

**Antiretroviral drugs and the prevention of
mother-to-child transmission of HIV infection
in resource-limited settings**

Report of a Technical Consultation, Geneva, Switzerland,
5–6 February 2004

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Acronyms and abbreviations

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

Introduction

Most children infected with HIV acquire infection from their mothers during pregnancy, labour and delivery or by breastfeeding. In 2003, an estimated 700 000 children were newly infected with HIV. One of the goals of the June 2001 Declaration of Commitment of the United Nations General Assembly Special Session on HIV/AIDS is to reduce the proportion of infants infected with HIV by 20% by 2005 and by 50% by 2010. To reach this goal, a comprehensive strategy to prevent HIV infection among infants and young children has been developed and promoted in an integrated approach to health service delivery. This strategy consists of the following elements: 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 infants and young children; and the provision of treatment, care and support to HIV-infected women, their children and families.

To prevent transmission from HIV-infected women to their infants, a WHO Technical Consultation in 2000 recommended that a short-course of antiretroviral (ARV) prophylaxis started in late pregnancy or during labour be included in programmes to prevent the mother-to-child transmission (MTCT) of HIV. These short-course regimens reduce the risk of peripartum transmission two- to three-fold. At that time, the recommended regimens included zidovudine (ZDV) alone or in combination with lamivudine (3TC) and nevirapine (NVP) alone. The simplest regimen consisted of single-dose NVP at the onset of labour plus a single dose for the infant soon after birth; MTCT-prevention programmes based on this regimen have been shown to be feasible

and acceptable and are being rapidly expanded.

Several years of experience have been obtained in implementing MTCT- prevention programmes and more results of research on other ARV drug regimens to prevent MTCT have become available since WHO issued the previous recommendations in 2000. In addition, further information is available on drug resistance induced by short-course MTCT-prevention regimens that do not fully suppress HIV, which has been a concern since early 2000. These concerns have centred on the potential impact on the effectiveness of subsequent ARV treatment for women or children infected with HIV who were exposed to short-course ARV prophylaxis. Throughout this document, ARV treatment refers to using potent combination ARV drugs to improve the quality of life and prolong life among HIV-infected children, adolescents and adults. Thus far, most HIV-infected people in resource-constrained settings have had limited access to ARV treatment. However, access to life-sustaining ARV treatment is rapidly expanding. Programmes for preventing MTCT provide an opportunity to identify people who could benefit from treatment. It is anticipated that the majority of HIV-infected women who have participated in such programmes will have access to ARV treatment. In this context, the potential impact of resistance is a far greater concern, but data to quantify the impact are lacking.

WHO convened a Technical Consultation in Geneva, Switzerland from 5–6 February 2004 with scientists, policy-makers, programme managers and community representatives to review recent experience with MTCT prevention programmes and new evidence on the safety and efficacy of various 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 simplified and standardized drug regimens. Prior to the Consultation, draft recommendations had been issued for public comment. Comments received on the draft recommendations together with the conclusions reached during the Consultation (as summarised in this report) will be used to develop recommendations on ARVs for treating pregnant women and preventing HIV infection in infants, together with the scientific basis for the recommendations. In particular, it will provide options for selecting ARV prophylaxis regimens to be included in programmes for preventing MTCT after taking into account the needs and health system constraints in different settings. Further, it will provide guidance on ARV treatment in pregnant women and women of childbearing age with indications for treatment.

The recommendations primarily target national-level programme planners and managers responsible for designing services for preventing MTCT and providing ARV treatment for women. It may also be a useful resource for health service providers involved in efforts to reduce HIV infection among infants and young children and to provide treatment and care support for HIV-infected women.

Summary of presentations

James McIntyre chaired the meeting, which began with an overview of the WHO 3 by 5 Initiative and the 2003 revised WHO ARV treatment guidelines¹ (Joseph Perriens and Marco Vitoria). This was followed by a review of progress and challenges in implementing programmes to prevent HIV infection among infants and young children (Ngashi Ngongo) and a comparative analysis of the efficacy of various interventions to prevent MTCT (François Dabis). Lynne Mofenson and Marie-Louise Newell reviewed the safety of ARV drugs used for preventing MTCT or providing treatment for pregnant women, and Mary Glenn Fowler provided an update on current evidence on drug resistance following short-course ARV regimens used for preventing MTCT.

Halima Dao and Tim Farley presented the draft WHO recommendations and various clinical scenarios that were used to focus the discussion and assist in formulating recommendations. Paulo Teixeira, Director of the WHO Department of HIV/AIDS, addressed the meeting and formally closed the proceedings.

Expanding antiretroviral treatment – the 3 by 5 Initiative

Joseph Perriens reminded the meeting that an estimated 8000 people die of AIDS in poor countries every day, largely due to lack of access to life-sustaining ARV treatment. Access to ARV treatment is considered a human right. Only 400 000 of an estimated 6 million people in resource-constrained settings who could benefit from ARV treatment are currently being treated. This lack of access to ARV drugs -- or treatment gap -- has been declared a global health emergency. In response, WHO and its partners launched the “Treat 3 Million by 2005” Initiative. Given the proven feasibility of treating people living with HIV/AIDS in developing and industrialized countries, a global target of treating 3 million people in resource-limited countries with ARV drugs by the end of 2005 is a necessary, achievable target on the way to the ultimate goal of universal access to ARV treatment for everyone who requires it. To reach this target, strong partnerships with all interested parties across many sectors are essential. It is envisaged that WHO country offices will play a pivotal role in supporting the 3 by 5 Initiative. Five strategic components have been identified as key to the success of the Initiative.

Pillar I: Global leadership, alliances and advocacy

Although supporting all countries to scale up activities, visible WHO leadership and commitment will focus on high-burden and strategic countries to achieve maximal impact. The rights-based 3 by 5 strategy is located within the broader development context and strongly emphasizes forging alliances and ongoing advocacy.

¹ *Preparing for 3 by 5: ARV treatment guidelines and technical and operational recommendations for ART.* Geneva, World Health Organization, 2003 (http://www.who.int/3by5/publications/briefs/en/arv_guidelines.pdf, accessed 27 April 2004).

Pillar II: Urgent sustained country support

Countries should be supported to build a comprehensive health-sector response to HIV/AIDS. This involves strengthening health systems, building human capacity and expanding community involvement.

Pillar III: Simplified, standardized tools for delivering ARV treatment

Procedures to identify individuals who need treatment have been simplified and ARV treatment regimens simplified and standardized to facilitate adherence and enable scaling-up. Tools for tracking programme performance and surveillance for drug resistance will provide assistance to ARV treatment programmes.

Pillar IV: Effective, reliable medicines and diagnostic supply

This includes country support for procuring and efficiently distributing low-cost medicines and diagnostics.

Pillar V: Rapidly identifying and reapplying new knowledge and success

The aim is to build on success stories and continuously learn by doing, in conjunction with ongoing evaluation and critical analysis of programme performance.

As part of efforts to expand access to ARV treatment, the WHO Department of HIV/AIDS and its partners have prepared the Global Health Sector Strategy for HIV/AIDS, guidelines for a public health approach to scaling up ARV treatment and a toolkit for planning ARV access. Ongoing 3 by 5 activities include country missions, advocacy, initial resource mobilization, developing partnerships and preparing operational guidelines. Processes for tracking and communicating 3 by 5 activities are being set up and training curricula are being developed.

Revised 2003 WHO Antiretroviral treatment guidelines

Marco Vitoria presented an overview of the 2003 revised WHO ARV treatment guidelines² intended primarily for use by national AIDS control programmes and other policy-makers involved in planning HIV treatment and care in resource-limited settings. The purpose of this revision is to provide an updated, simplified and standardized tool to guide the rapid expansion of ARV treatment.

² *Preparing for 3 by 5: ARV treatment guidelines and technical and operational recommendations for ART.* Geneva, World Health Organization, 2003
(http://www.who.int/3by5/publications/briefs/en/arv_guidelines.pdf, accessed 27 April 2004).

The guidelines describe in detail the WHO recommendations for initiating ARV treatment among HIV-infected children, adolescents and adults. For HIV-infected adults, if CD4 cell 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 counts of less than 350×10^6 cells/L to assist in decision-making; and
- WHO Stages I and II disease in the presence of a CD4 count of less than 200×10^6 cells/L.

If CD4 testing is unavailable, it is recommended to offered ARV treatment to patients with WHO Stages III and IV disease irrespective of total lymphocyte count or WHO Stage II disease with a total lymphocyte count of 1200×10^6 cells/L or less.

The recommended first-line triple-combination regimens for children, adolescents and adults are:

- stavudine (d4T) + 3TC + NVP;
- ZDV + 3TC + NVP;
- d4T + 3TC + efavirenz (EFV); or
- ZDV + 3TC + EFV.

Several considerations informed the selection of these first-line regimens, including potency, side effect profile, potential for maintaining future treatment options, anticipated adherence, availability of fixed dose combinations, coexistent illnesses (such as tuberculosis, hepatitis B virus or hepatitis C virus), pregnancy or potential thereof, concomitant medication use, presence of resistant viral strains, cost and drug availability, limitations in health service infrastructure and considerations specific to providing services in rural areas. In the event of treatment failure, the recommended triple drug second-line regimen for adults is tenofovir disoproxil fumarate (TDF) or abacavir (ABC), plus didanosine (ddI) and either lopinavir with a low-dose ritonavir (RTV) boost or saquinavir with a low-dose RTV boost (SQV/r) or nelfinavir (NFV). Apart from excluding TDF because data are lacking for use among children, the second-line ARV treatment regimens for children are the same as for adults. In settings that do not have a secure cold-chain, NFV is the preferred protease inhibitor.

WHO has tiered its monitoring recommendations for ARV treatment according to the health service level. These recommendations are designed for implementation at the community health centre and/or district hospital level working in concert and with regional referral hospital back up. Symptoms will be used to determine the need for monitoring and assessing drug toxicity among people receiving first-line drug regimens.

Recent progress and challenges in implementing programmes to prevent HIV infection among infants and young children

Ngashi Ngongo emphasized that all four components of the strategic approach to prevent MTCT need to be addressed in an analysis of progress and achievements. The components are:

- 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 infants and young children; and
- provision of treatment, care and support to HIV-infected women, their children and families.

One of the goals of the Declaration of Commitment of the United Nations General Assembly

Special Session on HIV/AIDS in June 2001 is that 80% of pregnant women accessing antenatal care should be offered information, counselling and HIV-prevention services. Several achievements related to this can be highlighted. Many countries have national policies to prevent MTCT in place. Some have made important strides in reaching HIV-infected pregnant women, and many high-burden countries are scaling up access to interventions to prevent MTCT. The uptake of HIV testing and counselling has improved over time, possibly due to the introduction of rapid HIV testing. Offering HIV testing and counselling should become standard practice in antenatal care. Efforts to integrate interventions to prevent MTCT with reproductive health and maternal and children's health services are ongoing.

Although much progress has been made, numerous challenges remain. In many countries, services to prevent MTCT are currently available to only a small fraction of the population. Poor-quality health services and inadequate community support for programmes to prevent MTCT remain major barriers to the uptake of services in some settings. To respond to these challenges, participants emphasized the importance of strategies that aim to increase community engagement.

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 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.

Although the current ARV regimens used to prevent MTCT are relatively simple and easy to use, administering infant doses has proven problematic. This is because of difficulties experienced

with communication of the maternal HIV status to health personnel responsible for care of the infant. Infant regimens that require continuous daily dosing may be especially difficult to administer. In addition, the medium- to long-term follow-up of HIV-exposed infants has presented many difficulties.

For an HIV-infected woman, balancing the risks and benefits of various infant feeding options is a complex but necessary task in resource-limited settings. Follow-up of HIV-infected women and their infants is essential for providing adequate support to HIV-infected women to enable them to choose the best infant feeding option according to their circumstances and to successfully carry out their choice.

Strong primary prevention efforts have been successful in some countries in reducing the prevalence of HIV among women of childbearing age and are a key component of global efforts to prevent HIV infection among infants and young children. Links between the prevention of MTCT, reproductive health and health services for mothers and children need to be enhanced. Similarly, links between prevention of MTCT and HIV treatment and care services are expected to enhance the effectiveness and long-term impact of programmes. Offering HIV testing and counselling

should be come standard practice in antenatal care.

To achieve the goals of the United Nations General Assembly Special Session on HIV/AIDS, the United Nations agencies and partners will have to work on strengthening health systems (infrastructure, staff, supplies, monitoring and evaluation, supervision and referral links) and improving the effectiveness of current interventions (ARV prophylaxis regimens, safer delivery practices and feeding strategies for infants and young children). Difficulties in forecasting demand and coordinating supplies, together with concerns regarding the long-term sustainability of drug supplies, pose challenges to the reliable supply of ARV drugs and diagnostics.

Strategic information needs to be disseminated through research and documentation of good practice. Participants emphasized the importance of timely and high-quality data for use in planning and advocacy.

Efficacy of antiretroviral drugs in preventing HIV infection in infants

François Dabis summarized the findings of trials investigating the efficacy of ARV regimens in reducing MTCT. He cautioned against comparing the results of individual trials directly because of methodological, diagnostic and other differences. Further, the distribution of risk factors for MTCT varies considerably in different populations, creating difficulty in comparing the results of studies conducted in different countries and even within the same country.

The risk of HIV transmission to infants and young children varies according to maternal viral load and immune status, even among women receiving ARV prophylaxis to reduce MTCT. The risk of MTCT is higher among women with clinical or immunological indications for initiating ARV treatment than among women without such indications.

The optimum method of reporting the relative efficacy of ARV regimens for preventing MTCT is unclear. The efficacy of ARV prophylaxis regimens can be expressed either as short-term (4–6 weeks) or long-term efficacy. Infant and young child feeding patterns and the infant mortality rate in a population influence the relationship between short-term efficacy and long-term efficacy. Infant feeding practices may also be relevant in comparing the short-term efficacy of ARV regimens, but differentiating between HIV transmission that occurs during labour and delivery and through breastfeeding is difficult. The efficacy demonstrated in randomized trials may differ from the level of effectiveness achieved in routine health services. Although several studies have evaluated long-term efficacy at 12, 18 and even 24 months, the impact of interventions to prevent MTCT on long-term child survival needs to be investigated.

In Europe and the United States, the use of triple-combination regimens during pregnancy and intrapartum is associated with lower levels of transmission than other drug regimens. To date, the efficacy and safety of triple-combination drugs in reducing MTCT has not been evaluated in resource-constrained settings.

Several trials evaluating the efficacy of short-course ARV prophylaxis have been conducted in resource-constrained settings. Short-term efficacy, as determined by infant infection status at 4–8 weeks of life, has been demonstrated for short-course prophylactic ARV regimens comprising: ZDV alone, ZDV together with 3TC, NVP alone (maternal and infant single-dose), ZDV plus NVP (maternal and infant single-dose) and ZDV + 3TC plus NVP (maternal and infant single-dose).

Marc Lallemand presented the preliminary results of the recently completed PHPT-2 trial among non-breastfeeding women in Thailand. The trial compared a regimen of ZDV alone, in which ZDV was given antepartum from 28 weeks, intrapartum and for one week to the infant, to the same ZDV regimen with the addition of single-dose maternal NVP in labour with or without infant single-dose NVP. The safety and efficacy of the regimen were assessed. At the first interim analysis, the ZDV-alone arm was stopped because of lower efficacy than the NVP-containing study arms. At that time, an 82% reduction in transmission was observed when comparing the ZDV-alone regimen to the ZDV plus maternal and infant NVP regimen. The overall risk of transmission with ZDV from week 28 plus single-dose NVP around the time of delivery was about 2%, and the regimen was well tolerated.

The efficacy of short-course ZDV prophylaxis plus single-dose mother and infant NVP was also studied in a breastfeeding population in Côte d'Ivoire. Women in the DITRAME Plus (ANRS 1201.0) trial received ZDV from 36 weeks plus single-dose maternal and infant NVP around the time of delivery; in a similar population, another trial assessed single-dose NVP added to ZDV and 3TC. Overall, these trials from Côte d'Ivoire and Thailand indicate that ZDV prophylaxis plus single-dose NVP around the time of delivery to woman and infant is highly efficacious and suggest that ZDV starting at 28 weeks is more efficacious than ZDV started later in pregnancy.

In a recent trial from Malawi infants born to women who had not received any 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.

The provision of ARV prophylaxis should be accompanied by interventions to reduce HIV transmission during breastfeeding to improve the effectiveness of efforts to reduce HIV transmission to infants and young children. The risk of HIV transmission during breastfeeding varies according to the duration of breastfeeding and the maternal plasma viral load and CD4 cell count. Other factors thought to influence HIV transmission during breastfeeding include: mastitis

and other breast conditions, the viral load of breast milk, the mode of infant feeding, nutritional status of the mother and infant factors (such as oral ulcers).

The potential role of infant or maternal ARV prophylaxis in preventing postnatal transmission of HIV is being investigated. Recently, preliminary results were presented from the SIMBA trial carried out in Rwanda and Uganda in which infants born to HIV-infected women who received ZDV + ddI from 36 weeks until one week postpartum were randomized to receive either daily NVP or 3TC to reduce the risk of infection during breastfeeding.

Safety and toxicity of antiretroviral drugs for pregnant women and infants

Lynne Mofenson and Marie-Louise Newell presented an update on the known and unknown risks to the pregnant woman, fetus and infant of ARV drugs for preventing MTCT or for treatment of maternal HIV disease.

The safety and toxicity considerations of ARV treatment for non-pregnant women of childbearing age include concerns of potential teratogenic risks to the embryo and fetus if they become pregnant while taking ARV drugs.

Safety concerns for women with antiretroviral use during pregnancy

MTCT prophylaxis with ZDV was not associated with short-term clinical or laboratory toxicity among pregnant women in several controlled trials, and no significant clinical or laboratory toxicity has been noted among more than 1600 women receiving single-dose NVP in controlled trials. Similarly, data on the safety of short-course combination regimens among women using ZDV and 3TC are reassuring.

In long-term follow-up of women, the progression of HIV-related disease does not appear to be altered by prophylactic ZDV regimens. Considerations relating to the potential long-term impact of viral resistance following short-course prophylaxis are discussed separately later.

Among pregnant women, several issues relating to the safety and toxicity of ARV treatment warrant additional consideration and may influence the choice of ARV treatment regimen. 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 and d4T (nucleoside reverse transcriptase inhibitors) and NVP (a non-nucleoside reverse transcriptase inhibitor).

However, pharmacokinetic studies with four of the protease inhibitors (SQV, RTV,

indinavir and NFV) indicate that dosing adjustments or low-dose RTV boosting may be necessary to achieve adequate drug levels during pregnancy. Adequate levels of drug exposure among HIV-infected pregnant women were demonstrated with SQV when administered with an RTV boost (SQV 800 mg and RTV 100 mg, twice daily) and with NFV when administered in higher, twice-daily doses (NFV 1250 mg twice daily).

WHO recommends NVP-based regimens as first-line treatment in resource-constrained settings during pregnancy or for women of childbearing age. NVP is a potent non-nucleoside reverse transcriptase inhibitor with demonstrated clinical efficacy, relatively easy to use and available as part of a three-drug fixed-dose combination.

Some reports suggest that the incidence of asymptomatic elevations of liver enzymes are similar for all ARV drugs. However, NVP-containing treatment regimens have been associated with a higher incidence of symptomatic hepatic events. Serious NVP-associated rash and hepatic toxicity, although uncommon, occur more often among women than among men (about 3–7 fold). Deaths from hepatic toxicity are rare (about 0.1%) but have been reported among HIV-infected pregnant women receiving NVP-based ARV treatment. It is unclear whether hepatic events are more common among pregnant women than among non-pregnant women.

The risk of severe hepatic toxicity and skin rash in 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 at the time NVP-based ARV treatment is started, including pregnant women initiating ARV treatment, are at a higher risk (about 10-fold) of severe symptomatic hepatotoxicity than women with lower CD4 counts. The risk is highest in the first six weeks of NVP treatment. NVP should be used with caution among pregnant women who are being started on triple-combination regimens solely for the purpose of preventing MTCT and who do not require ARV treatment for their own health.

Lactic acidosis and hepatic steatosis are rare but potentially life-threatening types of toxicity related to long-term (greater than six months) ARV treatment with nucleoside reverse transcriptase inhibitors that appear to be associated with mitochondrial dysfunction. Although these disorders are more common in women, it is unclear whether pregnancy predisposes to their development.

Three maternal deaths thought to be due to lactic acidosis have been reported among women on ARV treatment that included ddI + d4T who were receiving treatment at the time of conception and throughout pregnancy. Additional cases of nonfatal lactic acidosis have been reported among pregnant women receiving ddI + d4T. This combination should be used with caution and only when no other alternatives are available.

Hyperglycaemia and other metabolic disorders are associated with the chronic use of protease inhibitors. As pregnancy is also a risk factor for impaired glucose tolerance, the use of protease inhibitors during pregnancy could, in theory, increase the risk of pregnancy-associated

hyperglycaemia.

Safety of exposing fetuses and infants to ARV drugs

The extent of the risk of exposing the fetus and infant to ARV drugs is likely to vary according to the timing of exposure, duration of exposure and complexity of the drug regimen.

The use of ARV prophylaxis has prevented the transmission of HIV to a large number of infants. Although for infants the benefits of single-drug or combination MTCT prophylaxis clearly outweigh the potential adverse effects of drug exposure, monitoring for short- and long-term effects is recommended.

No significant clinical or laboratory toxicity has been seen among more than 1600 infants receiving single-dose NVP in randomized controlled trials.

In several placebo-controlled trials, no increase in serious adverse events was noted among infants receiving ZDV. However, mild transient anaemia has been reported among ZDV-exposed infants. More prolonged in utero (>1 month) and infant exposure to ZDV + 3TC has resulted in more severe neonatal anaemia and neutropaenia than observed with shorter ZDV exposure or exposure to ZDV alone.

Some reports have suggested that mitochondrial dysfunction is a rare though serious type of toxicity among infants exposed in utero or neonatally to nucleoside reverse transcriptase inhibitors (ZDV or ZDV + 3TC). However, other studies have not found this association. To date, no increased risk of carcinogenesis has been observed in the long-term follow-up of children exposed to ZDV. Further assessment of the long-term toxic effects of ARV drugs is required.

Studies of reproductive toxicology in animals have been conducted for all currently available ARV drugs. The studies compare the outcome of pregnancy in groups of animals receiving a range of drug doses during the period of organogenesis with the outcome in untreated control animals. The predictive value of studies in animals for adverse effects among humans is unknown. Thus, although studies in animals may identify teratogenic effects, extrapolating these effects to humans can be difficult.

For the most extensively studied drug, ZDV, neither prospective observational nor clinical trial data have found increased birth defects following in utero exposure. However, there are concerns regarding the effect of in utero exposure to certain ARV drugs. In utero exposure to EFV has been associated with teratogenicity in studies in monkeys. Significant central nervous system birth defects were observed in 3 of 20 (15%) infant cynomolgus monkeys with in utero exposure to doses comparable to therapeutic EFV levels in humans. In pregnancies reported prospectively to a registry of ARV drug use among pregnant women 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. These rates are similar to the prevalence of birth defects of 3.1% in the United States

population based on Centers for Disease Control and Prevention surveillance data. However, there are three retrospective case reports of neural tube defects with first-trimester EFV exposure. EFV should be avoided in the first trimester, which is the period of organogenesis.

Studies in monkeys have shown decreased fetal growth and reduction in fetal bone porosity with in utero exposure to TDF. Decreased bone mineral density with chronic use of TDF has also been noted in studies among HIV-infected children taking TDF-containing ARV treatment regimens.

Several reports from European studies have indicated that women receiving ARV treatment initiated before pregnancy or in early pregnancy are at an increased risk of premature delivery, especially when ARV treatment regimens include a protease inhibitor. However, this association has not been observed in studies in the United States. The reason for the difference between the studies in Europe and United States could be related to differences in underlying population characteristics and background rates of preterm delivery.

Short-course MTCT prophylaxis and viral resistance

Mary Glenn Fowler presented an overview of several issues pertaining to the selection of viral resistance with the use of MTCT prophylaxis. Although much evidence has been gathered, many questions remain unanswered and require further investigation.

Viral mutations that confer high-level resistance have been transiently detected among women receiving single-dose NVP or short-course 3TC to prevent MTCT. Resistance to NVP or 3TC occurs rapidly, as it requires only a single point mutation. In contrast, high-level ZDV resistance following short-course MTCT prophylaxis is rare, as multiple sequential mutations are needed to confer high-level resistance. High-level ZDV resistance generally does not occur until after several months of use.

Most studies have reported that a high maternal baseline viral load or low CD4 cell count is associated with an increased risk of resistance to any of the ARV drugs. In addition to viral load and CD4 cell count, other factors associated with the development of NVP resistance include viral subtype, the compartment (e.g. plasma or breast milk), the time elapsed between receiving single-dose NVP and sampling and the number of NVP doses the woman received during labour.

The HIVNET 012 study detected viral strains resistant to NVP at 6–8 weeks postpartum among 25% of women who received single-dose NVP. The SAINT study in South Africa found a 67% rate of NVP resistance at four weeks postpartum among women who had received two doses of NVP. Selection for NVP-resistant viral strains also occurs among women receiving combination ARV regimens that do not fully suppress viral replication. Viral resistance was detected among

33–53% of HIV-infected infants exposed to single-dose maternal and infant NVP. NVP resistance mutations differ between mothers and their infants. In most cases, infants with NVP resistance were infected with HIV at birth, suggesting that the resistance mutations were selected *de novo* in the infants when their actively replicating virus was exposed to NVP rather than being transmitted from the mother.

The risk of viral resistance to 3TC is correlated with the duration of drug exposure. A study conducted in France reported that resistance to 3TC was detectable in 50% (37 of 74) of women who received 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. Resistance to 3TC was detected among 12% of women in the multicentre PETRA study who had received combination ZDV and 3TC from 36 weeks of pregnancy, intrapartum and for one week postpartum.

The detection of either 3TC- or NVP-resistant strains among women is not associated with an increased risk of MTCT, although an association cannot be excluded.

The clinical significance of resistance following short-course MTCT prophylaxis is not clear. Although there is no conclusive evidence, there are concerns 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. The Consultation carefully considered the concerns about the impact of resistance to NVP and 3TC, especially given the recommendation by WHO that first-line ARV treatment regimens be based on non-nucleoside reverse transcriptase inhibitors and include 3TC.

Research is underway or being planned to address several issues related to the potential impact of NVP viral resistance:

- Does the selection or induction of resistance among women receiving single-dose NVP negatively affect their response to ARV treatment? If so, what is the nature and extent of the effect? Does the timing of initiating ARV treatment in relation to receiving single-dose NVP affect the outcome of treatment? What potential strategies can be explored for reducing any negative effect on treatment outcome?
- Do HIV-infected infants exposed to single-dose maternal and infant NVP have a diminished response to subsequent ARV treatment?
- How long does mutant virus persist after exposure to single-dose NVP? Are resistant strains archived in cell-associated virus?
- Will single-dose maternal and infant NVP show reduced efficacy if used to prevent MTCT in subsequent pregnancies?

The Consultation participants reviewed preliminary data from an observational study in Thailand. 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 in women who had received single-dose NVP, thus allowing women with and without NVP-resistant mutations to be compared. In all women in the study, non-nucleoside reverse transcriptase inhibitors based ARV treatment was initiated in the 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 NVP resistance mutation and 85% of the 27 women who did not receive single-dose NVP had a plasma viral load $\leq 400 \times 10^3$ copies/L ($P = 0.057$ for trend). For plasma viral load $\leq 50 \times 10^3$ copies/L, the percentages were 38%, 50% and 74% respectively ($P = 0.006$ for trend). The 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.

These findings suggest that an MTCT prophylaxis regimen of ZDV and single-dose NVP reduces viral response to ARV treatment if NNRTI-based treatment is initiated soon after delivery. Larger clinical trials are underway and others are planned that will 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.

Balancing risks and benefits

Halima Dao elaborated further on the rationale for the Consultation and provided an outline of the different scenarios contained in the draft recommendations on using ARV drugs to prevent MTCT. To set the background and foundations for further discussion, Tim Farley outlined the key issues, considerations and guiding principles for the selection of ARV regimens. These served as a framework on which the recommendations are built and summarize the key messages of the Consultation presentations.

Considerations regarding antiretroviral drug use among women of childbearing potential or women who are pregnant

Interventions to prevent MTCT should be part of an integrated continuum of HIV prevention, care and treatment services. Accordingly, the recommendations should adhere to the principles set out in the 2003 WHO ARV treatment guidelines and be consistent with the regimens chosen for first-line treatment.

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 ARV treatment guidelines. Potent combination treatment has substantial benefits for the health of a woman and is likely to provide enhanced protection against MTCT. All efforts should be made to ensure that all women who could benefit from ARV treatment can access it.

The selection of ARV treatment regimens for women of childbearing age 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 organ development and before a pregnancy is recognized. Similarly, the possibility of a future pregnancy should be considered when an ARV treatment regimen is selected for pregnant women.

The WHO-recommended first-line ARV treatment regimens for women who may become pregnant and who have indications for starting ARV treatment are ZDV + 3TC + NVP or d4T + 3TC + NVP. The non-nucleoside reverse transcriptase inhibitor component of these regimens is NVP, which is a potent non-nucleoside reverse transcriptase inhibitor with demonstrated clinical efficacy, is relatively easy to use and is available as part of a three-drug fixed dose combination. For non-pregnant women for whom effective contraception can be assured, EFV remains a viable option for the non-nucleoside reverse transcriptase inhibitor component of the regimen.

Drug interactions occur between many ARV drugs (especially some non-nucleoside reverse transcriptase inhibitors and protease inhibitors) and hormonal contraceptives, which may alter the safety and effectiveness of both hormonal contraceptives and 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.

Choice of MTCT prophylaxis regimen

Recommendations should be based on evidence as far as possible, and reviewed and updated, when warranted, as additional research becomes available. Numerous factors need to be taken into account in selecting an ARV regimen to prevent MTCT. A decision has to be made on which ARV drug or drugs to use, the choice of single-drug or combination ARV regimen and the period when the drugs are to be taken (early antenatal, peripartum, early postpartum or late postpartum).

Although regimens need to 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 with service delivery originate from programmatic issues linked to the health systems and the sociocultural context.

An MTCT-prevention programme that is not able to 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 a clinical trial.

The recommendations should be based on the relative safety of the various regimens, including analysing the known and potential implications of viral resistance induced by short-course ARV prophylaxis regimens, and the relative efficacy in reducing the transmission of HIV. 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 likely to influence adherence.

The comparative efficacy of different regimens suggests that prophylaxis should start as early in pregnancy as feasible, and for the same duration of prophylaxis, combination regimens are more efficacious than single drug regimens. However, such differences are difficult to quantify precisely, since they involve comparisons across trials, population groups and health-care settings.

Many studies have demonstrated a higher risk of MTCT among women with a high plasma viral load or low CD4 cell count, even if they receive short-course ARV prophylaxis. Further, the risk of developing NVP or 3TC resistance with short-course ARV prophylaxis regimens is greatest among women with a high plasma viral load or low CD4 cell count. As the risk of HIV transmission and the risk of drug resistance differ according to the stage of disease, the risk–benefit balance of alternative drug regimens for MTCT prophylaxis is not the same for all women.

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

In addition to substantial clinical experience with the use of ZDV among pregnant women and among infants, the efficacy and safety of ZDV prophylaxis has been more extensively studied than other ARV drugs. Therefore, when ARV treatment is initiated during pregnancy, ZDV should be included in the regimen whenever possible. Should it be necessary to initiate a protease inhibitor–based regimen during pregnancy, then SQV/r or NFV are the preferred options, as there are limited data available on the pharmacokinetics of other protease inhibitors in pregnant women.

Considerations on antiretroviral prophylaxis regimens for infants

Several ARV regimens for infants have been studied using different durations for 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 which ARV regimen the mother received.

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

When delivery occurs less than two hours after the mother received single-dose NVP, the infant should receive single-dose NVP as soon as possible after delivery and ZDV for one week. 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 infant NVP alone.

Considerations on HIV and infant feeding

The recommendations on HIV and infant feeding remain unchanged for women receiving ARV treatment. According to current UNFPA/UNICEF/UNAIDS/WHO guidelines, when replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life.

Conclusion

In this rapidly evolving field, many factors need to be considered in selecting an ARV regimen to prevent HIV infection among infants. Recommendations depend on when in pregnancy a woman is 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 achieving a balance between concerns of short- and long-term safety (including viral resistance) and clinical effectiveness. The ARV drug regimen(s) 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. In some resource-constrained settings, it may therefore be more feasible to initiate programmes to prevent MTCT with a simple regimen such as single-dose NVP and to introduce more complex regimens as infrastructure and programmatic capacity allow.

The following sections provide specific recommendations for the most frequently encountered clinical situations and are summarised in Table 1.

Recommendations on the use of antiretroviral drugs among pregnant women for their own health and to prevent HIV infection among infants

Clinical Situation A: HIV-infected women with indications for initiating antiretroviral treatment

who may become pregnant

The WHO-recommended first-line ARV treatment 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 treatment 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 organ development. There is concern that exposure to EFV during the first trimester may lead to central nervous system defects. When possible, drugs that are potentially teratogenic should be avoided if effective contraception cannot be assured.

Clinical Situation B: HIV-infected women receiving antiretroviral treatment who become pregnant

Although there are concerns relating to known and unknown 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 due to 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 CD4 count above 250×10^6 cells/L and recommended that a protease inhibitor, 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 clinical situation is the health of the woman and assuring 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 who are eligible for ARV treatment according to WHO guidelines can 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 gestation) 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 protease inhibitor–based regimen during pregnancy could be necessary, in which case SQV/r or NFV are the preferred protease inhibitors.

Treatment with EFV should not be initiated in the first trimester of pregnancy, as this is the main period of fetal organogenesis. There are theoretical risks to the fetal brain in later pregnancy, and hence EFV should only be used in pregnancy when 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 assured.

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 ZDV for four to six weeks in the infant 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, while others have given a double dose (600 mg) at onset of labour. Although these regimens have not been compared directly, there are similar reductions in HIV transmission rates. The double-dose regimen at 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 regimens. The development of MTCT-prevention programmes 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 during established labour should not be given 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 or 36 weeks of pregnancy and continued in the infant for one week after birth is highly efficacious and avoids the risk of drug resistance. Combination ZDV plus 3TC started at 36 weeks of pregnancy is more efficacious than ZDV alone but may result in viral resistance to 3TC in some of women who receive more than four weeks prophylaxis.

Triple-drug combination regimens for MTCT-prevention 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 perinatal MTCT. However, the safety and effectiveness of such regimens have not been established in resource-limited 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 NVP-based treatment who have a CD4 count above 250×10^6 cells/L. Until further data and clinical experience are available NVP-based triple-combination regimens should be used with caution in 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 (particularly 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 MTCT prevention in women without indications for ARV treatment then the recommended regimen is 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, or ZDV plus 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 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 who have 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 immunological 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 baseline 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 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. 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 assured postpartum. NVP-containing ARV treatment 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 tuberculosis disease do not initiate ARV treatment. Although there is significant interaction between rifampicin and NVP, the Technical Consultation concluded that 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 in labour of unknown HIV status. If this is not possible,

they 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 plus receive 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. Among women who have confirmed HIV infection and indications for ARV treatment, the WHO ARV treatment guidelines can be followed and ARV treatment can be 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 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 1. Clinical situations and recommendations for the use of antiretroviral drugs among 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	<p>First-line regimens: ZDV + 3TC + NVP or d4T + 3TC + NVP</p> <p>EFV should be avoided in women of childbearing age, unless effective contraception can be assured. Exclude pregnancy before starting treatment with EFV</p>
B: HIV-infected women receiving ARV treatment who become pregnant	<p>Women</p> <p>Continue the current ARV treatment regimen² unless it contains EFV, in which case substitution with a NVP or a protease inhibitor should be considered if the woman is in the first trimester. Continue the same ARV regimen during labour and after delivery</p> <p>Infants</p> <p>Infants born to women receiving either first- or second-line ARV regimens: ZDV for one week or single-dose NVP or single-dose NVP plus ZDV for one week</p>
C: HIV-infected pregnant women with indications for ARV treatment ¹	<p>Women</p> <p>Follow the treatment guidelines as for non-pregnant adults except that EFV should not be given in the first trimester</p> <p>First-line regimens: ZDV + 3TC + NVP or d4T + 3TC + NVP</p> <p>Consider delaying initiating ARV treatment until after the first trimester, although for severely ill women the benefits of early treatment clearly outweigh the potential risks</p> <p>Infants</p> <p>ZDV for one week or single-dose NVP or single-dose NVP plus ZDV for one week³</p>

<p>D: HIV-infected pregnant women without indications for ARV treatment¹</p>	<p>•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 week³</p> <p>Alternative regimens (not in any order of preference)</p> <p>•Women ZDV starting at 28 weeks or as soon as possible thereafter; continue in labour Infants ZDV for one week³</p> <p>•Women ZDV + 3TC starting at 36 weeks or as soon as possible thereafter; continue in labour and for one week postpartum Infants ZDV for one week + 3TC</p> <p>•Women Single-dose NVP Infants Single-dose NVP</p>
<p>E: HIV-infected pregnant women who have indications for starting ARV treatment¹ but treatment is not yet available</p>	<p>Follow the recommendations in clinical situation D, but preferably use the most efficacious regimen that is available and feasible</p>
<p>F: HIV-infected pregnant women with active tuberculosis</p>	<p>If ARV treatment is initiated, consider:⁴ ZDV+ 3TC + SQV/r or d4T+ 3TC + SQV/r</p> <p>If treatment is initiated in the third trimester, ZDV + 3TC + EFV or d4T + 3TC + EFV can be considered</p> <p>If ARV treatment is not initiated, follow the recommendations in clinical situation D</p>

<p>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 antepartum ARV</p>	<p>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</p> <p>Recommended regimens (not in any order of preference)</p> <p>•Women Single-dose NVP; if imminent delivery is expected do not give the dose but follow the recommendations in clinical situation H</p> <p>Infants Single-dose NVP</p> <p>•Women ZDV + 3TC in labour and ZDV for one week + 3TC postpartum</p> <p>Infants ZDV for one week + 3TC</p>
<p>H: Infants born to HIV-infected women who have not received any ARV drugs</p>	<p>Infants</p> <p>Single-dose NVP as soon as possible after birth plus ZDV for one week</p> <p>If the regimen is started more than 2 days after birth, it is unlikely to be effective</p>

- 1 WHO recommendations for initiating ARV treatment among 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 count, WHO Stage III disease with consideration of using CD4 counts of less than 350 10⁶ cells/L to assist decision-making and WHO Stage I and II disease in the presence of a CD4 count of less than 200 10⁶ 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 10⁶ cells/L .
- 2 Conduct clinical and laboratory monitoring as outlined in the 2003 revised WHO ARV treatment guidelines.
- 3 Continuing ZDV for four to six weeks in the infant can be considered if the woman received antepartum ARVs 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 treatment regimen can be initiated.

Annex 1. WHO statement

Antiretroviral drugs and the prevention of mother-to-child transmission of HIV infection in resource-limited settings

Expert Consultation, Geneva, 5–6 February 2004

A summary of main points from the Consultation

Background

WHO convened an Expert Consultation in Geneva on 5 and 6 February 2004 with scientists, policy-makers, programme managers and community representatives to review the experience with programmes and recent evidence on safety and efficacy of various antiretroviral (ARV) drug regimens for the prevention of mother-to-child transmission of HIV (MTCT). This information was reviewed in the context of rapid expansion of ARV treatment in resource-limited settings using simplified and standardized drug regimens. Prior to the Consultation, a draft set of recommendations had been issued for public comment, which is now being revised in the light of comments received and the recommendations made at the Expert Consultation.

Key recommendations

- Women who need ARV treatment for their own health should receive it, following the revised ARV treatment guidelines recently posted by WHO. The use of ARV treatment when indicated during pregnancy will improve the health of the mother and substantially decrease the risk of transmission of the HIV virus to the infant.
- Women who do not need treatment, or do not have access to treatment, should be offered ARV prophylaxis to prevent MTCT using one of a number of ARV drug regimens known to be safe and effective.
- The most efficacious regimen among those recommended for preventing MTCT among women with HIV who do not need ARV treatment is zidovudine (ZDV) from 28 weeks with single-dose nevirapine (NVP) at onset of labour for the mother and single-dose NVP plus one-week ZDV for the infant.
- Alternative but less efficacious regimens include one based on ZDV alone (from 28 weeks of pregnancy and through labour for the mother and for one week for the infant), one using the combination of ZDV plus lamivudine (from 36 weeks of pregnancy, through labour and one week postpartum for the mother and for one week for the infant) and a regimen comprising a single dose of NVP for the mother and for the infant (which does not need to be initiated until labour).

- The ARV drug regimen should be selected at the national level based on issues of efficacy, safety, drug resistance, feasibility and acceptability.

The Consultation participants made these recommendations based on a thorough review of the current evidence and careful consideration of issues of efficacy, safety and practicality.

New data reviewed

In particular, the Consultation participants reviewed available scientific evidence on the emergence of resistant HIV strains associated with use of some ARV drugs for prophylaxis, which has raised concerns about future ARV treatment options for the mother or, if infected, the infant. They felt, however, that the evidence regarding the degree of impact of such resistance is not as yet conclusive. New data from the observational study conducted by Lallemand et al. in Thailand suggest that the regimen of ZDV and a single dose of NVP could reduce the mother's response to ARV treatment initiated in the first months after delivery. These data were taken into account in developing the above recommendations. However, the Consultation participants felt that the implications of these preliminary data on subsequent treatment options for women were unclear and require further study. They noted that more definitive clinical trials assessing this issue are underway. Until further evidence is available, the group's expert opinion was that the ZDV plus single-dose NVP regimen can be recommended for the prevention of MTCT because of its considerable efficacy in reducing MTCT (by 80%, from the transmission rates observed with short-course ZDV alone, down to an absolute level under 2%), its simplicity and its safety profile for mother and infant. In view of these results, the Government of Thailand is implementing this regimen nationwide for the prevention of MTCT, alongside its efforts to scale up ARV treatment for all in need.

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³ The following participants declared interests related to the subject matter of the Technical Consultation: Prof. Joep Lange has been an adviser/consultant for the following companies: Agouron Pharmaceuticals Inc./Pfizer Inc., Bayer Pharmaceuticals Corporation, Boehringer Ingelheim, Bristol-Meyers Squibb, GlaxoSmithKline, Merck Sharp & Dohme Limited, Roche, Schering-Plough, Shire Pharmaceuticals Group plc and Virco-Tibotec. Dr James McIntyre worked on an expert report on nevirapine for Boehringer Ingelheim in 2003, and his institution currently receives research funds from Boehringer Ingelheim