HPTN 046 - Phase III Trial to Determine the Efficacy and Safety of an Extended Regimen of Nevirapine in Infants Born to HIV Infected Women to Prevent Vertical HIV Transmission During Breastfeeding - *Summary of Results*

2 March 2011

Results of HPTN 046, a Phase III, randomized, placebo-controlled trial designed to determine the efficacy and safety of an extended daily regimen of nevirapine (NVP) in infants born to HIV-infected women to prevent vertical HIV transmission during breastfeeding, were released on 2 March 2011 at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

HPTN 046 compared nevirapine (NVP) given to breastfeeding infants born to HIV infected mothers through 6 weeks of age to an extended regimen given through 6 months of age or cessation of breastfeeding, whichever was earliest.

Other studies have shown that giving daily infant NVP for 6 weeks, 14 weeks or 6 months to breastfeeding infants reduces HIV transmission through breast milk compared to single dose NVP, but no other study has directly compared 6 weeks of NVP to 6 months of NVP to determine if the longer regimen is better for prevention of HIV transmission through breast milk.

In HPTN 046, all breastfeeding HIV-exposed infants received daily Nevirapine (NVP) from birth to age 6 weeks, at which point, those who were determined to be HIV-uninfected and otherwise eligible (n=1,522) were randomized to receive either daily extended NVP (n=759) or placebo (n=763) through age 6 months or through cessation of breastfeeding, whichever was earliest. Randomization was stratified by maternal antiretroviral drug use (29% of mothers were receiving antiretroviral drugs for their own health at the time of randomization). At 3 months, 95% of infants in each arm were reported to be exclusively breastfeeding; over 90% stopped breastfeeding between 6 and 9 months of age, with no difference between study arms. Adherence to the study drug was 88-96% through six months of age and balanced between arms. Retention was 97% at 6 months. Complete data for the primary (6-month) endpoints are available and were included in the analyses. Follow-up is ongoing and is expected to be completed in July 2011 when the last randomized infant reaches 18 months of age.

The study found that the overall risk of HIV transmission through breast milk at age 6 months was lower with extended daily infant NVP, 1.1%, compared to 2.4% in infants in the placebo arm who had only 6 weeks of NVP (p=0.048). The study also demonstrated that extended infant NVP is most important for infants of mothers with high CD4+ cell counts ($\geq$ 350 cells/mm^3) who are not receiving antiretroviral therapy for their own health; among these infants, breast milk transmission was much lower with 6 months of NVP, 0.7%, compared to 2.8% of infants in the placebo arm who received only 6 weeks of NVP (p=0.014). If the mother was receiving antiretroviral drugs for treatment at the time of randomization, transmission through breast milk was very low overall and did not differ by study arm. Infants born to mothers not receiving antiretroviral drugs for treatment who had a low CD4 count (< 350 cells/mm^3) - those for whom WHO recommends antiretroviral therapy for their own health - had much higher rates of breast milk HIV transmission overall, and the transmission rates did not differ significantly between the study arms.

Extended daily NVP was also found to be safe and well-tolerated by infants through 6 months of age, with no significant difference in adverse events (including serious adverse events) between infants receiving between infants who received 6 months of NVP and infants in the placebo arm who received only 6 weeks of NVP. Mortality risk was similar between the study arms; however, two-thirds of deaths occurred after age 6 months, when the majority of mothers had reported cessation of breastfeeding.

This study supports the benefits and safety of extended infant NVP to prevent breast milk transmission overall, particularly in infants of HIV-infected mothers who do not yet require antiretroviral therapy for their own health (those

with CD4 ≥ 350 cells/mm^3) and provides additional information to allow policy makers to make decisions about the use of extended NVP by breastfeeding infants born to targeted groups of HIV-infected women.

Infant Postnatal MTCT or Death (%, 95%CI) in Infants Uninfected at 6 Weeks by Infant Age, Study Arm and Maternal CD4 Count in Mothers not on HAART

	Age 6 mos	Age 9 mos	Age 12 mos
	Overall HIV MTCT after 6 wks		
Ext NVP	1.1 (0.3-1.8)	1.5 (0.6-2.4)	2.0 (1.0-3.1)
PL	2.4 (1.3-3.6)	2.9 (1.7-4.1)	3.0 (1.8-4.3)
p value	0.048	0.078	0.218
	HIV MTCT after 6 wks, maternal CD4 < 350 not on ART		
Ext NVP	4.8 (0.2-9.4)	7.5 (1.7-13.3)	8.9 (2.6-15.2)
PL	8.1 (1.3-14.8)	8.1 (1.3-14.8)	10.0 (2.4-17.6)
p value	0.438	0.901	0.831
	HIV MTCT after 6 wks, maternal CD4 > 350 not on ART		
Ext NVP	0.7 (0-1.5)	0.9 (0-1.9)	1.5 (0.3-2.7)
PL	2.8 (1.3-4.4)	3.3 (1.7-4.9)	3.3 (1.7-4.9)
p value	0.014	0.014	0.079
	Overall death after 6 wks		
Ext NVP	1.2 (0.4-2.0)	2.2 (1.1-3.3)	3.1 (1.7-4.5)
PL	1.1 (0.3-1.8)	2.6 (1.5-3.8)	3.7 (2.3-5.2)
p value	0.86	0.62	0.55

The study is being conducted at sites in four African countries:

- Durban, South Africa: Prince Myshiyeni Hospital
- Dar es Salaam, Tanzania: Muhimbili Hospital
- Kampala, Uganda: MUJHU Clinic/Mulago Hospital
- Chitungwiza, Zimbabwe: Chitungwiza Clinics

Study products were provided free of charge by Boehringer Ingelheim Pharmaceuticals.

Sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the study was initially designed in the HIV Prevention Trials Network (HPTN) and later transitioned to the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group.

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NIAID Press Release