Pediatric HIV Overview

Tess Barton, MD
Associate Professor
Pediatric Infectious Diseases
Objectives

• Basic HIV overview
• Clinical manifestations of HIV in children
• Recommendations for HIV treatment
• Prevention of mother-to-child HIV transmission (PMTCT)
Estimated Children (<15 years) Living with HIV, 2010

Total: 3.4 million [3.0 million – 3.8 million]
Estimated Children <15 Years, Newly Infected with HIV, 2010

- Sub-Saharan Africa: 350,000 (300,000 – 410,000)
- Middle East & North Africa: 6,800 (4,800 – 8,800)
- Caribbean: 1,200 (<1,000 – 1,700)
- Latin America: 3,500 (2,100 – 5,000)
- Western & Central Europe: <100 (<200)
- Eastern Europe & Central Asia: 2,200 (1,700 – 2,900)
- East Asia: 2,100 (<1,000 – 3,800)
- South & South-East Asia: 20,000 (14,000 – 28,000)
- Oceania: <1,000 (<500 – <1,000)

Total: 390,000 (340,000 – 540,000)

44 children infected every hour in Sub-Saharan Africa
Estimated number of children (<15 years) newly infected with HIV, 2008

Total: 430 000 (240 000 – 610 000)
Estimated Deaths Due to AIDS in Children <15 Years, 2010

Total: 250,000 [220,000 – 290,000]
Estimated deaths of children (<15 years) due to AIDS, 2008

Total: 280,000 (150,000 – 410,000)
Impact of HIV/AIDS in Children

• HIV infection
  – Illness and opportunistic infections
  – Malnutrition and growth failure
  – Shortened lifespan

• Maternal AIDS
  – AIDS orphans
  – Loss of food security
  – Loss of educational opportunities

• Community Impact
  – Loss of young adult workers
  – Expenditures on HIV care instead of other health or food programs
Human Immunodeficiency Virus

Source: National Institute of Allergy and Infectious Diseases
How HIV Works

• Glycoproteins on the viral surface bind to surface of human CD4 cell
• HIV uses the cell to make new virus copies
• CD4 cells die
• CD4 cells are responsible for giving instructions to the rest of the immune system
Immunologic Consequences

• **Destruction or depletion of CD4+ lymphocytes**
  – Helper CD4+ cells - responsible for recognizing pathogens and displaying them to other parts of the immune system
  – Memory CD4+ cells

• **T-cell deficiency**
  – T-cells are crucial to fighting viral and fungal infections
  – *Opportunistic infections* — infections with organisms from one’s own body or the environment that would not cause disease in people with healthy immune systems

• **B-cell dysfunction**
  – T-cells tell B-cells what to do
  – B-cells make antibodies that help fight bacterial infections
Natural History of HIV Infection

Typical Course of HIV Infection

CD4+ T Lymphocyte Count (cells/mm³) vs. Weeks

- Primary infection
- Acute HIV syndrome
- Wide dissemination of virus
- Seeding of lymphoid organs
- Opportunistic diseases
- Constitutional symptoms
- Death

HIV RNA Copies per ml Plasma

Course of Pediatric HIV

• Rapid Progressors (10-30%)
  – symptomatic within first year of life
• Less Rapid Progressors (70-85%)
  – symptomatic within the first 5 years
• Long Term Survivors (<5%)
  – symptomatic within 8-10 years
HIV Disease in Infancy

- 15% of HIV-infected children progress to AIDS or death in the first 12 months of life
- 50% develop moderate immune suppression by 12 months
- 20% develop severe immune suppression
- Before HAART, mortality was 90% by age 10 years
- Progression difficult to predict
  - HIV-RNA levels less predictive
  - HIV disease and opportunistic infections can progress even with normal CD4+ cell counts
Mortality in HIV-Infected Children

HIV Paediatric Prognostic Markers Collaborative Study Group
### Immune Categories (CDC)

<table>
<thead>
<tr>
<th>Category</th>
<th>0-12 months</th>
<th>1-3 years</th>
<th>3-6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1. No immune suppression</td>
<td>≥1500</td>
<td>≥1000</td>
<td>≥500</td>
</tr>
<tr>
<td>Category 2. Moderate immune suppression</td>
<td>750-1499</td>
<td>500-999</td>
<td>200-499</td>
</tr>
<tr>
<td>Category 3. Severe immune suppression</td>
<td>&lt;750</td>
<td>&lt;500</td>
<td>&lt;200</td>
</tr>
</tbody>
</table>

- CD4 counts change with age
- Young children should have higher CD4 levels
- CD4% is more reliable to estimate immune status
### WHO Clinical Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td><strong>Persistent generalized lymphadenopathy (PGL)</strong></td>
</tr>
<tr>
<td>Stage 2</td>
<td><strong>Hepatomegaly</strong></td>
</tr>
<tr>
<td></td>
<td>Papular pruritic eruptions</td>
</tr>
<tr>
<td></td>
<td>Seborrheoeic dermatitis</td>
</tr>
<tr>
<td></td>
<td>Extensive human papilloma virus infection</td>
</tr>
<tr>
<td></td>
<td>Extensive molluscum contagiosum</td>
</tr>
<tr>
<td></td>
<td>Fungal nail infections</td>
</tr>
<tr>
<td></td>
<td>Recurrent oral ulcerations</td>
</tr>
<tr>
<td></td>
<td>Lineal gingival erythema</td>
</tr>
<tr>
<td></td>
<td>Angular cheilitis</td>
</tr>
<tr>
<td></td>
<td><strong>Parotid enlargement</strong></td>
</tr>
<tr>
<td></td>
<td>Herpes zoster</td>
</tr>
<tr>
<td></td>
<td>Recurrent or chronic URTIs (otitis media, <strong>otorrhoea</strong>, sinusitis)</td>
</tr>
</tbody>
</table>
Stage 2 Conditions

Seborrhea

Papular pruritic eruption
Stage 2 Conditions

Molluscum contagiosum
Stage 2 conditions

Herpes zoster
Stage 2 Conditions

- Recurrent oral ulcerations
- Angular cheilitis
- Molluscum contagiosum
- Parotid enlargement
<table>
<thead>
<tr>
<th>Stage 3</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate unexplained <strong>malnutrition</strong>, not adequately responding to standard therapy</td>
</tr>
<tr>
<td></td>
<td>Unexplained persistent diarrhea (14 days or more)</td>
</tr>
<tr>
<td></td>
<td><strong>Unexplained persistent fever</strong> (intermittent or constant for longer than one month)</td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis (outside the neonatal period)</td>
</tr>
<tr>
<td></td>
<td>Oral hairy leukoplakia (OHL)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td></td>
<td><strong>Severe recurrent presumed bacterial pneumonia</strong> (2 or more episodes in 6 months)</td>
</tr>
<tr>
<td></td>
<td>Acute necrotizing ulcerative gingivitis/periodontitis</td>
</tr>
<tr>
<td></td>
<td><strong>Lymphoid interstitial pneumonia</strong> (LIP)</td>
</tr>
<tr>
<td></td>
<td>Unexplained anemia (&lt;8gm/dl), neutropenia (&lt;500/mm3) or thrombocytopenia (&lt;30000/mm3)</td>
</tr>
</tbody>
</table>
Stage 3 Conditions

- Pulmonary tuberculosis
- Oral candidiasis (thrush)
Stage 3 Conditions

Lymphoid interstitial pneumonitis
### WHO Clinical Classifications

<table>
<thead>
<tr>
<th>Stage 4</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexplained <strong>severe wasting or malnutrition</strong></td>
</tr>
<tr>
<td></td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td></td>
<td>Recurrent severe bacterial infections (excluding pneumonia)</td>
</tr>
<tr>
<td></td>
<td>Chronic herpes simplex infection (more than one month)</td>
</tr>
<tr>
<td></td>
<td>Extrapulmonary Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Kaposi Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Esophageal candidiasis (or candida of the trachea, bronchi or the lungs)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus infection (age over one month)</td>
</tr>
<tr>
<td></td>
<td>Central nervous system toxoplasmosis (after the neonatal period)</td>
</tr>
<tr>
<td></td>
<td>Extrapulmonary cryptococcosis, including meningitis</td>
</tr>
<tr>
<td></td>
<td><strong>HIV encephalopathy</strong></td>
</tr>
<tr>
<td></td>
<td>Disseminated endemic mycosis</td>
</tr>
<tr>
<td></td>
<td>Chronic cryptosporidiosis</td>
</tr>
<tr>
<td></td>
<td>Chronic isosporiasis</td>
</tr>
<tr>
<td></td>
<td>Disseminated non-tuberculous mycobacteria infection</td>
</tr>
<tr>
<td></td>
<td>Cerebral or B cell non-Hodgkin lymphoma</td>
</tr>
<tr>
<td></td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>HIV-associated cardiomyopathy or nephropathy.</td>
</tr>
</tbody>
</table>
Stage 4 Conditions

Extrapulmonary TB
Miliary TB
Stage 4 Conditions

Severe malnutrition

Cryptococcosis

©Universidad Peruana Cayetano Heredia
Kaposi Sarcoma
Lipodystrophy

Tony Cenicola, New York Times
When to suspect HIV in a child

- Severe respiratory illness (pneumonia)
- Malnutrition
- Any tuberculosis
- Death of a parent
- Thrush after 6 months of age
- Persistent adenopathy
Diagnosing HIV in children

• Rapid tests, ELISA screen
  – False-positives in <18 months of age due to maternal Ab
  – May only diagnose maternal infection
  – Identifies HIV exposure

• Virologic tests

• Ab + Ag tests
HIV Treatment

USAID

NGOs

Health Ministry

PEPFAR
WHO Guidelines for Starting Treatment of HIV in Children

- <24 months: start regardless of clinical or immunologic status
- 24-59 months:
  - Clinical Stage 3 and Stage 4 disease
  - CD4 <25% or CD4 count <750
- >60 months
  - Clinical Stage 3 and Stage 4 disease
  - CD4 count <350
Early vs. Deferred Therapy (CHER Study, South Africa)

• Early therapy: 76% reduction in infant mortality; 75% reduction in HIV progression

Violari et al, NEJM 2008
Antiretrovirals
HAART (Highly Active Antiretroviral Therapy)
First-line HIV Treatment Regimens

**NNRTI**
- NEVIRAPINE (<3 years)
- EFAVIRENZN (≥3 years)

**NRTI**
- ZIDOVUDINE + LAMIVUDINE
- Abacavir + lamivudine also ok
Non-nucleoside RTIs (NNRTIs)

- Nevirapine
  - Available in liquid formulation
  - Used in perinatal prevention protocol
  - Severe hepatotoxicity
- Efavirenz
  - Once daily
  - Not available in liquid
  - CNS side effects (nightmares, hallucinations)
- Class resistance + resistant forever
Stevens-Johnson Syndrome
When to Choose Second-line Regimen

• Treatment failure
  – Viral load still >5000 after 6-12 months of treatment

• Toxicity of NNRTI
  – Hepatitis
  – Stevens-Johnson syndrome

• Consider in infants who only received single-dose Nevirapine (sdNVP)
Alternative HIV Treatment Regimens

- **PI**
  - **NRTI**
  - **NRTI**

  - **LOPINAVIR/ RITONAVIR**

  - **ZIDOVUDINE + LAMIVUDINE**

  Abacavir + lamivudine also ok
Ritonavir

- **Serious or life-threatening adverse effects:**
  - Alfuzosin, amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, methylergonovine, midazolam, pimozide, propafenone, quinidine, terfenadine, triazolam, voriconazole

- **Increases serum concentrations or toxic effects of:**
  - Meperidine, warfarin, desipramine, trazodone, ketoconazole, clarithromycin, rifabutin, cholesterol-lowering agents (concurrent use of lovastatin or simvastatin is not recommended; use lowest possible dose of atorvastatin and carefully monitor patient; consider use of pravastatin or fluvastatin for concurrent use with ritonavir); sildenafil, fluticasone

- **May increase the serum concentration or adverse effects of the following drugs (use with caution):**
  - atorvastatin, bupropion, buspirone, carbamazepine, clonazepam, clorazepate, cyclosporine, diazepam, digoxin, diltiazem, disopyramide, dexamethasone, dronabinol, estazolam, ethosuximide, flurazepam, itraconazole, lidocaine, methamphetamine, metoprolol, mexiletine, nefazodone, nifedipine, perphenazine, prednisone, propoxyphene, quinine, risperidone, sirolimus, SSRIs, tacrolimus, TCAs, thioridazine, timolol, tramadol, verapamil, zolpidem.

- **Ritonavir significantly decreases serum concentrations:**
  - Theophylline, methadone, ethinyl estradiol, oral or transdermal contraceptives (use additional or alternative contraceptive measures), phenytoin, valproic acid, lamotrigine, atovaquone

- **Ritonavir levels decreased:**
  - St John's wort (*Hypericum perforatum*), rifampin
  - Ritonavir formulations contain alcohol and may produce disulfiram-like reaction when coadministered with disulfiram or metronidazole.
Preventing Infant HIV (PMTCT)
Successful Reduction of Perinatal HIV Transmission in US

Estimated Number of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2006—United States and Dependent Areas

Year of diagnosis

Note: Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.
More than Just PMTCT Protocols

- Prevention of HIV in Women
- Preventing Unwanted Pregnancies
- ARV Prophylaxis
- Care & Treatment for HIV+ Women
Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment

Figure 1. Kaplan-Meier Plots of the Probability of HIV Transmission, According to Treatment Group.
Timing of HIV Transmission

- **Antenatal Pregnancy**: 10-25%
- **Intrapartum Labor & Delivery**: 40-60%
- **Postpartum Breast-feeding**: 15-25%

Treatment options:
- Maternal AZT + 6 weeks infant AZT
- Maternal AZT + sd-NVP + extended infant AZT/NVP
- Maternal therapeutic HAART
HIV Treatment in Pregnancy (WHO)

<table>
<thead>
<tr>
<th>CD4 cell count available</th>
<th>CD4 $\leq$350 cells/mm$^3$</th>
<th>CD4 $&gt;$350 cells/mm$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART</td>
<td>ART</td>
<td>ART</td>
</tr>
<tr>
<td>Regardless of clinical</td>
<td>If symptomatic (stage 3 or 4)</td>
<td></td>
</tr>
<tr>
<td>stage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO clinical stage</th>
<th>ART</th>
<th>ARV prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>ARV prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>ARV prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>ART</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>ART</td>
<td></td>
</tr>
</tbody>
</table>

- Any woman with CD4 $<350$ should receive HAART
- Any woman at WHO Stage 3 or 4 should receive HAART
- Healthy women with CD4 $>350$ can receive less intensive therapy
WHO PMTCT Recommendations

<table>
<thead>
<tr>
<th>Option A: Maternal AZT</th>
<th>Option B: Maternal triple ARV prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOTHER</strong></td>
<td><strong>MOTHER</strong></td>
</tr>
<tr>
<td>- Antepartum AZT (from as early as 14 weeks gestation)</td>
<td>- Triple ARV from 14 weeks until one week after all exposure to breast milk has ended</td>
</tr>
<tr>
<td>- sd-NVP at onset of labour*</td>
<td>- AZT + 3TC + LPV/r</td>
</tr>
<tr>
<td>- AZT + 3TC during labour and delivery*</td>
<td>- AZT + 3TC + ABC</td>
</tr>
<tr>
<td>- AZT + 3TC for 7 days postpartum*</td>
<td>- AZT + 3TC + EFV</td>
</tr>
<tr>
<td>*sd-NVP and AZT+3TC can be omitted if mother receives &gt;4 weeks of AZT antepartum</td>
<td>- TDF + 3TC (or FTC) + EFV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INFANT</th>
<th>INFANT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breastfeeding infant</strong></td>
<td><strong>Breastfeeding infant</strong></td>
</tr>
<tr>
<td>Sd-NVP at birth plus daily NVP from birth until one week after all exposure to breastmilk has ended</td>
<td>AZT or NVP from birth until 4 to 6 weeks</td>
</tr>
<tr>
<td><strong>Non-breastfeeding infant</strong></td>
<td><strong>Non-breastfeeding infant</strong></td>
</tr>
<tr>
<td>Sd-NVP at birth plus AZT or NVP from birth until 4 to 6 weeks</td>
<td>AZT or NVP from birth until 4 to 6 weeks</td>
</tr>
</tbody>
</table>
Global PMTCT Success

Estimate of the annual number of infant infections averted through the provision of antiretroviral prophylaxis to HIV-positive pregnant women, globally, 1996–2008

2009 AIDS epidemic update  Figure II
Use of Antiretrovirals in Pregnancy

Share of HIV-infected women ages 15–49 who received antiretroviral regimens for prevention of mother-to-child transmission, high-HIV-burden Countdown countries, 2006 and 2008

<table>
<thead>
<tr>
<th>Country</th>
<th>2006</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point estimate</td>
<td>Range estimate</td>
</tr>
<tr>
<td>Botswana</td>
<td>95</td>
<td>95–&gt;95</td>
</tr>
<tr>
<td>Cameroon</td>
<td>22</td>
<td>18–30</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>18</td>
<td>16–20</td>
</tr>
<tr>
<td>Gabon</td>
<td>4</td>
<td>3–5</td>
</tr>
<tr>
<td>Kenya</td>
<td>48</td>
<td>42–59</td>
</tr>
<tr>
<td>Lesotho</td>
<td>17</td>
<td>15–18</td>
</tr>
<tr>
<td>Malawi</td>
<td>14</td>
<td>12–16</td>
</tr>
<tr>
<td>Mozambique</td>
<td>13</td>
<td>11–15</td>
</tr>
<tr>
<td>South Africa</td>
<td>50</td>
<td>43–60</td>
</tr>
<tr>
<td>Swaziland</td>
<td>62</td>
<td>57–69</td>
</tr>
<tr>
<td>Tanzania, U. Rep.</td>
<td>15</td>
<td>14–16</td>
</tr>
<tr>
<td>Uganda</td>
<td>25</td>
<td>22–28</td>
</tr>
<tr>
<td>Zambia</td>
<td>35</td>
<td>31–39</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>17</td>
<td>16–19</td>
</tr>
</tbody>
</table>

— is not available.

PEPI-Malawi Study

- N=3016 infants
- Randomized:
  - SD NVP + 1 week ZDV (control)
  - NVP x 14 weeks (control)
  - NVP + ZDV x 14 weeks

Significantly lower transmission rates with extended infant therapy, compared to control.

No difference between extended treatment arms.

<table>
<thead>
<tr>
<th>At 9 months:</th>
<th>Control</th>
<th>ExtNVP</th>
<th>ExtNVP/ZDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>13.0%</td>
<td>7.2%</td>
<td>8.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p = 0.0004 vs control)</td>
<td>(p = 0.014 vs control)</td>
</tr>
<tr>
<td>Death</td>
<td>8.9%</td>
<td>6.8%</td>
<td>6.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p = 0.12 vs control)</td>
<td>(p = 0.05 vs control)</td>
</tr>
<tr>
<td>HIV infection or death</td>
<td>17%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p = 0.0009 vs control)</td>
<td>(p = 0.0043 vs control)</td>
</tr>
</tbody>
</table>

Taha, et al. CROI 2008. #42LB
Testing Infants for HIV

- IgG antibodies passed from mother to infant after 32 weeks gestation
- HIV Ab screens (ELISA, Oraquick, etc) will be positive in nearly all HIV-exposed infants
- Virologic testing necessary until 12-18 months of age
  - HIV PCR
  - P24 Antigen
Testing Infants for HIV

- **Presumptive Exclusion of HIV:**
  - 2 negative virologic tests @ >14 days and >4 weeks, OR
  - 1 negative virologic test >2 mo, OR
  - 1 negative HIV Ab test >6 mo

- **Definitive Exclusion of HIV**
  - 2 negative virologic tests @ >1 mo and >4 mo
  - 2 negative Ab tests @ >6 mo
Table 7.2.1a: Who needs co-trimoxazole prophylaxis?

<table>
<thead>
<tr>
<th>Situation</th>
<th>Infants and children confirmed to be living with HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-exposed infants and children</td>
<td>&lt; 1 year</td>
</tr>
<tr>
<td>Co-trimoxazole prophylaxis is universally indicated, starting at 4-6 weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection.</td>
<td>Co-trimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status</td>
</tr>
</tbody>
</table>

Once a child with HIV infection is started on co-trimoxazole, prophylaxis should continue until five years of age regardless of clinical symptoms or CD4 percentage.
Immunizations

• HIV+ children can (and should!) receive most routine childhood immunizations

• Live virus vaccines
  – MMR: Safe except in the advanced immunosuppression categories (Category 3)
  – VZV: Safe in asymptomatic children with good CD4+ (Category 1)
    • VZIG following chicken pox exposure in others

• Annual influenza vaccine

• Pneumococcal vaccine
  – Prevnar if <5 years, Pneumovax if > 2 years

• Hepatitis A

• Hepatitis B – check titers to verify response to vaccine and revaccinate if necessary
Summary

• HIV+ children may present with a broad variety of illnesses & infections
  – Always consider HIV with malnutrition or diarrhea > 1 month
• HIV+ children should be treated as early as possible
• Watch for drug interactions and side effects of HIV medications
Summary

• PMTCT programs work, and can eliminate HIV transmission to infants
  – True elimination requires increased testing of pregnant women, early in pregnancy

• Virologic testing is necessary to determine if an infant is HIV+
THANK YOU!