PLENARY 2

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"Development and Acceptability of a biodegradable implant for LA delivery of ARVs"

RTI technology development incorporates an end-user component to help developers select product characteristics.

Early engagement of end-users includes people who might use the implant, healthcare providers (HCPs), and other key stakeholders.

- In-depth interviews, focus group discussions, discrete choice experiments, and questionnaire surveys help discern barriers and contextual factors associated with a particular product, including cultural differences and other trade-offs that should be considered during product design.
- RTI studies with collaborators: TIP (young cis-women and men/male partners; HCPs); SCHIELD (reproductive-aged cis-women [18 to 30y]); iPrevent (MSW, MSM, cis-women); SAMURAI (young MSM and MSW [18 to 24y]); AMBER (MSM, TGW, and cis-women at risk for HIV); daisy (HCPs and caregivers of CLWH [2 to 5y]).

Delivery of ARVs via Implantable Systems for Young children (Daisy) explored HCP views on a LA implant for HIV treatment in children aged 2 to 5 years (Scorgie et al AIDS Patients Care 2022).

- Qualitative in-depth interviews were conducted among 24 HCPs living in South Africa.
  - HCPs viewed implant prototypes and visual cue cards depicting different implant parameters.
  - Feedback sought on: size/length; color/transparency; geometry; dosing interval; biodegradability; retrievability; replacement; trocar characteristics; patient challenges with placement; and body location.
- Key results – the ARV implant should be:
  Discreet (Less visible to mitigate stigma); Easy-to-administer (ease the burden on HCPs and health systems); and Child-friendly (HCPs valued child comfort and the ability to play like other children/preferred implants that would not inhibit movement or be painful).
  *For children living with HIV, we may need to consider locations other than the arm.

Technological aspects of the RTI reservoir-style ARV implant.

Drug delivery platform.

- A formulated API core is surrounded by a polymeric membrane.
- Biofluids flow into the implant, dissolve the API, then dissolved API flows out of the membrane.
- Release kinetics are based on biofluid transport in and out of the membrane – zero-order release kinetics can be achieved in many instances, depending on the formulation.
- Multiple APIs are possible (i.e., for HIV treatment).

Product development – tunable characteristics.

- API formulation (drug selection/particle size; excipient selection/ratios).
  - ARVs; Other APIs/treatment indications are possible.
- Polymer design (polymer selection; molecular weight, crystallinity; biodegradation timeframe).
  - Polycaprolactone (PCL) is a biodegradable polyester with a melting point at 60°C.
  - Slow, tunable degradation profile.
- Implant dimensions (surface area; wall thickness; compatibility with existing trocar systems).
  - Rod-shaped L40mm/OD 2.5mm form factor is compatible with commercially available trocars.
  - Tunable surface area (SA) and wall thickness (70, 100, 200 μm with fixed OD 2.5mm).
- Manufacturing (scalable fabrication; mechanical integrity testing; GMP/medical grade materials).
  - PCL is being used in FDA-approved applications, including medical sutures (monocryl, glycolon) and root canal filling (Resilon).

Tunability of the RTI ARV implant.

Implant dimension parameters (SA and wall thickness) modulate ARV release rate.

- *in vitro* studies – Bictegravir (BIC).

  - Greater implant surface area (L 40mm vs L 10mm) resulted in a higher release rate (cumulative release vs time).
  - Average daily release rate decreased with increasing implant wall thickness (70 to 300 μm).
- *in vivo* studies – PK of ISL (low, mid, high dose) implant in NHPs (Daly et al Pharmaceutics 2023).
  - Three dose groups demonstrate the impact of implant surface area.
  - Plasma ISL and PBMC ISL-TP (active moiety) concentrations were assessed in each dose group over 90d.
  - All dose groups had sustained ISL release; the high-dose group achieved the PrEP target (50 fmol ISL-TP/10^6 PBMCs).

PCL characteristics modulate the biodegradation profile (implant duration).

- PCL degradation is a two-stage process.
  - Molecular scale degradation via decreases in polymer chain length.
    Implant remains intact, and drug delivery continues.
  - Macro-scale degradation (mass loss) via cellular degradation.
    Begins when the polymer reaches a certain molecular weight (5kDa); The implant can be removed or left to biodegrade.
- Changes in PCL chain length and molecular weight can slow degradation for implant duration up to 1-2 years.

Other programs.

New biodegradable polymer formulations for implants and other drug delivery systems**.**

- Goal: tailor polymer degradation profiles to align with desired implant duration for different medical indications.
- Investigating numerous polymers with different compositions (PC17, PCL-C18-PEG, FD92PM, PHBV, PCLX, FZ71PM).
  - Polymer compositions affect implant performance *in vitro* (i.e., release rate, mechanical properties).
  - All polymers are compatible with gamma sterilization.
  - Biodegradation studies are still underway in preclinical and accelerated *in vitro* models.

Empiric and predictive modeling to potentially streamline product development decisions.

- Goal: Predict performance of implants/drug delivery systems with new drug formulations without *in vitro* studies (money and time savings).
- Developed models for Dk (diffusion) in a reservoir system as a function of API properties (MW, solubility [CsE, CsP], pKa, and logP)(Li, Lying et al Pharmaceuticals 2022).
  - Used experimental data (cumulative release of ARV over time) and fit the Dk value to yield predicted release rates.
  - The model readily determines empirical parameters that define membrane-controlled (zero order) release.
  - Need to develop better models to predict non-zero-order drug release (e.g, burst release or long tail depletion profile).

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