XV International AIDS Conference, Bangkok, July 2004

The Effectiveness of Combination ART Prophylaxis Regimens for Preventing MTCT of HIV in Resource-limited Settings in Eurasia

V. Zaporozhan, **S. Posokhova**, I. Boichenko, O. Lutsenko, N. Govorovskaya
Odessa Oblast Hospital, Odessa, Ukraine

BACKGROUND

The HIV/AIDS epidemic has engulfed dozens of countries, including Ukraine, over the past decade. Data from The European Center for Epidemiological Monitoring of HIV/AIDS show that Ukraine has the highest prevalence of HIV in the European region, with 1% of the adult population infected.[1] Each year in Ukraine, more than 2,000 children are born to HIV+ mothers.[1]

The rate of mother-to-child transmission (MTCT) of HIV is 1-2% in European countries and the United States, compared to 25-40% for Africa and Asia.[2-4] The prevalence of MTCT of HIV has decreased in many economically developed countries due to the use of highly-effective antiretroviral therapy (ART) during pregnancy.[2, 4, 5] The main aims of this approach are to decrease MTCT by reducing viral load (the number of viral copies in 1 µL of blood); improving immune function; providing prophylaxis for opportunistic infections; and maintaining a woman's overall health.[6, 7]

ART REGIMENS

ART was initially used in 1994 for the prophylaxis of MTCT in the United States in accordance with Protocol 076, developed by the US Centers for Disease Control and Prevention (CDC). Protocol 076 calls for the prescription of 500 mg of zidovudine, initiated at 14-34 weeks of pregnancy up to delivery. The drug is administered intravenously intrapartum, 2 mg/kg in the first hour, then 1 mg/kg each hour up to delivery. The newborn is given zidovudine syrup 6 hours after birth, 2 mg/kg every 6 hours for 6 weeks. The introduction of Protocol 076 has led to a 67.5% reduction in the MTCT rate, from 25.5% in the placebo group to 8.3% in the test group.[2, 8, 9] In resource-limited countries, a less expensive short-course prophylactic regimen has been proposed based on data showing that HIV transmission occurs most often during the third trimester of pregnancy and intrapartum. The short-course regimen includes the use of zidovudine, starting at week 36, 600 mg/day, intrapartum, 300 mg every 3 hours up to delivery. This regimen has been shown to reduce the HIV transmission rate by 50%.[10]

In recent years, studies in Uganda have demonstrated the efficacy of a one-time dose of 200 mg of nevirapine (Viramune) administered to an HIV+ woman at the onset of labor and prior to Cesarean section (C-section), as well as the administration of Viramune syrup to the newborn, 2 mg/kg once in the first 48-72 hours of life.[11] The use of Viramune intrapartum reduced the MTCT rate by 47%.[11] This regimen can be used effectively for pregnant women who have not been receiving ART. European studies have demonstrated the efficacy of combined ART with the inclusion of protease inhibitors during pregnancy. Reductions in the MTCT rate to below 1-2% have been achieved.[4, 11]

About 70% of all cases of vertical transmission of HIV occur intrapartum.[2, 12-14] There is a 4-fold increase in the concentration of HIV in cervical and vaginal secretions during pregnancy, heightening the risk of fetal infection through contact with maternal secretions.[13, 15] Many investigators have demonstrated the prophylactic role played by elective C-section in reducing the MTCT rate, especially in combination with ART.[2, 12, 16-18]

This study was designed to compare the efficacy of a combined ART regimen for mother and infant (zidovudine + nevirapine) with available monotherapy regimens—zidovudine or nevirapine—in relation to reducing the rate of MTCT of HIV.

PROJECT DESCRIPTION

From 1996 to 2003, 519 HIV-positive pregnant women were evaluated before and after they gave birth to live infants; the infection status for all of these babies has definitively been established by the Odessa Oblast Maternity Hospital. The pregnant subjects were divided into two groups.

Group 1 consists of 335 women who received ART according to the following regimens:

Group 1A (75 women)
- did not receive treatment during pregnancy
- were prescribed a single 200 mg dose of nevirapine (Viramune) at the onset of labor or 4-6 hours before C-section
- had Viramune syrup given to their newborn, 2 mg/kg in the first 48-72 hours of life

If a member of group 1A was admitted less than 2 hours before delivery, the newborn was prescribed Viramune syrup in the same 2 mg/kg dose immediately after birth, and then again after 48-72 hours.

Group 1B (98 women)
- received a short course of zidovudine (Retrovir) starting at 34-36 weeks of pregnancy (600 mg/day prior to labor, 300 mg intrapartum every 3 hours up to delivery)
- did not have treatment prescribed for their infant

Group 1C (162 women)
- received a combined ART regimen
  - Retrovir 600 mg a day starting at 34-36 weeks of pregnancy, 300 mg intrapartum every 3 hours up to delivery
  - a one-time 200 mg dose of nevirapine (Viramune) prescribed at the onset of labor or 4-6 hours before C-section
- had Viramune syrup given to their newborn, 2 mg/kg in the first 48-72 hours of life and Retrovir syrup, 4 mg/kg, twice a day for 7 days

Group 2 (184 women)
- did not receive ART for various reasons

All parturient subjects did not breast feed because it is known that the HIV transmission rate is as high as 12-30% with breastfeeding.[2, 13, 18]

The clinical laboratory battery included routine immunological, bacteriological, virological, serological, ultrasound, and statistical studies. The definitive diagnosis regarding the infant's infection status was established after the results of the polymerase chain reaction (PCR), which indicates the presence of viral antigens, were obtained at 1 and 3 months, as well as by enzyme immunoassay (EIA), which indicates the presence of HIV antibodies, at 12 and 18 months. The infant is considered HIV- if there are two negative PCR results at 1 and 3 months or two negative EIA results at 12 and 18 months.

FINDINGS AND DISCUSSION

Evaluated women ranged in age from 16-39 years; 22.6 ± 2.2 years on average. Prior to pregnancy, 24% of the women in **Group 1** and 32.1% of those in **Group 2** were injecting drug users (IDUs). Only 4.8% of **Group 1** and 13.3% of **Group 2** were active IDUs during their pregnancies.

Among all of the evaluated women, 493 (95%) were at the asymptomatic carrier stage, with a mean CD4+ lymphocyte count greater than 600 cells per µL of blood. Viral load was not determined. Opportunistic infections such as tuberculosis were diagnosed in 10 (1.9%) cases. Hepatitis B and C virus carrier state was observed in 25% of **Group 1** and 33% of **Group 2**.

There was a problematic obstetrical history, such as medical and spontaneous abortions, among 57.5% of **Group 1** and 67.6% of **Group 2**; this is a risk factor for the development of a number of obstetrical complications intrapartum and in the postpartum period.

In terms of extragenital pathology, a high incidence of anemia was observed: 72% in **Group 1** and 84% in **Group 2**. Kidney diseases (13.5%) were diagnosed with equal frequency; other extragenital diseases were noted in a very small number of women.

Sexually transmitted infections (STIs) were identified in the majority of women in both groups:
- 28.5% were diagnosed with trichomoniasis
- 40.2% with candidiasis
- 6.9% with syphilis
- 2.5% with genital herpes

This suggests a high risk of intranatal fetal infection and the development of postpartum purulent-septic complications.

More than 50% of the women had not been treated for their STI(s) during pregnancy, or treatment had not been effective. Chorioamnionitis and premature rupture of membranes occur more often with STIs and the post-rupture period increases, thereby increasing the MTCT rate.[2, 13, 15]

A high incidence—42.5%—of placental insufficiency and fetal intrauterine growth retardation (IUGR) syndrome was noted among the complications of pregnancy for **Group 2**; this rate is 1.5 times higher than for **Group 1**. Amnion pathology such as oligohydramnios was diagnosed in 33% of the women in both groups. It is hypothesized that oligohydramnios, placental insufficiency, and IUGR in HIV-positive pregnant women are risk factors of intrauterine fetal infection. The positive influence of ART is reflected in reduced viral load; this improves the functioning of the uteroplacental complex and decreases the rate of intrauterine fetal infection. The above data confirm this hypothesis.

Among the complications during the course of pregnancy and labor, premature rupture of the membranes was noted in 20% of the women; this is an unfavorable factor, lengthening the post-rupture period and increasing the rate of intranatal fetal infection.

A high relative proportion—9.4%—of premature births was noted in **Group 2**; this is three times greater than for **Group 1**. Premature and immature infants do not possess resistance to HIV and are susceptible to intranatal fetal infection to a greater degree.[2, 13] ***Study results have shown that ART did not increase the birth rate of premature and immature infants.***

The relationship of the MTCT rate to the use of ART and method of delivery in the evaluated groups is given in **Table 1.**

As the results of this assessment indicate, combined ART (zidovudine + nevirapine) for mother and fetus reduced the MTCT rate 4.2 times compared with the rate for women who did not receive treatment (**Group 2**).

The MTCT rate was 1.8 times lower with combined therapy than in pregnant women who received nevirapine (**Group 1A**) and 1.3 times lower than in **Group 1B,** who only received the short-course zidovudine (Retrovir) regimen.

	Group 1A (n=75)		**Group 1B** (n=98)		**Group 1C** (n=162)		**Group 2** (n=184)	
Labor	62		76		50		158	
C-section	13		22		112		26	
	labor	C-section	labor	C-section	labor	C-section	labor	C-section
Healthy children	87.1% (54)	92.4% (12)	89.5% (64)	95.5% (21)	88% (44)	95.5% (107)	68.4% (108)	92.4% (24)
Ill children*	12.9% (8)	7.6% (1)	10.5% (8)	4.5% (1)	12% (6)	4.5% (5)	31.6% (50)	7.6% (2)
MTCT rate**	12% (9)		9.2% (9)		6.7% (11)		28.2% (52)	

*difference significant (p<0.05); ** (p <0.01)

Table 1: MTCT rates for HIV+ pregnant women subjects.

In addition, this study demonstrates the role played by elective C-sections in reducing the rate of MTCT of HIV. For delivery by elective C-section, the MTCT rate was only 4.5% in **Group 1B** and **Group 1C**; this is 2.6 times lower than for vaginal births, and 1.6 times lower than for **Group 1A.** The role played by elective C-section was dramatically demonstrated in **Group 2** women who did not receive ART. In **Group 2,** the MTCT rate for C-section is 4.2 times lower than for vaginal births. However, when performing a C-section, the risk of postoperative complications for the mother must be considered.

CONCLUSIONS

- Prescribing zidovudine (Retrovir) 600 mg/day starting at 34 weeks of pregnancy plus 200 mg of nevirapine at the onset of labor or 4-6 hours before C-section, as well as Retrovir syrup, 4 mg/kg twice a day plus nevirapine syrup, 2 mg/kg in the first 48-72 hours of life to newborns, reduced the rate of MTCT of HIV to 6.7%; this is 1.3 times lower than a short-course Retrovir treatment, 1.8 times lower than with nevirapine alone intrapartum, and 4.2 times lower than for women who did not receive any therapy (**Group 2**).
- The combined regimen of prophylactic ART presented above can be recommended for countries with limited resources when it is not possible to carry out highly-effective ART during pregnancy, intrapartum, and for the newborn.

REFERENCES

1. А.М. Щербінська *et al.*, Система офіційної реєстації ВІЛ-інфікованих та хворих на СНІД в Україні та необхідність створення національної комп'ютеризованої системи офіційної реєстрації випадків ВІЛ/СНІД / Проблеми ВІЛ-інфекції, наркоманії та інфекцій, що передаються статевим шляхов в Україні. Інформаційний бюлетень. Київ.- 2003. –с. 14. [A.M. Shcherbinskaya *et al.*, The system of official registration of HIV+ individuals and AIDS patients in Ukraine and the necessity of creating a computerized system of official registration of HIV/AIDS cases, The problem of HIV infection, substance abuse, and sexually transmitted infections in Ukraine, Information bulletin, Kiev (2003) p.14].
2. ВИЧ-инфекция в перинаталогии /Под. ред В.Н. Запорожана, Н.Л. Аряева. К.:Здоровье (2001) с.70. [HIV infection in perinatology, V.N. Zaporozhan and N.L. Aryaev (Eds.). Kiev: Zdorovye (2001) p.70.]
3. E.M. Connor *et al.*, Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment, N. Engl. J. Med., **331** (18), pp.1173-1180 (1994).
4. L. Kuhn *et al.*, "Timing of maternal-infant HIV transmission: associations between intrapartum factors and early polymerase chain reaction results," AIDS (1997) **11,** pp. 429-435.
5. R. Ndauti, for the Nairobi Breastfeeding Study. Program and abstracts of the 2nd Conference on Global Strategies for the Reduction of Mother to Child Transmission of HIV: September 1-5, 1999: Montreal, Canada. Abstract 47.
6. J.S. Currier, Challenges to managing therapy during pregnancy, Program and abstracts of the 9th Conference on Retroviral and Opportunistic Infection, Feb. 24-28, 2002; Seattle, Washington, Abstract S19.
7 European Collaborative Study, "Maternal viral load and vertical transmission of HIV-1: An important factor but not the only one," AIDS (1999) **13,** pp. 1377-1385.
8. R.S. Sperlin, "Maternal zidovudine treatment and the risk of human immunodeficiency virus type 1 from mother to infant," Pediatric AIDS Clinical Trial Group Protocol 076 Study Group, N. Engl. J. Med., **335** (22), pp. 1621-1629 (1996).
9. C. Thorne, for the European Collaboration Study, Antiretroviral therapy and Cesarean section to reduce vertical transmission of HIV in Europe. Program and abstracts of the XIII International AIDS Conference; July 9-14, 2000; Durban, South Africa. Abstract
10. R.J. Simonds, "Impact of zidovudine use on risk and risk factors for perinatal transmission of HIV. Perinatal AIDS Collaboration Transmission Studies," AIDS **12**, (3), pp. 301-308 (1998).
11. M.G. Fowler *et al.*, Effect of nevirapine (NVP) for perinatal HIV prevention appears greatest among women with most advanced disease: Subgroup analyses of HIVNET 012, Program and abstracts of the 9th Conference on Retroviral and Opportunistic Infection; Feb. 24-28, 2002; Seattle, Washington, Abstract 120.
12. European Collaborative Study, "Vertical Transmission of HIV-1: Maternal immune status and obstetric factors," AIDS **10,** pp. 1675-1681 (1996).
13. I. Loussert-Ajaka *et al.*, "HIV-1 detection in cervicovaginal secretions during pregnancy," AIDS **11** (13), pp. 1575-1581 (1997).
14. L.E. Riley and M.F. Greene, "Elective Cesarean delivery to reduce the transmission of HIV," N. Engl. J. Med. **340** (13), pp. 1032-1033 (1999).
15. J. Montaner *et al.*, "Antiretroviral Treatment in 1998," Lancet **352**, p.1919 (1998).
16. M.T. Halpern *et al.*, "Cost-effectiveness of Cesarean section delivery to prevent mother-to-child transmission of HIV-1," AIDS **14**, pp. 691-700 (2000).
17. N. Shatter *et al.*, "Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A randomised controlled trial," Lancet **353,** pp. 773-780 (1999).
18. M.L.Newell, "Mechanisms and timing of mother-to-child transmission of HIV-1," AIDS **12,** pp. 831-837 (1997).