The effectiveness of highly active antiretroviral therapy among HIV-infected children in Asian countries

Torsak Bunupuradha, Linda Aurpibul, Jintanat Ananworanich, Thanyawee Puthanakit

aThe HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT)-Thai Red Cross Aids Research Center (TRCARC), Bangkok 10330, bResearch Institute for Health Sciences, Chiang Mai University, Chiangmai 50200, cSoutheast Asia Research Collaboration with Hawaii (SEARCH), Bangkok 10330, Thailand

Background: Worldwide, there are an estimated 2.1 million children under 15 years of age living with HIV infection. In the past five years, there has been significant progress in providing antiretroviral therapy (ART) to children in resource-limited countries. According to the World Health Organization, an estimated 200,000 children were receiving ART by the end of 2007.

Objective: To conduct a general review of pediatric ART effectiveness in Asian countries.

Methods: Published articles in PubMed and abstracts from the international HIV conferences were searched for articles related to pediatric ART in Asian countries from 1999 up to 2008.

Results: Available reports consistently demonstrated beneficial outcomes of first-line antiretroviral therapy, including significant reductions in mortality and hospitalization rates, and good immunological and virological outcomes. However, there were limited data on the availability of second-line ART and the management of children who failed first-line regimens. There was also a need for improved access to early diagnostic testing and treatment in infancy, and more data on ART selection for children exposed to antiretrovirals for prevention of mother to child transmission.

Conclusion: The highly active antiretroviral therapy is effective among HIV-infected children in Asia. Strategies for improved diagnosis and implementation of the life-saving antiretroviral programs including second-line ART, throughout Asia is encouraged.

Keywords: Antiretroviral therapy, Asia, human immunodeficiency virus, pediatric.
from the national AIDS program. In Vietnam, the national program has set a target of providing treatment to 70% of adults and 100% of children who are eligible by the year of 2010. With support from PEPFAR and GFATM, the number of Vietnamese children receiving treatment has significantly increased from 42 children in year 2005 to 789 children by the end of 2007. In China, the Ministry of Health launched a pilot project of ART in 2005 and as of October 2007, 805 children had received ART.

In general, after HIV-infection, children should start ART sooner than adults because HIV disease progression is more rapid and laboratory monitoring parameters are less predictive of risk of disease progression. Current treatment guidelines are based on the progressive risk of developing AIDS and death by age and CD4 level. A comparison of the different criteria to initiate treatment of the Pediatric European Network for Treatment of AIDS (PENTA) [4], the World Health Organization (WHO) [5] and the United States (US) Department of Health and Human Services [6] is shown in Table 1. For infants younger than one year of age, all treatment guidelines recommend initiating treatment as soon as possible after diagnosis. For older children, the decision to start ART is based on clinical symptoms and CD4 level. For children aged between one to three years, consider treatment when CD4 <25%. For children between 3-5 years of age, there is some discrepancy among threshold to initiate treatment, varies from CD4 20-25%. For children older than 5 years of age, the CD4 cell count is used rather than CD4%. In the US and PENTA guidelines, CD4 <350 cells/mm³ is used as a threshold to start treatment, while in the WHO guidelines, CD4 <200 cells/mm³ is used. In the PENTA and US guidelines, plasma HIV RNA level >100,000 copies/mL is an added marker that predicts a more rapid disease progression and is used as one of the criteria to consider initiating treatment.

The current preferred first-line ART regimens include two nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r). Like in other resource-limited settings, the most commonly used pediatric first-line regimen includes an NNRTI and not a PI due to its lower cost. This regimen has been prioritized by the WHO and adopted by national programs throughout Asia. However, second-line regimens are less accessible owing to limited pediatric formulations and availability of safe and effective drugs for children. We conducted a review of available literature on pediatric ART outcomes in Asia to review ART efficacy of first and second line ART.

<table>
<thead>
<tr>
<th>Table 1. Comparison of current PENTA, WHO and US treatment thresholds.</th>
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<tr>
<td>------------------</td>
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<tr>
<td>0-11 months</td>
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<tr>
<td>12-35 months</td>
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<tr>
<td>Immunological</td>
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<tr>
<td>CD4% / count</td>
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<tr>
<td>Virological</td>
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<tr>
<td>36-59 months</td>
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<tr>
<td>Immunological</td>
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<td>Virological</td>
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<tr>
<td>&gt;5 years</td>
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<td>Immunological</td>
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<td>Virological</td>
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Methods
Published articles indexed in PubMed and abstracts from the international HIV conferences (International AIDS Society, Conference on Retroviruses and Opportunistic Infections, and Pharmacology of HIV Therapy) were searched for articles relating to pediatric ART in Asian countries from 1999 up to 2008. The terms used to search were HIV-infected children, highly active antiretroviral therapy (HAART), antiretroviral treatment, second-line, protease inhibitor.

Results
Search results
Twelve cohort studies were identified describing first-line ART from four countries: China, India, Cambodia, and Thailand (Table 2). Two multicenter studies involving data from several countries (Cambodia, Laos, Myanmar, China) also described experiences with first-line regimens [7-18]. Data on second-line ART was limited to three published studies and presentations all being from Thailand [19-23].

Effectiveness of first-line ART in children
Studies were conducted in various health care settings, including a rural regional clinic in China, district hospitals in Cambodia, tertiary care hospitals in India, and general and university hospitals in Thailand. Baseline characteristics, antiretroviral (ARV) regimens used, and treatment outcomes are shown in Table 2.

Clinical outcomes
Mortality rates significantly decreased after initiation of ART. Overall mortality rates after ART ranged from 3-6%, with most deaths occurring within the first six months. Reported lost-to-follow-up rates were less than 2% except in the large multicenter studies that combined sites from other regions where the rate was around 8% [10, 11].

After treatment initiation, there was a decrease in the need for hospital admissions. Data from a Thai cohort reported that the hospitalization rate decreased with time after initiation of HAART from 30.7% in the first 24 weeks (mostly as a result of pneumonia and other bacterial infection in 61.7%, and immune reconstitution syndrome in 23.4%) to 2% at 120 weeks of treatment and thereafter [24]. The study from North India [16] also reported a decrease in mean number of unscheduled out-patient visits as well as episodes requiring hospital admissions. The clinical symptoms developed during the first few months after initiation of ART, could be opportunistic infections or immune reconstitution inflammatory syndrome (IRIS). One study in Thailand showed the incidence of IRIS of 19% at a median onset of 4 weeks (range 2-31) after HAART initiation [25].

Antiretroviral drugs-related toxicity
The reported adverse effects of ART included acute NNRTI-related toxicity. In those receiving nevirapine (NVP)-based regimen, rash was reported in 2-25%. In a Thai cohort 23% had a grade 2 rash and 8% had a severe drug reaction which was accompanied by mucosal involvement, fever, neutropenia, or elevated liver enzyme [13]. In another Thai cohort, 10% of cases on NVP developed rash with almost all also having fever, hepatitis, or mucous membrane involvement in which switching to efavirenz (EFV) was warranted [7]. No rash progressed to Stevens-Johnson syndrome. Treatment of skin rash, apart from drug interruption, included antihistamine and prednisolone. In a few cases, re-challenging with the same drug was done successfully.

EFV-related toxicity, mostly CNS disturbance specified as headache, dizziness, vomiting, somnolence, sleep problems, and vivid dreams/nightmares occurred in 5-26% of Thai children; all documented in the first two weeks. Side effects spontaneously subsided and EFV could be continued in most patients [13]. Hepatitis diagnosed by increased liver enzymes was reported in 4-15% of children on NNRTI-based ART in Thailand. Most were asymptomatic while some had concomitant skin rash [13]. Gastritis, hepatitis, and pancreatitis were also reported from Indian cohorts [8, 16]. Data on incidence of zidovudine (ZDV)-related anemia is limited as the majority of studies used stavudine (d4T). In the 3 studies that used ZDV, anemia was diagnosed in 4.5% of South Indian children [8] while no anemia greater than grade 2 occurred in a Thai cohort (67% received ZDV) [26]. In the Chinese study, there were no reports of anemia or any other side effects from ART which led to changing drug regimens [17].

It was evidenced that most side effects were considered minor, and did not require regimen modification. Severe adverse effects including unspecified toxicity which led to the necessity for drug switching were seen in 2-9% according to the MSF, Thai, and Cambodian studies [10-14]. The
Table 2. (continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Location, time frame</th>
<th>Clinical response(^a)</th>
<th>Immunologic response</th>
<th>Virologic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapphra et al.[7]</td>
<td>Thailand 1996-2006</td>
<td>Improve WAZ and HAZ</td>
<td>Median CD4 gain 12-15% (500-600) at 12 months</td>
<td>NA</td>
</tr>
<tr>
<td>Kumarasamy et al.[8]</td>
<td>South India 1996-2008</td>
<td>Improve mean WHZ at 1 year</td>
<td>Median CD4</td>
<td>NA</td>
</tr>
<tr>
<td>Lodha et al.[9]</td>
<td>India 1996-2003</td>
<td>Increase WHZ, BMI2</td>
<td>Mean 14.4 ± 45.7</td>
<td>NA</td>
</tr>
<tr>
<td>Bunupuradah et al.[18]</td>
<td>Thailand 2001-2006</td>
<td>Increase weight (kg) and height (cm) at 96 weeks</td>
<td>Median CD4 22% at 48 weeks 26% at 96 weeks</td>
<td>85% and 70% having HIV RNA &lt;400 and &lt;50 copies/ml respectively at week 96</td>
</tr>
<tr>
<td>O’Brien et al.[10]</td>
<td>8 countries 2001-2005</td>
<td>NA</td>
<td>Median CD4 gain 12-18% at 12 months</td>
<td>NA</td>
</tr>
<tr>
<td>O’Brien et al.[11]</td>
<td>14 countries 2002-2006</td>
<td>Decrease proportion of patients with WHZ &lt;-2</td>
<td>Median CD4 gain 12-18% at 12 months</td>
<td>NA</td>
</tr>
<tr>
<td>Puthanakit et al[13, 24]</td>
<td>Thailand 2002-2004</td>
<td>Increase WAZ, HAZ 48 weeks</td>
<td>Median CD4</td>
<td>HIV RNA &lt;50 copies/mL 69% at 48 weeks 70% at 192 weeks</td>
</tr>
<tr>
<td>Puthanakit et al[30]</td>
<td>Thailand 2002-2007</td>
<td>Increase WAZ, 24 weeks HAZ, 48 weeks</td>
<td>Mean CD4 17% (11-20) at 48 weeks Mean CD4 27% (SD 7) at 144 weeks</td>
<td>HIV RNA &lt;400 copies/mL</td>
</tr>
<tr>
<td>Janssens et al.[14]</td>
<td>Cambodia 2003-2005</td>
<td>Increase WHZ 12 months</td>
<td>Median CD4</td>
<td>HIV RNA &lt;400 copies/mL 73% at 48 weeks</td>
</tr>
<tr>
<td>Safim et al.[15]</td>
<td>Thailand 2003-2008</td>
<td>NA</td>
<td>Median CD4</td>
<td>74% at 12 months</td>
</tr>
<tr>
<td>Natu et al.[16]</td>
<td>India 2004-2006</td>
<td>Increase weight (kg)</td>
<td>Mean CD4</td>
<td>NA</td>
</tr>
<tr>
<td>Zhang et al.[17]</td>
<td>China 2005-2006</td>
<td>Increase WAZ, 12 months</td>
<td>Mean CD4</td>
<td>HIV RNA &lt;400 copies/mL</td>
</tr>
</tbody>
</table>

\(^a\) increase referred to changes marked as statistical significant (P<0.05), improve referred to the changes without statistically significant. WAZ: weight for age z-score; HAZ: height for age z-score; WHZ: weight for height z-score; BMI2: Body mass index z-score; NA: not available.
most common practice was a replacement of NVP with EFV or vice versa. There was a wide range of variation between cohorts regarding drug tolerability as the study from South Indian reported as high as 25% of the children needing to switch due to drug toxicity [8], while all Chinese children could tolerate their first ART regimen throughout the 12-month follow-up period [17].

Certain long term adverse events were reported as well. According to a study from Bangkok, Thailand, 5% of the children developed peripheral lipoatrophy after receiving ART regimen including d4T for more than 28 months [7]. Data from Chiangmai, Thailand reported lipodystrophy (LD) diagnosed by waist-to-hip ratio and LD check list in 9% of the children after 48 weeks of d4T-based regimens [28]. Later on, the prevalence increased in this cohort to 47 and 65% at 96 and 144 weeks, respectively. The most common type was lipohypertrophy (46%) [28]. Dyslipidemia was reported from two Thai cohorts: one cohort had 61% with hypercholesterolemia, 33% with hyper-LDL and 19% with hypo-HDL while the other cohort reported 12% hypertriglyceridemia and 11% hypercholesterolemia [7, 28]. Insulin resistance detected by homeostasis model assessment (HOMA-IR), abnormal c-peptide and/or insulin level was reported in 6.5% of HIV-infected children on HAART for 96 weeks; all had normal fasting plasma glucose levels [29].

A significant improvement in physical growth has been documented at 12 months following ART initiation through different means of measurement: weight for age z-score in a Chinese study [17], weight for height z-score in Cambodian [14] and Indian studies [9], and both weight for age and height for age z-score in Thai studies [13, 30]. In MSF report [11], the proportion of patients with weight for height z-score below 2 standard deviation of normal decreased from 12-27% to 0-3% at 12 months after ART. Some studies in India [16] and Thailand [18] reported growth improvement after HAART in terms of weight in kilograms and/or height in centimeters. A significant increase in body mass index z-score and an improvement in HIV clinical staging after 6 months on ART were also documented in studies from India. The mean hemoglobin level which was low at baseline (10.1-10.7 g/dL) showed improvement after HAART in 2 out of 3 studies [8, 13, 18].

**Immunological outcomes**

In 9 of 12 reviewed cohorts, except the Indian studies, ART was initiated when children met WHO criteria, i.e. had CD4 cell percentage ≤15% or had advanced or severe symptoms (WHO clinical stage 3 or 4) with any CD4 level.

At 12 months of treatment, immune recovery was evidenced. The median CD4 significantly improved to between 22-31%. The CD4 gain within one year ranged from 6 to 18%. The findings of each study are summarized in Table 2.

**Virological outcomes**

The proportion of children with virological success defined as plasma HIV RNA <400 copies/mL at 12 months of treatment as 55% in China [17], 73% in a young Thai cohort [30], 74% in Cambodia [14], and 85% in Thailand [18]. In another Thai study which used a lower cut-off value of plasma HIV RNA <50 copies/mL, the achievement of virological success was 69%, and 70% at 48 weeks and 192 weeks respectively [13]. In the Indian, MSF, and one of 5 Thai studies, there were no plasma HIV RNA data available.

**Virological failure in the first line regimen**

Virological failure was defined as plasma HIV RNA level >1,000 copies/mL after at least 6 months of treatment. The proportion of children with virological treatment failure after 12 months on HAART as 15.5% in the Cambodian [14], and 37% in the Chinese studies [17]. In the study from south India with longer follow-up time beyond 18 months, 19% of the children needed second-line PI-containing regimens [8]. A comparison of studies from Thailand has shown that the rate of virological failure was higher in young children at a rate of 25% compared to 13% in older children [13, 30].

**Effectiveness of second-line ART in children**

The recommended second-line regimen in children who failed first-line NNRTI-based ART is boosted PIs with NRTI. According to the WHO guidelines, the recommended NRTIs are didanosine (ddI) and abacavir (ABC). However, there is limitation in clinical practices due to the high cost and unavailability of ABC in many national programs, and also the poor tolerability to ddI. In some circumstances, the recycling
Table 3. Pediatric HIV-infected children treated with boosted protease inhibitors as second line regimens in Asian countries.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Location, time frame</th>
<th>Median duration of follow up</th>
<th>N (%male)</th>
<th>Median age at entry (IQR)</th>
<th>Median %CD4 (IQR)</th>
<th>Median CD4 count (cells/mm³) (IQR)</th>
<th>Median HIV-RNA log10 (IQR)</th>
<th>Previous regimen</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunupuradah et al. [19]</td>
<td>Thailand 2003-2007</td>
<td>96 weeks</td>
<td>50 (44)</td>
<td>9.3 years (7-11)</td>
<td>7 (3-10)</td>
<td>160 (44-287)</td>
<td>4.8 (4.5-5.1)</td>
<td>Failed NNRTI HAART or dual NRTI</td>
<td>Standard dose of LPV/r (230 mg/m²/dose Q 12 hours) + SQV (50 mg/kg/dose Q 12 hrs) + 3TC</td>
</tr>
<tr>
<td>Van de Lugt J. et al. [23]</td>
<td>Thailand 2006-2008</td>
<td>24 weeks</td>
<td>23 (65%)</td>
<td>9.4 years (3.2-15.6)</td>
<td>Mean 16 (10)</td>
<td>NA</td>
<td>Mean 4.5 (0.5)</td>
<td>Failed NNRTI HAART</td>
<td>Standard or low dose (70% of standard dose) LPV/r solution+ ZDV + 3TC</td>
</tr>
<tr>
<td>Plipat et al. [20]</td>
<td>Thailand 48 weeks</td>
<td>48 weeks</td>
<td>19 (74)</td>
<td>9.7 years (8-12)</td>
<td>3.3% (1.3-5.2)</td>
<td>70 (29.3-275)</td>
<td>4.8 (4.4-5.4)</td>
<td>Dual NRTI or NNRTI HAART</td>
<td>IDV/r (weight 14-35 kg received 200/100, &gt;35 kg received 400/100) plus NRTI and/or NNRTI</td>
</tr>
</tbody>
</table>

LPV/r: lopinavir/ritonavir; SQV: saquinavir; IDV/r: indinavir/ritonavir; ZDV: zidovudine; 3TC: lamivudine.

**Clinical response**

- Increase WAZ, HAZ at 96 weeks
- Increase 14% (IQR 7 to 19) and 558 (308 to 782) cells at 96 weeks
- 2 children were excluded due to poor adherence
- Mean CD4% 23% (9) at 24 weeks
- NA

**Immunological response**

- Proportion of HIV RNA <50 copies/mL
- 74% at 96 weeks
- Mean CD4% 23% (9) at 24 weeks
- NA

**Virological response**

- Proportion of HIV RNA <400 copies/mL
- 76% (16/21 children) at 24 weeks
- Proportion of HIV RNA <400 copies/mL, 89.5% at 17 months (11 patients at 6 months, 5 patients at 11 months, and 1 patient at 17 months)

*a* include only changes marked as statistically significant (P<0.05); NA: not available
NRTIs, i.e. AZT plus 3TC in combination with boosted PI was selected for children with few thymidine analog mutations (TAMs), or double boosted PIs regimen for children with multi-resistance to NRTIs. There are three studies relating to the second-line boosted-PI in children, one study with double boosted PI with 3 sequential publications [19, 21, 22] and two studies with boosted-PI HAART [20, 23]. The baseline characteristics and treatment outcomes are shown in Table 3.

**Clinical, immunological and virological outcomes of second-line PI therapy**

The majority of deaths and hospitalizations occurred during the first few months after switching to boosted PI based regimen [21, 22], mostly from opportunistic infections. Common adverse events of PI were diarrhea and increased cholesterol and triglyceride [19, 21].

Significantly, increases in weight for age Z-score and height for age Z-score, and CD4 have been reported in one study [19]. The proportion of children treated with single boosted PI who had virological success defined as plasma HIV RNA <400 copies/mL was 89.5% at 17 months [20]. Using lower cut-off value defined as plasma HIV RNA <50 copies/mL, the achievement of virological success was 74% at 96 weeks after double boosted PI in Thai children [19].

**Virological failure and resistance on second line PI regimens**

In a double boosted PI regimen of saquinavir/lopinavir/ritonavir, over 96 weeks, 10 out of 50 children had virological failure, defined as having two consecutive HIV-RNA >400 copies/mL after 12 weeks. None had major PI mutations and all had minor PI mutations [19].

**Discussion**

Assessment of ART programs for HIV-infected children in Asia is important to improve care and treatment outcomes. We reviewed the efficacy of pediatric ART programs in Asia. Despite the limited number of available reports, the favorable results indicate that programs in Asia could achieve good treatment outcomes similar to those in developed countries.

The mortality rate after initiation of ART was low, ranging from 3-6%. However, we have to be aware that death might have been underreported. Many children particularly young infants with severe HIV disease might have died before ART was widely accessible. The lost-to-follow-up rates were surprisingly low when compared to studies in the past or even current studies in other regions [31, 32]. This may be explained by the fact that HIV treatment is more acceptable nowadays for people in Asian countries. In addition, almost all reviewed studies were conducted in research settings which might differ from routine clinical practices with more intensive patient and family education, and better trained personnel and retention plan and follow-up strategy. These supportive factors should be encouraged in routine health service systems as well.

The growth of HIV-infected children after initiation of HAART was substantially improved and comparable to those seen in many studies from other parts of the world [11, 33-35]. Doubling in the amount of CD4 T lymphocytes was evidenced in almost all studies at 12 months after HAART. The efficacy of treatment in terms of immunological and virological outcomes was comparable to other studies in HIV-infected children both in resource-limited and resource-rich settings [35-38]. Furthermore, the results were not inferior to adult studies using HAART in resource limited settings [39-41].

The interesting public health issue is that several studies in Asia have shown satisfactory short-term outcomes of generic adult fixed-dose combination (FDC) antiretroviral tablets for treatment of children. This success is despite several important limitations that might lead to under- or overdosing of children: inaccurate dosing with the cut adult tablets and inaccurate dosing per weight of each of the three components. However, there is a substantial advantage in using adult FDC antiretroviral drugs. First, they are now available in most adult ART programs in resource-limited settings which are always larger and better established compared to pediatric programs. This increases the accessibility of children to ART. Second, they are in generic form and are less costly and more affordable for scaling-up on a national level. Third, the use of adult FDCs significantly reduces the pill burden when pediatric FDCs are not widely available. This facilitates treatment adherence and consequently a reduced risk of antiretroviral resistance development. Fourth, tablets have a more acceptable taste, are easier to swallow, crushed or mixed with food, when compared to liquid formulations. Finally, drug storage
and distribution is simpler and no refrigerator is needed. Recently, pediatric FDC has become available commercially with pharmacokinetic data from Zambia supporting its use in children weighing 6 kg or more [42].

Adverse effects occurred after HAART. However, most children were able to continue treatment. No life-threatening complications were reported from the use of antiretroviral agents. The need for hospital admission was high in the first few months of treatment, due to pneumonia and bacterial infections, which was explained by opportunistic infections and immune reconstitution syndrome. The hospitalization rate declined thereafter when children were stable on HAART. Despite no study in Asian countries comparing hospitalization rate of HIV-infected children before and after HAART, all clinicians working with this population could perceive a dramatic reduction in HIV-related morbidity and mortality including the number of severely ill children, length of hospital stay, and incidence of new opportunistic infections. The decrease in hospitalization rate after HAART was similar to reports from the US, Romania, and Spain [43-46].

The study of young children below two years of age in Thailand has shown the efficacy of HAART in terms of clinical, immunological, and virological success. There is a need for improved access to early HIV diagnostic testing, e.g. HIV-DNA PCR in the infancy period in order to initiate treatment as soon as possible, which has been shown to significantly reduce morbidity and mortality. More data on how to select ART for children exposed to antiretrovirals to prevent mother to child transmission is needed. There is a report of high incidence of NNRTI resistant mutation in new perinatally HIV-infected infants since single dose NVP has been widely used as part of HIV mother to child transmission prophylactic regimen. From the meta-analysis, 52.6% of infants exposed to single dose NVP alone had NNRTI resistance while only 16.5% of infants who received single dose NVP with other antiretroviral drugs developed resistance [47].

Only a few publications related to second-line boosted PI in Asian children are available. We hypothesized that this might be explained by the limited access to plasma HIV-RNA monitoring to detect treatment failure early, limited access to second-line regimen or lack of systematic data collection. Data of the boosted-PI regimens in Asian children have shown good virological efficacy; 74-90% of patients were able to suppress their viral load to an undetectable level. Interestingly, two studies also investigated the use of lower doses of boosted indinavir [20] and boosted lopinavir [23]. The results showed that lower doses also provided adequate plasma PI levels and good treatment efficacy. More research studies should be done to address this issue. There is also a need for more data on the use of new PI in children, e.g. darunavir, tipranavir and also new antiretroviral drug classes, e.g. intergrase inhibitors and chemokine receptor inhibitors.

**Conclusion**

Available reports consistently demonstrated beneficial outcomes of first-line antiretroviral therapy for HIV-infected children in Asian countries. There is an urgent need for improved access to early HIV diagnostic testing and treatment for infants, and more data on which to base ART selection for children exposed to antiretrovirals for prevention of mother-to-child transmission. The implementation of life-saving antiretroviral programs throughout Asia is encouraged. There was limited information about the management of children who failed first-line NNRTI regimens and more studies to address second-line treatment for Asian children are needed.

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