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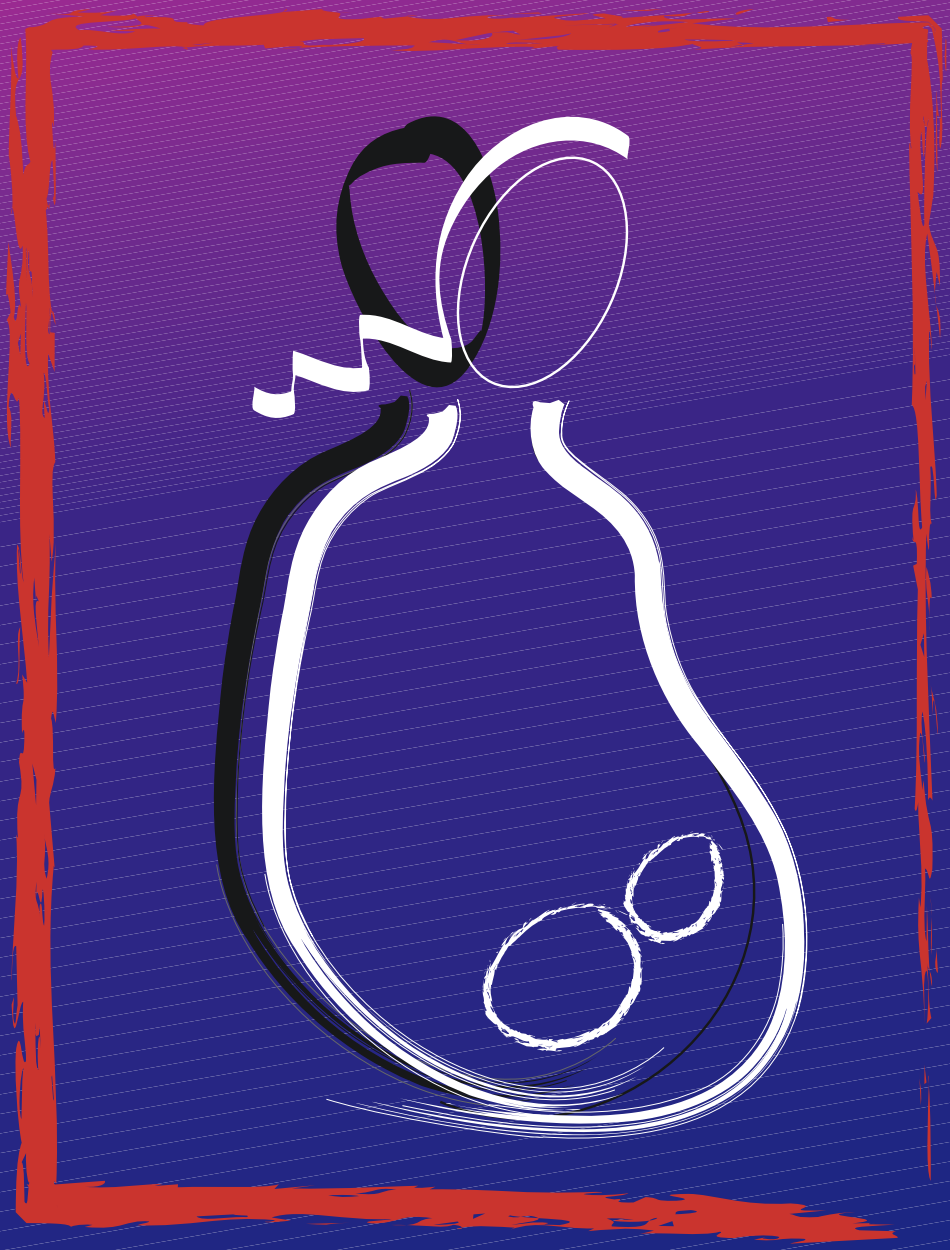

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV:

SELECTION AND USE OF NEVIRAPINE

TECHNICAL NOTES

Department of HIV/AIDS
Department of Reproductive Health and Research
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LIST OF ACRONYMS

ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
DITRAME	Diminution de la Transmission Mère-Enfant du VIH en Afrique
DNA	Deoxyribonucleic acid
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HIVNET	HIV Network Prevention Study
MTCT	Mother-to-child transmission
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PACTG	Pediatric AIDS Clinical Trials Group
PEP	Post exposure prophylaxis
PETRA	Perinatal Transmission Study
PHPT	Perinatal HIV Prevention Trial
PI	Protease inhibitors
SAINT	South Africa Intrapartum Nevirapine Trial
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization

PREFACE

A technical consultation on the prevention of mother-to-child transmission (MTCT) of HIV was convened by WHO in Geneva from 11-13 October 2000 on behalf of the United Nations Interagency Task Team on Mother-to-Child Transmission of HIV Infection. Participants reviewed available evidence on the efficacy and safety of antiretroviral prophylactic regimens used for MTCT-prevention in resource-limited settings. They concluded that all the regimens that have been shown to be effective in controlled clinical trials can be recommended for use in MTCT-prevention programmes in such settings.[1] These regimens include zidovudine alone, zidovudine plus lamivudine, and nevirapine alone. The experts agreed there was no longer any justification to restrict use of any of these regimens to pilot project or research settings.

There is considerable interest currently in the use of nevirapine for MTCT-prevention because of the low cost and simplicity of this regimen. Furthermore, a manufacturer has announced that it will offer nevirapine free of charge to developing countries for preventing MTCT for a period of five years.[2]

These technical notes are intended for the guidance of policy makers, programme managers and practitioners who are considering the use of nevirapine in MTCT-prevention programmes. The notes provide basic information on:

- the design of a comprehensive MTCT-prevention programme;
- the choice of antiretroviral regimens for preventing MTCT;
- the efficacy and safety of nevirapine for preventing MTCT;
- the efficacy and safety of nevirapine for the prevention and treatment of HIV/AIDS;
- the management of nevirapine donations.

1. BACKGROUND

1.1 MAGNITUDE OF THE PROBLEM

MTCT is the most significant source of HIV infection in children below the age of 15 years. Since the beginning of the pandemic, an estimated 5.1 million children worldwide have been infected, almost all through MTCT. In the year 2000, more than 600,000 children became infected, 90% of whom were in Africa.[3]

1.2 RISKS OF TRANSMISSION

HIV can be transmitted from an infected mother to her child during pregnancy, labour and delivery, or through breastfeeding. In the absence of breastfeeding, most infections occur during labour and delivery (Table 1). Reported transmission rates ranged from 13 to 32% in industrialized countries, and from 25 to 48% in developing countries.[4]
In breastfeeding populations, up to 20% of infants born to HIV-infected mothers may acquire HIV through breastfeeding, depending on the duration of breastfeeding and other risk factors such as the presence of mastitis, breast abscess and other local factors.[5]

Table 1. Estimated risk and timing of mother-to-child transmission of HIV

	Transmission rate (%)		
Timing	**No breastfeeding**	**Breastfeeding through 6 months**	**Breastfeeding through 18 to 24 months**
During pregnancy	5 to 10	5 to 10	5 to 10
During labour	10 to 20	10 to 20	10 to 20
Through breastfeeding			
Early (first 2 months)		5 to 10	5 to 10
Late (after 2 months)		1 to 5	5 to 10
Overall	15 to 30	25 to 35	30 to 45

Source: De Cock KM et al. 2000.[5]

1.3 STRATEGY FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION

The United Nations agencies recommend a three-pronged strategy to prevent transmission of HIV to infants:

- Primary prevention of HIV among parents-to-be;
- Prevention of unwanted pregnancies among HIV-infected women;
- Prevention of HIV transmission from HIV-infected women to their infants through the provision of antiretroviral drugs to HIV-infected pregnant women and their infants, safe delivery practices, and counselling and support for safer infant feeding practices.

1.4 COMPONENTS OF A COMPREHENSIVE MTCT-PREVENTION PROGRAMME

Prophylactic use of an antiretroviral regimen is just one component of an MTCT-prevention programme (Table 2). While the focus on the use of such regimens increases public awareness that transmission of HIV to infants can be prevented and provides a catalyst to action, the other components should not be neglected. MTCT-prevention programmes are often limited to interventions delivered to HIV-infected women during pregnancy and around the time of delivery. A significant and sustainable impact will only be achieved when all components of the comprehensive programme are in place and functioning. Furthermore, many of these other components are themselves key strategies in the broader HIV prevention effort.

Table 2. MTCT-prevention programme components and their contribution to the three-pronged strategy

	Primary prevention of HIV among parents-to-be	Prevention of unwanted pregnancies among HIV-infected women	Prevention of HIV transmission from HIV-infected pregnant women to their infants
■ Information, education and counselling on HIV prevention and care including approaches to MTCT-prevention	✓	✓	✓
■ Condom promotion	✓	✓	✓
■ Voluntary counselling and testing	✓	✓	✓
■ Family planning services		✓	
■ Treatment of sexually transmitted infections	✓		
■ Antenatal care			✓
■ Prevention of transmission with prophylactic antiretroviral regimens			✓
■ Safe delivery practices			✓
■ Counselling and support for safer infant feeding practices			✓
■ Community action to reduce stigma and discrimination and increase support for HIV prevention and care interventions	✓	✓	✓

It is also important to provide and improve care and support services for HIV-infected individuals and their families, especially:

- care of the HIV-infected mother;
- psychosocial support for the mother and her family;
- planning for the long-term care and support for HIV-infected and affected children in the family.

The integration of basic MTCT-prevention interventions within maternal and child health services with linkages to a broader array of interventions may not be achieved immediately but should be sought over the longer term to enhance programme impact and sustainability.

2. USE OF ANTIRETROVIRAL DRUGS FOR MTCT-PREVENTION

Primary prevention of HIV infection among future parents and avoidance of unwanted pregnancies among women infected with HIV are fundamental long term strategies in the prevention of transmission of HIV to infants. However, many HIV-infected women become pregnant and others may acquire HIV infection during pregnancy. The use of antiretroviral drugs during pregnancy and delivery has been shown to be effective in reducing the transmission of HIV from mothers to infants. These regimens reduce the risk of MTCT by decreasing viral replication in the mother and through prophylaxis of the infant during and after exposure to the virus.

This section reviews the evidence available to date on efficacy and safety of antiretroviral regimens, including those based on nevirapine, for MTCT-prevention.

2.1 EFFICACY

Remarkable reductions in paediatric HIV infection rates have been observed in industrialized countries since 1994 when the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 showed that administration of zidovudine to women from the fourteenth week of pregnancy and during labour, and to the newborn decreased the risk of MTCT by nearly 70% in the absence of breastfeeding.[6] When combined with elective caesarean section this regimen resulted in a transmission rate of 2% or less, in non-breastfeeding populations.[7,8] The use of combination antiretroviral regimens, known as highly active antiretroviral therapy or HAART, for the treatment of HIV-infected individuals has resulted in similar low vertical transmission rates when used by pregnant women.[9]

The cost and complexity of these regimens have restricted their use in resource-poor settings. However, from 1998, a shorter zidovudine alone regimen starting from 36th week of pregnancy was shown to reduce the risk of transmission of HIV at 6 months by 50% in a non-breastfeeding population[10] and by 37% in breastfeeding populations.[11,12] Other clinical trials have shown that short course antiretroviral regimens using the combination zidovudine and lamivudine,[13] or nevirapine alone[14] also substantially decrease the risk of HIV transmission (Table 3).

Table 3. Use of antiretroviral regimens for MTCT-prevention

Regimen (Reference)	Schedule	Cost	Efficacy	Practicality	Efficacy*/Transmission Rates/Comments
NON-BREASTFEEDING POPULATIONS					
Regimens starting in early pregnancy					
ACTG076/ ANRS024[6] ZDV	**Pregnancy: from wk 14** 100mg 5 times dly, **Intrapartum**: 2mg/kg intravenous (IV) infusion over 1 h, continuous hly IV infusion of 1 mg/kg **Postpartum Infant:** 2 mg/kg orally 6 hly for 6 wks	+++	++++	+	18-mth efficacy 68% 18-mths transmission rate 8% Original regimen. Requires extensive resources.
Regimens starting in late pregnancy					
'Thai short course'[10] ZDV	**Pregnancy: from wk 36** 300mg twice dly **Intrapartum**: 300mg 3 hly	++	+++	+++	6-mth efficacy 50% 6-mths transmission rate 9%
PHPT, Thailand[17] ZDV	Long-Short, Long-Long **Pregnancy: from wk 28** 300mg twice dly **Intrapartum**: 300mg 3 hly **Postpartum Infant:** 2mg/kg 6 hly for 3 days or 6 wks	++	+++	++	6-mths transmission rate 6% May be slightly better than 'Thai short course'
	Short-Long **Pregnancy: from wk 35** 300mg twice dly **Intrapartum**: 300mg 3 hly **Postpartum Infant**: 2mg/kg 6 hly for 6 wks	++	+++	+++	6-mths transmission rate 8% Similar to 'Thai short course'
BREASTFEEDING POPULATIONS					
Regimens starting in late pregnancy					
CDC, W Africa[12] ZDV	**Pregnancy: from wk 36** 300mg twice dly **Intrapartum**: 300mg 3 hly	++	++	+++	6-mth efficacy 37% 3-mths transmission rate 17%
DITRAME/ ANRS 049a W Africa[11] ZDV	**Pregnancy: from wk 36** 300mg twice dly **Intrapartum**: 600mg **Postpartum mother**: 300mg twice dly for 1 week	++	++	++	6-mth efficacy 38%; 6 mths transmission rate 18% Pooled 24-mth W African data CDC/DITRAME: 28% efficacy and transmission rate 22%
PETRA Arm A[13] ZDV+3TC	**Pregnancy: from wk 36** ZDV+3TC twice dly **Intrapartum**: ZDV 3hly/ 3TC twice dly **Postpartum mother**: ZDV+3TC twice dly for 1 wk **Postpartum Infant**: ZDV+3TC twice dly for 1 wk	++	+++	++	6-wk efficacy 54% 6-wks transmission rate 7%
Regimens starting in labour					
PETRA Arm B[13] & **SAINT**[18] ZDV+3TC	**Intrapartum**: ZDV 3hly/ 3TC twice dly **Postpartum mother**: ZDV/3TC twice dly for 1 wk **Postpartum Infant**: ZDV+3TC twice daily for 1 wk	++	++	+++	PETRA: 6-wk efficacy 39% 6-wk transmission rate 10% SAINT: 6-wk transmission rate 10% Programmatically attractive because of simplicity and relatively low cost.
HIVNET 012[14] & **SAINT**[18] NVP	**Intrapartum**: 200mg at start of labour (HIVNET) or at hospital intrapartum (SAINT) **Postpartum mother**: 200mg stat (SAINT only) **Postpartum Infant**: 2mg/kg stat within 48 hrs (SAINT) or 72 hrs (HIVNET 012)	+	++	++++	HIVNET 012: 14-16-wk efficacy 47%; 6-wks transmission rate 12% 12-mth efficacy 42%; 12-mths transmission rate 16% SAINT: 8-wks transmission rate 13% Programmatically very attractive because of simplicity and very low cost. Concerns over drug resistance in women who have access to ARV therapy.

Efficacy: Percentage reduction in HIV transmission rate in active arm compared with placebo, except for NVP which was compared in HIVNET012 with a probably ineffective regimen consisting of intrapartum ZDV for the mother and 1 week post-partum for the infant
ZDV: Zidovudine **3TC**: Lamivudine **NVP**: Nevirapine **ARV**: Antiretroviral
Adapted from: Efficacy of Antiretroviral Regimens for the Prevention of Mother to Child Transmission of HIV and Some Programmatic Issues : Farley T, Buyse D, Gaillard P, Perriens J. Background documents for WHO Technical Consultation October 2000.[1]

Short term efficacy as determined by infant's infection status at 6-8 weeks of life has been demonstrated for the short course prophylactic regimens comprising zidovudine alone, zidovudine plus lamivudine, or nevirapine alone. Long term efficacy as determined by the child's infection status at 24 months of age has been evaluated for the short course zidovudine regimen, and at 18 months of age for the nevirapine regimen, in breastfeeding populations.[15,16] Available data indicate that the proportion of children acquiring HIV through breastfeeding was comparable in both these regimens and the early difference in reduction of HIV transmission persisted despite continued exposure to HIV through breastfeeding. Assessment of the long-term efficacy of the zidovudine plus lamivudine regimen in such populations is still in progress.

All regimens include an intrapartum component, with varying duration of antepartum and/or postpartum prophylaxis. While the efficacy of the more complex regimens which include antepartum, intrapartum and postpartum components is somewhat higher, the single dose nevirapine regimen provided during labour to the mother and postpartum to the infant has also been shown to be efficacious and is more practical.

2.2 SAFETY

For women and infants who are offered antiretroviral prophylaxis of MTCT, the risk associated with exposure to one or more drugs must be weighed against the benefit of reducing the risk of transmission to infants of a fatal infection. Short-term safety and tolerance of the antiretroviral prophylactic regimens has been demonstrated in all the controlled clinical trials on MTCT-prevention. Collection of data on long-term safety and on patterns of resistance to the antiretroviral drugs is ongoing.

2.3 CHOICE OF ANTIRETROVIRAL REGIMEN(S)

The choice of regimen(s) to be included in a MTCT-prevention programme should be determined by assessment of feasibility, efficacy, acceptability and cost. However, it should be noted that drug costs may represent only a fraction of the costs of the services that are required for an effective MTCT-prevention programme.

Practical considerations in choosing antiretroviral regimens for MTCT-prevention

- Availability of voluntary counselling and testing services
- Proportion of HIV-infected women who are aware of their serostatus at different stages of pregnancy
- Patterns of initiation of antenatal care
- Frequency of antenatal visits
- Quality of antenatal care
- Proportion of births occurring in health care facilities
- Access to early postnatal care
- Acceptability and ease of dosage schedules
- Access to and cost of drugs

2.4 USE OF NEVIRAPINE FOR MTCT-PREVENTION

In recent years, the use of nevirapine has attracted considerable attention because of its demonstrated efficacy in clinical trials in reducing MTCT, low cost and ease of use in MTCT-prevention programmes. Further information about its use for this purpose is provided below.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that binds directly to HIV-1 reverse transcriptase, slowing the rate of viral DNA synthesis and thereby inhibiting viral replication. Nevirapine is rapidly absorbed when given orally to adults, and has a long elimination half-life $t_{1/2}$ of approximately 40 hours. Nevirapine crosses the placenta efficiently after a single oral 200 mg dose to the mother at the onset of labour. In infants, median $t_{1/2}$ ranges from 45 to 72 hours for elimination of the maternal nevirapine, and from 37 to 46 hours for the elimination of a single 2mg/kg neonatal dose.[19]

Short-term safety and tolerance of single dose nevirapine has been demonstrated in clinical trials. Data from 38 women and infant pairs enrolled in the initial phase I trials, PACTG 250 and HIVNET 006, showed no rash or serious adverse events detected either through laboratory tests of through observation of clinical symptoms in women or infants, attributable to nevirapine. In the HIVNET 012[14] and SAINT studies,[18] 960 women and infant pairs were exposed to the intrapartum/newborn nevirapine regimen; there were no significant differences in serious toxicity, occurrence of rash, anaemia, liver abnormalities or death between nevirapine and short course regimens of zidovudine or zidovudine/lamivudine in women or infants. In the PACTG 316 study, 1506 women

receiving antiretroviral treatment (usually combination therapy) were randomized to receive an extra dose of nevirapine or placebo at the time of delivery. There was no difference in maternal or infant toxicity between the two study arms.[20] Collection of long-term safety data following administration of single dose nevirapine is ongoing.

Selection of resistant virus has been observed among some women and infants who received single dose nevirapine[21,22] or lamivudine.[22,23] for preventing MTCT. The resistant virus will revert to wild type susceptible strains within 12 to 24 months after stopping the treatment with nevirapine. The clinical significance of the emergence of resistance in the context of MTCT prevention programmes is as yet unknown, particularly with regard to future treatment options for the mother or the child, or to the outcome of prophylaxis during a subsequent pregnancy if the same drug is used. The WHO Technical Consultation in October 2000 carefully reviewed the available information and concluded that the benefit of decreasing mother-to-child HIV transmission with these antiretroviral drug prophylaxis regimens greatly outweighed concerns related to development of drug resistance.[1]

Nevirapine and zidovudine were included in the WHO Model List of Essential Drugs in 1999, solely for the indication of MTCT prevention of HIV.[24] The HIVNET 012 regimen of nevirapine used for MTCT-prevention is a single 200 mg oral tablet to be taken by the mother at the onset of labour and a single oral dose of nevirapine in suspension (2 mg/kg) to be given to the newborn within 72 hours of birth.

Experience in the field suggests that the oral tablet for the mother can be taken at home at onset of labour. However, it is essential that the child should be brought to a health facility within 72 hours of birth for the oral dose of nevirapine in suspension.

3. USE OF NEVIRAPINE FOR OTHER INDICATIONS

This section provides basic information on the use of nevirapine in the long-term treatment of HIV disease and for post exposure prophylaxis, for the guidance of programme managers considering the procurement of nevirapine for use in HIV/AIDS programmes and of practitioners who may be asked to provide nevirapine for these indications.

3.1 USE OF NEVIRAPINE FOR LONG-TERM TREATMENT OF HIV

A number of antiretroviral drug regimens are currently available for use in the long-term treatment of adults infected with HIV (Table 4).

Table 4. Available antiretroviral drugs

Reverse Transcriptase Inhibitors		Protease Inhibitors
Nucleoside reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Zidovudine (AZT, ZDV)	Nevirapine (NVP)	Saquinavir (SQV)
Didanosine (ddI)	Efavirenz (EFV)	Ritonavir (RTV)
Zalcitabine (ddC)	Delavirdine (DLV)	Indinavir (IDV)
Stavudine (d4T)		Nelfinavir (NFV)
Lamivudine (3TC)		Amprenavir (APV)
Abacavir (ABC)		Lopinavir/ritonavir

Nevirapine must only be used in combination with other effective antiretroviral drugs in the long-term treatment of HIV infection in adults and children. In patients commencing antiretroviral treatment for the first time, the combination of nevirapine with two nucleoside reverse transcriptase inhibitors (NRTIs) is an effective antiretroviral regimen. Possible combinations for nevirapine-based initial regimens are:

- Nevirapine/zidovudine/lamivudine;
- Nevirapine/stavudine/didanosine;
- Nevirapine/stavudine/lamivudine.

Nevirapine can also be used in a variety of second line therapeutic combinations. The second line combinations are used when an initial regimen using drugs from the other two classes is either ineffective or poorly tolerated.[25]

Patients taking antiretroviral regimens including nevirapine must be closely monitored for adverse affects. The most frequent adverse effect of nevirapine is skin rash, which occurs in 16% of individuals who start long-term therapy. The risk of rash from nevirapine is greatest during the first six weeks of treatment and diminishes thereafter. Most cases of rash are mild to moderate and either subside spontaneously or are manageable without discontinuation of treatment.[26] Practitioners should familiarize themselves with prescribing information and the evaluation of severity of rash.

Nevirapine along with NRTIs (e.g., zidovudine, didanosine, and stavudine) has been associated with hepatotoxicity. The most common laboratory abnormality observed during nevirapine therapy is an elevation of hepatic transaminase enzyme levels. Cases of overt hepatitis, some of them fatal, have also been associated with nevirapine and NRTI treatment. The incidence of nevirapine related hepatitis reported from comparative clinical trials of HIV disease treatment regimens is 1%. The majority of cases of hepatitis occurred within the first eight weeks of treatment.

Selection for pre-existing resistant viral populations or development of new mutations may occur with all antiretroviral drug regimens. However, this is more likely to occur rapidly with drugs in which a single mutation is associated with drug resistance; such drugs include nevirapine and lamivudine, particularly when used in monotherapy regimens. This pattern of resistance mutations selected by nevirapine is similar to those selected by other NNRTIs, but is distinct from those of NRTIs and protease inhibitors.

3.2 USE OF NEVIRAPINE FOR POST EXPOSURE PROPHYLAXIS

Though not approved for use in post exposure prophylaxis (PEP), nevirapine has been used for this purpose for some years in combination with other antiretroviral drugs following occupational or sexual exposures to HIV. There has been a recent report of serious adverse events (including liver damage and skin reactions) attributed to multiple doses of nevirapine given over several days to several weeks for PEP.[27] Considerations about the use of nevirapine for PEP must balance the risk of HIV transmission represented by the exposure against the potential toxicity of the specific drugs used. In many circumstances, the risks associated with multiple dose of nevirapine as part of a PEP regimen outweigh the anticipated benefits. The use of nevirapine should therefore be avoided for PEP, especially as other effective antiretroviral regimens are currently available for this indication.

4. MANAGING NEVIRAPINE DONATIONS

It is recommended that a working group be appointed to assess the need for nevirapine use in MTCT-prevention programmes, and if required, to facilitate applications for and coordination of nevirapine donations. All parties interested in benefiting from donations should be represented. These might include not only governmental organisations and institutions but also non-governmental organisations, charitable organisations and academic institutions. This working group should look into issues such as national drug policy, patent status and registration of nevirapine in the country, guidelines for MTCT-prevention programmes, drug distribution channels, monitoring and evaluation of programme activities and other practical issues.

4.1 BASIC PRINCIPLES

Interagency Guidelines for Drug Donations[28] have been drawn up to improve the quality of drug donation programmes. Based on this document, the following conditions require special attention in the case of the nevirapine donation:

- The drug donation should be based on an expressed need and should not be sent without prior consent of the recipient country;
- Nevirapine should be approved for the indication of MTCT-prevention in the recipient country; it should appear on the national list of essential drugs (though, if a national list is not available, it is sufficient that the drug appears on the WHO Model List of Essential Drugs, which nevirapine does);
- After arrival in the recipient country the donated drugs should have a remaining shelf-life of at least one year;
- All drugs should be labelled in a language that is easily understood by health professionals in the recipient country;
- The donated drugs should be packed in accordance with international shipping regulations and be accompanied by a detailed packing list which specifies the contents of each numbered carton by International Nonproprietary Name (INN) or generic name, dosage form, quantity, batch number, expiry date, volume, weight and any special storage conditions.

4.2 SPECIAL CONSIDERATIONS REGARDING DONATIONS OF SINGLE SOURCE PHARMACEUTICALS

As the donation of nevirapine represents a single-source donation (a donation from a single pharmaceutical company), there are a number of additional issues that need to be considered by the recipient to prevent unnecessary misunderstandings and potential disturbance of the market:[29,30]

- The donation programme should aim to assist countries in their efforts to achieve equitable and sustainable access to essential health care, including essential drugs;
- The programme should not be promotional in character, or increase market opportunities for a specific commercial enterprise to the detriment of others;
- The donation should be based on a sound analysis of the recipient country's needs, and the selection and distribution of nevirapine must fit within existing policies and guidelines on MTCT-prevention; the standards of the MTCT-prevention programme must be promoted; health workers must be trained and systems for supervision, and monitoring and evaluation must be put in place;
- The systems for nevirapine supply, distribution, prescription, dispensing and reporting must be defined in advance;
- The additional costs to the recipient country should be calculated in advance and funding arrangements made;
- Financing mechanisms for ensuring sustained access to nevirapine beyond the five years of the donation programme should be defined.

4.3 REGISTRATION OF NEVIRAPINE

Drug registration is the system which subjects all pharmaceutical products to pre-marketing evaluation, marketing authorisations and post-marketing review to ensure that they conform to required standards of quality, safety and efficacy. Registration is the responsibility of national drug regulatory authorities and is undertaken on the basis of a specific application and documentation submitted by an interested company.

WHO advises that no pharmaceutical product should be exempted from the drug registration process, although normal drug registration procedures can be waived or simplified under exceptional circumstances.[31,32] In the case under consideration, nevirapine should preferably be registered for the indication of MTCT-prevention, even if it is already registered for the treatment of HIV disease.

4.4 INTELLECTUAL PROPERTY RIGHTS

Drug prices are often related to the patent status of a drug in a particular country.[33] In the selection of antiretroviral regimens for use in MTCT-prevention programmes, in planning for the procurement of essential drugs and deciding whether to request donations of nevirapine for MTCT-prevention purposes, countries need to carefully consider drug prices. Despite its low unit cost, price remains an issue for nevirapine, with respect to its future use in large scale MTCT-prevention programmes, and in long-term HIV/AIDS treatment programmes.

Drug prices are often related to their patent status in a particular country. When a drug is not patent protected in a country, a generic alternative may be registered, imported from other sources or produced in the country. Nevirapine's substance patent was filed by Boehringer Ingelheim on November 16, 1990 in Europe (Application number 90121954.3). Nevirapine's patent status should be verified at the local patent office when investigating possible legal sources of nevirapine in a particular country. Generic nevirapine is now available in India and will be soon produced in Brazil. A market information service developed by UNAIDS, UNICEF, WHO, and Médecins Sans Frontières, may be consulted to obtain information on generic sources, prices and supplies.[34]

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