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
RIP
Matt Arch

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

Drug entity	Drug substance ED_{100}	Formulated drug ED_{100}
Tenofovir	>1000 µM	700 µM
IQP-0528	10 µM	10 µM
Dapivirine	10 µM	0.8 µM
Maraviroc	100 µM	10 µM
Griffithsin	10 µM	0.5 µM

Dezzutti CS, et al. Unpublished data

Drug Safety

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

	Gene expression	
	Up	Down
N9	60	56
Tenofovir	138	490
HEC	12	4
No Rx	17	6

Adverse Event Profile

- MTN-007
- 1 weekxposure
- 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?

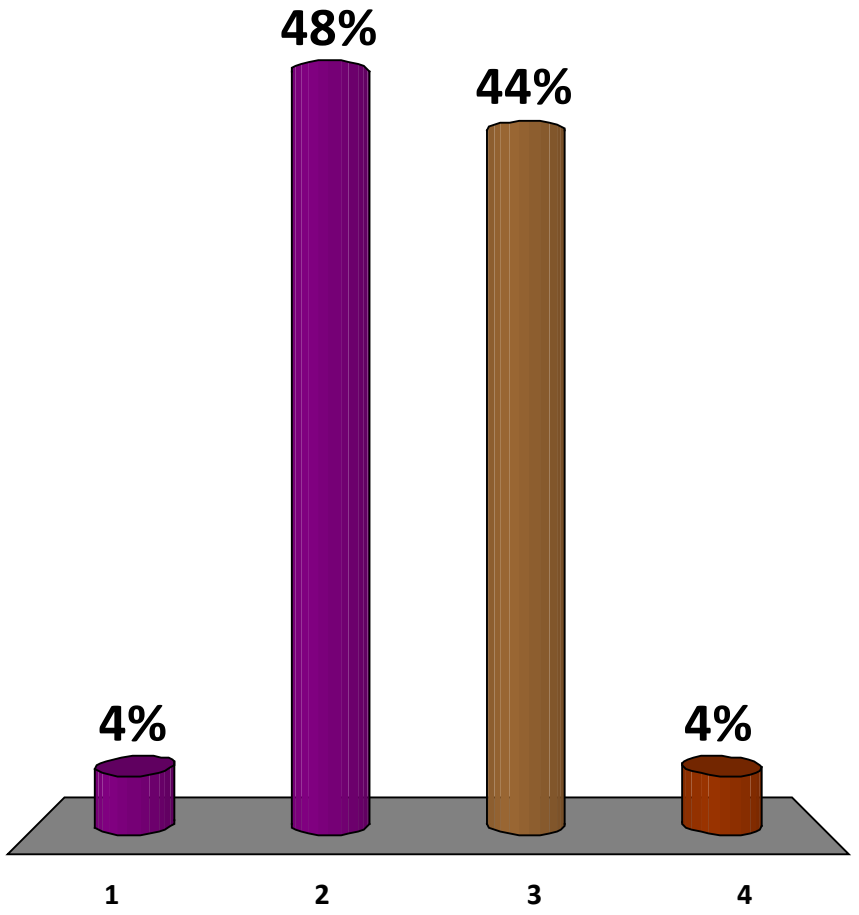
The HTI Vaginal Applicator

The CONRAD Applicator

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 get 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.

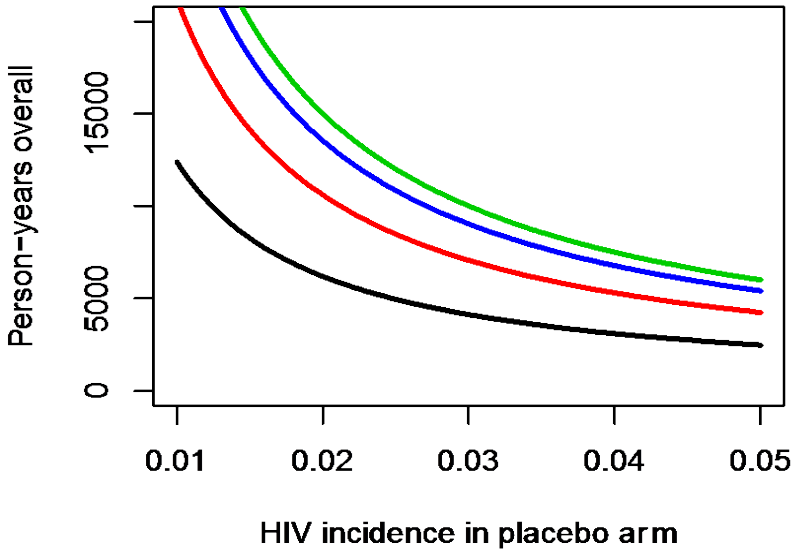
Estimating Baseline Incidence

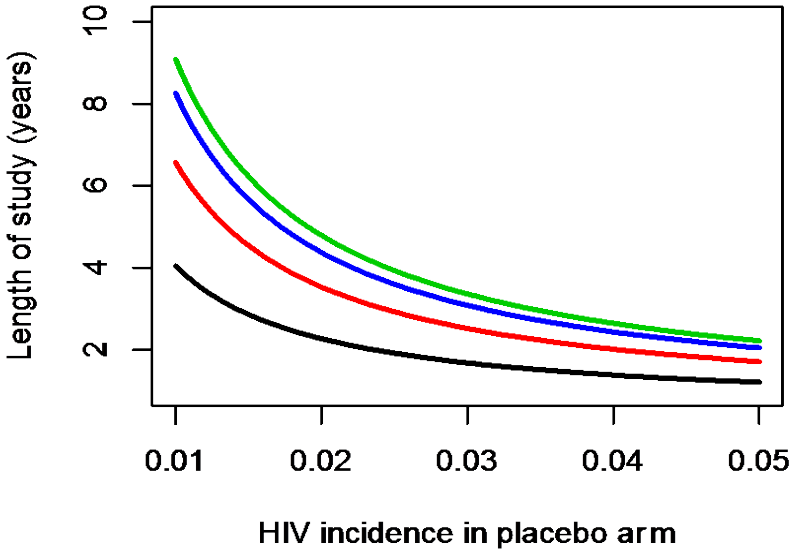
Propose: use information from iPrEx and iPrEx OLE

- 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





Rule out	Detect
0%	50%
15%	50%
15%	45%
20%	55%

Assumes 3500 participants enrolled over one year.

Placebo-Controlled Design Summary

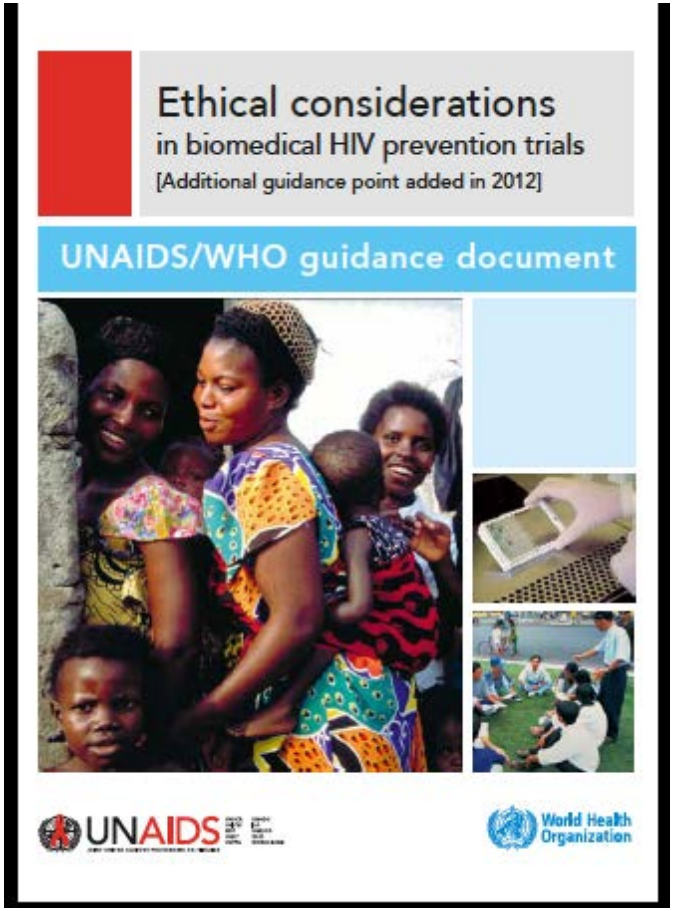
- Feasible both with and without background oral PrEP
- Likely will have to be larger than previous prevention trials but still feasible
- Possible extensions:
  - Enrichment designs
  - Stratified designs (by oral PrEP use)

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

UNAIDS Guidance

- 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

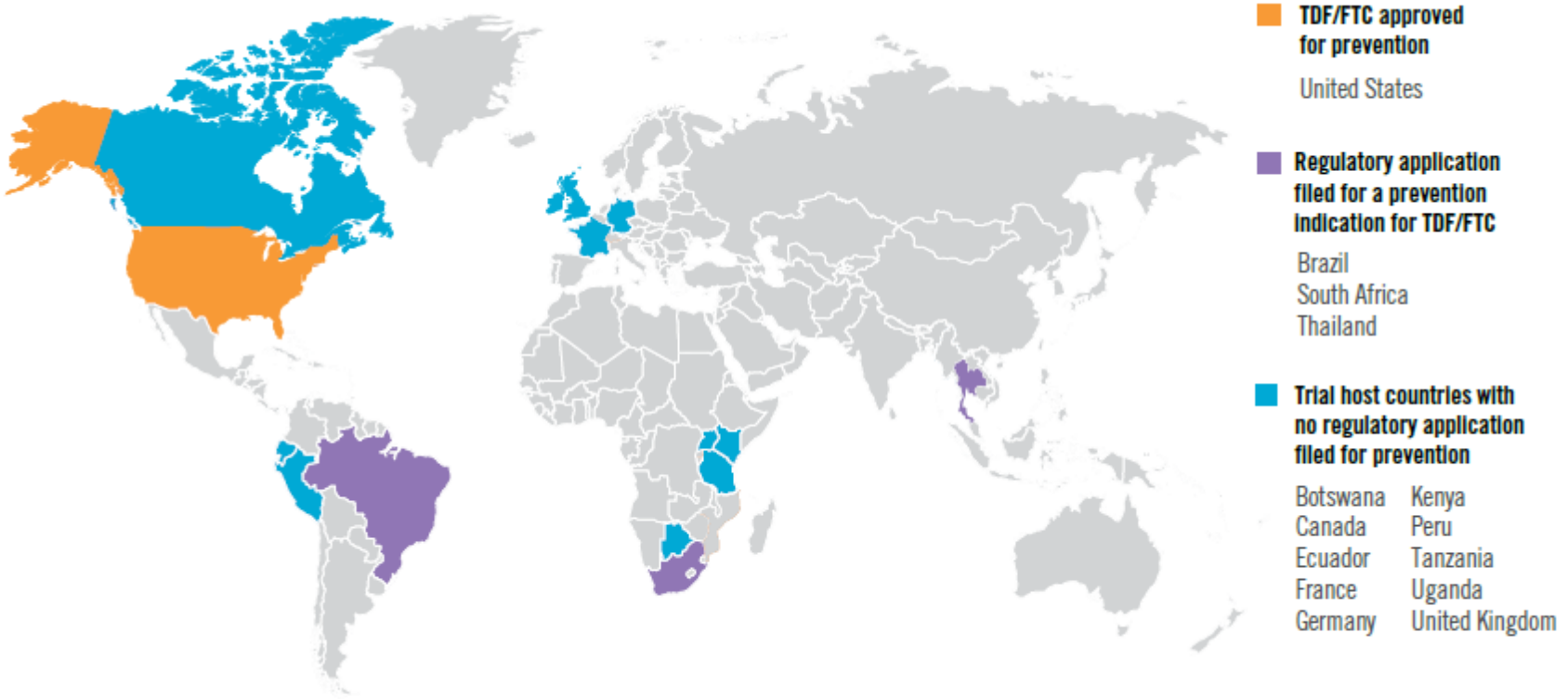
Effect Size

iPrEx OLE → 44%

IPERGAY un essai ANRS Intervention Préventive de l'Exposition aux Risques avec et pour les GAYS → 86%

KEEP CALM AND TAKE PrEP → 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

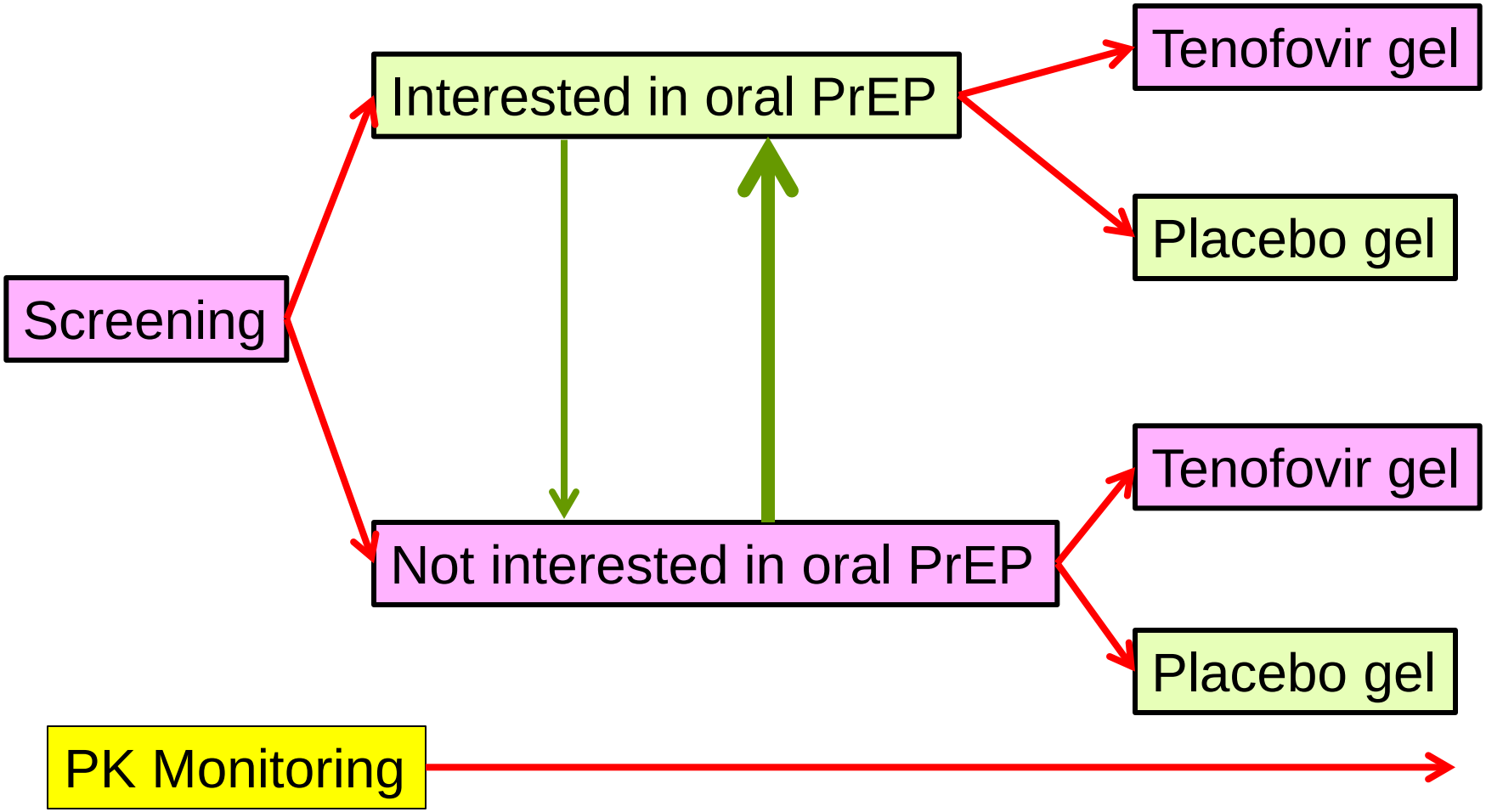
Potential Scenarios

- 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

	2015	2016	2017	2018	2019	2020	2021	2022
MTN-017								
Phase 2A/2B/3								
Review								
OLE								
Available								

Possible Phase 2A Trial Design



Possible Adonis Study Design

HIV negative MSM

Product taken with and without sex

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

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  - Ethics consultation participants
  - Community consultation participants
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Thank You