Advances in Cure Research Across the Lifespan

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HIV Cure through the Ages

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Disclosures

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  - Gilead
  - GlaxoSmithKline
  - Merck
  - ViiV

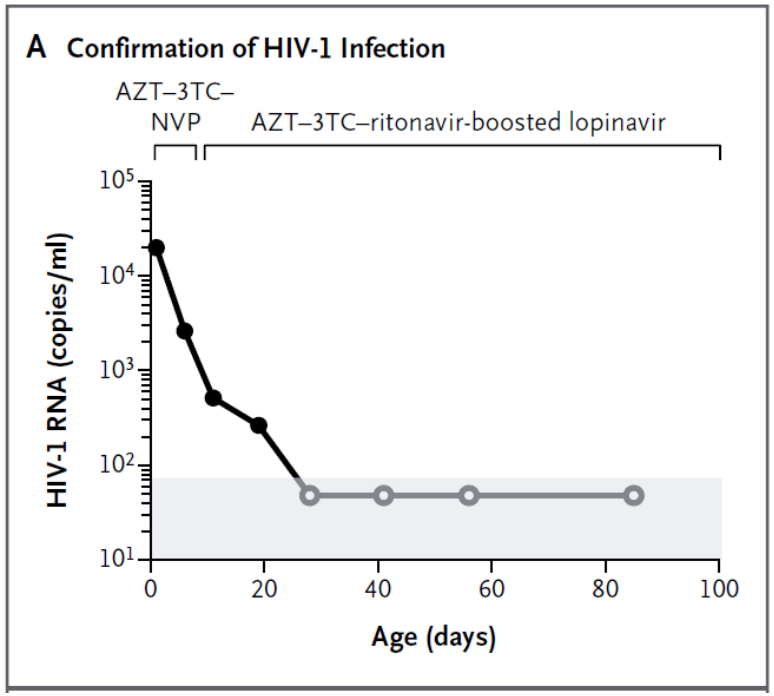
Timing of mother-to-child HIV transmission

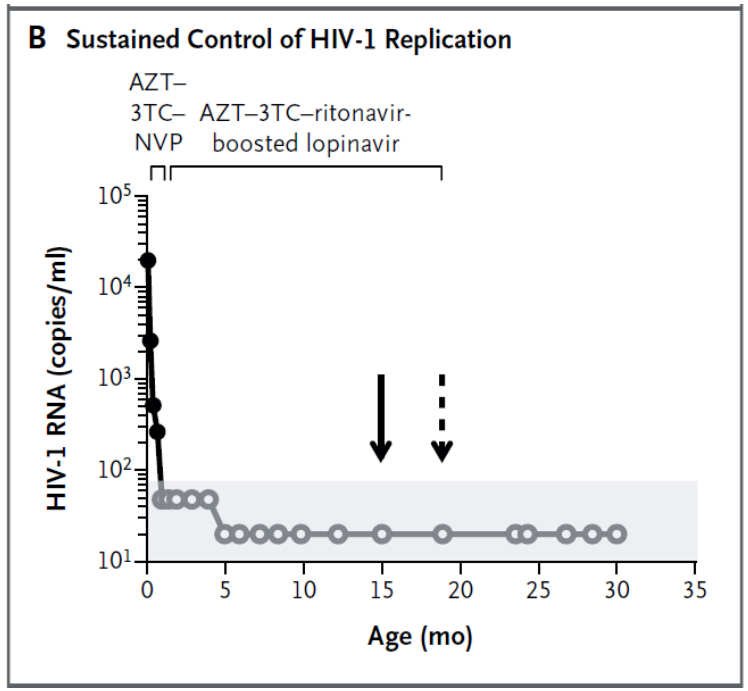
Timing	Route	Virologic testing
In utero	Trans-placental	HIV-1 DNA/RNA positive at birth
Peripartum	Oral/mucosal	HIV-1 DNA/RNA negative at birth positive at 1 month
Post-partum	Breastfeeding	HIV-1 DNA/RNA negative at birth and at 1 month; positive at later timepoints

Unique features of peri-natal HIV infection re: cure

- Timing of infection relatively well-defined
- Low levels of CCR5 expression on CD4+ T-lymphocytes
- Opportunity for immediate intervention with suppressive ART
- Early intervention may limit reservoir size
- Developing immune system may offer unique opportunities for boosting HIV-specific immunity

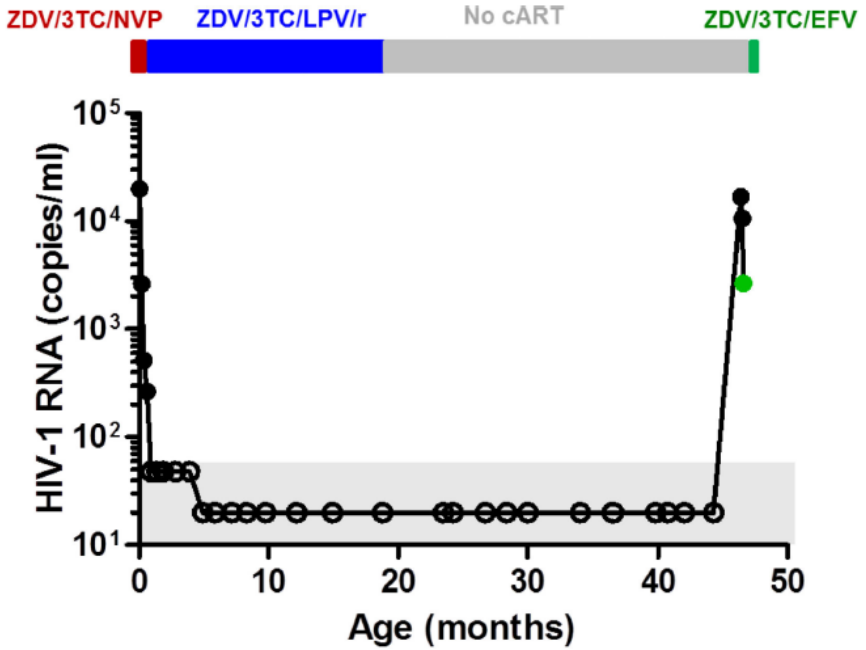
Mississippi baby: initial control of HIV-1 replication





Persaud D et al N Engl J Med 2013

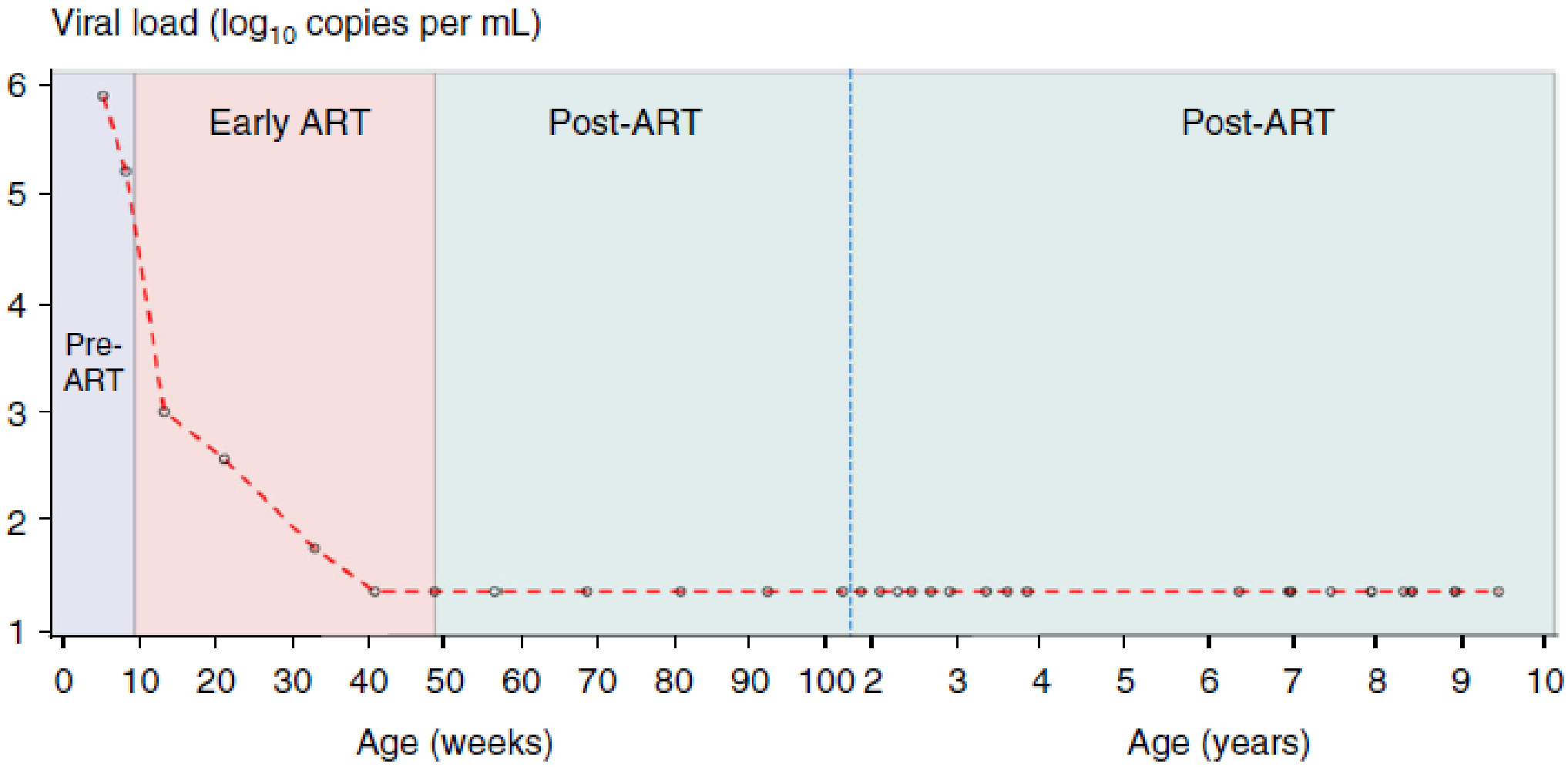
Long-term follow-up of the Mississippi baby



- **Last sample obtained 4 weeks prior to rebound was positive for 2-LTR circles**
  - SCA → 9.9 c/mL (retrospective testing)
- **Rebound associated with seroconversion**
  - WB+ at time of rebound

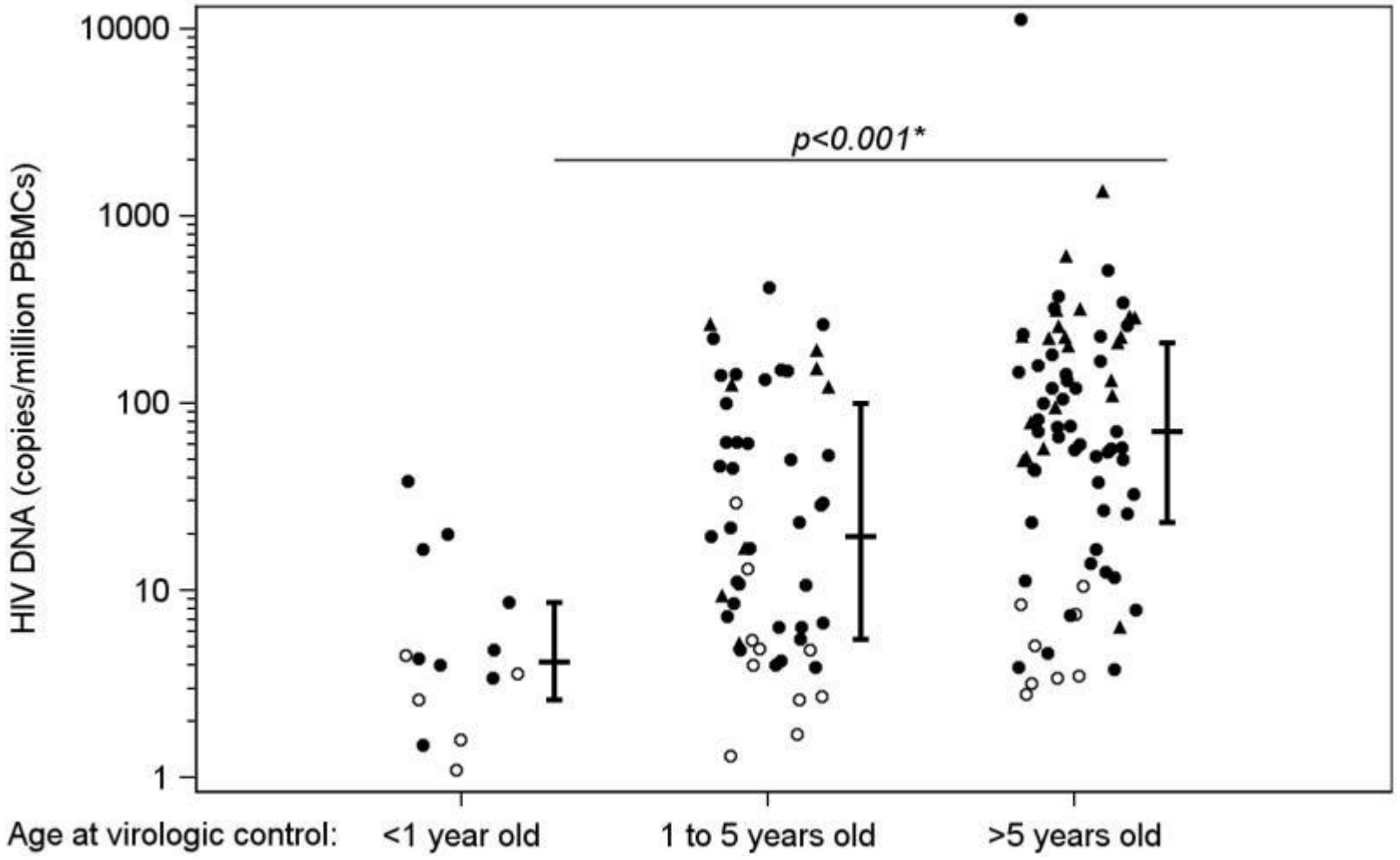
Luzuriaga et al N Engl J Med 2015

Long-term control post-ART control in a patient with perinatal HIV-1 infection



Violrari A et al Nature Commun 2019; 10:412

Age at virologic control predicts reservoir size in perinatally infected adolescents



Persaud D et al JAMA Pediatrics 2014

Challenges of conducting HIV cure research in infants

- **Safety and PK in infants, children, adolescents of many candidate interventions unknown**
- **Limitations on blood volume sampling for reservoir assays**
- **Most candidate therapeutic vaccines not studied in persons younger than 18 years**
- **Risk/benefit of most approaches using genetic modified peripheral lymphocytes or stem cells not suitable for study in children**

Early Infant Treatment (EIT) Study Design

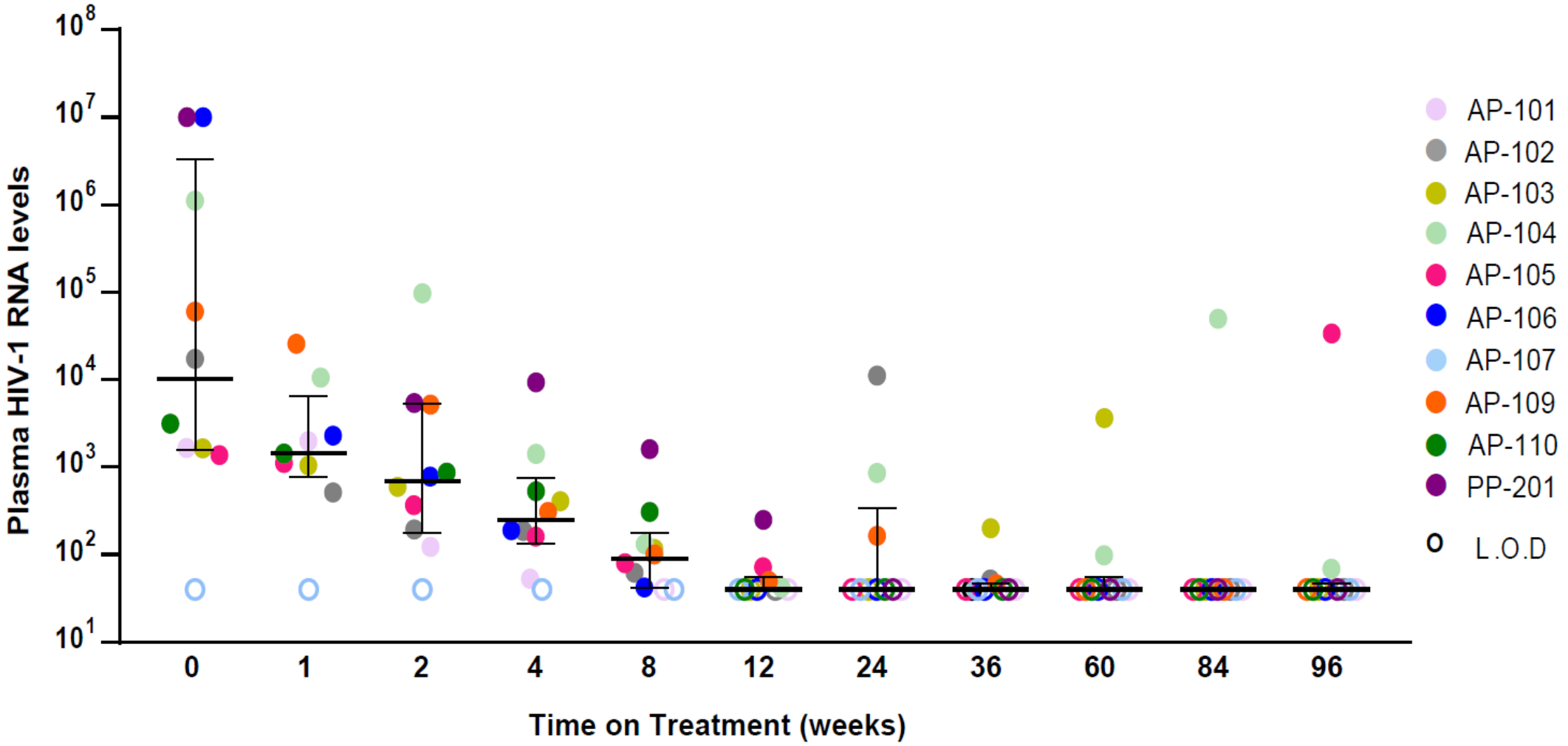
- **Single-arm non-randomized clinical trial of early ART in antepartum and peripartum infection**
- **Population: HIV+ children < 7 days of life if antepartum infection, < 57 days of life if peripartum infection.**
- **Sites: Gaborone and Francistown regions of Botswana**
- **Sample Size: up to 30 in antepartum cohort, up to 20 in peripartum cohort, up to 20 controls (on ART currently, started in 1st year of life but beyond criteria for early treatment)**
- **Duration: 96-192 weeks**
- **Study Regimen:**
  - At < 2 wks / 40 wks GA equivalent: NVP/ZDV/3TC
  - Thereafter, LPV/r/ZDV/3TC (current Botswana ART guidelines)

EIT Study Screening and Enrollment

- **>9100 newborns screened**
  - ~30% of all HIV-exposed infants in Botswana
- **Overall rate of confirmed HIV infection 0.4%**
- **40 children enrolled (plus 23 controls)**
- **30 of 40 had reached week 84 of follow-up**
  - 14/30 (47%) had sustained negative HIV-1 RNA from weeks 24-84
  - 16/30 (53%) had at least intermittent detectable viremia (>40 c/mL)

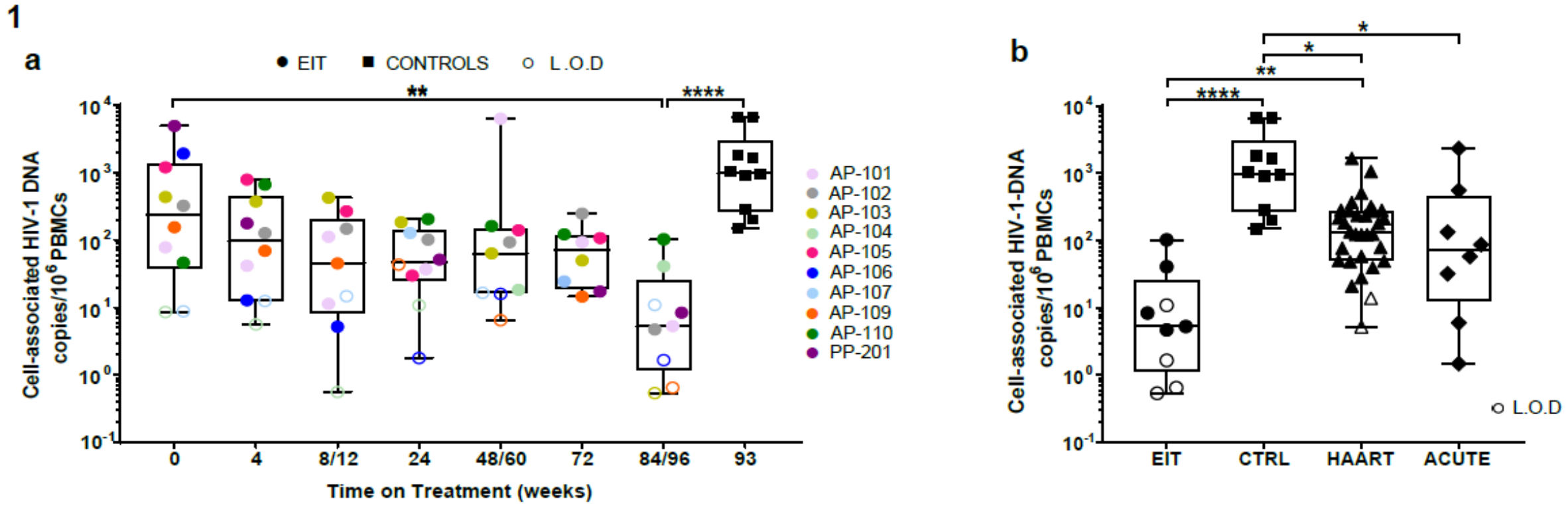
Shapiro R et al 25th CROI, 2018, Boston

Plasma HIV-1 RNA levels over time on ART



Gacrcia-Broncano P et al Sci Transl Med 2019

CA-HIV DNA in EIT participants versus controls and other cohorts



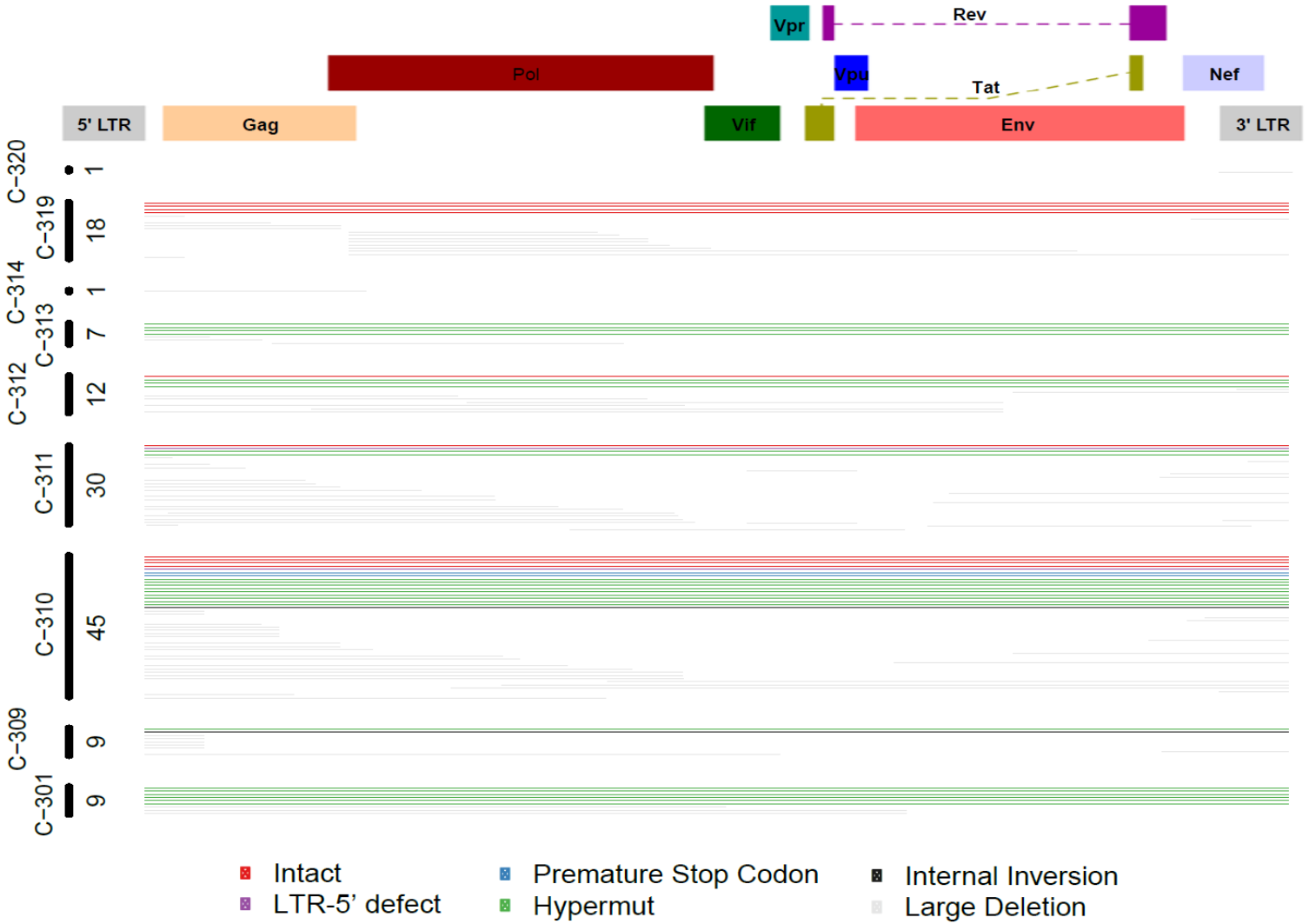
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, L.O.D. = limit of detection

Garcia-Broncano P et al Sci Transl Med 2019

Analysis of near full-length proviral sequences from early-treated HIV-1-infected neonates

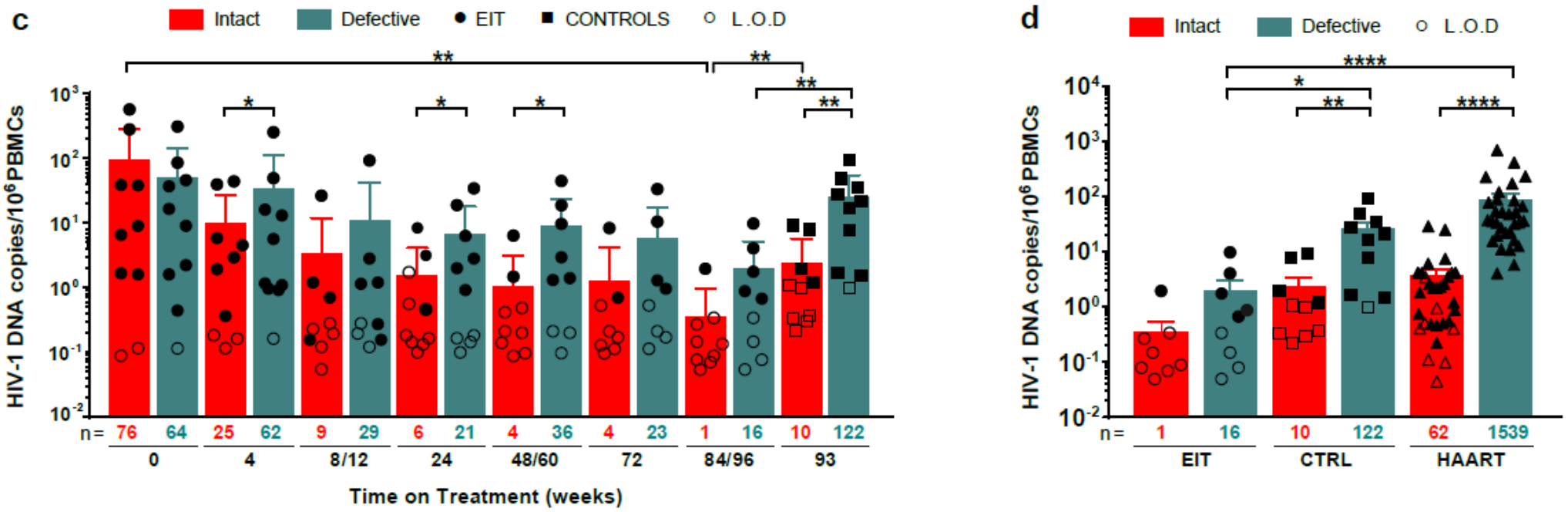
Garcia-Broncano P et al Sci Transl Med 2019

Analysis of near full-length proviral sequences from control HIV-1-infected neonates



Garcia-Broncano P et al Sci Transl Med 2019

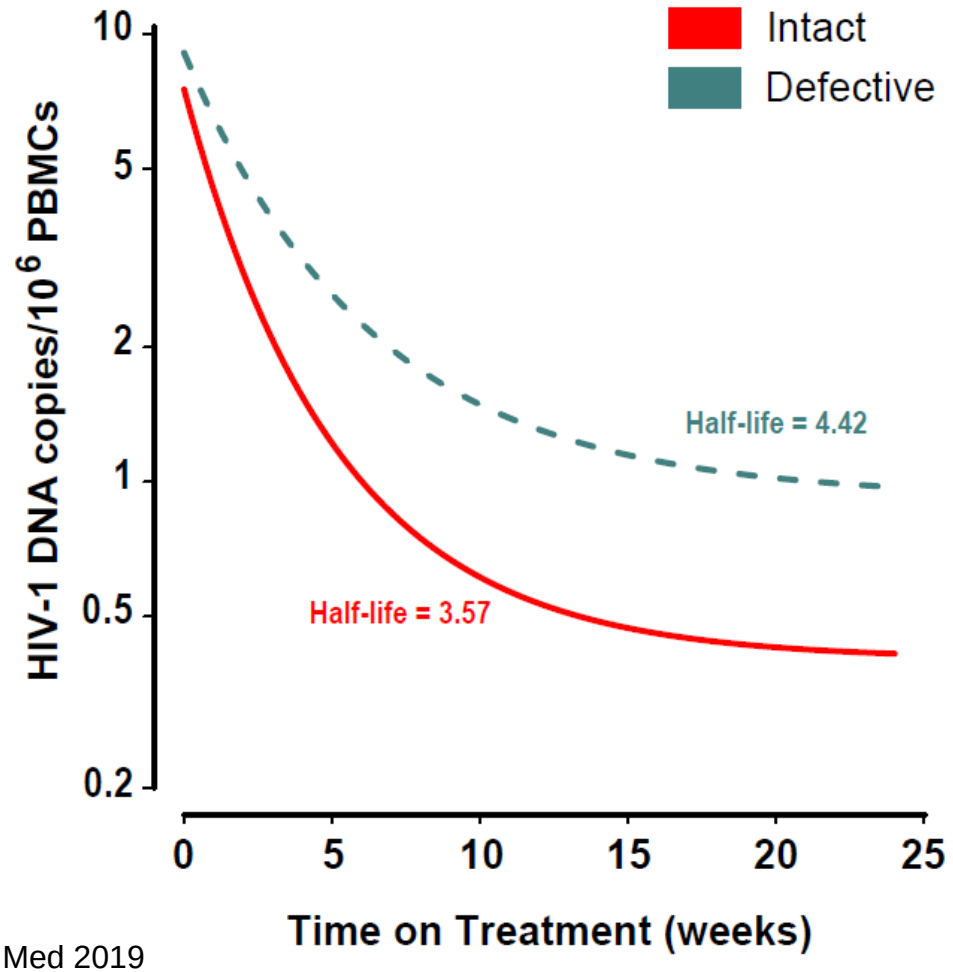
Intact versus defective proviral genomes



*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, L.O.D. = limit of detection

Garcia-Broncano P et al Sci Transl Med 201.

Decay rates of intact and defective proviral HIV-1 sequences following ART initiation



p=0.0002

Garcia-Broncano P et al Sci Transl Med 2019

- **Relationship between plasma viremia and EIA positivity at Week 84**

	Plasma HIV RNA by Week of ART							Week 84 EIA Antibody
	0	4	12	24	36	60	84	
A	1661	53	<40	<40	<40	<40	<40	-
B	17244	186	<40	11182	52	<40	<40	+
C	1636	408	<40	<40	<200	3648	<40	+
D	1111950	1413	42	860	<40	98	49993	+
E	1375	161	72	<40	<40	<40	<40	+/-
F	>10000000	191	<40	<40	<40	<40	<40	-
G	<40	<40	<40	<40	<40	<40	<40	-
H	60247	307	50	164	46	<40	<40	-
I	3145	533	<40	<40	<40	<40	<40	-
J	1005	561	42	<40	<40	<40	<40	+/-
K	272	6591	<40	735	55	106	339	+
L	1314	<40	<40	<40	<40	<40	319	+
M	23686	<40	<40	<40	<40	<40	<40	-
N	20291	12315	145164	1595770	133084	<40	7114	+
O	<200	<40	<40	<40	<40	<40	<40	-
P	12984	<40	<40	<40	<40	<40	<40	-
Q	315020	1051	97	300	166	<40	<40	-
R	79	66	77	<40	<40	<40	<40	-
S	11677	<40	<40	<40	<40	<40	<40	-
T	224127	388	163	<40	<40	<40	<40	-
U	143616	46	<40	<40	3966	<40	<40	+
V	8548	487	<40	<40	<40	<40	<40	-
W	33502	628	<40	76	<40	<40	<40	-
X	1837	118	166	5019	15325	23868	69549	+
Y	88885	456	45	<40	<40	28822	358491	+
Z	2279	<40	<40	<40	<40	<40	<40	-
AA	31708	350	<40	<40	89356	<40	<40	+/-
BB	114	105	<40	41	52	<40	<40	-
CC	276	743	310	255	31341	<40	<40	+
DD	292	41	59	<40	<40	364	<40	-
EE	15327	9082	93	<40	52080	713	<40	+
FF	25507	42	<40	<40	<40	<40	<40	-
GG	381	<40	<40	<40	<40	<40	<40	-
HH	>10000000	474	106	<40	17222	43871	54695	+
II	389270	1410	632	<40	121	<40	67	-
JJ	310	271	166	143	55	<40	<40	-
KK	10993	445	78	481050	5630	29932	71499	+
LL	706316	2252	<40	<40	<40	15609	1194	+

Ajibola G et al 27th CROI 2020

Conclusions

- **Early initiation of ART in HIV-infected neonates significantly limited establishment of a reservoir of PBMC harboring intact proviruses.**
- **Cells harboring intact proviruses decayed more rapidly than cells harboring defective proviruses.**
- **Maintaining a virus load <200 prevented development of humoral immune response**
- **These data provide strong empiric evidence supporting the immediate initiation of antiretroviral therapy for HIV-1-infected neonates.**

Next Steps

- **What additional interventions are available and appropriate for use in infants/young children?**
  - ~~Latency reactivating agents~~
  - ~~Therapeutic vaccines~~
  - ~~Checkpoint inhibitors~~
  - ~~Cell-based therapies~~
  - Broadly neutralizing antibodies
- **Can a dual bNAb combination sustain viral suppression in HIV-infected infants who initiated ART in the first days of life?**

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