

Meeting Minutes

STAKEHOLDER MEETING

AIDS 2014

20 July 2014, Melbourne, Australia



1 About

During the 20th International AIDS Conference (AIDS 2014) in Melbourne, Australia, CIPHER convened a stakeholder meeting (on 20 July 2014). The CIPHER Scientific Technical and Advisory Committee (STAC), cohort representatives, grantees and key stakeholders were convened to review CIPHER's programme and the year's developments, to discuss next steps and to network.

These minutes provides a summary of the information provided during the meeting and links to the supplementary information and meeting reports.

2 Update on CIPHER

Speaker: Marissa Vicari, CIPHER Project Manager, IAS

Marissa Vicari opened the meeting by welcoming everyone and thanking them for attending. An overview of the evolution of CIPHER, from a two-year research initiative to an IAS Priority, was presented:

- 2012: CIPHER was established as a two-year flagship paediatric initiative, with the support of an unrestricted educational grant of £1.5 million from ViiV Healthcare.
- Activities developed in 2012-2013:
 - Needs Assessment
 - Research Grant Programme
 - Global Cohort Collaboration
 - Online Paediatric HIV Cohort Database
 - JIAS special issue: Perinatally HIV-infected adolescents.
- End 2013: Paediatrics becomes an IAS Priority, branded as CIPHER.
- ViiV Healthcare renews the original grant of £1.5 million for 2014-2015.

2.1 Research Grant Programme

CIPHER has established a competitive grant programme in paediatric HIV. In 2013, the grant programme attracted overwhelming interest.

- Thanks to re-funding from ViiV Healthcare, CIPHER was able to award two more grants in 2014.
- The 2014 grantees (see next section) were selected from the 2013 shortlist.
- Thanks again to strong support from ViiV, CIPHER launched a [new round of grants for 2015](#) at AIDS 2014.

2.2 Global Cohort Collaboration

The CIPHER Global Cohort Collaboration brings together the largest paediatric HIV cohorts and networks worldwide¹, representing approximately 250,000 children and adolescents.

- CIPHER organized a kick-off meeting on 3 April 2014 at CROI, which was attended by more than 60 participants. WHO and PEPFAR have both shown interest in the collaboration and joined the meeting.
- A technical meeting on 27 April at IWHOD followed up the kick-off discussion, focusing on the concept notes. CIPHER used the opportunity to discuss synergy with the IWHOD organizers. During the IWHOD plenary, the need for paediatric and adult cohorts to collaborate on the issue of adolescents transitioning into adult care was discussed, and CIPHER was identified as a suitable convening mechanism. CIPHER will organize a workshop on adolescent transition next year.
- Next year's cohort collaboration annual meeting will be organized alongside the PENTA-ID meeting, 4-5 May 2015, where progress on current projects, research gaps and potential new projects will be discussed.

¹ Cohorts in the network: leDEA (Southern, Central, West and East Africa; CCASAnet; TREAT Asia), EPPICC (including PMTCT and Eastern European cohorts), Médecins Sans Frontières (MSF), Baylor International Pediatric AIDS Initiative (BIPAI), International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1074, Pediatric HIV/AIDS Cohort Study (PHACS) and Optimal Models/ICAP.

2.3 Online Paediatric HIV Database

The [CIPHER Online Paediatric HIV Database](#) was launched on World AIDS Day 2013.

- The database is an online searchable platform for cohort collaboration.
- It provides a profile of the registered cohorts, their objectives, the kind of data they are collecting and number of subjects, disaggregated by sex, age and route of transmission.
- Currently, about 30 cohorts are registered, representing around 250,000 infants, children and adolescents in 59 countries.

The database has generated a lot of positive feedback and will be continuously developed and improved. The database could become a useful tool for a broader audience, e.g., policy makers, industry and funders.

2.4 Priority development and future directions

The IAS has been restructured, and paediatric HIV has become one of three priorities in the organization; the other two are Key Affected Populations (KAPs) and Towards an HIV Cure. CIPHER is positioned as the branding of the paediatrics priority. These changes provide new possibilities for consolidating all activities in paediatrics under one umbrella. Towards this, CIPHER has:

- Adapted its logo
- Reformed the STAC
- Created synergy across IAS activities: the IAS-Industry Liaison Forum (IAS-ILF), KAPs and HIV Cure Priorities, with:
 - An IAS-ILF/CIPHER Thematic Roundtable on Paediatric HIV (see next section)
 - A JIAS special issue on young key populations (for release in the first quarter of 2015).
- Welcomed the IAS-ILF Viral Load Monitoring Working Group into

CIPHER. This group will be re-focused on paediatrics.

- Developed an advocacy and outreach component, including representation of the IAS on relevant international committees/working groups.

To strengthen and expand CIPHER, various activities are planned for the remainder of 2014 and throughout 2015:

- [CIPHER Grant Programme](#): exploring opportunities for expansion and updating research priorities for future rounds
- [Global Cohort Collaboration](#): exploring outcomes of the IAS-ILF/CIPHER Thematic Roundtable on Paediatric HIV (see next section) and ways to make the collaboration sustainable
- JIAS: continuing the JIAS tradition of publishing an annual CIPHER special issue
- Look into new activities, with a focus on adolescent transition
- The Viral Load Monitoring Working Group: this programme was handed to CIPHER from the IAS-ILF. Future activities focusing on early infant diagnosis will be explored
- IAS-ILF/CIPHER Thematic Roundtable: another meeting in 2015 to explore collaboration with partners
- Stakeholder meeting at IAS 2015: expanding participation of the group.

Linda-Gail Bekker concluded by stating that the IAS was committed to growing the funding base of CIPHER and confirmed the strong support of the IAS Governing Council.

3 Global Cohort Collaboration

Speaker: Pablo Rojo, CoRISpe and EPPICC

Pablo Rojo, an investigator in the CIPHER Global Cohort Collaboration, was invited to provide an update on the collaboration and the two projects underway:

- The durability of first-line antiretroviral treatment (ART) in children in resource-limited settings
- The global epidemiology of perinatally infected adolescents.

CIPHER is supporting the collaboration through a grant to three major data centres, including a partner from a resource-limited country with a high burden of paediatric HIV:

- Centre for Infectious Disease Epidemiology and Research, University of Cape Town, South Africa
- Paediatric HIV/AIDS Cohort Study Data and Operations Center, Harvard School of Public Health, USA
- Medical Research Council Clinical Trials Unit at University College London, UK.

The approach to data management and analysis for the CIPHER project is collaborative, focuses on capacity building, and includes a scholarship for a PhD/post-doc mentored by lead paediatric HIV cohort statistician. One of the big challenges foreseen is the combining of data across multiple cohort networks with different structures. This is a big job and is very complex. The team is working with an existing protocol (HIV Cohorts Data Exchange Protocol) for data harmonization, so the work can be used for future projects beyond CIPHER. Collaborative development of the protocol for data transfer has laid groundwork that will provide a good foundation for future collaborative projects. This collaboration is the first to include such a broad range of participating paediatric cohorts.

Timeline: The data transfer will take place in December 2014, with preliminary results available in October 2015.

4 Grantees' presentations

The two CIPHER grantees from 2014 presented their projects and two 2013 grantees shared their preliminary findings and had the opportunity to receive feedback from the STAC.

4.1 Tavitiya Sudjaritruk (2014)

[Tavitiya Sudjaritruk](#) from the Research Institute for Health Sciences, Chang Mai University, Thailand, presented her project: *Liver injury and long-term metabolic complications among perinatally HIV-infected children and adolescents receiving antiretroviral therapy in Thailand and Indonesia.*

- This study focuses on long-term complications of HIV infection and ART among perinatally HIV-infected children and adolescents.
- The aim is to determine the prevalence of non-alcoholic fatty liver disease (NAFLD), ranging from fatty liver to steatohepatitis (nonalcoholic fatty liver disease), fibrosis and cirrhosis, and long-term metabolic complications, including diabetes mellitus (DM), dyslipidemia, obesity and hypertension in perinatally HIV-infected youths.
- Additionally, the associated risk factors of NAFLD and the relationships between NAFLD and metabolic syndrome, particularly insulin resistance, will be identified.

The research project builds on data collected as part of the prospective observational cohort, TREAT Asia Paediatric HIV Observational Database (TApHOD), which has routinely collected data on demographic characteristics, clinical information and treatment outcomes of children with HIV in Thailand and other Asian countries. Three of the TApHOD sites in Thailand, including the Research Institute for Health Sciences, the HIV Netherlands Australia Thailand Research Collaboration and Khon Kaen University, will participate in the research project, leveraging the harmonized longitudinal data from TApHOD together with the new data that will be collected.

The study design is an age-matched case-control study. The aim is to enrol 150 HIV-infected children and adolescents receiving successful ART.

Participants will be classified into two groups: cases (n=50) defined as having abnormal liver function test (LFT) at least

once within the past 12 months and controls (n=100) defined as having normal LFT. All participants will be extensively evaluated for NAFLD and metabolic complications using well-established serum biomarkers and non-invasive radiologic tools. As a result, the research project will fill research gaps about the burden, impact and relationships of liver injury and metabolic syndrome on ART-experienced HIV-infected children and adolescents, especially in resource-constrained countries, who are now living longer with HIV in the ART era.

4.2 Eric McCollum (2014)

[Eric McCollum](#) from John's Hopkins School of Medicine, USA, presented his project: *Bubble CPAP treatment in hospitalized African infants failing standard pneumonia care in a high HIV prevalence country in Malawi.*

Pneumonia is the most common cause of death in children younger than five years worldwide. Pneumonia mortality rates in Africa are high and have increased even more in HIV-infected children. Bubble continuous positive airway pressure (bCPAP) is an innovative, effective, low-cost, simple, non-invasive ventilation approach to treat severe paediatric respiratory illnesses.

- This study will assess bCPAP effects on mortality and physiology in children failing standard pneumonia treatment to inform current care and potential refinements to bCPAP technology.
- The research project will conduct a prospective observational study to determine bCPAP outcomes, differentiated by HIV antibody status, of 400 hospitalized Malawian infants failing standard pneumonia care.

The hypothesis is that both HIV antibody-positive and HIV antibody-negative infants failing standard pneumonia care will benefit from bCPAP. McCollum and his team will test the hypothesis in two ways. First, they will compare precise bCPAP mortality rates between 200 HIV antibody-positive and 200 antibody-negative infants,

as well as identify predictors of bCPAP mortality. Second, they will study the physiologic effects of bCPAP use in hospitalized African infants, differentiated by HIV antibody status, failing standard pneumonia therapy.

4.3 Rebecca Hodes (2013)

[Rebecca Hodes](#) from the University of Cape Town, South Africa, provided an enthusiastic update on the Mzantsi Wakho project: *Promoting adolescent antiretroviral adherence and sexual and reproductive health uptake in South Africa: How can health and social protection services collaborate programmatically with HIV-positive adolescents?*

The study uses both qualitative and quantitative methods to achieve two aims:

- To identify and investigate risk and resilience-promoting factors for ART adherence and access to SRH services among HIV-positive teenagers, through linked qualitative and quantitative studies
- To collaborate with HIV-positive adolescents, health care and social service providers to design support tools to improve adolescent ART adherence and SRH service uptake.

The qualitative arm of the study is now the largest of its kind ever conducted, with a cohort of more than 50 HIV-positive adolescent and more than 70 caregivers. In-depth interviews, focus groups and a range of participatory methods have provided insights into adolescent adherence to antiretroviral treatment and use of sexual and reproductive health services. Key findings include the association between ART defaulting, delayed disclosure of HIV status (both to teenagers and by teenagers), and a lack of understanding of the transmission and treatment of HIV and sexually transmitted diseases. Among sexually active teenagers in the study, unprotected sex (i.e., sex without condoms) was common, and the fear of pregnancy generally outweighed concerns about HIV reinfection and transmission.

The quantitative arm of the study is progressing with Year 1 data collection, with 402 HIV-positive adolescents interviewed to date. The participants for the quantitative study have been recruited from more than 21 facilities (primary health clinics, community health centres and hospitals) in East London, King William's Town and surrounds. Just over half of the 402 participants (n=221, 54.9%) were female. More than two-thirds (n=280, 69.6%) knew their status. Slightly more than one-third of the sample (n=152, 37.8%) were older teenagers (15-19).

Rebecca Hodes has been appointed as the chair of the Social Sciences, Economics and Human Rights Track for the forthcoming International AIDS Conference, to be held in Durban, South Africa, in 2016.

4.4 Nelleke Langerak (2013)

[Nelleke Langerak](#) from the University of Cape Town, South Africa, presented her project: *HIV encephalopathy: definition of the natural history, physical characteristics and imaging findings in a group of children with gait abnormalities*.

This project focuses on children with HIV encephalopathy (HIVE) and spastic dysplasia who initiated ART before one year of age or from one year of age, and aims to determine:

- The degree of physical disability by three dimensional gait analyses and physical examination
- The relation between physical disabilities and CNS abnormalities by 3DGA, PE, brain and spine MRI scans
- The stability of physical disabilities and CNS abnormalities.

From the 210 children included in the original database, the research team concluded that 42 children were diagnosed with HIVE and spastic dysplasia, of whom 34 fulfilled the selection criteria based on the medical records information. Twelve of these children moved to the Eastern Cape province or were lost to follow up, which

resulted in 22 children being screened for eligibility. Surprisingly, only six of these children fulfilled all the strict selection criteria and could be included in the study, with the other 16 children being excluded (e.g., resolved increased muscle tone, not ambulant).

Due to the difficulties in recruiting children who are eligible for the research project, researchers applied to the Department of Education for permission to recruit children from nine specialized schools; this was recently approved. The informed consent procedure with parents has been completed and assessments with children from three schools have started.

One of the challenges is the many assessments involved in the project, which make logistical arrangements complicated. To ensure data collection is as smooth as possible, it is necessary to take special care regarding planning/bookings, organizing transport, translators, refreshments and incentives.

- In all, 29 children have been recruited; the informed consent procedures and intake with the parents/caregivers and children have been completed. Except for two children, all of the recruited and included children have completed the GMFM assessments at RXH or school.
- Twenty of them have visited at Medical Campus of Stellenbosch University and have undertaken the gait analysis, physical examination and Purdue Pegboard test.
- Three children are being assessed and 20 have been booked for scanning in the coming months. Nineteen children completed the neurocognitive testing with a psychology student.

Observations suggest that an increased tone in the lower limbs in children with HIVE may resolve over a period of months or years on standard ART regimens. However, children presenting with spastic dysplasia do not seem to show the same improvement over time. Although further investigation of the natural history of HIVE and spastic dysplasia is required to confirm these findings, the current observations may be of immediate

relevance to health care professionals, who may wish to consider the current findings when assessing the prognosis and treatment options for children with HIV who present with increased tone in the lower limbs.

The CIPHER project is a result of a pilot study published in 2013. The project has just received Human Research Ethics Committee (HREC) approval and secured funding for a follow-up study.

5 IAS-ILF/CIPHER Thematic Roundtable on Paediatric HIV

Speaker: Shaffiq Essajee, STAC member

Shaffiq Essajee provided an update on the roundtable, which held on the previous evening, on 19 July 2014, in Melbourne, Australia.

The IAS-ILF Thematic Roundtable series is aimed at bringing together scientific and technical experts from industrial and non-industrial organizations to discuss topics relevant to HIV where a multi-stakeholder approach can lead to solutions. The first of the series was entitled *Paediatric antiretrovirals: The barriers to and solutions for improved access to optimal drugs in resource-limited settings* (27 November 2013, Geneva, Switzerland). It brought together industry and non-industry stakeholders to discuss challenges facing the paediatric HIV market and ways forward. The Melbourne roundtable was a follow up to that discussion and included participation from CIPHER cohort investigators.

The main focus of the roundtable was on identifying the areas of synergy and collaboration between industry and cohorts to help address some of the obstacles identified, with the overall aim of progressing paediatric HIV and making adequate treatment options available.

The topics discussed were:

- New-born prophylaxis and treatment

- Next steps on harmonizing around age/weight bands
- FDC ratios – how can we come up with rational ratios?
- Post-marketing surveillance and pharmacovigilance collaborations.

In particular, the following issues were addressed:

- Assisting industry in developing child-friendly formulations
- Recruiting children under 12 years in clinical trials
- Informing industry on most appropriate:
 - Formulations
 - FDC ratios
 - Age bands
 - Weight bands.
- Providing clinical data (e.g., PK) for generic production or formulations
- Providing accurate post-marketing surveillance data.

During the discussion, challenges and opportunities were identified. The participants also reflected on how CIPHER cohorts could help address these challenges and opportunities:

- Challenges around FDC ratios and age/weight bands for different approval processes and between originators and generics
- Opportunities to stabilize the paediatric market when implementing new-born triple-ARV prophylaxis and the difficulty of recruiting very young children in trials
- Challenges in pharmacovigilance and the development of requirements for reporting.

Finally, participants also made concrete suggestions on how to include cohorts in organized collaborations:

- Perform more modelling/simulations and convene industry in technical meetings to agree on who does what (which drug/formulation/ratio/dosage) to catalyze development
- Inform industry about the hot spots where these populations are located so they can be included in trials

- Develop templates for pharmacovigilance (general questions + specific questions along drug characteristics) and set up sentinel networks in resource-limited settings.

Please access the meeting report [here](#).

To further develop effective and innovative responses to the paediatric gap, to maximize investments and to increase impacts it is of great importance to the IAS to continue engaging with stakeholders. Therefore we look forward to engaging and collaborating with stakeholders in the future.

Annex 1

CIPHER Stakeholder Meeting 2014 – Attendance	
Name	Affiliation
Appolinaire Tiam	Elizabeth Glaser Pediatric AIDS Foundation, STAC
Bernard Kadasia	The International AIDS Society
Carina Sorensen	The International AIDS Society
Celia Christie-Samuels	University of West Indies, IAS Governing Council, STAC
Chewe Luo	UNICEF/ IATT, STAC
Eric McCollum	John's Hopkins School of Medicine
Erika Lundström	The International AIDS Society
George Siberry	US National Institutes for Health, NICHD
Helen McDowell	ViiV Healthcare
Jack Downey	The International AIDS Society
Karen Manson	Janssen
Katy Hayward	ViiV Healthcare
Linda-Gail Bekker	Desmond Tutu HIV Centre, University of Cape Town, IAS President-Elect, STAC
Lucie Cluver	University of Cape Town
Lynne Mofenson	Elizabeth Glaser Pediatric Aids Foundation, STAC
Marissa Vicari	The International AIDS Society
Martina Penazzato	WHO, HIV Department, STAC
Nelleke Langerak	University of Cape Town
Owen Ryan	International AIDS Society
Pablo Rojo Conejo	Hospital 12 de Octubre Madrid, Spain
Perry Mohammed	Janssen
Rebecca Hodes	University of Cape Town
Shaffiq Essajee	Clinton Health Access Initiative, STAC
Sine Gyruup	The International AIDS Society
Tavitiya Sudjaritruk	Research Institute for Health Sciences, Chang Mai University