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

Recommendations for a public health approach

2010 version

World Health Organization

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
CNS	central nervous system
d4T	stavudine
ddI	didanosine
EFV	efavirenz
FTC	emtricitabine
GRC	WHO Guideline Review Committee
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDU	injecting drug-user
IDV	indinavir
INH	isoniazid
IQR	interquartile range
LPV/r	lopinavir/ritonavir
MCH	maternal and child health
MTCT	mother-to-child transmission (of HIV)
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
PI	protease inhibitor
PICO	population, intervention, comparison and outcomes
PMTCT	prevention of mother-to-child transmission (of HIV)
RIF	rifampicin
sd-NVP	single-dose nevirapine
SQV/r	saquinavir/ritonavir
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
WHO	World Health Organization

SUMMARY OF RECOMMENDATIONS

Significant progress is being made in the global scale-up of prevention of mother-to-child transmission of HIV (PMTCT), including in high burden and resource-limited settings. For the first time, the elimination of mother-to-child transmission of HIV (MTCT) is now considered a realistic public health goal and an important part of the campaign to achieve the millennium development goals. In the light of the global effort, it is critically important to provide the best evidence-based interventions to reduce the risk of transmission from an HIV-infected mother to her newborn child, while at the same time promoting the health of both the mother and the child.

Since WHO issued revised guidelines in 2006, important new evidence has emerged on the use of antiretroviral (ARV) prophylaxis to prevent MTCT, including during breastfeeding, on the optimal time to initiate antiretroviral therapy (ART) in individuals who need treatment, and on safe feeding practices for HIV-exposed infants. This evidence forms the basis for the new recommendations contained in these 2010 revised guidelines and summarized in preliminary form in the 2009 *Rapid Advice: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants* (http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf). The *Rapid Advice* gives a list of the key recommendations whereas the full guidelines document presents in detail the scientific evidence and rationale supporting these recommendations. The detailed guidelines document provides the necessary information for countries to adapt the WHO recommendations to their local settings.

The 2010 guidelines are developed to 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. Once implemented, these recommendations could reduce the risk of MTCT to less than 5% (or even lower) in breastfeeding populations from a background risk of 35%, and to less than 2% in non-breastfeeding populations from a background risk of 25%, and will ensure increased maternal and child survival.

The 2010 revision of the WHO guidelines on PMTCT complies with the recently updated WHO guidelines development process, which requires systematic review of new evidence for key questions and recommendations, as well as a consideration of programme feasibility and the cost implications of potential new recommendations. WHO has simultaneously revised guidelines for adult ART as well as HIV and infant feeding. All three sets of guidelines were updated in a harmonized fashion.

The 2010 revised PMTCT recommendations are based on two key approaches:

1. **Lifelong ART** for HIV-infected women in need of treatment for their own health, which is also safe and effective in reducing MTCT.
2. **ARV prophylaxis** to prevent MTCT during pregnancy, delivery and breastfeeding for HIV-infected women not in need of treatment.

These revised recommendations emphasize the need to have a unified approach to preventing MTCT throughout pregnancy, labour and delivery, postpartum, and the breastfeeding period. For the first time, evidence allows new recommendations on ARV prophylaxis to either the mother or infant during breastfeeding, in areas where breastfeeding is judged to be the most appropriate choice of infant feeding for HIV-infected women. This is a major paradigm shift, allowing for more effective and safer postpartum interventions. This also emphasizes that PMTCT is not an intervention that stops at delivery, but includes postpartum and breastfeeding follow up and interventions for both the mother and infant.

To maximize prevention of HIV transmission and maternal and infant survival, it is critical that care of both the mother and the infant is optimized. A key issue in deciding what ARV regimen to choose for an HIV-infected pregnant woman is whether the ARVs are being provided for treatment of the woman's HIV disease or solely for prophylaxis of MTCT. In the former case, treatment means that ARVs are started during pregnancy and continued throughout life, whereas ARVs given solely for prophylaxis are stopped when the risk of MTCT is no longer present. In both cases, effective linkages between PMTCT services and HIV care and treatment programmes are needed.

Since the majority of HIV-infected pregnant women are asymptomatic or have only mild symptoms, it is critical that services provide access to CD4 counts to determine which women should initiate lifelong ART. Prophylaxis interventions, which are provided solely for the prevention of transmission and stop after transmission risk has ceased (e.g. on complete cessation of breastfeeding or after delivery if replacement feeding is used), would therefore be restricted to women who are not eligible for treatment according to current recommendations.

Pregnant women eligible for ART

For HIV-infected pregnant women, the initiation of ART for their own health is recommended for all women who have CD4 cell counts of ≤350 cells/mm^3, irrespective of WHO clinical staging, and for all women in WHO clinical stage 3 or 4, irrespective of the CD4 cell count. These criteria for initiating ART for pregnant women are the same as for non-pregnant women. The available data show that maternal ART during pregnancy and continued during breastfeeding is the most effective intervention for maternal health and is also efficacious in reducing the risk of HIV transmission and infant death in this group of women with the highest risk of MTCT. Therefore, HIV-infected pregnant women in need of treatment for their own health should start ART irrespective of gestational age and should continue with it throughout pregnancy, delivery, during breastfeeding (if breastfeeding) and thereafter. The timing of ART initiation for HIV-infected pregnant women is the same as for non-pregnant women, i.e. as soon as the eligibility criteria are met. The preferred first-line ART regimen in pregnancy comprises of an AZT + 3TC backbone combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI): AZT + 3TC + NVP or AZT + 3TC + EFV (Table 1). Alternative recommended regimens are TDF + 3TC (or FTC) + NVP and TDF + 3TC (or FTC) + EFV. The preferred first-line ART regimens recommended for HIV-infected pregnant women are the same as for non-pregnant women, and for adults in general. However, EFV should not be started in the first trimester, and NVP should be used instead. EFV may be used in the second and third trimesters. The decision should be guided by the capacity and experience of maternal, newborn, child health and HIV/AIDS programmes, the readiness of PMTCT services, cost and operational feasibility.

Maternal ART should be coupled with the daily administration of NVP or twice-daily AZT to infants from birth or as soon as feasible thereafter until 4 to 6 weeks of age, irrespective of the mode of infant feeding.

Table 1. Antiretroviral treatment options recommended for HIV-infected pregnant women who are eligible for treatment

Maternal ART + infant ARV prophylaxis
Mother
Maternal antepartum daily ART, starting as soon as possible irrespective of gestational age, and continued during pregnancy, delivery and thereafter. Recommended regimens include: AZT + 3TC + NVP or AZT + 3TC + EFV* or TDF + 3TC (or FTC) + NVP or TDF + 3TC (or FTC) + EFV*
Infant
Daily NVP or twice-daily AZT from birth until 4 to 6 weeks of age (irrespective of the mode of infant feeding).

* Avoid use of EFV in the first trimester and use NVP instead.

Maternal and infant ARV prophylaxis to prevent MTCT for HIV-infected pregnant women who do not need treatment for their own health

All HIV-infected pregnant women who do not need ART for their own health require an effective ARV prophylaxis to prevent HIV transmission during pregnancy, labour and delivery, postpartum *and* during the breastfeeding period. ARV prophylaxis should be started from as early as 14 weeks of gestation (second trimester) or as soon as possible thereafter if women present later in pregnancy, in labour or at delivery. Despite the lack of direct clinical trial evidence showing the advantage of ARV initiation before 28 weeks, there are observational data that suggest starting ARV prophylaxis earlier in pregnancy may be more effective in reducing MTCT. Current programme experience shows that many women are started on prophylaxis after 28 weeks of pregnancy despite being identified earlier. In recommending earlier initiation of prophylaxis, instead of delaying until the third trimester, a high value was placed on reducing the risk of in utero transmission while decreasing the probability of women being lost to follow-up before starting any intervention to prevent MTCT. This recommendation will therefore minimize delays between HIV testing in pregnancy and the initiation of ARV prophylaxis.

For all HIV-infected pregnant women who are not in need of ART for their own health, a choice of one of two equally efficacious ARV prophylaxis options is recommended (Table 2). There is a strong benefit in providing effective and sustained ARV prophylaxis to women not eligible for ART during pregnancy, labour and delivery, and to either the women or their infants throughout breastfeeding. Both recommended options provide a significant reduction in the risk of MTCT. There are advantages and disadvantages of both options, in terms of feasibility, acceptability and safety for mothers and infants, as well as cost.

The choice for a preferred option should be made and supported at the country level, after considering the capacity of the country and the advantages and disadvantages of the option and the specific regimens.

Table 2. ARV-prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health

Maternal AZT + infant ARV prophylaxis (Option A)	Maternal triple ARV prophylaxis (Option B)
Mother	**Mother**
Antepartum twice-daily AZT starting from as early as 14 weeks of gestation and continued during pregnancy. At onset of labour, sd-NVP and initiation of twice daily AZT + 3TC for 7 days postpartum. (Note: If maternal AZT was provided for more than 4 weeks antenatally, omission of the sd-NVP and AZT + 3TC tail can be considered; in this case, continue maternal AZT during labour and stop at delivery).	Triple ARV prophylaxis starting from as early as 14 weeks of gestation and continued until delivery, or, if breastfeeding, continued until 1 week after all infant exposure to breast milk has ended. Recommended regimens include: AZT + 3TC + LPV/r or AZT + 3TC + ABC or AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV
Infant	**Infant**
For breastfeeding infants Daily NVP from birth for a minimum of 4 to 6 weeks, and until 1 week after all exposure to breast milk has ended. *Infants receiving replacement feeding only* Daily NVP or sd-NVP + twice-daily AZT from birth until 4 to 6 weeks of age.	*Irrespective of mode of infant feeding* Daily NVP or twice daily AZT from birth until 4 to 6 weeks of age.

Option A: Maternal AZT + infant ARV prophylaxis

This option includes maternal antepartum twice-daily AZT starting from as early as 14 weeks of gestation (or as soon as possible thereafter) and continued during pregnancy (Table 2). At the onset of labour, single-dose NVP (sd-NVP) is administered with initiation of twice-daily AZT + 3TC, which should be continued for 7 days postpartum. If maternal AZT was provided for more than 4 weeks antenatally, the omission of the sd-NVP and AZT + 3TC tail can be considered, while continuing maternal AZT during labour and stopping it at delivery. For breastfeeding infants, maternal prophylaxis should be coupled with daily administration of NVP to the infants from birth (within 6–12 hours) or as soon as feasible thereafter, until 1 week after all exposure to breast milk has ended or, if breastfeeding stops before the age 6 weeks, for a minimum of 4 to 6 weeks following birth. In infants receiving replacement feeding only, maternal ARV prophylaxis should be coupled with daily administration of infant NVP or sd-NVP plus twice-daily AZT from birth (within 6–12 hours), or as soon as feasible thereafter, until 4–6 weeks of age.

Option B: Maternal triple ARV prophylaxis

This option consists of triple ARV drugs provided to the HIV-infected pregnant woman starting from as early as 14 weeks of gestation (or as soon as possible thereafter) until delivery, or, if breastfeeding, continued until one week after all infant exposure to breast milk has ended (Table 2). Recommended regimens include: AZT + 3TC + LPV/r, AZT + 3TC + ABC, AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV. Irrespective of the mode of infant feeding, the maternal triple ARV prophylaxis should be coupled with daily administration of NVP or twice-daily AZT to the infant from birth (within 6–12 hours) or as soon as feasible thereafter until 4 to 6 weeks of age.

Conclusion

The recommended treatment options for HIV-infected pregnant women who are eligible for treatment are summarized in Table 1.

The two recommended ARV prophylaxis options for HIV-infected pregnant women who are not eligible for ART are summarized in Table 2.

A comparison of the main changes of the revised 2010 recommendations with the 2006 recommendations is provided in Table 3.

A summary of the key 2010 recommendations and the strength of recommendations and quality of evidence is provided in Table 4.

A schematic algorithm of the 2010 recommendations for ARV drugs for pregnant women and preventing HIV infection in infants is provided in Fig. 1.

These 2010 revised recommendations propose earlier initiation of ART (lifelong treatment) for a larger group of HIV-infected pregnant women, with the goal of directly benefiting the health of the mothers and maximally reducing HIV transmission to their children. In addition, they recommend a choice of two highly effective ARV prophylaxis options, to be started early in pregnancy, for HIV-infected pregnant women who do not need ART for their own health. Both the provision of ART and the provision of option A or option B prophylaxis address the continuum of MTCT risk during pregnancy, labour, delivery, postpartum, and the breastfeeding period. For the first time, recommendations are being made to provide prophylaxis postpartum to the mother or child to reduce the risk of HIV transmission during the breastfeeding period.

There is a clear benefit in providing ART to pregnant women who are eligible for treatment, and, for those not eligible for ART, in providing highly effective ARV prophylaxis during pregnancy, labour and delivery, as well as throughout breastfeeding, with either option A or option B. Even in resource-limited settings, with full implementation of the new recommendations and scale-up to universal access, nearly all new paediatric infections from MTCT can be prevented.

Table 3. Key revisions in the recommendations from 2006 to 2010

2010 recommendations	2006 recommendations
1. ANTIRETROVIRAL THERAPY FOR HIV-INFECTED PREGNANT WOMEN WHO NEED TREATMENT FOR THEIR OWN HEALTH	
ARV eligibility criteria	
• All women with CD4 of ≤350 cells/mm^3, irrespective of clinical staging • All women with clinical stage 3 or 4, irrespective of CD4 cell count	• Women in clinical stage 1 and 2 with CD4 of <200 cells/mm^3 • All women in clinical stage 4, irrespective of CD4 cell count • Women in clinical stage 3, with CD4 of <350 cells/mm^3, if available; if the CD4 cell count is not available, all women in stage 3 should be treated
When to start ART in pregnant women	
• As soon as feasible	• As soon as feasible
Recommended first-line regimens for pregnant women	
• AZT + 3TC + NVP or • AZT + 3TC + EFV or • TDF + 3TC (or FTC) + NVP • TDF + 3TC (or FTC) + EFV	• AZT + 3TC + NVP
Prophylaxis for infants born to pregnant women on ART	
All infants regardless of infant feeding mode • NVP or AZT for 4 to 6 weeks	• AZT for 7 days
2. ANTIRETROVIRAL PROPHYLAXIS FOR PREGNANT WOMEN WHO DO NOT NEED TREATMENT FOR THEIR OWN HEALTH	
When to start ARV prophylaxis	
• As early as 14 weeks of pregnancy	• Starting at 28 weeks of pregnancy
Prophylaxis regimens for the mother	

2010 recommendations	2006 recommendations
Option A: • AZT during pregnancy plus • sd-NVP + AZT + 3TC tail during labour and delivery plus • AZT + 3TC for 7 days postpartum (may omit sd-NVP and intrapartum and postpartum AZT + 3TC if >4 weeks AZT; in this case, continue maternal AZT twice daily during labour and stop at delivery) Option B: • AZT + 3TC + LPV/r or • AZT + 3TC + ABC or • AZT + 3TC + EFV or • TDF + 3TC (or FTC) + EFV	• AZT during pregnancy plus • sd-NVP + AZT + 3TC during labour and delivery plus • AZT + 3TC for 7 days postpartum
Prophylaxis regimens for exposed infants	
Option A: Breastfeeding infants • NVP from birth until 1 week after all exposure to breastfeeding Non-breastfeeding infants • NVP or sd-NVP + AZT for 4 to 6 weeks Option B: All infants regardless of infant feeding mode • NVP or AZT for 4 to 6 weeks	• sd-NVP + AZT for 7 days
Related infant feeding recommendation for known HIV-infected women	
National authorities should decide whether health services will principally counsel mothers to either breastfeed and receive ARV interventions or avoid all breastfeeding, as the strategy that will most likely give infants the greatest chance of HIV-free survival Where breastfeeding is judged to be the best option: • Exclusively breastfeed for the first 6 months, introduce appropriate complementary food thereafter, and continue breastfeeding for 12 months • Wean gradually within 1 month	• Exclusive breastfeeding for the first 6 months unless replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS) • At 6 months, continue breastfeeding with additional complementary food if AFASS is not met • Wean within a period ranging from about 2–3 days to 2–3 weeks

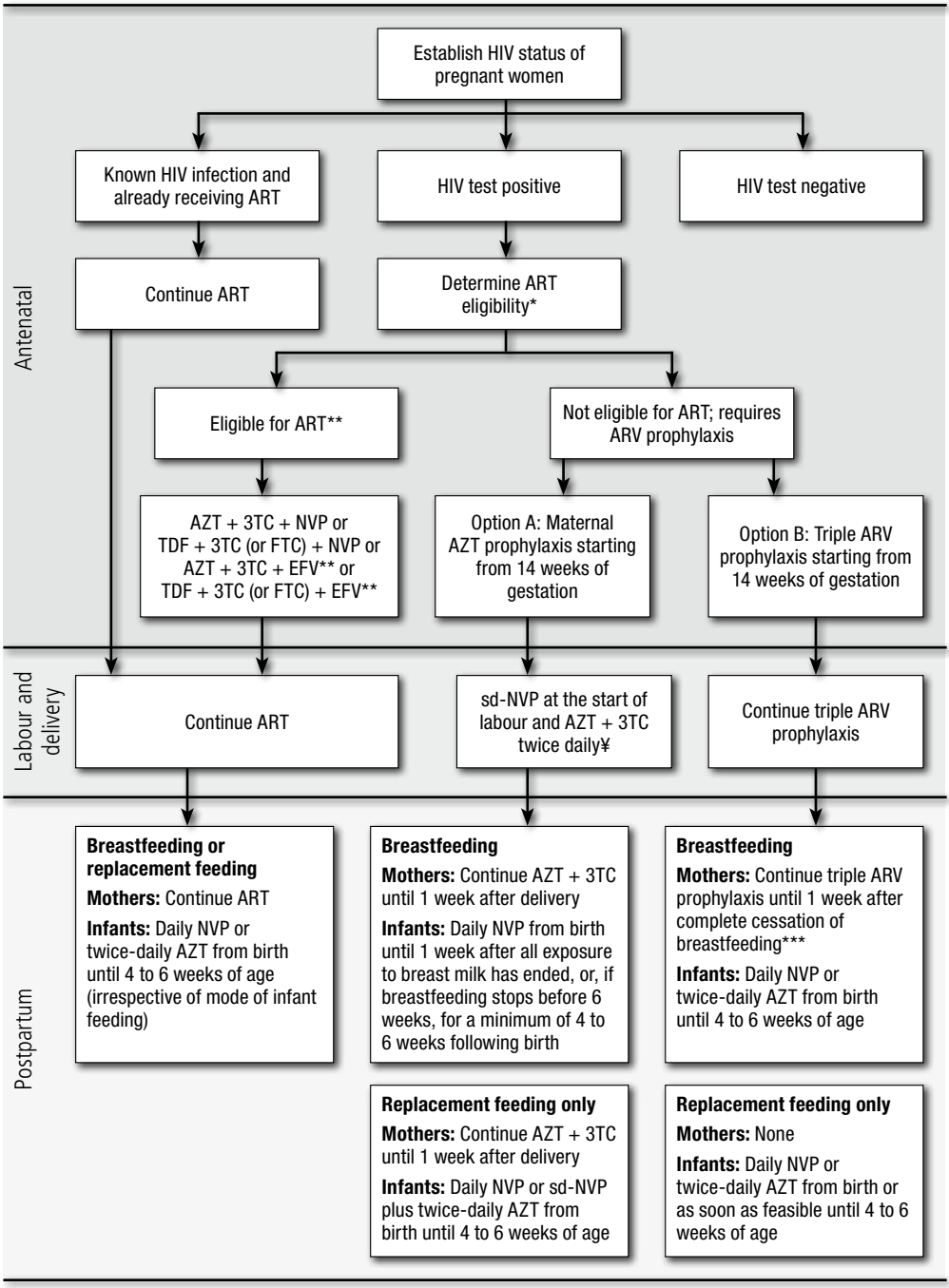
Table 4. Recommendations for treating pregnant women and preventing HIV infection in infants

Recommendation	Strength of recommendation	Quality of evidence
ART for pregnant women for their own health and to prevent MTCT		
For pregnant women with confirmed HIV status, initiation of antiretroviral therapy for their own health is recommended for all with a CD4 cell count of ≤350 cells/mm^3, irrespective of WHO clinical staging, and for all in WHO clinical stage 3 or 4, irrespective of CD4 cell count.	Strong	Moderate
HIV-infected pregnant women in need of ART for their own health should start ART as soon as feasible irrespective of gestational age and continue throughout pregnancy, delivery and thereafter.	Strong	Moderate
For pregnant women in need of ART for their own health, the preferred first-line ART regimen should include an AZT + 3TC backbone combined with an NNRTI: AZT + 3TC + NVP or AZT + 3TC + EFV. Alternative recommended regimens include TDF + 3TC (or FTC) + EFV and TDF + 3TC (or FTC) + NVP.	Strong	Low
Breastfeeding infants born to HIV-infected women receiving ART for their own health should receive daily NVP or twice-daily AZT from birth or as soon as feasible thereafter until 4 to 6 weeks of age.	Strong	Moderate
Infants receiving only replacement feeding, and born to HIV-infected women receiving ART for their own health, should receive daily NVP or twice-daily AZT from birth or as soon as feasible thereafter until 4 to 6 weeks of age.	Conditional	Low

Recommendation	Strength of recommendation	Quality of evidence
Maternal and infant ARV prophylaxis to prevent MTCT for HIV-infected women not in need of treatment for their own health (two equally efficacious options are recommended)		
For HIV-infected pregnant women who are not in need of ART for their own health and whose infants require effective ARV prophylaxis to prevent HIV transmission, ARV prophylaxis should be started from as early as 14 weeks of gestation (second trimester) or as soon as feasible thereafter in pregnancy, during labour or delivery, or after delivery, to prevent HIV transmission to their infants.	Strong	Low
Option A		
For HIV-infected pregnant women who are not eligible for ART for their own health, maternal ARV prophylaxis option A consists of antepartum twice-daily AZT plus sd-NVP at onset of labour[1] plus twice-daily AZT + 3TC during labour and delivery, continued for 7 days postpartum.	Strong	Low
In breastfeeding infants, daily NVP should be given to the infant from birth until 1 week after all exposure to breast milk has ended or, if breastfeeding stops before the age of 6 weeks, for a minimum of 4 to 6 weeks.	Strong	Moderate
In infants receiving only replacement feeding, daily NVP or sd-NVP plus twice-daily AZT should be given to the infant from birth until 4 to 6 weeks of age.	Conditional	Low
Option B		
For HIV-infected pregnant women who are not eligible for ART for their own health, maternal ARV prophylaxis option B consists of antepartum daily triple ARV prophylaxis until delivery, or, if breastfeeding, until 1 week after all exposure to breast milk has ended. Recommended regimens include AZT + 3TC + LPV/r, AZT + 3TC + ABC, AZT + 3TC + EFV, or TDF + 3TC (or FTC) + EFV.	Strong	Moderate
In breastfeeding infants, maternal triple ARV prophylaxis should be coupled with daily NVP or twice-daily AZT to the infants from birth until 4 to 6 weeks of age.	Strong	Low
In infants receiving only replacement feeding, maternal triple ARV prophylaxis should be coupled with daily NVP or twice-daily AZT to the infants from birth until 4 to 6 weeks of age.	Conditional	Low

[1] Omission of sd-NVP and the AZT + 3TC intrapartum and postpartum tail can be considered if the mother receives more than 4 weeks of AZT during pregnancy. In this case, continue maternal AZT twice daily during labour and stop at delivery.

Fig. 1. Algorithm for the 2010 PMTCT recommendations



* Start ARV prophylaxis while waiting to determine ART eligibility.

** Avoid use of EFV in first trimester; use NVP instead.

*** When stopping any NNRTI-based regimen, stop the NNRTI first and continue the two NRTIs for 7 days and then stop them to reduce the chance of NNRTI resistance

¥ If AZT was taken for at least the last 4 weeks before delivery, omission of the maternal sd-NVP and accompanying tail (AZT + 3TC) can be considered. In this case, continue maternal AZT twice daily during labour and stop at delivery.

Introduction

The human immunodeficiency virus (HIV) epidemic continues to take a heavy toll on women and children worldwide. In 2008, 33.4 million individuals were living with HIV, of whom 15.7 million were women and 2.1 million were children under 15 years of age [1]. Globally, HIV is the leading cause of death in women of reproductive age. Since nearly all HIV infections in children are acquired from their mothers, the global epidemiology of HIV in children reflects that of HIV in women. It has been estimated that, in 2008, 1.4 million HIV-infected women gave birth in low- and middle-income countries and that there were 430 000 new paediatric infections. Nearly all such infections can be prevented by PMTCT programmes providing highly effective ART and ARV prophylaxis interventions.

In the absence of any intervention a substantial proportion of children born to women living with HIV acquire the virus from their mothers during pregnancy, labour, delivery and breastfeeding. Without intervention, the risk of transmission is 15–30% in non-breastfeeding populations. Breastfeeding by an infected mother adds an additional 5-20% risk for an overall transmission rate of 20–45% [2]. The use of ARV drugs for PMTCT has been shown to be effective since the mid-1990s in multiple clinical trials and programmes. The use of sd-NVP, which is still being used in many settings, significantly reduces peripartum transmission but is associated with the acquisition of viral resistance and is much less effective than combination and longer ARV prophylaxis regimens. Moreover, this regimen does not cover the breastfeeding period. Postnatal transmission of HIV continues to be a major problem in sub-Saharan Africa and other resource-limited settings where the vast majority of women practise breastfeeding for long durations. Alternatives to prolonged breastfeeding can dramatically reduce this risk, but they require substantial care and nutritional counselling to be practised safely, and therefore are untenable at the population level in many developing countries [3]. For example, several studies from various African countries have demonstrated an increased risk of mortality in HIV-exposed uninfected children who stopped breastfeeding at the age of 4 to 6 months [4-8].

The 2006 WHO guidelines, *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants*, represented a major advance from previous recommendations by emphasizing a public health approach and highlighting the importance of providing lifelong ART to eligible pregnant women for their own health and thereby preventing MTCT for these women with the highest risk of transmission [9]. They also moved beyond sd-NVP to recommend a combination of ARVs for more effective prophylaxis during the last trimester of pregnancy and early postpartum. These 2006 guidelines are currently the technical backbone of most national PMTCT policies, particularly in high-burden countries in sub-Saharan Africa, where more than 90% of HIV-positive pregnant women reside. However, the 2006 guidelines recommended ART to a limited number of pregnant women, recommended prophylaxis strategies that only focused on the last trimester of pregnancy, and did not recommend ARV interventions during breastfeeding.

The last few years have seen unprecedented political and community mobilization in response to the HIV pandemic, with new funding opportunities and a revitalized public health approach. These have included considerable efforts to expand programmes aimed at preventing MTCT and guaranteeing access to ART for pregnant and postpartum HIV-infected women. This recent roll-out of ART in resource-constrained countries has changed the paradigm of PMTCT in these settings and has

raised the possibility of reducing MTCT to very low levels and achieving the virtual elimination of vertical transmission.

However, despite unprecedented efforts and important progress in the past several years, global PMTCT service coverage remains unacceptably low in many high burden countries [10]. According to the 2009 progress report Towards universal access, an estimated 45% of HIV-positive pregnant women received some regimen of ARVs for PMTCT in 2008, up from 35% in 2007 and 10% in 2004 [11]. In the 2009 report, of all women receiving a PMTCT intervention, 31% received only sd-NVP (down from 49%). While this progress has been encouraging, reliable data were not available on the proportion of eligible pregnant women receiving ART, or even combination prophylaxis, making it difficult to estimate the effectiveness of most programmes to reduce MTCT. These data highlight the need for accelerated scale-up of simple, standard and effective regimens, particularly in resource-limited settings.

From a programmatic perspective it is now crucial to speed up the transition from research to national programmes based on innovative, simplified and highly effective interventions that address the overall MTCT risk from pregnancy to the cessation of breastfeeding. Specific strategies for the prevention of MTCT must therefore take into account whether the mother is eligible for ART for her own health and whether breastfeeding is practised.

Since the 2006 PMTCT guidelines were issued, important new evidence has emerged on the use of ARV prophylaxis to prevent MTCT, including during breastfeeding, on the optimal time for ART initiation for individuals who need treatment, and on safe feeding practices for HIV-exposed infants. This has warranted the development of the revised 2010 guidelines.

A schematic algorithm for the 2010 revised recommendations on the use of antiretroviral drugs for PMTCT and for the treatment of pregnant women is provided in Fig. 1. Once implemented, these recommendations can significantly reduce maternal morbidity and mortality, particularly in high burden settings. Wide-scale implementation of these recommendations can also reduce the risk of MTCT to less than 5% (or even lower) in breastfeeding populations (from a background risk of 35%) and to less than 2% in non-breastfeeding populations (from a background risk of 25%). For the first time, evidence-based recommendations can now be made for resource-limited settings which can eliminate MTCT [12].

Objectives of the guidelines

In the light of new evidence and programme experience, these revised guidelines were developed to:

- Update recommendations for the use of ARV drugs in pregnant women for their own health and for preventing HIV infection in infants and young children;
- Simplify and standardize current recommendations to support the global scale-up of more effective interventions aimed at eliminating MTCT in resource-limited settings.

Target audience

The 2010 revised guidelines are meant for use by managers of national HIV and AIDS programmes, maternal, newborn and child health programmes and reproductive health programmes that are responsible for establishing national policies and standards and for designing and implementing national PMTCT services. The guidelines are also meant for local programme managers and health-care providers to ensure quality services across the different levels of the health system. In addition, the guidelines are intended to establish global standards for international and bilateral funding agencies and implementers.

SECTION II. DEVELOPMENT OF THE GUIDELINES AND GUIDING PRINCIPLES

Development of the guidelines

WHO has a mandate to define evidence-based global health norms and standards and to help countries adapt international recommendations according to their national circumstances. Recommendations for the use of antiretroviral drugs for PMTCT were first issued by WHO in 2000 and were revised in 2004 and 2006. The 2010 revised guidelines address issues related to ARV drug regimens for pregnant women with regard to eligibility criteria for ART, as well as prophylaxis for mothers and their exposed infants in order to prevent MTCT.

The 2010 revised guidelines were developed to meet the urgent need for updated guidance on the use of ARVs for the treatment of pregnant women and the prevention of HIV infection in infants, in both breastfeeding and non-breastfeeding populations. For this purpose, WHO initiated a revision process that culminated in a guidelines review meeting in October 2009. The 2010 revision of the WHO guidelines on PMTCT complies with the recently updated WHO guidelines development process, which requires systematic review of new evidence around key questions and recommendations, as well as a consideration of programme feasibility and the cost implications of potential new recommendations.

This publication is part of a trilogy of closely related guidelines. WHO has also revised *Antiretroviral therapy for HIV infection in adults and adolescents* [13] and *Principles and recommendations on HIV and infant feeding* [14]. All three guidelines followed a similar review process and have been updated in a harmonized fashion.

Revision process

Reviewing, summarizing and presenting the evidence

WHO convened an initial expert consultation in November 2008 to review new evidence accumulated since the 2006 guidelines. The aim was to determine whether there was enough new evidence to warrant their revision. After reviewing significant new research evidence and new studies nearing completion, WHO decided to proceed with a full review of the guidelines.

The scope of work was drafted and key questions were developed in accordance with the PICO format (population, intervention, comparison and outcomes) as follows:

a. When to start ART in pregnant women and what regimen to give to pregnant women eligible for ART?
b. When to start ARV prophylaxis for PMTCT in pregnant women and what regimen to give pregnant women for ARV prophylaxis?
c. What ARV prophylaxis regimen to give newborn infants born to HIV-infected mothers in the immediate postpartum period?
d. What regimen to use for preventing breastfeeding transmission of HIV beyond the immediate postpartum period?

Based on the PICO questions, a systematic review of peer-reviewed literature and abstracts was performed through a collaborative effort between the University of California, San Francisco (UCSF),

the US Centers for Disease Control and Prevention (CDC) and WHO. The HIV/AIDS Cochrane Collaborative Review Group search strategy (http://www.cochrane.org/cochrane-reviews/review-structure) was used for each of the four key questions. Standard search terms were defined and entered into multiple medical literature databases, conference proceedings and clinical trials web sites to identify both published reports and ongoing trials. Where appropriate, investigators of major trials were contacted to assess whether any relevant manuscripts were in preparation or in press and whether there were any significant updates in data analysis and conclusions. References of published articles were hand-searched for additional pertinent materials. Given the anticipated limited number of controlled studies which addressed the specific PICO questions and defined outcomes of interest, observational studies meeting the inclusion criteria were covered in addition to randomized controlled trials. Systematic reviews and meta-analyses addressing interventions of interest were reviewed in detail. The searches were limited to studies published from 1994 to the present.

After the initial search and screening of references, two reviewers independently double-coded and entered extracted information on standardized data extraction forms. Extracted information included study details (e.g. study design and location), participant details (e.g. study population inclusion and exclusion, population size, attrition rate, details of HIV diagnosis and disease and any clinical, immunological or virological staging or laboratory information), intervention details (e.g. PMTCT drug regimens, dosages) and outcome details (e.g. mortality, clinical disease progression, treatment response, serious adverse events, and resistance). For each of the included studies, an assessment of the risk of bias using the standard Cochrane format was completed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used. GRADE review outcomes for each specific question as defined in the PICO tables were assessed and the quality of evidence was ranked as high, moderate, low or very low. GradePro 2008 software was used to produce the summary of findings and grade evidence profile tables. Summary statistics using meta-analysis methods were included, where applicable, in the GRADE summary of findings and GRADE evidence profile tables (Annex 2). The full compilation of GRADE tables, systematic reviews, and associated summaries of evidence are available on the WHO web site (http://www.who.int/hiv/topics/mtct/en/index.html).

Feasibility assessment

Various meetings and presentations addressed the feasibility of potential new recommendations. An informal two-day meeting was held in September 2009 with implementing agencies and other key stakeholders, co-hosted by PEPFAR. The meeting, which included direct input from several country programmes, discussed and summarized issues that needed to be taken into account to implement new recommendations, including current challenges to programme implementation, and cost and feasibility implications.

A second feasibility assessment was made through a rapid assessment of relevant country-specific policies and barriers. This was done by sending out a structured questionnaire to 12 countries with high PMTCT burdens, countries not participating in the guideline review meeting, and countries from all six WHO regions. The survey reviewed the status of current national PMTCT guidelines, the time required to revise the guidelines, the coverage of PMTCT services, adult and infant HIV testing policies, and the availability of CD4 testing. Additional considerations of the feasibility of relevant

PMTCT interventions were provided through a presentation on health-systems issues of PMTCT programmes at the guidelines review meeting.

Current cost information for key ART and ARV prophylaxis regimens was prepared by WHO, taking into account differential pricing in low-, lower-middle- and upper-middle-income countries. Pricing information was based on the Global Price Reporting Mechanism (GPRM, http://apps.who.int/hiv/amds/price/hdd/). Cost implications of the proposed recommendations were presented and discussed during the guidelines review meeting.

Consensus on revised recommendations, external review and publication

A guidelines review meeting on the use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants was held in Geneva from 19–21 October, 2009. Participants represented four key areas of expertise (see Acknowledgments): people living with HIV (PLHIV), content experts, country programme experts, and implementing partners. Attention was given to ensuring regional diversity among the country programme experts. The chair of the meeting was Professor J. McIntyre. The sessions and group work were organized around the four PICO questions. Each session included presentations on the related GRADE evidence, current and proposed recommendations, cost implications and a risk-benefit analysis of the key question. Discussions started with a review of proposed recommendations from WHO in the group work. The group went through each proposed recommendation and took into consideration the quality of evidence, the balance between benefits and harms, the balance between values and preferences, cost, feasibility and related factors to formulate the final recommendation. The strength of the recommendations was determined in accordance with the basis of the findings. The resulting recommendations from the group work were presented in plenary, and, in a few cases where there was no initial consensus, further discussions were held and decisions were reached by voting.

Key recommendations were summarized in risk-benefit recommendation tables (Annex 3). The summary recommendations and Grade Evidence Profile Tables were sent for peer review to six independent reviewers and the six WHO regional offices. The reviewers were selected for their technical expertise and programmatic experience in the area of PMTCT. Feedback was received in writing from all reviewers, who provided strong overall support for the proposed recommendations.

A summary of the recommendations was published as Rapid Advice on 30 November, 2009 on the WHO website (http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf) after receiving approval from the Guidelines Review Committee (GRC). A core writing group comprising three external experts who were part of the review meeting, two writers and WHO technical staff developed the current guidelines. The full guidelines are a more comprehensive document presenting all background scientific and related information regarding the recommendations.

These 2010 guidelines will be reviewed by the Department of HIVAIDS, WHO, in 2012, unless significant new evidence warrants earlier review. The Department is responsible for keeping track of ongoing research, and systematically monitors emerging new evidence and evaluates the need to update recommendations on the use of ARV drugs for PMTCT.

Conflict of interest

All individuals participating in the October 2009 review meeting or commenting as peer reviewers were asked to complete the standard GRC declaration of interest form. Five individuals declared possible conflicts of interest, including present and past external research funding (three people) and direct support to national public health authorities (two people). All instances of declared financial support were standard publicly-funded research support; there were no declarations of support from any pharmaceutical companies. For the individuals participating in the October 2009 review meeting, the names of individuals with a declared possible conflict of interest, as well as the actual conflict, were shared with all participants. The meeting participants and the WHO Secretariat did not feel that any of the declared conflicts of interest would lead to biased contributions towards the development of the guidelines, and all individuals proceeded with full participation in the review meeting. Similarly for the peer reviewers, the WHO Secretariat did not feel that the declared conflicts of interest from two individuals were serious enough to warrant non-participation and all individuals proceeded with the review process.

From evidence to recommendations

The participants in the guideline review meeting reached consensus on the content, the strength of each recommendation, and the quality of evidence related to each recommendation detailed in Sections III to VI. The higher the quality of evidence, the more likely a strong recommendation could be made. The assessment of both strength of recommendation and quality of evidence is detailed in Tables 5 and 6. A standard risk-benefit table (Annex 3) listing the domains and considerations, e.g. quality of evidence, risks and benefits, values and acceptability, cost, and feasibility, was used to formulate the recommendations and assess the strength and quality of the recommendations.

Table 5. Assessment of the strength of recommendations

Strong recommendation	Conditional recommendation	No recommendation possible
The panel was confident that the desirable effects of the recommendation would outweigh any undesirable effects and that most individuals should receive the intervention.	The panel concluded that the desirable effects of the recommendation probably outweighed any undesirable effects but the group was not confident about these trade-offs. The majority of well-informed individuals would want the suggested intervention, but an appreciable proportion might not.	Further research was required before any recommendation could be made.

Table 6. Assessment of the quality of evidence

Evidence level	Rationale
High	Further research was very unlikely to change the panel's confidence in the estimate of effect.
Moderate	Further research was likely to have an important impact on the panel's confidence in the effect.
Low *	Further research was very likely to have an important impact on the panel's confidence in the effect.
Very low *	Any estimate of effect was very uncertain.

* Low or very low quality of evidence does not necessarily imply that the studies were conducted poorly but that the data were not optimal for developing a recommendation.

Guiding principles

The participants in the guidelines review meeting agreed on a set of principles to be used in developing international and national recommendations, particularly for resource-limited settings. The WHO guidelines were revised in accordance with the following guiding principles.

1. A public health approach for increasing access to PMTCT, and HIV treatment, care and prevention services

The public health approach seeks to ensure access to high-quality services at the population level, while striking a balance between the best proven standard of care and what is feasible on a large scale in resource-limited settings.

2. Integrated delivery of the WHO comprehensive strategic approach to the prevention of HIV infection in infants and young children within maternal and child health services

Interventions to prevent MTCT should be integrated within maternal and child health services and programmes for HIV treatment and care, and provide the essential package of antenatal and postnatal services (Annex 1). Services to prevent MTCT must be implemented and scaled up both as important prevention interventions and as access points for the treatment, care and support of women living with HIV, their children and families.

3. Continuity of HIV prevention and care services for postpartum women and their children

PMTCT interventions do not stop at delivery. Continued interventions and support of the mother and her child are needed for at least the first year after delivery. The goal is to improve both maternal and child health by providing ART for eligible women, assuring effective ARV prophylaxis during

breastfeeding, providing effective linkages to care and support, including reproductive health care and family planning, determining the final infection outcome of the HIV-exposed child, and facilitating access to early treatment for infants who become infected with HIV despite prophylaxis (Annex 1).

4. Rapid assessment of maternal CD4 cell count soon after diagnosis of HIV infection is critical for guiding decisions on HIV prevention, treatment and care

The CD4 cell count must be assessed, wherever possible, in order to determine maternal eligibility for lifelong ART. To ensure that all pregnant women who require ART are identified, CD4 testing should be included in the essential package of care for HIV-infected pregnant women.

5. Provide highly effective ARV-based interventions for all HIV-infected pregnant and breastfeeding women

a. Women in need of treatment for their own health should receive lifelong ART. This is the best intervention for improving the health of mothers, while providing maximum protection against HIV infection in their children.

b. Women not in need of ART should receive effective ARV-based prophylaxis during pregnancy, labour and delivery. If breastfeeding, a mother or her infant should receive effective ARV prophylaxis during the entire breastfeeding period in order to decrease MTCT and allow safer breastfeeding practices.

6. Simple unifying principles for different country settings

In resource-limited settings, PMTCT programmes should be based on standardized regimens and simplified approaches suitable for the majority of women. This evidence-based standardization facilitates the effective training, management and delivery of key interventions. While a simplified approach can address the needs of most women, consideration is also needed for special circumstances, including HIV-infected pregnant women with severe anaemia, coinfection with tuberculosis (TB) or HIV-2, and drug toxicity.

SECTION III. ANTIRETROVIRAL DRUGS FOR TREATING PREGNANT WOMEN FOR THEIR OWN HEALTH AND TO PREVENT HIV INFECTION IN THEIR INFANTS

Key recommendations

When is ART indicated
In pregnant women with confirmed HIV infection, the initiation of ART for maternal health is recommended for all women with CD4 cell counts of ≤350 cells/mm^3, irrespective of the WHO clinical staging, and for all women in WHO clinical stage 3 or 4, irrespective of the CD4 cell count.
When to start ART in pregnancy
HIV-infected pregnant women in need of ART for their own health should start ART as soon as feasible regardless of gestational age and continue throughout pregnancy, childbirth, breastfeeding (if breastfeeding), and thereafter.
What ART regimen to initiate
In pregnant women in need of ART for their own health the preferred first-line ART regimen should include an AZT + 3TC backbone combined with an NNRTI: AZT + 3TC + NVP or AZT + 3TC + EFV. Alternative recommended regimens are TDF + 3TC (or FTC) + EFV and TDF + 3TC (or FTC) + NVP. (*Note: avoid the use of EFV in the first trimester and use NVP instead.*)
What ARV prophylaxis to give infants of HIV-infected women receiving ART
All infants (regardless of whether breastfeeding or receiving only replacement feeding) born to HIV-infected women receiving ART for their own health should be given daily NVP or twice-daily AZT from birth or as soon as feasible thereafter until 4 to 6 weeks of age.

Every effort should be made to ensure that all women who require ART have access to it. As in non-pregnant individuals, ART significantly reduces HIV disease progression and decreases morbidity and mortality in pregnant women. For a pregnant woman in need of treatment, ART is also the most effective method of preventing MTCT and, by improving the health of the mother, improves the chances of survival of her child. Thus, treating a pregnant woman living with HIV not only addresses her individual health needs but also dramatically reduces the risk of MTCT, particularly for a woman with advanced disease and a higher risk of transmission. The benefits of ART for the health of the mother outweigh any potential risks for the well-being of the fetus and of potential drug toxicity, drug resistance and additional cost. A schematic algorithm for the use of antiretroviral drugs to prevent MTCT and for the treatment of pregnant women is provided in Fig. 1.

ART eligibility for pregnant women

Recommendations for the initiation of ART among adults, including pregnant women, are described in detail in the 2010 revised WHO adult treatment guideline *Antiretroviral therapy for HIV infection in adults and adolescents* [13]. The criteria for initiating ART for pregnant women are the same as for non-pregnant women. The recommendations prioritize the health of women over potential risks and

increased cost. The initiation of ART is therefore recommended in all pregnant women in need of ART for their own health.

When a pregnant woman is identified with HIV, the criteria for initiating ART in resource-limited settings are based on both the CD4 cell count and WHO clinical staging [15]. Assessment of the CD4 cell count is currently the cornerstone of determining ART eligibility and is strongly recommended for a public health approach to ART in all areas where ARVs are being provided. CD4 cell counts guide decisions about when to initiate ART as well as when to switch ART. In settings where CD4 cell counts are available, the WHO clinical stage can provide additional information about ART eligibility. In settings where CD4 cell counts are not available, evaluation of the WHO clinical stage alone can be used to determine ART eligibility.

The initiation of ART for the health of the HIV-infected pregnant woman is recommended for those with CD4 cell counts of ≤350 cells/mm^3, irrespective of WHO clinical staging, and for women in WHO clinical stage 3 or 4, irrespective of the CD4 cell count (Table 7).

Pregnant women eligible for ART for their own health should start treatment as soon as feasible irrespective of gestational age and continue in pregnancy, delivery, during breastfeeding (if breastfeeding) and throughout life. Women should be made aware of the potential benefits and implications of beginning ART for both themselves and their babies. Women presenting very late in pregnancy who are not able to initiate ART before delivery should receive ARV prophylaxis for PMTCT while plans are made to start ART for the mother as soon as possible after delivery.

Table 7. Eligibility criteria for initiating antiretroviral treatment or prophylaxis in HIV-infected pregnant women based on CD4 cell count and WHO clinical stage

	CD4 cell count not available	CD4 cell count available	
		CD4 ≤350 cells/mm^3	CD4 >350 cells/mm^3
WHO clinical stage 1	ARV prophylaxis	ART	ARV prophylaxis
WHO clinical stage 2	ARV prophylaxis	ART	ARV prophylaxis
WHO clinical stage 3	ART	ART	ART
WHO clinical stage 4	ART	ART	ART

ART regimens for pregnant women eligible for treatment

The recommended first-line ART regimens for eligible HIV-infected pregnant women are the same as for non-pregnant women and are discussed in detail in the adult ART guidelines [13]. The recommended regimens have been selected after considering potency, the safety profile, future treatment options, anticipated adherence, availability of fixed-dose combinations, and coexisting

health conditions (e.g. TB, HBV or HCV). Among the recommended regimens a systematic review did not find superiority of one regimen over another with regard to the critical outcomes of mortality, clinical response, disease progression and serious adverse events, and the important outcomes of virological response, adherence, tolerance and retention (Annexes 2 and 3).

In pregnant women in need of ART for their own health the preferred first-line ART regimen should include an AZT + 3TC backbone in combination with an NNRTI: AZT + 3TC + NVP or AZT + 3TC + EFV. Alternative recommended regimens are TDF + 3TC (or FTC) + EFV and TDF + 3TC (or FTC) + NVP. The primary benefit of the recommendation is the effective reduction in maternal HIV mortality and morbidity, particularly that attributable to TB. Secondary benefits include the reduction in MTCT and the decrease in infant mortality at 12 months of age. The recommended regimens have been shown to be acceptable to pregnant women and clinicians. Acceptability of the regimen further depends on ease of formulation and dosing (e.g. fixed-dose combination), ease of packaging and availability. Fixed-dose combinations or co-packaged formulations are therefore recommended wherever possible. The choice of regimen should be guided by the experience, availability, feasibility, and potential toxicity of the regimens in pregnancy.

Recommendations for first-line ART in pregnant women take into account two specific concerns: increased NVP hepatotoxicity in women with higher CD4 counts and potential teratogenicity of EFV. While long term use of NVP is not recommended in women with CD4 counts >350 cells/mm^3, there are conflicting data on whether there is an increased risk of hepatotoxicity with NVP in women with CD4 counts between 250 and 350 cells/mm^3. In the case of women who require ART for their own health, including pregnant women, it was felt that the benefits of using NVP outweighed the risks of not initiating ART. Close clinical monitoring (and laboratory monitoring, if feasible) during the first 12 weeks of therapy is recommended when NVP is initiated in women with a CD4 cell count of 250 to 350 cells/mm^3.

EFV should not be initiated in the first trimester of pregnancy but may be initiated in the second and third trimesters. There is conflicting evidence of very low quality on the risks of EFV causing neural tube defects [16]. The rates of overall birth defects reported in association with EFV, NVP, LPV/r or TDF appear similar and are consistent with rates reported in congenital defects registries in general populations. However, neural tube birth defects are rare, with an incidence in the range of 0.1% in the general population. Prospective data currently are insufficient to provide an assessment of neural tube defect risk with first-trimester EFV exposure, except to rule out a potential tenfold or higher increase in risk (i.e. an increase in risk from 0.1% to >1%). Since neural tube closure occurs by approximately 28 days of gestation and very few pregnancies are recognized by this time, the potential risk with the use of EFV is primarily in women who become pregnant while already receiving the drug.

Table 8. Considerations for the choice of first-line ART for HIV-infected pregnant women*

Recommended regimens	Dosing	Feasibility and operational considerations	Safety considerations
AZT + 3TC + NVP	AZT 300 mg twice daily 3TC 150 mg twice daily NVP 200 mg twice daily	• Regimen could potentially be provided as a fixed-dose combination • Extensive experience with AZT + 3TC backbone in pregnancy • Hb assessment is recommended (but not necessary) before use of AZT • Favourable cost of regimen • Need for close clinical toxicity monitoring for first 12 weeks with use of NVP • NVP dose escalation from once-daily to twice-daily regimen after 2 weeks	• Risk of anaemia with prolonged use of AZT • Risk of hepatotoxicity and hypersensitivity with use of NVP resulting in need for close clinical observation for first 12 weeks • Not recommended in pregnant women with CD4 >350 cells/mm^3
AZT + 3TC + EFV	AZT 300 mg twice daily 3TC 150 mg twice daily EFV 600 mg once daily	• Extensive experience with AZT + 3TC backbone in pregnancy • Hb assessment is recommended (but not necessary) before use of AZT • Effective contraception after delivery is required to prevent (subsequent) pregnancy with use of EFV • EFV is recommended for women presenting with TB	• Risk of anaemia with prolonged use of AZT • Potential risk (probably <1%) of neural tube defect with use of EFV in first month of pregnancy (before 6 weeks of gestation)

Recommended regimens	Dosing	Feasibility and operational considerations	Safety considerations
TDF + 3TC (or FTC) + EFV	TDF 300 mg once daily 3TC 300 mg once daily EFV 600 mg once daily or TDF 300 mg once daily FTC 200 mg once daily EFV 600 mg once daily	• Could be given as once-daily regimen in a fixed-dose combination • Effective contraception after delivery is required to prevent (subsequent) pregnancy with use of EFV • EFV use is recommended for women presenting with TB • TDF + 3TC (or FTC) use is recommended for women with HBV infection requiring HBV treatment	• Risk of nephrotoxicity with use of TDF • Limited data available on potential maternal and infant bone toxicity with use of TDF • Potential risk (probably <1%) of neural tube defect with use of EFV in first month of pregnancy (before 6 weeks gestation)
TDF + 3TC (or FTC) + NVP	TDF 300 mg once daily 3TC 150 mg twice daily NVP 200 mg twice daily or TDF 300 mg once daily FTC 200 mg once daily NVP 200 mg twice daily	• Need for close toxicity monitoring for 12 weeks with use of NVP • NVP dose escalation from once-daily to twice-daily regimen after 2 weeks • TDF + 3TC (or FTC) use is recommended for women presenting with HBV infection requiring treatment	• Risk of nephrotoxicity with use of TDF • Limited data available on potential maternal and infant bone toxicity with use of TDF • Risk of hepatotoxicity and hypersensitivity with use of NVP resulting in need for close clinical observation for first 12 weeks

* NNRTI drugs, such as NVP or EFV, are not recommended for women with HIV-2 infection alone.

Alternative combinations, such as a triple NRTI regimen or a PI-based regimen, can be considered if a recommended antiretroviral regimen is not indicated or not available.

Recommendations for the choice of ART regimen in pregnant women who require treatment and have had prior exposure to antiretrovirals for PMTCT

Resistance to NNRTI drugs is an important concern for PMTCT regimens. The long half-life of NVP and its low genetic barrier to resistance means that detectable drug levels persist for 2–3 weeks in the presence of active viral replication following a single maternal dose [17-19]. EFV also has a long half-life, with detectable drug levels for more than 21 days following discontinuation [20]. This has clinical relevance in pregnancy where antiretroviral drugs may be provided solely for prophylaxis against perinatal transmission and discontinued after delivery or after breastfeeding. In a meta-

analysis of 10 studies, the prevalence of NVP resistance in women 4 to 8 weeks following sd-NVP was 35.7% [21]. Additionally, NNRTI resistance can develop in women receiving NNRTI-based triple-drug prophylaxis regimens following discontinuation of prophylaxis, particularly if all drugs are stopped simultaneously [22]. In most women, resistant virus can no longer be detected 6 to 12 months after exposure. However, low levels of viral resistance can persist for longer periods and in some cases can remain present in latently infected cells [23-25].

Data suggest that women starting NNRTI-based ART within 6-24 months of sd-NVP exposure have higher rates of viral failure than those without sd-NVP exposure. A definite relationship between time from sd-NVP exposure to starting NNRTI-based ART has been observed but has varied between studies, with a significant improvement in response if there were more than 12 months between sd-NVP exposure and start of therapy [26-33]. A tail regimen for a minimum of 7 days is recommended following sd-NVP or cessation of NNRTI-based triple prophylaxis. The tail regimen is provided in order to suppress virus and prevent persistent single drug NNRTI exposure. Much lower NNRTI resistance rates of 0% to 7% at 2 to 6 weeks postpartum have been reported with the use of various tail regimens [34-39].

The choice of ART regimen for pregnant women who require treatment for their own health but who have had exposure to ARV drugs for PMTCT prophylaxis in earlier pregnancies will therefore depend on the time since ARV PMTCT drug exposure at the time ART is being initiated, and whether a tail regimen was used for prevention of resistance following exposure to sd-NVP (given alone or in combination with other ARVs). As discussed in the revised 2010 guidelines, *Antiretroviral therapy for HIV infection in adults and adolescents* [13], viral load testing, if available, is particularly useful for monitoring response to treatment in this special situation.

A non-NNRTI-based ART regimen (e.g. a LPV/r-based regimen) is recommended for women who require ART for their own health who have received, within 12 months of initiating treatment, sd-NVP alone or in combination with other drugs *without* an NRTI tail. If a non-NNRTI-based regimen is not available, an NNRTI-based regimen may be started, but it is recommended that viral load testing (if available) be performed after 6 months of ART and, if the viral load is greater than 5000 copies/ml a switch to a boosted PI regimen (e.g. LPV/r) is recommended.

For women who have received sd-NVP alone or in combination with other drugs *with* a tail within 12 months of starting treatment, the initiation of a standard NNRTI-based ART regimen is recommended. Viral load testing (if available) is recommended after 6 months of ART and, if the viral load is greater than 5000 copies/ml a switch to a boosted PI regimen (e.g. LPV/r) is recommended.

For women who have received sd-NVP (alone or in combination with other drugs) more than 12 months before starting treatment (with or without a tail), a standard NNRTI-based ART regimen is recommended. As in the other scenarios above, if available, the viral load should be evaluated after 6 months of ART, and if greater than 5000 copies/ml a switch to a boosted PI regimen (e.g. LPV/r) is recommended.

Table 9. Choice of ART regimen for HIV-positive women with prior exposure to PMTCT prophylaxis

Characteristics of previous PMTCT ARV exposure	Recommendation
sd-NVP (+/- short-course AZT) with no NRTI tail within the last 12 months	• Initiate a non-NNRTI regimen • 2 NRTIs + PI preferred over 3 NRTIs
sd-NVP (+/- short-course AZT) with an NRTI tail within the last 12 months	• Initiate an NNRTI regimen • If available, check viral load at 6 months and if >5000 copies/ml, switch to second-line ART with PI
sd-NVP (+/- short-course AZT) with or without an NRTI tail more than 12 months before	• Initiate an NNRTI regimen • If available, check viral load at 6 months and if >5000 copies/ml, switch to second-line ART with PI
All triple ARV regimens, irrespective of duration of exposure and time since exposure	• Initiate NNRTI regimen • If earlier triple ARV regimen was NNRTI-based and was stopped without administration of an NRTI tail, check viral load at 6 months, if available, and if >5000 copies/ml, switch to second-line ART with PI

ART regimens for women of childbearing age receiving treatment for their own health

Women of childbearing age receiving ART should continue treatment and monitoring as recommended in the revised adult ART guidelines [13]. Contraceptive counselling is an essential component of care for HIV-infected women of reproductive age. Effective and appropriate contraceptive methods should be provided [40] as part of ART services wherever possible, in order to prevent unintended pregnancy, taking into consideration potential interactions of antiretroviral drugs with hormonal contraceptives that could lower contraceptive efficacy [41].

For women planning a pregnancy or who become pregnant while receiving ART, some additional clinical and treatment considerations should be taken into account for the health of the woman and the fetus. Such considerations mainly include the choice of regimen based on gestational age, the clinical and laboratory findings and the risk of MTCT. Known benefits and potential risks of antiretroviral use during pregnancy (particularly during the first trimester) should be discussed with all women. The interruption of treatment among eligible women receiving ART for their own health who have a good immune response to ART has been associated with viral rebound and renewed CD4 cell decline, increasing the risk of MTCT and HIV disease progression [42, 43]. Discontinuing treatment before or during pregnancy is therefore not recommended.

Women receiving ART and planning to become pregnant

Although the primary aim of ART remains the health of the woman, an additional important benefit of ART for women planning a pregnancy includes the reduced risk of HIV transmission to her infant. Counselling before conception should cover the risk of infant HIV infection, risk factors and PMTCT,

potential drug toxicity for mother and infant, safer sexual practices to prevent sexually transmitted infections (STIs), and other general health messages.

It is recommended that there be fully suppressive ART before conception and that it be maintained during pregnancy, labour, delivery and breastfeeding. Preferred ART regimens in such situations should have minimal teratogenic potentials for infants. Women who are planning to become pregnant should use a regimen that does not include EFV, in order to avoid the highest risk period of in utero EFV exposure (conception to day 28 of gestation). For women receiving an EFV-based regimen and who plan to become pregnant, substitution of NVP in the place of EFV for at least the periconception period is recommended. Pharmacokinetic data indicate that women should immediately start NVP at 200 mg twice a day, as half NVP dosing before escalation is associated with subtherapeutic NVP levels in individuals substituting NVP in the place of EFV [44]. Alternatively, a triple NRTI or PI-based regimen can be given.

Some concerns exist about exposure to TDF in utero and the risks of abnormal fetal bone development. However, for women requiring ART and receiving TDF who become pregnant, the benefits of continuing treatment are likely to outweigh the theoretical risks of toxicity for the infant. Further safety data are awaited.

Women receiving ART who become pregnant

HIV-infected women already receiving ART and who become pregnant require appropriate antenatal counselling, which should cover the risk of infant HIV infection, risk factors and PMTCT, potential drug toxicity for mother and infant, safer sexual practices to prevent STIs, and other general health messages.

Most women are not enrolled in antenatal care during the early stages of pregnancy, when most organogenesis occurs (i.e. the first trimester). Since the neural tube closes at approximately 28 days of gestation, fetal exposure to EFV during the risk period for neural tube defects will have occurred before the recognition of pregnancy in the vast majority of women. If a woman receiving EFV is recognized as pregnant before 28 days of gestation, EFV should be stopped and substituted with NVP or a PI. If a woman is diagnosed as pregnant after 28 days of gestation, EFV should be continued. There is no indication for abortion in women exposed to EFV in the first trimester of pregnancy.

Antiretroviral prophylaxis for infants born to women receiving ART

A short duration of antiretroviral prophylaxis (for 4-6 weeks) is indicated for infants born to HIV-infected women receiving ART, to further reduce peripartum and postpartum HIV transmission, in addition to the protection received from the mother's ART regimen (Table 10). Regardless of infant feeding choice, infant prophylaxis provides added protection from early postpartum transmission, particularly in situations where women have started ART late in pregnancy, have less than optimal adherence to ART and have not achieved full viral suppression [45]. The choice of infant prophylaxis should be guided by national programme considerations with regard to experience, availability, feasibility and potential toxicity.

Table 10. Considerations for choice of infant prophylaxis when mother receives ART for her own health

Infant prophylaxis	Dose and duration	Feasibility and operational considerations	Safety considerations
AZT	15 mg per dose twice daily if birth weight >2500 g (or 10 mg per dose twice daily if birth weight ≤2500 g) from birth until 4 to 6 weeks of age	• Twice-daily regimen • Substantial experience among infants receiving replacement feeding	• Potential risk of anaemia (reversible)
NVP	15 mg once daily if birth weight >2500 g (or 10 mg once daily if birth weight ≤2500 g) from birth until 4 to 6 weeks of age	• Once-daily regimen • Limited safety monitoring required • Substantial experience among breastfeeding infants • No evidence assessing the efficacy among infants receiving replacement feeding for any duration beyond a single dose at birth • NVP is not recommended for infants born to mothers infected solely with HIV-2	• Risk of acquired drug resistance for infants becoming infected despite interventions • Potential risk for NVP toxicity if mother receives NVP-based ART regimen during breastfeeding (there is some passage of NVP to the infant through breast milk)

Infants should receive either twice-daily AZT or daily NVP from birth (within 6–12 hours) or as soon as feasible thereafter until 4 to 6 weeks of age.

Table 11. Clinical scenarios and recommendations for antiretroviral treatment and infant

Clinical scenario	Woman / infant regimen	Recommended drug regimen
Pregnant women tested HIV-infected and eligible for ART	Woman	AZT + 3TC + NVP or TDF + 3TC (or FTC) + NVP or AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV
	Infant	AZT or NVP

This is a strong recommendation with a moderate quality of evidence (for breastfeeding infants), and a conditional recommendation with a low quality of evidence (for non-breastfeeding infants) for the duration of prophylaxis and the choice between available regimens. The recommendation is based on programmatic issues that would facilitate its implementation in the field: 6 weeks is often the time of the first immunization visit and the target date for early diagnosis testing for HIV-exposed children in most settings, implying that most children will have an opportunity to be seen and re-evaluated at that age. The recommendation for use of daily NVP or twice-daily AZT until 4 to 6 weeks of age in infants of mothers receiving ART is made irrespective of the infant feeding option (breastfeeding or replacement feeding) and the duration for which the mother received ART. Although some data suggest that a shorter duration of infant prophylaxis may be adequate if the mother has received more than 4 weeks of antepartum drugs [45], a single recommended duration for infant prophylaxis in national programmes is programmatically easier to implement and will also compensate if maternal antepartum adherence to drugs has been suboptimal.

MTCT prophylaxis for women who require treatment for their own health

Timing and duration of ARV interventions			Notes on recommendations
Antepartum	Intrapartum	Postpartum (and irrespective of mode of infant feeding)	
Initiate ART irrespective of gestational age	Continue ART	Continue ART	Avoid EFV in first trimester and use NVP instead. EFV can be recommended after the first trimester. After delivery, EFV should be combined with proper use of contraceptives to avoid conception while receiving EFV. Avoid the use of drugs with known adverse potential, including ddI/d4T and AZT/d4T.
		From birth until 4 to 6 weeks of age	Infant prophylaxis should be given irrespective of infant feeding option (breastfeeding or replacement feeding) and duration of maternal ART.

Clinical scenario	Woman / infant regimen	Recommended drug regimen
Pregnant women eligible for ART but **exposed to sd-NVP without dual NRTI tail in last 12 months**	Woman	Non-NNRTI regimen
	Infant	AZT or NVP
Pregnant women eligible for ART **who have clinically significant or documented severe anaemia (Hb <7g/dl)**	Woman	TDF + 3TC (or FTC) + EFV or TDF + 3TC (or FTC) + NVP
	Infant	AZT or NVP
Pregnant women eligible for ART with **HIV-2 infection alone**	Woman	AZT + 3TC + ABC or AZT + 3TC + LPV/r
	Infant	AZT
Pregnant women eligible for ART with **TB coinfection**	Woman	AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV
	Infant	AZT or NVP

Clinical scenario	Woman / infant regimen	Recommended drug regimen
Pregnant women eligible for ART with **HBV coinfection requiring HBV treatment**	Woman	TDF + 3TC (or FTC) + EFV or TDF + 3TC (or FTC) + NVP
	Infant	AZT or NVP
Non-pregnant women of childbearing age who are eligible for ART and who **may become / plan to become pregnant**	Woman	AZT + 3TC + NVP or TDF + 3TC (or FTC) + NVP
	Infant	AZT or NVP
Women receiving ART who become pregnant	Woman	Continue same ART
	Infant	AZT or NVP

Clinical and laboratory monitoring of pregnant women receiving ART for their own health and their infants

Clinical and laboratory monitoring of HIV-infected pregnant women should be done as is recommended for non-HIV-infected pregnant women [13] and should be part of a package of care interventions as described in the 2008 WHO guidelines on essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings [46]. Particular attention should be given to signs of clinically significant anaemia among HIV-infected pregnant women [47].

HIV disease stage and potential disease progression can be monitored through assessment of the WHO clinical stage. Weight loss is one of the conditions used to determine the WHO clinical stage but can be difficult to assess in pregnancy and postpartum. When defining the clinical stage of a pregnant woman, health-care providers may need to take into consideration her expected weight gain in relation to the gestational age of the pregnancy and her potential weight loss from HIV.

The monitoring of immunological status through measurement of the CD4 cell count is not essential for monitoring patients on ART, but can be used to confirm clinical treatment failure [48-51]. However, the absolute CD4 cell count decreases during pregnancy because of pregnancy-related haemodilution; after delivery, body-fluid changes normalize to the non-pregnant state, and CD4 levels may rise by 50–100 cells/mm^3 [30-33]. A decrease in the absolute CD4 count of a pregnant woman from her CD4 values before pregnancy should therefore be interpreted with caution.

Additional monitoring of adverse reactions related to antiretroviral drugs should be based on the potential adverse reactions of the antiretroviral agents used (Table 19). It is unknown whether pregnancy predisposes to the development of NRTI-associated lactic acidosis; cases have been reported in late pregnancy. Any new symptoms in pregnant women receiving NRTIs should be evaluated thoroughly.

Treatment success, as well as effective prevention of infant HIV infections, is dependent on antiretroviral drug adherence. Regular assessment and support of drug adherence is recommended.

SECTION IV. MATERNAL AND INFANT ARV PROPHYLAXIS TO PREVENT MTCT FOR HIV-INFECTED PREGNANT WOMEN WHO DO NOT NEED TREATMENT FOR THEIR OWN HEALTH

Key recommendations

Eligibility for ARV prophylaxis

HIV-infected pregnant women who are not in need of ART for their own health require effective ARV prophylaxis to prevent HIV infection in their infants. ARV prophylaxis should be started from as early as 14 weeks of gestation (second trimester) or as soon as feasible during pregnancy, labour and delivery or thereafter.

What ARV prophylaxis regimen to give women and their infants

Two options are recommended for HIV-infected pregnant women who are not eligible for ART: option A is maternal AZT + infant ARV prophylaxis; option B is maternal triple ARV prophylaxis.

Option A: maternal AZT + infant ARV prophylaxis

For HIV-infected pregnant women who are not in need of ART for their own health, ARV prophylaxis option A consists of antepartum twice-daily AZT, plus sd-NVP at the onset of labour[1], plus twice-daily AZT + 3TC during labour and delivery and continued for 7 days postpartum.

In breastfeeding infants, daily administration of NVP to the infant from birth until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding stops before 6 weeks (but at least 1 week after the early cessation of breastfeeding), is recommended.

In infants receiving only replacement feeding, daily administration of NVP from birth or sd-NVP at birth plus twice-daily AZT from birth until 4 to 6 weeks of age is recommended.

Option B: maternal triple ARV prophylaxis

For HIV-infected pregnant women who are not eligible for ART for their own health, ARV prophylaxis option B consists of antepartum daily triple ARV prophylaxis until delivery, or, if breastfeeding, until 1 week after all exposure to breast milk has ended. Recommended regimens include AZT + 3TC + LPV/r, AZT + 3TC + ABC, AZT + 3TC + EFV, or TDF + 3TC (or FTC) + EFV.

In infants, regardless of infant feeding practices (breastfeeding or replacement feeding), the maternal triple ARV prophylaxis should be combined with the daily administration of NVP or twice-daily AZT to the infant from birth until 4 to 6 weeks of age.

Although women with higher CD4 counts who do not yet require ART for their own health are at lower risk of transmitting HIV to their infants, they need an efficacious ARV regimen (either option A or option B) to prevent infection in their infants. Optimal prophylaxis should be based on a combined

[1] sd-NVP and the AZT + 3TC intrapartum and postpartum tail can be omitted if the mother received more than 4 weeks of AZT during pregnancy; in this case continue maternal AZT twice daily during labour and stop at delivery.

approach of prophylaxis to both the mother and the infant, and should provide appropriate protection against postpartum transmission (with either maternal or infant prophylaxis) in settings where breastfeeding is the best infant feeding option.

ARV prophylaxis for women and their infants to reduce perinatal HIV transmission

All HIV-infected pregnant women who are not in need of ART for their own health require an effective ARV prophylaxis strategy to prevent HIV transmission to their infants. ARV prophylaxis should start from as early as 14 weeks of gestation (i.e. during the second trimester of pregnancy), or as soon as possible thereafter. For women presenting late, prophylaxis can be started in the second trimester, labour or at delivery, or even postpartum, but the principle that should be followed is that *as much as possible of the full prophylaxis regimen should be given*. Despite the lack of direct clinical trial evidence showing the advantage of ARV initiation before 28 weeks, observational data suggest that starting ARV prophylaxis earlier in pregnancy may be more effective in further reducing MTCT [52-54]. Current programme experience shows that many women are started on prophylaxis after 28 weeks of pregnancy despite being identified earlier. In recommending earlier initiation of prophylaxis, instead of delaying until the third trimester, a high value was placed on reducing the risk of in utero transmission while decreasing the probability of women being lost to follow up before starting any intervention to prevent MTCT. This recommendation will therefore minimize delays between HIV testing in pregnancy and the initiation of ARV prophylaxis.

Two prophylaxis options are recommended. The currently available scientific and programmatic data do not demonstrate that one strategy is more efficacious than the other. Hence there was consensus that both options should be strongly recommended without preferring one over the other. At a national and programmatic level, the decision for one option should be made according to local circumstances, weighing feasibility, acceptability, values and cost.

Maternal AZT plus infant ARV prophylaxis to prevent MTCT (option A)

The maternal component of this ARV prophylaxis strategy is based on the same regimen as previously recommended in the 2006 guidelines [9], i.e. antepartum daily AZT plus sd-NVP at onset of labour plus AZT + 3TC during labour and delivery and for 7 days postpartum. However, the revised recommendation now encourages starting the maternal AZT earlier in pregnancy in order to further decrease the chance of in utero transmission and to limit missed opportunities of starting maternal prophylaxis. As in the previous guidelines, the revised recommendation notes that consideration can be given to omitting maternal intrapartum and postpartum sd-NVP and the AZT + 3TC tail if the mother has been documented as receiving more than 4 weeks of AZT during pregnancy. In this case, continue maternal AZT twice daily during labour and stop at delivery.

The available observational studies show the benefits of starting prophylaxis early. This will minimize delays between HIV testing in pregnancy (recommended at the first antenatal care visit) and initiation of ARV prophylaxis. Given the median time of the first antenatal visit in most settings, it is recognized that most women would not start ARV prophylaxis at 14 weeks, but the goal is for a majority of

women to start prophylaxis during the second trimester rather than in the third trimester. For women not eligible for ART, this maternal ARV prophylaxis regimen is highly effective in preventing most in utero HIV transmission. The addition of sd-NVP helps to prevent HIV transmission around the time of delivery, while the administration of a short dual NRTI tail following sd-NVP minimizes the risk of emergence of viral resistance to NVP [55-57]. In the Kesho Bora study, women with CD4 counts of 200–500 cells/mm^3 were randomized between 28 and 36 weeks of gestation to initiate maternal triple ARV prophylaxis or AZT plus sd-NVP with an AZT + 3TC tail for 1 week [58]. Infection rates at birth were 1.8% (IQR = 0.8–3.7%) with maternal triple ARV and 2.2% (IQR = 1.2–4.3%) with AZT plus sd-NVP and AZT + 3TC, which were not significantly different.

For breastfeeding infants, the option A maternal ARV prophylaxis should be linked with daily administration of NVP to the infant from birth or as soon as feasible thereafter, until 1 week after all exposure to breast milk has ended, or until 4 to 6 weeks of age if breastfeeding stops very early (but always continue for 1 week after breastfeeding ends). Several randomized clinical trials as well as observational studies demonstrate the benefits of extended ARV prophylaxis to breastfeeding infants (Table 12). In the PEPI study (Malawi), infants born to mothers who had received sd-NVP were randomized to receive either sd-NVP and 1 week of AZT (group 1, control) or 14 weeks of daily infant NVP prophylaxis (group 2) or 14 weeks of daily NVP + AZT (group 3) [59]. At 9 months of age the risk of HIV infection in infants uninfected at birth was 10.6% in group 1, 5.2% in group 2 and 6.4% in group 3. However, at 18 months, HIV infection rates were as high as 13.9% in group 1, 10.1% in group 2 and 10.2% in group 3. Thus, postnatal transmission was significantly lower in the intervention arms as compared to the control group during the period of prophylaxis, but, after prophylaxis was discontinued, infections occurred at similar rates in the control and intervention groups. In the SWEN study (Ethiopia, India, and Uganda), 6 weeks of infant post-exposure prophylaxis with daily NVP from birth was assessed in breastfed children, and compared to sd-NVP (all mothers also received sd-NVP) [60]. The 6-week transmission rate in infants uninfected at birth in the 6-week extended-NVP arm was 2.5% vs. 5.3% in the sd-NVP arm ($p = 0.009$). However, as in the PEPI study, after prophylaxis was discontinued, postnatal transmission continued to occur in infants who continued to breastfeed. The 6-month HIV transmission rate was similar in both study arms: 8.9% in the extended-NVP arm vs. 6.9% in the sd-NVP arm ($p = 0.16$). In the MITRA study (Tanzania), breastfed children received daily 3TC from birth until six months of age, while their mothers received daily AZT + 3TC from the third trimester of pregnancy until 1 week postpartum [61]. Overall HIV-transmission rates were 3.8% and 4.9% at 6 weeks and 6 months of age, respectively. However, the breastfeeding duration was considerably shorter (median, 18 weeks) than usual African practices and only 15% of children were still breastfed at 6 months. Finally, the BAN trial (Malawi) showed a strong protective effect and no significant difference between 6 months of infant NVP prophylaxis and 6 months of maternal triple ARV prophylaxis [62, 63]. Among women with high CD4 counts (entry CD4 of >250 cells/mm^3; median 440 cells/mm^3), the postnatal MTCT rate at 6.5 months in infants uninfected at 2 weeks was 1.7% in the infant extended-NVP group vs. 2.9% in the maternal triple ARV group ($p = 0.1$); both rates were significantly lower ($p<0.009$) than that of the control arm of sd-NVP + 1 week AZT + 3TC (5.7%).

Table 12. MTCT risk, and risk of infection or death with the provision of antiretroviral extended prophylaxis to the breastfed infant

Note: transmission rates cannot be directly compared between studies because they represent different populations with different CD4 cell counts and different ARV interventions given for different durations of time, and because HIV transmission rates were assessed at different times.

Study	Antiretroviral intervention		MTCT risk (95% confidence interval)	Infant infection or death
	Maternal regimen	Infant regimen		
SIMBA, Rwanda [64] (Vyankandondera)	AZT + ddI from 36 weeks of gestation to 1 week postpartum	Daily NVP or daily 3TC * from birth up to 6 months	Overall: 6.9% at 1 mo (4.4–9.4) ** 7.7% at 6 mo (5.1–10.5)**	Not available
MASHI, Botswana [65] (Thior)	AZT + sd-NVP from 36 weeks of gestation to 1 week postpartum	Daily AZT from birth up to 6 months	Overall 4.6% at 1 mo ** 9.0% at 7 mo ** 9.5% at 18 mo **	6.1% at 1 mo** 12.9% at 7 mo** 15.1% at 18 mo**
MITRA, Tanzania [61] (Kilewo)	AZT + 3TC from 36 weeks of gestation to 1 week postpartum	Daily 3TC from birth up to 6 months	Overall 3.8% at 1.5 mo (2.0–5.6) 4.9% at 6 mo (2.7–7.1)	4.5% at 1.5 mo (2.4–6.5) 8.5% at 6 mo (5.7–11.4)
PEPI, Malawi [59] (Kumwenda)	sd-NVP at onset of labour	Daily NVP or NVP/AZT from birth up to 14 weeks	Among infants who were HIV-uninfected at birth Infant NVP prophylaxis 5.9% at 9 mo (3.9–7.0) Infant NVP/AZT prophylaxis 6.4% at 9 mo (4.9–8.3)	10.6% at 9 mo 11.2% at 9 mo
SWEN, Ethiopia, Uganda, India [60] (SWEN Study Team)	sd-NVP at onset of labour	Daily NVP from birth up to 6 weeks	Among infants who were HIV-uninfected at birth 2.5% at 1.5 mo ** 6.9% at 6 mo **	3.7% at 1.5 mo** 8.1% at 6 mo**

Study	Antiretroviral intervention		MTCT risk (95% confidence interval)	Infant infection or death
	Maternal regimen	Infant regimen		
BAN, Malawi [62, 63] (Chasela)	sd-NVP at onset of labour + AZT + 3TC during labour to 1 week postpartum	Daily NVP from birth up to 6 months	Among infants who were HIV-uninfected at age 2 weeks 1.7% at 6.5 mo **	Among infants who were alive and HIV-uninfected at age 2 weeks 2.6% at 6.5 mo**

* Similar MTCT rates were observed in both groups.

** Confidence interval was not available.

Median breastfeeding durations were: 14 weeks in the SIMBA study; unknown in the MASHI study (mothers instructed to wean at 5 months); 18 weeks in the MITRA study; unknown in the PEPI study (most infants were weaned between 6 and 9 months of age); unknown in the SWEN study (most infants were weaned between 14 weeks and 6 months of age); unknown in BAN (exclusive breastfeeding for 24 weeks with weaning over 4 weeks was promoted).

In conclusion, the available data suggest that postnatal infant ARV prophylaxis during breastfeeding is efficacious in reducing HIV transmission and infant death. A high value was placed on an intervention that would allow safer breastfeeding practices in settings where breastfeeding was the norm and where replacement feeding was not considered safe or feasible. To be maximally effective, ARV prophylaxis would have to be maintained throughout the period of breastfeeding exposure. Although data are only available for the provision of NVP to breastfed infants up to 6 months of age, there is a need to provide ARV prophylaxis throughout the breastfeeding period to minimize the overall risk of HIV transmission. Daily infant NVP prophylaxis given for up to 6 months in 3016 infants in the SWEN, PEPI, SIMBA and BAN trials appears safe for the infants compared to control interventions, with the exception of a slightly higher number of rashes seen in the BAN study (incidence of grade 3 or 4 rash with infant NVP in the BAN study was <2%; all resolved when switched to daily 3TC). Since most NVP toxicity occurs early (i.e. in the first 12 weeks of use) it was felt that the risk of increased toxicity with 12 months of extended infant NVP prophylaxis (as opposed to 6 months) was low and that the value of preventing postnatal transmission and providing an option for safer breastfeeding outweighed the potential risk of adverse events.

The infant prophylaxis dosing for extended NVP and for up to 6 weeks of AZT depends on the age and weight of the infant and is recommended in the following simplified dosing schedules (Tables 13 and 14). Low birth weight infants needing care in specialized settings should receive mg/kg dosing. For NVP, the starting dose is 2 mg/kg per day, with therapeutic drug monitoring. For AZT, infants born before 35 weeks of gestation needing care in specialized setting should receive 1.5 mg/kg intravenous, or 2 mg/kg oral every 12 hours, increased to every 8 hours at 2 weeks of age (neonates ≥30 weeks gestational age) or at 4 weeks of age (neonates <30 weeks gestational age).

Table 13. Extended simplified infant NVP dosing recommendations*

Infant age	NVP daily dosing
Birth** to 6 weeks • Birth weight 2000–2499 g • Birth weight ≥2500 g	 10 mg once daily 15 mg once daily
>6 weeks to 6 months	20 mg once daily
>6 months to 9 months	30 mg once daily
>9 months to end of BF	40 mg once daily

* Based on the dosing required to sustain exposure in the infant of >100 ng/ml with the least dose changes.

** Low birth weight infants should receive mg/kg dosing, suggested starting dose is 2 mg/kg once daily. Therapeutic drug monitoring is recommended

Adapted from: Mirochnick M. et. al. [66].

Table 14. Simplified infant AZT dosing recommendations*

Infant age	AZT daily dosing
Birth to 6 weeks • Birth weight 2000–2499 g • Birth weight ≥2500 g	 10 mg twice daily 15 mg twice daily

* Low birth weight infants should receive mg/kg dosing.

For infants receiving replacement feeding only, peripartum and post-exposure prophylaxis for 4–6 weeks with either daily-NVP or sd-NVP plus twice-daily AZT is recommended. There is no evidence assessing the efficacy of daily NVP for any duration beyond a single dose in infants with only replacement feeding. However, there is a high quality of evidence that 6 weeks of daily infant AZT prophylaxis in conjunction with maternal antepartum AZT prophylaxis for more than 4 weeks significantly prevents the risk of HIV transmission around the time of delivery [45]. There is additional evidence that giving AZT for 6 weeks to the infant provides significant protection when mothers have received less than 4 weeks of antepartum prophylaxis. There is evidence that, when pregnant women had received more than 4 weeks of antepartum prophylaxis, shorter durations of infant AZT were also effective. The safety of 6 weeks of infant NVP has been demonstrated in the trials mentioned above in breastfeeding infants. This recommendation is conditional because of the lack of data distinguishing between a 4-week and 6-week duration of infant prophylaxis and the lack of data comparing NVP and AZT prophylaxis in infants receiving replacement feeding. This recommendation, which gives countries the option of using NVP or AZT prophylaxis for 4–6 weeks in infants receiving replacement feeding, was based primarily on programmatic considerations that would facilitate its implementation in the field: 6 weeks is also the time of the first immunization visit and the target date for early diagnosis testing for HIV-exposed children in most settings, and hence most children will have an opportunity to be seen and re-evaluated at that age.

Maternal triple ARV prophylaxis to prevent MTCT (option B)

The provision of maternal triple ARV prophylaxis during pregnancy in women who are not eligible for ART results in very low in utero and peripartum transmission rates. A high value is also placed on the simplicity of the intervention as it contains only one maternal and one infant regimen and may be available as a once-daily fixed-dose combination. The recommended maternal triple ARV regimens include AZT + 3TC + LPV/r; AZT + 3TC + ABC; AZT + 3TC + EFV; and TDF + 3TC (or FTC) + EFV. NVP-based regimens are not recommended because of the risk of hepatotoxicity for women with high CD4 counts (>350 cells/mm^3).

For breastfeeding infants the maternal triple ARV prophylaxis should be coupled with the daily administration of NVP or twice-daily AZT to the infant from birth (within 6 to 12 hours) or as soon as feasible thereafter until 4 to 6 weeks of age. The available evidence shows the benefits of the provision of maternal triple ARV prophylaxis when children are breastfeeding (Table 15).

The Kesho Bora randomized controlled trial conducted in Burkina Faso, Kenya and South Africa assessed the efficacy of maternal triple antiretroviral prophylaxis started between 28 and 36 weeks of pregnancy and continued during breastfeeding until 6 months post-delivery compared to short-ARV prophylaxis [58]. Women with CD4 cell counts between 200 and 500 cells/mm^3 were enrolled. Three-quarters of infants were breastfed in both arms, for a median duration of 21.4 weeks. At birth, infant infection rates were similar in the two groups, 1.8% in mothers in the triple ARV arm and 2.2% in mothers in the short infant prophylaxis arm. However, in mothers randomized to triple ARV prophylaxis, the cumulative life table HIV infection rate of infants at 12 months was 5.5% (95% CI = 3.6%–8.4%), a risk reduction of 42% compared to infants in the short-ARV prophylaxis arm. The largest effect of triple ARV prophylaxis occurred among women with baseline CD4 cell counts between 200 and 350 cells/mm^3 and between 6 weeks and 6 months post-delivery. In these women, cumulative infant HIV infection rates at 6 months post-delivery were 5.5% and 10.5% among women in the triple ARV prophylaxis arm and short ARV prophylaxis arm respectively. In contrast, in women with CD4 cell counts of 351–500 cells/mm^3, cumulative infant HIV infection rates at 6 months post-delivery were 4.1% and 5.9% among women in the triple ARV prophylaxis arm and short infant prophylaxis arm respectively. In the open-label Dream study in Mozambique, a maternal triple ARV regimen was provided to both ART-eligible and non-eligible women from the third trimester of pregnancy and throughout breastfeeding exposure. The cumulative postnatal HIV transmission rate (between 1 and 12 months) was 2.8% [67]. The open-label AMATA study in Rwanda demonstrated very low transmission rates after 6 months of breastfeeding exposure (and then stopping breastfeeding) and maternal triple ARV prophylaxis [68]. In the Mma Bana study, high levels of viral suppression and very low overall transmission rates (1.1%) were reported at 6 months postpartum in Botswana among women with CD4 values of ≥200 cells/mm^3 who received triple ARV prophylaxis (either a triple NRTI or PI-based regimen) from 26 weeks of gestation [69, 70]. As discussed earlier, the BAN trial, which compared 6 months of extended NVP prophylaxis in infants to maternal triple ARV prophylaxis (and to a control regimen) during breastfeeding in women with CD4 values of >250 cells/mm^3, found that both regimens had significantly lower postnatal transmission rates than the control arm, with an infant infection rate of 2.9% in the maternal triple ARV group at age 6 months among infants uninfected at the age of 2 weeks [63] .

Table 15. MTCT risk, and risk of infection or death, with the provision of maternal triple ARV prophylaxis during pregnancy and breastfeeding to mothers who did not require ART for their own health

Note: transmission rates cannot be directly compared between studies because they represent different populations, different interventions and different methods, and because HIV transmission rates were assessed at different times.

Study	Antiretroviral intervention		MTCT risk according to baseline maternal CD4 count (95% confidence interval)	Infant infection or death according to baseline maternal CD4 count (95% confidence interval)
	Maternal regimen *Infant regimen*	Duration		
Kisumu, Kenya [71] (Thomas)	CD4 ≥250 cells/mm^3 AZT + 3TC + NVP * *sd-NVP for infants*	From 34 weeks of gestation until 6 months postpartum	Among women with CD4 ≥250 cells/mm^3: 3.8% at 1 mo (2.2–6.3) 4.9% at 6 mo (3.1–7.7) 5.5% at 12 mo (3.6–8.4)	Not available
Kesho Bora, Burkina Faso, Kenya, South Africa [58] (De Vincenzi)	CD4 200-500 cells/mm^3 AZT + 3TC + LPV/r *sd-NVP + 1 week of AZT for infants*	From 28 to 36 weeks of gestation until 6 months postpartum	Among women with CD4 200<CD4<500 cells/mm^3: 4.9% at 6 mo (3.1–7.5) 5.5% at 12 mo (3.6–8.4)	8.3% at 6 mo (6.0–11.5) 10.4% at 12 mo (7.7–13.9)
AMATA, Rwanda[68] (Peltier)	CD4<350 cells/mm^3: d4T + 3TC + NVP CD4≥350 cells/mm^3: AZT + 3TC + EFV *sd-NVP + 1 week of AZT for infants in both groups*	From 28 weeks of gestation until 7 months postpartum Stop breastfeeding at 6 months	Overall: 1.3% at 1 mo (0.4–4.1) 1.8% at 9 mo (0.7–4.8)	Overall: 5.0% at 9 mo (3.0–9.0)
MITRA-PLUS, Tanzania [72] (Kilewo)	All women: AZT + 3TC + NVP *1 week of AZT + 3TC for infants*	From 34 weeks of gestation until 6 months postpartum Continued if mother eligible for treatment at 6 months	Among women with CD4 ≥200 cells/mm^3: 4.1 % at 1.5 mo (2.1–6.0) 5.3% at 6 mo (2.9–7.6) 6.2% at 12 mo (3.6-8.7)	Not available

Study	Antiretroviral intervention		MTCT risk according to baseline maternal CD4 count (95% confidence interval)	Infant infection or death according to baseline maternal CD4 count (95% confidence interval)
	Maternal regimen *Infant regimen*	Duration		
Dream cohort, Mozambique[67] (Palombi)	All women: AZT + 3TC + NVP *sd-NVP for infants*	From 15 weeks of gestation	Overall: 1.2% at 1 mo ** 2.2% at 6 mo ** 2.8% at 12 mo **	Not available
Mma Bana, Botswana [70] (Shapiro)	CD4 ≥200 cells/mm^3 ABC + AZT + 3TC or AZT + 3TC + LPV/r	From 26 to 34 weeks of gestation until 6 months postpartum	Among women with CD4 ≥200 cells/mm^3: 1.1% at 6 mo (0.5–2.2)	Not available
BAN, Malawi [62, 63] (Chasela)	CD4 >250 cells/mm^3 AZT + 3TC + LPV/r	From labour until 6 months postpartum	Among women with CD4 >250 cells/mm^3: 2.9% at 6 mo in infants uninfected at 2 weeks	Infants uninfected and alive at 2 weeks: 4.1% at 6 mo

* Half-way through the Kisumu study, NVP was replaced by nelfinavir (NFV) among women with CD4 of >250 cells/mm^3.

** Confidence interval was not available.

Median breastfeeding durations were: unknown in Kisumu study, Kesho Bora trial, AMATA study and DREAM study (exclusive breastfeeding for 24 weeks followed by weaning was promoted in each study); 24 weeks in the MITRA-PLUS study; unknown in Mma Bana (71% breastfed >5 months but <1% breastfeeding at 6 months); unknown in BAN (exclusive breastfeeding for 24 weeks with weaning over 4 weeks was promoted).

As summarized in Table 15, the available data suggest that maternal triple ARV prophylaxis that started in pregnancy and continued during breastfeeding was efficacious in reducing HIV transmission and infant death. A high value was placed on providing an intervention that would allow safer breastfeeding practices.

For infants receiving only replacement feeding, the maternal triple ARV prophylaxis should be coupled with daily administration of NVP or twice-daily AZT to the infant from birth (within 6 to 12 hours) or as soon as feasible thereafter until 4 to 6 weeks of age. This conditional recommendation was primarily based on programmatic issues that would facilitate its implementation in the field: 6 weeks is the time of the first immunization visit and the target date for early diagnosis testing for HIV-exposed children in most settings, implying that most children will have an opportunity to be seen and re-evaluated at that age.

Table 16. Considerations for the choice of maternal triple ARV prophylaxis for HIV-infected pregnant women who are not in need of treatment for their own health

Recommended regimens	Dosing	Feasibility considerations	Safety considerations
AZT + 3TC + LPV/r	AZT 300 mg twice daily 3TC 150 mg twice daily LPV/r 400/100 mg twice daily	• Extensive experience with AZT + 3TC backbone in pregnancy • Hb assessment is recommended (but not necessary) before use of AZT • Relatively high cost of regimen • High pill burden	• Risk of anaemia with AZT
AZT + 3TC + ABC	AZT 300 mg twice daily 3TC 150 mg twice daily ABC 300 mg twice daily	• Regimen could be provided as a fixed-dose combination • Hb assessment is recommended (but not necessary) before use of AZT	• Risk of anaemia with AZT • Risk of hypersensitivity reaction with ABC
AZT + 3TC + EFV	AZT 300 mg twice daily 3TC 150 mg twice daily EFV 600 mg once daily	• Extensive experience with AZT + 3TC backbone in pregnancy • Hb assessment is recommended (but not necessary) before use of AZT • Effective contraception after delivery is required with use of EFV to prevent (subsequent) pregnancy • EFV use is recommended for women presenting with TB	• Risk of anaemia with use of AZT • Potential risk (probably <1%) of neural tube defect with use of EFV in first month of pregnancy (before 6 weeks of gestation)

Recommended regimens	Dosing	Feasibility considerations	Safety considerations
TDF + 3TC (or FTC) + EFV	TDF 300 mg once daily 3TC 150 mg twice daily EFV 600 mg once daily	• Effective contraception after delivery is required with use of EFV to prevent (subsequent) pregnancy • EFV use is recommended for women presenting with TB • TDF + 3TC use is recommended for women with hepatitis B infection requiring HBV treatment	• Risk of nephrotoxicity with use of TDF • Limited data available on potential maternal and infant bone toxicity with use of TDF • Potential risk (probably <1%) of neural tube defect with EFV use in first month of pregnancy (before 6 weeks of gestation) • Potential risk of hepatic flare in HBV-coinfected women after TDF + 3TC is discontinued after weaning
TDF + FTC + EFV	TDF 300 mg once daily FTC 200 mg once daily EFV 600 mg once daily	• Could be given as once daily regimen in a fixed-dose combination • Effective contraception after delivery is required with use of EFV to prevent (subsequent) pregnancy • EFV use is recommended for women presenting with TB • TDF + FTC use is recommended for women presenting with hepatitis B infection requiring HBV treatment • Relatively high cost of regimen	• Risk of nephrotoxicity with use of TDF • Limited data available on potential maternal and infant bone toxicity with use of TDF • Potential risk (probably <1%) of neural tube defect with use of EFV in first month of pregnancy (before 6 weeks of gestation) • Potential risk for hepatic flare in HBV-coinfected women after TDF + FTC is discontinued after weaning

Considerations for each of the two recommended ARV prophylaxis options for breastfeeding infants

A high value was placed on reducing the risk of HIV transmission to all HIV-exposed infants and providing effective prophylaxis during the breastfeeding period in settings where this practice was the preferred infant feeding option for HIV-exposed infants. There is therefore a strong benefit in

providing effective and sustained prophylaxis to women not eligible for ART during pregnancy, labour and delivery, as well as throughout the period when the infant is exposed to any breastfeeding. Both recommended options provide a significant reduction of the MTCT risk in the presence of breastfeeding. There are advantages and disadvantages for both options, in terms of feasibility, acceptability, cost and safety for mothers and infants.

The acceptability of both options in programme settings and at the population level is unknown. In particular, although the acceptability of giving daily infant ARV prophylaxis for up to 6 months has been shown in several research settings [59, 61, 62, 64, 65], the feasibility of giving daily infant ARV prophylaxis for longer periods (between 6 and 12 months in most settings), as well as the additional needed programme support are unknown. Similarly, while the acceptability of continuing maternal triple ARV regimens throughout the breastfeeding period among women with high CD4 counts (i.e. in women not in need of ART for their own health) for up to 6 months has been demonstrated [63, 70, 71], the acceptability and feasibility of providing maternal triple ARV prophylaxis for longer periods (antepartum plus up to 12 months post-delivery), followed by discontinuation, is also not known.

At the country level the extended ARV prophylaxis for all infants (daily NVP) is a significantly less costly option than the provision of a triple ARV regimen to all mothers. However, the maternal triple ARV option could be seen as a universal approach that might facilitate its implementation at the population level: both eligible and ineligible women (for ART) could then potentially receive the same ARV regimen, including one that might be available as a once-daily fixed-dose combination. It is important to note that a triple ARV regimen used solely for prophylaxis in women with a CD4 >350 cells/mm^3 would be stopped after the risk of MTCT has ceased, based on current recommendations and thresholds for ART eligibility. A thorough clinical and immunological assessment of the pregnant woman's need for ART for her own health is a critical component of decision-making on the choice of ARV regimen and whether it should be continued or stopped after delivery (i.e. after the infant has ceased breastfeeding).

The initiation of triple ARV prophylaxis among all pregnant women and its continuation throughout breastfeeding exposure, following option B, would not only prevent MTCT and enable safer breastfeeding practices, but might also improve maternal health while it is being received. However, if all pregnant women were offered triple ARV regimens, the question of whether and when to stop this intervention in women who are not eligible for ART according to current international guidelines is to date unanswered. The risk for maternal health of stopping prolonged maternal triple ARV prophylaxis after breastfeeding cessation among women with high CD4 counts is unknown. In contrast, this risk would not be present in option A, where infant rather than maternal prophylaxis is given.

Uncertainties, expected benefits and risks of the two options of prolonged prophylaxis during breastfeeding are outlined in Table 17. The choice for a preferred option should be made at country level, after having considered the local situation and the balance of the expected benefits and risks.

Table 17. Uncertainties, expected benefits and risks of the two ARV prophylaxis interventions for women who are not eligible for ART

	Expected benefits	Uncertainties and expected risks
Maternal AZT plus infant ARV prophylaxis (option A)	• Significant reduction of the MTCT risk. • Low rate of maternal NNRTI resistance with use of AZT + 3TC tail. • Low rate of adverse events in infants. • The long half-life of NVP allows the infant to potentially miss some of the daily doses while still maintaining adequate drug levels.	• The peripartum maternal regimen is more complex, requiring administration of AZT + 3TC tail if sd-NVP is given. Likelihood of NNRTI resistance in most infants who are infected despite prophylaxis. • Safety, effectiveness and feasibility of daily infant NVP beyond 6 months of age is unknown. • The maternal and infant acceptability of daily infant prophylaxis for a long period is unknown.
Maternal triple ARV prophylaxis (option B)	• Significant reduction of the MTCT risk. • Low rate of adverse events in infants. • May be easier to implement: both eligible and ineligible women receiving the same triple ARV regimen (note: NVP-containing regimens should not be used for women with CD4 >350 cells/mm^3). • No change in regimen between antepartum and postpartum periods. • Strategy may improve maternal health during the period woman is receiving the regimen.	• Need to know maternal CD4 count to be able to determine whether maternal triple ARV prophylaxis can be discontinued after breastfeeding cessation. • The risk for maternal health of stopping prolonged (e.g. 12–18 months) maternal triple ARV prophylaxis after breastfeeding cessation is unknown. • Potential risk of multi-ARV resistance in mother if she does not adhere to the regimen. • Likelihood of drug resistance (NRTI, NNRTI) in infants who are infected despite prophylaxis. • Some data suggest increased risk of adverse pregnancy outcomes (e.g. preterm birth, low birth weight) with triple ARV. • Monitoring visits are required to assess both maternal and infant safety. • The maternal acceptability of prolonged use (antepartum and up to 12 months postpartum) of triple ARV regimens followed by discontinuation among women with high CD4 counts is unknown, and acceptability in programme settings is unknown. • Option B is likely to be more costly than option A.

Table 18. Clinical scenarios and recommendations for the use of antiretroviral prophylaxis

Clinical scenario		Woman / infant regimen	Preferred recommended drug regimen and dosing
Pregnant woman tested HIV-infected and not in need of treatment; **infant is breast-fed**	Option A	Woman	AZT sd-NVP * AZT + 3TC *
		Infant	NVP
	Option B	Woman	AZT + 3TC + LPV/r or AZT + 3TC + ABC or AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV
		Infant	AZT or NVP

to prevent MTCT for women not in need of lifelong treatment for their own health

Timing and duration of peripartum ART			Notes on recommendations
Antepartum	Intrapartum	Postpartum (and irrespective of mode of infant feeding)	
AZT from as early as 14 weeks of gestation	sd-NVP at start of labour; daily AZT + 3TC from start of labour*	AZT + 3TC until 7 days after delivery*	* If maternal AZT was provided for more than 4 weeks antenatally, consideration may be given to omitting the sd-NVP and AZT + 3TC and to continuing AZT alone during labour and delivery
		From birth until one week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding ceases before 6 weeks	
Initiate triple ARV prophylaxis from as early as 14 weeks of gestation	Continue triple ARV prophylaxis	Continue triple ARV prophylaxis until one week after all exposure to breast milk has ended	NVP-containing regimens are not recommended
		From birth until 4 to 6 weeks of age	

Clinical scenario		Woman / infant regimen	Preferred recommended drug regimen and dosing
Pregnant woman tested HIV-infected and not in need of treatment; **infant receives replacement feeding only**	Option A	Woman	AZT sd-NVP * AZT + 3TC *
		Infant	Sd-NVP plus NVP or AZT
	Option B	Woman	AZT + 3TC + LPV/r or AZT + 3TC + ABC or AZT + 3TC + EFV or TDF + 3TC (or FTC) + EFV
		Infant	AZT or NVP
Pregnant woman requiring prophylaxis with **clinically significant or documented severe anaemia (Hb <7g/dl)**		Woman	TDF + 3TC (or FTC) + EFV
		Infant	AZT or NVP
Pregnant woman requiring prophylaxis infected with **HIV-2 alone**	Option A	Woman	AZT
		Infant	AZT

Women diagnosed during labour or immediately postpartum

Women may first be diagnosed with HIV infection during labour or immediately postpartum, in which case antepartum ARVs cannot be given. However, the intrapartum-postpartum components of option A or B prophylaxis or the postpartum component of option A or B prophylaxis alone can reduce MTCT and should be provided to women who present to the health care system in labour or immediate postpartum.

Although a clinical assessment can be used to determine if a woman has WHO stage 3 or 4 disease and therefore should start on ART, a CD4 count will likely not be immediately available. Prophylaxis is required, however, to prevent MTCT. Prophylaxis should be initiated immediately and the regimen modified postpartum if the mother is found to require ART for her own health.

It is important to note that maternal triple-drug prophylaxis option B requires several weeks (or more) to significantly lower the maternal viral load, making the infant NVP component of prophylaxis critically important in terms of providing immediate protection to the infant. Thus, for women identified as HIV-infected in labour or immediately postpartum, daily infant NVP prophylaxis as in option A may be a better approach to postnatal prevention than maternal triple drug prophylaxis option B.

Should the mother be found to require ART for her own health, she should be initiated on triple drug ART. Because of the time lag to reduction in viral load, the infant should continue daily NVP until the mother has received at least 6 weeks of ART before infant prophylaxis is discontinued.

Women diagnosed with HIV infection in labour

Option A (Maternal AZT plus infant ARV prophylaxis)

Mother: sd-NVP as soon as possible during labour and AZT + 3TC twice daily for 1 week

Infant (if breastfeeding): daily NVP from birth until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding ceases before 6 weeks (always continue for 1 week after all exposure to breast milk has ended).

Infant (not breastfeeding): sd-NVP plus twice daily AZT or daily NVP from birth until 4 to 6 weeks of age.

A clinical assessment should be done postpartum and a CD4 count obtained. Women who are found to require ART for their own health should be started on an appropriate life-long ART regimen. Because of the time lag to reduction in maternal viral load, if breastfeeding, the infant should continue daily NVP until the mother has received at least 6 weeks of ART before discontinuing infant prophylaxis.

Option B (maternal triple ARV prophylaxis, relevant only if breastfeeding)

Mother: Triple ARV prophylaxis during labour until 1 week after all exposure to breast milk has ended.

Infant: daily NVP from birth until 6 weeks of age (since the infant is breastfeeding and immediate protection is desirable, NVP would be the preferred infant prophylaxis and given for a full 6 weeks).

A clinical assessment should be done postpartum and a CD4 count obtained. Women who are found to require ART for their own health should not discontinue their triple drug ARV regimen but continue on an appropriate life-long ART regimen.

Women diagnosed with HIV infection immediately postpartum

Option A (infant ARV prophylaxis)

Infant (if breastfeeding): daily NVP from birth until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding ceases before 6 weeks.

Infant (not breastfeeding): sd-NVP plus twice daily AZT or daily NVP from birth until 4 to 6 weeks of age.

A clinical assessment and CD4 count should be done postpartum. Women who are found to require ART for their own health should be started on an appropriate life-long ART regimen. Because of the time lag to reduction in maternal viral load, the infant should continue daily NVP until the mother has received at least 6 weeks of ART before discontinuing infant prophylaxis.

Option B (maternal triple ARV prophylaxis, relevant only if breastfeeding)

Mother: triple ARV prophylaxis until 1 week after all exposure to breast milk has ended, or for 4 to 6 weeks if breastfeeding ceases before 6 weeks (always continue for 1 week after all exposure to breast milk has ended).

Infant: daily NVP from birth until 6 weeks of age (since the infant is breastfeeding and immediate protection is desirable, NVP would be the preferred infant prophylaxis and given for a full 6 weeks).

A clinical assessment should be done postpartum and a CD4 count obtained. Women who are found to require ART for their own health should not discontinue their triple drug ARV regimen but continue on an appropriate life-long ART regimen.

Clinical and laboratory monitoring of pregnant women receiving ARV prophylaxis and their infants

Maternal monitoring of immunological status through the measurement of CD4 cell counts should be done every 6 months for women receiving prophylaxis (both options A and B) in order to determine possible need for treatment. If, during this ongoing monitoring, the mother meets eligibility criteria for treatment, she should be initiated on ART. Additional clinical and laboratory monitoring of adverse reactions related to the antiretroviral drugs should be based on the potential adverse reactions of the drugs used.

Effective prevention of infant HIV infections depends on ARV drug adherence of both mothers and infants. Regular assessment of drug adherence is recommended for women and infants receiving option A or option B.

This section briefly outlines scenarios that need special consideration and attention. It summarizes recommendations that are already addressed in other WHO guidelines and documents or have been stated in previous sections of the present guidelines.

ARV regimens for women previously exposed to antiretroviral drugs

For women previously exposed to an ARV prophylaxis regimen for PMTCT in an earlier pregnancy and who are not in need of treatment for their own health, the recommendations for ARV prophylaxis in a subsequent pregnancy are the same. These are detailed in Section III of this guideline. For women who initiate ART within 12 months after sd-NVP exposure, a non-NNRTI-based regimen is recommended (Table 9).

Women who acquire primary infection during pregnancy or breastfeeding

Women who become infected with HIV during pregnancy or while breastfeeding have a very high risk of transmitting the virus to their infants. In a meta-analysis the risk of transmission to infants was about 30% among women who acquired HIV infection during breastfeeding [73]. Retesting of women late in pregnancy is therefore important in order to identify those with recent HIV infection who can benefit from access to HIV prevention and care interventions. In high-prevalence and generalized epidemic settings, women who tested negative early in pregnancy should be systematically offered repeat HIV testing in the third trimester of pregnancy, as recommended in the WHO 2010 HIV counselling and testing guidelines [74]. There are currently no data that indicate which ARV prophylaxis regimen is most efficacious for a pregnant woman with primary HIV infection. Consequently, standard ARV prophylaxis regimens for PMTCT should be used, as described in Section IV.

Women with anaemia

Anaemia is common in pregnant women, particularly HIV-infected pregnant women in resource-limited settings. HIV infection, in combination with other contributory factors such as malaria, worm infections, nutritional deficiencies and pregnancy itself, can severely exacerbate anaemia in women. Severe anaemia (Hb <7g/dl) in turn increases the risk of an adverse maternal outcome of delivery. Prevention, screening and treatment of anaemia and its contributory factors are therefore important components of essential antenatal care for all pregnant women, including HIV-infected pregnant women, as outlined in the WHO 2009 *guide for essential practice during pregnancy and postpartum* [47]. The package of preventive measures includes iron and folate supplementation during pregnancy for all women in areas with high prevalence of iron deficiency, irrespective of haemoglobin levels. Iron supplementation is recommended during the first 3 months after delivery [75]. The prevention and treatment of malaria and worm infections is also essential in high-prevalence areas.

In addition to standard prevention activities, routine screening for anaemia among pregnant women during antenatal care is recommended [75]. Screening of anaemia preferably includes laboratory monitoring of haemoglobin levels but can be done by clinical assessment if this is not available. Any

sign of anaemia, and particularly any clinically significant anaemia, should be routinely treated as part of ANC.

Pregnant or breastfeeding women eligible for ART who have clinically significant or severe anaemia should be started on a non-AZT-containing regimen while anaemia is being corrected. In such cases, AZT can be replaced with TDF or d4T, as recommended in the 2010 WHO Antiretroviral therapy for HIV infection in adults and adolescents [13].

For women not eligible for ART who have clinically significant or severe anaemia (Hb <7g/dl), a non-AZT-containing regimen should also be considered, e.g. TDF + 3TC (or FTC) + EFV. Alternatively, AZT-based prophylaxis (either option A or B) could be initiated after the severe anaemia has been corrected.

A study in Botswana among breastfed infants born to women receiving triple ARV prophylaxis suggested that infant haematological (and hepatic) toxicities associated with antenatal and postnatal exposure to maternal ARV were minimal, with the exception of increased early neutropenia that did not persist beyond one month of age [70, 75]. This study did not find any excess infant anaemia related to either in utero or breastfeeding exposure to maternal ARVs [76]. Similarly, the use of daily infant NVP prophylaxis was not associated with infant haematological or hepatic toxicities compared to the control regimens in clinical trials.

Women with HIV-2 infection

HIV-2 is endemic in West Africa and foci of infection occur in countries such as India and Portugal. Because no new evidence on HIV-2 infection was available, the guidance on pregnant women living with HIV-2 has not changed from the 2006 PMTCT ARV guidelines. In settings where HIV-2 is prevalent, testing for both HIV-1 and HIV-2 is recommended before initiating a PMTCT ARV intervention. HIV-2 may also progress to AIDS, although progression is generally much slower [77]. HIV-2 has the same modes of transmission as HIV-1 but has been shown to be much less transmissible from mother to child (transmission risk 0–4%) [78, 79].

NNRTI drugs, such as NVP and EFV, are not effective against HIV-2 [76]. For women who are infected with HIV-2 alone and eligible for treatment (based on the same eligibility criteria as for HIV-1), a triple NRTI regimen is therefore recommended as the first-line ART regimen (e.g. AZT + 3TC + ABC) [13]. Women with HIV-1 and HIV-2 coinfection should receive one of the ART regimens recommended for women with HIV-1 infection alone.

Pregnant women living with HIV-2 alone who are not eligible for treatment for their own health should receive an ARV prophylaxis intervention consisting of AZT from 14 weeks of pregnancy (or as soon thereafter as possible) and continuing during labour and delivery. This maternal intervention should be coupled with twice-daily AZT given to infants from birth until 4 to 6 weeks of age. In view of the low risk of transmission, the lack of any clinical trial data or programme experience with maternal triple ARV prophylaxis or extended infant prophylaxis, and the lack of effectiveness of NNRTI drugs, the additional interventions recommended for women with HIV-1 infection are not recommended for women with HIV-2 infection alone.

Women with active tuberculosis

It is estimated that TB accounted for more than a quarter (26%) of deaths among people living with HIV in 2008 [80]. The risk of active TB is approximately 10 times higher in HIV-infected pregnant women than in HIV-uninfected women and has been reported to account for about 15% of maternal mortality in some settings [81]. TB in pregnant women is also associated with prematurity, low birth weight, and perinatal tuberculosis. All HIV-infected women should be assessed for TB at each visit, and those presenting with a cough, fever, night sweats and weight loss should be evaluated for TB and started on TB treatment when indicated [82].

In accordance with the recommendations for HIV/TB coinfection, detailed in *Antiretroviral therapy for HIV infection in adults and adolescents* [13], HIV-infected pregnant women with active TB should start ART, irrespective of the CD4 cell count. The TB treatment should be started first, and followed by ART as soon as clinically possible (within 8 weeks after the start of TB treatment). Drug interactions between rifampicin and some of the antiretroviral drugs (i.e. the boosted protease inhibitors) complicate simultaneous treatment of the two diseases. As for all adults, EFV is the preferred NNRTI for HIV/TB co-infected pregnant women (starting after the first trimester). For those HIV/TB coinfected women not able to tolerate EFV, an NVP-based regimen or a triple NRTI regimen (e.g. AZT + 3TC + ABC or AZT + 3TC + TDF) can be used. In the presence of rifampicin, no lead-in dose of NVP is required.

Women with hepatitis B or hepatitis C virus coinfection

ART should be started in all pregnant women coinfected with HIV and HBV when treatment is required for the HBV infection,[i] irrespective of the CD4 cell count or the WHO clinical stage [83]. Coinfected pregnant women requiring ART and HBV treatment should receive a regimen containing TDF and 3TC (or FTC). These recommendations are the same as those for all adults [13, 84].

An elevation in hepatic enzymes following the initiation of ART may occur in HIV/HBV-coinfected women because of an immune-mediated flare in HBV disease secondary to immune reconstitution with therapy, particularly in women with low CD4 cell counts [85]. HBV infection may also increase the risk of hepatotoxicity with certain antiretroviral drugs, specifically NVP and protease inhibitors. Pregnant women with HIV/HBV coinfection should be counselled about signs and symptoms of liver toxicity.

When coinfected pregnant women do not require HBV treatment, ART or ARV prophylaxis should follow the general recommendation for HIV-infected pregnant women. However, it is important to note that in HIV/HBV-coinfected pregnant women who do not require treatment of HBV and also do not require lifelong ART for their own health, hepatic flares may occur with the use of maternal triple ARV for prophylaxis of MTCT (option B) when the triple ARVs are stopped. Option A (maternal AZT

(i) Anti-HBV therapy should be considered for all women coinfected with HIV and hepatitis B virus with any evidence of liver disease (i.e. elevated transaminase levels, elevated HBV-DNA titres, necro-inflammatory lesions or fibrosis on liver biopsy).

and extended infant prophylaxis), which does not contain drugs with anti-HBV activity, may therefore be preferred if HBV treatment is not needed and lifelong ART is not planned.

HCV is also increasingly recognized as an important coinfection with HIV. However, no specific changes in treatment are recommended in the adult ART treatment guidelines [13]. Pregnant women coinfected with HIV and HCV should receive ART or ARV prophylaxis according to the general recommendations for HIV-infected pregnant women. Those women on ART require careful clinical and laboratory monitoring, irrespective of the ARV regimens.

Coinfection with HIV and HBV or HCV is common among IDUs. Hence, all women living with HIV who are recognized to be IDUs should routinely be offered testing for hepatitis B and hepatitis C infections and monitored according to WHO guidelines.

Pregnant women living with HIV who are injecting drug-users

Health-care providers should ask pregnant women about current and past alcohol and injecting or other drug use. A comprehensive package of nine interventions for the prevention, treatment and care of HIV among IDUs is needed, including targeting co-morbidities such as hepatitis and TB [84]. Substance-using women may perceive HIV testing and counselling during pregnancy as a threat because of potential stigmatization, discrimination, prosecution or loss of custody of their children. Access to care for women who use drugs is often hampered by factors such as stigmatizing attitudes among health-care providers and a lack of coordination between obstetric-care providers and health-care workers in drug dependence treatment and harm reduction programmes.

Pregnant women require counselling about the effects of alcohol and other drugs on the growth and development of the fetus and the benefit of harm reduction services. If women meet the criteria for opioid dependency they should be offered counselling and opioid substitution therapy. Methadone substitution treatment is currently recommended for opioid-dependent pregnant women as outlined in *Guidelines for the psychologically assisted pharmacological treatment of opioid dependence* [84]. Data are limited on the use of buprenorphine (a semisynthetic opiate used to treat opioid addiction) in pregnancy. Comprehensive care is required throughout the continuum of pregnancy and postpartum, addressing HIV, obstetrical and IDU-related needs through the co-management of services and referrals. Obstetric-care providers should assess all HIV-infected female substance users for trauma and physical and/or sexual abuse. Opioid substitution therapy should be combined with psychosocial counselling, including support groups, community reinforcement, contingency treatment and motivational therapy and similar modalities.

In general, the same recommendations for ART or ARV prophylaxis for pregnant women living with HIV apply to those who are also IDUs. For pregnant women already on or starting ART, drug interactions may be a concern. Interactions between methadone and ARV drugs are the same in pregnant women as in other patients. Drug interactions may result in decreased methadone levels or raised ARV levels, increasing the risk of methadone withdrawal or ARV-related side-effects. NNRTIs significantly decrease the methadone level and can precipitate withdrawal symptoms. In a case series of chronic methadone recipients being started on NVP, 50–100% increases in daily methadone doses were required to treat opiate withdrawal. If a pregnant woman receives an NNRTI-based

intervention the dose of methadone should be increased and the woman should be monitored closely. Withdrawal symptoms generally occur 3–8 days following the start of NNRTI-based interventions. Methadone raises the concentration of AZT by 29–43%, and this may increase the risk of adverse effects (e.g. bone marrow suppression and anaemia) and therefore requires close monitoring. LPV/r slightly reduces the levels of methadone; titrating to methadone response might be necessary and monitoring is required. Buprenorphine can be used when methadone is not available. There are limited data on the safety and efficacy of the use of buprenorphine in pregnant women and neonates. The use of methadone is sufficient to prevent withdrawal symptoms in opioid-dependent women presenting around labour.

The neonatal withdrawal syndrome comprises the signs and symptoms exhibited by newborn infants cut off abruptly after prolonged exposure to drugs during pregnancy. Initially, it referred only to withdrawal from opioids, but the definition now includes manifestations of withdrawal from cocaine, amphetamine and alcohol. The syndrome occurs in about 60% of neonates who have been exposed to these drugs, usually during the first 48–72 hours of life, although methadone withdrawal can occur up to 2 weeks after birth. Health-care providers should ensure that all newborn infants of women living with HIV who are IDUs are provided with appropriate neonatal withdrawal syndrome management care in accordance with national guidelines.

SECTION VI. SAFETY AND RISK OF RESISTANCE TO ANTIRETROVIRAL DRUGS IN PREGNANT WOMEN AND THEIR INFANTS

Women and their infants receiving ARV drugs receive important benefits from reduced risk of HIV disease progression and death as well as reduced risk of MTCT. These benefits need to be balanced against the risks of drug toxicity and potential development of drug resistance. Pregnancy, delivery and breastfeeding raise additional issues regarding toxicity and drug resistance for women and their infants, and these concerns should be considered in the context of ensuring optimal treatment to preserve the mother's health and reduce the risk of infection in infants.

All ARV drugs are associated with toxicity to some extent, which may be transient or longer-term. Host factors and physiological changes that occur during pregnancy may affect the absorption, distribution, metabolism and elimination of drugs, making it difficult to predict ARV pharmacokinetics and potential toxicity. The severity of ARV toxicity for the pregnant woman and the fetus/infant varies with the choice and number of drugs to which the woman and infant are exposed as well as with the timing and duration of exposure. ARV drugs taken by lactating mothers can be found in breast milk in amounts that vary with different ARVs, and the plasma concentrations of these drugs in breastfeeding infants vary accordingly [86-88]. A study in Kenya showed that 3TC and NVP, but not AZT, were transmitted through breast milk to infants in biologically significant concentrations when their mothers received these drugs [87]. In Mozambique, detectable concentrations of ARV drugs in breast milk were found 1 week after delivery in women treated with ART from 28 weeks of gestation, despite some of the women having undetectable plasma levels at the same time [86]. This suggests a possible lag in the elimination of ARV drugs in breast milk. Current knowledge suggests that the transfer of LPV/r and TDF into breast milk is very limited. In one small study that evaluated TDF levels in breast milk of mothers who received a single dose of TDF intrapartum, TDF was detectable in 4 of 25 (16%) breast milk samples collected during the first week postpartum at very low levels. Because of chemical changes, it is not known whether these substrates would be bioavailable to infants when ingested [89].

In 2007, Thorne and Newell published an extensive literature review of the evidence for short-term to medium-term potential adverse effects and toxicities of exposure to ARV drugs in utero and in the neonate (including haematological, mitochondrial, teratogenic and carcinogenic effects) [90]. They concluded that the immense benefits of antiretroviral prophylaxis in PMTCT far outweighed the potential for adverse effects. However, they also noted that these adverse effects required further and longer-term monitoring, because some adverse effects might occur later in childhood. These key safety concerns are summarized in Table 19.

It is important to educate and prepare mothers regarding HIV and antiretroviral treatment and prophylaxis before the initiation of any ARV intervention [91, 92]. Failure to do so could lead to suboptimal adherence, potentially increased rates of HIV transmission and the development of drug resistance.

Drug resistance continues to be an important concern during the prolonged use of different ART regimens (compounded by suboptimal adherence) and during ARV prophylaxis with non-suppressive regimens. There is also wide variability in the half-lives of different drugs and ongoing exposure after the discontinuation of prophylaxis.

Safety and risk of resistance to nucleoside reverse transcriptase inhibitors (NRTIs)

Pregnant women

There has been extensive experience in pregnancy with the use of AZT and 3TC and these have been shown to be well tolerated. The combination of AZT + 3TC is therefore the preferred NRTI backbone in pregnancy for women receiving ART or triple ARV prophylaxis (option B). The major toxicity of AZT is haematological, including the risk of anaemia and neutropenia. In pregnant women with clinically significant anaemia or documented severe anaemia (haemoglobin <7 g/dl), consideration should therefore be given to the use of alternative drugs instead of AZT (e.g. TDF or d4T) or to delaying initiation of the ART or ARV drug intervention until after correcting the anaemia.

Resistance to AZT requires multiple sequential drug mutations; the development of resistance is associated with an advanced disease stage and a low CD4 cell count [93]. Early studies of patients receiving AZT alone demonstrated that while resistance emerged in a significant proportion of patients with late-stage HIV disease and low CD4 cell counts after more than 6 months of treatment, it took 9–12 months or more for resistance to emerge in asymptomatic patients with high CD4 cell counts [94-96]. Since the use of AZT prophylaxis (as a single drug) is only recommended for women who do not require therapy for their own health (CD4 of >350 cells/mm^3), the available evidence suggests that the time-limited use of AZT monotherapy during pregnancy for prophylaxis (for approximately 6 months, or less) should not be associated with a significant risk of developing AZT resistance.

In contrast, resistance to 3TC is associated with a single mutation, and rapid development of genotypic resistance to 3TC has been observed when 3TC has been given alone or as part of a prolonged non-suppressive dual NRTI regimen (AZT + 3TC) in pregnant women for PMTCT. In a study in France, where 3TC was added to AZT after 32 weeks of gestation, 39% of 132 women had detectable high-level resistance to 3TC at 6 weeks postpartum, and 2 of 5 infants who were infected despite prophylaxis had 3TC resistance [97]. Maternal 3TC resistance was only detected in women who had received 3TC for 4 weeks or longer during pregnancy. 3TC resistance was also detected at 1 week postpartum in 12% of women receiving 4 weeks of AZT + 3TC for PMTCT in the PETRA study [98]. However, no AZT or 3TC resistance was observed with intrapartum and 1-week-postpartum maternal AZT + 3TC [98, 99].

Alternative NRTI drugs for first-line ART and ARV regimens include TDF and FTC. There is only limited experience with the use of TDF in pregnancy. Studies in infant monkeys exposed in utero to TDF have shown decreased fetal growth and a reduction in fetal bone density within 2 months of the mother starting therapy [100, 101]. Bone demineralization has been observed in some studies of infected children receiving chronic TDF-based therapy but not in others [102-104]. The clinical significance of these findings for children exposed to TDF in utero is unknown but is currently being evaluated. For women receiving TDF-based ART who become pregnant or who start TDF-based ART or ARV regimens during pregnancy, the benefits of treatment or prophylaxis are likely to exceed the theoretical risks of toxicity for the infant. Further safety data are awaited.

Pharmacokinetic studies among pregnant women indicate that no dosing adjustments are required in pregnancy for AZT, 3TC, FTC and TDF [105-107].

The use of abacavir (ABC) has been associated with the risk of serious and sometimes fatal hypersensitivity reactions. Hypersensitivity to ABC is a multi-organ clinical syndrome. ABC should be permanently discontinued (and not restarted) if a hypersensitivity reaction is suspected. Hypersensitivity with ABC has been reported in 5–8% of non-pregnant women [108]. It is not known whether similar rates can be expected among pregnant women. Women receiving ABC should be informed and educated about the symptoms of a potential hypersensitivity reaction.

Two NRTI drugs, d4T and ddI, have been associated with the development of lactic acidosis. For this reason they are no longer being recommended as preferred options for ART in the revised WHO adult ART guidelines [13].

Infants

There is a consistent body of evidence (of low to high quality) showing that a short period of AZT prophylaxis (up to 6 weeks) for neonates, with various combinations of maternal ARV prophylaxis, does not result in significantly increased rates of severe side-effects, with the exception of mild transient anaemia [45, 54, 109]; the anaemia that is observed rapidly reverses after the AZT is stopped. There is limited experience with the use of 3TC for infant prophylaxis [64]. However, the use of AZT + 3TC for infant prophylaxis appears to result in increased rates of haematological toxicity in infants (anaemia, neutropenia) compared to AZT alone [97].

Although rare, mitochondrial toxicity has been described with in utero exposure to NRTI drugs, particularly when used in combination regimens. In a cohort of 4392 HIV-exposed but uninfected children followed in the French paediatric cohort, the 18-month incidence of clinical symptoms of mitochondrial toxicity was 0.26%, with a mortality risk of 0.07% [110]. The children presented with neurological symptoms and/or episodes of significant hyperlactataemia, and had deficits of mitochondrial respiratory chain complex enzyme function on muscle biopsy.

Safety and risk of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Pregnant women

Nevirapine is associated with systemic symptoms, increases in hepatic transaminase enzymes and skin rash, mainly in the first 18 weeks after starting treatment. Systemic symptoms may be non-specific, including nausea, vomiting, malaise, fatigue, anorexia, jaundice, liver tenderness and hepatomegaly with or without increases in hepatic transaminases. Although uncommon, NVP-related rash and hepatotoxicity can be life-threatening, particularly among pregnant women with CD4 counts of >250 cells/mm^3. Data are conflicting (and limited) on whether there is an increased risk of hepatic toxicity in women with CD4 counts between 250 and 350 cells/mm^3 [111]. A summary analysis of various clinical trials reported a 9.8-fold increase in symptomatic rash-associated, NVP-related hepatotoxicity as well as severe skin rash among women with CD4 cell counts above 250 cells/mm^3 as compared to women with lower CD4 cell counts (most severe reactions occurred in women with higher CD4 counts. NVP should only be used, therefore, in women with high CD4 cell counts if the benefits clearly outweigh the risks.

For women who require ART for their own health, including pregnant women, it was felt that the benefits of using NVP outweighed the risks of not initiating ART. Close clinical monitoring (and laboratory monitoring, if feasible) during the first 12 weeks of therapy is recommended, particularly when NVP is initiated in women with CD4 counts of 250 to 350 cells/mm^3. To decrease toxicity, reduced lead-in dosing is recommended for the first 2 weeks when starting NVP. Because of concerns of toxicity, NVP is not recommended for women with CD4 counts of >350 cells/mm^3, either as part of an ART regimen or as part of a regimen for option B maternal ARV prophylaxis.

EFV is primarily associated with toxicities related to the central nervous system (CNS), rash and possible teratogenicity (if taken during the first trimester of pregnancy). The rash is generally mild and self-resolving and usually does not require discontinuation of therapy. The CNS symptoms are common. While they typically resolve after 2 to 4 weeks, they can persist for months and require discontinuation of the drug. EFV should be avoided in patients with a history of psychiatric illness, when there is a potential for pregnancy (unless effective contraception can be assured) and during the first trimester of pregnancy.

A single mutation can confer resistance to NNRTI drugs such as NVP and EFV. These drugs have a long half-life; detectable drug levels persist for up to 2 weeks for NVP following a single dose and for 3 weeks or more for EFV following discontinuation of the drug. The persistence of subtherapeutic drug levels in the face of active viral replication is associated with the rapid development of NNRTI resistance among a significant proportion of women receiving sd-NVP. In most women, resistant virus can no longer be detected 6 to 12 months after exposure. However, low levels of viral resistance can persist for longer periods and in some cases remain present in latently infected cells [23-25]. A dual NRTI regimen (e.g. AZT + 3TC) for at least 7 days is recommended to provide a suppressive tail of ARV coverage following sd-NVP at labour and when NNRTI-based triple-ARV prophylaxis is stopped. Much lower NNRTI resistance rates of 0% to 7% at 2 to 6 weeks postpartum have been reported with the use of various tail regimens [34-39, 57]. Similarly, if EFV is used as a component of a triple ARV regimen for prophylaxis of MTCT in women who do not require treatment for their own health (option B), it is recommended to continue the dual NRTI backbone for 1 to 2 weeks following discontinuation of EFV to avoid the development of NNRTI resistance when discontinuing prophylaxis after HIV transmission risk has ceased.

Animal and some human data have raised concerns regarding the potential for neural tube defects with exposure to EFV early in the first trimester. In the US Antiretroviral Pregnancy Registry, overall birth defects with first-trimester EFV exposure occurred in 14 of 477 (2.9%) prospective pregnancies, similar to the prevalence rate in the overall US population (2.7%), and appeared consistent with the rates for women with NVP, LPV/r or TDF exposure. However, neural tube birth defects are rare, with an incidence of approximately 0.1% in the general population. Prospective data currently are insufficient to provide an assessment of neural tube defect risk with first-trimester exposure, except to rule out a potential tenfold or higher increase in risk (i.e. an increase in risk from 0.1% to >1%). Given that the neural tube closes by day 28 of gestation, most women who become pregnant while on EFV will have passed the risk period for neural tube teratogenicity prior to diagnosing pregnancy. It is recommended that EFV should not be initiated during the first trimester of pregnancy. If a woman already on EFV is diagnosed as pregnant before 28 days of gestation, EFV should be stopped and substituted with NVP or a PI. If a

woman is diagnosed as pregnant after 28 days of gestation, EFV should be continued. There is no indication for abortion in women exposed to EFV in the first trimester of pregnancy.

Infants

Available data from birth until 6 months of age suggest that daily provision of NVP to infants receiving breast milk is safe [59, 60, 62]. However, the safety of daily infant NVP beyond 6 months of age is not known. There is a strong consensus based on data from birth to 6 months that toxicity and adverse events are expected to be minimal beyond 6 months. Caution is indicated for infants receiving daily NVP (one of the recommended options for up to 4–6 weeks of age) when the mother is receiving an NVP-based ART regimen while breastfeeding. Mothers receiving NVP-based ART have NVP concentrations in breast milk of 60–75% of maternal plasma levels [86, 88, 89, 112, 113]. Breastfeeding infants of mothers on NVP-based ART have biologically significant serum concentrations of 900–1200 ng/ml with just breastfeeding ingestion, about 10% of maternal levels [87, 88, 114]. These levels are comparable to those expected with the use of daily NVP infant prophylaxis. Combined intake of NVP as part of infant ARV prophylaxis for 4-6 weeks and through ingestion of NVP-containing breast milk may result in increased NVP levels, although these levels should be lower than the trough level achieved with therapeutic dosing of NVP for treatment of an infected infant (about 3000 ng/ml) and is associated with relatively few adverse effects [115].

Because of the low genetic barrier of NVP, development of NNRTI drug resistance frequently occurs in infants that become infected despite NVP-based interventions. In the SWEN study, extended infant postexposure prophylaxis with daily NVP from birth to six weeks was assessed in breastfed children, and compared to sd-NVP [60]. Nearly all (92%) infants who became infected in the extended-NVP arm developed NNRTI resistance mutations [114]. However, the absolute number of HIV-infected infants was low because of the extended infant NVP prophylaxis. For infants who do become infected despite sd-NVP or extended infant NVP prophylaxis, the WHO 2010 paediatric ART guidelines recommend a PI-based, non-NVP-containing regimen, because of presumed resistance [116].

Resistance has also been observed in infants who become infected despite maternal ART or triple ARV prophylaxis. In the KIBS study of maternal triple ARV prophylaxis in Kenya, 67% of infants who became infected despite prophylaxis had drug resistance, some to both NNRTI and NRTI drugs [117]. In another study of 7 breastfeeding infants whose mothers started NVP-based ART postpartum and who became infected, all the infants had NNRTI resistance, 6 also had the M184V NRTI resistance mutation (primarily associated with 3TC), and thymidine analogue mutations (associated with AZT and d4T) were detected in 3 of 7 infants [118]. In a third study of 4 breastfeeding infants whose mother received NVP-based ART postpartum and who became infected, all the infants had NNRTI resistance and 3 had NRTI resistance mutations (M184V, K65R) [119].

Safety of protease inhibitors (PIs)

Pregnant women

The most frequent side-effects of LPV/r consist of weakness, headache and moderate digestive disorders (diarrhoea, nausea, abdominal pain, vomiting) [120]. LPV/r can also induce metabolic

complications such as insulin resistance, fat maldistribution and dyslipidaemia. Although a causal relationship to LPV/r has not been established, some cases of serious hepatotoxicity and pancreatitis have been observed in patients taking LPV/r in combination with other ARVs. Reduced plasma LPV/r concentrations were reported during the third trimester of pregnancy in studies using soft-gel capsules, but did not appear to be associated with impaired clinical efficacy [121, 122]. Associations between PIs and increased risks of low birth weight and preterm birth have been reported; in the Mma Bana trial, preterm delivery was observed in 23% of mothers who received LPV/r triple ARV prophylaxis compared to 15% of those receiving a triple NRTI prophylaxis regimen [70]. LPV/r has limited placental transfer (neonate/maternal ratio ~20%) and may therefore be less likely to be associated with fetal toxicity [123].

Infants

It is not known whether LPV/r is excreted in breast milk. No safety issue was reported in a recent trial evaluating early antiretroviral therapy with LPV/r in infants 6–12 weeks of age [124]. The potential toxicity in infants exposed to LPV/r in breast milk, if there is passage, is therefore expected to be small.

Table 19. Maternal and infant safety concerns of recommended and alternative antiretroviral drugs for pregnant women and their infants

Antiretroviral agent	Maternal antiretroviral intervention during pregnancy, labour, delivery and thereafter			Infant prophylaxis Infant concerns
	Maternal concerns	Placental passage	Infant concerns	
Nucleoside reverse transcriptase inhibitors				
Abacavir (ABC)	Risk of hypersensitivity reactions (5–8% of non-pregnant women; rate in pregnancy unknown)	Yes	Limited data available; animal studies suggest potential skeletal malformations with in utero exposure to drug levels 35 times that of human exposure	Not recommended
Emtricitabine (FTC)	No specific concerns	Yes	No specific concerns	Not recommended
Lamivudine (3TC)	Favourable safety profile; concern of hepatitis B flare if mother is HBV-coinfected and drug is stopped	Yes	Favourable safety profile	Limited safety data available

Antiretroviral agent	Maternal antiretroviral intervention during pregnancy, labour, delivery and thereafter			Infant prophylaxis Infant concerns
	Maternal concerns	Placental passage	Infant concerns	
Tenofovir (TDF)	Risk of renal toxicity warrants monitoring; concern of hepatitis B flare if mother HBV-coinfected and agent stopped postpartum	Yes	Concern of fetal bone defects; potential concern of low birth weight	Not recommended
Zidovudine (AZT)	Well tolerated; risk of anaemia	Yes	Favourable safety profile	Favourable safety profile, may be associated with anaemia that is reversible once stopped
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz (EFV)	Associated with rash, neuropsychiatric disturbances	Yes	Potential risk (probably <1%) of teratogenicity in first trimester of pregnancy; use of EFV after the first trimester can be considered	Not recommended
Nevirapine (NVP)	Potential risk of hypersensitivity reactions including rash and hepatic toxicity; incidence in women with CD4 between 250 and 350 cells/mm^3 unknown but strong consensus that benefit exceeds risk in women requiring ART; not recommended in women with CD4 >350 cells/mm^3 because of higher toxicity risk	Yes	Favourable safety profile	Favourable safety profile, including during extended dosing (documented until 6 months) in infants receiving breast milk
Protease inhibitors				
Lopinavir/ ritonavir (LPV/r)	Well tolerated; concern of hyperlipidaemia, insulin resistance, hyperglycaemia, and, rarely, diabetes mellitus	Yes (but low, ~20%)	Concern of preterm delivery	Not recommended

These 2010 revised guidelines define a new standard of care and provide a clear basis for countries to update their national PMTCT guidelines. Additional adaptation and implementation tools will be available as practical guides for national-level programme planners and managers responsible for designing and implementing services for PMTCT and ART. The revised guidelines provide a number of different options; the choice of specific options should take into account the capacity, needs and constraints of national and local health systems. These guidelines are cognizant of the realities of maternal and child health delivery systems in a variety of different settings where such interventions are implemented, and recognize that interventions must be kept simple. During the guidelines review, an assessment of health-systems considerations for PMTCT programmes concluded that PMTCT was a complex intervention, requiring multiple discrete processes separated in time and location, often with several decision branch points, and different treatment and prophylaxis options for women and infants [125]. Health systems will need to be adapted and strengthened to ensure that the additional PMTCT interventions included in the guidelines and adopted by country programmes are effectively implemented.

The new guidelines depend on more active and earlier identification of pregnant women who are HIV-infected, improved screening and rapid initiation or referral of women eligible for ART, effective linkages between PMTCT and ART services, longer duration of ARV prophylaxis during pregnancy, and, for women not on ART, ongoing prophylaxis of mothers or infants if the infants are exposed to HIV through breastfeeding. These key activities could burden health systems (including health facilities and health-care workers) or could fail to be implemented unless simple new health system protocols and practices are tested locally and put in place. Simple, reliable systems at the health facility level are needed to ensure that all mothers are tested for HIV, that all HIV-infected mothers are triaged to ARV prophylaxis or treatment according to CD4 count or WHO clinical staging, and that the risk of postnatal transmission is reduced with newly available strategies.

The quality of implementation of the PMTCT programme, including these new guidelines, will also depend on the effectiveness of the data systems that track the multiple steps of the PMTCT pathway, the ability of these data systems to inform health workers and their managers of the effectiveness of the programme, and the willingness of health-care workers to use this information to improve the standard of care. The safety of ARV prophylaxis and ART programmes should be assured through effective monitoring, including pregnancy registries and pharmacovigilance focusing on mothers and infants.

Despite the multiple constraints in low- and middle-income countries where national PMTCT programmes are most needed, the modifications to treatment and prophylaxis recommended in the revised guidelines should not place a significant additional burden on existing health systems. The key elements of the programme have already been established in previous guidelines; the new guidelines recommend more efficacious interventions at many steps in the PMTCT pathway. However, careful planning and local adaptation will be required to enable the implementation and scale-up of these more effective interventions. Adaptation, simplification (such as the use of fixed-dose formulations), standardized and clear protocols at the facility level, and standardization of the recommendations in line with national contexts are strongly advisable and will further increase the feasibility and acceptability (and ultimately the effectiveness) of the interventions. In some settings,

major challenges exist to effective implementation of MCH and PMTCT programmes; in these instances, health-systems support for countries seeking to implement or improve PMTCT programmes should be encouraged.

It should be noted that the recommendations were not based on cost. Although current cost of drugs was considered, no formal cost-effectiveness analysis was performed. The total costs of programmes will inevitably increase since the recommended strategies imply procurement of more ARV drugs for HIV-infected pregnant and postpartum women and their exposed infants and a clear target of initiating significantly more pregnant women on ART. The costs of ARV regimens have been decreasing, and the benefits of ART for the health of the pregnant woman eligible for lifelong treatment clearly outweigh the costs. Similarly, preventing HIV infection in infants with the use of effective ARV prophylaxis interventions outweighs the cost of such interventions. A cost saving can theoretically be expected as more adult and infant lives will be saved, thereby reducing the cost for HIV care and support services and increasing productive and healthy life-years.

ANNEX 1. PACKAGE OF ESSENTIAL SERVICES FOR PREGNANT AND POSTPARTUM WOMEN AND THEIR CHILDREN

Source: Guidance on global scale-up of the prevention of mother-to-child transmission of HIV: towards universal access for women, infants and young children and eliminating HIV and AIDS among children. Interagency Task Team on Prevention of HIV Infection in Pregnant Women, Mothers and their Children. World Health Organization, 2007 (http://www.who.int/hiv/pub/mtct/pmtct_scaleup2007/en/index.html).

Package of essential services for quality maternal care
Package of routine quality antenatal and postpartum care for all women, regardless of HIV status
1. Health education, information on HIV and STI prevention and care including safer sex practices, pregnancy including ANC, birth planning and delivery assistance, malaria prevention, optimal infant feeding; family planning counselling and related services
2. Provider-initiated HIV testing and counselling, including HIV testing and counselling for women of unknown status at labour and delivery, or postpartum
3. Couple and partner HIV testing and counselling, including support for disclosure
4. Promotion and provision of condoms
5. HIV-related gender-based violence screening
6. Obstetric care, including history-taking and physical examination
7. Maternal nutritional support
8. Infant feeding counselling
9. Psychosocial support
10. Birth planning, birth preparedness (including pregnancy/postpartum danger signs), including skilled birth attendants
11. Tetanus vaccination
12. Iron and folate supplementation
13. Syphilis screening and management of STIs
14. Harm reduction interventions for injecting drug users
Additional package of services for HIV-positive women
1. Additional counselling and support to encourage partner testing, adoption of risk reduction and disclosure
2. Clinical evaluation, including clinical staging of HIV disease
3. Immunological assessment (CD4 cell count) where available
4. ART when indicated
5. Infant feeding counselling and support based on knowledge of HIV status
6. ARV prophylaxis for PMTCT provided during the antepartum, intrapartum and postpartum periods
7. Co-trimoxazole prophylaxis where indicated
8. Additional counselling and provision of services as appropriate to prevent unintended pregnancies
9. Supportive care, including adherence support
10. Additional counselling and provision of services as appropriate to prevent unintended pregnancies
11. TB screening and treatment when indicated; preventive therapy (INH prophylaxis) when appropriate
12. Advice and support on other prevention interventions, such as safe drinking water
13. Supportive care, including adherence support, and palliative care and symptom management

Package of essential services for quality maternal care

Additional package of services for all women regardless of HIV status in specific settings

1. Malaria prevention and treatment
2. Counselling, psychosocial support and referral for women who are at risk of or have experienced violence
3. Counselling and referral for women with history of harmful alcohol or drug use
4. De-worming
5. Consider retesting late in pregnancy where feasible in generalized epidemics

Essential postnatal care for HIV-exposed infants and young children

1. Completion of ARV prophylaxis regimen
2. Routine newborn and infant care, including routine immunization and growth monitoring
3. Co-trimoxazole prophylaxis
4. Early HIV diagnostic testing and diagnosis of HIV-related conditions
5. Continued infant feeding counselling and support, especially after early HIV testing
6. Nutritional support throughout the first year of life, including support for optimal infant feeding practices and provision of nutritional supplements and replacement foods if indicated
7. ART for HIV-infected children, when indicated
8. Treatment monitoring for all children receiving ART
9. INH prophylaxis when indicated
10. Adherence support counselling for caregivers
11. Malaria prevention and treatment where indicated
12. Diagnosis and management of common childhood infections and conditions and integrated management of childhood illness (IMCI)
13. Diagnosis and management of TB and other opportunistic infections

ANNEX 2. EXAMPLES OF GRADE EVIDENCE PROFILES FOR THE KEY PICO QUESTIONS

Note: The full compilation of GRADE tables, systematic reviews, and associated summaries of evidence are available on the WHO web site (http://www.who.int/hiv/topics/mtct/en/index.html).

Should maternal AZT to prevent MTCT be started before or after 28 weeks of pregnancy?

Quality assessment						
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Infections at 4-8 Weeks - Antepatum AZT ≥28 Weeks						
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none
Infections at 4-8 Weeks - Antepatum AZT <28 Weeks						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Infections at 4-8 Weeks Indirect comparisons (Test for Interaction Between Antepartum AZT≥28 Weeks vs						
5	randomised trials	no serious limitations	no serious inconsistency	serious	serious[1]	none
Maternal Severe Adverse Events - Antepartum AZT ≥28 Weeks						
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Maternal Severe Adverse Events - Antepatum AZT <28 Weeks						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Maternal Severe Adverse Events Indirect comparisons (Test for Interaction Between Antepartum						
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Infant Severe Adverse Events - Antepartum AZT ≥28 Weeks						
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Infant Severe Adverse Events - Antepatum AZT <28 Weeks						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Infant Severe Adverse Events Indirect comparisons (Test for Interaction Between Antepartum AZT≥28 Weeks						
3	randomised trials	no serious limitations	serious[9]	serious	serious	none

1 Few number of total events and/or estimate includes the null.

2 Proportions were calculated using either ITT analysis or available case analysis.

3 2 of 3 studies included either breastfeeding or mixed feeding populations.

4 Numbers of participants with event and total participants were not used to calculate the ratio o relative effects.

5 The relative effect reported is actually an indirect measure of interaction between subgroups (RRR=ratio of relative risks).

Summary of findings					Importance
No of Patients		Effect		Quality	
Treatment	Comparison	Relative (95% CI)	Absolute		
74/623 (11.9%)[2]	119/626 (19%)[2]	RR 0.57 (0.42 to 0.79)[6]	82 fewer per 1000 (from 40 fewer to 110 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
7/180 (3.9%)[2]	24/183 (13.1%)[2]	RR 0.27 (0.11 to 0.64)	96 fewer per 1000 (from 47 fewer to 117 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Antepartum AZT <28 Weeks)					
–	–	RR 2.11 (0.83 to 5.38)[5,7]	–	⊕⊕◯◯ LOW	–
8/335 (2.4%)[2]	10/341 (2.9%)[2]	RR 0.81 (0.33 to 2)[8]	6 fewer per 1000 (from 20 fewer to 29 more)	⊕⊕⊕◯ MODERATE	CRITICAL
18/239 (7.5%)[2]	17/238 (7.1%)[2]	RR 1.05 (0.56 to 2)	4 fewer per 1000 (from 31 fewer to 71 more)	⊕⊕⊕◯ MODERATE	CRITICAL
AZT≥28 Weeks vs Antepartum AZT <28 Weeks)					
–	–	RR 0.77 (0.26 to 2.32)[3,5]	11 fewer per 1000 (from 35 fewer to 62 more)	⊕⊕◯◯ LOW	–
9/336 (2.7%)[2]	21/337 (6.2%)[2]	RR 0.44 (0.21 to 0.94)[7]	35 fewer per 1000 (from 4 fewer to 49 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
44/150 (29.3%)[2]	24/149 (16.1%)[2]	RR 1.82 (1.17 to 2.84)	132 fewer per 1000 (from 27 more to 296 more)	⊕⊕⊕◯ MODERATE	CRITICAL
vs Antepartum AZT <28 Weeks)					
–	–	RR 0.24 (0.1 to 0.58)[3,5]	–	⊕⊕◯◯ LOW	–

6 2 of 4 studies inclued either breastfeeding or mixed feeding populations.

7 2 of 4 studies inclued either breastfeeding or mixed feeding populations.

8 Studies included either breastfeeding or mixed feeding populations.

9 PACTG 076 reported a significant increase in infant SAE while the remaining two studies reported non-significant decrease in infant SAEs.

Are antenatal triple-drug regimens superior to AZT alone?

Quality assessment						
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Infections at birth						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none
Infections at 4-8 Weeks						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Infections at 18 months						
0	no evidence available					none
Maternal Response to Subsequent ART (Better indicated by lower values)						
0	no evidence available					none
Maternal Resistance						
0	no evidence available					none
Infant Resistance						
0	no evidence available					none

1 Few number of total events and/or estimate includes the null.

2 Proportions were calculated using either ITT analysis or available case analysis.

3 Studies included either breastfeeding or mixed feeding populations.

Ref: De Vienzi I; Kesho Bora Study Group. Triple-antiretroviral (ARV) prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-tochild transpission of HIV-1 (MTCT): the Kesho Bora randomized controled clinical trial in five sites in Burkina Faso, Kenya [Abstract LBPEC01]. 5th IAS Conference on HIV Pathogenesis and Treatment, Cape Town, South Africa, 19-22 July 2009.

Can sd-NVP be omitted from intrapartum prophylaxis?

Quality assessment						
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Infections at 4-8 weeks - primary analysis (NVP vs nothing)						
2[10]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none
Infections at 4-8 weeks - sensitivity analysis (NVP vs ZDV)						
6[11]	randomised trials	no serious limitations	no serious inconsistency	serious[4]	serious[1]	none
Maternal resistance - primary analysis (NVP vs nothing)						
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none
Maternal resistance - sensitivity analysis (NVP vs ZDV)						
0	no evidence available					none

1 Few number of total events and/or estimate includes the null.

2 Proportions were calculated using either ITT analysis or available case analysis.

3 2 of 3 studies included either breastfeeding or mixed feeding populations.

4 The sensitivity analysis includes studies that have somewhat dissimilar treatments.

5 3 of 4 studies included either breastfeeding or mixed feeding populations.

6 Studies included either breastfeeding or mixed feeding populations.

7 No resistance testing in comparison group performed.

10 Studies include: Mashi and PACTG 316.

11 Studies include: Chung 2005, HIVNET 012, Kiarie 2003, Mashi, PACTG 316 and SAINT.

Direct comparisons:

Dorenbaum A, et al. *JAMA* 2002;288:189-98;
Shapiro RL, et al. *AIDS* 2006;20:1281-8.
Lallement M, et al. *N Engl J Med* 2004;351:217-28

Indirect comparisons:

Guay L, et al. *Lancet* 1999;354:795-802.
Kiarie JN, et al. *AIDS* 2003;17:65-71.
Chung MH, et al. *AIDS* 2005;19:1415-22.
Moodley D, et al. *J Infect Dis* 2003;187:725-35.

Risk-benefit table 1.
When to start ART in HIV-1-infected pregnant women

Recommendations

1. Treat all HIV-infected pregnant women with CD4 count ≤350 cells/mm^3, irrespective of WHO clinical stage (Strong recommendation, moderate quality of evidence)
2. Treat all HIV-infected pregnant women with WHO clinical stage 3 and 4, irrespective of CD4 count (Strong recommendation, moderate quality of evidence)

Domains and considerations

Quality of evidence

High/moderate quality of evidence supports strong recommendations for these clinical and immunological criteria for ART initiation considering reduction in absolute risk of death, disease progression, including tuberculosis, occurrence of severe adverse events and transmission of HIV (sexual and mother-to-child).

One randomized clinical trial (RCT) specifically aimed to answer the PICO question: *When is the optimal time to initiate ART in asymptomatic, treatment-naïve, HIV-infected adults?* (CIPRAHT001 2009). This single-centre trial in Haiti demonstrated a 4-fold increased risk of death and 2-fold increased risk of TB disease in patients who deferred treatment initiation until CD4 count fell below 200 cells/mm^3 compared to those who started treatment at CD4 200-350 cells/mm^3. One sub-group post hoc analysis nested in a RCT (SMART trial; a multicentre study in 33 predominantly high income countries) reported reduction of disease progression and serious non-AIDS events when ART was initiated at a CD4 cell count <350 cells/mm^3 compared with <250 cells/ mm^3.

In the GRADE profile, pooled data from the RCT (816 participants) and the sub-group post hoc analysis (248 participants) provide moderate evidence that starting ART at CD4 levels higher than 200 or 250 cells/mm^3 reduces mortality rates in asymptomatic, ART-naive, HIV-infected people. Evidence regarding a reduction in morbidity is less strong, due to the relatively small number of events. Imprecision (only one RCT) and indirectness (post hoc subset analysis) are reported in the GRADE profile.

The RCT results are consistent with previous observational cohort studies both from high-income and low-income countries, which showed that early initiation of ART reduces mortality and morbidity (Sterne 2009; Moh 2007; Badri 2004; Wong 2007). No GRADE tables were produced for these four studies identified in the systematic review as it was felt unlikely they would increase the overall quality of evidence. Additional observational and modelling data suggest a strong reduction in TB morbidity with initiation of treatment.

There is no **specific** evidence supporting initiation of ART among **pregnant women** (as a subset population of all adults) at CD4 cell count <350 cells/mm^3, irrespective of WHO clinical staging or with WHO clinical stage 3 or 4, irrespective of CD4 cell count, for improved mortality. However, moderate quality evidence supports the initiation of ART among pregnant women with CD4 cell count <350 cells/mm^3, irrespective of WHO clinical staging to reduce mother-to-child HIV transmission (Kesho Bora). In addition, there is low quality evidence supporting initiation of ART among pregnant women with CD4 cell count < 350, irrespective of WHO clinical staging to reduce infant mortality (Kesho Bora). Observational and modelling data strongly suggest that pregnant women with CD4 <350 cells/mm^3 are at highest risk of transmitting HIV to their newborn, that this group accounts for up to 85% of MTCT risk, and that the benefit of initiating ART in this group would be strong in terms of decreasing transmission risk both during pregnancy and postpartum during breastfeeding.

It was felt that there was no evidence to consider pregnant women differently from non-pregnant adults in terms of criteria on when to start ART, and that the criteria for pregnant women should be consistent with the criteria for all adults. There was no evidence to show a benefit for starting ART in pregnant women with clinical stage 1 and 2 in the absence of CD4 counts.

No uncertainty about the quality of evidence

Risks/benefits

Benefits

The primary benefit of the recommendation is the improvement in health of HIV-infected mothers and the contribution to further reduction in adult HIV-related mortality and morbidity, particularly with reference to TB. Additional important benefits for pregnant women include the reduction in MTCT and the decrease in infant mortality at 12 months of age.

Risks

A risk of the recommendation includes ART drug toxicity potentially affecting the woman as well as the fetus/infant. (Note- as detailed in the adult ART guidelines, it is recommended that EFV-based regimens should not to be initiated during the first trimester of pregnancy). A risk of inequity in ART access and potential displacement of sicker patients should be prevented. Women who are not able to adhere to the drug regimen could develop ART drug resistance.

Uncertainty about the balance of benefits versus harms and burdens: No

Values and acceptability

In favour

The recommendation places a high value on the health of the woman and promotes wide implementation and access to CD4 testing in antenatal care, in order to promote optimal eligibility screening. All pregnant women with indications for ART for their own health should receive ART, irrespective of gestational age. Also, a high value was placed on keeping the recommendation for pregnant women in line with the recommendations for non-pregnant women, as outlined in the adult ART guidelines.

Against

The recommendation places relatively low value on the potential ART drug toxicity risks for the mother and unborn infant (although drug choices need to consider toxicity profiles for these populations) and higher value on the benefits of preventing MTCT.

Uncertainty or differences in values: No

Cost

Total costs for programmes will increase as more pregnant women (and adults in general) become eligible for life-long ART. A cost saving can theoretically be expected as more adult and infant lives will be saved, thereby reducing the cost for HIV care and support services. However, the anticipated cost implications remain a concern.

Uncertainty about whether the net benefits are worth the costs: No

Feasibility

Availability of CD4 cell count analysis is one of the cornerstones of initiating ART in HIV-infected pregnant women, as it is with all adults. The CD4 cell count is much more sensitive than clinical staging for determining ART eligibility. The implementation of the recommendation will require increased capacity, including human resources and laboratory infrastructure, at all levels of the health system in order to provide CD4 testing and ART to an increasing number of people. Particular challenges exist in testing for eligibility and initiating ART in HIV-infected pregnant women at primary care level and in remote areas.

Eligible HIV-infected pregnant women require prioritization for ART initiation in order to prevent delays and reduce the risk of MTCT. The ability to address this prioritization at the district and health facility levels, and the degree of coordination with ART programmes, will impact on feasibility.

A stronger link between MTCT programmes and ART programmes will improve feasibility. The development of an implementation tool and clear protocols and procedures at the facility level would further facilitate implementation

Uncertainty: No

Gaps and research needs

Programmes should monitor and evaluate indicators for the number of pregnant women initiating ART, as well as their adherence and response to treatment, in terms of their own health and the health of their children. The impact on health services should also be monitored.

Final comments

This is a strong recommendation. The benefits to maternal health of initiating ART according to the proposed eligibility criteria outweigh the potential risks and increased costs. The recommendation places a high value on the health of the women. It was concluded that the proposed eligibility criteria were acceptable and feasible for implementation. This is supported by the experience of several countries where these recommendations are already being implemented with success. An implementation tool and standardized protocols adapted to local settings would further facilitate successful implementation.

Risk-benefit table 2.
What ART to give to HIV-infected pregnant women in need of treatment for their own health and what to give their infants

Recommendations
1. HIV-infected pregnant women A. One of the following regimens should be used for ART-naive pregnant women initiating ART. • AZT + 3TC + NVP (preferred) • AZT + 3TC + EFV (preferred) • TDF + 3TC (or FTC) + EFV • TDF + 3TC (or FTC) + NVP (Strong recommendation, moderate quality of evidence) B. An EFV -based ART regimen should not be initiated during the 1st trimester of pregnancy. (Strong recommendation, low quality of evidence) 2. Infants born to HIV-infected mothers on ART One of the following regimens should be given to all infants born to mothers on ART, regardless of feeding method. • NVP once daily from birth until 4 to 6 weeks of age • AZT twice daily from birth until 4 to 6 weeks of age (Strong recommendation, low quality of evidence)
Domains and considerations
Quality of evidence
Maternal ART AZT + 3TC + NVP is the most common drug regimen used in pregnant women, and is recommended as the preferred first-line regimen for them. There is no GRADE profile as no RCTs were identified for the use of AZT + 3TC + NVP specifically in pregnant women. Cohort studies report a reduction in MTCT or death. When compared with short-course regimens, AZT + 3TC + NVP starting at 34 weeks was shown to reduce HIV-transmission or death at 7 months (Hwan-Bae 2008). There is no evidence for this regimen that evaluates maternal severe adverse events or the maternal response to ART. All four adult first-line regimens are recommended as options for ART for pregnant women. The systematic review showed no evidence from RCTs, non-randomized trials or observational studies from low and middle-income countries that clearly indicated the superiority of one regimen over another, among the four first-line regimens, or specific comparisons with d4T- and ABC-based ART regimens for treatment-naive patients. On the question of **whether TDF is superior to AZT** in a dual NRTI backbone, the quality of evidence for all but mortality outcomes is moderate to high. The evidence review found no evidence of superiority from three RCTs (Gallant 2004, Rey 2009, Arribas 2008) and one observational study with regard to mortality, serious adverse events or virological response. Taken together, this literature is of moderate quality, with two large studies with 144-week follow up adding to its precision and at least some patients enrolled from Latin American countries. The PEARLS study (AACTG 5175), an RCT of once-daily PI/NNRTI-containing therapy in Africa, Asia, Haiti, South America, and the USA (estimated completion 2010) will add to this literature by providing a direct comparison of AZT and TDF in dual NRTI backbones with EFV.

On the question of **whether EFV is superior to NVP** in combination with two NRTIs, the quality of evidence is moderate; the evidence review found no evidence of superiority from six RCTs and 24 observational studies. The observational studies reviewed from low and middle-income countries were unable to confirm the superiority of EFV, which has been reported from some studies in high-income countries.

Animal and some human data have raised concerns regarding the potential for neural tube defects with exposure to EFV early in the first trimester (the neural tube closes within the first 28 days of gestation). Based on the incidence of neural tube defects and the number of prospective first-trimester exposures in the antiretroviral pregnancy registry, there is sufficient data to rule out a 10-fold or higher increase in risk with first-trimester EFV exposure. Thus, if there is an elevated risk, it is likely to be <1%. Nevertheless, there are continued concerns about newly initiating EFV-based regimens during the first trimester.

When choosing an ARV regimen for women of childbearing age who are not yet pregnant, consideration should be given to the benefits and potential risks, as well as to the availability of alternative agents. If EFV-based ART regimens are used, adequate contraception should be provided and women should be informed about the potential risk of birth defects with first-trimester exposure and advised that, if pregnancy is desired, EFV should be discontinued before conception and another drug, such as NVP, substituted.

Infant prophylaxis

Breastfeeding infants

There is high-quality evidence that NVP regimens for 6 weeks or longer [6 weeks (SWEN); 14 weeks (PEPI-Malawi)] are efficacious and safe in reducing HIV transmission or death and infant mortality compared to sd-NVP given only at birth. There is moderate-quality to high-quality evidence that daily NVP regimens are associated with an increased risk of acquired resistance (in the lower number of infants who are infected) compared to sd-NVP (6 weeks; SWEN). Maternal ART provides protection against postnatal transmission to the infant, and hence prolonged extended NVP (beyond 6 weeks) is not needed if the mother is receiving ART. However, a short infant prophylaxis regimen of 4 to 6 weeks) is recommended even when women are receiving ART, in order to provide peripartum protection, especially where maternal viral suppression has not yet been achieved.

Non-breastfeeding infants

There is no evidence assessing the efficacy of daily NVP for any duration beyond a single dose at birth in non-breastfed infants born to HIV-infected women. However, there is substantial high-quality evidence of the efficacy of daily NVP in breastfeeding infants with ongoing exposure to HIV. There is high-quality evidence that 6 weeks of daily infant AZT prophylaxis in conjunction with maternal antepartum AZT prophylaxis for more than 4 weeks as used in the PACTG 076 and PHPT-1 trials (Connor, 1994; Lallemant, 2000) significantly prevents HIV MTCT. The PHPT-1 trial showed that a 6-week AZT regimen in the infant was beneficial if the mother started to take AZT late in pregnancy but that it might be unnecessary when the mother started AZT 4 weeks or earlier before delivery. Although the evidence base for the exact duration of infant prophylaxis is unclear, 4 to 6 weeks of AZT prophylaxis to non-breastfeeding infants has been and continues to be a standard part of the PMTCT regimen in Western countries, e.g. the USA and France, based on the original 076 trial.

There is a consistent body of evidence of high to low quality showing that a short period of AZT prophylaxis (up to 6 weeks) for newborns with various combinations of maternal prophylaxis does not incur significantly increased rates of severe side-effects, including anaemia (PACTG 076, PHPT-1, PETRA); the anaemia that is observed rapidly reverses after infant AZT is stopped. There are no data comparing the efficacy of infant AZT for 1 vs. 4 weeks, or for 4 vs. 6 weeks.

Uncertainty about the quality of evidence: No

Risks/benefits

Benefits

Maternal regimen

With each of the proposed regimens, the primary benefit is treatment for the mother's health. These ART regimens result in a reduction in maternal HIV mortality and morbidity, including a reduction in TB. Important secondary benefits include the reduction in MTCT in this group with the highest MTCT risk, and a decrease in infant mortality at 12 months of age. Globally, there is significantly more experience in pregnancy with AZT + 3TC, and it is the preferred NRTI backbone option in pregnant women. There is potential for administering one pill once daily if using fixed-dose combinations such as TDF + FTC + EFV. Fixed-dose combinations or co-packaged formulations, with simplified daily regimens, should be used whenever possible and feasible (as per the adult ART guidelines).

Infant regimen

Infant prophylaxis has been shown to be effective in preventing the peripartum transmission of HIV, especially where the mother has not yet achieved full viral suppression with her ART regimen at the time of delivery.

Risks

Maternal regimen

The risks of the proposed regimens include potential ART drug toxicity, including anaemia with AZT-based regimens, renal toxicity with TDF-based regimens, and hypersensitivity and hepatotoxicity with NVP-based regimens (particularly among pregnant women with higher CD4 cell counts). While the use of NVP in women with higher CD4 counts is still a concern, recent observational data from multiple sources suggest that this is not a significant problem in women with CD4 <350 cells/mm^3. There is still limited data on the use of TDF in pregnancy and the effects on maternal and infant bone toxicity. While there is a potential risk with the use of EFV of neural tube defects in the first month of pregnancy (first 28 days of gestation), the magnitude of this risk appears small (probably <1%) and virtually all pregnancies will be recognized and treatment started after this period, when the risk has passed.

Infant regimen

Among infants receiving daily NVP as short-course prophylaxis and where the mother is receiving an NVP-based ART regimen during breastfeeding, doubling-up of NVP requires clinical monitoring for toxicity. Infants receiving daily NVP who become infected despite maternal and infant ARV interventions are likely to develop drug resistance, and should be started on a PI-containing first-line ART regimen (per current paediatric ART treatment guidelines).

Uncertainty about the balance of benefits versus harms and burdens: No

Values and acceptability

In favour

The recommendation places a high value on the health and well-being of the woman, by providing the best possible treatment for her advanced HIV disease, and on decreasing maternal morbidity and mortality. A high value is also placed on the additional benefit of significantly reducing transmission to the infant among this group of women (eligible for treatment) who have the highest risk of transmission. There is extensive experience with the use of AZT + 3TC + NVP (twice daily) in HIV-infected women in need of ART for their own health, including in pregnant women, and this regimen has been shown to be effective (achieving viral suppression), well-tolerated and acceptable to pregnant women and clinicians. The acceptability of the other regimens appears promising, and depends in part on some of the additional advantages of being able to provide them in once-daily, fixed-dose combinations and on their increasing availability as part of first-line treatment for adults.

The benefits of ART for the health of the mother outweigh the potential risks, particularly as alternative regimens are available in the event of toxicity. Also, a high value was placed on keeping the same regimens for pregnant women in line with the recommendation for non-pregnant women, as outlined in the adult ART guidelines.
For infant prophylaxis, high value was placed on the demonstrated efficacy of the prophylaxis regimens in reducing peripartum and postpartum HIV transmission. Even when the mother is on triple ART, infant prophylaxis for 4 to 6 weeks is recommended because of uncertainties about maternal adherence and the length of time on ART, i.e. the infant prophylaxis provides back-up protection if the mother has not been on ART long enough to reduce the viral load to a level that would provide maximum protection in order to prevent transmission to the infant. Additional values in favour of infant prophylaxis include the facts that this is standard care in the West and that prophylaxis for 6 weeks would link to the first well-child immunization visit in most countries.

Against
The recommendation places relatively low value on the potential ART drug toxicity risks for the mother and unborn infant. Acceptability of the proposed regimens might be compromised because of potential ART toxicity.

Uncertainty or differences in values: No

Cost

Costs of the proposed ART regimens have been decreasing rapidly in the past several years. However, current costs vary widely for different countries, depending on their access to discount pricing. Currently, the AZT + 3TC + NVP regimen has the lowest cost (US $143–161 per year). The costs of other recommended regimens are in the range of $200–600 per year. A cost saving can theoretically be expected as more adult and infant lives will be saved, thereby reducing the cost for HIV care and support services and increasing productive and healthy life-years. However, it should be noted that the recommendations were not based on cost, as no formal cost-effectiveness analysis was performed. Costs are changing rapidly and vary between countries, and the benefits of ART for the health of HIV-infected pregnant women were felt to outweigh the costs.

Uncertainty about whether the net benefits are worth the costs: No

Feasibility

Extensive experience with the use of AZT + 3TC + NVP in HIV-infected women needing ART for their own health has shown this regimen to be feasible in low and middle-income countries. On a programmatic level, and presumably also at the individual patient level, simple formulations (i.e. fixed-dose combinations taken once or twice daily) will increase feasibility and adherence.
Potential drug toxicity continues to be a concern in pregnant women, especially with limited monitoring at the primary care level. Increased capacity at the health facility level is needed in order to monitor ART safety and effectiveness, including CD4 cell count analysis, and promote adherence. Development of an implementation tool and simple, standardized protocols adapted to local settings, would further facilitate implementation.
In terms of implementation of the recommendation, the provision of ART in ANC and MCH services must be built up. Linkages with the ART programme and clinics should be strengthened, and pregnant women should be given priority for treatment.

Uncertainty: No

Gaps and research needs

- Further research is needed to assess the CD4 cell count distribution for each of the WHO clinical stages, particularly stage 2 in pregnant women
- Potential risk of NVP toxicity in women with CD4 cell counts of 250-350 cells/mm3 and >350 cells/mm3
- Adverse effects in pregnant women and their infants with the use of ARV regimens
- Contraception acceptability and efficacy and use of ARV drugs (and interactions with ARVs)
- Better information on safety related to TDF and teratogenicity of EFV use during pregnancy

Final comments

The benefits to maternal health of using any of the recommended ART regimens, in order to provide the mother with the best possible treatment for her advanced HIV disease, outweigh the potential risks of drug toxicity. ART for eligible women also provides the very strong secondary benefit of giving the best possible ARV drug intervention to decrease the MTCT risk (both during pregnancy and postpartum if there is breastfeeding) in this group of women with very high transmission risk; who are estimated to account for up to 75% of all MTCT. Similarly, the added benefits of a peripartum short course of infant ARV prophylaxis in preventing infant HIV infection outweigh the potential risks of drug toxicity and provide additional protection if the mother has started ART late, or does not have high adherence, and has not achieved full viral suppression.

Risk-benefit table 3.
When to start maternal ARV prophylaxis in pregnancy for women not eligible for treatment

Recommendations

Give ARV prophylaxis to all HIV-positive pregnant women not eligible for ART, starting as early as 14 weeks gestation (second trimester) and while awaiting determination of treatment eligibility. Give prophylaxis as soon as possible when women present late in pregnancy, labour or delivery.
(Strong recommendation, low quality of evidence)

Domains and considerations

Quality of evidence

The 2006 recommendations are to start prophylaxis at 28 weeks gestation. The PICO question for this recommendation was around the evidence for starting earlier than 28 weeks. There is low-quality evidence from the earliest studies of AZT prophylaxis that starting AZT earlier is associated with lower rates of intrauterine transmission (Connor, 1994; compared to Shaffer, 1999; Wiktor, 1999; Dabis, 1999; and Limpongsanurak, 2001). There is also low-quality evidence from a single trial that found lower rates of intrauterine transmission in women who began AZT at 28 weeks of gestation compared to those who began at 35 weeks of gestation (Lallemant, 2000). However, there is no direct evidence to assess the additional benefit of starting AZT (or other prophylaxis) before 28 weeks of gestation vs. starting it at 28 weeks of gestation or later in women with >350 CD4 cells/mm^3. Despite these uncertainties in the systematic evidence review on specific comparisons in the duration of antenatal prophylaxis and in this subpopulation (i.e. women not eligible for treatment) there is well-established evidence of a risk of intrauterine transmission throughout pregnancy (although a greater risk in late pregnancy and around the time of delivery) and that extending prophylaxis provides additional benefit based on the dose-response principle of covering as much of the period of risk as possible.

Uncertainty about quality of evidence: Yes

Risks/Benefits

Benefits

Starting prophylaxis earlier in the mother would lower the risk of in utero infection during the second trimester and the early third trimester and would reduce vertical transmission. Additional observational evidence shows the programmatic benefit of an earlier start of prophylaxis. Pregnant women are generally tested for HIV at the first antenatal visit and the ability to start the regimen earlier will lessen the time delays between HIV testing and ARV prophylaxis initiation and will potentially reduce the number of pregnant women lost to follow up (between HIV diagnosis and the start of the prophylaxis intervention). It will also avoid delays resulting from the current recommendation to start at 28 weeks. In practice, in programmes following current recommendations, many HIV-infected pregnant women start on prophylaxis after 28 weeks and therefore do not have adequate prevention of transmission risk during the early or middle third trimester.

Risks

The longer prophylaxis might result in adherence issues. There is also increased risk for AZT-related maternal anaemia with the longer regimen compared to shorter regimens and some concern about AZT resistance (although AZT resistance is usually not seen in the first 6 months of monotherapy in individuals with no or minimal symptoms and higher CD4 (e.g. >350 cells/mm^3).

Uncertainty about the balance of benefits versus harms and burdens: Yes

Values and acceptability

In favour

This recommendation will avoid situations reported after the implementation of the 2006 guidelines, when women were seen in the early second trimester of pregnancy (e.g. before 28 weeks of gestation) and sent back home without prophylaxis, resulting in either: starting prophylaxis well after 28 weeks or not starting at all because of loss to follow-up. It will also allow starting prophylaxis with AZT alone (or other prophylaxis) while awaiting the CD4 result to determine maternal eligibility for ART.

This recommendation promotes wide implementation of early and active enrolment into PMTCT programmes and access to CD4 testing in antenatal care.

There will be a need to combine the dispensing of prophylaxis with the routine antenatal visit.

Against

It is not known whether starting ARV prophylaxis for PMTCT from 14 weeks of gestation would be acceptable to women. The emphasis on an earlier start might limit the additional counselling which some programmes provide. In well-developed and successful PMTCT programmes in some countries, AZT is provided from 28 weeks of gestation and nearly all pregnant women are receiving >4 weeks before delivery. In this situation, starting earlier at 14 weeks may not add more benefit.

Uncertainty or differences in values: No

Cost

Total costs for programmes will increase as maternal ARV prophylaxis will start earlier. A cost saving and measurable health benefit can theoretically be expected as vertical transmission will decrease and more infant lives will be saved.

Uncertainty about whether the net benefits are worth the costs: No

Feasibility

Although the new recommendation is to start as early as 14 weeks of gestation (at the beginning of the second trimester), the likelihood of this being implemented depends on when pregnant women present at ANC. Late attendance in antenatal clinics may hinder feasibility. In many settings, the median time for the first antenatal visit is the mid-second trimester, so the hope is that these women would still start prophylaxis before 28 weeks. More challenges exist in reaching rural women and for women who register very late for antenatal care. However, the feasibility of intervention will increase if AZT (or other prophylaxis) is started as soon as the HIV test in pregnancy is positive and while waiting for CD4 to determine ARV treatment eligibility.

More drugs may mean that there is a need for the mother to return more frequently to clinic for picking up the ARV prophylaxis, resulting in the need for an increased capacity of the health system to provide ARVs. Maternal/infant HIV drug kits (PMTCT "mother-baby packs") are now being developed to provide standardized packages of drugs and allow mothers to have access to drugs for an extended period without the need for frequent visits to the clinic. A programme tool would facilitate implementation.

Uncertainty: No

Gaps and research needs

There is a crucial need for more pregnancy outcome and later infant outcome data with longer in utero exposure to ARVs, particularly for combination ARVs and newer ARV drugs with less experience during pregnancy. There is also a need for more information about how to promote adherence for longer drug regimens and how to more effectively integrate antenatal prophylaxis into routine antenatal and maternal and child health care.

Final comments

The panel placed a high value on reducing the potential lost to follow-up and delayed start of ARV prophylaxis which now occurs by waiting until the third trimester (observed in many programme settings). The current target of starting at the beginning of the third trimester has inadvertently resulted in many women starting in the middle of the third trimester, or later. The risk of vertical transmission decreases as more ARV coverage is provided throughout the in utero period of risk.

Risk-benefit table 4.
What ARV prophylaxis to give to pregnant women for PMTCT (for women not eligible for ART, with unknown eligibility or when ART is not available)

Recommendations	
Two options are recommended	
Option A - "Maternal AZT + infant ARV prophylaxis"	Option B - "Maternal triple ARV prophylaxis"
Mother • Antepartum: daily AZT starting from as early as 14 weeks of gestation • Intrapartum: AZT and sd-NVP at onset of labour (if antenatal AZT <4 weeks) • AZT + 3TC during labour and delivery* • Daily AZT + 3TC for 7 days postpartum* Strong recommendation * omit AZT + 3TC "tail" if sd-NVP at onset of labour is not given; in this case, continue maternal AZT twice daily during labour and stop at delivery.	**Mother** • Maternal triple ARV starting from as early as 14 weeks of gestation until one week after all exposure to breast milk has ended Recommended regimens – AZT + 3TC + LPV/r – AZT + 3TC + ABC – AZT + 3TC + EFV – TDF + 3TC (or FTC) + EFV Strong recommendation
Infant ***Breastfeeding infant*** • Daily NVP from birth until one week after all exposure to breast milk has ended Strong recommendation ***Non-breastfeeding infant*** • Daily NVP or sd-NPV + AZT from birth until 4 to 6 weeks of age Conditional recommendation	**Infant** ***Breastfeeding infant*** • Daily NVP or AZT from birth for 4 to 6 weeks Strong recommendation ***Non-breastfeeding infant*** • Daily NVP or AZT from birth for 4 to 6 weeks Conditional recommendation
Domains and considerations	
Quality of evidence	
1. Maternal AZT option for breastfeeding infants ***Maternal component*** The maternal component of this regimen is the same as the current WHO 2006 guidelines and was based on prior studies. Review of evidence was not done to look at this regimen alone. The systematic review looked at comparing maternal option A vs. B There is moderate quality evidence from one trial (Kesho Bora; de Vincenzi 2009) that AZT beginning at 28 weeks, sd-NVP + AZT + 3TC intrapartum and AZT + 3TC x 7 days postpartum results in a similar rate of intrauterine and intrapartum transmission as that seen with AZT + 3TC + LPV/r beginning at 28-36 weeks (both regimens had transmission rates of <1% at birth and approximately 3% at 6 weeks in women with CD4 >350 cells/mm^3). **Infant component** There is high-quality evidence that daily infant NVP regimens for 6 and 14 weeks (SWEN), (PEPI-Malawi) are efficacious in reducing HIV transmission or death and infant mortality, compared to sd-NVP given only at birth. There is moderate- to high-quality evidence that extended-NVP regimens are associated with an increased risk of acquired resistance in the smaller number of infants who may get infected, compared to sd-NVP (6 weeks; SWEN).	

There is high-quality evidence that an extended infant NVP + AZT regimen [dual prophylaxis for 14 weeks (PEPI-Malawi)] is efficacious in reducing HIV transmission or death and infant mortality, compared to sd-NVP. However, there was moderate-quality evidence for no significant differences in HIV transmission or infant mortality between the extended NVP arm and the extended-dual prophylaxis arm, and low quality of evidence for an increase in probably-related serious adverse events in the NVP+AZT arm (PEPI-Malawi).

Newly available data from the BAN study (Malawi) evaluated extended NVP to the infant for 6 months vs. three-drug maternal ARV prophylaxis for 6 months during breastfeeding. Although this study was not able to be included in the systematic review, preliminary, unpublished data (presented at an international conference and manuscript submitted for publication) indicate a strong protective effect for both maternal and infant prophylaxis strategies, good adherence and a trend towards a better outcome in infants receiving daily NVP prophylaxis. [Note: the BAN study was published (Chasela et al. NEJM, 2010) after the risk-benefit tables were finalized and before the full guidelines were published; the published study is referenced in the full guidelines).

There are no data regarding extended-NVP regimens beyond 6 months. However, data from clinical trials extending the use of NVP in infants from a single dose at birth to 6 weeks, 14 weeks, and 6 months show clear dose-response protection for the increasing time of coverage during breastfeeding, and low adverse events. An additional review of toxicity and pharmacological modelling show that most adverse events in infants are likely to occur early and that extended prophylaxis at the sub-therapeutic doses required for infant prophylaxis during breastfeeding are likely to be well-tolerated.

Uncertainty about the quality of evidence: No

2. Maternal triple ARV prophylaxis option for breastfeeding infants

Antepartum prophylaxis with triple ARV

There is moderate quality evidence from one trial (Kesho Bora; de Vincenzi 2009) that AZT + 3TC + LPV/r beginning at 28-36 weeks is associated with a similar rate of intrauterine and intrapartum transmission as AZT beginning at 28 weeks, sd-NPV + AZT + 3TC intrapartum and AZT + 3TC for 7 days postpartum (both <1% at birth and both approximately 3% at 6 weeks) in women with CD4 values of >350 cells/mm^3.

Postpartum

The Kesho Bora study evaluated AZT+3TC+LPV/r given to mothers for 6.5 months postpartum compared to a maternal AZT short-course regimen without postnatal prophylaxis after 1 week. There is moderate-quality evidence of trends at different time points of decreased risk of HIV transmission or death, moderate-quality evidence for a trend towards reduction in HIV transmission, and very low-quality evidence for no difference in maternal severe adverse events (SAEs) between the two regimens. HIV transmission or death at 12 months was statistically significant; other outcomes were not statistically significant.

From the Mma Bana study which evaluated maternal AZT+3TC+LPV/r compared to co-formulated AZT+3TC+ABC to 6 months postpartum, there is low-quality evidence of no difference in HIV transmission or death, moderate-quality evidence of no difference in HIV transmission, and low-quality evidence of no difference in maternal severe adverse events between the two regimens.

Uncertainty about the quality of evidence: No

3. Both options for non-breastfeeding infants

There is no evidence assessing the efficacy of daily NVP for any duration beyond a single dose at birth in non-breastfed infants born to HIV-infected women, and there are no data comparing 6 weeks of infant NVP vs. 6 weeks of infant AZT in non-breastfeeding infants.

There is high-quality evidence that 6 weeks of daily infant AZT prophylaxis in conjunction with maternal antepartum AZT prophylaxis for more than 4 weeks (Connor, 1994; Lallemant, 2000) significantly prevents HIV MTCT. The PHPT-1 trial showed that a 6-week AZT regimen in the infant is beneficial if the mother starts to take AZT late in pregnancy but may be unnecessary when the mother starts AZT 4 weeks or earlier before delivery.
There is a consistent body of evidence of low to high quality showing that giving AZT to newborns with various combinations of maternal prophylaxis does not incur significantly increased rates of severe adverse events including anaemia (which is rapidly reversible) (PACTG 076, PHPT-1, PETRA).
There are no data comparing the efficacy of AZT for 1 week vs. 4 weeks, or for 4 weeks vs. 6 weeks.

Uncertainty about the quality of evidence: No

Risks/Benefits

1. Maternal AZT option for breastfeeding infants

Intrapartum prophylaxis - relevance of the AZT + 3TC "tail"

Benefits
The addition of an intrapartum and short postpartum tail to the mother has been shown to significantly reduce NVP drug resistance among both mothers and infants who have received sd-NVP at labour and birth.

Risks
Severe adverse events were not associated with the tail in the published studies. This additional tail is part of the 2006 recommendations and no change is proposed.

Postpartum / postnatal strategy in breastfeeding infants

Benefits
The use of daily infant NVP allows missing one or two doses because of its long half-life. Minimal monitoring is needed; available data suggest minimal toxicity for daily NVP to 6 months. The provision of ARV prophylaxis throughout the breastfeeding period will significantly reduce postpartum HIV transmission to the infant, allow safer infant feeding practices in resource-limited settings, and greatly increase the survival rate of exposed infants.
Note: Recommendations on the duration of breastfeeding in the presence of ARV prophylaxis are being addressed in a separate review process and a separate guidelines document on HIV and Infant Feeding.

Risks
The safety of daily infant NVP for 12 months or more is not known (although based on data to 6 months, toxicity/adverse events are expected to be minimal). There is a likelihood of resistance in most infants who are infected despite prophylaxis (although the number of infants infected is expected to be significantly lower, and first-line paediatric treatment in infants exposed to any NVP, including sd-NVP, is a PI-based, non-NVP-containing regimen, because of presumed resistance).

Uncertainty about the balance of benefits versus harms and burdens: No

2. Maternal triple ARV prophylaxis option for breastfeeding infants

Antepartum prophylaxis with triple ARV

Benefits

The study that compared antepartum triple-drug ARV to antepartum AZT alone (de Vincenzi, 2009) found no differences between the regimens for the outcomes of infection at birth (RR 1.0, 95% CI 0.14-7.03) and infection at 4-8 weeks (3.3% vs. 4.7%, RR 0.67, 95% CI 0.33-1.36).

Risks

None of the studies that compared antepartum AZT alone to AZT + 3TC or triple-drug ART found elevated risks of maternal severe adverse events The other two studies found no evidence of increased adverse events in infants.

Postpartum / postnatal strategy in breastfeeding infants

Benefits

Provision of maternal ARV prophylaxis throughout the breastfeeding period will significantly reduce the transmission of HIV to the infant and greatly increase the survival rate of the exposed infant.

Risks

The risk of stopping maternal triple ARV prophylaxis after prolonged use during pregnancy and breastfeeding cessation is unknown. There may also be difficulties in reassessing "eligibility" for treatment after prolonged three-drug prophylaxis.

Uncertainty about the balance of benefits versus harms and burdens: No

Values and acceptability

1. Maternal AZT option for breastfeeding infants

In favour

The infant provision of NVP can be linked to multivitamin administration and/or co-trimoxazole prophylaxis to the infant and can use the same visit schedule. The long half-life of NVP allows missing a day or two, as levels are maintained for several days. There is no need for close monitoring of infant safety.

Against

The antepartum maternal regimen, including the tail, is complex. There is a lack of efficacy, safety and feasibility data on daily infant NVP use beyond 6 months. There is no reported information on the maternal acceptability of extended infant prophylaxis outside of clinical trials.

Uncertainty or differences in value: No

2. Maternal triple ARV prophylaxis option for breastfeeding infants

In favour

The strategy (with single FDCs) is simple to implement but more costly. The same regimen to the mother will be used during using antepartum and after delivery. There is a high probability of reaching an undetectable viral load at delivery by giving triple ARV to the mother and continuing viral suppression during breastfeeding, thus reducing the risk of transmission to the infant.

Against

Since it is a triple drug regimen, there may be a need for referral for initiation of prophylaxis. It will be critical to have a CD4 count in order to determine if the mother should stop triple ARV postpartum or continue treatment for her own health. Multiple monitoring visits are required to assess maternal safety. Also, it will be necessary to strengthen the capacity of the health facility, including drug procurement.

Uncertainty or differences in value: No

Cost

The total costs for programmes will increase as both strategies imply the procurement of additional ARV drugs, for both mothers and infants, in this population of women who are not eligible for ART. A cost saving can theoretically be expected as more infant, and possibly adult, lives will be saved and there will be more healthy and productive life-years. At current prices, the maternal AZT + infant ARV prophylaxis option is significantly less costly than the maternal triple ARV prophylaxis option.

Uncertainty about whether the net benefits are worth the costs (both options): No

Feasibility

1. Maternal AZT option for breastfeeding infants

Administration of infant NVP prophylaxis appears similar to multivitamin administration. The compliance to infant daily NVP was not reported in the trials assessing infant prophylaxis strategies, although the strong protective effects for transmission suggest high compliance. The feasibility is unknown in large-scale programme settings.

Uncertainty: No

2. Maternal triple ARV prophylaxis option for breastfeeding infants

Outside of clinical trials, the maternal acceptability of continuation of triple-ARV during breastfeeding among women with high CD4 counts, as well as stopping after breastfeeding, is unknown.

Uncertainty: No

Gaps and research needs

- More definitive data comparing postnatal prophylaxis with infant NVP vs. maternal triple ARVs during breastfeeding are urgently needed. Such information may allow the ranking of the two options.
- Safety of 12 months (or longer duration) of daily infant NVP should be systematically assessed.
- Effect of triple maternal ARV on pregnancy outcome should be better assessed (e.g., preterm delivery or low birth weight infants).
- Safety and clinical effect of prolonged maternal antepartum and postnatal use of triple ARV and stopping after breastfeeding cessation should be carefully addressed.
- Long-term safety of in utero exposure to multiple drugs in the infant when used solely for prophylaxis should be evaluated.

"Maternal triple ARV prophylaxis" option: programme guidance is needed on how and when to stop maternal ARV after breastfeeding cessation.

Final comment

Final comment

There is a strong benefit in providing effective and sustained prophylaxis to women not eligible for ART during pregnancy, labour and delivery, and throughout breastfeeding in settings where breastfeeding is the preferred practice. Both options included in this recommendation provide significant protection; there are advantages and disadvantages for each of the options and the panel felt that the choice for a preferred option should be made at the country level.

The panel placed a high value on reducing the risk of HIV transmission to exposed infants, and providing effective prophylaxis during breastfeeding in settings where this is preferred.

ANNEX 4. PRIORITIES FOR RESEARCH

This annex is based on important gaps and needs in the available evidence and programme experience, as revealed by the systematic review conducted during the preparation of these guidelines, and identifies relevant priorities for research.

Safety of starting and stopping triple ARV prophylaxis

Available evidence on ART interruption among persons in need of treatment for their own health shows reduced treatment efficacy. However, there is no evidence on the potential concerns of starting and stopping triple ARV prophylaxis among women who do not require treatment for their own health and who have CD4 cell counts of >350 cells/mm^3. In addition, programme guidance and programme experience is needed on how and when to stop maternal ARV prophylaxis after the cessation of breastfeeding.

Use of the WHO-recommended interventions in future trials

A systematic review around the key questions identified important gaps in evidence for key questions, partly attributable to the use of a large variation of interventions and controls (or comparison groups) in PMTCT trials. It is therefore recommended to use the WHO-recommended interventions as the control arm in future studies.

Seroconversion during pregnancy

There are currently no data that indicate which ARV prophylaxis regimen is most efficacious for a pregnant woman with primary HIV infection. Research to identify the optimal intervention to prevent MTCT in women identified to seroconvert during pregnancy or during breastfeeding is desirable.

Safety and efficacy of extended infant prophylaxis during breastfeeding after 6 months of age

The new guidelines recommend extended infant prophylaxis with NVP during breastfeeding for up to 12 months, or longer. This is based on strong safety and efficacy data in multiple trials of postpartum prophylaxis for up to 3–6 months. Safety and efficacy data on extended prophylaxis, at least up to 12 months, as well as analysis of required programme support and methods to promote adherence, are needed.

Safety and efficacy of extended maternal prophylaxis during breastfeeding after 6 months of age

The new guidelines recommend extended maternal ARV prophylaxis during breastfeeding for up to 12 months, or longer. This is based on strong safety and efficacy data in multiple trials of maternal postpartum prophylaxis for up to 6 months. Safety and efficacy data on extended prophylaxis, at least up to 12 months, as well as analysis of required programme support and methods to promote adherence, are needed.

More reliable data comparing Option A and Option B prophylaxis

What is the relative effectiveness of Option A and B in women not eligible for ART? What is the relative effectiveness in populations where ART eligibility can not be determined easily or where there is limited access to ART (ie. in populations who are primarily of unknown eligibility status)?

Impact of ART and ARV prophylaxis on infant feeding practices

In settings where breastfeeding is recommended as the best infant feeding option, assessments are needed of the impact of ART and ARV postpartum prophylaxis (both maternal and infant prophylaxis options) on infant feeding practices.

Assessment of proposed strategies to provide ART (lifelong) to all HIV-infected pregnant women

What is the feasibility, cost and cost-savings, safety, prevention-benefit ("ART for prevention"), spill-over, long-term adherence, impact in relation to repeat pregnancies, etc? What are the most appropriate fixed-dose combinations that could be used with such an approach (i.e. safe toxicity profile during pregnancy, safe and low risk of resistance during chronic use, safe for use in women with high CD4 count, etc)?

Outcome measures - programme transmission rates and HIV-free survival

Standardized methodologies are needed to assess programme transmission rates (early and late transmission) and HIV-free survival, both for local programmes and for national estimates.

Safety of tenofovir

Some concerns exist about exposure to TDF in utero and risks of abnormal fetal bone development. However, for women requiring ART and receiving TDF-based regimens who become pregnant, the benefits of continuing treatment are likely to exceed the theoretical risks of toxicity for the infant, but further safety data are needed.

Safety of efavirenz

More reliable data on the safety and risk of teratogenicity of EFV use during pregnancy is needed.

Monitoring and evaluation of ART and PMTCT programmes

Better programme methods are needed to monitor and evaluate indicators for the number of pregnant women initiating ART, as well as their adherence and response to treatment, in terms of their own health, MTCT transmission rates, and the health of their children. The impact on health services, including examples of how best to link these services, should also be monitored.

Further research is needed to assess the CD4 cell count distribution for each of the WHO clinical stages, particularly stage 2 in pregnant women

Some data suggest that up to 50% of pregnant women with stage 2 have CD4 counts of <350 cells/mm^3. However, in the current recommendations, these women would not receive ART, if a decision is only based on clinical staging and CD4 count is not available. There is a need for better information on the distribution and relationship of CD4 and clinical stage and how to improve clinical staging at the primary health care level.

Further operational research and new technologies are needed to improve access to CD4 testing for pregnant women, to determine ART eligibility, at all levels of the health care system.

CD4 testing is currently the key laboratory test for determining ART eligibility. However, it is not generally available in many resource-limited settings, and particularly at primary care level. Simple, reliable and affordable point-of-care CD4 testing is needed. In settings where CD4 testing is limited during antenatal care, can women be started on triple ARV prophylaxis and can ART eligibility (CD4 testing) be determined around the time of delivery?

Potential risk of NVP toxicity in women with CD4 cell counts of >250 cells/mm^3

There is still some concern about increased risk of toxicity in women with CD4 count of 250–350 cell/mm^3. Additional safety data are needed.

Safety and adverse effects in pregnant women and their infants with the expanded use of ARV regimens

The new guidelines recommend a significant increase in the use of ARVs (both ART and ARV prophylaxis) during pregnancy. Additional data are needed on the safety and acceptability of different regimens, including any effects on pregnancy outcome and the long-term effects on the infant of in utero exposure to prolonged ARVs.

Crucial need of more pregnancy outcome and later infant outcome data (pharmacovigilance) with longer in utero exposure to ARVs (both ART and ARV), particularly for combination ARVs and newer ARVs with less experience during pregnancy

Need for more information about how to promote adherence for longer drug regimens for pregnant and postpartum women and their infants and how to more effectively integrate antenatal and postpartum prophylaxis into routine antenatal and maternal and child health care

More definitive data comparing postpartum prophylaxis with infant NVP vs. maternal triple ARVs during breastfeeding are urgently needed

Comparisons are needed for efficacy, field effectiveness, acceptability, safety profiles and requirements of the health system. Such information may allow the ranking of the two options.

ARV drug resistance in infants

Further studies are needed to determine the incidence and type of ARV resistance in infants who become infected despite maternal ART or triple ARV prophylaxis. The available data suggest that multi-class drug resistance may be observed in infants who become infected despite triple ARV drug regimens.

ANNEX 5. GLOSSARY

Breastfeeding: As these guidelines focus on PMTCT and as there remains a transmission risk of HIV with the ingestion of any breast milk, the term breastfeeding here refers to exclusive or partial breastfeeding and therefore covers infants who receive breast milk for comforting or after expression.

Replacement feeding: In the context of this document, infants in the replacement feeding group are those receiving any replacement feeding but no breast milk.

Antiretroviral treatment: An intervention (normally lifelong) for HIV-infected persons to primarily treat the HIV disease for their own health. Additional secondary effects such as a reduced risk of HIV transmission to an infant are of added value to the intervention.

Antiretroviral prophylaxis: A short-term intervention to primarily reduce the risk of HIV transmission to an infant. This intervention could be given to an HIV-infected pregnant woman and/or to an uninfected but exposed infant and is not for the treatment of HIV disease.

Clinically significant or severe anaemia: Signs consist of severe conjunctival or palmar pallor, or any pallor combined with >30 breaths per minute, tiring easily or breathlessness at rest. In pregnant women, when Hb testing is available, severe anaemia is defined at Hb < 7g/dl.

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