Rectal Compartment Pharmacodynamics

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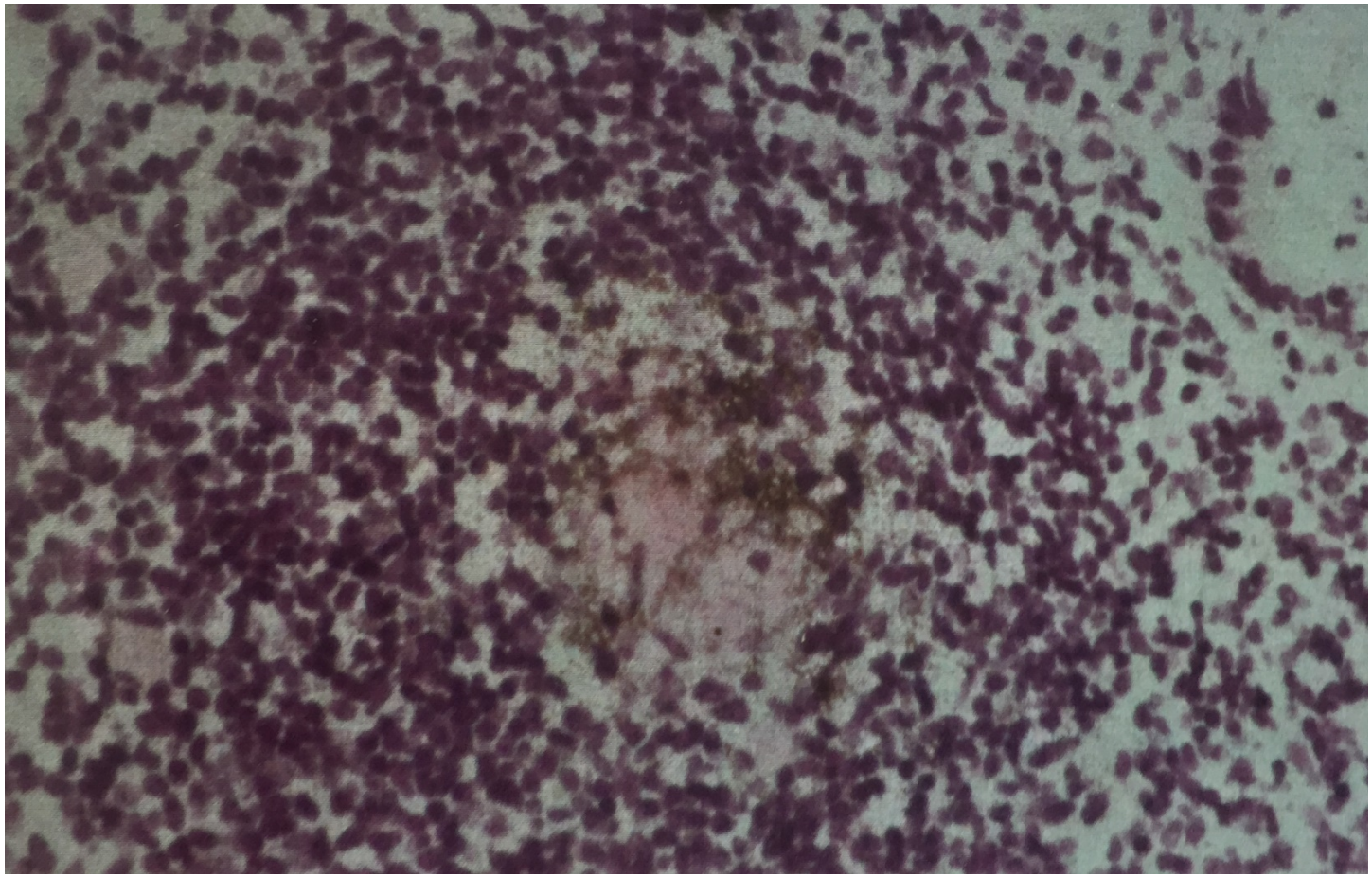
HIV and the Gut



McGowan I and Kotler DP unpublished data 1995

Introduction

- Rectal pharmacodynamics (PD) assays
- Rectal PD data from completed studies
  - HIV-1 p24
  - Molecular assays
- Lessons learned and questions for the future

Rectal Pharmacodynamic Assays

- Explant infection
  - *In vitro, ex vivo / in vitro* infection
  - Surgical tissue or endoscopic biopsies
  - Polarized or non-polarized assays
  - Choice of virus
  - Supernatant HIV-1p24
  - Supernatant RNA, explant RNA/DNA
- Rectal fluid PD

Explant Standardization

- Multisite comparison of anti-human immunodeficiency virus microbicide activity in explant assays using a novel endpoint analysis
- Key recommendations
  - Use of standardized endpoints
  - Drugs and/or virus reagents are centrally sourced
  - The same explant tissue and method used

Richardson-Harman N et al. J Clinical Microbiol 2009

Studies with Rectal PD

- RMP-01
  - UC781 gel (Phase 1)
- RMP-02 / MTN-006
  - TFV gel & oral (Phase 1)
- CHARM-01
  - TFV gel (Phase 1)
- MWRI-01
  - Rilpivirine LA
- Ipergay
  - Oral TDF/FTC
- MTN-017
  - TFV gel/oral (Phase 2)
- CHARM-03
  - Maraviroc gel & oral (Phase 1)
- HPTN-069
  - Oral TFV, MVC, FTC (Phase 2)

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RMP-01

- Population
  - HIV-negative (N=36)
- Center(s)
  - Single
- Sampling
  - Colon
  - 10 cm and 30 cm
  - BL, post single dose, and post seven doses
- Products (1:1:1)
  - UC781 gel (0.1%)
  - UC781 gel (0.25%)
  - HEC placebo
- Explant infection
  - 10 cm and 30 cm
  - HIV-1_{BaL}
  - 10^4 and 10^2 $TCID_{50}$
  - Cumulative D14 p24
  - No PK/PD data

Anton PA et al. PLoS One 2011

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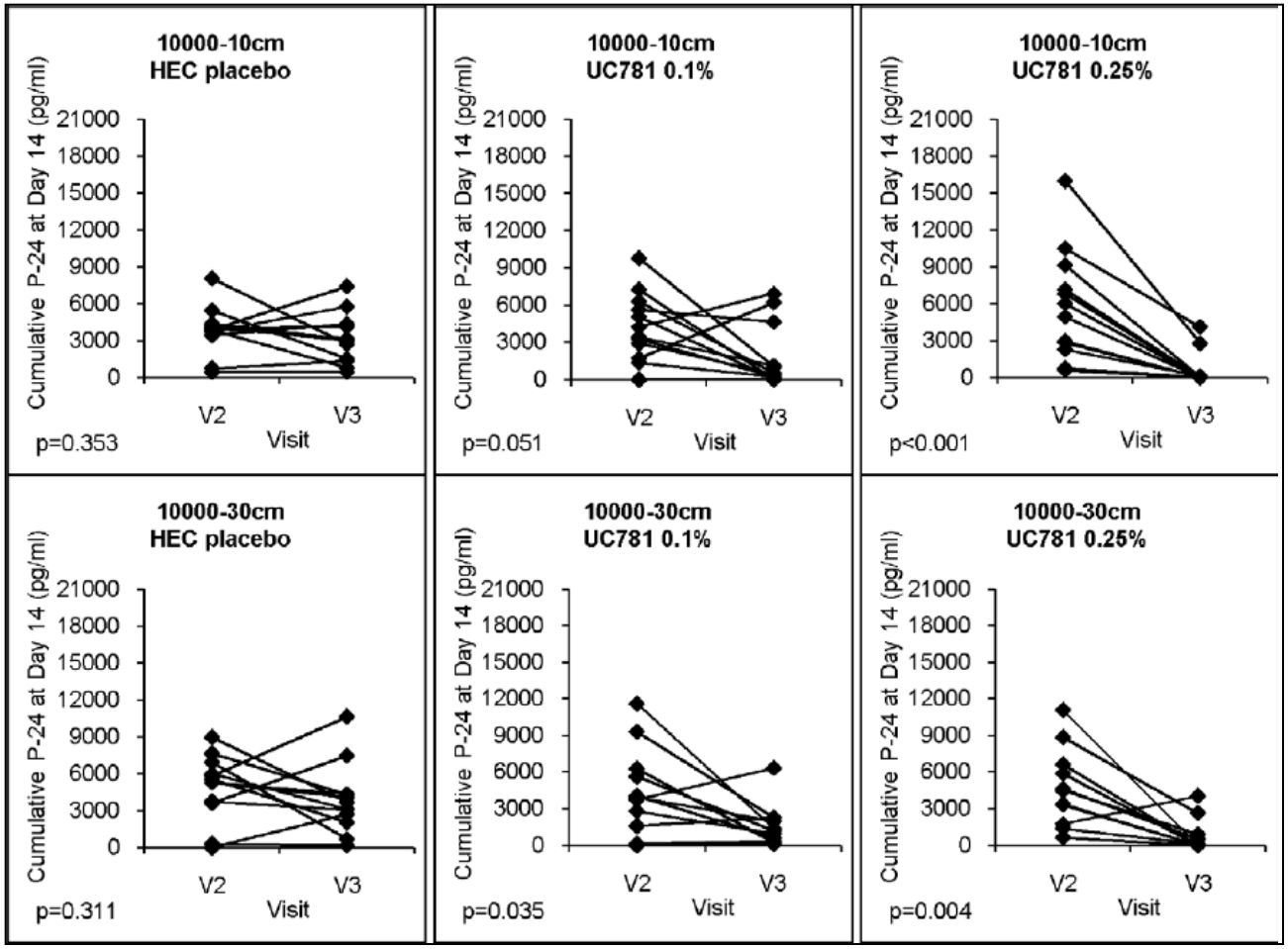
RMP-01 Results

- Infection rates at Baseline
  - HIV-1_{BaL} (10^4 $TCID_{50}$): 35/36 (97%)
  - HIV-1_{BaL} (10^2 $TCID_{50}$): 22/36 (61%)
- No difference in infection rates between 10 cm and 30 cm explants
- Significant suppression with single dose of UC781 0.25% gel
- No suppression seen with 7 daily (self administered) doses

RMP-01



Anton PA et al. PLoS One 2011

RMP-02 / MTN-006

- Population
  - HIV-negative (N=18)
- Center(s)
  - 2 sites
  - Samples shipped to UCLA for analysis
- Sampling
  - Colon (15 cm)
  - BL, post single dose, and post seven doses; 30 min + Days 1-3, 4-6, 7-9, 10-12
- Products (2:1)
  - TFV gel (1%)
  - HEC placebo
- Explant infection
  - 10 cm and 30 cm
  - HIV-1_{BaL}
  - 10^4 $TCID_{50}$
  - Cumulative D14 p24
  - PK/PD data

Anton PA et al. AIDS Res Hum Retroviruses 2012

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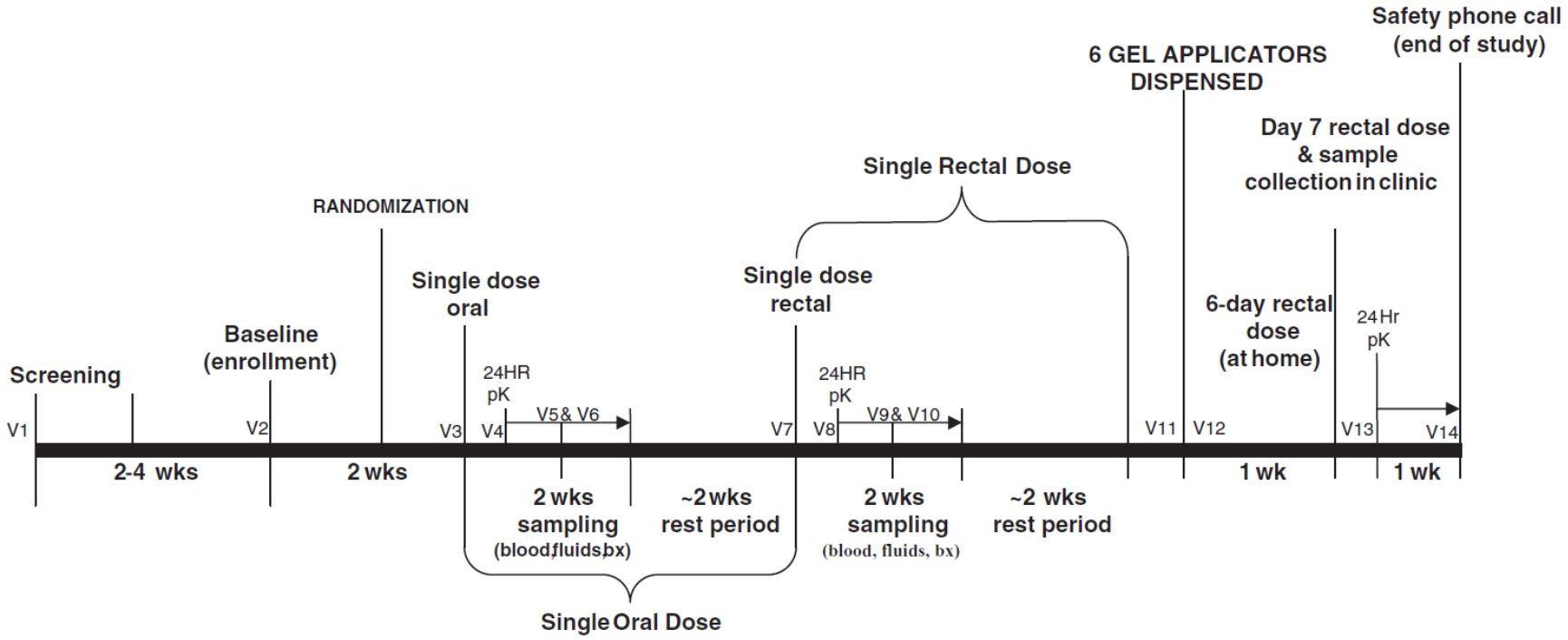
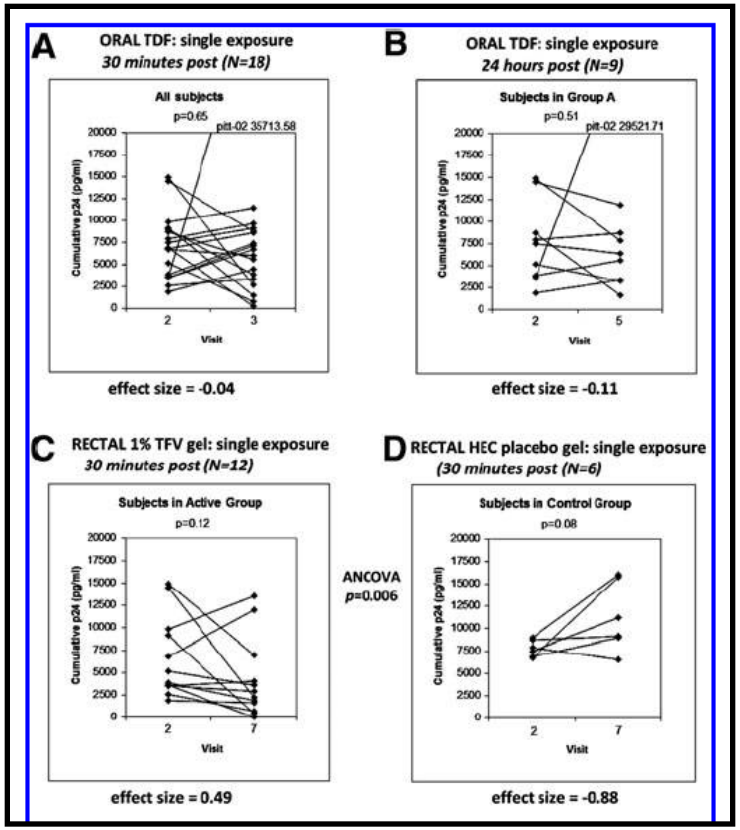
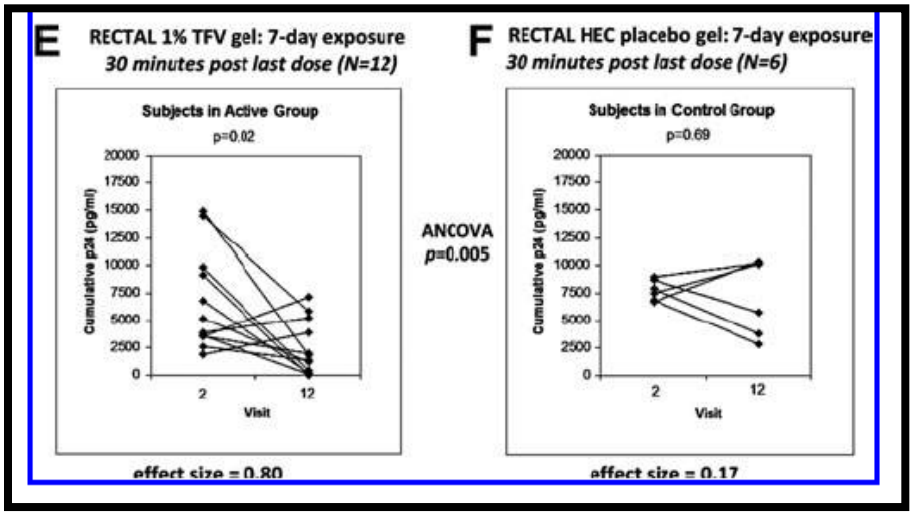
RMP-02/MTN-006 Study Design



RMP-02 / MTN-006



Single dose data (p = NS)



7 daily gel doses data (p = 0.02)

Anton PA et al. AIDS Res Hum Retroviruses 2012

CHARM-01

- Population
  - HIV-negative (N=14)
- Center(s)
  - 2 centers
  - Samples shipped to Pittsburgh
- Sampling
  - Flex sig (15 cm)
  - BL, and post 7D of each formulation
- Products (crossover)
  - TFV gel (1.0%)
  - RG TFV gel (1.0%)
  - RS TFV gel (1.0%)
- Explant infection
  - 15 cm
  - HIV-1_{BaL}
  - 10^4 $TCID_{50}$
  - Weight adjusted cumulative D14 p24
  - PK/PD data

McGowan I et al. PLoS One 2015

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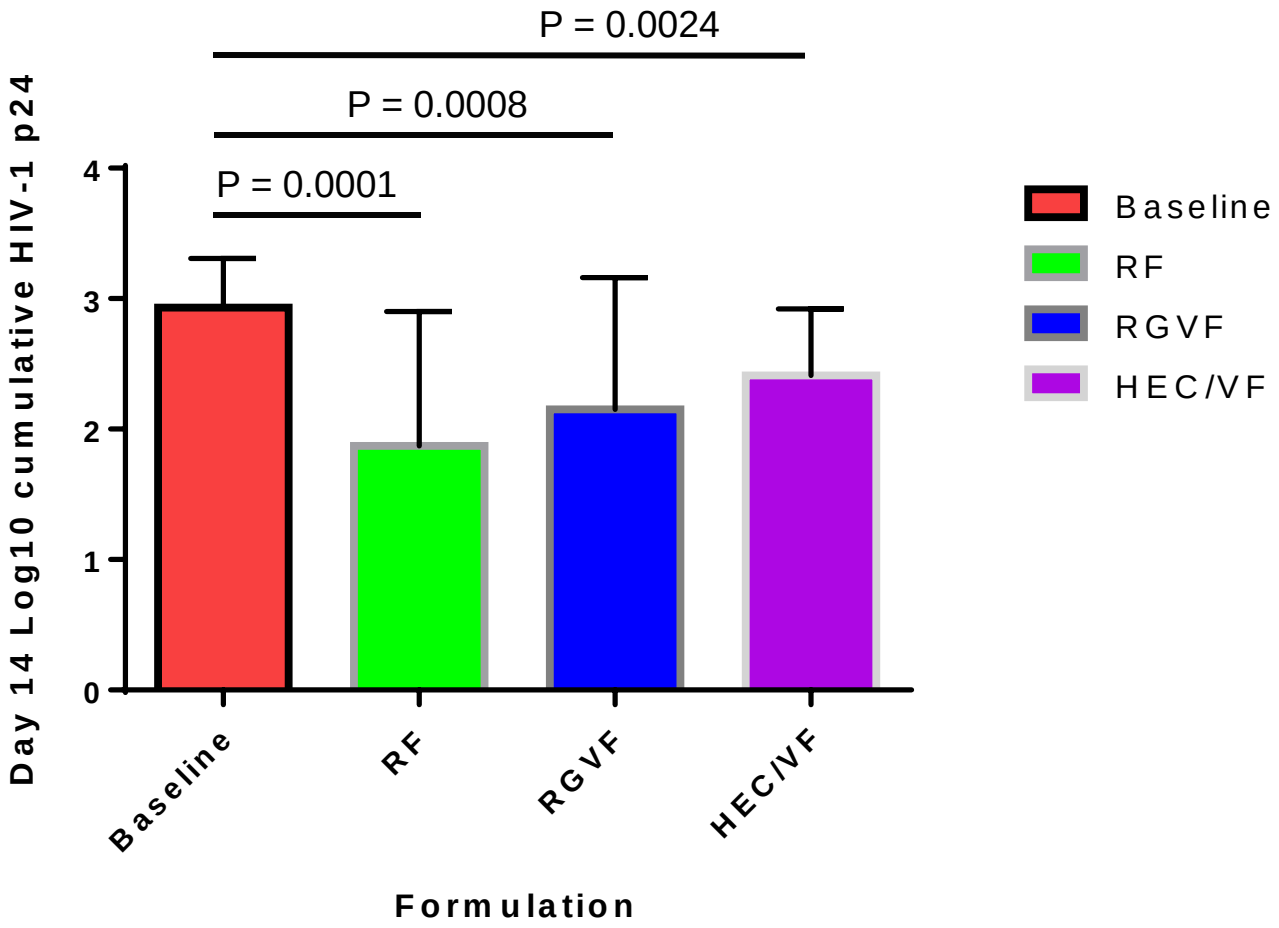
CHARM-01 Explant Data



McGowan I et al. PLoS One 2015

MWRI-01 / Single Dose

- Population
  - HIV-negative (N=36)
- Center(s)
  - 1 center
- Sampling
  - Flex sig (15 cm)
  - Cervicovaginal tissue
  - BL, and +1, 2, 3, 4, 5, 6 months after IM injection
- Products (1:1)
  - Rilpivirine LA 1200 mg
  - Rilpivirine LA 600 mg
- Explant infection
  - 15 cm
  - HIV-1_{BaL}
  - 10^4 $TCID_{50}$
  - Weight adjusted cumulative D14 p24
  - PK/PD data

McGowan I et al. HIV R4P 2014

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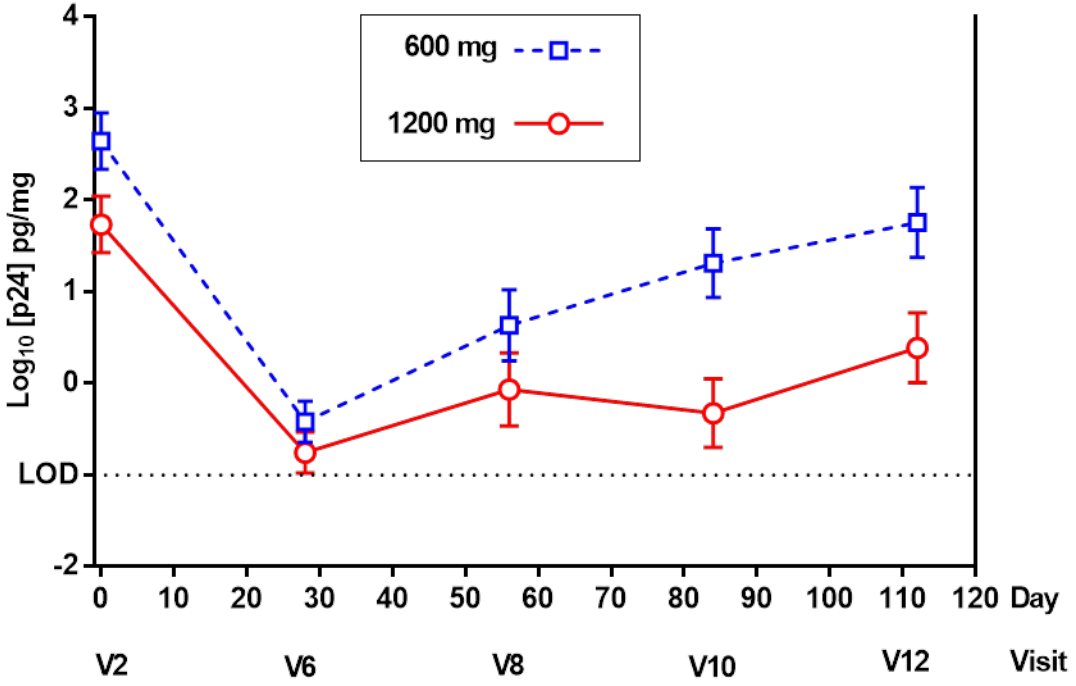
MWRI-01 SD Explant Data



Dose Effect *P* = 0.0009
Visit Effect *P* <0.0001
Dose*Visit Interaction *P* = 0.2131

McGowan I et al. HIV R4P 2014

Ex Vivo HIV-1 Infection of Rectal Biopsies

- Four biopsies obtained prior and after treatment (30 min, 1h, 2h, 4h, 8h, and 24h) biopsies gently disrupted with a small disposable pestle.
- 50 ng p24 of the R5-tropic HIV-1 reference strain NL-AD8 were added. Twenty hours after exposure to virus, the cells were treated with trypsin-EDTA to inactivate residual extracellular virus.
- The cell pellet was resuspended in medium containing 100U IL-2 and $5x10^5$ MT4-R5 cells and cultured over an 8 day period. Supernatants were collected every day between day 3 and day 8, and at days 9, 10 or 11. ELISA p24 (Innotest, Ingen)

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

Ex Vivo HIV-1 Infection of Rectal Biopsies

- 10 participants had biopsies assessable at both time points with 4 biopsies per time point and per participant
- Before drug intake all participants had at least 1 biopsy infected (10/10) vs 6/10 after drug intake ($p<0.07$, Mac Nemar test for clustered data)
- Using a quantitative infectivity score (0: no infection to 6: infection detected at D4) median difference of mean scores: 1.38 (IQR: 0.25 -1.75), $p<0.07$, Wilcoxon sign rank test)
- Trend towards partial protection of rectal biopsies from HIV-infection after intake of a double-dose of TDF/FTC
- Need for additional post-exposure doses

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

Ongoing Studies

MWRI-01 / Multiple Dose

- Population
  - HIV-negative (N=12)
- Center(s)
  - 1 center
- Sampling
  - Flex sig (15 cm)
  - Cervicovaginal tissue
  - BL, and +1, 2, 3, 4, 5, 6 months after IM injection
- Product
  - Rilpivirine LA 1200 mg
  - IM x 3 every 2 months
- Explant infection
  - 15 cm
  - HIV-1_{BaL} / Clade C
  - 10^4 $TCID_{50}$
  - Weight adjusted cumulative D14 p24
  - PK/PD data

McGowan I et al. HIV R4P 2014

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MTN-017

- Phase 2 expanded safety rectal microbicide study
- Crossover design with 8 week dosing periods
  - Oral TDF
  - Topical TFV gel daily
  - Topical TFV gel with sex
- Tissue substudy (N=36)
  - Bangkok
  - Pittsburgh
- Assays
  - Compartmental PK
  - Explant infection
  - Rectal fluid PD
- BL & end of each dosing period
- Explant infection
  - 15 cm / HIV-1_{BaL}
  - 10^4 $TCID_{50}$
  - WA D14 HIV-1 p24

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HPTN-069

- Phase 2 comparison of four oral PrEP regimens
- N = 600
- 48 week exposure with 1 week washout period
- Treatment arms:
  - MVC
  - MVC + FTC
  - MVC + TDF
  - FTC + TDF
- Sample collection
  - BL, +24, +48, +49 weeks
- Tissue substudy
  - N = 120
  - Rectal and cervical
- Explant infection
  - 15 cm / HIV-1_{BaL}
  - 10^4 $TCID_{50}$
  - WA D14 HIV-1 p24

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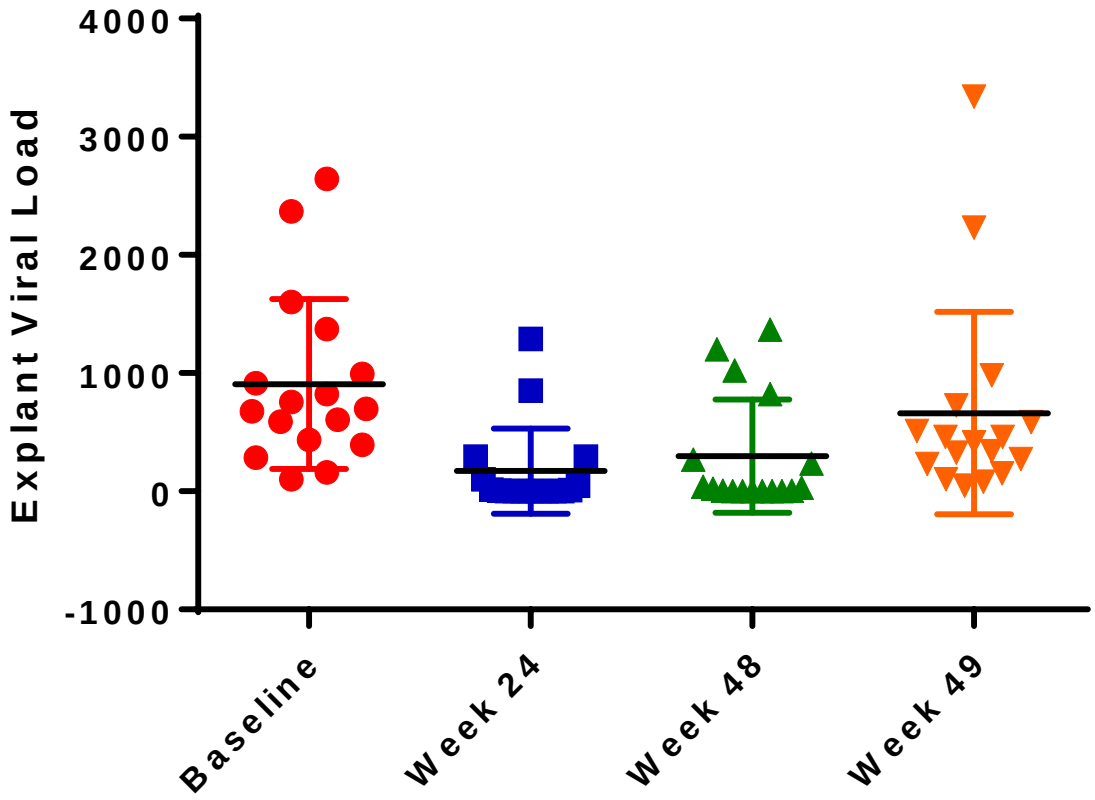
HPTN-069 Single Site Data



CHARM-03

- Population
  - HIV-negative (N=19)
- Center(s)
  - Single center
- Sampling
  - Flex sig (15 cm)
  - BL, and post 7D of each formulation
- Products (crossover)
  - Oral MVC
  - Rectal MVC gel
  - Vaginal MVC gel
- Explant infection
  - 15 cm
  - HIV-1_{BaL}
  - 10^4 $TCID_{50}$
  - Weight adjusted cumulative D14 p24
  - PK/PD data

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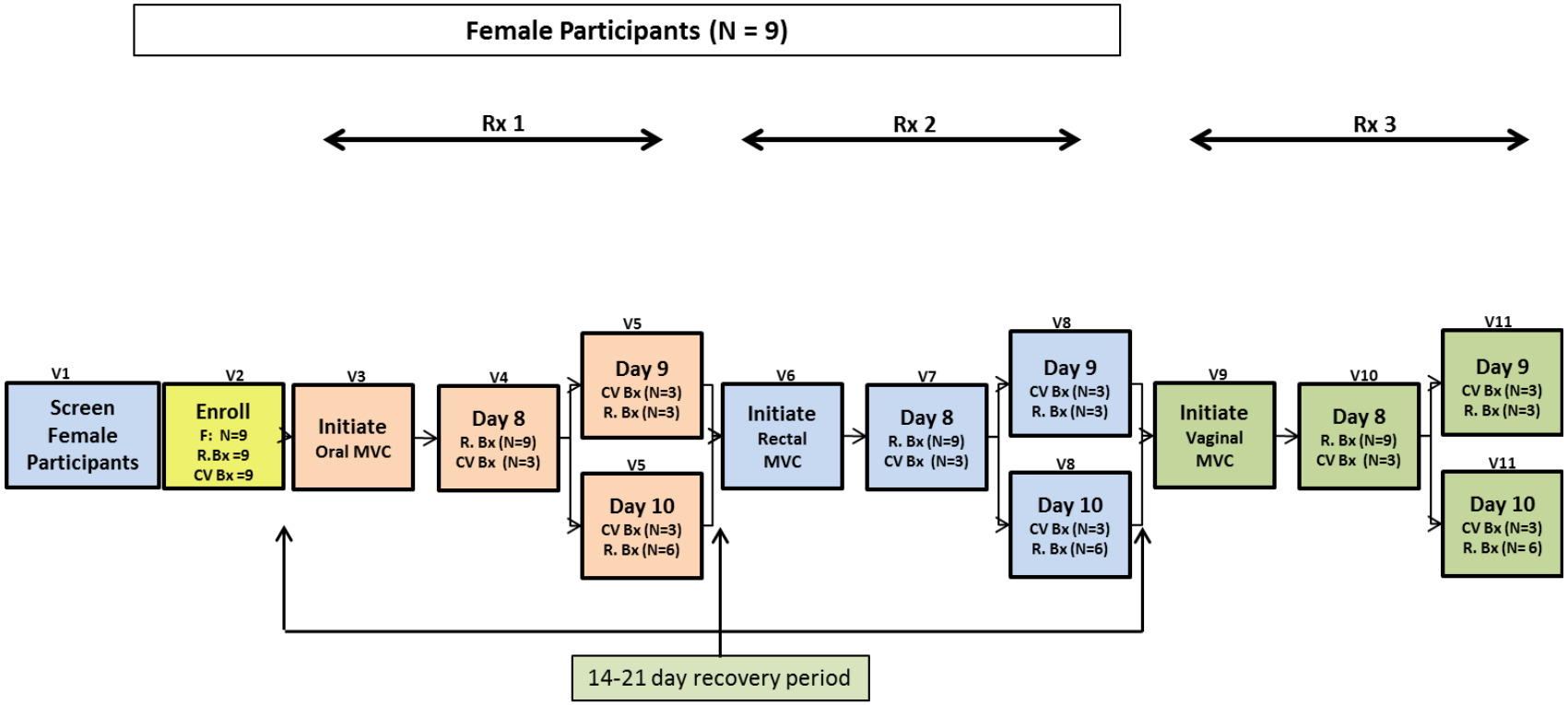
CHARM-03 Design



Rx= Treatment; F= Female; R= Rectal; Bx= Biopsies & CV= Cervical; N = number of participants having rectal or cervical biopsies
Participants will be randomized to product sequence and mucosal sampling schedule at Visit 2 (Enrollment)

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MTN-033 (Adonis) Study

- Phase 1 PK assessment of single dose TFV and dapivirine (DPV) gels
- N = 24
- Gels delivered by application or by digital/phallic insertion

- Compartmental PK
- Rectal fluid PD
- Explant infection
  - 5 cm & 15 cm
  - HIV-1_{BaL}
  - 10^4 $TCID_{50}$
  - Weight adjusted cumulative D14 p24

In Development

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Molecular Assays

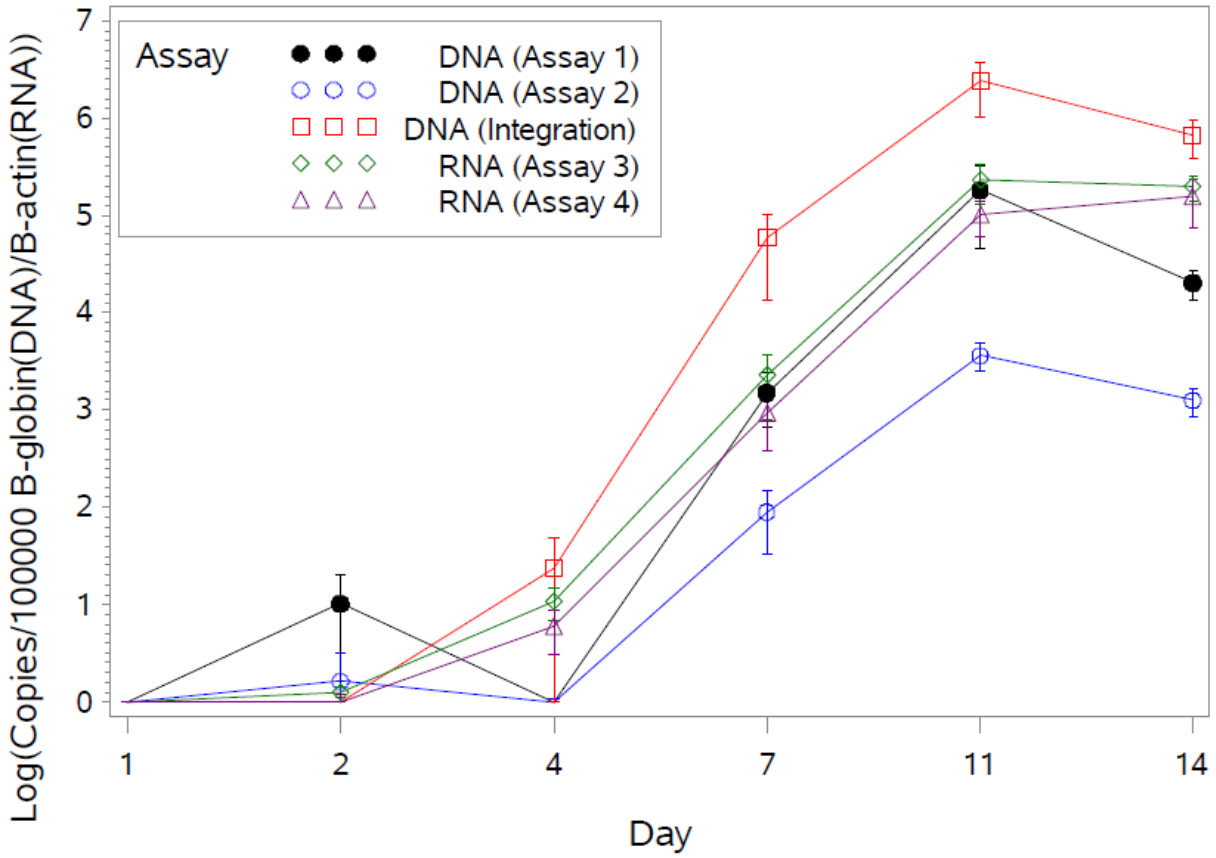
Molecular Assays

- Cumulative Day 14 HIV-1 p24 routinely used to quantify explant infection but has some limitations
  - Explant need to be cultured for 2 weeks
  - Assay sensitivity limited
  - Samples may need to be diluted for quantification
- Quantification of HIV-1 nucleic acids in supernatant and tissue is an alternative

Molecular Assay Study

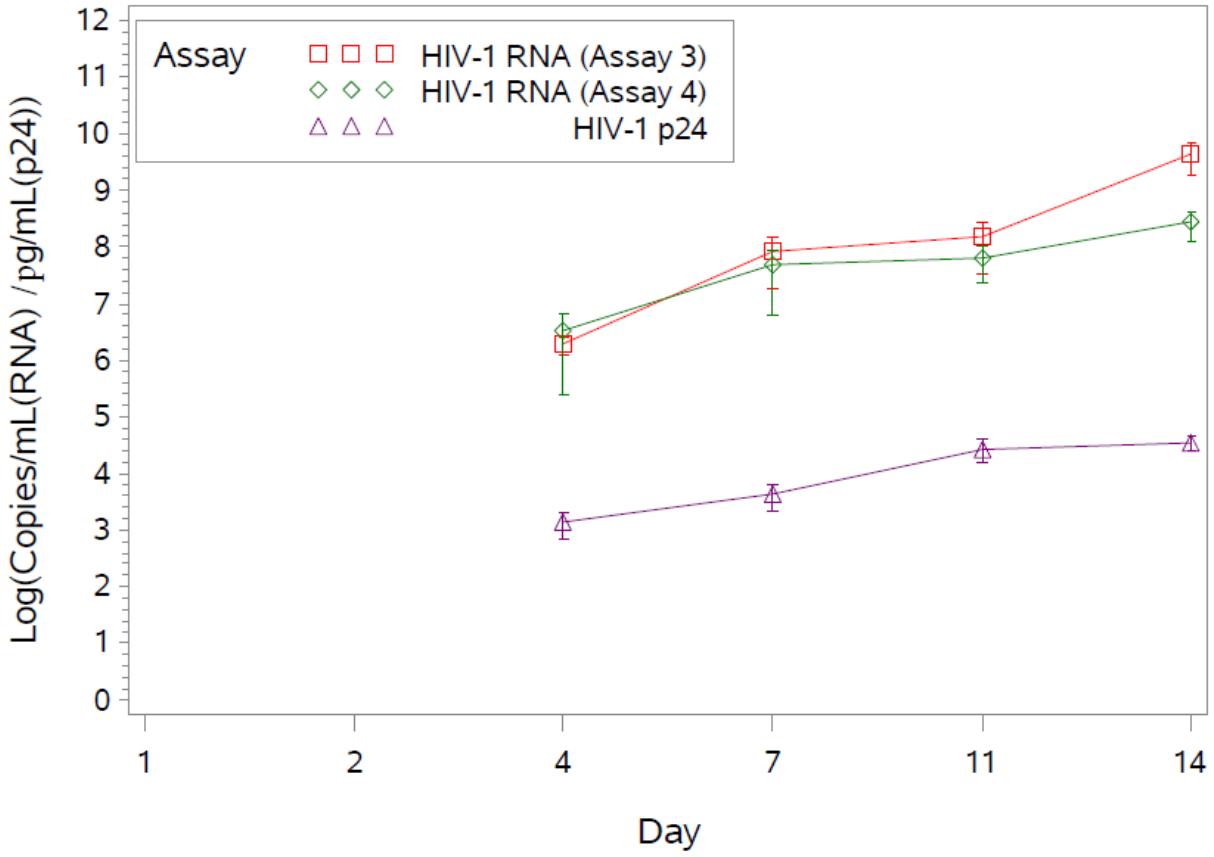
- Goal was to determine whether molecular assays provide a more sensitive approach to the quantification of explant infection
- Explants collected from 8 healthy volunteers and challenged with HIV-1_{BaL} or HIV-1_{CHO77}
- Supernatant and tissue harvested over 14 day period

Tissue Viral Kinetics



Janocko L et al. AIDS Res Hum Retroviruses 2015

Supernatant Viral Kinetics



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Lessons Learned

Lessons Learned

- *Ex-vivo* / *in vitro* explant studies are now being used to characterize antiretroviral efficacy in multiple PrEP studies
- Assay performance improved by using standardized assays, endpoints, and viral stocks
- Explant viral kinetics vary according to the virus used

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Future Questions

Future Questions

- What is the role (if any) of molecular assays in characterizing explant infection?
- What is the most relevant virus to use in explant infection studies?
- Can resistant virus replicate in explant tissue?
- Would MMC challenge studies diminish assay variability?

Acknowledgements

- Professor Jean-Michel Molina

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