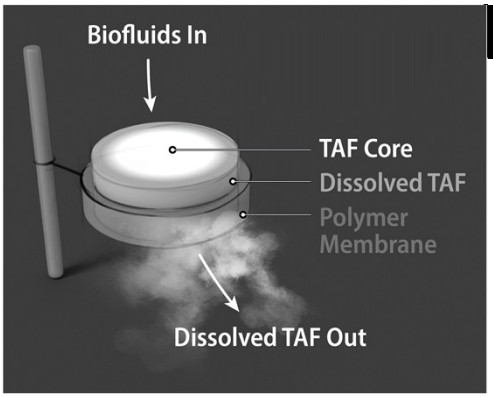
A Biodegradable, Implantable Polymer Device for Long-Acting HIV Prevention

The TIP Program is developing a novel, biodegradable and reversible implantable device with long-acting (LA) antiretroviral (ARV) release for HIV pre-exposure prophylaxis (PrEP).

To date, the program has:

- Achieved tunable drug release from 0.1 to 1 mg/day with a single rod in vitro and in vivo
- Down-selected optimal device parameters: polymer type, excipient, wall thickness
- Demonstrated that the platform is drug agnostic by achieving constant release (6-12 months) with ARVs from multiple drug classes including the prodrug tenofovir alafenamide (TAF)
- Optimized fabrication for scale and subcutaneous delivery of device with existing applicator systems
- Evaluated the safety, efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and insertion/retrievability of devices in exploratory preclinical studies



TIP Implantable Device

The TIP implantable device is a membrane-controlled reservoir system comprised of a formulated drug core encapsulated in an extruded polycaprolactone (PCL) tube.

- Drug passively diffuses through the membrane at a constant rate, offering sustained zero-order release of drug for LA prevention.
- PCL is biocompatible and biodegradable. The device is removable through therapeutic duration.

Human Centered Product Development

Efforts at RTI place an emphasis on early-stage feedback from potential end-users and health care providers to inform product development. Key findings to date include:

- Preference for longer duration (≥ 6 months) over size of device or number of rods
- Interest in a biodegradable system (no removal of device needed)
- Importance of a neat rod geometry & relative flexibility of device
- Providers preference for use of commercially available trocars for insertion

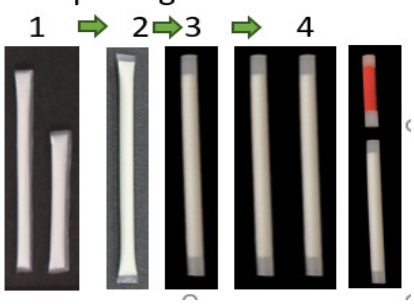
Device form factor and materials have been selected to ensure alignment with scale-up manufacturing needs &clinical translation. Devices have been engineered to incorporate:

- Manufacturing scale-up considerations
- Compatibility with approved trocars
- Formulations with greater aqueous stability

Primarily qualitative

Primarily quantitative

Implant generations:

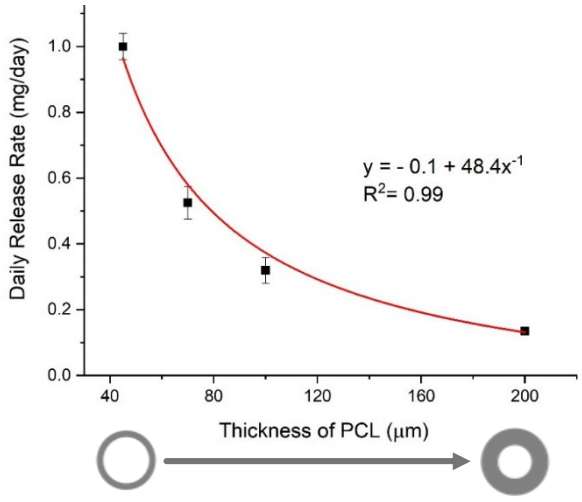


Discrete Choice Experiment randomly combines levels of attributes to generate hypothetical product profiles and choice sets from which participants choose their preference. We will assess key preferences and implant characteristics and estimate tradeoffs among attributes among young women in sub-Saharan Africa.

Lead candidate ARV, the NRTI prodrug tenofovir alafenamide (TAF)

TAF Implantable Devices In-Vitro Summary

Release of TAF scales inversely with wall thickness; demonstrated tunable release from ~0.1 → 1 mg/day



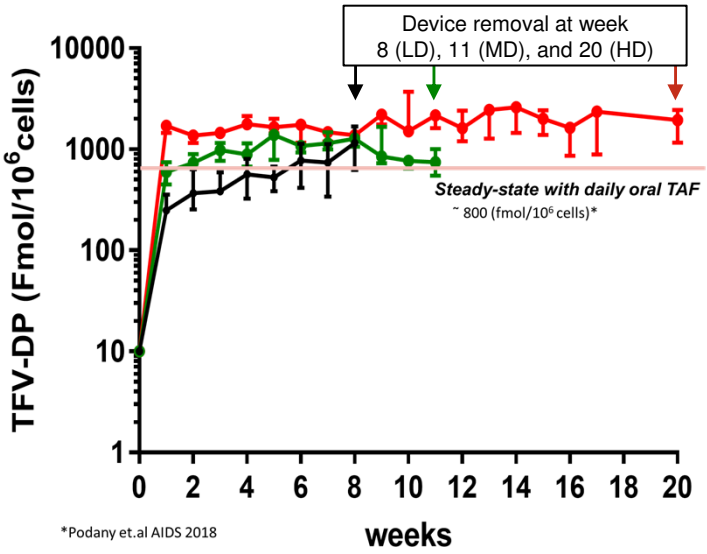
- Demonstrated tunable release rates from devices based on adjusting wall thickness and core formulation with both TAF salt (hemifumarate) and TAF base
- Dosing range compatible with estimates for HIV prevention
- Device (2.5mm x 40mm) loaded with TAF releasing at mid dose level (~0.35mg/day) is expected to last 1 year
- Showed high stability in storage under accelerated conditions (40°C/75% RH in closed foil pouches)
- Showed 6-month stability during administration under physiological conditions (37°C, pH7.4 in an aqueous buffer)

Next steps:

- **Evaluation of other drug classes in animal models**
- **Assess dual drug release from platform**
- **Prepare for first in human trials**

TIP Program In-Vivo Summary

Subcutaneous Delivery of TAF in Pigtail Macaques: PBMC concentrations of TFV-DP for three dose levels



*Podany et.al AIDS 2018

Dose Groups	Study duration (weeks)	Median TFV-DP (fmol/10^6 cells)
Low dose (LD)	8	378.5 (87-1196)
Mid dose (MD)	11	868.5 (206-1669)
High dose (HD)	20	1619 (395-3710)

TAF devices demonstrate favorable systemic PK in macaques:

- High and sustained TFV-DP in PBMCs that exceeded daily oral TAF at a fraction of the oral dose
- Dose proportionality in PBMCs provides flexible scalability.
- Estimated in vivo release rate is in high agreement with measured in vitro release rate.
- Device designs were compatible with an approved contraceptive trocar for insertion.
- Devices remained intact at retrieval after up to 180 days.

Selected Publications and Presentations

- Li L, et al. ***Performance and Stability of Tenofovir Alafenamide Formulations within Subcutaneous Biodegradable Implants for HIV Pre-Exposure Prophylaxis (PrEP).*** Pharmaceutics. Nov 5, 2020. https://pubmed.ncbi.nlm.nih.gov/33167509/
- Krogstad E, et al. ***How would South African health care providers design an implant for HIV prevention?*** AIDS Patient Care and STDs 2019. https://www.ncbi.nlm.nih.gov/pubmed/30932697
- Johnson LM, et al. ***Characterization of a Reservoir-Style Implant for Sustained Release of Tenofovir Alafenamide (TAF) for HIV Pre-Exposure Prophylaxis (PrEP).*** Pharmaceutics. July 4, 2019. https://pubmed.ncbi.nlm.nih.gov/31277461/
- Krogstad E, et al. ***Perspectives of South African youth in the development of an implant for HIV prevention.*** JIAS 2018. https://www.ncbi.nlm.nih.gov/pubmed/30152004
- Johnson L and van der Straten A. ***Implants for Delivery of Antiretroviral Drugs for HIV Pre-Exposure Prophylaxis.*** Contagion. June 20, 2018. https://www.contagionlive.com/publications/contagion/2018/june/implants-for-delivery-of-antiretroviral-drugs-for-hiv-preexposure-prophylaxis
- Lykins W, et al. ***Long Acting Systemic HIV Pre-Exposure Prophylaxis: An Examination of the Field.*** Drug Deliv Transl Res 2017. https://www.ncbi.nlm.nih.gov/pubmed/28612340
- Schlesinger E, et al. ***A Tunable, Biodegradable, Thin-Film Polymer Device as a Long-Acting Implant Delivering TAF for HIV Pre-exposure Prophylaxis.*** Pharm Res 2016. https://www.ncbi.nlm.nih.gov/pubmed/26975357

Selected Presentations

- Massud I, et al. ***Pharmacokinetics and safety of long-acting tenofovir alafenamide implants in macaques for HIV prevention.*** Presented at the 23rd International AIDS Conference (AIDS 2020) July 6-10, 2020. Available online.
- Gatto GJ, et al. ***Sustained 6-month Release Of Tenofovir Alafenamide (TAF) From A Biodegradable Implant For Long-acting (LA)-HIV Pre-Exposure Prophylaxis (PrEP).*** Presented at CRS June 29 - July 2, 2020.

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To Learn More

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