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

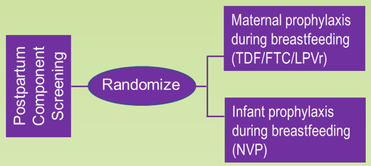
Patricia M. Flynn *[1], MD, Taha E Taha *[2], MD, Mae Cababasay, MS[3], Kevin Butler, MS[3], Mary Glenn Fowler, MD,[4] Lynne M. Mofenson, MD[5], Maxensia Owor, MD[6], Susan Fiscus, PhD[7], Lynda Stranix-Chibanda, MD[8], Anna Coutsoudis, PhD[9], Devasena Gnanashanmugam, MD[10], Nahida Chakhtoura, MD[11], Katie McCarthy, BS[12], Cornelius Mukuzunga, MD[13], Bonus Makanani, MD[14], Dhayendre Moodley, PhD[15], Teacler Nematadzira, MD[16], Bangini Kusakara, MD[16], Sandesh Patil, MD[17], Tichaona Vhembo, MD[16], Raziya Bobat, MD[18], Blandina T Mmbaga, MD[19], Maysseb Masenya, MD[20], Mandisa Nyati, MD[21], Gerhard Theron, MD[22], Helen Mulenga, MD[23], David E. Shapiro, PhD[3] and the PROMISE Study Team

[1]Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN,[2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [3]Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, MA, [4]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Elisabeth Glaser Pediatric AIDS Foundation, Washington, DC, [6]Makerere University - Johns Hopkins University Research Collaboration, Kampala, Uganda, [7]Department of Microbiology and Immunology, University of North Carolina School of Medicine, Chapel Hill, NC, [8]Department of Paediatrics and Child Health, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe, [9]Department of Pediatrics and Child Health, University of KwaZulu-Natal, Durban, South Africa, [10]Division of AIDS, National Institute of Allergy and Immunology, National Institutes of Health, Bethesda, MD, [11]Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD, [12]FHI 360, Durham, NC, [13]University of North Carolina - Lilongwe, Lilongwe, Malawi, [14]Department of Obstetrics and Gynecology, College of Medicine, University of Malawi, Blantyre, Malawi, [15]Centre for the AIDS Programme of Research in South Africa and School of Clinical Medicine, College of Health Sciences, University of KwaZulu Natal, Durban, South Africa, [16]University of Zimbabwe-University of California, San Francisco, Harare, Zimbabwe, [17]Department of Obstetrics and Gynecology, Byramjee Jeejeebhoy Government Medical College and Johns Hopkins Clinical Trials Unit, Pune, India, [18]Department of Pediatrics and Child Health, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa, [19]Department of Pediatrics, Kilimanjaro Christian Medical Centre, Moshi, Tanzania, [20]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [21]Perinatal HIV Research Unit, Chris Baragwanath Hospital, Johannesburg, South Africa, [22]Department of Obstetrics and Gynecology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, [23]George Clinic, Centre for Infectious Diseases Research in Zambia, Lusaka, Zambia

BACKGROUND

- Increased maternal viral load (MVL) and decreased CD4 cell counts (CD4) have been associated with increased risk of perinatal HIV-1 transmission
- The PROMISE 1077BF study included three sequential randomizations: antepartum, postpartum during breastfeeding, and maternal health following breastfeeding
- The PROMISE 1077BF study also included a group of mothers close to or after delivery who were not randomized in the antepartum component but who were eligible for postpartum randomization if eligibility criteria were met (late presenters)
- In the postpartum component, mother-infant (M-I) pairs were screened 4 -14 days postpartum and eligible M-I pairs were randomized at 6 – 14 days postpartum to a maternal three-drug antiretroviral combination regimen (TDF/FTC/LPVr preferred, mART) arm or infant nevirapine (iNVP) arm (Figure 1)

Figure 1. Randomization scheme of the PROMISE Postpartum Component



- Randomized regimens were continued until 18 months postpartum, unless stopped earlier due to cessation of breastfeeding, infant HIV-1 infection, or toxicity
- The primary analysis of the postpartum component has been reported
  - 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

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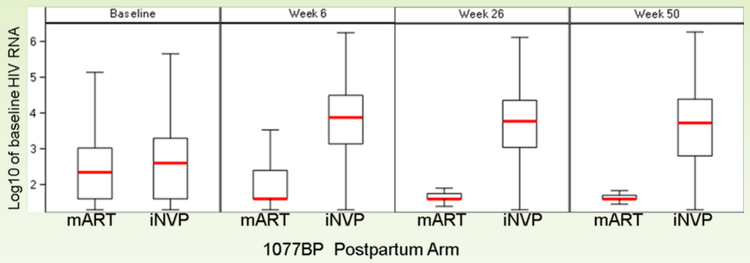
METHODS

- The Postpartum Component of PROMISE was conducted in 14 sites in India, Malawi, South African, Tanzania, Uganda, Zambia, and Zimbabwe
- 2,431 mothers with HIV-1 infection and CD4 counts ≥350 cells/mm3 (or above country-specific guidelines) and their HIV-1-uninfected infants were randomized at 6-14 days postpartum to mART (n=1,220) or iNVP (n=1,211) between June 2011 and October 2014
- MVL was analyzed real-time for mothers on ART and batch-tested retrospectively for mothers not receiving ART; specimens were collected at entry (7-14 days postpartum) and weeks 6, 14, 26, and 50 postpartum
- CD4 was measured real-time at entry and weeks 14, 26, 38, and 50 postpartum
- Infant HIV-1 NAT specimens were collected and assayed real-time at weeks 1 (entry), 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 and CD4 with transmission risk were assessed using proportional hazards regression models by randomized treatment arm, with MVL categorized as ≥1,000 or <1,000 copies/ml and CD4 categorized as ≥500 or <500 cells/mm3, and adjustment for randomization to the mART arm during the antepartum component of PROMISE
- 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 (Figure 2)

Figure 2. MVL at Baseline and Postpartum Visits by Treatment Arm



RESULTS

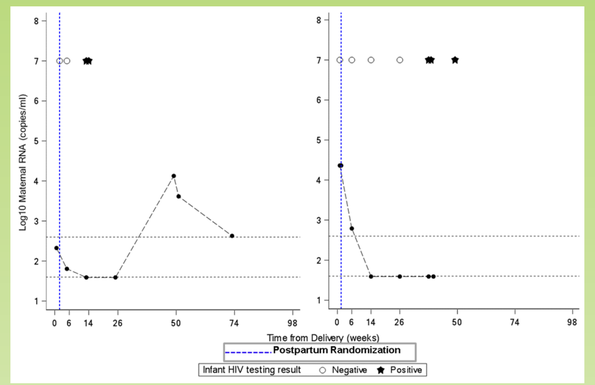
- Baseline MVL (p=0.11) and CD4 (p=0.51) (Table 1) were not significantly associated with infant HIV-1 transmission

Table 1. 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%)

- Time-varying MVL was significantly associated with infant HIV-1 infection in the mART arm (hazard ratio (95% CI): 13.96 (3.12, 62.45)) but not in the iNVP arm (hazard ratio (95% CI): 1.04 (0.20 – 5.39))
- Time-varying CD4 was significantly associated with infant HIV-1 infection in the mART arm (hazard ratio (95% CI): 0.18 (0.03-0.93)) but not in the iNVP arm (hazard ratio (95% CI): 0.38 (0.08-1.77))
- However, when both time-varying RNA 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 component did not change the finding
- There were seven infants with HIV-1 infection in each treatment group
  - In the mART arm, the median infant age at first positive HIV-1 NAT test was 38 weeks (range, 13-50 weeks)
  - In the iNVP arm, the median infant age at first positive HIV-1 NAT test was 26 weeks (range, 6 – 74 weeks)
  - In the mART arm, MVL closest and prior to first infant HIV-1 NAT ranged from not detected to 52,000 copies/mL
  - In the iNVP arm, MVL closest and prior to first infant HIV-1 NAT ranged from 815 – 153,963 copies/mL
- 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 (Figure 3)

Figure 3. Timing of MVL and infant HIV-1 NAT testing in two infants with HIV-1 transmission during breastfeeding



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

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