Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2011;40:15–24
doi:10.1093/ije/dyp358

COHORT PROFILE

Cohort Profile: The TREAT Asia Pediatric HIV Observational Database

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Accepted 5 November 2009

How did the study come about?

The Therapeutic Research, Education and AIDS Training (TREAT) Asia Pediatric human immunodeficiency virus (HIV) Observational Database (TApHOD) is a collaborative cohort of HIV-infected children in the Asia–Pacific region. TApHOD was established in 2007 in response to a need for better information about treatment and care of HIV-infected children living in this region. Its aim is to examine the natural history of HIV disease, monitor antiretroviral therapy (ART) and prophylactic treatments, monitor toxicities related to ART and develop capacity for standardized and systematic data collection that will lead to improved management of children living with HIV.

In Asia and the Pacific, approximately 140 000 children are living with HIV; the number has risen dramatically in recent years.[1] In 2004, an estimated 37 000 children died of AIDS-related illnesses in South and Southeast Asia and 51 000 became infected with HIV.[2] Over the past few years, the use of ART has been shown to slow disease progression and lower mortality in children.[3–6] Despite the few reports of efficacy of ART in HIV-infected children in Thailand, China, Cambodia and India,[7–15] there are limited data on the natural history of HIV, ART practices and clinical outcomes of these Asian children infected with HIV.

In 2001, The Foundation for AIDS Research, amfAR, in consultation with physicians, researchers and community groups across Asia and Pacific, formed a multinational network called TREAT Asia. The mission of the collaboration is to build capacity and promote safe and effective HIV/AIDS treatment and care (the members of the The TREAT Asia Paediatric HIV Network 2008 is given in Appendix 1; Asterisks, dagger and double dagger indicates TApHOD Steering Committee member, Current Steering Committee chair and co-chair). The network now encompasses 22 adult and 22 paediatric sites. In 2006, the paediatric programme of TREAT Asia launched TApHOD to gather regional paediatric data from clinical and research centres. TApHOD is a member cohort of the International Epidemiologic Databases for the Evaluation of AIDS (IeDEA).[16]

The organizational structure of TApHOD includes: a project management/administrative team, a data management/biostatistics team and a steering committee consisting of representatives from the former two groups and from all the participating sites (principal investigators). The project management centre is located at TREAT Asia's Bangkok office and is responsible for the administrative and operational functions of the study. The data management centre, located at the National Centre in HIV Epidemiology and Clinical Research (NCHECR), University of New South Wales

in Sydney, coordinates data collection and management and provides support of analytic activities at various stages of the research project.

The TApHOD study is funded by amfAR, the Austrian AIDS Life Association and the US National Institutes of Health, through the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases as part of IeDEA.

What does the study cover?

Currently, there is limited information available regarding HIV disease progression, ART regimens being used, treatment outcomes and mortality in children living with HIV in many countries in the Asia–Pacific region. Such data are important for improving paediatric HIV medical care. The objectives of the TApHOD study, therefore, are to:

(i) examine HIV natural history, including relationship between access to ART and paediatric disease progression;
(ii) develop capacity for systematic and standardized paediatric HIV clinical data collection in countries of the Asia–Pacific region;
(iii) monitor antiretroviral (ARV) and prophylactic treatments as related to demographics and markers of HIV disease stage in paediatrics;
(iv) monitor toxicity to ART in children; and
(v) assist in evaluation of new paediatric HIV treatments in the Asia–Pacific region.

Who are in the sample?

TApHOD is a multi-site, open observational cohort study of infants and children living with HIV in the Asia–Pacific. The study enrolls:

(i) children aged $\leqslant$18 years who are conclusively diagnosed with HIV using age-appropriate diagnostic tests: positive HIV virologic test [DNA polymerase chain reaction (PCR), RNA PCR or ultrasensitive p24 antigen assay (Up24)] at any age, or positive antibody testing at age $\geqslant$18 months; and
(ii) children with severe HIV disease (presumptive diagnosis): HIV antibody-positive at any age (or recent HIV-related maternal death or advanced HIV disease in mother) and CD4 <25%.

A child is excluded or removed from the study if he/she previously was included based on presumptive diagnostic criteria and then has a negative HIV test at $\geqslant$18 months of age.

The study participants are recruited from TREAT Asia clinical sites following approval from local governing ethics committees or institutional review boards (IRBs). The first site received IRB approval for the TApHOD protocol in December 2007. Any data collected after a site obtained ethics approval are considered prospective. For patients included in the prospective follow-up, all retrospective data are collected from the date of first entry into the clinic. The date of the earliest enrolment determines the commencement of retrospective data for each site. Sites are also required to provide data for those who died and lost to follow-up during the retrospective period.

Participating sites were selected from major paediatric HIV clinical centres in resource-limited countries in Asia based on their capacity to provide clinical care to children with HIV. Some of these sites are tertiary care referral hospitals and some are primary care centres. Children are referred to these sites from local and district hospitals, medical clinics and maternal–child health clinics, although referrals from other services do occur. Many of the children have their first point of HIV testing/clinical contact directly at the sites.

Currently, 14 sites in six countries (Figure 1) have agreed to participate and 12 sites transferred their data to the data management centre for aggregation. Each clinical site will enroll and continuously follow all HIV-infected children receiving care at the facility. Since data are anonymously forwarded to the data coordinating centre, informed consent is not a requirement, except if required by a site's local ethics committee.

How often have patients been followed up?

The cohort participants are followed as to the standard of care for paediatric HIV infection at the clinical site attended. The data contributed by each site are determined by ongoing patient care and, therefore, the timing of clinic visits and scope of data collection are determined by the nature of the health-care services provided.

Characteristics of participating sites

In March 2008 each participating site completed a site survey to assess its geographic and demographic attributes, clinical care and diagnostic capacity and access to ART. Selected characteristics of the participating sites are summarized in Table 1. The participating sites are predominantly public, university-based clinics and hospitals located in urban areas. ART access was first implemented in Thailand (1994–2002) and Malaysia (1995–97). Other participating sites implemented ART programmes between 1998 and 2005. At the time of survey, 2765 HIV-infected children were on ART in these sites with an average of 198 children per site [median 168; inter-quartile range (IQR) 103–228]. $CD4^+$ cell counts are used routinely in all sites (Table 2). All sites reported access to HIV RNA testing, although three sites reported that access was limited. The sites in India and Indonesia charge a fee for $CD4^+$

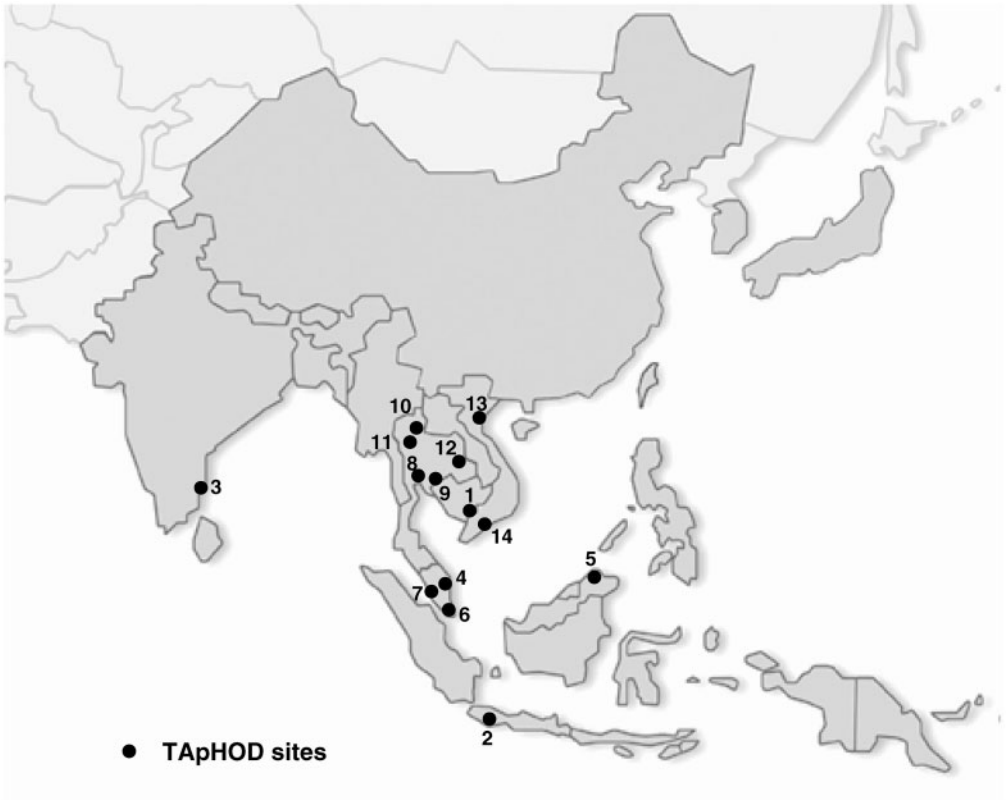

Figure 1 Geographical location of the participating sites in TApHOD

cell count and HIV RNA tests. Paediatric ART is free of charge at all sites except for India.

Criteria for starting ART changed with time. Currently all sites use three age bands for initiation of treatment: infants aged <12 months, children aged 1–3 years and children and adolescents aged >3 years. They initiate therapy:

- in children with AIDS or significant symptoms (WHO stage 3, 4), regardless of CD4 percentage/count or plasma HIV RNA level; and
- in children who have met the age-related CD4 threshold for initiating treatment (CD4 < 25% for children aged <1 year, <20% for children 1–3 years and <15% for children >3 years), regardless of symptoms or plasma HIV RNA level.

All sites use non-nucleoside reverse transcriptase inhibitor (NNRTI) containing regimens as first-line therapy and protease inhibitor- (PI) based regimens as the second-line (Table 3).

Patient characteristics

The TApHOD database currently includes information on 2280 children who enrolled during a period for which we also have complete data on those who died and lost to follow-up. The earliest visit to the clinic was in 1991. Of 2280 children, 549 (24.1%) were lost to follow-up. Table 4 shows the characteristics of the study participants at the time of first clinic visit. Children range from newborns to adolescents aged 17 years; the majority were of school age (5–13 years). There are 1122 (49.2%) females. Perinatal exposure was the dominant mode (>90%) of HIV transmission. $CD4^+$ cell percentage at baseline (first clinic visit) was available for 1169 children. Approximately 61% of these children were severely immunosuppressed, based on $CD4^+$ cell percentage (<15%) at baseline. WHO clinical stage was available for 1241 children. Of these children, 797 (64.2%) were WHO stage III and IV at baseline before initiation of ART. There were some significant differences between patients lost to follow-up and those remaining in the cohort. Those lost to follow-up were less likely to use ARV treatment (49.9 vs 85.4%, $P < 0.0001$), less likely to have an AIDS-defining illness when they first entered care (19.3% *vs* 27.7%, $P = 0.008$), more likely to receive prophylactic treatment (52.8 vs 41.0, $P < 0.0001$), more likely to experience *maternal* or *infant ARV* intervention and more likely to belong to a particular ethnic group.

What has been measured?

All of the participating sites collect demographic, treatment, laboratory and clinical data as part of their routine clinical care of HIV patients (Table 5).

Table 1 Profile of participating sites

Country, city, clinic	Location type	Site type	Public clinic?	Year of ART introduction	Children on ART	Use of generic drugs?	ARV payment
Cambodia							
1 Phnom Penh, National Centre for HIV/AIDS, Dermatology and STI, National Pediatric Hospital	Urban	University-based clinic	Yes	2002	656	Yes	Site/funder
Indonesia							
2 Jakarta, Cipto Mangunkusumo Hospital	Urban	University-based clinic	Yes	2002	170	No	Site/funder
India							
3 Chennai, YRG care	Urban	Non-university clinic	No	1998	125	Yes	Site and patient
Malaysia							
4 Kota Bharu, Hospital Raja Perempuan Zainab II	Mixed	Non-university clinic	Yes	1997	68	Yes	Site/funder
5 Kota Kinabalu, Hospital Likas	Mixed	Non-university clinic	Yes	2001	24	Yes	Site/funder
6 Kuala Lumpur, Hospital Kuala Lumpur	Urban	Non-university clinic	Yes	1995	96	Yes	Site/funder
7 Penang, Penang Hospital	Urban	Government clinic	Yes	1996	17	Yes	Site/funder
Thailand							
8 Bangkok, HIV-NAT	Urban	University-based clinic	Yes	2000	153	Yes	Site/funder
9 Bangkok, Siriraj Hospital	Urban	University-based clinic	Yes	1994	231	Yes	Site/funder
10 Chiang Rai, Chiang Rai Regional Hospital	Urban	Government clinic	Yes	2002	381	Yes	Site/funder
11 Chiang Mai, Chiang Mai University	Urban	University-based clinic	Yes	2002	220	Yes	Site/funder
12 Khon Kaen, Khon Kaen University	Mixed	University-based clinic	Yes	1995	212	Yes	Site/funder
Vietnam							
13 Hanoi, National Hospital of Pediatrics	Urban	University-based clinic	Yes	2005	166	No	Site/funder
14 Ho Chi Minh City, Children's Hospital No.1	Urban	University-based clinic	Yes	2005	246	No	Site/funder

Because there are no scheduled visits for the purpose of this study, the frequency of clinic visits and laboratory testing depends on the clinic's standard practice patterns. The participating sites are requested to extract variables from their existing clinic databases or their medical records, and to put them into a Microsoft Access database, which has been designed for TApHOD. These data are then forwarded electronically to the NCHECR for aggregation. Aggregated data are updated in March and September each year. Tailored computer programmes are used to assure data consistency and accuracy following each transfer. All potential errors are addressed by the site personnel and data are then updated prior to the next transfer.

In addition, on an annual basis, as a quality assurance measure, the TApHOD coordinator at the NCHECR randomly selects 10% of patients from each site and retrieves their data from the previous 12 months. The site coordinator checks these data against the medical record or clinic database for accuracy and identification of errors. If >10% of the total data points are in error, the site is asked to conduct an additional 10% data check. If the proportion of error remains >10%, all data at the site are checked for accuracy.

Table 2 Participating sites current access to diagnostic testing

Country, city, clinic	Access to RNA test	Access to DNA test	Viral load frequency	Access to $CD4^+$ count	CD4+ count frequency	Access to $CD4^+$ percentage	Access to Lymphocyte count	$CD4^+$ payment	Viral load payment
Cambodia									
Phnom Penh, National Centre for HIV/AIDS, Dermatology and STD, National Pediatric Hospital	Sometimes	Always	Every 6–12 months	Always	Every 6–12 months	Always	Always	Site/funder	Site/funder
Indonesia									
Jakarta, Cipto Mangunkusumo Hospital	Sometimes	No	Not routinely done	Always	Every 6–12 months	Always	Always	Site and patient	Patient
India									
Chennai, YRG care	Always	Always	Not routinely done	Always	Every 3–6 months	Always	Always	Site and patient	Patient
Malaysia									
Kota Bharu, Hospital Raja Perempuan Zainab II	Always	Always	Every 6–12 months	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Kota Kinabalu, Hospital Likas	Always	Always	Every 3–6 months	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Kuala Lumpur, Hospital Kuala Lumpur	Always	Always	Every 3–6 months	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Penang, Penang Hospital	Always	Always	Every 3–6 months	Always	Every 3–6 months	No	Always	Site/funder	Site/funder
Thailand									
Bangkok, HIV-NAT	Always	Always	Every 6–12 months	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Bangkok, Siriraj Hospital	Always	Always	Every 6–12 months	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Chiang Mai, Chiang Mai University	Always	Always	Every 6–12 months	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Chiang Rai, Chiang Rai Regional Hospital	Always	Always	Every 12–24 months	Always	Every 6–12 months	Always	Always	Site/funder	Site/funder
Khon Kaen, Khon Kaen University	Always	Always	Every 12–24 months	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Vietnam									
Hanoi, National Hospital of Pediatrics	Sometimes	Sometimes	Not routinely done	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder
Ho Chi Minh City, Children's Hospital No.1	Always	Always	Only to assess treatment failure	Always	Every 3–6 months	Always	Always	Site/funder	Site/funder

Always (Diagnostic test always available if requested by clinicians); Sometimes (25–50% of children can access this test).

Table 3 Type of first- and second-line regimens currently used by the participating sites

Country, city, clinic	First-line regimen	Second-line regimen
Cambodia		
Phnom Penh, National Centre for HIV/AIDS, Dermatology and STD, National Pediatric Hospital	AZT/d4T + 3TC + NVP/EFV	ABC + ddI + LPV/r
Indonesia		
Jakarta, Cipto Mangunkusumo Hospital	AZT/d4T + 3TC + NVP/EFV	TDF + ddI + LPV/r
India		
Chennai, YRG care	AZT + 3TC + NVP/EFV	TDF/ABC + 3TC/FTC + LPV/r
Malaysia		
Kota Bharu, Hospital Raja Perempuan Zainab II	AZT + 3TC + NVP/EFV	d4T/ddI + LPV/r
Kota Kinabalu, Hospital Likas		
Kuala Lumpur, Hospital Kuala Lumpur	AZT/d4T + 3TC + NVP or AZT/ddi + NVP/EFV	2NRTI + LPV/r
Penang, Penang Hospital	AZT/d4T + 3TC + NVP	2NRTI + LPV/r
Thailand		
Bangkok, HIVNAT	AZT/d4T + 3TC + NVP/EFV PI-based for infants exposed to NVP	NRTI + boosted PI/double boosted PI depends on drug resistance
Bangkok, Siriraj Hospital	AZT/d4T + 3TC + NVP/EFV	PI-based regimen (LPV/r)
Chiang Mai, Chiang Mai University	AZT/d4T + 3TC + NVP/EFV	2NRTI + LPV/r or double boosted PI
Chiang Rai, Chiang Rai Regional Hospital	AZT/d4T + 3TC + NVP/EFV	2NRTI + LPV/r
Khon Kaen, Khon Kaen University	AZT + 3TC + EFV if < 3 years: AZT + 3TC + NVP	3TC + EFV + LVR/r
Vietnam		
Hanoi, National Hospital of Pediatrics	AZT/d4T + 3TC + NVP/EFV	ABC + ddI + LPV/r/NFV
Ho Chi Minth City, Children's Hospital No.1	AZT/d4T + 3TC + NVP/EFV	ABC + ddI + LPV/r/NFV

AZT: aidovudine; d4T: stavudine; 3TC: lamivudine; NVP: nevirapine; EFV: efavirenz; DDI: didanosine; ABC: abacavir; TDF: tenofovir; LPV/r: lopinavir\ritonavir low dose; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

We also assessed the quality of the transferred data by computing the percentage of missing key variables (age, sex, clinical stage of HIV infection, $CD4^+$ cell percent and year of ART initiation). The median (IQR) percentage of missing data at the time of first clinic visit was 59% (IQR 33–68%) per site for $CD4^+$ cell percent and 44% (IQR 30–64%) per site for clinical staging. The number of missing values declined with increasing time after enrolment; 29% (IQR 16–45%) for $CD4^+$ cell percent and 5% (IQR 0–14%) for clinical staging at the time of last visit. There were no missing values for age, sex and year of ARV start.

What has been found?

The focus of the project is currently on collecting and combining data for research questions identified by the Steering Committee. The first formal data transfer took place in March 2008. Three manuscripts are in progress to address scientific questions that focus on ART outcomes including survival, shift in opportunistic infections and the experience of adolescents in Asian HIV care and treatment programmes. TApHOD aims to develop scientific collaboration with other paediatric cohorts involved in the IeDEA such as The Paediatric Antiretroviral Treatment Programmes in Lower-Income Countries (KIDS-ART-LINC).[17] By merging and analysing data from different regions we will be able to address new hypothesis and provide the evidence needed for appropriate management of HIV children.

What is attrition like?

Loss to follow-up in our study is defined as the proportion of children who did not attend the clinic during the subsequent year after their last visit. We are in the early stage of data collection and it is not possible for us to estimate attrition. However, we

Table 4 Demographic characteristics of 2280 TApHOD patients at the time of first clinic visit[a]

Demography	Retained in the programme ($n = 1731$)	Lost to follow-up ($n = 549$)[b]	*P*-value[c]
Age (years)			0.197
<1	252 (14.6)	78 (14.2)	
1–4	505 (29.2)	184 (33.5)	
5–9	663 (38.3)	208 (37.9)	
10–14	296 (17.1)	74 (13.5)	
⩾15	15 (0.9)	5 (0.9)	
Median age, years (IQR)	5.8 (2.4–8.9)	5.3 (2.2–8.3)	
Sex			0.197
Female	865 (50.0)	257 (46.8)	
Male	866 (50.0)	292 (53.2)	
Ethnicity			<0.0001
Thai	1123 (64.9)	283 (51.6)	
Indian	197 (11.4)	203 (37.0)	
Indonesian	132 (7.6)	16 (2.9)	
Malay	115 (6.6)	12 (2.2)	
Khmer	86 (5.0)	15 (2.7)	
Chinese	22 (1.3)	3 (0.6)	
Other/unknown	56 (3.2)	17 (3.1)	
Mode of exposure			0.047
Perinatal	1628 (94.1)	470 (85.6)	
Blood products	19 (1.1)	15 (2.7)	
Sexual intercourse/ abuse	9 (0.5)	2 (0.4)	
Other/unknown	75 (4.3)	62 (11.3)	
Infant ARV exposure			0.004
Yes	184 (10.6)	31 (5.7)	
No	968 (55.9)	86 (15.7)	
Unknown	579 (33.5)	432 (78.7)	
Maternal ARV exposure			0.015
Yes	156 (9.0)	26 (4.7)	
No	1000 (57.8)	94 (17.1)	
Unknown	575 (33.2)	429 (78.1)	
CD4$^+$ cell percent			0.449
<10	429 (24.8)	125 (22.8)	
10–14	130 (7.5)	33 (6.0)	
15–24	208 (12.0)	75 (13.7)	
⩾25	130 (7.5)	39 (7.1)	
Unknown	834 (48.2)	277 (50.5)	
Median %CD + (IQR)	10.0 (3.0–20.0)	11 (4.0–19.9)	
WHO clinical staging[d]			0.008
Stage I/II	357 (20.6)	87 (15.8)	
Stage III	326 (18.8)	152 (27.7)	
Stage IV	262 (15.1)	57 (10.4)	
Unknown	786 (45.4)	253 (46.1)	
Severe anaemia[e]			0.641
Yes	61 (3.5)	19 (3.5)	
No	951 (54.9)	261 (47.5)	
Unknown	719 (41.5)	269 (49.0)	
Mean haemoglobin, Hb (SD)	10.4 (1.9)	10.5 (1.9)	
ART[f]			<0.0001
Mono or dual therapy	182 (10.5)	90 (16.4)	
HAART-NNRTI	1219 (70.4)	163 (29.7)	
HAART-NNRTI\PI	7 (0.4)	0	
HAART-NRTI	3 (0.2)	1 (0.2)	
HAART-PI	67 (3.9)	20 (3.6)	
No ART	253 (14.6)	275 (50.1)	
Prophylactic treatments			<0.0001
Yes	709 (41.0)	290 (52.8)	
No	1022 (59.0)	259 (47.2)	

Values are numbers (percentages) unless stated otherwise.
Percentages may not add up to 100% due to rounding.
[a]For CD4$^+$ the closest value within the 3 months before the date of enrolment is used. For haemoglobin and prophylactic treatment the closest value within the 3 months before and one month after enrolment in the clinic are used.
[b]Includes those who have been transferred to other clinics or temporary involved in another study.
[c]Excluding the unknown categories.
[d]Maximum stage before enrolment is used.
[e]Severe anaemia was defined according to US guidelines: Hb <10 g/dL for children <21 days; Hb < 8 g/dL for children between 22 and 35 days; Hb < 7 g/dL for children between 36 and 56 days; Hb < 7.5 g/dL for children ⩾57 days.
[f]Refers to the first ART regimen.
SD: standard deviation.

examined the proportion of children lost to follow-up among the 2280 children who enrolled in the participating sites for HIV care and are included in the TApHOD database. The median duration of follow-up was 3.0 years (IQR 1.1–4.9). A total of 549 (24.1%) children were identified as lost to follow-up. The median percent of lost to follow-up across different sites is thus 19.1% (IQR 10.7–24.1%; range 2.3–51.4%) or 7.3 (6.7–7.9) per 100 child. The reasons for lost to follow-up were not collected systematically for

Table 5 Data collected for TApHOD

Category	Variables
Demographic, background information	Sex, date of birth, date of first clinic visit, date of the most recent contact, ethnicity, HIV exposure category, maternal and infant ARV exposure for PMTCT, date lost to follow-up, date and cause of death
HIV diagnostic testing	DNA PCR, RNA PCR, Up24, ELISA <18 months, ELISA ⩾18 months, other antibody test (and date), clinical presumptive diagnosis
Family history	HIV status of biological mother and father, vital status of biological mother and father, primary caretaker, orphan status, disclosure to child and date, residential status, school attendance and school grade
Serology—hepatitis and syphilis	Hepatitis B vaccination, HBV surface antigen, HBV e antigen, HBV core antibody, HCV antibody, syphilis RPR, syphilis VDRL, syphilis TPHA, syphilis other tests
Opportunistic infection	Date of diagnosis, CDC category, WHO staging, WHO event, diagnosis, outcome, immune reconstitution syndrome
$CD4^+$/HIV testing	Test date, $CD4^+$ count, $CD4^+$ percentage, $CD8^+$ count, $CD8^+$ percentage, total lymphocyte count, viral load (HIV RNA)
Other laboratory and physical examination	Test date, height, weight, haemoglobin, haematocrit, platelet count, ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, cholesterol, HDL, glucose, triglycerides, creatinine
ART	ART treatment and date started and stopped, dosage, frequency, formulation, generic or patent drug, part of a fixed dose combination, reason ARV stopped
Prophylaxis	Prophylactic treatment and start and stop date, primary or secondary
Adverse events	Adverse events, onset date and stop date, hopitalization for adverse events, admission and discharge date, discharge diagnosis

ELISA: enzyme-linked immunosorbent assay; HBV: hepatitis B virus; HCV: hepatitis C virus; CDC: US Centres for Disease Control; RPR: rapid plasma regain; VDRL: venereal disease research laboratory; TPHA: treponema pallidum hemagglutination assay; ALT: alanine aminotransferase also called SGPT: serum glutamic-pyruvic transferase; AST: aspartate transaminase also called SGOT: serum glutamic oxaloacetic transaminase; HDL: high-density lipoprotein; PMTCT: preventing mother-to-child transmission.

children and reported only for 153 of them. The reported reasons include: transfer to adult or another ART programme (22.6%), enrolled temporarily in a clinical trial or other studies (4.6%), moved to a new country (0.7%) and unknown (72.1%). Loss to follow-up is important and might bias results if it is associated with mortality or other outcomes. Currently there is no procedure in our participating clinics for tracing patients lost to follow-up in order to ascertain their vital status. A goal for TApHOD is to reduce the number of patients lost to follow-up by strengthening referral systems and regular exchange of information between different clinics, together with patient education and regular updates of contact details.

What are the main strengths and weaknesses?

TApHOD is the first collaborative cohort describing HIV care for infants and children in resource-limited settings in the Asia–Pacific region. This study will provide an important resource to help develop optimal management strategies for HIV-infected children in the region. The main strength of the study is the inclusion of multiple sites from different countries across the region. Four of the participating clinics are located in countries with high Human Development Index (HDI range ⩾0.750) and 10 are from countries with a medium HDI (range 0.500–0.749). This makes our study population relatively heterogeneous with respect to demographics, health status, education and social factors. Other strengths include a prospective study design, collection of detailed demographic and clinical data at baseline as well as throughout the follow-up period, a high level of quality control, and a common protocol and manual of operation for defining components of data collection and to maximize consistency of data over time. TApHOD can make unique contributions to the understanding of the epidemiology of paediatric HIV nationally, regionally and globally.

The primary limitation of this study is that participating study sites are mainly university-based clinics and/or referral centres, and the extent to which the findings of this collaboration can be generalized to other more primary-care-focused clinical centres cannot be fully ascertained. Another limitation relates to non-standardization of retrospective data.

All clinics enrolled patients before TApHOD was initiated, without a common protocol. This has the potential to introduce bias in the results if outcome or exposure of interest is verified differently between clinics or at different times within the same clinic. Moreover, retrospective data from medical record extraction may be imperfect due to the nature of routine care that may lack some documentation needed. Loss to follow-up and the difficulty of tracing our children is another concern. It is also important to note that the number of infants in our cohort is relatively small. Infants with HIV infection have higher rates of disease progression and mortality than older children[18–20] even without evidence of clear immune suppression (i.e. $CD4^+$ above WHO thresholds). Approximately 18% of our children are <18 months of age. In other words, it is probable that there is a survivor bias in our cohort that may lead to an underestimate of the mortality and disease progression in our cohort. Moreover, the wide implementation of PMTCT programme in this region has also decreased the risk of infection in infants, and resulted in lower number of infected young children.

Can I get hold of data? How can I collaborate?

TApHOD is an ongoing study. Each participating clinical site maintains ownership of data it contributes. Collected data are maintained and stored electronically at the NCHECR. Priorities for data analyses are subject of a concept sheet process. Concepts are accepted from people external to TApHOD if submitted in collaboration with one or more TApHOD site principal investigators. All concepts are subject to Steering Committee review and approval, and prioritized according to interest and resources. Under current TApHOD working procedures, raw data would not be made available to external researchers for analysis. Data summaries would be provided for approved concepts. Any question, research concepts or request on the data should be posted to Ms Joselyn Pang at TREAT in Asia's Bangkok office (joselyn.pang@treatasia.org).

Funding

TREAT Asia is a programme of The Foundation for AIDS Research, amfAR. The TREAT Asia Pediatric HIV Observational Database is supported in part by grants from the Austrian AIDS Life Association and the US National Institutes of Health, through the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases through the International Epidemiologic Databases to Evaluate AIDS (IeDEA; U01-AI069907). The National Centre in HIV Epidemiology and Clinical Research is funded by The Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, The University of New South Wales.

Acknowledgements

The authors wish to thank all the children and the staff in the participating centres who have given their time so generously during the course of this project.

Conflict of interest: None declared.

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Appendix 1

The TREAT Asia Paediatric HIV Network 2008

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