FORUM

The case for Option B and Optional B+: Ensuring that South Africa's commitment to eliminating mother-to-child transmission of HIV becomes a reality

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In a previous issue of the *Southern African Journal of HIV Medicine*, Pillay and Black summarised the trade-offs of the safety of efavirenz use in pregnancy (Pillay P, Black V. Safety, strength and simplicity of efavirenz in pregnancy. *Southern African Journal of HIV Medicine* 2012;13(1):28-33.). Highlighting the benefits of the World Health Organization's proposed options for the prevention of mother-to-child transmission (PMTCT) of HIV, the authors argued that the South African government should adopt Option B as national PMTCT policy and pilot projects implementing Option B+ as a means of assessing the individual- and population-level effect of the intervention. We echo this call and further propose that the option to remain on lifelong antiretroviral therapy, effectively adopting PMTCT Option B+, be offered to pregnant women following the cessation of breastfeeding, for their own health, following the provision of counselling on associated benefits and risks. Here we highlight the benefits of Options B and B+.

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In a recent issue of the *Southern African Journal of HIV Medicine*, Pillay and Black[1] summarised the trade-offs surrounding the safety of efavirenz (EFV) use in pregnancy. Highlighting the benefits of each option for the prevention of mother-to-child transmission (PMTCT) of HIV proposed by the World Health Organization (WHO), the authors argued that the South African (SA) government should consider the adoption of Option B as national PMTCT policy, and pilot projects implementing Option B+ as a means of assessing the individual- and population-level effect of the intervention. We echo this call and further recommend that '*optional B+*' (i.e. the option to stay on lifelong antiretroviral therapy (ART), effectively adopting PMTCT Option B+) be offered to pregnant women for their own health after the cessation of breastfeeding, following counselling on the benefits and risks of the intervention. In this article we highlight the benefits of Options B and B+.

In April 2012, WHO released a programmatic update to the use of antiretrovirals (ARVs) for PMTCT and the treatment of HIV-positive pregnant women.[2] The key findings indicate that Options B and B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons. While all options recommend initiating triple ARV therapy in HIV-positive pregnant women with a CD4 count <350 cells/mm^3,

their recommendations differ for CD4 counts >350 cells/mm^3. For the latter, Option A promotes: the use of zidovudine (AZT) from 14 weeks' gestation, single-dose nevirapine (NVP) at birth, and 7 days of AZT/lamivudine (3TC) postpartum for the mother; and daily NVP for the infant until the cessation of breastfeeding or until 4 - 6 weeks of age if the mother is receiving antiretroviral therapy (ART) or is not breastfeeding. Option B recommends ART for the mother from 14 weeks' gestation until birth or the cessation of breastfeeding, and the use of NVP for the infant until 4 - 6 weeks of age. Option B+ advocates lifelong ART, and NVP for the infant as for Option B. The rationale behind these recommendations stems from increasing evidence at clinical and programme levels highlighting the benefits of a single, standardised regimen to serve PMTCT and the treatment of HIV-positive pregnant women. The WHO update reflects earlier recommendations from major donors such as the United States President's Emergency Plan for AIDS Relief (PEPFAR),[3] and has led to the adoption of Option B+ by other high-burden African countries including Malawi, Kenya, Uganda, Swaziland and Rwanda, with pilots underway in several others.[4] Further support for PMTCT Options B and B+ are echoed in a newly released report by the United Nations Children's Fund (UNICEF), the Business Leadership Council and the Clinton Health Access Initiative.[5] WHO further highlights that this suggested approach would strengthen the effectiveness of the PMTCT programme through improved linkages with ART programmes.

Options B and B+ are simpler, probably safer, and less resource-intense than Option A

Numerous challenges have been experienced with the implementation of Option A. In addition to requiring drug changes across the continuum of care (antenatal, delivery and postpartum care),[1,6] the option necessitates the use of different ARVs depending on CD4 count. Option A also involves a long period of AZT monotherapy with associated potential for developing thymidine analogue (TAM) mutations, and it complicates clinical management and delays treatment initiation, mostly where access to CD4 count measurement is scarce.

The provision of effective care in SA is challenged by congested health facilities and a lack of human resources. Appropriately, Options B and B+ reduce the burden on healthcare workers. Option B simplifies the delivery of care by ensuring that the same regimen offered to pregnant women is the first-line regimen for all adults, with the WHO recommendation of EFV for all stages of pregnancy.[7] A standardised fixed-dose ARV combination throughout antenatal, delivery and postpartum care would not only improve continuity of care, but also simplify drug forecasting, procurement, supply chain management, and stock-out monitoring. The current first-line regimen in SA is tenofovir (TDF)/lamivudine (3TC)/efavirenz (EFV); generic single-pill fixed-dose combinations are registered and most likely to be included in SA's ARV tender for 2013. Despite reassurance from the 2010 Medical Research Council (MRC) survey showing a reduction of mother-to-child transmission of HIV in SA to 2.7%,[8] there are concerns regarding the feasibility and acceptability of the daily administration of nevirapine (NVP) syrup, including multiple reports of associated delivery problems. With the hasty cessation of the provision of free formula in the public sector, there may be a future increase in breastfeeding transmission rates. Strangely enough, this seems to have been accepted as a fatality by the National Strategic Plan (NSP) 2012 - 2016 target of <2% at birth and <5% at the end of breastfeeding.

For even further programmatic simplification, Option B+ would altogether send one simple and strong message to patients: 'ART for life' – promoting good adherence and successful ART. Stopping ART after the cessation of breastfeeding is likely to lead to confusing messages for HIV-infected individuals, their communities and health workers. Moreover, there is a risk of developing non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance if ART is stopped without tail protection (i.e. continuing the 2 remaining ARV drugs for 7 days after withdrawal of an NNRTI). The possible field implications of this are not yet well understood. While Option B remains simpler than Option A, it requires that primary healthcare services: determine the HIV status of women at each pregnancy; determine the CD4 count/HIV clinical stage before ART initiation at each pregnancy; ensure timeous ART initiation at each pregnancy for HIV-positive women; identify intent to breastfeed and the duration thereof after each delivery (taking into consideration that women are known to breastfeed beyond the initially intended period); and ensure that ART is ceased safely after each pregnancy, with CD4 count follow-up. Each additional step in the treatment cascade increases the risk of patient attrition. A study in SA demonstrated a 33% retention rate from first CD4 count to ART initiation.[9] Option B also recommends ART initiation from 14 weeks' gestation – assuming that women present for care early in pregnancy. Programme data, however, show that the majority of women present much later in pregnancy. Many of these challenges would be overcome with Option B+.

Treatment interruptions may be harmful

The national fertility rate in SA is 2.5.[10] With multiple pregnancies, typical in developing countries, women identified as HIV-positive tend to be exposed to the potentially harmful repeated initiation and discontinuation of ARVs. This is particularly pertinent in other sub-Saharan countries with much higher fertility rates than SA (e.g. in Malawi, with 5 - 6 births per woman).[11] In a recent systematic review,[12] unstructured treatment interruptions were associated with a higher risk of death and opportunistic infection, a lower probability of increased CD4 cell counts, a higher prevalence of neurocognitive impairment, a lower health-related quality of life, and an increased risk of virological failure and drug resistance. Earlier trials demonstrated that structured treatment interruptions were harmful to patients.[13,14] Consequently, many experts endorse continuous ART for pregnant women, rather than stopping and starting therapy with each pregnancy.[6]

Early initiation on ART may improve outcomes for mothers

Following increasing supporting evidence and expert opinion, initiation of ART at a CD4 count >350 cells/mm^3 to reduce morbidity and mortality (outside the context of pregnancy) is now recommended in US and European guidelines.[15,16] However, there is ongoing controversy in this regard. While the debate remains open about the individual benefits of ART initiation above a CD4 count of 500 cells/mm^3, a special case could be made for women of childbearing age in an African context. Multiple pregnancies and increased infectious risks serve to predispose these women to a rapid decline in CD4 count; hence, there is a relatively short time period within which the women's CD4 counts are high enough for the benefits of ARV initiation to be questionable. In a study from Zimbabwe, the peri-partum mortality of women with CD4 counts of 400 - 600 cells/mm^3 was 5.4 times higher than for their HIV-negative counterparts.[17] Furthermore, continual increases in maternal mortality in SA have been attributed to the AIDS epidemic.[18]

Option B+ could reduce early *in utero* HIV transmission

Option B+ ensures that women are already receiving ART for subsequent pregnancies, covering the initial weeks and maintaining a higher CD4 count. Several studies have demonstrated that the lowest risk of transmission is among women who have initiated ART before conception in comparison with those who initiate ART during pregnancy. The reduced risk of transmission is believed to be as a result of reducing the risk of early *in utero* transmission.[19,20]

Horizontal transmission to HIV-negative partners

The HIV prevalence among women during their reproductive years is particularly high in SA. A study among couples across eastern and southern Africa demonstrated a prevalence of stable HIV-discordant partnerships of 8 - 31%, with 49% serodiscordance among couples with at least one HIV-infected partner.[21] In a meta-analysis in sub-Saharan Africa, the proportion of HIV-positive women in stable HIV-serodiscordant relationships was 47%, demonstrating that women are just as likely as men to be the index partner.[22] As demonstrated in the HPTN 052 trial,[23] ART decreases transmission in HIV-serodiscordant couples by 96%. Continuing ART in women between pregnancies during their reproductive years would also serve to protect their HIV-negative partners. This is in line with the new WHO recommendations that HIV-positive individuals in serodiscordant partnerships be given ART regardless of CD4 count.[24]

Cost-effectiveness of treatment scale-up

The expected reductions in the number of infections, morbidity and mortality, both in children and adults, through the provision of Option B+, will contribute to a decline in overall treatment cost after initial funding.[25]

Challenges and arguments against Option B+

Several arguments against the adoption of Option B+ must be discussed when considering the roll-out of this intervention.

Adherence

Adherence among HIV-infected pregnant women is probably the most challenging issue, for short-course (Option A/B) and lifelong therapy.[26-29] In a recent meta-analysis of ART adherence during and after pregnancy, ART adherence was well below what was recommended for adequate virological suppression, especially during the postpartum period.[30] This has significant implications for the success of lifelong treatment, as recommended with Option B+. Loss to follow-up among pregnant women initiating ART across SA was found to be the greatest in the first 3 months after ART initiation, with differences diminishing over time.[31] This highlights where adherence support is most required. New innovative strategies need to be identified and piloted to address this, including: simpler and more tolerable ART regimens (TDF – fixed dose and combination); a reduced number of clinic visits and time associated with such visits; and adherence support clubs to optimise peer support.

We suggest an 'opt-out' option at the end of the breastfeeding period for women with a CD4 count >350 cells/mm^3 who do not want to remain on ART, allowing structured ART cessation with tail protection.

Cost

ARV drug cost was a major determinant in the decision of many sub-Saharan countries to implement PMTCT Option A. In 2009, the average drug cost for implementing Option B was 3 - 5 times higher than that of Option A. However, by the end of 2011, the cost was only twice as high.[2] The annual cost of the TDF/3TC/EFV first-line regimen in SA is R1 361.45 (approximately US$162) per patient. A single-pill fixed-dose regimen costs only marginally more: R1 424.88 (approximately US$172) per patient.[32] The lowest international price is R828 (US$100) per patient, and further reductions are expected. With the opening of the SA ARV tender in October 2012, fixed-dose combination drugs are likely to become available in the public sector. Further studies by the United States Centre for Disease Control (CDC) show that Option B+ would cost marginally more than Option B (incremental cost of $270 at 5 years) in the case of multiple pregnancies.[33]

Risk of renal toxicity from TDF

TDF has the potential for renal toxicity. While pregnancy-related conditions such as hypertension, pre-eclampsia and diabetes increase the risk of renal impairment,[34] this is offset by the young age of pregnant women. Furthermore, Option B+ policy ensures that most women start ART early in their HIV infection. Concerns remain surrounding the effect of TDF exposure on infant growth, with limited available data.[35]

Conclusion

Recently, SA's National Strategic Plan considered the evidence to be insufficient to warrant a change from the current PMTCT Option A protocol. The WHO programmatic update concludes that both Options B and B+ offer programmatic and operational advantages that would go towards the elimination of mother-to-child HIV transmission. The implementation of Option B+ would require increased adherence support mechanisms, funding, and scale-up at the primary healthcare level, including the adoption of task-shifting for ART initiation. However, this would result in the best protection for the health of pregnant women and infants, and contribute to reduced HIV transmission among sero-discordant couples according to the latest evidence.[23] In the medium term, this strategy is highly likely to be cost-effective.

Further research is required to address the challenges faced by PMTCT programmes while drawing on the latest scientific evidence to ensure that it is translated into policies reflecting the needs and realities of the millions of women living with HIV and their children. SA's PMTCT programme must ensure the delivery of the best care possible and move towards the elimination of paediatric HIV. A more aggressive PMTCT option such as B+ should be tested urgently, as it may be a necessary step to reach this goal.

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