



Challenges in the Procurement and Development of Paediatric Antiretroviral Formulations

SESSION REPORT

Public Satellite Session at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011)

17 July 2011
Rome, Italy

Co-hosted by IAS-ILF, CHAI, & UNICEF



Background

In 2010, the International AIDS Society (IAS)-Industry Liaison Forum (ILF) jointly with UNICEF, the Clinton Health Access Initiative (CHAI), and 13 other organizations (including WHO, UNAIDS, pharmaceutical companies, non-governmental organizations and community groups) 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. Two recommendations within that statement call specifically for investment in innovative drug manufacturing and delivery systems (e.g., dissolvable films, microtablets) to address the need for appropriate paediatric formulations and for the evaluation of a range of weight-adjusted dosage recommendations and fixed-dose combinations (FDCs).

As part of the effort to promote HIV research related to the treatment needs of children and highlighted in the consensus statement, the ILF, UNICEF, and CHAI organised a satellite session at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011), entitled “Challenges in the Development and Procurement of Paediatric Antiretroviral Formulations”. The objective of this session was to explore the pertinent market dynamic issues on supply and procurement for paediatric antiretroviral (ARV) formulations affecting resource-limited settings. Furthermore, it explored the particularities related to the current and future pipeline of paediatric formulations, including FDCs. The session further provided insight into the feasibility of developing new formulations that are pharmacologically relevant and easily administered to and accepted by children. The session also included two panel discussions, including one that brought together both originator and generic ARV manufacturers, where industry perspective was shared with the greater public.

There is currently a spectrum of issues in the development and distribution of ARVs for paediatric patients. From a procurement standpoint, a range of challenges have been identified that compromise the future of the paediatric ARV market. Importantly, the development of optimized antiretroviral regimens for HIV-infected children remains one of the key pillars of the World Health Organization’s (WHO’s) new Treatment 2.0 initiative. Importantly, the subject of research and development (R&D) into paediatric formulations is inadequately addressed, and a wide range of clinical research gaps associated with HIV-1 paediatric infection remains.



The session was co-chaired by Celia Christie-Samuels (University of the West Indies and member of the ILF Advisory Group) and Marc Cotton (Stellenbosch University and Tygerberg Hospital). Christie-Samuels welcomed participants to the satellite session and outlined the mission of the ILF, while highlighting its role and commitment to advancing the global research agenda on paediatric

HIV infection. Cotton followed by underscoring how the key to treatment after diagnosis is to proceed with the use of a formulation, outcome. He described some of the challenges in treating children, including storage issues and the phasing out of d4T. Cotton also noted that in nevirapine-exposed infants and children, lopinavir/ritonavir (LPV/r) is the drug of choice in his native South Africa, although indicating it is not particularly tolerable. Notably, the tablet formulation of LPV/r for older children is not a split tablet and is “difficult to swallow”. Before introducing the first speaker of the session, Cotton also commented on the challenge for TB-HIV co-infected paediatric patients and the associated obstacles in their clinical management.

Market dynamics of paediatric ARV formulations

Overview

By Joanna Sickler, CHAI



Joanna Sickler provided an overview of the market dynamics of paediatric ARVs, by highlighting the primary factors associated with supply risks and also expanding on some of the exciting developments in the field. When carefully examining the paediatric market over the course of the past six years, Sickler commented on the impressive increase in treatment coverage for both infants and children, with one in four treatment-eligible children receiving ARVs (Fig. 1). Furthermore, she pointed out that the increase is not just in terms of quantity, but also

in the quality of drugs that have become available to paediatric patients, which in turn has led to “better options” for this patient population.

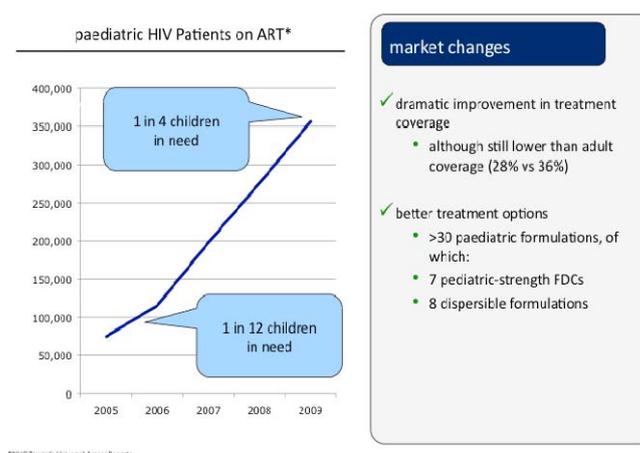


Figure 1. ARV treatment coverage

Despite “the good news” on treatment coverage, Sickler cautioned that there are persistent and serious challenges in paediatric HIV care, given the inherent nature of the market as both fragmented and small (~355,000 patients) relative to the adult market. In terms of what is currently procured, there are also more products for children with respect to the range of formulations and dosage (fragmented into subgroups by age and weight bands). In contrast, Sickler commented, adult procurement is effectively much more focused (Fig. 2). The slow transition to new products further fragments volumes, and products tend to be added and not removed at a country level. All these issues result in low volume orders by HIV national programmes, which Sickler described as the “crux of the challenge” for the paediatric ARV market. As a consequence, the size and the fragmented nature of this market make it inherently risky and difficult to sustain.

Adult Product Procurement	Paediatric Product Procurement
1. AZT 300 mg	1. AZT 50 mg/5 ml
2. AZT/3TC 300/150 mg	2. AZT 100 mg
3. AZT/3TC/NVP 300/150/200 mg	3. AZT/3TC 60/30 mg
	4. AZT/3TC/NVP 60/30/50 mg
	5. AZT 300 mg
	6. AZT/3TC 300/150 mg
	7. AZT/3TC/NVP 300/150/200 mg

Figure 2. Adult and paediatric product procurement

In response to low volume orders, Sickler discussed UNITAID and CHAI successfully pooling volumes as part of a coordinated effort, pointing out that this is a time-limited programme. There is currently a transition of the procurement responsibilities to the Global Fund by the end of 2012. Sickler added that positive mobilizations have taken place in recent months, and outlined the two major steps: the coordination of procurement, and product consolidation.

Countries and global stakeholders are partnering to ensure a smooth transition to new funders. In terms of coordinated procurement, the Global Fund approved Market Dynamics and Commodities Ad-hoc Committee (MDC) recommendations mandating coordination through a subset of procurement agents. Notably, the vast majority of paediatric programmes are also expected to transition to the Global Fund. In terms of product optimization, the Inter-agency Task Team is leading development of a global paediatric ARV formulary list now endorsed by Global Fund recommendations. Furthermore, there are “ongoing country-level efforts to consolidate formularies around newer products that provide adherence advantage”.

Sickler’s departing message underscored that the challenges, albeit notably significant, are not insurmountable in securing the future of the paediatric ARV market.

“Together we can secure the paediatric market and ensure paediatric HIV patients continue to be able to access optimal treatment options.”

Panel discussion on market dynamics

Panel moderator:

Shaffiq Essajee WHO

Panel participants:

Brenda Waning	UNITAID
Chewe Luo	UNICEF
Joanna Sickler	CHAI
Martin Auton	Global Fund
Nandita Sugandhi	CHAI
Angelina Namiba	Positively UK



Following Sickler’s overview, a panel discussion on the market dynamic issues for ARVs was moderated by a paediatric HIV expert, **Shaffiq Essajee** from WHO. The panel consisted of leading experts in global procurement of HIV paediatric ARV products. Essajee noted that “paediatric treatment is in peril”, and described how the current initiative towards elimination of vertical transmission of HIV does not consider treatment of HIV-infected infants and children. Recognizing the obvious need to terminate new cases of sexual transmission and mother to child transmission (MTCT) worldwide, he said that such efforts should not disregard the commitment to fund paediatric HIV treatment programmes. Essajee also emphasized that the paediatric field has to come up with “ways to do with less”, and called for FDC development that will result in less costly and simpler treatment regimens.

Brenda Waning, representing UNITAID, commented on her organization’s ongoing work with CHAI on paediatric procurement, and described the merit of this collaborative project. She underscored the challenge of countries’ small-volume orders, and commented on the impact of prevention of mother to child transmission (PMTCT) in eliminating paediatric HIV infection. Waning stressed that the procurement mechanisms of CHAI/UNITAID should be transitioned

strategically to the Global Fund, and also indicated that it has been relatively difficult to introduce new paediatric formulations outside the CHAI/UNITAID partnership.

Martin Auton, representing the Global Fund's Pharmaceutical Procurement Support Services, explained that his team has the task of sustaining the paediatric market by securing financing. He also described the Global Fund's ongoing work on ensuring adequate national programmatic capacities to sustain the supply of paediatric ARV products to patients, and its efforts to coordinate the ordering of ARVs.

Chewe Luo, senior advisor for HIV/AIDS at UNICEF, highlighted her organization's role in the paediatric ARV market, stating that "they buy for everybody". Luo argued that the absence of procurement guidance and standards at a country level results in the purchase of all types of formulations (unnecessarily). She also voiced UNICEF's concerns over how to deal with the component of paediatric treatment in the context of developing the MTCT elimination plan, referring to the "difficult negotiation about what we do with children". Underscoring the global community's greater focus on PMTCT and elimination, Luo cautioned that this approach has to be observed carefully by stakeholders.

Providing the insight of a provider, **Nandita Sugandhi**, currently responsible for HIV paediatric ARV drug optimization at CHAI, described her previous work as a paediatrician on the ground. Interestingly, Sugandhi commented that prescribers often do not think about how their decision making and prescribing practices can impact the global marketplace. There is currently no guidance/standard for what formulations should be prescribed (echoing Luo's earlier comments), but only for what regimen should be prescribed to patients. Sugandhi strongly emphasized the importance of having "a discussion with everyone in the room".

Angelina Namiba, representing the HIV charity organization, Positively UK, offered the unique perspective of a caregiver and a person living with HIV. Importantly, she spoke about the issue of parents and caregivers wanting better formulations for their HIV-infected children. Namiba also commented on how status disclosure to a child remains incredibly difficult and how it can have an impact on his/her adherence to ARV treatment. Furthermore, one of her key messages to the audience was the real fear that mothers and caregivers have over the impact that ARVs can have on child development.



When the floor was open to questions and comments, an audience member from Uganda voiced her concerns with the transitioning of UNITAID/CHAI procurement responsibilities to another

organization, given the strong and positive relationship between her country and CHAI. A paediatrician from South Africa indicated that stakeholders need to “get smarter”, and shared his concern over a disconnect between country-level guideline committees and stakeholders/normative agencies. In reference again to the UNITAID transition to the Global Fund, a representative from Roche Diagnostics cautioned that the cost would increase if a responsible partner were not involved in this process. A representative from Matrix Laboratories in India also expressed his concern about manufacturing, emphasizing that pooled procurement for children remains the only option, and that any other model “makes no sense”.

In addressing concerns over global procurement, Waning assured everyone that coordinated and careful steps are being taken to ensure a smooth and effective transition from UNITAID to the Global Fund. The emerging theme from the later discussion was how the transition can be made “least painful for manufacturers who are not making huge profits” and simultaneously does not affect patient access to needed formulations. Auton also commented that a procurement consortium will be established which will ensure that batch sizes are met.

Panel moderator Essajee posed the question to both Sugandhi and Luo of how one can communicate more effectively to national programmes and clinicians on the ground. Luo responded by stressing that the current global discourse does not connect with countries, and commented on countries not having experience to provide adequate and robust data to industry. Sugandhi, in bringing the panel discussion to a close by arguing that “this is a critical point for paediatrics”, offered an anecdote from Malawi, where the practice of splitting adult tablets was prevalent despite a memo having been issued to prescribe paediatric FDCs (but not reaching providers).

Developing child-appropriate formulations: what is in the research pipeline for paediatric ARVs?

Overview

By Elaine Abrams, Columbia University



Elaine Abrams, outlining the research issues related to the development of optimal paediatric FDCs, prefaced her talk by describing children’s dependence on caregivers in the context of receiving and adhering to ARVs. Furthermore, Abrams pointed to the unique challenges that are presented during adolescence, a period marked by rapid physical growth, organ maturation, and psychological development and individualization. She also noted that paediatric ARV formulations, although effective, are limited.

In setting the scene for what is currently in the R&D pipeline (Table 1), Abrams commented on how difficult it is to design drug studies for infants and

children. She also described the significant body of work underway to ensure that more antiretroviral drugs are available in paediatric populations. There are multiple paediatric pharmacokinetic (PK/safety) studies of ARVs underway through the IMPAACT network, including a study to determine efavirenz dosing for children under three years of age. Abrams indicated that Professor Di Gibb (from the UK's Medical Research Council) will initiate a study of lopinavir/ritonavir (LPV/r) sprinkles in Uganda, and also referred to the emerging data from research on darunavir for children. Ritonavir sprinkles, which are also under development, are urgently needed, according to Abrams. Raltegravir is "very exciting as a likely option" for paediatric treatment, with ongoing PK/safety studies underway, along with a paediatric formulation that is either chewable or in solution. Lastly, Abrams mentioned promising work around tenofovir tablets/powder, and the application for these formulations to the US Food and Drug Administration (FDA).

Drug/Formulation		Age
Efavirenz : open capsules with and without rifampin	PK , safety, pharmacogenetics	3 months - 3 years
Efavirenz oral solution and sprinkle	PK, safety	3 months - 6 years
Etravirene	PK and safety	2 months - 6 years 6 -18 years
Rilpiverine (TMC 278) Once daily	PK and safety in adolescents	
Lopinavir/ritonavir liquid and paediatric tabs	PK of WHO weight band dosing	Weight bands; 3 -25 kg
Lopinavir/ritonavir sprinkles	PK and safety	Trial to begin in Uganda: infants, young children
Atazanavir	PRINCE I & II	3 months - 8 years
Darunavir Requires boosting	PK, safety, efficacy	3 - 6 years 12 -18 years
Ritonavir sprinkles		Under development
Raltegravir Twice daily, no boosting	PK and safety	4 weeks - 19 years Paediatric formulations: chewable & solution
Dolutegravir: GSK1349572	PK and safety	6 weeks - 19 years Paediatric formulation in development
Elvitegravir Once daily, needs boosting	PK and safety	Adolescents; Paediatric development planned
Maraviroc CCR5 antagonist	PK and safety	2 - 18 years
Tenofovir powder		Application to US FDA 2 - 5 years
Tenofovir tablets 150 mg, 200 mg, 250 mg		Application to US FDA 2 - 12 years

Table

1. Paediatric-specific formulations currently in the pipeline (adapted from presenter's slides)

Abrams referred to the important work by the patient-driven Drugs for Neglected Diseases Initiative (DNDi). She commented the initiative's expansion of its portfolio to develop a first-line combination therapy for use in infants and children. In terms of medium-term priorities (stating that this is an area "near and dear to her heart"), Abrams noted that there is serious concern over children failing PI-based therapy. She made a call for the window of opportunity to make current adult options readily available for children in need of ARV treatment. Abrams concluded by highlighting the long-term priorities for paediatric ARV R&D (Table 2), and provided the attributes for an ideal formulation.

Once-daily dosing	Low toxicity profile
Age-weight appropriate, heat-stable formulations (sprinkles, dispersible tablets, breakable tablets)	Highly potent
Fixed-dosed combination	No drug-drug interactions
Low Cost	High genetic barrier

Table 2. Long-term priorities for paediatric ARV drugs

Panel discussion on research pipeline

Panel moderator:

Elaine Abrams Columbia University

Panel participants:

Anirudh Deshpande	Matrix Laboratories
Daniel Seekins	Bristol-Myers Squibb (BMS)
JA Gogtay	Cipla
Jim Rooney	Gilead Sciences
Sandra Lehrman	Merck
Michael Norton	Abbott Laboratories
Perry Mohammed	Janssen
Shailesh Pednekar	Ranbaxy
John Pottage	ViiV Healthcare

Following her insightful presentation, Abrams welcomed nine representatives from industry to a panel discussion. The distinctive panel consisted of both originator companies (US and European based) and three generic ARV manufactures from India. Each industry representative had the opportunity to give an overview of his or her company's ongoing research activities related to paediatric ARV formulations and to comment on some of the R&D issues raised by Abram.

Anirudh Deshpande from Matrix described how his company is currently involved in examining its portfolio to address future product pipeline. Matrix currently has nine drugs in its

paediatric portfolio, all of which have been approved by the US Food and Drug Administration (FDA) and WHO. In addition, Deshpande indicated that his company is actively developing three other products, all of which are dispersible and in combination.



Shailesh Pednekar from Ranbaxy commented on how paediatric formulations for HIV treatment is a small business area, and in response, his company has focused on prioritizing products for R&D. Pednekar also noted that Ranbaxy has some dispersible products in its portfolio.

Cipla's representative, **JA Gogtay**, underscored the need to be much more focused on how paediatric ARVs can move across all weightbands, for both regulatory approval and ultimate commercialization. Gogtay also spoke about his company's efforts to collaborate with and support its international partners, including WHO.

Michael Norton from Abbott commented on LPV/r and his company's approach to the paediatric HIV epidemic. The Abbott approach has been to provide extensive clinical trial support. Currently, Abbott is funding more than 20 paediatric HIV clinical trials. In addressing concerns over LPV/r palatability, Norton indicated that Abbott recognizes the limitations on tolerability associated with the current liquid LPV/r formulation. At the IAS 2011 Conference, Abbott announced that it is conducting development work exploring a potential LPV/r sprinkle formulation.

Perry Mohammed from Janssen described his company's current R&D efforts in HIV paediatrics (for both treatment-naïve and experienced patients) by highlighting three drugs

under development, including a second-generation NNRTI (25mg tablet under investigation) that is dispersible in water.

Dan Seekins from BMS (whose company is establishing doses for atazanavir and efavirenz in smaller children) highlighted the challenge of conducting quality pharmacokinetic studies in the US, given the limited number of paediatric patients. He also referred to the relative paucity of treatment options for small children, who are unable to take FDCs. With respect to what an ideal formulation for children may look like, Seekins noted that “liquids used to be the way to go”, and noted that the current trend is that “taste is everything”. In response, R&D efforts, he argued, should focus much more on dispersible formulations.

John Pottage, from ViiV Healthcare (a joint venture of GSK and Pfizer) described his company’s significant work around the development of integrase inhibitors, and commented on the company’s development of dispersible and granular formulations for younger paediatric patients in particular. Pottage also touched on ViiV’s interest in developing subcutaneous or muscular injections of ARV formulations (with a back-up integrase inhibitor) that can be longer acting.

Sandra Lehrman from Merck commented on her company’s collaborative work with Sharon Nachman (professor of paediatrics at Stony Brook University Medical Center), which has been looking at age-appropriate formulations, including the current tablets being marketed (e.g. raltegravir chewable tablets). Lehrman also noted how it takes a while to get to the youngest children, and explained that one needs to do pharmacodosing (“de-escalating”; safety studies first in older children, and then in infants). In addition, she emphasized that early infant diagnosis is critical since children should be treated earlier on in infection. Recognizing the challenge of treatment management (i.e., adherence), Lehrman said that it is important to “think outside the box”, and referred to the possibility of monthly injections of ARVs for children.

Jim Rooney from Gilead Sciences (and current ILF Industry Co-chair) highlighted his company’s active paediatric development programme for TDF, noting that this drug has been approved already in the US for use in adolescents. In June, Gilead submitted for approval in the US two different TDF formulations (sprinkle, reduced mass tablets) for the 2-12 year old age group. Rooney described how the sprinkle formulation requires a relatively large mass, and issues over storage and distribution present a challenge for resource-limited countries (although reduced mass tablets could provide an alternative option). Gilead has also submitted for approval of a sprinkle formulation and a reduced-dose tablet. Lastly, Rooney commented on the potential use of Gilead’s fixed-dose single-tablet “Quad” regimen of elvitegravir, GS 9350 (cobicistat), emtricitabine and tenofovir disoproxil fumarate.

During the question and answer period, there was reference to the need for a boost that is *not* ritonavir, given its recognized long-lasting lipid effects (coupled with its taste). There was particular excitement over ViiV's development of long-acting depot formulations, and the general push to a more active portfolio in HIV paediatrics by the company. Shirin Heidari from the IAS raised the question of how industry and non-industry stakeholders can work together early on more effectively to identify long-term priorities for developing a list of priority drugs that would prevent future market demands from facing similar challenges. Rooney referred to the experience of Gilead, which has collaborated with Merck and BMS, in developing Atripla, which has wide use in resource-limited settings. In addition, he noted the recent agreement with Janssen for darunavir.

Sandra Lehrman commented on a need to balance capacity and immediate priorities, particularly as children move past first-line regimens and require second-line options. Further to that point, John Pottage spoke of emerging data on parenterals and their potential role in more effective paediatric treatment. Daniel Seekins also referred to the collaborative work of BMS and Matrix, and commented about how companies are both exploring the future needs of paediatric patients and examining the supply needs of the current market. Notably, Anirudh Deshpande argued that we do have the capacity in place to improve paediatric formulations. In closing the panel discussion, Elaine Abrams emphasized that finding the right dose is "hard work", and that taste is not the only issue to consider in formulation development.

Closing remarks

Commenting that "children need us as adults", session Co-chair Celia Christie-Samuels summarized some of the points raised over the course of the satellite, including the challenges in getting an ideal formulation in the presence of a whole set of issues (i.e., taste, treatment simplification, PK dosing studies and age-appropriate formulations, and transition from syrup/granular to injectable). Marc Cotton summarized the highlights of the session and the panels. Cotton argued that ongoing communication is critical to advancing the research agenda, and commended the ILF and its partners for fostering this very important conversation.

About the ILF

The Industry Liaison Forum (ILF) is an initiative of the International AIDS Society (IAS) that brings together industry, independent investigators, non-governmental organizations, foundations and other stakeholders to enhance HIV treatment access and outcomes in resource-limited settings, with a particular focus on the role and responsibilities of industry. The ILF provides the unique platform that allows industry to engage, communicate and collaborate with other stakeholders to enhance HIV research, and thereby promote evidence-based health policy and health delivery in resource-limited settings.

The ILF fulfils its mission by: identifying research gaps; promoting targeted research; identifying challenges and best practices; analyzing available data and evidence; disseminating information; consulting and convening stakeholders; providing industry expertise; and supporting capacity building for research and health delivery.

As part of its new Strategic Plan (2012-2014), the ILF is committed to focusing on scientific, ethical and policy issues related to HIV research for women and children by identifying research gaps in this area.

For more information regarding ILF activities, please visit our website at <http://www.iasociety.org/ilf.aspx>, or follow us on Facebook & Twitter:



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