Attrition and Mortality of Children Receiving Antiretroviral Treatment through the Universal Coverage Health Program in Thailand

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Objective To assess mortality and loss to follow-up of children with HIV infection who started antiretroviral therapy (ART) through the Universal Coverage Health Program (UC) in Thailand.

Study design Children with HIV infection who initiated ART at age <15 years through the UC between 2008 and 2013 were included in the analysis. Death was ascertained through linkage with the National Death Registry. A competing-risks method was used to calculate subdistribution hazard ratios (SHRs) of predictors for loss to follow-up. Death was considered a competing risk. Cox proportional hazards models were used to assess predictors of mortality.

Results A total of 4618 children from 497 hospitals in Thailand were included in the study. Median age at ART initiation was 9 years (IQR, 6-12 years), and the median duration of tracking was 4.1 years (a total of 18 817 person-years). Three hundred and ninety-five children (9%) died, for a mortality rate of 2.1 (95% CI, 1.9-2.3) per 100 person-years, and 525 children (11%) were lost to follow-up, for a lost to follow-up rate of 2.9 (95% CI, 2.7-3.2) per 100 person-years. The cumulative incidence of loss to follow-up increased from 4% at 1 year to 8.8% at 3 years. Children who started ART at age ≥12 years were at the greatest risk of loss to follow-up. The probability of death was 3.2% at 6 months and 6.4% at 3 years. Age ≥12 years at ART initiation, lower baseline CD4%, advanced HIV staging, and loss to follow-up were associated with mortality.

Conclusion The Thai national HIV treatment program has been very effective in treating children with HIV infection, with low mortality and modest rates of loss to follow-up. *(J Pediatr 2017;188:210-6).*

In 2012, approximately 56 401 children with HIV infection aged <15 years were receiving antiretroviral treatment (ART) in south and southeast Asia.[1] Most of the current pediatric patients with perinatally acquired HIV were born before the effective prevention of mother-to-child transmission (PMTCT) program[2] was implemented, and approximately two-thirds have since grown to adolescence. Few previous studies have assessed retention in the care of children with HIV infection and adolescents in Thailand. A study conducted between 2000 and 2007 through the National Access to Antiretroviral for Persons Living with HIV/AIDS Program reported a mortality rate of 5.2 (95% CI, 4.6-5.8) per 100 person-years of follow-up, and 10.1% of children were loss to follow-up from the last visit.[3] A recent study in large referral centers in Thailand by 2011, including approximately 10% of Thai HIV pediatric patients, reported lower mortality rates of children with HIV infection (1.3 per 100 person-years; 95% CI, 1.1-1.6), reflecting the effectiveness of ART.[4]

The number of Thai children with HIV infection receiving ART was 6510 in 2011 and increased to 12 468 in 2014 after the National HIV/AIDS treatment program was expanded at the end of 2007 through the Universal Coverage Health Program (UC), administered by the National Health Security Office (NHSO).[5] All children with HIV infection in Thailand were eligible for free ART from this time according to national guidelines. CD4% and HIV-RNA testing to monitor ART treatment was provided at 6-month intervals for CD4% and at 6 months post-ART and annually thereafter for HIV-RNA. The preferred first-line ART regimen for

ART	Antiretroviral treatment
aSHR	Adjusted subdistribution hazard ratio
CDC	Centers for Disease Control and Prevention
NHSO	National Health Security Office
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NRTIs	Nucleoside reverse-transcriptase inhibitors
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission
SHR	Subdistribution hazard ratio
UC	Universal Coverage Health Program

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untreated children with HIV infection consisted of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) for those who were exposed to nevirapine from the PMTCT program.[6] These ART guidelines are generally in line with World Health Organization guidelines. Demographic and HIV clinical data of patients with HIV infection are systematically collected in real time through the NHSO database as a part of the UC.

The objective of this study was to assess mortality and loss to follow-up of all Thai children with HIV infection who were receiving treatment and care through the UC between 2008 and 2014. The results of this study will inform stakeholders about the quality of the pediatric National HIV program in Thailand.

Methods

Thai children with HIV infection were registered into the UC program to receive treatment and care. Demographic and HIV clinical data were systematically recorded into the NHSO database at registration and at any follow-up visits by the HIV coordinators at hospitals in Thailand. The CD4% and HIV-RNA (viral load) test results were collected by laboratory staff. These data had to be included in the database for reimbursement of laboratory testing.[7] Children with HIV infection are offered free monitoring twice-yearly for CD4% testing, and at 6 months post-ART and annually thereafter for HIV-RNA testing. The children were scheduled for follow-up every 3-6 months for ART prescription and monitoring.

This study included children with HIV infection who initiated ART at age <15 years between January 1, 2008, and November 5, 2013, with follow-up until November 5, 2014. This ensured at least 12 months of follow-up for the children included in the analysis, which allowed sufficient time for a child to become lost to follow-up according to our definition. The NHSO database also has been linked with the Thai national death registry twice monthly since the beginning of 2008 to ascertain the vital status of all children regardless of follow-up status.

For this study, ART was defined as a regimen including at least 3 drugs, 1 of which was a NNRTI or PI, plus 2 or 3 NRTIs. Baseline was defined as the date of ART initiation. Children who initiated ART before enrollment in the UC or started ART before 2008, those who were aged ≥15 years at ART initiation (who are considered adults in the Thai healthcare system, classified by an identity card issued at age 15 years), those who received an ART regimen that did not meet our criteria for ART, and those with incomplete demographic data for the study period were excluded from the analysis.

The attrition outcomes analyzed were mortality and loss to follow-up of children after ART initiation. A clinic visit was defined as either a prescription for ART or laboratory testing (CD4%). Children without a clinic visit for more than 12 months were classified as lost to follow-up, irrespective of whether or not they later returned to care. The loss to follow-up event was taken to be the latest clinic visit. A child who died more than 12 months from the last clinic visit was considered lost to follow-up in our lost to follow-up analysis after the last clinic visit. The loss to follow-up analysis included only the first occasion of loss to follow-up for each child. In the mortality analysis, death was assigned when a confirmed death date was included in the death registry.

Statistical Analyses

Descriptive statistics were used to report baseline characteristics by baseline age group including demographic data, year of ART initiation, regions of the country, antiretroviral regimens, Centers for Disease Control and Prevention (CDC) classification stage, and CD4%. Person-years of follow up were calculated from baseline to endpoints (ie, loss to follow-up or death) or censored at the last contact visit of patients who had no events. The competing-risks method of Fine and Gray[8] was used to calculate the subdistribution hazard ratios (SHR), to assess the factors associated with loss to follow-up, with death considered a competing risk. The competing-risk estimators were used to calculate the cumulative incidence of loss to follow-up after ART initiation. Predictor covariates were explored in univariate models, including baseline age, sex, CDC stage at baseline, baseline CD4%, first ART regimen, calendar year (fitted as a time-dependent covariate), and region of Thailand in which the child received care. Covariates including sex, CDC stage, ART regimens, and region were analyzed as categorical variables. Continuous covariates, including age at ART initiation and baseline CD4%, were also analyzed as categorical variables, using the cutpoints conventionally used in the HIV literature. Each calendar year was fitted as a separate category.

For the mortality analysis, there was no event that precluded the occurrence of death in this study, so competing-risks methods were not used. Cox proportional hazards models were used to assess predictors of mortality. The covariates included baseline age, sex, calendar year (fitted as a time-dependent covariate), baseline CD4%, region of the country, first ART regimen, and loss to follow-up. Loss to follow-up was not considered a competing event in the mortality model, in which vital status was ascertained by the national death registry. Loss to follow-up was included as a time-updated covariate in the mortality model. Loss to follow-up was defined as 0 at baseline for all children, and changed to 1 (with an episode of loss to follow-up) for children who were lost to follow-up. The Kaplan-Meier method was used to estimate the probability of death, both overall and by baseline CD4% group.

Variables with $P < .10$ in univariate analyses were included in the multivariate models. Statistical significance was defined as a 2-sided P value <.05. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and Stata version 14 (StataCorp, College Station, Texas). The database was collected by NHSO who administered all schemes of UC under the Ministry of Public Health, Thailand, which was funded by the Royal Thai Government and approved by