Progress in Very Early ART for Newborns: IMPAACT P1115 in 2022

Ellen G. Chadwick for
the P1115 Team
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EGC's spouse is an AbbVie stockholder

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ANNUAL MEETING
2022

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 → lifelong ART
- 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

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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

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Persaud D et al. CROI 2013; NEJM 2013

P1115 Study Design

Cohort 1

- High risk infants born to mothers untreated with ART during pregnancy
- Initiated pre-emptive ART within 48 hours of birth
- Those with *in utero* infection continued ART on-study

Cohort 2

- Infants diagnosed with *in utero* infection enrolled ≤10 days of age
- Initiated NVP-based triple-ARV prophylaxis within 48 hours of birth
- Transitioned to study ART regimen at enrollment

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ART Regimens

Version 1 (2014-2018)

- 2 NRTIs
- NVP until 12 weeks post VL < level of detection
- LPV/r at >42 weeks postmenstrual age

Version 2 (2019-)

- 2 NRTIs
- NVP until 12 weeks post VL < level of detection
- Raltegravir
- +/- VRC01 (selected by site)

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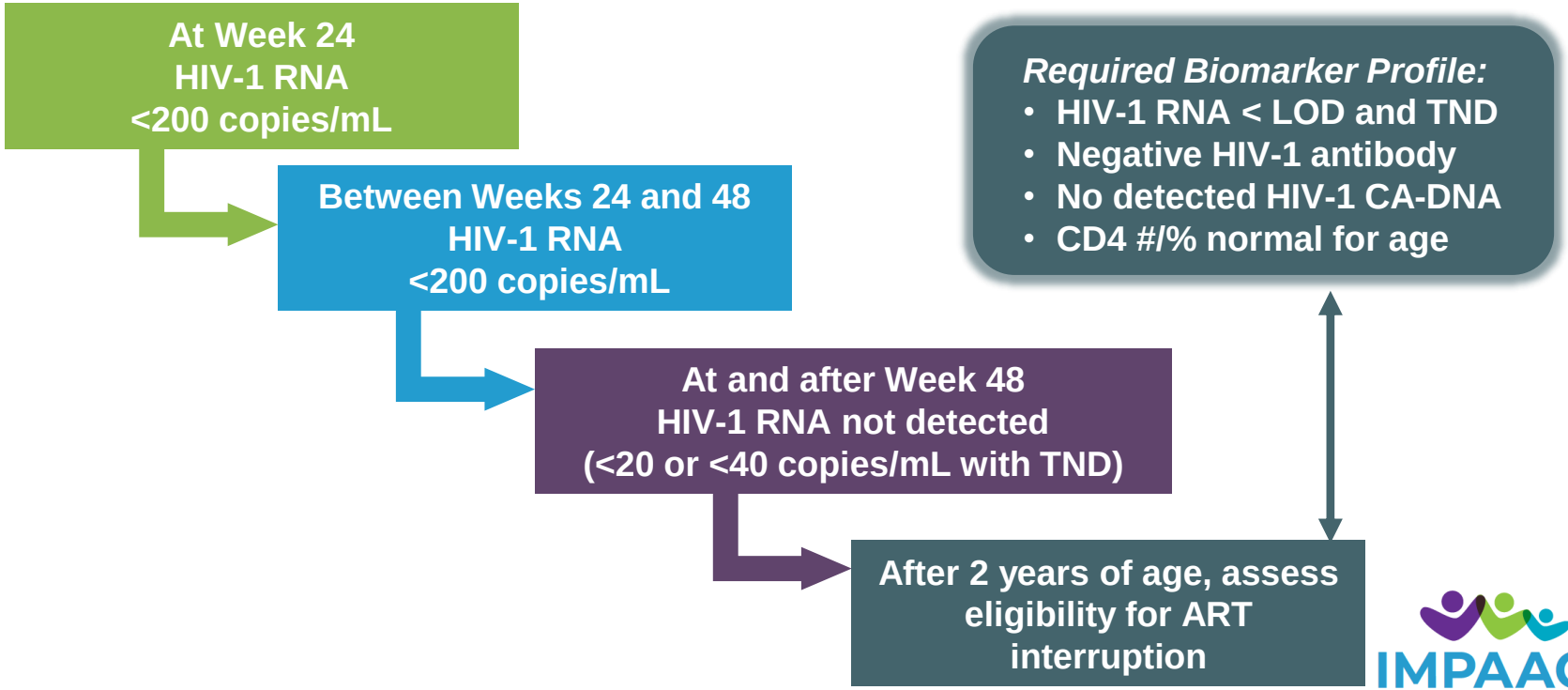
Virologic Suppression Criteria for Evaluation for ART-Free Remission



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Infants with *in utero* HIV Who Continued in Follow-up

Version 1 (N=54 of 460 enrolled)	
Africa	47 (87%)
Asia	1 (2%)
North America	2 (4%)
South America	4 (7%)

Version 2 (N=10 of 239 enrolled)	
Africa	10 (100%)
Asia	—
North America	—
South America	—

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What Has P1115 Contributed Thus Far?

Feasibility of early infant diagnosis
Safety and dosing of neonatal ARVs
PCP guidelines
Virology

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Feasibility of Early Infant Diagnosis

- Site engagement: 27 sites able to collect specimens for 2 NATs within 48 hours of age
  - Median 8 days of age at confirmed diagnosis (V2)
  - Challenges:
    - Newborn phlebotomy, limited allowable blood volume
    - NAT run failures
    - Resolving discordant NAT results (3/239 in V2)

Safety and Dosing of Neonatal ARVs

- Nevirapine
  - Pharmacokinetic modeling to predict/test treatment dose for newborns
  - Safety and dosing established *(Chadwick et al IAS 2015, Chadwick et al Int Ped HIV Wkshp 2017, Ruel et al Lancet HIV 2021)*
  - Treatment dose added to DHHS Perinatal and Pediatric Treatment Guidelines
- Raltegravir
  - 239 newborns treated for at least 1-2 weeks
  - No safety concerns assessed as related to RAL

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Safety and Dosing of Neonatal ARVs

- mAb VRC01
  - Excellent tolerability
    - 123 newborns received one dose; 8 received four doses over 12 weeks
    - No injection site reactions
- Maraviroc
  - Worked with IMPAACT Treatment Committee to establish dosing for use in infants with resistant HIV
    - Added to DHHS Pediatric Treatment Guidelines

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PCP Prophylaxis?

- CD4 counts and percentages of Version 1 participants tracked through first year of life
- At Weeks 24 and 48, ≥80% had CD4 count ≥1500 cells/mm^3 and CD4% ≥25%

Is cotrimoxazole still needed for early-treated infants in settings without malaria or high rates of bacterial infection?

Nelson et al CROI 2022

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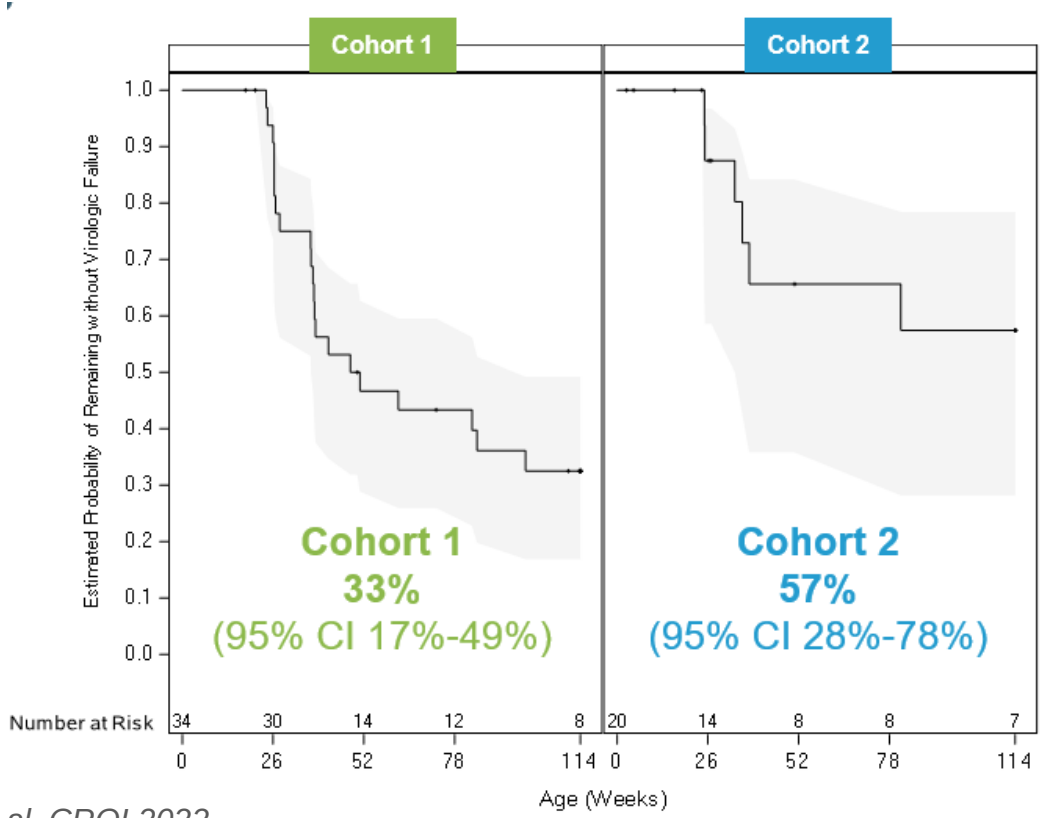
Virology

- Viral load decline in very early treatment
- Limitation of viral reservoir
- Biomarker profile to determine eligibility for treatment interruption

Estimated Probability of Remaining Free of Virologic Failure at 2 Years of Age on a LPV/r-based regimen (V1)



Virologic Failure:
>200 copies/mL at week 24 or detectable viremia ≥ week 48

Persaud et al, CROI 2022

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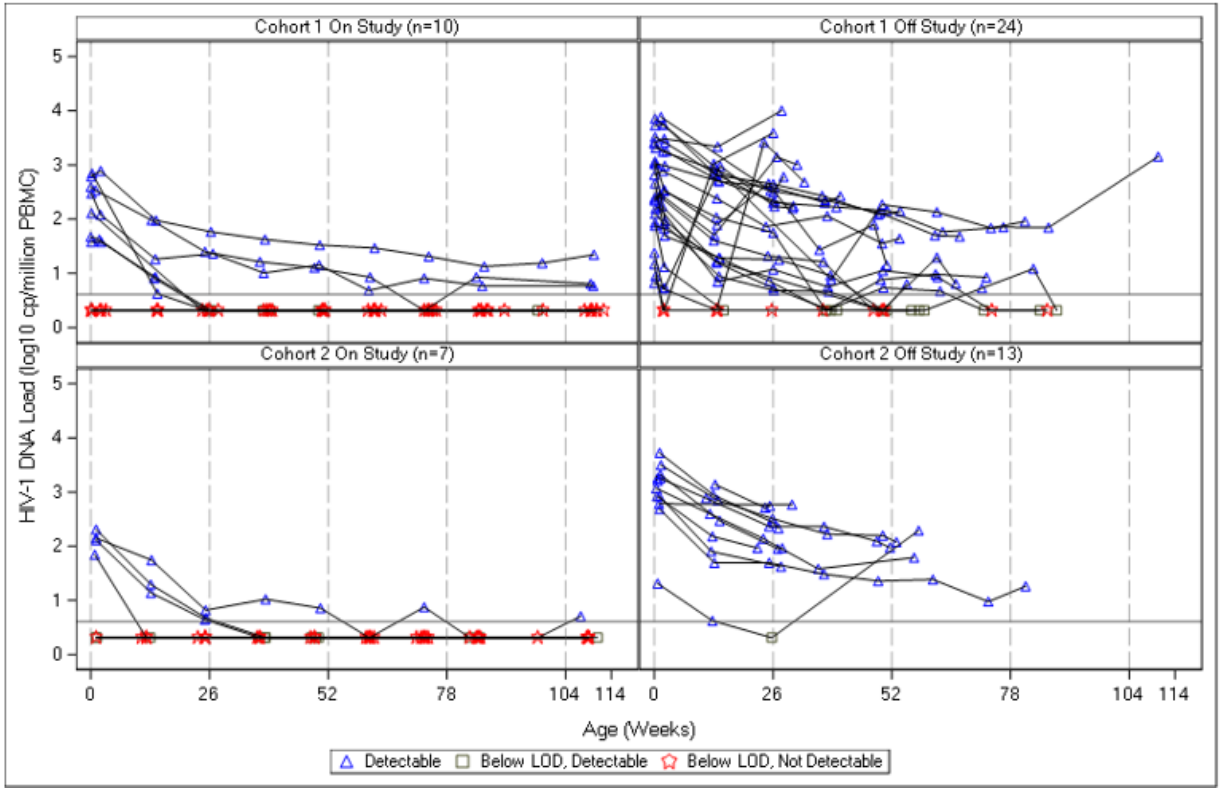
4 participants maintained nondetectable HIV DNA from baseline → excellent candidates for remission



- DNA measured by droplet digital PCR
- Assay LOD = 4.09 copies/10^6 PBMC

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Biomarker profile to identify V1 candidates for treatment interruption to investigate remission

At Study Week 108:

HIV-1 antibody negative
10/12 (83%) in Cohort 1
7/7 (100%) in Cohort 2

Non detectable cell Associated DNA
7/11 (64%) in Cohort 1
5/7 (71%) in Cohort 2

CD4 count/% normal for age
11/12 (92%) in Cohort 1
7/7 (100%) in Cohort 2

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6 participants from V1 currently eligible for ART interruption

1 recently interrupted ART

Summary

- P1115 has advanced knowledge about neonatal ARV safety/dosing/implementation/management in very early ART.
- Low reservoir size is achievable with very early ART, 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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https://www.verywellfamily.com/ava-meaning-origin-popularity-5119619

THANKS!

Any questions?

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