Initiation of Antiretroviral Treatment with Dual Nucleoside Reverse Transcriptase Inhibitors in Human Immunodeficiency Virus-Infected Infants with Less Advanced Disease in a Resource-Limited Setting: A Multi-Center Study in Thailand 1998-2000

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Objectives: *To evaluate the feasibility, duration of efficacy, and outcome of therapy with dual nucleoside reverse transcriptase inhibitors (NTRI) initiated in HIV-infected infants with mild to moderate disease.*

Material and Method: *During 1998-2000, a multi-center prospective open-labeled operational study was conducted. Antiretroviral naôve HIV-infected infants were enrolled in seven hospitals to receive either zidovudine (AZT) plus lamivudine (3TC) or AZT plus didanosine (ddI). Infants who were in CDC stage "C3" were excluded from the study.*

Results: *Of the 88 infants, the mean age of treatment initiation was 6.8 months, and the mean initial CD4 was 1538 cells/mm³ (21.4%). The z-scores for weight and height increased after 4-8 months of treatment, and by the 24th month, were +0.89 and +0.69 higher than at enrollment. The CD4% peak increased at 8 months of treatment, by a mean increment of 4.19%, but decreased to the level of 1.08% above baseline by the 24th month of treatment. Three (3.4%) infants died, 11 (12%) had disease progression, 7 (8%) was prematurely discontinued from the study protocol due to poor compliance, and 37 (42%) were lost to follow-up. At the end of 24 months, all remaining 30 children were in stable condition with a chance of clinical and immunological stability of 34% and 68% by intention-to-treat and on-treatment analysis, respectively.*

Conclusion: *Clinical and immunological benefit from dual NRTI was limited. Treatment of HIV-infected infant with mild to moderate disease in a resource-limited setting may have limited feasibility due to the high drop-out rate.*

Keywords : *HIV-infected infants, Antiretroviral therapy, Dual NRTI*

Antiretroviral therapy (ART) is an important part of management of HIV-infection. Effective ART

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prolongs healthy life, prevents opportunistic infections and improves long-term survival [1, 2]. Initiation of ART soon after acquiring infection is advantageous in preserving immune function and effectively suppresses viral replication, which may result in a better prognosis [3-5]. With these potential benefits, infants who have acquired perinatal HIV deserve ART once the infection is confirmed. Earlier studies have shown that early ini-

tiation of ART in infants can induce long-term viral suppression and preserve immune function [6-8]. Perinatal infection is generally more severe than infection in adults [9]. The HIV RNA pattern in untreated infants has been shown to be persistently high in the first year of life, probably due to the immature status of their immune systems to control viral replication [9-11]. Therefore, the benefits of ART should be more pronounced. A recent study has shown a 70% reduction of mortality in HIV-infected infants with triple combination antiretroviral therapy [12]. Because of the potential benefits and the less predictive value of the available virological and immunological parameters [10, 11], most treatment guidelines recommend a lower threshold for treatment initiation in infants than in older children [13-15]. Highly active antiretroviral therapy (HAART), generally composed of 3 antiretroviral drugs, has been recommended as the initial ART regimen in children [13-15]. Antiretroviral regimens composed of two nucleoside reverse transcriptase inhibitors (NRTI) have been known to be less effective in suppression of viral replication [16]. However, many children who were on dual NRTI were clinically and immunologically stable despite the presence of plasma HIV RNA [1, 2]. In settings where HAART is not feasible, dual NRTI may be an option especially in infants with less advanced stage. In 1998-2000, antiretroviral (ARV) drugs available in Thailand by the national program were mostly limited to NRTI that were locally produced. The authors conducted a prospective study to evaluate the feasibility, as well as the magnitude and duration of efficacy, of dual NRTI regimens initiated in infants with mild to moderate stages of HIV disease. The results of the study should be useful for consideration of initiation of treatment in infants.

Material and Method

A multi-center prospective open-labeled operational study was conducted in 7 hospitals in Thailand. The participating hospitals were Siriraj, Pramokutklao, Queen Sirikit National Institute of Child Health, Charoenkrung-Parchoruk, Vachira, Chulalongkorn and Hat-Yai Hospitals. The study protocol was approved by the Ethical Review Board of the Ministry of Public Health and the Faculty of Medicine Siriraj Hospital. Infants younger than 12 months of age, who were diagnosed with HIV infection, whose family could not afford triple antiretroviral regimen and who were committed to return for long term follow-up in one of the participating hospitals, were eligible. HIV-infection was defined as a positive HIV PCR in at least 2 separate blood samples, with or without symptoms. Once these infants reached the age of 18 months, they were required to have HIV infection confirmation by the presence of anti-HIV antibody. The enrollment required an informed consent by the parent or an authorized caregiver.

The exclusion criteria at enrollment were age older than 12 months or stage C3 according to the CDC classification system [17].

The infants with odd enrollment numbers were assigned to receive zidovudine (AZT) 100-120 mg/M^2/dose every 8 hours plus didanosine (ddI) 100 mg/M^2/dose every 12 hours. The infants with even enrollment numbers were assigned to receive AZT at the above described dosage, plus lamivudine (3TC) 4 mg/kg/dose every 12 hours. Those infants who were unable to tolerate their assigned medication of 3TC or ddI were switched to the other medication. The infants who were unable to tolerate both 3TC and ddI, or AZT or who did not take the medicine regularly for any reason were excluded from the study. The antiretroviral drugs were sponsored by the Ministry of Public Health of Thailand.

All the studied children were followed every 1-2 months, with a physical examination and general check-up. The disease staging was determined by using the CDC classification system [17]. The complete blood counts and CD4 levels were measured every 4 months. Other laboratory investigations were performed when clinically indicated. Verification of adherence was through self-report and left-over pill counts. Counseling on adherence was repeated periodically by assisting nurses. Children with obvious poor adherence or frequently missed pills even after counseling, as judged by the study physicians, were prematurely discontinued from the study.

The study was planned for 24 months of treatment. After the study ended, children who remained in stable condition were continued on the treatment they were receiving. Children who failed were offered salvage treatment available through the MOPH program. Other treatments such as vaccination and opportunistic infection prophylaxis were offered according to the standard of care in Thailand. Formula was offered free of charge from birth to at least 12 months of age. The study was integrated into the routine HIV care performed at these 7 hospitals in Thailand without other incentives, with the exception of the antiretroviral drugs, vaccines and formula.

Analysis of data

The tolerance of the treatment regimen was descriptively analyzed. The outcomes were measured in terms of CD4 lymphocyte percentage gain, and weight and height z-score gain every 4 months. Data of those infants who were lost to follow-up before 12 weeks of treatment were excluded from the analysis. Because of the natural decline of CD4 lymphocyte count with age in young children, CD4 lymphocyte counts may not rise even with clinical improvement. Therefore, CD4 lymphocyte count was not used in the analysis. This study did not intend to compare the treatment outcome of the two regimens, which would require a much larger sample size. The Kaplan-Meier survival analysis was performed for the proportion of patients who were in stable condition without disease progression or death after treatment with the use of two methods. The first was the intention-to-treat (ITT) method, in which all the patients that were lost to follow-up or who were prematurely terminated were counted as a failure. The second was the on-treatment (OT) method, in which the patients who were lost to follow-up or who were prematurely terminated were not counted. The characteristics that might correlate with disease progression or death, including the age at enrollment, baseline CD4 and disease stage, baseline weight and height z-scores, and CD4 gain after 4 and 8 months of treatment, were also analyzed.

Because the clinical and immunological status of HIV-infected infants will variously progress over time without treatment, benefits of the treatment strategy were measured by comparison of disease progression with a group of infants with similar ages and staging who did not receive treatment. A subset of children in this study were age and disease stage-matched at the initiation of treatment, with a ratio of 1:1, with HIV-infected children in a previous long term cohort conducted at 2 study centers, Siriraj Hospital and Queen Sirikit National Institute of Child Health Hospital. This control cohort included children who were born before 1990 and who were generally not given antiretroviral therapy unless they were moderately or severely symptomatic, and the treatment available was either AZT or ddI mono-therapy. Each child was matched only once. There were 37 children with a complete record from the previous cohort who were available for matching. The age of the patient matched was within one month difference, and the stage of disease was initially the same. Using Kaplan-Meier survival analysis, a comparative analysis was performed to evaluate the difference of time from the beginning of treatment of the patient in this study, with equal age in the matched control, to the time of clinical stage change (to a poorer category), or to immunological stage change (to a poorer category), or to death. The numbers of days and episodes of hospitalization during the comparison period were also analyzed.

Results

A total of 107 infants were enrolled in this study. Of these infants, 15 were lost to follow-up within 12 weeks of treatment (7 received AZT + 3TC, and 8 received AZT + ddI). These children were excluded from analysis. Additionally, there were 4 children who
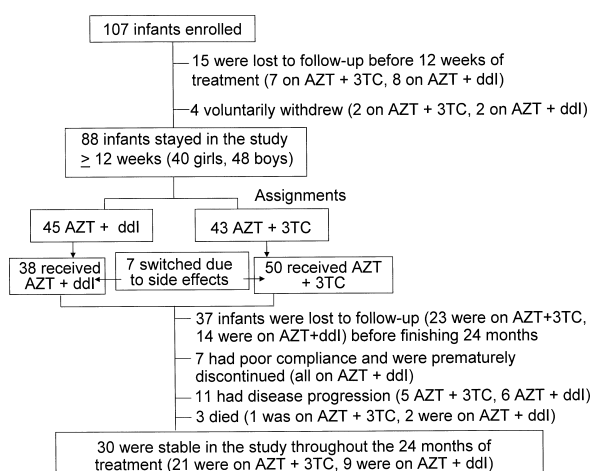

Fig. 1 The Diagram of the study patients

voluntarily withdrew soon after enrollment due to: (1) hepatitis and hemolysis of an unknown cause (receiving AZT + ddI for one month), (2) persistent vomiting probably from the treatment (soon after receiving AZT + 3TC), (3) thrombocytopenia of an unknown cause (receiving AZT+3TC for one month), and (4) a family who decided that they were unable to adhere to the treat-

Table 1. Drop-out and end-point events during 24 months of treatment

Events	0-4	5-8	9-12	13-16	17-20	21-24	Total
	------------------------Months------------------						
Premature disconfirmation from:							
Lost to follow up	4	6	6	9	7	5	37 (42%)
Poor adherence	5	-	1	1	-	-	7 (8%)
Disease progression	1	4	2	-	3	1	11 (12%)
Death	1	2	-	-	-	-	3 (3.4%)
Total	11	12	9	10	10	6	58 (66%)

ment (receiving AZT + ddI). Eighty-eight children remained in the study for at least 12 weeks of treatment with at least one follow-up blood draw after treatment (Fig. 1).

Of the 88 infants, 40 were girls and 48 were boys. 45 were assigned to receive AZT + ddI and 43 were assigned to receive AZT + 3TC. Seven children who were assigned to AZT + ddI were unable to tolerate ddI because of vomiting or diarrhea, and were switched to AZT + 3TC without problems. None of the children receiving 3TC needed to switch to ddI. There were no serious adverse events in these 88 children.

At enrollment, the mean age was 6.81 (SD = 3.68) months and the clinical stages were: 20 (23%) in clinical category N, 38 (43%) in category A, 30 (34%) in category B, and 4 (5%) in category C. The mean CD4 lymphocyte count at enrollment was 1,538 (SD = 985) cells/mm^3 and a mean CD4 lymphocyte percentage was 21.4% (SD = 7.8). Fifteen children (18%) had a baseline CD4 lymphocyte percentage of less than 15%. During the study period 3 children (3.4%) died from pneumonia (2), and sepsis (1). Their durations of treatment before death were 4, 6, and 6 months, and their disease stages at enrollment were A2, B2 and B2 respectively.

There were 37 infants (42%) lost to follow-up before reaching an end-point and before finishing 24 months of the study (23 receiving AZT + 3TC, 14 receiving AZT + ddI) as shown in Table 1. Seven infants (8%) were found to miss many doses of their medication, mostly within the first 4 months of treatment, and their families decided to prematurely discontinue their participation after counseling. All of
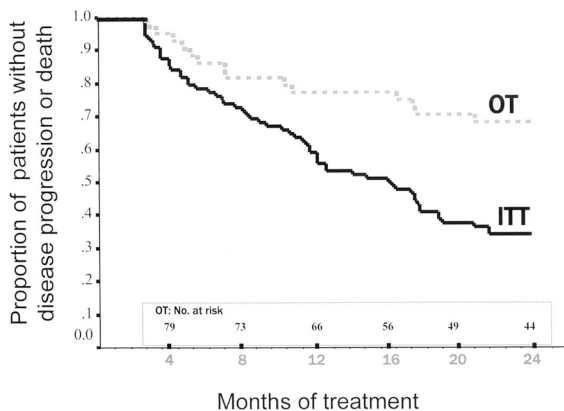
them were receiving AZT + ddI. Eleven children (12%), (5 receiving AZT + 3TC, 6 receiving AZT + ddI) had disease progression before finishing 24 months of treatment (Table 1). At 24 months of treatment 30 children (34%) remained in stable condition with the same or improved status compared with that at enrollment (21 were receiving AZT + 3TC and 9 were receiving AZT + ddI). The group of children who remained stable at 24 months was significantly older at enrollment than those who had disease progression or death (7.53 vs 4.5 months, p=0.005), and tended to gain more CD4 lymphocyte percentage at 4 months of treatment (mean gain = 4.67% vs 0.98%, p=0.29). The proportion of patients in the study without disease progression or death over the treatment period by ITT analysis and OT analysis are shown in Fig. 2, with the
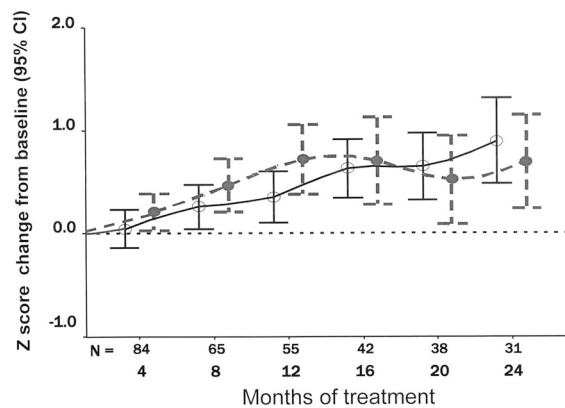

Fig. 3　Change of z-score of height (solid line) and weight (dashed line) for age after treatment

Fig. 2　Kaplan-Meier plot of patients without disease progression or death after AZT + 3TC or AZT + ddl therapy analyzed by intention-to-treat method (solid line) and on-treatment method (dashed line)

probability of 34% by ITT and 68% by OT at 24 months of treatment. Due to the high rate of infants lost to follow-up, a comparison analyses was performed between the 37 children who were lost to follow-up and the 30 children who were stable through the 24 months of treatment. There were no significant differences in age, disease staging, or weight and height z-scores at enrollment.

The effect of treatment on weight and height is demonstrated in Fig. 3. The increased z-scores of weight and height were clearly seen after 4 months of treatment. At 24 months of treatment, the mean changes from the baseline z-scores of weight and height were +0.89 and +0.69. The CD4 lymphocyte percentage was found to increase from the baseline at the 4th month of
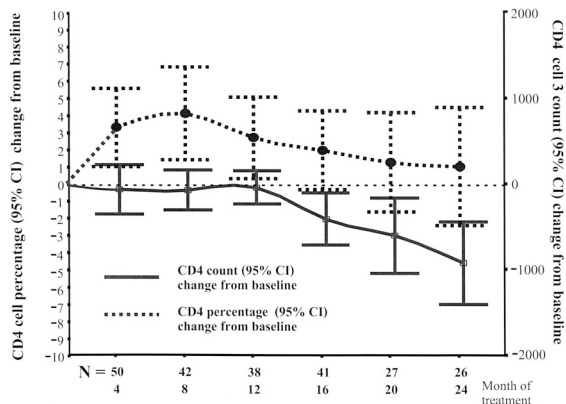
Fig. 4 Change from baseline in CD4 cell count (solid line) and percentage (dashed line) after treatment

treatment and reached its peak of mean increment of 4.19% at the 8th month of treatment, before slowly decreasing thereafter. At 24 months of treatment, the CD4 lymphocyte percentage was 1.08% above the level at enrollment. The CD4 lymphocyte count was stable up to 12 months of treatment and gradually dropped thereafter (Fig. 4).

In the matched-pair analysis, the duration of comparative analysis was 777 days. Of the 37 children in the previous cohort, 3 had antiretroviral treatment initiated before 12 months of age and 9 initiated treatment at 13-24 months of age. The antiretroviral medication used was either AZT or ddI monotherapy. The
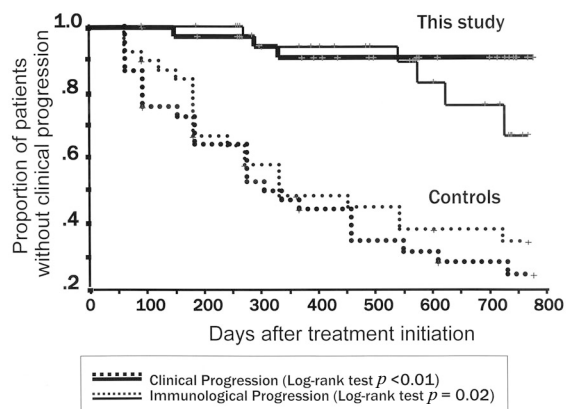

Fig. 5 Kaplan-Meier plots of 37 matched pairs without clinical and immunological progression between this cohort (solid lines) and the historical cohort (dashed lines). The immunological progression was presented in thin solid and dashed lines, and the clinical progression was presented in thick solid and dashed lines. The Log-rank tests were between this study cohort and the historical cohort.

median age at the start of matched-pair analysis was 6 months, with 21 pairs starting before 6 months of age. The mean CD4 lymphocyte count at the start showed no statistical difference (1,939 cells/mm^3 in this cohort vs. 2074 cells/mm^3 in the previous cohort, p=0.55). There were 2 deaths in this cohort compared with 6 in the previous cohort (p=0.19). There were more children in the previous cohort who developed clinical progression (26 vs. 3, p<0.01) and immunological progression (26 vs. 6, p=0.02) than in this cohort (Fig 5). There were more episodes, number of days, and a higher rate of hospitalization in the previous cohort compared to this cohort (37 vs. 9 episodes, 379 vs. 80 hospitalization days, and 7.661 vs. 4.286 hospitalization days per 1000 child-days).

Of the 32 children who were stable at the end of the study, 6 children were lost to follow-up soon after the study ended, 2 children had changed the regimen to HAART within 6 months, and 24 were still on the dual regimen with stable condition for at least 2 years.

Discussion

ART during infancy protects the immature immune system of the infants. It is expected that the outcome of early initiation of ARV in infants would result in benefits similar to treatment in adults with primary infection, in which the studies have confirmed clinical, immunological, and virological benefits[18-19]. Limited studies also supported the benefit of antiretroviral treatment in infants[6, 20]. Younger age of initiation of treatment correlates with the magnitude of recovery of naïve CD4 lymphocyte counts[21]. This could completely change the course of the disease in these patients. However, long-term medical treatment in infants is complicated. Adherence to treatment could be problematic in the chaotic atmosphere often found within HIV-infected families. Long-term therapy may also bring a higher incidence of adverse effects such as metabolic problems, osteopenia and mitochondrial dysfunction. Finally, the cost of treatment can be a significant barrier. Therefore, the benefits of treating these infants, especially those who are asymptomatic or mildly symptomatic, must be weighed against the risks of the aforementioned potential problems.

HAART, including two NRTI plus one PI or nevirapine (NVP), is generally recommended as the initial regimen in infants [13-15]. However, the available PI for infants, ritonavir (RTV), lopinavir/ritonavir (LPV/r), or nelfinavir (NFV), are mostly unaffordable in settings with limited resources. They are not palatable and fre-

quently cause gastrointestinal side effects. Nevirapine is less expensive and may be locally produced, but may cause significant adverse events including hepatitis and rashes in 15-20%. Dual NRTI regimens might be an option for those who are unable to take PI or NNRTI when the benefits outweigh the risks of sub-optimal viral suppression and risk of treatment failure from development of resistance.

Dual NRTI regimens are less potent and may result in failure more quickly than triple regimens [16, 22-24]. The clinical and immunological benefits of dual NRTI regimens have been clearly demonstrated in many pediatric studies [1, 2, 25, 26]. The relative magnitude of benefits if treatment is started in infancy with less advance disease stages, however, has not been well determined. A population-based study in Italy has found limited benefits of dual NRTI in the reduction of mortality in treated children [12], however, about half of the children in that study were in advanced stages of HIV and the median age of treatment initiation was 2.1 years.

In the settings where HAART regimens were very limited available, such as the situation during the study period in Thailand, it is still not established whether or not to delay treatment in HIV-infected infants. The authors of this study hypothesize that initiation of ARV in the early stages of HIV disease in infants, even with dual NRTI, may prolong the healthy period and reduce unnecessary mortality and morbidity. It may be more appropriate to initiate early dual NRTI therapy, rather than to delay treatment while the disease quickly progresses in infants [9, 27, 28].

This study demonstrated that implementation of ARV in infants in a developing country is challenging. Because the patients participated in operational research, they were treated in routine service, without other incentives more than the free ARV, vaccines and formula. This approach is more likely to simulate actual situations than with most clinical trials. About half of the infants were lost to follow-up. This drop out rate is markedly higher than with the routine service in older children at Siriraj Hospital, in which the rate has been less than 10% per year. From patient interviews, it was found that most of the infants lost to follow-up had been relocated, to be taken care of by their grandparents outside of Bangkok. The parents opted to return to work as their infants appeared healthy and the pressure to return for follow-up appointments seemed to decrease. Approximately 80% of the HIV-infected patients hometowns in this study are outside of Bangkok.

The data from this study suggested that the clinical benefits on growth of dual NRTI in infants are not different from that found in the cohorts of older children [1, 25]. In this study, the CD4 lymphocyte percentage gain from baseline peaked of 4.19% at 8 months of treatment, similar to the PENTA-4 trial [25, 31] that found a gain of 3% at 24 months, after adding 3TC into the stable regimens of mono or dual NRTI. We found that the CD4 lymphocyte percentage gain no longer persisted in most children at 24 months of treatment.

In the comparative analysis with the previous cohort before 1990, in which only monotherapy was given in very few infants, the dual NRTI performed in this study reduced disease progression and hospitalization up to 24 months. The mortality in this study was also less, although did not reach statistical significance. Previous studies without treatment found a mortality rate of 9% in Italy [28] in the 1st year of life, and 45% at the 2nd year of life in Rwanda [9]. The rate of 3 (3.4%) deaths during 2 years of treatment in this study is lower than in these other studies. This study confirmed the clinical and immunological benefits of dual NRTI regimens, although with limited duration. By ITT analysis, only 34% of children were stable at 24 months of treatment.

A previous study suggested that AZT + 3TC is more efficacious than AZT + ddI [32]. It was found in this study that 3TC is better tolerated than ddI. All of the children who prematurely discontinued the study, because of poor adherence, were receiving AZT + ddI.

In conclusion, this study has demonstrated limited benefit of dual NRTI regimens in infants, and revealed that initiation of treatment in HIV-infected infants in less advanced disease stages is usually not feasible due to the high rate of lost to follow-up. Currently, NNRTI-based HAART is widely available in Thailand, precluding the need to use dual NRTI regimens. Implementing regimens of HAART in infants with a potentially high drop-out rate, will result in an even more impact from viral resistance than dual NRTI regimens. Attempts with other measures, such as providing social workers to stay in close contact with the family, home visits, free transportation and parent-education, should be corporate in the treatment strategy.

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การเริ่มรักษาเด็กที่ติดเชื้อเอชไอวี โดยใช้ยานูคลิโอไซด์ รีเวอร์สทรานสคริปเตส 2 ตัว ในที่ที่มีทรัพยากรจำกัด: การศึกษาในหลายสถาบันในประเทศไทย

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ทวี โชติพิทยสุนนท์, ปิยาภรณ์ บวรกีรติขจร, ฤดีวิไล สามโกเศศ, อุไรวรรณ ตะรุโรทัย, เสน่ห์ เจียสกุล

วัตถุประสงค์: เพื่อประเมินความเป็นไปได้ ประสิทธิภาพ และผลลัพธ์ของการใช้ยาต้านไวรัสเอชไอวีชนิดนูคลิโอไซด์ รีเวอร์สทรานสคริปเตส 2 ตัว ในการเริ่มรักษาเด็กติดเชื้อเอชไอวี อายุต่ำกว่า 1 ปี ที่มีอาการน้อย หรือปานกลาง ในช่วงที่มียาต้านไวรัสจำกัด

วัสดุและวิธีการ: เป็นการศึกษาร่วมจากหลายสถาบัน ในปี พ.ศ 2541-2543 ชนิดไปข้างหน้าแบบเปิดเผย ซึ่งทำควบคู่ไปกับการปฏิบัติงานตามปกติในการดูแลผู้ป่วย เด็กอายุต่ำกว่า 1 ปี ที่ติดเชื้อเอชไอวีจะได้รับเข้าร่วมโครงการศึกษาโดยให้ยาไซโดวูดีน (AZT) ร่วมกับลามิวูดีน (3TC) หรือ AZT ร่วมกับไดแดนโนซีน (ddI) นาน 24 เดือน เด็กที่มีอาการหนักอยู่ในระยะสุดท้ายของโรค (C3) จะถูกคัดออก

ผลการศึกษา: ในจำนวนเด็ก 88 รายที่เข้าศึกษา เริ่มได้รับยาต้านไวรัสเมื่ออายุเฉลี่ย 6-8 เดือน และมีค่ามัธยฐานของระดับเซลล์ CD4 เท่ากับ 1538 เซลล์/ลบ.มม.(ร้อยละของ CD4 เท่ากับ 21.44) หลังจากได้รับยานาน 4-8 เดือน พบว่าค่า ซี-สกอร์ (z-score) ของน้ำหนัก และความสูงมีค่ามากขึ้นกว่าจุดเริ่มต้น +0.89 และ + 0.69 ตามลำดับ ระดับเซลล์ CD4 เพิ่มขึ้นสูงสุดหลังรักษาได้ 8 เดือน โดยมีค่าเฉลี่ยของร้อยละ CD4 ที่เพิ่มขึ้นเท่ากับ 4.19 หลังจากนั้น ค่าร้อยละของ CD4 ค่อยๆ ลดลงจนเมื่อเดือนที่ 24 ของการรักษามีค่าเฉลี่ยสูงกว่าจุดเริ่มต้นเท่ากับ 1.08 มีเด็ก 3 คน (ร้อยละ 3.4) เสียชีวิต, เด็ก 11 คน (ร้อยละ 12) มีการดำเนินโรคเลวลง, เด็ก 7 คน (ร้อยละ 8) หยุดยาก่อนเดือนที่ 24 เพราะไม่กินยาต่อเนื่อง และเด็ก 37 คน (ร้อยละ 42) ไม่มาติดตามรักษาต่อเนื่อง เมื่อวิเคราะห์ผลลัพธ์ ณ เดือนที่ 24 มีเด็ก 30 คน ยังอยู่ในสภาวะที่ดี นับว่าสูตรยา 2 ตัว ทำให้ร้อยละ 34 และ ร้อยละ68 ของเด็กมีอาการ และระดับ CD4 อยู่ในสภาวะดี โดยวิเคราะห์แบบ intention-to-treat และแบบ on-treatment analysis ตามลำดับ

สรุป: ยาสูตรนูคลิโอไซด์ รีเวอร์สทรานสคริปเตส 2 ตัว มีประโยชน์ทั้งด้านอาการและระดับ CD4 แต่เพียงช่วงจำกัด อย่างไรก็ดี การศึกษานี้แสดงให้เห็นว่าการรักษาด้วยยาต้านไวรัสในเด็กเล็กที่ยังมีอาการไม่มาก อาจทำไม่ได้ เพราะมีเด็กที่ไม่มาติดตามรักษาต่อเนื่องค่อนข้างมาก