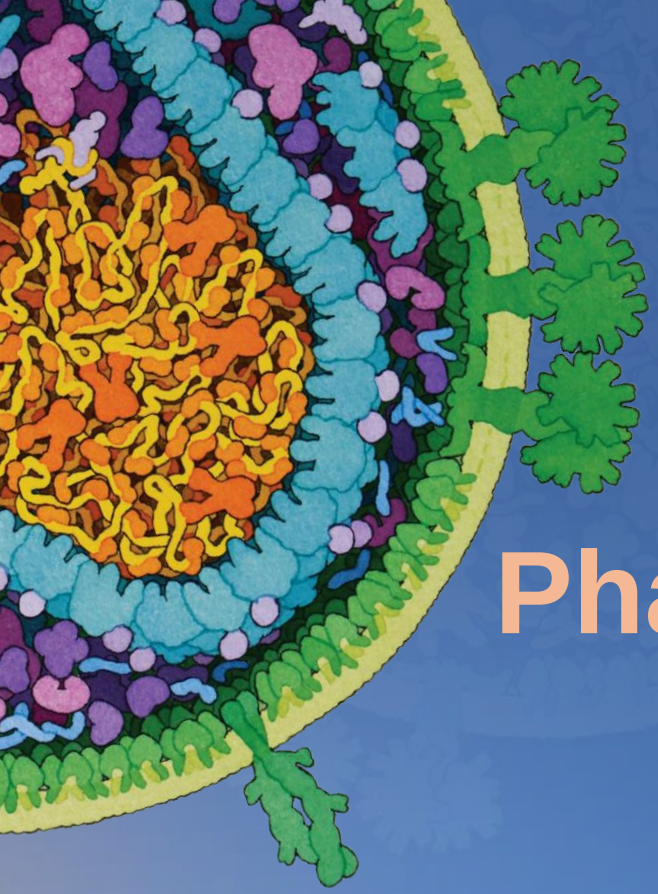

SCIENCE SPOTLIGHT™

Cabotegravir Population Pharmacokinetic (PPK) Simulation to Inform Q2M Strategies Following Dosing Interruptions

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Abstract # 1327

CROI 2021

Cabotegravir (CAB) for HIV Treatment and PrEP

- CAB is an integrase strand transfer inhibitor formulated as a long-acting (LA) injection for treatment and prevention of HIV, and as a daily tablet for use as oral lead-in and bridging therapy for LA injection interruptions.
  - Monthly IM injection regimen of CAB LA and rilpivirine (RPV) LA was non-inferior to standard oral therapy in maintaining HIV-1 suppression for HIV treatment in 2 Phase 3 studies [1,2] (approved in US, Europe and Canada).
  - Q2M treatment regimen of CAB LA and RPV LA was non-inferior to QM treatment regimen [1,2] in Phase 3 study [3] (approved in Europe).
  - CAB LA as a single agent administered Q2M was superior to daily standard-of-care oral TDF/FTC for PrEP in men and transgender women who have sex with men and in cisgender women in 2 Phase 3 PrEP studies [4,5].
- One-week delay of injection was generally permitted in Phase 3 studies. Longer delays are expected to lower drug exposure, and may be managed by oral CAB+RPV bridging therapy during the period of delay (oral bridging).
- In this analysis, CAB concentration-versus-time profiles following injection delays ranging from 1 to 12 weeks at various injection visits were simulated using CAB population pharmacokinetic (PPK) model.
- The aim was to inform strategies for managing CAB LA dosing interruptions for the Q2M regimen. Recommendations for managing RPV LA dosing interruptions are presented separately (CROI 2021 abstract #1189).

FTC: Emtricitabine; IM: intramuscular; LA: long-acting; PrEP: pre-exposure prophylaxis; Q2M: once every 2 months; RPV: rilpivirine; TDF: Tenofovir Disoproxil Fumarate.

1. Swindells et al. *N Engl J Med*. 2020;382:1112-1123. **2.** Orkin et al. *N Engl J Med*. 2020;382:1124-1135. **3.** Overton et al. CROI 2020. Slides 3334. **4.** Landovitz et al. AIDS 2020; Virtual. Slides OAXLB01. **5.** ViiV Healthcare. www.viivhealthcare.com/en-gb/media/press-releases/2020/november/viiv-Healthcare-announces-investigational-injectable-cabotegravir-is-superior-to-oral-standard-of-care-for-HIV-prevention-in-women. Accessed January 23, 2021.

Injection Delays

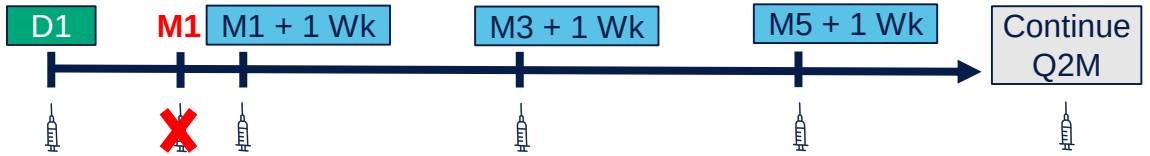
- 1 to 12 weeks of delay in dosing of the 2nd, 3rd, and 4th injection were simulated. Q2M dosing was resumed after delay. All injections were 3 mL (600 mg CAB).
- Oral bridging for a duration of 1 – 2 months starting at the time when the scheduled injection was missed was simulated. The 3rd injection was delayed and considered representative of any injection delay.
- CAB concentrations simulated using CAB population pharmacokinetic model (see Backup slide 1 and 2) must meet **all** 3 criteria to be considered acceptable:
  - Approximately ≥95% of simulated subjects should maintain concentrations of ≥0.65 µg/mL (CAB Phase 3 benchmark).
  - 100% of simulated subjects should maintain concentrations of ≥0.166 µg/mL (in vitro PA-IC90).
  - Median simulated CAB concentration should be ≤13.1 µg/mL.

Initiation injection (1 month before next injection)
Maintenance injection (2 months before next injection)
Continue injection Q2M (once every 2 months)
Oral bridging (30 mg CAB tablet daily)

M: month. Wk: week. See Backup slide 2 for full list of simulations.

Simulation 1: No delay

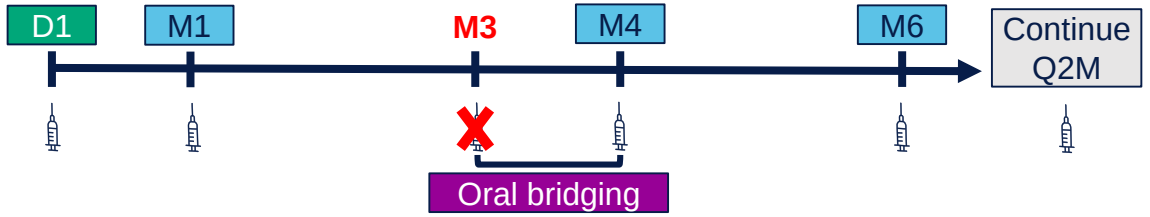
Simulation 2: 1-week delay of injection 2



Simulation 5: 4-week delay of injection 2

Simulation 6: 4-week delay of injection 2 and re-initiate Q2M dosing

Simulation 35: 4-week oral bridging for delay of injection 3



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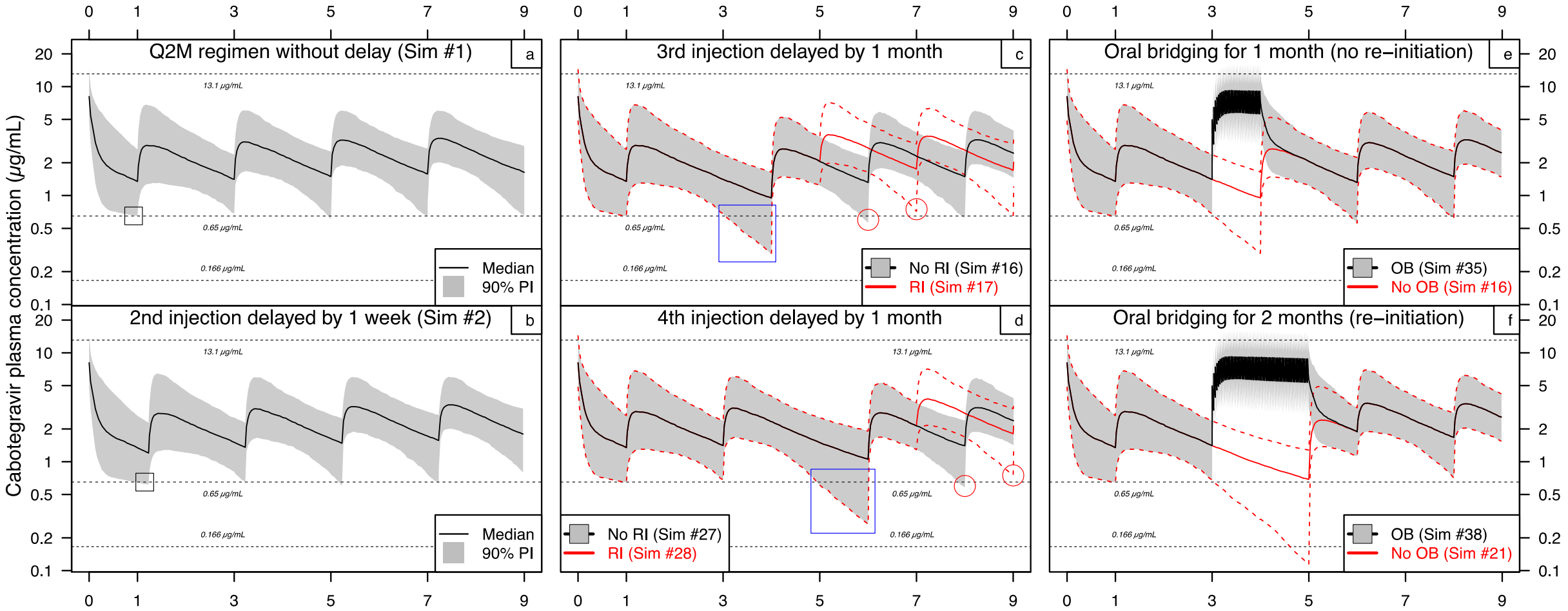
Simulated CAB Concentration-versus-Time Profiles

Figure a & b: Delays of ≤1 week provided similar exposure to the standard Q2M regimen (☐)

Figure c & d: Longer delays = exposure below benchmark (☐); Re-initiation = exposure above benchmark (O)

Figure e & f: Oral bridging provided therapeutic and safe exposure for planned injection interruptions



OB: oral bridging; PI: prediction interval; RI: Re-initiate Q2M regimen.

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Predicted % of Subjects Above CAB Phase 3 Benchmark 0.65 µg/mL

- Target (■): ~95% of subjects above benchmark.
- Delays of ≤1 week (■): proportion of subjects above benchmark remained <95% for 5 days and fell to 93.6% temporarily. The difference between 93.6% and 95% was deemed minimal and was judged to have little impact on efficacy due to the short duration.
- Delays of >1 week (■): proportion of subjects above benchmark fell to as low as 9.6%. After resuming the delayed injection:
  - Delays of 2 – 4 weeks (■): ≥92.8% of subjects above benchmark. The difference between 92.8% and 95% was deemed to be minimal and have little impact on efficacy due to the short duration.
  - Delays of >4 weeks (■): >95% of subjects above benchmark only achievable with re-initiation of Q2M regimen. Considering the low CAB exposure prior to resuming the delayed injection, re-initiation of Q2M regimen is recommended.
- Similar results were obtained for delaying the 3rd and 4th injections (Backup slide 3). Interpretations made based on delays of the 4th injection are applicable to subsequent injections.

Length of Delay of 2nd Injection	Time Point of CAB Trough Concentration	
	Trough prior to resuming the delayed injection	Trough after resuming the delayed Injection [a]
No Delay	95.0	95.6
1 Week	93.6	94.8
2 – 4 Weeks	77.4 – 91.4	92.8 – 94.2
4 – 12 Weeks	9.6 – 77.4	91.2 – 92.8
		96.0 – 96.2 (re-initiation)

a. Injections continue Q2M without re-initiating the Q2M regimen unless specified otherwise.

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Conclusions

- Adherence to the dosing schedule of Q2M regimen is strongly recommended.
- CAB injection delays of up to 1 week were predicted to have minimal impact, but longer delays have a greater impact, particularly for the 2nd injection.
- CAB oral bridging was predicted to provide therapeutic and safe exposure for planned interruptions in CAB LA IM injection.
- Regardless of oral bridging, CAB simulations support:
  - ≤2 months between the 1st and 2nd injections or ≤3 months between subsequent injections (i.e., injection is delayed by ≤1 month): resume 3 mL injections Q2M as soon as possible.
  - >2 months between the 1st and 2nd injections or >3 months between subsequent injections (i.e., injection is delayed by >1 month): re-initiate the Q2M regimen beginning with an initiation injection of 3 mL followed by a 2nd injection of 3 mL one month later and injections of 3 mL Q2M thereafter.
- Guidance for resuming CAB LA injections following injection delays and CAB oral bridging is aligned with RPV as part of a complete HIV treatment regimen.

CAB: cabotegravir; IM: intramuscular; LA: long-acting; PrEP: pre-exposure prophylaxis; Q2M: once every 2 months.