Dose-Ranging Pharmacokinetics and Efficacy of a 90-Day Multipurpose IVR Delivering Islatravir

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Priya Srinivasan[1], Jasmine L. King[2], Jining Zhang[1], Isabella C. Young[3], Dawn Little[4], Mackenzie L. Cottrell[5], Craig Sykes[5], James Mitchell[1], Angela D. M. Kashuba[5], Gerardo Garcia-Lerma[1], **S. Rahima Benhabbour[2,3]**, James Smith[1]

[1]Lab Branch, Division of HIV Prevention, Centers for Disease Control and Prevention, Atlanta, GA; [2]Lampe Joint Department of Biomedical Engineering, North Carolina State University and The University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Division of Pharmacoengineering and Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Katmai Government Services (KGS), Anchorage, AK; [5]Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC

BACKGROUND

Multipurpose prevention technologies (MPTs) are important to protect women from unintended pregnancy and sexually transmitted infections.

Uniquely designed, geometrically complex 3D printed intravaginal rings (IVRs) represent an attractive long-acting delivery platform that can provide superior control of drug release and product user characteristics.

To optimize the delivery of Islatravir (ISL) from our MPT IVR, IVRs containing 15, 30, and 60 mg of ISL were evaluated for their pharmacokinetics (PK) in pigtailed macaques.

We further investigated the efficacy of a 60 mg, 90-day ISL IVR against vaginal SHIV infection in macaques.

METHODS

- IVRs containing 15, 30, and 60 mg ISL were inserted for 28 days into pigtailed macaques (n=8) in a crossover design;
- The 15 and 60 mg ISL IVRs were subsequently investigated for 90-day PK studies (n=3 macaques each);
- Based on the total amount of ISL released over the 90-day period, we initiated a vaginal SHIV challenge study with a 60 mg IVR in sexually mature, normal cycling pigtailed macaques;
- Six ISL IVR-treated macaques received weekly low dose SHIV162p3 inoculations starting 3 days after IVR insertion for a total of 12 weeks;
- Two untreated controls received the same weekly challenges;
- The rings were removed on Day 90 (week 13.5) and the macaques followed for an additional 9.5 weeks.

RESULTS

Pharmacokinetics

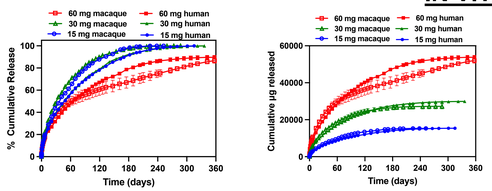
- 15, 30 , and 60 mg ISL in vitro release kinetics were similar between the human and macaque size rings.
- Systemic plasma ISL concentrations were within the levels seen with the safe 0.25 mg once-daily oral ISL human dose.
- The 60 mg IVR maintained ISL triphosphate (ISL-TP) at or above established ISL-TP benchmark levels needed for protection (50 fmol/10^6 cells) for over 90 days.
- Residual drug analysis revealed the 15 mg rings released 94% of their ISL payload over 90 days while the 60 mg IVRs released 56% over 90 days.
- Frequency of CD4, and CD8+ T cells was found to be stable, with no statistically significant changes, with a sustained release of ISL over 90 days in macaques.

Efficacy

- All ISL IVR macaques remain SHIV RNA negative after 12 weekly vaginal SHIV162p3 exposures and 9.5 weeks after ring removal.

First ever PrEP of a *90-day ISL IVR* demonstrating **complete protection** from 12 weekly exposures of SHIV162p3 in pigtailed macaques.

IN VITRO RELEASE



Amount ISL loaded in IVR (mg)	Burst at 24h (%)	Burst at 24h (µg)	% Cumulative Release	Zero-order release rate (µg/day)
Macaque: 60 Human: 60	Macaque:6.50±0.28 Human: 6.04±0.11	Macaque: 4032.3±174.8 Human: 3381.9±59.8	% release at day 342 Macaque: 85.68±1.94 Human: 89.60±1.81	Day 2-49 Macaque: 508 Human: 433 Day 49-342 Macaque: 75 Human: 91
Macaque: 30 Human: 30	Macaque: 7.13±0.22 Human: 5.93±0.17	Macaque: 2182.1±68.5 Human: 1896.3±54.1	% release at day 336 Macaque: 100% Human: 100%	Day 2-49 Macaque: 292 Human: 264 Day 49-336 Macaque: 38 Human: 50
Macaque: 15 Human: 15	Macaque: 6.34±0.38 Human: 5.72±0.29	Macaque: 1077.3±65.4 Human: 915.4±46.31	% release at day 315 Macaque: 100% Human: 100%	Day 2-49 Macaque: 151 Human: 136 Day 49-315 Macaque: 31 Human: 39

Figure 1. In vitro release of macaque vs. human IVRs at macaque pH 8.

PK STUDY DESIGNS

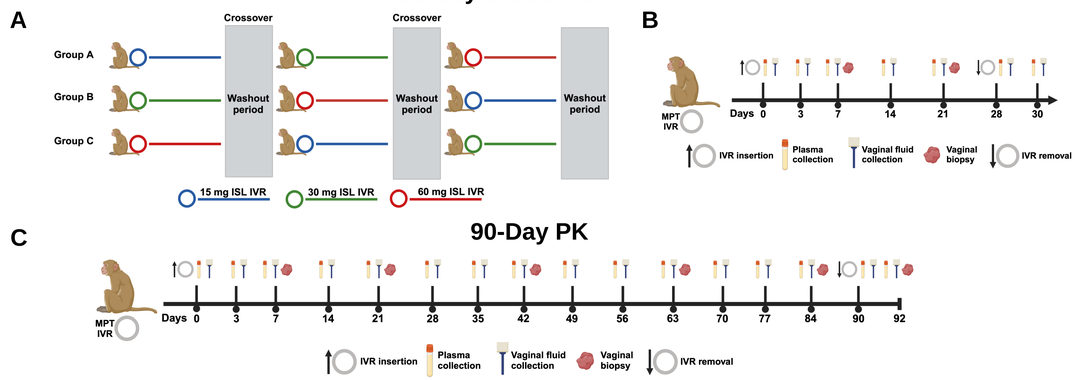


Figure 2. PK study design for A-B) 30-day ISL IVR crossover study (n=8) and C) 90-day ISL IVR study (n=3).

PK SUMMARY

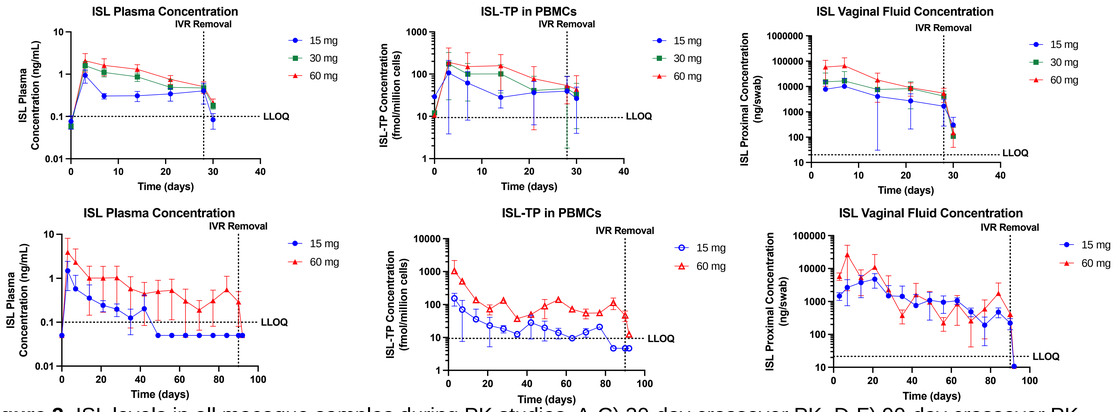


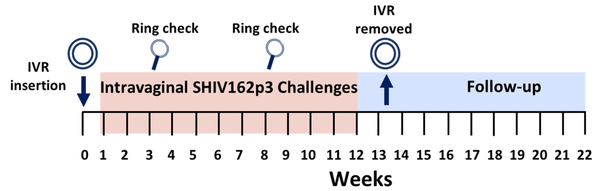
Figure 3. ISL levels in all macaque samples during PK studies. A-C) 30-day crossover PK. D-F) 90-day crossover PK.

RESULTS CONT'D

Table 1. Percentage of ISL released during PK study period.

Study period	Dose	Percentage (%) of ISL Released
30	15	55.7 (48.9 - 73.7; n=8)
	30	55 (53.2 - 69.8; n=8)
	60	48 (46.3 - 70.2; n=8)
90	15	93.8 (92.4 - 94.0; n=3)
	60	56.1 (49.1 - 59.6; n=3)

EFFICACY AGAINST REPEAT LOW DOSE CHALLENGE



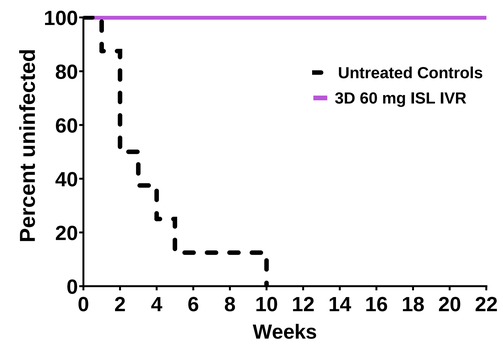


Figure 5. In vivo efficacy of ISL-treated macaques following SHIV162p3 challenges. A) Efficacy study design. B) Percent uninfected macaques post IVR insertion. (n=2 real time, n=6 historical controls, n= 6 3D 60 mg ISL IVR).

Table 2. Percentage of ISL released during efficacy study period.

Animal ID	043	173	334	156	138	407
% of ISL Released	67.9	59.2	53.1	61.8	69.6	68.4

CONCULSIONS & NEXT STEPS

- We completed the first ever pre-exposure prophylaxis (PrEP) efficacy evaluation of a 90-day IVR in preventing vaginal SHIV162p3 acquisition in a repeat low-dose weekly challenge macaque model;
- We demonstrated complete protection from 12 weekly exposures (22 weeks including follow up);
- Advance and translate first-in-line 3D printed IVR as a three-month MPT using optimized ARV/hormone dosages.

CONTACT INFO:
Priya Srinivasan, pvs6@cdc.gov
Rahima Benhabbour, benhabs@email.unc.edu

Lampe Joint Department of Biomedical Engineering

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