

PREVENTION OF
MOTHER-TO-CHILD TRANSMISSION OF HIV
USE OF NEVIRAPINE AMONG WOMEN OF UNKNOWN SEROSTATUS



REPORT OF A TECHNICAL CONSULTATION
5-6 DECEMBER 2001, GENEVA

DISCUSSION PAPER SERIES



WORLD HEALTH ORGANIZATION

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World Health Organization
Department of HIV/AIDS
Family and Community Health Cluster



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CONTENTS

EXECUTIVE SUMMARY	vii
1. INTRODUCTION AND BACKGROUND	1
2. KEY POLICY AND PROGRAMME ISSUES	4
2.1. Policy considerations in Botswana	4
2.2. Uptake and adherence in Lusaka, Zambia	5
2.3. Modelling approaches to scaling-up in Uganda	6
3. REVIEW OF NEVIRAPINE TOXICITY AND RESISTANCE	9
3.1. Toxicity in long-term treatment	9
3.2. Toxicity of single-dose prophylaxis	9
3.3. General issues related to resistance	9
3.4. Resistance associated with single-dose prophylaxis	10
4. CONCLUSIONS AND RECOMMENDATIONS	11
4.1. Definitions	11
4.2. Balancing risks and benefits	14
4.3. Recommendations on programme design	15
4.4. Research priorities	19
REFERENCES	21
APPENDIX	25



LIST OF ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
HIV	Human Immunodeficiency Virus
HIVNET	HIV Network Prevention Study
NNRTI	Non-nucleoside reverse transcriptase inhibitor
WHO	World Health Organization



EXECUTIVE SUMMARY

At this time, there is considerable support for accelerating and intensifying efforts to prevent HIV infections in infants, especially in countries most affected by the HIV/AIDS epidemic. Programmes using antiretroviral drugs to reduce HIV transmission from women known to be HIV-infected to their infants are being introduced or taken to scale in a number of countries. A two-dose regimen of nevirapine (single dose to the mother at onset of labour and single dose to the infant within 72 hours of birth) is increasingly being used because of its low cost and simplicity. The use of nevirapine among women of unknown serostatus at the time of labour and delivery has also been proposed, especially in settings with high HIV prevalence among pregnant women and limited availability or low uptake of programme activities for the prevention of mother-to-child transmission, such as voluntary counselling and testing and antiretroviral prophylaxis.

WHO convened a meeting in Geneva on 5 and 6 December 2001 to consider issues surrounding the use of nevirapine for the prevention of mother-to-child transmission among women of unknown serostatus. The participants discussed policy considerations in the context of national programmes to prevent HIV infections in Botswana and Uganda; they reviewed the results of research on uptake and adherence with different approaches to delivery of nevirapine in Zambia, and considered recent data on drug safety and resistance.

The participants identified and described three possible scenarios for the provision of nevirapine to prevent mother-to-child transmission:

- (1) targeted antiretroviral prophylaxis programmes, representing the current standard, in which HIV-infected women are identified through voluntary counselling and testing, and are offered antiretroviral prophylaxis and other specific prevention interventions;
- (2) combined antiretroviral prophylaxis programmes in which nevirapine would be offered as a “safety net” for women whose serostatus remains unknown at the time of delivery despite targeted programme inputs, and
- (3) universal nevirapine prophylaxis programmes, which would cover all women in situations where counselling and testing is not available.



They noted that there is no documented programme experience at this time with implementation of approaches to provide nevirapine to women of unknown serostatus.

In considering the above programme scenarios, the participants discussed three sets of issues related to use of nevirapine in women of unknown serostatus: drug safety, drug resistance, and programme implications. On drug safety, the participants concluded that the evidence to date indicates that the risk of serious adverse effects of a single dose of nevirapine is low, though very rare adverse effects cannot be ruled out, and they agreed that this possibility should not delay implementation of programmes that can prevent HIV transmission to infants, including programmes that provide nevirapine in selected circumstances to women of unknown HIV serostatus. The participants noted that concerns about drug resistance apply only to HIV-infected women because an uninfected woman cannot develop resistant virus. They endorsed the recommendations of a previous technical consultation which concluded that the benefit of antiretroviral drug (including nevirapine) prophylaxis in HIV-infected women greatly outweighed concerns related to the development of drug resistance and its impact on long-term treatment choices. They felt therefore that concerns about drug resistance should not determine decisions about the prophylactic use of nevirapine among women of unknown status.

After discussing programme design and implementation issues, the participants recommended that the targeted programme approach should remain the primary means of providing antiretroviral prophylaxis to prevent mother-to-child transmission of HIV. This approach represents the current standard that has now been successfully applied in a number of countries. It retains counselling and testing as the key entry point for positive women to a range of services to prevent ongoing transmission to their infants, including antiretroviral prophylaxis and infant feeding counselling and support. It thereby limits any risks of antiretroviral drug use to women who are already infected and their infants. In addition, this approach provides a range of other important benefits for the mother and her family, and the community at large.

The participants agreed that the combined programme approach represents a potential way to improve the coverage and effectiveness of targeted programmes, particularly in high prevalence settings. However, as there are no available data on potential risks and benefits, the implementation of the combined approach should involve operational research and careful evaluation.



The participants did not endorse the universal approach to the implementation of nevirapine prophylaxis programmes outside of research settings. They recognised that this programme approach was in principle more simple and affordable, and would ensure high coverage of antiretroviral prophylactic interventions for the prevention of peripartum HIV transmission. They noted however that it would not prevent postnatal transmission of HIV through breastfeeding, and that it might unnecessarily expose large numbers of HIV-negative women to a small, but still uncertain risk of drug toxicity.

Overall the participants therefore felt that programme efforts at this time should focus on the rapid scaling up of interventions to increase access to counselling and testing; on the expansion of targeted antiretroviral prophylaxis programmes; and on the controlled introduction of combined programmes in selected circumstances with supporting research to better document their risks and benefits. However, arguments were also made in favour of the universal approach, particularly in high-prevalence settings or where such an approach would be the only feasible option for preventing mother-to-child transmission.

Finally, the participants made recommendations on priority research topics.



1. INTRODUCTION AND BACKGROUND

The short-term efficacy results of the HIVNET 012 study conducted in Uganda were released in mid-1999.¹ In brief, this randomised clinical trial evaluated a simple antiretroviral drug regimen to prevent the transmission of HIV-1 from an infected mother to her child in a breastfeeding population. The main drug regimen under study consisted of a single oral dose of 200 mg nevirapine given at the onset of labour to HIV-infected pregnant women, combined with a single oral dose of nevirapine (2 mg/kg) given to the neonate within 72 hours of birth. The comparison group received a zidovudine regimen consisting of a maternal oral dose of 600 mg followed by 300 mg every three hours during labour, combined with a neonatal zidovudine regimen of 4 mg/kg twice daily during the first week of life. The nevirapine regimen reduced the mother-to-child transmission risk by 47% (95% confidence interval [CI]: 20-64%) at 14-16 weeks compared to the zidovudine regimen. In absolute terms, the cumulative transmission rate at that age was 13% in those receiving nevirapine versus 25% in those receiving zidovudine. The transmission rate in the zidovudine group was comparable to those observed in the placebo groups of other randomised clinical trials conducted in breastfeeding populations.² Subsequent data showed that although transmission continued to occur as exposure to breastfeeding continued, the reduction in transmission with this nevirapine regimen was observed at least until the age of 18 months, at which time the transmission rate was 16% in the nevirapine group and 28% in the zidovudine group.³ Economic analyses conducted at the time of release of the HIVNET 012 results concluded that the use of nevirapine to prevent mother-to-child transmission of HIV was cost-effective.⁴

At this time, programmes using either zidovudine (in short-course regimens of demonstrated efficacy) or nevirapine to reduce HIV transmission from women known to be HIV-infected to their children are being introduced or taken to scale in a number of countries. The nevirapine regimen is increasingly used in many settings because of its low cost and simplicity. Nonetheless, several obstacles are persistently being identified. The main difficulty seems to be a high drop out during voluntary HIV counselling and testing in antenatal care clinics, such that a large proportion of women in need are not identified and do not benefit from antiretroviral prophylaxis.⁵



WHO organised a technical consultation in October 2000 to review the most recent scientific data on the use of antiretroviral regimens to prevent mother-to-child transmission of HIV. The meeting concluded that any of the antiretroviral prophylactic regimens shown to be effective in randomised clinical trials, including the HIVNET 012 nevirapine regimen, could be recommended for general implementation, and that there was no justification to restrict their use to pilot projects or research settings.⁶ However, participants at the meeting acknowledged the need for further research on the clinical significance of transient drug resistance following single-dose nevirapine. The use of antiretroviral prophylaxis among women of unknown HIV serostatus for the prevention of HIV infections in infants was not discussed.

The Declaration of Commitment endorsed by 189 countries at the United Nations General Assembly Special Session on HIV, 25-27 June 2001, set the goal of reducing the proportion of infants infected with HIV by 20% by the year 2005 and by 50% by the year 2010.⁷ To reach these goals the challenge will be to scale up programme implementation with much improved levels of coverage and uptake of a broad array of interventions that seek to achieve primary prevention of HIV among women, prevention of unintended pregnancies among HIV-infected women, and, through specific measures including antiretroviral prophylaxis, the reduction of HIV transmission from infected women to their infants.

At present, the use of the HIVNET 012 nevirapine regimen among women of unknown serostatus at the time of labour and delivery is being proposed with increasing frequency, especially in settings with high prevalence of HIV among pregnant women and limited availability or low uptake of programme activities for the prevention of mother-to-child transmission, such as voluntary counselling and testing and antiretroviral prophylaxis.

WHO convened a meeting in Geneva on 5-6 December 2001, to review and discuss issues arising from the use of nevirapine for the prevention of mother-to-child transmission among women of unknown serostatus. The specific objectives of the meeting were:

- (1) to summarise the evidence on risks and benefits,
- (2) to summarise the policy considerations and
- (3) to outline the priority research questions to be addressed.



Participants included scientists, policy makers and programme managers. The list of participants is provided at the end of the report (see Appendix). A background paper on drug safety and resistance issues was prepared for the meeting.⁸ An update on the Botswana national programme for the prevention of mother-to-child transmission, the results of a study on the use of nevirapine among women of unknown serostatus in Lusaka, Zambia, and relevant economic analyses performed in the context of the Uganda programme, were presented and discussed during plenary sessions of the meeting. A summary of these presentations is given below.



2. KEY POLICY AND PROGRAMME ISSUES

2.1. POLICY CONSIDERATIONS IN BOTSWANA

Botswana is experiencing one of the most severe HIV epidemics in the world, which is leading to a considerable burden of HIV infections in children. It is estimated that the HIV prevalence among antenatal clinic clients averages 40%, and in the absence of any programme interventions, up to 16% of 60,000 infants born each year are infected with HIV: approximately 9,600 infants per year, in a population of 1.7 million. The national programme for the prevention of mother-to-child transmission was established in September 1998 and now covers all districts.

The programme aims to reduce mother-to-child transmission rates from current levels of up to 40% to 10% by the year 2005 through a six-component strategy that includes community information, education and mobilisation; counselling and voluntary testing; provision of a short-course zidovudine regimen; replacement feeding advice and support; modified obstetric practices to minimize risk of transmission; and care and support to women known to be HIV-infected. So far, programme uptake has remained low, with only 15% of the women who test positive and enter the intervention programme receiving an adequate dose of zidovudine.

There have been recent discussions in Botswana about the possible provision of nevirapine to all pregnant women who test HIV-positive (regardless of whether or not they receive zidovudine), and to women whose serostatus remains unknown at time of labour. The implementation of the ongoing programme combined with nevirapine provision to all delivering mothers and newborns whatever their testing experience, could avert larger numbers of infections in infants than the current approach. Concerns have been raised about drug safety, especially for HIV-negative women who would be unnecessarily exposed to nevirapine, as well as about the potential weakening of voluntary testing and counselling efforts thereby foregoing their benefits, including those associated with counselling HIV-infected mothers on safer infant feeding options to prevent HIV transmission through breastfeeding. No policy decision had been reached at the time of the meeting.



2.2. UPTAKE AND ADHERENCE IN LUSAKA, ZAMBIA

The Center for Infectious Disease Research in Zambia is conducting studies to assess uptake and adherence to methods of delivering nevirapine for the prevention of mother-to-child transmission of HIV in high prevalence settings with severe resource constraints. Two approaches are being assessed: HIV testing with provision of nevirapine only to seropositive women (targeted approach) or provision of nevirapine to all pregnant women without HIV testing (mass approach).

In an initial survey, a structured questionnaire was administered to women presenting for care at two public antenatal clinics in Lusaka. Respondents were asked which approach they would choose for themselves if resources were available to provide HIV testing and nevirapine to all women at the clinic. They were also asked which approach they would favour as a policy if resource constraints required a choice between offering nevirapine to all pregnant women or targeted HIV testing and nevirapine prophylaxis to only half.⁹

When presented with a personal choice in the setting of unconstrained resources, most women (74%) preferred the targeted approach, that is provision of nevirapine only to women testing HIV-positive. However, when resource constraints required a choice between mass prophylaxis for all women or targeted prophylaxis for only half, most women (60%) preferred mass prophylaxis.

A trial to test these two approaches was conducted in two clinics in Lusaka Health District where HIV prevalence among antenatal clients ranged between 26% and 31% in the year 2000. The preliminary findings were presented at the meeting.¹⁰ The researchers postulated that uptake (the proportion of women who agree to participate in the intervention programme) would be higher for the mass approach than for the targeted, since it does not require a woman to undergo HIV counselling and testing. On the other hand, they postulated that adherence (the proportion of women who actually take the drug) would be higher in the targeted approach, since knowledge of HIV status could motivate better adherence. A crossover design was used so that each clinic had experience with both intervention approaches. Uptake was 70% (492 out of 700) among the women offered enrolment into the mass approach and 59% (435 out of 732) among women offered enrolment into the targeted approach ($p < 0.01$). Adherence was assessed among HIV-positive women by measuring nevirapine in cord blood at delivery. Based on cord blood detection of nevirapine, adherence was 79% (87 out of 110) with the targeted approach versus 69% (70 out of 102) with the mass approach ($p = 0.11$).



When studying the determinants of uptake, an important finding was that key indicators of programme performance were higher in one clinic, leading to higher provider and client satisfaction and higher uptake of counselling and testing services.¹¹ This resulted in a similar uptake of programme inputs using the targeted and the mass approach in this clinic (70% vs. 71%).

In conclusion, the uptake of the intervention appears comparable using either approach in clinics with adequate counselling and testing services, while the mass approach might result in higher uptake in less well-functioning clinics. Adherence, on the other hand, may be lower among women who do not know their HIV status.

Further research is planned to compare the uptake of counselling and testing and the population coverage of nevirapine between a strategy where the drug is provided only to women identified as infected through counselling and testing, and a strategy in which nevirapine is offered both to those testing positive and to those who decline testing.

2.3. MODELLING APPROACHES TO SCALING-UP IN UGANDA

The goal of the Ugandan national programme for the prevention of mother-to-child transmission is to provide a comprehensive package of antenatal care to pregnant mothers in order to reduce the risk of HIV transmission to infants. Currently, three antiretroviral prophylactic regimens, including the HIVNET 012 nevirapine regimen, are recommended by the Ministry of Health. Pilot projects began in February 2000 and seven are now operational. Up to November 2001, 27,076 of 54,057 women seeking antenatal care in the pilot project clinics (50%) accepted counselling and testing, and of the 3,613 who tested positive, 1,963 (54%) initiated one of the recommended antiretroviral prophylactic regimens. The low levels of provision and acceptance of voluntary counselling and testing, and of prevention interventions, remain constraints for the rapid expansion of the programme.

A modelling exercise to examine options for scaling-up the Ugandan national programme for the prevention of mother-to-child transmission was performed in 2001 under the auspices of the Elizabeth Glaser Pediatric AIDS Foundation, with an emphasis on assessing the costs and implications of nevirapine distribution to women of unknown HIV status.¹² This exercise did not consider the possible benefits of programme interventions on outcomes other than prevention of HIV infections in infants.



It is estimated that in the year 2005, 27,000 HIV-infected children would be born in the absence of antiretroviral-based interventions. Five programme options were examined, using different assumptions (Table 1).

Table 1. Summary of the assumptions underpinning five scaling-up options

Option	Women		VCT?	Field-based service?	Community mobilization?
	receiving services by 2005	% of pregnant women in Uganda			
(1) Women delivering in district hospitals, with current intervention inputs	163,261	12.3%	Yes	No	No
(2) Women delivering at any health facility, at the current level of facility-based deliveries, and with additional intervention inputs	505,364	38%	Yes	No	Moderate
(3) Same as above, with increased use of facility-based deliveries	1,196,995	90%	Yes	No	Extensive
(4) Women who make at least one antenatal care visit offered counselling and testing, and those who test positive offered home-based administration of nevirapine with support from an outreach worker	1,196,995	90%	Yes	Yes	Moderate
(5) Option 1, plus women who make at least one antenatal care visit offered counselling, but no testing, and all those who consent provided nevirapine for self-administration at home	1,196,995	90%	C: Yes T: No	Yes	Moderate

In the costing parameters, the cost of voluntary counselling and testing was estimated to be US\$ 8.12 per woman. The first two programme options yielded costs per paediatric HIV case averted in the year 2005 of US\$ 312 and 464 respectively, but the coverage levels (proportion of HIV-infected women who receive nevirapine) remained low at 7.6 and 23.6% respectively. Cost-effectiveness parameters of the third and fourth options remained in the same range as for the second option (US\$ 437 and 418 per case averted, respectively), but coverage reached 55.8% in both instances. The fifth option yielded an estimated coverage of 79.1% and the total costs of the programme are transformed into net savings.



The overall analysis did not take into account the possible drop in adherence associated with the provision of nevirapine to all pregnant women, but a sensitivity analysis showed that an adherence figure as low as 30% would not affect the main conclusions. The conclusions remain similar at HIV prevalence as low as 2.5%. The potential foregone benefits of voluntary counselling and testing in preventing HIV transmission in the adult population and HIV transmission associated with prolonged breastfeeding were not, however, considered in this analysis.





3. REVIEW OF NEVIRAPINE TOXICITY AND RESISTANCE

3.1. TOXICITY IN LONG-TERM TREATMENT

The main toxic manifestations of nevirapine that are of clinical concern are rash and hepatic toxicity. Rash usually occurs during the first two to four weeks of treatment in about 17% of patients, with serious (grade 3 or 4) rash requiring treatment discontinuation in about 6–8%.^{14,15} Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis have rarely been reported. A hypersensitivity syndrome with fever, myalgia, arthralgia, hepatitis and eosinophilia may or may not precede the rash. Hepatotoxicity can occur in the absence of rash or the hypersensitivity syndrome. Most of this toxicity occurs within the first 12 weeks of treatment. Some reports have suggested a possible increased rate of rash¹⁶ or hepatic toxicity¹⁷ among women.

3.2. TOXICITY OF SINGLE-DOSE PROPHYLAXIS

Safety of single-dose nevirapine regimens has been evaluated in two phase I safety and pharmacokinetic studies in the USA¹⁸ and Uganda¹⁹ and in three large, randomised, comparative, phase III clinical trials in Uganda¹; in the USA, Europe, Brazil and the Bahamas²⁰; and in South Africa²¹. Altogether, nevirapine for prevention of mother-to-child transmission has been studied in comparative clinical trials in over 1,600 HIV-infected women and their infants. No significant clinical or laboratory toxicity has been observed. Moreover, there were no differences in the rate of occurrence or type of clinical or laboratory toxicity in either women or their infants comparing single-dose nevirapine to either placebo, zidovudine or zidovudine + lamivudine.

3.3. GENERAL ISSUES RELATED TO RESISTANCE

Nevirapine resistance is an issue only among HIV-infected women, because an uninfected woman clearly cannot develop resistant virus. Resistance can be conferred by a single genetic mutation of the viral reverse transcriptase enzyme, most frequently at K103N and Y181C.¹⁴ The Y181C mutation conferring resistance has been found to be present in approximately one in every 1,000 copies of HIV in the plasma of drug-naive patients.²² Nevirapine has a prolonged half-life that could result in prolonged exposure to sub-therapeutic levels as drug concentrations decrease, potentially increasing selection pressure for nevirapine-resistant virus.



3.4. RESISTANCE ASSOCIATED WITH SINGLE-DOSE PROPHYLAXIS

In phase I and III studies, primary resistance mutations have been detected at six weeks postpartum in about 20% of women receiving a single dose of nevirapine.^{23,24} In follow-up samples available at 12 to 18 months postpartum, the resistance mutations were no longer detectable and wild-type virus again predominated. Infants who became infected were also evaluated for nevirapine resistance.²⁴ Nevirapine resistance mutations were detected in 46% of these infants. When both mother and infant had detectable resistance, the pattern of mutations differed, with most mothers having the K103N mutation and most infants having the Y181C mutation. These data suggest that nevirapine resistance in these infants was likely selected *de novo* when they received single-dose nevirapine in the presence of already replicating virus.^{24,25} As observed for mothers, nevirapine resistance in infected infants was transient, and had no effect on mortality of untreated HIV-infected children. The clinical consequences of transient selection of nevirapine-resistant virus with single-dose prophylaxis are uncertain.

Nevirapine-resistant virus may be selected with a single dose of nevirapine even in women receiving other antiretroviral drugs if viral replication is not fully suppressed.^{26,27} The temporary selection of resistant virus induced by a single dose of nevirapine during labour is not expected to lead to emergence of nevirapine-resistant strains in the population²⁸, though data in this area are lacking.

Another concern has been whether the efficacy of single-dose nevirapine prophylaxis will be decreased in subsequent pregnancies. However, it is highly likely that resistant virus will no longer be detectable at the time the single dose is used again. Thus, the efficacy of the prophylactic nevirapine regimen in subsequent pregnancies may be retained, though again this needs to be confirmed through research.



4. CONCLUSIONS AND RECOMMENDATIONS

Following the plenary presentations, the participants met in two working groups to discuss issues related to toxicity, resistance and access to future treatment, and to review programme considerations. The conclusions and recommendations of the working groups were then presented and debated in a final plenary session. The overall conclusions and recommendations of the meeting are presented below.

4.1. DEFINITIONS

The participants considered the advantages and disadvantages of providing nevirapine to women of unknown serostatus for the prevention of mother-to-child transmission of HIV. They recognized that these depend on the programmatic conditions in which the nevirapine is provided. They identified three possible scenarios based on access to HIV testing and access to antiretroviral prophylaxis, noting that the last two scenarios were theoretical, as there is no documented programme experience to draw upon at this time. Table 2 provides definitions of the three scenarios.

4.1.1. TARGETED ANTIRETROVIRAL PROPHYLAXIS PROGRAMMES

Targeted programmes represent the current standard. The aim of a targeted programme is to identify HIV-infected women through voluntary counselling and testing, and to offer them antiretroviral prophylaxis and other specific prevention interventions. Antenatal counselling and testing is the entry point and key building block of the programme. In this scenario, antiretroviral drugs (usually zidovudine or nevirapine) are offered only to women who test HIV-positive, following a discussion of the risks and benefits. Nevirapine may in some cases be offered to provide optimal antiretroviral prophylactic coverage to HIV-positive pregnant women (and their infants) who have received a sub-optimal zidovudine regimen. Women of unknown serostatus are not given antiretroviral prophylaxis.

Current guidelines for counselling on infant feeding options are as follows. Among women known to be HIV-infected, avoidance of all breastfeeding is recommended when replacement feeding is acceptable, feasible, affordable, sustainable and safe; otherwise exclusive breastfeeding is recommended during the first months of life. To minimize HIV transmission risk, breastfeeding should be discontinued as soon as feasible, taking into



account local circumstances, the individual woman's situation and the risks of replacement feeding.⁶ Uninfected women and women of unknown HIV status are encouraged and assisted to exclusively breastfeed during the first six months of the infant's life, with introduction of complementary foods and continued breastfeeding thereafter till 24 months.^{29,30}

4.1.2. COMBINED ANTIRETROVIRAL PROPHYLAXIS PROGRAMMES

The combined programme has been proposed as a “safety net” for women whose serostatus remains unknown at the time of delivery despite targeted programme inputs. This may be the case among women who decline HIV testing, or who for any other reason are not tested or are not provided their test result, for example, if they present to the health services during labour.

The combined prophylaxis programme contains the basic elements of the “targeted” programme with antenatal counselling and testing either in place, in the process of being set up, or available off-site. Antiretroviral prophylaxis is offered to all HIV-infected women, usually in the form of a short course of zidovudine or a single dose of nevirapine for both the mother and the infant. In addition, nevirapine is also offered, following a discussion of its risks and benefits, to women whose serostatus is unknown, to be taken during labour and given to the infant. In this way, women who decline antenatal HIV testing or who otherwise remain of unknown serostatus at the time of labour are given access to nevirapine if they wish. Women of unknown status are encouraged to accept counselling and voluntary testing offered after delivery, so they can make informed decisions about infant feeding options and benefit from care and support services.

Infant feeding counselling follows the usual guidelines. In particular, women of unknown status are encouraged to exclusively breastfeed for the first six months of the infant's life and continue breastfeeding thereafter until 24 months.

4.1.3. UNIVERSAL NEVIRAPINE PROPHYLAXIS PROGRAMME

This would apply in situations where counselling and testing is not provided in the antenatal care setting, and is generally not available off-site. In a universal nevirapine prophylaxis programme, every pregnant woman receives basic information on HIV, the risk of mother-to-child transmission and the risks and benefits of nevirapine prophylaxis. Nevirapine is then offered to all women, who can choose to take it or not. Again, breastfeeding is promoted and supported for all women whose HIV status is unknown.



The participants agreed that the expression “mass treatment”, sometimes used to describe the “universal” approach, should no longer be used.

Table 2. Definitions of programme scenarios according to the strategies for counselling and testing, and nevirapine delivery

Programme scenario	Characteristics
“Targeted”	<ul style="list-style-type: none"> ■ Offer of voluntary counselling and testing to all pregnant women ■ Provision of antiretroviral prophylaxis and other specific prevention interventions (including infant feeding counselling and support) only to HIV-positive women, with information about risks and benefits ■ No provision of antiretroviral drugs to women of unknown serostatus ■ Possible provision of nevirapine to known HIV-infected women who have received a sub-optimal dose of zidovudine
“Combined”	<ul style="list-style-type: none"> ■ Background of a targeted antiretroviral prophylaxis programme for pregnant women ■ Provision of nevirapine to women of unknown HIV status (who were not offered testing, declined testing or did not receive test results prior to the beginning of labour) and their infants (HIVNET 012 regimen) with information about risks and benefits ■ Offer of postpartum voluntary counselling and testing on-site or through a referral link ■ Infant feeding guidance for women of unknown serostatus as for uninfected women
“Universal”	<ul style="list-style-type: none"> ■ Unavailability of counselling and testing either in the antenatal care setting or off-site ■ Basic information on HIV, the risk of mother-to-child transmission and the risks and benefits of nevirapine provided to all pregnant women ■ Offer of HIVNET 012 nevirapine regimen to all women and their infants ■ Infant feeding guidance as for uninfected women

In all of these scenarios, women’s right to decline or opt out of the prevention intervention would be maintained, as for any other medical intervention. All women would be provided basic knowledge of the programme and the benefits and risks of intervention procedures, which enable them to provide informed consent. Measures would be taken to encourage uptake of effective interventions, and to gain the support of the community for efforts to prevent mother-to-child transmission.



4.2. BALANCING RISKS AND BENEFITS

In considering the above programme scenarios, the participants discussed the risks of providing single-dose nevirapine to women of unknown serostatus, with a focus on drug toxicity and resistance, in relation to possible benefits.

4.2.1. RISKS

The participants noted that drug safety considerations apply to all women, regardless of their infection status. They agreed that the evidence to date indicates that the risk of serious adverse effects of a single dose of nevirapine is low, but that very rare adverse effects cannot be ruled out. Such rare events may only be detected with wide-scale programme implementation and single-dose nevirapine use by large numbers of mother-infant pairs. The participants concluded that the possibility of a very rare adverse effect of a single dose of nevirapine should not delay implementation of programmes that can prevent HIV transmission to infants, including programmes that provide nevirapine in selected circumstances to women of unknown HIV serostatus. Monitoring of adverse events should be conducted as part of large-scale programmes to ascertain the frequency and types of toxicity associated with single-dose nevirapine.

On the other hand, the participants noted that concerns about drug resistance apply only to HIV-infected women and agreed that issues related to resistance are the same whether nevirapine prophylaxis is provided to known HIV-infected women or women of unknown serostatus. Experts at a previous technical consultation concluded that the benefit of antiretroviral drug (including nevirapine) prophylaxis in HIV-infected women in reducing the risk of a fatal infection in the infant greatly outweighed concerns related to the development of drug resistance and its impact on long-term treatment choices.⁶ The participants therefore felt that concerns about drug resistance should not determine decisions about the prophylactic use of nevirapine among women of unknown status. Sentinel surveillance of drug resistance should be considered in all settings where antiretroviral drugs are used in programmes to prevent mother-to-child transmission.

4.2.2. BENEFITS

The benefits of nevirapine prophylaxis accrue to the infant and not to the mother. The HIVNET 012 two-dose drug regimen reduces intrapartum and early postpartum transmission of HIV by nearly 50% though it does not prevent later transmission through breastfeeding. Whereas the risks of toxicity associated with nevirapine prophylaxis apply evenly to all women whether or not they are aware of their serostatus, the benefits for the



child vary according to the mother's serostatus. Experts at a previous technical consultation concluded that the benefit of antiretroviral prophylaxis in known HIV-infected women in reducing the risk of a fatal infection in the infant "greatly outweighs any potential adverse effects of drug exposure".⁶ For women of unknown serostatus, however, the benefits vary according to their risk of infection; the higher the risk (e.g., the higher the prevalence of HIV among antenatal clients), the greater the potential benefit.

4.3. RECOMMENDATIONS ON PROGRAMME DESIGN

The participants discussed programme design issues, identified potential advantages and disadvantages of the different programme approaches (as summarised in Table 3), and made the following recommendations.

The targeted programme approach should remain the primary approach. This approach represents the current standard that has now been successfully applied in a number of countries. It retains counselling and testing as the key entry point for positive women to a range of services to prevent ongoing transmission to their infants, including antiretroviral prophylaxis and infant feeding counselling and support. It thereby limits any risks of antiretroviral drug use to women who are already infected and their infants. In addition, this approach provides a range of other important benefits for the mother and her family, and the community at large. In particular, the counselling and testing services should strengthen other prevention efforts, serve as an entry point into care and support services for infected women and their families, and may serve in the long term to address denial, stigma and discrimination at community level.

The circumstances for optimal implementation of this type of approach include:

- Availability of a robust health service infrastructure and adequate financial and human resources;
- Good access to and use of antenatal care services;
- High access to and uptake of HIV counselling and testing in antenatal care settings;
- Good level of deliveries attended by a skilled health care worker (while this is not strictly necessary, it will facilitate antiretroviral drug administration and infant feeding counselling and support);
- Strong community mobilization and support for the programme and low levels of stigma and discrimination against persons living with HIV/AIDS^{15 a};
- High level of commitment among local policy-makers, programme managers and local staff.

^a This applies to all approaches, but may be most important for targeted programmes in overcoming barriers to uptake of antenatal care and voluntary counselling and testing.



The combined programme approach merits attention as a potential way to improve the coverage and effectiveness of targeted antiretroviral prophylaxis programmes, particularly in high-prevalence settings. This approach may be helpful in providing a “safety net” in settings where counselling and testing services are still under development or where uptake of HIV testing remains low. This approach preserves the existing benefits of counselling and testing and of infant feeding counselling for those who test positive. However, because there is no documented experience with the implementation of the combined approach and therefore no available data on risks and benefits, implementation should be combined with operational research and careful evaluation^b.

The most suitable circumstances for the introduction of a combined approach include:

- High HIV prevalence^c among antenatal care clients;
- Persistent low uptake of HIV testing;
- High level of institutional deliveries or deliveries attended by a skilled health care worker to facilitate
 - (a) the provision of a single dose of nevirapine to the mother during labour and a single dose to the baby within 72 hours of delivery, and
 - (b) postpartum counselling and testing

The participants felt that this approach should be accompanied by efforts to develop and promote counselling and testing services, seeking to increase the number of women who use these services before and after delivery, and who can therefore make informed decisions about infant feeding options, and take advantage of care and support services. The provision of opportunities for postpartum counselling and testing may increase the number of women who are aware of their serostatus. However, concerns remain that, overall, the efforts to increase the number of women who know their serostatus may be undermined, as women are provided access to antiretroviral prophylaxis without HIV testing.

The participants did not endorse the universal programme approach to the implementation of nevirapine prophylaxis. They recognised that this programme approach was in principle more simple and affordable, and would ensure high coverage of antiretroviral prophylactic interventions for the prevention of peripartum HIV

^b In most countries nevirapine is only registered for prevention of mother-to-child transmission among HIV-positive women. Programmes should therefore seek approval for use among women of unknown serostatus from national regulatory bodies.

^c “High” prevalence is not quantified as this would need modeling, but in the context of a safety-net approach the higher the prevalence the greater the benefit to be drawn from the programme.



transmission. They noted however that it would not prevent postnatal transmission of HIV through breastfeeding, and that it might unnecessarily expose large numbers of HIV-negative women to a small, but still uncertain risk of drug toxicity.

Overall the participants therefore felt that programme efforts at this time should focus on the rapid scaling up of interventions to increase access to counselling and testing and thus knowledge of serostatus, which carries many benefits beyond the prevention of HIV infections in infants; on the expansion of targeted antiretroviral prophylaxis programmes; and on the controlled introduction of combined programmes in selected circumstances with supporting research to better document their risks and benefits. Some participants were concerned that the development of universal nevirapine prophylaxis programmes would divert attention from these pressing programme priorities, and felt that the universal approach should be implemented only in research settings where rigorous monitoring and evaluation can provide data, which is currently lacking, on its possible role, risks and benefits. However, arguments were also made in favour of the universal approach, particularly in high-prevalence settings or where such an approach would be the only feasible option for preventing mother-to-child transmission.



Table 3. Potential advantages and disadvantages of “targeted”, “combined”, and “universal” antiretroviral prophylaxis

Type of programme	
Advantages	Disadvantages
“Targeted”	
<ul style="list-style-type: none"> ■ Enables all benefits of knowledge of serostatus, including support for other prevention efforts and entry into care and support for those already infected ■ Permits infant feeding counselling to reduce the risk of transmission through breastfeeding ■ Improves adherence with programme interventions ■ May help to promote counselling and testing services as part of routine care ■ May help to de-stigmatize HIV in the long term 	<ul style="list-style-type: none"> ■ Places high demands on financial and human resources ■ Requires trained counsellors ■ Suffers from low uptake in settings where women do not want to know their HIV status ■ Is undermined where stigma and discrimination are a barrier to programme entry, uptake, and adherence
“Combined”	
<ul style="list-style-type: none"> ■ Increases the coverage and effectiveness of the antiretroviral prophylactic intervention when used as a “safety net” ■ Prevents more infections in infants ■ Preserves existing benefits of counselling and testing, and infant feeding counselling for those who test positive ■ May serve as an interim step while counselling and testing services are developed in antenatal care services 	<ul style="list-style-type: none"> ■ May undermine efforts to increase voluntary counselling and testing ■ Does not prevent postnatal transmission through breastfeeding ■ May lead to complacency in scaling up targeted programmes ■ May cause confusion among health providers with respect to infant feeding recommendations ■ Unnecessarily exposes HIV-negative women to any nevirapine toxicity
“Universal”	
<ul style="list-style-type: none"> ■ Ensures high coverage of antiretroviral prophylactic interventions ■ May prevent more peripartum infections ■ May be more acceptable ■ Will be easier to implement ■ Relatively cheap 	<ul style="list-style-type: none"> ■ May undermine efforts to introduce voluntary counselling and testing services and thereby foregoes their benefits ■ Does not prevent postnatal transmission through breastfeeding ■ Precludes access to care and support for HIV-infected persons ■ May suffer from low adherence with nevirapine use ■ May undermine commitment to HIV prevention programmes ■ Unnecessarily exposes a large number of HIV-negative women to any nevirapine toxicity



4.4. RESEARCH PRIORITIES

The participants agreed that many questions remain unanswered and that there is an urgent need for further research. They identified the following research topics. Topics considered of highest priority are marked with an asterisk (*).

4.4.1. PROGRAMME DESIGN AND IMPLEMENTATION

- *Factors influencing women's decision-making related to HIV testing in the context of different programme approaches
- Levels and determinants of adherence to antiretroviral prophylactic regimens in the context of different programme approaches
- Approaches to increase partner, family and community involvement in programmes to prevent mother-to-child transmission
- *Benefits, risks and appropriate approaches to implement combined antiretroviral prophylaxis programmes, including impact on (a) uptake of and adherence to nevirapine prophylaxis; (b) estimated coverage of nevirapine prophylaxis among HIV-infected women; (c) access to and uptake of antenatal and postnatal HIV counselling and testing; (d) infant feeding choices; (e) access to care for HIV-infected women and their families; (f) adoption of preventive behaviour
- Impact of use of nevirapine in women of unknown serostatus on infant feeding choices and practices for individuals and communities
- *Effectiveness and cost-effectiveness of various approaches to providing nevirapine prophylaxis in large-scale programme settings

4.4.2. EFFECTS AND RISKS OF NEVIRAPINE PROPHYLAXIS

- *Effect of timing of nevirapine administration on HIV transmission risk
- *Pharmacovigilance studies to determine the frequency and types of toxicity associated with nevirapine prophylaxis, in HIV-infected women and women of unknown status, and their infants



- *Sentinel drug-resistance surveillance by type of programme in populations where nevirapine prophylaxis is used, and where nevirapine is used for treatment
- Incidence of genotypic and phenotypic resistance associated with nevirapine prophylaxis in mother and infant
- *Kinetics and durability of resistance associated with nevirapine prophylaxis in mother and infant
- Prevalence and kinetics of viral resistance in breast milk associated with nevirapine prophylaxis, and dynamics of breast milk transmission of resistant virus
- Dynamics of sexual transmission of resistant virus
- Effect on viral, immune and clinical response to future NNRTI-based antiretroviral therapy for the infected mother and infant
- Effect on efficacy of antiretroviral prophylaxis in subsequent pregnancies



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