Haematological Toxicity & Neonatal Prophylaxis in Infants at High MTCT Risk

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BACKGROUND

- Guidelines recommend use of combination neonatal prophylaxis (CNP) with 2 or 3 drugs in specific high risk situations.
- We have previously found that use of CNP in high-risk situations is increasing in Europe (EPPICC, AIDS 2013)
- However, data on safety of neonatal prophylaxis (NP), particularly CNP, are limited

AIM

- **To identify whether NP type is associated with**

1. **severe or potentially life-threatening anaemia or neutropenia in the first 6 months of life and**
2. **haemoglobin (Hb) levels and neutrophil counts (NC) at ages 0-18 months**

METHODS

- An individual patient-data meta-analysis was conducted within 6 cohorts within EPPICC
- The Italian Register for HIV infection in children (ITLR); the Madrid Cohort of HIV-infected Children ; the Catalan Cohort of HIV-infected Children (CoRISPE-Cat); the 'Victor Babes' Hospital Cohort, Bucharest, Romania; the Swiss Mother and Child HIV Cohort Study (MoCHiV) and the European Collaborative Study (ECS) (considered as 2 separate studies, the Western-ECS and Ukraine-ECS).
- Infants born 01/01/96 to 30/06/10, at high risk for acquiring HIV (defined according to US Guidelines) and with HIV status, haemoglobin and neutrophil count measures available were included.
- CNP was defined as ≥2 antiretrovirals for PMTCT
- Haemoglobin and neutrophil count were graded using 2004 DAIDS paediatric toxicity tables
- Logistic regression models assessing risk of grade 3-4 anaemia / neutropenia in the first 6 months of life were adjusted *a priori* for cohort (as a random effect), calendar period, infant HIV and in utero ART exposure.
- Mixture models of 1) Hb levels and 2) log10-transformed NC were conducted to explore associations with NP type at ages 0-18 months.

RESULTS

Infant characteristics

- Of the 1836 infants, 969 were male and 25% (468/1836) were born preterm (<37 weeks)
- Of 1299 infants with maternal delivery VL data available, in 409 (31%) maternal VL was <50 copies/ml and in 444 (34%) it was 50-399 copies/ml
- 1149 (63%) infants were exposed in utero to cART (4% (n=48) for ≤4 weeks and 85% (n=977) >4 weeks, 124 had unknown cART duration) ,155 (8%) to monotherapy, 133 (7%) to dual therapy and 365 (20%) to no ART (34 missing data)
- Of the cART-exposed, 350 (74%) infants received 1 drug NP, 398 (22%) received CNP, 64 (3.5%) received no NP and for 24 there was no data
- Of the infants receiving CNP, 270 (68%) received two drugs and 126 (32%) three drugs (2, missing data)
- The most common combinations were ZDV+sdNVP (124 infants), ZDV+3TC (123 infants), ZDV/3TC/NVP (111 infants)
- Median duration of NP was 5.7 weeks (IQR 4–6) for one drug NP and 5.9 weeks (IQR 4–6) for CNP

Anaemia or neutropenia in the first six months of life

- Nadir haemoglobin level and neutrophil count up to age six months were available for 1737 and 1544 infants respectively
- Overall, 117 (6.7%) infants had Grade 3-4 anaemia at age 0-6 months and 140 (9.1%) had Grade 3-4 neutropenia

Table 1: Anaemia and neutropenia grades, expressed as nadir value in the first 6 months of life, by number of NP drugs and gestational age

	One drug NP		Two drugs NP		Three drugs NP	
	Grade 0-2	Grade 3-4	Grade 0-2	Grade 3-4	Grade 0-2	Grade 3-4
Anaemia (n=1737); N (%)						
All#	1185 (93.1)	88 (6.9)	247 (93.2)	18 (6.8)	110 (90.9)	11 (9.1)
≤32 weeks GA	41 (87.2)	6 (12.8)	15 (93.8)	1 (6.3)	10 (83.3)	2 (16.7)
33-36 weeks GA	536 (91.2)	52 (8.8)	78 (89.7)	9 (10.3)	46 (86.8)	7 (13.2)
≥ 37 weeks GA	592 (95.2)	30 (4.8)	145 (95.8)	8 (5.2)	50 (96.2)	2 (3.8)
Neutropenia (n=1544); N (%)						
All##	1050 (90.5)	110 (9.5)	197 (92.5)	16 (7.5)	90 (86.5)	14 (13.5)
≤32 weeks GA	34 (85.0)	6 (15.0)	13 (81.3)	3 (18.7)	6 (60.0)	4 (40.0)
33-36 weeks GA	492 (90.6)	51 (9.4)	69 (92.0)	6 (8.0)	36 (87.8)	5 (12.2)
≥37 weeks GA	510 (90.6)	53 (9.4)	109 (94.0)	7 (6.0)	45 (91.8)	4 (8.2)

GA (gestational age); # 29 infants missing GA; ##24 infants missing GA

Factors associated with anaemia or neutropenia in first 6 months

Unadjusted analysis

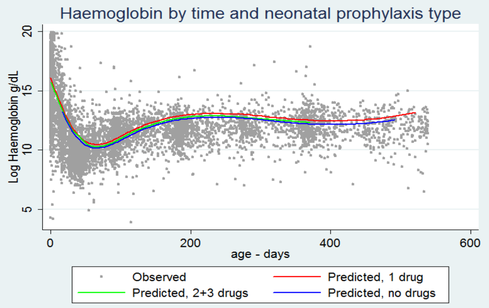
- Birth calendar period, gestational age and delivery viral load were significantly associated with increased risk of Grade 3-4 anaemia and of Grade 3-4 neutropenia
- Antenatal ART exposure was significantly associated with increased risk of anaemia (OR 4.47 [95% CI 2.19, 9.11] for dual therapy vs none; no other significant associations), but not with neutropenia

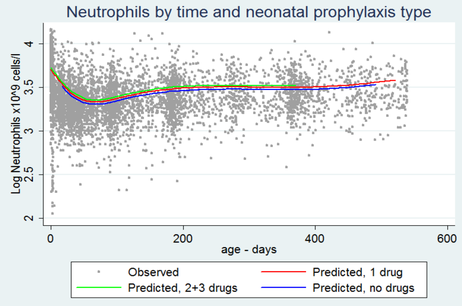
Adjusted analysis

- Grade 3-4 anaemia was not associated with NP type (AOR 1.14 [95% CI 0.63, 2.06] for 1 drug and 1.55 [95% CI 0.65, 3.69] for 3 drugs vs 2 drug NP, p>0.05)
- Infants receiving no NP were at increased risk of grade 3-4 neutropenia (AOR 3.42 [95% CI 1.08, 10.84] vs 2 drug NP, p=0.04),
- Preterm infants were at increased risk of grade 3-4 anaemia (AOR 1.88 [95% CI 1.24, 2.81] for 33-36 and 2.73 [1.28, 5.81] for ≤32 weeks vs term) as were infants with in utero exposure to dual therapy (AOR 4.36 [1.89, 10.0] vs no antenatal ART).

Haematological markers in the first 18 months of life

- 7746 results were available for 1836 infants; median per child = 3 (IQR: 1-6)
- No significant differences in predicted haemoglobin levels or the predicted neutrophil counts in the first 18 months of life were apparent by NP type
- **Haemoglobin**: coefficient -0.189 [95% CI: -0.38 to 0.007], p=0.102 for CNP vs. one drug NP; coefficient -0.35 [95%CI: -0.75 to 0.05], p=0.090 considering no NP vs one drug NP; **Neutrophil count**: coefficient 0.02 [95% CI: - 0.01 to 0.03], p= 0.178) considering CNP vs. one drug NP; coefficient -0.03 [95%CI: -0.10 to 0.04], p=0.366 considering no NP vs one drug NP)





CONCLUSIONS

- A small proportion of infants experienced grade 3-4 haematological toxicity in their first 6 months of life
- Risk of anaemia was not associated with type of NP exposure in adjusted analysis, whilst among infants receiving NP, there was no significant difference in risk of neutropenia by number of NP drugs

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