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A Bayesian Analysis of Prenatal Maternal Factors Predicting Nonadherence to Infant HIV Medication in South Africa

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Abstract

While efforts to prevent mother-to-child transmission of HIV been successful in some districts in South Africa, rates remain unacceptably high in others. This study utilized Bayesian logistic regression to examine maternal-level predictors of adherence to infant nevirapine prophylaxis, including intimate partner violence, maternal adherence, HIV serostatus disclosure reaction, recency of HIV diagnosis, and depression. Women (N = 303) were assessed during pregnancy and 6 weeks postpartum. Maternal adherence to antiretroviral therapy (ART) during pregnancy predicted an 80% reduction in the odds of infant nonadherence [OR = 0.20, 95% posterior credible interval (.11, .38)], and maternal prenatal depression predicted an increase [OR = 1.04, 95% PCI (1.01, 1.08)]. Results suggest that in rural South Africa, failure to provide medication to infants may arise from shared risk factors with maternal nonadherence. Intervening to increase maternal adherence and reduce depression may improve adherence to infant prophylaxis and ultimately reduce vertical transmission rates.

Keywords

Adherence; Women; Infants; HIV; South Africa

Introduction

While the occurrence of mother-to-child transmission of HIV (MTCT) has been reduced to about 1% in most high-income countries, unfortunately, the same cannot be said for many

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developing countries. (1) In some districts in South Africa, where the HIV prevalence among expecting mothers is estimated to be as high as 30%, MTCT has been reduced to less than 3%. (2) However, this success has occurred mostly in urban areas and in the Western Cape; MTCT rates in many rural areas can remain unacceptably high. (3) Prevention of MTCT (PMTCT) requires health officials, lay healthcare workers, and mothers to follow a complex protocol of HIV testing and treatment, and failure to achieve the goals of the protocol occurs at many stages of the process. (4)

The 2014 South African PMTCT protocol was based on Option B guidelines, which recommended that all HIV-infected pregnant women take antiretroviral medication pre-and post-partum, and all breastfeeding infants born to HIV-positive mothers receive daily nevirapine prophylaxis for the first 6 weeks of life. (5) South Africa has since adopted the Option B+ guidelines, and pregnant women are initiated on lifelong ART (infant ART recommendations remain the same). However, women may fail to take HIV medication or provide medication to their newborn for a myriad of reasons, e.g., recency of HIV diagnosis, failure to disclose their HIV status to their male partner, depression, and physical intimate partner violence (IPV). (6-15) Studies have found that adherence to antiretroviral therapy (ART) declines during the postpartum period, especially among women who were diagnosed with HIV during their pregnancy. (16) As formula feeding is often not feasible in rural South Africa and a substantial proportion of MTCT occurs postpartum (17), it is critical that new mothers maintain adherence to both their own and their infant's medication regimens. Yet, many studies estimating the impact of risk and protective factors on adherence have focused on the mother's adherence to her own ART regimen and have not considered adherence to the infant's regimen. (15, 18)

The limitations of conventional ("frequentist") statistical significance testing have long been recognized. The practice of significance testing reduces information contained in the data to a single index which mixes effect size and precision, the p value. Although p values can be useful statistical tools, they are commonly misused and misinterpreted. For example, a p value does not represent the probability that results occurred "by chance," nor does a small p value indicate a large or meaningful effect. Often, little attention is paid to the appropriateness of the assumptions underlying the calculation and interpretation of p values. Many researchers, including those from the American Statistical Association, have highlighted these limitations and emphasized the need to look beyond p values when evaluating and interpreting scientific research. (19-21)

Bayesian statistics offer an alternative to overcome some of the challenges associated with conventional statistical estimation and hypothesis testing techniques. (19, 20) A Bayesian analysis applies the axioms of probability theory to combine "prior" information with data to produce "posterior" estimates. In a Bayesian analysis, a researcher specifies his or her beliefs about a parameter estimate of interest before seeing the study data (the "prior") and then uses the study data to "update" their beliefs about the estimate (the "posterior"). (22) Researchers have increasingly recommended the use of Bayesian methods in social science research to enhance the interpretation of results. (19, 23-25), and tools for Bayesian analysis have become increasingly accessible. For example, Bayesian modeling frameworks are available in SAS PROC MCMC (26), STATA (27), R (28), and a large number of programs

that can be accessed through statistical software [e.g., WinBugs (29), JAGS (30), STAN (28)]. Many share syntax with familiar frequentist procedures, and thus should be accessible to users of these software packages. In addition, a number of introductory guides to carrying out Bayesian analyses have been published. (22, 28, 31)

This study applied Bayesian statistical techniques to examine longitudinal maternal-level predictors of failure to provide HIV medication to newborn infants during the 5th week of life (hereby referred to as “infant nonadherence”). It was hypothesized that prenatal failure to disclose HIV-positive status or disclosure with a negative reaction from the male partner, physical IPV, depression, maternal nonadherence, and recency of maternal HIV diagnosis would all increase the risk of infant nonadherence.

Methods

Study design, participants and procedures

Data were collected from April 10, 2014 to July 25, 2016 as part of a longitudinal clinical trial of a behavioral intervention to promote PMTCT uptake in 12 community health clinics (CHCs) in rural South Africa. The full trial protocol has been published elsewhere (32); briefly, the trial aimed to enroll 720 pregnant, HIV-positive women individually, followed by separate enrollment of 720 couples. Potential participants were eligible for the study if they were > 18 years of age, currently pregnant, HIV-seropositive, and had a male sex partner (in the second phase, the male partner must also be willing to participate). Participants were randomized to the intervention or control conditions between 6 - 30 weeks gestation and followed through delivery of the infant and for one year postpartum. The primary outcomes of the trial were maternal adherence and infant HIV seroconversions. Currently, the women-only phase of the trial has concluded and the couples phase is underway.

The study population for this manuscript included a cohort of women in the control condition who delivered a live infant and attended a study visit at 6 weeks postpartum (N = 303 included; a total of 485 control condition women were enrolled and eligible for a 6 week study visit; n = 19 data were lost due to computer error, n = 17 withdrew from the study, n = 30 were lost to follow-up, and n = 116 did not attend the 6 week visit, although they may have returned for later visits). Women were assessed using Questionnaire Development System® Audio Computer-Assisted Self-Interview software (ACASI) after informed consent was obtained. ACASI data collection was used to accommodate all levels of literacy and increase the disclosure of sensitive information, e.g., IPV, and of behaviors that participants may have perceived as socially undesirable, e.g., nonadherence. (33) Study personnel instructed participants on the use of ACASI using demographic questions. Once the participant understood the procedure, study personnel retreated to a separate room nearby and made themselves available for any participant questions that arose. Prior to study onset, ethics review and approval was obtained by the South Africa and US sites. The clinical trial is registered at [Clinicaltrials.gov](https://clinicaltrials.gov), number NCT02085356.

Measures

Outcome—The outcome, self-reported infant nonadherence during the 5th week of life, was assessed at 6 weeks postpartum by combining two measures. Two adherence measures were used given that combining, or triangulating, the results of complementary scales may enhance the accuracy of adherence measurement. (34, 35) The first was a visual analogue scale (VAS) (36) assessing the amount of medication given to the infant each day of the week preceding assessment, and the second was the ACTG 4-day adherence instrument (37), adapted to infant medication dosing. If anything less than perfect adherence was reported on either scale (i.e., not all of the medication was given in the past 7 days or at least one dose was skipped in the past 4 days), the participant was coded as nonadherent. The threshold of 100% was used because participants who missed even one dose in the past 4 or 7 days would have fallen below recommended adherence levels for effective therapy. (38)

Predictors measured at 32 weeks gestation—Physical IPV was measured using the mild and severe violence subscales of the Conflict Tactics Scale (CTS) (39); responses were collapsed to a dichotomous variable for any physical experience of IPV in month preceding the assessment at 32 weeks of pregnancy. Although the CTS typically assesses IPV in the past 12 months, for the present study it was adapted for past-month experiences given the proximity between study timepoints. HIV disclosure was a combination of whether or not the woman reported having disclosed her HIV status to her partner, and if so, whether the partner had 1) a positive or neutral reaction or 2) a negative reaction (40). Two dichotomous predictors were thus included: one indicator for disclosure with a positive or neutral reaction and one for disclosure with a negative reaction. Self-reported maternal adherence was measured using the same instruments (VAS and ACTG) as infant nonadherence and coded dichotomously using the same strategy in reverse: maternal adherence was coded as one if adherent, zero otherwise. All of the above variables were also measured at study entry; if a woman missed her 32-week study visit, the baseline values of these variables were used instead (17% of participants missed the 32-week visit).

Predictors measured at study entry only—Recent diagnosis was a dichotomous indicator of whether the woman was diagnosed as HIV-positive during the current pregnancy or previously. Depression was measured using the 10-item Edinburgh postnatal depression scale adapted for prenatal use (41), and retained as a continuous variable.

Statistical Analyses

This study utilized a fully Bayesian logistic regression analysis. A technique called “expert elicitation,” the process of consulting authorities in the scientific discipline and summarizing their beliefs into prior probability distributions, was used to obtain the prior information needed for the analysis (42). A pseudo-dataset with seven hypothetical study subjects was created, each with a unique combination of predictor values, and six experts were asked to estimate the probability that each “participant” would fail to provide at least one dose of HIV medication to her infant in seven days. Figure 1 shows the “dataset” and an example item from the questionnaire. Utilizing a “data augmentation” strategy, the experts' probability estimates were mathematically transformed into prior information about β coefficients. The strategy is so named because it is roughly equivalent to augmenting the

data with “prior observations.” (43, 44) At the time of prior elicitation, no experts had seen the data utilized in the analysis, nor had the researcher performing the elicitation process. Additional (nontechnical) detail on the prior specification process is presented in Supplemental Digital Content 1; for a more technical overview, see Bedrick et al (45).

After the prior information was obtained, the analysis was conducted using Just Another Gibbs Sampler (JAGS) v.4.2.0 (30) called with R2jags (46). Model convergence was verified using diagnostic plots generated with the ggcmc package (47); autocorrelation and time-series plots for the model parameters revealed excellent convergence. Analogous to classical logistic regression, parameter estimates are reported both on the logit scale and transformed into odds ratios with 2.5th and 97.5th quantiles of the transformed posterior distribution [95% posterior “credible” intervals (CI)]. For each parameter estimate, Bayes factors (BF) are also reported. BF represent the posterior odds of the null hypothesis, i.e., the ratio of the probability that the null hypothesis is true given the data to the probability that the null hypothesis was true before taking the data into account; $BF_i = \frac{\Pr(\beta_i = 0|y)}{\Pr(\beta_i = 0)}$. (48, 49)

Accordingly, $BF > 1$ indicate that the data increased support for the null hypothesis ($H_{0i}: \beta_i = 0$), $BF < 1$ indicate the data increased support for the alternative hypothesis ($H_{1i}: \beta_i \neq 0$), and $BF = 1$ indicate that the data did not change the probability of the null hypothesis. Bayes factors were computed with the Savage-Dickey ratio method (50) using MCMC samples from the prior and posterior densities. A Bayesian analogue of the two-sided p value was also computed as $2 \cdot \min(\Pr(\beta_i < 0), \Pr(\beta_i > 0))$. For comparison, a classical logistic regression (using maximum likelihood estimation) was also conducted, and odds ratios, confidence intervals, and p values are reported. All statistical analyses were completed using R v.3.2.5. (51)

Results

Women in this study ($N = 303$) were 18 to 43 years of age (mean = 28.4, $sd = 6$) with 0 to 10 years of education (mean = 5.6, $sd = 1.6$). The majority of women were unemployed ($n = 224$, 74%) and not looking for work. Per enrollment criteria, all women reported having a primary male partner; most were unmarried and not living with their partner ($n = 150$, 50%) or unmarried but living together ($n = 92$, 30%). By their own estimation, women entered into the study between 6 and 30 weeks gestation (mean = 18.6, $sd = 5.2$).

Just over half ($n = 162$, 54%) were diagnosed with HIV during the current pregnancy; among those diagnosed earlier, the mean number of years living with HIV was 4.2 (range = less than one year to 15 years, $sd = 3$). One hundred seventy women (56%) indicated that they had disclosed their serostatus to their male partner and received a positive reaction, 12 (4%) reported disclosure with a negative reaction, and 121 (40%) had not disclosed their serostatus. Forty-three women (14%) reported experiencing physical IPV in the month preceding assessment and 80 (26%) had missed at least one dose of their own HIV medication in the past seven days. Mean reported depression was 9.8 ± 6.2 in this sample; 98 (32%) women reported clinically significant levels of depression (Edinburgh depression scale total score > 12). Eighty-seven percent ($n = 262$) of study participants reported

consistent adherence to the infant medication regimen, while 41 women reported that they had missed at least one dose of their infant's medication over the past seven days (13%).

Table 1 presents the results of the analysis of factors predicting infant nonadherence. As can be seen in the table, maternal adherence had a strong protective effect against infant nonadherence. The posterior estimate of the odds ratio comparing adherent mothers to nonadherent mothers was 0.20, indicating that maternal adherence reduced the odds of infant nonadherence by 80% [posterior credible interval = (0.11, 0.38), BF = .001]. Conversely, depression multiplicatively increased the odds of nonadherence by about 4% per one-point increase in depression [OR = 1.04, 95% credible interval = (1.01, 1.08), BF = 0.64]. Although the posterior credible interval was mostly positive, suggesting that physical IPV during pregnancy may increase the odds of infant nonadherence [OR = 2.0, 95% CI = (0.92, 4.34)], the BF indicated fairly high posterior support for the null hypothesis of no impact (BF = 2.3). Diagnosis of HIV during the current pregnancy and disclosure of serostatus to the male partners, regardless of partners' reaction, did not clearly impact infant nonadherence in one direction or the other. Posterior density plots of β parameters and their associated priors are shown in Figure 2. For comparison, the results of the classical (maximum likelihood) logistic regression are also included in table 1.

Discussion

This study examined maternal-level predictors of failure to provide HIV medication to newborn infants during the 5th week of life. As hypothesized, HIV-infected mothers who reported taking all of their own medication and those who were less depressed were more likely to give their infants all of their prescribed HIV medication. In rural South Africa, and in other sub-Saharan African regions, women's nonadherence and failure to provide medication to infants may arise from shared risk factors, such as challenges to accessing medication, low health literacy, and nondisclosure to family members. (6, 8) Similarly, prenatal depression has been previously identified as a risk factor for nonadherence (14, 52), and this risk appears to generalize to women's adherence behavior with their newborns in this sample.

It was also hypothesized that failure to disclose HIV-positive status or disclosure with a negative reaction from the male partner, experience of physical IPV and maternal HIV diagnosis during the current pregnancy would all increase the risk of infant nonadherence. Although data were not conclusive, physical IPV may also increase the risk of infant nonadherence, which would be consistent with previous studies identifying IPV as a risk factor for nonadherence in pregnant women. (10) In contrast, disclosure to male partners did not influence infant adherence, as in previous research in Zimbabwe. (53) This outcome was surprising as women who have not disclosed their HIV status face additional challenges to medication use, including hiding medication bottles and covertly taking pills, challenges which did not generalize to providing medication to their infants. (54) However, if adherence behavior by a mother generalizes to her infant, mothers may capably address these barriers to adherence for themselves and their babies. Finally, although it was theorized that newly diagnosed women would be at increased risk for infant nonadherence, no such relationship was discovered. In fact, though previous research has found adherence behavior to be

negatively influenced by denial-based coping (13, 55), adherence behavior has also been found to decrease over time (56), which may counterbalance the influence of time of diagnosis on this sample.

The results of the Bayesian analysis do not deviate substantially from the conventional analysis, although if one is strictly following hypothesis testing rules (i.e., $p < .05$ equals significance), a frequentist analysis would discount the influence of depression, a finding that is supported by numerous studies suggesting that depression has a negative impact on adherence. (14, 15, 52, 57) One additional strength of Bayesian analysis and BF is that they can be used to measure support in favor of the null hypothesis, a property that is often incorrectly attributed to high p values (21). The high BF observed for positive disclosure and recency of HIV diagnosis indicate that the data provide evidence that these variables do not impact infant adherence, relative to what was thought before seeing the data (although commonly misinterpreted this way, high p values would not provide this evidence).

This analysis was primarily limited by the small percentage of women who reported any nonadherence and the use of self-reported adherence data. Although an ACASI system was used to reduce bias (33), results should be interpreted with caution. In light of the possible social desirability bias associated with reporting infant adherence behaviors, it is probable that the proportion of infant nonadherence was underreported. Additionally, the use of an “informative” prior in Bayesian statistics is controversial, as it introduces an element of subjectivity into the results. For this analysis, a prior elicitation strategy that is designed to be more intuitive and understandable was utilized in order to obtain higher-quality prior information. A classical logistic regression was conducted and only minor deviations from the results were noted, demonstrating that no significant subjectivity was introduced by the prior. Also, because of lack of data, we were unable to control for structural barriers to adherence such as medication stock-outs, which could potentially confound the maternal-infant nonadherence relationship. Finally, because of the prior elicitation strategy utilized in this study, it was not possible to apply a model selection strategy or otherwise add or remove predictor variables from the final model. After the data had been analyzed, it would be inappropriate to revise “prior” beliefs.

Limitations notwithstanding, this analysis provides information on important risk and protective factors for infant nonadherence that should continue to be addressed in future research and intervention programs. Perhaps most significantly, this study demonstrates a strong correlation between maternal adherence behavior during the pregnancy and adherence to the infant's medication regimen postpartum, highlighting the importance of establishing adherence behavior among mothers during pregnancy. In rural South Africa, pregnancy provides a unique opportunity for intervention, as it facilitates and increases contact between women and healthcare providers which may be otherwise limited or nonexistent. In fact, simply providing nevirapine suspension or tablets to women during antenatal care has been associated with improved infant adherence in Zimbabwe. (53) Results provide further evidence that identifying and intervening to increase adherence to ART and reduce depression during pregnancy may improve infant medication treatment rates postpartum, and ultimately reduce mother-to-child transmission of HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Case	Any IPV in past month	Disclosure to partner	Reaction to disclosure	HIV diagnosis during current pregnancy	Depression	100% maternal adherence
1	No	Yes	Negative	No	Low	Yes
2	No	Yes	Positive	No	High	Yes
3	Yes	Yes	Negative	Yes	High	No
4	No	No		No	Low	No
5	Yes	No		Yes	High	Yes
6	No	Yes	Positive	Yes	Low	No
7	Yes	No		No	High	No

For the following 7 hypothetical female participants, please provide an estimated probability that she will **fail to give at least one medication dose** to her infant in a week. You can give the same probability for two or more cases.

1. Was diagnosed with HIV before this pregnancy,
Has not experienced IPV in past month,
Has disclosed to her partner and got a negative reaction from him,
Reports low levels of depression,
Took all of her own medication in the past week.

_____ probability of failure to give at least one dose to her infant

Figure 1. Seven prototypical cases and example questionnaire item

Figure 2.

Prior and posterior densities for β coefficients (logit scale). Prior densities show the range and likelihood of parameter values, according to experts, before seeing the data. Posterior densities illustrate the probability of these values after taking the data into consideration. Maximum density heights indicate the most likely values of the parameters.

Disc - Pos = Disclosure to male partner with a positive partner reaction

Disc - Neg = Disclosure to male partner with a negative partner reaction

Mat Adh = Maternal ART adherence during pregnancy

Results of Bayesian and classical (maximum likelihood) logistic regression analyses of factors impacting adherence to infant ART prophylaxis

Table 1

Bayesian Analysis									
Parameter	Mean of posterior density	SD	OR	2.5 th quantile (OR)	97.5 th quantile (OR)	"p"	Bayes Factor		
Intercept	-0.84	0.306							
Physical IPV ^a	0.707	0.397	2.027	0.916	4.343	.077		2.31	
HIV disclosure to partner with positive reaction ^b	0.061	0.322	1.063	0.576	2.02	.862		10.15	
Disclosure with negative reaction ^b	-0.184	0.656	0.832	0.207	2.853	.803		2.33	
Recent HIV diagnosis ^c	-0.312	0.304	0.732	0.391	1.318	.3		5.72	
Depression	0.042	0.018	1.043	1.007	1.081	.027		0.64	
Maternal adherence ^d	-1.605	0.313	0.201	0.109	0.375	<.001		<0.01	
Classical analysis									
Parameter	Estimate	SE	OR	Lower CL	Upper CL	p			
Intercept	-1.112	0.395							
Physical IPV	0.802	0.425	2.231	0.944	5.061	.059			
Disclosure with positive reaction	0.253	0.375	1.288	0.623	2.737	.501			
Disclosure with negative reaction	-0.838	1.114	0.433	0.022	2.710	.452			
Recent HIV diagnosis	-0.286	0.359	0.751	0.369	1.516	.424			
Depression	0.056	0.030	1.058	0.997	1.122	.063			
Maternal adherence	-1.406	0.362	0.245	0.119	0.497	<.001			

^aReference = no physical IPV in past month

^bReference = no HIV serostatus disclosure to partner

^cReference = HIV diagnosis prior to current pregnancy

^dReference = At least one missed dose in past 7 days