Journal of Virus Eradication 2015; **1**: 192–195

The long-term outcomes of antiretroviral treatment initiated with mono or dual nucleoside reverse transcriptase inhibitors in HIV-1-infected children: an Asian observational study

Orasri Wittawatmongkol[1], Thahira J Mohamed[2], Thoa PK Le[3], Vibol Ung[4], Alan Maleesatharn[1], Rawiwan Hansudewechakul[5] Lam V Nguyen[6], Nagalingeswaran Kumarasamy[7], Pagakrong Lumbiganon[8], Tavitiya Sudjaritruk[9], Torsak Bunupuradah[10] Nik KN Yusoff[11], Nia Kurniati[12], Moy S. Fong[13], Revathy Nallusamy[14], Azar Kariminia[15], Annette H. Sohn[16] Kulkanya Chokephaibulkit[1]; for the TREAT Asia Pediatric HIV Observational Database

[1]Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2]Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [3]Children's Hospital 1, Ho Chi Minh City, Vietnam
[4]University of Health Sciences and National Pediatric Hospital, Phnom Penh, Cambodia; [5]Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand
[6]National Hospital of Pediatrics, Hanoi, Vietnam; [7]YRGCARE Medical Centre, CART CRS, Chennai, India
[8]Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[9]Faculty of Medicine and Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand
[10]HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [11]Hospital Raja Perempuan Zainab II, Kelantan, Malaysia
[12]Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; [13]Hospital Likas, Kota Kinabalu, Malaysia; [14]Penang Hospital, Penang, Malaysia
[15]The Kirby Institute, UNSW Australia, Sydney, Australia; [16]TREAT Asia/amfAR —The Foundation for AIDS Research, Bangkok, Thailand

Abstract

After a median of 115.9 months of follow-up, 90% of 206 HIV-1-infected children in a cohort in Asia who initiated antiretroviral treatment (ART) with mono or dual nucleoside reverse transcriptase inhibitors were alive and had comparable immunological and virological outcomes as compared to the 1,915 children who had started with highly active antiretroviral regimens. However, these children had higher rates of treatment-related adverse events, opportunistic infections, and cumulative mortality, and were more likely to require protease inhibitor-containing regimens or other more novel ART–based regimens.

Keywords: dual NRTI regimens, antiretroviral treatment, HIV-infected children, Asia

Introduction

Before the era of highly active antiretroviral therapy (HAART), the use of mono or dual nucleoside reverse transcriptase inhibitor (NRTI) regimens (mono/dual NRTI) was common in HIV-infected children and adults. This was subsequently found to lead to suboptimal virological responses resulting in treatment failure and development of drug resistance [1].

With the availability of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), it was recommended to patients who were receiving mono/dual NRTI to switch to HAART regimens including at least two drug classes. In a previous report of children in the TREAT Asia Pediatric HIV Observational Database (TApHOD), 12% of HIV-infected children in eight Asian countries had started treatment with mono/dual NRTI. After switching to HAART, these children were shown to have an increased risk of virological failure at 12 months of treatment [2]. However, the long-term clinical, immunological and virological outcomes of these children have not been fully described. This study therefore aims to evaluate the long-term outcomes in these Asian children who had initiated treatment with mono/dual NRTI in comparison with those who had started with HAART regimens.

Methods

Data collection and participating sites

TApHOD is a regional database collecting information on demographics, socio-economics, clinical outcomes, laboratory monitoring, treatment and adverse events in HIV-infected children from 16 paediatric centres in six countries in Asia (Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam). Data were collected during the course of routine clinical care and submitted electronically twice a year to the data management and biostatistical analysis centre at the Kirby Institute, University of New South Wales, Sydney, Australia for cleaning and analysis. Standardised quality control interventions have been established to ensure the integrity of data across sites [3].

Data analysis

In this analysis, we have included data from September 1991 to March 2010. HIV-infected children who had initiated antiretroviral therapy (ART) and continued taking their first regimen for at least 6 months were included in the analysis. The outcomes analysed were clinical stage, CD4 T cell count levels, HIV RNA levels (viral load, VL), and growth parameters at multiple time-points: ART initiation, 12, 36 and 60 months of ART, and at the last reported clinic visits. Data collected within a 90-day window period and closest to the target date of each time-point were used.

Growth parameters were assessed using the WHO 2006/2007 Child Growth Standards for height-for-age z scores (HAZ) and the World Health Organization (WHO) 1977 Standards for weight-for-age z scores (WAZ) [4,5]. Treatment switch was defined as changing at least one drug to another class and continuing the new regimen for at least 6 months, after having been on a previous regimen for at least 6 months. Loss to follow–up was defined as an absence of reported clinical data for at least 12 months since the last clinic visit.

We compared differences between children who had started with mono/dual NRTI (mono/dual group) or HAART (HAART group), which included at least two drug classes, at each time-point by using non-parametric statistics (chi-squared test, Fisher's exact test or Mann–Whitney rank sum test as appropriate). We have

*Corresponding author: Kulkanya Chokephaibulkit
Division of Infectious Diseases, Department of Pediatrics
Faculty of Medicine Siriraj Hospital, Mahidol University
Bangkok 10700, Thailand
E-mail: kulkanya.cho@mahidol.ac.th

used Kaplan–Meier curves to compare the rate of opportunistic infections (OIs) and hospitalisations per 1,000 person-months among groups over time, and the cumulative mortality rate. We used STATA version 9.2 (StataCorp LP, College Station, Texas, US) for all statistical analyses. The significance level was set at $P<0.05$.

Results

A total of 2,121 HIV-infected children were included in the analysis. Of these, 206 children initiated treatment with mono/dual NRTI at a median age of 2.1 [interquartile range (IQR) 0.8–4.6] years and 1,915 children were initiated with HAART at a median age of 6.4 (IQR 3.6–9.2) years (Table 1). By March 2010, the median follow-up was 115.9 (IQR 92.2–140.0) months in the mono/dual group and 45.1 (IQR 30.3–63.4) months in the HAART group.

Zidovudine plus lamivudine was the most commonly initiated mono/dual NRTI regimen (41.3%). The most frequently used HAART regimen was NNRTI based (95.1%): mainly stavudine (d4T) plus lamivudine and nevirapine (51.5% of all the patients receiving HAART). d4T was used for more than 6 months in 60.2% of mono/dual NRTI and 69.3% of HAART patients. Children in the mono/dual group had higher rates of regimen switches due to treatment failure than the HAART group: 9% *vs* 1.5% at 12 months of treatment, 37% *vs* 8% at 36 months of treatment, and 60% *vs* 18% at 60 months of treatment ($P<0.001$ at every time-point). The median duration of mono/dual NRTI treatment to the first regimen switch was 42.5 (18.4–68.1) months and at the most recent visit, in March 2010, 79.6% of the mono/dual group had switched to a HAART regimen, the proportions of children receiving PIs being 11.9% in the HAART group and 44.5% in the mono/dual group.

Immunological and virological outcomes

At treatment initiation, 37% of children in the mono/dual group had a CD4 T cell percentage below 15, as compared to 76% in the HAART group ($P<0.001$). In addition, the median CD4 T cell percentage at treatment initiation was higher in the mono/dual group (17.8% *vs* 8%, $P<0.001$), but became comparatively lower at 60 months of treatment (23.9% *vs* 28.0%, $P=0.001$), although there was no difference at the most recent visit (25% *vs* 27%, $P=0.147$).

Children in the mono/dual group had a significantly higher VL than the HAART group at all visits, resulting in treatment switch to HAART over time. At the most recent visit, two children were still on mono/dual regimens. Similarly high proportions of children in both groups achieved VL below 400 copies/mL (78% *vs* 85%, $P=0.27$).

Growth status

At initiation of treatment, children in the HAART group had a lower median WAZ and HAZ than children in the mono/dual group ($P<0.001$; Table 1). After starting treatment, the median WAZ and HAZ in both groups increased. At the end of the follow-up period, the median HAZ of children in the HAART group was persistently lower than children in the mono/dual group ($P=0.016$), but there was no statistical difference in the median WAZ between the groups.

Opportunistic infection and adverse events

The rate of OIs among children in the mono/dual group was significantly higher than those in the HAART group (the rates per 1,000 person-months were 22.0 *vs* 12.9, $P=0.002$, by 12 months of ART; 12.8 *vs* 6.8, $P<0.001$, between 12 and 36 months of ART; and 11.8 *vs* 5.4, $P<0.001$, between 36 and 60 months of ART, respectively. The overall rates of OIs over the follow-up period were 9.9 per 1,000 person-months in the mono/dual group compared to 5.0 per 1,000 person-months in the HAART group ($P<0.001$). Among children in the mono/dual group, 51.9% experienced OIs, whereas only 20.1% of children in the HAART group did. Anaemia, hepatotoxicity, hypersensitivity and clinical lipodystrophy were reported more frequently in children in the mono/dual group than in the HAART group by the 60-month visit and at the end of follow-up. The cumulative mortality rate by the most recent follow-up was higher in the mono/dual group (9.9% *vs* 4.1%, $P=0.004$; Figure 1).

Discussion

Mono/dual NRTI regimens were prescribed for children during the early stages of ART availability, and used more often in referral centres where the antiretroviral drugs were available. Once access to HAART had increased, this practice was abandoned. However, there remains a small subset of mono/dual NRTI-treated adolescents who have experienced a long duration of suboptimal antiretroviral exposure. We have found that children who had started ART with mono/dual NRTI regimens in our cohort had initiated treatment at a younger age and with a higher CD4 T cell count than those who had started later with HAART. This could be related to the limited availability of HAART, meaning that this type of treatment was prioritised for the sicker children who were generally older. The children in the mono/dual group were eventually switched to HAART at a median of 42.5 months of treatment, but 52% experienced OIs and 10% died. For those who had survived at the end of almost 10 years of follow-up for the mono/dual group, and up to almost 4 years of follow-up for the HAART group, children in both groups had similar CD4 T cell count levels and proportions of virological suppression. However, the mono/dual group had a better HAZ from the beginning of treatment to the end of follow–up than the HAART group. Starting ART earlier was associated with higher HAZ than for children initiating HAART later in life and at a more advanced stage of the HIV infection. This finding was in line with the results of the PREDICT study, which found that earlier ART initiation did not affect mortality but had an impact with better preserved growth [6]. Moreover, the mono/dual NRTI group was more likely to receive PI treatment, and experienced more adverse events than the HAART group.

Despite the relatively greater delay in treatment initiation, and the lower baseline CD4 T cell count, children initiated on HAART had less than half the level of OIs and mortality rate. At the end of the follow-up period, there were no significant differences in long-term immunological and virological outcomes among those

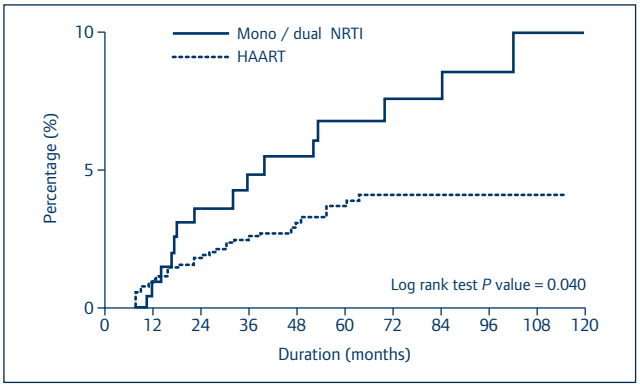

Figure 1. Kaplan–Meier curve of cumulative mortality rates (death as of 31 March 2010) by initial antiretroviral therapy regimen

Table 1. Characteristics and outcomes of children by their initial treatment regimens

Characteristics	*n*	Mono / dual NRTI	*n*	HAART	*P* value
At initiation	*206*		*1915*		
Age (months), median (IQR)		2.1 (0.8–4.6)		6.4 (3.6–9.2)	<0.001
CD4%, median (IQR)	141	17.8 (12.0–23.7)	1533	8 (2.9–14.3)	<0.001
Viral load (copies/mL), median (IQR)	23	543960	704	131890	<0.001
		(247420–1426300)		(38510–500000)	
WAZ, median (IQR)	121	–1.9 (–3.4 to –0.6)	1657	–2.7 (–4.0 to –1.5)	<0.001
HAZ, median (IQR)	115	–1.9 (–2.9 to –0.8)	1544	–2.5 (–3.4 to –1.5)	<0.001
At 12 months	*194*		*1786*		
Age (months), median (IQR)		3.1 (1.8–5.7)		7.4 (4.7–10.1)	<0.001
CD4%, median (IQR)	127	21.0 (13.0–27.5)	1415	21.0 (15.3–27.0)	0.369
Viral load (copies/mL), median (IQR)	23	31100	785	250	<0.001
		(3169–238952)		(50–400)	
WAZ, median (IQR)	125	–1.3 (–2.2 to –0.5)	1553	–1.9 (–2.9 to –1.0)	<0.001
HAZ, median (IQR)	116	-1.5 (-2.3 to -0.6)	1503	-2.2 (-3.0 to -1.3)	<0.001
At 60 months	*135*		*502*		
Age (months), median (IQR)		7.3 (5.8–9.6)		12.1 (10.1–14.8)	<0.001
CD4%, median (IQR)	108	23.9 (16.0–27.9)	415	28.0 (23.2–32.0)	<0.001
Viral load (copies/mL), median (IQR)	37	5790	299	50	<0.001
		(526–29575)		(50–399)	
WAZ, median (IQR)	109	–1.4 (–2.3 to –0.6)	428	–1.7 (–2.5 to –0.9)	0.049
HAZ, median (IQR)	106	–1.4 (-2.1 to –0.6)	420	–1.7 (–2.4 to –0.9)	0.016
Regimen:					
Mono/dual NRTI	50	37.0%	2	0.4%	
NNRTI-based HAART	60	44.5%	398	79.3%	
PI-based/advanced HAART	11	8.2%	59	11.7%	
Other regimens	8	5.9%	18	3.6%	
3TC monotherapy	0	—	0	—	
No ART	6	4.4%	25	5%	
At the end of follow-up	*117*		*1564*		
Age (months), median (IQR)		12.5 (10.5–14.4)		10.5 (7.2–13.5)	<0.001
CD4%, median (IQR)	71	25 (21.6–31.0)	806	27 (22–32)	0.147
Viral load (copies/mL), median (IQR)	41	40 (40–149)	424	250(50–399)	<0.001
WAZ, median (IQR)	100	–1.5 (–2.6 to -0.3)	1333	–1.7 (–2.6 to –0.8)	0.141
HAZ, median (IQR)	99	–1.3 (–2.3 to –0.8)	1293	–1.8 (–2.6 to –1.0)	0.016
Regimen:					
Mono/dual NRTI	2	1.7%	4	0.2%	
NNRTI-based HAART	41	35.1%	1301	83.2%	
PI-based/advanced HAART	52	44.5%	187	11.9%	
Other regimens	20	17.1%	54	3.5%	
3TC monotherapy	1	0.8%	6	0.4%	
No ART	1	0.8%	12	0.8%	
Duration of follow-up (months), median (IQR)	117	115.9	1564	45.1	<0.001
		(92.2–140.0)		(30.3–63.4)	

3TC, lamivudine; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; HAZ, height-for-age z scores; IQR, interquartile range; NNRTI, non–nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; WAZ, weight-for-age z scores

who had survived. Overall, the children who had initiated treatment with mono/dual NRTI and were still in active follow-up had good immunological, virological and growth outcomes, but had more treatment-related complications.

Our study had several limitations. Observational cohort data depend on what is reported by the participating sites and are subject to missing data. The small sample size of the mono/dual NRTI group precluded comparison between the NRTI drug regimens.

In conclusion, children who had started treatment with mono/dual NRTI had higher risks of OIs and mortality compared to those who had initiated treatment with HAART. Those who had survived to be switched to HAART had good long-term immunological, virological and growth outcomes, but experienced more treatment-related adverse effects and were more likely to require PI-containing regimens than those who had started on

HAART. These children are now adolescents, and their treatment experience reflects the legacies of the pre-HAART era. Despite the suboptimal regimens they were started on, these drugs have kept many of them alive until better options became available.

Sources of Funding

The TREAT Asia Pediatric HIV Observational Database is an initiative of TREAT Asia, a program of amfAR, the Foundation for AIDS Research, with support from the US National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Cancer Institute as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; U01AI069907), and the AIDS Life Association. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above.

Acknowledgements

The TREAT Asia Pediatric HIV Network: CV Mean, V Saphonn*, S Sarun;

National Centre for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia: V Ung* , M Pok, Y Kdan, B Chan;

National Pediatric Hospital, Phnom Penh, Cambodia: J Tucker;

New Hope for Cambodian Children, Phnom Penh, Cambodia: FJ Zhang;

Beijing Ditan Hospital, Capital Medical University, Beijing, China: N Kumarasamy*, S Saghayam, E Chandrasekaran;

YRGCARE Medical Centre, CART CRS, Chennai, India: DK Wati*, LPP Atmikasari, IY Malino;

Sanglah Hospital, Udayana University, Bali, Indonesia: N Kurniati*, D Muktiarti;

Cipto Mangunkusumo General Hospital, Jakarta, Indonesia: SM Fong*, M Thien, M Lim, F Daut;

Hospital Likas, Kota Kinabalu, Malaysia: Nik KN Yusoff*, P Mohamad;

Hospital Raja Perempuan Zainab II, Kelantan, Malaysia: KA Razali*, TJ Mohamed, NF Abdul Rahman, NADR Mohammed;

Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia: R Nallusamy*, KC Chan;

Penang Hospital, Penang, Malaysia: T Sudjaritruk*, V Sirisanthana, L Aurpibul, P Oberdorfer;

Faculty of Medicine and Research, Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand: R Hansudewechakul*, S Denjanta, W Srisuk, A Kongphonoi;

Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand: P Lumbiganon*, P Kosalaraksa, P Tharnprisan, T Udomphanit;

Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand: G Jourdain; PHPT-IRD UMI 174 (Institut de recherche pour le développement and Chiang Mai University), Chiang Mai, Thailand: T Bunupuradah*, T Puthanakit, W Prasitsuebsai, W Chanthaweethip;

HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand: K Chokephaibulkit*, K Lapphra, W Phongsamart, S Sricharoenchai;

Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand: KH Truong* , QT Du, CH Nguyen:

Children's Hospital 1, Ho Chi Minh City, Vietnam; VC Do*,TM Ha, VT An:

Children's Hospital 2, Ho Chi Minh City, Vietnam; LV Nguyen*, DTK Khu, AN Pham, LT Nguyen:

National Hospital of Pediatrics, Hanoi, Vietnam; ON Le:

Worldwide Orphans Foundation, Ho Chi Minh City, Vietnam; AH Sohn*, N Durier, C Sethaputra:

TREAT Asia/amfAR – The Foundation for AIDS Research, Bangkok, Thailand; DA Cooper, MG Law*, A Kariminia: The Kirby Institute, UNSW Australia, Sydney, Australia.

* TApHOD Steering Committee member
Current Steering Committee Chair
Current Steering Committee Co-Chair

References

1. Nachman SA, Stanley K, Yogev R *et al*. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. JAMA 2000; 283: 492–498.
2. Hansudewechakul R, Sirisanthana V, Kurniati N *et al*. Antiretroviral therapy outcomes of HIV-infected children in the TREAT Asia pediatric HIV observational database. *J Acquir Immune Defic Syndr* 2010; **55**: 503–509.
3. Kariminia A, Chokephaibulkit K, Pang J *et al*. Cohort profile: the TREAT Asia pediatric HIV observational database. *Int J Epidemiol* 2011; **40**: 15–24.
4. World Health Organization. The WHO Child Growth Standards, 2006. Available at: www.who.int/childgrowth/en/ (accessed May, 2015).
5. Kuczmarski RJ, Ogden CL, Guo SS *et al*. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 11 2002; **246**: 1–190.
6. Thanyawee P, Vonthanak S, Jintanat A *et al*. Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial. *Lancet Infect Dis* 2012; **12**: 933–941.