



Challenges in Pediatric and Adolescent HIV Care

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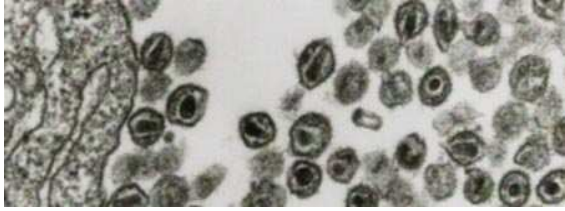




Implications of Perinatally-Acquired HIV Infection

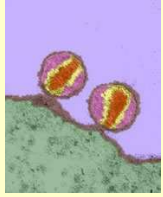


- Infection in children is acquired primarily through mother to child transmission, with primary infection around birth.
- Infection occurs in an immature immune system but with an active thymus. Implications:
 - Immune reconstitution may be better in younger children
 - However, high viral load may make control more difficult
 - Disease progression faster in children



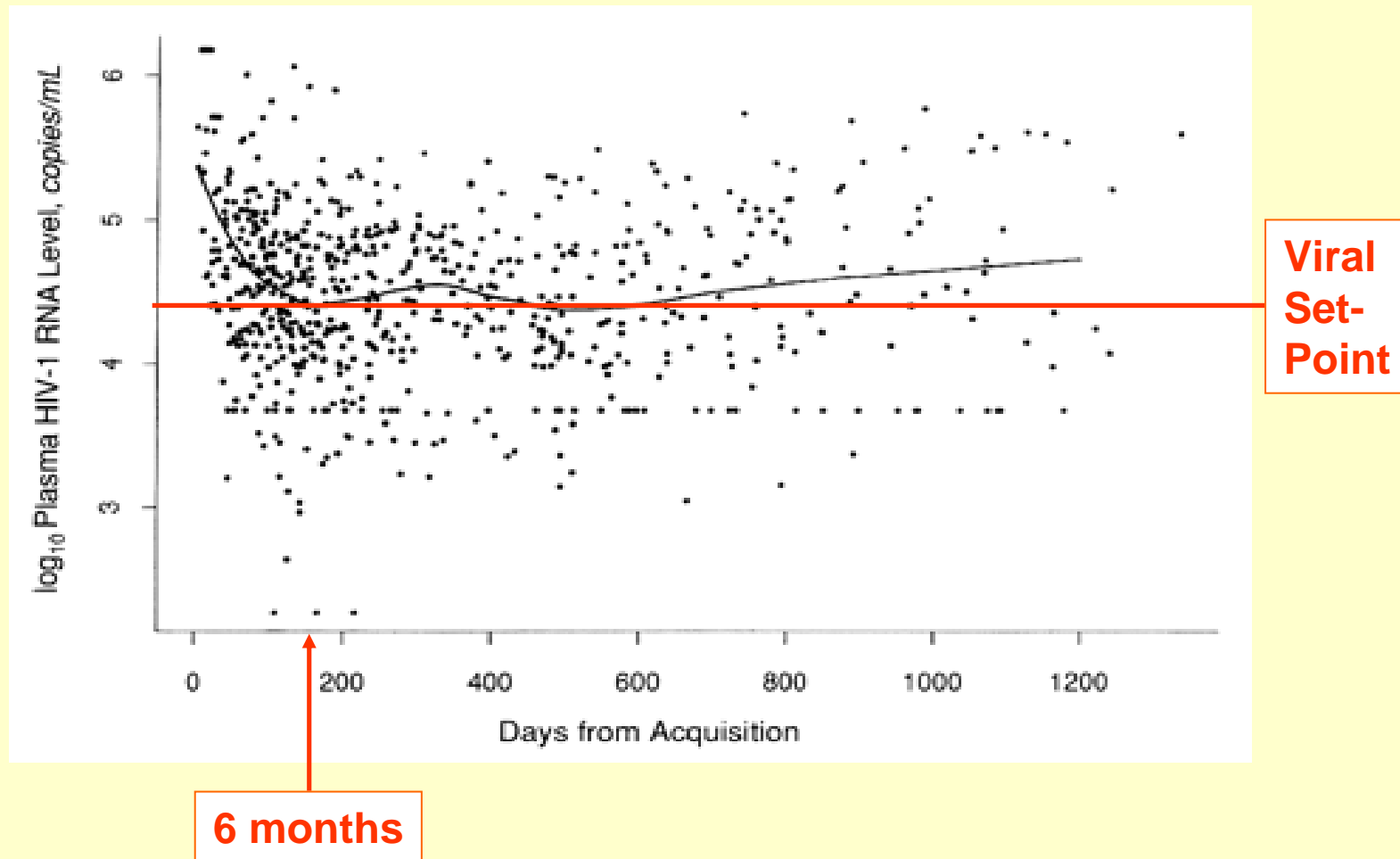
“Natural History” of Viral Load in Children Differs from Adults

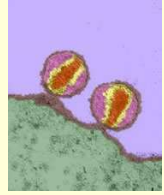
- **Generally low levels at birth (unless *in utero* infection), rise to several million copies/mL within the first months of life.**
- **Without treatment, very slow decline over several years before reach “set point”.**
- **“Set point” in children may be higher than in adults.**



Adult HIV Infection: Initial Viral Burst followed by Decrease to “Set Point” by 6-9 Months After Infection

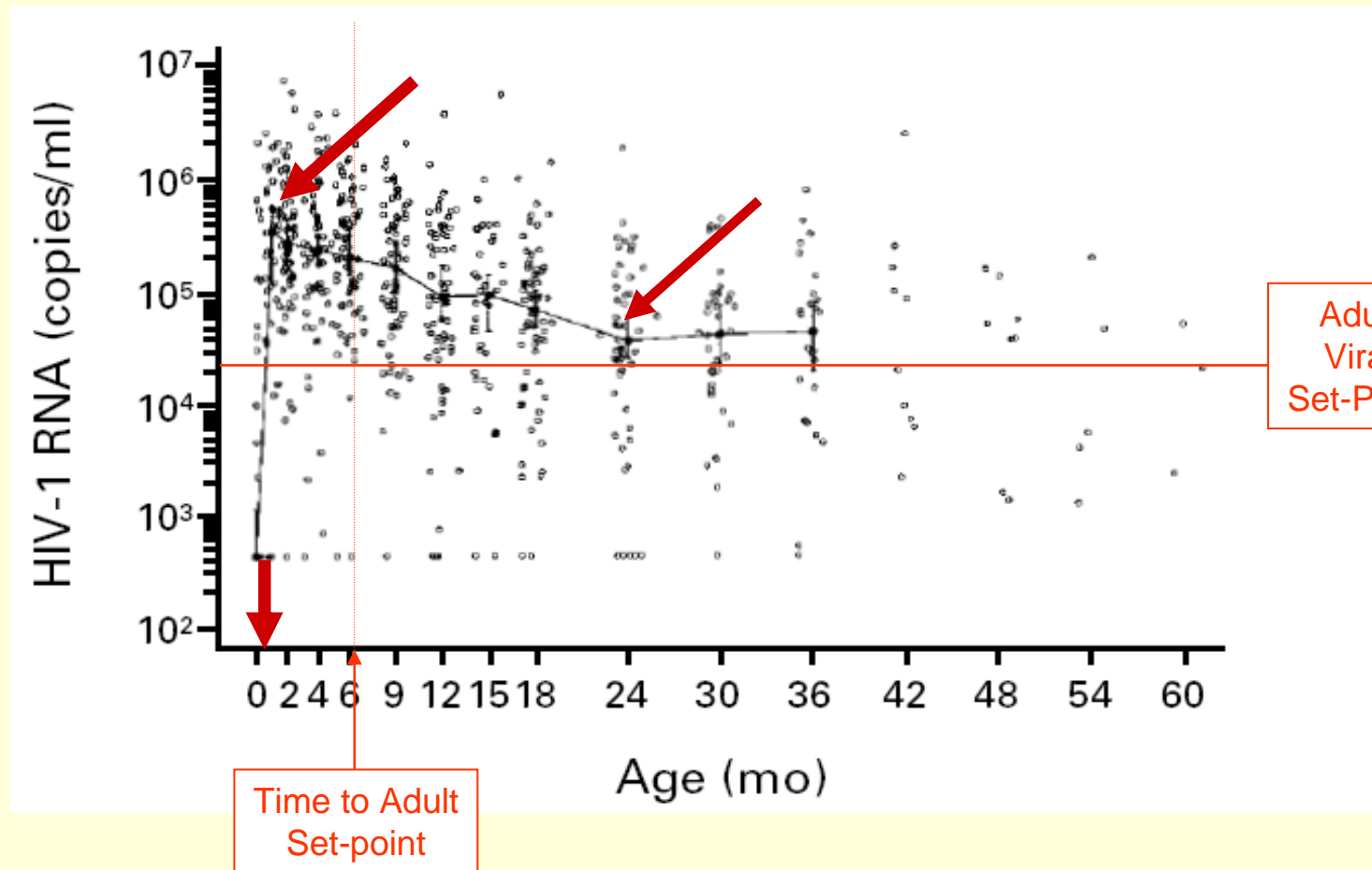
Schacker TW et al. Ann Int Med 1998;128:613-20





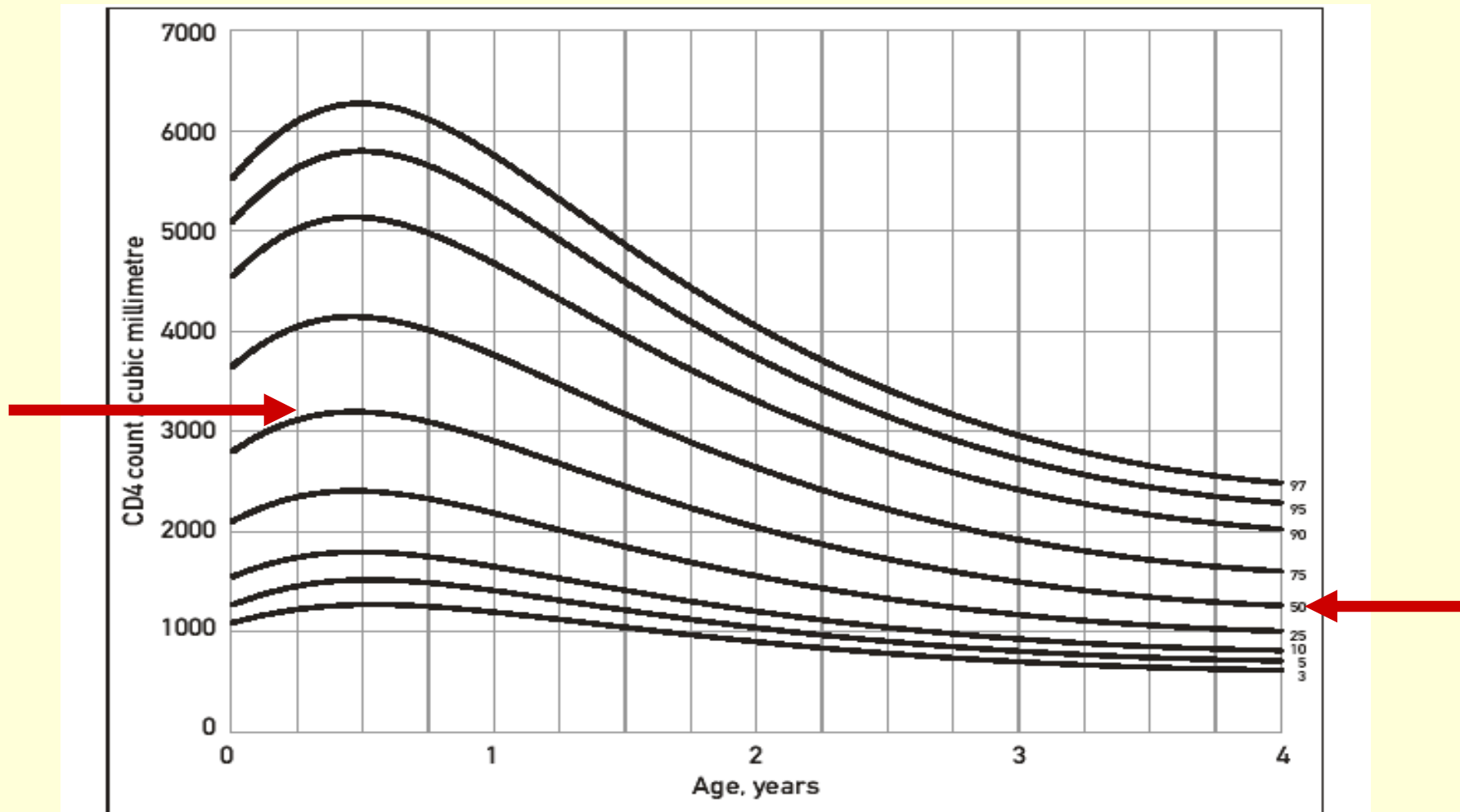
HIV RNA Levels Are High in Children with Perinatal Infection and Decrease to “Set Point” Slowly in Untreated Infants Over First Two Years of Life

Shearer WT et al. NEJM 1997;336:1337-42



Normal CD4 Count in Uninfected Children is Higher than in Adults and Slowly Decline to Adult Value by Age 5 Years

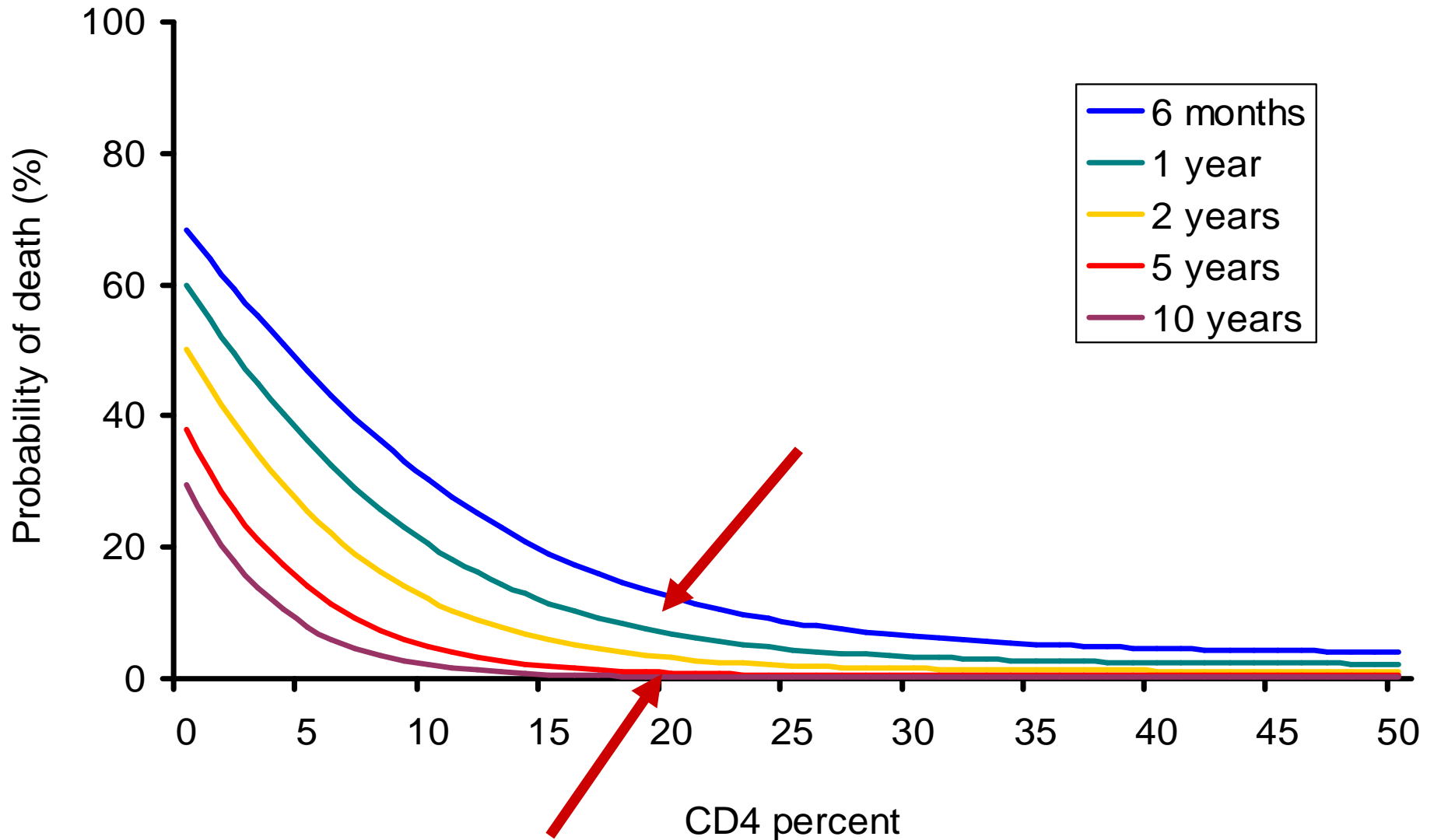
(ECS PIDJ, 1992, 11: 1018-1026, Shearer et al J All Clin Immunol 2003, 112: 973-980)

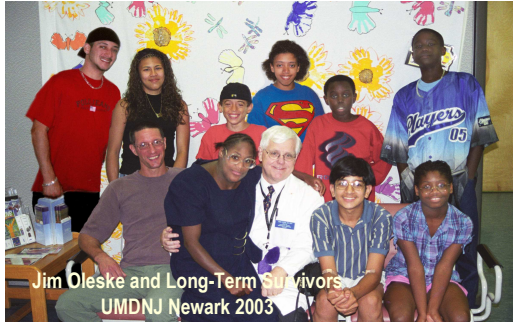


Pediatr Infect Dis J, 1992; 11: 1018-1026

Probability of Death in 12 Months by Age and CD4% in HIV-Infected Children on No Therapy or AZT Alone

HIV Pediatric Prognostic Marker Collaborative Study, Lancet 2003;362:1605-11





Courtesy Jim Oleske

Pediatric HIV Infection in the United States

- **With effective prevention of most new perinatal HIV infection, it is estimated that <250 newly infected infants are born annually in the U.S.**
- **Effective therapies for HIV in children have prolonged life and quality of life** (*Lee GM et al. Pediatrics 2006;117:273-83*).
- **The median age of over 3,500 HIV-infected children followed at pediatric clinical trials sites is 14.8 years** (*219 study summary July 23 2007*).



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

February 28, 2008

Developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children

François-Xavier Bagnoud Center, UMDNJ
The Health Resources and Services Administration
The National Institutes of Health

Use of antiretrovirals in pediatric patients is evolving rapidly. These guidelines are updated regularly to provide current information. The most recent information is available at <http://AIDSinfo.nih.gov>.



Guidelines available: <http://AIDSinfo.nih.gov>



2008 Revised US Pediatric ARV Guidelines

Initiation of HAART is Recommended



Age	Criteria
<12 months	<u>Regardless</u> 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



Why Initiate Treatment In All Infants Age <12 Months?

- Youngest children are at **greatest risk of rapid disease progression and death.**
- However, clinical & laboratory markers (CD4, RNA) are **poor indicators of risk for rapid progression in such infants.**
- **Therefore, more aggressive treatment may be considered.**
- However, limited data on efficacy of early treatment of asymptomatic infants and limited drug formulary for young infants.



Small Number of Observational Studies of Early HAART at Age <3-12 Months

Study	N	Age Start HAART
Belgium <i>Van der Linden PIDJ 2007</i>	17	<2.5 mos
PACTG 356 <i>Luzuriaga NEJM 2004</i>	25	<3 mos (median 2 mos)
PENTA 7 <i>PENTA AIDS 2004</i>	20	<5 mos (median 2.5 mos)
Italian Register <i>Chiappini AIDS 2006</i>	30	<6 mos (median 3.6 mos)
PACTG 1030 <i>Chadwick AIDS 2008</i>	21	<6 mos (median 3.7 mos)
French Perinatal <i>Faye PIDJ 2002</i>	31	<12 mos (median 3.7 mos)



Studies Early HAART at Age <3-12 Months Show Viral Suppression in 18%-73%

Study	N	Age Start HAART	Viral Response
Belgium <i>Van der Linden PIDJ 2007</i>	17	<2.5 mos	<50, 71% at 4.7 yrs
PACTG 356 <i>Luzuriaga NEJM 2004</i>	25	<3 mos (median 2 mos)	<400, 60% at 4 yrs
PENTA 7 <i>PENTA AIDS 2004</i>	20	<5 mos (median 2.5 mos)	<400, 44% at 1.5 yrs
Italian Register <i>Chiappini AIDS 2006</i>	30	<6 mos (median 3.6 mos)	Undetect 73% at 4 yrs
PACTG 1030 <i>Chadwick AIDS 2008</i>	21	<6 mos (median 3.7 mos)	<400, 53% at 6 mos
French Perinatal <i>Faye PIDJ 2002</i>	31	<12 mos (median 3.7 mos)	<500, 18% at 2 yrs



Early HAART at Age <3-12 Months is Associated with No AIDS Progression and Maintenance of Immune Reconstitution

Study	N	Age Start HAART	Viral Response	Other
Belgium <i>Van der Linden PIDJ 2007</i>	17	<2.5 mos	<50, 71% at 4.7 yrs	<ul style="list-style-type: none"> • No AIDS • 82% CD4 >25%
PACTG 356 <i>Luzuriaga NEJM 2004</i>	25	<3 mos (median 2 mos)	<400, 60% at 4 yrs	<ul style="list-style-type: none"> • No AIDS, 4 yr
PENTA 7 <i>PENTA AIDS 2004</i>	20	<5 mos (median 2.5 mos)	<400, 44% at 1.5 yrs	<ul style="list-style-type: none"> • No AIDS, 1.5 yr • 90% CD4 >25%
Italian Register <i>Chiappini AIDS 2006</i>	30	<6 mos (median 3.6 mos)	Undetect 73% at 4 yrs	<ul style="list-style-type: none"> • No AIDS, 4 yr • 97% CD4 >25%
PACTG 1030 <i>Chadwick AIDS 2008</i>	21	<6 mos (median 3.7 mos)	<400, 53% at 6 mos	
French Perinatal <i>Faye PIDJ 2002</i>	31	<12 mos (median 3.7 mos)	<500, 18% at 2 yrs	<ul style="list-style-type: none"> • No AIDS, 2 yr • 88% CD4 >25%

CHER Schema

HIV infection diagnosed before age 12 weeks and CD4 \geq 25%
(All get CTX and pneumococcal vaccine)

CHER Schema

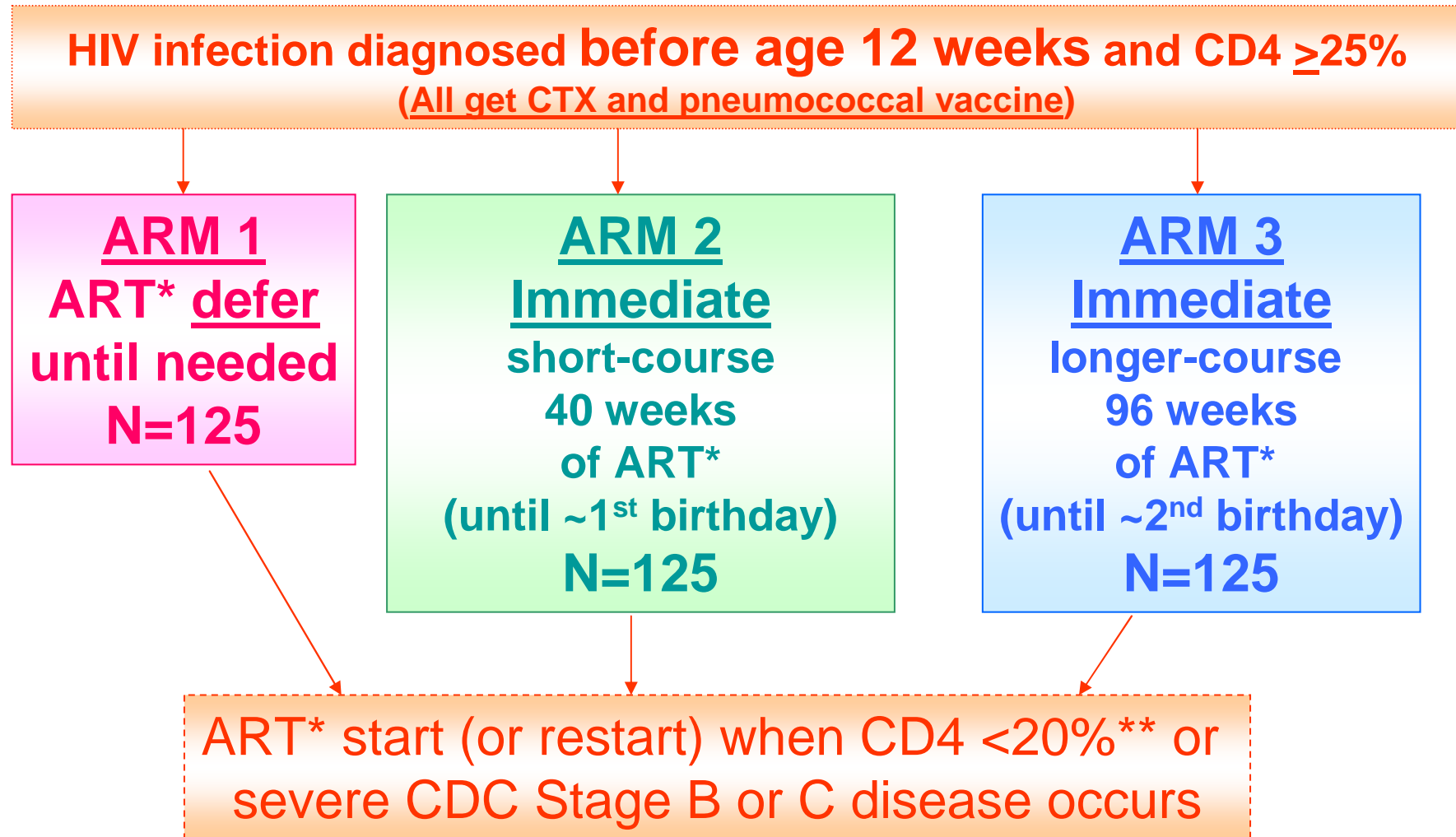
HIV infection diagnosed before age 12 weeks and CD4 \geq 25%
(All get CTX and pneumococcal vaccine)

ARM 2
Immediate
short-course
40 weeks
of ART*
(until ~1st birthday)
N=125

ARM 3
Immediate
longer-course
96 weeks
of ART*
(until ~2nd birthday)
N=125

*ART = AZT/3TC/LPV/r

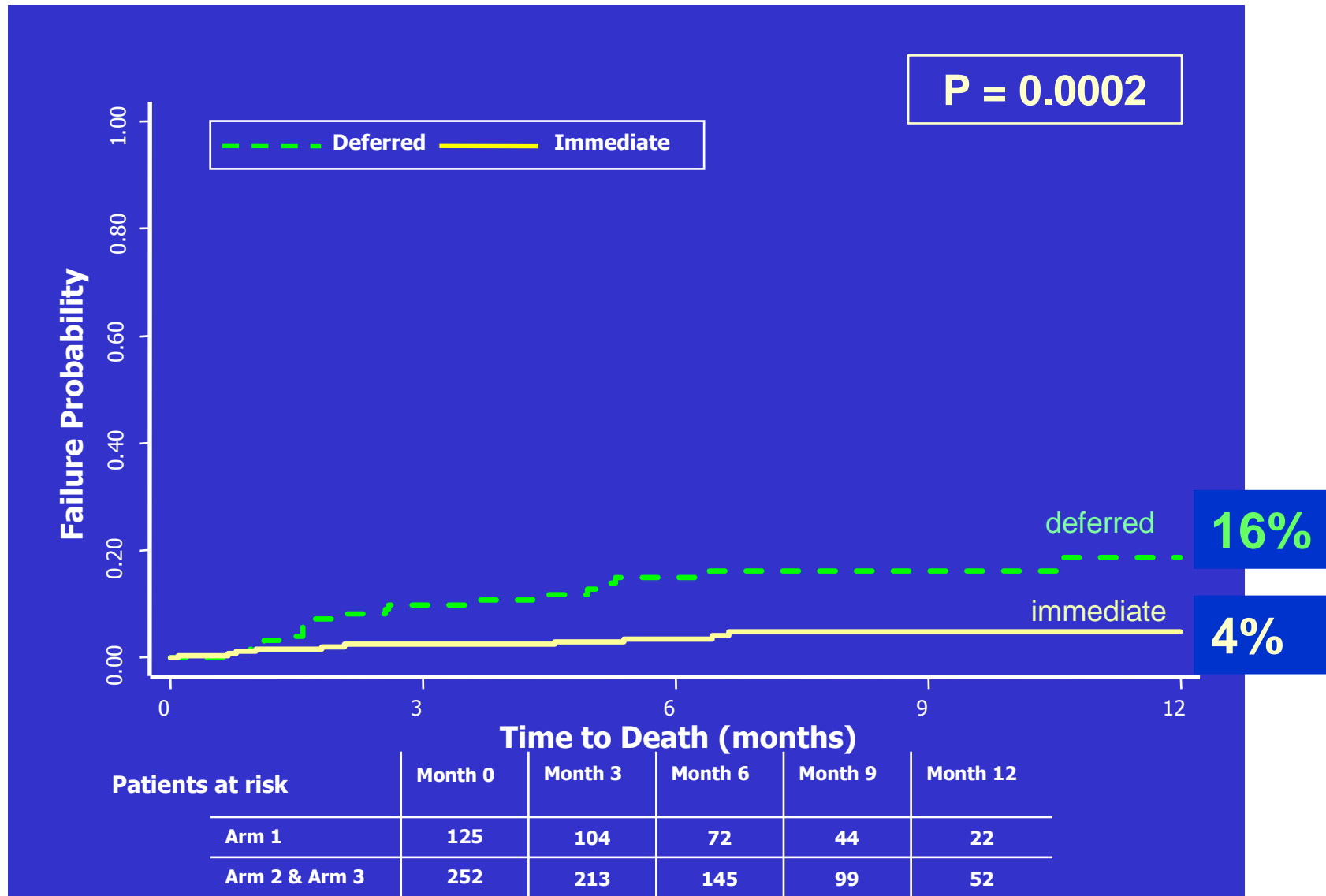
CHER Schema



*ART = AZT/3TC/LPV/r

**August 2006 changed to <25%

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

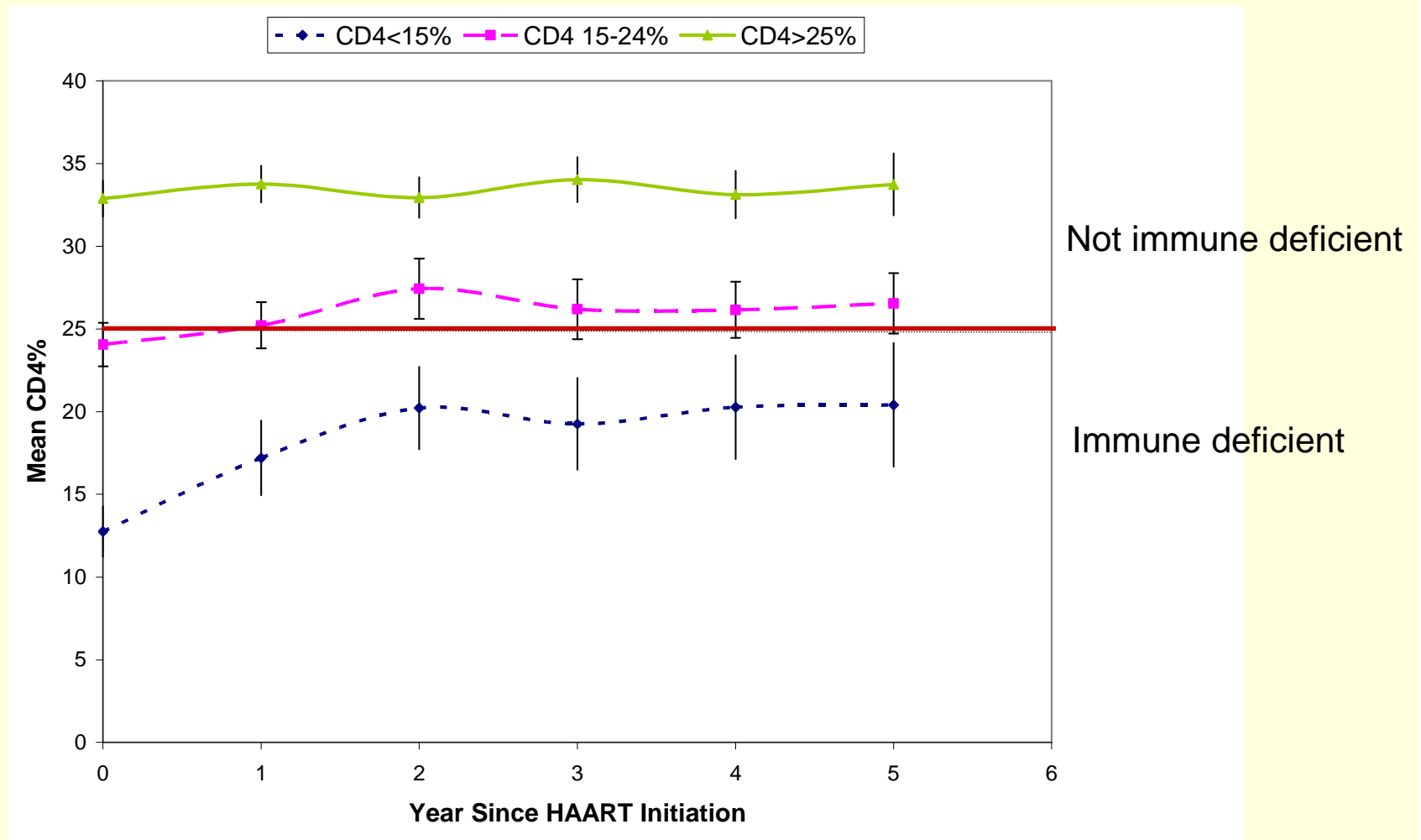


CHER: 76% Reduction in the Risk of Death with Immediate (Arms 2 & 3) Compared to Deferred (Arm 1) HAART



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

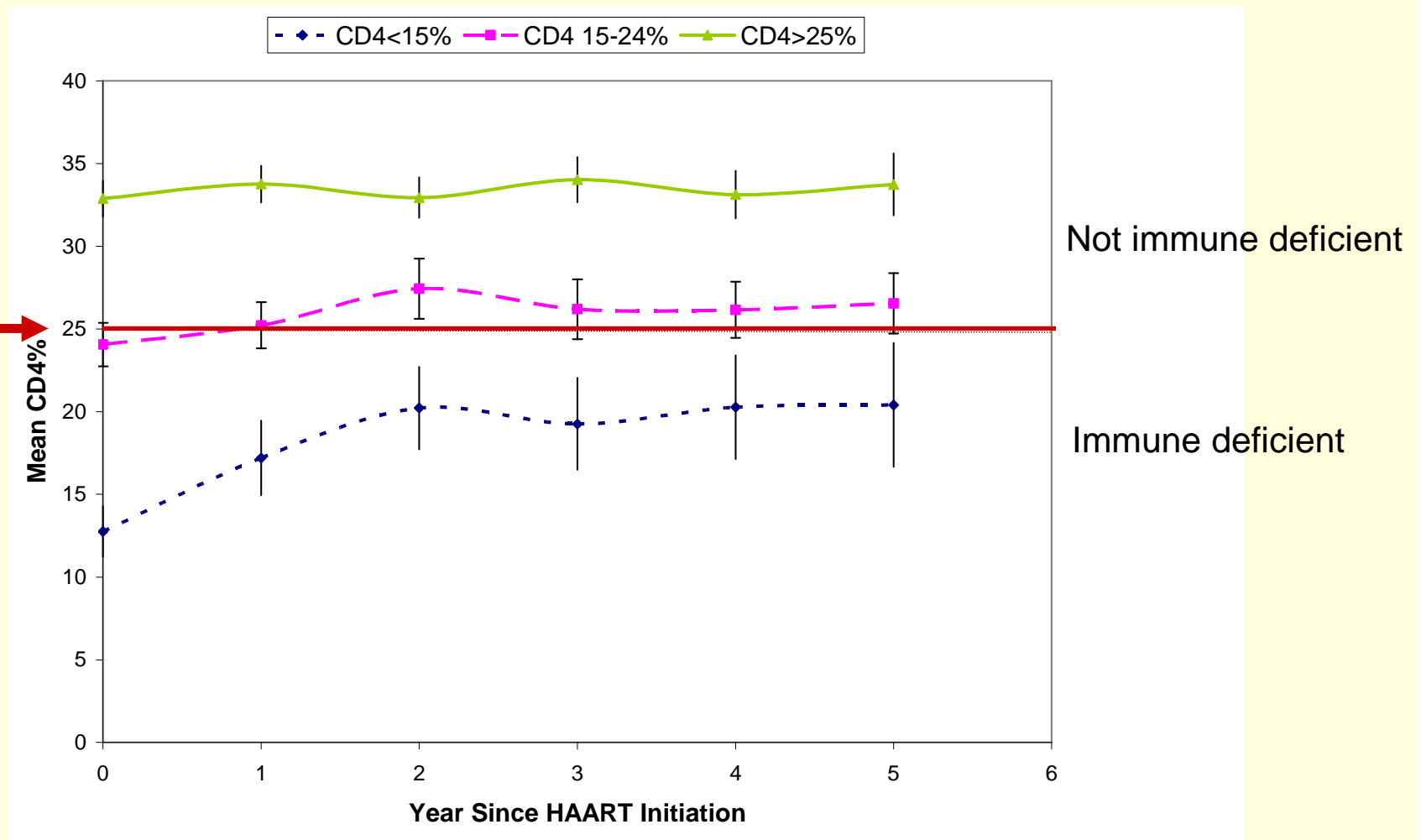
Patel K et al. Clin Infect Dis 2008 (in press)



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

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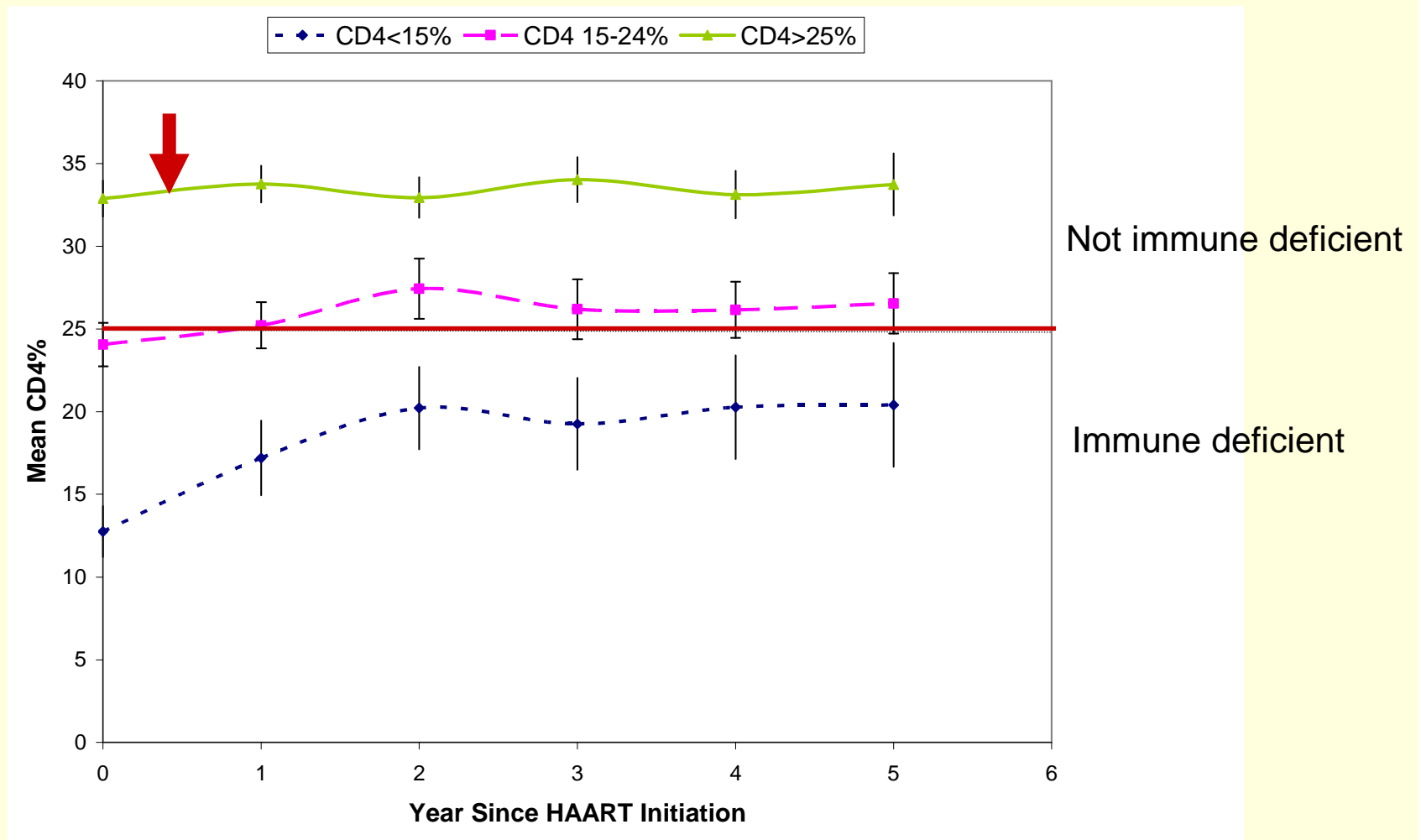
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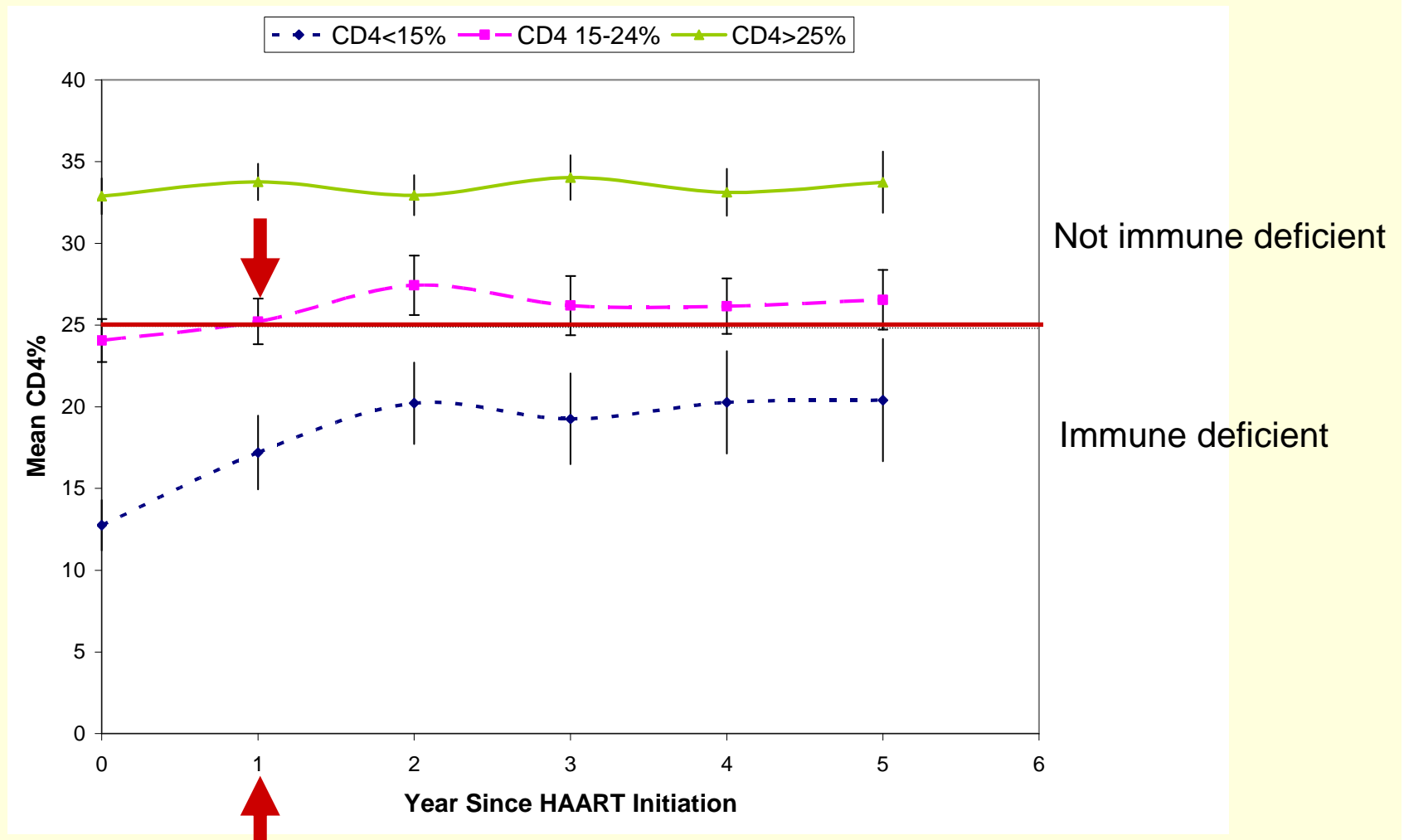
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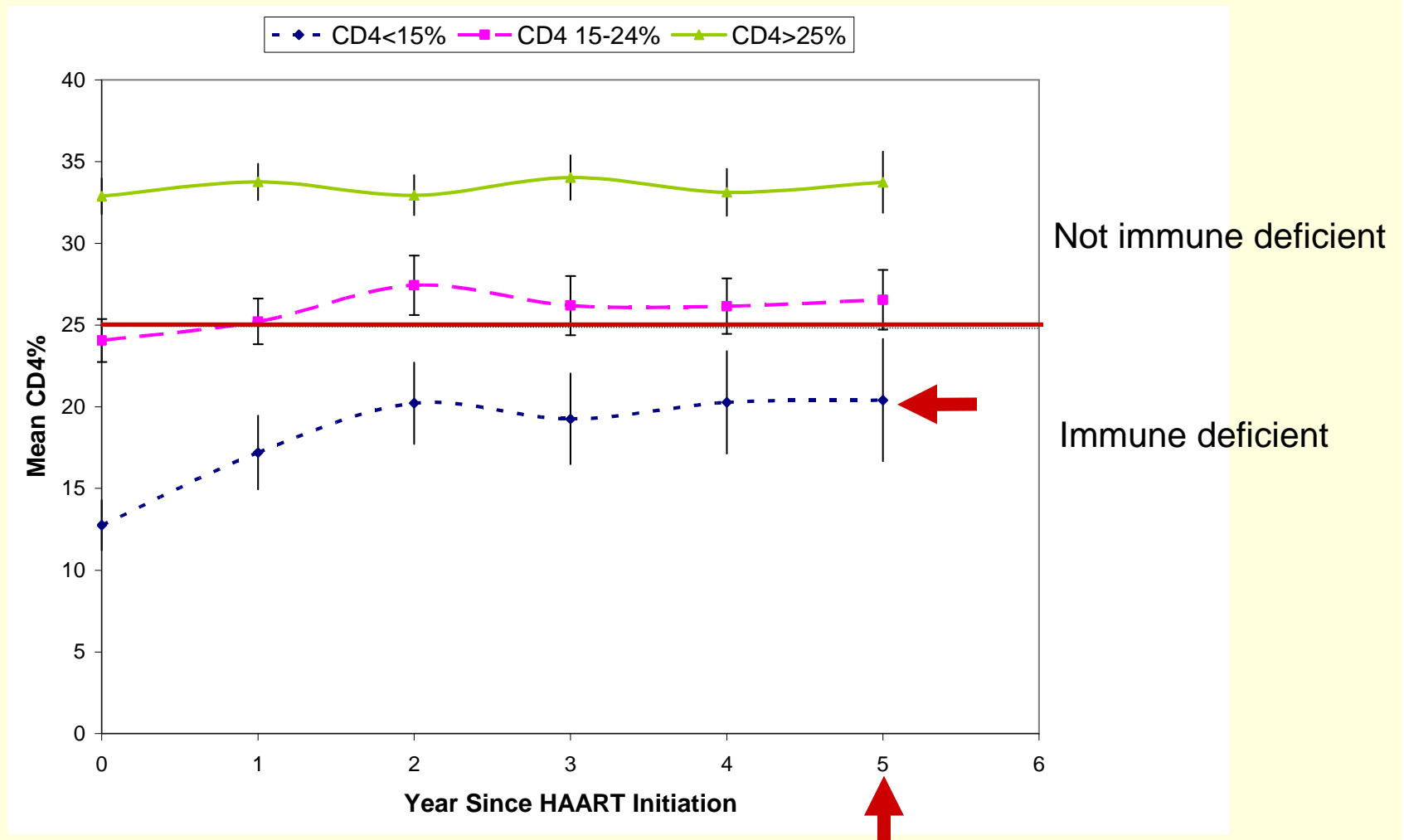
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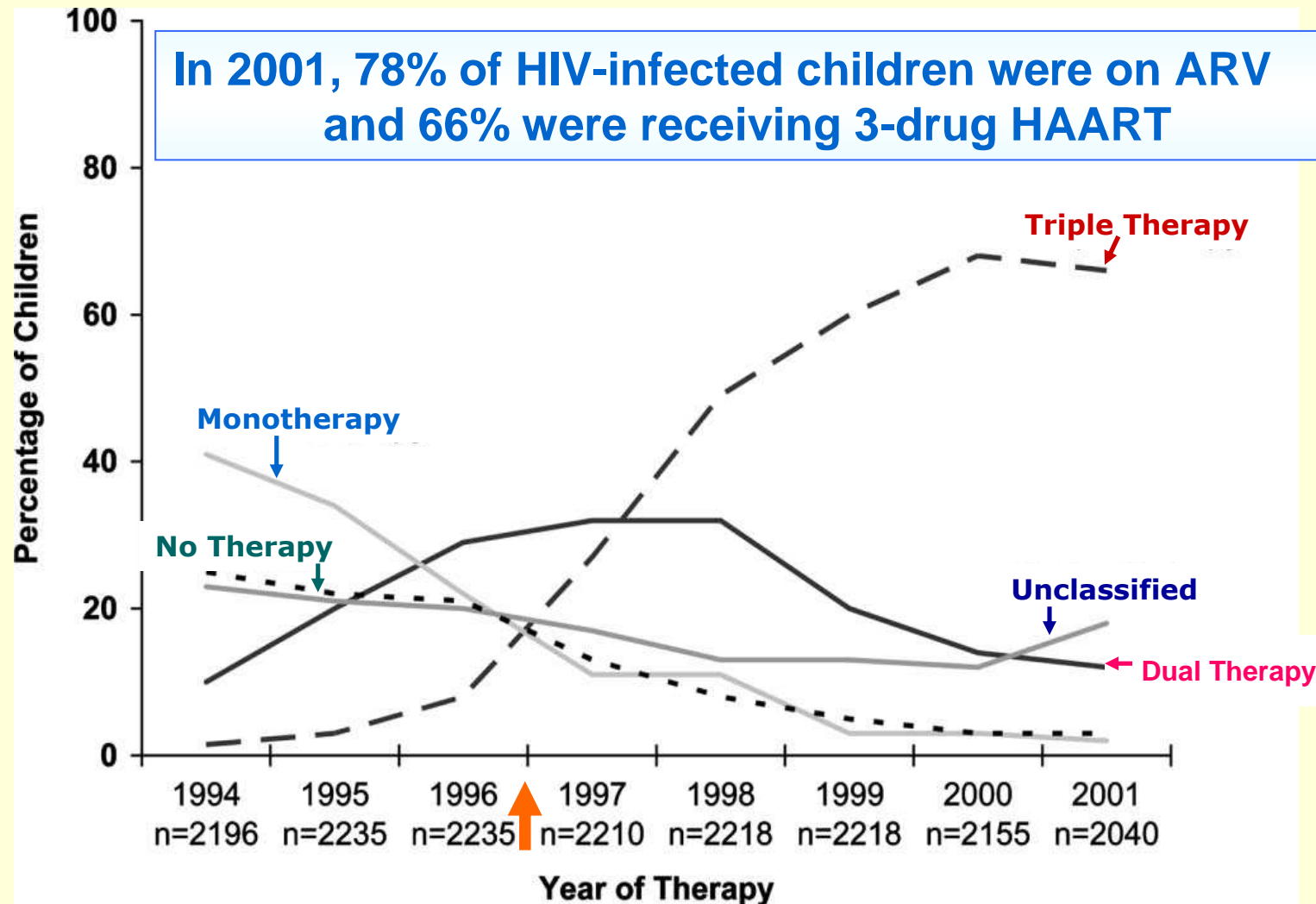
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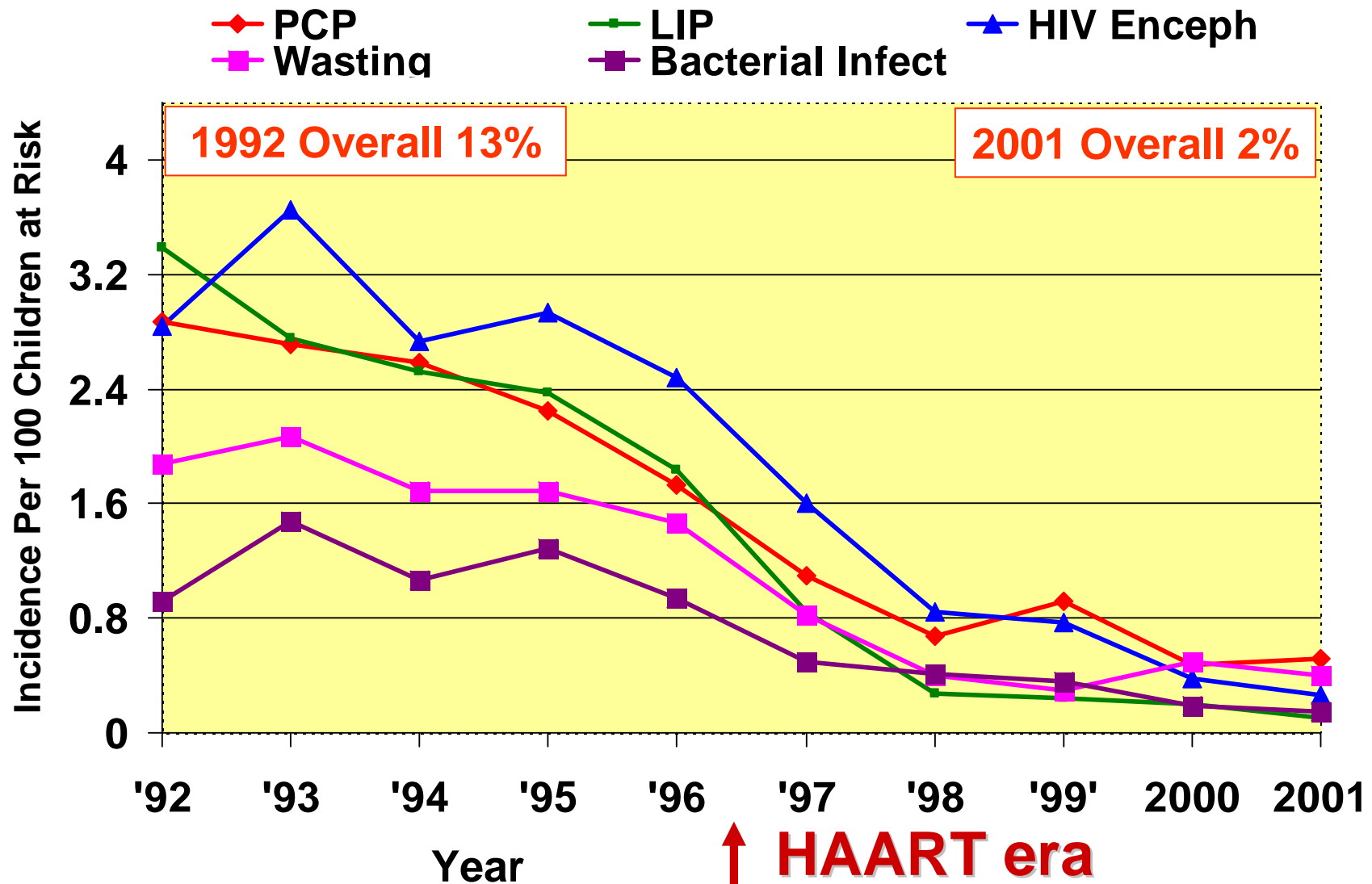
In the United States, the Majority of HIV-Infected Children Are Receiving Antiretroviral Therapy

Pediatric Spectrum of Disease Project, 1994-2001



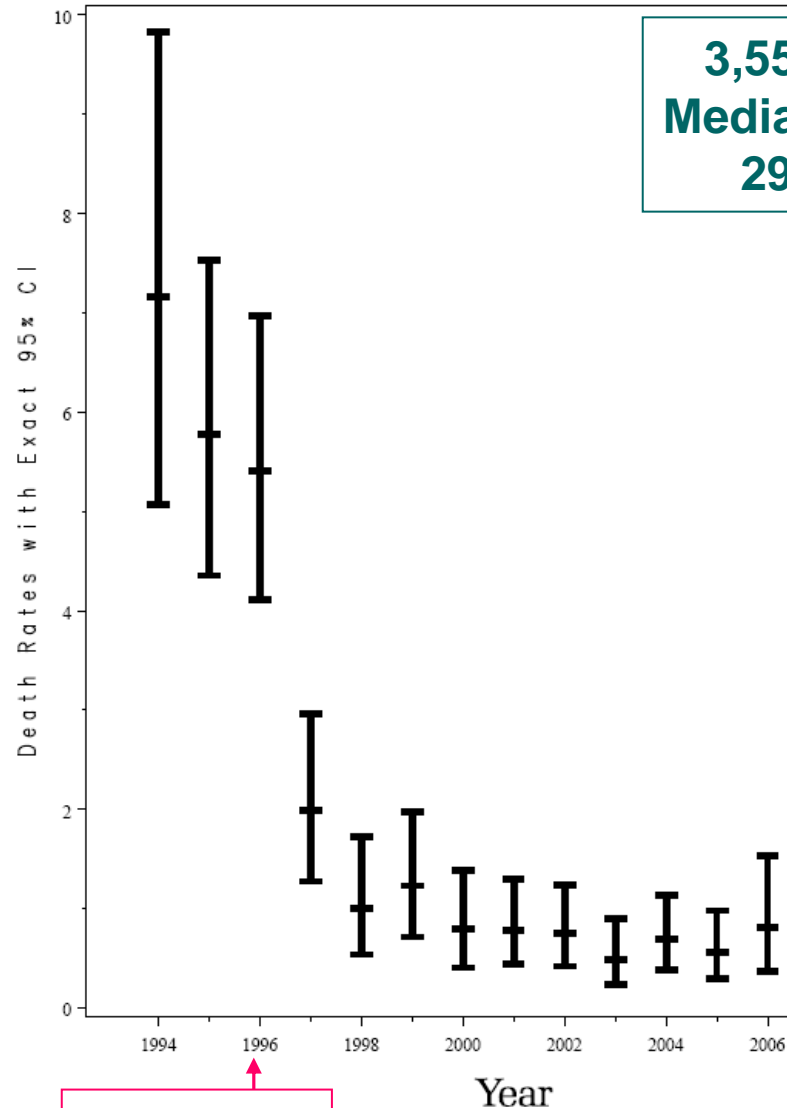
McConnell M et al. *JAIDS* 2005;38:488-94 – PSD includes over 2,000 children from 6 areas US

Incidence of Selected AIDS-Defining Conditions Per 100 HIV-Infected Children at Risk, U.S. *Pediatric Spectrum of Disease Project, 1992-2001*



Yearly Mortality (1994-2006) in HIV-Infected Children Enrolled in PACTG 219 Long-Term Follow-Up Study

Death Rates for Infected Children



**Death rate
in 1994:
7.2/100 pt-yrs**

**3,553 children
Median f/u 5.3 yrs
298 deaths**

**Death rate
in 2006:
0.6/100 pt-yrs**

HAART Era



Challenges in the Treatment of Pediatric HIV Infection in High Resource Settings



**Effective Therapy is Prolonging Life
Spectrum of Disease Changed**

- **Drug resistance: primary, acquired**
- **Lack salvage drugs for children**
- **Complications of therapy**
- **Adherence**
- **Mental health**
- **Adolescence - transition to adult care**

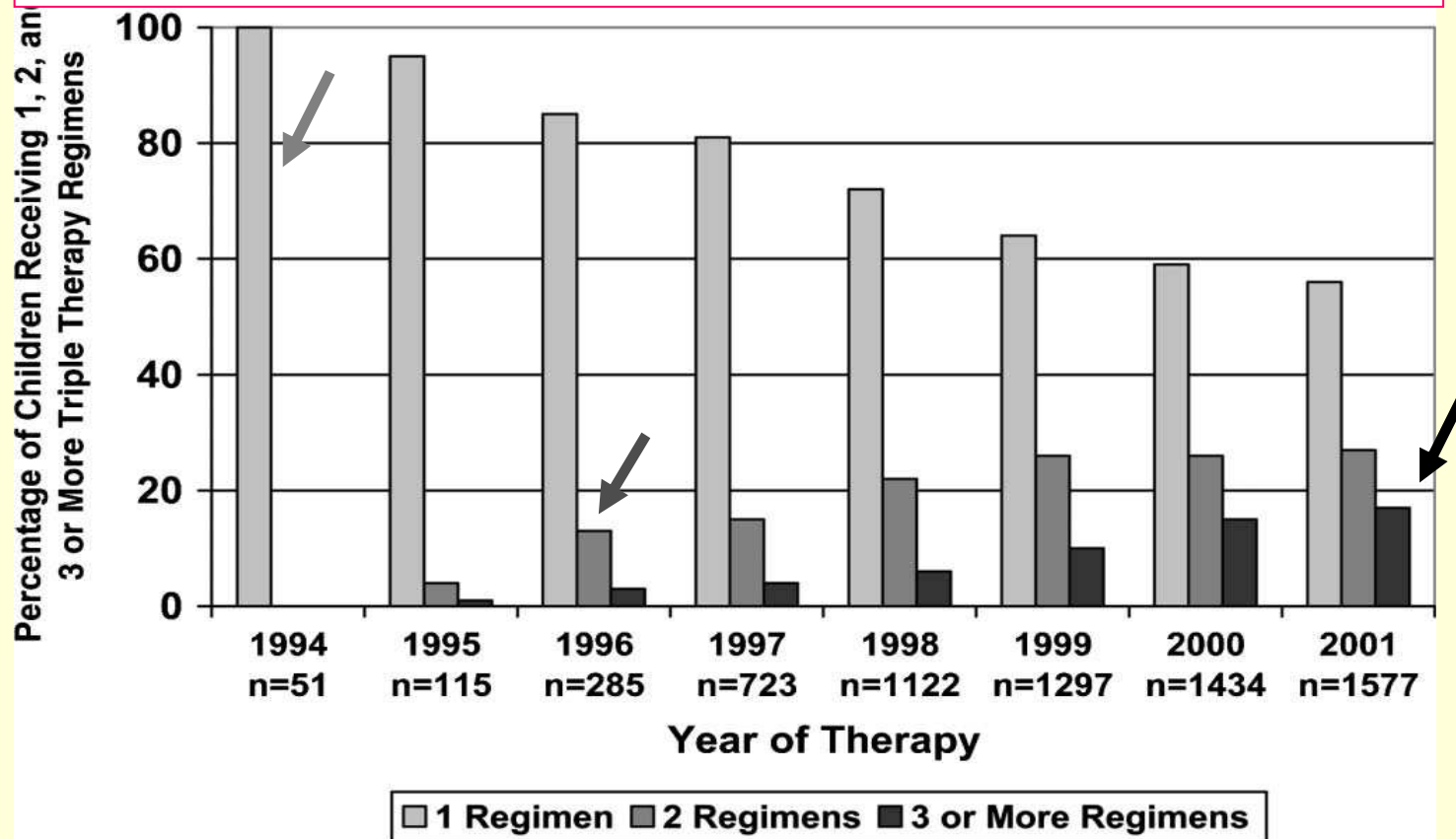
Acquired Drug Resistance

- Many older children had sequential mono and dual therapy prior to starting HAART, and may have had periods of inadequate adherence
 - Leads to the development of multi-drug resistant virus which -
 - Limits choices for effective therapy
 - Necessitates more complex regimens
 - However -
 - Newer drugs used for salvage in adults often not available in children
 - Lag in development of pediatric formulations

Increasing Number of Children on Triple Therapy Have Gone Through Two or More HAART Regimens

Pediatric Spectrum of Disease Project, 1994-2001

In 2001, 44% of children were on 2nd or greater triple drug regimen (3% on 5th or more)





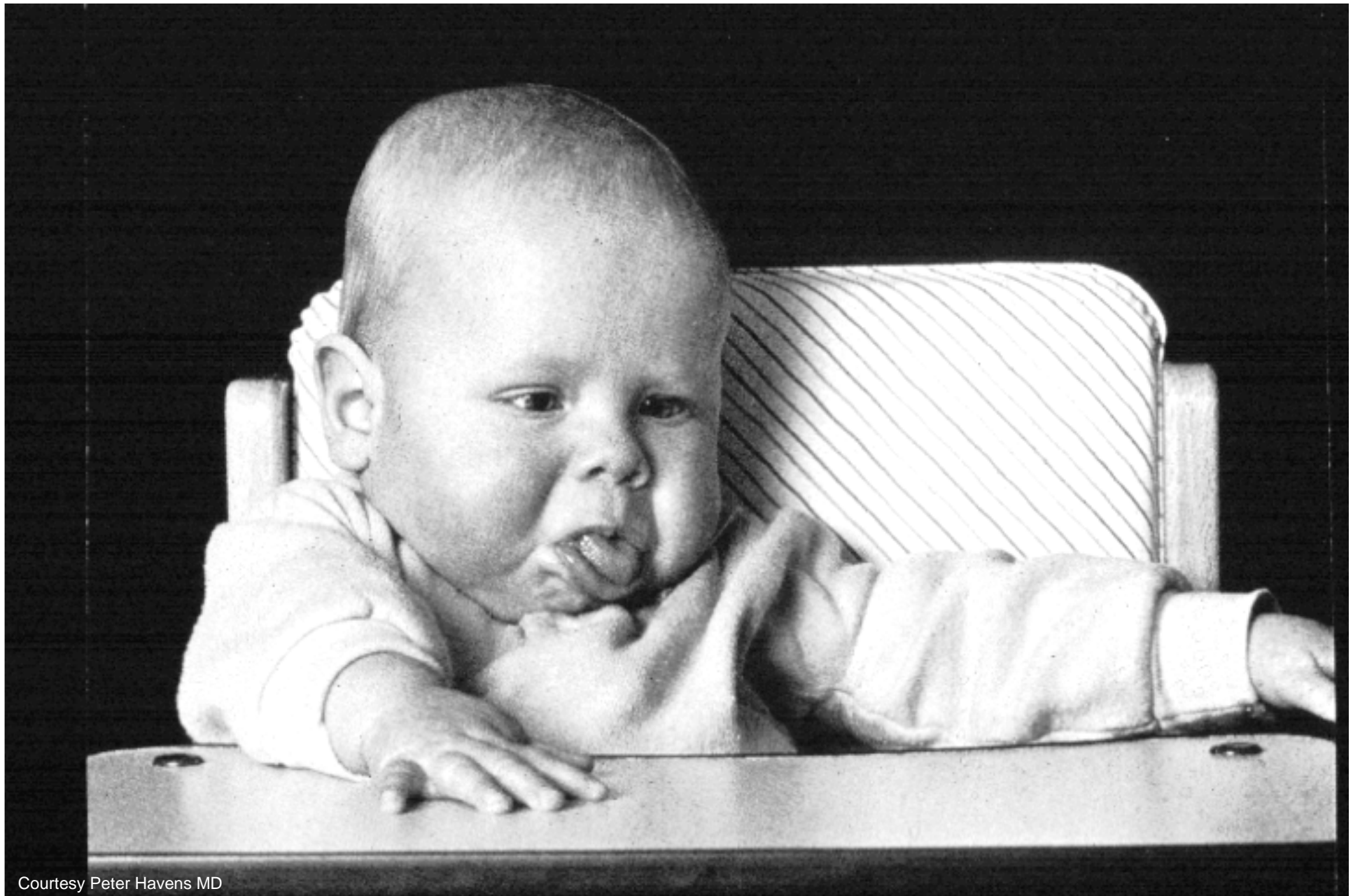
Metabolic Complications of Antiretroviral Therapy in Children

- Metabolic disorders reported in HIV-infected children on antiretroviral therapy:
 - Lipodystrophy reported in 6-47%
 - Hyperlipidemia reported in 13-67%
 - Insulin resistance 0-13%, with hyperinsulinemia reported in 60%
- Puberty is time when children are most likely to develop metabolic complications.

Tassiopoulos K et al. *JAIDS*. 2008; in press
Vigano A et al. *Antivir Ther*. 2007;12:297-302
Ene L et al. *Eur J Pediatr*. 2007;166:13-21
Ergun-Longmire B et al. *Endocr Prac*. 2006;12:514-21
Dzwonek AB et al. *JAIDS*. 2006;43:121-3

Carter RJ et al. *JAIDS*. 2006;41:453-60
Farley J et al. *JAIDS*. 2005;38:480-7
Beregszaszi M et al. *JAIDS*. 2005;40:161-8
European Paediatric Lipodystrophy Group. *AIDS*. 2004;18:1443-1451
McComsey G et al. *Pediatrics*. 2003;111:e275-81

Pediatric Adherence Challenges



Courtesy Peter Havens MD

Adherence is Critical for HAART Success, But Multiple Added Barriers to Adherence in Children

- **Reliance on parent/guardian administration in younger children**
- **Multiple medications given at least once daily, generally twice daily**
- **Limited number of child-friendly formulations**
- **Adherence fatigue with lifelong treatment in seemingly well child/adolescent**
- **Side effects, particularly body image in youth**
- **Adolescence (need one say more?)**

Mental Health in HIV-Infected Children and Youth

Scharko AM. AIDS Care 2006;18:441-5

- **Review of 8 studies including 328 HIV-infected children age 4-21 years; data were compared to prevalence in overall population.**
- **Prevalence of mental health disorders:**
 - **Attention deficit disorder: 24%**
 - **6.0-fold increased risk ratio**
 - **Anxiety disorder: 29%**
 - **3.8-fold increased risk ratio**
 - **Depression: 25%**
 - **7.1-fold increased risk ratio**



Challenges in Adolescent HIV Care

- Knowledge of HIV infection.
- Linking to (and retaining in) health care.
- Accepting (and adhering to) therapy.
- Mental health issues.
- Complexities of transition to adult care.
- High risk population for HIV transmission.
 - 40-60% of HIV-infected adolescents continue to engage in unprotected sex.
 - High rate substance use, smoking.

Rice E et al. Prospect Sex Repro Health 2006;38:162-7

Murphy DA et al. J Adol Health 2001;29S:57-63

Sturdevant MS et al. J Adol Health 2001;29S:64-71

Kadivar H et al. AIDS Care 2006;18:544-9

Rotheram-Borus M et al. J Adoles 2001;24:791-802

Lightfoot M et al. Am J Health Behav 2005;29:162-71.



Challenges in Management of Pediatric HIV Infection in Low Resource Countries



#1 Challenge in Low Resource Countries:

Continued HIV Transmission to Women



and

Poor Implementation of PMTCT

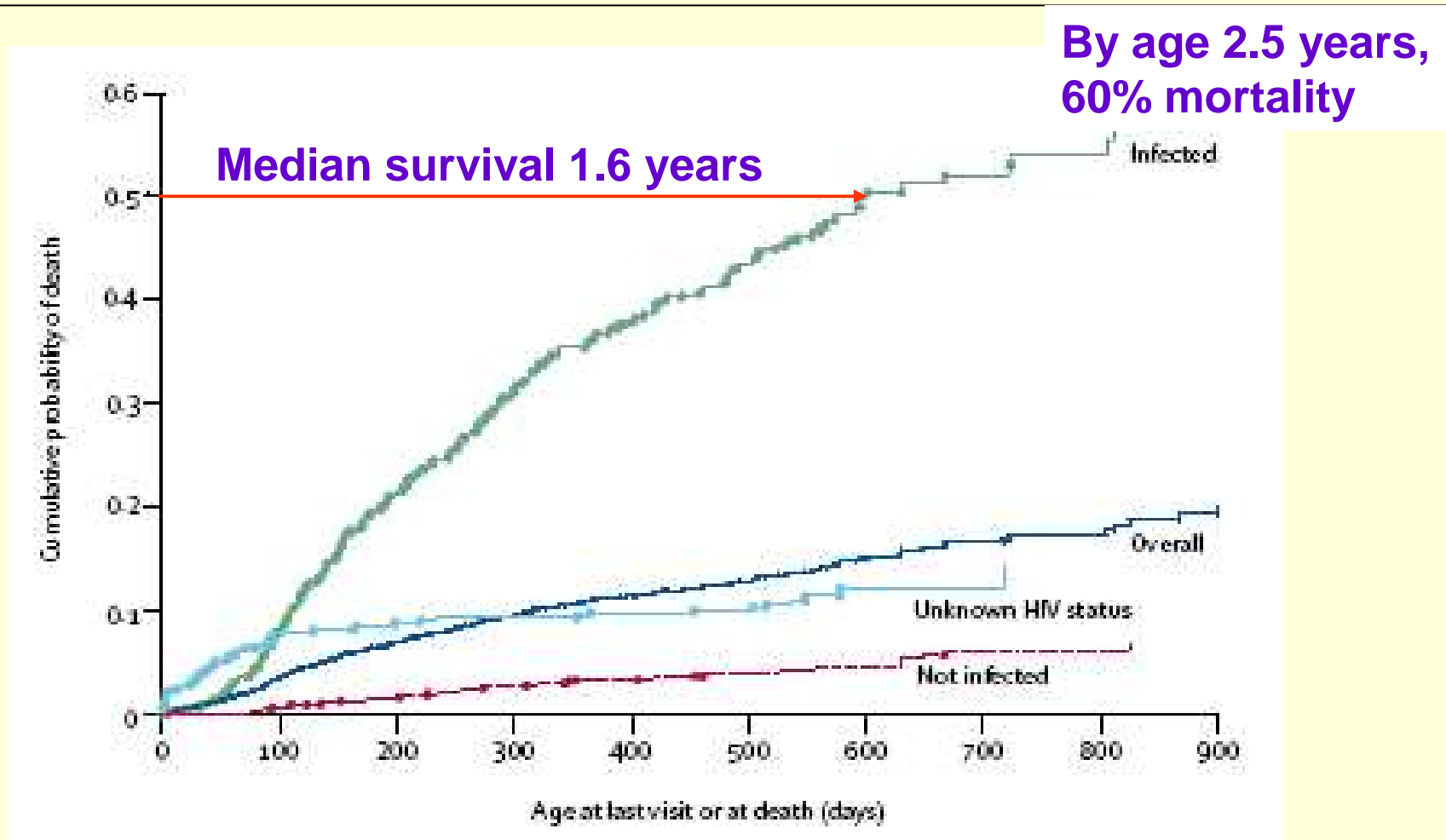




The Challenge of Pediatric HIV Infection in Resource-Poor Countries

- **While high rates of HIV infection in women, few women know they are infected and there is poor access to ARV to prevent MTCT.**
- **Children often present to health system with advanced disease.**
- **Rapid progression and high mortality due to HIV in children, yet few receive treatment.**
- **Early treatment would prevent many deaths but infant diagnosis not available.**

Data from African Perinatal Prevention Trials from Breastfeeding HIV Transmission Study Meta-Analysis: Mortality in Infected Children was 53% at 2 Years of Age
Newell et al. Lancet 2004;364:1236-43





Children in Resource-Limited Countries Respond to HAART as Well as in 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 N=876	70% <400 (6 mos)



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)
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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)
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Challenges in Drug Formulations & Dosing



Courtesy Peter Havens MD



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...)**

Pediatric Treatment in Low Resource Countries

What is Available for Adults



FDCs that allow one pill once or twice daily

Pediatric Treatment in Low Resource Countries

What is Available for Adults



FDCs that allow one pill once or twice daily

What has been Available for Children



Giving 3 different liquids hard to transport/store/give



Splitting adult tablets, risking inappropriate dose and associated risk toxicity or underdosing=resistance

Pediatric Treatment in Low Resource Countries

What is Available for Adults



FDCs that allow one pill once or twice daily

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What is Becoming Available for Children --- BUT NEED

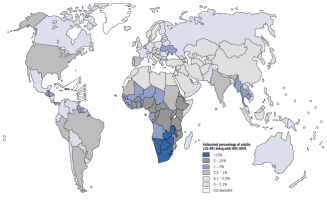
CIPLA

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	1:5:6.3	



- More than d4T/3TC/NVP preparations
- Crushable and dispersible tablets/granules
- Appropriate drug ratios for children based on PK
- Dual as well as triple FDC
- To be affordable

Scored crushable FDCs



Two 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

**Thank You For
Your Attention**

**And For Caring
For Children With
HIV Infection**

