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Development of a culturally appropriate health-related quality of life measure for human immunodeficiency virus-infected children in Thailand

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Abstract

Aim—Develop a reliable and valid self-report health-related quality of life (HRQOL) instrument for human immunodeficiency virus (HIV)-infected children in Thailand.

Methods—The Thai Quality of Life for HIV-infected Children instrument, the ThQLHC (an HRQOL measure that uses the Pediatric Quality of Life Inventory as a generic core and a 17-item HIV-targeted scale), was developed and administered cross-sectionally to 292 HIV-infected children in Thailand. The disease-targeted scale included HIV-related symptoms, ability to adhere with their treatment regimens and self-image. The internal consistency reliability (Cronbach's α) and construct validity of the ThQLHC scales were then evaluated.

Results—Internal consistency reliability coefficients ranged from 0.57 to 0.82, with four of five scales reaching the minimal acceptable level (>0.70). Significant associations were found between poor HRQOL and poor self-rated disease severity, care giver's rated overall quality of life, cluster of differentiation (CD) 4 percent and plasma HIV ribonucleic acid level.

Conclusion—Reliable and valid disease-targeted HRQOL measures for HIV-infected children are essential in the assessment of therapeutic effectiveness. The findings of this cross-sectional survey provide support for the reliability and validity of the ThQLHC as an HRQOL outcome measure for HIV-infected Thai children.

Keywords

child; health-related quality of life (HRQOL); HIV

Although numerous human immunodeficiency virus (HIV)-targeted health-related quality of life (HRQOL) instruments have been developed for clinical applications, such as the HIV adaptation of the Medical Outcomes Questionnaire,¹ the Acquired Immune Deficiency Syndrome (AIDS) Health Assessment Questionnaire,² the HIV/AIDS-Targeted Quality of

Life instrument,³ the HIV-QL31 (HIV-Quality of Life – 31 items),⁴ the General Health Self-Assessment⁵ and the Multi-dimensional Quality of Life Questionnaire for HIV/AIDS,⁶ very few are for the paediatric population. The General Health Assessment for Children was developed by Gortmaker *et al.*⁷ for assessment of potential long-term effects of anti-retroviral (ARV) therapies in AIDS Clinical Trial Protocol 219. Another existing HIV-targeted HRQOL instrument in children was developed by Nicolas *et al.*,⁸ which was designed for those caring for HIV-infected children in Europe. Little is known about the applicability of these instruments to those living in developing countries with different cultural and economic contexts.^{9,10} In addition, no paediatric HIV-targeted HRQOL instrument is currently available for children in Thailand. The purpose of this study was therefore to develop a self-reporting HRQOL instrument appropriate for HIV-infected children in Thailand and to evaluate the reliability and validity of the instrument.

Patients and Methods

The first phase of the study employed qualitative methods to generate content for items in the HIV-targeted scale. The instrument was then tested and refined by cognitive interviews. The second phase was designed to evaluate reliability and validity of the instrument generated from phase 1.

Phase I: development of the HRQOL instrument

Detailed study procedures and qualitative finding have been described elsewhere.¹¹ In brief, subjects in the first phase were a convenience sample of HIV-infected children and their primary care givers from an urban paediatric HIV specialty clinic in Bangkok. All recruitment followed approval of the protocol by the University of California, Los Angeles (UCLA) and local institutional review boards. HIV-infected children were eligible if they were aged 8 years or older and had never been diagnosed with a neurological, developmental or psychiatric disorder. Eligibility criteria for primary care givers included: (i) providing care for an HIV-infected child aged 8 years or older; (ii) being aged 18 years or older; (ii) ability to give informed consent; and (iv) being a native Thai speaker.

We conducted individual in-depth interviews with 34 HIV-infected children (mean age 12.5 (standard deviation (SD) = 2.2) years (range 8–16 years)) and 35 primary care givers (mean age 43.1 (SD = 11.5) years (range 27–66 years)) at the Infectious Disease and Immunology Clinic, Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand. The interviews were conducted using a semi-structured interview guide by a group of health-care workers who have experience in working with sick children. The semi-structured protocol was developed by a paediatric HIV specialist (WP) to obtain information regarding the patients' and the care givers' illness perceptions, major impact of their illness on daily functioning and well-being, future plans and concerns, and disclosure status. The interview sessions were audiotaped and transcribed verbatim.

In addition, we conducted a literature search to identify relevant previously published generic and HIV-targeted HRQOL instruments that could be adapted to and/or included in the instrument. Data from individual interviews, literature reviews and expert consultants were employed in the formation of specific items in the disease-targeted scale of the instrument. This scale was then combined with the generic core of the Pediatric Quality of Life Inventory (PedsQL) to yield an HIV-targeted HRQOL instrument for Thai children called the Thai Quality of Life for HIV-infected Children (ThQLHC). The PedsQL contained 23 questions (eight for one subscale, physical functioning; and five for another three subscales including emotional functioning, social functioning and school functioning).¹² Support for the reliability and validity of PedsQL has been provided in numerous paediatric patient populations and medical conditions.^{12–15}

Initial administration of the ThQLHC instrument was tested in face-to-face cognitive interviews of 10 HIV-infected children. 16–18 Cognitive interview participants completed the instrument and were then interviewed to obtain information regarding the suitability of the instrument. The information obtained from this process formed the basis for questionnaire revision before the larger scale survey in phase 2.

Phase II: evaluation of the psychometric properties

Subjects in the second phase of the study were also convenience samples of HIV-infected children and their primary care givers from two urban paediatric HIV specialty clinics in Bangkok (QSNICH and Siriraj Hospital). Recruitment was in accordance with the institutional review board-approved protocol. Inclusion and exclusion criteria were the same as those for phase 1.

Each subject was asked to complete the newly developed HIV-targeted HRQOL questionnaire (ThQLHC) with an individual interview by a research team member for those who were 8–11 years and a self-administered questionnaire for those 12 years or older. They were also asked to rate their HIV disease severity on a visual analogue scale from 0 to 10. Their primary care givers were also asked to complete a questionnaire that assessed demographic data and number of disability days in the past month, and rated their child's overall quality of life on a 10-point visual analogue scale. Certain clinical parameters, such as the current viral load (VL), CD4 cell counts and clinical staging, were obtained by a medical record review.

Scores on all of the scales were linearly transformed to a score ranging 0–100 (higher values indicating better HRQOL). The internal consistency reliability of the ThQLHC for multi-item scales was estimated using Cronbach's α .¹⁹

To evaluate construct validity, we estimated associations between HRQOL scale scores and the Centers for Disease Control and Prevention (CDC)²⁰ clinical staging, CD4 cell counts and log VL. We also estimated associations between HRQOL scale scores and self-rated severity of disease symptoms, and number of disability days within the prior 30 days.

We attempted to determine whether the disease-targeted scale provided unique HRQOL information beyond that of the PedsQL generic core by conducting backward stepwise regression analyses to see if the ThQLHC scale scores accounted for significant unique variance in two global validity variables: (i) self-reported severity of disease; and (ii) log VL.

All analyses were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). A P -value ≤ 0.05 was considered to be statistically significant.

Results

Sample characteristics

From April 2007 to March 2008, a total of 316 HIV-infected children attending the Infectious Disease Immunology Clinic at the QSNICH and Siriraj Hospital were approached to participate in the study. Of 316 children approached, 292 subjects were recruited (92.4% participation rate). Mean age (SD) of the children at the time of interview was 10.9 (2.27) years. Socio-demographic information of the sample population is provided in Table 1.

The HIV-targeted scale of the ThQLHC instrument includes 17 items (Table 2). In addition, we included two separate single items for care givers: (i) number of days their child missed at school and usual activity within the past month because of illness; and (ii) rating of their

child's overall quality of life. We also included one separate single item for children, a self-rating of the overall severity of HIV-related symptoms within the past month.

Descriptive statistics and reliability

The mean self-reported time required to complete the ThQLHC was 11.3 min (SD = 2.8 min) for those who read and completed the form themselves, and 10.75 min (SD = 1.8 min) for those to whom it was read. Rates of missing data were relatively low. A small proportion (11.6%) of subjects missed one or more items of the ThQLHC.

Descriptive statistics and reliability coefficients for the PedsQL generic core and the disease-targeted scales of the ThQLHC are provided in Table 3. Internal consistency reliability coefficients were >0.70 for all except for the school functioning scale ($\alpha = 0.57$).

Construct validity

Construct validity assessments are reported in Table 4. Statistically significant relationships ($P \leq 0.05$) were found consistently between self-rated disease severity markers and the five scales. Care giver ratings of their child's overall quality of life significantly correlated with both the school functioning and the HIV-targeted scale. In addition, log VL and CD4 cell counts were also found to be significantly correlated with the HIV-targeted scale. Nevertheless, there were no statistically significant relationships between socio-demographic variables (household income and care giver's education level) and any of the five scales.

In summary, poorer HRQOL was related to poorer self-rated severity of HIV disease symptoms, care giver rating of their child's overall quality of life, CD4 cell counts and log VL. Furthermore, the HIV-targeted scale, as well as the total HRQOL score, consistently correlated with the above clinical parameters (Table 4). We compared mean scores of each HRQOL scale between different disease stages categorised by the US CDC classification system, including asymptomatic (N), mildly (A), moderately (B) and severely (C) symptomatic.²⁰ One-way analysis of variance (ANOVA) was used to assess the differences of the mean scores among groups, but the groups did not differ significantly (Table 5).

Unique associations of scale scores with validity variables

Using stepwise regression analyses, initial variables in the model included each of the five ThQLHC scales, CD4 cell counts, CDC clinical staging and age (in years), we found that unique and significant information was obtained from the disease-targeted scale of the ThQLHC in predicting log VL. Specifically, we found that the HIV-targeted scales were significantly associated with log VL (t -statistic -2.152 ; $P = 0.032$). Using logistic regression analysis, we also found that the HIV-targeted scale was significantly associated with VL detectability: Odds ratio (95% confidence interval) and P -values are 0.973 (0.952, 0.995) and <0.001 , respectively. Using self-rated severity of HIV disease as a validity variable, only the school functioning scale and log VL were significantly associated (Table 6).

Discussion

This study describes the development of an HRQOL for children with HIV/AIDS. Using the PedsQL as a generic core supplemented by a disease-targeted scale, the ThQLHC encompasses a five multi-item scale evaluating HIV-related symptoms and well-being.

We estimated internal consistency reliability of multi-item scales using Cronbach's alpha. All but the school functioning scale satisfied the 0.70 reliability standard for group

comparisons.²¹ The coefficient α for quality of school functioning is somewhat lower (0.572). Further study is needed to improve the reliability of this particular dimension.

In our current sample, the distributions of the five scale scores were aggregated to the right of the mean (negatively skewed); that is, the majority of children reported good health. In fact, 1–28.4% received the highest possible score on any of the five scales, whereas none of the subjects received the lowest possible score (Table 3). One plausible reason is that the study population was limited to outpatient settings; only those who had access to health care were included. Thus, they were relatively unaffected in several dimensions of HRQOL. Although up to 18% and 28% of these children had the highest possible scores on the emotional and social functioning scales, respectively, only 36% of these children had had their HIV status disclosed to them by the time of study. Nevertheless, we did not detect any significant difference between median ThQLHC scores of participants who had and had not received disclosure ($P = 0.67$). The ceiling effect among children who exhibit functioning or well-being that is as good as the best function measured by a particular dimension is a cause of concern, because it limits responsiveness, an important psychometric property of disease-targeted instruments. A scale or dimension with ceiling effects is unable to detect further improvement of functioning and/or health status.²² On the contrary, as our subjects' health would be expected to deteriorate over time, the skewed distribution of scores at baseline is unlikely to hinder the detection of worsening HRQOL (i.e. no floor effect).²³

We further hypothesised that poor HRQOL would be significantly associated with poor self-rated severity of disease symptoms, poor care giver's rating of child's overall quality of life, higher level of VL, poorer socio-economic status and a greater number of self-reported disability days within the preceding month. We found statistically significant associations between each of the HRQOL scale scores with self-rated severity of the illness. Additionally, the HIV-targeted scale scores were found to be significantly associated with care giver's rating of child overall quality of life, CD4 cell count and log VL. Furthermore, using multivariate regression analysis, we demonstrated that the HIV-targeted scale of the ThQLHC was able to provide unique information in predicting log VL and VL predictability that a generic instrument alone would not capture in HIV-infected children. However, the R -square, the extent to which the variance is explained by this model, was relatively low (16% and 12% for log VL and VL predictability, respectively). Nonetheless, this finding supports the value of the disease-targeted dimension in providing such additional HRQOL information.

We hypothesised that if this instrument accurately assessed health, then the scale scores would be related to the clinical staging of the illness as determined by the CDC classification system for HIV infection,²⁰ and the magnitude of these relationships would be higher for the physical functioning and the HIV-targeted scale. However, our expectations concerning associations of the scale scores with this measure were generally not supported. We also expected the HIV-targeted scale scores to provide unique information about self-rated severity of disease, but it appeared that the school functioning scale rather than the HIV-targeted scale did so. Using multivariate analysis, the HIV-targeted scale was not retained in the final model for predicting the self-rated severity of the illness. It is plausible that these children may view school functioning as a more important indicator of their disease severity compared with their experience of disease-related symptoms.

Several of our findings are worthy of further comment. First, there is no significant correlation between the CDC clinical staging and child self-rated severity of the illness. This suggests that the clinical parameter used to predict survival may not be sensitive enough to capture the patients' perceptions of their health and well-being. Similar to other reports, assessment of biological variables and clinical parameters provides different information

than patient reports of health.²⁴ Research in other chronic illnesses indicates that the associations of HRQOL and disease severity indices do not always show consistent results.^{25–28}

Among those reporting significant results, the magnitude of these associations was not always necessarily large.²⁶ Other reports have not found significant associations between disease severity indices and HRQOL.²⁹ Second, although the strong correlation between the CDC classification staging and mortality was established in the early HIV literature,^{30–33} its relationship with HRQOL may not be consistent during the period when highly active ARV therapy has substantially improved the survival of these children. For example, children who had been classified as having AIDS or clinical category C in the previous year, after being switched to a salvage or more potent ARV regimen, might become asymptomatic or relatively healthy during the time of the interview. However, individuals whose VL is recently brought under control and CD4 count rises within a short period may suffer from immune reconstitution syndrome.^{34–37} Therefore, it is possible that the lack of significant finding here is because of the measured variable that was neither specific nor sensitive enough to permit the detection of associations. However, it is also possible that the five scales may not possess differential predictive validity for these children. An appropriate test of these possibilities will require: (i) use of more sophisticated validation measures of disease severity, such as the recently developed multidimensional AIDS severity adjustment for paediatric HIV infection, the Pediatric AIDS Severity Score;³⁸ and (ii) study of different groups of children, perhaps both inpatients and outpatients, and those who have and do not have access to health care.

Another unexpected finding was the lack of relationship of HRQOL scores with socio-economic status. Previous studies have reported significant associations between socio-economic status and HRQOL scores.^{39–41} One plausible reason is that our sample was overly homogeneous in this aspect; that is, 74% of subjects reported a household income of less than 10 000 Thai baht (approximately \$300 US)/month. This population, despite being unable to afford the treatment, had access to treatment under the government's universal coverage health scheme.

The strengths of this study include the use of a qualitative approach to maximise content validity of the instrument, a large sample size, two participating medical centres and different levels of disease severity based upon both the CDC classification system and patients' self-rating, as well as laboratory parameters. There are, however, limitations to this study. This survey was conducted cross-sectionally; thus, the instrument responsiveness (the ability to detect change in HRQOL over time) cannot be assessed.^{18,42} In addition, the sample population studied was limited to only ambulatory patients regularly visiting the clinic. Therefore, the results may have limited generalisability to only those with access to health care.

In conclusion, despite the fact that not all of our findings provide strong evidence of validity, the traditional measures of disease severity should be supplemented with HRQOL assessment, using ThQLHC in evaluating the effectiveness of a treatment intervention in Thai HIV-infected children. This field test and its preliminary data provide partial support for the psychometric properties of the ThQLHC for HIV-infected children. In terms of applicability, children deemed the instrument comprehensive, culturally appropriate and comprehensible. It is short (can be completed in about 10–12 min) and had high completion rates. The ThQLHC may thus be useful in determining the treatment effectiveness in terms of HRQOL outcomes of this population. More work is needed to improve this new measure. Additional studies should address the responsiveness to change in clinical status and the

ability to predict disease progression and/or survival. As a result, potential users are asked to bear in mind that additional work and analyses, and therefore revision(s), are to be expected.

What is already known on this topic

1. Few human immunodeficiency virus (HIV)-targeted health-related quality of life (HRQOL) instruments have been developed for the general paediatric population; the existing ones have been developed and tested in the Western cultural context.
2. Support for the reliability and validity of the Pediatric Quality of Life Inventory (PedsQL) generic core as an HRQOL measure has been provided in numerous paediatric patient populations and medical conditions. However, there is limited information regarding its applicability to the translated version for HIV-infected children in Thailand.
3. Data on level of HRQOL from the PedsQL generic core enable the comparison of HRQOL level between a particular group of patients with that of the general population and/or other groups of patients. Supplemented by the disease-targeted scale, an instrument is expected to have enhanced specificity and sensitivity for detecting changes in level of HRQOL at different disease stages.

What this paper adds

1. With the use of the cognitive interview, we were able to adapt the translated version of the PedsQL and supplement it with the newly developed HIV-targeted scale for the evaluation of the HRQOL among HIV-infected children in Thailand.
2. The school functioning domain of the instrument requires additional work, given its failure to reach the acceptable level of internal consistency reliability coefficients.
3. The association between the HRQOL score and the self-rated disease severity, caregiver's rated overall quality of life, CD4 percent, and plasma HIV RNA level provide support for this instrument as an HRQOL outcome measure for HIV-infected Thai children.

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Table 1

Sample characteristics

Characteristics	<i>n</i> (%)
Male gender	160 (54)
Clinical staging (<i>n</i> = 279)	
N (asymptomatic)	109 (37.3)
A (mildly symptomatic)	60 (20.9)
B (moderately symptomatic)	59 (20.2)
C (severely symptomatic)	51 (17.5)
Immunologic classification (<i>n</i> = 279)	
1 (CD4 counts \geq 25%)	87 (25.4)
2 (CD4 counts 15–24%)	72 (24.7)
3 (CD4 counts <15%)	133 (45.5)
Children whose HIV status had been disclosed	107 (36)
Living with infected care givers	107 (36)
Care giver's median age, year (IQR)	41.5 yrs (20)
Care giver's education level (<i>n</i> = 274)	
Less than 4 years	36 (13.1)
4–6 years	120 (43.8)
Some high school	48 (17.5)
High school diploma	25 (9.1)
Vocational school or some college	27 (9.8)
College degree	18 (6.5)
Total monthly household income in Thai baht	
<5000 (<143 USD)	118 (40.4)
5000–10 000 (143–286 USD)	100 (34.2)
10 001–25 000 (287–714 USD)	34 (11.6)
25 001–50 000 (715–1426 USD)	10 (3.4)
>50 000	2 (0.7)
Not sure	28 (9.6)

CD, cluster of differentiation; HIV, human immunodeficiency virus; IQR, interquartile range; USD, United States dollar.

Table 2
The human immunodeficiency virus (HIV)-targeted scale of the Thai Quality of Life for HIV-infected Children

Symptoms, feelings (problems with...)	Never	Almost never	Sometimes	Often	Almost always
1 Numbness or tingling in hands or feet	0	1	2	3	4
2 Dizziness or light-headedness	0	1	2	3	4
3 Fever, chills	0	1	2	3	4
4 Rash, itching or other skin problem	0	1	2	3	4
5 Common cold, sinus symptoms	0	1	2	3	4
6 Earache, draining ear, hearing problem	0	1	2	3	4
7 Eye trouble, problem with vision	0	1	2	3	4
8 Nightmares	0	1	2	3	4
9 Losing weight or weight loss	0	1	2	3	4
10 Toothache, dental caries	0	1	2	3	4
11 Painful oral lesion, difficulty swallowing	0	1	2	3	4
12 Loss of appetite	0	1	2	3	4
13 Nausea, vomiting	0	1	2	3	4
14 Diarrhoea	0	1	2	3	4
15 Worrying about one's appearance	0	1	2	3	4
16 Bed wetting	0	1	2	3	4
17 Failure to take regular medications	0	1	2	3	4

Table 3
Descriptive statistics and internal consistency reliability estimates of the Thai Quality of Life for HIV-infected Children

Scale	Number of items	Mean score	Standard deviation	Minimum score	Maximum score	% scoring of floor	% scoring of ceiling	Cronbach's alpha
Physical functioning	8	75.8	15.6	34.4	100	0	5.9	0.749
Emotional functioning	5	77.4	18.7	20	100	0	17.9	0.739
Social functioning	5	82.7	17.5	25	100	0	28.4	0.724
School functioning	5	68.6	15.9	15	100	0	1.0	0.572
Human immunodeficiency virus-targeted scale	17	79.8	12.2	47.1	100	0	1.7	0.819

All correlations are significant at the 0.01 level (two-tailed).

Correlations of the ThQLHC scales with self-rated disease severity, care giver rating of child's overall quality of life, clinical parameters and indicators of socio-economic status

Table 4

	Self-rated disease severity (P-value) [†]	Care giver rating of child's overall quality of life (P-value) [†]	Disability days [‡]	CD4 cells [‡]	CD4% [‡]	Log VL [‡]	CDC clinical classification [†]	Household income [‡]	Care giver's years of education [‡]
Physical functioning	-0.211 **	0.115	-0.104	0.109	0.217 **	-0.047	-0.088	0.009	-0.108
Emotional functioning	-0.224 **	0.068	-0.081	0.055	0.100	-0.105	-0.121	-0.046	-0.004
Social functioning	-0.174 **	0.092	-0.115	-0.062	0.005	-0.106	-0.042	-0.076	-0.053
School functioning	-0.296 **	0.148 *	-0.093	0.073	0.116	-0.190 *	-0.042	-0.057	-0.073
HIV-targeted scale	-0.297 **	0.157 **	-0.047	0.057	0.120 *	-0.172 **	-0.038	-0.083	-0.039
Total score	-0.297 **	0.157 **	-0.047	0.057	0.120 *	-0.172 **	-0.103	-0.083	-0.039

* Correlation is significant at $P < 0.05$;

** $P < 0.01$.

[†] Spearman rank correlation coefficient.

[‡] Pearson correlation coefficient. CD, cluster of differentiation; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; ThQLHC, Thai Quality of Life for HIV-infected Children; VL, viral load. Statistically significant values are in bold.

Table 5

Mean scale scores by different CDC clinical classifications

	N (n = 109)	A (n = 60)	B (n = 59)	C (n = 51)	F (P-value)
Physical functioning	76.77	73.62	76.48	72.75	0.348
Emotional functioning	79.44	78.05	76.86	71.80	0.116
Social functioning	82.98	81.50	82.54	82.54	0.964
School functioning	67.47	70.58	70.50	65.20	0.196
HIV-targeted scale	80.84	78.33	79.12	78.08	0.456

CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

Table 6

Stepwise regression analysis of the ThQLHC scales

Dependent variable	Independent variable	Unstandardised beta coefficient	Statistics	P-value	R ²
Log viral load	HIV-targeted scale	-0.012	-2.152*	0.032	0.162
	CD4 cell percent	-0.051	-6.184	<0.001	
	Constant	5.168	11.034	<0.001	
Viral load [†] (detectable vs. undetectable)	HIV-targeted scale	-0.027	6.024 [‡]	0.008	0.124
	CD4 percent	-0.064	-14.629	<0.001	
	Constant	3.378	12.673	<0.001	
Self-rated severity of HIV disease	School functioning scale	-0.044	-4.708*	<0.001	0.122
	Log viral load	0.332	2.668	0.008	
	Constant	4.499	5.567	<0.001	

* *t*-statistics.[†] Logistic regression analysis.[‡] Wald statistics. CD, cluster of differentiation; HIV, human immunodeficiency virus; ThQLHC, Thai Quality of Life for HIV-infected Children.