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Impact of Antiretroviral Therapy on Opportunistic Infections of HIV-Infected Children in the TREAT Asia Pediatric HIV Observational Database

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Abstract

Background—There are limited data on opportunistic infections (OI) and factors associated with their occurrence after highly active antiretroviral therapy (HAART) in Asian children. The use of HAART in Asia started much later than in developed countries and therefore reported findings may not be fully applicable to the pediatric HIV epidemic in Asia.

Methods—Retrospective and prospectively collected data from the TREAT Asia Pediatric HIV Observational Database cohort study from March 1993 to March 2009 were analyzed. OIs were defined according to WHO clinical staging criteria, and incidence rates calculated. Factors associated with the incidence of severe OIs were analyzed using random effects Poisson regression modeling.

Results—Of 2280 children in the cohort, 1752 were ever reported to have received ART, of whom 1480 (84%) started on HAART. Before commencing any ART, OIs occurred at a rate of

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89.5 per 100 person-years. The incidence rate was 28.8 infections per 100 person-years during mono- or dual-therapy, and 10.5 infections per 100 person-years during HAART. The most common OIs both before and after ART initiation were recurrent upper respiratory tract infections, persistent oral candidiasis, and pulmonary tuberculosis. The incidence rates of WHO clinical stage 3 or 4 OIs after HAART were highest among children <18 months of age and those with low weight-for-age z scores, CD4 cell percentage <15%, and WHO stage 3 at HAART initiation.

Conclusions—Despite dramatic declines in their incidence, OIs remained important causes of morbidity after HAART initiation in this regional cohort of HIV-infected children in Asia.

Keywords

Asia; pediatric HIV; HAART; opportunistic infection

INTRODUCTION

In the past decade, dramatic declines in the incidence of and mortality related to opportunistic infections (OI) in HIV-infected adults^{1, 2} and children³⁻⁶ have been observed. These reductions have resulted from the advent of highly active antiretroviral therapy (HAART) in the mid-1990s and routine use of antimicrobial prophylaxis. In Switzerland, Ledergerber, *et al* examined a population-based prospective cohort of 2410 adults starting therapy between 1995 and 1997 and found that the incidence of any OI decreased from 15.1 per 100 person-years in the six months before therapy to 7.7 in the first three months after starting treatment and to 2.6 in the following six months.¹ The US Perinatal AIDS Collaborative Transmission study, in an analysis of 364 HIV-infected children 17 years or younger, reported that incidence rates for all documented OIs had decreased from 14.4 per 100 person-years during the pre-HAART era to 1.1 after HAART.⁴ In Brazil, the incidence of OIs among children and adolescents was 18.3 per 100 person-years in the pre- and 2.6 in the post-HAART periods.⁵

In Asia, regional HAART scale-up in HIV-infected children began according to the current World Health Organization (WHO) and United States Department of Health and Human Services (US DHHS) recommendations in early 2000s. A number of studies have reported a decline in mortality and hospitalizations after receiving HAART in Asian children within individual site cohorts.^{7, 8} Specific data regarding regional trends in OIs and the factors associated with their occurrence after HAART are limited. In this study we examined the incidence rates and patterns of OI occurrence, and risk factors for developing OIs in HIV-infected children followed in the Therapeutic Research, Education and AIDS Training (TREAT) Asia Pediatric HIV Observational Database (TApHOD).

MATERIALS AND METHODS

TApHOD is an ongoing collaborative observational cohort study of infants and children with HIV in the Asia-Pacific region which has been described elsewhere.⁹ This analysis included patient data from 14 participating clinics in Cambodia (n=3), India (n=1), Indonesia (n=1), Malaysia (n=4), and Thailand (n=5). Patients were eligible for inclusion in TApHOD if age ≥ 18 years and conclusively diagnosed with HIV, using age-appropriate

testing or through a presumptive clinical diagnosis of HIV infection defined as meeting WHO criteria for initiating antiretroviral therapy (ART) ¹⁰. Prospective data collection for TApHOD commenced in 2008, with retrospective data provided where available. Data collection included information on demographic characteristics, anthropometric parameters, CD4 T cell and HIV viral load levels, other laboratory tests, ART histories, OIs, and causes of death. Data were anonymized and transferred to the Kirby Institute, Sydney, Australia, every six months for quality control and assurance procedures to verify the consistency and reliability of data. Ethical approval was obtained from all related institutional review boards (IRB) for the participating sites; and the data management (Kirby Institute) and the coordinating centers (TREATAsia/amfAR). Because data were observational and anonymously collected, informed consent was waived unless locally required. The study population for this analysis included all patients enrolled in TApHOD between March 1993 and March 2009.

ART regimens were classified as mono- or dual-nucleoside reverse transcriptase inhibitor (NRTI) therapy, and HAART as triple-NRTI therapy, or two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI). OIs were those used to define WHO clinical stages 2, 3 and 4.¹¹ Severe anemia was defined according to US DHHS guidelines as a hemoglobin level <7.5 g/dL.¹² For height-for-age z score (HAZ), the WHO 2006/2007 Child Growth Standards¹³ were used. WHO 1977 Standards were used for weight-for-age z scores (WAZ), to allow for scoring children >10 years of age.¹⁴ Baseline values were taken as the values most closely preceding the HAART initiation date within the prior three months. For reporting CD4 percent at the time of a specific OI, the closest value within three months before and one month after the occurrence of that OI was used.

Statistical Methods

Baseline values at the time of ART initiation were reported as means (standard deviation, SD) and frequencies (%), and the differences between groups (started on HAART vs. mono- or dual-therapy) were tested using Chi-squared tests (Fisher's exact or Cochran-Armitage test for trend) and Kruskal Wallis testing as appropriate. The incidence of OI was calculated by dividing the total number of events observed by the total person-years of observation forming the risk period. Children were considered at risk for developing OIs from the date of starting their first ART regimen or their first clinic visit for those who never received ART, until their death or their last reported clinic visit. The OI incidence rate (IR) was calculated: (1) during the period of not receiving any ART (2) during HAART use for children who started their treatment with these regimens and (3) during mono- or dual-therapy for children who started their treatment with these regimens. For children who started on mono- or dual-therapy and later switched to HAART, the date of switch was considered the end of study follow-up. We calculated the probability of developing stage 3 and 4 OIs during the HAART period using the Kaplan-Meier method. These estimates were plotted by baseline CD4 percentage strata.

We assessed factors associated with increased incidence of severe OI infections (WHO stage 3 and 4) by using random effects Poisson regression modeling in order to allow for the repeated-event nature of the data for children with multiple OI events. Covariates assessed

for inclusion in the multivariate model were sex, age, HAART regimen, CD4 percentage and cell count, WHO clinical staging, WAZ, HAZ, and anemia. CD4 percentage was considered a time-dependent variable and the remaining variables were fixed factors assessed at baseline. Only patients who initiated their first treatment with HAART were included in the risk factor analysis. Covariates were entered into the model if they had a P value of <0.10 in the univariate analysis. The forward step-wise method was used to assess the contribution to the model. Independent variables were considered significant at the P value <0.05 level. Stata version 9 (StataCorp LP, College Station) was used for all statistical analyses.

RESULTS

Demographic information

Between March 1993 and March 2009, 2280 children were enrolled in TApHOD, of whom 1752 (77%) had ever received ART. Of these, 1480 (84%) initiated treatment with HAART and 272 (16%) started with mono- or dual-NRTI therapy (Table 1). Eighty-nine percent of children on mono- or dual-therapy started their first treatment between 1995 and 2004, while most of patients who started with HAART (1444; 97.5%) received their first regimen after 2002. Those who started with HAART were significantly older than those on mono- or dual-therapy (median age: 7.0 vs 3.3 years; $P < 0.0001$); a higher proportion had pre-ART CD4 counts of <50 cells/mm³ (26.2% vs 7.7%; $P < 0.0001$), pre-ART CD4 <15% (59.4% vs 5.4%; $P < 0.0001$), experienced WHO clinical stage 4 (27.3% vs 14%; $P < 0.0001$), and had lower WAZ and HAZ ($P < 0.002$ and $P < 0.03$, respectively). At the closure of the dataset for analysis, 26% of the children who started with mono- or dual-therapy had remained on mono- or dual-therapy.

Incidence of OIs

There were 1637 OI events in 866/2280 children (median event 1, IQR 0-1; IR 89.5 per 100 person-years) during a median pre-ART follow-up time of 2.4 months; 226 events among 114/272 children (median 0, IQR 0-1; IR 28.8 per 100 person-years) during mono-dual treatment with a median follow-up time of 2.4 years, and 462 events in 279/1480 children (median event 0, IQR 0-0; IR 10.5 per 100 person-years) during a median follow-up time on HAART (Table 2). The most common OIs were recurrent upper respiratory tract infection, oral candidiasis, and pulmonary tuberculosis. The IR of all OIs combined in the first six months after starting treatment compared to the subsequent time period after the first six months went from 25.4 per 100 person-years to 7.7 for children started with HAART, and 66.2 per 100 person-years to 21.8 during the mono-dual- period for those who started with these regimens (Table 3).

There were 99 deaths after HAART, and 36 during the period prior to any ART. Overall, the reported cause of death was OI (63% of the cases) and other infections, or unknown (37%); 80% of all deaths occurring in the first six months of ART were OI-related. The IRs of all deaths decreased from 8.2 per 100 person-years to 1.1 after six months of HAART, and 1.7 per 100 person-years to 1.1 after six months of mono- or dual-therapy (Table 3).

Risk factors for OIs

Of 462 OIs documented in 1480 children initiating treatment with HAART, 264 OI events (57%) were WHO stage 3 or 4 defining. In multivariate Poisson regression analyses, time-dependent lower CD4 percentage, younger age, WHO clinical stage 3, and lower WAZ at baseline were associated with development of OIs after HAART. Compared with children with CD4 >25%, the relative risk for developing OIs was 21.0 (95% CI: 11.8-37.1) for CD4 <15%, and 2.7 (95% CI: 1.4-5.1) for CD4 15-24%. The median CD4 cell counts at OI diagnosis were 91 (IQR 16-208) cells/mm³ for oral candidiasis, 191 (IQR 68-621) cells/mm³ for pulmonary tuberculosis (TB), and 102 (IQR 27-500) cells/mm³ for severe recurrent bacterial pneumonia. Children <18 months of age at initiation of HAART had the highest risk of having severe OIs of any age group. Those with a baseline WHO clinical stage 3 were 3.7 times more likely to develop severe OIs after HAART than those with baseline clinical stage 1 and 2. The risk of OI decreased with increasing baseline WAZ (RR: 0.8; 95% CI: 0.7-0.9). The risks of OIs in those who started with a PI-based regimen were not different to that for children who started with an NNRTI-based regimen (Supplemental Digital Content 1).

Kaplan-Meier analyses showed that children who started their therapy at a baseline CD4 <15% had a higher frequency of OIs, especially during the first year of HAART, as compared with those with a baseline CD4 15-24% (Figure 1). Of 68 children with a baseline CD4 >25%, 13 (19%) experienced 15 events of severe OI infections after HAART; 14 happened in the first year of treatment. Of these 13 children, eight were <18 months at HAART initiation.

DISCUSSION

In this regional cohort, we found a substantial reduction in the incidence rates of OIs from 89.5 per 100 person-years during the pre-treatment period to 66.2 per 100 person-years in the first six months after mono- or dual-therapy, and 25.4 per 100 person-years after six months of HAART. The incidence rates further declined to 21.8 (18.5-25.7) and 7.7 (6.9-8.7) per 100 person-years beyond six months of mono- or dual-therapy and HAART. Although these results were in agreement with previous studies in adults and children from other settings and within our region,^{1, 3-5, 15} our OI incidence after HAART was of higher magnitude. This may have been caused by cross-cohort differences, including levels of immunosuppression and differences in intensity of reporting and analytical method. In this study we did not censor data after the first OI event in a given patient, but continued follow-up, allowing for a more complete assessment of the longer-term impact of ART on OI incidence.

It is also noteworthy that the spectrum of infection and the relative frequencies of OIs have not changed after starting ART. Recurrent upper respiratory tract infections, persistent oral candidiasis, and pulmonary TB continued to be the most common OIs. CDC stage 2 or 3 bacterial infections and non-TB infections accounted for the most of OIs among a US and European children cohort in both the pre- and post-HAART periods.^{3, 4, 16-19} However, the rates of TB infection in our study and in the region were much higher than in the US and Europe. This information is similar to previous reports in Asia which have shown that TB

has been the most common co-infection in HIV-infected patients.²⁰⁻²³ This likely reflects the higher burden of TB in Asia. Although ART had a significant impact on lowering TB incidence in our cohort, the more rapid TB disease progression seen in HIV-infected children makes it essential that HIV programs prioritize prophylaxis and screening of TB in children.²⁴⁻²⁶ Additionally, although the rates of recurrent bacterial infections have markedly decreased after HAART, they remained persistent which is similar to findings from the US and Europe cohorts.^{4, 19, 27}

Our study showed low incidences of preventable OIs, such as *Pneumocystis jirovecii* pneumonia (PCP) and Mycobacterium avium complex (MAC) infection. Although this could be attributable to primary and secondary chemoprophylaxis, our study was not able to examine the relationship between chemoprophylaxis and OIs and the lower incidence of MAC could be due to surveillance bias, as there was limited access to sensitive mycobacterial culture systems in the region during the pre-HAART era. Another study in an adult regional cohort showed that cotrimoxazole prophylaxis is still not consistently provided in all regional programs.²⁸

The overall rate of OIs after HAART was found to be lower than after mono- or dual-therapy (10.5 vs. 28.8 per 100 person-years), as OI incidence fell with time after initiating ART and children who were receiving HAART had a longer period of follow-up than those who received mono- or dual-therapy. Most of the children who received mono- or dual-therapy were switched to HAART and were then censored from the analysis.

The OI-related death rate among children who started with HAART was higher than among children who started with mono- or dual-therapy (7.2 vs. 2.0 per 100 person years), and higher than in the period prior to ART. Reasons for this could be that children started with HAART were in a more advanced stage of HIV with lower CD4 levels than those who started with mono/dual therapy, and were consequently at higher risk of immune reconstitution syndrome (IRIS). An earlier study in Thai children reported an incidence of IRIS of 19%.²⁹

Poor immunological status, younger age, and lower weight for age z score at the start of ART were significant risk factors for developing OIs after initiation of HAART. Similar to findings from The Children with HIV Early Antiretroviral Therapy (CHER) trial in South Africa on early infant diagnosis and treatment³⁰, our results also emphasize the importance of earlier identification of children with HIV and initiation of ART before advanced disease progression and concomitant higher risk of OIs. Although national programs in Asia are currently moving towards treating all infants under 12 months of age, implementation of this policy will require stronger linkages between obstetric and pediatric services in order to achieve this goal.

This study provides useful insights into the evolution of the pediatric HIV epidemic and treatment scale-up in Asia. Local production of fixed-dose combination (FDC) since the early 2000s led to greater access to lower-cost antiretrovirals in the Asia-Pacific region.³¹ In this study, only 6% of children were initiated with PI-based HAART. However, we did not find a difference in the rate of OIs by initial HAART regimen. Although the P1060 and

CHER trials in Africa have shown a mortality benefit to PI-based HAART in young children in largely resource-limited settings^{30, 32}, the PENPACT-1 study of children across Europe and America reported no difference in clinical, immunological and virological outcomes between children starting with PI-based vs. NNRTI-based regimens.³³

The primary limitation of this study is that data are observational and collected through the course of routine care. Our analysis is further limited by inclusion of children primarily receiving care at university-based clinics and/or referral centers, which usually have greater availability of human and treatment-related resources and accessibility to ART. Therefore, children in this study may not be fully representative of HIV-infected children in primary care centers or in rural areas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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References

1. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA. 1999; 282:2220–2226. [PubMed: 10605973]

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2. Etard JF, Ndiaye I, Thierry-Mieg M, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. *AIDS*. 2006; 20:1181–1189. [PubMed: 16691070]
3. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA*. 2006; 296:292–300. [PubMed: 16849662]
4. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the preand post-highly active antiretroviral therapy eras among HIV-infected children in the Perinatal AIDS Collaborative Transmission Study, 1986–2004. *Pediatrics*. 2007; 120:100–109. [PubMed: 17606567]
5. Candiani TM, Pinto J, Cardoso CA, et al. Impact of highly active antiretroviral therapy (HAART) on the incidence of opportunistic infections, hospitalizations and mortality among children and adolescents living with HIV/AIDS in Belo Horizonte, Minas Gerais State, Brazil. *Cad Saude Publica*. 2007; 23(Suppl 3):S414–423. [PubMed: 17992347]
6. Brady MT, Oleske JM, Williams PL, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. *J Acquir Immune Defic Syndr*. 2010; 53:86–94. [PubMed: 20035164]
7. Puthanakit T, Aupibul L, Oberdorfer P, et al. Hospitalization and mortality among HIV-infected children after receiving highly active antiretroviral therapy. *Clin Infect Dis*. 2007; 44:599–604. [PubMed: 17243067]
8. Lumbiganon P, Kariminia A, Aupibul L, et al. Survival of HIV-infected children: a cohort study from the Asia-Pacific region. *J Acquir Immune Defic Syndr*. 2011; 56:365–371. [PubMed: 21160429]
9. Kariminia A, Chokephaibulkit K, Pang J, et al. Cohort profile: the TREAT Asia pediatric HIV observational database. *Int J Epidemiol*. 2011; 40:15–24. [PubMed: 20100820]
10. World Health Organization. Antiretroviral therapy of HIV infection in infants and children: Towards Universal Access (2006 revision). World Health Organization; Geneva: 2006.
11. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. World Health Organization; Geneva: 2007.
12. [10 May, 2011] The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 1.0. Dec. 2004 Clarification August 2009 2009. Available at: http://rsc.techres.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf.
13. De Onis, M.; World Health Organization. Dept. of Nutrition for Health and Development. WHO child growth standards : length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age : methods and development. World Health Organization; Geneva: 2006.
14. Kuczmarski RJ, Ogden CL, Guo SS, et al. CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 11. 2000; 2002:1–190.
15. Lian YL, Heng BS, Nissapatorn V, Lee C. AIDS-defining illnesses: a comparison between before and after commencement of highly active antiretroviral therapy (HAART). *Curr HIV Res*. 2007; 5:484–489. [PubMed: 17896968]
16. Dankner WM, Lindsey JC, Levin MJ. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. *Pediatr Infect Dis J*. 2001; 20:40–48. [PubMed: 11176565]
17. Abellan-Martinez J, Guerra-Vales JM, Fernandez-Cotarelo MJ, Gonzalez-Alegre MT. Evolution of the incidence and aetiology of fever of unknown origin (FUO), and survival in HIV-infected patients after HAART (Highly Active Antiretroviral Therapy). *Eur J Intern Med*. 2009; 20:474–477. [PubMed: 19712847]
18. Kapogiannis BG, Soe MM, Nesheim SR, et al. Trends in bacteremia in the pre- and post-highly active antiretroviral therapy era among HIV-infected children in the US Perinatal AIDS Collaborative Transmission Study (1986–2004). *Pediatrics*. 2008; 121:e1229–1239. [PubMed: 18450865]

19. Guillen S, Garcia San Miguel L, Resino S, et al. Opportunistic infections and organ-specific diseases in HIV-1-infected children: a cohort study (1990-2006). *HIV Med.* 2010; 11:245–252. [PubMed: 20050937]
20. Zhou J, Elliott J, Li PC, et al. Risk and prognostic significance of tuberculosis in patients from The TREAT Asia HIV Observational Database. *BMC Infect Dis.* 2009; 9:46. [PubMed: 19383122]
21. Rajasekaran S, Jeyaseelan L, Raja K, Ravichandran N. Demographic & clinical profile of HIV infected children accessing care at Tambaram, Chennai, India. *Indian J Med Res.* 2009; 129:42–49. [PubMed: 19287056]
22. Shah NS, Anh MH, Thuy TT, et al. Population-based chest X-ray screening for pulmonary tuberculosis in people living with HIV/AIDS, An Giang, Vietnam. *Int J Tuberc Lung Dis.* 2008; 12:404–410. [PubMed: 18371266]
23. Gupta A, Nadkarni G, Yang WT, et al. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis. *PLoS One.* 2011; 6:e28691. [PubMed: 22220193]
24. Muga R, Ferreros I, Langohr K, et al. Changes in the incidence of tuberculosis in a cohort of HIV-seroconverters before and after the introduction of HAART. *AIDS.* 2007; 21:2521–2527. [PubMed: 18025889]
25. Braitstein P, Nyandiko W, Vreeman R, et al. The clinical burden of tuberculosis among human immunodeficiency virus-infected children in Western Kenya and the impact of combination antiretroviral treatment. *Pediatr Infect Dis J.* 2009; 28:626–632. [PubMed: 19451858]
26. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. *Clin Infect Dis.* 2010; 50(Suppl 3):S184–194. [PubMed: 20397947]
27. Chiappini E, Galli L, Tovo PA, et al. Changing patterns of clinical events in perinatally HIV-1-infected children during the era of HAART. *AIDS.* 2007; 21:1607–1615. [PubMed: 17630556]
28. Lim PL, Zhou J, Ditango RA, et al. Failure to prescribe pneumocystis prophylaxis is associated with increased mortality, even in the cART era: results from the Treat Asia HIV observational database. *J Int AIDS Soc.* 2012; 15:1. [PubMed: 22281054]
29. Puthanakit T, Oberdorfer P, Akarathum N, et al. Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected thai children. *Pediatr Infect Dis J.* 2006; 25:53–58. [PubMed: 16395104]
30. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008; 359:2233–2244. [PubMed: 19020325]
31. Welch S, Sharland M, Lyall EG, et al. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Med.* 2009; 10:591–613. [PubMed: 19878352]
32. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med.* 2010; 363:1510–1520. [PubMed: 20942667]
33. Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. *Lancet Infect Dis.* 2011; 11:273–283. [PubMed: 21288774]

Note: cd4pc: CD4 T cell percentage ; OI: opportunistic infection; HAART: highly active antiretroviral therapy

Figure 1.

Cumulative proportion of opportunistic infection WHO stage 3 and 4-free children stratified by CD4 level at the time of HAART initiation

Table 1

Characteristics of HIV-infected children at antiretroviral therapy initiation in TApHOD

Characteristics	HAART (n=1480)	mono/dual NRTI (n=272)	P-value
Sex: Male	748 (50.5)	141 (51.8)	0.7
Age			<0.0001
<18 months	159 (10.7)	117 (43.0)	
18-59 months	313 (21.2)	84 (30.9)	
60-155 months	930 (62.8)	64 (23.5)	
156 months	78 (5.3)	7 (2.6)	
Mean age, years	7.0 (3.8)	3.3 (3.3)	
Ethnicity			<0.0001
Thai	1061 (71.7)	205 (75.4)	
Indonesian	113 (7.6)	21 (7.7)	
Indian	86 (5.8)	37 (13.6)	
Malay	85 (5.7)	4 (1.5)	
Khmer	68 (4.6)	1 (0.4)	
Others	45 (4.5)	4 (1.5)	
CD4 cell count (cells/mm³)			<0.0001
0-49	387 (26.2)	21 (7.7)	
50-199	284 (19.2)	20 (7.4)	
200	521 (35.2)	138 (50.7)	
Unknown	288 (19.5)	93 (34.2)	
Mean CD4 count (cell/mm ³)	326.4 (488.2)	932.1 (957.2)	
CD4 cell percentage			<0.0001
<15%	879 (59.4)	69 (5.4)	
15-24%	191 (12.9)	64 (23.5)	
25%	68 (4.6)	35 (12.9)	
Unknown	342 (23.1)	104 (38.2)	
Mean (SD)	9.1 (8.4)	16.9 (10.2)	
WHO clinical staging			<0.0001
Stage 1/2	406 (27.4)	50 (18.4)	
Stage 3	411 (27.8)	85 (31.3)	
Stage 4	404 (27.3)	38 (14.0)	
Unknown	259 (17.5)	99 (36.4)	
Weight for age Z score (n=1121)	-2.9 (2.0)	-2.5 (2.1)	0.002
Height for age Z score (n=1026)	-2.4 (1.7)	-2.1 (1.6)	0.03
First ART regimen			
HAART-NNRTI	1382 (93.4)	0	
HAART-PI	87 (5.9)	0	
HAART-others	11 (0.8)	0	
Mono- NRTI therapy	0	47 (2.7)	
Dual-NRTI therapy	0	225 (12.8)	

Note: Data shown in number (%) or mean (SD, standard deviation), Statistical test performed on non-missing values

ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors.

Table 2

Incidence rate (IR per 100 person-years) of opportunistic infection-related events among HIV-infected children in TApHOD

Opportunistic infections	<i>Before ART N=2129</i> *			<i>After HAART N=1480</i>		
	N	IR (95% CI)	N	IR (95% CI)	N	IR (95% CI)
WHO stage 2	440	24.05 (21.90-26.41)	198	4.50 (3.92-5.17)	79	10.05 (8.06-12.53)
recurrent upper respiratory tract infections	402	22.0 (19.9-24.2)	188	4.27 (3.71-4.93)	76	9.67 (7.72-12.11)
fungal nail infections	23	1.26(0.84-1.89)	5	0.11(0.05-0.27)	1	0.13(0.02-0.90)
extensive Molluscum contagiosum	10	0.55(0.29-1.02)	3	0.07 (0.02-0.21)	1	0.13(0.02-0.90)
extensive wart virus infection	5	0.27(0.11-0.66)	2	0.05 (0.01-0.18)	1	0.13(0.02-0.90)
WHO stage 3	1017	55.59 (52.27-59.11)	197	4.48 (3.90-5.15)	135	17.18 (14.51-20.33)
oral candidiasis	376	20.55(18.58-22.74)	47	1.07(0.80-1.42)	50	6.36(4.82-8.39)
pulmonary tuberculosis	336	18.37(16.50-20.44)	71	1.61(1.28-2.04)	25	3.18(2.15-4.71)
diarrhea	154	8.42(7.19-9.86)	23	0.52(0.35-0.79)	20	2.55(1.64-3.94)
severe recurrent bacterial pneumonia	90	4.92(4.00-6.05)	44	1.00(0.75-1.34)	26	3.31(2.25-4.86)
lymph node tuberculosis	33	1.80(1.28-2.54)	5	0.11(0.05-0.27)	10	1.27(0.69-2.37)
lymphoid interstitial pneumonitis	25	1.37(0.92-2.02)	7	0.16(0.08-0.33)	3	0.38(0.12-1.18)
Acute necrotizing ulcerative gingivitis/periodontitis	3	0.16 (0.05-0.51)	0	-	1	0.13(0.02-0.90)
WHO stage 4	180	9.84 (8.50-11.39)	67	1.52 (1.20-1.94)	12	1.53 (0.87-2.69)
Pneumocystis pneumonia	60	3.28(2.55-4.22)	8	0.18(0.09-0.36)	1	0.13(0.02-0.90)
extrapulmonary or disseminated tuberculosis	23	1.26(0.84-1.89)	9	0.21(0.11-0.39)	1	0.13(0.02-0.90)
cytomegalovirus retinitis or cytomegalovirus infection	18	0.98(0.62-1.56)	8	0.18(0.09-0.36)	3	0.38(0.12-1.18)
disseminated mycosis	16	0.88(0.54-1.43)	10	0.23(0.12-0.42)	0	-
extrapulmonary cryptococcosis	15	0.82(0.49-1.36)	6	0.14(0.06-0.30)	0	-
chronic herpes simplex infection	15	0.82(0.49-1.36)	3	0.07(0.02-0.21)	1	0.13(0.02-0.90)
recurrent severe bacterial infection	12	0.66(0.37-1.16)	10	0.23(0.12-0.42)	2	0.25(0.06-1.02)
esophageal candidiasis	7	0.38(0.18-0.80)	2	0.05 (0.01-0.18)	1	0.13(0.02-0.90)
disseminated mycobacteriosis	6	0.33(0.15-0.73)	7	0.16(0.08-0.33)	2	0.25(0.06-1.02)
central nervous system toxoplasmosis	5	0.27(0.11-0.66)	2	0.05 (0.01-0.18)	0	-
chronic cryptosporidiosis	2	0.11(0.03-0.44)	2	0.05 (0.01-0.18)	1	0.13(0.02-0.90)
Kaposi's sarcoma	1	0.06(0.01-0.39)	0	-	0	-

ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; IR: incidence rates; CI: confidence interval

* 151 children were not included as they started their antiretroviral therapy before their first clinic visit.

Table 3

Incidence rates (IR per 100 person-years) of opportunistic infection-related events and mortality during and after the first six months of starting antiretroviral therapy

	Before ART	Mono- or dual-therapy		HAART	
		During the first 6 months	After the first 6 months	During the first 6 months	After the first 6 months
Follow-up	1830	121	665	693	3702
All OIs	89.5 (85.2-93.9)	66.2 (53.2-82.5)	21.8 (18.5-25.7)	25.4 (21.9-29.5)	7.7 (6.9-8.7)
WHO stage 2	24.1 (21.9-26.4)	17.4 (11.3-26.7)	8.7 (6.7-11.3)	7.5 (5.7-9.9)	3.9 (3.4-4.6)
WHO stage 3	55.6 (52.3-59.1)	45.5 (35.0-59.3)	11.9 (9.5-14.8)	12.3 (9.9-15.2))	3.0 (2.5-3.6)
WHO stage 4	9.8 (8.5-11.4)	3.3 (1.2-8.8)	1.2 (0.6-2.4)	5.6 (4.1-7.7)	0.8 (0.5-1.1)
OI-related death	0.9 (0.6-1.5)	1.7 (0.4-6.6)	0.3 (0.1-1.2)	6.6 (5.0-8.9)	0.6 (0.4-0.9)
All causes of death	2.0 (1.4-2.7)	1.7 (0.4-6.6)	1.1 (0.5-2.2)	8.2 (6.3-10.7)	1.1 (0.8-1.5)

ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; OI: opportunistic infection