

Update: What is New in U.S. Pediatric Antiretroviral Guidelines



October 26, 2006
<http://AIDSInfo.nih.gov>

Lynne M. Mofenson, M.D.
Pediatric, Adolescent and Maternal AIDS Branch
National Institute of Child Health and Human Development
National Institutes of Health
Department of Health and Human Services

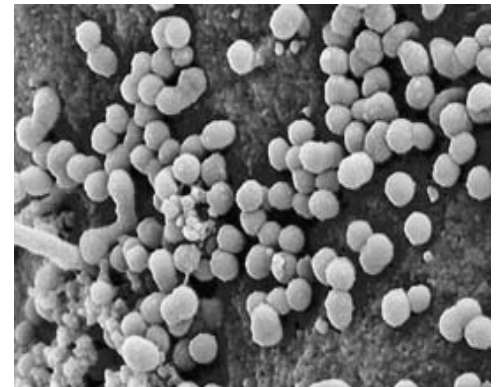
Overview: Discussion of What is New in Pediatric Antiretroviral Guidelines

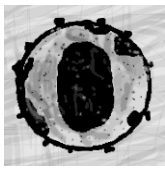


- **Recommendations for resistance testing in treatment-naïve children.**
- **Changes in CD4 and RNA age-related thresholds for when to start therapy in children.**
- **Newer data on response to therapy in children.**



Antiretroviral Drug Resistance Testing in Treatment-Naive Children





Antiretroviral Drug Resistance



- **Drug resistant virus found in 6-16% of naïve adults, and drug resistance testing is now recommended prior to starting treatment in all treatment naïve-adults.**
- **Data on primary resistance in children are limited.**
- **In New York, where universal newborn screening, viruses from infants with newly diagnosed perinatal infection in 1998-1999 and 2001-2002 were genotyped and extent of resistance examined.**

Prevalence of Drug Resistance in Infants with Perinatal HIV Infection, New York State

Parker MM et al. JAIDS 2003;32:292-7

Karchava M et al. JAIDS 2006;42:614-9

Type of Resistance	1998-1999 N=91	2001-2002 N=42
Any resistance	12.1%	19.1% 58% increase 1998-99 to 2001-02
NRTI	7.7%	7.1%
NNRTI	3.3%	11.9%
PI	3.3%	2.4%
≥2 classes	2.2%	2.4%

Non-subtype B virus found in 4.4% of infants born 1998-1999 and 16.7% of infants born 2001-2002.

Prevalence of Drug Resistance in Infants with Perinatal HIV Infection, NYS

Parker MM et al. JAIDS 2003;32:292-7

Karchava M et al. JAIDS 2006;42:614-9

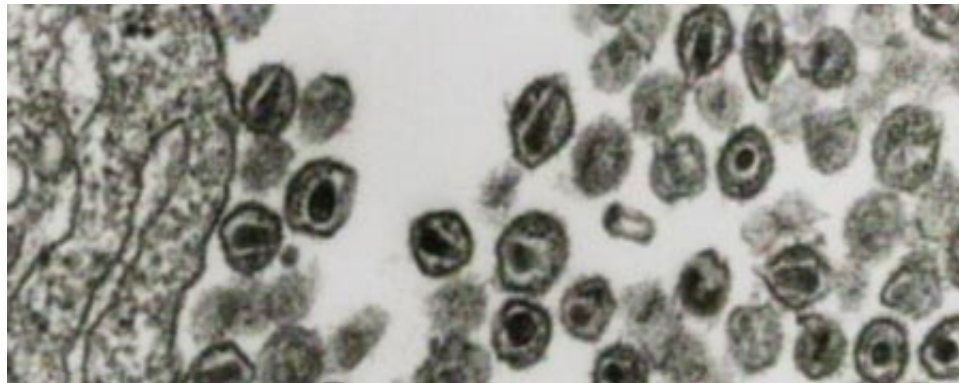
- **The presence of resistance in the infant did not always correlate with perinatal antiretroviral exposure history.**
- **45-50% of infants with resistance had either no maternal/infant antiretroviral exposure or only infant AZT exposure (none were resistant to AZT).**
- **In infants with perinatal antiretroviral drug exposure, mutations were not necessarily to drugs they were exposed to (in 20% of cases, did not correlate).**

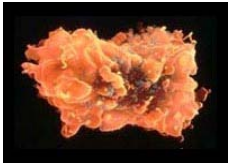
Drug Resistance Testing of Antiretroviral-Naïve Infected Children

- **Prevalence of infants infected with antiretroviral drug-resistant virus may be increasing in infants with perinatal infection.**
- **Resistance may not be predicted by the drug prophylaxis regimen received by the mother or infant.**
- **Therefore, antiretroviral drug resistance testing is now recommended prior to initiation of therapy in all treatment-naïve children, similar to recommendations in adults.**



Changes in CD4 and HIV RNA “Thresholds” for Starting Treatment in Children



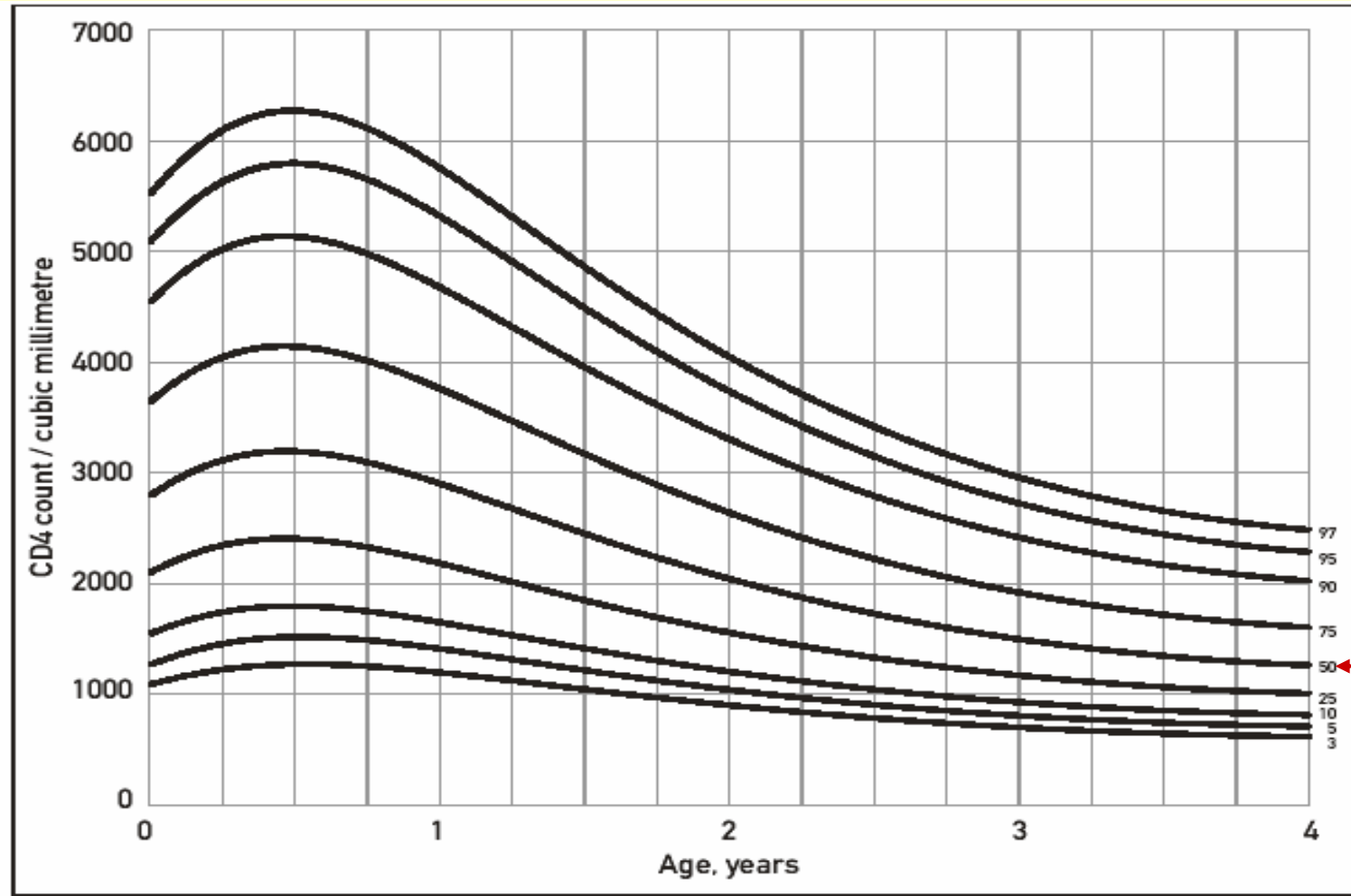


Immunologic Parameters in Children

- **Absolute CD4 counts in healthy uninfected children are much higher than in adults.**
- **Normal absolute CD4 counts slowly decline to adult levels by age 4-6 years.**
- **CD4% is less variable and more stable in younger children.**
- **Prognostic value of CD4 % or count varies with age.**
- **If using CD4 % or count for ARV decisions, use age-appropriate levels.**

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

(European Collaborative Study *Pediatr Infect Dis J*, 1992, 11: 1018-1026)



50th %ile

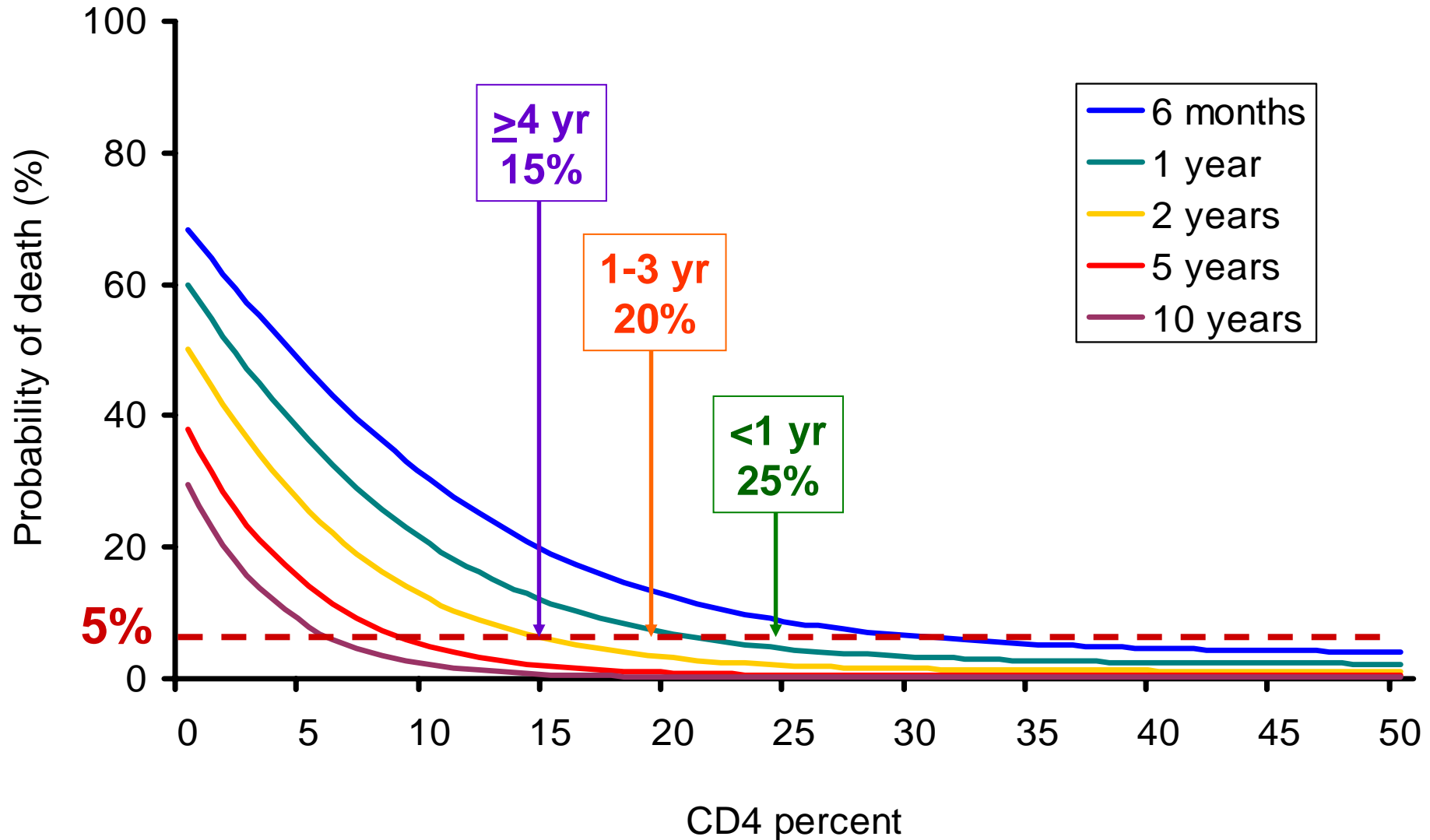
HIV Paediatric Prognostic Marker Collaborative Study (HPPMCS)

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

- **Individual patient meta-analysis of longitudinal data from 8 cohort studies and 9 randomized trials in the U.S. and Europe.**
- **Included 3,941 children receiving no therapy or AZT alone.**
- **The study analyzed the association of the most recent CD4%/count and HIV RNA level with short-term, 12-month risk of progression to AIDS or death, stratified by age of the child.**

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



Deaths/100 Pt-Yrs by Age & Current Absolute CD4 Count:

Children (HPPMCS) and Adults (Cascade)

CD4 Count & Short-Term Risk Death Similar in Children >5 Yrs & Young Adults

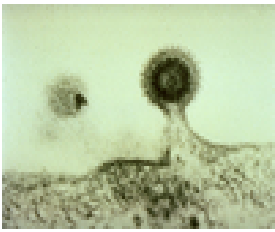
HIV Pediatric Prognostic Marker Collaborative Study, CROI 2007, Los Angeles CA, Abs. 700

CD4 Absolute Cell Count (cell/mm³)

		CD4 Absolute Cell Count (cell/mm ³)					
		<50	50-99	100-199	200-349	350-499	500+
HPPMCS	Age						
	0-4 yrs	59.3	39.6	25.4	11.1	10.0	3.5
	5-10 yrs	28.9	11.8	4.3	0.9	0	0
CASCADE	15-24 yrs	34.7	6.1	1.1	0.7	0.6	0.7
	25-34 yrs	47.7	10.8	3.7	1.1	0.4	0.2
	35-44 yrs	58.8	15.6	4.5	0.9	0.7	0.9
	45-54 yrs	66.0	18.8	7.7	1.8	1.3	0.86
	55+ yrs	91.3	21.4	17.6	3.8	2.5	0.9

CD4 <200

CD4 <350

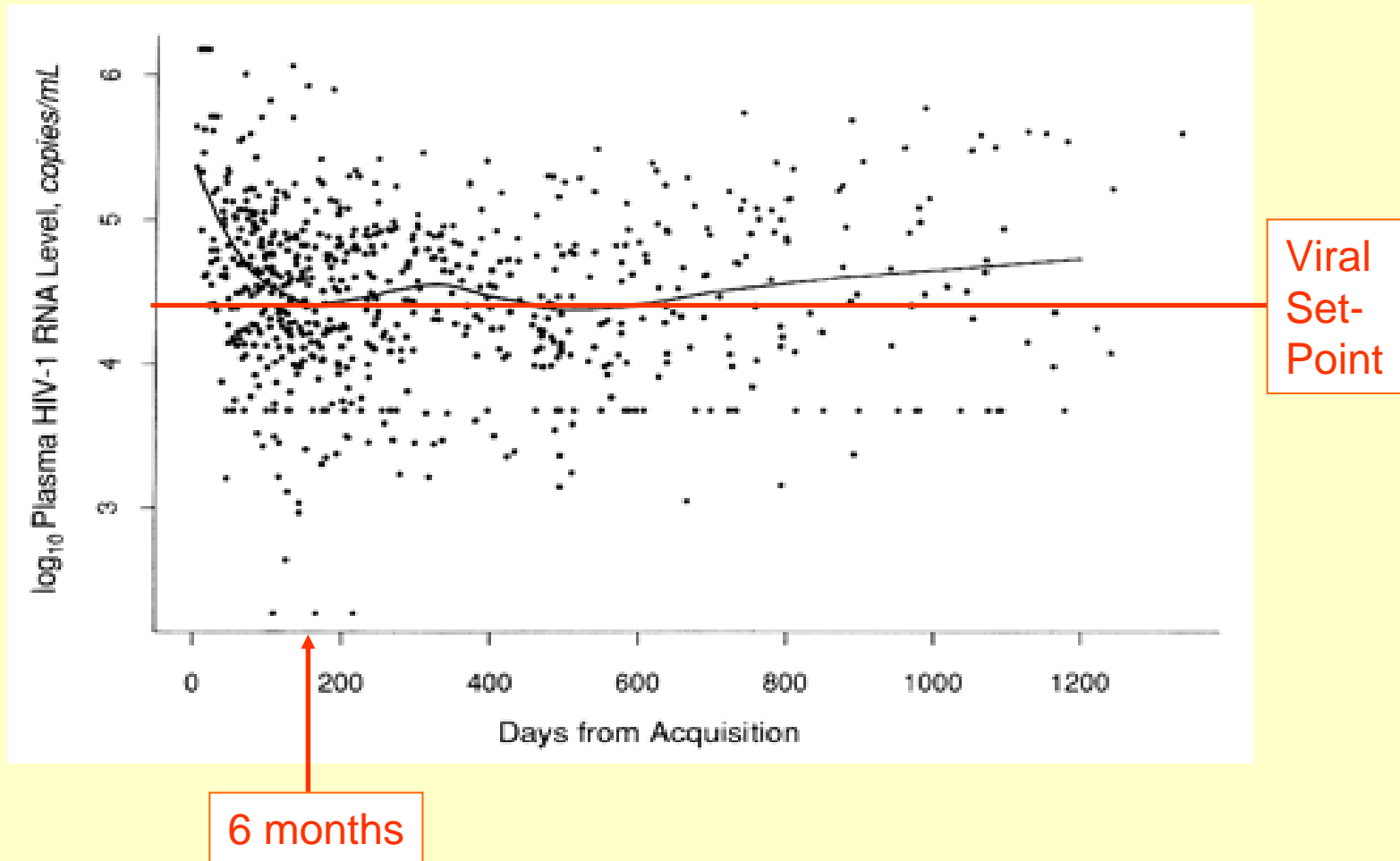


Viral Load in Children

- **Generally low levels at birth (unless *in utero* infection), rise to several million copies/mL within the first 1-2 months of life.**
- **Without treatment, very slow decline over several years before reach “set point”.**
- **RNA levels and changes have prognostic value but vary by age of child.**
- **As in adults, RNA and CD4 count have independent prognostic value.**

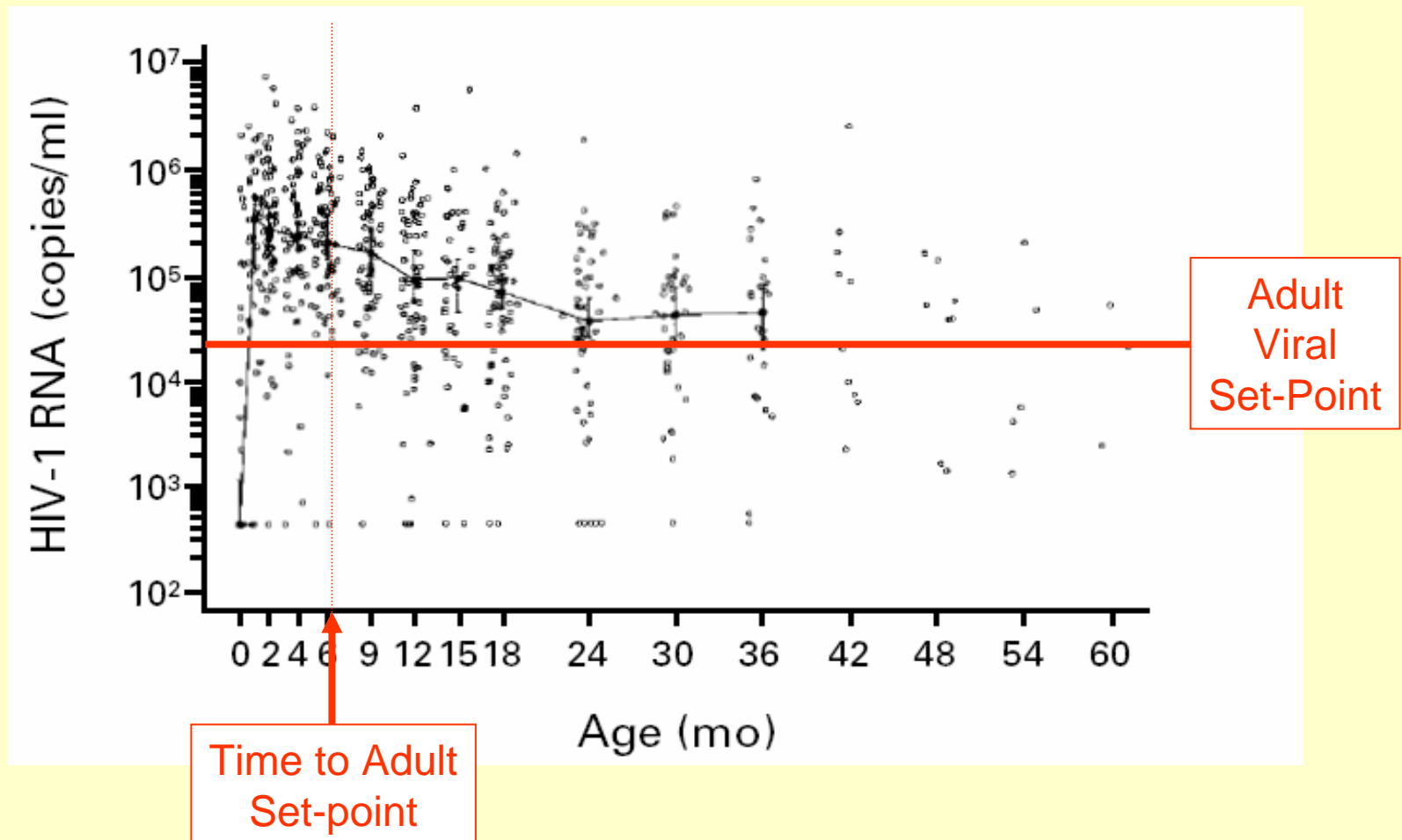
Adult HIV Infection: Initial Viral Burst followed by Decrease to “Set Point” by 6-9 Months After Infection

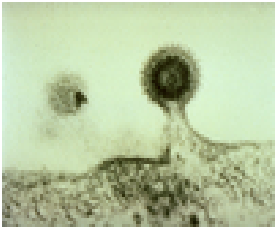
Schacker TW et al. Ann Int Med 1998;128:613-20



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



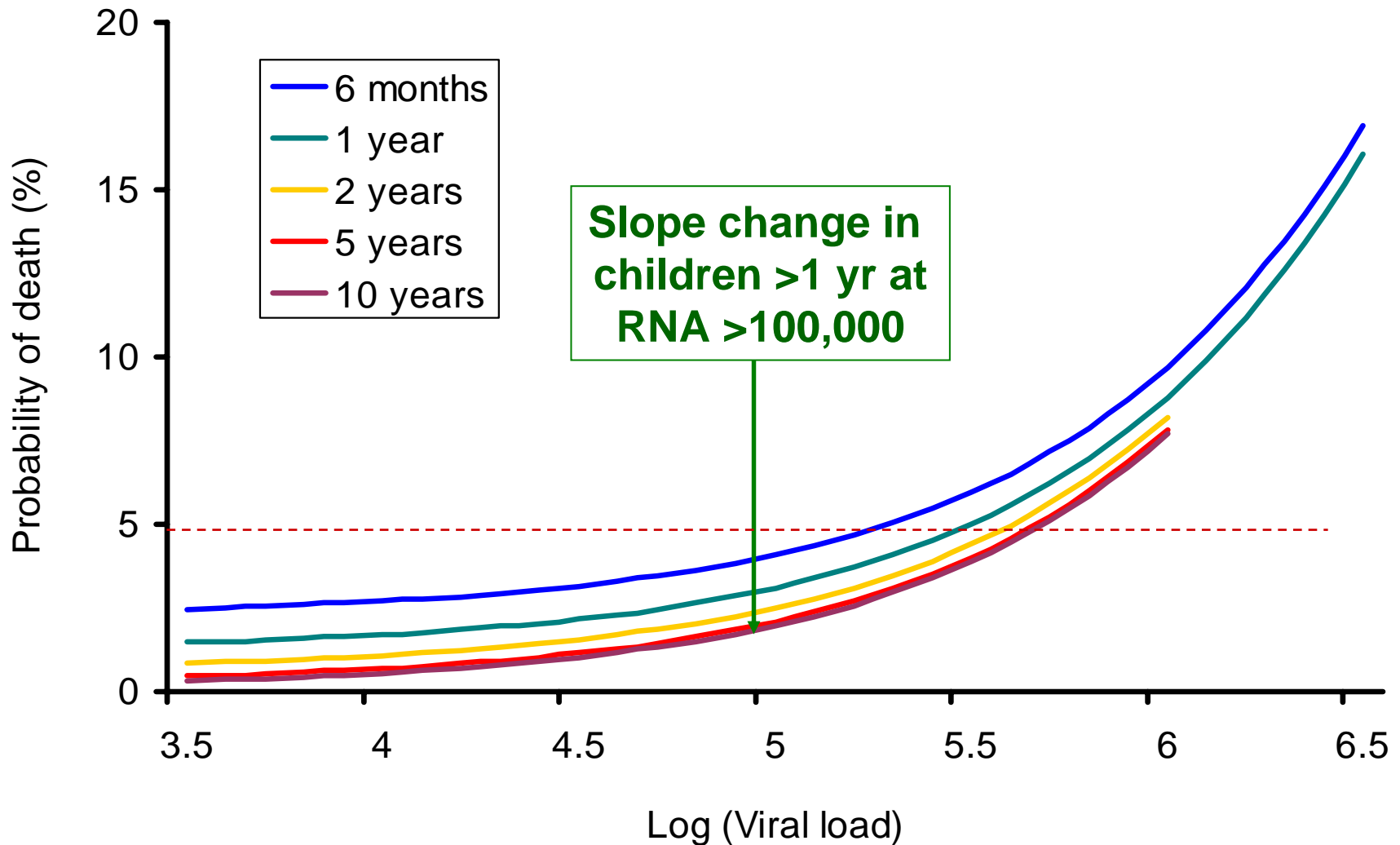


Viral Load and Progression in Children

- **High HIV RNA associated with higher risk for disease progression and death.**
 - **However, like CD4, predictive value of HIV RNA in infants age <12 months is much lower than older children.**
 - **In infants age <12 months, HIV RNA levels overlap in rapid & nonrapid progressors.**
 - **CD4 % more useful than HIV RNA in evaluating risk in infants <12 months; in older children both parameters are useful.**

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

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



Changes in Pediatric Guidelines

- **CD4% is recommended in children to 4-6 years; count can be used in older children.**
- **Age-related CD4%/count “thresholds” for when to start have been modified into 4 age groups to reflect the HPPMCS meta-analysis.**
 - **<12 months**
 - **1-<4 years**
 - **4-12 years**
 - **≥13 years**
- **RNA “threshold” for when to start used only in children >1 year and increased to >100,000 copies/mL.**

Recommendations on Starting ART in HIV-Infected Children





Initiation of ART: 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 infants so more aggressive treatment may be considered.**
- **However, few data on efficacy of early treatment of asymptomatic infants.**
- **Limited information on appropriate ARV dosing for young infants/neonates.**

Age <1 Year:

**TREAT if Any HIV-Related Symptoms
or if Asymptomatic & Severe Immune Deficiency**

Age	Recommend Treatment: HIV-Related Symptoms ¹ <u>Regardless</u> of CD4/RNA OR Asymptomatic <i>plus</i> Severe Immune Deficiency
<1 year	CD4 <25%

¹ HIV-Related Symptoms: CDC class C (AIDS) or CDC Class B (moderate) or A (mild) symptoms

Age <1 Year:
**CONSIDER ART if Asymptomatic and
Has Adequate Immune Status**

Age	Consider Treatment: <i>Asymptomatic plus Adequate Immune Status</i>
<1 year	CD4 \geq25%



Initiation of ART: Children Age 1 Year & Older

- **Risk of disease progression is lower for older children than for infants.**
- **In children >12 months, plasma HIV RNA may provide information about progression risk as an adjunct to clinical and immune parameters and can assist in making ARV decisions.**

Age >1 Year: **TREAT** if Significant Symptoms or if Asymptomatic & Severe Immune Deficiency

Age	Recommend Treatment: Significant Symptoms ¹ <u>Regardless</u> of CD4/RNA OR Asymptomatic or Mild Symptoms ² plus Severe Immune Deficiency
1-<4 years	CD4 <20%
≥4 to 12 years	CD4 <15% (or CD4 <200-300 in upper end age category)
≥13 years	CD4 <200

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

² Mild symptoms: CDC Class A or LIP, single episode bacterial pneumonia

Age >1 Year: **CONSIDER ART if Asymptomatic & Moderate Immune Deficiency or High Viral Load**

Age	Consider Treatment: Asymptomatic or Mild Symptoms ² plus Moderate Immune Deficiency OR High HIV RNA
1-<4 years	CD4 20-24% <u>or</u> RNA \geq100,000
\geq4 to 12 years	CD4 15-24% <u>or</u> RNA \geq100,000
\geq13 years	CD4 201-350 <u>or</u> RNA \geq100,000

² Mild symptoms: CDC Class A or LIP, single episode bacterial pneumonia

Age >1 Year: DEFER ART if Asymptomatic & Adequate Immune Status and Lower Viral Load

Age	Defer Treatment: Asymptomatic or Mild Symptoms plus Adequate Immune Status <u>and</u> Lower HIV RNA
1-<4 years	CD4 \geq 25% <u>and</u> RNA <100,000
\geq 4 to 12 years	CD4 \geq 25% <u>and</u> RNA <100,000
\geq 13 years	CD4 \geq 350 <u>and</u> RNA <100,000

² Mild symptoms: CDC Class A or LIP, single episode bacterial pneumonia

Newer Data on Response to Treatment in Children





Implications of Perinatal Infection for Treatment Response



- **Perinatal infection occurs in immature immune system with active thymus. Implications:**
 - Immune reconstitution may be best in younger children.
 - Virologic control in young children may be more difficult.
 - Immune reconstitution with treatment in children is with naïve CD4 cells.
 - Treatment is best initiated before immune suppression occurs.

Short-Term CD4 Response to HAART by Age at Initiation of HAART:

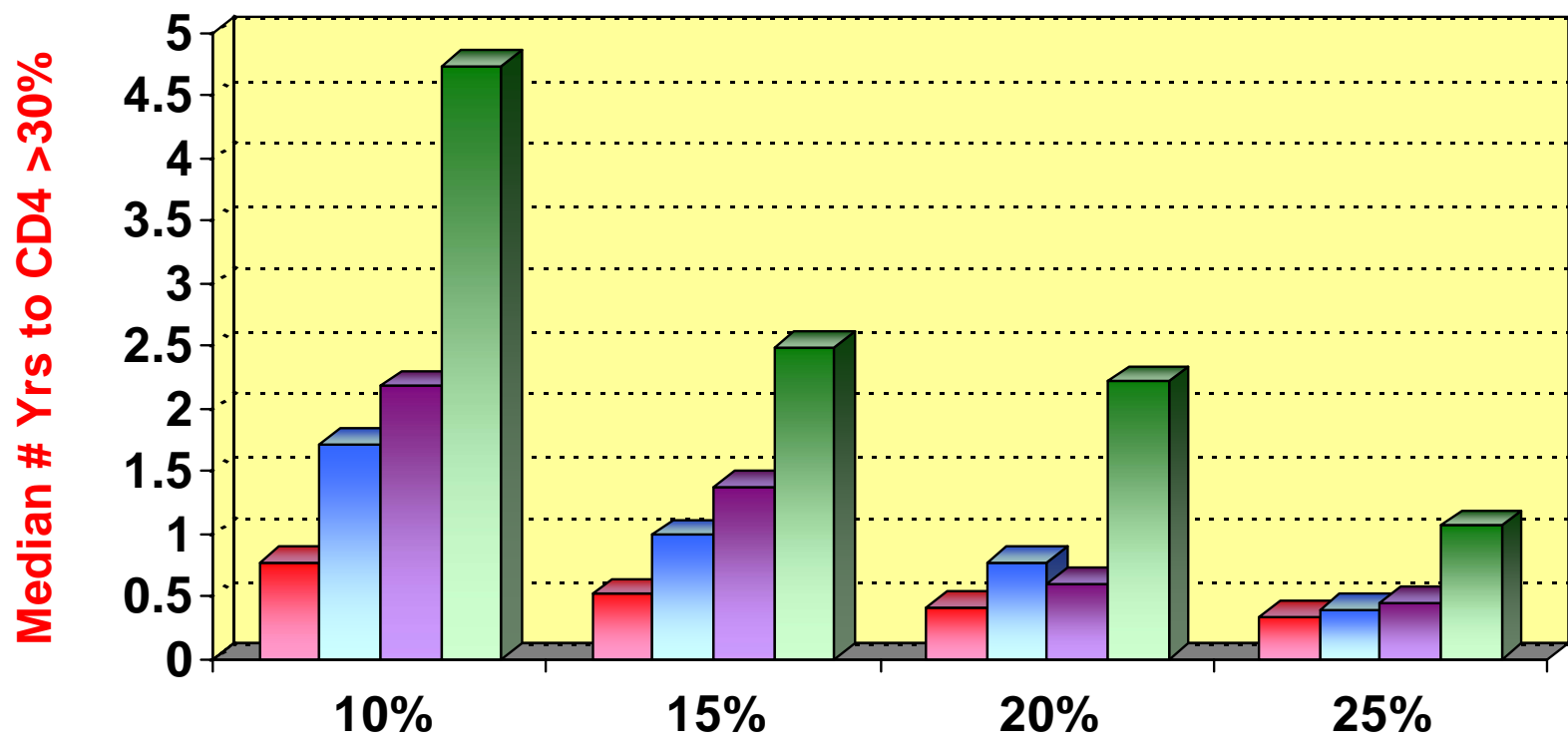
Younger Children have Better Immune Response

CHIPS UK Cohort: Walker AS et al AIDS 2004, 18: 1915 -1924

CD4% after 6 Months HAART

Age at Starting HAART	Increase by >10%	Increase to \geq 30%
<2 years (61)	46%	49%
2-5 years (57)	46%	24%
5-9 years (56)	32%	21%
>9 years (37)	24%	3%
All children (211)	38%	25%
P value for trend	0.01	0.01

Children <2 Yrs Have Shorter Time to Normalize CD4 than Older Children Regardless of CD4% at Start HAART
For Children >2 Yrs, the Lower the CD4% at Time HAART Started, the Longer it Takes to Normalize



CD4% at Initiation of HAART

CHIPS Cohort: Walker AS et al AIDS 2004, 18: 1915 -1924

Short-Term HIV RNA Response to HAART by Age at Initiation of HAART:

Younger Children have Poorer Virologic Response

Walker AS et al AIDS 2004, 18: 1915 -1924

HIV RNA after 6 Months HAART

Age at Starting HAART

<400 copies/mL

<50 copies/mL

<2 years (61)

48%

20%

2-5 years (57)

61%

23%

5-9 years (56)

63%

29%

>9 years (37)

76%

43%

All children (211)

60%

27%

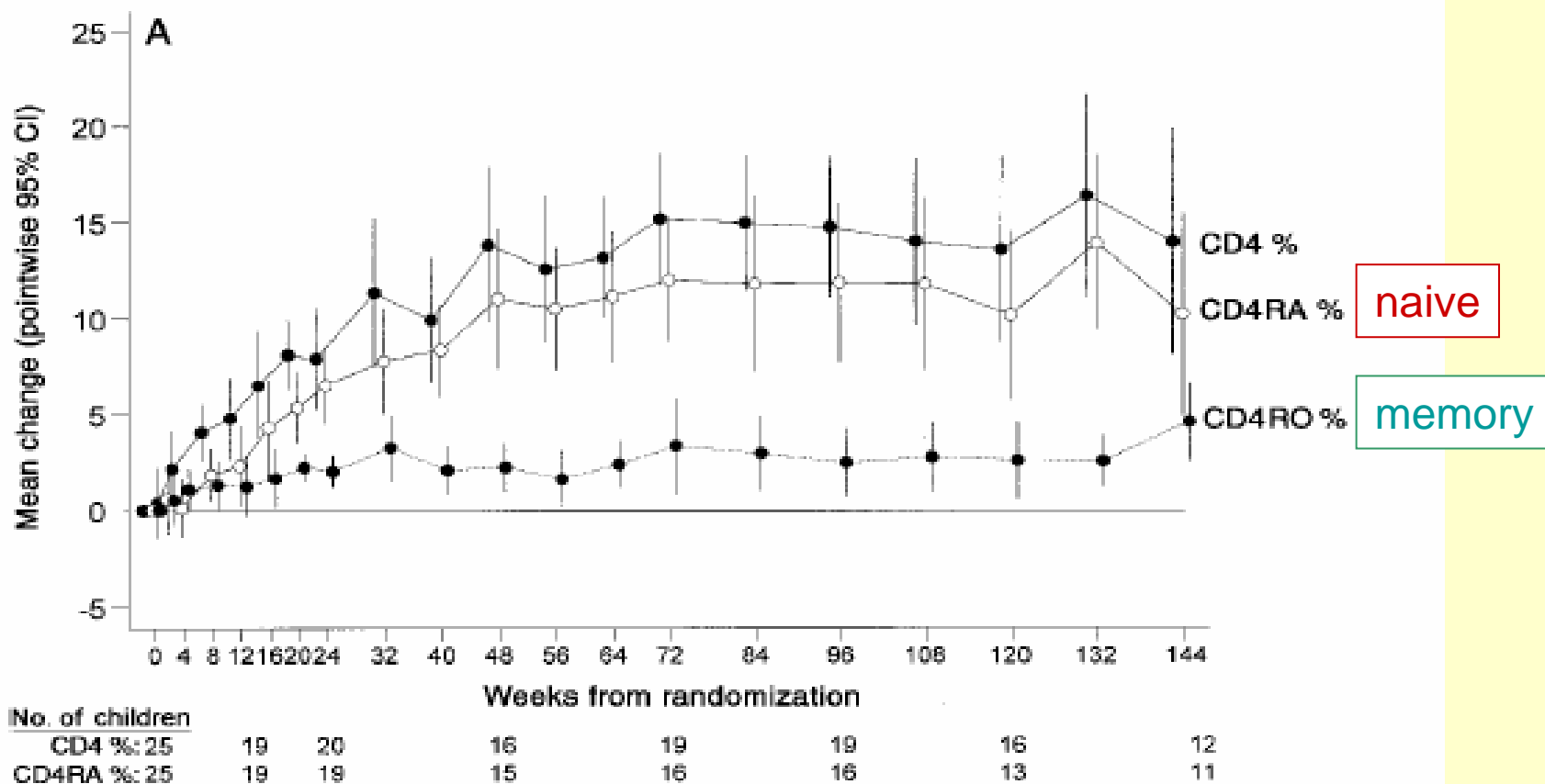
P value for trend

0.02

0.01

In Contrast to Adults, HIV-Infected Children Reconstitute With Naive CD4 Cells with HAART

De Rossi A et al. JID 2002;186:312-20



PENTA-5 Trial

Response to ART is Better in Children Started Before Development of Severe Immune Deficiency

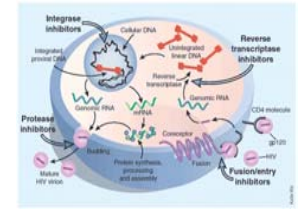
Arrive E et al. 14th CROI, Los Angeles, CA, 2007 Abs. 727

Months from ART start	Probability of Death	
	Immune Deficient at Start ART	<u>Not</u> Immune Deficient at Start ART
6 months	7.8%	1.8%
12 months	8.2%	2.2%

- Meta-analysis 1,195 children from 8 clinical trials in Africa.
- 53% >5 years of age, 66% severe age-related immune deficiency
 - ARV: NNRTI-based 58%, PI-based 37%
- Status at 1 year: dead 4.4%, lost to follow-up 12.2%



Choice of Initial Regimen



- **Combination therapy with at least 3 drugs.**
- **Preferred initial regimen is similar to adults, but fewer drug choices in children:**
 - **Protease inhibitor (PI)**
OR
 - **Non-nucleoside reverse transcriptase inhibitor (NNRTI)**
PLUS
 - **Two nucleoside reverse transcriptase inhibitors (NRTIs) (dual NRTI backbone)**
- **Therapy goal: reduce HIV RNA levels to below the level of detection & preserve immune function for as long as possible.**

Antiretroviral Drugs in Children: NRTI, NtRTI, NNRTI

Drug	Pediatric label	Pediatric formulation	Neonate/ infant dose
NRTI	Abacavir	Yes (>3 mos)	No
	Zidovudine	Yes	Yes
	Didanosine	Yes	Yes
	Zalcitabine	No	No
	Stavudine	Yes	Yes
	Emtricitabine	Yes (>3 mos)	No
	Lamivudine	Yes	Yes
NtRTI	Tenofovir	No	No (research)
	Delavirdine	No	No
NNRTI	Efavirenz	Yes (>3 yrs)	No (research)
	Nevirapine	Yes	Yes

Antiretroviral Drugs in Children: PI, Fusion Inhibitor

	Drug	Pediatric label	Pediatric formulation	Neonate/ infant dose
Protease Inhibitors	Amprenavir	Yes (>4 yrs)	Yes	No
	Atazanavir	No (in trials)	No	No
	Darunavir	No	No	No
	Fos-amprenavir	No (in trials)	No (research)	No
	Indinavir	No	No	No
	Lopinavir/ritonavir	Yes (>6 mos)	Yes	No (in trials)
	Nelfinavir	Yes (>2 yrs)	Powder	No
	Ritonavir	Yes (>1 mo)	Yes	No
	Saquinavir	No	No	No
	Tipranavir	No (in trials)	No	No
Entry Inhib	Enfuvirtide (T-20)	Yes (>6 yrs)	No	No

**Thank you for your attention
and for caring for children with HIV infection!**

