

Models and correlates of intact and defective HIV DNA decay in Kenyan children over 8 years of ART



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Children are *especially* valuable and relatively understudied population for cure

- **Generally smaller reservoirs and do decay** -- *Violari et al. 2008, Persaud et al. 2012, Jain et al. 2013, Luzuriaga et al. 1999*
- **Date of acquisition better-known**
- **Mortality still can be high in certain populations** -- *Tagarro et al. 2024*
- **Different immune milieu/inducibility?** -- *Ásbjörnsdóttir et al. 2018, Berendam et al. 2020, Dhummakupt et al. 2020*
- **Lifetime ART prognosis with associated challenges** -- *Zhou et al. 2024*
- **Lifetime of possible benefit (lifetime survivors!)** -- *Luzuriaga et al. 2015*

Optimizing pediatric HIV (OPH) cohort multi-data modeling study

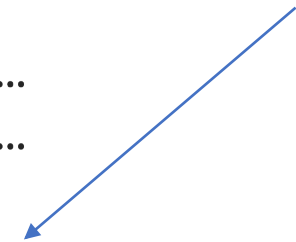
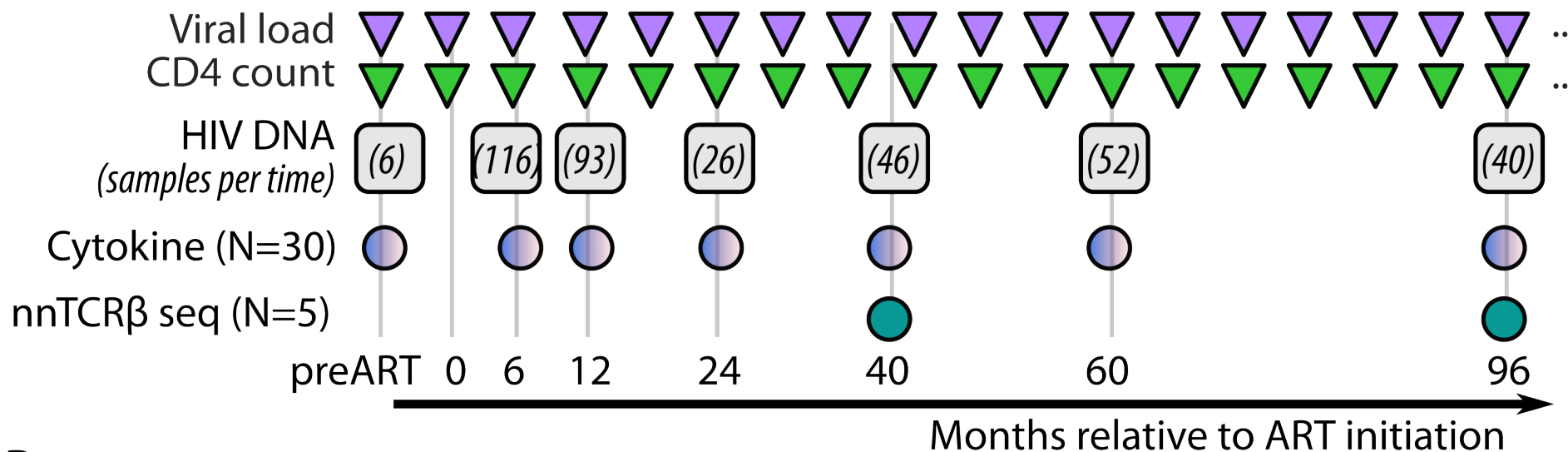
- 120 children in Nairobi Kenya who acquired HIV at or proximal to birth (subtype A and D)
- Very regular RNA and CD4 sampling over 8-10 years after birth
- CS-IPDA to estimate intact reservoirs



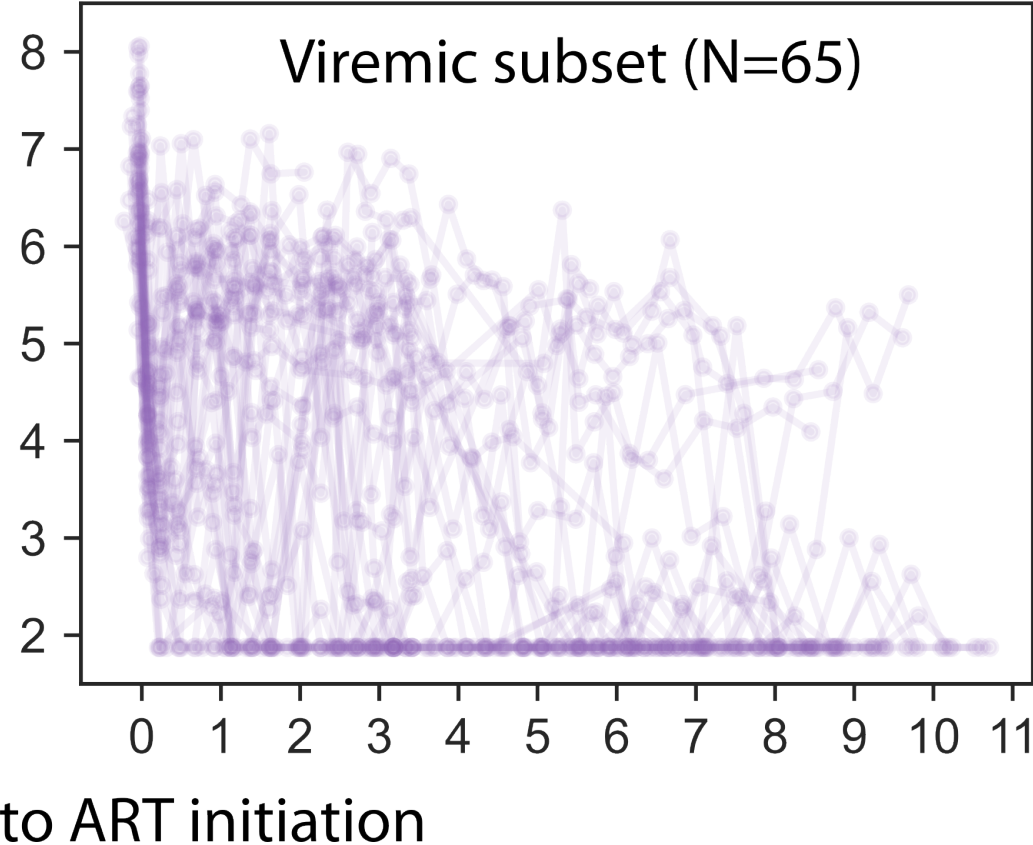
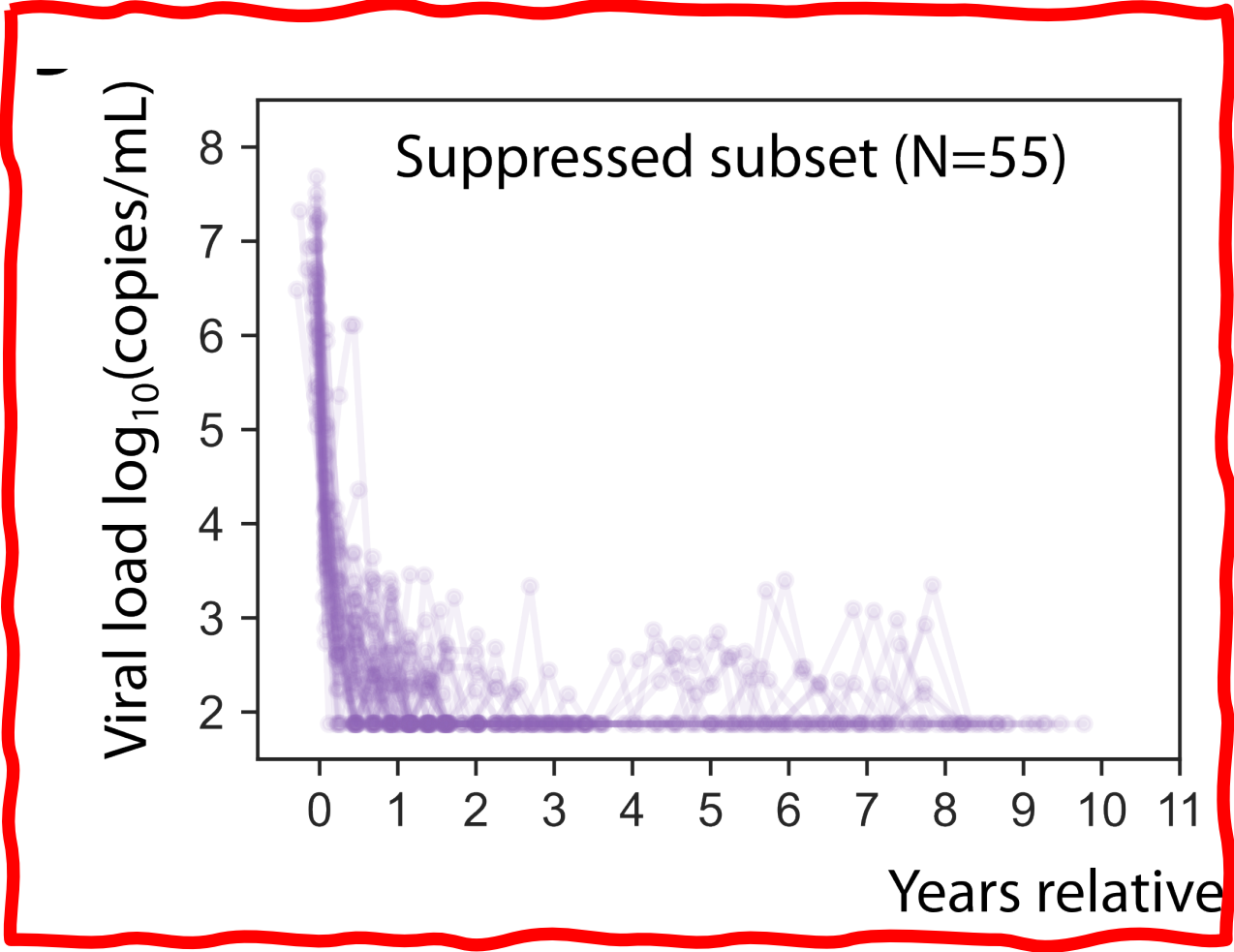
Cassidy et al. iScience 2022

Fish et al. STAR Protocols 2022

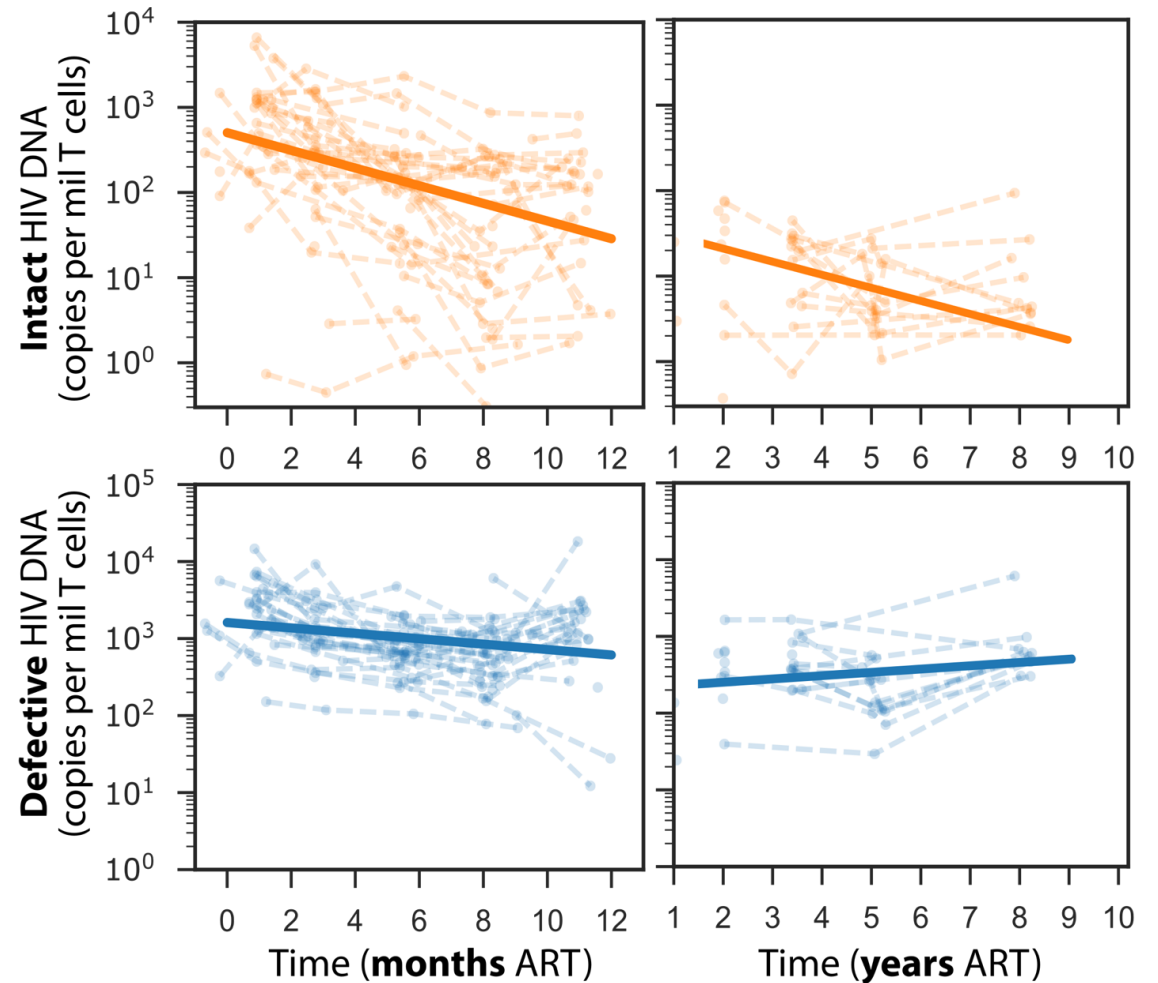
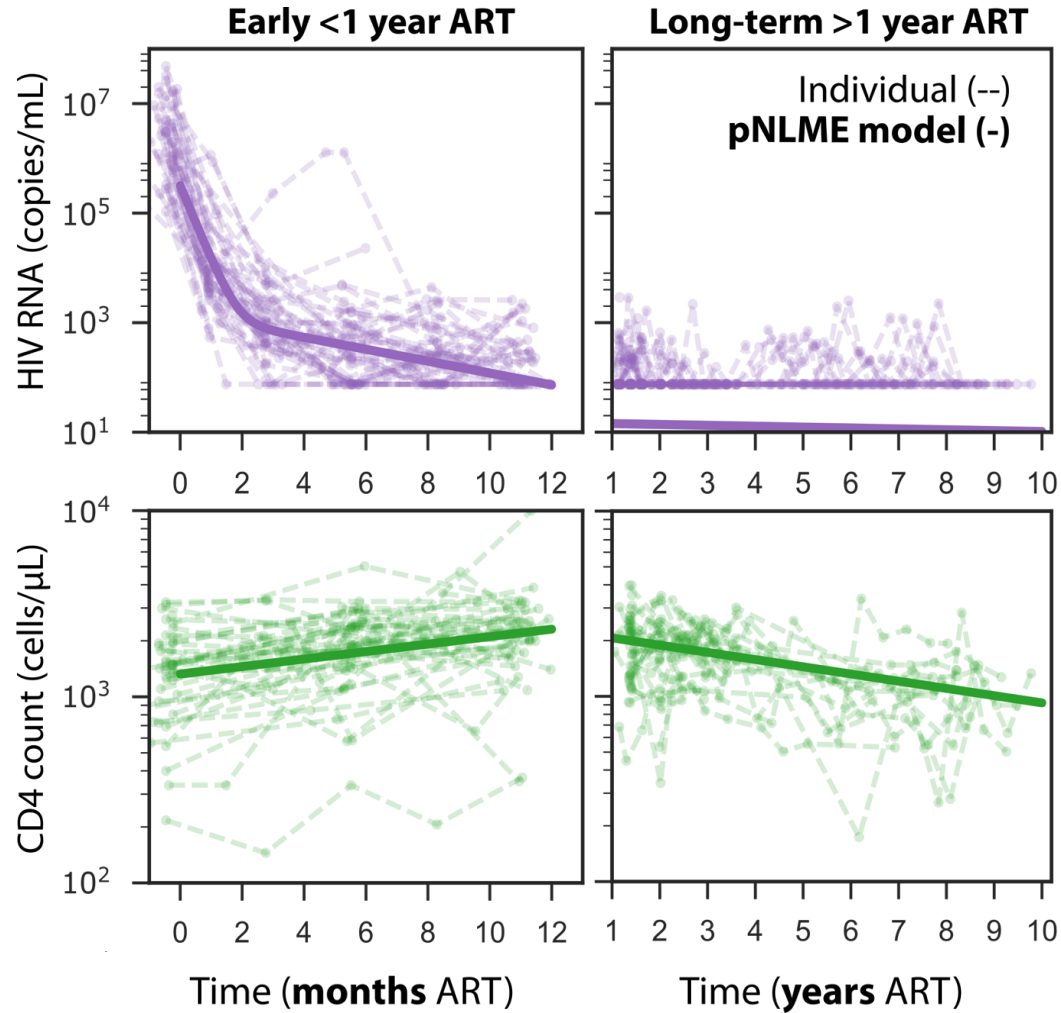
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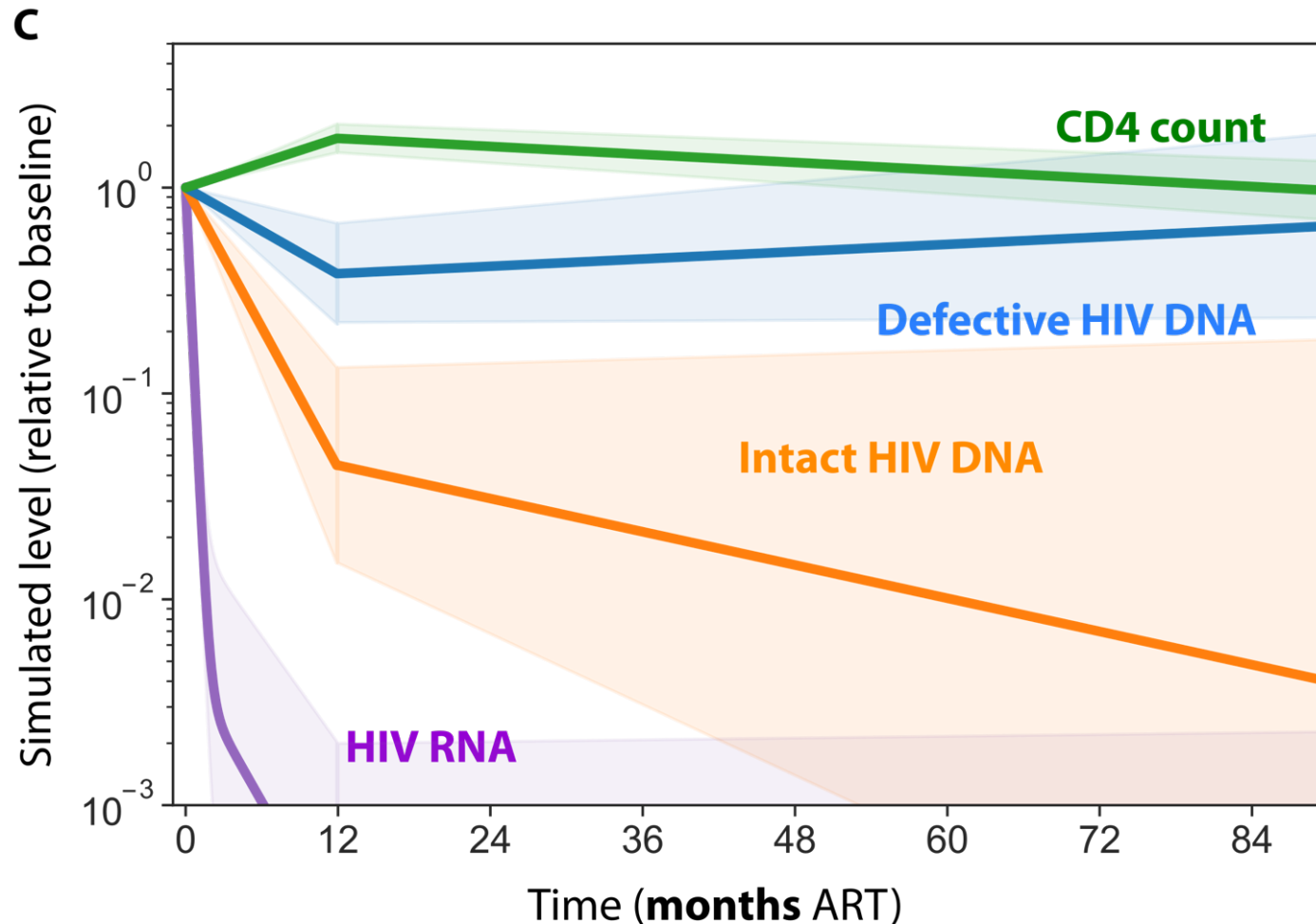
HIV RNA kinetics in suppressed and viremic subsets in the OPH cohort



Estimating kinetics from suppressed OPH subset



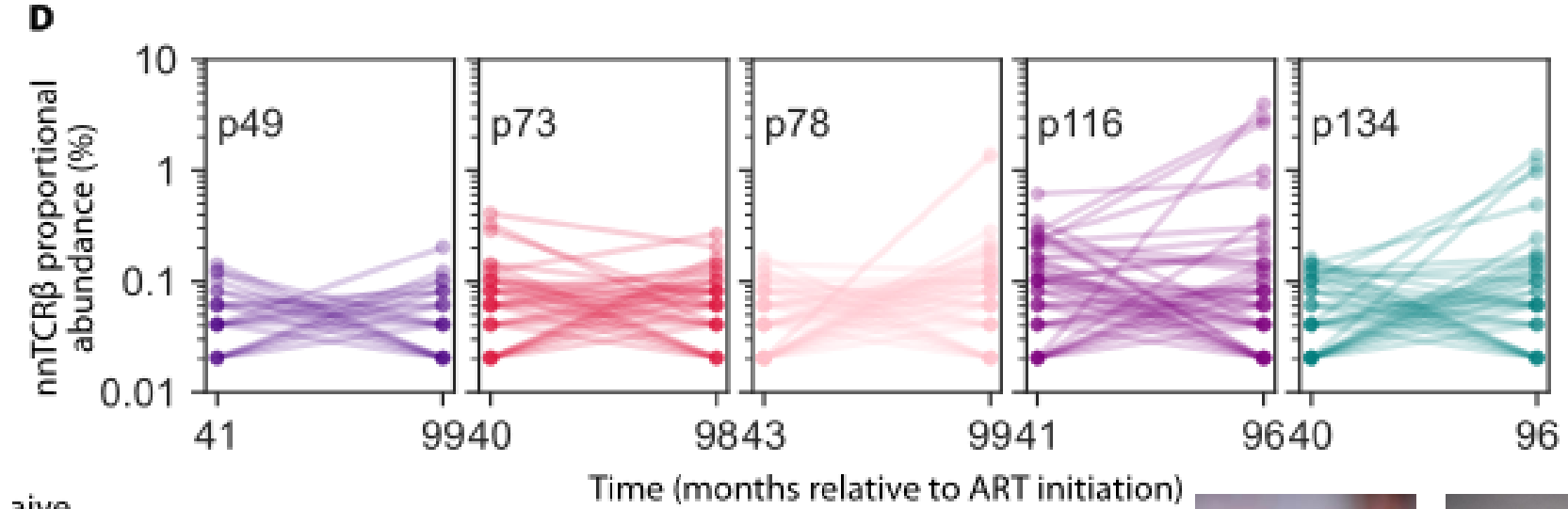
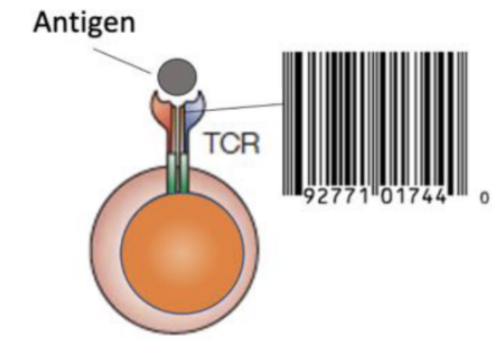
Summarizing kinetic rates of cells, HIV RNA and HIV DNA in this pediatric population



- RNA drops very rapidly in 2 phases
- DNA similar to RNA in first year
- CD4 count kinetics similar to previous data from HIVneg children
- Differential Int vs Def decay in first year
- Pediatric intact decay after 1 year overlaps with estimates from adults (~44mo)

Investigating an immunological correlate:

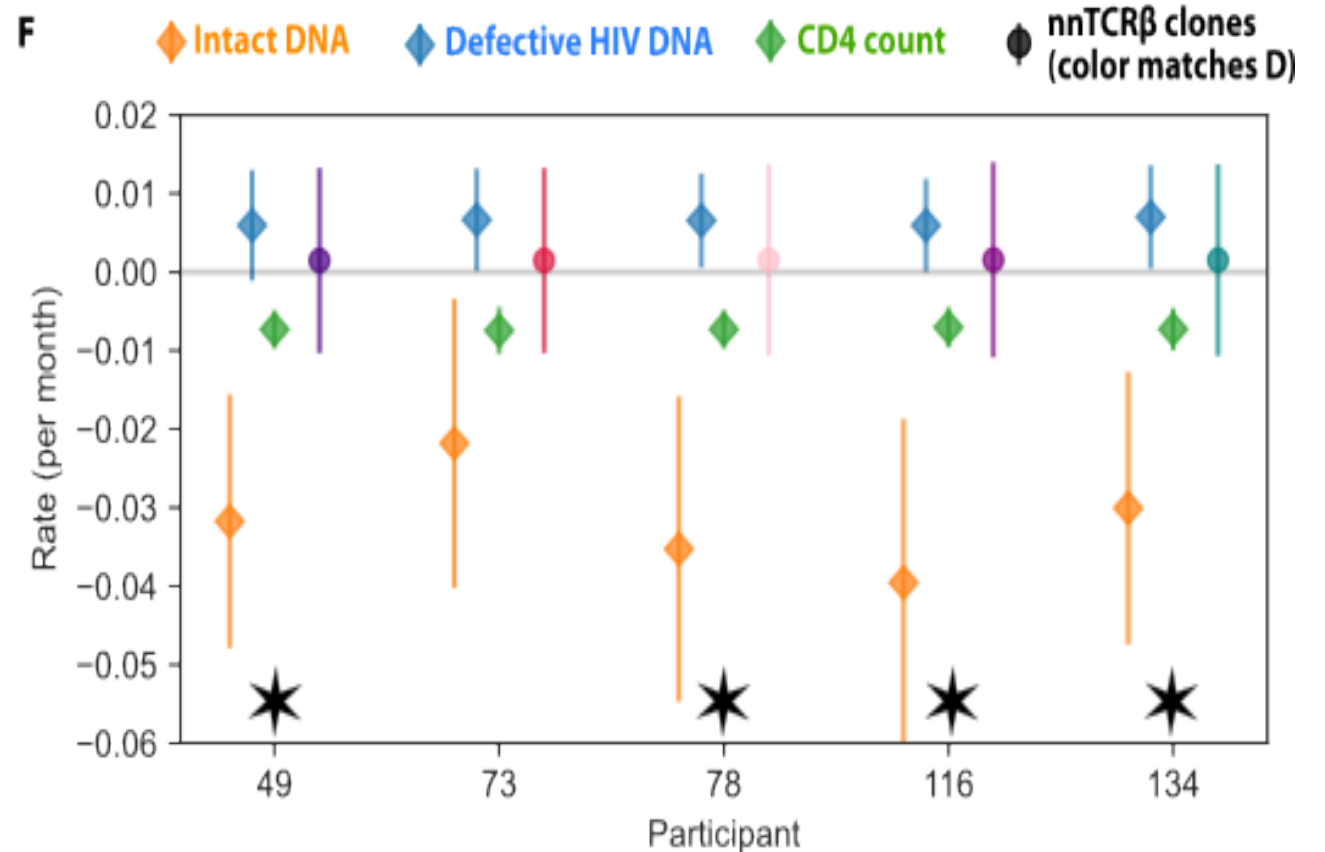
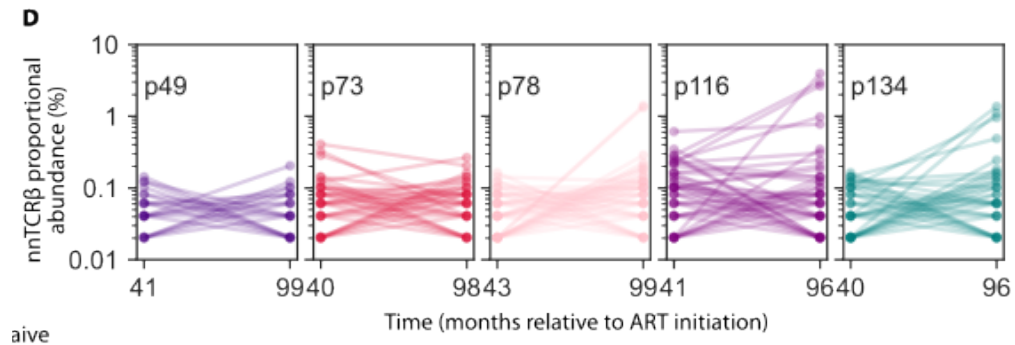
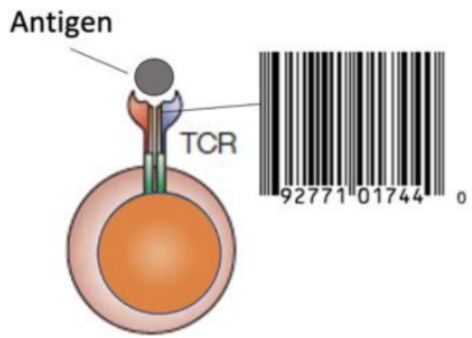
Non naive CD4+ T cell clonal kinetics do not explain intact HIV DNA decay in children with HIV



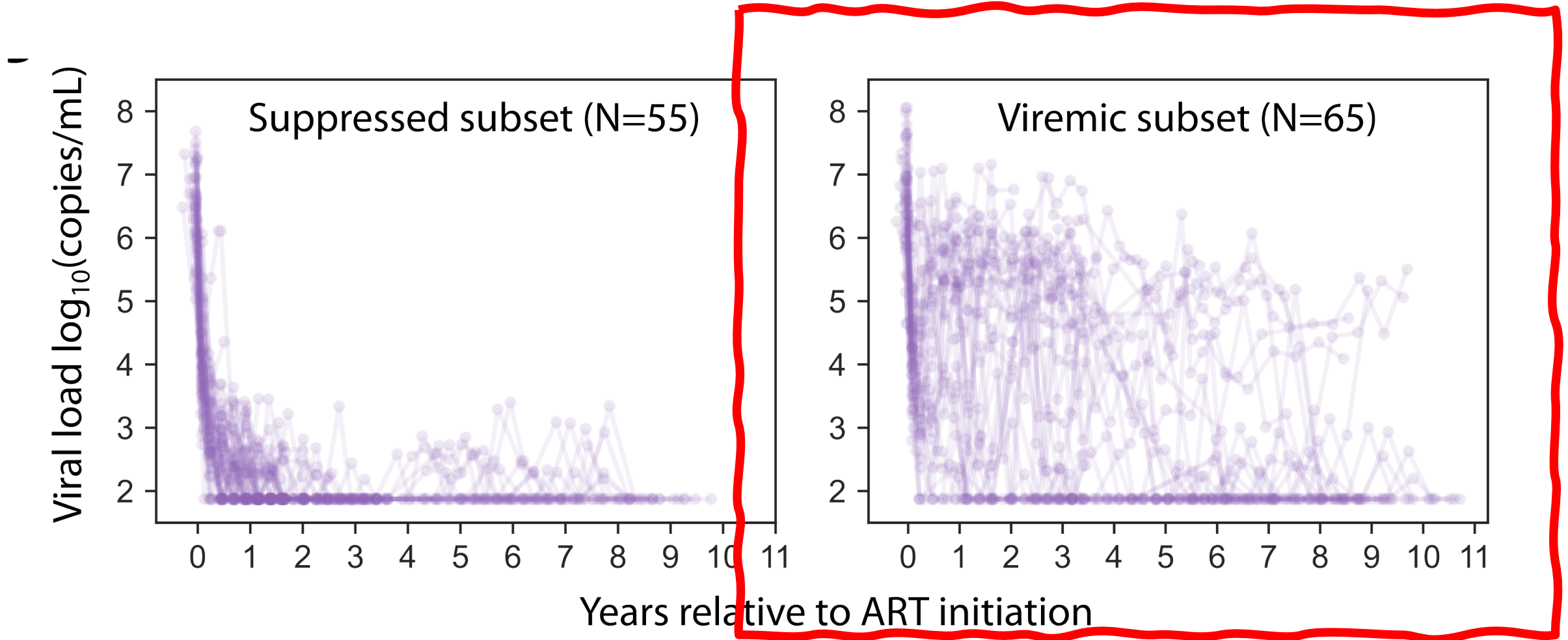
aive



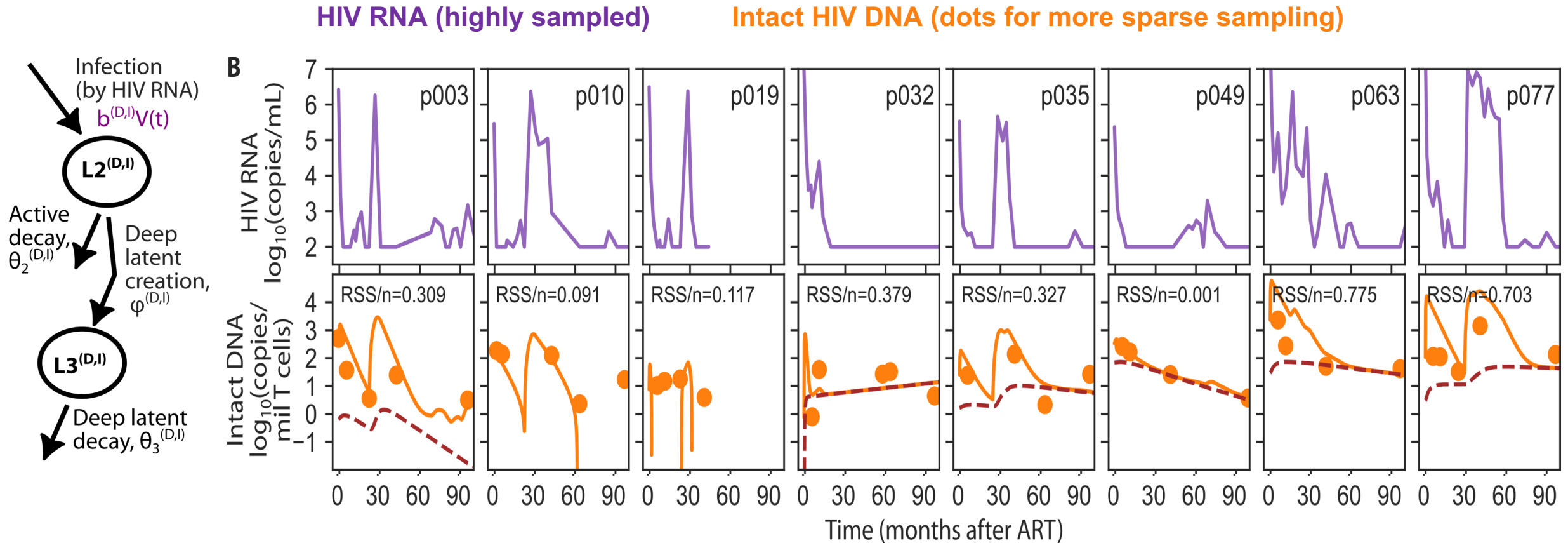
Non naive CD4+ T cell clonal kinetics do not explain intact HIV DNA decay in children with HIV



Linking HIV RNA kinetics in viremic subsets to HIV DNA via mechanistic modeling



Modeling decay in viremic participants (8/65 examples)



Transient viremia doesn't have a sustained reservoir impact

Acknowledgments

- I acknowledge we are on the unceded traditional land of the Miccosukee, Seminole and Tequesta peoples. I honor with gratitude this gorgeous land itself and its stewards.*
- I am extremely grateful to the human beings who generously shared their time, energy, and bodies for this research*



Agnes Lachat
Helen Moraa
Daisy Chebet




National Institute of
Allergy and
Infectious Diseases

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The passenger hypothesis - CD4+ T dynamics quantitatively explain the clonality and clonal dynamics of HIV DNA proviruses?

“Mild selection”, quantitating the influence of intact HIV on the fate of the cells

Mild HIV-specific selective forces overlaying natural CD4+ T cell dynamics explain the clonality and decay dynamics of HIV reservoir cells

Daniel B. Reeves, Danielle N. Rigau, Arianna Romero, Hao Zhang, Francesco R. Simonetti, Joseph Varriale, Rebecca Hoh, Li Zhang, Kellie N. Smith, Luis J. Montaner, Leah H. Rubin, Stephen J. Gange, Nadia R. Roan, Phyllis C. Tien, Joseph B. Margolick, Michael J. Peluso, Steven G. Deeks, Joshua T. Schiffer, Janet D. Siliciano, Robert F. Siliciano,  Annukka A. R. Antar

doi: <https://doi.org/10.1101/2024.02.13.24302704>

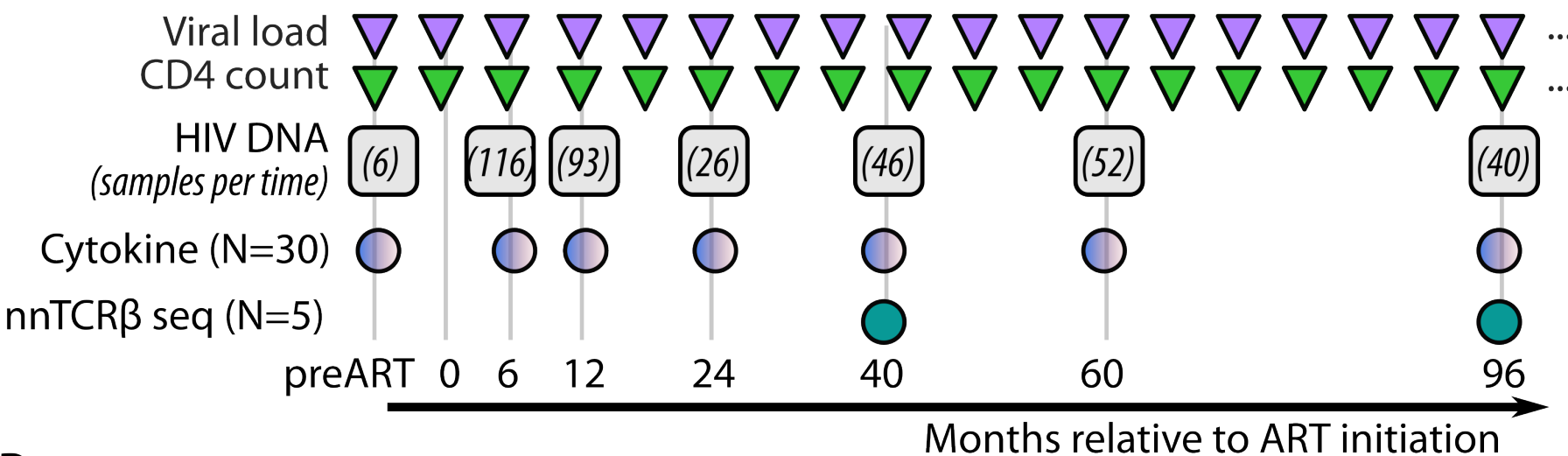


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“Correlates” of decay using multitype data

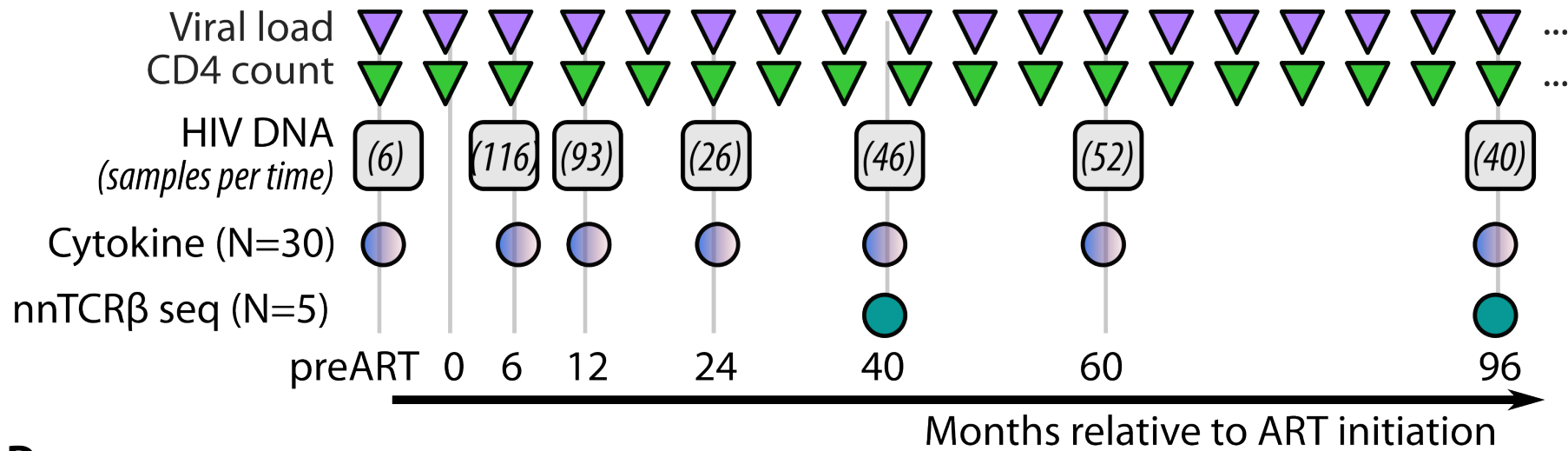
- Cross subtype IPDA Assay
- CD4+ T cell kinetics
- 4 cellular cytokines (IL2, IL7, IL15, GzB)
- Non naïve CD4+ TCR β sequencing
- HIV RNA kinetics

Levy et al. Cell Rep Med 2021
Cassidy et al. iScience 2022
Fish et al. STAR Protocols 2022



Poster number on CS-IPDA

“Correlates” of decay using multitype data



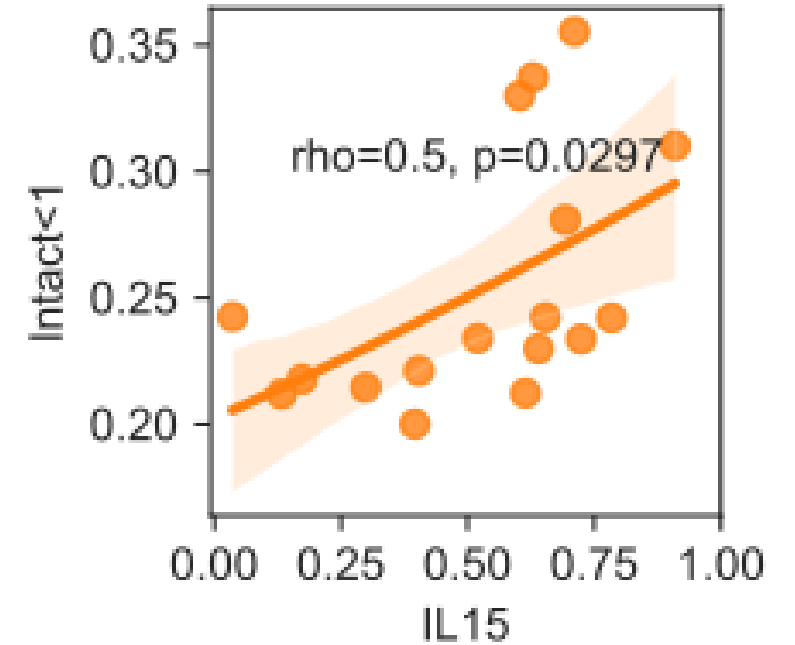
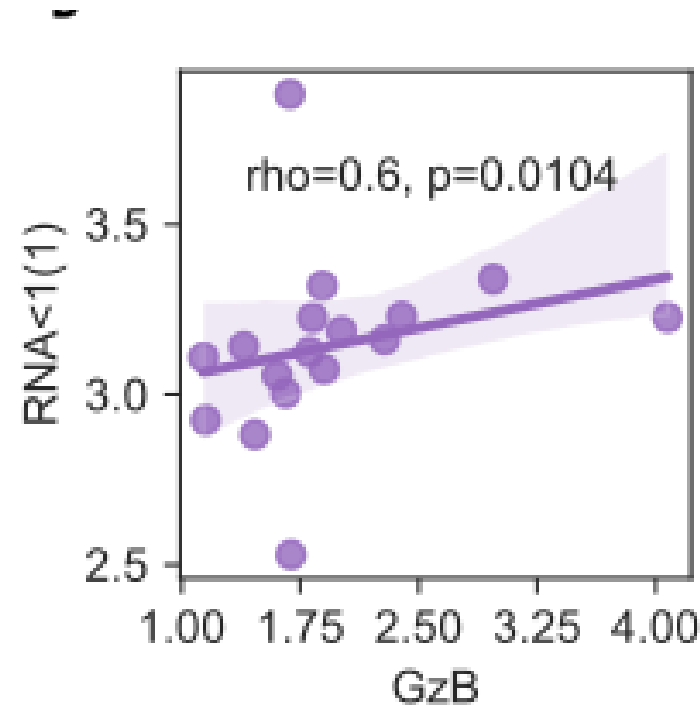
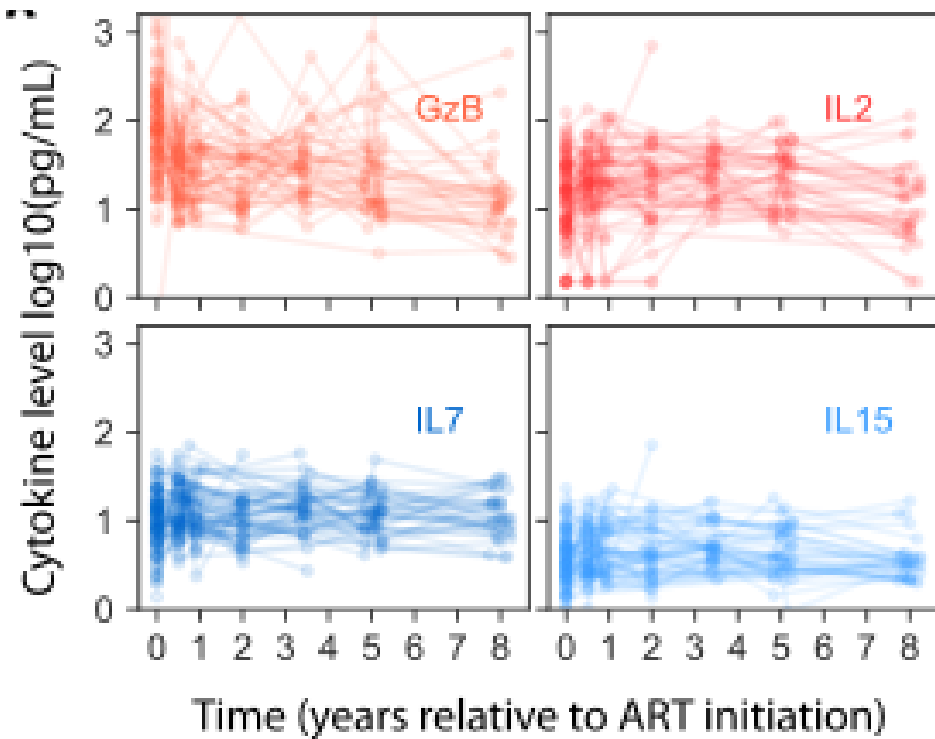
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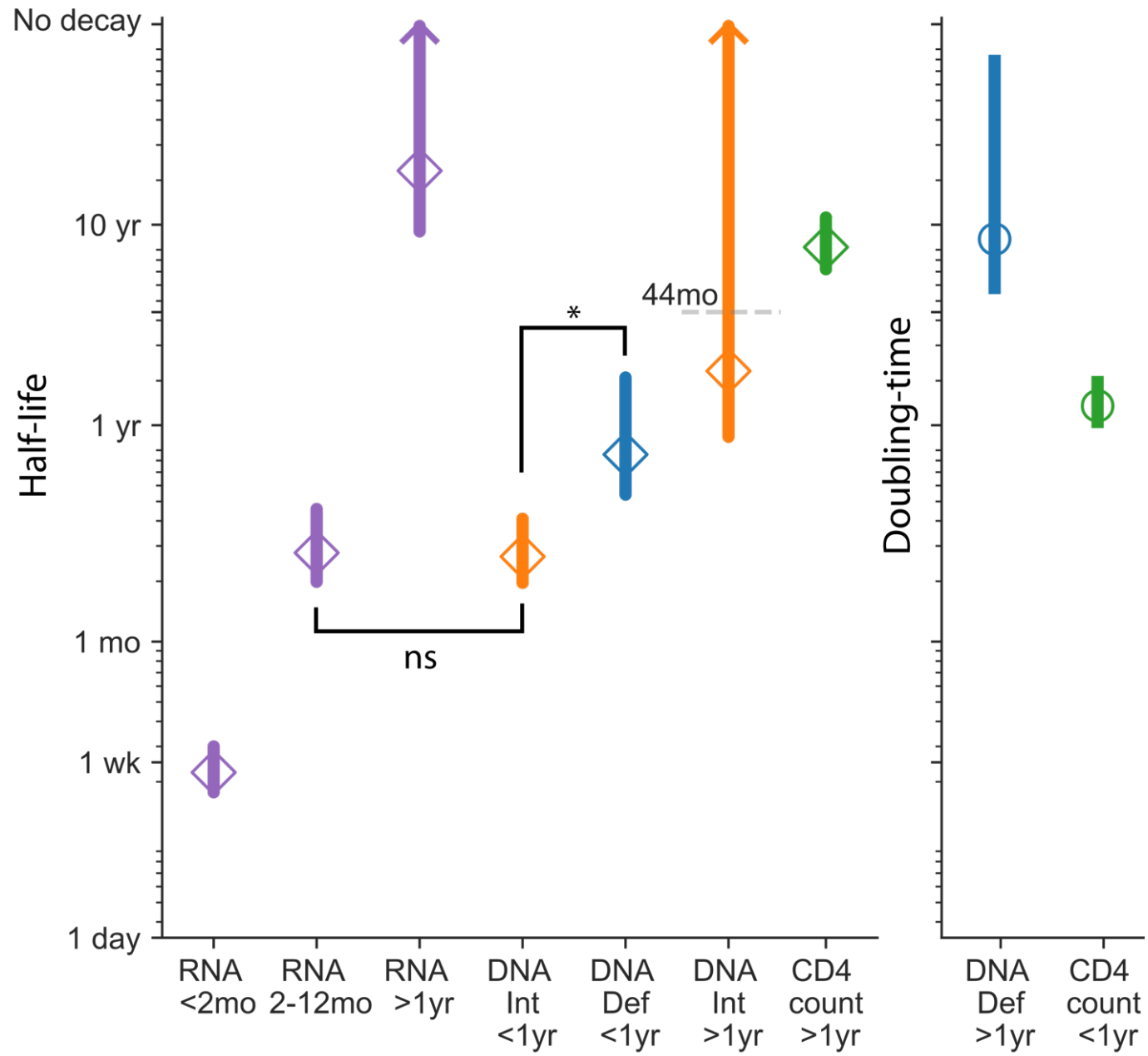
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Poster number on CS-IPDA



No strong cytokine correlates of decay





Thanks again



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This finding could reconcile data on long-term ART studies that show intact decay decelerates (though an open question about assay remains...)

