

***Ex Vivo* HIV-challenge of *in vivo* exposed colorectal explants may be an important predictor of microbicial effectiveness**

**Early blinded explant results from a Phase 1 Rectal Microbicide Trial of UC-78 (blinded data from 75% completed)**

---

J Elliott, I McGowan, A Adler, EJ Johnson, K Tanner, D Cho, T Saunders, E Khanukhova, C Mauck, P Anton

UCLA, NIH, CONRAD



# Study Outline

---

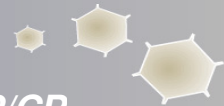
- **Study Population:** HIV negative men and women with RAI history
- **Study Size:** 36 participants (men and women) in 3 arms (12/arm)
- **Agent:** UC-781 (NNRTI) microbicide gel, vaginally-formulated, rectally applied
- **3 Groups:** UC-781 gel-high dose (0.25%)  
UC-781 gel-high dose (0.1% gel)  
Placebo (Universal)
- **Primary objectives:** Safety (# AE) and acceptability
- **Secondary objectives:** many (some novel) assays. 1<sup>st</sup> use of explants in Phase 1 trial: ? Efficacy indicator/? Early biomarker
- **ALL DATA / INTERPRETATION STILL BLINDED**
- **Accrual:** 9-12 months
- **Duration:** 18 months (last subject enrolled; completion date: mid 3/08)



# Trial Objectives and Indices

---

- **Secondary Objectives**: To determine whether use is associated with rectal mucosal damage (immunotox):
  - Epithelial sloughing
  - Histopathology
  - Mucosal mononuclear cell phenotype (flow)
  - Mucosal cytokine mRNA (tissue)
  - Mucosal cytokines (secreted)
  - Mucosal immunoglobulins
  - Fecal calprotectin
  - Explants- susceptibility to HIV infection



# Explants: process

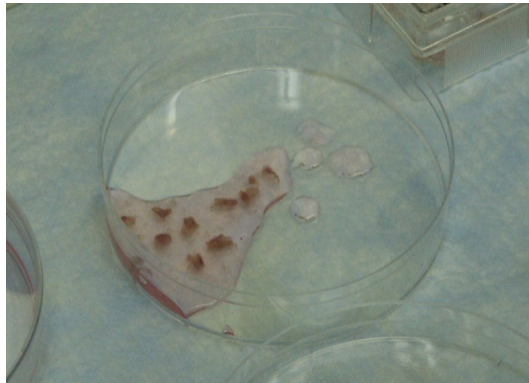
---

- **Samples acquired (large-cup forceps): 14 biopsies at each site (10cm and 30cm)**
- **NO procedure-related AE; no withdrawal / loss to follow-up**
- *NO Microbicide DRUG ADDED (except at V2): all drug is applied **IN VIVO***
- **To laboratory and set up within 2 hours max.**
- **HIV applied and left incubating for 2 hours: all washed and then incubated for 12-14 days. Controls: media (uninfected control); UC-781 at baseline visit only to demonstrate *in vitro* efficacy**
- **Supernatants for p24 taken every 3 days; each time point is mean of 2 biopsies pooled; cumulative profile graphed**

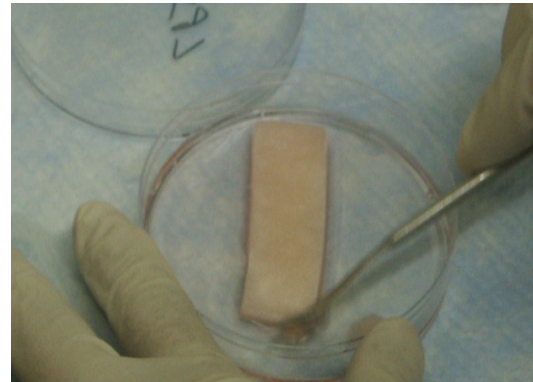


# Colorectal explants (10 cm and 30 cm)

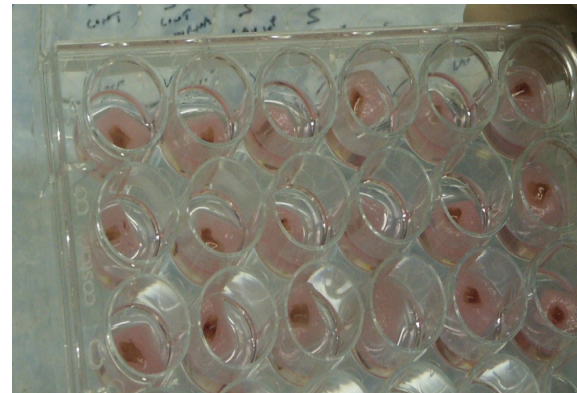
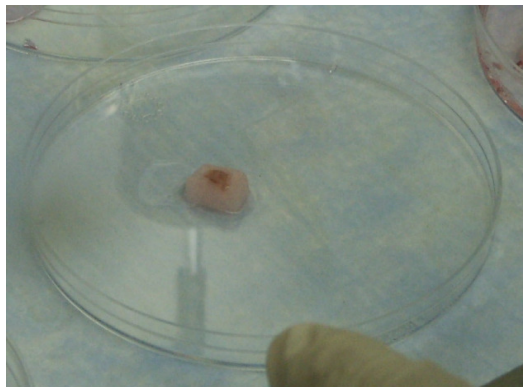
---



**Endoscopic biopsies**



**+ Absorbable gelatin sponge**

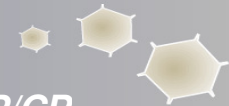


**= Happy Explants**

# Explants: (i) prior experience with UC-781 (ii) specifics of design plan

---

- EXPLANTS are proven/published model:
    - Margolis et al. J Clin Invest 1998
    - Fletcher et al. J Virol. 2005
    - Fletcher et al. AIDS 2006
  - UC-781 has been shown to suppress/reduce explant HIV infection *in vitro, ex vivo*:
    - Fletcher et al. J Virol. 2005 (UC-781 inhibits infection in cervical explant model)
    - Abner et al. J Infect Dis. 2005 (UC-781 inhibits infection in cervical explant model)
    - Gupta et al. AIDS Res Hum Retroviruses. 2006 (frozen/fresh explants with UC-781)
    - Van Herrewege et al. Antiviral Res. 2007 (cell line/chamber model with UC-781)
    - Cummins et al. Antimicrob Agents Chemother. 2007 (cervical explant model: inhibition with UC-781)
- 
- Explants from 2 sites (10 cm and 30 cm)
  - Explants from 3 visits: Baseline, post single exposure, post 7-day exposure
  - Each exposed to same laboratory viral strain: *only* R5 HIV<sub>bal</sub>
  - Two viral concentrations used to ensure infectivity and assess threshold:  
TCID<sub>50</sub>: 10<sup>4</sup> and 10<sup>2</sup>
  - CONTEXT: in our hands, 10<sup>4</sup> always causes infection (no intra-subject variability) while 10<sup>2</sup> can vary

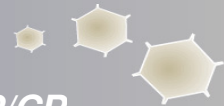


# Presentation Focus

---

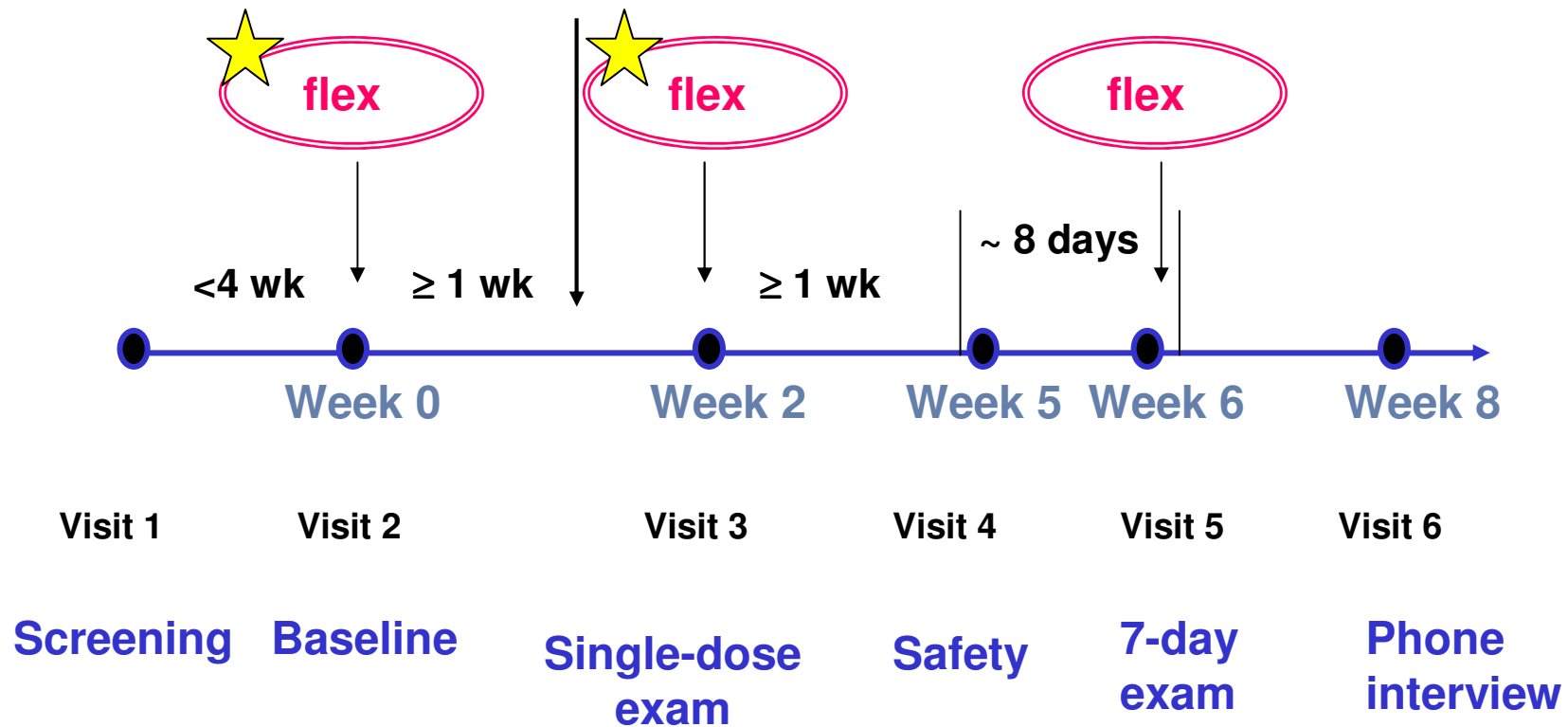
**Due to short presentation time AND still blinded nature of data:  
Only most controlled data will be presented now.**

- **Data at 10 cm (*clinically relevant*)**
- **Data at Visit 3: single dose exposure (*controlled*)**
- **Data from  $10^4$  viral infection *ex vivo* (*ensure baseline infection*)**

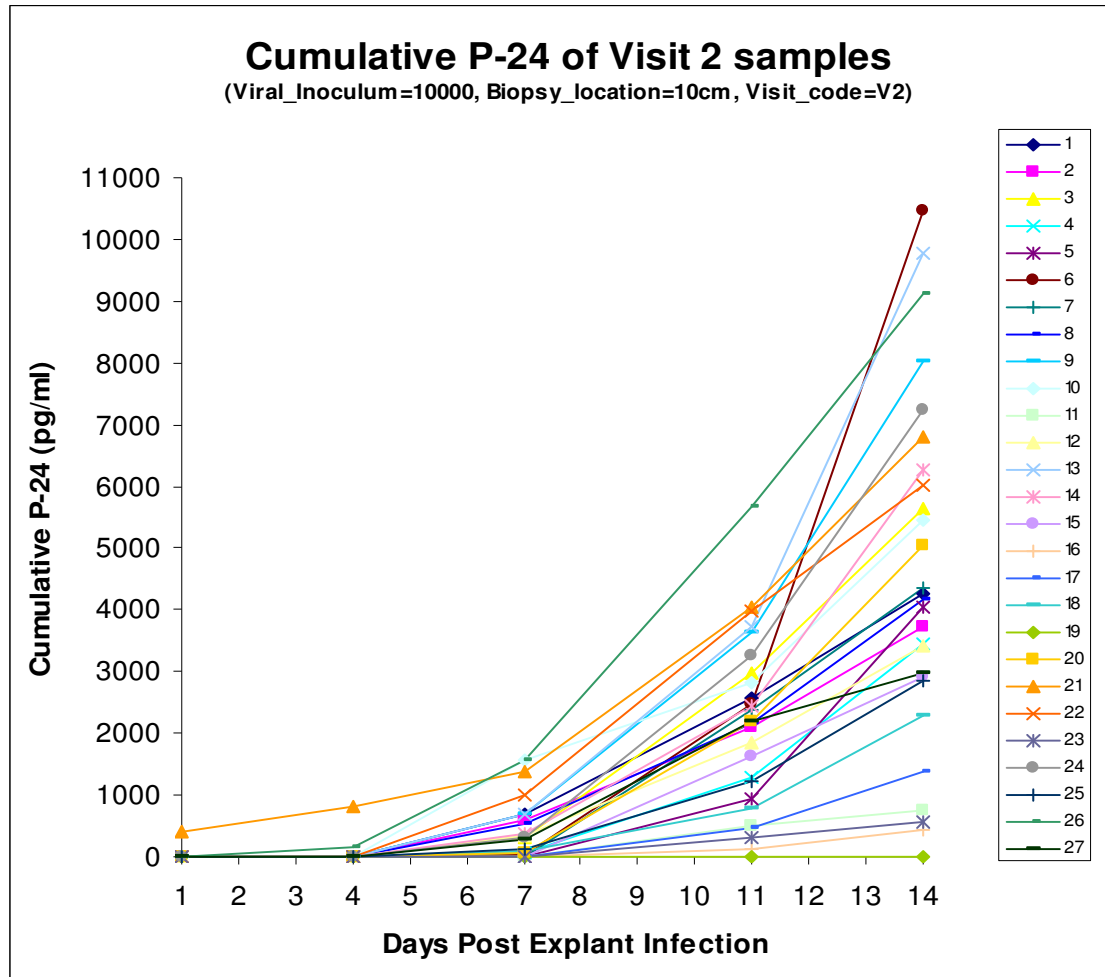


# RM Phase 1 Trial Design

Randomization: 0.1% UC-781, 0.25% UC-781, or placebo



# At Baseline (V2), 26/27 of subject's explants infectible with HIV<sub>BaL</sub> 10<sup>4</sup> TCID<sub>50</sub> (10 cm)



NB: All data recoded so PI/Team blinded from Laboratory identification

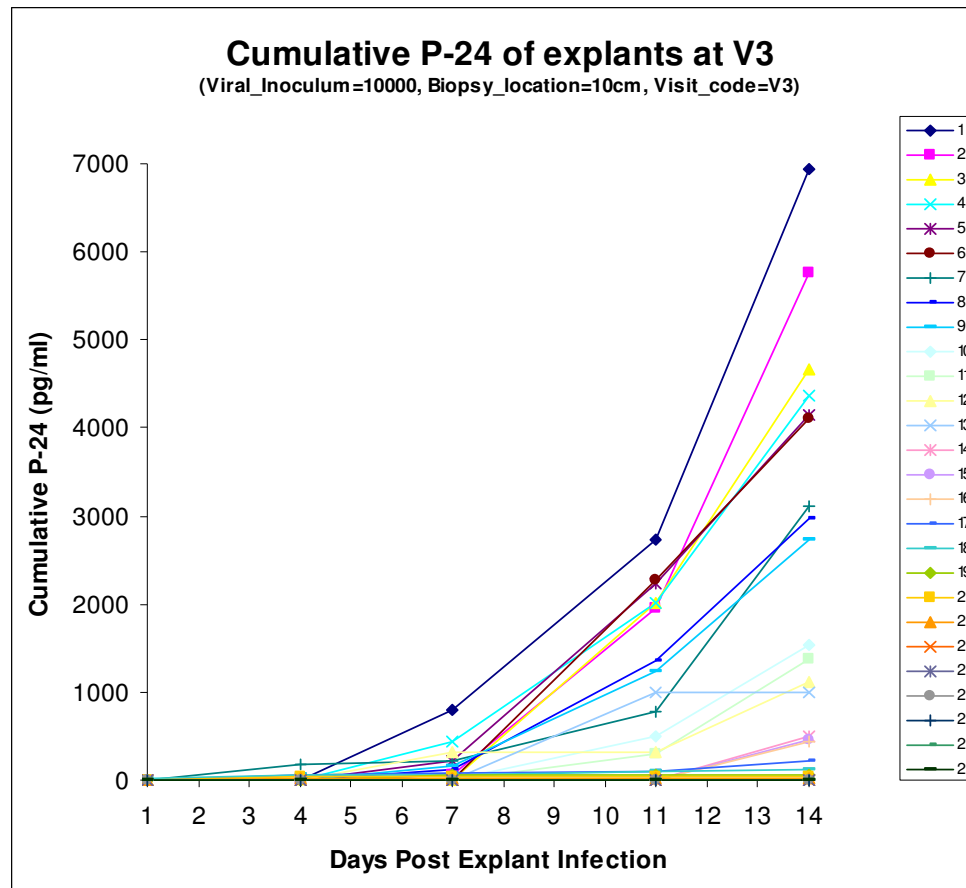
# Explant infectibility at each visit

---

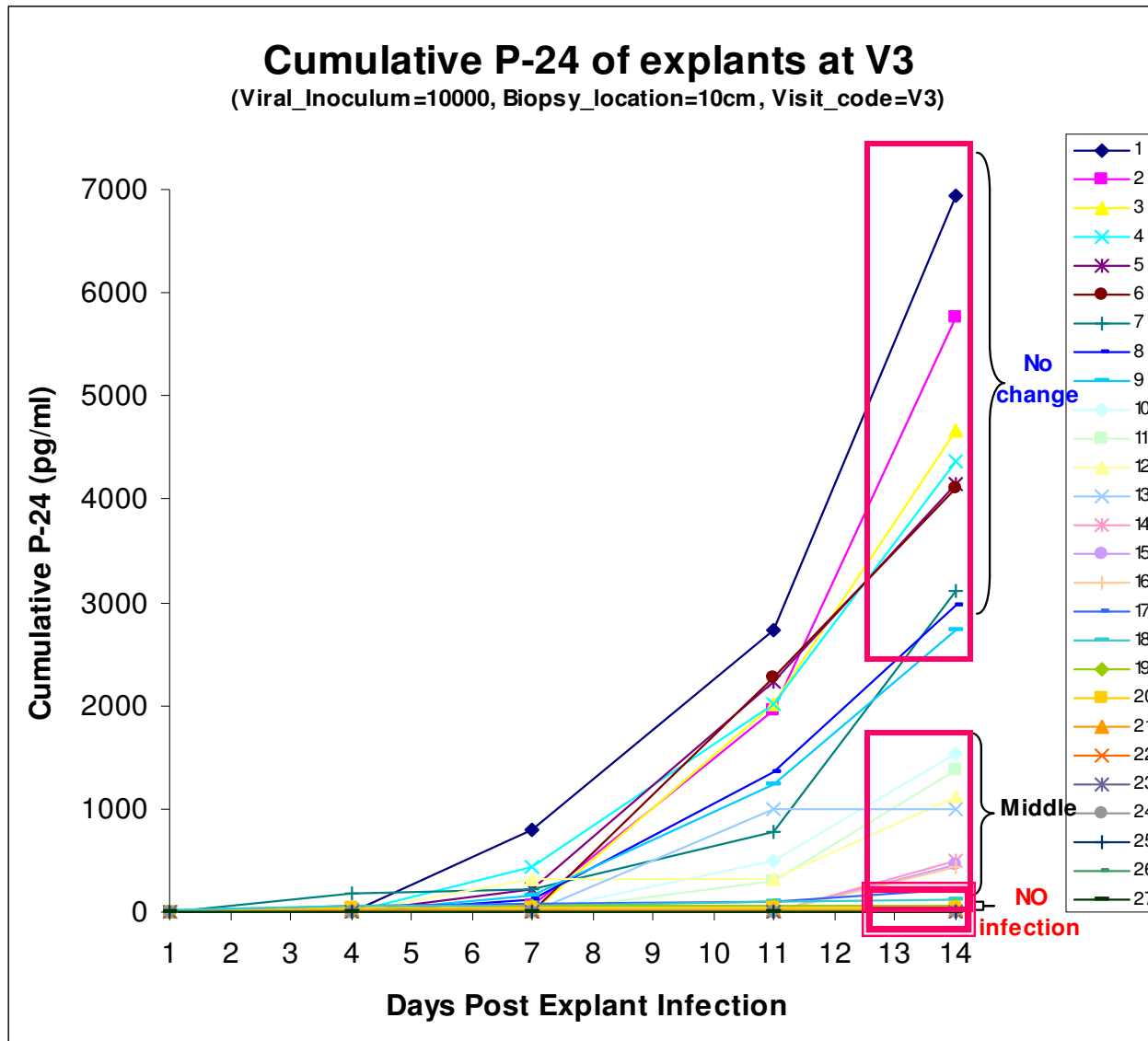
	Baseline		Post single dose		Post 7-day	
	TCID <sub>50</sub> 10 <sup>4</sup>	TCID <sub>50</sub> 10 <sup>2</sup>	TCID <sub>50</sub> 10 <sup>4</sup>	TCID <sub>50</sub> 10 <sup>2</sup>	TCID <sub>50</sub> 10 <sup>4</sup>	TCID <sub>50</sub> 10 <sup>2</sup>
% infected (N) at 10 cm	96% (26/27)	63% (17/27)	66% (18/27)	30% (8/27)	96% (26/27)	44% (12/27)
% infected (N) at 30 cm	96% (26/27)	66% (18/27)	74% (20/27)	33% (9/27)	78% (21/27)	63% (17/27)

## Visit 3 Results (single dose; samples acquired at 30')

- 18/27 (66%) subject's explants infectible, to some degree, with HIV<sub>BaL</sub> 10<sup>4</sup> TCID<sub>50</sub>
- 9/27 (33%) subject's explants unable to establish infection with HIV<sub>BaL</sub> 10<sup>4</sup> TCID<sub>50</sub>
- One subject (#19) never established infection (FACS shows +CCR5)



# Visit 3 Results (single dose; samples acquired at 30')



- 33% with NO INFECTION
- 33% with NO CHANGE
- 33% in MIDDLE

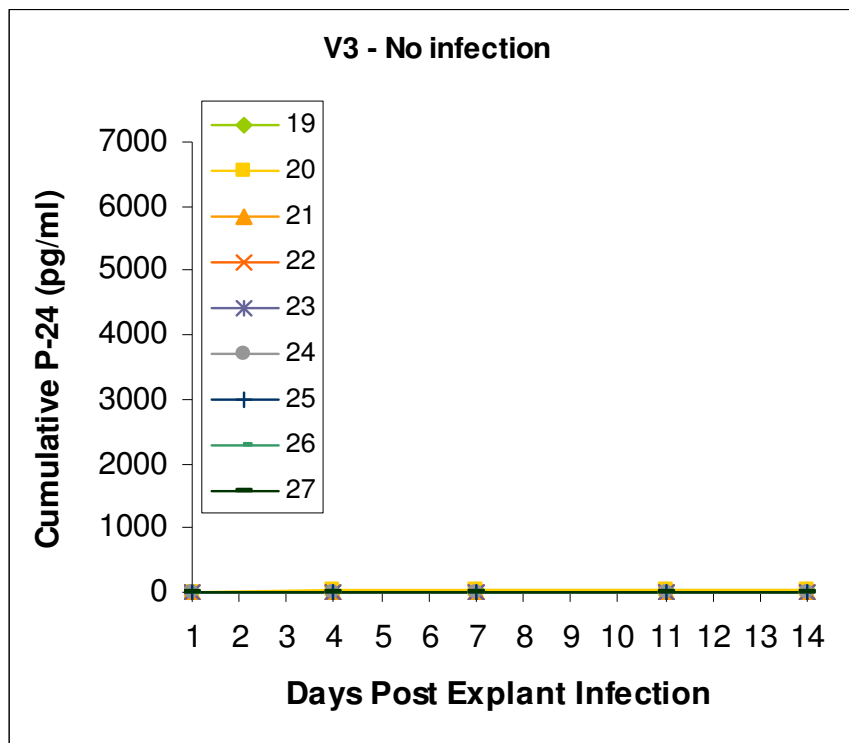
BLINDED

1 non-responder  
 in "NO infection"  
 group

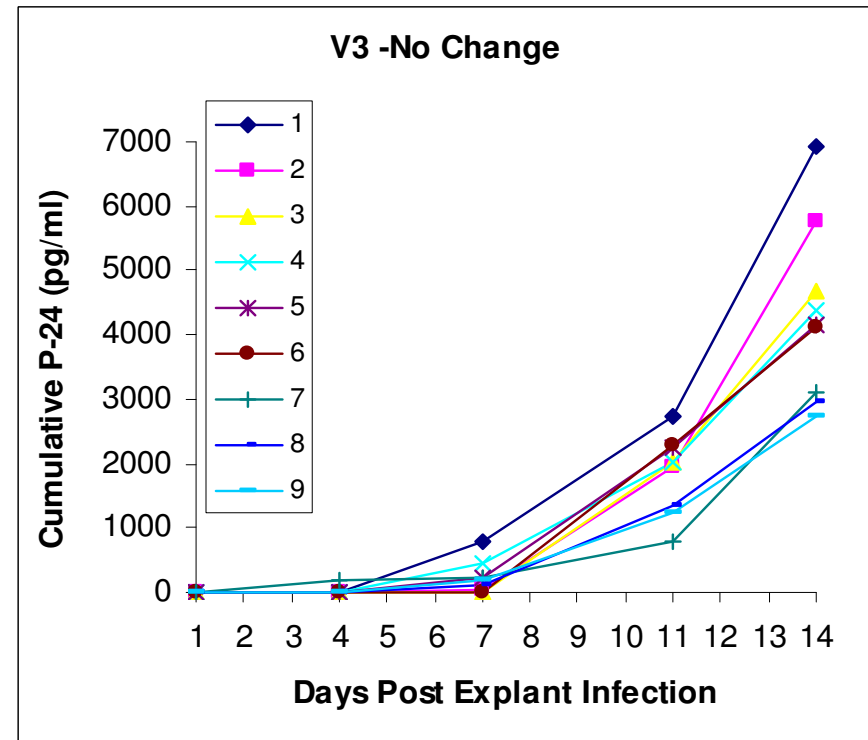
## BLINDED Data UC-781 RM Trial:

Expanded view of 33% subjects showing “No infection”  
and 33% subjects showing “No change” (Visit 3)

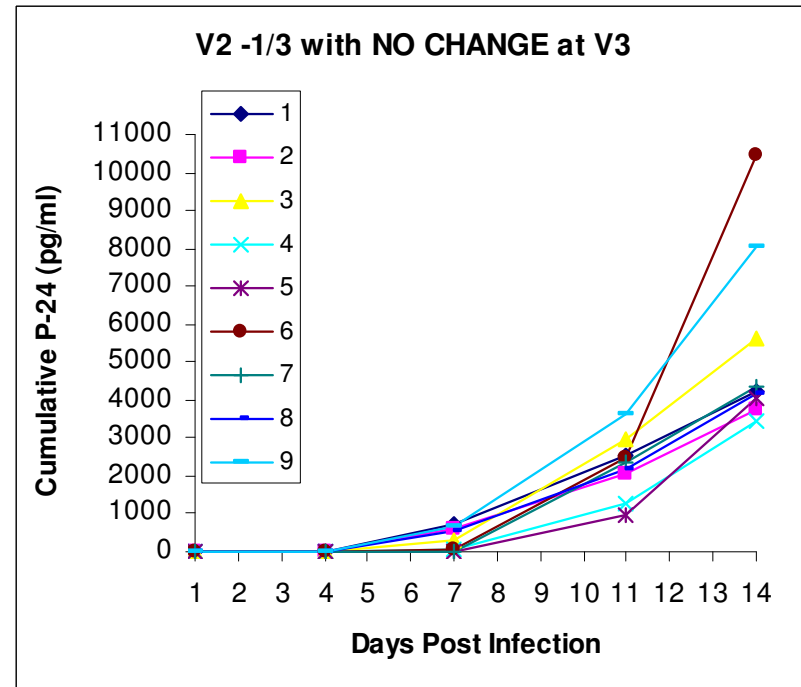
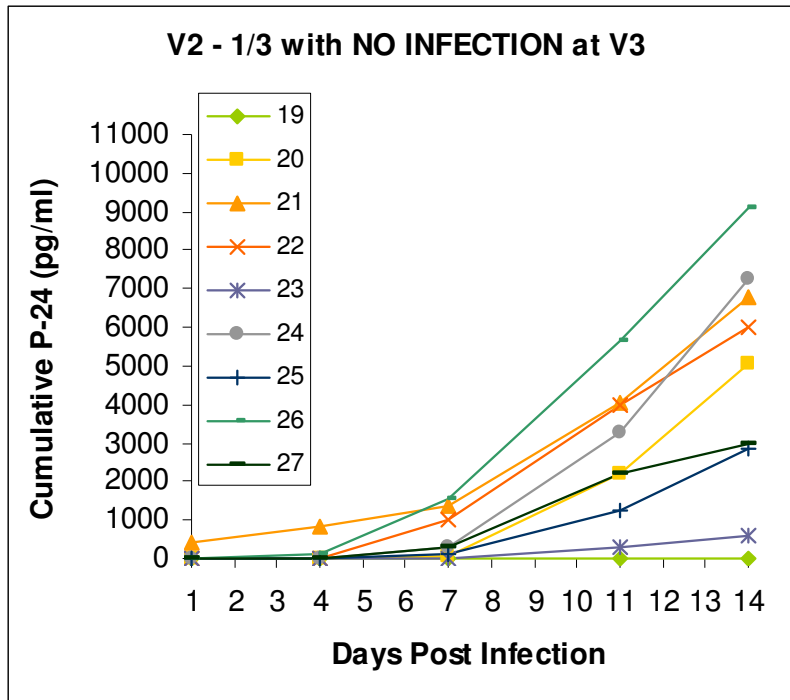
A



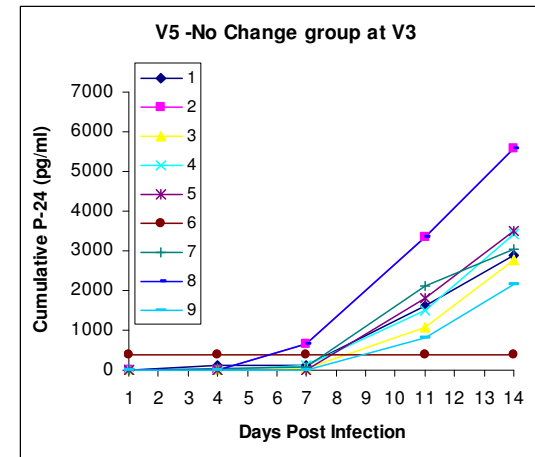
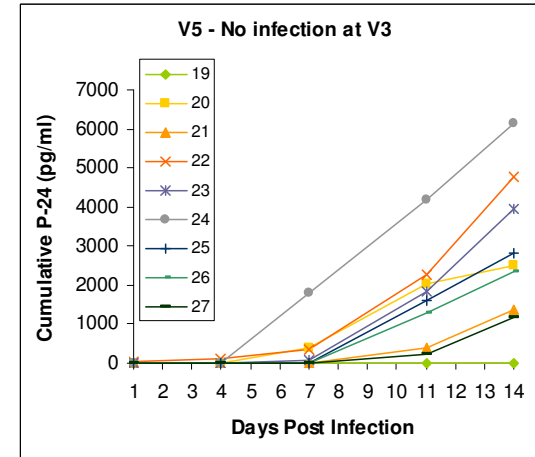
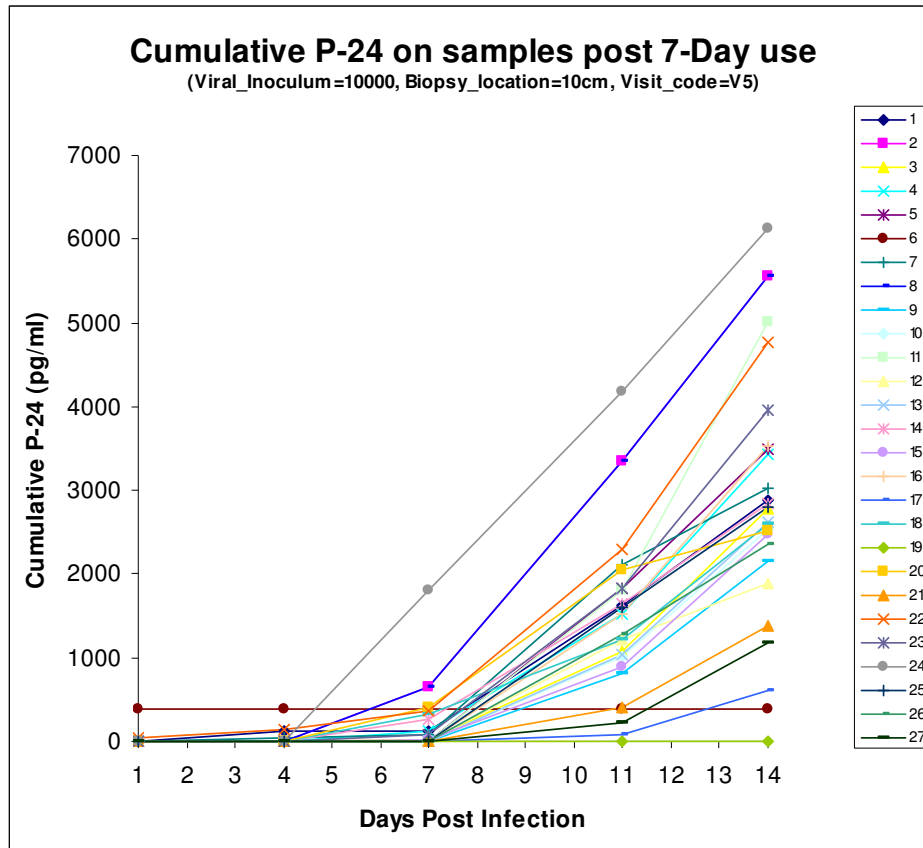
B



# No differences appreciated at Baseline between the 33% “no infection” and the 33% “no change” groups



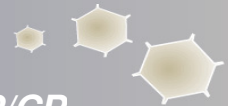
# Following 7 days of daily dosing (V5), no emerging pattern of response was evident.

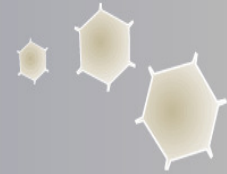


# Interpretations

---

- Data (75% reported here) all still blinded
- Nearly all explants infectible at Baseline (26/27; 96%)
- 3 study groups: placebo, high-dose UC-781, low-dose UC-781
- Important observation: **Not all results the same after single exposure**
- Convenient to anticipate that high drug dose are group that showed **no response** to  $10^4$  HIV infection *ex vivo*; even MIDDLE group demonstrated some reduction in infection...**need to await unblinding.**
- If so: (i) potentially important biomarker, especially for Phase 1 trials  
(ii) remarkable that a “clinically-safe”, rectally-applied drug dose could retain efficacy in assay of *ex vivo* tissue infection, using clinically excessive doses of laboratory viral strain (R5 only)





•NIH NIAID U19 IP/CP #AI060614: “Microbicide Development Program”

Biosyn, Inc

Anne Marie Corner  
Linda Knapp  
Linda Kristekas

CONRAD

Henry Gabelnick  
Christine Mauck  
Tim McCormick  
Marianne Callahan

UCLA

Ian McGowan (U Pitt)  
Chomchay Siboliban  
Amy Adler  
Terry Saunders  
Elena Khanukhova  
Charlie Price  
Julie Elliott  
John Boscardin  
Ying Zhou  
Daniel Cho  
Karen Tanner  
Elizabeth Johnson  
Alexis Dominguez  
Julia Klein

NIH

Jim Turpin  
Jeanna Piper  
CherylInn Mathias  
Grace Chow

Consultants

Alex Carballo-Dieiguez  
Ana Vetuneac

**VOLUNTEERS!**

