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

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PrEP 2.0 – Second generation HIV prevention drugs

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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
  - 90% Reduction in HIV risk
  - PrEP reduces HIV risk
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Population</th>
<th>Location</th>
<th>Primary outcome(s)</th>
<th>Completion date</th>
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[https://clinicaltrials.gov](https://clinicaltrials.gov)
# Clinical trials of investigational PrEP drugs – injectable long-acting

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<td>CAB LA</td>
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<td>Women</td>
<td>Sub-Saharan Africa</td>
<td>Safety Tolerability Efficacy</td>
<td>July 2020</td>
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[https://clinicaltrials.gov](https://clinicaltrials.gov)
Oral PrEP drugs
Tenofovir alafenamide (TAF) for PrEP

- Nucleoside reverse transcriptase inhibitor
  - Prodrug of tenofovir diphosphate (TFV-DP)
  - Converted to TFV-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

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
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 tolerability

- 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

Spreen et al., JAIDS 2014; McGowan et al., AIDS 2016
Emergence of K101E resistance during the RPV LA pharmacokinetic tail
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

ampstudy.org
Timeline for completion of PrEP clinical trials

- VRC01: Phase 1
- RPV LA: Phase 2
- CAB LA: Phase 3
- TAF/FTC: Phase 1
- VRC01/M: Phase 2
- CAB LA: Phase 3
- VRC01/W: Phase 1
- TAF/FTC: Phase 2

Years:
- 2016
- 2017
- 2018
- 2019
- 2020
- 2021
Low TDF/FTC uptake in the United States
An increasing number of persons initiating PrEP, United States 2012–2015

79,684 unique individuals started FTC/TDF for PrEP:
1,671 in Q4 2012 → 14,000 in Q4 2015

738% increase

McCallister et al., IAS 2016
Why do we need both PrEP and TasP?

Percent of HIV-infected persons

<table>
<thead>
<tr>
<th>Status</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>On ART, not virally suppressed</td>
<td>70%</td>
</tr>
<tr>
<td>In care, not on ART</td>
<td>64%</td>
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<tr>
<td>Linked, not retained in care</td>
<td>61%</td>
</tr>
<tr>
<td>Diagnosed, not linked to care</td>
<td>19%</td>
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<tr>
<td>Undiagnosed HIV</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

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)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.