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Characterizing HIV Manifestations and Treatment Outcomes of Perinatally Infected Adolescents in Asia

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Abstract

Background—More perinatally HIV-infected children in Asia are reaching adolescence.

Methods—We analyzed data from July 1991 to March 2011 reported by 18 clinics in six countries of children age >12 years.

Results—Of 1,254 adolescents, 33 (2.6%) died, and 52 (4.2%) were lost to follow-up within 2.4-year (3566 person-years) median follow-up period. Of 1,061 adolescents under active follow-up, 485 (46%) were male, median (IQR) age was 14.7 (13.3–16.4) years, 73% had lost a parent(s), 93% attended school, and 62% were aware of their HIV status. At the most recent evaluation, 93% were receiving highly active antiretroviral therapy (ART), 71% (N=737/1035) had CD4 >500 cells/mm³ and 86% (N=718/830) had viral load (VL) <400 copies/mL. Current CD4 >200 cells/mm³, no previous WHO stage 3 or 4, and being on a first-line regimen were independently associated with recent VL <400 copies/mL. Current age <15 years, VL <400 copies/mL, CD4 15–24% (vs. <10%) at ART initiation, no previous WHO stage 3 or 4, and ART duration of >1 year were associated with recent CD4 >500 cells/mm³. Primary causes of death after age 12 were opportunistic infections (N=15/33) and other AIDS- or treatment-related conditions (N=9/33). Those at age 12 with CD4 <200 vs. >500 cells/mm³ and those with VL >10,000 vs. <10,000 copies/mL were 17.4 and 4.76 times more likely to die in adolescence, respectively.

Conclusion—Adolescents in this cohort have been successfully maintained in HIV care. Initiating treatment at earlier stages of disease was associated with immune recovery and virologic suppression during adolescence.

Keywords

adolescents; pediatric HIV; Asia; antiretroviral therapy

Survival among perinatally HIV-infected children and youth has greatly improved since the advent of highly active antiretroviral therapy (HAART). Adolescents who have grown up with HIV are facing health problems and stigma in addition to the usual challenges HIV-uninfected youth face in transitioning to adulthood and emotional maturity. Adolescents have been reported to have a lower rate of virologic suppression and immunologic recovery than adults, and higher loss to follow-up rates.^{1,2} In a long-term follow-up study of a cohort of more than 2000 perinatally HIV-infected children in the US (PACTG 219), adherence rates were found to decline with age, with the worst adherence rates of 76% among 15–18 year olds as compared with 83%–89% for younger children.³ In previous reports, about two-thirds of perinatally infected adolescents in France and the United Kingdom were on highly active regimens, and only around 40–60% of US and European adolescents had undetectable viral loads.^{2,4,5} However, there have been few studies on perinatally HIV-infected adolescents in Asia.

Understanding the epidemiology of life-long HIV of this growing population would better guide clinicians to plan ahead for providing the support and care necessary to help adolescents reach adulthood with stable HIV disease. We aimed to describe adolescent HIV treatment outcomes in a regional observational cohort in Asia.

METHODS

The TREAT Asia (Therapeutic Research, Education, and AIDS Training in Asia) Pediatric HIV Observational Database (TApHOD) is the first regional database of HIV-infected children and adolescents in Asia and a member cohort of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) global consortium.⁶ Through March 2011, TApHOD included children and adolescents receiving care at 18 pediatric clinics in Cambodia (n=3),

India (n=1), Indonesia (n=2), Malaysia (n=4), Thailand (n=5), and Vietnam (n=3). These sites are predominantly public or university-based pediatric HIV referral clinics, located in urban or semi-rural areas. HIV-infected children are typically seen in these sites every three months, with biannual CD4 count monitoring. Routine viral load testing is available at sites in Thailand and Malaysia, with less frequent testing at other sites.

For this analysis, we included adolescents age 12 years or older at the time of their most recent clinic visit, who were ascertained by their primary HIV providers to have acquired infection either perinatally or during early childhood, and who had at least six months of follow-up. This age group was chosen *a priori* by the TAPHOD Steering Committee to focus on those most likely to be coping with long-term HIV infection and ART in the context of the emerging personal independence associated with adolescence.

Retrospective and prospective observational data are anonymized and entered into a standard TAPHOD Access database or a comparable clinical database, and transferred every six months to the Kirby Institute for Infection and Immunity in Society, University of New South Wales, Sydney, for quality control and analysis. Institutional review board approval is obtained at the sites, TREAT Asia, and the Kirby Institute. Patient consent and assent requirements are deferred to the individual institutional review board.

Data Analysis

Adolescents were considered in active follow-up if they had at least one clinic visit in the previous 12 months of data submission. We described characteristics of adolescents in our cohort at ART initiation and at their most recent clinical evaluation. We then reported cross-sectional associations between some of these characteristics and optimal immunological response (CD4 cell counts ≥ 500 cells/ μ L) or virologic response (HIV RNA viral load <400 copies/ml) using logistic regression.

For laboratory measurements around the most recent clinical evaluation and ART initiation, we used the closest result within the six months prior to and on the date of the last visit or start of ART. Lipid testing represented a combination of fasting and non-fasting values. WHO clinical stage was the highest stage experienced within 12 months prior to the last visit. Mono- or dual-therapy was defined as using one or two NRTIs or one drug of other class. HAART was defined as therapy with a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen, or two NRTIs plus an NNRTI or PI in antiretroviral-naïve children or adolescents. The transition from first-line HAART to second-line HAART was defined as when two drugs were changed, one of which represented a class switch from NNRTI to PI or PI to NNRTI, and the class switch was not reverted for at least 24 weeks. For HAZ, we used the WHO 2006/2007 Child Growth Standards.⁷ WHO 1977 growth standards were used for WAZ, to allow for scoring children >10 years of age.^{7,8} Loss to follow-up (LTFU) was defined as having no reported clinical visits within 12 months after the previous visit.

For mortality rate calculations, person-years of observation were calculated from the date a child reached age 12 years until death or the last reported clinic visit. Cox proportional hazard regression was used to examine the relationship between mortality and baseline factors at age 12 years. Time on ART and CD4 values were considered time-dependent variables; viral load was the closest value within six months prior to age 12 years. Mortality rates and effect estimates accounted for left truncation, which occurred because children enrolled in the clinics at different ages and a proportion of them came under observation after the age of 12 years. As children who entered the cohort after age 12 could not have had an event between age 12 and study enrollment, they were removed from the data set between the two time points. For these children, their first clinic visit was considered as their

baseline. A sensitivity analysis excluding children who entered the cohort after age 12 was performed.

In all analyses, factors found to be significant at the $p < 0.10$ level in univariate analysis were subsequently tested in multivariate analysis. Forward step-wise methods were used to assess the contribution to the model, and independent variables were considered significant at the $p < 0.05$ level. Stata version 9 (StataCorp LP, College Station) was used for all statistical analyses.

RESULTS

Of the 4,045 HIV-infected children with available data enrolled into TApHOD clinics between 1991 and 2011, 1,354 (33.7%) were >12 years at the time of their last clinic visit. Of these, we excluded 68 adolescents with an unknown mode and timing of HIV transmission, 31 with less than six months of follow-up, and one with unknown ART information. The analysis included 1,254 adolescents; 95% had ever received ART (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/B653>). More than two-thirds were in Thailand (79%), 584 (47%) were male, 1,060 (85%) were <12 years of age at cohort entry, and the median (IQR) time in follow-up during the adolescent period was 2.4 (1.2–4.2) years. By the end of March 2011, 1061 (85%) adolescents were currently under active follow-up, 33 (2.6%) died, 52 (4.2%) were lost to follow-up and 108 (8.6%) were transferred to other clinics.

Compared to adolescents who died after the age of 12 years, those who remained in follow-up received ART at younger ages (median 8.8 vs. 12.2 years; $p < 0.0001$), and initiated at higher CD4 percentages (7.0% vs. 3.0%, $p < 0.018$). They also had higher median CD4 count nadirs (122 vs. 14 cells/mm³; $p = 0.0003$) and a smaller proportion had experienced WHO clinical stage 4 events before ART initiation (20.5% vs 35.5%; $p = 0.044$). The initial ART regimens were mono- or dual-NRTI for 16.3% (167 of 1024) of adolescents who received ART and were still in follow-up, and for 12.9% (4 of 31) of those who received ART and died during adolescence ($p = 0.612$). Adolescents who died after the age of 12 years had higher rates of opportunistic infections (18.5 vs. 0.66 per 100 person-years; $p < 0.0001$) and hospitalization (4.34 vs. 0.49 per 100 person-years; $p = 0.001$) than those still alive. Of 1,061 adolescents in active follow-up, by their last clinic visit, 73% had lost one or both parents, 62% were disclosed to about their own HIV status; 93% were attending school.

Of the 1,024 adolescents who were receiving ART at their last clinic visit, 983 (96%) had been on HAART for a median (IQR) duration of 6.0 (4.3–7.5) years; 85% were on first-line regimens. Of the current HAART regimens used, 3% were mono-therapy with ritonavir-boosted lopinavir, and 1% were dual-NRTI regimens. The frequencies of antiretroviral drugs currently in use in any combination were: NRTI class – lamivudine 90%, zidovudine 63%, stavudine 12%, tenofovir 15%, didanosine 5%, abacavir 1.8%; NNRTI class – nevirapine 43%, efavirenz 27%; PI class - ritonavir-boosted lopinavir 26%, ritonavir-boosted atazanavir 2.7%, and ritonavir-boosted darunavir 1.6%.

Among the adolescents who remained in follow-up, the most recent median (IQR) CD4 cell count was 657 (470–862) cells/mm³, and 718 of 830 adolescents tested (86%) had HIV RNA <400 copies/mL. Of 37 adolescents who had not yet been started on ART, 33 (89%) had CD4 counts >350 cells/mm³. The most recent median (IQR) WAZ of the adolescents who remained in follow-up was -1.7 (-2.6 to -0.8), HAZ was -1.7 (-2.5 to -1.0). Within the previous 12 months, hypercholesterolemia (>200 mg/mL) was found in 210 of the 686 patients tested (31%); all were currently on ART. Of the 226 adolescents tested who were

receiving ritonavir-boosted PIs, 38% had hypercholesterolemia. Of the 464 adolescents ever tested for hepatitis B surface antigen (HBsAg), 30 (6.5%) were positive.

Factors associated with immunologic and virologic treatment responses

In multivariate analyses of the 935 adolescents with viral load measurements at their last visit, having the most recent CD4 >200 cells/mm³, no experience with WHO stage 3 or 4 events, and currently being on first-line HAART (vs. second-line or no treatment) were significantly associated with viral load <400 copies/mL. In analyses of the 1194 adolescents with CD4 counts at their last visit, current age <15 years, viral load <400 copies/mL, CD4 15-24% (vs. <10%) at ART initiation, no experience with WHO stage 3 or 4 events, and an ART duration of >1 year were factors predicting CD4 >500 cells/mm³ (see Table, Supplemental Digital Content 2, <http://links.lww.com/INF/B655>).

Factors associated with mortality after 12 years of age

The adolescent mortality rate in our cohort was 0.93 (95% confidence interval 0.66-1.30) per 100 person-years. Of the 33 children who died after 12 years of age, 15 (45%) were male and 31 (94%) had been receiving ART for a median (IQR) duration of 15.8 (13.5-16.6). The median age at death was 15.0 (13.3-16.6) years. The main reported causes of death were related to opportunistic infections in 15 (45%), non-infectious AIDS-related conditions in 9 (27%), and reasons unrelated to HIV in 4 (12%). In multivariate analysis, adolescents who were receiving second-line by the age of 12 years, had a viral load of >10,000 copies/mL or CD4 <500 cells/mm³ at age 12, had an increased chance of dying during adolescence (see Table, Supplemental Digital Content 3, <http://links.lww.com/INF/B656>). Results were similar in the sensitivity analysis that excluded children who entered cohort after age 12.

DISCUSSION

This is the first regional report of outcomes of perinatally HIV-infected adolescents in Asia. Of those who were in active follow-up after age 12, we found the majority were relatively healthy, but weight and height parameters continued to be poor despite multiple years of ART. Mortality and loss to follow-up during adolescence were low. More than two-thirds of adolescents had lost one or both parents, and more than half were cared for by grandparents or other relatives. Our disclosure rates for older adolescents were low compared to Western cohorts. Although not associated with virologic outcomes in our study, there are increasing efforts to standardize disclosure procedures within the regional social and cultural contexts.

Of the 78% with recent viral load tests, 87% were <400 copies/mL. Of the 98% with recent CD4 tests, 85% were >350 cells/mm³. Treatment, immunologic recovery, and virologic suppression rates were comparable or higher than those reported in European data, where more adolescents may have stopped taking ART (France 16%, UK, 25%) or have required third-line or even more complex ART regimens after a longer history of taking ART and accumulation of resistance.^{4,5,9}

In looking for factors associated with successful treatment in adolescents, we found that still being on first-line regimens, starting treatment at less advanced clinical and immunologic stages, and longer times on ART were protective. Notably, only 5% of adolescents in our cohort started ART before two years of age, the current WHO-recommended age by which perinatally infected infants should initiate treatment. These results point to the need for earlier initiation of ART in Asian infants and children and the importance of prolonging the time on virologically suppressive first-line regimens for as long as possible.

Hypertriglyceridemia and hypercholesterolemia were found at high rates in those who were tested, but the true prevalence across the cohort is unknown. Hepatitis screening of

adolescents in the cohort was also inconsistent, which was available in between 11-80% of patients by country. As children age into adolescents and become sexually active, confirming their hepatitis B protection status and revaccinating after severe immune suppression should become a higher priority.¹⁰

Overall mortality in our cohort was much lower than that reported in Uganda of 3.65 per 100 person-years¹¹ and close to the 0.8 per 100 person-years reported in the US.¹² One-third of deaths were related to HIV- or treatment-related organ dysfunction, which may be an indicator that adolescents in Asia may becoming similar to those in the US where causes of death have shifted to more chronic diseases.¹³ We found those who died in adolescence initiated ART at older ages, lower CD4 levels, poorer WHO stages, and at lower CD4 nadirs. In addition, those who had CD4 <200 cells/mm³ at age 12 years were about 17 times more likely to die in adolescence than those who had CD4 >500 cells/mm³, and those who had viral loads of >10,000 copies/mL at age 12 were about 5 times more likely to die than those with <10,000 copies/mL. These data show that immunologic and virologic status at age 12 can be prognostic indicators during adolescence.

The high retention rate and the low mortality rate in our cohort may be related to the nature of the participating sites. Although urban referral centers are more likely to manage severely ill patients, they also have a concentration of highly trained staff and access to treatments to manage both HIV and its complications.

Study limitations are primarily related to its observational nature. Multiple variables related to drug toxicity were not consistently collected. Earlier data were retrospectively collected before some sites had standard data collection forms or electronic databases. In addition to the lack of adherence data, neuropsychological development currently is not assessed in this cohort. Because of inter-country variability, country was not included as a covariate in the risk factor analysis.

In conclusion, adolescents in this regional Asian cohort with perinatally acquired HIV infection were consistently in stable health and receiving ART. However, growth parameters remained poorer than expected after multiple years of ART. In children reaching adolescence, we found that earlier treatment initiation led to lower subsequent mortality, and being able to remain on first-line regimens was associated with longer-term virologic suppression. Successful outcomes in adolescence require successful treatment from early childhood. Further research and data collection that includes reliable adherence assessments and more consistent monitoring of chronic disease outcomes and treatment toxicities would better inform long-term outcomes of adolescents transitioning to adulthood in Asia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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