Moving Beyond Truvada: The (Current) Future Pipeline for PrEP

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2 Million New Infections in 2014
5,600 New Infections per Day

Prevention Modalities

Clinical Trial Evidence for HIV Prevention Options (February 2016)

Prevention of sexual transmission

Adapted from: Salim S. Abdool Karim, CAPRISA

Effectiveness (%)

Prevention in people who inject drugs

Effect size (CI)

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

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)

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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)

Total Incidence and Growth Trend of FTC/TDF for PrEP

Unique individuals initiating FTC/TDF for PrEP, n


Total FTC/TDF for PrEP Utilization Compared With Population and New HIV Infections

FTC/TDF for PrEP use among AA and Hispanics is low relative to the rate of new HIV infections

Bush S, et al. ASM/ICAAC 2016; Boston, MA. #2651
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/ÉCLAIR
  - Immunotherapies – VRC01
  - Implantable devices
- More on Intermittent (i)PrEP
- Special populations
  - HPTN 073 – BMSM
  - ATN 110/113 – Youth
- Combinations of interventions

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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?

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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 trop-</th>
<th>Genotypic drug resis-</th>
<th>Plasma drug conc. at serocon-</th>
<th>Visit (ng/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20, black MSM MVC+ TDF</td>
<td>4</td>
<td>122,150</td>
<td>R5</td>
<td>none</td>
<td>MVC=0† TFV=0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>61, Asian MSM MVC alone</td>
<td>16</td>
<td>981</td>
<td>294</td>
<td>R5</td>
<td>none</td>
<td>MVC=145</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21, mixed MSM MVC alone</td>
<td>24</td>
<td>106,240</td>
<td>325</td>
<td>R5</td>
<td>none</td>
<td>MVC=0†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>35, white MSM MVC alone</td>
<td>32</td>
<td>13,626</td>
<td>828</td>
<td>R5</td>
<td>none</td>
<td>MVC=6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36, black MSM MVC alone</td>
<td>48</td>
<td>52,191</td>
<td>804</td>
<td>R5</td>
<td>none</td>
<td>MVC=0.7†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* expected pre-dose steady state MVC = 32 ng/mL
† undetectable plasma drug concentrations at every study visit

Note: 2 others with new HIV infection had undetectable study drug at every visit.
Pre-Clinical and Animal Models of TAF for PrEP

Will it be equi-efficacious as TDF-based PrEP?

Perhaps
Perhaps not

Prodrug Pharmacology of TDF and TAF

TFV 25 mg results in >90% lower TFV plasma levels

Concentrations of TFV and TFV-DP in Female Mucosal Tissues After Single Dose of TAF

<table>
<thead>
<tr>
<th>Tissue Samples</th>
<th>BLQ, %</th>
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<th>BLQ, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital Tissue</td>
<td>6</td>
<td>75</td>
<td>16</td>
</tr>
<tr>
<td>Rectal Tissue</td>
<td>0</td>
<td>63</td>
<td>8</td>
</tr>
</tbody>
</table>

BLQ = below the level of quantification. All the samples had detectable TFV (none were BLQ)
F/TAF for PrEP in SHIV-Challenged Macaques

- F/TAF prevents rectal SHIV infection in macaques to a degree similar to that previously found with F/TDF but with a substantially reduced TFV dose:
  - F/TAF protected 100% of macaques (N=6) challenged with SHIV in a similar, pre-clinical trial.

SHIV challenges (weeks, n)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>FTC/TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

RILPIVIRINE: 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>Daily oral TMC278</td>
<td>Six injections of TMC278 LA placebo every 8 weeks</td>
<td></td>
</tr>
<tr>
<td>ARM 2</td>
<td>N = 45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HPTN 076 – STUDY SITES AND STATUS

US Sites
- Newark, NJ
- Bronx, NY

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

- Viral load
- Plasma (RPV)
- 45% (b)
CABOTEGRAVIR

Formerly known as GSK1265744
Or "744"

Cabotegravir (GSK 1265744) development

Early Phase

NHP Models
First-in-human/Phase 1
Cardiac Safety, DDI

Indication

Treatment
Prevention cis women
Prevention MSM/TGW

Phase 2a

LATT-1
LATTE-2
Pivotal Phase 3

Phase 2b ± 3

HPTN 077*
HPTN 084
ECLAIR
HPTN 083

*INCLUDES BOTH MEN AND WOMEN

CAB LA PrEP Phase 2 Safety and PK Studies

Follow-Up Phase

- HIV negative, at-risk adults (excluding high risk)
- Drug PK sampling (blood plasma) in all study participants

VIV ECLAIR Study (NCT02076178)
- n=226 (all injections complete)
- 800 mg IM
- 3:1 randomization
- Men including MSM
- US only (10 sites)

HPTN 077 Study (NCT02178800)
- n=200 (110 Cohort 1; 90 Cohort 2)
- Two Cohorts (800 and 600 mg IM)
- 3:1 randomization
- 67% enrolment of women
- US, Brazil, SA, Malawi (8 sites)
Plasma CAB Conc-Time Profiles following 800mg IM Q12W in ÉCLAIR

- Simulated CAB 800mg IM Q12W (index, n=96)
- Observed CAB 800mg IM Q12W (ÉCLAIR, n=94)
- 8xPA-IC90 (1.35 µg/mL)
- 4xPA-IC90 (0.664 µg/mL)
- 1xPA-IC90 (0.166 µg/mL)

HPTN 083
A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral TDF/FTC for the Prevention of HIV Infection in Cisgender Men and Transgender Women who have Sex with Men

Target enrollment: 4,500 HIV-uninfected cisgender men and transgender women who have sex with men
Primary outcome: HIV Prevention effectiveness of cabotegravir compared to daily oral TDF/FTC

ClinicalTrials.gov Identifier: NCT02720094

HPTN 083: Study Schema

Step 1
- Oral TDF/FTC
- Placebo for CAB

Step 2
- CAB injection
- Oral TDF/FTC
- Placebo for CAB

Step 3
- Oral TDF/FTC
- Placebo for CAB

Key:
- CAB injection
- Oral TDF/FTC
- Placebo for CAB
Immunotherapies: VRC01

The AMP Study (HVTN 704/HPTN 085)

AMP is the first trial to assess if antibodies can be used to prevent HIV infection, similar to how antibodies are used to prevent other infectious diseases.

Study Schema for The AMP Study

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1500</td>
<td>4200</td>
</tr>
</tbody>
</table>

10 infusions total & infusions every 8 weeks
Study duration: 22 months
Pre-Clinical and Animal Models of TAF for PrEP

Will it be equi-efficacious as TDF-based PrEP?

Perhaps

Perhaps not

Prodrug Pharmacology of TDF and TAF

TAF 25 mg results in >90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.
Concentrations of TFV and TFV-DP in Female Mucosal Tissues After Single Dose of TAF

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<tr>
<th>Tissue Samples</th>
<th>TFV BLQ, %</th>
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<th>Tissue Samples</th>
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<th>TFV-DP BLQ, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVF</td>
<td>58</td>
<td>n/a</td>
<td>TFV</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>Genital Tissue</td>
<td>40</td>
<td>23</td>
<td>TFV-DP</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Rectal Tissue</td>
<td>0</td>
<td>63</td>
<td>TFV</td>
<td>0</td>
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Conclusions

- We did not stop with drug development when we had AZT for HIV treatment
  - We have only experienced “first generation PrEP” to date
  - The many exciting pharmaco-chemical and bio-engineering/delivery opportunities are being investigated
- We need better insights into how to market, equally (appropriately) deploy, and scale up these interventions
Thank you! Questions?

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