Safety of 6-week triple antiretroviral prophylaxis in high risk HIV-exposed infants

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BACKGROUND

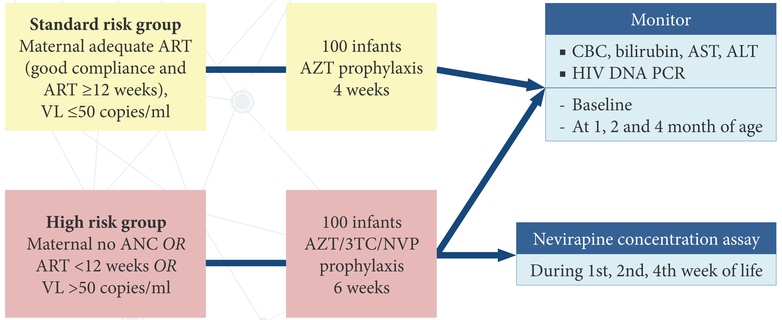
Triple-drug antiretroviral prophylaxis of zidovudine (AZT)/lamivudine (3TC)/nevirapine (NVP) for high risk HIV-exposed neonates is recommended within the Thai national program. However, there are limited data about the safety and drug concentration achieved with this regimen initiated at birth.

OBJECTIVES

To evaluate the safety of combination neonatal prophylaxis regimen and to describe nevirapine concentration levels during the first 4 weeks of life.

METHODS

- Prospective cohort of infants born from HIV-infected pregnant women in 4 clinical sites in Thailand.
- Neonates with high risk of HIV transmission (mother has HIV RNA >50 copies/mL prior to delivery or received ART <12 weeks) received AZT and 3TC twice daily, plus NVP (4 mg/kg/dose) once daily, for 6 weeks. As a control group, neonates with standard risk of HIV transmission who received 4-week of AZT were also enrolled.
- Blood for complete blood count, aspatate transaminase (AST), alanine transaminase (ALT) were drawn at birth, aged 1, 2 and 4 month.
- Adverse events were graded according to DAIDS toxicity table 2014.
- Sparse plasma NVP concentrations were collected at week 1, 2 and 4 and assayed by a validated liquid chromatography-triple quadrupole mass spectrometry assay. Target NVP plasma trough concentration for prophylaxis was >100 ng/mL.



RESULT

- From October 2015 to August 2016, 94 infants were enrolled.
- 31 neonates received triple ARV prophylaxis and 63 infants received AZT only.
- Characteristics of HIV-exposed infants and mothers are shown in table 1.
- Overall, median (IQR) gestational age and birth weight were 38 (37-39) weeks and 2.8 (2.5-3.2) kg, respectively.

Table 1. Characteristics of HIV-exposed infants and mothers

	Total (n=94)	4-week AZT prophylaxis (N = 63)	6-week AZT/3TC/NVP prophylaxis (N =31)	*p*-value
Mothers				
Gestational age at delivery, weeks (IQR)	38 (37-39)	38 (37-39)	38 (36-39)	0.29
Median of maternal age, years (IQR)	30 (21-34)	32 (26-36)	21 (19.5-29)	<0.001
Premature (<37 weeks), N (%)	16 (17.2)	6 (9.5)	10 (33.3)	0.004
Maternal antiretroviral therapy regimen, N (%)				
AZT-based	31 (33)	24 (38.1)	7 (22.6)	0.13
TDF-based	55 (58.5)	35 (55.6)	20 (64.5)	0.41
PI-based	26 (27.7)	18 (28.6)	8 (25.8)	0.78
NNRTI-based: NVP, EFV	60 (63.8)	44 (69.8)	16 (51.6)	0.08
Infants				
Sex, male (%)	46 (48.9)	34 (54)	12 (38.7)	0.16
Median of birth weight, kg. (IQR)	2.8 (2.5-3.2)	2.9 (2.6-3.2)	2.7 (2.4-2.9)	0.02
Birth weight <2.5 kg, N (%)	22 (23.4)	11 (17.5)	11 (35.5)	0.05
Median of height, cm. (IQR)	49.3 (48-52)	50 (48-52)	49 (46-52)	0.17
Median of circumference, cm. (IQR)	33 (32-34)	33 (32-34)	32 (31-33)	0.02

- There was no difference in adverse event rates between triple and AZT prophylaxis (**Table 2**).
- No infants were diagnosed HIV-infected at age 4 months.

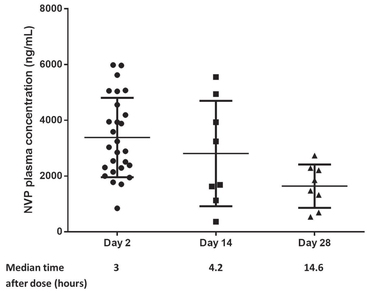


Figure 1. Nevirapine plasma concentrations (ng/mL) stratified by timing of plasma collection

Table 2. Adverse events in HIV-exposed infants stratified by risk group

	Overall (N = 94)	4-week AZT prophylaxis (N = 63)	6-week AZT/3TC/NVP prophylaxis (N =31)	*p*-value
All grade anemia (Hb <11 g/dL at age 1 month, Hb <10.4 g/dL at age 2-4 months)	41.1%	39.9%	43.6%	0.55
Grade 3-4 anemia (Hb <8 g/dL at age 1 month Hb <8.5 g/dL at age 2-4 months)	3.1%	3.1%	3.2%	
All grade neutropenia (ANC <1000/mm^3)	3.1%	3%	3.2%	0.94
Grade 3-4 neutropenia (ANC <600/mm^3)	0.5%	0.3%	1.1%	
Abnormal AST	1.4%	1.5%	1.1%	0.76
Abnormal ALT	3.8%	4%	3.2%	0.72
Median (IQR) Hb at 1 mo, g/dL	10.4 (9.3-11.7)	10.6 (9.6-12)	9.7 (8.8-11.2)	0.39
Median (IQR) Hb at 4 mo, g/dL	11.7 (11.2-12.3)	11.7 (11.4-12.3)	11.2 (10.6-12.1)	

- NVP concentrations were available from 18 infants: geometric mean (%CV) plasma NVP concentrations were 3075 (67), 2109 (92) and 1438 (72) ng/mL at weeks 1, 2 and 4, respectively. All infants maintained nevirapine concentrations >100 ng/mL during the first 4 weeks (Figure 1).

CONCLUSIONS

Triple ART infant prophylaxis with 6-weeks of AZT/3TC/NVP in high risk HIV-exposed infants appears to be safe with high NVP concentrations being rapidly achieved and maintained during the first 4 weeks of life.

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