

Model-Based Estimates of Cabotegravir Efficacy for Long- Acting PrEP by Time Since Injection

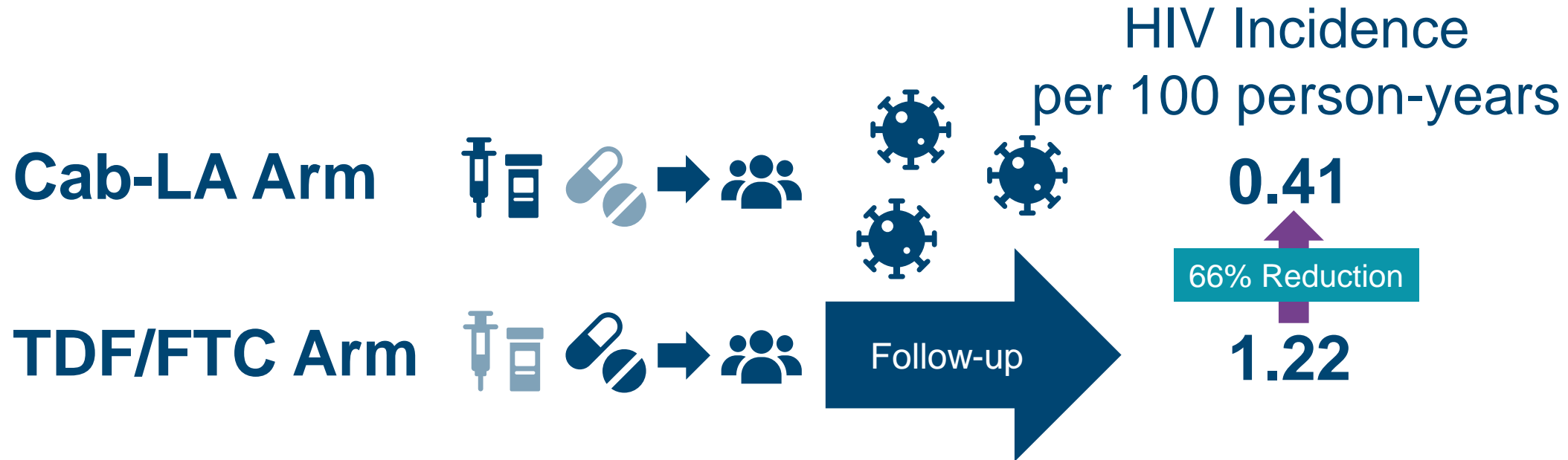
Mia Moore

Fred Hutch Cancer Center

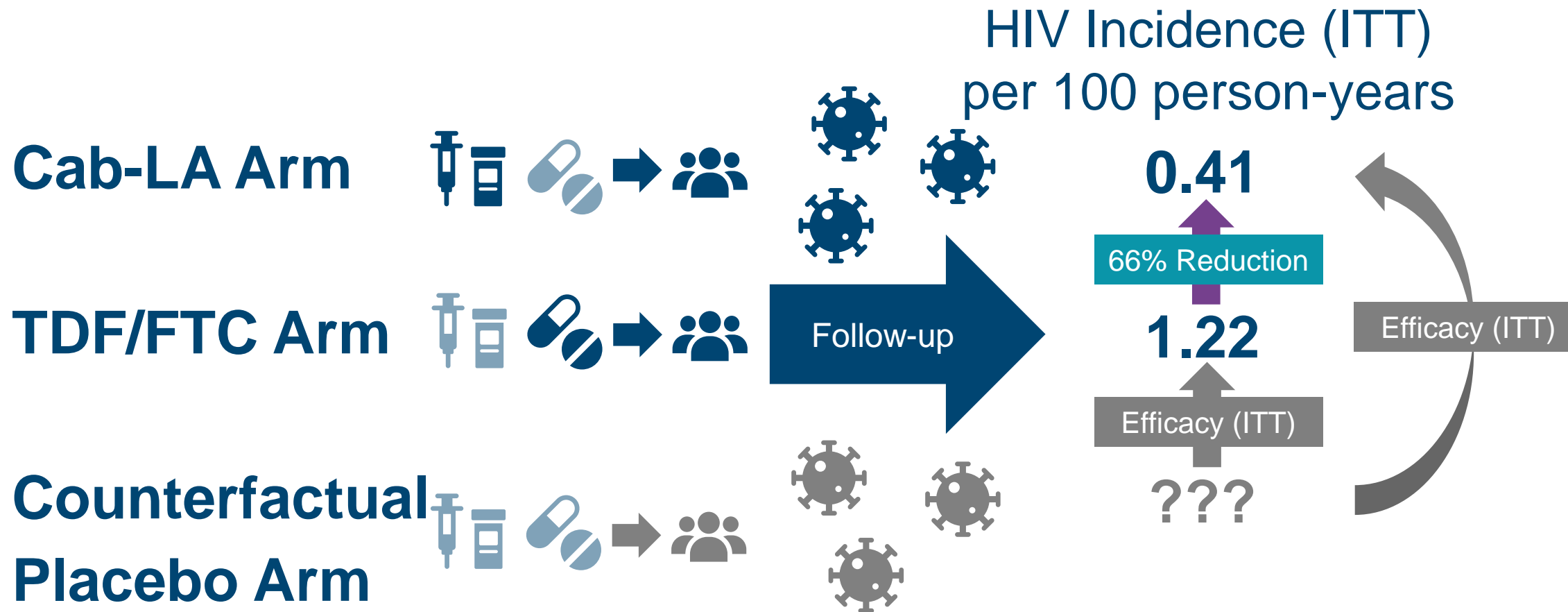


1. **Question: How does HIV protection wane following cabotegravir injection?**
2. We **propose a methodology** that creates a curve representing **efficacy vs time since injection** in men and transgender women who have sex with men (MSM/TGW).
3. **Preliminary results** suggest HIV incidence is reduced 97% in weeks 1 to 8.
4. Can use this curve to project intervention effectiveness from injection frequency

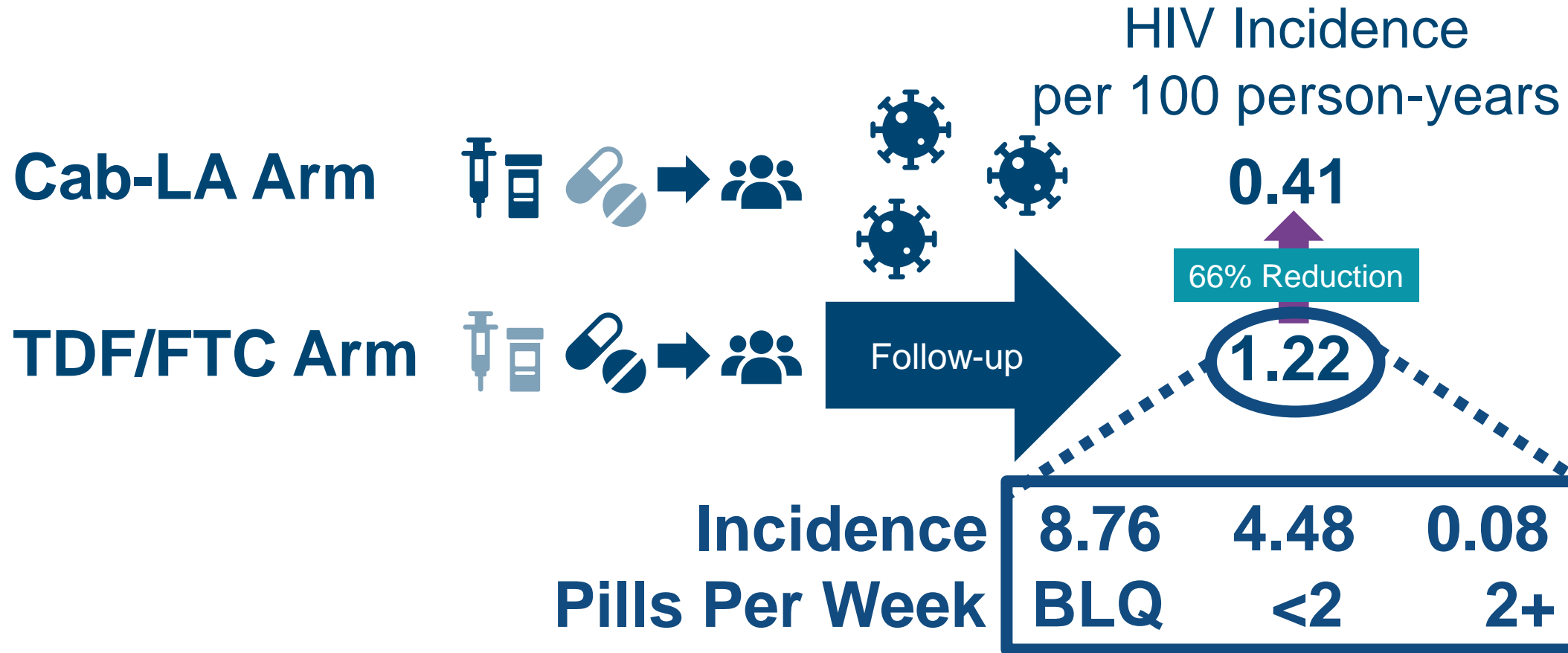
Efficacy estimates from HPTN 083



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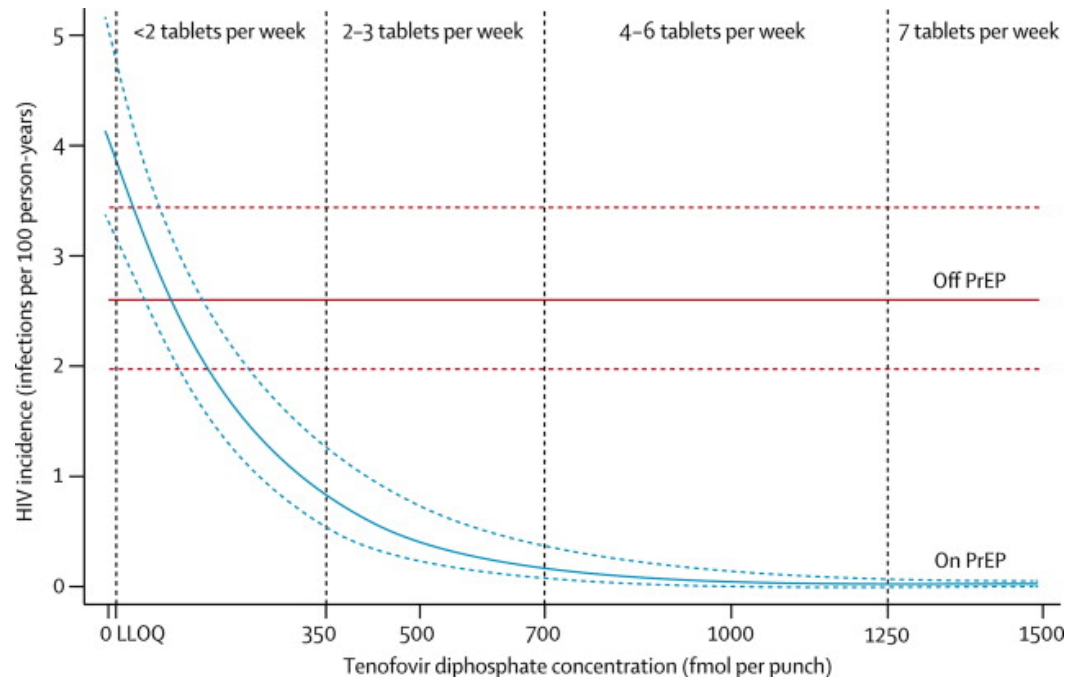


Anderson et al, Clinical Infectious Disease, 2023
doi:10.1093/cid/ciad021

Modeling Adherence/Efficacy Curves

Oral TDF/FTC

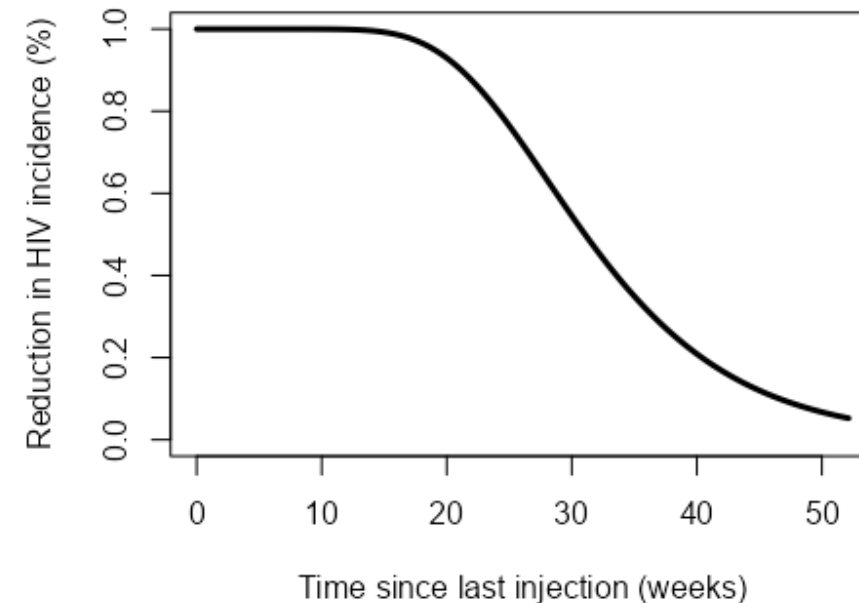
- Depends on number of pills per week
- Curve estimated using data from iPrEX OLE (below)
- Still being updated with data from new trials such as HPTN 083 (previous slide)



Grant et al, Lancet Infectious Disease, 2014
doi:10.1016/S1473-3099(14)70847-3

Injectable CAB-LA

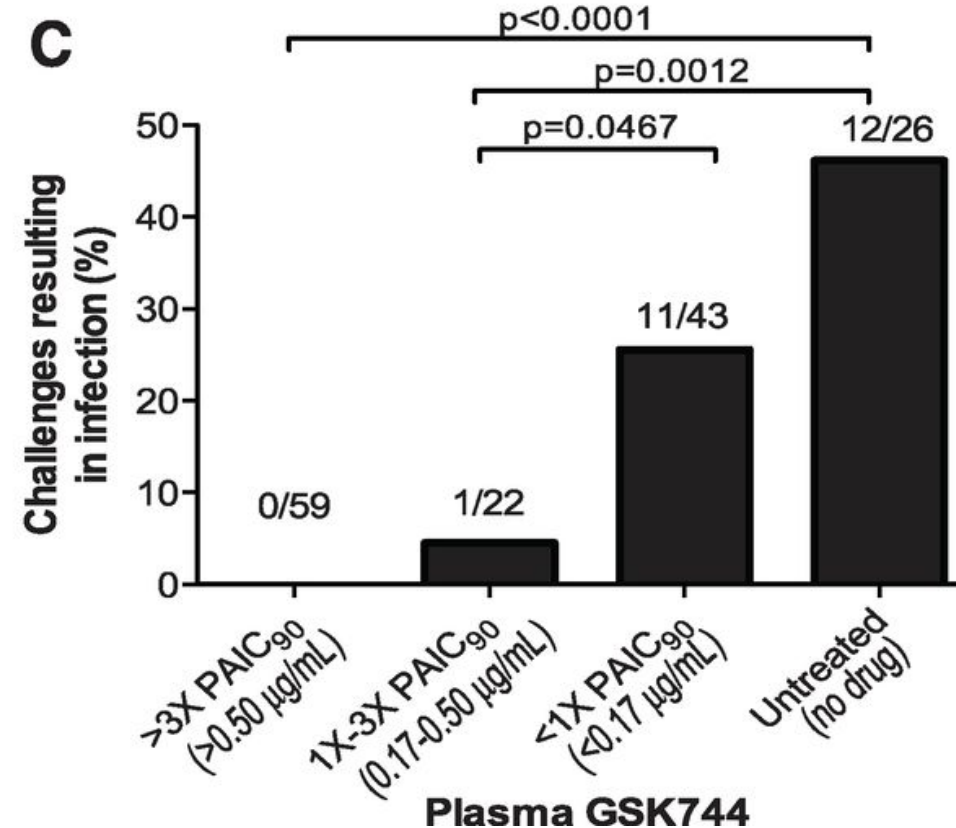
- Depends on time since injection
- Proposed curve based on non-human primate data and Phase 2 trials (below)
- We have updated this curve with data from HPTN 083



Adapted from
Marshall et al, Lancet HIV, 2018
doi:10.1016/S2352-3018(18)30097-3

Evidence from NHP studies

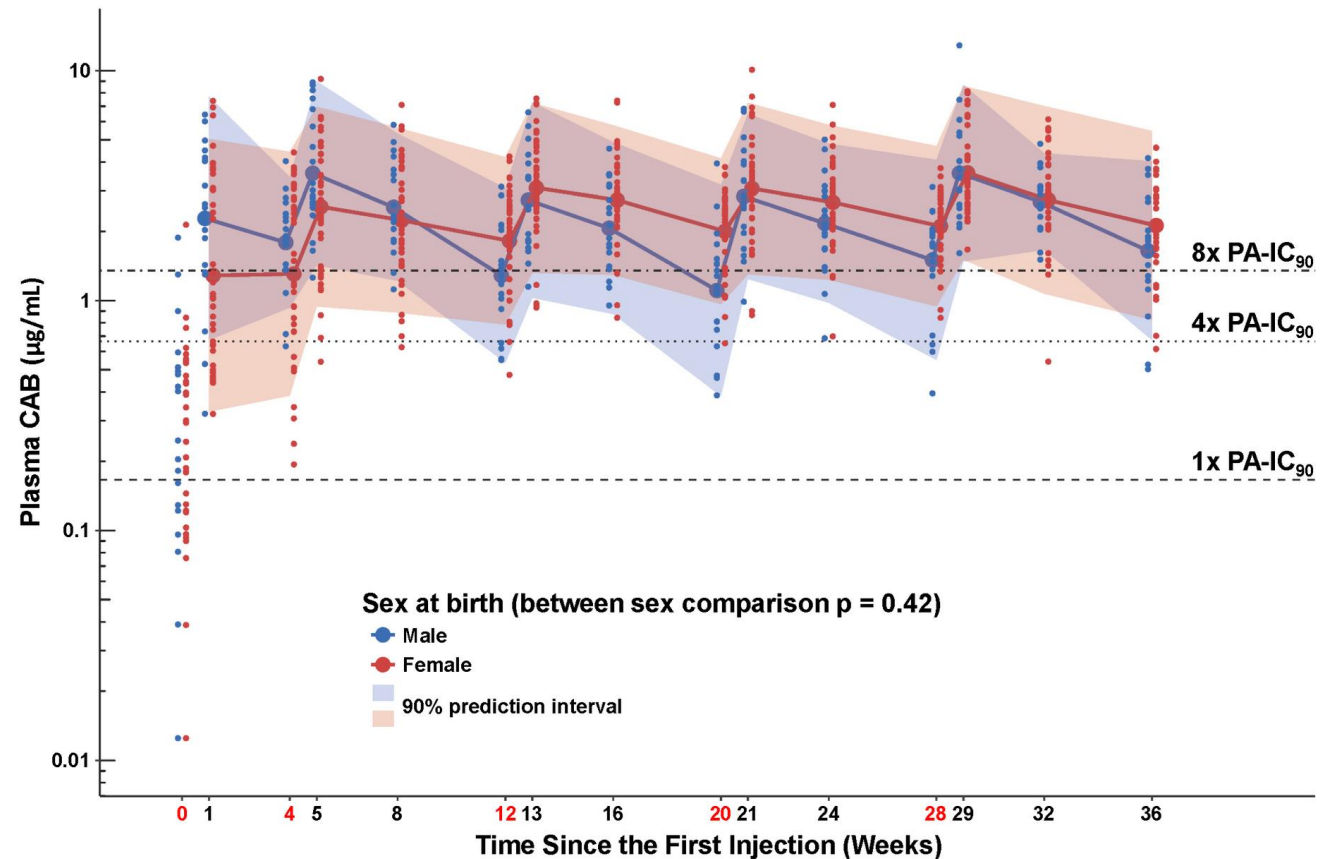
- PAIC90:= 166ng/ml in plasma (Target concentration derived from in-vitro assays (Yoshinaga, 2014))
- Assessment of concentration-efficacy in macaques(Andrews, 2014)
 - Initial injection of cabotegravir, waning over the course of several weeks
 - Macaques had weekly rectal challenges with simian HIV (SHIV)
 - 28-fold reduction in SHIV incidence with >1 PAIC90
 - 2-fold reduction in SHIV incidence with <1 PAIC90



Andrews et al, Science, 2014
doi:10.1126/science.1248707

Pharmacokinetics from Phase 1/2 studies

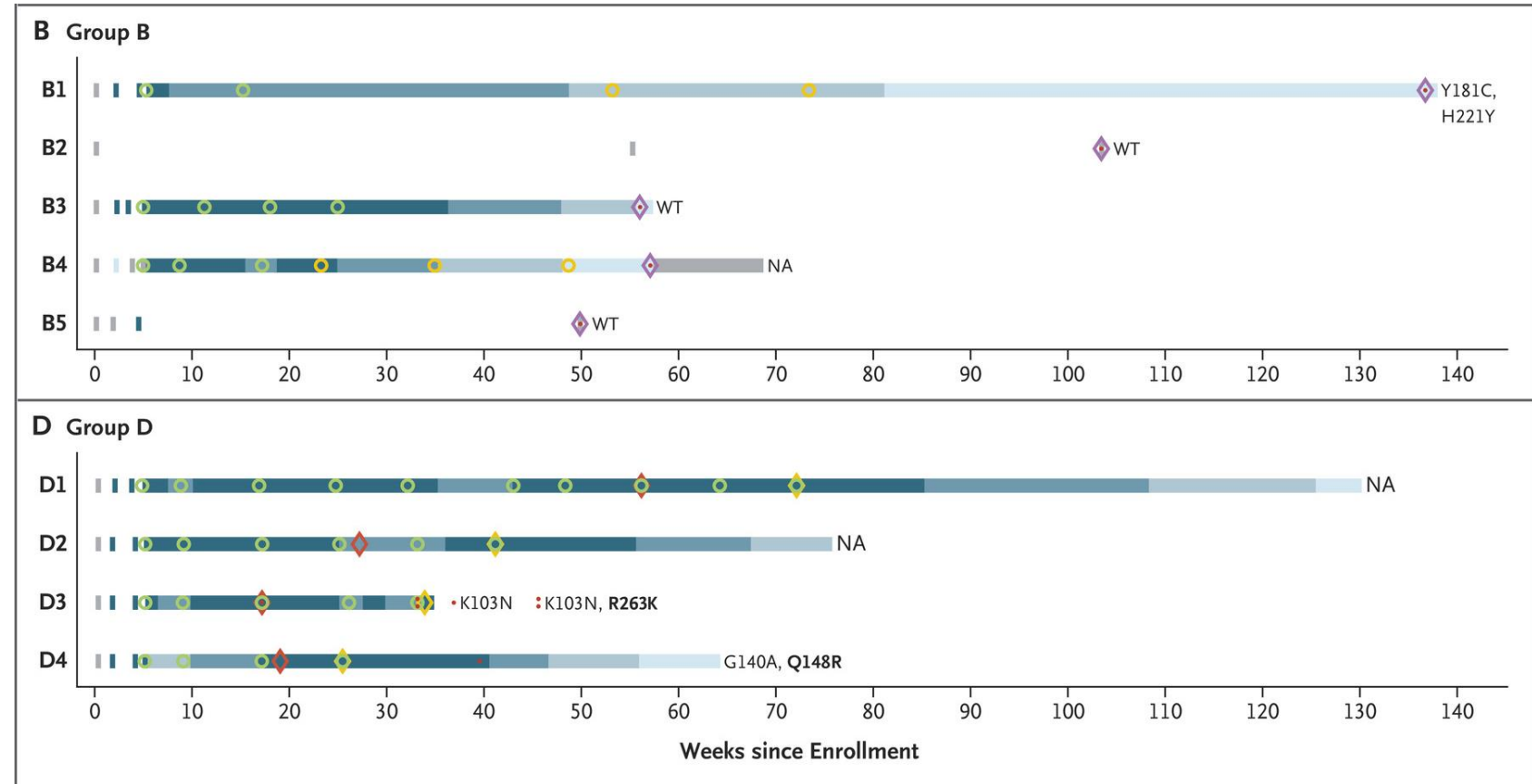
- Pharmacokinetic study of Regular Injections (Landowitz, 2018)
 - Phase II study quantifying pharmacokinetics of regimen used in HPTN 083 (600mg,
 - Mean trough plasma concentration in mean remains above 8x PAIC90
- Combined with the NHP data suggests a sigmoidal curve (**two parameters to be estimated from HPTN 083**)



Landowitz et al, PLOS Medicine, 2018
doi:10.1371/journal.pmed.1002690

Calibration of CAB-LA efficacy curve

- Example: In HPTN 083 there were 8* infections following ~20K injections
- Group B had **no recent exposure** to cabotegravir.
- Group D were acquired HIV despite receiving **appropriately timed** cabotegravir injections.

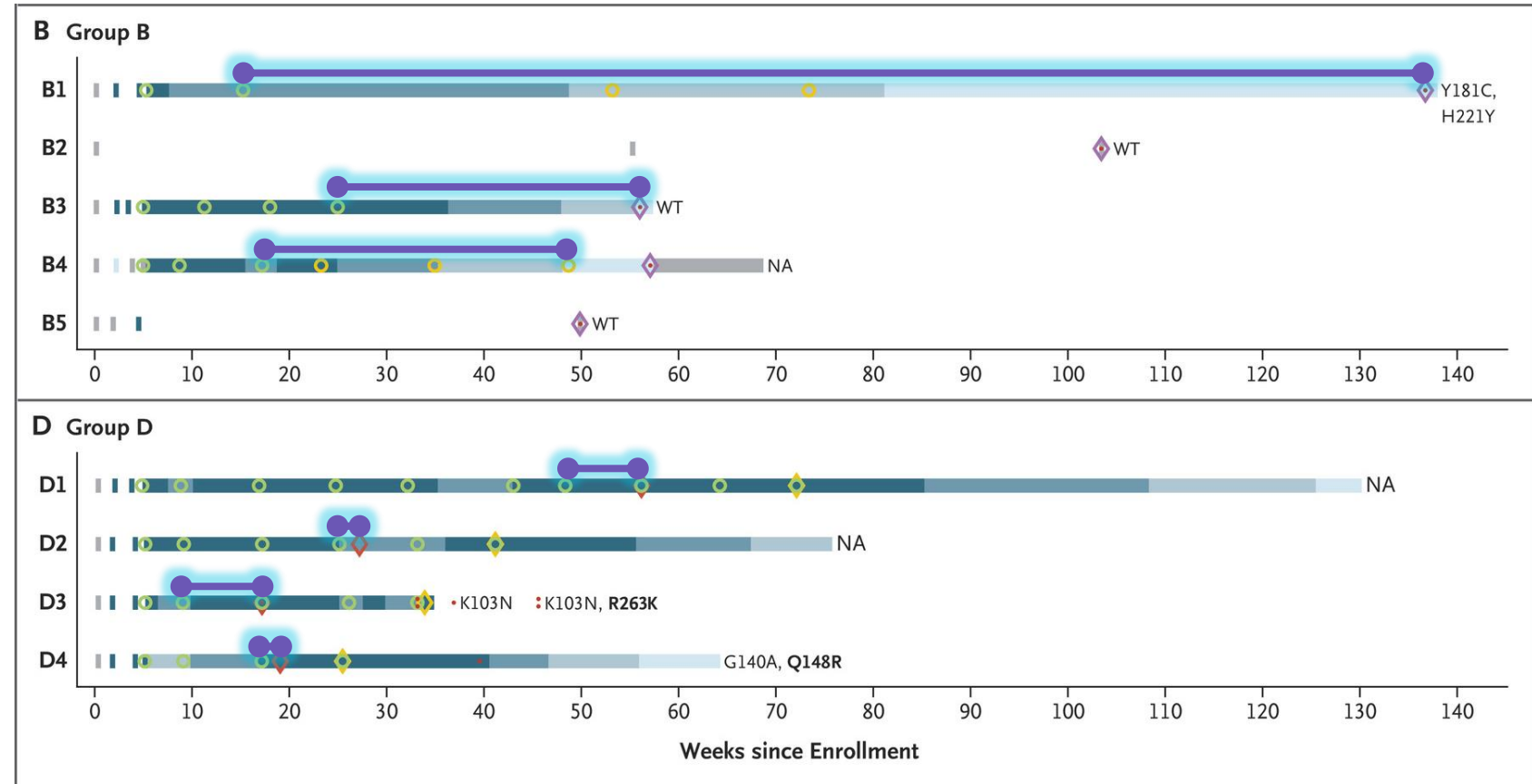


*Readjudicated to 7, but we're in this analysis we're using 8

Landowitz et al, NEJM, 2021 doi: 10.1056/NEJMoa2101016

Proposed endpoint analysis

- In HPTN 083 there were 8* infections following ~20K injections
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- Time between **most recent injection** and first HIV-positive visit **highlighted**

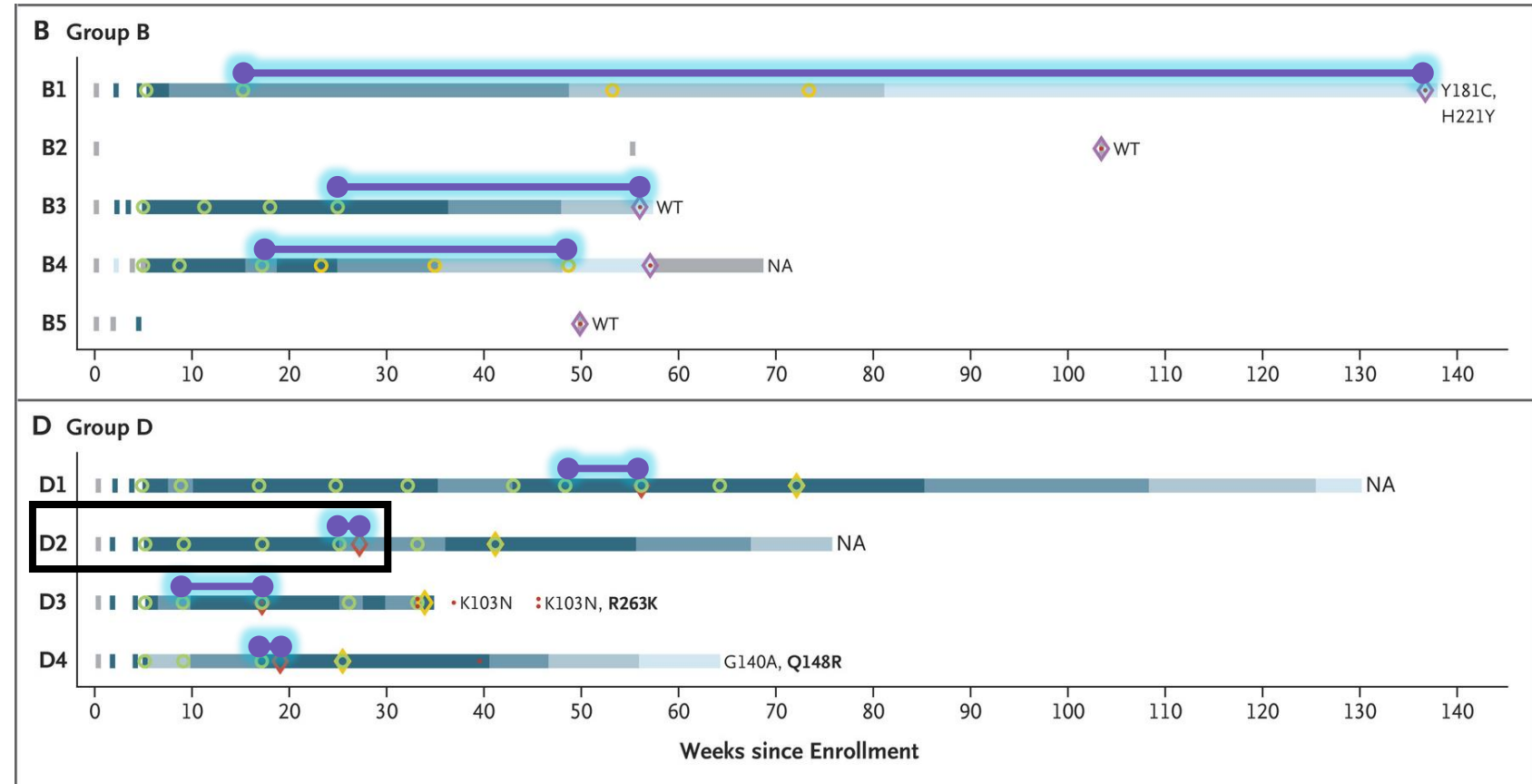


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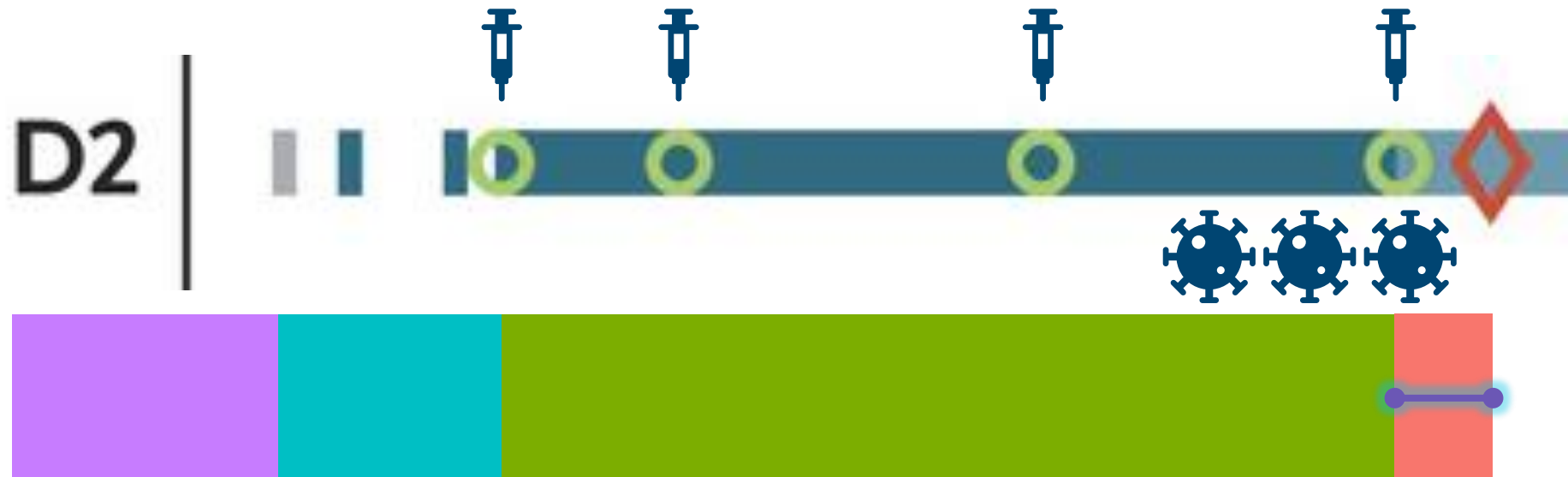
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HPTN 083 endpoints



- Patient D2 had their first HIV-positive visit **two weeks following injection**
- Their date of HIV exposure was **likely prior to their most recent injection**

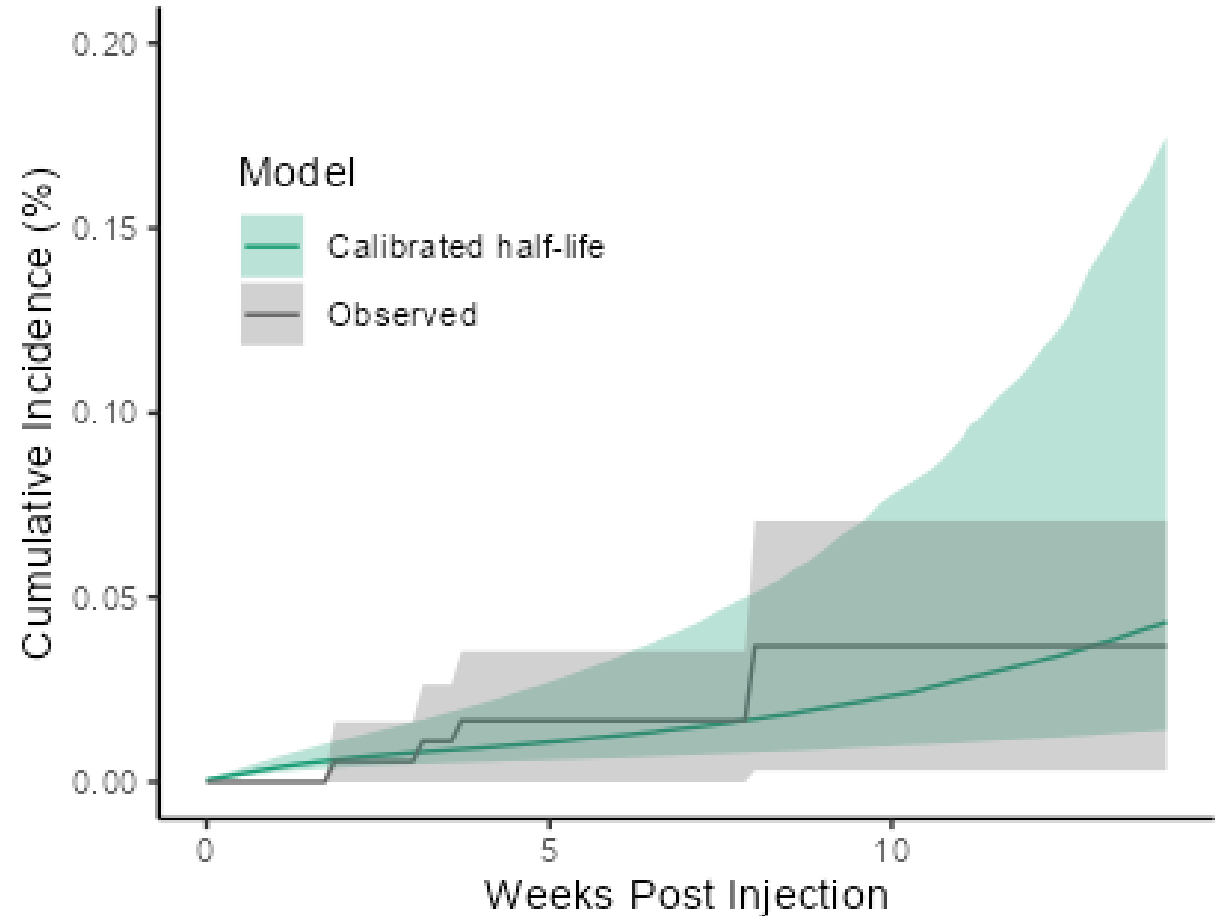
Time of exposure

- Since most recent injection
- Tail of previous injection
- Oral phase
- Before enrollment (off PrEP)

Histogram from
Delaney et al, Clin Infect Dis., 2017
doi:10.1093/cid/ciw666

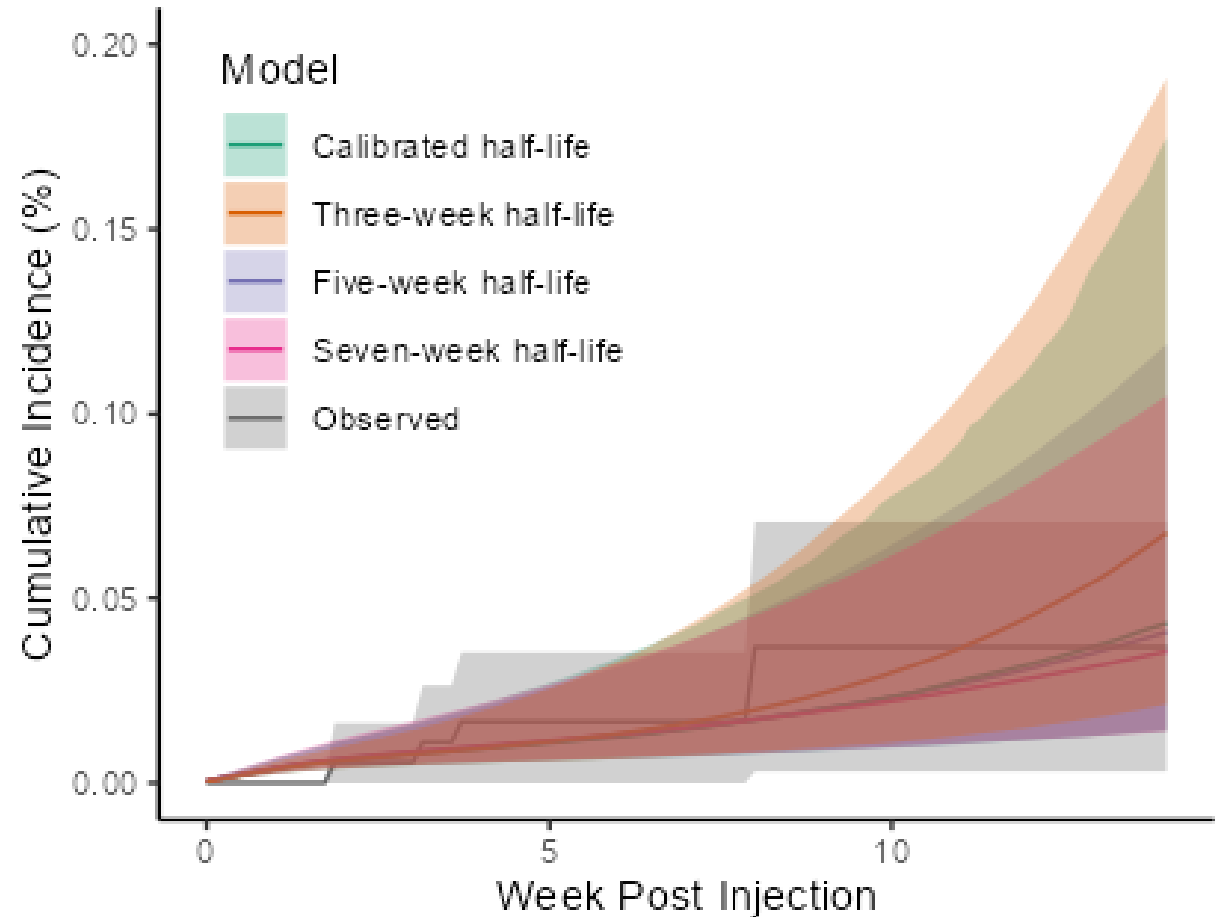
Calibration of Models to data

- We **calibrate** our model by
 - **Propose** potential values for the parameters describing the efficacy curve
 - **Simulate** dates of infection and detection
 - **Evaluate** the simulation and keep parameters with good agreement
- **Visualize** the fit (right) by comparing the cumulative HIV incidence
 - Observed in HPTN 083 (grey)
 - Simulated using the model (green)



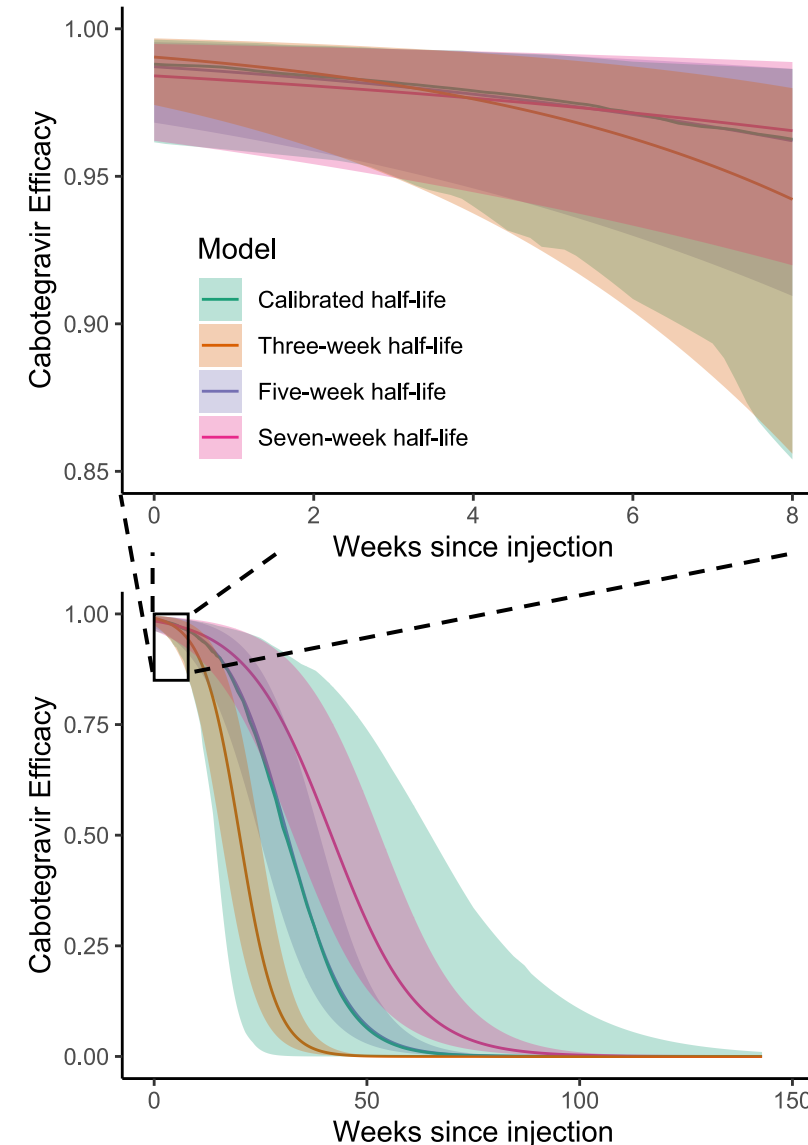
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- **Visualize** the fit (right) by comparing the cumulative HIV incidence
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- We also **fix** one of the parameters (**half life of the protection**) to either by **three**, **five**, or **seven** weeks.



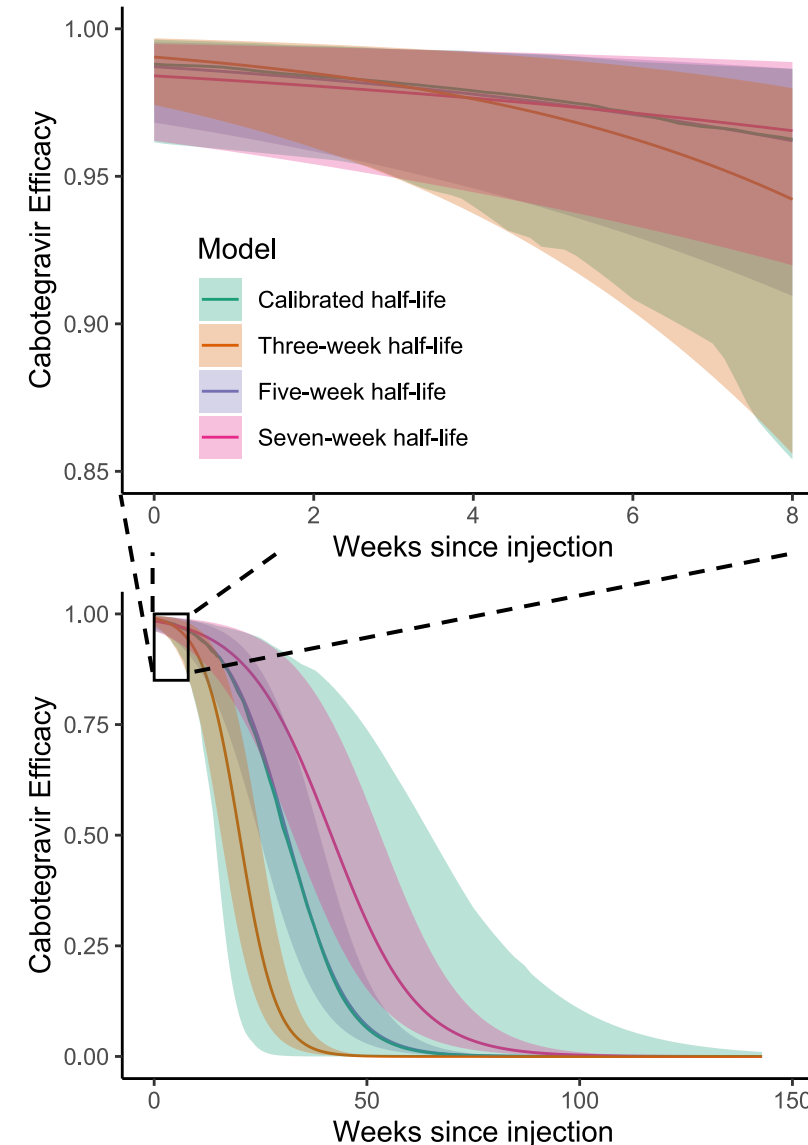
Estimates of Cabotegravir Efficacy

Weeks	Calibrated Half Life	Fixed Half Life		
		Three	Five	Seven
1 to 8	97.8 (93.1 – 99.2)	97.3 (93.1 – 99.1)	97.7 (94.4 – 99.2)	97.6 (94.4 – 99.2)
9 to 10	95.8 (82.4 – 98.5)	92.9 (82.7 – 97.4)	95.7 (89.8 – 98.5)	96.2 (91.3 – 98.8)
11 to 12	94.1 (73.9 – 98.2)	89.2 (75.0 – 96.0)	94.4 (87.0 – 98.0)	95.4 (89.6 – 98.5)
13 to 14	92.4 (60.8 – 97.8)	83.8 (65.5 – 93.9)	92.7 (83.5 – 97.3)	94.5 (87.6 – 98.2)
15 to 16	90.4 (43.8 – 97.3)	76.6 (54.5 – 90.7)	90.6 (79.3 – 96.5)	93.4 (85.2 – 97.8)



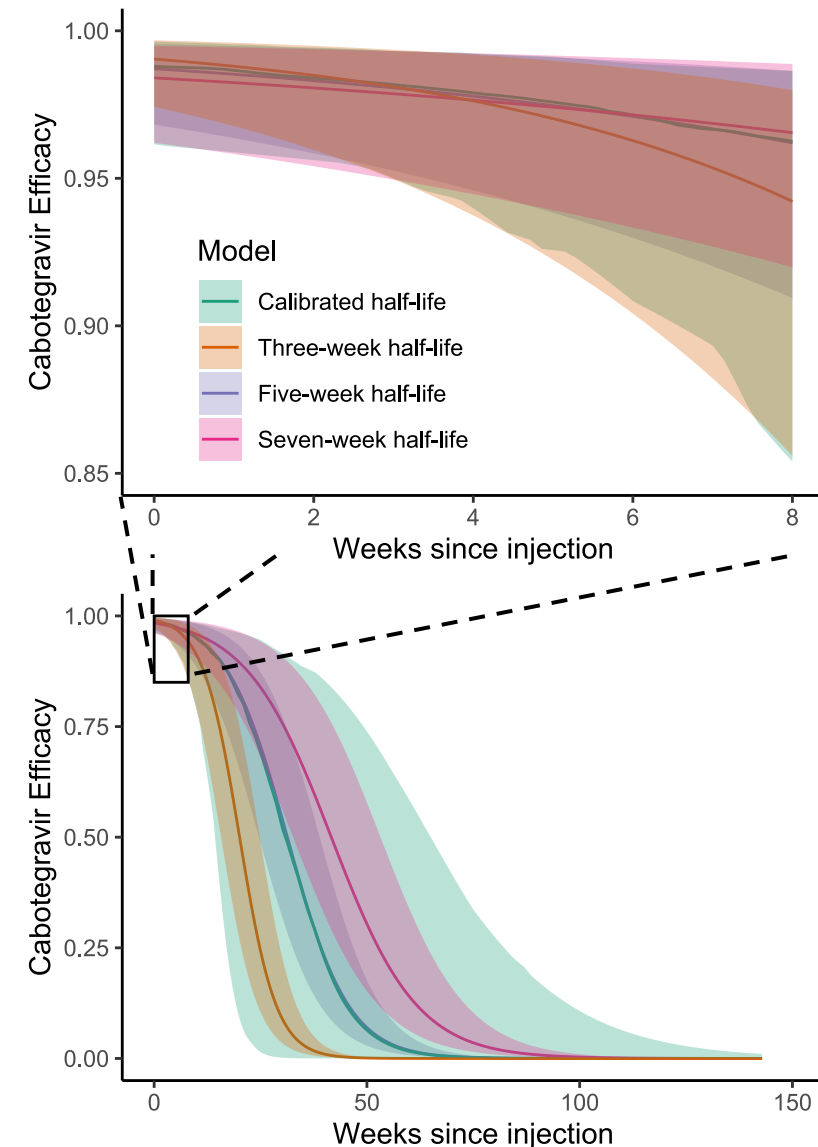
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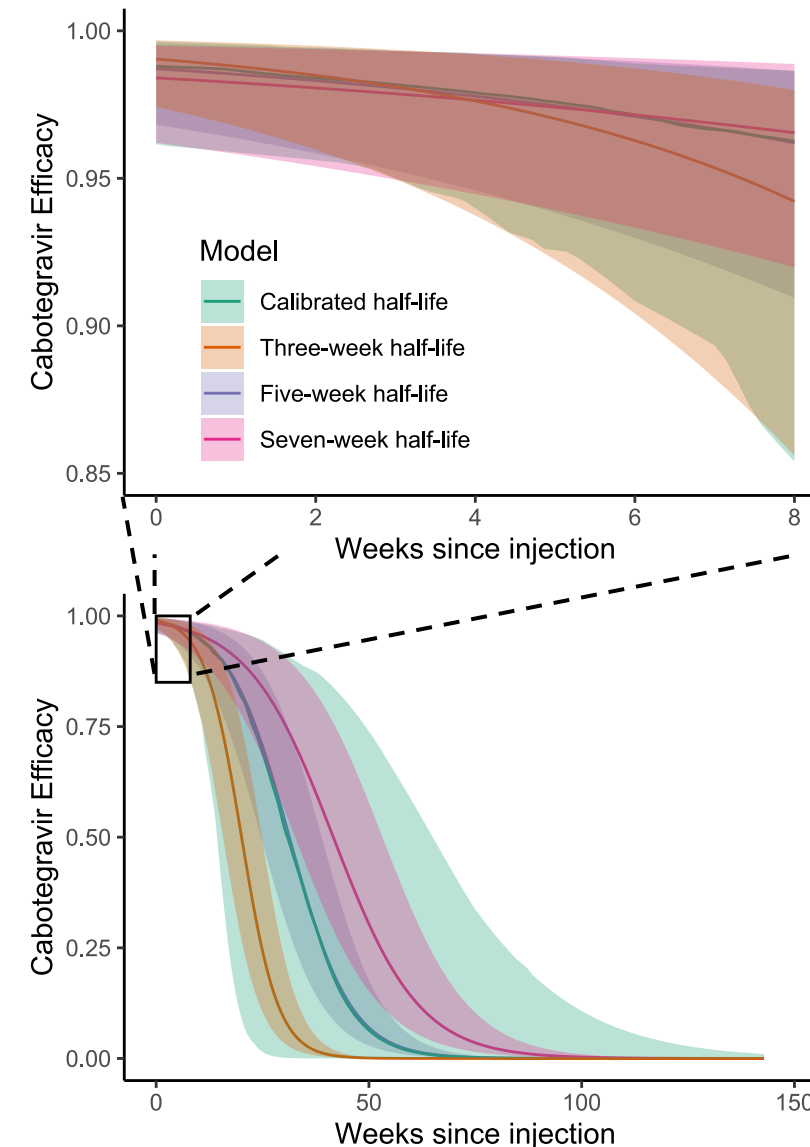
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Acknowledgments

- HPTN 083 Study Team
- HPTN Statistics and Data Management Center
- **HPTN Modeling Center**
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- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

