Original Article

Depressive Disorders and Virologic Failure in Adolescents with Perinatally Acquired HIV in Northeast Thailand

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Background: Children with perinatally acquired HIV, growing into adolescence, go through a period of change during which adherence to antiretroviral therapy can decrease, and mental health disorders are most often diagnosed for the first time.

Objective: To investigate the prevalence of depressive disorders and factors associated with virologic failure in adolescents with perinatally acquired HIV under care at a tertiary hospital in Northeast Thailand.

Materials and Methods: The present study was a cross-sectional study conducted between June 2017 and October 2018 at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. Participants with perinatally acquired HIV aged 12 to 24 years old who disclosed their HIV status and had been taking antiretroviral therapy for at least one year were interviewed by the psychiatrist, using DSM-5 criteria of depressive disorders. The diagnosis was made concurrently with psychiatric interventions in those who met indications for treatment. Virologic failure was defined as plasma HIV-1 RNA greater than 1,000 copies/mL. Factors associated with virologic failure were evaluated by univariable and multivariable analyses.

Results: Seventy-nine participants were enrolled. Their median age was 17.5 years old, with an interquartile range of 14.9 to 18.9, and 57% were female. Nine had virologic failure and 14 (17.7%) were diagnosed with depressive disorders. On multivariable analysis, depressive disorders were associated with virologic failure (adjusted odds ratio 7.55, 95% CI 1.65 to 34.65).

Conclusion: The prevalence of depressive disorders in adolescents with perinatally acquired HIV was 17.7%. Depressive disorders were found to be one of the factors associated with virologic failure.

Keywords: Depressive disorders; Adolescents; Perinatally acquired HIV; Virologic failure

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Antiretroviral therapy (ART) has allowed children with perinatally acquired HIV to grow up into adolescents. This is a period of changes in their life when they transition from dependence on caregivers to being responsible for their own HIV treatment. The problems of poor medication taste, secrecy, or stigma, especially the needs to take medications at school or at work can contribute to poor adherence. This transition period also is the time that they are vulnerable to develop depression[1-3]. The prevalence of depressive symptoms among children and adolescents living with HIV in a matched case-control study in Tanzania was 27% compared to 5.8% in a control group[3]. A cross sectional study among 82 adolescents with HIV in urban Uganda found depression in 40.8%[4]. A cross-sectional study in 224 adolescents living with HIV in a rural Uganda found that 16% had major depressive disorder. Stigma and bullying were strongly associated with major depressive disorder and suicidality[5]. A study in 195 adolescents and young adults with perinatal HIV in Thailand and Cambodia measured depression using the Child Depression Inventory for children younger than 15 years, or the Center for Epidemiologic Studies Depression Scales for youth of 15 years or older, found depressive symptoms in 34.7% among those with HIV-related enacted stigma compared to

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16.0% in those without[6]. Recently, a study from two pediatric HIV centers in Thailand among 149 participants aged 15 to 25 years, in which 94% were perinatal HIV, found prevalence of depressive symptoms at 11% by using PHQ-9 as the screening tool[7], and only those who had PHQ-9 scores of 9 or more were later interviewed by psychiatrists to confirm the diagnosis but the association of mental problems with virologic failure were not investigated. There was no report on the overall prevalence of depressive disorders diagnosed by psychiatric interview in Thai adolescents with perinatal HIV.

Factors that can contribute to virologic failure include drug resistance, drug toxicity, non-disclosure of HIV status, lack of family support, and poor adherence to ART[8,9]. A systematic review and meta-analysis of 95 studies conducted among children and adults found that depression was significantly associated with non-adherence to ART[10]. Early detection of depression and appropriate intervention can improve adherence and therefore, HIV treatment outcomes[11].

There are different methods used to measure adherence to ART and the results can significantly vary[12,13]. A study that compared three different adherence monitoring tools in Thai and Cambodian children with HIV age 1 to 12 years found that only the child self-report of any missed dose since the previous clinic visit showed a strong association with virologic failure[14]. However, there is no gold standard for assessing ART adherence in routine clinical practice and virologic failure is often used as a reference standard for adherence[15].

Srinagarind Hospital, Khon Kaen University is a tertiary-care referral center in Northeast Thailand for HIV-positive children and adolescents who experienced treatment failure. After achieving virologic resuppression, some patients develop virologic failure, despite extensive adherence counselling and support. The authors used pill counts and self-report of any missed doses in the past week to monitor adherence, but could not detect any adherence problem, leading to the authors' exploration on mental health issue. The present study aimed to determine the prevalence of depressive disorders in adolescents with perinatal HIV by psychiatric interview to concurrently provide psychiatric support and intervention in adolescents who need this support, especially those with virologic failure. The authors also investigated the association of depressive disorders with virologic failure.

Materials and Methods

A cross-sectional study was conducted between June 2017 and October 2018 at the Pediatric HIV Clinic, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. During a regular clinic visit, adolescents with perinatally acquired HIV, age 12 to 24 years old, who had been taking ART for at least one year and disclosed their HIV status were invited to participate in the present study. Adolescents who had already received treatment for psychiatric disorders, those who had significant hearing loss, other neurological disorders such as cerebral palsy, seizure disorders, history of severe head trauma, and stroke, and severe intellectual disability were excluded. Written informed consent was obtained from eligible adolescents or from a parent or legal custodian for adolescents less than 18 years of age by a research nurse. Adolescents were classified as perinatally-acquired HIV if they had known exposure to maternal HIV infection or were diagnosed with HIV before the age of 13 years old without other risk factors such as blood transfusion or sexual abuse. One of the three psychiatrists interviewed the participants using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria[16] of the following depressive disorders, 1) major depressive disorder, 2) persistent depressive disorder, 3) disruptive mood dysregulation disorder, 4) other specified depressive disorder, and 5) unspecified depressive disorder. The psychiatrists were unaware of the viral load test results of the patients. Then the psychiatrist recorded the diagnosis, notified pediatrician if the participant needed further follow-up or treatment such as antidepressant medication. Psychiatric follow-up was scheduled within three months. The present study was approved by the Khon Kaen University Ethics Committee in Human Research (COA No. HE 601179).

Demographic data including age, gender, duration of ART, highest level of education, parental status, and relationship of caregiver and the participant were collected. The authors used the Centers for Disease Control and Prevention (CDC) Classification System to define the most severe clinical categories that the participants ever experienced[17]. The most recent CD4 and viral load were the closest results such as within three to six months before the psychiatric evaluation. The ART regimen was the most recent regimen the patient took prior to the time of the psychiatric evaluation. First line and second line regimens were defined as two nucleoside reverse-transcriptase inhibitors plus a non-nucleoside

Table 1. Characteristics of study participants

Variable	Total (n=79)	Depressive disorders		p-value[a]
		No (n=65)	Yes (n=14)	
Sex; n (%)				0.56
Male	34 (43.0)	27 (41.5)	7 (50.0)	
Female	45 (57.0)	38 (58.5)	7 (50.0)	
Age at test (years); median (IQR)	17.5 (14.9 to 18.9)	17.25 (14.9 to 18.9)	18.7 (16.0 to 20.5)	0.09
Duration on ART (years); median (IQR)	12.0 (9.5 to 14.6)	11.4 (9.5 to 14.2)	13.3 (11.6 to 14.6)	0.26
Most recent CD4 count (cells/mm^3); median (IQR)	641 (468 to 753)	654 (502 to 747)	500 (305 to 775)	0.14
ART regimen; n (%)				0.93
First line	37 (46.8)	31 (47.7)	6 (42.9)	
Second line	27 (34.2)	22 (33.8)	5 (35.7)	
Third line	15 (19.0)	12 (18.5)	3 (21.4)	
Most recent viral load; n (%)				0.007
<1,000 copies/mL	70 (88.6)	61 (93.8)	9 (64.3)	
>1,000 copies/mL	9 (11.4)	4 (6.2)	5 (35.7)	
Highest CDC clinical category ever; n (%)				1.00
A	21 (26.6)	17 (26.2)	4 (28.6)	
B	42 (53.2)	35 (53.8)	7 (50.0)	
C	16 (20.2)	13 (20.0)	3 (21.4)	
Vital status of mother; n (%)				0.89
Alive	37 (46.8)	31 (47.7)	6 (42.9)	
Died	35 (44.3)	28 (43.1)	7 (50.0)	
Unknown	7 (8.9)	6 (9.2)	1 (7.1)	
Vital status of father; n (%)				0.86
Alive	27 (34.2)	23 (35.4)	4 (28.6)	
Died	38 (48.1)	31 (47.7)	7 (50.0)	
Unknown	14 (17.7)	11 (16.9)	3 (21.4)	
Caregiver; n (%)				0.76
Family member	48 (60.8)	40 (61.5)	8 (57.1)	
Group home	31 (39.2)	25 (38.5)	6 (42.9)	
Highest education; n (%)				0.19
Primary school	15 (19.0)	13 (20.0)	2 (14.3)	
Secondary school	57 (72.1)	48 (73.8)	9 (64.3)	
Higher than secondary	7 (8.9)	4 (6.2)	3 (21.4)	

ART=antiretroviral therapy; CDC=Centers for Disease Control and Prevention; IQR=interquartile range

[a] Data compared using Pearson's chi-squared test or Fisher exact test as appropriate for categorical variables and Wilcoxon rank sum test for continuous variables

reverse-transcriptase inhibitor, and any regimen plus a ritonavir-boosted protease inhibitor, respectively, whereas third line regimen was defined as any drug plus an integrase inhibitor. Virologic failure was defined as plasma HIV-1 RNA of more than 1,000 copies/mL. Factors associated with virologic failure including duration on ART, vital status of parents, types of caregivers, level of education, and presence of depressive disorders were evaluated by using univariable analysis and variables with a p-value of less than 0.2 were considered in multivariable analysis with level of significance at p-value less than 0.05. Statistical analyses were conducted using Stata, version 10 (StataCorp LP, College Station, TX, USA).

Results

One hundred five adolescents with HIV were being followed up at the authors' clinic, 103 cases were perinatally acquired HIV (98.1%), 79 of these 103 (76.7%) participated in the present study. The median age was 17.5 years old (IQR 14.9 to 18.9, min-max 12.0 to 22.8) and 45 (57.0%) were female. Characteristics of the study participants are presented in Table 1. The median duration of ART was 12.0

Table 2. Factors associated with virologic failure (VL >1,000 copies/mL) by univariable and multivariable analysis

Variable	Virologic failure		Univariate analysis		Multivariate analysis	
	n/N	%	OR (95% CI)	p-value	aOR (95% CI)	p-value
Sex						
Male	3/34	8.8	Ref.			
Female	6/45	13.3	1.59 (0.37 to 6.87)	0.53		
Age (years)						
12 to <18	3/41	7.3	Ref.			
>18	6/38	15.8	2.38 (0.55 to 10.26)	0.23		
Duration on ART						
<9 years	1/18	5.6	Ref.			
>9 years	8/61	13.1	2.57 (0.30 to 22.02)	0.34		
ART regimen						
First + second	7/64	10.9	Ref.			
Third	2/15	13.3	1.25 (0.23 to 6.74)	0.80		
Highest CDC clinical category ever						
A	2/21	9.5	Ref.			
B/C	7/58	12.1	1.30 (0.25 to 6.84)	0.75		
Vital status of mother						
Alive	4/37	10.8	Ref.			
Died	4/35	11.4	1.06 (0.24 to 4.63)	0.93		
Unknown	1/7	14.3				
Vital status of father						
Alive	3/27	11.1	Ref.			
Died	4/38	10.5	0.94 (0.19 to 4.59)	0.94		
Unknown	2/14	14.3				
Caregiver						
Family member	7/48	14.6	Ref.			
Group home	2/31	6.5	0.40 (0.08 to 2.09)	0.25		
Education						
≤ Secondary	7/72	9.7	Ref.		Ref.	
> Secondary	2/7	28.6	3.71 (0.60 to 22.83)	0.19	2.22 (0.30 to 16.70)	0.44
Depressive disorders						
No	4/65	6.2	Ref.		Ref.	
Yes	5/14	35.7	8.47 (1.91 to 37.57)	0.02	7.55 (1.65 to 34.65)	0.01

OR=odds ratio; aOR=adjusted odds ratio; CI=confidence interval; ART=antiretroviral therapy; CDC=Centers for Disease Control and Prevention

years (IQR 9.5 to 14.6) and more than half of them were on second- or third-line regimen. Twenty percent of them had experienced AIDS-defining opportunistic infections in the past. Forty-eight (60.8%) participants lived with their family members and 64 (81.0%) attended or completed secondary school or higher. Nine participants had virologic failure (11.4%; 95% CI 5.3 to 20.5), with a median viral load of 69,936 copies/mL (IQR 13,195 to 92,341). All had genotypic drug resistance testing, and none had detectable resistance to their current regimens. No participants had any drug toxicity or drug interaction due to their ART regimens. Fourteen participants (17.7%; 95% CI 10.0 to 27.9) were diagnosed with depressive disorders, in which five had virologic failure (5/14, 35.7%). Among 65 participants with no depressive disorders, four (6.2%) had virologic failure. The diagnosis of depressive disorders included major depressive disorder in one case, persistent depressive disorder or dysthymia in seven cases, and there were three cases each of other specified depressive disorder and unspecified depressive disorder. All of them were advised by the psychiatrist on their diagnoses and plan of follow up.

Variables with a p-value of less than 0.2 by univariable analysis were education higher than secondary school with odds ratio (OR) 3.71 (95% CI 0.60 to 22.83, p=0.19), and depressive disorders (OR

8.47, 95% CI 1.91 to 37.57, p=0.2), respectively. In multivariable analysis, depressive disorders were the significant variable associated with virologic failure (adjusted OR 7.55, 95% CI 1.65 to 34.65, p=0.01) (Table 2).

The five participants who had both depressive disorders and virologic failure were advised to take antidepressants. Three of them agreed to start the treatment. At one year follow-up, two of these three had HIV viral load tests of less than 1,000 copies/mL, the third patient's viral load was 14,655 copies/mL, and had no change from the pre-antidepressant level. Of the two participants who declined antidepressant treatment, one had viral suppression and the other had persistent virologic failure at 8,215 copies/mL.

Discussion

In the present study, the prevalence of depressive disorders in adolescents with perinatally acquired HIV was 17.7%, which was found to be associated with virologic failure. A study in Uganda among a sample of 336 adolescents living with HIV reported prevalence of depressive symptoms as 45.8% (95% CI 40.5 to 51.2) using the CES-D self-reported inventory scale, but they did not confirm whether those adolescents had a diagnosis of depressive disorder after screening[18]. In the study of 562 adolescents living with HIV in Malawi using a clinician interview hand-rated instrument tool called the Children's Depression Rating Scale, Revised (CDRS-R), 18.9% were found to have depression[2]. While the prevalence of depression or depressive disorders can vary depending on the instrument used and the characteristics of the study population, the high rates of depressive symptoms and disorders in adolescents and youth with HIV are concerning and contribute to their struggles with life-long adherence to HIV treatment[19,20].

Factors associated with ART adherence are pill burden, disclosure status, stigma, family support, and mental health problems such as depression[13,20]. Treatment of depression in adults has been associated with improved mental health and improved ART adherence and treatment outcomes[21,22], but few studies have been done in adolescents[23].

The strength of the present study is the use of psychiatric interview to diagnose depressive disorders to concurrently provide psychiatric support and intervention to those who need it. The limitations of the present study were 1) the time consuming of psychiatric interview and intervention. This might not be feasible in setting with many patients and limited availability of psychiatric personnel, in which other screening tools should be used. 2) The present study was a cross sectional study, so the temporal sequence of depression and virologic failure could not be ascertained. 3) Factors that were reported to be associated with depression and ART adherence such as internalized stigma and bullying or other types of mental disorders such as anxiety were not screened for. 4) The authors assessed the prevalence of depression in only adolescents with perinatal HIV because this clinic had only two cases of non-perinatally acquired HIV and they were doing well with virological suppression. 5) The sample size was small because the authors included only those who were treated at the present study clinic, so the result could not be generalized to other population.

However, the present study findings highlight the importance of depressive disorders as one of the factors associated with virologic failure in adolescents living with HIV. Further study on mental health issues such as stigma, bullying, and depressive and anxiety disorders in a larger sample of HIV positive youth is needed.

Conclusion

The prevalence of depressive disorders in adolescents with perinatally acquired HIV was 17.7%. Depressive disorders were found to be one of the factors associated with virologic failure.

What is already known on this topic?

Depressive disorders are common among adolescents living with HIV. This can contribute to non-adherence.

What this study adds?

Success for HIV care in adolescent includes HIV medication, adherence support, and more importantly mental health intervention in those who need it for sustaining medication adherence and achieving viral suppression.

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Conflicts of interest

No potential conflict of interest was reported by the authors.

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