Update on Pediatric Antiretroviral Therapy

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HIV-Infected Children are Not Little HIV-infected Adults

- Age-related differences in risk of HIV disease progression and surrogate markers such as CD4
- Dosing is complex - needs adjustment as child grows to avoid under-dosing and resistance
- Differential maturation of organs leads to age-related pharmacokinetics changes and age-specific dosing
- More limited drug formulary because pediatric drug formulations are needed
- Concern regarding ARV toxicities in growing child (e.g., TDF and bone in pre-pubertal child)
HIV-Infected Children Are Not a Uniform Group: Age-Related Differences

- **Infants and children - <2 years**
  - High viral load
  - Rapid progression and high mortality with no good surrogate markers
  - PMTCT ARV drug exposure and resistance – may affects ART response
  - Fewest options – liquid/dispersible needed
  - Major changes organ development/metabolism - affect dosing
HIV-Infected Children Are Not a Uniform Group:
Age-Related Differences

- **Age 2-5 years**
  - Progression lower but still high, surrogate marker better predictors but complicated by age-related change in CD4
  - Pediatric formulations needed, palatability issues

- **Age >5 years**
  - Progression more like adults, CD4 similar to adults
  - Generally can take solid tabs/caps but still need lower dose ped formulation
For any given CD4% marked difference in mortality risk by age
For any given CD4 count and age, mortality risk is higher in resource-limited than resource-rich counties.
For children over age 5 years, risk of AIDS/death similar to that in younger adults.
What Can We Learn From Resource Rich Countries?
In the United States, the Majority of HIV-Infected Children Are Receiving Antiretroviral Therapy: PHACS/AMP Study

Van Dyke R et al. JAIDS 2011;57:165-73

451 perinatally-infected children from 15 US sites

At entry:
- Median age 12 yrs
- Median ART duration 11.4 yrs
- Median # individual ARVs taken: 7

In 2008, 93% of HIV-infected children were on treatment
More Recent Birth Cohorts More Likely to Have Suppression of Viral Replication than Earlier Cohorts

Van Dyke R et al. JAIDS 2011;57:165-73

PHACS/AMP: 451 perinatally-infected children from 15 US sites

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage RNA &lt;400 c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>68%</td>
</tr>
<tr>
<td>1991-1993</td>
<td>60%</td>
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<tr>
<td>1994-1995</td>
<td>58%</td>
</tr>
<tr>
<td>1996-1997</td>
<td>76%</td>
</tr>
<tr>
<td>1998-2001</td>
<td>78%</td>
</tr>
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</table>
More Recent Birth Cohorts Have Better Immune Function (Higher CD4) Over Time than Earlier Cohorts

Van Dyke R et al. JAIDS 2011;57:165-73

PHACS/AMP
451 perinatally-infected children from 15 US sites

At entry:
- Median CD4 33%
- 78% had CD4 ≥25%
Recovery of Immune Status with Potent Therapy is Dependent on CD4% at Time Therapy is Initiated


1,236 children enrolled in PACTG 219 not on therapy at study initiation
Recovery of Immune Status with Potent Therapy is Dependent on CD4% at Time Therapy is Initiated


1,236 children enrolled in PACTG 219 not on HAART at study initiation
Significant Decline in Mortality in HIV-Infected Children Over Time Associated with Better Therapies

Death rate 1994: 7.2/100 pt-yrs

Death rate 2006: 0.6/100 pt-yrs

Death rate 18/100 pt-yrs

HAART Era

PACTG 219, observational study: 3,553 children
Brady M et al. JAIDS 2010;53:86-94

PACTS, birth cohort: 364 children
Kapogiannis B et al. CID 2011;53:1024-34
# In U.S., ART is Individualized with Intensive Monitoring

**November 1, 2012 US Pediatric Guidelines**

| Table 15 | Schedule of Monitoring HIV-Infected Children Before and During ART |

<table>
<thead>
<tr>
<th></th>
<th>Entry Into Care</th>
<th>Monitoring Pre-Therapy</th>
<th>ART Initiation</th>
<th>1–2 Weeks on Therapy</th>
<th>4–8 Weeks on Therapy</th>
<th>Every 3–4 Months</th>
<th>Every 6–12 Months</th>
<th>ARV Switch</th>
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<tbody>
<tr>
<td>Clinical History</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Physical Exam²</td>
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<td>CBC w/ Differential</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Chemistries⁴</td>
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<td>Electrolytes</td>
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<td>Glucose</td>
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<td>X</td>
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<tr>
<td>AST/ALT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X⁴</td>
<td>X⁴</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Bilirubin</td>
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<tr>
<td>BUN/ Creatinine</td>
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<td>X</td>
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<td></td>
</tr>
<tr>
<td>Albumin/Total Protein</td>
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<td></td>
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<td></td>
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<tr>
<td>Ca/Phosphate</td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>CD4 Count/%</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X⁶</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>HIV RNA</td>
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<td>X</td>
<td>X</td>
<td>X²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Resistance Testing</td>
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<td>X</td>
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<td>Urinalysis</td>
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<td>X</td>
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</tbody>
</table>
What About ART in More Resource-Limited Countries?
% Children and Adults Eligible for ART Who Are Receiving ART in Low and Middle-Income Countries, 2009-2011

Clinical Response to ART in Children in Low Resource Countries is Good

- Significant declines in mortality with ART in children in Lesotho, Malawi, and Swaziland; most deaths (78%) in 1st year ART.

Kabue et al. Pediatrics 2012;120:e591

- Significant declines in hospitalization/ cost in children on ART in Thailand; most occur in 1st yr ART.

Collins et al. AIDS 2012;26:1943-52
Viral Suppression in Developing vs Developed Countries


**Developing Countries**
- Mean age: 5.7 yrs
- Baseline RNA: 5.5 log c/mL
- Majority studies used NNRTI-based regimens
- 12 mos ART: 65% suppressed
- P=0.40

**Developed Countries**
- Mean age: 6.7 yrs
- Baseline RNA: 4.7 log c/mL
- Majority studies used PI-based regimens
- 12 mos ART: 49% suppressed
CD4% Levels Post ART in Developing vs Developed Countries


Developing Countries

Baseline CD4% 12%

12 mos ART: Mean CD4 24%

P=0.03

Developed Countries

Baseline CD4% 23%

12 mos ART: Mean CD4 27%
Mortality on ART in Developing vs Developed Countries

*Peacock-Villada E et al. Pediatrics 2011;127:e423*

<table>
<thead>
<tr>
<th>Country and First Author</th>
<th>N=</th>
<th>Time, mo</th>
</tr>
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<tbody>
<tr>
<td>Burkina Faso (Hien)</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td>Kenya (Nyandiko)</td>
<td>279</td>
<td>Med. 34</td>
</tr>
<tr>
<td>Kenya (Song)</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Kenya (Van Winghem)</td>
<td>648</td>
<td>12</td>
</tr>
<tr>
<td>Kenya (Waramalwa)</td>
<td>67</td>
<td>6</td>
</tr>
<tr>
<td>Lesotho (Cohen)</td>
<td>283</td>
<td>12</td>
</tr>
<tr>
<td>Lesotho (Leyenaar)</td>
<td>284</td>
<td>14</td>
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<tr>
<td>Malawi</td>
<td>436</td>
<td>6</td>
</tr>
<tr>
<td>Malawi</td>
<td>233</td>
<td>12</td>
</tr>
<tr>
<td>Mozambique (Marazzi)</td>
<td>207</td>
<td>6</td>
</tr>
<tr>
<td>Rwanda (van Griensven)</td>
<td>315</td>
<td>24</td>
</tr>
<tr>
<td>South Africa (Barth)</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td>South Africa (Eley)</td>
<td>407</td>
<td>12</td>
</tr>
<tr>
<td>South Africa (Jaspan)</td>
<td>391</td>
<td>12</td>
</tr>
<tr>
<td>South Africa (Jooste)</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>South Africa (Smit)</td>
<td>615</td>
<td>12</td>
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<td>Tanzania (Blé)</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td>Uganda (Karrya)</td>
<td>250</td>
<td>12</td>
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<tr>
<td>Zambia (Bolton-Moore)</td>
<td>2938</td>
<td>36</td>
</tr>
<tr>
<td>Zambia (Walker)</td>
<td>93</td>
<td>24</td>
</tr>
</tbody>
</table>

**Africa Mean**
- IPENTA: 103 48wk
- Denmark (Bracher): 49 108
- France (Thuret): 22 Med. 16
- Netherlands (Fraaij): 31 48
- Switzerland (Rudin): 133 86
- USA (McKinney): 27 24
- USA (Patel): 866 Med. 70

**Europe/US Mean**

Post-ART mortality rates in Africa were 8-fold higher than in US/Europe

- Africa: 7.5/100 child-years
- Europe/US: 0.9/100 child-years

Post ART Deaths per 100-Child Years
When to Start
### WHEN TO TREAT: Infants - <2 Years
2010 WHO Pediatric HIV Recommendations

**Table 6:** Recommendations for initiating ART in infants and children; revised in 2010

<table>
<thead>
<tr>
<th>Age</th>
<th>Infants and children &lt;24 months of age&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>≥24 months of age to 59 months of age</th>
<th>Five years of age or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>%CD4+</td>
<td>All&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤25</td>
<td>NA</td>
</tr>
<tr>
<td>Absolute CD4</td>
<td>All&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤750 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≤350 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(As in adults)</td>
</tr>
</tbody>
</table>

**Table 7:** Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and immunological markers

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Immunological</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 months</td>
<td>Treat all</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td></td>
</tr>
<tr>
<td>Stage 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Treat all&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Treat all</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Treat if CD4 below age-adjusted threshold</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Don’t treat if no CD4 available:</td>
</tr>
</tbody>
</table>
Early Treatment in Infants Reduces Disease Progression and Death: CHER Trial

Compared starting treatment in asymptomatic HIV+ infants with CD4 >25% aged <4 months vs deferring until met standard criteria

75% Reduction in Mortality: 4% vs 16% for Early vs Deferred ART

77% Reduction in Death/Progression: 6% vs 26% for Early vs Deferred ART
Early HAART in HIV-Infected Infants Associated with Improved Neurodevelopmental Outcome: CHER and Control Children

Laughton B et al.  AIDS 2012;26:1685-90

Griffiths Mental Development Scales given at median age 11 mos to deferred vs early patients, HIV-exposed uninfected, & HIV-unexposed children

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deferred ART</th>
<th>Early ART</th>
<th>HIV-exposed uninfected</th>
<th>HIV-unexposed</th>
<th>P Value Defer vs Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26</td>
<td>64</td>
<td>28</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Mean Motor</td>
<td>88.9</td>
<td>97.7</td>
<td>105.3</td>
<td>101.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean General</td>
<td>100.1</td>
<td>106.3</td>
<td>105.6</td>
<td>106.9</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CHER Trial: Enrolled HIV-infected infants <12 weeks of age and randomized to deferred vs immediate ARV.
WHEN TO TREAT: ≥2 Years
2010 WHO Pediatric HIV Recommendations

Table 6: Recommendations for initiating ART in infants and children; revised in 2010

<table>
<thead>
<tr>
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<td>NA</td>
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<td>Absolute CD4</td>
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<td>≤750 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≤350 cells/mm&lt;sup&gt;3&lt;/sup&gt; (As in adults)</td>
</tr>
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</table>

Table 7: Recommendations for initiating ART in HIV-infected infants and children according to clinical stage and immunological markers

<table>
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<tr>
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<th>Immunological</th>
</tr>
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<tbody>
<tr>
<td>&lt;24 months</td>
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<td>Stage 4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stage 3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Treat if CD4 below age-adjusted threshold</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Don’t treat if no CD4 available:</td>
</tr>
</tbody>
</table>
PREDICT Study Design
Pediatric Randomized of Early vs Deferred Initiation in Cambodia and Thailand

Immediate (Early) ART (N=149)
Deferred ART (CD4 <15%* or CDC C) (N=150)

Children age 1-12 yrs with CD4 15-24% and CDC A or B (n=300)
Baseline (mean):
Age 6.4 yr
CD4 20%/619

*April 2009: Immunological Criteria to start ART in children aged from 1-3 years change to CD4 < 20%

Primary Endpoint
AIDS-free survival at week 144 and neurodevelopmental outcome
PREDICT Study: AIDS-Free Survival

AIDS-free survival week 144
- Early: 98.7%
- Defer: 97.9%

Survival (%) vs Time (weeks)

- Early treatment
- Deferred treatment

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Defer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>AIDS</td>
<td>3</td>
<td>2</td>
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</table>

*p = 0.6*
PREDICT Study: Death or Progression to CDC Class B or C

Lancet Infect Dis 2012;12;933-41

<table>
<thead>
<tr>
<th>Rate/100 pt-yr</th>
<th>Early</th>
<th>Defer</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class B (any)</td>
<td>8.8</td>
<td>11.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Low platelet</td>
<td>0.3</td>
<td>2.4</td>
<td>0.03</td>
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<tr>
<td>VZV zoster</td>
<td>0.5</td>
<td>3.2</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\[ p = 0.3 \]
Intelligence Scores Were Not Different Between Immediate vs. Deferred ART

Puthanakit T. 19th CROI, Seattle, WA, March 2012 (Abs 24)

Intelligence Scores Were Lower In HIV-Infected Children Compared to HIV-Uninfected Controls
CD4 and Height Better with Early ART


- Median CD4 at week 144 was 33.2% in early vs 24.8% in deferred arms (p<0.0001)

- While no difference btn arms for weight, mean height gain per year was 5.4 cm in early vs 4.9 cm in deferred arm (p=0.001)
Over the 3 year study period, 46% of deferred arm children started ART (96% for immunologic criteria).

For children with at least 48 weeks of ART, no difference in rates of viral suppression between arms: 81% of early vs 85% of deferred children had RNA <50 copies/mL.

Overall 9% in the early vs 6% in the deferred group switched to 2\textsuperscript{nd} line (p=0.59).

17% of children in the early vs 10% in the deferred arm had grade 3 or 4 events secondary to ART (p=0.19)
What to Start

Tenofovir
Preferred First-Line Pediatric ARV Regimens: 2010 WHO Pediatric HIV Recommendations

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Standard first-line regimen</th>
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<tbody>
<tr>
<td>INFANTS</td>
<td></td>
</tr>
<tr>
<td>Infant or child &lt;24 months not exposed to ARVs</td>
<td>NVP + 2 NRTI</td>
</tr>
<tr>
<td>Infant or child &lt;24 months exposed to NNRTI</td>
<td>LPV/r + 2 NRTI</td>
</tr>
<tr>
<td>Infant or child &lt;24 months with unknown ARV exposure</td>
<td>NVP + 2 NRTI</td>
</tr>
<tr>
<td>CHILDREN</td>
<td></td>
</tr>
<tr>
<td>Children 24 months to 3 years</td>
<td>NVP + 2 NRTI</td>
</tr>
<tr>
<td>Children &gt;3 years</td>
<td>NVP or EFV + 2 NRTI</td>
</tr>
</tbody>
</table>

Box 4: Recommended alternative ARV regimen for infants and children to simplify management of toxicity, comorbidity and drug – drug interaction

AZT or d4T\(^a\) + 3TC\(^b\) + ABC

\(^a\): 3TC = lamivudine, d4T = stavudine

\(^b\): ABC = nevirapine, efavirenz
With Scale-Up of PMTCT, Smaller Number of Perinatally-Infected Infants but Greater Proportion with ARV Drug Resistance

Proportion of Newly Infected Children with NNRTI Resistance

PMTCT Scale-Up With Effective Regimens

Current Number of New Pediatric HIV Infections

Projected Number of New Pediatric HIV Infections

Affects choice of first-line ART
P1060: NVP vs LPV-r HAART in HIV-Infected Infants Under 3 Years

**Cohort 1**

*Palumbo P et al. NEJM 2010;363:1510-20*

- ART-naïve children, age 6 mos-3 yrs meeting criteria for ART with prior SD NVP exposure (n=288)
- Randomise
- NVP + AZT/3TC
- LPV/RTV + AZT/3TC
- Time to Viral Failure/ Off Drug/ Death

**Cohort 2**

*Violari A et al. NEJM 2012;366:2380-9*

- ART-naïve children, age 6 mos-3 yrs meeting criteria for ART without prior SD NVP exposure (n=288)
- Randomise
- NVP + AZT/3TC
- LPV/RTV + AZT/3TC
- Time to Viral Failure/ Off Drug/ Death
**P1060 Results: Comparing Cohorts**

**Cohort 1: NVP-exposed**
- Combined Endpoint: 39.6%
- Viral Failure: 21.7%

**Cohort 2: No NVP Exposure**
- Combined Endpoint: 40.8%
- Viral Failure: 19.3%

**Combined endpoint= Viral Failure, Off Study Drug, or Death**

- Similar rates of overall failure (combined endpoint) & viral failure in NVP-exposed AND -unexposed cohorts.
- Suggests PI (LPV/r) superior to NNRTI (NVP) for children <3 years old, regardless of past NNRTI exposure
NNRTI vs PI-Based ART in HIV-Infected Children and Malaria, Toro, Uganda

Achan J et al. NEJM 2012 Nov 29 in press

- 170 children aged 2 mo-5 yrs (median age ~3 yrs) randomized to initiate NNRTI vs LPV-based ART and followed for median 366 days; primary endpoint malaria incidence.

<table>
<thead>
<tr>
<th></th>
<th>NNRTI</th>
<th>LPV</th>
<th>HR</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Malaria incidence</td>
<td>2.25</td>
<td>1.32</td>
<td>0.59 (0.36-0.97)</td>
<td>0.04</td>
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<tr>
<td>(episodes pt-yr)</td>
<td></td>
<td></td>
<td>41% decrease</td>
<td></td>
</tr>
<tr>
<td>63-day risk of</td>
<td>54.2%</td>
<td>28.1%</td>
<td>0.41 (0.22-0.76)</td>
<td>0.004</td>
</tr>
<tr>
<td>recurrent malaria</td>
<td></td>
<td></td>
<td>59% decrease</td>
<td></td>
</tr>
</tbody>
</table>
Risk of recurrent malaria following treatment with AL

Recurrent Malaria in HIV-Infected Children on LPV/rtv vs NNRTI-Based HAART, Toro, Uganda

Achan J et al. NEJM 2012 Nov 29 in press

- LPV associated with a 59% decrease in recurrent malaria after artemether-lumefantrine (AL) rx (HR=0.41, 95% CI 0.22-0.76, p=0.004)
- RTV inhibits CYP 3A4 pathway involved in lumefantrine metabolism

<table>
<thead>
<tr>
<th></th>
<th>LPV/r –based ART</th>
<th>NNRTI-based ART</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median day 7 lumefantrine level ng/ml (IQR)</td>
<td>926 (473-1910)</td>
<td>200 (108-510)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
NNRTI vs PI as Initial Therapy in Older Children: A Different Trial with a Different Story to Tell….

PENPACT-1/ PACTG 390
(Europe & Americas)
- Initial Therapy
- VL for switching
266 ART naïve children requiring therapy

PENPACT-1/ PACTG 390

1st-line ART

- PI + 2 NRTIs
- PI + 2 NRTIs
- NNRTI + 2 NRTIs
- NNRTI + 2 NRTIs

Switch criteria: Confirmed VL at/after week 24 (or AIDS)

- Switch when VL>1,000 c/ml
- Switch when VL>30,000 c/ml

2nd-line ART (“strongly encouraged”)

- NNRTI + 2 new NRTIs
- NNRTI + 2 NRTIs
- PI + 2 new NRTIs
- PI + 2 new NRTIs

Minimum follow-up:
4 years

Primary Endpoint:
Change in VL from baseline to 4 years
ART naïve children requiring therapy

**PENPACT-1/ PACTG 390**

1\(^{st}\)-line ART

- PI + 2 NRTIs
  - Switch when VL > 1,000 c/ml

Switch criteria:
Confirmed VL at/after week 24 (or AIDS)

2\(^{nd}\)-line ART (“strongly encouraged”)

- NNRTI + 2 new NRTIs

Minimum follow-up: 4 years

**Randomize**

ART naïve children requiring therapy

- NNRTI + 2 NRTIs
- Switch when VL > 30,000 c/ml

Primary Endpoint:
Change in VL from baseline to 4 years

- 2 NRTIs + PI (N=131)
  - LPV/r 49%
  - NFV 48%
  - Other PI 2%

- 2 NRTIs + NNRTI (N=132)
  - EFV 61%
  - NVP 38%

- PI + 2 new NRTIs

DOMIZE + 2 NRTIs

- LPV/r 49%
- EFV 61%
- NFV 48%
- NVP 38%
- Other PI 2%
PENPACT-1/PACTG 390: Proportion with HIV-1 RNA <50 c/ml

70% still on 1st line ART at 4 years

Primary Endpoint
Change log_{10} RNA baseline to 4 yrs:
NNRTI: -3.31
PI: -3.16
p=0.26
4-year viral load suppression was not significantly different with initial regimen being NNRTI- or PI- containing HAART (same results for CD4 count, not shown)

Primary Endpoint
Change log$_{10}$ RNA baseline to 4 yrs:
- NNRTI: -3.31
- PI: -3.16
  p=0.26
P1060 #2 (not NVP exposed) vs. PENPACT-1: Conflicting Results for PI vs NNRTI-based HAART

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P1060 Cohort 2</th>
<th>PENPACT/PACTG 390</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (Range)</td>
<td>1.7y (0.5-3y)</td>
<td>6.5 y (0.1-17.8y) 26% ≤3 yo</td>
</tr>
<tr>
<td>NNRTI</td>
<td>100% NVP</td>
<td>38% NVP; 61% EFV</td>
</tr>
<tr>
<td>PI</td>
<td>100% LPVr</td>
<td>49% LPVr; 48% NFV</td>
</tr>
<tr>
<td>Previous NVP exp</td>
<td>None</td>
<td>2%</td>
</tr>
<tr>
<td>Subtype B</td>
<td>None</td>
<td>41%</td>
</tr>
</tbody>
</table>

- Preferred initial regimens for younger (≤ 3 yr old) and older (> 3 yr old) children may be different
- May get different results depending on which drug(s) used in NNRTI or PI class
- Differences by host and virus genetics?
Other Strategies?

Would NVP work better once virologic suppression is achieved on a PI regimen?
323 sdNVP-exposed children <24 months of age
Started PI-based regimen: LPV/r, 3TC, D4T. Johannesburg, SAfr

38 (11.8%) died, 40 (12.5%) lost to follow-up, 50 (15.5%) not eligible
195 randomized

Suppressed <400 cpm > 3 months by 52 weeks

99 Stay on LPV/r
96 Switch to NVP

52 weeks
52 weeks

FU 18-53 months
FU 18-53 months

Coovadia et al. JAMA 2010;304:1082-90
Proportions of Children with RNA <50, 51-1000 or >1,000 c/mL at Each Visit through 148 Weeks

LPV

NVP Switch

NVP switch arm significantly more likely to have RNA<50: 48% NVP vs 34% LPV @ 156 wks (p=0.01)
Proportions of Children with RNA <50, 51-1000 or >1,000 c/mL at Each Visit through 148 Weeks

In children who don’t suppress, LPV arm more likely to blip 50-1,000 and go down again.

While children who don’t suppress in NVP arm more likely to fail with confirmed RNA >1,000. 22% NVP vs 10% LPV (p=0.009).
Viral Failure in Switch Arm Primarily Secondary to Pre-ART Drug Resistance Frequency ≥25%


Failure NVP switch with no resistance 14% vs LPV 10% (p=0.34)

- Low frequency resistance not associated with failure
- 3.5-fold higher risk failure in children with >25% resistant virus
Other Strategies?

Induction with 4 drugs?

Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants


Early antiretroviral therapy in HIV-1-infected infants, 1996-2008: treatment response and duration of first-line regimens

The European Pregnancy and Perinatal HIV Cohort Collaboration (EPFCC) study group in EuroCoord

AIDS Issues Volume 25(18), 28 November 2011, p 2279-2287
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Publication Type: [CLINICAL/science]
DOI: 10.1097/QAD.0b013e32834d614c
ISSN: 0269-9370
Accession: 00020202-20111128-00010
Keywords: antiretroviral therapy, drug switching, Europe, infant
Early Viral Suppression with 3-Class ART in HIV-Infected Infants Exposed to SdNVP

*Prendergast A et al. AIDS 2008;22:1333-43*

- In Durban, South Africa, infants exposed to sdNVP received AZT/3TC/NFV/NVP at median age 42 days.
- NNRTI resistance mutations were found in 39%.
- Of 49 infants on ART, all had RNA <400 and 94% <50 within a year of starting ART
- No significant difference in time to undetectable in infants with and without resistance
Can Early ART Be Safely Interrupted?

Early Antiretroviral Therapy and Mortality among HIV-Infected Infants

Children with **HIV Early AntiRetroviral Therapy (CHER)** Study

HIV infection diagnosed before age 12 weeks and CD4 >25%

**Immediate N=250**

**ARM 1**
ART* Defer Until Needed
N=125

**ARM 2**
Immediate “Short” ART for 40 weeks*
(until ~1st birthday)
N=125

**ARM 3**
Immediate “Longer” ART for 96 weeks*
(until ~2nd birthday)
N=125

**ART* start (or restart) when CD4 <20%** or severe CDC Stage B or C disease occurs

*ART = AZT/3TC/LPV/r
CHER: Disease Progression (Severe B or C) or Death
ART-Deferred vs ART-40 wk vs ART-96 wk
Cotton M et al. 19th CROI, Seattle, WA, March 2012 (Abs 28LB)

Disease Progression or Death

HR (95% CI) relative to ART-Deferred

ART-40 wk: 0.5 (0.3-0.8, p=0.005)
ART-96 wk: 0.4 (0.3-0.7, p=0.0003)
• Early ART until 1\textsuperscript{st} or 2\textsuperscript{nd} birthday followed by interruption compared to deferred ART appears safe in children with regular CD4 and clinical monitoring and results in less ART exposure (potential cost-saving).

• Early ART for 2 years compared to 1 year results in longer subsequent interruption and rrend toward fewer clinical events.

• Further analysis needed to evaluate viral suppression, resistance, immune response and neuro-developmental consequences after ART restart.
You Can’t Treat Pediatric HIV Without Drugs!
Critical Need for New Drug Formulations in Children

Pediatric Antiretroviral Drugs

What is Available and Needed
What is Available for Adults

FDCs that allow one pill once daily

4-drugs in one – once daily
What is Available in Children

- d4T 5 mg/ml
- 3TC 10 mg/ml
- NVP 10 mg/ml

30 mg/20 mg/ml Kaletra® oral solution
What We Need for ARVs in Children

- Fentanyl lollipop
- FDCs that allow one pill daily
- Triaminic orange flavor chewables
- Dextromethorphan dissolvable strip
- Triaminic patch
- Sachet

We Can
Summary

- Resource-rich countries most children are receiving ART with an individualized intensive monitoring approach.
- In resource-limited countries, progression is more rapid and while children respond well to ART, therapy started at older age and low CD4, resulting in higher mortality on ART than in rich countries.
- Initiation of ART in early infancy is optimal but complicated by drug resistance from exposure to PMTCT drugs.
- While NNRTI-based ART seems effective in older children, PI-based ART appears optimal for infants.
- Use of switch or induction strategies requires further study.
- More drug choices and formulations needed in children!
Thanks For Your Attention

Special thanks to: George Siberry