

# MTN-007: Integrating systems biology into microbicide trials

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# Background

- **Rectal microbicides are being developed to prevent HIV transmissions associated with anal intercourse**
- **Tenofovir 1% gel has been evaluated for safety in two Phase 1 studies:**
  - **RMP-02/MTN-006**
  - **MTN-007**
- **Tenofovir was well tolerated and safe by established general and mucosal safety parameters**

# Mucosal safety biomarkers

- **Current approaches depend on evaluation of predefined parameters:**
  - **Histology**
  - **Flow cytometry**
  - **Luminex**
  - **RT-PCR**
- **Evaluation of a broader array of parameters may identify unexpected but potentially important mucosal responses to the study product**

# Systems biology

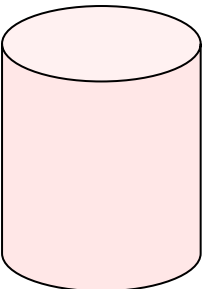
**“Systems biology is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a more holistic approach (instead of the more traditional reductionism) to biological and biomedical research”**

**Wikipedia**

# Methods

HumanHT12 v4 Expression  
BeadChips (Illumina)

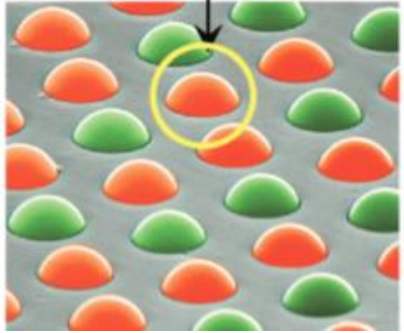
Complete rectal  
biopsy



→ RNA later → RNA →



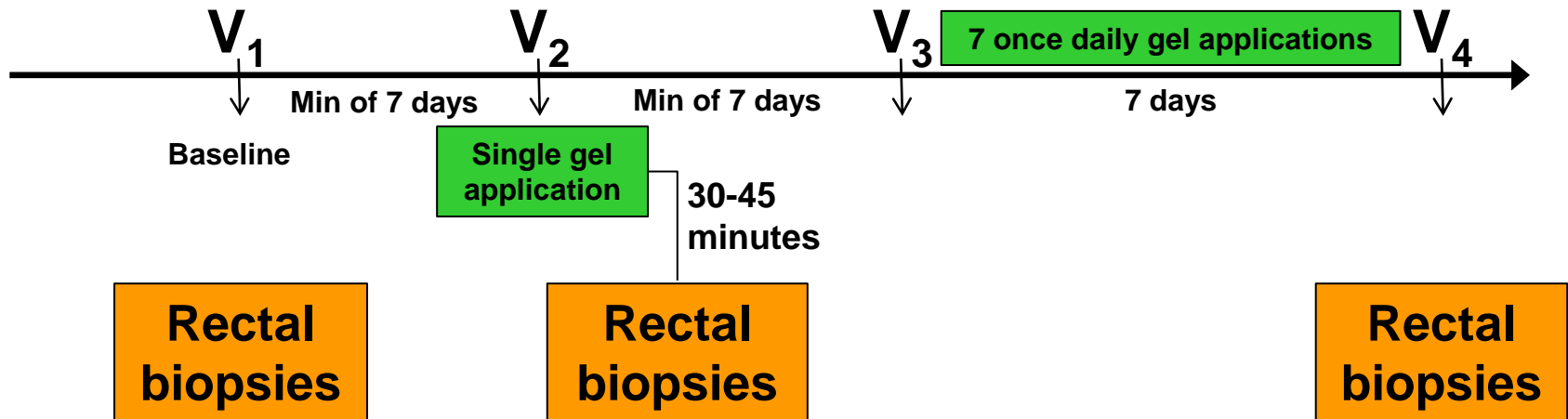
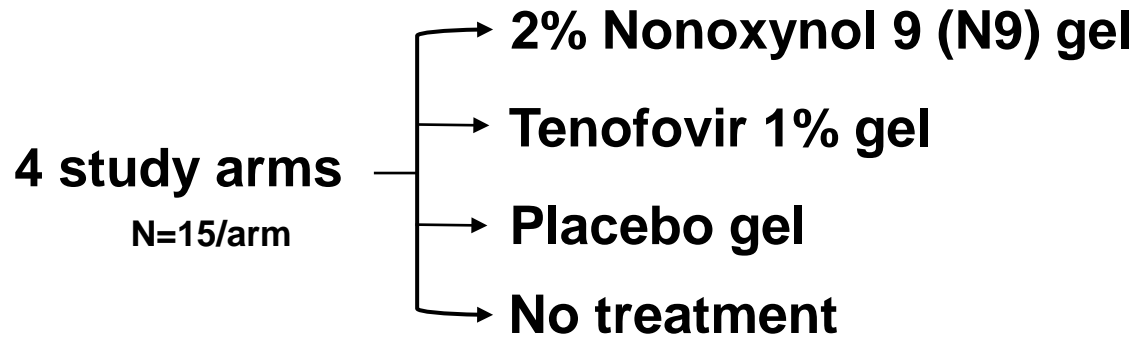
~40,000 genes



Data analysis



# MTN-007 study design



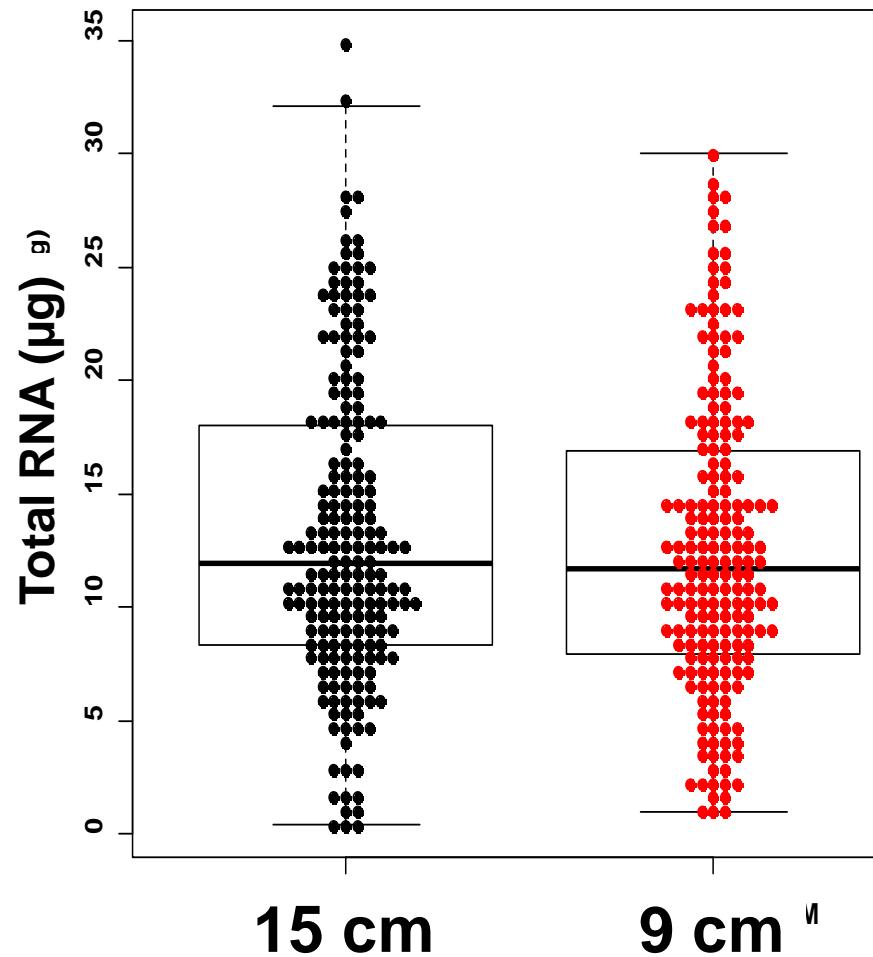
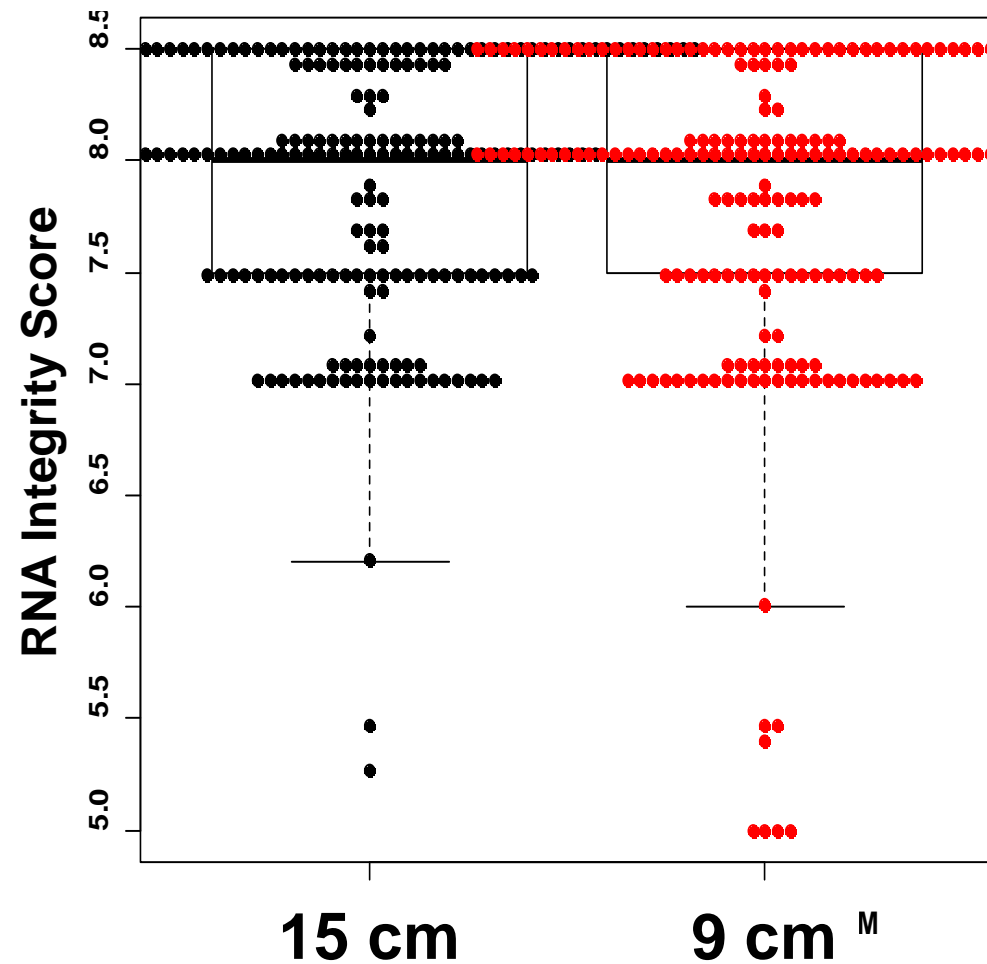
Microarrays:

8 subjects

RT- ddPCR assays:

7 additional subjects

# MTN-007 rectal biopsies yielded excellent RNA quality and quantity

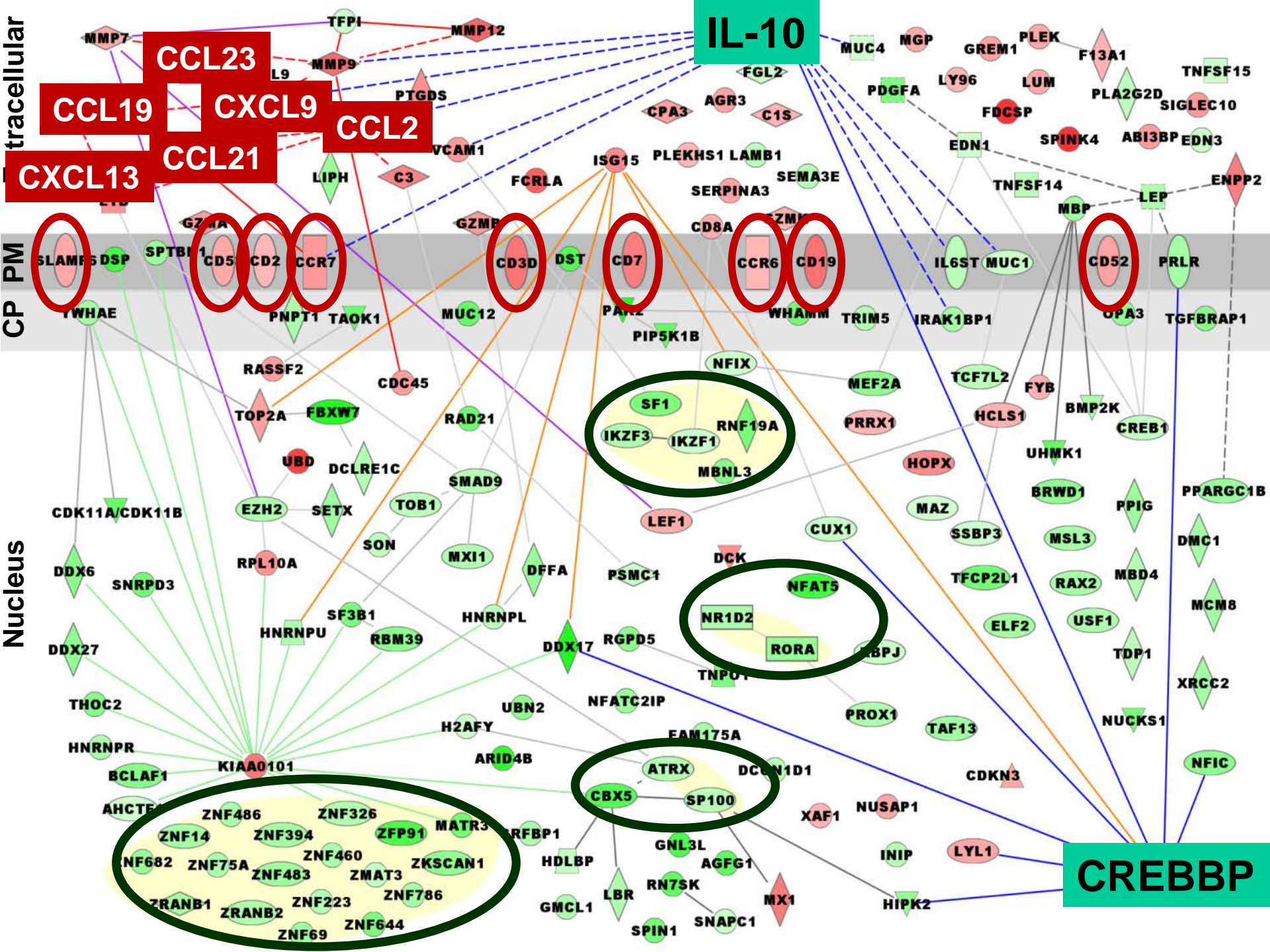


n=381

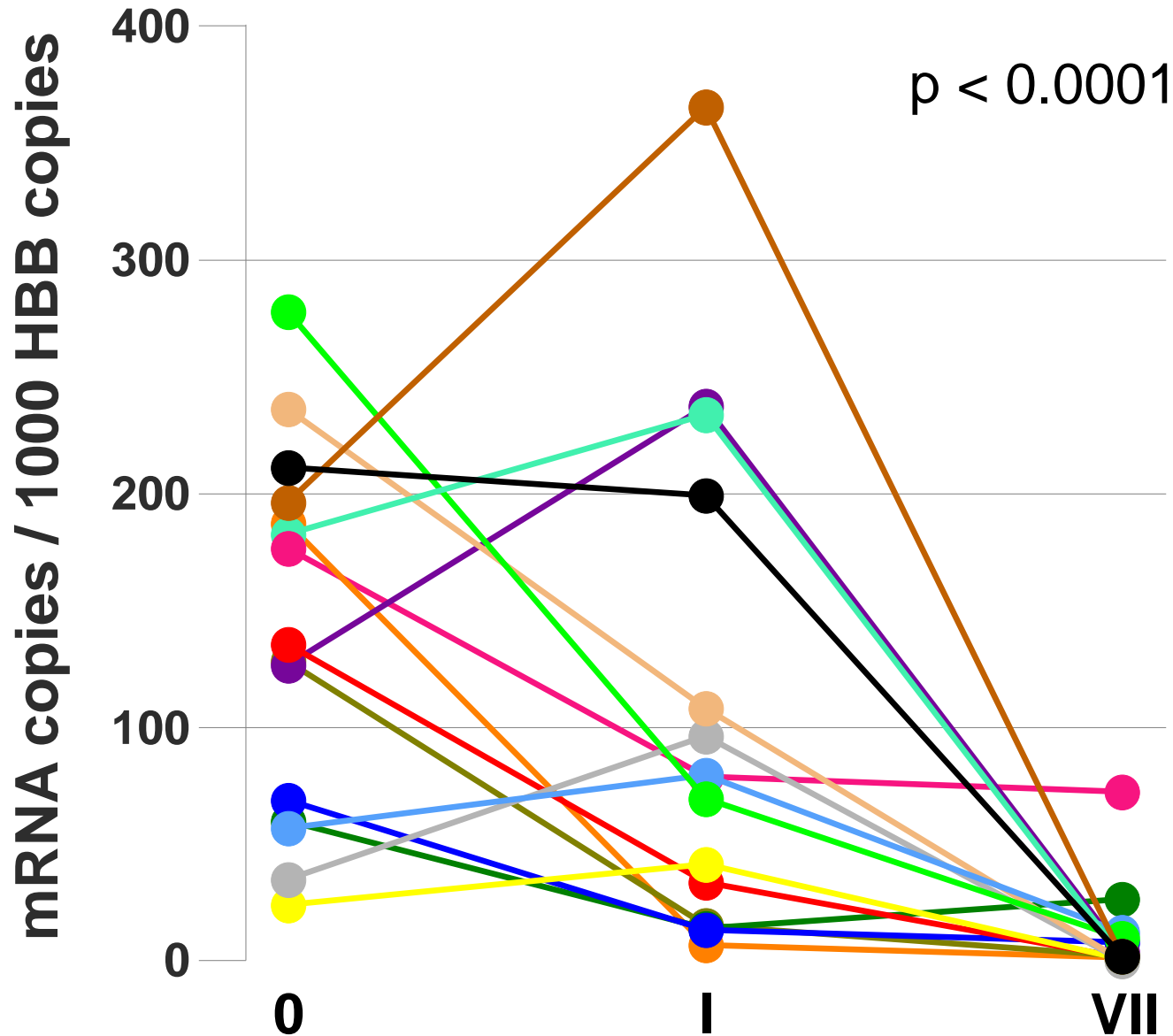
# Number of genes changing expression after 7 days of treatment

	<b>Up</b>	<b>Down</b>
<b>Nonoxynol-9</b>	60	56
<b>Tenofovir</b>	137	505
<b>HEC</b>	12	4
<b>No treatment</b>	17	6



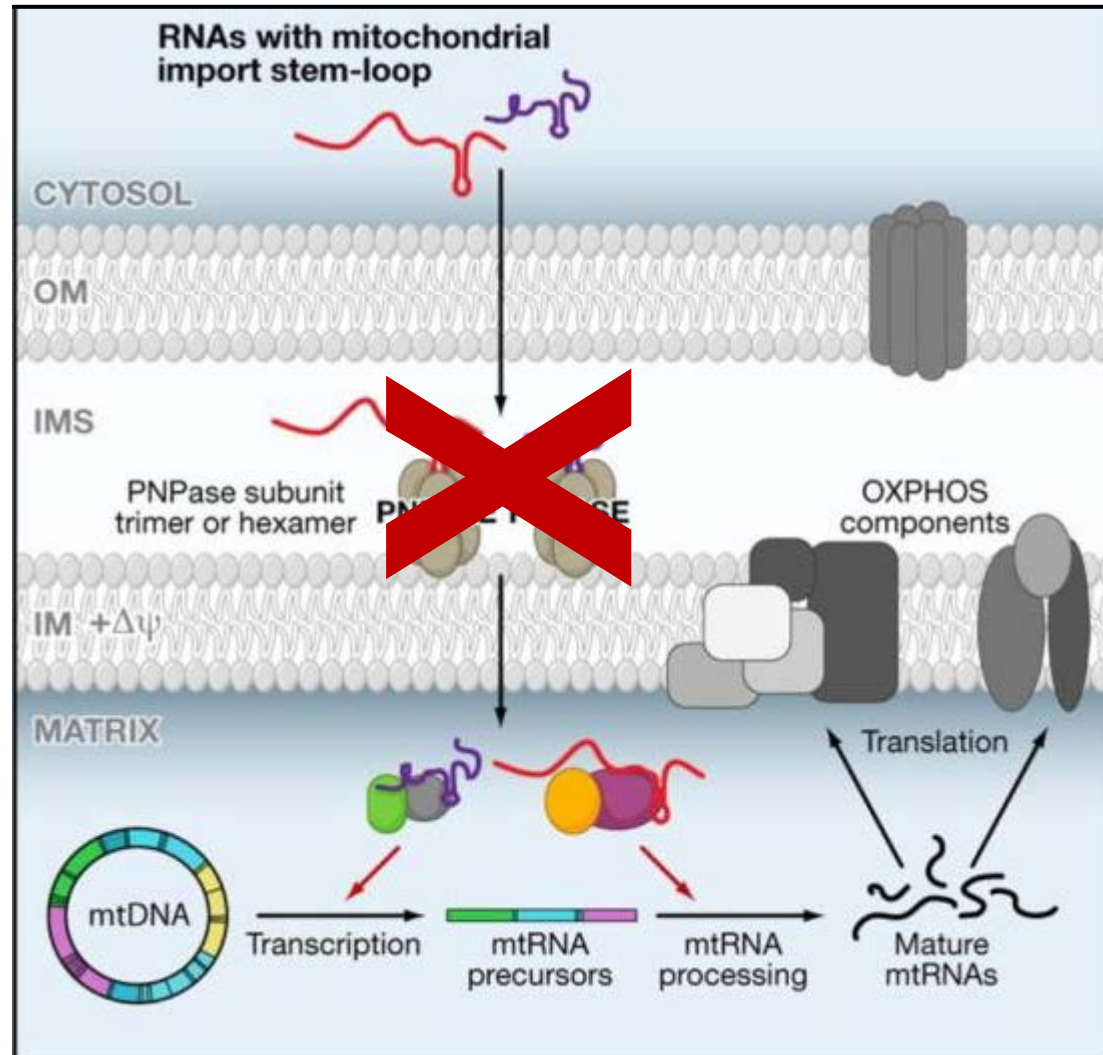


# Suppression of PNPT1 by tenofovir



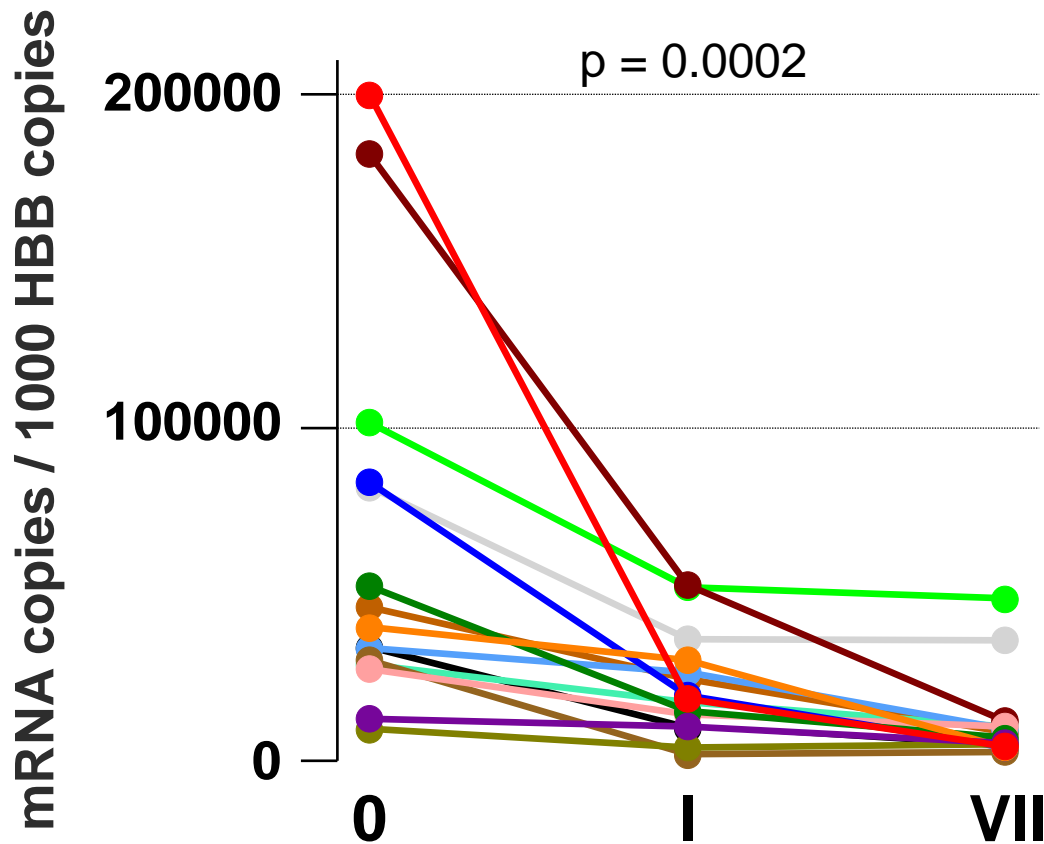
# Polynucleotide phosphorylase (PNPT1) imports RNA into mitochondria

Tenofovir

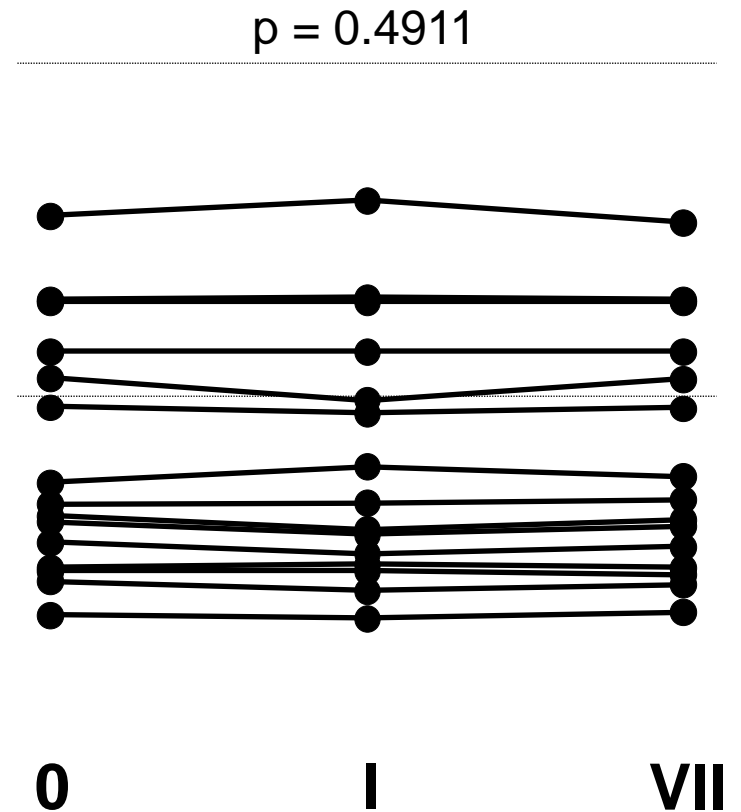


# Suppression of mtATP6 by tenofovir

## Tenofovir



## Nonoxynol 9



# Summary

- **The MTN-007 study demonstrated that rectal use of a reduced glycerin formulation of tenofovir 1% gel was associated with excellent general and mucosal safety**
- **However, use of microarray technology and confirmatory PCR demonstrated significant changes in a number of genes associated with mitochondrial and immune function**
- **These microarray data generate several hypotheses that will be investigated in future studies:**
  - Project Gel
  - CHARM Program
  - MTN-017
  - MTN-014



# Study limitations

- **The clinical significance of these data is not known especially as the safety profile in MTN-007 was excellent and conventional mucosal safety testing was normal**
- **Microarray data from MTN-007 will need to be validated in a second population**
- **Microarray technology provides comprehensive data on gene expression but additional studies looking at the biological consequences of these changes are required:**
  - Proteomics
  - In vitro studies

# Acknowledgments

- **Funding**
  - National Institute of Allergy and Infectious Diseases (grant UM1 AI068633)
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  - National Institute of Mental Health
- **Study participants**
- **Clinic staff**
- **Co-authors** (please see our poster)