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Health-related quality of life of perinatally HIV-infected adolescents.

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Abstract

Background: With effective Antiretroviral Treatment (ART), HIV infection is now considered to be a chronic disease requiring long-term care. This study aims to assess the health-related quality of life (HR-QOL) of perinatally HIV-infected adolescents growing-up with HIV.

Method: A cross-sectional survey in HIV-infected adolescents receiving ART was conducted at Chiang Mai University Hospital. Controls were age- and gender-matched healthy adolescents from the same geographic location and adolescents with hematologic malignancies. HR-QOL was assessed in adolescents using the Pediatric Quality of Life Inventory (PedsQL™); their parents also completed the assessment independently. HIV-related clinical characteristics were extracted from medical records.

Results: From July 2014 to February 2015, sixty-five HIV, 130 healthy and 30 hematologic malignancy adolescents were enrolled. Their mean age was 14.6 ± 2.2 years. The HIV group has been on ART for 8.9 ± 3.1 years. Their mean CD4 lymphocyte count was 662 ± 265 cells/mm^3; 82% had HIV RNA level <40 copies/ml. From self-reporting, the HR-QOL of HIV-infected adolescents was not different from that of the control and the hematologic malignancy group (mean total score of 78.19 ± 15.58 vs. 78.00 ± 12.04 and 79.78 ± 11.76, respectively; p=0.932). However, the parent-proxy report showed a higher perceived HR-QOL in the HIV vs. the control group in all domains. The age and CD4 were independently associated with QOL scores of infected adolescents in the simple linear regression, but not significant in multiple regression models.

Conclusion: With increasing accessibility to ART and comprehensive care, the HR-QOL of perinatally HIV-infected adolescents was improved and found to be comparable to non-HIV infected peers. Further study to identify clinical and psychosocial factors potentially associated with QOL in this population is warranted.

Keywords: Quality of life, Adolescent, HIV, Antiretroviral treatment.

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Introduction

With effective Antiretroviral Treatment (ART), children who acquired HIV infection from mother-to-child transmission can survive into, to date, at least the second decade of life [1,2]. In Thailand, the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) was launched by the Thai Ministry of Public Health in 2002. All Thai HIV-infected patients with severely immune suppression have had access to ART since that date. Currently they are considered to be a group of patients with chronic disease requiring long-term care. During childhood, HIV-infected children can catch-up on growth and developmental milestones which are similar to their uninfected peers. However, growing-up with HIV is still challenging in various aspects, especially in the transitional period of adolescence [3]. Past experiences of HIV–related illnesses, medical interventions and the need to adhere to life-long ART could interfere with their mental development and neurocognitive functioning, as well as mental and physical resilience and their overall Quality of Life (QOL) could consequently be affected. Certain health issues which have not previously been addressed as the earlier focus was just on survival, are now becoming issues of concern in adolescents including their final height, reproductive health, bone health, organ function such as heart, lung and liver disease, as well as metabolic diseases and abnormalities of body figure [4-8]. In addition, the need to keep up with hospital appointments and to take medication at exactly the same time everyday can lead to a feeling of compromise and being different from others. Maintaining adherence to treatment often becomes more

challenging during adolescent life, and can inadvertently affect QOL during these critical years [9].

Health-related Quality of Life (HR-QOL) is one psychosocial assessment method used to assess a child's well-being which is an important component/outcome of health care treatment which could be affected by their disease [10,11]. The Pediatric Quality of Life Inventory 4.0 Scales (PedsQL 4.0) is a brief, practical and reliable assessment for measuring quality of life which can be assessed by either self- or proxy-reports [12]. PedsQL 4.0 measures various areas of functioning in physical and psychosocial health, in both children and adolescents, whether healthy or with acute and chronic health conditions [13,14]. The scale was previously used in measuring QOL of Thai children with thalassemia [15]. It is essential that health care providers working with perinatally HIV-infected adolescents learn about their clients' perceptions in order to promote psychosocial health and facilitate the transitional period to adulthood. Similar to findings from adult studies, pediatric studies have shown that HIV-infected children who did not, for whatever reason, have antiretroviral treatment had lower quality of life scores than uninfected controls [16]. However, existing data on the QOL of HIV-infected adolescents who are taking ART remains scarce.

The objectives of this study are to assess HR-QOL of perinatally HIV-infected adolescents growing-up with HIV, and to compare HR-QOL with those of healthy HIV-uninfected controls. We also explored whether their QOL would be different from adolescents with other chronic illnesses. Factors potentially associated with HR-QOL of perinatally HIV-infected adolescents were also determined.

Patients and Methods

A cross-sectional study in HIV-infected adolescents was conducted at Chiang Mai University Hospital, Chiang Mai, Thailand. Inclusion criteria were: 1) having perinatal HIV infection; 2) aged from 10 - 18 years; 3) being clinically stable while receiving antiretroviral treatment and 4) having parent (s) or accompanying caregivers who knew the patients. Those who had other significant concurrent illnesses, physical disabilities and those who resided in orphanage or group homes without individual caregivers were excluded. A convenience sampling strategy was employed. Potential participants were approached during their outpatient clinic visits for HIV treatment. They were enrolled onto the study for the duration of the period from July 2014 to February, 2015. Adolescents with hematologic malignancies who were clinically stable after completed courses of chemotherapy were enrolled in a similar manner during their outpatient clinic visits. Age- and sex-matched healthy adolescents from the same geographic location were enrolled as a comparison group. Demographic characteristics of the adolescents and their families were obtained from interviews. HIV-related clinical characteristics were extracted from medical records. Informed consent and assent were obtained from either the parent (s) or caregiver(s) and all participants. The study was approved by the local Ethics Committee.

HR-QOL was assessed using the Pediatric Quality of life inventory (PedsQL 4.0) which consists of 23 items which measuring core domains in physical (8), emotional (5), social (5) and school (5) functioning [13]. The psychosocial functioning scores were the sum of the emotional, social and school functioning scores. The total score was obtained from the sum of the physical and psychosocial health functioning scores. The PedsQL 4.0 consists of developmentally appropriate forms for a particular age; the questionnaires tailored towards 13 to 18 years old were used in this study. A user agreement was signed with the MAPI Research Institute, prior to using the questionnaires. A high PedsQL score indicated a better quality of life. Both caregivers and adolescents were asked to respond independently to the survey. The PedsQL4.0 self-report form was filled in with adolescents in study and control groups, while the PedsQL 4.0, proxy-report form was completed by their caregivers. Sample sizes were estimated using guidance from the study by Norman et al., which showed that an effect size of about 0.5 SDs was reasonable for most quality of life scores [17]. From the statistics table for sample size determination, with 80% power at the 5% significance level, 65 cases of HIV-infected adolescents and 130 controls were required in this study. Data were analyzed using SPSS 22.0 software. Mean, Standard Deviation (SD) and percentage were calculated for analysis in this study. Independent t-tests and either chi square or Fisher exact tests were used to compare continuous and categorical variables, as appropriate. A simple linear regression analysis was used to assess variables potentially associated with HR-QOL scores. Variables included age, weight- and height-for-age z-score, body mass index, age at ART initiation, duration on ART, regimen used, family status, family income, current CD4 lymphocyte count and virologic suppression. Variables with a p-value <0.2 were included in the multiple linear regression analysis. A p-value of less than 0.05 was considered to be statistically significant.

Results

From July, 2014 to February, 2015, sixty-five HIV-infected, 130 healthy HIV-uninfected and 30 hematologic malignant adolescents were enrolled. The characteristics of each group are shown in Table 1. In the HIV-infected group, 52% were males. Their mean (± SD) age at ART initiation and duration on ART were 6.0 ± 3.6 years and 8.9 ± 3.1 years, respectively. At the time of study, 44 (67%) remained on the first-line non-nucleoside reverse transcriptase inhibitor based regimen, while 21(33%) were on second -line regimens; 53 (82%) had HIV RNA level <40 copies/ml and their mean ± SD current CD4 lymphocyte count was 662 ± 265 cells/mm^3. The mean ± SD current weight- and height-for-age z-scores were -0.22 ± 2.26 and -0.84 ± 1.24, respectively; their body mass index was 19.36 ± 4.63 kg/m^2. In the hematologic malignant group, 70% were male; their median age was 12.7 years (interquartile range, IQR 11.4-14.3) and the

Table 1. *Characteristics of perinatally HIV-infected adolescents, healthy controls and adolescents with hematologic malignancies*

Characteristics	HIV-Infected Group (N=65)	Healthy Control Group (N=130)	Hematologic Malignancies Group (N=30)	P-Value
Male Gender	34 (52)	67 (52)	21 (70)	0.18
Age, Years	14.9 (12.9-16.8)	14.9 (12.9-16.8)	12.7 (11.4-14.3)	0.01
13-15 Years	33 (51)	66 (51)	25 (83)	
>15-18 Years	32 (49)	64 (49)	5 (17)	
Family Status				
Living with Biological Parents	14 (22)	83 (64)	21 (70)	<0.01
Living with Single Parents	27 (41)	47 (36)	9 (30)	
Living with Other Relatives	24 (37)	0	0	
Family Income (Thai Baht*)	7,000 (5,000-10,000)	15,000 (10,000-30,000)	12000 (6,000-20,000)	<0.01
≤ 10,000	51 (81)	43 (36)	13 (43)	
>10,000	12 (19)	76 (64)	14 (47)	
Date in median (interquartile range), or number (%) as appropriate				
* At the time of study enrollment, 10,000 Thai baht=314 US dollars				

median duration from the first diagnosis was 3.3 years (range 0.2-9.5). The diagnoses included acute leukemia (n=18), lymphoma (n=7), chronic leukemia (n=2) and others (n=3). The characteristics of each group are shown in Table 1. A significantly lower proportion of HIV-infected patients were living with their biological parents; 14 (22%) vs. 83 (64%) and 21 (70%) of healthy HIV-uninfected and hematologic malignant patients, respectively. The median family income of the HIV-infected group was significantly lower than the other two groups.

The results of the self-report showed that the perceived HR-QOL of HIV-infected adolescents was no different to that of the control and hematologic malignant group (mean ± SD total scores of 78.19 ± 15.58 vs. 78.00 ± 12.04 and 79.78 ± 11.76, respectively; p=0.93). Among the five domains, the mean social functioning score (83.46 ± 17.98) was the highest followed by the physical health score (79.95 ± 17.93). When compared in each domain, there was no difference in the scores between the HIV-infected and healthy control group. However the mean emotional functioning score of the HIV-infected group was found to be significantly lower than the hematologic malignant group (73.85 ± 18.72 vs. 82.67 ± 15.91, p=0.03), but did not differ from that of the control group (Table 2).

The parent-proxy reports showed that the total score of HIV-infected group was no different from that of the healthy control, while that of hematologic malignant group was significantly higher (66.66 ± 20.71, 61.54 ± 15.45 and 79.42 ± 12.45, respectively, p<0.01). Among the five domains, parent-proxy report scores in emotional (74.77 ± 19.71) and social (71.38 ± 22.56) functioning were the highest and second highest, respectively. When compared to the control group in each domain, parents of the HIV-infected group gave significantly higher scores in psychosocial health (69.54 ± 19.58 vs. 63.56 ± 13.35, p=0.03) and emotional functioning (74.77 ± 19.71 vs. 65.12 ± 17.57, p=0.01). As perceived by parents, the hematologic malignant group had higher scores in physical health, psychosocial health and social functioning domains than the HIV-infected group (Table 2).

Focusing on the HIV-infected group, a moderate correlation was observed between adolescent self-reports and parent proxy-reports for the total (r=0.46) and physical health scores (r=0.49), but rather weak correlations were observed for psychosocial health (r=0.38), emotional (r=0.40), social (r=0.342) and school functioning (r=0.21). The CD4 lymphocyte count was positively associated with total HR-QOL scores according to the simple linear regression, while increased age and family status (living with biological parents) had a slight positive association. Virologic non-suppression had a trend towards a negative association. However, there was no significant relationship demonstrated for any factors in multiple regression models (Table 3).

Discussion

Increased access to ART has changed the natural history of HIV infection and allowed perinatally HIV-infected children to survive becoming adolescents. Thus, the psychosocial well-being of these HIV-positive adolescents has become another concern to be addressed. In this study we found that the overall perceived HR-QOL of perinatally HIV-infected adolescents was reasonably good and similar to that recorded in healthy control and hematologic malignant groups. Clinical and demographic factors including age, sex, growth parameters, duration on treatment, immunologic/virologic treatment outcomes and socioeconomic status of family were not significantly associated with HR-QOL in this population.

Our study participants have been on ART for nearly a decade. Improvement in quality of life of children living with HIV/AIDS has been consistently reported from developed countries like the US since the early ART era. Data from PACTG219c, an observational prospective cohort study in the US assessed the long term outcomes of HIV-infected and -exposed children in the

Table 2. *Comparison of HR-QOL scores in perinatally HIV-infected adolescents, healthy controls and adolescents with hematologic malignancies*

HR-Qol	HIV-Infected Group	Correlation Coefficient[a], *R*	Healthy Control Group	Correlation Coefficient[a], *R*	P-Value[b]	Hematologic Malignant Group	Correlation Coefficient[a], *R*	P-Value[c]	P-Value[d]
Number of Study Participants	65		130			30			
Adolescent Self-Report									
Total Score	78.19 (15.58)	0.46	78.00 (12.04)	0.56	0.93	79.78 (11.76)	0.62	0.58	0.80
Physical Health Score	79.95 (17.93)	0.49	81.62 (13.37)	0.43	0.51	81.77 (12.64)	0.52	0.57	0.74
Psychosocial Health Score	77.26 (15.86)	0.38	76.28 (13.13)	0.56	0.67	78.72 (12.55)	0.57	0.63	0.67
Emotional Functioning	73.85 (18.72)	0.40	70.50 (16.85)	0.52	0.21	82.67 (15.91)	0.56	0.03	<0.01
Social Functioning	83.46 (17.98)	0.34	81.46 (15.63)	0.39	0.42	83.00 (14.30)	0.31	0.90	0.69
School Functioning	73.69 (17.44)	0.21	76.50 (14.49)	0.46	0.24	70.50 (14.70)	0.55	0.39	0.12
Parent Proxy-Report									
Total Score	66.66 (20.71)		61.54 (15.45)		0.08	79.42 (12.45)		<0.001	<0.01
Physical Health Score	61.25 (25.38)		57.65 (22.14)		0.33	81.25 (16.47)		<0.001	<0.01
Psychosocial Health Score	69.54 (19.58)		63.56 (13.35)		0.03	78.46 (12.13)		0.008	<0.01
Emotional Functioning	74.77 (19.71)		65.12 (17.57)		0.001	74.50 (17.83)		0.95	<0.01
Social Functioning	71.38 (22.56)		66.77 (17.40)		0.12	91.67 (9.86)		<0.001	<0.01
School Functioning	62.62 (24.91)		58.81 (18.46)		0.23	68.67 (20.38)		0.26	0.05

HR-QOL Health-Related Quality of Life

[a] correlation between adolescents and parent scores in each domain

[b] comparison between HIV and healthy control groups

[c] comparison between HIV and hematologic malignant group

[d] comparison between all 3 groups

US. The findings of the study demonstrated significantly worse mean adjusted scores for health perceptions, physical resilience, physical functioning and social/role functioning in HIV-infected children of 5-11 years of age when compared to an uninfected group in the same cohort [18]. With continued follow-up in the groups of children ≥ 12 years, better scores were seen in those initiated onto ART when compared to those who were not, regardless of the drug regimens used. Similarly, in Asian countries, the PREDICT study in Thai and Cambodian HIV-infected young children (mean age 6.3 ± 2.8 years) identified a lower QOL in HIV-infected children when compared to a control uninfected group. Significantly higher QOL scores in all domains were observed after 144 weeks of HIV clinic attendance with either early or deferred ART initiation [16]. Our results were also in line with the study in Northern India which was carried out among younger HIV-infected children (mean age 8.98 ± 3.49 years, median duration on ART 16.5 months) using the same tools [19]. They reported significantly better QOL in psychosocial, emotional and the school functioning domain in HIV-infected children when compared with age- and gender-matched children with other chronic medical illnesses. Factors including age, sex, socio-economic status, clinical and immunological staging did not significantly influence QOL scores.

Although not perfectly correlated (correlation coefficient ranged between 0.21-0.48), information from both parents' and adolescents' point of view was useful in completing the assessment of QOL outcomes. Both adolescent self- and parent-proxy reports showed a trend towards higher psychosocial health, emotional and social functioning scores than the healthy control group. It may be that HIV-infected adolescents have better access to health services and social support, which somehow affected their perceived HR-QOL. The previous study in 2011 using the youth self-report and Child Behavior Checklist indicated that HIV-infected adolescents had more psychosocial problems than healthy controls, with lower competence scores in sport, social, and school activities [20]. The

Table 3. *Predictors of health-related quality of life scores in HIV-infected adolescents (N=64)**

	Simple Linear Regression			Multiple Linear Regression**		
Variables	**ß**	**95% CI**	**P-Value**	**ß**	**95% CI**	**P-Value**
Male Gender	0.47	-6.80, 7.74	0.90			
Age	1.61	-0.02, 3.23	0.05	0.87	-0.93, 2.68	0.34
Body Mass Index	0.02	-1.11, 1.16	0.97			
Duration of ART (Years)	0.55	-0.66, 1.76	0.37			
ART Regimen	-1.76	-6.28, 2.77	0.44			
Current CD4 Lymphocyte Count	-0.02	-0.03, -0.001	0.03	-0.01	-0.03, 0.003	0.12
Current Virologic Non-Suppression	-8.05	-17.15, 1.06	0.08	-6.18	-15.23, 2.97	0.18
Family Status	2.08	-1.02, 5.17	0.19	0.74	-2.64, 4.13	0.66
ß unstandardized regression coefficients; ART antiretroviral therapy; CI confidence interval						
** An outlier was excluded*						
*** Variables with p-value <0.2 from simple linear regression were included*						

difference between this study and the findings of our current one may be explained by the change in the social and medical norm and the social acceptance of HIV with time. While a study into Thai adults living with HIV/AIDS in Northern Thailand suggested that community acceptance was important for mental aspects of their QOL irrespective of the disease stages, growing up in Northern Thailand where HIV is classified as an epidemic might allow those children and adolescents to lead a nearly normal social life. The results may not be generalizable to other parts of Thailand or other countries with different community environments [21].

We observed quite similar or slightly better scores within the HIV-infected group in all domains except school functioning, which was lower but not significantly different from the control groups. Missing school to attend clinic and past illnesses/opportunistic infections which affected learning capability might be a part of the explanation. In the hematologic malignant patients scores in all domains were higher when compared to either the HIV or healthy control groups. The most probable explanation for this is the fact that the study was carried out in the outpatient setting which is when the hematologic malignant patients have already undergone the worst part of their treatment i.e. frequent hospitalization, chemotherapy with side effects or medical procedures. Thus, they felt much better coming to hospital for follow-up appointments. Meanwhile, most HIV-infected patients had to come to clinic regularly without any turning point to offer them a feeling of improvement or relief. Another difference was that higher proportion of adolescents in hematologic malignant group was <15 years and being male, young boy might perceive less compromise QOL than mid-adolescent girls. It was difficult to find an appropriate population for comparison as each disease/condition has a different nature. Moreover, the effect of illnesses on overall health and also the burden of treatment varied tremendously between conditions. However, we can now reassure patients regarding the long term benefits of ART for perinatally HIV-infected adolescents, not only regarding measurable clinical outcomes, but also improving self-reported HR-QOL.

Regarding parental perception on the QOL of the adolescents who have been on ART since early childhood, growing-up as an HIV-infected youth may perform better and have more favorable outcomes than their parents/caregivers have expected; while parents of adolescents in the healthy control may have expected a more ideal QOL. Parents of adolescents with hematologic malignancies may have lower expectations as their children were diagnosed with dreadful, critical conditions. Only a moderate correlation (Table 2) was found between adolescents and parents in this study. An Australian epidemiological study stated that adolescents were found to be much less optimistic about their health and well-being than their parents [22]. In this study we found that our adolescents were more optimistic.

Factors associated with better mental health in the Ugandan study among 614 HIV-infected adolescents aged 16.2 ± 2.1 years receiving ART, were achievement in secondary or tertiary education and the desire to have child in future [23]. Future hope may affect present QOL; however, we did not ask the question in our study and it would be useful to follow-up this line of investigation in the future. The Kenyan study reported that HR-QOL in adults decreased with the time the patients were on ART [24]. The Vietnamese study reported gender differences in QOL outcomes of HIV treatment in adults; males had better scores in morbidity, environment and psychological dimensions, while women had better scores in the performance domain [25]. We did not see such association or any gender difference in the present study. More in-depth studies might be warranted to explore related factors in order to plan for age- appropriate intervention for our population.

Several study limitations merit a mention. First was the age difference between the HIV-infected and hematologic malignant group. The latter group was younger and the findings may not be directly comparable in certain domains. Secondly was the difference in the natural history of the disease and course of treatment that might not allow fair comparison between the two groups. However, it is apposite to mention several strengths of this study. First, the calculated number of the sample size was actually enrolled; secondly, we obtained information from interviews of both parents and adolescents and thirdly our

study participants were homogenous, all were perinatally HIV-infected population in the age group of adolescence.

In summary, when increased accessibility to ART has changed the natural history of disease caused by HIV and allowed perinatally HIV-infected children to survive to become adolescents, the study results support the impact of ART on HR-QOL of developing perinatally HIV-infected adolescents. A follow-up study with more in-depth exploration, as well as further research to identify potentially modifiable factors associated with QOL in this population are warranted.

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