

PROGRAMMATIC UPDATE

**USE OF ANTIRETROVIRAL DRUGS
FOR TREATING PREGNANT WOMEN
AND PREVENTING HIV INFECTION IN INFANTS**

EXECUTIVE SUMMARY

APRIL 2012

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Recent developments suggest that substantial clinical and programmatic advantages can come from adopting a single, universal regimen both to treat HIV-infected pregnant women and to prevent mother-to-child transmission of HIV. This streamlining should maximize PMTCT programme performance through better alignment and linkages with antiretroviral therapy (ART) programmes at every level of service delivery. One of WHO's two currently recommended PMTCT antiretroviral (ARV) programme options, Option B, takes this unified approach.

Now a new, third option (Option B+) proposes further evolution—not only providing the same triple ARV drugs to all HIV-infected pregnant women beginning in the antenatal clinic setting but also continuing this therapy for all of these women for life. Important advantages of Option B+ include: further simplification of regimen and service delivery and harmonization with ART programmes, protection against mother-to-child transmission in future pregnancies, a continuing prevention benefit against sexual transmission to serodiscordant partners, and avoiding stopping and starting of ARV drugs. While these benefits need to be evaluated in programme settings, and systems and support requirements need careful consideration, this is an appropriate time for countries to start assessing their situation and experience to make optimal programmatic choices.

This programmatic update is meant to provide a current perspective for countries on the important changes and new considerations arising since publication of WHO's PMTCT ARV guidelines, 2010 version, especially as a number of countries are now preparing to adopt Option B+. WHO has begun a comprehensive revision of all ARV guidelines, including guidance on ARVs for pregnant women, planned for release in early 2013.

Prevention of mother-to-child transmission of HIV (PMTCT) is a dynamic and rapidly changing field. Current World Health Organization (WHO) PMTCT antiretroviral (ARV) guidelines on treating pregnant women and preventing infection in infants (1), issued in 2010, were a major step towards more efficacious regimens. The WHO guidelines emphasize the importance of providing lifelong antiretroviral therapy (ART) to all HIV-infected pregnant women eligible for such treatment and recommend two short-term antiretroviral prophylaxis options (Option A and Option B) for women not eligible under current criteria, as determined by CD4 count, for treatment for their own health (Table 1). Recently, a third option, to provide lifelong ART to all HIV-infected pregnant women, regardless of CD4 cell count, has emerged (Option B+), and a number of countries are already adopting or considering this approach.

Although many low- and middle-income countries are still in early stages of implementing the 2010 guidance, new evidence and recent experience warrant a programmatic update to reassess preferences between Options A and B for prophylaxis in HIV-infected pregnant women who do not need treatment for their own health and to weigh the potential advantages and considerations of the new Option B+ approach in a public health perspective.

Current WHO guidance on ARV use in HIV-infected pregnant women

The 2010 WHO PMTCT ARV guidelines are based on the need to distinguish between treatment and prophylaxis. Consistent with the 2010 WHO adult ART guidelines (2), they recommend and prioritize starting all women with CD4 counts ≤ 350 cells/mm³ or WHO Stage 3 or 4 disease (approximately 40–50% of all HIV-infected pregnant women) on ART for life for their own health as well as for the prevention of infant HIV infection. For women with CD4 counts > 350 cells/mm³, who are not eligible for treatment according to current criteria, the PMTCT ARV guidelines recommend starting ARV prophylaxis early in pregnancy and, in breastfeeding settings, providing extended ARVs to either the mother or child during the postpartum risk period.

The two recommended prophylaxis options, A and B, are quite different programmatically but were judged to be equally efficacious, *if implemented appropriately*, in reducing the risk of infant infections for women with CD4 counts > 350 cells/mm³. Because of the difference in the prophylaxis options, it is sometimes not well understood that Options A and B include both treatment and prophylaxis components, as shown in Table 1. The overall effectiveness, both for the mother's health

Table 1. Three options for PMTCT programmes

	Woman receives:		Infant receives:
	Treatment (for CD4 count ≤350 cells/mm ³)	Prophylaxis (for CD4 count >350 cells/mm ³)	
Option A^a	Triple ARVs starting as soon as diagnosed, <i>continued for life</i>	<i>Antepartum:</i> AZT starting as early as 14 weeks gestation <i>Intrapartum:</i> at onset of labour, sdNVP and first dose of AZT/3TC <i>Postpartum:</i> daily AZT/3TC through 7 days postpartum	Daily NVP from birth through 1 week beyond complete cessation of breastfeeding; or, if not breastfeeding or if mother is on treatment, through age 4–6 weeks
Option B^a	<i>Same initial ARVs for both^b:</i>		Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
	Triple ARVs starting as soon as diagnosed, <i>continued for life</i>	Triple ARVs starting as early as 14 weeks gestation and <i>continued intrapartum and through childbirth if not breastfeeding or until 1 week after cessation of all breastfeeding</i>	
Option B⁺	<i>Same for treatment and prophylaxis^b:</i>		Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method
	Regardless of CD4 count, triple ARVs starting as soon as diagnosed, ^c <i>continued for life</i>		

Note: "Triple ARVs" refers to the use of one of the recommended 3-drug fully suppressive treatment options.

^a Recommended in WHO 2010 PMTCT guidelines

^b True only for EFV-based first-line ART; NVP-based ART not recommended for prophylaxis (CD4 >350)

^c Formal recommendations for Option B+ have not been made, but presumably ART would start at diagnosis.

and for preventing new infant infections, of implementing either of the options depends on providing both ARV treatment to those with low CD4 counts and prophylaxis to those with higher CD4 counts. Countries were asked to weigh the benefits and uncertainties of the two approaches, particularly the operational issues, in order to determine the best approach for their national programme.

Rationale for this update

In the short time since the 2010 PMTCT ARV guidelines were developed, the context and expectations for PMTCT programmes have changed considerably. Major changes include:

- the ambitious goals for eliminating paediatric HIV infection of the new *Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive* (3), together with substantial progress in the global scale-up of PMTCT and ART coverage (4);
- new evidence to support ARV treatment as HIV prevention—notably that provision of ART to HIV-infected individuals with higher CD4 cell counts, who are not eligible for treatment, significantly reduces sexual transmission to a serodiscordant (uninfected) partner (5); this evidence has led to new WHO recommendations on couples

counselling and treatment for serodiscordant couples regardless of CD4 count (6);

- increasing country experience with operational and programme implementation challenges with both Option A and Option B;
- the proposal by some countries to move to the new Option B+ approach of lifelong ART for PMTCT for all HIV-infected pregnant women, rather than stopping ARVs for women not eligible for treatment, as in both Option A and Option B (7);
- the launch of the Treatment 2.0 Initiative to simplify and optimize the use of ARVs and standardize the first-line treatment regimen (8,9);
- reassuring data on the safety of efavirenz in pregnancy (10); and
- the decreasing cost of ARV drugs (11,12).

In addition, concerns have been raised that WHO's recommendation of two different options for PMTCT prophylaxis for HIV-infected women who do not require treatment for their own health might be confusing and should be reconsidered in light of newly recognized potential benefits, operational experiences and the programme requirements of the various options.

This programmatic update, while not presenting new guidelines, reviews the currently recommended Options A and B, discusses the rationale for Option B+, and provides an update from WHO indicating and weighing preferences as much as possible among the range of options. This update summarizes key issues that need to be addressed in field settings and in national programmes. It also highlights evidence gaps that need to be addressed to build a base for future revision of guidelines.

Key findings

This programmatic update indicates that Options B and specifically B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons. 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. In contrast, Option B and Option B+ start all HIV-infected pregnant women on triple ARV regimens without need for an initial CD4 cell count (although CD4 testing is still needed in Option B and desirable in Option B+). Thus, Options B and B+ provide greater assurance that women in need of treatment receive a fully suppressive triple ARV regimen, to minimize the risks of infant infection and maximize the benefit to their own health, and avoid inadvertently receiving a sub-optimal ARV prophylaxis intervention, particularly in settings with limited access to CD4 testing. Limited access to timely, reliable CD4 testing, and thus the inability to identify women in need of treatment and to initiate treatment, is a major concern in many resource-constrained settings, especially at the primary care level, where most women obtain maternal and child health (MCH) care.

Regimen efficiency and simplification. Another key advantage of Options B and B+ is greater efficiency, very much in accord with Treatment 2.0 principles. First, the same simplified, fixed-dose combination ARV regimen can be used throughout the PMTCT intervention. Further, it is possible, and highly desirable, to provide the same regimen both for PMTCT and as the first-line national ART regimen for non-pregnant individuals. The ability to use the same regimen for PMTCT and for first-line ART considerably simplifies drug forecasting, procurement, supply to facilities, and drug stock monitoring. The first-line regimen of tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) is available as a single-pill fixed-dose combination and has been recommended recently as the optimized regimen for first-line adult treatment, including for pregnant women (9). An important advantage of efavirenz in the first-line regimen is that it can be used in all women, regardless of CD4 count (unlike nevirapine, which cannot be used in women with high CD4 counts). Although concerns remain about the safety of efavirenz in early pregnancy, and enhanced pharmacovigilance monitoring is needed, review of recent data is reassuring, and benefits are likely to outweigh risks (10).

Many HIV high-burden countries initially chose Option A because of limited PMTCT programme support, challenges of

scale-up, lower drug costs, ease of adding on to prior PMTCT approaches and training, and limited capacity to provide triple ARVs in MCH settings. However, these factors are changing, and a number of high-burden countries are considering moving from Option A to Option B or B+.

Costs. The cost of ARV drugs was a major determinant in countries' choice of a PMTCT option. In 2009 the average ARV drug cost of Option B was three to five times higher than the cost of Option A (depending on regimen and assuming the provision of both ART and prophylaxis). However, by the end of 2011, this differential had diminished to two times higher. The annual cost of two-pill formulations of TDF/3TC/EFV has decreased by 30% over the past three years and is now US\$150; the newer TDF/3TC/EFV single-pill fixed-dose regimen costs approximately US\$180 per year (11,12). Further declines are anticipated. With the differing initial cost of drugs now less of a factor, analyses of long-term costs, cost-benefit and cost-effectiveness will be more appropriate for guiding policy decisions than per person initial cost.

Option B+ advantages. The Option B+ approach of life-long ART for all HIV-infected pregnant women, regardless of CD4 count, has important advantages over both Options A and B (*if viral suppression is maintained*) but needs to be evaluated in programme and field settings. These advantages include:

1. further simplification of PMTCT programme requirements—no need for CD4 testing to determine ART eligibility (as required in Option A) or whether ART should be stopped or continued after the risk of mother-to-child transmission has ceased (as in Option B) (although CD4 counts or viral load assays are still desirable for determining baseline immunological status and monitoring response to treatment);
2. extended protection from mother-to-child transmission in future pregnancies from conception;
3. a strong and continuing prevention benefit against sexual transmission in serodiscordant couples and partners;
4. likely benefit to the woman's health of earlier treatment and avoiding the risks of stopping and starting triple ARVs, especially in settings with high fertility; and
5. a simple message to communities that, once ART is started, it is taken for life.

Challenges and questions. Still, there are important programmatic, operational and clinical challenges and questions about Option B+ that need to be addressed, including service organization and service delivery of ART in MCH and primary care settings, cost and sustainability, ARV adherence and retention in care, referral mechanisms and transitions from the PMTCT programme to HIV care and treatment programmes, concerns about HIV drug resistance with long-term use of ART when initiated in early HIV disease, safety of increased ARV exposure for the fetus/infant, acceptability and equity. Thus, countries implementing Option B+ or planning demonstration projects should be supported to monitor this approach closely to address these issues and assess the feasibility, cost-benefit and public health impact of Option B+.

WHO advice to countries

In light of global and country commitments to elimination of new paediatric infections and the changes outlined in this programmatic update, all countries should examine their own policy, goals and implementation experiences and assess how they can better simplify, optimize and integrate their PMTCT and ART programmes. Countries that are successfully implementing Option A and achieving their targets of decreasing mother-to-child transmission of HIV and treating mothers eligible for ART do not need to plan an immediate change to Option B or B+. Countries that are considering changing their PMTCT guidelines should anticipate and prepare adequately for the changes, to assure that clear policy, implementation strategy, proper messaging, training and an ARV demand forecasting and supply system are in place.

Options B and specifically B+ seem to offer important programmatic and operational advantages and thus could accelerate progress towards eliminating new paediatric 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.

There is an urgent need to assess country experiences and evidence that address the preferences among Options A, B and B+ outlined here. Evidence on the operational advantages of providing triple ARVs to all HIV-infected pregnant women (Options B and B+), on how to best meet the programme requirements of these approaches, and on the acceptability, effectiveness and prevention impact of providing lifelong ART to all HIV-infected pregnant women (Option B+) will help inform upcoming guidelines revision.

This programmatic update is meant to provide a current perspective for countries on the important changes and new considerations arising since the 2010 PMTCT ARV guidelines, especially as a number of countries are now preparing to adopt Option B+. WHO has begun a comprehensive revision of all ARV guidelines, including guidance on ARVs for pregnant women, planned for release in early 2013.

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Programmatic update on ARVs for pregnant women and PMTCT: Key points

- **Time to reassess.** New developments warrant reassessment of current PMTCT and treatment options. WHO is not changing its guidance now but will review its PMTCT ARV guidelines as part of a comprehensive review and consolidation of all ARV-related guidance in 2013.
- **Options B and B+ have advantages.** WHO recognizes that in many settings there are likely to be important clinical and programmatic advantages to the currently recommended Option B (maternal triple ARVs for all HIV-infected pregnant women and continued lifelong for those eligible for treatment) and the emerging Option B+ (lifelong treatment for all HIV-infected pregnant women, regardless of CD4 count) over Option A (ART for pregnant women eligible for treatment; AZT antenatal single-drug prophylaxis and infant prophylaxis during breastfeeding).
- **Options B and B+ better assure treatment.** While current data do not indicate differences in the efficacy of Options A and B when used as prophylaxis for women not eligible for treatment, Options B and B+ provide greater assurance that women in need of treatment, especially in settings with limited access to CD4 testing, receive a fully suppressive triple ARV regimen to minimize the risk of infant infection and to benefit their own health.
- **Benefits beyond PMTCT.** Option B and particularly Option B+ offer women benefits beyond PMTCT, including likely additional benefit for women's own health by starting treatment earlier and prevention of sexual HIV transmission to uninfected partners, including the common situation of HIV serodiscordant couples.
- **Higher cost but more cost-effective?** Initial drug costs are higher for Options B and B+ than for Option A, but the cost of the drugs is decreasing. The benefits gained for the costs expended are likely to be much greater.
- **Options B and B+ simpler for programmes.** These regimens are, in many aspects, simpler for programmes—the same regimen could be given to all HIV-infected pregnant women (available as a once-daily fixed-dose combination); there is no initial distinction between treatment and prophylaxis; CD4 counts are not needed for starting ARVs; there is no change in regimen during the pregnancy/postpartum period (as in Option A); and the regimen could be harmonized with adult ART regimens for easier logistics if an efavirenz-based regimen is used.
- **Option B+ has further advantages.** Compared with Option B, Option B+ would provide protection against sexual transmission of HIV that extends past the period of risk for mother-to-child transmission, protect the next pregnancy starting from conception, and avoid stopping and restarting ARVs with the next pregnancy or when CD4 count later drops below 350 cells/mm³.
- **More countries moving toward Option B or B+.** Many high-burden countries in sub-Saharan Africa initially favoured Option A, due to lower drug cost and continuity with prior PMTCT recommendations, but some are now reassessing this choice. Countries with lower prevalence or more developed infrastructure tended to choose Option B. Malawi was the first to adopt Option B+, for its ease of implementation and potential prevention benefit; additional countries are now considering Option B+.
- **Easier implementation could expand services.** Reported difficulties with implementing PMTCT programmes, including the challenge of providing ARV treatment in MCH settings and at the primary care level, highlight the importance of simplifying drug regimens and operational delivery, as exemplified by Options B and B+. Easier implementation should facilitate expansion of services and more effective programmes. This will, however, require strengthened antenatal services, task-shifting, more effective ARV service delivery in MCH settings and direct linkages with ART programmes.
- **Unknowns need research.** Concerns and unknowns with Options B and B+ include possible increased ARV multi-drug resistance in women due to poor adherence and in infants infected despite maternal ART, and the acceptability and feasibility for women of remaining in care and on lifelong ART, especially for women starting treatment earlier than is currently recommended for adults generally. In particular, rapid scale-up of ARVs, including efavirenz, for pregnant women will greatly increase early fetal exposure, including exposure from conception in future pregnancies, and prolonged exposures during breastfeeding. Pharmacovigilance, drug resistance monitoring, implementation research and programme monitoring are necessary.
- **No easy fix.** Moving from current Option A or Option B to Option B+ will not, on its own, resolve the key challenges and problems of expanding coverage and successfully transitioning pregnant women from PMTCT programmes to HIV care and treatment programmes. Well-supported referral systems and strong MCH and ART programme linkages are essential.
- **Adherence and retention crucial.** Postpartum drop-out rates in PMTCT programmes are especially high, in part due to weak postpartum services. PMTCT interventions during breastfeeding have yet to be fully implemented successfully with any option. Maintenance of viral suppression with ARV treatment—achieved by supporting continued adherence to the ART regimen—is crucial to the additional benefits of the Option B and B+ interventions and to minimizing adverse consequences.
- **And especially with Option B+.** While programmes need to provide effective support for adherence and retention in care with all three PMTCT options, additional support will be required for Option B+. It is particularly important for programmes implementing Option B+ to develop strong systems to support adherence and retention and to build evidence of successful practices through implementation science.
- **Family planning still essential.** Even in the context of expanded access to ART for HIV-infected pregnant women, family planning services still need to be strengthened to avoid unintended pregnancies.
- **Quality assurance needed for HIV testing.** Reliable HIV rapid testing in antenatal settings is important for all options, as the entry point to PMTCT interventions. Robust quality assurance systems and confirmatory testing will be especially important in the context of Option B+, where every pregnant woman who tests HIV-positive is started on treatment for the rest of her life.