

# Fertility intentions of prenatal and postpartum HIV-positive women in primary care in Mpumalanga province, South Africa: a longitudinal study

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**Introduction:** This study aimed to assess fertility intentions (planning to have more children in the future) and associated factors among pregnant and postpartum HIV positive women in rural South Africa.

**Methods:** In a longitudinal study, as part of a prevention of mother to child transmission (PMTCT) intervention trial, 699 HIV positive prenatal women, were systematically recruited and followed up at 6 months and 12 months postpartum (retention rate = 59.5%).

**Results:** At baseline, 32.9% of the women indicated fertility intentions and at 12 months postnatal, 120 (28.0%) reported fertility intentions. In longitudinal analyses, which included time-invariant baseline characteristics predicting fertility intention over time, not having children, having a partner with unknown/HIV-negative status, and having disclosed their HIV status to their partner, were associated with fertility intentions. In a model with time-varying covariates, decreased family planning knowledge, talking to a provider about a future pregnancy, and increased male involvement were associated with fertility intentions.

**Conclusion:** Results support ongoing perinatal family planning and PMTCT education.

**Keywords:** fertility intentions, family planning, HIV infection, pregnancy, South Africa, male involvement

## Introduction

South Africa had an estimated 6,300,000 people living with HIV (PLHIV) in 2013<sup>1</sup> and HIV prevalence among pregnant women attending antenatal clinics was 29.7%.<sup>1</sup> Antiretroviral therapy (ART)<sup>2</sup> and interventions to prevent mother-to-child transmission (PMTCT) of HIV<sup>3</sup> have greatly reduced the impact of HIV on health and life expectancy for mothers, children, and sexual partners.<sup>4</sup> With the appropriate resources and support, having a healthy pregnancy and HIV-negative child are now attainable goals, and understanding and supporting the fertility intentions, that is, desire to have children, of PLHIV can improve linkages to and effectiveness of these services.

Understanding factors related to motivation for childbearing may guide health care providers as they initiate discussions regarding childbearing intentions and may help them to address topics such as safer conception and pregnancy planning. Discussing reproductive desires with a health care provider is an element of the PMTCT guidelines and has been associated with increased fertility intentions,<sup>5,6</sup> though PLHIV have reported that reproductive discussions with their health care providers are infrequent.<sup>7-9</sup>

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Many PLHIV also report a lack of trust that their health care providers will provide unbiased information and support.<sup>10–12</sup>

Conflicting evidence exists regarding the influence of HIV-specific factors on fertility intentions among PLHIV, that is, the length of time since HIV diagnosis,<sup>13–16</sup> time since ART initiation,<sup>7,14,17</sup> disclosure of HIV serostatus to partners,<sup>16,18,19</sup> the HIV serostatus of partners,<sup>7,18,20,21</sup> level of education,<sup>15,22,23</sup> income,<sup>24–26</sup> and PMTCT knowledge.<sup>11,19,27,28</sup> Similarly, concerns regarding welfare of the family, including potential HIV transmission to infants<sup>21,29,30</sup> or partners,<sup>10,21,31</sup> monetary concerns,<sup>29,32,33</sup> and fears regarding maternal mortality<sup>10,31,33–35</sup> have been reported as considerations among PLHIV with regard to future pregnancies. Cultural factors, spousal, familial, and societal support, social expectations and attitudes, including stigma, also impact fertility intentions.<sup>30</sup> However, these issues underscore the importance of the relationship between fertility intentions and the level of importance the individuals place on these factors.

Relationship factors, such as intimate partner violence (IPV) and male involvement during pregnancy planning and perinatal care, play a potential role in fertility intentions due to their impact on relationship quality. Depression, which has been associated with IPV,<sup>36</sup> may also impact fertility intentions, which require future-oriented thinking.<sup>37</sup> In addition, HIV and family planning knowledge may influence fertility intentions as concerns with regard to the risk of HIV transmission during pregnancy have been reported.<sup>21,29</sup> Factors related to prior pregnancies, including unplanned pregnancy and HIV diagnosis during pregnancy, appear likely to also influence attitudes and plans with regard to future pregnancy.

Despite the volume of research on fertility intentions among PLHIV, studies have neglected the potential changes that occur in intentions following delivery. Rather, the few longitudinal studies of intentions among PLHIV have focused on comparisons between HIV-infected and HIV-uninfected women, for example,<sup>38</sup> or the relative influence of ART. This study seeks to address this gap in research by exploring factors associated with existing or changing fertility intentions during the antenatal and/or postnatal period, addressing understudied factors associated with relationships, health, and knowledge. Care during the perinatal period provides a window of opportunity for linkage to and uptake of HIV treatment services,<sup>39</sup> and information, therefore, regarding intentions assessed throughout the perinatal period may be especially important.

## Patients and methods

### Study design

This study is drawn from an ongoing longitudinal clinic-randomized PMTCT-controlled trial with 2 assessments

prenatally (8–24 and 32 weeks pregnant) and 2 assessments during the postnatal period (6 and 12 months). The trial is aimed at increasing PMTCT uptake, family planning, and male partner participation in the antenatal and postnatal process in 12 randomly selected community health centers in Gert Sibande and Nkangala districts in Mpumalanga province, South Africa. Further details about the study design, staff training, subject recruitment, and procedures have been previously reported.<sup>40</sup>

### Ethical approval

Ethical approval was granted by the Human Sciences Research Council (HSRC) Research Ethics Committee (REC), protocol approval number REC4/21/08/13, and the University of Miami Miller School of Medicine Institutional Review Board (IRB ID: 20130238) (CR00006122). Study approval was also obtained from the Department of Health and Welfare, Mpumalanga Provincial Government, South Africa. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants.

### Sample and procedure

Eligible women were HIV-seropositive pregnant women with partners, between 8 and 24 weeks pregnant, the typical time of entry into antenatal care, and aged  $\geq 18$  years. Candidates agreeing to participate were enrolled following provision of written informed consent. There were no exclusions based on literacy as all assessments were administered using an audio computer-assisted self-interview (ACASI) system.

After enrollment, all women completed study measures in their preferred language (English, isiZulu, or seSotho) using ACASI to enhance disclosure, accommodate all levels of literacy, and reduce interviewer bias. To familiarize participants with the computer system, assessors completed the demographic component of the questionnaire with participants prior to completion of all other assessments. In addition, an on-site assessor was available to assist where necessary and answer any questions.

### Measures

Fertility intentions were assessed with the question, “Are you planning to have more children in the future?” (response option, yes, no). Sociodemographic factors assessed included age, education, income, partner status, and number of chil-

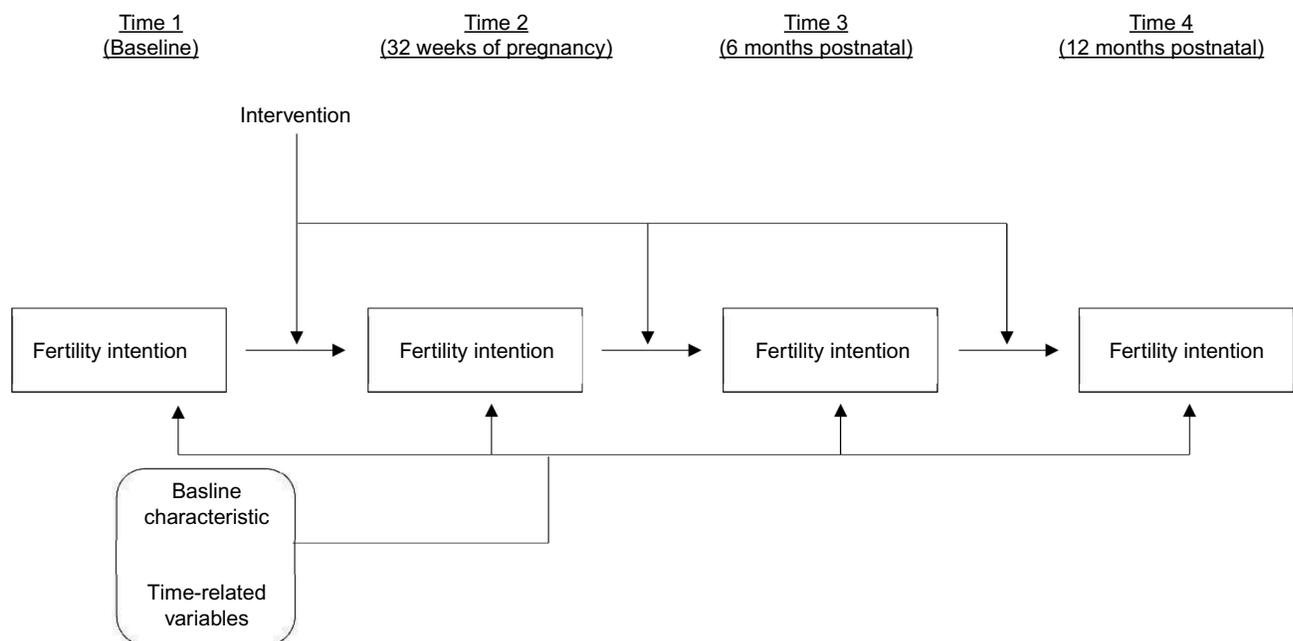
dren. Reproductive issues assessed included planning of the current pregnancy, talking to a health care provider about future pregnancy, and an 8-item measure of family planning knowledge.<sup>40</sup> Family planning knowledge items assessed perception of risk of transmission to the partner during pregnancy as well as knowledge of the fertility cycle and ideal time to conceive, with heterogeneous response options. Knowledge of safer conception practices was also assessed.<sup>41</sup> HIV-specific issues assessed included date of HIV diagnosis, a 12-item measure on HIV knowledge (Cronbach's  $\alpha=0.69$ , 0.64, 0.52, and 0.65 at the 2 prenatal and postnatal assessment points, respectively) using an adaptation of the AIDS-Related Knowledge Test to South African context; items reflect information about HIV transmission, reinfection with resistant virus, and condom use knowledge.<sup>42</sup> Partner-specific issues assessed included disclosure of HIV status to partner, HIV status of partner, consistency of condom use, and an 11-item male involvement index<sup>40</sup> (Cronbach's  $\alpha=0.83$ , 0.82, 0.84, and 0.82 at the 2 prenatal and postnatal assessment points, respectively). IPV was assessed using an adaptation of the Conflict Tactics Scale 18,<sup>43</sup> which included a 9-item partner psychological victimization subscale (Cronbach's  $\alpha=0.76$ , 0.66, 0.83, and 0.83 at the 2 prenatal and postnatal assessment points, respectively), and a 9-item partner physical violence subscale (Cronbach's  $\alpha=0.92$ , 0.89, 0.94, and 0.94 at the 4 assessment points). Emotional status was assessed at baseline with the Edinburgh Postnatal Depression Scale 10 (EPDS-10).<sup>44</sup> The EPDS-10 is a 10-item instrument asking

participants to rate how often they have experienced different symptoms associated with depression in the past 7 days. Scores range from 0 through 30; the validated cut-off score for South African populations is 12.<sup>45</sup> Cronbach's  $\alpha$  for the EPDS-10 scale ranged from 0.66 to 0.70 at the different assessment points in this study sample.

## Data analysis

Statistical analyses included descriptive statistics (such as means, SDs, frequencies, and percentages), Student's *t*-tests or its non-parametric alternative (Mann–Whitney *Z*-test), as well as chi-square or Fisher's exact tests. The dependent variable consisted of women living with HIV and whether they had a desire to have more children at baseline, 32 weeks assessment, and 6 and 12 months assessments.

To investigate patterns the participants' binary responses (yes/no) for fertility intention between 2 adjacent time points (time and time +1), we used the autoregressive model (also known as "Markov chain model"),<sup>46</sup> which tested how fertility intention at one time point predicted fertility intention at the next time point. Then, using multigroup test approach, we investigated the effects of intervention on response changes in fertility intention. The hypothesized autoregressive model for fertility intention continuity is presented in Figure 1. According to this approach, the same autoregressive model was estimated using 2 groups (standard of care vs. enhanced intervention) simultaneously. Multigroup analysis is useful to test for differences ( $\Delta$ ) using the "parameter invariance"



**Figure 1** Hypothesized autoregressive model for fertility intention continuity.

method.<sup>47</sup> Given the categorical (binary) outcomes, logistic regression coefficients were estimated with odds-ratios (ORs, as effect sizes of logistic coefficients).<sup>48</sup> To estimate unique autoregressive associations of fertility intention, the current model used several time-invariant (baseline demographic variables) and varying covariates as control variables. In addition, to account for lack of independence between observations within multiple sites, we used a sandwich estimator to adjust for underestimated standard errors and bias in chi-square computation.<sup>49</sup> Missing data were handled using multiple imputation<sup>50</sup> after comparing it with inverse-probability treatment weighting, specifying 10 imputed datasets. All data analyses were conducted using Mplus (version 7.4).<sup>51</sup>

## Results

### Sample characteristics at baseline

In all, 699 women living with HIV were enrolled during pregnancy (8–24 weeks) and completed assessments at baseline; 61.7% of the sample completed assessments at 32 weeks pregnant; 50.6% postnatal at 6 months; and 59.5% at 12 months. At baseline, 224 women (32.9%) indicated that they were “planning to have more children in the future” (fertility intentions).

Attrition analyses indicated that women with more education, those who already had children, and those who had an HIV-infected infant (OR=0.64,  $p<0.10$ ) were less likely to drop out of the study over time, and these variables were accounted for in all subsequent analyses. Other demographic and psychosocial variables, such as age, income, HIV-infected partner, disclosure of HIV status to partner, depression, and relationship status were not found to predict missing data over time.

Table 1 describes baseline characteristics, overall and by fertility intention. Women were, on average, aged 28.4 years, the majority (71.1%) had grade 10–11 education, 51.1% had a household income of  $\geq 600$  Rand a month, 20.2% had no children, and 53.0% reported that the current pregnancy had been unplanned. Almost half (47.1%) had talked to their health care provider about trying to get pregnant in the future. Slightly more than half (54.1%) of women had been diagnosed with HIV during this pregnancy. As a requirement of eligibility, all women had a partner; 41.1% were married or cohabiting, 59.0% had disclosed their HIV status to their partners, and 25.1% of their partners were known to be infected with HIV. Fertility intentions were more likely to be reported by younger women, those with more education, those having lower income, those with no children or

only one child, those having been diagnosed with HIV during this pregnancy, those having a partner and family with high-fertility desires, and those having less HIV and family planning knowledge (Table 1).

### Transition patterns of fertility intention and moderating effects of intervention across 4 time points

Transition patterns showed that overall; women who reported planning to have children at Time 1 were more likely to report planning to have children in all future time points (see ORs in Table 2). Similar response patterns were detected even after adjusting the effects of all time-invarying (baseline characteristics) and varying covariates (see AORs in Table 2). Next, to examine the intervention effects on the transition frequencies for fertility intention, these ORs were compared by condition. After adjusting for time-varying covariates, participants in the experimental group were less likely to plan to have children in the future from time points 1–2 (AORs=13.17 [standard of care] vs 10.26 [enhanced intervention]; Wald-test=6.42,  $p<0.05$ ) and from time points 3–4 (AORs=4.74 [standard of care] vs 3.99 [enhanced intervention]; Wald-test=4.88,  $p<0.05$ ) compared with those in control group.

### Effects of baseline characteristics and time-varying covariates on fertility intention across time

In longitudinal analyses, in Model 1, which included time-invariant predictors (at baseline) of fertility intention assessed over 4 time periods, not having children (AOR=0.61,  $p<0.001$ ), having a partner with unknown/HIV-negative status (AOR=0.76,  $p<0.01$ ), and having disclosed their HIV status to their partner (AOR=1.25,  $p<0.05$ ) were associated with fertility intentions. In Model 2, which included time-varying covariates, decreased family planning knowledge (AOR=0.84,  $p<0.001$ ), talking to a provider about a future pregnancy (AOR=1.34,  $p<0.01$ ), and increased male involvement (AOR=1.01,  $p<0.01$ ) were associated with fertility intentions (Table 3).

## Discussion

The study examined fertility intentions among women living with HIV during the pre- and postnatal periods, and found less than one-third of women intended to have more children, as previously found.<sup>30</sup> As in earlier studies,<sup>14,19,23,30,52</sup> younger age and having fewer or no children were associated with intentions to conceive again in the future.

**Table 1** Fertility intention by socioeconomic, reproductive, HIV, partner and mental health characteristics prenatal at baseline

Characteristics	All	No fertility intention (n=457)	Fertility intention (n=224)	p-value
	Mean (SD), n (%)	Mean (SD), n (%)	Mean (SD) n, (%)	
Socioeconomic status				
Age	28.4 (5.7)	29.2 (5.8)	26.8 (5.2)	<0.001
Education				
Grade 0–9	149 (21.5)	111 (75.0)	37 (25.0)	0.016
Grade 10–11	344 (49.6)	229 (67.6)	110 (32.4)	
Grade 12 or more	200 (28.9)	117 (60.3)	77 (39.7)	
Monthly household income (South African Rand)				
<600 (~ US\$50)	339 (48.9)	202 (59.9)	135 (40.1)	<0.001
≥600	354 (51.1)	255 (74.1)	89 (25.9)	
Reproductive issues				
Number of children				
None	140 (20.2)	64 (46.0)	75 (54.0)	<0.001
One	270 (39.0)	167 (62.8)	99 (37.2)	
Two or more	283 (40.8)	226 (81.9)	50 (18.1)	
Pregnancy unplanned				
No	320 (47.0)	223 (69.7)	97 (30.3)	0.177
Yes	361 (53.0)	234 (64.8)	127 (35.2)	
Family planning knowledge <sup>#</sup>	4.5 (1.3)	4.6 (1.4)	4.3 (1.3)	0.010
Discussed with health care provider trying to get pregnant in the future				
No	360 (52.9)	249 (69.2)	111 (30.8)	0.226
Yes	321 (47.1)	208 (64.8)	113 (35.2)	
HIV issues				
Diagnosed during this pregnancy				
No	318 (45.9)	224 (71.3)	90 (28.7%)	0.031
Yes	375 (54.1)	233 (63.5)	134 (36.5%)	
HIV knowledge <sup>#</sup>	13.8 (3.2)	14.0 (3.2)	13.4 (3.2)	0.010
Partner issues				
Partner status				
Married or cohabiting	285 (41.1)	194 (69.8)	84 (30.2)	0.217
Having partner (not married/cohabiting)	408 (58.9)	263 (65.3)	140 (34.7)	
Disclosure of HIV serostatus (to partner)				
No	279 (41.0)	183 (65.6)	96 (34.4)	0.483
Yes	402 (59.0)	274 (68.2)	128 (31.8)	
HIV serostatus of spouse/partner				
Negative/do not know	510 (74.9)	334 (65.5)	176 (34.5)	0.121
Positive	171 (25.1)	123 (71.9)	48 (28.1)	
Study condition				
Standard of care	357 (51.1)	250 (72.5)	95 (27.5)	0.003
Enhanced intervention	342 (48.9)	207 (61.6)	129 (38.4)	

Notes: <sup>#</sup>Mann–Whitney tests were used for median comparison of groups and chi-square tests for differences in proportions.

In contrast with previous research, neither educational level<sup>15,22,53</sup> nor income<sup>24,26</sup> was associated with reproductive desires. This may have been due to a lack of educational and socioeconomic variability in this rural sample, with a largely low-income sample with the majority having attained 10 or 11 years of education. As found in previous studies,<sup>20,21,54,55</sup> partner's HIV-positive status was negatively associated with fertility intentions. Disclosure of HIV serostatus to partners at the baseline assessment, as found previously,<sup>16,18,19</sup> was positively associated with fertility

intentions. Male involvement was associated with fertility intentions, showing the important role of male partners in fertility desires and the promotion of male involvement in the mother and child care continuum.<sup>56</sup> Inconsistent condom use was not associated with fertility intentions in this study, as seen in previous studies.<sup>21,57–59</sup> This finding may have been associated with local beliefs that women are less likely to conceive following childbirth or due to concerns about insisting on condom use being associated with HIV, as noted previously.

**Table 2** Transition frequencies (probabilities) of fertility intention and moderating effects of intervention across four timepoints

Fertility intention	No	Yes	Row total	OR (95% CI)	Time-varying AOR <sup>a</sup> (95% CI)	Time-invariant AOR <sup>b</sup> (95% CI)
<b>(a) Overall Sample (n=699)</b>						
Time 2						
Time 1	No	377 (80.7%)	90 (19.3%)	467 (100.0%)	9.89 (7.16–13.67)	10.31 (7.33–14.48)
	Yes	69 (29.7%)	163 (70.3%)	232 (100.0%)		
Time 3						
Time 2	No	361 (80.9%)	85 (19.1%)	446 (100.0%)	3.65 (2.36–5.66)	2.67 (1.87–3.80)
	Yes	136 (53.8%)	117 (46.2%)	253 (100.0%)		
Time 4						
Time 3	No	393 (79.1%)	104 (20.9%)	497 (100.0%)	3.85 (2.59–5.73)	3.55 (2.58–4.89)
	Yes	100 (49.5%)	102 (50.5%)	202 (100.0%)		
<b>(b) Standard of care (n=357)</b>						
Time 2						
Time 1	No	213 (82.6%)	45 (17.5%)	258 (100.0%)	10.38 (6.44–16.73)	11.30 (8.33–15.33)
	Yes	31 (31.3%)	68 (68.7%)	99 (100.0%)		
Time 3						
Time 2	No	194 (79.5%)	50 (20.5%)	244 (100.0%)	2.29 (1.29–4.07)	2.07 (1.14–3.77)
	Yes	71 (62.8%)	42 (37.2%)	113 (100.0%)		
Time 4						
Time 3	No	210 (79.2%)	55 (20.8%)	265 (100.0%)	3.66 (1.79–7.43)	3.42 (2.13–5.48)
	Yes	47 (51.1%)	45 (48.9%)	92 (100.0%)		
<b>(c) Enhanced intervention (n=342)</b>						
Time 2						
Time 1	No	164 (78.5%)	45 (21.5%)	209 (100.0%)	9.11 (6.24–13.30)	8.91 (5.33–14.88)
	Yes	38 (28.6%)	95 (71.4%)	133 (100.0%)		
Time 3						
Time 2	No	167 (82.7%)	35 (17.3%)	202 (100.0%)	5.51 (3.10–9.77)	2.97 (2.25–3.94)
	Yes	65 (46.4%)	75 (53.6%)	140 (100.0%)		
Time 4						
Time 3	No	183 (78.9%)	49 (21.1%)	232 (100.0%)	4.01 (2.69–5.98)	3.88 (2.26–6.67)
	Yes	53 (48.2%)	57 (51.8%)	110 (100.0%)		

**Notes:** Total sample size (n=699) was used after utilizing multiple imputation for missing cases. <sup>a</sup>AORs were estimated after adjusting the effects of baseline characteristics (time invariance covariates). <sup>b</sup>AORs were estimated after adjusting the effects of all-time varying covariates. All ORs were significant at  $p < 0.00$ .

**Abbreviations:** AOR, adjusted OR; OR, odds-ratio.

Furthermore, the study found an association between discussing family planning with a health care provider and fertility intentions, as in previous research.<sup>60</sup> These findings have been confirmed in several other studies,<sup>5,6</sup> and show the importance of the South African Department of Health guidelines in helping facilitate the initiation of discussions about fertility intentions by health care providers with PLHIV. In contrast, family planning knowledge and participation in an enhanced PMTCT intervention, which included information on family planning, were associated with decreased fertility intention. It is possible that better family planning knowledge and having received information on family planning from interventionists may have heightened awareness of risks of HIV transmission during pregnancy or consideration of other issues associated with pregnancy, such that knowledge may be necessary but not sufficient to arrive at fertility intentions.

Surprisingly, IPV during the perinatal period, unplanned pregnancy, time since HIV diagnosis, and depression (analysis not shown) were not associated with fertility intentions, contrary to previous research.<sup>60</sup> Future research should examine the relative trade-offs in reproductive decision making among this vulnerable population.

## Study limitations

Study follow-up rates were lower than the original target and those previously achieved in our pilot studies, and results may have been influenced by self-selection among women who were followed to 12 months postpartum. The high level of attrition and low clinic attendance may have been related to the need for many women to travel long distances to reach the health facility, migration arising from economic necessity, and culturally condoned migration of women during

**Table 3** Effects of baseline characteristics and time varying covariates on fertility intention across time (n=699)

Fertility intention	$\beta$	AOR (95% CI)
<b>Model 1: Baseline characteristics</b>		
<b>Education</b>		
Grade 0–9 (reference)	–	–
Grade 10–11	0.01	1.01 (0.83–1.23)
Grade 12 or more	0.09	1.10 (0.89–1.36)
<b>Income (South African Rand)</b>		
600 or more (reference)	–	–
<600	–0.05	0.95 (0.74–1.22)
<b>Partner status</b>		
Married or cohabitating (reference)	–	–
Having partner (not married/cohabitating)	–0.01	0.99 (0.84–1.17)
<b>Children</b>		
None (reference)	–	–
At least one	–0.49***	0.61 (0.52–0.72)
<b>Partner HIV status</b>		
Negative or unknown (reference)	–	–
Positive	–0.26**	0.76 (0.65–0.91)
<b>Disclosure of HIV status to partner</b>		
No (reference)	–	–
Yes	0.22*	1.25 (1.03–1.51)
<b>Model 2: variables assessed at four assessments</b>		
<b>Knowledge</b>		
HIV knowledge	0.00	1.00 (0.97–1.03)
Family planning knowledge	–0.18***	0.84 (0.77–0.91)
Talked to health care provider about future pregnancy	0.29**	1.34 (1.12–1.61)
<b>Partner issues</b>		
Disclosed HIV status to partner	–0.09	0.92 (0.76–1.11)
Consistent condom use	–0.09	0.92 (0.76–1.10)
Male involvement	0.07**	1.07 (1.03–1.11)
Psychological partner violence	–0.02	0.98 (0.97–1.00)
Physical partner violence	0.02	1.02 (0.99–1.04)

**Notes:** Logistic regression coefficients were held equal across all four timepoints. Also, all logistic regression coefficients were estimated after adjusting the intervention effects. \* $p < 0.05$ . \*\* $p < 0.01$ . \*\*\* $p < 0.001$ .

**Abbreviation:** AOR, adjusted odds-ratio.

the perinatal period to their mothers' homes.<sup>61</sup> The inclusion criteria for the study participants were limited to women who had a partner, preventing generalization to women without partners. The content of discussions about fertility and pregnancy between couples and with health care providers was not assessed, and should be considered in future studies to gain more insight in fertility and reproductive intentions and their influence by providers.

## Conclusion

This study of pregnant women living with HIV demonstrated declining fertility intentions from the prenatal to postnatal period. PMTCT and family planning knowledge, along with sociodemographic factors, were associated with

fertility intentions, and individual discussions between patients, providers, and interventionists were associated with diminished desire for more children. Factors identified related to motivation for childbearing may be useful in helping health care providers to initiate and explore fertility-related discussions, and in developing and providing effective and suitable strategies for contraception, safer conception, and pregnancy planning. Future studies should explore the role of culture in fertility intentions, and potential moderation of its influence in the uptake of clinical guidance by providers.

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## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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