# Oral PrEP – New Drugs

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# Criteria for Oral PrEP

- Safe
- Penetrates target tissues
- Protects against HIV infection in tissues
- Long-lasting activity for convenient dosing
- Unique resistance profile or high barrier to resistance
- No significant drug-drug interactions
- Possibly, not a part of current rx regimens
- Affordable, easy to use and implement

DAIDS Working Group Report 4/09

# Antiretroviral Drugs: 2013

## nucleoside/tide RTIs (NRTIs)

- zidovudine (ZDV, AZT)
- didanosine (ddI)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TDF)

## NNRTIs

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)

## protease inhibitors (PIs)

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

## entry inhibitors (EIs)

- enfuvirtide (T-20, fusion inh)
- maraviroc (MVC, CCR5 inh)

## integrase inhibitors (IIs)

- raltegravir (RAL)
- elvitegravir (EVG)

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## integrase inhibitors (IIs)

- raltegravir (RAL)

# Investigational ART (partial list)

| | NRTI | NNRTI | PI | EI | II |
|---|---|---|---|---|---|
| Phase 3 | | | | | elvitegravir<br>dolutegravir |
| Phase 2 | apricitabine<br>DAPD<br>dexelvucitabine<br>festinavir<br>GS-7340 | BILR 355<br>lersivirine<br>UC-781 | | BMS-663068<br>cenicriviroc<br>PF-232798 | |
| Phase 1/2 | amdoxovir<br>elvucitabine | GSK 2248761<br>RPV-LA | TMC 310911 | HGS004<br>ibalizumab | S/GSK‘744 |
| Phase 1 | | RDEA 806 | CTP-298<br>CTP-518<br>PPL-100<br>SPI-256 | SCH-532706<br>VIR-576 | BI 224436<br>INH-1001 |

# MVC for PrEP: Advantages


- HIV entry inhibitor – CCR5 antagonist
- FDA-approved 2007
- Safety profile X 5+ years Gulick IAS 2012
- Achieves high tissue levels
  - 3X higher in vaginal secretions Dumond JAIDS 2009
  - 8-26X higher in rectal tissue Brown JID 2011
- Once-daily dosing Rosario Brit J Clin Pharm 2008
- Drug resistance is uncommon
- Used uncommonly for HIV treatment
- Prevented HIV infection in mouse model Neff PLoS One 2010

# MVC for PrEP: Disadvantages


- Limited clinical safety data in HIV-uninfected individuals
- Increased pathogenicity with Δ32 deletion of some viral infections (e.g., West Nile virus)
- Other theoretical safety risks
- Not labeled for once-daily dosing
- Failed to prevent SHIV in monkey model
  Massud IAS 2012
- Some potential for drug-drug interactions
- Not active against X4 virus

# HPTN 069: NEXT-PrEP

- **Design: Phase II, 4-arm, multisite, study**
- **Study population (N=400)**
  - **At-risk HIV-negative gay men**
- **Study Treatment:**
  - **MVC monotherapy**
  - **MVC + FTC**
  - **MVC + TDF**
  - **TDF + FTC (control)**
- **Duration: 48 weeks**
- **Primary endpoint: Grade ≥3 toxicities; time to study treatment discontinuation**


Amendment:
Cohort of 200 women

# RAL for PrEP: Advantages

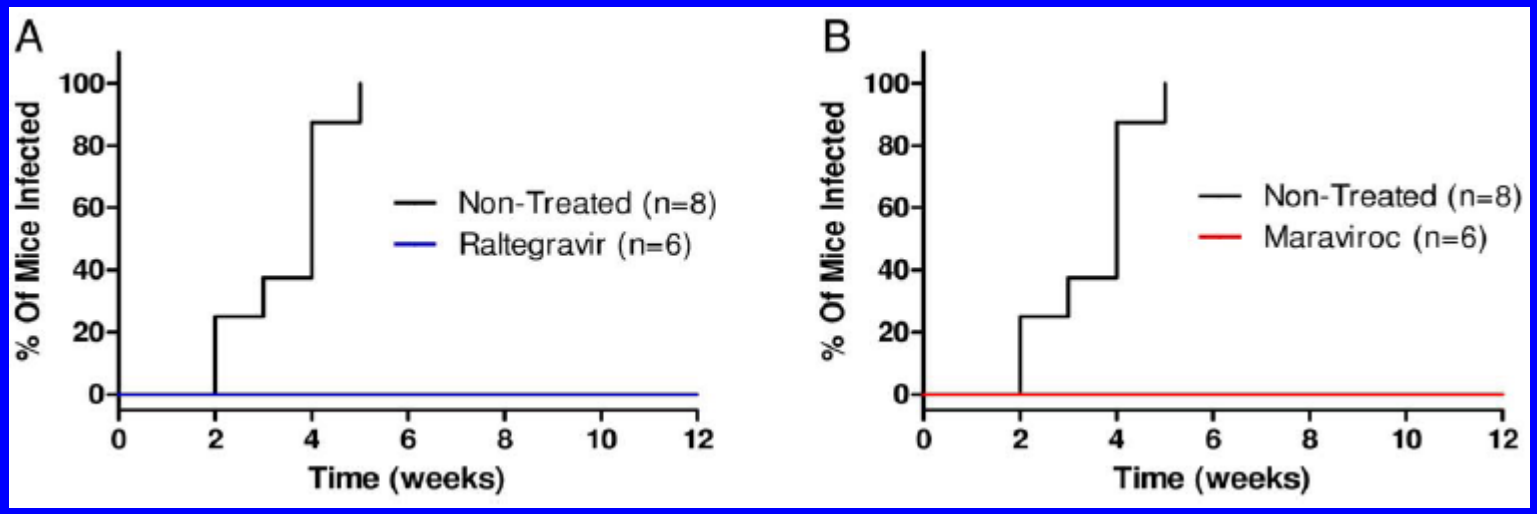

- HIV integrase inhibitor
- FDA-approved 2007; safety profile X 5+ years
- Safety/tolerability as PEP Mayer JAIDS 2012
- Achieves tissue levels
  - ~93% in vaginal secretions Jones PK Workshop 2009
  - 1.5-7X higher in GALT Patterson PK Workshop 2012
- Few drug-drug interactions
- Prevented HIV infection in mouse model Neff PLoS One 2010

# RAL for PrEP: Disadvantages


- Twice-daily dosing (as treatment)
- Low barrier to drug resistance
- "Preferred drug" in HIV treatment guidelines; used commonly
- No current PrEP clinical studies

# Animal Study: MVC and RAL PrEP

- Humanized mouse model (RAG-hu mice)
- Orally administered MVC or RAL daily X 7 days (6 mice/group)
- Vaginal HIV-1 challenge on day 4




Neff, et al. PLoS One 2010;5:e15257

# RPV-LA for PrEP: Advantages

- HIV NNRTI
- FDA-approved 2011; safety profile X 2+ years
- RPV-LA single-dose clinical study (N=33)
  Jackson CROI 2012 #35
- RPV-LA achieves tissue levels
  - 10X higher in LN (animals) v'ant Klooster AAC 2010
  - CVF and RT =, VT lower, RF much lower
    Else PK Workshop 2012
- RPV-LA once-monthly dosing possible
  Baert Eur J Pharm Biopharm 2009
- Pilot combo safety study with '744 as PrEP enrolling (N=40) www.clinicaltrials.gov

# RPV-LA for PrEP: Disadvantages

- Investigational formulation (phase 1)
- Very limited safety clinical data
- Some drug-drug interactions
- Low barrier to drug resistance; cross-resistance to other NNRTI
- “Alternative drug” in HIV treatment guidelines; used commonly

# ‘744 for PrEP: Advantages

- HIV integrase inhibitor
- Clinical data (N=48 healthy volunteers)
  Min ICAAC 2009 #H-1228
- Long half-life (30 hours); infrequent parenteral dosing possible
  Spreen IAS 2012 #TuPE040
- Higher barrier to resistance than other II
- Few drug-drug interactions
- Pilot combo safety study with RPV-LA as PrEP enrolling (N=40) www.clinicaltrials.gov

# ‘744 for PrEP: Disadvantages

- Investigational drug and formulation (phase 2a)
- Very limited clinical safety data
- No available tissue PK data (?)
- Other integrase inhibitors (RAL, EVG) used commonly in HIV treatment

# Ibalizumab for PrEP: Advantages

- HIV entry inhibitor -- CD4 attachment antagonist
- Monoclonal antibody
- Clinical phase 2b studies in HIV-infected individuals completed Khanlou ICAAC 2011 #H2794b
- Drug resistance not expected
- No drug-drug interactions
- Pilot phase 1 safety study of three-doses, given once-weekly SC, as PrEP completed (N=25) www.clinicaltrials.gov

# Ibalizumab for PrEP: Disadvantages

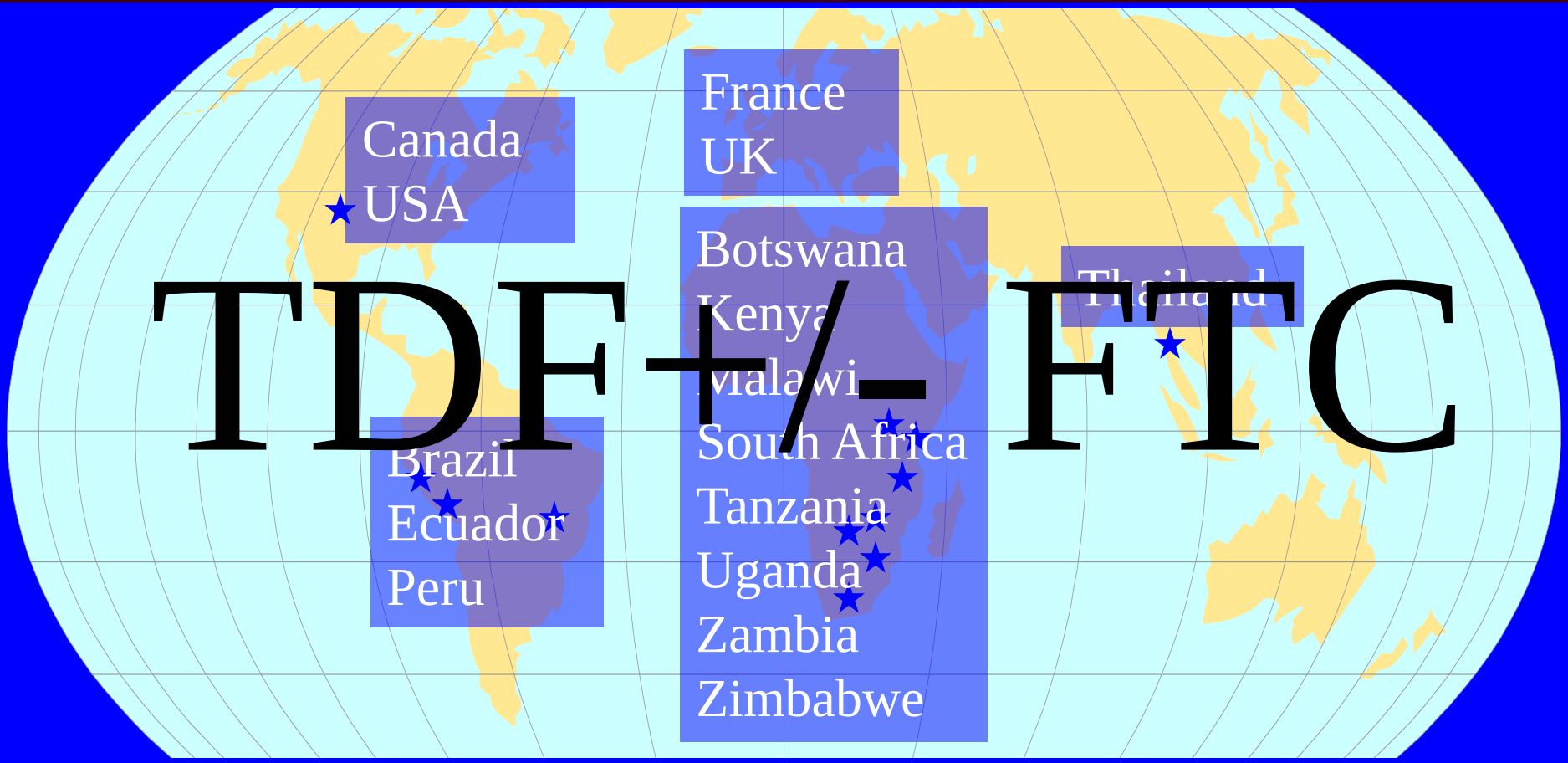
- Investigational drug – phase 1-2
- Limited safety data in HIV-uninfected individuals
- Theoretical safety risks
- No tissue PK data
- Parenteral administration once every 1-4 weeks

# Summary: New PrEP Drugs

| | mechanism | dosing route | dosing frequency | PrEP stage |
|---|---|---|---|---|
| MVC | CCR5 antagonist | oral | once daily | Phase 2 |
| RAL | II | oral | twice daily | -- |
| RPV-LA | NNRTI | injectable, SC | once monthly | Phase 1/2 pilot |
| ‘744 | II | injectable, SC | once monthly (or less) | Phase 1/2 pilot |
| ibalizumab | CD4 attachment inhibitor | injectable, SC | once every 1-4 weeks | Phase 1 pilot |


THANK
YOU

# Completed and Current Studies of Oral PrEP




**14 studies and projects, up to 16 countries**

**32,000+ participants**