




Advances in Pediatric and Adolescent HIV Care

MILLER
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XIV Seminario Integral del SIDA

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¿Which of the following is true concerning current treatments of HIV-infected children?

a) Dose adjustments of available HAART medications are necessary based on physical growth and developmental parameters.
b) Children do not exhibit lipid or cardiovascular side effects of HAART drugs.
c) Adolescent females with HIV infection do not require contraception for sexual activity, since they are sterile.
d) Maternal breast feeding is recommended for HIV exposed infants.
e) All of the above.
f) I do not know, I'm coming to learn.

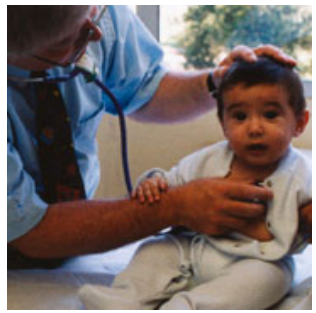
Pediatric HIV Infection

- **Pediatric HIV infection is a world-wide public health challenge disproportionately affecting children in poorest parts of the world.**

- **Dramatic advances in prevention/treatment of pediatric HIV infection in high resource countries, but only 1% of the 2.3 million HIV-infected children live in these regions.**

- **Thus, there have evolved two pediatric HIV epidemics, one in high resource countries and one in low resource countries.**

Example of the Epidemic
in High Resource Countries



Pediatric HIV Infection in the United States

A Success Story

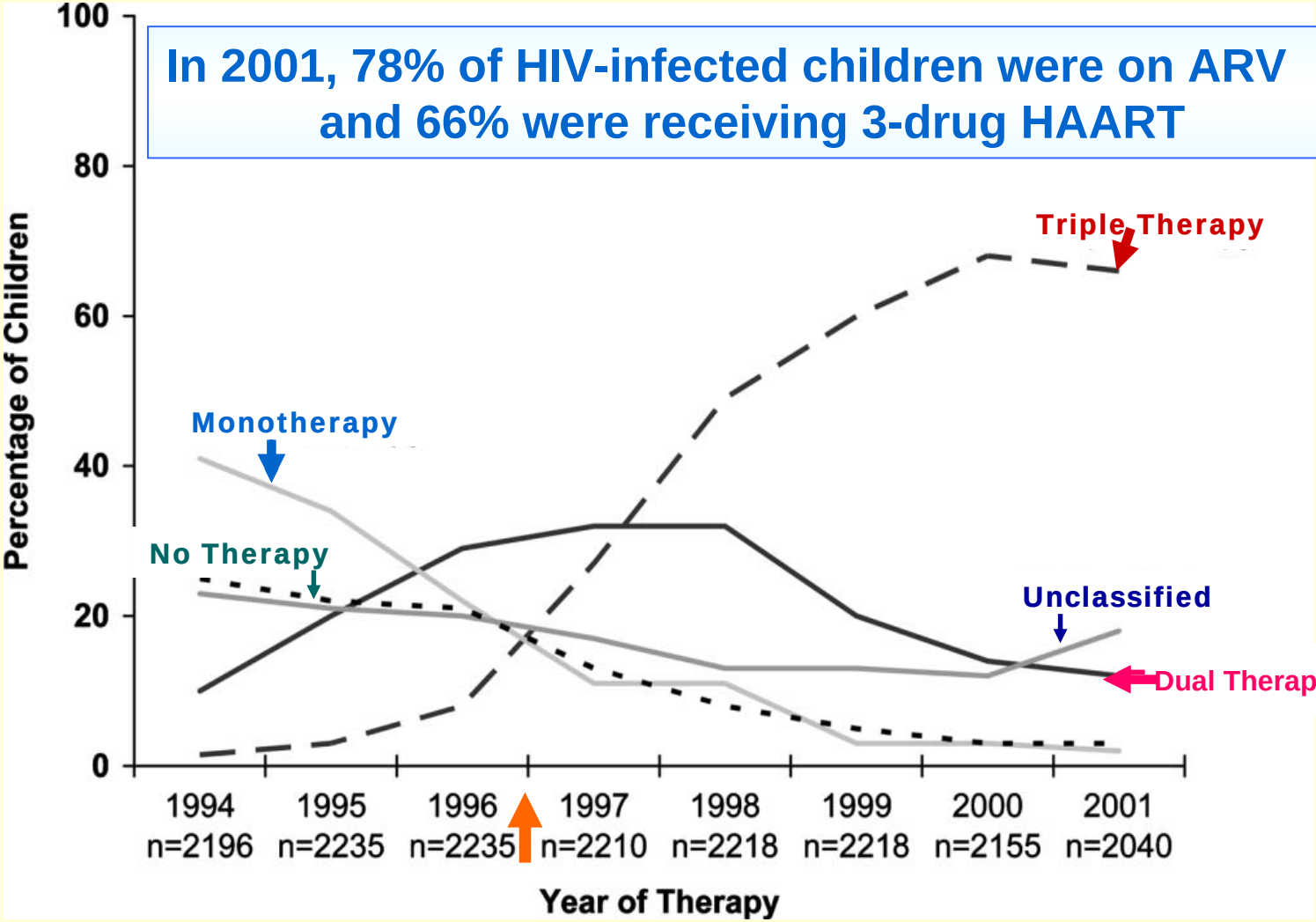
Courtesy Jim Oleske

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. (<2% MTCT rate)**
- **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)*.**

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

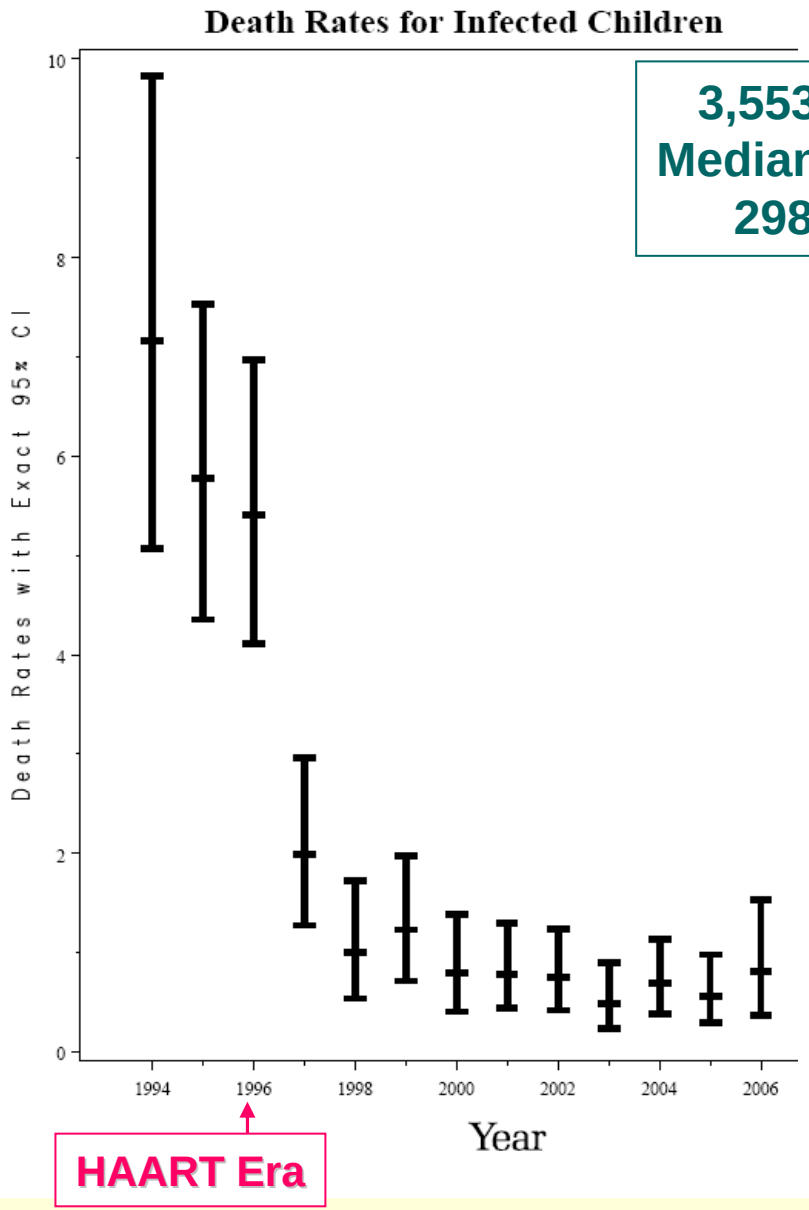
Pediatric Spectrum of Disease Project, 1994-2001



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

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

Death rate in 1994: 7.2/100 pt-yrs



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

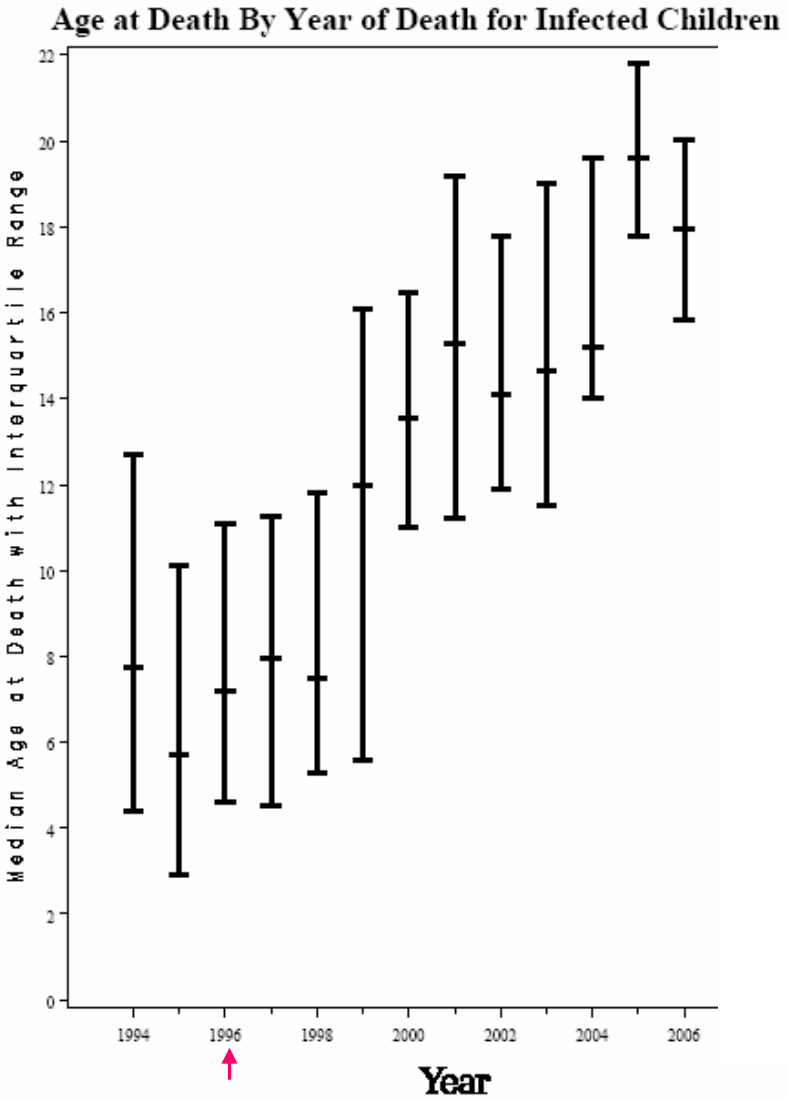
Death rate in 2006: 0.6/100 pt-yrs

National Institute of Child Health and Human Development (NICHD)

Courtesy Mike Brady, Paige Williams

Age at Death (1994-2006) in HIV-Infected Children Enrolled in PACTG 219 Long-Term Follow-Up Study

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



Mean age at death 2006: 18.2 years

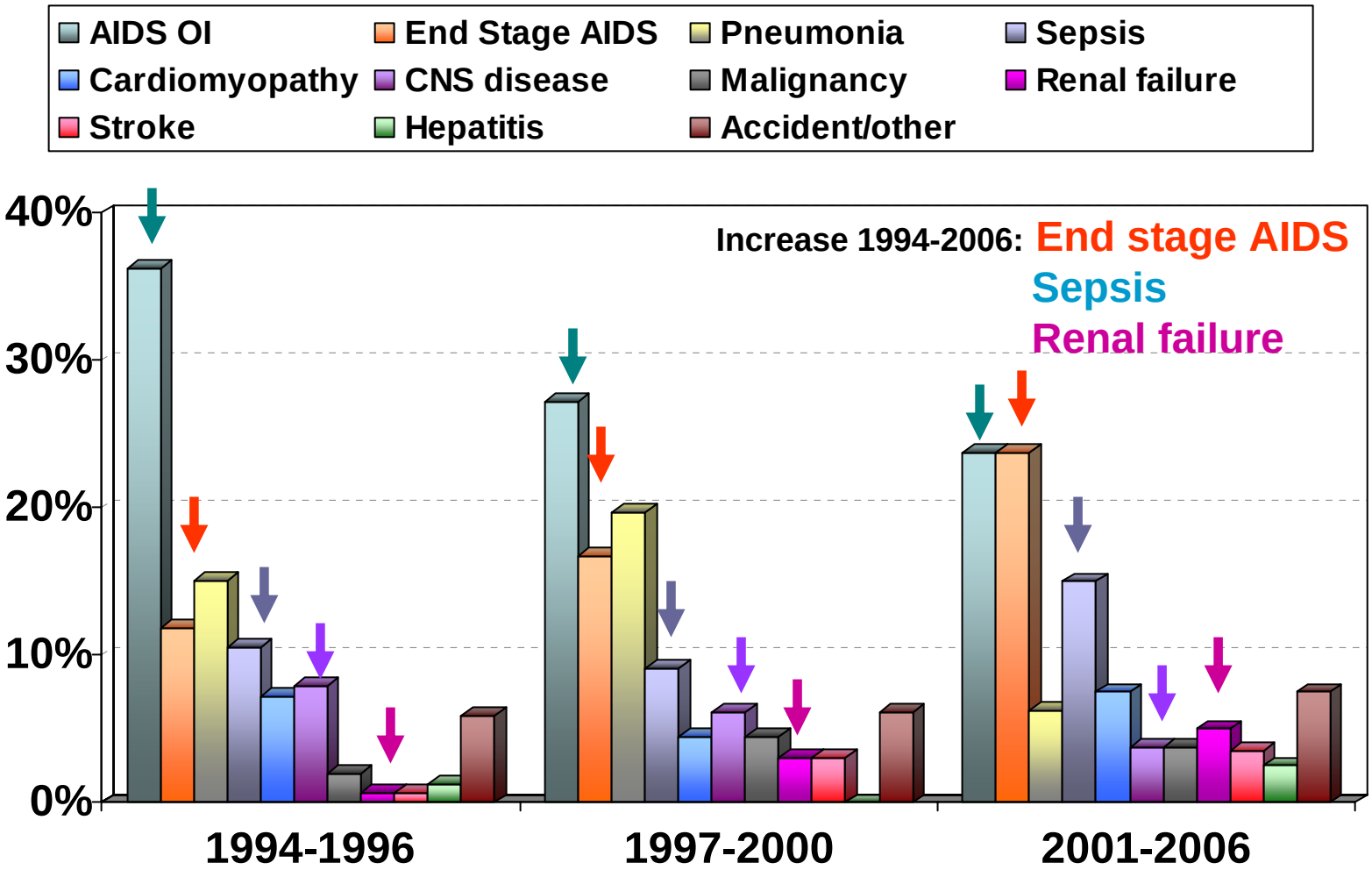
Mean age at death 1994: 8.9 years

HAART Era

Courtesy Mike Brady, Paige Williams

National Institute of Child Health and Human Development (NICHD)

Primary Causes of Death (1994-2006) in HIV-Infected Children Enrolled in PACTG 219



3,553 children
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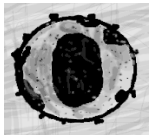
Courtesy Mike Brady, Paige Williams

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



Prevalence of Transmitted Primary ARV Drug Resistance in New Perinatal HIV Infection

Type of Resistance	NY* 98-99[1] (N=91)	NY* 01-02[2] (N=42)	US 02-05[3] (N=21)
Any resistance	12.1%	58% increase → 19.1%	23.8%
NRTI	7.7%	7.1%	14.3%
NNRTI	3.3%	11.9%	19.0%
PI	3.3%	2.4%	0%
≥2 classes	2.2%	2.4%	9.5%

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

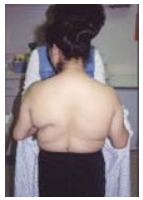
[1]Parker MM, et al. *JAIDS* 2003;32:292-7.
[2]Karchava M, et al. *JAIDS* 2006;42:614-9.
[3]Persaud D, et al. *J Infect Dis* 2007;195:1402–10.

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**

Long-term Complications of HIV Infection and of Antiretroviral Therapy in Children

- **Metabolic complications**
  - **Abnormal fat accumulation & wasting**
  - **Abnormal lipid profiles**
  - **Insulin resistance**
  - **Osteopenia/bone disease**
- **Mitochondrial toxicity**
- **Liver disease**
- **Renal disease**
- **Adolescent obesity**



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 hyper-insulinemia 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 Lipdystrophy Group. *AIDS*. 2004;18:1443-1451
McComsey G et al. *Pediatrics.* 2003;111:e275-81

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.**

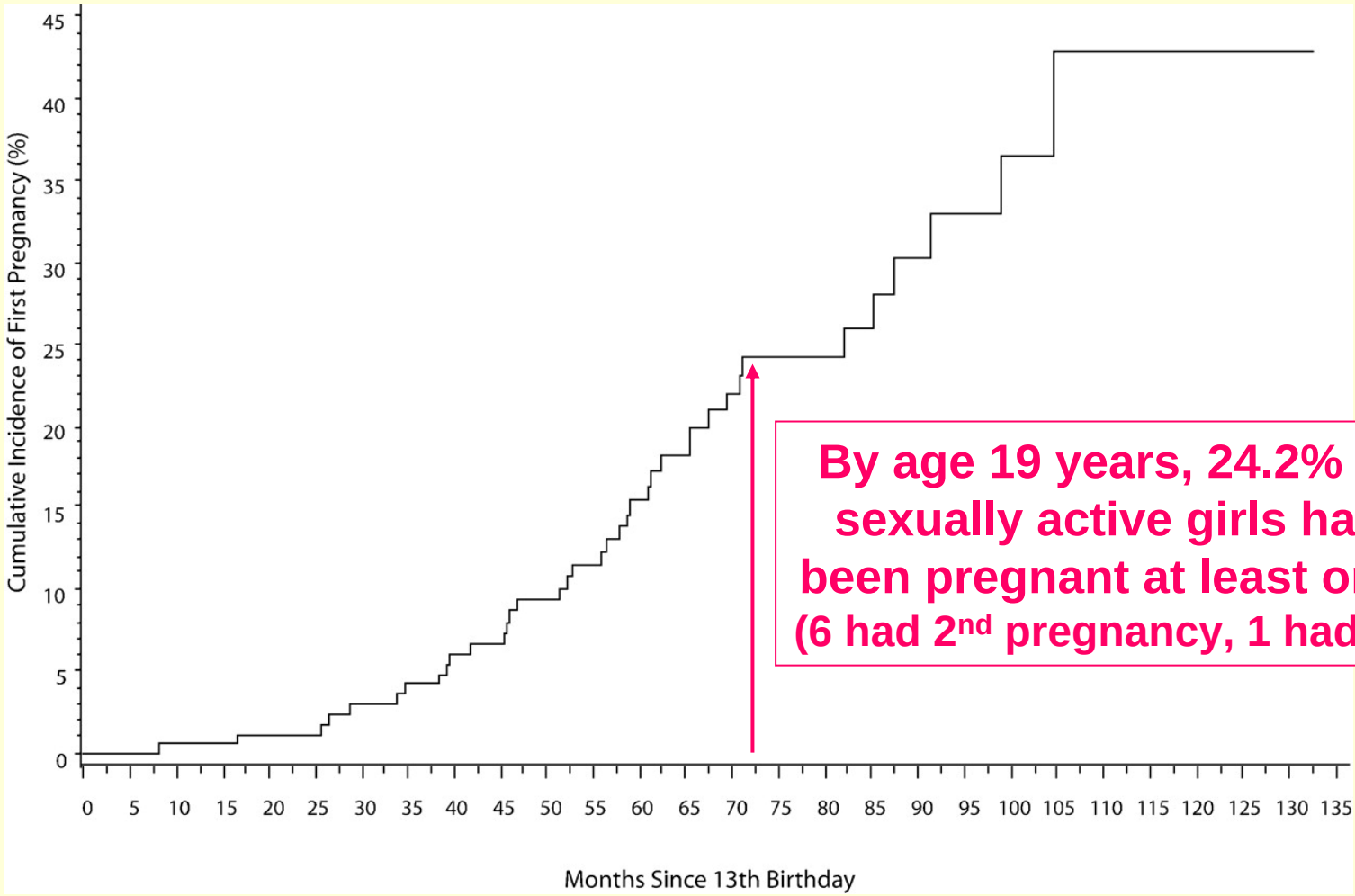
Rice E et al. Prospect Sex Repro Health 2006;38:162-7
Murphy DA et al . J Adol Health 2001;29S:57-63
Sturdevant MS et al. J Adol Health 2001;29S:64-71
Kadivar H et al. AIDS Care 2006;18:544-9
Rotheram-Borus M et al. J Adoles 2001;24:791-802
Lightfoot M et al. Am J Health Behav 2005;29:162-71.

Considerations for Treatment of Adolescents

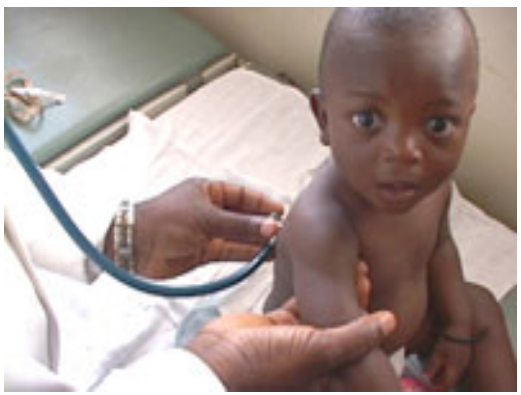
- **Provide counseling on contraception & safer sex**
- **Avoid efavirenz in girls who may become pregnant by choice or through inconsistent use of birth control**
- **Be aware of drug interactions between oral contraceptives & certain PIs & NNRTIs**
  - **Depending on the specific interaction, may lead to failure of the contraceptive or of ART; in some cases, may cause toxicity**
  - **Efficacy of injectable progestogen contraceptives in women on ARVs is unclear**
  - **No data on hormonal contraceptive patch or vaginal ring**

Cumulative Incidence of First Pregnancy in 174 Perinatally HIV-Infected Sexually Active Girls Age >13 Years, PACTG 219C

Brogly SB et al. Am J Public Health 2007;97:1047-1052



Challenges in Management of Pediatric HIV Infection in Low Resource Countries

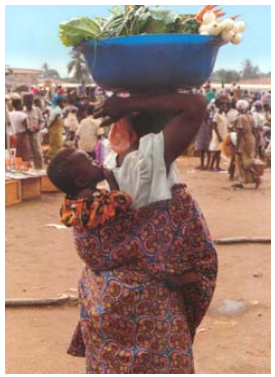


#1 Challenge in Low Resource Countries:

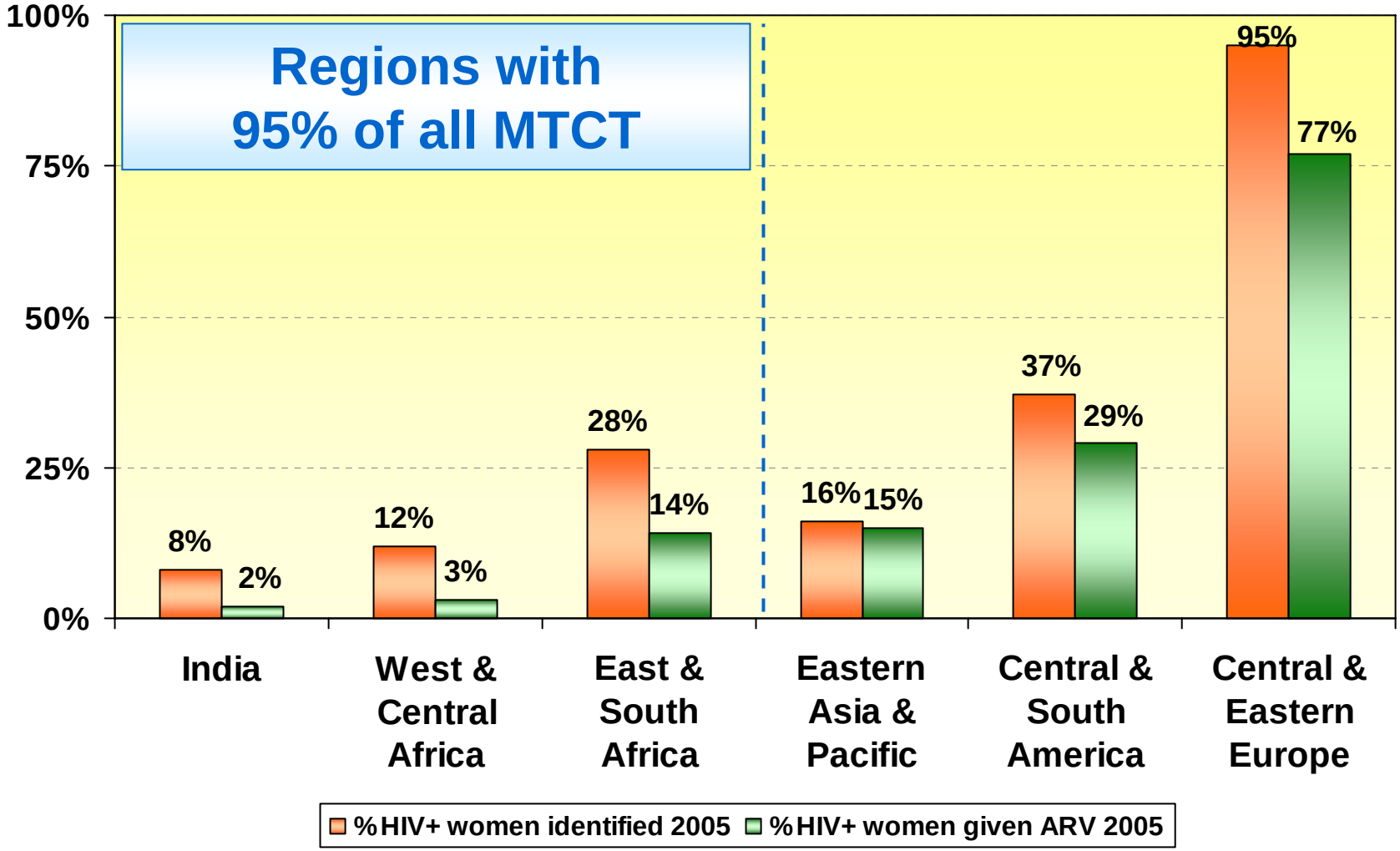
Continued HIV Transmission to Women

and

Poor Implementation of PMTCT



Despite Effective Regimens to Prevent MTCT, Globally Only 11% of Women Receive ARV Prophylaxis



Interagency Task Team on PMTCT Report Card Feb 2007 UNICEF/WHO/UNAIDS

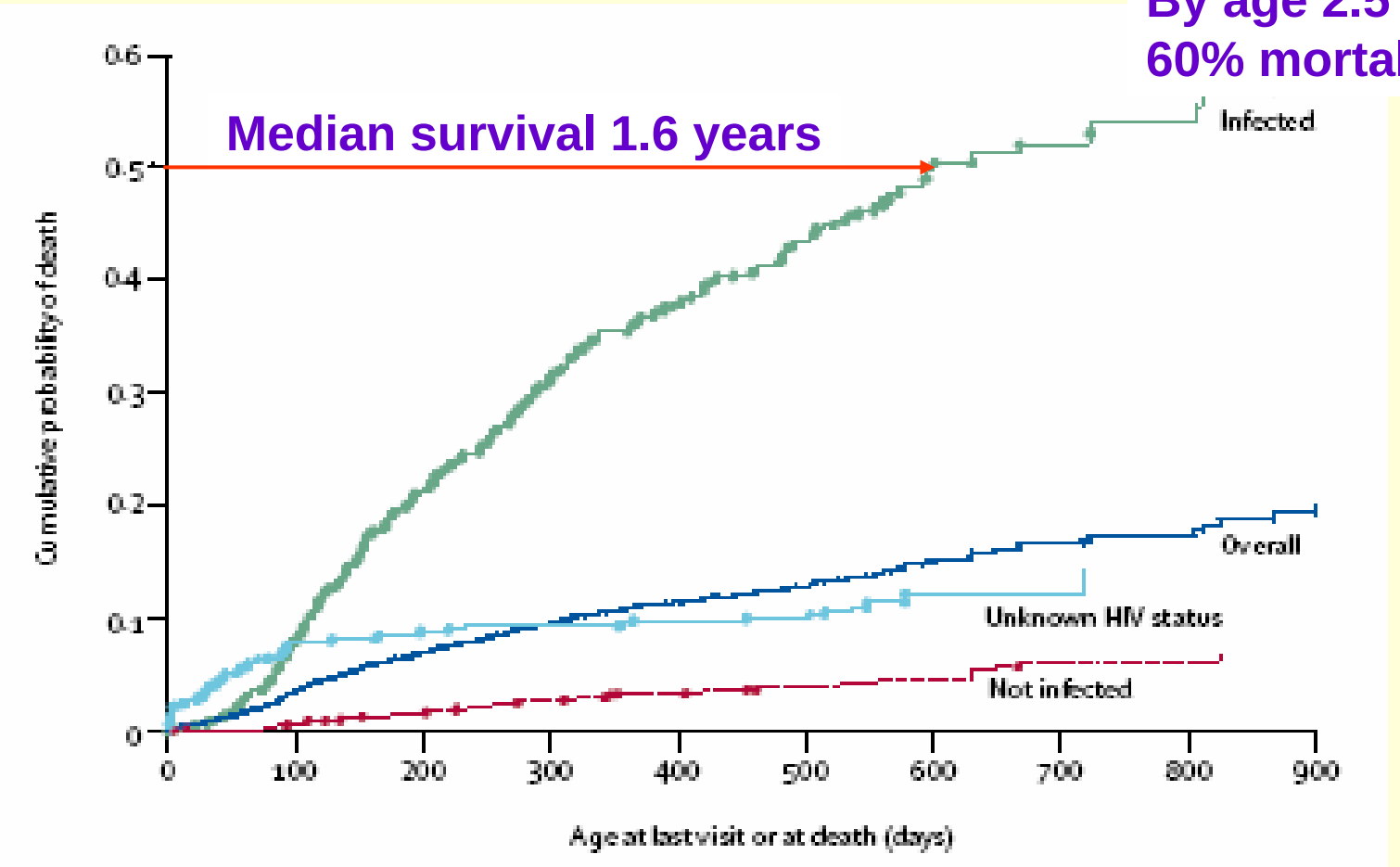
The Challenge of Pediatric HIV Infection in Resource-Poor Countries

- **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

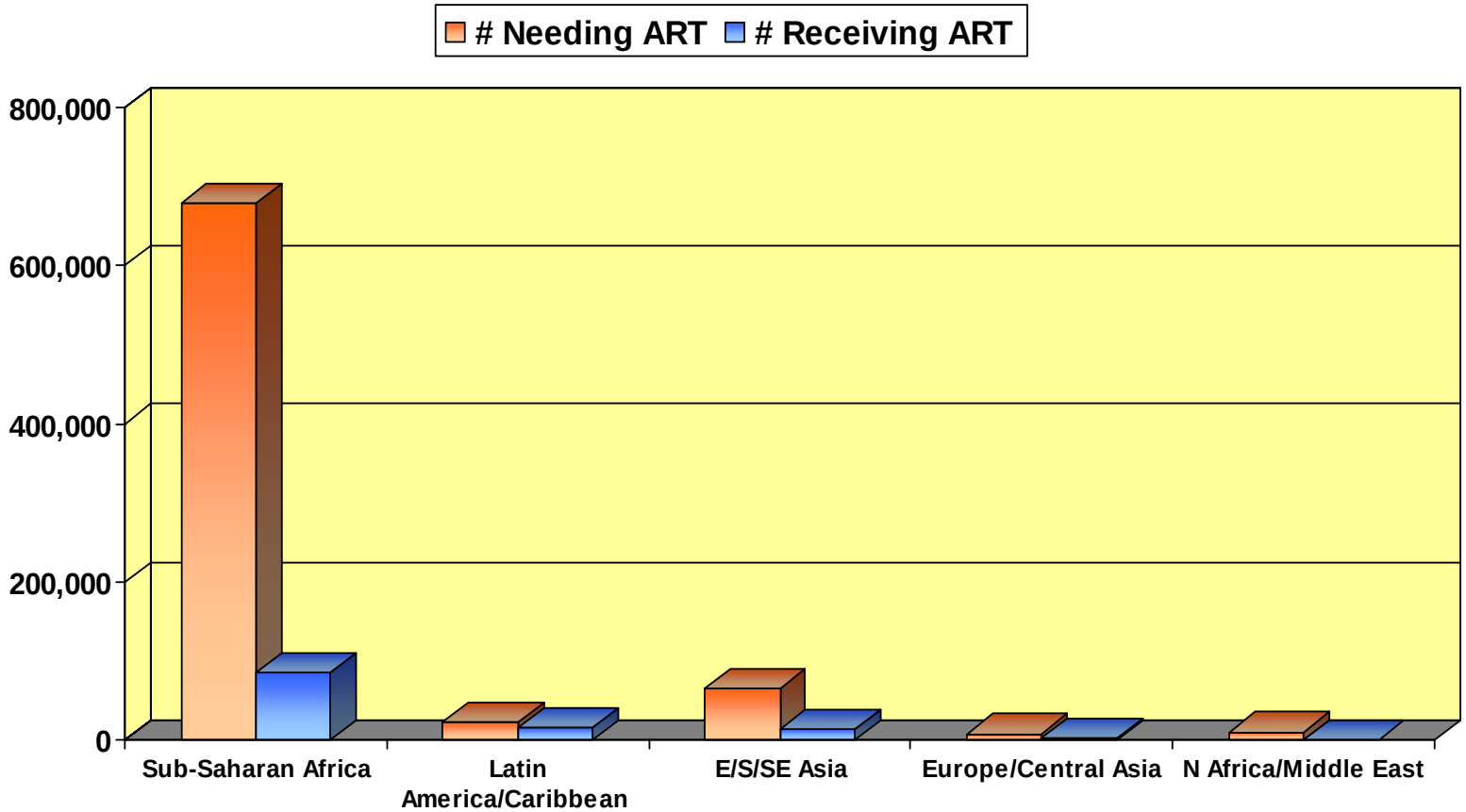
Newell et al. Lancet 2004;364:1236-43

By age 2.5 years, 60% mortality



Estimated Number of HIV-Infected Children Needing and Number Receiving Antiretroviral Treatment

By Region as of December 2006



ARV Coverage	13%	67%	21%	20%	<1%

Source: World Health Organization, April 2007

World Health Organization UNAIDS

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 *Abs 584* 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)
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)

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)

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 ***Van der Linden PIDJ 2007***	17	<2.5 mos	<50, 71% at 4.7 yrs	• No AIDS • 82% CD4 >25%
PACTG 356 ***Luzuriaga NEJM 2004***	25	<3 mos (median 2 mos)	<400, 60% at 4 yrs	• No AIDS, 4 yr
PENTA 7 ***PENTA AIDS 2004***	20	<5 mos (median 2.5 mos)	<400, 44% at 1.5 yrs	• No AIDS, 1.5 yr • 90% CD4 >25%
Italian Register ***Chiappini AIDS 2006***	30	<6 mos (median 3.6 mos)	Undetect 73% at 4 yrs	• No AIDS, 4 yr • 97% CD4 >25%
PACTG 1030 ***Chadwick AIDS 2008***	21	<6 mos (median 3.7 mos)	<400, 53% at 6 mos	
French Perinatal ***Faye PIDJ 2002***	31	<12 mos (median 3.7 mos)	<500, 18% at 2 yrs	• No AIDS, 2 yr • 88% CD4 >25%

Why Consider Stopping HAART in Children?

- **Biphasic disease progression with high risk first year of life, slower progression later.**
- **Treatment of neonate more analogous to treatment of acute primary infection.**
- **Children have developing immune system and greater capacity to regenerate immune system with treatment due to active thymus.**
- **Life-long treatment starting in infancy raises significant issues of long-term drug toxicity, adherence, resistance.**

Ongoing Pediatric Treatment Interruption Trials

	Age Starting HAART	Duration HAART Pre-Interrupt	Immune Criteria to Interrupt	Criteria to Restart HAART
CHER S. Africa (N=250)	<12 wks	1 or 2 yrs	CD4 ≥25%	CD4 <25%, Clinical
OPH03 Kenya (N=100)	<12 wks	2 yrs	CD4 ≥25% and normal growth	CD4 <15% or ↓>⅓ of peak, Clinical
BANA II* Botswana (N=600)	**6 mos-13 yrs**	**>6 mos**	**CD4 ≥25% (CD4 Immune 1)**	**CD4 <25% (CD4 Immune 2/3)**
PENTA 11* Europe/US (N=100)	**2-15 yrs**	**>6 mos**	**CD4 ≥30% (age 2-6 yrs); CD4 ≥25% and CD4 >500 (age 7-15 yrs)**	**CD4 <20% (age 2-6 yrs); CD4 <20% or CD4 >350 (age 7-15 yrs)**

*** Require HIV RNA undetectable prior to interrupt**

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

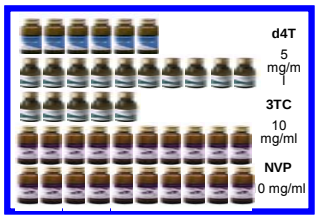
- **Pediatric formulations**
  - **Fewer ARV approved in children**
  - **More costly than adult preparations**
  - **FDC just becoming available**
- **Dosing weight/size based, change as child grows, problems for busy health clinic.**
- **Liquid drugs transport/storage problems.**
- **Complexity of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

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

What is Becoming Available for Children --- BUT NEED

Scored crushable FDCs

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

Conclusion

- **Clinical care and treatment evolves rapidly**
- ***U.S. Pediatric Guidelines Working Group* meets monthly, reviews clinical trials results, and updates guidelines**
- ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*—February 28, 2008**
- **Published text posted on www.aidsinfo.nih.gov**
- **AIDS Education and Training Center—National Resource Center has fact sheets and slide presentations for education at www.aids-etc.org**

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**

¿Which of the following is true concerning current treatments of HIV-infected children?

a) Dose adjustments of available HAART medications are necessary based on physical growth and developmental parameters.
b) Children do not exhibit lipid or cardiovascular side effects of HAART drugs.
c) Adolescent females with HIV infection do not require contraception for sexual activity, since they are sterile.
d) Maternal breast feeding is recommended for HIV exposed infants.
e) All of the above.
f) I'm sorry, I did not learn.

Thank You For Your Attention

National Institute of Child Health and Human Development (NICHD)

Thanks to
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