Gearing up for PrEP 2.0 – Can scientific and other innovations transform PrEP into a more powerful game changer across key populations?

Karen Hoover, MD, MPH
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention

CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS
Progress, Risks, and Opportunities | 13-14 October 2016

PrEP 2.0 – Second generation HIV prevention drugs

Karen Hoover, MD, MPH

Lead, Health Services Research for Prevention with Negatives

IAPAC 2016

October 14, 2016

Overview

- Oral PrEP medications
  - Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)
  - Tenofovir alafenamide/emtricitabine (TAF/FTC)
  - Maraviroc (MVC)
- Injectable PrEP medications
  - Cabotegravir long-acting (CAB LA)
  - Rilpivirine long-acting (RPV LA)
  - VRC01
- PrEP implementation in the United States

TDF/FTC as a daily pill to prevent HIV is effective

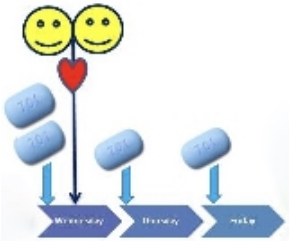
- Safe, well tolerated, highly effective when taken daily
  - Long half-life with protection from 4 doses per week

- Why do we need 2nd generation PrEP medications?
  - Infrequent toxicity with TDF/FTC
    - Renal function
    - Bone density
  - Challenges with adherence to daily oral PrEP

European studies demonstrated efficacy of TDF/FTC in MSM

- PROUD
  - Open-label randomized clinical trial in 13 sexual health clinics
  - Control arm that deferred access to PrEP for one year
  - Reduced risk of HIV infection by 86%

- IPERGAY
  - Event-driven 3-day regimen of TDF/FTC before and after sex
  - Reduced risk of HIV infection by 86%; 97% reduction in open-label extension
  - Study participants took TDF/FTC 4 times per week
  - Equipoise exists for whether efficacy would be as high with less frequent sexual encounters



McCormack et al., Lancet 2016; Molina et al., NEJM 2015

Clinical trials of investigational PrEP drugs – oral

Drug	Sponsor	Phase	Population	Location	Primary outcome(s)	Completion date
Oral drugs						
TAF/FTC	CONRAD	1	Women	United States Dominican Republic	Pharmacokinetics Pharmacodynamics	December 2017
TAF/FTC	Gilead Sciences	3	MSM TGW	United States Canada Europe	Safety Efficacy	September 2020
MVC	NIAD	2	MSM Women	United States Puerto Rico	Safety Tolerability	November 2015

https://clinicaltrials.gov

Clinical trials of investigational PrEP drugs – injectable long-acting

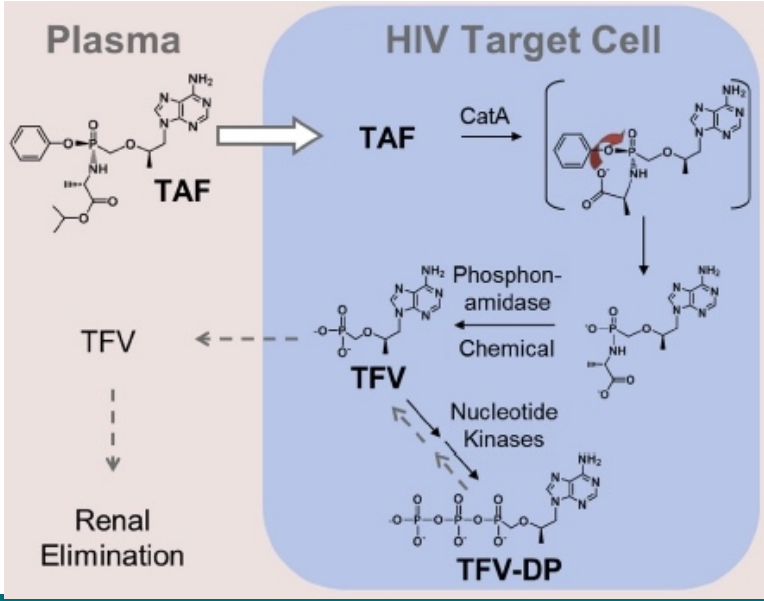
Drug	Sponsor	Phase	Population	Location	Primary outcome(s)	Completion date
Injectable drugs						
CAB LA	ViiV Healthcare	2a	Men	United States	Safety Tolerability	February 2016
CAB LA	ViiV Healthcare	1	Men Women	United States	Pharmacokinetics Safety Tolerability	December 2017
CAB LA	NIAD	2b/3	MSM TGW	United States	Safety Efficacy	June 2020
RPV LA	PATH	2	Women	United States South Africa Zimbabwe	Safety	October 2017
VRC01	NIAID	1	Men Women	United States	Safety Tolerability	August 2017
VRC01	NIAID	2b	MSM TGW	North America South America Switzerland	Safety Tolerability Efficacy	July 2019
VRC01	NIAID	2b	Women	Sub-Saharan Africa	Safety Tolerability Efficacy	July 2020

https://clinicaltrials.gov

Oral PrEP drugs

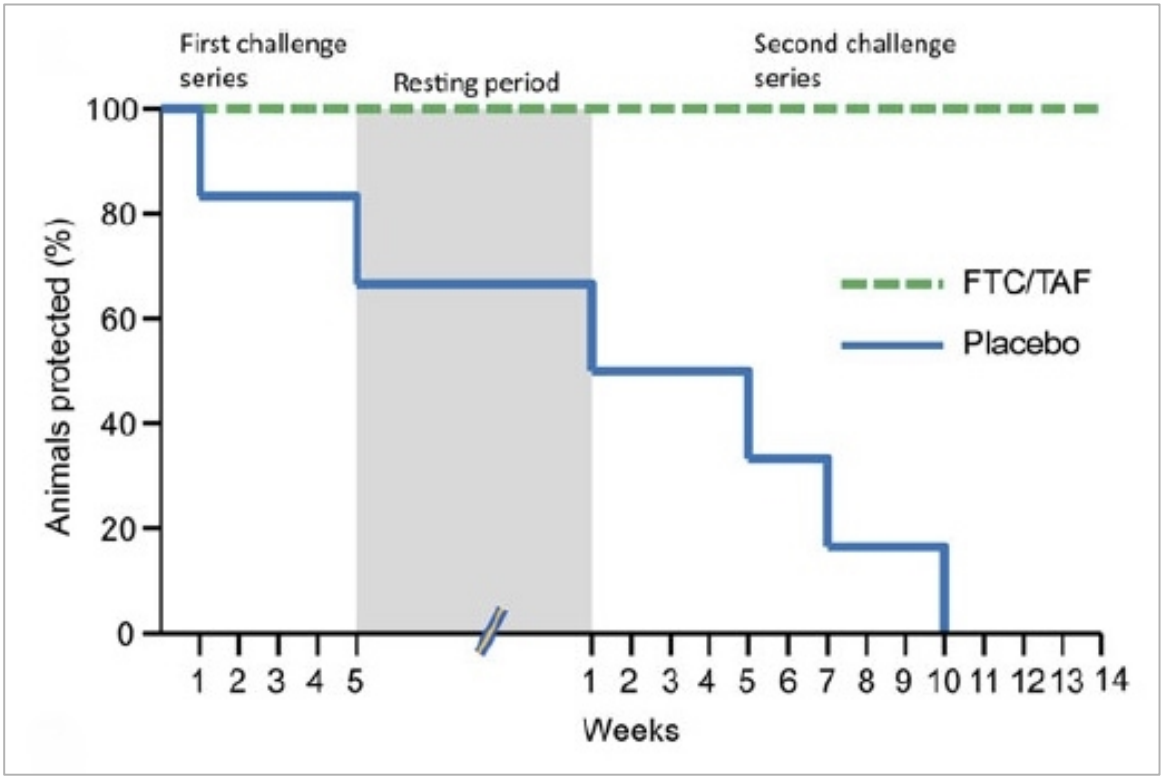
Tenofovir alafenamide (TAF) for PrEP

- Nucleoside reverse transcriptase inhibitor
  - Prodrug of tenofovir diphosphate (TVF-DP)
  - Converted to TVF-DP in PBMC
  - 90% lower drug concentrations in blood and tissue
    - Less renal toxicity
    - Less bone toxicity
    - Fewer side effects
  - Allows 10-fold lower dose



Ray et al., Antiviral Research 2016

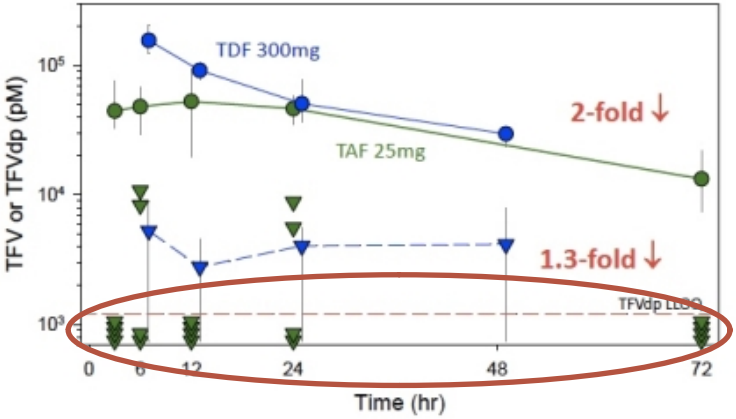
Oral TAF/FTC prevented SHIV infection in macaques



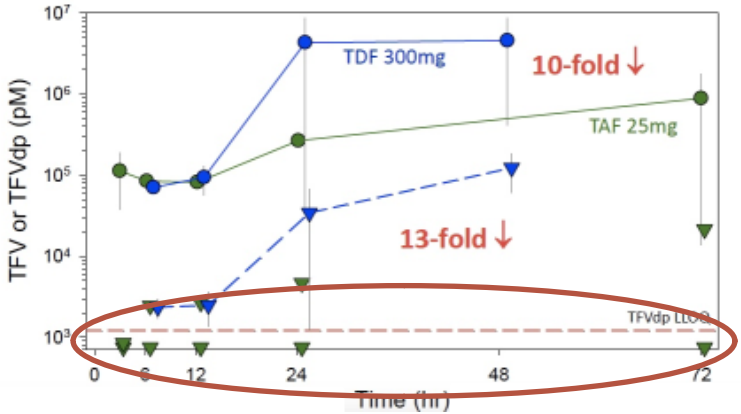
Massud et al., JID 2016

Lower than expected tissue levels in women after a single dose of TAF vs. TDF

Cervicovaginal



Rectal



Garrett et al., CROI 2016

Phase 1 PK/PD study of TAF/FTC for PrEP in women – not yet recruiting

- Sponsored by CONRAD in collaboration with USAID and Agility Clinical, Inc.
  - ClinicalTrials.gov identifier: NCT02904369
  - Drugs: TAF/FTC 10/200 mg, TAF/FTC 25/200 mg, TDF/FTC 300/200 mg
  - Estimated enrollment: 72
  - Locations: United States (2 sites) and Dominican Republic (1 site)

- Primary outcome
  - Concentrations after single dose, and during and after 2 weeks of daily dosing
    - Plasma, PBMC, cervicovaginal and rectal fluid, and cervicovaginal tissue

- Secondary outcomes
  - Grade 2 or higher adverse events; gastrointestinal adverse events; lab abnormalities; and anti-HSV activity

Phase 3 clinical trial of TAF/FTC for PrEP in at-risk MSM and TGW – recruiting

- Sponsored by Gilead Sciences
  - ClinicalTrials.gov identifier: NCT02842086
  - Drugs: TAF/FTC 25/200 mg, TDF/FTC 300/200 mg
  - Estimated enrollment: 5000
  - Locations: United States (54 sites), Canada (6 sites), and Europe (32 sites)
  - Follow-up: Up to 96 weeks
  - Open-label extension planned with TAF/FTC

- Primary outcome
  - Incidence of HIV infection

- Secondary outcomes
  - Renal and bone toxicity measures; and adverse events and laboratory toxicities

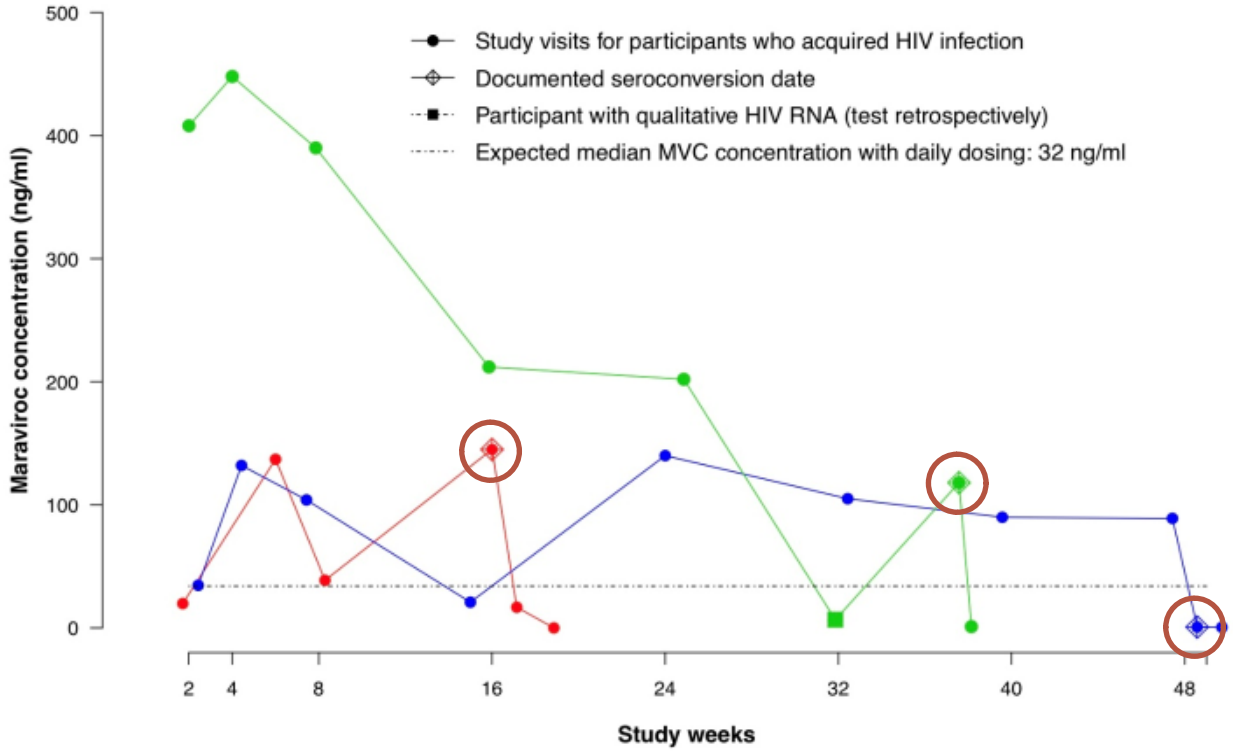
Phase 2 clinical trial of MVC for PrEP in at-risk MSM and women – completed

- Sponsored by NIAID in collaboration with HPTN and ACTG
  - ClinicalTrials.gov identifier: NCT01505114
  - Drugs: MVC 300 mg, MVC/FTC 300/200 mg, MVC/TDF 300/300 mg, TDF/FTC 300/200 mg
  - Estimated enrollment: 594
  - Locations: United States (12 sites) and Puerto Rico (1 site)
  - Follow-up: 48 weeks

- Primary outcomes:
  - Grade 3 or higher adverse events
  - Tolerability

- Secondary outcomes:
  - Renal, lipid, and bone toxicity measures; adherence; concentrations in plasma, PBMC, and rectal and vaginal tissue

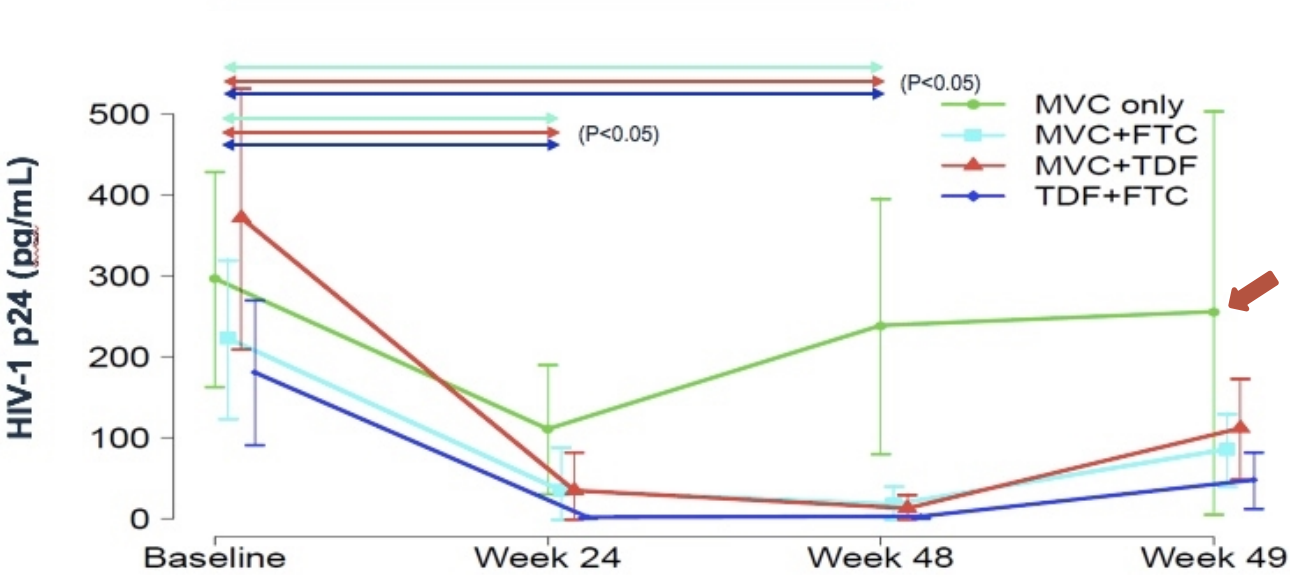
HIV seroconversions in persons with low and variable serum maraviroc concentrations



2 persons had no MVC not detected at any time point

Gulick et al., CROI 2016

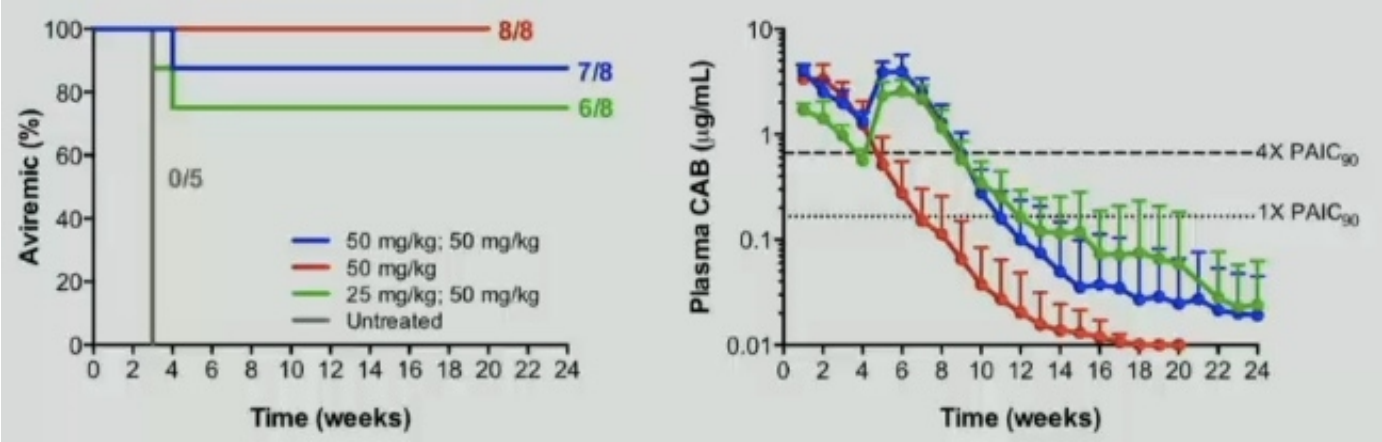
Maraviroc plus TDF or FTC suppresses HIV replication in colorectal explants better than maraviroc alone



McGowan et al., CROI 2016

Injectable PrEP drugs

CAB LA prevented infection in macaques with intravenous exposure to SHIV



Andrews et al., CROI 2016

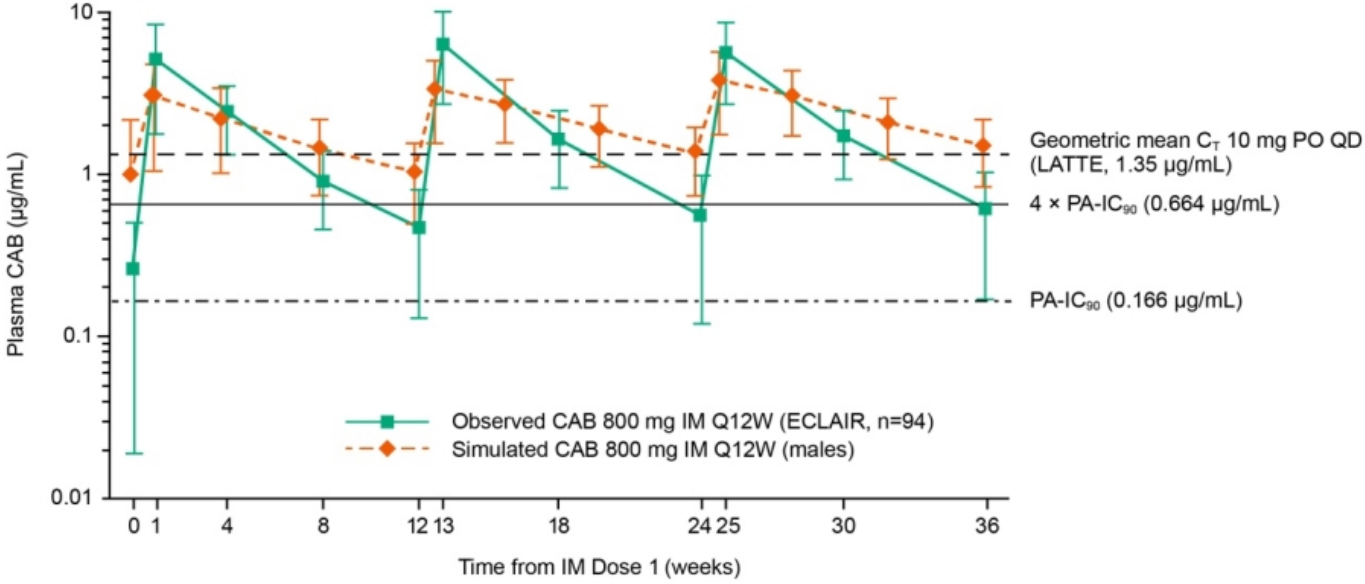
Phase 2 clinical trial of CAB LA for PrEP in men (ÉCLAIR) – completed

- Sponsored by ViiV Healthcare in collaboration with GlaxoSmithKline
  - ClinicalTrials.gov identifier: NCT02076178
  - Drugs: CAB LA 800 mg every 12 weeks for 3 doses
  - Oral run-in: CAB 30 mg tablets daily for 4 weeks
  - Estimated enrollment: 127
  - Location: United States (10 sites)

- Primary outcomes
  - Safety and tolerabiltiy

- Secondary outcome
  - Plasma pharmacokinetic parameters
  - Acceptability

Cabotegravir 800 mg every 12 weeks results in high peaks and low troughs



Dosing of 600 mg every 8 weeks

2 seroconversions:
Placebo and 24 weeks post-dose

Markowitz et al., CROI 2016

Phase 1 clinical trial of CAB LA in healthy men and women – not yet recruiting

- Sponsored by ViiV Healthcare
- ClinicalTrials.gov identifier: NCT02478463
  - Drugs: CAB LA 600 mg single dose
  - Oral run-in: CAB 30 mg daily for 28 days
  - Estimated enrollment: 16
  - Location: not announced
- Primary outcomes
  - CAB concentration in plasma; vaginal, cervical, and rectal tissue; and cervicovaginal and rectal fluid
- Secondary outcomes
  - Adverse events and serious adverse events
  - Safety
  - Tolerability

Phase 2/3 clinical trial of CAB LA for PrEP in at-risk MSM and TGW – not yet recruiting

- Sponsored by NIAID in collaboration with ViiV Healthcare and Gilead Sciences
  - ClinicalTrials.gov identifier: NCT02720094
  - Drugs: CAB 30 mg oral run-in,CAB LA 600 mg, TDF/FTC 300/200 mg
  - Estimated enrollment: 4500
  - Location: United States (8 sites)

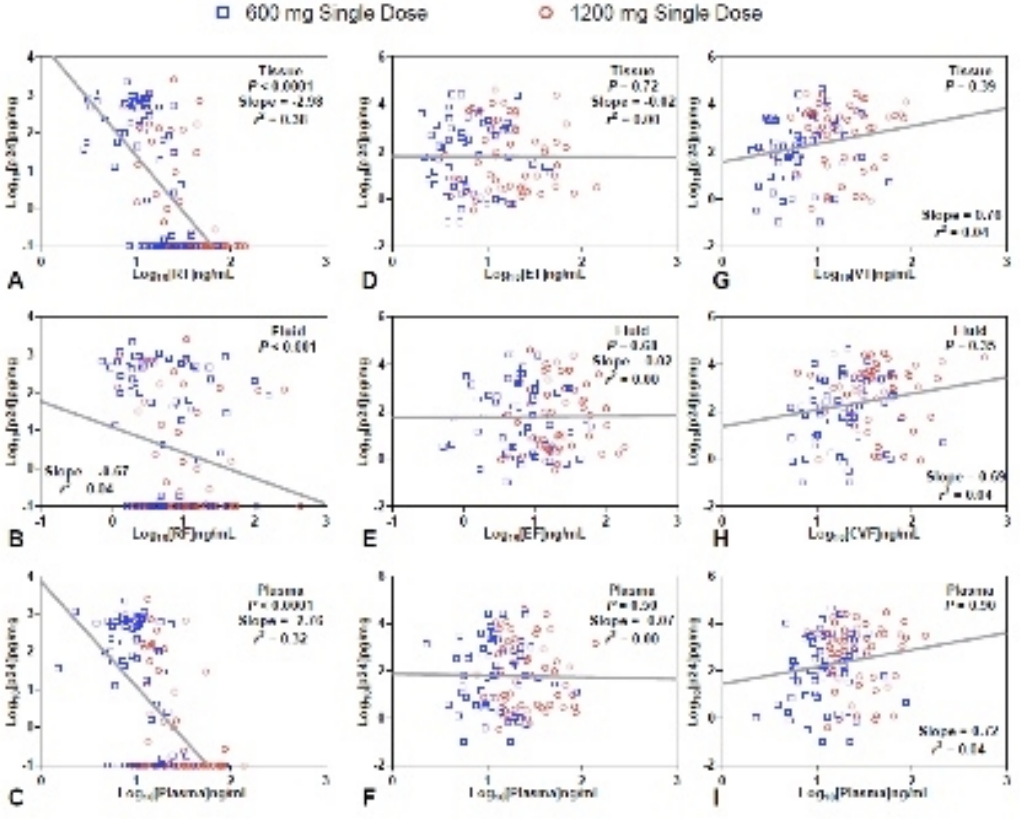
- Primary outcomes
  - Incidence of HIV infection
  - Grade 2 or higher clinical and laboratory adverse events

- Secondary outcomes
  - Changes in renal function, Z-score, and DXA criteria for osteopenia and osteoporosis
  - Grade 3 or 4 liver-related adverse events
  - Incidence of resistance mutations

Phase 1 PK/PD clinical trial of RPV LA for PrEP in men and women – completed

- Sponsored by Janssen Research & Development, LLC
- ClinicalTrials.gov identifier: NCT01656018
- Drugs: RPV LA dose-ranging
- Estimated enrollment: 90
  - Location: United States (1 site)
- Primary outcomes
  - Adverse events
  - Acceptability
- Secondary outcomes
  - RPV concentration in plasma; endocervical, vaginal, and rectal fluid; cervical, vaginal, and rectal tissue
  - Ex vivo pharmacodynamics

HIV replication vs. RPV concentration in rectal, cervical, and vaginal explants



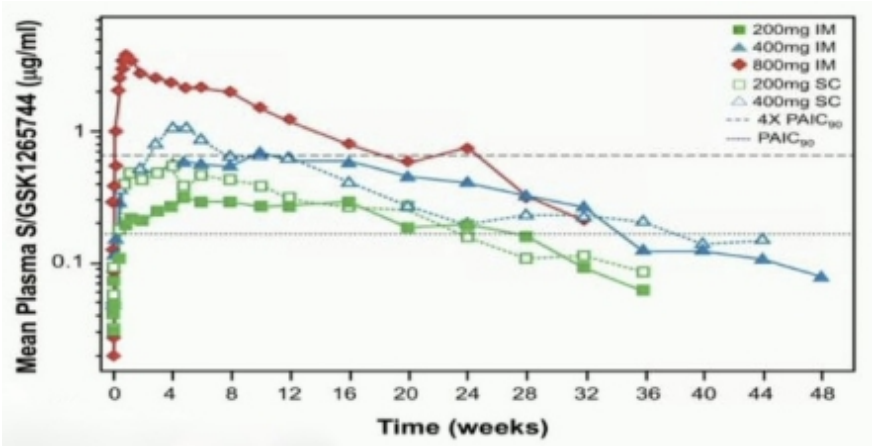
McGowan et al., CROI 2016

Phase 2 clinical trial of RPV LA for PrEP in women – ongoing

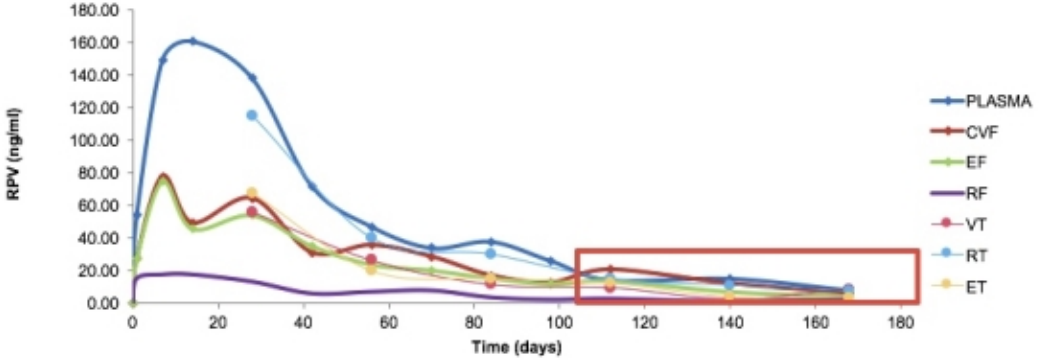
- Sponsored by PATH in collaboration with Bill and Melinda Gates Foundation, NIAID, and NIH
- ClinicalTrials.gov identifier: NCT02165202
- Drugs: RPV LA 1200 mg IM every 8 weeks for 6 doses
- Estimated enrollment: 132
- Location: United States (2 sites), South Africa (1 site), Zimbabwe (1 site)
- Primary outcomes
  - Adverse events
- Secondary outcomes
  - Tolerability
  - RPV LA concentration in cervicovaginal fluid, rectal fluid, and cervicovaginal tissue
  - Incidence of HIV infection

Nanosuspensions of PrEP drugs have long pharmacokinetic tails

Cabotegravir

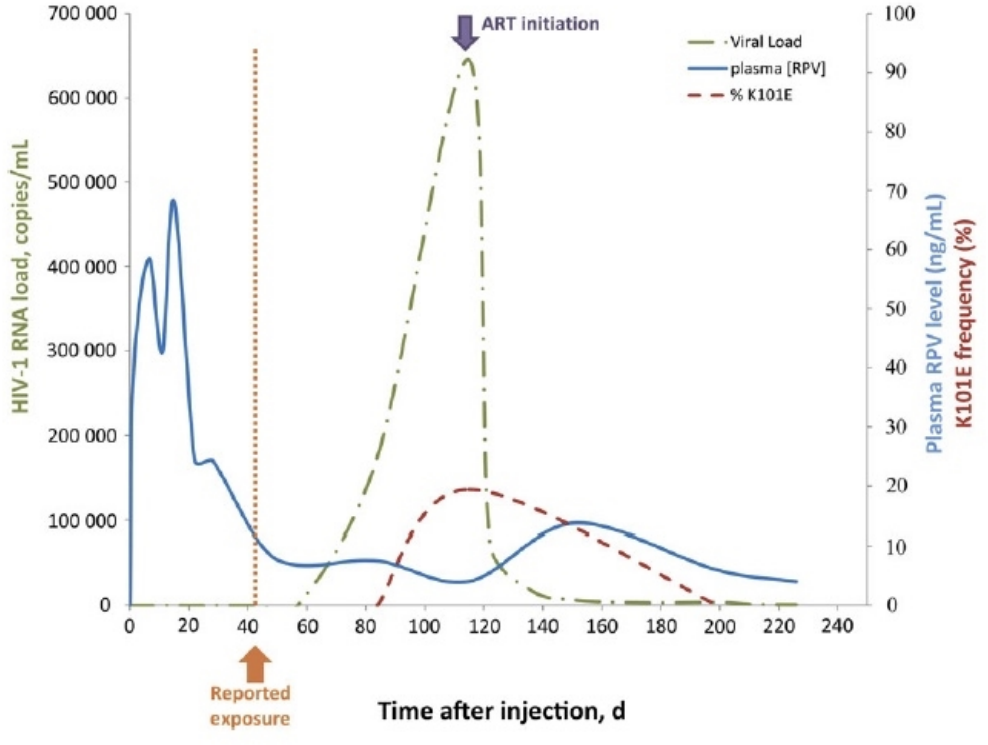


Rilpivirine



Spreen et al., JAIDS 2014; McGowan et al., AIDS 2016

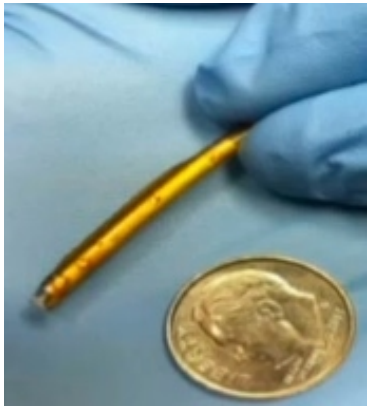
Emergence of K101E resistance during the RPV LA pharmacokinetic tail



Penrose et al., JID 2016

Implantable devices containing TAF in pre-clinical development

Implantable and removable



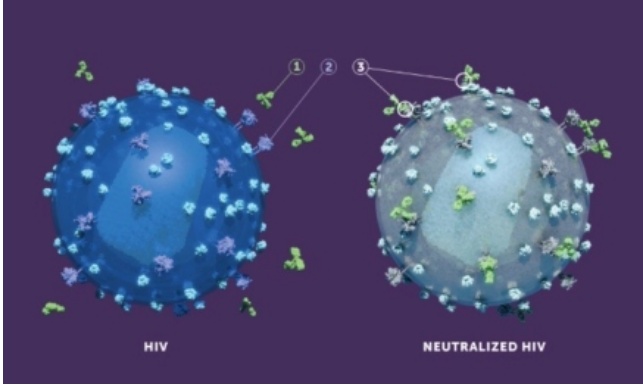
Implantable and biodegradable

Day 0

Day 14

Gunawardana et al., Antimicrobial Agents and Chemotherapy 2015; Schlesinger et al., CROI 2016

VRC01 (3BNC117) – Broadly neutralizing antibody



- Undergoing studies for use both as PrEP and HIV treatment
- Safe and well tolerated administered intravenously or subcutaneously in phase 1 study
- Ongoing phase 1 studies with IV and SC dosing
  - VRC01 dose-ranging
  - VRC01LS – longer half-life than VRC01
- PrEP studies with broadly neutralizing antibodies can inform HIV vaccine development

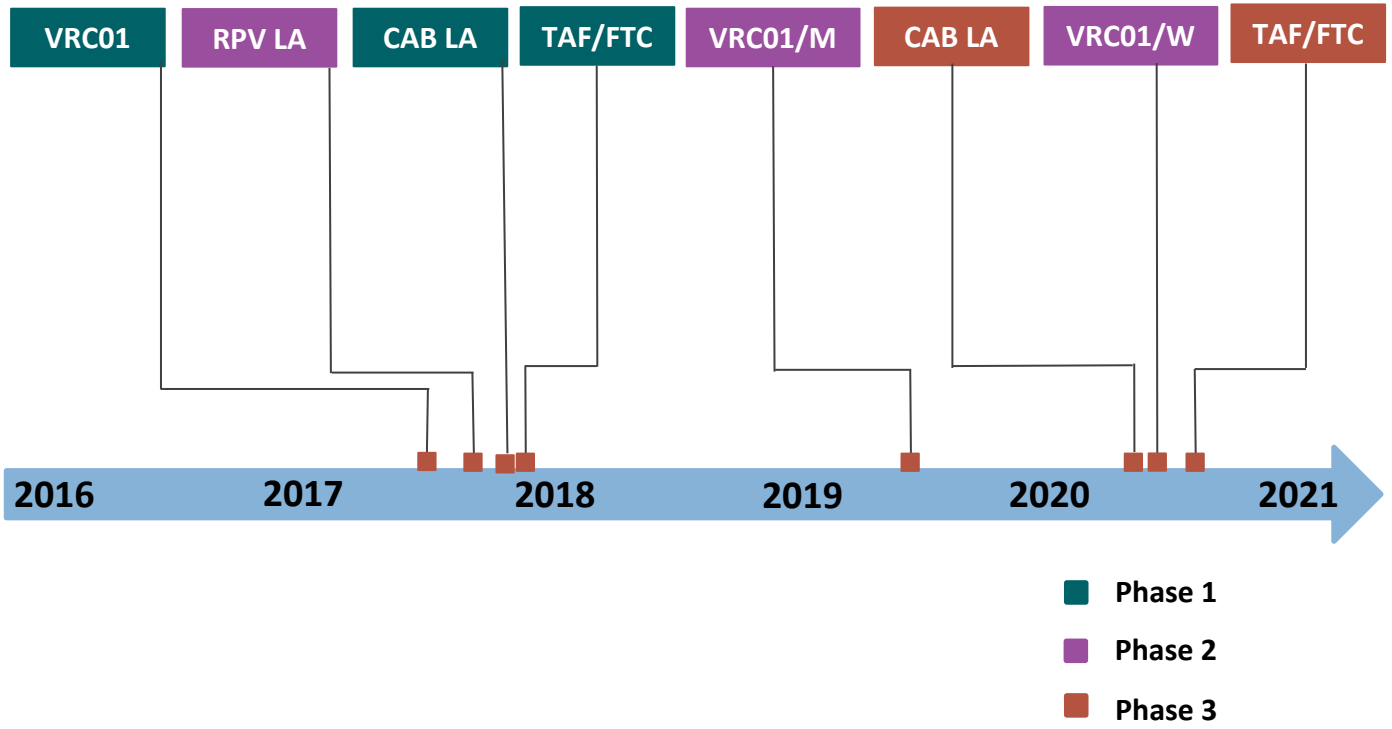
Phase 2 Antibody Mediated Protection (AMP) study in at-risk men and women – recruiting

- Phase 2 studies of safety and efficacy
  - HVTN 704/HPTN 085 (NCT02716675)
    - MSM and TG women in the United States (19 sites) and Peru (2 sites)
  - HVTN 703/HPTN 081 (NCT02599896)
    - Sexually active women in Botswana (1 site), Kenya (1 site), and South Africa (6 sites)

- Intravenous infusion: 10 doses of VRC01 30 mg/kg, VRC01 10 mg/kg, or saline every 8 weeks, follow-up for 20 weeks

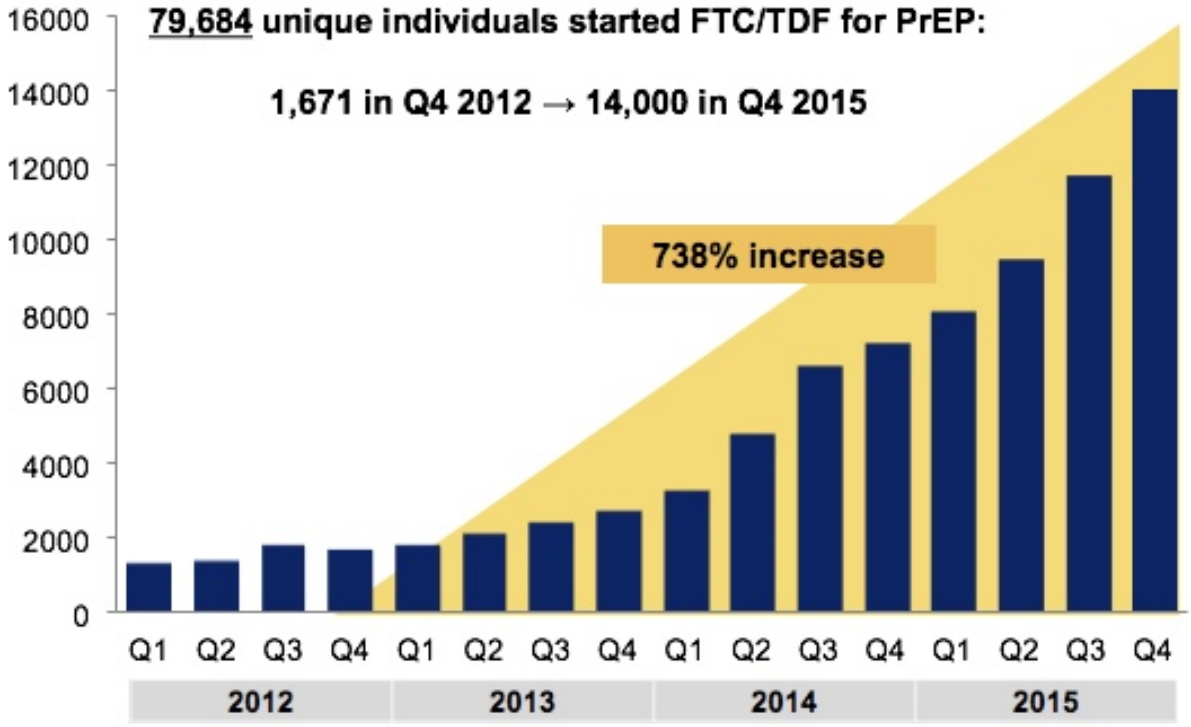
- Primary outcomes
  - Adverse events
  - Incidence of HIV infection

Timeline for completion of PrEP clinical trials



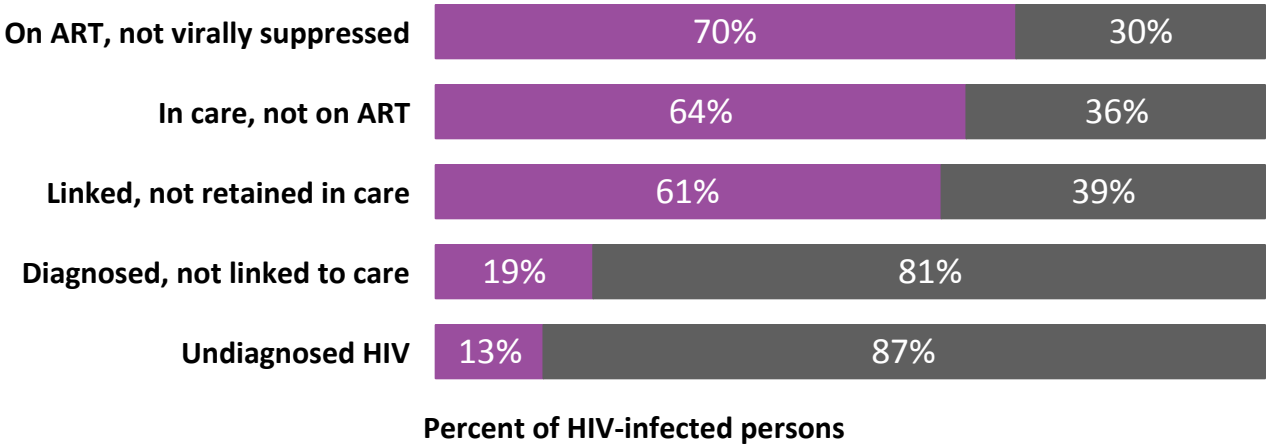
Low TDF/FTC uptake in the United States

An increasing number of persons initiating PrEP, United States 2012–2015



McCallister et al., IAS 2016

Why do we need both PrEP and TasP?



www.aids.gov/federal-resources/national-hiv-aids-strategy/nhas-update-5-things.pdf

Global statistics of HIV care continuum compared to gaps to reach UNAIDS 90-90-90 targets

http://www.unaids.org/sites/default/files/media_asset/MDG6Report_en.pdf

Summary

- Focus on implementation of TDF/FTC as we await availability of second generation PrEP drugs
  - TAF/TDF
  - CAB LA
  - VRC01
- Injectable PrEP might help those who have trouble taking a daily pill, but not a panacea
  - Oral run-in for 30 days might be needed to assess tolerability and adverse events
  - Oral PrEP tail coverage might be required for several months after discontinuing
  - Might be problematic for individuals with adherence challenges
- Broadly neutralizing antibodies exciting option for PrEP
  - Early in development
  - Help to guide vaccine studies

Thank you!

Email: khoover@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov