UPDATE ON PEDIATRIC HIV

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Assistant Professor of Pediatrics
9/5/12
DID YOU KNOW?

• HIV/AIDS was identified in 1981—31 years this June
• USA has over 1 million individuals living with HIV and estimated that more than 20% are unaware of their diagnosis—and there are 56,000 new infections each year (JAMA, 2008)
• High Incidence States include: NY, FL, TX, CA, and NJ.
History of Pediatric AIDS in USA

- 1981  First cases in adults
- 1983  First cases in children
- 1985  HTLV III antibody test available
- 1988  9th leading cause of death in 1-4 yr olds
- 1992  Peak # of perinatal AIDS cases
- 1992  7th leading cause of death in 1-4 yr olds
- 1994  ACTG 076  landmark study
- 1996  Decline in perinatal AIDS cases begins
HISTORY OF PEDIATRIC HIV/AIDS (2)

- First cases in children identified in Newark, NJ and New York
- Children were often identified with PCP and other opportunistic infections-
- First medication available to treat disease in 1989—liquid preparation available in 1990
- Development of highly active antiretroviral therapy—(HAART) in mid 1990’s
HIV in the 21st Century is a chronic illness

• Viral replication is controlled with antiretroviral medications
• With less virus in the body---there are less opportunistic infections—
• Lifelong treatment with medications—and now there is decreased pill burden
• Increased longevity
• Improved quality of life
Robert Wood Johnson AIDS Program

1. Established in 1983 when first children were identified with HIV/AIDS in NJ
2. Part of statewide network funded to provide care for HIV infected women, infants, children and youth
3. Provides comprehensive integrative care for patients (every patient assigned a care team)
New Jersey Statewide Family Centered HIV Care Network

1. FXB Center
   University of Medicine and Dentistry of NJ
   Newark
2. Newark Beth Israel Medical Center
   Newark
3. Jersey City Medical Center
   Jersey City
4. St. Joseph’s Hospital and Medical Center
   Paterson
5. Robert Wood Johnson AIDS Program
   UMDNJ/RWJMS
   New Brunswick
6. Jersey Shore Medical Center
   Neptune
7. Cooper Hospital/University Medical Center
   Camden
Five Patient Categories

1. Perinatally HIV infected infant/child/youth
   - birth – 24 yrs of age and up to 26 years of age

2. HIV exposed infants
   - birth to 18 mos

3. HIV infected women –collaborate with RWJMS Adult ID physicians and Dept. of OB/GYN
   - pregnant and non-pregnant

4. Behaviorally Acquired-HIV Infected Youth---

5. Affected family members—caretaker, guardian, siblings
Integrative Care Model

- Psychologist
- Nurse case manager
- Physician
- Family case manager
- Pharmacist
ACTG 076: Results

66% reduction in risk of transmission (P = <0.001)

Transmission Rate (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Transmission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>22.6%</td>
</tr>
<tr>
<td>ZDV</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

n=184 for Placebo, n=180 for ZDV
PREVENTION OF MOTHER TO CHILD TRANSMISSION in NJ

• 1995: Law passed to test pregnant women for early identification

• 2003: First state to implement a **Rapid HIV Test** (venipuncture—results in one hour for women who present in labor with unknown status)

• 2008: Prenatal testing law changed: test in the first and third trimester of pregnancy
Factors Influencing Perinatal HIV Transmission

• Maternal Factors
  – low CD4 count
  – advanced disease/high viral load
  – co-infection/chorioamnionitis (Bacterial Vaginosis, CMV)
Maternal-Child HIV Transmission

- Antenatal 30-40%
- Intrapartum 60-70%
- Postpartum (breastfeeding) 5-15%
Evidence for Intrauterine Transmission

- HIV identified in placenta (>8 weeks gestation)
- In Vitro infection of placenta-derived cells
- HIV identified in fetal tissue (>10 weeks gestation)
- HIV identified in amniotic fluid
- HIV identified in fetal blood specimens
- Virus identification at birth in a subset suggestive of in-utero infection
Factors Influencing Perinatal HIV Transmission

Fetal

- Infant’s immune response
- Prematurity
Goal of Treatment

• Survival
• Slow disease progression
• Decrease opportunistic infection
• Maintain growth and development

Markers of Successful Treatment

• Increased CD4 count
• Decreased viral load

Effective treatment results in reduction of viral load by .75 – 2.0 log over 24 weeks.

Current Antiretroviral (drugs)

• Nucleoside Reverse Transcriptase Inhibitors (NRTI)
• Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
• Protease Inhibitors (PI)
• Entry Inhibitors

Choice of Antiretroviral Therapy (ART)

• Early combination therapy with at least three drugs is recommended.
• The goal is to suppress viral replication, preferably to undetectable levels.
• Combination of PI and 2 NRTI's are considered first choice to accomplish this.
• Alternatively 2 NRTIs and 1 NNRTI or 3 NRTIs can be used

Predictors of Antiretroviral Failure

• High baseline viral load
• Low baseline CD4 count
• Non-adherence
• Addition of one new drug to a pre-existing suboptimal regimen
• Inadequate regimen

Possible Outcomes Perinatal HIV Exposure

Mother 1

Baby 1
Positive ELISA & WB
Received HIV Antibody Only
Does NOT have HIV Infection
Will Sero-revert before 2 Years Old
70%

Mother 2

Baby 2
Positive ELISA & WB
Received HIV Virus & Antibody
DOES have HIV Infection
Will Develop Symptoms of Illness Over Time
30%
1. Combivir: contains Zidovudine (Retrovir) and Lamivudine (Epivir) (2-nucleosides)
2. Kaletra: contains lopinavir and ritonavir (protease inhibitor)
   • Medications are taken **only** two times a day—
   • Primary focus on adherence and monitor side effects
ACTG 076
THREE PART REGIMEN
TO PREVENT MOTHER TO CHILD TRANSMISSION

<table>
<thead>
<tr>
<th>14-34 weeks</th>
<th>Prior to Delivery</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV Two-times/day</td>
<td>ZDV infusion 1mg/kg/hr-first hour is 2mg/kg/hr</td>
<td>ZDV 4mg/kg/dose PO 6 wks</td>
</tr>
</tbody>
</table>

Pregnancy
Labor and Delivery
Infancy
CARE FOR HIV EXPOSED INFANTS

• WHO ARE YOU GOING TO CALL AFTER THE BABY IS BORN?
  1. PEDS ID ATTENDING---(732) 235-7894
     VERIFY WHAT BLOOD WORK IS NEEDED ON THE INFANT
  2. CLINICAL CARE COORDINATOR-Blanca Jackson (732)
     235-6142

• WHAT DO YOU NEED TO DO FOR THE BABY’S DISCHARGE?
• Resident to make referral to the Social Worker and Outcomes Manager to arrange for Visiting Nurse
CARE OF NEWBORN AT BIRTH

1. Consult with Peds ID—-re: mode of delivery, ROM, mother’s viral load and treatment---(infant may need more than one medication)

2. Obtain newborn labs
   - Venipuncture: HIV DNA PCR and CBC w/diff for baseline (3 ml purple tube) (PRIORITY)
   - Cord Blood: Elisa and Western Blot (2 ml red tube)
   - Urine for CMV
   If not obtained on mother—via Cord Blood: CMV serology (Ig G) and Hepatitis C antibody

3. START AZT 6-12 hours after birth
   - STANDARD DOSE—REVISED IN 2011---
     - FULL-TERM
       - PO: 4 mg/kg/dose every twelve hours
       - IV: 3.0 mg/kg/dose every 12 hours

     - PREMATURE INFANTS (< 35 weeks)
       - ORAL: 2 mg/kg/dose every 12 hours—and increased at 2 wks and 4 wks depending on GA (30 weeks)

       - IV: 1.5 mg/kg every 12 hours and increased at 2 wks and 4 wks depending on GA (30 weeks)
INFANT MEDICATION OPTIONS

• A one time dose of Nevarpine may be given to the infants 48 hours after birth depending on mothers’ status

• Mothers may have been late to enter prenatal care or to start prenatal treatment infant may have Epivir added for one week in addition to the six week course of Zidovudine and a one-time does of Nevirapine
DISCHARGE PLAN FOR INFANT

1. Write script for AZT and give to caretaker to obtain (required to have prior to discharge)
2. Resident to refer to SW for VNA Referral for medication administration
3. Confirm mother/caretaker has oral AZT prior to discharge – re-check medication dose, check medication bottle for correct dosing and medication formulation
4. Peds ID nurse and Nursery will review proper medication administration and provide a set of syringes (1 ml)

5. Peds ID team will make two-week follow-up appointment for follow-up CHINJ (89 French St)
6. Resident to make one-week appointment with Pediatrician
HIV EXPOSED INFANT FOLLOW-UP

• Infants are followed by Peds ID for 18 months
• Visits at 2 weeks, 6 weeks, 8 weeks, 4 months, 6 months, 12 months and 18 months
Need to have antibody tests performed to confirm seroreversion (no detection of maternal antibodies)
Provide teaching and support to parent/caretaker---
GENERAL HIV TESTS

• **Antibody detection tests**
  – HIV Elisa –confirmed by HIV Western Blot
  
  – Rapid HIV test—(two types—one-hour venipuncture and 15 minute fingerstick (for ages 13 and above only)

• **Virus detection tests**
  – HIV DNA PCR --QUALITATIVE (results + or -)

  – HIV RNA PCR --QUANTITATIVE TEST (results: viral load—copies)
HIV EXPOSED STATUS

• Definitive exclusion of HIV infection is based on **two or more negative virologic tests** performed at > one month **and** > 4months

• Viral load performed at 2 weeks

• Bactrim prophylaxis is not needed if the infant has had 2 negative PCR’s tests at more than 8 weeks of age
Pathogenesis of HIV Infection

Infection of CD₄ cells → Destruction of CD₄ cells

↓          ↓

Immune Activation   Immune Deficiency

↓          ↓

Autoimmune Phenomena   Opportunistic and Serious Infections
STATUS OF PERINATALLY INFECTED CHILDREN IN USA

• Improved survival and quality of life

• Mortality in behaviorally infected children declined greater than 90%

• Mean age of death has doubled from ~ 9 years of age in the pre-HAART era to greater than 18 years of age by 2006

• Cause of death shifted from opportunistic infections to end-stage AIDS, sepsis and renal failure

• Mortality remains 10 to 30 fold higher in similarly aged children (3)
Pediatric HIV Infection

Common Signs & Symptoms

• Failure to thrive
• Lymphadenopathy
• Persistent oral candida
• Developmental delay
• Recurrent bacterial infections
• L.I.P., Parotitis
• Chronic diarrhea
• Opportunistic Infections
Perinatal HIV Infection

Diagnosis: Basics

• HIV infection is diagnosed by two positive HIV DNA PCR tests performed on separate samples

• Persistence of HIV antibody beyond 18-24 months
ADDITIONAL TESTS TO CONFIRM DIAGNOSE HIV INFECTED INFANT

• HIV RNA PCR (QUANTITATIVE) Test—viral load
• CD-4/T-cell: need to use percentage and number
• Genotype: to evaluate if there is medication resistance transmitted from the mother
# AIDS-defining Conditions Most Commonly Reported for Children <13 Years of Age, Cumulative through 2007
United States and Dependent Areas

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

*1 diagnosis reported for some children; 9,590 children have been reported with AIDS through 2007.
Pneumocystis carinii Pneumonia (PCP)
PREVENTION OF PCP

• Most cases occur in children not known to be HIV exposed/infected
• Lack of a well established, reliable CD4 “cut off” for PCP risk
• All children born to HIV infected mothers should receive PCP prophylaxis after the age of 6 weeks if HIV infection has not been presumptively ruled out
• Preventable
  – TMP-SMZ is highly effective prophylaxis for children with cancer and adults with AIDS
INITIAL WORK-UP  HIV INFECTED CHILD/YOUTH

• Viral load—quantitative RNA
• CD-4 count—percentage
• GART-Genotype Antiretroviral test-evaluates for medication resistance
• Hepatitis A, B, C
• Toxoplasmosis Titer
• Echocardiogram /EKG/Chest-X-ray
• Sexually transmitted infections (for older patients)
# Vaccinations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Administer</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>Yes</td>
</tr>
<tr>
<td>DTP</td>
<td>Yes</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Yes</td>
</tr>
<tr>
<td>IPV</td>
<td>Yes</td>
</tr>
<tr>
<td>MMR</td>
<td>Yes*</td>
</tr>
<tr>
<td>HIB</td>
<td>Yes</td>
</tr>
<tr>
<td>Varicella</td>
<td>Yes*</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Yes</td>
</tr>
<tr>
<td>Influenza (inactivated)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Except in severely immune suppressed
HAV, HPV vaccine –Yes
Rota --No
HIV Treatment Principles

• Combination treatment using drugs from at least two classes is essential to achieve the goal of total viral suppression
• Non suppressive treatment rapidly leads to viral resistance due to mutations in the virus
• Once a mutation develops it is never lost – archived resistance
• For the first regimen important to keep in mind the next few choices in case of failure
• When changing regimens, always use at least two active drugs to assure maximal suppression
• Toxicity and adherence monitoring are essential
HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

• Combination of at least three medications
• Complex regimens—now simplified to once a day for eligible patients: Example: Trizivir includes Abacavir/Lamivudine/Zidovudine
  Atripla includes Efavirenz/Emtriva/Tenofovir
  New quad pill for treatment naïve patients
<table>
<thead>
<tr>
<th><strong>NRTI</strong></th>
<th><strong>PI</strong></th>
<th><strong>Fusion Inhibitor</strong></th>
<th><strong>Integrase Inhibitor</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Abacavir (ABC)</td>
<td>✓ Atazanavir (ATV)</td>
<td>✓ Enfuvirtide (ENF, T-20)</td>
<td>✓ Raltegravir (RAL)</td>
</tr>
<tr>
<td>✓ Didanosine (ddI)</td>
<td>✓ Darunavir (DRV)</td>
<td>✓ Selzentry-Maraviro</td>
<td>✓ MULTICLASS</td>
</tr>
<tr>
<td>✓ Emtricitabine (FTC)</td>
<td>✓ Fosamprenavir (FPV)</td>
<td>✓ ATRIPLA-</td>
<td>✓ (EFV, FTC, TDF)</td>
</tr>
<tr>
<td>✓ Lamivudine (3TC)</td>
<td>✓ Indinavir (IDV)</td>
<td>✓ Complera</td>
<td>✓ (FTC, TDF, RIL)</td>
</tr>
<tr>
<td>✓ Stavudine (d4T)</td>
<td>✓ Lopinavir /Ritonavir (LPV) KALETRA</td>
<td>✓ NEW --QUAD PILL –</td>
<td>✓ COBICISTAT</td>
</tr>
<tr>
<td>✓ Tenofovir (TDF)</td>
<td>✓ Nelfinavir (NFV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Truvada (TRV)</td>
<td>✓ Ritonavir (RTV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Zidovudine (AZT)</td>
<td>✓ Saquinavir (SQV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Combivir</td>
<td>✓ Tipranavir (TPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Trizivir</td>
<td>✓ Prezista (PRZ)</td>
<td></td>
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</tr>
</tbody>
</table>

**NNRTI**

- Delavirdine (DLV)
- Intelence (ETR)

- Efavirenz (EFV)

- Nevirapine (NVP)

February 2009

2.09 AETC National Resource Center, www.aidsetc.org
Monitoring of Children on HAART

• Within 2 weeks of starting new ARV regimen
  – Screen for side effects, assess adherence
• Assess child’s initial response within 4-8 weeks
  – Screen for side effects, monitor adherence
  – Laboratory evaluation (CD4, HIV RNA, toxicity screening-- LFT’s, BUN, Creatinine)
• For stable patients, schedule visits at least every 3-4 months
• More frequent evaluation may be needed (4)
SPECIAL CONSIDERATIONS FOR PERINATALLY INFECTED ADOLESCENTS

• Tend to have more advanced disease
• Majority born before ZDV monotherapy was available for children
• Received sequential mono—dual---triple --therapy
• Heavily ARV experienced with multiple mutations/resistance
• Treatment fatigue
• Medications are a daily reminder of disease
METABOLIC ABNORMALITIES FROM HAART

- Protease inhibitors and nucleoside reverse transcriptase inhibitors effect fat distribution and lipid metabolism
- Fat redistribution syndrome: abnormal alterations in body shape: loss of subcutaneous fat (lipoatrophy) from the face, limbs, or buttocks
- Increase of fat deposition lipohypertrophy centrally, with increased abdominal girth due to visceral fat accumulation, breast enlargement, dorsocervical fat accumulation (buffalo hump) (3)
METABOLIC ABNORMALITIES (2)

• Development of lipomas
• Combination of lipoatrophy and lipohyperatrophy--LIPODYSTROPHY
• Peripheral wasting and central obesity not always associated with weight gain
• Occur independently of dyslipidemia and altered glucose metabolism
• Fat distribution most commonly appears as children progress through puberty
Lipodystrophy
CENTRAL NERVOUS SYSTEM

• Pre-HAART—HIV encephalopathy-
• Etiology: viral replication on developing brain, chronic inflammation, antiretroviral therapy, drug toxicity, social factors, and prenatal exposure to substances
• Manifestations: behavioral problems, learning disorders, attention deficit disorder/hyperactivity, impaired executive functioning
DISEASE CO-MORBIDITIES

• Development of cancers: lymphomas, anal and cervical cancers
• Females: need to have annual pap smears-gyn specialists
• Males: need to anal paps
• Type II Diabetes: 2011—young female (identified during routine blood test)—
• Patients referred to Endocrine—insulin resistance
• Hepatitis C: identified in a newly diagnosed young male (ymsm)
MENTAL HEALTH CONCERNS

• Study with cohort of 9 to 16 year-olds increased rates of psychiatric disorders
• RWJAP patients greater than 50% have a DSM IV diagnosis and more than 30% on medications
• Lack of resources for mental health treatment
• Psychologist---on team
CURRENT CHALLENGES

• Only group growing up with HIV/AIDS—no information on long-term effects
• Long-term morbidities of disease—does HIV increase aging process
• Preconception planning—decision to have children
RECENT PERINATAL TRANSMITTED CASES

- **2008**
  - Admitted for weight loss, skin lesions, fever, and abscess
  - CD-4 count: 5/1.6 %
  - Viral load: 16,000
  - Required PCP prophylaxis, MAI prophylaxis
  - HAART Initiated: Atripla
  - Patient adherent
  - Identified that mother learned of her status and thought it would go away
  - Younger sibling tested positive

- **2011**
  - Mother received prenatal care at HROB Clinic—had period of non-adherence in early pregnancy
  - Viral load undetectable at delivery
  - Infant ‘s HIV DNA PCR was positive
  - HAART Initiated- 3-liquids
  - Zerit, Epivir Viramune
  - Poor compliance
  - DYFS referral for Direct Observed Therapy (DOT)
  - Total of 3 regimens to date
CASE OF PCP IN 2011

• 13 year old male presented to off-site ER with SOB, tachypnea, and fever
• CXR—read as PCP
• Peds ID Attending called and transferred patient to BMSCH
• Tested for HIV—positive (Mother was not tested during pregnancy)
• Successfully treated with Bactrim and steroids
• HAART started
OTHER RECENT PATIENTS

• Acute Retroviral Syndrome (ARS)-early stage of infection-two males identified in 2010
• Patient A—low CD-4 and high viral load—presented with vomiting, abdominal pain and renal failure
• Patient B—low CD-4 and high viral load—presented with 30 lb. weight loss, throat abscess, mono-like symptoms
GOING FORWARD

• Begin the conversation- Take time with your patients to inform them about the importance of HIV testing, how HIV can be prevented-and how to protect themselves
• Call Blanca to test your patients with STD’s in the ED or on the floor
• Help make a generation AIDS free--
Percentage HIV/AIDS Diagnoses by Facility Type New Jersey, 2004 - 2009

- Inpatient: 29
- Private physician: 18
- CTS: 16
- Outpatient: 10
- HIV Clinic: 9
- Other/Unknown: 8
- ED: 6
- Corrections: 4
REFERENCES


• 2. Havens and Mofenson, Evaluation and Management of the Infant Exposed to HIV-1 in the United States, Pediatrics 2009;123;175

• 3. Guidelines for Use of Antiretroviral Agents in Pediatrics- AIDS Education Training Center, National Resource Center ;2009
RESOURCES

• http.aidsinfo.nih.gov – for medication guidelines
• http://www.cdc.gov/mmwr - for HIV testing information
• www.state.nj.us/health/aids - for NJ HIV/AIDS statistics
• www2.umdnj.edu/pidweb for more information about RWJAP