A CASE FOR OPTIONS B AND B+

TO ELIMINATE MOTHER TO CHILD TRANSMISSION OF HIV BY 2015

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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% HIV infections annually.\(^1\) Without intervention, the risk of mother-to-child transmission of HIV (MTCT) can be as high as 45%, however successful implementation of prevention of mother-to-child transmission (PMTCT) programs can reduce this risk to around 2% in non-breastfeeding populations and less than 5% in breastfeeding populations.\(^2\) Eliminating MTCT and protecting 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 collective action across all four prongs of PMTCT\(^1\) has substantially reduced HIV transmission rates among infants. In low and middle-income countries, the percentage of HIV positive pregnant women receiving antiretrovirals (ARVs) for PMTCT increased from 9% in 2004 to 61% in 2011.\(^3\) Transmission to infants is highest (about 80%) in HIV positive pregnant women in need of treatment for their own health.\(^4\) These women make up 40-60% of women accessing PMTCT services\(^5\). Yet on 2011, less than half of eligible pregnant women living with HIV (48%) received ART for their own health\(^6\). Transmission rates have therefore remained high,\(^7\) with the number of annual new infant infections only falling from approximately 570,000 to 273,000 between 2001 and 2011.\(^8\)

The Global Plan Towards Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive\(^9\) 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 HIV-related maternal deaths by 50%. Within these targets, the Global Plan aims to reduce MTCT to less than 5%.\(^10\) These are ambitious yet achievable targets.

The pace of decline in new HIV infections in children—roughly 14% annually from 2009 to 2011—suggests that we may have already fallen behind the Global Plan’s target of reducing the estimated number of new HIV infections in children by 25% from the 2010 level.\(^11\) During 2011-12, some countries have made remarkable improvements while others are lagging behind. The cumulative effect however, sets a pace that will not get us to our 2015 goal.

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\(^1\) 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.
To achieve the 2015 goal, we must take rapid and collective action. One major driver of the trajectory towards virtual elimination of new HIV infections in infants is the choice of PMTCT protocol and selected drug regimen. In practice, the drug regimen options provided to HIV positive pregnant women vary across settings—which affects service coverage, retention and adherence rates, and, ultimately, impacts on transmission. Most priority countries targeted by the Global Plan are currently implementing Option A of the 2010 World Health Organization (WHO) guidelines. A few countries have had relative success with Option A or earlier treatment protocols prior to the 2010 WHO guidance. For example, Botswana, South Africa and Namibia have achieved overall MTCT rates of 4%, 11%, and 12%, respectively. This success can be attributed to national governments and implementing

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

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**ii** Option A: zidovudine during pregnancy/infant NVP during breastfeeding for women without advanced HIV disease; lifelong 3-drug antiretroviral therapy (ART) for women with advanced disease

**iii** Latest available country listing provided in Appendix I of this document.

**iv** 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%.

**v** 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.
partners working aggressively to overcome implementation challenges, including increasing access to services for women and their families and improving retention in services and treatment 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 continuum of clinical services. Exhibit 2 shows an illustrative cascade, based on data from a number of Southern African countries.

The retention challenges associated with treatment 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, and if eligible, initiated for treatment. Access to CD4 testing remains limited and in 2010 only 37% of HIV positive pregnant women received CD4 screening. These services are often not located within ANC and HIV testing services, and as a result there is often attrition of pregnant women between HIV diagnosis and CD4 testing. In addition, due to the long turnaround times for CD4 test results,

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vi These include Zambia, Lesotho, Malawi, Zimbabwe, and South Africa.
women who may be eligible for treatment—and at most risk of vertical transmission due to their advanced disease—may be lost between CD4 testing and initiation of treatment. A cohort in South Africa estimated an overall retention rate of only 33% between the first CD4 test and the initiation of antiretroviral therapy.26

- **Unavailability of labor and delivery treatment regimen at birth site.** The risk of MTCT is highest during labor and delivery at 10-20%. An estimated 35-45% of MTCT occurs during this time period. In many countries, significant portions of women do not deliver at health facilities.27 Because Option A requires a switch in regimen and additional drugs, women who do not deliver in a health facility may not receive the prophylaxis needed for labor and delivery.

- **Higher risk of transmission during breastfeeding.** Option A requires 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.28 During this extended breastfeeding period, countries have experienced high rates of loss to follow-up,29 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 healthcare systems:

- **Procurement and supply chain management difficulties.** Because Option A requires a variety of drugs across the continuum of care, it is more difficult to forecast and manage drug stock. Furthermore, Option A requires large amounts of infant nevirapine (NVP) syrup throughout the breastfeeding period. Managing and distributing the syrup as well as ensuring use before the expiry date is difficult.

- **Complex patient management.** With Option A, patients are given different drug regimens through pregnancy, labor and delivery, and postnatal periods. This requires multiple visits with physicians and healthcare workers for counseling and consultation. In addition, multiple drug regimens may present challenges 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 addressing these challenges, it is not easy to reduce transmission. In 2008, the Malawi Ministry of Health, in partnership with the Clinton Health Access Initiative (CHAI), began a three-year pilot programme in the Machinga District, a highly populated rural district with high HIV-prevalence. Based on modeling,$^{30}$ at the start of the program Machinga had an estimated 18% transmission rate at 6 weeks after an infant's birth and 32% transmission rate at 18 months of age. The targets of the programme were to increase access to PMTCT services for HIV positive pregnant women from 24% to 80%, and to decrease the rate of MTCT at 18 months to 15-22%. The programme focused on improving multiple aspects of the healthcare system, including transportation, lab networks, training, testing technology, and maintaining buffer stock. Over the course of the programme, the modeled transmission rate at 6 weeks decreased to 7.3% and the transmission rate at 18 months decreased to less than 20%.$^{31}$

Because the Machinga programme was implemented before the 2010 WHO guidelines$^vii$ were available, the programme used Option A as recommended in the 2006 guidelines,$^viii$ and therefore did not provide extended prophylaxis throughout the breastfeeding period. If extended prophylaxis had been provided, the modeled transmission rates would have dropped to 12% at 18 months.$^{32}$

Although the Machinga programme substantially reduced the number of new infections in infants, the transmission rate at 18 months remained well above the Global Plan’s 5% target for the 22 PMTCT priority countries$^ix$, suggesting that programmes implementing Option B and B+ could result in additional impact.

A programmatic update released by WHO in April 2012$^{34}$ highlights the challenges associated 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

$vii$ Following the introduction of the 2010 WHO guidelines, Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, 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.

$viii$ The 2006 recommendations 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.

$ix$ The 22 PMTCT priority countries: Angola, Botswana, Burundi, Cameroon, Chad, Cote d’Ivoire, Democratic Republic of Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, United Republic of Tanzania, Uganda, Zambia, Zimbabwe
testing to determine which women should initiate ART for their own health...Options B and specifically B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons.\(^{65}\)

Many countries are therefore considering transitioning to Options B and B+. Updated WHO guidelines scheduled to be released mid-2013 are expected to strongly recommend Options B and B+.

Section 2 of this discussion document explores the benefits of using Options B and B+, and Section 3 explores the financial impact of implementing these options.

**SECTION 2: WHY OPTIONS B AND B+?**

**Safety, regulatory and cost barriers to implementation of Options B and B+ have been overcome.**

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

- **Reduced concern about the safety of efavirenz.** Guidelines issued by the United Kingdom in January 2012 recommend the use of tenofovir disoproxil fumarate/lamivudine/efavirenz (TDF/3TC/EFV) for pregnant women.\(^{36}\) 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.\(^{37}\) Several other systematic analyses of EFV in pregnancy have reached the same conclusion.\(^{38}\) Additionally, the WHO 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.”\(^{39}\)

- **Approval of TDF/3TC/EFV fixed dose combination.** The FDA first approved the three-drug combination in 2006 and FDA tentative approval of a generic supply of the fixed-dose combination (FDC) was granted in September 2009.\(^{40}\) This single pill once-a-day regimen can be used for all adults.\(^{41}\) Two suppliers have received tentative FDA 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 recommended combinations for Options B and B+ make these protocols more viable.\(^{42}\)
**Affordability of TDF/3TC/EFV fixed dose combination.** Between 2007 and 2011, the price of the generic TDF/3TC/EFV tablet dropped by 59%, making it more affordable for countries. According to the Global Price Reporting Mechanism for HIV, tuberculosis and malaria, the price of standard regimen TDF/3TC/EVF ranged from USD$140 to $165 per year in 2012, depending on the country. Averaged across the 22 PMTCT priority countries, annual cost would be $158, or $0.43 per day. In the next few years, further reductions are likely to bring a year’s supply to $100.

**Options B and B+ facilitate operational simplifications.** Options B and B+ have significant operational advantages over Option A that include:

- **Simplifications for the mother.** In Options B and B+ if a pregnant woman tests positive for HIV, she receives treatment immediately (rather than requiring an additional step of initiating treatment only after receiving CD4 results). This decreases the required number of clinic visits, helps reduce loss to follow up, and allows for earlier initiation of treatment in pregnancy. A blood sample for CD4 testing should still be taken after an HIV 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. Simplification of the regimen and decreasing the number of times a woman must switch medications, could have a positive effect on retention and adherence during and after pregnancy.

- **Simplifications for the infant.** The principal mechanism of prophylaxis for Options B and B+ is maternal treatment—a single pill, once a day. Infant prophylaxis is also recommended for 4-6 weeks, regardless of infant feeding method. In contrast, for women with CD4 cells/mm$^3$ > 350, Option A depends solely on infant prophylaxis for the duration of the breastfeeding period. Retention of infants on Option A is challenging, as it requires parents to return to the clinic for regular refills of NVP syrup (which is often difficult to stock and distribute), and administer daily doses of the syrup to the infant for the duration of the breastfeeding period.

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$x$ Loss to follow up is likely reduced at this initial step in the cascade due to the removal of gating CD4 testing. Further research is needed to better understand loss to follow up through the remainder of the cascade.

$xi$ Total volume consumed depends on several factors including a child’s weight distribution over the length of breastfeeding and the concentration of NVP syrup dispensed.
• **Simplifications for the provider.** Unlike Option A, in Options B and B+ a single regimen can be used for the entire adult population, which simplifies operations, procurement and supply management. The 2012 WHO programmatic update states that this streamlining will “maximize program performance through better alignment and linkages with antiretroviral therapy (ART) programs at every level of service delivery.”

While the operational advantages of Options B or B+ are also considerable, shifting from Option A will require country preparation and planning, including 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 effectiveness benefits.**

When compared to Option A, the operational simplifications of Options B and B+ are likely to result in higher retention rates and improved clinical benefits. Implementing Options 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 has resulted in a significant increase in the number of pregnant and breastfeeding women starting ART. After only three months of nationwide implementation, the government saw a greater than five-fold increase in the number of pregnant women enrolled on ART. 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+.

Post-partum retention and adherence on Options B and B+ will 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 stockouts of ARVs, and drive down costs. Money saved can be invested in mechanisms that 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.

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xii These hypotheses should be studied in settings where Options B or B+ are being implemented. As part of the evaluation of whether and when to adopt the options, country-specific hypotheses on the magnitude of the effect of these options on retention rates should be modeled to anticipate the associated impact on transmission rates.

xiii 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.
The clinical benefits of Options B and B+ are illustrated in Exhibit 3 below.

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.** When compared with Options A and B, the total number of new infant infections averted is likely to be higher with Option B+, as more women will already be receiving lifelong treatment initiated during earlier pregnancies.\(^{xiv}\)

- **Improved maternal health.** Option B+ is better for the mother’s health.\(^{xv}\) Introducing mothers to triple ARVs early in their reproductive lives may decrease HIV related morbidity due to opportunistic infections such as tuberculosis.\(^{52}\) Continued adherence to Option B+ will likely increase maternal life expectancy.\(^{53}\) This will have an indirect effect on reducing under-5 mortality, as HIV-positive status of a parent is associated with a 20-40% increase in the risk of mortality in under-5 children.\(^{54}\)

\(^{xiv}\) Due to normal loss in retention, not all women will still be on treatment between pregnancies; the subset of women who do continue to take their ARVs between pregnancies and into the next pregnancy will see this benefit.

\(^{xv}\) Known to be the case for women with CD4 counts < 350; observational evidence only for women with CD4 counts > than 350.
children under-5 regardless of their HIV status. Increasing maternal life expectancy also reduces the number of orphans needing support.

- **Lower transmission to HIV-negative male sexual partners.** Option B+ puts more HIV-positive women on lifelong ART sooner than Options A or B. The HPTN 052 study clearly demonstrates a statistically significant difference in transmission rates to HIV negative male partners of women that are initiated early on ART (i.e., at CD4 counts > 350). An increase in the number of adult infections averted significantly reduces the amount of money spent on HIV care and on treating opportunistic infections such as tuberculosis and pneumonia. This also results in increased productivity as fewer work hours will be spent managing HIV-related ailments and care.

Option B+ likely results in more infections averted and maternal life years saved when compared with Option A or Option B.

**Option B/B+ in the Context of Humanitarian Emergencies**

Options B and B+ also have implications for service delivery in countries prone to humanitarian emergencies. In emergency situations, access to health care can be significantly limited. CD4 testing is often not available and adherence rates can drop due to factors such as inaccessible services, population movement, and service disruption. Because Option A is a more complicated treatment regimen, is more difficult to deliver in humanitarian settings, which may hinder uptake and adherence. Option B+ is simpler to administer and facilitates rapid initiation of treatment.

By providing Option B+ at the decentralized level, at all facilities providing MNCH, emergency-affected women can potentially continue access to their treatment or at least know where they can continue to access care. Standardizing PMTCT protocols between countries will also mitigate the impact of population movement, especially if Option B+ is adopted in neighbouring countries with the potential to host to pockets of populations from the emergency-affected country. This will also reduce the burden of responsibility on the woman to remember her specific regimen if displaced or if attending a different clinic.

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xvi Theoretically all women under all of the options will ultimately be put on ART.

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

xviii These hypotheses should be studied in settings where Options B or B+ are being implemented.
Human Rights Implications of Option B+ for Pregnant Women Living with HIV

Ensuring the rights of women and children in the context of HIV demands an understanding of how HIV-related stigma and discrimination creates or exacerbates human rights violations. In many settings, HIV-related stigma and discrimination fuel the human rights violations which restrict coverage, access and quality of services for women and children, particularly among vulnerable and marginalized groups.

The EMTCT agenda offers an opportunity to address the complexities of ensuring human rights protections. A critical step to a human rights focused implementation of Option B+ is to place women and children at the centre of the decision-making process, and secondly, for stakeholders to work together to determine the best course of action.

Duty bearers including national governments, the United Nations and other partners must actively engage with communities affected by HIV and ensure that EMTCT programmes address the rights of pregnant women and are implemented in a way that protects and preserves those rights. EMTCT programs are the opportunity to create partnerships between all these sectors, including women and children affected by HIV, and define the best ways forward.

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

Malawi is the first of the 22 priority countries of the Global Plan to adopt and implement Option B+. A number of other countries including Uganda, Namibia and Tanzania have received MOH approval for Option B+ and are currently working on developing costed operational plans for implementation. Additional countries including Zambia, South Africa, Mozambique and Kenya are having high-level MOH discussions about changing PMTCT guidelines to Option B+, however the most frequently cited barrier to implementing Options B or B+ is cost.

For example, although Option B+ is included in national guidelines in Uganda, in practice it has only been implemented at pilot sites supported by non-government organizations, due to funding shortages.”

Therefore, accurate costed operational plans are an important part of the PMTCT guidelines process.

Most cost evaluations focus on the immediate cash flow challenges associated with treating more HIV-positive pregnant women, and as a result, the full financial cost-benefit of Option B+ is obscured. A more comprehensive picture of cost includes the incremental cost incurred to administer Option B or B+,
the cost of failure (i.e., the increased number of new infections and their associated costs) in Option A in the short and medium term, and the additional benefits and cost-savings from Option B and B+.

**Cost over time**

Comprehensive cost is evaluated in two ways: the near-term, focused on the incremental cost of paying for Options B or B+ versus Option A; and the long-term, focused on the aggregate cost over time of paying for the full set of benefits and costs accrued under Options B or B+ compared to Option A.

Concern about short-term cost is valid. Both Options B and B+ require spending in the short-term in order to accrue results in the medium and long-term. This incremental direct cost per mother-baby pair in Option B 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,\(^{\text{ix}}\) shows incremental direct costs of treating all\(^{\text{xx}}\) mother-infant pairs on Option B instead of on Option A of approximately $350 million per year. While this is not an insignificant amount of money, it pales in comparison to the $15 billion\(^{\text{59}}\) total global expenditures in HIV in 2010.

Concerns related to long-term costs can be simplified to a single question: *Does the incremental cost required to implement Options B or B+ exceed the “cost of failure” associated with Option A?* The long-term cost calculation must reflect the relationship between the increased costs incurred by more HIV+ pregnant women receiving treatment and the related cost savings of 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 occur under Option A.

Many groups are working to analyze this question in different ways\(^{\text{xxi}}\) (e.g., country-specific vs. not, theoretical coverage and retention levels vs. operational realities, how cost compounds over time, etc.), but initial analyses consistently point to the importance of looking at the full picture over a longer timeframe to see true costs or cost savings of Options B and B+ over Option A. The U.S. Centers for

\(^{\text{ix}}\) 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.

\(^{\text{xx}}\) 100% coverage of mother-infant pairs is, of course, unrealistic; maximum coverage used here to estimate maximum cost.

\(^{\text{xxi}}\) 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.
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.

Relative cost of each Option

In an effort to better understand how the costs of Options B and B+ compare to those of Option A over time, a rapid modeling exercise has been conducted by CHAI, BLC and UNICEF. 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 contextsxxii.

The logic and framing described below is not intended to provide any authoritative answers. The purpose is to inform the ongoing conversations about a large scale shift away from Option A. The intent is also to inform country participation to help evaluate Options B and B+ for individual country settings.

This review of the costs incurred from the three Options presents a telling story about the relative aggregate cost over time. All HIV+ pregnant women, regardless of CD4 count at the time of their pregnancies will require treatment at some point to prevent vertical transmission. It is necessary therefore, to estimate the absolute cost incurred for the total number of people receiving prophylaxis and/or treatment across the options. It is also 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, the approach of determining relative aggregate cost over time includes costs for HIV+ pregnant women and their infants on Options A and B who initiate treatment after their interactions with the PMTCT cascade. For example, this would include the lifetime absolute cost of an HIV+ woman whose CD4 count is >350 cells/mm³ 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.

xxii Options B and B+: Model Methodology, UNICEF, BLC, CHAI 2012
There are three types of people affected in this scenario: 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 their infants generate direct drug costs for prophylaxis and/or treatment over time and through multiple pregnancies. Serodiscordant partners of HIV+ pregnant (or formerly pregnant) women generate treatment costs if they are infected. All three groups have associated non-drug related 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 continuum 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, but significant drop-offs in client retention through subsequent care). For Options B and B+, it assumes that drop-offs between testing and initiation of ARVs are reduced. However, the travel that is often required from ANC to ART clinics to initiate ARVs will still result in some women being lost in the process. These assumptions remain conservative, using real world data showing current PMTCT and treatment coverage rates that remain static over time.

**Incremental spending 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. Triple ARVs used for prophylaxis in Option B cost more than the ARVs prescribed for prophylaxis to HIV+ pregnant women and their infants in Option A.

Option A, however, leads to more infant infections, which are primarily driven by two factors:

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xxiii 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.

xxiv 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 Option A higher.
• 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; and

• The difficulties associated with administering daily NVP syrup to infants leads to disproportionately high attrition of breastfed infants during prophylaxis phase.

Given this higher rate of infection after the initial years, the total cost per year of Option A is higher than Option B. The cost of failure (i.e. HIV+ infants) in Option A compounds over time as more and more children require. This is true even under extremely conservative treatment coverage assumptions for children (assumed to be roughly 25% in this case). The 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.

Considering the cumulative direct costs of both Options over several years,\textsuperscript{xxv} implementing Option B saves more money than Option A.

\textit{Incremental spending on Option B+ as compared to “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 higher than Option A and incrementally higher than Option B, due to sustained ART coverage for HIV+ pregnant women.

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\textsuperscript{3} implies more women are eligible for treatment in Option A) and actual treatment coverage of those women. As treatment coverage increases rapidly in many countries, the differential cost of Option B versus B+ may not be dramatic over time.

In addition to the cost differences between Option B and B+, Option B+ results in financial benefits above and beyond Option B. The benefits include lower rates of transmission to infants due to protection from ART initiated in the previous pregnancy, reduced transmission rates to HIV negative

\textsuperscript{xxv} Definitive modeling must be conducted to determine this time frame using country-specific assumptions. 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 on a country-by-country basis.
male sexual partners, improved maternal health and associated productivity gains, lower morbidity and associated secondary and tertiary care costs, and potentially lower non-drug related direct and indirect costs of delivery (including cost of fewer CD4 tests, lower costs from switching on and off treatment over time).

Modeling the transition from Option A to Option B+ involves accounting for the incremental cost of sustained treatment weighed against the unique financial benefits of Option B+. A number of variables are critical to this cost-benefit equation and most cannot be modeled quickly or without country participation. 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 started on treatment and how long these infants continue on treatment. Higher rates of pediatric treatment will result in higher total system costs under Option A, thereby 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 partner infected by an HIV+ positive woman. The HPTN052 study demonstrated a significant decrease in transmission rates to male partners for HIV+ pregnant women who initiate ART early (i.e., with CD4 >350). Pregnant women with CD4>350 cells/mm$^3$ will have a lower transmission rate on Option B+ than on Option A (or on 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. Transmission rate is also heavily associated with sexual behavior (e.g., condom use) as well as prevalence of male circumcision in a particular population.

**Non-drug related direct (and indirect) costs:** Non-drug related direct treatment costs are mainly lab and human resource costs. These costs will differ across options based on testing, training and patient counseling requirements. For example, as 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 may lead to lower non-drug related direct costs per
patient for Option B+. Non-drug related 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. They will 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 depends on the country context. These costs would be higher for Option A than B
or B+, as Option A leads to 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 in countries, to result in Option B+ becoming cost
neutral relative to Option A. In Malawi, 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.xxvi These results should be modeled on a country-specific basis to enable
governments to make a balanced choice between which options they can implement.

**Looking beyond cost to implementation**

The realities of implementation are a critical consideration in any country’s decision to implement one of
the options. These implementation challenges should not to be ignored or minimized. No option is easy
to implement. Each option requires concerted effort, resources, reorganization, program scale-up, and
troubleshooting from the government, implementing partners, funders, and policy-makers. To achieve
the target of virtually eliminating MTCT, all options require certain pre-requisites to be in place. Pre-
requisites include decentralization of services to the primary care and community levels, task shifting of
nurses and community health workers, strengthened engagement of family planning services,

xxvi An article by Fasawe et al (2013), examines the cost-effectiveness of Option B+ for prevention and treatment of mothers and children
Malawi. 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.
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 pre-requisites, the ability to manage the change required, and the degree of commitment to eliminating new pediatric infections will ultimately form the basis of which option that country chooses as well as the timing of implementation.

The assumption is that the resources expended on these system changes and improvements will reap easier and greater benefits under Option B and even more under Option B+. According to the April 2012 WHO programmatic update:

"Options B and specifically B+ 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."61

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: Status of adoption of WHO 2010 Guidelines (as of April 2013)

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