0792 - EXTENDED PROPHYLAXIS WITH NEVIRAPINE DOES NOT AFFECT GROWTH IN HIV-EXPOSED INFANTS

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Background

Current WHO guidelines for HIV-infected pregnant women recommend that antiretroviral therapy (ART) should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued for life. Further guidance recommends that HIV-infected mothers should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer while on ART.

With regard to infant prophylaxis, current guidelines recommend that infants of mothers on ART and breastfeeding should receive 6 weeks of infant prophylaxis with daily nevirapine. Additional recommendations for breastfeeding infants who are considered at high risk of acquiring HIV, state that the infant prophylaxis should continue for an additional 6 weeks using either nevirapine (once daily) or zidovudine (ZDV) (twice daily).

The widespread implementation of these guidelines especially in resource-limited settings is resulting in unprecedented numbers of children being exposed to antiretroviral (ARV) medications in utero —over 1 million per year. There is limited information on the effect of extended ARV exposure on growth among HEU infants in the postpartum period, including whether there is an effect of infant ARV prophylaxis on growth outcomes.

To address this research question, we evaluated the effect of an extended course of infant prophylactic nevirapine given daily from 6 weeks to 6 months on the growth of HEU breastfeeding infants, while adjusting for other known risk factors for adverse growth outcomes.

METHODS

- This is a secondary data analysis of data from the HIV Prevention Trials Network (HPTN) 046 trial, a phase three, randomized, double-blind, placebo-controlled trial conducted in four countries in east and southern Africa.
- This trial assessed the efficacy and safety of extending once-daily nevirapine from 6 weeks to 6 months of age or until cessation of breastfeeding when compared to only 6 weeks of neonatal prophylaxis, for prevention of transmission among HIV-exposed breastfeeding infants (all of whom had received nevirapine prophylaxis until the age of 6 weeks)

Study Setting

- The study was conducted at research sites in Durban, South Africa, in Kampala, Uganda, in Dar es Salaam, Tanzania and in Chitungwiza, Zimbabwe where HIV infected women were provided infant feeding counseling and received the local standard of care for PMTCT at the time. Majority of the women in this study were not receiving ART either antepartum or postpartum as it was not the standard of care at the time.
- Informed consent was obtained from the eligible women who chose to breastfeed as the preferred mode of infant feeding prior to study participation.
- Infants were eligible if they had an HIV DNA PCR negative result from a blood specimen obtained within 7 days of birth, a birth weight of at least 2000 grams, were breastfeeding and did not have any life threatening conditions.
- All mother-infant pairs were recruited and followed up between June 2008 and March 2010.

Randomization

- At enrollment, all infants received open label daily oral nevirapine for the first 6 weeks (42 days) of life.
- After the 6 week period of open label nevirapine, between 6-8 weeks, eligible infants were randomized within strata of maternal ART use (i.e. maternal ART for treatment of HIV or no maternal ART for treatment of HIV at time of randomization) to one of two arms; either extended nevirapine or placebo once daily from 6 weeks to 6 months or through cessation of breastfeeding, whichever was earliest.

Study Procedures

- Baseline socio-demographic data, medical and pregnancy history were collected from the women at screening and enrollment.
- Infant examinations were conducted within 7 days post birth, at 2, 5, 6, and 8 weeks, and at 3, 4, 5, 6, 9, 12, and 18 months.
- At each infant scheduled study visits, physical examinations were performed including the recording of anthropometric measurements which were done by trained nurses using standardized instruments.
- Length was measured using a measuring board to the nearest 0.1 centimeter
- Weight readings were taken using a pediatric weighing scale to the nearest 0.1 kilograms.
- Head circumference was measured using tape measure to the nearest 0.1 centimeter
- Information regarding breastfeeding status and practices was assessed by interview
- All infants received prophylactic co-trimoxazole treatment from 6 weeks of age to the time of confirmed HIV uninfected status following breastfeeding cessation.
- Mothers were counselled to exclusively breastfeed for 6 months as per the contemporaneous WHO infant feeding guidelines however, the mother determined the timing of breastfeeding cessation.

Analysis Outcomes

- Study endpoints were standardized growth indicators or standardized normal deviates (Z scores) computed from the measurements of weight, length and head circumference for each infant based on the infant's gender and age in months using the (WHO) Child Growth Reference Standards
- Measures of adverse growth outcomes included the following: underweight (WAZ<-2 SD), stunting (LAZ <-2 SD), wasting (WLZ< -2 SD) and low head circumference (HCZ < -2 SD).

Statistical Analysis

- Medians and inter-quartile ranges (IQR) are presented as a summary description of average and variation of some quantitative variables.
- Proportions were used to describe categorical variables presented.
- The intent to treat (ITT) approach to examine study intervention effect on growth outcomes for weight, length and head circumference.
- Linear mixed effects models were used to compare the rate of change in infant growth outcomes (WAZ, LAZ, WLZ, and HCZ) between the two study arms. Each infant was modelled as a random effect nested within treatment group. Time was modelled as a continuous variable.
- Using Poisson Regression models the incidence of adverse growth outcomes (underweight, stunting, wasting and low head circumference)were calculated as the ratio of the total number of infants with a first event (e.g. wasting) to the total person time at risk
- Univariable Cox proportional hazard regression models were used to identify the maternal and infant correlates of adverse growth outcomes.
- A likelihood ratio test p-value of less than 0.1 in the univariable model was used as the cut-off for including variables in the multivariable models.
- Final multivariable Cox models included variables significant at 0.05 level
- The statistical package used for analysis was R package nlme

RESULTS

In HPTN 046, a similar number of mother-infant dyads were randomized to the extended nevirapine group (751) and placebo study group (752).

Characteristics	Extended NVP arm N= 751	Placebo arm N= 716
Mother's age, years median [IQR]	26 [21 - 30]	27 [23 - 31]
Years of education (median [IQR])	10 [7 - 11]	10 [7 - 11]
Number of pregnancies (median [IQR])	3 [2 - 3]	3 [2 - 3]
Number of Live births (median [IQR])	1 [1 - 2]	1 [1 - 2]
Work outside home (n (%))		
Yes	206 (27.4)	197 (26.2)
No	545 (72.6)	556 (73.8)
Vaginal delivery (n (%))		
Yes	621 (82.7)	615 (81.7)
No	130 (17.3)	138 (18.3)
Mother died (n (%))		
Yes	7 (0.9)	8 (1.1)
No	744 (99.1)	745 (98.9)
Mother's CD4 count, cells/mm³ (median [IQR])	528.5 [371 - 721.75]	534.5 [360 - 732]
Mother CD4 category, cells/mm³ (n (%))		
<200	39 (5.2)	29 (3.9)
201-350	124 (16.5)	106 (14.1)
>350	587 (78.3)	615 (82)
World Health Organization (WHO) Clinical Staging of HIV Disease (n (%))		
I	615 (81.9)	630 (83.7)
II	105 (14)	96 (12.7)
III	29 (3.7)	24 (3.1)
IV	3 (0.4)	1 (0.1)
Marital status (n (%))		
Divorced/separated/Widowed	22 (2.9)	23 (3.1)
Married/Living with Partner	494 (65.8)	504 (66.9)
Single	235 (31.3)	226 (30)
Mother on ART (n (%))		
Yes	220 (29.3)	221 (29.9)
No	531 (70.7)	522 (70.7)
Birth weight, g (median [IQR])	3100 [2800 - 3400]	3100 [2850 - 3400]
Low birthweight (<2500g) (n (%))	46 (6.1)	48 (6.4)
Infant's sex (n (%))		
Male	360 (47.9)	393 (52.2)
Female	391 (52.1)	360 (47.8)
Any Breastfeeding (n (%))		
≤ 3 months	44 (5.9)	51 (6.8)
> 3 months	707 (94.1)	702 (93.2)
Exclusive Breastfeeding Duration, days (median [IQR])	183 [167-189]	183 [167-188]
Any Breastfeeding Duration, days (median [IQR])	184 [180-190]	183 [180-189]

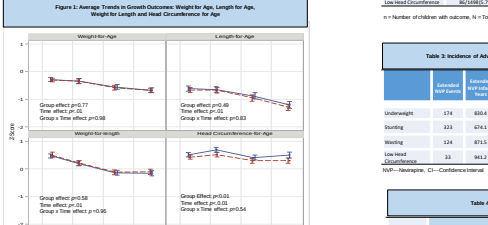
NVP = Nevirapine, *IQR=Interquartile Range, n=number, % = percent, ART = Antiretroviral Therapy, g = grams

- The overall median maternal age was 27 years (interquartile range: 23-31)
- Parity of the women in both groups was similar with a median of three pregnancies and median of one live birth
- Most of the women (95%) were in Immune Category 1 and 2 of the CDC Classification System for HIV Infection (14) showing normal immune function to moderate suppression as evidenced by the absolute CD4 cell counts
- The median duration of breastfeeding was six months with 94% of infants' breastfed for more than 3 months.

Mean Trajectories of Child Growth Outcomes

- Overall, the mean trajectories of WAZ, LAZ, and WLZ did not differ between infants assigned to extended nevirapine versus placebo (treatment x time interaction: p=.05; Fig 1)but declined over time in both groups (time effect p=.01)
- Significant group differences in mean HCZ were observed between the extended nevirapine and placebo groups (Fig 1)
- Mean HCZ was significantly higher among the infants randomized to extended nevirapine when compared with infants randomized to placebo particularly at six months (group effect p=0.01) and 18 months (group effect p=0.01)
- Maternal ART exposure did not modify treatment effects on growth outcomes (i.e. maternal ART x treatment: p=.05)

Figure 1: Average Trends in Growth Outcomes: Weight for Age, Length for Age, Weight for Length and Head Circumference for Age



*Maternal ART exposure did not modify treatment effects on growth outcomes (Maternal ART x treatment: p=0.05). Maternal ART Strata, therefore combined in plots above

Prevalence and Incidence Rate of Adverse Growth Outcomes

- At baseline (6 weeks post-delivery randomization), there were no differences in growth outcome measures between the study arms (Table 2).
- Overall, prevalence of stunting, underweight, wasting and low head circumference at randomization were 14.8%, 5.4%, 3.9% and 1.0%, respectively
- At 18 months the prevalence of stunting, underweight, wasting and low head circumferencewere 58.1%, 27.7%, 20.3%, and 5.7% respectively (Table 2).
- The incidence rates of the adverse growth outcomes increased substantially over the study period from 6 weeks to 18 months.
- The highest incidence rate among the different types of adverse growth outcomes was observed for stunting and it was not different between the two treatment arms (47.9/100 years in the extended NVP arm versus 48.3/100 years in the placebo arm).
- Similarly, the incidence rates for underweight, wasting and low head circumferencedid not differ between study arms (p>.05; Table 3).

Table 2: Prevalence of Adverse Growth Outcomes among HIV Exposed Uninfected Infants

Randomization	Overall n/N (%)	Extended NVP n/N (%)	Placebo n/N (%)	p-value
Underweight	81/1501 (5.4%)	43/748 (5.7%)	38/753 (5%)	0.63
Stunting	222/1499 (14.8%)	107/748 (14.3%)	115/751 (15.3%)	0.64
Wasting	58/1499 (3.9%)	29/748 (3.7%)	30/751 (4%)	0.91
Low Head Circumference	15/1498 (1.0%)	6/748 (0.8%)	9/750 (1.2%)	0.61
Randomization	Overall n/N (%)	Extended NVP n/N (%)	Placebo n/N (%)	p-value
Underweight	416/1501 (27.7%)	217/748 (29%)	199/753 (26.4%)	0.26
Stunting	871/1499 (58.1%)	436/748 (57.5%)	441/751 (58.7%)	0.64
Wasting	306/1499 (20.3%)	152/748 (20.3%)	152/751 (20.2%)	0.96
Low Head Circumference	86/1498 (5.7%)	39/748 (5.2%)	47/750 (6.3%)	0.36

n = Number of children with outcome, N = Total Number of children, NVP = Nevirapine, % = Percent

Table 3: Incidence of Adverse Growth Outcomes by Study Arm from 6 weeks to 18 Months

	Extended NVP Events	Extended NVP Infant Years	Extended NVP Rate/100 Infant Years (95% CI)	Placebo Events	Placebo Infant Years	Placebo Rate/100 Infant Years (95% CI)	p-value
Underweight	174	830.4	21 (18 -24.3)	161	837.3	19.2 (16.4 – 22.4)	0.642
Stunting	323	674.1	47.9 (42.8-53.4)	326	674.7	48.3 (43.2 – 53.9)	0.902
Wasting	124	871.5	14.2 (11.8 – 17)	122	865.4	14.1 (11.7-16.8)	0.948
Low Head Circumference	33	941.2	3.5 (2.4 – 4.9)	38	941.2	4 (2.9 – 5.5)	0.55

NVP= Nevirapine, CI – Confidence Interval

Table 4: Predictors of Risk of Adverse Growth Outcomes

	Underweight		Stunting		Wasting		Low Head Circumference	
	(WAZ<-2 SD)		(LAZ<-2 SD)		(WLZ<-2 SD)		(HCZ<-2 SD)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Site								
Chitungwiza	1.00 (ref)	-	1.00 (ref)	-	1.00 (ref)	-	1.00 (ref)	-
Dar es Salaam	0.90 (0.61, 1.30)	0.59	0.63 (0.47, 0.86)	0.003*	0.82 (0.54, 1.25)	0.36	1.33 (0.63, 2.81)	0.45
Durban	0.16 (0.09, 0.27)	<0.01*	0.27 (0.19, 0.37)	<0.01*	1.23 (0.88, 1.70)	0.22	0.33 (0.12, 0.88)	0.02*
Kampala	0.69 (0.53, 0.92)	0.01*	0.81 (0.65, 1.00)	0.05*	0.29 (0.19, 0.43)	<0.01*	0.97 (0.53, 1.79)	0.93

SD - Standard Deviation, CI - Confidence Interval, *Significant at 0.05 level, ART—Antiretroviral Therapy

SUMMARY

- Extended course of prophylactic nevirapine given daily from six weeks to six months does not adversely affect growth (WAZ, LAZ, WLZ, and HCZ) in HEU breastfeeding infants.
- Male sex, short duration of breastfeeding, lack of maternal ART exposure may increase risk for growth compromise in HEU infants.
- Targeted interventions among HEU infants may curtail the incidence of adverse growth outcomes

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