With better knowledge and availability of antiretroviral treatments, the Thai National HIV Guidelines Working Group has issued treatment guidelines for children in Thailand in March 2010. The most important aspects of these new guidelines are detailed below.

ART should be initiated in infants less than 12 months of age at any CD4 level regardless of symptoms and in all children at CDC clinical stage B and C or WHO clinical stages 3 and 4. For children with no or mild symptoms consider CD4-guided thresholds of CD4 ≤ 25% (children aged one to five years) or CD4 ≤ 350 cells/mm$^3$ (children 5 years or older). The preferred first-line regimen in children aged < 3 years is AZT+3TC+NVP. For children ≥ 3 years of age the preferred regimen is AZT+3TC+EFV. If an infant has previously been exposed to NVP perinatally, use AZT+3TC+LPV/r as empirical first regimen. In adolescents, consider TDF+3TC+EFV.

The preferred ARV treatment in children who failed first line regimens of 2NRTI+NNRTI (Salvage treatment) comprises 2NRTI (guided by genotype) +LPV/r, and an alternative regimen is 2NRTI (guided by genotype) +ATV/r (use in cases with dyslipidemia who are six years or older). In cases with extensive NRTI resistance with no effective NRTI option available, double boosted PI with LPV/r+SQV or LPV/r+IDV can be considered. Consultation with an expert is recommended.

Laboratory monitoring is recommended for CD4 and every six months. Viral load at least at 6 and 12 months after initiation or change of regimen, then yearly thereafter. More frequent viral load monitoring is advised for cases with unsuccessful virologic response, infants, children with imperfect adherence, or those using of third line regimens. Toxicity monitoring depends on the drug received, at least every six months, and more often as clinically indicated. These include, but are not limited to, complete blood count, renal function tests, liver function tests, urinanalysis, and lipid profiles. Therapeutic drug monitoring is recommended in cases that have ARV-related toxicity, receiving non-standard dosing or regimens, using double boosted PI, and in those with renal or hepatic impairment.

Keywords: HIV, pediatrics, Thai guidelines
to antiretroviral therapy (ART) and monitoring for more than 10 years. The National Guidelines have been updated as knowledge and availability of treatment and care have improved. The Thai National HIV Guidelines Working Group is composed of pediatricians, academicians, researchers, and nongovernment organizations (NGOs) with expertise in HIV and AIDS, and is supported by the Bureau of AIDS, TB, and STD, and Ministry of Public Health (MOPH). Representatives from the NHSO and the MOPH have joined the Working Group. The guidelines were issued in March 2010.

The treatment guidelines presented here aim to provide a summary of recommendations for treating HIV-infected children and adolescents in Thailand. The Working Group reviewed and made recommendations based upon data from Thai children and from recently published WHO [1], PENTA [2] and US guidelines [3].

**Current situation of Pediatric HIV/AIDS in Thailand**

The major route of HIV infection in Thai children is mother to child transmission. The cumulative numbers of perinatally HIV-infected Thai children are estimated to be 15,000 to 20,000, of which more than 8,000 children have received antiretroviral therapy through the National program. HIV prevalence among pregnant women at antenatal care clinics has been reduced from about 2% in 1999 to 0.74% in 2009. There are about 6,000 infants born to HIV-positive mothers each year, leading to 200-400 newly HIV-infected infants annually.

**Diagnosis of HIV in children younger than 18 months of age**

HIV infection should be diagnosed early in life to provide appropriate treatment and care. The diagnosis can be made by positive HIV RNA or DNA polymerase chain reaction (PCR) as early as one month of age.

HIV infection can be excluded if a child had either 1) two negative HIV PCR tests, of which the first test is performed at > one month of age and the second test is performed at > four months of age; 2) two negative HIV antibody test after six months of age; or 3) one negative PCR at > four months of age and one negative HIV antibody test after six months of age plus no clinical signs or symptoms compatible with HIV infection [4].

In the clinical care for infants born from HIV-positive mother in Thailand, it is recommended to have at least one HIV antibody test preferable at 18 months to definitely exclude HIV infection. At 12 months, the majority of infants who are not infected have negative HIV antibody tests. However, 5-10% of HIV uninfected infants may have persistent maternal antibodies. The infants with positive HIV antibody tests at 12 months should have the test repeated at 18 months. It is noted that combination serologic tests (antigen-antibody combined tests) may be able to detect very low levels of HIV antibodies and report positive results in some HIV-uninfected children at 18 months of age. Therefore, it is recommended not to use the combination test for diagnosis of perinatal infection.

**Baseline evaluations before the initiation of ART**

A detailed history of any possible previous exposure to ART in a child should be documented. Children should be examined and evaluated for opportunistic infections (OI), especially tuberculosis. Cotrimoxazole (TMP/SMX), is recommended in all HIV-exposed infants until HIV infection is excluded and in all HIV-infected infants regardless of CD4 levels. TMP/SMX is also recommended in HIV-infected children younger than five years of age who have CD4 percentage lower than 15%, and in older than five years who have CD4 count less than 200 cells/mm³. The common side effects of TMP/SMX are rash or cytopenia, which might be confused with ART toxicity if started at the same time. Baseline pre-ART evaluations should include CD4 cell count and percentage, hematology, biochemistry, (e.g. AST, ALT), and profile testing for other blood-borne infections, especially hepatitis B. Moreover, the evaluation of psychosocial aspects including whether the child has been informed about their HIV status and their readiness to take antiretroviral therapy are crucial. Clinical monitoring and measurements of CD4 level should be repeated every six months in well children who do not need to start ART, and more frequently in infants and in older children approaching treatment thresholds.

**When to start antiretroviral therapy (ART)**

Because disease progression among HIV-infected infants is unpredictable and has high morbidity and mortality, ART should be started urgently in all infants, as soon as the diagnosis of infection is confirmed.
irrespective of the clinical or immunological stage [5]. ART should be initiated in all children with symptomatic diseases (CDC clinical stage B or C or WHO stage 3 or 4) who are > one year of age. For children who have minor symptoms, ART initiation should be based on age-specific CD4 thresholds (Table 1). Baseline viral load is not recommended as criteria to initiate ART. Importantly, issues likely to affect adherence should always be considered and addressed before starting therapy.

**What antiretroviral regimens to start with**

The current preferred first-line ART regimen for previously untreated children comprises two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI). The preferred NRTI combination is zidovudine (ZDV) and lamivudine (3TC) and the alternative combination is stavudine (d4T) and lamivudine (3TC). AZT is preferred because it has less long-term toxicities, such as lipodystrophy, compared to stavudine. However, children with low baseline hemoglobin <8 g/dL should start with d4T and switch to AZT after 6-12 months of treatment. In adolescents who weigh > 40 kg or with Tanner stage IV, tenofovir (TDF) and 3TC is a preferred because the dosing is once daily, which may improve adherence (Table 2).

The preferred NNRTI is nevirapine (NVP) for children age < 3 years, and efavirenz (EFV) for older children. NVP has benefits over EFV in terms of formulations available, i.e. syrup, tablet, and fixed dose combination GPOvir (d4T/3TC/NVP) or GPOvir-Z (AZT/3TC/NVP). However, NVP has more side effects such as rash and hepatotoxicity [6]. Some reports showed better virological efficacy of EFV over NVP [7].

Infants who are exposed to NVP as part of prevention of mother to child transmission have 20-57% risk of harboring NVP resistance [8, 9]. Therefore, the first line regimen should be two NRTIs and boosted lopinavir (LPV/r), the only protease inhibitor (PI) available for infants [10]. Genotypic testing for drug resistance prior to initiating ARV is recommended. After the first six months of treatment with a PI-based regimen, if the patient has viral suppression and the genotypic testing of the sample prior to ARV initiation has no evidence of NVP resistance, the regimen can be switched to NNRTI-based regimen.

For children who had recent opportunistic infections, there are some special considerations such as timing of the start of antiretroviral drugs, drug interactions, and the risk of developing immune reconstitution inflammatory syndrome (IRIS). In general, antiretroviral therapy should be initiated within

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### Table 1. Criteria for initiation of antiretroviral therapy among HIV-infected children.

<table>
<thead>
<tr>
<th>Age &lt;1 year</th>
<th>Age 1-5 years</th>
<th>Age &gt; 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical staging criteria</td>
<td>CDC category B, C or WHO stage 3, 4</td>
<td>CDC category B, C or WHO stage 3, 4</td>
</tr>
<tr>
<td>Immunological criteria</td>
<td>%CD4 &lt;25</td>
<td>CD4 &lt;350 cells/mm³</td>
</tr>
</tbody>
</table>

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### Table 2. The recommended first line regimen in Thai children.

<table>
<thead>
<tr>
<th>Age &lt;3 years</th>
<th>Age &gt;3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred regimens</td>
<td>AZT+3TC+NVP</td>
</tr>
<tr>
<td>Preferred regimens for adolescents (weight &gt;40 kg or Tanner stage IV)</td>
<td>AZT+3TC+EFV</td>
</tr>
<tr>
<td>Alternative regimens</td>
<td>d4T+3TC+NVP</td>
</tr>
</tbody>
</table>

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two to eight weeks after starting treatment for OI. Among children who have a low baseline CD4 level, the risk of developing IRIS is about 20% [11]. However, this should not be a reason to delay initiation of antiretroviral treatment when indicated. The most problematic drug interactions with ART are with rifampicin in children with tuberculosis (TB) co-infections. Rifampicin reduces EFV levels by 25%, however data from Thai HIV-infected adult patients showed that the standard dose of EFV provide adequate plasma levels [12]. Recent data also showed that despite drug interactions between rifampicin and NVP, the standard dose of NVP could be used [13]. However, rifampicin significantly reduces PI levels and these drugs must not be used together. In case patients need PI, the treatment option depends on immune status. If a patient has a low CD4 level and needs a PI-containing salvage regimen, the antiretroviral drug has a higher priority. Therefore, one should avoid rifampicin and modify anti-tuberculous drugs using quinolones or aminoglycosides. If a patient has a high CD4 level, PI-based antiretroviral treatment initiation should be postponed until the completion of a two-month intensive anti-tuberculous treatment with rifampicin. The maintenance phase without rifampicin should be used with PI containing regimens.

Monitoring while on ART

The first six months after initiation of treatment is a vulnerable period due to potential drug toxicity, IRIS, or poor adherence. It is crucial to monitor for clinical response, which would include confirming general well being, changes in body weight, and problems related to ART or IRIS. Follow-up visits should be scheduled every month until stable, then extended to every two to three months. It is important to specifically check for adherence to therapy at every clinic visit.

The CD4 cell count should be monitored every six months. Plasma HIV viral load should be monitored at least at 6 months and 12 months after treatment initiation and yearly thereafter. In cases where the virologic response is not as successful as expected, more frequent virologic monitoring is required. More frequent clinical and laboratory monitoring are required in infants, as well as in cases of imperfect adherence, especially at the start or change of therapy.

Serum testing for drug toxicity should be done routinely every six months. It should include complete blood count, liver function tests, renal function tests, and lipid profile. Some antiretroviral drugs have specific drug toxicities which require monitoring, such as NVP (alanine aminotransferase, ALT, at two to four weeks after initiation), AZT (complete blood count after three months after initiation), indinavir (IDV), and TDF (urinalysis and creatinine every three months).

**Diagnosis of treatment failure**

Treatment failure can be detected through virologic, immunologic, or clinical criteria [3]. Virologic failure is usually detected earlier than immunologic failure. However, the lapsed time differs in each individual ranging from few months to few years. Clinical failure usually occurs after a period of immunologic failure. Immunologic failure or clinical failure must concur with virologic failure in order to indicate treatment failure.

1) Clinical failure is defined as one of the following:
- Abnormal or regression of developmental milestones.
- Poor growth without other causes.
- Appearance of new, or progression of, HIV-related conditions or opportunistic infections. Due to the high prevalence of tuberculosis in Thailand, tuberculosis of the lung or lymph node does not necessarily indicate clinical failure, especially if there is an otherwise good response to treatment.

2) Immunologic failure is determined based on at least two measurements of CD4, at least one week apart. Some acute conditions or infections may cause a transient drop in CD4. Immunologic failure is defined as one of the following:
- Inadequate immunologic response to treatment:
  - For children younger than five years with baseline CD4<15%, an increase of CD4 percentage of less than five after one year of treatment
  - For children five years or older with baseline CD4 <200 cells/mm³, an increase of CD4 of less than 50 cells/mm³ after one year of treatment.
- Decrease of CD4 levels:
  - For those with baseline CD4 percentage <15%, a sustained decrease of at least 5% after treatment initiation, i.e., decrease from 15% to 10%.
  - Any decrease in CD4 percentage or count of more than 30% over a six-month period.

3) Virologic failure is defined as one of the following:
- Inadequate virologic response to treatment
  - In infants younger than 12 months of age, the HIV RNA level (viral load) is >50 copies/mL after one year of treatment.
• In children older than one year of age, the viral load is >50 copies/mL after six months of treatment

• Increase of viral load to >1,000 copies/mL in those who previously had good viral suppression. The viral load of 50-1,000 copies/mL may be a transient viral blip from imperfect adherence or other temporary effects. In such cases, the viral load measurement should be repeated at one to three months after adherence counseling.

Antiretroviral treatment in children with treatment failure

Most treatment failures are caused by poor adherence. Therefore, adherence must be evaluated and counseling must be provided to patients and their families. Treatment failure may be from inappropriate treatment regimens, e.g., dual NRTI that was commonly used when antiretroviral drugs were not widely available. Some children may acquire resistant virus from the beginning, such as infants exposed to perinatal single dose NVP. These children are at risk for treatment failure with NNRTI regimens. A baseline genotypic assay is a useful guide to treatment in such cases.

The new treatment regimen should be guided by genotypic assay results. In Thailand, it is recommended to perform a genotypic assay when the viral load is >2,000 copies/mL and the child has been receiving treatment or discontinued treatment no longer than one month.

It is important that the new treatment or salvage regimen be started soon after virologic failure to prevent accumulation of resistance mutations. Prolonged use of failing regimens causes selective pressures that result in more resistance mutations and may jeopardize future options. For example, prolonged use of NRTI in patients with thymidine analogue mutations (TAMs) will cause accumulation of more TAMs; and prolonged use of NNRTI in patients who have NNRTI resistance mutations may cause further resistance to etravirine, (a new NNRTI drug) [14]. However, the new treatment regimen should not be started until good adherence is ensured.

Choosing the new regimen in children who fail 2NRTI+1NNRTI regimens (Fig. 1)

• Preferred regimen: 2NRTI plus LPV/r[15] (selection of NRTI guided by genotype)

• Alternative regimens: 2NRTI plus boosted atazanavir (ATV/r). Selection of NRTI is guided by genotype (see below). ATV is approved in children six years or older. This regimen is most appropriate in those with dyslipidemia [16].

Double boosted PI with boosted lopinavir and saquinavir (LPV/r+SQV) [17] or boosted lopinavir and indinavir (LPV/r+IDV) [18], with or without NRTI. These regimens are considered only in children who have no effective NRTI available, i.e., with extensive NRTI resistance mutations and cannot use TDF or ABC. Initiating these regimens requires expert consultation. Children receiving double boosted PI must be closely monitored for toxicities, especially metabolic and renal. Children who receive these regimens and had complete viral suppression for more than one year should be considered to switch to a regimen comprising a single boosted PI plus NRTI(s).

Selection of NRTI for the new regimen guided by genotypic assay

The genotypic resistance testing reports include the gene mutations and the interpretation of ARV drug susceptibility. The principles of interpreting genotypic assay in order to select NRTI in the new regimen are as follows [19]:

• Resistance mutations in reverse transcriptase (RT) genes that confer resistance to most NRTIs, except 3TC and FTC, are called TAMs. When number of TAMs is >4, most of the NRTIs will not be effective except that TDF, ABC, and ddI may still be useful if without K65R.

• The other multi-NRTI mutations are T69i and Q151M. They confer resistance to all NRTIs. The exception is that virus with Q151M are still susceptible to TDF.

• The K65R mutation confers resistance to TDF, ABC, and ddI, but is susceptible to AZT.

• The L74V and K65R mutations confer resistance to ddI and ABC.

• The M184V mutation confers resistance to 3TC and FTC. However, the virus with M184V is a less fit virus, and therefore keeping the patient on 3TC or FTC to sustain this mutation may have clinical benefits. The M184 mutation also causes hyper-susceptibility to AZT or TDF.

The guide to selecting NRTIs in the new regimen in combination with LPV/r or ATV/r is as follows (Fig. 1):

a) When there are <4 TAMs and without Q151M or T69i.
The 2NRTI selected for new regimens after failing AZT/d4T+3TC may be ddI+3TC, ddI+AZT, ABC+3TC or ABC+ddI.

b) When there are >4 TAMs or with Q151M or T69i, but without K65R.

The new regimen may be TDF+3TC or TDF+ABC or TDF+AZT. Some experts recommend TDF+AZT+3TC because AZT may prevent development of K65R, and 3TC may decrease viral fitness. TDF should only be used for salvage treatment in children >30 kg or with Tanner stage IV. TDF should not be used with ddI.

c) When there are >4 TAMs and with K65R but unable to use TDF (e.g. too young)

There will be no effective NRTI available. In this case, the regimens with double boosted PI should be considered. 3TC may be added to reduce viral fitness. However, some experts may consider the 2NRTIs as in a) plus single boosted PI (LPV/r, ATV/r) with closely viral load monitoring.
Salvage regimens in children who are infected with three classes of resistance mutations [20]

Children experiencing extensive antiretroviral therapy and have resistance mutations to NRTIs, NNRTIs, and PIs, have been identified more often in older children. The principle in designing the salvage regimen is to use at least two active drugs plus recycle NRTIs because NRTIs may still be useful even with resistance mutations. The aim is to achieve complete viral suppression. New drugs, such as darunavir, maraviroc, etravirine, or raltegravir, may be needed in compassionate programs or study trials. Expert consultation is recommended.

In case new effective regimens are not available in the near future, and the patient has a high CD4 level (e.g. over than 200 cells/mm³), 3TC monotherapy may be considered to slow the disease progression, yet not select further resistance mutations that may jeopardize future options. The salvage regimen should be initiated as soon as possible.

Salvage regimens in children who fail dual NRTI regimens

Dual NRTI regimens (AZT or d4T + 3TC or ddI) were often used in the past when ART availability was limited. Children receiving dual NRTI regimens will have virologic failures at some points. However, there are many children who have been receiving dual NRTIs with stable CD4 and clinical status. These children should be tested for viral load and viral resistance. Whenever possible, the treatment regimen should be switched to highly active antiretroviral therapy (HAART) to prevent emerging of resistance even though their viral load is suppressed. For children who had incomplete viral suppression, the genotypic assay should be used to guide the design of the new regimen. The following points are guides to formulate the new regimen:

- If the RT mutations are not extensive, TAMs <4 (please see above for NRTI selection), the preferred new regimen is 2NRTIs+LPV/r.
- If there are >4 TAMs especially with K65R or unable to use TDF, the preferred regimen is NNRTI (prefer EFV) +LPV/r with or without NRTI.

Monitoring in children receiving salvage regimens

Monitoring for efficacy and safety of treatment

During the early phases of the new treatment regimen, patients should be closely monitored for adherence and potential side effects. The CD4 and viral load should be monitored at least at six months and 12 months after switching to the new regimens. The salvage regimens containing PI that may cause metabolic side effects should be monitored for fasting glucose and lipid levels. Children who receive TDF and IDV should be monitored for renal function (electrolytes, BUN, creatinine, and urinalysis). The tests for safety monitoring should be performed every three to six months or as clinically indicated.

Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring is useful for patients who receive IDV, double boosted PI regimens, or drugs that may have interact with each other. Moreover, patients using drugs at dosages different from what is recommended, and patients with underlying kidney or liver diseases should receive TDM. The drug level monitored is the trough level after at least two weeks of treatment. However, TDM in the patients receiving IDV should also include the peak level at two to four hours after drug administration, which correlates with kidney toxicity. Expert consultation is required for drug or dose adjustments.

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References


