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Original article

Non-Nucleoside Reverse Transcriptase Inhibitor–Based Antiretroviral Therapy in Perinatally HIV-Infected, Treatment-Naïve Adolescents in Asia

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A B S T R A C T

Purpose: About a third of untreated, perinatally HIV-infected children reach adolescence. We evaluated the durability and effectiveness of non-nucleoside reverse-transcriptase inhibitor (NNRTI)–based antiretroviral therapy (ART) in this population.
Methods: Data from perinatally HIV-infected, antiretroviral-naïve patients initiated on NNRTI-based ART aged 10–19 years who had ≥6 months of follow-up were analyzed. Competing risk regression was used to assess predictors of NNRTI substitution and clinical failure (World Health Organization Stage 3/4 event or death). Viral suppression was defined as a viral load <400 copies/mL.
Results: Data from 534 adolescents met our inclusion criteria (56.2% female; median age at treatment initiation 11.8 years). After 5 years of treatment, median height-for-age *z* score increased from −2.3 to −1.6, and median CD4+ cell count increased from 131 to 580 cells/mm^3. The proportion of patients with viral suppression after 6 months was 87.6% and remained >80% up to 5

IMPLICATIONS AND CONTRIBUTION

Little is known about how perinatally HIV-infected, antiretroviral therapy–naïve adolescents respond to treatment. This work shows that they achieve good height-for-age and CD4+ recovery and a high rate of virological suppression. Earlier ART initiation

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years of follow-up. NNRTI substitution and clinical failure occurred at rates of 4.9 and 1.4 events per 100 patient-years, respectively. Not using cotrimoxazole prophylaxis at ART initiation was associated with NNRTI substitution (hazard ratio [HR], 1.5 vs. using; 95% confidence interval [CI] = 1.0–2.2; $p = .05$). Baseline CD4+ count ≤200 cells/mm^3 (HR, 3.3 vs. >200; 95% CI = 1.2–8.9; $p = .02$) and not using cotrimoxazole prophylaxis at ART initiation (HR, 2.1 vs. using; 95% CI = 1.0–4.6; $p = .05$) were both associated with clinical failure.

Conclusions: Despite late ART initiation, adolescents achieved good rates of catch-up growth, CD4+ count recovery, and virological suppression. Earlier ART initiation and routine cotrimoxazole prophylaxis in this population may help to reduce current rates of NNRTI substitution and clinical failure.

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Of the 35 million people living with HIV, an estimated 2.1 million are adolescents (aged 10–19 years) living in low- or middle-income countries, and approximately 230,000 under the age of 15 years are living in the Asia Pacific region [1,2]. Despite a perception in earlier stages of the HIV epidemic that very few perinatally HIV-infected (paHIV) children could survive to adolescence without treatment, data from Sub-Saharan Africa indicate that about a third live beyond the age of 10 years [3,4]. Consequently, until early infant diagnosis and linkage to HIV care improves, the number of paHIV adolescents presenting for treatment is likely to continue increasing.

The World Health Organization (WHO) preferred first-line antiretroviral therapy (ART) regimen for adolescents includes two nucleoside reverse-transcriptase inhibitors (NRTIs) and a non-NRTI (NNRTI) [5]. Maximizing the durability of first-line ART in adolescents is crucial given the length of time they will require treatment and the high cost and poorer tolerability of second-line protease inhibitors. Although NNRTI-based ART is generally very safe and efficacious, initiation and maintenance of HIV treatment may be complicated by the difficult physical, emotional, and social changes that take place during the transition to adulthood. Furthermore, prescribers must consider the pubertal delay and organ damage that is common in paHIV adolescents [6–8]. Studies from resource-limited areas have found that adolescents tend to have high rates of poor treatment adherence, treatment failure, and loss to follow-up [9–12]. A global effort is now underway to bring greater attention to this unique population; however, to improve the current situation, we need to understand which treatment interventions are most likely to be effective.

This analysis evaluated the durability and effectiveness of NNRTI-based ART in paHIV adolescents receiving care in low- and middle-income countries in Asia. Specific outcomes evaluated included height-for-age recovery, immunological recovery, virological suppression, NNRTI substitution, and clinical failure.

Methods

The study population consisted of HIV-infected patients enrolled in the TREAT Asia Pediatric HIV Observational Database (TApHOD) which contributes to the International Epidemiologic Databases to Evaluate AIDS global consortium. Recruitment started in 2008 and as of March 2014, TApHOD included data from 5,511 children and adolescents who had ever received care at one of 16 pediatric clinics in Cambodia (n = 1), India (n = 1), Indonesia (n = 2), Malaysia (n = 4), Thailand (n = 5), or Vietnam (n = 3). These sites are predominantly public or university-based pediatric HIV referral clinics. Ethics approval was obtained at the sites, TREAT Asia/amfAR (coordinating center), and the Kirby Institute (data management and statistical analysis center). Patient consent is deferred to the individual participating sites and their institutional review boards; some sites require informed consent, and others do not.

Data collection in TApHOD is based on a standardized set of demographic, monitoring, and treatment variables that have been described previously [13]. The distinction between behavioral and perinatal HIV infection is made by study site investigators based on the clinical information available to them at the time of clinic entry. In general, documentation of perinatal infection is based on a combination of the following criteria: (1) infection identified in early childhood; (2) known or suspected parental HIV; (3) no history of blood transfusion; and (4) no documented or suspected history of sexual abuse.

Data from PaHIV, ART-naive children who started NNRTI-based ART (defined as a triple regimen containing two NRTIs and an NNRTI) aged 10–19 years on or after January 1, 2003, and who had at least 6 months of follow-up on NNRTI-based ART were included in this analysis. Patients exposed to mono/dual therapy before starting triple therapy were excluded. Baseline date was the date of ART initiation. Treatment breaks <14 days, and NRTI modifications were ignored.

The window period for baseline height, weight, CD4+ cell count, hemoglobin, and alanine aminotransferase measurements was within 3 months before or after ART initiation. For baseline viral load, the window period was between 3 months before and 2 weeks after treatment started. Measurements taken closest to the baseline date were used. Alanine aminotransferase upper limit of normal was consistent with the age- and sex-specific ranges defined by the Harriet Lane Handbook 20th Edition [14]. Severe anemia was defined as hemoglobin <7.5 g/dL [15]. HIV disease staging was based on the WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children [16]. The highest WHO stage documented before or at ART initiation was considered the baseline HIV disease severity.

Weight and height measurements were converted into age- and sex-standardized z scores. Height-for-age z scores were calculated using the WHO 2007 child growth standards and macros (ages 5–19 years) [17]. Weight-for-age z scores were calculated using the WHO child growth standards and macros for 1977 [18]. The 1977 standards were used because the WHO 2007