TWO YEAR VIROLOGIC OUTCOMES OF VERY EARLY ART FOR INFANTS IN THE IMPAACT P1115 STUDY

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www.impaactnetwork.org/studies/p1115

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HIV-1 Reservoir as Barrier to Remission and Cure

- The latent reservoir for HIV-1 in resting memory CD4+ T cells is a major barrier to remission and cure making ART lifelong
- Smaller reservoir size is associated with several cases of ART-free remission where rebound viremia is delayed for years off ART
- Efforts are underway to identify strategies to restrict and eliminate the latent reservoir

Reviewed in Deeks et al., Nature Medicine, December 2021.

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Ongoing Prospective Phase I/II Proof-of-Concept Study of Early Intensive ART to Achieve ART-Free HIV-1 Remission in Infants

Goal: to replicate the "Mississippi "Baby who experienced 27 months of remission with very early ART initiated at 30 hours of life

NCT02140255; Persaud D et al. CROI 2013; NEJM 2013.

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IMPAACT P1115: Accrual

460 infants enrolled in two cohorts at 30 sites in 11 countries between January 2015 and December 2017

Cohort 1

N=440 high-risk infants, initiated on pre-emptive ART within 48 hours of birth

↓

34 of 36 diagnosed with *in utero* infection continued ART on-study

Cohort 2

N=20 infants diagnosed with *in utero* infection enrolled within 10 days of age and continued ART on-study
(initiated NVP-based triple-ARV regimen within 48 hours of birth)

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NCT02140255; Ruel et al Lancet HIV 2021.

Study Regimen

NRTI	Two nucleoside reverse transcriptase inhibitors
NVP	Nevirapine at treatment doses until 12 weeks after HIV-1 RNA confirmed below the limit of detection
LPV/r	Lopinavir/ritonavir added at 14 days of age and 42 weeks postmenstrual age

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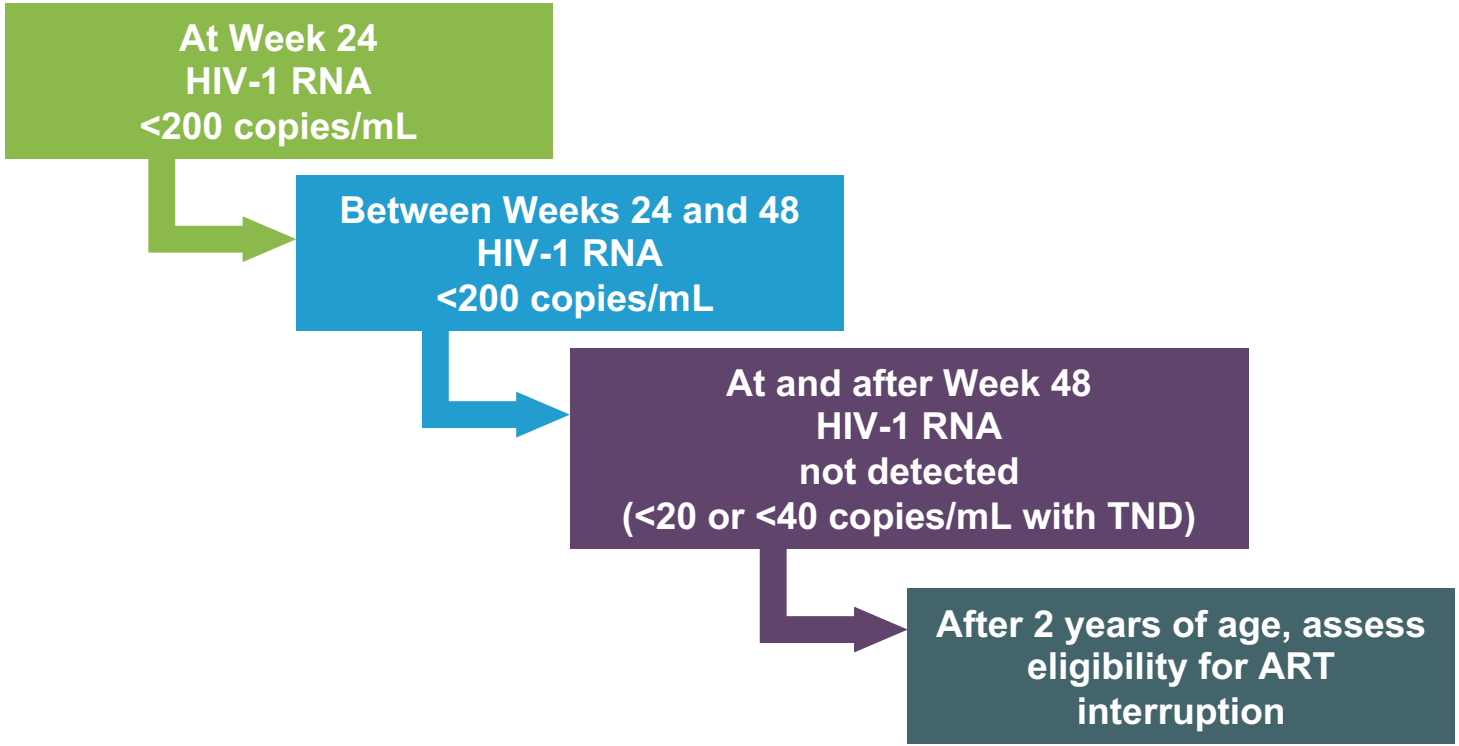
Virologic Suppression Criteria to Remain on Study



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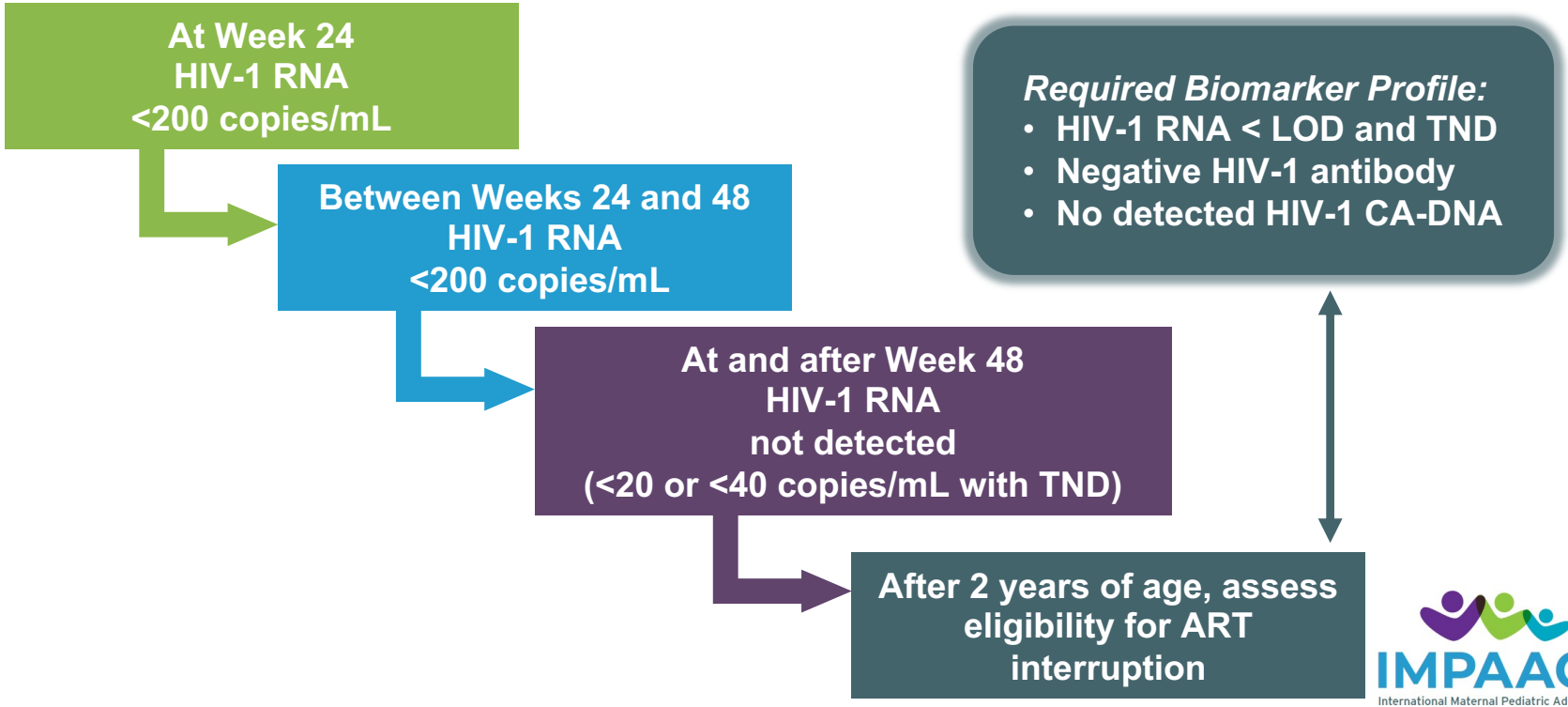
Virologic Suppression Criteria for Evaluation for ART-Free Remission



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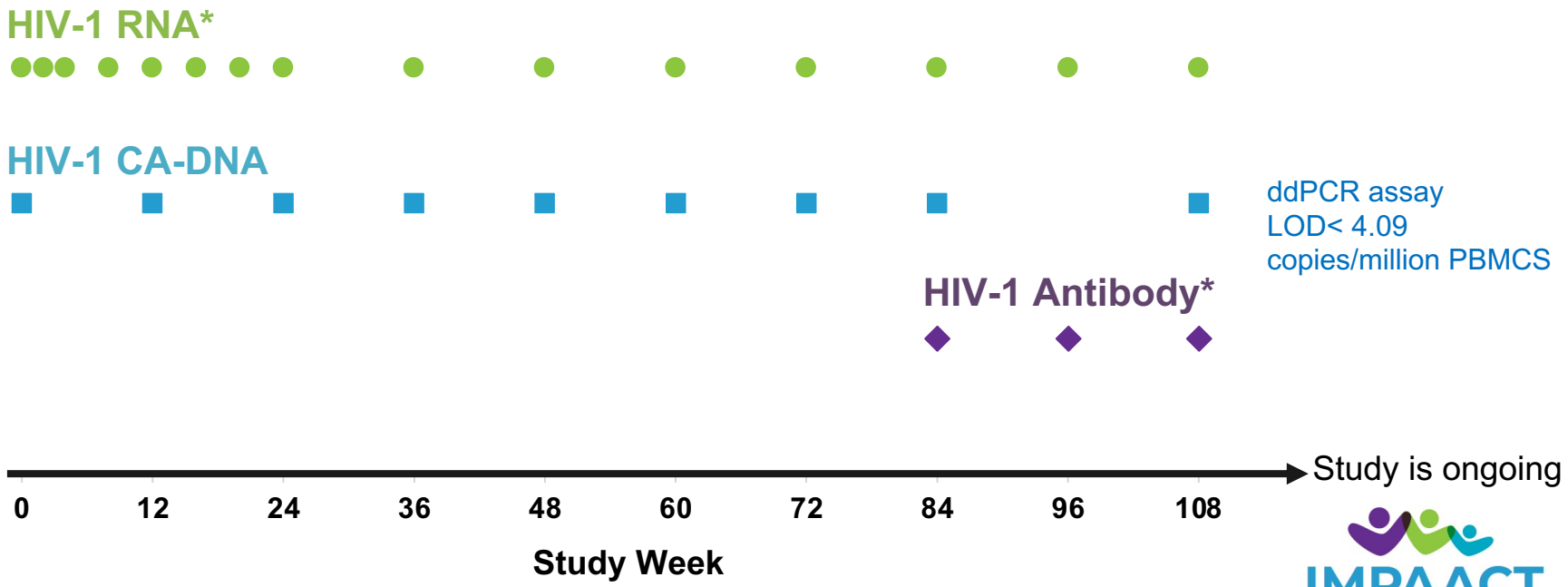
Frequency of Key Evaluations



*real time

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Statistical Analyses

- Estimation with Kaplan-Meier (KM) based survival probabilities and exact binomial proportion confidence intervals (CI)
- Univariable Cox proportional hazards regression (Hazard Ratio (HR))

Results

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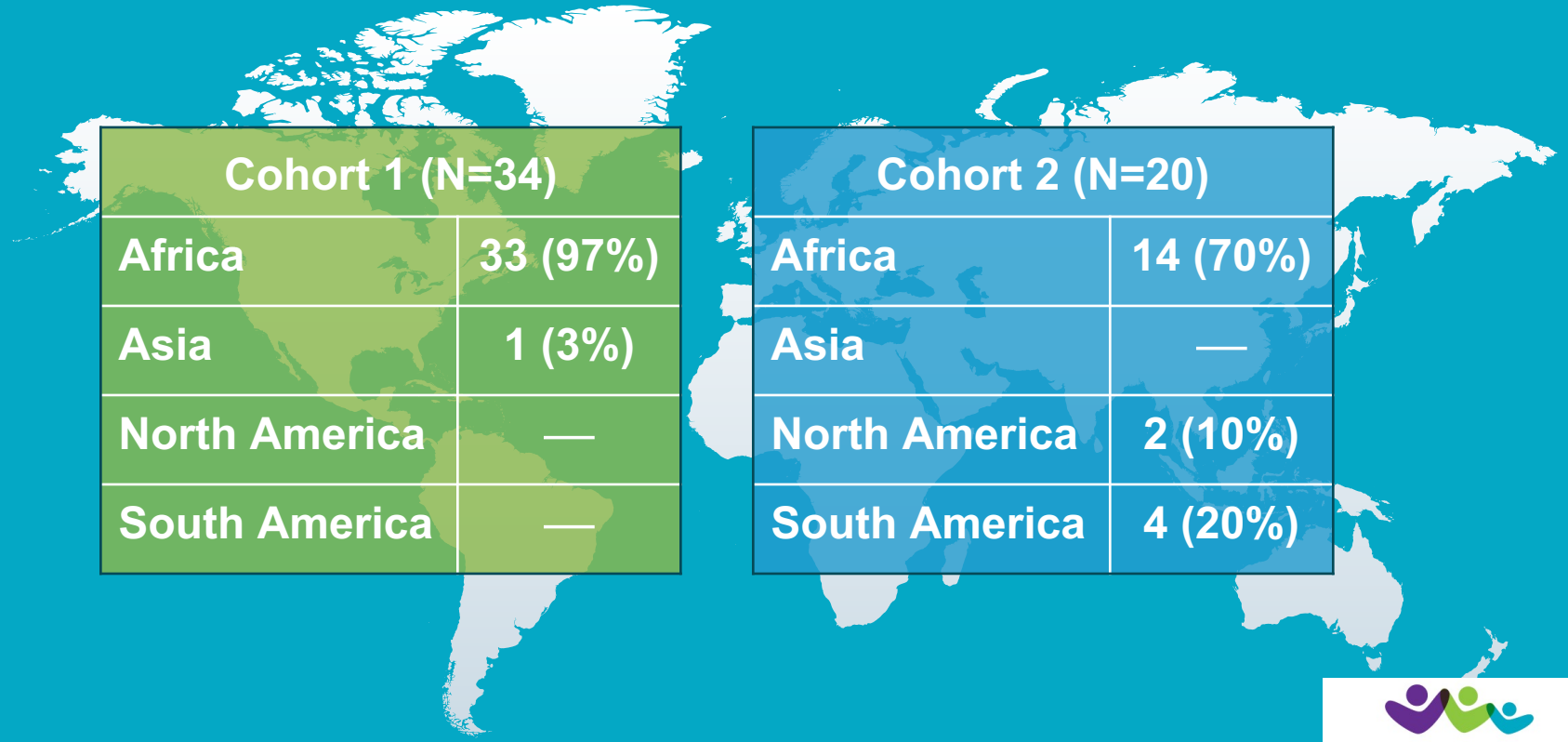
Infant Characteristics



Cohort 1 (N=34)	
Africa	33 (97%)
Asia	1 (3%)
North America	—
South America	—

Cohort 2 (N=20)	
Africa	14 (70%)
Asia	—
North America	2 (10%)
South America	4 (20%)

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Infant Characteristics

	Cohort 1 (N=34)	Cohort 2 (N=20)
	Median (Q1-Q3) or n (%)	
Age at Study Entry	22.2 (12.6-32.6) hours	8 (5.5-8) days
Age at first ARV (hours) (1)	7.3 (1.8-21)	32.8 (1.1-40.1)
Female Sex	23 (68%)	10 (50%)
Breastfed	33 (97%)	13 (65%)
Earliest HIV RNA VL (log_{10} c/mL)	4.9 (4-5.3)	4.1 (3.2-5.2)
Earliest HIV DNA Load (log_{10} c/10^6 PBMC) (2)	2.4 (1.7-3.0)	2.8 (1.8-3.3)
Earliest CD4% (3)	50.4 (42-57.5)	53.5 (45-59)
Maternal ARV Exposure During Pregnancy and Delivery (4)	0 (0%)	7 (37%)

(1) *Cohort 2 N=17.*
(2) *Cohort 2 N=19.*
(3) *Cohort 1 N=32; Cohort 2 N=18.*
(4) *One set of twins in Cohort 2 [$N_{mothers}$=53].*

See CROI Poster #0718 by Nelson et al.

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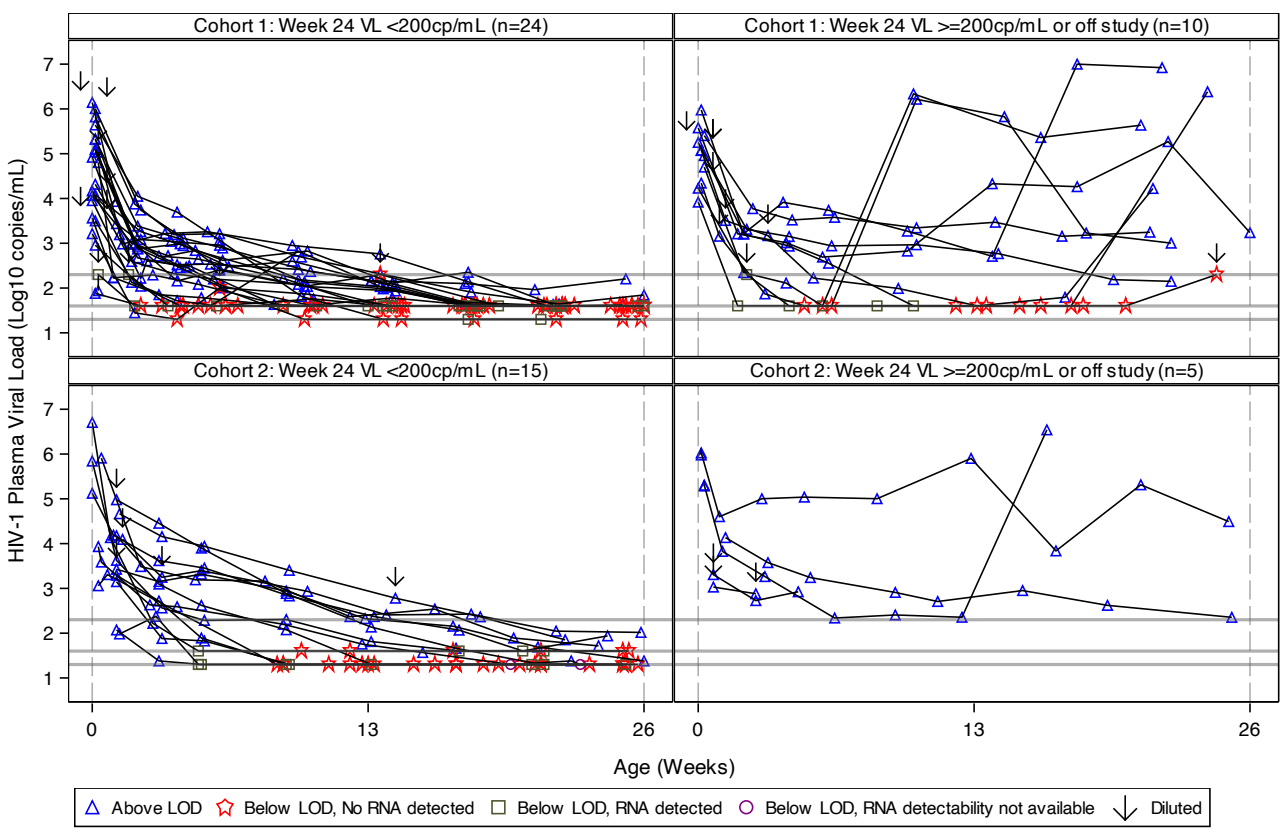
Plasma HIV-1 RNA through 26 Weeks of Age with Very Early ART

Cohort 1

Cohort 2



At Study Week 24:
75% in Cohort 1
(24/32, 95% CI 57%-89%)
and
88% in Cohort 2
(15/17, 95% CI 64%-99%)
had HIV-1 RNA <200 copies/mL

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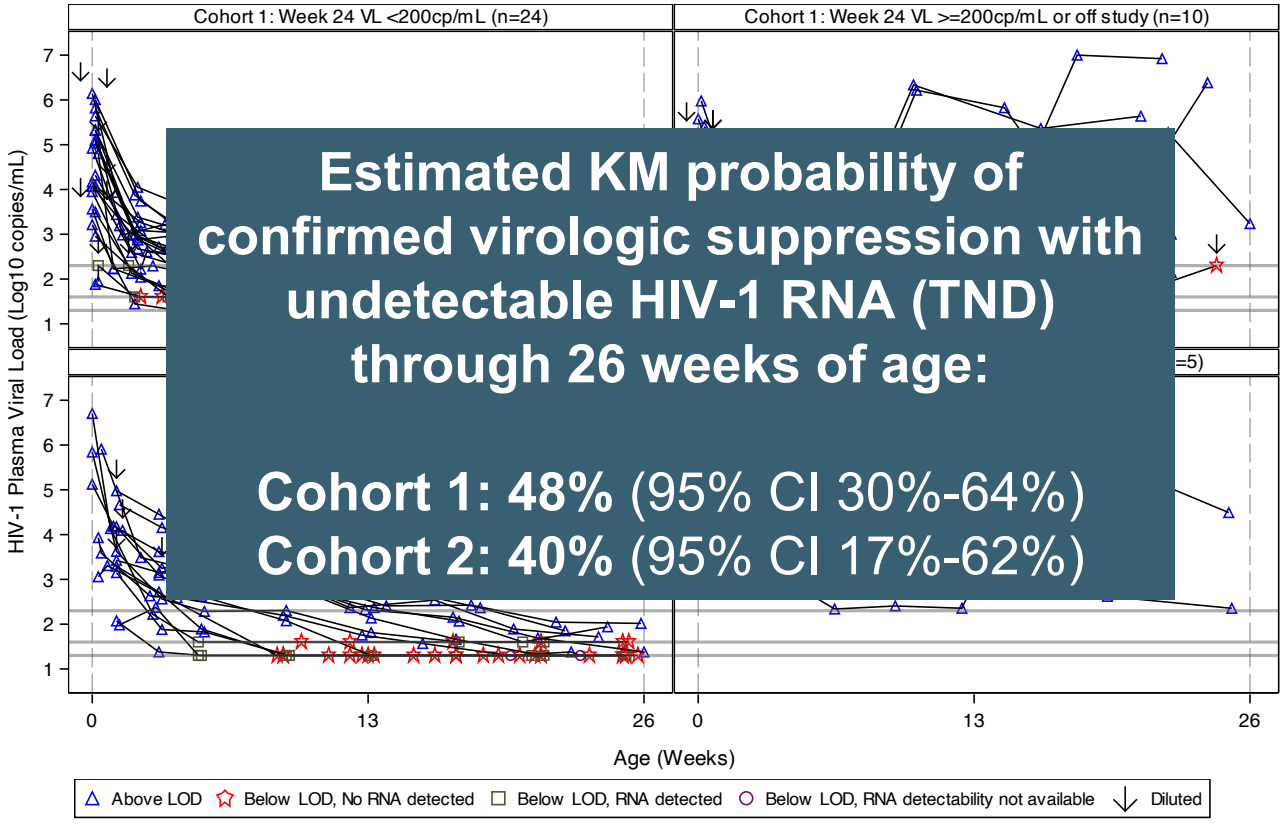
Plasma HIV-1 RNA through 26 Weeks of Age with Very Early ART

Cohort 1

Cohort 2



Estimated KM probability of confirmed virologic suppression with undetectable HIV-1 RNA (TND) through 26 weeks of age:

Cohort 1: 48% (95% CI 30%-64%)
Cohort 2: 40% (95% CI 17%-62%)

At Study Week 24:
75% in Cohort 1
(24/32, 95% CI 57%-89%)
and
88% in Cohort 2
(15/17, 95% CI 64%-99%)
had HIV-1 RNA <200 copies/mL

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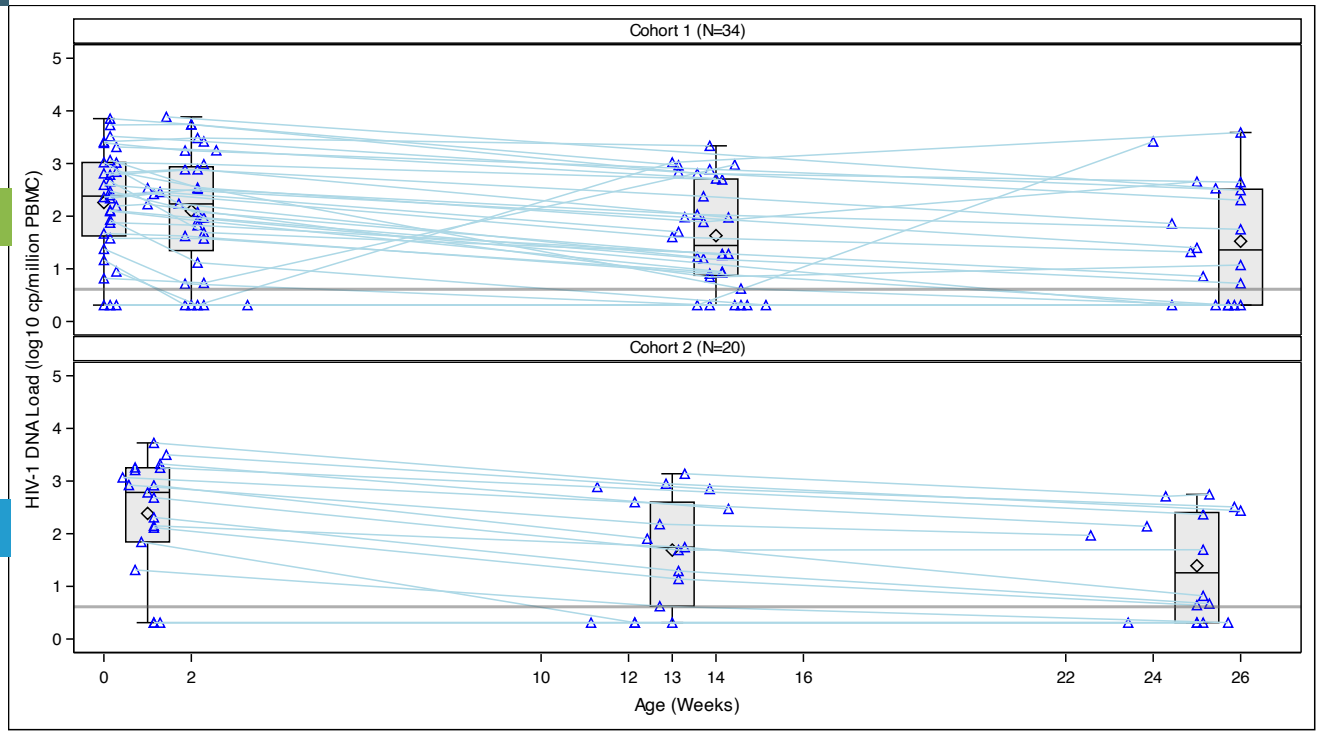
HIV-1 CA-DNA through 26 Weeks of Age with Very Early ART

Cohort 1

Cohort 2



At Study Week 24 :

- **CA-DNA declined a median of 1.0 log_{10} copies/million PBMCs from earliest measurement in each Cohort**
- **19%** (6/31) **in Cohort 1 and 22%** (4/18) **in Cohort 2 had no CA-DNA detected**

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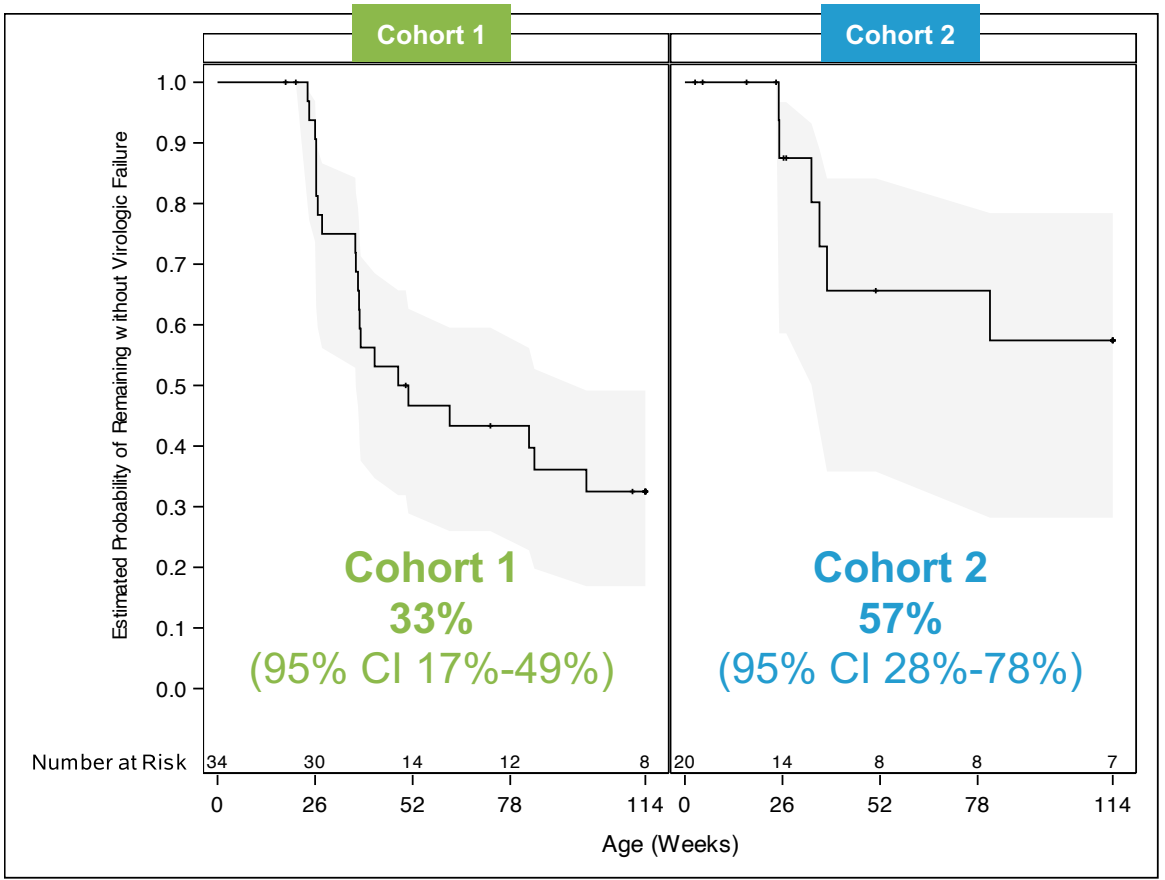
Estimated Probability of Remaining Free of Virologic Failure at Two Years of Age



Virologic Failure: >200 copies/mL at week 24 or confirmed detectable viremia thereafter.

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Univariable Associations of Baseline Factors with Delayed Time to Virologic Failure Through Two Years of Age

	Cohort 1	Cohort 2
	Hazard Ratio (HR) (95% CI)	
Normal Gestational Age (ref. Small for Gestational Age*)	0.6 (0.2-1.7)	—
Male Sex (ref. Female)	**0.3 (0.1-0.9)**	1.5 (0.3-7.4)
ART Initiation 24-48 Hours of Age (ref. 0-24 Hours)	**0.1 (0.02-0.9)**	0.2 (0.04-1.2)
Earliest HIV-1 RNA VL (per 1 $\log_{10}$ c/ml lower)	**0.6 (0.4-0.9)**	0.7 (0.4-1.3)
Earliest HIV-1 CA- DNA Load (per 1 $\log_{10}$ c/million PBMC lower)	0.6 (0.4-1.0)	**0.1 (0.03-0.8)**
Earliest CD4% (per 10% higher)	0.9 (0.6-1.3)	0.4 (0.2-1.0)
Earliest CD8% (per 10% lower)	0.7 (0.5-1.1)	—
Earliest CD4%/CD8% Ratio	0.8 (0.6-1.2)	—
Maternal HIV-1 RNA VL at entry (per 1 $\log_{10}$ c/ml lower)	0.8 (0.5-1.3)	0.9 (0.4-2.0)
No Maternal ARV Exposure During Pregnancy	—	0.9 (0.2-5.0)

Boldface *indicates CI excludes HR=1.*
Dash (—) indicates not collected.
**INTERGROWTH score*

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Biomarker Profiling at 2 Years of Age in Infants with Sustained Virologic Suppression

At Study Week 108:

HIV-1 Antibody negative

83% (10/12, 95% CI 52%-100%) **in Cohort 1**

100% (7/7, 95% CI 59%-100%) **in Cohort 2**

Non detectable CA-DNA

64% (7/11, 95% CI 31%-89%) **in Cohort 1**

71% (5/7, 95% CI 29%-96%) **in Cohort 2**

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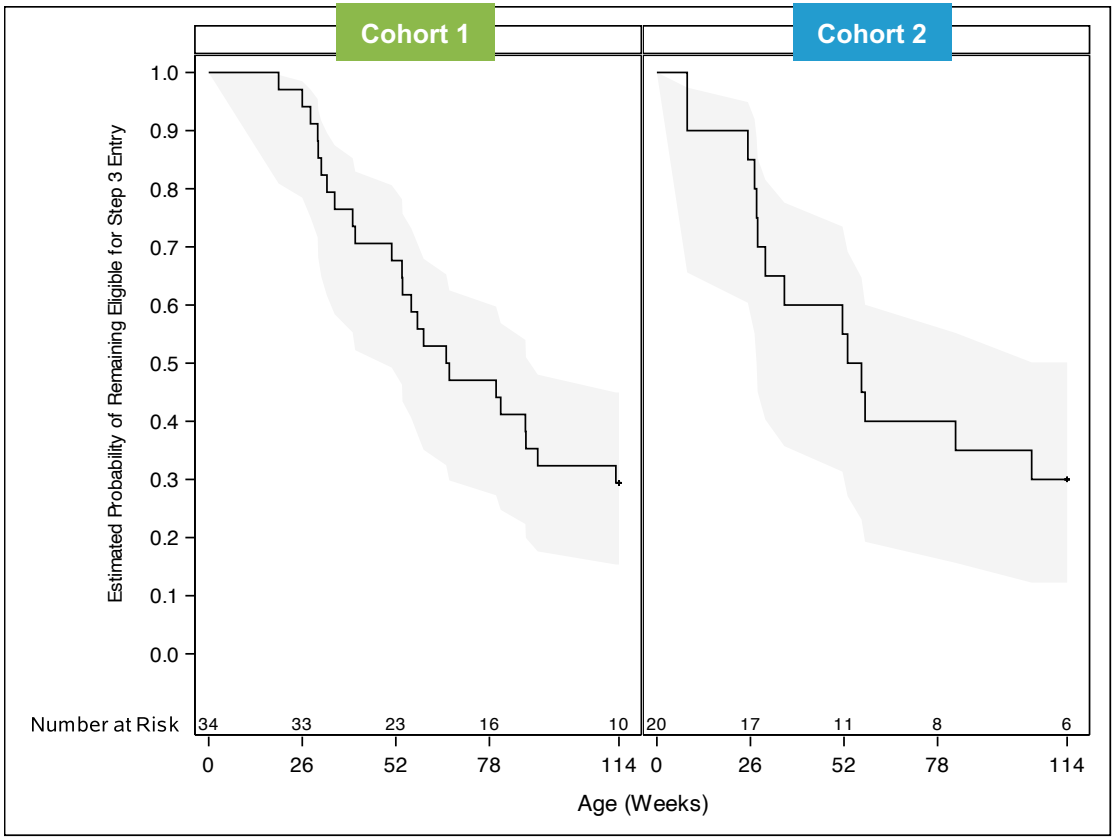
Potential Eligibility for ART Interruption through Two Years of Age



Estimated Probability of Remaining Potentially Eligible at two years of age:

Overall:
30% (95% CI 18%-42%)

Cohort 1:
29% (95% CI 15%-45%)

Cohort 2:
30% (95% CI 12%-50%)

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Study Limitations

- Virologic suppression criteria in the study were stringent
  - leading to early loss of study participants who may have suppressed later
  - limiting assessment of the long-term response to very early nevirapine-LPV-ritonavir based ART in infants
- Options have now expanded to include more potent antivirals such as integrase inhibitors and broadly neutralizing antibodies with follow-up of all infants on study ART

Summary

- A substantial proportion of infants in IMPAACT P1115 who maintained virologic suppression through two years of age, achieved low reservoir size potentially enabling ART-free remission.
- Assessments of eligibility for ART cessation and ART-free remission are underway.
- Findings will be important for informing biomarker profiling and HIV-1 remission potential with very early ART in perinatal infection.

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