IN SITU FORMING IMPLANTS WITH CABOTEGRAVIR FOR ULTRA LONG-ACTING PREP

ID 00855

I Massud[1], M Kovarova[2], A Wong-Sam[1], C Dinh[1], E Edwards[1], V Mrotz[1], J Mitchell[1], W Heneine[1], I C Young[4], R Shrivastava[3], J V Garcia[2], C Dobard[1], G García-Lerma[1], S R Benhabbour[3,4]

[1]Centers for Disease Control and Prevention, Atlanta, GA, United States.

[2]International Center for the Advancement of Translational Science, Division of Infectious Diseases, Center for AIDS Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

[3]Joint Department of Biomedical Engineering, North Carolina State University and The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

[4]Division of Pharmacoengineeing and Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

BACKGROUND

- Bi-monthly Cabotegravir long-acting (CAB LA) is available as a new option for HIV prevention. Biodegradable in situ forming implants (ISFI) releasing CAB represent an attractive ultra long-acting delivery platform that can provide sustained drug release for several months to years but can be removed to terminate treatment if needed. We evaluated drug release, drug tail after removal, and PrEP efficacy of CAB ISFIs in macaques.

METHODS

Safety and PK analysis:

- Two 1-mL injections of CAB ISFI (500 mg/mL CAB) were administered to the back of 6 rhesus macaques
- Plasma CAB levels were monitored weekly for up to 6 months and in tissues monthly for up to 3 months.
- Implants were retrieved at week 12 in two animals to assess the CAB tail after implant removal.
- ISFI injection sites were monitored weekly (up to 12 weeks) for presence of local skin reactions.

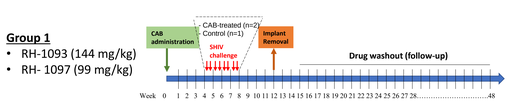
Efficacy:

- Efficacy was evaluated in two groups of 2 macaques when plasma CAB levels were >4x PA-IC_{90}.
- Group 1 animals were challenged with $SHIV_{162p3}$ twice-weekly between **weeks 4-8** and group 2 were challenged between **weeks 12-16**. One animal in group 2 received 6 additional SHIV challenges between **weeks 24-27.**
- Infection outcomes were compared to two untreated animals challenged during the same time period.

Efficacy Study Design

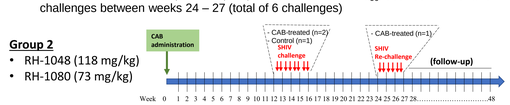
I. Short-term efficacy with implant removal

- CAB-treated (n=2) and untreated control (n=1)
- Twice-weekly rectal challenges between weeks 4 – 8 (total of 8 challenges)



II. Long-term efficacy

- CAB-treated (n=2) and untreated control (n=1)
- Twice-weekly rectal challenges between weeks 12 – 16 (total of 8 challenges)
- One CAB-treated animal (RH 1048) w/ plasma CAB >4x PA-IC_{90} received additional SHIV challenges between weeks 24 – 27 (total of 6 challenges)



ISFIs releasing CAB were safe and fully protected macaques from rectal SHIV infection for up to 6 months

Figure 1.

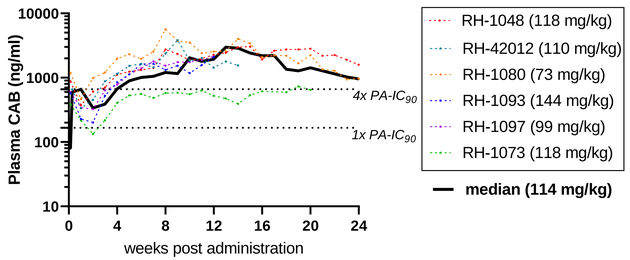


Figure 1. CAB levels in plasma up to 6 months after CAB ISFI administration. Dotted black lines represent 4x PA-IC_{90} (664 ng/mL) and 1x PA-IC_{90} (166 ng/mL).

Table 1. Median (range) CAB concentrations in plasma (n= up to 6) and tissues (n=3)

	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Plasma ng/mL	338 (216-464)	982 (406-1,977)	1,950 (578-5,628)	2,270 (1,430-2,553)	2,003 (1,923-2,083)	2,528 (2,828-2,227)	1,278 (971-1,585)
Vaginal tissue ng/g (n=3)		293 (BLOQ-356)	849 (238-1,016)	822 (265-9,577)			
Rectal tissue ng/g (n=3)		333 (256-1,034)	1,004 (699-4,554)	713 (615-1,377)			

Figure 2.

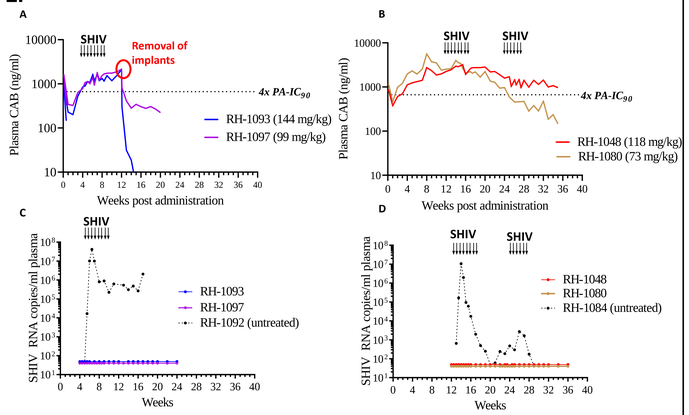


Figure 2. (A) Short-term efficacy: CAB plasma levels during challenge weeks 4-8 (n=2) and following implant removal at week 12. **(B) Long-term efficacy:** CAB plasma levels during challenge weeks 12-16 (n=2) and weeks 24-27 (n=1). Time and frequency of rectal SHIV exposures indicated by arrows. **(C-D) Virological outcome:** SHIV RNA detected in plasma of untreated (n=2) and not detected in CAB-treated animals (n=4)

Figure 3.

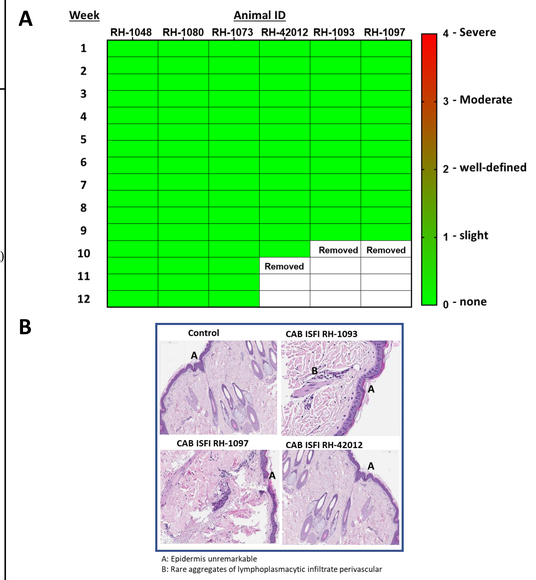


Figure 3. (A) Skin reactions were assessed visually and graded based on the Draize scale (0-4) **(B)** H&E stain of skin biopsies collected in the back (control) or near the ISFI administration site.

RESULTS

- Median (range) **plasma CAB levels** were high at week 4 [982 ng/mL (406-1,977)] and **remained ~1.9-fold above the 4x PA-IC_{90} for up to 6 months** post administration [1,278 ng/mL (971-1,585)] (**Fig 1**).
- **Median CAB levels in vaginal and rectal tissues** were 293 ng/g and 333 ng/g at week 4, respectively, and **increased more than 2-fold** by week 12 (822 and 713 ng/g, respectively). (**Table 1**).
- **Implant removal** in 2 macaques at week 12 **resulted in a rapid decline** in plasma CAB levels within 3 days (mean of 2,128 ng/mL at the time of removal to 179 ng/mL at day 3 after removal). CAB levels fell below the limit of detection (5 ng/mL) by week 3 post removal in the animal (RA-1093), suggesting a **short CAB tail** following complete ISFI removal. Notably, CAB levels remained detectable in animal RA-1097, likely due to residual CAB ISFI following incomplete ISFI removal (**Fig 2A**).

RESULTS (CONTINUED)

- **CAB ISFI-treated animals** exposed twice-weekly to SHIV starting at week 4 (n=2) or week 12 (n=2) post administration (**Fig 2A and 2B**, respectively) **were fully protected** after 8 SHIV exposures (total of 32 exposures). Plasma CAB levels in animal RA-1048 remained above 4x PA-IC_{90} at week 24 and **maintained full protection** following an additional 6 SHIV exposures (**Fig 2B).**
- The two untreated animals were infected with SHIV after one rectal challenge (**Fig 2C and 2D**).
- **No skin reactions or safety concerns** were observed at the implant sites in any of the CAB ISFI treated animals (**Fig 3A**).
- **H&E staining** of skin biopsies collected 12 weeks post administration were **unremarkable (Fig 3B).**

CONCLUSIONS

- CAB ISFIs provided sustained release of CAB above established PrEP benchmarks for up to 6 months.
- CAB ISFIs conferred high and durable protection against SHIV infection in a validated macaque model of rectal HIV transmission.
- CAB ISFIs were safe and resulted in a short drug tail following complete removal.
- Our findings describe a novel biodegradable and removable CAB formulation for long-acting PrEP and supports clinical advancement in humans.

ADDITIONAL KEY INFORMATION

Author contact information: **vve9@cdc.gov**

ACKNOWLEDGEMENTS:

We would like to thank:

- Amy Martin for diagnostic drug level testing.
- Dr. Nascimento Seixas for the histological assessment.
- The study was possible thanks to the support of NIH-NIAID R01AI131430

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention