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19th Annual HIV CONFERENCE
May 14-15, 2010 • Orlando, FL

Is an AIDS-Defining Condition the End of the Road?

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Objectives

- Compare the impact of early vs. late initiation of HAART in morbidity and mortality outcomes in pediatric HIV.
- Examine the differences in major clinical outcomes after initiation of HAART between HIV-infected children from developed countries vs. resource-limited countries.
- Describe the effects of AIDS in immunological recovery.



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HIV/AIDS and Children

- An estimated 2.7 million people were infected with HIV in 2007, including 370,000 children **under age 15.** (*Global AIDS Alliance*)
- **80 % of children with HIV die by age five without treatment; 80 % are alive at age six with ARV treatment.** (*Global AIDS Alliance*)
- Every minute, one child under age 15 dies from AIDS or an AIDS-related illness.
(UNICEF)



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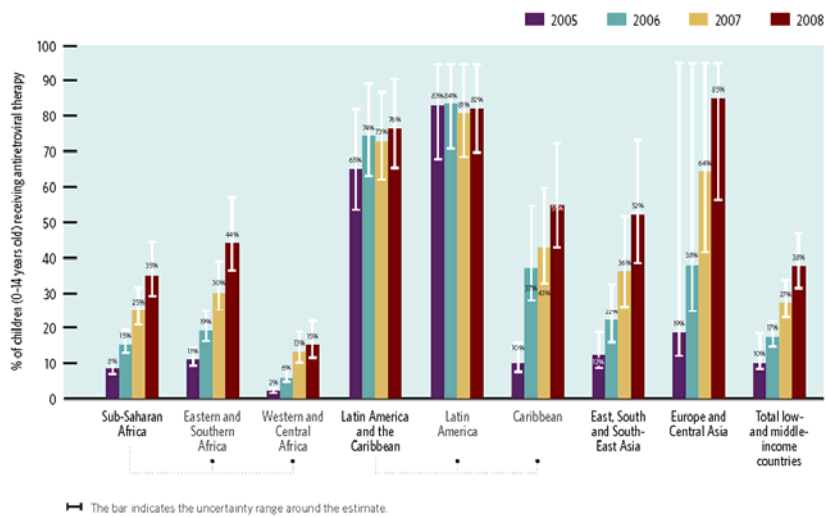
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Prognosis of HIV-infected Children in Resource-Limited Countries

- **Poorer prognosis than in developed countries for several reasons:**
 - **Child survival lower in Africa in general**
 - Malnutrition and/or poverty
 - Concurrent infections (malaria, TB, diarrhea)
 - **Health systems are weaker**
 - Lack of access to health care services
 - Delayed laboratory diagnosis; PCR not available
 - Lack of access to basic HIV care and ART



Percentage of children receiving antiretroviral therapy in low- and middle-income countries, 2005–2008



CHER Trial

- **Children with HIV Early Antiretroviral Therapy**
- **Phase 3, randomized, open label trial**
- **Addressed the optimal time of initiation and duration of ART in infants with in utero or intrapartum HIV-1 infection**
- **Conducted in two centers in South Africa, in Soweto and Cape Town.**
- **Between 8/05 and 2/07, 377 infants were enrolled:**
 - 125 randomly assigned to the deferred-therapy group
 - 252 randomly assigned to the early-therapy groups

Violari, A et al. *NEJM* 2008;359:2233-44.



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CHER Trial

- **Early mortality was reduced from 16% to 4% (relative reduction of 76%) when ART begun at median age of 7 wks, compared to starting ART according to threshold CD4 % or clinical progression of HIV dz.**
- **In the deferred-therapy group:**
 - Rapid decrease in CD4 values
 - Rapid dz progression (32 pts vs 16 in early tx group)
 - Excess deaths could not be prevented



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Severe Acute Malnutrition

- Malawi, cohort of 454 children with SAM, 17% HIV infected, all of them w/o ART.
- HIV-infected children are more likely to die than HIV-uninfected children (35% vs. 14%).
- Those HIV-infected children with advanced disease and low CD4% were at a **higher risk of mortality**
- Children with CD4% < 20% gained weight less rapidly than those with a CD4% > 20% (7.6 g/kg/d vs 11.9 g/kg/d, NS).
- HIV-infected children with severe acute malnutrition who survive nutritional rehabilitation achieve and maintain nutritional recovery as well as HIV uninfected children.

Fergusson, P et al. *Arch Dis Child* 2009;94:512–516.



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Survival into Adulthood of Perinatally HIV-infected Youth

- **Encourages expansion of pediatric treatment programs in low-resource countries.**
- **Provides lessons about how the epidemic changes with increasing access to ART for children.**



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Continuing Improvement in Survival for Children with AIDS in Brazil

- **Probability of survival to 60 months increased steadily over the years.**
 - Cases diagnosed from 1997 to 1998 had a probability of survival of 74.7%
 - Cases diagnosed from 1999 to 2002, probability of survival increased to 86.3%
- More consistent and effective use of HAART: free universal access in Brazil since 1996.
- Wider access to early diagnosis and treatment of HIV and OIs.
- Comparable to survival rates from affluent countries.



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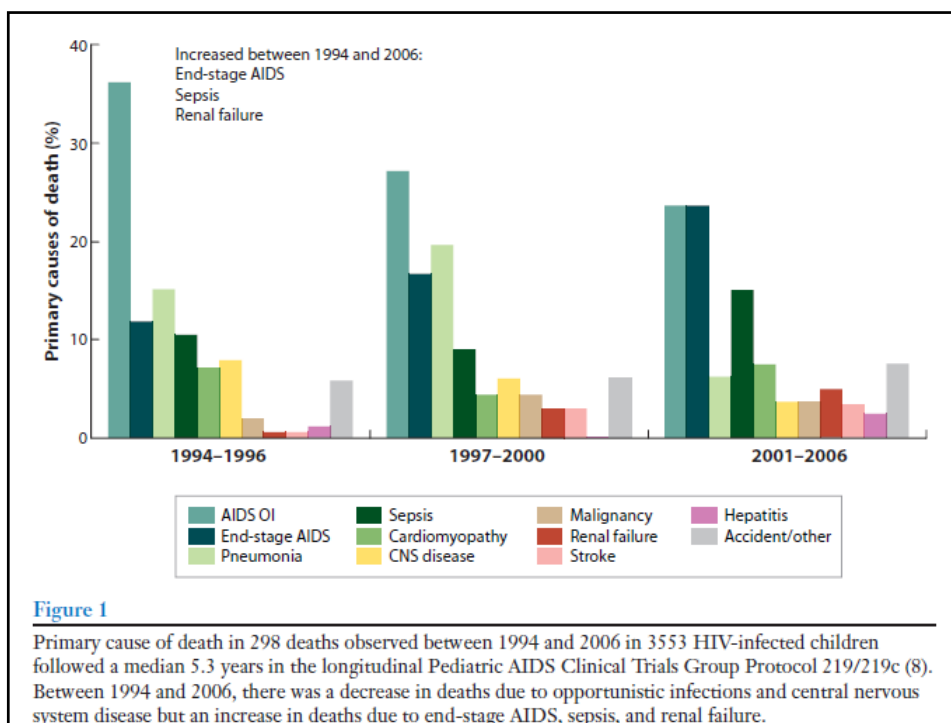
Pediatric HIV Care

- **Now focuses on morbidity related to long-term HIV infection and its treatment.**



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Nationwide Trends in Hospitalizations HIV-Infected Children (1994-2003)

- **Data from the Nationwide Inpatient Sample**
 - 71% decrease in number of hospitalizations of HIV infected children ≤ 18 y/o
 - In 1994 11,785 hospitalizations
 - In 2003 3,419 hospitalizations
 - Inpatient fatality rate decreased from 5% in 1994 to 1.8% in 2004.

Kourtis, AP et al. *Pediatrics* 2007;120:e236-e243



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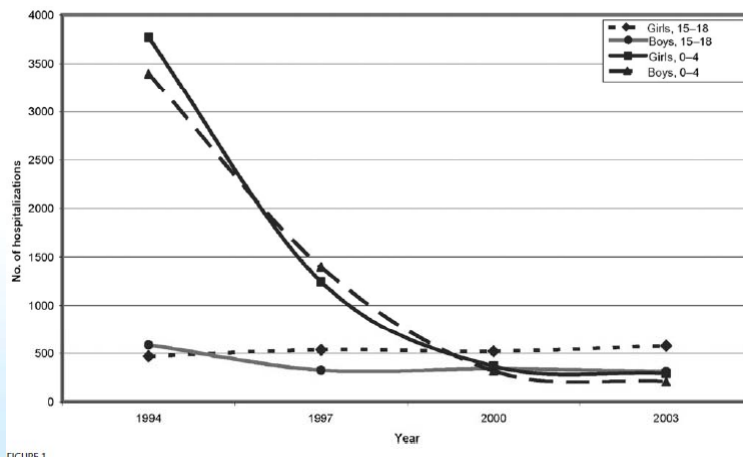
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Decrease in Number of Hospitalizations

- Most profound decrease for infants and young children.
- The number of hospitalizations for adolescents has not decreased.
- The number of hospitalizations among adolescent girls actually increased.
 - Alarming increase in the number of newly acquired HIV infections among adolescents.
 - Increase in the survival of perinatally infected children in the US.

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Number of hospitalizations of HIV-infected boys and girls: United States, 1994 –2003.



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Significant Decrease in Number of Hospitalizations

- *Pneumocystis jiroveci*
- Bacterial infections
- Sepsis
- Fungal infections
- Encephalopathy
- FTT
- Lymphocytic interstitial pneumonitis

- No significant change for pneumococcus or CMV

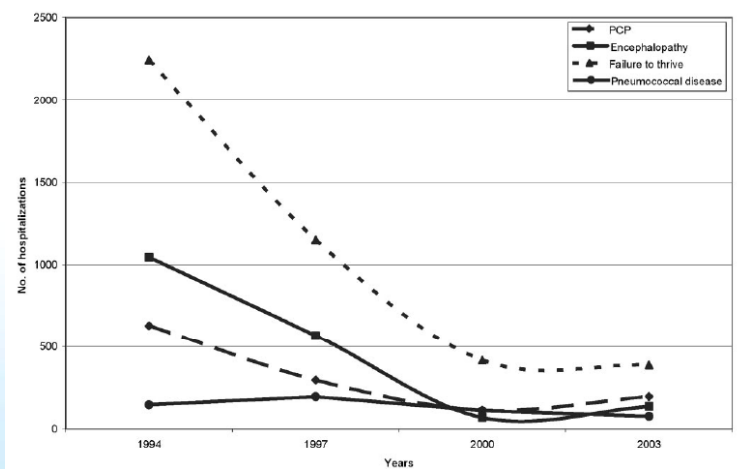
Kourtis, AP et al. *Pediatrics* 2007;120:e236-e243.



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**Number of pediatric hospitalizations for selected
HIV-related conditions: U S 1994 –2003**





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Cancer Rates After Year 2000 Significantly Decrease in Children With Perinatal HIV Infection

- **Observational population study: 1,190 perinatally HIV-infected children enrolled onto the Italian Register for HIV Infection in Children from 1985 to 2004**
- **Cancer rates (per 1000 children per year):**

1985-1995	4.49
1996-1999	4.09
2000-2004	0.76
- **The cancer incidence in HIV-infected children after year 2000, remained ~5x higher than in the general population.**

Chiappini et al. *Journal of Clinical Oncology*, 2007;25:97-101



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Continuous improvement in the immune system of HIV-infected children on prolonged antiretroviral therapy

- **Robust immune reconstitution on HIV-infected children in response to 3 years of effective HAART.**
 - Cohort of 37 children receiving their first HAART regimen.
 - All were perinatally infected.
 - Limited or no prior exposure to ARV.
 - ddl + FTC + EFV once per day.
 - Best predicted by the baseline immunologic characteristics of the patients.
 - Baseline CD4+% predicted the recovery of CD4+ T-cell numbers and function in response to HAART.
 - Thymic output in response to HAART increased with higher thymic function at the initiation of therapy.

Weinberg, A et al. *AIDS* 2008; 22:2267-77.



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Immune Reconstitution

- HIV-infected children undergo progressive immune reconstitution in response to HAART that could potentially lead to normalization of immune parameters.
- Not only CD4+ T cells, but **also functional and phenotypic immune measures** continue to improve in HIV-infected children over 3 years of effective HAART



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Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland

- **944 children with perinatally acquired HIV were reported in the United Kingdom and Ireland by October 2002**
- **Mortality was stable before 1997 at 9.3 per 100 child years at risk but fell to 2.0 in 2001-2**

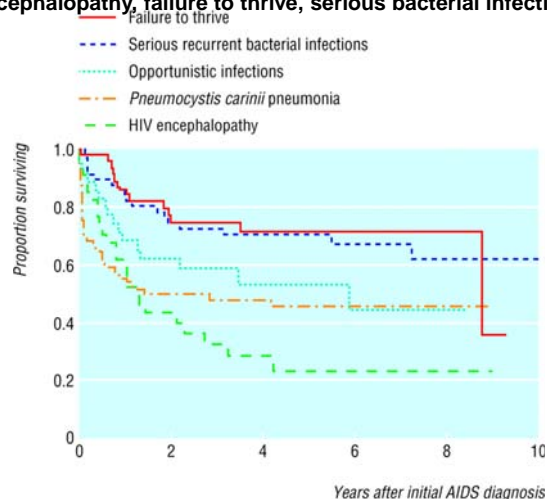
Gibb, D M et al. BMJ 2003;327:1019



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Fig 2 Survival after initial AIDS diagnosis, by presenting indicator disease. Six cancer cases are excluded. Only one indicator disease is shown for children presenting with more than one according to hierarchy: *P. carinii* pneumonia, other opportunistic infection, HIV encephalopathy, failure to thrive, serious bacterial infections



Gibb, D M et al. BMJ 2003;327:1019

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Patient P.

- **21 y/o BM with perinatally acquired HIV infection**
- intrauterine exposure to cocaine
- mother had chronic active hepatitis B, which he also acquired perinatally.
- 11/98: presumptive *Mycobacterium avium complex* because of multiple rectal and colonic ulcerations were visualized during lower endoscopic procedure as part of a diagnostic investigation for chronic diarrhea

P.

- 9/99: colonic perforation during colonoscopy
 - VL >750,000, CD4 161 (10%)
 - Reanastomosed on 10/09, but developed fistulae, requiring diverting colostomy.
- Coagulopathy, superior vena cava syndrome, DVT. On lovenox for lifetime.
- FSIQ = 70
- Adherent to HAART (d4T+ TDF + LPV/r), VL <400, CD4 383 (22%). Pull through of colostomy.
- Stopped taking meds. Nadir of CD4= 27 (3%) in 3/09.



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P.

- Weakness, blurred vision, dysdiadochokinesis, dysarthria. Progressed to inability to ambulate w/o assistance.
- MRI brain (3/30/09): Multifocal cortical/subcortical areas of subtle high signal abnormality c/w progressive multifocal leukoencephalopathy .
 - PCR from plasma and CSF detected presence of JC virus.
- Reinstitution of HAART with (TDF +FTC) + LPV/r
- VL ,48 since 5/09; CD4= 169 (9%) in 11/09.



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Patient S.

- 18 y/o WF with perinatally acquired HIV
- Recurrent bacterial infections
- FTT
- Cryptosporidiosis
- Esophagitis by *Candida* and CMV at 4 y/o
- CD4 206 (5%), VL 280,000
- Short stature – growth hormone injections
- FSIQ =89



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S.

- Immune reconstitution
 - CD4=1814 (46%), VL undetectable since 12/01
 - d4T + EFV + LPV/r – switch 2ry to lipodystrophy
 - Remains on (FTC + TDF)+ LPV/r since 9/05



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Patient E.

- 20 y/o BM from Congo
- Transferred to JMH for tx of “infection on leg”
- Diagnoses of Kaposi sarcoma, bacillary angiomatosis, cellulitis of leg.
- In 11/06: CD4 = 190 (12%), VL 15,000
- Started chemotx 12/06
- ART: (ZDV + 3TC) + LPV/r
- Intermittently non-adherent.
 - CD4= 396 (17%), VL 350.



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New Challenges as Perinatally HIV-Infected Youth Survive into Adulthood

- **Maintaining adherence to long-term, life-long therapy**
- **Selecting successive antiretroviral drug regimens**
 - Limited availability of pediatric formulations
 - Lack of pharmacokinetic and safety data in children
- **Overcoming extensive drug resistance in multi-drug experienced children**



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AIDS is Not a Death Sentence

“Given that medicine can turn AIDS from a death sentence into a chronic illness and reduce mother-to-child transmission, our withholding of treatment will appear to future historians as medieval, like bloodletting.”

--William J. Clinton (NYT, 12/1/02)



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