THE PATH TO ADULTHOOD: HIV, ADOLESCENTS & TRANSITION

Elaine Abrams, MD
HIV & Women Workshop
The Path to Adulthood

- Epidemiologic snapshot
- Biomedical health outcomes
- Psychosocial & behavioral outcomes
- Sexual & reproductive health
- Transition from childhood to adulthood and pediatric to adult care

To acquaint the adult HIV community with the emerging health issues of this growing population as they transition into adult care
GLOBAL OVERVIEW
Epidemiologic snapshot: HIV infection among adolescents

• Globally, it is estimated that there are approximately 2.1 million adolescents (10-19 years) living with HIV
  – Includes perinatal and behavioral acquisition
  – 58% of adolescents with HIV are female
  – There were an estimated 250,000 new HIV infections among adolescents (15-19yrs) in 2013
    • 2/3 of all new adolescent infections occurred among girls
  – Approximately 80% live in Sub Saharan Africa

Estimated number of adolescents living with HIV by UNICEF region, 2013
HIV-related mortality remains high among adolescents

- There were ~120,000 AIDS-related deaths among adolescents in 2013
  - HIV/AIDS 2nd leading cause of death among adolescents globally, following road traffic injuries
- From 2005-2013, modeling suggests a 50% increase in HIV-related mortality among adolescents
  - Only group in which deaths have risen

Numbers of HIV-related deaths among adolescents and new child infections

Projected number of children with HIV in 21 priority countries, Sub Saharan Africa

~750,000 adolescents, 10-14 years of age

WHO March 2014 Supplement to 2013 Guidelines
Age distribution of 1131 HIV+ children in CHIPS cohort, UK

Bamford, Arch Dis Child 2015
A snapshot of perinatal HIV in the US

10,798 persons with perinatal HIV living in the US in 2010

NYC: 2,449 children with living with perinatal HIV (NYCDOH, 2011)
- 13% < 13 years
- 76% - 13-24 years
- 11% > 24 years

CDC HIV Surveillance Report 2011
BIOMEDICAL HEALTH OUTCOMES
Biomedical profile of youth with perinatal HIV infection

• Two overlapping cohorts of perinatally HIV-infected adolescents
  – Aging children identified and treated during infancy and/or childhood
  – Newly identified during adolescence
    • It is estimated untreated infants with perinatal infection have a ~ 20-30% probability of survival to >10 years
    • Asymptomatic or with history of multiple nonspecific health conditions (URI, skin disease, recurrent diarrhea, recurrent infections)

• Among those who survive, globally, youth with perinatal HIV have multiple health problems as a consequences of:
  – Late identification and late ART availability/initiation
  – Suboptimal regimens during early childhood
  – Antiretroviral-associated toxicities
Common conditions among adolescents with untreated perinatal HIV

- **Chronic lung disease**: untreated lymphocytic interstitial pneumonia with bronchiectasis and cor pulmonale; small airways disease with constrictive obliterative bronchiolitis
- **Cardiac disease**: dilated cardiomyopathy, pericardial effusion, LV diastolic dysfunction, increased LV thickness, decreased LV fractional shortening, pulmonary hypertension
- **Growth Failure**: stunting and pubertal delay
- **Opportunistic infections**: crypto, TB, vaccine preventable illnesses
- **Malignancies**: Burkitts lymphoma and Kaposi Sarcoma
- **Skin disease**: nonspecific rashes, papular pruritic eruptions, angular cheilitis, molluscum contagiosum, herpes zoster, warts
- **Other**: HIV nephropathy, low bone mineral density

Lowenthal et al, Lancet 2014
Complications of HIV and ART for adolescents with perinatal HIV

- Metabolic complications
- Bone disease
- Mitochondrial toxicity
- Liver disease
- Renal Disease
- Cardiovascular disease
- CNS dysfunction
- Behavioral Challenges
An emerging picture of elevated cardiovascular risk among HIV+ youth

- High rates of hypercholesterolemia (17-44%) among children on ART in multiple studies
- High rates of insulin resistance (7-33%) also reported among children on ART in variety of studies
- Sustained elevation of immune activation markers in children regardless of durable long term ART (Persaud, *JAMA Pediatr* 2014)
- Application of PDAY (pathological determinants of atherosclerosis in youth) suggests increased CVD risk in 48% of HIV+ youth studied (Patel, *Circulation* 2013)
- Several studies report increased carotid intimal media thickness among HIV+ youth (Sainz, *JAIDS* 2013)
Findings suggest possible increased risk of CVD in adulthood

• Cardiovascular events are unusual in children & adolescents with perinatal HIV
• Emerging profile of lipid abnormalities, insulin resistance, elevated inflammatory and vascular markers
  – No clear sex differences have yet been identified
• These findings suggest possible increased risk of CVD in adulthood
  – Will perinatal HIV with 1-2 decades of ART become an ‘additional’ risk factor for adult CVD or will it fade against more traditional CVD risk factors (smoking, obesity, etc.)
• Risk reduction and monitoring particularly important
Adolescence: transitioning from childhood to young adulthood

**Childhood**
- Dependence on parent/family/adults
- Physical and emotional growth and development
- Adult supervision and decision-making
- Education and learning
- No sex, substances (alcohol, drugs, cigarettes)
- Supervised healthcare

**Adulthood**
- Independence
- Education complete
- Employment
- Residential independence
- Dating/partner/marriage
- Pregnancy/parenthood
- Sexual relationships
- Healthcare self-management

**Adolescence**
- Significant physical, emotional and social change

**Perinatal HIV Infection**
Risky behavior and adolescence: Blame it on the brain

• Increase in morbidity and mortality during adolescence associated with rise in risk behaviors:
  – Substance abuse, unprotected sex, antisocial acts, reckless & drunk driving

• Emerging data suggests risk-taking can be attributed to:
  – Immature/evolving neural system integration and efficiency, prefrontal cortex, limbic system, related structures
  – Limitations in executive function (cognitive processes associated with ability to carry out goal-directed behavior, impulse control, self-monitoring)
  – Personality traits of impulsivity, sensation-seeking, aggression and sociability were related to increased levels of risky behavior
  – “The brain’s inhibitory system does not match the demands of the excitatory or sensation-seeking systems, resulting in increased participation in risky behaviors.”

Pharo, 2011
Psychiatric disorders among HIV+ youth

- P1055 (Gadow, 2012)
- CASAH (Mellins, 2009, 2011)
- General Population (NCS-A, Kessler, 2012; n=10,148)
Substance use among HIV+ youth

P1055 (Williams, 2010); CASAH (Elkington, 2009); PHACS (Mellins, 2011); General Population (2009 Youth Risk Behavior Systems Survey; YRBSS; n=15,425)
Sexual risk behavior increases over time and with substance use

- In several studies, reports of onset of sexual activity and unprotected sex on last encounter were similar to uninfected cohorts.
- The proportion of youth who were sexually active increased with increasing age.
- The odds of engaging in unprotected sex over time were over 4 times greater if youth reported using alcohol (AOR 4.19; 95% CI [2.08, 8.44], p < .001) and twice as great if youth used marijuana (AOR = 2.29; 95% CI [1.05, 5.02], p < .05).

PHACS (Tassiopoulos, 2011; Mellins, 2011); CASAH (Bauermeister, 2009); General Population (2012 Youth Risk Behavior System Survey; YRBSS) Elkington 2009, Bauermeiser, 2011
Systematic review and meta-analysis of ART adherence in adolescents

<table>
<thead>
<tr>
<th></th>
<th>Number of studies</th>
<th>% adherence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>50</td>
<td>62.3</td>
<td>57.1–67.6</td>
</tr>
<tr>
<td>North America</td>
<td>22</td>
<td>52.7</td>
<td>46.5–59.0</td>
</tr>
<tr>
<td>Africa</td>
<td>8</td>
<td>83.8</td>
<td>78.9–88.7</td>
</tr>
<tr>
<td>Asia</td>
<td>3</td>
<td>83.9</td>
<td>76.8–91.0</td>
</tr>
<tr>
<td>Europe</td>
<td>12</td>
<td>62.0</td>
<td>50.7–73.3</td>
</tr>
<tr>
<td>South America</td>
<td>5</td>
<td>62.8</td>
<td>46.6–77.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% female</td>
<td>27</td>
<td>65.6</td>
<td>58.8–72.4</td>
</tr>
<tr>
<td>&lt;50% female</td>
<td>15</td>
<td>54.3</td>
<td>45.9–62.7</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents [12–29]</td>
<td>34</td>
<td>60.1</td>
<td>53.3–67.0</td>
</tr>
<tr>
<td>Young adults [20–24]</td>
<td>10</td>
<td>67.9</td>
<td>58.6–77.3</td>
</tr>
<tr>
<td>Study year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 2005</td>
<td>22</td>
<td>59.3</td>
<td>49.2–69.4</td>
</tr>
<tr>
<td>2005 onwards</td>
<td>16</td>
<td>77.0</td>
<td>72.0–82.0</td>
</tr>
<tr>
<td>Adherence measure&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load</td>
<td>36</td>
<td>62.2</td>
<td>56.0–68.4</td>
</tr>
<tr>
<td>Self-report</td>
<td>20</td>
<td>59.1</td>
<td>51.8–66.4</td>
</tr>
</tbody>
</table>

Kim, AIDS 2014
Challenges of adherence accentuated during adolescence

• Barriers to adherence cited by adolescents: forgetting, not wanting to be reminded about HIV, not wanting to take medications
  – Drug holidays (unplanned ART interruptions) not uncommon

• Few interventions have been demonstrated to improve adolescent adherence
  – Suggested benefit of adherence support devices (such as medication boxes and beepers), cell phone support, and offering individual and group support and motivational interviewing

• Adolescent perspectives imply importance of: improving knowledge, better, long-acting formulation, additional adherence support, earlier disclosure
Rates of viral suppression among 649 perinatally infected youth, US

Kahana, JAIDS, 2015
ART exposure among adolescents with perinatal infection

- Oldest youth are often highly drug experienced with history of sequential monotherapy, non-suppressive regimens, inadequate adherence and MDR HIV
- Among younger youth there is generally less historic drug exposure having initiated ART with more potent, forgiving and tolerable regimens
- Adolescents, unlike young children, are often able to benefit from introduction of new drug classes and simplified regimens approved for adult therapy
  - Few meaningful pharmacologic/dosing differences
  - Lingering concerns re: toxicities during puberty
  - Each new ‘drug’ saves a few more adolescents who burned through existing options
  - *Still have to take a pill at least once daily*
**Genotype of 17 year old with perinatal HIV, NYC**

| PI Major Resistance Mutations: | G48V, I54V, V82A, I84V |
| PI Minor Resistance Mutations: | L10I, V11I, Q58E, A71V |
| Other Mutations: | I13V, M36I, L63P, N83S |

**Protease Inhibitors**
- atazanavir/r (ATV/r) High-level resistance
- darunavir/r (DRV/r) Low-level resistance
- fosamprenavir/r (FPV/r) High-level resistance
- indinavir/r (IDV/r) High-level resistance
- lopinavir/r (LPV/r) High-level resistance
- nevirapinavir (NFV) High-level resistance
- saquinavir/r (SQV/r) High-level resistance
- tipranavir/r (TPV/r) High-level resistance

| NNRTI Resistance Mutations: | V108I, E138Q, Y181C |
| Other Mutations: | None |

**Nucleoside RTI**
- lamivudine (3TC) Low-level resistance
- abacavir (ABC) High-level resistance
- zidovudine (AZT) High-level resistance
- stavudine (D4T) High-level resistance
- didanosine (DDI) High-level resistance
- emtricitabine (FTC) Low-level resistance
- tenofovir (TDF) High-level resistance

**Non-Nucleoside RTI**
- efavirenz (EFV) Intermediate resistance
- etravirine (ETR) Intermediate resistance
- nevirapine (NVP) High-level resistance
- rilpivirine (RPV) Intermediate resistance
SEXUAL AND REPRODUCTIVE HEALTH
# Pregnancy in perinatally-infected females

Between 1998-2013, 16 publications on 277 pregnancies in 231 perinatally-infected girls.

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Year (place)</th>
<th># Perinatal Girls</th>
<th># Pregnancies</th>
<th># Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crane Ob/Gyn</td>
<td>1998 (Boston)</td>
<td>Case rpt: 1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CDC MMWR</td>
<td>2003 (Puerto Rico)</td>
<td>Case rpt: 8</td>
<td>10</td>
<td>0/7 live birth</td>
</tr>
<tr>
<td>Chibber Arch Gyn/Ob</td>
<td>2005 (India)</td>
<td>Case rpt: 30</td>
<td>30</td>
<td>0/26 live birth</td>
</tr>
<tr>
<td>Bernstein J Adol Health</td>
<td>2006 (Wash DC)</td>
<td>Cohort: 6/43 (14%)</td>
<td>6</td>
<td>Unk</td>
</tr>
<tr>
<td>Ezeanolue J Adol Health</td>
<td>2006 (Newark)</td>
<td>Cohort: 5/28 (18%)</td>
<td>5</td>
<td>Unk</td>
</tr>
<tr>
<td>Levine J Adol Health</td>
<td>2006 (Philadelphia)</td>
<td>Case rpt: 2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Koenig Am J Ob/Gyn</td>
<td>2007 (US)</td>
<td>Case rpt: 15</td>
<td>15</td>
<td>Unk</td>
</tr>
<tr>
<td>Thorne AIDS</td>
<td>2007 (Europe)</td>
<td>Case rpt: 9</td>
<td>11</td>
<td>0/8 live birth</td>
</tr>
<tr>
<td>Meloni AIDS Care</td>
<td>2009 (Italy)</td>
<td>Case rpt: 2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Williams Am J Ob/Gyn</td>
<td>2009 (Newark)</td>
<td>Case rpt: 10</td>
<td>13</td>
<td>1/7 live birth</td>
</tr>
<tr>
<td>Kenny J HIV Med</td>
<td>2012 (UK/Ireland)</td>
<td>Cohort: 30/252 (12%)</td>
<td>42</td>
<td>0/3 live birth</td>
</tr>
<tr>
<td>Jao AIDS</td>
<td>2012 (NYC)</td>
<td>Case rpt: 14</td>
<td>17</td>
<td>0/17 live birth</td>
</tr>
<tr>
<td>Millery J Ass Nurs AIDS Care</td>
<td>2012 (NYC)</td>
<td>Cohort: 25/97 (26%)</td>
<td>33</td>
<td>0/19 live birth</td>
</tr>
<tr>
<td>Croucher Sex Trans Inf</td>
<td>2013 (UK)</td>
<td>Cohort: 6/31 (19%)</td>
<td>8</td>
<td>0/3 live birth</td>
</tr>
<tr>
<td>Munjal Adol Health Med Th</td>
<td>2013 (Bronx)</td>
<td>Case rpt: 30</td>
<td>37</td>
<td>1/37 live birth</td>
</tr>
</tbody>
</table>
Between 1998-2013, 16 publications on 277 pregnancies in 231 perinatally-infected girls.

- Majority of pregnancies were unplanned.
- Elective termination was not uncommon (15%-42% in 5 studies reporting).
- Repeat pregnancy was not uncommon: 32 had 2 pregnancies; 4 had three pregnancies.
- Adverse pregnancy outcomes: miscarriage (6-14% 4 studies), preterm (7-44% 4 studies), SGA (47% 1 study), low birth weight (1 study).
- MTCT uncommon (3 infections/159 live birth, 2%)
### Pregnancy in perinatally-infected adolescents in the UK

**759 females born before 2001**

<table>
<thead>
<tr>
<th>Details</th>
<th>Number/Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 (6%) have had at least 1 pregnancy, 19 had 2 pregnancies, 4 had 3 or 4 pregnancies</td>
<td></td>
</tr>
<tr>
<td>9 terminations, 2 miscarriages, 51 live births, 5 continuing to term</td>
<td></td>
</tr>
<tr>
<td>Median age at conception was 19 years</td>
<td></td>
</tr>
<tr>
<td>36% with CD4 &gt;500; 15% CD4 350-499; 49% CD4 &lt;350</td>
<td></td>
</tr>
<tr>
<td>71% were on ART at conception</td>
<td></td>
</tr>
<tr>
<td>VL at delivery &lt;50 copies/mL in 64%, 51-1000 in 31% and &gt;1000 in 5%</td>
<td></td>
</tr>
<tr>
<td>44% delivered by elective CS, 27% by emergency CS, 27% by planned vaginal delivery and with one unplanned vaginal delivery; 1 pediatric infection to date</td>
<td></td>
</tr>
</tbody>
</table>

Byrne JIAS, 2014
# Complex health profile of pregnant women with perinatal infection

<table>
<thead>
<tr>
<th></th>
<th>Women with perinatal HIV (n=16)</th>
<th>Women with behaviorally acquired HIV (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>20 (19-23)</td>
<td>30 (23-37)</td>
</tr>
<tr>
<td><strong>Substance use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to pregnancy</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>During pregnancy</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Hx of OI</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Nadir CD4 during pregnancy (cells/mm)</td>
<td>231 (38-374)</td>
<td>391 (286-544)</td>
</tr>
<tr>
<td>Nadir CD4 ≤200 during pregnancy</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Viral suppression at delivery</td>
<td>10</td>
<td>52</td>
</tr>
<tr>
<td>Second line ART</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>SGA infant</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>
Impact of HIV infection on pregnancy and maternal health

- All pregnancies at two Bronx, NY hospitals (37 pregnancies to 30 PHIV, 40 pregnancies in 35 BHIV) through 1 year postpartum period: less robust immunologic and virologic responses
- Followed 10 PHIV and 21 BHIV women for 4 more years. Mortality outcomes:
  - No deaths BHIV
  - 4 deaths (13%) in the PHIV with complications of HIV: 3 with CD4 < 50 cells/µL and VL log10 > 4.7 copies/mL at 1yr postpartum.

Munjal Adolescent Health, 2013
TRANSITION
Meeting the needs of adolescents living with HIV infection

- Generally children with perinatal HIV infection have received lifelong care in pediatric settings
  - Dedicated child-focused, comprehensive HIV service programs with pediatric care specialists and multidisciplinary teams
- It is not uncommon for pediatric programs to expand service delivery to meet needs of the growing adolescent population
  - Expansion often organic and unplanned
  - Biomedical and psychosocial legacy of HIV infection necessitate specific services (Reproductive and sexual health needs)
Essential services for adolescents living with HIV infection

- Informed health care workers
- Advanced HIV management
  - Suitable ARV regimens,
  - Treatment of OI & complications
- Adherence support
- Sexual and reproductive health services (SRH)
  - Contraception & pregnancy care
- Prevention with positives
- Peer education and support services

- Mental health services
- Training in treatment and health literacy
- Community-based services
  - Access to housing, legal services
- Harm reduction
- Life skills training
What is successful transition and how do we measure it?

- **Ultimately the goal is successful engagement and retention in adult HIV services**
- Critically important to define outcomes
  - Retained in care?
  - Adherent to ART? Viral suppression?
  - Uses contraception? Planned pregnancies? Uses condoms?
- Important to monitor individual outcomes post-transition
  - To support optimal health outcomes
  - Consider implications of early treatment and perinatally acquired disease
  - Assess program strengths and weaknesses
Transition outcomes for HIV+ adolescents in Argentina

Transition of the patients

- Successful transition: 94
- Non successful transition: 28
- Not evaluable Transition: 77
- To be transfered in the next 3 months: 22
- Still in The Transition Program to be prepared: 8

Total: N=130

72.3% Transitioned

Caillaud, IAS 2014
Complex medical and psychosocial issues in perinatally infected young adults – 82% of deaths associated with poor adherence and advanced HIV disease, 9 with mental health diagnoses and 2 deaths due to suicide!
In Conclusion

• Large numbers of children with perinatal HIV infection are entering adolescence, a period of rapid and complex physical and emotional growth and development

• These youth faced a broad array of health and behavioral challenges as a consequence of complications of the disease as well as the treatments

• We are now challenged with both defining and meeting these health needs to ensure a safe and successful passage into adulthood

• Adult HIV programs will inherit this legacy as well as the responsibility of caring for these young people in the decades to come
Acknowledgements

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