ANTIRETROVIRAL DRUGS FOR TREATING PREGNANT WOMEN AND PREVENTING HIV INFECTION IN INFANTS IN RESOURCE-LIMITED SETTINGS

TOWARDS UNIVERSAL ACCESS

Recommendations for a public health approach

2006 version

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This publication is part of a trilogy of guidelines published at the same time by the World Health Organization (WHO) and its partners which provide recommendations supporting the public health approach to the use of antiretroviral (ARV) drugs in resource-limited settings. The guidelines are based on the work of a group of experts, who participated in several technical consultations on the use of ARV drugs for treating pregnant women and preventing HIV infection in infants and young children.

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ABBREVIATIONS AND ACCRONYMS

ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ANC	Antenatal care
ARV	Antiretroviral
ART	Antiretroviral therapy
ATV/r	Atazanavir/ritonavir
AZT	Azidothymidine
ddI	Didanosine
d4T	Stavudine
EFV	Efavirenz
fos-APV/r	Fosamprenavir/ritonavir
FTC	Emtricitabine
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDU	Injecting-drug user
IDV	Indinavir
LPV/r	Lopinavir/ritonavir
MCH	Maternal and child health
MTCT	Mother-to-child transmission
NFV	Nelfinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OST	Opioid substitution therapy
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission
RIF	Rifampicin
Sd-NVP	Single-dose nevirapine
SQV/r	Saquinavir/ritonavir
STI	Sexually transmitted infection
TB	Tuberculosis
TDF	Tenofovir
3TC	Lamivudine
UN	United Nations
UNGASS	United Nations General Assembly Special Session
WHO	World Health Organization

I. INTRODUCTION

The human immunodeficiency virus (HIV) pandemic is one of the most serious health crises the world faces today. AIDS has killed more than 25 million people since 1981 and an estimated 38.6 million people are now living with HIV, about 2.3 million of whom are children *(1)*. Since 1999, primarily as a result of HIV, average life expectancy has declined in 38 countries. In the most severely affected countries, average life expectancy is now 49 years – 13 years less than in the absence of AIDS *(2)*. A disproportionate burden has been placed on women and children, who in many settings continue to experience high rates of new HIV infections and of HIV-related illness and death. In 2005 alone, an estimated 540 000 children were newly infected with HIV, with about 90% of these infections occurring in sub-Saharan Africa *(1)*.

Most children living with HIV acquire the infection through mother-to-child transmission (MTCT), which can occur during pregnancy, labour and delivery or during breastfeeding. In the absence of any intervention the risk of such transmission is 15–30% in non-breastfeeding populations. Breastfeeding by an infected mother increases the risk by 5–20% to a total of 20–45% *(3)*. The risk of MTCT can be reduced to under 2% by interventions that include antiretroviral (ARV) prophylaxis given to women during pregnancy and labour and to the infant in the first weeks of life, obstetrical interventions including elective caesarean delivery (prior to the onset of labour and rupture of membranes), and complete avoidance of breastfeeding *(4–6)*. With these interventions, new HIV infections in children are becoming increasingly rare in many parts of the world, particularly in high-income countries.

In many resource-constrained settings, elective caesarean delivery is seldom feasible *(7)* and it is often neither acceptable nor safe for mothers to refrain from breastfeeding. In these settings, the efforts to prevent HIV infection in infants initially focused on reducing MTCT around the time of labour and delivery, which accounts for one to two thirds of overall transmission, depending on whether the mother breastfeeds. Recently, to increase the effectiveness of PMTCT (prevention of mother-to-child transmission) programmes, many countries with a heavy burden of HIV have adopted more effective ARV regimens, beginning in the third trimester of pregnancy, which can reduce the risk of transmission during pregnancy and childbirth to 2–4% *(8,9)*. Even when these regimens are used, however, infants remain at substantial risk of acquiring infection during breastfeeding. Research is ongoing to evaluate several new approaches to preventing HIV transmission during breastfeeding *(10)*.

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 introduce and expand PMTCT programmes. These programmes have been shown to be feasible, acceptable and cost-effective, yet despite significant progress, they have not been implemented widely in resource-constrained settings *(11)*. The shift from donor-funded projects and pilot initiatives towards national programmes has been slow and the majority of low- and middle-income countries have not achieved the goals

adopted by the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) in June 2001. By 2005, only 9% of pregnant women living with HIV were receiving ARV prophylaxis for PMTCT *(11)*. As with other HIV services, there is a striking variation in coverage between countries: in Botswana, for example, the prevention services reach at least 50% of all pregnant women living with HIV. Countries in eastern Europe and Latin America have also achieved high coverage.

Renewed efforts are urgently required to increase access to comprehensive and integrated programmes to prevent HIV infection in infants and young children. These programmes serve as a unique entry point for women to access the services they need to improve their own health and prevent transmission of HIV to their infants *(12)*. Several recent initiatives have presented an opportunity for countries to increase the coverage and effectiveness of PMTCT programmes. The international community re-energized the fight against the HIV pandemic through a commitment to universal access to prevention, care and treatment services when, at a summit in July 2005, the Group of Eight nations[1] issued a remarkable communiqué making a series of profound commitments, including a declaration of commitment on HIV/AIDS:

> We will work to achieve these aims by … with the aim of an AIDS-free generation in Africa, significantly reducing HIV infections and working with WHO, UNAIDS and other international bodies to develop and implement a package for prevention, treatment and care, with the aim of as close as possible to universal access to treatment for all those who need it by 2010.

Further, WHO Member States attending the United Nations Summit in September 2005 reaffirmed their commitment fully to implement all goals in the 2001 UNGASS Declaration of Commitment, which included reducing the proportion of infants infected with HIV by 50% by 2010. In line with these initiatives, the Inter-Agency Task Team on Prevention of HIV Infection in Pregnant Women, Mothers and their Children organized a high-level global partners forum in Abuja, Nigeria from 1 to 3 December 2005 to: (i) review progress towards the achievement of UNGASS targets for preventing HIV infection in infants and young children, and (ii) build consensus on priority action that global partners, national governments and all implementers could take to move faster towards achieving universal access by 2010. At the forum, a Call to Action Towards an HIV-free and AIDS-free Generation was issued by representatives of governments, multilateral agencies, development partners, research institutions, civil society and people living with HIV. This Call to Action expresses the commitment and political will of global partners, national governments and civil society to work collectively with the aim of accelerating action to achieve the goal of eliminating HIV infection in infants and young children.

1 Canada, France, Germany, Italy, Japan, the Russian Federation, the United Kingdom and the United States.

Abuja Call to Action: Towards an HIV-free and AIDS-free Generation

Those present recognized that:

- *evidence confirms that effective large scale programmes to prevent MTCT of HIV can be implemented in settings with limited resources;*
- *15% of new HIV infections each year are caused by MTCT and that elimination of HIV infection in infants and young children would serve to accelerate global HIV prevention efforts;*
- *aggressive efforts to reduce mother-to-child-transmission of HIV and eliminate HIV infection in infants and young children would also help to hold families together, benefit communities and reduce the stigmatization of people living with HIV;*

and called upon *other governments, development partners, civil society and private sector to join this Call to Action, and move swiftly towards supporting the measures needed to eliminate HIV in infants and young children and clear the way for a worldwide HIV-free and AIDS-free generation.*

GOAL: *Elimination of HIV infection in infants and young children to pave the way towards an HIV-free and AIDS-free generation across the globe.*

Regional and national consultations are taking place to identify specific obstacles in the way of universal access and concrete action to overcome them. A consultation involving representatives from 53 African countries held in Brazzaville, Republic of Congo, in March 2006, adopted the Brazzaville Commitment which set an agenda for action to scale up a comprehensive HIV response in Africa aiming at universal access to HIV prevention, treatment, care and support by 2010.

The implication of these commitments is that national governments, with support from development partners and donors, must now accelerate their efforts to expand and improve the effectiveness of PMTCT programmes and to achieve universal access for all who need these and related services, in accordance with the Abuja Call to Action.

II. OBJECTIVES OF THE GUIDELINES

These revised guidelines on ARV Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants in Resource-Limited Settings are consistent with, and aim to support, the Call to Action Towards an HIV-free and AIDS-free Generation. The document is one of a trilogy of guidelines published at the same time which provide recommendations developed by WHO and its partners in support of the public health approach to antiretroviral therapy (ART) in resource-constrained settings.[2] It contains recommendations for the use of ARV drugs in pregnant women for their own health and for preventing HIV infection in infants and young children, and a summary of the scientific rationale for the recommendations. In particular, the publication aims to provide guidance to assist national ministries of health in the provision of ART for pregnant women with indications for treatment, and in the selection of ARV prophylaxis regimens to be included in programmes to prevent MTCT, taking into account the needs and constraints on health systems in various settings.

The guidelines primarily target national-level programme planners and managers responsible for designing services for PMTCT and provision of ART for women. It should also be a useful resource for health care workers involved in efforts to reduce HIV infection in infants and young children and to provide treatment and care for women living with HIV.

2 The others are: (i) Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access *(15)*; and (ii) Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access *(16)* (referred to in this document as the WHO adult and paediatric guidelines, respectively).

III. DEVELOPMENT OF THE GUIDELINES

WHO first issued recommendations for the use of ARV drugs for PMTCT in 2000 *(13)*. Those recommendations were revised in 2004 with the adoption of simplified and standardized regimens *(14)*. Since then, important evidence has become available on more potent ARV prophylaxis regimens, the effectiveness of ART in preventing MTCT, the safety of ARV drugs for pregnant women, and resistance following ARV prophylaxis among mothers and its implications for their future treatment options. In addition, considerable experience has accumulated in implementing and scaling up programmes to prevent MTCT of HIV. In this context, WHO convened a Technical Consultation in Geneva, Switzerland, on 28 and 29 June 2005 to review new evidence and programmatic experience and to update the guidelines on the use of ARV drugs for treating pregnant women and preventing HIV infection in infants. The guidelines were reassessed in the context of expanding access to ARV drugs for treating pregnant women and increasing the use of highly effective regimens for preventing HIV infection in infants.

The Consultation also considered the need to harmonize these guidelines with the WHO adult and paediatric HIV treatment guidelines and to simplify them to facilitate implementation at country level. Further, special attention was given to factors related to the health system and to patients that can hinder the uptake of interventions for the prevention of MTCT and affect the quality of services provided. These include the strength of the health service infrastructure, the availability of human and financial resources, the accessibility and use of health services such as antenatal care, and the proportion of deliveries attended by a skilled health professional. Sociocultural factors and specific conditions and circumstances that influence the uptake and quality of services were also considered.

Following the June 2005 Consultation, draft guidelines were developed and presented at a Consensus Meeting held in Geneva, Switzerland on 18–19 May 2006. This Meeting reviewed evidence that had accumulated in the interim and aligned recommendations with the international commitment to universal access to HIV prevention, care, treatment and support services as well as the Abuja Call to Action.

The recommendations are based on evidence from randomized controlled trials, high-quality scientific studies for non-treatment-related options, observational cohort data, or expert opinion where evidence is lacking or inconclusive. The strength of the recommendations has been indicated to guide the degree to which they should be considered in country programmes (Table 1).

Table 1. Grading of recommendations and levels of evidence

STRENGTH OF RECOMMENDATION	LEVEL OF EVIDENCE TO GUIDE RECOMMENDATIONS
A. Recommended – should be followed B. Consider – applicable in most settings C. Optional	I. At least one randomized controlled trial with clinical, laboratory or programmatic endpoints. II. At least one high-quality study or several adequate studies with clinical, laboratory or programmatic endpoints. III. Observational cohort data, one or more case-controlled or analytical studies adequately conducted. IV. Expert opinion based on evaluation of other evidence.

Sources: adapted from The British HIV Association (BHIVA) treatment guidelines for 2005 *(17)*; Developing an evidence-based guide to community preventive services – methods *(18)*; WHO Evidence Network *(19)*; EBM guidelines: evidence-based medicine *(20)*.

Throughout this publication, ART refers to the use of triple combination ARV regimens primarily to improve quality of life and prolong life in children, adolescents and adults living with HIV. It should be distinguished from ARV prophylaxis for PMTCT, which refers to the use of ARV drugs solely for reducing the risk of such transmission.

IV. GUIDING PRINCIPLES

1. A public health approach for increasing access to PMTCT services

The prevention of HIV infection in infants and young children is an evolving area from both a scientific and programmatic standpoint. The public health approach proposed in these guidelines builds on previous and emerging scientific evidence and programmatic experience from low- as well as middle- and high-income countries. The main purpose of adopting a public health approach is 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-constrained settings.

PMTCT programmes should aim to deliver ART for pregnant women living with HIV who require treatment for their own health or, for those who do not yet require such therapy, to provide highly effective prophylactic treatment to prevent MTCT. To achieve this, recommendations for a public health approach are provided to assist countries in developing practical standardized protocols for ensuring the optimal use of scarce human and financial resources, simplified clinical and laboratory monitoring, sustainable programmes and the highest achievable effectiveness within existing constraints.

In the public health approach, PMTCT programmes are built around standardized regimens and simplified approaches suitable for the majority of women. This evidence-based standardization and simplification facilitates the expansion and management of programmes and training and the development of skills. Provision is also made for many specific circumstances which arise, for example for women with severe anaemia or co-infection with tuberculosis (TB) and HIV, or drug toxicity.

2. The WHO comprehensive strategic approach to the prevention of HIV infection in infants and young children

WHO promotes a comprehensive strategic approach to the prevention of HIV infection in infants and young children, consisting of four components:

1. primary prevention of HIV infection;
2. prevention of unintended pregnancies among women living with HIV;
3. prevention of HIV transmission from mothers living with HIV to their infants;
4. care, treatment and support for mothers living with HIV, their children and families *(12)*.

All four components must be implemented in order to optimize the effectiveness of programmes and reach the overall goal of improving maternal and child health (MCH) in the context of HIV. This comprehensive approach is built around the routine offer of HIV testing and counselling to

all pregnant women, ARV prophylaxis for PMTCT and counselling and support for infant feeding, and is underscored by ART, care and support for women living with HIV, their children and families (Annex 1). In this strategy, special attention is given to primary prevention services for women identified as HIV-negative (the majority of women in almost all settings) and strengthening linkages with other sexual and reproductive health services, particularly family planning. The provision of family planning counselling and services is especially important during the postpartum period for women living with HIV who choose not to breastfeed or who stop breastfeeding early as they have a shorter duration of lactational amenorrhea.

In many resource-constrained settings, PMTCT programmes have not paid adequate attention to services for women who test HIV-negative. These women require access to essential primary prevention services, especially during pregnancy and lactation, as both biological and behavioural factors may increase a woman's risk of acquiring HIV at this time *(21,22)*. Innovative approaches should be identified according to local epidemiological and socioeconomic contexts to address the prevention needs of these women and their partners.

The main focus of these guidelines is the last two components of the strategy. Other guidelines are available covering the first two components *(23,24)*.

3. Integrated delivery of interventions for PMTCT within maternal and child health services

Programmes to prevent HIV infection in infants and young children are a rallying point for enhanced care for women and children and an opportunity to strengthen related health systems. The aim of improving the quality of MCH services and integrating a set of key interventions to prevent MTCT into these services is to ensure that women (i) have greater access to high-quality antenatal, labour, delivery and postpartum care, including counselling and support for infant feeding, and (ii) use existing services more frequently and earlier in pregnancy than is currently the case.

The comprehensive strategic approach aims to respond to the wide range of health needs of women and their children and families. Within this approach, a set of key interventions to prevent MTCT need to be implemented as integral components of essential MCH services. HIV testing and counselling as the pivotal component of programmes to prevent MTCT is essential for identifying women who can benefit from ART and care either immediately or later, or benefit from interventions to prevent HIV infection in their infants. The effectiveness of such programmes is initially determined by the proportion of pregnant women who have an HIV test. The routine offer of HIV testing and counselling for all pregnant women – preferably as early in pregnancy as possible – should, therefore, now be considered an integral component of essential care during pregnancy. For those who miss this, HIV testing and counselling for women in labour or shortly after childbirth can also facilitate their entry into PMTCT services as well as other HIV prevention, treatment and

care services. In many resource-constrained settings, a substantial proportion of women present at the time of labour without having previously accessed HIV testing and counselling services. If conditions permit, HIV testing and counselling should, therefore, also now routinely be offered to all women in labour whose HIV status is unknown. Should this not be possible, testing and counselling can be provided shortly after delivery. Similarly, identification of women living with HIV in the postpartum period, preferably early on, also enables them to access HIV-related services and to receive counselling on infant feeding, with the aim of reducing the transmission of HIV to infants and young children. It is also necessary to integrate the routine offer of HIV testing and counselling into other health services attended by pregnant women and women of childbearing age, including services for well or sick children and clinics for family planning and for sexually transmitted infections (STIs). Rapid HIV testing with results available the same day is preferred; this reduces delay and increases the proportion of women who receive test results. Minimizing delay in obtaining test results is especially critical for HIV testing during labour or shortly after childbirth.

Women living with HIV require additional services during pregnancy, labour and delivery and the postpartum period. A woman's clinical stage and, where available, her CD4 cell count must be assessed in order to determine her eligibility for ART. CD4 cell counts form a critical link between antenatal care and ART services, especially for asymptomatic women. To ensure that all pregnant women who require ART are identified, efforts should be made to include the CD4 cell count measurement in the essential package of care for pregnant women. During pregnancy, women living with HIV require either ART or ARV prophylaxis for PMTCT (depending on whether they have indications for ART), cotrimoxazole prophylaxis (if they are eligible), screening for and treatment of TB infection, counselling and care relating to nutrition and psychosocial support. In areas with stable malaria, women living with HIV require access to insecticide-treated nets and effective case management of malaria illness as well as either intermittent preventive treatment with at least three doses of sulfadoxine-pyrimethamine or daily cotrimoxazole prophylaxis *(25)*. MCH services need to pay particular attention to safer delivery practices and counselling and support on infant feeding for women living with HIV.

A woman living with HIV may experience many emotional and social problems that affect her health and well-being. These can include concerns about disclosing her HIV status and difficulties in coping with uncertainty about the HIV status of her child. Thus in addition to short- and long-term medical care, women attending MCH services may require psychosocial support.

The increasing momentum created by access to treatment and care offers a crucial opportunity for strengthening prevention programmes. The creation of a link between prevention and treatment will increase the uptake of essential prevention services and ensure the long-term sustainability of care, treatment and support services. In addition to the moral and ethical imperatives, it is essential that new HIV infections in infants and adults are prevented to ensure that treatment and care services are not overwhelmed in the long run.

In sum, programmes to prevent MTCT must be implemented and scaled up both as important prevention interventions and as access points for care, treatment and support for women living with HIV, their children and families. For this to happen, interventions to prevent MTCT need to be integrated into MCH services and programmes for HIV treatment and care.

4. Women's health as the overarching priority in decisions about ARV treatment during pregnancy

For a pregnant woman with indications for ART, such treatment reduces maternal mortality and morbidity, is the most effective method of preventing MTCT of HIV and, by securing the health of the woman, 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 at an advanced stage of disease who has a higher risk of such transmission. In many settings, the survival of the mother is a strong predictor of the child's survival *(26,27)*. The progression of disease in or death of the mothers may undermine any improvement in survival of the infants following ARV prophylaxis for preventing MTCT.

For these reasons, but particularly for the woman's benefit, every effort should be made to ensure that all women who require ART have access to it. The primary purpose of ART in this situation is to improve and protect the health of the woman. Although the overarching consideration is the woman's health and ensuring that she receives optimal treatment, decisions about treatment for a woman of childbearing potential or who is pregnant also need to consider fetal well-being, the gestational age of the pregnancy and potential side-effects, particularly those related to pregnancy.

5. Necessity for highly effective ARV regimens for eliminating HIV infection in infants and young children

If the goal of eliminating HIV infection in infants and young children is to be achieved, all pregnant women eligible for ART must have access to it, and countries must adopt more efficacious ARV regimens for preventing MTCT among pregnant women who do not yet require ART. National programme managers are strongly encouraged to develop their capacity to implement the recommended regimen for preventing MTCT. This consists of: antepartum – azidothymidine (AZT) from 28 weeks of pregnancy (or as soon as possible thereafter); intrapartum – AZT and lamivudine (3TC) plus a single dose of nevirapine (Sd-NVP); and postpartum – AZT and 3TC for seven days for women and Sd-NVP and AZT for one week for infants. Widespread implementation of this regimen will dramatically reduce the number of new HIV infections in infants and young children and result in low levels of HIV viral resistance.

The length of the prophylactic regimen and optimum choice of drugs can vary depending on when a woman is identified as infected with HIV. HIV testing may have taken place before pregnancy or may occur at different times during pregnancy, at the time of labour and delivery, or postpartum. A PMTCT programme based on a regimen starting at 28 weeks of pregnancy requires that women attend antenatal care services early in pregnancy. Current recommendations do, however, take into account situations where women present later in pregnancy or around childbirth, including those women who deliver at home.

Operational contexts vary considerably between countries and even within a country. In settings that do not currently have the capacity to deliver the recommended prophylactic regimen to prevent MTCT, it may be necessary – as an absolute minimum – to implement the single-dose (mother and infant) NVP regimen. However in these circumstances, the specific obstacles to delivering more effective regimens should be identified and concrete action taken to overcome them. The expansion of PMTCT programmes using Sd-NVP should be considered a short-term interim measure while steps are being taken to enable more effective regimens to be delivered.

V. CLINICAL AND IMMUNOLOGICAL ASSESSMENT OF WOMEN IDENTIFIED AS HIV-INFECTED

The 2006 revised WHO adult guidelines *(15)* describe in detail the WHO recommendations for initiating ARV treatment among children, adolescents and adults living with HIV. The recommendations in this publication adhere to the principles set out in those guidelines and are consistent with the regimens recommended for first-line therapy. Similarly, the WHO adult guidelines take into consideration actual or potential pregnancies *(15)*. At country level, it is also necessary to harmonize guidelines for PMTCT and for ART for adults and children.

When a woman is identified with HIV, her clinical stage and, where available, her CD4 cell count must be assessed to determine whether she is eligible for ART. The WHO recommendations for a public health approach to ART emphasize the benefits of wider availability of CD4 testing to guide decisions about when to initiate ART as well as when to switch or salvage ART regimens. In resource-constrained settings, the criteria for initiating ART are based on WHO clinical staging criteria alone (where the CD4 cell count is not available) or on both WHO clinical staging plus the CD4 cell count (when the latter is available) (Table 2). Weight loss is one of the conditions used to determine clinical stage, but an assessment of weight loss during pregnancy can be difficult. 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.

Table 2. Recommendations for initiating ARV treatment in pregnant women based on clinical stage and availability of immunological markers[a]

WHO CLINICAL STAGE	CD4 TESTING NOT AVAILABLE	CD4 TESTING AVAILABLE
1	Do not treat **(Level A-III recommendation)**	Treat if CD4 cell count <200 cells/mm^3 **(Level A-III recommendation)**
2	Do not treat **(Level B-III recommendation)**	
3	Treat **(Level A-III recommendation)**	Treat if CD4 cell count <350 cells/mm^3 **(Level A-III recommendation)**
4	Treat **(Level A-III recommendation)**	Treat irrespective of CD4 cell count **(Level A-III recommendation)**

[a] Women have lower CD4 cell counts during pregnancy compared to postpartum, partly due to pregnancy-related haemodilution. The impact of this on using the CD4 350 threshold in pregnant women, especially in those in clinical stage 1 or 2, is not known.

The criteria for initiating ART for pregnant women are the same as for non-pregnant women, with the exception that initiation of such therapy is recommended for pregnant women who have clinical stage 3 disease and a CD4 cell count below 350 cells/mm^3 (Table 2). ART for pregnant women is therefore recommended for:

- all women in clinical stage 4 irrespective of the CD4 cell count;
- women in clinical stage 3, with the CD4 <350 cells/mm^3 count, if available; if the CD4 cell count is not available, all women in stage III should be treated;
- women in clinical stage I and 2 with a cell count of CD4 <200 cells/mm^3.

The main purpose of this recommendation is to address the health of the pregnant woman herself. The additional benefits of providing ART to this group of women are: (i) substantially reducing the risk of MTCT, and (ii) minimizing the consequences of resistance to NVP from the use of Sd-NVP-containing ARV prophylactic regimens for the prevention of MTCT.

The optimal time to initiate ART when the CD4 cell count is between 200 and 350 cells/mm^3 is unknown. There are accumulating data that if non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART is initiated in women less than six months following exposure to Sd-NVP, viral suppression may be compromised, and it is likely that many women with CD4 cell counts between 200 and 350 cells/mm^3 may need therapy to start within the first year postpartum. This justifies the start of ART in women in stage 3 with a CD4 count of between 200 and 350 cells/mm^3. Some experts suggest that ART should be considered for pregnant women with stage 1 or 2 and a CD4 count of <350 cells/mm^3, particularly for women with a CD4 cell count nearing the threshold of 200 cells/mm^3.

However, in pregnancy, haemodynamic changes occur in all women, whether or not they are living with HIV. Women have lower CD4 cell counts during pregnancy compared to the postpartum period, partly due to pregnancy-related haemodilution *(28–32)*. Thus, CD4 levels will rise after the end of pregnancy. The impact of this on using the CD4 350 cells/mm^3 threshold (determined during pregnancy) is not known. Further data are needed as to whether particular corrections need to be made. The CD4 cell percentage may be subject to less variation during and after pregnancy than the absolute count *(33)*. Until additional evidence becomes available, however, it is recommended that absolute CD4 cell counts continue to guide treatment decisions for pregnant women.

A woman living with HIV who has not begun ART prior to delivery requires continued HIV-related care and support in the postpartum period, including clinical and immunological assessments to determine when ART is needed for her own health. It is anticipated that these women will have access to ART in PMTCT programmes or, linked through well-functioning referral systems, in ART services.

VI. WOMEN WHO BECOME PREGNANT WHILE RECEIVING ARV TREATMENT

The overarching consideration for a woman receiving ART who becomes pregnant is her health and ensuring that she receives optimal treatment. Clinical decisions also need to take into account the gestational age of the pregnancy, the clinical findings and the regimen being used. The benefits of ART in this situation include a reduction in the risk of HIV transmission to infants.

When a pregnancy is recognized during the first trimester, the potential benefits and risks of ART for the health of the woman and the fetus (the risk of MTCT and in utero exposure to ARV drugs) should be considered. The risk of birth defects induced by ARV drugs has been assessed through the Antiretroviral Pregnancy Registry. Among prospectively followed pregnancies, the prevalence of birth defects in infants who were exposed to ARV drugs during the mother's pregnancy did not differ significantly from rates in the general population *(34)*. Concerns remain about efavirenz (EFV)-induced fetal effects, however, and EFV should only be used during the first trimester of pregnancy if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without any other therapeutic options. For women receiving EFV who become pregnant and this is recognized during the first trimester, it is recommended that NVP be substituted for EFV, or alternatively a triple nucleoside reverse transcriptase inhibitor (NRTI)- or a protease inhibitor (PI)-based regimen can be given. Although NVP-related symptomatic hepatotoxicity has primarily been observed in patients who are ARV-naïve when ART is started, if NVP is substituted for EFV then close monitoring is needed in the first 12 weeks of therapy for women who have established a good immune response to EFV-based treatment (e.g. a CD4 cell count >250 cells/m^3). Pharmacokinetic data indicate that when NVP is substituted for EFV, women should immediately commence NVP at 200 mg twice a day, as an escalation in the dose of NVP is associated with sub-therapeutic NVP levels in these individuals *(35)*.

Most women will not realize they are pregnant during this early period and if the patient is already in the second or third trimester when her pregnancy is recognized, EFV could be continued, given that the high-risk exposure has already occurred *(36,37)*. Based on current evidence of the extent of risk of EFV-induced fetal effects, exposure to EFV during pregnancy should not be viewed as an indication for abortion. It is important to note that an exaggerated perception of fetal risk can result in a woman terminating an otherwise wanted pregnancy *(38)*.

Although women who become pregnant while receiving EFV may consider temporarily suspending treatment, this is not recommended. Discontinuing treatment during pregnancy has been associated with viral rebound and renewed CD4 cell decline *(39)*, possibly compromising a woman's health and increasing the risk of MTCT. Further, data indicate that an interruption in treatment among adults receiving ART for their own health, who have a good immune response to ART, increases their risk for HIV-related disease *(40,41)*.

There are concerns about a potential association between exposure to tenofovir (TDF) in utero and abnormal fetal bone development. However, for women receiving TDF who become pregnant,

the benefits of continuing treatment are likely to exceed the theoretical risks of toxicity for the infant. Further safety data are awaited.

Pregnancy-associated nausea and vomiting may affect a woman's ability to adhere to ART and occasionally require that treatment be temporarily suspended. If nausea and vomiting are significant problems and not amenable to medication, a temporary suspension of treatment may be necessary until the symptoms are controlled.

The ARV dose for women during labour is likely to be especially important for reducing MTCT at this time. During labour, therefore, women receiving ART should continue to adhere to their ART regimen, whenever possible.

Key recommendations

- *For women who become pregnant while receiving an EFV-containing regimen and are in the first trimester of pregnancy, NVP should be substituted for EFV, with close monitoring of those women who have higher CD4 cell counts. Alternatively a triple NRTI- or PI-based regimen could be used* ***(Level A-IV recommendation).***
- *Women who are receiving EFV and are in the second or third trimester of pregnancy can continue the current regimen* ***(Level A-IV recommendation).***
- *Exposure to EFV during pregnancy is not an indication for abortion* ***(Level A-III recommendation).***
- *For women who become pregnant while receiving a TDF-containing regimen, the benefits of continuing the regimen are likely to outweigh the risks of toxicity for the infant and drug substitution is not recommended* ***(Level A-IV recommendation).***
- *Infants born to women who are receiving antiretroviral therapy should receive AZT for seven days* ***(Level A-IV recommendation).***

VII. PREGNANT WOMEN WITH INDICATIONS FOR ARV TREATMENT

ARV treatment for pregnant women not only addresses their health and well-being but also dramatically reduces the risk of MTCT, particularly for women who are at an advanced stage of disease. Treatment decisions for pregnant women should be based on their need and eligibility for ART. Additional consideration is needed of the well-being of the fetus, the gestational age of pregnancy and potential side-effects, particularly those related to pregnancy. The possibility of a future pregnancy should also be considered when selecting an ARV regimen for a pregnant woman. With more advanced disease and higher viral load, pregnant women who require ART are at the highest risk for MTCT and of developing resistance to NVP following Sd-NVP alone or in combination with AZT given as prophylaxis for PMTCT. For these women, the most effective method of preventing MTCT and eliminating the risk of resistance to NVP is to start fully suppressive ART. Women need to be informed and aware of the potential benefits and implications of beginning ART both for themselves and their fetuses.

When a pregnant woman is in need of ART according to the national guidelines, treatment should be started as soon as practicable even if she is in the first trimester of pregnancy. In some circumstances, delaying the start of treatment may be desirable for a woman in the first trimester of pregnancy, although should her clinical or immune status suggest that she is severely ill, the benefits of early treatment clearly outweigh any potential risks to the fetus and therapy should not be delayed in such cases.

The first-line ART regimens recommended for adults and adolescents are selected with consideration for their potency and side-effect profile, the potential for maintenance of future treatment options, anticipated adherence to them, the availability of fixed-dose combinations, co-existent health conditions (such as TB, hepatitis B virus or hepatitis C virus) and actual or potential pregnancy. From these first-line regimens, the recommended regimen for pregnant women is AZT + 3TC + NVP (Table 3).

Table 3. Recommended first-line ARV regimens for treating pregnant women[a] and prophylactic regimen for infants

Mother	
Antepartum	AZT + 3TC + NVP twice daily[b]
Intrapartum	AZT + 3TC + NVP twice daily
Postpartum	AZT + 3TC + NVP twice daily
Infant	AZT × 7 days[c]

[a] For alternative regimens see the 2006 revised WHO adult guidelines *(15)*.

[b] When NVP therapy is started, NVP should be given in half of the total daily dose once a day for 14 days (e.g. 200 mg once daily), with escalation to standard twice the daily dose (e.g. 200 mg twice daily) after 14 days if there are no side-effects.

[c] If the mother receives less than four weeks of ART during pregnancy, then four weeks, instead of one week, of infant AZT is recommended.

1. Nucleoside reverse transcriptase inhibitor-based treatments

The preferred NRTIs for pregnant women are AZT and 3TC. The safety of AZT for pregnant women and infants has been more extensively studied than other ARV drugs and it has been shown to reduce significantly the risk of MTCT. When ART is started during pregnancy, therefore, AZT should be included in the regimen whenever possible. Alternative NRTI drugs for use in pregnancy include ABC and stavudine (d4T).

Because of the lack of data on the use of TDF in pregnancy and concern regarding potential fetal bone effects, TDF should be considered as a component of initial ART for pregnant women when other alternatives are not available or are contraindicated.

2. Non-nucleoside reverse transcriptase inhibitor-based treatments

NVP is the NNRTI drug of choice for ART in pregnancy because of the substantial clinical experience gained among pregnant women and its efficacy in reducing MTCT. However, there are concerns about toxicity, including hepatitis, in women starting NVP-containing ART with a CD4 cell count between 250 and 350 cells/mm^3 (see section IX). There are a number of approaches to the treatment of pregnant women with a CD4 cell count in this range, including: initiation of an NVP-containing regimen with close monitoring in the first 12 weeks of therapy, as the benefit may outweigh the risk in this situation; starting an EFV-containing regimen if the woman is in the second or third trimester of pregnancy and effective contraception can be assured postpartum; or giving a triple NRTI- or a PI-based regimen. Each of these approaches has advantages and disadvantages (Table 4) and there are currently no data to favour one approach over the other.

Table 4. Approaches to selecting an ARV treatment regimen for pregnant women with a CD4 cell count between 250 and 350 cells/mm^3 who have indications for treatment[a]

APPROACH	ADVANTAGES	DISADVANTAGES
Begin NVP-based therapy with close observation over the first 12 weeks	• Reserves PI for second-line regimens • Consistent with standard recommendations	• Potential elevated risk of severe hepatic toxicity (extent of which is undefined for women with CD4 restricted to 250–350 cells/mm^3)
Begin EFV-based therapy if woman is in second or third trimester, and effective contraception can be assured postpartum	• Reserves PI for second-line regimens • Consistent with standard recommendations • Less risk of hepatic toxicity	• Potential risk of teratogenicity if subsequent pregnancy occurs
Begin triple NRTI therapy[b]	• Reserves PI for second-line regimens • Less risk of hepatic toxicity	• Studies suggest less potent than NNRTI-based regimens • Unknown safety in pregnancy for TDF
Begin PI-based therapy	• Less risk of hepatic toxicity	• No second-line treatment options exist
Delay three-drug therapy until the CD4 count drops below 250 cells/mm^3. Give short course AZT + Sd-NVP and AZT/3TC tail for prophylaxis against MTCT	• No risk of hepatic toxicity with Sd-NVP and minimal risk with short-course AZT	• Potential for development of NVP resistance • Risk of progression of disease, particularly if symptomatic

[a] The CD4 350 ceiling in pregnancy may represent a higher CD4 level postpartum because of pregnancy-induced haemodilution.

[b] Choice of regimens is AZT + 3TC + ABC or AZT + 3TC + TDF.

When NVP-containing ART is initiated in a pregnant woman with a CD4 cell count above 250 cells/mm^3, close monitoring of clinical symptoms and, where available, hepatic transaminases is recommended during the first 12 weeks of therapy. This includes informing the woman about symptoms for which she should seek care urgently (such as yellow eyes, skin rash, fever or abdominal pain); more frequent visits in the first weeks of therapy (e.g. every two weeks); and, if available, evaluation of liver enzymes at baseline and frequently in the first 12 weeks (e.g. 2, 4, 8 and 12 weeks) with symptom-directed evaluation thereafter. If liver enzymes increase to grade 3 or higher (alamine transaminase and/or aspartate transaminase >5 times the upper limit of normal) without an alternative explanation, NVP should be permanently discontinued and an alternative ARV drug substituted. Similarly, NVP should be substituted for if symptoms of hepatic toxicity develop, particularly if there is a rash.

During the first trimester of pregnancy EFV should only be used if the potential benefit justifies the potential risk to the fetus, such as in a pregnant woman without any other therapeutic options. EFV remains an option for the NNRTI component of a first-line regimen for pregnant women in the second or third trimester of pregnancy who cannot receive NVP (e.g. a pregnant woman with severe NVP toxicity or who has TB). Women who start EFV during pregnancy require family planning counselling and effective contraceptive methods in the postpartum period.

3. Women presenting late in pregnancy or during labour

Women with indications for ART who present very late in pregnancy should be started on ART, irrespective of the gestational age of the pregnancy. If however, it is not possible to begin treatment prior to delivery, ARV prophylaxis for PMTCT should be given while plans are made to start ART for the mother as soon as possible after delivery (see Table 5). If an NVP-containing prophylaxis regimen is used, women should, wherever possible, receive AZT and 3TC intrapartum, continued for seven days postpartum to reduce resistance. However, if only Sd-NVP is available it should be given.

During labour, women receiving ART should continue adhering to their ART regimen whenever possible and such therapy should be maintained postpartum.

4. Therapy for infants

The recommended regimen for infants is AZT for one week. If the mother receives less than four weeks of antenatal ART, then four weeks rather than one week of AZT is recommended for the infant. The recommendation for longer dosing of the infant when the mother has received only a short course of antenatal therapy is based on the Thailand HIV Perinatal Prevention Trial (PHPT-1), in which a regimen of AZT starting at 36 weeks of pregnancy and given to the infant for 4–6 weeks was superior to a regimen of AZT starting at 36 weeks gestation and given to the infant for 3 days *(42)*.

VIII. ARV PROPHYLAXIS FOR PREVENTING HIV INFECTION IN INFANTS

For the goal of eliminating HIV infection in infants and young children to be achieved, all pregnant women eligible for ART must be started on treatment, and pregnant women who do not yet need ART must be given highly effective ARV prophylaxis to prevent MTCT. Various ARV drugs, including NRTIs such as AZT and 3TC, and the NNRTI NVP, either alone or in combinations of two or three drugs, have been shown to reduce MTCT *(6,42–55)*. Over the years, trials have built on each other and a large number of ARV regimens have been evaluated (Annex 2). These regimens reduce the risk of MTCT by decreasing viral replication in the mother and through prophylaxis for the fetus and infant during and after exposure to the virus.

The first major breakthrough in the prevention of MTCT came in 1994 with the three-part Pediatric AIDS Clinical Trials Group (PACTG) 076 trial, which demonstrated that long-course AZT prophylaxis given early in pregnancy and intravenously during delivery to the mother and for six weeks to the infant dramatically reduced the risk of vertical transmission from 25% to 8% *(45)*. Although the PACTG 076 AZT regimen was rapidly introduced into practice in Europe and North America, it was costly and too complex for many parts of the world where there is a high prevalence of HIV. Shorter and simpler ARV regimens have thus been evaluated in trials in low- and middle-income countries. Almost all regimens evaluated to date include an intrapartum component and varying duration of antepartum and/or postpartum prophylaxis for the infant (and sometimes for the mother). These studies have been conducted in settings where antenatal care coverage is sometimes inadequate, a significant proportion of births are not attended by skilled health personnel, elective caesarean section is rarely carried out and nearly all infants are initially breastfed, with most continuing to be breastfed until at least six months of age and often into the second year of life. In the late 1990s, a study among non-breastfeeding women in Thailand *(52)* and two studies among breastfeeding populations in West Africa *(47,55)* found that AZT regimens begun late in pregnancy and given during labour either with no prophylaxis for the infants or with one week of prophylaxis for the mothers were effective in reducing MTCT. Following this, a number of trials evaluated whether a two-drug combination regimen, such as short-course AZT combined with 3TC, or an easier to implement simpler regimen such as Sd-NVP would be at least as effective as short-course AZT alone *(43,48)*. Several other clinical trials and open-label studies among non-breastfeeding as well as breastfeeding populations have confirmed the efficacy of various ARV regimens including AZT alone *(42,56)*, AZT + 3TC *(51,57,44)*, Sd-NVP *(51)* and, more recently, combinations of AZT + Sd-NVP *(9,46,40)*, or AZT and 3TC + Sd-NVP *(46)*.

Based on this evidence, recommendations for prophylactic ARV regimens for the prevention of MTCT using the public health approach are shown in Table 5.

Table 5. Recommended prophylactic ARV regimens for pregnant women who are not yet eligible for ART[a]

Mother	
Antepartum	AZT starting at 28 weeks of pregnancy or as soon as feasible thereafter
Intrapartum	Sd-NVP[b] + AZT/3TC[b]
Postpartum	AZT/3TC × 7 days[b]
Infant	Sd-NVP + AZT × 7 days[c]

[a] Alternative regimens for programmes with more limited infrastructure are shown in Table 6.

[b] If the woman receives at least four weeks of AZT during pregnancy, omission of the NVP dose may be considered for her. In this case, the NVP dose for the infant must be given immediately at birth, and four weeks instead of one week of AZT is recommended for the infant. If the NVP dose is not given to the mother, she will not require intrapartum 3TC as well as postpartum AZT and 3TC.

[c] If the mother receives less than four weeks of AZT during pregnancy, four weeks instead of one week of AZT is recommended for the infant.

Research in high-income countries has focused on more complex regimens and has shown that triple-ARV combinations given to women during pregnancy and labour can reduce the risk of transmission to under 2% *(5,6,58)*. These regimens are discontinued after childbirth for women without indications for ART. Since around 1998 *(5,59)*, triple-ARV combinations have increasingly been used to prevent MTCT; currently the majority of pregnant women living with HIV in Europe and North America receive such regimens *(5,60)*. In these settings and without breastfeeding, HIV infection in infants has been nearly eliminated. More recently, triple-ARV prophylactic regimens to prevent MTCT have been widely recommended and used in Brazil and other South American countries, with levels of effectiveness comparable to those observed in high-income countries *(4,61)*. In many high-income countries, however, PI-based or triple NRTI-based regimens rather than NVP-based regimens are now being used in women to whom drugs are being given solely for PMTCT, because of concern related to the increased risk of hepatotoxicity with chronic NVP therapy in women with higher CD4 cell counts (see section IX). In lower-income countries, the choice of drugs for such women is more problematic, as PI drugs are reserved for second-line therapy.

Countries with a high burden of HIV initially focused their efforts to prevent HIV infection in infants on reducing MTCT around the time of labour and delivery. More recently, building upon early experience, some of these countries have also begun to consider using ARV prophylactic regimens in the third trimester of pregnancy which, together with intrapartum and postpartum prophylaxis, can reduce the risk of transmission during pregnancy and childbirth to 2–4% *(8,9)*. Several projects and clinical studies in these settings have also evaluated the use of triple-ARV

prophylactic regimens *(62–66)*. However, to date it is unclear what additional benefit may be gained by implementing more complex, costly and intensive prophylactic regimens. Where ART is initiated in all pregnant women in need of treatment as recommended, triple-ARV prophylaxis in pregnant women for whom ART is not yet indicated might not bring significant additional benefit in reducing MTCT compared to use of the simpler and less costly AZT from 28 weeks of pregnancy plus Sd-NVP. In a study in Cote d'Ivoire, the administration of ART to women who met the WHO criteria for being started on therapy and short-course ARV prophylaxis, plus Sd-NVP to women who did not require therapy for their own health, resulted in MTCT rates of 2–4%. These did not significantly differ between groups *(66)*. Additionally, the use of the PI class of drug, which is reserved for second-line therapy, for prophylaxis for PMTCT may also be problematic. Further comparative data, especially in breastfeeding populations, are required before these can be considered for more general use.

In sum, short-term efficacy, as determined by the infant's infection status at 6–8 weeks of life, has been demonstrated for prophylactic ARV regimens comprising:

- AZT alone,
- AZT together with 3TC,
- NVP alone (single dose for mother and infant),
- AZT + Sd-NVP for mother and/or infant,
- AZT + 3TC plus Sd-NVP for mother and/or infant, or
- triple-ARV combination regimens.

Concerns remain that the development of viral resistance with increased use of partly suppressive ARV prophylaxis – especially regimens containing Sd-NVP – may have a negative impact on future ART options for women and infants who become infected. Accruing data suggest that the incidence of resistance may be decreased by giving dual NRTI drugs intrapartum and for a short period postpartum following Sd-NVP *(57,67,68)*. As NVP has a long half-life, with drug levels persisting for up to three weeks after women receive Sd-NVP, giving dual NRTI drugs for a period after exposure to Sd-NVP is expected to suppress viral replication and decrease the risk of developing resistance.

Despite limitations on comparing studies directly *(69)*, several conclusions can be made by drawing on existing evidence about the relative efficacy of ARV prophylaxis options. Longer regimens starting earlier in pregnancy are more efficacious than shorter regimens. A randomized four-group trial in a non-breastfeeding population in Thailand investigated the efficacy of AZT prophylaxis given for varying durations to pregnant women and infants *(42)*. Transmission was lower in the study group where AZT was given to women from 28 weeks of pregnancy and to

infants for six weeks (6.5%) compared with the study group in which women received AZT from 35 weeks of pregnancy and infants were given only three days AZT (10.5%). The study also showed that more prolonged ARV prophylaxis for the infant is not a substitute for longer duration of the component for the mother. Longer prophylaxis appeared beneficial for the infant, however, when the antenatal component for the mother was short (for example, starting at 35 weeks of pregnancy). Data from the meta-analysis of individual records of African studies also suggests longer regimens are more efficacious than shorter regimens. In this analysis, a combination of AZT and 3TC initiated at 36 weeks of pregnancy was significantly more efficacious than the same combination started during labour *(70)*.

In general, combination regimens are more efficacious than single-drug regimens. A meta-analysis of an individual record *(70)* of data from several African MTCT-prevention trials indicated that the combination of AZT and 3TC from 36 weeks of pregnancy had greater efficacy in preventing MTCT than ARV monotherapy with either AZT from 36 weeks of pregnancy or Sd-NVP. Studies in high-income countries also indicate that a combination of ARV drugs is more efficacious than single-drug regimens *(50)*. In a cohort study in the United States, the risk of MTCT was 10.4% among women receiving AZT monotherapy, 3.8% among those receiving dual ARV regimens and 1.2% in women receiving triple-ARV regimens *(58)*.

Studies in Botswana, Côte d'Ivoire and Thailand have assessed the efficacy of adding Sd-NVP to an AZT regimen given to the mother antepartum for varying durations as well as intrapartum, and postpartum to the infant *(8,9,46,63)*. These studies have shown that this regimen is highly efficacious and achieves lower rates of MTCT than with either AZT or Sd-NVP alone. The risk of MTCT in the PHPT-2 trial in a non-breastfeeding population in Thailand, in which women were given AZT from 28 weeks of pregnancy and Sd-NVP and AZT during labour, and infants received Sd-NVP + AZT for one week, was about 2%, similar to transmission rates achieved with the use of triple-ARV regimens *(9)*.

A study in Botswana suggests that Sd-NVP for the mother may be omitted if she receives at least four weeks of AZT during pregnancy and the infant is given Sd-NVP immediately after birth plus AZT for four weeks *(8)*. While this option removes the risk of mothers developing resistance to NVP, further evidence is needed to clarify the relative importance of Sd-NVP for mother and infant in the context of short-course AZT regimens.

Among breastfeeding women, the long-term efficacy of ARV prophylactic regimens is diminished due to the risk of postpartum transmission throughout the breastfeeding period. Long-term efficacy in breastfeeding women, as determined by the child's infection status at 18–24 months of age (which accounts for the continued risk of acquiring HIV infection during the breastfeeding period) has been confirmed, although it is reduced for short-course AZT *(71)*, single-dose NVP for mothers and infants *(49)*, and for a combination of AZT and 3TC from 36 weeks of pregnancy

(43). Although direct comparisons between studies are difficult, the decrease in long-term efficacy in breastfeeding women appears more marked with short-course AZT and combined AZT and 3TC regimens than with Sd-NVP. Where breastfeeding is common, it is particularly important to include Sd-NVP as a component of prophylactic regimens to prevent MTCT because the long half-life of NVP prevents early postnatal transmission through breast milk, a significant component of postnatal transmission. This effect is not observed with AZT prophylaxis *(72,73)*.

1. ARV prophylactic regimens for preventing HIV infection in infants among women seen during pregnancy

The recommended ARV regimen for preventing MTCT among women who do not have indications for ART consists of: antepartum – AZT from 28 weeks of pregnancy or as soon as possible thereafter; intrapartum – AZT and 3TC + Sd-NVP; and postpartum – AZT and 3TC for seven days for women, and for infants Sd-NVP and one week of AZT (Table 5). Widespread implementation of this regimen will dramatically reduce the number of new HIV infections in infants and young children and result in low levels of HIV viral resistance.

Where adequate capacity exists, national programmes are strongly encouraged to adopt and implement the recommended ARV regimen for PMTCT. Operational contexts vary considerably between countries and even within a country. In some settings additional inputs may be necessary to develop capacity to implement this regimen. Where capacity is very limited, it may be necessary – as an absolute minimum – to implement the single-dose regimen for mothers and infants. However, in these circumstances, the specific obstacles to delivering more effective regimens should be identified and action taken to address them. The expansion of PMTCT programmes using Sd-NVP should be considered a temporary and interim measure while steps are being taken to enable more effective regimens to be delivered.

The recommended AZT regimen is initiated at 28 weeks of pregnancy. If this is not possible, AZT should be started as soon as feasible thereafter. Several studies have shown that starting AZT later in pregnancy is also efficacious and may be necessary for women presenting for antenatal care late in pregnancy *(8,46)*. AZT and 3TC given to women intrapartum and for seven days postpartum is recommended to reduce viral drug resistance when Sd-NVP is given either alone or in combination with AZT. In some studies AZT was administered every three hours during labour; in others a double dose (600 mg) was given at the onset of labour. Although these regimens have not been directly compared, they result in a similar reduction in HIV transmission rates. The double-dose regimen at the onset of labour may be more practical and preferred for wide-scale implementation. Although data on the use of AZT and 3TC for mothers intrapartum and postpartum to reduce resistance were obtained from the use of Sd-NVP alone *(57)*, it is reasonable to assume the same regimen may reduce resistance to NVP when Sd-NVP is given together with short-course AZT. Although administration of AZT/3TC alone can be associated with the development

of resistance to 3TC, this would be unlikely with limited exposure (seven days), whereas resistance may be seen in up to 40% of women who receive AZT/3TC for four weeks or more *(50,74)*. Thus, although the NVP drug levels can persist in some women for up to 21 days, for prevention of resistance to NVP following Sd-NVP the seven-day postpartum tail AZT/3TC is recommended to avoid inducing a resistance to 3TC that might occur with a longer postpartum tail.

Omission of the NVP dose for the mother may be considered if she has received AZT for at least four weeks during her pregnancy. If the NVP dose is not given to the mother, or delivery occurs less than two hours after she is given the labour dose, the infant must receive Sd-NVP immediately after birth and be given AZT for four weeks instead of one week *(8,75,76)*. If the NVP dose is not given to the mother, she must be given AZT intrapartum but she will not require 3TC intrapartum or the AZT and 3TC regimen postpartum. Thus, avoiding the NVP dose for the mother removes the risk of her becoming resistant to NVP but increases the overall complexity of the prophylactic regimen, which needs to be considered when programme decisions are made.

In settings without adequate capacity to deliver the recommended regimen, it may be necessary to use other regimens (Table 6). Programme managers may opt to administer a regimen of AZT from 28 weeks of pregnancy and intrapartum, and for seven days to the infant plus Sd-NVP, without the seven-day tail of AZT/3TC. However, while this regimen is still as effective as the combination of AZT and Sd-NVP plus the seven-day tail of 3TC, it is associated with a higher risk of resistance to NVP. In circumstances where the infrastructure does not allow for longer antepartum regimens to be implemented, Sd-NVP can be given to prevent MTCT. Sd-NVP is an effective regimen, reducing transmission by over 40% *(48,49)*, but it is less effective than the recommended regimen. If Sd-NVP is used, it is better if possible to include AZT and 3TC given intrapartum and for seven days to the woman because this reduces resistance *(57)*. AZT and 3TC are available in a fixed-dose combination, simplifying administration even in sites with limited infrastructure. If the infrastructure does not permit the AZT and 3TC component to be given to the mother, Sd-NVP alone should be administered.

Although several ARV regimens for infants have been studied using different durations of either single or combined drugs, it is still not known which regimen achieves the largest reduction in MTCT, and the optimal regimen for an infant may depend on the ARV regimen that the mother received. Although the NVP dose can be given to the infant up to 72 hours after childbirth, administering it immediately after childbirth is preferable and many PMTCT programmes have found this more practical.

If a woman is given AZT and Sd-NVP but receives less than four weeks of AZT during pregnancy, the AZT prophylactic regimen for the infant should be increased from one to four weeks. This is ased on a trial in Thailand in which women received AZT from 35 weeks of pregnancy and the risk of HIV infection was lower in infants given AZT for six weeks than in infants given it for three days *(42)*.

In programmes where it is only possible to administer Sd-NVP, the addition of AZT for the infant is not recommended for programme purposes. Sd-NVP would only be given in places with limited infrastructure. The administration of additional drugs to the infant other than Sd-NVP requires the availability of education for the mother plus a liquid preparation, which may not be available. Further, as shown in a trial in Malawi when the woman and infant both received Sd-NVP, the addition of AZT for one week to the infant did not provide any additional efficacy over that seen with Sd-NVP alone *(77)*.

While the giving of AZT or AZT/3TC for one week to infants who receive Sd-NVP may reduce the risk of resistance to NVP in infants who become infected *(57,78)*, it is also not being recommended for programme purposes. In addition to the reasons given above, there is no fixed-dose preparation of AZT and 3TC for infants and the infant would therefore have to receive three separate drugs, complicating administration. Additionally, in contrast to the giving of an AZT/3TC tail to women who receive Sd-NVP, all of whom are infected and at risk of becoming resistant to NVP, the majority of infants who would be exposed to the drugs would not be infected and hence not at risk of developing such resistance.

Key recommendations

- *Programmes for the prevention of MTCT are strongly encouraged to implement the recommended ARV regimen for preventing such transmission among women who do not have indications for ART, consisting of AZT starting from 28 weeks of pregnancy (or as soon as possible thereafter); AZT and 3TC + Sd-NVP intrapartum; and AZT and 3TC postpartum for seven days for women, and for infants Sd-NVP and AZT for one week* ***(Level A-I recommendation)****.*
- *Omission of the NVP dose for the mother may be considered for women who receive at least four weeks of AZT before delivery (Level C-I recommendation).*
- *The NVP dose can be given to an infant up to 72 hours after childbirth but should preferably be given as soon as possible after delivery* ***(Level A-II recommendation)****.*
- *If the mother receives less than four weeks of AZT before delivery, the AZT dose for the infant should be extended to four weeks* ***(Level A-I recommendation)****.*
- *When Sd-NVP is used to prevent MTCT, either alone or in combination with AZT, women should be given AZT and 3TC intrapartum and for seven days postpartum to prevent resistance to NVP* ***(Level A-I recommendation)****.*
- *When delivery occurs within two hours of a woman taking Sd-NVP, the infant should receive Sd-NVP immediately after delivery and AZT for four weeks* ***(Level A-I recommendation)****.*

2. Women living with HIV who are in labour and who have not received ARV prophylaxis

Several ARV regimens given during labour and postpartum have been shown to have an impact in reducing MTCT. The meta-analysis of individual records *(70)* of data from African MTCT prevention trials indicated that a combination of AZT and 3TC started during labour has similar efficacy to Sd-NVP in preventing MTCT. ARV prophylaxis regimens and the advantages and disadvantages of each regimen are outlined in Table 7.

Many women in these circumstances may only have been identified as being HIV-infected during labour. Particular efforts are needed to ensure that they receive HIV-related services, including clinical and immunological assessments to determine their eligibility for ART as part of postpartum follow-up services.

The recommended ARV regimen for preventing MTCT among women in labour who have not received antenatal ARV prophylaxis consists of Sd-NVP + AZT and 3TC intrapartum, and a seven-day tail of AZT + 3TC for the mother, and for the infant Sd-NVP and AZT for four weeks (Table 7). The recommendation to add four weeks of AZT for the infant to Sd-NVP is based on extrapolation from a Thai study *(42)* that demonstrated that longer prophylaxis was more effective than shorter for the infant if the mother had received antepartum therapy for less than four weeks. Because in this situation the mother receives no antepartum therapy, and even though data on added efficacy are limited, it is recommended that the infant is given AZT for four weeks as the preferred component of the regimen, when possible.

An alternative regimen would be AZT intrapartum for the mother, and 3TC + AZT and 3TC postpartum for one week for both mother and infant. This intrapartum/postpartum regimen was shown to be effective in reducing transmission and to have equivalent early efficacy to Sd-NVP alone in the South African Intrapartum NVP Trial (SAINT) *(43,51)*. In programmes without an adequate capacity to deliver the recommended regimen, Sd-NVP alone should be administered (Table 7).

Key recommendations

- *The recommended regimen for women living with HIV who are in labour and who have not yet received ARV drugs is: intrapartum – Sd-NVP + AZT and 3TC; postpartum – AZT and 3TC given to the woman for seven days, plus for the infant Sd-NVP immediately after delivery and AZT for four weeks.* ***(Level A-I recommendation)****.*
- *If delivery is expected imminently, the NVP dose for the mother should be omitted, and the same recommendations and considerations apply as for infants born to women living with HIV who do not receive antenatal or intrapartum ARV prophylaxis.* ***(Level A-II recommendation)****.*
- *When delivery occurs within two hours of the woman taking NVP, the infant should receive Sd-NVP immediately after delivery and AZT for four weeks.* ***(Level A-I recommendation)****.*

3. Infants born to women living with HIV who have not received ARV drugs during pregnancy or labour

The efficacy of infant-only regimens was evaluated in a South African trial which compared Sd-NVP with six weeks of AZT in infants *(73)*. No difference was detected in cumulative transmission at 12 weeks of age. However, a clinical trial in Malawi has shown that if the mother does not receive any ARV drugs, then Sd-NVP and AZT given to the infant for one week is more efficacious than Sd-NVP alone *(53)*. Further, based on the Thai study referred to above, a regimen consisting of Sd-NVP and AZT for four weeks for the infant is likely to be more effective than Sd-NVP and one week of AZT, although the data on the additional efficacy of four weeks compared to one week of AZT in this situation are limited (see Table 8).

The recommended regimen for prophylaxis for the infant when the mother has not received any ARV prophylaxis is Sd-NVP plus four weeks of AZT, when possible. In programmes without adequate capacity to deliver the recommended regimen, Sd-NVP with one week of AZT or Sd-NVP alone should be administered.

For infants born to women living with HIV who do not receive any ARV prophylaxis, the administration of ARV drugs to infants immediately after delivery solely for post-exposure prophylaxis is likely to result in a larger reduction in transmission than giving the drugs later. When feasible, ARV prophylaxis should be initiated for the infant as soon as he or she can tolerate oral feeding and within 12 hours following delivery. If ARV prophylaxis is delayed for more than two days, it is unlikely to have any benefit.

Key recommendations

- *Sd-NVP immediately after delivery and AZT for four weeks are recommended for infants born to women living with HIV who do not receive any ARV prophylaxis, because this regimen results in a greater reduction in transmission than just Sd-NVP for the infant.* ***(Level A-III recommendation)****.*
- *ARV prophylaxis for infants born to women living with HIV who had not received antenatal or intrapartum ARV prophylaxis should begin immediately after delivery or within 12 hours after delivery, if possible.* ***(Level A-III recommendation)****.*

Table 6. Different approaches to the use of ARV prophylaxis to prevent HIV infection in infants

RANKING	TIME OF ADMINISTRATION			ADVANTAGES	DISADVANTAGES
	PREGNANCY	LABOUR	POSTPARTUM		
Recommended	AZT (≥28 weeks gestation)	Sd-NVP[a] + AZT/3TC	***Mother:*** AZT/3TC × 7 days[a] ***Infant:*** Sd-NVP[a] + AZT × 7 days[b]	• Highly effective regimen • Substantially reduces in utero and intrapartum transmission • The AZT/3TC tail given to the mother reduces the development of her becoming resistant to NVP • AZT given to infants reduces the risk of resistance to NVP in those who become infected	• Longer and more complex than other regimens
Alternative	AZT (≥28 weeks gestation)	Sd-NVP	***Infant:*** Sd-NVP + AZT × 7days[b]	• Highly effective regimen • Substantially reduces in utero and intrapartum transmission • AZT given to infants reduces the risk of resistance to NVP in those who become infected	• High risk of resistance to NVP • Probable sub-optimal viral response if NNRTI-ART is initiated in women within 6 months of childbirth

Minimum	–	Sd-NVP + AZT/3TC	***Mother:*** AZT/3TC × 7 days ***Infant:*** Sd-NVP	• Effective in reducing MTCT • The AZT/3TC tail given to the mother reduces the development of her becoming resistant to NVP	• Less effective than recommended regimen • Does not reduce in utero transmission • More complex to deliver than Sd-NVP alone
Minimum	–	Sd-NVP	***Infant:*** Sd-NVP	• Effective in reducing MTCT • Simplest regimen to administer	• Less effective than recommended regimen • Does not reduce in utero transmission • High risk of resistance to NVP • Probable sub-optimal viral response if NNRTI-ART is initiated in women within 6 months of childbirth

Note: for doses see Annex 3.

[a] If the woman receives at least four weeks of AZT during pregnancy, omission of the NVP dose for mothers may be considered. In this case the NVP dose must be given to the infant immediately after birth, AZT is recommended for four weeks instead of one week, and the mother will not require 3TC during labour as well as AZT and 3TC postpartum.

[b] If the mother receives less than four weeks of AZT during pregnancy, AZT is recommended for four weeks instead of one week.

Table 7. ARV prophylaxis regimens for PMTCT among pregnant women living with HIV who have not received antepartum therapy or prophylaxis

RANKING	TIME OF ADMINISTRATION		ADVANTAGES	DISADVANTAGES
	LABOUR	**POSTPARTUM**		
Recommended	Sd-NVP + AZT/3TC	***Mother***: AZT/3TC × 7 days Infant: Sd-NVP + AZT × 4 weeks[a]	• Sd-NVP is effective in reducing MTCT • The AZT/3TC tail given to the mother reduces the development of her becoming resistant to NVP • In breastfeeding women, NVP-based regimen may be advantageous in reducing early postpartum transmission • Consistent with recommended regimen for PMTCT when mother receives antepartum prophylaxis • AZT given to infants reduces the risk of resistance to NVP in those who become infected	• More complex to deliver than Sd-NVP alone
Alternative	AZT/3TC	***Mother:*** AZT/3TC × 7 days Infant: AZT/3TC × 7 days	• Equivalent efficacy to Sd-NVP alone intrapartum/postpartum • No risk of resistance to NVP in women or infants should they become infected	• More complex to deliver than Sd-NVP alone

Minimum	Sd-NVP + AZT/3TC	***Mother:*** AZT/3TC × 7 days Infant: Sd-NVP[a]	• Sd-NVP is effective in reducing MTCT • The AZT/3TC tail given to the mother reduces the development of resistance to NVP	• More complex to deliver than Sd-NVP
Minimum	Sd-NVP	***Infant:*** Sd-NVP	• Single-dose NVP is effective in reducing MTCT • Simplest regimen to administer	• High risk of resistance to NVP, with sub-optimal viral response if NNRTI-based ART is initiated in women within 6 months of childbirth

Note: for doses see Annex 3.

[a] Data on added efficacy of four weeks of infant AZT in this situation are limited.

Table 8. ARV prophylaxis regimens for infants born to women living with HIV who have not received antepartum or intrapartum therapy or prophylaxis

RANKING	POSTPARTUM	ADVANTAGES	DISADVANTAGES
Recommended	***Infant:*** Sd-NVP immediately after birth + AZT × 4 weeks[a]	• Sd-NVP + AZT given to the infant is more effective in reducing MTCT than just Sd-NVP • Consistent with recommended regimen for PMTCT when mother receives antepartum or intrapartum prophylaxis • AZT given to the infant reduces his/her risk of becoming resistant to NVP	• More complex to deliver than Sd-NVP alone
Alternative	***Infant:*** Sd-NVP immediately after birth + AZT × 1 week	• Clinical trial data demonstrate that Sd-NVP + AZT for one week given to the infant is more effective in reducing MTCT than just Sd-NVP • AZT given to the infant reduces his/her risk of becoming resistant to NVP	• More complex to deliver than Sd-NVP alone
Minimum	***Infant:*** Sd-NVP immediately after birth	• Prophylaxis with Sd-NVP for the infant is equivalent to six weeks of AZT • Simplest regimen to administer	• Risk of resistance to NVP in infants who become infected despite NVP prophylaxis

Note: for doses see Annex 3.

[a] NVP administered immediately after birth, if possible within 12 hours after delivery, is likely to result in a larger reduction in transmission than starting it later. Data on added efficacy of four weeks of AZT for infants in this situation are limited.

IX. SAFETY OF ANTIRETROVIRAL DRUGS FOR PREGNANT WOMEN AND THEIR INFANTS

ARV drugs may be used during pregnancy as part of a triple-combination regimen for a woman who requires treatment for her own health or as short-term ARV prophylaxis given to a woman and/or her infant to prevent MTCT. Pregnancy and breastfeeding raise additional issues regarding the prevention of HIV transmission to infants and of toxicity for the woman and child which can affect ARV drug selection, but these concerns should be dealt with in the context of ensuring optimal treatment to preserve the woman's health. All ARV drugs are known to be associated with some toxicity, which may be transient or longer-term and may potentially affect both the woman and the child. For a woman receiving ART, the benefits of the drugs include reducing the risk of progression of her disease and death as well as preventing MTCT. When ARV drugs are used to prevent MTCT, the potential risk of exposure of the woman and infant to one or more drugs for a limited period of time must be weighed against the benefit of preventing such transmission.

The extent of risk for the pregnant woman, fetus and infant from ART or prophylaxis varies according to the timing and duration of exposure and the number of drugs to which the woman and infant are exposed. Further, physiological changes that occur during pregnancy may affect the absorption, distribution, metabolism and elimination of drugs, making it difficult to predict the ARV pharmacokinetics.

1. Safety of ARV drugs for treating pregnant women

The WHO adult guidelines *(15)* contain a more detailed discussion of toxicities of ARV drugs for non-pregnant individuals. This section specifically addresses safety issues related to pregnancy.

1.1. Nucleoside and nucleotide analogue reverse transcriptase inhibitors

The NRTI drugs with which the most extensive clinical experience has been gained in pregnant women are AZT and 3TC, and these are the preferred NRTIs for pregnant women. Alternative NRTI drugs for first-line ART regimens are ABC, d4T and emtricitabine (FTC). Pharmacokinetic studies among pregnant women indicate that no dosing adjustments are required for AZT, 3TC, ABC and d4T *(79–81)*. Data on the use of FTC in pregnancy are limited, although data on 3TC, a structurally similar drug, suggest that standard dosing is adequate.

The major toxicity of AZT is haematological (anaemia and neutropenia). Thus, in pregnant women with severe anaemia (haemoglobin <7 g/dl), the use of other NRTI drugs such as d4T or ABC should be considered. So far only minimal experience has been gained with the use in pregnancy of TDF, a nucleotide analogue drug which is included as a possible option for first-line ART regimens in adults. Studies in infant monkeys exposed in utero to TDF have shown decreased fetal growth and a reduction in fetal bone porosity within two months of the mother starting therapy *(82,83)*. Bone demineralization has been observed in some studies of infected children

receiving chronic TDF-based therapy but not in others *(84–86)*. The clinical significance of these findings for children exposed to TDF in utero is unknown but is currently being evaluated.

A woman may be given didanosine (ddI) in second-line ART regimens. Studies with this drug in pregnant women suggest that the dosage does not need to be modified during pregnancy *(87)*. However, there have been several case reports of lactic acidosis among pregnant women receiving ddI in combination with d4T, some resulting in the death of the mother and, in some cases, the fetus. All the women had received this combination prior to conception and continued during pregnancy, and all presented with symptoms of lactic acidosis late in pregnancy *(88,89)*.

A sufficient number of prospectively followed pregnancies with first trimester exposures have been monitored to detect a one and a half-fold increase in overall risk for birth defects with exposure to AZT and 3TC and a two-fold increase in overall risk with ABC *(34)*. No such increases have been detected. Birth defects were observed in 13 out of 205 (6.3%) live-born infants following first-trimester exposure to ddI compared with 2 out of 190 (1.1%) infants exposed to ddI later in the pregnancy *(34)*. Although no pattern of birth defects was noted, continued monitoring of rates and types of defect is needed.

1.2. Non-nucleoside analogue reverse transcriptase inhibitors

NVP is the NNRTI drug of choice for ART in pregnancy because of substantial clinical experience with pregnant women and its proven efficacy in reducing MTCT *(49,51)*. The most frequent adverse effects of NVP are hepatotoxicity and cutaneous rash. Although uncommon, symptomatic hepatic or serious cutaneous toxicity with chronic NVP therapy is more frequent in women than in men and most often occurs during the first 6–12 weeks of therapy. It is likely that hepatic toxicity is in part an immune-mediated phenomenon, as it is more common in women who are started on NVP-based ART when they have a CD4 cell count greater than 250 cells/mm^3 and in men with a count greater than 400 cells/mm^3 *(90–93)*. In an analysis of several studies in the United States that included approximately 600 women with a range of CD4 cell counts, symptomatic hepatic toxicity was observed in about 10% and fatal hepatic toxicity in 0.7% of women with a CD4 cell count above 250 cells/mm^3 at the time NVP was begun, compared with 1–2% symptomatic hepatitis, and no cases of fatal hepatic toxicity were seen in women with a CD4 cell count below 250 cells/mm^3 *(91,93)*. Although cases have been reported in pregnant women, it is not known whether pregnancy further predisposes women to these toxicities *(94–96)*.

There are concerns about initiating NVP-containing ART in women with a CD4 cell count in the range 250–350 cells/mm^3. This situation may arise as ART is recommended for pregnant women who have a CD4 cell count of less than 350 cells/mm^3 and WHO clinical stage 3 disease. The exact risk of NVP-associated symptomatic hepatitis or fatal hepatitis for women in this CD4 cell count range is unclear, as data have only been presented for toxicity in approximately

200 women with CD4 cell counts in the range 250–399/mm^3 in high-income countries. Fatal symptomatic hepatitis was observed in 0.4% of women with a CD4 cell count in this range; in contrast, mortality was highest (1.1%) in women with a CD4 cell count greater than 400 cells/mm^3. In published reports of chronic NVP toxicity that include data on CD4 cell count, many (although not all) women with symptomatic or fatal hepatic toxicity had a CD4 cell count above 350/mm^3. It is likely that there is a gradient of toxicity risk in women with a CD4 cell count higher than 250/mm^3, with the greatest risk in women with a higher CD4 cell count and more normal immune status, as observed in women without HIV infection who received NVP-based post-exposure prophylaxis *(97,98)*.

Some studies in resource-constrained settings, predominantly among pregnant women, have suggested that the risk of NVP-related hepatic toxicity is lower than reported in high-income countries. These studies have reported grade 3 or 4 elevations in hepatic enzymes in about 4% to 7% of women with a range of CD4 cell counts *(62,63,65,99,100)*. By contrast, however, one study in South Africa found higher rates of symptomatic, severe hepatic toxicity in non-pregnant women in a trial where the CD4 cell count had to be higher than 200 cells/mm^3 on entry into the study (the median CD4 cell count in patients with early hepatotoxicity was 406 cells/mm^3) *(101)*. Data on women receiving NVP in resource-constrained settings remain relatively limited and there is a pressing need for better information about NVP toxicity in these settings.

Data from the Antiretroviral Pregnancy Registry have not detected any increase in the overall risk of birth defects following first-trimester exposure to NVP *(34)*. However, there are concerns that EFV (the alternative NNRTI for first-line therapy) increases the risk of birth defects. Significant malformations (anencephaly, anophthalmia, cleft palate) have been observed in infant monkeys with in utero exposure to EFV at drug levels similar to therapeutic ranges in humans *(102)*. However, the predictive value of animal studies for humans is unknown, making it difficult to translate animal risks into an assessment of teratogenic risk in humans. Thus far in humans, four retrospective cases have been reported of central nervous system defects in infants exposed in the first trimester to EFV (three infants with meningomyelocele and one with a Dandy-Walker malformation) *(103–105)*.

In a prospective pregnancy registry, where women are enrolled before the outcome of pregnancy is known and prior to tests such as antenatal ultrasound, birth defects were observed in 5 out of 228 (2.2%; 95% confidence interval: 0.7–5.1%) live-born infants following first-trimester exposure to EFV *(34)*. None of the prospectively reported anomalies in this study were similar to those in the animal trial or the case reports. A sufficient number of live births have been monitored to detect a two-fold increase in overall risk for birth defects following first-trimester exposure to EFV; no such increase has been detected *(106)*. However, larger studies are required to evaluate the risk for specific congenital anomalies such as neural tube defects, as current prospective studies have inadequate power to draw conclusions about these risks *(107)*.

EFV is classified by the United States Food and Drug Administration as a Category D drug: "Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks." *(103)*. Thus, EFV is not recommended for women with childbearing potential unless effective contraception can be assured. EFV remains a viable option for the NNRTI component of a first-line regimen in women with childbearing potential for whom effective contraception can be assured or pregnant women in the second or third trimester who cannot receive NVP (e.g. a pregnant woman with severe NVP toxicity or who has TB). When an EFV-based regimen is started in a woman with childbearing potential, she should not become pregnant before she begins ART.

Women who are receiving ART containing EFV require access to effective contraceptive methods to reduce the likelihood of unintended pregnancy. Follow-up counselling and support for effective contraception may be necessary. In a recent study among 548 women receiving EFV in Côte d'Ivoire, with family planning counselling and use of hormonal contraception the annual incidence of pregnancy was 2.6% *(108)*.

1.3. Protease-inhibitor drugs

Recommendations regarding second-line therapy in pregnant women are complicated by more limited experience with PIs in pregnancy. The PIs that have yielded the most experience and safety data in pregnancy are SQV/r and nelfinavir (NFV) *(109,110)*. No dosing adjustment is necessary with SQV/r during pregnancy *(109)*. While standard dosing of NFV (1250 mg twice daily) has been shown to produce acceptable drug levels in pregnant women, a number of studies have suggested that NFV levels are highly variable during pregnancy *(111–113)*. Some data suggest that drug levels of the capsule formulation of lopinavir with a ritonavir boost (LPV/r) may be lower in pregnant women during the third trimester than postpartum *(114,115)*; however, another study showed adequate plasma levels in the majority of women with standard dosing *(116)*. There are no data on drug levels of the heat-stable LPV/r tablet drug formulation in pregnancy; until further data are available, standard doses of this formulation can be given. Drug levels of indinavir (IDV) are lower during pregnancy than postpartum *(112,117)*, but limited data suggest that IDV with low dose ritonavir boosting may result in adequate levels *(118)*. There are no data on atazanavir with a ritonavir boost (ATV/r) or fosamprenavir with a ritonavir boost (fos-APV/r) in pregnant women, and until more data are available, these drugs should only be used if no alternative is available.

There are conflicting data regarding the potential effects of PI-based ART during pregnancy on pregnancy outcomes. Some studies have suggested an increased risk of preterm delivery in pregnant women receiving PIs during pregnancy, while other studies have not reported this *(110,119–122)*. There are very few data on risks associated with the use of ART during pregnancy in resource-constrained settings. Observational studies from Cote d'Ivoire and Thailand found similar rates

of preterm delivery between women given ART and those receiving single- or dual-drug ARV prophylaxis regimens *(63,66)*. Although initial data suggested that the use of PIs in pregnancy might be associated with increased risk of gestational hyperglycemia or diabetes, more recent studies have not shown the use of PIs to be associated with higher risk. Some data suggest that women living with HIV may have a higher rate of gestational diabetes than those without HIV infection *(123,124)*. There is also conflicting information about the relationship of PI use in pregnancy and pre-eclampsia *(124–126)*. For women who require second-line therapy and either become pregnant while receiving PI-based therapy or need to change drugs during pregnancy, the benefits of therapy to the mother outweigh the theoretical risks of an adverse pregnancy outcome, and therapy should be initiated or continued as needed. A sufficient number of first trimester exposures to NFV and RTV have been monitored to detect at least a two-fold increase in the risk of overall birth defects; no such increase has been detected to date *(34)*. Not enough pregnancies have been followed to make any observations with other PI drugs.

1.4. Long-term effects of exposure of the infant to ARV drugs in utero

The long-term effects of exposure of the infant in utero to combination ARV regimens require further study. Data from high-income countries are conflicting. In reports from a large French cohort, clinical symptoms of mitochondrial dysfunction were observed in 0.26% of infants who were not infected but born to women living with HIV who had received ART during pregnancy, with a mortality of 0.07% *(127)*. The children had primarily neurological symptoms, sometimes accompanied by significant hyperlactatemia, and abnormal mitochondrial respiratory chain enzyme function on biopsy. However, this has not been reported from other cohorts in Europe and the United States *(128,129)*. Several research groups have reported persistent, although clinically asymptomatic, haematological abnormalities in uninfected infants exposed to ART in utero *(129,130).* Further long-term follow-up of uninfected infants born to women living with HIV who had received ART during pregnancy is ongoing so as to improve evaluation of the risk of such exposure for the infant.

2. Safety of ARV drugs used as prophylaxis for preventing HIV infection in infants

In clinical trials on the prevention of MTCT, short-term toxicity is uncommon with use of the ARV prophylaxis regimens recommended for resource-constrained settings *(131)*. In women, the use of AZT for PMTCT has not been associated with clinical and laboratory toxicity in several controlled trials and long-term follow-up *(45,132)*, although safety data are missing for longer AZT regimens in Africa where anaemia is common. Trials in Thailand suggest that serious anaemia in women receiving AZT from 28 weeks of pregnancy is rare; no increase in haematological toxicity was observed with AZT started at around 36 weeks of pregnancy in trials in Africa *(9,42,46,47,52,55)*. Although these trial data are reassuring, it is not known whether AZT from 28 weeks of pregnancy will result in severe anaemia in settings where anaemia is common and women are not screened.

In a French study, the combination of AZT and 3TC given to women for PMTCT from the early second trimester of pregnancy and to the infant for six weeks was associated with higher rates of infant anaemia and neutropenia than were observed in infants exposed to AZT alone *(50)*. In ARV prophylactic regimens recommended for preventing MTCT in resource-constrained settings, exposure to AZT and 3TC during pregnancy and by the infant are more limited, and severe haematological toxicity appears uncommon *(43,44,46,131)*.

Sd-NVP has been associated with minimal toxicity in all clinical trials to date *(131)*. Clinical trials involving over 1600 women and infants who received Sd-NVP have demonstrated no significant toxicity with this regimen. In particular, hepatic toxicity and rash were unusual in women and their infants and did not differ between Sd-NVP and comparison groups (placebo, AZT alone, or AZT and 3TC) *(6,37,39,131)*. More recent studies that have combined Sd-NVP with antenatal AZT, or AZT and 3TC, have similarly not observed significant maternal or infant toxicity *(9,46,63)*. Five-year follow-up of infants enrolled in the HIVNET 012 trial using Sd-NVP in Uganda has observed no long-term effects of exposure to prophylaxis.

In a study of prophylaxis for infants with Sd-NVP alone or in combination with AZT, transient mild (grade 1) haematological and liver enzyme abnormalities were observed at six weeks of age in infants who had received Sd-NVP plus seven days of AZT prophylaxis compared to those receiving Sd-NVP alone *(133,134)*.

Thus, the risk of short- and medium-term toxicity to the woman or her infant with the current WHO recommended ARV prophylaxis regimens is minimal and appears to be limited to mild, transient haematological abnormalities. The major concern related to use of these regimens is selection for viral resistance and its implications for future treatment options for both women and HIV-infected infants (see section X).

X. RESISTANCE TO DRUGS FOLLOWING ARV PROPHYLAXIS FOR PREVENTION OF HIV INFECTION IN INFANTS

1. Background

Resistance to HIV drugs may emerge in women receiving triple-combination regimens but occurs more frequently with single- and dual-drug regimens. Viral resistance is a potential problem for women after short-term exposure to ARV drug regimens to prevent MTCT and for infants who become infected. This is particularly the case for NVP and 3TC, drugs for which a single mutation leads to high-level resistance, whereas multiple sequential mutations are needed to confer resistance to AZT.

Partly suppressive regimens favour replication of resistant virus over wild-type virus, and the amount of virus containing resistance mutations rises. When the drug is discontinued, selective pressure is no longer present and wild-type virus again becomes the predominant strain. Low-level viral resistance can, however, persist for a prolonged period of time. The clinical consequences of selection of resistance mutations in terms of response to future ART are being studied.

Resistance to AZT is usually only observed after several months of partly suppressive therapy *(135,136)*. It emerges more rapidly among individuals with more advanced HIV disease. Studies to date show a low prevalence of resistance to AZT after short-course AZT to reduce the risk of MTCT. Exposure to AZT in regimens recommended to prevent MTCT is unlikely to affect future ART options.

Resistance to 3TC can develop more rapidly, even when it is given in combination with AZT. The risk of viral resistance to 3TC is correlated with the duration of drug exposure. In a study of a cohort in France, an overall resistance rate of 39% was observed among women six weeks after childbirth. In this study, resistance to 3TC was detectable among 50% (37 out of 74) of women receiving 3TC for more than two months, 20% (14 out of 70) of those receiving it for one to two months and none of the 12 women receiving 3TC for less than one month *(38)*. In the multicentre Petra study, 12% of women who received AZT and 3TC antenatally from 36 weeks, intrapartum and for one week postpartum showed detectable resistance when tested one week after delivery *(74)*. However, no resistance to AZT or 3TC was observed when this combination was only given intrapartum and for one week postpartum *(74,137)*.

NVP has a prolonged half-life, with detectable levels persisting in some women who have received Sd-NVP for up to 21 days postpartum *(138)*. The prolonged half-life is beneficial in that, in addition to preventing intrapartum transmission, NVP can prevent MTCT occurring postnatally during the first few weeks of life *(72)*. However, the woman is also exposed to a prolonged period of non-suppressive drug levels, promoting the development of resistance to drugs. The risk of resistance to NVP following exposure to a single dose of it is most strongly related to the mother's plasma viral load and CD4 cell count at the time of exposure *(139)*. Other factors associated with the development of resistance to NVP following prophylactic treatment to prevent MTCT include

viral subtype (more common in women infected with subtype C than D and A) *(140,141)*, the compartment (such as plasma or breast milk), the number of NVP doses the woman received during labour and the time since Sd-NVP was received. The risk of resistance to NVP following administration of two doses of it to the mother is about twice as high as that observed with a single dose *(137)*.

It is difficult to compare directly the rates of resistance reported in different studies, as the mothers' plasma viral loads and CD4 cell counts, the viral subtypes and types of assay used to detect resistance and other factors vary between studies. While resistance to NNRTI can be detected using standard genotyping in around a quarter to half of women given Sd-NVP, more sensitive techniques such as real-time polymerase chain reaction have shown that resistance to NVP may occur in as many as 60–89% of women given Sd-NVP *(142–145)*. The proportion of viral variants with resistance to NVP declines over time but, with sensitive assays, low levels of resistant viral populations can be detected in women for a year or more after exposure. Resistance to NVP usually confers cross-resistance to EFV.

NVP-resistant viral strains are also selected for among women who receive NVP in addition to other ARV drugs for preventing MTCT, although the rates may be lower than in those exposed to Sd-NVP alone. Additionally, if a triple-drug regimen that includes NVP is given and then stopped postpartum, there is a risk of development of resistance to NVP because it has a longer half-life than the NRTI drugs. In a study in Ireland where NVP-based triple-ARV regimens were given to pregnant women for PMTCT and then stopped postpartum, resistance to NVP was detected in 15% of the women *(146)*.

When mutations resistant to NVP have been detected in both mother and infant, the mutations differ. Viral resistance was detected among 33–53% of infants with HIV when both they and their mothers were exposed to Sd-NVP *(68,139)*. In most cases, infants with resistance to NVP were noted to be infected at birth, suggesting that the resistance mutations were selected de novo among the infants when their actively replicating virus was exposed to NVP, rather than being transmitted from the mother. The transmission of resistant viral strains to infants therefore appears to be uncommon.

2. Prevention of resistance to NVP

The risk of resistance to HIV drugs is strongly associated with the mother's plasma viral load and CD4 cell count at the time of exposure. Thus, women at the highest risk of developing resistance to NVP with exposure to a single dose of it are those with more advanced HIV disease for whom ART is recommended. The most important method of preventing resistance to NVP is to assess the eligibility of all pregnant women for ART, optimally including CD4 cell count evaluation with clinical staging, and to give ART to those women who require it. Resistance following Sd-NVP is

less common among women who do not have indications for ART. These women are unlikely to require ART within six months of childbirth, and some studies suggest that exposure to Sd-NVP does not adversely affect the outcome of ART begun after this period.

Accumulating data suggest that the incidence of resistance may be decreased if dual NRTI drugs are given intrapartum and for a short period postnatally following Sd-NVP *(57,67,68)*. As NVP has a long half-life and drug levels persist for up to three weeks, it is expected that giving dual NRTI drugs for a period after the women receive Sd-NVP will suppress viral replication and decrease the risk of developing resistance. A randomized trial in South Africa *(57)* demonstrated that the giving of AZT and 3TC during labour at the same time as Sd-NVP, followed by AZT and 3TC for four to seven days postpartum, reduces the development of resistance to NVP from 60% to about 10%. While a longer duration of dual NRTI may seem attractive due to the prolonged half-life of NVP, a longer duration of the AZT/3TC tail may run the risk of development of resistance to 3TC. The optimal ARV regimen and duration of administration to reduce the development of resistance to NVP is not yet known, and studies are ongoing *(57,67)*.

3. Implications of resistance to drugs

The development of either 3TC- or NVP-resistant strains with short-course ARV prophylaxis has not been associated with an increased risk of MTCT in that pregnancy. Further, recent studies in Côte d'Ivoire, South Africa and Uganda have shown that prior exposure to Sd-NVP does not reduce the efficacy of Sd-NVP in subsequent pregnancies *(147,148)*.

Limited data are available on the outcome of ART in women who had previously received prophylactic regimens for PMTCT. A study in Thailand suggested that maximal viral suppression might be decreased in women who receive Sd-NVP and are later given NVP-based ART, although in the study the clinical and immunological responses did not differ from those in women who had not been exposed to Sd-NVP *(149)*. The length of time between exposure to Sd-NVP and beginning NNRTI-based ART may be important and affect treatment decisions (see Table 9). A reduced viral response to NNRTI-based ART may be more likely if ART is started less than six months after receiving Sd-NVP. However, recent studies from Botswana, Cote d'Ivoire, South Africa and Zimbabwe suggest that if ART is started 6–18 months after exposure to Sd-NVP, the virological and immunological response to ART appears to be the same as in women without previous exposure *(150–153)*.

Table 9 presents the advantages and disadvantages of ARV treatment regimens for women who have received prophylactic regimens containing Sd-NVP for PMTCT and who subsequently require ARV treatment.

Table 9. ARV treatment regimens for women who have previously received Sd-NVP-containing prophylactic regimens for PMTCT

TIME SINCE EXPOSURE TO SD-NVP	RANKING	OPTIONS	ADVANTAGES	DISADVANTAGES
Less than six months	Recommended regimen	Two NRTIs + NNRTI	• Reserve PIs for second-line regimens • Consistent with standard recommendations	• Potential for reduced viral response to ART
	Alternative regimen	Three NRTIs	• NNRTI resistance not an issue • Reserve PIs for second-line regimens	• Studies suggest may be less potent than NNRTI- or PI-based regimens
	Alternative regimen	Two NRTIs + PI	• NNRTI resistance not an issue	• No second-line treatment options exist
More than six months	Recommended regimen	Two NRTIs + NNRTI	• Consistent with standard recommendations • Accumulating data suggest that viral response is not compromised	• Potential for reduced viral response to ART

Key recommendations

- *Women who have previously received Sd-NVP for PMTCT should be considered eligible for NNRTI-based antiretroviral therapy and not be denied access to life-sustaining therapy.*
- *For women receiving Sd-NVP who are in false labour, a repeat NVP dose should not be given during established labour, as the risk of viral resistance is higher following two doses of NVP. In such situations, the infant should receive NVP as soon as possible after birth as well as AZT for four weeks* ***(Level A-III recommendation)****.*
- *A triple NRTI- or PI-based regimen can be considered as an alternative to NNRTI-based treatment if ART is started within six months of exposure to Sd-NVP* ***(Level B-IV recommendation)****.*
- *Use of an NNRTI-based regimen is recommended for women who are started on ART more than six months after exposure to Sd-NVP* ***(Level A-III recommendation)****.*
- *Pregnant women who have received ARV prophylaxis in a previous pregnancy can receive the same ARV regimens recommended for PMTCT as for women with no prior ARV exposure* ***(Level A-III recommendation)****.*

XI. SPECIAL CONSIDERATIONS

1. Pregnant women living with HIV who have anaemia

Anaemia is common among pregnant women, particularly in resource-constrained settings. HIV, anaemia and, in many settings, malaria may occur in the same individual, interacting in several ways and exacerbating the effects of individual diseases. Hookworm and low dietary intake of iron and folate are also important contributory factors.

The prevention, diagnosis and treatment of anaemia are key components of routine antenatal care in resource-constrained settings. As part of a strategy to prevent anaemia and its adverse effects, WHO recommends the routine use of iron and folate supplementation for all pregnant women living in areas with a high prevalence of iron deficiency. Iron supplementation is also recommended during the postpartum period. In addition, the prevention and case management of malaria is important for reducing anaemia among pregnant women living in malaria-endemic areas.

Although anaemia may occur with long-term use of AZT, PMTCT regimens containing AZT have been well tolerated by women living with HIV and their infants.

Key recommendations

- *Women with indications for ART who have severe anaemia (Hb <7g/dl) should be started on a non-AZT-containing regimen and receive treatment for anaemia. The alternatives to AZT are d4T or ABC.*
- *For pregnant women living with HIV without indications for ART, the priority is to treat the severe anaemia. AZT-containing prophylactic regimens should only be initiated after severe anaemia has been corrected (Hb >7g/dl). Alternatively the antenatal component of prophylaxis could be avoided and women receive only ARV prophylaxis, beginning in labour. This will not, however, be as efficacious for preventing MTCT.*

2. Pregnant women living with HIV who have active tuberculosis

All women with a cough that has lasted for more than 2–3 weeks should be screened for active TB. In pregnant women living with HIV with active TB, the first priority is to treat the TB. With careful clinical management, however, a woman with TB can receive ART at the same time as treatment for the TB. The optimum time to give ART will depend on the CD4 cell count, tolerance of TB treatment and other clinical factors. Drug interactions between some ARV drugs and rifampicin (RIF) complicate the choice of ARV drug regimens for pregnant women who have active TB and require ART. If a pregnant woman receiving ART develops TB, such therapy should be continued, although drug–drug interactions may make it necessary to use other ARV drugs.

An EFV-based regimen is the recommended first-line treatment for patients with TB and HIV. If a pregnant woman is in the second or third trimester of pregnancy, an EFV-based ART regimen can be considered; effective contraception would need to be assured postpartum. Changing from an EFV-based to NVP-based ART regimen could be considered when the TB treatment is completed.

NVP-containing ARV regimens can be started during the continuation phase of TB treatment if these do not include RIF. An alternative for women with tubercular disease would be a triple NRTI regimen such as AZT + 3TC + ABC. In this situation, the use of TDF can also be considered (TDF + 3TC (or FTC) + AZT).

The use of PI drugs for initial treatment regimens is not recommended for adults with TB *(154)*. SQV/r was previously recommended as an alternative regimen for women of childbearing age and pregnant women with tubercular disease; significant hepatotoxicity has, however, been described in individuals receiving concurrent RIF and SQV/r (1000 mg/100 mg twice daily) *(155)*. If pregnant women receiving second-line PI-based regimens develop TB, or if TB is the event that signifies failure of a first-line ART regimen, then an LPV/r (400mg/400mg twice daily) or SQV/r (400 mg/400 mg twice daily) regimen should be used with careful clinical and laboratory (alamine transaminase) monitoring for toxicity.

The recommendations for ARV prophylactic treatment for PMTCT should be followed if women living with HIV who have active TB are not given ART (see section VIII).

3. Management of injecting drug-using pregnant women living with HIV

Obstetrical care providers should ask about alcohol or drug use (injecting drug use or other drug use) among pregnant women living with HIV. Substance-using women may perceive HIV testing and counselling during pregnancy as a potential risk factor for stigmatization, discrimination, prosecution or losing custody of their children.

Injecting drug use (IDU) with contaminated equipment is a major mode of HIV transmission in many countries in Europe, Asia and Latin America. In these settings, particular attention is needed to address the needs of female drug users living with HIV, especially during pregnancy. The access to care for women who use drugs is often hampered by factors which include 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.

National programmes should ensure that antenatal care, labour and delivery and postpartum services provide a user-friendly environment for women living with HIV who are IDUs. Women require counselling about the effects of alcohol and other drugs on growth and development of the fetus and the benefit of harm reduction services. If opioid drug-using women meet the criteria for dependency, opioid substitution therapy should be offered, the patient counselled about the risks and benefits of such therapy and agreement reached about a treatment programme and adherence to it. Methadone substitution treatment is currently recommended for opioid substitution therapy for opioid-dependent pregnant women. Data are limited on the use of buprenorphine in pregnancy. Comprehensive care is required throughout the continuum of pregnancy and postpartum period addressing HIV, obstetrical-gynaecological and IDU-related needs through co-management, improved coordination and referral mechanisms. Obstetrical care providers should assess all female substance users living with HIV 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 principles for clinical and immunological assessment of pregnant women living with HIV apply for injecting drug-using pregnant women living with HIV. For pregnant women already on or starting ART, drug interactions may be a concern. For injecting drug-using pregnant women living with HIV who are not yet eligible for ART, the same ARV prophylactic regimens for PMTCT are recommended as for women who are not IDUs.

Interactions between methadone and ARV drugs are the same in pregnant women as in other patients (see national guidelines). Drug interactions can potentially result in decreased methadone levels or in increased ARV levels, increasing the risk of 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 the daily methadone doses were required to treat opiate withdrawal. If a pregnant woman receives NNRTI- (NVP- or EFV-) based ART, the dose of methadone must be increased. Withdrawal symptoms generally occur 4–8 days following the start of NVP-based ART. Methadone significantly increases concentrations of AZT (up to 43%), which may increase the risk of adverse effects from the AZT and therefore requires close monitoring. SQV/r slightly reduces the levels of

methadone; no methadone dosage adjustment is necessary, however, and only close 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 who receive ARV prophylaxis at the onset of labour.

Co-infection with HIV and the hepatitis B or C virus is common among IDUs. Pregnant women living with HIV and co-infected with the hepatitis C virus who are receiving ART require careful clinical and laboratory monitoring, irrespective of the ARV regimens. All injecting drug-using women living with HIV should routinely be offered testing for hepatitis B and C infections and monitored according to the WHO guidelines.

Neonatal withdrawal syndrome refers to the signs and symptoms exhibited by newborns cut off abruptly after prolonged exposure to drugs during pregnancy. Initially, it was used to describe withdrawal from opioids, but the definition now includes manifestations of withdrawal from cocaine, amphetamine and alcohol. Neonatal withdrawal syndrome occurs in about 60% of all fetuses exposed to these drugs, usually within the first 48–72 hours of life, although methadone withdrawal can occur up to two weeks after birth. Health care providers should ensure that all newborns of injecting drug-using women living with HIV are provided with appropriate neonatal withdrawal syndrome management care according to national guidelines.

4. Pregnant women with HIV-2 infection

HIV-2 is endemic in West Africa and foci of infection also occur in countries such as India and Portugal. HIV-2 has the same modes of transmission as HIV-1 but it has been shown to be less transmissible from mother to child than HIV-1, with rates of MTCT of 0–4% among breastfed infants in the absence of any interventions *(156,157)*. HIV-2 may also progress to AIDS with similar opportunistic infections, although progression is generally much slower than observed with HIV-1 *(158)*. In settings where HIV-2 is prevalent, testing for both HIV-1 and HIV-2 is recommended prior to the administration of ART or ARV prophylaxis for PMTCT. Laboratory tests and testing algorithms for differentiating between HIV-1 and HIV-2 are necessary.

It is important to note that NNRTI drugs, such as NVP, are not effective against HIV-2. For a woman living with HIV-2 only, ART for her health as well as ARV drugs for PMTCT should therefore not include NNRTIs. Women living with HIV-2 in need of ART should be given treatment. Triple NRTIs are recommended as the first-line ARV regimens for treating individuals living with HIV-2 *(15)*. Pregnant women living with HIV-2 for whom ART is not yet indicated should be considered for ARV prophylactic treatment to prevent MTCT (see Table 10).

Table 10. ARV regimens for prophylaxis to prevent MTCT of HIV-2 in pregnant women living with HIV-2 alone[a]

	MATERNAL ART INDICATED	MATERNAL ART NOT INDICATED
Mother		
Antepartum	AZT + 3TC + ABC[b]	AZT starting at 28 weeks gestation or as soon as feasible thereafter
Intrapartum	AZT + 3TC + ABC	AZT
Postpartum	AZT + 3TC + ABC	
Infant	AZT × 7 days	AZT × 7 days

[a] Women living with HIV-1 and HIV-2 co-infection should receive prophylaxis as recommended for HIV-1 (see Tables 6–8).

[b] For alternative regimens see the WHO adult guidelines *(15)*.

Pregnant women living with HIV-2 only can be given AZT to reduce MTCT with prophylaxis from 28 weeks of pregnancy (or as soon as feasible thereafter) and intrapartum and for seven days to the infant. As the risk of MTCT of HIV-2 is relatively low, the benefits of giving ARV prophylaxis may be outweighed by the risks of drug toxicities and, in some circumstances, it may be considered not to give a prophylactic regimen. Women need to be informed of the potential benefits and risks of this option. As with HIV-1, women living with HIV-2 who have symptomatic disease, a compromised immune system and high HIV-2 ribonucleic acid viral loads are at greater risk of MTCT of HIV-2 than asymptomatic women, and the benefit of prophylaxis for prevention of HIV-2 MTCT is likely to be greatest in this group when ART is not yet indicated or initiated. Current WHO recommendations on HIV and infant feeding also apply to women with HIV-2.

Women living with both HIV-2 and HIV-1 should receive appropriate ARV prophylaxis as per the guidelines for prevention of HIV-1 infection. The risk of MTCT of HIV-1 is much higher than for HIV-2, and the combination of Sd-NVP and short-course AZT is the most effective prophylaxis regimen to prevent MTCT of HIV-1.

5. Women with primary HIV infection during pregnancy

Women who become infected with HIV during pregnancy or while breastfeeding are likely to 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 *(159)*.

Retesting of women late in pregnancy may identify those with recent HIV infection who can benefit from access to HIV prevention and care interventions. Thus where resources permit, it may be beneficial for women who test negative early in pregnancy to be offered repeat HIV testing in the third trimester of pregnancy. This strategy has been used for pregnant women who live in high-prevalence areas, pregnant women living in low-prevalence areas who are at higher risk of exposure to HIV (such as women with a history of an STI, female sex workers and IDUs) and for pregnant women in a discordant couple.

There are currently no data that indicate which ARV prophylactic regimen is most efficacious for a pregnant woman with primary HIV infection. Standard ARV prophylactic regimens for PMTCT should, therefore, be used as described in section VIII.

XII. ANTIRETROVIRAL DRUGS FOR PREVENTING HIV TRANSMISSION DURING BREASTFEEDING

To minimize the risk of HIV transmission to infants during breastfeeding while at the same time not increasing their risks of exposure to other causes of morbidity and mortality, the current WHO recommendations state that when replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by mothers living with HIV is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life and should then be discontinued as soon as feasible. The recommendations further state that when mothers living with HIV choose not to breastfeed from birth, or stop breastfeeding later, they should be provided with specific guidance and support for at least the first two years of the child's life to ensure adequate replacement feeding *(13)*.

The efficacy and safety of ARV drugs for preventing breast-milk transmission in mothers living with HIV who do not have indications for first-line ART remain a question for research. It is hypothesized that ARV drugs given to breastfeeding women will reduce the risk of postnatal transmission of HIV. Several ongoing studies are evaluating the effect of single or combination ARV regimens given to breastfeeding women and/or the infant to prevent early and/or late postnatal transmission *(10)*. Additional evidence is needed of the safety of ARV prophylaxis given to women or infants for preventing HIV transmission during breastfeeding. The optimal duration of ARV prophylaxis is unknown and there are concerns that viral rebound following cessation of prophylaxis may lead to a high risk of MTCT for infants who continue to be breastfed after prophylaxis has stopped and may also be detrimental to the mother. There are limited data about the penetration of ARV drugs into breast milk; if there is differential penetration, there may be high levels of some drugs while others may show low or undetectable levels in breast milk. Data from a study in Botswana indicated that levels of NVP in the breast milk of women receiving NVP-based ART were lower than in the mothers' plasma, while levels of 3TC and AZT in the breast were about three times as high *(160)*. Sub-optimal concentrations of ARV drugs in breast milk may select for resistant virus in this compartment. A study in Zimbabwe among women exposed to Sd-NVP suggests that resistance to NVP is more frequently found in breast milk than in the mothers' plasma and that there are divergent resistance mutations found between breast milk and plasma *(161)*. Finally, the safety of prolonged exposure of breastfeeding infants to ARV drugs in breast milk needs to be evaluated. In a small study, ARV drug concentrations in breastfeeding infants of mothers who were receiving ART were higher than expected, with NVP levels in the breastfeeding infant comparable to those achieved with NVP doses for infants *(160)*.

Women living with HIV who require ART for their own health and are breastfeeding should, however, continue to receive such therapy, as the benefit to the health of the woman outweighs the potential risks to the infant.

Overall, preliminary initial data from observational studies in several African countries of ARV prophylaxis provided to the breastfeeding infant for preventing postnatal transmission are promising *(54,162,163)*. Several randomized controlled clinical trials are in progress and should

yield results in the near future. There is currently not enough evidence to conclude that ART for or provision of ARV prophylaxis to the mother and/or the infant during the breastfeeding period reduces HIV transmission to infants during breastfeeding. The risks and benefits of ARV drugs used solely for preventing breast-milk transmission need to be more fully elucidated before this approach can be recommended.

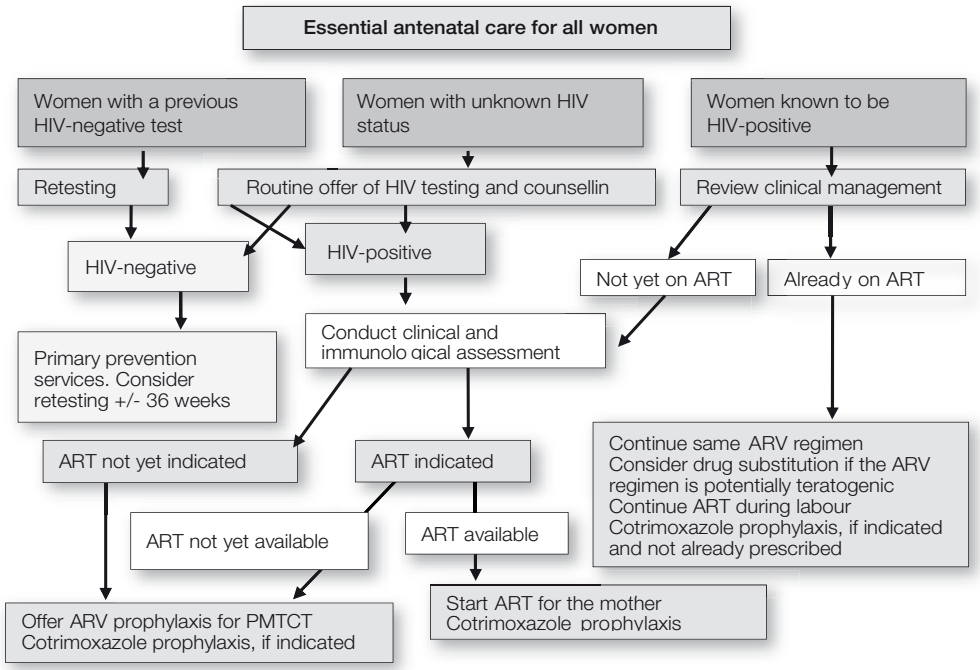
Key recommendations

- *Current United Nations recommendations on HIV and infant feeding remain valid, irrespective of whether a woman is receiving ART.*
- *Women receiving ART who are breastfeeding should continue their ARV regimen* ***(Level A-IV recommendation)****.*
- *The use of ARV drugs in the mother and/or baby solely to prevent transmission through breastfeeding is currently not recommended* ***(Level A-IV recommendation)****.*

ANNEX 1 Comprehensive services for the prevention of mother-to-child transmission

The following figures summarize the package of comprehensive services to be provided to pregnant women and their children in the context of prevention of MTCT. Fig. 1 describes services for women seen during pregnancy and distinguishes between pregnant women with a previously HIV-negative test, those with unknown HIV status and those known to be HIV-positive. Fig. 2 describes services for women seen during labour.

Fig. 1. Comprehensive services for the prevention of MTCT: women seen during pregnancy



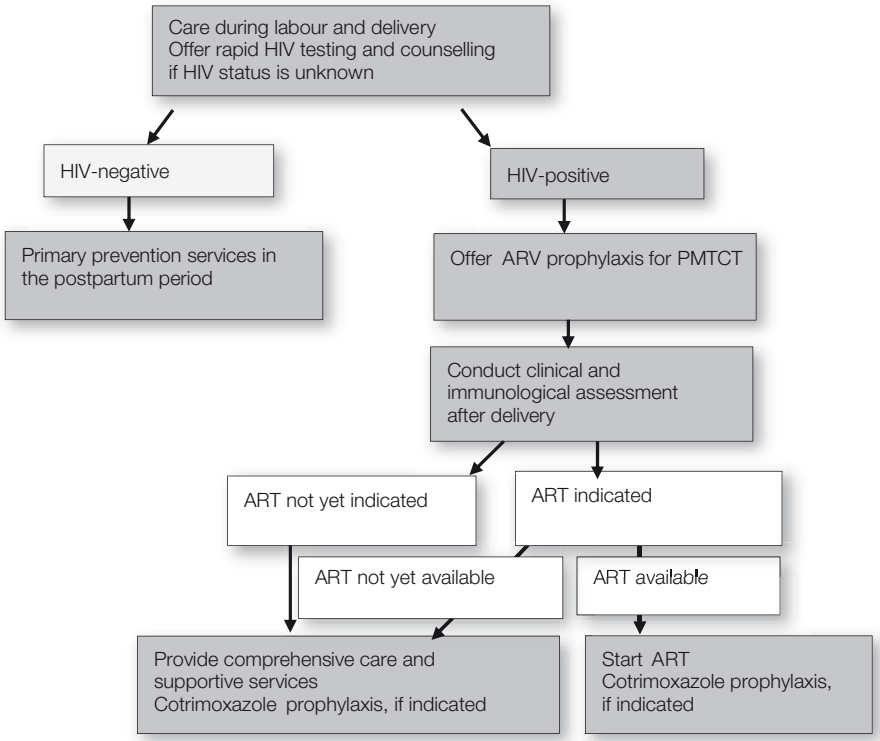
Package of services for antenatal care

1. Essential antenatal care services, including routine offer of HIV testing and counselling
2. Management of malaria in stable malaria areas
3. Clinical and immunological assessment of HIV-positive women
4. Screening, prevention and treatment of TB
5. Screening for and management of liver diseases
6. Screening, prevention and management of STIs
7. Screening for and management of injecting drug use
8. Initiation of ART and ARV prophylaxis for PMTCT
9. Cotrimoxazole and isoniazid prophylaxis
10. Counselling and support on nutrition
11. Counselling and support on infant feeding

For all HIV-positive women in the postpartum period

1. **Provide counselling and support on infant feeding**
2. **Provide follow-up care for mother and infant:**
   - HIV-related care and ART when indicated
   - Cotrimoxazole prophylaxis for women and their infants
   - Sexual and reproductive health services
   - Counselling and support on nutrition
   - Diagnosis of HIV infection in infants
3. **Adherence support for women receiving ART**

Fig. 2. Comprehensive services for prevention of MTCT: women seen during labour



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ANNEX 2 Outcome and characteristics of studies investigating the efficacy of long- and short-course antiretroviral regimens for preventing mother-to-child transmission of HIV

STUDY	DRUGS	ANTENATAL AND INTRAPARTUM	POSTPARTUM	ESTIMATED MEDIAN MATERNAL CD4+ AT ENROLMENT[A] 10^6 CELLS/L	MODE OF INFANT FEEDING	VERTICAL TRANSMISSION RATE AND EFFICACY
Pediatric AIDS Clinical Trials Group (PACTG) 076 / ANRS 024 trial, USA and France *(45)*	AZT vs placebo	Long (from 14 weeks); intravenous intrapartum	Long (6 weeks), infant only	550	Replacement feeding	8.3% in intervention group vs 25.5% in placebo group at 18 months (68% efficacy)
CDC short-course ZDV trial, Thailand *(52)*	AZT vs placebo	Short (from 36 weeks); oral intrapartum	None	419	Replacement feeding	9.4% in intervention group vs 18.9% in placebo group at 6 months (50% efficacy)
DITRAME (ANRS 049a) trial, Côte d'Ivoire, Burkina Faso (47,71)	AZT vs placebo	Short (from 36 weeks); oral intrapartum	Short (1 week), mother only	545	Breastfeeding (96%)	18.0% in AZT group, 27.5% in placebo group at 6 months (38% efficacy); 21.5% vs 30.6% (30% efficacy) at 15 months 22.5% vs 30.2% (26% efficacy) in pooled analysis at 24 months[b]

CDC short-course ZDV trial, Côte d'Ivoire (55,71)	AZT vs placebo	Short (from 36 weeks); oral intrapartum	None	538	Breastfeeding (100%)	16.5% in intervention group vs 26.1% in placebo group at 3 months (37% efficacy) 22.5% vs 30.2% (26% efficacy) in pooled analysis at 24 months[b]
Petra trial, South Africa, Tanzania and Uganda *(43)*	Antenatal, intrapartum and postpartum AZT + 3TC vs intrapartum and postpartum AZT + 3TC vs intrapartum AZT + 3TC vs placebo	Short (from 36 weeks); oral intrapartum	Short (1 week), mother and infant	448	Breastfeeding (74%, median duration 28 weeks) and replacement feeding	5.7% at 6 weeks for antenatal, intrapartum and postpartum AZT + 3TC, 8.9% for intrapartum and postpartum AZT + 3TC, 14.2% for intrapartum AZT + 3TC only and 15.3% for placebo (efficacy compared with placebo:63%, 42% and 0%, respectively) 14.9% at 18 months for antenatal, intrapartum and postpartum AZT + 3TC, 18.1% for intrapartum and postpartum AZT + 3TC, 20.0% for intrapartum AZT + 3TC only and 22.2% for placebo (efficacy compared with placebo: 34%, 18% and 0%, respectively)

STUDY	DRUGS	ANTENATAL AND INTRAPARTUM	POSTPARTUM	ESTIMATED MEDIAN MATERNAL CD4+ AT ENROLMENT[A] 10^6 CELLS/L	MODE OF INFANT FEEDING	VERTICAL TRANSMISSION RATE AND EFFICACY
HIVNET 012 trial, Uganda (48,49)	NVP vs AZT	No antenatal ARV; oral intrapartum: Sd-NVP 200 mg vs oral AZT	Single-dose NVP 2 mg/kg within 72 hours of birth (infant only) vs AZT (1 week), infant only	443	Breastfeeding (99%, median duration 9 months)	11.8% in NVP group vs 20.0% in AZT group (42% efficacy) at 6–8 weeks; 15.7% in NVP group vs 25.8% in AZT group (41% efficacy) at 18 months
SAINT trial, South Africa *(51)*	NVP vs AZT + 3TC	No antenatal ARV; oral intrapartum: Sd-NVP 200 mg vs AZT + 3TC	Single NVP dose within 48 hours of birth (mother and infant) vs AZT + 3TC (1 week), mother and infant	394	Breastfeeding (42%) and replacement feeding	12.3% in NVP group vs 9.3% in AZT + 3TC group at 8 weeks (difference not statistically significant, p=0.11)
Perinatal HIV Prevention Trial (PHPT-1), Thailand *(42)*	Four AZT regimens with different durations of antepartum and infant postpartum administration, no placebo	Long (from 28 weeks), short (from 36 weeks); oral intrapartum	Long (for 6 weeks), short (for 3 days), infant only	365	Replacement feeding	Short-short group was stopped at interim analysis (10.5%); vertical transmission rate 6.5% in long-long group vs 4.7% in long-short group and 8.6% in the short-long group at 6 months (no statistical difference); in utero

						transmission significantly higher with short vs long maternal therapy regimens (5.1% vs 1.6%)
PACTG 316 trial, Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, USA *(6)*	Sd-NVP vs placebo among women already receiving AZT alone (23%) or AZT plus other ARV drugs (77% combination therapy)	Antenatal: non-study ARV regimen; oral intrapartum placebo vs single NVP dose 200 mg, plus intravenous AZT	Placebo vs single NVP dose 2 mg/kg within 72 hours of birth plus non-study ARV drugs including AZT, infant only	434	Replacement feeding	77% of women received dual or triple-combination ARV regimens during pregnancy Trial stopped early due to very low vertical transmission rate in both groups: 1.4% in intervention group vs 1.6% in placebo group (53% of the vertical transmission was in utero)
Perinatal HIV Prevention Trial (PHPT-2), Thailand (9)	AZT alone vs AZT plus maternal and infant NVP vs AZT plus maternal NVP	Antenatal: AZT from 28 weeks; oral intrapartum AZT alone or AZT plus Sd-NVP at onset of labour	AZT for 1 week with or without Sd-NVP, infant only	372	Replacement feeding	AZT-alone group was stopped due to a higher transmission rate than the NVP–NVP group (6.3% vs 1.1%). In groups in which the mother received Sd-NVP, the vertical transmission rate did not differ significantly between the infant receiving or not receiving Sd-NVP (2.0% vs 2.8%)

STUDY	DRUGS	ANTENATAL AND INTRAPARTUM	POSTPARTUM	ESTIMATED MEDIAN MATERNAL CD4+ AT ENROLMENT[A] 10^6 CELLS/L	MODE OF INFANT FEEDING	VERTICAL TRANSMISSION RATE AND EFFICACY
French AZT + 3TC (ANRS 075) trial, France *(50)*	Open label, non-randomized AZT + 3TC	AZT + 3TC (added from 32 weeks on); intravenous AZT intrapartum	AZT + 3TC for 6 weeks, infant only	426	Replacement feeding	1.6%; historical control group receiving standard long PACTG 076 AZT only had vertical transmission rate of 6.8%
Thai AZT + 3TC trial, Thailand *(44)*	Open-label, nonrandomized AZT + 3TC	AZT + 3TC (from 34 weeks), oral AZT + 3TC intrapartum	AZT for 4 weeks, infant only	274	Replacement feeding	2.8% at 18 months; historical control groups receiving short AZT only had vertical transmission rate of 9.4% to 11.7%
DITRAME Plus (ANRS 1201.0) trial, Abidjan, Côte d'Ivoire *(46)*	Open-label, AZT plus Sd-NVP	AZT from 36 weeks; intrapartum: oral AZT plus Sd-NVP at onset of labour	Sd-NVP, plus AZT for 1 week, infant only	370	Breastfeeding (54%) and replacement feeding	6.5% at 6 weeks; historical control group receiving short AZT only had vertical transmission rate of 12.8% (98% breastfed in historical control group)
DITRAME Plus (ANRS 1201.1) trial, Abidjan, Côte d'Ivoire *(46)*	Open-label, AZT + 3TC plus Sd-NVP	AZT + 3TC from 32 weeks (stopped at day 3 postpartum); intrapartum: oral AZT + 3TC	Sd-NVP, plus 1 week AZT, infant only	412	Breastfeeding (66%) and replacement feeding	4.7% at 6 weeks; historical control group receiving short AZT only had vertical transmission rate of 12.8% (98% breastfed in historical control group)

		plus Sd-NVP at the onset of labour				
NVAZ trial, Malawi *(53)*	Neonatal NVP vs NVP + AZT	None (latecomers)	Sd-NVP with or without AZT twice daily for one week, infant only	Not reported	Breastfeeding (100%)	15.3% in NVP + AZT group and 20.9% with AZT only at 6–8 weeks; vertical transmission rate at 6–8 weeks among infants who were not infected with HIV at birth 7.7% and 12.1%, respectively (36% efficacy)
Postnatal NVP + ZDV trial, Malawi *(77)*	Neonatal NVP vs NVP + AZT	Intrapartum: Sd-NVP	Sd-NVP with or without AZT twice daily for one week, infant only	Not reported	Breastfeeding (100%)	14.1% in NVP-alone group and 16.3% in NVP + AZT group at 6–8 weeks (difference not statistically significant). Vertical transmission rate at 6–8 weeks among infants who were not infected with HIV at birth 6.5% and 16.9%, respectively

STUDY	DRUGS	ANTENATAL AND INTRAPARTUM	POSTPARTUM	ESTIMATED MEDIAN MATERNAL CD4+ AT ENROLMENT[A] 10^6 CELLS/L	MODE OF INFANT FEEDING	VERTICAL TRANSMISSION RATE AND EFFICACY
Infant post-exposure prophylaxis trial, South Africa *(73)*	Neonatal NVP vs AZT	None (latecomers)	Sd-NVP or twice daily AZT for 6 weeks, infant only	480.5 NVP study group and 448.5 AZT study group	84% replacement feeding	At 12 weeks, infection rate in the NVP group 14.3% and AZT group 18.1% (difference not statistically significant) but at 12 weeks, among infants not infected at birth, 7.9% additional infections occurred in the NVP group and 13.1% in the AZT group (p=0.06).
SIMBA trial, Rwanda, Uganda *(54)*	NVP vs 3TC postnatally in breastfeeding infants born to women who received AZT + ddI antenatally and one week postpartum	AZT + ddI from 36 weeks; intrapartum: oral AZT + ddI	AZT + ddI for 1 week (mother); NVP once daily for 14 days then twice daily vs 3TC twice daily while breastfeeding, infant only	427	Breastfeeding (median 3.5 months, interquartile range 2.9 –5.1 months)	6.9% at 4 weeks and 7.8% at 6 months (difference not statistically significant); transmission rate 2.4% between day 3 and 6 months
MASHI, Botswana *(8)*	Initial: short-course AZT with/without maternal and	First randomization: AZT from 34	Second randomization: breastfeeding	372	Randomiza-tion: 50% breastfeeding (median	Initial design: In formula feeding group, vertical transmission rate at 1 month: 2.4%

	infant NVP and with/without breastfeeding Revised: short-course AZT and infant NVP with/without maternal NVP and with/without breastfeeding; CD4 <200: highly active ART for the mother	weeks plus oral AZT intrapartum and either Sd-NVP at onset of labour or placebo	+ AZT (infant) 6 months + Sd-NVP, infant only, vs formula feeding + AZT (infant) 4 weeks + Sd-NVP, infant only		duration 5.8 months), 50% formula feeding	in maternal and infant Sd-NVP group, 8.3% in placebo group (p=0.05); in breastfeeding + infant AZT group, vertical transmission rate: 8.4% in Sd-NVP group, 4.1% in placebo group (difference not statistically significant) Revised design: Overall vertical transmission rate at 1 month: 4.3% in maternal and infant Sd-NVP group and 3.7% in maternal placebo and infant Sd-NVP group (no significant difference; no interaction with mode of infant feeding) Vertical transmission rate at 7 months: 9.1% in breastfeeding + AZT group and 5.6% in formula feeding group; mortality at 7 months: 4.9% breastfeeding vs 9.3% formula feeding; HIV-free survival at 18 months: 15.6% breastfeeding vs 14.2% formula feeding

STUDY	DRUGS	ANTENATAL AND INTRAPARTUM	POSTPARTUM	ESTIMATED MEDIAN MATERNAL CD4+ AT ENROLMENT[A] 10^6 CELLS/L	MODE OF INFANT FEEDING	VERTICAL TRANSMISSION RATE AND EFFICACY
MITRA, Tanzania *(163)*	Open-label, AZT + 3TC, and 3TC for infant	AZT + 3TC from 36 weeks; intrapartum oral AZT + 3TC	Maternal and infant AZT + 3TC (1 week); 3TC for 6 months, infant only	Unknown	Breastfeeding (median 20 weeks)	3.4% at 6 weeks and 5.1% at 3 months among infants who were not infected with HIV at birth
Cote d'Ivoire *(66)*	Open-label, NVP highly active ART for women who meet WHO criteria for therapy. Short AZT/3TC + Sd-NVP for women who do not require therapy	Women needing therapy: AZT + 3TC + NVP during pregnancy and orally intrapartum Women not needing therapy: AZT + 3TC from 32 weeks; intrapartum: oral AZT plus Sd-NVP	Women needing therapy: women continue AZT + 3TC + NVP; Sd-NVP plus1 week of AZT, infant only Women not needing therapy: 3 days AZT + 3TC; Sd-NVP plus 1 week AZT, infant only	189 469	Primarily replacement feeding Primarily replacement feeding	*Women needing therapy:* vertical transmission rate: 2.4% (95% confidence interval 0.3–8.5%) at 4–6 weeks *Women not needing therapy:* vertical transmission rate: 3.8% (95% confidence interval 1.0–9.5%) at 4–6 weeks No significant difference between groups (p=0.70)

DREAM cohort, Mozambique *(62)*	Open-label NVP highly active ART	D4T or AZT + 3TC + NVP from 24 weeks, continued orally intrapartum	Mother if breastfeeding continue d4T or AZT + 3TC + NVP regimen until weaning, then stop ARV drugs; Sd-NVP + 1 week AZT, infant only	492	Primarily replacement feeding	Transmission rate: 10 out of 331 infants at 18 months (3%; 95% confidence interval 1.1–4.9%)

[a] Median or geometric mean of medians if more than the study group is included.

[b] Included in the pooled analysis.

Annex 3 Doses of antiretroviral prophylaxis drugs for the prevention of mother-to-child transmission of HIV

All regimens are administered by mouth. Paediatric formulations exist for the main drugs used in current prophylactic regimens to prevent MTCT (AZT, NVP and 3TC)

REGIMEN	ANTENATAL	INTRAPARTUM	POSTPARTUM	POSTNATAL
REGIMENS WITH ANTE-, INTRA- AND POSTPARTUM COMPONENTS				
AZT **PLUS** **Sd-NVP**	Mother: AZT 300 mg twice a day starting at 28 weeks or as soon as possible thereafter	Mother: AZT 600 mg at onset of labour **OR** AZT 300 mg at onset of labour and every 3 hours until delivery **PLUS** Sd-NVP 200 mg at onset of labour	None	Infant: NVP 2 mg/kg oral suspension or 6 mg at once immediately after birth[a] **PLUS** AZT 4 mg/kg twice a day for 7 days[b] **OR** NVP 2 mg/kg oral suspension immediately after birth
Seven-day tail of AZT + 3TC	None	**Mother:** 3TC 150 mg at onset of labour and every 12 hours until delivery[c]	AZT 300 mg twice a day for 7 days **PLUS** 3TC 150 mg twice a day for 7 days	

REGIMEN	ANTENATAL	INTRAPARTUM	POSTPARTUM	POSTNATAL
REGIMENS WITH INTRAPARTUM AND POSTPARTUM COMPONENTS				
AZT **PLUS** **Sd-NVP**	None	**Mother:** AZT 600 mg at onset of labour **OR** AZT 300 mg at onset of labour and every 3 hours until delivery **PLUS** Sd-NVP 200 mg at onset of labour	None	**Infant:** NVP 2 mg/kg oral suspension immediately after birth **PLUS** AZT 4 mg/kg twice a day for 4 weeks
AZT **PLUS** **3TC**	None	**Mother:** AZT 600 mg at onset of labour **OR** AZT 300 mg at onset of labour and every 3 hours until delivery **PLUS** 3TC 150 mg at onset of labour followed by 3TC 150 mg every 12 hours until delivery	**Mother:** AZT 300 mg twice a day **PLUS** 3TC 150 mg twice a day for 7 days	**Infant**: AZT 4 mg/kg twice a day **PLUS** 3TC 2 mg/kg twice a day for 7 days

REGIMEN	ANTENATAL	INTRAPARTUM	POSTPARTUM	POSTNATAL
Sd-NVP	None	NVP 200 mg at onset of labour	None	**Infant:** NVP 2 mg/kg oral suspension immediately after birth
REGIMEN WITH ONLY THE INFANT COMPONENT				
AZT **PLUS** **Sd-NVP**	None	None	None	**Infant:** NVP 2 mg/kg oral suspension immediately after birth **PLUS** AZT 4 mg/kg twice a day for 4weeks

[a] Infants prescribed Sd-NVP can receive the dose immediately after delivery or within 72 hours. Giving the infant NVP dose as soon as possible after childbirth and before discharge from the health facility is preferable, and many programmes to prevent MTCT have found this more practical than administering the dose 48 or 72 hours after delivery.

[b] If the mother receives less than four weeks of AZT during pregnancy, four weeks instead of one week of AZT is recommended for the infant.

[c] The seven-day tail includes AZT given during labor in addition to 3TC

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