Predictors of HIV Rebound after Interruption of Antiretroviral Therapy (ART) Started During Primary HIV Infection

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BACKGROUND

Understanding factors that affect timing of viral rebound after antiretroviral treatment (ART) interruption will accelerate efforts toward inducing sustained HIV remission.

STUDY GOAL

To evaluated whether size, activity, and molecular diversity of proviral DNA as well as peripheral T cell phenotypes prior to treatment interruption predict time to HIV RNA rebound in individuals interrupting ART initiated during primary infection.

METHODS

Cohort. The Zurich Primary HIV Infection Cohort (ZPHI) enrolled people with HIV (PWH) who started ART during primary infection and interrupted therapy after a median of 18.4 months of suppression.

Sampling. We selected stored samples (pre-ART interruption between 2002-2007) from 73 ZPHI participants. **Figure 1**.

Flow cytometry. Frequencies of T cell maturation subsets, T cell activation (HLA-DR$^+$CD38$^+$), exhaustion (PD-1$^{+,}$ TIGIT$^+$), cycling (Ki67$^+$) degranulation/cytotoxicity (CD107a$^+$) and regulatory CD4$^+$ T Cells (CD25$^+$FoxP3$^+$). **Figure 2**.

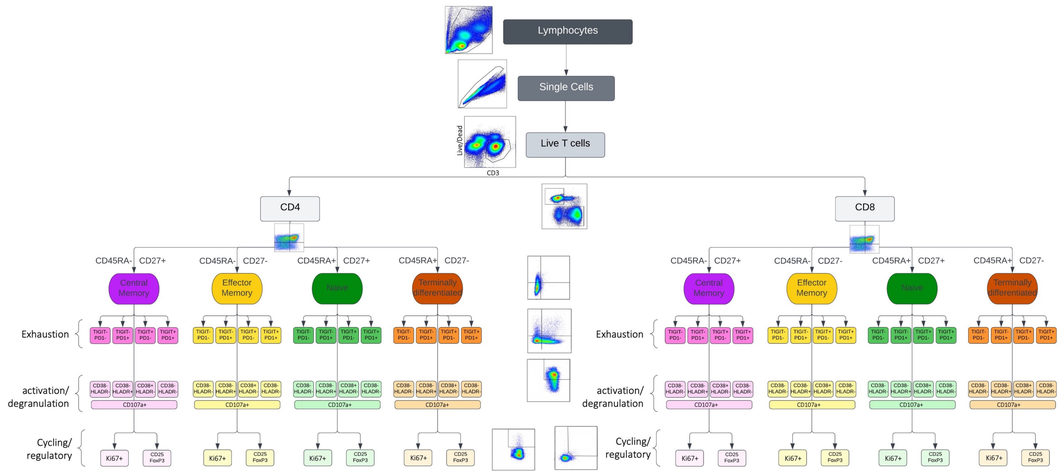
HIV reservoir measures. Levels of cellular HIV DNA (gag, N=67), HIV RNA (spliced and multiple spliced encoding *tatrev*, N=66) by digital droplet (dd)PCR, and molecular diversity by deep sequencing of HIV DNA by Illumina platform (full length envelope, N=40). **Figure 3.**

Statistics: We evaluated associations between time to rebound (i.e., reaching 1,000 copies/ml) and each clinical, virologic and immunologic factors using univariate Cox proportional hazard models for interval censored outcomes without adjusting for multiple comparisons.

Smaller and Less Diverse HIV Reservoir as well as Less Activated and Cytotoxic T Cells are Associated with Longer Time to Viral Rebound

A Combination of Viral and immune Factors are Likely Needed to Predict Time to HIV RNA Rebound after ART interruption

Figure 2. Flow Cytometry Panel and Gating Algorithm



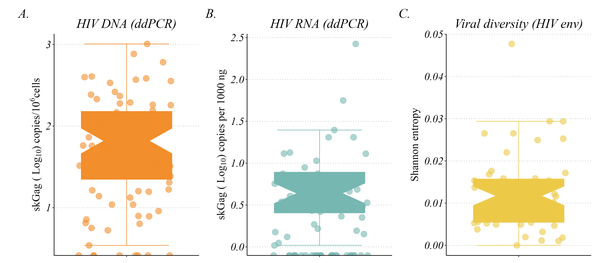
RESULTS

Viral reservoir predictors: Lower HIV DNA levels and lower molecular diversity of HIV DNA (envelope) pre-ART interruption was significantly associated with longer time to rebound (p=0.04 and p=0.05 respectively), but not the activity (cellular HIV RNA) of the HIV reservoir.

Immune predictors. Lower percentage of effector and terminally differentiated CD4$^+$ and CD8$^+$ T cells expressing markers of activation and degranulation/cytotoxicity were consistently associated with longer time to rebound (all P<0.05, **Table 2**).

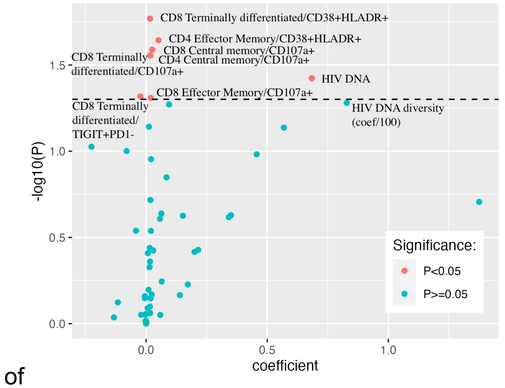
Clinical predictors. None of the clinical predictors (listed in Table 1) were associated with time to rebound. **Figure 4** provides an overview of all predictors

Figure 3. HIV DNA and RNA levels and Diversity



Legend: Levels of cellular HIV DNA (gag, N=67), HIV RNA (spliced and multiple spliced encoding tatrev, N=66) were generated by digital droplet PCR, and molecular diversity by deep sequencing of HIV DNA by Illumina platform (full length envelope, N=40), Figure show Median and Interquartile Range.

Figure 4. Predictors overview



Legend: *-log10(P):* P-values scaled by -log10. The dashed line indicates -log10(0.05). *coefficient:* the estimated effect size of a predictor on the hazard of viral rebound.

CONCLUSIONS

We found a combination of viral and immune factors associated with longer time to rebound after ART interruption in PWH starting ART during early infection.

Smaller and less diverse HIV reservoirs as well as less activated and cytotoxic T Cells are associated with longer time to viral rebound

Additional studies are needed to validate the immune and reservoir mediators of delayed HIV rebound that may act as predictive biomarkers and targets for interventions.

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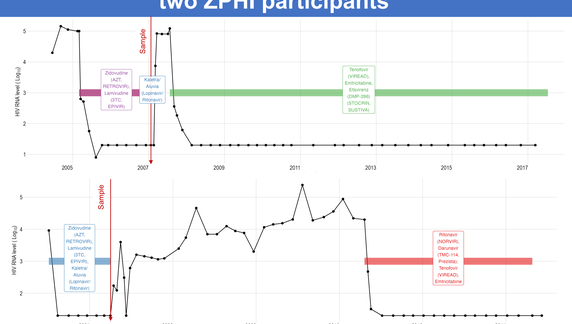
Figure 1. Example of HIV RNA trajectories and ART intake for two ZPHI participants



Legend: Red arrow marks time of sample selection

Table 1. Cohort Characteristics

Characteristics	N (%) or Median [IQR]
Male Sex	64 (87.7%)
Mode of infection	
Homosexual contact	55 (75.3)
Heterosexual contact	17 (23.3)
Other	1 (1.37)
Age at the time of diagnosis	37.1 [30.0; 45.4]
White Ethnicity	67 (91.8)
CD4 T Cell count at enrollment	418 [167;841]
CD8 T Cell count at enrollment	726 [224;3982]
Time from EDI to ART initiation (months)	1.4 [1.15, 2.0]
Time on ART (months)	18.4 [13.6; 21.0]

Table 2. Factors Significantly Predictive of Shorter Time to Viral Rebound

Factors	Estimate	95% CI	p-value
Terminally differentiated CD8 T Cells –(CD38 and HLA-D)+	0.0163	(0.003, 0.03)	0.02
Effector memory CD4 T Cells – (CD38 and HLA-DR)+	0.0511	(0.007, 0.095)	0.02
Central memory CD8 T Cells – (CD107a)+	0.0252	(0.003,0.047)	0.03
Terminally differentiated CD8 T Cells – (CD107a)+	0.0164	(0.002,0.031)	0.03
Central memory CD4 T Cells - (CD107a)+	0.0181	(0.002,0.034)	0.03
Effector memory CD8 T Cells – (CD107a)+	0.0196	(0,0.039)	0.05
Mean molecular diversity HIV DNA (env)	82.85	(-0.862, 166.56)	0.05
HIV DNA levels	0.6841	(0.039,1.330)	0.04

Legend: *Estimate:* the estimated effect sizes of the factors on the hazard of viral rebound. An estimated effect greater than zero indicates that as the factor increases, the hazard of viral rebound increases and thus the time to rebound decreases.