Florida/Caribbean AETC AIDS Education and Training Center
19th Annual HIV CONFERENCE
May 14-15, 2010 • Orlando, FL

HIV in Children: Thirty years of Discovery and Challenges

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USF HEALTH

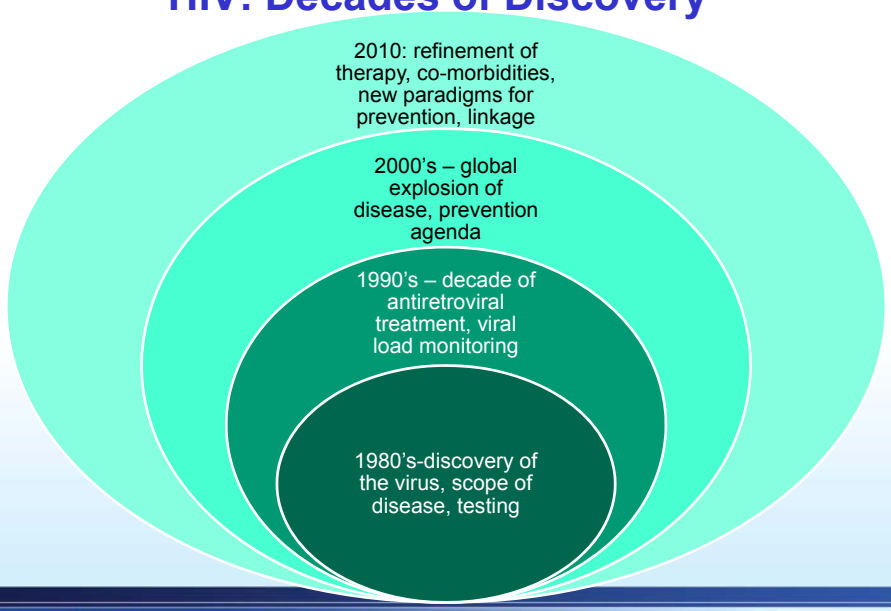
Disclosure of Financial Relationships

This speaker has the following significant financial relationships with commercial entities to disclose:

- **Advisory Board: American Academy of Pediatrics – Committee on Pediatric AIDS**

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

HIV: Decades of Discovery



Objectives

- Review the history of the HIV epidemic in children in the U.S. and advances and challenges in the prevention of Mother to Child Transmission (MTCT) of HIV.
- Discuss the natural history of HIV infection in children and success of treatment in developed world.
- Highlight evolving concepts of antiretroviral treatment and acute and long term complications.

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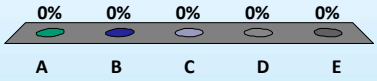
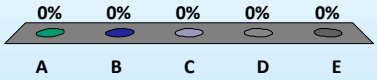
What is your role?

A. Nurse
B. Case manager
C. Social worker
D. Physician
E. ARNP/PA



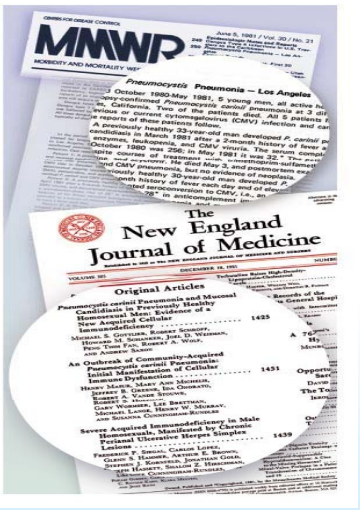
How long have you been involved in care or prevention of HIV?

A. One year or less
B. One to Five years
C. Between five and ten years
D. Before protease inhibitors were developed
E. Since before someone shot JR on Dallas



Milestones in Pediatric HIV

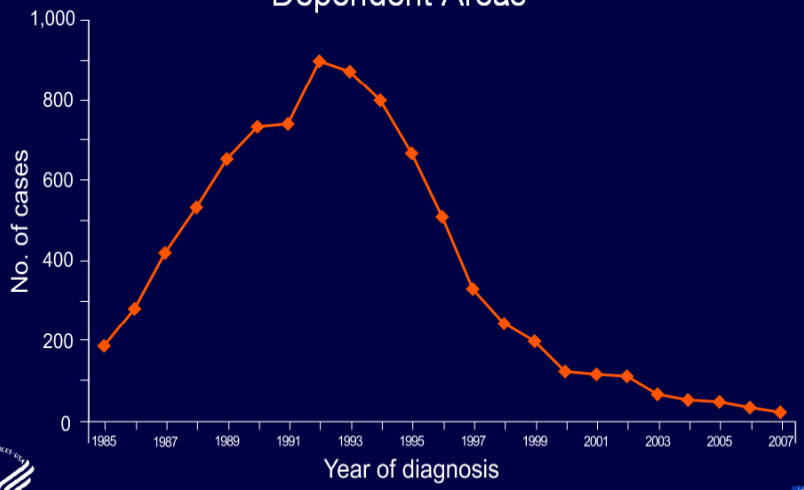
- First cases of PCP pneumonia described in MSM in 1981.
- In 1983, Dr Scott reported 14 infants with an acquired immunodeficiency syndrome. The findings included failure to thrive, oral Candidiasis, infiltrates, HSM, lymphadenopathy, and diarrhea. Later studies showed most infections were transmitted vertically.
- 1988: Pizzo reports on use of Zidovidine in kids; 1989:Retrovir syrup approved.
- 1994: Results of PACTG 076 are released.
- 1995: Protease inhibitors begin large phase 3 testing.



Scott, GB,N Engl J Med. 1984 Jan 12;310(2):76-81.

Gottlieb M. N Engl J Med 2001;344:1788-1791

Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas



Note. Data have been adjusted for reporting delays and missing risk-factor information.

"Dramatic success; but every HIV positive infant should be considered a failure"

Groups still at risk:

- **Late presenters without prenatal care and those with acute seroconversion during pregnancy.**
- **Women seen in antenatal care but not offered voluntary counseling/testing**
- **HIV infected pregnant women who were prescribed but did not take antiretrovirals**
- **Those with substance abuse and mental health co-morbidities**
- **Unexplained "failures"**

Time of Maternal HIV Testing among Children with Perinatally Acquired AIDS, HIV Exposure or HIV Infection Reported in 2007—United States and Dependent Areas

	Perinatally Acquired AIDS N=73		HIV Exposure* N=2,361		HIV Infection† N=529	
Time of maternal HIV test	No.	%	No.	%	No.	%
Before or at birth	28	38	2,240	95	213	40
After birth	29	40	47	2	138	26
Unknown	16	22	74	3	178	34

*From 33 areas that report perinatal exposure.
†From 53 areas with confidential name-based HIV infection reporting.

In the State of Florida, Counseling and HIV Testing For ALL Pregnant Women is the LAW!

- **A practitioner attending a pregnant women should provide counseling and offer HIV testing:**
  - -At the initial prenatal care visit,
  - -At 28 to 32 weeks gestation for all pregnant women, regardless of risk behaviors.
- **"Opt-out"**-HIV testing is a routine part of prenatal screening, a woman can opt-out, in writing.
- Confidential, culturally sensitive and non judgmental
- Rapid testing during labor for women without documented HIV status
- Immediate postpartum maternal test or newborn HIV test if no previous results available
  - •Initiate prophylaxis and confirm positives

Evaluation of HIV exposed infant

Action[a]	Infant Age						
	Birth	14 d	4 wk	6 wk	8 wk	4 mo	12–18 mo
History and physical examination[b]	X		X				
Assess risk of other infections	X						
ARV prophylaxis[c]	→	→	→	→			
Recommend against breastfeeding	X→						
Hemoglobin or complete blood cell count	X		X[d]		X[d]		
HIV-1 DNA PCR or RNA assay[e]	[f]	X[g]	X		[h]	X	
Initiate PCP prophylaxis[i]				X			
Enzyme immunoassay for antibody to HIV-1[j]							X

AAP, Pediatrics, 2008

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Diagnostic Testing in Infants

- **Presumptive rule-out of HIV infection**
  - 2 or more negative virologic tests
    - One at age ≥14 days and one at ≥1 month; or
    - One negative virologic test at ≥2 months; or
    - One negative HIV antibody test ≥6 months
- **Definitive rule-out of HIV infection**
  - 2 or more negative virologic tests
    - One at ≥1 month; or
    - One negative virologic test at ≥4 months; or
    - 2 negative HIV antibody tests ≥6 months
- **No other laboratory or clinical evidence of HIV infection**

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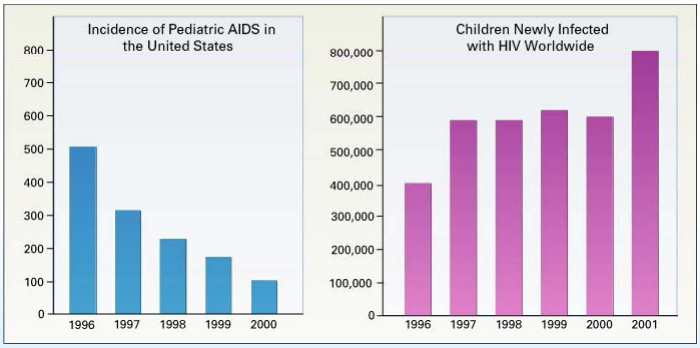
Diagnostic Testing in Infants

- **If any of the HIV-1 virologic test results are positive, immediately repeat to confirm the diagnosis of HIV-1 infection.**
- **Criteria for HIV diagnosis:**
  - 2 positive HIV virologic tests (NAAT-HIV-1 DNA or RNA) on separate blood samples (regardless of age)
  - Positive HIV antibody test with confirmatory Western blot (or IFA) at age ≥18 months

U.S. data are from the Centers for Disease Control and Prevention, and international data are from the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization



Steinbrook R. N Engl J Med 2002;346:1842-1843

The NEW ENGLAND JOURNAL of MEDICINE

What is the approximate percent of pregnant women get routine prenatal HIV testing in the US?

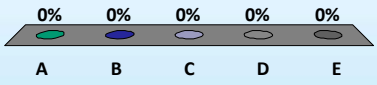
A. 20%

B. 40%

C. 60%

D. 80%

E. >95%



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What is the approximate percent of pregnant women tested for HIV in Africa?

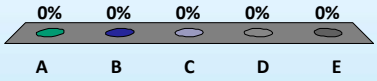
A. <10%

B. 20%

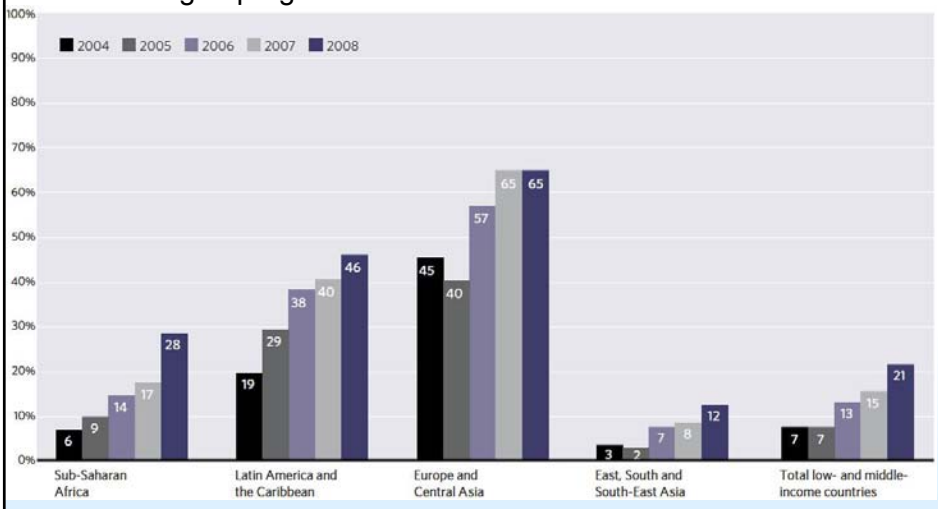
C. 40%

D. 60%

E. >80%



HIV testing of pregnant women in low and middle income countries



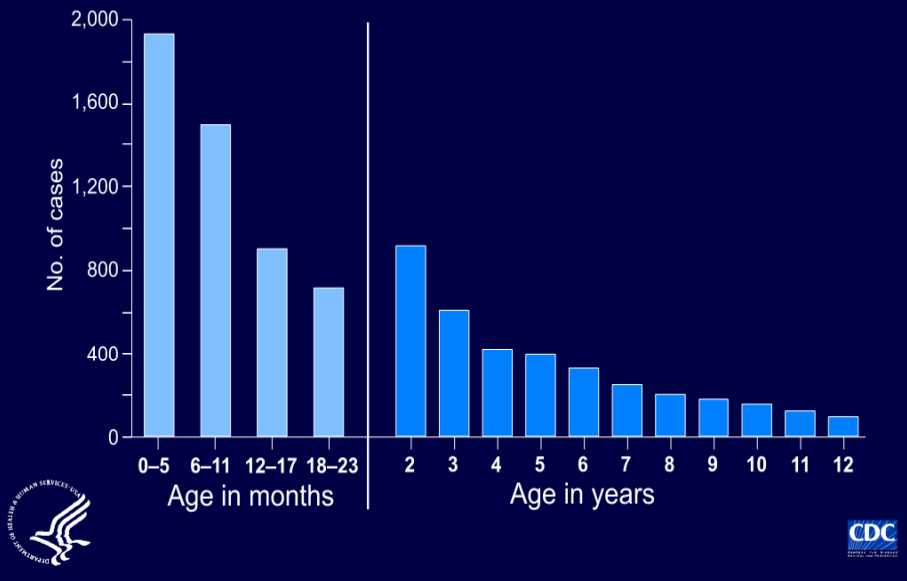
WHO, UNAIDS, UNICEF. *Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report 2009.*

Natural History of HIV-Infected Children
(US and Europe pre HAART)

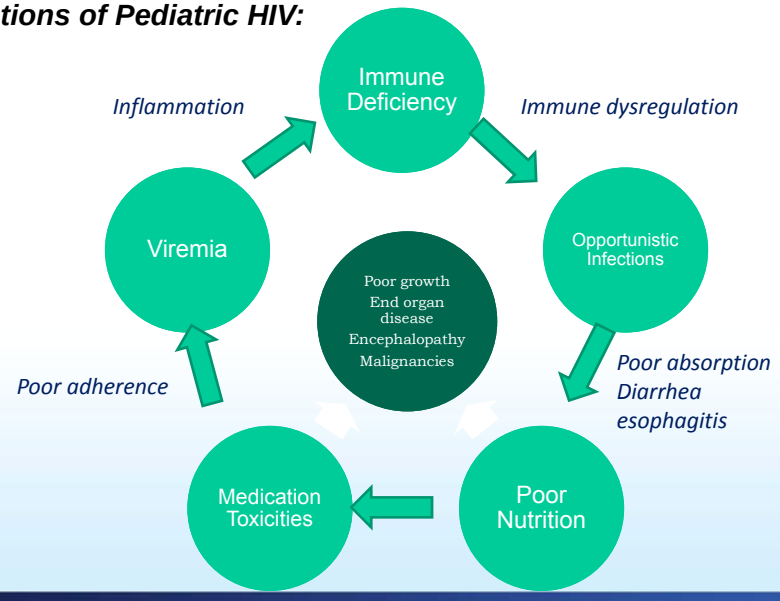
- Rapid progressors - 20% of patients
- Intermediate/slow progressors - 60-75%
- Long term survivors/late progressors - 5-10%
- Overall median survival time for perinatal infection is 8 to 9 years
- Immune status poorly reflects clinical status

Pediatrics 2001;108:116 –122
CID 2007 ; 45; 785-794

Reported Perinatally Acquired AIDS Cases, by Age at Diagnosis
Cumulative through 2007—United States and Dependent Areas



Complications of Pediatric HIV:

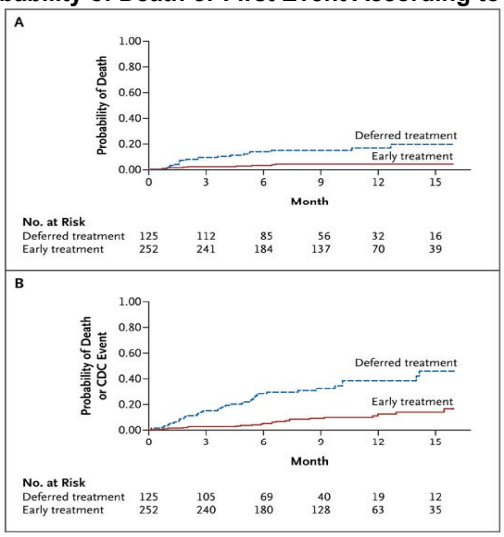


Symptomatic HIV in the First Year

- **Failure to thrive**
  >50% will have Wt & Ht < 5%
- **Developmental Delay**
  30% will have HC < 5%
  20% will have cortical atrophy on CT
  40% will have abnormal motor function
- **Opportunistic infections**
  PCP, Candidiasis, diarrhea
- **AIDS defining illness in first year associated with median survival 7 months**

Englund PIDJ,1996
Pediatrics 2001;108:116 –122

CHER Study: Probability of Death or First Event According to Treatment Group



Violari A et al. N Engl J Med 2008;359:2233-2244

The NEW ENGLAND JOURNAL of MEDICINE

ART Initiation: Infants <12 Months

- Youngest children are at greatest risk of rapid disease progression
- Clinical and laboratory markers are poor indicators of risk of rapid progression in infants
- Limited data suggest early ART reduces risk of HIV progression and death
- Limited information on appropriate ARV dosing

- ***Recommended* for infants regardless of clinical status, CD4 %, or viral load**
  - Assess and discuss adherence issues before initiation
  - It is not known whether ART begun in early infancy can safely be discontinued after months or years of therapy

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Types of Initial ART Regimens

- **NNRTI-based**

  (1 NNRTI + 2 NRTI backbone)
- **PI-based**

  (1 or 2 PIs + 2 NRTI backbone)
- **3 NRTIs**

  (ZDV + 3TC + ABC for use only in special circumstances)

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What antiretrovirals have dosing for infants under 3 months?

A. Zidovidine, Lamuvidine

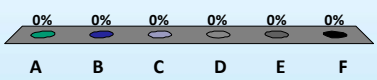
B. Lopinavir

C. Efavirenz

D. Nevirapine

E. 1,2,4

F. All of the above



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Current ARV Medications

NRTI
- ✓ Abacavir (ABC)
- ✓ Didanosine (ddI)
- ✓ Emtricitabine (FTC)
- ✓ Lamivudine (3TC)
- ✓ Stavudine (d4T)
- ▪ Tenofovir (TDF)
- ✓ Zidovudine (AZT, ZDV)

NNRTI
- ▪ Delavirdine (DLV)
- ✓ Efavirenz (EFV)
- ▪ Etravirine (ETR)
- ✓ Nevirapine (NVP)

PI
- ✓ Atazanavir (ATV)
- ✓ Darunavir (DRV)
- ✓ Fosamprenavir (FPV)
- ▪ Indinavir (IDV)
- ✓ Lopinavir (LPV)
- ✓ Nelfinavir (NFV)
- ✓ Ritonavir (RTV)
- ▪ Saquinavir (SQV)
- ✓ Tipranavir (TPV)

Fusion Inhibitor
- ✓ Enfuvirtide (ENF, T-20)

CCR5 Antagonist
- ▪ Maraviroc (MVC)

Integrase Inhibitor
- ▪ Raltegravir (RAL)

✓ = FDA approved for pediatric treatment

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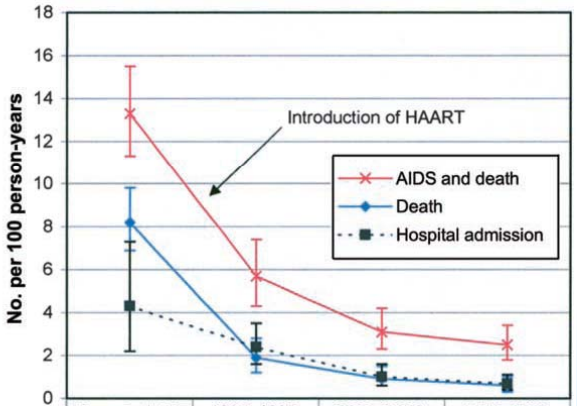
Clinical Course

- **Once past the first few years of life, the clinical visits are more often asymptomatic, in both treated or untreated patients.**
- **Treatment with HAART before AIDS defining illness associated with significantly slower progression.**

With HAART:
- 75% decrease in hospitalization rates
- Marked improvement in survival
- Early HAART-75% decrease in early death in CHER study

Pediatrics 2007;120;e236-e243
Pediatrics 2001;108:116 –122

Morbidity and Mortality in Children with HIV



	Through 1996[a]	1997–1999	2000–2002	2003–2006
AIDS and death	13.3	5.7	3.1	2.5
Death	8.2	1.9	0.9	0.6
Hospital admission	4.3	2.4	1.0	0.7

Judd, CID, 2007

ART: Age ≥12 Months

- **Risk of disease progression is lower for older children than for infants**
- **Optimal time to initiate therapy in asymptomatic children or those with high CD4 counts or % is not known**
- **Data suggest immune response to ART is better when treatment is initiated at higher CD4 % or count**
- **HIV RNA may provide information about progression risk as an adjunct to clinical and immune parameters**
- **Factors to consider in deciding when to initiate therapy**
  - Increasing HIV RNA levels (e.g., approaching 100,000 copies/mL)
  - Rapidly declining CD4 count or % to values approaching severe suppression
  - Development of clinical symptoms
  - Ability of caregiver and child to adhere to regimen

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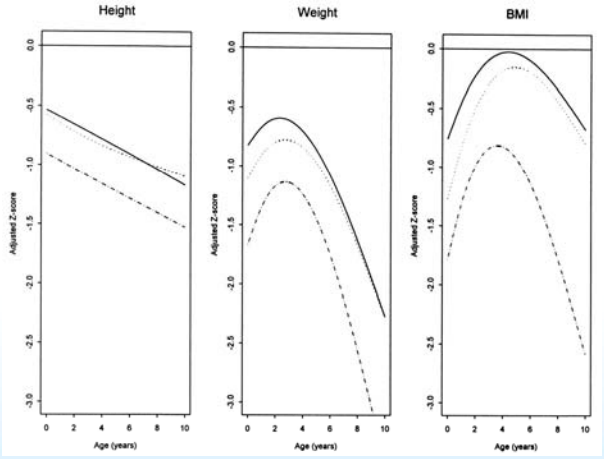
Impact of HIV Disease Category on Growth- z scores



The European Collaborative Study, Paediatrics 2003;111:e52-e60

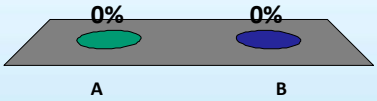
PEDIATRICS

Solid line-asymptomatic; dots –moderate; dashes – Category C

Children respond to ART treatment at the same level as adults

A. True

B. False



Clinical Considerations

- HIV RNA and CD4 count or % are independently predictive of risk of disease progression
- Both help determine when to start and when to change ART
- CD4 count and % may be more useful than HIV RNA in evaluating risk in infants <12 months of age; in older children, both parameters are useful
- A 5-fold (.7 $\log_{10}$) change in HIV RNA copies/mL in infants or 3-fold (.5 $\log_{10}$) change in children aged ≥2 years is biologically and clinically significant

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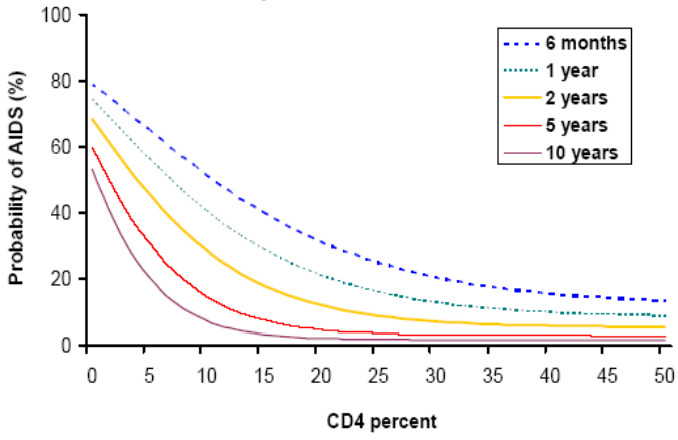
Estimated Probability of AIDS within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

(Appendix Figure 1, *Pediatric ARV Guidelines*)



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CDC CLINICAL CATEGORIES

Category N: Not symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only *one* of the conditions listed in category A.

Category A: Mildly Symptomatic

Children with two or more of the following conditions but none of the Conditions listed in category B or C:

- Lymphadenopathy (>0.5 cm at 2 or more sites; Bilateral=1 site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent URI, sinusitis or otitis media

Category B: Moderately Symptomatic

Children who have symptomatic conditions (other than in A or C), that are related to HIV infection, e.g. Bacterial meningitis, pneumonia or sepsis (single episode); Cardiomyopathy; LIP; etc.

Category C: Severely symptomatic

Children with any condition listed in the 1987 surveillance case definition For acquired immunodeficiency syndrome, with exception of LIP.

AIDS-defining Conditions Most Commonly Reported for Children <13 Years of Age, Cumulative through 2007 United States and Dependent Areas

Condition	No.	%*
Pneumocystis jirovecii	3,316	35
Lymphoid interstitial pneumonitis	2,201	23
Recurrent bacterial infections	1,999	21
HIV wasting syndrome	1,801	19
HIV encephalopathy	1,670	17
Candida esophagitis	1,619	17
Cytomegalovirus disease	1,040	11
Mycobacterium avium infection	847	9
Severe herpes simplex infection	512	5
Cryptosporidiosis	489	5
Pulmonary candidiasis	363	4

*>1 diagnosis reported for some children; 9,590 children have been reported with AIDS through 2007.

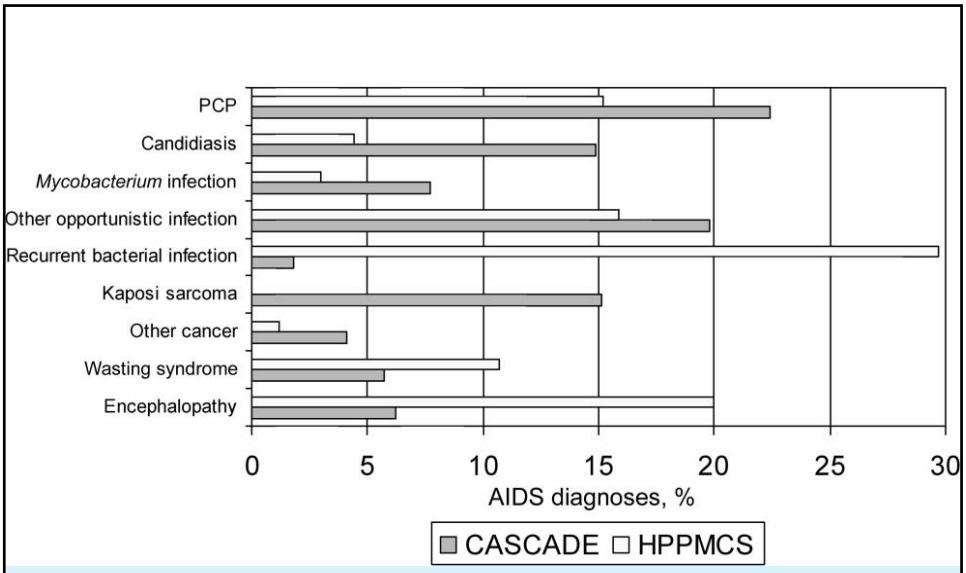

Figure 2. Distribution of AIDS-defining conditions in the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) and the Concerted Action

JID 2008:197 (1 February) ● Dunn et al.

Infectious Complications

- **Throughout Immune Categories:**
  - Bacterial infections: Bacteremias, meningitis, pneumonia with common pediatric pathogens
  - Tuberculosis
  - Candidiasis
- **Advancing Immunodeficiency:**
  - Opportunists: PCP, Mycobacterium avium, Herpes simplex and zoster, Cryptococcus, CMV

Pediatrics 2005;115;e488-e494;
Pediatrics 2007;120;e236-e243

Presentation of late perinatally infected disease

- **Children who present after 6-10 years of age with previous unrecognized HIV infection. May be relatively asymptomatic until sentinel event.**
  - Cryptococcal meningitis
  - Wasting and chronic diarrhea
  - Symptomatic Cardiomyopathy
  - CNS Vasculitis and encephalopathy
  - Immune thrombocytopenia, severe anemia
  - Severe HSV
  - Recurrent bacterial parotitis, lymphadenitis
- **Maternal death, change in guardianship**

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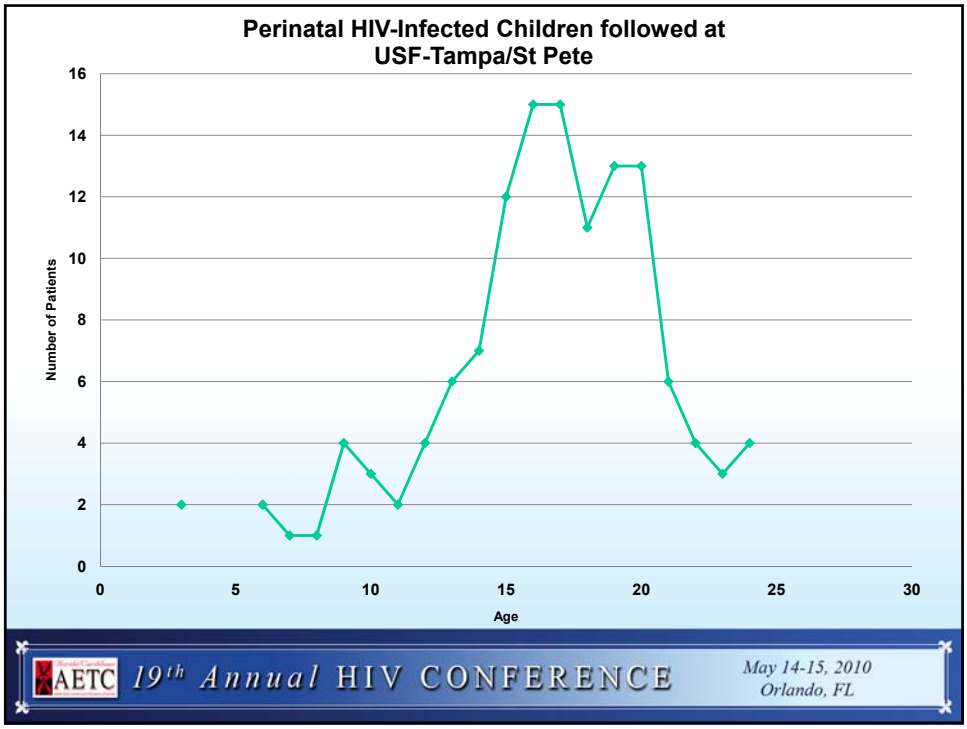

Long Term Complications of HIV

- Growth and Metabolic issues
- Cardiovascular
- Neurodevelopmental
- Renal
- Bone
- Malignancy

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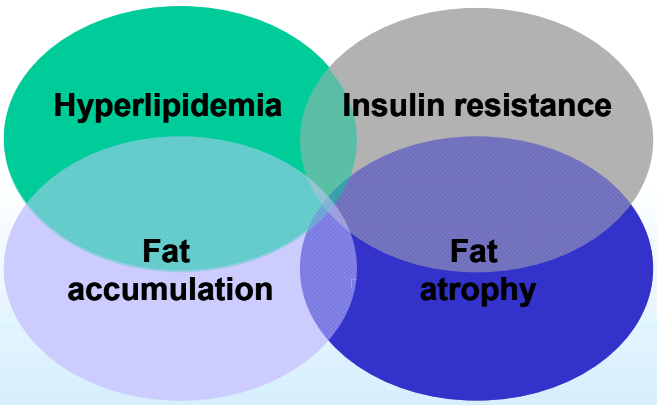
HIV-Associated Lipodystrophy



Fat Abnormalities in HIV-infected Children

- **Lipoatrophy and lipodystrophy are distinct clinical syndromes that can co-exist in the same patient.**
- **Lipoatrophy:**
  - The loss of subcutaneous fat from the cheeks produces an emaciated appearance.
  - Subcutaneous tissue is depleted from the arms, shoulders, thighs, and buttocks (peripheral wasting), with prominence of the superficial veins in these sites.
- **Lipohypertrophy:**
  - The dorsocervical fat pad becomes variably enlarged (ie, buffalo hump).
  - The circumference of the neck expands by 5-10 cm.
  - Breast hypertrophy occurs.
  - Abdominal visceral fat accumulation (protease belly)

Treatment Options:

- **Lipoatrophy:**
  -Switch from "D-drugs"

- **Lipohypertrophy:**
  - Exercise
  - Thiaglitazones ?, GH
  - Change from Protease inhibitors

PEDIATRICS Vol. 111 No. 3 March 2003, pp. e275-e281
Fisher M et al. 11th European AIDS Conference; 2007; Madrid, Spain. Abstract PS5/7.

Spectrum of Renal Disease

- Incidence of renal disease lower in vertical acquired HIV. Less co-morbidities and confounders such as hepatitis co-infection, iv drug use, smoking
- HIVAN – advanced immunosuppression, high viral loads, proteinuria, progression to ESRD. Seen primarily in Black race.
- An American study (Andiman et al, 2009) showed that among the 2102 HIV-infected children, nearly 22% developed persistent abnormalities of renal function over a period of 30 months or more. More common in patients on Tenofovir, Ind, antinfectives

HIV Renal Disease

- Retrospective cohort study from 1998-2007 of perinatal population- 33% had proteinuria and 11% in nephrotic range. Degree of proteinuria correlated with viral load.
- Responded to HAART and decrease in viral load. Untreated progressed to ESRD.
- Control of viral load with highly active antiretroviral therapy appears to prevent the progression of HIV associated renal disease and improve survival rates in infected children.

Chaparro, J Pediatr 2008;152:844-9

Renal Disease and HAART

- **Unanswered questions:**
  - Long term consequences of early therapy
  - Increase early use of Tenofivir
  - Cumulative exposure to multiple anti-infectives and other drugs
  - Genetic and cardiovascular impact

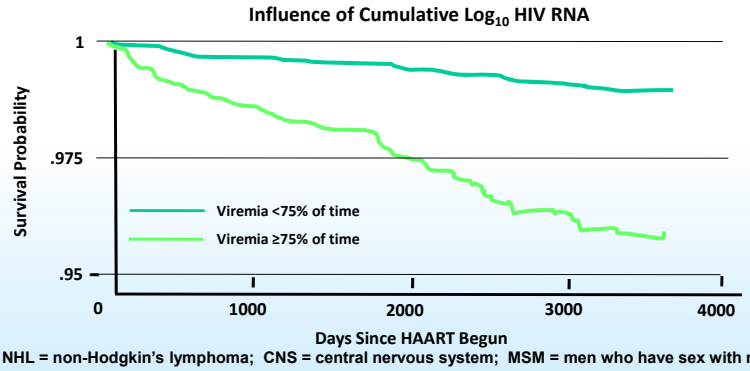
HIV and Malignancies

- An overall cancer incidence of 1.56/1000 person-years was documented in the PACTG 219c study. (1993-2003) Rates were higher for all cancers in the HIV-infected population compared to uninfected.
- Lymphoma (83%), Leiomyosarcoma, Kaposi's sarcoma most common cancers
- In multivariate regression, the cancer rate was 3.09 (95% CI 1.22,7.85) times higher in children with < 2 years of HAART use than in children with >2 years of HAART and 3.20 (95% CI 1.32, 7.76) times higher in children with < CD4 15% at cohort enrollment than in children with >CD4 15%
- In Italian perinatal cohort, cancer incidence rate dropped from 4.49/1000 person-years to 0.76/1000 person-years over 2 decades.

PIDJ, March, 2005
J Clin Oncol., 2007

Risks of Ongoing Virus Replication

- Retrospective analysis of German CLINSURV Cohort, n=6458
- Inclusion: Initiation of HAART until development of lymphoma or 12/31/06
- 94 lymphomas: 78 NHL and 16 primary CNS lymphoma
- Independent risks for lymphoma: MSM, older age, CD4+ count <200 cells/mm^3, viremia (VL >500 c/mL) ≥75% of time



NHL = non-Hodgkin's lymphoma; CNS = central nervous system; MSM = men who have sex with men.

Zoufaly A et al. 15th Conference Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 16.

Take Home Messages

- Every positive infant is a sentinel event for a community.
- Make diagnosis early, initiate treatment and aggressively monitor adherence.
- Amazing progress has been made, many new treatment options on horizon but still limited data in children
- Long term complications are evolving, requires continued vigilance.

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Dedicated to all of the children and families who contributed to the knowledge presented here and the pioneers who cared for them.

THANK YOU

Disclosure of Financial Relationships

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- **Advisory Board: American Academy of Pediatrics – Committee on Pediatric AIDS**

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

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