HIV, ART and Adolescence - The Perfect Storm

Elaine Abrams
ICAP, Columbia University
The Path to Adulthood

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

• To review the global estimates for adolescents, 10-19 years of age, living with HIV infection
• To describe biomedical conditions and outcomes of adolescents with perinatal HIV infection
• To describe psychosocial and behavioral outcomes of adolescents with perinatal HIV infection
• To identify the contributions of HIV, antiretroviral treatment (ART) and the developmental stage of adolescence to health outcomes among adolescents with perinatal HIV infection
GLOBAL OVERVIEW
Global summary of the AIDS epidemic | 2013

| Number of people living with HIV | Total       | 35.0 million [33.2 million – 37.2 million] |
|                                 | Adults      | 31.8 million [30.1 million – 33.7 million] |
|                                 | Women       | 16.0 million [15.2 million – 16.9 million] |
|                                 | Children (<15 years) | 3.2 million [2.9 million – 3.5 million] |

| People newly infected with HIV in 2013 | Total       | 2.1 million [1.9 million – 2.4 million] |
|                                        | Adults      | 1.9 million [1.7 million – 2.1 million] |
|                                        | Children (<15 years) | 240 000 [210 000 – 280 000] |

| AIDS deaths in 2013                  | Total       | 1.5 million [1.4 million – 1.7 million] |
|                                      | Adults      | 1.3 million [1.2 million – 1.5 million] |
|                                      | Children (<15 years) | 190 000 [170 000 – 220 000] |
Epidemiologic snapshot: HIV infection among adolescents

- Globally, it is estimated that there are approximately 2.1 million adolescents (10-19 years) living with HIV
  - Overlapping definitions of adolescents (10-19 yrs) and youth (15-24 yrs).
    - 10-15 yrs included with children; 15-19 yrs included with adults
    - Includes perinatal and behavioral acquisition
  - 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
  - Approximately 58% of adolescents with HIV are female

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

Number of children & adolescents (10-14yrs) with HIV projected in 21 priority countries in Sub Saharan Africa in 2020.

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

WHO March 2014 Supplement to 2013 Guidelines
A snapshot of perinatal HIV in the US

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

- 24% < 13 years
- 76% >= 13 years

NYC: 2,449 children with living with perinatal HIV (NYCDOH, 2012)
- 13% < 13 years
- 76% - 13-24 years
- 11% > 24 years
Age distribution of 1131 HIV+ children in CHIPS cohort, UK

Bamford, Arch Dis Child 2015
BIOMEDICAL HEALTH OUTCOMES
Demographic profile of adolescents with perinatal HIV infection

- Globally, vulnerable families, often affected by poverty, violence, limited health care and educational resources
- Disruptions in caregiving due to parental illness, death and poverty
- In some countries, parental substance abuse and untreated mental illness have decimated families
- In many countries, youth with perinatal HIV are from ethnic minorities and other disenfranchised populations who have cope[d with racism and discrimination, and now must cope with HIV stigma
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 obliterator 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
CARDIOVASCULAR HEALTH
Hypercholesterolemia Rates (>200mg/dL) in HIV-Infected Children

Rates of Insulin Resistance in HIV-Infected Children

Sustained Elevation of Immune Activation Markers Regardless of Durable Long-term ART

Persaud, JAMA Pediatr 2014

P-value PHIV+ vs HEU: <0.001 <0.001 0.004

- soluble CD14 (x10^6 pg/ml)
- GMCSF (pg/ml)
- IL-1beta (pg/ml)

< 1 yr (N=14) 1-5 yrs (N=53) >5 yrs (N=77) HEU
Early evidence of cardiovascular disease: Carotid Intimal Media Thickness (cIMT)

- Measured carotid IMT in 150 HIV+ adolescents and 150 age- and sex-matched controls (age 14.6 years; 63% F)
- HIV: 97% perinatal; 97% on ART; 76% VL<50; 17% smokers
- IMT higher in HIV+ vs. HIV- overall and HIV w/VL < 50 vs. HIV-
- NO association of IMT with CRP or T cell activation/senescence
Pathobiological Determinants of Atherosclerosis in Youth (PDAY)

- Determined aggregate risk of cardiovascular disease among adolescents with perinatal HIV in the PHACS cohort using PDAY
  - Estimates risk of currently having atherosclerotic lesions in the coronary arteries or abdominal aorta
  - PDAY developed using autopsy data from over 1100 15-34 year olds
    - based on lipids, glucose, smoking, BP, and BMI
- In this cohort, 48% of HIV+ youth and 24% HIV-controls had scores > 0, indicating CVD risk
  - Higher risk among boys vs. girls

Patel, Circulation 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
• 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 should be routine part of HIV care
BONE HEALTH
Evidence suggests an increased risk of fractures in adults with HIV infection.

All fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Incidence rate ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnsten et al. 2007</td>
<td>9.0%</td>
<td>1.16 [0.57, 2.35]</td>
</tr>
<tr>
<td>Hansen et al. 2012</td>
<td>45.2%</td>
<td>1.55 [1.44, 1.66]</td>
</tr>
<tr>
<td>Yin et al. 2010</td>
<td>24.8%</td>
<td>1.28 [0.93, 1.78]</td>
</tr>
<tr>
<td>Young et al. 2011</td>
<td>21.1%</td>
<td>2.41 [1.64, 3.54]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>1.58 [1.25, 2.00]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.03; Chi² = 6.97, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 3.80 (P = 0.0001)

Fragility fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>Incidence rate ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen et al. 2012</td>
<td>25.1%</td>
<td>1.90 [1.70, 2.12]</td>
</tr>
<tr>
<td>Volk et al. 2011</td>
<td>26.5%</td>
<td>1.27 [1.20, 1.35]</td>
</tr>
<tr>
<td>Walker-Harris et al. 2012</td>
<td>13.8%</td>
<td>0.95 [0.65, 1.40]</td>
</tr>
<tr>
<td>Womack et al. 2011</td>
<td>25.5%</td>
<td>1.32 [1.19, 1.46]</td>
</tr>
<tr>
<td>Yin et al. 2010</td>
<td>9.2%</td>
<td>1.09 [0.64, 1.88]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>1.35 [1.10, 1.65]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.04; Chi² = 44.58, df = 4 (P = 0.00001); I² = 91%
Test for overall effect: Z = 2.91 (P = 0.004)
Bone Mineral Density (BMD) through puberty

236 HIV-infected and 143 uninfected youth 7-24 years of age

Significant and widening differences between HIV+ and HIV- boys through puberty

Jacobson D et al, AIDS 2010
Prevalence of low bone mineral density among HIV+ adolescents

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Duration of ART (years)</th>
<th>Findings</th>
<th>Associated factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiMeglio</td>
<td>$N = 350$</td>
<td>9.5 years (IQR 9.1–11.3)</td>
<td>Total body Z-score $&lt; -2.0$; 7% versus 1% in HIV-negative peers</td>
<td>Higher peak viral load and CD4%</td>
</tr>
<tr>
<td></td>
<td>Mean age 12.6 years</td>
<td></td>
<td>LS Z-score $&lt; -2.0$; 4% versus 1% in HIV-negative peers</td>
<td>Ever used indinavir</td>
</tr>
<tr>
<td></td>
<td>Black 66%, Hispanic</td>
<td></td>
<td>Spinal BMD Z-score $&lt; -2.0 = 8%$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26% and white 8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bunders</td>
<td>$N = 66$</td>
<td>3.4 years (IQR 1.5–5.2)</td>
<td>LS Z-score $&lt; -2.0$; 24%</td>
<td>Height-for-age</td>
</tr>
<tr>
<td></td>
<td>Mean age 6.7 years</td>
<td></td>
<td></td>
<td>Z-score $&lt; -1.5$</td>
</tr>
<tr>
<td></td>
<td>Black 62%</td>
<td></td>
<td></td>
<td>Ever have WHO stage 4</td>
</tr>
<tr>
<td>Puthanakit</td>
<td>$N = 100$</td>
<td>7.0 years (4.3–8.7)</td>
<td>Low total body or lumbar spine in 32.4% of cohort</td>
<td>Weight, BMI, nutrition, use of tenofovir and protease inhibitors</td>
</tr>
<tr>
<td></td>
<td>Age 14.3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thai 100%</td>
<td></td>
<td>Use of TDF is associated with lower lumbar spine Z-score:</td>
<td></td>
</tr>
<tr>
<td>Schtscherbyna</td>
<td>$N = 74$</td>
<td>11.1 years (SD 3.5)</td>
<td>$-1.8 (1.1)$ vs. $-1.3 (0.9)$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age 17.3 (SD 1.8) years</td>
<td></td>
<td>Use of protease inhibitor is associated with LS Z-score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White 36.5%</td>
<td></td>
<td>$-1.7 (1.1)$ vs. $-1.1 (0.9)$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-white 63.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age 17.3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Black 71%, Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26% and white 23%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Puthanakit & Siberry, JIAS, 2013
Lower number of circulating osteogenic precursors in adolescents with perinatal HIV

Circulating Osteogenic Precursors
(%LIN-OCN+RUNX2+)

Perinatal   Adolescence   HIV-

P<0.05

Manavalan, CROI 2014, abstract #132
Lower peak bone mass and abnormal trabecular and cortical microarchitecture in young men infected with HIV early in life.

Yin, AIDS 2014

HIV+ 24-year-old man

HIV-24-year-old man

Yin, AIDS 2014
Does HIV infection early in life prevent attainment of a genetically-determined “peak bone mass”?

# Prevention strategies to optimize bone health in perinatally HIV+ youth

<table>
<thead>
<tr>
<th>Prevention strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium + vitamin D</td>
<td>Ensure adequate intake of calcium (1300mg/day) and vitamin D (600IU/day) in adolescents</td>
</tr>
<tr>
<td>Promote healthy lifestyle</td>
<td>Good nutrition; avoid cigarette smoking; avoid/limit alcohol consumption</td>
</tr>
<tr>
<td>Exercise</td>
<td>Encourage high-intensity impact activities (running, jumping, gymnastics, basketball) for 10-20 min/day, 3 days/wk</td>
</tr>
<tr>
<td>Effective ART</td>
<td>Regardless of regimen, ART that achieves virologic suppression, preserves/restores immunologic function should have positive effect on bone health</td>
</tr>
<tr>
<td>Avoid bone ‘unfriendly’ medications</td>
<td>Individualized risk-benefit assessment critical. Minimize use of systemic corticosteroids. For youth with multiple risk factors for poor bone health, consider avoiding TDF, boosted PIs, medroxyprogesterone</td>
</tr>
</tbody>
</table>

Puthanakit & Siberry, JIAS, 2013
PSYCHOSOCIAL AND BEHAVIORAL OUTCOMES
Adolescence: transitioning from childhood to young adulthood

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

**Adulthood**
- Independence
- Education complete
- Employment

**Adolescence**
- Transitioning from childhood to young adulthood
- Significant physical, emotional and social change
- Separation/individual from parents
- Peers increasingly important
- Social need to fit in
- Risk taking and experimentation

**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, Behav Neurosci 2011
Psychiatric disorders among HIV+ youth

P1055 (Gadow, 2012); CASAH (Mellins, 2009, 2011); General Population (NCS-A, Kessler, 2012; n=10,148)
Psychiatric disorders among HIV+ and HIV-exposed & HIV-affected youth

Gadow, J Dev Behav Ped, 2010
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 among HIV+ youth

Onset of Sexual Activity

- PHACS (10-18): 58%
- CASAH (14-18): 46%
- YRBSS (14-18): 53%

Unprotected Sex Last Occasion

- PHACS (10-18): 42%
- CASAH (14-18): 54%
- YRBSS (14-18): 47%
- General Population (2012 Youth Risk Behavior System Survey; YRBSS): 74%

- PHACS (Tassiopoulos, 2011; Mellins, 2011); CASAH (Bauermeister, 2009); General Population (2012 Youth Risk Behavior System Survey; YRBSS)
Sexual risk behavior increases over time and with substance use

• In the CASAH cohort, as expected, the proportion of youth who were sexually active increased with increasing age.
  – The odds of having unprotected sex was more than twice as great at each additional follow-up visit.

• 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).

Elkington 2009, Bauermeiser, 2011
Viral resistance in sexually active youth with HIV RNA >5000 copies/ml (n=38), PHACS

- 42% of 92 sexually active ≥1 VL >5000 copies/ml
- 81% had resistance to ≥1 ARV class
- 24% had some resistance to drugs in all 3 classes
- 63% with resistance reported unprotected sex

Tassiopoulos et al. (2013)
Reported non-adherence in the last month among HIV+ youth

PHACS (Mellins, 2011; Usitalo, 2009); CASAH (Marhefka, 2009); P1055 (personal communication, Kacanek, 2013); Other illnesses (Bender, 2000; Johnson, 2002)
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 measurea</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>
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 formulations, additional adherence support, earlier disclosure
Rates of viral suppression among 649 perinatally infected youth, US

Proportion of adolescents

Time since diagnosed with HIV

Kahana, JAIDS, 2015
Rates of viral suppression among 1547 youth with behaviorally acquired HIV, US

Proportion of youth

Time since diagnosed with HIV

0-1yr | 2yrs | 3-4yrs | >5yrs

Proportion of youth

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

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Resistance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>atazanavir/r (ATV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>darunavir/r (DRV/r)</td>
<td>Low-level resistance</td>
</tr>
<tr>
<td>fosamprenavir/r (FPV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>indinavir/r (IDV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>lopinavir/r (LPV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>nevirapavir (NFV)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>saquinavir/r (SQV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>tipranavir/r (TPV/r)</td>
<td>High-level resistance</td>
</tr>
</tbody>
</table>

#### NRTI Resistance Mutations:

<table>
<thead>
<tr>
<th>Mutation</th>
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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>V108I, E138Q, Y181C</td>
</tr>
</tbody>
</table>

#### Other Mutations:

None

#### Nucleoside RTI

<table>
<thead>
<tr>
<th>RTI</th>
<th>Resistance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamivudine (3TC)</td>
<td>Low-level resistance</td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>zidovudine (AZT)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>stavudine (D4T)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>didanosine (DDI)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td>Low-level resistance</td>
</tr>
<tr>
<td>tenofovir (TDF)</td>
<td>High-level resistance</td>
</tr>
</tbody>
</table>

#### Non-Nucleoside RTI

<table>
<thead>
<tr>
<th>RTI</th>
<th>Resistance Level</th>
</tr>
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<tbody>
<tr>
<td>efavirenz (EFV)</td>
<td>Intermediate resistance</td>
</tr>
<tr>
<td>etravirine (ETR)</td>
<td>Intermediate resistance</td>
</tr>
<tr>
<td>nevirapine (NVP)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>rilpivirine (RPV)</td>
<td>Intermediate resistance</td>
</tr>
</tbody>
</table>
Drug resistance mutations among adolescents transitioning to adult services

- 112 adolescents transferring to adult HIV care services underwent genotypic analysis
- 63/112 had genotypes available
  - 5 ART-naive (no primary mutations)
  - 58 ART-experienced
- Median duration of ART: 13.5y
- Drug resistance:
  - 51% PI mutations
  - 77% NRTI mutations
  - 37% NNRTI mutations

De Mulder, *PLOS ONE* 2012
Lifetime adherence to ART – are we asking the impossible?

• Adherence is a formidable challenge for adolescents
  – Highly vulnerable to normal adolescent developmental

• Challenges of daily medication administration are accentuated during adolescence

• Adherence is not static: good today, gone tomorrow

• No perfect (and few good) measures of adherence

• Many are studying approaches to optimize ART adherence
BREATHER (PENTA 16)
Randomised 48week trial of weekend breaks in viral load suppressed young people 8-24 years on efavirenz

- Non-inferiority of VL suppression in young people on EFV-based 1st line ART was demonstrated for Short Cycle therapy (weekend breaks) vs. Continuous therapy
- 2-year follow-up as randomized continuing

Butler K. 38LB CROI 2015
What did young people say?  
Breather Social Science Substudy

40 young people were interviewed about what it was like being in the trial. You said:
To begin with starting and stopping was confusing and made you worry. But once you got used to it and found a routine, you liked it and it was better than always taking medicine.

Some of you said:
Sometimes you forgot to take your medicine when you were supposed to, but you did not always tell your doctor or nurse. This happened before and during the trial, but being in the trial helped some of you to remember.

IMPORTANT things to know:
We need to CARRY ON this research to check whether having a break at weekends is safe over a longer time, so it’s important this trial keeps going and we need you for this to happen. This means coming to your clinic visits and continuing to take your medicines as agreed by you and your doctor.

It made your social life better as you could stay over at friend’s houses and you didn’t worry about having to take medicine.

You worry that other HIV positive young people might try it when they don’t take Efavirenz and then get ill.

You sometimes felt side effects from Efavirenz (feeling dizzy, not being able to concentrate or not feeling yourself) and you did not always tell your doctor or nurse about this. Those of you who had the weekend off taking your medicine, felt better on those two days.
I have an adolescent, very smart, meth addicted, patient ... she seems to genuinely want to take his meds, but just goes on benders and forgets. I asked him, “If had an injectable form of the medicines that you get once a month or every other month instead of taking pills, would that interest you? She said “ABSOLUTELY” ... when I asked if the pain of the shots would be a deterrent. She said definitely not, shoots up, no fears about needles, etc ... but then, fast forward 10 minutes later into our visit, we move to one of his next problems ... early latent syphilis. To this she says, “no way, if you make me get it, I am leaving right now, is there anything we can do by pill?” ... so I call her on it, I say, you just told me that shots aren’t a problem? “yes but that one hurts a lot” ... After several minutes of my trying to convince her about PCN, I concede to doxy BID. She tries for 3 days, gets too much GI upset, comes in a gets PCN IM.
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

<table>
<thead>
<tr>
<th>759 females born before 2001</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>
</tr>
<tr>
<td>9 terminations, 2 miscarriages, 51 live births, 5 continuing to term</td>
</tr>
<tr>
<td>Median age at conception was 19 years</td>
</tr>
<tr>
<td>36% with CD4 &gt;500; 15% CD4 350-499; 49% CD4 &lt;350</td>
</tr>
<tr>
<td>71% were on ART at conception</td>
</tr>
<tr>
<td>VL at delivery &lt;50 copies/mL in 64%, 51-1000 in 31% and &gt;1000 in 5%</td>
</tr>
<tr>
<td>44% delivered by elective CS, 27% by emergency CS, 27% by planned vaginal delivery and with one unplanned vaginal delivery</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Experience</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 (43%)</td>
<td>31 (52%)</td>
</tr>
<tr>
<td>During pregnancy</td>
<td>1 (7%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Hx of OI</td>
<td>6 (43%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td><strong>Nadir CD4 during pregnancy</strong></td>
<td>231 (38-374)</td>
<td>391 (286-544)</td>
</tr>
<tr>
<td><strong>Nadir CD4 ≤200 during pregnancy</strong></td>
<td>9 (64%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td><strong>Viral suppression at delivery</strong></td>
<td>10 (71%)</td>
<td>52 (87%)</td>
</tr>
<tr>
<td><strong>Second line ART</strong></td>
<td>6 (43%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>SGA infant</strong></td>
<td>8 (47%)</td>
<td>12 (12%)</td>
</tr>
</tbody>
</table>

Jao AIDS 2013
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
- 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.
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

• Increasingly large numbers are aging into adolescence, a stage of great risk and resiliency

• Biomedical and psychosocial legacy of HIV infection necessitate specific services
  – Reproductive and sexual health needs
Talking about ‘transition’…
What exactly do we mean?

• It is not uncommon for pediatric programs to expand service delivery to meet needs of the growing adolescent population
  – Expansion often organic and unplanned

• Many programs are simultaneously exploring how best to transition youth to adult service programs
  – Transition is defined as a purposeful process that addresses the medical, psychological and educational/vocational needs of adolescents and young adults with chronic physical and medical conditions as they move from child-centered to adult-oriented health care systems (National Service Framework www.dh.gov.uk/publications)
  – Transition is the purposeful and planned movement of adolescents from child-centered to adult-oriented services (http://apps.who.int/adolescent/hiv-testing-treatment/page/Transition)
  – Transition is the process that maximizes resiliency, minimizes risks, promotes personal growth and strengthens the ability to self-manage
What do we know about models for transition?

• No ‘tested’ models; several piloted; several described
  – Most programs introduce adolescents to adult care services through visits, joint clinics, or assisted referral
  – Toolkits, tools, supportive materials available, generic and program specific, common recommended program elements

• Transition between services must be
  – Tailored to the local situation
  – Individualized to the child, family and community context
  – Include core set of services addressing the specific needs of the population, particularly young women

• Ultimately the goal is successful engagement and retention in adult HIV services
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?

• Critically important to define outcomes
  – Retained in care?
  – Adherent to ART?
  – Uses contraception?
  – Uses condoms (secondary prevention)?

• Critically important to monitor individual outcomes post-transition
  – To support optimal health outcomes
  – Assess program strengths weaknesses
Transition outcomes HIV+ adolescents in Argentina

Transition of the patients

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

Transitioned N=130

72.3%

Caillaud, IAS 2014
Transition to adult care: mortality in perinatally-HIV+ youth in UK/Ireland

• Evaluated mortality 2006-2011 in UK/Ireland in 996 perinatally-infected youth ≥13 years, including 248 cared in 14 adult clinics.
• Median age at transfer 17 years (range 15-21) and at death 21 years (range 17-24)
• Estimated minimum mortality by age and type care in perinatally HIV-infected young people UK/Ireland:

<table>
<thead>
<tr>
<th>Age Group/ Type Care</th>
<th>Number of deaths n=11</th>
<th>Mortality Rate/ 100 pt-yr</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-15 years, Pediatric</td>
<td>3</td>
<td>0.2 (0.1-0.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>16-20 years, Pediatric</td>
<td>2</td>
<td>0.3 (0.1-1.0)</td>
<td>1.3 (0.2-8.6)</td>
</tr>
<tr>
<td>16-20 years, Adult</td>
<td>4</td>
<td>0.5 (0.2-1.3)</td>
<td>2.7 (0.6-12.2)</td>
</tr>
<tr>
<td>&gt;21 years, Adult</td>
<td>4</td>
<td>0.9 (0.3-2.3)</td>
<td>4.9 (1.1-22.0)</td>
</tr>
</tbody>
</table>

Fish, HIV Med 2014
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 are faced with 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 and will be responsibility addressing the next many years of treatment that lie ahead for these young people
Acknowledgements

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