Challenges in Management of Pediatric HIV/AIDS: Thailand Perspective

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Recently, a report suggested that the epidemic of human immune deficiency virus (HIV) infection may have reached its peak. Although the number of new cases is reducing, the number of people living with HIV has not decreased as the patients survive in this era in which effective antiretroviral therapy has been widely accessible. The knowledge about HIV disease has never been this immense. The challenges facing us have changed from treating the dying diseased cases complicated with opportunistic infections to dealing with the problems related to long-term treatment including life-long adherence, drug adverse effects, drug resistance, and the need for a newer generation with less toxic drugs. In children, additional challenges are related to adolescent problems. This review summarizes the challenging issues of this era in treating HIV-infected children.

The overview disease burden

In 2009, there were 33.3 million people living with HIV worldwide, of which 5-10% were children.[1] The majority of them are living in Sub-Saharan Africa. In Thailand, an estimated 400,000 infected people with HIV were reported in 2009, of which approximately 15,000-20,000 were children. Nearly all of them were acquired perinatally. The prevalence of HIV infection among pregnant women in Thailand has declined from 1.74% in 1999 to 0.64% in 2009. After the implementation of a nation-wide prevention-of-mother-to-child-transmission (PMTCT) program, the rate of perinatal transmission has decreased from 25% to 2-4%.[2]

Diagnosis of HIV infection in perinatally HIV-exposed infants

Virologic assay, either HIV DNA-PCR or RNA-PCR assay, can be used for diagnosis of HIV infection in infants. Because of the maternally transferred anti-HIV antibody, the serologic test causes a false positive in uninfected young infants. The PCR is recommended to be performed at least 2 times at age 1-2 months and 4-6 months. At age 12-18 months of age, the HIV antibody test should always be performed to confirm the diagnosis regardless of the results of prior virologic tests. HIV infection can be definitely diagnosed by the presence of HIV antibody in children aged ≥ 18 months. Definitive exclusion of HIV infection can be made by no clinical or virologic evidence of HIV infection plus one of the following criteria: 1) at least two negative HIV PCR assays which are performed at age ≥ 1 month and ≥ 4 months, 2) at least two negative HIV antibody tests at ≥ 6 months of age, 3) one negative HIV PCR at age ≥ 4 months and absence of HIV antibody after 6 months of age.[3]

Management of HIV-infected children: the current Thai guidelines

HIV-infected children require routine care and anticipatory guidance similar to normal children. All HIV-infected children should be immunized with the same schedule as uninfected children except that children with severe immune suppression (CD4 percentage < 15% or CD4 count < 200 cells/mm^3) or severely symptomatic disease status should not receive live-attenuated vaccine such as mumps-measles-rubella or varicella vaccine. Moreover, all HIV-exposed infants with unknown infection status from 4-6 weeks of age, should receive chemoprophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) until HIV infection can be excluded. Cotrimoxazole is the drug of choice. Likewise, infected children younger than 12 months or those with CD4 < 15%; or < 200 cells/mm^3 in children older than 5 years, should also receive PCP prophylaxis. This is because the risk of PCP development is quite high in HIV-infected infants < 12 months regardless of their CD4 levels.

Highly active antiretroviral therapy (HAART) has been the principle of treatment of HIV infection. HAART normalizes immunologic function, prevents opportunistic infection and mortality. With HAART, HIV has been changed from a deadly disease to a chronic disease in which patients can live a very normal life. HAART is generally composed of three drugs from at least two classes. The aims of antiretroviral therapy are to minimize viral load, maintain viral suppression, preserve immune function, maintain normal growth and development, and improve the quality of life.

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The evaluation of adherence to life-long antiretroviral treatment is crucial. Poor adherence may lead to the development of drug-resistant HIV. Before initiation of antiretroviral therapy, the caregivers and children should be assessed for factors associated with adherence and counseled to understand the importance and how to maintain long-term adherence. Moreover, children with CD4 <15% or < 200 cells/mm^3 in those older than 5 years should be evaluated and treated for the pre-existing opportunistic infections (OI) before initiation of antiretroviral therapy to provide a plan of treatment and prevent immune reconstitution inflammatory syndrome (IRIS).

When to initiate antiretroviral therapy in Thailand

The risk of disease progression is highest in young children. The early mortality rate has been substantially reduced from 16% to 4% among asymptomatic HIV-infected infants starting antiretroviral therapy prior to 12 weeks of age.[4] Therefore, all HIV-infected infants should receive antiretroviral therapy as soon as possible. This can only be possible with the availability of PCR for early diagnosis. For children aged 12 months or more, antiretroviral therapy should be initiated if the child has significant clinical symptoms (CDC clinical stage B or C[5] or WHO stage 3 or 4[6]) regardless of CD4 levels. The initiation of antiretroviral therapy is also recommended for children with no or minor symptoms who have CD4 levels below age-specific thresholds as shown in Table 1. The treatment guideline in Thailand does not recommend using plasma HIV RNA level as a criterion for starting antiretroviral therapy.[7]

Antiretroviral therapy can be started while treating OI, usually soon after the patients are assured to tolerate OI treatment well. In children with tuberculosis, HAART should be started within 2-8 weeks after starting anti-tuberculosis treatment.

First line antiretroviral regimens for HIV-infected children in Thailand

The preferred initial antiretroviral regimen for ARV-naïve children is a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP) for children age < 3 years and efavirenz (EFV) for children age ≥ 3 years. For perinatal NVP exposed children, a NNRTI-based regimen should be avoided because of the high rate of development of NVP resistance leading to treatment failure.[8,9] In these infants, lopinavir/ritonavir (LPV/r) with two NRTIs is recommended as the preferred first-line therapy.

The preferred first line two NRTIs combination to use in the regimen is zidovudine (AZT) plus lamivudine (3TC). In the children who cannot tolerate AZT or have significant anemia, stavudine (d4T) should replace AZT. Stavudine should be switched to AZT after resolution of anemia to prevent lipodystrophy from prolonged use. In adolescents tenofovir (TDF) plus 3TC in combination with EFV is the preferred combination as they can be administered once daily and so help to improve adherence.

The fixed dose combinations (FDC) of AZT/3TC/NVP (GPOvir-Z) and d4T/3TC/NVP (GPOvir-S) have been available in Thailand for adult patients, and can be applied for use in children with proven adequate pharmacokinetic and efficacy.[10,11] The FDC reduced pill burden helps adherence in children. The pediatric FDC is under development. Due to potential toxicity, NVP should not be used as initial therapy for adolescent girls with CD4 > 250 cells/mm^3. Adolescent girls who are sexually active should not use EFV without two methods of contraception because EFV may have teratogenicity.[12,13]

In Thailand, tuberculosis co-infection is a common problem. Because rifampicin is a potent CYP3A inducer, protease inhibitor levels are reduced substantially and thus must not be used together. Rifampin minimally interferes with NNRTIs levels and therefore can be used together without dose adjustment.[14,15]

Monitoring children receiving antiretroviral therapy

Children receiving antiretroviral therapy should be regularly monitored for immunologic and virologic response, side effects, and adherence. Toxicities and adherence should be cautiously focused during the first few months. Growth and development can affect clinical response and should be monitored. Children who have low baseline CD4 may have IRIS which usually occurs within 12 weeks of starting HAART and may be severe.

For laboratory monitoring, CBC and CD4 count/percentage should be assessed every 6 months. HIV viral load should be evaluated at 6-12 months after initiating HAART and then annually. In the case of suboptimal adherence or suspected treatment failure, additional CD4 count/percentage and HIV viral load assessment are required. Monitoring of drug toxicities including CBC, liver enzymes, and lipid profile should be performed every 6 months. In addition, renal function should also be monitored in children receiving TDF, and fasting blood sugar in those receiving protease inhibitors.

The challenging issues in management of HIV-infected children, the era of HAART

As children survive with near normal lives from effective antiretroviral therapy, the challenges come along with long term treatment as these children grow up. There are four challenging issues to discuss as follows.

1. Drug resistance in long term treatment experienced children

Poor adherence to ARV is a major cause of acquired drug resistance, which results in treatment failure. Virologic monitoring can help early detecting treatment failure

TABLE 1. Indications for initiation of antiretroviral therapy in HIV-infected children in Thailand.

Age	Criteria
< 12 months	• All
1- < 5 years	• CDC clinical stage B or C or • WHO clinical stage 3 or 4 • CD4 < 25%
≥ 5 years	• CDC clinical stage B or C or • WHO clinical stage 3 or 4 • CD4 < 350 cells/mm^3

TABLE 2. First line antiretroviral regimens for HIV-infected children recommended in Thailand.

Age	Preferred regimen	Alternative regimen
< 3 years	AZT+3TC+NVP	d4T+3TC+NVP
≥ 3 years	AZT+3TC+EFV	AZT+3TC+NVP d4T+3TC+NVP d4T+3TC+EFV
Adolescents	TDF+3TC+EFV	-

and prevent extensive resistance from prolonged use of failing regimens. A genotypic assay is helpful to guide a selection of a new treatment regimen. In Thailand, the preferred regimen in children who failed first line regimens of 2NRTI+NNRTI comprises 2NRTI (guided by genotype) plus LPV/r. Ritonavir boosted atazanavir (ATV/r) is an alternative to LPV/r in children with dyslipidemia who are six years or older.

The children in the early era of antiretroviral therapy may have experienced dual NRTIs regimens, which could lead to extensive NRTI mutations. Studies from Thailand showed that 96-96.8% of children on dual NRTIs had viral resistance, 39-40% were high grade resistance (≥4 nucleoside analogue mutations (NAMs) ± Q151M or 69 insertion complex), and 56-60% were low grade resistance (< 4 NAMs).[16,17] The salvage regimens for these children who failed NNRTI regimens are challenging. The regimens including double boosted PI, LPV/r plus indinavir or saquinavir, are effective,[18,19] and may be considered if there is no NRTI option available. However, these regimens require close monitoring for adverse events, especially renal toxicity from indinavir, and should be switched to a safer regimen as soon as it becomes available.

Resistance to three drug classes, NRTI, NNRTI, and PI, has emerged recently. The children who have several years experience of treatment are at risk of carrying three drug class-resistant viruses. The HIV-infected infants who were exposed to a perinatal single dose of NVP for prevention of mother-to-child-transmission have a 46%-87% chance of developing NVP resistance at baseline[20,21] and require LPV/r as the first line regimen. They also may develop three drug class-resistance in childhood. The regimens to treat these children require more potent newer, so called third line drugs. The third line drugs recently available in adults are darunavir, etravirine, and raltegravir. Only darunavir is approved in children ≥ 6 years of age. Unfortunately, they are not available in the free access national program. In real life, the children with three drug class-resistance may need to stay on a failing regimen or holding regimen, i.e, 3TC mono-therapy just to slow down the disease progression, until these salvaging third line drugs are available.

There is increasing evidence that resistant strains of HIV are being transmitted in various parts of the world including Thailand.[8,22-26] The World Health Organization (WHO) has responded to this concern by establishing the Global HIV Drug Resistance Surveillance Network to assist countries in monitoring for the emergence of HIV drug resistance.[27] It is mandatory to establish strategies aimed at minimizing the magnitude of the drug resistance problem. These strategies include careful review of ARV history and initiating only effective and less toxic HAART for newly diagnosed HIV-infected individuals, baseline genotypic assay before initiation of HAART in places with a high prevalence of primary drug resistance, simplification of regimens to promote adherence, and scaling up HAART for all HIV-infected pregnant women to minimize the use of single dose NVP which may induce NNRTIs resistance in mothers and infants.

Strategies to promote adherence include regimen simplification and psychosocial interventions which are important to prevent development of drug resistance. Practical regimen simplifications are the change to once daily dosing regimen and reduction of pill burden by using FDC. The drugs that can be used once daily are TDF, abacavir (ABC), 3TC, EFV, LPV/r, and ATV/r. Didanosine (ddI) tablets can be used once daily, but have food interference and bad taste, and so should not be used as the first choice in children.

2. Long term toxicity of antiretroviral therapy

Children are at higher risk of long term toxicity from antiretroviral therapy as they will need to stay on treatment for a longer time in life than adults. However, children have less underlying diseases and may be more tolerant to some toxicity than adults. Of these, lipodystrophy, dyslipidemia, and disorders of glucose metabolism, as well as osteopenia and renal dysfunction, are the main challenges.

HIV-associated lipodystrophy syndrome

Fat redistribution can manifest as central lipohypertrophy, facial/peripheral lipoatrophy, or a combined type. The prevalence of clinical lipodystrophy in HIV-infected children receiving HAART has been reported in 5.6-28.2%.[28-31] However, a study from Chiang Mai showed that as many as 65% of HIV-infected children receiving non-nucleoside analogue reverse transcriptase inhibitors (NNRTI)-containing HAART developed lipodystrophy assessed by waist-to-hip ratio and LD checklist at 144 weeks after HAART initiation.[32] D4T containing FDC had been commonly used in their cohort. Taylor et al reported that the onset of fat redistribution and dyslipidemia peaked between 10-15 years of age suggesting that physiologic changes associated with puberty may predispose adolescents to developing lipodystrophy syndrome.[33] Treatment with thymidine analogue NRTI or protease inhibitors has significantly been associated with the presence of physical changes.[31,34] Facial/peripheral lipoatrophy has been found significantly with prolonged use of d4T while central lipohypertrophy was most associated with PIs and EFV, and can occur even in the absence of HAART.[35] HIV-associated facial lipoatrophy is a major stigma that can have dramatic effects on their self-esteem, social habits, and medication compliance.[36] Careful monitoring and early detection are important. Partial improvement of lipoatrophy has been reported after substitution of d4T with either abacavir or tenofovir. Various reconstructive procedures have been shown to be effective in adults and are well-tolerated, but their use has been limited by their expense[37-40] and very limited experience in HIV-infected children. Recently, WHO recommend to phase-out d4T use to prevent this facial lipoatrophy.[41] The current guideline in Thailand recommends d4T as the alternative regimen.

Dyslipidemia

Up to 67% of HIV-infected children receiving HAART developed lipid abnormalities.[28,33,42,43] These abnormalities consist of elevated triglyceride and total cholesterol levels, as well as low high density lipoprotein (HDL) levels. Changes in low-density lipoprotein (LDL) levels are less noteworthy, but can occur.[44] Although many reports demonstrated that PI-containing HAART is a major risk factor of dyslipidemia,[42,43,45] it can also be found in HIV-infected children who are receiving NNRTI-containing HAART.[32] Among the PIs, ATV appears to have fewer lipid side effects than LPV/r.

Dyslipidemia increases the risk of cardiovascular disease in HIV patients, as it does in non-HIV-infected adults. In adults patients with HIV are at higher risk for cardiovascular morbidity and mortality.[46-48] Long-term studies are needed to document the cardiovascular disease

burden in children with HIV-associated dyslipidemia.

Children receiving a PI containing regimen should have lipid profiles monitored including triglyceride, total cholesterol, LDL-C, and HDL-C which should be monitored every 6-12 months, or more often if indicated. The first step intervention for children with dyslipidemia includes lifestyle modification (low fat diet, exercise, reduced television watching, smoking cessation) and switching to a new HAART regimen that is less likely to cause lipid abnormalities. Lipid levels may improve with substitution of an NNRTI for a PI in NNRTI-naive patients.[37,49] Similarly, substitution of RTV-boosted ATV for other PIs has led to improved lipid profiles.[50] Switching from d4T to TDF or ABC has resulted in improvement in lipid profiles without the loss of viral suppression.[35,51] Fenofibrate can be use in cases with persistent high triglyceridemia, but there has been no drug approved to treat hypercholesterolemia in children.

Disorders of glucose metabolism

A spectrum of disorders of glucose metabolism has been associated with HIV infection and HAART. These abnormalities include 1) insulin resistance (target tissues of insulin action fail to respond appropriately to insulin, resulting in increased pancreatic insulin production), 2) impaired fasting plasma glucose (FPG), defined as a FPG of 100-125 mg/dl, 3) impaired glucose tolerance (OGTT), defined as an elevated blood glucose of 140-199 mg/dl 2 hours after a standard OGTT, and 4) diabetes mellitus (DM is defined as either FPG ≥ 126 mg/dl, a random plasma glucose ≥ 200 mg/dl in a patient with hyperglycemic symptoms, a hemoglobin A1C of > 6.5%, or a 2-hour plasma glucose after OGTT ≥ 200 mg/dl.[35,40,52] In contrast to the high prevalence of dyslipidemia, insulin resistance, impaired glucose tolerance and DM have been found to be relatively uncommon in HIV-infected children. Furthermore these glucose metabolism abnormalities especially DM are less common in HIV-infected children compared to adults.[43,52] A cross-sectional multicenter study of a cohort of 396 children and adolescents from 37 PACTG sites demonstrated that rates of impaired FPG (100-125 mg/dl; 5% and 7%) and 2-hour glucose level (140-199 mg/dl; 4% and 4%) in patients taking PI and non-PI were low and similar to HIV-negative children (7% and 1%).[43] Though an association between PIs and abnormal glucose homeostasis remains unclear, ATV has a minimal effect on glucose tolerance and ritonavir (RTV) boosting may modestly increase insulin resistance.[40] A 4-year study of glucose homeostasis found treatment switched substantially in favor of NNRTI showed an improvement in insulin sensitivity. Puberty was associated with a significant decrease in insulin sensitivity.[53]

The presence of insulin resistance, dyslipidemia, and the significant correlation of reduced insulin sensitivity with increased visceral adipose tissue content has suggested that PI-containing HARRT is associated with the emergence of early features of a metabolic syndrome-like phenotype.[54] A study of insulin resistance at 96 weeks of treatment with NNRTI-based HAART among HIV-infected children in Thailand revealed a low prevalence at 6.5%. No child had impaired fasting glucose (≥ 110 mg/dl). No associations between insulin resistance and lipodystrophy or treatment regimen were detected.[55]

Children receiving a PI-containing regimen should be monitored for hyperglycemic symptoms (polyuria, polydipsia, and polyphagia), and acanthosis nigricans. A random plasma glucose (RPG) level should be obtained 3-6 months after initiation of HAART, and annually thereafter. If RPG is ≥ 140 mg/dl, they should obtain a fasting plasma glucose and see an endocrinologist if laboratory abnormality is confirmed.[35]

Osteopenia and osteoporosis

Osteopenia, osteoporosis, and impairments of bone metabolism have been recently reported as frequent findings in HAART-treated patients, however, fracture is rare.[56,57] Although the definitive cause for bone mass and bone metabolism alterations have been uncertain, studies have suggested several factors which may contribute, such as the use of HAART (PIs, TDF), development of lipodystrophy, nutritional and hormonal factors, and HIV infection *per se*.[56,58,59] Studies on the impact of TDF on bone mineral density (BMD) in highly antiretroviral-experienced children demonstrated that TDF use was associated with decreases in absolute BMD and BMD z score, with an increase in bone markers and calcium excretion.[60,61] The magnitude of spinal bone loss was lower in adults (2-3%),[62] compared with > 6% loss in pediatric patients. This difference is likely attributable to lower rates of bone turnover in older adolescents and adults, who have completed their skeletal growth.[60] Therefore, TDF should be used with caution in growing children. Careful monitoring of HIV-infected children who require treatment with TDF is warranted. The BMD at baseline and every 6-12 months may be checked. Ensuring adequate vitamin D and calcium intake, and supplementing these nutrients when necessary, may ameliorate some of the bone density effects.

Kidney dysfunction

Many antiretroviral drugs are nephrotoxic and may be implicated in causing both acute and chronic kidney disease. TDF is associated with glomerular and proximal tubular toxicity. A study in adults found 1.6% prevalence of TDF-associated renal toxicity. Patients may present with proteinuria, reduced tubular transport of phosphate, glycosuria, or Fanconi syndrome.[63] The renal safety of TDF in HIV-infected children and adolescents has not been well documented. A prospective, 96-week longitudinal study found no significant decrease in glomerular filtration rate (GFR) or tubular dysfunction.[64] However, the renal safety of TDF in the long term in children needs further study.

Crystalluria, crystal nephropathy and nephrolithiasis have been established with IDV. Acute interstitial nephritis, although not common among antiretroviral agents, is seen with IDV and ATV in HIV-infected patients. Kidney damage related to antiretroviral therapy is typically reversible with early recognition and timely discontinuation of the offending agent.[65,66]

3. Disclosure of HIV diagnosis to children and adolescents

Grown up children with HIV infection must be informed about their diagnosis at the appropriate timing with an appropriate process to help them develop coping with positive attitude and able to live normal lives. Disclosure opens the opportunity to provide HIV related health education and proper self care, as well as infection control. Disclosure when a child is too young may create false conception, fear, and the child may not be able to keep the secret. On the other hand, too late disclosure may cause the feeling of mistrust, and may miss the chance of preventing poor adherence or risk of transmission from

lack of knowledge. Disclosure helps improving childs self-esteem, and promoting trust and family communication.[67-69] A study found 85% of caretakers and 97% of the children felt more comfortable after disclosure.[70]

The appropriate timing for disclosure varies in each individual child and is affected by the childs maturity, environment, and attitude of caretakers. The American Academy of Pediatrics recommended that school-age children and adolescents with HIV should be informed about their diagnosis.[67] It is very important that the child must be disclosed before adolescence, the time of highest risk behavior. We found 80% of children older than 7 years with HIV in Bangkok were not aware of their diagnosis.[71] Most of the reasons for not disclosing were the feeling that the child was too young, that the child might be mentally traumatic, that the child might be unable to keep the secret, and that the child might have bad feelings to the mother who transmitted the virus to them.[69,72,73] All these must be taken into consideration when making diagnosis disclosure. Appropriate disclosure should result in a positive attitude, improve familial relationship and bonding, and able to make the child cope with infection with good self care. Disclosure should be provided as a careful process ideally in the style of patient and family center. It should also take into account of the family socio-cultural and beliefs.

With several years of experience, Siriraj Hospital and Queen Sirikit National Institute of Child Health, the two large referral centers for pediatric HIV, and the Thai MOPH-U.S. CDC Collabooration[53] have developed the first disclosure model for Thai children with HIV implemented in the year 2005. The model which is counseling based consists of 4 steps as follows:

Step 1: Eligibility screening: the provider team offers the service to children who are in school age, e.g. 7 years and older in this model, and have no severe illness or in need of hospitalization in either the child or the caretakers, and the child does not have mental retardation or severe psychological problem.

Step 2: Readiness assessment and preparation for disclosure: this step composes of assessing the childs coping skill and learning about the family environment. The caretakers are given the knowledge and discussion about the HIV, disclosure, how to respond to the childs emotion, and their concerns. The caretaker will make the decision when to be ready for the disclosure with the guidance by the counselor. This step may take several months, although, it must be very brief in some instances such as the child is having high risk behavior, or refuses to take medications, or accidentally knows about the diagnosis or has a strong desire to learn the diagnosis.

Step 3: Provider-assisted disclosure session: this is a scheduled session for the provider to give the knowledge of HIV diagnosis to the child with the presence of caretaker(s). It is important that all HIV related health knowledge and appropriate self care, as well as the psychological support including the handling of the secret must be discussed. The model provides the list of information that needs to be given to the child. Picture drawing is helpful in younger children. In the cases that caretakers want to tell the diagnosis by themselves, this session will be scheduled as soon as possible right afterwards to ensure that each child will receive the complete information from the provider team.

Step 4: Post disclosure assessment: this step is to monitor the effect of disclosure to the child and family.

In the case that the child is too young to understand about HIV, but there are other needs to disclose (such as the child refuses to take the medicine), partial disclosure is useful. This includes all the steps above, but the information given to the child is limited to the need to take medication and self care for a chronic illness without telling the name HIV or AIDS. The way to deliver information to the child depends on the child's maturation and ability to understand.

Currently, more than 200 children were disclosed using this model. The outcomes have been highly satisfactory.[74] This model has been adopted and applied in several centers in Thailand. With the appropriate process, HIV-infected children will be able to grow physically and mentally healthy into adulthood.

Disclosure of their HIV status to the community is another issue. At the present time, HIV infection is still a poor stigma in most settings. HIV-infected children must be protected from stigmatization and prejudice which could prevent them from a healthy environment to grow up. Therefore, disclosure of HIV infection of a child to the community is generally not suggested. The community needs to be educated and learn to live with HIV-infected people, regardless of their disclosure status.

4. Adolescents with HIV

Being adolescent is challenging in everyone's life. HIV infection makes the adolescent period even more complicated. Adolescents who grow up with HIV experience long term treatment and disclosure may be able to cope with the infection better than those who acquired infection from high risk behavior. Nevertheless, adolescents in both groups have similar adaptive and emotional challenges. Adolescents have problems with adherence to treatment despite their previous excellent adherence in childhood,[75] and have worse treatment outcomes with a higher chance of virologic failure compare to adults.[76] Lipodystrophy from long term treatment with d4T and other NRTIs may cause frustration to adolescents and may lead to poor adherence. Despite the knowledge about disease, studies have shown that HIV-infected adolescents still engage in high risk behavior with multiple sexual partners.[77] In the US, a quarter of HIV infected girls who were sexually active have been pregnant at least once by 19 years of age.[78] Thailand has a younger cohort of adolescents, but tends to have the same feature.

Guiding adolescents into the right direction as well as supporting them to comply with treatment are not easy. Apart from counseling and providing constructive activities to help adolescents cope and understand, simplification of antiretroviral therapy is an important strategy. The regimen of once daily such as TDF+3TC (or FTC)+EFV is the most ideal first line regimen in resource limited settings, but requires monitoring for kidney toxicity, neuropsychiatric side effects, and effective contraceptive methods. We found double methods including contraceptive implantation plus condoms are the most acceptable. The second line treatment regimen is more difficult to simplify. ATV/r can be given once daily with TDF and 3TC (or FTC), but may cause jaundice and result in poor adherence. A once daily LPV/r regimen is an option if the patients have limited or no PI resistant mutations. Continuous counseling and guidance are needed in adolescents, although the affect to the treatment outcome may be guarded.

It is important to prepare the children and adolescents with HIV for adulthood. Transition of care requires a good team work of pediatricians and internists. It is expected

that these children and adolescents can live a long life, may be close to a normal population, and can contribute greatly to the society they live in.

CONCLUSION

In this era, to normalize the long-term health, lifestyle and life expectancy of the HIV-infected children have become the challenges. More understanding and resources are required. These grown up HIV-infected children and adolescents will become quality adults with appropriate management.

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