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
Completed and Current Studies of Oral PrEP

14 studies and projects, up to 16 countries
32,000+ participants

TDF +/- FTC
# Antiretroviral Drugs: 2012

## 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)
Antiretroviral Drugs: 2012

nucleoside/tide RTIs (NRTIs)
- lamivudine (3TC)
- emtricitabine (FTC)
- tenofovir (TDF)

entry inhibitors (EIs)
- maraviroc (MVC, CCR5 inh)

integrase inhibitors (IIs)
- raltegravir (RAL)
## Investigational ART (partial list)

<table>
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<tr>
<th>Phase</th>
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<th>PI</th>
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</table>
MVC for PrEP: Advantages

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

- Limited clinical safety data in HIV-uninfected individuals
- Increased pathogenicity with ∆32 deletion of some viral infections (e.g., West Nile virus)
- Other theoretical safety risks
- Not labeled for once-daily dosing
- Some potential for drug-drug interactions
- Not active against X4 virus
HPTN 069/ACTG 5305: NEXT-PrEP

Novel Examination of Therapies for PrEP

• Design: Phase II, 4-arm, 12-site, study
• Study pop: 400 at-risk HIV-negative MSM
• Study Treatment (blinded, placebo-controlled):
  • 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 planned
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 animal 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

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  
  Min ICAAC 2009 #H-1228
- 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 in progress (N=24) [www.clinicaltrials.gov](http://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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dosing Route</th>
<th>Dosing Frequency</th>
<th>PrEP Stage</th>
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<tbody>
<tr>
<td>MVC</td>
<td>CCR5 antagonist</td>
<td>Oral</td>
<td>Once daily</td>
<td>Phase 2</td>
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<tr>
<td>RAL</td>
<td>II</td>
<td>Oral</td>
<td>Twice daily</td>
<td>?</td>
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<td>RPV-LA</td>
<td>NNRTI</td>
<td>Injectable, SC</td>
<td>Once monthly</td>
<td>Phase 1 pilot</td>
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<tr>
<td>‘744</td>
<td>II</td>
<td>Injectable, SC</td>
<td>Once monthly (or less)</td>
<td>Phase 1 pilot</td>
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<tr>
<td>ibalizumab</td>
<td>CD4 attachment inhibitor</td>
<td>Injectable, SC</td>
<td>Once every 1-4 weeks</td>
<td>Phase 1 pilot</td>
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THANK YOU