CIPHER
Paediatric HIV Matters

INDUSTRY LIAISON FORUM

Meeting Report

ILF/CIPHER Thematic Roundtable on Paediatric ARVs

Aligning, coordinating and accelerating actions to provide better ARVs for children

18 March, 2015, Geneva, Switzerland

Acknowledgments

This report is the outcome of a thematic roundtable organized by the International AIDS Society's (IAS's) Industry Liaison Forum (ILF) and Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) in Geneva, Switzerland, on 18 March 2015. The ILF and CIPHER would like to extend their gratitude to the body of experts and key informants who participated in this meeting and provided invaluable insight and feedback.

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Background and objectives

The Industry Liaison Forum (ILF) Thematic Roundtable Series is aimed at convening scientific and technical experts from industry and non-industry organizations to discuss topics relevant to International AIDS Society (IAS) member priorities (Paediatric HIV, Key Populations, HIV Cure and HIV Co-infections) where a multi-stakeholder approach can lead to better alignment of efforts and ultimately to novel solutions.

The first of the paediatric antiretrovirals (ARVs) series took place in November 2013 and identified challenges and barriers to industry in making optimal paediatric drugs available at various levels such as: research and development (R&D), normative guideline formulation, regulatory approval, production, forecasting and supply chain (see meeting report). Specifically, this meeting identified a need for industry to be more informed of the guideline development process so that changes and new recommendations do not come as a surprise and are feasible.

At the 20th International AIDS Conference in Melbourne, Australia, in July 2014 (AIDS 2014), investigators from the IAS Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration and regulatory authorities were invited to join the discussion in a follow-up roundtable that focused on exploring collaborative solutions to some of the identified R&D and regulatory challenges (see meeting report). The meeting highlighted the common goal shared by stakeholders: contributing to the development and distribution of better ARV regimens to more infants, children and adolescents. Challenges and opportunities were emphasized, as well as several avenues for follow up, including some specifically through the CIPHER Global Cohort Collaboration.

The ILF and CIPHER joined forces again by organizing a third roundtable in this series on Wednesday, 18 March 2015. As a direct response to the need for industry to be more informed of the guideline revision process, the main objective of this roundtable was to provide a forum to report back in depth on the December 2014 Paediatric ARV Drug Optimization 2 (PADO 2) meeting, working up to the next WHO consolidated ARV guidelines revision. The diverse group of experts convened had the opportunity for more in-depth discussion on the work being done in the paediatric space on optimal drug formulation (Paediatric HIV Treatment Initiative), coordinated procurement and global supply of paediatric ARVs, and efforts towards alignment of regulatory requirements.

This thematic roundtable provided a forum for substantive discussion and feedback to enhance stakeholder effectiveness and synergy.

Rationale of roundtable convening

In welcoming participants, **Owen Ryan** (IAS, Executive Director) recognized the IAS team behind this thematic roundtable. He highlighted the increasing role of the IAS in advocacy within the HIV space and how the IAS has distinguished itself as a voice of HIV professionals globally. In recent years, the IAS has made its mark by having a constructive public presence in paediatric HIV through its two hallmark initiatives, CIPHER and the ILF.

Marissa Vicari (IAS, CIPHER Manager) outlined the architecture of CIPHER and its overarching programmatic activities since its creation in 2012. The key activities of CIPHER, steered by a group of HIV paediatric clinical and technical experts, include a research grant programme, a global cohort collaboration and an online paediatric HIV cohort database. In addition, CIPHER focuses on research dissemination through a variety of vehicles, including special issues published by the Journal of the International AIDS Society (JIAS). The online cohort database is an open access, collaborative tool that maps and provides profiles of paediatric HIV cohorts worldwide. CIPHER has also launched the largest paediatric HIV cohort collaboration to date, representing over 250,000 infants, children and adolescents

affected by HIV. The group is currently exploring two critical topics: time on first-line ARVs in children; and global epidemiology of perinatally HIV-infected adolescents.

Sébastien Morin (IAS, ILF Research Officer) provided an overview of the ILF. He commented on how negative perceptions of industry lead to the exclusion of originator and generic manufacturers from key discussions around HIV treatment policy. In response, the ILF provides a platform that enables industry to take part in technical conversations. In the first ILF roundtable on paediatric HIV in November 2013, the following areas of challenge were identified and prioritized for promotion of more optimal drugs for children living with HIV in resource-limited settings:

1. Developing child-friendly formulations and recruiting children under 12 years in clinical trials
2. Consulting industry during the revision process of WHO ARV treatment guidelines
3. Harmonizing regulatory processes
4. Disseminating accurate forecasts to plan production
5. Post-marketing surveillance and pharmacovigilance collaborations.

At AIDS 2014, the ILF and CIPHER held a roundtable to foster discussion with paediatric HIV cohorts. It was at that meeting that representatives from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) clarified some processes. The CIPHER Global Cohort Collaboration was then clearly identified as a potential vehicle for responding to some of the challenges identified by industry, particularly in helping identify neonates to enroll in studies and in addressing industry queries.

The present roundtable providing feedback from the Paediatric ARV Drug Optimization 2 meeting (PADO 2) was a direct follow-up to the call from industry to be more engaged in the key discussions around treatment guidelines and optimizing paediatric drug development.

Report from PADO 2 and lead up to the next WHO guidelines

Martina Penazzato (WHO) provided background and history on work around two paediatric drug optimization consultations, Paediatric ARV Drug Optimization (PADO) 1 and PADO 2, which will impact the 2015 revision of the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Given the unacceptable treatment gap between children and adults persists and the absence of appropriate drugs and formulations for children living in resource-limited settings, WHO and partners started discussions around paediatric ARV drug optimization in 2011. In 2013, PADO 1 triggered a number of important follow-up activities, including determining weight-based dosing with existing drugs and developing implementation tools targeted at health care workers and HIV programme managers. PADO 1 discussions also resulted in a set of concrete mid- and long-term priorities for new drugs and formulation development, and a roadmap to streamline access and uptake of optimal products.

Other successful collaborative efforts by WHO include the Paediatric ARV Working Group (PAWG), which has served as a critical technical enabler for formulation development in establishing dosing ratios for paediatric fixed dose combination tablets (FDCs). In addition, research networks have been instrumental in examining the pharmacokinetics (PK) to establish simplified weight-band dosing for drugs such as darunavir. The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) has been a critical platform for WHO and other partners to help identify optimal drug formulations for use in paediatric treatment of HIV infection (Table 1)[1]. WHO has also responded to immediate needs through policy briefs addressing supply issues such as the phaseing out of stavudine (d4T) and didanosine (ddI).

[1] The full policy brief (including also the list of limited-use paediatric ARV formulary) is available at http://www.emtct-iatt.org/wp-content/uploads/2015/05/Updated-Formulary-04012015.pdf

Table 1. 2015 optimal paediatric ARV formulary

Drug Class	Drug	Dosage Form	Strength
NNRTI	EFV	Tablet (scored)	200 mg
NNRTI	NVP	Tablet (dispersible, scored)	50 mg
NNRTI	NVP	Oral liquid*	50 mg / 5 mL, 100 mL
PI	LPV/r	Tablet (heat stable)	100 mg / 25 mg
PI	LPV/r	Oral liquid	80 mg / 20 mg/mL
FDC	AZT/3TC	Tablet (disp, scored)	60 mg / 30 mg
FDC	AZT/3TC/NVP	Tablet (disp. scored)	60 mg / 30 mg / 50 mg
FDC	ABC/3TC	Tablet (disp. scored)	60 mg / 30 mg, 120 mg / 60 mg

* For infant prophylaxis during PMTCT

Source: Update to the Optimal List of Paediatric ARV Formulations, Geneva, Switzerland, 2015. http://www.emtct-iatt.org/wp-content/uploads/2015/05/Updated-Formulary-04012015.pdf

To better understand the trajectory of the HIV epidemic in children, a WHO and UNAIDS Reference Group technical consultation on modeled estimates for children in need for ARVs over the next decade took place in London in 2014, and ongoing efforts have been exploring how to modify the currently used software Spectrum[2] to model additional nuances (e.g., age groups). These estimates are critical in incentivizing manufacturers to remain in the paediatric ARV market and invest in the development of more appropriate drug formulations as well as help production planning and securing supply chains.

New energies, new coordination and new collaboration

In opening conversation with manufacturers through the ILF roundtables, there has been growing recognition that such collaboration can eventually help close the treatment gap. Platforms have been formed to accelerate R&D for paediatric HIV products, such as the Paediatric HIV Treatment Initiative (PHTI), and for increasing advocacy for better alignment between WHO treatment recommendations and regulatory bodies. This new wave of collaboration has taken place by leveraging pre-existing mechanisms of collaboration, namely: PADO; the WHO guidelines; PAWG; the IATT Optimal Formulary; and the Paediatric ARV Procurement Working Group (PAPWG) (Figure 1).

To further the communication and coordination of efforts, a series of meetings took place in December 2014 in Geneva, Switzerland, which included PADO 2, a PHTI meeting on developing priority medicines, a PAPWG meeting and an IATT Formulary revision.[3] In PADO 2, the key directions for priority products were unchanged from PADO 1, with specific advice given to WHO's Guideline Development Group (GDG) around the following three topics:

- **Adolescents:** This population is challenging to treat; there is a need to move towards more effective and forgiving regimens, and for more information to support the adoption of lower doses of EFV in first-line treatment.
- **Neonates:** A lack of appropriate formulations and dosing guidance remain key barriers for optimal use of drugs in neonates and young infants.

[2] Country teams use the software tool, Spectrum (http://www.futuresinstitute.org), and its AIDS Impact Module to estimate the impact of the HIV epidemic. Every two years, UNAIDS and partners conduct regional workshops, training national personnel and technicians on the specific tools and methodologies used to produce the national estimates.

[3] One concrete outcome was updating the IATT ARV Formulary, which now includes eight products (as opposed to 10 previously), see Table 1.

- **Second- and third-line:** The integrase inhibitor class was identified having a more prominent role, particularly for children failing treatment after initiating a protease inhibitor-based regimen.

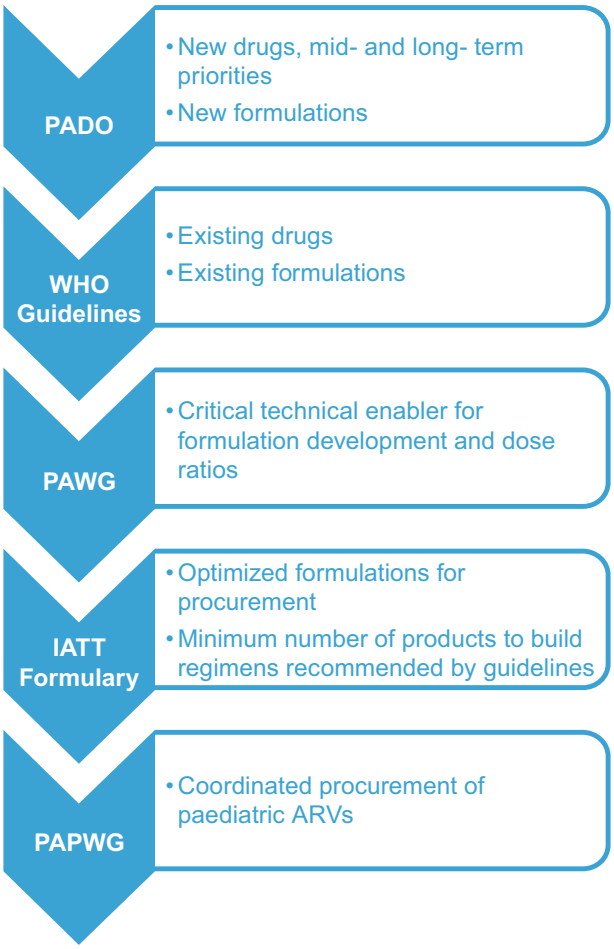

Figure 1. Global paediatric HIV treatment initiatives and activities

Priorities for drug development (Table 2), included TAF/3TC/DTG as a long-term first-line regimen for children for all age groups. Importantly, it was recognized that in order to acheive harmonization, paediatric drug development must align with development plans for adults while considering the unique needs of infants and children. Key research gaps flagged at PADO 2 included: a) safety and efficacy of ARVs for new-borns; b) adolescent-specific acceptability and toxicity profiles of new drugs and formulations; and c) value of performing genotyping.

Table 2. PADO 1 and 2 priorities for paediatric drug development over the next 10 years

	0-3 years	3-10 years	10 years +
FIRST-LINE			
Mid-term (5 years)	ABC/3TC/DTG		TAF/3TC/DTG
Long-term (10 years)	TAF/3TC/DTG		
SECOND-LINE			
Mid-term (5 years)	AZT/3TC/RAL or LPV/r	AZT/3TC/DRV/r	TAF/3TC/DRV/r
Long-term (10 years)	AZT/3TC/LPV/r	RPV/DRV/r or AZT/3TC/DRV	

Source: PADO 2 meeting report (WHO). http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization/en/

To follow up PADO 2, WHO and its partners have released a meeting report to disseminate outcomes of the meeting to manufacturers. In addition, PAWG is set to endorse weight-band dosing in accordance with requirements of regulatory authorities for key ARVs, namely RAL and DTG. In terms of the WHO guidelines, a technical meeting of the GDG is scheduled to take place on clinical and operational issues in June 2015. The key questions for guidelines revisions will include when to initiate treatment (e.g., all children) and what drugs to use in specific contexts, such as: a) postnatal prophylaxis (e.g., multi-drug regimens for high-risk babies); b) as the NRTI backbone; c) first-line in adolescents; and d) second- and third-line regimens. Notably, WHO is also revisiting simplification strategies as part of the revision of its guidelines.

Innovative regulatory thinking to advance paediatric product development

John Gordon (WHO) presented an overview of the WHO Prequalification of Medicines Programme (PQP), the objective of which is to ensure quality products are provided for UN procurement. Inferior quality medicines are associated with a spectrum of serious consequences, and sophistication of regulatory systems worldwide varies significantly. For example, an estimated 50% of countries have varying capacity and level of development in regulatory systems, while 30% have minimal or limited regulation. Importantly, the PQP has been successful in driving demand for generic ARV products.

The WHO PQP focused initially on drugs to treat HIV infection and then expanded into other diseases, including malaria, TB and influenza. The scope of prequalification is limited to priority medicines and active pharmaceutical ingredients (APIs).[4] As part of a portfolio of key outputs by the PQP, there is a published list of prequalified medicinal products. Medicines eligible for prequalification are determined by WHO disease-oriented programmes, and most products are generic. Only products are prequalified, not the companies themselves.

Although paediatric products are produced for the markets of stringent regulatory authorities (SRAs), the rate of development and approval within these markets is insufficient to meet the urgent need for such products in developing countries. The WHO PQP has made efforts to fill this gap between need and availability by encouraging industry's submission of paediatric products. Paediatric products available on SRA markets are often liquids, such as oral solutions and syrups, which are not well suited for available storage conditions. In addition, a pharmaceutically equivalent comparator is frequently not available for the development of monocomponent or fixed-dose combination (FDC) multisource products. One way to remedy this is to have greater flexibility in the design of comparative bioavailability studies (e.g., multiple units of paediatric strength vs. single unit of adult strength).

Another approach employed by the PQP is the Biopharmaceutics Classification System (BCS)-based biowaiver, a system for classifying APIs and evaluating finished pharmaceutical products, which is applicable to situations where paediatric strengths of comparator products exist. In cooperation with the scientific community, the PQP is seeking to understand how it might be possible to apply the principles of BCS-based biowaivers in situations where a pharmaceutically equivalent paediatric comparator does not exist. The approach involves the introduction of a solubility criterion that accounts for differences in gastrointestinal tract conditions between paediatric and adult populations.

Guidance to inform future paediatric drug development research does exist, including the ICH E11 guideline for Clinical Investigation of Medicinal Products in the Pediatric Population. Paediatric drug development has been enhanced by advancements in several areas of general adult drug development since the ICH E11 was adopted in 2000. Importantly, the EU and the USA currently have permanent legislation in place that mandates plans for paediatric development

[4] As published in Invitations for Expression of Interest on the WHO PQP website (http://apps.who.int/prequal).

as part of an overall product development strategy. As E11 is currently under review, an expert working group on paediatric drug development is addressing the following areas of the guidance documentation:

- Formulation challenges in paediatric drug development
- Types of studies and methodology of clinical trials
- Age classification and paediatric subsets, including neonates
- Timing of paediatric development milestone agreements with regulators and "commonality of content"
- Ethical considerations in paediatric studies
- Extrapolation of data
- Model-Informed Drug Discovery Development (MID3).

Supply and global volumes of paediatric ARVs

Wesley Kreft (PFSCM) outlined the role of the PAPWG and its impact in convening and coordinating activities of key procurement stakeholders for paediatric ARVs. More specifically, the PAPWG has been responsible for:

- Active engagement with countries and partners to adopt/transition to the prescribed IATT Formulary to guide selection and procurement of paediatric ARVs around a subset of optimal products[5]
- Forecasts communicated to WHO/AMDS, with anticipated orders by Procurement Consortium members
- Ongoing monitoring of market challenges and continued engagement with suppliers to manage exits, transitions, bottlenecks, etc.
- Implementation of reporting indicators to track PAPWG progress; these indicators are relevant for industry in particular (Table 3)
- Development of communication tools and procurement analytics to support coordination efforts at country and global levels, as well as interaction with the paediatric HIV initiatives.

[5] Optimal formulation orders are growing in volume. The list of optimal paediatrics ARV formulary is available in Table 1.

Table 3. PAPWG reporting indicators

Indicator categories
1. Supply security • Average lead time for Procurement Consortium member orders [SA] • Average delay in delivery for Procurement Consortium member orders [SA] • % of delayed deliveries for Procurement Consortium member orders [SA]
2. Consolidated order management • % of tracked products with validated batch sizes information [A] • % of products able to complete a full batch for Procurement Consortium [A]
3. Anticipated demand • Volume of ARVs procured by the Procurement Consortium [A] • Value of ARVs procured by the Procurement Consortium [A] • % of products in quarterly order cycle where orders are in line with anticipated demand forecast [Q]
4. Product selection and optimization • Number of countries procuring optimal and limited-use ARVs exclusively (as part of the Procurement Consortium)[SA] • Number of countries that have transitioned from non-essential to optimal ARVs (as part of the Procurement Consortium) [A]
5. PAPWG reach • Number of children reached by the Procurement Consortium [A] • Number of countries part of the Procurement Consortium [A] • Number of countries outside of the Procurement Consortium that are using the designated ordering cycle dates [A]

• Completed Q – quarterly SA – semi-annual A – annual

Source: Wesley Kreft (PFSCM), ILF/CIPHER Thematic Roundtable on Paediatric ARVs, Geneva, Switzerland, 2015

In 2014, the PAPWG purchased more than 10.6 million packs of medicines valued at US$35.8 million, with 90% (9.5 million) listed on the IATT Optimal Paediatric ARV Formulary (Table 1). An estimated 8% of packs purchased were from the limited use list of ARVs needed for special circumstances. Notably, the PAPWG is actively working with a variety of suppliers in order to prevent supply disruptions, and is also encouraging countries to select optimal formulations. Seventy-five countries participated in the Procurement Consortium in 2014.

Paediatric HIV Treatment Initiative

To scale up treatment for children, UNITAID, the Drugs for Neglected Diseases initiative (DNDi), The Clinton Health Access Initiative (CHAI) and the Medicines Patent Pool (MPP) established the Paediatric HIV Treatment Initiative (PHTI) last year. **Fernando Pascual** (MPP) provided an introduction to this dynamic new platform, which focuses on overcoming the barriers to developing and delivering specific priority paediatric formulations appropriate for children.

The structure is central to the PHTI's activities, which are carried out by product-specific teams. These teams are made up of technical experts, drug companies and PHTI members, working with WHO and PADO and take the lead in technical guidance. The PHTI is identifying work needed to fill gaps in formulation development in order to improve ARV access to children.

Some of the PHTI's key projects include work around ABC + 3TC + EFV where generic partners have been invited for production, along with development efforts on DRV/r. Their concrete deliverables are still in the planning stage. An FDC should take 18 to 24 months to develop if everything works well.

Table 4: PHTI's efforts to close treatment gap between adults and children living with HIV

Reasons for the treatment gap	Public health impact of PHTI
Perception of shrinking market (35% decline in newly infected children from 2009 to 2012. Target zero new infections by 2015. Still around 1.5 million children living with HIV in need of treatment by 2020)	PHTI offers a viable business model for paediatric formulations, thus attracting interest from industry
Lack of coordination among partners to boost development of appropriate formulations	PHTI creates a platform for industry, drug development organizations, financing organizations, civil society, etc.
Uninteresting/fragmented market (45 different formulations available; only 10 categorized as "optimal" for procurement)	PHTI focuses only on WHO priority products, thus contributing to rationalize the market
Lack of suboptimal formulations (e.g., LPV/r only as an unpalatable oral solution that requires refrigeration)	PHTI delivers optimal formulations
Paediatric HIV is neglected	Overall, PHTI engages public health actors involved in paediatric HIV

Source: Fernando Pascual (MPP), ILF/CIPHER Thematic Roundtable on Paediatric ARVs, Geneva, Switzerland, 2015

The PHTI is addressing PADO 2 product priorities, with recognition that drug development takes time. Under the guidance of the PHTI, clinical dosing for some formulations has been determined. The MPP has also achieved progress in licensing nearly all specific products prioritized at PADO 2, with the exception of DRV/r which is currently being assessed. The PHTI remains cognizant of the impact that regimen trends will have on the medium- and long-term prospects of putting more children on optimal regimens. It is also putting in place mechanisms to accelerate development and market uptake of products needed for smaller specific groups (e.g., DRV/r for patients failing LPV/r).

The PHTI will continue to foster its partnerships, especially in close collaboration with WHO, and the intent is to prevent further market fragmentation.

The Global Pediatric ARV Commitment-to-Action

PEPFAR's **Paul Zeitz** provided brief remarks on the Global Pediatric Antiretroviral (ARV) Commitment-to-Action. On World AIDS Day 2014, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the Pediatric HIV Treatment Initiative (PHTI) [a collaboration of UNITAID, the Clinton Health Access Initiative (CHAI), Drugs for Neglected Diseases initiative (DNDi) and the Medicines Patent Pool (MPP), which includes the World Health Organization (WHO) as a technical partner], and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) announced a new Global Pediatric Antiretroviral (ARV) Commitment-to-Action (Commitment-to-Action). The HIV Medicines Research Industry Forum endorsed the Commitment-to-Action on the same day. The Commitment-to-Action brings together leading organizations to accelerate the development of new, high-priority pediatric ARV co-formulations for first- and second-line treatment by 2017. The objectives of the Commitment-to-Action are:

1. Accelerate the development of new, high-priority, and child-adapted formulations
2. Support rapid and streamlined regulatory approval
3. Ensure that new formulations of pediatric ARVs are promptly eligible for procurement
4. Support product-specific demand forecasts and market-sizing data on priority products

5. Track financing commitments for procurement
6. Support demand creation and uptake of optimal formulations.

The consortium of partners that is supporting the Global Pediatric ARV Commitment to Action is undertaking an independent review of the current ecosystem of paediatric-related activities in advancing treatment coverage.

Roundtable discussion: Aligning, coordinating and accelerating actions to provide better ARVs for children

"Nothing is possible without manufacturers"

Nandita Sugandhi (CHAI) opened the roundtable discussion, underscoring the value of establishing constructive partnerships by key stakeholders in HIV paediatrics, including drug developers, and described how "nothing is possible without manufacturers". The energy around PEPFAR's efforts through the Accelerating Children's HIV/AIDS Treatment (ACT) Initiative, which aims to double the number of children receiving ART in selected countries, could serve as a catalyst to drive further advances in treatment optimization. The global collaborative spirit over the past few years has resulted in the convening of a specific set of technical groups and consultations to address some of the critical issues in access to paediatric ARV drug formulations. In addition to PADO 1 and 2, the formation of the PAPWG, the IATT Optimal Formulary List and the ACT initiative, there is also PHTI's emerging work as well as the New Horizons Programme, sponsored by Janssen, to donate paediatric formulations of darunavir to stimulate the development of third-line ART programmes in resource-limited settings. In mapping out the concept of an "HIV paediatric ecosystem", the priority issues include:

- Development of optimal HIV paediatric drug formulations
- Alignment of regulatory requirements
- Supply and global volume forecasts, production planning and capacity
- Opportunities and challenges from the manufacturer's perspective to guide discussions in the lead up to the development of the 2015 WHO ARV guidelines.

Challenges in clinical trials: from recruitment to approval of studies

Manufacturers highlighted some of the complexities and concerns in conducting research to develop new formulations and drugs for children. Participants shared some of the challenges in identifying eligible children for participation in clinical trials, and addressing issues of consent. An important point raised was the frequent reluctance of parents and caregivers to expose their children to interventions of unknown benefit, especially when available treatment is going well. CIPHER is examining how to support the identification and recruitment of infants into clinical research through its Global Cohort Collaboration. A number of industry representatives recognized that the need to understand what is suitable for children in terms of drug/formulation issues remains equally important to industry.

In advancing the drug and formulation agenda, industry participants commented that regulatory plans traditionally driven by the FDA have not often been suitable for populations in resource-limited settings. Nonetheless, the FDA has become increasingly sensitive and understanding of the needs of children living with HIV outside the US, as was the

case in the approval of raltegravir. Industry participants also described the challenges in getting approval for intensive two-stage PK studies. For example, for the P1093 study in Latin America, some countries rejected the stage 1 study, which is critical for dose selection, but were receptive to the stage 2 (safety) study.

Signals of toxicity in one age group can greatly impact and restrict the evaluation of drugs in other age groups. Compassionate-use programmes and expanded-access programmes may be a source of valuable information to fill in this knowledge gap, particularly in small children (e.g., programme has data for children up to four years of age). However, from the regulatory perspective, this information cannot be solicited although the group felt, as with phase IV data, that such data would still have value (e.g., TDF data is being examined in groups for which the drug is not approved). Physicians and researchers that use drugs in compassionate-use programmes could share data in such platforms as the CIPHER Cohort Collaboration or another repository. Nonetheless, regulators would have to be engaged in such discussions. It was also noted that different compassionate-use programmes have different criteria (e.g., the type of patients eligible), and one should be aware of the demographics of children in these programmes. Apart from compassionate-use and expanded-access programmes[6], data from children on off-label use would be difficult to obtain.

How to educate stakeholders on clinical trials in children

Approving and launching clinical studies in paediatric populations in resource-limited settings, as seen with a recent adolescent HIV vaccine study in South Africa, is challenging. One proposal called for the creation of a multi-stakeholder task force that could inform and educate Institutional Review Boards (IRBs) and other stakeholders on practical issues in the conduct of paediatric clinical trials (e.g., how much blood to draw from subjects). From an ILF perspective, training and education is a valuable strategy and the feasibility of developing this task force should be discussed at greater length. Of note, JIAS could have a special issue on the challenges of paediatric clinical trials, which could serve as one set of tools developed by this proposed task force. Some participants noted that it would be important to map out what other groups are already doing in this area; for example, there is currently an advisory group in the US that is addressing the topic. One industry representative indicated that there is data showing a decline in the number and size of clinical trials in paediatric populations over the past decade. The reasons for this decline may be associated with trust by study participants (parents), IRBs and also technical issues.

Feedback on recent paediatric initiatives: are they useful to industry?

Industry representatives at the roundtable provided positive feedback regarding global efforts to provide better direction for formulation development. There was particular appreciation for the medium- and long-term priorities for first- and second-line regimens from PADO 2 (see Table 2) and dissemination of the IATT Optimal and Limited Formularies. The transparency and openness of those engaged in PADO and other initiatives were constructive aspects of the process. Originator representatives commented that it would also be helpful to have a sense of where not to invest R&D, for example, if a drug or formulation will not be prioritized for use in a certain setting.

Determining the appropriate paediatric dosage strength of a drug formulation remains one of the biggest challenges for drug developers, as is the case with EFV. Forecasting data is also important for manufacturers in the context of scaling up treatment in high-burden countries. Some participants described the lack of consolidated forecasting as a critical barrier. One generic representative underscored the fact that companies would like to have a market visibility

[6] Expanded access mechanisms are designed to make promising products available as early in the drug evaluation process as possible to patients withoutew therapeutic options, either because they have exhausted or are intolerant of approved therapies, and cannot enter a clinical trial. Expanded access refers to access to investigational medical products outside of a clinical trial, where the intent is a potential treatment, rather than research. Source: FDA website: http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm134331.htm

of 5-10 years for use of their products in WHO-recommended regimens, and that this would incentivize companies to invest in HIV paediatric R&D. When looking at new products on the market, generic companies are examining what originators have already done on that drug in children. Overall, there was a sense that PADO 2 and PHTI provided reassurance and clarity on what products remain relevant and important for the medium and long terms.

From a procurement perspective, the various initiatives have been very helpful, with one participant commenting on how there is a natural flow from PADO ("blue-sky level") down to the PAPWG ("transactional level"). Forecasting for new product launches remains extremely difficult, but for established products and how they are being used, the current structures are very helpful. How transitions are managed (e.g., new guidelines, small number of optimal products) will remain of importance to this group. It was also noted that the phasing out of a particular product is easier than introducing a new product. Significant improvements on the procurement front were also evident since procurement agents are aligning their orders. This has resulted in meeting the minimum batch sizes and supplies, and consequently, lead times have been reduced.

Some meeting participants requested more information on the current investment in paediatric R&D as the future investment targets of some of the companies in the paediatric arena are not particularly clear.

Meeting participants also voiced concern over educating providers on how to use new products recommended by the WHO guidelines, given the greater sensitivities in making product changes for children. In addition, there was some discussion around the adoption and implementation of the 2013 WHO guidelines. WHO commented that despite the rapid adoption, the reality in the field may not be consistent with a country's formal declaration on having transitioned to new treatment recommendations for children often because the optimal formulations are not available, and thus, much could be resolved if the appropriate formulation was developed.

It was reassuring to see data from the PAPWG showing adoption of the optimal formulations by countries in 2014. Again, advocacy was raised as an important element, and it was emphasized that organizations within countries could support governments in effective transitions. The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) noted the concerns of their country programmes about rapid changes in new guidelines and formulation preferences. WHO's Martina Penazatto noted that the next wave of guidelines would not likely have dramatic shifts in recommended regimens, as was the case in 2013.

Participants also expressed the need to have a more accurate sense of how quickly HIV programmes and countries can adopt a recommendation (and a new product). It was noted that strong communication efforts were made to inform countries of the IATT Optimal Paediatric ARV Formulary, including the use of social media and a suggestion was made on taking a similar approach in guidelines dissemination. More specifically, there was a call for the various stakeholders to coordinate to develop a communication plan for all ongoing activities and initiatives.

Despite these efforts, political will was also recognized as critical in securing the paediatric HIV market, with more engagement at country level needed. There was also a sense that more grassroots work was needed, as well as more interactions with Ministries of Health. One recommendation was to have a presence at the regional meetings that HIV programme managers attend, and to invite the "unusual suspects", namely industry representatives, as fostered by the ILF.

Conclusion and next steps

The third ILF Thematic Roundtable on Paediatric ARVs concluded with recognition that paediatric initiatives, such as PADO 2, and tools, such as the IATT Optimal Formulary, have been very helpful in securing access to paediatric ARVs. It welcomed global efforts towards simplification and coordination. Nonetheless, there are concerns over implementation challenges with the 2013 WHO guidelines, and product availability from a supply standpoint remains an issue. Participants clearly indicated that it was useful to have feedback from the variety of stakeholders, and that the ILF platform for discussion provided insight into the guideline revision process. The room gave a resounding "YES" when asked if the ILF and CIPHER should continue to organize such feedback meetings.

As with the previous two roundtables, the spirit of the discussion was important in driving forward priority activities, even in the wake of the challenges articulated. There were some unique messages that stood out from this meeting that had not been raised in the previous roundtables, notably:

- **Advocacy:** There was consensus on the need to focus on countries, particularly Ministries of Health, in advocating for more optimal paediatric ARV options for children and for adoption of WHO guidelines. Furthermore, advocating for the use of the IATT Optimal Formulary will be a critical action point in the coming months.
- **Clinical trials:** There is currently a gap in awareness, education and training on the complexities of clinical trials in children. One key activity would be to target IRBs as they are the key actors responsible for ethical approval of drug studies. Given the sensitivities and concerns around study protocols in children, particularly in intensive PK studies where repeated blood draws are required, the development of training material that addresses these issues should be a priority.
- **Missing partners:** Participants recognized the need to identify key partners who are currently not engaged in the ongoing discussions around HIV paediatrics.
- **Communication plan:** A call was made to have stakeholders support the development of a communication plan for all the ongoing activities and initiatives. In addition, the use of social media is an untapped vehicle that has yet to be realized, and should be integrated into this broader communication plan.
- **Industry feedback:** The meeting participants recognized the value of having industry feedback as part of the WHO guidelines development process, and this should be advanced.

Stronger Together Against **Paediatric** HIV

Appendix A: Agenda

Thematic Roundtable on Paediatric ARVs: Aligning, coordinating and accelerating actions to provide better ARVs for children

Organized by the International AIDS Society's Industry Liaison Forum (ILF) and the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER).

Wednesday, 18 March 2015, 13:00 – 17:00 CET
Geneva, Switzerland

13:00 – 13:20	**Welcome and roundtable introduction** Owen Ryan (IAS) / Executive Director Marissa Vicari (IAS) / Manager, CIPHER Sébastien Morin (IAS) / Research Officer, ILF
13:20 – 13:40	**Overview presentation I: Report from PADO2 and lead up to the next WHO guidelines** Martina Penazzato (WHO) / CIPHER Executive Committee
13:40 – 14:00	**Overview presentation II: Innovative regulatory thinking to advance paediatric product development** John Gordon (WHO)
14:00 – 14:20	**Overview presentation III: Supply and global volumes of paediatric ARVs** Wesley Kreft (PFSCM)
14:20 – 14:30	**Overview presentation IV: Paediatric HIV Treatment Initiative (PHTI)** Fernando Pascual (MPP)
14:30 – 15:00	Coffee break
15:00 – 16:45	**Roundtable discussion: Aligning, coordinating and accelerating actions to provide better ARVs for children** • Development of paediatric formulations • Alignment of regulatory requirements • Supply and global volume forecasts – Production planning and capacity • Leading up to 2015 WHO Guidelines – Opportunities and challenges from the manufacturer's perspective Facilitator: Nandita Sugandhi (CHAI)
16:45 – 17:00	**Closing** Marissa Vicari (IAS) / Manager, CIPHER Sébastien Morin (IAS) / Research Officer, ILF

Appendix B: List of participants

Participants from industry

ARV / generics	Cipla	**Denis Broun** – *Global Director for Access and Public Affairs*	
ARV / generics	Cipla	**Rahul Lande** – *Export Manager, NGO and Institutional Business*	
ARV / generics	Cipla	**Sharadd Jain** – *Head, Global Institution Business for Formulations*	
ARV / generics	Emcure	**Utharadhi Devbalaji Balaji** – *Senior Director, Global HIV/AIDS Initiatives*	
ARV / generics	Macleods Pharmaceuticals	**Rohini Karde** – *Deputy Manager, Institutional Business*	
ARV / generics	Mylan Laboratories	**Kedar Madhekar** – *Assistant General Manager*	
ARV / generics	Strides Arcolab	**Vinod Nair** – *Vice President (Marketing)*	
ARV / originator	AbbVie	**Joshua Mugo Muiruri** – *Tender Manager*	
ARV / originator	AbbVie	**Matthew Hamada** – *Senior Product Manager, Virology*	
ARV / originator	Gilead Sciences	**James Rooney** – *Vice President, Medical Affairs*	ILF
ARV / originator	Gilead Sciences	**Valeriy Marinin** – *Manager, Analytics & Forecasting, Access Operations & Emerging Markets*	
ARV / originator	Janssen	**Karen Manson** – *Communications Leader, Global Citizenship*	
ARV / originator	Janssen	**Luc Denys** – *Senior Director, Global Access & Partnership Program*	
ARV / originator	Janssen	**Perry Mohammed** – *Global Medical Affairs Lead, HIV, Global Public Health*	ILF
ARV / originator	Merck	**Isabelle Girault** – *Director, Global Marketing*	
ARV / originator	ViiV Healthcare	**Helen McDowell** – *Director, Government Affairs, Access and Patient Advocacy*	
ARV / originator	ViiV Healthcare	**Tia Vincent** – *Global Scientific Lead, Dolutegravir*	
Diagnostics	Sysmex Partec	**Francesco Marinucci** – *Director, Essential Healthcare*	ILF

Appendix B: List of participants (continued)

Other participants

Clinton Health Access Initiative	**Cebele Wong** – *Global Market Associate*	
Clinton Health Access Initiative	**Marianne Gauval** – *HIV Pediatric Indication Manager*	
Clinton Health Access Initiative	**Nandita Sugandhi** – *Clinical Advisor*	
Desmond Tutu HIV Centre	**Linda-Gail Bekker** – *Deputy Director*	ILF/GC
Drugs for Neglected Diseases initiative	**Janice Lee** – *Project Manager*	
Elizabeth Glaser Pediatric AIDS Foundation	* **Lynne Mofenson** – *Senior HIV Technical Advisor*	
Elizabeth Glaser Pediatric AIDS Foundation	**Bethany Corrigan** – *Programme Officer*	
Elizabeth Glaser Pediatric AIDS Foundation	**Natella Rakhmanina** – *Director of Technical Leadership*	
Elizabeth Glaser Pediatric AIDS Foundation	**Tamar Gabelnick** – *Policy Advisor*	
Independent	**Colleen Daniels** – *Independent*	ILF
International AIDS Society	**Birgit Poniatowski** – *Director, Development*	IAS
International AIDS Society	**Jeanne Mencier** – *Associate Development Officer*	IAS
International AIDS Society	**Leah Brodbeck** – *ILF Intern*	IAS
International AIDS Society	**Lochan Shah** – *CIPHER Intern*	IAS
International AIDS Society	**Marissa Vicari** – *Manager, CIPHER*	IAS
International AIDS Society	**Owen Ryan** – *Executive Director*	IAS
International AIDS Society	**Sébastien Morin** – *Research Officer, Industry Liaison Forum*	IAS
International AIDS Society	**Tamara Torri** – *Project Manager, HIV Programmes*	IAS
International AIDS Society	**Yannis Mameletzis** – *CIPHER Advisor*	IAS
Médecins Sans Frontières	**Arax Bozadjian** – *Campaigns for Access to Essential Medicines*	
Médecins Sans Frontières	**Jessica Burry** – *Pharmacist*	
Medicines Patent Pool	**Fernando Pascual** – *Pharmaceutical Consultant*	
Office of the U.S. Global AIDS Coordinator	**Paul Zeitz** - *Senior Advisor for Strategy*	
Partnership for Supply Chain Management	**David Jamieson** – *Deputy Director, Project Planning and Global Partnerships*	
Partnership for Supply Chain Management	**Dominic Farrugia**- *Procurement Specialist Lead*	
Partnership for Supply Chain Management	**Wesley Kreft** – *Deputy Director*	
The Global Fund to Fight AIDS, Tuberculosis and Malaria	**Mireille Muhimpundu** – *Associate Specialist, Sourcing Department*	
UNITAID	**Jane Galvão** – *Technical Officer HIV/AIDS*	
U.S. Food and Drug Administration	* **Linda Lewis** – *Medical Officer*	
USAID	**Christine Malati** – *Pharmaceutical Advisor*	
WHO	**Martina Penazzato** – *Paediatric Technical Advisor, HIV/AIDS Department*	
WHO	* **John Gordon** – *Consultant: Lead Bioequivalence, Prequalification of Medicines Programme*	

ILF: ILF Advisory Group member
GC: IAS Governing Council member
IAS: IAS Secretariat
*: Attending remotely through WebEx

Appendix C: List of acronyms

3TC	Lamivudine
ABC	Abacavir
ACT	The Accelerating Children's HIV/AIDS Treatment (ACT) Initiative
AIDS 2014	20th International AIDS Conference
AMDS	AIDS Medicines and Diagnostics Service
APIs	Active pharmaceutical ingredients
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
BCS	Biopharmaceutics Classification System
CHAI	Clinton Health Access Initiative
CIPHER	Collaborative Initiative for Paediatric HIV Education and Research
d4T	Stavudine
DNDi	Drugs for Neglected Diseases initiative
DTG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FDC	Fixed-dose combination
GDG	Guideline Development Group
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
IAS	International AIDS Society
ILF	Industry Liaison Forum
IATT	Interagency Task Team (on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children)
IRB	Institutional Review Board
JIAS	Journal of the International AIDS Society
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MPP	Medicines Patent Pool
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
PADO	Paediatric ARV Drug Optimization
PAPWG	Paediatric ARV Procurement Working Group
PAWG	Paediatric ARV Working Group
PEPFAR	President's Emergency Plan for AIDS Relief
PFSCM	Partnership for Supply Chain Management
PHTI	Paediatric HIV Treatment Initiative
PI	Protease inhibitor
PK	Pharmacokinetic
PMTCT	Prevention mother-to-child transmission of HIV
PQP	WHO Prequalification of Medicines Programme
R&D	Research and development
RAL	Raltegravir
SRAs	Stringent regulatory authorities
TAF	Tenofovir alafenamide fumarate
TDF	Tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	US Agency for International Development
WHO	World Health Organization

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