

FROM RESEARCH TO PRACTICE: USE OF SHORT COURSE ZIDOVUDINE TO PREVENT MOTHER-TO-CHILD HIV TRANSMISSION IN THE CONTEXT OF ROUTINE HEALTH CARE IN NORTHERN THAILAND

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Abstract. Thailand has made remarkable progress in battling the HIV epidemic, as the decreases in HIV prevalence and changes in sexual behavior attest. Yet, in Phayao, a northern province severely affected by HIV, approximately 280 HIV-infected women, or 5% of all pregnant women, gave birth to an estimated 70 infected children in 1997. As many of these infants die within their first year of life, the infant mortality rate is on the rise after years of decline.

The province, however, responded quickly to this crisis. Since July 1997, the Ministry of Public Health (MOPH) offers through Phayao's seven public hospitals a short regimen of zidovudine to all consenting HIV-infected women to prevent mother-to-child transmission of the virus. The overall prophylactic coverage for the province reached 68% of all HIV-infected pregnant women in the fourth quarter of 1997, either through the MOPH program or through the North Thailand Perinatal HIV Prevention Trial, the parallel clinical trial conducted by the MOPH and the Ministry of University Affairs. Analysis of the data collected showed that compliance to the intervention was excellent, around 90%. This was achieved at an additional cost of US\$ 0.13 per capita per year, affordable even in the context of the economic crisis, and represents less than 1% of public health expenditures in Thailand. The cost per Disability Adjusted Life Years saved is approximately US\$35, making it highly cost-effective.

In less than a year, the MOPH implemented this program on a large scale in this relatively poor province, with limited external support. Women receive pretest counseling at their first prenatal visit, are offered HIV testing and, if they accept, return for posttest counseling two weeks later. In the case of a positive test result, a confirmation test is performed at the provincial hospital. HIV-infected women are offered zidovudine the 34th week of pregnancy or as soon as possible thereafter. Before starting treatment, the women's hemoglobin, CBC and platelets are measured. Infants begin taking oral zidovudine shortly after birth and continue until they are one week old. Subsequently, health centers regularly follow the infants, and volunteers provide case management of childhood illness, nutrition problem solving, childhood immunizations and home visits. Mothers feed the infants breastmilk substitutes, and women with insufficient income receive the substitutes free of charge.

The northern Thailand experience provides important insights into the feasibility of large scale interventions to prevent perinatal HIV, such as the need for the reorganization of the delivery of health care and quality counseling. On the basis of this experience, a simplified schedule of three intervention phases (Screen, Treat and Care), which can be incorporated into routine mother and child health care, is proposed. Follow-up of the child, however, will require more frequent and intensive contact with health care services than usual. At a time when many countries are reevaluating their health care systems, these insights should be considered, so as to additionally better the needs of HIV-infected women during pregnancy and beyond.

INTRODUCTION

In 1994, the results of the AIDS Clinical Trial Group (ACTG) 076 clinical trial showed a 67.5%

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decrease in HIV transmission from mother to child (25.5%, placebo vs 8.3%, zidovudine), when HIV-infected women took the drug during pregnancy (Connor *et al*, 1994). Women began the study treatment between the 14th and 34th week of gestation. The regimen consisted of antepartum oral zidovudine (ZDV) and an intrapartum intravenous loading dose of ZDV for the mothers, while

newborns received a six week treatment of ZDV syrup. Tolerance to the treatment was excellent for both the mothers and the infants, and long term follow-up the infants showed no adverse effects. Development of resistance was uncommon. This trial and all subsequent studies have confirmed the safety and efficacy of ZDV monotherapy during pregnancy (Simonds *et al*, 1998; Thomas *et al*, 1994; Blanche *et al*, 1997; Mofenson, 1997; Aleixo *et al*, 1997). They also indicated the likely efficacy of a short treatment beginning at a late stage of pregnancy. Furthermore, recent evidence has confirmed the efficacy of a short course of zidovudine. According to data released by the US Centers for Disease Control and Prevention (CDC, 1998), a trial conducted in central Thailand showed that a regimen of ZDV shortened to one month for the mother only decreased vertical HIV transmission by 50% (9%, ZDV vs 18%, placebo).

Although it is not known how its efficacy compares with treatments in use in industrialized countries, such a short course is simpler, easier to follow and less costly than the ACTG 076 regimen. In addition, it permits women to begin treatment at a later stage in their pregnancy. This raises the hope that ZDV prophylaxis could be made readily available to most HIV + pregnant women worldwide. However, regardless of the treatment program, some key implementation issues must be addressed in order to achieve this goal. This paper aims to delineate these issues on the basis of the experience of Phayao, a northern province of Thailand, where a long or a short regimen of ZDV has been offered to all identified HIV-infected pregnant women since July 1997.

THE EFFECTIVENESS OF REDUCING HIV TRANSMISSION IN A FIELD SETTING: THE PHAYAO EXPERIENCE

The HIV epidemic in Phayao

The HIV epidemic has severely affected the women and children in Thailand's six northern provinces: Chiang Mai, Chiang Rai, Lampang, Phayao, Lamphun, and Mae Hong Son. Between 1989 and 1995, the HIV prevalence among pregnant women rose steadily in this area, from less than 1% to more than 7% (Fig 1). In Phayao, the

province most affected by HIV, the prevalence among pregnant women has progressed at an even faster rate, from about 3% in 1989 and 1990 to a peak of 11% in 1993. It was estimated that approximately 350 of 6,473 infants were born to HIV-infected mothers in 1997 in this province. Pediatric AIDS is likely to be the sole explanation for the recent increase in infant mortality, according to the

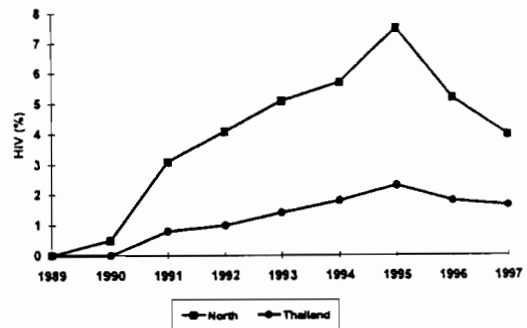


Fig 1—HIV prevalence among pregnant women in Thailand and in the upper regions of the country, 1989 - 1997.

provincial public health authorities.

A study of a population of infants born to HIV+ mothers conducted in Phayao hospital in 1991 and 1992 showed a rate of vertical transmission of 37% (Sirisanthana, 1997). This high transmission rate is explained in part by the fact that most women breastfeed their infants. When women do not breastfeed, transmission occurs in about 25% of cases (Fowler *et al*, 1997; Kreiss, 1997). Shortly thereafter, the Ministry of Public Health (MOPH) recommended that HIV-infected mothers formula feed their infants, despite its active promotion of breastfeeding for the general population. Thus, free infant formula is provided to the poorest HIV-infected mothers for the first year.

Northern Thailand responded strongly to the epidemic. As a result of comprehensive action, including dissemination of information to the public through all media and condom promotion among commercial sex workers and their customers, positive results have been observed. The prevalence among young military conscripts dropped from more than 20% in 1992 to about 7.7% in 1996. The median HIV prevalence among pregnant women in

the six northern provinces decreased to 5.2% in 1996. In Phayao specifically, serosurveillance data showed a decrease of HIV prevalence among pregnant women from 11% in 1995 to approximately 5% three years later. In other regions of the country, however, especially in the northeast, the prevalence of HIV among pregnant women is still rising.

Specific interventions to decrease mother-to-child transmission (MCT) were implemented in most of Northern Thailand. HIV testing and counseling programs have been offered in antenatal clinics since 1993, and HIV-infected mothers now feed their newborns breastmilk substitutes. As a result, based on a study of 302 women conducted by the Provincial Health Office, it is estimated that the vertical transmission rate decreased to approximately 23% in 1994. Despite this progress, however, the number of AIDS cases diagnosed in pediatric wards continued to increase. As soon as results of the ACTG 076 were released, implementation of this intervention was set as the next priority.

Two approaches to reduce vertical transmission

After ACTG 076, the AIDS Division of the MOPH decided to reevaluate its therapy program. In mid-1995, the World Bank and the World Health Organization assisted the MOPH in analyzing the economics of antiretroviral therapy. They concluded that, given the Ministry's antiretroviral budget and the quality of Thailand's health care infrastructure, ZDV prophylaxis for HIV-infected pregnant women and their newborns was feasible, affordable and by far the most cost-effective way to use the budget (Prescott and Periens, 1996). At about this time, the Thai Food and Drug Administration approved the use of ZDV for the prevention of perinatal HIV. In 1997, the Thai Red Cross, using funds from donations, provided ZDV prophylaxis to more than 1,500 women and their infants throughout the country (Phanuphak, 1998).

Early in 1997, evidence of the likely efficacy of a shorter course of ZDV prompted the local health authorities in the upper north region of Thailand to extend ZDV treatment to all HIV-infected pregnant women through two programs. The North Thailand Perinatal HIV Prevention Trial (NTPHPT) would evaluate the efficacy of a short ZDV treatment relative to a longer ACTG 076-like regimen in collaboration with the MOPH, while the latter would

also offer a short course ZDV regimen through the Z10 program to all women not included in the study. All key individuals involved in the prevention of MCT in the six northern provinces of Thailand were invited to discuss the implementation of the Z10 program in January 1997. The most important issues included availability of resources, counseling and laboratory services, as well as the ability of families and communities to provide continuous support and care for the mothers and their future infants.

In July 1997, the public health authorities of the province of Phayao, population 517,000, launched the Z10 program. Presently, the provincial hospital and the six district hospitals offer HIV testing and counseling, as well as a short course ZDV prophylaxis (Z10). This provides an opportunity for all HIV-infected pregnant women to receive open label ZDV. At the same time, a joint research team (Harvard University, MOPH, Chiang Mai University, Mahidol University, and the Institut de Recherche Scientifique pour le Développement en Coopération) started the North Thailand Perinatal HIV Prevention Trial in the northern regions. Women are randomly assigned at the 28th week of pregnancy to either an ACTG 076-like ZDV regimen or a short course regimen. Through this trial, approximately 30% of HIV-infected pregnant women in the Phayao province receive treatment.

The Z10 program

The Z10 treatment included six weeks of oral ZDV, 600 mg per day, starting the 34th week of pregnancy and 300 mg of ZDV every three hours from the onset of labor to delivery. Oral ZDV, 8 mg/kg/day, was given to the infants from twelve hours to seven days after birth. For mothers, the required number of visits was usually seven: four antenatal visits, delivery, and two postnatal visits. Six out of seven are incorporated into the routine schedule of maternal care. One additional antenatal visit was necessary for all pregnant women for posttest counseling, two weeks after the first visit. Group or individual counseling was offered to HIV-infected pregnant women at each visit. Infants were seen when one week old, then subsequently at one month, three, four, six, twelve, fifteen and eighteen months. Only the one visit at day seven, at the end of the treatment, is added to the routine schedule for healthy babies in order to discuss formula feeding.

Laboratory examinations included rapid HIV tests during the first antenatal visit that were analyzed at the district level (50,000 to 70,000 inhabitants) and, if initial results were positive, confirmation testing at the provincial level (500,000 inhabitants). Determination of the hematological parameters necessary to initiate treatment, CBC and platelet count, were performed at the district level. In the case of severe anemia or neutropenia, the ZDV treatment was postponed. CBC and platelet counts were measured three times: before ZDV prophylaxis, after four weeks, and at delivery. (Note: An objective of the program in Phayao was to provide additional monitoring, so as to ensure that ZDV prophylaxis is safe. If incorporated into routine health care, this would not be necessary, except perhaps during the initial phase of a program). Newborns were measured before initiation of the seven-day treatment. When the infants were eighteen months of age, they were tested for HIV by ELISA.

Z10 was offered at the hospital level, primarily in district hospitals, the most decentralized level at which both sufficient laboratory and counseling capacity is available. This led to two major organi-

zational changes: i) all pregnant women have to go to the district hospital, rather than to the health center, for the first two antenatal visits; and ii) only HIV-negative women then go to a health center for antenatal care follow-up, while HIV-positive women receive all antenatal, delivery and postnatal care at the district hospital level.

Success of the Z10 program

The intervention was established from July 1997 to October 1997, when it became fully operational. Between July and December 1997, 1,177 pregnant women attended the hospital antenatal clinics for their first visit, and almost 100% of these women were tested for HIV. As a result, the hospitals identified 65 HIV-infected women (Table 1). Sixty returned for the posttest and initiated the ZDV treatment. Of those, 24 were given a short course of ZDV through the MOPH program, while 29 enrolled in NTPHPT. Five did not go back for a confirmation test or chose to terminate their pregnancy. None of the women was unable to take ZDV due to anemia. One woman delivered prematurely, before starting treatment, and thus was un-

Table 1

HIV-infected pregnant women enrolled in the Z10 and NTPHPT programs Phayao Province.

	October to December 1997	
	Cases	%
Pregnant women who went to an antenatal clinic	1,177	100
Confirmed HIV+ pregnant women	65	5.5
HIV+ pregnant women	65	100
- who did not return for a confirmation test or ended their pregnancy	5	7.7
- who took ZDV	53	81.5
- through Z10 program	24	36.9
- through NTPHPT	29	44.6
Reasons women did not start or complete treatment	7	10.8
- Fetus death in utero	1	1.5
- Migration to another province	1	1.5
- Drug intolerance	1	1.5
- Start of antenatal care after 34 th week	1	1.5
- Delivery before 34 th week	1	1.5
- Infrequent attendance at antenatal clinic	2	3.1

able to participate in the program. Tolerance to the treatment was good; only one of the women had to stop treatment due to reported intolerance. Out of 53 women, only two did not get the full treatment. Consequently, the overall coverage for the whole province, through both programs, was 68% of all HIV-infected pregnant women in the province by the fourth quarter of 1997 and exceeded 80% during the first quarter of 1998. PCR diagnosis of the first forty infants born to HIV-infected women in the program showed that only ten had become infected.

Neighboring provinces of the northern region of Thailand, administratively called Region 10, also introduced ZDV as routine treatment, and their results are displayed in Table 2. In all of these provinces, more than 95% of pregnant women attend antenatal clinics, and more than 90% of those women were tested for HIV. In three of these five provinces, Chiang Rai, Lampang, and Mae Hong Son, more than 60% of the pregnant women identified as HIV-infected received the ZDV treatment. In the other two provinces, the intervention was still in the start-up phase early 1998 and will need to be

evaluated in the following months. Results of the implementation of the ZDV prophylactic treatment in neighboring provinces showed effects comparable to the Phayao experience. Acceptance rates for the ZDV prophylactic treatment were high, 75% or higher for four out of the five provinces. Compliance was also particularly high. According to the interviews of women who underwent the routine treatment, more than 90% have taken the ZDV treatment from the 34th week of pregnancy to delivery at adequate dosage.

Cost of the Z10 program

Some of the costs to implement the intervention were start-up costs, incurred only once to initiate the activities, and include the expansion or development of adequate counseling and laboratory services. The cost of the ZDV tablets and syrup for the short course of treatment was estimated at US\$60 (all costs are presented in US dollars) per mother-child pair. The estimated cost for the HIV testing procedures was US\$3 for both the initial HIV test

Table 2

Prevention of MCT in Northern Thailand: initial results of the other northern provinces, October 1997 - March 1998.

	Chiang Mai	Chiang Rai	Lampang	Lamphun	Mae Hong Son
Total results					
Identified HIV + pregnant women	108	253	125	48	7
Women who initiated ZDV treatment as part of research project or routine health care	33	164	101	16	7
Total ZDV treatment initiation rate	31%	65%	81%	33%	100%
Results of routine PMCT HIV prophylaxis					
HIV+ pregnant women proposed ZDV prophylactic treatment as part of routine health care	106	184	109	25	8
Women who accepted treatment	61	158	109	23	6
Acceptance rate	58%	86%	100%	92%	75%
HIV + pregnant women who received starting dose of ZDV	33	72	101	14	6
% who initiated treatment	31%	39%	93%	56%	75%
Women who have delivered (as of April 98)	32		123	14	
Women who fulfilled criteria for full compliance	32		112	14	
% compliance	100		91	100	

for all pregnant women and the ELISA confirmation test for those who tested positive. The estimated cost of each laboratory test (Hb, CBC, and platelet count) was about 20 cents.

Though district hospitals already had sufficient laboratory capacity to perform simple tests, such as Hb, CBC and platelet count, it was still necessary to standardize technics and train staff. Laboratory technicians required two days of training, while, at each hospital, counselors involved in the program needed three days of training. Furthermore, the provincial hospital laboratory was upgraded to act as a referral center for the ELISA tests.

Funding for the program comes from central, regional and provincial levels. The National AIDS program provides the HIV tests. The MOPH supplies the ZDV, while national and local funds cover the cost of breastmilk substitutes. Some funding is also mobilized at the community (Tambon) level and by people with AIDS groups (PWAs). For example, while access costs are usually borne by the patients themselves, peer support groups may be able to generate income through their own activities, while upgrading laboratory capacity can only be achieved through the Ministry of Public Health.

LESSONS LEARNED FROM THE PHAYAO EXPERIENCE

Overall, the Phayao experience proved quite successful in terms of acceptance of HIV testing, prophylactic coverage, and compliance to treatment. Factors explaining this high level of acceptance of HIV testing all over Thailand are: the quality of information and counseling provided during the pretest; the commitment of women to comply with an effective intervention that reduces the risk of death for their children; social and peer pressure, as group pretests are usually conducted. As for compliance, interviews of the women who received Z10 showed a 90% rate of full compliance *ie* daily drug intake without interruption. Reasons may include: 1) the treatment schedule requires few visits and laboratory examinations; 2) pregnant women are convinced that it is a safe, effective treatment; and 3) pregnant women are followed by local staff in a familiar setting, obviating the need for contact with an external team. Similarly high compliance with the ZDV treatment has been found

in studies subsequent to ACTG 076, which often leads to a lower rate of transmission, about 5%, than initially found in ACTG 076.

However, the Z10 program also raised some interesting issues. In this approach, the district hospital conducts most of the prevention of mother-to-child transmission (PMCT) activities, while the health center's role is limited to follow-up. Hence, several challenges arise. First, it "recentralizes" part of the provision of antenatal care back to the hospital, where all pregnant women now have to go for first and second antenatal visits. This can increase the travel time and costs involved for some of the women. These costs are even higher for HIV-infected women, who must be followed up regularly at the district hospital level to receive treatment. Second, the program reduces local health center involvement in the PMCT activities. Health center staff have to ensure adequate follow-up of the child and the mother without having been involved in antenatal and delivery care. Follow-up in district hospitals can also sometimes disconnect patients from the local support of community organizations.

Third, though health managers saw the hospital-based approach as a good way to ensure confidentiality, this does not prove very effective in practice. Health center staff might not be informed officially of a pregnant woman's HIV-infected status yet it becomes obvious when a woman goes to the hospital for follow-up antenatal visits and later feeds her newborn formula instead of breastmilk. Furthermore, the lack of formal recognition of a woman's HIV-infected status hampers the health center staff's involvement in the follow-up and counseling. Health workers should be aware that, if only HIV-infected pregnant women attend all prenatal clinics at the hospital, while HIV-uninfected women use community services, this may lead to breach of confidentiality and, consequently, discrimination.

Improvements in confidentiality, quality of follow-up, and efficiency will require adaptation and modification of current approaches. This will include changes in the role of the health center from disease control to support of families in adopting healthy behaviors. Simplifying the intervention to prevent MCT, expanding the health center to provide more testing and counseling services, and increasing acceptance of HIV-infected people in communities will support the necessary prevention

services at the health center level. This would have multiple positive benefits: increased confidentiality; a reduction in transportation costs and traveling time for pregnant women; a continuum of care with provision of integrated care at the subdistrict level, involving health staff and health volunteers; and an increase in local support to HIV-infected women and families by community organizations.

FEASIBILITY OF SCALING UP: THREE CORE PHASES

On the basis of the northern Thailand experience, it is possible to propose a simplified scheme of three key phases for the prevention of mother-to-child transmission, which could provide the foundation for a schedule adapted to local conditions in countries with less developed health systems than Thailand. This schedule is only possible if the first line facilities – the health centers – are upgraded. Table 3 describes the activities as they should occur in terms of quantity, timing and quality of services. The schedule serves as a basis for monitoring and evaluating the activities and identifying key obstacles; thus it needs not be followed rigidly. For example, women who present themselves for antenatal care after the 34th week should be studied, so that steps can be taken to improve the accessibility of the intervention.

Phase I screening of all pregnant women

During the first antenatal visit, all pregnant women are encouraged to go to the health center, the first level of interface between the user and the health system where rapid HIV testing and pretest and posttest counseling are available. The HIV screening test is recommended to all pregnant women during this visit, and if they consent, one blood sample is taken. One or two rapid tests are conducted on this sample. All pregnant women receive a treatment of iron and folic acid for one to three months to prevent anemia. HIV-uninfected women are encouraged to breastfeed exclusively for the first four to six months after the baby is born. They receive information and counseling about the benefits and management of breastfeeding.

During the second contact, a confirmation test is performed for women who tested positive. HIV-

infected women then benefit from extensive qualified counseling. They are informed of the choices available to them and about the steps to follow to reduce the risk of HIV transmission to their baby. They are informed of, and potentially referred to, existing support organizations: peer support groups, non-governmental organizations (NGOs), community organizations, etc. They also receive information about the use of condoms and are requested to encourage their partner to come in for testing. For women at a pregnancy stage of less than 34 weeks gestation, an appointment is scheduled for them during the 34th week. For those in their 34th week or later, treatment can be initiated immediately.

A potential issue for Phase I is the timing of the posttest and the announcement of HIV status. The posttest and counseling are usually conducted during the second visit, following confirmation of the HIV-infected status on a second sample. Another approach would be to conduct the pretest, test, posttest and counseling during the first antenatal visit. Confirmation of status with an additional sample is conducted later during the second antenatal visit, during which the treatment is initiated. This approach is based on the following rationale: 1) the combination of two rapid tests is highly sensitive and specific, and 2) the results of the test could be disclosed immediately to HIV-infected pregnant women. These women would be told that they “probably” or “very likely” are HIV-infected. They would be encouraged to return for a confirmation test and ZDV prophylactic treatment. (Note: The Centers for Disease Control and Prevention now recommend that, in some instances, health care providers release early results of HIV tests rather than have patients wait two weeks while a test to confirm the results is performed. Such early disclosure may be made available to patients at tuberculosis and sexually transmitted disease clinics, to women in labor with no history of prenatal care and uncertain HIV status, and to healthcare workers who have either been stuck by a needle or who are involved in high risk situations (Anonymous, 1998).

This approach has several advantages. First, it reduces the risk of human error in the management of the tests results, especially due to confusion of names or loss of records kept by the pregnant women, which in many countries can account for a much larger error than that attributable to insufficient sensitivity or specificity of the HIV test.

Table 3

Three phases to prevent MCT.

	Required visits	Who	When gestational age	Where	Lab tests and exams	Intervention activities
Phase I screening	1. Identification	all pregnant women	Antenatal visit 1, up to 34 weeks	Health center	- HIV testing (1 or 2 rapid tests)	- group pretesting-counseling - anemia prophylaxis by iron folic acid
	2. Confirmation	all pregnant women	Antenatal visit 2, two weeks later	Health center	- HIV confirmation (1 rapid test) - interview - physical exam	- individual posttest-counseling - consent to undergo ZDV treatment - counseling for HIV-pregnant women - regarding breastfeeding
Phase II ZDV treatment	1. Initiation	HIV+ pregnant women	Antenatal visit 2, as of 34 weeks	Health center	- interview - physical exam - CBC - Platelet count	- individual counseling - consent for treatment - ZDV 600 mg per day for six weeks - testing of partner
	2. Follow-up	HIV + pregnant women	38 weeks	Health center	- interview - physical exam	- individual counseling
	3. Delivery	HIV + pregnant women	Delivery	Health Center	- interview - physical exam	- oral ZDV 300mg every 3 hours from labor until delivery - individual counseling - family planning - promotion of condom use
Phase III Caring	EPI	infants born to HIV + mothers	Delivery	Health center	- physical exam - CBC	- formula feeding - ZDV syrup 8 mg/kg/day for 7 days - BCG
	Integrated Management of Ill child	all infants	according to EPI schedule	Health center	- immunization status check - growth monitoring	- DPT1, DPT2, DPT3 - measles
		all infants	whenever illnesses occur	Health center	- interview - physical exam using symptomatic approach - growth monitoring	- treatment of infections - nutritional counseling
	Nutritional counseling	all infants fed breast milk substitutes	according to EPI schedule	Health center	- interview - physical exam - growth monitoring	- nutritional rehabilitation
	Promotion of condom use	all HIV + mothers				- distribution of condoms
	Family planning	mothers		Health center		- local
	Counseling, psychological support	HIV + mothers		Health facility Community organizations		- counseling - peer support
	Support of caring practices	all infants fed breast milk substitutes	monthly	Home visits	- interview - growth monitoring	- support of adequate feeding and infant caring practices
	Support for family affected by AIDS	all affected by HIV	monthly	Home visits		- nutritional counseling

Second, it increases the feasibility of the intervention in settings where the majority of women attend antenatal clinics only one or two times their pregnancy. Third, it may also reinforce the responsibility of the counselor conducting the pretest and test, who will know he/she will have to speak with the woman about the results of the test and cannot expect another colleague to handle the sensitive situation. With such an approach, the confirmation step of the screening phase could be combined with the initiation of treatment step, reducing the number of required contacts.

Phase II: prophylactic ZDV treatment to prevent MCT

Only HIV-infected women go on to the second phase, which includes three steps: initiation of antenatal treatment, follow-up, and delivery. During the next antenatal visit (second visit at minimum, as of the 34th week), CBC and platelets are assessed. A confirmation test can be conducted, if it has not yet been done. If the hematological indicators are satisfactory (including Hb > 8g/dl and neutrophil count > 750/ml), the treatment of 600 mg of ZDV per day is initiated. Treatment is given for a period of four weeks until the next visit. Counseling is again offered at this stage. Testing and counseling of the partner can be also conducted at this time. In the 38th week of pregnancy, women come back for follow-up, including an interview and physical examination. Counseling is offered for psychological support, along with information about the subsequent steps in the treatment. ZDV treatment is given for the following two weeks.

From the onset of labor to delivery, the pregnant woman receives an intensive treatment of 300 mg of ZDV every three hours. A CBC is conducted for the newborn. When the hematological parameters are satisfactory, the newborn receives 8 mg/kg (2 mg/kg four times a day) of ZDV syrup beginning at the 12th hour of life for seven days. If bottle feeding is a safe alternative, and conditions for follow-up are in place according to Phase III requirements, the mother refrains from breastfeeding. As mothers do not breastfeed exclusively and therefore do not benefit from the contraceptive effect of breastfeeding, an appropriate family planning method has to be recommended. Use of condoms is promoted, especially in the case of discordant couples.

Phase III care: counselling for mothers and caring for infants

This phase aims at providing adequate support for the HIV-infected mother and her infant over the first two years of life of the baby. Mothers will need counseling for social and psychological support, and infants born to HIV+ mothers will require adequate follow-up. Proper care practices have to be ensured at the household level, including sufficient dietary intake, hygiene, and bonding. Infants' nutritional status has to be monitored, and adequate counseling and/or supplementation provided when needed. Infants fed by breastmilk substitutes will probably display a relatively larger number of infections requiring health care. Regular follow-up can be conducted during routine visits for growth monitoring and immunization. However, additional visits will be needed in case of an illness; estimates show a two to threefold increase in the number of infections for breastmilk substitute-fed infants as compared to exclusively breastfed infants in developed countries (Cunningham, 1981), and even more in developing countries (Cunningham, 1984). Thus, this phase should include: counseling, vaccination under the Expanded Program on Immunization (EPI), growth monitoring, nutritional rehabilitation and integrated management of health care for the sick child at the health center level or through outreach strategies; community support to families affected by AIDS; and individual counseling and support for family caring practices, such as formula feeding and management of child illness.

In some countries, such as Thailand, the interface between the health system and households is already strong. A comprehensive network of health centers and community volunteers ensures outreach activities, active tracking and home visits. In other countries, public health systems which have succeeded in increasing childhood immunization and oral rehydration coverage to more than 80% have already developed strategies to increase utilization of services or ensure continuity with active channeling and canvassing. Most of these strategies will be the same to ensure compliance and follow-up of prevention of mother-to-child transmission.

Implementation of the three phases

For children to benefit from PMCT, managers have to ensure that several critical conditions are met. These conditions include not only availability of resources, access to care, acceptability, quality and continuity of services, but also equity and autonomy vis-à-vis those services. These conditions have guided this analysis of PMCT in northern Thailand. Operational strategies for putting those conditions in place are country specific, and indeed specific to local conditions, and should be designed with this in mind. Still, this experience can provide important lessons for other countries embarking on large-scale PMCT implementation:

Availability of key resources is a necessary condition for an operational intervention. An uninterrupted supply of HIV tests, ZDV, and laboratory supplies must be guaranteed. This requires either procurement through the usual channels of drug supply or the establishment of a parallel system; for example, when funding for ZDV is channeled through an organization such as the Red Cross.

Physical accessibility is also an issue. Women have to be able to get the place where testing, counseling and ZDV treatment is offered. In Phayao, antenatal care is routinely conducted at the health center level. Requesting all pregnant women to go to the district hospital outpatient ward for the first and second antenatal visit can increase the difficulty of seeking care, as the amount of travel time and cost of transportation increase.

Initial use of services must also be ensured. When utilization of antenatal care is low, specific strategies to increase it have to be designed. This may include community-based problem solving and monitoring, education or social mobilization. When utilization is high, specific attention should be given to avoid the creation of additional obstacles to use by introducing HIV testing. Due to fear or discriminatory attitudes, women may choose not to attend antenatal clinics anymore.

Continuity of care and compliance is one, if not the most important, issue the system must address successfully. First, women have to return to obtain the result of their HIV test. Then, they have to go back for each of the important subsequent steps. Finally, they have to comply with their treatment. For fulfillment of each of these critical steps, specific strategies can be implemented.

Quality of the services provided is a major element of the final effectiveness of the intervention. Standard procedures have to be designed well and respected. Personnel must be positive, empathetic, and compassionate. Criteria for counseling quality must be met.

Autonomy and self-reliance of recipients is an important goal to pursue. Concurrent with providing adequate services, the health care system should aim at building personal responsibility. In order to ensure compliance and therefore the maximum effectiveness of the intervention, women must be provided with complete, accurate information and be able to decide for themselves whether they wish to participate in the intervention.

Equity of coverage in the intervention is also to be considered. Even if a large proportion of HIV+pregnant women benefit from the intervention and are followed, some groups may remain excluded. The health care system should be able to identify these groups and take action to reach them in an effective way.

Strategies to optimize effectiveness

It is possible to identify some operational problems in fulfilling the conditions influencing final effective coverage. Table 4 describes the operational strategies that can be developed to ensure genuine implementation of the intervention to prevent MCT. This table is based mainly on the Phayao experience, but has been adapted to incorporate potential generic problems, causes and corrective strategies to address the problems encountered.

Affordability of ensuring PMCT

Health care services will require additional resources to fulfill these conditions. Table 5 displays the categories of additional cost linked to the implementation of the intervention. To calculate these costs, three basic indicators are needed: the HIV prevalence rate among pregnant women, the number of births per year and the utilization rate of the intervention. These costs are calculated for Phayao, with a population of 517,000 inhabitants, a crude birth rate of about ten per thousand, and an HIV seroprevalence of 5.1%.

Table 4
Operational strategies for PMCT.

	Problems	Causes	Strategies	Implementation issues
Target population	- problems in identifying HIV + women	- insufficient serosurveillance data	- all HIV + pregnant women	
Availability of resources	- shortages of essential resources	- parallel procurement mechanism for ZDV - high cost of procurement - insufficient lab capacity - insufficient training of lab technician	- procurement of ZDV through international bidding	
Physical access	- low access, women live too far from the facility where the services are offered	- long distances, high cost of transport - change of antenatal care focus from health center to district hospital	- offer screening and treatment in all districts hospitals of the province	- subsidies for transportation? - decentralization of follow-up at health center level?
Initial utilization	- women do not go to antenatal care visits - HIV + women do not go, although others attend - HIV+ pregnant women go, but refuse the HIV test	- acceptability of services is low - fear of discriminatory attitudes - fear of insufficient confidentiality - insufficient quality of pretest	- referral of pregnant women by the health centers to the district hospital for the first visit - reduction of discrimination by ensuring confidentiality, empathy and caring attitude of personnel	- persistent discrimination - reluctance to use services - decentralization of some activities
Continuity	- HIV + women do not go back for posttest - HIV + pregnant women refuse to initiate ZDV treatment - HIV + pregnant women do not complete treatment - newborns do not complete treatment	- inadequate quality of pretest - choice of women to have an abortion - adverse effect of drugs lead to abandonment of treatment	- training of personnel for counseling - fixed appointments for HIV pregnant women - involvement of health center personnel to actively channel women to required visits - support through peer and group counseling during antenatal visits	- insufficient counseling capacity - low integration of professional counseling and peer support
Quality	- HIV+ pregnant women complain about services - standards of quality of counseling are not followed - standard procedures for lab testing are not followed	- no standard procedures for treatment - insufficient development of lab standard procedures - insufficient supervision - lack of monitoring - lack of refresher training	- clear definition of schedule for visits - establishment of standardized protocol for treatment - regular refresher courses for counseling - training of laboratory technicians - supervision of laboratory technicians - nutritional education	- difficulties in designing quality criteria for counseling - insufficient supervision capacity for laboratory technicians - insufficient supervision for counseling
Autonomy	women do not attend peer support meetings	- schedule of meetings are not convenient	- information to all women - informed consent - referral to PWAs groups	- meeting place for PWAs group not available, or far from hospital
Equity	some groups remain untouched, although the majority of women get adequate prophylaxis	- difficulties in identifying vulnerable groups - necessity of designing specific strategies	- subsidy for breastmilk substitutes for one year to low income women - identification of non users by health center staff/ health volunteers - close follow-up of specific groups by health volunteers	- duration of period in which artificial milk is necessary - identification of excluded groups

Table 5

Additional costs to implement intervention for approximately 200 HIV-infected pregnant women.

Stages of production of effective coverage	Categories of additional costs	Cost to treat 60% of HIV + pregnant women (US \$)	Cost to treat 100% of HIV + pregnant women (US \$)	Implementation issues
Availability of resources	- upgrade laboratories - initial training of 7 lab technicians - initial training of personnel for counseling	2,000 140 700	2,000 140 700	
Physical access	- transportation for additional visits to hospital	10	15	- lower cost in decentralizing follow-up at health center level
Initial utilization	- HIV test - other lab tests - zidovudine - breast milk substitutes (BMS) for one year (\$150 per child)	12,000 200 13,000 32,000	14,000 300 16,000 42,000	- possibility of price decrease of ZDV - possibility of lowering cost of BMS by international bidding
Continuity	- active tracking of defaulting women	500	900	
Quality	- technical training for standards - regular refresher courses for counseling - nutritional education	300 500 200	300 500 200	
Autonomy	- information leaflets - information to communities - information activities for women in villages - development of support groups	50 500 1,400 1,400	50 500 1,400 1,400	- many common costs to be shared with other HIV interventions
Equity	- actions to identify excluded women - active channeling of vulnerable women - intensive follow-up of vulnerable women	200 300 200	300 300 200	- duration of period in which formula milk is necessary
Total		65,600	81,205	
Total per capita		0.13	0.16	

No additional cost was linked to the increased number of visits, *ie*, no additional personnel were hired, and no overtime was paid.

The additional cost of implementing this intervention is estimated to be US\$65,000 per year for the Phayao Province. This includes the cost of HIV testing of all pregnant women visiting the health services in the provinces, ZDV for both pregnant women and provision of breastmilk substitutes to all mothers of an HIV-infected child for one year. The cost per HIV-infected women treated is about

US\$309. Some of these costs may be overestimated. For example, the cost of breastmilk substitutes (BMS) for all HIV-infected pregnant women followed has been included. In practice, a large part of these costs are already incurred, as many women in Thailand offer mixed feeding to their infants. Cost of community mobilization might also be lower, as these costs are largely common costs to be

shared among several interventions.

The cost per of life saved can be estimated to be around US\$2,600, on the basis of a transmission rate of 25% and a conservative hypothesis of a reduction in transmission of 50%. Given an average life expectancy of 69 years, this represents a cost per Disability Adjusted Life Years (DALY) of approximately US\$35 to US\$40. In comparison, the total cost per DALY for antenatal and delivery care was estimated at about US\$25 to US\$30 in low-income countries (World Bank, 1993). This cost per DALY does not, however, include the potential additional benefits of testing and counseling a large number of women/couples on reducing HIV transmission through sexual behavioral changes.

This additional cost is equivalent to about 13 cents per capita per year. This represents less than 1% of the public health expenditures of Thailand, around US\$30 per capita per year, and less than 0.1% of overall health expenditures, estimated at US\$97 per capita. Increasing the intervention's coverage to 100% would raise the cost to about 16 cents per capita per year. In comparison, the cost per capita of EPI in low-income countries is estimated to be 5 cents (World Bank, 1993).

Assuming similar unit costs, it is possible to estimate the potential addition cost of this intervention in other contexts. Cost increases linked to treating a larger number of pregnant women can be estimated in calculating the increase in variable costs (mainly tests, drugs and Breast Milk Substitutes) and the increase of some fixed costs to raise utilization, continuity and equity. For example, in a context where the crude birth rate is about 5%, and the seroprevalence among pregnant women is around 10%, the additional cost would increase to 50 cents per capita for coverage of 60% of the women.

REMAINING ISSUES

Other interventions may have to accompany PMCT. Many couples are discordant, so HIV testing and counseling could be offered more systematically to partners. The additional cost of testing partners is very low, as it concerns only the partners of identified HIV+ pregnant women. Beyond activities already conducted, the Phayao Province plans to reinforce community-based problem solving, as well as the education of school children. Implementation of premarital counseling has also

been discussed. Establishing programs to prevent MCT is likely to have additional benefits in terms of prevention of HIV transmission. Pretesting sessions permit the dissemination of information to a large number of women. Finally, the ZDV regimen should not preclude the follow-up of the mother's health, the treatment of her opportunistic infections and the social and psychological support she will need after pregnancy. The prevention of MCT, therefore, has to be an element of a more holistic approach to community care than that which is presently provided in Phayao.

CONCLUSION

The MOPH program in the northern provinces of Thailand had shown the feasibility of offering a simplified regimen of ZDV to HIV-infected pregnant women on a large scale to prevent vertical transmission. The Phayao experience demonstrates in particular that it is possible to integrate this activity into routine mother and child health (MCH) services, with limited external support. Based on this evidence, it is clearly possible to achieve a high level of coverage at a very affordable cost with short course ZDV therapy, leading to a significant reduction in vertical HIV transmission. Analysis of this experience enabled the identification of a simplified approach, consisting of three phases, which can be implemented as an integral part of existing MCH services on a large scale in most countries. Furthermore, the analysis has revealed a series of key conditions to ensure the effectiveness, efficiency and financial viability of these interventions in other settings. As most of these obstacles are common to the three phases of the intervention, but also to many other interventions, support for health care reform strategies will be necessary to accelerate the implementation of the effective prevention of vertical transmission.

Other countries developing operational strategies can greatly benefit from the Thailand experience through inter-country networking and on-site support. This gives rise to the hope that the experiences of ACTG 076 and subsequent studies can soon be translated into large-scale, sustainable interventions, so that, before the end of the century, those who have been most affected by the HIV epidemic - women and their children in developing countries - can benefit from this life saving strategy.

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REFERENCES

- Aleixo LF *et al.* Zidovudine administered to women infected with human immunodeficiency virus type 1 and to their neonates reduces pediatric infection independent of an effect on levels of maternal virus. *J Pediatr* 1997; 130 : 960-14.
- Anonymous. CDC launching new era in testing by giving OK to rapid screening testes. *AIDS Alert* 1998 ;13: 25.
- Blanche S, Mayaux MJ, Mandelbrot L, *et al.* Acceptability and impact of zidovudine prevention on mother to child HIV-1 transmission in France. 4th Conference on Retroviruses and Opportunistic Infection, 1997.
- Centers for Disease Control and Prevention, Atlanta. Administration of zidovudine during late pregnancy and delivery to prevent perinatal transmission - Thailand 1996-1998. *MMWR* 1998 ;47 :151-4.
- Connor EM, Sperling RS, Gelber R, *et al.* Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994;331:1173-80.
- Cunningham AS. Breastfeeding and morbidity in industrialized countries: an update. In: Jelliffe DB, Jelliffe EFP, eds. *Advances in International Maternal and Child Health*, Vol 1. Oxford: Oxford University Press 1981: 1.
- Cunningham AS. Breastfeeding and illness. *Pediatrics* 1984;73:416.
- Fowler MG. Update: transmission of HIV-1 from mother to child. *Curr Opin Obstet Gynecol* 1997: 9 : 343-8.
- Kreiss J. Breastfeeding and vertical transmission of HIV-1. *Acta Paediatr* 1997;421 (suppl):113-7.
- Mofenson LM. Mother-child HIV-1 transmission : Timing and determinants. *Obstet Gynecol Clin North Am* 1997;24:759-84.
- Phanuphak P. Ethical issues in studies in Thailand of the vertical transmission of HIV. *N Engl J Med* 1998;338:834-5.
- Prescott N, Periens J. Affordability and cost-effectiveness of antiretrovirals in Thailand. 1996.
- Simonds RJ, *et al.* Impact of zidovudine use on risk and risk factors for perinatal transmission of HIV. Perinatal AIDS Collaborative Transmission Studies. *AIDS* 1998;12:301-8.
- Sirisanthana V. Perinatal HIV-1 transmission rate in Thailand. Second International Symposium on Pediatric AIDS in Thailand. Chiang Mai, Thailand. March 24-26, 1997.
- Thomas P, Singh T, Bornschlegel K, *et al.* Use of ZDV to prevent perinatal HIV in New York City. 4th Conference on Retroviruses and Opportunistic Infections, 1994.
- World Bank. Investing in health. World Development Report. Washington DC, 1993.