Should nevirapine be used to prevent mother-to-child transmission of HIV among women of unknown serostatus?*
Tin Tin Sint,1 François Dabis,2 Claude Kamenga,3 Nathan Shaffer,4 & Isabelle F. de Zoysa5

Abstract At present, HIV testing and counselling during pregnancy represent the key entry point for women to learn their serostatus and for them to access, if they are HIV-positive, specific interventions to reduce mother-to-child transmission (MTCT) of HIV. However, the provision and uptake of testing and counselling services are inadequate, and many pregnant women in countries most affected by the HIV/AIDS epidemic remain unaware of their HIV status. The offer of single-dose nevirapine prophylaxis to women whose HIV status is unknown at the time of delivery has been proposed to circumvent these problems in high-prevalence settings. The potential advantages and disadvantages of three different programme approaches are considered: targeted programmes in which antiretroviral drugs are offered only to women who are known to be HIV-positive; combined programmes in which nevirapine prophylaxis is offered to women whose serostatus remains unknown at the time of delivery despite targeted programme inputs; and universal nevirapine prophylaxis programmes in which HIV testing and counselling are not available and all pregnant women, regardless of their serostatus, are offered nevirapine prophylaxis.

Keywords Nevirapine/therapeutic use; HIV infections/prevention and control; Disease transmission, Vertical/prevention and control; Health status; Pregnancy; Risk assessment (source: MeSH, NLM).

Mots clés Névirapine/usage thérapeutique; Infection à VIH/prévention et contrôle; Transmission verticale maladie/prévention et contrôle; État sanitaire; Grossesse; Evaluation risque (source: MeSH, INSERM).

Palabras clave Nevirapina/uso terapéutico; Infecciones por VIH/prevención y control; Transmisión vertical de enfermedad/prevención y control; Estado de salud; Embarazo; Medición de riesgo (fuente: DeCS, BIREME).

Introduction
Globally, about 700 000 children became newly infected with HIV in 2003 (1), mainly as a result of mother-to-child transmission (MTCT). In the absence of specific interventions, the estimated rate of MTCT of HIV ranges from 14–25% in developed countries to between 13% and 42% in the developing world (2).

In June 2001, the United Nations General Assembly Special Session on HIV/AIDS set the goal of reducing the proportion of infants infected with HIV by 20% by 2005 and by 50% by 2010 (3). To reach these goals, a number of programme elements need to be in place. WHO recommends four strategic approaches: primary prevention of HIV infection; prevention of unintended pregnancies among HIV-infected women; prevention of HIV transmission from HIV-infected women to their infants; and provision of care and support to HIV-infected women, their infants and family (4). Measures to reduce transmission from HIV-infected women to their infants include specific interventions such as antiretroviral treatment or prophylaxis, safer delivery practices, and infant feeding counselling and support. HIV testing and counselling during pregnancy provide a key entry point for women to learn their serostatus and for them to access these interventions if necessary.

Experience from the field, however, points to persistent problems with programme implementation. In particular, the provision of testing and counselling in antenatal care settings is often inadequate, and — even where services are available — uptake often remains low. In addition, in some settings antenatal care is not available or accessed, and in many places the link between antenatal care and labour and delivery is weak. The HIVNET 012 regimen, which comprises a single oral dose of nevirapine given to the mother at onset of labour and a single dose to the infant within 72 hours of birth, has been proposed when a woman’s HIV status remains unknown at the time of labour and delivery. This approach has the potential

1 Technical Officer, Department of HIV/AIDS, World Health Organization, 1211 Geneva 27, Switzerland. Correspondence should be sent to this author (email: sintt@who.int).
2 Professor, Institut de Santé Publique, Epidémiologie et Développement (ISFED), Université Victor Segalen Bordeaux 2, Bordeaux, France.
3 Technical Officer, HIV/AIDS Prevention and Care Department, Family Health International, Arlington, TX, USA.
4 Chief, MTCT Section, Global AIDS Program, Centers for Disease Control and Prevention, Atlanta, GA, USA.
5 Senior Adviser for HIV/AIDS, Office of the Assistant Director-General (FCH), World Health Organization, Geneva, Switzerland.

* The views contained in this paper are those expressed by participants in two WHO consultations: Use of nevirapine among women of unknown serostatus (2002) and antiretroviral drugs and prevention of mother-to-child transmission of HIV in resource-limited settings (2004); they are not necessarily those of WHO.

Ref. No. 03-008276
(Submitted: 8 October 2003 – Final revised version received: 3 June 2004 – Accepted: 2 July 2004)
to increase programme coverage and effectiveness, especially in settings with limited availability or uptake of HIV testing services and high HIV prevalence among pregnant women. The regimen is simple, affordable (US$ 0.50) (5) and has moderate efficacy (47%) for the prevention of peripartum HIV transmission (6, 7).

Models suggest that the provision of nevirapine to all women of unknown status and their infants is cost-effective and should be considered as an approach for the prevention of MTCT in sub-Saharan Africa (8). Research in Zambia suggests, however, that this approach may not be the preferred option for all women (9) and may not necessarily result in higher levels of use of nevirapine by those in need. This research indicates that a programme strategy in which nevirapine is offered to all pregnant women without testing leads to increased uptake (measured by the proportion of women who accept enrolment in the programme) but, in the absence of observed therapy, lower adherence (measured by the proportion of women who actually ingest the nevirapine tablet at onset of labour) compared with a strategy in which nevirapine is offered only to seropositive women who have been identified through testing and counselling (10).

Programme approaches

In this context, three possible approaches can be considered for the provision of single-dose antiretroviral prophylaxis to prevent MTCT of HIV (11), as shown in Table 1: targeted programmes, combined programmes, and universal nevirapine prophylaxis programmes.

Targeted programme

Targeted antiretroviral prophylaxis programmes represent the current standard of care. Antiretroviral drugs, such as nevirapine, and other specific interventions are offered only to women who are known to be HIV-positive. Women of unknown serostatus are not given any antiretroviral drugs.

Combined programme

Not all women living in high-prevalence settings who are offered HIV testing and counselling agree to be tested, and some who do may not receive their test results in time. In these cases a combined programme approach has been proposed as a safety net for women whose serostatus remains unknown at the time of delivery, despite the availability of testing and counselling. The combined programme contains the basic elements of the targeted programme, and antiretroviral prophylaxis is offered to all pregnant women known to be HIV-positive. In addition, nevirapine is offered to women whose serostatus is unknown, after discussion of its risks and benefits.

This approach provides women who decline antenatal HIV testing, or whose serostatus remains unknown at the time of labour for any other reason, with access to nevirapine if they wish. Women could be offered nevirapine to take at home at the onset of labour or to take under observation in the labour ward or at home with a birth attendant. These women are encouraged to accept voluntary testing and counselling after delivery, so that they can make informed decisions about feeding options. Mothers thus identified with HIV will also benefit from treatment, care and support services as required.

Universal programme

Provision of nevirapine prophylaxis to all women regardless of their serostatus could apply in high-prevalence situations where HIV testing and counselling are not provided in the antenatal setting and are not available off-site. In this programme approach, all pregnant women receive basic information on HIV, the risks of MTCT and the risks and benefits of nevirapine prophylaxis, and nevirapine is offered to all women and their infants.

Balancing risks and benefits

The risks of providing nevirapine to women of unknown serostatus in relation to possible benefits need to be taken into consideration. The benefits of nevirapine accrue to the infant and not to the mother, and vary according to the mother’s risk of infection (there is, of course, no benefit for infants of uninfected mothers). Drug toxicity is a concern for both HIV-infected and uninfected mothers. This approach provides women who decline antenatal testing and counselling after delivery, despite the availability of testing and counselling. The combined programme contains the basic elements of the targeted programme, and antiretroviral prophylaxis is offered to all pregnant women known to be HIV-positive. In addition, nevirapine is offered to women whose serostatus is unknown, after discussion of its risks and benefits.

This approach provides women who decline antenatal HIV testing, or whose serostatus remains unknown at the time of labour for any other reason, with access to nevirapine if they wish. Women could be offered nevirapine to take at home at the onset of labour or to take under observation in the labour ward or at home with a birth attendant. These women are encouraged to accept voluntary testing and counselling after delivery, so that they can make informed decisions about feeding options. Mothers thus identified with HIV will also benefit from treatment, care and support services as required.

Balancing risks and benefits

The risks of providing nevirapine to women of unknown serostatus in relation to possible benefits need to be taken into consideration. The benefits of nevirapine accrue to the infant and not to the mother, and vary according to the mother’s risk of infection (there is, of course, no benefit for infants of uninfected mothers). Drug toxicity is a concern for both HIV-infected and uninfected women and their infants, though serious adverse events after a single dose of nevirapine have not been reported so far (12, 13).

Table 1. Characteristics of three approaches to the provision of antiretroviral prophylaxis for the prevention of mother-to-child transmission of HIV

<table>
<thead>
<tr>
<th>Type of programme</th>
<th>Targeted</th>
<th>Combined</th>
<th>Universal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Offer of voluntary testing and counselling to all pregnant women</td>
<td>• Offer of nevirapine to women of unknown serostatus (who were not offered testing, declined testing or did not receive test results prior to the beginning of labour) and their infants, with information about risks and benefits</td>
<td>• Background of a targeted programme</td>
<td>• Unavailability of testing and counselling either in the antenatal care setting or off-site</td>
</tr>
<tr>
<td>• Provision of antiretroviral drugs and other specific prevention interventions (including infant feeding counselling and support) only to HIV-positive women, with information about risks and benefits</td>
<td>• Offer of postpartum counselling and testing on-site or through a referral link</td>
<td>• Basic information on HIV, the risk of MTCT and the risks and benefits of nevirapine provided to all pregnant women</td>
<td></td>
</tr>
<tr>
<td>• No provision of antiretroviral drugs to women of unknown serostatus</td>
<td>• Infant feeding guidance for women of unknown serostatus as for uninfected women</td>
<td>• Offer of nevirapine to all women and their infants</td>
<td>• Infant feeding guidance as for uninfected women</td>
</tr>
</tbody>
</table>

Concerns about drug resistance apply to HIV-infected women and children and therefore arise in all three programmes where single-dose nevirapine is offered. Drug resistance is an important issue in the context of accelerated access to antiretroviral treatment. A recent study reported that nevirapine mutations after exposure to zidovudine and nevirapine during pregnancy reduced the virological response to subsequent non-nucleoside reverse transcriptase inhibitor containing antiretroviral therapy in women (14).

Several studies have looked at nevirapine-induced genotypic resistance in women exposed to single-dose nevirapine-only prophylaxis. Viral resistance after single-dose nevirapine seems to be transient in the absence of continued exposure. In one study, the detectable resistance in women, initially 43% at 4–6 weeks postpartum, decreased to 24% at 10–36 weeks postpartum (15); in another study, resistance was no longer detectable in women by 12–24 months after delivery (16). Resistance may therefore have some limits on the effectiveness of single-dose nevirapine in subsequent pregnancies.

Based on potential implications of viral resistance, experts participating in the most recent WHO consultation recommended a disease-adapted approach in the provision of antiretroviral drugs to reduce MTCT of HIV (17). Antiretroviral treatment should be the standard of care for HIV-infected women who need antiretroviral drugs for their own health. For HIV-positive women who do not meet the eligibility criteria for treatment, or do not have access to treatment, zidovudine plus single-dose nevirapine is the regimen of choice. Alternatively, zidovudine alone, zidovudine plus lamivudine, or single-dose nevirapine may be offered.

Although these recommendations apply only to women who are known to be HIV-positive, some policy-makers and programme managers may consider including the use of single-dose nevirapine for women of unknown serostatus among various options for the delivery of antiretroviral drugs for the prevention of MTCT of HIV. In doing so, they should carefully weigh the potential advantages and disadvantages of the different programme approaches (see Table 2). The points raised need to be considered in the context of a comprehensive HIV prevention, treatment and care programme in which knowledge of HIV status may lead to multiple benefits for women, their families and the community at large, including access to treatment for those in need.

### Conflicts of interest

None declared.

---

**Table 2. Potential advantages and disadvantages of different approaches to the provision of antiretroviral prophylaxis for the prevention of mother-to-child transmission of HIV**

<table>
<thead>
<tr>
<th>Antiretroviral prophylaxis</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeted programme</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Enables all benefits of knowledge of HIV status, including support for other prevention efforts and entry into care, treatment and support programmes for those already infected</td>
<td>• Places high demands on financial and human resources</td>
<td></td>
</tr>
<tr>
<td>• Permits infant feeding counselling and support to reduce the risk of transmission through breastfeeding</td>
<td>• Requires trained counsellors</td>
<td></td>
</tr>
<tr>
<td>• Improves adherence with programme interventions</td>
<td>• Tends to suffer from low uptake in settings where women do not want to know their HIV status</td>
<td></td>
</tr>
<tr>
<td>• May help to promote testing and counselling services as part of routine care</td>
<td>• May be undermined where stigma and discrimination are barriers to programme entry, uptake, and adherence</td>
<td></td>
</tr>
<tr>
<td>• May help to destigmatize HIV in the long term</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined programme</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increases the coverage of the antiretroviral prophylactic intervention when used as a safety net</td>
<td>• May undermine efforts to promote HIV testing and counselling</td>
<td></td>
</tr>
<tr>
<td>• Has the potential to prevent more peripartum transmission</td>
<td>• Does not provide for infant feeding counselling and support of untested HIV-infected women who refuse testing after delivery, in order to reduce postnatal transmission</td>
<td></td>
</tr>
<tr>
<td>• Preserves the existing benefits of testing and counselling, and infant feeding counselling and support for those who test positive</td>
<td>• May lead to complacency in scaling-up targeted programmes</td>
<td></td>
</tr>
<tr>
<td>• May serve as an interim step while testing and counselling services are developed in antenatal care and labour and delivery services</td>
<td>• May cause confusion among health providers with respect to infant feeding recommendations</td>
<td></td>
</tr>
<tr>
<td>• May help to improve uptake of testing and enable more women to receive benefits</td>
<td>• Unnecessarily exposes uninfected women to any nevirapine toxicity (none currently recognized for single-dose administration)</td>
<td></td>
</tr>
<tr>
<td><strong>Universal programme</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ensures high coverage of antiretroviral prophylactic interventions</td>
<td>• May undermine efforts to introduce HIV testing and counselling services and thereby denies their benefits</td>
<td></td>
</tr>
<tr>
<td>• Has the potential to prevent more peripartum transmission</td>
<td>• Does not prevent postnatal transmission through breastfeeding</td>
<td></td>
</tr>
<tr>
<td>• May be more acceptable</td>
<td>• Precludes access to treatment, care and support for HIV-infected persons</td>
<td></td>
</tr>
<tr>
<td>• May be easier to implement</td>
<td>• May suffer from low adherence with use of nevirapine</td>
<td></td>
</tr>
<tr>
<td>• May be less costly</td>
<td>• May undermine commitment to HIV prevention programmes</td>
<td></td>
</tr>
</tbody>
</table>

Résumé

Devrait-on faire appel à la névirapine pour prévenir la transmission mère-enfant du VIH dans le cas des femmes dont le statut sérologique est inconnu ?

Actuellement, le dépistage du VIH et les conseils proposés pendant la grossesse représentent le point d’accès principal permettant aux femmes de connaître leur statut sérologique et d’accéder, si elles sont séropositives, à des interventions spécifiques pour limiter la transmission mère-enfant (TME) du VIH. Cependant, l’offre de services de dépistage et de conseil et le recours à ces services sont insuffisants et de nombreuses femmes des pays les plus touchés par l’épidémie de VIH/SIDA restent sans connaître leur statut VIH. Il a été suggéré de proposer un traitement prophylactique constitué d’une dose unique de névirapine aux femmes dont le statut VIH n’est pas connu au moment de l’accouchement, afin de contourner cette difficulté dans les pays à forte prévalence. Les auteurs envisagent les avantages et les inconvénients potentiels de différentes approches programmatiques : programmes ciblés dans lesquels on ne propose des antirétroviraux qu’aux femmes dont on sait qu’elles sont séropositives, programmes combinés dans lesquels on propose aux femmes dont le statut sérologique reste inconnu un traitement prophylactique par la névirapine au moment de l’accouchement, malgré des intrants de programme ciblés, et programmes de prophylaxie généralisée par la névirapine, dans lesquels les femmes ne peuvent disposer d’un dépistage du VIH et de conseils et où toutes les femmes enceintes, indépendamment de leur statut sérologique, se voient proposer un traitement prophylactique par la névirapine.

Resumen

¿Debe usarse la nevirapina para prevenir la transmisión del VIH de la madre al niño entre las mujeres de estado serológico desconocido?

Actualmente el asesoramiento y las pruebas de detección del VIH durante el embarazo representan el punto de acceso fundamental de las mujeres al conocimiento de su serología y a la posibilidad de, si son VIH-positivas, beneficiarse de intervenciones específicas de reducción de la transmisión del VIH de la madre al hijo. Sin embargo, la oferta y la utilización de los servicios de pruebas y asesoramiento son insuficientes, y muchas mujeres embarazadas de los países más afectados por la epidemia de VIH/SIDA siguen sin saber si son seropositivas. Se ha propuesto que se ofrezca una dosis única de nevirapina como tratamiento profiláctico a las mujeres cuya serología VIH se desconozca en el momento del parto, a fin de evitar esos problemas en los entornos de alta prevalencia. Se examinan aquí las posibles ventajas e inconvenientes de tres tipos de programas: programas focalizados que sólo ofrecen antirretrovirales a las mujeres demostradamente VIH-positivas; programas combinados que ofrecen profilaxis con nevirapina a las mujeres cuya serología sigue sin conocerse en el momento del parto a pesar de las medidas de obtención de información que contemplan dichos programas; y programas de profilaxis universal con nevirapina, en los que, no disponiéndose de servicios de asesoramiento y pruebas del VIH, se ofrece tratamiento profiláctico con nevirapina a todas las mujeres embarazadas, con independencia de su serología.

References


Routine provision of nevirapine to women of unknown serostatus: at best a temporary solution to prevent MTCT

Marie-Louise Newell1

Mother-to-child transmission (MTCT) is the dominant mode of acquisition of HIV infection for children worldwide. The risk of peripartum MTCT can be reduced with antiretroviral prophylaxis given to HIV-infected women in late pregnancy and during labour and delivery; prevention of MTCT depends also on avoiding infections in women of childbearing age (1). Current MTCT prevention programmes do not reach many of the women who need them, partly because the provision of prophylaxis is conditional on the identification of HIV infection in pregnant women after voluntary HIV counselling and testing services outside the antenatal setting (2). Rapid testing with results available the same day also increases the number of women being tested, and decrease stigma attached to HIV testing, an opt-out approach — in which everyone is tested unless someone specifically asks not to be — would normalize HIV testing and reach more women than the current widely used opt-in approach (6). Rapid testing with results available the same day also increases the number of women whose HIV infection status is known (7). Provision of voluntary counselling and testing services outside the antenatal setting would have the benefit of making the services more relevant and accessible for men and women of all ages. These services should aim to identify not only infected but also uninfected people, and to provide appropriate support for both groups.

1 Professor of Paediatric Epidemiology, Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, England (email: m.newell@ich.ncl.ac.uk).

Ref. No. 04-017186
Tin Tin Sint et al.

Nevirapine prophylaxis for MTCT of HIV

peripartum MTCT in settings with high neonatal and infant mortality, high HIV prevalence and limited mother and child health services (3) may be a way forward, but only as a temporary measure. There is considerable benefit to be derived from individual voluntary counselling and testing for all women, with appropriate and optimal support depending on the test result. Recent evidence of the substantial effectiveness of postexposure prophylaxis for the neonate alone using one week zidovudine and single-dose nevirapine highlight the continued benefit of identifying infected women even during delivery (J). Furthermore, a combination of short-course regimens of antiretrovirals is substantially superior to single-dose nevirapine in reducing MTCT, while single-dose nevirapine may impact on future treatment options for infected women (J). Therefore, universal prophylaxis programmes should not replace efforts to increase voluntary counselling and testing services and to improve support for both infected and uninfected women.

Conflicts of interest: none declared.

References