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Factors associated with high rates of antiretroviral medication adherence among youth living with perinatal HIV in Thailand

Dr. Ezer Kang, *Howard University*

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Ezer Kang[1], Darcie AP Delzell[2], Manik Chhabra[3] and Peninnah Oberdorfer[4]

Abstract

Antiretroviral medication adherence behaviour among Thai youth with perinatal HIV in Thailand has received growing attention. However, few studies have examined individual predictors of antiretroviral adherence using multiple self-reports. A convenience sample of 89 Thai youth (interquartile range 14–16 years) with perinatal HIV at three paediatric programmes in Chiang Mai completed a structured questionnaire and reported their antiretroviral adherence in the past one, seven and 30 days using count-based recall and a visual analog scale. Mean self-reported adherence rates ranged from 83.5% (past 30 days) to 99.8% (yesterday) of the time. One-inflated beta regression models were used to examine the associations between antiretroviral adherence outcomes, treatment self-efficacy, depression, anxiety, social support and beliefs/attitudes about medications. Higher percentage of medications taken in the past 30 days was independently associated with higher treatment self-efficacy and fewer symptoms of depression. Adherence monitoring would benefit from focal assessment of youth depression and perceived capacity to follow their antiretroviral regimen.

Introduction

Since Thailand launched the national Access to Care programme in 2000, an estimated 8000 (out of approximately 15,000–20,000) youth living with perinatal HIV (PHIV) in Thailand have received antiretroviral (ARV) treatment, resulting in decreased paediatric HIV mortality and morbidity.[1,2] This has spurred a growing interest in understanding patterns of paediatric ARV medication adherence, particularly as an increased number of youth are surviving into adolescence.[3] Several studies have reported high adherence rates among Thai youth, ranging from 94% based on self-reports among 17- to 24-year-old youth,[4] to 100% based on reports from caregivers ($n = 30$; mean age = five years old),[5] to 98% or greater based on pill counts ($n = 29$; median age = six years old).[6] Although these findings were limited by small samples and

measurement variability, they were consistent with multisite study findings showing that low- and middle-income countries reported comparably greater paediatric adherence than high-income countries.[7,8] Based on caregiver reports, for example, 26% reported

[1]Department of Psychology, Wheaton College, Wheaton, IL, USA
[2]Department of Mathematics and Computer Science, Wheaton College, Wheaton, IL, USA
[3]Department of Internal Medicine, School of Medicine, Yale University, New Haven, CT, USA
[4]Division of Pediatric Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Corresponding author:
Peninnah Oberdorfer, Division of Pediatric Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, 502000, Thailand.
Email: aoberdor@med.cmu.ac.th

non-adherence among HIV-infected youth in the United States and European countries compared to 1% in Thailand.[8] Based on a paediatric prospective cohort study, an analysis of 260 Thai youth and adolescents living with HIV (median age = 14.8 years), the median percentage adherence based on pill count was 99.2% (interquartile range (IQR) 94.7–100%).[9] However, a retrospective analysis of clinical data (2008–2011) from a multisite study of 1139 youth (IQR 3.3–5.5 years) living with HIV in Bangkok and northern Thailand indicated that out of 919 under active follow-up, 21% ($n = 193$) of the youth were on second-line protease inhibitor-based highly active antiretroviral treatment (HAART), and 2.4% were on third-line regimens.[10] The number of youth treated with salvage ARV regimens suggested the likelihood of questionable adherence to first and second-line regimens.

Numerous studies in the United States have cited potential factors associated with poor paediatric ARV medication adherence including low self-efficacy, depression, behavioural challenges, pill burden, younger age, stressful events and low levels of social support.[11–14] Consistent with these findings, a systematic review of studies conducted in low- and middle-income countries including Thailand found that family factors (lack of caregiver availability, parent–child conflicts, poor adult coordination of medication supervision), socio-economic indices (family poverty, low parental educational level) and ARV medication burden were associated with poor paediatric adherence rates.[7] Some have also suggested that since youth in Thailand have taken ARV medications for a shorter period of time than their counterparts in the United States and Europe due to medication availability, they may be less affected by treatment fatigue and side effects of earlier ARV regimens.[8] Moreover, caregivers likely prioritised ARV medication adherence with their children after years of witnessing family members die from AIDS when ARV medications were not yet available.

Few studies have specifically examined emotional–behavioural predictors of ARV adherence among Thai youth with PHIV. If adherence rates are indeed high among this cohort in Thailand, what are potential explanations? Moreover, given the lack of a single optimal assessment of adherence,[15] would multiple subjective measures of adherence confirm the rates reported to date in Thailand? To address these questions, this study will examine potential relationships between established individual predictors (HIV treatment self-efficacy, depression, anxiety, social support and beliefs and attitudes about medications) and ARV medication adherence rates based on subjective self-reports among a cohort of Thai youth receiving ARV treatment in Chiang Mai.

Methods

Participants

Thai-speaking youth living with PHIV, aged 13–21 years receiving HAART medications from three paediatric HIV medical programmes in Chiang Mai were invited to participate in this study between April 2010 and June 2011. Eligibility criteria for participation included: (a) born to an HIV-seropositive mother; (b) confirmed seropositive for HIV and (c) engaged in medical care and/or having a complete medical record available. Overall, we were able to interview 77% (92/119) of eligible families who were approached in the three clinics. In addition to declining participation due to living too far from the clinic, several families cancelled their scheduled interviews due to family illness. During the informed consent process, the youth and their guardians were reassured that their participation was voluntary and refusal to participate did not jeopardise their services at the clinic.

Procedure

The Research Ethics Committees (REC) of each participating site approved the research protocols. Site medical providers identified potential participants by reviewing patient charts and medical appointment schedules for eligibility requirements. Legal guardians provided written informed consent for youth participation, and the youth provided written assent in accordance with the institutional REC guidelines. Viral load (VL) and $CD4^+$ counts at the time of the interview were obtained by reviewing the youths' medical charts (window included six months prior to and one month after adherence interview).[16]

Validated instruments from published adherence studies were translated from English to Thai by a translator and back translated to English by a second independent translator. The medical site staff (i.e. caseworkers, nurses) were trained to explain the informed consent protocol and administer the face-to-face individual interviews with youth during their routine medical appointments. Participants received 300 baht ($10) to cover their transportation expenses to the clinic.

Measures

Dependent variables

Medication adherence. Self-reported medication adherence was measured in two ways.[17] First, participants rated the percentage of time they took their prescribed dosage of ARV medication in the past 30 days

by indicating their responses on a visual analog scale (VAS$_{dose}$) ranging from 0% to 100% ('mark the percentage that matches with your habit of taking your medications last month. 0% means that you have taken no medications; 100% means you have taken every single dose of medications'). VAS$_{dose}$ was analysed as a continuous variable. Second, based on the standard adherence measure used in the Pediatric AIDS Clinical Trials Group (PACTG),[12,18] participants indicated the number of medications, frequency of administering each medication in their daily regimen and whether they had forgotten to take those medications during the past month (yes/no). They then reported the number and frequency of taking each medication the day before and seven days prior to study interview ('how many pills did you take yesterday and this past week [per time/times per day]?'). An adherence percentage rate was calculated that reflected the total number of dosages taken relative to the total number of doses (pills) prescribed over the assessed time period.

Independent variables

HIV treatment self-efficacy. The HIV treatment adherence self-efficacy scale (HIV-ASES)[19] is a 12-item scale used to assess participants' self-perceived confidence in taking their prescribed ARV medications when faced with different barriers. Responses on a Likert scale ranged from 1 (*cannot do it at all*) to 10 (*certain you can do it*). A summative score ranging from 12 to 120 was calculated with higher summative scores indicating higher treatment self-efficacy. Cronbach's alpha for this sample was .89.

Depression. The Center for Epidemiological Studies-Depression Scale (CES-D)[20] is a 20-item self-report symptoms rating scale of depressive symptoms. Respondents rate how often they experience each symptom on a 4-point scale, 0 (*rarely or none of the time*) to 3 (*most or all of the item*), resulting in a summary score ranging from 0 to 60. For this study sample, the Cronbach's alpha was .70.

Anxiety. Two subscales from the Reynolds and Richmond youth's manifest anxiety scale (CMAS),[21] a widely used measure in youth anxiety and paediatric HIV[13,22] adherence studies were administered. Youth responded yes or no to experiencing 10 physical anxiety and 11 worry/oversensitivity questions. The overall score ranged from 0 to 21 and was treated as a continuous variable. Cronbach's alpha for this sample was .80.

Social support. Thirteen items from the social provision scale (SPS)[23] were used to assess the extent to which participants felt supported in their different relationships. Responses on a Likert scale ranged from 1 (*strongly disagree*) to 4 (*strongly agree*). The summative score ranged from 13 to 52 with higher scores indicating more social support. Cronbach's alpha for this sample was .83.

Beliefs and attitudes about medications. Ten items adapted from the Beliefs About Medications Questionnaire[24] were used to measure participants' held beliefs about ARV medications on a Likert scale ranging from 1 (*strongly disagree*) to 4 (*strongly agree*), resulting in a summary score ranging from 10 to 40, with a higher score indicating more positive beliefs and attitudes about ARV medications. In the analysis, a weighted average score was used because many subjects had missing data for some of the individual items. Cronbach's alpha for this sample was .72.

Demographic information. Participant's socio-demographic information was collected, which included age, sex, type of household (e.g. kin or orphanage), guardian HIV-serostatus and education level.

Data analysis

The number of subjects who reported 100% medication adherence for the previous day and past seven days was very high (97% in both cases). However, the mean percentage of adherence reported for the past 30 days (VAS$_{dose}$) was 84% (SD = 0.194). We chose VAS$_{dose}$ as the dependent variable of interest not only because of its sufficient variance but also due to reports that suggested greater accuracy of patient recall of adherence over a long period of time using VAS-based measures.[17] This was further confirmed given that 19% of the youth reported missing doses within the last month. The independent variables considered to potentially affect VAS$_{dose}$ were social support, age, depression, anxiety, self-efficacy and attitude and beliefs about medication. The dependent variable is a proportion, with 35% of the values at 100%. We desired to (a) investigate factors that might influence 100% adherence separately from less-than-100% adherence and (b) use an analysis method that modelled the dependent variable as a proportion (bounded between 0 and 1). We therefore chose to model VAS$_{dose}$ using a one-inflated beta regression model. This regression technique uses a mixture distribution which assumes a beta distribution for values less than 1 and a degenerate distribution with a probability mass parameter for values equal to 1 (this mass parameter gives the probability of a subject having 100% adherence). Beta distributions can take on a variety of shapes, so they are more flexible in modelling proportion data and do not have the symmetry assumption necessary for ordinary

regression. In one-inflated beta regression, three generalised linear models are fit using maximum likelihood with a Newton–Raphson/Fisher scoring algorithm. These three functions model (a) the mean of the beta distribution with a logit link, (b) the precision of the beta distribution with a log link and (c) the probability mass parameter with a logit link. It is not required that the same independent variables influence these three parameters. Therefore, stepwise regression was used for all three models simultaneously with a combination of forward and backward steps, using the generalised Akaike information criterion for variable selection.[25] Additionally, we analysed the same data using a two-part fractional regression model for comparative purposes.[26] For this comparison, we used the same set of explanatory variables that were present in the beta regression model. All modelling was performed using the R programming environment.

Results

Participant characteristics

Ninety-two youths living with PHIV consented to participate in this study. Of those 92, three subjects' data had missing values for age, social support or depression and were removed for all analyses and descriptive statistics calculations resulting in a final sample of 89. Forty-eight percent were men ($n = 43$) and 52% women ($n = 46$) with a median age of 15 years (IQR 14–16 years). Forty percent ($n = 36$) lived with kin-family members, 30% ($n = 27$) in orphanages and 25% ($n = 22$) lived with their biological parent. Fifteen percent of the adult caregivers were HIV-seropositive. Ninety-four percent of the youth were attending school. At the time of the interview, 84% of the youth were treated with first-line ARV medications which comprised of two nucleoside reverse transcriptase inhibitors with a non-nucleoside reverse transcriptase inhibitor.[27] The median duration of time that the youth were on ARV medications was seven years (IQR = 7–8 years) at the time of the interview.

Adherence indicators, VL, CD4$^+$ measures

Descriptive data for all measures are presented in Table 1. Females participants reported higher levels of depression [$t(87) = -2.14$, $p < .05$] and anxiety [$t(87) = -2.59$, $p < .05$] than men. Mean self-reported ARV adherence rates ranged from 83.5% (percentage of medications taken in past 30 days) to 99.8% (percentage taken yesterday; see Table 2). VL and CD4$^+$ counts and percentages within six months prior to and one month after the adherence assessment were retrieved retrospectively from medical records.[16] Fifty-five percent ($n = 49$) of the reviewed charts recorded laboratory values within this time period. For the 49 youths, the median duration of time between the adherence assessment and the VL used in the analysis was two months (IQR 2–4 months). The median CD4$^+$ percentage was 28.0% (IQR 24.0–32.0%) and the median CD4$^+$ count was 646.0 copies/mL (IQR 401.5–840.0 copies/mL). Ninety-two percent ($n = 45$) had VL<400 copies/mL.

Table 1. Descriptive statistics of study variables.

Measure	Women ($n = 46$)	Men ($n = 43$)
Treatment self-efficacy (HIV-ASES)	83 (7.2)	79 (12)
Depression (CES-D)	17 (6.2)	14 (5.7)*
Anxiety (CMAS)	6.7 (4.1)	4.5 (3.7)*
Social support (SPS)	41 (3.9)	39 (4.1)
Beliefs/attitudes about medications (scaled)	31 (3.4)	31 (2.8)
% ARVs taken in past 30 days (VAS$_{dose}$)	88% (16)	79% (22)

Note. Scales with higher numbers indicating a higher level of the construct being measured. Standard deviations are given in parentheses. HIV-ASES: HIV treatment adherence self-efficacy scale; CES-D: Center for Epidemiological Studies-Depression; CMAS: youth's manifest anxiety scale; SPS: social provision scale; VAS: visual analog scale; ARV: antiretroviral.
*$p < 0.05$.

Table 2. Self-reported ARV medication adherence measures.

Measure	Mean (SD)	Counts of % adherent			
		≥95%	90–94%	80–89%	<80%
% of ARVs taken in past 30 days (VAS$_{dose}$)	83.5% (19.4)	34	20	11	24
% of ARVs taken yesterday (PACTG)	99.8% (7.7)	87	0	1	1
% of ARVs taken in past 7 days (PACTG)	99.1% (5.9)	87	0	0	2
Forgot to take medications in past month	No ($n = 72$) Yes ($n = 17$)				

ARV: antiretroviral; VAS: visual analog scale; PACTG: Pediatric AIDS Clinical Trials Group.

ARV medication adherence

The covariates affecting the mean and probability mass parameters of the final model are shown in Table 3. The pseudo-R^2 for the model fit was 0.24. Age and gender were controlled for in the model, as they exhibited evidence of relationship with the dependent variable, VAS_{dose}. Higher mean percentage of medications taken in the past month (VAS_{dose}) was independently associated with higher treatment self-efficacy and lower levels of depressive symptoms (this is reflected in the signs of the parameter estimates for μ seen in Table 3). Furthermore, higher treatment self-efficacy increased the probability of 100% adherence (this is reflected in the signs of the parameter estimate for ν seen in Table 3). To further explain the effect of the parameter estimates on VAS_{dose} with an example, the first two rows of Table 4 show the effect of an increase in age (13–20 years) on predicted VAS_{dose} when treatment self-efficacy (85) and depressive symptoms (15) are held constant (men only in this example). The result is an increase in predicted adherence rate

Table 3. Model results for the one-inflated beta regression model and the two-part fractional regression model.

Parameter	Regressor	Beta regression Estimate (SD)	Fractional regression Estimate (SD)
Mean (μ)	Treatment self-efficacy	0.03 (0.01)***	0.02 (0.01)**
	Age	0.14 (0.05)***	0.16 (0.07)**
	Depression	−0.06 (0.02)***	−0.06 (0.02)****
	Gender	0.41 (0.21)*	0.55 (0.26)**
Probability mass (ν)	Treatment self-efficacy	0.13 (0.04)***	0.13 (0.04)***

*$p < 0.1$, **$p < 0.05$, ***$p < 0.01$, ****$p < 0.001$.

Table 4. Predicted values of adherence for men for various values of the independent variables (for illustrative purposes).

Treatment self-efficacy	Child age	Depression	% ARVs taken past 30 days (VAS_{dose})
85	13	15	69.7
85	20	15	85.8
95	13	15	75.8
85	13	20	63.5

Note. The values for treatment self-efficacy, age and depression are example scores entered into the fitted model, resulting in the VAS_{dose} percentages.
ARV: antiretroviral; VAS: visual analog scale.

(69.7%–85.8%). Similarly, an increase in depression score (see rows 1 and 4) corresponds to a decrease in predicted adherence rate when age and treatment self-efficacy are held constant. No significant associations were found between mean VAS_{dose} and social support, anxiety and beliefs/attitudes about medications.

Discussion

Based on self-reported recall measures of ARV medication adherence, our findings suggest that, on an average, youth with PHIV take their prescribed ARV regimen 83.5% (in the past 30 days) to 99.8% (yesterday) of the time. Moreover, fewer depression symptoms and higher medication self-efficacy were associated with higher self-reported ARV adherence. Although these finding are consistent with previous United States-based studies, it is important to consider several implications in the context of Thai families.

First, the relationship between depressive symptoms and poor ARV medication adherence has been well established in adult and paediatric studies. DiMatteo[28] suggested that depressive markers of hopelessness, social isolation and difficulties with concentration and decision making render daily administration of medications a formidable challenge – especially for youth who concurrently navigate developmental milestones.[29] In a study examining depressive symptoms among Thai high school students in Chon Buri province, negative thinking was the best predictor of depressive symptoms.[30] This is noteworthy given the confluence of illness-specific and developmental stressors that potentially foster negative thinking for youth with PHIV. Moreover, in a study comparing emotional–behavioural problems between youth living with HIV ($n = 50$) and a control group of healthy youth randomly selected from a local school ($n = 56$) in Chiang Mai, caregivers reported more social withdrawal among HIV-infected youth.[31] This highlights the importance of interventions tailored to address *specific* presentations of depression among Thai youth with PHIV.

Second, consistent with previous findings in the United States, high self-efficacy was correlated with medication adherence.[32] The perceived capacity to follow a daily medication regimen is a well-established predictor of adherence and in part can be explained by the information-motivation-behavioural skills model (IMB).[33] The IMB model proposes that medication adherence is largely influenced by information one holds about medication treatment (e.g. drug interaction, side effects), beliefs and attitudes about ARV medication adherence which influences personal (and social) motivation and the requisite behavioural skills and resources to consistently follow one's medication

regimen. However, recent studies in Bangkok proposed broadening the construct of motivation beyond the individual to include social and interrelational motivation.[34] Cultural and developmental scripts that inform the practice of familial and communal responsibilities, especially for an emerging young adult, recast ARV medication adherence as a behaviour that affects not only oneself but also one's family and community. Moreover, Thai-Buddhist cultural scripts that emphasise social and familial obligations further motivate the development of personal sense of efficacy in adhering to medications. This perhaps partially accounts for why social support was not associated with ARV medication adherence in this study. The concern with unduly burdening others with expectations of supporting their adherence behaviour is consistent with the mindset of not negatively affecting the family or community networks with one's illness.

Self-report anxiety was not associated with adherence behaviour. A potential explanation is drawn from studies suggesting that compared with youth in the United States, Thai youth reported higher levels of self-control, emotional restraint and behavioural inhibition.[35,36] Moreover, given that the CMAS used in this study measured underlying anxiety traits, future studies might consider the potential influence of acute or state-based anxiety on adherence behaviour. Attitudes and beliefs about medications were also not associated with ARV medication adherence. The providers at the study sites suggested that medication administration has essentially become routine and normalised to the extent that youth follow their medication regimen not necessarily because of a specific set of personal beliefs about medications, but rather due to a process of accepting that is part of their daily routine.

This raises a final noteworthy point. High and consistent rates of ARV medication adherence among Thai youth with PHIV are unquestionably promising. However, previous adherence studies and provider reports caution that stable adherence does not necessarily imply that the *process* of taking medication is easy, particularly for older youth.[29,37] As such, it is recommended that providers assess for medication adherence behaviour (e.g. did you take your medication in the past two days?) and invite youths to discuss their *experiences* of following their daily regimens (e.g. how has it been taking your medications this week?). This provides a richer contextual understanding of factors that potentially impede or facilitate adherence behaviour for Thai youth.

Several limitations of this study were noteworthy. First, findings from this cross-sectional study represented retrospective recall of ARV medication adherence at a single point in time and did not allow us to determine the temporal influences of select predictors on adherence outcomes. Second, participants in this study were sampled from families actively receiving and engaged with medical care at paediatric HIV programmes in Chiang Mai. As such, the findings could not be generalised to Thai youth living with PHIV who might not be linked with medical services due to illness condition, or logistic barriers to accessing and engaging in care. Presumably, families who are actively engaged in medical care at the study sites are perhaps more involved in the child's overall care – including oversight of medication administration. Moreover, 30% of the youth in this study lived in orphanages, where staff generally monitor and supervise the residents' daily medication administration in a structured manner. This potential selection bias should be accounted for when interpreting the high rates of self-reported ARV medication adherence in this study. Third, the use of youth self-report measures without corroborating guardian and medical provider reports potentially provides a less comprehensive account of adherence rates. Moreover, the small variation in reported adherence rates coupled with a moderate sample size could mask or hide stronger effects of the predictor variables on adherence outcomes. Fourth, self-reports have the potential for inaccurate recall and social desirability bias – especially since the participants were interviewed by the medical staff. To minimise this common limitation in adherence studies, we assessed for both general and specific estimates of missed medication dosages within short (yesterday) and longer periods time (past 30 days) with multiple questions. Finally, due to the nature of a retrospective medical chart review, several objective indices that would validate self-reports of adherence were unavailable, including VL at the start of ARV treatment and within two to four weeks of adherence assessment, and markers of medication resistance. Notwithstanding these limitations, this is the first study to our knowledge to examine individual emotional–behavioural predictors of ARV medication adherence, suggesting that most Thai youth living with PHIV who are actively receiving medical care are following their ARV medication regimen as prescribed based on validated adherence assessments.[38] Theoretical models informed by both quantitative and qualitative studies are needed to further *explain* the relationships between adherence and factors such as depressive symptoms and self-efficacy, in order to continue supporting Thai youth as they navigate the daily demands of taking their medications.

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