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

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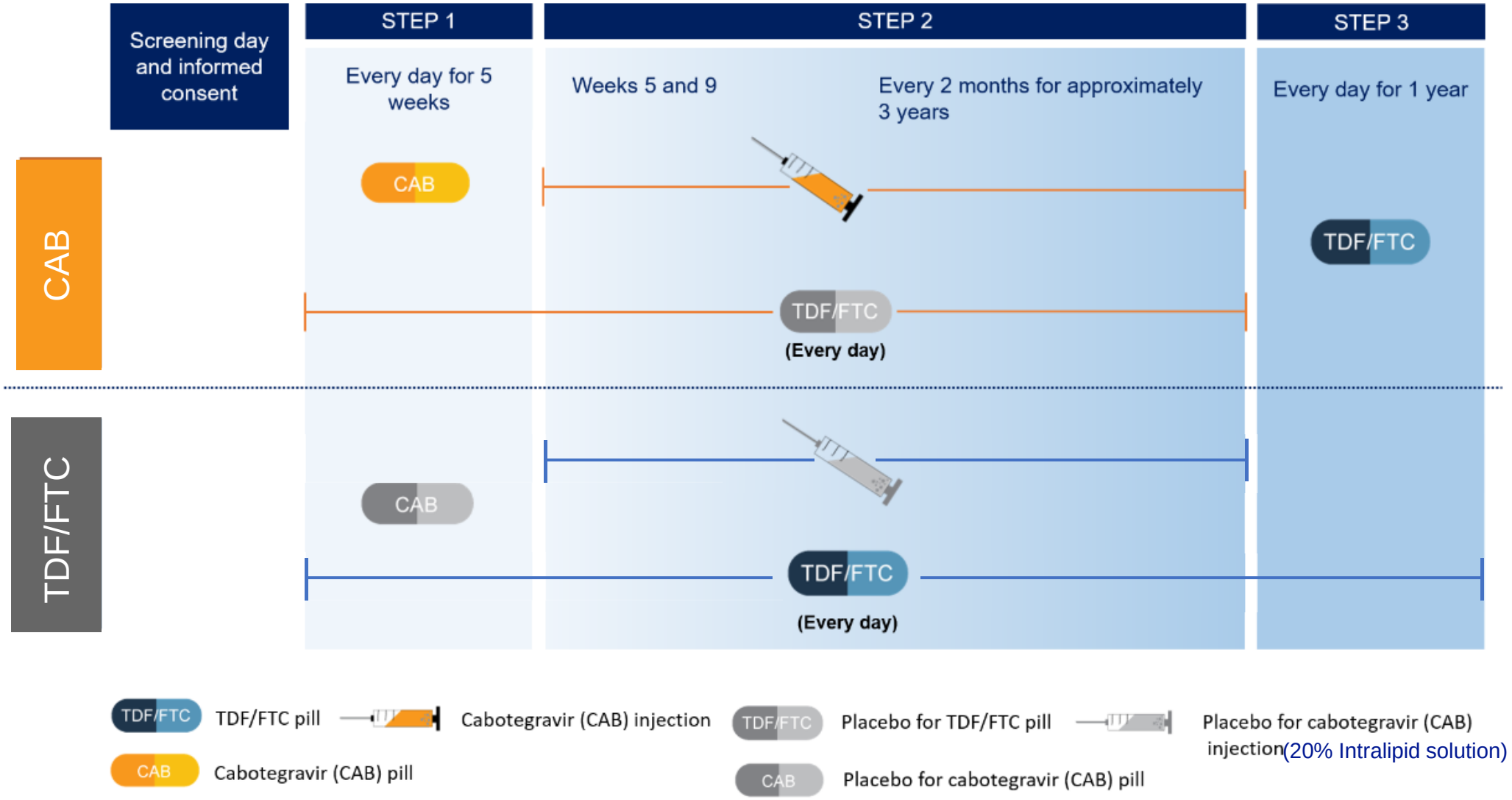
Equitable LAI PrEP Workshop, February 27, 2023

# Disclosure

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

# HPTN 083/084 Study Design

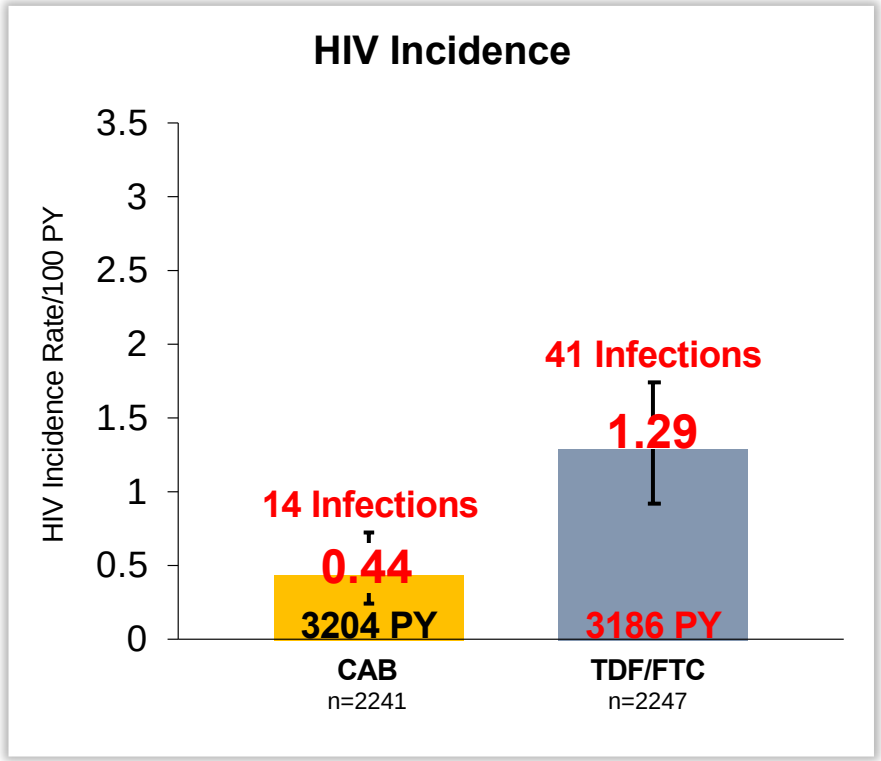


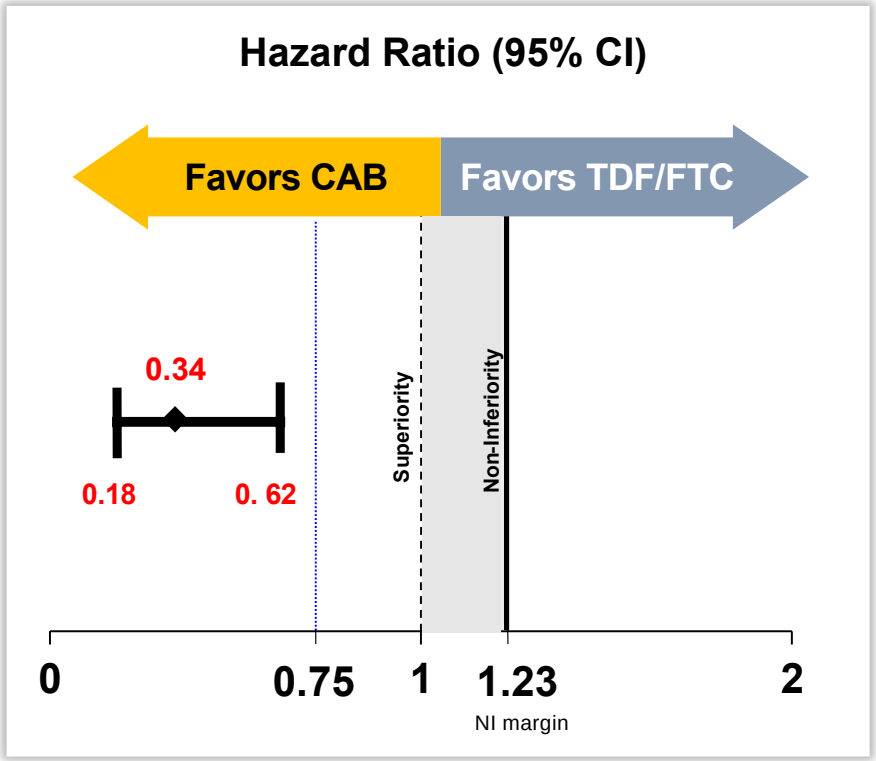

Landovitz RJ et al. AIDS 2020, #OAXLB0101

# EFFICACY

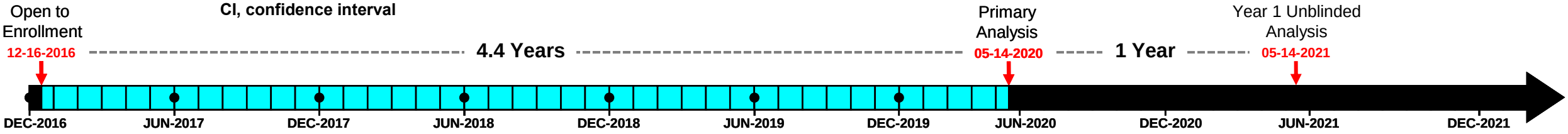
# HPTN 083 HIV Incidence: CAB vs. TDF/FTC

Primary blinded period, through May 2020



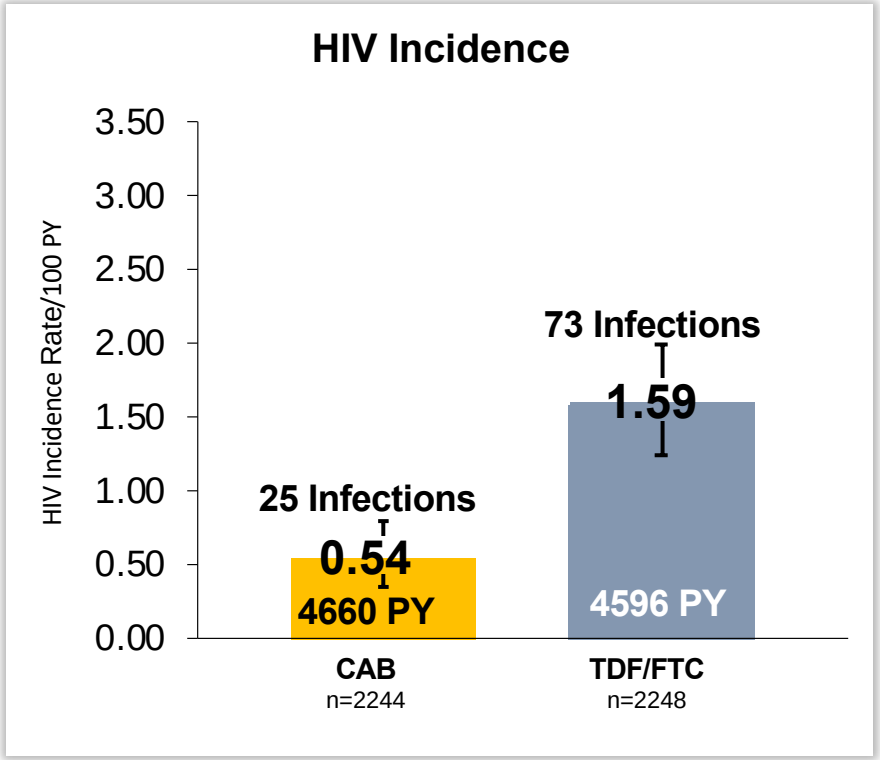

CI, confidence interval

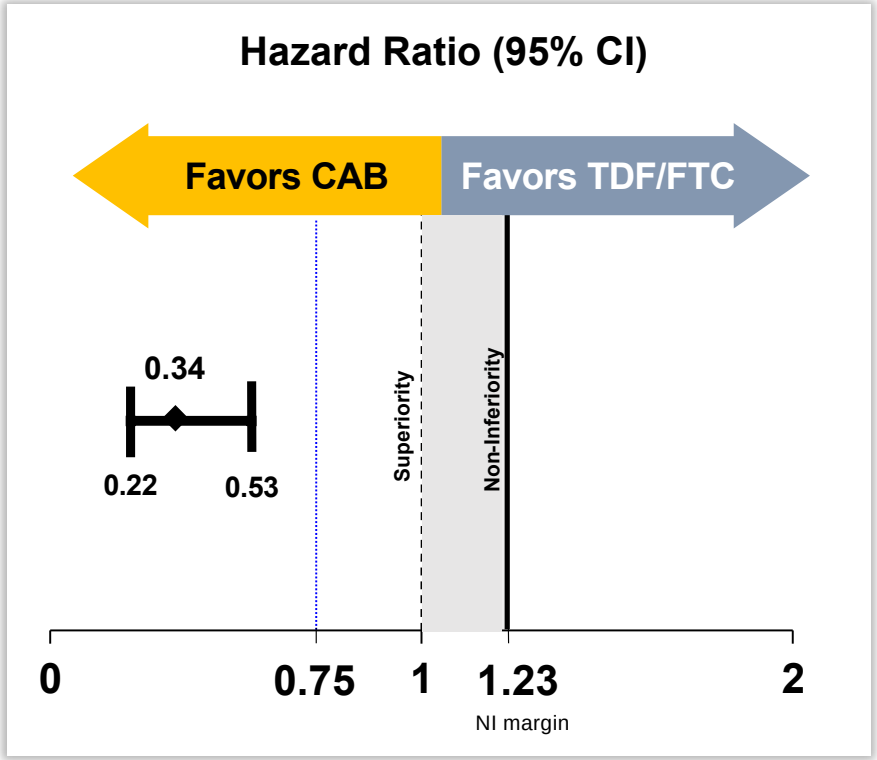



Landovitz, R. HIV Glasgow 2022.

# HPTN 083 HIV Incidence: CAB vs. TDF/FTC

Combined blinded and unblinded period, through May 2021

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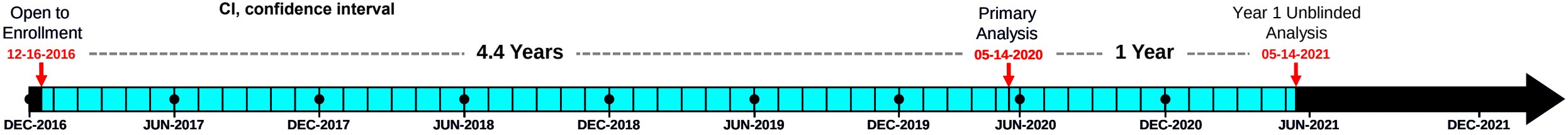
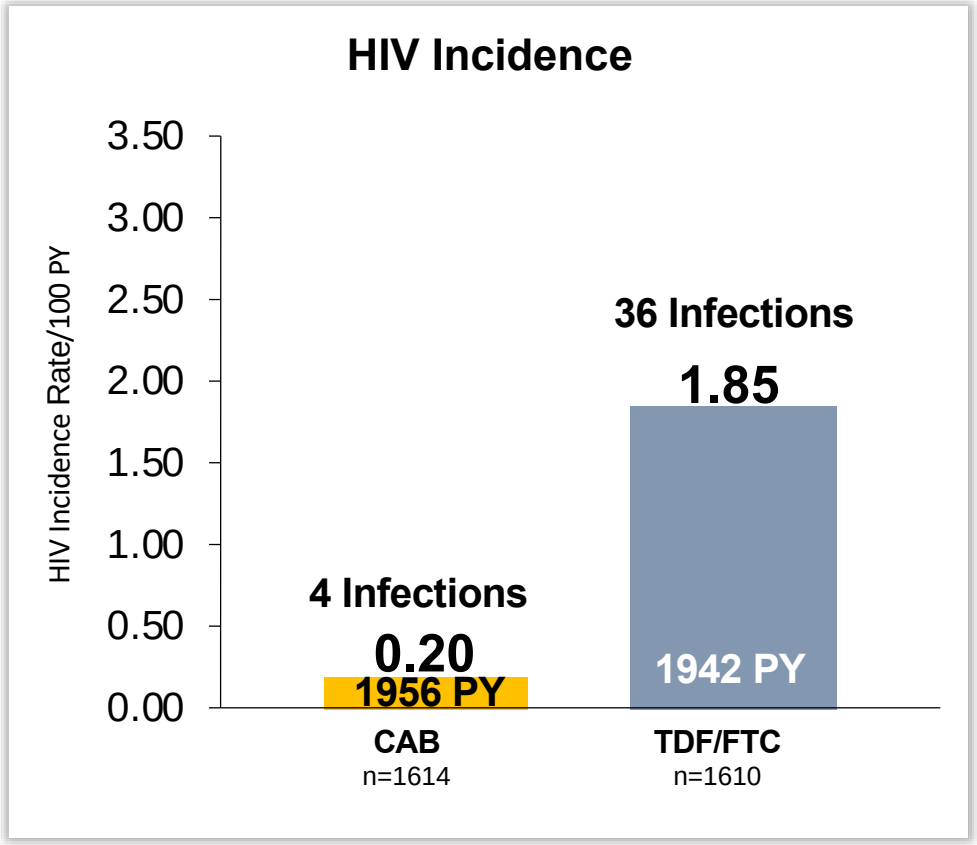
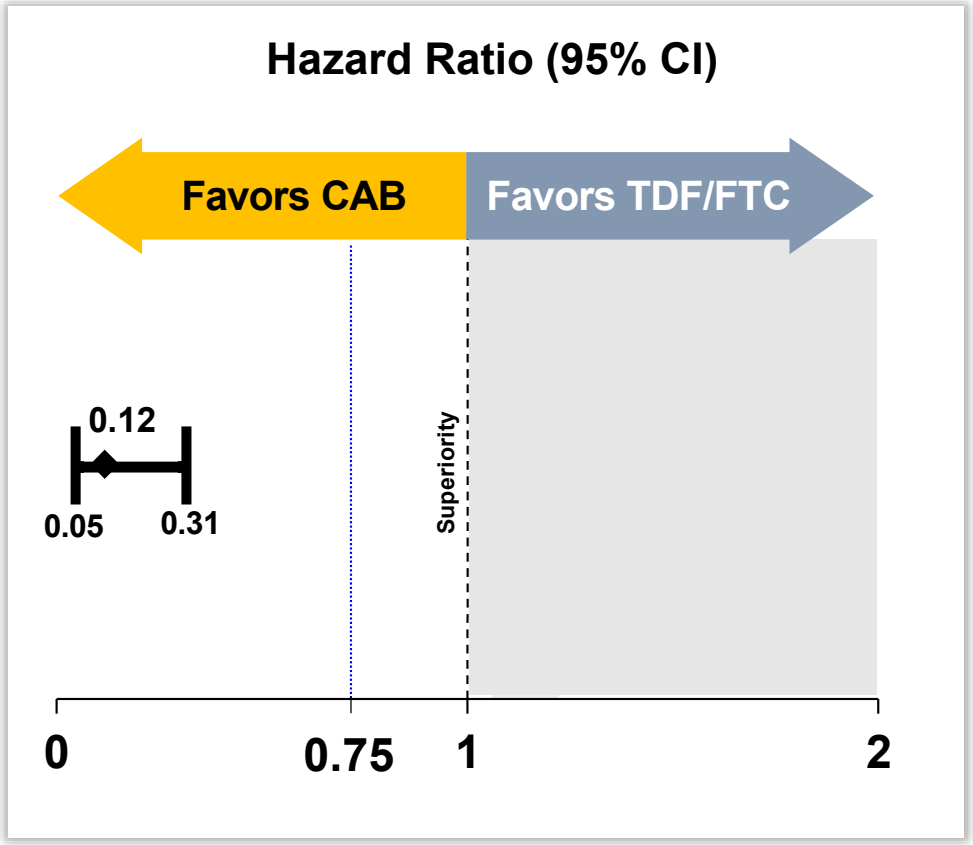



Landovitz, R. HIV Glasgow 2022.

# HPTN 084 HIV Incidence: CAB vs. TDF/FTC

Blinded period, through Nov 2020

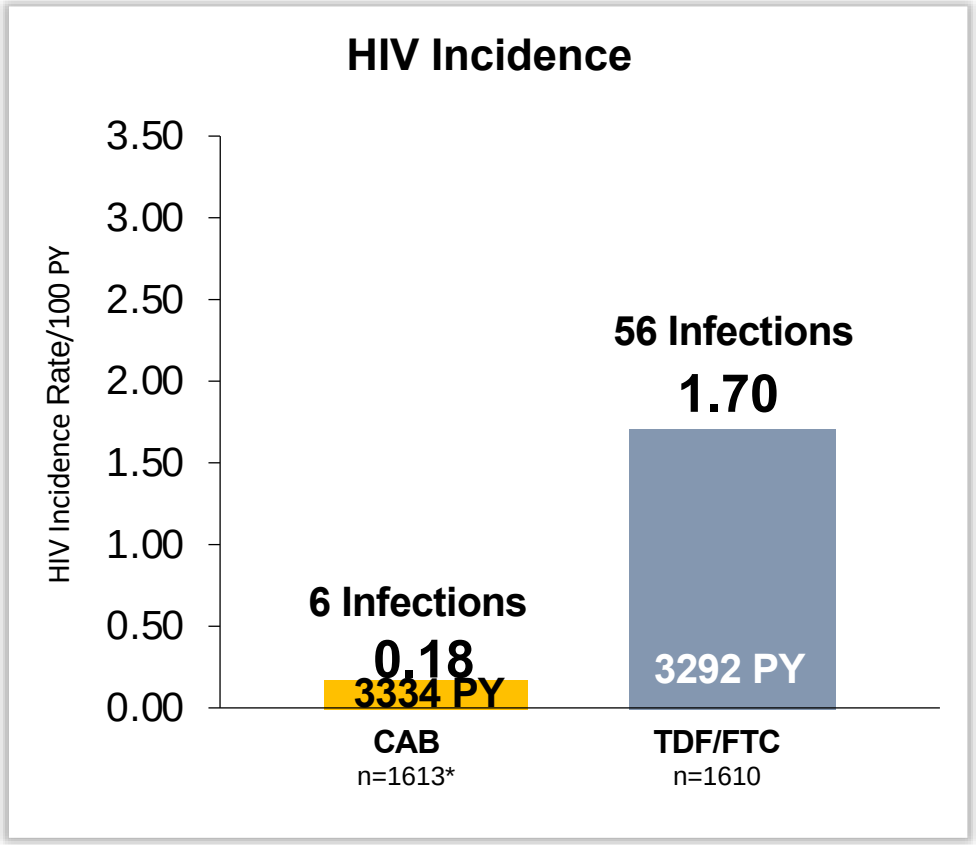


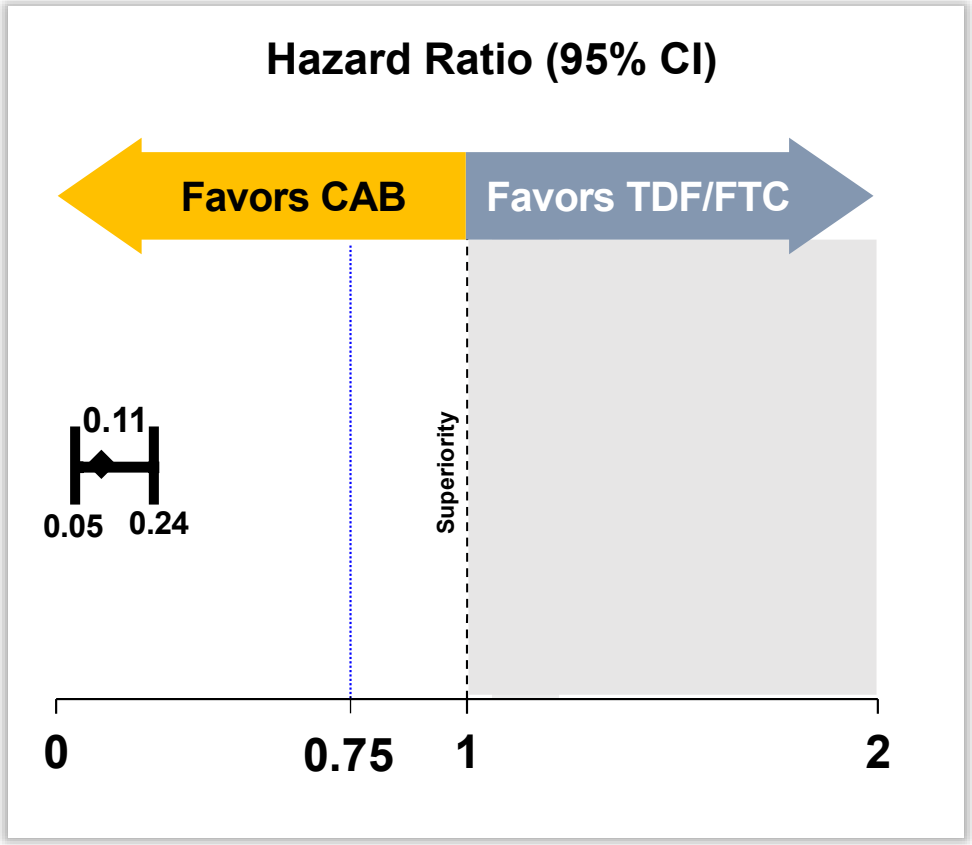




CI, confidence interval

# HPTN 084 HIV Incidence: CAB vs. TDF/FTC

Combined blinded and unblinded period, through Dec 2021




CI, confidence interval

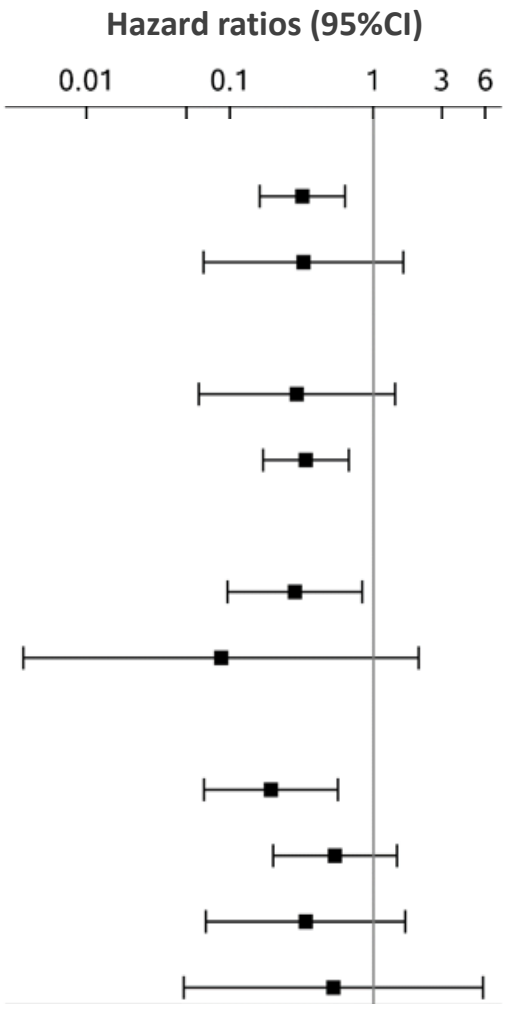
*Excludes 1 baseline infection from the blinded period

# 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

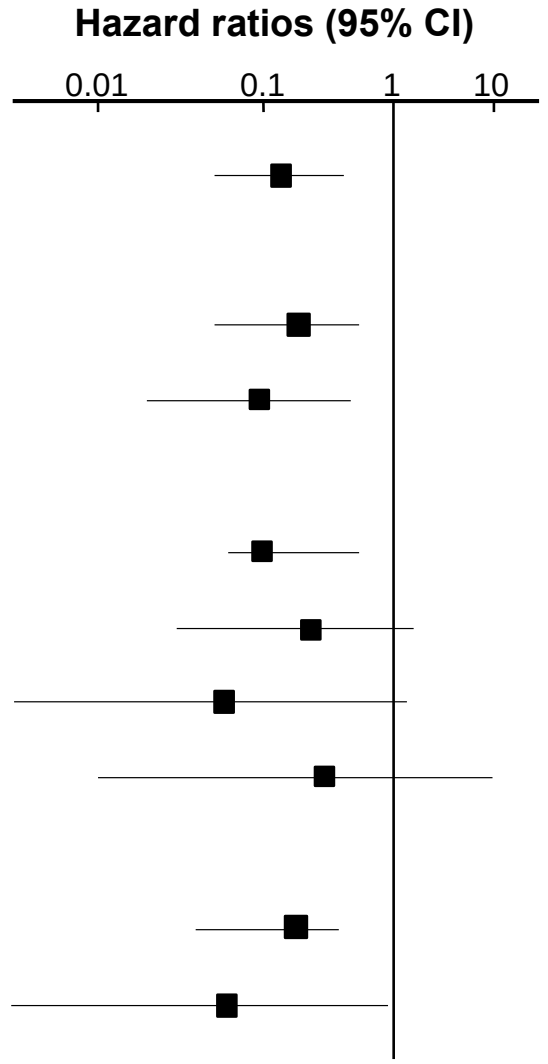
| Subgroup | CAB Events/PY (IR%) | TDF/FTC Events/PY (IR%) | HR (95%CI) |
|---|---|---|---|
| **Age** | | | |
| ≤30 | 11/2185 (0.50) | 33/2114 (1.56) | 0.32 (0.16, 0.63) |
| >30 | 2/1016 (0.20) | 6/1071 (0.56) | 0.33(0.07, 1.61) |
| **Cohort** | | | |
| TGW | 2/368 (0.54) | 7/383 (1.83) | 0.29 (0.06, 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) |



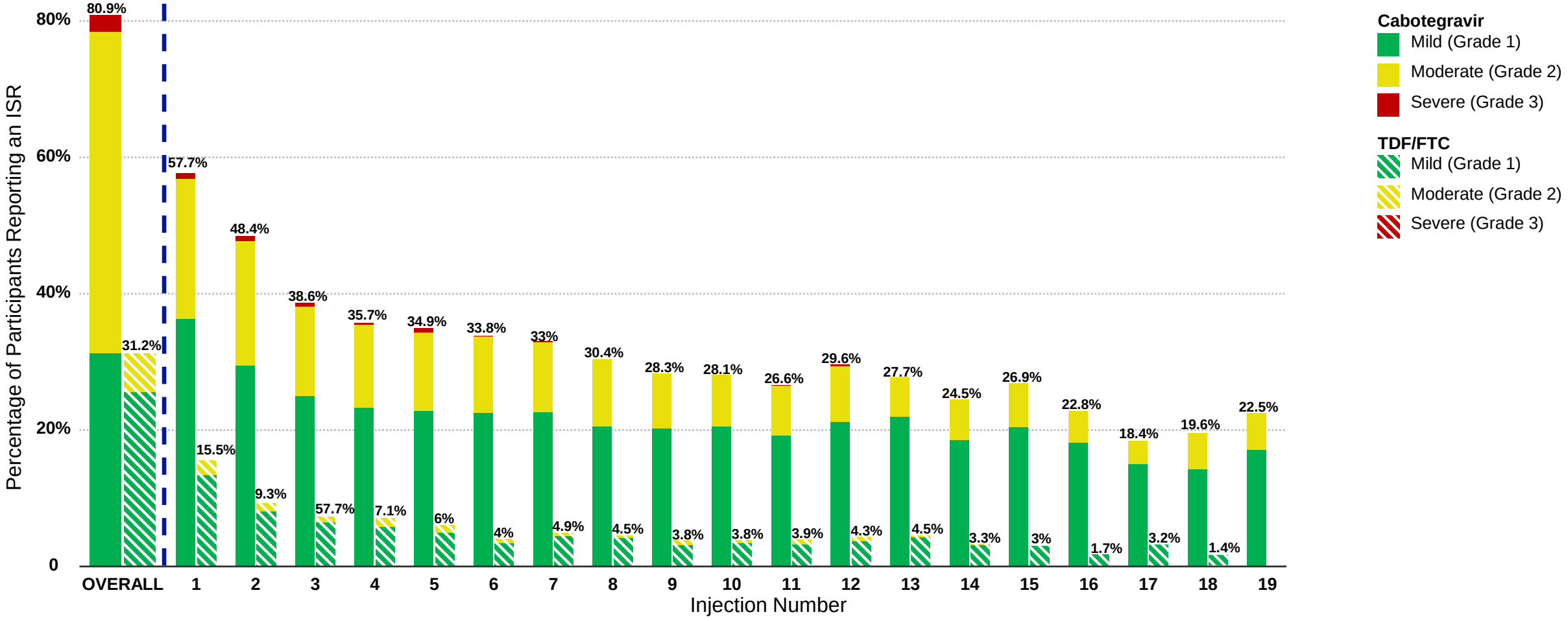

Delany-Moretlwe, S et al. Lancet. 2022.

# 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

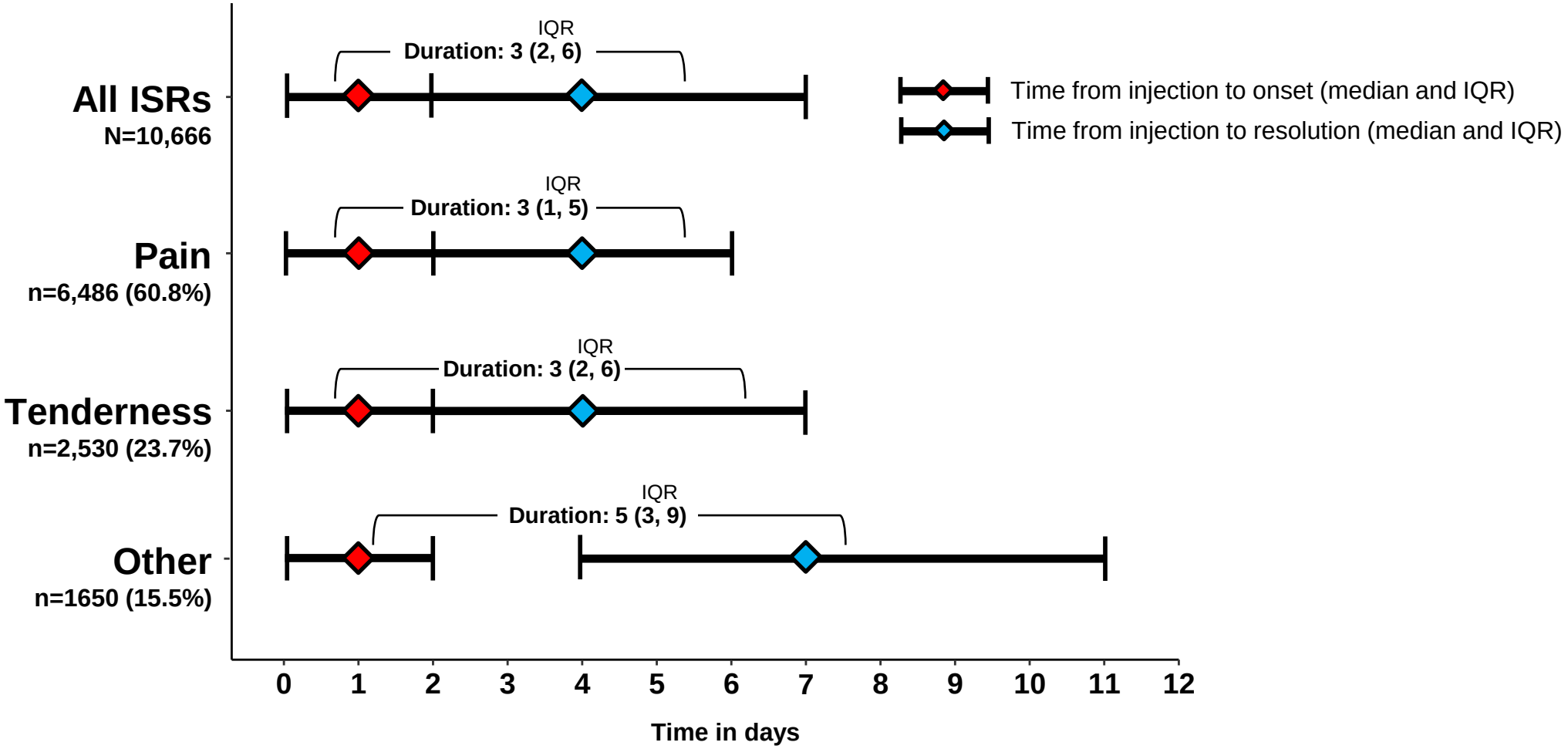
# HPTN 083: Injection Site Reactions




| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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**

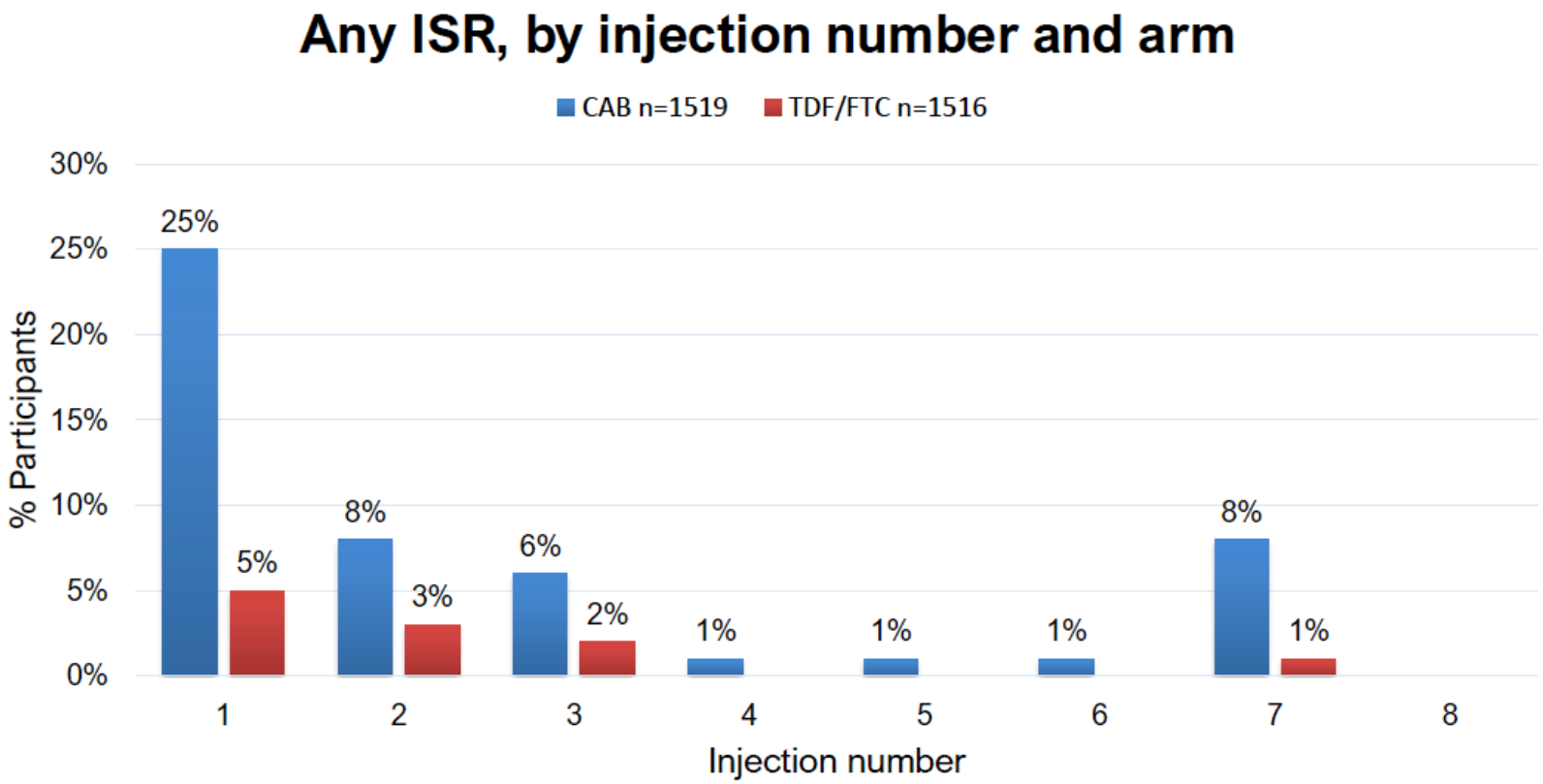
# HPTN 083: Injection Site Reactions




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

Landovitz RJ et al. NEJM 2021

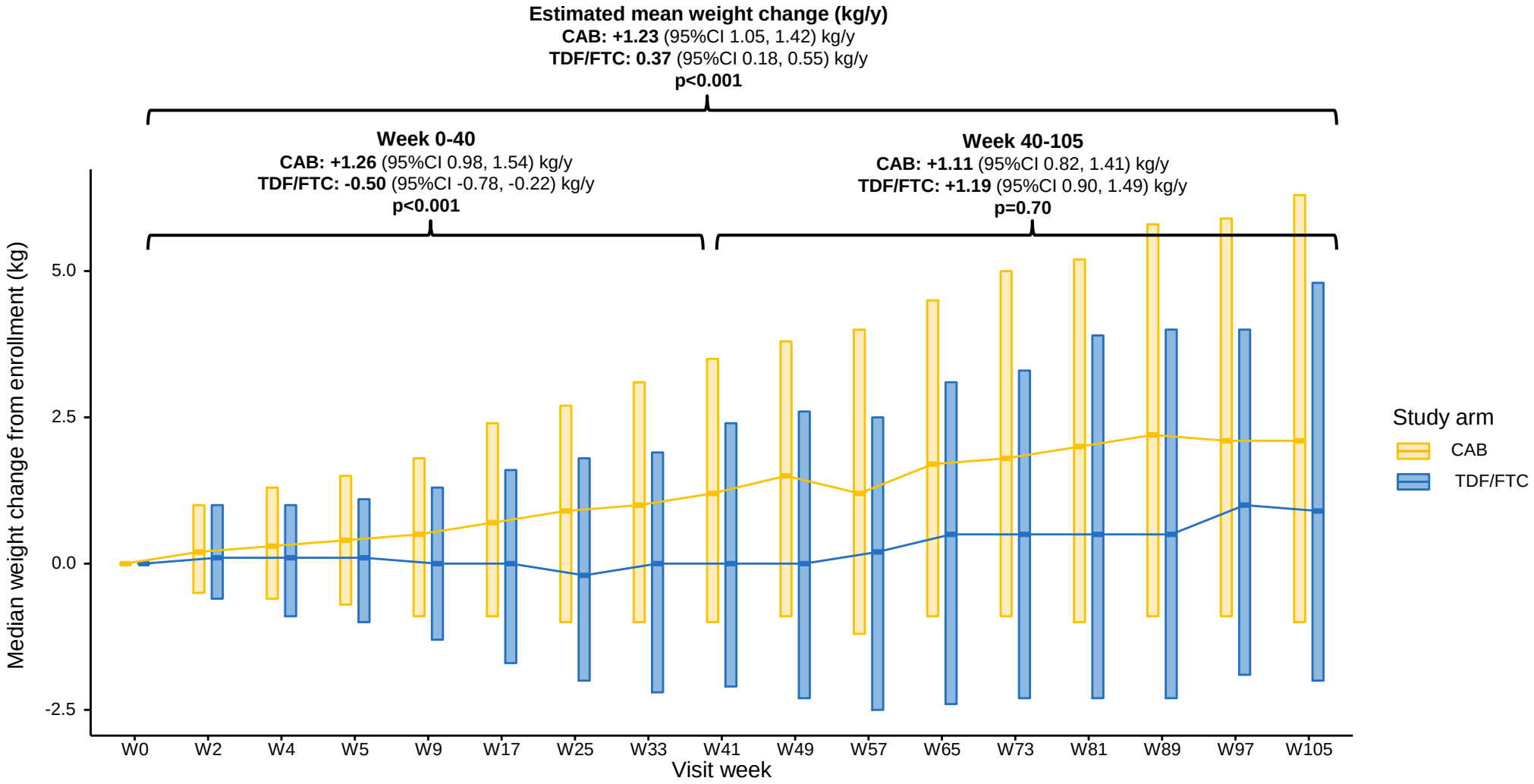
# HPTN 084: Injection Site Reactions




- 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

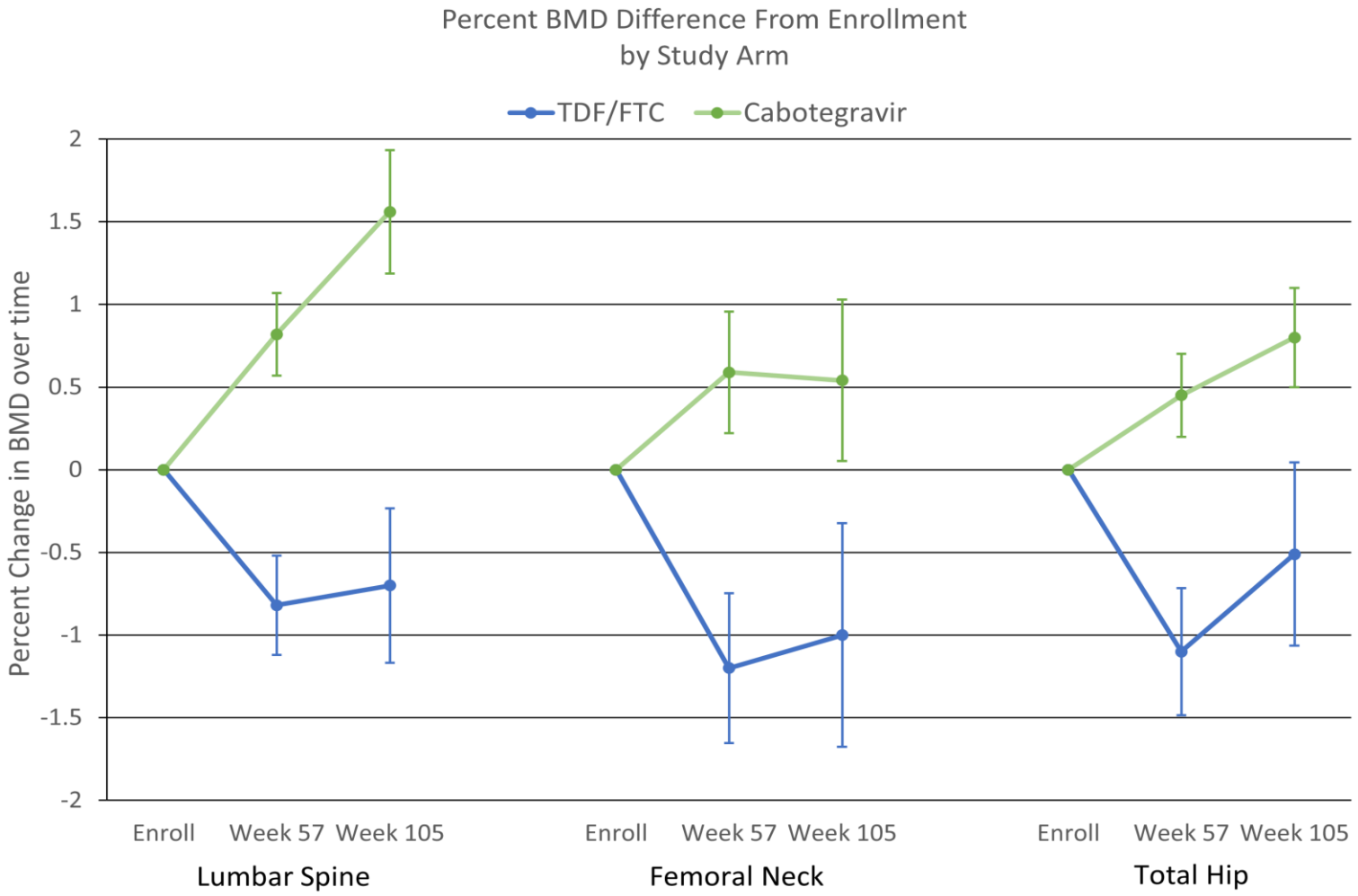
Delany-Moretlwe, S. HIV R4P 2021. #LB1479

# 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 |

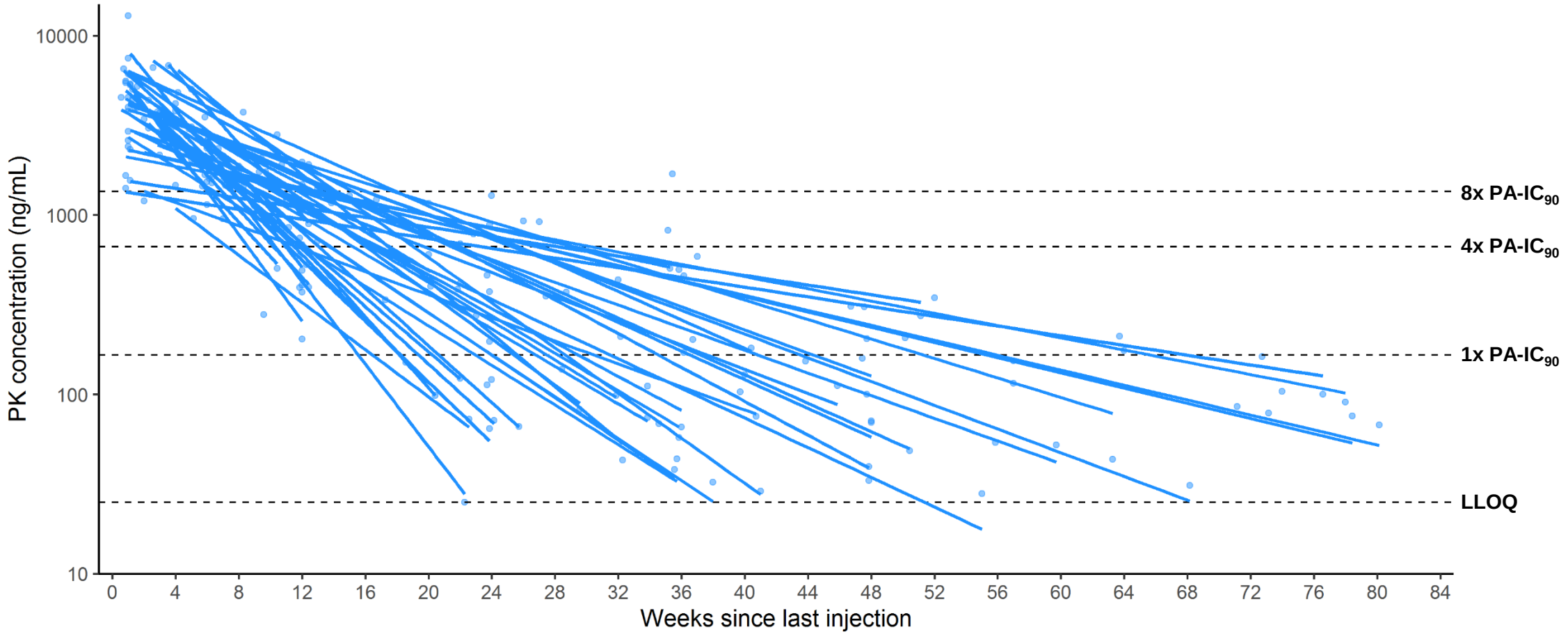
**includes multiple births*
***includes ectopic pregnancy, elective and spontaneous abortion*

# 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

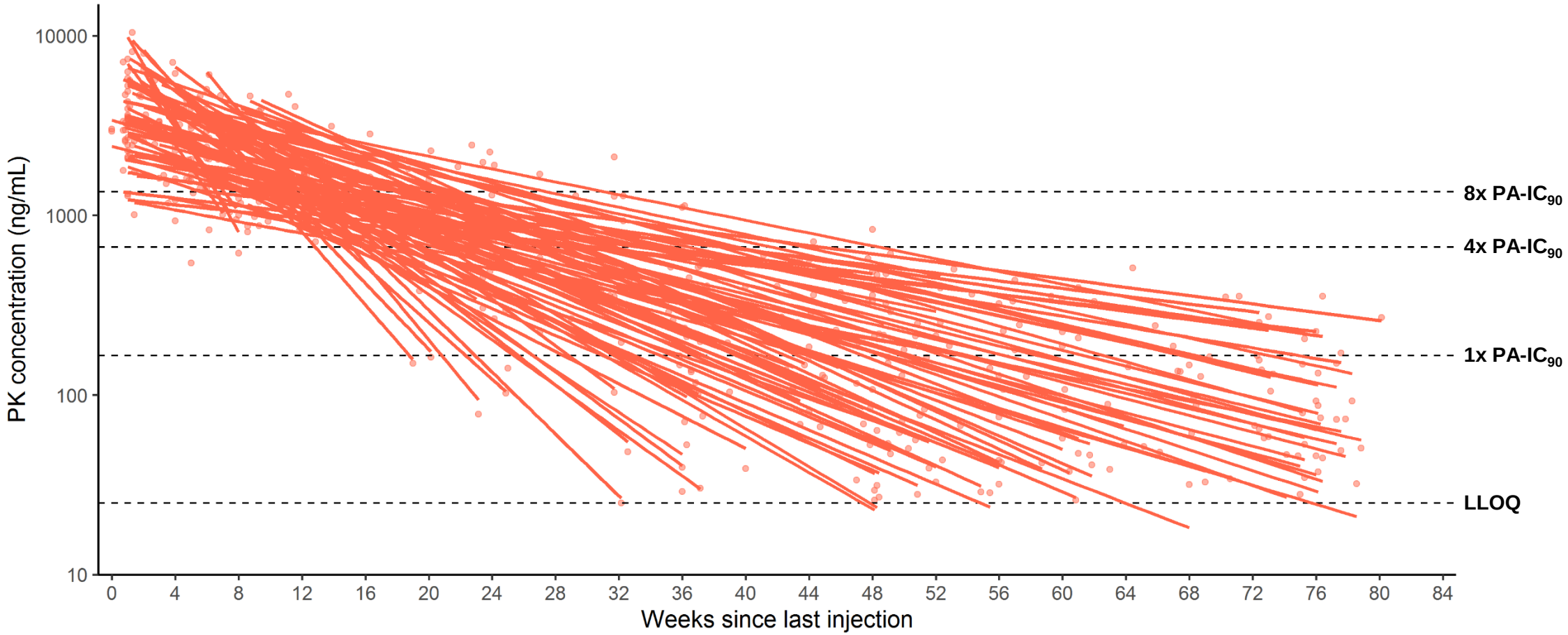
# PHARMACOKINETICS

# CAB Subsequent to Final Injection (Log Scale)
## Males



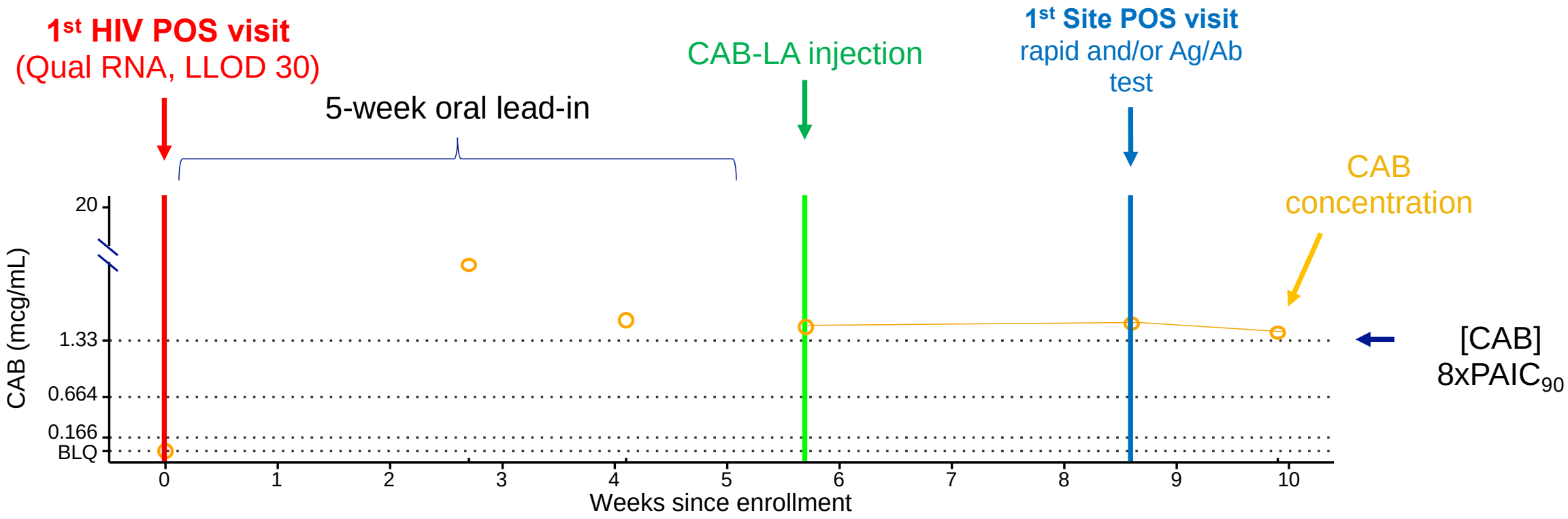

Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

# CAB Subsequent to Final Injection (Log Scale)
## Females

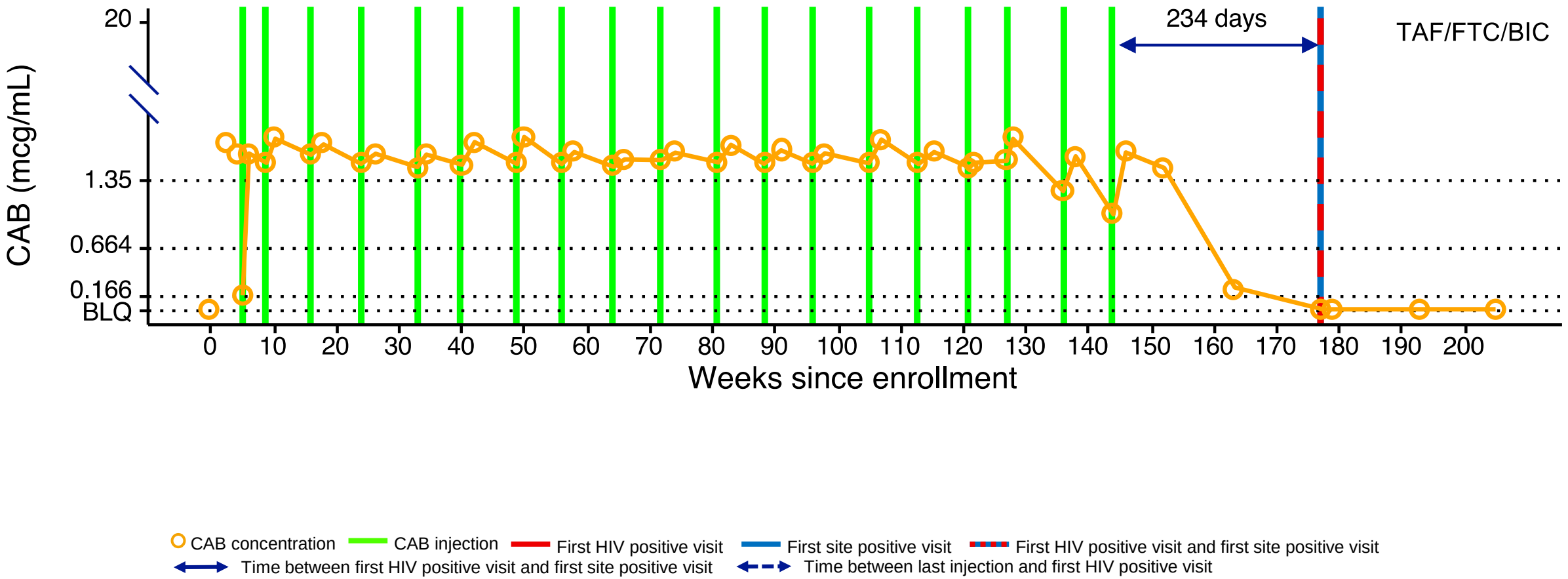



Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

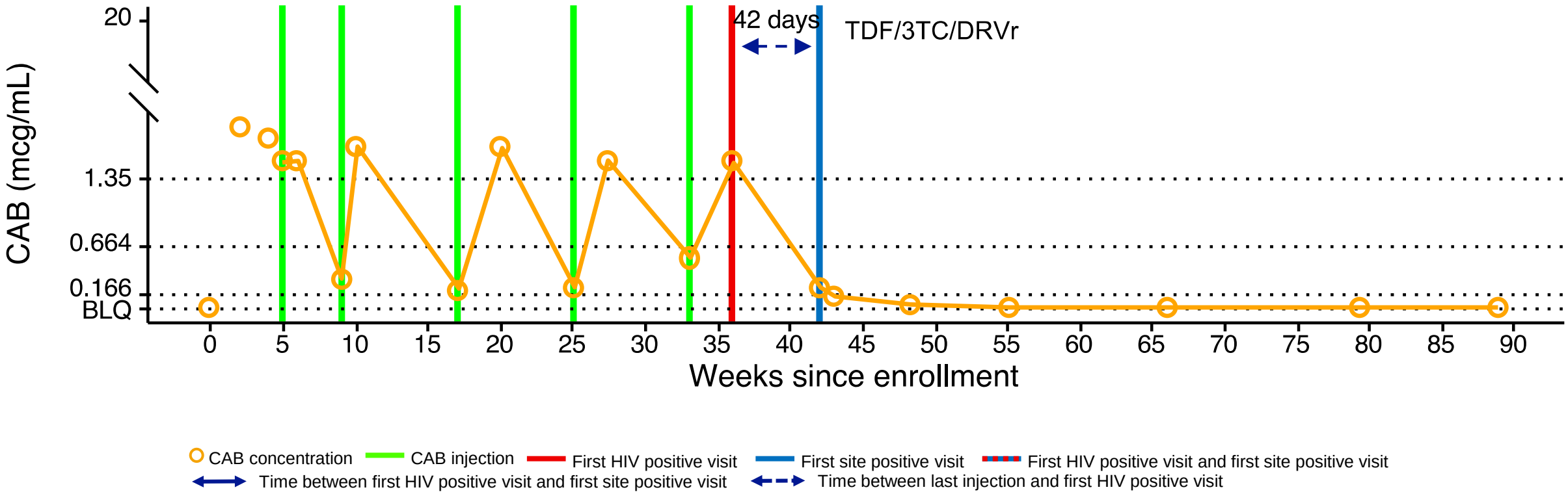
# Schematic for Seroconversions



# Expected Pattern of CAB Concentrations



# Fast Elimination – One case so far



# The Bottom Line:
## Pharmacokinetics in Men and Women

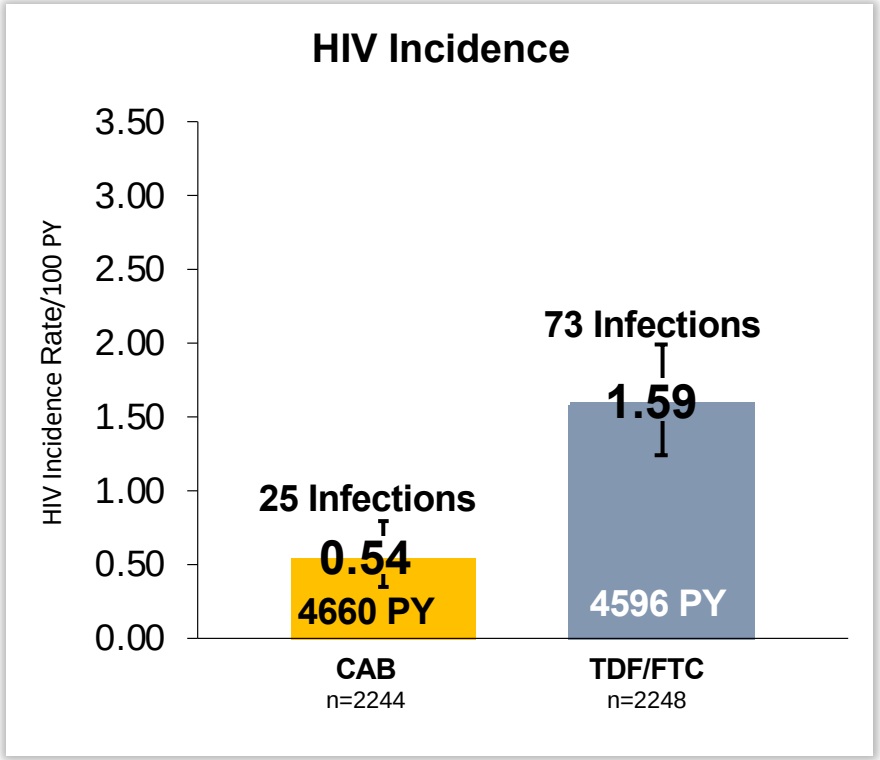
- **People born male**: the median time from the last injection to the time when CAB concentration fell below the LLOQ was 10.1 Months
- **People born female**:  the median time from the last injection to the time when CAB concentration fell below the LLOQ was 1 year and 3.5 months
- Higher BMI associated 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

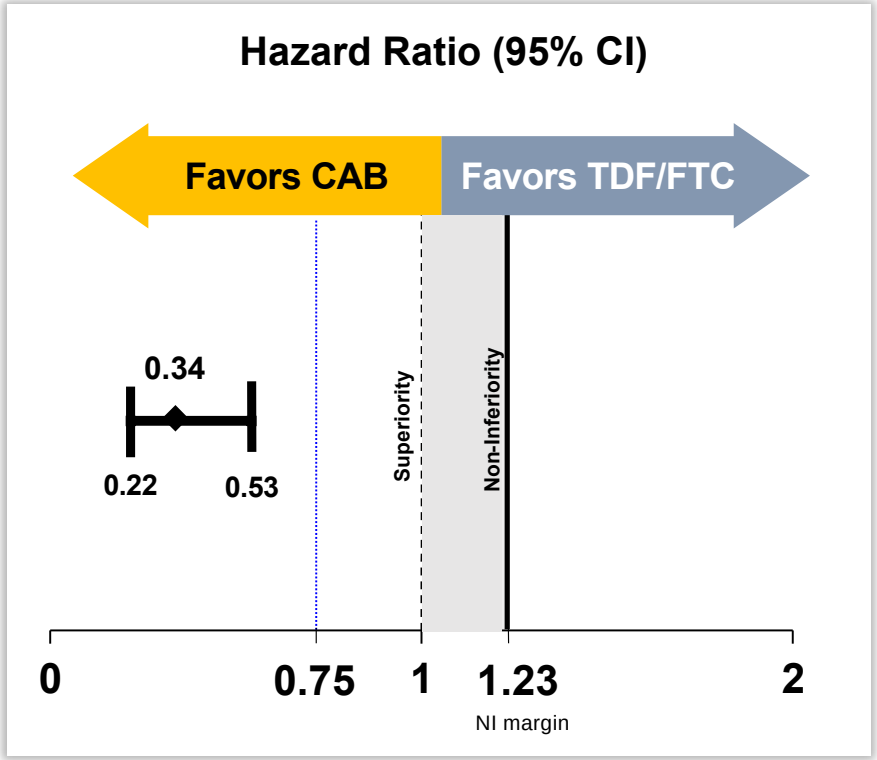
Landovitz, R. Lancet HIV. 2020.

# FAILURES

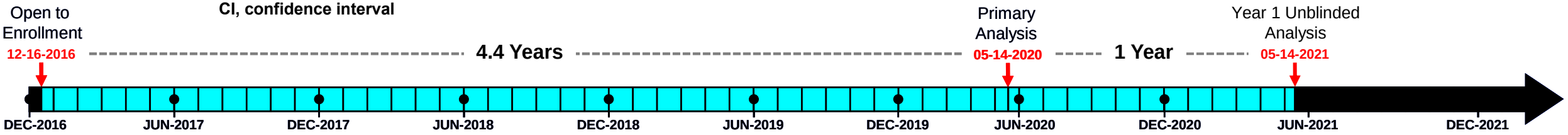
# REMINDER: BOTH PrEP MEDICATIONS WORK *EXTREMELY* WELL

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**

# FAILURE GROUPS IN HPTN 083

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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

- **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 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

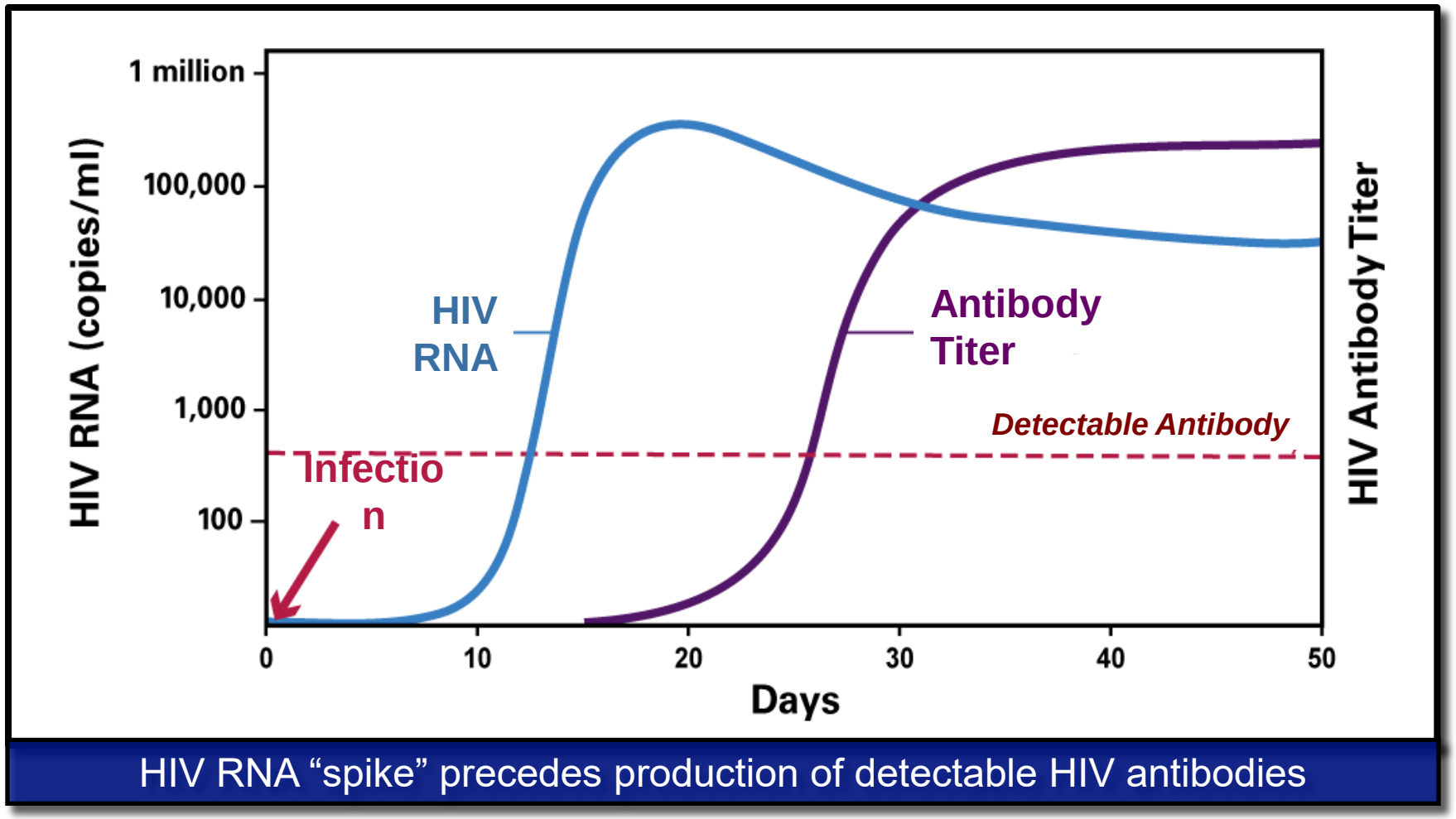
# Bottom Line: Summary of HPTN 083 resistance

| CAB INITIATED OR RE-INITIATED WITH OCCULT HIV INFECTION | | |
|---|---|---|
| | **N (%)** | **Integrase Resistance** |
| 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

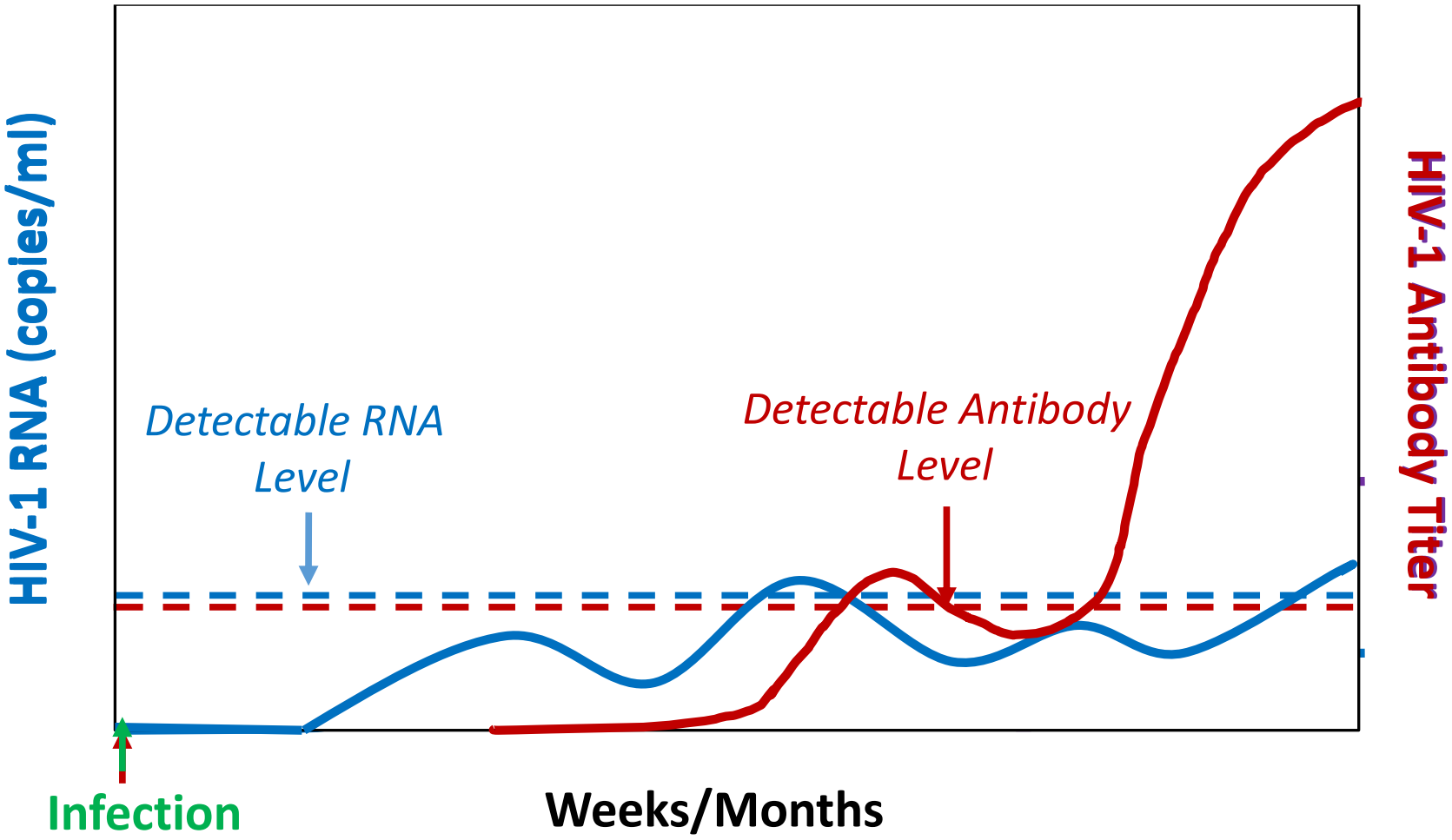
# TESTING DELAYS

# 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?

# CAB PrEP Implementation (similar issues for CAB/RPV for ART)

**Insurance variability**

- **Coverage**
- **Residence in pharmacy vs. medical benefit**
  - **Share-of-cost implications thereof**
- **Requirement for Buy-and-Bill vs. Specialty Pharmacy**
- **CMS reimbursement not clear until J-code July 1, 2022**

**Institutional Requirements**

- **Institutional support for Buy-and-Bill**
- **Institutional allowance of Brown/White/Clear Bagging**

US CDC, DHHS. PrEP for the prevention of HIV infections in the United States – 2021 Update

# CAB PrEP Implementation (similar issues for CAB/RPV for ART)

**Clinic Requirements**

- Operations/Work flow for administration
- Patient Tracking
- Bridging with missed doses (inconsistency between RCTs and PI)
- Reloading (inconsistency between RCTs and PI)

**Provider Hesitancy**

- Which to recommend?
- How to counsel re: Onset? Durability?
- Resistance and options for ART choice in breakthrough
- Complexity (and anguish!) of discordant results

US CDC, DHHS. PrEP for the prevention of HIV infections in the United States – 2021 Update

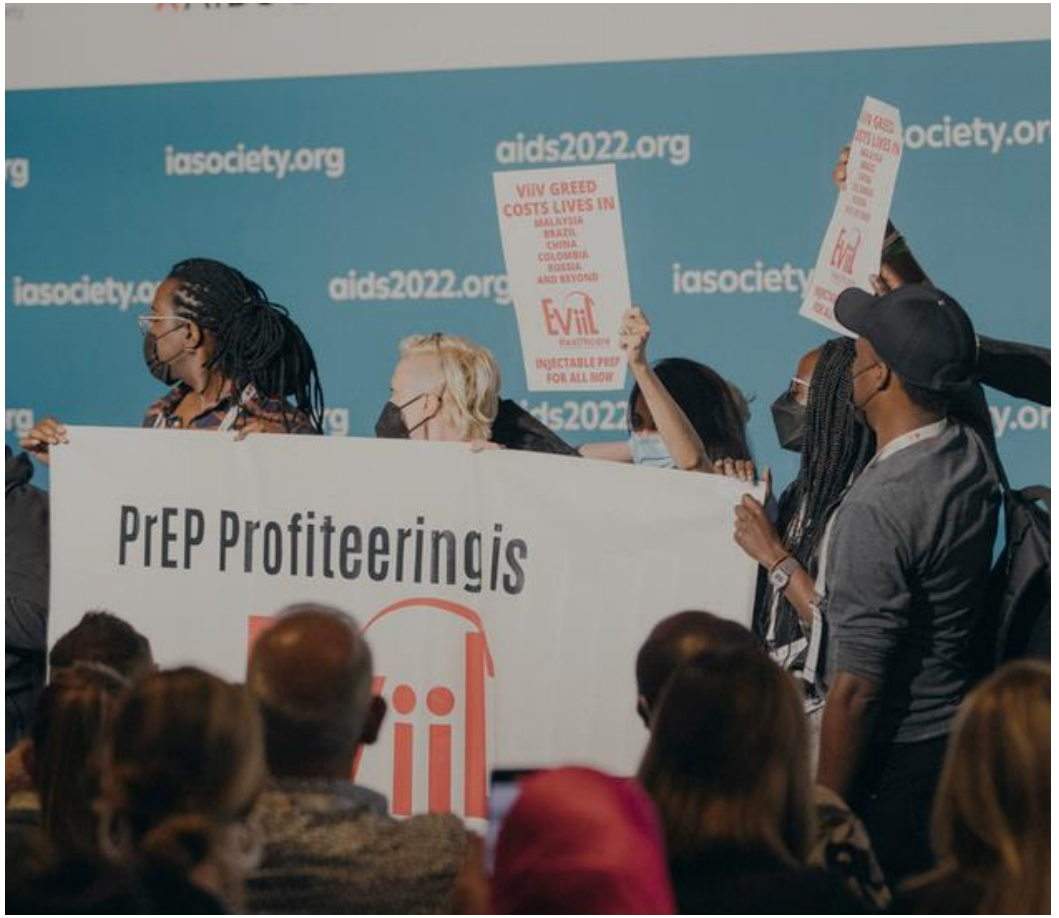
# Can CAB be given at other anatomic sites?

- 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?

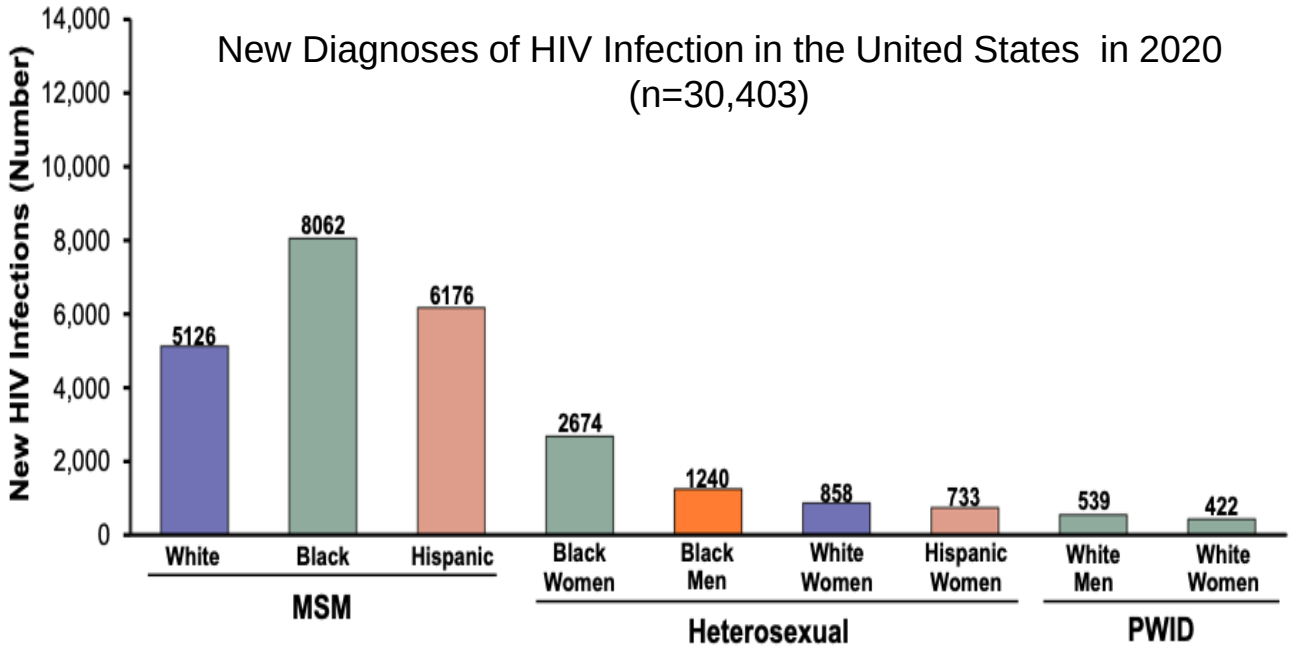
- Cabotegravir is currently priced at $22,200 per year
  - >185 times higher than the $60–$119 estimated cost-effectiveness threshold for middle-income countries (MICs)
- ViiV recently provided access to generic versions in 90 countries with the Medicines Patent Pool (MPP), including all African nations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

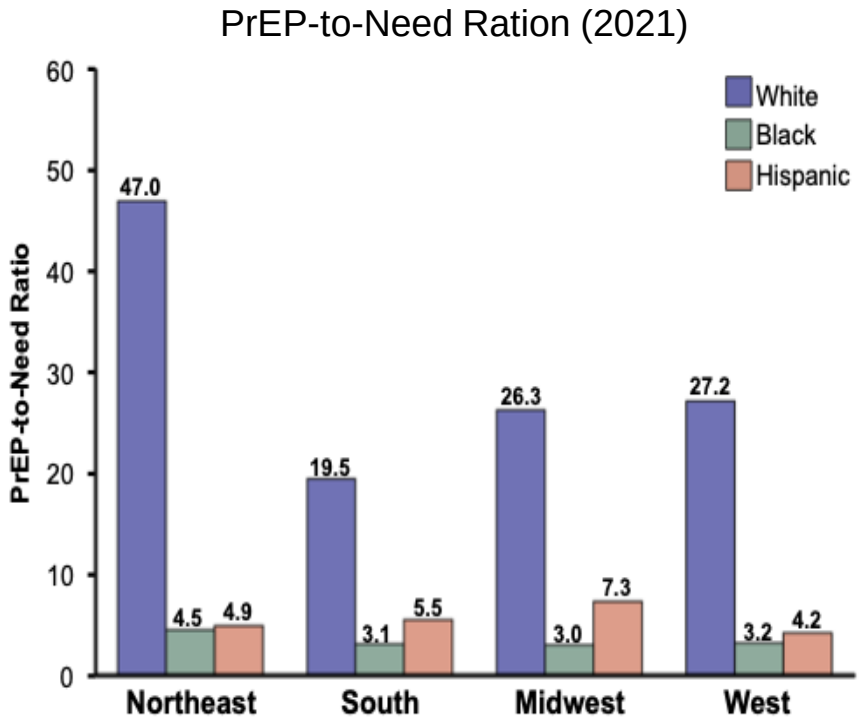



Pepperell T, et al. OFID. 2022.

# 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**




CDC. HIV Surveillance Report, 2020. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published May 2022.
Sullivan P, et al. J Int AIDS Soc. 2022;25(suppl 3): 227. Abstract OALBX0106.

# 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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