Putting the Rectal Microbicide Puzzle Together

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"How lucky I am to have something that makes saying goodbye so hard"
- Winnie the Pooh
Some Questions to Consider

- Do we need rectal microbicides?
- Is tenofovir 1% gel the best candidate to move into later stage development?
- Is a vaginal applicator the best way to deliver a microbicide?
- What is the best dosing regimen?
- What is the best study design?
Phase 3 RM Planning Meetings

- Background
  - MTN-017 will be completed in June 2015
  - General safety profile and adherence patterns very good
  - What is the next step?

- Consultations
  - Clinical trial design meeting
  - Ethics consultation
  - Community consultation
Is Tenofovir Gel the Best Product to Move into Later stage Development?
## Drug Potency

<table>
<thead>
<tr>
<th>Drug entity</th>
<th>Drug substance $ED_{100}$</th>
<th>Formulated drug $ED_{100}$</th>
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<tbody>
<tr>
<td>Tenofovir</td>
<td>$&gt;1000 \mu M$</td>
<td>700 $\mu M$</td>
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<tr>
<td>IQP-0528</td>
<td>10 $\mu M$</td>
<td>10 $\mu M$</td>
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<td>Dapivirine</td>
<td>10 $\mu M$</td>
<td>0.8 $\mu M$</td>
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<td>Maraviroc</td>
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<td>10 $\mu M$</td>
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<td>Griffithsin</td>
<td>10 $\mu M$</td>
<td>0.5 $\mu M$</td>
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Dezzutti CS, et al. Unpublished data
Drug Safety

- What are the long-term consequences of repeated mucosal exposure to tenofovir gel?

<table>
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<tr>
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<th>Gene expression</th>
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<tr>
<td></td>
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<tr>
<td>N9</td>
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<tr>
<td>Tenofovir</td>
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<td>HEC</td>
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<td>No Rx</td>
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Adverse Event Profile

- **MTN-007**
  - 1 week exposure
  - GI adverse events
  - Placebo gel (N =16)
    - G1: 13 events
  - Tenofovir gel (N =16)
    - G1: 15 events
  - Flatulence
    - Placebo: 12%
    - Tenofovir: 36%

- **UC781**
  - 1 week exposure
  - GI adverse events
  - Placebo gel (N = 12)
    - G1: 0 events
  - UC781 gel (N =24)
    - G1: 1 event
  - Flatulence
    - Placebo: 0%
    - UC791: 0%
Is a Vaginal Applicator the Best Way to Deliver a Microbicide?
The HTI Vaginal Applicator
The CONRAD Applicator

Glide Push: Overview

Used Glide Push Stored

Glide Push Loaded

Glide Push Dispensed
What is the Best Dosing Regimen?
Which Dosing Regimen Would You Use in a Phase 3 Study?

1. Daily rectal gel
2. Rectal gel before sex
3. Rectal gel before and after sex
4. Other regimen
What is the Best Phase 2A/2B/3 Study Design?
Clinical Trial Design Meeting

- 18th / 19th February, 2015
- Approximately 25 attendees
- Clinical trial researchers, epidemiologists, community advocates, statisticians, FDA, ethicists, and NIH staff
- Delegates from the US, Thailand, South Africa, and Peru
Possible Trial Design Options

- Placebo controlled trial
  - ± oral PrEP
- Non-inferiority trial
- Superiority trial
- Deferred access
  - e.g. PROUD study
- Counterfactual design
Placebo-Controlled Designs

- **Advantages:**
  - Provides answer to the critical questions
  - Easily interpretable
  - "Gold-standard"

- **Disadvantages:**
  - In a trial with no enhanced prevention package for both trial arms, placebo group will experience high (similar to baseline) HIV risk
Placebo-Controlled Designs

- How does provision of oral PrEP impact trial design?
  - In an event driven design, no impact on number of events.
  - Will decrease background incidence rate, requiring more participants and/or longer follow-up time to observe the required number of events.
Estimating Baseline Incidence

Propose: use information from iPrEx and iPrEx OLE

- Placebo arm (iPrEx): 3.93
- Between iPrEx end and start of iPrEx OLE: 3.81
- PrEP initiators (iPrEx OLE): 1.8 (1.3, 2.6)
- PrEP decliners (iPrEx OLE): 2.6 (1.5, 4.5)

Conservative Estimate: 2 infections/100 person-years
Study Size & Duration

Assumes 3500 participants enrolled over one year.
Placebo-Controlled Design Summary

- Feasible both with and without background oral PrEP
- Likely will have to be larger than previous prevention trials but still feasible
- Possible extensions:
  - Enrichment designs
  - Stratified designs (by oral PrEP use)
Phase 3 Ethics Meeting

- 13th March, 2015
- Approximately 10 attendees
  - Ethicists from the US, Thailand, Zimbabwe, and Peru
  - MTN staff
  - NIH staff
- Ethical review of potential Phase 2A/2B/3 study designs
Guidance point 13

- Study participants should be provided with access to “all state of the art risk reduction methods”
- “New methods should be added… as they are scientifically validated or approved by the relevant authorities”
Oral PrEP Trials in MSM

- iPrEx OLE: Effect Size 44%
- IPERGAY: Effect Size 86%
- KEEP CALM AND TAKE PrEP: Effect Size 86%
Oral PreP Availability

AVAC, October 2014
Primary Ethics Recommendations

- The majority felt that moving forward with tenofovir gel was appropriate but
- It was premature to undertake a Phase 3 study
- A phase 2A expanded safety design appropriate (N = 600)
- Access to oral PrEP should be provided during future studies
- Post trial access of oral PrEP less clear
Community Consultation

- Approximately 35 delegates
  - Community advocates / activists from the US, Peru, Thailand, and South Africa
  - MTN staff
  - NIH staff

- Primary goal to update the community on
  - Rectal microbicide development
  - Feedback from clinical design meeting and ethics consultation
  - Potential designs for future studies
Community Recommendations

- Prioritize development of lubricant rather than applicator based intervention
- Provide oral PrEP in the context of future studies
- Concerns about people using studies to access PrEP
- Some people will not want to use oral PrEP
- Strong support for Adonis study
Potential Scenarios

- Complete MTN-017 and move to Phase 2A
- Complete MTN-017 and move to Phase 2B
- Complete additional studies and then progress to Phase 3
- Initiate development pathway for dapivirine gel
- Consider other formulations / API
Complete MTN-017 / Phase 2A/2B/3

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Possible Phase 2A Trial Design

Screening

Interested in oral PrEP
  - Tenofovir gel
  - Placebo gel

Not interested in oral PrEP
  - Tenofovir gel
  - Placebo gel

PK Monitoring
Possible Adonis Study Design

- HIV negative MSM
  - Screening
  - Baseline
  - Stage 1: Applicator delivery of tenofovir gel
  - Stage 2: Digital / penile delivery of tenofovir gel 2 x 4 mL
  - Stage 3: TFV or TAF FDT

- Phase 1 (N = 24 couples)
- Objectives
  - Safety & acceptability
  - PK including “mapping” of product distribution
  - PD
Acknowledgements

- Our clinical trial participants
- Rectal Phase 3 Meetings
  - Clinic trial design participants
  - Ethics consultation participants
  - Community consultation participants
  - Clare Collins and Liza Dawson
  - Elizabeth Brown
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Thank You