



**Catching children before they fall:
Addressing the urgent drug development needs of
children living with HIV**

MEETING REPORT

Public Satellite Session at AIDS 2012
Washington, DC, USA
22 July 2012

INTRODUCTION

Although antiretroviral (ARV) treatment coverage for adults living with HIV has been steadily climbing and has now reached approximately half of those in need, coverage for the world's 3.4 million HIV-infected children lags far behind at less than 25%. In high-income countries, new infant infections have largely been eliminated due to effective prevention of mother to child transmission (PMTCT) interventions. However, in low- and middle-income countries, many pregnant women do not have access to testing and timely, effective PMTCT or maternal antiretroviral therapy (ART). As a result, in 2011, 330,000 children became infected with HIV, and 230,000 children died of AIDS-related complications¹

The global strategy to eliminate new infant infections through PMTCT by 2015, while laudable, fails to take into account the reality that some children will continue to be infected and will urgently need access to early diagnosis and immediate safe, potent, child-friendly ARV treatment. Without this treatment, half of the children born with HIV will die before their second birthday. A critical barrier to access to treatment for children is, among others, the lack of appropriately adapted formulations. The World Health Organization (WHO) recommends immediate ART for all HIV-infected children less than two years old, and a protease inhibitor-based regimen is recommended, particularly for HIV-infected infants and children who have very high viral loads and may have been exposed to ARVs for PMTCT. However, challenges in implementing these recommendations include the poor taste of some of the existing paediatric formulations, impractical multiple liquid preparations that require refrigeration, and undesirable interactions with tuberculosis (TB) drugs.

Two years ago, the International AIDS Society-Industry Liaison Forum (IAS-ILF), with 15 other organizations (including WHO, UNAIDS, pharmaceutical companies, non-governmental organizations and community groups), jointly released a consensus statement, [Asking the Right Questions: Advancing an HIV Research Agenda for Women and Children](#), which outlined 20 recommendations to advance HIV research for women and children. Six of those recommendations call for more investment in clinical research related to the unique needs of paediatric populations. To continue highlighting the recommendations in the consensus statement, the IAS-ILF and Drugs for Neglected Diseases initiative (DNDi) jointly organized a public satellite session at the XIX International AIDS Conference (AIDS 2012) to draw attention to the drug development needs of children with HIV. The session provided insight into the drug development process, outlined some of the key practical and technical challenges of formulation development for HIV-infected children, and discussed ways to overcome scientific, financial and policy barriers to accelerating the development and implementation of more optimal treatment options for children.

The session was co-chaired by Celia Christie-Samuels (IAS-ILF Co-chair and Professor of Paediatrics at the University of West Indies) and Bernard Pécoul (DNDi Executive Director). In her opening remarks, Christie-Samuels presented a brief overview of the IAS-ILF's mission and efforts to accelerate HIV clinical and

¹ World AIDS Day Report. *UNAIDS*. 2012. http://issuu.com/unaid/docs/20121128_jc2434_worldaidsday_results?mode=window&backgroundColor=%23222222

operational research in children living with HIV in resource-limited countries. Bernard Pécoul presented DNDi's mission to focus on developing new treatment for the most neglected patients, including paediatric HIV treatment, specifically in young children.

Keynote address *Paediatric HIV – a neglected disease?*

Stephen Lewis, *Co-director, AIDS-Free World*

Long recognized as a champion in the HIV response in Africa, Stephen Lewis provided the keynote address of the satellite session. Lewis evoked the urgency in developing appropriate antiretroviral drug formulations for young children living with HIV, most of who reside in sub-Saharan Africa.

Lewis commented on the slow progress by global health actors, and noted that the global community itself should have developed a plan to eliminate new HIV paediatric infections much earlier. Describing paediatric HIV as “becoming a back-story”, he noted that 3.4 million children living with HIV is a function of an inadequate response. Lewis stated that no one would argue with the elimination plan, but “we’re late with it by 2011”. Furthermore, he argued against the notion that we can eliminate HIV in children and “keep mothers alive” at the expense of treating children. In his parting thoughts, Lewis referred to the importance of this satellite session, and declared that children are not “expendable casualties just because they didn’t fit into prevention strategies”.

For the full speech, please go to: <http://www.aidsfreeworld.org/Publications-Multimedia/Speeches/~//media/Files/Speeches/IAC%20DNDi%20Session%202012-07-22.pdf>

A dream formulation for infants in the developing world? A paediatrician's experience

Adeodata Kekitiinwa-Rukyalekere, Mulago National Hospital “dream” formulation

Offering a clinician's perspective, Adeodata Kekitiinwa-Rukyalekere provided a snapshot of the characteristics for an “ideal” paediatric ARV formulation. Kekitiinwa-Rukyalekere prefaced her talk by underscoring how global ART coverage for children lags behind that of all adults (echoing Stephen Lewis' comments), and described how children are not virologically suppressed like adults, even when on treatment.

The evolution of drug development has its roots in the early days when clinicians “struggled with tablets”. Although pharmaceutical companies responded by developing syrups/suspensions, providers and caregivers soon recognized the challenges even with these formulations. Kekitiinwa-Rukyalekere spoke about the issue of the poor taste of the lopinavir/ritonavir (LPV/r) syrup, and noted how such issues as lack of refrigeration in many resource-limited regions constrain its use. Furthermore, single paediatric tablets became problematic since they are associated with a high pill burden, and the challenge of fixed-dose combination (FDC) development (especially for children under the age of three years) has served as a major barrier for formulation experts.

Kekitiinwa-Rukyalekere made reference to study PI060, where LPV/r was shown to be superior to nevirapine (NVP) as a first-line regimen, and underscored the important implications of this study in light of the dialogue for developing a “dream” formulation. Formulation development also has to consider the critical element of patient acceptability. More recently, CHAPAS-2 examined pharmacokinetics and acceptability of LPV/r sprinkles in infants younger than one year and children older than four years (presented as a late breaker at the International Paediatric Workshop)². In older children taking LPV sprinkles, LPV exposure was lower when compared with use of tablets (Table 1). In infants, LPV sprinkle exposure was comparable with syrup. Interestingly, caregivers reported that the sprinkles were more acceptable for infants, but not for older children (taste being the primary issue in the older group) (Figure 1). Results from the ARROW Trial showed tablets being the preferred option for treatment of younger children³. Kekitiinwa-Rukyalekere noted that supply chain management is a critical aspect of paediatric HIV treatment, citing data from Uganda, where five of 14 health facilities had stock outs for paediatric formulations, but not for adult formulations (based on a comprehensive baseline survey between November 2011 and March 2012)⁴.

	Tablets	Sprinkles	GMR (90% CI)	Historical data in children
PK parameter	GM (95% CI)	GM (95% CI)	Sprinkle:tablet	
AUC _{0-12h} (h.mg/L)	115.6 (103.3-129.8)	83.1 (66.7-103.5)	0.72 (0.60-0.86)	72.6 (41.5-103.7)
C _{max} (mg/L)	13.9 (12.9-15.1)	10.3 (8.6-12.2)	0.74 (0.64-0.85)	8.2 (5.3-11.1)
C _{12h} (mg/L)	4.4 (3.3-5.9)	2.6 (1.7-4.1)	0.59 (0.43-0.81)	3.4 (1.3-5.5)

Table 1. LPV exposure in older children enrolled in CHAPAS-2

² Musiime V, FillekesQ, KasiyreP, et al. Pharmacokinetics and acceptability of a new generic lopinavir/ritonavir sprinkle formulation compared with syrup/tablets in African, HIV-infected infants and children according to WHO weight-band dose recommendations (CHAPAS-2). 4th International Workshop on HIV Pediatrics; 2012 July 20-21; Washington DC.

³ Nahirya – Ntege et al. *PLoS ONE* 7(5): e36186.

⁴ <http://www.dignitasinternational.org/cms/content/Lablite%20-%20baseline%20mapping%20survey%20of%20decentralised%20ART%20service%20provision%20in%20Malawi,%20Uganda%20and%20Zimbabwe.pdf>

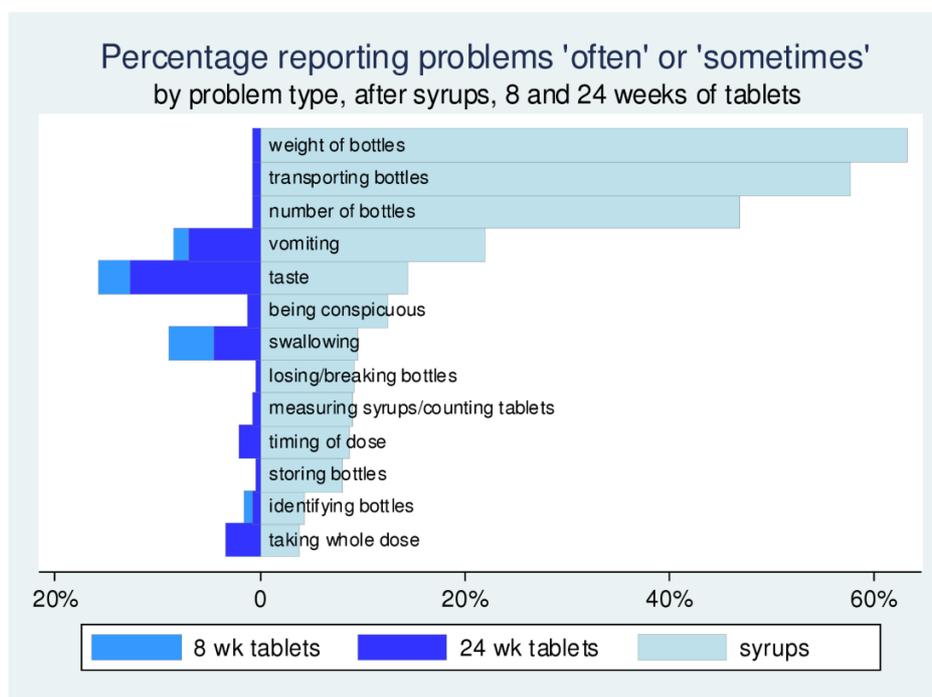


Figure 1. Acceptability of caregiver for formulation in CHAPAS-2

Kekitiinwa-Rukyalekere concluded by outlining some of the “dream attributes” of future formulations, which include simplified administration (e.g. an FDC in a single tablet with reduced pill burden). FDCs, if scored, would be an acceptable and efficacious option that would meet the needs of all age groups and weight bands. Formulations that can be delivered as sprinkles or smaller granules or that are dispersible could cater for younger children, and such sprinkle formulations should have favourable PK parameters across all age ranges with minimal/no toxicity.

A “layman’s guide” to paediatric formulation development

Karen Thompson, Senior Investigator, Pharmaceutical Research, Merck

Martin Gartland, Global Medical Lead – Kivexa/Epzicom, ViiV Healthcare

Aiming to provide a more generalized overview on the technical process of developing and manufacturing a paediatric formulation and receiving regulatory approval, Karen Thompson from Merck and Martin Gartland from ViiV Healthcare co-presented a talk on behalf of the industry members of the IAS-ILF. Thompson opened the presentation by outlining the science of paediatric formulations. In terms of the molecule itself, many factors have to be considered, including the mechanism of action. For development of an FDC, two different molecules may not have the same absorption. Notably, the maturation of enzymes in metabolizing drugs changes with age, and there are particular taste preferences according to age. Thompson also stressed the need to assess appropriate dose requirements in children in different age groups, a process that is particularly challenging for infants under two years of age (Table 2).

Formulation options involve a range of factors, including route of administration, dosing flexibility and safety. Thompson noted that sprinkles are particularly challenging from dose adjustment perspective., and any taste-masking excipients must be examined for any potential negative effects (e.g., there is a database for monitoring, although data is based on information from adults).⁵ ⁶ The manufacturing processes for formulation products included quality assurance, while supply assurance is a critical area (e.g. adequate shelf life and assurance of integrity of product from production to patient). Thompson noted that paediatric drug development should be approached with the same rigor as adult drug development including controlling the supply chain, stability and quality to protect. highly vulnerable paediatric population.

Physiology	Age-related changes
Gastric emptying time	Pre-term gastric emptying is slow and linear, approaches adult levels within first six to eight months of age.
Gastric pH	At birth, pH is neutral, falls to 1-3 within 24 hours after birth, returns to neutrality by day 10 and slowly declines to adult values. By age three, gastric acid/kg body weight like adult.
Intestinal transit	Transit time is prolonged in the neonate, and reduced in older infants. Immature secretion and activity of bile and pancreatic fluids in neonate and infants over first few months, immaturity of the intestinal mucosa, immaturity of transport systems. Reduced first pass metabolism.
Renal blood flow	At birth, 5% to 6% of cardiac output, 15% to 25% by one year of age, reaches adult values after two years. Renal clearance reaches adult levels after two years of age.
Percutaneous adsorption	Permeability rates are 100 to 1,000 fold greater before 30 weeks of gestation; full-term neonates have three- to four-fold greater permeability than adults.

Table 2

Ongoing efforts in paediatric development include the effort to standardize taste evaluation tools for children and the need to define better *age appropriateness*. Thompson underscored the need to obtain data for mini-tabs as there is concern over whether children can choke.

Martin Gartland embarked on describing the clinical and regulatory challenges after a formulation has been successfully developed. Gartland outlined the regulatory processes in place by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Figure 2), and highlighted the European Union paediatric investigation plan (PIP) which is introduced very early in the clinical research process, as it needs to

⁵ Issues in the formulations of drugs for oral use in children. Role of excipients. *Drugs* **4**(6) (2002) 371-379.

⁶ Benzyl Alcohol: *N. Engl. J. Med.* **307**(2) (1982) 1384-1388; *Lancet* **I** (1982) 1250-1251.
Propylene glycol: *J. Pediatrics* **77**(5) (1970) 877-878; *Ped.* **72** (1983) 353-355.

be in place to proceed (at Phase I). He also commented that PIP remains one of the key regulatory challenges as drug developers may not have extensive data on a given formulation. Furthermore, he highlighted how differences between EU and FDA processes (e.g. different age cohorts and different PK requirements/endpoints) must be incorporated into a company's development plan.

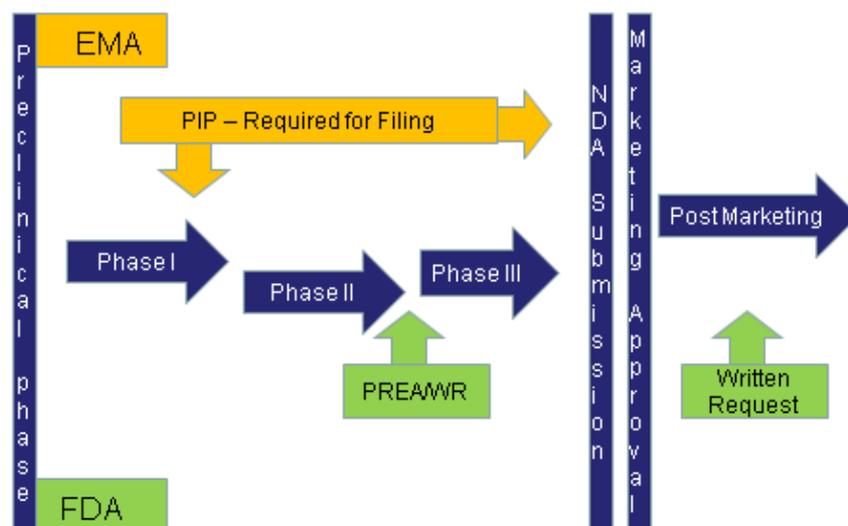


Figure 2. Schematic of topline regulatory process

Lastly, Gartland outlined some successes in the paediatric formulation pipeline. Abbott has been developing a heat-stable formulation of ritonavir that could be sprinkled over food or added to liquid. Gilead had recent approval of tenofovir paediatric powder (micro encapsulation for taste masking), and ViiV/GSK had recent FDA approval of fosamprenavir oral suspension down to four weeks of age (and also a partnership with Matrix/CHAI in development of a dispersible formulation of ABC/3TC). Merck had the recent FDA approvals for raltegravir in a paediatrics chewable formulation.

Addressing the drug development needs of infants and young children: DNDi's Paediatric HIV Programme

Shing Chang, Scientific Advisor, DNDi

Shing Chang offered an overview of DNDi's paediatric HIV programme, and described a new partnership with the Indian generic manufacturer, Cipla, in developing a new FDC. The paediatric HIV challenge is characterized by an interplay of a very aggressive viral infection in children with rapid developmental changes in the context of fewer ARV options based on limited safety data, and even fewer available formulations (with only two, LPV/r and fosamprenavir, being approved for infants/young children).

Children are “not small adults”, and many adult formulations are not suitable for use in certain paediatric populations. Furthermore, he noted the particular challenge of liquid formulations that can lead to sub-optimal adherence and dosing when not taken appropriately by children.

Chang described the Cipla-DNDi partnership (Figure 3), which aims to develop and produce an improved first-line FDC ARV regimen adapted to meet the specific needs of infants and younger children living with HIV. The concept is based on a sachet containing four drugs, which would require no cold chain, making it particularly useful in remote areas of many countries. The four drugs would be in a taste-masked granular or “sprinkle” form, and they could be mixed into food or liquids, such as water or even breast milk. Each sachet would constitute a fixed dose of LPV/r, lamivudine and either abacavir or zidovudine.

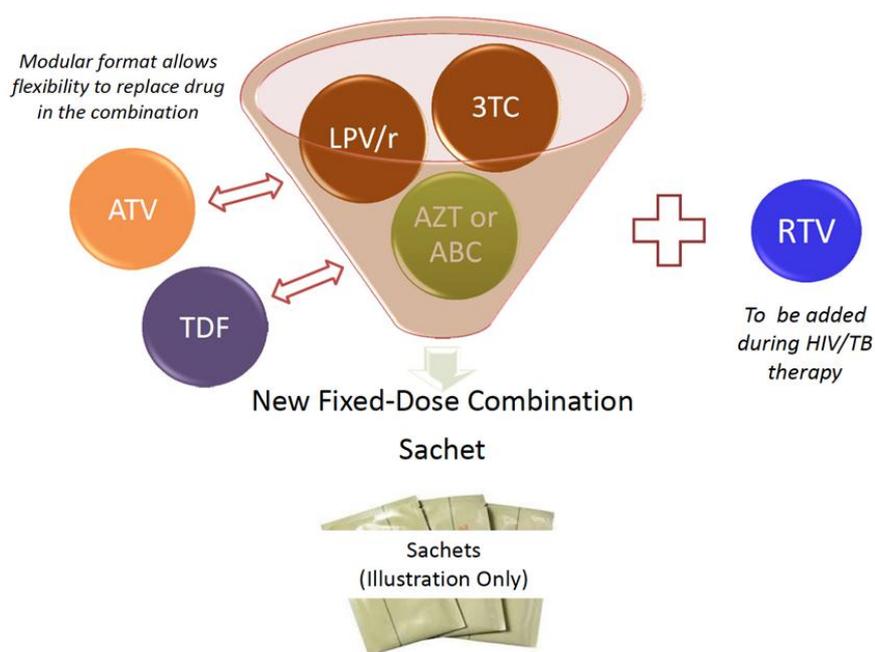


Figure 3. “4-in-1” sachet-based FDC, built on the current Cipla LPV/r sprinkles product

Chang also outlined the many advantages in dose adjustment, whereby one can add extra ritonavir for boosting in children receiving treatment for their TB. Chang’s parting message was that despite more work needed to optimize the 4-in-1 sachet, greater support is also needed from other partners and manufacturers to provide suitable formulations.

PANEL DISCUSSION I:

How do we address the technical challenges to paediatric formulation development?

Moderators:	Lynne Mofenson (NIH) and Polly Clayden (HIV i-Base)
Panel participants:	
Jaideep Gogtay	Head of Medical Services, Cipla (India)
Adeodata Kekitiinwa-Rukyalekere	Associate Professor of Pediatrics, Baylor College of Medicine; Senior Consultant Pediatrician, Department of Pediatrics and Child Health at Mulago National Hospital, Uganda
Karen Thompson	Senior Investigator, Pharmaceutical Research, Merck
Martin Gartland	Global Medical Lead – Kivexa/Epzicom, ViiV Healthcare
Shing Chang	Scientific Advisor, DNDi

Lynne Mofenson and **Polly Clayden** co-moderated a panel discussion and fielded questions to speakers in light of the presentations, with the aim of addressing the technical challenges in ARV product development for infants and children. Mofenson commented that despite our efforts to reduce new HIV infections in infants by 90%, there will still be estimated 70,000 to 100,000 children with HIV who need optimized treatment. She underscored the importance that AIDS 2012 re-emphasize the needs for children living with HIV, stating that “the more people advocate, the better”. Mofenson also emphasized that dosing must be established for pre-term infants as only AZT and NVP exist for this vulnerable population.

Cipla’s **Jaideep Gogtay** was invited to provide remarks from a generic manufacturers’ perspective. Gogtay re-emphasized the challenge in developing FDCs as it is much more complicated than developing a single drug agent. Cipla has examined a variety of options, from improving the taste of liquid formulations to exploring the feasibility of crushed tablets. One consideration has been a combination of three to four drugs in a sprinkle formulation, which ultimately led to the collaboration with DNDi, described previously by Chang. He noted that the coming two years will be critical in terms of formulation R&D, and emphasized the need to prioritize the development of a formulation for infants and young children.

Echoing the theme of collaboration, Kekitiinwa-Rukyalekere explained how paediatricians have to work constructively with drug developers. Although exclusive breastfeeding is being promoted, there are outstanding questions about the interaction of ARV drugs and breast milk. There is a spectrum of clinical issues to be addressed, and technical issues can be overcome through collaborative ventures. Partnerships can be also innovative, not just technical, according to Martin Gartland.

Mofenson enquired about the development of longer lasting formulations and the application technologies, such as nanotechnology. Panellists agreed that a DEPO formulation would be very difficult to develop. **Karen**

Thompson indicated that film is an appropriate technology for low-dose administration; however, she stated that dose adjustment for body surface area (BSA) for children is much more challenging.

Audience perspective

Heddy Tepler from Merck asked how DNDi anticipated adjusting for dose/weight for the sachet. Chang commented that “the beauty of the sachet” was in dispensing particles in different sizes, and stated how from a manufacturing point of view, the sachet provides this flexibility, instead of drugs being locked into a tablet. A physician from Jamaica spoke of infants having a “virgin tongue”, and consequently, LPV/r does not bother them and the concern of palatability is more for older children. Concerns were also raised over under-dosing with a sprinkle formulation if a child does not consume his/her food.

Diana Gibb of the MRC argued that PK studies must be linked to acceptability studies, as was undertaken in CHAPAS -2, as relatively little literature exists in terms of what families/caregivers prefer. Gibb also commented that if a mother does not wish to carry syrup bottles, then a practical issue is in fact a treatment issue. In response to the issue of toxicity, Chang stated that all drugs are expected to have some level of toxicity, particularly in special populations (e.g., young patients). There is an inherent challenge in developing and testing paediatric treatments in any setting, as children cannot provide feedback the way that an adult can (e.g., was nausea due to gastrointestinal problems or to bad taste). Gartland, in response to a question by an MSF representative, stated that an affordable ABC/3TC formulation is being developed by ViiV Healthcare for use in resource-limited settings.

PANEL DISCUSSION II

Overcoming the barriers: What can be done to accelerate the entry of improved paediatric HIV therapies?

Moderators: Lynne Mofenson (NIH) and Polly Clayden (HIV i-Base)

Panellists:

Lulu Muhe	Medical Officer, Maternal, Newborn, Child and Adolescent Health (MCA), World Health Organization, Switzerland
Benedict Xaba	Minister of Health, Ministry of Health, Swaziland
Lihle Dlamini	Treatment Action Campaign, South Africa
Shaffiq Essajee	Senior HIV Advisor, Clinton Health Access Initiative, USA

A second roundtable discussion followed, with the aim of identifying the strategies needed to create an enabling environment to accelerate development and uptake of paediatric HIV drugs in resource-limited settings.

Shaffiq Essajee commented that drug developers are risk averse, noting the real risks in undertaking research in younger children. Furthermore, Essajee emphasized the need to conduct research in infants, and argued that manufacturers should be more conscious of the clinical needs of paediatric populations. **Lulu Muhe** described how WHO has been active in convening stakeholders to address paediatric formulations (e.g. defining criteria for optimizing and evaluating available paediatric formulary products), and called for constructively supporting companies sensitizing them to the needs of patients and caregivers.

Lynne Mofenson made reference to the superior efficacy of LPV/r demonstrated in PI060, and asked Muhe to explain why WHO has yet to recommend a protease inhibitor-based first-line regimen for children. Muhe stated that WHO's treatment guidelines revisions are based on input by international experts, and is currently collecting evidence for children younger than three years to determine if PI-based regimens will ultimately be recommended as first-line regimens. Mofenson and Muhe also echoed concern over NNRTI resistance in infants born to mothers being treated with EFV.

The challenge over expediting the drug approval process was also mentioned. The representative from Treatment Action Campaign, **Lihle Dlamini**, commented on South Africa's Medicines Control Council (MCC) and its delayed registration of a tenofovir vaginal gel for HIV prevention. Minister **Benedict Xaba** underscored the need for WHO member states to better understand the R&D process as a critical component of their decision making on, for example, procurement. Xaba emphasized the need for governments to commit financially to sustain treatment programmes. In the case of Swaziland, the ARV procurement is done by state budget, and is not funded by external donors. Xaba argued for the need for innovative funding mechanisms, and called for negotiating on cost with drug manufacturers.

Rachel Cohen of DNDi noted that representatives from donor agencies (e.g., the Global Fund) were not able to participate in the panel discussion, and commented on how PEPFAR itself has become more focused on eMTCT. Cohen, however, questioned whether donors are addressing paediatric treatment needs in resource-limited countries, an issue raised earlier by Mofenson. Essajee highlighted the need to manage the

transition of pooled procurement of paediatric ARVs from UNITAID to Global Fund/PEPFAR in order to ensure that no child is left without treatment. Stating that we are still only “scratching the surface”, Essajee commented on the urgency to identify funds to break past the 25% coverage rate for ARVs in children. Clayden made reference to the newly published [i-Base/TAG2012 Pipeline Report](#), which describes treatment advances in HIV, HCV, and TB, and which includes a section on the paediatric drug pipeline (e.g. including a list of approvals of new drugs from innovator companies by the FDA).

In closing, session co-chairs highlighted the need for ways to produce more affordable and child-friendly drugs and to think strategically with regulatory stakeholders in expediting access to new formulations for children.

ABOUT IAS-ILF

The Industry Liaison Forum (ILF) is an initiative of the International AIDS Society (IAS) that brings together industry, independent investigators, community, non-governmental organizations, normative agencies, and other stakeholders to enhance HIV research and thereby promote evidence-based health policy and health delivery in resource-limited settings. Founded in 2001, the IAS-ILF is part of the IAS's Research Promotion Department, which includes the *Journal of the International AIDS Society* (JIAS), the Fellowships & Grants Programme, and Research Prizes & Awards.

The IAS-ILF strives to fulfil its mission by: identifying research gaps; promoting targeted research; identifying challenges and best practices; disseminating information; conducting analyses; consulting and convening stakeholders; providing industry expertise; and supporting capacity building for research and health delivery. The IAS-ILF is a unique collaboration between stakeholders in the global response to HIV and serves as a platform for creative thinking and constructive dialogue around HIV research. The IAS-ILF Advisory Group consists of senior clinicians and public health experts from the pharmaceutical and diagnostic industry, academia, non-governmental organizations, community, international organizations and UN agencies.

As part of its new ILF Strategic Plan 2012-2014, the IAS-ILF will continue to prioritize prevention and treatment for women and children in resource-limited settings, with an emphasis on prevention and treatment outcomes, as well as access. The IAS-ILF will support research and other strategies to: enhance treatment management; scale up prevention of mother to child transmission programmes; improve prevention and treatment access and outcomes for these vulnerable populations; optimize the potential of pre-exposure prophylaxis and other chemoprevention interventions; and support best practices in public health policy and delivery.

For more information regarding IAS-ILF activities and its relevant publications, please visit our website at: <http://www.iasociety.org/ilf.aspx>.

Contact information:

International AIDS Society
Industry Liaison Forum
Avenue de France 23
CH-1202
Geneva, Switzerland
ilf@iasociety.org