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Predictors of Nonadherence to Single-Dose Nevirapine Therapy for the Prevention of Mother-to-Child HIV Transmission

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Abstract

Background—Adequate adherence is required for prevention of mother-to-child transmission of HIV (pMTCT) programs to be effective. We investigated predictors and extent of nonadherence to single-dose nevirapine.

Methods—Data on nevirapine intake and possible predictors were collected among 760 HIV-positive women with liveborn babies enrolled in a study in Lusaka, Zambia.

Results—Most (94%) women took nevirapine before delivery, and most (91%) newborns received it soon after delivery. Maternal nonadherence was associated with home births (odds ratio [OR]: 3.2; 95% confidence interval [CI]: 1.3 to 7.4), no high school education (OR: 2.4; 95% CI: 1.1 to 5.3), and low newborn birth weight (OR: 4.6; 95% CI: 1.3 to 20.1). Disclosure of HIV status and couples counseling was only associated with adherence among home births. Failure to administer nevirapine to the newborn was associated with birth at the tertiary hospital (OR: 7.2; 95% CI: 3.7 to 13.8), lower 5-minute Apgar scores (OR: 0.5; 95% CI: 0.4 to 0.7), and neonatal death (OR: 5.8; 95% CI: 2.0 to 16.3).

Conclusions—Excellent adherence to single-dose nevirapine for pMTCT can be achieved. Nonadherence seems to be affected by place of birth and by poor health status of the newborn. Procedures to ensure that viable yet ill neonates receive nevirapine should be part of clinical protocols and training within pMTCT programs.

Keywords

perinatal HIV transmission; nevirapine; adherence; prevention

In a landmark study, a 50% reduction in mother-to-child transmission (MTCT) of HIV was reported for a single dose of nevirapine administered to the mother, followed by a single dose

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administered to the newborn.¹ In an 18-month follow-up of the same cohort, rates of MTCT remained low.² The efficacy of this simple intervention is encouraging for resource-poor settings with a high HIV seroprevalence, because the relatively low cost and simplicity of the intervention make high population coverage under operational conditions a potentially achievable objective. In addition to high coverage, adequate adherence to the regimen is essential for population effectiveness.

Few studies have investigated correlates of nonadherence to prevention of mother-to-child transmission of HIV (pMTCT) interventions. In a Kenyan study, adherence to single-dose nevirapine was higher than to a short-course zidovudine regimen (87% vs. 41%; $P < 0.001$) and adherence was associated with partner notification and partner willingness to go for HIV testing.³ In a separate report from the same group, couples counseling was associated with high uptake of nevirapine,⁴ although we did not find this association among 9409 women offered pMTCT services in Zambia.⁵ A qualitative report from Zambia identified fear of partner abuse or desertion and stigma as potential reasons for nonadherence to nevirapine.⁶ It is unclear whether these studies adequately distinguished predictors of nonadherence to the drug regimen from factors associated with participation in pMTCT programs in general, specifically with agreement to be tested for HIV.

Here, we investigated predictors of nonadherence to the maternal and newborn components of single-dose nevirapine within a cohort of HIV-positive women in Lusaka, Zambia who had tested for HIV during their pregnancy and agreed to take nevirapine for pMTCT.

METHODS

A pMTCT program was established in Lusaka at 2 clinics that provide antenatal and maternity services. Voluntary counseling and HIV testing were offered to all women antenatally, and all HIV-positive women were offered single-dose nevirapine. Active community outreach to male partners was implemented, and couples counseling was made available and promoted. Nurse midwives dispensed a 200-mg nevirapine tablet to consenting women at the time of posttest counseling and instructed women to take it at the onset of labor. When women presented at the labor and delivery ward, midwives on all shifts were trained to ask whether the women had remembered the tablet; if they had not, a replacement was given. Before discharge, babies born to HIV-positive women were administered a 0.6-mL dose of nevirapine suspension. It was incumbent on women to bring their patient-held record to identify themselves when admitted for delivery. Home deliveries were unanticipated, and no newborn nevirapine suspension was provided to be given at home.

Here, we report on a subset of HIV-positive women who enrolled into the Zambia Exclusive Breastfeeding Study (ZEBS), a clinical trial of short exclusive breast-feeding.⁷ These women consented to HIV testing, accepted nevirapine as an intervention for pMTCT during posttest counseling (median = 26 weeks of gestation, interquartile range: 21–32 weeks), met inclusion criteria, and agreed to study requirements. More than 11,000 women were counseled at the 2 clinics over the time frame: uptake of HIV testing was 84%, HIV seroprevalence was 27%, and 25% of HIV-positive women were eligible and consented to study enrollment. For ZEBS enrollees, the midwives on duty in the labor and delivery ward were trained to record information about nevirapine adherence and obstetric and newborn details onto study forms that were checked daily. If mothers delivered at another site, study staff visited the site to collect as much information as possible from records. Health care providers at the tertiary referral hospital where most of the off-site deliveries occurred also received training in the pMTCT protocol and were aware of the study. Women were counseled that if they delivered at home, they should bring their baby to the clinic as soon as possible to receive nevirapine and bacillus Calmette-Guérin (BCG) vaccine. Nevirapine adherence and other clinical data were collected

at this visit. At enrollment during pregnancy, maternal blood was tested for CD4 cell counts (FACSCount; Becton Dickinson, San Jose, CA). Detailed social and clinical data were collected, including disclosure of HIV status and whether antenatal couples counseling had occurred.

This analysis includes 760 HIV-positive women enrolled in the ZEBS who delivered liveborn babies between May 2001 and August 2003. Descriptive analyses first considered the extent of nonadherence to maternal and newborn doses. Nonadherence was defined as lack of consumption of nevirapine regardless of timing. Women who had not taken nevirapine before admission but who ingested a replacement after admission for the delivery were included as adherent. Next, associations between nonadherence, the adequacy of the timing of nevirapine consumption, and characteristics of the mother-child pairs were investigated. For crude analyses, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All independent variables that were statistically significant (Wald χ^2 , $P < 0.05$) in crude analyses were included in multiple logistic regression models to calculate adjusted ORs. Statistical analyses were conducted using SAS Version 9.0 (SAS Institute, Cary, NC).

RESULTS

Descriptive Characteristics

Of the 760 HIV-positive women with liveborn babies, 74.1% gave birth at the clinic where they received antenatal care, 10.1% delivered at home, and 14.5% delivered at the referral tertiary care hospital in Lusaka. More than half (52.8%) had disclosed their HIV status to their partners. Socioeconomic parameters reflected the disadvantaged communities where the clinics are located (Table 1).

Most women (93.6%) took nevirapine before delivery, and almost all (98.4%) took it within 48 hours of delivery. More than 90% of newborns were given nevirapine after delivery, and 98.3% of neonates received it within the protocol-specified 72 hours (89.5% received it within 8 hours of delivery). Full adherence to the maternal and newborn components within the required time frames was achieved among 84.9% of mother-child pairs (Table 2). Of note, maternal intake tended to be close to delivery. Almost half (44.8%) of women took nevirapine ≤ 3 hours before delivery, and 16% took it ≤ 1 hour before delivery. If adequate timing is redefined to include only mothers who took nevirapine > 1 hour before delivery (but < 48 hours before delivery), maternal adherence is reduced to 78%.

Predictors of Nonadherence

Maternal nonadherence (no nevirapine consumption) was associated with home births (OR = 3.15, 95% CI: 1.34 to 7.38), no high school education (OR = 2.35, 95% CI: 1.05 to 5.25), and low newborn birth weight (OR = 4.57, 95% CI: 1.04 to 20.14). Among those who took nevirapine, home birth (OR = 2.09, 95% CI: 1.08 to 4.08) and low birth weight (OR = 2.33, 95% CI: 1.35 to 4.02) were associated with taking the drug too close (< 1 hour) to delivery. Failure to administer nevirapine to the newborn was significantly associated with birth at the tertiary hospital (OR = 7.17, 95% CI: 3.73 to 13.78), lower 5-minute Apgar scores (OR = 0.47, 95% CI: 0.35 to 0.63), and neonatal death (OR = 5.76, 95% CI: 2.03 to 16.32) (Table 3). Other factors investigated, including disclosure of HIV status to one's partner, couple HIV testing, gestational age at nevirapine dispensing, maternal age, parity, history of death of a previous child, and low CD4 cell count; socioeconomic markers, including food security, source of water, and maternal and paternal employment, were not associated with maternal or newborn nonadherence.

Predictors of nonadherence were examined stratified by site of delivery. Among clinic deliveries ($n = 563$), the results were similar to those of the overall study population. An

exception was the association between maternal nonadherence and low birth weight. Within clinic deliveries, maternal non-adherence was only increased when birth weight was <1500 g. Maternal nonadherence was similar if birth weight was in the range of 1500 to 2500 g compared with higher birth weights.

Among home deliveries (n = 76), lack of disclosure of HIV status to one's partner emerged as a significant predictor of maternal nonadherence. Maternal nonadherence occurred among 6.1% of those who had disclosed compared with 25.6% of those who had not disclosed (OR = 5.33, 95% CI: 1.09 to 26.01). Approximately half (48.8%) of women who had disclosed had originally been counseled as part of a couple in the antenatal clinic (25.7% of the study population had been through couples counseling). All women who had received couples counseling and delivered at home took nevirapine, whereas maternal nonadherence occurred among 21% of women counseled individually. This is in contrast to findings among clinic deliveries, where maternal nonadherence was not associated with disclosure or couples counseling. Among home deliveries, there was a weak nonsignificant trend toward greater adherence to newborn nevirapine among those who had disclosed (18.2%) compared with those who had not disclosed (25.6%). For home deliveries, the newborn dose required that the baby be brought to the clinic. For deliveries in the hospital or other locations (n = 117), results were similar to those of the overall analysis.

DISCUSSION

Nonadherence to single-dose nevirapine for pMTCT was low in this study population of HIV-positive women and their newborns, although nonadherence increased when defined to include adequately timed intake by mother and child. These findings are comparable to those of other studies,^{1,3} but nonadherence may be considerably higher in operational settings. Our study population may not be generalizable because it included only women who had already agreed to take nevirapine and were self-selected for compliance by being willing to enroll in a prospective study.

Of concern, however, were the marked differences in nonadherence by place of delivery. Maternal and newborn nonadherence was 4 times higher with home births than with delivery at the clinic where antenatal care had taken place, and births at the tertiary hospital were associated with significantly less chance that the newborn would receive nevirapine. Other studies have alluded to problems associated with home deliveries with reference to uptake of pMTCT interventions.³ We identify, in addition, barriers for pMTCT programs associated with referral of high-risk pregnancies to tertiary level health care facilities other than those where antenatal care (and, usually, pMTCT programs) are based. Tertiary hospital staff may be somewhat neglected with respect to pMTCT training and support, and maternal or newborn complications prompting referral to the tertiary center may interfere with implementation of routine protocols.

Related to this, we observed that the health of the newborn affected its access to nevirapine. Newborns with lower Apgar scores and who were at risk for subsequent neonatal death were significantly less likely to receive nevirapine. This may not be attributable to the newborn's health status per se but possibly to health care interventions, consultations, or referrals that may disrupt routine care in the nursery. Similar issues may explain the association between birth at the tertiary hospital and infant nonadherence. Whereas operational difficulties may interfere with nevirapine access for these high-risk neonates, prophylaxis is particularly important for these survivors, who are the most vulnerable to HIV transmission.⁸ Markers of newborn health were also, although less strongly, associated with maternal nonadherence. In part, this may be accounted for by preterm deliveries (onset of unexpected labor), because the association in the

clinic deliveries was confined to newborns with a very low birth weight (<1500 g), who are also almost all preterm.

Past studies of adherence to pMTCT interventions have focused on factors relating to maternal adherence, with an implicit assumption that newborn adherence would be similar. Here, we observed that predictors of maternal and newborn nonadherence were somewhat different. For example, maternal education was associated with maternal but not newborn non-adherence. Our results suggest that treatment of the neonate is primarily associated with the functioning of health service systems and is less dependent on the motivation or characteristics of the mother.

Successful pMTCT prophylaxis depends not only on adherence but on adequate timing of drug dosing. Maternal ingestion of nevirapine 1 hour or less before delivery may result in subtherapeutic maternal blood levels (<100 ng/mL), which may increase the likelihood of transmission.⁹ Although adherence was high, more than 15% of women ingested nevirapine late in labor and may not have obtained the full benefit of prophylaxis. Grand multiparous women (6 or more deliveries), who are at increased risk of very rapid labor, may benefit from being counseled to take nevirapine at the first onset of labor.

It was surprising that disclosure of HIV status, male participation in HIV testing, and socioeconomic status were not predictive of adherence in our study population. Other studies have attributed lack of uptake to women's reluctance to notify their partners and fear of spousal interference.^{10,11} One study of nevirapine specifically noted the importance of partner disclosure.³ In our study, even though only half of the women had disclosed their HIV status to their partner, high levels of adherence to nevirapine were reported. Disclosure and partner involvement may be more relevant for longer anti-retroviral regimens that cannot be hidden as easily. We observed that nondisclosure was significantly associated with maternal nonadherence among the subgroup who delivered at home. This seems plausible, because the presence of the woman's partner in the home could negatively influence her decision to take the medication if she had not disclosed her status.

There are some limitations of this study worth noting. In the subgroups of home and hospital deliveries, small numbers place limits on our power to detect associations. The measurement of nonadherence relied on accurate recording of the attending midwife, who, if the mother did not ingest nevirapine in front of her, in turn, relied on adequate reporting by the mother. If a large number of women who failed to take nevirapine falsely claimed otherwise, this could affect our ability to detect associations and result in an underestimation of nonadherence. Given that the women were enrolled in a clinical study, higher levels of motivation as well as better access to health care and information about HIV may set this sample apart from the rest of the population in the area.

The population effectiveness of pMTCT programs is affected by coverage (the proportion of the population with access to the services), uptake (the proportion accepting counseling and HIV testing), and adherence (the proportion actually taking the drugs). Our data suggest that in this cascade, the simplicity of single-dose nevirapine allows nonadherence to play only a minor role in reducing the population effectiveness of pMTCT programs. We identified poor neonatal health and place of delivery as influential factors in determining whether nevirapine was administered. Programs should review clinical protocols and referral patterns of high-risk neonates within their communities to ensure that health service systems beyond the routine care of healthy term newborns do not interfere to deny nevirapine to these babies. Procedures relating to the administration of nevirapine to a viable yet ill neonate should be developed and incorporated into pMTCT protocols and training to ensure that all newborns are given the opportunity to benefit from an intervention that can reduce the likelihood of HIV transmission.

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TABLE 1
 Characteristics of 760 HIV-Positive Women and Their Liveborn Babies in Lusaka, Zambia

Subject Characteristics	n	%
Place of delivery		
Clinic	563	74.1
Home	77	10.1
Tertiary/referral hospital	110	14.5
Other	10	1.3
Infant birth weight (g)		
<1500	14	1.9
1500–2500	125	16.9
>2500	602	81.2
Mother's age (y)		
<20	76	10.0
20–29	512	67.4
30–39	162	21.3
>40	10	1.3
Parity		
0	121	15.9
1	187	24.6
2	171	22.5
3+	281	37.0
Prior newborn/child mortality	293	46.1
Maternal CD4 count (cells/mL)		
<200	175	23.0
200–350	232	30.5
>350	353	46.5
Disclosed status to partner	401	52.8
Married	623	83.7
High school education		
Yes (>grade 8)	325	42.8
No (≤grade 8)	435	57.2
Source of drinking water		
In home	51	6.7
On property	103	13.6
Shared/community	606	79.7
Days last month with no food		
None	574	75.5
1 or more	186	24.5
Baby's father employed	659	86.7
Baby's mother employed	231	30.4

TABLE 2

Extent of Nonadherence to Maternal and Newborn Single-Dose Nevirapine Among 760 HIV-Positive Women and Their Liveborn Babies in Lusaka, Zambia

Maternal and Infant Adherence	n	%
Maternal nevirapine intake		
Yes	711	93.6
No	45	5.9
Don't know	4	0.5
Maternal dosing before delivery (h) *		
0–1	98	15.6
2–3	184	29.2
4–8	199	31.6
9–12	64	10.2
13–24	56	8.9
25–48	19	3.0
>48	10	1.6
Infant nevirapine intake		
Yes	688	90.5
No	63	8.3
Don't know	9	1.2
Infant dosing after birth (h)		
<8	614	89.2
9–24	37	5.4
24–48	14	2.0
48–72	9	1.3
>72	12	1.7
Don't know	2	0.3
Maternal and infant nevirapine intake		
Yes	656	86.3
No	94	12.4
Either or both unknown	10	1.3
Maternal and infant nevirapine intake and timing adequate †		
Yes	645	84.9
No	115	15.1

* Data were missing for 81 records.

† Timing was defined as adequate if the maternal dose was taken within 48 hours of delivery and the infant dose was taken within 72 hours of delivery.

TABLE 3

Predictors of Nonadherence to the Maternal and Newborn Dose of Nevirapine Among 760 HIV-Positive Mothers and Their Babies

Variable	N	n	%	Crude Analysis		Adjusted Analysis*	
				OR	95% CI	OR	95% CI
Maternal nevirapine nonadherence							
Place of delivery							
Clinic	563	25	4.4				
Home	76	13	17.1				
Hospital or other	117	7	6.0	4.44	(2.16 to 9.12)	3.15	(1.34 to 7.38)
High school education (≥ 8 y)				1.37	(0.58 to 3.25)		
Yes	285	8	2.8				
No	471	37	7.9	2.95	(1.35 to 6.43)	2.35	(1.05 to 5.25)
Birth weight (g)							
>1500	14	3	21.4				
1500–2500	125	14	11.2	6.55	(1.71 to 25.01)	4.57	(1.04 to 20.14)
>2500	600	24	4.0	3.03	(1.60 to 6.03)	2.68	(1.29 to 5.57)
Neonatal death <28 d							
Yes	29	5	17.2				
No	727	40	5.5	3.58	(1.30 to 9.87)	2.37	(0.75 to 7.49)
Infant nevirapine nonadherence							
Place of delivery							
Clinic	563	20	3.6				
Home	76	17	22.4				
Hospital or other	112	26	23.2	7.82	(3.88 to 15.76)	1.33	(0.38 to 4.67)
Birth weight (g)				8.21	(4.39 to 15.35)	7.17	(3.73 to 13.78)
<1500	14	5	35.7				
1500–2500	121	9	7.4	8.95	(2.85 to 28.14)	2.55	(0.63 to 10.31)
>2500	599	35	5.8	1.3	(0.61 to 2.77)	0.75	(0.32 to 1.76)
Apgar score at 5 min [†]	684			0.47	(0.35 to 0.63)	—	—
Neonatal death <28 d							
Yes	27	9	33.3				
No	724	54	7.5	6.2	(2.66 to 14.47)	5.76	(2.03 to 16.32)

* Adjusted odds ratios are calculated from multivariable logistic regression models, including all the variables shown.

[†] As a continuous variable in the crude analysis (ie, higher 5-minute Apgar scores are associated with less nonadherence) but not included in the multivariable model because of missing data.