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

GUIDELINES ON CARE, TREATMENT AND SUPPORT FOR WOMEN LIVING WITH HIV/AIDS AND THEIR CHILDREN IN RESOURCE-CONSTRAINED SETTINGS

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WORLD HEALTH ORGANIZATION
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Contents

Abbreviations and acronyms

3TC	lamivudine
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ARV	antiretroviral
d4T	stavudine
ddI	didanosine
EFV	efavirenz
HIV	human immunodeficiency virus
LPV/r	lopinavir with a low-dose ritonavir boost
MTCT	mother-to-child transmission of HIV
NFV	nelfinavir
NRTI	nucleoside analogue reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NVP	nevirapine
PI	protease inhibitor
RTV	ritonavir
TDF	tenofovir disoproxil fumarate
SQV	saquinavir
SQV/r	saquinavir with a low-dose ritonavir boost
ZDV	zidovudine

PREFACE

HIV is the greatest health crisis the world faces today. An estimated 40 million people are now living with HIV and, in 2003, the pandemic led to 5 million new infections and claimed 3 million lives. An increasing burden is being placed on women and children, who are experiencing growing rates of AIDS-related illness and death in many settings. Globally, about half of all adults living with HIV are women and 2.5 million children are living with the virus. A total of 700 000 children were newly infected in 2003, mainly through mother-to-child transmission of HIV. In the most severely affected countries, AIDS is wiping out families, destroying communities and threatening the social, economic and political gains of recent decades.

This crisis has led to unprecedented political and community mobilization, new funding opportunities and a renewed public health response seeking to scale up key prevention, care, treatment and support interventions so that they become available to all. Over the past few years, considerable efforts have been made to introduce and expand programmes to prevent mother-to-child transmission of HIV. These programmes provide HIV testing and counselling in antenatal care settings and serve as a unique entry point for women with HIV to access the services they need in order to improve their own health and prevent transmission of HIV to their infants.

WHO issued recommendations on the use of antiretroviral drugs for preventing mother-to-child transmission of HIV in 2000. Those recommendations have been reassessed in the context of rapidly expanding antiretroviral treatment programmes using simplified and standardized regimens. In addition, considerable experience in implementing programmes to prevent

mother-to-child transmission of HIV in resource-constrained settings has accumulated since 2000 as well as further evidence on the safety and effectiveness of various antiretroviral regimens.

This publication summarizes existing evidence on the use of antiretroviral drugs for preventing mother-to-child transmission of HIV and makes recommendations on the choice of regimens in the context of expanding access to antiretroviral treatment.

It is part of a series of modules comprising guidelines on care, treatment and support for HIV-infected women and their children in resource-constrained settings being developed by WHO and its partners.

The recommendations complement revised guidelines for antiretroviral treatment that have been issued in support of the 3 by 5 Initiative. The target of treating 3 million people in developing countries with antiretroviral therapy by the end of 2005 is a necessary, achievable target on the way to the ultimate goal of universal access to antiretroviral treatment for everyone who requires it.

Executive summary

Mother-to-child transmission (MTCT) is the most important source of HIV infection in children. In 2001, the United Nations General Assembly Special Session on HIV/AIDS committed countries to reduce the proportion of infants infected with HIV by 20% by 2005 and by 50% by 2010. Achieving this urgently requires an increase in access to integrated and comprehensive programmes to prevent HIV infection in infants and young children. Such programmes consist of interventions focusing on primary prevention of HIV infection among women and their partners; prevention of unintended pregnancies among HIV-infected women; prevention of HIV transmission from HIV-infected women to their children; and the provision of treatment, care and support for women living with HIV/AIDS, their children and families.

WHO convened a Technical Consultation on Antiretroviral Drugs and the Prevention of Mother-to-child Transmission of HIV Infection in Resource-limited Settings in Geneva, Switzerland on 5–6 February 2004. Scientists, policy-makers, programme managers and community representatives reviewed the most recent experience with programmes and evidence on the safety and efficacy of various antiretroviral (ARV) regimens for preventing HIV infection in infants. This information was reviewed in the context of the rapid expansion of ARV treatment in resource-constrained settings using standardized and simplified drug regimens. Prior to the Technical Consultation, a draft set of recommendations had been issued for public comment.

Women may receive ARV drugs during pregnancy as part of potent combination regimens used to treat their HIV infection or as prophylaxis to prevent HIV infection in infants. ARV treatment for women benefits their health but also substantially reduces the risk of MTCT. All efforts should be made to ensure that all women who require ARV treatment have access to it.

Therapeutic decisions relating to ARV treatment for women should be based on their need and eligibility for such treatment. However, ARV regimens for women of childbearing age should be selected considering the possibility of a planned or unintended pregnancy and considering that ARV drugs may be taken in the first trimester of pregnancy, before a pregnancy is recognized.

Short courses of ARV drugs started in late pregnancy or during labour reduce the risk of in utero and peripartum HIV transmission two- to three-fold; in 2000, WHO recommended that they be included in programmes to prevent MTCT. At that time, the recommended regimens included zidovudine (ZDV) alone or in combination with lamivudine (3TC) and nevirapine (NVP). The simplest regimen consisted of single-dose NVP at the onset of labour plus a single dose for the infant soon after birth. Programmes to prevent MTCT based on this regimen have been shown to be feasible and acceptable. There have been several years of experience in implementing such programmes. In addition, the results of research on other ARV regimens for preventing MTCT have become available since WHO issued recommendations in 2000.

The efficacy of ZDV plus single-dose maternal and infant NVP has been examined in several settings. Although directly comparing studies is difficult, a combination regimen of ZDV plus single-dose maternal and infant NVP is more efficacious than single drug regimens and, in general, longer regimens are more efficacious than shorter regimens.

Although triple-combination regimens are widely used in industrialized countries for preventing MTCT in women who do not yet require ARV treatment for their own health, their safety and effectiveness have not been assessed in resource-constrained settings. There is serious concern about risk to the woman if possible toxicity cannot be carefully monitored.

Information on the safety of various ARV regimens shows that short-course regimens are, in general, well tolerated, with few mild and transient side-effects for the woman and her infant. There is more concern about the safety of ARV drugs taken by pregnant women for extended periods, especially those who do not yet require ARV treatment. Among women who require ARV treatment for their HIV disease, the benefits to the women's health outweigh the known and theoretical adverse effects.

Drug resistance induced by short-course regimens to prevent MTCT that do not fully suppress the virus has been a concern since early 2000. As MTCT-prevention and ARV-treatment programmes expand and programmes to prevent MTCT identify women needing treatment (either immediately or at a later time), potential resistance has become a far greater concern. Viral resistance has also been detected in HIV-infected infants exposed to short-course ARV regimens. Resistance to NVP develops rapidly and has been noted following single doses of NVP. ZDV resistance usually only emerges after several months of partly suppressive therapy. Resistance to 3TC has not been detected when it has been used in combination with ZDV for short periods but has been detected following longer periods of exposure (more than four weeks). The clinical consequences of viral resistance following short-course MTCT

prophylaxis are unclear. The concern about resistance should be balanced with the programmatic simplicity and practicality of the single-dose NVP regimen compared with other regimens and the urgent need to expand programmes to prevent MTCT.

Successful programmes to prevent MTCT are complex interventions, of which the ARV regimen is but one component. Although regimens based on ZDV plus single-dose maternal and infant NVP are highly efficacious, providing twice-daily ARV prophylaxis to pregnant women from 28 weeks of pregnancy increases the burden on programmes and on the women who participate. ARV prophylaxis using single-dose maternal and infant NVP remains a practical alternative when regimens based on ZDV plus single-dose maternal and infant NVP are not acceptable or feasible. Progress in implementing programmes to prevent MTCT based on single-dose maternal and infant NVP or other short-course regimens should not be undermined.

Although considerable progress has been made in understanding the factors associated with HIV transmission during breastfeeding, reliably preventing transmission during this period remains a challenge in places where infant formula cannot be safely provided. The potential role of infant and/or maternal ARV prophylaxis in preventing postnatal transmission of HIV is being investigated.

In the light of the scientific evidence available and the programmatic experience accumulated, the participants at the Technical Consultation recommended specific ARV regimens according to different clinical situations. These guidelines are based on those recommendations and expert opinion where evidence was lacking. Key recommendations in the guidelines are as follows.

1. Women who need ARV treatment for their own health should receive it in accordance with the WHO guidelines on ARV treatment. The use of ARV treatment, when indicated, during pregnancy substantially benefits the health of the woman and decreases the risk of HIV transmission to the infant

2. HIV-infected pregnant women who do not have indications for ARV treatment, or do not have access to treatment should be offered ARV prophylaxis to prevent MTCT using one of several ARV regimens known to be safe and effective:

   - ZDV from 28 weeks of pregnancy plus single-dose NVP during labour and single-dose NVP and one-week ZDV for the infant. This regimen is highly efficacious, as is initiating ZDV later in pregnancy.
   - Alternative regimens based on ZDV alone, short-course ZDV + 3TC or single-dose NVP alone are also recommended.

3. Although expanding access to programmes to prevent MTCT presents many challenges and single-dose maternal and infant NVP is the simplest regimen to deliver, programmes should consider introducing more complex ARV regimens where possible. The expansion of programmes to prevent MTCT using single-dose NVP should not be hindered while necessary improvements in health systems are taking place to enable more complex ARV regimens to be delivered.

WHO will regularly review the evidence base for these guidelines and will issue updated recommendations when warranted by new information.

1. Background to HIV infection in infants and young children

In 2003 an estimated 700 000 children were newly infected with HIV, about 90% of these infections occurred in sub-Saharan Africa *(1)*. In contrast, new HIV infections in children are becoming increasingly rare in many parts of the world. In 2003, less than 1000 children were estimated to have become infected with HIV in North America and western Europe and less than 100 in Australia and New Zealand *(1)*. Most HIV-infected children acquire the infection through mother-to-child transmission (MTCT) of HIV, which can occur during pregnancy, labour and delivery, or during breastfeeding. In the absence of any intervention, the risk of MTCT of HIV is 15–30% in non-breastfeeding populations; breastfeeding by an infected mother increases the risk by 5–20% to a total of 20–45% *(2)*.

The risk of MTCT can be reduced to below 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 membrane rupture) and completely avoiding breastfeeding *(3–5)*.

In resource-constrained settings, elective caesarean delivery is seldom available *(6)* and/or safe, and refraining from breastfeeding is often not acceptable, feasible or safe. To date, efforts to prevent MTCT in resource-constrained settings have mostly focused on reducing MTCT around the time of labour and delivery, which accounts for one third to two thirds of overall transmission, depending on whether or not breastfeeding occurs. ARV prophylaxis around the time of delivery alone can reduce the risk of MTCT in a breastfeeding population almost two-fold following vaginal

delivery (41– 47% reduction in risk) *(7,8)*. If ARV prophylaxis is extended to include the last month of pregnancy, efficacy at six weeks can be as high as 63% *(9)*. However, even when peripartum ARV prophylaxis is used, 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)*.

At the United Nations General Assembly Special Session on HIV/AIDS in June 2001, governments from 189 countries committed themselves to a comprehensive programme of international and national action to fight the HIV/AIDS pandemic by adopting the Declaration of Commitment on HIV/AIDS. The Declaration established specific goals, including reducing the proportion of infants infected with HIV by 20% by 2005 and by 50% by 2010.

Although programmes to prevent MTCT have been shown to be feasible, acceptable and cost-effective, interventions to reduce MTCT have not yet been implemented on a wide scale in resource-constrained settings *(11,12)*. Renewed efforts are urgently required to increase access to comprehensive and integrated programmes to prevent HIV infection in infants and young children. Offering HIV testing and counselling to pregnant women should become standard practice in antenatal care. Failing that, offering HIV testing and counselling to women shortly after delivery is also an important entry point for MTCT-prevention and other HIV-related prevention, treatment, care and support services. Interventions focusing on the prevention of HIV transmission from infected women to their children need to be complemented by interventions that address primary prevention of HIV infection, especially among women of child-bearing age and their partners, prevention of unintended pregnancies among HIV-infected women and the provision of care, treatment and support for HIV-infected women, their children and families *(13)*.

This publication contains recommendations for ARV use in pregnant women and a summary of the programmatic considerations and scientific rationale for the recommendations. In particular, it aims to provide guidance to assist national departments of health in selecting ARV prophylaxis regimens to be included in programmes to prevent MTCT after taking into account the needs and health system constraints in various settings. In addition, it contains recommendations for ARV treatment for pregnant women and women of childbearing age who have indications for treatment. These recommendations have been made following a review of evidence, supplemented by expert opinion where evidence was lacking or inconclusive, at the Technical Consultation on Antiretroviral Drugs and the Prevention of Mother-to-child Transmission of HIV Infection in Resource-limited Settings in Geneva, Switzerland on 5–6 February 2004 convened by WHO.

This publication primarily targets national-level programme planners and managers responsible for designing services for MTCT prevention and ARV treatment of women. It may also be a useful resource for health service providers involved in efforts to reduce HIV infection in infants and young children and to provide treatment and care for women living with HIV/AIDS. Throughout this publication, ARV treatment refers to the use of potent combination ARV regimens to improve the quality of life and prolong life in children, adolescents and adults living with HIV/AIDS. It should be distinguished from the use of ARV drugs with the objective of reducing the risk of MTCT (ARV prophylaxis to prevent MTCT).

2. Review of antiretroviral regimens for preventing HIV infection in infants

ARV drugs, including nucleoside analogue reverse transcriptase inhibitors (NRTIs) such as zidovudine (ZDV) and lamivudine (3TC) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (NVP), either alone or in combinations of two or three drugs, have been shown to be effective in reducing MTCT (Table 1). These regimens reduce the risk of MTCT by decreasing viral replication and through prophylaxis of the fetus and infant during and after exposure to the virus.

Randomized clinical trials, open-label trials and observational studies have provided evidence of the effectiveness of ARV prophylaxis *(3,7–9,14–26)*. Research to evaluate ARV prophylaxis in the United States and Europe has focused on long ARV regimens and has been set against a background of high levels of antenatal service coverage with early initiation of antenatal care, high rates of elective caesarean section deliveries for HIV-infected women and avoiding breastfeeding.

Observational studies in industrialized countries, where MTCT rates are now below 2%, have shown that triple-ARV combinations given to HIV-infected women during pregnancy and labour are highly effective in reducing MTCT *(3–5)*. In industrialized countries, triple-combination regimens are increasingly used to prevent MTCT among women who have HIV RNA levels exceeding 10^6 copies/L *(27)*. However, there is no evidence yet from resource-constrained settings, where breastfeeding is common, that such combination regimens would produce similar levels of efficacy.

Research in Africa has focused on short-course regimens of peripartum ARV drugs and has been conducted in settings where antenatal care coverage is sometimes inadequate, a significant proportion of births are not attended by a skilled practitioner, elective caesarean section is rarely carried out and nearly all infants are initially breastfed, with most continuing breastfeeding until at least six months of age and often into the second year of life. Table 1 summarizes the efficacy of the various short-course ARV drug regimens for the prevention of HIV infection in infants.

Short-term efficacy, as determined by infant infection status at 6–8 weeks of life, has been demonstrated for long- and short-course prophylactic ARV regimens comprising:

- ZDV alone *(15,16,18,20)*;
- ZDV together with 3TC *(9,19,22)*;
- NVP alone (single dose for mother and infant) *(8,19)*;
- ZDV plus single-dose maternal and infant NVP *(23,28,29)*; and
- ZDV and 3TC plus single-dose maternal and infant NVP *(24)*.

In a non-breastfeeding population in Thailand, the PHPT-2 trial compared long-course ZDV alone given from 28 weeks of pregnancy, intrapartum and to the infant for the first week of life, to the same ZDV regimen with the addition of single-dose maternal NVP with or without single-dose NVP for the infant. At the first interim analysis, the ZDV-alone study arm was stopped because of lower efficacy than the NVP-containing study arms. At that time, an 82% reduction in MTCT rate was observed from the ZDV-alone regimen to the ZDV plus maternal and infant NVP regimen *(30)*. In the final analysis, HIV transmission in the arm in which both the mother and infant received single-dose NVP in addition to maternal and infant ZDV (transmission rate 2.0%) did not differ significantly from the arm in which only the mother received single-dose NVP in addition to maternal and infant ZDV (transmission rate 2.8%) *(29)*. All regimens were well tolerated.

In addition to the PHPT-2 trial in Thailand, the efficacy of short-course ZDV plus single-dose maternal and infant NVP has also been examined in a population in Côte d'Ivoire in which about 60% of the infants were breastfed *(23)*. Women in the DITRAME Plus (ANRS 1201.0) study received ZDV from 36 weeks plus single-dose maternal and infant NVP around the time of delivery; in a similar population, another study assessed single-dose NVP added to ZDV and 3TC *(24)*. Overall, these studies from Côte d'Ivoire and Thailand indicate that ZDV plus single-dose NVP around the time of delivery to the woman and infant is highly efficacious and suggest that ZDV starting at 28 weeks is more efficacious than ZDV started later in pregnancy.

In contrast to these studies, in the PACTG 316 study *(3)* that evaluated adding single-dose maternal and infant NVP to the standard ARV regimens used in high-income countries (antenatal, mostly dual or triple combination ARV; intravenous ZDV during labour; and ZDV for the infant for six weeks), adding single-dose maternal and infant NVP did not appear to provide additional

Table 1. Outcome and characteristics of studies investigating the efficacy of long- and short-course ARV regimens for preventing MTCT

Study	Drugs	Antenatal and intrapartum	Postpartum
PACTG 076 / ANRS 024 trial, USA, France *(14)*	ZDV versus placebo	Long (from 14 weeks), intravenous intrapartum	Long (six weeks), infant only
Bangkok CDC short-course ZDV trial, Thailand *(15)*	ZDV versus placebo	Short (from 36 weeks) intrapartum	None
DITRAME (ANRS 049a) trial, Côte d'Ivoire, Burkina Faso *(16,17)*	ZDV versus placebo	Short (from 36 weeks) intrapartum	Short (one week), mother only
Côte d'Ivoire CDC short-course ZDV trial, Côte d'Ivoire *(17,18)*	ZDV versus placebo	Short (from 36 weeks) intrapartum	None
Petra trial, South Africa, Tanzania and Uganda *(9)*	Antenatal, intrapartum and postpartum ZDV + 3TC versus intrapartum and neonatal ZDV + 3TC versus intrapartum ZDV + 3TC versus placebo	Short (from 36 weeks and intrapartum)	Short (one week), mother and infant
HIVNET 012 trial, Uganda *(7,8)*	NVP versus ZDV	No antenatal ARV; intrapartum: single-dose NVP 200 mg versus oral ZDV	Single-dose NVP 2 mg/kg within 72 hours of birth (infant only) versus ZDV (one week), infant only

benefit; the transmission rate was 1.4% in the NVP arm versus 1.6% in the placebo arm. Adding NVP around the time of delivery does not therefore appear to increase efficacy when using drug regimens that fully suppress viral replication.

Maternal CD4+ count at enrolment[a] 10^6 cells/L	Mode of infant feeding	Vertical transmission rate and efficacy
550	Replacement feeding	8.3% in intervention arm versus 25.5% in placebo arm at 18 months (68% efficacy)
419	Replacement feeding	9.4% in intervention arm versus 18.9% in placebo arm at 6 months (50% efficacy)
551	Breastfeeding	18.0% in ZDV arm, 27.5% in placebo arm at 6 months (38% efficacy); 21.5% versus 30.6% (30% efficacy) at 15 months 22.5% versus 30.2% (26% efficacy) in pooled analysis at 24 months[b]
538	Breastfeeding	16.5% in intervention arm versus 26.1% in placebo arm at 3 months (37% efficacy) 22.5% versus 30.2% (26% efficacy) in pooled analysis[b]
448	Breastfeeding	5.7% at six weeks for antenatal, intrapartum and postpartum ZDV + 3TC, 8.9% for intrapartum and postpartum ZDV + 3TC, 14.2% for intrapartum ZDV + 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 ZDV + 3TC, 18.1% for intrapartum and postpartum ZDV + 3TC, 20.0% for intrapartum ZDV + 3TC only and 22.2% for placebo (efficacy compared with placebo: 34%, 18% and 0%, respectively)
443	Breastfeeding	The placebo arm was stopped; vertical transmission rate 13.1% in NVP arm versus 25.1% in ZDV arm (47% efficacy) at 14–16 weeks; 15.7% in NVP arm versus 25.8% in ZDV arm (41% efficacy) at 18 months

Study	Drugs	Antenatal and intrapartum	Postpartum
SAINT, South Africa *(19)*	NVP versus ZDV + 3TC	No antenatal ARV; intrapartum: single dose NVP 200 mg versus ZDV + 3TC	Single NVP dose within 48 hours of birth (mother and infant) versus ZDV + 3TC (one week), mother and infant
Thai Perinatal HIV Prevention Trial (PHPT-1), Thailand *(20)*	Four ZDV regimens, no placebo	Long (from 28 weeks), short (from 36 weeks)	Long (for six weeks), short (for three days), infant only
PACTG 316 trial, Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States *(3)*	NVP versus placebo among women already receiving ZDV or ZDV plus other ARV drugs	Antenatal: non-study ARV regimen; intrapartum: placebo versus single NVP dose 200 mg, plus intravenous ZDV	Placebo versus single NVP dose 2 mg/kg within 72 hours of birth plus non-study ARV drugs including ZDV (infant only)
Thai Perinatal HIV Prevention Trial (PHPT-2), Thailand *(29)*	ZDV alone versus ZDV plus maternal and infant NVP versus ZDV plus maternal NVP	Antenatal: ZDV from 28 weeks. Intrapartum: ZDV alone or ZDV plus single-dose NVP at onset of labour	ZDV for one week with or without single-dose NVP (infant only)
French ZDV + 3TC (ANRS 075) trial, France *(21)*	Open label, nonrandomized ZDV + 3TC	ZDV + 3TC (from 32 weeks)	ZDV + 3TC for six weeks (infant only)
Thai ZDV + 3TC trial, Thailand *(22)*	Open-label, nonrandomized ZDV + 3TC	ZDV + 3TC (from 34 weeks)	ZDV for four weeks (infant only)
DITRAME Plus (ANRS 1201.0) trial, Abidjan, Côte d'Ivoire *(23,38)*	Open label, ZDV plus single-dose NVP	ZDV from 36 weeks plus single-dose NVP at onset of labour	Single-dose NVP, plus ZDV for one week (infant only)
DITRAME Plus (ANRS 1201.1) trial, Abidjan, Côte d'Ivoire *(24,38)*	Open label, ZDV + 3TC plus single-dose NVP	ZDV + 3TC from 32 weeks (stopped at day 3 postpartum) plus single-dose NVP at the onset of labour	Single-dose NVP, plus one week ZDV (infant only)

Maternal CD4+ count at enrolment[a] 10^6 cells/L	Mode of infant feeding	Vertical transmission rate and efficacy
394	Breastfeeding (42%) and replacement feeding	12.3% in NVP arm versus 9.3% in ZDV + 3TC arm at eight weeks (difference not statistically significant)
365	Replacement feeding	Short-short arm was stopped at interim analysis (10.5%); vertical transmission rate 6.5% in long-long arm versus 4.7% in long-short arm and 8.6% in the short-long arm at 6 months (no statistical difference); in utero transmission significantly higher with short versus long maternal therapy regimens (5.1% versus 1.6%)
432	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 arms (53% of the vertical transmission rate in utero) Vertical transmission rate 1.4% in intervention arm versus 1.6% in placebo arm
Not reported	Replacement feeding	ZDV-alone arm was stopped due to a higher transmission rate than the NVP–NVP arm (6.3% versus 1.1%); in arms in which the mother received single-dose NVP, the vertical transmission rate did not differ significantly between the infant receiving or not receiving single-dose NVP (2.0% versus 2.8%)
426	Replacement feeding	1.6%; one fifth that of historical controls receiving ZDV only
274	Replacement feeding	2.8% at 18 months
370	Breastfeeding and replacement feeding	6.5% at six weeks
412	Breastfeeding and replacement feeding	4.7% at six weeks

Study	Drugs	Antenatal and intrapartum	Postpartum
NVAZ trial, Malawi *(25)*	Neonatal NVP versus NVP + ZDV	None (latecomers)	Single-dose NVP with or without ZDV twice daily for one week (infant only)
Postnatal NVP + ZDV trial, Malawi *(33)*	Neonatal NVP versus NVP + ZDV	Single-dose NVP	Single-dose NVP with or without ZDV twice daily for one week (infant only)
SIMBA trial, Rwanda, Uganda *(35)*	NVP versus 3TC postnatally in breastfeeding infants born to women who received ZDV + ddI antenatally and one week postpartum	ZDV + ddI from 36 weeks	ZDV + ddI for one week (mother), NVP once then twice daily versus 3TC twice daily while breastfeeding (infant)

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

[b] Included in the pooled analysis.

Almost all regimens evaluated to date include an intrapartum component and varying duration of antepartum and/or infant (and sometimes maternal) postpartum prophylaxis. Available data from these trials individually suggest that regimens using a combination of ARV drugs, such as ZDV plus single-dose maternal and infant NVP, may be more effective than single-drug regimens in reducing MTCT and that longer courses are more effective than shorter courses, but directly comparing trials is difficult *(31,32)*. The rate of transmission is associated with maternal, delivery and infant characteristics that differ by site and population. Further, the methods of assessing the efficacy of an intervention vary between studies, which can affect the results *(32)*. An individual record meta-analysis of data from the African MTCT-prevention trials is underway to allow direct comparison of the efficacy (MTCT rates at 6–8 weeks) of ARV regimens starting antenatally or intrapartum and using ZDV alone, NVP alone and ZDV + 3TC.

In a trial in Malawi *(25)*, infants born to women who had received neither antenatal nor intrapartum ARV prophylaxis were given either single-dose NVP or single-dose NVP plus ZDV for one week. The combination of NVP and ZDV was more efficacious than NVP alone. In contrast, a further trial in Malawi showed no benefit of adding ZDV for one week to neonatal single-dose NVP when the mother had received intrapartum NVP *(33)*.

Maternal CD4+ count at enrolment[a] 10^6 cells/L	Mode of infant feeding	Vertical transmission rate and efficacy
Not reported	Breastfeeding	Overall vertical transmission rate at 6–8 weeks 15.3% in NVP + ZDV arm and 20.9% with ZDV only. Vertical transmission rate at 6–8 weeks among infants who were negative at birth 7.7% and 12.1%, respectively (36% efficacy)
Not reported	Not reported	Overall vertical transmission rate at six weeks 14.1% in NVP-alone arm and 16.3% in NVP + ZDV arm (difference not statistically significant)
427	Breastfeeding (median 3.5 months, interquartile range 2.9–5.1 months)	Vertical transmission rate 6.9% at four weeks and 7.8% at 6 months (difference not statistically significant); transmission rate 2.4% between day 3 and 6 months

Many women do not know their HIV status at the time of delivery. HIV testing and counselling around the time of labour or shortly thereafter is an important entry-point for women to interventions to prevent MTCT, including ARV prophylaxis for the infant, and other HIV-related treatment and care services. Offering HIV testing and counselling shortly after delivery has been shown to be feasible *(25,34)*.

In breastfeeding populations, the impact of ARV prophylaxis given to pregnant women on the long-term risk of MTCT is less because of the continuing risk of MTCT in the postnatal period. Several ongoing and planned trials will assess the impact of ARV drugs given to the mother and/or the infant during the breastfeeding period *(10)*. Preliminary results have been presented from the SIMBA trial carried out in Rwanda and Uganda in which infants born to HIV-infected women who received ZDV plus didanosine (ddI) from 36 weeks of pregnancy until one week postpartum were randomized to receive either daily NVP or 3TC for up to seven months to reduce the risk of HIV transmission during breastfeeding *(35)*. The median duration of breastfeeding was 3.5 months *(26)*. In this study, the risk of postnatal transmission between week four and month six was 1.0% (95% confidence interval 0.0–2.0%). In comparison, when neither mother nor infant receives ARV prophylaxis during breastfeeding and if the infant breastfeeds for a full six months, the risk of postnatal transmission

occurring between four weeks and six months of age is estimated to be 4.2% (95% confidence interval 1.8–6.7%) *(36,37)*. Determining which element of the SIMBA intervention (ARV prophylaxis given to the mother, ARV prophylaxis for the infant or infant feeding counselling resulting in high rates of exclusive breastfeeding and early cessation of breastfeeding) had the greatest effect on the postnatal transmission rate is difficult.

Long-term efficacy in breastfeeding populations, 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 for short-course ZDV *(17)* and for NVP (single-dose maternal and infant) regimens *(7)*. To date, the only combination drug regimen that has been assessed for long-term efficacy at 18 months in a breastfeeding population is ZDV and 3TC, given in three different regimens *(9)*. Only the regimen that targeted the antenatal, intrapartum and postpartum period demonstrated a sustained, although reduced, effect at 18 months (Table 1).

Efficacy demonstrated in randomized trials may differ from the level of effectiveness in routine health services. Poor-quality health services and inadequate community support for programmes to prevent MTCT remain major barriers to the uptake of services in some settings. Further, in some areas with high levels of antenatal care coverage, the number of deliveries attended by a skilled practitioner remains disproportionately low. Women who deliver at home may not receive adequate intrapartum ARV prophylaxis, and providing postpartum care for these women and their children may be difficult. This hinders adherence to ARV prophylaxis and the follow-up and care of HIV-infected women and HIV-exposed infants.

The impact of interventions to prevent MTCT on child survival needs to be quantified. High levels of child mortality, high rates of postpartum acquisition of HIV infection during breastfeeding and lack of access to life-sustaining ARV treatment for women diminishes the long-term impact of peripartum interventions. In addition, for equity, humanitarian and moral reasons, women must have access to ARV treatment when required.

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

All ARV drugs are known to be associated with some toxicity. ARV drugs may be used during pregnancy:

- as potent combination treatment for maternal HIV disease if the woman requires treatment for her own health; or
- as single, dual or triple drug prophylaxis given to prevent HIV infection in infants.

The extent of risk to the woman, fetus and infant from ARV prophylaxis varies according to the timing of exposure, duration of exposure and the number of drugs to which the woman and infant are exposed. The risk of adverse events when short-course ARV regimens with one or two drugs are used for a limited period of time in pregnancy to prevent peripartum MTCT is likely to be less than when combinations of drugs are used for longer periods. Similarly, the potential toxicity to infants exposed to short courses of ARV drugs is expected to be less than when they are exposed for longer periods.

For women receiving ARV treatment for HIV disease, the benefits of the drugs include reducing maternal morbidity and mortality as well as preventing MTCT. When ARV drugs are used during pregnancy for preventing 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 reducing the risk of MTCT.

All the controlled clinical trials on MTCT prevention *(7,8,15,16,18,19,22)* have demonstrated the short-term safety and tolerance of short-course ARV regimens used for a limited period of time in pregnancy and/or in the infant for preventing MTCT. However, information is still lacking on the effects of short courses of ARV drugs to prevent MTCT on the long-term health of the infected mother (and that of her infant) or on future ARV treatment options, but research is ongoing. The issue of viral resistance and its potential implications for subsequent treatment outcome are discussed below.

The physiological changes that occur during pregnancy affect the absorption, distribution, metabolism and elimination of drugs, making predicting ARV pharmacokinetics difficult. Pharmacokinetic studies conducted to date suggest

that no dosing adjustments are required for ZDV, 3TC, ddI, stavudine (d4T) (NRTI drugs) or NVP (an NNRTI drug). However, pharmacokinetic studies on four of the protease inhibitors (PI) (saquinavir (SQV), ritonavir (RTV), indinavir and nelfinavir (NFV)) indicate that dosing adjustments or low-dose RTV boosting may be necessary to achieve adequate drug levels during pregnancy *(39,40)*. The possible and serious consequences of changes in pharmacokinetics during pregnancy include increased drug toxicity or viral resistance, which can emerge if drug levels are lowered. Additional pharmacokinetic studies among pregnant women are urgently required.

Toxicity and the contraindications to ARV drugs used for preventing MTCT and for ARV treatment are summarized below.

3.1 Nucleoside and nucleotide analogue reverse transcriptase inhibitors

Short-course ARV prophylaxis regimens that include nucleoside analogue drugs generally contain ZDV, or both ZDV and 3TC. The most frequent side-effects of ZDV and 3TC are nausea, headache, myalgia and insomnia; the incidence of these side-effects usually decreases with time. Contraindications to ZDV or ZDV plus 3TC for MTCT prophylaxis include known allergy to these drugs, severe disorders of the blood and blood-forming organs (haemoglobin <70 g/L or severe neutropaenia with neutrophils <750 10^6 cells/L) and severe liver or kidney dysfunction.

MTCT prophylaxis with short-course ZDV was not associated with short-term clinical or laboratory toxicity among pregnant women in several controlled trials and long-term follow-up. Trials from Thailand suggest that serious anaemia in women receiving ZDV from 28 weeks of pregnancy is rare and no increase in serious haematological toxicity was observed with ZDV started at 36 weeks in trials in Africa. Although these trial data are reassuring, it is not known whether ZDV from 28 weeks in Africa will result in serious anaemia in programmes where anaemia is common and women are not screened. HIV-related disease progression does not appear to be altered by receiving ZDV prophylaxis *(41)*.

Women may experience rare but more serious toxic effects with more prolonged use of combination drug regimens that include ZDV and 3TC or other nucleoside analogue drugs for treatment of HIV disease and/or as prophylaxis for preventing MTCT. These include lactic acidosis, hepatic steatosis, pancreatitis and other disorders associated with mitochondrial dysfunction. Although evidence suggests that lactic

acidosis occurs more commonly among women than men, whether pregnancy augments the incidence of this syndrome is unclear. There have been several case reports of lactic acidosis among pregnant women receiving ARV combinations including ddI + d4T, some resulting in maternal and in some cases, also fetal, death; all women had received this combination prior to conception and continued during pregnancy, and all presented with symptoms of lactic acidosis late in pregnancy *(42,43)*. Whenever possible, the ddI + d4T combination is recommended to be avoided in ARV treatment regimens, especially during pregnancy *(44–46)*.

The major short-term toxicity among infants exposed to prophylactic ZDV to reduce MTCT is anaemia, which is greater for longer exposures. However the effect is usually mild and reversible after treatment is interrupted *(9,15,16,18,47,48)*. More prolonged in utero exposure to ZDV administered during this period may result in a small but significant and durable effect on haematopoiesis for all exposed infants, infected or not, up to the age of 18 months, but the clinical significance of this observation is unknown *(49)*. More prolonged in utero (greater than one month) and infant exposure to ZDV and 3TC has resulted in more severe neonatal anaemia and neutropaenia than observed with shorter ZDV exposure or with ZDV exposure alone *(21,50)*. However, severe blood toxicity was not observed in studies in which infants were exposed to shorter ZDV and 3TC combination regimens *(9,19,22)*.

Clinical trials and prospective observational data have shown no evidence of an increased risk of congenital malformations associated with exposure to ZDV prophylaxis *(14,51,52)*. A greater than two-fold increase in the risk of birth defects following first-trimester exposure to ZDV, 3TC and d4T (NRTIs), NVP (an NNRTI) and NFV (a PI) have been excluded in an evaluation of outcomes of prospectively followed pregnancies in the United States Antiretroviral Pregnancy Registry *(51)*.

Although ZDV may theoretically have mutagenic and carcinogenic effects *(53,54)*, no trial or study on ZDV-exposed children has reported any malignancy *(47,55,56)*. A study in France identified clinical findings of mitochondrial dysfunction, manifested primarily as nervous system symptoms such as seizures with or without hyperlactataemia, among 7 (0.26%) of 2644 uninfected children with in utero and post-delivery ARV drug exposure *(57)*, but other studies *(58–60)* have not confirmed an increased rate of serious clinical manifestations.

There is concern that in utero exposure to tenofovir disoproxil fumarate (TDF), a nucleotide analogue drug, may result in abnormal bone

development. Studies on monkeys have shown decreased fetal growth and a reduction in fetal bone porosity with in utero exposure to TDF *(61,62)*. Studies on HIV-infected older children receiving TDF treatment have also identified decreased bone mineral density with chronic use *(63)*.

3.2 Non-nucleoside reverse transcriptase inhibitors

The WHO-recommended first-line ARV treatment regimens are NNRTI based (containing either efavirenz (EFV) or NVP), and NVP is the NNRTI drug most commonly used for MTCT prophylaxis. Contraindications to NVP use include the presence of known allergy to NVP or to benzodiazepine derivatives, which could result in an idiosyncratic allergic reaction regardless of the dose received.

Short-course ARV prophylaxis with NVP involves administration of a single dose of NVP to women during labour and to the newborn infant. No significant clinical or laboratory toxicity has been observed with the use of this regimen among more than 1600 women and infants participating in comparative clinical trials *(64)*.

The most frequent adverse effects of long-term NVP treatment are hepatotoxicity and cutaneous rash. One review *(65)* suggested that the incidence of asymptomatic elevations of liver enzymes is similar for all ARV drugs. However, a more detailed analysis showed a significantly higher rate of asymptomatic liver toxicity among NVP-exposed patients than among controls and that NVP-containing treatment regimens are associated with a higher incidence of symptomatic hepatic events *(66)*. The risk is highest in the first six weeks of NVP treatment. Starting NVP at half the normal dose during the first two weeks minimizes the risk of rash and hepatotoxicity. Serious NVP-associated rash and hepatic toxicity, although uncommon, may occur about 3- to 7-fold more often among women than among men *(67)*. Cases of fatal hepatotoxicity (fulminant hepatitis) and/or rash (Stevens–Johnson syndrome and toxic epidermal necrolysis) have been reported among women receiving NVP-based ARV treatment, including pregnant women, although these have been rare *(64)*. It is not known whether pregnancy increases the risk of hepatic toxicity among women receiving NVP.

The risk of severe hepatic toxicity and skin rash with NVP-based treatment varies according to the CD4 cell count at the time treatment is initiated. Women with CD4 counts greater than 250 10^6 cells/L when NVP-based ARV treatment starts, including pregnant women initiating

ARV treatment, have about a 10-fold higher risk of severe symptomatic hepatotoxicity than women with lower CD4 counts *(66, 68)*.

Among infants, prolonged exposure to NVP may be associated with infant haematological toxicity, including neutropaenia *(69)*. Rash and hepatic toxicity have also been reported among children receiving chronic NVP for treatment of HIV infection. However, serious toxicity has not been reported among infants receiving only single-dose NVP *(64)*.

First-trimester exposure to EFV has been associated with teratogenicity in studies in monkeys. Significant central nervous system defects (anencephaly, anophthalmia, microophthalmia and cleft palate) were observed in 3 of 20 (15%) infant cynomologus monkeys with in utero exposure to doses comparable to therapeutic EFV levels in humans *(70)*. The predictive value of animal reproductive toxicology studies among humans is unknown, and although studies in animals may identify teratogenic effects, extrapolating these effects to humans can be difficult *(71)*.

Among pregnancies reported prospectively to an ARV pregnancy registry in the United States, birth defects were observed in 4 of 142 (2.8%) live births following exposure to EFV-based regimens in the first trimester of pregnancy *(51)*. These rates are similar to the prevalence of birth defects in the United States population (3.1%), based on surveillance data from the United States Centers for Disease Control and Prevention. However, there are three retrospective case reports of neural tube defects with first-trimester EFV exposure *(72,73)*. Treatment with EFV should be avoided in the first trimester, which is the period of organogenesis; EFV is not recommended for use among women of childbearing potential unless effective contraception can be ensured. Women of childbearing potential should undergo pregnancy testing prior to initiating EFV.

3.3 Protease inhibitors

None of the current short-course ARV regimens used for preventing MTCT in resource-constrained settings includes PI drugs. Although PI drugs are highly potent antiviral agents when used in combination regimens and can significantly lower maternal viral load, the PI drugs do not cross the placenta and therefore do not provide prophylaxis to the fetus, unlike ZDV, 3TC and NVP.

Most ARV treatment guidelines do not consider PIs part of first-line regimens, due to higher pill counts, increased food and water

requirements, significant drug interactions, metabolic abnormalities, need for a cold chain for RTV-boosted regimens and a high cost relative to NNRTI-based regimens *(44,46,74)*. However, when a PI-based regimen is used during pregnancy, SQV with a low-dose RTV boost (SQV/r) and NFV are preferred choices, as data on the pharmacokinetics of other PI drugs among pregnant women are limited.

Long-term use of PIs can be associated with a variety of metabolic disorders, including lipodystrophy, hyperglycaemia, onset or exacerbation of diabetes mellitus and diabetic ketoacidosis. Pregnancy itself is a risk factor for hyperglycaemia, and using PIs during pregnancy could increase the risk for pregnancy-associated hyperglycaemia *(75)*.

In industrialized countries, the increasing use of complex and potent ARV combinations, especially those including PIs, has raised questions regarding the effect of such exposure on pregnancy outcome, especially exposure during the early weeks of pregnancy. In an analysis of European data on nearly 2500 uninfected children born to HIV-infected women, use of antenatal combination treatment with a PI drug was associated with a 4.1-fold increased risk of premature delivery compared with no treatment *(47)*. There have been other reports of an increased risk of premature delivery, predominantly associated with the use of PI drugs in early pregnancy *(76,77)*. However, a meta-analysis of data from seven studies including over 3200 women-child pairs from the United States did not report an increased incidence of prematurity *(78)*. The reason for the difference between the European and United States studies is unclear and could be related to differences in underlying population characteristics and background rates of preterm delivery *(79)*. The association between ARV treatment and preterm delivery observed in the European studies has been suggested to be due to immune modulation induced by combination treatment *(80)*.

4. Antiretroviral resistance following short-course prophylaxis for preventing MTCT

Viral resistance may emerge during ARV treatment and occurs more frequently with single- and dual-drug regimens. Viral resistance is a potential problem for women after short-term exposure to ARV drugs to prevent MTCT and for infants who become infected despite ARV prophylaxis *(21,45,64,81)*.

Before ARV drugs are received, HIV that contains drug mutations associated with viral resistance is present at low levels not detectable using standard resistance assays. Partly suppressive regimens favour replication of resistant virus over wild-type virus, and the amount of virus containing resistance mutations rises. However, after the drug is discontinued, the selective pressure is no longer present, wild-type virus again becomes the predominant strain and resistant virus is no longer detectable. The clinical consequences of such resistance are unclear at present.

Pre-existing resistant viral populations may be selected for or new mutations may develop with any ARV drug or drug regimen that does not fully suppress viral replication. Most studies have reported that a high maternal plasma viral load or low CD4 cell count are associated with an increased risk of resistance to any ARV drug. NVP and 3TC are drugs for which a single mutation leads to high-level resistance, whereas multiple sequential mutations are needed to confer resistance to ZDV.

Resistance to ZDV is usually only observed after several months of partly suppressive therapy. It emerges more rapidly among individuals with more advanced HIV disease. Studies to date show a low prevalence of ZDV resistance after short-course ZDV to reduce the risk of MTCT *(82–84)*. Exposure to short-course ZDV in programmes to prevent MTCT is unlikely to affect future ARV treatment options.

Resistance to 3TC can develop more rapidly, even when it is given in combination with ZDV. The risk of viral resistance to 3TC is correlated with the duration of drug exposure. In the multicentre Petra study, 12% of women who received ZDV + 3TC antenatally from 36 weeks, intrapartum and for one week postpartum had detectable resistance when tested one week after delivery *(81)*. In a cohort study in France, an overall resistance rate of 39% was observed

among women six weeks after delivery. In this study, resistance to 3TC was detectable among 50% (37 of 74) of women receiving 3TC for more than two months, 20% (14 of 70) of those receiving it for one to two months and none of the 12 women receiving 3TC for less than one month *(21)*. To date, 3TC has not been used extensively in programmes to prevent MTCT, and the impact of 3TC resistance on MTCT prevention and ARV treatment options is thus currently limited. However, this may change as ARV regimens containing ZDV, 3TC and NVP become more widely used in first-line treatment options and for preventing MTCT.

In addition to plasma viral load and CD4 cell count, other factors associated with the development of NVP resistance following MTCT prophylaxis include viral subtype, the compartment (such as plasma or breast milk), the time since single-dose NVP was received at which sampling is done and the number of NVP doses the woman received during labour. Directly comparing the rates of resistance reported in different trials is difficult, as the maternal plasma viral load and CD4 cell count, type of assay used to detect resistance and other factors vary between studies.

Viral strains resistant to NVP were detected at 6–8 weeks postpartum among 25% of women who received single-dose NVP in the HIVNET 012 study *(85)*. In this study, the rate of NVP resistance was higher among women infected with subtype D (36% resistance) compared with those infected with subtype A (19% resistance). In a study in South Africa, where subtype C virus is predominant, 39% of women had detectable resistance at seven weeks postpartum *(86)*. The SAINT study, also conducted in South Africa, found a 67% rate of NVP resistance at four weeks postpartum among women who had received two doses of NVP *(87)*. NVP-resistant viral strains are also selected for among women who received NVP in addition to other ARV drugs for preventing MTCT *(88)*. For example, NVP resistance was identified at four weeks postpartum among 17% of Thai women who received combination ZDV plus single-dose NVP *(28)* and at four weeks postpartum among 33% of women receiving a similar regimen in Côte d'Ivoire *(89)*.

The predominant NVP resistance mutation appears to shift at different time points, with the Y181C mutation predominant one week postpartum and K103N predominant by 6–8 weeks postpartum among women. In addition, when NVP resistance mutations have been detected among both mother and infant, the mutations differ. Viral resistance was detected among 33–53% of HIV-infected infants who were exposed to single-dose maternal and infant NVP *(86,87,90,91)*. In most cases, infants with NVP resistance 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.

The detection of either 3TC- or NVP-resistant strains among women is not associated with an increased risk of MTCT, although such an association cannot be excluded. The implications of transient selection of NVP-resistant virus with single-dose prophylaxis for subsequent ARV treatment remain uncertain, but research is ongoing to clarify this issue. Although there is no conclusive evidence, there is concern that viral resistance may negatively affect the response to subsequent ARV treatment that includes the same drug or a drug that may have cross-resistance.

An observational study in Thailand *(88)* assessed the response to ARV treatment among women who had previously received single-dose NVP for MTCT prophylaxis. Women receiving ARV treatment who had previously received single-dose intrapartum NVP were compared with women who had never been exposed to NVP. Viral resistance studies were conducted 10 days postpartum among women who had received single-dose NVP, thus allowing women with and without detectable NVP-resistant mutations to be compared. For all women in the study, NNRTI-based ARV treatment was initiated at a median of 6.1 months following delivery. In the preliminary results of the study, after six months of ARV treatment, 68% of the 50 women who received single-dose NVP and had at least one NVP resistance mutation, 80% of the 92 women who received single-dose NVP but did not have a detectable mutation and 85% of the 27 women who did not receive single-dose NVP had a plasma viral load $\leq 400\ 10^3$ copies/L (*P* for trend = 0.057); plasma viral load $\leq 50\ 10^3$ copies/L: 38%, 50% and 74%, respectively (*P* for trend = 0.006). Immune response was similar between groups, with a median CD4 count increase of about $100\ 10^6$ cells/L after six months of ARV treatment.

The findings of this study suggest that a MTCT prophylaxis regimen of ZDV plus single-dose NVP reduces the viral response to ARV treatment if NNRTI-based treatment is initiated soon after delivery. Larger clinical trials are underway and others are planned to provide more definitive data on the clinical implications of this finding. These studies will also investigate interventions to reduce the development or impact of such resistance.

The NNRTI drugs NVP and EFV have a longer half-life than NRTI drugs. NVP levels greater than 50 g/L can persist up to three weeks following discontinuation of NVP *(92)*. Thus, if a triple-drug regimen that includes NVP or EFV is given to prevent MTCT, continuing the dual NRTIs for a period after discontinuing the NNRTI drug could decrease the risk of developing NNRTI resistance. In one study, continuing ZDV + 3TC for five days after discontinuing NVP did not prevent the development of NVP resistance *(93)*. EFV also has a prolonged half-life and therefore could have a similar risk for inducing NNRTI resistance mutations. Several studies are evaluating whether

administering one or two NRTIs after NVP is stopped will reduce the incidence of resistance mutations, but data are not yet available.

It is unknown whether ARV treatment choices should be modified for HIV-infected children who have been exposed to ARV drugs in utero, neonatally or during breastfeeding. Studies are in progress among children to assess whether single-dose NVP prophylaxis compromises their response to subsequent ARV treatment with NNRTI-based regimens. Until additional data are available, HIV-infected women and children exposed to single-dose NVP prophylaxis should be considered eligible for NNRTI-based regimens as recommended in the revised 2003 WHO guidelines for ARV treatment in resource-constrained settings *(74)*.

5. Considerations regarding antiretroviral drugs for treating pregnant women and women of childbearing potential

Interventions to prevent MTCT should be part of an integrated continuum of HIV prevention, care and treatment services. Providing care and, when indicated, ARV treatment for women living with HIV/AIDS is a key component of strategies to prevent MTCT *(13,94)*. In many settings, maternal survival is a strong predictor of child survival *(95–97)*, and disease progression or deaths among mothers may undermine any improvement in child survival due to ARV prophylaxis for preventing MTCT *(96)*. A study in rural Uganda found that the death or terminal illness of a mother was an independent predictor of mortality among children *(95)*.

Programmes to prevent MTCT provide a key opportunity for identifying people who could benefit from ARV treatment either immediately or later, and most women living with HIV/AIDS who have participated in such programmes are anticipated to have access to treatment. Accordingly, the recommendations in this publication adhere to the principles set out in the 2003 WHO ARV treatment guidelines *(74)* and are consistent with the regimens chosen for first-line therapy. The guiding principle for ARV treatment among women is that therapeutic decisions should be based on their need and eligibility for ARV treatment according to the WHO treatment guidelines. Potent combination treatment substantially benefits the health of a woman and reduces the risk

of MTCT. All efforts should be made to ensure that all women who require ARV treatment have access to it.

The 2003 revised WHO treatment guidelines for ARV treatment in resource-constrained settings *(74)* describe in detail the WHO recommendations for initiating ARV treatment among children, adolescents and adults living with HIV/AIDS. If CD4 testing is available, WHO recommends offering ARV treatment to adolescents and adults with: WHO Stage IV disease irrespective of CD4 cell count, WHO Stage III disease with consideration of using CD4 cell counts less than 350 10^6 cells/L to assist decision making, and WHO Stages I and II disease in the presence of a CD4 cell count less than 200 10^6 cells/L. If CD4 testing is unavailable, WHO recommends offering ARV treatment to adolescents and adults with WHO Stages III and IV disease irrespective of total lymphocyte count or WHO Stage II disease with a total lymphocyte count less than 1200 10^6 cells/L.

The WHO-recommended first-line ARV regimens for adolescents and adults consist of a five-drug formulary, with a triple combination of ZDV + 3TC + NVP or d4T + 3TC + NVP or ZDV + 3TC + EFV or d4T + 3TC + EFV. These regimens were chosen following consideration of potency, side-effect profile, potential for maintenance of future treatment options, anticipated adherence, availability of fixed-dose combinations, coexistent health conditions (such as tuberculosis, hepatitis B virus or hepatitis C virus) and pregnancy or potential thereof. In the event of treatment failure, the recommended triple-drug second-line regimen is TDF or abacavir (ABC), plus ddI and either LPV/r or SQV/r or NFV. NFV is the preferred PI drug in settings that do not have a secure cold chain.

The selection of ARV regimen for women should consider the possibility of a planned or unintended pregnancy and that ARV drugs may be received in the first trimester of pregnancy during the period of organogenesis and before a pregnancy is recognized. Similarly, the possibility of a future pregnancy should be considered in selecting an ARV regimen for pregnant women. In addition to substantial clinical experience with the use of ZDV among pregnant women and among infants, the efficacy and safety of ZDV prophylaxis have been more extensively studied than those of other ARV drugs. When ARV treatment is initiated during pregnancy, ZDV should therefore be included in the regimen whenever possible.

Among women of childbearing potential or pregnant women who are eligible for ARV treatment, based on the same criteria as for non-pregnant women, the first-line ARV regimens are ZDV + 3TC + NVP or d4T + 3TC + NVP. The NNRTI component of these regimens is NVP, which is a potent drug with demonstrated clinical efficacy, is relatively easy to use and is available as part of a three-drug fixed-dose combination.

Alternative ARV drugs have limitations. EFV, an NNRTI drug, is considered potentially teratogenic and is not recommended in the first trimester of pregnancy. If EFV has to be used, then it should only be taken after the first trimester of pregnancy and avoided among women of childbearing age unless effective contraception can be ensured. Among non-pregnant women using effective contraception, EFV remains a viable option for the NNRTI component of the regimen.

ARV drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. The limited data available suggest that drug interactions between many ARV drugs (especially some NNRTIs and PIs) and hormonal contraceptives may alter the safety and effectiveness of both the hormonal contraceptives and the ARV drugs. It is not known whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medroxyprogesterone and norethisterone enantate) would be compromised, as these methods provide higher blood hormone levels than other progestogen-only hormonal contraceptives and than combined oral contraceptives. Thus, if a woman on ARV treatment decides to initiate or continue hormonal contraceptive use, the consistent use of condoms is recommended for preventing HIV transmission and may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

The dual NRTI combination d4T + ddI should be avoided in pregnancy because the risk of lactic acidosis is potentially increased with this combination. Should it be necessary to initiate a PI-based regimen in pregnancy, then SQV/r or NFV are the preferred PI drugs, as limited data are available on the pharmacokinetics of the other PI drugs among pregnant women.

6. Balancing risks and benefits in selecting an antiretroviral regimen for preventing HIV infection in infants

For pregnant women who do not yet need or have access to ARV treatment for their own disease, the use of ARV prophylaxis for preventing MTCT is recommended. Lack of availability of ARV treatment should not hinder the development of programmes to prevent MTCT based on short-course ARV prophylaxis.

Numerous factors need to be taken into account when selecting an ARV regimen for preventing MTCT. Decisions must be made regarding which ARV drug or drugs to use, the choice of single or combination drugs and the period when the drugs are to be taken (early antenatal, peripartum, early postpartum or late postpartum).

Although ARV regimens should be simplified and standardized as far as possible, issues relating to feasibility and acceptability, in addition to cost–benefit considerations, need to be taken into account in different settings. Many of the difficulties experienced by programmes in expanding access to MTCT interventions originate from health system constraints and the sociocultural context. A programme to prevent MTCT that cannot deliver or ensure adherence to a complex prophylaxis regimen will be less effective than a programme that implements the simpler single-dose (maternal and infant) NVP regimen, even though the more complex regimen may have shown greater efficacy in clinical trials.

The best choice of prophylactic regimen depends on when HIV testing and counselling can be performed. Women may be identified as HIV-infected before pregnancy, at different times during pregnancy, at the time of labour and delivery or postpartum.

Practical considerations in choosing ARV regimens for the prevention of MTCT include:

- the availability of HIV testing and counselling services;
- the proportion of HIV-infected women who are aware of their serostatus at various stages of pregnancy;

- the proportion of women seeking antenatal care;
- the timing of the first antenatal visit;
- the frequency of antenatal visits;
- the quality of antenatal care;
- the proportion of births occurring in health care facilities;
- access to early postpartum care;
- the acceptability and ease of dosage schedules; and
- the efficacy and safety of different ARV drug regimens, including their potential to compromise future treatment options.

ZDV, 3TC and NVP are the drugs of first choice in preventing MTCT. They have been formally assessed for safety and efficacy in many clinical trials. Administering them is relatively simple. All three drugs can be taken twice daily, and appropriate infant formulations are available. To further simplify prophylaxis, ZDV and 3TC are available in a co-formulation, thus reducing the number of pills to be taken. Finally, NVP can be used in a single-dose formulation for intrapartum use only. NVP is expected to be available soon in a single-dose formulation for infant use.

Whenever possible, ARV drug regimens should be chosen based on evidence of the relative safety of the various regimens (including the potential implications of viral resistance induced by short-course ARV), the relative efficacy in reducing the transmission of HIV from women to infants (Table 1) and the capacity of the health system to deliver the regimen. An attempt should be made to minimize the risk of adverse effects of ARV prophylaxis while maximizing the efficacy of the intervention, in addition to considering factors that may influence adherence.

Many studies have demonstrated an increased risk of MTCT in women with a high plasma viral load or low CD4 cell count, even if they receive short-course ARV prophylaxis. In the HIVNET 012 study, the rate of MTCT at six weeks in women with a CD4 count below 200 10^6 cells/L who had received short-course NVP prophylaxis was 21.7% and 31.6% at 18 months. The rate of MTCT among women with a CD4 count above 500 10^6 cells/L was 8.9% at six weeks and 11.2% at 18 months *(98)*. The DITRAME Plus (ANRS 1201.0) study in Côte d'Ivoire observed a six-week transmission rate of 18.6% among women with a CD4 count below 200 10^6 cells/L *(23)*. Women in that study received ZDV from 36 weeks and intrapartum ZDV plus single-dose NVP, and infants received single-dose NVP after delivery and ZDV for one week. In a pooled analysis from two trials in West Africa comparing maternal short-course ZDV to placebo, advanced maternal disease was associated with a substantial reduction in efficacy at 24 months. At 24 months, among children born to women with

CD4 counts below 500 10^6 cells/L, the risk of MTCT at 24 months was similar – 39.6% in the ZDV group and 41.3% in the placebo group. However, among children born to women with CD4 counts above 500 10^6 cells/L, the risk of MTCT were 9.1% in the ZDV group and 22.0% in the placebo group (a 59% reduction in risk of MTCT) *(17)*. The risk of developing NVP or 3TC resistance following short-course ARV regimens is greatest in women with high plasma viral load or low CD4 cell count. As the risk of HIV transmission, the efficacy of the regimen and the risk of drug resistance differ according to stage of disease, the risk–benefit balance of alternative drug regimens for MTCT prophylaxis is not the same for all women.

Several infant ARV regimens have been studied using different durations of either single or combination drugs. However, it is still not known which infant regimen achieves the largest reduction in MTCT, and the optimal infant regimen may depend on the ARV regimen that the mother received.

Although a formal pharmacokinetic evaluation has not been conducted, the February 2004 Technical Consultation considered the pharmacokinetic characteristics of NVP *(99)* and recommended that infants prescribed single-dose NVP can receive the dose shortly after delivery or before discharge from the health facility. Many programmes to prevent MTCT have found this more practical than administering the dose at 72 hours after delivery.

When delivery occurs within two hours of the mother taking NVP, the infant should receive single-dose NVP as soon as possible after delivery and ZDV for one week. If ZDV syrup for infants is not available, then the infant should receive NVP as soon as possible after delivery and a dose of NVP at 72 hours after birth. A clinical trial has shown that, if the mother did not receive any ARV drugs, then single-dose NVP and ZDV given to the infant for one week is more efficacious than single-dose NVP alone *(25)*. However, adding ZDV for one week had no effect when the mother and the infant had both received single-dose NVP *(33)*.

Although most rapid HIV tests detect HIV-1 and HIV-2, most do not differentiate between them. Several reports indicate that the rates of MTCT of HIV-2 are between 0% and 4% among breastfed infants in the absence of any interventions *(100–102)*. As the risk of MTCT is much lower for HIV-2 than HIV-1, recommendations for the use of ARV drugs to reduce MTCT also apply in settings with coexisting HIV-1 and HIV-2 infection. However, in such settings, HIV-1 and HIV-2 may need to be differentiated before initiating ARV treatment in women with indications for starting treatment, since NNRTI drugs are ineffective against HIV-2.

7. Safety and efficacy of antiretroviral drugs for reducing HIV transmission during breastfeeding

HIV transmission during breastfeeding has reduced the overall effectiveness of efforts to prevent MTCT. Research is ongoing to evaluate several new approaches to prevent HIV transmission during breastfeeding *(10)*.

The efficacy of ARV drugs in preventing postnatal transmission during breastfeeding is not yet known. A number of international clinical trials are evaluating the effect of ARV prophylaxis on the risk of early and/or late postnatal transmission in women who do not yet require treatment for their own health. In these studies, ARV drugs are provided to the woman during the breastfeeding period to reduce the risk of HIV transmission.

An alternative approach to preventing MTCT may be ARV prophylaxis given to the infant during breastfeeding. This approach was used in the SIMBA study *(35)* and is being investigated in several other trials. The timing of the postpartum interventions explored in these trials includes ultra-short regimens given in the first week of life to prevent transmission by colostrum or early breast-milk. They also include interventions covering the first 6–12 weeks of breastfeeding and interventions that provide ARV prophylaxis to the infant through the first six months of life accompanied by early cessation of breastfeeding.

Clinical trials are also studying the safety for both the mother and infant of (single and combination) ARV regimens given to breastfeeding women to prevent postnatal MTCT. ZDV, 3TC and NVP are detected in human breast-milk at concentrations that would achieve drug levels among children that are 5–10% of the therapeutic drug concentrations. Thus, breastfed infants of women receiving ARV drugs during the postnatal period would have potential ARV exposure but at subtherapeutic doses in terms of viral inhibition. It is not known whether PIs are excreted into breast-milk in humans, although some PIs can be detected in the milk of lactating animals.

Women with indications for ARV treatment and who are breastfeeding should continue their ARV regimen. The current United Nations recommendations *(103)* on HIV and infant feeding remain unchanged for women receiving ARV treatment, that is, HIV-infected women should avoid all breastfeeding when replacement feeding is acceptable, feasible, affordable, sustainable and safe. Otherwise, exclusive breastfeeding is recommended during the first months of life.

8. Recommendations for the use of antiretroviral drugs in pregnant women for their own health and to prevent HIV infection in infants

In this rapidly evolving field, many factors need to be considered in selecting an ARV regimen to prevent HIV infection in infants. Recommendations depend on when in pregnancy a woman is first identified as HIV-infected and on her need for ARV treatment. Programmatic considerations and the reality of weak health systems in most high-burden countries increase the difficulty of balancing short- and long-term safety (including viral resistance) and clinical effectiveness. The ARV drug regimen or regimens should be selected at the national level based on issues of efficacy, safety, drug resistance, feasibility and acceptability. Several drug regimens are likely to be more effective but more complicated to administer in resource-constrained settings. Initiating MTCT prevention programmes with a simple regimen such as single-dose NVP and introducing more complex interventions to prevent MTCT as infrastructure and programmatic capacity allow may therefore be more feasible in some resource-constrained settings.

The following sections provide specific recommendations for the most frequently encountered situations and are summarized in Table 2.

Clinical situation A: HIV-infected women with indications for initiating antiretroviral treatment who may become pregnant

The WHO-recommended first-line ARV regimens for women who may become pregnant and who have indications for starting ARV treatment are ZDV + 3TC + NVP or d4T + 3TC + NVP. The choice of ARV regimen for women with the potential to become pregnant must consider the possibility that the ARV drugs may be received during the first trimester: before pregnancy is recognized and during the period of organogenesis. There is concern that exposure to EFV during the first trimester may lead to central nervous system birth defects. When possible, drugs that are potentially teratogenic should be avoided if effective contraception cannot be ensured.

CLINICAL SITUATION B: HIV-INFECTED WOMEN RECEIVING ANTIRETROVIRAL TREATMENT WHO BECOME PREGNANT

Although there are concerns relating to potential effects of ARV drugs on the developing fetus, suspending treatment during the first trimester is generally not recommended. However, in the first trimester, EFV should be avoided and replaced by NVP, NFV or SQV/r because of a possible risk of central nervous system birth defects. A decision to substitute EFV in women should be evaluated on a case-by-case basis and consider the theoretical risks of central nervous system defects as well as the potential complications resulting from ARV substitution.

Women initiating NVP-based ARV treatment with a CD4 count above 250 10^6 cells/L are at an increased risk of symptomatic hepatotoxicity compared with women who are more immunosuppressed. It is not known whether this risk also applies when NVP is substituted for EFV in women who have established a good response to EFV-based ARV treatment. Nevertheless, the Technical Consultation cautioned against substituting with NVP in the first trimester of pregnancy in women with a CD4 count above 250 10^6 cells/L and recommended that a PI drug, such as SQV/r or NFV, could be substituted for EFV in such situations.

Women receiving TDF as part of a second-line ARV treatment regimen are recommended to continue the regimen during pregnancy. The benefits of continuing treatment are likely to exceed the risks to the fetus from a potential association between TDF and abnormal bone development.

Pregnancy-associated nausea and vomiting may affect a woman's ability to adhere to ARV treatment and occasionally require that treatment be temporarily discontinued. If treatment is discontinued, all ARV drugs should be stopped simultaneously and restarted together to decrease the risk of developing drug resistance.

ARV treatment with the full regimen should continue during labour. Infants born to women receiving ARV treatment can receive ZDV for one week or single-dose NVP or both single-dose NVP and ZDV for one week. The current recommendations on HIV and infant feeding remain unchanged for women receiving ARV treatment.

Clinical situation C: HIV-infected pregnant women with indications for antiretroviral treatment

The overarching consideration in this situation is the health of the woman and ensuring that she receives optimal treatment. However, pregnancy and breastfeeding raise additional safety concerns for the woman and her child. Potent combination treatment has substantial benefits for the woman's health and is likely to provide enhanced protection against MTCT. All efforts should be made to ensure that pregnant women eligible for ARV treatment according to WHO guidelines have access to it.

For eligible women, ARV treatment should generally be started as soon as possible during pregnancy. Delaying the start of treatment may be desirable if a woman is in the first trimester of pregnancy, although if a woman's clinical or immune status suggests that she is severely ill, the benefits of early treatment outweigh the potential risks to the fetus.

If an HIV-infected woman with indications for treatment is first seen very late in pregnancy (beyond 36–38 weeks of pregnancy) and treatment cannot be initiated prior to delivery, the recommendations for clinical situation E for preventing MTCT should be followed while planning to initiate ARV treatment for the woman as soon as possible after delivery.

When ARV treatment is initiated during pregnancy, ZDV should be included in the regimen whenever possible. If NVP-based regimens are contraindicated, initiating a PI-based regimen during pregnancy could be necessary, in which case SQV/r or NFV are the preferred PIs.

Treatment with EFV should not be initiated in the first trimester of pregnancy, as this is the period of organogenesis. There are theoretical risks to the fetal brain in later pregnancy, and hence EFV should only be used in pregnancy when the potential benefits justify the potential risks to the fetus. In addition, the future possibility of pregnancy should be considered, and EFV-based treatment should only be initiated if effective postpartum contraception can be ensured.

Treatment should continue during labour and the postpartum period, and infants should receive ZDV for one week or single-dose NVP or both single-dose NVP and ZDV for one week. Continuing the infant on ZDV for four to six weeks can be considered if the woman received less than four weeks of antepartum ARV treatment. Administering a more prolonged infant ARV regimen is logistically more complex, and the infant dose of ZDV may need to be adjusted as the infant gains weight.

The current recommendations on infant feeding remain unchanged for women receiving ARV treatment.

CLINICAL SITUATION D: HIV-INFECTED PREGNANT WOMEN WITHOUT INDICATIONS FOR ANTIRETROVIRAL TREATMENT

A number of regimens are recommended. A regimen consisting of ZDV starting from week 28 of pregnancy, single-dose NVP and ZDV during labour, and single-dose NVP plus ZDV for one week given to the infant is highly efficacious. Several trials indicate that starting ZDV later in pregnancy is also efficacious and may be more feasible in some settings. In addition to single-dose NVP at the onset of labour, women should continue to receive ZDV during labour.

Some studies have administered ZDV every three hours during labour; others have given only a double dose (600 mg) at the onset of labour. Although these regimens have not been compared directly, there are similar reductions in HIV transmission rates. The double-dose regimen at the onset of labour may be more practical and preferred in some circumstances.

Several regimens can be considered as alternatives to the ZDV plus single-dose NVP regimen starting from week 28. They differ in practicality and the problem of resistance and are not presented in any order of preference.

Many challenges are involved in expanding access to MTCT prevention programmes, and single-dose (maternal and infant) NVP is the simplest regimen to deliver. However, where feasible, programmes should plan to introduce more complex and efficacious ARV regimens. The development of programmes for preventing MTCT that use single-dose NVP should not be delayed nor hindered while necessary improvements to infrastructure or health systems are taking place to enable the delivery of more complex ARV regimens.

Circumstances may arise in which ARV prophylaxis cannot be started before labour. For many women, HIV testing and counselling may occur late in pregnancy or during labour. If starting ARV prophylaxis before labour is not practical or feasible, then single-dose maternal and infant NVP can be used. The single-dose NVP alternative is the simplest regimen to provide and is the preferred regimen in settings with a limited capacity for delivering health services and is an important option when HIV infection is identified late in pregnancy or during labour.

For women receiving single-dose 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 NVP doses. In such situations, the infant should receive NVP as soon as possible after birth as well as ZDV for one week.

Alternative regimens that do not contain NVP avoid the potential adverse effects of NVP resistance on subsequent ARV treatment. ZDV alone started from 28 weeks of pregnancy or as soon as feasible thereafter and continued in the infant for one week after birth is efficacious and avoids the risk of drug resistance. Combination ZDV + 3TC started at 36 weeks of pregnancy is more efficacious than ZDV alone but may result in viral resistance to 3TC in some women who receive more than four weeks prophylaxis.

Triple-drug combination regimens for preventing MTCT can be considered. The use of a fully suppressive triple-drug regimen, such as the WHO-recommended first-line and second-line regimens, is expected to prevent the emergence of resistance and also be highly effective in reducing MTCT. However, the safety and effectiveness of such regimens in women who do not yet require ARV treatment have not been established in resource-constrained settings.

Although cases of severe symptomatic hepatotoxicity among women receiving NVP-based ARV treatment are rare, an increased risk has been reported among women receiving daily NVP-based treatment who have a CD4 count above 250 10^6 cells/L at the time treatment is initiated. Until further data and clinical experience are available, NVP-based triple-combination regimens should be used with caution among women who do not require ARV treatment for their own health, especially those with a good immune system.

In Europe and the United States, triple-combination regimens have been associated with lower rates of transmission compared with other drug combinations. However, the increased complexity of these regimens (especially PI-based regimens), increased exposure to potential drug toxicity and lack of evidence on the efficacy and safety of these regimens for preventing MTCT in resource-constrained settings need to be considered. If triple-combination regimens are used for preventing MTCT among women without indications for ARV treatment then the recommended regimens are ZDV + 3TC + SQV/r or ZDV + 3TC + NFV. If the woman is in the third trimester of pregnancy (and hence past the period of concern for teratogenicity), an alternative regimen containing ZDV + 3TC + EFV could be considered.

If a triple-drug combination is used, the regimen should be continued during labour but discontinued after delivery if the woman does not have an indication for ARV treatment. All the drugs should be stopped simultaneously to decrease the risk of viral resistance.

The recommended ARV regimens for infants include single-dose NVP, ZDV for one week, single-dose NVP plus ZDV for one week or ZDV and 3TC for one week. The choice depends on the ARV regimen taken by the mother. More intensive (dual) infant regimens are recommended when the mother has received a suboptimal antepartum and/or intrapartum regimen. Programmes that have selected a ZDV-based maternal regimen can consider continuing the infant on ZDV for four to six weeks if the mother received ZDV for less than four weeks. Administering a more prolonged infant ARV regimen is logistically more complex, and the infant dose of ZDV may need to be adjusted as the infant gains weight.

Clinical situation E: HIV-infected pregnant women with indications for starting antiretroviral treatment but treatment is not yet available

The same recommendations and considerations apply as in clinical situation D, except that the most efficacious regimen available should be selected for these women wherever possible. A high rate of MTCT is observed in women who have clinical or immune indications for ARV treatment but do not initiate triple-drug treatment during pregnancy, even if they receive short-course ARV prophylaxis. Further, most studies have reported that a high maternal plasma viral load or low CD4 cell count is associated with an increased risk of resistance. All efforts should be made to ensure that all women who need ARV treatment according to WHO guidelines have access to it.

Clinical situation F: HIV-infected pregnant women with active tuberculosis

All women with a cough for more than 2–3 weeks should be screened for tuberculosis. Among HIV-infected pregnant women with active tuberculosis, especially smear-positive pulmonary tuberculosis, the priority is to treat tuberculosis. However, with careful clinical management, women with HIV-associated tuberculosis can receive ARV treatment at the same time as tuberculosis treatment. The

optimum time to initiate ARV treatment depends on CD4 cell counts, tolerance of tuberculosis treatment and other clinical factors. Potential drug interactions between anti-tuberculosis drugs and some ARV drugs complicate the choice of ARV drug regimen. A regimen consisting of ZDV or d4T plus 3TC plus SQV/r can be considered for a pregnant woman initiating ARV treatment while receiving rifampicin-based anti-tuberculosis treatment *(74)*. Pharmacokinetic data are limited regarding the use of SQV/r and concomitant rifampicin among women. Additional pharmacokinetic studies are needed to determine the optimal ARV treatment regimen for pregnant women receiving rifampicin-based anti-tuberculosis treatment. Although ABC and rifampicin can be used concomitantly, experience with ABC during pregnancy is limited. In the third trimester, an EFV-based regimen could be considered. When EFV-based regimens are initiated, the future possibility of pregnancy should be considered, and EFV should only be used if effective contraception can be ensured postpartum. NVP-containing ARV regimens can be initiated during the rifampicin-free continuation phase of tuberculosis treatment. As there is more experience with the use of ZDV than d4T among pregnant women and infants, ZDV is preferred in pregnancy.

The recommendations for short-course ARV prophylaxis as described in clinical situation D can be followed if HIV-infected women with active tuberculosis do not initiate ARV treatment. Although there is significant interaction between rifampicin and NVP, this is unlikely to result in decreased efficacy of single-dose NVP among women receiving rifampicin.

Clinical situation G: Pregnant women of unknown HIV status at the time of labour or women in labour known to be HIV-infected who have not received antiretroviral drugs before labour

In many settings, a substantial proportion of women present at the time of labour without previously accessing HIV testing and counselling services. Identifying HIV-infected women around the time of labour or shortly after delivery is an important entry point into services for preventing MTCT and accessing HIV-related treatment and care. If there is time, HIV testing and counselling should be offered to women of unknown HIV status in labour. If this is not possible, testing and counselling can be offered shortly after delivery. Rapid HIV tests should be used for women agreeing to be tested.

Single-dose NVP should be offered to HIV-infected women in labour who have not received antenatal ARV prophylaxis, and the infant should receive single-dose NVP. If imminent delivery is expected, the maternal NVP dose should be omitted, and the infant should receive NVP as soon as possible after birth and ZDV for one week. If ZDV syrup for infants is not available, then the infant should receive NVP as soon as possible after delivery and a dose of NVP at 72 hours after birth. An alternative regimen starting during labour is ZDV + 3TC and continued for one week for the mother and the infant. In women who have confirmed HIV infection and indications for ARV treatment, the WHO treatment guidelines can be followed and ARV treatment initiated postpartum.

Infants born to HIV-infected women who did not receive antenatal or intrapartum ARV prophylaxis should receive single-dose NVP as soon as possible after birth plus ZDV for one week as detailed in clinical situation H.

Clinical situation H: Infants born to HIV-infected women who have not received any antiretroviral drugs

Identifying HIV-infected women shortly after delivery is potentially an important entry point into services to prevent MTCT and to provide HIV treatment and care, as a substantial proportion of women deliver without accessing HIV testing and counselling.

ZDV for one week and single-dose NVP are recommended for infants born to HIV-infected women who did not receive any ARV prophylaxis because this regimen results in a greater reduction in transmission than single-dose NVP for the infant alone.

NVP and ZDV prophylaxis for infants should begin as soon as possible after delivery. ARV drugs initiated immediately or soon after delivery are likely to result in a larger reduction in transmission than later initiation. If ARV prophylaxis is delayed more than two days, it is unlikely to have any benefit.

Table 2. Clinical situations and recommendations for the use of antiretroviral drugs in pregnant women and women of child-bearing potential in resource-constrained settings

Clinical situation	Recommendation
A: HIV-infected women with indications for initiating ARV treatment[1] who may become pregnant	First-line regimens: ZDV + 3TC + NVP or d4T + 3TC + NVP EFV should be avoided in women of childbearing age, unless effective contraception can be ensured. Exclude pregnancy before starting treatment with EFV
B: HIV-infected women receiving ARV treatment who become pregnant	**Women** Continue the current ARV regimen[2] unless it contains EFV, in which case substitution with NVP or a PI should be considered if the woman is in the first trimester. Continue the same ARV regimen during the intrapartum period and after delivery **Infants** Infants born to women receiving either first- or second-line ARV treatment regimens: ZDV for one week or single-dose NVP or single-dose NVP plus ZDV for one week
C: HIV-infected pregnant women with indications for ARV treatment[1]	**Women** Follow the treatment guidelines as for non-pregnant adults except that EFV should not be given in the first trimester First-line regimens: ZDV + 3TC + NVP or d4T + 3TC + NVP Consider delaying initiating ARV treatment until after the first trimester, although for severely ill women the benefits of initiating treatment early clearly outweigh the potential risks **Infants** ZDV for one week or single-dose NVP or single-dose NVP plus ZDV for one week[3]

Clinical situation	Recommendation
D: HIV-infected pregnant women without indications for ARV treatment[1]	• **Women** ZDV starting at 28 weeks or as soon as feasible thereafter; continue ZDV during labour, plus single-dose NVP at the onset of labour **Infants** Single-dose NVP plus ZDV for one week[3] Alternative regimens (not in any order of preference) • **Women** ZDV starting at 28 weeks or as soon as feasible thereafter; continue in labour **Infants** ZDV for one week[3] • **Women** ZDV + 3TC starting at 36 weeks or as soon as feasible thereafter; continue in labour and for one week postpartum **Infants** ZDV + 3TC for one week • **Women** Single-dose NVP **Infants** Single-dose NVP
E: HIV-infected pregnant women who have indications for starting ARV treatment[1] but treatment is not yet available	Follow the recommendations in clinical situation D, but preferably use the most efficacious regimen that is available and feasible
F: HIV-infected pregnant women with active tuberculosis	If ARV treatment is initiated, consider:[4] ZDV + 3TC + SQV/r or d4T + 3TC + SQV/r If treatment is initiated in the third trimester, ZDV + 3TC + EFV or d4T + 3TC + EFV can be considered If ARV treatment is not initiated, follow the recommendations in clinical situation D

Clinical situation	Recommendation
G: Pregnant women of unknown HIV status at the time of labour or women in labour known to be HIV-infected who have not received ARV drugs before labour	If there is time, offer HIV testing and counselling to women of unknown status and if positive initiate intrapartum ARV prophylaxis. If there is insufficient time for HIV testing and counselling during labour, then offer testing and counselling as soon as possible postpartum and follow the recommendations in clinical situation H Recommended regimens (not in any order of preference) • **Women** Single-dose NVP; if imminent delivery is expected do not give the dose but follow the recommendations in clinical situation H **Infants** Single-dose NVP • **Women** ZDV + 3TC in labour and ZDV + 3TC for one week postpartum **Infants** ZDV + 3TC for one week
H: Infants born to HIV-infected women who have not received any ARV drugs	**Infants** Single-dose NVP as soon as possible after birth plus ZDV for one week If the regimen is started more than two days after birth, it is unlikely to be effective

[1] WHO recommendations for initiating ARV treatment in HIV-infected adolescents and adults. If CD4 testing is available it is recommended to offer ARV treatment to patients with: WHO Stage IV disease irrespective of CD4 cell count, WHO Stage III disease with consideration of using CD4 cell counts less than 350 10^6 cells/L to assist decision-making and WHO Stage I and II disease in the presence of a CD4 cell count less than 200 10^6 cells/L. If CD4 testing is unavailable, it is recommended to offer ARV treatment to patients with WHO Stage III and IV disease irrespective of total lymphocyte count or WHO Stage II disease with a total lymphocyte count less than 1200 10^6 cells/L.

[2] Conduct clinical and laboratory monitoring as outlined in the 2003 revised WHO treatment guidelines *(74)*.

[3] Continuing the infant on ZDV for four to six weeks can be considered if the woman received antepartum ARV drugs for less than four weeks.

[4] ABC can be used in place of SQV/r; however, experience with ABC during pregnancy is limited. In the rifampicin-free continuation phase of tuberculosis treatment, an NVP-containing ARV regimen can be initiated.

References

1. UNAIDS and World Health Organization. AIDS epidemic update: 2003. Geneva, UNAIDS, 2003 (http://www.unaids.org/Unaids/EN/Resources/Publications/corporate+publications/aids+epidemic+update+-+december+2003.asp, accessed 7 June 2004).

2. De Cock KM et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. Journal of the American Medical Association, 2000, 283(9):1175–1182.

3. Dorenbaum A et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. Journal of the American Medical Association, 2002, 288(2):189–198.

4. Cooper ER et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2002, 29(5): 484–494.

5. Thorne C, Newell ML. Are girls more at risk of intrauterine-acquired HIV infection than boys? AIDS, 2004, 18(2):344–347.

6. Buekens P, Curtis S, Alayon S. Demographic and health surveys: caesarean section rates in sub-Saharan Africa. British Medical Journal, 2003, 326(7381):136.

7. Jackson JB et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. Lancet, 2003, 362(9387):859-68.

8. Guay LA et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet, 1999, 354(9181):795–802.

9. The Petra study team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. Lancet, 2002, 359(9313):1178–1186.

10. Gaillard P et al. Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2004, 35(2): 178-87.

11. Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. Lancet, 2002, 359(9323):2097–2104.

12. Progress report on the global response to the HIV/AIDS epidemic, 2003. Geneva, UNAIDS, 2003 (http://www.unaids.org/ungass/en/global/ungass00_en.htm, accessed 7 June 2004).

13. Strategic approaches to the prevention of HIV infection in infants: report of a WHO meeting, Morges, Switzerland, 20–22 March 2002. Geneva, World Health Organization, 2003 (http://www.who.int/hiv/pub/mtct/en/StrategicApproachesE.pdf, accessed 7 June 2004).

14. Connor EM et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. New England Journal of Medicine, 1994, 331(18):1173–1180.

15. Shaffer N et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet, 1999, 353(9155):773–780.

16. Dabis F et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. DIminution de la Transmission Mere-Enfant. Lancet, 1999, 353(9155): 786–792.

17. Leroy V et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. AIDS, 2002, 16(4):631–641.

18. Wiktor SZ et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. Lancet, 1999, 353(9155):781–785.

19. Moodley D et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. Journal of Infectious Diseases, 2003, 187(5):725–735.

20. Lallemant M et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. New England Journal of Medicine, 2000, 343(14):982–991.

21. Mandelbrot L et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. Journal of the American Medical Association, 2001, 285(16):2083–2093.

22. Chaisilwattana P et al. Short-course therapy with zidovudine plus lamivudine for prevention of mother-to-child transmission of human immunodeficiency virus type 1 in Thailand. Clinical and Infectious Diseases, 2002, 35(11):1405–1413.

23. Dabis F et al. A short course of zidovudine + peripartum nevirapine is highly efficacious in preventing mother-to-child transmission of HIV-1: the ARNS 1201 DITRAME Plus study. 10th Conference on Retroviruses and Opportunistic Infections, Boston, Massachusetts, USA, 10–14 February 2003 (Abstract 854).

24. Dabis F et al. Effectiveness of a short course of zidovudine + lamivudine and peripartum nevirapine to prevent HIV-1 mother-to-child transmission. The ANRS DITRAME Plus trial, Abidjan, Côte d'Ivoire. Antiviral Therapy, 2003, 8 (Suppl. 1): S236–S237.

25. Taha TE et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. Lancet, 2003, 362(9391):1171-7.

26. Vyankandondera J et al. Reducing risk of HIV-1 transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA). 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 13–16 July 2003 (Abstract LB7).

27. United States Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Washington, DC, United States Department of Health and Human Services, 2003 (http://www.aidsinfo.nih.gov/guidelines/perinatal/PER_112603.pdf, accessed 7 June 2004).

28. Chalermchokcharoenkit A et al. Combination short-course zidovudine plus 2-dose nevirapine for prevention of mother-to-child transmission: safety, tolerance, transmission, and resistance results. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 96).

29. Lallemant M et al. A randomized, double-blind trial assessing the efficacy of single-dose perinatal nevirapine added to a standard zidovudine regimen for the prevention of mother-to-child transmission of HIV-1 in Thailand. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 40LB).

30. Lallemant M et al. Nevirapine (NVP) during labor and in the neonate significantly improves zidovudine (ZDV) prophylaxis for the prevention of perinatal HIV transmission: results of PHPT-2 first interim analysis. 14th International Conference on AIDS, Barcelona, Spain, 7–12 July 2002 (Abstract LbOr22).

31. Alioum A et al. Estimating the efficacy of interventions to prevent mother-to-child transmission of HIV in breast-feeding populations: development of a consensus methodology. Statistics in Medicine, 2001, 20(23):3539–3556.

32. Alioum A et al. Estimating the efficacy of interventions to prevent mother-to-child transmission of human immunodeficiency virus in breastfeeding populations: comparing statistical methods. American Journal of Epidemiology, 2003, 158(6): 596–605.

33. Taha TE et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: Randomized controlled trial. JAMA, 2004 (in press)

34. Chersich MF et al. Initiating early postpartum voluntary counselling and testing in a resource-constrained setting. 14th International Conference on AIDS, Barcelona, Spain, 7–12 July 2002 (Abstract TuPeF5398).

35. Vyankandondera J et al. Reducing risk of HIV-1 transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA-study). 13th International Conference on AIDS & STIs in Africa, Nairobi, Kenya, 21–26 September 2003.

36. Richardson BA et al. Breast-milk infectivity in human immunodeficiency virus type 1-infected mothers. Journal of Infectious Diseases, 2003, 187(5):736–740.

37. Breastfeeding and HIV International Transmission Study (BHITS) Group. Late postnatal transmission of HIV-1 in breastfed children: an individual patient data meta-analysis. Journal of Infectious Diseases (in press).

38. Dabis F et al. Effectiveness of short-course combinations of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum transmission of HIV: the ANRS 1201 Ditrame Plus study, Abidjan, Côte d'Ivoire. Submitted.

39. Acosta EP et al. Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. Antimicrobial Agents and Chemotherapy, 2004, 48(2):430-6.

40. Bryson Y et al. Pharmacokinetics, antiviral activity, and safety of nelfinavir (NFV) with ZDV/3TC in pregnant HIV-infected women and their infants: PACTG 353 Cohort 2. Ninth Conference on Retroviruses and Opportunistic Infections, Seattle, Washington, USA, 24–28 February 2002 (Abstract 795-W).

41. Bardeguez AD et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2003, 32(2): 170–181.

42. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. Sexually Transmitted Infections, 2002, 78(1):58–59.

43. Mandelbrot L et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. AIDS, 2003, 17(2):272–273.

44. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Washington, DC, United States Department of Health and Human Services, 2003 (http://www.aidsinfo.nih.gov/guidelines/adult/AA_032304.pdf, accessed 7 June 2004).

45. Coll O et al. Pregnancy and HIV infection: a European consensus on management. AIDS, 2002, 16(Suppl. 2):S1–S18.

46. British HIV Association (BHIVA) Writing Committee on behalf of the BHIVA Executive Committee. British HIV Association guidelines for the treatment of HIV-infected adults with antiretroviral therapy. London, British HIV Association, 2003 (http://www.bhiva.org/guidelines/2003/hiv/gindex.html, accessed 7 June 2004).

47. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2003, 32(4):380–387.

48. Taha TE et al. Effect of HIV-1 antiretroviral prophylaxis on hepatic and hematological parameters of African infants. AIDS, 2002, 16(6):851–858.

49. Le Chenadec J et al. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. AIDS, 2003, 17(14): 2053–2061.

50. Lambert JS et al. A pilot study to evaluate the safety and feasibility of the administration of AZT/3TC fixed dose combination to HIV infected pregnant women and their infants in Rio de Janeiro, Brazil. Sexually Transmitted Infections, 2003, 79(6):448–452.

51. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989 through 31 July 2003. Wilmington, NC, Registry Coordinating Center, 2003.

52. Lambert JS et al. Risk factors for preterm birth, low birth weight, and intrauterine growth retardation in infants born to HIV-infected pregnant women receiving zidovudine. Pediatric AIDS Clinical Trials Group 185 Team. AIDS 2000, 14(10): 1389–1399.

53. Toltzis P et al. Zidovudine-associated embryonic toxicity in mice. Journal of Infectious Diseases, 1991, 163(6):1212–1218.

54. Olivero OA et al. Incorporation of zidovudine into leukocyte DNA from HIV-1-positive adults and pregnant women, and cord blood from infants exposed in utero. AIDS, 1999, 13(8):919–925.

55. Hanson IC et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 1999, 20(5): 463–467.

56. Culnane M et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. Journal of the American Medical Association, 1999, 281(2):151–157.

57. Barret B et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. AIDS, 2003, 17(12):1769–1785.

58. Lindegren ML et al. Drug safety during pregnancy and in infants. Lack of mortality related to mitochondrial dysfunction among perinatally HIV-exposed children in pediatric HIV surveillance. Annals of the New York Academy of Sciences, 2000, 918: 222–235.

59. Dominguez K, Bertolli J, Fowler M, et al. Lack of definitive severe mitochondrial signs and symptoms among deceased HIV-uninfected and HIV-indeterminate children < or = 5 years of age, Pediatric Spectrum of HIV Disease project (PSD), USA. Annals of the New York Academy of Sciences, 2000, 918:236–246.

60. Chotpitayasunondh T et al. Safety of late in utero exposure to zidovudine in infants born to human immunodeficiency virus-infected mothers: Bangkok. Bangkok Collaborative Perinatal HIV Transmission Study Group. Pediatrics, 2001, 107(1):E5.

61. Tarantal AF et al. Administration of 9-[2-(R)-(phosphonomethoxy)propyl]aden ine (PMPA) to gravid and infant rhesus macaques (Macaca mulatta): safety and efficacy studies. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 1999, 20(4):323–333.

62. Tarantal AF et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2002, 29(3):207–220.

63. Hazra R et al. Safety, tolerability, and clinical responses to tenofovir DF in combination with other antiretrovirals in heavily treatment-experienced HIV-infected children: data through 48 weeks. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 928).

64. Mofenson LM, Munderi P. Safety of antiretroviral prophylaxis of perinatal transmission for HIV-infected pregnant women and their infants. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2002, 30(2): 200–215.

65. Stern JO et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2003, 34(Suppl. 1):S21–S33.

66. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2004, 35(5): 538–539.

67. Bersoff-Matcha SJ et al. Sex differences in nevirapine rash. Clinical and Infectious Diseases, 2001, 32(1):124–129.

68. Important new safety information. Re: Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE (nevirapine). Ingelheim, Boehringer Ingelheim, 2004.

69. Shetty AK et al. Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2003, 34(5):482–490.

70. From the Food and Drug Administration. Journal of the American Medical Association, 1998, 280(17):1472.

71. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. New England Journal of Medicine, 1998, 338(16):1128–1137.

72. Fundaro C et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. AIDS, 2002, 16(2):299–300.

73. De Santis M et al. Periconceptional exposure to efavirenz and neural tube defects. Archives of Internal Medicine, 2002, 162(3):355.

74. Scaling up antiretroviral therapy in resource-constrained settings: treatment guidelines for a public health approach. Geneva, World Health Organization, 2003 (http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf, accessed 7 June 2004).

75. Chmait R et al. Protease inhibitors and decreased birth weight in HIV-infected pregnant women with impaired glucose tolerance. Journal of Perinatology, 2002, 22(5):370–373.

76. Thorne C, Newell M. Pregnancy outcome in ART-treated HIV-infected women in Europe. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 98).

77. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. AIDS, 2000, 14(18): 2913–2920.

78. Tuomala RE et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. New England Journal of Medicine, 2002, 346(24):1863–1870.

79. Thorne C, Fiore S, Rudin C. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. New England Journal of Medicine, 2003, 348(5):471–472; author reply 471–472.

80. Fiore S. Treatment, immunological changes and pregnancy outcome. 10th Conference on Retroviruses and Opportunistic Infections, Boston, Massachusetts, USA, 10–14 February 2003 (Abstract 354).

81. Giuliano M et al. Selection of resistance mutations in pregnant women receiving zidovudine and lamivudine to prevent HIV perinatal transmission. AIDS, 2003, 17(10): 1570–1572.

82. Cunningham CK et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. Journal of Infectious Diseases, 2002, 186(2):181–188.

83. Nolan M, Fowler MG, Mofenson LM. Antiretroviral prophylaxis of perinatal HIV-1 transmission and the potential impact of antiretroviral resistance. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2002, 30(2): 216–229.

84. Ekpini RA et al. Changes in plasma HIV-1-RNA viral load and CD4 cell counts, and lack of zidovudine resistance among pregnant women receiving short-course zidovudine. AIDS, 2002, 16(4):625–630.

85. Eshleman et al. Characterization of nevirapine resistance mutations in women with subtype A vs. D HIV-1 6–8 weeks after single-dose nevirapine (HIVNET 012). Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 2004, 35(2):126–130.

86. Martinson N et al. HIV resistance and transmission following single-dose nevirapine in a PMTCT cohort. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 38).

87. Sullivan J. South African Intrapartum Nevirapine Trial: selection of resistance mutations. 14th International Conference on AIDS, Barcelona, Spain, 7–12 July 2002 (Abstract LbPeB9024).

88. Jourdain G et al. Exposure to intrapartum single-dose nevirapine and subsequent maternal 6-month response to NNRTI-based regimens. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 41LB).

89. Chaix ML et al. Genotypic resistance analysis in women who received intrapartum nevirapine associated to a short course of zidovudine to prevent perinatal HIV-1 transmission: The Ditrame Plus ANRS 1201/02 Study, Abidjan, Côte d'Ivoire. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 657).

90. Chaowanachan T et al. Resistance mutations following a single-dose intrapartum administration of nevirapine to HIV-infected Thai women and their infants receiving short-course zidovudine. 10th Conference on Retroviruses and Opportunistic Infections, Boston, Massachusetts, USA, 10–14 February 2003 (Abstract 855).

91. Eshleman SH et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). AIDS, 2001, 15(15):1951–1957.

92. Muro E et al. Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose NVP: implications for intervention studies. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 891).

93. Lyons F et al. Emergence of genotypic resistance in HIV-1-infected pregnant women taking HAART to reduce mother-to-child transmission of HIV-1. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 892).

94. Saving mothers, saving families: the MTCT-Plus Initiative. Geneva, World Health Organization, 2003 (http://www.who.int/hiv/pub/prev_care/pub40/en, accessed 7 June 2004).

95. Nakiyingi JS et al. Child survival in relation to mother's HIV infection and survival: evidence from a Ugandan cohort study. AIDS, 2003, 17(12):1827–1834.

96. Songok EM et al. The use of short-course zidovudine to prevent perinatal transmission of human immunodeficiency virus in rural Kenya. American Journal of Tropical Medicine and Hygiene, 2003, 69(1):8–13.

97. Newell ML and Ghent IAS Working Group on HIV Infection in Women and Children. Mortality among infected and uninfected infants born to HIV-infected women in Africa: infants, HIV, and mortality in Africa study. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 8–11 February 2004 (Abstract 155).

98. Nakabiito C et al. Effect of nevirapine (NVP) for perinatal HIV prevention appears strong among women with advanced disease: subgroup analyses of HIVNET 012. 14th International Conference on AIDS, Barcelona, Spain, 7–12 July 2002 (Abstract TuOrB1174).

99. Mirochnick M et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. Journal of Infectious Diseases, 1998, 178(2): 368–374.

100. O'Donovan D et al. Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in the Gambia. MRC/Gambia Government/University College London Medical School working group on mother-child transmission of HIV. AIDS, 2000, 14(4):441–448.

101. Andreasson PA et al. A prospective study of vertical transmission of HIV-2 in Bissau, Guinea-Bissau. AIDS, 1993, 7(7):989–993.

102. Poulsen AG et al. Lack of evidence of vertical transmission of human immunodeficiency virus type 2 in a sample of the general population in Bissau. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 1992, 5(1): 25–30.

103. New data on the prevention of mother-to-child transmission of HIV and their policy implications. WHO Technical Consultation on Behalf of the UNFPA/UNICEF/WHO/UNAIDS Inter-Agency Task Team on Mother-to-Child Transmission of HIV, Geneva, Switzerland, 11–13 October 2000. Geneva, World Health Organization, 2001 (WHO/RHR/01.28; http://www.who.int/child-adolescent-health/publications/NUTRITION/New_data.htm, accessed 7 June 2004).