Safety of Triple Drug Antiretroviral Prophylaxis in High Risk HIV-Exposed Neonates

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Background: PMTCT in Canada

Vertical transmission in Canada 1997-2011

(Canadian Perinatal HIV Surveillance Database, n=2495 MIP)

- 2.7% vertical transmission overall
- 0.3% (5/1780) with >4 weeks of cART in pregnancy
- **10.7 %** (12/112) with <4 weeks of cART in pregnancy
- 0.5% with undetectable maternal VL close to delivery (<50 or <40 c/ml)
- **3.1%** with maternal VL 40 - 1000 c/ml close to delivery

How should infants of mothers with suboptimal virologic control be managed?

Department of Health & Human Services recommendations for "high risk" infants:

- If no antepartum maternal treatment given
  - **Zidovudine** for 6 weeks PLUS
  - Three doses of **nevirapine** in first week of life (birth, 48 hours later, and 96 hours after second dose; AI)
- *"…the decision to combine other drugs should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by counseling of the mother on potential risks and benefits… (BIII)"*

http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf

Standard Practice 4 Canadian Centers

- Triple cART has been given to neonates born to mothers with sub-optimal viral control for over 10 years
- 2 most common regimens

  ZDV/3TC/Nelfinavir

  ZVD/3TC/Nevirapine

Dosing (term infants)

ZDV: 4mg/kg BID

3TC: 2mg/kg BID

Nelfinavir: 40-50mg/kg/BID

or

NVP: 150mg/m^2 daily, increased to BID dosing after two weeks of age

SickKids

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STOLLERY CHILDREN'S HOSPITAL

Study Rationale

Objective:

To determine the safety of triple cART at treatment doses in HIV-exposed newborn infants

Specific outcomes:

- Incidence of anemia and neutropenia among cART vs ZDV treated infants
- Incidence of treatment discontinuation due to adverse events
- Growth parameters among cART vs ZDV treated infants at 1 and 6 months of age

Methods

- Retrospective review of all HIV exposed infants born at 4 Canadian Hospital Centers between 1997-2012

- Eligibility criteria for infants
  - Born to HIV infected mother and initiated on cART at treatment doses within 72 hours of birth*
  - Single or three dose nevirapine regimens excluded

- Controls
  - All ZDV treated infants followed at the Hospital for Sick Children over three year period (2010-2012)

*Per institution protocol, majority started within 12 hours of birth

Results

- 148 infants received triple cART
  - ➢ Rationale for cART
    - Documented detectable maternal viral load (78.4%)
    - Other overlapping factors: poor adherence (45%), late diagnosis (20%), no antenatal care (8%), refused treatment (8%)
  - ➢ Regimens
    - 59 – Zidovudine, Lamivudine & Nevirapine
    - 82 – Zidovudine, Lamivudine & Nelfinavir
    - 7 – Zidovudine, Lamivudine & Lopinavir/r
- 145 zidovudine monotherapy recipients as comparison group

Baseline Characteristics

Variable	cART	Zidovudine	p value
Maternal age (years)	29.3 ± 5.0	33.7 ± 5.1	0.02
Maternal viral load (c/mL)	9806±34,539	<50±137	0.003
Maternal CD4 count (cells/μL)	411 ±258	519 ±220	0.003
Timing of Diagnosis			
Prior to pregnancy	61.9%	88.3%	<0.001
During pregnancy	34.7%	11.7	
At delivery	3.4%	0	
Mode of Delivery			
Vaginal	37.8%	60.7%	<0.001
C/section Elective	46.6%	26.9%	
C/Section: Emergency	15.4%	12.4%	
Infant sex (% female)	48.9%	54.5%	NS
Gestational age (weeks)	37.7±2.53	38.4±1.94	0.02
Premature (< 37 weeks; %)	20%	11.8%	0.06

§ Only one with a viral load > 1000 copies/mL

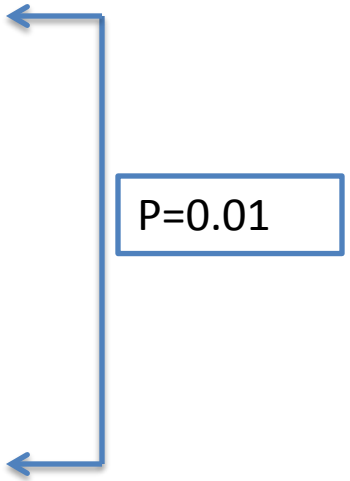
Vertical transmission

- cART Recipients
  - Vertical transmission in **8.8%** (13/148)
  - 46% likely infected *in utero:* DNA PCR positive within 48 hours of birth in 6 of 13
  - 13 infected infants who had started cART at birth for prophylaxis:
    - Sustained virological suppression achieved in 4 cases (Oral Abstract #TUAB0206LB)
    - 9 never suppressed: Failure associated with poor adherence, treatment interruptions or intermittent viral load blips
- None of ZDV treated infants infected

Clinical adverse events

- Non-specific symptoms/signs in cART recipients:15.5%
  - "Related to cART": Irritability (0.68%), jitteriness (1.35%), vomiting (3.38%), diarrhea (2.70%), rash (2.70%)

- Treatment discontinuation
  - cART recipients (n=14) (9.5%)
    - Possible medication toxicity (n=10)
    - Stopped by parents; no toxicity (n=4)
  - ZDV recipients (n=3) (2.1%)
    - Anemia in all 3; hemoglobin < 80 g/L in 2

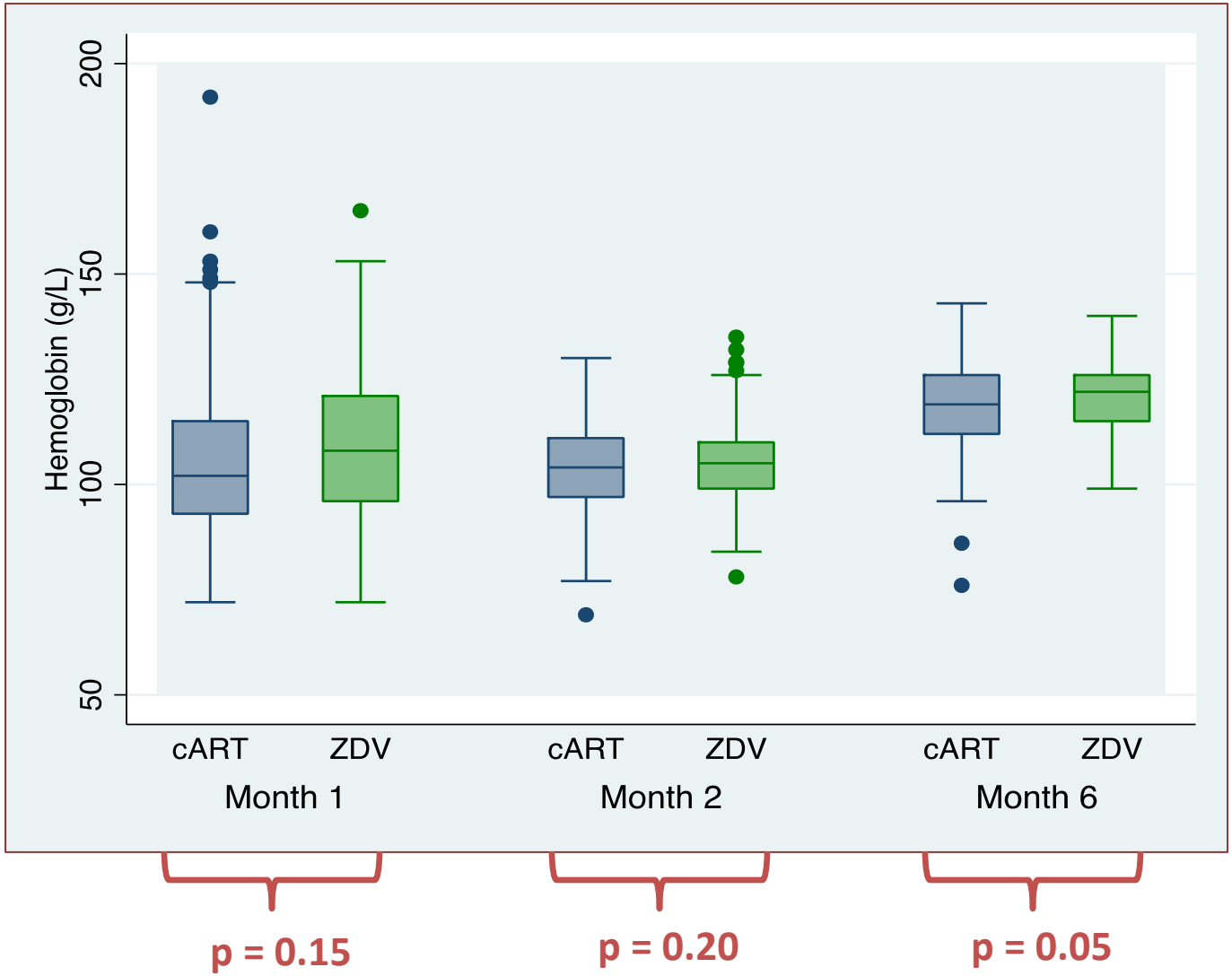


Treatment discontinuation due to possible adverse events in cART recipients

Case	Regimen	Adverse event
1	ZDV/3TC/NVP	Rash, vomiting, diarrhea at 7 days §
2	ZDV/3TC/NVP	Rash at 10 days
3	ZDV/3TC/NVP	Hemoglobin 62 g/L at 2 weeks; transfused PRBC
4	ZDV/3TC/NLF	Hemoglobin 76 g/L at 4 weeks
5	ZDV/3TC/NLF	Neutropenia (0.4 cells/mm^3) at 4 weeks
6	ZDV/3TC/NLF	Persistent vomiting at 3 weeks
7	ZDV/3TC/NLF	Possible pancreatitis (lipase 162 U/L) at 2 weeks
8	ZDV/3TC/NLF	Elevated GGT (494 U/L) on day 10
9	ZDV/3TC/NLF	CPK 1243 U/L at 4 weeks
10	ZDV/ABC/LPV	Hemoglobin 92 g/L at 4 weeks

§ Likely secondary to viral illness; brother with similar symptoms

Impact of treatment on hemoglobin



Laboratory measures at 6 months of age

Variable (mean+ SD)	cART	ZDV	p value
Leukocyte count (x10^9/L)	9.50±3.10	9.50±2.60	0.96
Neutrophil count (x10^9/L)	2.09±1.24	2.04±1.38	0.75
Hemoglobin (g/L)	118±11	121±8	0.05
Platelet count (x10^9/L)	432±139	425±113	0.66
ALT (units/L)	24.7±15.9	22.4±9.30	0.89
Lactate (mmol/L)	1.94±0.90	1.76±0.73	0.18

Impact of treatment on hemoglobin

	1 MONTH		2 MONTHS		6 MONTHS	
	cART	ZDV	cART	ZDV	cART	ZDV
Normal	49.3 %	60.7 %	46.3%	56.8 %	85.8 %	94.0 %
Mild	25.7%	17.9 %	35.8%	33.1 %	8.5 %	5.4 %
Moderate	21.6 %	20.0 %	16.3%	9.4 %	3.8 %	7.8%
Severe	3.4 %	1.4 %	1.6 %	0.70	0.20%	0
p value §	0.03		NS		NS	

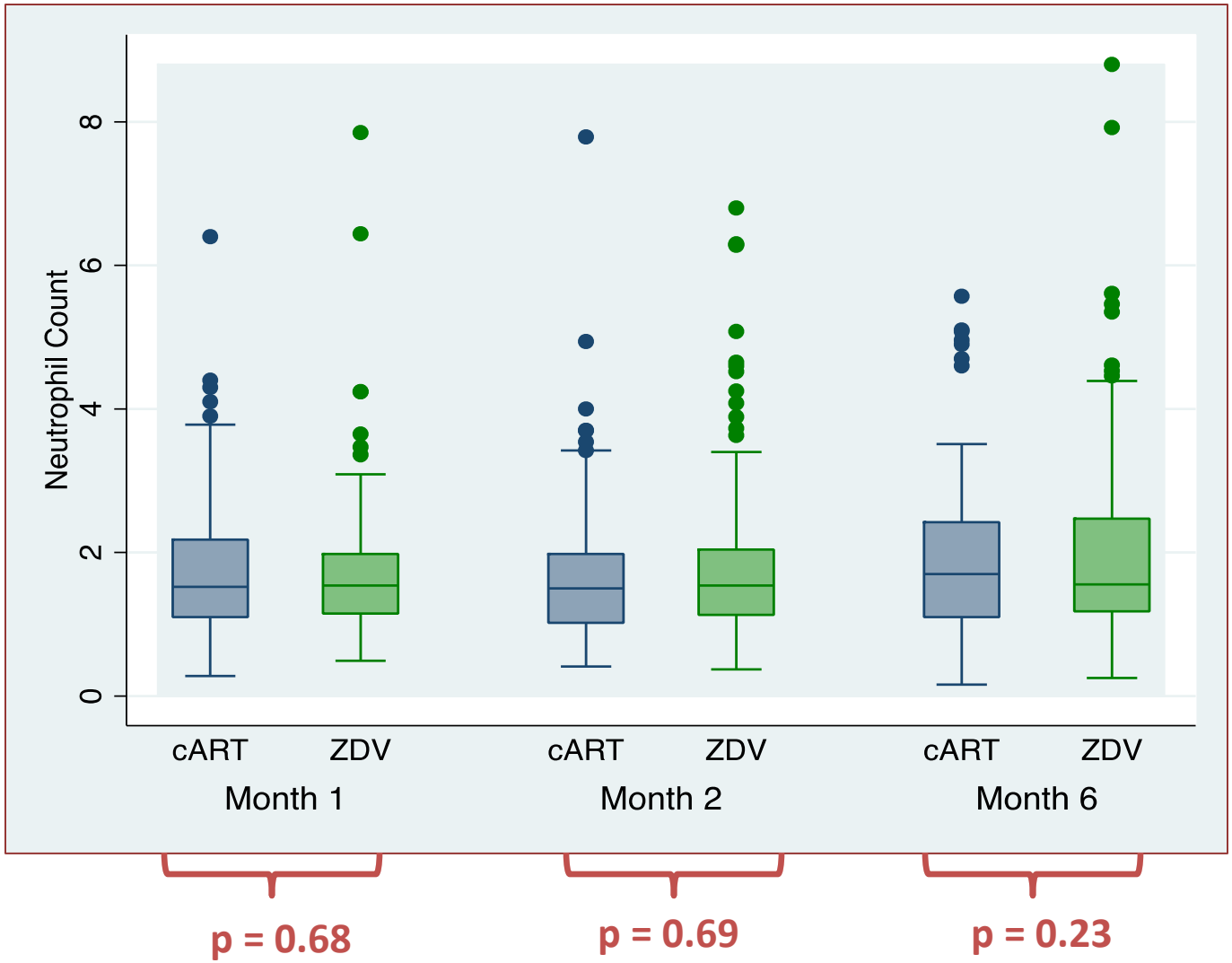
Grading of anemia:

At 1 month: mild = 95-105 g/L; moderate = 80-94 g/L; severe < 80 g/L

At 2 & 6 months: mild = 85-100 g/L; moderate = 75-84 g/L; severe < 75 g/L

§ Mantel-Haenszel χ^2

Impact of treatment on neutrophil count



Impact of treatment on neutrophil count

	1 MONTH		2 MONTHS		6 MONTHS	
	cART	ZDV	cART	ZDV	cART	ZDV
Normal	67.2 %	67.0 %	71.3 %	66.9 %	73.3 %	69.5 %
Mild	14.1 %	23.2 %	13.9 %	13.0 %	16.2 %	14.1 %
Moderate	10.2 %	7.9%	8.1 %	12.9 %	6.7%	10.9 %
Severe	8.6 %	2.9 %	6.5 %	7.2 %	3.8 %	5.5 %
p value §	0.04		NS		NS	

Impact of Treatment on Growth

	cART	ZDV	p
Birthweight (gm)	2920±580	3093±560	0.02
1 month measures			
Weight (gm)	3920±610	4170±590	<0.001
Length (cm)	51.7±2.71	52.3±272	0.06
Head Circumference (cm)	36.7±1.50	37.2±1.30	0.002
6 month measures			
Weight (gm)	8000±1120	8230±1140	NS
Length (cm)	67.0±2.84	68.2±3.30	0.002
Head Circumference (cm)	43.6±1.86	44.2±1.76	0.009
Δ Weight 1-6 months	4090±922	4070±939	NS
Δ Height 1-6 months	15.5±2.68	15.9±2.81	NS
Δ HC 1-6months	7.07±1.32	7.00±1.44	NS

WHO Z-Score Differences

	cART	ZDV	P
1 month Z Score			
Weight	-0.84 ± 1.19	0.31 ± 1.03	<0.001
Height	-1.29±1.36	-0.94±1.38	0.05
Weight <-2 SD (n,%)	19 (15.4%)	8 (5.6%)	<0.001
6 month Z Score			
Weight	0.38±1.16	0.71±1.43	0.06
Height	0.16±0.19	0.76±1.42	<0.001
Weight<-2SD (n,%)	1 (0.3%)	2 (0.7%)	NS
Weight>2 SD		55 (20.2%)	

Summary & Conclusions

- Despite triple cART PEP, the vertical transmission rate was 8.8% in these high risk situations

- Triple cART in neonates was generally well tolerated
  - No significant differences in absolute laboratory measures at 1,2 and 6 months of age
  - Possible increase in severe symptoms (*sample size limitations) at 1 month of age*
  - No significant differences in grade II or higher anemia or neutropenia at 2 and 6 months of age

Summary & Conclusions

However…

- Higher incidence of early treatment discontinuation among cART treated infants (9.5% vs 2.2%)

- cART treated infants
  - Lower birth weight, higher rate pre-term delivery
  - Lower growth parameters at birth and 1 month of age, but "Catch up" at 6 month of age

Further Directions

- Close monitoring and long term follow-up of cART treated infants is necessary
- There remain practical & knowledge gaps regarding neonatal cART
  - Limited availability of newborn-friendly formulations
  - Options for PMTCT of drug resistant virus
  - Pharmacokinetic studies of antiretroviral medications in neonates & pre-term infants

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