

Early management of young HIV-infected infants

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Children's Infectious Disease

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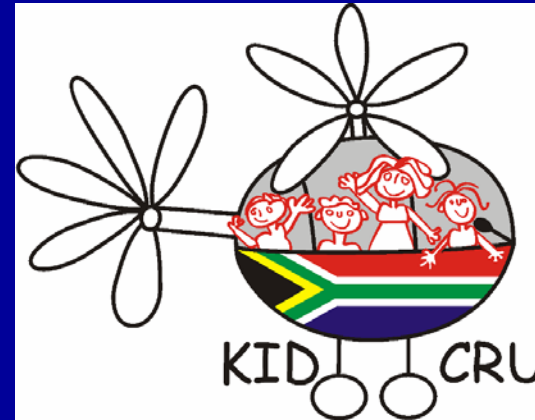
(KID-CRU)

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Stellenbosch University

Tygerberg Children's

Hospital



Natural History of HIV

Rich et al Pediatrics 2000; 105

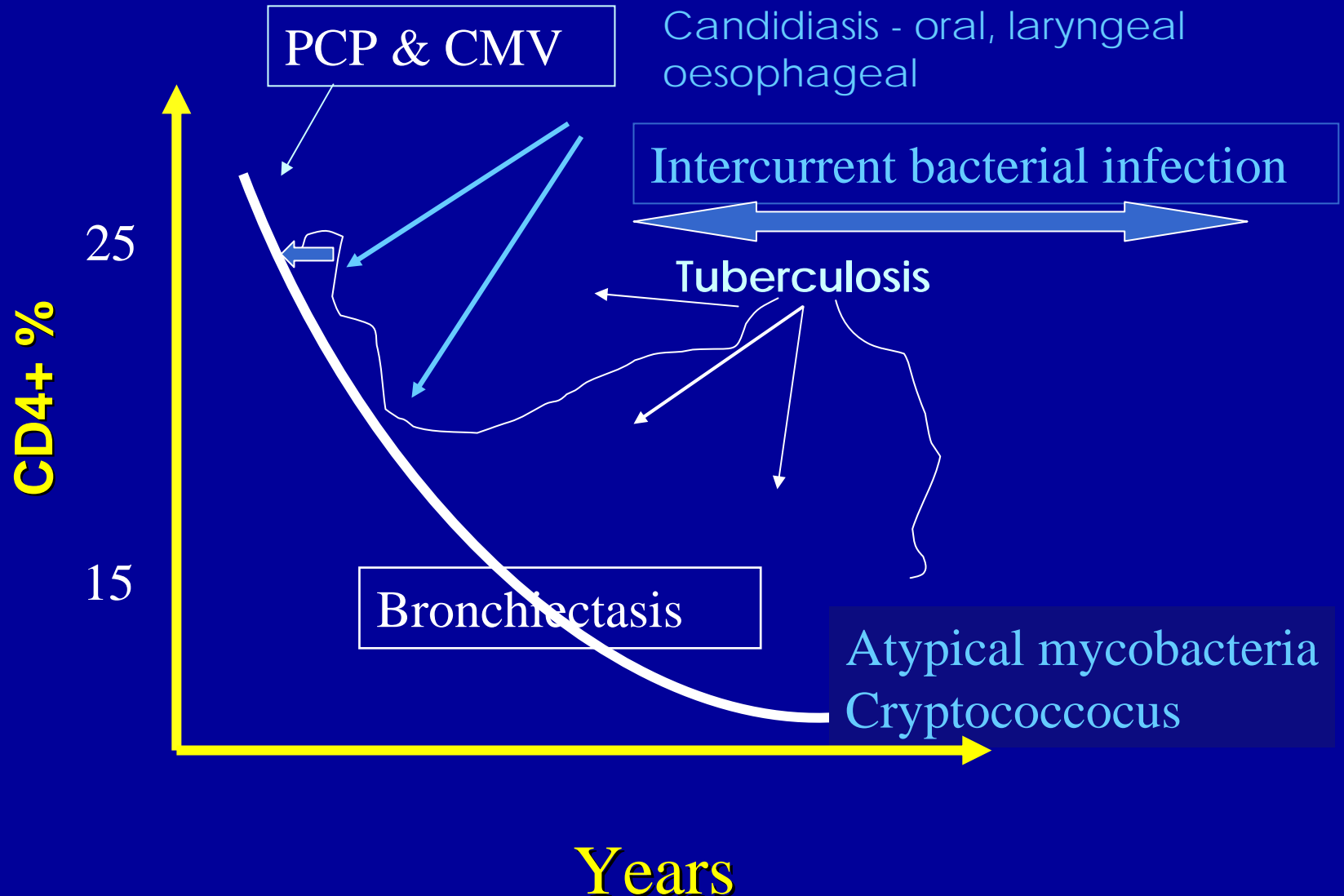
- WITS study 122 infants
- Pre-1996
- Clinical progression - Death or CDC “C”
 - 15% by 6m
 - 32% by 18m

Progression in HIV CDC USA 1982-1993

Barnhart HX Pediatrics 97 710 06

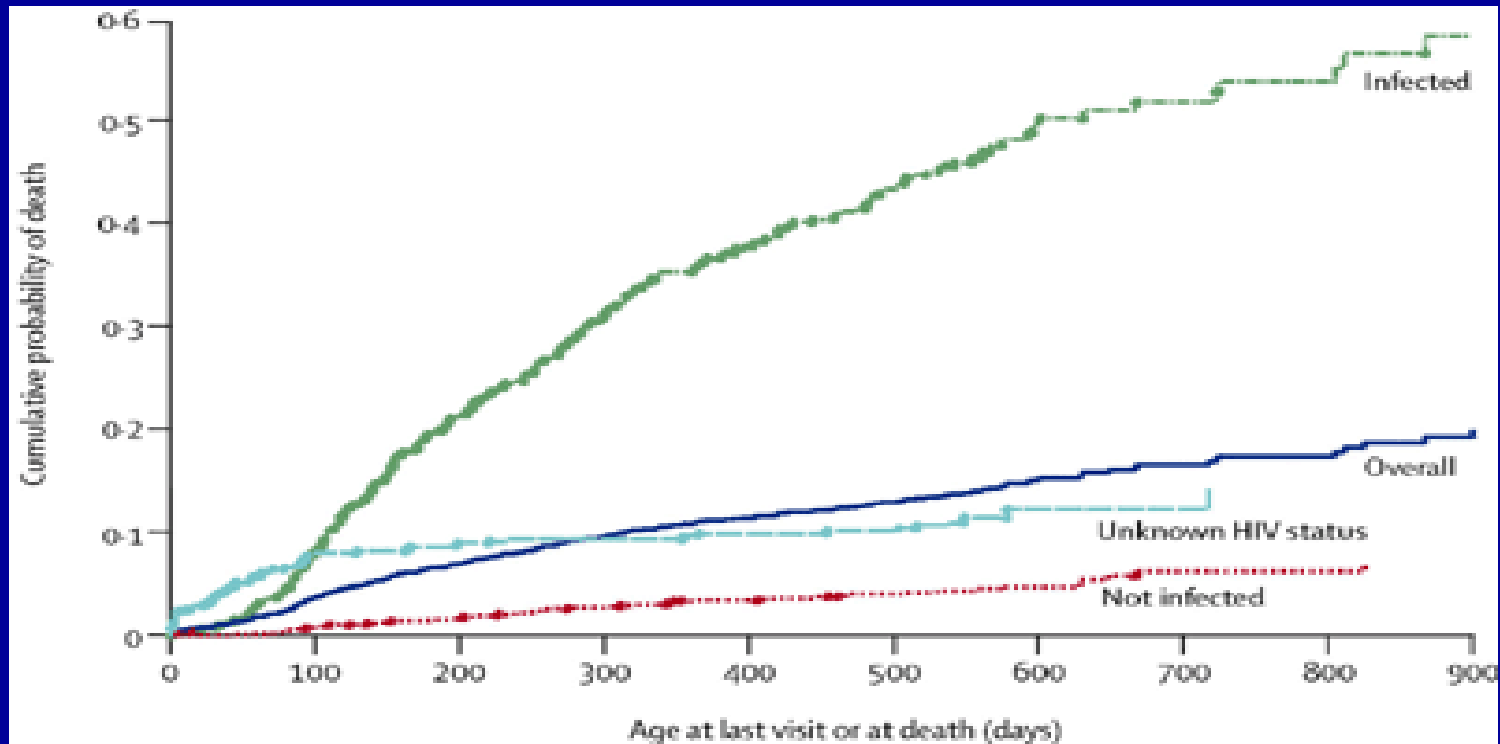
	Time in category	Time to C	% C in 5y	% surviving 5y	Median survival
N	10m	6.6y	50	75	8y
A	4m	5.7y	58	67	7.1y
B	65m	5.4y	60	65	6.8y
C	34m			17	1.9y

CD4% in HIV+ infants



Cumulative mortality of HIV- infected African infants

Newell ML et al
Lancet 2004; 364: 1236-43



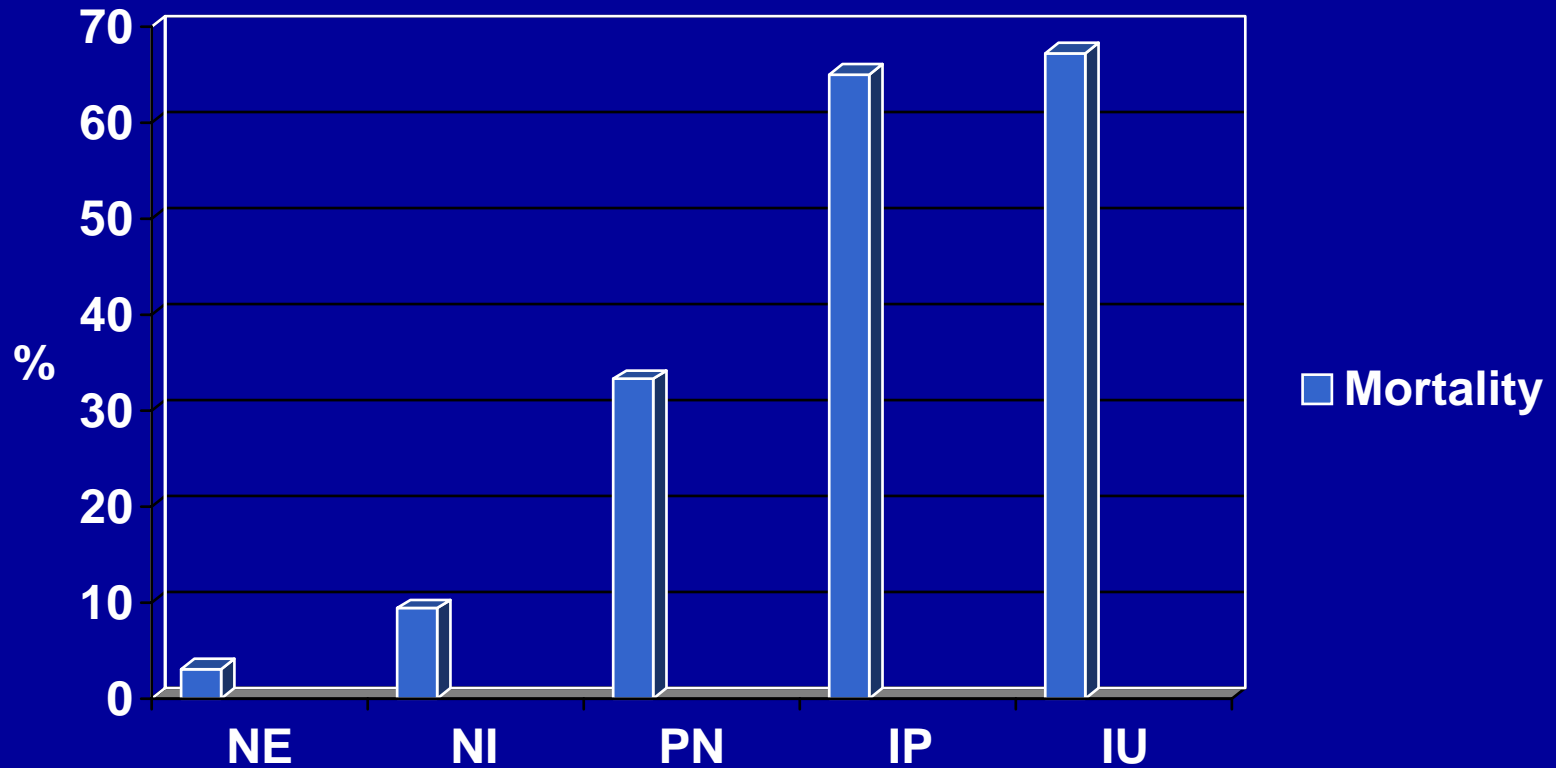
Children at risk	1 day	7 days	28 days	365 days	730 days
Overall	3330	3269	3212	2063	297
p (death)	0.002	0.006	0.008	0.110	0.174
Infected	693	691	681	299	54
p (death)	0.0015	0.003	0.008	0.352	0.525
Uninfected	2127	2114	2078	1364	211
p (death)	0.0005	0.003	0.006	0.049	0.076

Child mortality according to maternal and infant HIV status in Zimbabwe

E. Marinda¹, J.H. Humphrey², P.J. Iliff³, K. Mutasa³, E.G. Piwoz⁴,,
ZVITAMBO Study Group

- Death in children enrolled in ZVITAMBO trial
- 1998 – 2000
- Cause of death - hospital records or verbal autopsy
- Population
 - HIV-negative (NE, n=9510)
 - HIV-exposed uninfected (NI, n=3135)
 - Infected in-utero (IU, n=381)
 - Intrapartum (IP, n=508)
 - Postnatal (PN, n=258)

2 year mortality



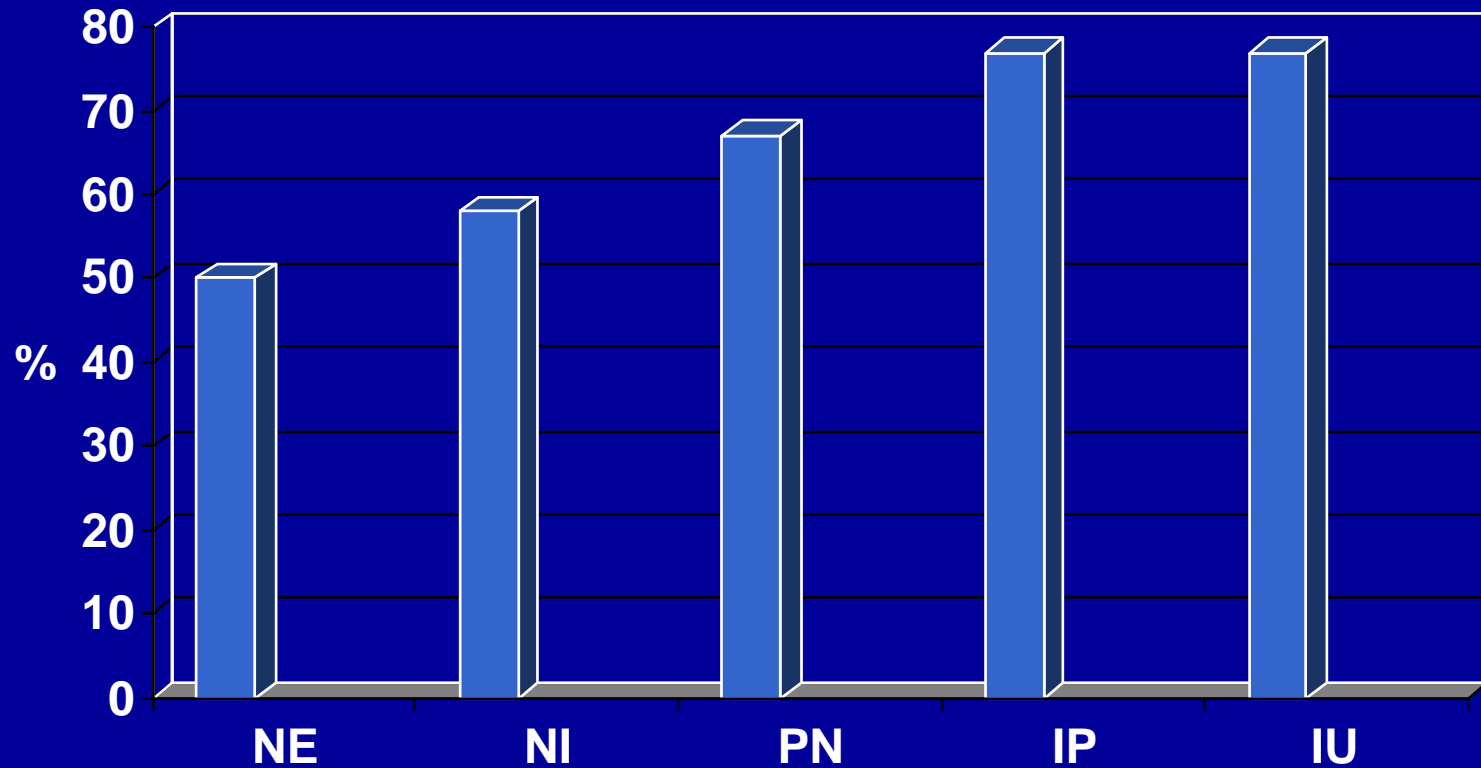
Results

- Median time from infection to death
 - 208d IU
 - 380d IP

Among NI children - predictors of mortality

- indicators of maternal severity of illness (death, anemia, low arm circumference, low CD4)
- social vulnerability (unmarried and low income)

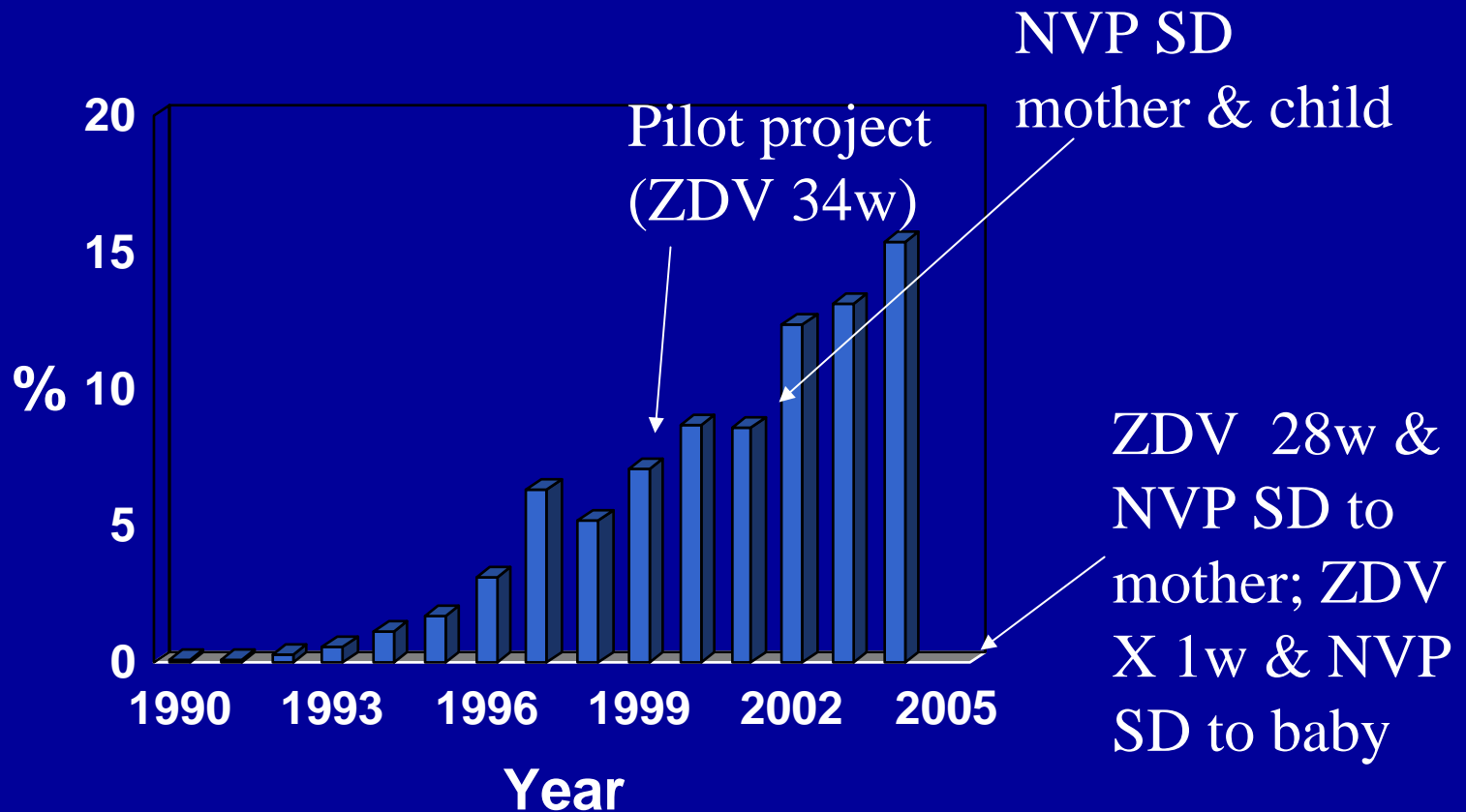
Acute respiratory infection causing death



Conclusions

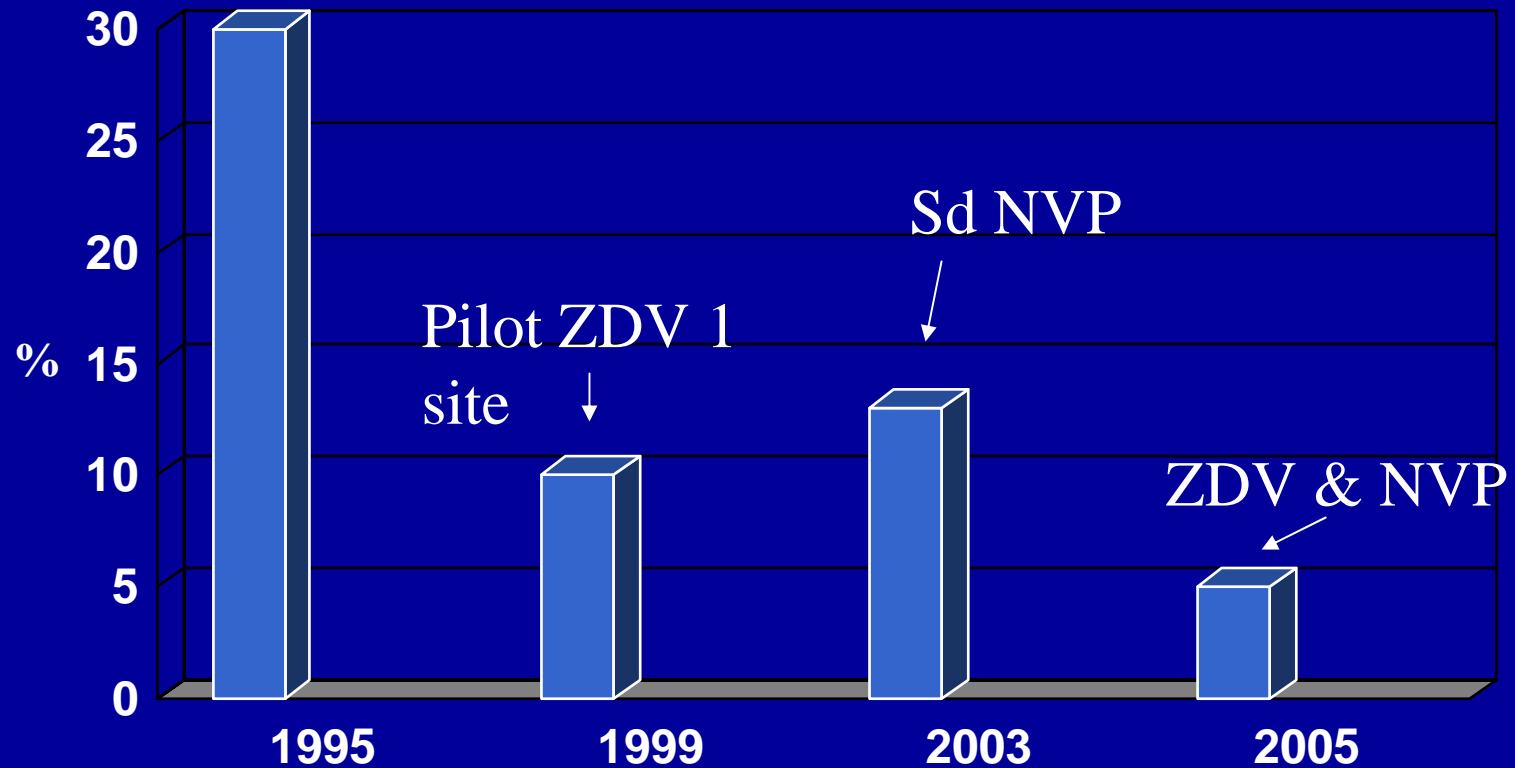
- Mortality is exceedingly high among HIV-infected children
- The earlier children are infected, the faster they die
- Respiratory infection major cause deaths
- Need for timely ARV and cotrimoxazole prophylaxis

W Cape: HIV infection in antenatal clinic attendees and programs to reduce vertical transmission



SD - single dose Nevirapine - NVP

Vertical transmission - W Cape

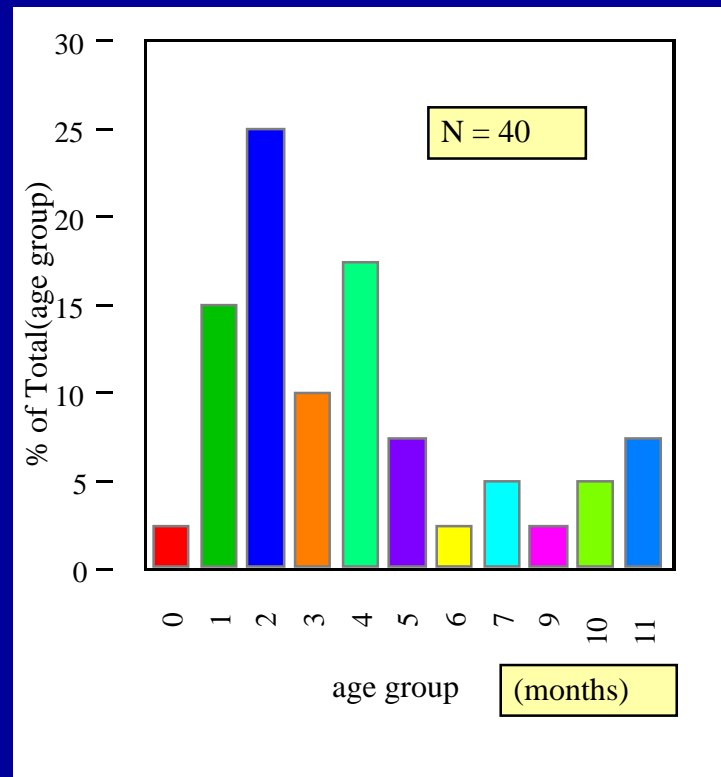


Infant diagnosis

- When do you do a PCR?
- 14w W Cape
- 6w National

At what age do infants present with severe disease?

Age of infants needing PCR's at TCH - 2005



Infants <6m of age in TCH -

week of 30/1/06 - 3/2/06

Burden of disease

- 25 infants
- Median age 4m (IQ: 2.4 - 4.8)
- HIV-exposed - 15 (60%)
- HIV+ - 6 (24%)

Temporal Trends in Early Clinical Manifestations of Perinatal HIV Infection in a Population-Based Cohort

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WORLDWIDE, APPROXIMATELY 2.5 million children are infected with the human immunodeficiency virus (HIV),¹ and approximately 1700 new perinatal infections occur daily.² In the United States, more

Context The effect of early antiretroviral therapy (ART) on the early progression of perinatal human immunodeficiency virus (HIV) infection is not well defined.

Objective To examine early disease progression and survival in a population-based cohort with perinatal HIV infection in relation to year of birth and use of ART.

Design, Setting, and Patients Retrospective study of temporal trends in early progression of perinatal HIV infection among 205 HIV-infected children in Northern California born between January 1, 1988, and December 31, 2001, and followed up through age 3 years.

Main Outcome Measures Prevalence of and age at progression to a first US Centers for Disease Control and Prevention category C diagnosis relative to year of birth, type of ART, and age at initiation of therapy.

Results Of 205 children, 134 (65%) received ART and/or *Pneumocystis jiroveci* pneumonia prophylaxis. By age 3 years, 81 (40%) progressed to a category C diagnosis, 41 (51%) of whom died. Untreated children were significantly more likely to progress to a category C diagnosis (62% [44/71] untreated vs 28% [37/134] treated children, $P < .001$); none of 23 infants who received triple ART progressed to category C. However, even without triple ART, very early mono/dual ART (by age 2 months vs 3-4 months) was associated with delayed and decreased progression to category C ($P = .02$). Of 33 children born between January 1, 1996, and December 31, 2001, only 7 (21%) progressed to category C ($P = .02$ compared with 1988-1995), 6 of 7 of whom received no therapy. More recent year of birth and more advanced therapy were associated with improved survival.

Conclusions This population-based cohort demonstrated decreased early HIV progression and improved survival at age 3 years, associated with more advanced therapy. Although limited by small sample size, the findings suggest that very early treatment, even without triple ART, was associated with improved outcome.

JAMA. 2005;293:2221-2231

www.jama.com

Early versus Late therapy

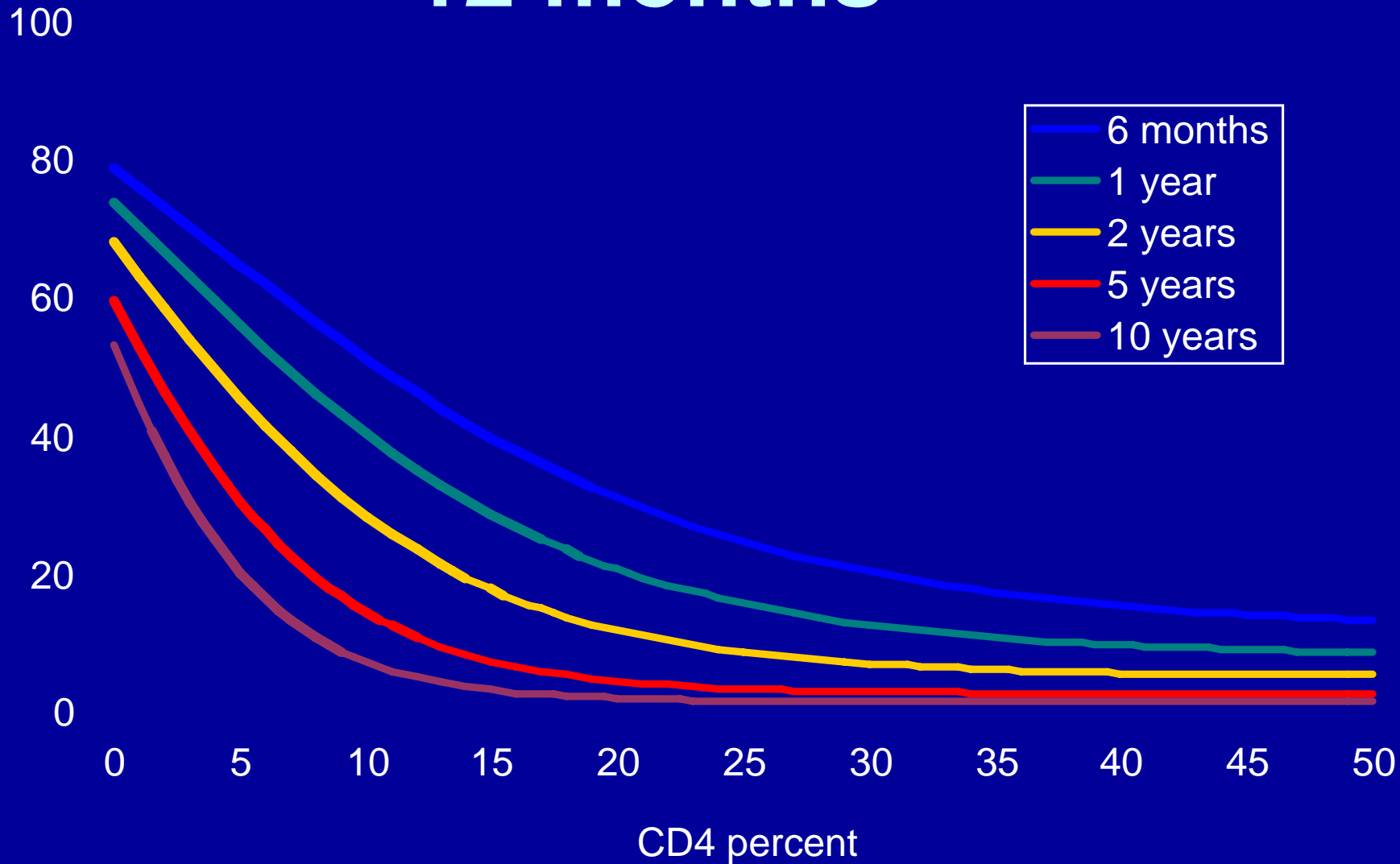
Faye Clin Infect Dis 2004; 39: 1692-8

- 83 HIV-infected infants born in 1996 (when HAART became available) or later
- 40 early Rx \leq 6m
 - None developed OI or encephalopathy in 1st 24m
- 43 after 6m
 - 6 had AIDS-associated events (P=.01)
 - 3 encephalopathies (P=.08)

Comprehensive Program for Research in AIDS (CIPRA-SA)

- When do you start ART in HIV-infected infants? (CHER study)
 - Do you start immediately or can you wait
 - If you start immediately, can you stop for a few years once the child is older
 - Does ART make vaccination against pneumococcus & haemophilus work better?
- TCH & PHRU (Avy Violari)

Probability of AIDS within 12 months



WHO Classification of immunodeficiency in children

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤11 months (%)	12–35 months (%)	36–59 months (%)	≥5 years (cells/mm ³)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

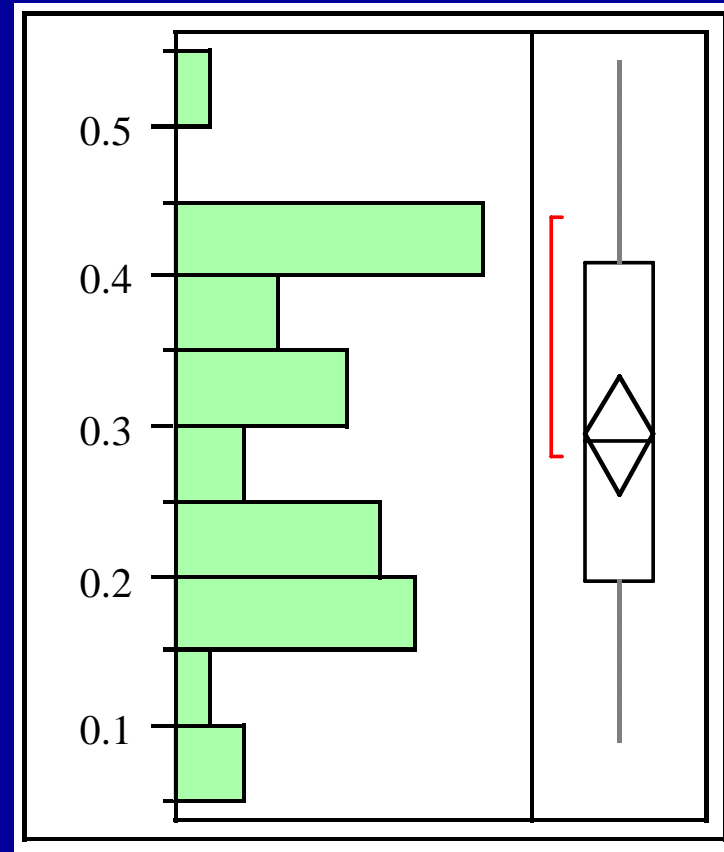
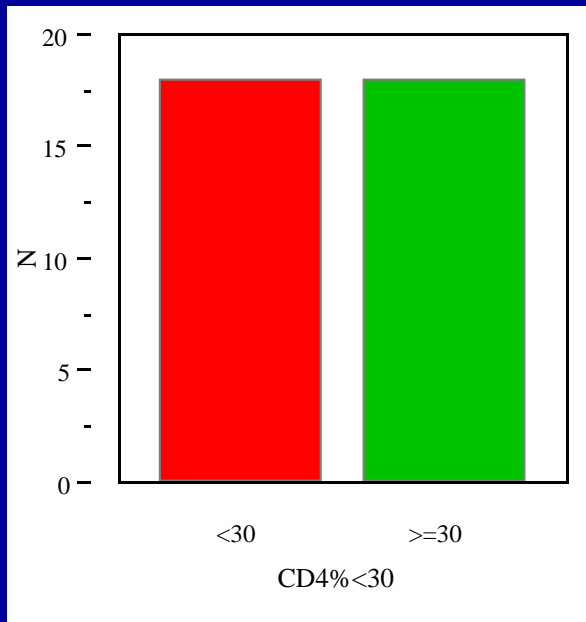
Source: Based on WHO global and regional consultations and data from references (45, 174).

HIV-infected infants seen at TCH for possible enrolling in CHER study

- N = 42
- Median age - 6.5 (IQ: 5.4 - 9.5) weeks

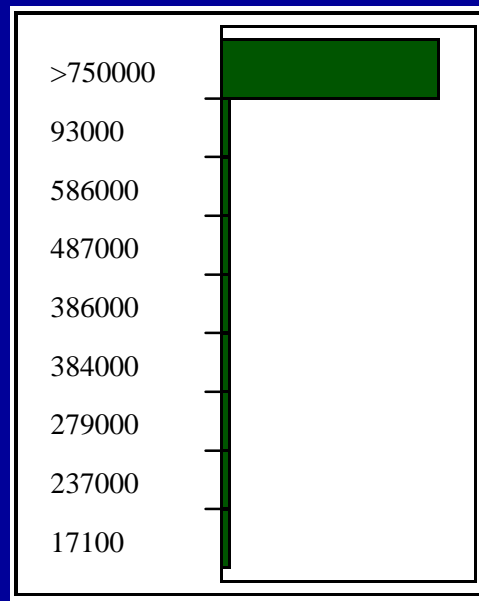
CD4%

- Median 29.1%
- IQ - 19.8 - 40.1%

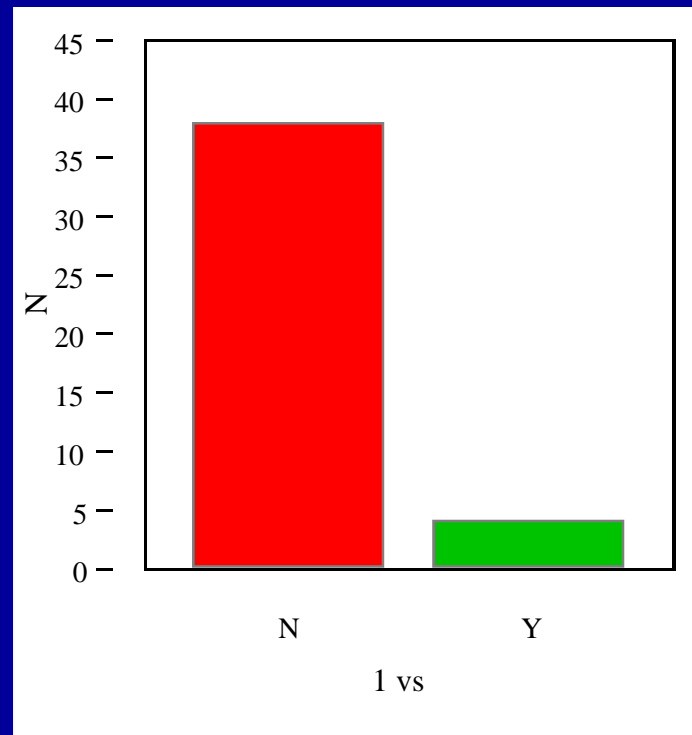


Plasma HIV RNA at screening

Copies/ml



WHO stage 1 at 1st evaluation



Conclusions

- Infants symptomatic from an early age
- CD4 depletion evident early

Recommendation

- Early diagnosis - from 2 weeks?
- Needs evaluation & rapid implementation
- Many infants require early ARVs

Acknowledgements

- Morna Cornell - CIPRA-SA
- Avy Violari - Co-PI, CHER
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- KID-CRU team