

ART initiated before 12 weeks
reduces early mortality in
young HIV-infected infants:
evidence from the Children with HIV Early
Antiretroviral Therapy (CHER) Study

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Rationale

- Treatment of HIV-infected infants is complex
 - High risk of death & disease progression in infancy
 - CD4 & viral load poor predictors of disease progression or death in infants
 - Initiation of ARVs commits to lifelong therapy
- No comparative prospective data to inform ART guidelines
- Approaches (2007):
 - Consider treatment for all infants as soon as identified (US Guidelines)
 - Treat all infants <1y (Feb 2008)
 - Treat when reach CD4 or clinical criteria (WHO Guidelines)
 - Either of the above, and include viral load criteria (European PENTA Guidelines)
 - Under revision

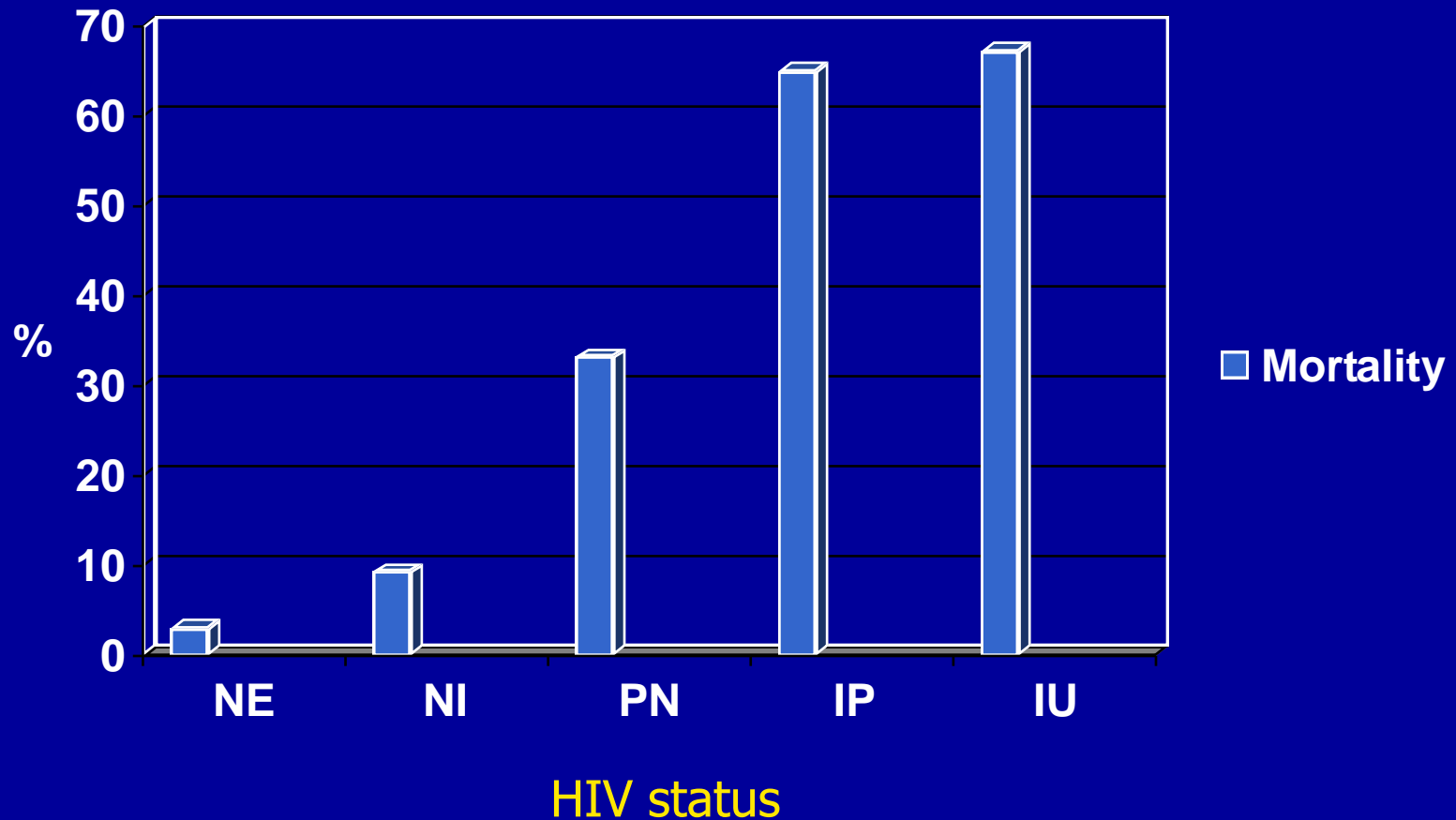
Child mortality according to maternal and infant HIV status in Zimbabwe

Marinda et al. *Pediatr Infect Dis J* 2007; 26: 519-26

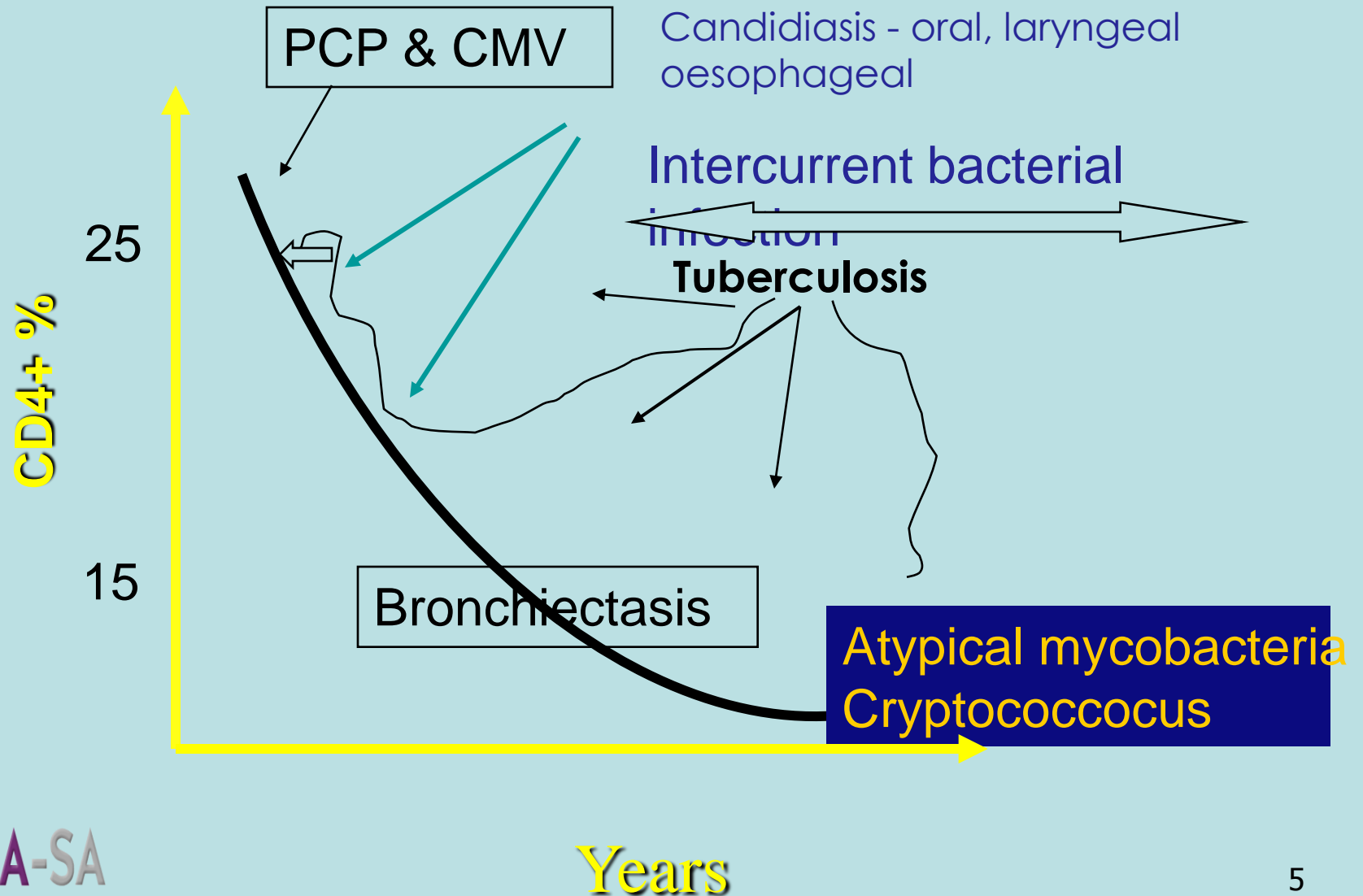
- Death in children enrolled in ZVITAMBO trial
- 1998 – 2000
- Cause of death - hospital records or verbal autopsy
- Population
 - HIV-negative (NE, n=9510)
 - HIV-exposed uninfected (NI, n=3135)
 - Infected in-utero (IU, n=381)
 - Intrapartum (IP, n=508)
 - Postnatal (PN, n=258)

2 year mortality

NE - not exposed; NI - HIV-exposed uninfected; PN - postnatal, IP - intrapartum; IU - *in utero*

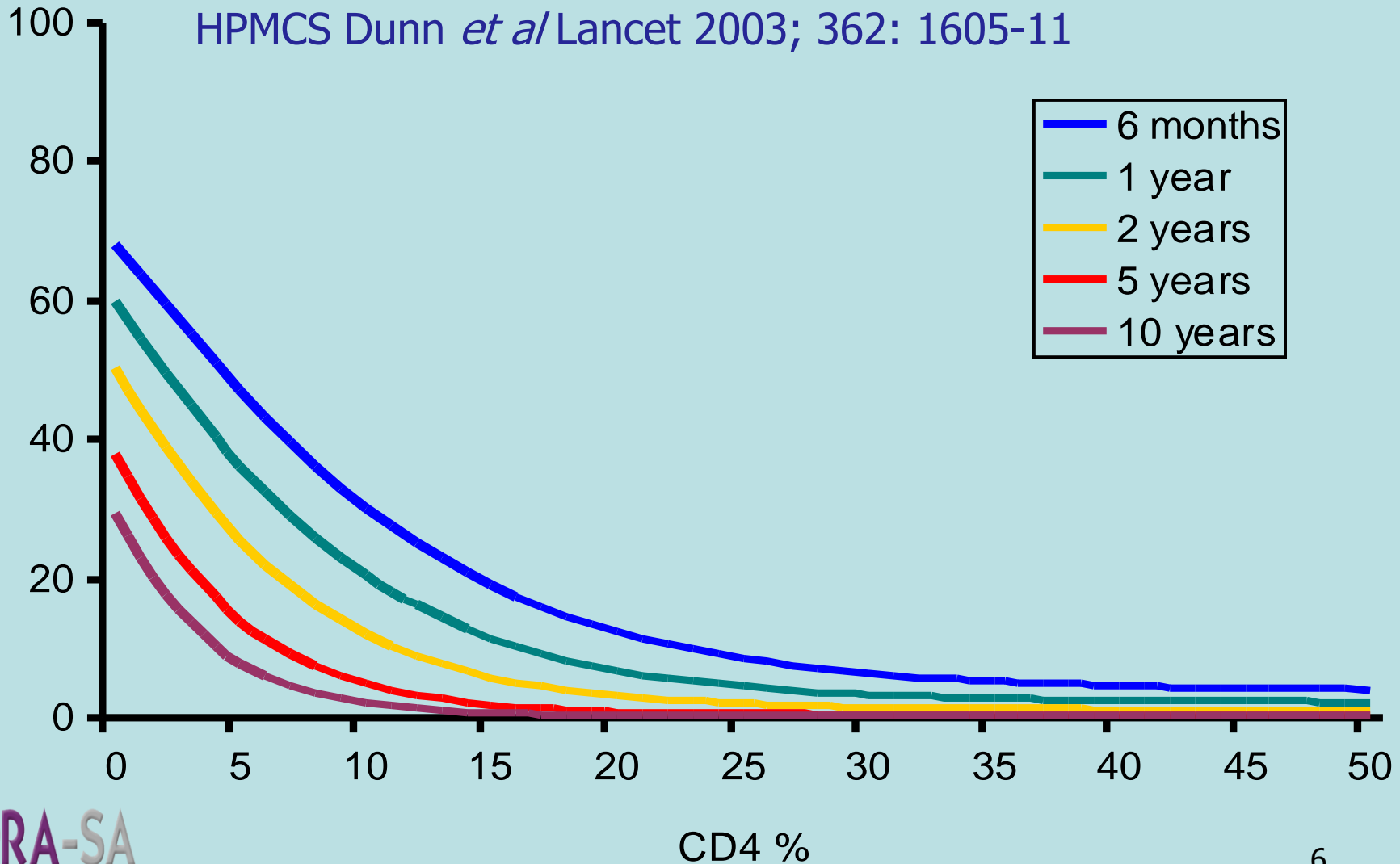


CD4% & disease in HIV+ infants



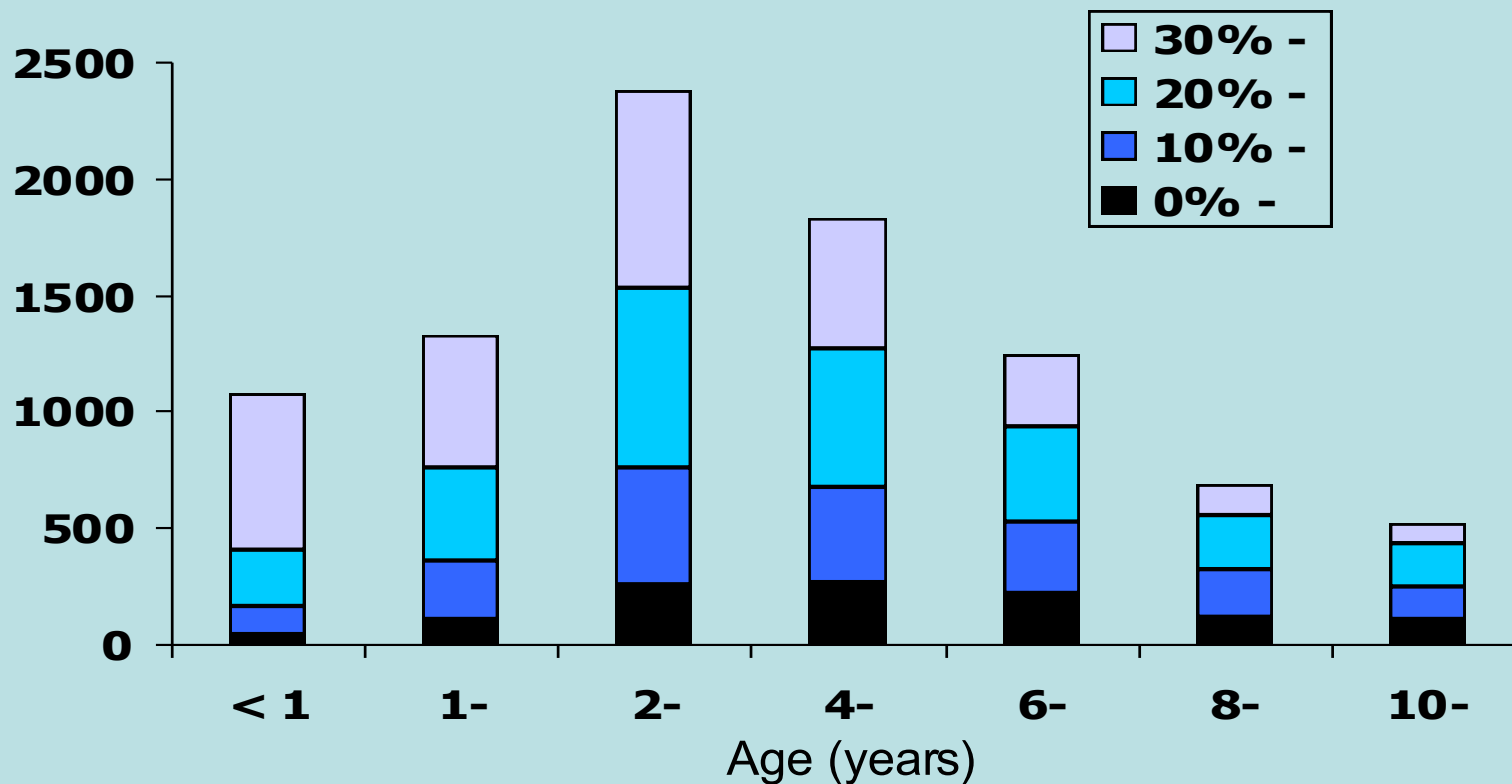
Probability of death within 12 months

HPMCS Dunn *et al*/Lancet 2003; 362: 1605-11



CD4% & death

HPMCS Dunn *et al*/Lancet 2003; 362: 1605-11



Number of Deaths

30% -	59	14	11	2	2	0	0
20% -	43	21	8	3	0	0	0
10% -	31	26	31	5	4	3	3
0% -	24	53	90	50	44	26	15

European & N American experience over 20 years

- Since 1995 (HAART)
 - Dramatic reductions in death and progression to AIDS
 - Infants and children started earlier did better
 - <3m; <6m

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)

ART started <3m better virological outcome than >3m

Luzuriaga et al N Engl J Med 2004; 350: 2471-80

- N = 52
- D4T, 3TC, NVP, NFV
- Viral suppression at 48w (<400 copies)
 - <3m - 15 (60%)
 - >3m - 11 (41%)

CHER Trial - Hypothesis

- Early limited ART until 1st or 2nd birthday will:
 - Have long-term benefit by delaying disease progression
 - And delaying the need for long-term continuous ART

CHER Trial Part A n= 375

HIV infection diagnosed before 12 weeks and CD4% >25%

Arm 1
Deferred
treatment
N=125

Arm 2
Short course
(to first birthday)
N=125

Arm 3
Long course
(to second birthday)
N=125

ART (start or re-start) when CD4% <20% or clinical event
(<25% from August 2006)

FOLLOW UP
For a minimum of 3.5 years

CHER Trial Design (Part A)

- **Inclusion:**
 - DNA PCR confirmed HIV infection
 - CD4 >25%
 - ART naïve except for pMTCT
 - Age <12 weeks
- ART: ZDV + 3TC + LPV/r
- All children received Co-trimoxazole and Pneumococcal vaccine
- **Endpoints:**
 - **Primary:** Death OR failure of 1st line ART regimen
 - **Secondary, including:**
 - Cumulative rate of disease progression and hospitalisation
 - Grade 3 & 4 adverse events
 - Development of ART Resistance

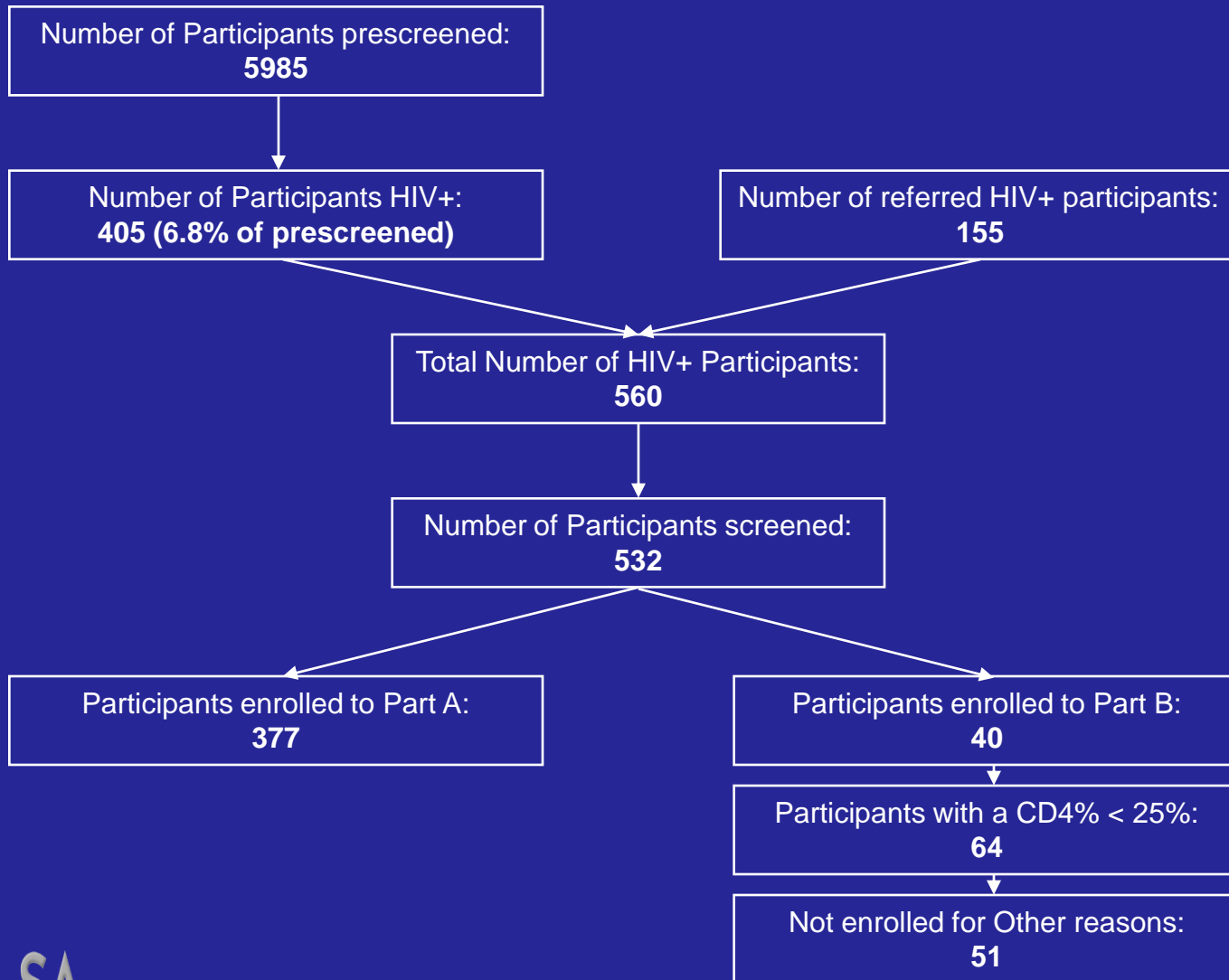
Criteria for starting ART in Arm 1

- Immunological criteria
 - CD4% <20% (WHO guidelines 2003)
Then from August 2006:
 - CD4% <25% or CD4 count <1000cells/mm³ if age <12mo
- Clinical Criteria
 - CDC Stage C
 - Selected Stage B:
 - Severe lung disease including LIP
 - Nephropathy
 - Cardiomyopathy
 - FTT in absence of remediable causes
 - Recurrent bacterial pneumonia
 - Severe or recurrent oral candidiasis

DSMB Review (20 June 2007)

- DSMB recommended modification of the study
 - release results of Arm 1 versus Arms 2&3 combined
 - infants in Arm 1 not already on ART should be urgently recalled and assessed for ART
 - trial follow-up to continue
- Interim data presented after median follow-up of 32 (*IQR: 20-48) weeks

Screening & Enrolment



Baseline characteristics

Variable	Arm 2 & 3		Arm 1	
Number of participants enrolled	252		125	
Sex: Female (%)	147	(58.3 %)	74	(59 %)
Age (weeks, median (IQR))	7.4	(6.6 - 8.9)	7.1	(6.4 - 8.9)
Mother receiving ART for PMTCT				
No Therapy	26	(10.3 %)	15	(12 %)
NVP (%)	162	(64.3 %)	72	(58 %)
AZT (%)	8	(3.2 %)	5	(4 %)
AZT + NVP (%)	51	(20.2 %)	26	(21 %)
HAART (%)	2	(0.8 %)	5	(4 %)
Weight (Median IQR (kg))	4.4	(4.0 - 4.9)	4.5	(4.0 - 5.0)
CDC Classification				
Class N & A (%)	237	(94.0 %)	121	(96.8 %)
Class B (%)	11	(4.4 %)	3	(2.4 %)
CD4 % (median (IQR))	35.1	(29.1 - 40.8)	35.6	(29 -43.8)
CD4 Count (cells/mm ³) median (IQR)	2035	(1519-2754)	2044	(1585-2960)

Breast Feeding

- 20% in each arm

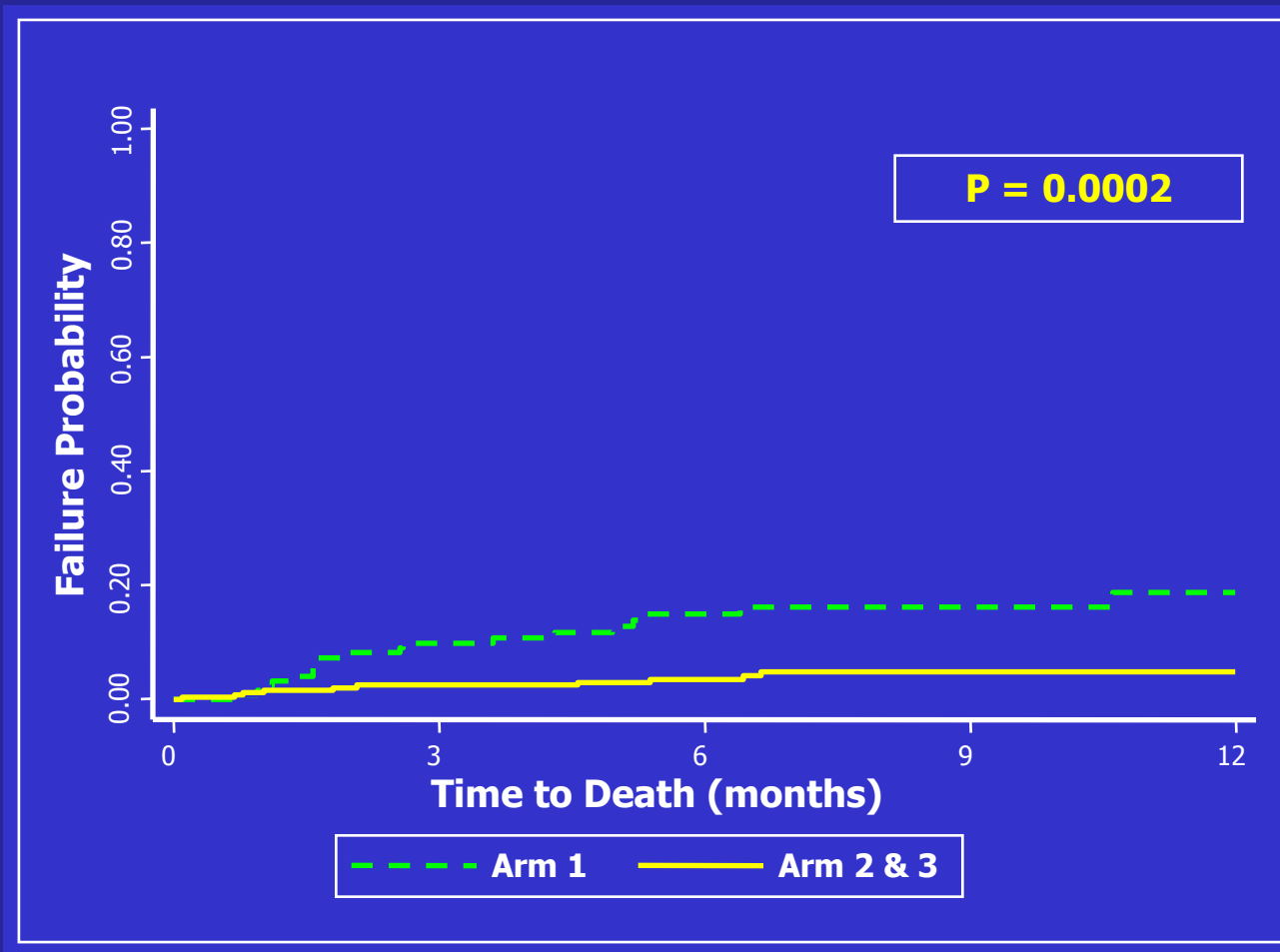
Follow-up and use of ART

Variable	Arm 2 & 3 n = 252	Arm 1 n = 125
Lost to follow-up	10 (4.0 %)	4 (3.2 %)
No. of participants initiating ART	250	76 (60.8%)
Participants on ART at:		
Week 12	98.2 %	18.1 %
Week 24	96.5 %	48.8 %
Week 32	95.6 %	59.0 %
Week 40	95.0 %	52.3 %
% time spent on ART by week 40	98.6 %	32.0 %

Mortality Rates

Variable	Arm 2 & 3 n = 252	Arm 1 n = 125	Total n = 377
Died (%)	10 (4%)	20 (16%)	30 (8%)
Person Years of follow-up	167	79	246
Rate per 100 PY (95% CI)	6.0 (2.9; 10)	25.3 (15.5; 39.0)	12.2 (8.2; 17.4)
Hazard Ratio			0.24 (0.11; 0.51)
P - value			0.0002

Time to Death



Patients at risk

	Month 0	Month 3	Month 6	Month 9	Month 12
Arm 1	125	104	72	44	22
Arm 2 & Arm 3	252	213	145	99	52

Risk of death

Death rate per **100 person-years** (Arm 2&3 vs 1)

– 3 months 10 vs 41

– 3 to 6 months 4 vs 23

– 6 to 12 months 3 vs 9

Causes of Death

Variable	Arm 2 & 3	Arm 1	Total
Died at home/unknown	4	8	12 (40%)
Gastroenteritis	4	4	8
Pneumonia/sepsis	0	5	5
PCP /CMV	0	3	3
SIDS	1	0	1
Liver failure	1	0	1
Total	10	20	30

Disease progression in all patients

Variable	Arm 2 & 3 n = 252	Arm 1 n = 125	Total
Failure to thrive	18	19	37
Developmental delay	0	8	8
PCP	0	5	5
Oesophageal candidiasis	0	2	2
Extrapulmonary TB	1	1	1
CMV colitis	0	1	1
CMV pneumonia	0	2	2
CMV Hepatitis	0	1	1
Pneumococcal disease	0	2	2
Number Events	19	41	60
Number patients	19 (7.5%)	38 (30.4%)	57

Summary & Conclusions

- Starting ART before 12 weeks of age reduces early mortality by 75%
- Findings have implications for guidelines on timing of ART in early infancy
- Results support need for enhanced pMTCT programs, early infant diagnosis & effective transition to care

Programmatic issues

- Single policy easy to implement
- Majority infants need HAART in 1st year of life
- Easier to manage if low transmission rates
- Can implement without waiting for CD4 results
- ARV education should start antenatally & must be “fast-tracked when +ve PCR
- Mothers have many issues that need to be addressed
 - Own health
 - Disclosure
 - Infant feeding
 - TB exposure
 - Socio-economic

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