Rectal Microbicide Development:
- How Did We Get Here?
- What Have we Learned?

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Disclosures

- ViiV/GSK: Clinical research contract managed through JHU
- Gates Foundation: Clinical trial simulation project contract managed through JHU
- NIH/DAIDS: clinical research funding managed through JHU
Objectives

- **Behavioral Understanding**
  - What have we learned about relevant behavior & desired product attributes?

- **Method Development**
  - What new tools were needed to ask essential questions?

- **Product Development**
  - How do drugs and formulations stack up against desired product attributes?
Behavioral Understanding
Behavioral & Preference Questions

- Quantifying sexual behavior
  - Sexual practices
    - Lubricants
    - Rectal douche
  - Inform user desires & method development (contextually appropriate)

- Applicator preferences
  - Most studies used vaginal applicator
  - Project gel – directly compared vaginal applicator & rectal specific applicator

- Volume acceptability
  - Gel volume escalation to 50 mL
Example: Douche Behaviorally-Congruent


Douche & Lube Development Concerns

• Lube use near universal with great product variety
• Water-based hyperosmolar lube most commonly used (iRMA Lube Survey 2008)
• Hyperosmolar gels damage epithelial, not iso-osmolar (Fuchs 2007, Dezzutti 2012)

• Rectal douching increased risk for HIV transmission (Coates 1988, Moss 1988)
• Douching v. common (50-75%) and highly acceptable (many papers)
• Tap water (hypo-osmolar) and Fleet enema (hyper-osmolar) most commonly (Hylton 2007)
• Tap water & hyper-osmolar enemas epithelium damage (Schmelzer 2004, Leyva 2014)

• Product Development: Lube & Douche need careful attention to reduce toxicity & contextual acceptability in addition to usual drug development
Method Development
Method Development

- HIV surrogate distribution as target
- Cellular & tissue pharmacology
- Toxicity assessment
- Surrogates of Efficacy
Locating HIV in the Colorectal Lumen

Quantifying distance of highest concentration to guide study design*

<table>
<thead>
<tr>
<th></th>
<th>$^{111}$In (Cell-assoc)</th>
<th>$^{99m}$Tc (Cell-free)</th>
<th>P value*</th>
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<tbody>
<tr>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
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<tr>
<td>1 hr</td>
<td>6.15 (5.22, 8.51)</td>
<td>7.08 (5.45, 7.57)</td>
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<td>4 hr</td>
<td>4.96 (4.25, 7.27)</td>
<td>6.00 (4.85, 8.68)</td>
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<tr>
<td>8 hr</td>
<td>7.07 (5.74, 7.89)</td>
<td>5.53 (2.75, 6.62)</td>
<td>0.19</td>
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</table>

*Sigmoidoscope distance adds 4 cm

Surrogates dosed in “ejaculated” semen

SPECT (color) & CT (grayscale)

Louissaint JID 2012; Weld IAS 2017
Co-localizing Rectal Microbicide & “HIV”

“Microbicide” $(^{111}\text{In-DTPA})$

“HIV” $(^{99m}\text{Tc-SC})$ in Ejaculate

Concentration-Distance-Time

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

Evolution of Toxicity Assessment

- Colonoscopy (macro structure)
- Histology (micro structure)
- Cytokines (inflammation)
- Permeability (functional)
- ‘Omics
  - Transcriptomics (MTN-007)
  - Proteomics (MTN-007, Project Gel)
  - Metabolomics (DREAM 01)

David Gorski, Science Based Medicine 2011 (https://sciencebasedmedicine.org/woo-omics/)
Pharmacodynamics: Efficacy Surrogates

Which Target Concentration: EC$_{90}$?

- Cell Culture HIV replication
- Humanized Mouse HIV Rectal Challenge
- Macaque SIV/SHIV Rectal Challenge
- Human tissue explant HIV challenge
  - O single oral; □ single rectal; ▼ 7-day rectal
- EC$_{90}$ Clinical (seroconversion) MSM/TGW
  - iPrEx 4/day PBMC (>EC$_{90}$) → HPTN 066 4/day PBMC → Tissue PK

Colon Tissue CD4+ Cells

EC$_{90}$: Concentration with 90% Effect

Product Development
Vehicle: Integrating Safety, Acceptability, PK

- Toxicity
- Distribution
- Acceptability

9 men, single dose cross-over
- Hyper-, iso-, hypo-osmolar enema
- Luminal PK, histology, acceptability favor iso-osmolar

Leyva, et al. ARHR 2013
Exploring Behaviorally-Congruent Formulations

- **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?
Exploring Behaviorally-Congruent Formulations

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

- **Applicator Gel**
  - HEC 10 mL

- **Manual Lube Application**
  - Wet™ 10 mL

- **Retention**
  - 60%
  - 95%
  - 3%

- **Distribution**
  - 60 cm
  - 5.9–7.4 cm
  - 4.4–15.3 cm
CHARM TFV: Gel Vehicle & Sex Impact

- TFV 1% gel Product Comparison (osmolality key variable)
  - VF: 3,111 mOsm/kg
  - RGVF: 836 mOsm/kg
  - RF: 479 mOsm/kg

- Acceptability: RF = RGVF > VF
- Plasma TFV: VF > RGVF > RF; no Sex impact
- Colon TFV-DP: VF > RGVF = RF
- Lumen: VF > RGVF = RF; Sex neutralized
- Coincident Distribution: 86% “HIV” & “Microbicide”
- Explant: RF > RGVF > VF

CHARM-01: McGowan PLOS One 2015; CHARM-02: Hiruy ARHR 2015
# Development Pipeline

- **Drugs:** 7
- **Formulations:** 4
- **Start:** All by 2018*

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Rectal Formulation</th>
<th>Dose Levels</th>
<th>Doses or Conditions (x prod's)</th>
<th>N drug (total)</th>
<th>TOX</th>
<th>PK</th>
<th>PD</th>
<th>ACC</th>
<th>Status</th>
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<td>MTN-035</td>
<td>no API</td>
<td>insert, douche</td>
<td>NA</td>
<td>RAI(8w)</td>
<td>(150)</td>
<td>-</td>
<td>x</td>
<td></td>
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<td>DREAM 01</td>
<td>TFV</td>
<td>douche iso, hypo</td>
<td>3</td>
<td>1x3</td>
<td>18</td>
<td>-</td>
<td>x</td>
<td></td>
<td>x</td>
<td>enrolling</td>
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<tr>
<td>MTN-039</td>
<td>EVG</td>
<td>inserts</td>
<td>1</td>
<td>1</td>
<td>30</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>CHARM 03</td>
<td>MVC</td>
<td>gel hyper (+vag, +oral)</td>
<td>1</td>
<td>8x2(or 3)</td>
<td>19</td>
<td>9</td>
<td>x</td>
<td></td>
<td>x</td>
<td>analysis</td>
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<tr>
<td>IQP DuoGel</td>
<td>IQP 0528</td>
<td>gel iso</td>
<td>1</td>
<td>1</td>
<td>16</td>
<td>8</td>
<td>x</td>
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<td>MTN-037</td>
<td>MIV-150/Zn/Carag</td>
<td>gel iso, 3 volumes</td>
<td>3</td>
<td>1x3</td>
<td>12</td>
<td>6</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>start 2017</td>
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<tr>
<td>MTN-026</td>
<td>DPV</td>
<td>gel (HEC)</td>
<td>1</td>
<td>1,7</td>
<td>18(27)</td>
<td>-</td>
<td>x</td>
<td></td>
<td></td>
<td>development</td>
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<tr>
<td>MTN-033</td>
<td>DPV</td>
<td>gel (appl v manual)</td>
<td>1</td>
<td>1x2</td>
<td>16</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>development</td>
</tr>
<tr>
<td>PREVENT</td>
<td>Griffithsin</td>
<td>gel (iso, carbopol)</td>
<td>1</td>
<td>15 (DOT)</td>
<td>18</td>
<td>9</td>
<td>x</td>
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<td>Phase III</td>
<td>Clinical Trial Simulation: TFV Oral v. TFV Rectal, Compares Different Designs</td>
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*Fingers crossed*
Summary

- Behavioral Understanding
  - What have we learned about relevant behavior & desired product attributes?

- Method Development
  - What new tools were needed to ask essential questions?

- Product Development
  - How do drugs and formulations stack up against desired product attributes?
Thank You!
Are we there yet?
The long and winding rectal road...

IRMA policy and advocacy through the ages
7 August 2017
Marc-André LeBlanc
Today...

• IRMA:
  – Who is she?
  – What has she done?
  – What’s next on her busy agenda?
Who is IRMA?
IRMA, b.2005

4 people, 4 agencies, 2 countries
IRMWG Steering Committee

- Jonathan Berger, ALP, South Africa
- Manju Chatani, AMAG, Ghana
- JD Davids, CHAMP, US
- Jerome Galea, UCLA, Peru
- Pamina Gorbach, UCLA, US
- Bridget Haire, AFAO, Australia
- Anuchit Jittrathanakul, PSI, Thailand
- Rowena Johnston, amfAR, US
- Rick Jones, GNP+, Netherlands
- Jeremy Kwan, PT Foundation, Malaysia
- Marc-André LeBlanc, GCM, Canada
- Ian McGowan, UCLA, US
- Ken Mayer, Brown U., Fenway, US
- Kim Mulji, NAZ Foundation, UK
- Jim Pickett, AFC, US
- John Shaw, advocate, US
- Roy Wadia, BCCDC, Canada
AIDS Foundation of Chicago is the IRMA secretariat

1100+ advocates, scientists, funders, policymakers from 6 continents

AIDS Foundation of Chicago is the IRMA secretariat
Mission: support development of safe, effective, acceptable, and accessible rectal microbicides for all that need them

AIDS Foundation of Chicago is the IRMA secretariat
What do we do?

Advocacy
Advocacy priorities

- Increase and diversify funding
- Increase research activities
  - RM research, expand pipeline
  - Lubricant safety, lubricant access
- Increase knowledge
  - Heterosexual anal sex
  - Anal sex behaviours and practices in general
Advocacy priorities

• Recruit researchers, advocates
• Recognise anal intercourse as important driver in HIV epidemic among gay men, MSM, and heterosexuals
• Address burden of HIV among gay/MSM
• Promote anal health
What do we do?

A stroll down memory lane
Hello!

Having just launched our fresh site - rectalmicrobicides.org - in mid February, we thought it was about time to add a blog to our web presence.
11. **Definition.** — A course of action which induces a verbal or physical contract. It is the substance of the contract, inducing the parties to the contract.

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**Male circumcision**

![Image of male circumcision]
What do we do?

Some of our projects
IRMA-ALC – South America
tinyurl.com/rectalvid in English, Spanish, Thai
Global Call to Action on Lubricant Safety

- 2007 survey
- Key materials and updates
- Research agenda on lubricant safety
- Lube access
- Engage regulators, manufacturers, researchers

Lube Safety Working Group
Lessons learned
An act of unprotected anal intercourse is **10 to 20 times more likely** to result in HIV transmission than an act of unprotected vaginal intercourse.
Anal intercourse is a human behavior.
WELCOME

ALL SIZES
ALL COLORS
ALL AGES
ALL CULTURES
ALL SEXES
ALL BELIEFS
ALL RELIGIONS
ALL TYPES
ALL PEOPLE

SAFE HERE

“Turning the Tide Together” is:
HONEST DISCUSSION
OF
ANAL SEX

IRMA | international
rectal microbicide
advocates
MEN & WOMEN
DEMAND
RECTAL MICROBICIDES
Advocacy goals

Increase and diversify funding

Over the 11-year period of investments in RM research IRMA has tracked, the public sector has provided 97.3% of the funding (mostly from the U.S.), the philanthropic sector has provided 2.5% of funding, and the commercial sector has provided 0.2%.

Source: *From Promise to Product: Advancing Rectal Microbicide Research and Advocacy*
Advocacy goals

Projected funding needs

Source: From Promise to Product: Advancing Rectal Microbicide Research and Advocacy
Present and future challenges
• Is it time to retire IRMA? Is her agenda sufficiently taken up by others, making her obsolete?
• Is IRMA still relevant? What should our role be?
• Should our focus still be on people of all genders who have anal sex?
• Thinking about the next few years, what should IRMA’s top priorities be?
• What strategies should IRMA use to advance its agenda?
• Is there a way out of this conundrum of having the entire RM research field funded by one donor?
Questions? Thoughts?
Thank you

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