Vaginal PrEP Efficacy of Biodegradable Islatravir Implants in Macaques

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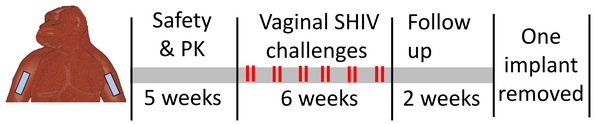
BACKGROUND

Long-acting pre-exposure prophylaxis (LA PrEP) with sustained delivery of antiretrovirals may promote adherence and increase PrEP efficacy. Islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor, has high potency and a long intracellular half-life making it an attractive candidate for LA PREP. **Here, we evaluated the safety, pharmacokinetics (PK), and vaginal efficacy of biodegradable implants releasing ISL in macaques.**

METHODS

Figure 1. Study Design and Methods

A) Two implants (n=6)



B) One implant (n=6)

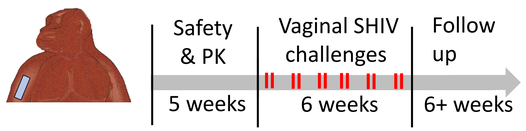


Figure 1. Reservoir-style implants (25 mm) comprised of poly(ε-caprolactone), a biodegradable polymer, were loaded with 46 ± 2 mg of ISL in PEG40-castor oil with a projected *in vitro* release rate (IVRR) of 83 µg/d. **(A)** Six macaques received two 25 mm implants, were monitored for safety and PK for 5 weeks, and then were exposed vaginally to $SHIV_{162P3}$ twice-weekly for 6 weeks (12 challenges). **(B)** One implant was removed from each animal and after a 5-week PK assessment animals were rechallenged with SHIV. Animals were sedated weekly, or biweekly during follow-up, to visually assess implant-site reactions (**Fig 2A,B**) and collect blood to monitor plasma ISL (**Fig 3A, C**) and SHIV RNA (**Fig 3B**). Infection outcome was compared to 6 untreated animals (**Fig 3D**). Skin biopsies (4mm) were taken at the time of implant removal (week 13) for H&E staining (**Fig 2C**).

Biodegradable islatravir (ISL) implants achieved clinically relevant plasma ISL levels and protected against vaginal SHIV infection.

RESULTS

Figure 2. Implant-site reactions

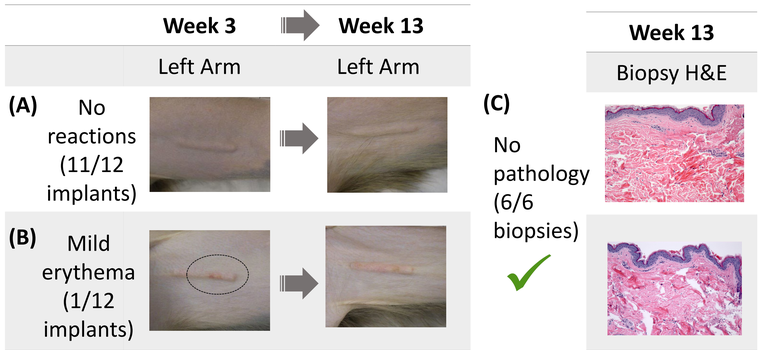


Figure 2. (A) No implant-site reactions were observed in 11/12 implants (representative photos). **(B)** Mild erythema observed in only 1/12 implants at week 3 **(C)** H&E stained skin biopsies from implant removal site (10X) were pathologically unremarkable in all samples.

Figure 3. Pharmacokinetics and vaginal PrEP efficacy of ISL implants

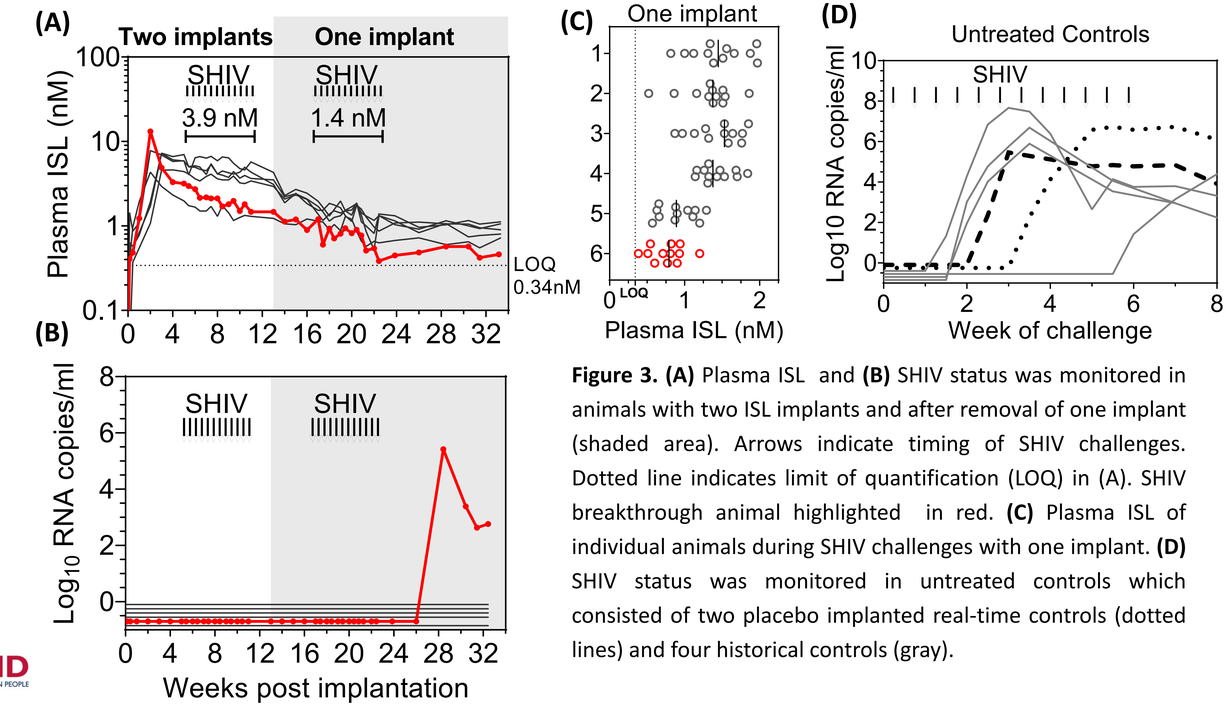


Figure 3. (A) Plasma ISL and **(B)** SHIV status was monitored in animals with two ISL implants and after removal of one implant (shaded area). Arrows indicate timing of SHIV challenges. Dotted line indicates limit of quantification (LOQ) in (A). SHIV breakthrough animal highlighted in red. **(C)** Plasma ISL of individual animals during SHIV challenges with one implant. **(D)** SHIV status was monitored in untreated controls which consisted of two placebo implanted real-time controls (dotted lines) and four historical controls (gray).

CONCLUSIONS

Safety

- Implant-site reactions were minimal for 33+ weeks, with mild erythema noted in only 1/12 implants.
- Implant-site skin biopsies taken after implant removal at week 13 were pathologically unremarkable.

Pharmacokinetics

- Plasma ISL concentrations were similar to once daily oral ISL dosing in humans (0.25 mg: 1.3 nM; 0.75 mg : 3.6 nM) [1].
- Concurrent *in vitro* studies determined ISL release rates were 77.6 and 45.1 µg/d at the time of SHIV challenges with two and one implant, respectively (data not shown).

Vaginal PrEP efficacy

- 6/6 animals with 2 ISL implants remained uninfected after 12 vaginal SHIV exposures and during follow-up (2-weeks). Median plasma ISL during challenges was 3.9 nM (1.2-6.7).
- 5/6 animals with one ISL implant remained uninfected after 12 vaginal SHIV challenges and during 10-weeks of follow-up. Median (range) plasma ISL of *protected* animals was 1.4 nM (0.9 - 1.5).
- A single breakthrough occurred 6 weeks after the last SHIV challenge. This animal had the lowest plasma ISL in the study group with a median (range) of 0.8 nM (0.4-1.2).

FUTURE DIRECTIONS

- Measure ISL-triphosphate (ISL-TP) levels in PBMCs.
- Remove remaining implants and confirm SHIV status of 5 uninfected animals after drug washout.
- Measure residual drug from removed implants to determine *in vivo* release rate.
- Expand safety assessments to include longitudinal monitoring of lymphocytes and CD4+ T cells.

REFERENCES

1. Matthews, et al. PMID: **34651606.** JAIDS, 2021.

ACKNOWLEDGEMENTS

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