

Risk of neutropenia, anemia, and skin rash among HIV exposed African infants on nevirapine and cotrimoxazole prophylaxis compared to those on cotrimoxazole prophylaxis alone.

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1. Background

- Based on WHO recommendations, HIV exposed uninfected (HIV-EU) infants receive co-trimoxazole (CTX) prophylaxis from 6 weeks through cessation of breast milk (BM) exposure. [WHO, 2006]
- CTX prophylaxis is highly effective against bacterial and protozoan opportunistic infections. [Grimwade et al, Chintu et al, Lancet 2004]
- Infant nevirapine (NVP) prophylaxis is recommended from birth through 1 week after all exposure to breast milk is stopped. [WHO Rapid Advice, 2009]
- This is based on evidence from several trials which demonstrated the benefits of extending infant prophylaxis in reducing BM transmission. [Six Week Extended-Dose Nevirapine (SWEN) Study Team, et al, Lancet. 2008; Kumwenda NI et al, N Engl J Med.2008; Chasela C et al, 2009].

2. Safety of CTX and NVP prophylaxis

- Extended infant NVP at prophylactic dosing levels is well tolerated with some reports of rashes and neutropenia. [SWEN, Lancet 2008]
- Frequently reported side effects with CTX include skin rash, neutropenia and anemia. [Chintu et al, Lancet 2004; Mermis et al, Lancet 2008]
- However, adult treatment with NVP has been associated with granulocytopenia, liver toxicity and severe skin rash. [Mirochnick et al, J Infect Dis 1998; Bardsley-Elliott et al, Paediatr Drugs 2000]
- To our knowledge, there are no studies looking at the safety of concurrent use of CTX and NVP prophylaxis among HIV-exposed infants.

3. HPTN 046 Trial-version 2.0

- Phase III, randomized, double blind, placebo-controlled trial.
- Evaluated the efficacy and safety of 6 months NVP for prevention of BM transmission of HIV.
- Recruitment began in Jan 2007, via PMTCT antenatal care clinics in Kampala, Uganda and Chitungwiza, Zimbabwe.
- Standard-of-care single dose NVP +/- one week zidovudine
- Enrolled and randomized on or before day 3 post birth.
- Follow up of mother/infant pairs through 18 months after birth.
- Design changes were implemented beginning 10 August 2007 based on the SWEN study results
 - Study recruitment, and infant randomization were stopped.
 - Randomized infants < day 42 old were unblinded and those on placebo switched to open label NVP taken through day 42.
 - All babies enrolled thereafter received 6 weeks extended infant NVP (SWEN).

4. Data analysis aim and objectives

- The overall aim of this analyses using data from the 2.0 version of HPTN 046 trial was to assess the potential interaction of CTX and NVP among breastfeeding HIV-EU infants with regard to:
- Overall risk of neutropenia, and/or anemia,
 - Risk of severe (grade 3 or higher) neutropenia, and/or anemia
 - Risk of severe (grade 2 or higher) skin rash.

5. Methods

- Secondary data analysis of the HPTN 046 trial, version 2.0.
- Compared infants on daily (NVP and CTX) versus CTX alone.
- Used the U.S. Division of AIDS (DAIDS) 2004 toxicity tables.
- The adverse event (AE) rate was calculated for specified intervals of age: < 6 weeks; 6 wk.–6 mo. and 6- 12 mo. by the treatment group: placebo, 6 month NVP or SWEN).
- A relative risk of AE was calculated using Poisson regression.
- Infant evaluations:

	weeks					months							
	birth	2	4	6	8	3	4	5	6	9	12	18	
Clinical data ¹	X	X	X	X	X	X	X	X	X	X	X	X	
CBC ²	X	X	X	X	X	X	X	X	X	X	X	X	
HIV DNA PCR	X	X	X	X	X	X	X	X	X	X	X	X	

¹Infant demographic and clinical data

²CBC: Complete Blood Count including differential

Figure 1: Trial profile

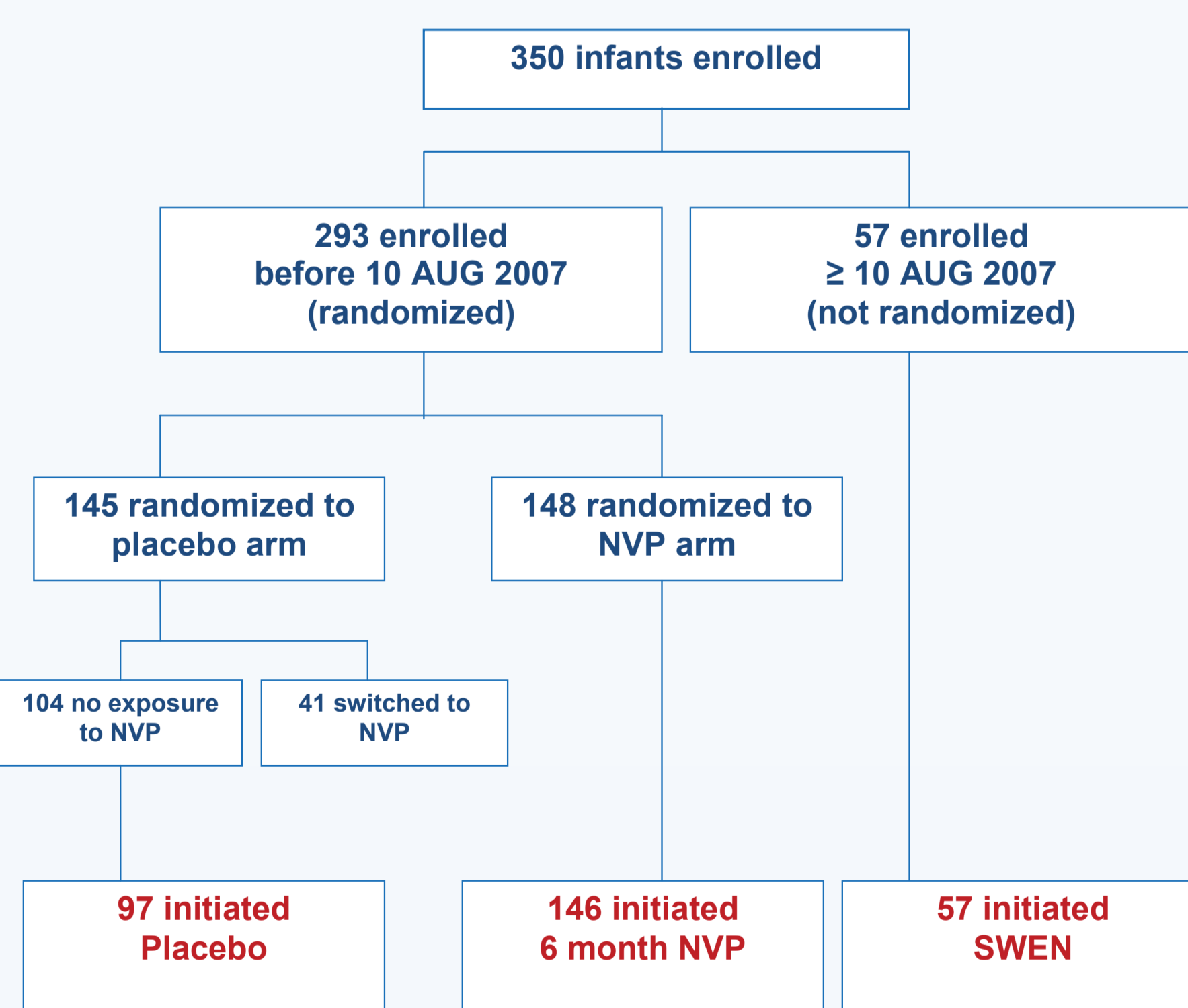


Table 1: Baseline characteristics of 298 infants at the week 6 visit by treatment group

Characteristic	Placebo (n=97)	6 month NVP (n=144)	SWEN ¹ (n=57)	P value ²
Gender (female), [n (%)]	44(45%)	75(52%)	24(42%)	0.36
Weight(kg), median (IQR) ³	5(4-5)	5(4-5)	5(4-5)	0.88
Antimicrobials ⁴	77(79%)	130(90%)	49(86%)	0.02
Hemoglobin(g/dl), median (IQR)	11.4(10.5-12.1)	10.7(9.7-11.6)	10.3(9.7-11.7)	0.002
ANC ⁵ (cells/mm ³), median (IQR)	1278(947-1920)	1370(990-1950)	1360(933-1919)	0.72
Skin rash	23(24%)	32(22%)	10(18%)	0.88
Mother on ART ⁶	20(21%)	31(22%)	0(0%)	0.87

¹SWEN (Six Weeks of nevirapine);

²P value comparing 6 month NVP vs. placebo;

³IQR (Inter quartile range);

⁴Antimicrobial drugs: systemic antibiotics, antifungal and antimicrobicides

⁵ANC: Absolute Neutrophil Counts

⁶Mother on antiretroviral therapy (ART) at time of randomization

Figure 2: Overall infants with at least one episode of adverse event

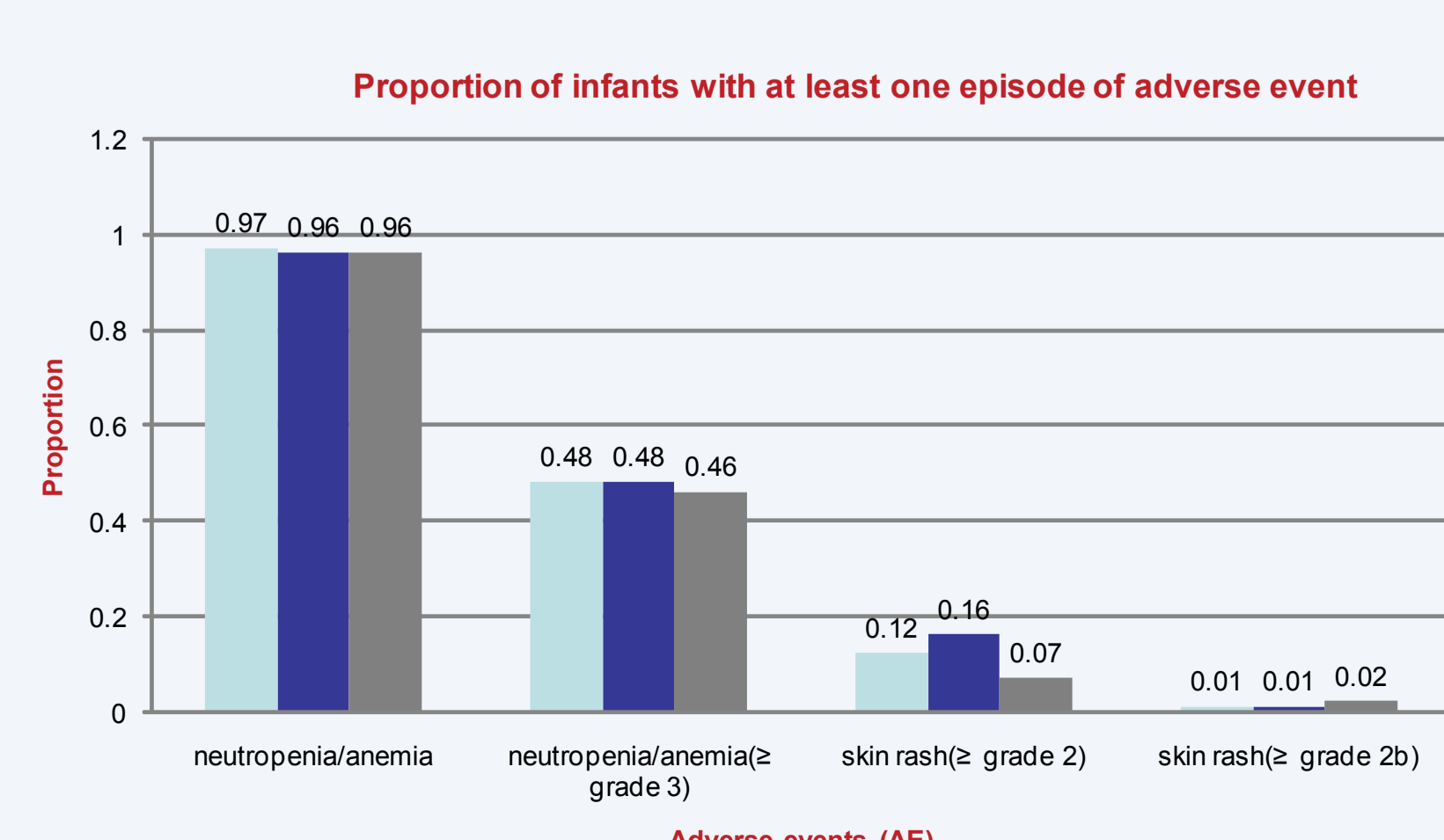


Figure 3: Absolute Neutrophil Count (ANC) Showing Nadir in the first 6 weeks Across Treatment Groups

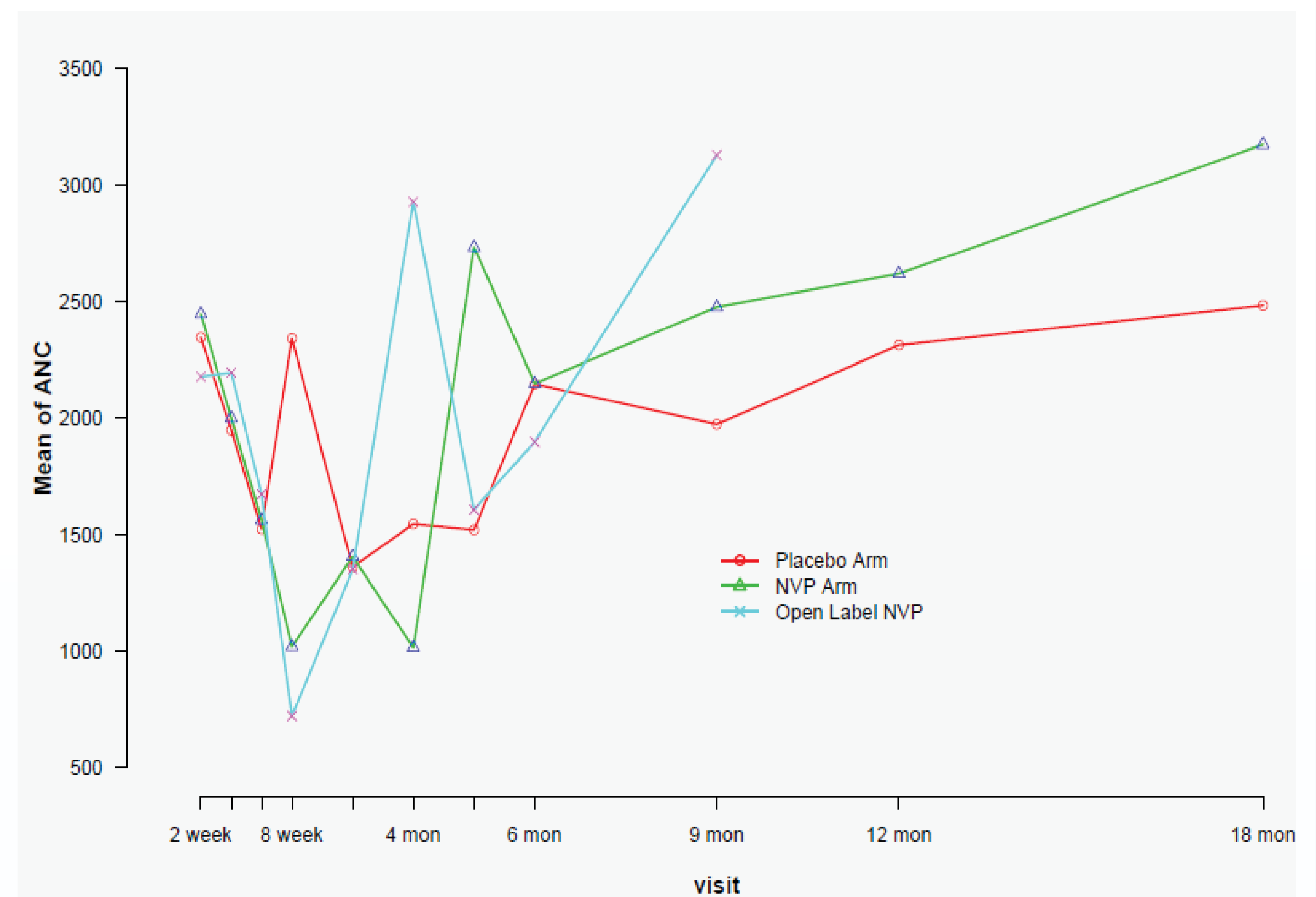


Figure 4: Proportion of infants with severe (≥ grade 3) neutropenia and/or anemia by treatment group

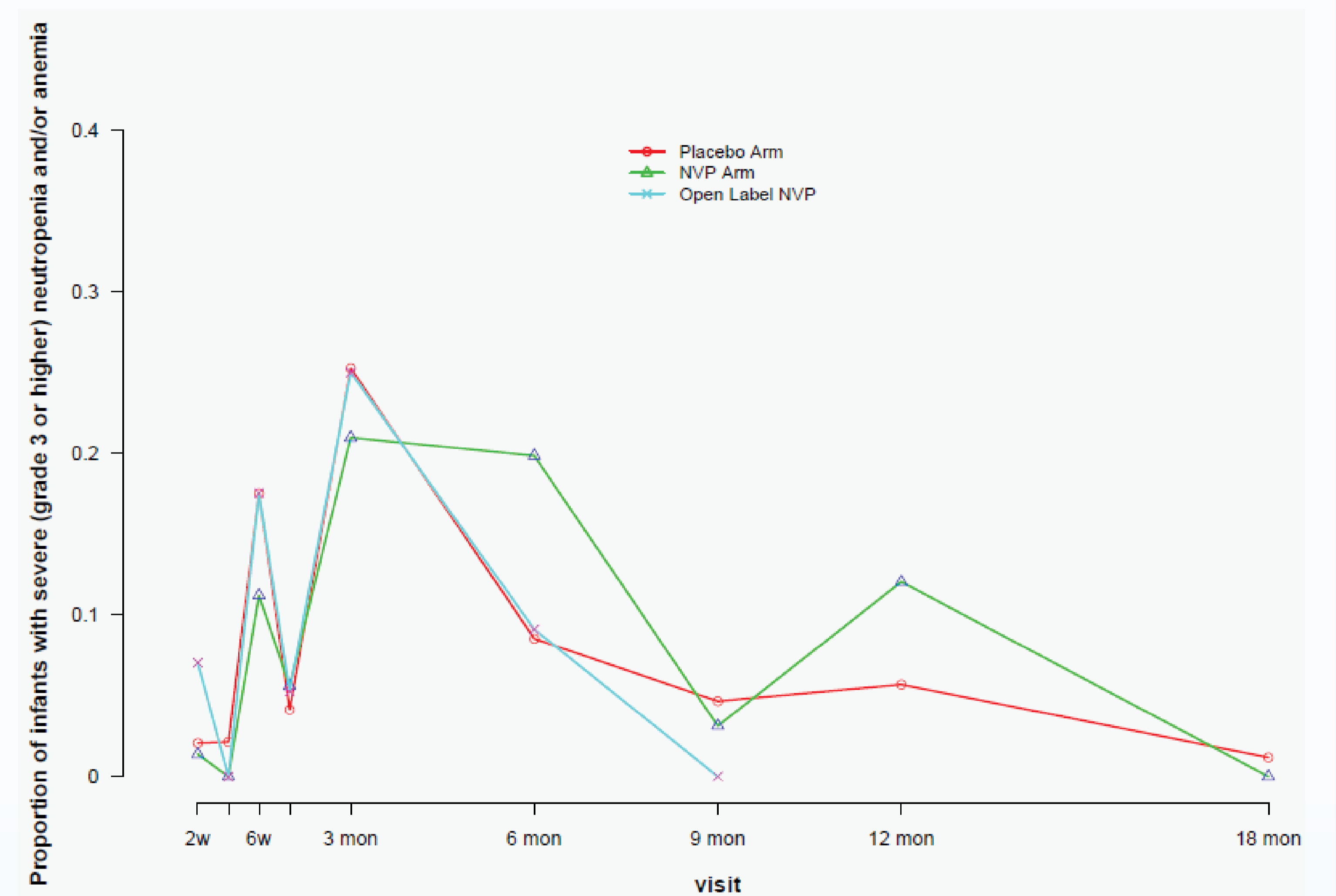


Table 2: Incidence rates of adverse events by treatment group

events/infant - months = incidence rate

	Placebo	6 month NVP	SWEN
Neutropenia/anemia			
<6 weeks	81/131=0.62	142/194=0.73	61/76=0.81
6 wk. - 6 mo.	176/435=0.41	278/652=0.43	100/259=0.39
6 mo. - 12 mo.	61/546=0.11	93/806=0.11	1/54=0.02
Neutropenia/anemia (≥ grade 3)			
<6 weeks	21/131=0.16	18/194=0.10	14/76=0.18
6 weeks - 6 months	40/435=0.10	75/652=0.12	22/259=0.08
6 months - 12 months	9/546=0.02	20/806=0.03	0/54=0
Skin rash (≥ grade 2)			
< 6 weeks	5/131=0.04	5/194=0.03	2/76=0.03
6 weeks - 6 months	9/435=0.02	13/652=0.02	2/259=0.01
6 months - 12 months	3/546=0.01	8/806=0.01	0/54=0

Table 3: Relative risk of adverse event comparing 6 month NVP (NVP/CTX) to placebo (CTX alone)

Rate Ratio (RR), 95% Confidence Interval

	6 weeks – 6 months	6– 12 months
Neutropenia and/or anemia (all grades)	1.05 [0.93, 1.20]	1.02 [0.80, 1.31]
Neutropenia and/anemia (≥ grade 3)	1.25 [0.83, 1.89]	1.50 [0.67, 3.37]
Skin rash (grade ≥2)	0.96 [0.42, 2.23]	1.80 [0.47, 6.92]

6. Summary and Conclusion

- We demonstrate a drop in ANC during the first 6 weeks of life of these breastfeeding HIV-EU infants.
- Using DAIDS Toxicity Tables, there were no significant differences in incident AE rates across treatment groups for those who got sdNVP, 6 weeks NVP or 6 months NVP
- AE rates were relatively higher during the first 6 weeks of life regardless of treatment group.
- Extended prophylaxis with NVP among HIV-EU infants receiving prolonged prophylaxis CTX did not appear to increase the immediate and long term risk of neutropenia, anemia or skin rash.

7. Acknowledgment

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