Global Challenges with Pediatric Formulations

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Outline

- Overview of HIV-infection in children
- Current treatment recommendations
- Challenges in pediatric formulations&dosing

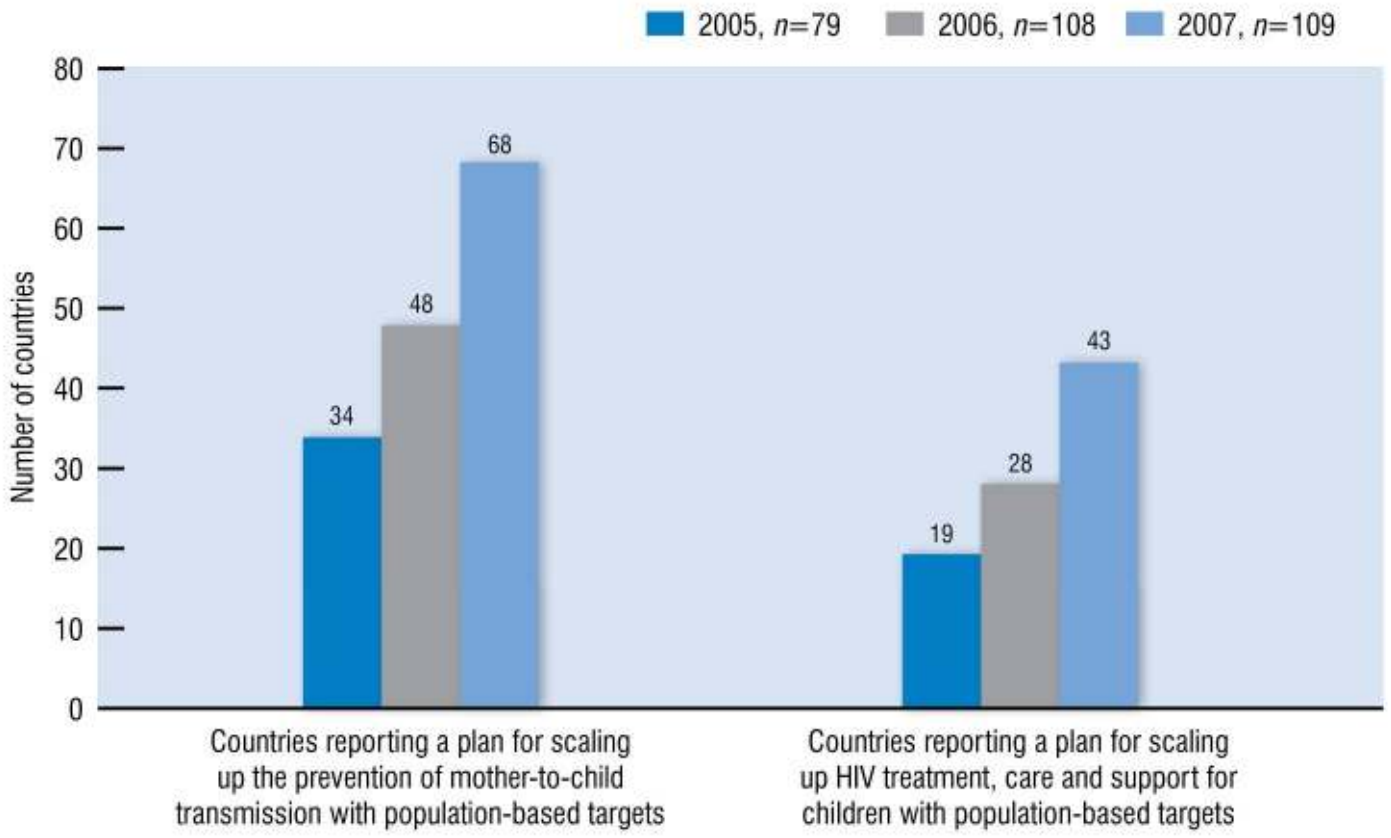
Two HIV Pediatric Epidemics

- High-resource countries
  - New perinatal infections are rare
  - Effective treatment available
  - Aging cohort of infected children
  - Concerns long-term complications of treatment
- Low-resource countries
  - 1,000 infants are newly infected each day
  - Diagnosis of infection in infants problematic
  - Problems with drug access
  - Treatment when available is started late

WHO/UNAIDS/UNICEF Estimates, 2007

- 2.1 million (1.9-2.4 million) children <15 yrs living with HIV
  - 90% living in sub-Saharan Africa
  - 6% of all HIV infections
  - 14% of all HIV-related mortality
- 420,000 new infections and 290,000 deaths
  - More than 90% infected through MTCT
  - Many of children who died never received an HIV diagnosis or entered into HIV care
- HIV is the leading cause of under-5 mortality in African countries with high HIV burden.

Number of countries with national scale-up plans and population-based targets for the prevention of mother-to-child transmission and HIV treatment, care and support for children, 2005–2007



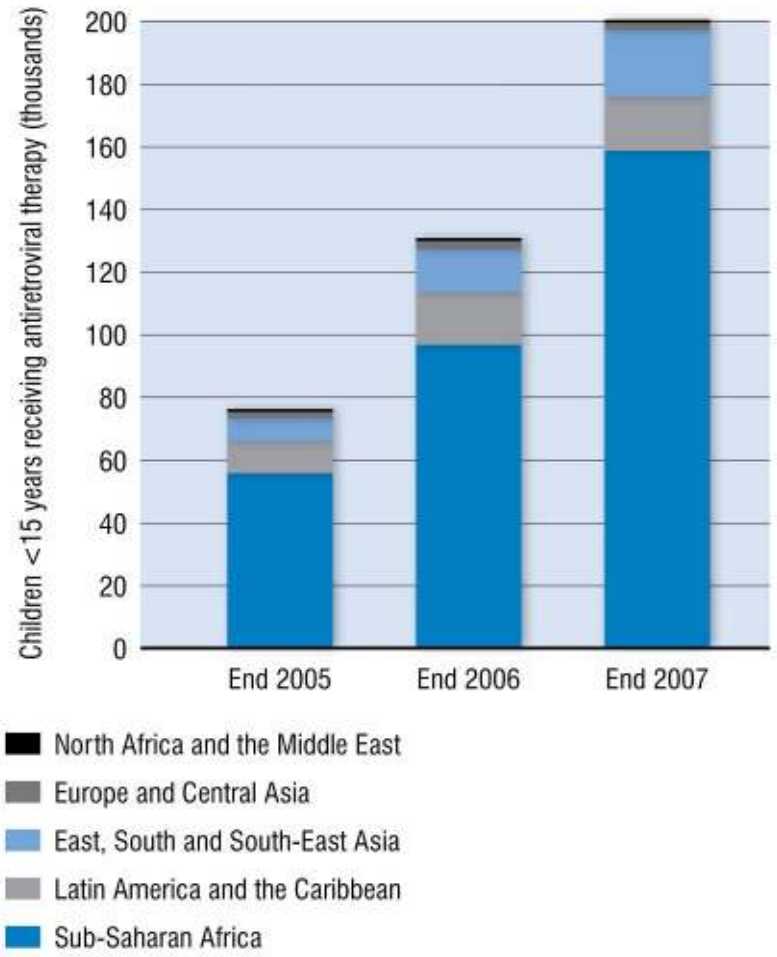
n: number of reporting countries

WHO/UNAIDS/UNICEF Progress Report 2008

Diagnosis of HIV infection in infants

- Essential to identify and ensure early initiation of care and treatment.
- In 2007, of the 715,000 infants born to women living with HIV in low and middle-income countries, only 8% were tested for HIV within 2 months of birth (WHO/UNAIDS/UNICEF Progress Report 2008)
- Most children are entering HIV care at older age, after becoming sick.

Number of children receiving antiretroviral therapy in low- and middle-income countries, 2005–2007



WHO/UNAIDS/UNICEF Progress Report 2008

Children in Resource-Limited Countries Respond to HAART as Well as Children in Resource-Rich Countries

	% RNA undetectable on HAART
Janssens/Cambodia 2007 **N=212**	**74% <400 (17 mos)**
George/Haiti 2007 **N=100**	**56% <50 (12 mos)**
Wamawala/Kenya 2007 **N=67**	**67% <400 (6 mos)**
Reddi/S Africa 2007 **N=151**	**80% <50 (12 mos)**
Puthanakit/Thailand 2007 **N=107**	**70% <50 (3.7 yrs)**
Kamya/Uganda 2007 **N=250**	**74% <400 (12 mos)**
Kekitiinwa/Uganda 2008 *Abs 584* **N=876**	**70% <400 (6 mos)**

L Mofenson, CROI 2008

However, Children in Low-Resource Countries Who Receive ART are Starting at Older Ages than High Resource Countries

	Baseline Median Age	% RNA undetectable on HAART
Janssens/Cambodia 2007 **N=212**	**6.0 yrs**	74% <400 (17 mos)
George/Haiti 2007 **N=100**	**6.3 yrs**	56% <50 (12 mos)
Wamawala/Kenya 2007 **N=67**	**4.4 yrs**	67% <400 (6 mos)
Reddi/S Africa 2007 **N=151**	**5.7 yrs**	80% <50 (12 mos)
Puthanakit/Thailand 2007 **N=107**	**7.7 yrs**	70% <50 (3.7 yrs)
Kamya/Uganda 2007 **N=250**	**9.2 yrs**	74% <400 (12 mos)
Kekitiinwa/Uganda 2008 ***Abs 584*** **N=876**	**7.6 yr**	70% <400 (6 mos)

L Mofenson, CROI 2008

Children in Low-Resource Countries Who Receive ART are Starting Treatment When Already Severely Immune Deficient

	Baseline Median Age	**Baseline Median CD4**	% RNA undetectable on HAART
Janssens/Cambodia 2007 **N=212**	6.0 yrs	**6%**	74% <400 (17 mos)
George/Haiti 2007 **N=100**	6.3 yrs	**12%**	56% <50 (12 mos)
Wamawala/Kenya 2007 **N=67**	4.4 yrs	**6%**	67% <400 (6 mos)
Reddi/S Africa 2007 **N=151**	5.7 yrs	**8%**	80% <50 (12 mos)
Puthanakit/Thailand 2007 **N=107**	7.7 yrs	**5%**	70% <50 (3.7 yrs)
Kamya/Uganda 2007 **N=250**	9.2 yrs	**8.6%**	74% <400 (12 mos)
Kekitiinwa/Uganda 2008 ***Abs 584*** **N=876**	7.6 yr	**8%**	70% <400 (6 mos)

L Mofenson, CROI 2008

Delay in Start ART Until Immune Deficient Results in Excess Mortality, Most in 1st 6 Mos Treatment

Arrive E et al. 14th CROI, Los Angeles, CA, 2007 Abs. 727

Months from ART start	Probability of Death After Starting ART	
	Immune Deficient at Start ART	**Not Immune Deficient at Start ART**
6 months	7.8%	1.8%
12 months	8.2%	2.2%

6% excess mortality

0.4% after 6 mos

0.4% after 6 mos

Meta-analysis 1,195 children from 8 African clinical trials.

- **53% >5 years of age, 66% severe age-related immune deficiency**
- **ARV: NNRTI-based 58%, PI-based 37%**

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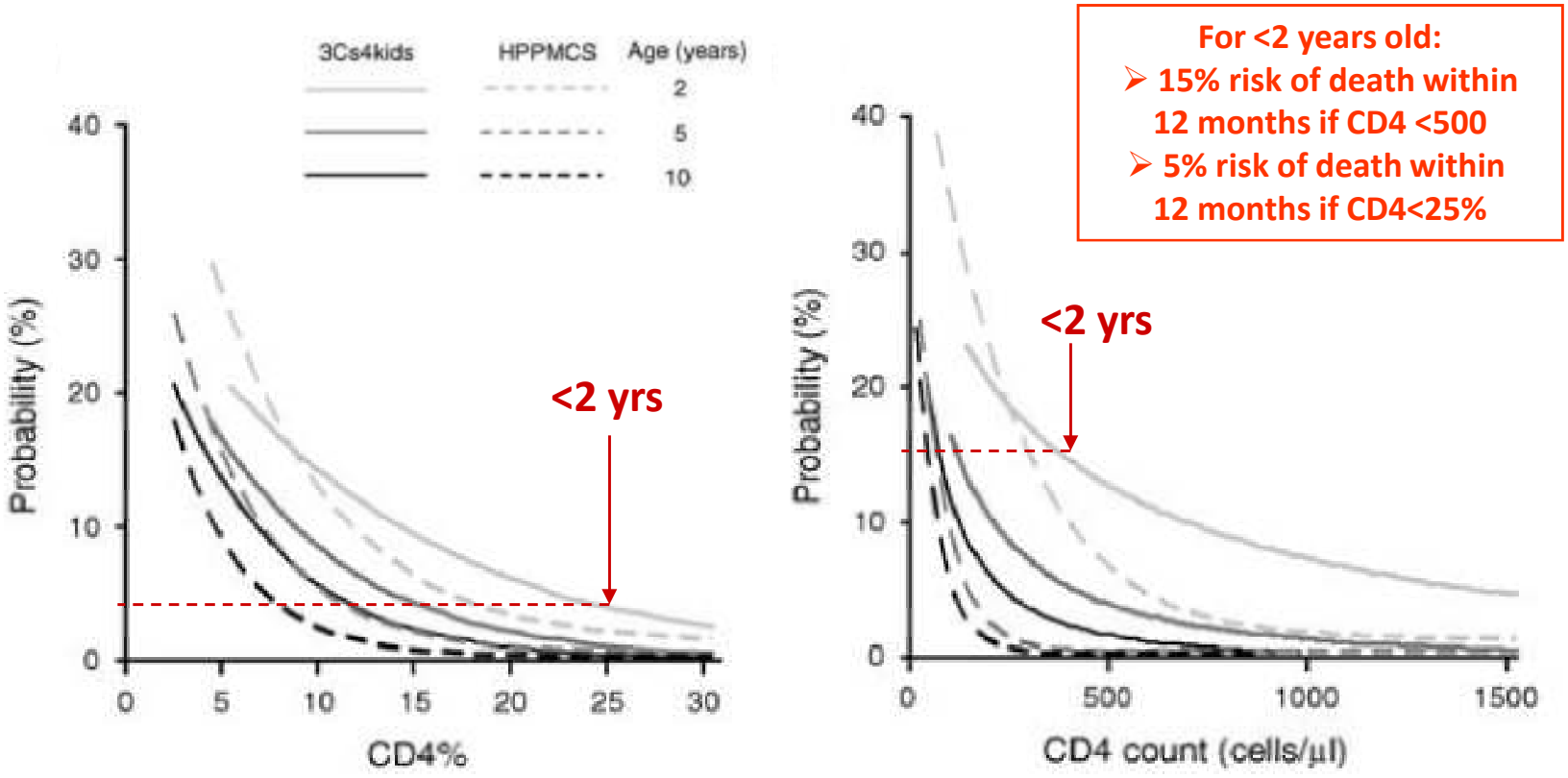
HIV+ Children <2 Years Have High Risk of Mortality Even at High CD4%/Count in Both Developed (HPPMCS) and Developing (3Cs4Kids) Countries

3Cs4Kids Collaboration. AIDS 2008;22:97-105

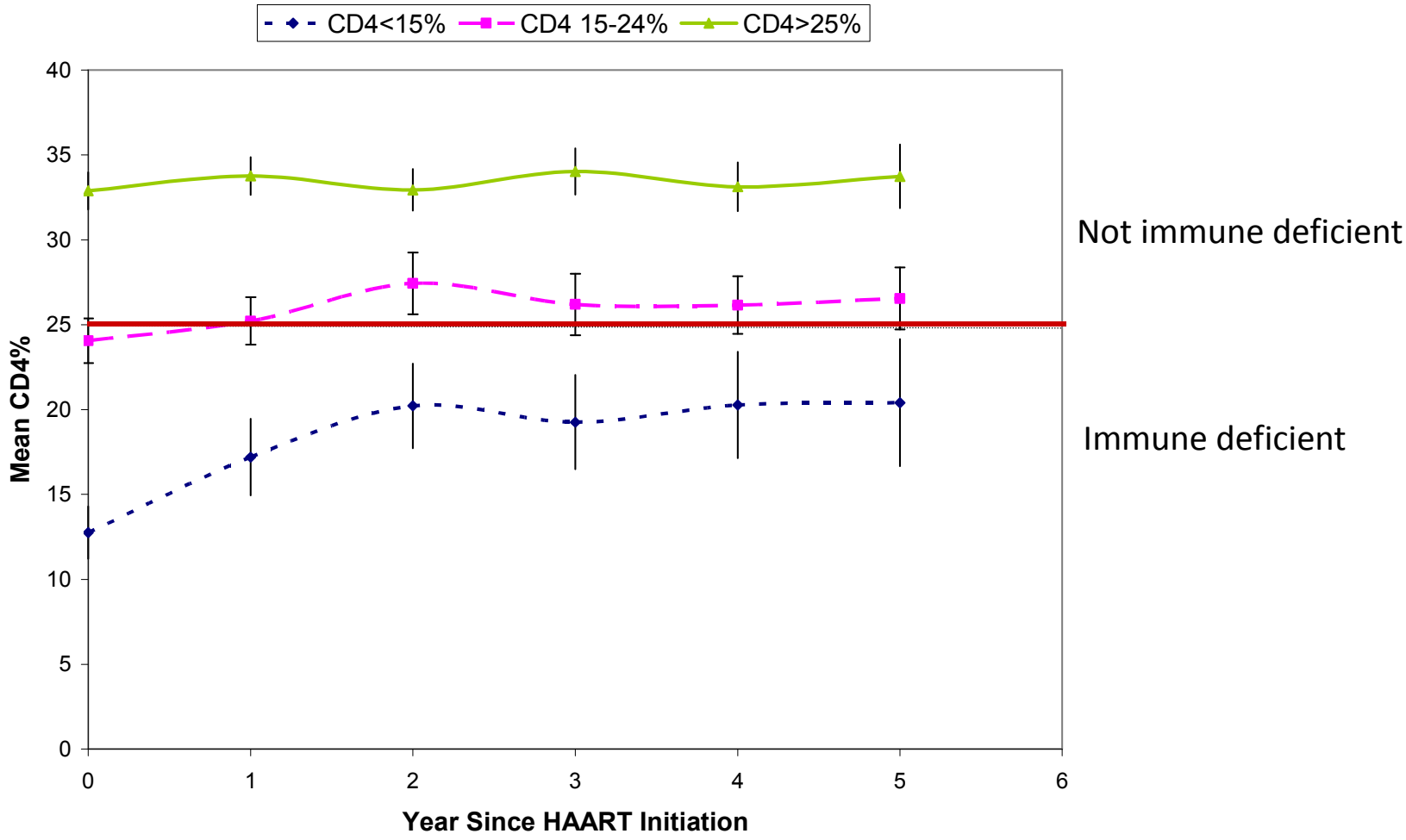


For <2 years old:
- **15% risk of death within 12 months if CD4 <500**
- **5% risk of death within 12 months if CD4<25%**

Estimated Probability of Death by Age and CD4% / Count in HIV+ Children in HPPMCS (US, Europe) vs 3Cs4Kids (Brazil, Africa)

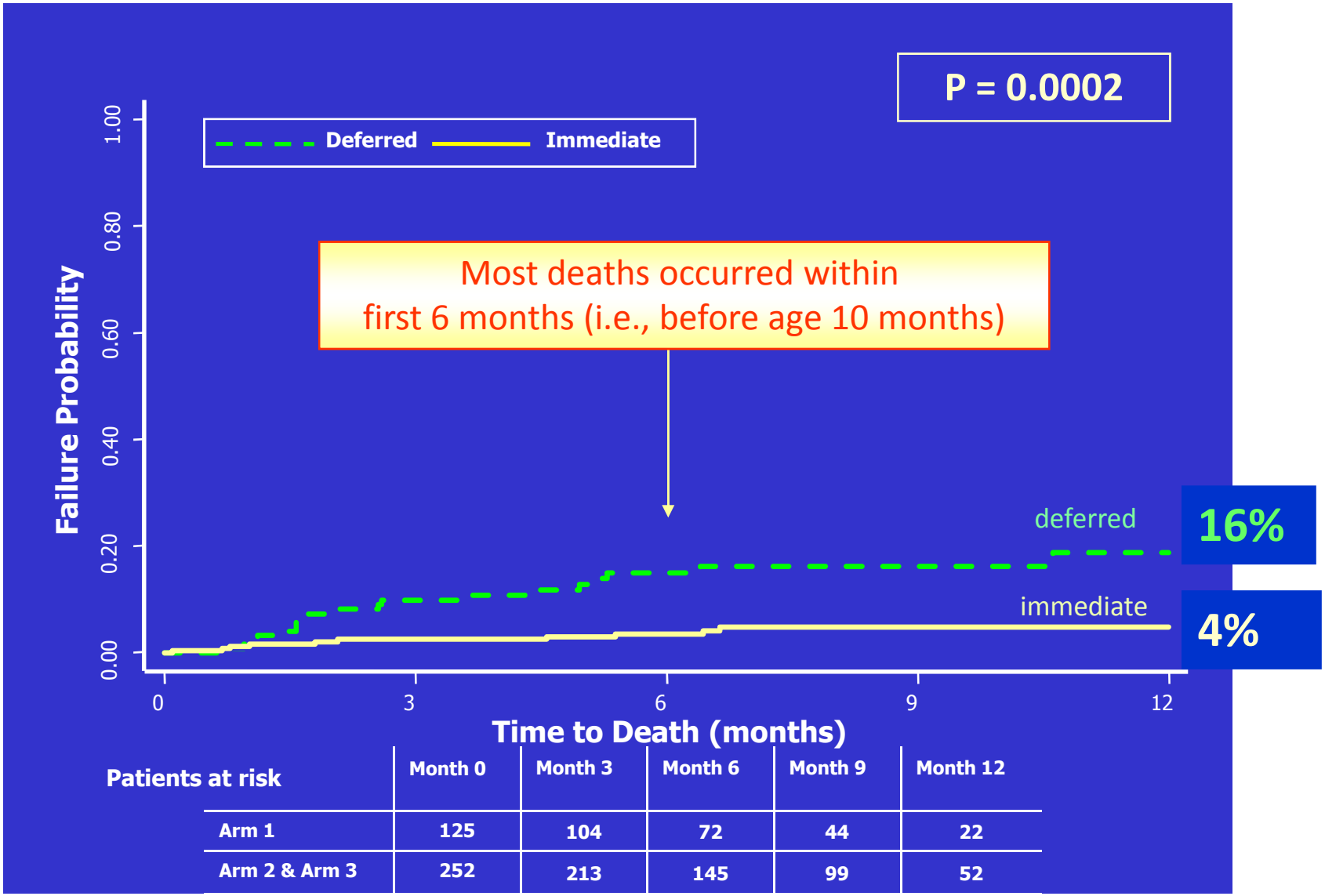
Recovery of Immune Status with HAART is Dependent on CD4% at Time HAART is Initiated

Patel K et al. Clin Infect Dis 2008



1,236 children enrolled in PACTG 219 not on HAART at study initiation

CHER: 76% Reduction in the Risk of Death with Immediate (Arms 2 & 3) Compared to Deferred (Arm 1) HAART



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

2008 Revised US Guidelines (29/Jul/08): Initiation of HAART is Recommended

Age	Criteria
<12 months	Regardless of symptoms, CD4, RNA
1 - <5 years	AIDS or significant HIV-related symptoms[1] *or* CD4 <25%
≥5 years	AIDS or significant HIV-related symptoms[1] *or* CD4 <350 cells/mm^3

[1] Significant symptoms: AIDS or CDC Class B conditions except LIP and single episode of bacterial pneumonia

WHO Antiretroviral Therapy for Infants and Children 2008—Criteria to Start ARV

(WHO, April 2008; available in http://www.who.int/hiv/paediatric/en/)

Age	<12 mos	12-35 mos	36-59 mos	>5 yrs
%CD4	All	<20	<20	<15
Absolute CD4		<750	<350	As in adults <200

What to start with?

NNRTI-based

2 NRTI + 1 NNRTI

NNRTI: ≤3 years: nevirapine (>300 mg/m^2)

>3 years: efavirenz

PI-based*

2 NRTI + 1 PI

PI: LPV/r

* WHO Guidelines: LPV/r if NVP-exposed for PMTCT, April 08

US Guidelines for the Use of ARV Agents in Pediatric HIV-infection, July 08

Update PENTA Guidelines 2007

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Ideal HIV Therapy for Children

Regimen:

- Durable and potent antiviral activity, with high threshold to development resistance esp. after MTCT ARV
- Minimal toxicity and drug-drug interactions
- Co-formulated or co-packaged
- Once or max twice daily dosing

Dosing forms:

- Sprinkable, granular crushable or dispersible solid forms
- No food restrictions
- Acceptable taste or masking
- Cheap
- Easy to store & no requirement for refrigeration
- Long shelf life at room temp

ICASA, Abuja 2005

Antiretroviral Drugs Approved in Adults

but Not Yet Approved in Children

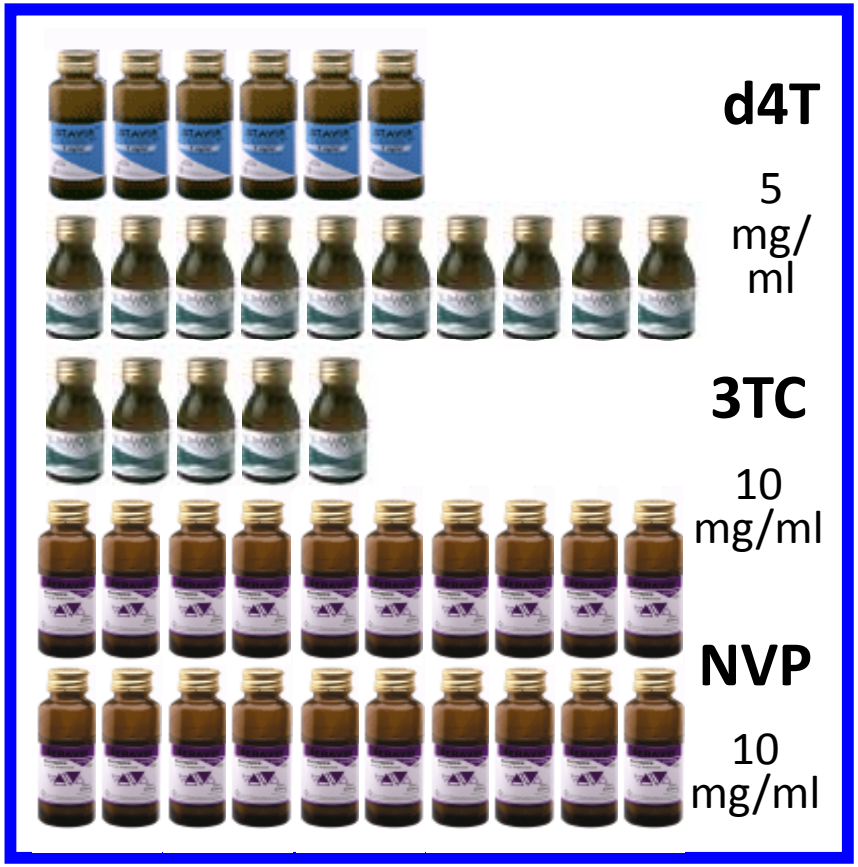
N(t)RTI	NNRTI	Protease Inhibitors	Entry/Fusion Inhibitors	Integrase Inhibitors
Abacavir	Efavirenz	Atazanavir	Enfurvirtide	Raltegravir
Didanosine	Nevirapine	Darunavir	Maraviroc	
Emtricitabine	Etravirine	Fosamprenavir		
Lamivudine		Indinavir		
Stavudine		Lopinavir/rtv		
Tenofovir		Nelfinavir		
		Ritonavir		
		Saquinavir		
		Tipranavir		

Challenges in Treatment of HIV-Infected Children in Low Resource Settings

- Pediatric formulations
  - Fewer ARV approved in children
  - More costly than adult preparations
  - FDC just becoming available
- Dosing weight/size based, change as child grows, problems for busy health clinic.
- Liquid drugs transport/storage problems.
- Complexity of therapy in context multiple co-morbidities (TB, malaria, malnutrition…)

What is available for Children?

Liquid formulations



Problems with storage, transportation, adherence

Splitting adult formulations

Risks of toxicity and resistance

Co-formulated pediatric solid preparations

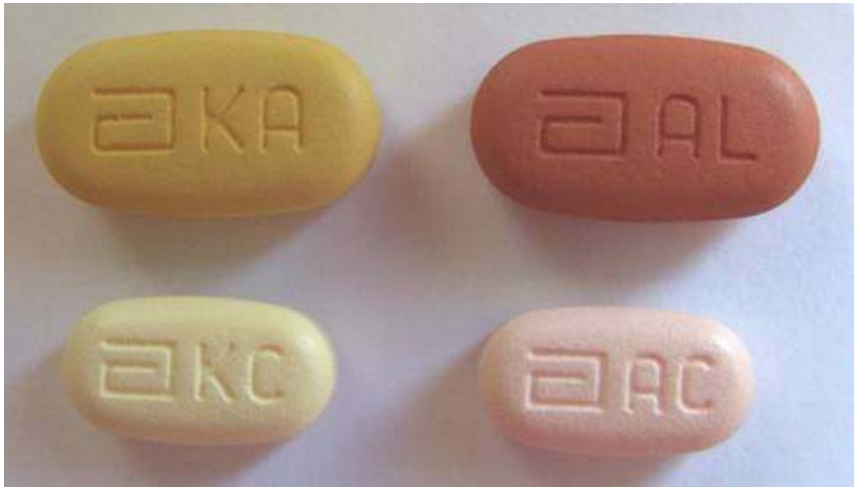
Scored crushable FDCs

CIPLA

D4T	30/40 mg	12 mg	6 mg
3TC	150 mg	60 mg	30 mg
NVP	200 mg	100 mg	50 mg
Ratio	1:5:6.6	1:5:8.3	

RANBAXY

LPV/r 100/25 mg, heat-stable tablet



WHO weight band dosing table

Drug	Strength of tab (mg) or liquid mg/ml	Number of tablets or ml by weight band (twice daily)													Strength of adult tab (mg)	Number of tablets by weight band (twice daily)	
		Children 6 weeks of age and above (0.75 BD is delivered as 1 tablet AM and 0.5 tablets PM and 1.5 BD is delivered as 2 tablets AM and 1 tablet PM)															
		3-3.9 kg	4-4.9 kg	5-5.9 kg	6-6.9 kg	7-7.9 kg	8-8.9 kg	9-9.9 kg	10-10.9 kg	11-11.9 kg	12-13.9 kg	14-16.9 kg	17-19.9 kg	20-24.9 kg		25-29.9 kg	30-34.9 kg
AZT	60	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300	1	1
AZT (new annex E)	300; 10 mg/ml	6 ml	6 ml	6 ml	9 ml	9 ml	9 ml	9 ml	12 ml	12 ml	12 ml	0.5	0.5	0.75	300	1	1
AZT/3TC	60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150/200	1	1
ABC	60	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300	1	1
ABC (new annex E)	300; 20 mg/ml	3 ml	3 ml	3 ml	4 ml	4 ml	4 ml	4 ml	6 ml	6 ml	6 ml	0.5	0.5	0.75	300	1	1
ABC/3TC	60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150	1	1
ABC/3TC/NVP	60/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150/200	1	1
ABC/AZT/3TC	60/60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/300/150	1	1
3TC	30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	150	1	1
3TC (new annex E)	150; 10 mg/ml	3 ml	3 ml	3 ml	4 ml	4 ml	4 ml	4 ml	6 ml	6 ml	6 ml	0.5	0.5	0.75	150	1	1
d4T	6	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30	1	1
d4T (new annex E)	various; 1 mg/ml	6 ml	6 ml	6 ml	9 ml	9 ml	9 ml	9 ml	1x15 mg	1x15 mg	1x15 mg	1x20 mg	1x20 mg	1x20 mg	30	1	1
d4T/3TC	6/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30/150	1	1
d4T/3TC/NVP	6/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30/150/200	1	1
NVP	50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	200	1	1
NVP (new annex E)	200; 10 mg/ml	5 ml	5 ml	5 ml	8 ml	8 ml	8 ml	8 ml	10 ml	10ml	10 ml	0.75	0.75	0.75	200	1	1
Lopinavir/ritonavir	100/25	n/r	n/r	n/r	n/r	n/r	n/r	n/r	1.5	1.5	1.5	2	2	2.5	100/25 * (paed)	3	3
Lop/rit (new annex E)	80/20 mg/ml	1 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	2 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	80/20 mg/ml	3.5 ml	4 ml

* 3 tablets BD of 100/25 may be substituted with 2 tablets am and 1 tablet pm of 200/50

Note: higher doses of Lop/rit may be required when co-administered with enzyme-inducing drugs such as NVP, EFV; fosamprenavir, rifampicin.

- Promote a standardized ARV treatment applicable in LRS
- Simplification of drug delivery
- Reduction of prescription errors

Summary

- Despite significant progress in treatment scale up, many children living with HIV are still not receiving treatment, and mortality among them remains high.
- Early diagnosis is critical to ensure timely initiation of treatment and care.
- Treatment when available is started late.
- Treat all children below 12 mos.
- Pediatric formulations of the currently available ARVs and development of more co-formulated preparations are urgently needed.