Impact of Vorinostat Treatment of Non-Hodgkin's Lymphoma on HIV-1 Latent Reservoir

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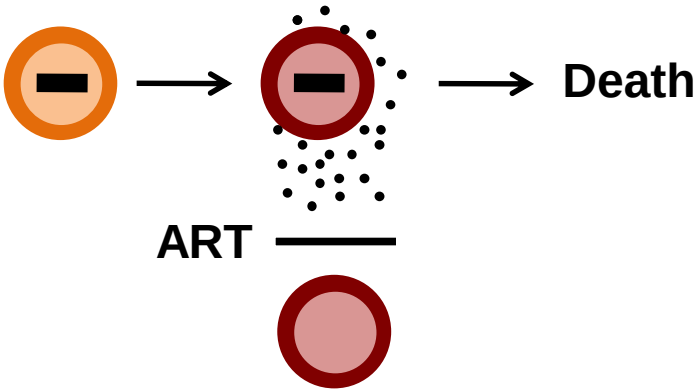
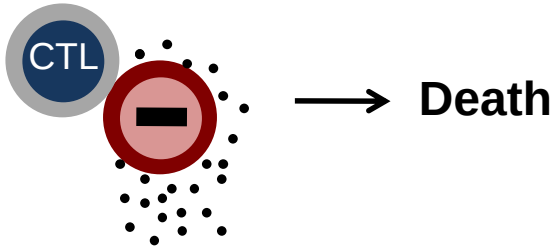
HIV Cure Strategies

- Major barrier to HIV cure is a latent reservoir of replication competent HIV in resting CD4+ T cells that persists despite ART
- “Shock and Kill” Strategy

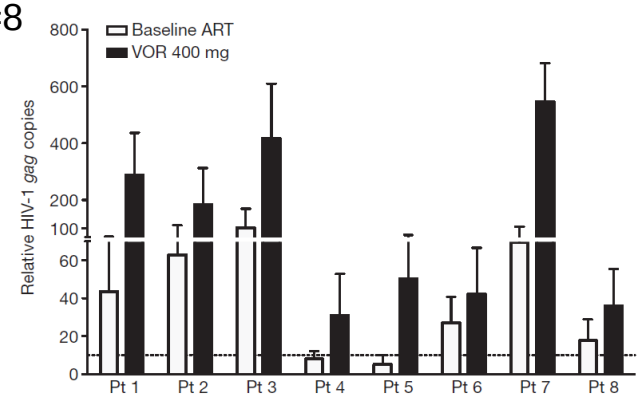




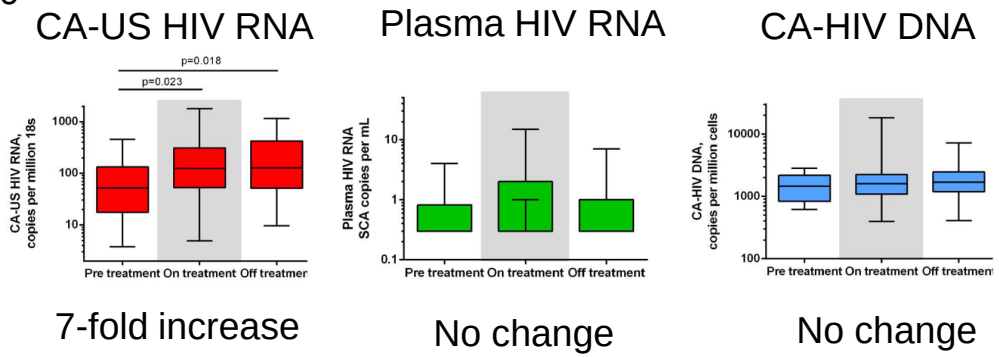
VOR in Cancer and HIV Cure

- Vorinostat (VOR) is a HDAC inhibitor that is approved for cancer treatment
- Identified as a potential latency reversing agent (LRA)
- Prior clinical studies looking at impact of VOR on HIV persistence
  - Increase of cell-associated HIV RNA
  - Did not report on changes in replication competent HIV in resting CD4 T cells measured by viral outgrowth
  - VOR is perturbing the latent reservoir

N=8



N=20



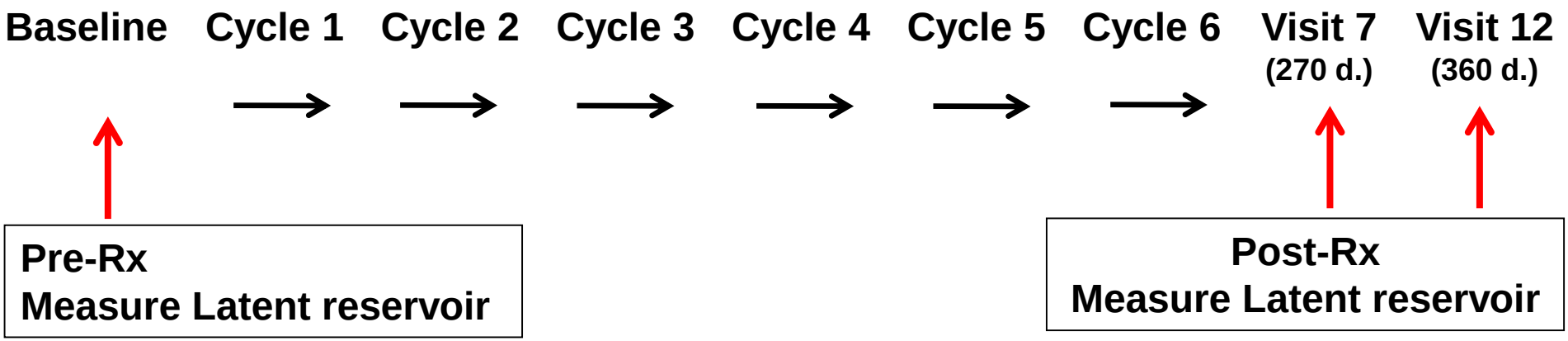
7-fold increase

No change

No change

AMC 075: VOR for HIV Lymphoma
Phase II, 90 participants

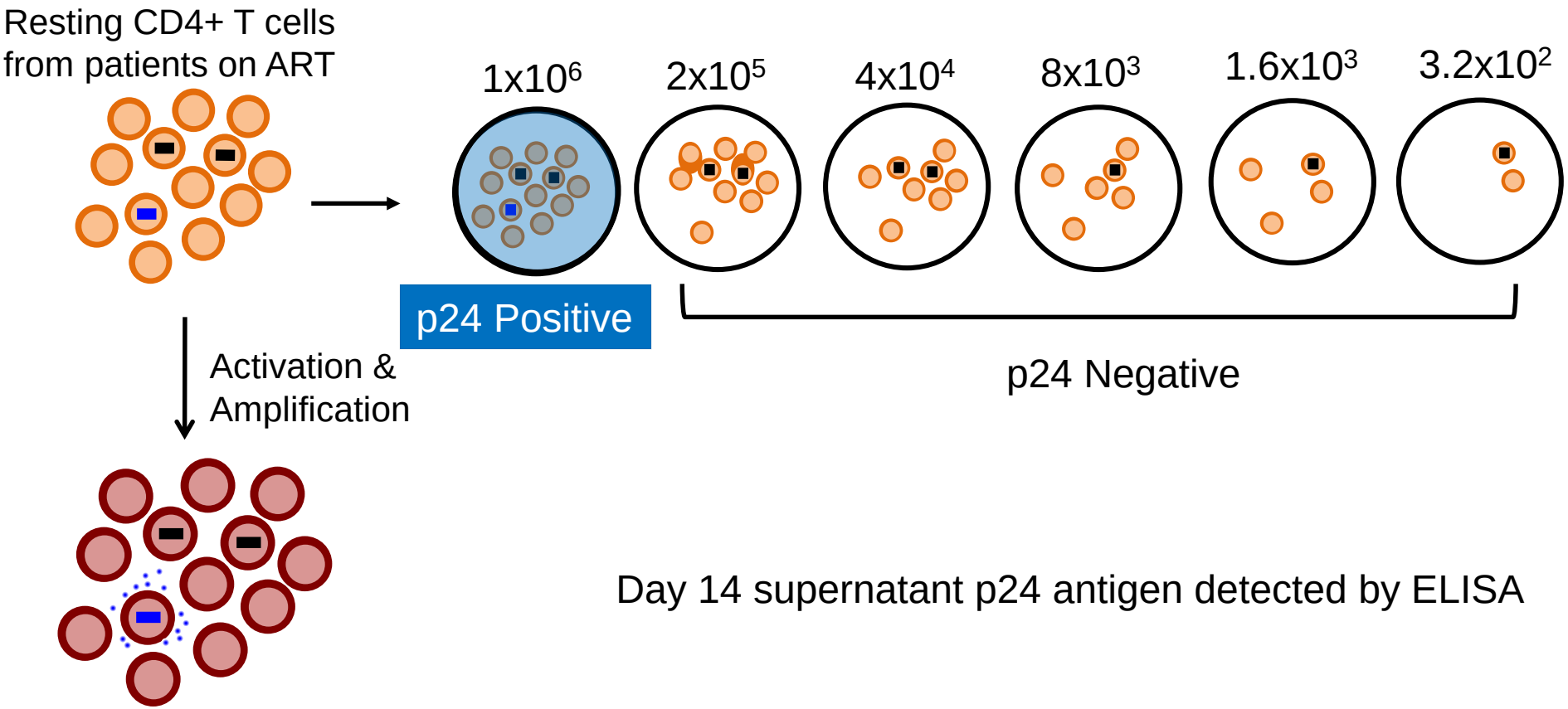
- Chemotherapy (R-EPOCH) with randomization +/- VOR
- VOR: 300 mg orally, day 1-5 of each 21 day cycle, for 6 cycles



- Latent reservoir was measured in a subset of patients whose HIV was suppressed at baseline and remained suppressed throughout study on ART

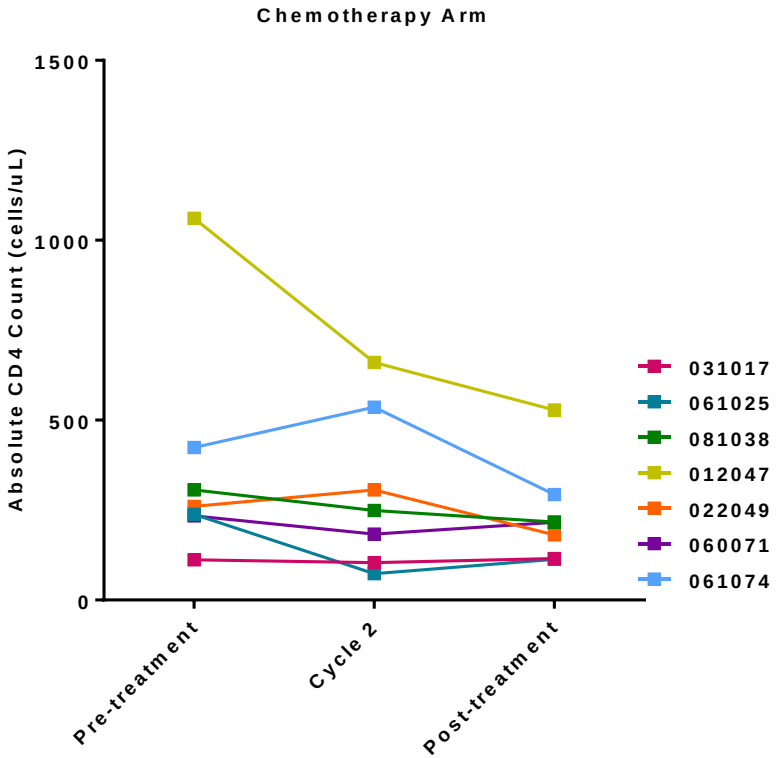
Quantitative Viral Outgrowth Assay

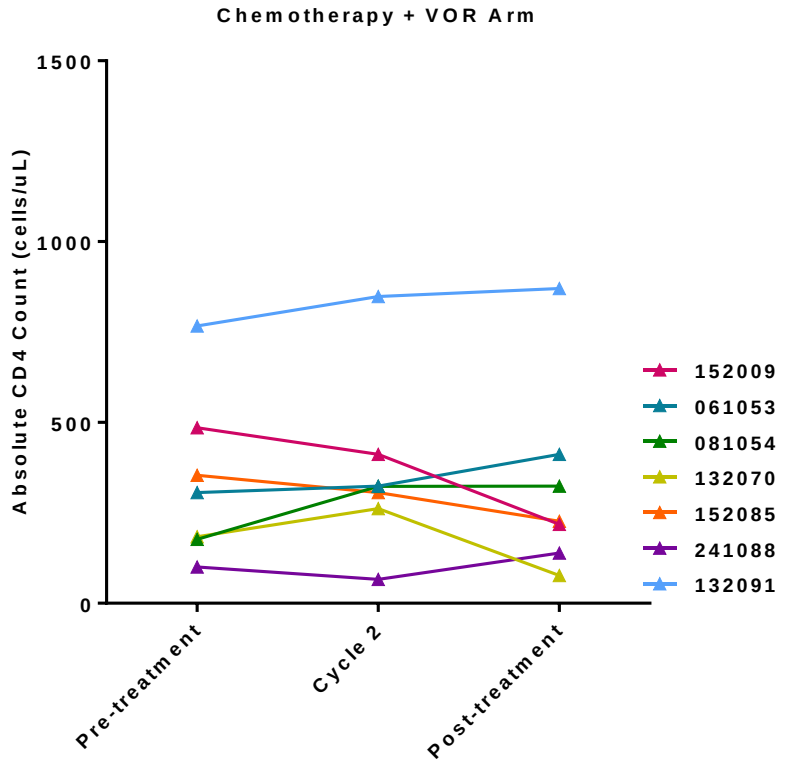
- Quantitative Viral Outgrowth Assay (QVOA)



- For statistics, a mixed effects Bayesian model

Impact of chemotherapy and VOR on CD4 counts



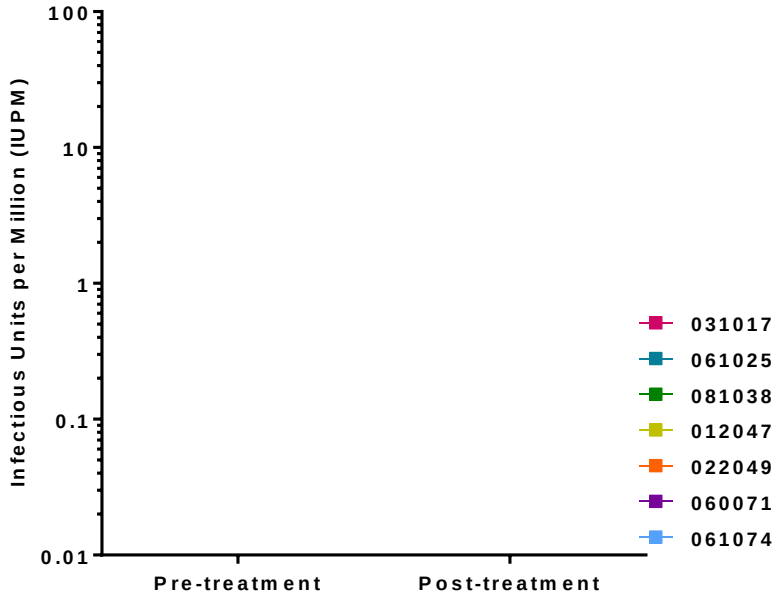


No significant change

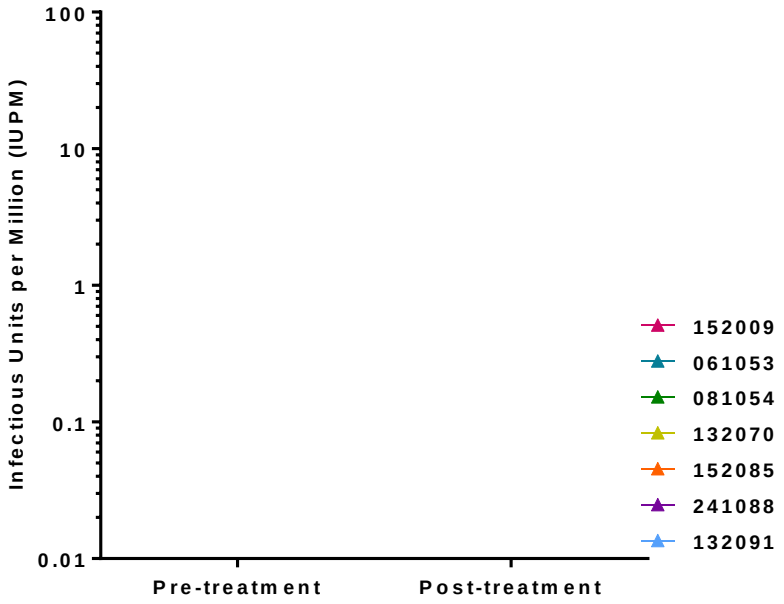
HIV LR Measurements (n =14)

Treatment Effect by Group

N =7

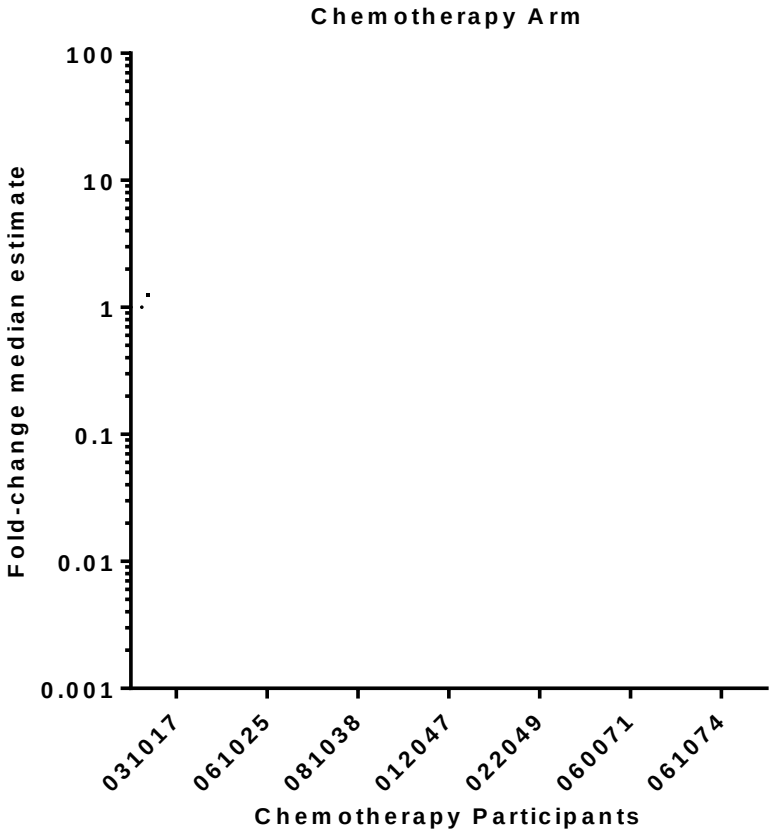


N =7



VOR Treatment Effect	Fold-change Median Estimate (95% CI)
Inter-patient average	1.08 (0.21, 5.13)

Individual treatment effect



Conclusions

- In a randomized trial of VOR plus chemotherapy, there were no significant changes detected in the HIV LR by qVOA in 14 patients
  - By group (fold-change 1.08) or by individual (fold-change range 0.48-2.70)

- Limitations:
  - Large confidence intervals with qVOA
  - Small N to date (anticipating 6 additional patients)
  - Did not looked specifically for a “shock” or HIV reactivation effect
  - Patients with malignancies receiving chemotherapy may not have effective CTL responses to eliminate latently infected cells even if HIV is reactivated

- Consistent with a recent new study by Archin/Margolis of 5 patients who received VOR 3 days per week x 8 weeks, no change in reservoir by qVOA measurements

Future Directions

- Need for more effective “kill” strategies

Acknowledgements

The AMC 075 Team

Juan Carlos Ramos
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Probability of VOR Effect

Participant	Fold-change Median Estimate (95% CI)	Probability that VOR increased IUPM	“p-value”
152009	0.85 (0.16, 4.72)	41%	0.82
061053	0.95 (0.13, 6.67)	47.7%	0.954
081054	2.20 (0.38, 14.96)	81.5%	0.37
132070	1.51 (0.23, 11.32)	71.6%	0.57
152085	0.48 (0.01, 3.56)	24.5%	0.49
241088	0.62 (0.07, 3.81)	27.5%	0.55
132091	2.70 (0.45, 23.28)	86%	0.28

How to measure treatment effect while controlling for temporal change?

Method: Mixed effects Bayesian model coded in Stan

Baseline IUPM for each participant (fixed effect)

Temporal fold-change in IUPM (random effect, applies to both arms)

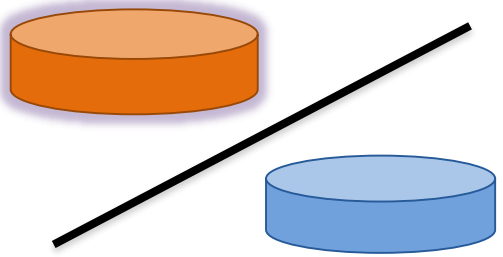
Treatment fold-change in IUPM (random effect, applies to treatment arm only)

"Effective IUPM" in well

×

cells in well (known)

Poisson likelihood that a well is positive / negative



Method adapted from Rosenbloom, Deng, ..., Busch, Bacchetti (in prep)