A Biodegradable Implant Releasing Low-Dose Islatravir Protects Macaques from Rectal SHIV Infection

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ABSTRACT

Background: Islatravir (ISL) is a potent nucleoside reverse transcriptase translocation inhibitor that was associated with lymphopenia in a dose-dependent manner in clinical studies. We recently showed that treatment with high ISL doses in macaques also resulted in lymphopenia[1]. Here, we evaluated preclinically a poly (ε-caprolactone) (PCL) implant designed to release low levels of ISL that are not predicted to cause lymphopenia. We investigated the safety and PK of ISL releasing implants and efficacy of low-dose ISL in protecting macaques against rectal SHIV infection.

Methods: Biodegradable PCL implants (25mm length,300 µm wall-thickness) were loaded with approximately 42 mg of ISL and the in vitro release-rate (IVRR) was determined under sink conditions. A single ISL implant was placed in the arm of each rhesus macaque (n=6) using a trocar. ISL-TP levels in PBMCs were measured weekly by LC-MS/MS. Implant site reactions were graded using a modified Draize scale (range: 0-5). Macaques underwent a 7-week conditioning phase to achieve steady-state ISL-TP in PBMCs prior to rectal exposure to SHIV162p3 twice - weekly during weeks 7-10 (up to 8 SHIV challenges). Macaques were monitored for SHIV infection during the challenge and follow-up period by RT-PCR. Infection outcomes were compared to 7 untreated animals.

Results: The estimated IVRR of ISL was 134.6 ± 12 µg/d, as calculated during the corresponding dates of the challenges. The median [range] ISL-TP levels in PBMCs during the conditioning phase was 136 fmol/10^6 cells [118-164]. During SHIV challenges, the ISL-TP level was 109 fmol/10^6 cells [76-141] or about 1 $\log_{10}$ lower than those seen in humans treated with 0.25 mg of once-daily oral ISL (1,140 fmol/10^6 cells) (Fig 1). ISL implants remained intact during the 5-month study period with no evidence of migration or implant-site reactions. The untreated controls were infected after a median of 1 SHIV challenge [range = 1-3]. In contrast, all ISL-treated macaques remained protected following repeated rectal SHIV challenges, resulting in an estimated efficacy of 100% (Fig 1).

Conclusions: ISL implants maintained structural integrity, provided sustained release of low-dose ISL, and showed no sign of local toxicities after 5 months. The ISL-TP levels in PBMCs remained below the clinical toxicity threshold and provided complete protection to macaques against rectal SHIV infection. Our study supports the development of a PCL implant that can deliver safe and effective ISL concentrations for ultra-long-acting HIV prevention.

METHODS

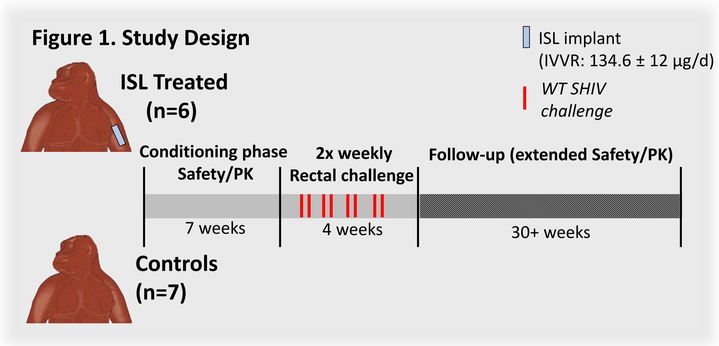


Figure 1. Reservoir-style implants comprised of biodegradable PCL and ISL core had an *in vitro* release rate (IVRR) of 134.6 ± 12 µg/d. Six macaques received ISL implants and were exposed twice-weekly to rectal $SHIV_{162P3}$ for 4 weeks (8 challenges) after a 7-week conditioning phase. Infection outcome was compared to 7 untreated animals. Blood was collected weekly to monitor for drug levels (ISL and ISL-TP) and SHIV infection by RT-PCR.

Implants releasing low-dose Islatravir (ISL) provide completed protection against Rectal SHIV exposure

RESULTS

Figure 1. ISL implants maintained clinically relevant ISL concentrations in plasma and PBMCs

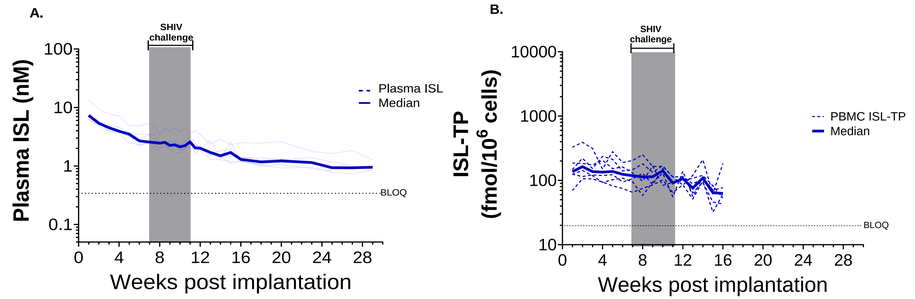


Figure 1. (A) Plasma ISL concentrations (nM) and **(B)** ISL-TP in PBMCs (fmol/10^6 cells) observed in macaques with ISL implants with an estimated in vitro release rate of 134.6 ± 12 µg/d. Solid and dotted lines denote the values from the median and individual animals, respectively. Shaded area indicates the timing of SHIV challenges.

Key Takeaway: ISL implants (134.6 ± 12 µg/d) achieved similar plasma ISL concentrations observed in humans with once-daily oral ISL dosing (0.25 mg ISL; 0.7-1.3 nM) [2]

Figure 2. Efficacy of ISL implants against rectal SHIV infection

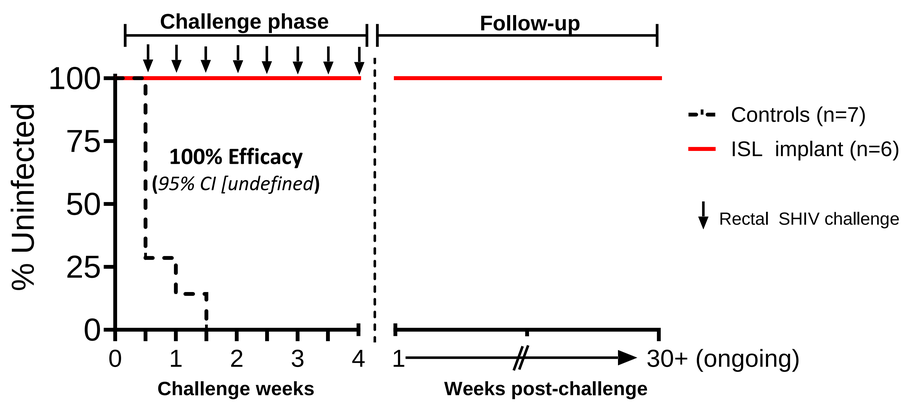


Figure 2. Protection against repeated rectal SHIV exposures in macaques with ISL implants (red line) compared to untreated controls (dotted black line). Rectal SHIV exposures denoted with black arrow. The estimated time of infection was defined as 1 week (or 2 challenges) prior to the first detection of SHIV RNA in plasma assuming a 1-week eclipse period between infection and detection of SHIV RNA

Figure 3. Safety assessment of ISL implants

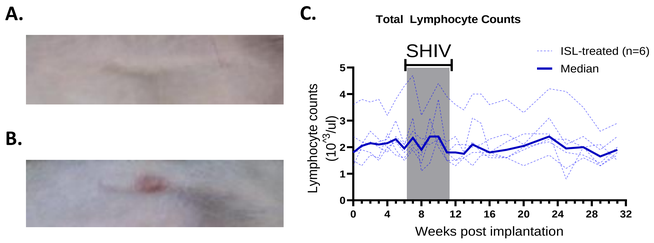


Figure 3. (A) ISL implants maintained structural integrity for more than 30 weeks (representative photo). **(B)** Mild erythema observed in one animal on day 175 **(C)** Longitudinal assessment of total lymphocytes counts (TLC) revealed no change in total lymphocyte in ISL-treated animals.

Key Takeaway: Implant site reaction occurred in 1 animal. Pathology findings of skin biopsies collected at the time of implant removal was unremarkable. Sustained release of ISL for 30+ weeks had no clinical impact on total lymphocyte counts.

CONCLUSIONS

Pharmacokinetics of ISL implants

- Achieved clinically relevant plasma ISL levels
- Provided sustained release of ISL for >10 months; anticipated to release for up to 1 year or longer

Efficacy

- Robust protection (100% efficacy) against repeated rectal SHIV exposures (0 infections per 48 total exposures)

Safety

- Implant site reactions were minimal
- Skin biopsies surrounding the ISL implant were pathologically unremarkable
- Overall, no impact on total lymphocytes

FUTURE DIRECTIONS

- Measure residual drug from recovered implants to determine *in vivo* release rate
- Challenge with $SHIV_{M184V}$ to determine if ISL implants are effective against ISL-resistant SHIV variants
- Expand safety assessments to include longitudinal monitoring of lymphocytes and CD4+ T cells

REFERENCES

1. Daly et al., HIV R4P 2024
2. Matthews, et al. PMID: 34651606. JAIDS, 2021.

ACKNOWLEGDEMENTS

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