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

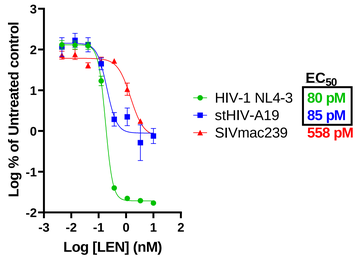
Methods

- 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

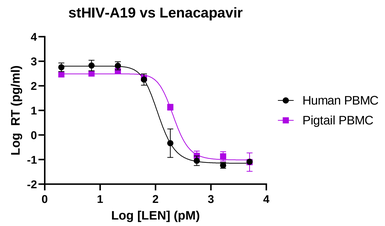
1. LEN Potency against stHIV In Vitro

SupT1-CCR5+ cells



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

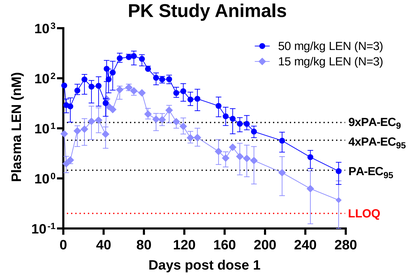
PTM PBMC



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

2. LEN Pharmacokinetics in PTMs

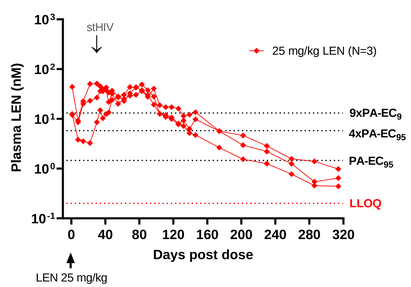
PK Study Animals



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

*Mean ± range of measured values shown

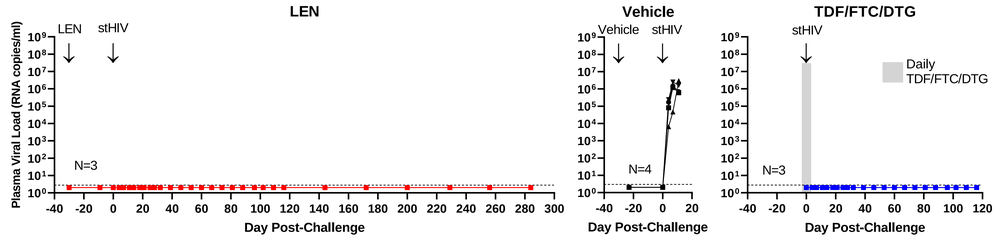
LEN PrEP Animals in IV Challenge Study



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

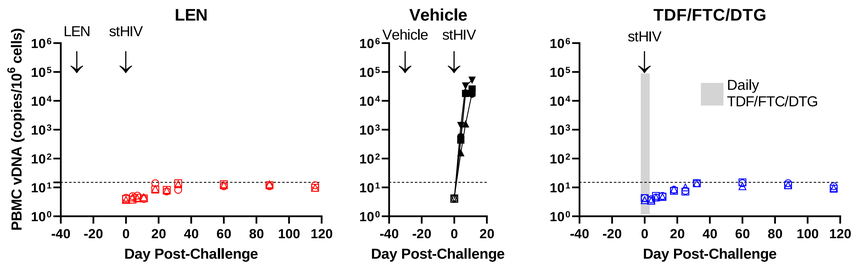
3. LEN PrEP vs IV stHIV Challenge

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; 45 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. **Funding:** This work was funded in part by the National Cancer Institute, NIH (contract No. 75N91019D00024). The content of this poster does not necessarily reflect the view or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. **Study approval:** All work involving research animals was conducted under a protocol approved by the Institutional Animal Care and Use Committee of the National Cancer Institute (protocol AVP-078) and adhered to the standards of the Guide for the Care and Use of Laboratory Animals in accordance with the Animal Welfare Act. Macaques were housed at the NIH and cared for in accordance with American Association for the Accreditation of Laboratory Animal Care (AAALAC) standards in an AAALAC-accredited facility (Animal Welfare Assurance number A4149-01).

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