What We Know and What We Do Not Know About Long-acting PrEP

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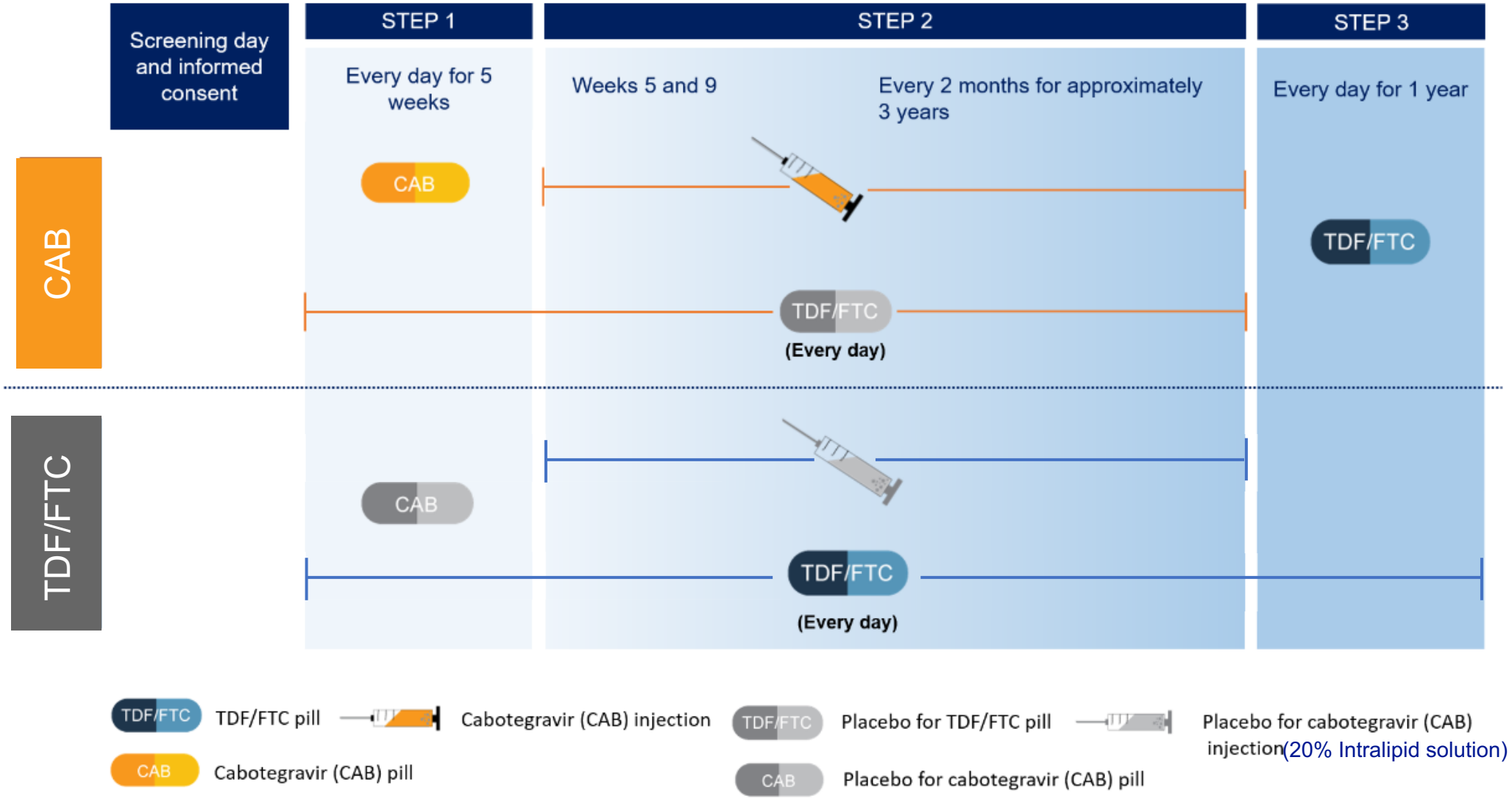
Equitable LAI PrEP Workshop, March 8, 2023

Disclosure

Raphael J. Landovitz has served on Scientific Advisory Boards for Merck.

HPTN 083/084 Study Design

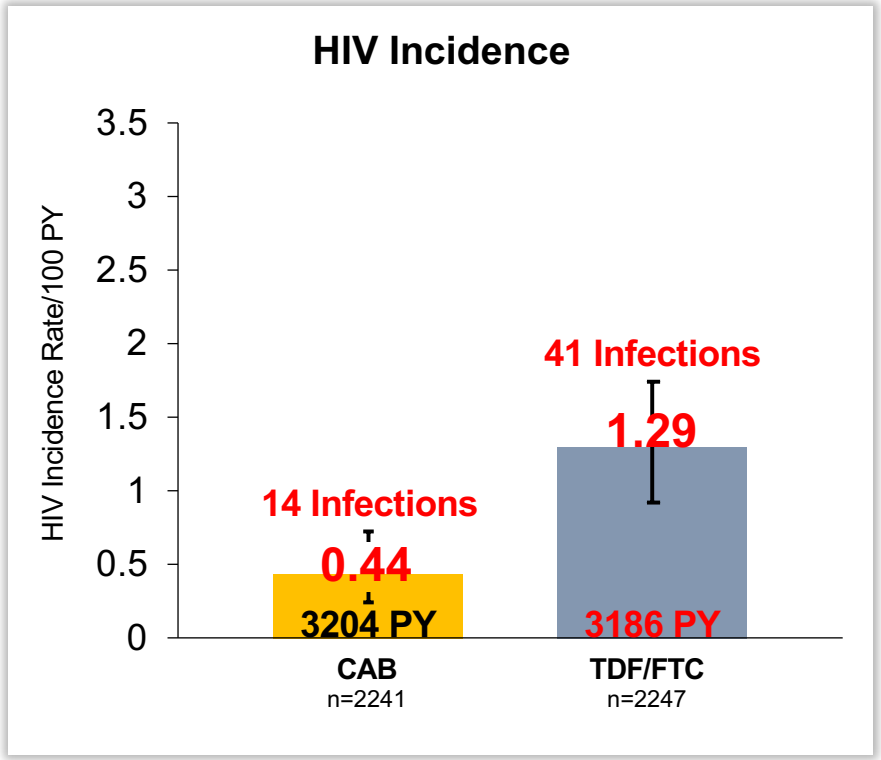


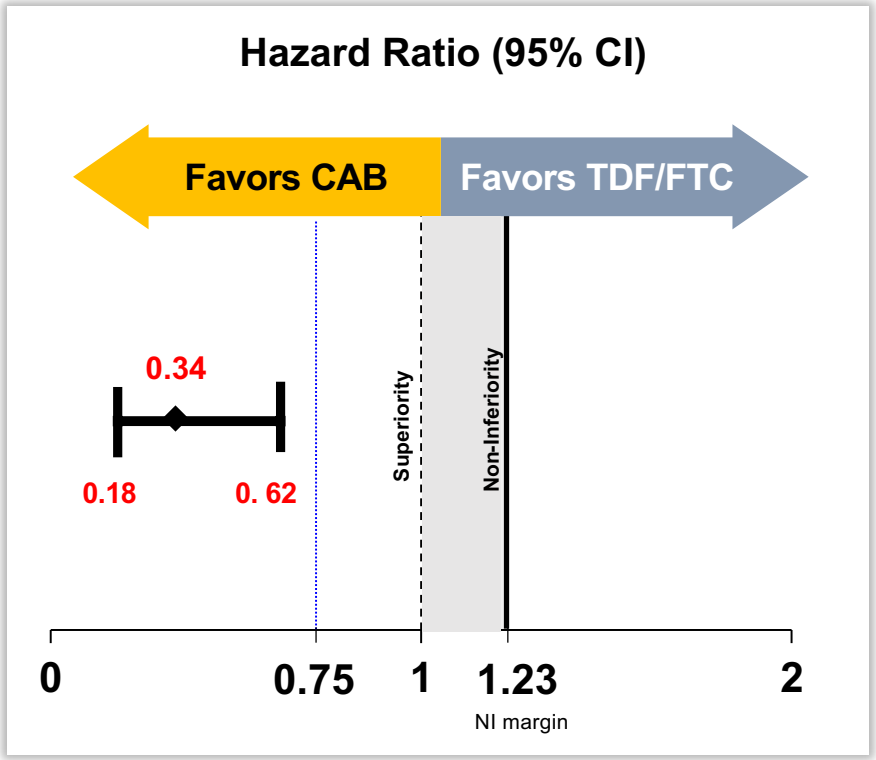
Landovitz RJ et al. AIDS 2020, #OAXLB0101

EFFICACY

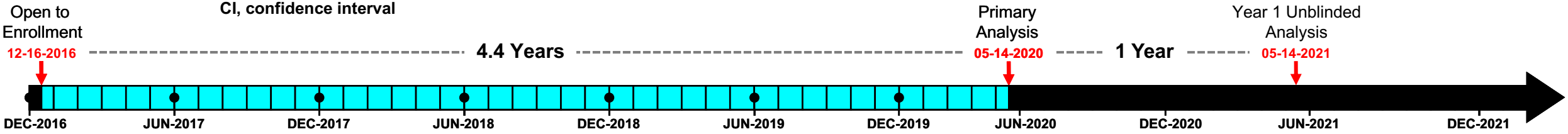
HPTN 083 HIV Incidence: CAB vs. TDF/FTC

Primary blinded period, through May 2020





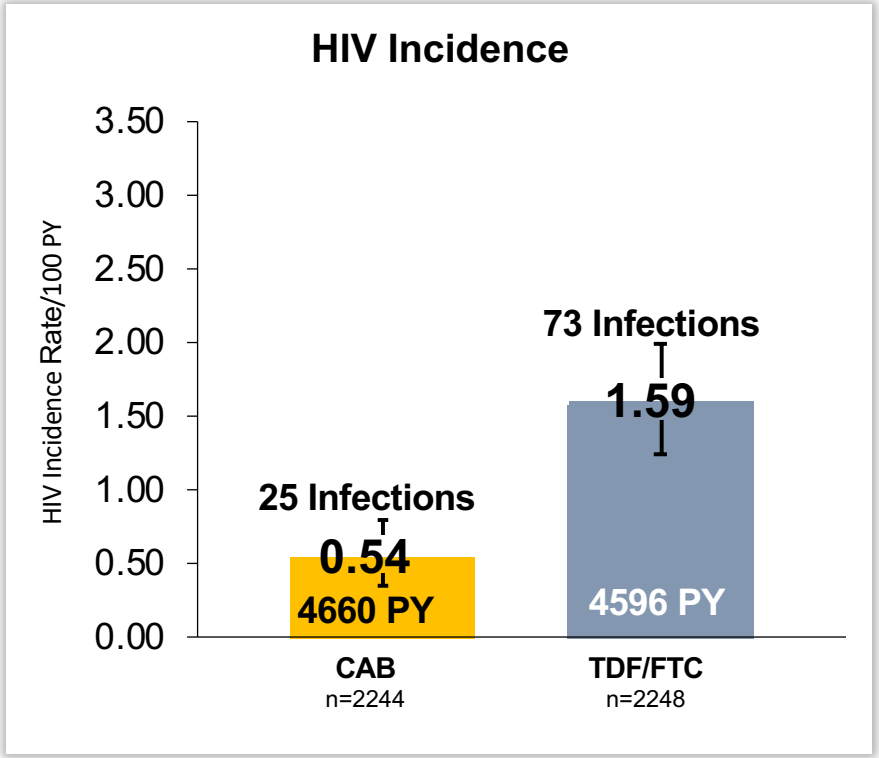
CI, confidence interval

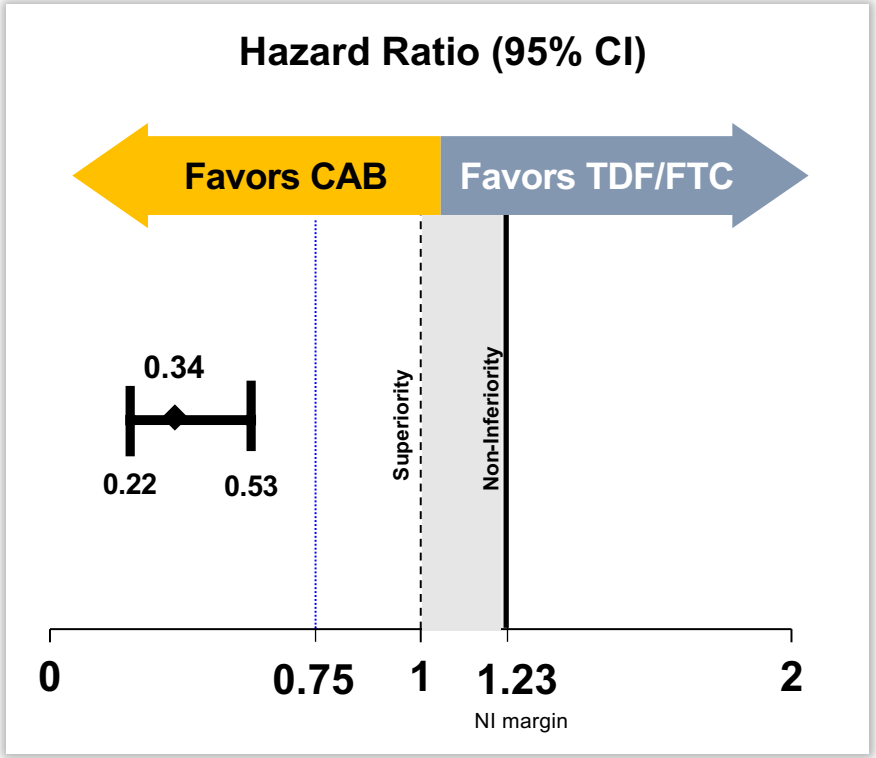


Landovitz, R. HIV Glasgow 2022.

HPTN 083 HIV Incidence: CAB vs. TDF/FTC

Combined blinded and unblinded period, through May 2021





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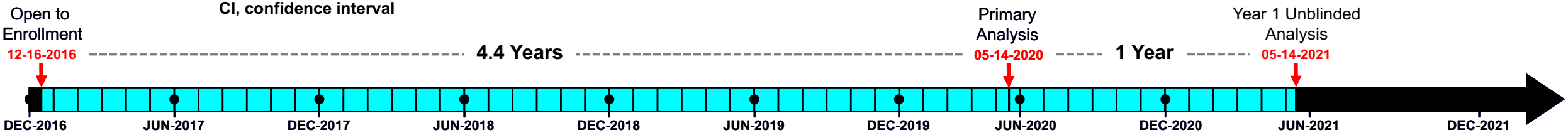
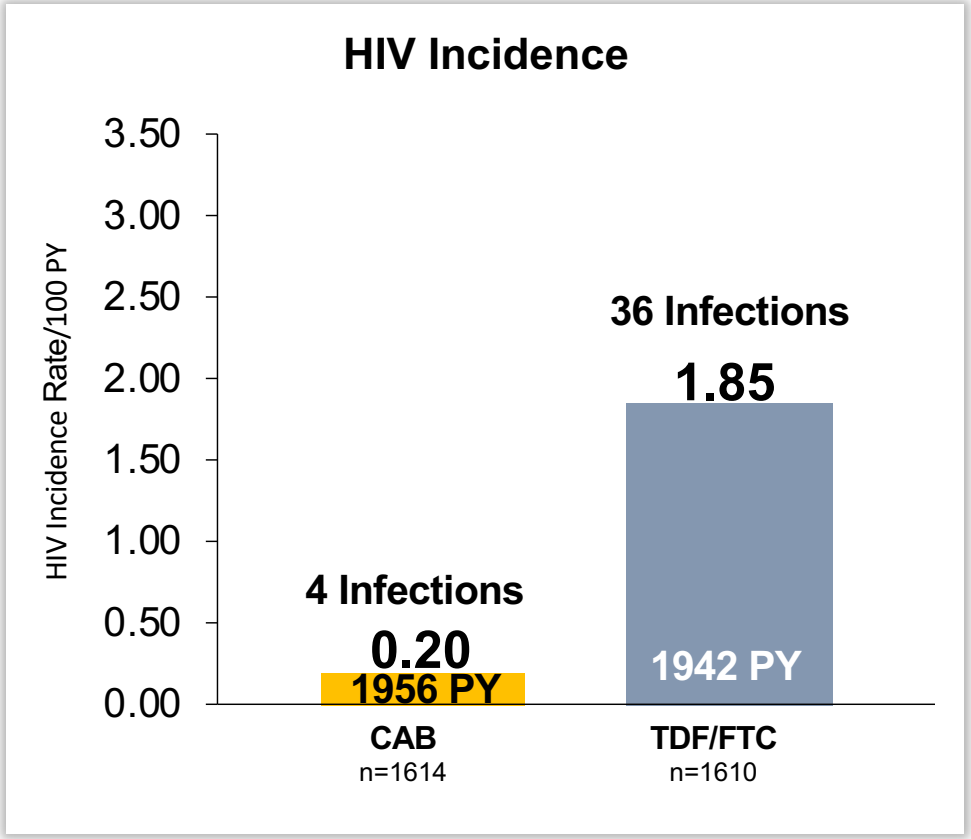
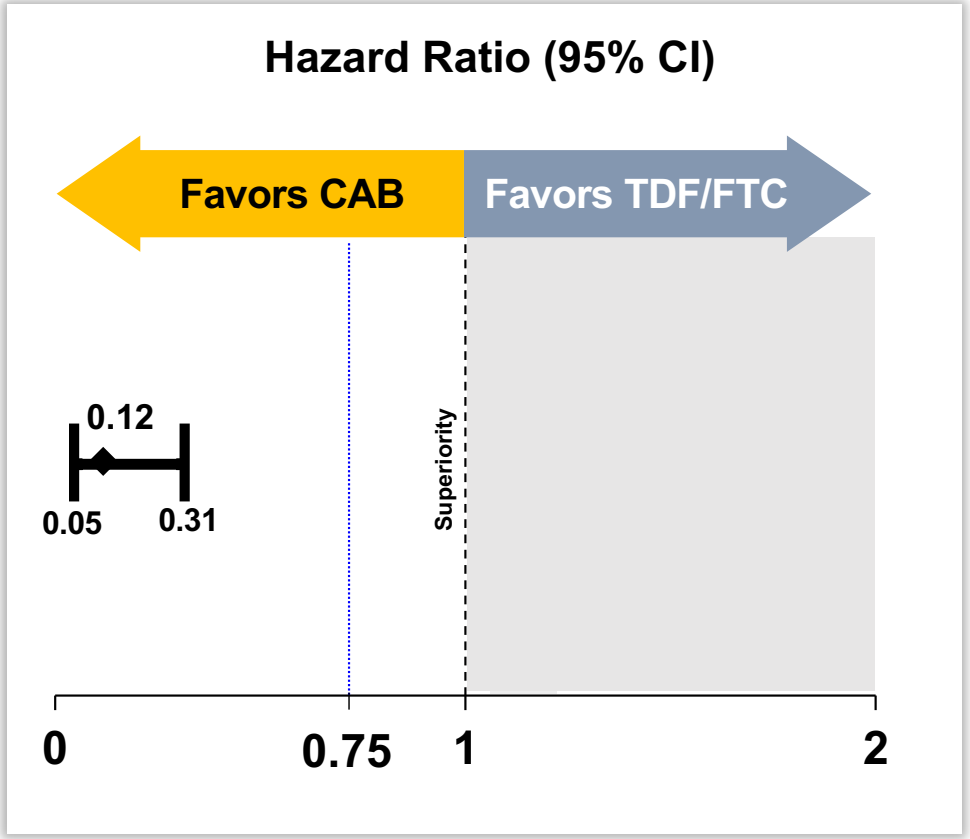


Landovitz, R. HIV Glasgow 2022.

HPTN 084 HIV Incidence: CAB vs. TDF/FTC

Blinded period, through Nov 2020

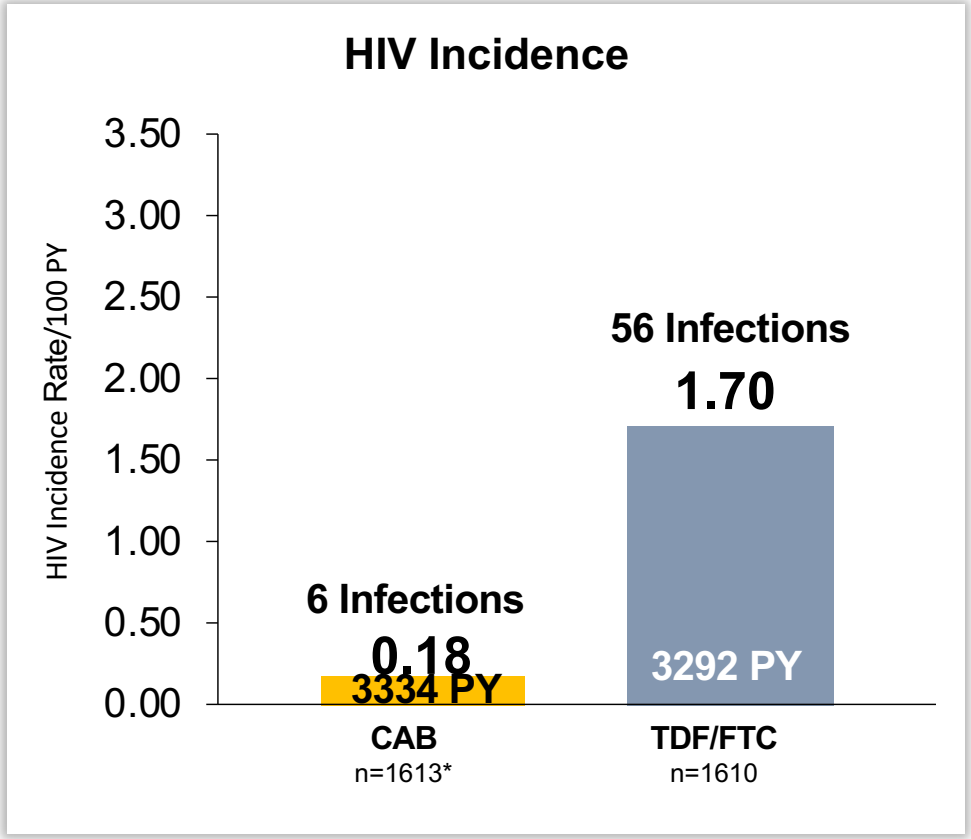


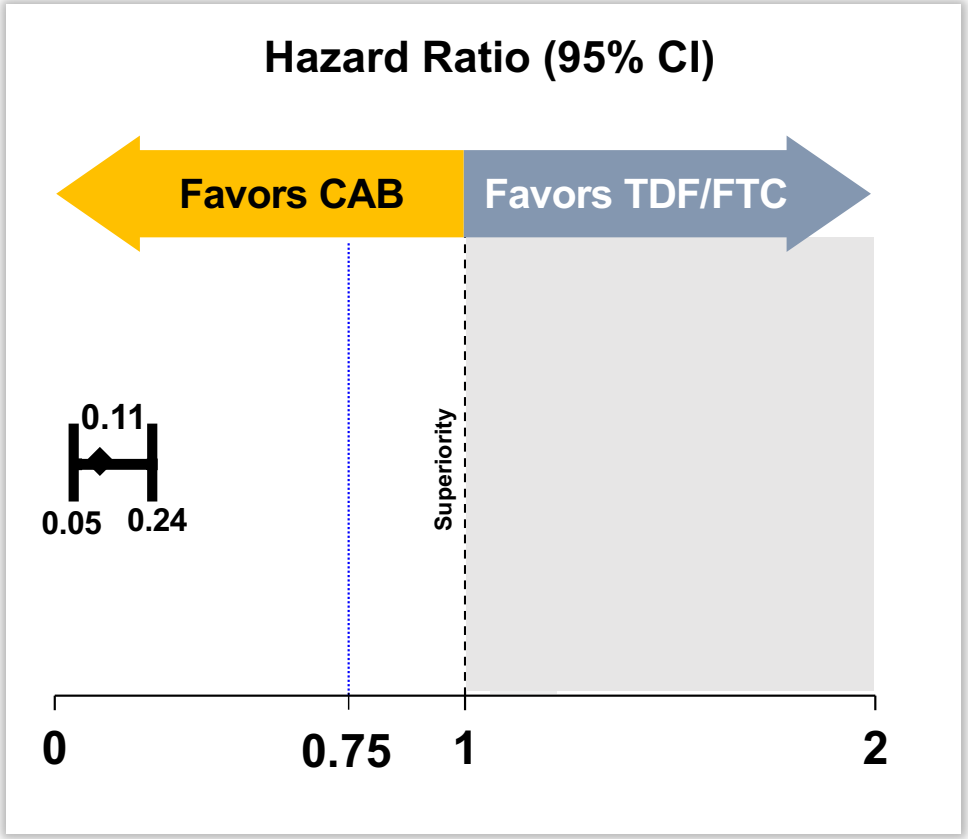


CI, confidence interval

HPTN 084 HIV Incidence: CAB vs. TDF/FTC

Combined blinded and unblinded period, through Dec 2021





CI, confidence interval

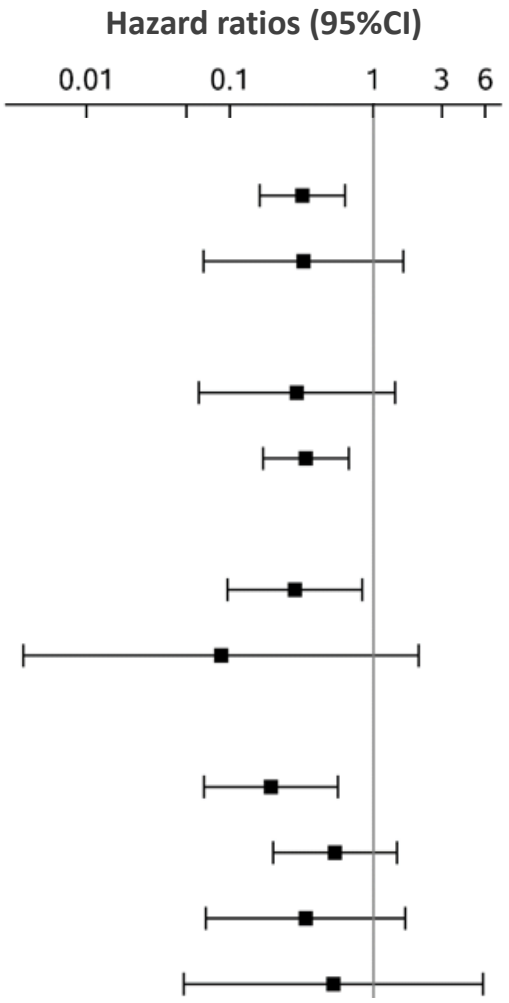
*Excludes 1 baseline infection from the blinded period

The Bottom Line: Efficacy

- Long-acting cabotegravir is very effective at preventing HIV in MSM, TGW, and cisgender women
  - 66% reduction in HIV infection when compared to MSM and TGW who were offered TDF/FTC
  - 89% reduction in HIV infection when compared to cisgender women who were offered TDF/FTC

HPTN 083 HIV Incidence by Subgroup CAB vs. TDF/FTC

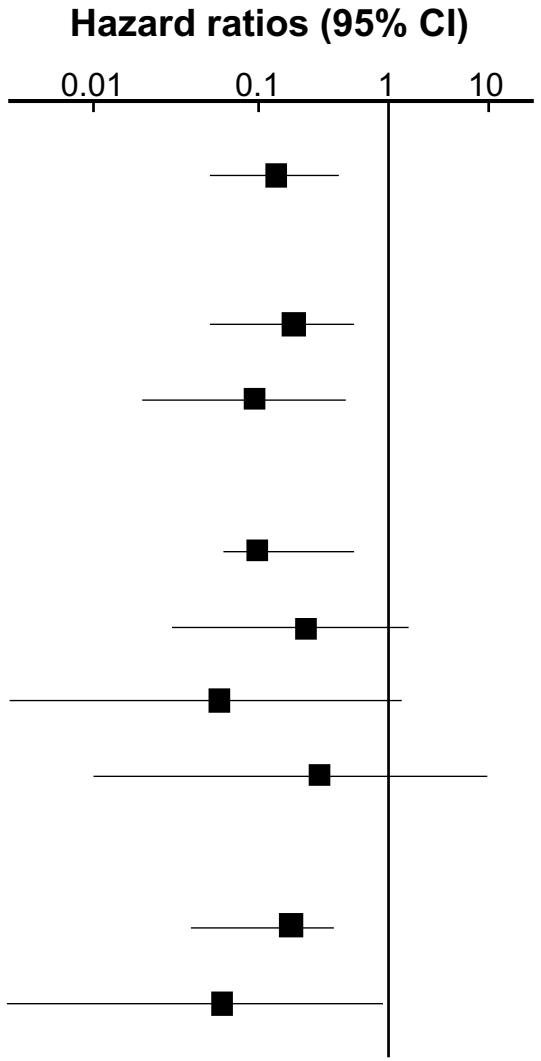
Subgroup	CAB Events/PY (IR%)	TDF/FTC Events/PY (IR%)	HR (95%CI)
Age			
≤30	11/2185 (0.50)	33/2114 (1.56)	0.32 (0.16, 0.63)
>30	2/1016 (0.20)	6/1071 (0.56)	0.33(0.07, 1.61)
Cohort			
TGW	2/368 (0.54)	7/383 (1.83)	0.29 (0.06, 1.41)
MSM	11/2829 (0.39)	32/2800 (1.14)	0.34 (0.17, 0.67)
Race			
Black/African-American	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)



Grinsztejn, B. AIDS 2022. #12707

HPTN 084 HIV Incidence by Subgroup CAB vs. TDF/FTC

Subgroup	CAB Events/PY (IR%)	TDF/FTC Events/PY (IR%)	HR (95%)
Overall	4/1956 (0·20%)	36/1942 (1·85%)	0·12 (0·05–0·31)
Age			
<25 years	3/866 (0·35%)	20/851 (2·34%)	0·17 (0·05–0·54)
≥25 years	1/1090 (0·09%)	16/1091 (1·47%)	0·09 (0·02–0·49)
Contraceptive Method			
DMPA	3/1009 (0·30%)	21/1000 (2·10%)	0·16 (0·05–0·53)
NET-EN	1/175 (0·57%)	6/182 (3·30%)	0·22 (0·03–1·48)
Implant	0	8/607 (1·32%)	0·06 (0·00–1·16)
Other	0	1/152 (0·66%)	0·32 (0·01–9·89)
BMI			
≤30 kg/m^2	4/1389 (0·29%)	27/1447 (1·87%)	0·16 (0·06–0·45)
>30 kg/m^2	0	9/495 (1·82%)	0·05 (0·00–0·96)



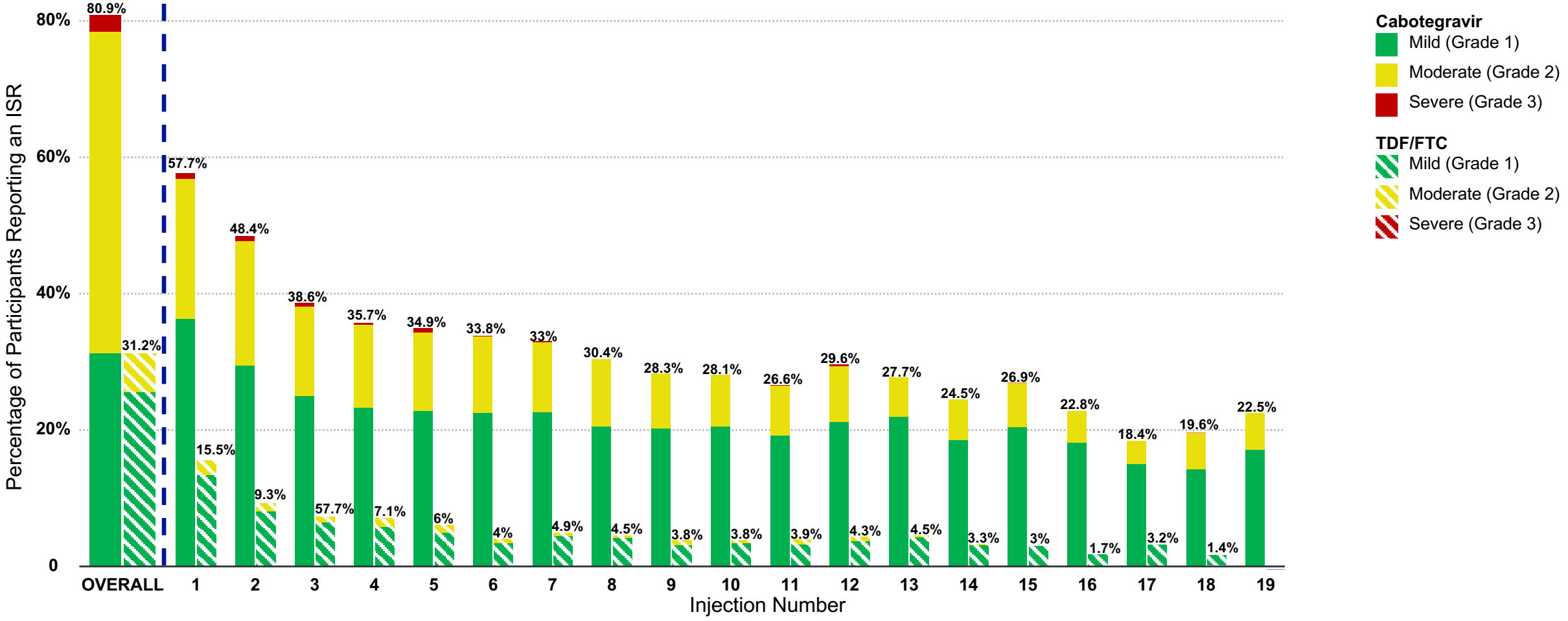
Delany-Moretlwe, S et al. Lancet. 2022.

The Bottom Line: Efficacy in specific populations

- Long-acting cabotegravir is also very effective at preventing HIV in:
  - Young individuals
  - Black individuals
  - Transgender women
  - Individuals from various regions of the world
  - Individuals using various contraceptive methods
  - Individuals with higher BMIs

SAFETY

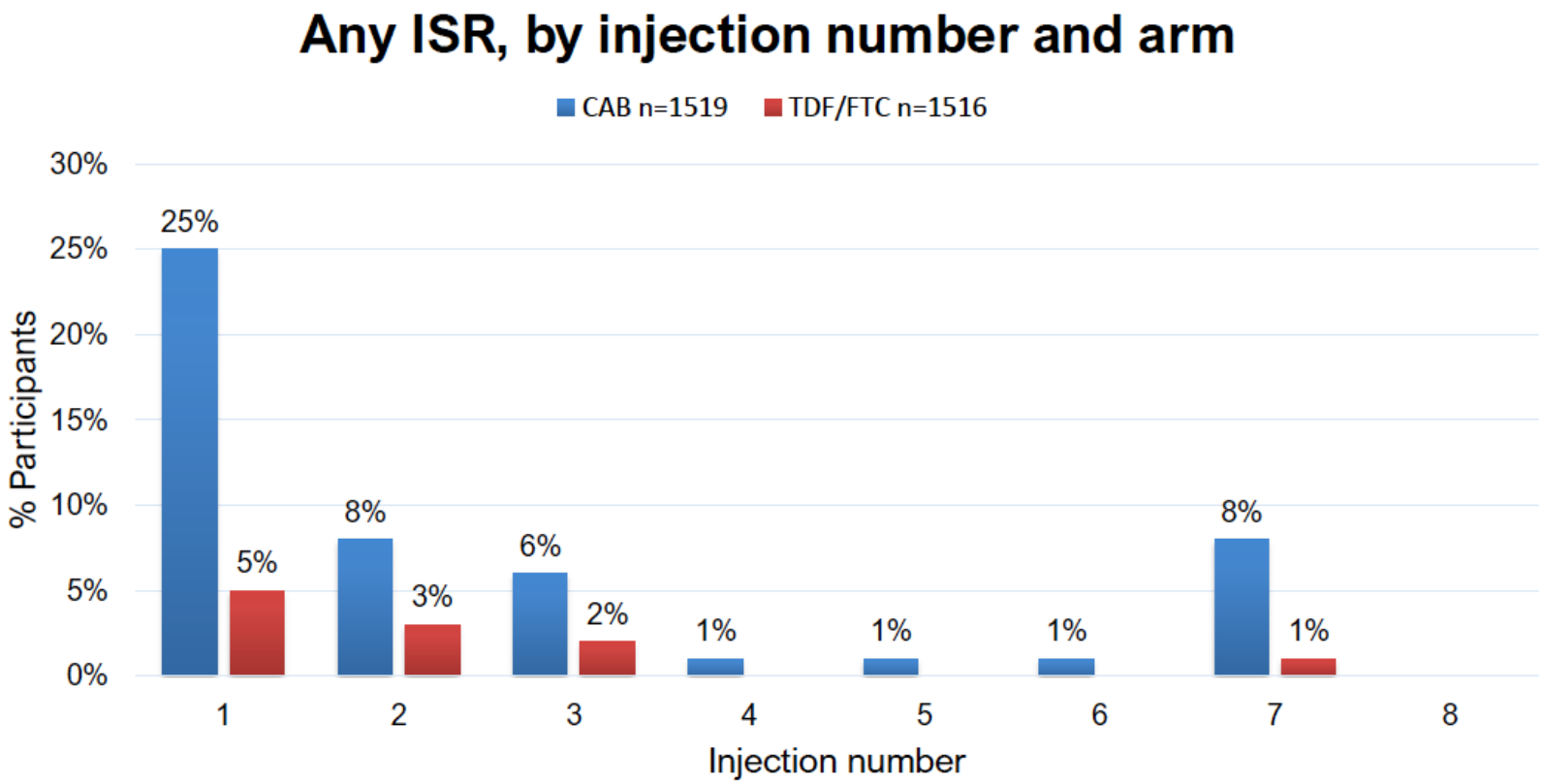
HPTN 083: Injection Site Reactions



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

Landovitz RJ et al. NEJM 2021

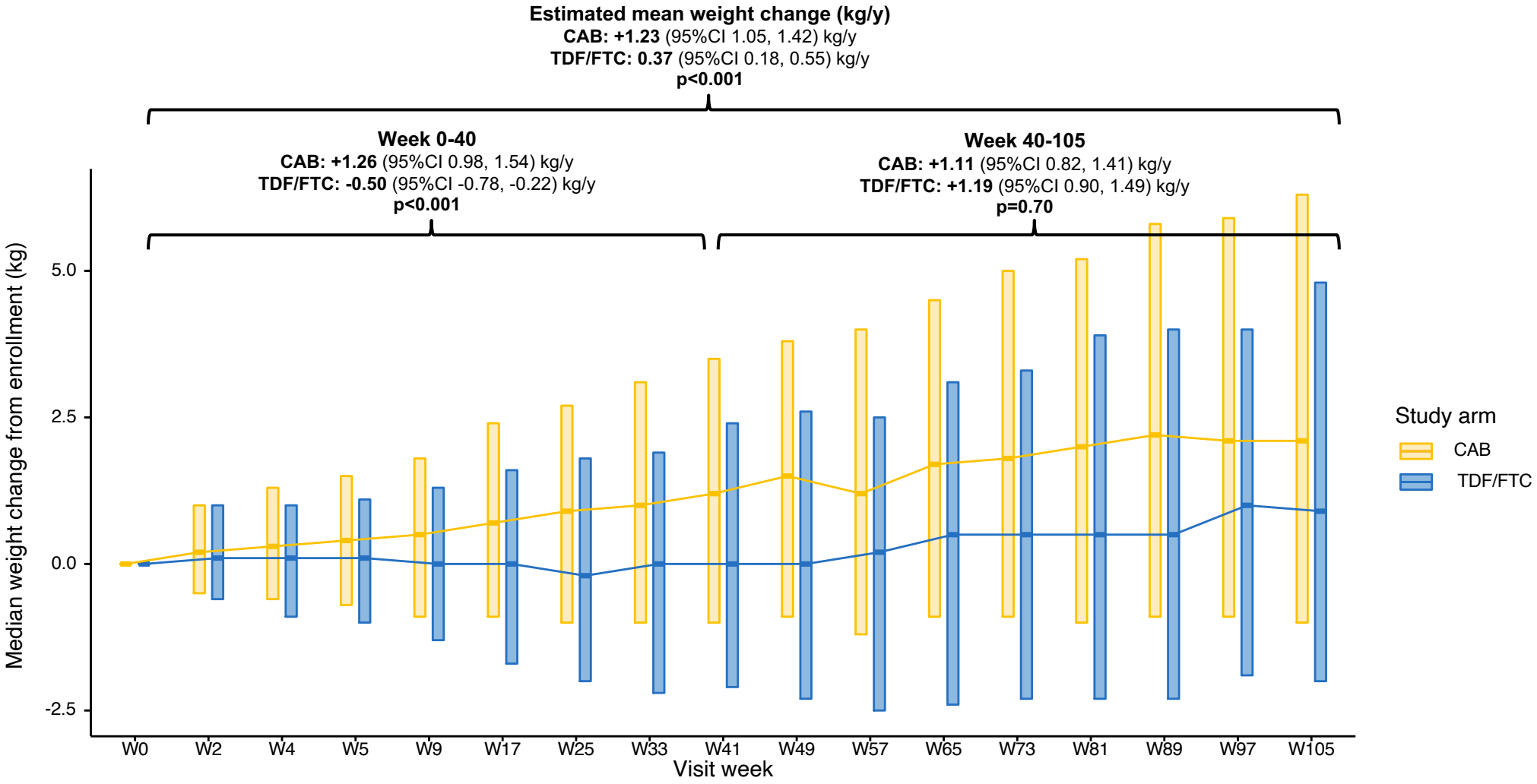
HPTN 084: Injection Site Reactions



- 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

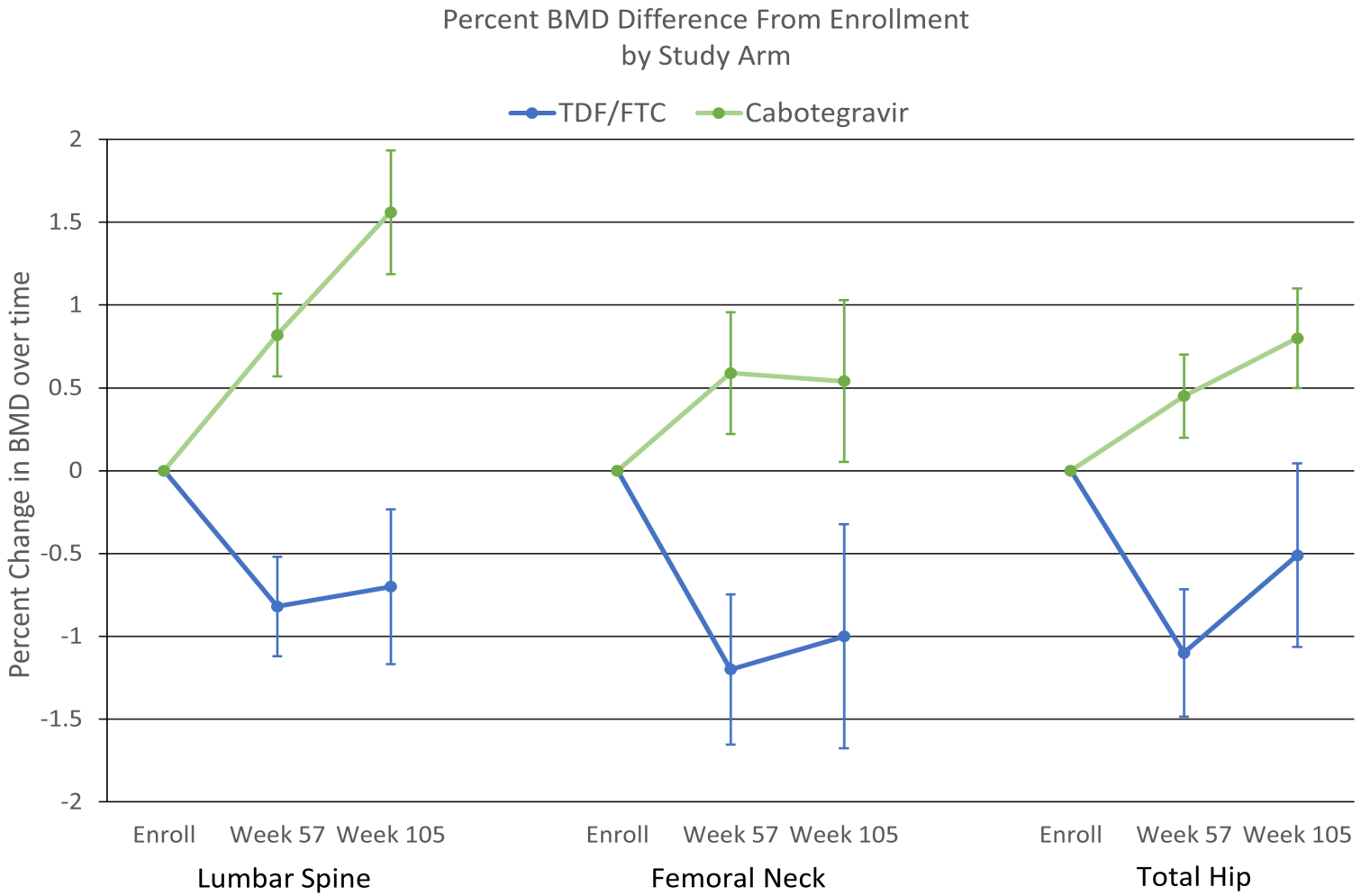
Delany-Moretlwe, S. HIV R4P 2021. #LB1479

HPTN 083: Median Change in Weight (kg)



Landovitz RJ et al. NEJM 2021

HPTN 083: DXA BMD change over time



- BMD decreased in the TDF-FTC arm by 0.5-1.0%
- BMD increased in CAB-LA arm 0.5-1.5%

Brown T et al. CROI 2023. Poster #987.

The Bottom Line: Safety

- Long-acting cabotegravir was safe and well tolerated
- The most common side effect was injection site reaction (ISR)
  - The majority were mild to moderate in severity
  - Reports of ISRs decreased over time
  - Very few ISRs led to the discontinuation of cabotegravir
- We're all gaining weight, people on CAB-LA and TDF/FTC at about the same rate EXCEPT for the first year, where TDF/FTC people LOST weight (but then gained thereafter)
- By DXA measurement, CAB-LA had better outcomes than TDF-FTC over two years; no clinical differences

HPTN 084 Cumulative Pregnancy Outcomes CAB vs. TDF/FTC

	Total n=132	CAB n=63	TDF/FTC n=69
Ongoing	57	23	34
Known pregnancy outcomes*			
Live births	61	31	30
Pregnancy loss			
≥37 weeks	0	0	0
20-36 weeks	3	1	2
<20 weeks**	13	9	4
Congenital anomalies	0	0	0

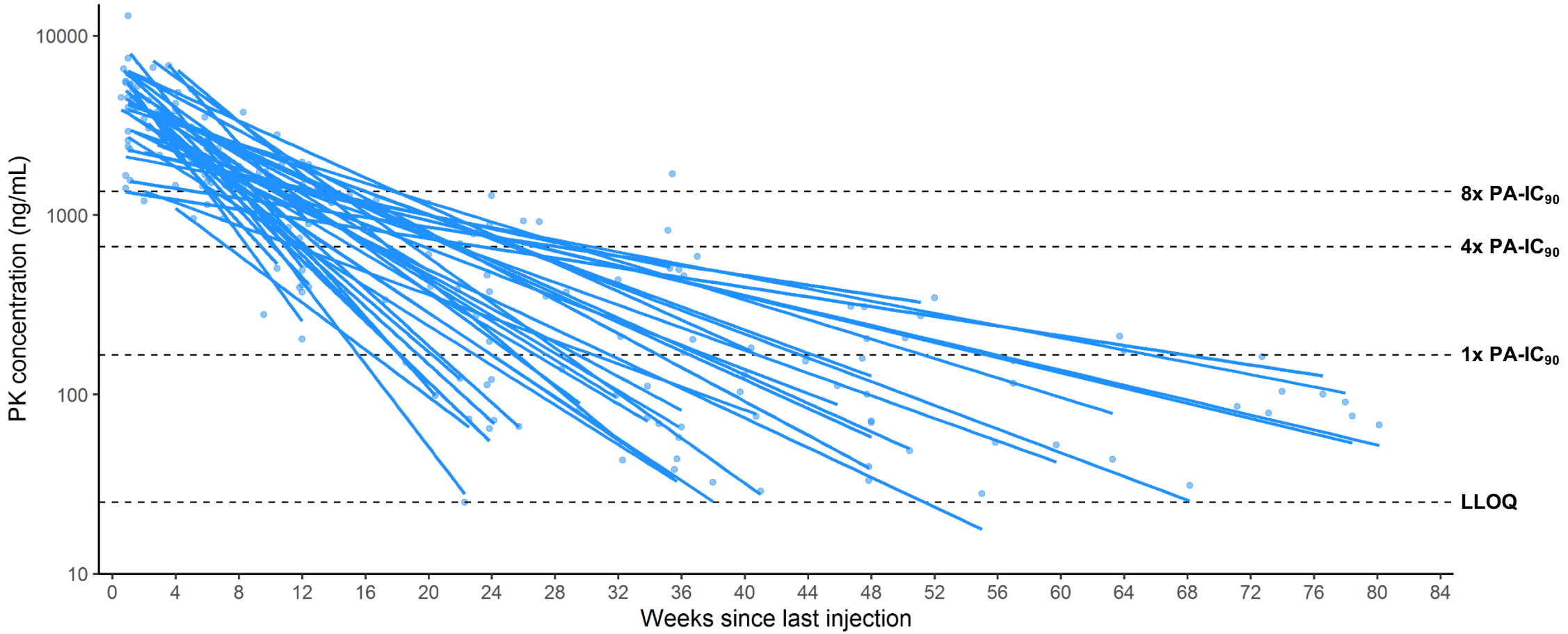
**includes multiple births*
***includes ectopic pregnancy, elective and spontaneous abortion*

The Bottom Line: Pregnancy

- Data are still being collected on the safety of cabotegravir during pregnancy and breastfeeding
- To date, data does not suggest there are any safety concerns

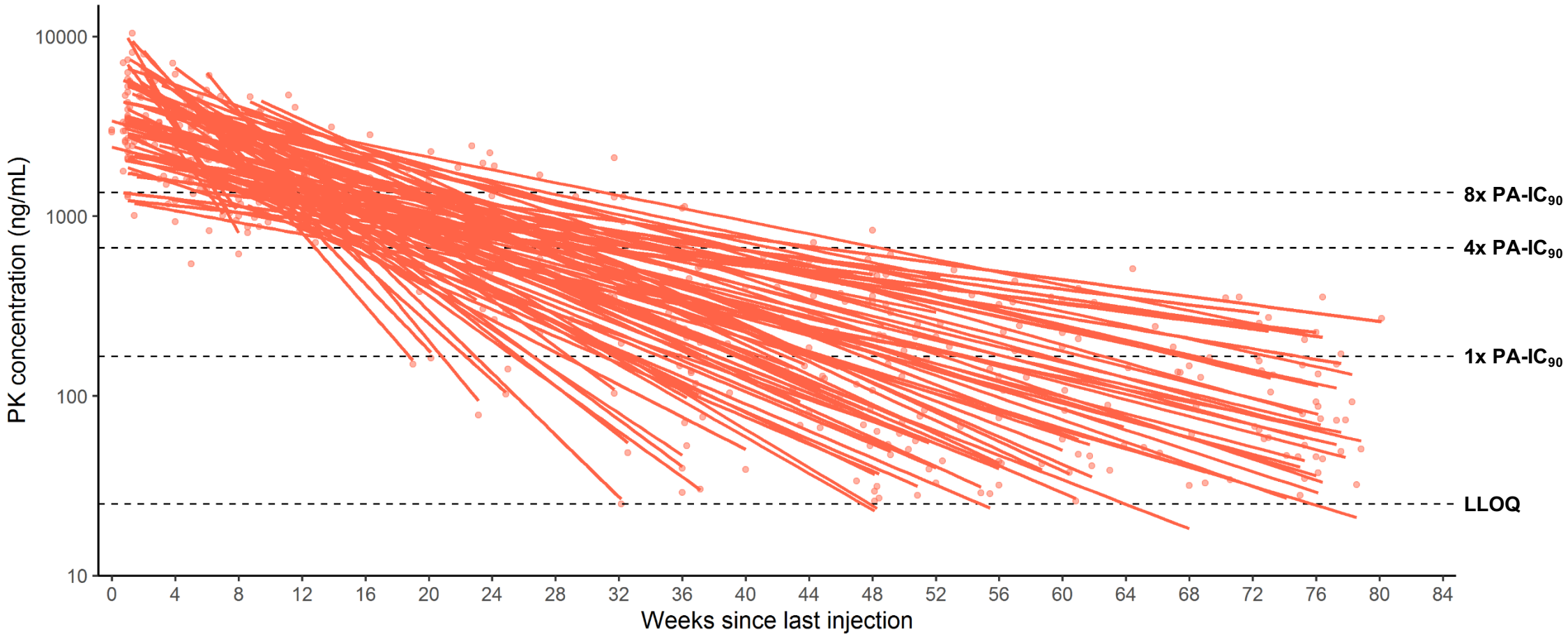
PHARMACOKINETICS (That's a Fancy word for 'drug levels')

CAB Subsequent to Final Injection (Log Scale)
Males



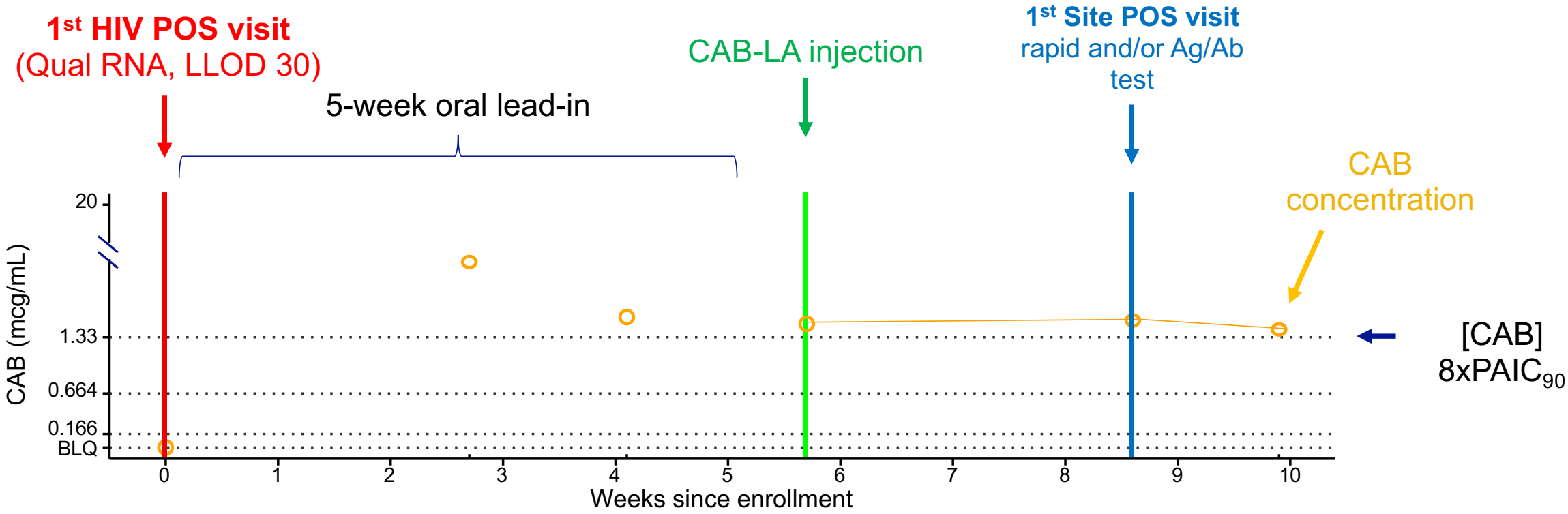
Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

CAB Subsequent to Final Injection (Log Scale)
Females

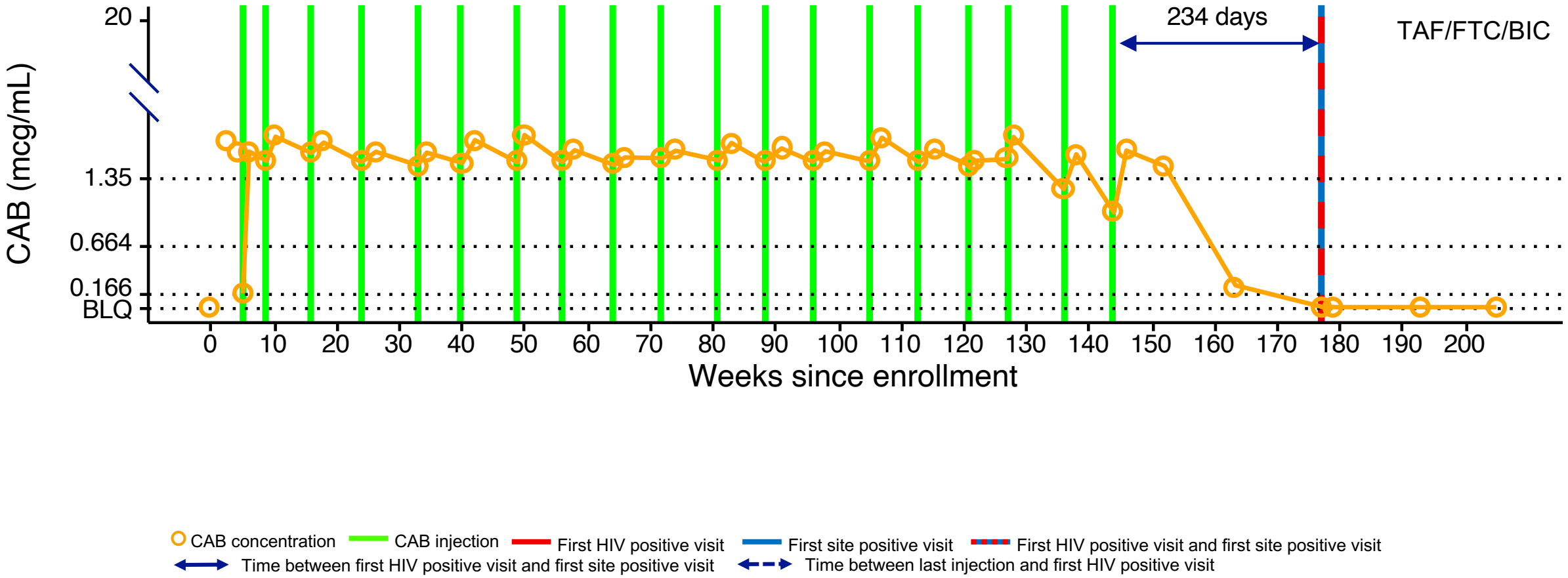


Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

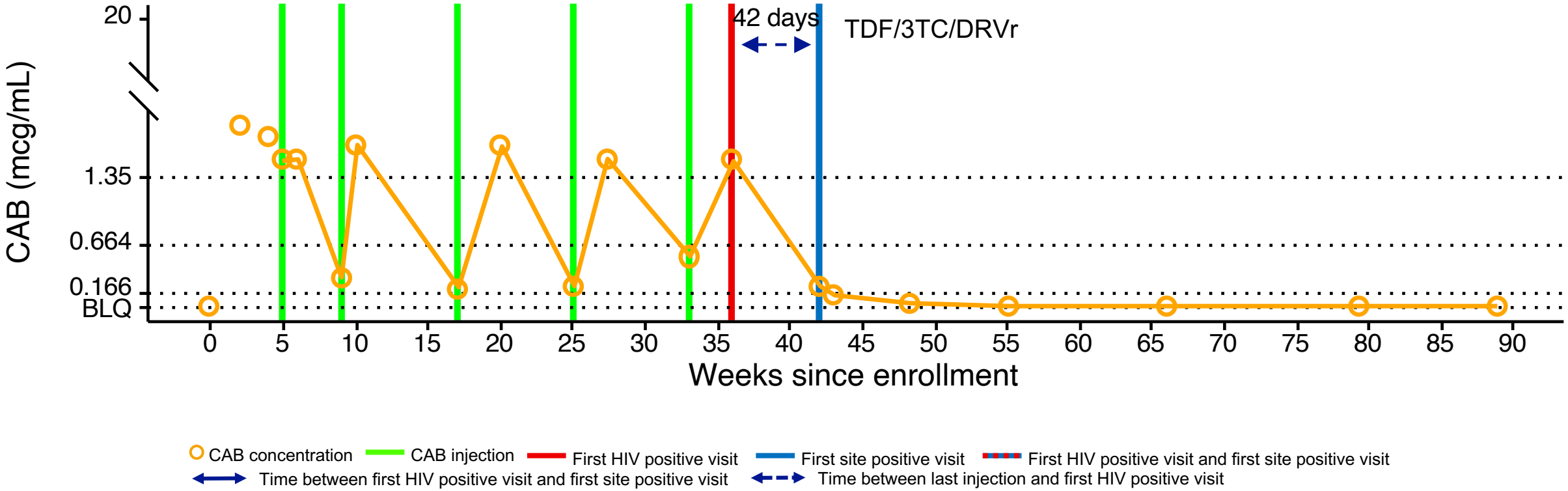
Schematic for Seroconversions



Expected Pattern of CAB Concentrations



Fast Elimination – One case so far



The Bottom Line:
Pharmacokinetics in Men and Women

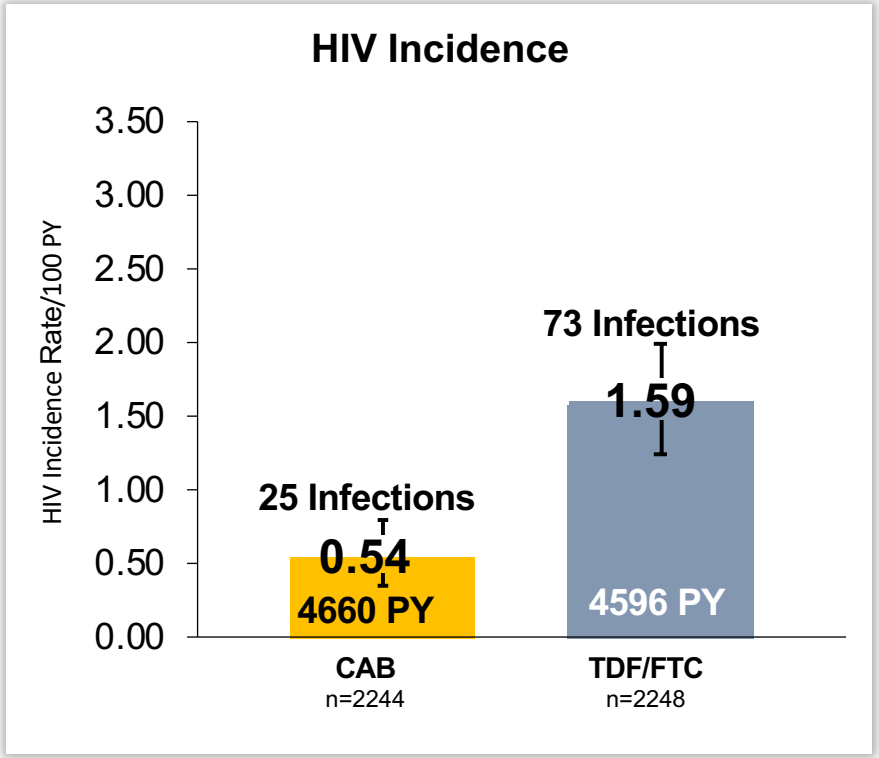
- **People born male**: the median time from the last injection to the time when CAB concentration fell below the LLOQ was 10.1 Months
- **People born female**: the median time from the last injection to the time when CAB concentration fell below the LLOQ was 1 year and 3.5 months
- Higher BMI associated with more prolonged period of exposure
- Rapid concentration decay in rare participants remains to be fully explained but likely is not a genetic “fast metabolizer” abnormality

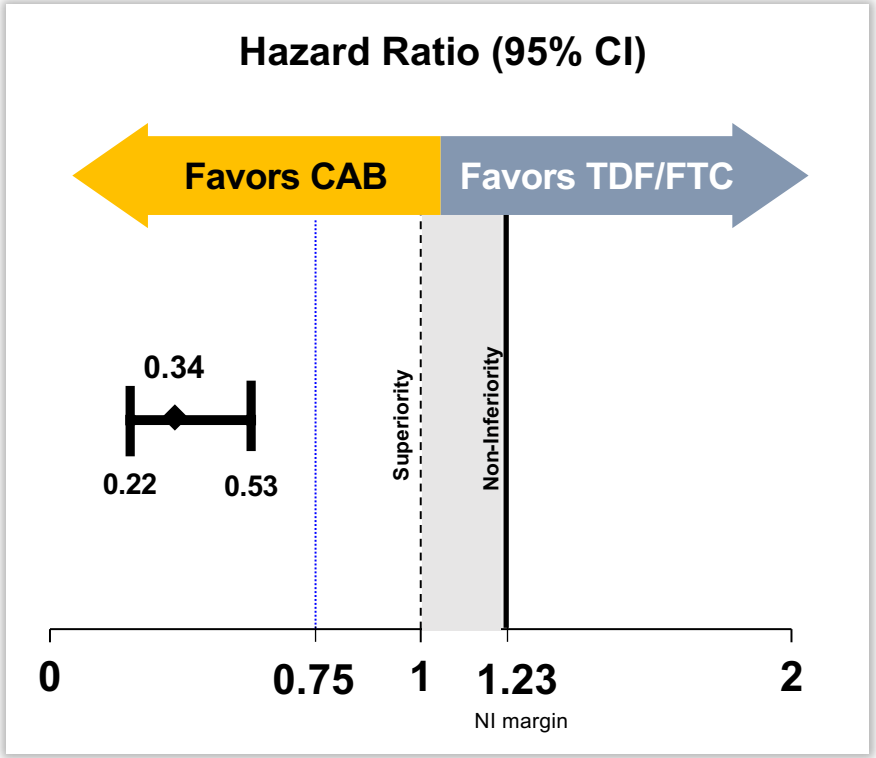
Landovitz, R. Lancet HIV. 2020.

FAILURES

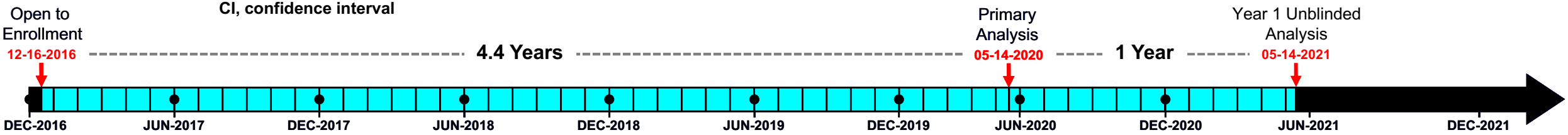
REMINDER: BOTH PrEP MEDICATIONS WORK *EXTREMELY* WELL

Combined blinded and unblinded period, through May 2021





CI, confidence interval



Landovitz, R. HIV Glasgow 2022.

FAILURE GROUPS IN HPTN 083

- **Group A cases:** HIV acquired at enrollment
- **Group B cases:** HIV acquired w/o recent CAB exposure
- **Group BR cases:** HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
- **Group C cases:** HIV acquired during oral lead-in
- **Group D cases:** HIV acquired in the setting of on-time CAB injections
- **Group DX cases:** HIV acquired while on CAB with at least one 10-week delayed injection

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CAB arm, Group A

What we learned:

- **If we do not diagnose HIV before PrEP agents start (acute or eclipse phase infection = very early infection), CAB can make it challenging to diagnose later**
- **Failure to diagnose HIV infection can lead to continued CAB administration, and even continued CAB injections**

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CAB arm, Group B & BR

What we learned:

- **If you don't take CAB, it doesn't prevent HIV infection**
- **In 3 participants, exposure and HIV acquisition during the "tail" did not result in CAB resistance**
  - **This is reassuring, but DOES NOT RULE OUT THAT IT CAN HAPPEN WE NEED MORE DATA**
  - **When CAB is restarted after prolonged hiatus, failure to diagnose interim newly acquired HIV can lead to INSTI resistance, much as "A" cases can**
- **When people were provided open-label TDF/FTC to "cover they tail" they did not take it – this likely contributed to HIV acquisition**

FAILURE GROUPS IN HPTN 083

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CAB arm, Group C

What we learned:

- If you don't take CAB, it doesn't prevent HIV infection
  - We don't know how "forgiving" it is to missed doses
- There is likely a "time to onset" of protection with oral CAB
  - We don't know how long
- If CAB delays new (incident) HIV detection by delaying testing, CAB injections can inadvertently be given
- As with the "A" Cases, viral "escape" at HIGH CAB levels can lead to CAB (and other integrase) resistance

FAILURE GROUPS IN HPTN 083

- **Group A cases:** HIV acquired at enrollment
- **Group B cases:** HIV acquired w/o recent CAB exposure
- **Group BR cases:** HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
- **Group C cases:** HIV acquired during oral lead-in
- **Group D cases:** HIV acquired in the setting of on-time CAB injections
- **Group DX cases:** HIV acquired while on CAB with at least one 10-week delayed injection

CAB arm, Group D & DX

What we learned:

- Delays in HIV tests detecting “new” HIV infections
- CAB levels in the blood were as expected
  - It wasn’t “unexpectedly” low concentrations of CAB that explain the PrEP failure
- If HIV “smolders” after a PrEP failure, it can lead to CAB (and other integrase) resistance
  - That resistance can be often avoided by earlier detection
- When delays occur, CAB levels can drop, losing protection – but not leading to INSTI resistance to-date

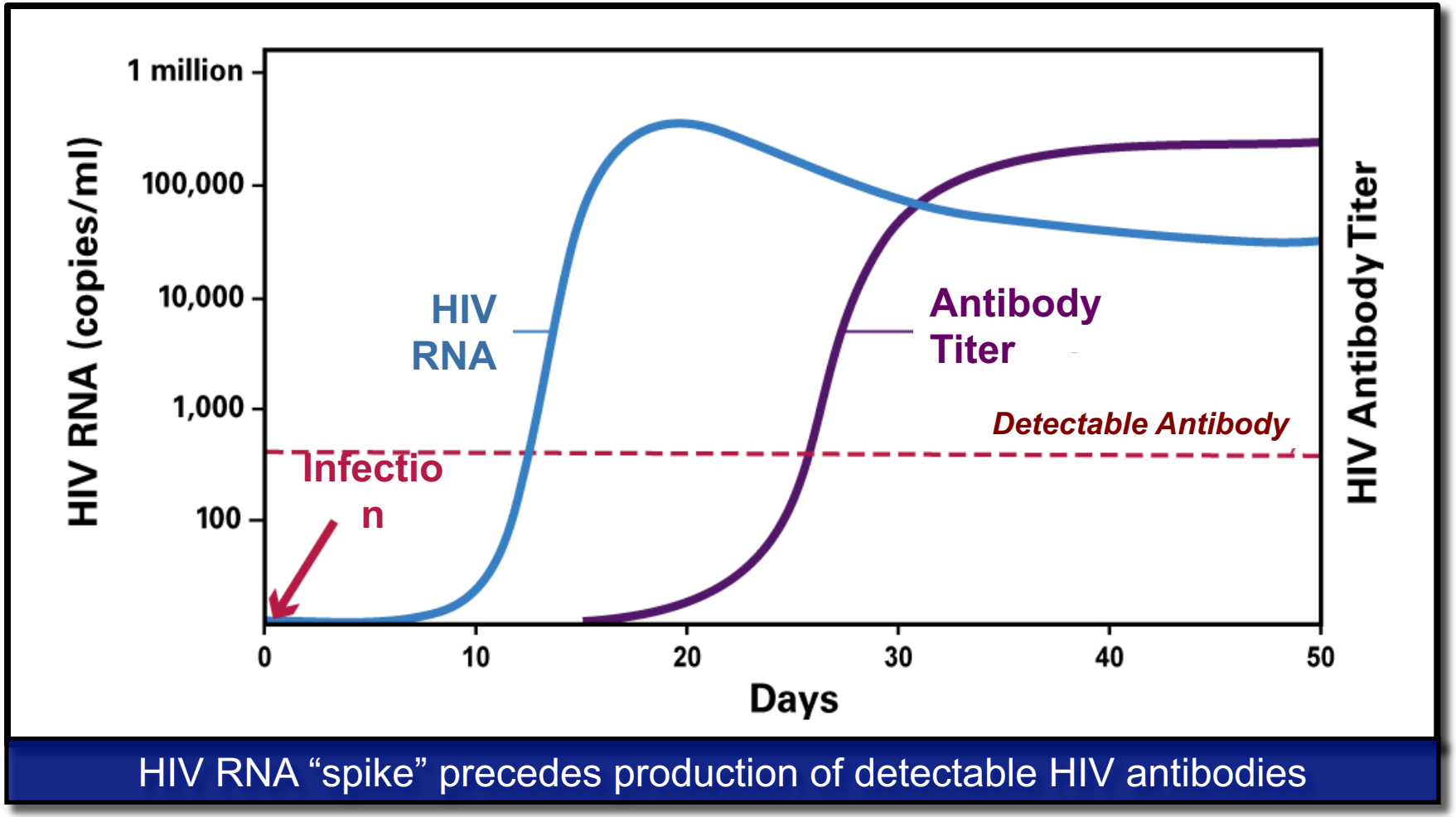
Bottom Line: Summary of HPTN 083 resistance

	N (%)	Integrase Resistance
CAB INITIATED OR RE-INITIATED WITH OCCULT HIV INFECTION		
Initiated	1 (25)	Yes
Restarted	1 (50)	Yes
HIV ACQUISITION DURING OLI		
During OLI	2 (66)	Yes
HIV BREAKTHROUGH INFECTION WITH ON-TIME INJECTIONS		
On-time failure	6 (100)	Yes
HIV BREAKTHROUGH INFECTION WITH AT LEAST ONE 10+ WEEK DELAY		
≥1 delay	0 (0)	No
HIV INFECTION 6+ MONTHS FROM LAST INJECTION		
Tail-phase*	0 (0)	No

*No result for one case

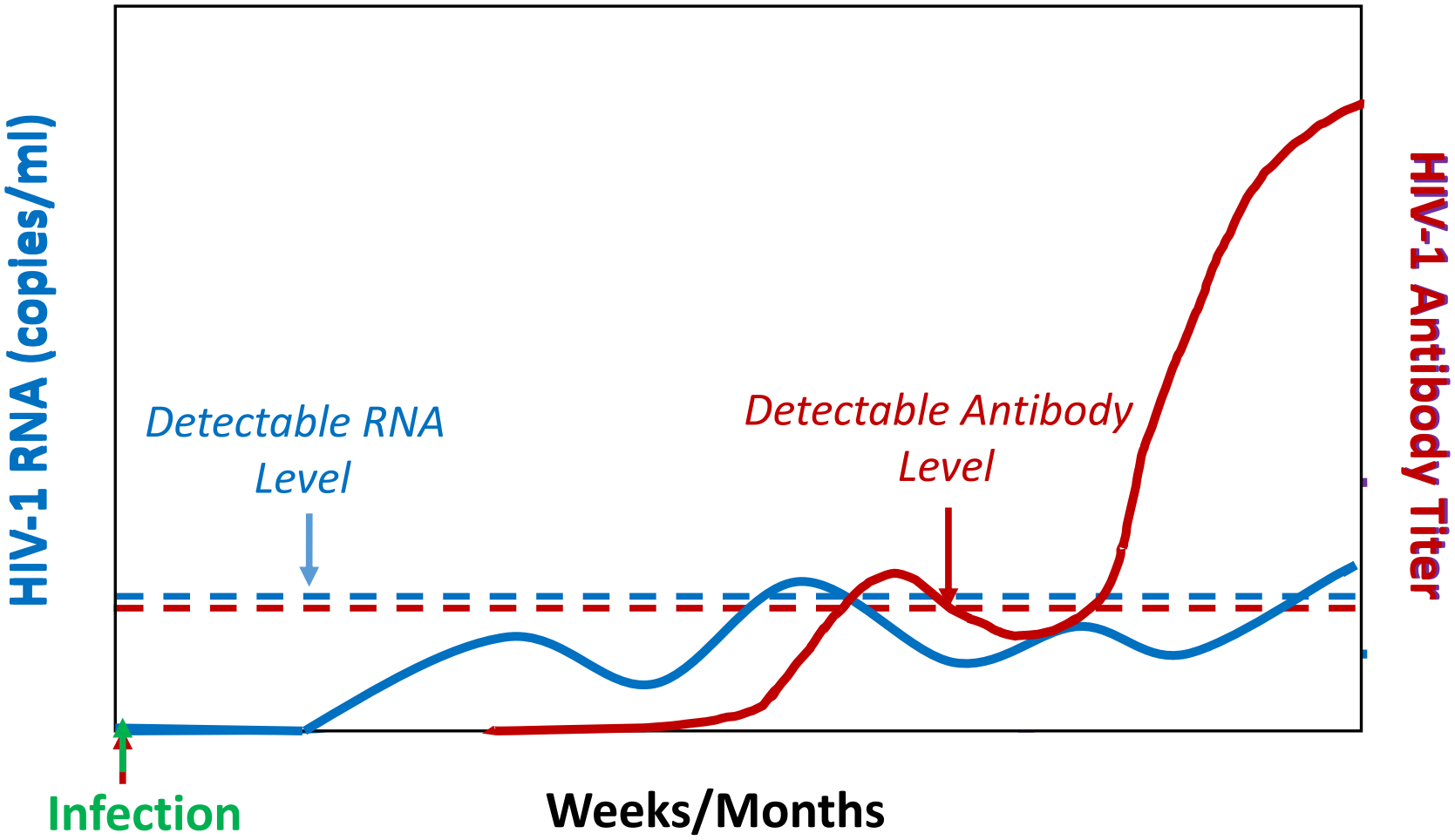
TESTING DELAYS

Diagnosing Acute HIV



HIV RNA "spike" precedes production of detectable HIV antibodies

Diagnosing Acute HIV



The Bottom Line:
Testing Delays

- RNA testing finds infections earlier, but is costly, may not be feasible in many settings, and may confuse patients and providers
  - This is being explored in HPTN 083 and 084 OLE'
- No delays seen in MSM/TGW when infection is acquired > 6 months after last injection
  - Likely a longer timeline for ciswomen/TGM

CLINICAL USE and IMPLEMENTATION

Making Good Decisions Absent Good Data

What to start?

- Whatever the patient will adhere/persist with best
- There is no ethical/moral “obligation” to use CAB

Onset of protection?

- PK suggests time from first injection (irrespective of OLI) to 8x PA-IC90 is median 2 days, 95% by 7 days
- Durability – incredibly interpatient variability (077 data), likely varies by sex (maybe BMI), wouldn’t assume more than 9-10 weeks for males, 12+ for females

Breakthroughs (nee: failures)

- Poorly understood to date
- Salvage with NNRTI or r/PI if infection likely to have occurred within 1 year, DTG/BIC-based ART >1 year?

Implementation

- Do we have the global, social, and political will to figure out how to use it?

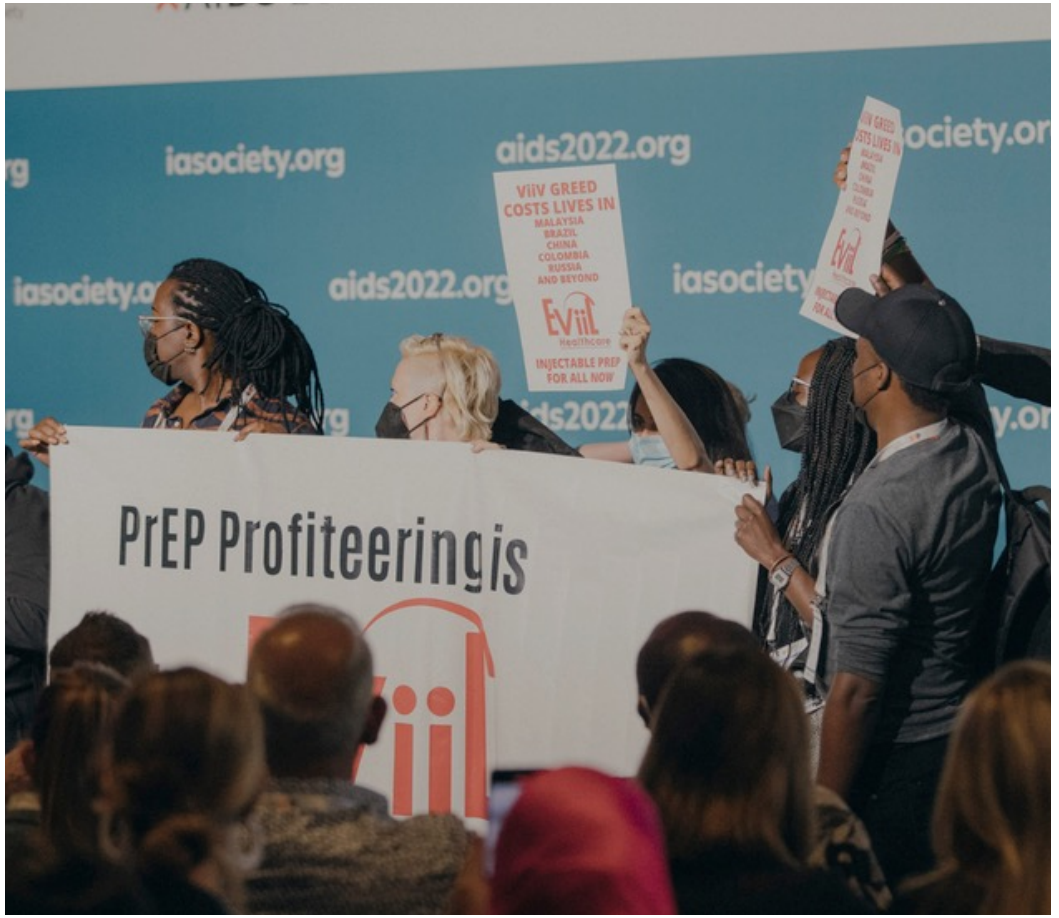
Can CAB be given at other anatomic sites?

- 118 participants enrolled in a ATLAS-2M substudy to evaluate the pharmacokinetics, safety, tolerability, and efficacy of CAB+RPV LA following short-term repeat IM thigh administration
- Across 704 thigh injections, 327 injection site reactions occurred
  - Most were Grade 1 (55–76%) or 2 (19–38%)
  - 4–7% were grade 3
- The median duration of ISRs was 3–3.5 days
- One Grade 2 ISR led to withdrawal
- Only 28–33% preferred thigh injections
  - This was largely due to ease of access

Felizarta, F et al. CROI 2023. Poster Session-H1.

How will it be paid for?

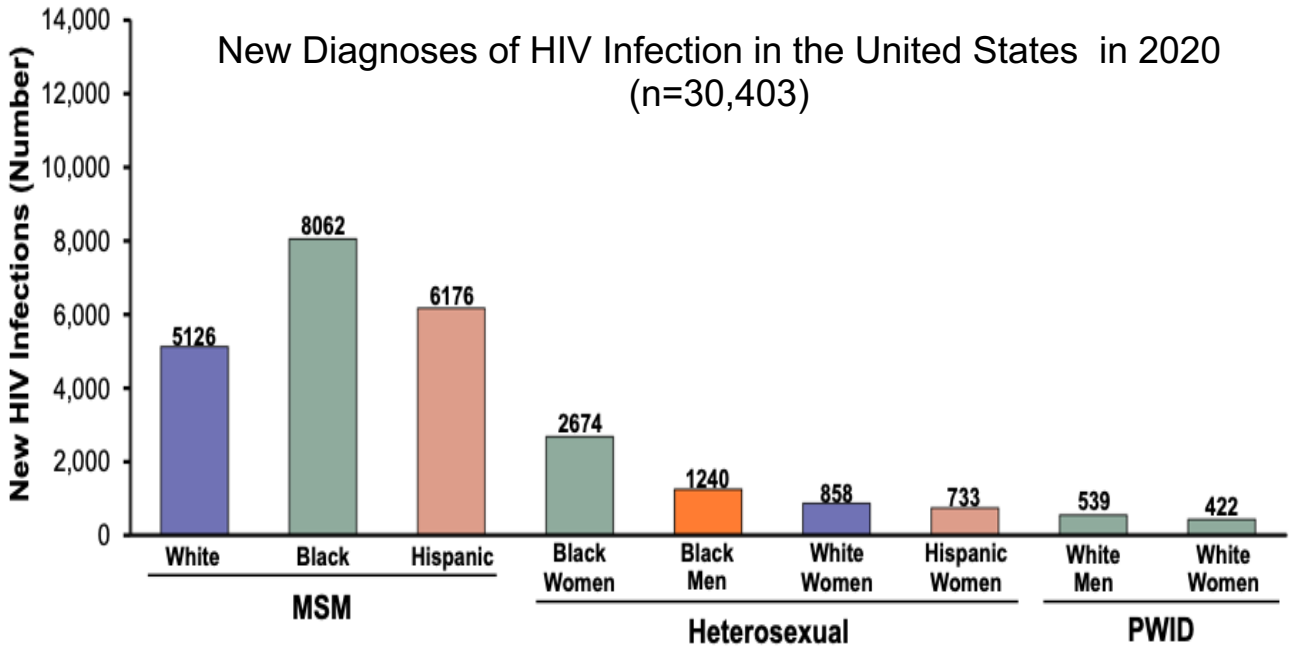
- Cabotegravir is currently priced at $22,200 per year
  - >185 times higher than the $60–$119 estimated cost-effectiveness threshold for middle-income countries (MICs)
- ViiV recently provided access to generic versions in 90 countries with the Medicines Patent Pool (MPP), including all African nations
  - Not applicable to all LMICS

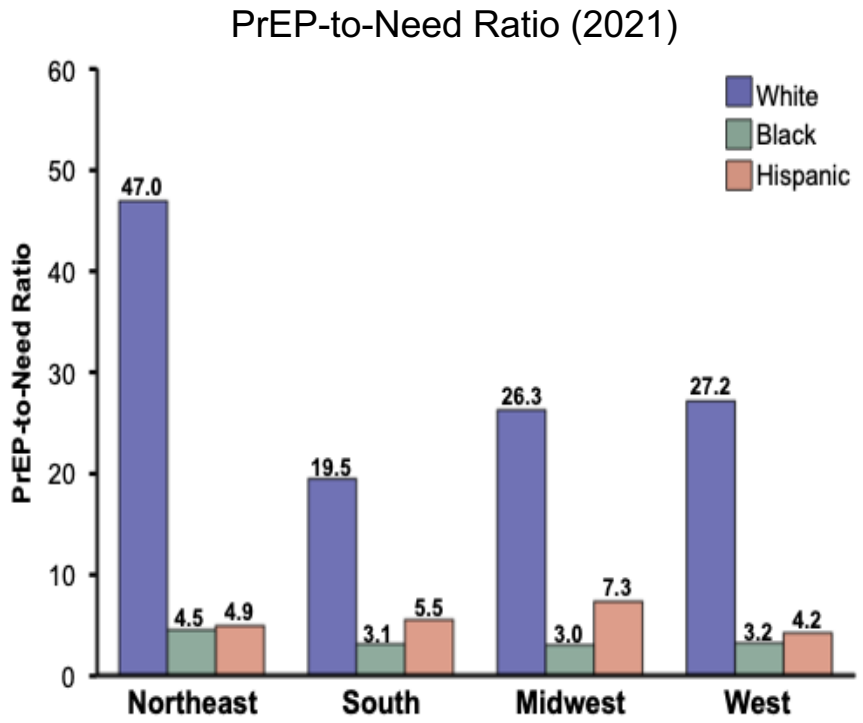


Pepperell T, et al. OFID. 2022.

Can we use it Equitably?

- **PrEP-to-need ratio**
  - Number of PrEP users divided by the number of new HIV diagnoses in that group in the same year
  - Equity metric, no "target" level
- **US prevention programs in all regions have demonstrated larger gaps in PrEP-to-need ratios by race/ethnicity**
  - Southern states lagged all other regions
- **Better programs are needed to provide PrEP to communities and people at greatest risk for HIV infection**





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Concluding Thoughts

- Long-acting cabotegravir is **highly effective** for prevention of HIV in MSM, TGW, cisgender women and various subgroups
  - **So is Tenofovir-based oral PrEP**
- CAB is safe, generally well-tolerated, and data does not suggest there are safety concerns for use during pregnancy or breastfeeding
- The washout period after last CAB injection is longer in individuals born female compared to individuals born male
- RNA testing finds CAB breakthrough infections earlier, and often before resistance, but high cost and may not be feasible in many settings
- We need strong community advocacy to **demand** programmatic implication and rapid generic production to bring costs down
- If we don't **demand** focus on making available biomedical prevention programs to most-affected communities, disparities will only widen
  - This is UNACCEPTABLE

Thank you!

Questions?

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