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Complex decisions: correlates of injectable contraceptive discontinuation following HIV-1 seroconversion in an HIV prevention trial

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Abstract

Contraceptive adherence during acute and recent HIV-1 infection is important to maternal and child health given the elevated risk of vertical HIV-1 transmission and additional complications of pregnancy. Injectable contraception (IC) is the most common non-barrier modern contraception method used in sub-Saharan Africa (SSA). Adherence to IC after HIV-1 seroconversion is not well understood. We examined factors associated with IC discontinuation among women in SSA diagnosed with HIV-1 infection while participating in a clinical trial of biomedical HIV-1 prevention. After diagnosis with HIV-1 infection in the VOICE trial, 255 women from South Africa, Uganda, and Zimbabwe enrolled in a longitudinal observational study (MTN-015). Contraceptive method was assessed at MTN-015 baseline and at 3, 12, and 24 months post-seroconversion. Correlates of IC discontinuation were examined by Cox proportional hazard modeling. IC use was reported at baseline by 78% of women enrolled (198/255), of which 92% (182/198) completed at least one follow-up visit. Two-thirds of women (66%, 121/182) continued on IC during the follow-up period (median 24 months). Lower rates of IC discontinuation were observed in women who reported having had at least one child (HR 0.39, 95% CI 0.20–0.82) or earning a personal income (HR 0.51, 95% CI 0.30–0.87) at baseline. These findings suggest that

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many women with HIV-1 infection face complex decision-making regarding family planning in the years that follow seroconversion and highlight that some women may discontinue IC use despite on-site provision of family planning services. Understanding the broader context of family planning choices in recently seroconverted women may be key to more effective linkages between family planning services and HIV-1 testing and care.

Keywords

Injectable; female contraception; HIV infection; Africa; seroconversion

Introduction

HIV/AIDS and maternal death remain the leading causes of death in women of reproductive age worldwide, and many of these deaths are preventable (World Health Organization [WHO], 2013). Universal access to sexual and reproductive health services, such as family planning, is a key global strategy to improving maternal health (United Nations [UN], 2017; WHO, 2015), particularly in regions of high HIV prevalence (Singh, Darroch, Ashford, & Vlassof, 2009). Family planning not only provides HIV-infected women with control over reproductive choices and protection from pregnancy-related and post-partum complications but also affords time for treatment of HIV-1 and other infections, thereby lowering further risk of complications in childbearing (Calvert & Ronsmans, 2013; Hladik, Stover, Esiru, Harper, & Tap-pero, 2009; Le Coeur et al., 2005; Zaba et al., 2013).

Injectable contraception (IC), namely noresthisterone enanthate (NET-EN) and depomedroxyprogesterone acetate (DMPA), is frequently used among women in sub-Saharan Africa (SSA) (Darroch & Singh, 2011), largely due to its ease of administration as an injection every 2–3 months, respectively, and provider preference in public health clinics. Despite the relative convenience of these injectable regimens, the estimated 12-month discontinuation rate of DMPA, for example, ranges from 22 to 75% depending on study population (Haddad et al., 2013a; Nanda et al., 2011; Peipert et al., 2011; Sangi-Haghpeykar, Poindexter, Bateman, & Ditmore, 1996; Smit & Beksinska, 2013; Westfall, Main, & Barnard, 1996). Apart from medication side effects, factors associated with HIV-1-infected women not using IC include: younger age (Hoyt, Storm, Aaron, & Anderson, 2012), lower education (Melaku & Zeleke, 2014; Polis et al., 2011), unmarried status (Polis et al., 2011), rural setting (Melaku & Zeleke, 2014), lack of parity (Haddad et al., 2013a; Maraux et al., 2015), unemployment (Maraux et al., 2015), and partner disapproval (Haddad et al., 2013a). Understanding how IC integrates into the lives of HIV-1-infected in SSA is critical to effectiveness of family planning programs.

Qualitative and survey studies have explored the impact of knowledge, or diagnosis, of HIV infection on contraceptive choices (Imbuki, Todd, Stibich, Shaffer, & Sinei, 2010; Magalhães, Amaral, Giraldo, & Simoes, 2002; Stifani, Mac-Carthy, Nunn, Benfield, & Dourado, 2018). Findings from focus group discussions and in-depth interviews of HIV-positive reproductive age women in Kenya suggested that perceptions of side effects, partner opinion, and HIV disease progression played a role in family planning choices; some women

noted that their HIV status directly influenced their contraceptive decisions, particularly concerning abstinence (Imbuki et al., 2010). A survey of Brazilian women found a notable decrease in highly effective contraception, including injectable formulations, following HIV diagnosis; younger age, lower income, and HIV positive partner or unknown partner status were associated with no method to prevent pregnancy after diagnosis. Of note, most respondents reported being greater than one year from diagnosis and on ART, and actual timing of seroconversion could not be determined from the survey (Stifani et al., 2018).

The period surrounding HIV-1 acquisition prior to viral suppression on ART is an important window for pregnancy prevention given the heightened risk for vertical transmission in acutely and recently seroconverted women who become or are already pregnant (Pilcher et al., 2004; Wawer et al., 2005). Factors affecting IC use in recently seroconverted women have not been well described, and examining patterns and predictors of IC discontinuation after HIV-1 seroconversion may aid in identifying women who are at higher risk of pregnancy and possible vertical transmission. We evaluated the demographic and behavioral factors associated with IC discontinuation after HIV-1 seroconversion among women who were followed longitudinally after acquiring HIV-1 infection during participation in the Vaginal and Oral Interventions to Control the Epidemic trial (VOICE/Microbicide Trials Network (MTN) 003) (Mar-razzo et al., 2015).

Methods

Study design, population, and procedures

The current study was a secondary analysis of data from women who enrolled in MTN-015 following acquisition of HIV-1 while participating in VOICE. Briefly, VOICE was a randomized, placebo-controlled trial conducted from September 2009 to August 2012 that assessed daily use of oral tenofovir disoproxil fumarate (TDF), oral tenofovir-emtricitabine (TDF-FTC), or 1% tenofovir (TFV) vaginal gel as PrEP against HIV-1 infection. MTN-015 is an ongoing multi-site, prospective, observational cohort study designed to follow women after HIV-1 seroconversion in VOICE and other parent MTN HIV-1 prevention trials of antiretroviral-based topical microbicide and oral pre-exposure prophylaxis (PrEP) in order to examine the nature of HIV-1 disease progression and treatment response in women acquiring HIV-1 under these conditions. Detailed trial methods are described elsewhere: MTN-003 (Marrazzo et al., 2015; Microbicides Trial Network [MTN] MTN-003, http//www.mtnstopshiv.org/studies/70) and MTN-015 (Rid- dler et al., 2016).

Women who seroconverted in VOICE enrolled in MTN-015 from 15 study sites in South Africa, Uganda, and Zimbabwe (Riddler et al., 2014). All MTN-015 sites offered on-site access to one or both injectable hormonal contraceptive formulations, DMPA or NET-EN, at no cost to the participants. NET-EN was only available in South Africa. Of note, VOICE involved the study of three investigational products and their placebo products, and thus, for enrollment in VOICE, participants were required to use reliable contraception defined as a hormonal method (e.g., injectable, pill, implant, or vaginal ring), intrauterine device, or sterilization of participant or partner, in order to prevent potential fetal exposure of unknown consequence. Since VOICE participants stopped study product at seroconversion, the need for contraception to prevent this exposure no longer existed, and therefore, enrollment in

MTN-015 did not require the use of reliable contraception although it remained part of services offered by trial sites. MTN-015 participants, however, did receive contraceptive counseling as part of the behavioral interventions at screening and enrollment, followed by additional counseling every six months post-seroconversion or after initiation of ART for the remainder of time in the study.

The current analysis included all MTN-015 participants from VOICE who completed an MTN-015 entry visit and at least one follow-up visit. Demographic data were collected at the MTN-015 entry visit. Behavioral questionnaires, which included assessment of contraceptive method by self-report, were administered via face-to-face interviews at MTN-015 baseline and at 3, 12, and 24 months post-seroconversion.

Local institutional review boards (IRB) and ethics committees at each participating site for VOICE and MTN-015 approved the protocol and study documents, and all participants provided informed consent. The University of California, Los Angeles, IRB additionally approved the current analysis.

Statistical analysis

The primary aim of this analysis was to examine correlates of IC discontinuation following HIV-1 seroconversion. The primary outcome was time from estimated HIV-1 seroconversion to IC discontinuation without substituting another non-barrier modern method. The date of HIV-1 seroconversion was estimated as the midpoint between the last HIV-1 negative test and the first positive rapid test date in VOICE. Contraceptive use at time of MTN-015 entry was treated as a surrogate for contraceptive use at time of seroconversion.

Participants were classified as IC “discontinuers” if they reported IC use at baseline and reported no use of IC or another form of non-barrier modern contraception at their last follow-up visit. In cases where multiple visits followed IC discontinuation, time of IC discontinuation was considered to be the first time point at which the participant reported not using IC. Baseline IC users who switched from IC to another non-barrier contraceptive were grouped as “continuers.” Baseline IC users who had multiple follow-up visits and reported discontinuing IC at one visit and resuming IC use at a following visit were considered “intermittent” users and also were grouped as “continuers” if they reported IC use at their final study visit. Participants who reported IC use at all attended visits were considered as “consistent” users and grouped as “continuers.”

Cox proportional hazard modeling was conducted to examine correlates of IC discontinuation. A sensitivity analysis excluding women with time from seroconversion to MTN-015 entry of greater than 6 months was performed in order to account for a prolonged interim period between studies. For this analysis, data were not available on contraceptive use during this interim period, and thus, the sensitivity analysis was performed to test effect of unmonitored time-off of study.

Variables of significance in the univariate models (p-value < 0.05) or known to be associated with IC discontinuation in published studies were candidates in the multivariate model, and the final multivariate model was obtained using step-wise variable selection, with inclusion

of variables where *p*-value remained less than 0.1. The mean of covariates method was used to calculate the adjusted survival curve for the combination of significant variables. Data were analyzed using JMP® Pro 12.0.1 (SAS Institute, Inc., Cary, NC, USA).

Results

MTN-015 enrolled 255 of 356 women (72%), who sero-converted in VOICE from February 2010 to May 2012. At MTN-015 baseline visit, 78% (198/255) of women reported IC use (Figure 1). Among women reporting IC use at baseline, 92% (182/198) had at least one additional follow-up visit and were included in this analysis. The median time from estimated seroconversion to MTN-015 entry was 3 months (interquartile range (IQR) 2–4 months), and the median total follow- up time from estimated seroconversion to last follow-up visit was 24 months (IQR 14–26 months). Participant demographic, behavioral, and HIV-1 disease characteristics are presented in Table 1. The majority of participants were from South Africa (95%), young (median age 23, IQR 21–26), and unmarried (95%). IC discontinuation was reported by 34% (61/182) of baseline IC users during follow-up. Among IC discontinues, the median time from seroconversion to IC discontinuation was 23.5 months (range of 3–41 months). The median overall survival, or IC use, was 27.4 months (95% CI 26.5–36.7) from time of seroconversion.

Correlates of IC discontinuation for the univariate models are shown in Table 2. Lower rates of IC discontinuation following seroconversion were observed in women with baseline characteristics of already having at least one child (HR 0.39, 95% CI 0.20–0.82, $p = 0.02$) or earning personal income (HR 0.51, 95% CI 0.30–0.87, $p = 0.01$). During follow-up, women who reported condom use at last vaginal sex (HR 0.47, 95% CI 0.300.87, $p = 0.02$) also showed lower likelihood of IC discontinuation compared to women who did not report condom use at last vaginal sex. Factors not associated with rate of IC discontinuation in univariate models included age, education, other partnership characteristics, or disclosure of HIV status. Age was explored in stratified quartiles, none of which correlated with IC use (data not shown).

With regards to HIV-1 disease characteristics, higher baseline HIV-1 viral load correlated with a lower likelihood of IC discontinuation (HR 0.78, 95% CI 0.61–0.99, $p = 0.04$). During follow-up, women who initiated ART (HR 0.51, 95% CI 0.26–0.95, $p = 0.03$) showed lower rates of IC discontinuation compared to women who did not initiate ART during follow-up; however, the hazard rate was not constant over time given that participants started ART at varying points during follow-up. Of the IC discontinuers who initiated ART during follow-up, 29% (5/17) started ART at a visit prior to reporting IC discontinuation, and 47% (8/17) reported having started ART and not using IC at the same visit.

The final multivariate model included baseline variables of earning personal income and having at least one child, adjusting for age at baseline and having any male partner in the prior 3 months at follow-up (Table 2). Small sample size limited inclusion of additional variables and interaction terms. Age was included given its significance in published literature despite lack of statistical significance in the univariate model. Both earning personal income and having at least one child at baseline were highly significant in the

univariate models and remained significant in the multivariate model. Having any male partner in the prior 3 months was not significant in univariate analysis and was included to adjust for reduced sexual activity, a potential confounding variable in a woman's decision to use long-acting contraception. Figure 2 illustrates the Kaplan-Meier survival curve for IC use among participants over time from seroconversion, adjusting for earning personal income and having at least one child.

After excluding women who enrolled in MTN-015 more than 6 months after seroconversion, having at least one child (HR 0.28, 95% CI 0.14–0.61, $p = 0.002$) and earning personal income (HR 0.46, 95% CI 0.27–0.80, $p = 0.01$) remained associated with lower rates of IC discontinuation. Initiation of ART (HR 0.60, CI 0.30–1.13, $p = 0.12$) was not significantly associated with IC discontinuation in the sensitivity analysis.

Discussion

In this analysis of over 200 women with recent HIV-1 infection and access to IC and contraceptive counseling, we observed that two-thirds of women on IC at time of seroconversion chose to continue IC during follow-up, while one-third of participants reported discontinuing IC without substitution of another non-barrier contraceptive method, the majority of whom were not on ART at the time of discontinuation. The duration of follow-up for our analysis was longer than previous studies, which estimated rates of DMPA discontinuation over the first 12-months of IC use, and thus exact comparisons cannot be made to other published data.

IC discontinuation following HIV-1 seroconversion in absence of ART initiation raises concern for women at potentially heightened risk of unintended pregnancy and HIV-1 vertical transmission. Although motivations for IC discontinuation were not directly assessed, other studies have described side effects, younger age, desire for fertility, or abstinence from sexual activity as reasons for contraceptive discontinuation among HIV-positive and negative women in SSA and beyond (Barden, Spei-zer, Calhoun, & Corroon, 2018; Haddad et al., 2013b; Imbuki, et al., 2010; Nanda et al., 2011). Female fertility intentions cited as wanting more children in the next year were strongly associated with IC downgrading to OCPs, condoms or no method in a cohort of HIV positive couples in Zambia (Haddad et al., 2013b). Further studies are needed to assess fertility desires in recently seroconverted women. Even so identifying correlates of IC discontinuation may aid in recognition of at-risk women who may benefit from additional counseling on family planning, alternative contraceptive options, and ART initiation.

Baseline demographic factors, such as age and level of education, were not associated with IC discontinuation in the current analysis; however, having at least one child and earning personal income were protective against IC discontinuation. Associations of parity and employment with continuation of hormonal contraception have been observed in other cohorts outside of the context of seroconversion (Maraux et al., 2015; Melaku & Zeleke, 2014). Although these associations may not be specific to the time period surrounding seroconversion, our observations suggest the significance of their role in decision-making regarding fertility even in the context of recent HIV-1 infection. Again, we did not assess

fertility desires directly; however, having no children at present has been shown to be associated with positive fertility desires and intentions in women living with HIV/AIDS (Hoyt et al., 2012). Employment is a factor indicative of female autonomy, and one speculative conclusion would be that women who have their own income might feel empowered to take control of their reproductive health and be less likely to discontinue IC.

We observed an association of starting ART with lower rates of IC discontinuation; however, given differing times of ART initiation for individuals, this association was not constant over the follow-up period. Of note, at the time of the VOICE study and MTN-015 follow-up, the WHO recommendation for ART initiation prior to 2015 depended on CD4 count (WHO, 2015 September); therefore, many women with recent seroconversion and well-preserved immunologic status may not have been offered ART as standard care. Further, in another recent analysis, population-based surveillance data on contraception in combination with data from the local ART program in KwaZulu-Natal, South Africa, were used determine contraceptive use in women as they progressed through the HIV treatment cascade. Although overall contraceptive use increased across the cascade, dual protection with condoms and hormonal contraception increased only after ART initiation (Raif-man et al., 2014). Association between family planning and ART may reflect engagement in care; women may be more likely to continue IC if they have regular access to HIV services, education and counseling.

We focused on IC for this analysis given its high baseline frequency among family planning methods self-reported by MTN-015 participants, as well as reported in the literature (Darroch & Singh, 2011). Small sample size limited performance of a similar analysis on oral contraceptive users. Data on contraceptive use prior to MTN-015 entry also were not available for inclusion in the current analysis; however, data on IC use relative to HIV-1 risk were previously published for the VOICE trial (Noguchi et al., 2015). The fact that the parent study required women to be on an effective form of contraception for enrollment potentially contributes to bias in the study population. Although contraceptive counseling and onsite IC availability continued, the “requirement” was lifted for enrolling into MTN-015; therefore, discontinuation may have been influenced by removal of this pressure rather than individual choice. Discontinuation of contraception may reflect a return to previous behaviors prior to trial entry. We did not have concomitant data in women who did not acquire HIV-1 during the VOICE trial for comparison.

The current analysis has several other limitations. The homogeneity of the study population in terms of factors, such as age and marital status, made detecting any difference among them difficult and thus lessened the study’s generalizability. Family planning method was assessed at study visits and not in real-time between visits. Data were collected by face-to-face interviews and from women in a clinical trial, presenting a potential reporting and social desirability bias whereby IC use is over reported. That said, if we assume that compared to real-world scenarios, these women were in a more ideal situation with access to contraceptive options and counseling, then we are controlling to some extent for potentially confounding variables such as resource availability. Without these resources, IC discontinuation rates, or even lack of use at baseline, would be potentially higher. We also have no quantitative or qualitative data as to why women stopped using IC.

Nevertheless, many women with recently acquired HIV-1 face complex decision-making regarding family planning, and integration of contraception into HIV care to provide women options should take into account variables that are not easily assessed but nonetheless important to treatment outcomes. Acknowledging the fertility desires of HIV-1-infected women is the first step toward building combined HIV and family planning programs to optimize women's health and eliminate mother-to-child transmission of HIV-1 infection. Furthermore, recognizing the impact of personal choice, cultural and socioeconomic pressures related to childbearing decisions of women with recent HIV-1 infection may aid in developing effective programs for linking family planning services and HIV testing and care. Future research is needed to evaluate interventions at both the program and individual level to provide support for these linkages.

Conclusion

Availability of contraception is an essential component of HIV care in reproductive-age women, particularly following recent infection and before viral suppression by antiretroviral therapy. Recognizing personal choice, cultural and socio-economic pressures involved in childbearing decisions, particularly in women who do not have children or earn their own income, may be key to effective support of linkages between contraceptive services and HIV diagnosis and treatment.

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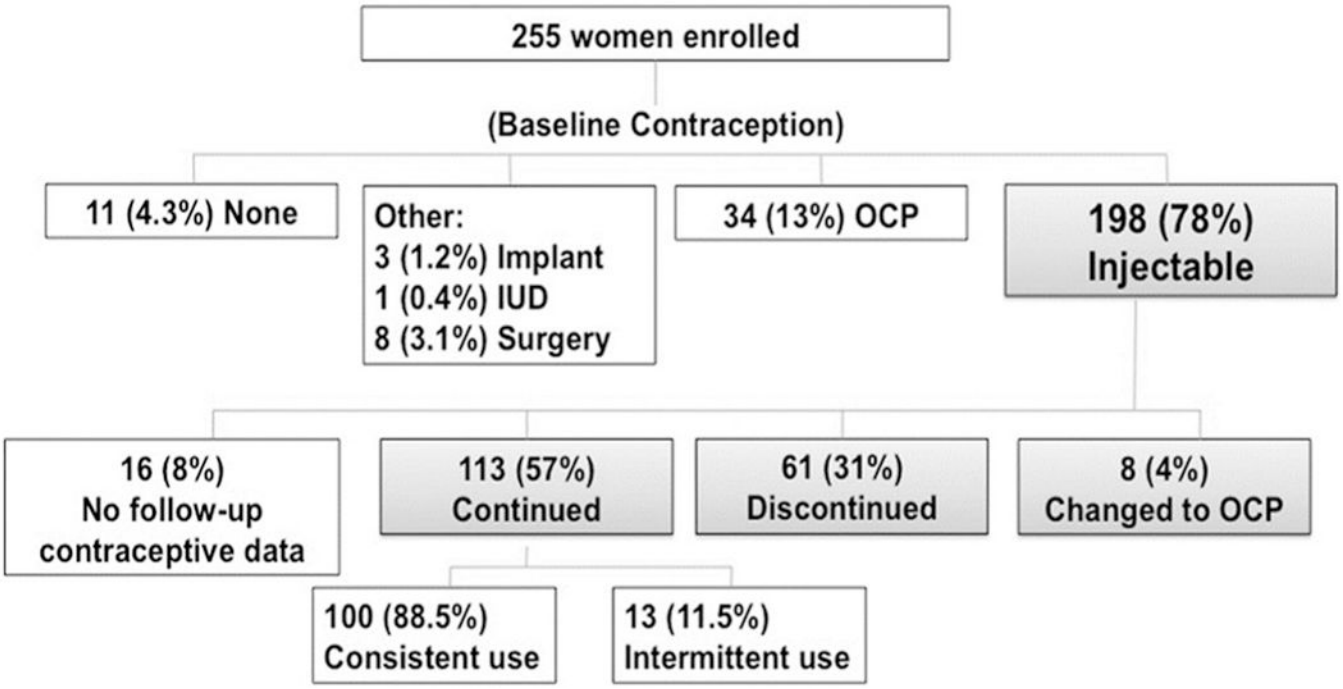

Figure 1.

Schematic of highly effective contraceptive use in women enrolled in the MTN-015 VOICE cohort. None = participants not reporting use of any other non-barrier form; OCP = oral contraceptive pill; IUD = intrauterine device; *gray* box = participants included in analysis.

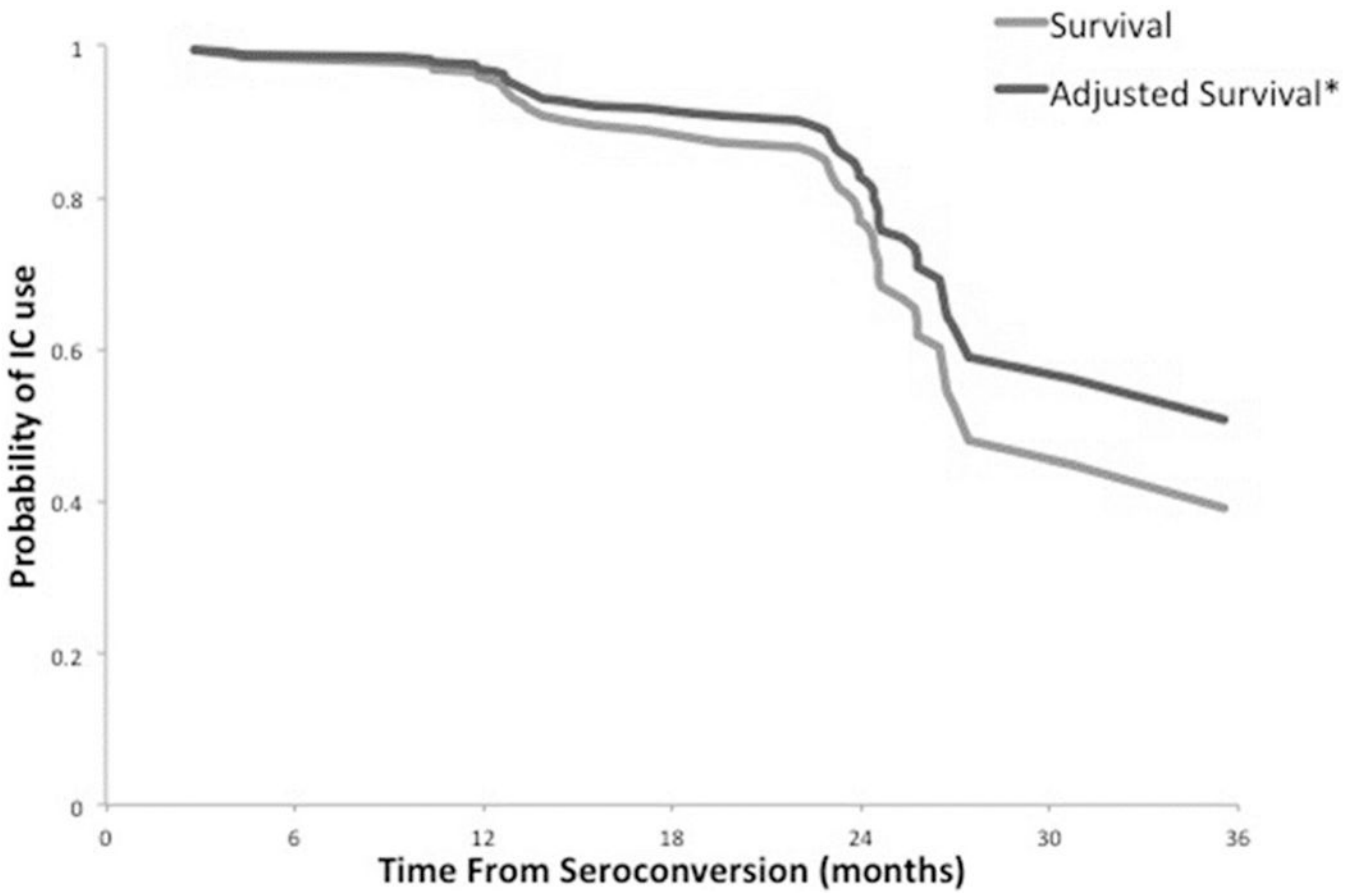

Figure 2.

Kaplan-Meier survival curves for IC use over time from seroconversion among participants overall (gray) and adjusted for having at least one child and earning personal income (black). *Adjusted by mean of covariates method for baseline variables of having at least one child and earning personal income.

Table 1.

Demographic, behavioral, and HIV-1-related characteristics of baseline IC users with follow-up data available (N = 182[#]).

Characteristic[^]	Count (%)	
Age, y median (IQR)	23	(21,26)[*]
Site: South Africa, n (%)	172	(95)
Education: Secondary school, n (%)	96	(53)
Parity: At least one child, n (%)	160	(88)
Socioeconomic Status, n (%)		
Owns a home	132/181	(73)
Earns personal income	109	(60)
Receives financial support from partner	145/168	(86)
Partnership characteristics		
Married, n (%)	10	(5)
Any male partner, n (%)	169	(93)
Any male partner in last 3 m at follow-up, n (%)	171	(94)
Number of partners in last 3 m, n median (IQR)	1	(1,1)[*]
Partner age, y median (IQR)	27	(24,30)[*]
Partner age at last vaginal sex >10y older, n (%)	103/181	(57)
Partner with known HIV status, n (%)	85/176	(48)
Partner with known HIV positive or unknown HIV status, n (%)	144/175	(82)
Partner with more than one partner, n (%)	108/168	(64)
Cohabitation with partner, n (%)	19/168	(11)
New partner during follow-up, n (%)	31/174	(18)
Intimate partner violence in last 12 m, n (%)	21/180	(12)
Sex for goods/money in last 3 m, n (%)	3/162	(2)
Condom use last vaginal sex at follow-up, n (%)	150/171	(88)
Disclosure of HIV status, n (%)		
To anyone	135/179	(75)
To partner	107/179	(60)
Immediate disclosure to partner	96/110	(87)

Characteristic^	Count (%)	
HIV-1 disease parameters		
HIV-1 viral load, log_{10} copies/mL median (IQR)	4.4	(3.6,5.0) *
CD4 absolute count, cells/mm^3 median (IQR)	558	(423,713) *
On ART, n (%)	2	(1)
Started on ART during follow-up, n (%)	43	(24)
Time from seroconversion to enrollment, m median (IQR)	3	(2,4) *
Total follow-up time from seroconversion, m median (IQR)	24	(14,26) *

Denominator listed for missing data when total N was less than 182.

^ Data collected at baseline unless otherwise specified as follow-up; m = months; y = years; n = count.

* Result expressed in median and interquartile range (IQR) rather than count and percentage as appropriate.

Table 2.

Univariate and multivariate hazard models of associations between covariates and time from seroconversion to IC discontinuation.

Variable^	Univariate models			Multivariate model*		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, y	1.03	(0.95–1.10)	0.37	1.06	(0.99–1.14)	0.08
Education: Secondary school	1.01	(0.61–1.69)	0.97			
Parity: At least one child	0.39	(0.20–0.82)	0.02	0.38	(0.17–0.91)	0.03
Socioeconomic Status						
Owns a home	0.87	(0.50–1.56)	0.61			
Earns personal income	0.51	(0.30–0.87)	0.01	0.58	(0.33–1.01)	0.05
Receives financial support from partner	0.66	(0.33–1.45)	0.28			
Partnership characteristics						
Married	1.21	(0.37–2.96)	0.72			
Any male partner	0.78	(0.36–2.05)	0.59			
Any male partner in last 3 m at follow-up	0.69	(0.28–2.28)	0.50	0.93	(0.33–2.62)	0.89
Partner age at last vaginal sex >10y older	0.63	(0.38–1.05)	0.08			
Partner with known HIV status	0.99	(0.59–1.64)	0.97			
Partner with more than one partner	1.11	(0.64–1.98)	0.71			
Cohabitation with partner	1.20	(0.52–2.42)	0.64			
New partner during follow-up	1.16	(0.60–2.09)	0.64			
Intimate partner violence in last 12m	0.61	(0.21–1.40)	0.27			
Sex for goods/money in last 3m	3.01	(0.73–8.30)	0.11			
Condom use last vaginal sex at follow-up	0.47	(0.26–0.93)	0.02			
Disclosure of HIV status						
To anyone	1.14	(0.65–2.15)	0.66			
To partner	1.08	(0.65–1.82)	0.77			
Immediate disclosure to partner	0.64	(0.25–2.17)	0.43			
HIV-1 disease parameters						
HIV-1 viral load, $\log_{10}$ copies/mL	0.78	(0.61 −0.99)	0.04			
CD4 absolute count, cells/mm^3	1.00	(1.00–1.00)	0.30			
Started on ART during follow-up	0.51	(0.26–0.95)	0.03			

^ At baseline unless otherwise specified; m = months; y = years

* See text for explanation of variable selection.