Clinical Pharmacology of HIV Pre-Exposure Prophylaxis (PrEP) – Where are we now?

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Disclosures

ViiV/GSK funded clinical trial managed through Johns Hopkins
Objectives

- Describe brief history of PrEP to date
  - Limitations to daily oral PrEP
  - Differential diagnosis vaginal product underperformance

- Innovations to broaden PrEP success
  - Long-acting PrEP
  - Vaginal microbicicides
  - Rectal microbicicide
HIV PrEP Development 2001-2018

- **2001-2009** Vaginal microbicides – 6 failed RCTs
- **2010** Vaginal Tenofovir gel heterosexual women
  - Modest protection, 3 RCTs (1 mITT, 2 post hoc)
  - Clinical Pharmacology demonstrated concentration-response
- **2010-2015** HIV PrEP Oral TFV ± FTC
  - MSM/TGW (N=3) modest to high level protection, sNDA
  - Hetero women & men (N=2), high protection, sNDA
  - PWID (N=1) protects
  - Heterosexual women (N=2) failed to protect
- **2016** HIV Dapivirine intravaginal ring (N=2)
  - Modest protection
  - EMA NDA under review 2017-2018

Abdool Karim Science 2010; Abdool Karim Lancet 2011; Grant NEJM 2010; Anderson STM 2012; Baeten NEJM 2012; Marrazzo NEJM 2015; van Damme NEJM 2012
HIV PrEP Development 2001-2018

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# Vaginal PrEP Underperformance

<table>
<thead>
<tr>
<th>PrEP Type</th>
<th>Study</th>
<th>RRR (%)</th>
<th>Post Hoc “Adherence” Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFV Vaginal Gel</td>
<td>CAPRISA 004</td>
<td>39%</td>
<td>40-88%</td>
</tr>
<tr>
<td></td>
<td>VOICE gel</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FACTS 001</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Dapivirine IVR</td>
<td>ASPIRE</td>
<td>27%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>The Ring Study</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>TDF/FTC Oral</td>
<td>iPrEx</td>
<td>42%</td>
<td>90-100%</td>
</tr>
<tr>
<td></td>
<td>Partners</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDC TDF2</td>
<td>62%</td>
<td></td>
</tr>
</tbody>
</table>

*mITT, modified intent to treat analysis; **RRR = relative risk reduction in HIV infection; ***assumes no microbiome effect
Differential Diagnosis

- **Adherence** doesn’t completely account for oral-vaginal outcome differences
- Women practicing **RAI** – certain, but variable effect
  - If 1/20 HIV exposures is anal & 20x anal HIV transmission risk, max RRR is 50%
  - Front door dose, no back door protection
- **Vaginal microbiome** may reduce TFV concentration with concomitant BV
- Polymorphic LOF kinase mutations impact NTP concentrations, but <10%
- **[Tissue] v. [Systemic] relative contribution** varies by route; unsettled
Long-Acting Formulations
Adherence: CAB-LA (2 months)

Problem being solved is daily oral adherence
- Solution requires some daily oral adherence
- *Oral lead-in – may be dropped with data*
- *Long tail – may be inconsequential for resistance*

Target Dosing based on Animal Model
- Confidence bolstered by Treatment Effectiveness
- But tissue concentrations poor relative to plasma
- HPTN 083/084 greatly inform target concentration issue
Adherence: bnMAbs (2 – 6 months)

- Neutralize virus (Env) & recruit effector cells to kill HIV infected cells
- Rare “elite” neutralizers: evolve nAbs which neutralize within & across clades
- Engineering improvements – increase coverage, potency, and half-life
  - Passive immunoglobulin low potency, narrow breadth
  - Early bnMAbs (from elite neutralizers) increase potency & breadth
  - Combinations broadens coverage *(move up)*
  - FcRn substitution increases half-life *(move right)*
- Treatment
  - Clinical transiently reduces viral load (VRC01)
- Prevention
  - High level SHIV vaginal/rectal protection macaques
  - 2 RCTs underway with VRC01 infusion
- Expensive vs. other approaches

Sok D. Immunity 2016;45(5):958-960 (Figure 1)
Adherence: Subdermal Implant Designs (1 year)

- TAF Oak Crest (removable)
  -Courtesy Marc M. Baum, Oak Crest Institute of Science; Gunawardana et al., AAC, 2015

- TAF RTI (biodegradable)
  -van der Straten LEAP 2018

- TAF or CAB SLAP-HIV (removable)
  -Hope/Kiser SLAP-HIV

Courtesy Marc M. Baum, Oak Crest Institute of Science; Gunawardana et al., AAC, 2015; Ariane van der Straten LEAP 2018; Thomas Hope SLAP-HIV.
Vaginal Microbicide Formulations
Adherence: Pod-IVR Design (1 month)

- ≤10 Polymer-coated drug “pods”
- An un-medicated, torus-shaped elastomeric support holds the pods
- Release rate controlled through delivery channels size
- Flexible drug combinations unlike matrix of single reservoir rings
- Phase I, 3 ARV study under review
- MPT (contraception/ARV) pre-clinical

Marc Baum & John Moss, Oakcrest Institute of Science
**Front Door-Back Door: Pod-IVR**

**Day 7 Rectal Fluid Concentrations**

- **In Vitro (µm)**
- **Pod-IVR (clinical : in vitro)**

<table>
<thead>
<tr>
<th>ARV</th>
<th>IC$_{50}$</th>
<th>IC$_{90}$</th>
<th>TDF</th>
<th>TDF FTC</th>
<th>TDF FTC MVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFV</td>
<td>0.5</td>
<td>3.9</td>
<td>2.2</td>
<td>81.0</td>
<td>0.81</td>
</tr>
<tr>
<td>FTC</td>
<td>0.6</td>
<td>0.35</td>
<td>-</td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>MVC</td>
<td>0.006</td>
<td>0.013</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

- Combinations complex
- Rectal fluid may provide protective levels
- Future Work
  - Rectal tissue cell active drug
  - Anterior & posterior colon wall
  - Relevant distance

Vincent K, et al. PLOS One (in review)
Multipurpose Prevention Technologies (MPT)

- **MPT: PrEP & (Other STI* +/- or Contraception)**
  - Complicated design, development, & partnerships
  - Balances limiting attributes of optimized single drug platforms with improved adherence with one device, two purposes

- **Product pipeline (22 products)**
  - Intravaginal ring – 4 pregnancy, 5 STI
  - Vaginal Gels – 3 pregnancy, 4 STI
  - Vaginal films – 2 STI
  - Fast dissolve insert – 3 STI
  - Barrier - 1 pregnancy/STI

- *Most STIs are HIV in combination with HSV-2 +/- or HPV, 2 products also cover chlamydia*
On Demand, Portable: Tenofovir Film

**Plasma**

- $T_{max}$ Film > Gel; C Film > Gel 8+ hrs

**Cervical Tissue Homogenate**

- Film > Gel (except RF, Plasma)

**Ex vivo HIV Tissue Challenge**

- BL v 5h NS; Film v. Gel any time NS

FAME Program: Robinson JAIDS 2018, Bunge JAIDS (in review); Also Dapivirine Bunge JAIDS 2016; Robinson ARHR 2016
### Systemic v. Tissue & Oral v. Topical Dosing

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen Duration</th>
<th>Serum or Plasma TFV ng/mL</th>
<th>VT TFV-DP fmol/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTN-001 TFV 1% VF</strong></td>
<td></td>
<td></td>
<td></td>
<td>1,807 (591, 5,860)</td>
</tr>
<tr>
<td><strong>MTN-014 TFV 1% RGVF</strong></td>
<td></td>
<td></td>
<td></td>
<td>166 (37, 2,377)</td>
</tr>
<tr>
<td>Pod-IVR TDF (OCIS)</td>
<td></td>
<td></td>
<td></td>
<td>303 (277,938)</td>
</tr>
<tr>
<td>Pod-IVR TDF-FTC (OCIS)</td>
<td></td>
<td></td>
<td></td>
<td>289 (110, 603)</td>
</tr>
<tr>
<td>Pod-IVR TDF-FTC-MVC</td>
<td></td>
<td></td>
<td></td>
<td>302 (177,824)</td>
</tr>
<tr>
<td>Reservoir IVR (Einstein)</td>
<td></td>
<td></td>
<td></td>
<td>120 (90, 550)</td>
</tr>
<tr>
<td>TFV Film 40 mg SD (FAME)</td>
<td></td>
<td></td>
<td></td>
<td>160 (27, 485)</td>
</tr>
<tr>
<td>TFV Film 40 mg MD (FAME)</td>
<td></td>
<td></td>
<td></td>
<td>937 (56, 1456)</td>
</tr>
<tr>
<td><strong>MTN-001 TDF oral</strong></td>
<td></td>
<td></td>
<td></td>
<td>BLQ (BLQ, BLQ)</td>
</tr>
<tr>
<td><strong>HPTN-066 TDF oral</strong></td>
<td></td>
<td></td>
<td></td>
<td>BLQ, 41 (2/2)</td>
</tr>
</tbody>
</table>

**Criteria to advance product?**
- Vaginal tissue TFV-DP? (vaginal dosing)
- PBMC TFV-DP? (oral dosing)
- Both? In what combination?

**How Long?** (on demand vs. IVR)

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*proven product effectiveness in primary (oral TDF 65% RRR) or post hoc (oral >90% RRR; vaginal 60-88% RRR)*
Evolving Thoughts on Target Concentration

• TDF/FTC Rx dose (conc’n) same for PrEP
  – refuted by protective doses in MSM v. women
• [Tissue] a/w successful oral PrEP predicts topical dosing target
  – refuted by vaginal gel underperformance despite high TFV [tissue]
• At least a [2-site] problem, [systemic] & [tissue] contribute, but in different proportion depending on dosing route
  – Supported by plasma conc’n-response
  – PK/PD model fit Improved by [tissue] & route of risk adjustment of [systemic] data
  – What is ΔEC90 for oral vs. Topical?
• Any resolution short of oral v. topical RCT?
Rectal Microbicide Formulations
On Demand Rectal Microbicide Feasibility

- **On demand** oral PrEP (Truvada) efficacy high
  - Ipergay 86% risk reduction

- **On demand** vaginal tenofovir efficacy modest
  - CAPRISA 004, FACTS 001 ~60% with good adherence

- **NHP Protection:**
  - Single dose rectal TFV protects rectal SHIV challenge

- **Behaviorally-congruent** formulations –
  - ARV-medicated sex lubricant or douche
  - “piggy-back” onto very common sex practices
  - Less demanding of behavior change
TFV Rectal Microbicide Development

Methods/Vehicle Development

- **JHU**
  - “HIV” surrogate distribution
- **JHU**
  - Tissue pharmacology
- **CDC/NIH**
  - Luminal PK-D imaging
- **NIH**
  - PD Surrogates: Explant, BLT, NHP
- **MDP 2/2b**
  - RF vehicle development
- **MDP 1**
  - Enema vehicle development
- **JHU**
  - Lube dosing feasibility
Does RM Outdistance & Outlast “HIV”? 

“Microbicide”\(^{\text{111}}\text{In-DTPA}\)  “HIV” \(^{99m}\text{Tc-SC}\) in Ejaculate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distance to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D_{\text{min}})</td>
<td>Most distal signal</td>
</tr>
<tr>
<td>(D_{\text{max}})</td>
<td>Maximum “concentration”</td>
</tr>
<tr>
<td>(D_{\text{max}})</td>
<td>Most proximal signal</td>
</tr>
</tbody>
</table>

Rectal TFV gel (0hr), simulated sex/ejaculation (1hr), SPECT/CT (2hr)

Hiruy, et al. ARHR 2015


Hendrix, et al. CPT 2008
TFV Rectal Microbicide Development

**Methods/Vehicle Development**
- JHU: “HIV” surrogate distribution
- JHU: Tissue pharmacology
- CDC/NIH: Luminal PK-D imaging
- NIH: PD Surrogates: Explant, BLT, NHP
- MDP 2/2b: RF vehicle development
- MDP 1: Enema vehicle development
- JHU: Lube dosing feasibility

**Drug Product Development**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Vaginal Formulation (VF)</th>
<th>Reduced Glycerin (RGVF)</th>
<th>Rectal Formulation (RF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>RMP-02/MTN-006</td>
<td>MTN-007</td>
<td>CHARM 01/02</td>
</tr>
<tr>
<td>Phase II</td>
<td>No Phase II • Safety/AEs</td>
<td>MTN-017</td>
<td>Safety/Accept</td>
</tr>
<tr>
<td>Phase III</td>
<td>No Phase III • Applicator <em>(Safety)</em></td>
<td></td>
<td>Future RCT? On Demand Lube</td>
</tr>
</tbody>
</table>

**Dosages**
- Vaginal Formulation (VF): 3,111 mOsm/kg TFV 1%
- Reduced Glycerin (RGVF): 836 mOsm/kg TFV 1%
- Rectal Formulation (RF): 479 mOsm/kg TFV 1%

**Future RCT?**
- On Demand Lube
Is Gel as Lube Feasible?

- Douche
  - Saline-like 125 mL

- Applicator Gel
  - HEC 10 mL

- Manual Lube Application
  - Wet™ 10 mL

- How much product is delivered?
- Where is the gel distributed?
Is Gel as Lube Feasible?

- **Douche**
  - Saline-like 125 mL

- **Applicator Gel**
  - HEC 10 mL
  - Retention: 95%  
  - Distribution: 5.9–7.4 cm

- **Manual Lube Application**
  - Wet™ 10 mL
  - Retention: 10% (3.5 mL gel)  
  - Distribution: 4.4–15.3 cm

- • Retention: 60%
- • Distribution: 60 cm
TFV Rectal Microbicide Development

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<tbody>
<tr>
<td>Phase I</td>
<td>RMP-02/MTN-006</td>
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</tr>
<tr>
<td>Phase II</td>
<td>No Phase II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Safety/AEs</td>
<td></td>
</tr>
</tbody>
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<table>
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<th>836 mOsm/kg</th>
<th>TFV 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>MTN-007</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>MTN-017</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>No Phase III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Applicator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*(Safety)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rectal Formulation (RF)</th>
<th>479 mOsm/kg</th>
<th>TFV 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>CHARM 01/02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TFV 10% RF Lube</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Safety/Accept</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>Future RCT ?</td>
<td></td>
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<tr>
<td></td>
<td>On Demand Lube</td>
<td></td>
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<table>
<thead>
<tr>
<th>Enema Formulation (EF)</th>
<th>Dose escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iso- or hypo-osmolar</td>
</tr>
<tr>
<td>Phase I</td>
<td>DREAM 01-03</td>
</tr>
<tr>
<td>Phase II</td>
<td>Safety/Accept</td>
</tr>
<tr>
<td>Phase III</td>
<td>Future RCT ?</td>
</tr>
<tr>
<td></td>
<td>On Demand Douche</td>
</tr>
</tbody>
</table>
Grindr Survey

Especially with sex product, Essential to build around user experience

- 4,751 Took Grindr Survey
  - 78% RAI last 3 months
  - 80% douche before RAI
  - 27% douche after RAI

Likelihood of using a microbicide douche (currently douche) 98%
Likelihood of using a microbicide douche (currently do not douche) 94%
Insertive partner supportive of RM douching partner 96%

Generally much higher than similar survey research for vaginal products
Interspecies TFV-DP Comparisons

- TFV, TDF, TAF, CMX-157 Comparison
  - Doses selected to achieve clinical target
  - No large differences in mice or NHP

- Advance TFV to Clinical development
  - Flexible formulations

- Hypo-osmolar formulation
  - NHP ~10-fold increase tissue TFV-DP

- Significant variability (1-2 log_{10} range)

- Colorectal tissue [TFV-DP] target (iPrEx reference) exceeded by all doses in NHP

Xiao et al AAC 2017; Ensign et al Eur J Pharm Biopharm 2018
TFV Douche: Macaque SHIV Challenge

Pharmacodynamics: SHIV Rectal Challenge
- Daily oral TDF vs. weekly rectal TFV
- Weekly intrarectal SHIV challenge (10^3 TCID50)
- Weekly plasma viral RNA by qPCR
- “Infected” = 2 vRNA values > 250/mL x 2 wks

Steady-state oral PK & Challenge Ongoing; Oral-Topical [target] conversion remains unclear
Phase I: Douche PK in NHP & Human

Macaque PK Colon Cell TFV-DP

Human PK Colon Cell TFV-DP

TFV-DP concentration in rectal CD4 cells (fmol/10^6 cells)

$p = 0.0005$

Daily Oral
7/wk
4/wk
2/wk
Colon Luminal HIV & Product Distribution

**Define HIV Distribution**

- HIV surrogates (SPECT, color) & anatomy (CT, grayscale)

<table>
<thead>
<tr>
<th></th>
<th>99mTc Cell-free</th>
<th>111In Cell-assoc</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 hr</strong></td>
<td>7 (5, 8)</td>
<td>6 (5, 9)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>4 hr</strong></td>
<td>6 (5, 9)</td>
<td>5 (4, 7)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>8 hr</strong></td>
<td>6 (3, 7)</td>
<td>7 (6, 8)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Sigmodoscopy distance adds 4 cm

**Compare to Product Distribution**

DREAM-01
TFV Douche Development

- Phase I
  - DREAM-01 – SAD (>90% complete)
  - DREAM-03 – MAD (NIH & FDA review)
  - DREAM-02 – Douche + sex sequencing (in development)

- Phase II/III
  - Extended safety convert to efficacy
  - Clinical trial simulation

- NDA & Market Planning
  - Negotiating with corporate partners
Summary

- **Long-Acting**
  - Injectables – RCTs, limits AEs, oral lead-in, long tail
  - Infusion bnMAbs – RCTs, future SC dosing?, less AEs, COST
  - Implantables – Pre-clinical, less frequent dosing, retrievable, bnMAb suitable

- **Vaginal Microbicides**
  - Vaginal gel & IVR underperformed in RCT
  - Novel formulations may enhance adherence, front-door back door issues
  - Uncertain cervicovaginal tissue concentration targets

- **Rectal Microbicides**
  - Behaviorally-congruent strategies - Lube feasible? Douche acceptable & exceeds [target]?
  - Uncertain rectal dosing target tissue concentration uncertain
  - Model building & Clinical Trial Simulation underway
Acknowledgements

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