Am. J. Trop. Med. Hyg., 69(1), 2003, pp. 8–13

THE USE OF SHORT-COURSE ZIDOVUDINE TO PREVENT PERINATAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS IN RURAL KENYA

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Abstract. To determine the feasibility of using short-course zidovudine (ZDV) to prevent mother-to-child transmission of human immunodeficiency virus (HIV) in a breastfeeding population in a rural area in Kenya, pregnant mothers attending clinics in seven health centers in western Kenya between 1996 and 1998 were requested to volunteer for participation in this study. The HIV-infected mothers were given a daily dose of 400 mg of ZDV starting at 36 weeks of gestation and another 300 mg every three hours intrapartum. After delivery, mothers and their children were followed-up and clinically monitored every 3–4 months for two years, and child and mother mortality rates were analyzed. Of the 825 mothers who consented, 216 (26.2%) were infected with HIV. Of those infected, 51 (23.6%) took the full prescribed dose, 69 (31.9%) took only the prenatal dose, and the remaining 96 (44.4%) did not take any dose. Failure to take ZDV was attributed mainly to delivery occurring earlier than expected, while non-compliance to the intrapartum dose was due to mothers giving birth at home and fear of traditional birth attendants. By the end of the second year, 75 HIV-exposed children (34.7%) and 33 HIV-infected mothers (15.3%) had died. The HIV-free survival of children at 24 months was significantly associated with mother survival ($P < 0.001$) and prenatal ZDV compliance ($P < 0.003$). Our findings suggest that implementation of programs for prevention of mother-to-child transmission of HIV in rural areas of Africa need to consider the various socioeconomic and cultural barriers that may prevent successful uptake of antiretroviral prophylaxes. Similarly, the rapid disease progression in mothers may eliminate the increase in child survival due to ZDV prophylaxis.

INTRODUCTION

Antiretroviral prophylactic therapies to prevent mother-to-child transmission of human immunodeficiency virus (HIV) came into use after the successful study done by the Pediatric AIDS Clinical Trial Group 076.[1] In this trial, which defines the current U.S, regimen,[2] zidovudine (ZDV) was given to mothers beginning at 14–34 weeks of pregnancy, intravenously during labor, and for six weeks to infants and resulted in a 68% reduction in mother-to-child transmission of HIV. Due to the high cost and complexity of the regimen, recommendations were made for shorter and simplified regimens to be tested in developing countries. A trial in Thailand showed a 50% reduction in mother-to-child transmission of HIV in non-breastfeeding women who took an exclusive oral ZDV regimen twice a day beginning at 36-weeks gestation and every three hours during labor.[3] An identical regimen on a breastfeeding population in two areas in west Africa had an efficacy of 37% and 38%, respectively, after 3–6 months.[4,5] In the perinatal transmission trial (PETRA) conducted in eastern and southern countries in Africa with various rates of caesarian births and breastfeeding to assess a combination of ZDV and lamivudine, the most efficient regimen (group A, from 36 weeks of gestation to the end of the first week postpartum for mother and child) had an efficacy of 65% at 18 months.[6] In the ultra-short nevirapine HIVNET 012 trial in Uganda, one dose given to the mother during labor combined with one dose given to the neonate within 72 hours of birth reduced three-month transmission by 47%.[7] These studies have formed the basis of recommendations for the use of short-course antiretroviral therapies for prevention of mother–to-child transmission of HIV in developing countries.[8–10]

However, data on the use of antiretroviral therapies for prevention of HIV transmission from mothers to their children are either from developed countries[1] or from urban areas of developing countries.[3–7] Countries experiencing the greatest burden of the HIV epidemic are in sub-Saharan Africa, where two-thirds of the population live in rural areas.[10]

In a preliminary report, we have shown the benefits of short-course ZDV in reducing child mortality in HIV-exposed children in Western Kenya.[11] However, there is a need for information to guide future implementation programs of antiretroviral prophylaxes in rural areas. Additionally, there has been a growing concern to link prophylaxis against mother-to-child transmission of HIV in developing countries with prolonging the lives of parents.[12,13] However, there are limited data on the role of maternal health on child survival in populations taking part in antiretroviral prophylactic studies.

We report here the findings of our attempt to implement the use of short-course ZDV to prevent mother-to-child transmission of HIV in a breastfeeding population in rural western Kenya and the observations we made over a follow-up period of two years.

MATERIALS AND METHODS

Between October and December 1996 and August and October 1998, antenatal clinic attendees in seven rural health centers in western Kenya were requested to volunteer for the program. Recruitment began by dissemination information on HIV/acquired immunodeficiency syndrome (AIDS) through village public meetings (*barazas*), re-training of field and health center staff, and equipping of antenatal and maternity clinics. The criteria for recruitment of volunteers were being married, having a gestational period of 18–22 weeks by the last menstrual period, an absence of life-threatening disease, and hemoglobin levels > 7 g/dL. Enrollment was done after counseling on HIV testing, use of ZDV, and risk of breastfeeding.

Blood samples were tested for antibodies to HIV using a particle agglutination test (Serodia, Fujirebio, Inc., Tokyo, Japan) and an enzyme-linked immunosorbent assay (Behringwerke, Marburg, Germany). Discordant test results were confirmed by Western blotting (Diagnostic Biotech, Singapore). Volunteers were considered HIV infected if they were antibody positive in two of the tests. The HIV-infected mothers were given a 100-mg tablet of ZDV four times a day starting at 36 weeks of gestation, followed by 300-mg dose at the start of labor and every three hours intrapartum as per a modified regimen according to the recommendations of the Centers for Disease Control.[2] Mothers were given a two-week supply of ZDV, and during each weekly follow-up they were examined, remaining pills were counted, and inquiries were made regarding symptoms and any missed doses. To compensate for possible deliveries occurring before arrival at the health center, mothers were given an intrapartum pack in addition to the two-week dose. At delivery, midwives at the health center administered the drug orally to the volunteers. Diagnosis and treatment of other infectious diseases were carried out as per the existing guidelines of the Kenya Ministry of Health.

After delivery, all mothers and their children irrespective of their HIV status or compliance with ZDV treatment were followed-up at the local health centers every 3–4 months for physical examination, treatment, and recording of morbidity data. To compensate for the cost of commutation to the health centers, volunteers were reimbursed with transport funds whenever they visited the clinics for their appointments. Failure to attend a routine clinic visit resulted in default tracing with field workers visiting the volunteers at home. The death of a child or mother was reported directly to the counselors at the clinic or to the field workers during home visits. In the cases where mothers and their children had moved away from the area, relatives provided information on whether child or mother was alive or dead. All HIV-exposed children surviving after 18 months of follow-up were bled and serologically tested for HIV as described earlier.

Where possible, outcomes were statistically analyzed by use of the Statistical Program for Social Sciences, version 10 (SPSS, Inc., Chicago, IL). Cumulative proportion curves for child mortality were constructed using the Kaplan-Meier method. For the analysis of mortality and survival rates, twins were treated as independent births.

Informed consent was obtained from all volunteers and the program received ethical clearance from the Kenya Medical Research Institute and the National Ethical Review Board.

RESULTS

Characteristics of the volunteers. Of 836 antenatal clinic attendees who were interviewed, 828 agreed to participate in the study, but three were not included after they were found not to be pregnant. The mean age of the volunteers were 23.2 years, with an ethnic distribution of Luo (604), Luyhia (199), and others (22). Six-hundred sixteen mothers were involved in a monogamous marriage, while 209 had legal co-wives (polygamous). Of those involved in polygamy, 46 (22%) had been widowed but remarried a married relative of her deceased husband (wife inheritance), while of those in the monogamous relationship, eight (1.3%) were a result of wife inheritance.

Prevalence of HIV and prenatal use of ZDV. Of 825 volunteers 216 (26.2%) were HIV positive. Irrespective of ethnic group, the highest prevalence of HIV was observed among 54 mothers who had been inherited (44.4%, 24 of 54; $P < 0.0003$) suggesting that the cause of death of their first husbands was probably due to HIV/AIDS. When these mothers were excluded from the analysis, no significant difference was observed in HIV prevalence between those practicing monogamous and polygamous relationships (147 of 608, 24.2% and 45 of 163, 27.6%; $P = 0.42$).

At the time of ZDV use, 96 HIV-infected mothers (44.4%) could not take the prophylaxis (non-ZDV group). Eighteen of them had moved from the area, mainly to urban areas to join their husbands, and four refused to comply. Table 1 shows a comparison between the remaining 74 mothers in the non-ZDV group and the 120 mothers who took ZDV (ZDV group). A significant difference was observed in the gestation period and mother's level of education between the two groups. The mean weeks of gestation in the mothers who did not take ZDV was 36.7 weeks, the time when the regimen was scheduled to begin. Among the ZDV group, there was variation in the duration of ZDV prophylaxis before delivery (median time = 32.5 days, range = 6.5–56.5 days).

As for education level, HIV-infected mothers who had attained more than six years of formal education had a significantly increased chance of using ZDV than their counterparts with a shorter period of formal education (79.3% and 54.4.1%, respectively; $P < 0.01$). Mother's age, ethnic group, and type of marriage had no significant influence on prenatal ZDV use.

Delivery outcome. There were 829 live births. Of them, 807 were single births 22 were twin births. Five second-trimester spontaneous abortions, one fetal death *in utero*, and one maternal death before labor were reported. Of the 829 live births, 507 (61.2%) were delivered at home under the care of traditional birth attendants. Of the 216 live births of HIV-infected mothers, 122 (56.5%) were delivered at home. None of the 69 mothers in the ZDV group who delivered at home took the prescribed intrapartum dose. The majority of them (59, 84.3%) reported that they could not take the intrapartum dose because of the presence of traditional birth attendants during delivery, and nine (12.8%) did not remember to take the dose. One mother shared the drugs with her husband and had none left at delivery. All HIV-infected mothers opted to breastfeed their infants.

TABLE 1

Comparison of factors influencing prenatal use of zidovudine (ZDV) among mothers infected with human immunodeficiency virus

Category	ZDV group (n = 120)	Non-ZDV group (n = 74)	*p*
Age (years)	23.8	22.1	0.531
Gestation weeks at delivery	39.5	36.7	0.002
Formal educational level			
≤6	74	62	0.008
>6	46	12	
Type of marriage			
Monogamous	77	46	0.839
Polygamous	42	28	
Ethnic group			
Luo	104	64	0.856
Luyhia	16	10	

Child mortality and HIV-free survival. Of the 829 children, 156 (18.8%) had died by the age of 24 months (Figure 1). Mortality among children born to HIV-infected mothers was significantly higher than those born to HIV-uninfected mothers (75 of 216, 34.7% and 81 of 613, 13.2%; $P < 0.01$). By 24 months of age, 42 of the 141 HIV-exposed children who were alive were unavailable for confirmation of HIV status; 18 children had moved from the area and mothers of the remaining 24 children refused to have them tested. When the surviving children whose status was unknown were excluded from the analysis, the overall HIV-free survival at 24 months was 47.1% (82 of 174). Expectedly, children of mothers who complied with prenatal ZDV prophylaxis had a significantly higher HIV-free survival rate (59.2%, 61 of 103) than children of HIV-infected mothers who did not take any ZDV (29.6%, 21 of 71) ($P < 0.0002$)

The probability of death of the children is shown in Figure 2. Mortality curves of the children in the ZDV group and those of HIV-uninfected mothers showed a similar trend during the first 12 months of life (16 of 120, 13.3% and 65 of 613, 10.6%; $P = 0.48$). However, they showed a significantly different trend by 24 months of age (34 of 120, 28.8% and 81 of 613, 13.2%; $P < 0.0005$).

Maternal mortality. By 24 months after delivery, 33 HIV-infected mothers in the program had died (Figure 1). Twenty-nine mothers died at the local district hospitals with a clinical diagnosis of one or a combination of the following: tuberculosis, pneumonia, malaria, wasting syndrome, chronic diarrhea, and cryptococcal meningitis, while one mother died at childbirth. No precise cause of death was available for three mothers who had moved from the study area. Most (21 of 33) of the maternal deaths occurred during the second year of follow-up. No significant association was observed among ZDV use, place of delivery, and maternal death. However, infant death and ages of the mothers were significantly associated with maternal mortality (Table 2). Of the mothers who died, 13 had infants still alive, of whom three were HIV infected. Fifteen mothers died after the death of their children, three died before the dead of their children, and two died in the same month as their children.

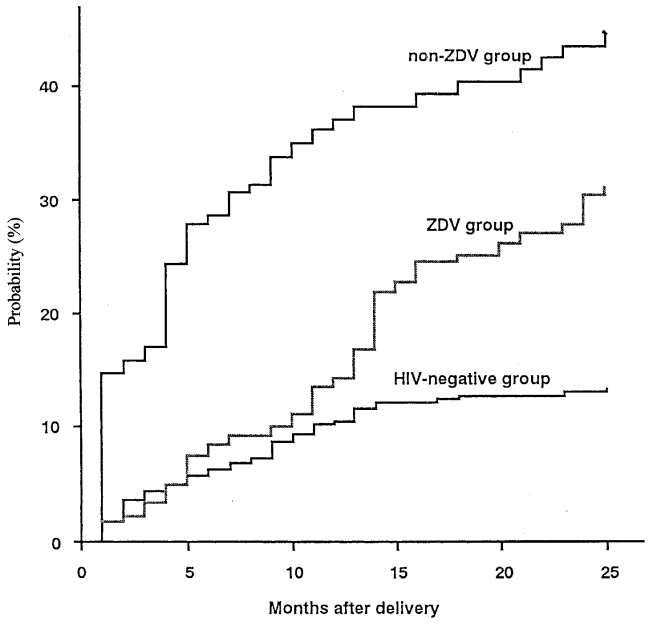

FIGURE 2. Probability of death of children born to human immunodeficiency virus (HIV)–infected mothers and to HIV-positive mothers with or without treatment with zidovudine (ZDV).

DISCUSSION

Our main objective in this program was to attempt to incorporate an effectively proven intervention strategy against mother-to-child transmission of HIV into clinical practice in a rural African environment. The seven health centers that we chose for the program were located away from the nearest urban centers and situated along the shores of Lake Victoria, an area notorious for high prevalence rates of HIV in

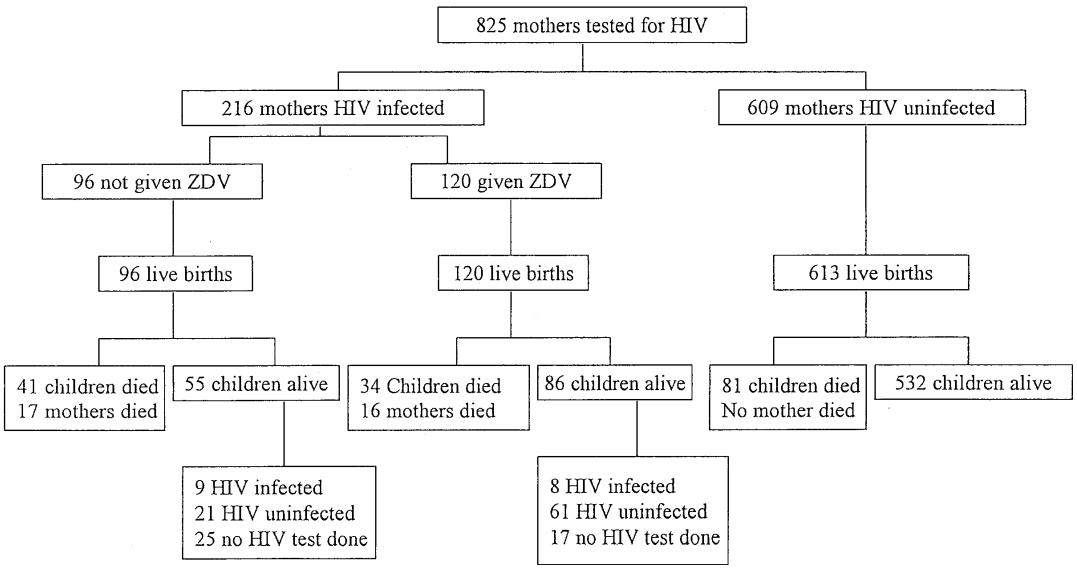

FIGURE 1. Summary outcome of a two-year follow-up study of children and mothers in the treatment program. HIV = human immunodeficiency virus; ZDV = zidovudine.

TABLE 2
Observed risk factors for mortality among mothers infected with human immunodeficiency virus*

	Alive (n = 183)	Dead (n = 33)	p
Prenatal ZDV use			
No	79	17	0.485
Yes	104	16	
Age (years)			
≤25	146	18	0.004
>25	37	15	
Status of index child			
Dead	55	20	0.001
Alive	128	13	
Place of delivery			
Home	103	19	0.957
Other	80	14	

* ZDV = zidovudine.

Kenya.[14,15] We observed an encouraging trend in the very high acceptance rate by mothers to undergo HIV testing and to return for their HIV test results. The high return rate may have been due to our use of field workers who visited them in the event of default or lateness, and our provision of reimbursements to aid in transportation to the health facility during appointments. In an attempt to protect confidentiality among the volunteers as much as possible in such a village environment, we chose to follow-up all mothers who consented to have an HIV test irrespective of their HIV status.

In our earlier study,[11] we reported the significant benefits on child survival by mothers in rural environments who used ZDV, confirming that, similar to mothers in urban environments, ZDV is effective in reducing mother-to-child transmission of HIV and thus child mortality. However, we encountered several obstacles that would act against successful implementation of short-course ZDV in rural Kenya. The inability of correct estimation of gestation period resulted in a high rate of non-adherence to prescribed prophylaxis. The use of the last menstruation period (LMP) is a common method for calculation of expected date of delivery (EDD) among antenatal care settings in developing countries. Reliable information on the actual date of LMP in Africa has been reported to be influenced by several factors, including mother's level of education.[16] In our study, we also observed a concurrent association of gestation period, mother's level of formal education, and ZDV use, confirming that low literacy levels adversely affect provision of correct LMP dates.[16] The use of alternative systems to estimate EDD, such as ultrasonography,[17] may be required in rural areas to support gestational dating by LMP and to avoid the high rate of non-adherence to ZDV. In absence of such facilities, provision of short-course ZDV would need to be started earlier in pregnancy.

We observed an inability of mothers who delivered at home to take the intrapartum prophylaxis. Most of them reported that the presence of traditional birth attendants discouraged them from taking the dose for fear of exposing their HIV status. Although suggestions have been made for traditional birth attendants to oversee the provision of antiretroviral prophylaxes to HIV-infected women who deliver at home,[18,19] it was apparent that traditional birth attendants contributed substantially to non-compliance of ZDV prophylaxis in our study. However, since home births will continue to be the preferred method in rural areas of sub Saharan Africa[18,20] and traditional birth attendants will always be needed, the use of alternative dosing regimens, such as non-intrapartum prophylaxes,[21] which have a lesser chance of jeopardizing the confidentiality of a mother's HIV status, needs to be further investigated. However, it should be noted that a positive effect of ZDV on child survival was observed even in absence of intrapartum dosing.[11]

The increase in mortality of children in the ZDV group after the first year of follow-up is consistent with trends noted on mortality of children born to breastfeeding HIV-infected mothers on antiretroviral prophylaxis in Africa. The PETRA study team reported diminished benefits of antiretroviral prophylaxis on the survival of children after 18 months of follow-up.[6] Similarly, the west Africa study noted a waning of the protective effect of ZDV on child survival after eight months.[22] These studies attributed this phenomena to postnatal infections arising from breastfeeding. Since cumulative transmission risks of HIV through breastfeeding has been shown to increase with time,[23] we postulate that effect of postnatal infections may have eliminated the increase in child survival due to ZDV prophylaxis in our study.

To our knowledge, the mortality rate at 24 months of age among children exposed to HIV in our study was the highest among reported studies on mother-to-child transmission of HIV and antiretroviral prophylaxis. Even among mothers who complied with prenatal use of ZDV, the effect on child survival was not only less than that in other ZDV-adherent populations in cities in west Africa,[24] but was also less than that of children born to mothers who did not use any antiretroviral prophylaxis in urban Kenya.[25] One possible explanation for the disparity is the higher maternal mortality observed in our study compared with the reported mortality rates of HIV-infected breastfeeding mothers in the urban Kenya study.[26] The poorer background health status in rural areas arising from limited food supply, poor sanitation, and high prevalence of other infectious diseases[27] may have significantly contributed to the fast progression to AIDS in the HIV-infected mothers. The strong association observed between the deaths of mothers and children supports the view that mothers who infect their children are often at an advanced stage of infection.[19,26,28]

The second possible explanation is the role played by malaria infection, a malady that is controlled in most urban areas of Africa. The location in which we carried out the program not only had a high prevalence of HIV, but also a high background child mortality due mainly to malaria.[29,30] We observed during our clinical evaluation periods that the majority of volunteers presented themselves with *Plasmodium falciparum* malaria. Mortality rates in infants born to mothers with both HIV-1 and placental malaria have been reported to be higher than those born to mothers with HIV alone.[31] Similarly, HIV viral load has been shown to be higher in HIV-infected blood donors with malaria than in those without malaria.[32] Thus, co-infection with *P. falciparum* malaria may have raised HIV viral load in mothers in our study, resulting in an increased risk of perinatal and postnatal transmission of HIV.

In conclusion, our findings suggest that design and implementation of programs for prevention of mother-to-child transmission of HIV in rural areas of Africa need to consider the various socioeconomic and cultural barriers that may pre-

vent successful uptake of antiretroviral prophylaxes. Similarly, the negative effect on child survival observed due to mothers' fast progression to AIDS would require supplementary interventions that reduce maternal morbidity and mortality.

Received October 14, 2002. Accepted for publication February 12, 2003.

Acknowledgments: We thank all the mothers and children who volunteered for the program, and all participants of the Kenya Medical Research Institute–Japan International Cooperation Agency Project for their services. Special thanks are given to Dr. Takahashi Kurimura and Dr. Davy Koech for their technical advice. We dedicate this work to all volunteers who died in the course of our study and to our colleagues James Njoroge and Judith Aketch, who passed away during their service to this project. This work is published with the permission of the Director of the Kenya Medical Research Institute.

Financial support: This work was supported by Japan International Cooperation Agency and in part by the Toyota Foundation (grant no. D01-A-057), and International Scientific Research Program (grant no. 14256005) from Monbu-Kagakusho (Japan Ministry of Education and Science).

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