Multi-Drug Resistant HIV-1 Reverse Transcriptase Genotype in Children Treated with Dual Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

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Background: *Multi-drug resistant HIV mutants have been reported after prolonged dual antiretroviral therapy.*
Objective: *To evaluate the prevalence and resistance pattern in HIV-infected children treated with dual NRTIs.*
Material and Method: *Records of HIV-infected children treated with dual NRTIs at Srinagarind Hospital, Khon Kaen University, Thailand, were reviewed for baseline data and their consensually-stored plasma were checked for the occurrence of HIV mutants by genotyping.*
Results: *Fifty-seven HIV-infected children were treated with dual NRTI regimens (27 males; 30 females). The median age and median CD4+ T-lymphocyte at genotypic testing were 83.5 months and 10.9%, respectively. The median duration of ARV therapy was 22 months. More than half the children (42) were on zidovudine and didanosine. A set of three or more nucleoside analog mutations (NAMs), conferring multi-dideoxynucleoside resistance, was found in 60% of the cases.*
Conclusion: *High percentages of NAMs were found in HIV-infected children previously on dual ARV therapy for long periods. Genotypic testing was helpful in designing the second antiretroviral regimen.*

Keywords: *HIV, Children, Drug resistance*

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The guideline for antiretroviral agents in pediatric HIV infection is a triple combination including two nucleoside reverse transcriptase inhibitors (NRTI) and one of the non-nucleoside reverse transcriptase inhibitors (NNTRI) or protease inhibitors (PI)[1]. The combination therapy, especially the protease inhibitor agents, is expensive, and most HIV-infected patients in developing countries cannot afford it.

Dual NRTI therapy had been used for HIV-infected patients in Thailand a few years ago. The combination of zidovudine (ZDV) or stavudine (d4T) plus didanosine (ddI) was safe, well-tolerated, and produced clinical, immunological, and virological responses in children[2-4]. The dual NRTI therapy is inexpensive; however, it does not result in sustained viral suppression and may result in the development of viral resistance after prolonged use[5].

Multi-drug resistant HIV mutants to NRTIs, such as a set of nucleoside analog mutations (NAMs) or Q151M, were observed after prolonged NRTI therapy[6-9]**.** These HIV mutants are resistant to most of the NRTIs, which obviates selection of an alternate antiretroviral regimen after therapeutic failure. Thus, resistance testing is advised when designing the second regimen.

The authors examined the resistance profiles in HIV-infected children using genotyping. The authors aimed to ascertain the prevalence of HIV mutants and

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the magnitude of resistance problems in the dual NRTI therapy in children, and how to design an effective second regimen.

Material and Method

Patients

The records of HIV-infected children treated with dual NRTI at Srinagarind Hospital, Khon Kaen University, from May 1998 to July 2003 were reviewed. Genotyping was checked from stored plasma samples for the occurrence of HIV mutants. Baseline data included age at ARV treatment, CD4 lymphocyte percentage at entry and at the time of genotyping, and the initial and last ARV regimens were recorded.

HIV genotyping

Viral RNA was isolated from stored plasma using the QIAamp viral extraction kit (Qiagen Inc., Chatsworth, California, USA). The TRUEGENE HIV-1 Genotyping Assay was used in conjunction with the Open Gene automated DNA sequencing system (Visible Genetics Inc., Toronto, Canada) to sequence the protease and RT regions of HIV-1 cDNA.

Tests involved simultaneous clip sequencing of protease and codons 35 to 244 of RT from amplified cDNA in both the 3′ and 5′ directions. Sequences were aligned and compared with a lymphoadenopathy-associated virus type 1 (HIV-B-LAV1) and consensus sequence using the Visible Genetics Gene Librarian software. Interpretation of genotypes in terms of drug-resistance was based on the Guide Lines T 6.0 Rules, approved by the US FDA.

Determination of CD4+ /CD8+T lymphocyte subset from whole blood

Three-color immunofluorescence staining was performed according to Pattanapanyasat et al[10] with some modification. All panels of fluorochrome conjugated monoclonal antibodies were purchased from Becton Dickinson. Stained samples were analyzed using FacsVantage Flow Cytometer (Becton Dickinson, San Jose, CA). Data were acquired with CellQuest software (Becton Dickinson, San Jose, CA). Instrument setting and three-color compensation were performed prior to running the samples, using CaliBRITE 3 beads (Becton Dickinson, San Jose, CA). A p-value of less than 0.05 was considered significant.

Results

Of the 61 HIV-infected children treated with dual NRTIs, 57 were tested for genotypic resistance (27 males; 30 females). Four plasma samples could not be amplified. Vertical transmission was the major infective route in 56 cases (98%), followed by one case (2%) from blood transfusion. The median age at the start of ARV and at genotypic testing was 63.1 and 83.5 months, respectively.

The median CD4 T-lymphocyte percentages at baseline and at genotyping were 6.2 and 10.9 percent, respectively and the median duration of ARV therapy

Table 1. Baseline clinical immunology of the 57 HIV-infected children

Characteristic	N = 57	
Sex (M/F)	27/30	
Duration of ARV exposure, months		
Mean ± SD	24.9 ± 4.1	
Median (range)	22.0 (8.5-53.7)	
	At ARV initiation	At genotyping
Age, months		
Mean ± SD	61.0 ± 26.4	85.9 ± 25.6
Median (range)	63.1 (4.6-137.4)	83.5 (27.2-163.6)
CD4+ T-lymphocyte		
Absolute, cells/cu mm		
Mean ± SD	285.6 ± 255.7	358.1 ± 291.3
Median (range)	169.0 (1.0-1,278.1)	252.0 (10.2-1,326)
Percentage, %		
Mean ± SD	9.2 ± 7.3	11.1 ± 7.3
Median (range)	6.2 (0.1-29.5)	10.9 (0.4-35.0)

Table 2. The antiretroviral regimen at the start and time of genotypic assay

ARV regimen	Number of patients (%)	
	At starting	At genotyping
ZDV + ddI	42 (73.7)	33 (57.9)
d4T + ddI	9 (15.8)	12 (21.1)
ZDV + 3TC	5 (8.8)	6 (10.5)
3TC + d4T	1 (1.8)	3 (5.3)
ddI + 3TC	0	1 (1.8)
d4T + 3TC + EFV	0	1 (1.8)
ddI + d4T + EFV	0	1 (1.8)
Total	57 (100)	57 (100)

was 22.0 months (Table 1). All patients underwent an initial ARV regimen with a dual NRTI therapy; mostly ZDV + ddI (42 cases), d4T + ddI (9 cases) (Table 2). The regimens at the time of genotyping were ZDV + ddI (33 cases), d4T + ddI (12 cases) (Table 2).

Genotyping showed that the 56 plasma samples (98%) had at least one NRTI mutation. One child had no mutations despite immunological failure. Mutations conferring resistance to ZDV such as M41L, D67N, K70R, T215F, T215Y, K219Q, L210W, T69D were found in 49.1, 73.7, 50.9, 35.1, 43.9, 45.6, 33.3, and 7.0 percent, respectively. Fifty patients (88.7%) had developed at least one NAM. The NAMs set of the combination of mutations in the RT gene (*i.e.* M41L, D67N, K70R, L210W, T215F, T215Y, K219Q, E44D, and V118I) were common and sets of more than three NAMs were found in 59.6% (Fig. 1). Notwithstanding, the Q151M mutant, one of the multidideoxynucleoside-resistant HIVs, was not detected. M184V, and/or M184I were found in nine patients and all of them had undergone lamivudine (3TC) therapy.

The NNRTI resistance mutations in the RT

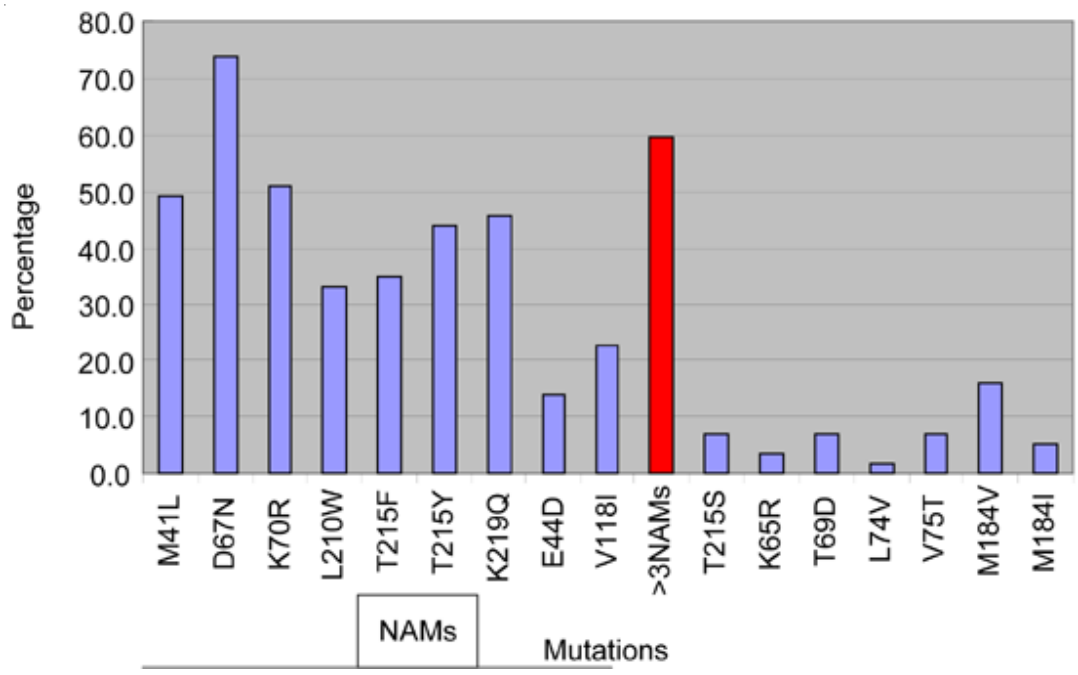

Fig. 1 NRTI mutations detected in the 56 children after dual NRTI therapy

Table 3. The number of NAMs and duration of therapy and immunological status

	3 NAMs or less	Over 3 NAMs	p-value
Duration of NRTI therapy	18.9 ± 9.1	27.9 ± 11.7	0.005
At baseline			
Absolute CD4	213 ± 337	322 ± 290	0.224
CD4 percentage	6.8 ± 7.7	10.4 ± 8.9	0.148
At genotyping			
Absolute CD4	398 ± 334	337 ± 353	0.535
CD4 percentage	10.6 ± 8.7	11.3 ± 9.1	0.803

codons, A98G, L100I, K103N, V108I, V179D, and Y188L, were found in 13 children. Single NNRTI mutation such as A98G, G190A, V108I, V179D or Y188L, was detected in 4, 4, 1, 1 and 1 NNRTI-na ve patients respectively. Each of the multiple NNRTI mutations (*i.e.* A98G + G190A and A98G + L100I + K103N) was found in nevirapine- and efavirenz-experienced patients, respectively.

Based on classification of 3-NAMs-or-less or over-3-NAMs, the authors found a significantly longer ARV exposure in the over-3-NAMs group (27.9 ± 11.7) than the 3-NAMs-or-less group (18.9 ± 9.1) (Table 3). However, there was no statistically significant difference among the number of mutations and the CD4 at the start of ARV or at genotyping (Table 3).

Discussion

Prevalence of NRTI mutations

The authors described the analysis of HIV-1 drug resistance mutations among 57 HIV-infected children; most presented late and had severe immunologic suppression at the start of ARV therapy (Table 1). The plasma viral load could not be checked in the present study due to limitation of resources. However, the authors assumed their plasma viral RNA was high due to their immunological failure.

The initial ARV regimen in most of these children was ZDV plus ddI. The dual NRTI therapy could suppress the virus at between 0.8 and 1.4 log10 but was insufficiently potent to suppress HIV to an undetectable level[11,12]. Therefore, though the dual therapy may be beneficial at an early stage of therapy, its potential for long term success is unlikely in patients with a higher viral load or advanced disease[4,8,11], as was the case in the presented children.

In general, ZDV and/or ddI-resistant HIV mutants usually develop after 6 to 12 months of therapy, the longer the exposure to ARV, the greater the frequency of resistance[13]. The presented children were on prolonged exposure to dual NRTIs due to the lack of alternative drugs at that time. All told, the use of less potent regimens, the severe immunological suppression at the time of treatment, and the long exposure to ARV, resulted in less potential to suppress the plasma HIV-RNA to an undetectable level, thereby giving the HIV occasion to develop drug resistant mutants.

The present study had a high percentage of NRTI mutants, especially more than 3NAMs (59.6%), similar to a study done in HIV-infected Thai adults and children[5,14]. The unavailability of a potent ARV and protease inhibitor, and the assiduous virological monitoring, might account for this phenomenon.

As *per* the *in vitro* and *in vivo* data, HIV developed more mutations under prolonged drug pressure[15] and the additional mutations made the HIV more resistant or 'fit'[15,16]. Changing to a more potent ARV early and correctly after virologic failure would reduce the opportunity for HIV to develop more mutations and enhance the duration of therapeutic benefit[17]. The presented patients were on prolonged dual therapy; median 22 months, which allowed HIV mutants to accumulate. Interestingly, the L74V mutation was found in only one child. This mutation is common in patients who were on ddI monotherapy[5,18-20] but uncommon in the ddI group of patients on combination therapy with ZDV or d4T[5,6], as was the case in the presented children.

The development of the E44D/A and V118I mutations conferred moderate lamivudine-resistance; that is, in the presence of the zidovudine-resistance mutation, and was strongly associated with M41L, D67N, L210W and T215Y[21,22]. Thymidine analogues (*i.e.* ZDV & d4T) and didanosine, but not lamivudine, could promote the development of these mutations[23]. Similarly, the authors found these mutations in the presented children with ZDV/d4T + ddI therapy, but not in those treated with 3TC (data not shown). The occurrence of E44D/A and V118I mutations with sets

of NAMs made these mutants resistant to ZDV, d4T, ddI and possibly 3TC.

In the presented NNRTI-na ve children, the prevalence of primary NNRTI-associated mutations in HIV-1 was 11/54(20%). Causes of NNRTI mutation might be explained from the NNRTI exposure or from the spontaneous mutation. The unrecognized NNRTI exposure was unlikely due to the unavailability of NNRTI use in children both for treatment or prevention of mother to child transmission. Therefore, the spontaneous mutation was the most likely explanation. Ninety-eight percent (56/57) of the presented patients had HIV-1 subtype AE infection. This primary NNRTI resistance mutation in the present study valued between subtype B (9.3%) and subtype C (33.1%)[24]. Although, RT substitutions at positions involved in NNRTI resistance were not associated with a significantly worse virologic outcome in NNRTI-treated patients[25], clinicians should be very cautious when using the NNRTI-based regime in this situation.

The importance of this finding

Heterogeneity exists among individual virologic responses to the zidovudine and didanosine combination therapy[26]. Cross-resistance between nucleoside analogues[27] deserves maximal attention to ensure optimal antiretroviral therapy and design algorithms for antiretroviral management based on genotypic antiretroviral resistance testing[7].

The second regimen must be carefully selected for patients who have experienced ZDV or d4T plus ddI failure. Of the NAMs, more than three in the present study, most of the NRTIs (*i.e.* ZDV, ddI, or d4T) lost their activities against these mutants so that the only effective NRTI left was 3TC, presuming no additional mutations (*i.e.* E44D or V118I) occur. The strategy of changing ARV regimen after treatment failure by choosing two new NRTIs and one NNRTI without doing resistance testing after the ZDV or d4T plus ddI failures is shortsighted. If multi-dideoxynucleoside mutants (> 3 NAMs) occur at a high percentage as in the present study, the second regimen with 2 new NRTIs and 1 NNRTI may have only 1 or 2 effective antiretroviral drug(s) (*i.e.* NNRTI and/or 3TC) resulting in a mono- or dual therapy, again. Moreover, the new drugs in the second regimen, 3TC and NNRTIs (*i.e.* efavirenz or nevirapine), have a low genetic barrier and HIV can rapidly develop resistance after only a single mutation[28,29].

The NNRTI mutations caused a cross resistance to the rest of the drugs in this group[30]. Patients might have clinical and immunological benefits from this ineffective second regimen for a short time, but would eventually experience therapeutic failure[31] as the HIV mutates. Using this strategy, the authors shall lose all antiretroviral drugs from both the NRTI and NNRTI classes.

Another approach without the genotyping is to design the second effective regimen using a PI-based regimen (*i.e.* 2 boosted PIs or 3TC + NNRTI + one PI). Even though the PI-containing regimen is effective for these children[32], it is expensive and beyond the means of most patients in developing countries. Therefore, the use of genotypic resistance testing in dual NRTI failure may prove beneficial and could help with the design of less expensive but effective regimens. In cases of no multi-NRTI resistant mutants, the authors may be able to use PI-sparing regimens (i.e. 2 new NRTIs and one NNRTI), that are less expensive and more cost effective in developing countries.

The present study was performed retrospectively from the storage plasma. Due to the lack of virological monitoring in the present study, the authors could use only immunological and clinical parameter to monitor the response of the antiretroviral therapy. The prevalence of drug resistance in the present study could represent the real situation in clinical practice at that period in the lack of virological and other antiretroviral drugs. The authors could not demonstrate the timing when mutation developed after initiation of antiretroviral treatment. To answer this question, the authors need to trace back to every storage plasma to check HIV-RNA and mutation that can be done in the future when the resource is available.

Conclusion

Several important observations were made in the present study. First, high percentages of NAMs were found in HIV-infected children on long-duration, dual NRTI therapy. Second, genotypic, antiretroviral drug testing should be considered for the design of better drug regimens to improve the management of dual NRTI failure in children. Third, the ARV regimen should be selected carefully as two new NRTIs with one NNRTI might not be a good choice without genotypic results.

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รูปแบบการดื้อยาต้านไวรัสหลายขนานในเด็กติดเชื้อเอชไอวีที่ได้รับยาต้านไวรัสสองชนิด

จุฬาพรรณ อิ้งจะนิล, ภพ โกศลารักษ์, วีระพงศ์ ลุลิตานนท์, ผกากรอง ลุมพิกานนท์, วสันต์ จันทราทิตย์

บทนำ: *เชื้อเอชไอวีสามารถเกิดการดื้อยาต้านไวรัสหลายชนิดได้ โดยเฉพาะในคนที่ได้รับการรักษาด้วยยากลุ่ม nucleoside reverse transcriptase (NRTI) เป็นเวลานาน*

วัตถุประสงค์: *เพื่อประเมินความชุกและรูปแบบการดื้อยาที่เกิดขึ้นในเด็กที่ได้รับการรักษาด้วยยาต้านไวรัสกลุ่ม NRTI 2 ชนิด*

วัสดุและวิธีการ: *ทำการเก็บข้อมูลพื้นฐานและข้อมูลการรักษาจากเวชระเบียน และนำเลือดที่เก็บไว้มาตรวจรูปแบบของการดื้อยาโดยวิธี genotypic assay*

ผลการศึกษา: *พบมีเด็กติดเชื้อเอชไอวีที่ได้รับการรักษาด้วยยาต้านไวรัสในกลุ่ม NRTI 2 ชนิด ในโรงพยาบาลศรีนครินทร์ จำนวน 57 ราย เป็นเพศชาย 27 รายและเพศหญิง 30 ราย มัธยฐานอายุเมื่อตรวจ genotype คือ 83.5 เดือน มัธยฐานร้อยละของ CD4+ T-lymphocyte เมื่อตรวจ genotype คือ 10.9 และมัธยฐานระยะเวลาที่ได้รับยาต้านไวรัสคือ 22 เดือน โดยได้รับยา zidovudine และ didanosine เป็นส่วนใหญ่ พบการกลายพันธุ์ที่ก่อให้เกิดการดื้อยาหลายชนิด (nucleoside analog mutations, NAMs) ร้อยละ 60*

สรุป: *การศึกษานี้พบมีความชุกของการเกิด NAMs สูงในเด็กที่ได้รับยาต้านไวรัสกลุ่ม NRTI 2 ชนิด เป็นระยะเวลานาน การตรวจหารูปแบบการดื้อยา (genotypic assay) จะช่วยแพทย์ในการเลือกยาต้านไวรัสที่มีประสิทธิภาพสูตรยาต่อไป*