Meeting Report

Beyond Option B+

A Satellite Session at IAS 2013, Kuala Lumpur, Malaysia
1 July 2013

Organized by the International AIDS Society’s Industry Liaison Forum and UNICEF
Acknowledgements

This report is the result of an official satellite event organized by the International AIDS Society’s Industry Liaison Forum (IAS-ILF) and UNICEF at the 7th IAS International Conference on HIV Pathogenesis, Treatment and Prevention, held 30 June to 3 July 2013 in Kuala Lumpur, Malaysia. The IAS-ILF would particularly like to thank Craig McClure (UNICEF), Chewe Luo (UNICEF), the experts and key informants that graciously provided their time and insight and Rodney Kort for leading the writing of this report.

IAS-ILF Secretariat
Bertrand Audoin
Bernard Kadasia
Shirin Heidari
Sébastien Morin
Carina Sorensen
Rodney Kort
Janette Bennett
International AIDS Society, Switzerland
International AIDS Society, Switzerland
International AIDS Society, Switzerland
International AIDS Society, Switzerland
Consultant, Canada
Copy Editor, South Africa

IAS-ILF Advisory Group
Anita Silva
Boris Renjifo
Catherine Hankins
Celia DC Christie-Samuels
Cheryl Smith
Elly Kataebra
Heidi Nass
Jim Rooney
Joel Gallant
Linda-Gail Bekker
Luc Denys
Michael Rabbow
Nicholas Hellmann
Perry Mohammed
Rahab Mwaniki
Sandra Nusinoff Lehrman
Scott Purdon
Roche Molecular Diagnostics, USA
AbbVie, USA
Amsterdam Institute for Global Health and Development, The Netherlands
University of the West Indies, Jamaica
Burkina Foundation, USA
Makerere Medical School, Uganda
AIDS Treatment Activists Coalition, USA
Gilead Sciences, USA
John Hopkins University, USA
Desmond Tutu HIV Foundation, South Africa
Janssen/Tibotec, Belgium
Boehringer Ingelheim, Germany
Elizabeth Glaser Pediatric AIDS Foundation, USA
Janssen/Tibotec, UK
National Empowerment Network of People Living with HIV/AIDS, Kenya
Merck, USA
ViiV Healthcare, UK

Support
The IAS-ILF is grateful for the support received from AbbVie, Boehringer Ingelheim, Gilead Sciences, Janssen, Merck, Roche and ViiV Healthcare.

Copyright
International AIDS Society, Switzerland

Produced by
International AIDS Society
Avenue de France 23
CH-1202 Geneva
Switzerland
Tel: +41 22 710 08 00
Fax: +41 22 710 08 99
info@iasociety.org
www.iasociety.org

Photo disclaimer: The photographs used in this publication are for illustrative purposes only; they do not imply HIV status, or any particular attitudes, behaviors, or actions on the part of any person who appears in the photographs.

Beyond Option B+
http://www.iasociety.org/ilf.aspx
Craig McClure welcomed participants to the session, noting that new WHO guidelines regarding the use of antiretrovirals (ARVs) to treat and prevent HIV infection include a number of new recommendations that will be discussed in this session, including offering all HIV-infected pregnant women lifelong antiretroviral therapy (ART), regardless of CD4 count (“Option B+”), and treating all children under the age of five, regardless of CD4 count. He noted the need to identify HIV-positive children early and link them to care, as well as the need to follow HIV-exposed and uninfected children, who we now know have poorer health outcomes compared with their HIV- and ARV-unexposed peers. He noted that there are a number of initiatives aimed at addressing a range of issues in maternal and paediatric diagnosis, care and treatment.

Elaine J Abrams highlighted important new recommendations from the WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, along with 2012 data from the WHO Treatment Update (see below, as well as Figures 1 and 2):

- ART is now recommended for all adults and adolescents who have CD4 counts of ≤500/mm$^3$ (prioritizing those who have counts of ≤350/mm$^3$).
- The guidelines no longer recommend “Option A” (ARV prophylaxis during pregnancy, delivery and breastfeeding to prevent vertical transmission) for pregnant or breastfeeding women.
- Option B (or B+) is now recommended for pregnant or breastfeeding women, with the decision regarding which approach to adopt to be made at the national level.
- All children below five years of age are recommended for ART initiation, regardless of CD4 count or WHO clinical staging.
- ART should be initiated in all children five years of age and older with a CD4 count of ≤500/mm$^3$.

She also noted the recommended first-line ARV regimens for children younger than three years (preferably with a lopinavir/ritonavir [LPV/r]-based regimen) independent of maternal ARV exposure, and for children three years of age and older (with efavirenz [EFV] as the preferred non-nucleoside reverse transcriptase inhibitor [NNRTI] for first-line treatment).

3. Option B: For women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of vertical transmission risk has ceased; Option B+ retains women on lifelong ART irrespective of CD4 count.
WHO 2013 ART Guidelines

When to Start: Pregnant & Breastfeeding Women

All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART

*strong recommendation, moderate-quality evidence*

For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment

*conditional recommendation, low-quality evidence*

In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased

*conditional recommendation, low-quality evidence*

---

Figure 1. WHO 2013 ART Guidelines – When to Start: Pregnant & Breastfeeding Women (Abrams EJ, Towards an AIDS-free Generation. IAS 2013, Kuala Lumpur, Malaysia)

WHO 2013 ART Guidelines

When to Start: Children

ART should be initiated in all children infected with HIV below five years of age, regardless of CD4 count or WHO clinical stage

- Infants diagnosed in the first year of life
  *(strong recommendation, moderate-quality evidence)*

- Children infected with HIV between one and below five years of age
  *(conditional recommendation, very low-quality evidence)*

ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≤500 cells/mm³, regardless of WHO clinical stage

- CD4 count ≤350 cells/mm³
  *(strong recommendation, moderate-quality evidence).*

- CD4 count between 350 and 500 cells/mm³
  *(conditional recommendation, very low-quality evidence).*

---

Figure 2. WHO 2013 ART Guidelines – When to Start: Children (Abrams EJ, Towards an AIDS-free Generation. IAS 2013, Kuala Lumpur, Malaysia)
Progress data on the Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive: 2011 – 2015\(^4\) included an estimated 800,000 paediatric infections prevented between 2005 and 2012 and a sharp increase in the number of pregnant women receiving ARVs for prevention of mother-to-child transmission (PMTCT), from 14% coverage in 2005 to 65% coverage in 2012.\(^5\) The number of new paediatric infections decreased from 330,000\(^6\) in 2011 to 290,000 in 2012. The estimated vertical transmission rate in 2012 was 17%, which represents important progress, although meeting the 2015 Global Plan\(^4\) target of 5% will require even more rapid scale-up efforts. However, not all countries are scaling up at the same rate. Figure 3 highlights key data from the progress report.

Option B+ was first implemented successfully by Malawi, and resulted in a rapid scale up in the number and proportion of pregnant or breastfeeding women initiating ART. A growing number of countries are planning or implementing Option B or B+ (see Figure 4). However, there remains a persistent and widening gap in ART access between children under 15 years of age (with 34% ART coverage in the 22 priority countries) and adults (with 63% coverage in the 22 priority countries). Post-natal PMTCT follow up is weak; access to early infant diagnosis (EID) testing and delays within the EID cascade are also resulting in missed opportunities to identify HIV-positive children at key health system entry points. While overall access to health sector interventions is improving for paediatric populations, there is significant variability between countries and retention in the cascade of care remains a major challenge. Abrams presented data from a number of countries indicating that while children were enrolling at younger ages than in previous years, many are not diagnosed until they present at clinics with significant HIV disease progression.

There is also a growing population of HIV-infected adolescents who are “falling between the cracks” of paediatric and adult programmes and are particularly vulnerable to loss to follow up (LTFU). Of particular concern are the psychosocial needs of adolescent populations. She noted that the increasing number of countries adopting Option B+ provides significant operational advantages and opportunities compared with previous approaches, along with the push to harmonization of regimens for adults and paediatrics. However, capitalizing on them will require renewed efforts to address LTFU at several points in the cascade of care and adequately resourced health systems to ensure retention in care. She encouraged innovation in EID and the rapid expansion of HIV diagnostic testing to ensure HIV-infected children are diagnosed and linked to care as early as possible.


Progress towards EMTCT Targets 2009 to 2012, 21 priority countries

UNAIDS 2013 Progress Report on the Global Plan

Figure 3. Progress Towards Elimination of Mother-to-Child Transmission (EMTCT) Targets: 2009 to 2012, 21 priority countries (Abrams EJ, Towards an AIDS-free Generation. IAS 2013, Kuala Lumpur, Malaysia)

PMTCT Approaches by Country, June 2013

*Piloting testing feasibility and acceptability of Option B+ in select regions; **Implementing Option A and B; ***National policy is Option B but not yet implementing
Implementation of new regimen (either Option B or B+) in select regions or nationally where implementation defined as: 1) sites selected; 2) staff training completed; 3) ART regimens available at site and supply chain management system in place.
Source: WHO, UNICEF, UNAIDS Global Update on HIV Treatment: Results, Impact and Opportunities, 2013 and IATT Secretariat

Figure 4. PMTCT Approaches by Country, June 2013 (Abrams EJ. Towards an AIDS-free Generation. IAS 2013, Kuala Lumpur, Malaysia)
Panel 1: Option B+, is it really simpler?

**Moderator:** Chewe Luo, UNICEF, USA

**Panellists:**
- Marc Lallemant, DNDi, Switzerland
- Moono Nyambe, GNP+, Zambia
- Nathan Shaffer, WHO, Switzerland
- Appolinaire Tiam, EGPAF, Lesotho

Craig McClure noted that some of the challenges on the road ahead will be addressed by two panels addressing two aspects of the elimination of mother-to-child transmission (EMTCT) and paediatric diagnosis, care, treatment and support. He noted that the increasing decentralization of HIV services and the engagement of communities and community systems are helping accelerate progress on targets in the Global Plan.

Chewe Luo noted the important progress outlined in Elaine J Abrams’ presentation, as well as the need for innovation as countries move increasingly to decentralized approaches in delivering HIV services. Thirteen countries are moving to Option B+ and, as services are decentralized, new challenges will emerge. The Inter-Agency Task Team (IATT), co-ordinated jointly by UNICEF and WHO, has developed a toolkit to support decision making at the national level regarding strategies for preventing paediatric infections, improving maternal health and ensuring that both mothers and children are retained in care. She invited panellists to comment on the evidence base for the new recommendations on lifelong ART for pregnant women, as well as their implications for the future of HIV care and treatment programmes.

Marc Lallemant indicated that there have been no clinical trials directly comparing Option A, Option B and Option B+. He noted that there is compelling evidence that ART initiated before conception is effective in reducing vertical transmission, and we know that Option A is much less permissive than Option B or B+ in terms of risk of transmission. In terms of maternal health, treating at CD4 counts below 500 cells/mm$^3$ is clinically beneficial, but we must be conscious of both the risks and benefits of adopting the new guidelines in terms of drug resistance, long-term physical and cognitive development, and other toxicities that must be monitored over the long-term. He noted that Option B+ is ambitious and exciting, but we will only reap the benefits if we do it right over the long term, emphasizing that community involvement will be extremely important in its success.

Luo referenced the fact that countries have complained that there are too many changes in guidance issued by normative agencies and asked Nathan Shaffer, the lead on PMTCT normative guidance at WHO, what he thought could be accomplished over the next year now that the new guidelines had been released.

Shaffer agreed that the focus of the past two to three years has been on developing guidance and policy options. He emphasized that there have been rapid changes in both the scientific evidence and resulting normative agency guidance. Now, the need is to focus on adopting the recommendations of the new consolidated guidelines, with a particular focus on Options B and B+. He noted that while some countries are actively planning for Option B+, they are still in early stages of adoption. Over the next year, countries should move from pilot projects and interim guidance to clear policies in response to the new guidelines, which will also put them in a good position to incorporate updates to the guidelines as they are developed. He noted that WHO, in partnership with the IATT, is developing tools for ART initiation, adherence and retention in care, and will work with its partners to identify other tools and resources that might be useful in rolling out the guidelines. There is also now an opportunity to simplify and clarify national monitoring and evaluation frameworks to track and report more accurately what is happening with ART and PMTCT rollout. He also emphasized the need to develop an implementation science research agenda to support implementation of the guidelines and address outstanding programmatic/service delivery questions.
In response to a query from Luo regarding whether, from the perspective of women living with HIV, Option B+ provides a simpler approach to ART for pregnant women, Moono Nyambe emphasized that while it may be simplified for some women, it is crucial that women be at the centre of all interventions affecting their health. There are still many evidence gaps and outstanding infrastructure issues that need to be addressed (e.g., access to viral load testing and EID), and therefore health care workers and health systems must work in partnership with individual women to determine the approach that achieves the best outcome for each woman and her child. Nyambe raised two key points: (1) how countries will interpret and implement the guidelines; and (2) how the environment and cultures affect how guidelines are implemented. She provided two examples, from Uganda and Malawi, of how good advice and intentions can be interpreted in ways that result in problematic outcomes for women living with HIV. In Uganda, recognizing that male involvement is important in retaining women in PMTCT programmes, some clinics interpreted this to mean that women were responsible for bringing their partners to the clinic. In practice, this meant women who attended the clinic with their partners received priority treatment over women attending without partners. As a result, there were a number of examples where women would hire a man to go to the clinic with them in order not to be de-prioritized.

In Malawi, in an attempt to reduce LTFU, undiagnosed women attending prenatal clinics would receive an HIV test and, upon diagnosis, would be initiated on ART the same day. The “fast-tracking” approach required newly diagnosed pregnant women to absorb an enormous amount of information in a very short time frame, with little consideration on how this information would be received when they returned home. Nyambe also noted that the changes in guidance on breastfeeding over the past decade (though they did not change in the 2013 guidelines) have been very confusing to women and left many uncertain regarding which breastfeeding practices place their infants at greatest risk of HIV transmission. She emphasized the need for programme managers and other implementers to take account of ethics and human rights considerations in the rollout of the guidelines to ensure improved health outcomes for women, their children and families.

Luo noted the recent drop off in Lesotho’s coverage numbers for maternal ART and asked Appolinaire Tiam whether this was partly a result of the transition to Option B+. Tiam explained that Lesotho started rolling out Option B+ between August 2012 and April 2013, following capacity building and training of health care workers. Part of the impetus behind the movement to Option B+ was stock-outs of nevirapine (NVP), which caused problems in ARV prophylaxis implementation. He also noted that 3.6% of women declined Option B+, which was unexpected, emphasizing that countries must consider contingency plans for women who decline ART. One reason women identified for declining Option B+ is the concern about the change in clinical advice from Option A to Option B+ and the fear of extended maternal ART on potential toxicities. Many women had been provided Option A previously and did not understand why that option was no longer relevant or effective. Finally, Tiam noted that laboratory infrastructure is a significant limiting factor to meeting 2015 EMTCT targets, with stock-outs of test kits and other problems with laboratory supply chain management. This has been the most significant reason for Lesotho’s ART coverage slowing recently.
RJ Simonds began by highlighting some of the well-known issues in paediatric care and treatment, including the increasing gap in ART access between children and adults, the limited availability of paediatric drug formulations, retention in care, and adherence (particularly in the growing population of adolescents on ART).

Meg Doherty noted that WHO estimates that adaptation of all recommendations in the new consolidated guidelines will avert three million deaths and 3.5 million infections, and will increase overall treatment-eligible numbers by approximately nine million worldwide (810,000 of whom are newly treatment-eligible children under five years of age). She noted that the trend in paediatric ART coverage is increasing (from 14% in 2009 to 34% in 2012), and that the intent is for the guidelines to get children treated earlier and help them survive longer.

Boris Renjifo noted that AbbVie was committed to developing paediatric formulations concurrently with adult formulations, such as heat-stable, half-strength tablets. AbbVie is also working to address some of the limitations of current formulations, such as developing a sprinkles powder of RTV to address the palatability of the liquid formulation, and to ensure an uninterrupted supply of its paediatric formulations. He noted that AbbVie is currently conducting approximately 60 clinical studies of various ARV formulations, 25% of which are parallel paediatric studies.

Denis Tindyebwa indicated that the number one problem in early diagnosis and treatment of children is the lack of implementation of HIV testing and counselling guidelines and access to test kits for pregnant women. He emphasized the need for better planning to ensure that supplies of test kits are available for both mothers and infants, along with improved counselling skills. He suggested that the model of care for children is disadvantaging them. It recommends that children identified as HIV infected at primary care centres be referred to an ART clinic, but this often does not happen and few ART sites provide paediatric ART. In addition, the inclusion of indicators to support monitoring of children in national monitoring and evaluation plans, along with a strong emphasis on identifying HIV-infected children as early as possible, will be crucial to progress in identifying and treating HIV-infected infants.

Angela Mushavi emphasized government leadership as critical in driving forward the children’s treatment agenda, noting that it is ultimately the government’s responsibility to ensure that the guidelines are adopted and implemented. Government also has an important role in driving the decentralization of HIV care to improve access to ART for children.

She noted the relative dearth of specialists (such as paediatricians) in low- and middle-income countries and therefore the need for task-shifting and other strategies to empower non-clinicians to deliver ART to children. Again, this is a policy issue that has to come from government. She also noted the need to challenge misconceptions in some communities that children cannot be infected with HIV. Communications that address such misconceptions, along with HIV-related stigma and discrimination, are needed to improve accurate information and awareness at the community level.
Discussion

One of the questions raised by session participants was what happens to women (and their infants) who decline ART. Participants underscored the need to support informed consent regarding individual treatment decisions, irrespective of national guidance on whether to implement Option B or B+.

Nathan Shaffer noted that the purpose of establishing a national decision on Option B or B+ is to ensure clarity regarding the recommendations and the required programmatic support. However, he emphasized that this does not presuppose individual decisions regarding whether to initiate ART (which may be most applicable to HIV-infected women with high CD4 counts), and that this decision can be reassessed at any time.

Denis Tindyebwa noted that in some cases, women need additional support and counselling in decision making. He noted that about 5% of adults decline ART for a variety of reasons, and that this is why additional support is required via programme counsellors, mother-to-mother (M2M) programmes and other community services aimed at supporting women’s health needs. This may ultimately mean placing women on Option A if that is their choice, even though this approach may not be part of national guidelines and is no longer recommended by WHO.

One of the participants also stressed the need to learn from experience, for example, asking programme managers which formulations women and their children find preferable (e.g., a syringe of liquid NVP or scored NVP tablets).

A question was also raised about the feasibility of “milk banks” of breast milk from HIV-negative women for HIV-infected women. Chewe Luo noted that, from the perspective of child survival, milk banks and wet nursing might be helpful, but it raises a number of programmatic challenges that would need to be thought through carefully.
Closing remarks

Co-Chair Craig McClure closed the session by summarizing eight key messages from the session:

1. Monitoring and evaluation plans must change as programmes evolve to ensure better tracking and monitoring of both mothers and children.

2. Male involvement in PMTCT interventions is crucial, but it should not be a barrier to accessing care.

3. Choice is important, but it is also important to ensure clear, simple messaging (treatment literacy) that addresses breastfeeding and the implications of initiating ART to ensure women make informed choices.

4. Strengthening laboratory infrastructure, procurement and supply chain management of HIV commodities (e.g., test kits, paediatric formulations) is critical; simplifying and harmonizing drugs and protocols will help, but procurement and supply chain management remains an important bottleneck to scaling up to meet the EMTCT targets.

5. The key message of updated WHO guidance for children less than five years of age is to initiate children on ART as early as possible and to reduce the number of children who “slip through the cracks” and do not present until they have advanced disease progression.

6. There is a need for new formulations for children, which countries are able to provide at affordable prices: this could be through the licensing of generics and new formulations (like LPV/r sprinkles).

7. Decentralization of HIV services by government to local levels require empowering district programme managers and communities to better monitor and adjust programmes.

8. There is a need to recognize the requirements of children and families beyond the health sector: social and economic support is likely best provided by community systems in collaboration with health sector actors.

Co-Chair Elly Katabira thanked the panellists and audience members for an excellent discussion.
IAS-ILF Mission

The mission of the Industry Liaison Forum is to accelerate scientifically promising, ethical HIV research in resource-limited countries, with a particular focus on the role and responsibilities of industry, namely pharmaceutical and diagnostic companies, as sponsors and supporters of research.

The IAS-ILF fulfills 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.