Skaggs School of Pharmacy
and Pharmaceutical Sciences
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Estimated onset and duration of PrEP activity for daily TDF/FTC using the EC_{90} from iPrEx

Sharon Seifert[1], David Glidden[2], Amie L. Meditz[3], Jose Castillo-Mancilla[4], Brandon Klein[1], Becky Kerr[1], L Anthony Guida[1], Jia-Hua Zheng[1], Lane Bushman[1], Peter L Anderson[1]

Department of Pharmaceutical Sciences[1] and
Division of Infectious Diseases[4] University of Colorado Denver,
University of California, San Francisco[2],
Beacon Center for Infectious Disease, Boulder, CO[3]

Introduction

- Truvada® received FDA approval for PrEP indication in 2012
  - Used in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk for exposure
    - No guidance on how many doses needed to confer protection after starting PrEP
    - Not known how long protection lasts after discontinuing PrEP

US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014

A CLINICAL PRACTICE GUIDELINE

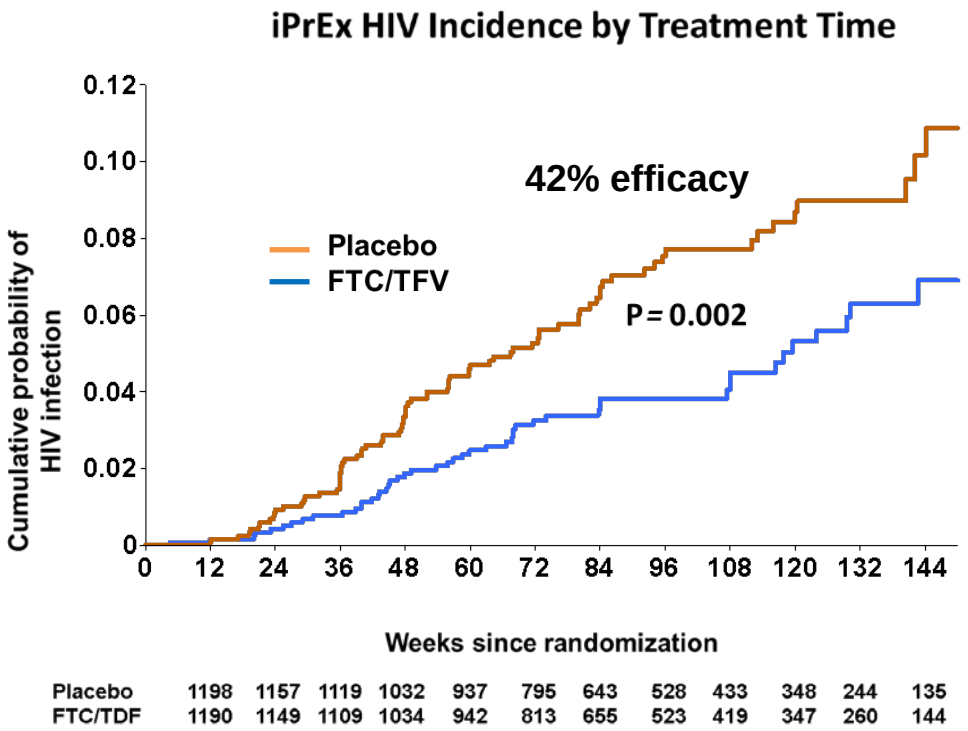
TIME TO ACHIEVING PROTECTION

The time from initiation of daily oral doses of TDF/FTC to maximal protection against HIV infection is unknown.

http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf

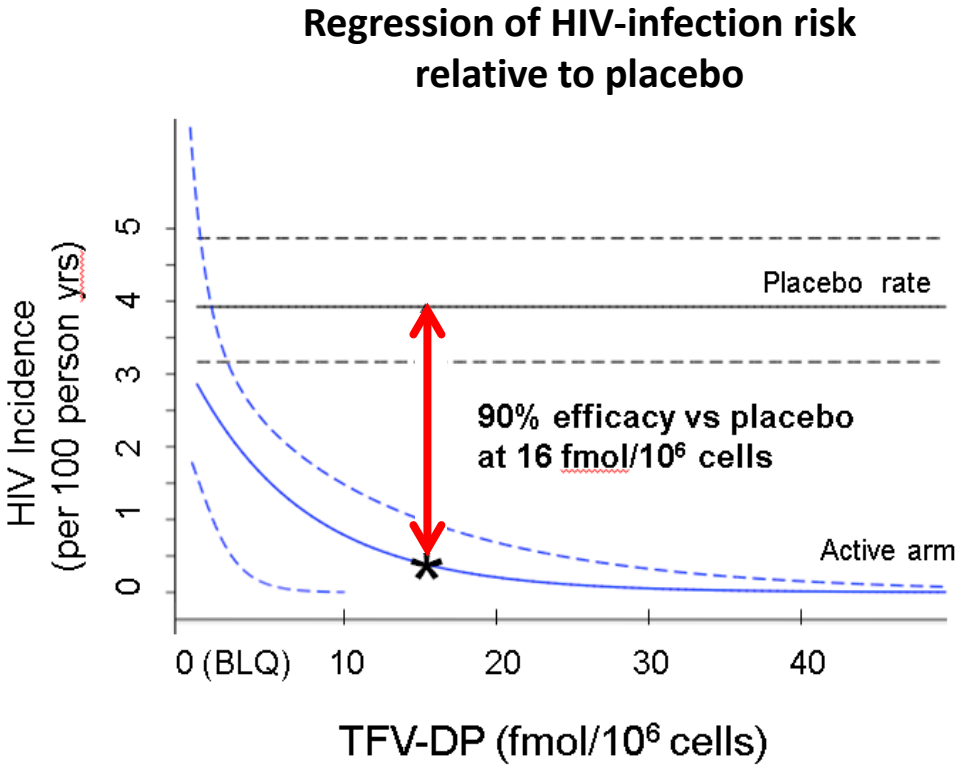
Background: iPrEx

- iPrEx Trial
  - 2499 MSM participants
    - 1251 in TDF/FTC arm
    - 1248 in placebo arm
  - Variable adherence
    - Wide gradient of drug exposures facilitated a concentration- effect analysis



Grant RM, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. The New Eng Journal of Med. Dec 30.2010 363:2587.
Grant RM, et al. Completed observation of the randomized placebo-controlled phase of iPrEx: daily oral FTC/TDF pre-exposure HIV prophylaxis among men and trans women who have sex with men. 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011). Rome, July 17-20, 2011. Abstract

Background: EC_{90}



- iPrEx post hoc analysis
  - Proportional hazards regression equation for HIV-infection risk relative to placebo
    - intracellular TFV-DP in vPBMC
  - EC_{90} = 16 fmol/10^6 cells (95% CI: 3 to 28)

Anderson, PL, et al. Sci Transl Med. 2012 September 12; 4(151) PMID: 22972843

Objectives

1. Determine the number of daily doses needed for a person initiating PrEP to reach the EC_{90}
   – Onset of action
2. From steady state conditions, determine how long after discontinuation of PrEP drug levels remain at or above the EC_{90}
   – Duration of action

Approaches

- Proportion of participants with concentrations > EC_{90}
- Inferred HIV risk reduction using the iPrEx regression equation
- Pharmacokinetic concentration-time profile in rectal tissue

Study Design

- Samples collected from HIV-negative adults enrolled in a pharmacokinetic trial (Cell PrEP) at the University of Colorado Denver
  - One rectal biopsy per participant collected while “on-drug”
- PBMC isolated, counted, and lysed prior to freezing
  - Exception: samples from visit 7 (doses 5, 6, or 7)
    - Half freshly lysed
    - Half viably cryopreserved = **RAW**

ClinicalTrials.gov Identifier: NCT01040091

Laboratory Methods

- PBMC samples
  - Freshly lysed vs viably cryopreserved
    - Conversion factor: median cryopreserved:fresh ratio = 0.43 (IQR: 0.32 to 0.69)
- Tissue samples
  - Rectal tissue samples subjected to collagenase
  - Mononuclear cells isolated
- Drug quantification using validated LC-MS/MS assays[1]

1. Bushman LR, Kiser JJ, Rower JE, Klein B, Zheng JH, Ray ML, Anderson PL. Determination of nucleoside analog mono-, di-, and tri-phosphates in cellular matrix by solid phase extraction and ultra-sensitive LC-MS/MS detection. J Pharm Biomed Anal. 2011 Sep 10;56(2):390-401

Statistical Analysis

- Multiple imputation used to generate full dataset (= **FULL**) with converted vPBMC concentrations
    - Accounts for variability in conversion factor and inter-individual differences
- Inferred HIV risk reduction calculated using iPrEx regression equation[1]

$$100\left(1-n_D^{-1}\sum_{i=1}^{n_D}\exp\{\widehat{\beta}_1+\widehat{\beta}_2 Z_{iD}\}\right)$$

Input average TFV-DP concentration

- Sensitivity analysis

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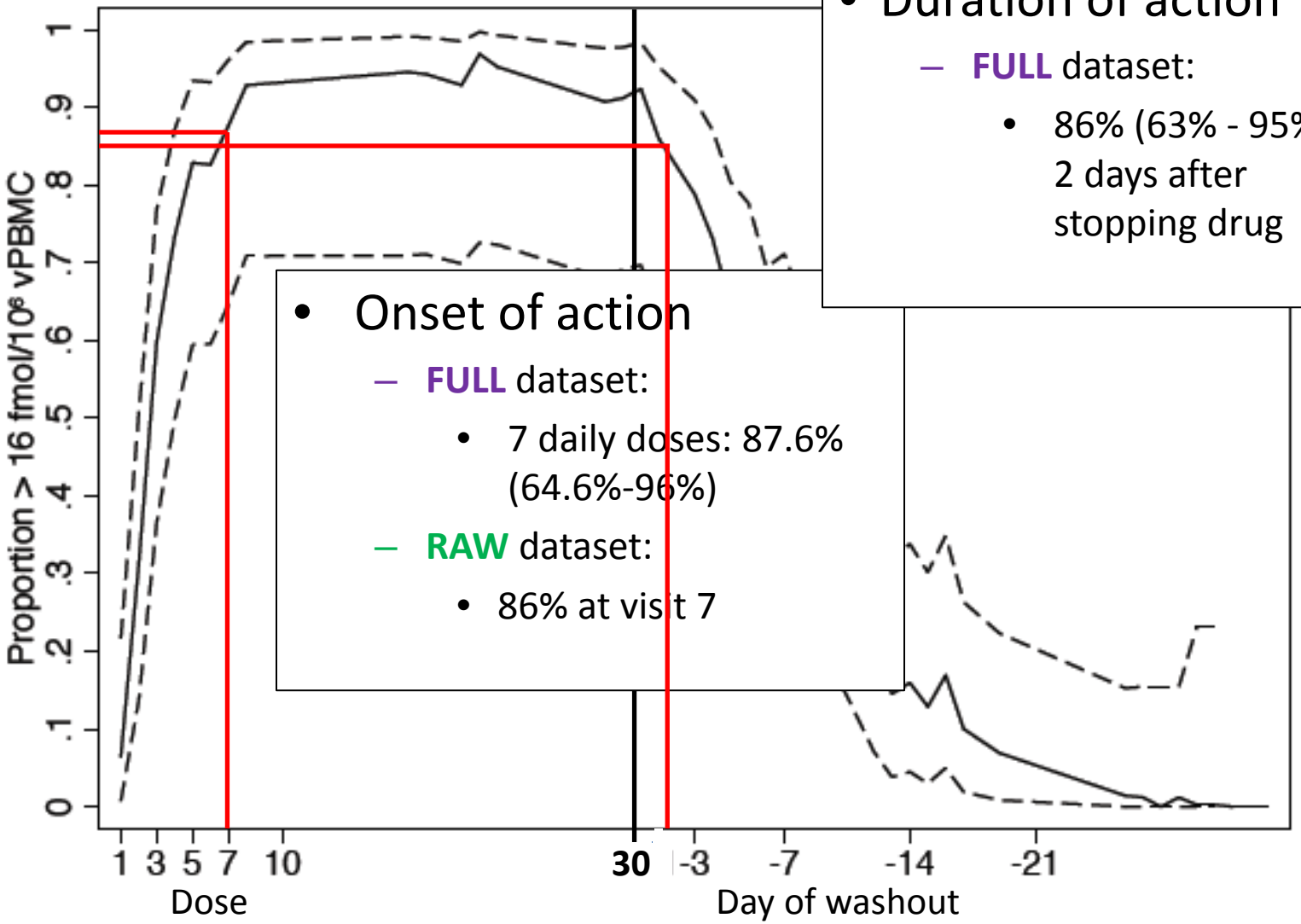
Results: Cell PrEP

N	**21**
Age(yrs) Median (range)	31 (20-47)
Gender N(%)	Male: 11(52.4) Female: 10 (47.6)
Race N(%)	Caucasian: 10 (47.6) Afr-American: 10 (47.6) Hispanic: 1 (4.7)
eGFR ($mL/min/1.73m^2$) Median (range)	93.3 (67.8 – 128.6)

- 410 PBMC samples from 21 participants analyzed
  - 19 participants completed all visits
  - Rectal tissue samples collected from 19 participants

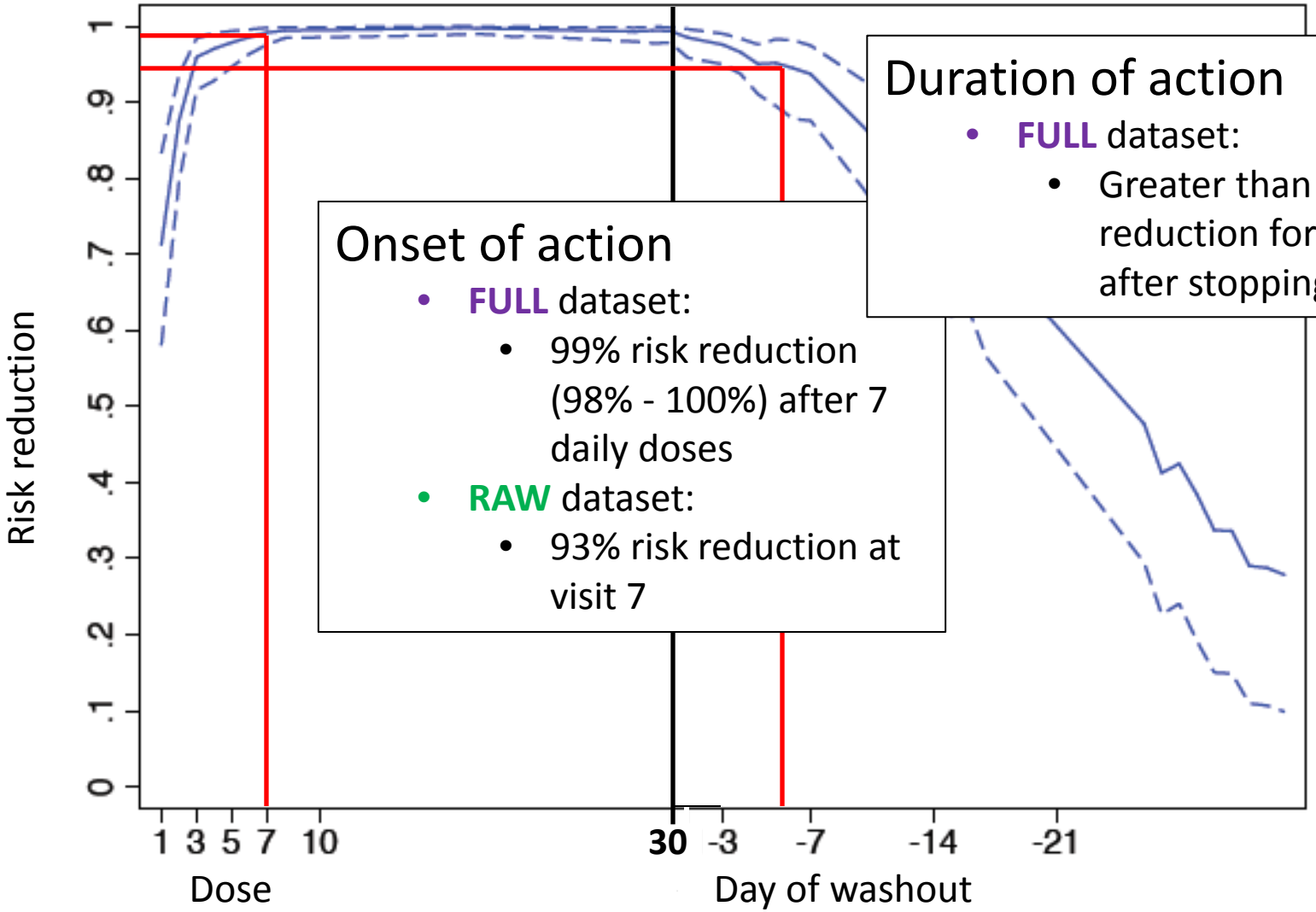
Results: Proportion > EC_{90}



- Duration of action
  - **FULL** dataset:
    - 86% (63% - 95%) 2 days after stopping drug

- Onset of action
  - **FULL** dataset:
    - 7 daily doses: 87.6% (64.6%-96%)
  - **RAW** dataset:
    - 86% at visit 7

Results: Inferred HIV Risk Reduction



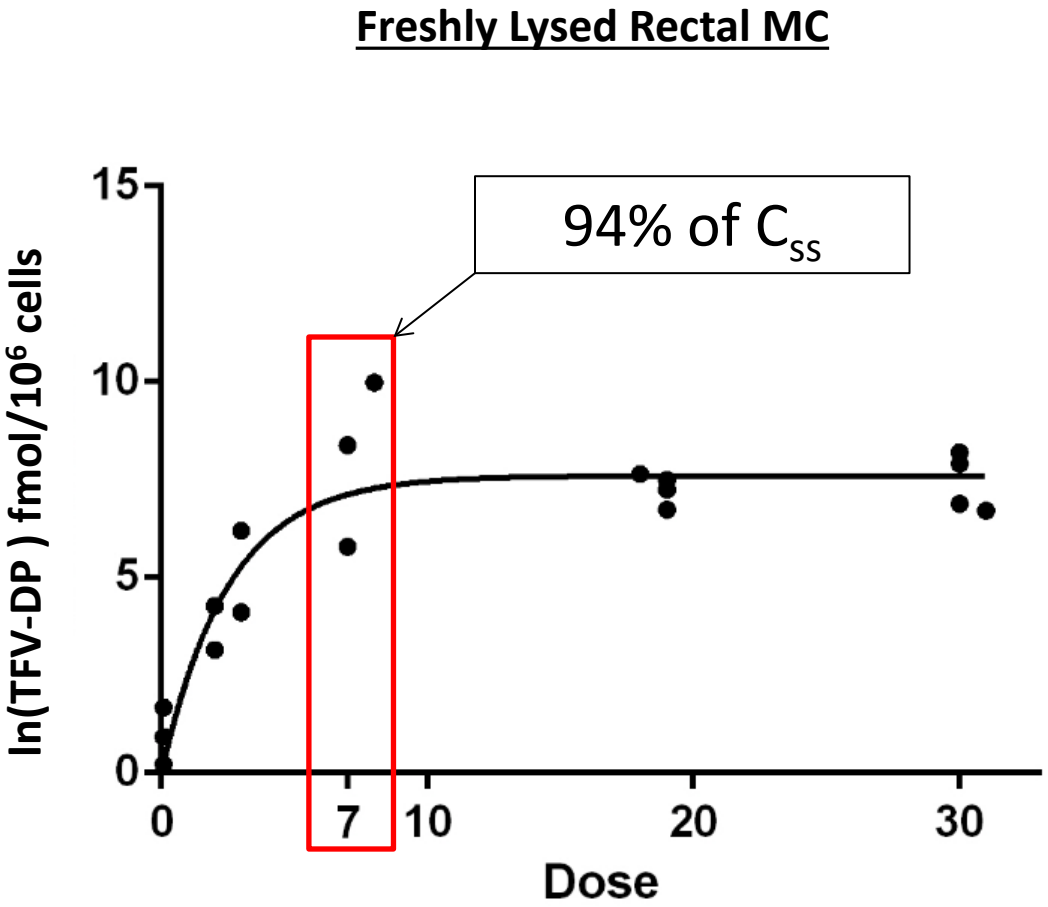
Onset of action

- **FULL** dataset:
  - 99% risk reduction (98% - 100%) after 7 daily doses
- **RAW** dataset:
  - 93% risk reduction at visit 7

Duration of action

- **FULL** dataset:
  - Greater than 95% risk reduction for 6 days after stopping drug

Results: Pharmacokinetics



At day 7 TFV-DP concentrations in rectal tissue approximate steady state concentrations

Conclusions

- Using the iPrEx EC_{90} established in MSM:
  - High PrEP efficacy and high rectal tissue concentrations can be achieved after approximately one week of daily dosing
  - Following daily dosing to steady state, a high level of protection may persist for several days after the last dose taken

Limitation: iPrEx EC_{90} only applies to MSM

Acknowledgments

CAVP Laboratory:

PL Anderson
JJ Kiser
LR Bushman
M Ray
LA Guida
JH Zheng
B Kerr
B Klein
L Jimmerson
H Chen
K Bushman
A Hodara
L Bechtel
JE Rower

Collaborators:

RM Grant and iPrEx study team
DV Glidden
J Castillo-Mancilla
E Gardner
C Wilson
S MaWhinney
J Predhomme

Funding:

Seifert 5 T32 AI 7447-22: Colorado HIV Research Training Program
Anderson U01 AI84735

Study Drug:

Gilead Sciences

Study Subjects:

All participants in Cell PrEP

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