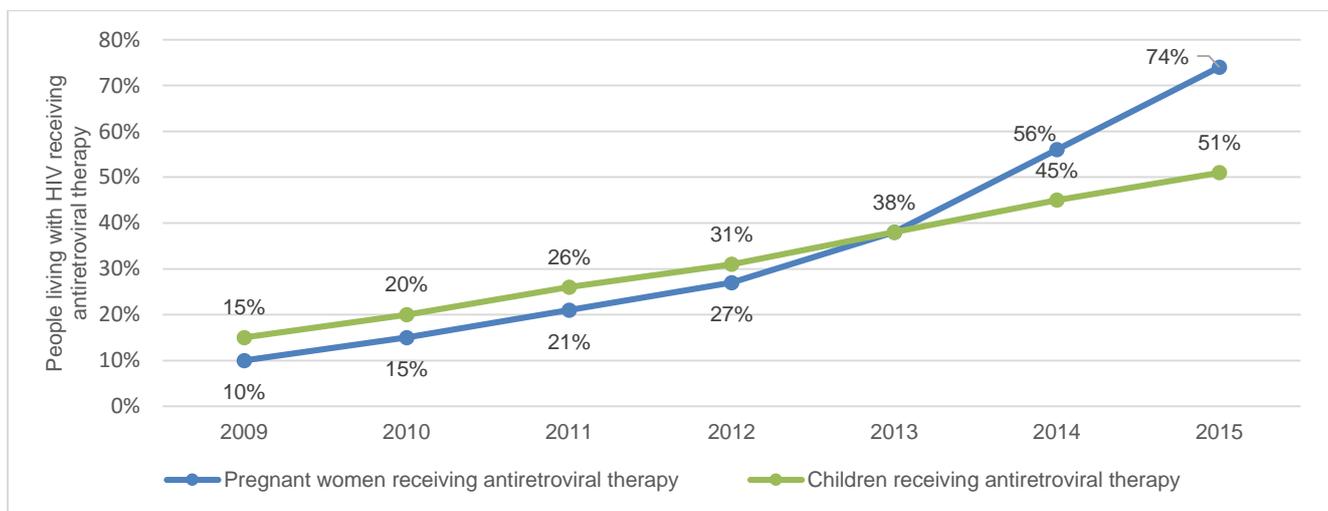


# CTA/ILF/CIPHER Thematic Roundtable on Paediatric ARVs: Fast tracking development of priority formulations

Saturday, 16 July 2016, 18:00 – 22:00  
The Royal Hotel, Prince Alfred Suites, 267 Anton Lembede Street, Durban, South Africa

## Background

Despite significant progress in scaling up HIV services for children, the treatment gap for paediatric HIV persists. In 2015, only 51% of children living with HIV received antiretroviral therapy, compared with 74% of pregnant women (Figure 1).

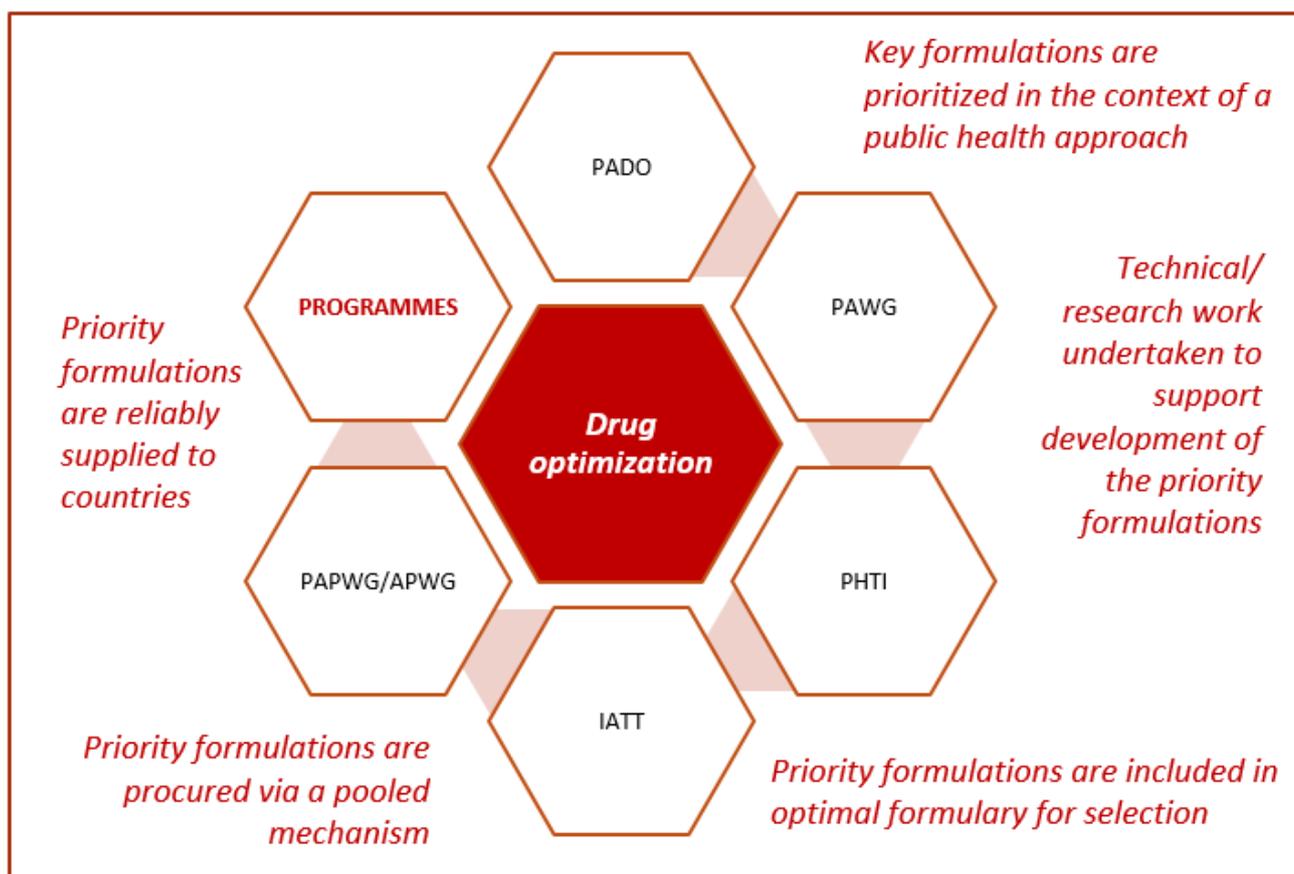


**Figure 1.** Treatment gap between pregnant women and children receiving antiretroviral therapy (Source: Global Plan Report, 2016)

Overall, a remarkable decrease in the number of new paediatric HIV infections has been reported in the 21 Global Plan priority countries, where a 60% decline in the number of new HIV infections among children has been estimated. Though this is a major success for the HIV/AIDS community, it highlights the urgency of acting now to address a need that is not expected to disappear, but rather to become increasingly difficult to tackle due to the challenges of conducting clinical studies in paediatric populations and the lack of incentives for industry to prioritize paediatric HIV drug development.

## Rationale and milestones

Over the past few years, key consultations have advanced the discussion on drug and formulations development for children, resulting in a more collaborative and coordinated response (Figure 2). The first Paediatric Antiretroviral Drug Optimization (PADO) meeting was held in 2013 to address the critical barrier to making paediatric formulations more accessible to children in need. PADO’s discussions prioritized drugs and formulations that are most needed in the context of a public health approach. This list was subsequently up taken by the Pediatric HIV Treatment Initiative (PHTI, a collaboration of UNITAID, CHAI, DNDi and MPP, and it includes WHO as a technical partner), which was launched in 2014 to ensure coordinated actions for developing priority paediatric products. In the same year, a second PADO meeting provided input to the development process of the 2015 WHO Consolidated Guidelines on the use of ARVs, highlighted critical research gaps and renewed the list for priority formulations (Table 1).



**Figure 2.** Drug optimization for Paediatric ARVs is the product of collaborative and coordinated action. PADO: Paediatric ARV Drug Optimization, PAWG: Paediatric ARV Working Group, PHTI: Pediatric HIV Treatment Initiative, IATT: Inter-Agency Task Team for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children, PAPWG: Paediatric ARV Procurement Working Group

PADO priority formulations and rationale for prioritization	
<b>LPV/r 4-in-1</b>	First line for under 3 years to address the lack of optimal formulations
<b>ABC/3TC/EFV</b>	First line 3-10 years to provide a fixed-dose combination (FDC) to maximize adherence and simplify procurement
<b>ATV/r and DRV/r</b>	Use in second- and third-line formulations and overcome issue with separate administration of RTV
<b>NVP/AZT</b>	Better dosage form to facilitate dosing for postnatal prophylaxis
<b>RAL dispersible tablets</b>	Use in infants and young children to enable rapid introduction of integrase inhibitors for use in first-line regimen
<b>DTG single or FDCs</b>	Identified as key drug to introduce integrase inhibitors in first line with potential for harmonization across the full age spectrum
<b>TAF in FDCs</b>	Key drug for future use in first line to minimize toxicity with potential for harmonization across the full age spectrum

**Table 1.** PADO 2 priorities for drug and formulation development, as reviewed in December 2015. Source: PADO 2 meeting report (WHO). PnP = postnatal prophylaxis. \*The two “LPV/r 4-in-1” combinations contain lopinavir/ritonavir + zidovudine + lamivudine (LPV/r/AZT/3TC) and lopinavir/ritonavir + abacavir + lamivudine (LPV/r/ABC/3TC), respectively.



Subsequent efforts promoted alignment of the PADO and PHTI work with additional work streams that have been supporting selection and effective procurement of optimal formulations for children; these are the Inter-Agency Task Team for Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) optimal formulary and Paediatric ARV Procurement Working Group (PAPWG)<sup>1</sup> pool procurement mechanism, respectively. As a result, the various work streams supported by several stakeholders are now effectively linked to ensure coordinated work from research and development to registration, selection, introduction, procurement and uptake (see Figure 2).

More effective communication and open dialogue between the stakeholders has been instrumental for generating convergence and fostering collaborations. A number of the International AIDS Society's (IAS's) joint Industry Liaison Forum (ILF) / Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) roundtables, for example, have provided forums for open dialogue with industry and for enhancing critical thinking around paediatric formulation development. This was further energized after the launch of the Global Paediatric Antiretroviral Commitment-to-Action (CTA) initiative, which has mobilized further efforts in promoting accountability and in addressing some of the remaining gaps in this area of work.

There has been recognition that there is a need for the formulation development process and the existing mechanisms to be faster, more efficient and more sustainable. Development of paediatric ARVs is currently required by the existing regulatory framework; however, clinical development of paediatric ARV formulations is currently inefficient, slow and substantially affected by industry's business model, which is not incentivized by the decreasing market for paediatric ARVs.

## Political commitment

A number of key events have created a favourable environment for triggering strategic changes and provide a platform to accelerate development of needed formulations. This is supported by clear political commitment as expressed by:

- **The 69<sup>th</sup> World Health Assembly (WHA)<sup>2</sup>**, which recently adopted a resolution on paediatric medicines to represent Member States' commitment to addressing the lack of paediatric medicines and the call for WHO and global actors to engage in concrete actions to improve the quality of research standards, improve regulatory pathways at global and national levels, and promote timely development of paediatric formulations.
- **Philanthropies** are demonstrating interest in setting up formulations technology platforms for paediatric medications and in enabling the creation of an innovative mechanism to develop priority formulations for HIV, as well as for other disease areas.
- The **Holy See and Caritas Internationalis** have convened high-level dialogues to call for accelerated action and promote a closer collaboration with industry in ensuring that critical commodities are available for scaling up HIV services for children.
- The **United Nations High-Level Meeting on Ending AIDS (HLM)** has provided the opportunity to officially endorse super-fast track targets and promote an implementation framework that recognizes the lack of paediatric formulations and calls for urgent actions at global and national levels.

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<sup>1</sup> The PAPWG's approach to improving supply security has been so successful that some paediatric ARVs no longer require the same level of support that they have previously received. Thus, in January 2016, the group approved the expansion of the scope of the PAPWG to include additional products facing similar market conditions. To reflect its broadened mission and scope, the PAPWG adapted its name from the Paediatric ARV Procurement Working Group to the ARV Procurement Working Group (APWG).

<sup>2</sup> The 69<sup>th</sup> World Health Assembly. Available at: <http://www.who.int/mediacentre/events/governance/wha/en/>

## Proposing a Global Accelerator for Paediatric Formulations

The overall goals of the Global Accelerator for Paediatric Formulations are to optimize and streamline existing regulatory frameworks, strengthen collaboration and ensure coordination between existing platforms, and develop a sustainable financing mechanism to develop new and needed formulations for paediatric HIV in a timely fashion. The key actors involved include:

- **Manufacturers:** Originators are required to develop paediatric plans, while generic manufacturers have no requirement to develop paediatric formulations and typically engage with paediatric development based on market incentives.
- **Regulators:** These include stringent regulatory authorities (SRAs), WHO Pre-Qualification Programme (WHO PQ) and national regulatory authorities (NRAs), which approve new drugs and formulations for use and market introduction. SRAs are the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA).
- **PADO:** The international group, convened by WHO, gathers scientific and programmatic expertise to inform drug optimization and drug prioritization.
- **PHTI:** The collaboration platform develops new formulations of ARVs prioritized by PADO by building upon the expertise and roles of the founding organizations (UNITAID, MPP, DNDi, CHAI and WHO as a technical partner).
- **Donors and various stakeholders:** These intervene at different points in the cascade from development to introduction.

The way these actors interact and contribute to the development and introduction of formulations differs, depending on whether a product is a new ARV or a new formulation of approved ARVs.

### New drugs

The USA and the EU have both developed specific legislation to incentivize and reward paediatric drug development. Paediatric studies are required as part of every new drug application to the FDA, and incentives for pharmaceutical companies are offered as a six-month period of marketing exclusivity called the “paediatric exclusivity”. In Europe, the Paediatric Regulation requires set up of a paediatric programme at an early stage in the drug development process and planning for paediatric trials at an earlier time.

As a result, originators submitting for market authorization of a novel compound need to develop a Paediatric Investigation Plan (PIP, for the EMA) or Pediatric Study Plan (PSP, for the US FDA) to submit to SRAs. In order to ensure that the data collected do not serve only populations in developed countries, but also address needs in developing countries where the majority of children with HIV live, originators could be invited/advised by SRAs to consult the research networks linked to the PADO group and obtain technical advice to develop their PIP/PSP.

Research networks could advise on the development of PIPs and PSPs based on the PADO principles and recommendations and offer a joint research platform to conduct studies in the best and most rapid way. The networks could operate jointly and maximize the enrolment capacity for key safety and dose-finding studies. Furthermore, priority could be given to the following approaches:

- Enrol children in different weight-band groups simultaneously irrespective of age.
- Ensure adequate number of subjects in each weight-band.
- Test weight-band dosing based on the use of the WHO generic tool with allometric scaling.
- Undertake pharmacokinetics (PK) sub-studies to address critical drug interaction, such as with rifampicin (RIF) in TB patients.
- Nest acceptability studies to ensure feasibility of administration and use.
- Explore opportunities to effectively link PIPs/PSPs to strategic trials (i.e., factorial and adaptive design).



This approach would not just ensure speed but also quality, and in this context, SRAs could consider a more rapid review. Periodic consultation between SRAs, in conjunction with streamlining and coordinating international development programmes, will ensure that requirements are met and that research efforts are maximized.

## New formulations of approved ARVs

The pathways for developing a new formulation of approved drugs would begin with a given formulation to be prioritized by the **PADO group**, which periodically evaluates clinical evidence, prioritizes harmonization with adult regimens, and evaluates global programmatic data and needs to generate a list of priority formulations. The PADO list is reviewed every year to ensure that the list is current and captures changes or advances in development of formulations. This typically includes FDCs of recommended drugs in first and second line, as well as better age-appropriate formulations to enable administration in children, infants and neonates. These formulations are then considered by the **PHTI**, which supports and facilitates the development of formulations by interacting with research networks, manufacturers (both originators and generics) and regulators.

The collaboration with **research networks** largely via the Paediatric ARV Working Group (PAWG), convened by WHO, is essential to inform drug ratios in FDCs, dosing, and characteristics of formulations to be developed. This happens in consultation with regulators to ensure that the approach is acceptable and meets regulatory requirements. Overall, existing research networks have the capacity to join forces and develop PK modelling, secondary analysis from clinical trials, review of observational datasets and pharmacovigilance studies, rigorous documentation of implementation experience and modelling to inform forecasting. All of these elements are critical for informing prioritized formulation development.

In interacting with **industry**, PHTI promotes and facilitates technology transfer and intellectual property sharing from originators to generics and supports generic manufacturers in development and seeking regulatory advice to undertake bioequivalence and studies (including biostability). If additional clinical studies are needed, PHTI can facilitate outreach to the research networks that are well placed to advise or undertake the studies required. Assistance is also provided by key PHTI partners to develop the submission for regulatory approval and to ensure that evidence and background information are adequately gathered (this sometimes requires involving key experts from the research networks). Another aspect of industry collaboration involves the development of appropriate data from clinical studies and modelling to justify doses. This may require that the originator of the clinical data (typically the innovator) shares the data, and that an appropriate regulatory filing be prepared to support the proposed dosing. Typically, generic manufacturers have little experience justifying dosing that is not aligned with the approved product. Therefore, a mechanism for this to occur has been developed such that all generic manufacturers can have access to the data: PHTI coordinates those activities.

**Regulators**, who have been engaged in the whole process and have provided feedback to research networks and to generic manufacturers via PHTI are already familiar with the content of the submission and the nature of the collaboration behind it; they could consider fast tracking the review process and enabling approval of priority formulations faster.

A critical step, once formulations are approved by SRAs, is to take them to countries and ensure registration via national regulatory authorities. This mechanism could be fast tracked for priority formulations. The paediatric regulators network (convened by WHO) could be leveraged to ensure that once SRAs have approved a given priority drug or formulation, more rapid in-country approval can immediately follow.

In consideration of the low volumes required for these products, rapid introduction of new optimal formulations in the **IATT Optimal Formulary**<sup>3</sup>, its adoption in countries and the consequent inclusion

<sup>3</sup> IATT Policy Brief. Update to the Optimal List of Paediatric ARV Formulations. March 2015. Available at: <http://www.emtct-iatt.org/wp-content/uploads/2015/05/Updated-Formulary-04012015.pdf>



of the priority products in the pooled procurement mechanism led by the **PAWPG** will be critical for consolidating demand and ensuring sufficient manufacturing and reliable procurement and supply.

## Sustainable financing mechanism

A core question for the global accelerator is how the mechanism could be funded sustainably in light of the uncertainties regarding future engagement of partners and donors. We assume that the development of new drugs will continue to be fully funded by innovators, but how can the paediatric ARV community fund the development of priority formulations, knowing that the market is not an incentive for manufacturers to develop them?

The proposed global accelerator would provide financing for paediatric ARV formulations development costs via a pooled fund. Currently, the US National Institutes of Health (NIH) and the European & Developing Countries Clinical Trials Partnership (EDCTP) fund research networks to conduct clinical studies to investigate new drugs and new formulations. In addition, funding for development and introduction of paediatric formulations of approved drugs is provided by UNITAID directly or via its grantees (i.e., DNDi, CHAI, MPP). However, it is unclear whether this is sufficient and sustainable in the long term.

A pooled funding mechanism could be established to streamline the funding process and optimize the resources towards what is needed to develop priority formulations. This pooled funding could be generated via contributions by manufacturers, complementing funding from private philanthropies and additional resources arising from specific initiatives, such as the Innovative Medicines Initiative (IMI) funded by the European Union.

Contributions from manufacturers could be provided via a number of approaches, including:

- A fixed amount per year
- A percentage of revenues from adult drugs
- Revenues from the generic production of paediatric formulations and/or a percentage of adult product revenues (or a fixed fee).
- Other approaches to be identified.

However, questions remain, and these will have to be addressed before such a pooled fund could be implemented. They include:

- What activities would the fund provide support for?
- Where would the fund sit?
- Who would manage the fund?
- How would the fund work?

## Conclusion and main messages

The global community has come a long way in expanding access to paediatric ARVs globally. However, important obstacles to provide most effective and least toxic drugs in the optimal formulations persist. Priorities for future development of paediatric ARV formulations have been identified through the PADO consultations, and mechanisms to support selection and procurement of existing products, as well as to facilitate development of age-appropriate formulations, have been put in place. However, there are many challenges to developing and making these formulations available where they are most needed, and in a timely manner.

Existing regulatory frameworks promote development of paediatric formulations, but implementation of those frameworks has been slow and sometimes ineffective, resulting in inefficient allocation of resources for paediatric formulation development. In addition, the success in preventing mother-to-child transmission has reduced the number of new HIV infections, making it increasingly challenging



to conduct clinical studies adequate to assess efficacy, safety and acceptability of new paediatric drugs and fixed-dose combinations across the age spectrum.

To help optimize global resources and efforts towards developing the most-needed paediatric ARVs formulations, alternative models of collaborations and innovative financing mechanisms that build on existing regulatory processes, optimize investments in paediatric ARVs and enable more sustainable development of prioritized products must be explored. This requires promoting an open dialogue between key stakeholders, such as drug manufacturers, policy makers, research networks, donors and regulatory agencies.

The Global Accelerator for Paediatric Formulations can be an innovative mechanism to ensure that future efforts are focused on priority paediatric ARV formulations. Via this form of collaboration, existing collaborative platforms, such as PHTI, can be strengthened to maximize the resources and the expertise available to develop new formulations and make them rapidly available in countries. Research networks could join forces to increase the quality and the speed of the research undertaken to inform drug development. Regulatory pathways could be sped up, optimized and potentially leveraged to generate additional resources. Manufacturers that continue to bring innovations could save resources and optimize their investment in paediatric development while receiving guidance and support from the global community.

## Advancing the dialogue and innovating global mechanism

The upcoming roundtable to be held at the 21<sup>st</sup> International AIDS Conference in Durban on 16 July 2016 will follow up from the ILF/CIPHER Thematic Roundtable on Paediatric ARVs: Stimulating development of the most needed formulations, which took place on 7 March 2016 in Geneva, Switzerland<sup>4</sup>. This roundtable provided the opportunity to collect initial feedback on alternative financing mechanisms and generated ongoing dialogue, which has contributed to informing further development of the Global Accelerator for Paediatric Formulations.

The upcoming roundtable will also build on the political commitment resulting from two high-level meetings on access to HIV testing and treatment, which were convened by The Pontifical Council for Justice and Peace, UNAIDS, PEPFAR and Caritas Internationalis in April and May 2016. It will also build on ongoing work conducted on paediatric ARVs by the PHTI, partner of the CTA.

The objectives of the thematic roundtable to be held in Durban are as follows:

- Share the outcome of the consultations that informed the development of the Global Accelerator for Paediatric Formulations.
- Discuss the challenges and opportunities outlined in the proposed approach and consider potential alternative options.
- Develop a shared vision for innovating existing mechanisms and fast track development of formulations.
- Reach a consensus on follow-up actions.

The expected output will be a meeting report and a white paper to document and disseminate the shared vision, as well as develop and inform subsequent steps for implementation. More detailed consultations within different constituencies will be held in the coming months. The Global Accelerator for Paediatric Formulations proposal, revised to reflect constituencies' input, will be outlined by December 2016. CTA partners and the IAS will review the final proposal at the beginning of the Paediatrics Week (5-9 December, Geneva) for official endorsement, with implementation of the structure of the Global Accelerator for Paediatric Formulations occurring throughout 2017.

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<sup>4</sup> ILF/CIPHER Thematic Roundtable on Paediatric ARVs: Stimulating development of the most needed formulations. Available at: <https://bit.ly/1S31ZML>



## About the convening partners

### About the Collaborative Initiative for Paediatric HIV Education and Research

[CIPHER](#) is aimed at optimizing clinical management and delivery of services to infants, children and adolescents affected by HIV in resource-limited settings through advocacy and research promotion. The content and structure of CIPHER is guided by experts in paediatric HIV convened by the IAS.

CIPHER is supported by its founding sponsor, ViiV Healthcare, and Janssen.

### About the Industry Liaison Forum

The [ILF](#) highlights the perspective of the HIV biomedical industry and catalyses multi-stakeholder dialogue and engagement, as well as reflections and actions to address barriers along the HIV cascade of prevention, diagnostics and treatment. Challenges around cross-cutting issues affecting industry's contribution to the HIV response are also of central importance. The work of the ILF is guided by a strong advisory group, which is composed of industry and non-industry representatives.

The ILF is grateful for the unrestricted support received from its Gold Partners (Gilead Sciences, MSD and ViiV Healthcare), its Silver Partners (AbbVie, Alere and Janssen) and its Bronze Partners (Abbott, bioLytical Laboratories, Cepheid, Cipla, Female Health Company, Omega Diagnostics, Roche Molecular Systems and Sysmex Corporation). This discussion is sponsored by ILF Gold and Silver Partners.

### About the Global Pediatric Antiretroviral Commitment-to-Action

On World AIDS Day 2014, PEPFAR, the Pediatric HIV Treatment Initiative (PHTI) and the Global Fund announced a new Global Pediatric Antiretroviral Commitment-to-Action (CTA). The PHTI is a collaboration of UNITAID, CHAI, DNDi and MPP, and it includes WHO as a technical partner. The CTA brings together these leading organizations to accelerate the development and uptake of new, high-priority paediatric ARV co-formulations for first- and second-line treatment by 2017. The CTA was launched to support, consolidate and catalyse existing efforts that support the following objectives:

1. **Accelerate the development of new, high-priority and child-adapted formulations** based on the WHO consolidated ARV guidelines and other technical advice issued by WHO with the aim of delivering the highest priority paediatric co-formulations for first- and second-line treatment by 2017 and beyond.
2. **Support rapid and streamlined regulatory approval** – globally and in-country – of new paediatric ARV formulations, especially for use in children 0 to 3 years of age.
3. **Ensure that new formulations of paediatric ARVs are promptly eligible for procurement** by supporting rapid national and global review of high-priority products for children and quick integration of new products into the Interagency Task Team (IATT) optimized formulary list.
4. **Ensure that product-specific demand forecasts and market-sizing data on priority products** are accurate, timely, coordinated and disseminated to key stakeholders, namely manufacturers.
5. **Track financing commitments for procurement** and uninterrupted supplies of priority paediatric ARVs by 2017, including use of pooled procurement to secure paediatric pipelines.
6. **Support demand creation and uptake of optimal formulations** by providing technical support to national programmes and by facilitating timely revisions of guidelines, dosing charts and training aides.

CTA partners leverage their unique expertise to provide strategic guidance and input on key decisions. Partners participate in monthly calls to provide updates on their respective work, coordinate efforts when needed and evaluate progress in order to achieve the CTA's objectives outlined here. In addition to providing this regular input, some partners have provided additional support. For example, [PEPFAR](#) and [WHO](#) are leading efforts to develop a new funding mechanism that could incentivize research and development of priority paediatric ARVs. [UNITAID](#) organized and funded a CTA side event at the 2015 International AIDS Society conference, where all CTA partners participated in a panel discussion on accelerating innovation for paediatric ARV formulations. The CTA also had a presence at the Accelerating Children's HIV/AIDS Treatment (ACT) Regional Workshop in Zambia in the fall of 2015 to ensure coordinated efforts between ACT and the CTA. It has also launched the Public Recognition Awards (PRAs) to recognize the pharmaceutical company and national AIDS programme that have made considerable progress towards making priority paediatric ARVs available. Most recently, the CTA has been working with ILF/CIPHER and other initiatives to develop a new funding mechanism that could incentivize companies to develop priority paediatric ARVs. This model will be presented and discussed at the 2016 International AIDS Conference in Durban with the support of the IAS. Through these efforts, the CTA has sustained momentum and moved towards achieving its overall goal of accelerating the development and country uptake of priority paediatric ARVs.