10. Response to Pediatric HIV Care and Support in Thailand - Dr. Rangsima Lolekha

Response to Pediatric HIV Care and Support in Thailand

Thailand MOPH – U.S. CDC Collaboration

Prepared for the UNICEF Pediatric HIV Consultation
October 20, 2004
Rangsima Lolekha
Global AIDS Program

Objectives of this Talk

- Introduction to the Global AIDS Program, Thailand MOPH – U.S. CDC Collaboration
- Describe TUC’s pediatric programs

GAP Countries

GAP/Thailand provides funding and technical collaboration to:
- Pilot new approaches in prevention, care, and surveillance for HIV/AIDS, TB, STD
- Scale up successful pilot projects to the provincial level and nationally
- Strengthen existing programs

Develop province-based networks for prevention, care, training, and surveillance

Networks

- Bangkok Metropolitan Administration
- Chiang Rai
- Ubon Ratchathani
- Phuket

Main Areas of Work for GAP/Thailand

- Training and health communications
- Care and counseling
- Prevention and care for families
- Prevention and care for special populations
- Surveillance, monitoring, and evaluation
- Laboratory services
- Information systems
- TB prevention and control

Several GAP Strategies Focus on the Pediatric Population

1. Diagnosis of pediatric HIV disease
2. Improving care and treatment services
3. Evaluating performance

1. Diagnosis of Pediatric HIV Disease
Outcome or impact monitoring

Perinatal HIV Outcome Monitoring (PHOMS) Surveillance system started in January 2001

6 sites are currently supported: Ubolratchathanee, Chiang Rai, Petchaburi, Songkla, Prae, Nhonkai

Outcome and Diagnosis of Pediatric HIV Disease

Objectives of the Surveillance System

- To report mother-to-child HIV transmission rate
- To monitor number of HIV-infected children who receive PMTCT regimen according to Thai national PMTCT guidelines
- To facilitate referral system for HIV-infected children to receive care and treatment through NAPHA program

Bureau of Epidemiology is now receiving support to use PCR for diagnosis of pediatric HIV infection through this program

Appropriate care for mothers and children

Enhancing HIV-Related and Treatment of HIV-Infected Mothers and Their families (ECAT)

Develop model for care and counseling of HIV-infected women, their partners and children

TUC supports pilot in 4 provinces

Department of Health expanding model to other regions

2. Improving Care and Treatment Services

2.1 Expanded Care and Treatment (ECAT) for Women, Partners and Children

HIV-infected women

- Enrolled at 6wks postpartum
- Health check up, CD4 count test and access to treatment and counseling
- Treatment for patients with CD4<200 or symptomatic
- Supportive counseling
- Health promotion education
- Vitamin and iron supplement
- OI prevention and treatment
- CD4 count every 6 months
- Family planning

HIV-infected partners

- Follow-up
- Supportive counseling
- Diagnosis of HIV infection
- OI prophylaxis
- Treatment as indicated
- HIV-infected children
- Supportive care for children affected by HIV

HIV-exposed infant

- Follow-up
- Supportive counseling
- Diagnosis of HIV infection
- OI prophylaxis
- Treatment as indicated
- HIV-infected children
- Supportive care for children affected by HIV

2.2 Care and Treatment Programs for HIV-Infected Children

- Chiang Rai
- Siriraj and Queen Sirikit National Institute of Child Health
- Ubolratchathanee

Network Model for Pediatric HIV Care from the Regional Hospital to District Hospitals

Chiang Rai Regional Hospital follows 170 children on ARVs

Observational and follow-up training will be provided to 16 district hospital teams

Approximately 70 children on ARVs will begin to receive care and treatment at their district hospitals

1. Develop provincial care and treatment guidelines
2. Improve capacity of health care workers in district hospital to care for HIV-infected children on ARVs
3. Monitor performance

Key Component: Focus on Adherence

Dr Rawiwan Hansudewethakul, Chiang Rai regional hospital

Adherence strategies implemented before children starts ARVs

1. Preparation before ARVs
2. Caregivers practice preparing drugs
Adherence Emphasized at Every Clinic Visit

Monitoring for non adherence
1. Pill count  
2. Patient recitation  
3. Pill box  
4. Diary  
5. DOT

Additional Adherence Strategies

Continue group process and counseling  
Day care activities
Care team meeting  
Home visit  
ART camp

Pediatric Adherence and Disclosure

Siriraj and Queen Sirikit National Institute of Child Health

- New project
- Assess baseline data on ARV access, antiretroviral adherence and disclosure status and practice of HIV-infected children and families in QSNICH and Siriraj hospital
- Develop disclosure guidelines/protocol for HIV-infected children and their care givers
- Develop adherence tool kit (e.g. educational materials etc) for health care providers, caretakers and children

System Development for HIV/AIDS Care in Day Care Centers, Chiang Rai province

Family camp activities

3. Evaluating Performance

HIVQUAL

- New York State AIDS Institute project for HIV clinical care improvement
- Began in 1995
- Widely applied in U.S.

HIVQUAL-T

2002-2004 Pilot in 8 hospitals in Chiang Mai, Chiang Rai, Poyao
2004- Expand to more than 30 hospitals in Northern Thailand

The HIVQUAL-T Project: Goals

- Build capacity and capability to sustain quality improvement
- Develop a sustainable quality improvement program structure that supports ongoing improvement in the quality of HIV care
- Promote quality improvement activities and self-reporting of HIV performance data

Improve the quality of care for persons with HIV
Main Menu

Enter Patient Identification and Random Samples

Example HIVQUAL-T adult
6 main indicators
1. Monitoring HIV status
2. ARV treatment
3. OI prophylaxis
4. TB/HIV
5. Syphilis
6. Care for women with HIV

Report on ARV and laboratory data (example)

President’s Emergency Plan for AIDS Relief

- Announced January 28, 2003
- 15 focus countries
- Goals:
  - Prevent 7 million new HIV infections
  - Treat 2 million HIV-infected people
  - Provide care for 10 million HIV-infected people and AIDS orphans

Overall budget for global AIDS: $15 billion over 5 years
($10 billion new money, including $1 billion for Global Fund)

Summary

- TUC will continue to focus pediatric care and treatment issues
- The Global AIDS Program activities throughout the world are expanding rapidly in this area

Thank you for your attention
11. Antiretroviral Therapy in Thai Children
Dr. Kulkanya Chokephaibulkit

Antiretroviral Therapy in Thai Children
Kulkanya Chokephaibulkit, MD.
Department of Pediatrics
Faculty of Medicine Siriraj Hospital
Mahidol University

Some Important Facts about HIV-Infected Children
Paediatric Times, 21(10), 1-17.

- Infection in young infants is equivalent to primary infection
- Viral load in infants is high and slowly decline
- Disease mostly run faster than adult but 40-50% survive to 10 year without ART (but mostly symptomatic)
- It takes longer time and less likely to achieve undetectable VL by HAART even in naive children (<50% vs >70% in adults)
- Great restoration and regenerative capacity (CD4 naïve recovery) if viral replication is under control
- Surrogate markers have different predictive values compared to adults

Survival Trends for 3 Birth Cohorts in US Pediatric Spectrum of Disease Project

Problems of Antiretroviral Therapy in Children
- Unpalatable drug formulation
- Limited PK data
- Limited clinical trials
- Some children are very difficult med takers
- Long-term adherence depend upon caregiver and difficult to most families
  ⇒ ART may disrupt normal family life
- Dysfunctional family (psychosocial/economic)

Before Initiating ART
- Take time to evaluate the indications
- Take time to evaluate caregivers / family status to ensure long-term adherence
- Take time to explain to caregivers / family comprehensively, and make them participate in decision of ART
- ART is not urgent, but need long-term commitment
- Defer ART if adherence is questionable

The Goal of Treatment in Children
- To maintain good immunological status
- To prevent disease progression
- To maintain good quality of life
- To maintain good family function (Regardless of achieving undetectable VL)

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- Limited clinical trials
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  ⇒ ART may disrupt normal family life
- Dysfunctional family (psychosocial/economic)

Some Important Facts about HIV-Infected Children

- It takes longer time and less likely to achieve undetectable VL by HAART even in naive children (<50% vs >70% in adults)
- Great restoration and regenerative capacity (CD4 naïve recovery) if viral replication is under control
- Surrogate markers have different predictive values compared to adults

Before Initiating ART

Start ARV 3 x 5
Salvage ARV 3 x 6
**Early Initiation**

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Better immune reconstitution with CD4 naïve cell</td>
<td>• Long-term adherence</td>
</tr>
<tr>
<td>• Possible improved long-term outcome</td>
<td>• Resistance</td>
</tr>
<tr>
<td>• Prevent morbidity (illnesses/hospitalization)</td>
<td>• Toxicity</td>
</tr>
<tr>
<td></td>
<td>• Uncertain dosing (Limited PK data)</td>
</tr>
<tr>
<td></td>
<td>• Loss HIV specific immune response</td>
</tr>
<tr>
<td></td>
<td>• Cost</td>
</tr>
</tbody>
</table>

**CDC Staging of Pediatric HIV**

- **Clinical categories**
  - N = Asymptomatic
  - A = Mildly symptomatic
  - B = Moderately symptomatic
  - C = Severely symptomatic (= AIDS)
  - “E” = Exposed (perinatally)
- **Immunological categories**
  - 1 = Normal
  - 2 = Moderate suppression
  - 3 = Severe suppression

**Pediatric HIV Classification**

<table>
<thead>
<tr>
<th>Age-Specific CD4 Count / Percentage</th>
<th>Immunologic Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 mo x10^9/L %</td>
<td>1: No suppression</td>
</tr>
<tr>
<td>≥ 1500 ≥ 25</td>
<td>2: Moderate suppression</td>
</tr>
<tr>
<td>≥ 1000 ≥ 25</td>
<td>3: Severe suppression</td>
</tr>
<tr>
<td>≥ 500 ≥ 25</td>
<td></td>
</tr>
<tr>
<td>&lt; 750 &lt; 15</td>
<td></td>
</tr>
<tr>
<td>&lt; 500 &lt; 15</td>
<td></td>
</tr>
<tr>
<td>&lt; 200 &lt; 15</td>
<td></td>
</tr>
<tr>
<td>750-1499 15-24</td>
<td></td>
</tr>
<tr>
<td>500-999 15-24</td>
<td></td>
</tr>
<tr>
<td>200-499 15-24</td>
<td></td>
</tr>
</tbody>
</table>

**Natural Course**

- At stage “B”, 65% survive more than 5 years
- Stage “C” is a good predictor for poor outcome

**Baseline CD4/VL vs Long-Term Risk for Death (mean F/U 5.1 yr)**

- VL ≤ 100,000: 15% Death
- VL > 100,000: 1% Death

**Baseline CD4% and Long-Term Risk for Death (mean F/U 5.1 yr)**

- CD4% < 5: 97% Death
- CD4% 5-9: 76% Death
- CD4% 10-14: 43% Death
- CD4% 15-19: 31% Death
- CD4% 20-24: 10% Death

Mofenson LM, JID 1997;175:1020.
CD4 Predicts Survival in Thai Children without ART

At any time point before 5 yo
CD4 < 22% 79% (N=24)
CD4 > 22% 0   (N=11)


Earlier HAART Initiation is Better
1173 patients initiating HAART at various CD4
CD4 < 200 – Threshold May Be Too Low!

Initiation of ARV In Infants
From Various Guidelines

US
Recommend
Stage A, B, C
CD4 <25%
Consider all esp. < 6M

EU
Recommend
Stage C
CD4 <20%
Rapid CD4 fall
VL > 6 log
Consider all esp. < 6M

WHO
Recommend
Stage III
CD4 <20%
Stage II with total L <2,500
/mm3

Dynamic of HIV-RNA in Infants
Peak, range 0-10x10^6
most > 100,000
Decline 0.6 log_10/yr
Stabilize after 24 mo (vs 6 m in adults)

HIV-RNA has low predictive value for subsequent disease progression/mortality
∴ VL decision to start ARV is uncertain

Initiation of ARV In Children
From Various Guidelines

US
Recommend
Stage C
CD4 <15%
Consider
Stage A, B
CD4 15-25%
VL>5 log

EU
Recommend
Stage C
CD4 <15%
Consider
Stage B
CD4 15-20%
VL>5 log

WHO
Recommend
Stage III
CD4 <15%
Stage II with total L <1,500
/mm3

When to Start Antiretroviral Therapy to Thai Children

• What is the appropriate clinical staging to start?
  - Stage B or C (Consider A)
  - All infants <12 M

• What is the appropriate CD4 level to start?
  ≤ 20%
  (Consider 20-25%)

Recommendation of When to Start ART

USA(2003)
Recommend
>Stage <12M: A,B,C
≤12M: C
CD4 <12 M: < 25%
≥12M: < 15%
Consider:
• All infants < 12 M
  (esp. < 6M)
  >12M: Stage A, B
  CD4 ≥ 25%
  VL ≤ 5 log

Def: Stage N
CD4 > 25%
VL ≤ 5 log

EU
Recommend
• Stage “C” any age
  • CD4 <12 M: <20%
  >12 M: <15%
  • Rapid full CD4 and/or VL >10

Consider:
• All infants < 12 M
  • >12M: Stage “B”
  CD4 15-20%
  VL ≤ 5 log

Def: Stage N
• Stage N, A
  • CD4 > 20%
  • VL ≤ 5 log

Thailand
Recommend
• Stage A/B
  • CD4 ≥ 20%
  • All infants < 12 M

Consider
• Stage A
  • CD4 > 20-25%

Consider other factors

What to Start
Major Targets of Antiretroviral Agents

**Protease Inhibitors**
- SQV, RTV, IDV, NFV, AMV, LPV/r

**NRTIs**
- Zidovudine (AZT)
- Didanosine (ddi)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)

**RT Inhibitors**
- NVP, DLV, EFV

**NTRTI**
- Tenofovir

**PIs**
- Saquinavir (SQV)
- Fortovase (SGC)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Lopinavir (LPV)
- Amprenavir (APV)

**Entry Inhibitors**
- CXCR4: AMD3100, T22
- CCR5: SCH-C, D; TAK779

**Fusion gp41**
- T20

**ARV drugs**
- Tenofovir (TDF)
- T-20 (Enfuvirtide)

**Drug Regimen Consideration**
- Schedule
- Formulation (Pediatric)
- Taste
- Drug-drug Interaction
- Tolerability, S/E
- Efficacy
- Cost

**CSF Penetration of ARV Drugs**

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT  60%</td>
<td>NVP 45%</td>
<td>SQV, RTV poor</td>
</tr>
<tr>
<td>d4T  55%</td>
<td>DLV 0.4%</td>
<td>IDV, NFV mod.</td>
</tr>
<tr>
<td>ddl  20%</td>
<td>EFV 0.7%</td>
<td></td>
</tr>
<tr>
<td>ddC  20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JTC  10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC  18%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Common side effects of NRTIs**

- **Suspected mitochondrial toxicities**
  - AZT: anemia, neutropenia, nausea, hepatitis, headache, malaise, myopathy
  - JTC: peripheral neuropathy
  - d4T: peripheral neuropathy, lipodystrophy (cheek atrophy, limb atrophy, bitemporal atrophy).
  - ddl: peripheral neuropathy, pancreatitis
  - Lactic acidosis in all NRTIs (esp. d4T)

**Common side effects of NNRTIs**

- Nevirapine: rash, hepatitis
- Efavirenz: dizziness, nightmare, transient rash (18%)

**Common side effects of PIs**

- Lopinavir, Ritonavir: nausea, vomiting, circumoral paresthesia, diarrhea, bitter taste
- Indinavir: kidney stone, hyperbilirubinemia (indirect), metallic taste
- Nelfinavir: diarrhea

**Problems of HAART in Children**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Liquid available</th>
<th>Taste</th>
<th>Cost</th>
<th>Schedule</th>
<th>S/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTV</td>
<td>y</td>
<td>Bad</td>
<td>High</td>
<td>BID</td>
<td>GI</td>
</tr>
<tr>
<td>LPV-r</td>
<td>y</td>
<td>Bad</td>
<td>High</td>
<td>BID</td>
<td>GI</td>
</tr>
<tr>
<td>NFV</td>
<td>y (powder)</td>
<td>OK</td>
<td>High-Med</td>
<td>TID</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>IDV</td>
<td>N</td>
<td>OK</td>
<td>High</td>
<td>TID</td>
<td>Renal Stone</td>
</tr>
<tr>
<td>SQV</td>
<td>N</td>
<td>OK</td>
<td>OK</td>
<td>TID</td>
<td>Fever, Flare</td>
</tr>
<tr>
<td>EFV</td>
<td>N</td>
<td>OK</td>
<td>Med</td>
<td>OD</td>
<td>CNS</td>
</tr>
<tr>
<td>NVP</td>
<td>y (powder)</td>
<td>OK</td>
<td>Low</td>
<td>(GPO)</td>
<td>GI (mod)</td>
</tr>
<tr>
<td>ABC</td>
<td>y</td>
<td>OK</td>
<td>High</td>
<td>BID</td>
<td>Hypersens</td>
</tr>
<tr>
<td>ddl</td>
<td>y (powder)</td>
<td>Bad (powder)</td>
<td>OK (tab)</td>
<td>Med</td>
<td>GI (powder)</td>
</tr>
</tbody>
</table>
Nelfinavir

**Ad**
- Powder formulation available
- Effective
- Different resistance pattern
- Well studied in children

**Disad**
- Diarrhea
- Expensive (GPO may produce)

Ritonavir & Lopinavir/r

**Ad**
- Liquid formulation available
- Effective
- High resistance barrier
- Well studied in children

**Disad**
- Bad taste, GI S/E
- Expensive

Indinavir

**Ad**
- Highly Effective
- High resistance barrier

**Disad**
- No pediatric formulation
- Less studied in young children
- Nephrolithiasis
- TID dosing (unless combine with RTV)
- Expensive

Saquinavir

**Ad**
- Effective

**Disad**
- No pediatric formulation
- Less studied in children
- Poor PK
- TID dosing

Efavirenz

**Ad**
- Once daily dosing
- Highly effective
- Well tolerate

**Disad**
- No liquid formulation
- Not approve in < 3y.o.
- Low resistance barrier
- CNS S/E

Nevirapine

**Ad**
- Cheap (by GPO)
- Liquid formulation available

**Disad**
- Low resistance barrier
- S/E esp. rash in 20%
- Less effective on viral suppression

Abacavir

- **Ad**
  - Liquid formulation available
  - Convenient bid dosing with AZT/3TC
  - Well tolerated
  - In interfere with Cy P450

- **Disad**
  - Hypersensitivity reaction in 5%
  - Less effective viral suppression in pediatric trial (VL<400 in only 10%)

What Regimen to Start For Thai Children

- **Stage ≤ B and CD4 ≥ 15%**
  - Triple: 2NRTI + PI or 2 NRTI + NNRTI
  - Dual 2NRTI if complianc for HAART is questionable

- **Stage C or CD4 < 15%**
  - Insist Triple: 2NRTI + PI or 2 NRTI + NNRTI

- **Choices**
  - PI: LPV/r, NFV, IDV/r (older children)
  - NNRTI: EFV, NVP

National Guideline 2002
Recommended Drug Regimen to Start

**USA (2003)**

<table>
<thead>
<tr>
<th>Stage B and CD4 &gt; 15%</th>
<th>2 NRTIs + PI or NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage C or CD4 &lt; 15%</td>
<td>2 NRTIs + PI or NNRTI</td>
</tr>
</tbody>
</table>

**Special Circumstances**

- 2 NRTIs

**Choices**

- PI: LPV/r, NFV, IDV
- NNRTI: EFV, NVP

- First choice
  - 2 NRTIs + PI or NNRTI

- Second choice
  - 2 NRTIs + ABC

- Strongly
  - 2 NRTIs + NFV or RTV
  - 2 NRTIs + LPV/r or NVP
  - 1 NRTI + EFV

- Alternative
  - 2 NRTIs + APV
  - 2 NRTIs + NVP

- Thailand

**In 11 infected mother-child pairs received NVP-NVP**

- 1 mother had K103N
- 4 infants had Y181C, 1 had K103N

Resistant in infants occur more frequent than mothers. Probably by de novo.

M. Gordon, ThPub2004, XV IAC Bangkok July 11-16, 2004

**Follow Up**

- Clinical and adherence check up
  - Q 1-2 mo
- Lab - CBC, CD4, (VL) Q 6 M
  - SGPT at 1, 6 M if take NVP
  - U/A if take IDV

**Criteria For Failure (US)**

- **Clinical**
  - Neurodevelopmental deterioration
  - Growth failure
  - Disease stage progression
    - A → B
    - B → C
    - C → new OI

- **Immunologic**
  - Immuno stage progression
  - CD4 count decline > 30% in 6 mo
  - % CD4 decline > 5% if baseline CD4% < 15%

- Persistent increase VL
  - However, VL failure only is not an absolute indication

**What to Switch To?**

- Failed Regimens
  - 2 NRTI
  - 2 NRTI + NNRTI
  - 2 NRTI + PI
  - 3 class resistance

- Regimens to switch to
  - NNRTI + (boosted) PIs
  - (double) boosted PI + NRTI
  - Mega HAART (> 5 drugs)

- Resistant test affect the decision

Ensure that the treatment failure is not from poor adherence
Changing of Regimen
After treatment failure
• Check of adherence
• Only if adherence is good ⇒ change regimen
Dual ⇒ Triple
Triple ⇒ boosted PI
⇒ Mega HAART (>5 drugs)
Change at least 2 new drugs

WHO Guidelines

Clinical stage I
1. Asymptomatic
2. Generalized lymphadenopathy
Clinical stage II
3. Unexplained chronic diarrhoea outside the neonatal period
4. Severe persistent or recurrent candidiasis outside the neonatal period
5. Weight loss or failure to thrive
6. Persistent fever
7. Recurrent severe bacterial infections
Clinical stage III
8. AIDS-defining opportunistic infections
9. Severe failure to thrive
10. Progressive encephalopathy
11. Malignancy
12. Recurrent septicaemia or meningitis

WHO STAGING
for Resource Limited Settings

Recommendation for Initiating ART
by WHO in Resource Limited Setting 2003

<table>
<thead>
<tr>
<th>CD4, available</th>
<th>Stage III or CD4 &lt; 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18 mo PCR®</td>
<td>Stage III with CD4 &lt; 20%</td>
</tr>
<tr>
<td>No PCR</td>
<td>Stage III or CD4 &lt; 15%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4 not available</th>
<th>Stage III only</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18 mo PCR®</td>
<td>No Rx at any stage</td>
</tr>
<tr>
<td>No PCR</td>
<td>Stage III only</td>
</tr>
</tbody>
</table>

Regimen: AZTord4T + 3TC + EFV or NVP (NVP if <3 yo or <10 kg)

Stage III only
No Rx at any stage
Stage III with CD4 < 20%
Stage III or CD4 < 15%

First-Line Regimen

<table>
<thead>
<tr>
<th>First-line regimen</th>
<th>Comment</th>
</tr>
</thead>
</table>
| d4T or ZDV + 3TC + NVP or EFV | NNRTI choice: if age <3 yr or wt <10 kg, use NVP; if age >3 yr or wt >10 kg, use NVP or EFV Regardless of perinatal NVP exposure
Concurrent RIF therapy, if age > 3 yo ⇒ EFV if age < 3 yo ⇒ ZDV/3TC/ABC

Comments: What if the < 3 yo child unable to tolerate NVP
Suggestions: Use NFV, use ABC (not avail in liquid, expensive)
>> Use dual NNRTI if no other drug available in symptomatic pts.?

Second-line Treatment Regimens for Infants and Children with Treatment Failure, 2003

• All drugs should be replaced

d4T or ZDV + 3TC + NVP or EFZ
Change to
ABC + ddI + LPV/r or NVP + SQV/r or RTV

CD4 available

Stage III or CD4 < 20%
Stage III with CD4 < 20%
Stage III or CD4 < 15%
Stage III only

Comments: What if the < 3 yo child unable to tolerate NVP
Suggestions: Use NFV, use ABC (not avail in liquid, expensive)
>> Use dual NNRTI if no other drug available in symptomatic pts.?

Changing ARV

• Clinical failure
• Immunological failure: CD4 counts/percentage
  - CD4 dropped ≤ baseline
  - > 50% fall from peak
Comments: > 50% drop is OK in most cases but may be too much in those with low peak response, or too less for the growing children with physiologic drop, esp without time frame

Suggest: =>50% drop should be confined to only CD4 percentage and only among those with the peak response >20%
<Other criteria should be added to help:
>> Rapid drop e.g. >30% in 6 months
>> Limited CD4 peak (<15%) after 6 M

Suggestions: Other regimens should be included as alternatives: e.g.
ddI+LPV/r+NFV
ddI+NFV+SQV/r
ddI+NFV+RTV

Depending upon availability locally!

Comment: ABC may not be available
**TB Disease and HIV Co-infection, 2003**

<table>
<thead>
<tr>
<th>CD4 (mm3)</th>
<th>TB and ART</th>
<th>Recommend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>1. Start TB Rx 2. Start ART as soon TB Rx tolerated</td>
<td>Recommend ART</td>
</tr>
<tr>
<td>&lt; 200 - 350</td>
<td>1. Start TB Rx 2. Start ART after initiation phase</td>
<td>Consider ART</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>1. Start TB Rx</td>
<td>Defer ART</td>
</tr>
</tbody>
</table>

**Suggestions:**
- NVP should be acceptable with RIF if no alternative available
- If RIF is co-administered with NVP, increased NVP around 20% would be prudent
Problems Causing Poor Adherence
- Lack of knowledge
- Chaotic family setting
- Care-givers not available to feed/F/U.
- Side effects
- Poor formulation/bad taste/complexity/etc.
- Difficult drug taker child

Problems Facing
- Growing children → Adolescent
  - Disclosure
  - Sexuality issues
  - High risk behaviors (less in perinatal cohort)
- What’s the next regimens? Who is going to pay?

Thank you
12. Pediatric HIV Projects at HIV-NAT and the Treatment of Orphans with HIV at Baan Gerda
– Dr. Jintanat Ananworanich

Pediatric HIV Projects at HIV-NAT and The Treatment of Orphans with HIV at Baan Gerda

October 20, 2004
Jintanat Ananworanich
HIV-NAT
jintana@chula.ac.th

Research Projects
- When to start ARV?
  - An on-going pilot study of 43 children
  - Awarded 5-year U19 NIH grant to perform the full study with 300 children
- How common is resistance in children treated with dual NRTI?
- What to do when children fail GPO-vir?

Prevalence of NRTI resistance on dual NRTI for at least 6 months (N = 95)

<table>
<thead>
<tr>
<th>NRTI</th>
<th>% of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine</td>
<td>96.8%</td>
</tr>
<tr>
<td>3TC</td>
<td>31.6%</td>
</tr>
<tr>
<td>ddI</td>
<td>1.1%</td>
</tr>
<tr>
<td>abacavir</td>
<td>2.4%</td>
</tr>
<tr>
<td>lamivudine</td>
<td>60%</td>
</tr>
<tr>
<td>NAMS &lt; 4</td>
<td>40%</td>
</tr>
</tbody>
</table>

Data from 95 children

Research Projects
- What is the correct dosing of ARVs in children?
  - Dual boosted PI with LPV/r/SQV
  - NFV based on either BSA or BW
- How well does HAART work in children?
- What are the factors that affect adherence and disclosure of HIV diagnosis to children?

What to do when children fail GPO-vir?
- 20 children
  - Failed NRTI/NNRTI
  - PI-naïve
  - Sick
    - CDC B and C
    - CD4 6.5% (129)
    - VL 4.9 log
  - Started LPV/r + SQV
  - 12-hours PK
  - 2-year follow up
    - CD4, VL, TDM
- Acceptable PK
  - Identify threshold for VL suppression and toxicity
  - At 24 weeks
    - Significant wt gain
    - CD4 rise of 6% (216)
    - VL drop 2.5 log
    - VL undetectability in 80%
    - No PI resistance
    - Significant rises of cholesterol and triglyceride

Coping and Living Issues Caregivers
- Stress, ability to cope and social support
  - Coping mechanisms
- Disclosure
- Adherence
  - Barriers to adherence
  - Methods to assess adherence
  - Biological vs non-biological caregivers

Baan Gerda
A family-style Thai community for orphans with HIV infection
In Lopburi
Issues

- Medical care
  - OI prophylaxis
  - ARV
  - Laboratory monitoring
  - Resistance
  - Medical care for opportunistic infections and other illnesses
  - Immunization, dental care
- Finding foster parents and change of parents
- Death in adults and children
- School, teenagers
13. Ensuring Secure and Reliable Supply and Distribution System in Developing Countries, in the Context of HIV/AIDS and PMTCT – Helene Moller

Overview of Presentation

- Background:
  - Access to ARVs, Access to Medicines
  - Supply Division involvement from 1997 to date
- Paediatric Formulations available (in the context of WHO guidelines for prevention and treatment)
- Procurement and Supply Logistics

BACKGROUND
Overview of HIV supply history

- 1997: UNICEF lead agency in PMTCT pilot programme: Implications for Supply Division
  - Zidovudine, nevirapine
  - HIV diagnostic tests
  - Breast Milk Substitute
- 2001/2002: MOU with Columbia University, to provide supply support to 8 countries, including Thailand:
  - Capacity to provide first, second line ARVs established
- GFATM, WHO 3 x 5, other NGOs: Product portfolio expanded:
  - ARVs 42 formulations in 75 different presentations, 30-40% can be used for children
  - HIV tests, CD4, CD8, Viral load including PCR equipment

CHALLENGE
Child mortality and morbidity

2/3 of deaths among children and young adults in Africa and South East Asia are due to 7 causes:

- AIDS 14%
- Malaria 9%
- TB 2%
- Diarrhoeal diseases 11%
- Malaria 6%
- Maternal & perinatal conditions 11%
- Other causes 35%

Prompt diagnosis and access to essential drugs could save 4 million lives a year in Africa and SE Asia alone.

ACCESS to DRUGS IMPROVED
but large gaps remain ....

In 32 countries 50% of the population lacks regular access:

- Public spending is insufficient and decreasing
- Limited health insurance coverage
- New essential drugs are costly
- Supply systems are often unreliable and poorly managed

What do we mean with ‘there is no access to Paediatric ARV Formulations’?

Access to paediatric ARV formulations depends on effective supply chain management
**DEMAND:**
When to start; What to start with …. 

**WHO Guidelines exist**
- For Prevention of Mother to Child Transmission:
  - Guideline for mothers with indications for initiation of treatment who may become pregnant
  - Mothers on ART who become pregnant, and infants
  - HIV infected pregnant women with or without indications for ART, and infants etc
- For Treatment and Care: First Line
  - Preferred option for children (zidovudine [ZDV]) + 3TC + NVP
  - Guideline for children on TB treatment regiments containing rifampicin, substitute NVP for EFV
- For Treatment and Care: Second Line
  - Guidelines for children with treatment failure (ABC + ddi + PI)

**FIRST LINE / PMTCT**
ARV Formulations are available …..

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Products available</th>
<th>Price (US $ / 100ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMTCT/1st Line</td>
<td>Innovator</td>
<td>Generic</td>
</tr>
<tr>
<td>D4T</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ZDV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3TC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NVP</td>
<td>Yes</td>
<td>Yes #</td>
</tr>
<tr>
<td>EFV</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Mostly current ACCESS prices unless range indicated.
# Not necessarily WHO prequalified

**SECOND LINE / PMTCT**
ARV Formulations are available …..

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Products available</th>
<th>Price (US $ / 100ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Line</td>
<td>Innovator</td>
<td>Generic</td>
</tr>
<tr>
<td>ABC</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ddi</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NFV</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Mostly current ACCESS prices unless range indicated.
# Not necessarily WHO prequalified

**Access to paediatric ARV formulations depends on effective supply chain management**

**DEMAND:**
When to start; What to start with …. 

- For Prevention of Mother to Child Transmission:
  - Zidovudine (ZDV): 4mg/kg 2x daily, for 1 week, 4-6 weeks
  - Nevirapine (NVP): single dose 0.6mg/kg
  - Lamivudine (3TC): 2mg/kg 2x daily, for 1 week

- Variations of:
  - stavudine (d4T): 1mg/kg/dose 2x daily
  - nevirapine (NVP): 4mg/kg 2x daily, then 4mg/kg 2x daily
  - efavirenz (EFV): 5mg/kg 2x daily

**DEMAND:**
When to start; What to start with …. 

- For Treatment and Care:
  - Zidovudine (ZDV): 4mg/kg 2x daily, for 1 week, 4-6 weeks
  - Nevirapine (NVP): single dose 0.6mg/kg
  - Lamivudine (3TC): 2mg/kg 2x daily, for 1 week

- Variations of:
  - abacavir (ABC): 8mg/kg 2x daily
  - didanosine (ddI): 50mg/m²/dose 2x daily
  - lamivudine: 90-120 mg/m²/dose 2x daily, or 240mg/m²/dose once a day
  - lopinavir/ritonavir: 225mg/m² LPV, plus 57.5 mg/m² ritonavir 2x daily
  - nelfinavir (NFV): 50mg/kg 3x daily, or 75mg/kg/dose bd

**DEMAND:**
When to start; What to start with …. 

- For Treatment and Care:
  - Variations of:
    - abacavir (ABC): 8mg/kg 2x daily
    - didanosine (ddI): 50mg/m²/dose 2x daily
    - lamivudine: 90-120 mg/m²/dose 2x daily, or 240mg/m²/dose once a day
    - lopinavir/ritonavir: 225mg/m² LPV, plus 57.5 mg/m² ritonavir 2x daily
    - nelfinavir (NFV): 50mg/kg 3x daily, or 75mg/kg/dose bd

- Variations of:
  - stavudine (d4T): 1mg/kg/dose 2x daily
  - nevirapine (NVP): 4mg/kg 2x daily, then 4mg/kg 2x daily
  - efavirenz (EFV): 5mg/kg 2x daily

---

*Oct 2004 Access to Paediatric ARV formulations*
Based on these recommended doses, how many bottles of ARVs do we need to buy if 100 children will need ART in 2005?

**FIRST LINE / PMTCT**

Operational Characteristics of available ARV Formulations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Products available (volume)</th>
<th>Storage &amp; other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMTCT/ 1st Line</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Innovator</td>
<td>Generic</td>
</tr>
<tr>
<td>ZDV</td>
<td>240ml</td>
<td>100, 200ml</td>
</tr>
<tr>
<td>d4T</td>
<td>200ml</td>
<td>-</td>
</tr>
<tr>
<td>FTC</td>
<td>240ml</td>
<td>100, 240ml</td>
</tr>
<tr>
<td>NVP</td>
<td>240ml</td>
<td>20*, 25, 100ml</td>
</tr>
<tr>
<td>EFV</td>
<td>180ml</td>
<td>No</td>
</tr>
</tbody>
</table>

* Only available in donation programme, with dispensing syringe

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**SECOND LINE**

Operational Characteristics of available ARV Formulations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Products available (volume)</th>
<th>Storage &amp; other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Line</td>
<td>Innovator</td>
<td>Generic</td>
</tr>
<tr>
<td>ABC</td>
<td>240ml</td>
<td>-</td>
</tr>
<tr>
<td>ddI</td>
<td>237ml</td>
<td>-</td>
</tr>
<tr>
<td>LPV/r</td>
<td>5x60ml</td>
<td>-</td>
</tr>
<tr>
<td>NFV</td>
<td>144g pwd</td>
<td>-</td>
</tr>
</tbody>
</table>

* Only available in donation programme, with dispensing syringe

---

**ARV liquid formulations can become expensive...**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost per month</th>
<th>Cost per day</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>21.69</td>
<td>0.72</td>
<td>200.67</td>
</tr>
<tr>
<td>ddI</td>
<td>53.61</td>
<td>1.79</td>
<td>514.36</td>
</tr>
<tr>
<td>LPV/r</td>
<td>24.94</td>
<td>0.83</td>
<td>217.75</td>
</tr>
</tbody>
</table>

---

**ARV Formulations available, but ....**

- More expensive than adult formulations
- No fixed dose combinations
- Estimating needs are problematic
- Weight guided dosing will assist care-givers
- Some need cold storage, shipment
- Distributing glass bottles has it’s problems
- Taste of formulations, bulk of supplies

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Access to paediatric ARV formulations depends on effective supply chain management

- **Monitoring**
  - We need partners to complete the cycle
- **Effective Use**
- **Product Selection**
- **Supplier Agreements**
- **Quality Assurance**
- **Forecasting**
- **Receipt, Storage, Distribution**
- **Product Procurement**
- **Pricing, Selection**
- **Effective Use**
14. Ensuring comprehensive care of children? - Kathleen Casey

Ensuring comprehensive care of children?
The unmet psychological needs of infected and affected children and their carers.
Kathleen Casey
Senior Technical Officer, Testing & Counseling

Balancing physical and psychological support
- Common psychological and behavioral presentations in pediatric infection
- Common issues confronting counsellors
- Children and treatment adherence
- Gaps in services in Thailand (case study)
- Implementation strategies: supporting comprehensive care

Psychological impact-behavioral
- Psychopathological abnormalities: 63% of cases
  - Hyperactivity
  - Delayed adaptive behavioural skills
  - Oppositional disorders
  - Avoidant disorders
  - Depression/withdrawal/anxiety
  - Autistic like behaviours
  - Substance dependence

Psychological and developmental impact
- Communication deficits in 80% cases
  - Expressive language delays
  - Receptive language delays
  - Impaired vocal capacity, oral-motor problems (articulation)

Infected children present special communication challenges to the counsellor and parents!

Key counseling tasks-children
- Supporting children - post disclosure
- Help the child work through feelings and beliefs about the illness
- Help children express feelings of grief and loss.
- Address issues around medical visits and hospitalisation (preparation strategies)
- Address issues around death and dying

Key counseling tasks -parents & carers
- Assisting parents & carers manage challenging behavioral disturbances
- Informed decision making – disclosure
- Family counseling post disclosure
- Managing treatment adherence challenges
**Key counseling tasks - parents & carers**

- Should the child be told (pros & cons)?
- When and by whom?
- How much information should be given?
- What if questions about death arise?
- What about the child’s capacity to manage the information and manage the “secret”?  
- Should the school be told?

**Our counsellors are unprepared!**

- Most counselor training in the region is VCT
- Where counsellors are trained to deliver ongoing counseling they are prepared for adult clients
- There is a widespread failure to address the psychological needs of both children & adults who are caring for them

**Adherence counseling tasks**

- Improving treatment literacy – carers
- Exploring parent & caregiver attitudes & beliefs related to treatment
- Problem solving adherence constraints
  - Planning schedules
  - Memory cues
  - Problem solving e.g. gag reflex


**Burden of care in Thailand**

- "Global ORPHANS Study for Thailand" I estimated that in 1998 there were 34,372 children under the age of 15 who had lost their mothers to AIDS, and 420,731 whose mothers were HIV positive but asymptomatic.
- A second data collection in the year 2000 counted 10,270 children, 35% of which are double orphans
- There are limited specialist services offered by NGOs.
- Orphan homes for HIV infected children provide psychosocial care and encourage volunteer support.

**Study size**

- 16 regional hospitals
- 50 general
- 451 community hospitals health centers
- 82 private hospitals
- 90 NGOs
- PLWHA 192

**Testing of children**

- Lack of clarity relating to policies related to testing of minors without parental consent
  - 43.8% of regional hospitals
  - 42% of general
  - 40% of community hospitals
  - 19% of private hospitals
  - Unattached minors and testing - No policy.

**Counselling of children**

- Institutions reporting staff trained to counsel children
  - 37.5% (n=16) regional hospitals
  - 38.0% (n=50) general hospitals
  - 37.9% (n=451) community
  - 22.3% (n=350) health center
  - 13.8% (n=80) private
  - 41.4% (n=185) NGOs
  - 51.8% (n=85) PLWHA
The burden of care in Thailand

- In the year 2003 - 4% of AIDS cases are children and 4,000 children are infected every year.
- >1/7th of all new infections are children

Strategies

- Clarify policies related to testing of minors, unattached minors and orphans
- Scale up “care counselor” training
- Develop curricula for counseling of children and parents
- Develop child support volunteer support & supervision networks programs
- Peer support facilitator curriculum to include child support and care issues
- Teacher HIV awareness programs
15. Challenges in paediatric HIV care, support and treatment – Arjan de Wagt

Technical issues - Diagnosis
- Diagnosis before 18 months is difficult without VL
- CD4 and VL testing expensive, often not available, decision on when to treat therefore difficult
- If VL available how to set up system for test analysis
- Counseling of families is complex
- How to test more women to identify exposed children: routine, pre-pregnancy etc?
- Guidance of disclosure of HIV status to children themselves, relatives, teachers

Technical issues - Management
- High levels of PEM among infected children, management is complex
- Guidelines on micronutrient supplementation among HIV infected children
- Pediatric care and treatment as part of a family response
- Support on how to care for infected children to care providers, e.g. grandparents
- Psychosocial impact and support to families and children is too limited

Programme issues – Prevention
- How to ensure that resources for treatment are not being taken from prevention
- How to use 3by5 as an opportunity of primary prevention
- How to accelerate PMTCT as part of 3by5
- Improve PMTCT follow up incl. PCP prophylaxis

Programme issues – Program management
- Regional coordination
- Programme indicators, benchmarks and targets are weak

Programme issues – Access
- Psychosocial issues, family support, access to education (discrimination)
- Post exposure prophylaxis for sexual assaulted children
- How to provide orphans with a home

Programme issues – Staff
- Need to strengthen knowledge and skills on HIV care/treatment
- Attitudes / discrimination by health workers
- Lack of adequately trained physicians and counselors
- What additional support (technical, psychosocial etc.) do health care workers dealing with paediatric HIV cases need. E.g. how to prevent burn out?

Programme issues – Adolescents
- Access (incl. legal) to services like testing and treatment
- HIV infected children growing up: sexual health, behavior and guidance