HIV R4P virtual conference,
27 January 2021
LB1479

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

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Disclosures

- I have served on MSD advisory boards
- I have received drug donations for research from Gilead Sciences

Background

- Antiretroviral-based pre-exposure prophylaxis can reduce HIV acquisition
- Women are disproportionately affected by HIV, esp. in sub-Saharan Africa where women experience individual and social barriers to consistent daily oral PrEP use
- Novel long-acting products e.g., CAB LA administered less frequently may simplify PrEP use and provide much needed HIV protection

Source: Fonner, AIDS 2016; UNAIDS, 2020; Celum, JIAS 2019; Landovitz, PLoS Med 2018

Primary Objectives

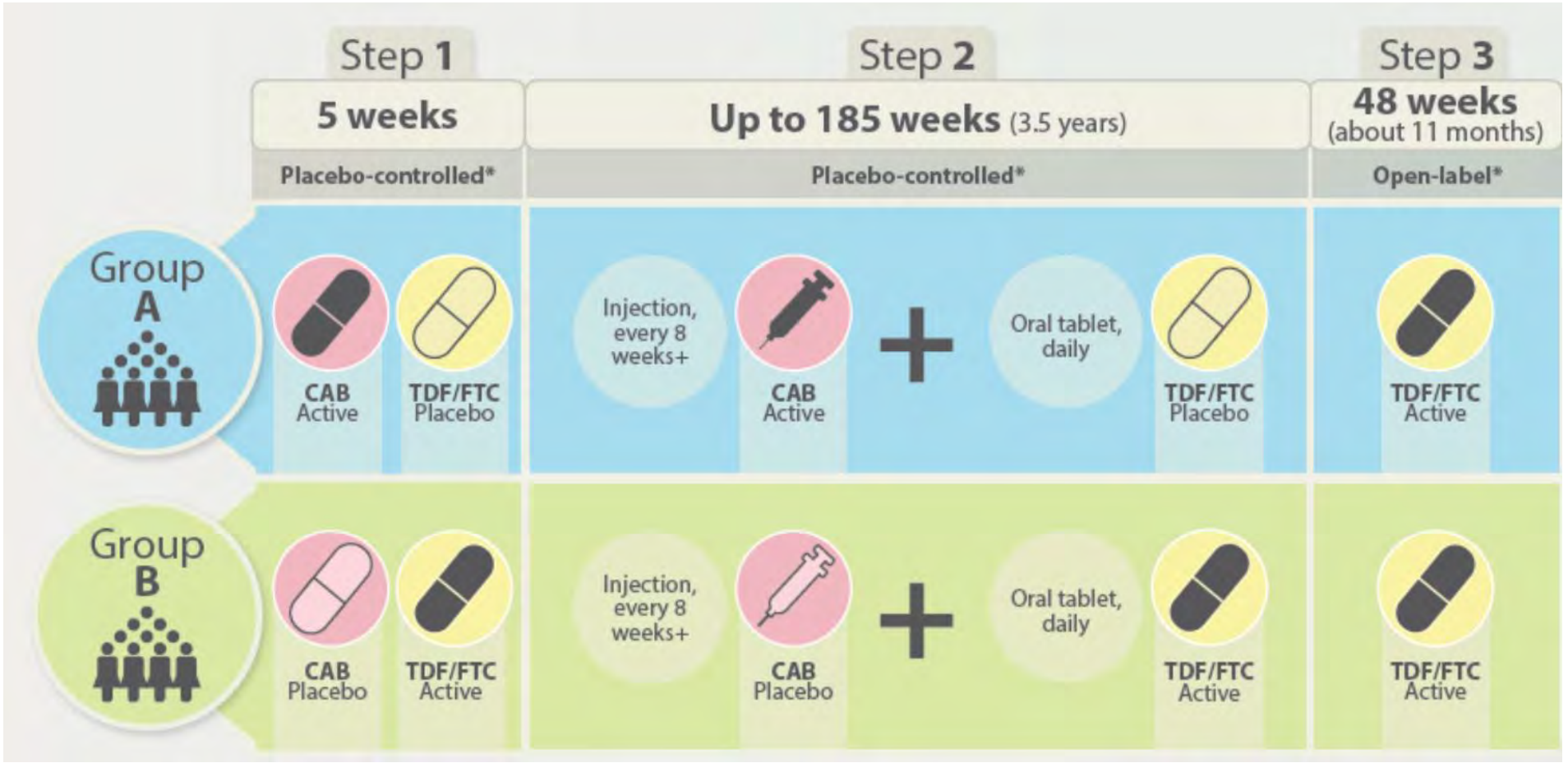
- To evaluate the relative efficacy of oral CAB/CAB LA vs. daily oral TDF/FTC for HIV prevention.

- 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, allergy
- Not pregnant or breastfeeding
- Use reliable form of modern contraception
  - From May 2018, only LARC with <1% failure rate

Study design

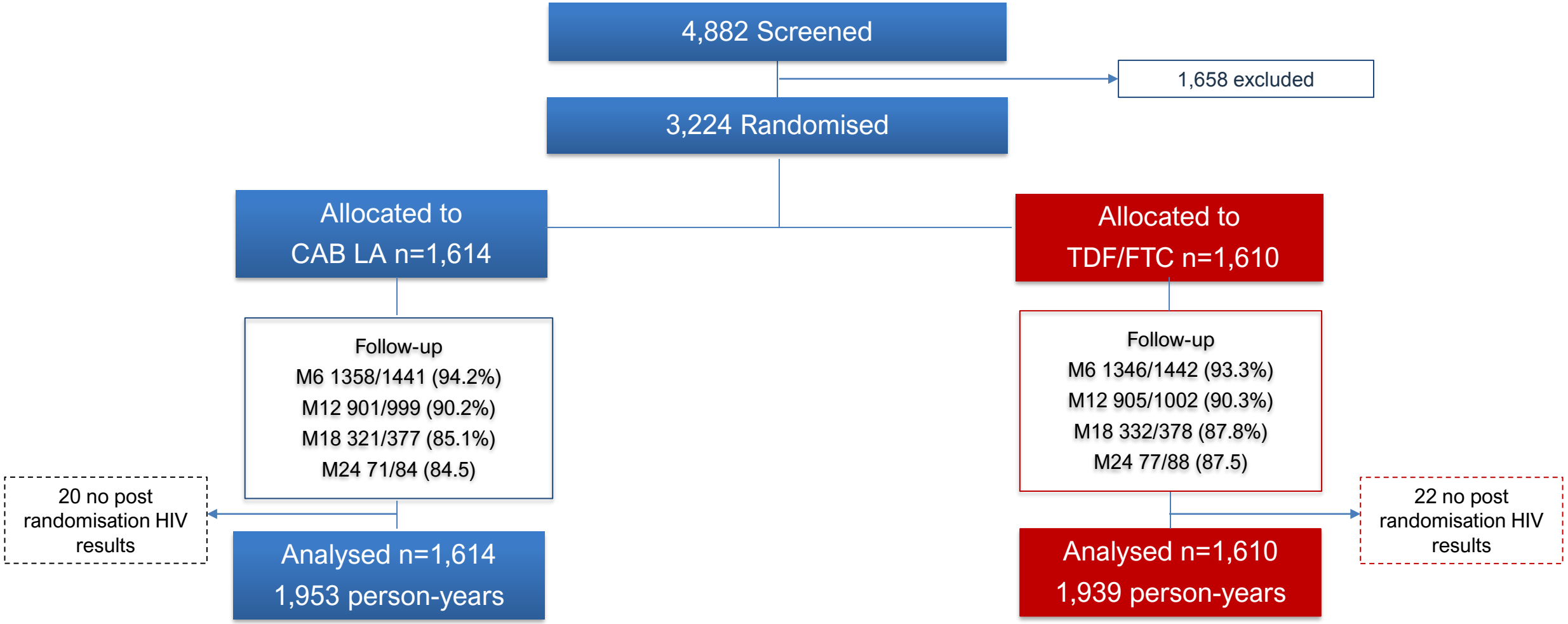


HIV, pregnancy testing and safety assessments at each product administration visit; additional post injection safety visits
Real-world adherence counselling support aligned with national guidelines

Statistical analysis

- Endpoint-driven trial (n=114)
  - Background HIV incidence in absence of PrEP 3.5% pa
  - CAB adherence 80-85%, TDF/FTC adherence 45-50%, LTFU 5% pa
  - 90% power, $\alpha = 0.05$ to detect RR 0.48-0.54
- Superiority analysis
  - HIV incidence during steps 1 and 2
  - Intent to treat, Cox proportional hazards model, stratified by site
- Interim reviews at 22%, 39%, 59%, 78% of information planned
  - Early stopping using an O'Brien-Fleming boundary for efficacy
  - Pre-specified stopping boundary crossed during planned interim review Nov 5, 2020

Screening, enrolment and follow-up



Participant baseline characteristics

	Total (n=3224) % or Median (IQR)	CAB (n=1614) n (%) or Median (IQR)	TDF/FTC (n=1610) n (%) or Median (IQR)
Median Age (years)	25 (22, 30)	25 (22, 30)	25 (22, 20)
≤ 25 years	57%	57%	57%
Not living with partner	82%	82%	82%
In the past month			
Partner HIV positive or unknown*	34%	34%	35%
≥ 2 sex partners*	54%	54%	55%
Transactional sex*	41%	41%	41%
Anal sex*	6%	5%	6%
Median VOICE risk score (IQR)	6 (5,7)	6 (5,7)	6 (5,7)
C. trachomatis	17%	17%	17%
N. gonorrhoeae	7%	7%	7%
BMI ≥ 25	55%	55%	56%

**Responses for 3210 participants, CAB n=1610 and TDF/FTC N=1600*

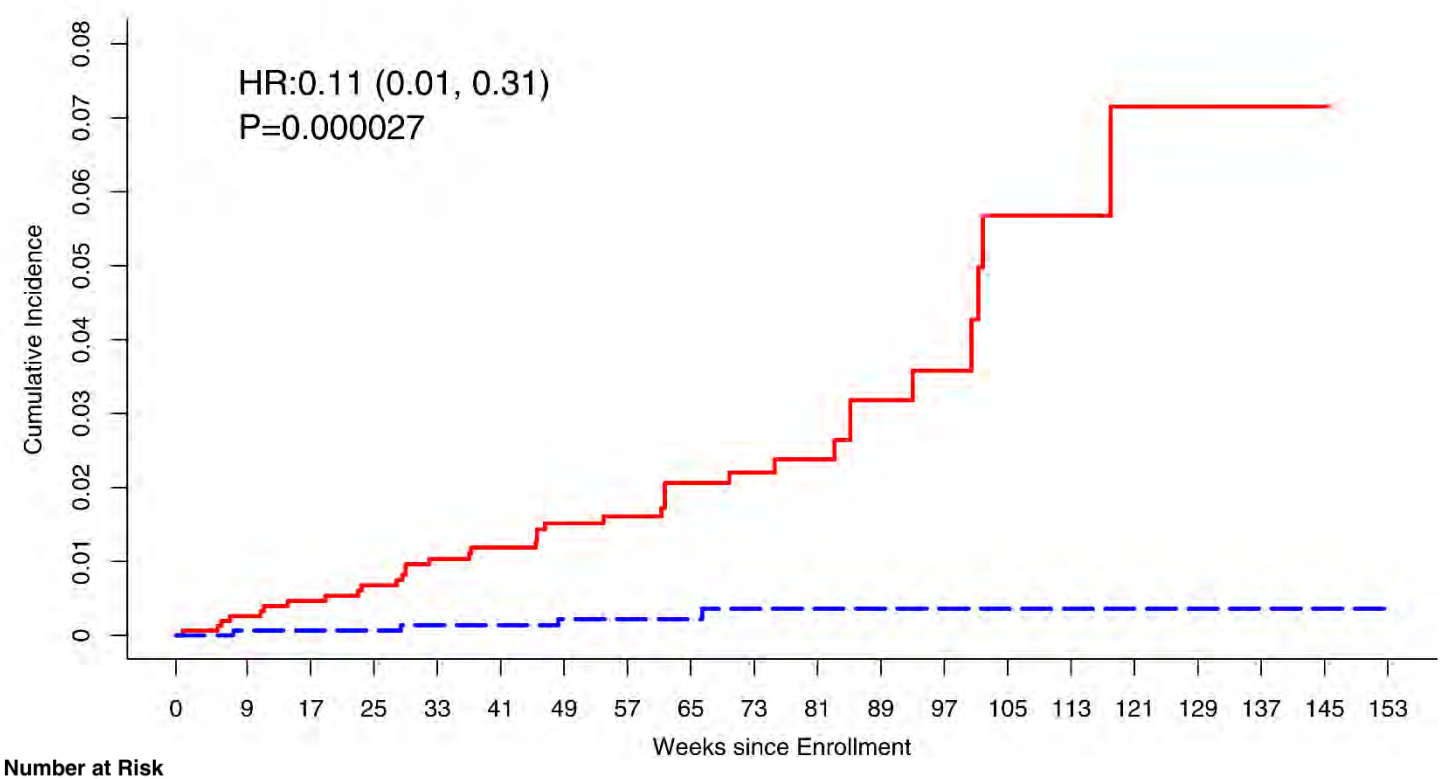
Primary outcome: HIV incidence

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

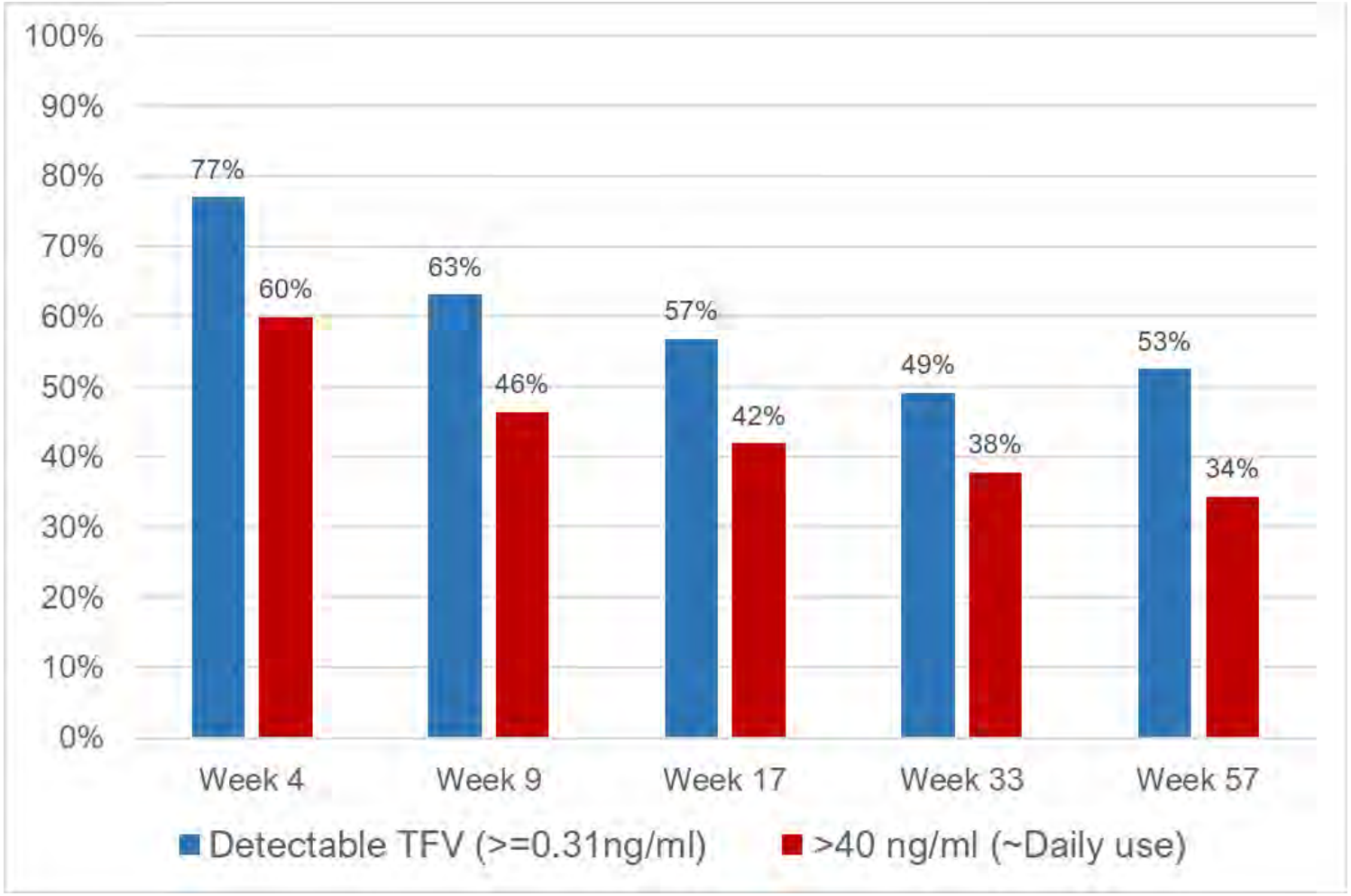
TDF/FTC	1609	1490	1429	1410	1351	1259	1158	982	799	655	482	306	201	113	70	63	52	22	3	0
Cabotegravir	1612	1485	1441	1429	1370	1279	1177	985	800	647	480	304	204	113	67	58	50	23	3	2

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

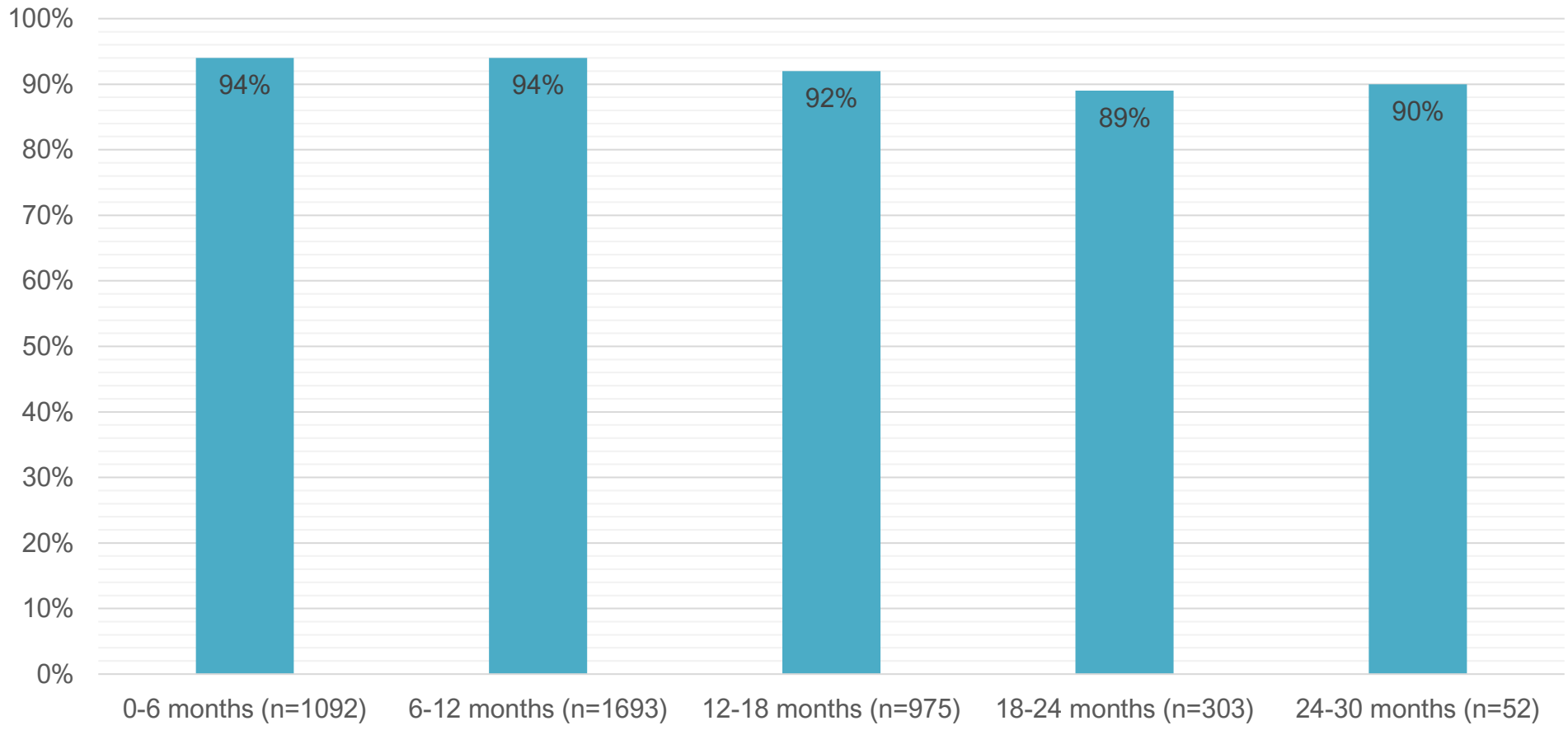
*Women in the CAB group had an **89% lower risk of HIV infection,** compared to TDF/FTC group*

TDF plasma concentrations – adherence subset (n=375)



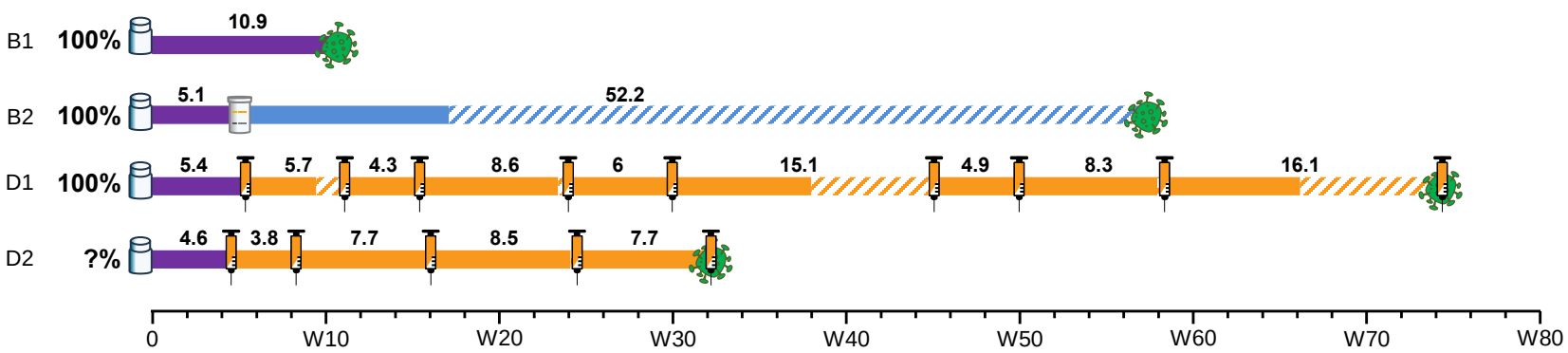
Overall,
62% detectable TFV
46% >40ng/ml

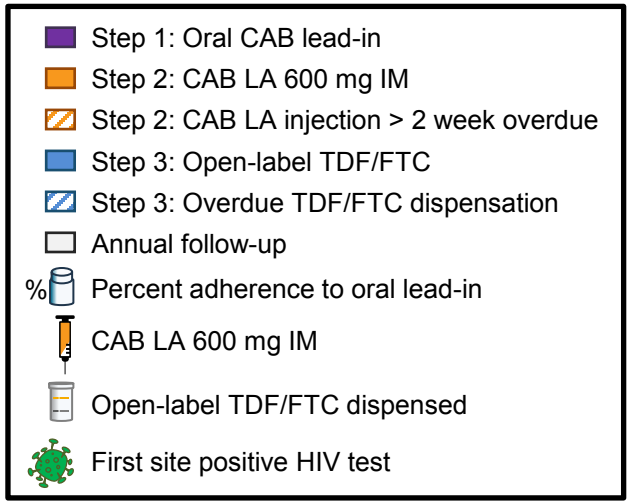
Injection coverage, 6-month intervals - all



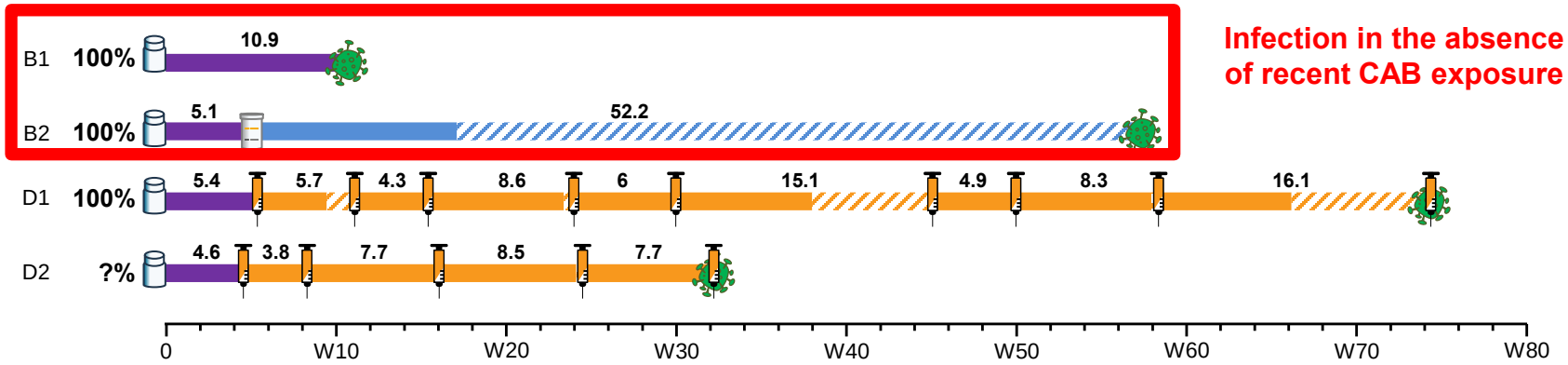
Injection coverage: injections administered as a proportion of total expected injection visits

Cabotegravir - 4 incident HIV Infections





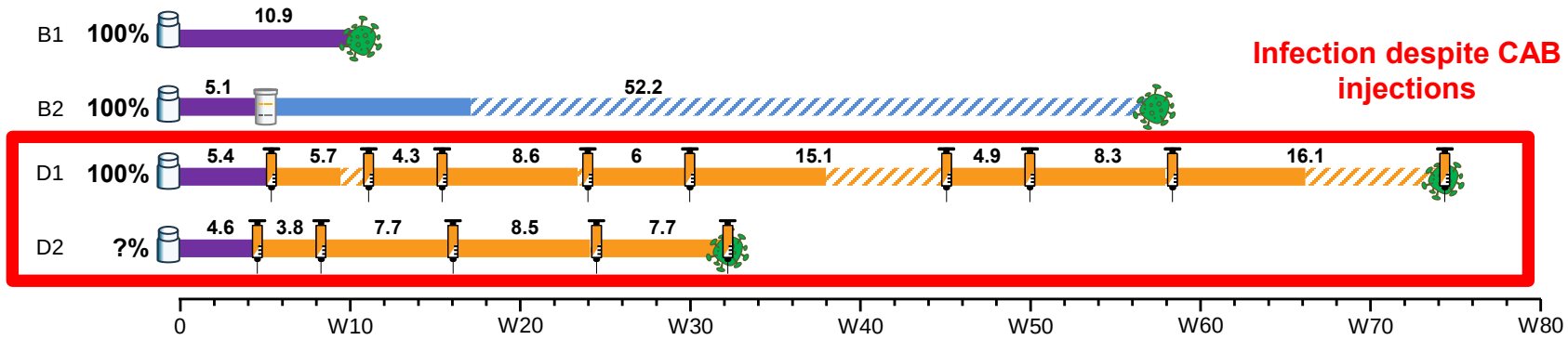
Cabotegravir - 4 incident HIV Infections

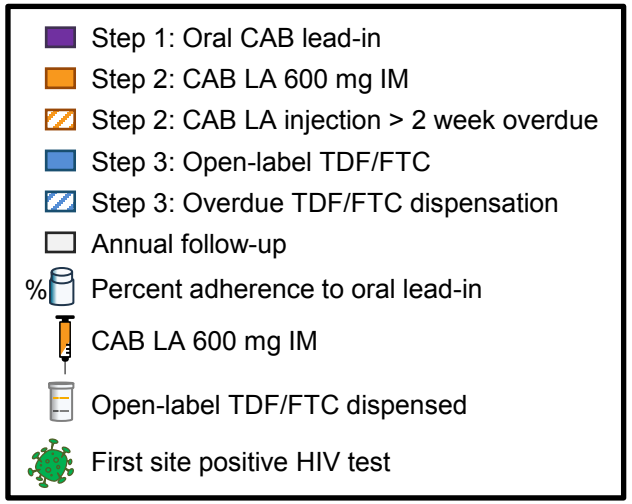


Infection in the absence of recent CAB exposure

- 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
- First site positive HIV test

Cabotegravir - 4 incident HIV Infections





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TDF/FTC - 36 Incident HIV Infections

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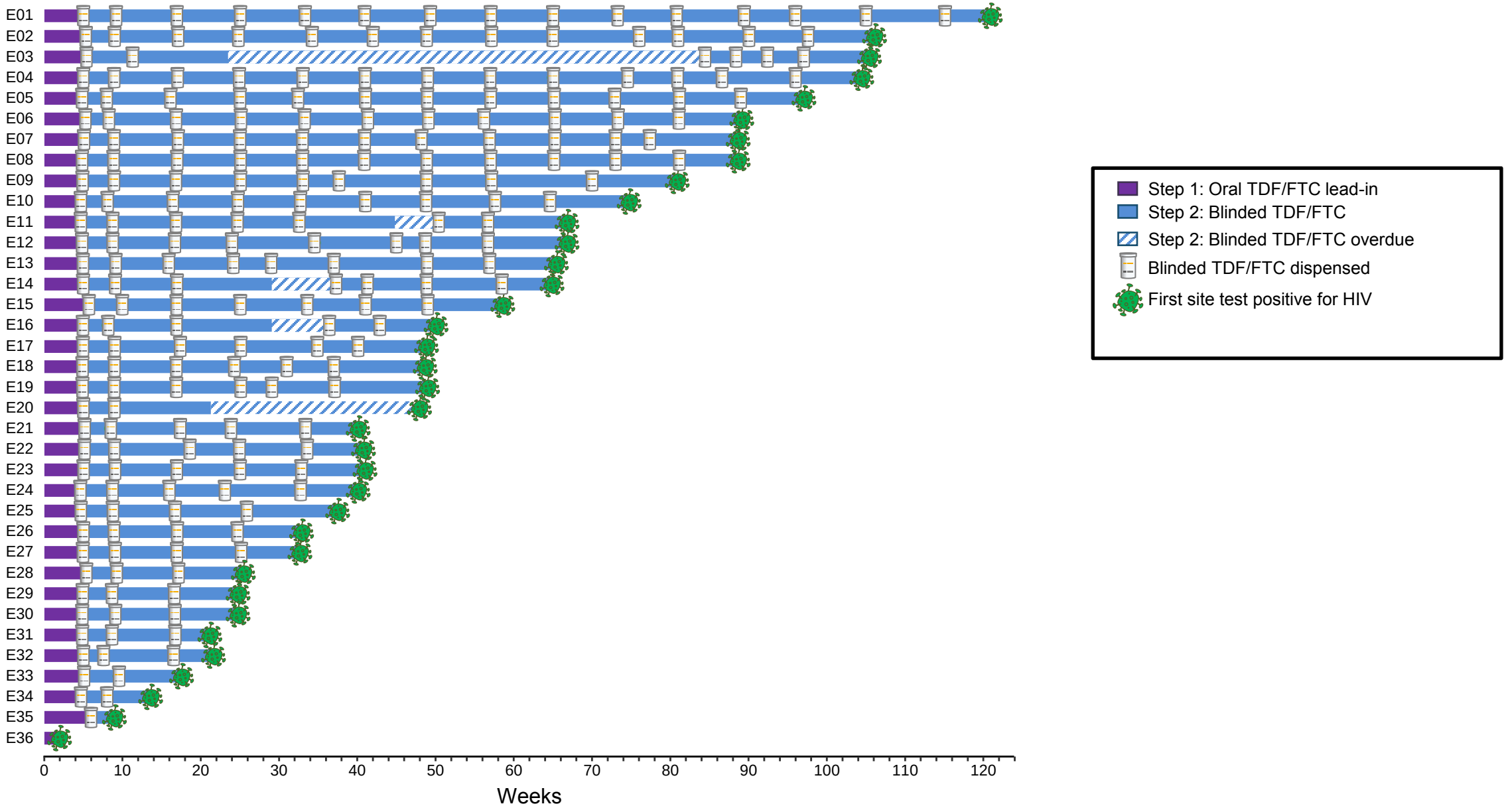
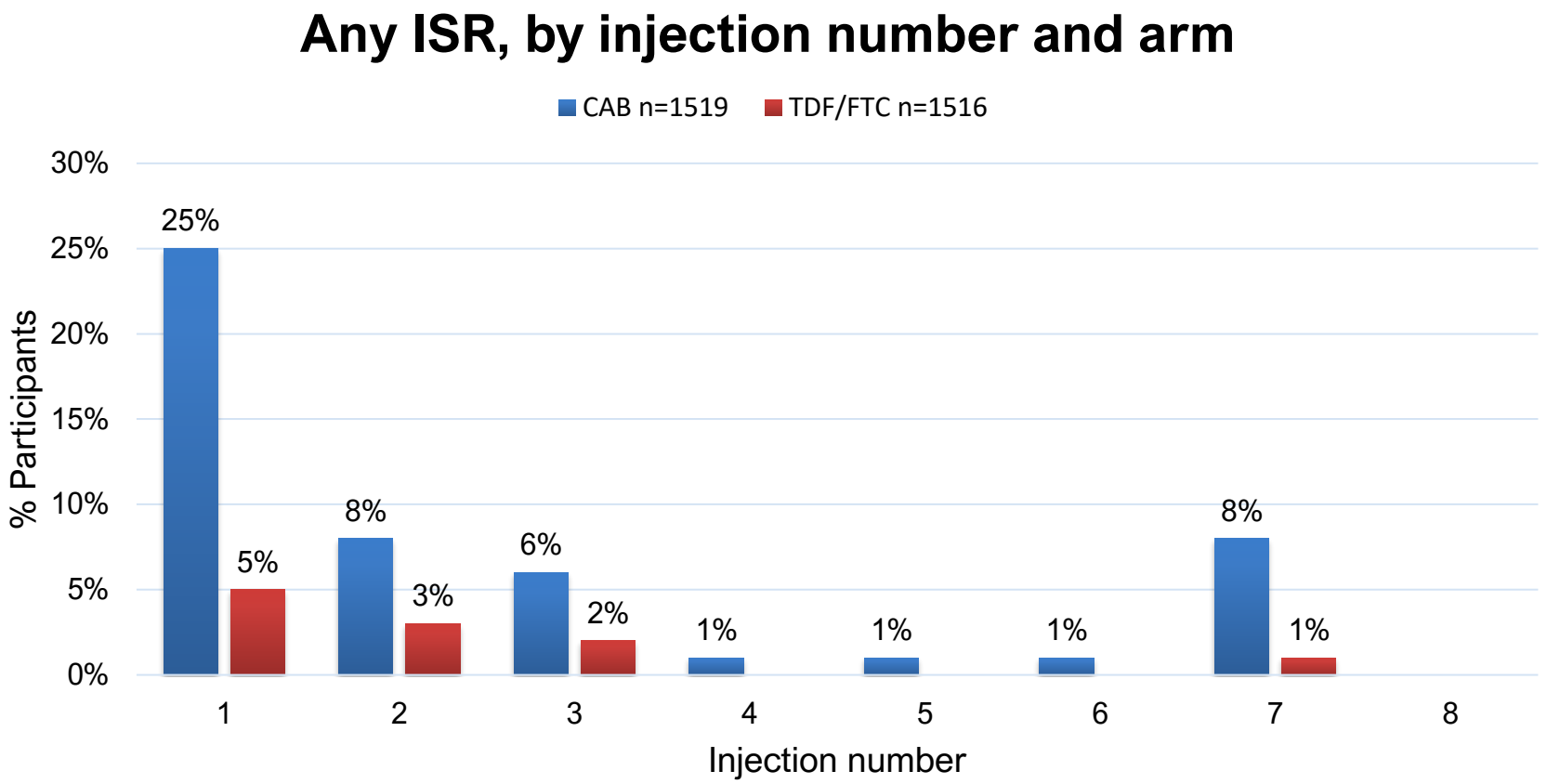


Additional testing among seroconverters, in progress

- HIV
  - Timing of first infection
- Drug concentrations
  - CAB all visits
  - TDF/FTC selected visits peri-infection
- Resistance profiles
  - HIV infection at time of first detection

Safety: Injection site reactions (ISR)

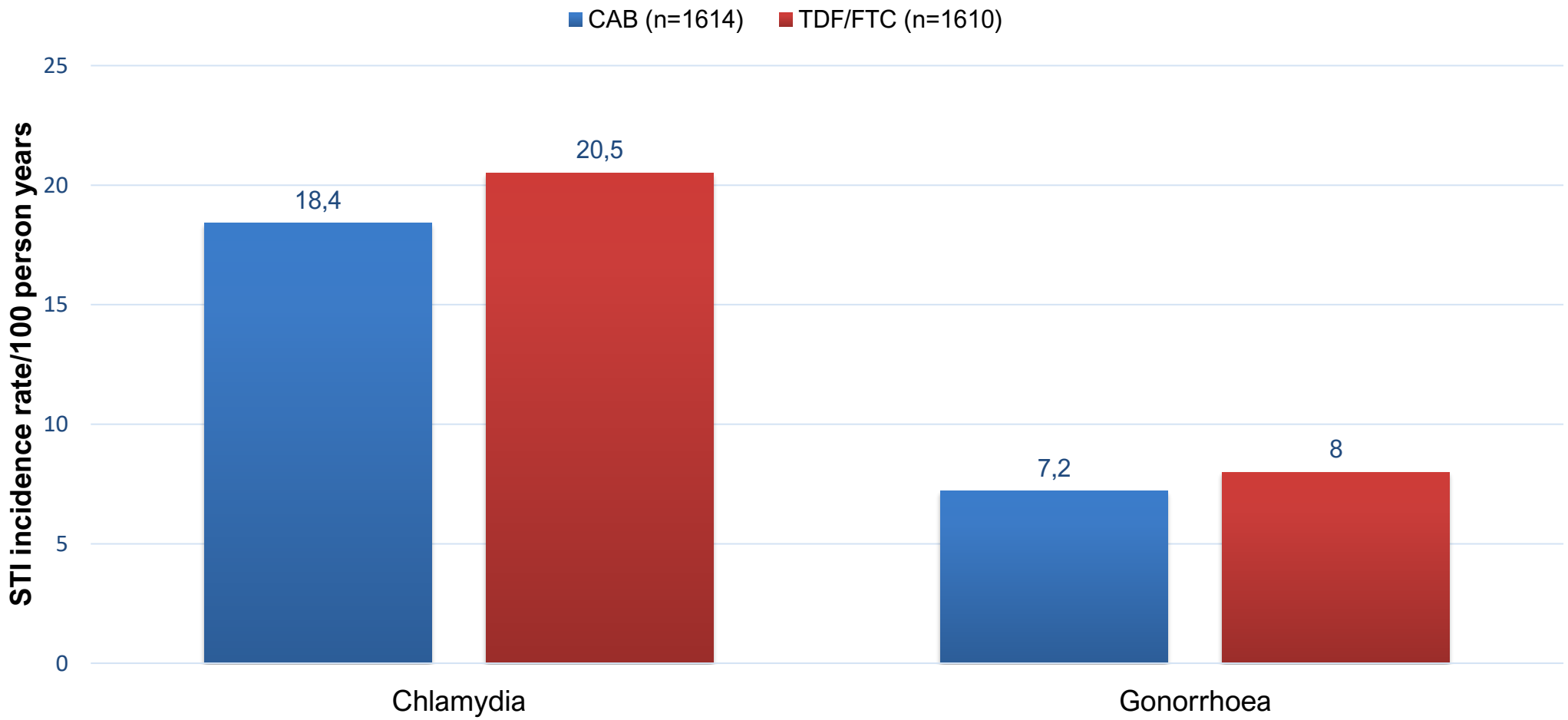


- 21% participants any ISR
  - 32% CAB vs. 9% TDF/FTC
- 4% participants Grade 2+ ISR
  - 7% CAB vs. 1% TDF/FTC
- Zero discontinuations d/t ISR

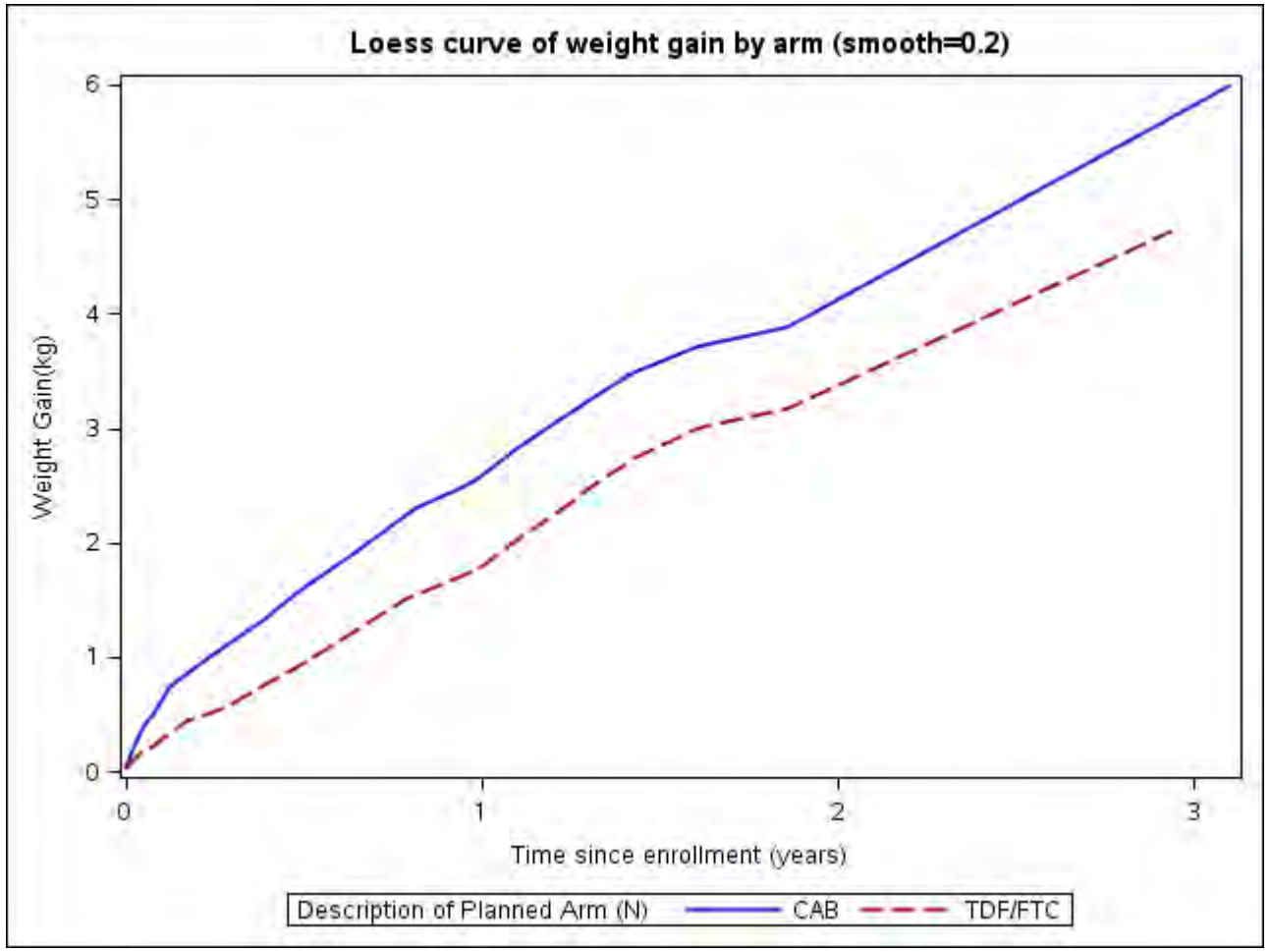
Safety: Grade 2+ adverse events - reported in ≥ 5%

Participants with ≥ Grade 2 events	Total (n=3224)		CAB (n=1614)		TDF/FTC (n=1610)	
	n	%	n	%	n	%
Any Grade 2+ events	2956	92%	1477	92%	1479	92%
Creatinine clearance decreased	2359	73%	1166	72%	1193	74%
Creatinine increased	664	21%	337	21%	327	20%
Gastrointestinal disorders	650	20%	309	19%	341	21%
Chlamydia infection	528	16%	253	16%	275	17%
Upper respiratory tract infection	509	16%	236	15%	273	17%
Urinary tract infection	409	13%	210	13%	199	12%
Amylase increased	320	10%	172	11%	148	9%
Blood glucose decreased	292	9%	146	9%	146	9%
Vulvovaginal candidiasis	267	8%	145	9%	122	8%
Trichomoniasis	230	7%	123	8%	107	7%
Back pain	188	6%	89	6%	99	6%
Abnormal loss of weight	177	5%	76	5%	101	6%
Menorrhagia	166	5%	81	5%	85	5%
Nasopharyngitis	159	5%	86	5%	73	5%
Metrorrhagia	155	5%	79	5%	76	5%
Any SAE/EAE	73	2%	32	2%	39	2%
Deaths	3	0,1%	3	0,1%	0	0

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



Changes in weight, kg – ITT (n=3,224)



Initial immediate increase in weight on CAB

- +0.42 kg CAB, (95% CI 0.30,0.54)
- **p <0.001**

Overall, increase in weight in both arms

- CAB +2.4 (95% CI 2.1, 2.7)kg/year
- TDF/FTC +2.2 (95% CI 2.0, 2.4)) kg/year
- **p=0.12**

Pregnancy incidence and outcomes - ITT

	Total n=3224	CAB n=1614	TDF/FTC n=1610
No. confirmed pregnancies	50	29	21
Person-years	3829.7	1914.5	1915.2
Incidence rate (95% CI)	1.3 (1.0, 1,7)	1.5 (1.0, 2.2)	1.1 (0.7, 1.7)

Pregnancy outcomes - ITT

	Total n=50	CAB n=29	TDF/FTC n=21
Ongoing	23	15	8
Known pregnancy outcomes n=27			
Live births	20	10	10
Pregnancy loss			
>=37 weeks	0	0	0
20-36 weeks	3	1	2
<20 weeks*	4	3	1
Ectopic	0	0	0
Congenital anomalies n=27			
No	23	11	12
Unknown	4	3	1

**includes elective terminations*

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
  - CAB LA 8-weekly likely provided an adherence advantage over daily oral TDF/FTC
  - Ongoing testing to fully understand reasons for breakthrough infections
- 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 PrEP agent for cisgender women

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