Issues in the Treatment of Pediatric HIV in the Resource Limited Setting

Theodore Ruel MD, Fellow, Division of Infectious Disease, Department of Pediatrics
University of California, San Francisco

December 2007

Outline

- A brief history of the epidemic in children
- Challenges in care and antiretroviral treatment
- Reports from the roll out ...
- Future Directions
The beginning (in the USA)

- 4 infants with immunodeficiency in 1982 in New York, New Jersey, and San Francisco (1)
- First transfusion associated case described in 1983 at UCSF (2)

As of 2005 …

<table>
<thead>
<tr>
<th>Transmission Category</th>
<th>2005</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Perinatally acquired</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>Transfusion-associated</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other/not reported</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

(1) MMWR 1982; 31(49): 665-7.
(2) MMWR 1983; 1(831) 956-8.

www.cdc.gov/hiv/topics/surveillance/resources/slides/pediatric/index.htm
Perinatal AIDS Cases

Estimated Number of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2005—United States Dependent Areas

Children (<15 years) newly infected with HIV in 2007

Total: 420,000 (350,000 – 540,000)
Children (<15 years) living with HIV in 2007

Total: 2.5 (2.2 – 2.6) million


Estimated total annual resources available for HIV/AIDS, 1996–2005

Lancet, 2006; 368: 526–30
## Overall Access to ART in 2005

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Number receiving ART</th>
<th>Estimated need</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>1 040 000</td>
<td>4 600 000</td>
<td>23%</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>345 000</td>
<td>460 000</td>
<td>75%</td>
</tr>
<tr>
<td>East, South and South-East Asia</td>
<td>235 000</td>
<td>1 440 000</td>
<td>16%</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>24 000</td>
<td>190 000</td>
<td>13%</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>4 000</td>
<td>75 000</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1 650 000</strong></td>
<td><strong>6 800 000</strong></td>
<td><strong>24%</strong></td>
</tr>
</tbody>
</table>

UNAIDS, 2006

## Children (<15 years) receiving and needing ART, December 2006

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Estimated number receiving ART</th>
<th>Estimated need</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>85 000</td>
<td>680 000</td>
<td>13%</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>15 500</td>
<td>23 000</td>
<td>67%</td>
</tr>
<tr>
<td>East, South and South-East Asia</td>
<td>13 300</td>
<td>64 000</td>
<td>21%</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>1 500</td>
<td>7 500</td>
<td>20%</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>&lt;100</td>
<td>10 000</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>115 500</strong></td>
<td><strong>780 000</strong></td>
<td><strong>15%</strong></td>
</tr>
</tbody>
</table>

WHO, 2007
Pediatric Roll Out – Funding and implementation

- PEPFAR
- Global Fund
- Clinton Foundation HIV/AIDS Initiative
- Elizabeth Glaser Pediatric AIDS Foundation
- Baylor International Pediatric AIDS Initiative
- National Programs

“Ten Point Management Plan”

- Early Diagnosis of HIV infection
- OI Prophylaxis and treatment
- Antiretroviral therapy as indicated
- Immunizations
- Growth and development monitoring
- Nutrition education and supplementation
- Psychosocial support
- Aggressive treatment of acute infections
- Adolescent care, treatment and support
- Mother and family care and treatment MTCT plus

Department of Pediatrics, Makerere University Kampala, Uganda
Challenge and importance of early diagnosis

- Many children only tested because they become symptomatic
- Diagnosis in < 18 mo difficult
  - Antibody based testing not reliable
  - DNA or P24 Ag testing limited
- Why it is so urgent?

Child mortality according to maternal and infant HIV status in Zimbabwe

E Marinda, J Humphrey, P Iliff, K Mutusa, E Piwoz, L Moulton, K Nathoo, P Salama, B Ward

ZVITAMBO Study Group

14,110 Mothers

4495 HIV-positive mothers

9562 HIV-negative Mothers

53 Indeterminate

9210 HIV (-) and not exposed

3135 Exposed but HIV(-)

1336 HIV (+)

353 seroconverted during follow-up

Infants

Mortality from birth to 24 mo.

Survival probability

Age in days

How do you deal with this?

- Increase testing and diagnosis …
  - Coordinated PMTCT programs
  - Active testing program in communities (eg Whole families)
  - DBS based DNA testing

- OI prophylaxis

- Antiretroviral Therapy
  - WHO Guidelines - other reasons to start
  - When to start?

“CHAP”

- Cotrimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial


Lancet 2004;364:1865-1871
Double-blind randomized placebo-controlled trial of co-trimoxazole vs placebo

534 HIV infected children

1-14 years

University Teaching Hospital, Lusaka, Zambia

Diversity of age and cd4, minority on ART (5-10%)

Death rate at median 19 mo f/u

- 74 (28%) children in co-trimoxazole group
- 112 (42%) in the placebo group
- Hazard ratio [HR] 0.57 [95% CI 0.43–0.77] p=0.0002.

Hospital admission rate (per child-year of follow-up)

- 48% in the co-trimoxazole group
- 63% in the placebo group (0.77 [0.62–0.95]; p=0.01).
CHAP - consequence

- Study stopped by DSMB in October 2003

- In 2004 WHO changed recommendations to include all HIV infants up 18 mo and any “symptomatic” HIV infected child with

- In 2006, WHO recommended for all children regardless of immune or clinical status …

Children with HIV and Malaria Project (CHAMP)

- Study of interactions between HIV and Malaria in children

- 300 HIV infected children recruited from pediatric HIV clinic at Mulago Hospital, Kampala, Uganda

- Parallel Cohort of 600 HIV (-) from same locale

AIDS, 2007; 15: 2059-66
Children with HIV and Malaria Project (CHAMP)

- 9 episodes of malaria among HIV-infected children (0.07/py)
- 440 episodes among children from the community (0.90/py)

- Insecticide-treated bednets (ITN)
  - 43% reduction in malaria incidence ($P < 0.001$)

- Combination of TMP/SMX + ITN
  - 97% reduction in malaria incidence ($P < 0.001$)

- *Malaria accounted for only 4% of febrile episodes in the HIV cohort in comparison with 33% in the community-based cohort ($P < 0.0001$).*

AIDS, 2007; 15: 2059-66

INH Prophylaxis

- Recommended in HIV-infected adults and children with pos. PPD skin test in USA

- Most national TB programs recommend INH for children < 5 yrs exposed to an adult with sputum + TB

- HIV infected children at **high risk** of developing TB

- No standard recommendation of INH in HIV infected children worldwide ...


Benefit of INH prophylaxis

- Isoniazid or placebo given with co-trimoxazole either daily or three times a week
- 263 children
  - 132 Received INH
- Median f/u 5.7 (2 - 9.7) months
- Mortality 8% in INH and 16% Placebo Arms
  - HR 0.46 by intention to treat analysis
  - TB incidence 5 cases INH and 13 cases PL (HR 0.28 p=0.005)


- Ideally CD4% and Clinical Stage

- Total Lymphocyte Count if CD4 not available

- Guidelines for “Presumptive” diagnosis in <18 mo
### ART Initiation Guidelines – WHO (2006)

#### Immunological marker

<table>
<thead>
<tr>
<th></th>
<th>Age-specific recommendation to initiate ART&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤11 months</td>
</tr>
<tr>
<td>%CD4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>CD4 count&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;1500 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

---

### ART Initiation Guidelines – WHO (2006)

#### WHO paediatric stage

<table>
<thead>
<tr>
<th>WHO paediatric stage</th>
<th>Availability of CD4 cell measurements</th>
<th>Age-specific treatment recommendation [A (0)]&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CD4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Treat all</td>
</tr>
<tr>
<td></td>
<td>No CD4</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Treatment unguided</td>
<td>Treat all, CD4-guided in those children with TB&lt;sup&gt;c&lt;/sup&gt;, LIP, OHL, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>No CD4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CD4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CD4-guided&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>No CD4</td>
<td>TLC-guided&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>CD4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CD4-guided&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>No CD4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Do not treat</td>
</tr>
</tbody>
</table>
Presumptive diagnosis of severe HIV disease

- **Confirmed** HIV antibody-positive AND

- Diagnosis of any AIDS-indicator condition can be made OR the infant is symptomatic with two or more of the following:
  - oral thrush
  - severe pneumonia
  - severe sepsis

Challenge

- Recognizing that high first year mortality many providers in USA will start **any** HIV infected children less than 1 year of age …

- But in RLS it is rare to be able to confirm diagnosis and those indications are non-specific, can you really start them all on ARV presumptively? And at what cost?

- Concerns of toxicity, drug resistance early in life, limited second line options …
Early vs. Deferred Treatment?

- **Children with HIV Early ART (CHER)**
  - South Africa
  - Recognition that CD4 and viral load poor predictors of disease progression in infants
  - Hypothesis: early ART with subsequent treatment interruption will delay disease progression and chronic ART
  - **All healthy children < 12 weeks old with CD4% > 25%**


---

Children with HIV Early ART (CHER)

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred ART</td>
<td>Short-course until 1y</td>
<td>Long-course until 2y</td>
</tr>
</tbody>
</table>

Treat, stop, and ART (re-start) when CD4% < 20% or clinical event (<25%)

Follow-up for > 3.5 years

**CHER - Interim Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Arm 2 &amp; 3</th>
<th>Arm 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N =</strong></td>
<td>252</td>
<td>125</td>
</tr>
<tr>
<td>Died (%)</td>
<td>10 (4)</td>
<td>20 (16)</td>
</tr>
<tr>
<td><strong>Person years of follow-up</strong></td>
<td>167</td>
<td>79</td>
</tr>
<tr>
<td><strong>Death Rate/ 100 PY (95% CI)</strong></td>
<td><strong>6.0</strong> (2.9, 10)</td>
<td><strong>25.3</strong> (15.5, 39.0)</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong>*</td>
<td><strong>0.24</strong> (0.11, 0.51)</td>
<td><strong>25.3</strong> (15.5, 39.0)</td>
</tr>
</tbody>
</table>

*Violari A, et al. IAS 07, WESS103.*

**CHER - Implications**

- **75% reduction** in mortality in infants started on ART at <12 weeks
  - DSMB closed deferral arm

- Impact on guidelines
  - Capacity issues: diagnostics, access to pediatric ARVs
  - Clinical issues: non-African settings, treatment interruption, consequences on long-term toxicity and resistance
When to start …

- Wait even longer? PREDICT study
  - Randomized trial of children with moderate immune failure (CD4 15-24%)
    - Immediate vs. deferred (<15%) ART

Which ARV to start …

- Standard first-line, WHO 06
  - 2 NRTI: AZT or d4T or ABC and 3TC
  - 1 NNRTI: NVP or EFV

- NRTI
  - Generally AZT unless anemic, then d4T
  - Thailand: 57% of children on d4T regimen had lipodystrophy by 144 weeks**

- Post NVP ART (IMPACT 1060)

Other issues with Pedi ART

- Inadequate number of trained health care workers comfortable with treating children
- Adherence dependant on the caregiver who may change from time to time
- Weight based dosing
  - Liquid suspensions
    - Expensive, harder to ship/distribute/store
    - Issues of compliance
  - Split adult tablets
    - Inappropriate doses for small children (<10kg)

Pill Cutting …
Reports from the rollout…

- Concerns about how well ART with children in these settings would work …

- Reports from:
  - BAPAI
  - Cote D’Ivoire
  - GHESKIO
  - Uganda

Baylor International Pediatric AIDS Initiative (BAPAI)

- Well resourced programs

- 10,000 children in Botswana, Uganda, Lesotho, and Malawi

- Botswana
  - 81% undetectable (<400 copies/mL) at 12 mo

Côte d'Ivoire

- National treatment program
- 395 children
  - 80% had a CD4% <15%, Median RNA 5.6 log
  - Median age was 7 years
- 54% undetectable at 12 mo


South Africa

- Sinikithemba HIV/AIDS clinic in KwaZulu-Natal, South Africa
- 151 children
  - median age 5.7 years (range 0.3–15.4)
  - median follow-up time 8 months
- At 6 mo, 84% undetectable ( < 50 c/ml)
- At 12 months, 80.3% undetectable ( < 50 c/ml)

Reddi et al. BMC Pediatr 2007;7:13
Haiti

- Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO), Haitian NGO

- 236 children started ART
  - Median viral load 5.30 log c/mL

- 56% (56/100) undetectable (< 50c/ml) at 12 mo

George et al. . JID 2007;195:1411-8

National Statistics: Uganda

- HIV prevalence: 6.4%
- Estimated number of HIV infected: 950,000
  - Paediatric HIV/AIDS patients: 140,000
- Total number requiring ART: 208,000
  - 43,700 (21%) requiring ART are children

- Number on ART: 100,000 (Apr07)
  - Children account for 10% of the 100,000
  - Only 20 % of eligible children are on ART
  - Mulago contributes 22% of all on ART
Uganda

- Makerere University, Mulago Hospital, Kampala Uganda
- 250 children
  - Median age 9.2 years
- 74% undetectable (< 400c/ml) at 1 year

Kamya, JAIDS 2007 46(2):187-93

Children with HIV and Malaria Project (CHAMP)

- Very well resourced clinic with aggressive follow up, Kampala Uganda
- Observational cohort of 300 HIV infected children enrolled at age 1-10 yrs
- 78 started ART on study
- 86% undetectable (< 400 c/ml) at 6mo
- 75% undetectable at 12 months
Future Directions

- Push for Early diagnosis
  - HIGH infant mortality
  - DBS based community testing
- Aggressive OI prophylaxis
- Increased access to ART
- Adherence programs
- More Treatment options (drug and formulation)
- More data
  - Timing - When to start, when to switch
  - Resistance and second line therapy

Children (<15 years) newly infected with HIV in 2005

Total: 540,000 (420,000 – 670,000)
Access to PMTCT services in sub-Saharan Africa, 2005

Mortality from birth to 24 mo.

UNAIDS, 2006

Call for Prevention

- Expand access to PMTCT for mothers
- Expand access to TREATMENT for mothers
- Higher goal – complete suppression
  - Lower transmission rates
    - Intrauterine
    - Peripartum
    - Breast milk
  - Improve health of their infants HIV (-) and (+)

Acknowledgement

- Philippa Musoke (Makerere University, Kampala)
- Annette Sohn (UCSF)
- Jean Humphrey (Zvitambo)
- CDC
- WHO
Web Resources

  - Pediatric guidelines per WHO

- www.aidsinfo.nih.gov/Guidelines
  - Pediatric Guidelines per NIH

- hivinsite.ucsf.edu

Bibliography


My Contact Information

- Theodore Ruel MD
- ruelt@peds.ucsf.edu