HIV Prevention 2020

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**Viewpoint**

March 8, 2019

**HIV in the United States**

Getting to Zero Transmissions by 2030

Ingrid Katz, MD, MHS\textsuperscript{1,2}; Ashish K. Jha, MD, MPH\textsuperscript{1,3}


**Editorial**

February 7, 2019

**Ending the HIV Epidemic**

A Plan for the United States

Anthony S. Fauci, MD\textsuperscript{1}; Robert R. Redfield, MD\textsuperscript{2}; George Sigounas, MS, PhD\textsuperscript{3}; et al

Black MSM accounts for most of the new HIV-1 diagnoses in the south, however, rates of new infections are surging among Hispanic/Latino MSM in the south in recent years.

New HIV diagnoses in Southern US, 2017. CDC
“Ending the HIV Epidemic”
Four Strategies

☑️ Increase Testing and Diagnosis
☑️ Improve the Treatment Cascade
☑️ PrEP to protect individuals at risk
☑️ Rapid detection and response to HIV-1 transmission outbreak clusters
Four Prevention Opportunities

Cohen et al, JCI, 2008
Cohen IAS 2008

UNEXPOSED

Safer Behaviors!
STI RX
Structural Circumcision
Condoms

EXPOSED (precoital/coital)
Vaccines
ART PrEP
Microbicides

EXPOSED (postcoital)
Vaccines
ART PEP

INFECTED
Treatment Of HIV Reduced Infectivity

YEARS
HOURS
72h
YEARS
Treatment as Prevention

Reduce HIV in genital secretions with ART!
“The results have galvanized efforts to end the world’s AIDS epidemic in a way that would have been inconceivable even a year ago”

Bruce Alberts, editor of Science
UNDETECTABLE ≡ UNTRANSMITTABLE
“End of AIDS on the horizon, but innovation is needed”
Community Based TasP

- ANRS South Africa \( (NEJM, NS) \)
- Botswana \( (IAS, 30\% \text{ Reduction}) \)
- SEARCH \( (IAS, 2018, NS) \)
- HPTN 071/POPART \( (CROI 2019) \)**

Treatment serves as prevention, but imperfectly.
Why is “Treatment as Prevention” Imperfect?

- Magnitude of Coverage
- ART Resistance
- Specific Untreated People
  - acute HIV
  - “in-migration” into a community
  - young men as a key population

ATTRIBUTABLE RISK FOR EACH?
TDF/FTC was FDA Approved for use for Prevention on July 16, 2012

- Success depends entirely on adherence
- Alternatives to daily dosing are possible
- Truvada PrEP uptake has been limited to date
- Perhaps longer acting agents will prove more attractive?
PrEP use has increased in the US...

177,268 recipients by end of 2017

Magnuson D. et al. IAS Amsterdam 2018
THE PHASE 3 DISCOVER STUDY: DAILY F/TAF OR F/TDF FOR HIV PRE-EXPOSURE PROPHYLAXIS

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F/TAF is non-inferior to F/TDF for HIV prevention

HIV Incidence

<table>
<thead>
<tr>
<th>HIV Incidence Rate/100 PY</th>
<th>F/TAF</th>
<th>F/TDF</th>
</tr>
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<tbody>
<tr>
<td>0.1</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>0.2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>0.3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Incidence Rate Ratio [95% CI]

- Favors F/TAF: RR = 0.19
- Favors F/TDF: RR = 1.15

Noninferiority margin: RR = 1, no difference

CI, confidence interval; RR, rate ratio.

Monthly Dapivirine Rings

- Flexible silicone vaginal ring developed

- Woman-initiated
  - Self-inserted monthly
  - Discreet

- Slowly releases the NNRTI dapivirine

- Reduced women’s HIV-1 risk by ~30% in 2 phase 3 trials

- Data from open-label studies show greater use and potentially greater risk reduction

- Under regulatory review??
  - NNRTI, non-nucleoside reverse transcriptase inhibitor

Nel A, et al. NEJM. 2016;375:2133-2143
Baeten J, et al. CROI 2018. #143LB
Nel A, et al. CROI 2018, #144LB
Long Acting Parenteral PrEP
Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084).

*In Steps 1 and 2, the tablets and the injections will look alike, so staff and participants will not know if they are getting the active or placebo products. In step 3, everyone will be given active TDF/FTC.
+In step 2 the first two injections are four weeks apart and 8 weeks apart thereafter.
HPTN 083

PHASE 2B/3 INJECTABLE CABOTEGRAVIR COMPARED TO DAILY ORAL TDF/FTC FOR PREP IN CISGENDER MEN AND TRANSGENDER WOMEN WHO HAVE SEX WITH MEN

Raphael Landovitz
Beatriz Grinjsten

NIAID/DAIDS DSMB
May 9, 2019
Status of Enrollment: n=4500

- 27 US sites
- 11 South American sites
- 4 Asian sites
- 1 African site

The study is essentially fully enrolled (!!) with additional enrollment of 500 subjects
Study Population

3,200 women who have sex with men

- Female
- HIV negative
- Age 18-45 years
- Sexually active (vaginal intercourse twice in past 30 days)
- **Modified VOICE Risk Score 3**
- Not pregnant or breastfeeding
- No previous enrollment in vaccine trial and no co-enrollment in other HIV prevention trials
- No contraindications to either agent
Challenges in Development of CAB-LA as PreP

- Recruitment and retention!
- **Reduced HIV incidence compromises anticipated endpoints**
- Will CAB-LA PrEP “overwhelm” STIs
- Analysis may be complicated: ITT vs “As treated”
MK-8591 at 3.9, 1.3, 0.43 and 0.1 mg/kg is highly protective against infection with SHIV109CP3 (Phase 2 study q month pill launching)

- Overall, treatment with MK-8591 at all 4 doses was associated with a 41.47-fold lower risk of infection, p<0.0001, log rank test
- Intracellular levels of MK-8591-TP at or above 24 fmol/10^6 PBMC is associated with 92% protection
- Animals treated with 0.1 mg/kg dose are 7.2-fold less likely to be infected, p=0.0004 log rank test
Safety and Pharmacokinetics of Oral Islatravir (MK-8591) Once Monthly in Participants at Low Risk of Human Immunodeficiency Virus 1 (HIV-1) Infection (MK-8591-016)

ClinicalTrials.gov Identifier: NCT04003103

Recruitment Status: Not yet recruiting
First Posted: July 1, 2019
Last Update Posted: August 15, 2019
Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention


Antimicrob Agents Chemother. 2018 Sep;62(10)
LA Implants

Matrix vs. Reservoir
Renewable vs. biodegradable

- MK-8591 (Islatravir)
- Cabotegravir (Northwestern, ViiV)
- TAF (Oakcrest, Houston, RTI, Northwestern)
- Dolutegravir (Sol-Gel)
Ultra Long-Acting Dolutegravir (sol-gel)

What is PrEP [DTG] target?

- [DTG] should be $\geq C_T$ observed at 10 mg once daily (0.30 mcg/mL)
- $= EC_{90}$ based on $E_{\text{max}}$ model from PK/PD analysis of monotherapy study
- With 50 mg daily, $C_T$ is 1.20 mcg/mL;
  - 0.30 mcg/mL is 25% of that value

Kovarova M et al., Nature Communications 2018
Van Lunzen Lancet ID 2012
Reese et al Drug Metab Disp 2013

Slide Courtesy of Ethel Weld
Ultra LA DTG Antiviral Effect

- BLT mice challenge

- 80% protection from repeated vaginal challenge (positive controls 4/5 HIV+)

Kovarova M et al., Nature Communications 9, (2018)
Vaccine Strategies 2019

Efficacy Studies

- P5 “Clade C” approach using ALVAC & gp120/MF59 (HVTN 702)
- Multi-clade approach using rAd26/MVA/gp140 trimer (Crucell/Janssen)
- Neutralizing antibody approach using VRC01 (AMP Trial: HVTN 703/HPTN 083, HVTN 704/HPTN 085)
Development of Broad Neutralizing Antibodies (BnABs)

The initial neutralizing antibody response to HIV "autologous nAb"
Continuum with 10~20% Broadly neutralizing antibodies

HIV-1

The transmitted-Founder virus
Escape virus

Antibody

The initial neutralizing antibody response to HIV "autologous nAb"
bnAb Activities

CD4bs
- VRC01, VRC07.523LS, 3BNC117, N6

V3 glycan
- 10-1074

MPER
- 10E8

V2 glycan/Apex
- CAP256

HIV-1 Trimer
VRC01 Protects against Mucosal SHIV162P3 Challenge in NHP

20 mg/kg infusion of VRC01

RECTAL CHALLENGE
4/4 protected

VAGINAL CHALLENGE
4/4 protected
The AMP Studies: Phase 2b Proof-of-Concept Trials
Designed to Test the Efficacy of VRC01 Antibody to Prevent HIV Acquisition

AMP = Antibody Mediated Prevention
Two harmonized protocols

HVTN 704/HPTN 085
(MSM and TG in the Americas & Europe)

HVTN 703/HPTN 081
(Women in sub-Saharan Africa)
The AMP Studies: phase 2b proof of concept trials designed to test the efficacy of VRC01 antibody to prevent HIV acquisition

AMP = Antibody Mediated Prevention

Two harmonized protocols:

• HVTN 704/HPTN 085 (MSM and TG in the Americas & Europe)

• HVTN 703/HPTN 081 (Women in sub-Saharan Africa)
### The AMP Studies: Highlights

<table>
<thead>
<tr>
<th>Cohort</th>
<th>IV Treatment</th>
<th>n=</th>
<th>Schedule</th>
</tr>
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<tbody>
<tr>
<td>North + South American MSM (2400)</td>
<td>VRC01 10 mg/kg</td>
<td>800</td>
<td>Every 8 wks x 10 doses</td>
</tr>
<tr>
<td>HVTN 704 / HPTN 085</td>
<td>VRC01 30 mg/kg</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Placebo Control</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan African women (1500)</td>
<td>VRC01 10 mg/kg</td>
<td>500</td>
<td>Every 8 wks x 10 doses</td>
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- Two different infusion doses:
  - Important to know if lower dose of 10 mg/kg can protect
- Powered to associate mAb serum level with protection
Study Designed with two dosages to span a range of VRC01 concentrations and power to detect reduced acquisition and sieving

Sieving:

All infection viral Envs are cloned and tested for neutralization sensitivity to VR01

Does VRC01 have the ability to exclude acquisition of HIV variants deemed as “sensitive” to the antibody
bNAbs

**Next-gen bNAbs:** re-engineered, more potent VRC07, combos of mAbs, combos of bnAbs with different specificities into single molecule, trispecific mAbs

**First-Gen: VRC01**
(HVTN 703/ HPTN 081 & HVTN 704/HPTN 085)

**Primary Objectives:**
- Safety
- Efficacy (Week 80)

**Secondary Objectives:**
- VRC01 concentration
- mAb effector functions
- Genotypes/ effector functions/ sensitivity to neutralization of breakthroughs
The Big Picture

• HIV prevention research results are driving global HIV prevention
• TASP and PrEP need to find their way(s) to INTEGRATED STRATEGIES
• Global HIV Prevention remains too unfocused for maximal benefit
• US End the Epidemic is a major attempt at an integrated strategy
THANK YOU FOR LISTENING