HIV Infection in Infants, Children and Adolescents

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Epidemiology

- HIV transmission during pregnancy, labor/delivery, and breastfeeding account for almost all new pediatric infections.

- Aggressive perinatal testing and use of HAART during pregnancy and avoidance of breastfeeding has had a dramatic impact in developing countries.

- In the US, fewer than 200 infants with perinatal transmission each year.
Perinatally Acquired AIDS Cases by Quarter-Year of Diagnosis* 1985-1998, United States

*Adjusted for reporting delays and redistribution of NIRs, data reported through December 1999
Epidemiology in Adolescents

- Adolescents are becoming infected via high risk behaviors
- Teens and young adults one of the most rapidly rising demographic among new infections
# Estimation of HIV Incidence in the US

<table>
<thead>
<tr>
<th>Table 1. Estimated Incidence of Human Immunodeficiency Virus Infection, 50 US States and the District of Columbia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stratified Extrapolation Approach</strong></td>
</tr>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td><strong>22 States, No. (%)</strong>^{a}</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong>^{b}</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
</tr>
<tr>
<td>13-39</td>
</tr>
<tr>
<td>30-39</td>
</tr>
<tr>
<td>40-49</td>
</tr>
<tr>
<td>50-69</td>
</tr>
<tr>
<td><strong>Transmission category</strong></td>
</tr>
<tr>
<td>MSM</td>
</tr>
<tr>
<td>IDU</td>
</tr>
<tr>
<td>MSM/IDU</td>
</tr>
<tr>
<td>Heterosexual</td>
</tr>
</tbody>
</table>

**Abbreviations:** BED, BED human immunodeficiency virus 1 capture enzyme immunoassay; CI, confidence interval; IDU, Injection drug use; MSM, men who have sex with men.


**Numbers do not count individuals diagnosed with AIDS at or within 5 mo after human immunodeficiency virus diagnosis; these were risk redistributed but not adjusted for reporting delay.

**Numbers for 2006 diagnoses were adjusted for reporting delay and risk redistribution.

**Confidence intervals reflect random variability affecting model uncertainty but may not reflect model assumption uncertainty; thus, they should be interpreted with caution.

**Race/ethnicity and transmission category subgroup numbers may not sum to the overall total because cases with unknown race/ethnicity or unknown transmission categories are excluded. However, percentages are adjusted for the exclusion and sum to 100%.

Hall, H. I. et al. JAMA 2008;300:520-529.
Survival of Perinatally-Infected Children

Median age of perinatally-infected children in US clinical trials was 14.8 years in 2007.

* $P$-value < 0.0001 for 1997-2001 birth cohort.
Life Expectancy in Perinatally-Infected Children

In both US and British/Irish cohorts, it is clear that deaths have decreased steadily over time.

Judd, CID 45:918, 2007 Patel, CID 46:507, 2008;
Life Expectancy in HIV-Infected Children

- In the US, the median age of death in 1994 was 7.2 years; in 2006, it had increased to 18.2 years.

- Mortality in HIV-infected children, 5 – 14 yrs, is 25-30x higher than uninfected (0.49/100 infected children vs. 0.02/100 uninfected).
Pediatric Spectrum of HIV Disease Consortium, US

Trends in Treatment of Pediatric HIV Infection

- Treatment of HIV infection with triple therapy
- Earlier treatment of infection
  - 5.8 years in 1980-90, 2.4 months in 2000-2003
- CHER study reinforces early HAART
- Use of new drugs in children within 1 year of licensing in adults
- Formulation less of an issue with aging population
- More changes of regimen with viral load monitoring
I’ve just taken my ritonavir!
Decreasing Options for Therapy in Aging-Up Perinatally-Infected Adolescents

- Most perinatally infected children entering adolescents have received each generation of ART
- Often have multiple resistance mutations, especially to NRTIs
- Not unlike adults on therapy for over 10 years
- Excitement about new agents and new drug classes
- Dose by pediatric or adult doses?
- Must balance potential toxicity with higher pediatric doses vs change for drug resistance and virologic failure with lower adult doses
- Interactions with puberty and concomitant medications, including illicit agents

Characteristics Associated with Reduced Adherence

**Patient Characteristics**
- Younger age
- Male sex
- Not in school
- Distrust of health care providers
- Lack of knowledge of HIV

**Structural Factors**
- Unstable housing
- Home in rural area
- Problems with insurance
- Transportation barriers

**ART Related Factors**
- Increasing regimen complexity (numbers and intervals)
- Side effects
- Longer time on ART

**Social Factors**
- Parent as caregiver
- Lower education level of caregiver
- Disorganized families
- Poverty
- Fear of stigma and discrimination
- Lack of disclosure
- Prior sexual abuse

**Mental Health Factors**
- Drug and alcohol use
- Depression
- psychic distress
- Decreased life satisfaction
- Decreased self efficacy
- Decreased outcome expectancy

What’s Different about Pediatric HIV?

- More rapid progression of disease in infants
- Two phenotypes of disease
CDC Surveillance Definition of Pediatric AIDS

- Additional criteria for AIDS in children < 13 years
  - Multiple bacterial infections
  - Growth failure
  - Lymphoid interstitial pneumonia
  - HIV encephalopathy manifestations
Multiple Serious Bacterial Infections

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
Bacterial Infections in Pediatric HIV

**Pathogens**
- S. pneumoniae - 31%
- CNS – 18%
- Enterics – 9%
- Other Strep – 9%
- Salmonella – 7%
- S. aureus – 7%
- H. influenzae – 4%

**Clinical presentation**
- Acute pneumonia – 60%
- Acute sinusitis – 36%

AIDS-Defining Criteria for Wasting Syndrome in Children < 13 Years

- Wasting syndrome in the absence of a concurrent illness that could explain the following findings:
  - Persistent weight loss >10% of baseline
  - Downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child >=1 year of age
  - <5th percentile on weight-for-height chart on two consecutive measurements, >=30 days apart

- PLUS
  - Chronic diarrhea (i.e., at least two loose stools per day for >30 days)
  - Documented fever (for >=30 days, intermittent or constant)
Impact of HAART on Growth

- Median age at entry was 6 years and observed for a median of 71 months on HAART
- Statistically significant rises in weight and height but not BMI Z-score
- Virologic non-responders had lower Z-scores for weight and height but not BMI
- No difference based on baseline CD4+ percentage

N=212

Lymphoid Interstitial Pneumonia

- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Still an AIDS defining condition
- But when present, only considered moderately symptomatic
AIDS-Defining Criteria for Encephalopathy (1994 definition)

- At least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness that could explain the findings:
  - Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests;
  - Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age);
  - Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
Incidence between 1993 to 2007 was 5.1 cases per 1,000 person years

10 fold decline observed beginning in 1996

HAART regimens with high CNS penetration resulted in substantial survival benefit (74% reduction)

8-year-old boy generalized brain atrophy. Cerebral atrophy is observed commonly among children with HIV-associated encephalopathy, but it also may be observed among children who are normal neurologically and developmentally.
CT scan of the brain of a 9-month-old girl with bilateral calcifications of the basal ganglia.
Neurocognitive Function in Pediatric HIV Infection

- Abnormalities include visuospatial and motor integration deficits, attentional dysregulation, language impairments and social-emotional deficits, memory, and adaptive functioning.
- Neurocognitive function more affected in children with advanced disease (AIDS).
- In some studies, those without AIDS perform as well as HIV-uninfected controls.
- Mean mental and motor scores of HIV-infected children were higher after PIs available compared to prior.
- In longitudinal studies, a trend toward improved scores post PI in young children.

Smith, Pediatr 2006;117-851-862; Willen, Ment Retard and Dev Disabil 2006; 12:223
Mental Health

Role of HIV infection in mental health disorders is still not clear.

Many risk factors for mental health disorders overlap with those for HIV (e.g., poverty, disrupted home life, history of mental illness or substance abuse).

HIV vs. Socioeconomic risks vs. Exposure to ART

Rigorous study designs using validated instruments are beginning to be available.

Emerging patterns likely different for aging up perinatally infected adolescents and those infected via high risk behaviors.
Mental Health Disorders in Perinatally Infected Children and Adolescents

- Baseline assessment of 193 perinatally-infected children and adolescents, age 9 – 16 years and 127 HIV uninfected controls
- Infected children had greater OR for any psychiatric condition, predominantly ADHD
- No difference for anxiety and mood disorders or substance abuse
- In follow-up of these patients, mental health disorders associated with sex and drug use risk behaviors

**Table 3** Rates of categories of psychiatric disorder by caregiver or youth report by HIV status

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Total N = 340</th>
<th>HIV+ N = 206</th>
<th>HIV- N = 134</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any psychiatric disorder</td>
<td>191 (56.2)</td>
<td>125 (60.7)</td>
<td>66 (49.3)</td>
<td>1.59*</td>
<td>1.03, 2.47</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>156 (45.9)</td>
<td>101 (49.0)</td>
<td>55 (41.0)</td>
<td>1.38</td>
<td>.89, 2.14</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>22 (6.5)</td>
<td>15 (7.3)</td>
<td>7 (5.2)</td>
<td>1.43</td>
<td>.57, 3.59</td>
</tr>
<tr>
<td>Behavioral disorder</td>
<td>85 (25.0)</td>
<td>53 (25.7)</td>
<td>32 (23.9)</td>
<td>1.10</td>
<td>.67, 1.83</td>
</tr>
<tr>
<td>ADHD</td>
<td>48 (14.1)</td>
<td>37 (18.0)</td>
<td>11 (8.2)</td>
<td>2.45*</td>
<td>1.20, 4.99</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>12 (3.5)</td>
<td>4 (1.9)</td>
<td>8 (6.0)</td>
<td>.31</td>
<td>.09, 1.06</td>
</tr>
</tbody>
</table>

* < .05, based on logistic regression

Mental Health Disorders in Adolescents Infected via High Risk Behaviors

- High rates of posttraumatic stress disorder, mood disorders also reported

St. Jude Clinic Experience
- 15% prior diagnosis of major depression
- 12% depressive thoughts on admission
- 8% prior suicidal ideation
- 5% suicidal ideation on clinic presentation

Martinez, AIDS Patient Care STD 23:469, 2009; Kadivar AIDS Care 18:544, 2006
**Substance Abuse Among HIV-Infected and Uninfected Adolescents**

<table>
<thead>
<tr>
<th></th>
<th>HIV-Infected</th>
<th></th>
<th>HIV-status Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wilson, 2001 (REACH cohort)</td>
<td>ATN Managerial Database, Perinatally-infected</td>
<td>ATN Managerial Database, 2001, High Risk Behaviors</td>
</tr>
<tr>
<td></td>
<td>n=235</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>45&lt;sup&gt;b&lt;/sup&gt;</td>
<td>78&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Marijuana Use</td>
<td>42&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>68&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cocaine Use</td>
<td></td>
<td>0.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hard Drug Use</td>
<td>&lt;sup&gt;8&lt;/sup&gt;&lt;sup&gt;a, e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injecting Drugs</td>
<td></td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined as use within the past 3 months,  
<sup>b</sup> Defined as ever used,  
<sup>c</sup> Defined as ≥ 1 drink on ≥ 1 of the 30 days prior to survey,  
<sup>d</sup> Defined as ≥ 1 times during the 30 days prior to survey,  
<sup>e</sup> Includes cocaine, heroin, crystal methamphetamine or hallucinogenic drug.
Substance Abuse in HIV Infected Adolescents

- Males more likely to smoke and use marijuana compared to females
- Hard drug use uncommon (≤ 8%) except for HIV-infected males where 17% reported use
- Less substance abuse in perinatally infected adolescents compared to those infected via high risk behaviors
- Increased use of OTC and prescription medications in perinatally infected
Ongoing Research

Large, long-term cohort studies are necessary to define the disease and therapy related complications that arise in perinatal HIV infection. These cohorts are very expensive and have limited ability to detect rare complications. In the US, the PACTG 219C cohort has been closed. Follow-up of some of the subjects through the NICHD funded Pediatric HIV/AIDS Cohort Study:
- Adolescent Master Protocol (AMP) (n=600 infected and 200 exposed children, age 7 – 16 years)
- Surveillance Monitoring for Antiretroviral Toxicities Study in HIV-Uninfected Children Born to HIV-Infected Women (SMARTT) (n=1845-2425)

European/South American cohorts and mechanisms to share data are critical. Cohort development in the developing world also necessary.
Thanks for Your Attention!