Mucosal Assays in Rectal Microbicide Trials

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Overview

- A brief history of rectal microbicide research
- Integration of mucosal assays into rectal microbicide research
- Lessons learned about the performance and utility of mucosal assays in rectal microbicide trials
A Brief History of Rectal Microbicide Research
Rectal Microbicide Timeline

1999
HIVNET-008 (Nonoxynol-9)

2003
HPTN-056

2006
RMP-01 (UC781)

2009
RMP-02
MTN-006 (Tenofovir)

2010
MTN-007 (Tenofovir)

2011
Project Gel (Tenofovir)

2012
CHARM-01
CHARM-02 (Tenofovir)

2012
MTN-017 (Tenofovir)

2015
CHARM-03 (Maraviroc)

2015
MTN-026 (Dapivirine)

2015
DREAM-01 (Tenofovir)
HIVNET-008

- Phase 1 evaluation of Advantage 24
  - 52.5 mg of N-9 in 1.5 ml of gel
- Conducted in Seattle during 1996 / 1997
- 35 seroconcordant sexually active couples
  - 25 HIV negative
  - 10 HIV positive
- Cohort dose escalation design
- Maximum exposure QD for five weeks + BID for one week
- Anal sex three times weekly

Tabet S et al. Sex Trans Dis 1999
RMP-01 (UC781)

Screening | Enrollment | Baseline Endoscopy | Randomization | Placebo

Single dose | 2nd Endoscopy | 7 single Doses | 3rd Endoscopy

Anton PA et al. PLoS ONE 2011
Baseline Evaluation

Open label Oral tenofovir (N = 18)

Single rectal tenofovir (N = 18) 2:1

7 Day Rectal tenofovir (N = 18) 2:1

Safety, PK / PD, acceptability

Anton PA et al. AIDS & Human Retroviruses 2012
MTN-007

- N=60
- 2% N-9 (N=15)
- 1% Tenofovir (N=15)
- HEC (N=15)
- No Treatment (N=15)
- Baseline Evaluation
- Single dose
- 7 day daily doses
- 7-14 day interval
- Endoscopy Safety/behavioral assessment

McGowan I et al. PLoS ONE 2013
DAIDS Integrated Preclinical Clinical Program for HIV Topical Microbicides

- Microbicide Development Program
- CHARM Program
- Dual compartment Program
- DREAM Program
- PREVENT Program
MDP Program

- First IPCP focusing on rectal microbicide development
- Provided proof of concept in the SIV NHP model and development of explant platform
- Phase 1 clinical trials of the vaginal formulation of tenofovir gel
  - UC781 (RMP-01)
  - Tenofovir (RMP-02/MTN-006)
- Behavioral correlates of RAI
CHARM Program

- Combination HIV Antiretroviral Rectal Microbicide Program
- NIAID/DAIDS Integrated Preclinical Clinical Program
- Consortium
  - University of Pittsburgh
  - UCLA
  - Johns Hopkins
  - UNC
  - CONRAD / Gilead

McGowan I: IPCP U19 AI082637 / September 2009
Pre-Phase dose comparison of current formulations of tenofovir 1% gel
- Vaginal formulation
- Reduced glycerin formulation
- Rectal specific formulation

Endpoints
- General and mucosal safety
- PK/PD

Current status
- Completed

McGowan I et al. PLoS ONE 2015
CHARM-02

- Pre-Phase 1 single dose comparison of current formulations of tenofovir 1% gel with and without simulated RAI

- Endpoints
  - Pharmacokinetics
  - Drug distribution using SPECT/CT imaging

- Current status
  - Completed

Hiruy H et al. AIDS Res Hum Retroviruses 2015
CHARM-03

- Pre-Phase 1 single dose comparison of oral and topical maraviroc
  - Rectal
  - Vaginal
- Endpoints
  - General and mucosal safety
  - PK/PD
- Current status
  - Enrolling
Dual Compartment Program

- Development and Evaluation of Dual Compartment Combination Microbicides
- Macaque, and human studies proposed
- Dual compartment and suppository formulations of IQP-0528 and tenofovir

PI: Robert Buckheit
Imquest Biosciences
Frederick, MD
Project start: June 2012
Project end: May 2017

Dezzutti CS et al. Antiviral Research 2012
DREAM Program

- Development of Rectal Enema As Microbicide
- Murine, macaque, and three human studies proposed
- Candidates include
  - Tenofovir
  - TFV alafenamide fumarate
  - CMX157

PI: Craig Hendrix
Johns Hopkins University
Baltimore, MD
Project start: July 2014
Project end: June 2019
PREVENT Program

- Griffithsin-based Rectal Microbicides for PREvention of Viral Entry
- To develop an antiviral lectin Griffithsin rectal gel
- Macaque, and one human study proposed

PI: Kenneth Palmer
University of Louisville
Louisville, KY
Project start: July 2014
Project end: June 2019
Project Gel

GUYS EXPERIENCING LUBE

project gel

IS NOW ENROLLING

Call 412.641.3380
or visit www.microbicides.us
for more information.

Microbicide Safety and Acceptability in Young Men
Project Gel

- NICHD R01
  - Pittsburgh, Boston, Puerto Rico
- Phase 1 safety and acceptability of tenofovir 1% gel
  - Ethnically diverse MSM (18-30)
  - Consensual RAI in last month
  - Unprotected RAI in last year

Carballo-Diéguez A et al. AIDS Behav 2014
# Integration of Mucosal Assays

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Lessons Learned
Epithelial Sloughing

Epithelial sloughing score

Baseline Single dose 7 doses

No treatment, HEC gel, Nonoxynol-9 gel, Tenofovir gel

Epithelial sloughing score

Baseline Single dose 7 doses

No treatment, HEC gel, Nonoxynol-9 gel, Tenofovir gel
Fecal Calprotectin

Baseline | Single dose | 7 doses

- No treatment
- HEC gel
- Nonoxynol-9 gel
- Tenofovir gel
Microarray Data

No Treatment

HEC placebo gel

Nonoxynol-9 gel

Tenofovir gel

Hladik F et al. Elife 2015
Summary

- Rectal microbicides have moved from preclinical to Phase 2 clinical evaluation
- The current design of rectal microbicide Phase 1/2 trials commonly includes:
  - Mucosal safety assays
  - Compartamental PK
  - Intestinal explant PD
- New assays under evaluation include transcriptomic and proteomic platforms
Acknowledgements

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