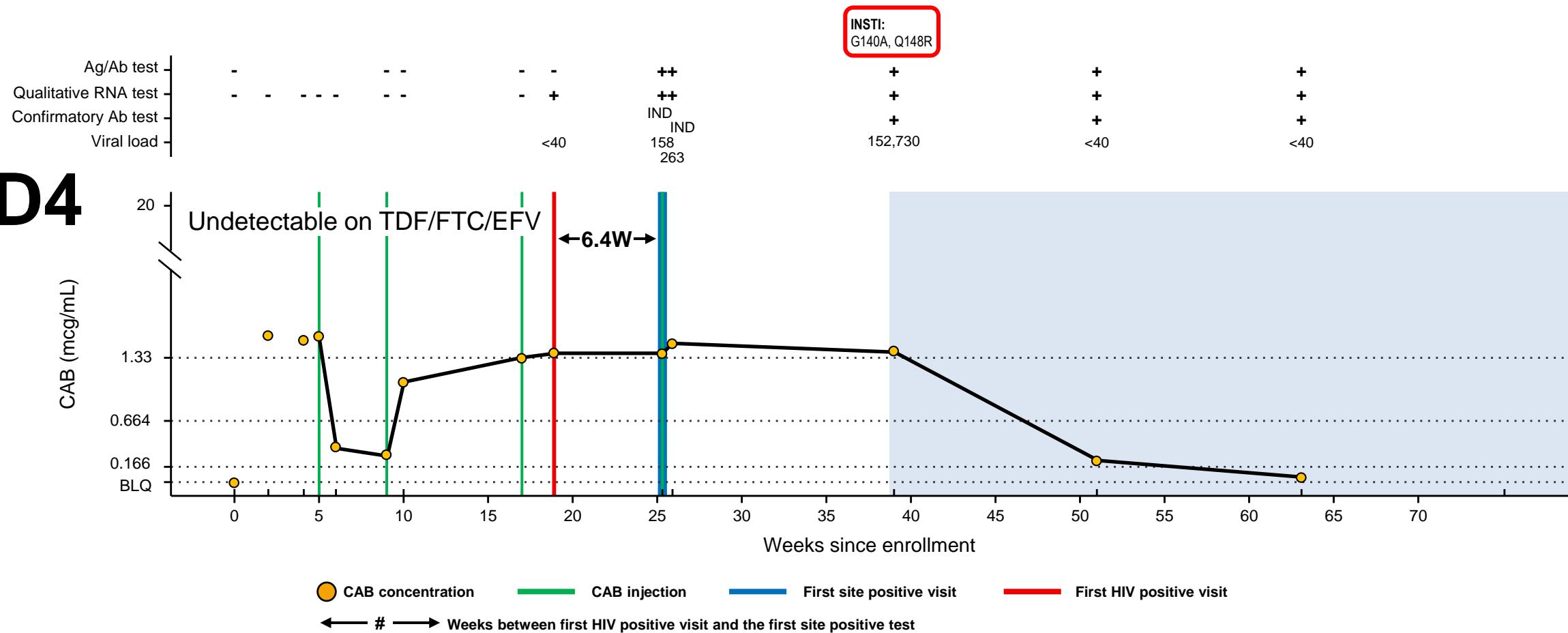
Marzinke et al, Journal of Inf Dis, 2021 in Press



The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press

# A Cautionary Tale



The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press

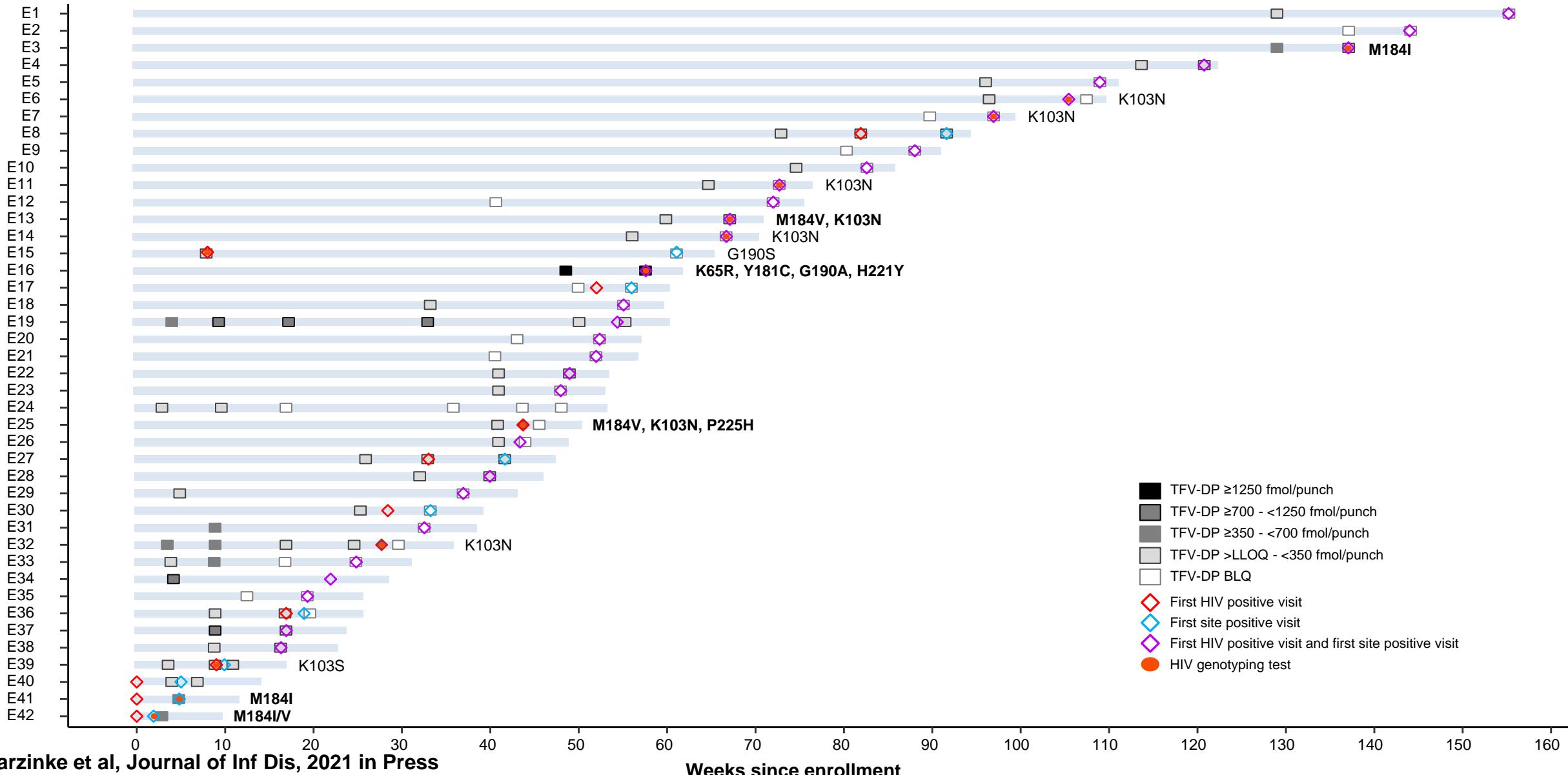
Case	Sample type	Visit type	Subtype	Drug resistance mutations <sup>a</sup>				INSTI Phenotype <sup>b</sup> (Fold change)
				NRTI	NNRTI	PI	INSTI	
A1	1 <sup>st</sup> viremic	Enrollment	B	K65R, M184V	L100I, K103N, I135T, P225H	L10V, I62V		N/A (assay failure)
A2	1 <sup>st</sup> viremic	Enrollment	C		I135T, 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 <sup>st</sup> viremic	Yearly 1	B		I135T, V179T, Y181C, H221Y	I62V		N/A (assay failure)
C1	1 <sup>st</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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 <sup>st</sup> 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

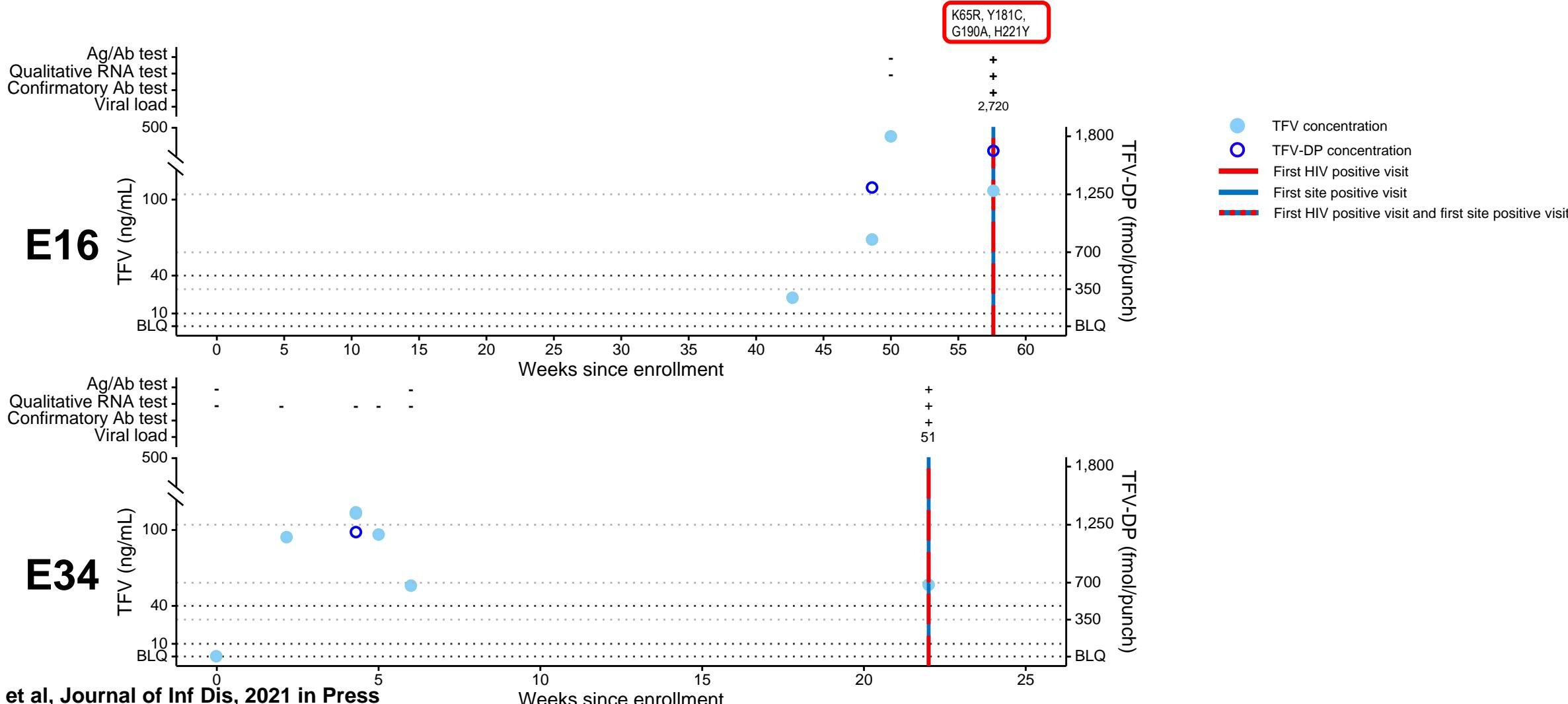
- **Extended testing identified earlier infection dates in many cases**
- **Virus loads were often low at the first HIV positive visit**
- **There was often a prolonged period of viral suppression after infection**
- **Antibody expression was diminished / delayed in many cases**
- **In some cases, RNA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

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**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%)**

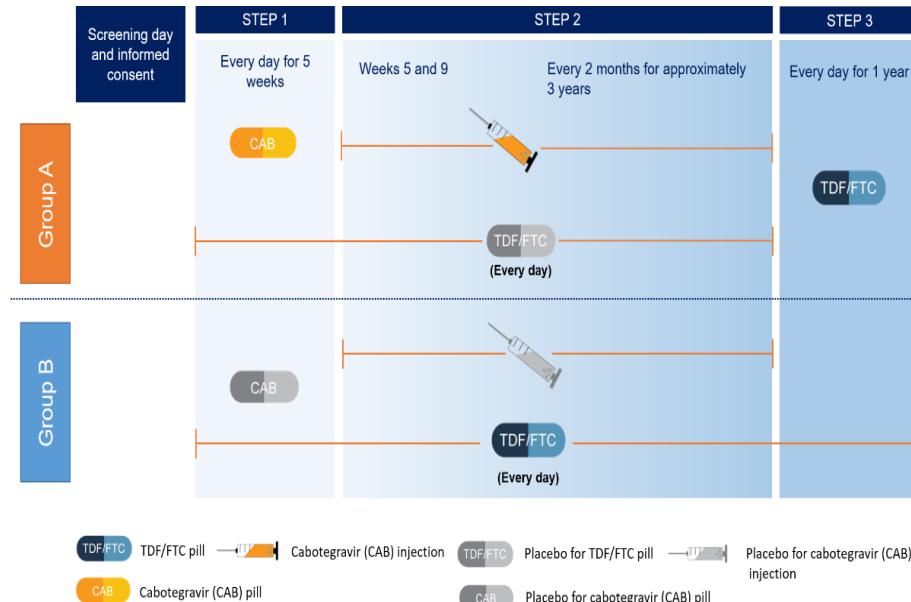
**CAB risk reduction (incidence 0.41%) compared to a counterfactual placebo would be estimated to be 91.5% (95% CI 82-96%)**

# 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-Moretliwe and Mina Hosseinpour, *Protocol Chairs*



Start Nov 2017  
Blinded Study halted by DSMB November 2020

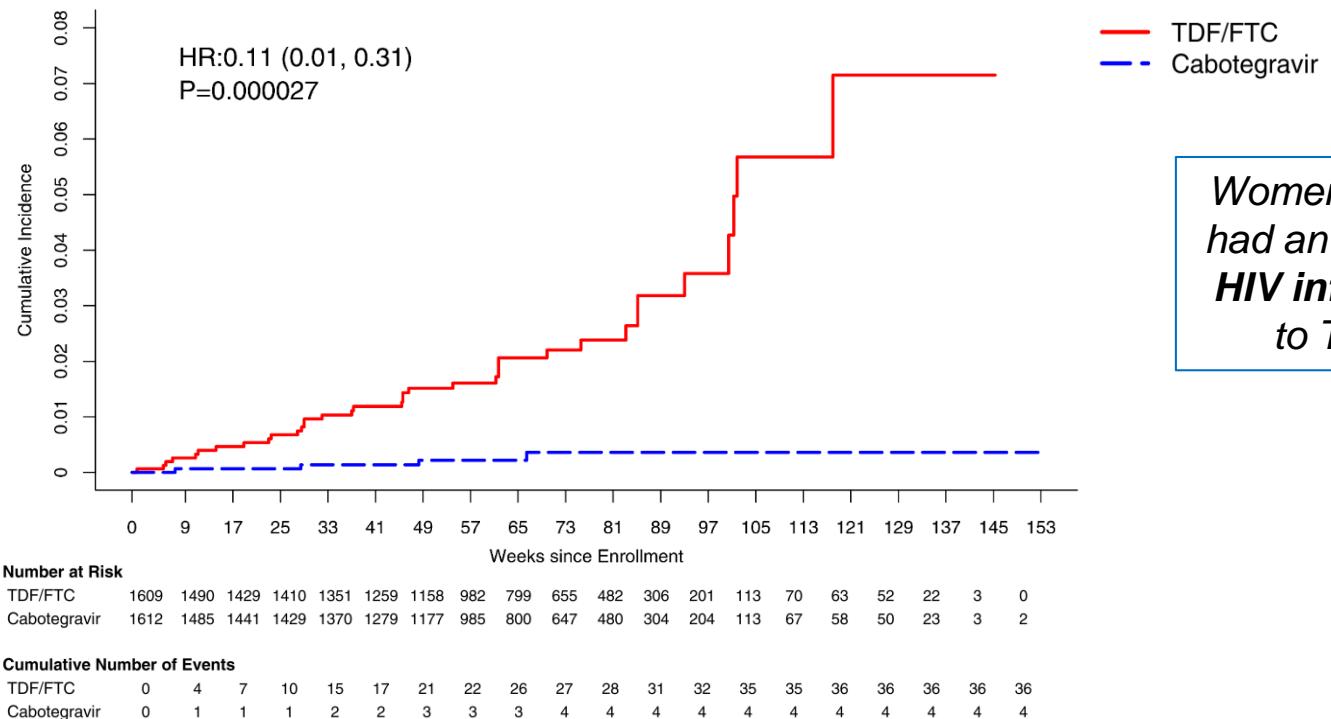
# Primary outcome: HIV incidence

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*

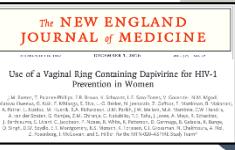
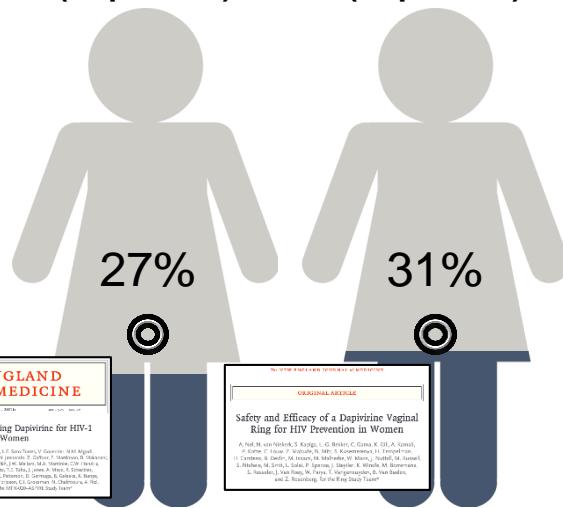
# Cumulative HIV incidence - ITT



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

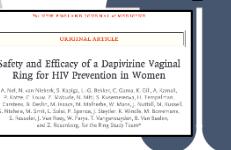
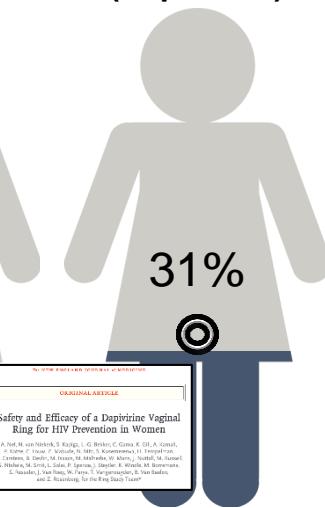
# “PrEP 3.0”: Trials of Novel PrEP Agents

**ASPIRE**  
(Dapivirine)



CI: 1 – 46

**Ring**  
(Dapivirine)



CI: 1 – 51

**DISCOVER**  
(TDF/FTC)      (TAF/FTC)



Incidence  
rate  
0.30%

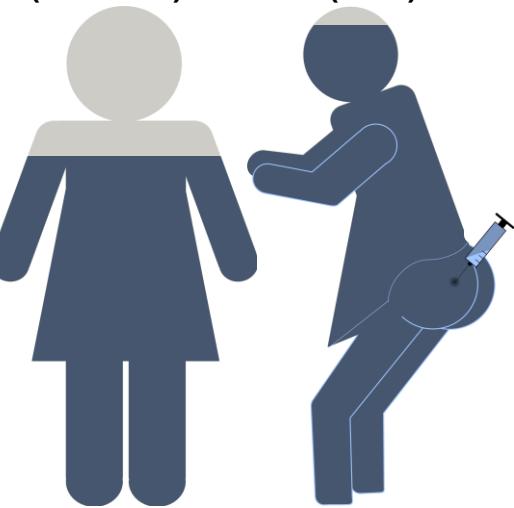
Incidence  
rate  
0.16%

**HPTN 083**  
(TDF/FTC)      (CAB)



Incidence  
rate  
1.22%  
Incidence  
rate  
0.41%

**HPTN 084**  
(TDF/FTC)      (CAB)



Incidence  
rate  
1.79%  
Incidence  
rate  
0.21%

# Conclusions

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- 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.

Questions? Email [rlandovitz@mednet.ucla.edu](mailto:rlandovitz@mednet.ucla.edu) or



@doc\_in\_a\_box

## HPTN 083 Study Team

**Community Program Managers  
Community Educators & Recruiters,  
CAB Members**

**Our 43 Sites in 7 countries**

**...and our Study Participants!**

