Rapidly-dissolving inserts for on-demand topical prophylaxis

- **On-demand topical prophylaxis**
  - Event-driven drug delivery- right place/right time
- **User-friendly**
  - Small, discreet, easy to carry
  - Self-administered; no applicator
  - Minimal leakage
  - Dual use; vaginal or rectal
- **Favorable safety profile**
  - Low systemic drug exposure/less toxicity
- **Potential for drug combinations**
  - More flexible dosing options (before or after sex)

USAID FROM THE AMERICAN PEOPLE PEPFAR

CONRAD is developing inserts containing Tenofovir Alafenamide (TAF) and Elvitegravir (EVG) for topical HIV and HSV prophylaxis

CONRAD
Leaders in Reproductive Health and HIV Prevention

Rationale for selecting TAF + EVG for inserts

❑ Tenofovir alafenamide (TAF)

- ✓ More potent than TFV and TDF
- ✓ Increased TFV-DP concentrations in HIV target cells
- ✓ Favorable safety profile with oral dosing
- ✓ Active against HIV and HSV

❑ Elvitegravir (EVG)

- ✓ Blocks viral integration (~8h after post viral entry)
- ✓ Potential for more flexible dosing regimen (PrEP/PEP)
- ✓ Demonstrated post-exposure protection with Raltegravir gel (up to 3h) in vaginal challenge macaque model[1]

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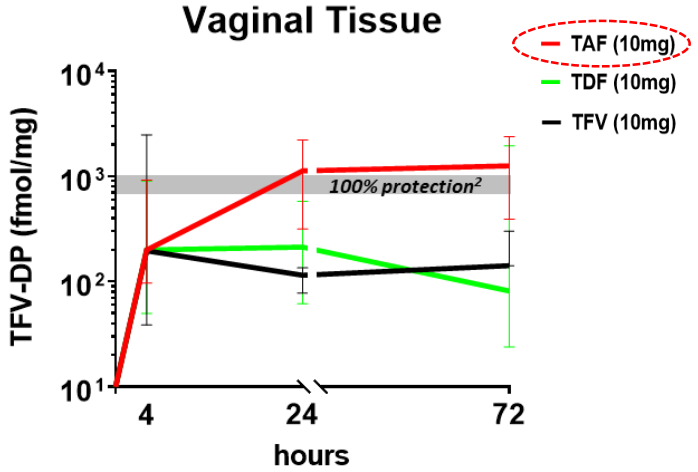
1-Dobard et al, Science Translational Medicine 2014

Preclinical Progression towards identifying lead TAF/EVG insert

Selection of Lead TFV Pro-drug

PK comparison
(single-drug inserts)

- TFV (10mg)
- TDF (10mg)
- TAF (10mg)



Key Finding:

- Increased tissue TFV-DP with TAF compared to TFV or TDF

Dobard et al, CROI 2019

Preclinical Progression towards identifying lead TAF/EVG insert

Selection of Lead TFV Pro-drug

PK comparison
(single-drug inserts)

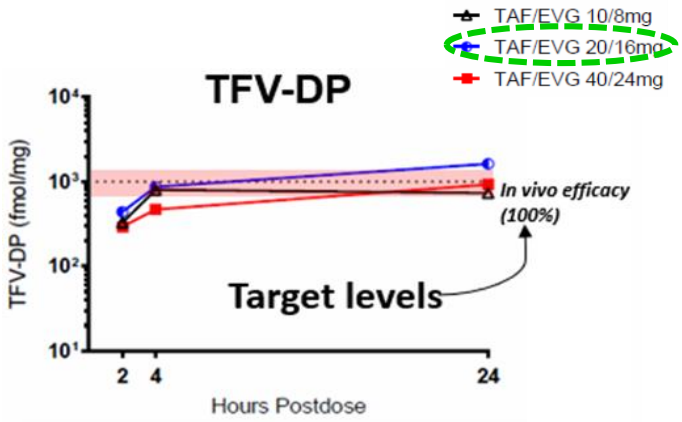
- TFV (10mg)
- TDF (10mg)
- TAF (10mg)

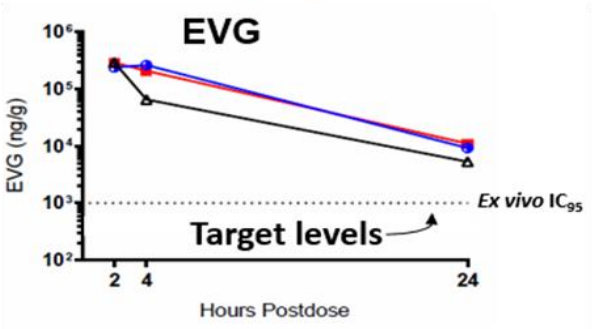
Fixed-Dose TAF/EVG Combination

Dose ranging PK

- TAF/EVG (10/8 mg)
- TAF/EVG (20/16 mg)
- TAF/EVG (40/24 mg)

Vaginal Tissue



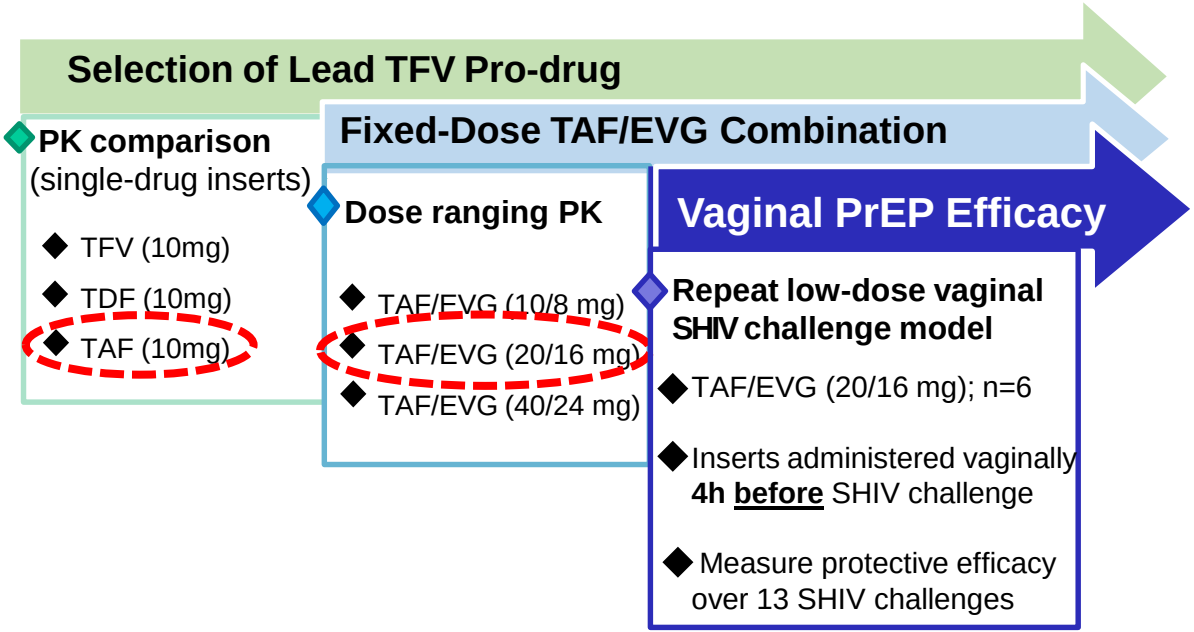


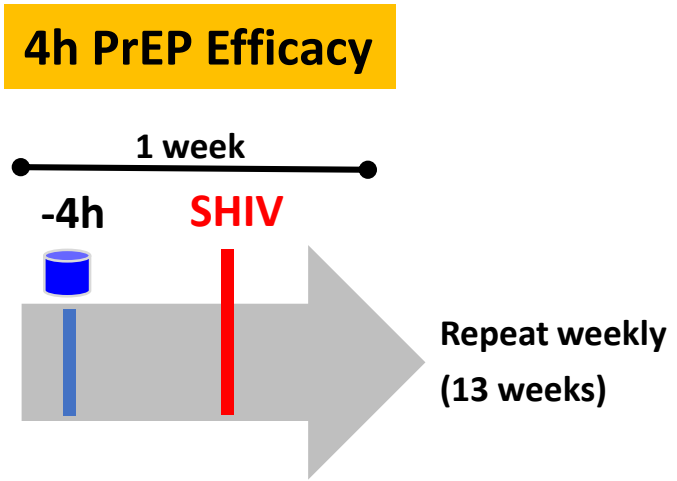
Key Finding:

- 20/16 mg TAF/EVG insert maintained the highest tissue [TFV-DP] and [EVG] over 24h

Dobard et al, CROI 2019

Preclinical Progression towards identifying lead TAF/EVG insert





Dobard et al, CROI 2019

Preclinical Progression towards identifying lead TAF/EVG insert

Selection of Lead TFV Pro-drug

PK comparison
(single-drug inserts)

- TFV (10mg)
- TDF (10mg)
- TAF (10mg)

Fixed-Dose TAF/EVG Combination

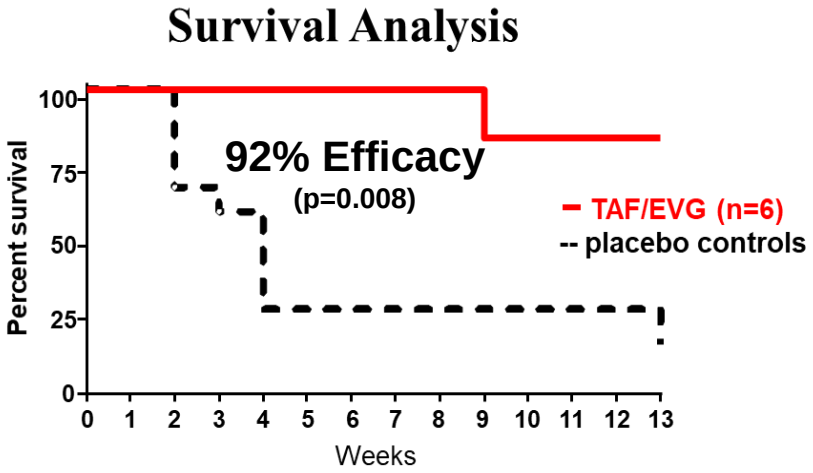
Dose ranging PK

- TAF/EVG (10/8 mg)
- TAF/EVG (20/16 mg)
- TAF/EVG (40/24 mg)

Vaginal PrEP Efficac

Repeat low-dose vaginal SHIV challenge model

- TAF/EVG (20/16 mg); n=6
- Administer inserts vaginally **4h <u>before</u>** SHIV challenge
- Measure protective efficacy over 13 SHIV challenges



Key Findings:

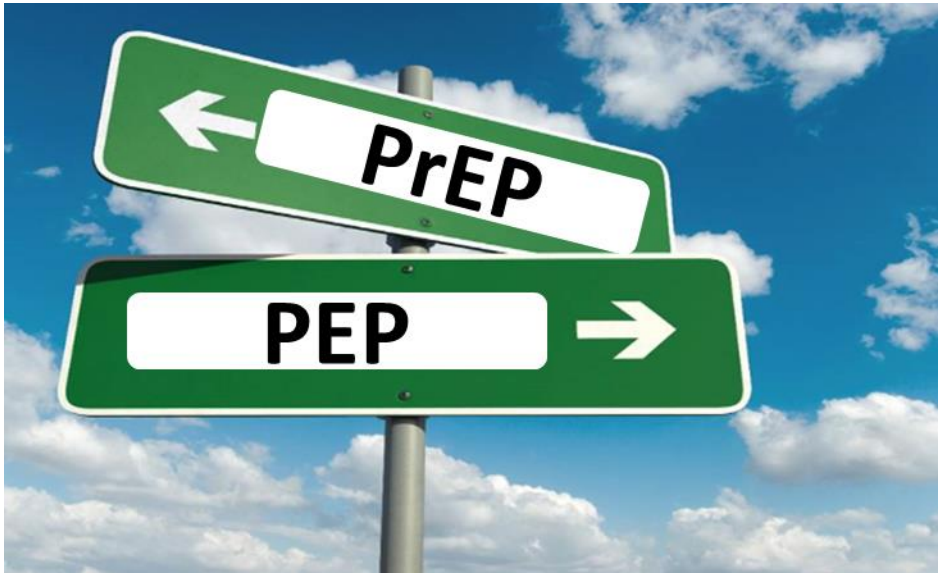
- **92% Efficacy (95%CI: 34.8%, 98.9%)**

Dobard et al, CROI 2019

Study Objectives

- Assess efficacy of TAF/EVG (20/16mg) inserts when administered as PEP **4h after** vaginal SHIV exposure

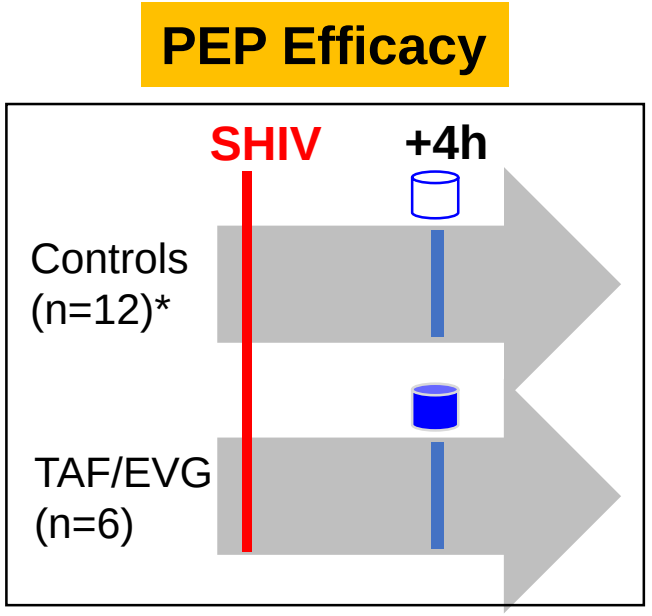
- Understand drug distribution in plasma and PBMCs after vaginal TAF/EVG dosing



PEP challenge design

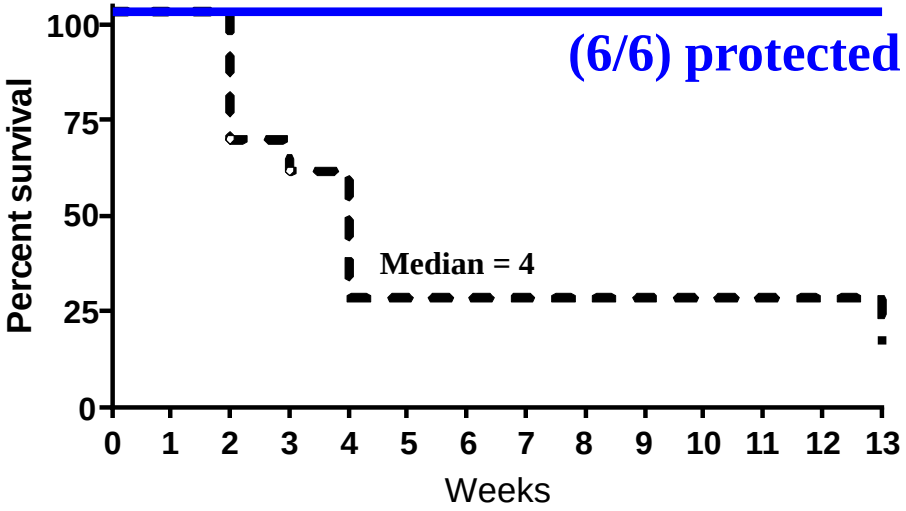
Study Design:

- Pigtailed macaques with regular menstrual cycles
- Vaginal SHIV challenges once per week for up to 13 weeks
- Inserts administered **4 hours after** SHIV challenge
- Blood collected prior to each SHIV inoculation to monitor for SHIV infection and drug concentrations



*5 real-time and 7 historical controls

PEP efficacy of TAF/EVG inserts administered 4h after SHIV exposure

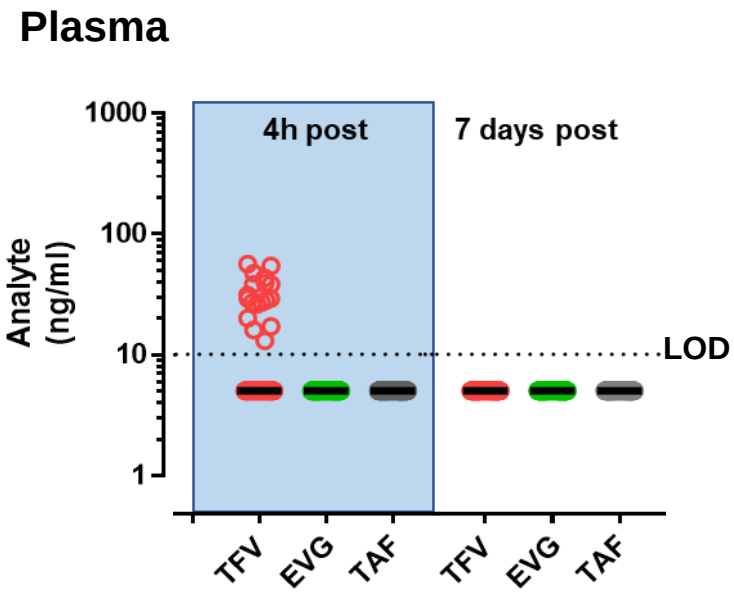


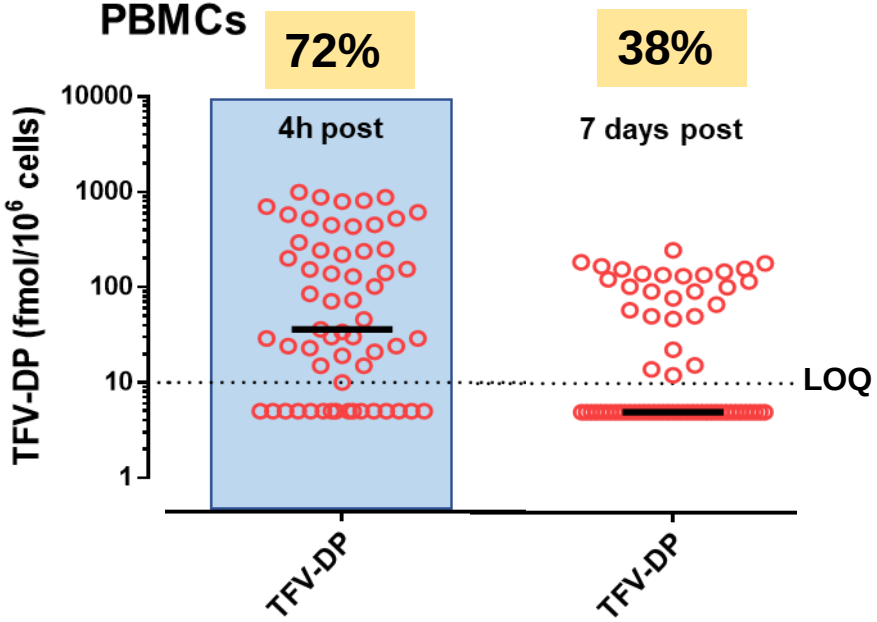
Combined controls (n=12)

4h PEP (n=6)

100% Efficacy (p= 0.009; log-rank test)

Drug exposures in plasma and PBMCs following vaginal dosing with TAF/EVG inserts





- Low drug exposure in plasma

- Median TFV-DP @ 4h = 36 fmol/10^6 cells
- Median TFV-DP @ 7d = <LOQ fmol/10^6 cells

Summary

- ❑ Vaginal administration of TAF/EVG (20/16mg) inserts provided high protection against vaginal SHIV infection when administered within a 4-hour window either before or after viral exposure
- ❑ High TFV-DP loading in PBMCs from topical delivery of TAF is unique; unclear role in protection
- ❑ Findings show proof of concept for vaginal TAF/EVG inserts for “on demand” topical **PrEP** or **PEP** and support clinical advancement
- ❑ First-in-human (Phase I) clinical studies to assess safety and PK of TAF/EVG (20/16mg) inserts:
  - ❑ CONRAD 146 (vaginal use) – study completed; results to be available mid-2020
  - ❑ MTN-039 (rectal use) – study ongoing

Acknowledgments

CDC DHAP LAB Branch
- Walid Heneine

Antiretroviral Prophylaxis Team
- **Kenji Nishiura**
- Mara Sterling
- Natalia Makarova
- Jim Smith
- Gerardo Garcia-Lerma

Analytical Chemistry team
- Angela Holder
- Amy Martin
- Chuong Dinh

Quantitative Sciences and Data Management Branch
- George Khalil

Pre-clinical evaluation team
- James Mitchell
- Shannon Ellis
- Frank Deyounks
- Kristen Kelley
- Ryan Johnson
- David Garber

CONRAD
- Melissa Peet
- Meredith Clark
- Gustavo Doncel
- Onkar N. Singh
- Vivek Agrahari
- Timothy McCormick

University of the Sciences
- Pardeep Gupta
- Sriramakamal Jonnalagadda

Disclaimer: The findings and conclusions in this presentation are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention or USAID

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