# *Asymptomatic Hematologic Toxicity with Very Early Combination Antiretroviral Therapy in In Utero HIV-infected Infants*

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# Disclosures

- Ownership of stock and stock options in Abbott Labs/AbbVie, Roche and Novartis
- No other disclosures

# Background

- The capacity of HIV to establish latency early  in long-lived cells or viral reservoirs precludes virus eradication and cure with current combination antiretroviral therapy (ART)
- Converging data in adult and children show that therapy during acute HIV infection (early therapy) quantitatively modifies HIV persistence and HIV-specific immune responses
  - Prolonged remission (27 months of sustained virologic control without ART) in an *in utero* HIV-infected infant ("Mississippi baby") suggests that very early ART may limit viral reservoir formation
- Further investigation prompted IMPAACT P1115: "Very Early Intensive Treatment of HIV-Infected Infants To Achieve HIV Remission: A Phase I/II Proof of Concept Study"

Blankson Ann Rev Med 2002  Ananworanich AIDS 2014  Luzuriaga JID 2014  Bitnun CID 2014  Persaud NEJM 2013

# P1115 Study Design

- Newborns enrolled
  - Cohort 1 -- high risk of HIV infection (mothers ARV untreated during gestation)
  - Cohort 2 – *in utero* HIV infection diagnosed before study entry
- ART (ZDV, 3TC, nevirapine at treatment doses) initiated within 48 hours of birth.

# P1115 Study Design

- *In utero* HIV infection (+ birth HIV PCR) identified by 2 weeks of age
  - Infected infants continue ART, adding LPV/r at ≥42 weeks gestation (= 4 drug ART)
  - Uninfected infants switch to standard country prophylaxis (ZDV or NVP); followed through 4 weeks
- Safety objectives:
  - Assess nevirapine dosing to achieve therapeutic drug levels
    - *Abstract LBPE011, AIDS 2016, Durban, South Africa*
  - To assess the safety of very early ART in neonates
    - Descriptive summary of hematology labs

# Safety Assessment

- Labs performed
  - CBC w/differential & platelets, ALT, AST in all, + lipase in infected patients
    - Uninfected: only at Week 2 except if Grade ≥1 → repeat at Week 4+
    - HIV-infected: every 2 to 4 weeks while on study
- Age-appropriate grading using DAIDS Toxicity table Version 1.0
  - Clinical monitoring committee (CMC) assessed relationship of possibly, probably or definitely related to ART
- *Routine monitoring led to an interim review of asymptomatic hematologic toxicity in all participants enrolled before March 1, 2017.*

# IMPAACT P1115 Registered Study Sites
# As of February 28, 2017 (enrollment ongoing)

# Selected Baseline Characteristics*

| | HIV Infected (n=30) | Uninfected (n=225) | Total (n=255) |
|---|---|---|---|
| Median Age (25-75%ile) | 2 days (1-6) | 1 day (1-2) | 1 day (1-2) |
| Male:female | 14:16 | 110:107 | 124:123 |
| Cohort 1 (% breastfed) | 18 (89%) | 225 (76%) | 243 (77%) |
| Cohort 2 (% breastfed) | 12 (58%) | NA | 12 (58%) |
| Gestational Age<br>Term (≥37 weeks)<br>Pre-term (34-37 weeks)<br>Not evaluated/unknown | <br>26<br>3<br>1 | <br>188<br>27<br>10 | <br>214<br>30<br>11 |
| Co-infection (syphilis or sepsis) | 5 | 13 | 18 |

*Study period: 1/23/15-2/28/17; baseline: at study entry

# Country of Enrollment

| Country | HIV-infected | Uninfected | Total |
|---|---|---|---|
| **Zimbabwe** | 9 | 75 | **84 (33%)** |
| **South Africa** | 7 | 66 | **73 (29%)** |
| Brazil | 3 | 20 | 23 |
| Malawi | 2 | 13 | 15 |
| Uganda | 4 | 10 | 14 |
| Haiti | 0 | 11 | 11 |
| Zambia | 0 | 10 | 10 |
| USA | 1 | 8 | 9 |
| Tanzania | 1 | 5 | 6 |
| Kenya | 2 | 4 | 6 |
| Thailand | 1 | 3 | 4 |
| *Total* | *30* | *225* | *255* |

# All ≥ Grade 3 Lab Toxicities after Entry Regardless of Relationship

| Toxicity | HIV Infected (n=30) | Uninfected* (n=225) | Total (n=255) |
|---|---|---|---|
| Lipase | 2 | NA | 2 |
| Hemoglobin | 8 | 9 | 17 |
| Absolute Neutrophil Count (ANC) | 16 | 18 | 34** |
| Platelets | 0 | 1 | 1 |

* 1 death

**21/34 (62%) of ANC events were from Zimbabwe: 7/9 HIV-infected, 14/75 uninfected

# ≥ Grade 3 Hematologic Toxicities

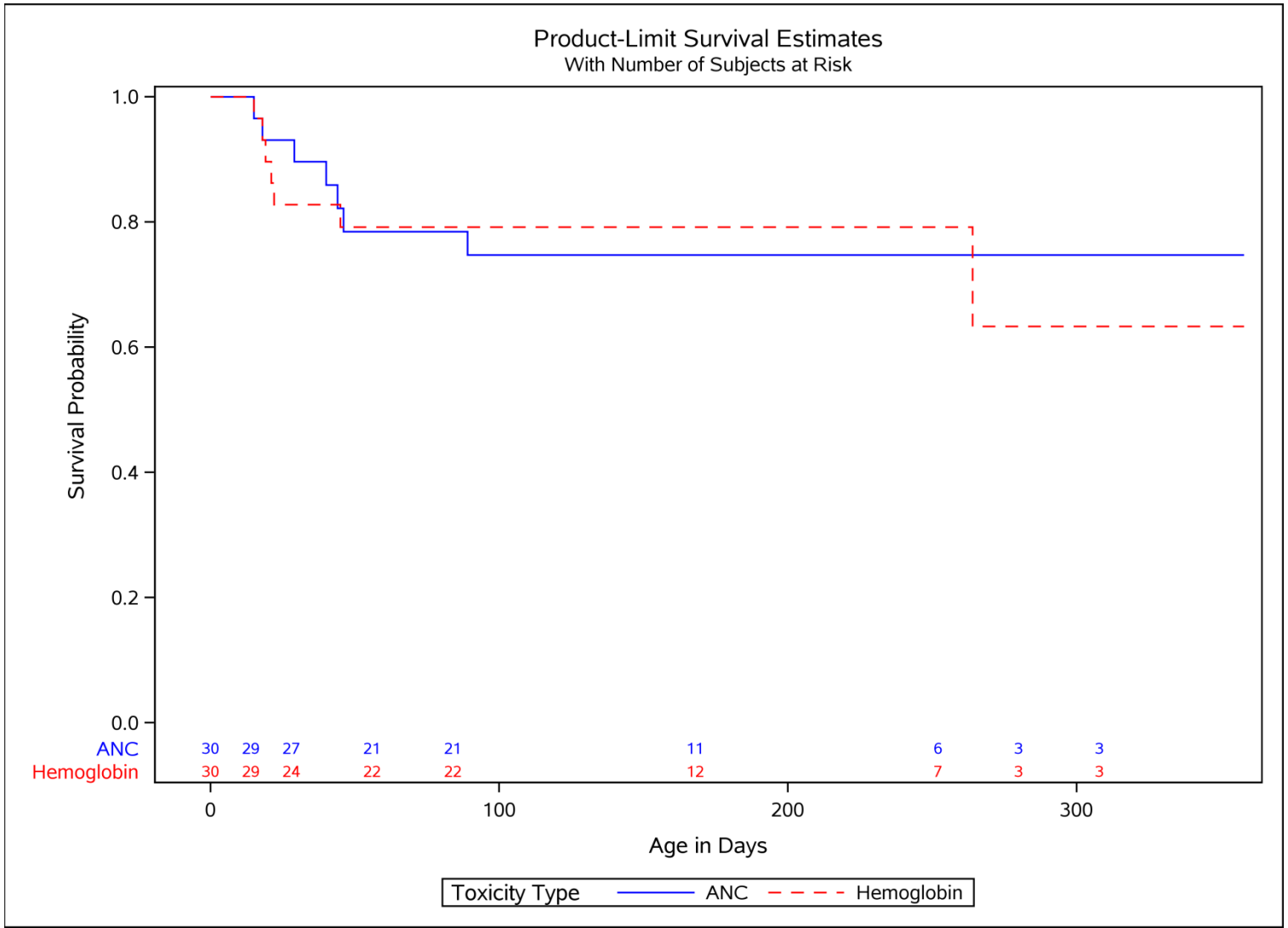
## *at Least Possibly Related to ARVs*

| Events | HIV infected (n=30) | Uninfected (n=225) | Total (n=255) |
|---|---|---|---|
| Hemoglobin | 7 (23%) | 4 (2%) | 11 (4%) |
| assoc. symptoms | 1 RBC transfusion | -- | 1 |
| ANC | 7 (23%) | 12 (5%) | 19 (7%) |
| assoc. symptoms | -- | -- | -- |
| Total # infants with events* | **13 (43%)** | **16 (7%)** | **29 (11%)** |

*12/13 infants discontinued ZDV, replaced with abacavir (10) or stavudine (2)

There were no Grade 3/4 sign/symptoms or diagnoses that were assessed as related by the CMC.

# Time to First Grade 3/4 Hematologic Toxicity Among HIV-infected Infants



# Outcomes in HIV-infected Infants

- Median time to improvement to ≤ Grade 2 after zidovudine discontinuation
  - Hemoglobin: 20 days (15-29 Q1-Q3)
  - ANC: 22 days (9-77 Q1-Q3)
- Mortality among *in utero* HIV-infected infants
  - **P1115: None (of 30) through median 23 weeks follow up**
  - ZVITAMBO study: 33% (of 381) by 16.4 weeks of follow up
  - HPTN 040: 15% (of 93) by median 15.6 weeks of age; median 24 weeks follow up

Marinda PIDJ 2007;26:519
Nielsen-Saines NEJM 2012;366:2368

# Limitations

- Number of HIV-infected infants is relatively small (n=30) and follow-up is limited
- Median duration ART for HIV-infected 13.9 weeks vs. 1.2 weeks for Uninfected
  - Short follow-up for hematology labs for Uninfected (only at Week 2 unless ≥ Grade 1)
- This is an interim, descriptive summary

# Conclusions

- Grade 3/4 asymptomatic ART-related hematologic toxicity is not uncommon in early treated HIV-infected newborns
  - Coincides with physiologic nadir of Hgb
- ZDV known to be associated with hematologic toxicity: early replacement of ZDV with abacavir may be a suitable strategy to manage hematologic toxicity in HIV-infected infants, but more data is needed
- Excellent survival and favorable clinical course supports ongoing study of very early ART in perinatal infection

# Thanks to the P1115 Team

Yvonne Bryson
Ellen Chadwick
Mark Cotton
Deborah Persaud
Patrick Jean-Philippe
Rohan Hazra
Theodore Ruel
Katherine Luzuriaga
Mark Mirochnick
Edmund Capparelli
Lynette Purdue
Amanda Zadzilka
Chivon McMullen-Jackson
Marie Theunissen
Anne Coletti
Charlotte Perlowski
Cheryl Jennings
Diane Costello
Camlin Tierney
Bryan Nelson
Min Qin
Bonnie Zimmer
Cristina Reding
Rebecca LeBlanc

**and all the patients, families and investigators who have participated in the protocol so far**

# Acknowledgements

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH).

The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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