Prevention of vertical transmission and beyond:
How to identify, enrol and retain children in treatment programmes in resource-limited settings

MEETING REPORT

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

INDUSTRY LIAISON FORUM
Linking Experts in HIV Research

INTRODUCTION

In June 2010, the Executive Directors of UNICEF and UNAIDS, the Director-General of the World Health Organization (WHO) and the Director of The United States President's Emergency Plan for AIDS Relief (PEPFAR) committed to work towards eliminating mother -to -child transmission of HIV by 2015. The political will to eliminate vertical HIV transmission by 2015 is welcome, but numerous practical hurdles to reach this goal remain. In the lead up to the XIX International AIDS Conference (AIDS 2012) in Washington, DC, UNAIDS launched a report entitled *Together we will end AIDS,* which provides the latest epidemiological data on HIV infections worldwide. This report highlights the growing and sobering gap: it estimates that by the end of 2011, only 57% of pregnant women living with HIV in low- and middle-income countries received effective prevention of mother to child transmission (PMTCT) services, and less than half of exposed infants had access to infant prophylaxis. Children with HIV also lag behind in treatment, with approximately a quarter of the children in need of ART receiving treatment by the end of 2011 compared with a nearly 57% coverage rate for adults.

As convener of the world's largest international conference on HIV research, the International AIDS Society (IAS) has long prioritized the needs of children living with HIV, particularly those in resource-limited countries. In 2010, 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. Eleven of those recommendations call for more investment in clinical and operational research related to PMTCT and the unique needs of paediatric HIV care and treatment.

At AIDS 2012, the IAS-ILF, with UNICEF and Management Sciences for Health (MSH), jointly organized a public satellite session as part of its efforts to promote and accelerate HIV research related to infants and children. Going beyond the recognized challenges in eliminating paediatric HIV, this session highlighted the practical options currently available to optimize prenatal/neonatal prophylaxis, postnatal case finding, and ways to improve antiretroviral treatment access for children infected with HIV, including presentation of a list of preferred ARV formulations for children developed by the Inter-Agency Task Team (IATT).

The session was co-chaired by Nick Hellman (Elizabeth Glaser Pediatric AIDS Foundation and member of IAS-ILF Advisory Group) and Rene Ekpini (UNICEF). Ekpini described the poor state of treatment coverage in children living with HIV as "unacceptable" as treatment scale up for adults exceeds the pace for infants and children in resource-limited settings. Hellman provided an overview of the IAS-ILF's mission, highlighting its work in raising awareness of the research gaps in clinical and operational research for children living with HIV.

Beyond Option B: discussion of B+ and other alternatives to prenatal and neonatal prophylaxis

Erik Schouten, *Principal Technical Advisor for HIV, Management Sciences for Health (MSH)*

Erick Schouten, as one of the primary architects of Option B+ in Malawi, presented an overview of this new public health strategy regarding PMTCT. Under Option B+, HIV-infected pregnant women receive lifelong triple ARV treatment, irrespective of their CD4 levels. Since WHO issued its *Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants*[1] in 2009, questions have emerged over whether PMTCT scale up is sufficient without the need for CD4 count testing. However, CD4 count testing is a "major bottleneck": an estimated 70% of women attending antenatal care sites do not have access to reliable CD4 tests. Malawi, a country with constrained capacity and limited resources, has responded by opting to rely only on a positive serological result. The rationale for Option B+ was published in *The Lancet* last year[2].

Schouten outlined the additional benefits of Option B+, including: improvement in maternal health; making breastfeeding safe; avoiding the start/stop approach to HIV treatment; reducing HIV sexual transmission risk; and reducing TB incidence. Describing Option B+ as "the only realistic option" for the elimination of vertical transmission in resource-limited settings, he noted how implementation will be central to its success. Schouten outlined some of the key implementation elements, including buy in from all stakeholders, forecasting who would need to start ART, costing, developing guidelines, and monitoring and evaluation (M&E) tools. Implementation of Option B+ began in Malawi in July 2011, with 3,366 health workers being trained. By March 2012, more than 528 sites had implemented the strategy across the country and the impact on increasing ART coverage in pregnant and breastfeeding women has been significant (Figure 1). Furthermore, the harmonization of PMTCT and ART programmes is imperative.

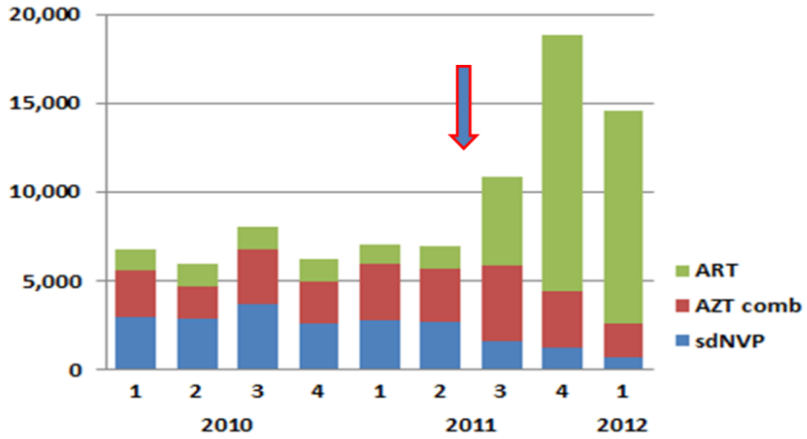

Figure 1. Change in type of ARV regimen for PMTCT provided to pregnant/breastfeeding women before and after the mid-2011 Option B+ implementation in Malawi

[1] World Health Organization. *Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants.* Publication date: November 2009.

[2] Schouten EJ, Jahn A, Midiani D, *et al*. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. *Lancet*. 2011 Jul 16;378(9787):282-4.

In closing, Schouten recognized some of the key challenges in rolling out Option B+, including the implications for scaling up treatment. Identifying mothers, identifying exposed/infected infants and children, and acceptance of ART also remain critical elements to the success of Option B+. Notably, he commented on how immunization clinics can be key entry points for identifying infants, and argued for elasticity in health systems. In his parting thoughts, Schouten described Option B+ as a "game changer", but "not a silver bullet".

Strategies for identifying HIV-exposed infants

***Angela Mushavi**, National PMTCT and Paediatric HIV/AIDS Care & Treatment Coordinator at the Ministry of Health and Child Welfare, Zimbabwe*

Angela Mushavi provided an overview of the challenges associated with identifying HIV-exposed infants and ensuring early diagnosis of those who are infected. Given the aggressive pathogenesis of HIV infection in newborns, Mushavi noted that in the absence of treatment, almost half of children die in the first two years of life, and the majority of those deaths occur in the first six months. Consequently, an early HIV diagnosis, coupled with early ART initiation, is critical. WHO currently recommends HIV testing for "all infants with unknown or uncertain HIV exposure being seen in health-care facilities at or around birth, at the first postnatal visit (usually 4-6 weeks), or other child health visit"[3]. Furthermore, the use of HIV virological assays is recommended for diagnostic testing at four to six weeks of age or at the earliest opportunity thereafter in exposed infants.

Mushavi outlined the range of techniques to assess HIV exposure status, including the maternal hand-held antenatal card and the maternal PMTCT status codes on a child's health card. Children should be screened at all entry points, including well-baby under-five clinics, malnutrition clinics, expanded programme on immunization (EPI) clinics, and adult ART/TB clinics. Data presented from Zimbabwe showed that 69% of tested infants were identified through well-baby under-five (U5) clinics[4]. Mushavi also highlighted a study from a Médecins Sans Frontières (MSF) programme in Bulawayo, demonstrating the impact of mentor mothers on other mothers, which resulted in an increase in HIV testing of infants[5].

When examining the PMTCT cascade, there is a significant gap between the number of positive infant HIV PCR test results at the laboratory and the number of such results that are received by the mother or caregiver, resulting in an estimated 51% of infants not completing this cascade stage. Mushavi spoke about the issue of long turnaround times for HIV PCR tests, but indicated ways of expediting the receipt of testing results. For example, Malawi has been using mobile phone technology to provide SMS reminders to caregivers for test results, which has been associated with a significant reduction in turnaround time (Figure 2). In closing, Mushavi called for newer technologies in point-of-care diagnostics, and emphasized how early infant diagnosis (EID) must be fully linked to HIV care and treatment for children.

[3] World Health Organization. *Antiretroviral therapy for HIV infection in infants and children: Towards universal access. Recommendations for a public health approach*: 2010 revision
[4] Courtesy of Clinton Health Access Initiative (CHAI)
[5] Courtesy of Médecins Sans Frontières (MSF)

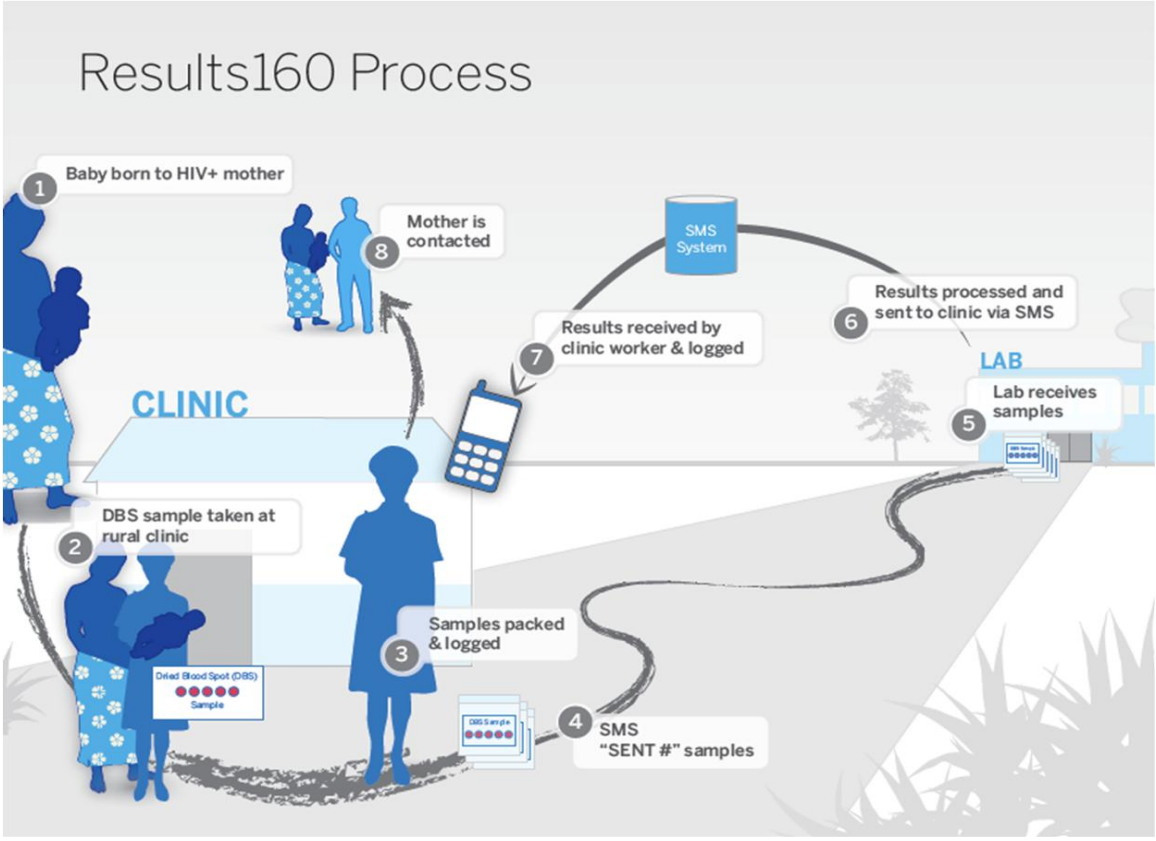

Figure 2. Use of mobile technology to reduce turnaround-time for PCR results in Malawi (courtesy of UNICEF Malawi)

Retention of children in HIV treatment and care programmes

Dorothy Mbori-Ngacha, *Senior HIV Specialist at UNICEF*

Dorothy Mbori-Ngacha provided an overview of children's enrolment and retention in HIV treatment and care programmes. Mbori-Ngacha first commented on the challenges of retaining pregnant women in care, particularly younger women, as evidenced by a Columbia University study (Figure 3). In addition, she said that there is minimal discussion over the lack of retention of non-pregnant women, and underscored the critical importance of retention of women in programmes as the momentum around Option B+ grows.

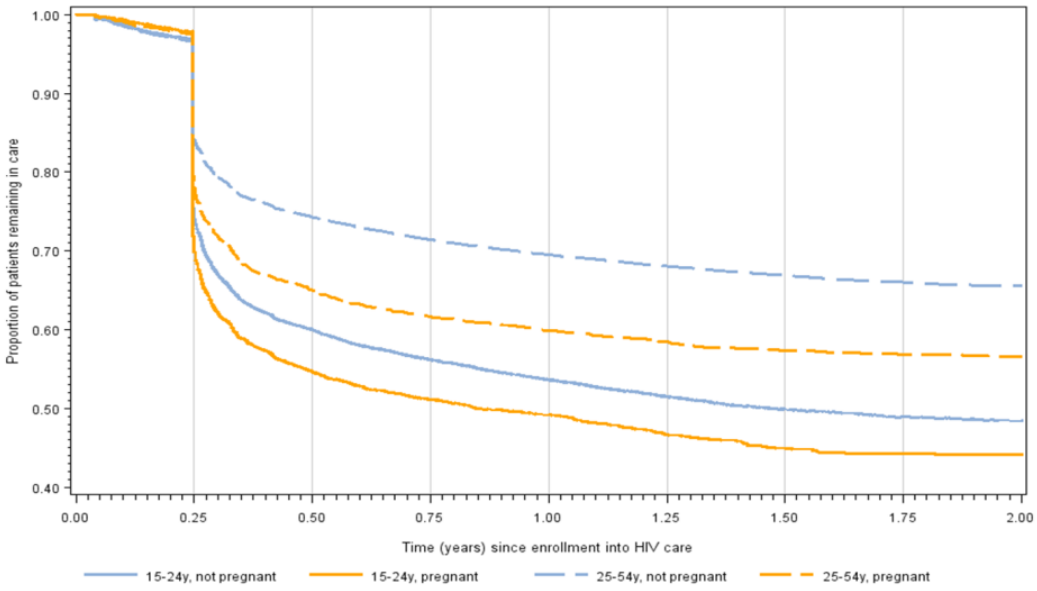

Figure 3. Pregnant women have worse rates of retention in HIV care than non-pregnant women in the same age group, and young pregnant women have the worst retention rate[6]

Mbori-Ngacha noted that HIV DNA PCR assays are particularly expensive (estimated at US$50 per test). Despite extensive testing in various countries, children are not being adequately enrolled and retained in treatment and care programmes, resulting in a poor return on investment. Alarmingly, an estimated 53% of children in the HIV paediatric care cascade are lost to follow up. Attrition from HIV treatment programmes is a phenomenon that extends beyond Africa. In Asia, the probability of loss to follow up of children on ARV treatment is estimated at approximately 15.1%, although rates are lower than those in Africa: west Africa's rate is 37.2%, east Africa's is 27.6%, and southern Africa's is 29.4%[7]. The effect of age on retention is also a key predictor, with younger children being more vulnerable to loss to follow up. Mbori-Ngacha argued that we should invest in promoting the retention of the youngest children (<2 years of age) and adolescents.

Limited research has been conducted to understand the underlying reasons for loss to follow up in children. More recently, Braitstein and colleagues identified some of the key factors in an HIV treatment programme in western Kenya, which included disclosure/fear of discrimination, death, transfer to another clinic, and transportation costs[8]. Mbori-Ngacha commented on the issue of faith healing in such countries as Zimbabwe, and underscored the need to understand cultural practices. As knowledge of best practices around retention in HIV care and treatment is growing (Figure 4), she encouraged the documentation of what works in the field. Community health volunteers have been shown to dramatically reduce loss to follow up (69% reduction) in Uganda. Other interventions have included transport vouchers, patient advocates, training providers and the use of mobile phones. Lastly, Mbori-Ngacha called for innovation and to "think outside the box" in order to maximize retention rates across paediatric programmes.

[6] ICAP study (Columbia University)
[7] V Leroy, et al AIDS 2010: XVIII International AIDS Conference: Abstract no. MOAB0202
[8] P Braitstein et al. JAIDS 2011

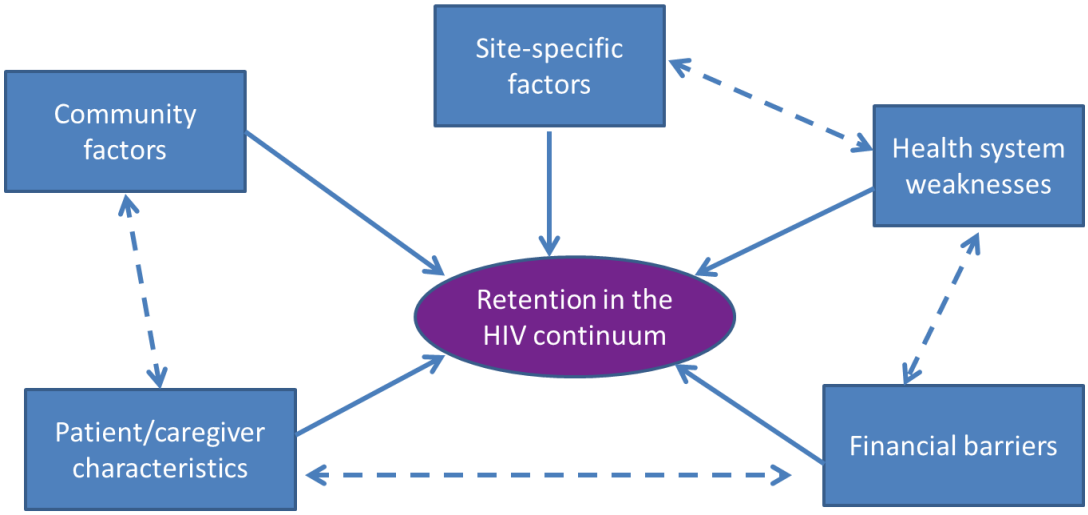

Figure 4. Factors affecting HIV care and treatment retention rates (adapted from WHO, 2011)

Optimizing paediatric ARV formulations: presentation of IATT optimized list of paediatric ARV formulations

***Nandita Sugandhi**, Clinical Advisor at the Clinton Health Access Initiative (CHAI)*

Nandita Sugandhi offered an overview of the complex challenges in "optimizing" paediatric ARV formulations. Despite an estimated half a million HIV-infected children receiving ARV treatment worldwide, coverage rates in children lag behind those of adults (Figure 5). Although the number of regimen options is low in resource-limited countries (e.g., only nine drugs are currently available in such settings), there has been a significant increase in the number of new paediatric formulations (e.g., dosage forms and strengths, and fixed-dose combinations). Countries are currently procuring 36 ARV formulations that are available.

Although WHO provides guidance on regimens, there are no recommendations on what formulations are preferable, and the proliferation of product choices over recent years has led to a "fragmented" market for paediatric ARV products. National programmes have not fully transitioned to procuring newer products, which has resulted in small paediatric drug procurement volumes distributed across too many products to be sustainable in the long term. From a clinician's standpoint, Sugandhi commented that the current portfolio of 36 formulary products does enable more individually tailored regimens, but further increases market fragmentation. The need to have separate formulations for differing weight bands and dose ranges in younger children also increases market fragmentation.

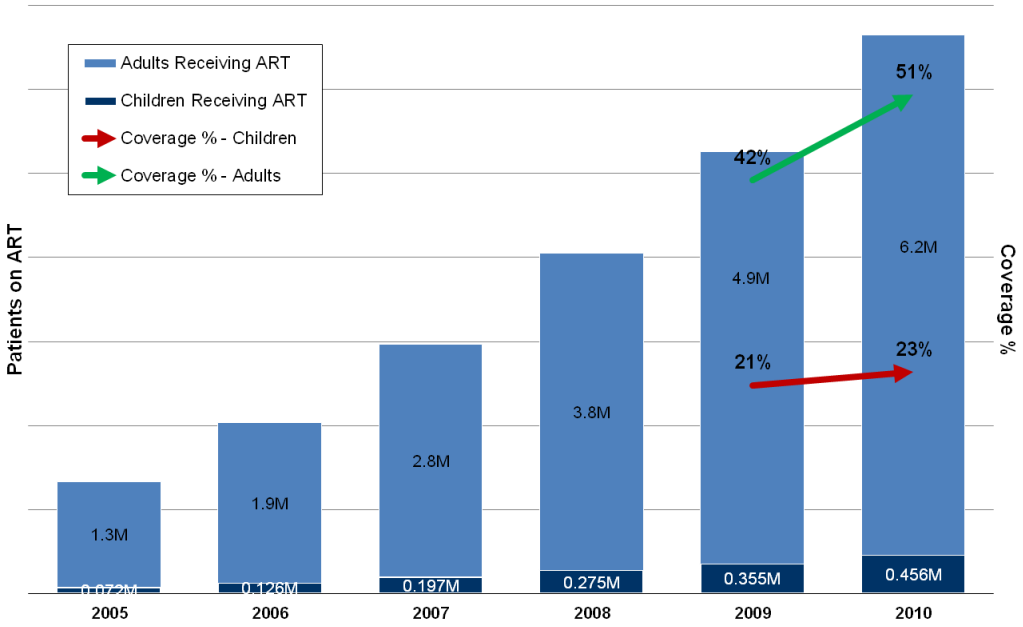

Figure 5. A dramatic scale up of children on ART has been achieved with improved treatment options introduced over the past five years. Paediatric scale up coverage is still half that of adults

In terms of the formulations being procured, Sugandhi noted that some countries are involved in uncoordinated transitions from syrups to other formulations. Importantly, as drug manufacturing is "not an overnight process", manufacturers have to meet a minimum batch requirement prior to actually producing the formulations. Sugandhi described one successful mechanism to meet such minimum batch sizes through pooled procurement, as coordinated by CHAI/UNITAID in recent years.

CHAI, as a member of the Inter-Agency Task Team (IATT), has sought to support a process of consolidating the current list of available ARV paediatric formulary products being procured by countries. This concept, nonetheless, is not new: WHO's Essential Medicines List has employed a similar approach. Sugandhi spoke about the issue of balancing the public health approach (e.g., addressing coverage and minimizing fragmented markets) versus ensuring choice for optimal treatment to the individual patient (e.g., focusing on child-appropriate FDCs that would meet the needs of all children).

On 23 April 2012, the IATT released a condensed paediatric ARV formulation list broken down into three categories: *optimal*, *for limited use*, and *non-essential*[9]. In outlining the process of developing this condensed list of 14 optimal formulations (down from a total of 43 formulations) by the IATT paediatric working group, Sugandhi described the criteria used, which included: a) the need to meet WHO standards; b) formulations already approved for use; c) easy for patients/health care workers (HCWs) to use; and d) cater for needs for children across all ages. The 14 products recommended as *optimal* paediatric ARV products (green) also cover the recommended WHO regimens across all weight bands (including two syrups for PMTCT) (Table 1).

[9] WHO Inter-Agency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children. Report of the Meeting of the Paediatric Working Group Developing an Optimized List of Paediatric ARV Formulations. Meeting Report. Geneva, Switzerland; May 5, 2011

IATT Optimal, For Limited Use and Non-Essential Pediatric Antiretrovirals

Item	Formulation	Dose(s)
Optimal		
ABC	Tablet (dispersible, scored)	60mg
ABC+3TC	Tablet (dispersible, scored)	30+60mg
ddI	Capsule (unbuffered, enteric coated)	125mg, 200mg
ddI	Tablet (buffered, chewable, dispersible)	25mg
EFV	Tablet (scored)	200mg
AZT+3TC+NVP	Tablet (dispersible, scored)	60+30+50mg
AZT+3TC	Tablet (dispersible, scored)	60+30mg
d4T+3TC+NVP	Tablet (dispersible, scored)	6+30+50mg
d4T+3TC	Tablet (dispersible, scored)	6+30mg
LPV/r	***Oral liquid****	***80+20mg/ml***
LPV/r	Tablet (heat stable)	100+25mg
NVP	Tablet (dispersible, scored)	50mg
NVP	Oral liquid**	50mg/5ml
AZT	Oral liquid**	50mg/5ml
LimitedUse		
ABC	Oral liquid	100mg/5ml
ATV	Solid oral dosage form	100mg, 150mg
DRV	Oral liquid	500mg/5ml
DRV	Tablet	75mg, 150mg
ddI	Powder for oral liquid*	2g, 4g bottle
3TC	Oral liquid	50mg/5ml
RTV	Oral liquid*	400mg/5ml
RTV	Tablet (heat stable)	100mg
d4T	Powder for oral liquid*	5mg/5ml

** Requires cold chain (2-8*C) for transport and/or storage and is not adapted for resource limited settings where refrigeration may not be accessible.*
*** Use should be reserved for PMTCT ONLY.*

Table 1

Sugandhi also underscored how this list can serve as a model for countries to examine their own procurement practices. In addition, she emphasized that some limited-use formulations were included as there are cases that will require special treatment.

The next steps include national-level adoption of this formulary list (Poster THPE704), which can effectively guide procurement, and the development of a standardized toolkit to assist national programmes in rationalizing their choice of products. In terms of a revision process, the IATT will include new products (e.g., LPV/r sprinkles), be adaptive to new treatment recommendations due to be released next year, and consider the evolving epidemic and programme needs. In light of Treatment 2.0 for children, optimal formulation development has to account for sustainable access to paediatric ARVs as scale up expands. Sugandhi called for creating a stable environment for further research and product development, which will ultimately translate into better treatment outcomes for children living with HIV.

PANEL DISCUSSION

Panel moderator:
Scott Kellerman Global Technical Lead for HIV, MSH (USA)

Panel participants:

Erik Schouten	Malawi
Angela Mushavi	Zimbabwe
Dorothy Mbori-Ngacha	South Africa
Pope Kosalaraska	Thailand
Mohammed Mahdi	Swaziland

Following the insightful presentations, **Scott Kellerman** from MSH moderated a panel discussion that included all four speakers and two additional representatives, Pope Kosalaraska (Thailand) and Mohammed Mahdi (Swaziland).

From identification to retention: what can we do better?

In addressing EID, **Angela Mushavi** highlighted the multiple entry points for capturing infants. She also spoke about the issue of mortality in children (particularly in young children under two years of age who do not receive ART), and commented on underlying malnutrition, which is a significant predictor of mortality. Mushavi also described how Zimbabwe has been addressing the issue of malnutrition in HIV-infected children more aggressively.

In Thailand's experience with PMTCT, **Pope Kosalaraska**, a paediatrician and Associate Professor at Khon Kaen University (Thailand), commented on how his country's experience has differed in some respects from the African context, but indicated that most HIV-infected pregnant women are identified in antenatal clinics, as is the case in Africa. Of note, Thailand has currently implemented Option B for PMTCT. **Mohammed Mahdi**, Country Director at EGPAF Swaziland, described the challenges for EID in Swaziland, particularly as most mothers often do not come back to receive the infant HIV PCR testing results. There are also questions among providers, according to Mahdi, about when to initiate ARV treatment in children. Notably, in a small pilot project, testing sites have started working with community-based organizations to identify and inform women who had infants tested for HIV, but did not return to obtain their results.

Regarding Option B+, **Erik Schouten** noted that longitudinal clinical monitoring for women on treatment takes place in ANC clinics. Schouten also commented on how Malawi is currently conducting a cohort analysis to examine retention of pregnant women following introduction of Option B+. This analysis will hopefully identify the elements that support adherence and retention, and factors that prevent women from coming back, both critical to the success of Option B+.

Nandita Sugandhi described the example of Malawi, where a review of UNITAID orders revealed that 23 different paediatric products were being procured. Consequently, CHAI/UNITAID held a meeting with clinicians, Malawi's Ministry of Health and pharmacists in order to better understand their experience in using paediatric formulations. Following systematic examination, it became apparent that many patients are

prescribed FDCs, and it was not necessary to procure many other products. For example, Malawi has been phasing out d4T, but has been continuing to procure FDCs with d4T.

Kellerman asked panelists how to increase retention in care. **Dorothy Mbori-Ngacha** noted that community involvement significantly enhances retention, although engaging community actors is often outside the comfort zone of providers and treatment programme implementers. **Angela Mushavi** emphasized that stigma remains a barrier to retention, and reiterated the added value of mentor mothers and village health workers to bring women into care ("we have to stop being health facility focused, but work with community").

Who is ready for Option B+?

Mahdi commented that Swaziland has started discussing the transition to implementing Option B+, and emphasized that the approach will have to engage all players in the country. Concurrently, Swaziland is trying to assess where it stands with Option A, and it will attempt to pilot Option B+ in selected sites. Mahdi noted that WHO can use some of this pilot evidence to support other countries as they consider transitioning to Option B+. **Kosalaraska** stated that Thailand has implemented Option B, with reliable CD4 testing in place. As such, changing PMTCT policies will be difficult in his country. **Mushavi** explained that Zimbabwe has an adaptation committee consisting of different stakeholders (clinicians, funders) to assess whether Option B+ can be sustained.

Offering institutional perspectives on the topic, **Mbori-Ngacha** mentioned how the "train is moving" and noted that it is important to have conversations at a country level about the relevance and capacity to implement Option B+. Although such countries as Swaziland are doing well under Option A, Option B+ may be important to also reduce incident infection (the *treatment as prevention* impact). **Sugandhi** indicated that Option B+ may be more viable for some countries, especially as the cost of ARV drugs is reduced over the coming years. **Schouten** underscored the need for good preparation (as was the case in Malawi's experience), especially as key policy makers, funders, the Global Fund and other key stakeholders must be convinced. He also reminded the audience that drug procurement is a process that takes up to nine months.

In closing, the panel agreed that global and local actors need to enhance the PMTCT and treatment cascade efficiency. With Option B+, there was the recognition that there is yet another tool in the arsenal. However, there was a collective sense, as pronounced by Sugandhi, that despite our best possible efforts to prevent vertical transmission, children who still become infected will require the most optimal treatment choices.

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.

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