PROMISE
IMPAACT 1077
Promoting Maternal and Infant Survival Everywhere

Association of Maternal Viral Load and CD4 Count with Perinatal HIV-1 Transmission Risk during Breastfeeding in the PROMISE Postpartum Component

10th Workshop on HIV Pediatrics
July 20-21, 2018
Amsterdam, the Netherlands

Patricia M. Flynn, MD, Taha E Taha, MD, Mae Cababasay, MS, Kevin Butler, MS, Mary Glenn Fowler, MD, Lynne M. Mofenson, MD, Maxensia Owor, MD, Susan Fiscus, PhD, Lynda Stranix-Chibanda, MD, Anna Coutsoudis, PhD, Devasena Gnanashanmugam, MD, Nahida Chakhtoura, MD, Katie McCarthy, MPH, Cornelius Mukuzunga, MD, Bonus Makanani, MD, Dhayendre Moodley, PhD, Teacler Nematadzira, MD, Bangani Kusakara, MD, Sandesh Patil, MD, Tichaona Vhembo, MD, Raziya Bobat, MD, Blandina T Mmbaga, MD, Maysseb Masenya, MD, Mandisa Nyati, MD, Gerhard Theron, MD, Helen Mulenga, MD, David E. Shapiro, PhD and the PROMISE Study Team

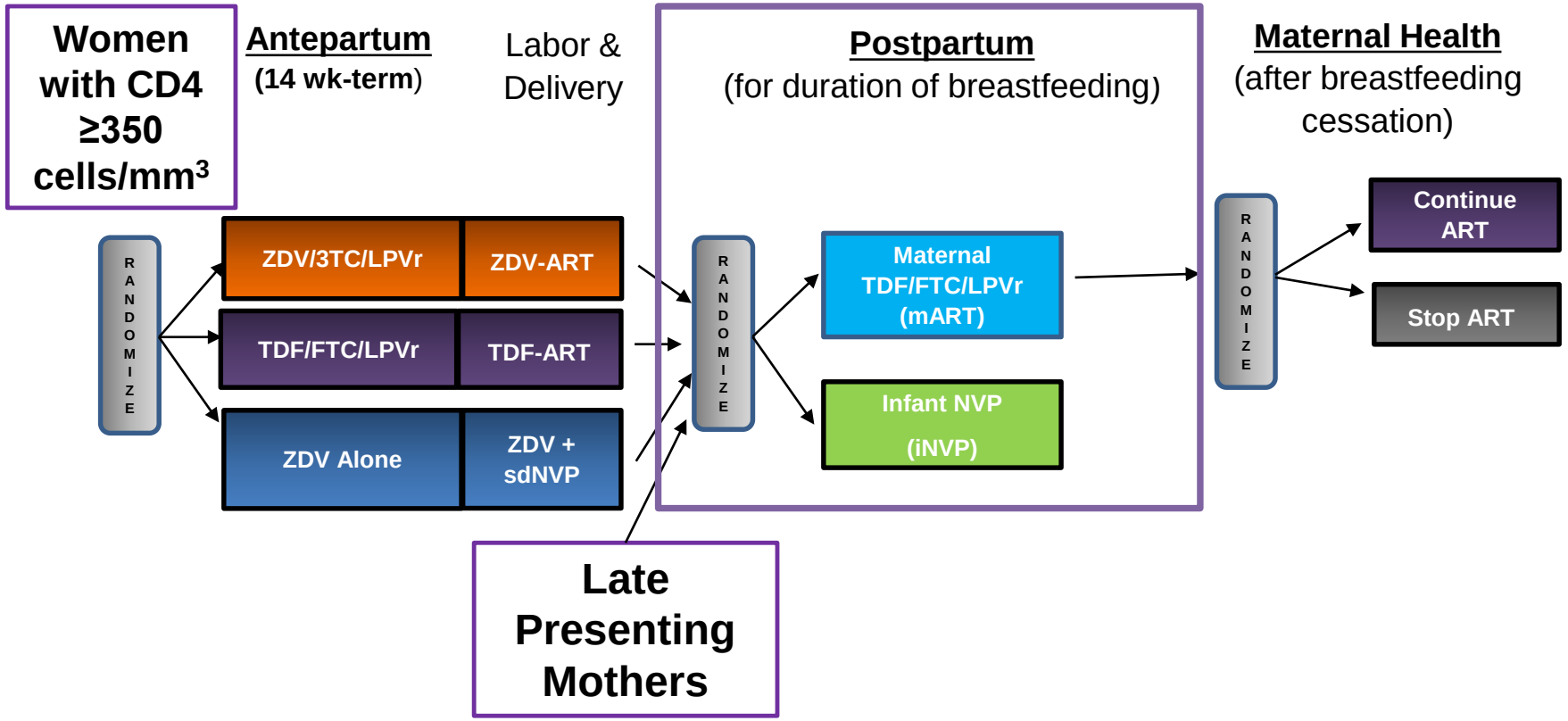
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

DISCLOSURES

Dr. Flynn is a paid consultant for Merck and receives royalties from Up to Date.

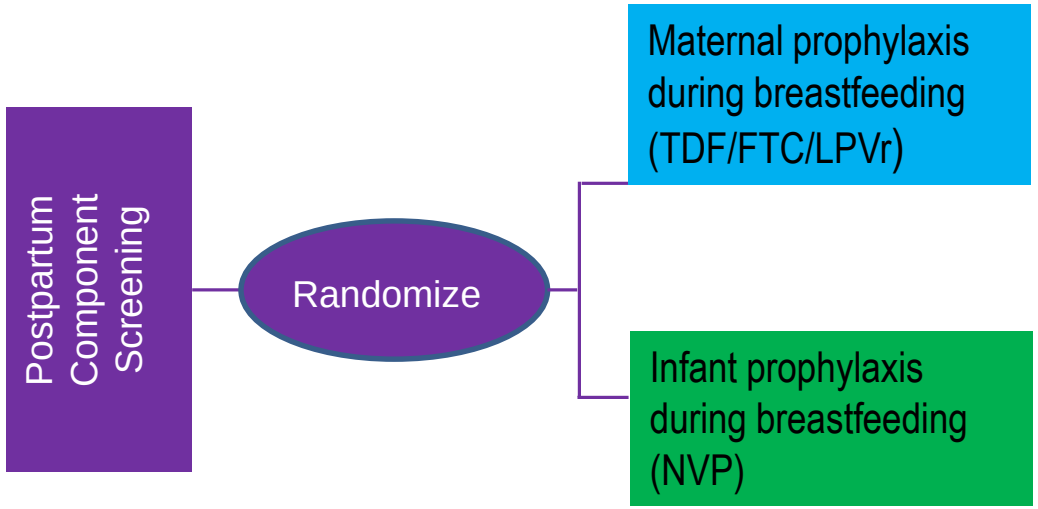
Background

- Increased maternal viral load (MVL) and decreased CD4 cell counts (CD4) have been associated with increased risk of perinatal and postnatal HIV-1 transmission



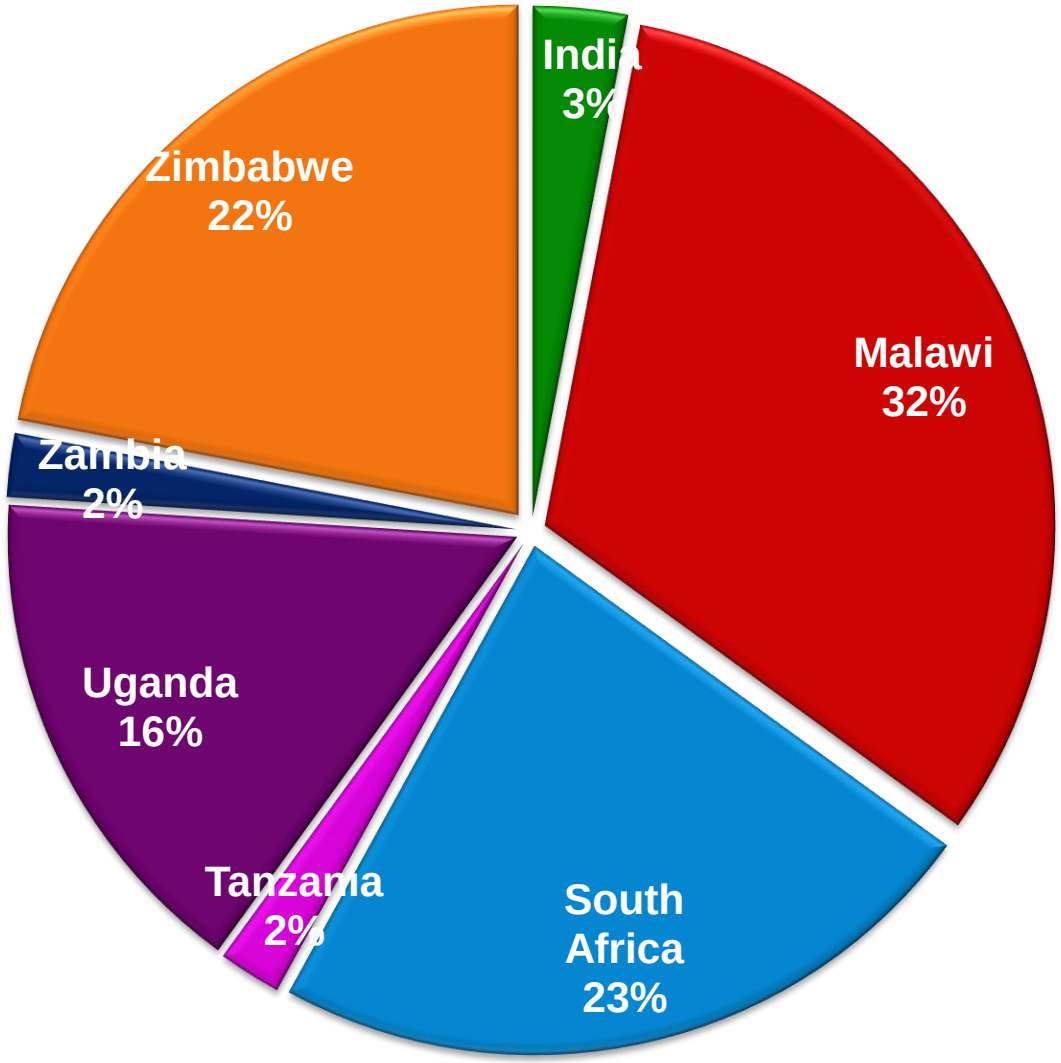
PROMISE – Postpartum Component

- Eligible mother-infant (M-I) pairs (maternal CD4 ≥ 350 cells/mm^3 or country-specific level and infant HIV-1 NAT negative and > 2 kg) were randomized at 6 – 14 days postpartum to a maternal three-drug ART regimen (TDF/FTC/LPVr preferred, **mART**) arm or infant nevirapine (**iNVP**) arm
- Infants in the **mART** arm also received NVP for 6 weeks
- Late-presenting women were enrolled during labor or within 6 days of delivery after assuring the mother's CD4 count met eligibility criteria and infant had a negative HIV-1 NAT



PROMISE – Postpartum Component

- 2,431 M-I pairs were randomized at 6-14 days postpartum to **mART** (n=1,220) or **iNVP** (n=1,211) at 14 sites in 7 countries
- 95% of the mothers had been enrolled in the antepartum component (42% ZDV and 53% mART)
- Randomized regimens were continued until 18 months postpartum, unless stopped earlier due to cessation of breastfeeding, infant HIV-1 infection, or toxicity



PROMISE – Postpartum Component, Primary Analysis Findings

- The primary analysis of the postpartum component has been reported (*J Acquir Immune Defic Syndr. 2018 Apr 1;77(4):383-392*)
  - Both regimens were safe and associated with very low postpartum transmission rates (mART , 0.57% and iNVP, 0.58%; hazard ratio [HR] 1.0, 96% repeated confidence interval 0.3-3.1)
  - Infant HIV-1-free survival was high (97.1%, mART and 97.7%, iNVP, at 24 months)
- This planned secondary analysis examines the relationship between MVL and CD4 with HIV-1 transmission during breastfeeding

Methods

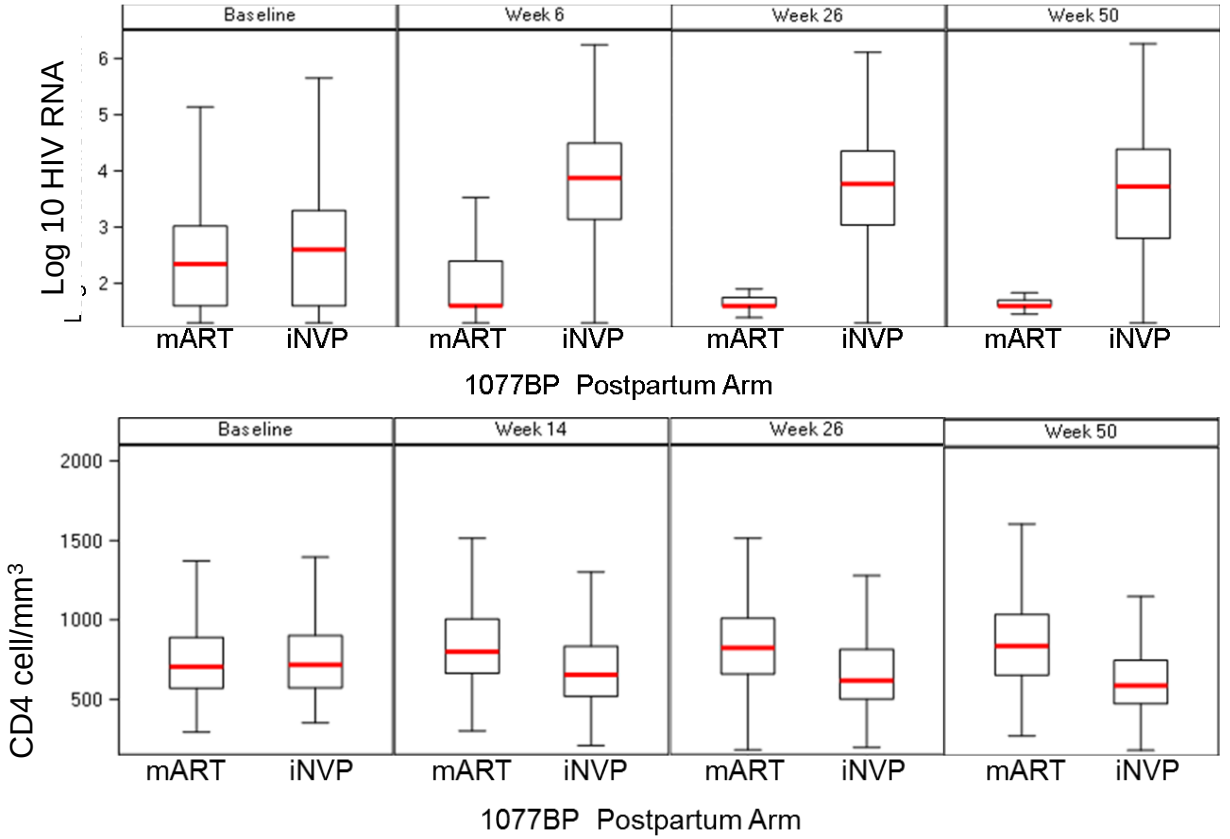
- Study Evaluations

Maternal Viral Load	Entry (6-14 days postpartum), weeks 6, 14, 26, and 50 postpartum
Maternal CD4	Entry, weeks 14, 26, 38, 50 postpartum
Infant HIV-1 NAT	Entry (6-14 days postpartum), week 6, every 4 weeks until week 26, then every 12 weeks

- Infant infection was defined as a positive HIV-1 NAT at any two post-entry timepoints
- The associations of baseline and time-varying MVL (<1000 or ≥1,000 copies/ml) and CD4 (< 500 or ≥ 500 cells/mm^3) with transmission risk were assessed using proportional hazards regression models and adjustment for randomization to the mART arm during the antepartum component of PROMISE

Analysis

- For analyses using time-varying MVL and CD4, each treatment arm was analyzed separately because the post-randomization visits showed little overlap between the two arms with respect to MVL and CD4 cell count



Results

Baseline MVL and CD4 cell count by Treatment Arm		
	mART n=1,220	iNVP n=1,211
Baseline Maternal Viral Load		
< 1,000 copies/mL	911 (75%)	814 (67%)
≥ 1,000 copies/mL	309 (25%)	397 (33%)
Baseline CD4 count		
< 500 cells/mm^3	162 (13%)	170 (14%)
≥ 500 cells/mm^3	1,058 (87%)	1,041 (86%)

- Baseline MVL (p=0.11) and CD4 cell count (p=0.51) were not significantly associated with infant HIV-1 transmission

Results, continued

- Time-varying MVL was significantly associated with infant HIV-1 infection in the **mART** arm but not in the **iNVP** arm
- Time-varying CD4 was significantly associated with infant HIV-1 infection in the **mART** arm but not in the **iNVP** arm
- Adjusting for whether or not the mother was randomized to the mART arm in the antepartum component of PROMISE component did not change these findings

	Hazards Ratio (95% Confidence Interval)	
	mART	**iNVP**
Time-varying MVL	**13.96 (3.12-62.45)**	1.04 (0.20-5.39)
Time-varying CD4	**0.18 (0.03-0.93)**	0.38 (0.08-1.77

Results, continued

- When both time-varying MVL and time-varying CD4 were in used in the model for infant HIV-1 infection in the **mART** arm, only MVL remained associated with infant HIV-1 infection (hazard ratio (95% CI): 11.57 (2.45,54.68)) and there was no association with maternal CD4 (hazard ratio (95% CI): 0.34 (0.06,1.88))
- Adjusting for whether or not the mother was randomized to the mART arm in the antepartum component of PROMISE did not change these findings

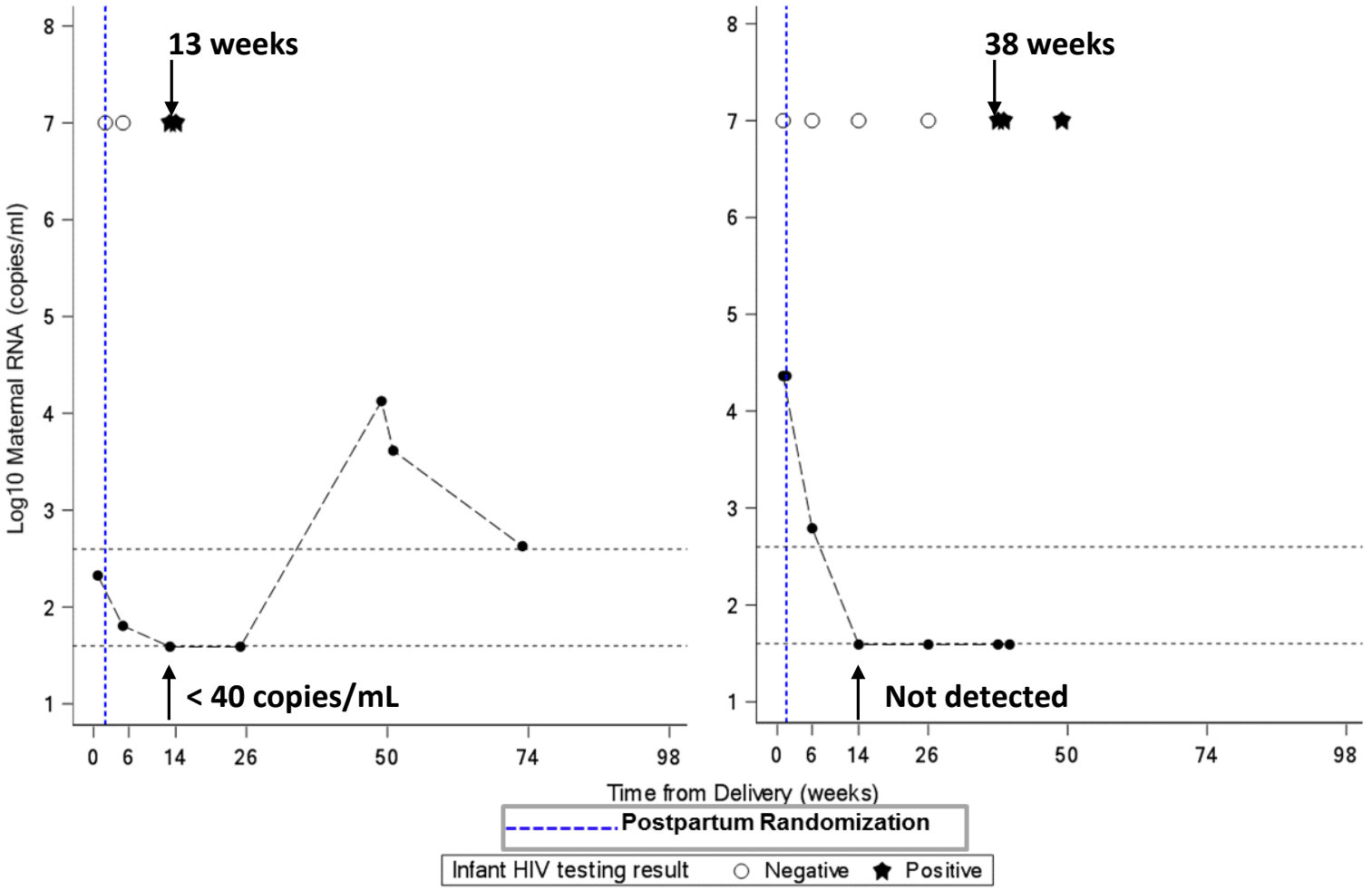
Infant HIV-1 Infections

- There were seven infants with HIV-1 infection in each treatment group

	mART	**iNVP**
HIV-1 infections	n=7	n=7
Median infant age at first positive HIV-1 NAT	38 weeks (range, 13-50 weeks)	26 weeks (range, 6-74 weeks)
MVL closest and prior to first positive infant HIV-1 NAT	Not detected – 52,002 copies/mL	815 – 153,963 copies/mL

Results, continued

- In the **mART** arm there were two infected infant cases where MVL was undetectable or < 40 copies/mL in assessments prior to first positive infant HIV-1 NAT



Conclusions

- In the **iNVP** arm, time-varying MVL and CD4 were not significantly associated with HIV-1 transmission during breastfeeding. However, in the **mART** arm, increased MVL and decreased CD4 during breastfeeding were associated with increased risk of infant HIV-1 infection
- Two infant transmissions were observed following periods of MVL that were < 40 copies/mL
- These data emphasize the important role of adherence to mART in controlling MVL and preventing infant HIV-1 infection and suggest that iNVP should be considered in situations with documented poor maternal ART adherence

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Acknowledgements

The PROMISE protocol team gratefully acknowledges the dedication and commitment of the more than 3,500 mother-infant pairs without whom this study would not have been possible.

Sponsors: US National Institutes of Health (K Klingman, R Browning, L Purdue, G Siberry); **Protocol Chair and Vice Chairs:** J McIntyre, T Chipato; **Operations Center:** M Allen, A Coletti, K George, M Valentine, V Toone; **Statistical and Data Management Center:** T Fenton, K Butler, M Qin, C Marr, C Tierney, S Brummel, K Angelidou, M Basar, L Marillo, A Manzella, A Zadzilka; **Laboratory Center:** A Loftis; **CMC:** D Bhattacharya, R Hoffman, A Gupta, G Theron, B Chi, P Flynn, J Currier

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) 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), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.