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# Prevention of Maternal HIV Transmission

## Practical Guidelines

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**Summary**

The recently published Protocol 076 study (ACTG 076/ANRS 024) showed that zidovudine significantly decreased the relative risk of maternal HIV transmission by 71.5% compared with placebo. Oral zidovudine 100mg five times daily until the onset of labour, followed by intravenous zidovudine 2 mg/kg over 1 hour then 1 mg/kg • h until delivery, or an identical placebo regimen were administered to HIV-infected pregnant women (14 to 34 weeks' gestation) with CD4+ counts > 200 cells/μl. 400 babies born to these women received zidovudine syrup 2 mg/kg or placebo administered 6-hourly for 6 weeks. The zidovudine regimens were well tolerated by both mothers and infants.

Further studies should aim to determine the mechanism by which zidovudine reduces the risk of maternal HIV transmission, the timing of HIV transmission, the efficacy of zidovudine in women not meeting the entry criteria for Protocol 076 and the long term effects of zidovudine during pregnancy on both mother and infant, and should examine the possibility of developing a simplified zidovudine regimen.

Following recent guidelines from the US and French public health services, the full Protocol 076 regimen should be given to all women fulfilling that study's entry criteria. This regimen should also be considered in women with more severe disease or in later stages of gestation. Clinical efficacy of zidovudine should be monitored closely in women and infants, who should also be followed up for long term adverse effects.

Unblinded screening for HIV in pregnant women in the USA is facing extreme opposition; nevertheless, guidelines on HIV counselling and HIV testing of pregnant women are currently being developed there in light of the Protocol 076 findings.

The prevalence of HIV infection among women of reproductive age is increasing, with up to 32% of women of child-bearing potential in some developing countries being HIV-positive.[1] The risk of vertical HIV transmission from mother to baby ranges from 7 to 40%,[2-5] and over 1 million children worldwide are infected with HIV.[6] Maternal HIV transmission is the primary means by which infants become infected;[7,8] prevention of maternal HIV transmission is of paramount importance.

Several risk factors possibly associated with HIV transmission from mother to child have been identified and include high viral-load levels, advanced clinical disease, low CD4+ counts, vaginal delivery, breast-feeding and the development of primary infection during pregnancy.[5,7,9]

This review focuses on the recently published results of the trial known as AIDS Clinical Trials Group (ACTG) 076 study in the USA and as ANRS 024 in France (hereafter referred to as

Protocol 076).[10] The implications of these results in terms of treatment guidelines and public health measures are addressed.

## 1. Protocol 076

### 1.1 Methods and Results

Protocol 076 was a phase III double-blind, randomised, multicentre, placebo-controlled trial designed to evaluate the efficacy and tolerability of zidovudine in the prevention of maternal HIV-1 transmission.[10]

HIV-infected pregnant women of 14 to 34 weeks' gestation were included in the study if they also met the following criteria:

- CD4+ counts > 200 cells/μl
- no contraindications for antiretroviral therapy
- no previous antiretroviral therapy, immunotherapy or anti-HIV vaccines during the pregnancy.

The results discussed in this overview are based on the findings from the first 400 infants born to these HIV-infected women and for whom data on at least 1 viral culture were available.

Because the timing of maternal HIV transmission is uncertain and since HIV-infected maternal cells may persist in the infant's circulation after birth, zidovudine was administered in the antepartum, intrapartum (during labour and delivery) and neonatal periods during the trial (table I). Breastfeeding was not allowed.

Overall, zidovudine significantly reduced the percentage of infants infected with HIV, compared with placebo (7.9 *vs* 27.7%, $p < 0.001$; fig. 1). This corresponds to a relative risk reduction of maternal HIV transmission of 71.5% with zidovudine compared with placebo.

Zidovudine was generally well tolerated by mothers and infants, with no short term toxicity in infants other than reversible mild decreases in haemoglobin levels (fig. 2).

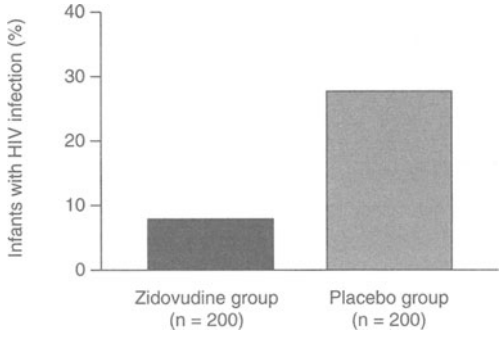


**Fig. 1.** Percentage of HIV-infected infants born to HIV-infected mothers, according to treatment regimen ($p < 0.001$).[10]

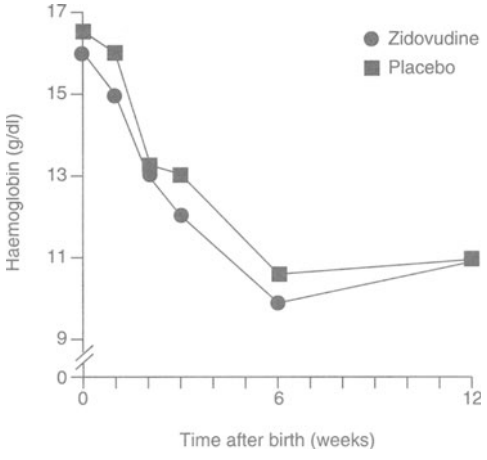


**Fig. 2.** Mean haemoglobin levels in infants in the zidovudine and placebo arms of Protocol 076.[10]

**Table I.** Treatment regimen in Protocol 076[10]

| | |
|---|---|
| **Antepartum period** | Zidovudine 100mg orally 5 times daily, or placebo, administered to the mother until the onset of labour for a median of 11 weeks |
| **Intrapartum period**[a] | Zidovudine 2 mg/kg intravenously over 1 hour then 1 mg/kg • h intravenously, or placebo, administered to the mother from the onset of labour until delivery |
| **Neonatal period** | Zidovudine 2 mg/kg syrup 6-hourly, or placebo, beginning 8 to 12 hours after birth, administered to the neonate for 6 weeks |

a During labour and delivery.

Protocol 076 was discontinued early because of the favourable results, and zidovudine was subsequently offered to all study participants and their neonates.

### 1.2 Unanswered Questions

While the results of Protocol 076 represent a breakthrough in the control of maternal HIV transmission, they raise the following questions and call for further studies.

- *What is the mechanism of action of zidovudine in reducing the risk of maternal HIV transmission?*

Our studies have shown that the mean HIV viral load [as measured by polymerase chain reaction (PCR) analysis] on the day of delivery in women who transmit HIV to their infants is greater than that in women who do not transmit the virus (fig. 3). Thus, in Protocol 076, it is possible that zidovudine may have prevented maternal HIV transmission by decreasing the maternal HIV viral load and consequently decreasing viral exposure to the fetus and/or infant, and that the drug may have prevented the establishment of HIV in the fetus.[11]

- *When does maternal HIV transmission occur?*

Maternal HIV transmission can theoretically occur *in utero*, during labour and delivery, or after birth (as a result of persistent exposure to maternal HIV-infected cells or through breast-feeding).

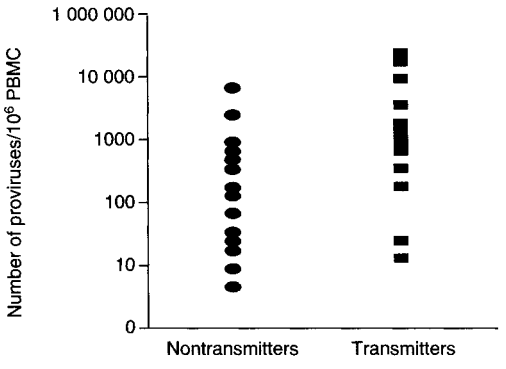


**Fig. 3.** Mean HIV viral load on the day of delivery in women who transmit the virus (mean = 735) to their infant versus those who do not (mean = 164). PBMC = peripheral blood mononuclear cells.

Because of the intensive treatment regimen in Protocol 076, it was not possible to determine the efficacy of zidovudine in reducing maternal HIV transmission during the individual antepartum, intrapartum and neonatal periods. No study to date has specifically addressed this issue.

Using viral data obtained during the first 3 months of life of 95 HIV-1–infected infants born to HIV-1–infected mothers, it was estimated that 65% of infants were infected with HIV on the day of birth or during delivery, whereas 35% were infected *in utero* in late pregnancy (fig. 4).[12] In those infants infected *in utero*, the median period between the time of infection and delivery was 14 days; 95% were infected < 59 days before delivery. These results are supported by those of other investigators which indicate that 50 to 70% of cases of maternal HIV transmission occur in late pregnancy or during labour or delivery.[5,12-20] Early intrauterine transmission may be more common in women with advanced disease than in those with less advanced disease.[5] In light of these findings, it would seem prudent to initiate zidovudine therapy at least 8 weeks before the anticipated delivery date.

- *Can zidovudine reduce maternal HIV transmission during breast-feeding?*

Breast-feeding was not allowed in Protocol 076: the effects of zidovudine on maternal HIV transmission during breast-feeding remain to be determined. However, avoidance of breast-feeding is a simple means of preventing one potential avenue of viral transfer, and consequently breast-feeding is not recommended in HIV-infected women in the USA.[11]

- *Can zidovudine reduce maternal HIV transmission in women who do not fulfil the entry criteria for Protocol 076, i.e. those with more advanced disease (CD4+ count < 200 cells/μl), those who have received long term zidovudine therapy, and those at > 34 weeks' gestation?*

The risk of maternal HIV transmission is known to be higher in women with advanced HIV disease than in those with less advanced disease, presumably because of the much higher viral load associ-

ated with late-stage disease.[12,15] As shown in figure 5, the risk of HIV transmission from mother to infant is inversely correlated with the CD4+ count. While the results of Protocol 076 confirm that maternal HIV transmission can be reduced with zidovudine in patients with a CD4+ count > 200 cells/μl, no study has addressed the effects of zidovudine on HIV transmission in women with a CD4+ count ≤ 200 cells/μl.

The risks and benefits of initiating zidovudine treatment during the first trimester of pregnancy and after 34 weeks' gestation are not known.

- *What are the long term effects of zidovudine during pregnancy on the mother and infant?*

There is some concern that zidovudine-resistant strains may become more of a clinical problem if short courses of zidovudine are used routinely during pregnancy or after birth. This could have a


**Fig. 4.** Percentage of infants (n = 95), born to HIV-infected women, in whom HIV was transmitted *in utero* or at the time of delivery.[12]

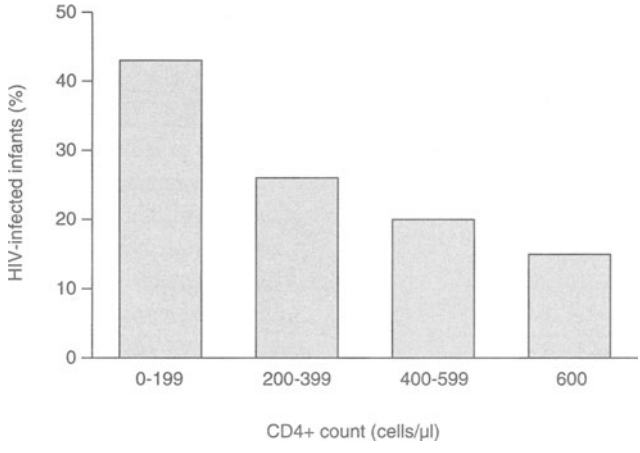


**Fig. 5.** The risk of maternal transmission according to maternal CD4+ counts.[21]

detrimental effect on the mother's subsequent response to therapy.[11,22] Furthermore, the long term effects, if any, of zidovudine therapy on future pregnancies are not known. Indeed, the long term outcome of the HIV-infected mother remains poor and more than one pregnancy is rare.

Although there have been no reports of neonatal malformations, premature births or fetal distress associated with the maternal use of zidovudine,[23] large numbers of infants need to be evaluated to determine whether zidovudine is associated with birth defects.[5,11] The effects of perinatal zidovudine in infants not infected with HIV are not known.[24]

- *Can the treatment regimen used in Protocol 076 be simplified?*

The development of a simplified zidovudine regimen (e.g. shorter treatment duration and the use of an oral rather than intravenous formulation during labour) is particularly important for developing countries in which the Protocol 076 regimen is not practical or affordable.

- *Why does maternal HIV transmission occur despite zidovudine therapy in some cases?*

Possible explanations for the occurrence of vertical transmission of HIV despite zidovudine therapy include particularly high maternal viral loads, the presence of resistant HIV strains, and transmission before the initiation of zidovudine therapy.

## 2. US and French Treatment Guidelines

On the basis of the results of Protocol 076, the US and French public health services have developed treatment guidelines for the use of zidovudine to reduce the risk of maternal HIV transmission.[25]

The recommendations of the US Public Health Service for the use of zidovudine according to various clinical situations are presented in table II. The full Protocol 076 regimen should be administered to all women meeting the study's entry criteria. In addition, the guidelines propose that zidovudine should be considered in patients not meeting the study's entry criteria for Protocol 076 (e.g. those with more severe disease or those at > 34 weeks' gestation), despite the anticipated lower efficacy of zidovudine in these patients. Additional information is needed to optimise the use of zidovudine in these patients. The results of Protocol 076 are not applicable to HIV-2–infected women: maternal HIV transmission rates are lower in patients with HIV-2 infection compared with those in patients infected with HIV-1.[26]

The final decision about treatment should be made by the woman in consultation with her healthcare provider after a detailed discussion of the risks, benefits and uncertainties of treatment, including the reduced but still possible risk of HIV transmission despite treatment with zidovudine and the unknown long term effects of such therapy.[25]

Zidovudine-associated toxicity, decreases in CD4+ counts and the development of zidovudine-resistant HIV strains should all be monitored in pregnant women receiving zidovudine.[25] Infants of HIV-infected mothers should receive routine checks to detect zidovudine-associated toxicity, to diagnose HIV infection early (although this is hampered by the presence of maternal HIV antibodies), to assess the development of opportunistic infections and to consider the possibility of initiating antiretroviral therapy.[5] The efficacy of early antiretroviral therapy in infants is not known, however.[25] Fetal monitoring should be performed only when clinically indicated (e.g. reduced fetal movements, inconsistent size compared with estimated gestation and maternal illness), not specifically because of maternal zidovudine use.

Routine follow-up is necessary to detect any potential long term adverse effects of zidovudine therapy in mothers (including the development of viral resistance and disease progression) and in both infected and noninfected infants (including organ system toxicity, adverse effects on neurodevelopment, pubertal changes and reproductive capacity, and development of neoplasms).[25] Surveillance mechanisms to monitor the long term effects of *in utero* exposure to zidovudine are also needed.[11]

The development and evaluation of other preventive strategies including vaginal lavage, other nucleoside analogue and non-nucleoside analogue

**Table II.** US Public Health Service recommendations for the use of zidovudine to reduce the risk of maternal-infant HIV transmission[25]

| Clinical situation | Recommendations[a] |
|---|---|
| **Pregnant HIV-infected women** | |
| • CD4+ counts ≥ 200 cells/μl<br>No contraindications for zidovudine<br>14 to 34 weeks' gestation<br>No history of extensive (> 6 months) prior antiretroviral therapy | Full Protocol 076 regimen[b]<br>Risk-benefit discussion |
| • > 34 weeks' gestation<br>No history of extensive (> 6 months) prior antiretroviral therapy<br>Zidovudine not required for the woman's health | Full Protocol 076 regimen[b]<br>Risk-benefit discussion |
| • CD4+ counts < 200 cells/μL<br>14 to 34 weeks' gestation<br>No other contraindications for zidovudine<br>No history of extensive (> 6 months) prior zidovudine use | Antepartum component of Protocol 076 regimen[b] for the woman's benefit<br>Intrapartum and neonatal components of Protocol 076 regimen[b] until further information is available<br>Risk-benefit discussion |
| • History of extensive (> 6 months) zidovudine and/or other antiretroviral therapy before pregnancy | Consider Protocol 076 regimen[b] on a case-by-case basis<br>Risk-benefit discussion including clinical and immunological stability on zidovudine, likelihood of being infected with a zidovudine-resistant strain, and her reasons for current use of an alternative antiretroviral if applicable<br>Discussion with HIV consultants may be warranted |
| • No antepartum zidovudine therapy<br>In labour | Risk-benefit discussion of intrapartum and neonatal components of Protocol 076[b]<br>Offer zidovudine when clinical situation permits |
| **Infants born to HIV-infected women** | |
| • No maternal intrapartum zidovudine therapy | Offer the postpartum component of Protocol 076 regimen[b] if zidovudine can be initiated within 24 hours of birth and if the clinical situation permits<br>Risk-benefit discussion |

a In all cases, inform the patient that the regimen may be less effective than in Protocol 076 because it will be started at a later stage.
b The Protocol 076 regimen is detailed in table I.

reverse transcriptase inhibitors and passive and active immunisation alone or in combination with zidovudine are needed.[5]

## 3. The French Response to Protocol 076

In contrast to the situation in the USA (see section 4), HIV screening is generally offered to all pregnant women in France. In addition, early diagnosis of HIV infection in infants (using viral culture or PCR) is available in most French centres.

The network of the National Cohort Studies in France covers more than two-thirds of the pregnancies among HIV-infected women.[27] Responses to a recent questionnaire sent to all physicians in the network indicated that zidovudine was suggested to all HIV-infected pregnant women, 90% of whom wanted to be treated with the drug (JF Delfraissy, personal communication). Importantly, the medical costs of treating HIV-infected women and their babies in France is covered by national health insurance.

## 4. The US Response to Protocol 076

Despite the significant benefits of zidovudine in reducing maternal HIV transmission in Protocol 076 (see section 1.1), mandatory unblinded testing of all pregnant women for HIV infection is facing extreme opposition in the USA. The main criticism comes from patient advocates and women's rights proponents on the grounds of privacy rights.[24] This reaction has been fuelled by the recent intense New York debate over the pro-

posed mandatory unblinded screening of neonates for HIV infection (which was ultimately rejected). Even advocates of mandatory screening of neonates do not support the compulsory HIV testing of pregnant women.

The principle of consent for both HIV screening and treatment is of utmost importance given the uncertainty about the long term consequences of zidovudine therapy during pregnancy (see section 1.2).[24] Ethical, social and economic problems as well as the benefits and potential risks (including discrimination) of routine HIV testing need to be considered.[11]

Given the failure of the US healthcare system to guarantee healthcare access for all, the concern that many women at risk of HIV receive no or inadequate prenatal care and the level of poverty of the majority of women infected with HIV, the practicality of HIV testing and treatment according to the Protocol 076 regimen would be fraught with difficulties.[24] Furthermore, the requirement for extensive counselling before HIV testing mandated by law in some states will make routine HIV testing a major challenge.

Nevertheless, the US Public Health Service is currently developing guidelines for HIV counselling and testing of pregnant women,[11] and an antiretroviral pregnancy registry has been set up.

## 5. Conclusions

The results of Protocol 076 clearly show that zidovudine, when administered in the antepartum, intrapartum and neonatal periods, significantly reduces the risk of maternal HIV transmission.

Based on the findings of Protocol 076, the US and French public health services have released recommendations on the use of zidovudine in the prevention of maternal HIV transmission. The zidovudine regimen used in Protocol 076 is recommended for all patients meeting the study entry criteria, i.e. HIV-infected pregnant women at 14 to 34 weeks' gestation with CD4+ counts > 200 cells/μl, no clinical indications for receiving zidovudine treatment and no prior use of antiretroviral therapy during the pregnancy. The regimen should also be considered in patients with more severe disease and in those at a later stage of gestation. Appropriate components of the Protocol 076 regimen should also be considered in HIV-infected pregnant women who have not received antepartum zidovudine therapy and who are in labour, and in neonates whose mothers have not received zidovudine therapy. Final treatment decisions should be made by the patient after a full risk-benefit discussion with their healthcare provider.

Future studies should investigate the mechanism by which zidovudine prevents maternal HIV transmission, the timing of vertical transmission, the efficacy of zidovudine in patients not meeting all the entry criteria for Protocol 076, the long term effects of zidovudine on the mother and infant, and the possibility of developing a treatment regimen. The effects of zidovudine on HIV transmission via breast milk and the reason for maternal HIV transmission despite zidovudine therapy in some cases also need to be determined. Finally, the development and evaluation of other preventative strategies alone or in combination with zidovudine are urgently required.

Expanded use of zidovudine in HIV-infected pregnant women represents a great challenge. This applies both to developed countries and to developing countries in which the regimen used in Protocol 076 would be difficult to employ. Thus, at the present time, the results of Protocol 076 would appear to have little or no impact in many developing countries in which the toll of HIV infection is the greatest.

Prior to Protocol 076, rates of vertical transmission of HIV from mother to baby were relatively high. Now the challenge for clinicians is to maximise the benefits of these findings, to expand their utility to greater numbers of pregnant women infected with HIV-1, and to implement effective, ethical and practical public health strategies.

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