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Lenacapavir Protects Against Rectal SHIV Acquisition in Macaque Model

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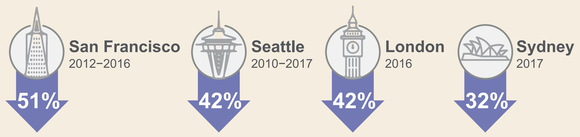
Introduction

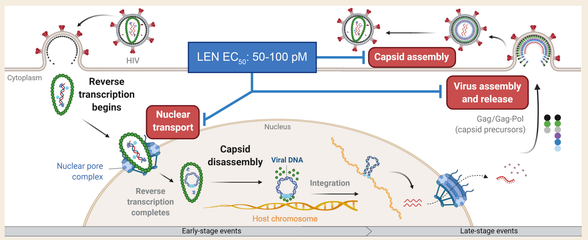
- Pre-exposure prophylaxis (PrEP) is an important strategy for HIV prevention

Where PrEP uptake has been high, there are significant population-level declines in new HIV infections[1-4]



- Not everybody is, however, benefiting from current PrEP options
  - In the US, < 25% of those who would benefit from PrEP (estimated 1.2M) are on daily oral PrEP
  - Worldwide, ~ 33% on PrEP of UNAIDS 2020 target of 3M
- Low uptake is related, in part, to challenges with:
  - Daily oral adherence and persistence, especially in younger people
  - Stigma (partners, family, community, and healthcare services)
  - Health system demands (more frequent clinical visits than people living with HIV)
- Significant unmet clinical need remains for those not benefiting from oral daily PrEP options
- Long-acting (LA) antiretroviral agents circumvent the requirement for daily dosing to achieve maximal protection and represent a promising new alternative to daily oral regimens

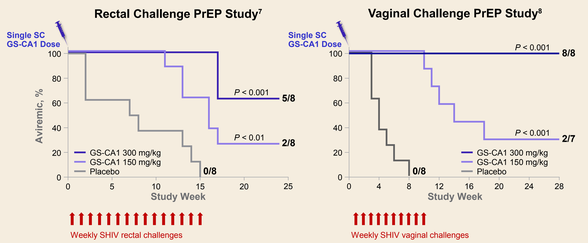
Capsid Inhibitors Like LEN and GS-CA1 Interfere With Multiple Steps of HIV Replication Cycle[5,6]



EC_{50} = half-maximal effective concentration; Gag = group-specific antigen; LEN = lenacapavir; Pol = polymerase.

- GS-CA1 and LEN are structural analogs and potent, multistage inhibitors of HIV capsid, with LA potential
- Q6M SC formulation of LEN was recently approved for the treatment of multidrug-resistant HIV infection in combination with other antiretrovirals
- Q6M SC formulation of LEN is in clinical development for PrEP

LA GS-CA1 Previously Shown to Reduce Risk of SHIV Infection in Repeat Mucosal Challenge NHP Models



NHP = nonhuman primate; SHIV = chimeric simian-human immunodeficiency virus.

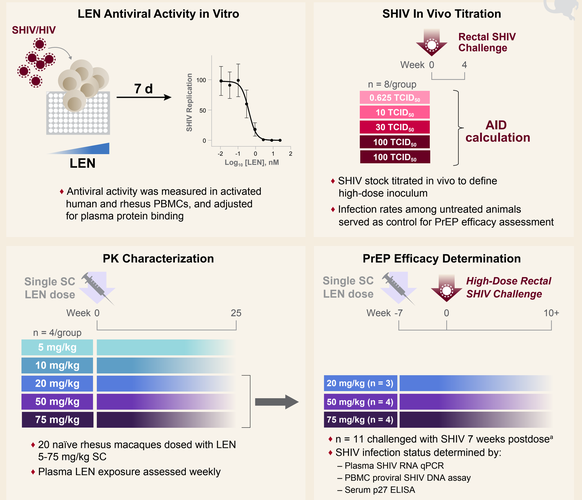
- Significant infection risk reduction was observed with GS-CA1 vs placebo in rectal and vaginal challenge models
- Infection-to-viremia delay complicated accurate estimation of protective drug exposures in repeat-challenge model

Objective

- To establish LEN pharmacokinetic (PK) profile in macaques and assess its efficacy as PrEP at clinically relevant exposures using a single high-dose SHIV rectal-challenge macaque model

Methods

Study Designs

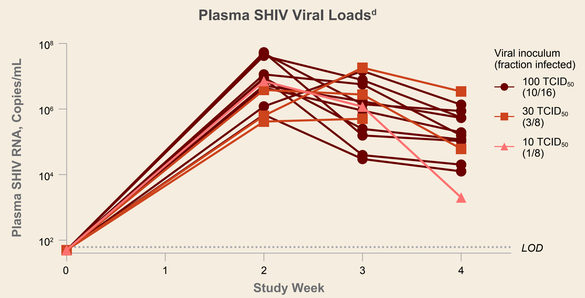


[a]Projected to have LEN exposures > 2x protein-adjusted 95% effective concentration ($paEC_{95}$) at time of challenge. AID = animal infectious dose; ELISA = enzyme-linked immunosorbent assay; PBMCs = peripheral blood mononuclear cells; qPCR = quantitative Pol chain reaction; $TCID_{50}$ = half-maximal tissue culture infectious dose.

Results

Titration of SHIV Infectivity Following Rectal Challenge in Rhesus Macaques

SHIV Inoculum, x $TCID_{50}$	Proportion of Challenged Animals Infected, n/n (%)[a]	AID_{50}[b]	% AID at 100 $TCID_{50}$ (95% CI)[c]
0.625	0/8	77 $TCID_{50}$	65.30 (40.3, 84.0)
10	1/8 (12.5)		
30	3/8 (37.5)		
100	4/8 (50)		
100	6/8 (75)		



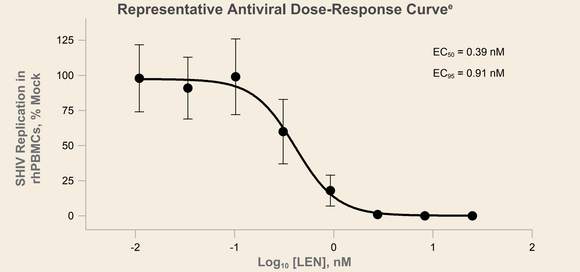
[a]Confirmed by plasma viral load assay; [b]Half-maximal AID (AID_{50}) computed via logistic regression analysis; [c]% of animals predicted by logistic regression analysis to become infected/challenge using 100 $TCID_{50}$ SHIV inoculum; [d]Measured by Gag reverse-transcription (RT)-qPCR among untreated rhesus macaques that became infected following single rectal challenge with specified SHIV inoculum; numbers of infections observed/total challenges performed with given inoculum are noted in *parentheses*; plasma viral RNA monitoring was performed through week 4 postchallenge, at which time, viremic animals were placed on combination antiretroviral therapy (ART); *horizontal dotted line* represents assay limit of detection (LOD; 62 copies/mL). CI = confidence interval.

- A SHIV inoculum of 100 $TCID_{50}$ was estimated to result in 65% infection per challenge and selected for the LEN efficacy study

Results (Cont'd)

Comparison of LEN Antiviral Activity in Rhesus and Human In Vitro

LEN Antiviral Potency	SHIV-Infected Rhesus PBMC	HIV-1-Infected Human PBMC
Mean EC_{50} ± SD, nM[a]	0.39 ± 0.16	0.05 ± 0.03
Mean EC_{95} ± SD, nM[b]	0.91 ± 0.38	0.12 ± 0.07
	Rhesus	**Human**
Plasma binding shift[c]	9.7	17.4
$paEC_{95}$ ± SD, nM[d]	8.80 ± 3.69	2.01 ± 1.22

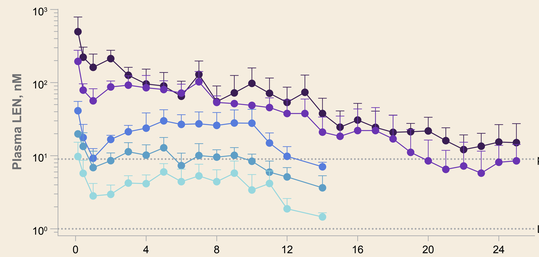


[a]7 half-maximal effective concentration (EC_{50}) measurements (n = 3 biological replicates each) across 2 independent experiments; [b]$EC_{95} = EC_{50} \times (95/5)^{1/n}$, where n represents Hill coefficient for LEN measured against HIV-1_{IIIB} in MT-4 cells (n = 3.51 ± 0.31); [c]Mean competitive equilibrium dialysis plasma shift assays determined from 3 independent experiments performed in singlet; [d]Derived from EC_{95} multiplied by corresponding plasma shift value; [e]Dose–response curve for LEN in rhesus PBMCs (rhPBMCs) acutely infected with SHIV-SF162P3; data are shown as mean ± standard deviation (SD) values from 1 of 7 assays (n = 3 biological replicates each).

- LEN was predicted to be ~4.4-fold less potent against SHIV vs HIV in vivo ($paEC_{95}$ 8.80 vs 2.01 nM)

LEN LA PK Profile in Rhesus Macaques

LEN Concentration-Time Curve[a]



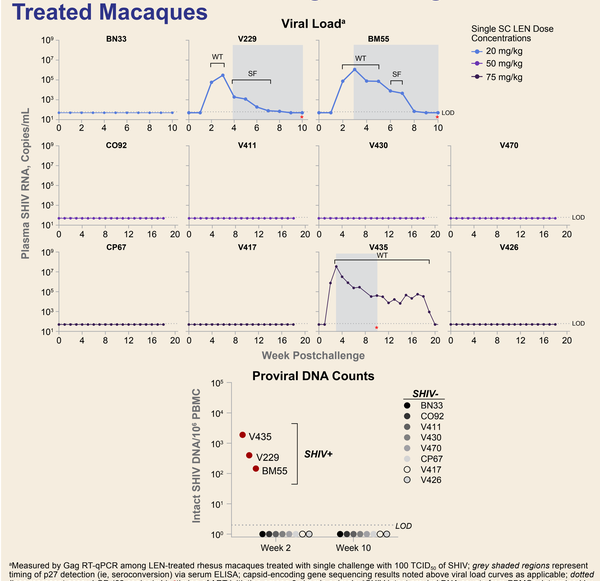
LEN PK Parameters

Mean ± SD (% CV)	LEN 5 mg/kg	LEN 10 mg/kg	LEN 20 mg/kg	LEN 50 mg/kg	LEN 75 mg/kg
AUC_{last}, μM•h	9.3 ± 1.9 (21)	20.3 ± 1.7 (8)	48.4 ± 17.9 (37)	179 ± 23 (13)	284 ± 126 (44)
AUC_{inf}, μM•h[b]	10.6 ± 1.7 (16)	23.8 ± 0.6 (2)	53.0 ± 16.7 (32)	243 ± 70 (29)	367 ± 239 (65)
$t_{1/2}$, h	17.2 ± 5.0 (29)	25.1 ± 9.1 (36)	18.7 ± 7.1 (35)	45.1 ± 19.8 (44)	53.1 ± 39.1 (74)
C_{max}, nM	10.5 ± 5.4 (51)	21.5 ± 2.0 (9)	42.5 ± 14.2 (33)	200 ± 74 (37)	530 ± 241 (45)
T_{max}, h	408 ± 736 (180)	240 ± 400 (167)	228 ± 408 (179)	102 ± 156 (153)	102 ± 156 (153)

[a]Plasma LEN levels measured by mass spectrometry following single SC challenge at specified dose levels (n = 4 /group); data represented as mean + SD values; LOD = 1nM; rhPBMC $paEC_{95}$ for LEN = 8.8 nM; [b]% of area under plasma concentration–time curve (AUC) extrapolated between AUC from time 0 to infinity (AUC_{inf}) and AUC to last measurable plasma concentration (AUC_{last}) ranged from 8.7% to 26.3%; analytes include AUC_{last}, AUC_{inf}, terminal half-life ($t_{1/2}$), maximal concentration (C_{max}), and time to reach C_{max} (T_{max}) determined by noncompartmental analysis using Phoenix® WinNonlin™ 6.4 build 8.1.0.3530 (Certara, Princeton, NJ). CV = coefficient of variation (100 X SD/mean). LOQ = limit of quantitation.

- LEN displayed dose-dependent increases in plasma exposure in macaques (dose proportional from 5 to 20 mg/kg and more than dose proportional from 50 to 75 mg/kg)
- The slow release of LEN was demonstrated by a long $t_{1/2}$ in the range of 17-53 days following a single SC dose

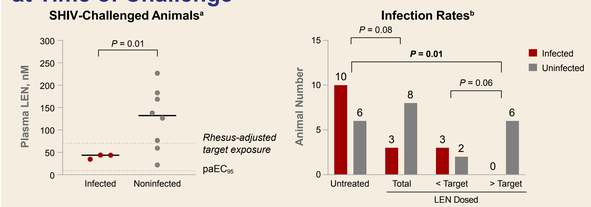
SHIV Infectivity, Seroconversion Status, and Capsid Resistance Profile After Single Challenge of LEN-Treated Macaques



[a]Measured by Gag RT-qPCR among LEN-treated rhesus macaques treated with single challenge with 100 $TCID_{50}$ of SHIV. *grey shaded regions* represent timing of p27 detection (ie, seroconversion) via serum ELISA; capsid-encoding gene sequencing results noted above viral load curves as applicable; *dotted lines* represent assay LOD (62 copies/mL); [b]timing of ART initiation among 3 viremic animals; [c]SHIV intact proviral DNA counts from PBMCs determined by intact proviral DNA assay among 11 SHIV-challenged rhesus macaques at indicated time points; *red symbols* represent animals that were viremic by qPCR and seropositive by p27 serum ELISA; *dotted line* represents assay LOD (2 copies/million PBMCs). SF = sequence failure; WT = wild-type sequence.

- Of 11 SHIV-challenged animals, 3 became infected and 8 remained protected as confirmed by plasma qPCR, cell-associated proviral DNA assay, and serology
- No capsid resistance to LEN emerged in the 3 infected animals

Animal Infection Status Relative to LEN Exposure at Time of Challenge



[a]Plasma levels measured by mass spectrometry among SHIV-challenged animals at time of challenge vs final infection status; *symbols* represent individual study animals; *P* value computed via unpaired t-test with Welch's correction; LEN $paEC_{95}$ = 8.8 nM; rhesus-adjusted clinical LEN target trough concentration (C_{trough}) = 70 nM; [b]*Bars* represent numbers of infected or uninfected study animals that were either untreated, all LEN treated, or LEN treated and split into those with exposures below or above adjusted LEN target C_{trough}; *P* values computed via Fisher exact test.

- Adjusting for LEN potency difference between HIV and SHIV, protection was computed above and below the clinical minimum LEN plasma target C_{trough} in this model (70 nM; derived by multiplying 16 nM [human target C_{trough} exposure] x 4.4 [fold lower LEN potency against SHIV in rhesus vs HIV in human cells])
- In animals with LEN above rhesus-adjusted target exposure, LEN demonstrated complete protection and was superior to the untreated group

Conclusions

- LEN displayed long-acting PK profile in rhesus macaques following a single SC administration
- LEN demonstrated effective SHIV prophylaxis in a stringent macaque model at clinically relevant LEN exposures
- These data support the ongoing clinical evaluation of LA LEN for HIV PrEP
  - LEN for PrEP is currently being evaluated in the phase 3 PURPOSE 1 (NCT04994509) and PURPOSE 2 (NCT04925752) clinical trials

References: **1.** Buchbinder SP, et al. CROI 2018, *abstr* 87; **2.** Grulich A, et al. Lancet HIV. 2018;5:e629-37; **3.** HIV/AIDS Epidemiology Unit, Public Health–Seattle & King County and the Infectious Disease Assessment Unit, Washington State Dept of Health. HIV/AIDS Epidemiology Report 2017:86; **4.** Nwokolo N, et al. Lancet HIV 2017;4:e482-3; **5.** Bester SM, et al. Science 2020;370:360-4; **6.** Link JO, et al. Nature 2020;584:614-8; **7.** Vidal SJ, et al. Nature 2022;601:612-6; **8.** Bekerman E, et al. IAS 2021, *abstr* 2474. **Acknowledgments:** The authors would like to thank members of BIOQUAL, Inc. (Rockville, MD) and Accelevir (Baltimore, MD) for performing the in-life portion of the animal studies and the cell-associated viral DNA analysis, respectively. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, NY, funded by Gilead. **Disclosures:** **E Bekerman, SR Yant, L VanderVeen, D Hansen, B Lu, W Rowe, K Wang, C Callebaut:** employees and shareholders of Gilead.

Presented at CROI 2023, 19-23 February 2023, Seattle, WA