

Prevention of mother-to-child transmission of HIV: challenges for the current decade

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Abstract In June 2001 the United Nations Special Assembly on HIV/AIDS set reduction targets of 20% and 50% for the numbers of children newly infected with HIV by 2005 and 2010 respectively. Are these targets achievable? Antiretroviral monotherapy during pregnancy, delivery, and the neonatal period can reduce the rate of mother-to-child transmission of HIV-1 by two-thirds in non-breastfeeding populations. Shorter and simpler regimens of monotherapy have been associated with a reduction of 50% in such transmission among non-breastfeeding populations and of up to 40% in breastfeeding populations. Delivery by elective caesarean section is associated with a halving of the risk of mother-to-child transmission. However, breastfeeding poses a substantial additional risk of acquisition of HIV, and if prolonged it more than doubles the overall rate of transmission. Rates below 2% are being reported from settings where combination therapy is applied during pregnancy and delivery, delivery is by elective caesarean section, and breastfeeding does not take place. In breastfeeding populations where elective caesarean delivery is not an option but peripartum antiretroviral therapy is used, rates at six weeks are about 10% but can be 25% or more after 18 months of breastfeeding. More widely applicable interventions are being developed, such as cleansing of the birth canal and antiretroviral therapy during the breastfeeding period.

Keywords Acquired immunodeficiency syndrome/transmission/drug therapy; Disease transmission, Vertical/prevention and control; Breast feeding/adverse effects; Caesarean section; Anti-HIV agents/pharmacology/adverse effects; Zidovudine/adverse effects; Nevirapine/adverse effects; Risk factors (*source: MeSH*).

Mots clés SIDA/transmission/chimiothérapie; Transmission verticale maladie/prévention et contrôle; Allaitement au sein/effets indésirables; Césarienne; Agents anti-HIV/pharmacologie/effets indésirables; Zidovudine/effets indésirables; Névirapine/effets indésirables; Facteur risque (*source: INSERM*).

Palabras clave Síndrome de inmunodeficiencia adquirida/transmisión; Transmisión vertical de enfermedad/prevenición y control; Lactancia materna/efectos adversos; Cesárea; Agentes anti VIH/farmacología/efectos adversos; Zidovudina/efectos adversos; Nevirapina/efectos adversos; Factores de riesgo (*fuentes: BIREME*).

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Introduction

Mother-to-child transmission (MTCT) of HIV-1 can occur before, during, and after delivery (1). Transmission is rare during early pregnancy and relatively frequent in late pregnancy and during delivery. Breastfeeding contributes substantially to the overall risk. In the absence of specific interventions the estimated rate of MTCT ranges from 15% to 40%, the differences between populations being largely associated with the prevalence of breastfeeding. Postnatal transmission from mother-to-child through breastfeeding remains important in cases where peripartum antiretroviral prophylaxis reduces the risk of vertical transmission late in pregnancy and during delivery (2, 3).

Risk factors for vertical transmission include maternal progression of infection, measured as the peripheral blood viral load or by clinical and immunological markers (2, 4). However, the RNA viral load in plasma, although important, is not the only factor associated with increased risk. Premature infants are more likely to be infected than full-term infants and the risk increases with the duration of membrane rupture (5). Elective caesarean section delivery approximately halves the risk of transmission, even in women with a low viral load, with high CD4⁺ T-cell counts, or on antiretroviral therapy (6, 7, Table 1).

Prevention of mother-to-child HIV transmission

Current interventions aimed at reducing MTCT target the peripartum period but their application in populations where breastfeeding is the norm presents considerable problems (2, 3). Effective interventions

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include the reduction of the maternal viral load through antiretroviral therapy, the avoidance of exposure to contaminated maternal secretions through delivery by elective caesarean section, and the avoidance of breastfeeding. Washing the birth canal with an antiseptic to reduce exposure to contaminated secretions also has some effect.

Antiretroviral prophylaxis

In 1994 there was a major breakthrough in the prevention of vertical acquisition of HIV. It was demonstrated that zidovudine monotherapy, given during the second and third trimester of pregnancy, administered intravenously during delivery, and given to infants for six weeks, reduced the risk in a non-breastfeeding population by two-thirds (8). This intervention was rapidly introduced with considerable success in industrialized countries (9, 10). Shorter, more practical regimens starting later in pregnancy have been shown to reduce peripartum transmission by 40–50% (11–15). The risk of acquisition of HIV through breastfeeding is unaffected by the use of peripartum antiretroviral therapy (16, 17).

Combination therapy with two (18) or more (19) antiretroviral drugs is assumed to be associated with a larger reduction in vertical transmission risk than monotherapy, although this has not been evaluated in comparative randomized trials. The evidence of effect comes from cohort studies (9, 10, 19). Rates as low as 2–4% have been reported with the use of combination therapy during pregnancy and delivery, often together with elective caesarean section and always in the absence of breastfeeding.

Adverse effects associated with antiretroviral therapy. The effect of short-term exposure to antiretroviral drugs on the progression of disease in HIV-infected women is not known. Nor is the long-term effect of fetal exposure to antiretroviral nucleoside analogues, although many infants born now to HIV-infected mothers are exposed during intrauterine and early neonatal life. There is a scarcity of data on the pharmacokinetics and safety of agents other than zidovudine during pregnancy. It is difficult to distinguish drug-induced mitochondrial toxicity from the effects of HIV infection. This is because mitochondrial dysfunction can occur in viral infections and other conditions, such as diabetes and heart disease (10, 20, 21).

Drug resistance. Concern has been expressed about the development of resistance following single-dose nevirapine and its possible long-term implications for the women treated and for its use in the prevention of MTCT. In a trial in Uganda, nevirapine resistance was detected in nearly 20% of a small number of women tested six weeks postpartum, but at 12 months only wild-type virus (i.e. nevirapine sensitive) was detectable (14). The clinical implications of this finding are unclear, although it could mean that future treatment options for the women are restricted. WHO/UNICEF recommendations issued in 2000

Table 1. Risk factors for mother-to-child transmission of HIV, strength of association, and impact on overall rate of transmission

Risk factor	Strength of association	Impact ^a
<i>Maternal</i>		
RNA viral load	Strong	Large
AIDS	Strong	Small to medium
Immune deficiency	Strong	Medium
Genetic	Weak	Small
Other sexually transmitted infections	Medium	Small to medium
Chorioamnionitis	Medium	Small
Vitamin A deficiency	Medium	Small
<i>Obstetric</i>		
Mode of delivery	Strong	Large
Duration of membrane rupture	Strong	Large
RNA in vagina/cervix	Medium	Medium
Invasive procedures	Strong	Small
<i>Paediatric</i>		
Prematurity	Strong	Medium
Breastfeeding	Strong	Large
Breast health	Strong	Small
Genetic	Weak	Small

^a The impact of a risk factor is not only determined by the strength of the association with the risk of transmission but also by the frequency of the factor in a population.

state that the advantages of nevirapine in reducing the risk of transmission far outweigh the possible disadvantages of resistance (22).

Drug safety. The safety of antiretroviral drugs is a key issue for the management of HIV-infected pregnant women. It was recently reported that there might be an increased risk of premature delivery associated with the use of combination therapy during pregnancy, especially when protease inhibitors were included (23). Three cases of lactic acidosis resulting in maternal deaths and four non-fatal cases in pregnant women have been reported; all the women received a combination of drugs including ddI (didanosine) and d4T (stavudine). Lactic acidosis is a known toxic effect of nucleoside analogues, but there are no data indicating whether the risk is higher in pregnant women than in non-pregnant women.

In some settings an increasing number of infants may be exposed to highly potent antiretroviral therapy from the start of pregnancy and possible adverse effects cannot be excluded (23–25). It has been suggested that it might be prudent to minimize the potential adverse events by using the simplest possible regimens and to save the more potent combination therapies for delaying the progression of disease in women until after pregnancy. However, this may not bring about the greatest possible reduction in risk of MTCT. Clinical decisions have to find the balance most favourable to individual women. If feasible, it is very important to conduct long-term follow-up of children born to HIV-infected women who have been exposed to antiretroviral therapy before and after delivery. This is especially important in relation to the increasing use

of combination therapies with three or more drugs, sometimes initiated before pregnancy.

Avoidance of exposure

Delivery by caesarean section was suggested as a possible intervention as early as the mid-1980s but reliable confirmation of the effect on the risk of vertical transmission was difficult to obtain. In the late 1990s the results of a randomized controlled trial in Europe (26) and of a large American–European meta-analysis (27) confirmed a reduction in risk exceeding 50% associated with elective caesarean section before labour and membrane rupture. Subsequent observations showed that the effect was also of this order in women with a low or high viral load and in those given antiretroviral monotherapy or combination therapy (6, 7). Elective caesarean section is a cost-effective intervention for the prevention of vertical transmission of HIV in a wide range of circumstances, even with a risk of 1% in vaginal deliveries, such as is achievable with highly active antiretroviral therapy (28). However, delivery by elective caesarean section is not an option in large parts of the world where HIV prevalence is highest, and even where the procedure is possible the increased risk of infectious morbidity has to be borne in mind. Nevertheless, these findings confirm the importance of the period during delivery for MTCT and highlight the need for further applied research aimed at making delivery safer, both generally and for reducing the risk of MTCT.

The use of antiseptic or antiviral agents to cleanse the birth canal during labour and delivery has been suggested as a possible way of reducing intrapartum transmission of HIV-1. Although the results from two randomized trials in sub-Saharan Africa showed that cleansing with chlorhexidine did not reduce the risk of MTCT overall, there may be some benefit for a subgroup of women or when increased concentrations of the agent are used (29, 30). In the trial in Malawi, the risk of transmission was substantially reduced as a result of vaginal cleansing in women for whom the duration of membrane rupture exceeded four hours. Furthermore, this cleansing was associated with significant reductions in neonatal morbidity and mortality as well as in maternal morbidity (31). In a trial in Kenya, a higher concentration of chlorhexidine seemed to be effective (30).

The need for further research aimed at identifying appropriate and applicable options for reducing risk at the time of delivery is highlighted by the large effect of the mode of delivery on the risk of vertical transmission, irrespective of other important risk factors, and by the evidence suggesting that cleansing the birth canal is beneficial in some circumstances.

Infant feeding

It is estimated that breastfeeding increases the overall risk of MTCT by 14% for women with established HIV infection and by 29% for women who become

infected during lactation (32). This demonstrates the importance of the primary prevention of HIV acquisition in lactating women. More recent data from a randomized controlled trial in which mothers were allocated to either breastfeeding or artificial feeding confirmed an additional absolute risk of vertical transmission through breastfeeding of 16% when follow-up was conducted after two years. In this trial, breastfeeding approximately doubled the overall rate of transmission (33).

However, exclusive breastfeeding is considered to be optimal for infants during the first six months of life. Furthermore, it helps to protect mothers against pregnancy. Optimal breastfeeding requires antenatal preparation and postnatal support for mothers in order to ensure that they understand the issues and have a good technique (22). Among HIV-infected women who choose to breastfeed, exclusive breastfeeding is recommended because of its general health advantages over mixed feeding. The suggestion that exclusive breastfeeding may be beneficial in reducing the risk of MTCT (34) requires confirmation by further studies.

Although transmission through breastfeeding does not negate the reduction in risk achieved through peripartum antiretroviral therapy, it does reduce the overall efficacy of peripartum interventions (12, 17). Research is being conducted with a view to making infant feeding safer in areas of high HIV prevalence, as regards both HIV transmission and general health benefits for all infants and their mothers.

Further analysis of the trial in Kenya (35) indicated that mortality was possibly higher among breastfeeding women than among those using formula feeding. It is important to realize that the analysis dealt with the intention to treat, that the hypothesis of an impact of breastfeeding on mortality in HIV-infected women was developed post hoc, and that only a small number of women died. Although the characteristics of the women in the two randomized groups were apparently similar at enrolment, the median plasma viral load was higher among those randomized to breastfeeding, and information on clinical progression was lacking. The rate of intrauterine transmission was increased in the breastfeeding group and there was thus a possibility of more advanced disease in these women. Loss to follow-up was substantial in both groups, occurring earlier in the formula-feeding group than in the breastfeeding group. Deaths in the formula-feeding arm were possibly underreported. Rather than the higher mortality in the breastfeeding group, it is the low mortality rate among the women in the formula-feeding arm which needs further investigation. No information was provided on the extent and quality of contact of the women with the health care services. Women in the intervention group, i.e. those randomized to formula feeding, might have attended the clinic between scheduled visits if they, or their infants, felt unwell. This could have resulted in

improved management of their HIV disease and might explain at least partly the low level of mortality in this group over the two-year period.

In a vitamin A intervention trial in South Africa, women made an informed choice on infant feeding (36). Those who chose to breastfeed were advised to do so exclusively. During a follow-up period averaging 11 months there was no evidence of increased mortality or morbidity in the exclusively breastfeeding group as compared with the non-breastfeeding group. Two of 410 exclusively breastfeeding mothers died, as did three of 156 non-breastfeeding women. Furthermore, there was no evidence of an association between clinical problems in the mothers and the duration of breastfeeding.

Current mother-to-child HIV transmission rates

Following the results of the American–French zidovudine trial (8), women in industrialized countries who are identified as HIV-infected are generally offered prophylaxis with this drug. However, because subsequent trials in Thailand and sub-Saharan Africa (12–18) have confirmed the effectiveness of shorter and less complex regimens of antiretroviral therapy, pilot programmes are being implemented to offer these peripartum interventions on a population basis.

The MTCT rate has declined substantially in the last few years in countries where interventions aimed at reducing the risk can be implemented. Rates of under 2% have been reported where there has been antiretroviral prophylaxis during pregnancy, delivery, and the neonatal period, elective caesarean section delivery, and no breastfeeding. Even where the avoidance of breastfeeding and/or elective caesarean section delivery are impossible, trials show (12–14) that peripartum antiretroviral prophylaxis can reduce the rate assessed at 2–3 months of age to less than 10%, although subsequent acquisition of HIV in breastfed infants remains a concern. However, there are few data on the effect of this intervention on a population basis other than in a research setting (Box 1).

Outlook for the prevention of mother-to-child transmission of HIV

Every year five million people acquire HIV and three million more die of AIDS. In many countries of sub-Saharan Africa about a third of the adult population is HIV infected and the prevalence of HIV infection in pregnant women reaches 40% in some places. In June 2001 the United Nations Special Assembly on HIV/AIDS set reduction targets of 20% and 50% for the numbers of children newly infected with HIV by 2005 and 2010 respectively. Are these targets achievable?

Box 1. Effective options for preventing mother-to-child transmission of HIV and associated problems

1. Prevention of acquisition of infection in women of childbearing age

- Behavioural changes, immediate and permanent

2. Prevention of transmission from HIV-infected women to their infants

- Voluntary counselling and testing services
- Identification of uninfected women
- Does it reduce child mortality?

2a. Reducing maternal peripheral viral load

- *Antiretroviral therapy during pregnancy, delivery and/or postpartum*
 - Monotherapy or combination therapy
 - Medium- or long-term adverse effects for mother and infant
 - Effect across all groups?

2b. Avoidance of exposure to contaminated maternal secretions

- *Delivery by elective caesarean section*
 - Safety in resource-poor settings
 - Effectiveness in women with undetectable viral load?
- *Cleansing of birth canal*
 - Limited effect on overall transmission risk
- *Modification of infant feeding practices*
 - Safety in many settings

2c. Boosting host defence

- *Micronutrient supplementation*
 - No evidence of effect on transmission risk
- *Immune therapy (passive or active)*
 - Not evaluated for effectiveness

Primary prevention

The most effective approach to preventing vertically acquired HIV infection in children is through primary prevention among women of childbearing age, and secondarily through the prevention of unwanted pregnancies among HIV-infected women and of MTCT. The primary prevention of infection in young adults would also result in parents living longer and in there being fewer orphans. It is necessary not only to induce behavioural change but also to sustain it in the long term.

A well-functioning, appropriate, and accessible voluntary counselling and testing service is a prerequisite for a successful programme of MTCT prevention. The antenatal setting, although convenient, may not be the most desirable. Initially, the main aim of voluntary counselling and testing for HIV infection in MTCT prevention programmes was to identify infected women and to offer interventions for the reduction of transmission. However, even in areas of high HIV prevalence most women attending antenatal care services are not infected. Consequently, it is just as important that voluntary counselling and testing should offer uninfected women guidance on how to prevent the acquisition of infection. Primary HIV infection during pregnancy and breastfeeding poses an increased risk of MTCT of HIV. Preventive interventions directed at preg-

nant and lactating women could make an important contribution to the reduction of MTCT.

Secondary prevention

In addition to the primary prevention of HIV infection in adults, the number of infected children can be reduced through the prevention of MTCT. It is vital to ensure that all HIV-infected women benefit from the available interventions, applied as appropriate in the settings where they live (37).

The ultimate goal of public health programmes for the prevention of MTCT is to save the lives of large numbers of children born to HIV-infected mothers. The success of these programmes should be measured in terms of lives saved rather than of infections prevented. Systems for measuring this effect should be established. The efficacy of interventions in reducing mortality among children under 5 years of age has not been reliably assessed.

Although there are no data on the relative effectiveness of interventions for different subgroups of HIV-infected women, the assessment of risk factors for vertical transmission suggests that differential effects occur. For example, it is highly likely that women with advanced HIV infection and a high viral load do not benefit, or benefit to a comparatively small extent, from zidovudine monotherapy given for a limited time. If confirmed, this would have substantial consequences in MTCT prevention programmes. Consideration would have to be given to screening women not only for HIV infection but subsequently also for markers of likely success of preventive interventions, or to providing triple antiretroviral therapy for all HIV-infected women. The cost would be substantial (Box 2).

Sustainability

In industrialized countries the sustainability of the current low MTCT rates is being questioned. MTCT prophylaxis in women who are being treated with antiretroviral therapy before becoming pregnant —

something that is happening increasingly in Europe and the USA (9, 10) — is not straightforward. In the USA there is a debate on the need for delivery by elective caesarean section in women who have an undetectable viral load attributable to highly active antiretroviral therapy. Resistance to drugs may develop quickly and it is unclear what this may mean in relation to the risk of MTCT. Primary infection with a drug-resistant strain is relatively rare but may become more common. Adult women are increasingly likely to receive highly active antiretroviral therapy before becoming pregnant, and there is some evidence that these women may be more likely to choose to carry their pregnancies to term rather than opting for a termination. Questions still remain: what are the adverse effects in the medium to long term of exposure to antiretroviral therapy in early life for the increasing number children who are exposed but uninfected? What does intervention against vertical transmission mean for the progression of disease in infected mothers?

Even away from research settings, rates of MTCT can be substantially reduced to very low levels through a combination of measures that include antiretroviral therapy, elective caesarean section, and avoidance of breastfeeding. However, even in countries where all these interventions are available there is a question as to whether low rates are sustainable in the long term.

Effect of lack of resources

Many of the ethical issues that have been raised in relation to HIV research and the conduct of clinical trials also have a bearing on programmes for the implementation of interventions aimed at reducing the risk of MTCT. There is a widening gulf between resource-rich and resource-poor countries. Whereas special attention is given in industrialized countries to the possibility of extremely rare side-effects of antiretroviral therapy and to minor adaptations to various regimens, in developing countries the prevention of peripartum MTCT through antiretroviral monotherapy is the current goal. It is unclear whether child deaths are being prevented. Moreover, there is no clear picture of the fate of the increasing number of orphaned children of HIV-infected parents. Although the trials carried out in Africa and Thailand suggest a substantial reduction in the risk of MTCT as a result of short courses of peripartum antiretroviral therapy, there is little evidence as to whether antiretroviral prophylaxis is effective for all HIV-infected women or whether it only benefits certain subgroups. If the latter were the case, programmes for the prevention of MTCT would have to be adapted for the groups likely to benefit. Alternative, more intensive therapy would have to be used for others. This would, of course, hugely complicate these public health initiatives and might even cast doubt on the whole endeavour.

Consideration needs to be given to the care of mothers and their infants after delivery. A further

Box 2. Questions for the future

- How sustainable are the low rates of MTCT^a of HIV obtained with application of a combination of programmes for the prevention of MTCT?
- Are the low rates achievable worldwide in every setting?
- What are the implications of the development of drug resistance?
- What is the effect of antiretroviral therapy on infected women and their exposed children?
- What action should be taken in further pregnancies?
- How can antiretroviral therapy be made available to women postpartum?
- How can MTCT preventive services be integrated into general maternal and child health care services?
- How can breastfeeding be made safer for HIV-infected mothers?
- How can effectiveness of MTCT programmes be demonstrated?

^a MTCT = mother-to-child transmission.

concern is that, for practical reasons, implementation studies tend to focus on sites where the right infrastructure is available rather than where the need is greatest. This tends to widen the gap within countries and limits the further extension of implementation programmes.

Conclusion

The targets set by the United Nations Special Assembly on HIV/AIDS in June 2001, while laudable, may be optimistic. Success largely

depends on primary prevention efforts among young adults. A 50% reduction in the number of newly infected children is more likely to be achieved if there is a rapid and substantial fall in the number of new infections in young women. Special attention should be given to this matter in the coming decade, together with the prevention of MTCT, in such a way as to cause minimal adverse effects for women who are already infected and their children. ■

Conflicts of interest: none declared.

Résumé

Prévention de la transmission du VIH de la mère à l'enfant : un défi pour cette décennie

En juin 2001, la session spéciale de l'Assemblée des Nations Unies sur le VIH/SIDA a établi comme cibles une réduction de 20 % d'ici à 2005 et de 50 % d'ici à 2010 du nombre d'enfants nouvellement infectés par le VIH. Ces cibles peuvent-elles être atteintes ? Une monothérapie antirétrovirale administrée pendant la grossesse, l'accouchement et la période néonatale peut réduire des deux tiers le taux de transmission du VIH-1 de la mère à l'enfant dans les populations qui ne pratiquent pas l'allaitement au sein. Des schémas de monothérapie plus courts et plus simples sont déjà associés à une réduction de 50 % de la transmission dans les populations ne pratiquant pas l'allaitement au sein et de 40 % dans les populations le pratiquant. L'accouchement par césarienne programmée est associé à une diminution de moitié du risque de transmission du VIH de la mère à l'enfant. En revanche, l'allaitement au sein augmente le

risque d'infection par le VIH et, s'il est prolongé, il peut plus que doubler le taux global de transmission. Des taux inférieurs à 2 % ont été rapportés dans des circonstances où une polythérapie antirétrovirale est appliquée pendant la grossesse et l'allaitement, où l'accouchement se fait par césarienne et où l'enfant n'est pas nourri au sein. Dans les populations pratiquant l'allaitement au sein et où la césarienne programmée ne figure pas parmi les options mais où une thérapie antirétrovirale est appliquée pendant le péripartum, les taux de transmission à six semaines sont d'environ 10 % et peuvent atteindre 25 % ou plus après 18 mois d'allaitement. Des interventions plus largement applicables sont actuellement envisagées, comme le lavage de la filière génitale au moment de l'accouchement et l'administration d'une thérapie antirétrovirale pendant la période d'allaitement.

Resumen

Prevención de la transmisión maternoinfantil del VIH: retos para la década entrante

En junio de 2001, en el período extraordinario de sesiones de la Asamblea General de las Naciones Unidas sobre el VIH/SIDA se establecieron metas de reducción del número de nuevas infecciones infantiles por el VIH, concretadas en el 20% y el 50% para los años 2005 y 2010 respectivamente. ¿Es posible alcanzar esas metas? La monoterapia antirretrovírica durante el embarazo, el parto y el período neonatal puede reducir la tasa de transmisión maternoinfantil de la infección por el VIH-1 en dos tercios en las poblaciones no alimentadas al pecho. Otros regímenes monoterápicos más breves y sencillos se han asociado a reducciones del 50% de esa transmisión en poblaciones no amamantadas, y del 40% en poblaciones amamantadas. El parto por cesárea optativa reduce a la mitad el riesgo de transmisión maternoinfantil. Sin

embargo, la lactancia materna entraña un riesgo adicional sustancial de contagio, y cuando se mantiene de forma prolongada duplica con creces la tasa global de transmisión. Se está informando de tasas inferiores al 2% en entornos donde se aplica la terapia combinada durante el embarazo y el parto, la cesárea electiva en el momento del alumbramiento y la evitación de la lactancia materna. En las poblaciones amamantadas nacidas en entornos que no ofrecen cesárea pero en los que se emplea terapia antirretrovírica perinatal, las tasas a las seis semanas son de un 10%, pero pueden alcanzar o superar el 25% tras 18 meses de lactancia. Se están desarrollando intervenciones aplicables de forma más generalizada, como la limpieza de la vía del parto y el tratamiento antirretrovírico durante el período de amamantamiento.

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