Size and Activity of the HIV Reservoir Predict Rebound Timing After ART Interruption

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Jonathan Z. Li[1], Autumn Kittilson[1], Meghan Melberg[1], Elizabeth Wonderlich[2], Jennifer Kinslow[3], Evgenia Aga[4], Ronald Bosch[4], Yijia Li[1], Mark Pilkinton[5], Lynsay MacLaren[6], Michael Keefer[7], Ed Acosta[8], Lawrence Fox[9], Liz Bar[10], John Mellors[11], Robert Coombs[12], Steven Deeks[13], Rajesh Gandhi[14], Michael Busch[15], Alan Landay[3], Bernard Macatangay[11], and Davey M. Smith[16] for the A5345 Study Team

[1]Brigham and Women's Hospital, Harvard Medical School, [2]Southern Research, [3]Rush University, [4]Harvard T.H. Chan School of Public Health, [5]Vanderbilt University Medical Center, [6]Whitman Walker Health, [7]University of Rochester, [8]University of Alabama, [9]National Institute of Allergy and Infectious Diseases, [10]ACTG Community Scientific Subcommittee, [11]University of Pittsburgh, [12]University of Washington, [13]University of California, San Francisco, [14]Massachusetts General Hospital, Harvard Medical School, [15]Vitalant Research Institute, [16]University of California, San Diego

BACKGROUND

- Strategies for ART-free HIV remission ultimately require validation through treatment interruption (TI) studies to confirm a delay in HIV rebound
- Identification of biomarkers predictive of time to rebound is essential for developing and evaluating promising treatment strategies
- AIDS Clinical Trials Group (ACTG) trial A5345 is a prospective TI study to determine associations between virologic, immunologic and host biomarkers and time to rebound
- We compared the timing of HIV rebound for early-treated and chronic-treated cohorts

A5345 STUDY DESIGN

Key Inclusion Criteria

- ART initiation:
  - Initiated ART >6 months after date of infection (Cohort A, chronic-treated) OR
  - Initiated ART during Fiebig stages III-V (Cohort B, early-treated)
- ≥2 years of suppressive ART

ART Restart Criteria

- HIV-1 RNA at ≥1,000 copies/mL on two consecutive measurements

Table 1: Participant Characteristics

	Overall (N=45)	Chronic (N=33)	Early (N=12)
Age (median years)	45	46	38
Sex			
Male	91%	88%	100%
Female	9%	12%	0%
Race/ethnicity			
White	56%	73%	8%
Black	9%	12%	0%
Hispanic	18%	12%	33%
Asian, Pacific Islander	13%	0%	50%
More than one race	4%	3%	7%
Country			
USA	87%	100%	50%
Thailand	13%	0%	50%
Baseline CD4 (cells/mm^3)	771	783	742
Pre-ART Viral Load (log_{10} copies/mL)	4.6 (N=35)	4.5 (N=23)	5.7 (N=12)

Laboratory Assays

- Pre-TI viral reservoir markers were quantified by the following assays:
  - Unspliced cell-associated RNA (CA-RNA)
  - Total HIV DNA (total-DNA)
  - Intact proviral DNA (IPD) by the IPDA
  - Residual viremia by the integrase single-copy assay (iSCA)
  - Infectious units/million rCD4 cells (IUPM) by the differentiation quantitative viral outgrowth assay (dQVOA)
  - T cell phenotyping and HIV-specific immune responses to Gag, Env, Pol (CD107a, TNFa, IL-2, IFNg)
  - Antibody levels (HIV-1+2 Ab, HIV Combo Ab, LAg-Avidity)

RESULTS

- Early-treated participants had smaller (lower HIV DNA, IUPM, IPD) and less transcriptionally active HIV reservoirs (lower CA-RNA) (**Figure 1**)
- Lower reservoir activity was modestly associated with a delay in HIV rebound including CA-RNA (Spearman's r = -0.26, p = 0.08), the pre-specified primary measure (**Table 2**)
- The strongest predictor of time to HIV rebound was IPD in chronic-treated participants and iSCA in early-treated participants (**Table 2**)
- Pre-treatment interruption, significant correlations were detected across multiple reservoir markers and CA-RNA strongly correlated with total-DNA but only modestly correlated with intact proviral DNA (**Figure 2**)
- A higher percentage of HIV gag-specific CD8+ T cell cytotoxic response (CD107a) was associated with a lower IPD (Spearman's *r* = -0.37, P=0.02)

Figure 1: Early-treated participant reservoirs are smaller and less active

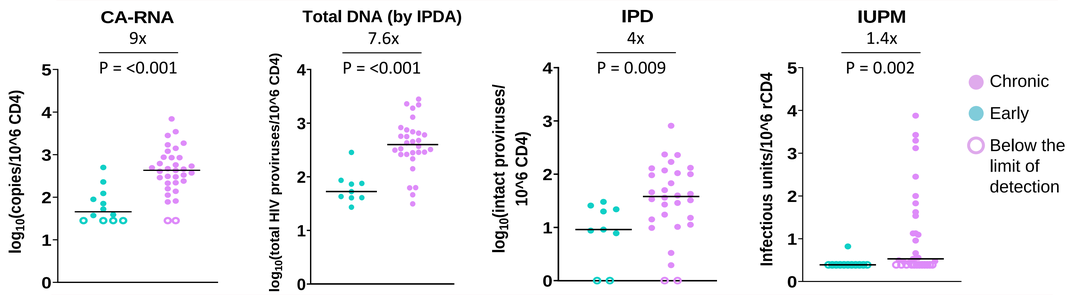
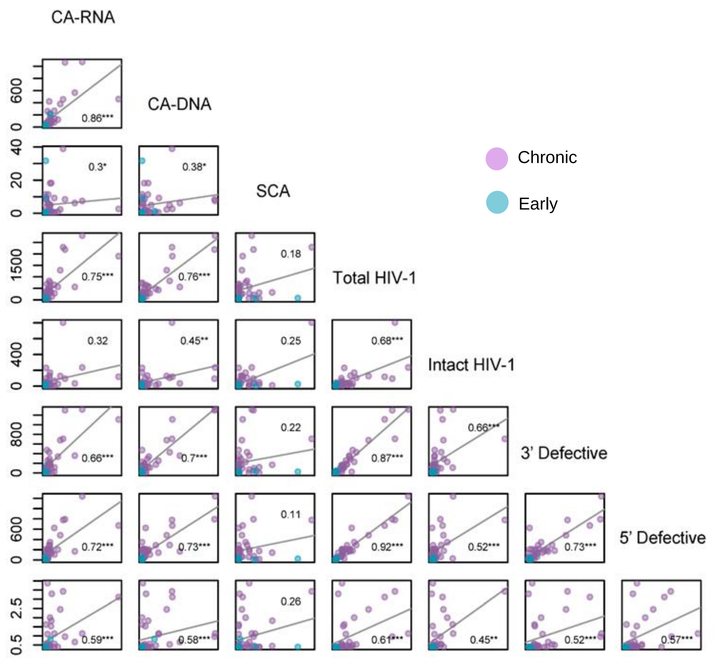


Table 2: Reservoir predictors of HIV rebound timing

	Overall			Chronic			Early		
	N	Spearman Correlation	p-value	N	Spearman Correlation	p-value	N	Spearman Correlation	p-value
CA-RNA (copies/10^6 CD4)	45	-0.26	0.08	33	-0.27	0.13	12	-0.31	0.33
Total DNA (copies/10^6 CD4)	39	-0.18	0.26	30	-0.26	0.17	9	-0.50	0.17
IPD (intact proviruses/10^6 CD4 cells)	39	-0.28	0.09	30	-0.37	0.044	9	-0.27	0.48
iSCA (copies/mL)	45	-0.28	0.06	33	-0.11	0.55	12	-0.68	0.015
IUPM (infectious units/10^6 rCD4 cells)	45	-0.18	0.25	33	-0.17	0.35	12	-0.18	0.58

Figure 2: Reservoir marker correlations



CONCLUSIONS

- The strongest predictors of time to HIV rebound are the size of the intact reservoir for chronic-treated individuals and HIV residual viremia for early-treated individuals
- Smaller reservoir size and lower transcriptional activity in early-treated participants suggests early ART may lower the barrier to HIV remission
- We identified key HIV-specific CD8 immune responses associated with a smaller intact HIV reservoir size

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