Abstract #: T- 114

Six Weeks of Extended NVP is Effective in Increasing HIV-free Survival among Low Birth Weight Infants of HIV infected Mothers Compared to Single Dose NVP

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Abstract

Background In many countries, infants born to HIV-infected mothers are low birth weight (LBW) and have a high risk of HIV acquisition & mortality. These babies may have different drug metabolism and response to prophylaxis, yet are often excluded from studies. We hypothesize that efficacy of six weeks of nevirapine (NVP) (SWEN) compared to single-dose (SD) NVP will vary by infant birth weight.

Methods In a NIH-funded randomized clinical trial, breastfeeding infants of HIV-infected women in Pune, India were a randomized to receive SDNVP or SWEN. Infants were classified in 3 birth weight (BW) categories <2.0, 2.0-2.5 & ≥2.5 kg. Efficacy outcomes were HIV infection, and HIV infection or death at 12 months. Kaplan-Meier method was used to estimate the probability of HIV infection & HIV infection or death. Differential effects of SWEN by LBW were examined using a Cox proportional hazard models with interaction for SWEN & LBW in an intention-to-treat analysis. The analysis was adjusted for maternal age, education, antenatal AZT, intrapartum NVP, CD4 counts & HIV viral load at delivery, duration of breastfeeding and infant's gestational age.

Results Among 732 infants, 364 (50%) randomized to SWEN, median BW was 2.6 kg (range 1.7-3.6). Median GA in each BW group was 36, 38 & 38 weeks. Kaplan-Meier estimate (95% CI) of probability of HIV infection and HIV infection or death at 12 months among LBW infants was 17% (13%-22%) & 20% (16%-26%) respectively compared to 14% (10%-19%) & 15% (11%-20%) among infants with BW ≥ 2.5 kg. SWEN decreased the risk of HIV infection by 81% (p=0.06); risk of HIV infection or death reduced by 83% (p=0.03) among infants with BW<2 kg compared to 45% & 11% among infants with BW 2.0–2.5 & ≥2.5 kg, respectively . Grade 3/4 adverse events were overall higher among infants <2.0 kg BW compared to infants with BW ≥ 2.5kg (77% vs 35%, p<0.0001). But, among infants <2.0 kg BW, SWEN was as safe as SDNVP (grade 3/4 AEs 72% vs 76%, p=0.75).

Conclusion Our results provide evidence for the use of SWEN prophylaxis compared SDNVP to reduce HIV transmissions & HIV infection or death (increase HIV free survival) among LBW infants born to HIV infected mothers.

Background & Research Questions

Background

- Low birth weight (LBW), defined as <2.5kg birth weight, is an import public health problem in middle- and low -income countries particularly in some African and Asian countries where incidence of LBW is as high as 40% among live-births.
- Maternal HIV infection, in addition to several maternal-fetal risk factors, is identified as an independent risk factor for LBW.
- LBW is an independent risk factor for HIV mother-to-infant HIV transmission (MTCT)
- Numerous studies have identified ARV prophylaxis, including provision of six weeks of extended Nevirapine (SWEN) to breastfed HIV-exposed infants, as critical interventions for reducing MTCT, however many of these studies excluded LBW infants.
- LBW infants are physiologically immature and may metabolize ARVs differently than normal birth weight infants; therefore safety and efficacy data of ARVs in LBW infants are needed.
- The SWEN – India study enrolled approximately 40% LBW infants hence presented an unique opportunity to evaluate the safety and efficacy of SWEN in LBW.

Research Questions

- Is there a differential efficacy of SWEN compared to SDNVP by infant birth weight?
- Is SWEN as safe as SDNVP by infant birth weight?

Methods

Study Population

- HIV-infected pregnant women from Pune, India who intended to breastfeed their infants
- Women were enrolled either in the antepartum, intrapartum , or within 1 week postpartum

Definitions:

Infant HIV infection:

- DNA PCR positive & confirmed HIV RNA> 5000 copies/ml

LBW

- LBW categorized in three groups
  ≤ 2 kg: very LBW
  >2 – 2.5 kg: LBW
  > 2.5 kg: Normal BW

Statistical Methods

Safety Endpoints: Poisson Regression

Efficacy Endpoints: Cox-Proportional Hazards Model

Study Design

- Secondary analysis using data from SWEN-India Randomized Control Trial
- All infants (n = 737) received SDNVP at birth and were randomized at 1 week post-partum to receive either multivitamins or SWEN (2mg/kg daily) + multivitamins
- Mothers and infants were followed for 12 months with 11 post-partum visits.

Outcomes:

Safety Endpoints (using DAIDS criteria):

- Grade 3 or 4 Adverse Events (AE)
- Grade 2 or higher Neutropenia

Efficacy Endpoints:

- HIV Infection at 6 wks, 6 mo and 12 mo
- Mortality at 12 mo
- HIV infection or death at 12 mo

Results

Table 1: Baseline Characteristics of Mothers and Infants by Infant Birth Weight

Characteristics	Overall	Infant Birth Weight			p-value
		≤ 2.0 Kg (n = 50)	> 2.0 & ≤ 2.5 Kg (n = 249)	> 2.5 Kg (n = 433)	
Maternal Baseline Characteristics					
Median Age, Yrs (IQR)	23 (21 – 25)	24 (21 – 26)	22 (21 – 25)	23 (21 – 25)	0.20
< Primary Education	292 (40%)	23 (46%)	113 (45%)	156 (36%)	**0.04**
Housewife	591 (81%)	33 (66%)	193 (78%)	365 (84%)	**0.002**
Primigravida	247 (34)	15 (30%)	89 (36%)	143 (33%)	0.67
Vaginal Delivery	587 (80%)	41 (82%)	198 (80%)	348 (80%)	0.94
Antepartum AZT	247 (34%)	4 (8%)	78 (31%)	165 (38%)	**< 0.001**
Intrapartum NVP	484 (66%)	15 (30%)	153 (61%)	316 (73%)	**< 0.001**
HAART	61 (8%)	6 (12%)	27 (11%)	28 (6%)	0.07
Median CD4 cells/μL (IQR)	466 (314 – 650)	504 (252 – 632)	445 (301 – 613)	472 (328 – 667)	0.24
Median log10 Viral Load, copies/ml (IQR)	3.7 (2.9 – 4.5)	4.11 (3.30 – 4.76)	3.98 (3.14 – 4.70)	3.56 (2.72 – 4.38)	**< 0.001**
Infant Characteristics					
Male Gender	388 (53%)	24 (48%)	116 (47%)	248 (57%)	**0.02**
Median Birth Weight , kg (IQR)	2.6 (2.4 – 3.0)	1.98 (1.75 – 2.00)	2.40 (2.25 – 2.50)	2.90 (2.70 – 3.10)	**< 0.001**
Median GA, wks (IQR)	38 (38 – 38)	36 (35 – 37)	38 (37 – 38)	38 (38 – 38)	**< 0.001**
SWEN	364 (50%)	25 (50%)	125 (50%)	214 (49%)	0.98
Breastfeeding duration < 4 Months 4 – 6 Months ≥ 6 Months	 403 (55%) 71 (10%) 258 (35%)	 27 (54%) 4 (8%) 19 (38%)	 138 (55%) 23 (9%) 88 (35%)	 238 (55%) 44 (10%) 151 (35%)	0.99

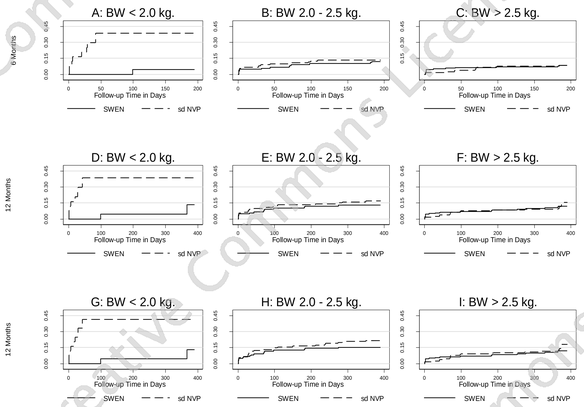
Results

- Proportion of AEs among infants with birth weight < 2.0 kg and 2.0 – 2.5 kg were similar in the SWEN and sSDNVP groups. However, among infants with normal birth weight in the SWEN arm reported significantly smaller number of SAE's (37% v/s 50%; p = 0.009).
- Among infants with birth weight < 2.0 kg, cumulative risk of HIV Transmission at 6 and 12 months and HIV infection or death at 12 months was significantly lower among infants in the SWEN groups compared to SDNVP (Figure 1 A ,D,G).
- Risk of HIV transmission, or HIV infection or death was similar in the SWEN and SDNVP groups among infants with birth weight > 2.0 kg.
- Gestational age of infants with birth weight < 2.0 kg were significantly smaller than those with birth weight > 2.0 kg (36 wks vs 38 wks; p < 0.001). However, differential effect of SWEN versus SDNVP by infant gestational age for HIV infection at any time, or HIV infection or death was not statistically significant (Data not shown, available upon request).

Table 2: Proportion of Grade 3 or 4 Adverse Events or Grade 2 or Higher Neutropenia with 95% CI by Infant Birth Weight (BW) Categories

Safety Endpoint	BW: ≤ 2.0 Kg			BW: > 2.0 & ≤ 2.5 Kg			BW: > 2.5 Kg		
	SDNVP	SWEN	p	SD NVP	SWEN	p	SD NVP	SWEN	p
Grade 3/ 4 AE or ≥Grade 2 Neutropenia	19 (76%) (58%, 94%)	18(72%) (53%, 91%)	0.99	61(49%) (42%,59%)	63 (50%) (42%,59%)	0.90	109(50%) (43%, 56%)	79(37%) (30%, 43%)	**0.009**

Figure 1: Kaplan-Meier Estimates for HIV Infection at 6 and 12 Months and HIV Infection or Death at 12 months by SWEN and Infant Birth Weight (BW)



Results

Table 3: Safety and Efficacy of SWEN versus SDNVP by Birth Weight Categories

Safety & Efficacy Endpoints	BW: ≤ 2.0 Kg		BW: > 2.0 & ≤ 2.5 Kg		BW: > 2.5 Kg	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Grade 3 or 4 AE or ≥ Grade 2 Neutropenia						
Risk Ratio	0.67	0.65	0.82	0.82	0.88	0.87
95% CI	0.38, 1.19	0.36, 1.16	0.63, 1.06	0.63, 1.07	0.70, 1.11	0.69, 1.10
p-value	0.17	0.15	0.13	0.14	0.29	0.24
HIV Transmission at 6 Weeks						
Hazard Ratio	**0.03**	**0.05**	**0.40**	0.48	0.88	1.01
95% CI	**0.003, 0.33**	**0.004, 0.71**	**0.16, 0.95**	0.20, 1.18	0.40, 1.97	0.44, 2.30
p-value	**0.004**	**0.03**	**0.04**	0.11	0.76	0.98
HIV Transmission at 6 Months						
Hazard Ratio	**0.12**	**0.17**	0.62	0.67	0.87	0.97
95% CI	**0.02, 0.67**	**0.03, 1.09**	0.31, 1.24	0.33, 1.37	0.46, 1.66	0.50, 1.88
p-value	**0.02**	**0.06**	0.18	0.28	0.68	0.94
HIV Transmission at 12 Months						
Hazard Ratio	**0.15**	**0.19**	0.59	0.62	0.93	1.03
95% CI	**0.03, 0.70**	**0.03, 1.04**	0.31, 1.13	0.32, 1.20	0.53, 1.62	0.59, 1.83
p-value	**0.02**	**0.06**	0.11	0.16	0.79	0.90
HIV Transmission or Death at 12 Months						
Hazard Ratio	**0.15**	**0.17**	0.57	**0.55**	0.79	0.89
95% CI	**0.03, 0.67**	**0.03, 0.85**	0.32, 1.01	**0.30, 1.00**	0.46, 1.36	0.51, 1.54
p-value	**0.01**	**0.03**	0.06		0.40	0.68
Mortality at 12 Months						
Hazard Ratio	0.06	0.06	0.45	0.45	0.55	0.60
95% CI	0.003, 1.20	0.002, 1.71	0.15, 1.34	0.14, 1.38	0.15, 2.0	0.16, 2.23
p-value	0.07	0.10	0.15	0.16	0.36	0.44

Conclusions and Implications

- **SWEN was as safe as SDNVP among infants with birth weight less than 2.5 kg, but was found to be safer among infants with normal birth weight.**
- **Though SWEN was protective, risk of HIV transmission at any time point and HIV transmission or death at 12 months was similar in SWEN compared to SDNVP among infants with birth weight > 2.5 kg.**
- **Differential efficacy of SWEN compared to SDNVP was highest among infants with BW < 2.0. In this group, SWEN was more efficacious than SDNVP, and significantly reduced the risk of HIV transmission at six weeks by 95% and HIV transmission or death at 12 months by almost 80%.**
- **Based on our data, SWEN at 2mg/kg dosed daily is safe and efficacious in LBW infants.**

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