

Should nevirapine be used to prevent mother-to-child transmission of HIV among women of unknown serostatus?*

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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; Etat 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 (*fuentes: DeCS, BIREME*).

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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 trans-

mission 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

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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 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

Type of programme		
Targeted	Combined	Universal
<ul style="list-style-type: none"> • Offer of voluntary testing and counselling to all pregnant women • 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 • No provision of antiretroviral drugs to women of unknown serostatus 	<ul style="list-style-type: none"> • Background of a targeted programme • 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 • Offer of postpartum counselling and testing on-site or through a referral link • Infant feeding guidance for women of unknown serostatus as for uninfected women 	<ul style="list-style-type: none"> • Unavailability of testing and counselling either in the antenatal care setting or off-site • Basic information on HIV, the risk of MTCT and the risks and benefits of nevirapine provided to all pregnant women • Offer of nevirapine to all women and their infants • Infant feeding guidance as for uninfected women

Source: Adapted from *Use of nevirapine among women of unknown serostatus. Report of a technical consultation, Geneva, 5–6 December 2001* (11).

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

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

Source: Adapted from *Use of nevirapine among women of unknown serostatus. Report of a technical consultation, Geneva, 5–6 December 2001* (11).

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.

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.

ملخص

هل ينبغي إعطاء دواء النفيرايين للمرأة التي لا يعرف نمطها المصلي لانتقال فيروس الإيدز من الأم إلى الطفل؟

تعاين من شدة انتشار العدوى. وتتناول هذه الدراسة المزايا والمساوئ المحتملة لثلاثة برامج مختلفة الأساليب: البرامج الموجهة التي يتم في إطارها إعطاء الأدوية المضادة للفيروسات القهقرية المضادة للإيدز للمرأة المعروف أنها إيجابية للعدوى؛ والبرامج المشتركة التي يتم في إطارها إعطاء دواء النفيرايين الوقائي للمرأة التي يظل وضعها المصلي مجهولاً في وقت الولادة بالرغم من مدخلات البرامج الموجهة؛ وبرامج الإعطاء الشامل لدواء النفيرايين الوقائي، وهي البرامج التي لا يتاح في إطارها إجراء اختبار تحري الفيروس أو النوعية بسبل الوقاية منه، ويُقدم النفيرايين الوقائي في إطارها لجميع الحوامل بغض النظر عن نمطهن المصلي.

ملخص: يعتبر اختبار تحري العدوى بفيروس الإيدز والتوعية بسبل الوقاية منه أثناء الحمل المنفذ الرئيسي الذي تعرف المرأة من خلاله نمطها المصلي، وتستفيد من خلاله المرأة الإيجابية لفيروس الإيدز من المداخلات النوعية التي تستهدف الحد من انتقال الفيروس من الأم إلى الطفل. غير أن تقديم خدمات الاختبار والتوعية والاستفادة منها يتسمان بعدم الكفاية، كما أن العديد من النساء الحوامل في البلدان الأشد تأثراً بوباء الإيدز والعدوى بفيروسه يجهلن وضعهن المتعلق بالعدوى بفيروس الإيدز. وقد اقترح إعطاء جرعة وقائية واحدة من دواء النفيرايين للمرأة التي لا يُعرف وضعها المتعلق بالعدوى بالفيروس في وقت الولادة، لتجنب هذه المشكلات في المناطق التي

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Commentary

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, which may not be acceptable, feasible or of perceived benefit (2).

Would routine provision of nevirapine to pregnant women ensure that more MTCT is prevented than is the case using the present targeted approaches (3)? Would routine provision mean less support for infected and uninfected women to remain healthy? Improving support services during and after delivery, in particular with antiretroviral treatment for infected women with more advanced disease (1), would directly benefit the mother and is likely to increase uptake of services. Maternal HIV has a major direct impact (through her vital status) and indirect impact (through MTCT) on infant and child mortality rates (4). Support for a mother in the years following delivery

would probably reduce the risk of her dying and thus make it less likely that her children, infected or not, die in childhood.

Could improvements to voluntary counselling and testing and MTCT intervention uptake be achieved in other ways? Involvement of the partner and family and provision of couple or family counselling (including testing of couples together) provide a more stable and supportive environment for the mother and child; such measures increase the likelihood that women identified as infected accept interventions to reduce MTCT, including appropriate infant feeding (5). To increase the number of pregnant 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.

To achieve the targets set by the United Nations, universal provision of nevirapine to all pregnant women to reduce

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