CROI 2021 Update: Evaluating Options for Long-Acting PreP

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Nicholas Yared, M.D.
Infectious Disease Senior Staff
Henry Ford Health System

HPTN 083 – Injectable Cabotegravir (CAB) for PrEP

- HPTN 083 showed 66% reduction in HIV incidence in men who have sex with men (MSM) and transgender women (TGW) randomized to CAB 600mg every 8 weeks vs. daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)
- 58 incident infections among 4566 participants
  - 13 in CAB group, annual incidence 0.41%
  - 39 in TDF/FTC group, annual incidence 1.22%
- Marzinke et al. used data from HPTN 083 to characterize the 58 cases where infection occurred

Marzinke M, et al. Laboratory analysis of HIV infections in HPTN 083: Injectable CAB for PrEP

Lab Analysis of HPTN 083 – Methods

- Plasma concentrations of CAB and TFV-diphosphate
- Concentrations from dried blood spots (DBS) using liquid chromatography-tandem mass spectrometry
- HIV Ag/Ab test, HIV discriminatory test, and RNA assays for HIV status and timing
- Resistance testing to look for resistance-associated mutations (RAMs) if HIV-1 RNA level > 500 copies/mL

Results of Lab Analysis of Incident HIV Cases in HPTN 083 – **Cabotegravir Arm**

- 12 incident infections
  - 5 with no recent CAB dosing
  - 4 occurred despite on-time CAB injections & targeted CAB concentrations
  - 3 occurred in oral lead-in phase (1 had no CAB detected)
- RAMs
  - 5 had INSTI-related mutations (Q148 or R263K)
  - 1 had NNRTI mutations only
  - 1 had NRTI & NNRTI mutations

Study Arm	CAB Arm	TDF/FTC Arm
Incident infections	12	39
Baseline infections	4	3
Total	16	42

Marzinke M, et al. Laboratory analysis of HIV infections in HPTN 083: Injectable CAB for PrEP

Results of Lab Analysis of Incident HIV Cases in HPTN 083 – **TDF/FTC Arm**

- 37 incident infections in patients with suboptimal drug concentrations
- 1 infection due to transmission of TDF/FTC-resistant HIV-1
- 1 infection occurred despite targeted drug concentrations
- RAMs
  - 7 had NNRTI mutations
  - 3 had NRTI mutations
  - 3 had both NRTI & NNRTI mutations

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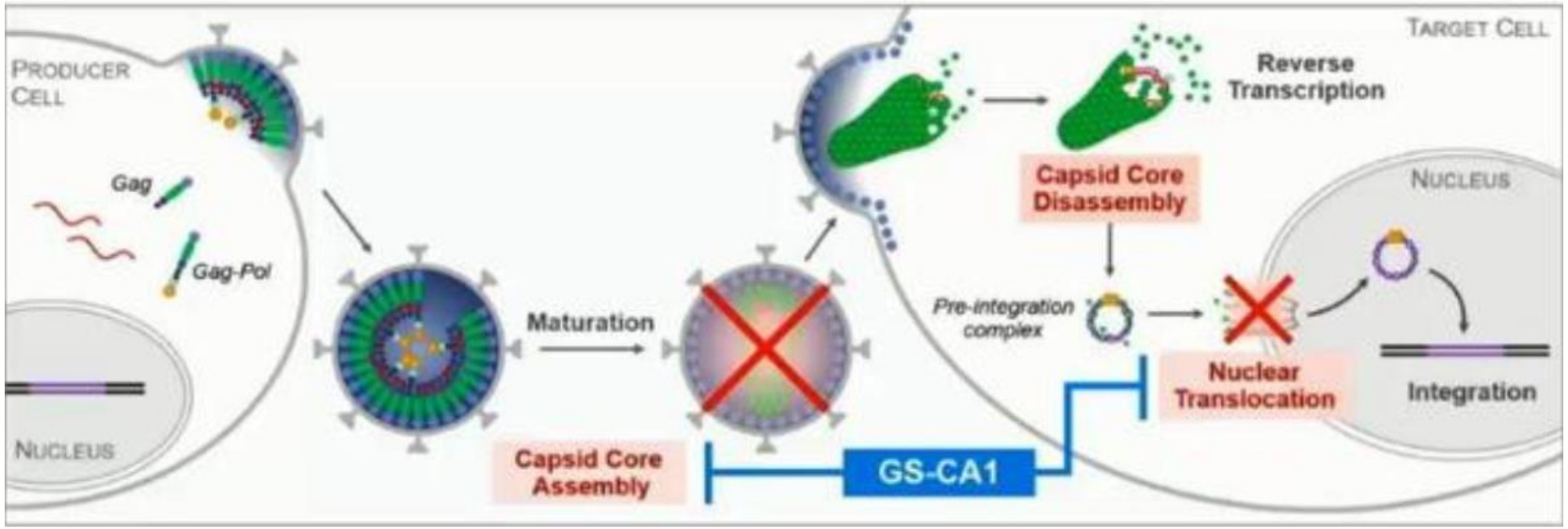
HPTN 083 Incident Infection Conclusions

- Both oral daily TDF/FTC and Q8 week injectable CAB were effective for PrEP in MSM and TGW
- **Integrase inhibitor resistance was encountered in some cases in the CAB arm**
- Incident infection in TDF/FTC arm primarily driven by oral pill non-adherence

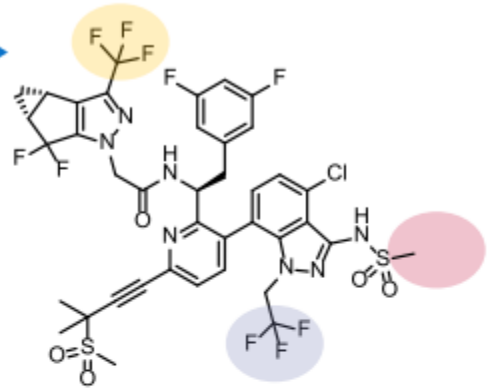
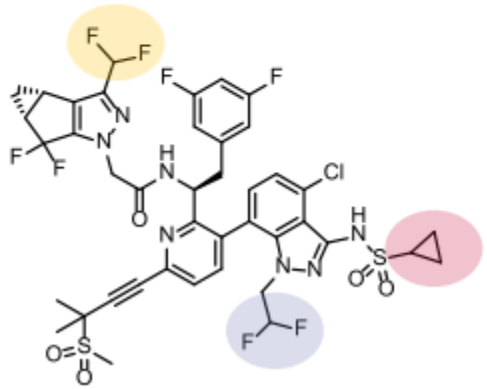
Lenacapavir

- First-in-class HIV capsid inhibitor
- HIV capsid protein = p24
  - Necessary for virion assembly
  - p24 conical structure needed for viral infectivity
- Single SC dose reduces plasma HIV viral load by 2.2 logs after 9 days
- Maintains sustained antiviral plasma concentrations for > 6 months



Link JO, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature 2020;584:614-18.

Lenacapavir and GS-CA1 Characteristics

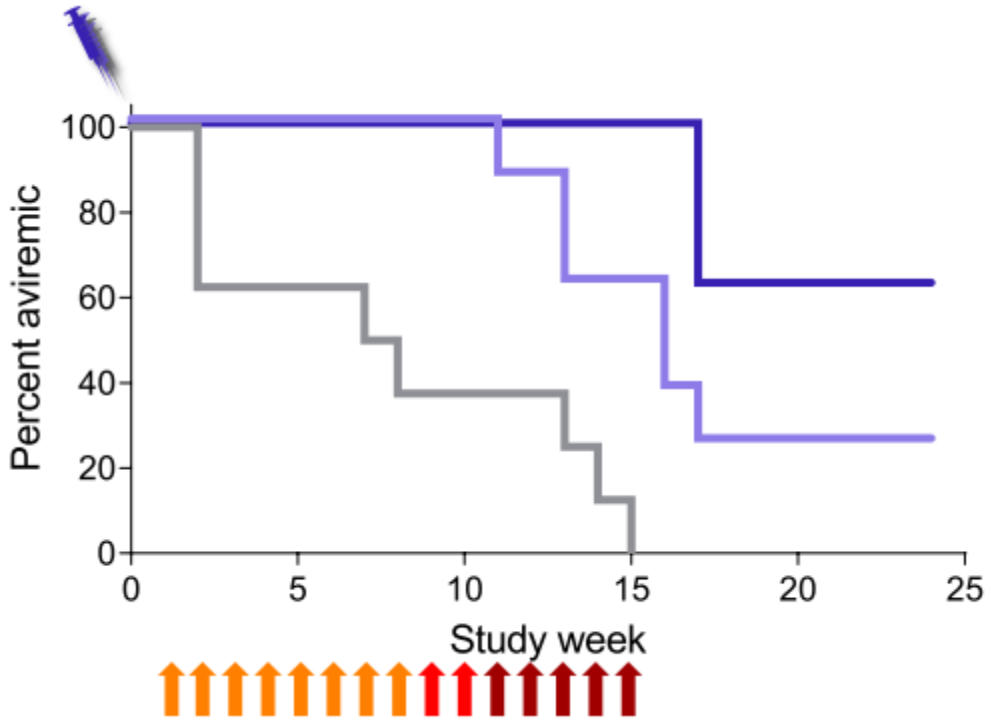
	Structure	Status	PBMC EC_{50} (nM)
LEN[1] (GS-6207)		• Favorable safety & tolerability profile in clinical trials* • 2.3-$\log_{10}$ HIV-1 RNA decline after 9 days of monotherapy* • Q6M formulation in Phase 2/3 trials in PLWH	HIV† 0.050 SHIV‡ 0.569
GS-CA1[2] (LEN analog)		• Preclinical efficacy in hu-mice • Tool compound for preclinical research studies	HIV† 0.130 SHIV‡ 0.748

GS-CA1 for PrEP – Repeat Mucosal Challenge Study

- Objective: Determine efficacy of GS-CA1 long-acting formulation to prevent infection after repeat SHIV exposure in rhesus macaques
- Groups
  - GS-CA1 300 mg/kg
  - GS-CA1 150 mg/kg
  - Placebo
- Single dose of GS-CA1 administered followed by weekly intrarectal SHIV challenges
- Monitored weekly plasma viral load (qRT-PCR) and serology
- Analysis of per-exposure risk reduction using Cox proportional hazard model

1.) Subbarao S, et al. J Infect Dis 2006. 2.) Garcia-Lerma JG, et al. PLoS Med 2008. 3.) Andrews CD, et al. Sci Transl Med 2015. 4.) Bekerman E, et al. J Antimicrob Chemother 2020.

GS-CA1 and Simian HIV Challenge Results

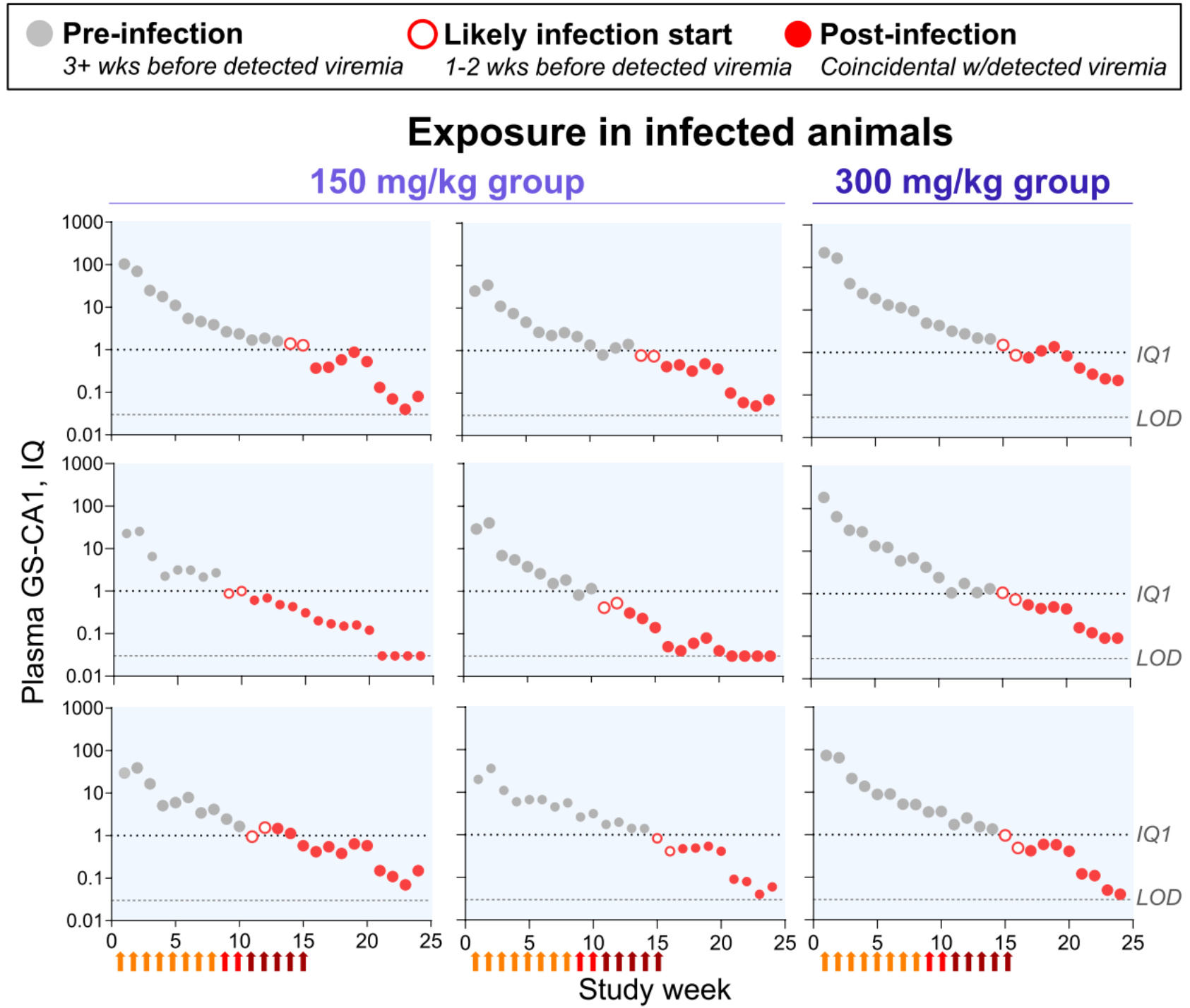


	No. Protected	Median Weeks to Infection (95% CIs)	Hazard Ratio	p-value
GS-CA1 300 mg/kg	5 / 8	Not reached (17, –)	0.038	**0.0002**
GS-CA1 150 mg/kg	2 / 8	16 (11, –)	0.141	**0.0061**
Placebo	0 / 8	7.5 (2,14)	1	

Hazard ratios, p-values calculated using Cox regression model.

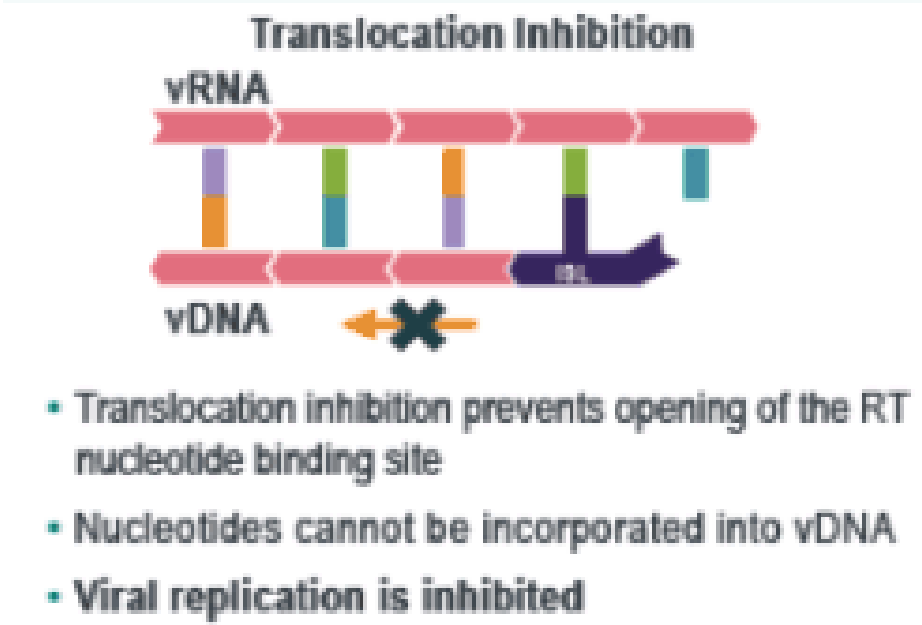
- Infection occurred in GS-CA1 groups after marked compound washout (~9-10 weeks)
- 86% risk reduction in infection in low-dose group
- 96% risk reduction in infection in high-dose group

IQ: Inhibitory Quotient, protein-adjusted 95% effective concentration



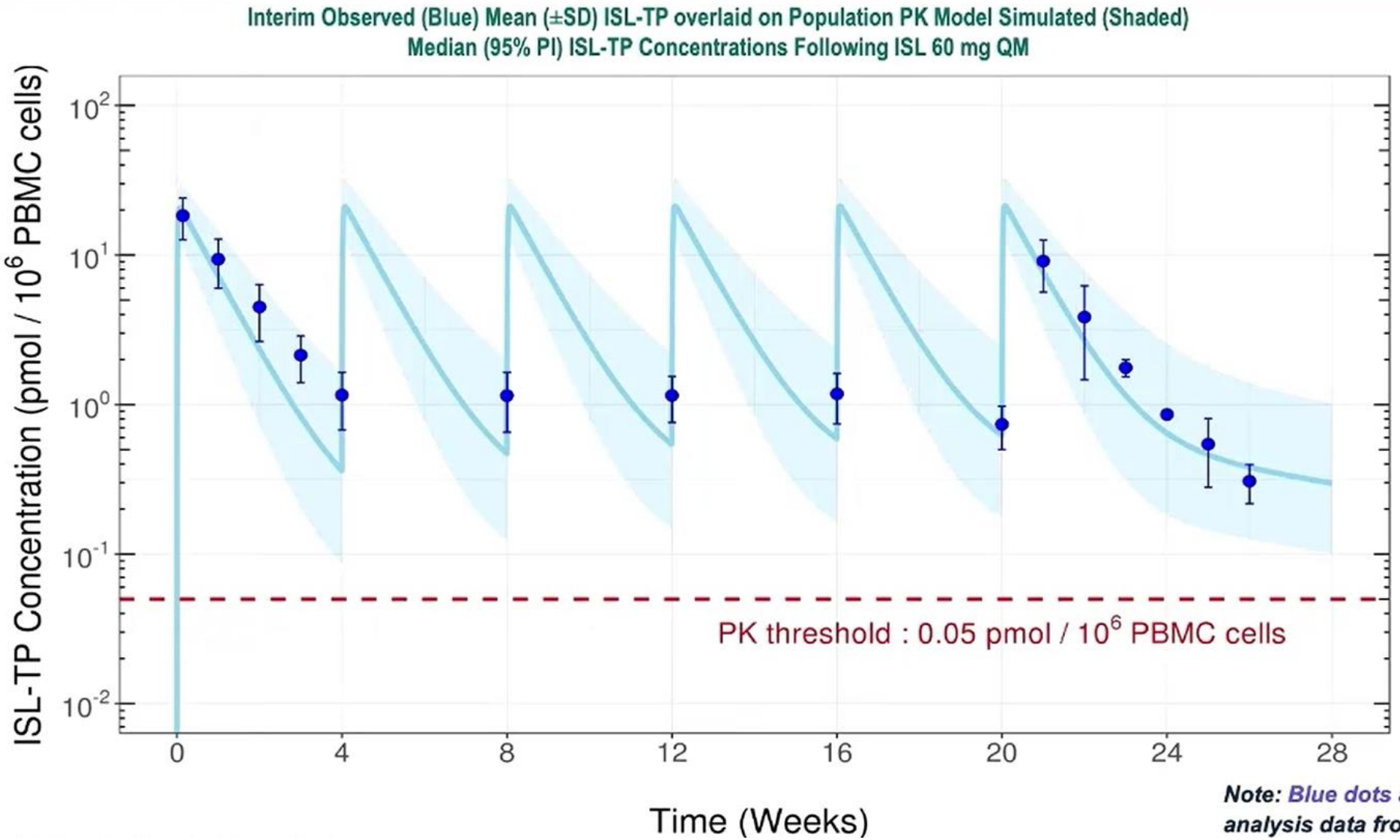
Nucleoside Reverse Transcriptase Translocation Inhibitors (NRTTIs)

- Islatravir (ISL)
  - First-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Active against common NRTI and NNRTI resistance-associated mutations
  - Half-life of approximately 190 hours of ISL-triphosphate, the active intracellular form
- MK-8507
  - Active against common NNRTI resistance-associated mutations
  - Half-life of approximately 70 hours



Rudd D, et al. Modeling-supported islatravir dose selection for phase III. Presented at CROI 2020; 2020 Mar 8-11; Boston, MA.

Monthly oral dose of ISL 60 mg is expected to maintain systemic ISL-TP concentrations above the PK threshold



***Note:** Blue dots and error bars represent observed Interim analysis data from an ongoing Protocol 016 Phase2a trial[1]*

- Double-blind placebo-controlled multicenter Phase I trial
- Groups
  - Single islatravir-eluting implant (48 mg, 52 mg, or 56 mg)
  - Placebo implant
- Implant placed in participants at low risk to acquire HIV for 12 weeks
- Active islatravir-TP levels above target for all implants throughout placement
- No dose-dependent difference in implant-related adverse events

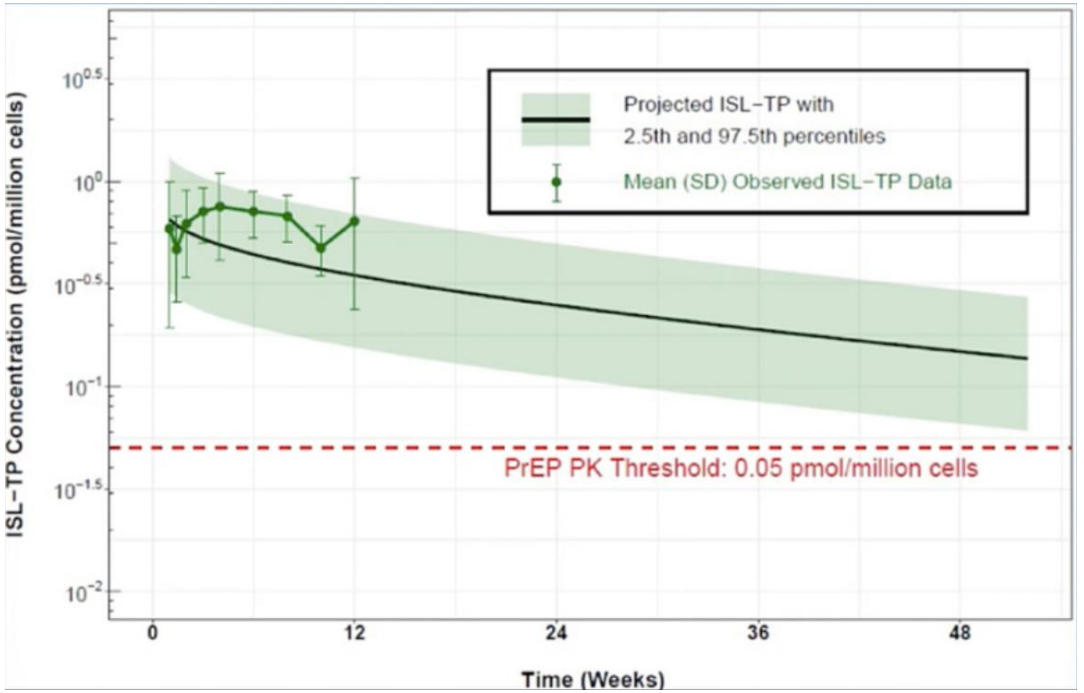


TABLE 1: A) Number of individuals reporting implant-related adverse events (% of total). Note this is blinded data. N=12 total per dose level; 8 on active and 4 on placebo. B) Mean islatravir-TP levels at 12 weeks.

A	48 mg	52 mg	56 mg
TOTAL	**8 (67)**	**6 (50)**	**8 (67)**
Hematoma	6 (50)	6 (50)	5 (42)
Erythema	5 (42)	3 (25)	5 (42)
Tenderness	3 (25)	6 (50)	5 (42)
Pruritis	6 (50)	3 (25)	7 (58)
Induration	4 (33)	5 (42)	5 (42)
B			
N	8	8	8
Geometric Mean C85d (%GCV) (pmol/10^6 cells)	0.118 (18.3)	0.198 (70.0)	0.620 (49.9)

Matthews R et al. Next-generation islatravir implants projected to provide yearly HIV prophylaxis. Presented at CROI 2021. 2021.

Questions?