Elevated Plasma IL-10 and Type I Interferon Predict Faster HIV Reservoir Decay in Acute Treated HIV

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BACKGROUND

- While antiretroviral therapy (ART) is able to suppress virus to undetectable levels, virus rapidly rebounds from latently-infected cells ("the HIV reservoir") within weeks of ART interruption.[1-2]
- A major goal of HIV cure is to reduce the HIV reservoir size to induce ART-free remission in people with HIV (PWH).[3]
- While there have now been a handful of studies modeling HIV reservoir decay during prolonged (~20 years) ART,[4-7] there have been no studies quantifying decay rates immediately after acute treated HIV infection.
- Here, leveraging >500 longitudinal samples from 67 PWH treated during acute HIV infection, we developed a novel mathematical model to predict peripheral CD4+ T cell reservoir decay using the intact proviral DNA assay (IPDA).[8]

METHODS

- Participants were sampled from the UCSF Treat Acute HIV study which enrolls individuals diagnosed with acute (<100 days) HIV.[9]
- Participants were provided immediate ART with TDF/FTC (later, TAF/FTC) + DTG, linked to clinical care, and followed monthly for 24 weeks, followed by every ~3 months thereafter.
- HIV intact and defective DNA was quantified using the IPDA at weeks 0, 2, 4, 8, 12, 16, 20, and 24.[8]
- High-sensitivity multiplex plasma cytokine assays (MesoScale Diagnostics) were performed from cryopreserved plasma samples across the same longitudinal timepoints.
- Semiparametric generalized additive models were fit to model HIV intact and defective decay rates over time.

$$\log_{10} \mathrm{I}_{it} \sim (T_{it} \wedge \tau) + (T_{it} - \tau)_+ + A_{it} + A_{it}(T_{it} \wedge \tau) + A_{it}(T_{it} - \tau)_+ + \mathrm{E}_i\,(T_{it} \wedge \tau) + E_i(T_{it} - \tau)_+ + \widehat{\beta}_i + s(V_i) + s(C_i) + \mu_i$$

where
I_{it} : Intact (or Total Defective) proviral HIV DNA Count
T_{it} : Weeks Since ART Initiation
A_{it} : Cytokine Concentration (pg/mL)
E_{it} : Estimated Delay in ART Initiation (Weeks)
β_i : Trend in CD4+ T-cell Count
C_i : Initial CD4+ T-cell Count
V_i : Pre-ART Viral Load
μ_i : Participant-level Random Effect
$(T_{it} \wedge \tau) = \min(T_{it}, \tau) = T_{it}\,1\{T_{it} < \tau\}$
$(T_{it} - \tau)_+ = \max(T_{it} - \tau, 0) = (T_{it} - \tau)\,1\{T_{it} - \tau > 0\}$
Continuous linear spline with one knot at τ
$s(x)$ cubic regression spline

RESULTS

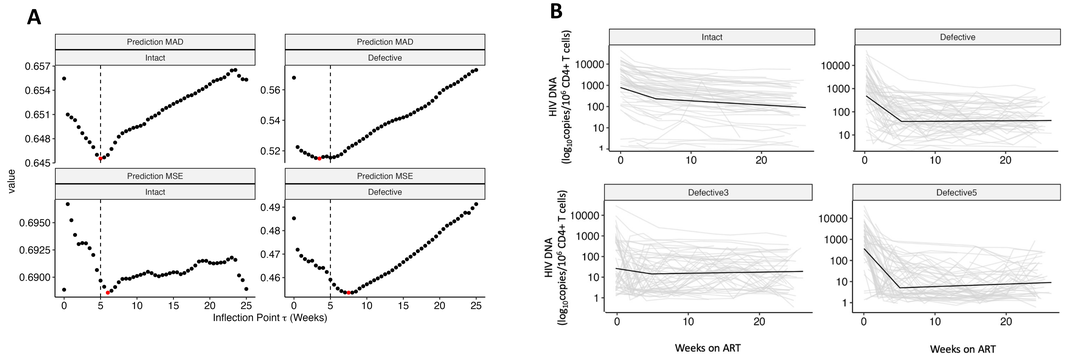
Table 1. Baseline characteristics of study population

Descriptive Characteristics	Total N=35
Sex at birth (% male)	35 (100%)
Age (years)	29 (25 – 36)
Initial CD4+ T-cell count (cells/mm^3)	418 (348 – 662)
Pre-ART plasma HIV RNA (log_{10} copies)	5.3 (4.4 – 5.9)
Race/Ethnicity (self-report)	
Caucasian (%)	9 (26%)
Latinx (%)	10 (29%)
Asian (%)	9 (26%)
African American (%)	6 (17%)
Other (%)	1 (3%)
Fiebig staging (HIV recency)	
I-III (%)	13 (37%)
IV-V (%)	22 (63%)
Timing of ART initiation (days from detected HIV)	40 (22 – 79)

Medians with interquartile ranges (or %). Fiebig stages were estimated as previously described.[10]

- Acute treated PWH with higher plasma **IL-10** and **IFN-β** demonstrated accelerated **HIV intact** and **defective** reservoir decay.
- IL-10 and type I interferons are well known to exert variable effects on the host immune response depending on stage of disease.
- Our findings highlight the need to consider potential stage-specific targeting of these complex signaling pathways in future HIV cure trials.

Figure 1. Rapid biphasic decay of HIV intact and defective decay was observed during acute treated HIV



A. *Visualization of the tuning of inflection points (tau, t) evaluated along a grid from 0 weeks to 24 weeks from semiparametric generalized additive models using data from the entire cohort (N=67). Results are shown for both intact (left) and defective (right) HIV DNA decay models, respectively. The biphasic decay model's inflection point was tuned by estimating the tau that minimized prediction error measured by leave-one-out mean absolute deviation (MAD, upper panels) and leave-one-out mean squared error (MSE, lower panels). The best tau for each loss is shown in relation to the final model's selected inflection point of ≒ 5 weeks as reference (vertical dashed line).* ***B.*** *Biphasic decay patterns were observed for HIV intact (upper left) and total combined defective (upper right), as well as for 3' plus 5' defective (lower panels). Grey lines represent observed patients, and black lines represent the fitted, average patient. Average predicted participant trajectories were generated by taking the mean of Ei (estimated time between HIV infection and ART initiation), Ci (initial CD4+ T cell count), and Vi (log_{10} pre-ART plasma viral load) across participants from our final model.* ***Of note: for the analyses including cytokine levels, we also included an additional term for the time-varying trend in CD4+ T cell count; this was to ensure that variations in CD4+ T cell counts (which could potentially affect or be affected by cytokine levels) were also accurately modeled in the biphasic decay.***

Table 2. Among 20 cytokines evaluated, plasma IL-10 and IFN-β levels significantly predicted accelerated HIV intact and defective reservoir decay rates during acute treated HIV

A Intact Phase 1

Cytokine	N	Estimate	SE	p	q	Change in $t_{1/2}$ (Weeks) per 2-Fold ↑Cytokine (95% CI)
IL-10	31	-0.067	0.021	0.0016**	0.066*	-0.43 (-0.76, -0.10)
IFN-β	31	-0.003	0.001	0.0026**	0.070*	-0.02 (-0.04, -0.002)

B Defective Phase 1

Cytokine	N	Estimate	SE	p	q	Change in $t_{1/2}$ (Weeks) per 2-Fold ↑Cytokine (95% CI)
IL-10	31	-0.046	0.051	0.3633	0.9032	-0.08 (-0.26, 0.10)
IFN-β	31	-0.007	0.002	0.0016**	0.0655*	0.02 (-0.03, 0.0004)

C Intact Phase 2

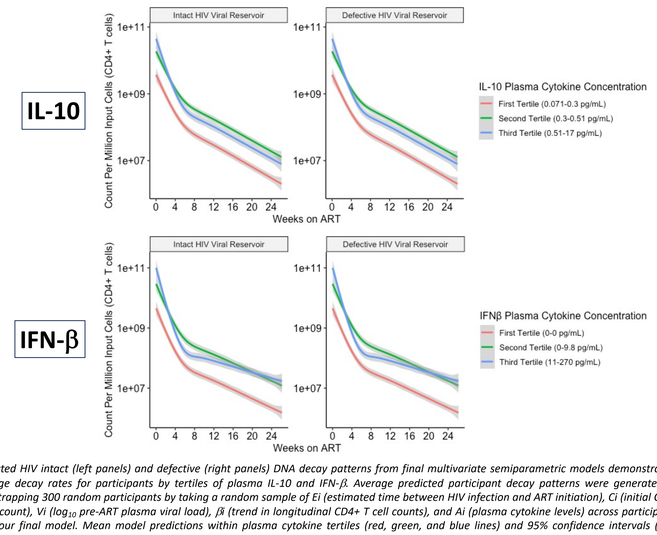
Cytokine	N	Estimate	SE	p	q	Change in $t_{1/2}$ (Weeks) per 2-Fold ↑Cytokine (95% CI)
IL-10	31	0.001	0.017	0.9640	0.9887	0.09 (-3.67, 3.83)
IFN-β	31	7.8e-5	3.4e-4	0.8182	0.9769	0.01 (-0.08, 0.10)

D Defective Phase 2

Cytokine	N	Estimate	SE	p	q	Change in $t_{1/2}$ (Weeks) per 2-Fold ↑Cytokine (95% CI)
IL-10	31	0.002	0.041	0.9560	0.9887	12 (-335, 359)
IFN-β	31	0.0004	0.001	0.6341	0.9475	2.5 (-26.2, 31.8)

*Among 20 plasma cytokines, concentrations of IL-10 and IFN-β (a type I interferon) during the first 24 weeks of acute treated HIV significantly predicted accelerated HIV reservoir decay, even after adjustment for initial CD4+ T cell count, time-varying CD4+ T cell count, pre-ART viral load, and timing of ART initiation. Tables show change in half-life estimates in reservoir decay rates for HIV intact (**A, C**) and defective (**B, D**) DNA per two-fold increase in plasma cytokine concentrations from final biphasic decay models. SE = standard error. P = two-sided p-value (** p<0.05, * p<0.10). Q = two-sided false discovery rate (FDR) Benjamini-Hochberg q-value (** p<0.05, * p<0.10). Half-life estimates denote the predicted additive adjustment to the HIV DNA decay half-life in weeks for every 2-fold increase in cytokine concentration.*

Figure 2. Fold-increases in plasma IL-10 and IFN-β predicted faster HIV intact and defective decay during acute treated HIV



Predicted HIV intact (left panels) and defective (right panels) DNA decay patterns from final multivariate semiparametric models demonstrating average decay rates for participants by tertiles of plasma IL-10 and IFN-β. Average predicted participant decay patterns were generated by bootstrapping 300 random participants by taking a random sample of Ei (estimated time between HIV infection and ART initiation), Ci (initial CD4+ T cell count), Vi (log_{10} pre-ART plasma viral load), β (trend in longitudinal CD4+ T cell counts), and Ai (plasma cytokine levels) across participants from our final model. Mean model predictions within plasma cytokine tertiles (red, green, and blue lines) and 95% confidence intervals (grey shaded regions) are shown for IL-10 and IFN-β.

CONCLUSION

- Individuals with higher plasma interleukin (IL)-10 and type I interferon (IFN-β) expression during the first 24 weeks of acute treated HIV demonstrated accelerated reservoir decay.
- Both IL-10 and IFN-β are cytokines are well known to exert variable effects on the host immune response depending on stage of disease (e.g., favorable during acute but detrimental during chronic infection).[11-12]
- The finding that IL-10 was significantly associated with accelerated decay of the early HIV intact DNA reservoir is novel; prior work suggests that during chronic infection, IL-10 may maintain the SIV DNA reservoir.[13]
- Our findings add insight into the complexity of these pleiotropic cytokines and highlight the need for potential stage-specific targeting of these cytokines in future HIV cure strategies.

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