Next-generation Islatravir/Etonogestrel/Ethinyl Estradiol MPT Intravaginal Ring

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BACKGROUND

- Condoms are the only available multipurpose prevention technology (MPT) but elicit poor user adherence and require partner cooperation
- Current intravaginal ring (IVR) technologies have limited ability to achieve target drug release kinetics and do not elicit 100% drug release.
- **Unmet Need: (1) Long-acting MPTs with high user adherence and acceptability for all women. (2) IVRs with facile ability to fine-tune drug release and promote complete drug release.**

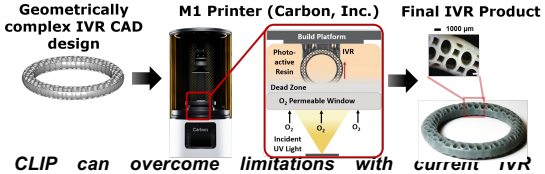
INNOVATION

3D-printed geometrically complex IVRs for the prevention of HIV and unplanned pregnancy

Structural and geometric complexity elicits tunable and complete drug release.

Continuous Liquid Interface Production (CLIP™) for 3D-Printed IVRs

- CLIP implements computer aided design (CAD) and a photoactive resin that solidifies upon selective UV exposure via free radical photopolymerization mechanisms.
- Incorporation of oxygen to inhibit polymerization, creating a "dead zone" for continuous and layerless production.



- ***CLIP can overcome limitations with current IVR manufacturing due its wide design space eliminating the ring's solid cross-section for targeted, tunable, and complete drug release.***

METHODS

Solid human-sized IVRs were manufactured using CLIP 3D-printing and Islatravir (EFdA), etonogestrel (ENG), and ethinyl estradiol (EE) were formulated individually or in combination **(Fig.1)**

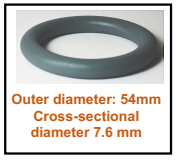


Fig. 1 Human-sized solid IVR generated with CLIP

First-in-line 3D-printed MPT IVR demonstrates sustained drug release and was well-tolerated in sheep and macaques

- 3D CLIP IVRs were loaded with EFdA, ENG, and EE (3.7 wt%, 0.19 wt%, and 0.04 wt% respectively) for in vitro release study in SVF (sheep pH 7). Release samples were collected and drugs quantified by HPLC. All drugs exhibited low burst in the first 24 h (<10%) and sustained zero order release over 180 day **(Fig.2).**

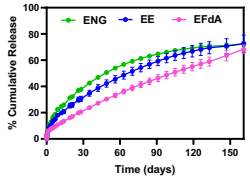


Fig. 2 In vitro release of EFdA/EE/ENG in simulated vaginal fluid (SVF, sheep pH 7) at 37℃.

- MPT IVRs were administrated to 4 female sheep (4.03-6.48 mg/kg EFdA, 0.2-0.3 mg/kg ENG, and 0.05-0.07 mg/kg EE) for a 21-day pharmacokinetic study. Plasma, vaginal biopsies, and fluids were collected **(Fig. 3).**
- Macaque-sized IVRs (25 mm OD & 6.0 mm CSD) with Islatravir were administered to 3 female non-human primates for a 30-day pharmacokinetic study. Plasma, PBMCs, vaginal biopsies, and fluids were collected. **(Fig. 4).**

Fig. 3

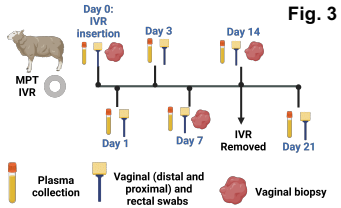
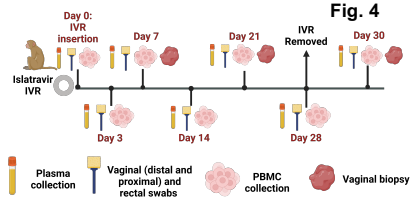


Fig. 4



RESULTS

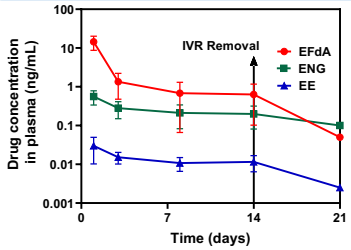


Fig. 5 Plasma concentrations (ng/mL) of EFdA, ENG, EE in sheep from MPT IVR

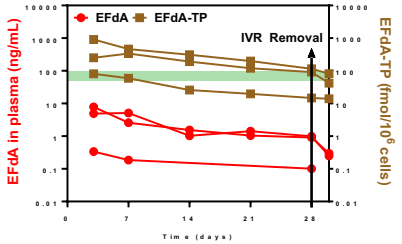


Fig. 6 Plasma concentrations (ng/mL) of EFdA and EFdA-triphosphate (TP) in macaques from EFdA IVR

Fluids (ng/swab)	Day 3 (ng/swab)			Day 7 (ng/swab)			Day 14 (ng/swab)		
	Vaginal (proximal)	Vaginal (distal)	Rectal	Vaginal (proximal)	Vaginal (distal)	Rectal	Vaginal (proximal)	Vaginal (distal)	Rectal
Sheep	422.5	144.2	0.443	136.6	184	0.3545	80.87	17.19	0.14
Macaque	16878	182111	121	1307	525	12.1	503	217	6.86

Table 1. Drug concentrations in vaginal and rectal fluids in sheep (MPT IVR) and macaques (EFdA IVR)

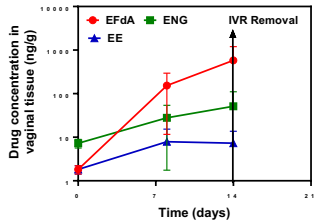


Fig. 6 Drug concentration in proximal vaginal tissue of EFdA, ENG, EE in sheep from MPT IVR

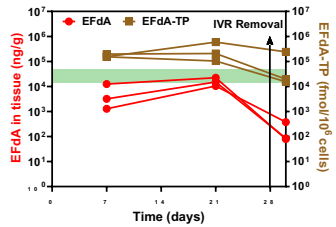


Fig. 7 Drug concentration in proximal vaginal tissue of EFdA and EFdA-TP in macaques from EFdA IVR

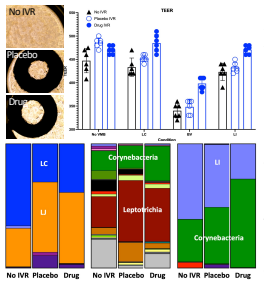


Fig. 8 Top left panels show matured air-interfaced VEC cultures in 24well format transwells. Triplicate cultures were incubated with or without the indicated IVRs for 48h before imaging at 4X magnification showing no obvious impact on the health or integrity of the multilayers. Top right shows the trans-epithelial electrical resistance (TEER) of 6 replicates for VEC cultures incubated with no IVR (black), a placebo mouse size (3 mm OD) IVR (open blue) or mouse size EFdA/ENG/EE IVR (filled blue) for 48h. Parallel transwell cultures were established with one of three selected vaginal microbiome (VMB) communities dominated by *Lactobacillus crispatus* (LC), bacterial vaginosis (BV) organisms or *L. iners* (LI). VMB communities were stabilized for 24h prior to placement of the IVR. After Teer measurements were obtained, DNA from the cultures were analyzed by qPCR array for community profiles (bottom panels) for each of the 3 VMB. LC = *L. crispatus*, LI = *L. jensenii*, LI = *L. iners*.

CONCLUSIONS

- Plasma EFdA levels (1-10 ng/mL) were maintained over 14 days in sheep and 28 days in macaques
- EFdA-TP levels were above oral benchmark of 50-100 fmol/10^6 PBMCs in macaques (green shaded region in Figures 6 & 7).
- MPT IVRs were well-tolerated in sheep and VEC cultures (Figure 8)
- Plasma ENG/EE levels were maintained over 14 days and comparable to NuvaRing levels

ADDITIONAL KEY INFORMATION

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