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H. W. REYNOLDS, O. GACHUNO, J. KAYITA, M. A. HAYS and J. RAKWAR,

ABSTRACT

Objective: **To test whether a single take home dose of infant nevirapine increased infant uptake without decreasing institutional deliveries.**
Design: **Cluster randomized post-test only study with control group.**
Setting: **Ten hospitals in urban areas of Coast, Rift Valley, and Western provinces, Kenya.**
Participants: **Pregnant women with HIV, 18 years and older, and at least 32 weeks gestation recruited during antenatal care and followed up at home approximately one week after delivery.**
Intervention: **In the intervention group, women were given a single infant's dose of nevirapine to take home prior to delivery. In the control group, no changes were made to the standard of care.**
Main outcome measures**: Mothers' reports of infant uptake of nevirapine and place of delivery.**
Results: **Uptake of the infant's nevirapine dose was high, 94% in the intervention group and 88% in the control group (p=0.096). Among women who delivered at home, uptake was higher significantly among infants whose mothers got the take home dose compared to women who did not get the dose (93% vs. 53%, p<0.01). The intervention did not influence place of delivery. Providers were positive about the take home dose concept; difficulties were attributed to HIV-related stigma.**
Conclusions: **Making take home infant nevirapine available, either as a single dose administered within 72 hours of birth or as part of a more complex six week postnatal regimen, will increase infant uptake especially among women who deliver at home without affecting place of delivery.**

INTRODUCTION

In 2008 45% of pregnant women living with HIV and 31% of infants born to women living with HIV received antiretroviral (ARV) drugs to prevent transmission of the virus from mother to child in sub-Saharan Africa (1). Although large gains in reaching HIV positive pregnant women with ARVs have been documented in the last few years, many countries still face major challenges. Of the 20 countries estimated to have the largest number of women needing ARVs to reduce perinatal HIV transmission, 12 countries currently reach less than 50% of the pregnant women estimated to need ARVs (1).

Efficacy of the ARV used to prevent perinatal HIV transmission depends on the drug regimen. Single dose nevirapine offers about a 50% reduction in risk (2). Since 2006, countries have been shifting to more efficacious regimens with combinations of two or three ARV drugs (1). Of pregnant women who tested HIV positive and received drugs in 2008, 31% received the single dose nevirapine regimen, while the rest received ARVs for their own health, more efficacious regimens, or the regimen was "uncategorised".

The World Health Organization (WHO) guidelines on the use of ARV drugs for treating pregnant women and preventing HIV infection in infants prioritise lifelong antiretroviral therapy (ART) to treat HIV in women (3). If women are not eligible for ART, then pre and peri-partum interventions should maximise the likelihood of reducing vertical HIV transmission and postpartum interventions

should facilitate safe breastfeeding. Although there has been a move away from single dose nevirapine for the mother's regimen, the recommendations strengthen the role of nevirapine for the infant (3). Daily administration of nevirapine to the infant is recommended from birth to six weeks for infants born to HIV-infected women receiving ART for their own health or until one week after all exposure to breastmilk for infants born to women not in need of ART. For nonbreastfeeding infants, the recommendations are nevirapine or zidovudine (AZT) until six weeks of age (3).

As a single dose regimen to mother and newborn, studies have demonstrated that nevirapine is an efficacious, low-cost, and practical prophylactic regimen for reducing mother-to-child transmission of HIV-1 in resource-limited settings (2,4). The single dose regimen includes a 200mg tablet of nevirapine taken by the mother at the onset of labour and a 0.6ml dose of oral suspension nevirapine syrup for the infant within 72 hours of delivery (2).

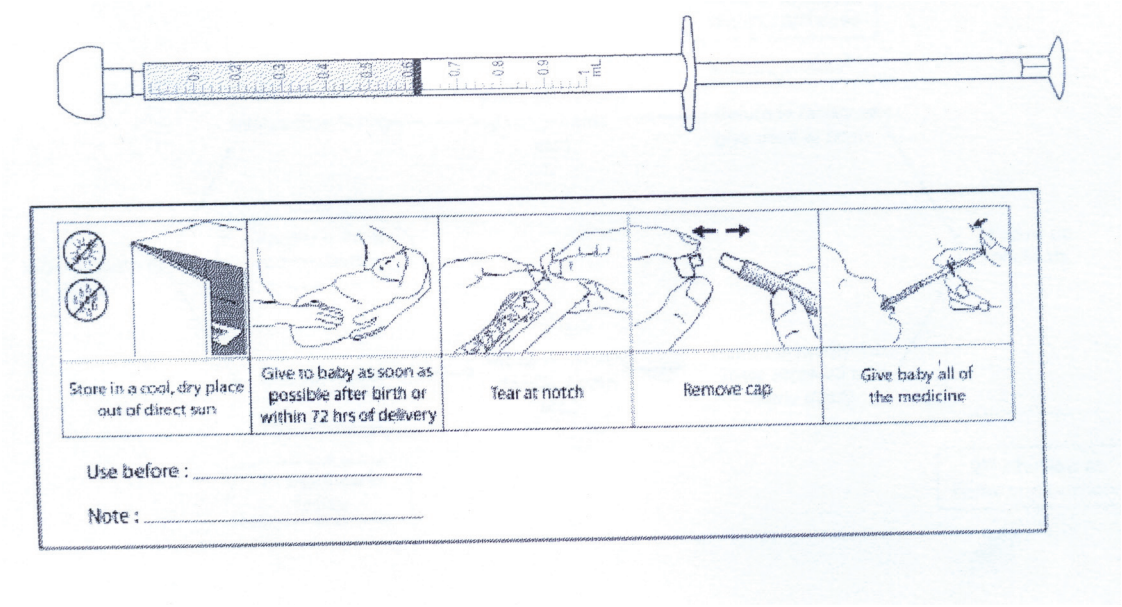
In Kenya in 2008, 56% of pregnant women living with HIV received ARVs for perinatal HIV prevention compared with 39% of their infants, and at the time of this study (2006) those proportions were slightly lower. Standard practice for administration of singledose nevirapine requires HIV positive women to deliver in health facilities or to return to the health facility within 72 hours after delivery so that the infant can get his/her dose of nevirapine. In many contexts, particularly rural locations, many births occur outside the health facility, which is the main barrier to uptake of the infant nevirapine dose (5). In Kenya, the prevalence of home births is 29% for urban women and 66% for rural women (6).

Allowing women to take the infant's nevirapine dose home from antenatal care (ANC), as is already done with the mother's dose, could increase infant's uptake. A study from Rakai, Uganda demonstrated the "proof of concept" of the infant take home dose (7). However, this study relied on at-home HIV testing and counseling and nevirapine provision by midwives which may not be particularly cost-effective, feasible, or even practiced outside of the Rakai context. Packaging of the infant nevirapine dose is important, since the paediatric formulation is viscous in nature and the nevirapine must be distributed into syringe dispensers. Nevirapine and the syringe dispenser are available at no-cost to participants of Boehringer Ingelheim (BI) Donations Program (Baxa Corporation, Denver, CO) (8).

To improve the packaging of the infant's nevirapine dose to facilitate taking it home, BI, the United States Agency for International Development (USAlb), and Program for Appropriate Technology in Health (PATH) developed a self sealing foil pouch to protect the filled Baxa Exacta-Med syringes dispenser (9). The nevirapine infant dose pouch's label provides pictorial instructions and expiry information (Figure 1). To help standardize the practice, PATH also developed a provider training manual (10). A pilot introduction of the pouch in Kenya found high acceptability by both providers and mothers, and mothers thought the pouch was easy to use (11). The nevirapine infantdose pouch has recently been made available at no-cost as part of the BI Prevention of Mother to Child Transmission (PMTCT) Donations Program (http://www.pmtctdonations.Ofg/en/products/pouch.aspx).

Figure 1

1 ml Baxa Exacta-Med Dispenser filled to .06 ml and English label for the NVP infant-dose pouch



One of the concerns about implementing this intervention was its potential effect on current delivery practices. With the introduction of the syringe, nevirapine infant dose pouch, instructions and training material, we conducted a study to examine whether offering the infant dose to take home increases uptake without decreasing institutional deliveries As a secondary objective, this study assessed providers' perspectives on the feasibility and acceptability of the take home dose.

MATERIALS AND METHODS

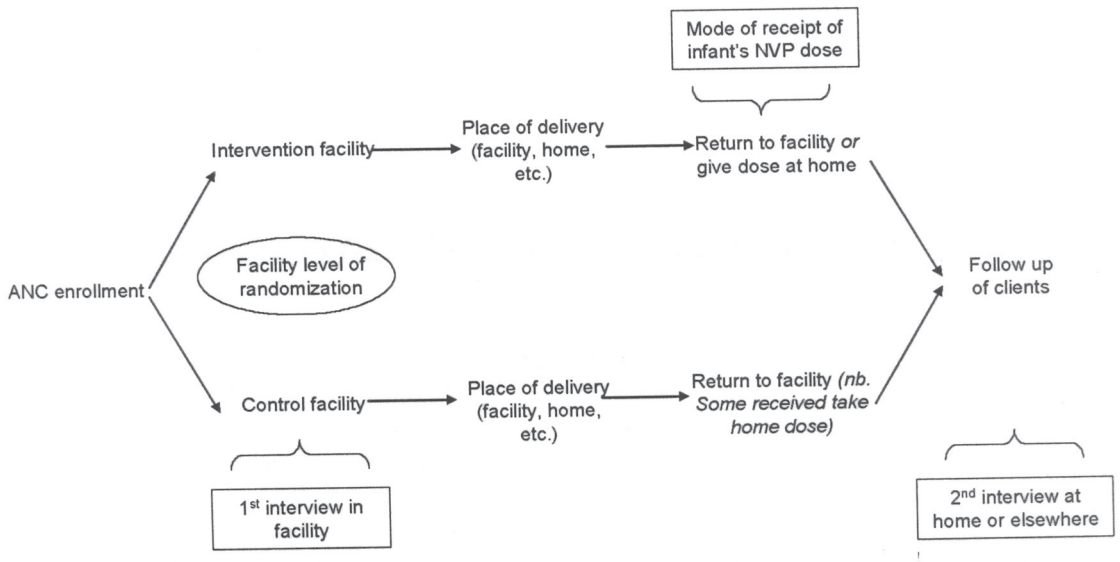
The study design was a cluster randomized post-test only with control group (Figure 2). Ten health facilities with high PMTCT client loads were matched on the following characteristics: province, type of facility, ANC client load, number of PMTCT trained providers, time since PMTCT implementation, and HIV testing uptake rate. Pairs of facilities were randomly assigned to intervention or control group. Facilities are all hospitals and are located in Coast, Rift Valley, and Western provinces of Kenya. Facilities with high client loads were chosen to keep research costs reasonable.

In the intervention facilities, PMTCT providers received training on how to repackage nevirapine syrup into the syringes, to seal the syringe with the pouch, to calculate the expiry date, and to counsel women on how to use the infant's dose. Women in the intervention sites were given explicit instructions on how to store the repackaged nevirapine, to read the expiry dates, to open the foil, and to administer the drug. They were instructed that if they did not deliver in a health facility or were discharged before administration of nevirapine to the baby, they were to administer nevirapine to the baby within the first 72 hours. No changes were made in the administration of the woman's nevi rapine dose; women still received their dose during ANC according to the national protocol.

In the control group, no changes were made to the standard of care. Women received their nevirapine dose during ANC as per the facility's protocol and were counseled to deliver in the health facility or to return within 72 hours of delivery so that their newborns could receive their nevirapine dose.

In an effort to standardize the care across sites, providers in both the intervention and control groups used a flow chart job aid that reviewed the process

Figure 2
Study design



In-use stability studies conducted at BI suggest that the infant nevirapine dose should be used within two months after filling the Baxa Exacta-Med syringe and putting it in the pouch (8), and this was the standard that was used in this study. In other words, to be eligible to receive the infant's dose to take home and to participate in the study, women had to be at least 32 weeks gestation (with an assumed estimated date of delivery of approximately 40 weeks).

of how to offer optout HIV testing and post-HIV test counseling including key points to remember during counseling. The intervention facilities differed only in that their flow chart contained information on how to offer the infant's dose. Women in all the facilities were encouraged to deliver in health facilities.

Antenatal mothers aged 18 years and above who were HIV infected, had attained a gestation

of 32 weeks, and gave signed informed consent to participate were enrolled in the study. Women participated in two interviews. The first interview took place at the time of recruitment into the study after their ANC visit. This interview contained information about how to contact the mother for the follow up interview, her estimated date of delivery, socio-demographic information, pregnancy and contraceptive use history and intentions, use of health services, history of HIV testing, HIV status disclosure, knowledge of when to take nevirapine and reports of providers' counseling on nevi rapine.

The second interview took place at the participant's home (or another location at the participant's suggestion) approximately one week after women delivered their infants. It investigated the factors associated with nevirapine administration, perspectives on administering nevirapine, HIV status disclosure, partners' approval of nevirapine, health services use and intention, and infant's nevirapine dose uptake. The details of nevirapine administration, including who administered it to the infant, where, and when, were based on mother's reports during the second interview.

Interviews with providers sought their perspectives of the feasibility and acceptability of the practice. Interviews were conducted near the end of participant recruitment so that providers in the training group had enough time to gain experience dispensing the infant's dose.

Sample size calculations determined that a sample of 190 women attending the 10 different facilities was needed to detect a 66% increase in uptake of the infant nevirapine dose (from 36% to 60%). This sample size assumed 80% power, a false positive rate of 5% (one-tailed), a loss-to-follow up of 30%, and and intraclass correlation of 0.002.

The main outcome of the study, infant uptake of nevirapine, was measured based on mothers' reports. Infant uptake of nevirapine was assessed by intervention or control group (intent-to-treat analysis) and by whether or not the mother received the take home dose. Due to the small cluster size by design, the data are analysed as if no matching occurred as suggested by Diehr *et al.* (12). Crude proportions of taking infant dose of nevirapine are calculated and compared by a 2x2 contingency table Pearson chi-square test. Then, the difference in the estimated proportions are tested using a generalised estimating equation (GEE) methods with the identity link function and binomial variance (SAS version 9.1.3). Only the GEE analyses account for clustering (at the facility level). We also analysed the bivariate relationship between maternal characteristics (age, education, employment, marital status, parity, number of ANC visits, and place of delivery) and infant uptake. All tests were conducted at the 0.05 significant level. Tests of the main outcome and group are one-sided, while tests of characteristics and the main outcome are two-sided. Finally, we conduct descriptive bivariable analyses (no statistical tests) of socio-demographic characteristics and reports of HIV testing, status disclosure, and partner perspectives stratified by group to help with the interpretation of the results. Provider perspectives on the take home dose concept are also presented.

Ethical approval to conduct this study was obtained from Institutional Review Boards of Family Health International and Kenyatta National Hospital.

RESULTS

The average time between the first and second interviews was 47 days in the intervention group (range 3-91 days) and 38 in the control group (range 7-81 days). Intervals between interviews were shorter in the control group. This was because two of the five control facilities started data collection late necessitating recruitment of mothers nearer to date of delivery.

Babies were slightly older on average in the intervention group when the interviewer visited for the second interview than babies in the control group (15 days [range 0-65] vs. 8 days [range 1-20] on average). The average in the intervention group is skewed by a few cases that were difficult to follow up. We were able to verify with the data collection instruments (which were based on mothers' reports) that all but one infant received their dose of nevirapine before the interviewer arrived to conduct the second interview. The one exception was where an infant in the intervention group received the nevirapine dose after the interviewer's visit, so we conservatively treated that case as not having received the nevirapine dose in the analysis. Almost all of the infants were still alive at the time of the interview (99% in both groups).

One hundred and sixteen clients in the intervention group and 87 in the control group agreed to the first interview. Of these 85 clients in the intervention group (73%) and 75 (86%) in the control group participated in second interviews. We included all clients who agreed to participate in the first interview regardless of their willingness to participate in the second interview. Many clients considered 'lost-to-follow up' had participated in the first interview, but refused to participate in the second interview from the outset (19 of 31 clients in the intervention group and 4 of 12 in the control group).

Clients' characteristics and health service use are presented in Table 1. Clients were in their mid 20's with one to two children on average. The majority of clients had completed primary education and most were married. Two-thirds of clients were unemployed. About half of clients sought four or more ANC visits. Few differences were noted between the

characteristics of those women in the intervention group compared to the control group.

There was no difference between intervention and control groups on place of delivery. The majority of women delivered in a health facility (Table 1). About one-third of clients in both groups delivered at home which is typical of Kenyan women in urban areas (6).

Uptake of the infant's dose of nevirapine was high in both groups, 94% in the intervention group and 88% in the control group (p=0.096) (Table 2). However, some women in the control facilities received the infant's take home dose in ANC. When analysed by whether or not the mother received the infant's nevirapine dose to take home, infant's uptake was borderline statistically significant (p=0.085). Of those women who delivered at home, uptake was highest among those whose mothers received the dose to take home (93% vs. 53%, p=0.008).

Table 1

Socio-demographic characteristics and health service use of clients who completed the follow-up' interview

Intervention Group (n=85)	Control Group (n=75)
Mean age (range)	27.4 (18-40)	28.4 (18-42)
Mean number of children (range)	1.6 (0-6) (%)	2.2 (0-9) (%)
Education		
None	16	19
Primary (up to grade 7/8)	58	51
Secondary (up to form 4/6)	19	25
Post-secondary/university	7	5
Marital status		
Married or living as married	81	81
Single	12	5
Divorced/separated/widowed	7	13
Employment status and income type		
Unemployed	76	76
Salaried/hourly[1]	7	9
Income based on sales or self-determined	15	15
Total number of ANC visits made during this pregnancy		
1	13	9
2	16	16
3	22	21
4+	47	53
Place of delivery		
Same health facility as recruited	44	44
Respondent's home /Another person's home	38	37
Another health facility	16	16
In transit to health facility	2	3

[1]Only one woman reported income type of 'hourly'

Table 2
Infant uptake of the nevirapine dose by study group and treatment population

	Infant took dose (%)	Infant did not take dose (%)	p-value & standard error[1]
Study group			
Intervention (n=85)	94	5	p-value = 0.096
Control (n=75)	88	12	SE=0.0469
Treatment population*			
Received dose to take-home (n=102)	95	5	p-value = 0.085
Did not receive dose to take-home (n=58)	86	14	SE=0.0576
Of clients who delivered at their home or at another person's home			
Received dose to take-home (n=45)	93	7	p-value = 0.008
Did not receive dose to take-home (n=15)	53	47	SE=0.1646

[1]The difference in the estimated proportions between intervention and control groups was tested using a generalized estimating equation (GEE) approach accounting for clustering.
*Some mothers in control group were given the NVP syrup take home by providers

A recalculation of the inter-cluster (facility) correlation using the kappa statistic yielded a kappa of 0.019 which is greater than the rho of 0.002 that we used to estimate sample sizes. While the inter-cluster correlation found in this study is still quite low, our underestimate of it during sample size calculations may have slightly underestimated the needed sample size. Nonetheless, the largest contributor to the lack of statistical significance comes from the fact that the differences between groups is smaller than what we estimated.

Few maternal characteristics were significantly associated with uptake of the infant's nevirapine dose. Infants who received their doses compared to those who did not were significantly more likely to be born to women who had four or more ANC visits (54% vs 14%, p=0.05) (results not shown). Mothers' age, education, employment, marital status, parity, and place of delivery were not significantly associated with infant uptake.

Despite random assignment, there were differences between intervention and control groups in terms of women's reports of previous HIV testing and HIV status disclosure, factors which may affect uptake of nevirapine. Women in the intervention group were 66% less likely to have ever been tested for HIV prior to the intervention (Table 3). Of those who had ever been tested, the intervention group was also less likely (on the order of 38 percentage points) to know that they were HIV positive.

Women in the intervention group were also less likely to disclose their HIV status or to talk with their partners about nevirapine. They were much less likely compared to the control group to have disclosed their HIV status, to know their partners' HIV status, to have talked with their partners about nevirapine, or to say that their partner strongly approved about using nevirapine (Table 3).

Almost all mothers reported taking their nevirapine dose, and almost all of those mothers took their dose within 24 hours of delivery. Similarly, all but one infant who got their dose received it within the first two days after delivery (Table 4). Fifty one percent of women in the intervention group reported giving the infants their dose compared to 17% in the control group. This was the case despite the majority of mothers delivering in health facilities where one would expect a provider to give the infant's dose.

Table 3
Women's reports of HIV testing, status disclosure and partners' feelings about nevirapine

	Intervention (%)	Control (%)
	(n=85)	(n=75)
Ever tested for HIV prior to pregnancy	24	40
Of those tested prior to pregnancy	(n=20)	(n=30)
Knew HIV + status	45	83
Disclosure about HIV status	(n=85)	(n=75)
No one	45	20
Husband/partner/boyfriend	39	65
Mother/father or mother/father in-law	11	33
Brother/sister	13	17
Friend	0	13
Other health care provider	0	16
Other*	3	4
Partner's HIV status	(n=85)	(n=75)
HIV positive	18	35
HIV negative	5	11
Don't know	78	55
Of women with partners	(n=75)	(n=66)
Woman talked with partner about NVP for baby	32	68
Of those who have talked with their partner	(n=24)	(n=45)
Partner's approval about using NVP for infant		
Strongly approve	54	87
Approve	29	11
Disapprove	8	0
Strongly disapprove	8	2

[1]"Other" category includes 'religious person' or 'other family member"

Table 4
Characteristics of nevirapine dose administration

	Intervention n=85 (%)	Control n=75 (%)
Mother took her dose	93	95
Of mothers who took dose	(n=79)	(n=71)
When before the infant was born did mother take dose		
Within 2 hrs	39	38
Within 1 day (2-24hrs)	57	61
More than 1 day (25 or more hours)	4	1
Of infants who got dose:[1]	(n=80)	(n=66)
When after delivery did the infant get His/her dose		
Less than 1 day	81	83
1-2 days	16	17
3 days	1	0
Person who gave infant his/her dose[1]		
Mother	51	17
Midwife/Nurse/Birth Attendant	43	80
Family member/Friend/husband	5	3

[1]One "don't know" response for the intervention group is not shown

Providers confirmed that prior to the intervention a minority of providers, and more often in the control group than intervention, were informally repackaging the infant nevi rapine dose for take home (Table 5). Only two-thirds of intervention group providers reported distributing the take home dose during the study because they worked in other areas of PMTCT where distribution of nevirapine was not part of their responsibilities.

Table 5
Providers' perspectives on the take-home nevirapine dose concept

	Intervention group (n=41) (%)	Control group (n=25) (%)
Perceived likelihood that a woman who receives a take-home dose of NVP will give it to her newborn according to instructions		
Very likely	37	44
Somewhat likely	39	44
Not very likely	7	4
Very unlikely	15	4
Don't know/No response	2	4
Perceived likelihood that a woman who was given the take home dose will return to the facility for delivery compared to a woman who is not given the take-home dose		
More likely	27	12
Less likely	29	64
No difference	44	24
Ease/feasibility of systematically distributing take-home infant NVP dose[1]		
Very easy/feasible	35	38
Somewhat easy/somewhat feasible	12	42
Somewhat challenging/not very feasible	39	17
Very challenging/not at all feasible	16	4
Prior to the intervention, frequency with which providers informally re-packaged the infants NVP dose to take home		
Very often	2	20
Somewhat often	2	8
Not very often	17	20
Never	78	52
Proportion of providers who distributed take-home dose during the intervention	63	n/a
Reasons given for not distributing infant take-home dose, among those who have not distributed the NVP dose (in the intervention clinics)[2]		
Work in other areas of PMTCT	47	n/a
Have not been oriented to distribute take-home dose	33	n/a
Have not had supplies to be able to distribute it	20	n/a
Other		
Administer it at delivery	7	n/a
Did not have repackaging materials	7	n/a
Expect mothers to deliver in hospital	7	n/a
Intervention group providers' perceptions	n=26	
Have time with women to counsel on the take home dose	46	n/a
Have time to fill and package syringe	92	n/a
Foil pouch is easy to use	100	n/a
Supplies of syringes are sufficient to always provide dose	58	n/a
Supplies of nevirapine are sufficient to always provide dose	54	n/a

[1]For providers in the intervention group, this question asked about "the ease of having distributed the infant's NVP dose", while the control providers were asked about "how feasible" this practice would be
[2]Multiple responses allowed
*Of providers who have ever distributed the infant NPV dose (n=26)

Providers who had distributed the dose felt that the foil pouch was easy to use and that they had time to fill and package the syringe. A majority of providers felt the supplies of syringes and nevirapine were always sufficient to provide the dose. However, less than half felt they had time to counsel women on the take home dose.

A majority of providers in the intervention group (55%) felt that systematically distributing the take home dose was challenging (Table 5). Providers attributed these difficulties to client factors, which would affect any prophylactic regimen or method of administration, rather than factors related to service delivery or provider skills. They reported that clients were afraid of their partners' responses or clients were in denial about their HIV status (results not shown).

DISCUSSION

The take home dose may increase infant uptake especially among women who deliver at home. Concerns that offering the infant dose to take home would encourage mothers to deliver at home were unfounded. Providers embraced the intervention; however, they felt that HIV stigma and fear faced by clients made systematically distributing the take home dose challenging. Combined with previous research (7,13), this study indicates that offering the infant nevirapine dose to take home will increase uptake.

Despite randomization, we found that the intervention group was much less likely to have ever been tested for HIV, to have disclosed their status to anyone much less their partners, to know their partners HIV status, or to talk with their partners about nevirapine for the baby. We hypothesize that the relatively higher levels of HIV status disclosure and communication with partners in the control group partially explains why the control group's uptake was similar to that for the intervention group. Although more information is needed to confirm that assumption, other studies have found that compliance with a PMTCT regimen is positively associated with partner notification and partner willingness to have an HIV test (14) and negatively associated with HIV fear and stigma and reluctance to notify partners (15-17).

The relatively short interval between recruitment into the study and delivery may also partially explain the relatively high uptake of nevirapine in both groups. Due to manufacturer requirements, our study's inclusion criteria required that women be at least 32 weeks gestation. Women who adhere to maternal nevirapine were more likely to have a shorter mean interval between HIV testing and delivery than women who did not adhere (18), and low nevirapine uptake has been attributed to a lag time between HIV testing and issue of nevirapine (19).

The results of this study have multiple applications. First, they are specifically relevant for contexts where single dose nevirapine is the only ARV option. Despite the WHO guidelines, some settings still do not have the capacity to deliver more efficacious regimens, some women will still attend ANC too late to start more efficacious regimens, and many women do not deliver in health facilities. This may be more likely the case for rural areas where home deliveries are more common. The findings of this study can also be extended to promoting the take home nevirapine dose to increase the feasibility and uptake of extended postnatal delivery of nevi rapine regimens for infants born to HIV-infected women. Finally, other groups, such as UNICEF, have drawn on the experiences developing the packaging for the infant's dose and aspects of testing in development of the Mother-Baby Pack, which contains all the ARVs and other drugs needed to prevent perinatal HIV transmission (20). Issues around packaging, information for mothers, and concerns about non-return of mothers and infants are as relevant as PMTCT programmes continue to evolve and improve.

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