Pharmacokinetic study of islatravir and etonogestrel implants in macaques

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BACKGROUND

Prevention of HIV and unintended pregnancies are public health priorities. Methods that provide sustained release of drugs can improve patient adherence and increase efficacy of medications that require consistent dosing. **Long-acting (LA)** implants have been successfully used for contraception including the FDA-approved Nexplanon implant which releases the hormone **etonogestrel (ENG)** to prevent unintended pregnancy for up to 3 years.

LA products for HIV **pre-exposure prophylaxis (PrEP)** are building upon these models**. Islatravir (ISL)** is a novel nucleoside reverse transcriptase translocation inhibitor that is phosphorylated within cells to the active metabolite **ISL-triphosphate (ISL-TP**). The long half-life and potency of ISL make it an attractive candidate for delivery by an implant for LA PREP.

Here, we evaluated safety and pharmacokinetics of ISL and ENG implants in female pig-tailed macaques.

METHODS

Figure 1. Study Design

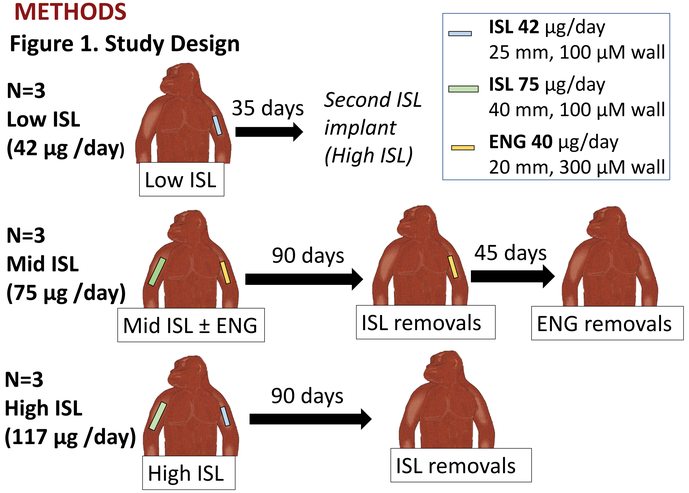


Figure 1. Implants were placed subcutaneously in the upper inner arms of macaques. Three **in vitro release rates of ISL were investigated**; low (42 µg/day), mid (75 µg /day), and high (42 + 75= 117 µg /day). **ENG implants** (40 µg/day) were evaluated concurrently in the mid ISL study group.

- Specimen collection: blood once a week, mucosal biopsies every two weeks.
- Drug level testing: ISL, ENG, and progesterone (p4) in plasma. Intracellular ISL-TP in peripheral blood mononuclear cells (PBMCs), and mucosal biopsies.
- Implant-site reactions: erythema and edema evaluated weekly by two veterinarians using a modified Draize scale.

Biodegradable implants with sustained delivery of **ISL** and **ENG** for >3 months in nonhuman primates show promise for multi-purpose prevention of HIV and pregnancy.

RESULTS

Figure 2. Concentrations of ISL-TP in PBMCs

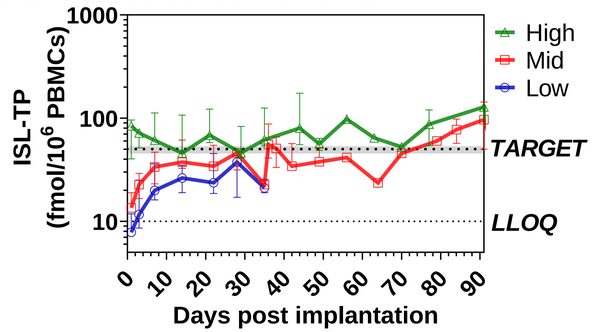


Figure 2. (Left) PBMC ISL-TP levels for the low (blue), mid (red) and high (green) ISL groups. The pharmacokinetic target of 50 fmol ISL-TP/10^6 PBMCs (Target) and lower limit of quantification (LLOQ) are shown with dashed lines.

Table 1. Concentrations of ISL in plasma and ISL-TP in PBMCs and rectal/vaginal tissues

ISL Cumulative IVRR		Duration (days)	Median [range]			
			Plasma ISL (ng/ml)	PBMC ISL-TP (fmol/10^6 PBMCs)	Vaginal ISL-TP (fmol/g)	Rectal ISL-TP (fmol/g)
Low	42 µg/day	35	0.39 [0.36 - 0.54]	26.7 [21.8 - 32.6]	8.7 [8.5 - 11.6]	19.7 [8.5 - 27.3]
Mid	75 µg/day	90	0.59 [0.49 - 0.75	42.5 [20.1 - 96.5]	10.6 [8.4 - 21.6]	29.3 [26.2 - 30.0]
High	117 µg/day	90	0.88 [0.66 - 3.4]	79.5 [46.5 - 229.0	16.5 [10.7 - 64.1]	39.3 [26.0 - 45.4]

Plasma ISL and PBMC ISL-TP values were calculated once steady state was achieved; Low ISL (day 7-35), Mid ISL (d7-90), High ISL (d7-90). Vaginal and rectal ISL-TP levels were determined at day 21 post implantation.

Figure 3. Concentrations of p4 and ENG in plasma

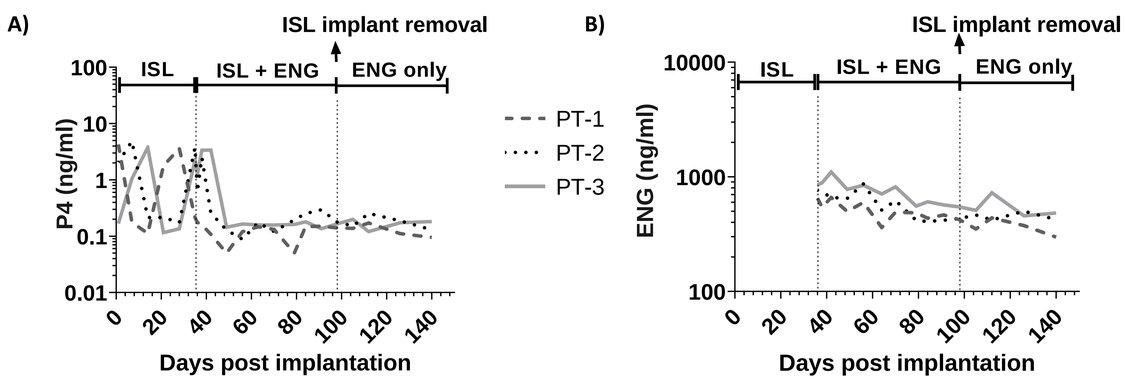


Figure 3. Plasma p4 **(A)** and ENG **(B)** in macaques that received an ISL implant (75 µg /day), followed by an ENG implant and lastly ISL implant removal. Data for each macaque, PT-1, PT-2, and PT-3, is shown.

Figure 4. Heat map of implant-site reactions

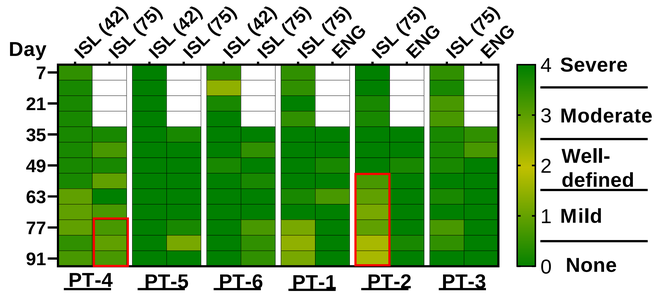


Figure 4. Implants for each animal (column) and the weekly Draize score (ranging from 0 - 4) are shown.

SUMMARY OF RESULTS

- Plasma ISL and ISL-TP in PBMCs were sustained for >3 months. Dose linearity was observed (**Fig 2, Table 1**).
- ISL-TP was detected in vaginal and rectal tissue (**Table 1**).
- ISL did not alter natural cycling of p4 (**Fig 3A,** day 0-35).
- ENG levels were stable and sufficient to suppress p4 production by day 14 post implantation (**Fig 3A and 3B**).
- Two ISL implants (75 µg/day) broke on day 49 and 56 and resulted in mild redness and swelling with a median Draize score of 1 (range 0.5-2) (**Fig 4**, red boxes). Samples collected after implants broke were excluded from PK analysis.
- No implant-site reactions were observed with intact ISL (n=7/9) and ENG (n=3/3) implants. H&E-stained skin biopsies collected at implant sites were pathologically unremarkable.

CONCLUSIONS

- Implants yielded stable plasma ISL and ISL-TP in PBMCs for >3 months with minimal implant-site reactions when intact.
- ISL-TP was present in tissues important for viral transmission.
- The sustained release of ISL is projected to last for >2 years.
- ENG suppressed p4 which will lead to inhibition of ovulation.
- Evaluation of optimized implants with increased wall thickness is underway for improved durability and vaginal efficacy as PrEP in a SHIV challenge model.

ACKNOWLEDGEMENTS

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