DIFFERENTIAL CLEARANCE OF INTACT AND DEFECTIVE HIV DNA IN THE PEDIATRIC RESERVOIR

00713

Session: *EARLY TREATMENT AND HIV RESERVOIRS IN CHILDREN - Poster-Q02*
(Tues 2/15, 2:00—4:00 PM MST)

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BACKGROUND/MOTIVATION

- HIV reservoirs are the fundamental barrier to cure [1]
- Children living with HIV (**CWH**) may have outsized benefit and potential for reservoir reduction [1]
- Assays that distinguish intact (replication-competent) and defective proviruses have shown "differential clearance" in the adult HIV reservoir with intact HIV proviruses cleared more rapidly than defective HIV proviruses. This raises at least 2 mechanistic hypotheses (**Fig 1**)
- HIV RNA clearance rates have been estimated in CWH [3,4]
- Studies of intact versus defective reservoir decay in children are limited [5]

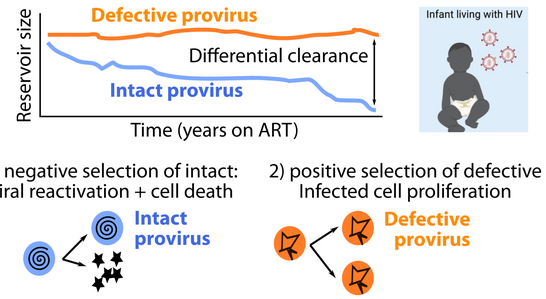
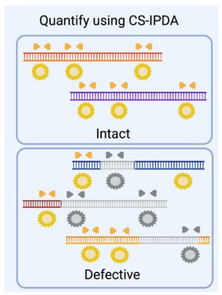


Fig 1. Differential clearance: *Schematic of study in a child with HIV (CWH) and 2 mechanistic hypotheses.*

METHODS



- A cross-subtype intact proviral DNA assay (CS-IPDA, [2]) was applied to longitudinal samples, months 0-96 post ART initiation, from a pediatric Kenyan cohort who initiated early ART
- For modeling, HIV DNA data was restricted to time points with undetectable viral replication: HIV RNA <150 copies/mL
- Half-lives were estimated by defining an optimal mathematical model and using population nonlinear mixed effects modeling to estimate model parameters

Fig 2. CS-IPDA schematic. *Cassidy et al. 2021 [2]*

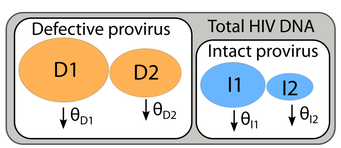


Fig 3. Schematic of mechanistic mathematical model selected. *D and I represent defective and intact HIV DNA, 1 and 2 represent clearance phase (1 and 3 phase models were also tested)*

Key takeaway: Among early-treated children on suppressive ART (N=120) intact proviruses decayed more rapidly than defective proviruses

RESULTS – Data analysis

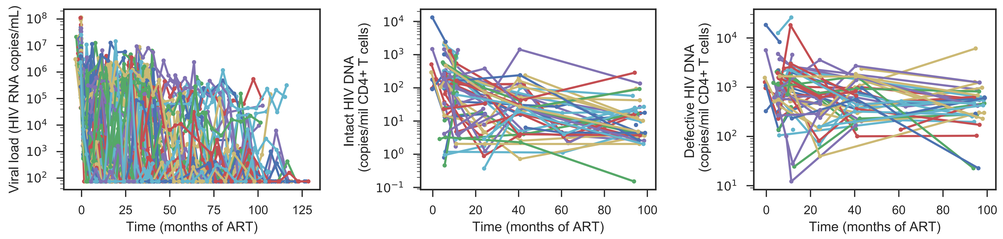


Fig 4. Raw Viral loads, intact HIV DNA and defective HIV DNA from 120 CWH

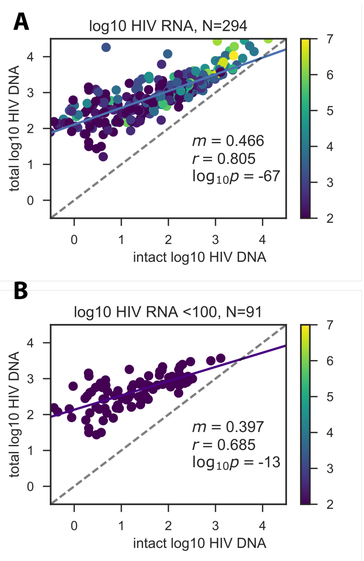


Fig 5. Evidence for differential decay in raw data. *A) All data points, and B) subset to HIV RNA < 150 copies/mL. In both figures, intact and total HIV do not have a 1:1 relationship. At low HIV DNA levels, a lower proportion of HIV DNA is genomically intact. Heatmap colors represent log10 HIV RNA*

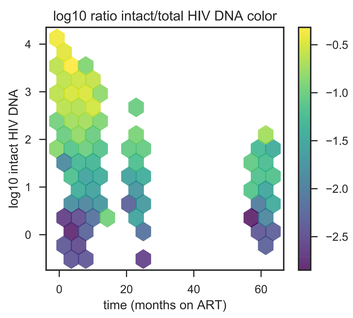


Fig 6. Time on ART is not the only predictor of intact:total ratio. *Log10 ratio (color bar) can be low (purple) at early and late time points.*

RESULTS – Mathematical modeling

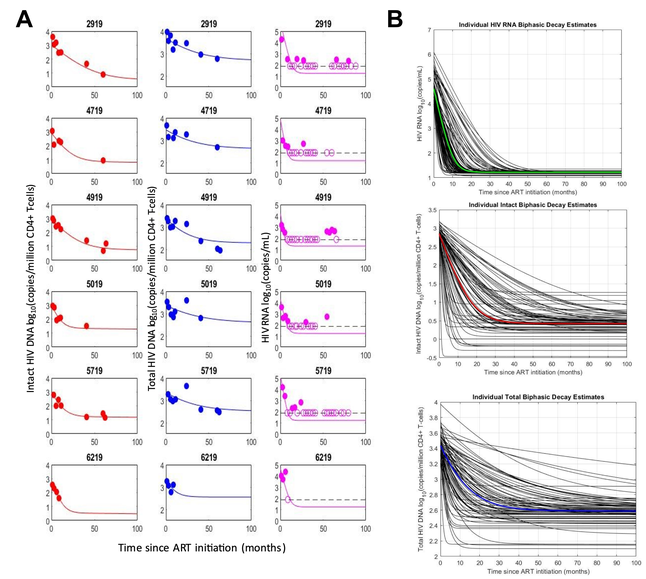


Fig 7. Mechanistic modeling reveals differential clearance*. A) 6 example fits of intact (red) and total (blue) HIV DNA and HIV RNA (pink) using the biphasic model of **Fig 3**. B) All best fits from all eligible participants (black), including average as a thick colored line. C) Box plots of estimated clearance rates. First phase (left panel) clearance rates are similar for intact and total HIV DNA, whereas HIV RNA is slightly faster. Second phase (right panel) clearance rates are significantly different, with intact HIV DNA having the fastest decay. RNA no longer decays as it is already cleared from blood.*

CONCLUSIONS

- **Intact HIV DNA level is predictive of total HIV DNA level**
- **At timepoints with undetectable viremia, each 1 log decrease in HIV DNA is associated with a ~2.5 log decrease in intact HIV DNA**
- **Long term clearance is significantly faster for intact HIV DNA, suggesting any immunological mechanisms driving differential clearance in adults may also exist in children.**

REFERENCES

[1] Goulder et al. *Nat Rev Immunol* 2016; [2] Cassidy et al. *iScience* 2021; [3] Morris et al. *JAIDS* 2020; [4] Luzuriaga et al. *JVI* 1999 [5] Garcia-Broncano et al. *Sci Trans Med* 2019

Acknowledgments. We gratefully recognize the study participants, as well as the clinical and administrative teams from the Optimizing Pediatric HIV (OPH) Cohort. Funding was provided by the NIH R01s HD023412 & HD094718