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Impact of Antiretroviral Therapy on Quality of Life in HIV-Infected Southeast Asian Children in the PREDICT Study

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Abstract

Quality of life (QOL) is an important antiretroviral treatment (ART) outcome. We compared QOL among 299 Thai and Cambodian children ages 1–12 years-old, CD4 15–24% randomized to early (ART at week 0, $N=149$) versus deferred groups (ART when at CD4 <15%, $N=150$) and also compared with QOL data from age-matched healthy controls ($N=275$). Primary caregivers completed PACTG QOL questionnaires at week 0 and every 24 weeks until 144 weeks. Children were enrolled during March 2006 to September 2008. Mean (SD) age of children was 6.3 (2.8) years, 58% were female, 60% were Thai, %CDC N:A:B:C was 2:62:36:0%. During 144 weeks, all children in the early-group and 69 (46%) of deferred-group children started ART. There was no significant difference of QOL scores between treatment groups at baseline (all $p>0.05$) and at week 144 (all $p>0.05$). By multivariate analysis, the early-group had higher QOL score changes in five domains, including health perception ($p=0.04$), physical resilience ($p=0.02$), psychosocial well-being ($p=0.04$), social and role functioning ($p<0.01$), and symptoms ($p=0.01$) compared to the deferred group. QOL of HIV-infected children in both groups were lower than healthy control in all 7 domains at baseline (all $p<0.05$) and 5 of 7 domains at weeks 144 ($p<0.01$). In conclusion, no significant difference of QOL scores between treatment groups. Early ART commencement associated with greater increase of QOL scores over 144 weeks. QOL scores in HIV-infected children were lower than healthy controls.

Introduction

Quality of life (QOL) represents general well-being of individuals. Living with a chronic illness can affect children's QOL.[1–3] Currently, HIV-infected children treated with highly active antiretroviral therapy (HAART) have increased life expectancy.[4–6] Deaths related to HIV/AIDS mortality have decreased significantly, but the non-AIDS-related conditions maintain a stable trend in children living with HIV-1 after treatment with HAART.[7] Unlike many other chronic illnesses, children with HIV infection are more likely to experience more difficulties in their daily lives (e.g., parental death from AIDS and social stigmatization[8,9]) which may worsen their QOL. Lee et al.[3] reported significantly lower QOL scores in HIV-infected children as compared to HIV-exposed but uninfected children. In addition,

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long-term requirement for life-saving antiretroviral therapy (ART) with pill burden and its side effects may affect children's QOL. The majority of QOL reports in HIV-infected children were from resource-rich settings, and conducted as cross-sectional studies in children already treated with ART.[3,10–12] There are limited data of QOL change before and after ART initiation in HIV-infected children without AIDS symptoms.[13]

Our team has conducted a multicenter, randomized, open-label study of early versus deferred ART among Thai and Cambodian ART-naïve HIV-infected children with CD4 15–24% (Pediatric Randomized of Early vs. Deferred Initiation in Cambodia and Thailand; The PREDICT study).[14] The baseline QOL, before ART, of these children has been previously reported showing relatively low QOL scores compared to previous reports from untreated HIV-infected children in Western countries, and also lower than ART-treated Thai HIV-infected children from Northern Thailand.[3,13,15] Higher CD4% and CD4 cell count were associated with higher QOL scores in the health perception domain in Thai and Cambodian HIV-infected children.[13] Here, we report the effect of ART initiation on QOL in children over 144 weeks in the PREDICT study.

Methods

This report is a substudy of the PREDICT study (clinicaltrials.gov identification number NCT00234091). PREDICT is an open label, randomized control trial to compare the timing of ART initiation in ART-naïve HIV-infected children over 144 weeks.[14] The eligibility criteria were HIV-infected children, aged 1–12 years, CDC clinical classification N (no HIV symptoms), A (mild HIV symptoms), or B (moderate HIV symptoms),[16,17] ART-naïve, CD4 15–24%, and no active opportunistic infections at screening visit.

Children were enrolled during March 2006 and September 2008 from seven sites in Thailand and two sites in Cambodia, and followed by scheduled visit every 12 weeks until 144 weeks. Children were randomized to the early-group (started ART at week 0) versus the deferred-group (started ART when a confirmed CD4 was <15% or development of a CDC classification C event). At each visit, the children had a medical history taken, body weight, height measurement, and physical examination. The complete blood count, CD4%, CD4 counts were performed every 12 weeks, and plasma HIV-RNA by Roche Amplicor assay (Palo Alto, USA) were performed every 24 weeks.

Due to limited data of QOL in healthy children, therefore, we also conducted a cross-sectional collection data of QOL in healthy children by enrolling age-matched HIV-negative Thai and Cambodian children, and asked their caregivers to complete the same QOL questionnaires. These healthy children were enrolled from PREDICT sites in Thailand and Cambodia with the same proportion of Thai/Cambodian (60:40) to proportion of HIV-infected children in PREDICT study. Their data were used as the control group. Information about the family, including education level of primary caregivers and biological or nonbiological caregivers and the self-reported monthly income were recorded. Biological caregiver was defined as father or mother. Self-reported monthly income was reported from perception of caregivers as below average, average, or above average. The study was approved by national and local institutional review boards. All caregivers of the HIV-infected children gave consent prior to enrollment.

Quality of life questionnaire and transformed scores

The primary caregiver completed the General Health Assessment for Children QOL questionnaire[3,13,18] at the baseline visit and every 24 weeks until weeks 144. There are three forms for children ages 6 month–4 years, 5–11 years, and 12–20 years, respectively. The Thai version of the QOL questionnaire, translated from the English version of General Health Assessment for Children QOL questionnaire, was validated with good reliability.[13,15] In addition, the English version of General Health Assessment for Children QOL questionnaire was used for translation and back translation of the Cambodian version which was previously validated and used.[13] It took 20–30 min per each visit to complete this questionnaire. The study nurses read the QOL questions to the caregivers and filled in their responses for illiterate caregivers. The primary caregiver responsible for each orphanage child completed the questionnaire.

There are seven QOL domains including: (1) health perception, (2) physical resilience, (3) physical functioning, (4) psychosocial well-being (for children 5–11 years old only), (5) social and role functioning, (6) health care utilization, and (7) symptoms. The raw scores in all seven domains had different minimum and maximum values, therefore, the raw scores were calculated to simple transformed scores of 0 to 100 with the following formula: transformed score = [(actual raw score – lowest possible raw score)/ (highest possible raw score – lowest possible raw score)] × 100].[3,10,13,19] For items with mixed or negative directionality, scores were reverse coded so that higher scores indicated higher QOL.[3,10,13]

Statistical analysis

We used descriptive statistics to summarize demographic and clinical characteristics of the HIV-infected children and healthy controls. The nonparametric Wilcoxon rank-sum test was used to compare continuous variables between treatment groups. Chi-square test was used in the case of categorical variables. Changes in QOL score from baseline to week 144 were assessed using the Wilcoxon matched-pairs signed-rank test. To evaluate the effect of timing of ART on QOL, we performed subgroup analysis only in the deferred group. We categorized deferred-group children according their ART status at weeks 144.

To identify the predictors of greater increase QOL score over time, random effect linear regression model of QOL score changes overtime were adjusted for baseline QOL score and study week. Predictors of mean change in QOL score were age, gender, CDC class, ethnic, weight, height, CD4%, HIV-RNA, HIV status disclosed, recent negative life events (i.e., parental job loss, divorce of parents, very ill family member, death in family; recent negative life events scores ranged from 0–18),[20] education of primary caregivers, biological or nonbiological caregiver, self-report monthly income by perception of caregivers, and treatment groups. All variables associated with QOL at the level of $p < 0.10$ in the univariate analysis were used to build the multivariate models. Statistical analyses were performed using STATA, version 11.2 (StataCorp, College Station, TX, USA).

Results

Patient demographics and clinical characteristics

Among 299 enrolled children, 149 children were randomized to the early group and 150 children were randomized to the deferred group. All were vertically HIV-transmitted children. The mean (SD) age was 6.3 (2.8) years, 58% were female, and proportion of children with CDC clinical classification N:A:B was 2:62:36%, respectively. Sixty percent were enrolled from Thai sites, and 29% were reported by their caregiver to know their HIV status. Five most common negative life events were death in family (11.7%), family member was hospitalized (11.6%), parent lost job (10.7%), family member was very sick (6.9%), and family member left home (5.2%). Thirty seven (12%) children were living in orphanages. The baseline characteristics are shown in Table 1.

The characteristics of 275 HIV-negative control group are; 58% were female, proportion of Thai versus Cambodian were 59:41%, mean (SD) age was 7.1 (3.1) years. The education levels of primary caregivers of this control group were; no education 8%, elementary school 40%, high school 30%, higher than high school 20%, and no data available 2%.

One hundred and forty-nine children in the early-group, and 69 children in the deferred-group received ART during the follow-up period. The reasons for starting ART in children in the deferred group were meeting immunologic criteria in 66 children and developing clinical events in 3 children (1 *Pneumocystis jiroveci* pneumonia and 2 severe thrombocytopenia). The mean (SD) CD4% at time of ART initiation in the deferred group was 14% (2.8). The ART regimens included zidovudine/lamivudine/nevirapine (201 children, 92.2%), zidovudine/lamivudine/lopinavir-ritonavir (10 children, 4.6%), and others (7 children, 3.2% with zidovudine/lamivudine/efavirenz or abacair//lamivudine/nevirapine).

At end of the study, 142 children (95%) in the early group and 147 children (98%) in the deferred group completed follow up at weeks 144. The mean (SD) CD4% at week 144 in the early group was 33.2% (6.4) and in the deferred group was 24.8% (7.4), $p < 0.001$.

Quality of life scores

Mean (SD) score of QOL domains for all children and by treatment arms at baseline and week 144 are presented in Table 2. There was no significant difference of QOL scores between treatment groups at baseline (all $p > 0.05$) and at week 144 (all $p > 0.05$). When QOL scores were compared between weeks 144 and baseline, children in early group had significantly increased scores in six domains, except social functioning (Table 2). Children in the deferred group also had significantly increased scores in four domains except physical resilience, psychosocial well-being, and social functioning (Table 2).

When compared with QOL data of healthy children, HIV-infected children had lower baseline QOL scores in all seven domains (all $p < 0.05$) (Table 2). At weeks 144, HIV-infected children in the early group and deferred group had lower QOL scores in five domains compared with QOL data of healthy children (all $p < 0.05$) (Table 2).

Quality of life scores in deferred group

The baseline mean QOL scores of 81 children in the deferred group who were still ART-naïve at week 144 was

Table 1. Demographic Characteristics of HIV Infected Children at Baseline

	Early group (N = 149)	*Deferred group (N = 150)*	*Total HIV-infected children (N = 299)*
% Female	52%	64%	58%
% Thai: Cambodian	60.: 40%	59:41%	60:40%
Age at baseline (years)	6.1 (2.8)	6.5 (2.8)	6.3 (2.8)
Weight for age z-score	−1.3 (1.1)	−1.3 (1.0)	−1.3 (1.0)
Height for age z-score	−1.6 (1.4)	−1.7 (1.3)	−1.6 (1.3)
Weight for height z-score	−0.5 (1.0)	−0.5 (1.0)	−0.5 (1.0)
Body mass index (kg/m^2)	15.3 (1.7)	15.1 (1.7)	15.2 (1.7)
%CDC category N:A:B	3:61:36	1:63:36	2:62:36
Baseline CD4%	19.4 (4.8)	20.6 (4.3)	20.0 (4.6)
Baseline HIV-RNA $\log_{10}$ copies/mL	4.7 (0.6)	4.6 (0.6)	4.6 (0.6)
HIV status disclose; *n* (%)	42 (28)	46 (31)	88 (29)
Recent negative life event score	1.4 (1.9)	1.3 (1.9)	1.4 (1.9)
% children living in orphanages	20 (14.4)	18 (12.4)	38 (13.4)
Biological caregivers as primary caregivers; *n* (%)	93 (62.4)	94 (62.6)	187 (62.5)
Education level of primary caregivers; n (%)			
No education	17 (11)	23 (15)	40 (13)
Elementary school	65 (44)	62 (41)	127 (42)
High school	40 (27)	42 (28)	82 (27)
Higher than high school	16 (11)	18 (11)	34 (13)
No data available	11 (7)	5 (5)	16 (5)
Monthly income by perception of primary caregivers; n (%)			
Below average	78 (52)	81 (54)	159 (53)
Average	38 (26)	40 (27)	78 (27)
Above average	2 (1)	2 (1)	4 (1)
No data available	31 (21)	27 (18)	58 (19)

Data are presented as mean (SD) or percentage; ART, antiretroviral therapy.

Table 2. Comparison of Quality of Life Scores Between HIV-Infected Children Categorized by Treatment Arms and Healthy Children

	Baseline						Week 144					
	Healthy children	*All HIV-infected children*	p^a	*Early*	p^a	*Deferred*	p^a	*All HIV-infected children*	p^a	*Early*	p^a	*Deferred*	p^a
Health perception	79.9 (13.2)	70.5 (17.4)	<0.01	69.6 (16.5)	<0.01	71.2 (18.2)	<0.01	77.2 (12.8)	<0.01	77.6 (12.1)[b]	<0.01	76.9 (13.5)[b]	<0.01
Physical resilience	77.3 (12.6)	70.4 (13.1)	<0.01	69.2 (13.2)	<0.01	71.6 (13.1)	<0.01	74.6 (12.1)	<0.01	75.8 (11.7)[b]	<0.01	73.5 (12.4)	<0.01
Physical functioning	90.4 (13.7)	87.2 (12.8)	<0.01	86.8 (12.5)	<0.01	87.7 (13.1)	<0.01	93.7 (11.4)	<0.01	94.1 (11.2)[b]	<0.01	93.4 (11.7)[b]	0.03
Psychosocial well-being	84.7 (11.7)	78.7 (15.8)	<0.01	77.4 (17.4)	<0.01	79.6 (14.4)	0.01	83.2 (14.9)	0.68	84.2 (13.6)[b]	0.87	82.7 (14.7)	0.41
Social functioning	98.4 (4.8)	96.5 (8.1)	0.01	96.3 (8.6)	0.03	96.7 (7.7)	0.03	97.3 (7.3)	0.24	97.4 (8.1)	0.77	97.4 (6.4)	0.10
Health care utilization	99.1 (3.1)	92.6 (7.1)	<0.01	93.0 (7.0)	<0.01	92.0 (7.4)	<0.01	96.1 (4.8)	<0.01	96.2 (4.8)[b]	<0.01	96.1 (4.9)[b]	<0.01
Symptoms	96.4 (4.4)	90.5 (7.7)	<0.01	91.1 (7.2)	<0.01	89.8 (8.3)	<0.01	94.3 (6.1)	0.01	95.0 (6.0)[b]	0.01	93.6 (6.3)[b]	<0.01

Data are presented as mean (SD). [a]p values were compared with QOL scores in age-matched healthy children. [b]When compared within this arm, the QOL scores in this domain increased significantly compared to baseline scores ($p < 0.01$).

higher in physical functioning ($p = 0.01$) and lower in social functioning ($p = 0.003$), as compared to 69 children in the deferred group who were started ART during study (Table 3). At week 144, there was no significant difference between QOL scores in all domains when comparing the deferred group children who started ART versus the deferred children who were still ART-naïve (all $p > 0.05$) (Table 3).

Predictors of change of QOL scores over 144 weeks

By multivariate analysis, the early group had a greater increase of QOL scores over 144 weeks in five domains; health perception ($p = 0.04$), physical resilience ($p = 0.02$), psychosocial well-being ($p = 0.04$), social and role functioning ($p < 0.01$), and symptoms ($p = 0.01$), as compared to the deferred group (Table 4). Caregivers of Thai children reported greater increase in health perception, but caregivers of Cambodian children reported more significant increases of three QOL domains (physical functioning and psychological well-being, social and role functioning, and symptoms). Older age of children at baseline was associated with a greater increase in two QOL domains (physical resilience and physical functioning). The other predictors of change of QOL scores over 144 weeks are shown in Table 4. No association of gender, living in orphanages, HIV disclosure status, recent negative life events, weight for age, and baseline CD4% with the changes of QOL was found.

Discussion

Our study compared QOL over 144 weeks among ART-naïve HIV-infected children who initiated ART when CD4 was between 15–24% and when CD4 was <15%. There was no significant difference of QOL scores between treatment groups at baseline and at week 144. By multivariate analysis, the early group had a greater increase of QOL scores in five domains over 144 weeks compared to the deferred group. When compared to age-matched healthy controls, the HIV-infected children in both treatment arms had significantly lower QOL scores in all domains.

In a cross-sectional study in the US, HIV-infected children who were receiving ART had higher QOL than children who were not receiving ART.[3] In contrast to that study,[3] the early group had higher QOL scores in all domains at weeks 144 but did not reach statistical difference compared to the deferred group. When compared QOL scores at weeks 144 to baseline scores within treatment groups (Table 2), children in the early group had significantly increased scores in six domains, and children in the deferred group also had significant increased QOL scores in four domains. In addition, children in the deferred group who were still ART-naïve at the end of the study had no significant difference in QOL scores in all domains at week 144 compared to children in the deferred group who started ART during the study (Table 3). It is possible that we enrolled HIV-infected children with quite good baseline clinical (no AIDS symptoms) and immunological status (CD4% 15–24%), therefore, they had no significant difference with one who started ART.

By multivariate analysis, children in the early group had a greater increase of QOL scores in five domains over 144 weeks. Xu et al.[21] reported low levels of agreement between QOL scores by self-reports from HIV-infected children and proxy reports from their caregivers and reliability diminishes with older children. Therefore, our findings should to be

Table 3. Quality of Life Scores in Deferred Group at Baseline and Week 144 by ART Status

Mean (SD) QOL in deferred group	Baseline: Started ART (N=69)	Baseline: Still ART-naïve at week 144 (N=81)	p	Week 144: Started ART# (N=59)	Week 144: Still ART-naïve at week 144 (N=81)	p
Health perception	67.9 (19.1)	73.6 (17.2)	0.06	77.8 (11.8)	76.3 (14.9)	0.53
Physical resilience	70.1 (12.1)	72.4 (72.4)	0.31	72.5 (10.4)	73.9 (14)	0.55
Physical functioning	84.3 (14.7)	90.2 (11.1)	0.01	91.4 (12.6)	95.0 (10.6)	0.07
Psychosocial well-being	78.2 (13.9)	79.8 (14.6)	0.59	82.7 (13.8)	82.0 (15)	0.99
Social functioning	98.9 (4.1)	95.1 (9.3)	0.003	98.2 (6.1)	96.6 (6.6)	0.20
Health care utilization	92.2 (7.9)	92.0 (7.1)	0.88	95.4 (5.3)	96.6 (4.4)	0.17
Symptoms	88.1 (8.4)	90.7 (7.9)	0.06	93.2 (6.1)	94.0 (6.4)	0.44

Data of children who started ART at least 12 weeks before week 144 were included.

interpreted carefully due to the caregivers answered the QOL questionnaires through their perception and the PREDICT study was not a blinded study, therefore, it is possible that caregivers tended to answer worse when they know their children are not getting ART. The knowledge of treatment in the early group could enhance a feeling of wellness versus the knowledge of no specific therapy in the deferred group.

There are limited data for the factors associated with QOL scores in HIV-infected children in under-resourced countries. In our study, several factors had been associated with higher QOL scores. Older age of children was associated with a greater increase of QOL scores in physical functioning, which is similar to our baseline report.[13] This may be explained by older children having more vigorous activity such as lifting heavy objects, participating in strenuous sports compared to younger children. Fewer co-morbid health problems had been associated with higher scores in physical functioning in South African HIV-infected adults receiving ART.[22] In our study, less severe HIV disease status was associated with a greater increase of QOL scores, whereas CDC clinical classification N and A was associated with higher scores in physical functioning domain.

In our study, nonbiological caregivers reported greater changes of QOL score in social and role functioning. Kuntawee et al.[23] reported that HIV-infected children who were cared for by caregivers aged >45 years had a better quality of life than those whose caregivers were 20–45 years old. However, we did not note the age of caregivers in this study. In general, the majority of nonbiological caregivers were the children's relatives (e.g., aunt and grandmother) who were older than their biological caregivers. Recent stressful life events were associated with poor adherence in children with HIV infection.[24] One or more negative life events had been associated with diminished QOL, especially in health perception domain from a cross

Table 4. Significant Predictors of Changes of Quality of Life Scores over 144 Weeks

Domain	Significant predictors factors from multivariate analysis	Mean change of QOL scores	95%CI	p Value
Health perception	Thai versus Cambodia	7.18	4.88 to 9.48	<0.01
	Early-arm versus deferred-arm[a]	1.74	0.08 to 3.41	0.04
Physical resilience	Age at baseline	0.37	0.05 to 0.71	0.03
	CDC class N or A versus B	1.82	0.23 to 3.41	0.03
	Education of caregivers higher versus lower	−3.07	−4.59 to −1.53	<0.01
	Early-arm versus deferred-arm[a]	1.84	0.32 to 3.36	0.02
Physical functioning	Thai versus Cambodia	−2.28	−4.04 to −0.53	0.01
	Age at baseline	1.06	0.68 to 1.42	<0.01
	CDC class N or A versus B	2.42	0.80 to 4.04	<0.01
	Monthly income higher versus lower	−2.56	−4.25 to −0.87	<0.01
Psychological well-being	Thai versus Cambodia	−6.42	−9.99 to −2.86	<0.01
	Monthly income higher versus lower	−3.38	−6.35 to −0.41	0.03
	Early-arm versus deferred-arm[a]	2.71	0.13 to 5.29	0.04
Social and role functioning	Thai versus Cambodia	−2.32	−3.11 to −1.52	<0.01
	Biological versus non-biological caregivers	−1.41	−2.27 to −0.54	0.02
	Early-arm versus deferred-arm[a]	0.74	0.13 to 1.36	<0.01
Health care utilization	HIV-RNA log10 copies/ml	−0.59	−1.09 to −0.10	0.02
	Education of caregivers higher versus lower	−1.05	−1.64 to −0.45	<0.01
Symptoms	Thai versus Cambodia	−2.47	−3.52 to −1.42	<0.01
	Early-arm versus deferred-arm[a]	1.11	0.29 to 1.92	0.01

Higher score indicated better quality of life. Education of caregivers; higher (high school or higher than high school) versus lower (primary school or no education). Monthly income; higher (average and above average) versus lower (below average). [a]Compared between treatment arms for the changes of QOL scores at week 144 to baseline.

study in US HIV-infected children.[25] Contrastingly, we failed to demonstrate this association in our study even the mean (SD) negative life events in our study was higher 1.4 (1.0) versus 0.8 (1.1) in US HIV-infected children.[25] This may be because the US children had worse clinical status than children in our study, as 39% of US children had AIDS symptoms and 56% had moderate to severe CD4% cell depletion.[25] Youth with perinatally acquired HIV who had been told their HIV status did not show an increase of psychological problems and had less anxiety than those who had not been told.[26] There are limited data of HIV disclosure status on QOL in HIV-infected children. In our study, the proportion of HIV disclosure status did not correlate with change of QOL scores, which is in agreement with another published report.[10]

Our study had some limitations. First, we assessed the QOL according to the perception of the caregivers, but we did not interview the children. Second, it is important to be cautious in interpreting nonsignificant data from our study as it was not powered on the QOL outcomes. Third, our study had a limited number of HIV-infected adolescents, aged more than 11 years old, which may be the most vulnerable group to psychosocial issues and low QOL. Nachman et al.[27] reported perinatally HIV-infected youth to have high rates of psychiatric symptoms, including depression. Children who had depression had poorer academic functional and overall QOL.[27] Last, monthly income in our study was a self-report from the perception of caregivers. We did not collect the actual monthly income. According to World Bank figures, average income might differ greatly among areas either in Thailand or in Cambodia.

The strength of our study is its randomized study design and prospective follow-up before and after ART, as well as the availability of HIV-negative controls and the unique population of Asian children without advanced HIV disease. To our knowledge, our study is the first report of QOL assessment in children randomized to starting ART at different CD4 thresholds. In addition, we also had the data from age-matched healthy control from Thailand and Cambodia. Further study should be evaluation of QOL from the children's perspective and find interventions (e.g., peer support) to improve QOL in children with HIV infection.

In conclusion, in this first QOL report in Asian ART-naive HIV-infected children without advanced HIV disease, no significant difference of QOL scores between treatment groups at baseline and at week 144 was found. Early ART commencement was associated with a greater increase of QOL scores over 144 weeks compared to defer ART. HIV-infected children had significantly lower QOL scores compared to the healthy controls.

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