Maternal Self-Medication and Provision of Nevirapine to Newborns by Women in Rakai, Uganda

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Summary: To assess the effectiveness of maternal self-administration of nevirapine for prevention of mother-to-child transmission (MTCT) of HIV, we conducted a program to provide maternal and newborn doses of nevirapine to pregnant women in rural Uganda. Women provided blood for HIV testing and were offered voluntary counseling and testing (VCT) during annual community HIV surveys. HIV-positive women who accepted VCT were offered nevirapine tablets and syrup. Blood samples were collected postpartum from women and their babies. Infants were tested for HIV by polymerase chain reaction (PCR), and a subsample of maternal and infant blood was assayed for nevirapine. Among the 981 women tested for HIV, 900 (91.7%) accepted VCT, of whom 105 (11.7%) were HIV-positive. Ninety-three women accepted nevirapine, of whom 81 (87.1%) were followed postpartum; 75 (92.6%) reported receipt of the drug, and 69 reported taking the tablets (85.2%). There were 81 liveborn babies (3 sets of twins), and 67 (84.8%) received the syrup. In a subsample of 25 mothers reporting receipt of the drug, nevirapine was detected in 22 (88.0%) and 24 (96.0%) babies tested. PCR of 67 infant blood samples identified 5 HIV-positive (MTCT rate = 7.5%, 95% confidence interval [CI]: 0.3%–16.6%). Mothers can administer nevirapine to themselves and their newborns and can achieve low rates of perinatal HIV infection.

Key Words: HIV/AIDS, mother-to-child HIV transmission, nevirapine, voluntary counseling and testing, Uganda

(*J Acquir Immune Defic Syndr* 2005;39:121–124)

Received for publication March 3, 2004; accepted October 12, 2004.

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Funded by the following grants: Elisabeth Glaser Pediatric AIDS Foundation Call to Action grant 26.5-PS-22108, Gates Institute for Population and Reproductive Health 117, Johns Hopkins Population Center grant P30HD06268, International Fogarty Center grant D43TW01508, and Walter Reed Medical Institute grant HMJF 5686.

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Surveillance of women attending antenatal clinics in Uganda has shown substantial declines in HIV prevalence over the past decade.[1] Nevertheless, in 2000, median HIV prevalence rates were approximately 11% in major urban areas and 5% in rural areas.[2] Approximately 85% of the Ugandan population resides in rural areas, and most mother-to-child transmission (MTCT) of HIV is likely to occur among rural mothers. The provision of nevirapine to women at onset of labor and to newborns within 72 hours of birth has been shown to reduce MTCT by 47%.[3] Services to provide nevirapine are only available in limited hospital settings, however. Although 91% of rural women report receiving antenatal care,[4] most deliver at home. In addition, voluntary HIV counseling and testing (VCT) and provision of MTCT prophylaxis are not available in most rural health facilities.

Current Uganda Ministry of Health policy recommends that women receive the maternal nevirapine dose during pregnancy to ensure that the medication is available for self-administration at onset of labor. Women are not provided with the newborn dose. Instead, they are encouraged to deliver at health facilities where health personnel administer the pediatric nevirapine syrup. Only 20% to 32% of rural mothers report delivering at a health facility,[4,5] however, and recent data from Uganda suggest that many mothers fail to return for the pediatric dose within the recommended 72 hours postpartum (Catherine Wilfert, MD, personal communication, 2003). Thus, provision of nevirapine syrup via obstetric services does not reach many of those in need.

To assess whether home-based newborn medication could improve coverage, we initiated provision of the maternal and newborn nevirapine dose to pregnant women enrolled in a rural community cohort study. Although the cohort is in a research setting, the innovations used to provide services to this rural population provide a "proof of concept" applicable to other rural regions.

METHODS

The Rakai Health Sciences Program (formerly called the Rakai Project) conducts annual home-based surveillance surveys on HIV, health, and behaviors in a cohort of more than 12,000 adults aged 15 to 49 years who reside in 56 villages in Rakai District, southwestern Uganda.[6,7] From October 2001 to February 2003, midwives located and screened 1070 pregnant

women, of whom 981 (91.7%) provided a blood sample for HIV testing. HIV was determined by 2 enzyme immunoassays (EIAs; Vironostika HIV-1, Organon Teknika, Charlotte, NC; Cambridge Biotech, Worcester, MA), and discordant EIA results or new seroconversions were confirmed by Western blot analysis (HIV-1 Western blot; Bio-Merieux-Vitek, St. Louis, MO). Rapid testing is not used during survey rounds because VCT cannot be provided at the time blood samples are collected.

For the home-based nevirapine study, project midwife-counselors were notified of pregnancies by the cohort survey team. The midwives visited women in their homes to verify pregnancy, to provide antenatal care and VCT, and, where indicated, to offer nevirapine. Pregnancy was diagnosed by history and examination, and in case of uncertainty, was confirmed by urinary human chorionic gonadotropin (hCG).

The 981 women who provided a blood sample for HIV testing were all provided with HIV education and were strongly encouraged to get their HIV results and counseling (VCT); 900 (91.7%) agreed to VCT. In this article, we report results on nevirapine uptake in the group of women who accepted VCT. HIV-positive women who accepted VCT were offered nevirapine tablets and syrup and instructed on drug storage and administration. If the pregnancy was at least 28 weeks of gestation, the women received a nevirapine tablet (200 mg) and pediatric syrup at the time of the midwife's visit. If the pregnancy was less than 28 weeks of gestation, women were advised to obtain the nevirapine after 28 weeks of pregnancy from depots maintained by 18 trained Rakai Health Sciences Program resident HIV counselors, who were readily accessible to all study participants. The rationale for this procedure was that women at 28 or more weeks of pregnancy would have nevirapine tablets available even if they experienced preterm labor. The medications were not immediately provided to women at less than 28 weeks of gestation to reduce the risk that the drugs could be lost or used by others if retained in the home for a prolonged period. All women were instructed to take the tablets at onset of labor. In case of false labor, they were advised to return to the resident HIV counselors for further supplies. Women were encouraged to deliver at government health facilities if at all possible.

The newborn syrup was repackaged for home-based administration. Nevirapine is routinely distributed in 240-mL containers, but a single dose for a typical newborn weighing 3000 g is 0.6 mL. We reformulated the syrup in 0.6-mL doses that were provided to mothers in a 3-mL amber, ultraviolet-opaque, capped syringe (Baxa Corp., Englewood, CO). Reformulation was carried out under a sterile hood. Before program initiation, the stability and sterility of the repackaged syrup for up to 6 months was assessed in the Research Pharmacy Department, Johns Hopkins Medical Institutions (Vivian Rexroad, PharmD, personal communication, 2003). Mothers were instructed to provide the newborn syrup within 72 hours of birth. In cases of multiple births, mothers were instructed to provide the syrup to the firstborn and to obtain an additional dose from the community depot for babies born second or later. Confidential storage of nevirapine would be difficult in the typical rural Rakai house. The nevirapine tablet and syrup were wrapped in aluminum foil and packaged in an opaque polythene bag. To avoid potential stigmatization of HIV-positive mothers and their babies, HIV-negative women were offered a syringe containing multivitamin syrup packed in an identical polythene bag. Both HIV-positive and HIV-negative women were offered multivitamin tablets. Thus, possession of tablets and syrup was not a marker of HIV infection. The women themselves were informed of which medication(s) they received, however.

Project midwives were notified of each birth and interviewed women in their homes within the first week postpartum to provide care and to ascertain compliance with the maternal and neonate medications. A comparable number of HIV-negative women were also followed and offered home-based postpartum care to avoid stigmatization of HIV-positive women and their babies. Maternal and newborn blood samples were obtained from HIV-positive mothers and their newborns to assess nevirapine levels. Nevirapine assays were performed at the Johns Hopkins Hospital Pharmacology Department using high performance liquid chromatography (HPLC) with a reverse phase column. The lower limit of detection was <25 ng/mL.

HIV-infected women and their babies were visited again at 4 to 6 weeks postpartum to obtain an infant heel stick blood sample for HIV testing by reverse transcriptase polymerase chain reaction (RT-PCR; Roche Amplicor 1.5; lower limit of detection of 400 viral copies/mL).

The project protocol was approved by the Institutional Review Board of the Uganda Virus Research Institute and the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health.

RESULTS

Of 981 women who provided blood (Table 1), 113 (11.5%) were HIV-positive. Among these 981 women, 900 (91.7%) accepted VCT, and 105 (11.7%) of this latter group were HIV-positive. Acceptance of VCT was similar among HIV-positive and HIV-negative women (92.9% and 91.9%, respectively). Twelve HIV-positive women who accepted VCT did not receive nevirapine because the drug or the test results were not available in time for their delivery. The remaining 93 HIV-positive women who received VCT were offered and accepted nevirapine. Thirty-nine women were $\geq$28 weeks of gestation and were provided with nevirapine immediately; another 54 women were given a referral slip and asked to procure nevirapine from resident HIV counselors once their pregnancies reached 28 weeks of gestation.

Of the 93 HIV-positive women who were offered nevirapine, 81 women (87.1%) were followed up postpartum, and three quarters were visited within 3 days of birth (75.3%). The 81 women reported 84 births, including 3 sets of twins. At the time of the postpartum interview, 79 (94.0%) of the 84 newborns were alive. Three of the 5 deaths were reported as stillbirths, and 2 were deaths of liveborn babies on the day of birth. Breast-feeding was initiated in 95.1% of liveborn babies.

Among the 81 HIV-positive women followed up postpartum, 75 (92.6%) reported receipt of nevirapine and 69 (85.2%) reported taking the maternal dose. Mothers reported that they provided the pediatric dose to 68 (84.0%) of the 81 liveborn babies (or 67 [84.8%] of 79 surviving newborns),

TABLE 1. Coverage of VCT and Nevirapine Utilization of HIV-Positive Women in Rakai District, Uganda

	Number	Percent
Screening/VCT and nevirapine provision		
Pregnant women screened and providing a blood sample	981	100.0
Accepted VCT among those screened	900	91.7
HIV-positive women among those accepting VCT	105	11.7
HIV-positive women delivered before NVP provided	12	1.3
HIV-positive women offered NVP	93	88.6
Accepted NVP among those offered treatment	93	100
Postpartum follow-up		
Women		
Women followed up postpartum among those offered NVP	81	100
Received NVP among women followed up postpartum	75	92.6
Took NVP among those offered NVP	69	85.2
Infants		
Liveborn infants identified at postpartum follow-up	81	100
Liveborn infants who received NVP*	68	84.0
Infants surviving at postpartum follow-up	79	100
Surviving infants who received NVP†	67	84.8
Infants followed up at 4–6 weeks postpartum and MTCT		
Infants surviving at 4–6 weeks postpartum follow-up	74	100
Infants with HIV-1 PCR results	67	90.5
HIV-positive infants among those with PCR results	5	7.5

*Sixty-eight of 81 eligible infants received NVP (2 sets of twins).
†Sixty-seven of 79 eligible infants received NVP (2 sets of twins).
NVP indicates nevirapine.

including 2 sets of twins. Approximately half of the women (52.2%) who took nevirapine reported self-medication with the tablets within 2 hours after the onset of labor, and 87% reported self-medication before rupture of membranes. Ninety-six percent (65 of 68) of newborns were reported to have been given nevirapine syrup on the day of delivery, and all but 1 of the newborns received their dose within 72 hours of birth. All newborns whose mothers attempted to administer the syrup ingested the entire dose.

The rates of reported symptoms were comparable between HIV-positive women who took nevirapine and 55 HIV-negative women followed postpartum. Among the 69 mothers who took nevirapine, 4.4% reported rash, 23.2% reported nausea and/or vomiting, and 2.9% reported jaundice. Among 55 HIV-negative women, 0% reported rash, 27.3% reported nausea and/or vomiting, and 3.6% reported jaundice. Mothers reported rash, nausea and/or vomiting, and jaundice in 2.9% of 68 newborns who consumed nevirapine syrup compared with 2.4% of 42 newborns born to HIV-negative women who gave their babies multivitamin syrup.

Serum from 25 women and newborns reported to have taken nevirapine was assayed, and the drug was detected in 22 women (88.0%) and 24 newborns (96.0%).

Seventy-four surviving infants born to HIV-positive mothers were followed up at 4 to 6 weeks postpartum. Most visits (88%) occurred at 28 days postpartum (range: 27–39 days), and all but 1 infant were still being breast-fed. Blood specimens were collected from 69 (93.2%) of 74 infants followed. Infant serum was assayed by RT-PCR for HIV-1 detection in 67 infants (1 sample had an insufficient quantity for analysis). Five infants were HIV-positive, resulting in an MTCT rate of 7.5% (95% confidence interval [CI]: 0.3%–16.6%).

DISCUSSION

This program of maternal self-medication with nevirapine tablets at onset of labor and maternal provision of nevirapine syrup to newborns resulted in a low rate of MTCT comparable to those observed in clinical trials.[3] The MTCT rate in this study population was 19.4% before initiation of the nevirapine program,[7] suggesting that this strategy may reduce MTCT by approximately 60% compared with historic levels. Two other programs observed MTCT rates of 11.2% and 13.0%, also suggesting the effectiveness of the drug in service settings.[8,9] Another program utilizing self-medication reported an MTCT rate of 11.9% at 6 weeks but an 18.1% rate at 14 weeks, however.[10]

In addition, high rates of VCT and nevirapine acceptance resulted in high service coverage in this rural population. The population of the community cohort study is atypical of rural Africa, however, in that more than 90% of residents have consented to provide blood for HIV testing and most also accept their HIV results and counseling. In Mombasa, Kenya, where prevention of perinatal MTCT used similar procedures for maternal self-medication, service coverage was low, largely because women failed to return for HIV test results and only 37.2% of 285 of HIV-infected

mothers who received nevirapine took the nevirapine dose provided.[11] Among 105 HIV-positive Rakai women who received their test results, 75 (71.4%) reported receipt of nevirapine and 69 (65.7%) subsequently reported taking the drug. Another study in Lusaka, Zambia, offered nevirapine services without requiring VCT (universal provision) in 1 clinic and after receiving VCT (targeted provision) in a second clinic. Nonadherence to medication was reported in 39% of women under the universal strategy and in 26% of women under the targeted strategy.[12] Thus, failure to take nevirapine was more frequent among women who were unaware of their HIV status (universal provision), but even among women who knew they were HIV-positive, nonadherence was higher than that observed in the present study (26% vs. ~15%).

The Rakai program used the HIVNET 012 nevirapine regimen, but mothers self-medicated and administered the drug to their newborns postpartum. Compliance with the maternal and newborn dose was high, and most mothers took their dose and administered a dose to their newborns within the recommended time limits. In fact, nearly all mothers reported giving their newborns the nevirapine dose within 24 hours of delivery. Guay et al[3] reported that the median time to dosing postpartum was 24 to 30 hours in their trial. Whether earlier provision of the newborn dose might have an impact on the effectiveness of the HIVNET 012 regimen on MTCT is still unknown.

Challenges of conducting the program in Rakai include the underserviced nature of the setting, where most deliveries occur in the home. Pregnant women participating in the present study were already enrolled in a longitudinal cohort; free VCT provided by community-based counselors was widely available and accepted; and midwife-counselors, backed up by the resident HIV counselors, may have enhanced nevirapine acceptance and compliance rates. Unfortunately, our inability to provide rapid testing led to some missed opportunities for provision of nevirapine to eligible women. Nevertheless, despite these programmatic challenges and differences from other African populations, the Rakai experience represents a "proof of concept" and suggests mechanisms by which prevention of MTCT may be provided in other settings. Mothers can be empowered to self-medicate themselves and their newborns and to reduce perinatal HIV infection. In circumstances where access to or utilization of supervised delivery care is poor, as is the case in most rural areas of sub-Saharan Africa, there is an urgent need to replicate this study in a more conventional service setting.

In conclusion, mothers can provide nevirapine to themselves and their newborns and can achieve low rates of perinatal HIV infection.

ACKNOWLEDGMENTS

The authors thank the women and newborns who participated in this project, the midwife-counselors who carried out project activities, Drs. Terri Parsons and Vivian Rexroad of the Research Pharmacy Department at the Johns Hopkins Medical Institutions for conducting the nevirapine assays, and Drs. Susan Fiscus and Constance Ducar for conducting the HIV PCR assay of infant samples.

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