Injectable Pre-Exposure Prophylaxis for HIV Prevention

Raphael J. Landovitz, MD MSc
Associate Professor of Medicine
UCLA Center for Clinical AIDS Research & Education
HPTN/IMPAACT Network Meeting 2016
Prevention of sexual transmission

PROUD – daily oral TDF/FTC (MSM – United Kingdom)

IPERGAY – event-driven TDF/FTC (MSM – Canada, France)

Partners PrEP – daily oral TDF/FTC (Serodiscordant couples – Kenya, Uganda)

Partners PrEP – daily oral TDF (Serodiscordant couples – Kenya, Uganda)

TDF2 – daily TDF/FTC (Heterosexual men and women – Botswana)

iPrEx – daily oral TDF/FTC (MSM – North and South America, South Africa, Thailand)

CAPRISA 004 – BAT-24 dosing vaginal tenofovir gel (Women – South Africa)

RV 144 – six injectable ALVAC/AIDSVAX (Heterosexual men and women – Thailand)

The Ring Study – monthly vaginal ring containing dapivirine (Women – South Africa, Uganda)

ASPIRE – monthly vaginal ring containing dapivirine (Women – Malawi, South Africa, Uganda, Zimbabwe)

MTN 003/VOICE – daily dosing vaginal tenofovir gel (Women – South Africa, Uganda, Zimbabwe)


FACTS 001 – event-driven vaginal tenofovir gel (Women – South Africa)

MTN 003/VOICE – daily oral TDF/FTC (Women – South Africa, Uganda, Zimbabwe)

MTN 003/VOICE – daily oral TDF (Women – South Africa, Uganda, Zimbabwe)

Prevention in people who inject drugs

Bangkok Tenofovir Study – daily oral TDF (PWID – Thailand)

Effect size (CI)

86% (58; 97)
86% (44; 99)
75% (55; 87)
67% (44; 81)
62% (22; 84)
44% (15; 63)
39% (6; 60)
31% (1; 51)
31% (1; 51)
27% (1; 46)
15% (-21; 40)
6% (-21; 40)
0% (-40; 30)
-4% (-49; 27)
-49% (-129; 3)
49% (10; 72)

Adapted from: Salim S. Abdool Karim, CAPRISA
The PrEP Pipeline: Looking past TDF/FTC

- Maraviroc – HPTN 069/ACTG A5305
- TAF – Macaque protection (?) but low tissue levels
- Long Acting Therapies
  - Rilpivirine (TMC278) – HPTN 076
  - Cabotegravir (GSK1265744) – HPTN 077/HPTN 083/ECLAIR
  - Immunotherapies – VRC01
  - Implantable devices
- More on Intermittent (i)PrEP
- Special populations
  - HPTN 073 – BMSM
  - ATN 110/113 – Youth
- Combinations of interventions

2. Garrett K, CROI 2016
The PrEP Pipeline: 
Looking past TDF/FTC

- **Maraviroc** – HPTN 069/ACTG A5305
- **TAF** – Macaque protection (?) but low tissue levels
- **Long Acting Therapies**
  - Rilpivirine (TMC278) – HPTN 076
  - Cabotegravir (GSK1265744) – HPTN 077/HPTN 083/HPTN 084/ÉCLAIR
  - Immunotherapies – VRC01
  - Implantable devices
- **More on Intermittent (i)PrEP**
- **Special populations**
  - HPTN 073 – BMSM
  - ATN 110/113 – Youth
- **Combinations of interventions**

2. Garrett K, CROI 2016
HPTN 069 / ACTG A5305

A phase 2 safety study designed to answer: Could daily oral maraviroc, a CCR5 receptor antagonist, be a next-gen PrEP agent for men and/or women?
Maraviroc – HPTN 069/ACTG A5305
HPTN 069 / ACTG A5305

Screening

Enrollment and Randomization
N = 600
(400 men; 200 women)

Arm 1, N=150
100 men; 50 women
MVC (active) +
FTC (placebo) +
TDF (placebo)

Tissue Subset
N = 30
15m; 15w

Drug Interaction Subset
N = 18

Arm 2, N=150
100 men; 50 women
MVC (active) +
FTC (active) +
TDF (placebo)

Tissue Subset
N = 30
15m; 15w

Drug Interaction Subset
N = 18

Arm 3, N=150
100 men; 50 women
MVC (active) +
FTC (placebo) +
TDF (active)

Tissue Subset
N = 30
15m; 15w

Drug Interaction Subset
N = 18

Arm 4, N=150
100 men; 50 women
MVC (placebo) +
FTC (active) +
TDF (active)

Tissue Subset
N = 30
15m; 15w

Drug Interaction Subset
N = 18
HPTN 069 / ACTG A5305: Participants

- **N = 406** individuals enrolled
- 100% male at birth; 7 (2%) transgender
- Median age 30 (range 18, 70)
- 28% black, 22% Latino, 62% white, 10% other (participants could report more than one)
- 20% high school education or less, 67% some college or more, 13% advanced degrees

- 31 (8%) had 34 STIs during study screening:
  - 15 (4%) chlamydia, 5 (1%) gonorrhea, 14 (3%) syphilis
HPTN 069 / A5305: Results

• No differences by study arm in:
  – proportion who discontinued study drugs (p=0.6)
  – time to permanent study drug discontinuation (p=0.6)

• There were 67 grade 3-4 AEs
  – No differences in occurrence or rate among the study arms (p>0.05 in pairwise comparisons)

• 90 (22%) had 115 STI diagnosed during study f/u

• Plasma Drug Concentrations:
  – Random subset across 4 study arms (n=160)
  – All study drugs in regimen detectable in 83% (week 24) and 77% (week 48)
    • No differences between the study arms (p>0.3)
**HPTN 069 / A5305: HIV Infections**

- 5 new HIV infections during the study
- Annual incidence rate 1.4% [95% CI: 0.8%, 2.3%]

<table>
<thead>
<tr>
<th>#</th>
<th>Demos. (age, race/ethnicity, HIV risk)</th>
<th>Study arm</th>
<th>First reactive HIV+ test (week)</th>
<th>HIV RNA (cps/mL)</th>
<th>CD4 cells (/mm³)</th>
<th>HIV tropism</th>
<th>Genotypic drug resistance</th>
<th>Plasma drug conc. at seroconversion visit (ng/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20, black MSM</td>
<td>MVC+ TDF</td>
<td>4</td>
<td>122,150</td>
<td>357</td>
<td>R5</td>
<td>none</td>
<td>MVC=0† TFV=0</td>
</tr>
<tr>
<td>2</td>
<td>61, Asian MSM</td>
<td>MVC alone</td>
<td>16</td>
<td>981</td>
<td>294</td>
<td>R5</td>
<td>none</td>
<td>MVC=145</td>
</tr>
<tr>
<td>3</td>
<td>21, mixed MSM</td>
<td>MVC alone</td>
<td>24</td>
<td>106,240</td>
<td>325</td>
<td>R5</td>
<td>none</td>
<td>MVC=0†</td>
</tr>
<tr>
<td>4</td>
<td>35, white MSM</td>
<td>MVC alone</td>
<td>32</td>
<td>13,626</td>
<td>828</td>
<td>R5</td>
<td>none</td>
<td>MVC=6.7</td>
</tr>
<tr>
<td>5</td>
<td>36, black MSM</td>
<td>MVC alone</td>
<td>48</td>
<td>52,191</td>
<td>804</td>
<td>R5</td>
<td>none</td>
<td>MVC=0.7</td>
</tr>
</tbody>
</table>

* expected pre-dose steady state MVC = 32 ng/ml
† undetectable plasma drug concentrations at every study visit
HPTN 069 / A5305: Study Drug Concentrations in New HIV Infections

Note: 2 others with new HIV infection had undetectable study drug at every visit.
HPTN 076

A phase 2 safety study designed to answer: Could injectable rilpivirine, a FDA-approved NNRTI in its oral formulation, be a useful sustained-release PrEP agent?
Long Acting Rilpivirine (TMC278)
HPTN 076: Phase 2 Safety

- TMC278 LA is a novel poloxamer 338-containing formulation of TMC278. TMC278 LA is long-acting suspension and well-suited for delivery via IM injection
- HPTN 076 enrolling at 4 sites, low-risk HIV-uninfected women (NY, NJ, Zim, SA)
- Fully enrolled, Data available 2017
### HPTN 076: Safety and acceptability of injectable rilpivirine (TMC278 LA) for PrEP

136 HIV-uninfected, women ages 18-45 years

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>52</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1</td>
<td>Daily oral TMC278</td>
<td>Six injections of TMC278 LA 1200 mg every 8 weeks</td>
<td>Follow-up phase (tail phase)</td>
</tr>
<tr>
<td>N = 91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM 2</td>
<td>Daily oral placebo</td>
<td>Six injections of TMC278 LA placebo every 8 weeks</td>
<td></td>
</tr>
<tr>
<td>N = 45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HPTN 076 – Study Sites and Status

US Sites
- Bronx, NY
- Newark, NJ

International Sites
- Cape Town, South Africa
- Harare, Zimbabwe

Primary Endpoint- September, 2016
Last Study Visit- February, 2017
SSAT040: Seroconversion Event During Washout of 300 mg

Summary: Drug Levels, Viraemia, Resistance

ART = antiretroviral therapy

Penrose K, et al. HIVR4P 2014. Abstract OA27.01
CABOTEGRAVIR

The artist formerly known as GSK1265744
Or “744”
Cabotegravir (GSK 1265744) development

Early Phase

NHP Models

First-in-human/Phase 1

Cardiac Safety, DDI

Indication

Treatment

LATTE-1

LATTE-2 Pivotal Phase 3

Phase 2a

Prevention cis women

HPTN 077*

HPTN 084

Prevention MSM/TGW

ECLAIR

HPTN 083

Phase 2b ± 3

*INCLUDES BOTH MEN AND WOMEN
HPTN 077

A phase 2 safety study designed to answer:
Could injectable cabotegravir, a NON-FDA-approved integrase inhibitor (currently being developed for HIV treatment in parallel) be a useful sustained-release PrEP agent in women (and men) globally?
Favorable attributes for PrEP:
• High genetic barrier to resistance
• PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation
## Long Acting Cabotegravir HPTN 077 – Phase 2a

A Phase 2a Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, Cabotegravir, in HIV-uninfected Men and Women

### Cohort 1

<table>
<thead>
<tr>
<th>Weeks</th>
<th>4</th>
<th>41</th>
<th>81</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARM 1</strong>&lt;br&gt;N = 79</td>
<td>Daily Oral 744 30mg</td>
<td>Injections of 744LA 800 mg every 12 weeks at three time points</td>
<td>Follow-up Phase (Tail Phase)</td>
</tr>
<tr>
<td><strong>ARM 2</strong>&lt;br&gt;N = 27</td>
<td>Daily Oral Placebo</td>
<td>Injections of 744LA placebo every 12 weeks at three time points</td>
<td></td>
</tr>
</tbody>
</table>

### Cohort 2

<table>
<thead>
<tr>
<th>Weeks</th>
<th>4</th>
<th>41</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARM 1</strong>&lt;br&gt;N = 66</td>
<td>Daily Oral 744 30mg</td>
<td>Injections of 744LA 600 mg every 8 weeks after monthly load at five time points</td>
<td>Follow-up Phase (Tail Phase)</td>
</tr>
<tr>
<td><strong>ARM 2</strong>&lt;br&gt;N = 22</td>
<td>Daily Oral Placebo</td>
<td>Injections of 744LA placebo every 8 weeks after monthly load at five time points</td>
<td></td>
</tr>
</tbody>
</table>
Fully Enrolled as of May 27, 2016
67% Women

Primary Endpoint - March, 2017
Last Study Visit - January, 2018
ECLAIR

A Viiv-sponsored phase 2 safety study designed to answer:

Could injectable cabotegravir, a NON-FDA-approved integrase inhibitor (currently being developed for HIV treatment in parallel) be a useful sustained-release PrEP agent in US-based men?
ÉCLAIR: Cabotegravir LA for PrEP in Low-Risk, HIV-Uninfected Men

**Phase 2a**

Double-blind
Men 18 to 65 years of age
Low-risk of acquiring HIV
No PEP or ART
No liver disease
5:1 randomization

**Oral Phase**

| Cabotegravir 30 mg qd (n=105) |
| Placebo (n=21) |

**Injection Phase**

| Cabotegravir LA 800 mg IM every 12 weeks (n=94) |
| Saline Placebo IM every 12 weeks (n=21) |

Week 0 4 5

Baseline characteristics (cabotegravir oral phase):
- Median age: 31 years.
- White/black race/ethnicity: 56%/31%.
- Hispanic/Latino race/ethnicity: 15%.
- Median height: 176 cm.
- Median BMI: 26 kg/m².
- Risk for HIV acquisition:
  - Homosexual contact: 85%.
  - Heterosexual contact: 21%.
  - Occupational exposure: 2%.

Mean (SD) Plasma CAB Conc-Time Profiles following 800mg IM Q12W in ÉCLAIR and Predicted in original Phase 2 Model (Sparse Time Points)

Simulated CAB 800mg IM Q12W (males, n=663)
Observed CAB 800mg IM Q12W (ECLAIR, n=94)
8x PA-IC90 (1.35 μg/mL)
4x PA-IC90 (0.664 μg/mL)
1x PA-IC90 (0.166 μg/mL)

Time (Weeks)
0 4 8 12 16 20 24 28 32 36
Plasma CAB (μg/mL)
0.01
0.1
1
10
Numbers of Subjects in CAB Concentration Ranges by Injection Visit - ÉCLAIR

- Injection 1: 24% <1 × PA-IC_{90}, 31% 1 × to <4 × PA-IC_{90}, 31% >4 × PA-IC_{90}
- Injection 2: 15% <1 × PA-IC_{90}, 32% 1 × to <4 × PA-IC_{90}, 37% >4 × PA-IC_{90}
- Injection 3: 45% <1 × PA-IC_{90}, 55% 1 × to <4 × PA-IC_{90}, 30% >4 × PA-IC_{90}
Multi-stakeholder Input to Dose-finding

HPTN 083 Team Leadership
HPTN Network Leadership
HPTN Laboratory Center Leadership
NIH/DAIDS
ViiV
Simulated Median (90% PI) Conc-Time profile following (CAB) LA 600mg IM at Day 1, Week 4 and Q8W thereafter in Males (Updated PopPK Model)
HPTN 083: Treatment Arms

Group A
- Cabotegravir (CAB) injection
- Cabotegravir (CAB) pill
- TDF/FTC pill
- Placebo for cabotegravir (CAB) injection
- Placebo for cabotegravir (CAB) pill
- Placebo for TDF/FTC pill

Group B
- Cabotegravir (CAB) injection
- Cabotegravir (CAB) pill
- TDF/FTC pill
- Placebo for cabotegravir (CAB) injection
- Placebo for cabotegravir (CAB) pill
- Placebo for TDF/FTC pill
HPTN 083: A “3 STEP” Study

**Screening day and informed consent**

**STEP 1**
- Every day for 5 weeks

**STEP 2**
- Weeks 5 and 9
- Every 2 months for 1 to 3.5 years

**STEP 3**
- Every day for 1 year

**Group A**

- **CAB**
- **TDF/FTC**

**Group B**

- **CAB**
- **TDF/FTC**

---

Cabotegravir (CAB) injection

- **CAB**

Cabotegravir (CAB) pill

- **CAB**

TDF/FTC pill

- **TDF/FTC**

Placebo for cabotegravir (CAB) injection

- **CAB**

Placebo for cabotegravir (CAB) pill

- **CAB**

Placebo for TDF/FTC pill

- **TDF/FTC**
Protocol Objectives

Primary Objectives
- Efficacy of CAB vs. TDF/FTC
- Safety of CAB vs. TDF/FTC

Secondary Objectives
- Efficacy in pre-specified subgroups of CAB vs. TDF/FTC
- Kidney, liver, and bone safety in CAB vs. TDF/FTC
- ART resistance in seroconverters on CAB vs. TDF/FTC
- HIV incidence based on strata of study product adherence
- Acceptability and preferences for oral vs. injectable PrEP

Tertiary Objectives
- Rates, patterns, correlates of adherence
- Changes in sexual risk behavior (self-report and biomarkers, i.e., STIs)
- Cost effectiveness considerations
Study Population

Cis-MSM and TGW, 18 yo or older, at high-risk for HIV acquisition defined as:

- In past 6 months: Any ncRAI; >5 partners; stimulant drug use; rectal or urethral STI

Enrollment goals:
- *Minimum* 50% of US enrollment BMSM (~ 950)
- Overall minimum 10% TGW (~ 450)
- Overall > 50% under age 30
HPTN 083 Sites

**South Africa**
- Groote Schuur HIV CRS

**Asia (Thailand and Vietnam)**
- CMU HIV Prevention CRS
- Silom Community Clinic CRS
- Thai Red Cross (TRC-ARC) CRS
- Yen Hoa Health Clinic CRS

**Latin America (Argentina, Brazil, Peru)**
- Fundación Huésped CRS
- Hospital General de Agudos JM Ramos Mejía CRS
- Instituto de Pesquisa Clinica Evandro Chagas (IPEC) CRS
- Hospital Nossa Senhora da Conceição CRS
- University of Sao Paulo CRS
- Centro de Referencia e Treinamento DST/AIDS CRS
- Asociacion Civil Selva Amazonica (ACSA) CRS
- Barranco CRS
- San Miguel CRS
- CITBM CRS
- Via Libre CRS

**United States**
- Alabama CRS
- Adolescent and Young Adult Research at the CORE Center (AYAR at CORE) CRS
- Bridge HIV CRS/ East Bay AIDS Center (EBAC) CRS
- Bronx Prevention Research Center CRS
- Chapel Hill CRS
- Children’s Hospital Colorado CRS
- Cincinnati CRS
- Fenway Health (FH) CRS
- George Washington University CRS
- Greensboro CRS
- Harlem Prevention Center CRS
- Hope Clinic of the Emory Vaccine Center CRS
- Houston AIDS Research Team (HART) CRS
- Johns Hopkins University CRS
- New Jersey Medical School CRS
- New Orleans Adolescent Trials Unit CRS
- New York Blood Center CRS
- Ohio State University CRS
- Penn Prevention CRS
- Ponce de Leon Center CRS
- St. Jude Children’s Research Hospital CRS
- UCLA CARE Center CRS
- UCLA Vine Street Clinic CRS
- UIC Project WISH CRS
- University of Miami AIDS Clinical Research Unit (ACRU) CRS
- Washington University Therapeutics (WT) CRS
- Weill Cornell Chelsea CRS
HPTN 083 Sites – Phase 2b/3
42 Sites in 7 Countries

Anticipated Start – 3rd Q 2016 US Sites
Non-US TBD*
*Based on local regulatory approvals
Antibody Mediated Prevention

HPTN 081/HVTN 703, HPTN 085/HVTN 704
How Do Antibodies Prevent Infection?
One Way: Neutralization
The 3 Study Groups

**North & South America:**

2700 Men and Transgender Individuals Who Have Sex With Men, age 18-50, HIV-negative

1. Lower dose VRC01, 10 mg/kg (900)
2. Higher dose VRC01, 30 mg/kg (900)
3. Placebo (900)
The 3 Study Groups in Africa

1500 HIV-negative Heterosexual Women, age 18-50

1. Lower dose VRC01, 10 mg/kg (500)
2. Higher dose VRC01, 30 mg/kg (500)
3. Placebo (500)
### AMP Study Arms

#### Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HVTN 704/HPTN 085 (MSM and transgender persons in N. &amp; S. America)</th>
<th>HVTN 703/HPTN 081 (Sub-Saharan African women)</th>
<th>Total</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>2,800</td>
<td>Infusions every 8 weeks through Week 72 (10 total infusions per participant)</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1,400</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1,400</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,700</td>
<td>1,500</td>
<td>4,200</td>
<td></td>
</tr>
</tbody>
</table>

Access to PrEP where possible
Thank You