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

HIV Incidence per 100 person-years

- Cab-LA Arm: 0.41 (66% Reduction)
- TDF/FTC Arm: 1.22

Follow-up

Landowitz et al, NEJM, 2021
doi: 10.1056/NEJMoia2101016
Efficacy estimates from HPTN 083

HIV Incidence (ITT) per 100 person-years

Cab-LA Arm

TDF/FTC Arm

Counterfactual Placebo Arm

0.41

1.22

???

66% Reduction

Efficacy (ITT)

Follow-up

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Efficacy estimates from HPTN 083

Cab-LA Arm

TDF/FTC Arm

HIV Incidence per 100 person-years

0.41

66% Reduction

Follow-up

Incidence Pills Per Week

8.76 4.48 0.08

BLQ <2 2+

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)

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

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

Marshall et al, Lancet HIV, 2018
doi:10.1016/S2352-3018(18)30097-3
• 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, 8x PAIC90)
  - 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

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.

Time between **most recent injection** and first HIV-positive visit highlighted.

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Proposed endpoint analysis

- 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.
- Time between **most recent injection** and first HIV-positive visit **highlighted**

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

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)
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)
- We also **fix** one of the parameters (**half life of the protection**) to either by **three**, **five**, or **seven** weeks.
## Estimates of Cabotegravir Efficacy

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<th>Fixed Half Life</th>
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<td>Three</td>
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### Graphical Representation

- **Model**: Calibrated half-life, Three-week half-life, Five-week half-life, Seven-week half-life
- **Axes**: Weeks since injection, Cabotegravir Efficacy
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Presentation Highlights

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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.