Meeting Report
Paediatric HIV Cohort Consultation
13 – 15 May 2013, Venice, Italy

Hosted by the Collaborative Initiative for Paediatric HIV Education and Research, a project of the International AIDS Society
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*Meeting participants.*
ABOUT CIPHER

While significant progress has been made in improving access to HIV prevention, diagnosis, treatment and care interventions for paediatric populations in resource-limited settings, global coverage continues to lag well behind adults, and significant knowledge gaps remain in both clinical management and service delivery to these vulnerable populations. As part of its work in advancing the global HIV paediatric research agenda, the International AIDS Society (IAS) launched the Collaborative Initiative on Paediatric Education and Research (CIPHER) in July 2012. The two-year initiative is supported by the Viiv Healthcare UK Paediatric Innovation Seed Fund and is aimed at answering outstanding clinical and operational research questions needed to optimize clinical management and delivery of HIV services for infants, children and adolescents. CIPHER has been guided by a Strategic and Technical Advisory Committee (STAC), comprised of key stakeholders and experts in HIV paediatric research from around the world. The STAC met in July 2012 in conjunction with the XIX International AIDS Conference (AIDS 2012) to provide strategic and technical input to the CIPHER Secretariat. CIPHER has two goals:

- **Goal 1: Invest in and promote priority paediatric research**
  Evidence for Action, a needs assessment based on a literature review and key informant interviews with technical experts, was developed to identify priority HIV paediatric research areas. An investigator-driven clinical and operations research grants competition was launched in September 2012, with full proposals due in February 2013. Seven successful applicants were selected through a peer-review process and were announced at the 7th HIV Pathogenesis, Treatment and Prevention Conference (IAS 2013) in Kuala Lumpur, Malaysia, on 30 June–3 July 2013. A special issue of the journal of the International AIDS Society, focusing on current issues related to perinatally HIV-infected adolescents, was also launched at IAS 2013. Additional information on the CIPHER Research Grants Programme is available on the CIPHER website.

- **Goal 2: Strengthen paediatric cohort collaboration**
  At the AIDS 2012 meeting between STAC members and paediatric cohort investigators, there was consensus that a stand-alone meeting with paediatric cohort investigators from around the world is desired to obtain in-depth knowledge about ongoing paediatric HIV cohorts around the world and to allow investigators to identify how best to strengthen paediatric cohort collaboration (Goal 2 of CIPHER). A STAC planning committee was established to develop the agenda and identify participants, chairs and presenters for the meeting, which was held on 13–15 May 2013 (see Annex 1: List of Participants), immediately prior to the Paediatric European Network for Treatment of AIDS (PENTA) meeting. This report summarizes the outcome of that consultation.
CIPHER Paediatric Cohort Consultation

Consultation Objectives

1. Establish a baseline of information on ongoing paediatric HIV cohort, current research agenda and extent of data collection.
2. Identify priority research gaps that can be addressed by cohort collaboration.
3. Identify mechanisms to address these gaps with the support of CIPHER.

The meeting which was co-chaired by Lynne Mofenson (National Institutes of Health, USA) and Linda-Gail Bekker (IAS Governing Council/Desmond Tutu AIDS Foundation, South Africa), included a series of cohort presentations, breakout groups and plenary report back, which resulted in discussion and consensus recommendations. The agenda was structured and chaired to best leverage the expertise of participants not only in developing recommendations for strengthening paediatric cohort collaboration, but also to encourage innovative ideas for research projects that are important and could be pursued through other funding channels (or in a second phase of CIPHER if funding becomes available). These are noted in the section Consensus Research Priorities, Parking Lot: Potential Future Projects.

Prior to the consultation, each of the participating cohorts submitted a cohort summary. Each summary provides an overview of the respective cohort, including its objectives, participant characteristics, data elements and analyses (including recent publications or papers), and the most significant challenges faced by cohort investigators and priorities for clinical or operational research. Information from the cohort summaries will be made available in the CIPHER paediatric cohort database.

Overview: Research Gaps

Rohan Hazra, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), provided an overview of the current clinical and programmatic challenges and outstanding research questions related to paediatric populations. While there has been significant progress in expanding coverage of PMTCT programmes, including diagnosis and treatment of HIV-infected infants, a number of outstanding questions remain.

Tenofovir disoproxil fumarate (TDF): The expanded use of TDF in both maternal and paediatric ART regimens has added urgency to the need to evaluate its short- and long-term impact on renal function and bone mineral density (BMD). Paediatric studies cited included: a PACTG study, indicating that 21.6% of participants had at least one persistent renal abnormality for which TDF was a major risk factor; the Collaborative HIV Paediatric Study (CHIPS) study, showing renal dysfunction in 3.7% (six of 159 study participants) with a median of 561 days of TDF exposure; and a Gilead study with discontinuation of therapy in 4.5% (four of 89) for renal tubular dysfunction after 48 weeks of TDF [1,2,3]. Studies that follow paediatric populations beyond the endpoints of short-term randomized clinical trials (RCTs) will be essential in determining the long-term impact of TDF on bone health and renal function.

Routine monitoring: Determining the most clinically relevant biomarkers and the frequency of monitoring will be key to tracking and evaluating ARV-related toxicities and adverse events; serum creatinine, urine protein, glucose and serum phosphate were all identified as potentially
important to follow. A PHACS study, for example, found that three years of TDF exposure was an independent predictor for cumulative risk of proteinuria of 22% and chronic kidney disease of 4.5% among a multi-ethnic cohort in the USA [4]. Assessment of BMD will likely only be possible in specific settings and cohorts.

**VL threshold for switching ART:** The WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection recommend reducing the viral load (VL) threshold for determining virological failure from >5,000 copies/mm$^3$ to >1,000 copies/mm$^3$, supported by low-quality evidence [5]. More robust evidence is needed to determine the optimal switch threshold, as well as to determine the rate and number of resistant mutations. A recent RCT, PACTG 390/PENPACT I, found good clinical and immunological outcomes after four years among all four arms of the trial, irrespective of whether >1,000 copies/mm$^3$ or >30,000 copies/mm$^3$ was used as the switch threshold or therapy was initiated with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor, with no difference in efficacy or adverse events among the four arms of the trial [6]. A 2010 study of routine VL monitoring found that >5,000 copies/mL was an independent predictor of clinical failure, while a subsequent analysis of that study found that two distinct VL thresholds (at 2,600 copies/mm$^3$ and 32,000 copies/mm$^3$) increased the risk of a WHO clinical event, irrespective of CD4+ count [7,8]. More robust evidence is clearly needed to determine the optimal switch threshold using immunological, clinical and resistance biomarkers, and to determine the optimal frequency of laboratory monitoring.

**Metabolic complications:** Hypercholesterolemia rates of 20% to 50% have been found among HIV-infected paediatric and adult cohorts. Conflicting results among different studies in HIV-infected adults have been seen regarding the correlation between abacavir (ABC) and cardiovascular risk [9,10,11,12]. While cardiovascular (CV) events are rare in children, CV risk factors associated with later risk of adult cardiovascular disease are seen beginning in youth. There is substantial concern that perinatally HIV-infected youth may be at higher risk of CV disease in early adulthood due to the effects of chronic inflammation, ARVs and high rates of traditional risk factors.

**Retention and transition to adult-based care:** Retaining paediatric populations through adolescence and transition to adult care was also identified as a priority concern. A United Kingdom study found a five-fold increase in mortality among HIV-positive youth reaching the age of 21 compared with their younger peers, and data from a United States study found that 10% of 18 year olds were lost to follow up at adult HIV sites, with a greater likelihood of attrition when transitioning youth from adolescent to adult programmes [13,14]. Another recent study on the impact of HIV-I and pregnancy on maternal health found significantly higher mortality among perinatally infected women compared with women who were behaviourally infected [15]. Drug resistance among perinatally infected youth at the time of transition to adult care is also a significant concern [16]. There are also significant psychosocial issues to consider in adolescence and young adulthood, including a developing sense of autonomy, personal identity, education, employment and intimate relationships, all of which must be negotiated in the context of living with HIV.

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1 Two ART regimens (PI+2 NRTIs or an NNRTI + 2 NRTIs) and two VL switch thresholds (>1,000 copies/mm$^3$ or >30,000 copies/mm$^3$) comprised the four arms of this study.
**Cohort Summaries**

Representatives of individual cohorts and cohort networks delivered presentations providing overviews of each respective cohort, which are summarized below. Additional information about the cohorts will be provided in the CIPHER paediatric cohort database.

**Médecins sans Frontières Epicentre**

In addition to direct medical humanitarian activities for populations in need, Médecins sans Frontières (MSF) conducts epidemiological and clinical research and delivers trainings to health care providers and researchers in resource-limited settings. One of MSF’s research partners, Epicentre (established in 1988), has established 48 active Follow-Up Care HIV/AIDS (FUCHIA) databases in 13 countries (29 projects in 11 African countries, two projects in India and 17 in Myanmar). There are 37,322 children under 15 years in MSF cohorts, including HIV-exposed uninfected (HEU) infants, with 15,721 under 12 months of age (as many as 50% of these are HEU).

**Challenges**

Not all MSF cohorts are followed by FUCHIA, and tracking them via FUCHIA is complicated by the requirements of national monitoring systems. The quality of data collection is uneven, and there is limited use of FUCHIA capacities for longitudinal follow up of PMTCT health outcomes. No exhaustive, multi-centric data analysis has been done, with each MSF section tending to analyze a limited amount of clean data linked to a specific research question. Retaining adolescents in care is a significant problem. Task shifting from physicians to nurses or other lower-level health cadres is still not achieved in many contexts where MSF works, and there is limited decentralization of paediatric care. Clinicians need new, simplified paediatric formulations to optimize paediatric treatment outcomes, and better quality data on the mid-term and long-term ARV toxicities would be helpful. MSF has a data-sharing agreement, established in 2012, to facilitate data collection and exchanges.

**Priority Research Questions**

- Interventions/models for improving adolescent retention in care
- Task shifting of paediatric care to nurses and decentralization of care
- New, simplified paediatric formulations
- Data on mid- and long-term side effects (particularly protease inhibitors and TDF).
**Baylor International Pediatric AIDS Initiative (BIPAI)**

The mission of Baylor International Pediatric AIDS Initiative (BIPAI) at Texas Children’s Hospital is to provide high-quality family-centred paediatric and adolescent health care, education and clinical research worldwide. It has nine cohort sites (international project offices and centres of excellence) located in nine African countries, one in Constanta, Romania, and one in Houston, Texas, USA. It has 15,579 active patients (2,237 HEU and 7,640 HIV-infected children under the age of 11, and 5,702 between 11 and 19 years of age). Services are also provided to a large number of patients through a variety of outreach efforts. Adolescent health care is a major focus of BIPAI. With more than 3,500 active members in six countries, BIPAI’s Teen Club International is the world’s largest network of support groups for adolescents living with HIV. Teen clubs provide psychosocial support and life skills training to adolescents living with HIV.

BIPAI has more than 23 years of experience conducting paediatric HIV-related research, including operational, behavioural, clinical, pharmaceutical and retrospective record reviews. All BIPAI sites collect ongoing data via its Electronic Medical Record. BIPAI sites have institutional review boards or work with government institutional review boards that hold active federal-wide assurance numbers from Health and Human Services. All personnel have successfully completed good clinical practice training. There are currently more than 60 active research projects within the BIPAI network. Currently, the patients in care at BIPAI are not part of a research cohort. However, given the number of children in care, there is interest in participating in future cohort research studies.

**Challenges**

The most significant clinical management challenges for BIPAI include ART adherence, HIV-related stigma, HIV disclosure, retaining patients in care, the development of viral resistance, limited second-line and third-line treatment options, and the diagnosis and management of co-infections, such as tuberculosis (TB).

**Priority Research Questions**

- Evaluation of viral resistance
- Best practices for second- and third-line treatment in resource-limited settings
- Best practices for early infant diagnosis, especially non-virologic algorithms for presumptive diagnosis in settings where there is limited access to DNA PCR
- Linkage to care following early infant diagnosis
- Best practices for transition from adolescent to adult care.
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)/INTERNATIONAL MATERNAL ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

PACTG/IMPAACT is a paediatric and maternal clinical trials network that includes 89 sites in the USA, Puerto Rico, South America, Africa and Thailand. Investigators presented on several PACT/IMPAACT protocols as follows.

Paediatric Late Outcomes Protocol (PACTG/IMPAACT 219/219c)

The objectives of the paediatric late outcomes protocol in the cohort study are: (1) to describe late outcomes among HIV-infected infants, children and adolescents, including survival, growth, neurologic, immunological and metabolic function, quality of life, organ system toxicity, and the development of opportunistic infections and malignancies; and (2) to determine if HEU children demonstrate any short- or long-term adverse clinical or laboratory effects due to exposure to ART or immune therapy/vaccines. The study, which is now closed, included 3,552 HIV-infected and 2,348 HEU infants, children and adolescents. Data for the paediatric late outcomes protocol is drawn from follow up of children from USA and Puerto Rico trials sites between 1993 and 2007.

Challenges

There was significant data loss when sites were defunded, and there were challenges in retaining individuals in the cohort. There are also challenges in maintaining support for the cohort database and conducting analyses.

Prospective Surveillance Study of Long-Term Outcomes in HIV-infected Infants, Children & Adolescents (IMPAACT 1074)

IMPAACT 1074 was established in 2009 with the primary objective of identifying long-term adverse outcomes of HIV infection, ART and other experimental interventions. Secondary objectives include combining data from this cohort with data from other cohorts to detect signals of adverse outcomes and to use the cohort as a basis for focused sub-studies on specific adverse outcomes. The cohort includes 1,185 individuals infected via both perinatal and horizontal transmission (no HEU), with the majority (70%) being 18 years of age or older. It includes 40 sites in the US, including Puerto Rico.

Challenges

The challenges include the relatively limited scope of data collected, with no protocol-specified evaluations or laboratory testing and no repository specimens. Investigators are also facing the potential loss of study sites with network re-competition and retaining subjects in the study.

Priority Research Questions

- Identification of uncommon and/or long-term adverse outcomes of HIV infection and/or ART (malignancy, end organ disease, metabolic disease, behavioural issues)
- Transition to adulthood and adult care
- Pregnancy outcomes among youth/adults with perinatal HIV infection.
**Pediatric HIV/AIDS Cohort Study (PHACS)**

The two primary study objectives of PHACS are: evaluating the long-term safety of fetal and neonatal exposure to HIV and ARV prophylaxis among HEU children through the Surveillance Monitoring for ART Toxicities (SMARTT) Study (currently n=2,960); and evaluating the effects of perinatally acquired HIV infection and ARVs in pre-adolescents and adolescents through the Adolescent Master Protocol (AMP) (n=671). The participants are enrolled and followed at 22 sites in the US.

**Challenges**

Challenges include recruitment and retention of study participants and the significant data collection burden on participants at study visits. Other issues include confounding factors and securing sufficient data to use causal methods.

**Priority Research Questions**

- Rare but serious adverse events among *in utero* ARV-exposed infants and children
- Resolving conflicting study results regarding the association between protease inhibitors and preterm birth
- The contribution of TDF to renal and bone complications
- When to start, when to switch, and HIV ARV resistance prevalence and patterns
- Transition to adult care
- Behavioural and neurodevelopmental risks and outcomes

**Optimal Models for HIV Care in Africa**

Project objectives are to: analyze routinely collected clinical data from HIV care and treatment; identify key facility-level factors associated with care and treatment outcomes across different types of health facilities and between countries; and strengthen in-country utilization of routinely collected data for programme evaluation and research. Participating countries include Ethiopia, Kenya, Rwanda, Mozambique and Tanzania, with the cohort comprising 53,761 participants from less than one year of age to 15 years of age at 268 sites.

**Challenges**

Challenges/limitations of this cohort include variability and quality of data, as well as missing data (there are no VL data for most children and up to 50% of children are missing data in key variables). As a result, the heterogeneity of effects across different cohorts may make combined results difficult to interpret.

**Priority Research Questions**
- Uptake and evaluating the impact of revised WHO recommendations for paediatric and adolescent treatment, particularly:
  - Identifying whether earlier ART initiation will improve health outcomes
  - Determining how new regimens will have an impact on health outcomes
  - Identifying factors associated with uptake of WHO recommendations and defined outcomes
- Determine HIV care and ART outcomes, such as identifying patterns of ART-related toxicities and growth outcomes

**EUROPEAN PREGNANCY AND PAEDIATRIC HIV COHORT COLLABORATION [EPPICC]**

EPPICC is a network of cohort studies from across Europe conducting epidemiological research on HIV-infected pregnant women and children, and children exposed to HIV in utero. The collaboration was established in 2009 and includes 18 cohorts from 15 countries. The participating paediatric cohorts included more than 7,000 children with HIV (ever enrolled) in 2012, while the pregnancy/MTCT cohorts include more than 44,000 mother-infant pairs. Participating cohorts maintain their own electronic study databases. Data are obtained by EPPICC through electronic data mergers, based on HICDEP (HIV Cohorts Data Exchange Protocol) data formats.

**Challenges**

There is no centralized or core dataset. Some cohorts have to go back to clinics to obtain specific variables for research projects. Data are only merged for specific projects. Paediatric cohorts are shrinking due to the success of PMTCT programmes in reducing vertical transmission and the transfer of individuals in paediatric cohorts to adult care. Funding for individual cohorts is increasingly fragile. The heterogeneity in the data can preclude some meta-analyses and there are significant barriers to data harmonization.

**Priority Research Questions**

- Factors regarding vertical transmission despite comprehensive PMTCT coverage
- Safety and use of ARVs during pregnancy
- Access to care and retention in HIV treatment and care for pregnant women
- Transition from paediatric to adult programmes
- Long-term virological and immunological response
- Mortality and AIDS-defining events
- Optimal timing for switch to second- and third-line ART
- Poor CD4 response during viral load suppression
Toxicities/adverse events related to TDF.

**EPPICC: EASTERN EUROPE**

Ukraine and Russia account for 90% of the HIV epidemic in eastern Europe. There are two EPPICC paediatric cohorts, with seven sites in Ukraine (more than 1,000 participants under 18 years of age) and four sites in Russia (approximately 1,079 participants under 18 years of age) enrolling only HIV-infected participants. The aim of the Ukraine cohort is to investigate HIV disease progression, treatment (uptake, response, toxicities, etc.), growth and co-infections in HIV-infected children and adolescents, with both the Ukrainian and Russian cohorts conducting cross-sectional studies on specific topics, such as HIV/HCV and HIV/TB co-infection.

**Challenges**

Language barriers (standard operating procedures must be translated into Russian), developing and maintaining electronic databases and limited experience in data management are significant challenges. Some sites have limited expertise in conducting research, and there is competition with industry projects that have substantial financial rewards for participation.

**Priority Research Questions**

- Prevalence of co-infections, especially with hepatitis C (HCV) and TB
- Evaluation of opportunities to engage with HIV-infected parents attending clinics with children
- Reasons for loss to follow up (LTFU)
- Future data mergers within EPPICC
- Long-term virological and immunological response
- Mortality and AIDS-defining events
- Switch to second- and third-line
- Suboptimal CD4 response during viral load suppression
- Predictors of poor CD4 response in children on ART.

**INTERNATIONAL EPIDEMIOLOGICAL DATABASES TO EVALUATE AIDS (IeDEA)**

IeDEA is a global network of observational cohorts that includes paediatric sub-cohorts located in Asia, the Caribbean, Central and South America, and central, east, southern and west Africa. The purpose of IeDEA is to create a platform to evaluate paediatric clinical outcomes, which can also be used in the evaluation of health care systems. IeDEA includes 110,180 HEU and HIV-infected infants, children and adolescents in 31 countries. Each IeDEA region conducts their own centralized data management through regional standard operating procedures, with data for
multiregional analyses merged for each concept-driven analysis. A Data Harmonization Working Group is developing an IeDEA Data Exchange Standard to facilitate the consistent collection of standardized core data at regular intervals. Data harmonization remains challenging given the time required to gather and validate data, with limited regional capacity for analyses of large data sets.

**Challenges**

Data harmonization among cohorts, the amount of time needed to collect data, and limited regional capacity for additional “big data” analyses were identified as key technical challenges. There are also inconsistencies in the data collected by different regional cohorts and significant differences in the frequency of data collection.

**Priority Research Questions**

- Long-term treatment outcomes of perinatally infected adolescents/young adults
- Drug resistance, third-line treatment options, chronic diseases, cognitive and functional development
- Drug toxicities, particularly TDF, abacavir (ABC) and integrase inhibitors
- Adherence, including assessment of effective interventions and tools

**IeDEA Southern Africa**

The goal of IeDEA Southern Africa is to conduct clinical, epidemiological and health services research to inform HIV service delivery in southern Africa, to increase the capacity for delivering ART and to improve the prognosis of people living with HIV. It includes six countries in southern Africa (Lesotho, Mozambique, Malawi, South Africa, Zambia and Zimbabwe), with 42,830 under 12 years of age at first visit, 12,744 who were 12-18 years of age at first visit (perinatally or behaviourally infected) and 1,200 HEU children.

**Challenges**

Retention in care (including transfer of care between sites) and determining health outcomes remain significant challenges, along with technical issues, such as data harmonization across sites and completeness of data collection. The time needed to collect and collate data, conduct analyses and collate data for multi-regional analyses is also a challenge.

**Priority Research Questions**

- Safety and effectiveness of different PMTCT and paediatric ART strategies
- How to implement PMTCT and paediatric ART effectively at scale in resource-limited settings
- Effects of long-term HIV infection and exposure to ART in perinatally infected adolescents
- Models of care for transitioning from paediatric to adolescent and ART care.
**IEDEA Central Africa**

The IEDEA Central Africa cohort investigates therapeutic and adverse responses to ART, cancers and other co-morbidities, conducts implementation science for HIV treatment and care, defines the epidemiology of unusual disease course and fosters translational studies. Four countries (Burundi, Democratic Republic of Congo, Cameroon and Rwanda) are involved, and the cohort includes 5,441 individuals under 15 years of age and 2,916 adolescents and young adults (15-24 years of age).

**Challenges**

Challenges include variable levels of expertise among data personnel at different sites (often very low level), harmonizing data from different clinical forms and databases, low data quality, limited access to laboratory monitoring and the relatively small size of the cohort (particularly the adolescent cohort).

**Priority Research Questions**

- Timing of ART initiation in children of one to four years of age
- Adherence and retention in PMTCT and HIV care
- Long-term treatment outcomes, including durability of first-line ART
- Cancers and other co-morbidities (including Burkitt’s lymphoma, KS, hepatitis).

**IEDEA West Africa**

The goal of IEDEA West Africa is to document the operational conditions of HIV care after rapid scale up and the long-term outcomes among HIV-exposed and HIV-infected children. IEDEA West Africa includes 11 cohorts in eight countries (Benin, Burkina Faso, Cote d’Ivoire, Ghana, Mali, Senegal, Togo and Nigeria), comprising 9,370 children, including 2,820 HEU children.

**Challenges**

One of the major challenges for IEDEA West Africa is improving the care of HIV-infected adolescents on ART, particularly in assessing the impact of disclosure to adolescents of their HIV status (including when and how to disclose) and facilitating the transfer of adolescents from paediatric to adult care.

**Priority Research Questions**

- Documenting the transition from paediatric to adult care
- Disclosure to adolescents process
- Drugs toxicities and pharmacokinetics
- Adherence.

**IEDEA EAST AFRICA**

The goals of IEDEA East Africa are to determine the short- and long-term outcomes of adults and children and examine patient and site-level factors associated with these outcomes, assess the coverage and outcomes of PMTCT programmes, and monitor the translation of evidence into practice for managing co-infections (especially HIV/TB) and epidemiological surveillance on the prevalence, incidence and outcomes of HIV-related malignancies. IEDEA East Africa includes sites in Kenya, Uganda and Tanzania comprising 42,214 individuals (up to 18 years of age), including 25,507 who are HIV infected and 15,707 who are HEU or of unknown sero-status.

**Challenges**

Missing data, data harmonization across IEDEA regions and insufficient funds for enhanced monitoring (including cardiac and cognitive evaluations) are key challenges. There are also no background incidence data.

**Priority Research Questions**

- Long-term effects of intra-uterine ART exposure on cardiac and cognitive function and bone health
- Optimal monitoring strategies for children
- Optimizing adherence in paediatric populations

**TREAT ASIA PAEDIATRIC HIV OBSERVATIONAL DATABASE: TAPHOD IEDEA ASIA-PACIFIC**

The purpose of TAPHOD-IEDEA Asia-Pacific is to examine the natural history of HIV, including the relationship between access to ART and disease progression, in paediatric populations in south and southeast Asia, and to improve capacity for systematic and standardized paediatric HIV clinical data collection. It includes 17 paediatric sites in six countries (Cambodia, India, Indonesia, Malaysia, Thailand and Vietnam), with a cohort of approximately 4,500 (under 18 years of age). HEU children are not followed once their HIV diagnosis is confirmed.

**Challenges**

Challenges include the many different patient and site staff languages (for example, Indonesian, Chinese, Khmer, Malay, Thai and Vietnamese), data quality, consistency and harmonization, differing regulatory requirements, English language scientific writing skills, and investigator time constraints.
Priority Research Questions

- Long-term complications and chronic disease outcomes on bone health, kidney, cardiovascular and neurocognitive function
- Protease inhibitor resistance and third-line treatment options
- Adolescent transition to adult programmes

**CARIBBEAN, CENTRAL AND SOUTH AMERICA NETWORK FOR HIV EPIDEMIOLOGY (CCASAnet)**

CCASAnet is a network of seven cohort sites in five countries (Argentina, Brazil, Haiti, Honduras and Peru) that is part of the leDEA network. The purpose of CCASAnet is to establish a network of participating sites in the Caribbean, Central and South America for sharing of existing research and clinical data related to the epidemiology of HIV and related disorders in children less than 18 years of age. The cohort includes 1,795 HEU and 3,780 HIV-infected participants.

**Challenges**

The primary challenge is developing a standardized database that will facilitate cross-regional data sharing.

Priority Research Questions

- Long-term non-infectious complications of perinatally infected children and adolescents: metabolic, cognitive and mental health
- ARV treatment issues, particularly genotypic resistance monitoring, access to third-line ART regimens (including outcomes and toxicities) and regimen simplification, paediatric fixed-dose combinations
- Adherence tools and interventions

**Chair’s Summary**

Meeting Co-Chair Lynne Mofenson summarized the research questions that were most consistently identified by cohorts:

- Adherence (particularly among older children and adolescents)
- Retention/loss to follow up (LTFU)
- Transition from paediatric to adult programmes
- ARV-related toxicities (especially renal, hepatic and metabolic function, bone mineral density and strength and neurodevelopmental and cognitive function)
- Co-infections (particularly TB, HBV, HCV and cryptococcus)
- Duration on first-line regimens/switch rates.

Disclosure issues were also seen as very important, particularly for adolescents. Technical issues, such as data quality, expertise in data management, and research and data harmonization, were also consistently identified as challenges across cohorts.
RESEARCH PRIORITIES

For the second objective of CIPHER, funding of US$500,000 is allocated for one or two key research questions that can be addressed collectively through cohort collaboration. Funding can be allocated to studies involving a global consortium of paediatric initiatives and cohorts that can collect and/or analyze data on health outcomes, adverse events, clinical management or operational/service delivery issues. Given the unique opportunity presented by the consultation, attention could also be devoted to brainstorming other research ideas, considering data harmonization issues, use of the CIPHER database, and novel ways for the global network to communicate and share information.

Three breakout groups were established and asked to identify two to four research priorities from among the priorities identified by individual cohort presenters and summarized by consultation Co-Chair Lynne Mofenson. An overview of participants in each breakout group is available in Annex 2. Chairs and rapporteurs for each breakout group were identified and were given directions to facilitate the group towards prioritizing research priorities, keeping in mind the available funding, feasibility of implementation through cohort collaboration, and impact.

RESEARCH PRIORITIES: BREAKOUT GROUP I

1. Transition from paediatric to adult care

Research is required to understand the challenges that HIV-infected adolescents face in transitioning to adult ART programmes, particularly given adherence challenges and retaining this population in care. Such research could potentially provide a long-term legacy for continuation of follow up (ongoing follow up with the vertically infected population) during adult care. A pilot survey being prepared by European cohorts could provide the basis for data collection. The study could also be essential for future studies on health outcomes (cancers, toxicities, fractures, pregnancy outcomes, etc.).

2. Retention/LTFU

A study aimed at understanding the factors leading to LTFU and low retention in care among paediatric patients could inform interventions aimed at retaining paediatric patients across the cascade of care through transition to adult programmes.

3. Pregnancies among perinatally infected adolescents

Determining pregnancy outcomes among perinatally infected girls and women remains an important and unanswered question. Limited data is available on the rate of pregnancies among this growing, sexually active population or the outcomes of pregnancies. Such a study would involve identifying pregnancy outcomes in both infants and their mothers.

4. HBV cross-sectional study to assess prevalence

A research study evaluating hepatitis B (HBV) prevalence among a cross-section of HIV-infected paediatric populations would provide important information on a potentially important co-morbidity in resource-limited settings and improve clinical management.
Parking Lot: Potential Future Studies

- Cost-effectiveness modelling: developing a paediatric cost-effectiveness model with data from large cohorts/pooled analyses.
- Mapping the use of ARVs: what formulations are being used, where they are procured from, and strategies for stock outs (this project would require the involvement of ministries of health).
- Disclosure: defining and piloting interventions to support disclosure, both by parents to HIV-infected children and by sexually active adolescents/young adults to sexual partners.
- Operational research on programmatic strategies to increase the proportion of HIV-exposed infants receiving early infant diagnosis.
- Studies to obtain more detailed information on physical and cognitive development among adolescents, such as evaluation of physical development/puberty onset using Tanner staging.
- Using HEU populations as controls for future studies of HIV-infected paediatric populations.

Research Priorities: Breakout Group 2

1. TDF toxicity monitoring

A large-scale study monitoring TDF toxicity would provide important data on the short- and long-term health impacts of this ARV among paediatric populations. Urinalysis evaluation for proteinuria is one approach to screening for TDF tubular toxicity (rather than creatinine screening, which identifies a late outcome); urinalysis may not predict just renal toxicity, but also bone toxicity since the presumed mechanism of bone loss is driven by renal phosphate wasting. One challenge for this research priority is that few patients in paediatric cohorts are using TDF and those that are would be using it with protease inhibitors (PIs) so the toxicity issues may be difficult to differentiate. It might be possible to get manufacturers to contribute to the costs as part of a post-marketing surveillance strategy.

2. HBV, HCV and cryptococcus co-infection among HIV-infected paediatric populations

A cross-sectional study of HBV, HCV and cryptococcus infections among cohorts would fill important knowledge gaps regarding the prevalence (and potential clinical impact) of these co-morbidities. While they are prevalent in many low- and middle-income countries (LMICs), it is not clear to what extent they are prevalent in HIV-infected paediatric populations. It might be possible to do a prospective cross-sectional survey of HBV/HCV sero-surveillance (the EPPICC cohort is conducting a survey to identify HCV co-infected patients to review treatment protocols, and the survey could be adapted for wider use). Drug manufacturers might have an interest in funding this area. A point-of-care (POC) cryptococcus antigen test is available, which is very sensitive and cheap and could be used in such a study, and there are POC HCV and HBV assays that are available and inexpensive. Conventional wisdom is that these are not common paediatric diseases, but there are no hard data available to determine the accuracy of this perception.
3. **Pregnancy outcomes among perinatally-infected adolescents**

There is little data on pregnancy outcomes among perinatally infected adolescents, which is an increasingly important knowledge gap given the rapidly expanding HIV-infected adolescent population in resource-limited settings who are (or will shortly become) sexually active. This research priority will likely require some prospective preparatory work as most clinics don’t routinely collect this information. Data on contraception use among perinatally infected girls and women is very poorly collected, and there is no good data on perinatally versus behaviourally acquired infections among pregnant HIV-positive mothers.

4. **Duration of first-line therapy in children/time to switch**

Duration of first-line ART in children and time until they switch to a second-line ART regimen is a critical question. Compared with other types of clinical data, there is probably better quality data on this issue since most programmes are heavily focused on ART reporting. In discussion, such a research study was also considered feasible to implement. Collection of data related to first-line ART regimens in children is already under way by iDeA globally and may also be relatively low cost to implement. The CHIPS cohort is also analyzing this data and this is about to be taken up as part of EPPICC, so a small amount of funding could potentially have a large impact given existing work in this research area. An activity like this could mobilize this global group and provide a baseline of data that could be built on (e.g., in the future, we could look at second-line and third-line switching).

One challenge is that different strategies for switching are used by different sites/clinics: some use VL, some use CD4 and some use WHO clinical staging and this can vary even between sites in a cohort. Such a study may need to define “switch”. For example, iDeA has a few definitions for a switch, including switching an NNRTI to a PI with the reason reported as treatment failure, or a switch from an NNRTI to a PI plus a switch in at least one NRTI. This project in theory could then evaluate how different strategies work. It might be possible to see differences between regions based on local drug availability and practice, and this could be extended to define not only duration of ART, but also to better understand why to switch and what regimens to use.

5. **Transition from paediatric to adult care**

This study would require descriptive mapping of the transition from adolescent to adult care. It might be possible to select a number of regionally and nationally representative sites or types of clinic that are especially good at this. This project would entail prospective qualitative data collection, but a survey would be relatively easy to do.

Breakout Group 2 indicated that the highest priority research questions were HBV co-infection prevalence, pregnancy outcomes, duration of first-line ART/time to switch, and transition from paediatric to adult care.
Parking Lot: Potential Future Studies

The group also proposed research ideas for future consideration, including cancer incidence among paediatric populations, which is not currently well collected and would be important information to collect in the future. They also suggested drug resistance profiling and monitoring of health outcomes among HEU children.

Research Priorities: Breakout Group 3

1. Optimizing switch strategies after first-line failure

The goal of this research project is to improve clinical and programmatic guidance with respect to optimal timing of switch in order to reduce the risk of second-line failure and the accumulation of additional resistance mutations. It includes: examining outcomes of children with varying times to virologic failure; examining laboratory markers, including CD4+, VL and (if available) genotyping; identifying WHO clinical events; determining response to second-line ART; and identifying ARV-related clinical outcomes.

2. Adolescent HIV outcomes and care support structures – “pre-transition”

There is an opportunity to pool global adolescent data to conduct standard HIV and ART outcomes analyses (including information on pregnancy outcomes). This project would require gathering operational data from participating clinical centres about current adolescent care and support services and pushing adult cohorts to specify if patients were perinatally infected in their databases. Data elements would include VL (if available), CD4 counts and ART regimen. In discussion regarding the age threshold (10 years of age or 12 years of age and older), participants suggested using the WHO definition of 10 years of age, which would also help in looking at disclosure issues.

3. Preparing for TDF

This study would evaluate the short- and long-term impact of TDF on physical and cognitive development among children. However, there are a relatively small number of children on TDF currently and time is required to identify population-level side effects. It might be possible to do power calculations in order to estimate what numbers/rates of children on TDF would be needed before meaningful analyses could be done. A TDF project could encourage sites within global cohorts to gather minimum pre-TDF data in order to facilitate future comparisons (e.g., creatinine, weight/height fracture data, and concurrent illnesses, such as TB).

4. Building data analysis capacity: junior investigators

This breakout group also suggested establishing a small portion of scholarship funding to support junior investigators from LMICs to work with the data analysis centre, using the CIPHER-supported analyses as an example.

Consensus Research Priorities

Following extensive discussion regarding the cost, implementation feasibility (particularly whether data were currently collected or whether a survey or other data collection tool could
provide a straightforward way of obtaining the required data) and scientific merits of the priority research questions presented by each of the three breakout groups, consultation participants agreed on the following research priorities with a strong recommendation to incorporate a capacity-building scholarship component (funding permitting) as part of these projects:

1. Adolescent transition to adult care
This priority research project could identify important factors in LTFU and the interventions/services (such as transition plans) that might ensure a smooth transition to adult programmes.

2. Duration on first-line ART to switch
This research project was seen as a high priority given its potential impact on informing clinical management and improving health outcomes of paediatric populations. Participants noted that it could also include mortality and LTFU data (note that EPPICC and iEDEA were both collecting these data and could leverage that work to produce a global analysis).

3. Pregnancy outcomes of perinatally infected adolescents
Determining pregnancy outcomes among HIV-infected adolescents (including the health status of infants) would require retrospective data collection (descriptive in nature), including characteristics and pregnancy outcome (HIV diagnosis, birth weight, other standard measures). It was noted that there is not a lot of a data available on this issue at the moment and it would require substantial work in determining data elements (therefore it was deemed a lower priority than the first two research projects mentioned).

Parking Lot: Potential Future Projects
Regarding an HBV and HCV cross-sectional survey, a cross-sectional prevalence blood testing survey using POC assays, in selected sites with regional representation, would provide important information to clinicians. In discussion, participants noted that the project is likely to require significant costs and so the decision was to table this project as a potential future project.
MECHANISM FOR ADDRESSING RESEARCH PRIORITIES

The purpose of the second breakout session was to determine the most appropriate mechanism and methodology for undertaking one or more of the identified consensus research priorities. Two breakout groups were established (see Annex 2) to develop recommendations on the most effective approach to collaboration and implementation of the research projects, with a final plenary discussion developing consensus agreement on the most appropriate mechanism.

PROPOSED MECHANISM: BREAKOUT GROUP 1

Adolescent Transition to Adult Programmes

This group noted that most data for this project is already collected and available at most sites, with some data also possible from adult-based HIV care sites. Site surveys will likely be required to address site-specific factors (such as transition to adult care policies/mechanisms).

Duration of First-line ART to Switch

Data are available for this project at most sites and the initial data collection could be the first stage of a multi-stage project. Data collection will include infant diagnosis and ART initiation.

Pregnancy Outcomes in Perinatally Infected Females

Data are generally not available to answer this question, but there is a lot of interest and potential. This group suggested establishing a working group to design data collection tools (building on PHACS, 219C/1025).

PROPOSED MECHANISM: BREAKOUT GROUP 2

A central data management and analysis centre will be essential for undertaking priority research projects. Considerations include:

- Establishing a data transfer agreement
- Data standard operating procedures
- Cleaning/validating and analyzing the data

The invitation/selection criteria for the data management centre should be determined by a working group, and will include the need for demonstrated experience in working with large data sets. Not all cohorts may be included in the research; it will depend on the cohort size, data quality, and other functional considerations. Funding will be for primary analysis (at the data management centre), for cohorts that need support for data extraction (e.g., institutional review board fees and staff time), and should include support for conference calls and, if required, face-to-face meetings.
Papers and Editorials/Commentaries in Peer-reviewed Publications

This group underscored the need to maintain connection among the global network of paediatric cohorts and to publish important clinical and operational issues relevant to the priority research projects. Examples include:

1. ARV exposure in infants that might be different in different regions because of genetic variation. We know that there is genotoxicity and sub-clinical metabolic problems. We need to determine what (if any) is the impact of these biological and molecular changes on long-term outcomes.

2. Commentary on retention in care and LTFU rates across paediatric programmes.

**Consensus: Collaborative Mechanism**

Consultation participants agreed to establish a CIPHER Executive Committee (with no cohort representatives to ensure that there are no conflicts of interest) that would then define the terms of reference for the data management centre responsible for undertaking the highest priority research projects and work with individual cohorts to collect and validate the data. Definitions of certain terms (such as “switch”), in particular, must be explored and harmonized given variability in how such terms are used in different clinical sites. Research centres with sufficient expertise and infrastructure to host the data management centre will be invited to submit proposals in response to the terms of reference. Working groups will be established for each research project, and will be responsible for drafting and revising the concept notes defining the research project, methodology and data elements and definitions. Participants also agreed, given the funding available, that the research projects be limited to the two projects that consultation participants identified as the highest priority: Transition from Adolescent to Adult Care; and Duration on First-line ART to Switch. The feasibility of collecting data on adolescent pregnancy outcomes (including determining data elements and data collection tools) will be considered in developing the concept note for the Transition from Adolescent to Adult Care research priority.

**Research on Adolescents Before Transition to Adult Care**

Participants recommended that this study consist of two elements (1) an initial survey of pre-transitional care and (2) obtaining the necessary data, including family information (primary caregiver, other family support structures/caregivers). The research should highlight whatever emerges in the evolution of care, tracking trending data within paediatric programmes from younger to older adolescents. The working group for this project will research and draft a literature review to explore what is currently known and unknown in this area. The Child Survival Working Group of the UN IATT is currently writing a similar paper for a special supplement in the journal, AIDS. The Perinatally-Infected Adolescents Working Group will identify any additional required data elements and then determine the approach to data collection, management and analysis.

**Duration on First-line ART to Switch**

The key issue in gathering data regarding duration on first-line and time to switch (given different guidance on when to switch) is to consider which data elements will help determine the extent of potential impact on future health outcomes given variable switch strategies and
definitions. Data elements would include current ART regimen, CD4, VL data (where available), and length of time on ART before 12 years of age. Additional data elements/analyses could be added in the survey phase of the project.

**Incorporating a Capacity-building Element for Junior Investigators in LMICs**

Participants strongly supported using some funding to support scholarships that would provide younger investigators from LMICs to work with mentors and senior staff in analyzing data at the site selected as the data management centre. The scholarships could dovetail with (and leverage funding from) the Harvard scholarship programme currently in development. It was suggested that a simple approach to capacity building is to require the contracted data centre to help support student(s) participate in data analysis/support. Shirin Heidari noted that if the scope is limited to support for a short period of time (travel/cost of living for a two-month period), it is possible that this could be supported via another programme budget. The terms of reference for the data centre management would include asking the organization how it could best support a capacity-building element.

Participants also noted that publishing papers and editorials on the significant number of adolescents who will shortly reach child-bearing age (transitioning out of paediatric and into adult cohorts) will be important in flagging this as an issue for ART programme managers and clinicians. Other papers and editorials on the consensus high-priority CIPHER research projects discussed at the meeting were also suggested for consideration. Publications coming out of the research projects will be published under group authorship, with authorship guidelines to be developed by the working group.
**CIPHER ONLINE DATABASE**

Carina Sorensen and Marissa Vicari from the IAS Research Promotion Department, presented the CIPHER paediatric cohort database, an online, searchable database that is being developed as part of CIPHER. The purpose is to establish a tool that will facilitate cohort communication and collaboration over the long term (beyond the two-year timeline of CIPHER). It includes an interactive map that displays an overview of paediatric HIV cohorts globally. A profile page outlines more detailed information about each cohort. The beta version is tentatively planned to be launched at IAS 2013.

Meeting participants were enthusiastic about the database, and provided useful suggestions to further improve it. Suggestions included noting the date and data source to ensure accuracy and sending out annual or semi-annual reminders to cohort leads to upload/update their information. A text box could also be included for explanatory purposes (e.g., explanation of age ranges in the cohort). Consultation participants agreed to establish a working group to develop the database and ensure that it meets the functional requirements of cohorts and cohort investigators.
**Next Steps**

Meeting chairs and IAS Secretariat staff thanked the participants for their active participation and for a productive meeting. The chairs summarized the conclusion of the meeting. Shirin Heidari explained the next steps:

**Meeting Report**

A meeting report on the consultation will be drafted and circulated to consultation participants for input hopefully by the end of June.

**CIPHER Executive Committee**

The group was also informed that a CIPHER Executive Committee was established chaired by IAS Governing Council representative Linda-Gail Bekker and including Lynne Mofenson, Shaffiq Essajee and Shirin Heidari. The role of the committee is to develop terms of reference for the data management centre, review the submitted proposals and oversee the implementation of the cohort mechanism agreed by the group.

**Cohort Steering Committee**

The steering committee will be comprised of diverse representatives of the paediatric HIV cohorts (defined as a cohort that is actively contributing to global cohort work/projects). Terms of reference will be developed by the executive committee, which will clarify the role and responsibilities of steering committee members.

**Two Working Groups**

An Adolescent Transition to Adult Programmes Working Group and a Duration on First-line ART to Switch Working Group will be formally established to develop a concept note for implementation of each research project.

**CIPHER Cohort Database Working Group**

A working group was established to support the IAS Secretariat in refining and improving the paediatric cohort database.

**Commentaries and Editorials**

Specific papers or editorials can be drafted based on the outcome of the meeting and perhaps to formally launch the global CIPHER paediatric cohort network. The executive committee will consult with the steering committee. A special issue on perinatally infected adolescents, guest edited by Lynne Mofenson and Marc Cotton, will be published in the *Journal of the International AIDS Society* in June and launched at IAS 2013.

**Long-Term Plans**

If additional funding is secured, there is a possibility for a second global meeting of paediatric cohort investigators in 2014.
## Annex 1: Paediatric Cohort Consultation Participants

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## ANNEX 2: BREAKOUT GROUP PARTICIPANTS

### Breakout Session 1: Identifying two to four priority research gaps

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* Group chair

### Breakout Session 2: Identifying collaborative mechanisms to address agreed research questions

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