HIV Infection among our youngest: knowledge, survival, resiliency, and opportunity

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Johns Hopkins Medical Institutions
NICHD Council Meeting
September 13, 2018
Disclosures

• Gilead scientific advisory board
• Merck HIV Global Therapeutic Expert Forum
### Global summary of the AIDS epidemic 2016

#### Number of people living with HIV

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>( millions) [ (range) ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>36.7</td>
<td>[30.8–42.9]</td>
</tr>
<tr>
<td>Adults</td>
<td>34.5</td>
<td>[28.8–40.2]</td>
</tr>
<tr>
<td>Women</td>
<td>17.8</td>
<td>[15.4–20.3]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>2.1</td>
<td>[1.7–2.6]</td>
</tr>
</tbody>
</table>

#### People newly infected with HIV in 2016

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>( millions) [ (range) ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.8</td>
<td>[1.6–2.1]</td>
</tr>
<tr>
<td>Adults</td>
<td>1.7</td>
<td>[1.4–1.9]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>160 000</td>
<td>[100 000–220 000]</td>
</tr>
</tbody>
</table>

#### AIDS deaths in 2016

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>( millions) [ (range) ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.0</td>
<td>[0.83–1.2]</td>
</tr>
<tr>
<td>Adults</td>
<td>890 000</td>
<td>[740 000–1.1]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>120 000</td>
<td>[79 000–160 000]</td>
</tr>
</tbody>
</table>
“Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. The cause of the outbreak is unknown, and there is as yet no evidence of contagion..

......no apparent danger to nonhomosexuals from contagion...... no cases reported to date outside the homosexual community or in women.

Nine of the victims tested had severe defects in their immunological systems...........”
The First Pediatric Cases

Fig 3. Pediatrics AIDS cases by year of transmission of human immunodeficiency virus. Includes children younger than 13 years of age in whom AIDS was diagnosed as of Dec 31, 1985. Year of transmission was considered year of birth for perinatally acquired cases and year of transfusion for transfusion-acquired cases.
The First Pediatric Cases

“Another 85 cases (not reviewed here) were reported in adolescents.”

**Fig 5.** Pediatric AIDS cases by child’s age at diagnosis. Includes children younger than 13 years of age in whom AIDS was diagnosed as of Dec 31, 1985.
Prognosis of perinatal HIV infection

- Symptoms develop over months to years
- 25% rapidly progress to AIDS (<1 year = highest risk)
- 75% experience slow progression
- 25% mortality by age five
- Annual rate of disease progression (6-8%)

“although they make up only 1% of AIDS patients, they have unique clinical, social, and public health problems that require special attention.” Rogers
Course of Untreated HIV

- **Primary Infection**
- **Acute HIV syndrome**
  - Wide dissemination of virus
  - Seeding of lymphoid organs
- **Clinical Latency**
- **Opportunistic Diseases**
- **Constitutional Symptoms**
- **Death**

**Graph:**
- **Y-axis:** CD4+ T Lymphocyte Count (cells/mm³)
- **X-axis:** Weeks and Years
- **HIV RNA Copies per ml Plasma**
  - $10^7$ to $10^2$ scale
CD4 level and Risk of Opportunistic Infections (OIs)
Goals of Therapy

1) ↓ HIV-associated morbidity, prolong duration and quality of survival

2) Preserve/restore immunologic function

3) Maximal and durable suppression of HIV viral load

4) Prevent transmission
   - Treatment as prevention (TasP)
   - Undetectable = Untransmittable (U=U)
Advances in management of HIV

- Diagnostic tools
- Opportunistic infection prophylaxis and treatment
  - Immunizations
- Antiretroviral treatment
- Identification, management, and prevention of co-morbidities

Unique clinical issues for children

- Prevention of mother to child acquisition
- Antiretroviral treatment for children
  - dosing, formulation, palatability, toxicity
- Prophylaxis of opportunistic infections
- Identification of co-morbidities
- Treatment of co-morbidities
- Immunizations
REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

Edward M. Connor, M.D., Rhoda S. Sperling, M.D., Richard Gelber, Ph.D., Pavel Kiselev, Ph.D., Gwendolyn Scott, M.D., Mary Jo O'Sullivan, M.D., Russell VanDyke, M.D., Mohammed Bey, M.D., William Shearer, M.D., Ph.D., Robert L. Jacobson, M.D., Eleanor Jimenez, M.D., Edward O'Neill, M.D., Brigitte Bazin, M.D., Jean-François Delfraissy, M.D., Mary Culnane, M.S., Robert Coombs, M.D., Ph.D., Mary Elkins, M.S., Jack Move, M.D., Pamela Stratton, M.D., and James Balsley, M.D., Ph.D.,

for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*
Risk of Perinatal Transmission Decreased

Intervention – ARV Prophylaxis

- No ARV: 25%
- ARV in Labor: 9-13%
- Optimal comb ARV (AP/±IP/PP): <2%
- Current rates: <1%

References:
- Wade, et al. 1998 NEJM 339;1409-14
- Guay, et al. 1999 Lancet 354;795-802
- Fiscus, et al. 2002 Ped Inf Dis J 21;664-668
- Moodley, et al. 2003 JID 167;725-735
no Child
born with HIV
by 20??

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.
<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>'80-'84</td>
<td>First AIDS cases reported in United States</td>
</tr>
<tr>
<td>'85-'89</td>
<td>* 1987 Zidovudine (NRTI)</td>
</tr>
<tr>
<td>'90-'94</td>
<td>1991 Didanosine (NRTI) 1992 Zalcitabine (NRTI) 1994 Stavudine (NRTI)</td>
</tr>
<tr>
<td>'00-'04</td>
<td>2000 Didanosine EC (NRTI) Kaletra (FDC) Trizivir (FDC) 2001 Tenofvir DF (NRTI)</td>
</tr>
<tr>
<td>'05-'09</td>
<td>2005 Tipranavir (PI) 2006 Atripla (FDC) Darunavir (PI) 2007 Maraviroc (EI) Raltegravir (INSTI) 2008 Etravirine (NNRTI)</td>
</tr>
<tr>
<td>'10-'14</td>
<td>2011 Complera (FDC) Nevirapine XR (NNRTI) Rilpivirine (NNRTI) 2012 Stribild (FDC) 2013 Dolastegavir (INSTI) 2014 Cobicistat (PE) Elvitegravir (INSTI) Triumeq (FDC)</td>
</tr>
<tr>
<td>'15-'16</td>
<td>2015 Evotaz (FDC) Genvoya (FDC) Prezemprix (FDC) 2016 Descovy (FDC) Odelsse (FDC)</td>
</tr>
<tr>
<td>2017</td>
<td>FDA APPROVED</td>
</tr>
<tr>
<td>2018</td>
<td>Raltegravir (Isentress HD)</td>
</tr>
</tbody>
</table>

**Needs:**
- Pediatric PK studies
- Access to FDA-approved agents
- Combination pills
- Suitable formulations
- Agents for highly treatment experienced children

**Drug Class Abbreviations:**

- **EI:** Entry Inhibitor
- **FDC:** Fixed-Dose Combination
- **PI:** Fusion Inhibitor
- **INSTI:** Integrase Inhibitor
- **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor
- **NRTI:** Nucleoside Reverse Transcriptase Inhibitor
- **PE:** Pharmacokinetic Enhancer
- **PI:** Protease Inhibitor

**Note:** Drugs in gray are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines.
Prevention of illness

- Optimization of OI prophylaxis
- Improve ab responses to vaccination
  - HPV
  - HBV
  - Meningococcus
  - Influenza
  - Rotavirus
  - RSV

- Aged <13 years
- Aged ≥13 years
Long-term Morbidity of HIV and/or ART

- Cardiovascular disease
- Malignancy
- Medication side effects:
  - Kidney, bone, liver
- Metabolic abnormalities:
  - Mitochondrial toxicity
  - Lipodystrophy
  - Lipoatrophy
- Longstanding inflammation
- CNS abnormalities
  - Strokes, cognitive effects, mental health
- Unknown?
  - Consequences of lifelong ART?
  - Consequences of lifelong HIV?

Age Distribution of Persons Living with Diagnosed Perinatally Acquired HIV Infection, Year-end 2015—United States and 6 Dependent Areas

N = 11,847
Diagnoses of HIV Infection among Children Aged <13 Years, by Age at Diagnosis, 2010–2014—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.
The First Pediatric Cases

"Another 85 cases (not reviewed here) were reported in adolescents."

Fig 5. Pediatric AIDS cases by child’s age at diagnosis. Includes children younger than 13 years of age in whom AIDS was diagnosed as of Dec 31, 1985.
Diagnoses of HIV Infection among Adults and Adolescents by Age at Diagnosis, 2016—United States

N = 39,660

Note. Data for the year 2016 are preliminary and based on 6 months reporting delay.
Adolescents and Young Adults Aged 13–24 Years Living with Diagnosed HIV Infection, by Sex and Race/Ethnicity, Year-end 2014—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.

- Includes Asian/Pacific Islander legacy cases.
- Hispanics/Latinos can be of any race.
Diagnoses of HIV Infection among Adolescents and Young Adults Aged 13–24 Years, by Transmission Category, 2010–2015—United States and 6 Dependent Areas

Note. Data have been statistically adjusted to account for missing transmission category. "Other" transmission category not displayed as it comprises less than 1% of cases.

*Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
Prevention...

When transgender women choose to take PrEP

How much does PrEP cost?

Will using PrEP cause problems with the hormones I am taking?

Would they even prescribe PrEP for a woman like me?

PrEP is a safe, daily pill that helps prevent HIV.

Find yours at PrEPForHer.com
# Medical challenges

<table>
<thead>
<tr>
<th>Disease</th>
<th>Perinatal</th>
<th>Non-perinatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced disease/immunosuppression</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>Co-morbidities ¹</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>Neurocognitive delay and dysfunction</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>Mental health (anxiety, depression, PTSD), substance use</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Delayed puberty and short stature</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Suboptimal responses to vaccines</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Perinatal</th>
<th>Non-perinatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment experienced</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>More complicated ART</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>Treatment fatigue</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug-resistant virus</td>
<td>X</td>
<td>*</td>
</tr>
</tbody>
</table>

*some NPHIV youth

Agwu & Fairlie JIAS 2013; Lee & Hazra JIAS 2013
### Psychosocial challenges

<table>
<thead>
<tr>
<th></th>
<th>Perinatal</th>
<th>Non-perinatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stigma (HIV, sexuality)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disclosure (HIV, sexuality)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Limited support systems</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical staff may be only reliable support</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Poor adjustment to illness/status, self efficacy, outcome expectancy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Denial/guilt</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Limited health literacy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Logistic barriers: insurance, childcare, transportation, poverty, legal</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Attempting to be “normal”</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Murphy JAMA 2003; Martinez Pediatrics 2014; Mofenson JIAS 2015; Rudy AIDS Pt Care 2009 & 2010; Lee & Hazra JIAS 2015
Clinical Observations ➔ Research Questions

- Youth presenting with advanced HIV
- Youth less likely to initiate ART
  - CD4 recovery not better
- Providers reluctant to start ART
- Youth have worse outcomes
  - poor virologic suppression
  - continuing failing ART
  - ART discontinuation
  - high hospitalizations
  - Poor retention in care
- Youth do better in pediatric & adolescent vs. adult settings
  - Differences in how providers of varied training interact with youth

Median CD4 Counts of nPHIV-infected Youth

- 40% CD4<350; 20% CD4<200


Agwu KL2, NIAID K23
“What are we missing?”

- Life is dynamic
- Adherence is hard & multifactorial
- Side effects
- Long term toxicity
- One size does not fit all
- Forever is a long time
- Fatigue
- Disclosure
- Stigma
- Mental health
- “I don’t want to be here?”
Simplifying treatment: better drugs

- Fewer pills
  - Combination pills
  - One-pill regimen options
  - Once daily options
- Smaller pill size
- More formulations
- More delivery options
- Better taste
- Higher barrier to resistance
- Fewer drug-drug interactions
- Fewer side effects
- Fewer dietary requirements
- More options for treatment-experienced individuals
Simplifying treatment: fewer agents?

- 2 drug regimens
- NRTI-sparing regimens
- Decreased drug interactions
  - Dolutegravir/rilpivirine (Juluca)
    - Non-inferior to 3-drug regimen
  - Dolutegravir/lamivudine
    - Adults: switch to 3TC/DTG → no VF, improved CD4, reduced cost
    - Pediatrics??

Maggiolo et al. BMC 2017
Simplifying treatment: are pills even needed?
Population: 309 treatment-naïve, HIV+ 
92% male; 15% AA, 79% White, median age 35, baseline CD4 489
Location: USA, Canada, Spain, France, and Germany
Meds: oral cabotegravir, rilpivirine, and abacavir
Intramuscular cabotegravir and rilpivirine (two 2 mL injections)- buttocks
Method:
   All start oral → suppress   → continue oral cabotegravir/rilpivirine/abacavir
   → IM cabotegravir/rilpivirine every 4 weeks
   → IM cabotegravir/rilpivirine every 8 weeks
Youth willingness to use LA-ART by frequency of administration

- Once every week (n= 254): 49.6%
- Once every two weeks (n= 252): 56.3%
- Once every month (n= 252): 86.1%
- Once every two months (n= 250): 86.8%
- Once every three months (n= 256): 90.2%

Weld et al. IAS 2017
Impact of non-adherence on interest among youth

*Impact of non-adherence on interest among youth.*

**Interest level of IM LAARV use by viral load**

(n=288)

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>Definitely not</th>
<th>Probably not</th>
<th>Probably would</th>
<th>Definitely not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable</td>
<td>7.1</td>
<td>7.1</td>
<td>28.8</td>
<td>57.1</td>
</tr>
<tr>
<td>Low Detectable</td>
<td>6.3</td>
<td>9.4</td>
<td>28.1</td>
<td>56.3</td>
</tr>
<tr>
<td>High Detectable</td>
<td>1.4</td>
<td>2.8</td>
<td>18.1</td>
<td>77.8</td>
</tr>
</tbody>
</table>

*p<0.05; significance tested by adjusted Poisson regression, robust variance*

Weld et al. IAS 2017
Development Pipeline for Long-Acting ART

- Cabotegravir & rilpivirine LA --Phase IIb
  - FLAIR
  - ATLAS
  - HPTN 083
  - HPTN 084
  - ACTG 5359
  - IMPAACT 2017
  - IMPAACT 2022*
- MK-8591 (EFdA)

*in development

Beyond ART
“Forever is a long time”
Beyond viral suppression as a destination....
Outcome Measure to Detect HIV-1 Remission: Time to Viral Rebound


Slide courtesy of Deborah Persaud
48 clinical trial sites in 13 countries

**October 2017:**
Version 1:
Step 1: Enrolled 440 mother-infant pairs
Step 2: 34 infected infants (Cohort 1)
Step 2: 18 infected infants (Cohort 1)
Step 3: ART cessation to detect remission
Step 4: Restart ART for viremic rebound

**December 2017:** Version 2
additional 445 mother-infant pairs (ARVs +/- bNAbs)
Where should the Science be moving?

- Multimodal strategies & approaches for treatment, prevention, remission
  - Biologics (e.g., monoclonal ab, activated T cells)
  - Other agents (e.g., latency reversing agents)
  - ART next gen (e.g., long-acting, different delivery modes)
- Predicting and addressing complications
  - Longitudinal cohorts, biomarkers, surrogates
- Behavioral and community interventions
  - Improved finding & targeting strategies
- Implementation science
- Optimizing care models
  - Rapid initiation
  - Alternative “venues” for care delivery
  - Tech
- Personalized medicine?
  - Proteonomics, Metabolomics, microbiome
Focusing on youth: JHU Projects and Initiatives

Multidisciplinary approaches
Multimodal, cross sector strategies
Relevant & specific
  Include youth and community voices
Real world
Creative & innovative
Increased targeted funding
Ethics & regulatory
Advocacy & guidelines
Acknowledgements

The Youth!!

ACE team
IPC/PAHAP
Bartlett Clinic (Keruly, Moore, Nolan)
JHU HIV Clinical Research team (IMPAACT, ATN, Cure)
  Trent, Persaud, Arrington-Sanders, Anderson, Collensen-Streng
  Farmer, Griffith, Lee, Hsu, Weld

HIV Research Network

Gebo, Moore, Fleishman, Yehia, Berry, Gaur, Korthuis, Rutstein,
  Voss, Monroe, co-investigators, sites, and participants

Funding:
No assumption of HIV status should be made; f