Viral and Immune Predictors of Time to Viral Rebound in SHIV-Infected Infant Macaques

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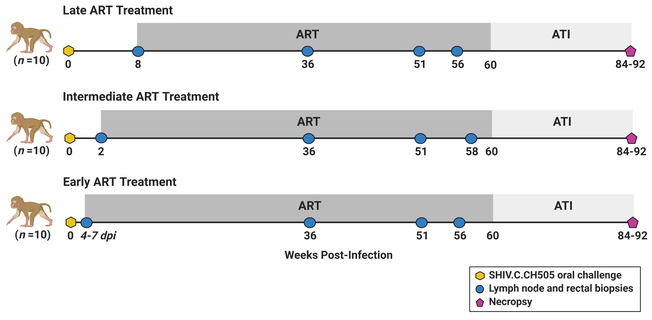
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BACKGROUND

Interruption of antiretroviral therapy (ART) to evaluate HIV remission in pediatric clinical trials presents ethical challenges. Determining a set of predictors of time to viral rebound (TTR) in a preclinical model could identify biomarkers to guide remission strategies and clinical trial design.

METHODS

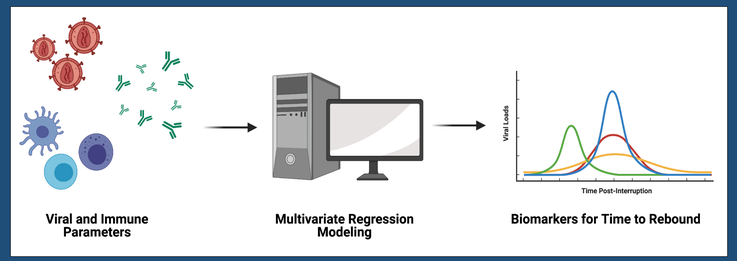
Study Design: 4-week-old rhesus macaques (RMs) were orally infected with SHIV.C.CH505.375H.dCT and placed on daily ART for 1 yr prior to analytical treatment interruption (ATI). Peripheral blood, lymph nodes (LN), and rectal biopsies (RB) were collected to quantify viral and immune (cellular and humoral) parameters pre-ART and pre-ATI.



Biomarker Analyses: Cox Proportional Hazards model with LASSO regularization was used to identify and rank parameters that predicted TTR, defined as the timepoint when PVL exceeded the LOD (60 copies/ml) for two consecutive samplings. Over 80 variables (summarized in Table 1) were pruned for multi-linearity using a Pearson correlation cutoff of 0.9. LOOCV deviance was used for selection of predictor variables (Table 2).

Table 1. Viral and immune measures evaluated as biomarkers for TTR

Viral Parameters	Immune Parameters
Plasma viral loads (PVL)	T cell subset frequency
Residual plasma viremia	T cell activation & exhaustion
Total cell-associated DNA & RNA	T cell responses
Intact proviral DNA	NK cell frequency
	NK cell activation
	Antibodies: binding, neutralizing, ADCC, & ADCP



Peak PVL pre-ART best described TTR,
but predictive strength increased with successive inclusion of 10 additional viral and immune parameters measured pre-ART and/or pre-ATI

RESULTS

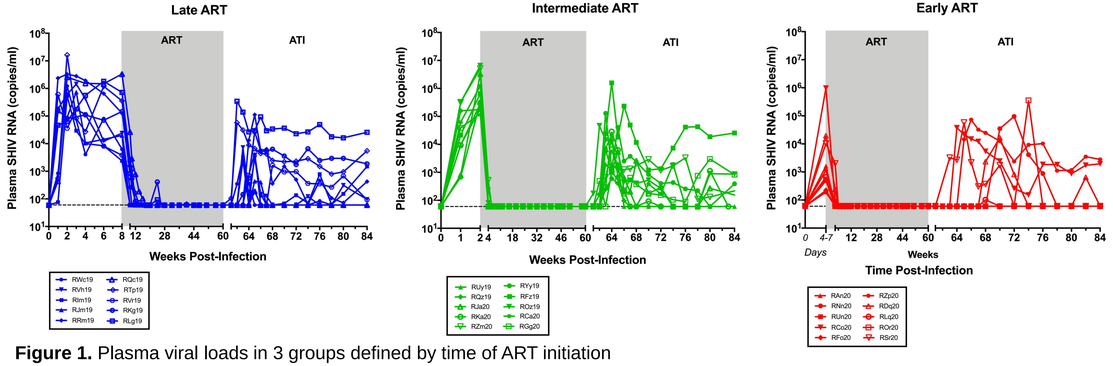


Figure 1. Plasma viral loads in 3 groups defined by time of ART initiation

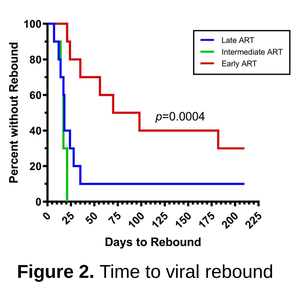


Figure 2. Time to viral rebound

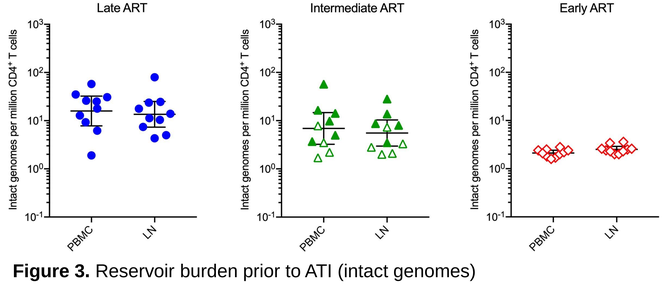


Figure 3. Reservoir burden prior to ATI (intact genomes)

Table 2. Selection of variables predicting TTR

Inclusion Rank	Predictor	LOOCV Deviance
1	Log peak PVL (Pre-ART)	4.03
2	Log RNA in blood CD4+ T (Pre-ART)	3.89
3	% Perf+ CD69+ NK in LN (Pre-ATI)	3.88
4	Intact genomes in LN CD4+ T (Pre-ATI)	3.84
5	Log RNA in RB CD4+ T (Pre-ATI)	3.82
6	% GzmB+ CD8+ T in LN (Pre-ATI)	3.81
7	ADCC levels (Pre- ATI)	3.72
8	% Antibodies binding infected cells (Pre-ATI)	3.67
9	% FoxP3+ CD4+ T in LN (Pre-ATI)	3.65
10	% Ki67+ Central Memory CD4+ T in LN (Pre-ATI)	3.64
11	Log RNA in blood CD4+ T (Pre-ATI)	3.63
12	Log RNA in LN CD4+ T (Pre-ATI)	3.67

Prediction Strength

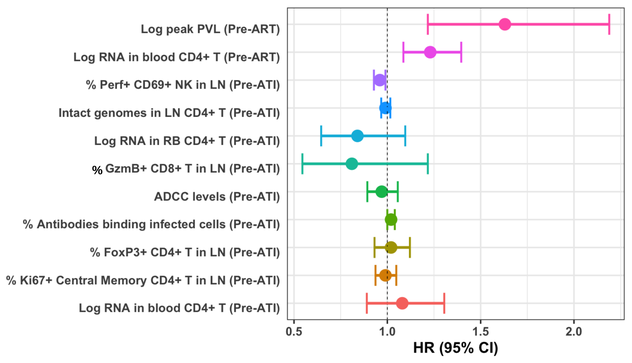


Figure 4. Marginal hazard ratios

CONCLUSIONS

- Reservoir size on long-term ART alone could not fully explain TTR
- Multivariate modeling identified viral and immune parameters that, in combination, provided the best prediction of TTR in SHIV-infected infant macaques
- Identified predictors should be explored as potential biomarkers to screen children being considered for ATI in studies of HIV remission approaches

ACKNOWLEDGEMENTS

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