Trajectories of fertility intentions among women living with HIV in South Africa

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ABSTRACT

Fertility intentions are thought to be dynamic among women of reproductive age, yet few studies have assessed fertility intentions over time among women with HIV. We examine temporal patterns of fertility intentions in women with HIV to assess the extent to which fertility intentions – and the corresponding need for safer conception and judicious antiretroviral therapy (ART) regimen selection – vary over time. 850 non-pregnant HIV-positive women aged 18–35 on or being initiated onto ART in Johannesburg, South Africa were enrolled into a prospective cohort study (2009–2010). Fertility intentions were assessed at enrollment and at 30-day intervals via an interviewer-administered questionnaire. We used group-based trajectory modelling to identify longitudinal patterns of fertility intentions over 12 months. We identified four patterns of fertility intentions, which we labelled "consistently low" (representing ~60% of the population), "low and increasing" (~23%), "high and increasing" (~12%), and "high and decreasing" (~5%). Our findings suggest that a single family-planning assessment at one time point is insufficient to fully identify and meet the reproductive needs of women with HIV. As HIV testing and treatment evolve in South Africa, routine screening for fertility intentions can offer important opportunities to optimize HIV treatment, prevention, and maternal and child health.

Introduction

Understanding reproductive goals and fertility intentions is important for optimizing the health of women and their children, including HIV treatment and prevention among couples affected by HIV. For women living with HIV wanting to avoid pregnancy, contraceptive counselling and care can minimize pregnancy-related morbidity and mortality, including mother-to-child transmission (Calvert & Ronsmans, 2013; Newell et al., 2004; Reynolds, Janowitz, Homan, & Johnson, 2006; Reynolds, Janowitz, Wilcher, & Cates, 2008; UNAIDS, 2015; Wilcher, Petruney, Reynolds, & Cates, 2008). For women and couples affected by HIV who desire a baby, safer conception services can help to ensure pre-conception viral suppression, which prevents both sexual transmission of HIV to uninfected partners and vertical transmission to infants (Bekker et al., 2011; Matthews et al., 2018; Schwartz et al., 2017, 2014).

Data from Botswana further underscore the importance of comprehensively assessing and addressing women's reproductive health needs within HIV treatment programmes. Preliminary findings from the Tsepamo Study indicated that women who conceive while taking dolutegravir may experience an increased risk for neural-tube defects in their newborns (Zash, Makhema, & Shapiro, 2018). The World Health Organization (WHO), the United States Food and Drug Administration, and the European Medicines Agency's Pharmacovigilance Risk Assessment Committee responded with a renewed focus on limiting dolutegravir use for women intending to become pregnant (European Medicines Agency, 2018; United States Food and Drug Administration, 2018; WHO, 2018). While recent date are more reassuring, prompting WHO to now recommend the use of dolutegravir for pregnant women and those of child-bearing potential (WHO, 2019), the prevalence of neural-tube defects remains greater in association with dolutegravir exposure than with other types of antiretrovirals (Zash, Holmes, et al., 2019).

Routine screening for fertility intentions during HIV treatment visits represents a potential opportunity to

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identify and meet the family planning needs of women living with HIV. Changes in life circumstances or health status may rapidly shift both short-term and long-term reproductive goals over the life course, irrespective of HIV status (Taulo et al., 2009; Yeatman, Sennott, & Culpepper, 2013). In general, few data have explored longitudinal changes in fertility intentions, particularly in sub-Saharan Africa (Kodzi, Casterline, & Aglobitse, 2010; Sennott & Yeatman, 2013). In South Africa, fertility intentions are infrequently assessed after initial antiretroviral therapy (ART) enrollment (Schwartz, Mehta, et al., 2012), and practical guidance and messaging around comprehensive assessment of fertility intentions remain sparse. New strategies are urgently needed to link women living with HIV to appropriate contraceptive and safer conception services (Black & Schwartz, 2018).

We have previously shown among women living with HIV in South Africa that unmet need for contraception can rapidly increase or decrease (Rucinski et al., 2018), indicating the need for routine monitoring of contraceptive needs to prevent unintended pregnancies and associated adverse events. In the current study, we examine trajectories of fertility intentions to assess the extent to which pregnancy desires and the corresponding need for safer conception and ART regimen selection vary over time.

Methods

Data were collected from a prospective cohort study of 12-month pregnancy incidence in HIV-positive women on ART. Detailed study procedures and eligibility criteria have been previously reported (Schwartz, Mehta, et al., 2012; Schwartz, Rees, et al., 2012; Schwartz, Taha, et al., 2012; Steiner, Black, Rees, & Schwartz, 2016; Rucinski et al., 2018, 2019). Briefly, 850 HIV-infected women on or initiating ART were recruited from four public-sector HIV outpatient clinics in Johannesburg and followed for 12 months between 2009 and 2011. Women were eligible for participation if they were 18–35 years old, not pregnant or breastfeeding and had not given birth in the last three months. Women with an infertility diagnosis and those who previously had a tubal ligation, hysterectomy or bi-lateral oophorectomy were ineligible. Study staff assessed pregnancy through urine-based pregnancy testing (One Step hCG Urine Pregnancy Test, Atlas Link Technology, Beijing). ART regimen, CD4 cell count and HIV viral load were confirmed through medical record review. After providing written informed consent, eligible women completed an interviewer-administered questionnaire assessing demographic and behavioural characteristics. Fertility intentions were measured at enrollment using three questions that asked about current and future childbearing plans. Women were first asked if they were currently trying to conceive at the time of interview (yes/no). Those answering "no" to the first question were asked if they planned to conceive in the next 12 months (yes/no/not sure). Those answering "no" or "not sure" to this second question were then asked if they desired a baby at some point in the future (yes/no/not sure). Follow-up visits occurred every 1–3 months during routine clinic visits, during which women provided updated information on whether they were currently trying to conceive (yes/no).

We constructed an analytic cohort in which we followed each woman from enrollment through 12 months of follow-up. We assessed current fertility intentions dichotomously every month for a total of up to 12 time points; women were considered as either actively trying to conceive or not within each month at which they had a visit. If a woman attended more than one routine HIV clinical care visit in a given month, corresponding to multiple assessments of fertility intentions in that month, we used her assessment of fertility intentions from the first visit only. Women without a visit in a given month were assigned a missing value for that month. Women with only an enrollment visit were excluded; the remaining women were censored at pregnancy, complete loss to follow-up, or the end of 12 months.

We used group-based trajectory modelling, which facilitates identification of latent groups of individuals whose outcomes of interest follow a similar trajectory over time (Nagin, 2005; Nagin & Odgers, 2010) to describe population patterns of fertility intentions over 12 months. We first fit a series of trajectory models to identify the most appropriate number of trajectory groups, considering up to five groups to allow for heterogeneity while maintaining interpretability. These models were fit using cubic polynomial terms, and the Bayesian Information Criterion (BIC) was used to select the trajectory model with the best fit (Nagin, 2005). After the best-fitting number of trajectories was selected, we then considered constant, linear, quadratic, and cubic specifications for each trajectory group, selecting a final model through visual inspection of the data and using the BIC.

Once we identified a final model, we assigned each woman in the cohort to a trajectory group using a maximum probability assignment rule, where each woman was categorized in the trajectory group for which her posterior probability was highest. To assess model adequacy, we examined the mean of the posterior probabilities of group membership, ensuring the mean was ≥ 0.70 for each group (Nagin, 2005). We then used descriptive profiles to summarize characteristics (captured at enrollment) for women in each group.

In sensitivity analyses, we re-estimated trajectories using quarterly assessments of fertility intentions, using the first visit within a given three-month period if women had multiple measurements in that quarter. We did this to account for missing observations, which resulted primarily from our choice to finely measure fertility intentions every month within an existing research programme where visits more or less every three months were standard. All models were fit using PROC TRAJ (https://www.andrew.cmu.edu/user/bjones/index.htm), a free downloadable SAS add-on package (SAS, version 9.4, Cary, NC).

Results

Overall, 850 HIV-positive women were enrolled. Twenty-one (2.5%) women completed a fertility intentions assessment at enrollment but did not return after their initial study visit and were thus excluded from further analyses (S1 Table). Among the remaining 829 women, median time on ART was 13 months (IQR 5, 24). Most women were in a relationship (93%) with a spouse, boyfriend, or regular sexual partner. Nearly all (92%) had previously been pregnant. Nearly half (43%) reported plans to conceive in the next 12 months; 12% were trying to conceive at enrollment.

In longitudinal analyses, a four-group model emerged as the best-fitting model to describe temporal patterns of fertility intentions over 12 months (Figure 1). Model fit statistics are presented in the supplemental materials (S2 Table). An estimated 60% of women were predicted to have a consistently low probability (between 0% and 3%) of trying to conceive over the study period. An estimated quarter (23%) were predicted to have a low but increasing probability (from 3% at enrollment to 47% at month 12), and an estimated 5% were predicted to have a high then decreasing probability (from 57% to ~85% over the first six months to <1% at month 12). Finally, an estimated 12% of women were predicted to have a consistently high – and increasing – probability of trying to conceive (from 64% at enrollment to 99% at month 12). We labelled these fertility intentions trajectories as "consistently low", "low and increasing", "high then decreasing", and "high and increasing", respectively.

Based on the maximum posterior probability assignment rule, 552 (67%) women were assigned to the consistently low group, 141 (17%) to the low and increasing group, 106 (13%) to the high and increasing group, and 30 (4%) to the high then decreasing group (Table 1). These percentages were similar to the trajectory group sizes estimated from the model's parameters. For all groups, the mean posterior probability of group membership was >0.80 and the median number of follow-up visits was ≥7 (Table 1).
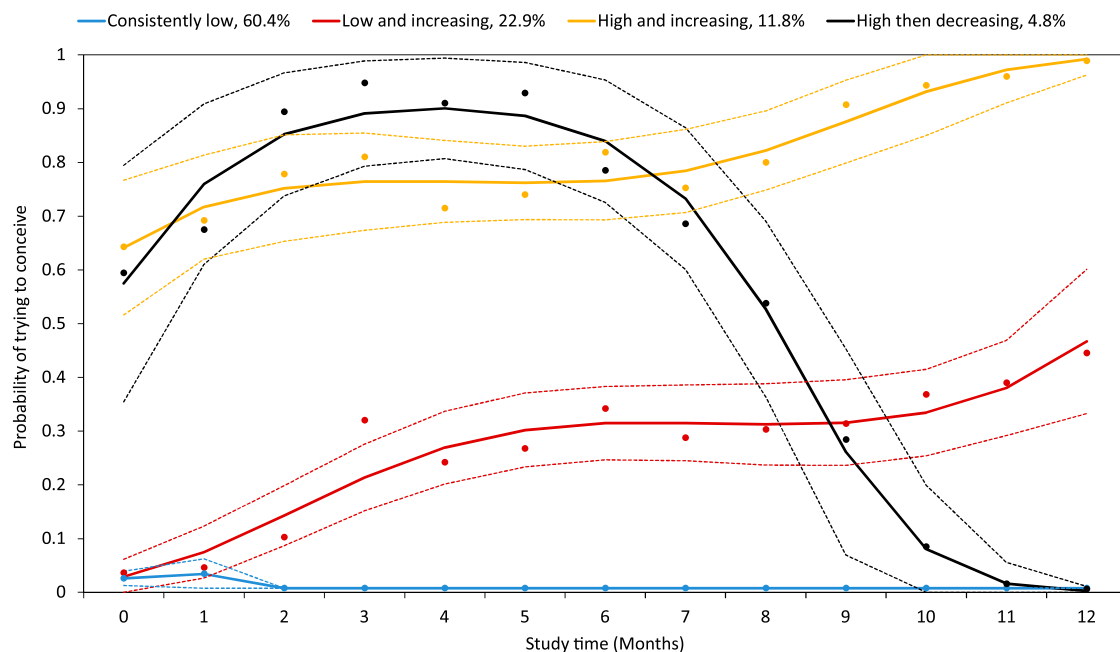

Figure 1. Predicted trajectories of fertility intentions for 829 women living with HIV in South Africa between 2009 and 2011. Points represent the observed proportions of women trying to conceive among those assigned to a given trajectory group on the basis of their maximum posterior group membership probability. Curves represent the proportion of women trying to conceive as estimated by the model for a given trajectory group and corresponding 95% confidence intervals (dashed lines). The "consistently low" and "high then decreasing" trajectories were each modelled using a quadratic term, and the "low and increasing" and the "high and increasing" trajectories each using a cubic term.

Table 1. Characteristics at enrollment of 829 women assigned to "consistently low", "low and increasing", "high and increasing", and "high then decreasing" trajectories of fertility intentions over 12 months[a].

	Consistently low N = 552 (66.6%)		Low and increasing N = 141 (17.0%)		High and increasing N = 106 (12.8%)		High then decreasing N = 30 (3.6%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Posterior probability of group membership	0.90	0.09	0.93	0.12	0.82	0.18	0.85	0.17
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Monthly follow-up visits	7.0	6–8	7	6–9	8	7–9	7	6–9
Age (years)	30.7	28–33	30.4	26–33	30.1	27–33	29	27–30
No. living children	1.0	1–2	1	0–1	1	0–1	0	0–1
Months since last pregnancy	36.0	15–84	60	24–96	72	30–108	64	20–108
CD4 count at enrollment (cells/μl)	326.0	195–475	256	169–404	295.5	172–460	291.5	153–410
Months on ART	14.2	6–27	8.6	3–20	11.1	5–22	6.5	4-18
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Married/cohabiting with a partner	231	41.9	61	43.3	64	60.4	12	40.0
In a relationship[b]	506	91.7	128	90.8	105	99.1	30	100
Pregnant at HIV diagnosis	204	37	36	25.5	17	16	5	16.7
Any living children	481	87.1	93	66	65	61.3	14	46.7
Trying to conceive, currently	10	1.8	4	2.8	70	66	18	60.0
Planning to conceive, next year[c]	148	26.8	79	56	103	97.2	29	96.7
Planning to conceive, ever[d]	18	85.7	130	92.2	106	100	30	100
Main partner desires a/another child[e]	315	70.3	110	94.8	97	97	30	100
Taking hormonal contraception	183	33.2	22	15.6	9	8.5	4	13.3
Fell pregnant during follow-up	102	18.5	20	14.2	25	23.6	2	6.7

Abbreviations; SD: Standard Deviation, IQR: Interquartile Range, ART: Antiretroviral therapy, No.: Number.
[a]Each woman was assigned to either the consistently low, low and increasing, high and increasing, or high then decreasing trajectory group using a maximum-probability assignment rule.
[b]Comprises women who were married/cohabiting with a partner, as well as those women who reported a boyfriend or regular sexual partner.
[c]Women who planned to conceive "in the next year" comprised those who reported they were already trying to conceive at enrollment and those who reported they were planning to conceive in the next 12 months.
[d]Women who planned to conceive "ever" comprised those who reported they were already trying to conceive at enrollment, those who reported they were planning to conceive in the next 12 months, and those who reported they desired a baby at some point in the future.
[e]Excludes women who were uncertain about their partner's fertility intentions.

Women assigned to the consistently low fertility intentions group had more recently given birth (median time since last birth: 36 months) compared to women assigned to the other three groups (low and increasing: median of 60 months; high and increasing: median of 72 months; high then decreasing: median of 64 months) (Table 1). More than a third (37%) of women assigned to the consistently low group had been pregnant at their initial HIV diagnosis, compared to 26% assigned to the low and increasing group, 16% assigned to the high and increasing group, and 17% assigned to the high then decreasing group. Most (87%) women assigned to the consistently low group had one or more living children, compared to 66%, 61%, and 47% of women assigned to the low and increasing, high and increasing, and high then decreasing groups, respectively. The percentage of women planning to conceive in the next year (as reported at enrollment) was lowest (27%) among those whose fertility intentions patterns led to assignment in the consistently low group, intermediate (56%) among those assigned to the low and increasing group, and highest (97%) among those assigned to the high and increasing or high then decreasing group. The percentage of women reporting hormonal contraceptive use at enrollment followed a roughly opposite pattern across these four groups (consistently low: 33%, low and increasing: 16%, high and increasing: 9%, high then decreasing: 13%).

In sensitivity analyses where we re-estimated trajectories using quarterly assessments, three trajectory groups emerged (S3 Figure). Results were broadly similar to those found in the main analysis, insofar as women predominantly were predicted to have a consistently low probability of trying to conceive, but an estimated quarter were predicted to have fertility intentions that changed over time.

Discussion

Supporting women living with HIV to safely realize their reproductive goals is important for HIV prevention and for women's and children's health more broadly. In this prospective cohort of South African women living with HIV, we found that although 60% of women reported consistently low fertility intentions, considerable changes in fertility intentions were seen in a sizeable subset of the cohort, even within a brief, 12-month period. Our findings affirm that routine assessment of fertility intentions during HIV clinical care visits should be prioritized

by HIV care providers to meet the contraceptive and safer conception needs for women living with HIV.

Though fertility intentions are generally recognized as being dynamic among women of reproductive age, few prior studies have assessed changes in fertility intentions over time among women living with HIV (Hoffman et al., 2008; Taulo et al., 2009). Furthermore, despite national recommendations to provide integrated family planning and HIV treatment services (Republic of South Africa Department of Health, 2012), fertility intentions are not routinely screened within ART services in South Africa. This lack of routine screening represents a critical gap in HIV prevention programming. We elucidate the potential size of this gap, estimating that nearly one-third of women had a marked increase over only 12 months in their predicted probability of trying to conceive.

Routine assessment of fertility intentions may offer an important opportunity for providers to mitigate HIV transmission risks by encouraging viral suppression and considering ART regimen switches if needed. As findings from Botswana still indicate a potential safety signal between dolutegravir taken at the time of conception and neural-tube defects, many countries have delayed or limited roll-out of dolutegravir to women or subsets of women while emphasizing the importance of contraceptive use for women of childbearing age. Previously, mixed messages around regimen management related to fears/signals of teratogenicity have resulted in irregular regimen management for women (Black & Schwartz, 2018; Schwartz, Taha, et al., 2012). Our findings indicate that a single assessment of childbearing plans at ART enrollment is likely insufficient to guide decisions around regimen switching, as women's fertility intentions may change, even over a 12-month period. Moreover, while characteristics of women assigned to each trajectory group differed in some instances, particularly with respect to measures of childbearing experience and the timing of HIV diagnosis, these differences should not be used to direct screening in clinical practice. Instead, routinely asking all women for updates on their childbearing plans each time they present to care – both for the immediate future and over the next year – may offer a measurable indication for pre-conception health optimization and safer conception counselling, including ensuring viral load monitoring is up to date.

This study has some limitations. Estimated trajectories reflect specifically the fertility intentions of women enrolled in this study, as the fertility intentions of partners were not assessed during follow-up. To the extent that decisions around childbearing reflect the fertility intentions of both women and their partners, the lack of information about partner intentions may limit our understanding of drivers behind the trajectories presented here. Approximately three percent of women did not return after their initial study visit, and although most characteristics of this small group of excluded women were similar to those included in trajectory analyses, their patterns of fertility intentions may have differed. Trajectories of fertility intentions may also have been more or less dynamic among women who reported to the clinic with less frequency, and for whom monthly assessments of fertility intentions were not fully observed. However, in sensitivity analysis where we used wider intervals (every three months) that resulted in less missing data, trajectories were generally similar. Our choice to classify women into trajectories for which their posterior probability of group membership was highest does not fully account for uncertainty in assignment (Clogg, 1995), and while this approach minimizes the number of incorrect assignments compared to other approaches (Goodman, 2007), some classification error may have occurred (Bray, Lanza, & Tan, 2015) in our descriptive presentation of group profiles. However, the mean of the posterior probabilities of group membership was generally high for each group, suggesting good assignment accuracy, and the proportion of women assigned to each group closely corresponded to the groups' estimated probability from the model's parameters. While the inclusion of multivariable analysis of potential predictors was beyond the scope of this brief manuscript, formal predictive modelling that characterizes distinct predictors of changing fertility intentions may be appropriate for future research. We were also not able to confirm the original treatment indication among ART-experienced women in this study, and non-pregnant women were only eligible for lifelong ART initiation with a CD4 count ≤200 cells/ml or WHO clinical stage 4 diagnosis at the time of enrollment. It is possible that trajectories of fertility intentions may differ in the current "treat all" era, and future studies should explore any temporal changes.

Despite these limitations, our findings strongly suggest that women living with HIV have diverse reproductive goals and needs that may change over the short-term. Routine assessment of fertility intentions – both at initial care presentation and throughout the HIV treatment process – can increase contraceptive use, referrals for safer conception counselling provision, and ART regimen changes as appropriate. As HIV testing and treatment evolve in South Africa, routine screening for fertility intentions can better direct care delivery, offering important opportunities to optimize HIV prevention and maternal and child health outcomes in this population.

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