Global Health and Special Populations

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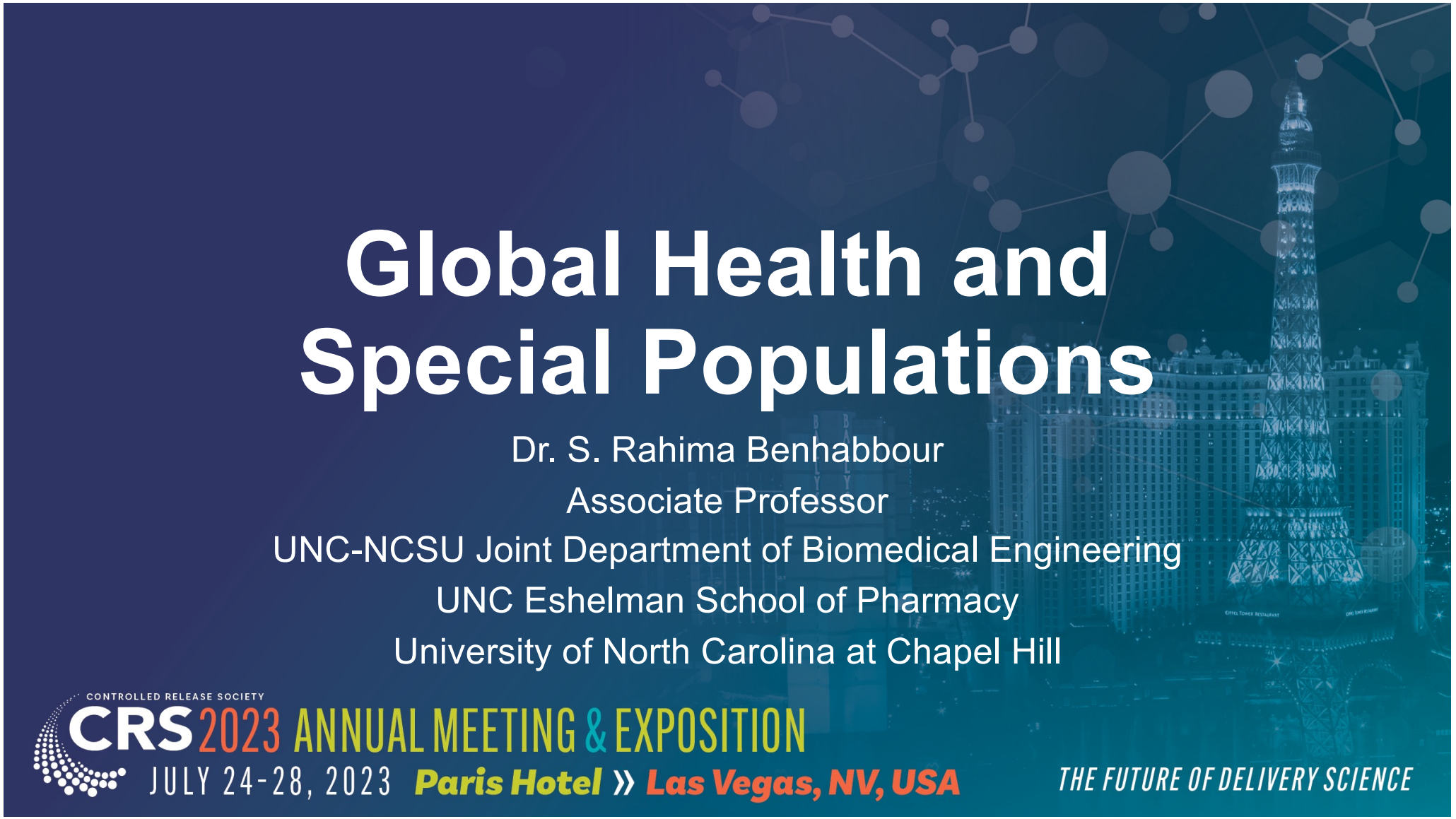
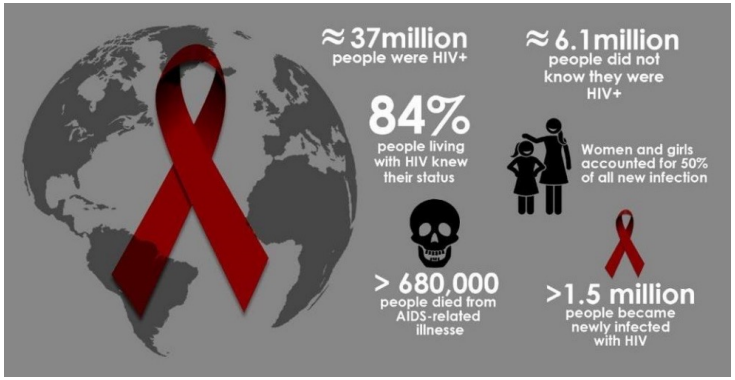


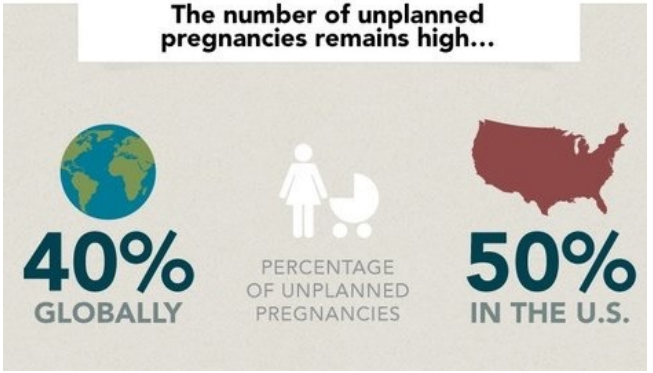
High global prevalence of HIV and unplanned pregnancy

HIV



- 38 million people are living with HIV
- 1.5 million people become newly infected in 2021
- 19.2 million women are living with HIV
- Sub-Saharan Africa accounts for 68% of global HIV infections

Unplanned Pregnancy



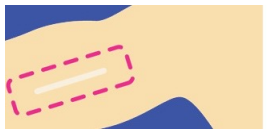
- 120 million unplanned pregnancies each year
- 65% of unplanned pregnancies arise from nonuse of contraceptive methods
- 14 million unplanned pregnancies in Sub-Saharan Africa
- 41% women discontinue short-acting birth control methods

UNAIDS (2021); CDC (2021)

Current Landscape of HIV PrEP and Contraception

Contraception

Short & long-acting contraceptive options in a variety of dosage forms

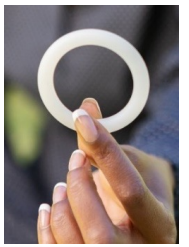


Nexplanon®
The Birth Control Arm Implant

HIV Prevention (PrEP)

- **Truvada® (2012)**
  - Effectiveness is strictly dependent on adherence
  - Drugs: tenofovir and emtricitabine

- **Apretude (2021)**
  - First long-acting injectable for HIV PrEP
  - Bimonthly i.m. injections of 600 mg/3 mL cabotegravir
  - Not removable - 30-day oral lead-in for safety recommended
  - PK tail for > 1-year post-discontinuation



- **30-day Dapivirine (DPV) vaginal ring (2020)**
  - NOT approved by the FDA for women in the USA
  - WHO has approved it and recommends it to women in EU and sub-Saharan Africa
  - 25 mg dapivirine releasing 4 mg over a month (**only 16% drug release**) with <50% efficacy

Unmet need for multipurpose prevention technologies (MPTs)

Condoms are the only marketed product to protect against **both** HIV and unplanned pregnancy
Poor user adherence and require partner cooperation

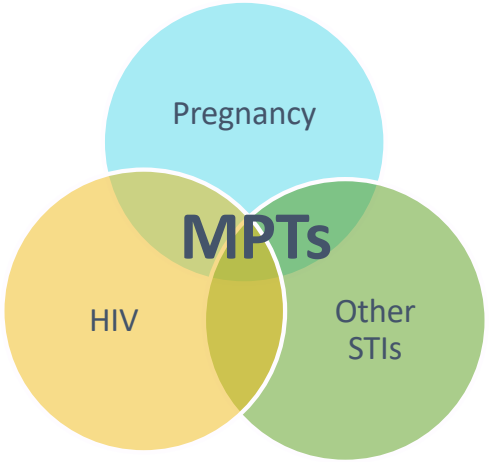
Multipurpose prevention technologies (MPTs) address at least two sexual or reproductive indications in a single technology

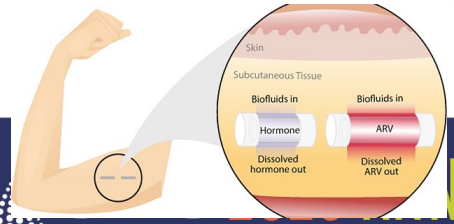
- Target population: women and girls in sub-Saharan Africa

Long-acting | User acceptability | Increase adherence
Discrete | Cost-effective | Ease of access

Combined Oral Contraceptives

Oral Pre-Exposure Prophylaxis (PrEP)

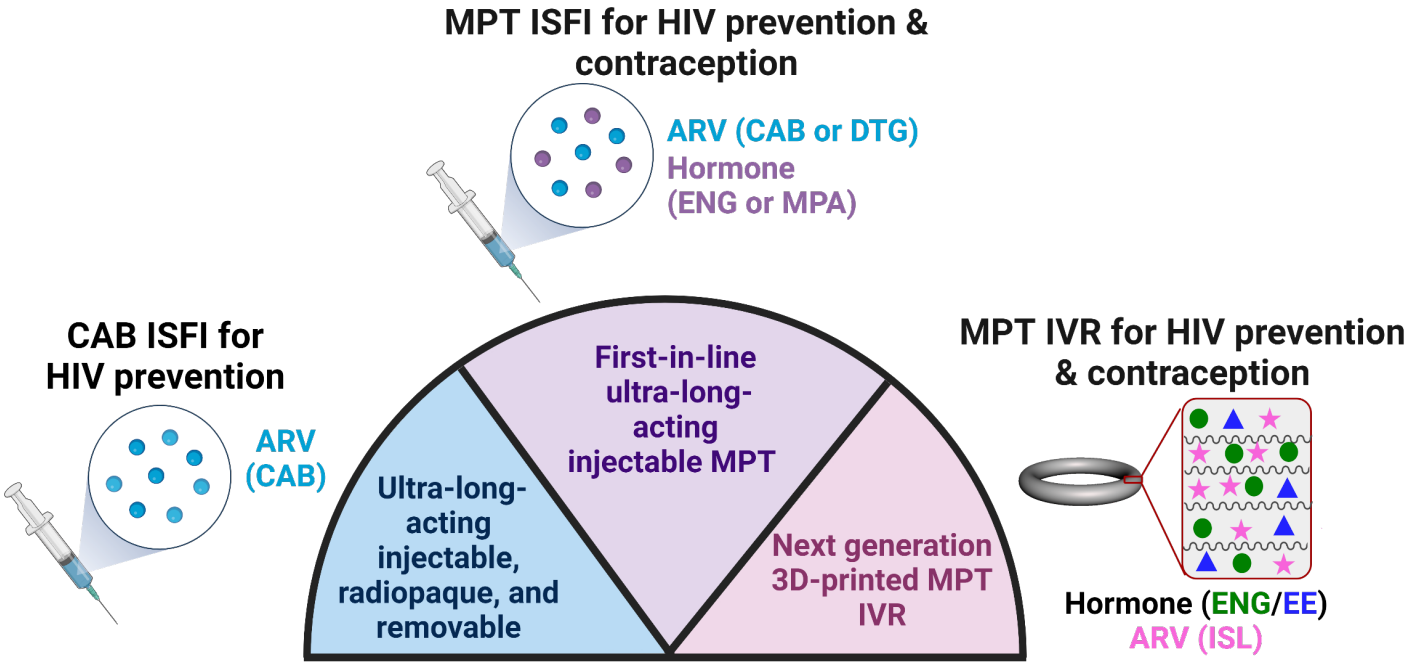




No published literature on injectable MPTs

Young, IC & Benhabbour S.R. "Multipurpose prevention technologies: Oral, Parenteral, and Vaginal Dosage Forms" (Review). *Polymers* 2021

Long-acting prevention technologies

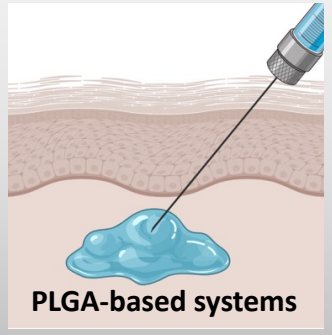


Expand preventative options, bring choice and empowerment to women and girls, and make a global impact in women's sexual and reproductive health

Ultra-Long-Acting Injectable PrEP & MPTs

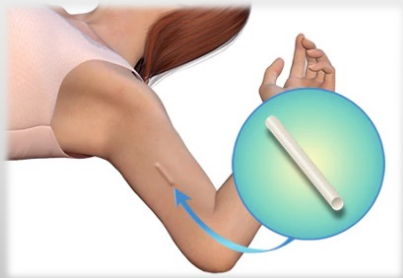
1

PLGA-based ISFIs for LA Delivery of DTG



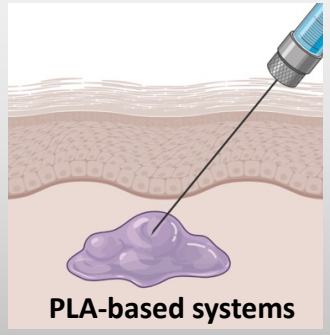
2

Solid Implants based ISFI technology for LA Delivery of DTG and/or RPV



3

PLA-based ISFIs for LA Delivery of EFdA



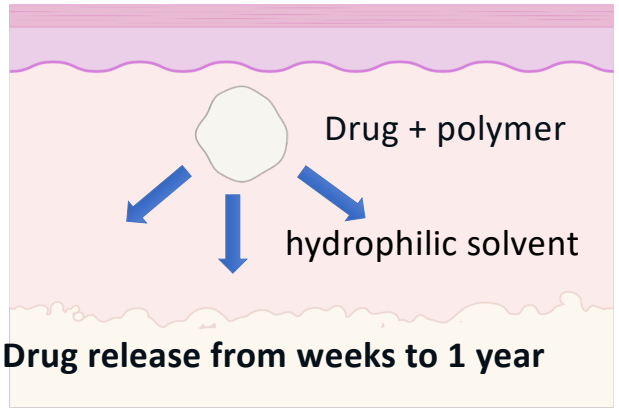
Ultra-Long-Acting ISFIs

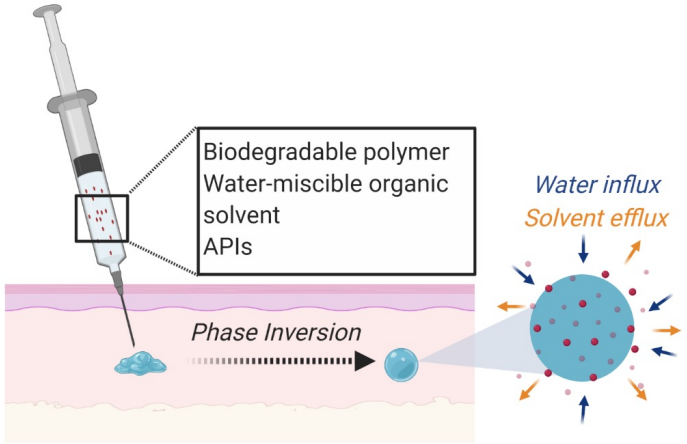
In situ forming implants (ISFIs) for sustained release of APIs

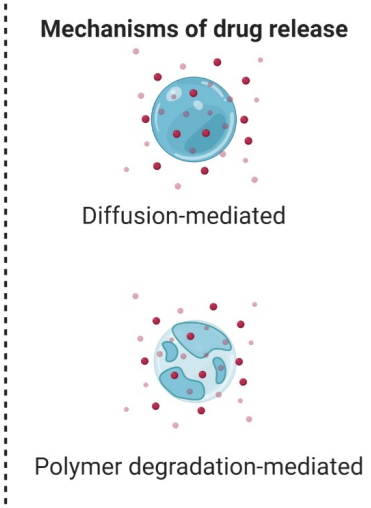
3 component system:
Drug + polymer (PLGA) + hydrophilic solvent (NMP)

Advantages: sustained release, tunable release kinetics , biodegradable, ability to remove (if needed)

Implant forming (phase inversion)







Minnis et al (2019) and van der Straten et al (2018)

Young, IC & Benhabbour S.R. "Multipurpose prevention technologies: Oral, Parenteral, and Vaginal Dosage Forms" (Review). *Polymers* 2021

Injectables are favored in areas where HIV prevalence is highest

Ultra-long-acting (ULA) CAB ISFI

NIH National Institute of Allergy and Infectious Diseases

NIH NIAID R01AI131430

nature communications

Article

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Ultra-long-acting in-situ forming implants with cabotegravir protect female macaques against rectal SHIV infection

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Check for updates

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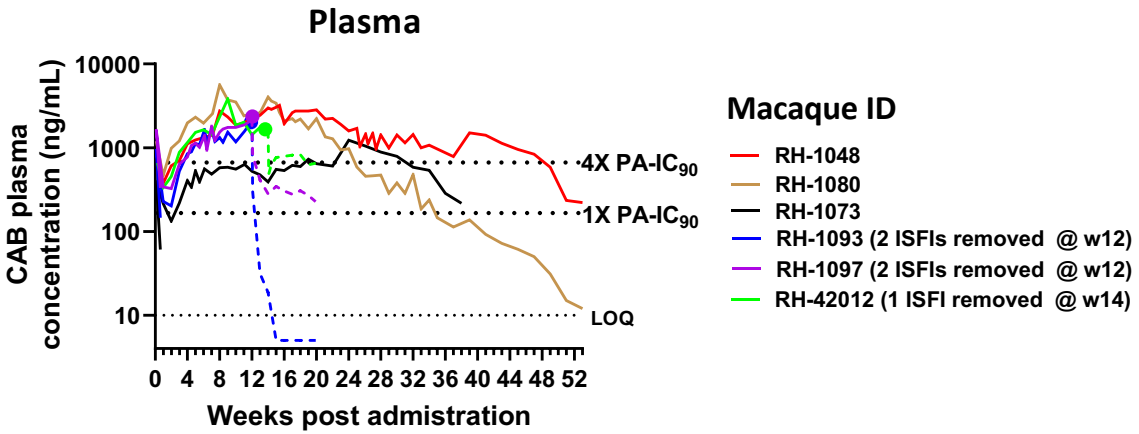
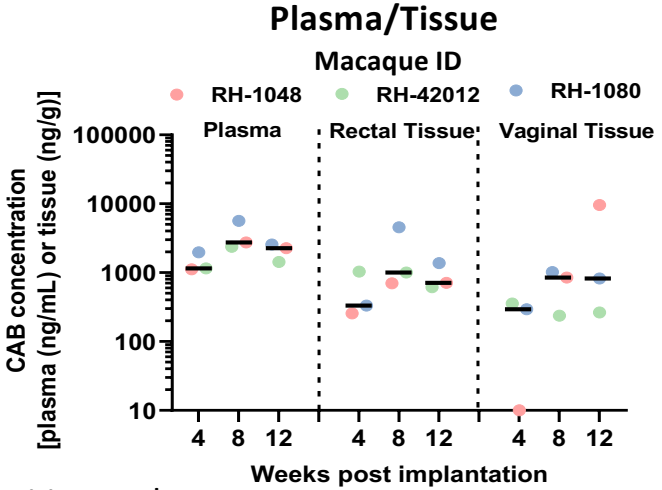
Editors' Highlights pages, which aims to showcase the 50 best papers recently published in an area: Microbiology and infectious diseases

PK of CAB ISFI in rhesus macaques

2× 1 mL injections of CAB ISFI was administered s.c. to six female rhesus macaques (113.8 mg/kg)





- CAB ISFI can achieve CAB levels in plasma above the 4X PA-IC90 for up to 6 to 11 months
- Median plasma concentration at week 28 (~6 months) was 886 ng/mL
- Removal of CAB ISFIs resulted in up to a 100-fold reduction of CAB concentration within 2 weeks
- Even distribution in vaginal and rectal tissues for 12 weeks

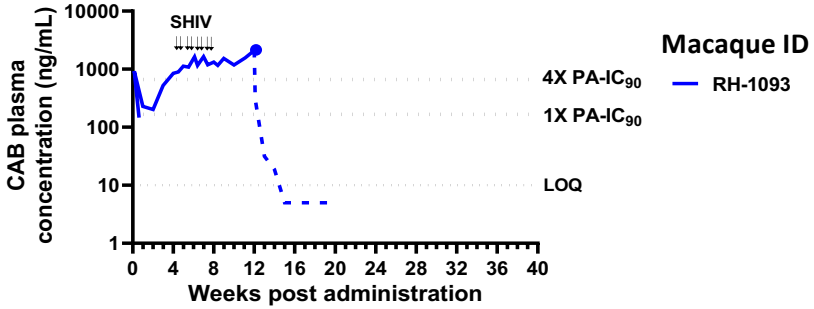
LOQ: limit of quantification. Concentrations below LOQ were represented as LOQ/2

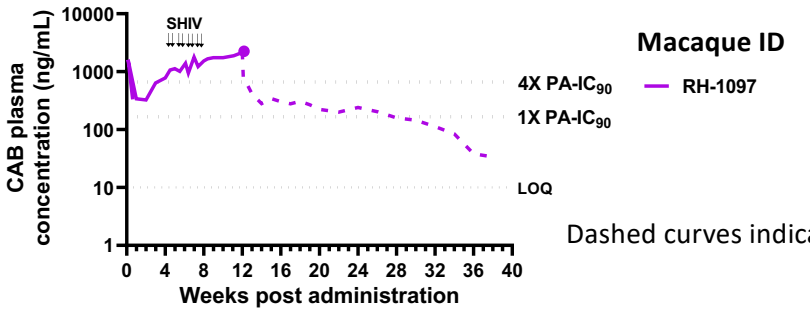
Young IC, Massud I *et al.* Nature Communications, 2023

Efficacy of CAB ISFI in rhesus macaques – short term protection

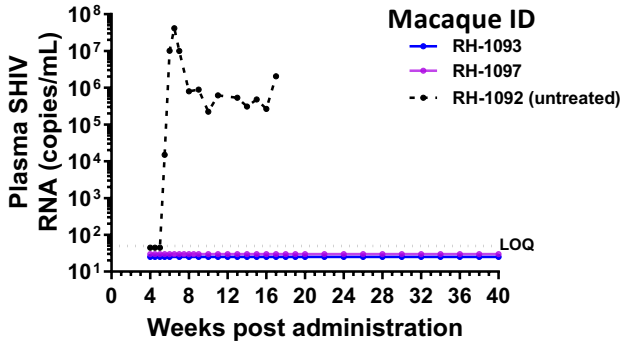
Rectal SHIV challenges (10 $TCID_{50}$ of SHIV163p3 – stock used to predict clinical efficacy of all currently approved PrEP products)

- 2 macaques were challenged twice weekly between weeks 4 and 8 (8 challenges per animal)





Dashed curves indicate ISFI removal



Single CAB ISFI treatment was completely protective against rectal SHIV exposures

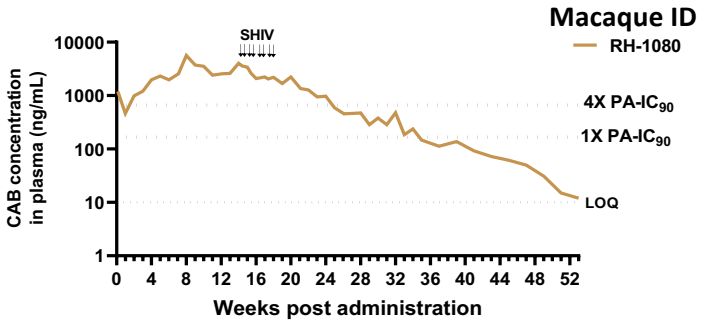
$TCID_{50}$: median tissue culture infectious dose; LOQ: limit of quantification. Concentrations below LOQ were represented as LOQ/2

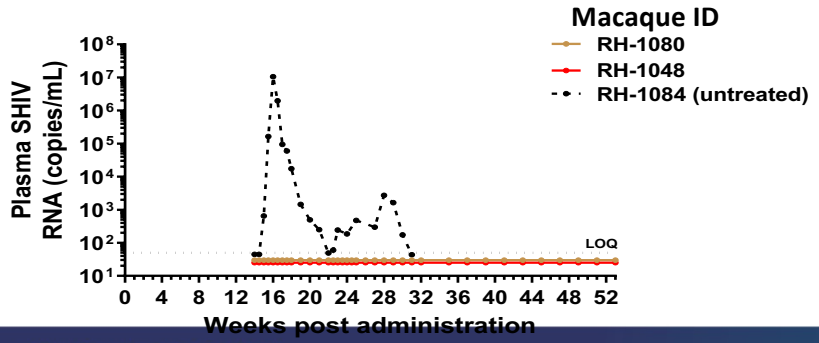
Young IC, Massud I *et al.* Nature Communications, 2023

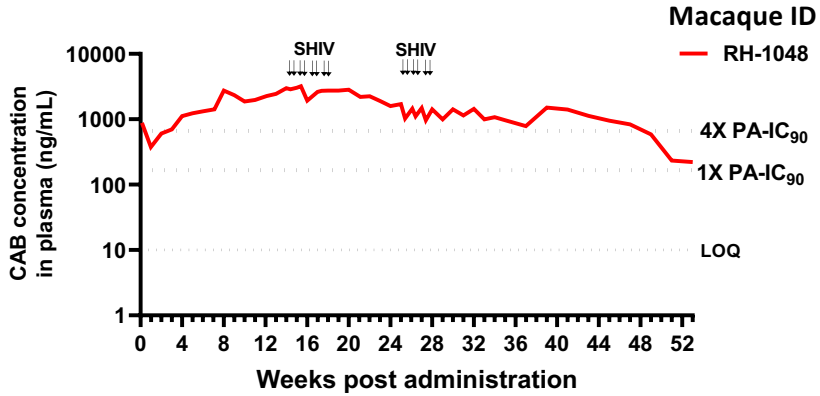
Efficacy of CAB ISFI in rhesus macaques – long term protection

Rectal SHIV challenges (10 $TCID_{50}$ of SHIV163p3 – stock used to predict clinical efficacy of all currently approved PrEP products)

- 2 macaques were challenged twice weekly between weeks 12 and 16 (8 challenges per animal); RH-1048 received 6 additional 6 SHIV challenges between weeks 25 and 28 (total of 14 exposures)







Long-lasting efficacy with a single CAB ISFI treatment against 38 rectal SHIV exposures - the longest documented PrEP activity seen with a single CAB administration.

$TCID_{50}$: median tissue culture infectious dose; LOQ: limit of quantification.
Concentrations below LOQ were represented as LOQ/2

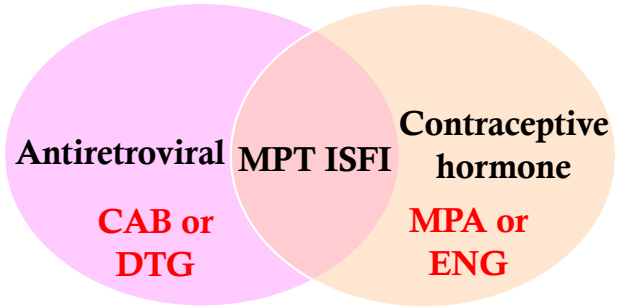
Young IC, Massud I *et al.* Nature Communications, 2023

Long-acting injectable multipurpose prevention technology

Develop and characterize an ISFI formulation that

1) can accommodate antiretrovirals in combination with a contraceptive drug at translatable human doses, provide sustained delivery over ≥ 3 months,

2) can further prevent pregnancy in addition to HIV.



NIH National Institute of Allergy and Infectious Diseases

NIH NIAID R01AI162246

Conclusions

- CAB plasma levels in mice and macaques were above 4X PA-IC90 for at least 6 months after a single injection → reduced dosing frequency
- CAB ISFIs are easily removable, if needed, and elicit potential for a short PK tail after removal
- First-in-line LA injectable MPT with sustained release of ARVs and hormones over 90 days
- MPT ISFIs were well-tolerated in mice and did not demonstrate chronic local or systemic inflammation
- No difference in ARV release when co-formulated with ENG or MPA
- Rapid decline of CAB and MPA after ISFI removal
- Potential to sustain release beyond 90 days

Acknowledgments

My Lab

Collaborators

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MATRIX Advancing R&D of Innovative HIV Prevention Products for Women

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