

The Use of Mucosal Assays in Microbicide Trials

Integrating PK/PD

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PD: Ex vivo p24 Imputations, Kinetics and Variability

Placebo/baseline (untreated) *ex vivo* p24 data from:

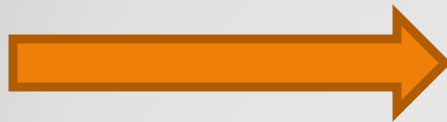
- 17 data sets, 10^4 TCID₅₀ HIV-1 BaL
- 4 Labs: Pitt, UCLA, CONRAD, Imperial
- 3 tissue types: rectal, cervical, vaginal
- 9 studies: UC781, Tenofovir, FAME01, FAME02, CHARM01, MTN013, CONRAD, MWRI01, Fox
- 700 tissue explants: 13% cervical, 72% rectal and 16% vaginal
- Coded C1-C4 (cervical), R1-R8 (rectal) and V1-V5 (vaginal).

Comparison of Imputation Methods

Method	Replace non-detectable with values....
Z (current)	$\frac{1}{2}$ LLOQ/LOD
A	Predicted from a non-linear mixed model
B	Predicted from (i) model of growth curve then (ii) non-linear mixed model
C	Predicted iteratively from model of growth curve and non-linear mixed model

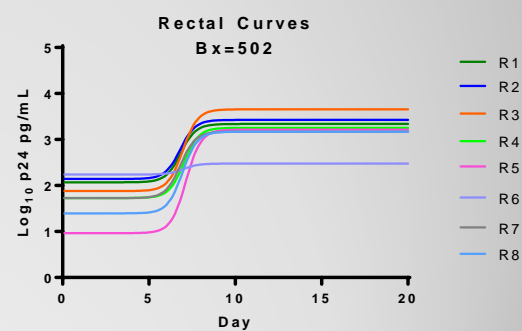
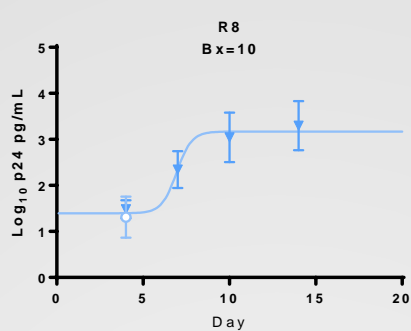
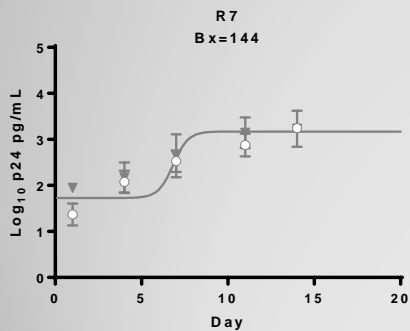
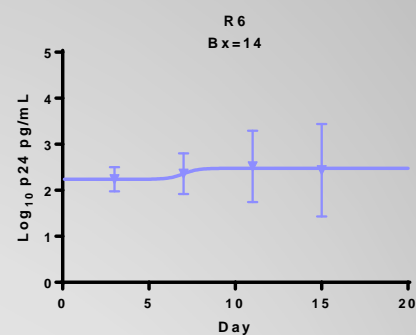
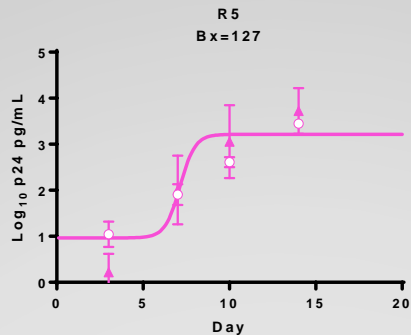
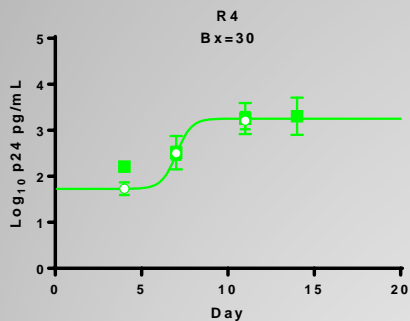
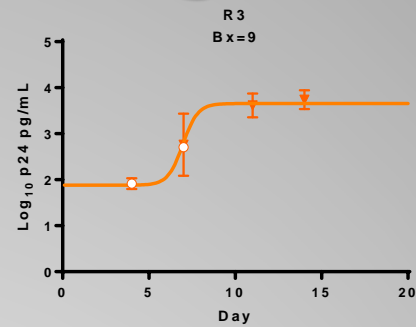
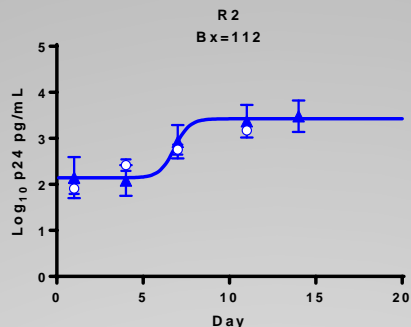
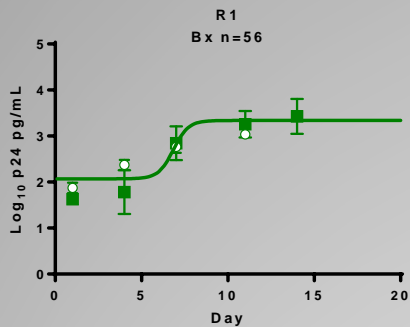
Comparison of Imputation Methods

Experiment	<500 SSI	≥ 500 SSI	Different to Z $P < 0.05$	Ease of Implementation Easy-Hard
R1	A,B and C	Z	A,B and C	Z-A-B-C
R2	A,B and C	Z	A,B and C	
R4	A,B and C	Z	A,B and C	
R7	A,B and C	Z	A,B and C	

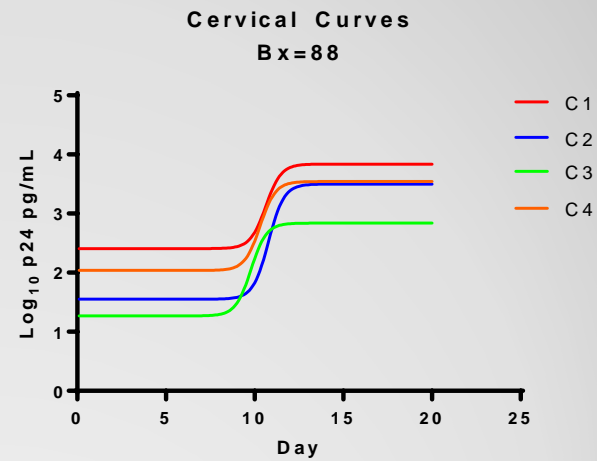
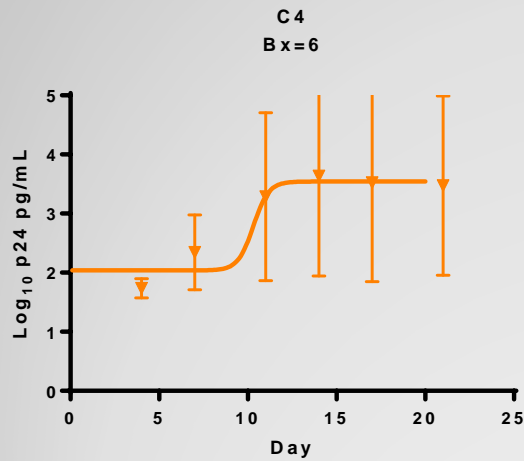
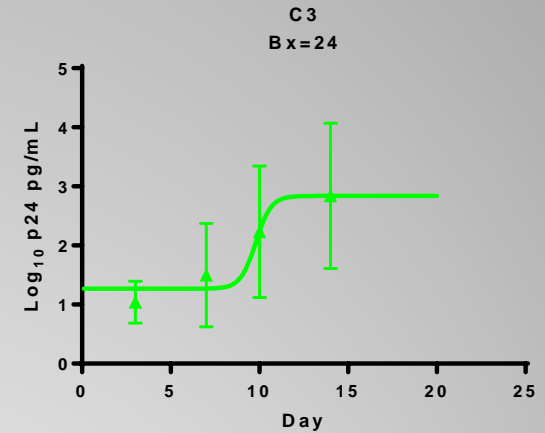
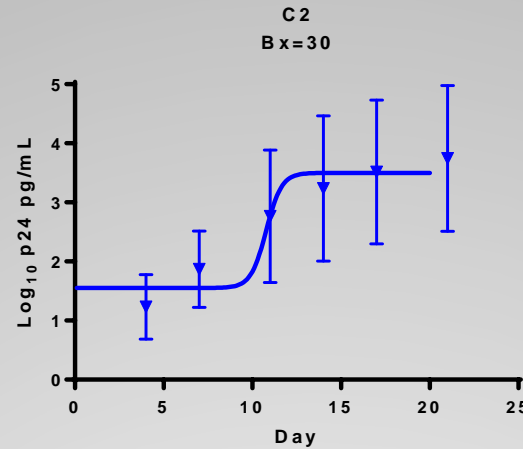
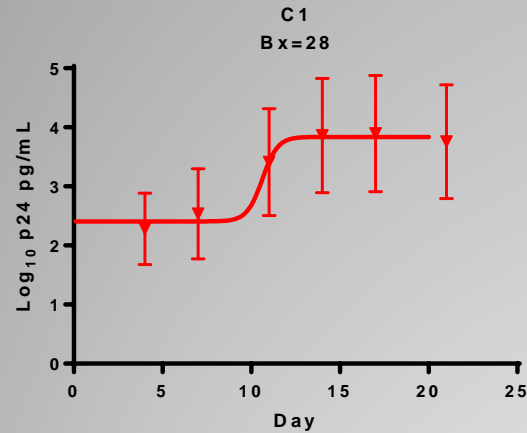


Move forward with Method A

Rectal *Ex vivo* Challenge

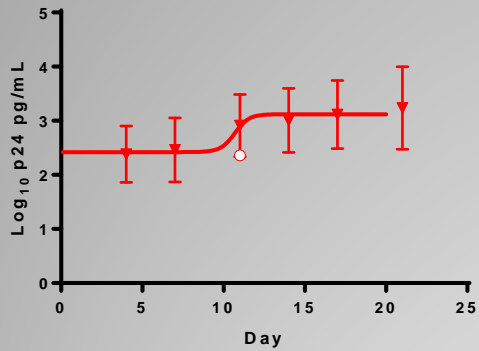


Cervical *Ex vivo* Challenge

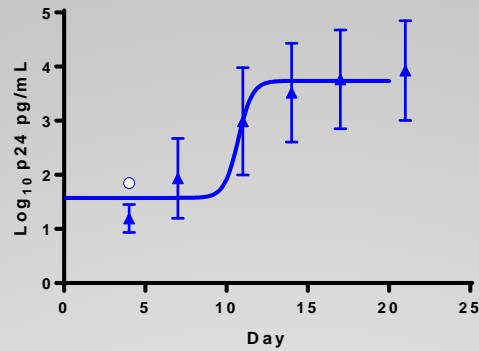


Vaginal *Ex vivo* Challenge

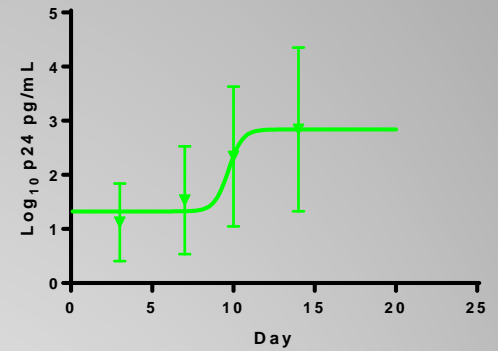
V1
Bx=29



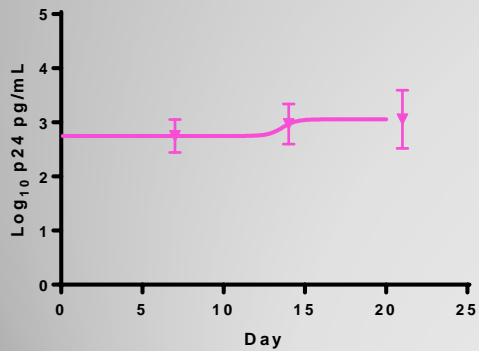
V2
Bx=30



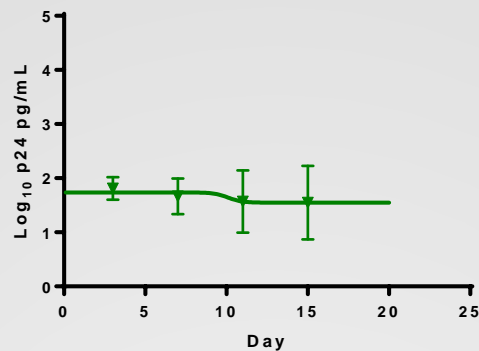
V3
Bx=24



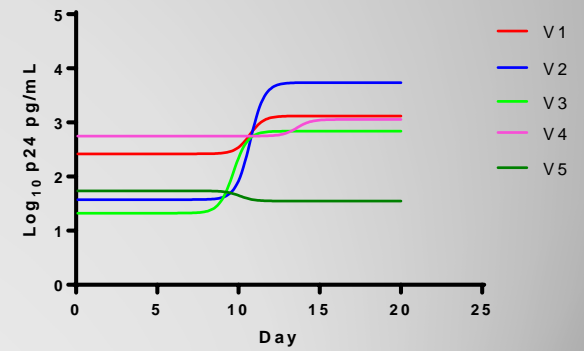
V4
Bx=19



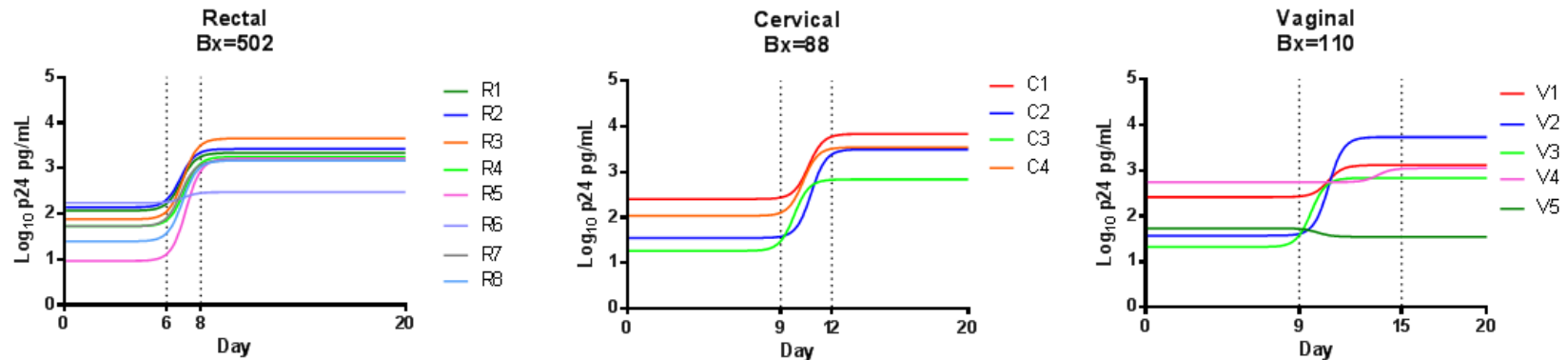
V5
Bx=8



Vaginal Curve
Bx=110



Ex vivo Growth Across Tissue Types and Implications for Experimental Design



Last Day	Rectal p24	N
14	5248	4
15 (R6 only)	1479	6

Last Day	Cervical p24	N
14	1318	19
21	21878	19

Last Day	Vaginal p24	N
14	1514	24
21	9120	10

p24 = geometric mean cumulative p24 pg/ml.

N = no. of tissues samples needed, per treatment group, to find a one log difference in p24 to be significant ($p < 0.05$) with 80% power.

Integrating PK/PD

PD

Determine PD endpoint (e.g. cumulative p24), log transform.

PK

Determine dose endpoint (e.g. concentration, C_{max}, AUC), log transform.

Integrate PK/PD

Pair contemporaneous PK/PD measurements (same subject/time)
Linear mixed model, is slope sig?

yes

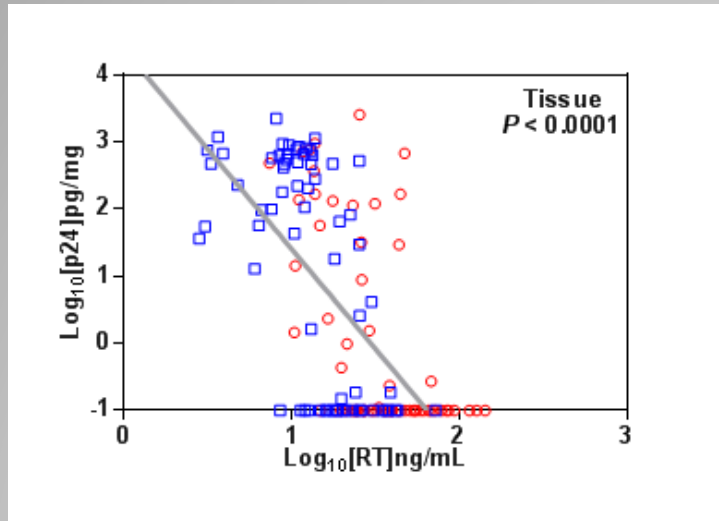
no

Non-linear model, calculate % virus control, EC₅₀.

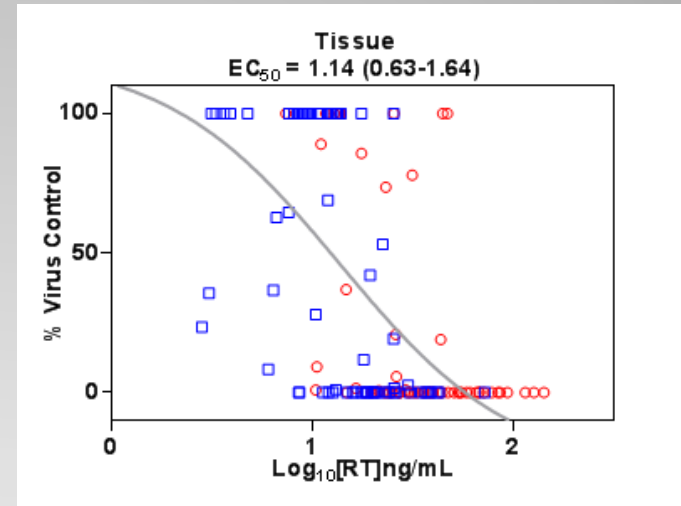
No PK/PD relationship

Integrating PK/PD in Rectal Tissue: 2 steps

1



2



□ 600 mg Single Dose

○ 1200 mg Single Dose

A Compartmental Pharmacokinetic and Pharmacodynamic Assessment of Rilpivirine LA Pre-Exposure Prophylaxis in HIV-Negative Volunteers

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