LONG ACTING LENACAPAVIR PROTECTS AGAINST INTRAVENOUS CHALLENGE WITH SIMIAN-TROPIC HIV

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Background

- Daily pre-exposure prophylaxis (PrEP) is highly effective but dependent on adherence.
- Lenacapavir (LEN) is a potent first-in-class HIV capsid (CA) inhibitor with long-acting pharmacokinetics (PK), making it attractive for PrEP[1].
- A less potent LEN analogue, GS-CA1, has recently shown efficacy in repeat SHIV rectal and vaginal challenge models in rhesus macaques[2,3].
- LEN and GS-CA1 both effectively inhibit HIV capsid nuclear import, virion assembly, and proper capsid core formation[1,4].
- We previously derived a simian-tropic HIV-1 infectious clone (stHIV-A19) that encodes HIV-1 CA and replicates to high titers in pigtail macaques (PTMs)[5,6].

stHIV-A19 CA Sequence

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HIV-1NL43 PIVQNLQGQM VHQAISPRTL NAWVKVVEEK AFSPEVIPMF SALSEGATPQ DLNTMLNTVG 60
stHIV-A19 ---------- ---------- ---------- ---------- ---------- ---------- 60
SIVmac239 -.--QIG-NY --LPL----- -----LI--- K-GA--V-G- Q-----C--Y -I-Q-----C-- 59

HIV-1NL43 GHQAAMQMLK ETINEEAAEW DRLHPVHAGP IAPGQMREPR GSDIAGTTST LQEQIGWM.T 119
stHIV-A19 ---------- ---------- ---------- N--------- ---------- -----A--.- 119
SIVmac239 D------IIR DI-----D- -LQ--QP-PQ ..Q--L---S --------S VD---Q--YR 117

HIV-1NL43 HNPPIPVGEI YKRWIILGLN KIVRMYSPTS ILDIRQGPKE PFRDYVDRFY KTLRAEQASQ 179
stHIV-A19 ---------- ---------- ---------- ---------- ---------- ---------- 179
SIVmac239 QQN-----N- -R---Q---Q -C----N--N ---VK----- --QS------ -S-----TDA 177

HIV-1NL43 EVKNWMTETL LVQNANPDCK TILKALGPGA TLEEMMTACQ GVGGPGHKAR VL 231
stHIV-A19 D--------- ---------- ---------- ---D------ ---------- -- 231
SIVmac239 A------Q-- -I-------- LV--G--VNP -----L---- ------Q--- LM 229
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*HIV-1 CA residues associated with LEN resistance (L56, N57, M66, Q67, K70, N74, T107) are highlighted in yellow, with those distinct from NL4-3 and stHIV-A19 highlighted in cyan

Objectives

- To comparatively evaluate LEN antiviral potency in vitro against stHIV, HIV-1, and SIVmac239
- To evaluate PK and efficacy of subcutaneous (SC) LEN PrEP in PTMs against a high-dose intravenous (IV) stHIV challenge

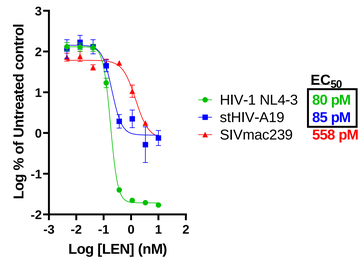
Methods

- LEN potency against stHIV-A19, HIV-1 NL4-3, and SIVmac239 was compared in SupT1-CCR5 cells (qRT-PCR readout 7 dpi). LEN potency against stHIV-A19 was then determined in PTM PBMCs (RT readout 7 dpi). After correcting for PTM plasma protein binding by competitive equilibrium dialysis, a plasma-adjusted (PA)-EC_{95} for LEN was derived.
- LEN PK was assessed in PTMs receiving two subcutaneous (SC) doses of LEN 6 weeks apart (15 mg/kg x 2, n=3; 50 mg/kg x 2, n=3). LEN plasma levels were determined by LC-MS.
- Prior to a single IV challenge with 10^5 infectious units of stHIV-A19, naïve PTMs received either: (1) a single SC injection of LEN (25 mg/kg, 30 days pre-challenge, n=3), (2) a single SC vehicle injection (30 days pre-challenge, n=4), or (3) 7 daily doses of a 3-drug control regimen[7] (TDF/FTC/DTG, starting 3 days pre-challenge, n=4). Plasma stHIV RNA (vRNA) and stHIV DNA (vDNA) in PBMCs were monitored by qRT-PCR and qPCR, respectively.

Results

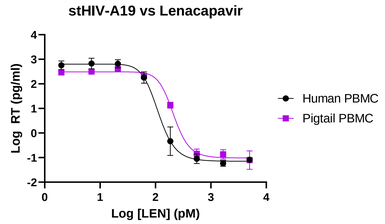
1. LEN Potency against stHIV In Vitro

SupT1-CCR5+ cells



- stHIV-A19 and HIV-1 equally sensitive to LEN
- LEN more potent against stHIV than SIVmac239

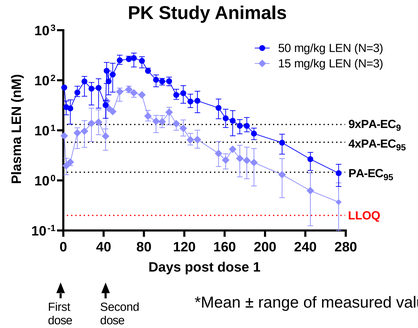
PTM PBMC



- LEN EC_{95} vs stHIV in PTM PBMCs = 150 pM
- **LEN PA-EC_{95} = 1.46 nM**

2. LEN Pharmacokinetics in PTMs

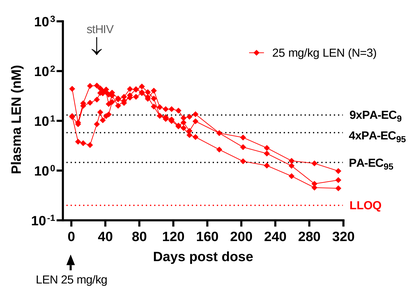
PK Study Animals



*Mean ± range of measured values shown

- Mean plasma LEN concentrations maintained above PA-EC_{95} for >145 and >200 days after 2nd 15 mg/kg and 50 mg/kg dose, respectively

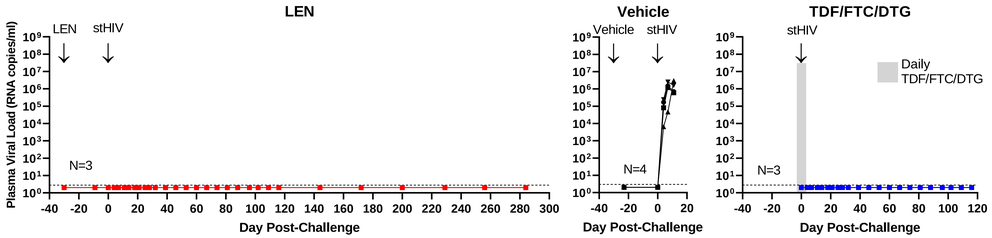
LEN PrEP Animals in IV Challenge Study



- Mean plasma LEN concentrations exceeded target protective levels (4x PA-EC_{95}) by day 1 post dose and at the time of challenge

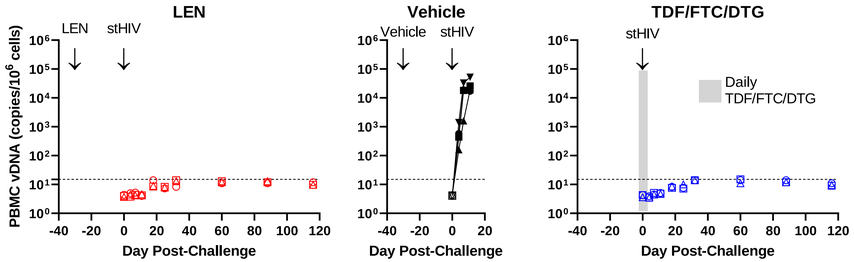
3. LEN PrEP vs IV stHIV Challenge

Plasma Viral Loads



*LOD = 2.8 vRNA copies/ml (dashed line)

vDNA in PBMC



*LOD = 15 vDNA copies/10^6 cells (dashed line); open symbols = no vDNA detected

- No evidence of infection in LEN or three-drug control animals (>8 months of follow-up for LEN animals)
- All 4 vehicle control animals infected

4. LEN Safety in PTMs

- No abnormalities or significant changes in complete blood counts (CBC) or blood serum chemistries in animals that received LEN injections
- Mild to moderate injection site reactions, which resolved without intervention, observed in some animals following some LEN injections or vehicle control injections

Conclusions

- A single subcutaneous LEN injection effectively prevented simian-tropic HIV infection in a stringent, high dose intravenous challenge model
- These findings highlight the utility of this stHIV/PTM model and support the ongoing clinical development of long-acting LEN for PrEP

References: 1. Link JO, et al. *Nature* 2020;584:614-8; 2. Vidal SJ, et al. *Nature* 2022;601:612-616; 3. Bekerman E, et al. *IAS Conference on HIV Science* 2021, July 18-21; 4. Yant SR, et al. *Nat Med* 2019;25:1377–1384; 5. Hatziioannou T, et al. *Science* 2014;344(6190):1401-5; 6. Schmidt F, et al. *PNAS* 2019;116(21):10504-10509; 7. Del Prete GQ, et al. *AIDS Res Hum Retroviruses* 2016;32(2):163-8.
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