Cure Research in Maternal/Pediatric Setting

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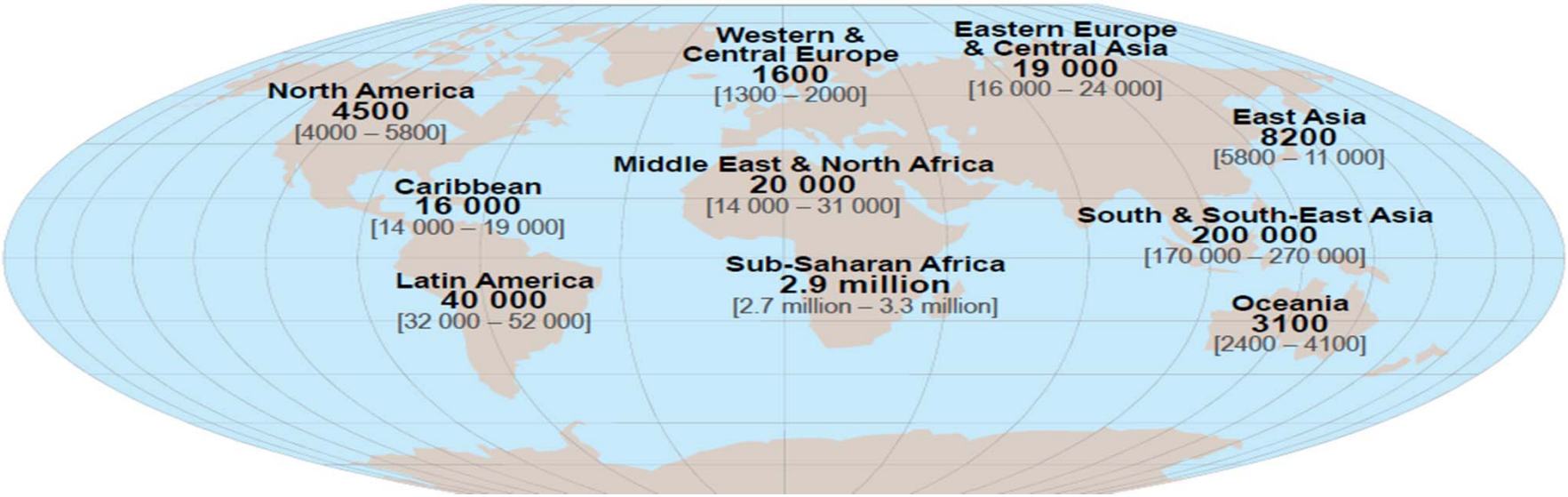
Chair, HIV Cure Scientific Committee

Forum for Collaborative HIV Research

June 17th, 2014

Global Impact of HIV/AIDS Epidemic in Children (<15 years)



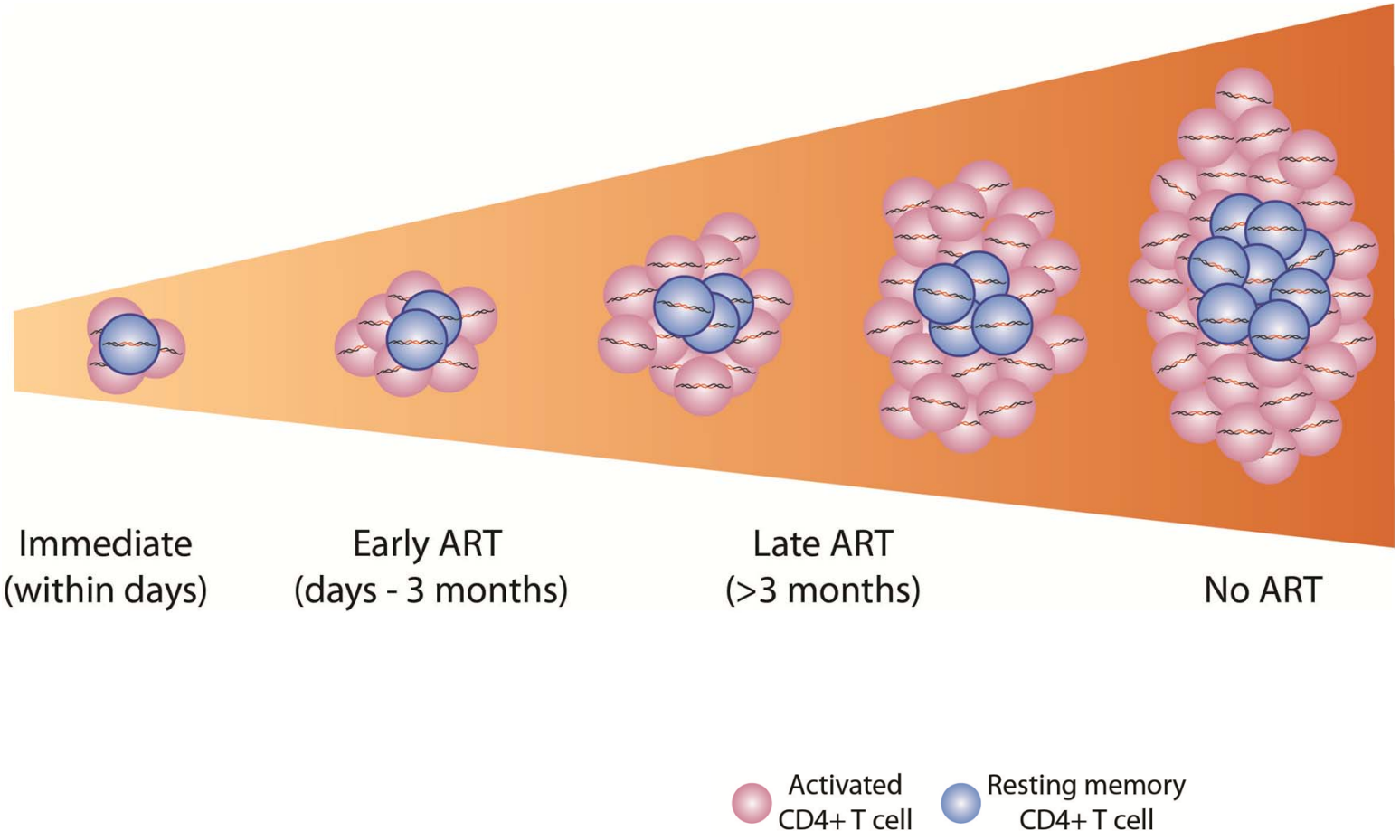
2012 global HIV and AIDS estimates
Children (<15 years)

Children living with HIV	3.3 million [3.0 million – 3.7 million]
New HIV infections in 2012	260 000 [230 000 – 320 000]
Deaths due to AIDS in 2012	210 000 [190 000 – 250 000]

52% reduction from 2001

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

Latent Reservoir Size and Timing of ART in Perinatal Infection



Model: Persaud D

Perinatal HIV Infection: Opportunity to Assess Immediate ART and Cure

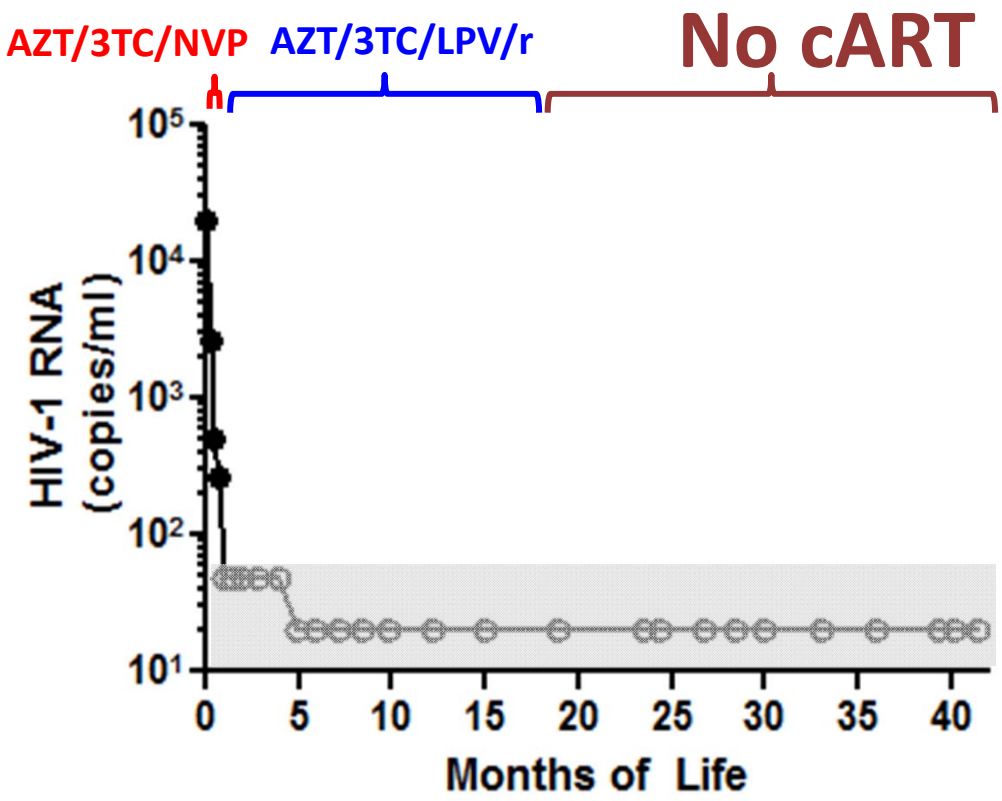
- Timing of HIV exposure is known
- Early reservoir formation may be restricted under routine antiretroviral prophylaxis to prevent mother-to-child transmission
- Reduced viral reservoirs may also occur from the underdeveloped and tolerogenic nature of the infant immune system

Sustained HIV Remission in a Perinatally-Infected Child

- Born in rural Mississippi (US)
- 35 weeks gestation; spontaneous vaginal delivery
- Mother positive for HIV during labor (rapid test)
- No antiretroviral prophylaxis during labor
- Post-exposure prophylaxis with a three drug regimen - AZT/3TC/NVP
- Nevirapine-twice daily dosing; started at 31 hours of age
- Managed at a tertiary care center (University of Mississippi Medical Center)

Persaud D, *Gay H, Ziemniak C, Chen YH, Piatak M, Chun T-W, Strain M, Richman D, Luzuriaga K. NEJM 2013:369 (19);1828-1835*

Sustained HIV Remission (23 months off cART)



Limit of Detection< 20 copies/mL

Persaud D, *Gay H, Ziemniak C, Chen YH, Piatak M, Chun T-W, Strain M, Richman D, Luzuriaga K. NEJM 2013:369 (19);1828-1835;* Persaud D et al.; CROI 2014

Remains under the care of Dr. Hannah Gay of the University of Mississippi Medical Center

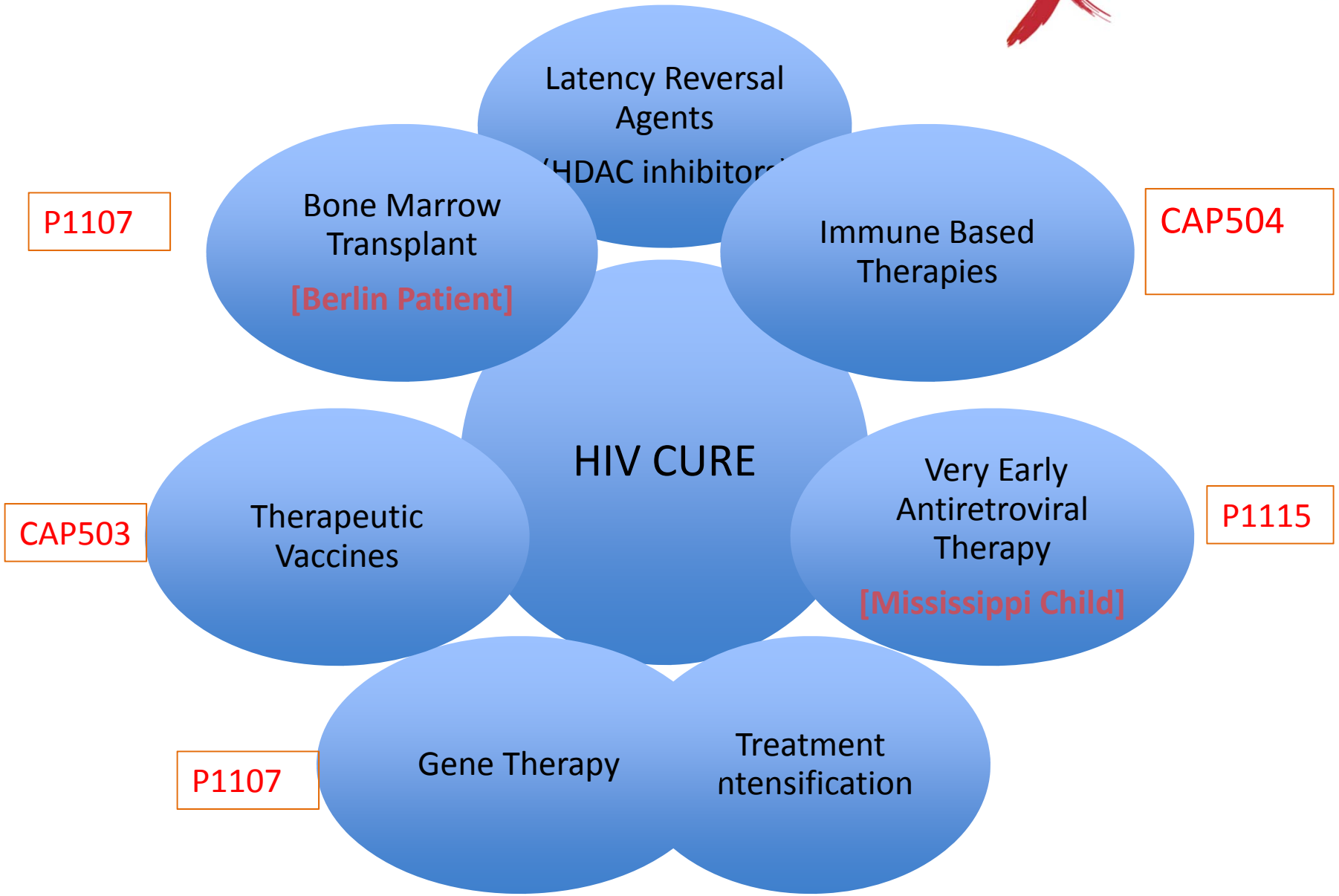
Implementing Immediate ART for HIV Cure Research

- Scalable
- Build on PMTCT programs
- Added value:
  - Focus on early infant diagnosis
  - Potential to enhance identification and treatment of HIV-infected infants
  - Promote retention in care
  - Prolong lives

Cure Scientific Agenda

- Evaluate very early ART to reduce viral reservoirs in neonates to achieve viral remission/cure
- Evaluate specific interventions in chronically infected- youth to reduce HIV reservoirs
  - HIV Vaccines
  - Immunomodulatory agents
  - Inflammatory blockade
- Elucidate relationships between viral reservoirs and the developing immune system

Approaches to HIV Cure



Summary

- HIV-infected children face a life-time of antiretroviral treatment (30 or more years)
- Medication fatigue, antiretroviral toxicities, stigma and social factors promote nonadherence and self-directed treatment interruption
- The developing immune system, opportunity for very early and early treatment, along with thymic reserve set pediatric HIV infection apart
- Provide the scientific rationale for simultaneous conduct of studies towards HIV cure or sustained remission in children
- Approaches guided by scientific reasoning with special attention to risks, benefits and false expectations

International Maternal Pediatric Adolescent AIDS Clinical Trials Group-HIV CURE Scientific Committee

Deborah Persaud (Chair); Ellen C Chadwick (Vice Chair)

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Mission

Identify interventions to block establishment and/or maintenance of HIV reservoirs in infected infants, children and adolescents, leading to cure

Acknowledgements

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Hannah Gay

Katherine Luzuriaga

Yvonne Bryson

Parents and their Children

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Ya Hui Chen
Kaitlin Rainwater-Lovett
Priyanka Uprety



National Institute of Allergy and Infectious Diseases

National Institute of Allergy and Infectious Diseases

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Group

IMPAACT P1115

Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study

Rationale

- HIV remission reported in a U.S. born child treated with a 3 drug ARV regimen by 31 hours of life for high-risk HIV-exposure from untreated maternal infection
- Emerging data that very early therapy during acute HIV infection in adults and children quantitatively modifies HIV persistence
- Hypothesis: very early ART in neonates with *in utero* HIV infection permits long-term control of HIV-1 replication off ART and leads to ***HIV remission***, defined as HIV RNA below the limit of detection (LOD) for 48 weeks following ART cessation

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P1115 Objectives

Primary Objective

- To assess ***HIV remission*** among HIV-infected neonates who initiate ART within 48 hours of birth

Secondary Objectives

- ***Safety*** of very early ART in neonates
- ***Pharmacokinetics*** in neonates/young infants
  - ***nevirapine*** (NVP) at treatment (i.e. higher than prophylaxis) doses
  - ***lopinavir exposures*** when dosed with NVP in neonates/young infants
- Relationship between ***time to reach plasma HIV RNA < LOD*** and achievement of virologic and immunologic criteria for ART cessation
- ***Extent of HIV persistence*** in infants who achieve HIV remission
- ***Immune activation*** and ***host and viral determinants***, including maternal factors and HIV-specific immune responses, associated with HIV remission

P1115 Study Design

- ***Four operational steps***

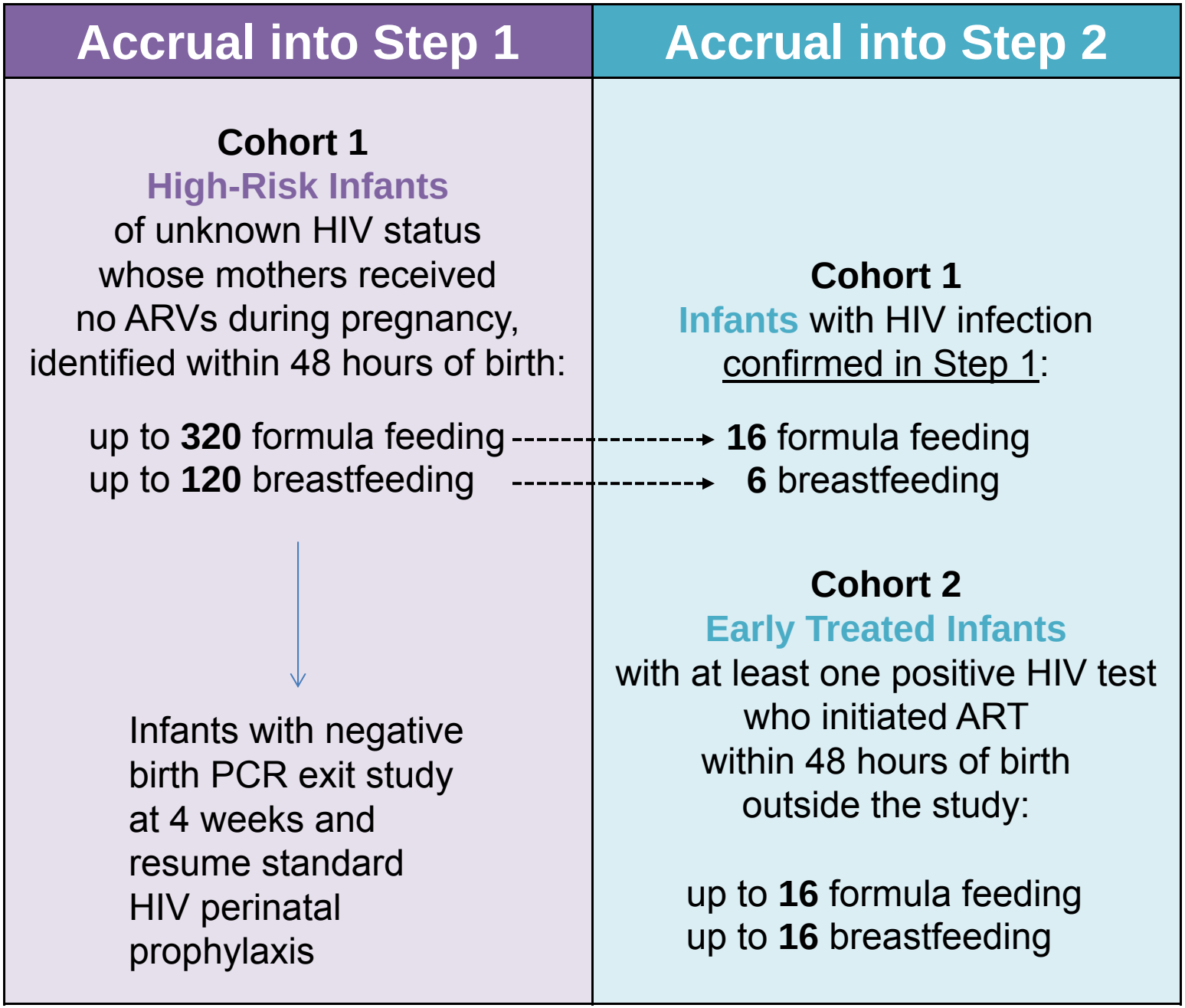
- ***Two cohorts*** of infants enrolled in pairs with their mothers (some breastfeeding, some formula feeding)

  – Cohort 1: (*High Risk*) Infants born to HIV+ mothers receiving no ART during gestation (except in labor/delivery)

  – Cohort 2: (*Early Treated*) Infants initiated ART <48 hrs as clinical care (outside study), and enrolled <10 days of age when birth PCR is positive

P1115 Study Steps

Step 1	Initiation of intensive ART for high-risk infants while awaiting HIV test results (if infected, enter Step 2; if uninfected, exit study after four weeks)
Step 2	Continued intensive ART for confirmed HIV-infected infants with monitoring to determine eligibility for cessation of ART between 2 and 4 years of age
Step 3	ART cessation with monitoring for viral rebound, followed through 5 years of age
Step 4	ART re-initiation for children who experience viral rebound, followed through 5 years of age


Accrual into Step 1
Accrual into Step 2
Cohort 1
High-Risk Infants
of unknown HIV status
whose mothers received
no ARVs during pregnancy,
identified within 48 hours of birth:
up to 320 formula feeding
up to 120 breastfeeding
Infants with negative
birth PCR exit study
at 4 weeks and
resume standard
HIV perinatal
prophylaxis
Cohort 1
Infants with HIV infection
confirmed in Step 1:
16 formula feeding
6 breastfeeding
Cohort 2
Early Treated Infants
with at least one positive HIV test
who initiated ART
within 48 hours of birth
outside the study:
up to 16 formula feeding
up to 16 breastfeeding

P1115 Study Drug Regimens

Step 1	2 NRTIs + NVP (6 mg/kg twice daily)
Step 2	***START WITH*** 2 NRTIs + NVP (6 mg/kg twice daily) ***ADD*** LPV/r at ≥14 days of age and ≥42 weeks postmenstrual age ***STOP NVP*** when HIV RNA <LOD for ≥12 weeks
Step 3	***No ARVS***
Step 4	Resume ART if viral rebound in Step 3

Eligibility for *Cohort 1*

Mother	Infant
• Presumed or confirmed HIV infection • No receipt of ARVs during *current* pregnancy	• **<u>Step 1: Cohort 1</u>** • ≤48 hours of age • ≥34 weeks gestational age at birth • No clinically significant diseases (other than HIV infection) that, in the investigator's opinion, would interfere with study participation or interpretation • **<u>Step 2: Cohort 1</u>** • Confirmed evidence of *in utero* HIV infection

Eligibility for *Cohort 2*

Mother	Infant
• Presumed or confirmed HIV infection • May have received ARVs during current pregnancy	• ≥34 weeks gestational age at birth • ≤10 days of age • ≥1 positive nucleic acid test for HIV infection on a sample collected within 48 hours of birth • Started ART within 48 hours of birth (clinical decision) and continued daily

Virologic Monitoring

Virologic Monitoring in Step 2

- HIV RNA PCR intensely followed and infants whose viral load is not suppressed <LOD by Week 24 exit the study
- After Week 24, infants with confirmed HIV RNA rebound will exit the study

Infants whose viral load remains suppressed <LOD through Step 2 Week 84 are evaluated for possible entry into Step 3

Criteria to Enter Step 3 and Cease ART

- Has reached Week 96 on study
- Has not breastfed for >6 weeks
- Achieved plasma HIV RNA <LOD by Week 24
- Has had no confirmed HIV RNA ≥LOD after Week 24

Lab Criteria to Enter Step 3 and Cease ART

- All of the following between Weeks 84 and 192
  - Two consecutive negative HIV antibody tests by ≥ third generation ELISA tests ≥8 weeks apart
  - Two consecutive negative HIV DNA tests ≥8 weeks apart
  - No detectable HIV RNA
  - CD4 ≥ 25% and normal for age

Monitoring in Steps 3-4

- Step 3: After ART cessation, HIV RNA PCR is intensely monitored
  - If HIV RNA ≥ LOD is confirmed on two consecutive tests, the infant enters Step 4
- Step 4: Participant re-initiates ART and is closely followed for virologic re-suppression

Safety Monitoring

- **Maximize safety for parts of the protocol outside of standard practice**
  - Investigational “treatment dosing” of NVP for first 2 weeks of life
  - 4 drug ART (LPV/r + NVP + 2NRTIs) until ~6 months
  - ART cessation
- **P1115 Clinical Management Committee** (subset of protocol team) will regularly review clinical and laboratory toxicity data reports
- **IMPAACT Study Monitoring Committee** (independent of protocol team) will review study data approximately every 6 months
  - Primary safety outcome data
  - Permanent discontinuations of ARVs for safety reasons

Guideline for Ad hoc SMC Review of ART Cessation

- Each cohort will be monitored separately
- If 10 out of the first 10 children in a cohort who cease ART have viral rebound, ART cessation will be suspended in that cohort
- If 5 children in a cohort do not re-suppress HIV by 6 weeks after ART re-initiation, ART cessation will be suspended in that cohort
- After any ART suspension, SMC will evaluate future direction of protocol

Panel Discussants

- Sandra Nusinoff Lehrman (Merck, Forum industry co-chair), moderator
- Yvonne Bryson (UCLA, P115)
- Ellen Chadwick (Northwestern, P115)
- Mark Cotton (UStellenbosch, P1115)
- Linda Lewis (CDER/FDA)
- Boris Renjifo (Abbvie)
- Seema Shah (DAIDS/NIH)