30th CROI 2023

Cabotegravir Pharmacology in the Background of Delayed Injections in HPTN 084

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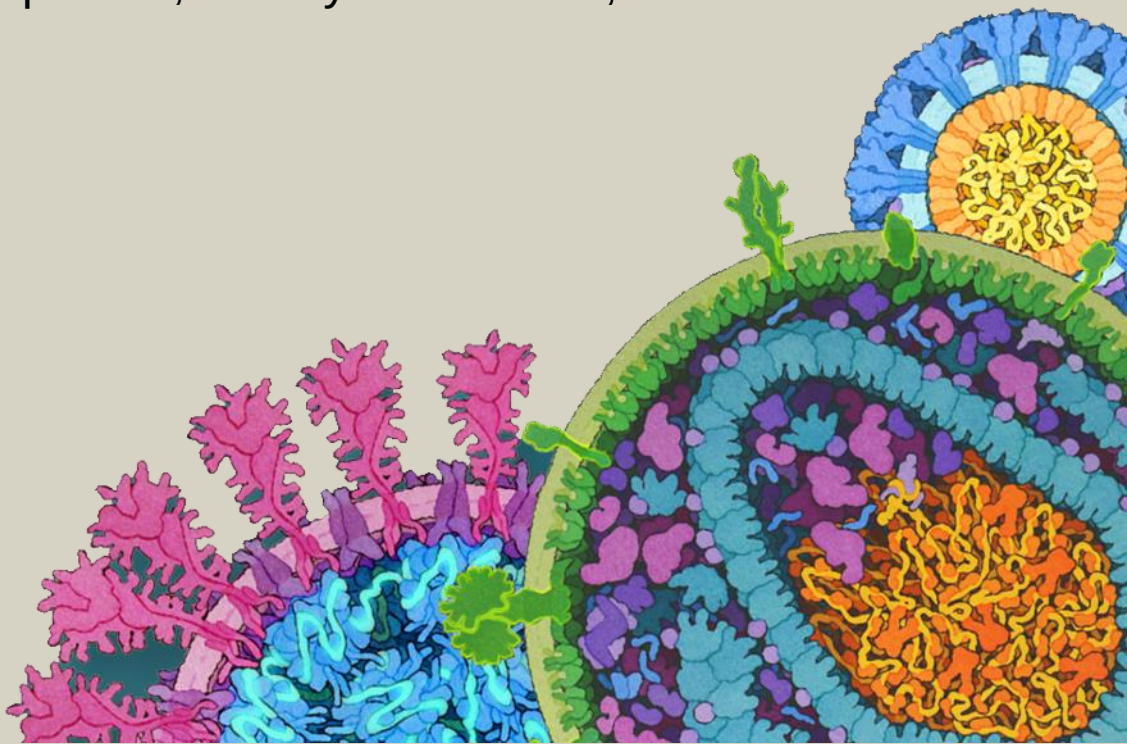


Overall Study Findings: HPTN 084

- HPTN 084 is an ongoing Phase 3 randomized controlled trial that demonstrated the superiority of long-acting injectable cabotegravir (CAB) compared to daily oral F/TDF for HIV prevention in individuals assigned female at birth.
  - HIV incidence CAB 0.20 vs F/TDF 1.85 per 100 py, HR 0.12; 95% CI 0.05 - 0.31

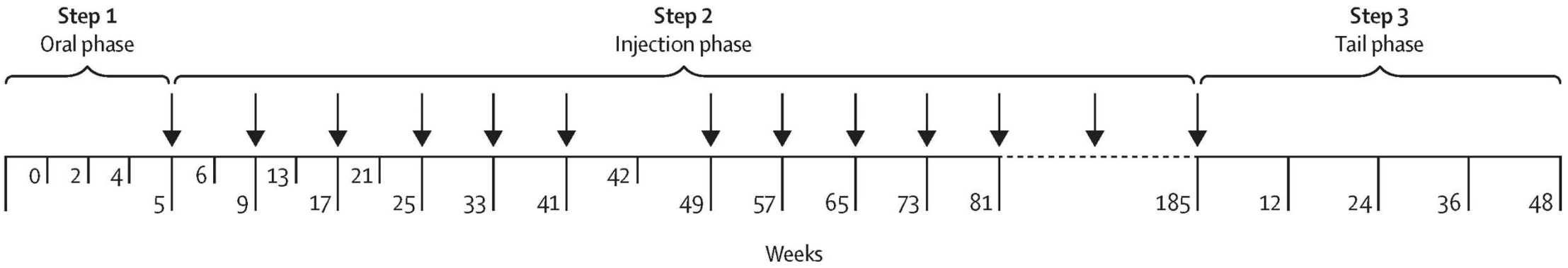
- The blinded portion of the trial was stopped at a planned interim review on 05Nov2020.

- Participants were subsequently unblinded and continued on their original randomized study regimen pending a protocol amendment to offer open-label CAB.

HPTN 084 Study Design

- Oral Lead-In: 30 mg CAB or oral F/TDF, placebo
- Injection Phase: 600 mg CAB-LA or oral F/TDF, placebo
- PK Tail Phase: Open-Label F/TDF

- The CAB-LA regimen was targeted to achieve concentrations >4x PA-IC_{90} (0.664 mcg/mL) in 80% of individuals, and >8x PA-IC_{90} (1.33 mcg/mL) in 50% of individuals



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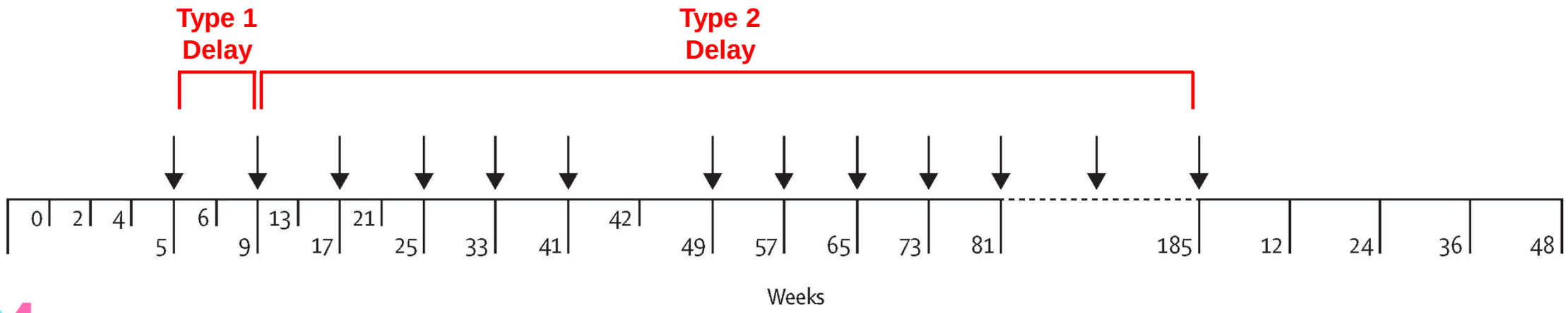
Evaluation of Delayed Injections in HPTN 084

- Interrogate the impact of delayed injections on CAB concentrations
  - Sampling was limited to participants randomized to the CAB study arm during the blinded phase of the trial
  - Sampling was limited to the following:
    - Type 1 Delay: If the second injection (week 9) took place **8-14 weeks** after the first injection (week 5)
    - Type 2 Delay: If any subsequent injection took place **12-18 weeks** after the last injection



Characteristics of Participants Who Received Delayed Injections

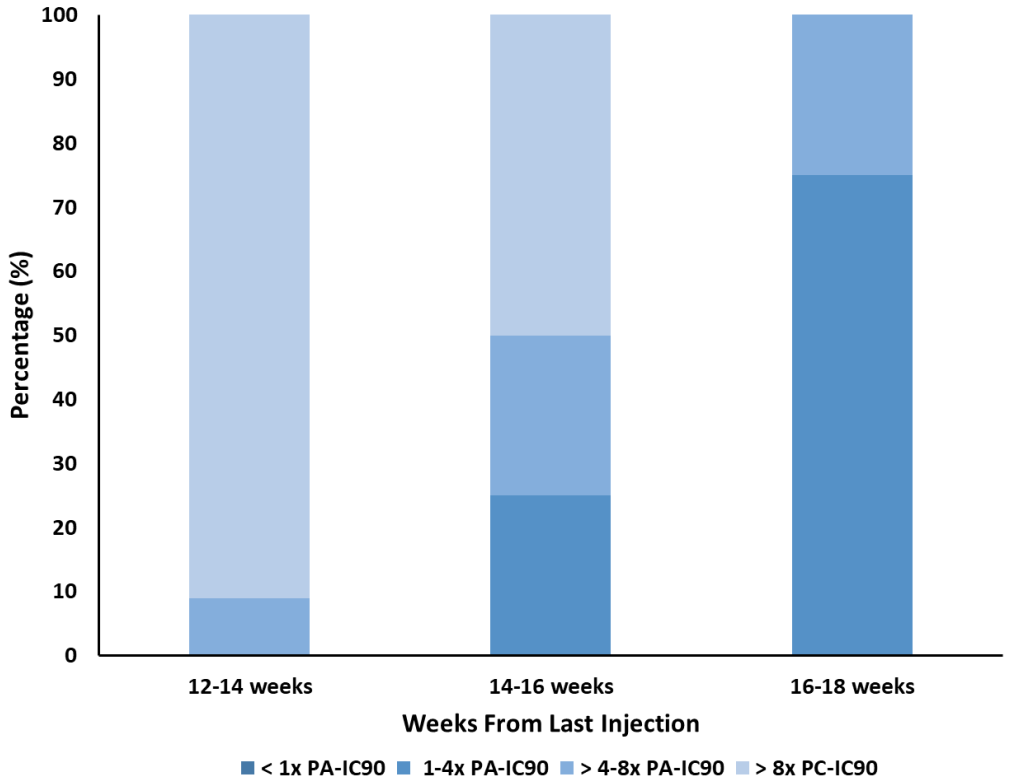
- 194/1614 participants (12%) had at least one delayed injection during blinded phase of HPTN 084; 224 total delays observed
  - 19 Type 1 Delays
  - 205 Type 2 Delays

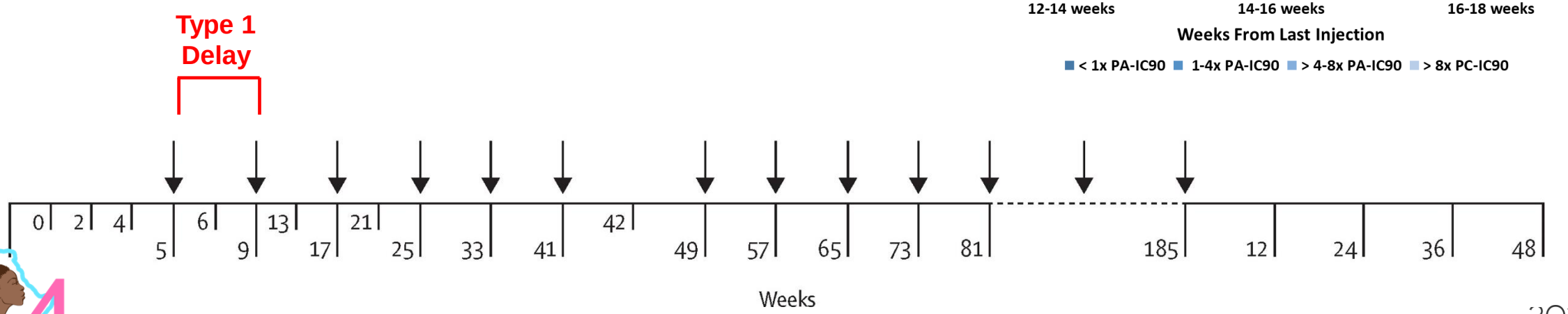
Country	Participants (n)	Percentage (%)
Botswana	8	4.1
Eswatini	7	3.6
Kenya	6	3.1
Malawi	10	5.2
South Africa	108	55.7
Uganda	26	13.4
Zimbabwe	29	15.0

- Participant Profile
  - Age (median): 25 years (18-44 years)
  - BMI (median): 26.3 (16.9-54.3)
  - Weight (median): 68 kg (40-146)

Injection Delays Between 1st and 2nd Injections (Type 1 Delays)

[CAB] Trough	8-10 weeks Between Injections	10-12 weeks Between Injections	12-14 weeks Between Injections
	N=11	N=4	N=4
>8x PA-IC_{90}	10 (91%)	2 (50%)	0 (0%)
>4-8x PA-IC_{90}	1 (9%)	1 (25%)	1 (25%)
1-4x PA-IC_{90}	0 (0%)	1 (25%)	3 (75%)
<1x PA-IC_{90}	0 (0%)	0 (0%)	0 (0%)





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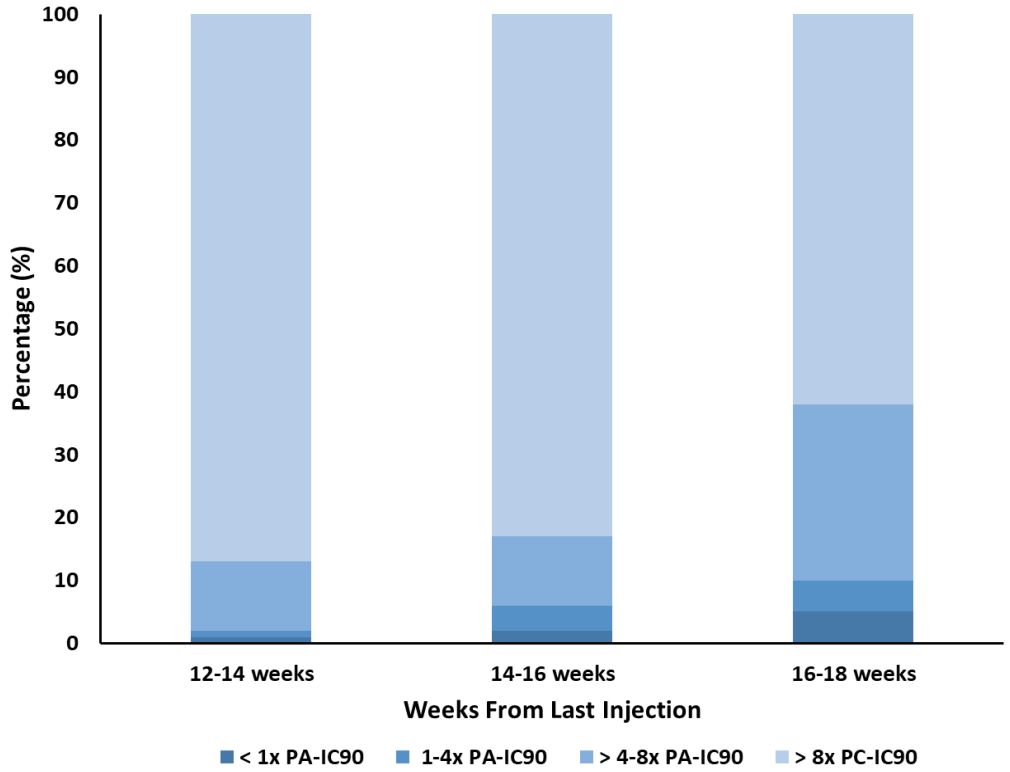
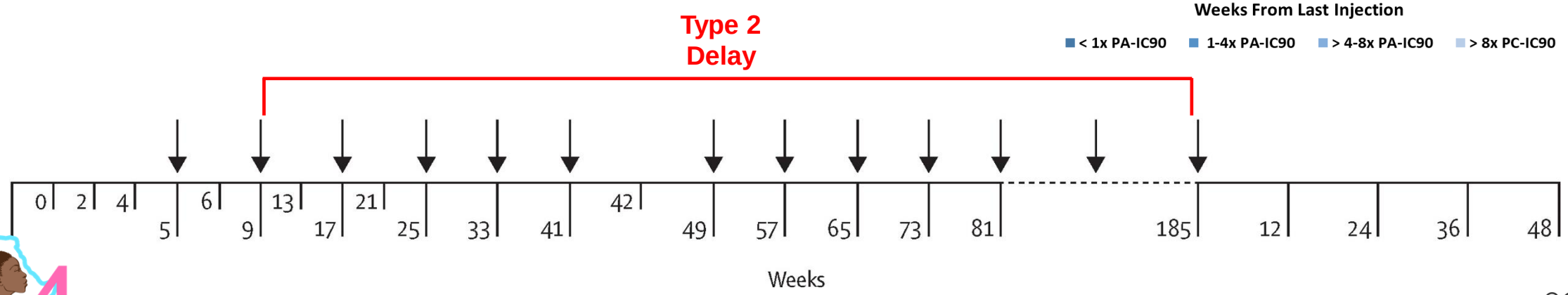
Injection Delays *After* the 2nd Injection (Type 2 Delays)

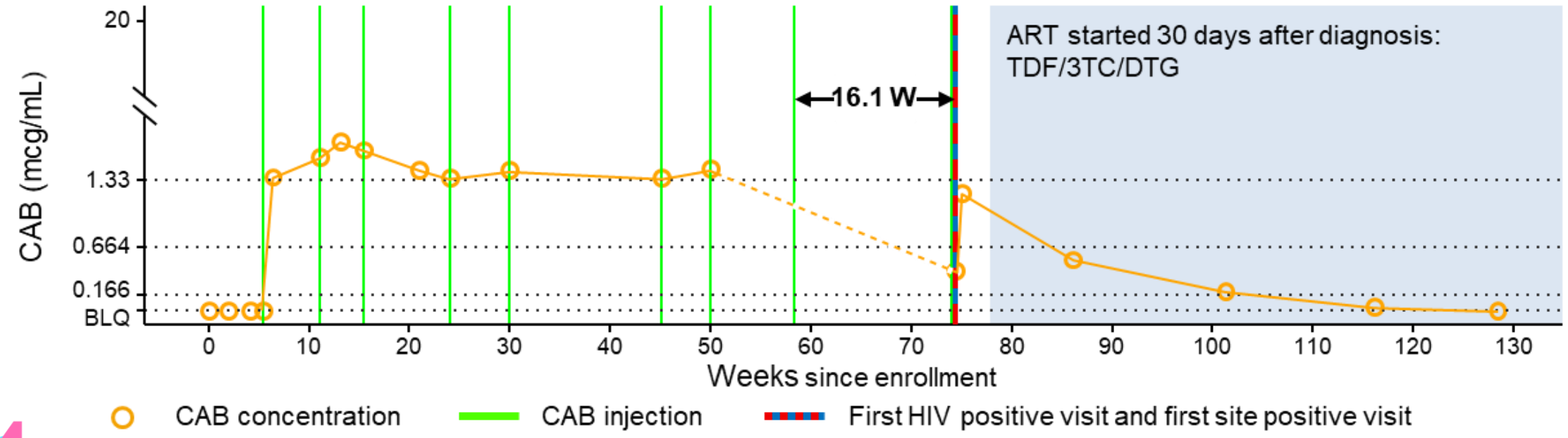
[CAB] Trough	12-14 weeks Between Injections	14-16 weeks Between Injections	16-18 weeks Between Injections
	N=109	N=57	N=39
>8x PA-IC_{90}	95 (87%)	48 (84%)	24 (62%)
>4-8x PA-IC_{90}	12(11%)	6 (11%)	11 (28%)
1-4x PA-IC_{90}	1 (1%)	2 (4%)	2 (5%)
<1x PA-IC_{90}	1 (1%)	1 (2%)	2 (5%)





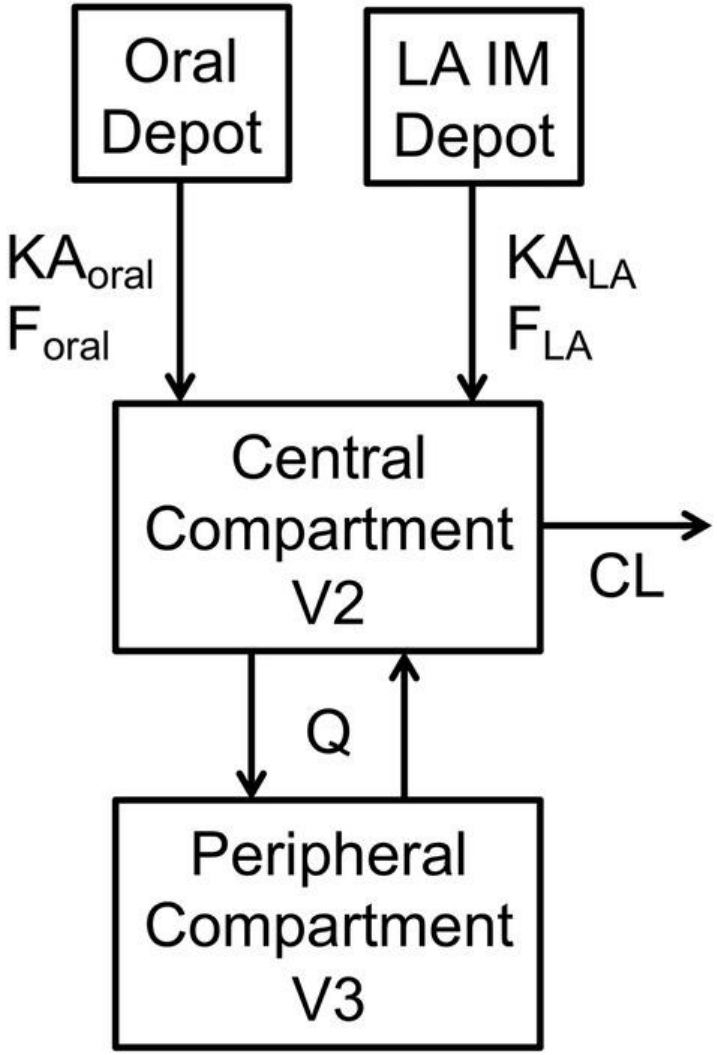
HIV Infections in Participant with Delayed Injections

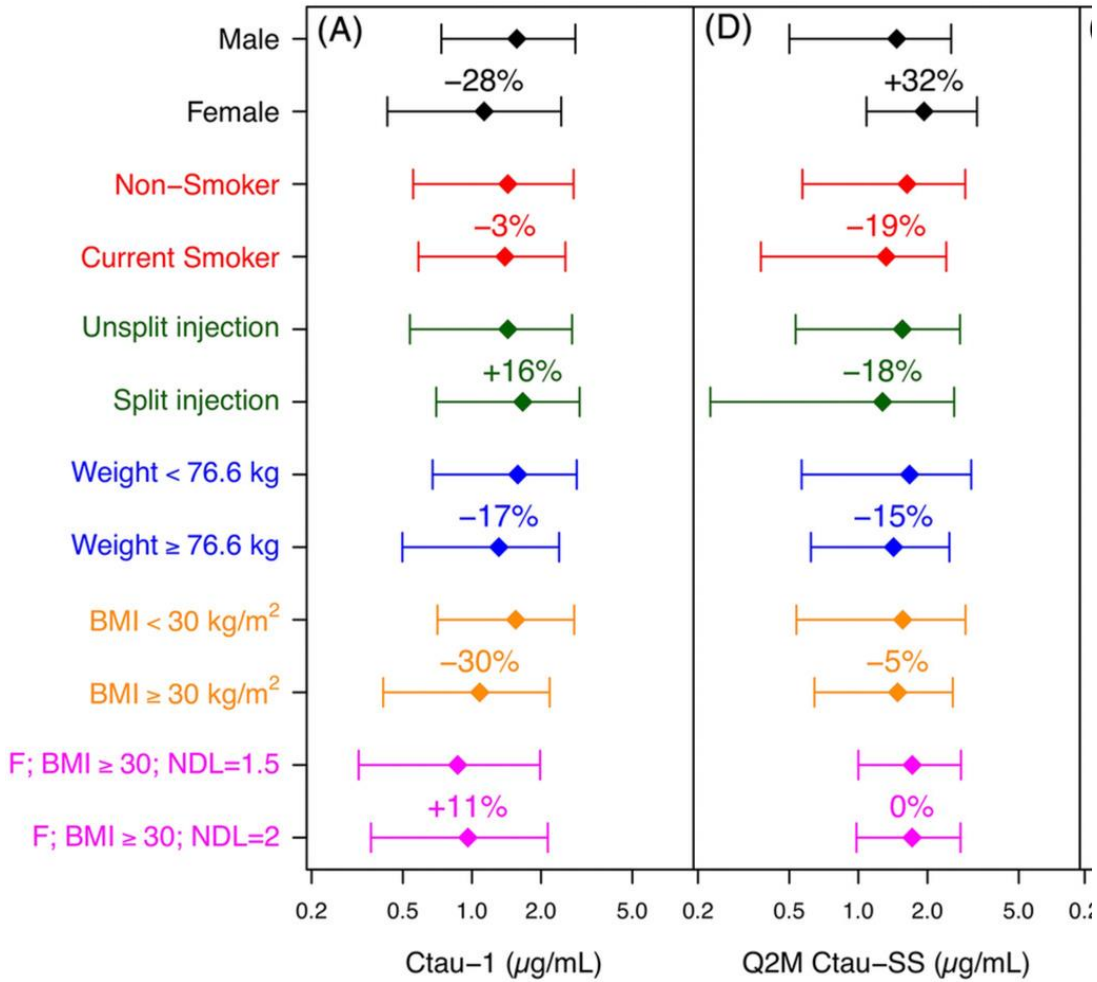
- During blinded phase of HPTN 084, one participant acquired HIV in the background of late injections
  - 3/9 injections occurred late (8.5, 15.1, 16.1 weeks)
  - CAB concentration at first HIV positive visit: 0.416 mcg/mL (<4x PA-IC_{90})



Delany-Moretlwe et al. Lancet. 2022; 399
Eshleman et al. J Infect Dis. 2022; 225(10)

CAB Population Pharmacokinetic (popPK) Model and Significant Co-variates





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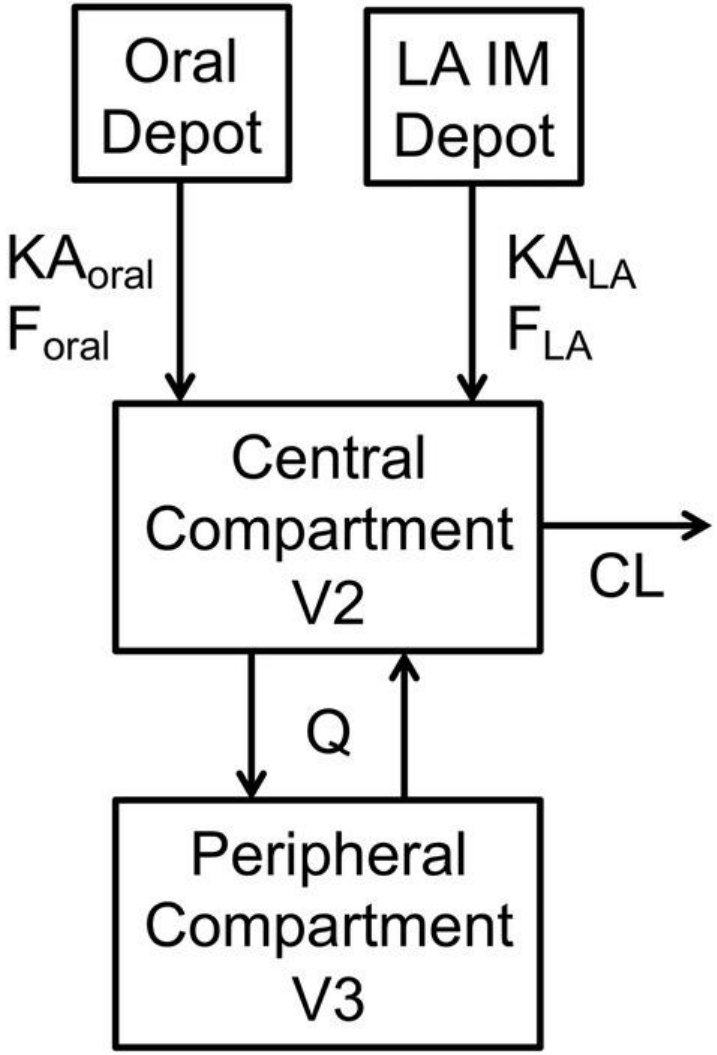

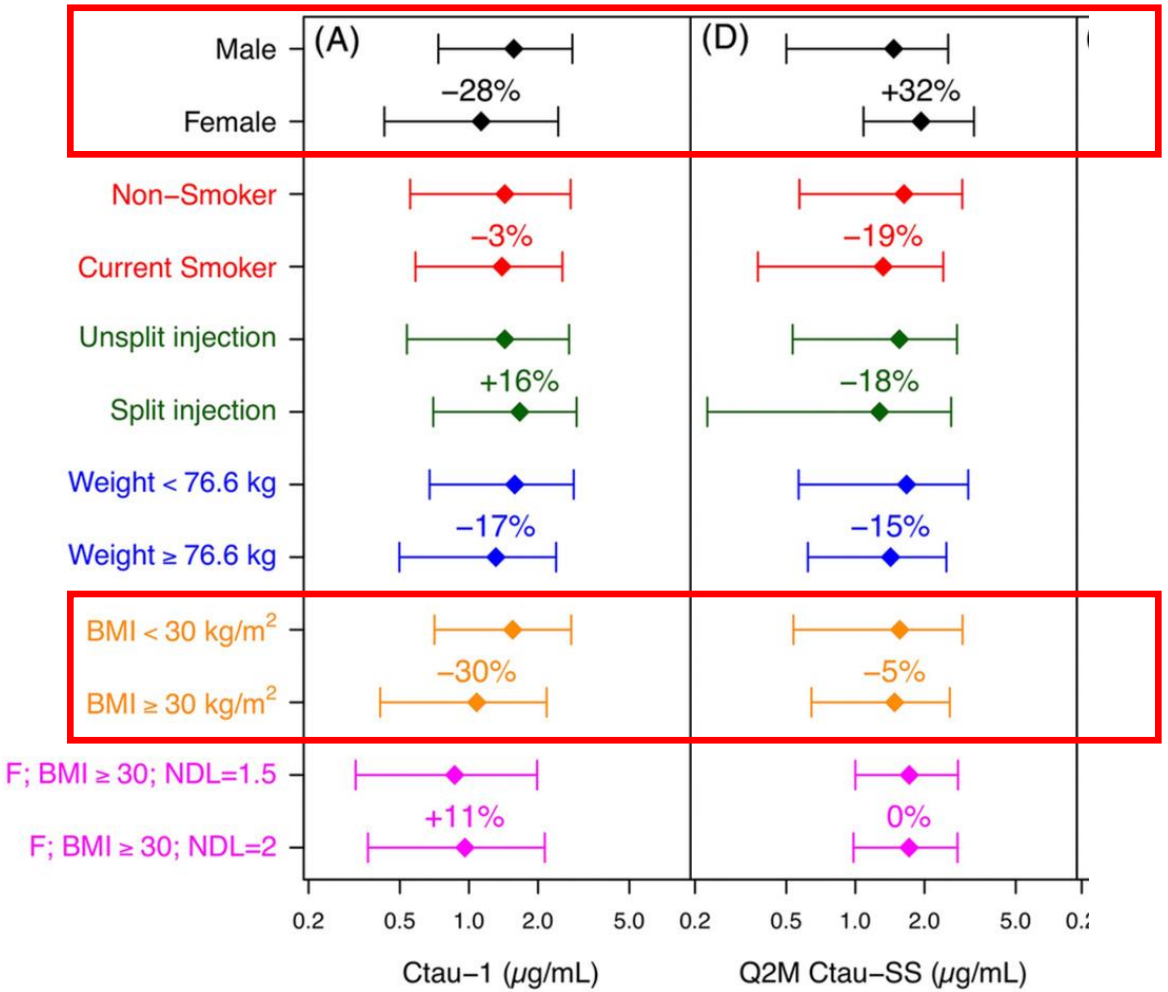

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Conclusions

- HPTN 084 participants on a CAB-LA 600 mg Q2M regimen who received late injections maintained CAB concentrations >4x PA-IC_{90} and >8x PA-IC_{90} 98% and 87% of the time, respectively, following a 6 week delay (12-14 weeks between injections)

- Data from HPTN 084 suggest that there may be up to 6 weeks of forgiveness in persons assigned female at birth who received delayed CAB injections.

Future Considerations

- While data suggest injection forgiveness in persons assigned female at birth, adoption of quarterly dosing (CAB-LA 600 mg Q3M) has not been evaluated for prevention
  - Q3M dosing should not be pursued in persons assigned male at birth
  - Empiric evidence to ensure target concentrations are achieved with alternative dosing regimens is needed

Acknowledgments

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- Gilead Sciences

HIV Prevention Trials Network

- Leadership and Operations Centre, FHI360
- Laboratory Centre (Johns Hopkins)
- Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchison Cancer Research Center
- HPTN Leadership

HPTN 084 Study team

- 20 sites in 7 countries in sub-Saharan Africa
- Community advisory boards and partners

… and our study participants!