A BUSINESS CASE FOR OPTIONS B AND B+

TO ELIMINATE MOTHER TO CHILD TRANSMISSION OF HIV BY 2015

BLC BUSINESS LEADERSHIP COUNCIL
For a Generation Born HIV Free
A PROJECT OF THE NBO Health Alliance

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SECTION 1: THE CASE FOR CHANGE

We are at a pivotal moment in the history of the HIV/AIDS epidemic – the science of what works to prevent HIV transmission, morbidity, and mortality is clear. New infections in children account for 15% of new HIV infections annually[i]. Without intervention, the risk of mother to child transmission of HIV (MTCT) can be as high as 45%; successful implementation of prevention of mother to child transmission (PMTCT) programs reduces this risk to around 2% in non-breastfeeding populations and less than 5% in breastfeeding populations[ii]. Eliminating MTCT and enhancing the health of infected mothers is the beginning of the end of AIDS.

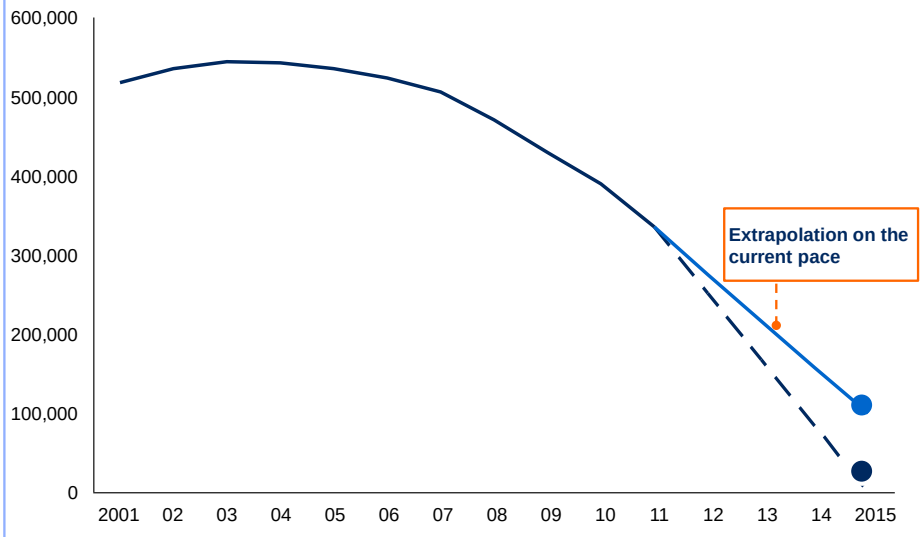
PMTCT has been a major priority for the global community over the last decade, and progress has been made in reducing the transmission rate at 18 months, stemming from action across all four prongs of PMTCT[1]. The percentage of HIV positive pregnant women receiving antiretrovirals (ARVs) for PMTCT increased from 9% in 2004 to 48% in 2010 in low and middle income countries[iii]. Transmission of infection to infants is highest (about 80%) in HIV positive pregnant women in need of treatment for their own health[iv]. These women make up 40-60% of women accessing PMTCT services. Only 23% of positive pregnant women receiving antiretrovirals received them for their own health. Transmission rates therefore have remained high[v], with the number of annual new infant infections falling from approximately 570,000 to 390,000 between 2001 and 2010[vi].

The Global Plan Towards Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive[vii] has put forth a clear set of targets for 2015: to reduce the number of new HIV infections among children by 90% and to reduce the number of AIDS-related maternal deaths by 50%. Within these targets, the Global Plan aims to reduce MTCT to less than 5% at 18 months[viii]. This is an achievable yet ambitious target, but we are already in danger of missing the mark.

[1] These prongs include 1) primary prevention of HIV among women of reproductive age, 2) providing appropriate counseling and support to women living with HIV to enable them make an informed decision about their future reproductive life, 3) for pregnant women living with HIV, ensure HIV testing and access to the antiretroviral drugs, and 4) better integration of HIV care, treatment and support for women found to be positive and their families.

The decline in new HIV infections in children – roughly 14% annually from 2009 to 2011, with 390,000 in 2010 - suggests that we have already fallen behind the Global Plan's May 2012 target that "the estimated number of new HIV infections in children is reduced by 25% from the 2010 level."[ix] Over the last year, some countries have made remarkable improvements while others are lagging behind, but the cumulative effect sets a pace that will not get us to our 2015 goal.

Exhibit 1: Estimated number of children newly infected with HIV in low- and middle-income countries

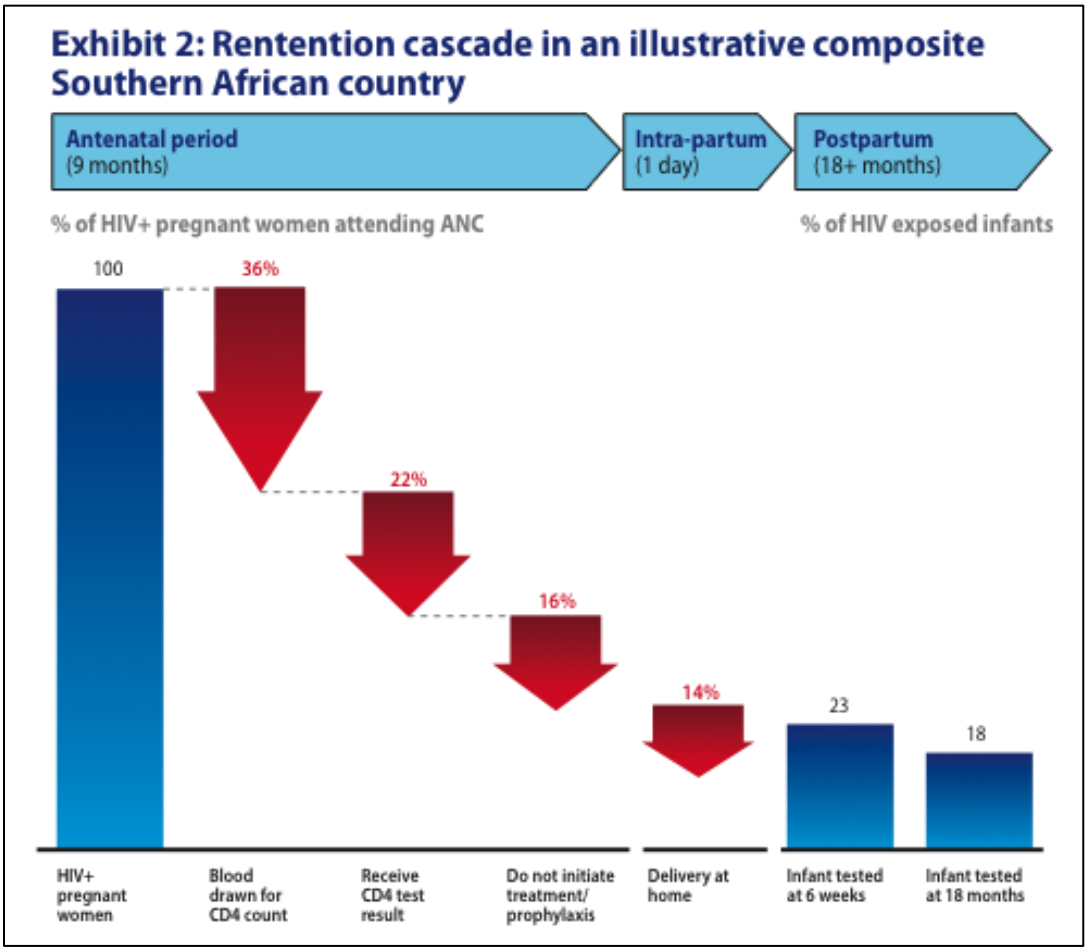


SOURCE: Progress report 2011: Global HIV/AIDS response; Epidemic update and health sector progress towards universal access

To achieve this, we must take rapid and collective action. One major driver of the trajectory towards virtual elimination is the choice of PMTCT protocol and selected drug regimen[x], given that, in practice, the Options vary with respect to operational complexity, resulting coverage, retention, and adherence rates, and, ultimately, impact on transmission. The WHO's 2012 Programmatic Updates addresses the question directly[xi]. Most priority countries targeted by the Global Plan are currently implementing Option A of the 2010 WHO guidelines[2]. A few countries have had relative success with Option A or previous versions of protocols prior to the

[2] Latest available country listing provided in Appendix I of this document

WHO guidance in 2010 (Botswana, South Africa and Namibia have realized overall MTCT rates of 4%[xii], 11%[xiii], and 12%[3,xiv], respectively[4]). This success can be attributed to national governments and implementing partners aggressively working to overcome execution challenges, including but not limited to increasing access to services for women and their families and improving retention and adherence. Other countries have had less promising results, largely due to these same operational challenges, which can lead to high rates of loss to follow-up across the cascade of clinical services. Exhibit 2 shows an illustrative cascade, based on data from a number of Southern African countries[xv,xvi,xvii,xviii,xix,xx,xxi,xxii,xxiii,xxiv][5].



[3] The recent MRC study released in June 2011 shows 3.5% MTCT at week 6 after birth; the study will repeat in 2011 and 2012 collect and analyze 18 month MTCT rates. The latest available estimates for 18 month MTCT in South Africa otherwise show 12%.

[4] Best available data; denominators are not always clearly described, though it appears that Botswana reports a denominator of the number of HIV+ pregnant women who present at antenatal care or at labor/delivery, South Africa reports a programmatic denominator (number of children tested via PCR), and Namibia used a population-based denominator modeled with Spectrum. However, in these three countries ANC coverage is high – above 80% and in most cases above 90% - and therefore the denominator used is likely to directionally reflect the population.

[5] These include Zambia, Lesotho, Malawi, Zimbabwe, and South Africa.

The retention challenges associated with Option A include:

- **Loss to follow up prior to initiation of treatment for eligible women.** Pregnant women must initially be tested for HIV; then clinically or immunologically staged based on CD4 testing; then initiated if treatment eligible. Access to CD4 remains limited and in 2010 only 37% of HIV positive pregnant women had CD4 screening. Further, because CD4 testing is often not co-located with ANC and HIV testing services, there is attrition of pregnant women between diagnosis with HIV and testing for CD4 count. In addition, due to the long turnaround times for CD4 test results, women who may be eligible for treatment–and thus at most risk of vertical transmission due to their advanced disease–may be lost to follow-up between CD4 testing and treatment initiation. A cohort in South Africa estimated an overall retention rate of 33% between the provision of a first CD4 count and the initiation of antiretroviral therapy[xxv].

- **Unavailability of labor and delivery regimen at birth site.** The risk of MTCT is highest during labor and delivery at 10-20%, and so an estimated 35-45% of MTCT occurs during this time period. In many countries, a significant portion of women do not deliver at health facilities[xxvi]. For women who do not return to healthcare centers for labor and delivery, the switch in regimen and the additional drugs required makes it difficult to ensure that they have the prophylaxis recommended in Option A for this stage of pregnancy.

- **Higher risk of transmission during breastfeeding.** Option A requires new mothers on prophylaxis to give nevirapine (NVP) syrup to their infants for the duration of breastfeeding. Nearly all of the 22 priority countries report breastfeeding durations of greater than 18 months[xxvii]. During this extended breastfeeding period, countries have experienced high rates of loss to follow-up [xxviii] which may contribute to high postnatal transmission rates. Visits for immunizations and other well-child care may not coincide with or be co-located with HIV-exposed infant care (including ARV refills), contributing to this postpartum loss to follow-up.

In addition to these drop off points for mothers and infants, Option A poses operational challenges to providers and the healthcare systems on which they rely:

- **Procurement and supply chain management difficulties.** Because Option A requires a variety of drugs across the continuum, it is more difficult to forecast and manage stock of multiple drug supplies. Furthermore, Option A requires large amounts of nevirapine syrup for the infants on prophylaxis. Managing and distributing the syrup as well as ensuring its use before the expiry date is difficult.

- **Complex patient management.** On Option A, patients are expected to adhere to different drug regimens through pregnancy, labor and delivery, and postnatal periods. This requires multiple engagements with physician and healthcare workers for counseling and consultation. In addition, multiple drug regimens create complexity for patient management, making it more difficult to decentralize treatment services and appropriately train lower level health care workers.

Even when concerted and prolonged effort is put toward improving service delivery and addressing some of these challenges, it is not easy to reduce transmission. For example, in 2008, the Malawi Ministry of Health in partnership with the Clinton Health Access Initiative (CHAI) began a three-year pilot program in the Machinga District, a highly populated rural district with high HIV-prevalence. Based on modeling[xxix], Machinga had an estimated 18% transmission rate at 6 weeks and 32% at 18 months at the start of the program. The targets of the pilot were to increase the percentage of pregnant women accessing the full range of PMTCT services from 24% to 80% who were tested for HIV, and to decrease, by at least 50%, the rate of MTCT at 18 months, to 15-22%. Dedicated resources went into improving multiple aspects of the system including basic transportation, lab networks, training, testing technology, and maintaining buffer stock. Over the course of the program, the modeled transmission rate at 6 weeks decreased to 7.3% and the transmission rate at 18 months decreased to less than 20%[xxx].

The Machinga program was implemented using a modified version of the 2006 guidelines[6] rather than the 2010 and therefore do not provide extended prophylaxis throughout the

[6] This included: women with CD4<350 or stage 3 -4, eligible for treatment, women with CD4>350, AZT at 28 weeks, SD-NVP + AZT + 3TC intra-partum and seven days of maternal AZT+3TC, infant received 6 weeks of AZT or NVP, no extended breastfeeding prophylaxis.

breastfeeding period. However, even if one were to assume that this had been provided, the modeled transmission rates still would have only been 12%[xxxi] at 18 months. Without a doubt, this effort averted a huge number of infections in infants. The MTCT reduction goals were met, and the achievements of this work should be applauded. The lesson, however, remains that even with an infusion of funding, devoted incremental human resources, and infrastructure improvements, the transmission rate at 18 months remained well above 5%. Further to this point, the World Health Organization (WHO) released a programmatic update in April 2012[xxxii]. This update builds on the 2010 recommendations[7], describing not only Options A and B but also Option B+, in which pregnant HIV-positive women are initiated on triple ARV treatment for life upon HIV diagnosis[8]. The update highlights the issues with Option A, stating

"While Option A has been successfully implemented in a number of high burden countries, generally it has been difficult to implement in many low-resource settings due to the changes in drugs delivered across the care continuum (antenatal, delivery and postpartum) and the requirement for timely CD4 testing to determine which women should initiate ART for their own health."[xxxiii]

The update goes further, saying

"Options B and specifically B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons.[xxxiv]

It is possible that the WHO guidelines to be released next year will take this statement even further and only recommend Options B and B+.

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[7] The 2010 guidelines provide international standards, primarily for low- and middle income settings, in support of the global scale-up of more effective interventions aimed at preventing MTCT in resource limited settings. They offer two treatment options (A and B), which recommend the same ARV treatments for women with low CD4 counts (≤350 cells/mm3). However, the options differ in treatment and prophylaxis for women with high CD4 counts, and in their approach to treating breast-fed infants. In Option A, the drugs provided for prophylaxis vary at different stages of the care continuum (antenatal, delivery and postpartum) as well as CD4 testing to determine which women should initiate ART for their own health. Option B recommends a triple ARV treatment until one week after end of breastfeeding for use as prophylaxis to prevent mother-to-child transmission of HIV. An additional clinical difference is that Option A requires breast-fed infants to be treated until one week after the end of exposure to breast milk, whereas Option B recommends treatment until 4 to 6 weeks of age irrespective of the feeding method.

[8] In wake of the WHO 2010 guidelines, Malawi revised its national PMTCT guidelines and adopted B+. Under Option B+, all pregnant women living with HIV are offered lifelong ART, irrespective of their CD4 count.

The rest of this discussion document paper makes the case for options B and B+. It explains their benefits (section 2) and describes the logic of their relative financial impact (section 3).

SECTION 2: WHY OPTIONS B and B+?

Options B and B+ are possible from a safety and regulatory perspective, enable significant operational simplifications, and result in indisputable clinical benefits.

Safety, regulatory, and operational barriers to implementation of Options B and B+ have been overcome

Options B and B+ are more viable options than they were when the WHO released its 2010 guidelines. Several factors contribute to this, including:

- **Reduction of concerns about the safety of efavirenz**. Guidelines, recently issued by the United Kingdom in January 2012, recommend the use of TDF/3TC/EFV for pregnant women[xxxv]. The guidelines note that, despite earlier warnings by the U.S. Food and Drug Administration (FDA) on the use of efavirenz (EFV), in the first trimester of pregnancy, real world experience suggests that it is safe for use[xxxvi]. Several other systematic analyses of EFV in pregnancy over the past few years have come to the same conclusion[xxxvii]. Similarly, the WHO, in its June 2012 Technical Update on Treatment Optimization, "provides further support for the use of EFV to optimize and simplify first-line treatment, including among pregnant women and those of reproductive age[xxxviii].

- **Approval of TDF/3TC/EFV fixed dose combination**. This three-drug combination was first approved by the FDA in 2006. FDA tentative approval of a generic supply of the FDC was granted in September 2009[xxxix]. This one pill once a day regimen can be used for all adult populations[xl]. Two suppliers have received FDA tentative approval or WHO prequalification for the analogous combination of TDF/FTC/EFV, and the two pill combination of TDF/3TC and EFV is now available from four generic suppliers. The growing number of quality-assured suppliers of the two and three-drug FDC that underlie Options B and B+ make these protocols more viable than ever[xli].

- **Affordability of TDF/3TC/EFV fixed dose combination**. The price of the generic TDF/3TC/EFV tablet dropped by 59% between 2007 and 2011, making it more affordable for countries[xlii]. Also, CHAI announced agreements in May 2012 to provide countries

participating in the CHAI Procurement Consortium a year's supply of the drugs for $159, or $0.44 per day[xliii]. Further reductions are likely, with the price likely to be approaching $100 in the next few years[xliv].

Options B and B+ facilitate operational simplifications

Options B and B+ have significant operational advantages over Option A that should be studied further in settings where they are being implemented. They include:

- **Simplifications for the mother**. Options B and B+ remove the gating CD4 step from the PMTCT cascade and enable a pregnant woman to receive an HIV test and, if she is positive, to receive treatment immediately. This decreases the number of unique interactions the woman must have with the system, helps to reduce loss to follow up at this point in the cascade (rather than requiring what would otherwise be an additional step of initiating treatment only after receiving CD4 results[9]), and allows for earlier initiation of treatment during pregnancy. It should be noted that a blood sample for CD4 testing should still be taken after diagnosis to provide a baseline CD4 count. However, the result is not required to initiate treatment and can be provided at a follow-up visit to the clinic at a later date. Concerns about retention and adherence during and after pregnancy must be addressed to achieve maximal benefit from any Option, though it is likely that simplification of the regimen itself, decreasing the number of times a woman must switch medications, could have a positive effect [xlv,xlvi,xlvii].

- **Simplifications for the infant**. The principal mechanism of prophylaxis for Options B and B+ is maternal treatment – one pill, once a day. Infant prophylaxis is recommended for 4-6 weeks, regardless of infant feeding method.[xlviii] In contrast, for women with CD4 cells/mm^3 > 350, Option A depends solely on infant prophylaxis for the duration of the breastfeeding period. Infant retention on Option A is fraught with challenges, including returning to the clinic for regular refills of a formulation (syrup) that is difficult to stock and distribute and

[9] It is likely that loss to follow up is reduced at this initial step in the cascade due to the removal of gating CD4 testing. However, further research must be done to better understand loss to follow up through the remainder of the cascade, for which retention is less well understood.

daily administration of this syrup to the infant for the breastfeeding period, amounting, in some cases, to over 2 liters of NVP[10].

- **Simplifications for the provider**. A unified regimen can be used for the entire adult population – pregnant and non-pregnant, male and female – simplifying operations, procurement and supply management. The 2012 WHO programmatic update postulates that this streamlining will *"maximize program performance through better alignment and linkages with antiretroviral therapy (ART) programs at every level of service delivery."*[xlix]

While the likely operational advantages of Options B or B+ are considerable, shifting from Option A will require consideration of country preparation and planning including, but not limited to, human resources training at the facility and community levels, supply chain management and demand creation to improve initiation, retention, and adherence.

These operational advantages are likely to have clinical benefit

The operational simplifications described above are likely to facilitate higher retention rates and improved clinical benefits on Options B and B+ compared to Option A[11]. Option B and B+ will likely increase the number of women who initiate treatment, resulting in overall lower transmission of HIV to infants. Early evidence of this has been observed in Malawi, where implementation of Option B+ for PMTCT[12] has resulted in a significant increase in the number of pregnant and breastfeeding women starting ART. In three months, the number of pregnant and breastfeeding women starting ART has jumped from 3,561 and 1,394, respectively, to 7,599 (2-fold increase) and 6,799 (5-fold increase), respectively (between Q3 and Q4 2011)[l]. This compares to a total of 1,200 pregnant women on ART under Option A in Q1 and Q2 2011. While these are early results and show only total volumes, they convey the direction and magnitude of the change associated with moving to Option B+.

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[10] Total volume consumed depends heavily several factors including a child's weight distribution over the length of breastfeeding and the concentration of NVP syrup dispensed.

[11] These hypotheses should be studied in settings where Options B or B+ are being implemented. Further, country-specific hypotheses about the magnitude of the effect of these Options on retention rates, for example, can and should be modeled to anticipate the associated impact on transmission rates, as part of the evaluation of whether and when to adopt the Options.

[12] The Government of Malawi has formally adopted universal roll-out of Option B+ (i.e., to all HIV+ individuals) but has had to devise a phased implementation approach due to the cost difference between TDF/3TC/EFV and d4T/3TC/NVP – beginning with HIV+ pregnant women, HIV+ persons living with tuberculosis, and HIV+ persons experiencing severe side effects from the D4T regimen.

Higher post-partum retention and adherence on Options B and B+ would reduce the number of infants that are infected during this period. In addition, simplifying operations, procurement and supply management could likely improve forecasting and reduce the risk of stockouts of ARVs. It can further drive down the costs due to negotiation leverage and operational infrastructure efficiencies. The money saved from such improvements could then be invested in mechanisms to increase retention, such as expanded community support services. As a result, Options B and B+ will likely result in a higher number of infections averted and reduced costs of HIV-related treatment and care.

Option B+ has additional benefits over both Options A and B

Beyond the clinical benefits it shares with Option B, Option B+ has three additional benefits.

- **Lower transmission to infants**. The total number of new infant infections averted is likely to be highest with Option B+ as compared to Options A and B because in subsequent pregnancies, more women will already be receiving lifelong treatment initiated during earlier pregnancies[13].

- **Improved maternal health**. Option B+ is better for the mother's health[14]. Placing mothers on triple ARVs early as treatment may decrease HIV related morbidity due opportunistic infections such as tuberculosis[li]. Option B+ will likely increase maternal life expectancy for those who adhere[lii]. This is likely to have an indirect effect on reducing under-5 mortality. (parental HIV-positive status is associated with a 20-40% increase in the risk of mortality in children under-5 regardless of their HIV status[liii].) Increasing maternal life years also reduces the number of orphans needing support. The annual cost of providing care to a child orphaned due to HIV/AIDS is estimated to be more than $200 per year; research shows this to be $45 per maternal life year saved[liv].

[13] Not all women will still be on treatment between pregnancies due to normal loss in retention; the subset of women who do continue to take their ARVs between pregnancies and into the next pregnancy will see this benefit.

[14] Known to be the case for women with CD4 counts < 350; observational evidence only for women with CD4 counts > than 350

- **Lower transmission to HIV-negative male sexual partners.** Option B+ puts more HIV-positive women on lifelong ART sooner than Options A or B[15]. The HPTN 052 study clearly demonstrates a statistically significant difference in transmission rates to HIV-negative partners for those individuals that are initiated early on ART (i.e., at CD4 counts > 350)[lv]. Adult infections are averted under Option B+ for those patients who would have otherwise received prophylaxis[16] and been taken off ARVs following the breastfeeding period under Options A and B. More adult infections averted significantly reduce the amount of money spent on HIV care and on treating opportunistic infections such as tuberculosis and pneumonia; further, this results in increased productivity gain as fewer work hours will be spent managing HIV-related ailments and care.

Taken together, Option B+ likely results in more infections averted and more maternal life years saved than either Option A or Option B[17]. Further, leveraging the close relationship between PMTCT and maternal, newborn, and child health programs offers an opportunity for a mutually enforcing effort.

The clinical benefits of Options B and B+, relative to Option A and relative to one another, are illustrated in the exhibit below.

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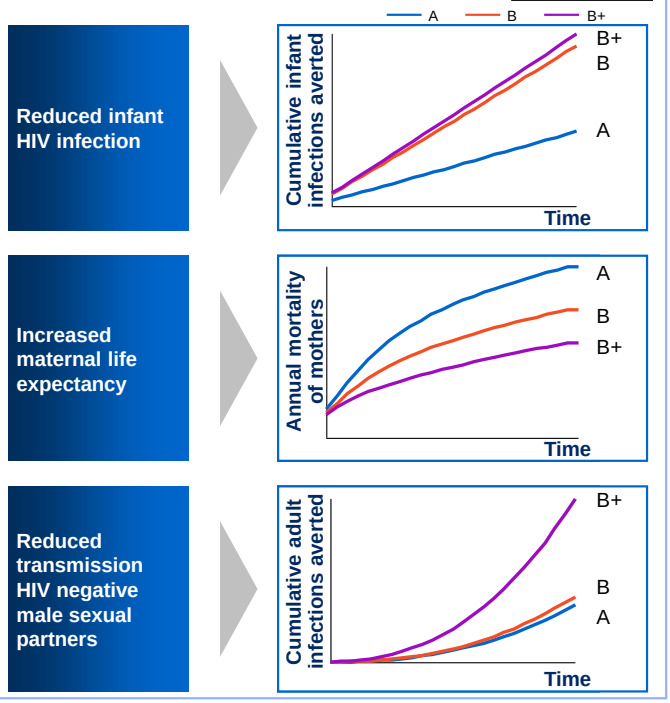
[15] Theoretically all women under all of the Options will ultimately be put on ART.

[16] Option B also averts some infections to serodiscordant partners during prophylaxis, when the mother will be administered triple ARVs. This protection ceases when she is taken off triple ARVs between pregnancies

[17] These hypotheses should be studied in settings where Options B or B+ are being implemented.

Exhibit 3: Clinical benefits of Options B and B+

ILLUSTRATIVE



SECTION 3: OVERCOMING THE BARRIERS TO OPTIONS B and B+

Despite these benefits, only one of the 22 focus countries of the Global Plan has already chosen to adopt and implement B+, with most currently costing new plans for Option A[lvi,18].

Concerns about cost are most frequently cited as the barrier to implementing Options B or B+; these eclipse the benefits accrued under B and even more so under B+. Though several countries have expressed interest in Options B or B+, none has yet transitioned fully away from A. Those potentially interested include, but are not limited to, Cameroon, Kenya, Mozambique, Namibia, South Africa, Swaziland, Uganda, Zambia and Zimbabwe[lvii]. In Uganda, "PMTCT Option B+ is included in [the] national guidelines. However, in practice it has only been implemented at pilot sites supported by non-government organizations, due to funding shortages." [lviii,lix]

However, most cost evaluations have only taken into consideration a narrow view of the issue. By focusing on the immediate cash flow challenges associated with treating more HIV-positive pregnant women, the full financial cost-benefit is obscured. It is necessary to think comprehensively about cost, including not only the incremental cost incurred to administer Option B or B+ but also the cost of failure (i.e., the greater number of infections and their associated costs) in Option A in the short and medium term and the additional benefits and cost-savings from B and B+.

Cost over time

Comprehensive cost should be understood on two time horizons: the near-term, focused on incremental cost of paying for Options B or B+ versus Option A; and the long-term, for which consideration should be given to aggregate cost over time of paying for the full set of benefits and costs accrued under Options B or B+ compared to Option A.

[18] Malawi is rolling out Option B+; countries including Burundi, Cote d'Ivoire, Chad, and parts of Nigeria are implementing Option B (which Botswana has already done quite successfully), with highly variable coverage. Other countries are also experimenting with B or B+ in pilot settings.

Concern about short term cost is valid. Both Options B and B+ require spending in the short-term in order to accrue benefits in the medium and long-term. This incremental direct cost per mother-baby pair in Option B over Option A, however, is small relative to total global investment in HIV/AIDS. A "back of the envelope" calculation, multiplying the total number of HIV+ pregnant women by the rough incremental direct cost of moving from Option A to Option B[19], shows the incremental direct costs of treating all[20] mother-infant pairs on Option B instead of on Option A would amount to approximately $350 million per year. While this is not an insignificant amount of money, it pales in comparison to the $15 billion[lx] total annual global investment in HIV in 2010.

The long term cost concern is considerably more complex, but can be simplified to a single question: **does the incremental spend required to implement Options B or B+ exceed the "cost of failure" associated with Option A?** In other words, the long-term cost calculus must reflect the relationship between increased cost incurred by placing more HIV+ pregnant women on treatment and the related cost savings from more infections averted and improved maternal health *as compared to* the cost associated with new infections of infants and male sexual partners and maternal deaths which would otherwise accrue under Option A.

Many groups are working to analyze this question in different ways[21] (e.g., country-specific vs. not, theoretical coverage and retention levels vs. operational realities, how does cost compound over time, etc.), but initial analyses consistently point to the importance of looking at the full picture over a long timeframe to see the true costs or cost savings of B and B+ over A. The U.S. Centers for Disease Control (CDC) and the Clinton Health Access Initiative (CHAI) co-chair the IATT Finance and Economics Working Group (FEWG), which plays a leading role in developing the definitive models and tools that can be used in country-specific contexts to examine this question.

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[19] Based on an incremental ~$250 per mother-infant pair in Option B over Option A in both drug- and non-drug direct costs (average difference across a number of models reviewed that were developed by CHAI, EGPAF, and NCGM). Non-drug direct costs vary in calculation by model but generally include consideration of human resources, labs, and shipping. Assumes 1.4 million HIV+ pregnant women.

[20] 100% coverage of mother-infant pairs is, of course, unrealistic; maximum coverage used here to estimate maximum cost.

[21] These groups and their associated models include, but are not limited to: Futures Institute/Spectrum, CDC, Clinton Health Access Initiative/PMTCT and Pediatrics Impact and Cost Model, National Center for Global Health and Medicine (NCGM) and the Pan American Health Organization (PAHO)/Costing Tool for Elimination Initiative, WHO Guidelines Technical Advisory Group at the Elizabeth Glaser Pediatric AIDS Foundation/PMTCT Cost Elimination Tool, MSH, Andrea Ciaranello et al at Harvard University.

Relative cost of each Option

A rapid modeling exercise has been undertaken in an effort to better understand how the costs of Options B and B+ compare to those of Option A over time. Complete methodology, assumptions, and sources are available alongside this discussion document and are intended to be tested, debated, and improved by the community and tailored to unique country contexts.

The logic and framing described below is not intended to provide any authoritative answers. It is intended to put forth a hypothesis to accelerate the ongoing conversations about a large scale shift away from Option A and to inform country participation in asking and answering the question – to evaluate Options B and B+ for individual country settings – with the IATT Finance and Economics Working Group (and others).

This review of the basic logic of the costs incurred presents a telling story about the relative aggregate cost over time of the three Options. The approach to this question is to estimate the absolute cost incurred for the total number of people receiving prophylaxis and/or treatment across the options - all HIV+ pregnant women, regardless of CD4 count at the time of their pregnancies, will require treatment at some point. It is necessary to account for the ART cost for all women under Options A and B to adequately compare the long-term costs with Option B+, as Option B+ only accelerates the pace at which a woman receives ART compared to the other options.

Therefore, this approach includes HIV+ pregnant women and their infants in Options A and B who initiate treatment after their interactions with the PMTCT cascade (i.e., the lifetime absolute cost of an HIV+ woman whose CD4 count is >350 cells/mm^3 during her childbearing years and therefore receives Option A prophylaxis for the duration of her pregnancies and breastfeeding periods, but who deteriorates in health and ultimately is initiated on triple ARV treatment later in life in a non ANC setting).

There are three types of people affected in this logic: a) HIV+ pregnant women who give birth to one or more children over the time period; b) infants born to these HIV+ pregnant women; c) the HIV-negative partners of these HIV+ pregnant women.

Each of these populations generates a set of costs over a lifetime of child bearing and sexual contacts. HIV+ pregnant women and the infants born to them generate direct drug costs for prophylaxis and/or treatment over time and through multiple pregnancies. Serodiscordant partners of the HIV+ pregnant (or formerly pregnant) women generate treatment costs if they are infected. All three groups have associated non-drug direct costs of service delivery (e.g., personnel salary and lab commodity costs) and indirect system costs (e.g., healthcare worker training and supply chain management).

This discussion focuses on the direct costs of each Option; these costs depend on a series of assumptions that have been made conservatively to ensure confidence in the hypotheses presented below. It assumes coverage and retention rates along the PMTCT cascade that reflect the operational realities seen on the ground in a generic Southern African country currently implementing Option A (e.g., relatively high coverage of ANC and HIV testing, significant drop-offs thereafter through CD4 testing and retrieving results, initiating on ARV prophylaxis or ART; low, but material, infant initiation on prophylaxis and then treatment). For Options B and B+, it assumes that the loss between testing and initiation is reduced because one is able to initiate in parallel to taking a baseline CD4 count but that there remains some loss because some portion of women will need to travel from ANC to an ART clinic to initiate and will be lost in the process[22]. These assumptions remain conservative, using real world data showing current PMTCT and treatment coverage rates that remain static over time.[23]

Incremental spend on Option B as compared to the "cost of failure" in Option A

When comparing the direct costs associated with each Option, Option B is more expensive than Option A in the first years, when HIV+ pregnant women are taking ARVs as outlined by the WHO 2010 guidelines for each Option. Triple ARVs used for prophylaxis in Option B cost more than the ARVs prescribed for prophylaxis to HIV+ pregnant women and their infants under Option A.

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[22] As described in Section 2, we hypothesize that mitigating the drop-off at CD4 testing is only the tip of the iceberg with respect to the operational simplifications of Options B and B+ over Option A.

[23] This steady state picture of the Options – with no scale up of coverage over time – presents a very conservative estimate of the relative costs. When used in a specific country, scale up must be accounted for, which will likely push the costs of A higher.

Option A, however, when implemented in the field, leads to more infant infections. These infections are primarily driven by two factors:

- Lower initiation rates for pregnant women due to the complexities associated with CD4 testing prior to treatment, leading to more untreated women and women incorrectly put on prophylaxis rather than treatment, as indicated by Option A guidelines; and

- Disproportionately high infant attrition during prophylaxis among breast fed infants due to the difficulty of administering daily NVP to an infant.

Given this higher rate of infection, after the initial years, the total cost per year of Option A is higher than that of Option B. By this time, the cost of failure (i.e., treating HIV+ infants) in Option A has begun to compound with more and more infants requiring treatment over time. This is true even under extremely conservative assumptions about treatment coverage for children (assumed to be roughly 25% here), and does not incorporate potential additional cost savings in Option B, such as from increased productivity. This cost is amplified further in countries with poor coverage of maternal ARV prophylaxis, poor coverage/ adherence on infant prophylaxis, good coverage of pediatric treatment, and/or lower child mortality.

Over several years[24], then, considering the cumulative direct costs of both Options, Option B is cost saving relative to Option A.

Incremental spend on Option B+ as compared to the "cost of failure" in Option A

The cost equation for Option B+ versus Option A is more complex. The short term costs of B+ are certainly higher than Option A and incrementally higher than Option B due to sustained ART coverage of treatment for HIV+ pregnant women, including women on treatment before they are otherwise clinically eligible.

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[24] Definitive modeling must be conducted to determine this time frame using country-specific assumptions and aspirations. Initial hypotheses resulting from the rapid modeling done to support this paper and described in the methodology document suggest that Option B quickly becomes less expensive than Option A on a *per-year* basis (within 5-10 years, if not sooner) and results in aggregate cost savings over a ~10-15 year timeframe. This is not an authoritative statement, however, and must be considered in more detail on a country by country basis.

However, the extent of this cost differential depends in part on the CD4 distribution of the HIV+ pregnant population (a greater proportion of women below 350 cells/mm^3 implies more women eligible for treatment in Option A) and actual treatment coverage of those women. As treatment coverage is increasing rapidly in many countries, the differential cost of B versus B+ may not be dramatic over time.

In addition to the cost differences between Option B and B+, Option B+, generates a set of financial benefits above and beyond Option B, such as lower transmission to infants due to protection from ART initiated in the previous pregnancy, reduced transmission to HIV negative male sexual partners due to the impact of treatment as prevention, improved maternal health and associated productivity gains, lower morbidity and associated secondary and tertiary care costs, and potentially lower non-drug direct and indirect costs of delivery (including cost of fewer CD4 counts, lower costs from switching on and off treatment over time).

Relative to the modeling of Option A compared to Option B, then, the modeling of Option A to Option B+ involves accurately accounting for the incremental cost of sustained treatment weighed against the unique financial benefits of Option B+. A number of variables contribute critically to this cost-benefit equation; most cannot be modeled quickly or without engagement in country. The following is a non-exhaustive list of relevant variables and how they affect the long-term calculation of the absolute costs of Option B+ in comparison to Option A.

Pediatric HIV treatment initiation and retention rates: As described earlier, Option B+ averts more infant HIV infections than Option A. There is an additional cost in the system for each infection not averted by Option A. The magnitude of this cost is determined by the percentage of infants that initiate treatment and how long these infants are retained on treatment. Higher rates of pediatric treatment will result in higher total system costs on Option A, reducing the difference in cost between Options A and B+.

Rate of transmission from HIV+ pregnant and previously pregnant women to HIV negative male sexual partners: There is a significant cost to the system for each male infected by an HIV+ positive woman. The HPTN052 [lxi] study demonstrated a significant decrease in transmission rates for individuals who initiate ART early (i.e., with CD4 >350).

Mothers with CD4>350 cells/ mm^3 will have a lower transmission rate on Option B+ than on Option A (or Option B, after the breastfeeding period). The difference in the number of men infected, and the resulting system cost, depends on the number of male HIV negative sexual partners per HIV positive woman and the transmission rate, which is heavily associated with sexual behavior (e.g., condom use), as well as male circumcision status, in a particular population.

Non-drug direct (and indirect) costs: Non-drug direct treatment costs mainly comprise lab and human resource costs. These will differ across options based on testing, training and patient counseling requirements. For example, since Option B+ is assumed to have higher retention rates and retains HIV+ women on treatment through successive pregnancies, less is spent on tests for HIV+ pregnant mothers (e.g., CD4 testing to re-stage women in successive pregnancies or for individuals who do not collect their results). These factors considered together may lead to a lower non-drug direct cost per patient for Option B+. Non-drug indirect costs are likely to further differentiate the Options, if the cost of scaling up Option A per patient exceeds that of scaling up Option B+.

Secondary and tertiary care for HIV-associated morbidity: Hospitalization and specialist care for HIV-associated morbidity, if quantified, would be an additional cost of failure for infected mothers, infants, and serodiscordant partners as they suffer from increasingly compromised immune systems over time, leading to opportunistic infections, and, ultimately, end of life care. The extent to which these costs are meaningful is highly dependent on country context. These costs would accrue more for Option A than B or B+, since Option A produces the least number of infections averted under current assumptions of coverage and retention across the cascade.

Productivity benefits: Productivity benefits, in particular from the increase in life years for mothers, dramatically increase the monetary benefits associated with Option B+. Higher retention of pregnant mothers and earlier initiation on ART treatment under Option B+ will drive lower mortality rates. These increased life years have a potential economic benefit. The country specific extent of this benefit will make B+ more cost effective vis-à-vis Option A.

These variables have the possibility, when tested on a country-specific basis, to result in Option B+ becoming cost neutral relative to A. For example, accounting for the productivity benefits accrued from improved maternal health and resulting life years saved has shown that Option B+ can produce cost savings over Option A[25] in Malawi. That said, it is important to refrain from broad conclusions on this point given the complexity and country-specific nature of the assumptions. These questions should be the focus of additional scrutiny and should be modeled on a country-specific basis to enable governments to make a balanced consideration of the choice between Options A, B, and B+.

Looking beyond cost to implementation

Of course, beyond cost, the realities of implementation are a critical consideration in any country's decision of Option and should not to be ignored or minimized. No Option is easy, as doing any of them well will require concerted effort, resources, reorganization, program scale-up, and troubleshooting on the part of the government, implementing partners, funders, and policy-makers. For optimal results and to achieve the target of virtually eliminating MTCT, all Options will require pre-requisites such as decentralization of services to the primary care and community levels and task shifting to nurses and community health workers, as well as strengthened engagement of family planning, expansion of community based support services and the provision of wrap-around services to provide the basic program activities that reduce HIV risk, transmission and morbidity and mortality.

A country's starting point with respect to these realities, ability to manage the change required, and degree of commitment to eliminating new pediatric infections will ultimately form the basis of which Option that country chooses and the timing of implementation.

That said, the hypothesis is that the resources expended on these system changes and improvements will reap easier and greater benefits under Option B and even more so under Option B+. The April 2012 WHO update makes the case, writing *"Options B and specifically B+*

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[25] A soon to be published article by Avila et al., examines the cost-effectiveness of Option B+ for prevention and treatment of mothers and children Malawi[25]. Concurrent with the logic presented above, this work finds that, while Option B+ requires greater upfront investment than the other Options, its return is also greater, especially when considering the gain in maternal life years and associated cost saved.

seem to offer important programmatic and operational advantages and thus could accelerate progress towards eliminating new pediatric infections. If Option B+ can be supported, funded, scaled up at the primary care level and sustained, it will also likely provide the best protection for the mother's health, and it offers a promising new approach to preventing sexual transmission and new HIV infections in the general population." In light of this statement and the growing evidence that addresses the concern about the costs of Options B and B+, the question is not if countries should transition to them, but when and how.

APPENDIX I

WHO 2010 Guidelines Adoption

Complete: Policy in line with WHO 2010 Guidelines Adopted. (*Implementation status not considered)
In process: Discussions regarding policy adoption are in process but policy has not yet been adopted.
Partial adoption: Do not intend to adopt full WHO recommendation
Insufficient Information

Priority Country	Status of adoption of 2010 WHO guidelines on ARVs PMTCT	Status of adoption of 2010 WHO guidelines on HIV & Infant Feeding
Angola	Partial	Partial
Botswana	Option B. Adoption complete	Adoption complete
Burundi	Option B. Adoption complete	Complete
Cameroon	Option A. Adoption complete	Adoption complete
Chad	Option B -Adoption complete	Adoption complete
Cote d'Ivoire	Option B. Adoption complete	Adoption complete
DRC	Option A - Adoption complete	Adoption complete
Ethiopia	Option A	Adoption complete
Ghana	Option A - Adoption complete	Adoption complete
India	Partial. Shifting to option B	Nutrition guidelines in line with WHO recommendation have been developed with support from UNICEF, WHO and WFP and a technical working group set up by NACO. The guidelines are in draft form pending final approval of Secretary NACO
Lesotho	Option A. Adoption and Roll Out well advanced	Adoption and Roll Out well advanced
Kenya	Option A. Adoption Complete	Adoption complete
Malawi	B+ -Adoption complete, being rolled out.	Adoption complete, being rolled out.
*Mozambique	Option A; national roll-out started July 2011	Fully integrated into the revised PMTCT guidelines
Namibia	Option A. Adopted, endorsed, and partial roll out Discussions to switch to Option B+ started late 2011. Government officially endorsed switch to Option B+ end of March 2012 and the PMTCT TWG has constituted a small group (Ministry + partners) to commence action on developing an operational plan	Adopted, endorsed, and partial roll out. With Option B+ now adopted, the revision of the PMTCT guidelines can be finalized to incorporate the Option B+ elements
Nigeria	A and B- Adoption complete	Complete
South Africa	Option A. Adoption complete	Complete. Aligned to option A
Swaziland	Option A. Adopted, endorsed, and partial roll out	Adopted, endorsed, and partial roll out
Tanzania	Option A. Adopted	Adopted (final guidelines being finalised)
Uganda	Option A. Adopted, endorsed, and roll out.	Adopted, endorsed, and l roll out
Zambia	* Option A. Completed	Completed
Zimbabwe	Option A. Adopted, endorsed, and partial roll out	Adopted, endorsed, and partial roll out
Summary status in March 2012	**20 Complete (91%)** **2 Partial adoptions (9%)**	**18 complete (82%)** **2 in process (9%)** **1 partial/no adoption** **1 insufficient information**
Summary status in May 2012	**20 Complete (91%)** **2 Partial adoptions**	**20 complete (91%)** **1 partial/no adoption** **1 in process**

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