Title
Correlates of Injectable Contraceptive Discontinuation following HIV Seroconversion in an HIV Prevention Trial

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Correlates of Injectable Contraceptive Discontinuation following HIV Seroconversion in an HIV Prevention Trial

A thesis submitted in partial satisfaction of the requirements

for the degree Master of Science in Clinical Research

by

Margaret Rae Caplan

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ABSTRACT OF THE THESIS

Correlates of Injectable Contraceptive Discontinuation
following HIV Seroconversion in an HIV Prevention Trial

by

Margaret Rae Caplan
Masters of Science in Clinical Research
University of California, Los Angeles, 2016
Professor Robert M. Elashoff, Chair

Background: Injectable contraception (IC) is the most common form of highly effective contraception currently used in sub-Saharan Africa; however, its use has not been well described in HIV-infected women in the post-seroconversion period. This analysis aimed to examine factors associated with IC discontinuation following HIV seroconversion in an HIV prevention trial.

Methods: Following HIV acquisition in a prevention trial, 255 African women were enrolled in a longitudinal observational study (MTN-015). IC use was evaluated at MTN-015 entry and at 3, 12, and 24 months. Correlates of IC discontinuation were examined by Cox proportional hazard modeling.

Results: Of baseline IC users, 34% (61/182) of women with follow-up data discontinued use of IC without a non-barrier substitution. Having at least one child (adjusted HR 0.38, *p*= 0.03) and earning personal income (adjusted HR 0.58, *p*= 0.05) were associated with lower rates of IC discontinuation.

Conclusion: IC discontinuation was common post-seroconversion in HIV-infected African women despite onsite contraceptive services. Many women with recently acquired HIV face complex decision-making regarding family planning.

The thesis of Margaret Rae Caplan is approved.

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2016

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CHAPTER ONE: MANUSCRIPT

The following manuscript was prepared in anticipation of submission to the journal *Contraception*.

Abstract

Objective: To examine predictors of discontinuation of injectable contraception (IC) among African women following HIV seroconversion in an HIV prevention trial.

Methods: African women were enrolled in a longitudinal observational study (MTN-015) after seroconversion during the VOICE trial (MTN-003). Contraceptive methods were assessed at MTN-015 entry and at months (m) 3, 12, and 24 post-seroconversion. Women reporting IC use at baseline were evaluated longitudinally for continued use from time of seroconversion. Correlates of IC discontinuation during follow-up were examined by Cox proportional hazard modeling.

Results: Of 255 women enrolled, IC use was reported at baseline by 198 (78%) women, and 182 (91%) had follow-up data available. During follow-up 34% (61/182) of women discontinued IC completely without substitution of another highly effective contraception (HEC) method. Lower rates of IC discontinuation were observed with having at least one child (HR 0.39, CI 0.20-0.82, p= 0.02) and earning personal income (HR 0.51, CI 0.30-0.87, p= 0.01) at baseline. Other baseline demographic factors, partnership characteristics, and disclosure of HIV status were not significantly associated with IC discontinuation by Cox proportional hazard modeling.

Conclusion: Discontinuation of IC was common post-seroconversion in HIV-infected women despite onsite provision of contraceptive services. Recognizing socioeconomic pressures involved in the childbearing decisions of recently HIV-infected women is key to developing effective interventions to support linkages between contraceptive services and HIV diagnosis and care.

Implications (50 words): Highly effective contraception is a critical component of HIV care in reproductive-age women, particularly following recent infection and prior to viral suppression by antiretroviral therapy. Recognizing socioeconomic pressures involved in childbearing decisions is key to developing effective interventions to support linkages between contraceptive services and HIV diagnosis and treatment.

Keywords (max 6): Injectable, female contraception, HIV, Africa, seroconversion

1. Introduction

HIV/AIDS and maternal death remain the leading causes of death in women of reproductive age 15 to 44 years worldwide, and many of these deaths are preventable.[1] A key global strategy to improve maternal health is ensuring universal access to sexual and reproductive health services, including family planning.[2,3] Family planning has well-established public health benefits to both maternal and child health, particularly in regions of high HIV prevalence.[4] By reducing unintended pregnancies and optimizing timing of pregnancy, family planning not only provides HIV-infected women with protection from pregnancy- and post-partum-related complications but also affords time to improve their own health through treatment of HIV and other infections, thereby lowering risk of complications in childbearing.[5-8] Family planning reduces childhood morbidity and mortality by preventing mother-to-child transmission (PMTCT) of HIV,[9,10] as well

as averting challenges from uninfected-infant HIV exposure and parental morbidity and mortality.[11,12]

Advances in antiretroviral therapy (ART) have improved maternal and child health through treatment and prevention of HIV infection. By improving overall health, HIV-infected women on ART have increased fertility compared with HIV-infected women not on ART.[13,14] Among HIV-infected women initiating ART in Uganda, nearly one-third of the women became pregnant within the three years of starting ART; however, within the same cohort, Matthews et al. observed an association between increased mortality and the pregnancy and post-partum period, particularly during early ART.[15] This association suggests that expansion of ART alone is not enough to reduce maternal deaths and that timing of pregnancy is key to reduce risk of pregnancy-related complications.

Provision of contraception is necessary but not sufficient for effective family planning or for HIV prevention. Enhancing access to ART and highly effective contraception (HEC) addresses only one barrier to care in sub-Saharan Africa (SSA) and other resource-limited settings that carry the highest burden of HIV/AIDS and maternal deaths globally.[1] Understanding how HEC integrates into the lives of HIV-infected or at-risk women in SSA is critical to implementation and effectiveness of HEC. Examples of HEC include hormonal methods and intrauterine devices (IUD), which provide enhanced efficacy compared with barrier protection such as condoms in preventing pregnancy. Progestin-only injectable contraception (IC), namely depomedroxyprogesterone acetate (DMPA) and noresthisterone enanthate (NET-EN), has become the most common form of hormonal contraception used in SSA,[16] largely due to its ease of administration as an injection every 3 months. Even without reliance on daily dosing, the estimated 12-month discontinuation rates of DMPA range from 22 to 75% depending on study population.[17-22] Apart from medication side effects, factors associated with HIV-infected women

not using IC include younger age,[23] lower education,[24,25] unmarried status,[25] rural setting,[24] lack of parity,[22,26] unemployment,[26] and partner disapproval.[22]

An important window for pregnancy prevention is the time period surrounding HIV acquisition given the heightened risk for vertical transmission in acutely and recently seroconverted women who become or are already pregnant.[27,28] IC use during this window has not been well described, and examining patterns and predictors of IC discontinuation after HIV seroconversion will aid in identifying women who are at higher risk of pregnancy and possible vertical transmission.

The Microbicide Trials Network 015: An Observational Cohort Study of Women following HIV-1 Seroconversion in Microbicide Trials (MTN-015) follows women who acquired HIV during HIV biomedical prevention trials and provides an opportunity to examine IC use following HIV seroconversion. For the current analysis, we aimed to examine demographic and behavioral factors associated with IC discontinuation after HIV seroconversion among a subset of women from one parent trial, Vaginal and Oral Interventions to Control the Epidemic (VOICE, MTN-003).[29]

2. Methods

2.1 Study design, population, and procedures

MTN-015 is a multi-site, prospective, observational cohort study designed to follow women after HIV seroconversion in parent MTN HIV prevention trials of antiretroviral-based topical microbicide and oral PrEP in order to examine the nature of HIV disease progression and treatment response in women acquiring HIV under these conditions. The current analysis

focused on one MTN parent trial, VOICE (MTN-003, study period from September 2009 to August 2012). Briefly, VOICE was a randomized, placebo-controlled trial to assess daily use of oral tenofovir disoproxil fumarate (TDF), oral tenofovir-emtricitabine (TDF-FTC), or 1% tenofovir (TFV) vaginal gel as pre-exposure prophylaxis (PrEP) against HIV infection. Detailed trial methods of MTN-003[31] and MTN-015[32] are described elsewhere. While participants in other parent trials completed follow-up prior to the start of the MTN-015 enrollment period, participants in VOICE were offered enrollment in MTN-015 upon coming off the parent study. Limiting this analysis to the VOICE cohort attempted to minimize the potential for the length of time that a participant spent off-study prior to enrollment in MTN-015.

MTN-015 enrolled women who seroconverted in VOICE from 15 study sites across South Africa, Zimbabwe, and Uganda and followed them between May 2010 and June 2014 for a planned minimum of 12 months after HIV seroconversion identification date.[30] 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, although use of HEC was not required for MTN-015 study participation. MTN-015 participants received 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. Of note, VOICE participants were required per protocol to use HEC defined as hormonal method (e.g. injectable, pill, implant, or vaginal ring), IUD, or partner sterilization for the duration of the VOICE study.

Only women with an MTN-015 entry visit and at least one follow-up visit were included in the current analysis. Demographic data were collected at the MTN-015 entry visit, which is also referred to as the “baseline” visit. Behavioral questionnaires, which included assessment of

contraceptive method by self-report, were administered via face-to-face interviews at MTN-015 entry 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.

2.2 Statistical Analysis

The primary aim of the current analysis was to examine correlates of IC discontinuation without substituting another HEC following HIV seroconversion in VOICE. The primary outcome was time from estimated HIV seroconversion to IC discontinuation. Date of HIV seroconversion was estimated from the midpoint between the last HIV 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 HEC 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 discontinuing IC use. Baseline IC users who switched from IC to another HEC also 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 were grouped as "continuers" if they reported IC use at their last visit. Participants who reported IC use at every attended visit were considered as "consistent" users and grouped as "continuers."

Cox proportional hazard modeling was conducted to examine correlates of IC discontinuation. Cox proportional hazard modeling that utilized the time from MTN-015 entry rather than from seroconversion to IC discontinuation also was performed. Sensitivity analyses excluding women with time from seroconversion to MTN-015 entry of greater than 6 months were performed.

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).

3. Results

3.1 Primary Analysis

MTN-015 enrolled 255 of 356 women (72%), who seroconverted in VOICE from February 2010 to May 2012. At MTN-015 study entry, 78% (198/255) of women who enrolled reported IC use (Figure 1).

Among women reporting IC use at baseline, 91% (182/198) had at least one additional follow-up visit after study entry and were included in the current analysis. The median time from estimated seroconversion to MTN-015 entry was 3 months (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).

Demographic, behavioral, and HIV-disease characteristics of women included in the current analysis 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 users during follow-up. The median time from seroconversion to IC discontinuation was 23.5 months (range of 3 to 41 months). In Figure 2, survival curves for IC use are shown for both time from HIV seroconversion and time from MTN-015 enrollment. The analysis using time from seroconversion takes into account additional lead-in time from the point at which seroconversion occurred in the parent trial to the point at which the participant enrolled in MTN-015. The overall shape of both curves is similar; however, given the additional lead-in time, the curve for time from seroconversion is shifted to the right compared with the curve for time from enrollment. This difference is most evident in the 24-month time point, where 51% of the baseline IC users remain at risk in the seroconversion curve (Figure 2A) compared to 18% of the baseline IC users in the enrollment curve (Figure 2B).

Correlates of IC discontinuation for the univariate models are shown in Table 2. Significantly 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 0.30-0.87, *p=0.02*) also showed lower rates 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 to partner or anyone.

The general relationship between variables and IC discontinuation did not change when we considered time from enrollment to discontinuation rather than time from seroconversion to discontinuation, although the distributions shifted right as previously noted when time from seroconversion was used rather than time from enrollment. Age was explored in stratified quartiles, which did not correlate with IC use (Figure 3). Figures 4 and 5 illustrate survival curves for IC use grouped by earning personal income and having at least one child at baseline, respectively.

With regards to HIV disease characteristics, higher baseline HIV viral load correlated with a lower rate 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, although the hazard rate was not constant over time as shown by crossing of survival curves in Figure 6. 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 discontinuation of IC, and 47% (8/17) reported starting ART and discontinuing 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 moths was not significant in univariate analysis (Figure 7) but was included to adjust for reduced sexual activity as

represented by lack of a partner, a potential confounding variable in a woman's decision to use contraception. Figure 8 illustrates the survival curve for IC use among participants over time from seroconversion, adjusting for earning personal income and having at least one child.

3.2 Sensitivity Analyses

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 significantly correlated with lower rates of IC discontinuation (Figure 9). 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.

4. Discussion

Over one-third (34%) of women in the current analysis discontinued IC use after HIV seroconversion without substitution of another HEC and despite onsite availability of IC and contraceptive counseling. Furthermore, the majority of women who stopped using IC were not on ART at the time of discontinuation and therefore were at high risk of pregnancy and subsequent maternal to child transmission of HIV infection if pregnancy were to occur. The horizon of follow-up for our analysis was longer than previous studies of estimated rates of DMPA discontinuation over the first 12-months of IC use and thus exact comparison cannot be made to published data.

Baseline demographic factors, such as age and marital status, were not shown to be associated with IC discontinuation; 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 also have been observed in other cohorts outside of the context of seroconversion.[24,26] Although these associations may not be specific to the time period surrounding seroconversion, our observations suggest that their potential significance in decision-making regarding fertility is consistent throughout women's lives even in the setting of recent HIV infection. We did not assess fertility desires directly; however, having no children at present has been shown to be a factor associated with positive fertility desires and intentions in women living with HIV/AIDS.[34] Employment is one factor associated with women's empowerment, and one speculative conclusion would be that women who have their own income thus 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 individual participants, the association was not constant over the follow-up period. In another recent analysis, Raifman et al. (2014) used population-based surveillance data on contraception in combination with data from the local ART program in KwaZulu-Natal, South Africa, to determine contraceptive use in women as they progressed through the HIV treatment cascade, from being unaware of infection to being virologically suppressed on ART. An increase in contraceptive use across the cascade was observed from less than 40% among HIV-infected women who did not know their status to greater than 70% among women who have been on ART for 4-7 years. Of note, these estimates were made from a composite of all contraception, including condoms. More effective methods with dual protection, including modern contraception, increased only after initiation of ART.[35] The latter conclusion is consistent with our finding of association between IC continuation and ART initiation at follow-up. Association between family planning and ART initiation may reflect

ongoing engagement in care; women may be more likely to continue using HEC if they have regular access to HIV services where they receive education and counseling.

We focused on IC for this analysis given its high baseline frequency as the HEC of choice among family planning methods self-reported by MTN-015 participants, as well as reported in the literature. A small sample size limited performance of a similar analysis on baseline oral contraceptive users. Data on contraceptive use prior to MTN-015 entry also were not available for this analysis; however, data on IC use relative to HIV risk have been previously published for the VOICE trial.[33] The fact that the parent study VOICE required women to be on an effective form of contraception potentially contributes to bias in the study population. Although contraceptive counseling and onsite availability of HEC continued to be provided, the "requirement" was lifted post-seroconversion upon enrolling into MTN-015, and 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 during the VOICE trial for comparison.

The current analysis has several other limitations. The study is observational with a small sample size relative to number of variables being explored, and the homogeneity of the study population in terms of factors, such as age and marital status, made detecting small differences among them difficult and lessens its generalizability. Family planning method was assessed at study visits and not in real-time between visits, and thus time from seroconversion to discontinuation was estimated based on an estimated seroconversion date and the study visit at which IC was already not being used. Data was collected by face-to-face interviews and from women in a clinical trial, presenting a potential reporting and social desirability bias.

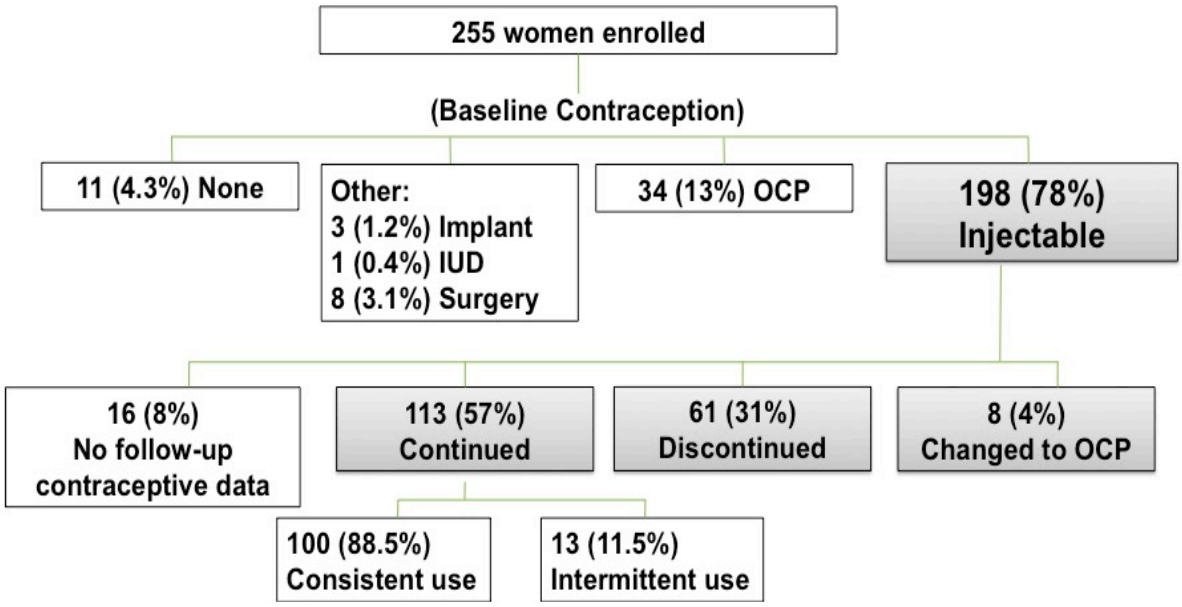
Nevertheless, if we assume that compared to real-world scenarios, these women were in a more ideal situation with access to contraceptive options and counseling, then we are controlling to some extent for confounding variables such as resource availability, and without these resources, the IC discontinuation rate, or even lack of use at baseline, would be potentially higher. The observation that over one third of women discontinued IC during follow-up is particularly concerning because fewer women overall may be using IC in practice.

Understanding demographic and behavioral factors associated with discontinuation of IC may help to identify women at risk of unplanned pregnancy and in need of additional interventions. Many women with recently acquired HIV face complex decision-making regarding family planning, and more effective integration of HEC into HIV care should take into account variables that are not easily assessed but nonetheless important to treatment outcomes. Acknowledging the fertility desires of HIV-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 infection. Furthermore, recognizing the socioeconomic pressures related to childbearing decisions of women with recent HIV infection may aid in developing effective programs for linking HIV testing, HIV/ART care and family planning services. Future research is needed to evaluate interventions at both the program and individual level to provide support for these linkages.

5. Acknowledgements

We thank the women who participated in this study. We also acknowledge the MTN-015 study team and study sites for their work on data and sample collection.

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.

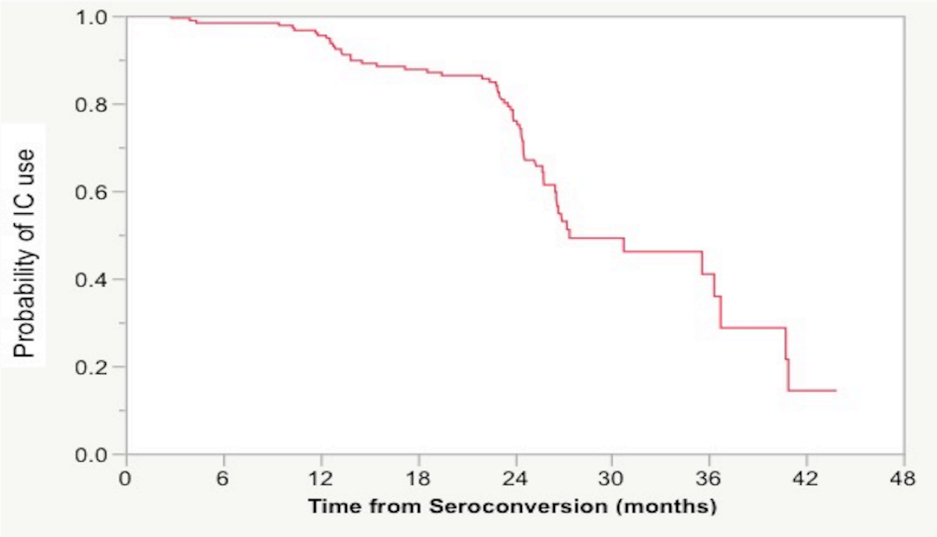
Table 1. Demographic, behavioral, and HIV-related characteristics of baseline IC users with follow-up data available (N=182[#])

Characteristic[^]	Count (%)	
Age, y median (IQR)	23	(21,26)*
Time from seroconversion to enrollment, m median (IQR)	3	(2,4)*
Total follow-up time from seroconversion, m median (IQR)	24	(14,26)*
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 3m at follow-up, n (%)	171	(94)
Number of partners in last 3m, 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 12m, n (%)	21/180	(12)
Sex for goods/money in last 3m, 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	(59)
Immediate disclosure to partner	96/110	(87)
HIV disease parameters		
HIV 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)

[#] 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.

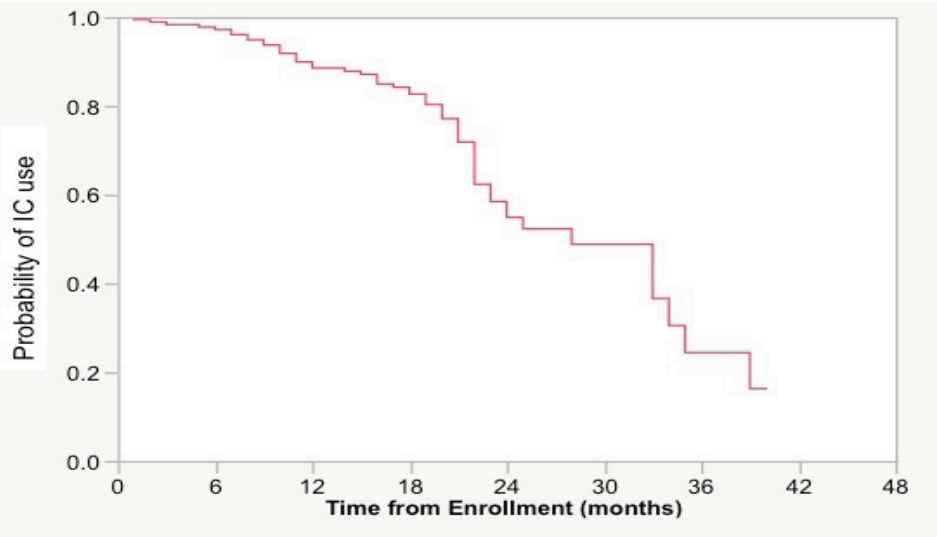
Figure 2. Kaplan-Meier (KM) survival curves for IC use over time from A) sercoconversion or B) MTN-015 enrollment among all participants reporting IC use at baseline visit (N=182).

A.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
IC users	182	177	164	126	92	19	5	3	0
(Percent of baseline)		97%	93%	69%	51%	10%	3%	2%	0%

B.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
IC users	182	172	131	110	33	13	5	3	0
(Percent of baseline)		94%	72%	60%	18%	7%	3%	2%	0%

Table 2. Univariate and multivariate hazard models of associations between covariates and time from seroconversion to IC discontinuation

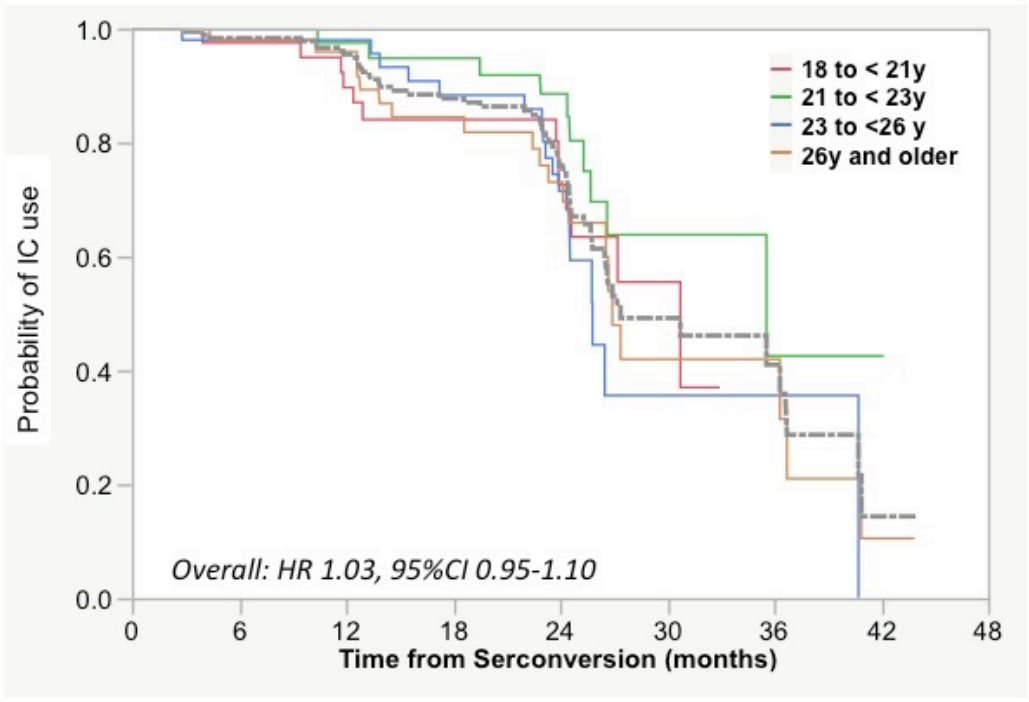
Variable[^]	Univariate models			Multivariate model[*]		
	HR	95% CI	p	HR	95% CI	p
Age, y	1.03	(0.95-1.10)	0.37	1.06	(0.99-1.14)	0.08
Education: Secondary school	1.01	(0.61-1.69)	0.97			
Parity: At least one child	0.39	(0.20-0.82)	0.02	0.38	(0.17-0.91)	0.03
Socioeconomic Status						
Owns a home	0.87	(0.50-1.56)	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 3m 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 disease parameters						
HIV 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.

Figure 3. KM survival curves for IC use grouped by age quartiles over time from A) seroconversion or B) MTN-015 enrollment (dashed line represents overall survival).

A.



B.

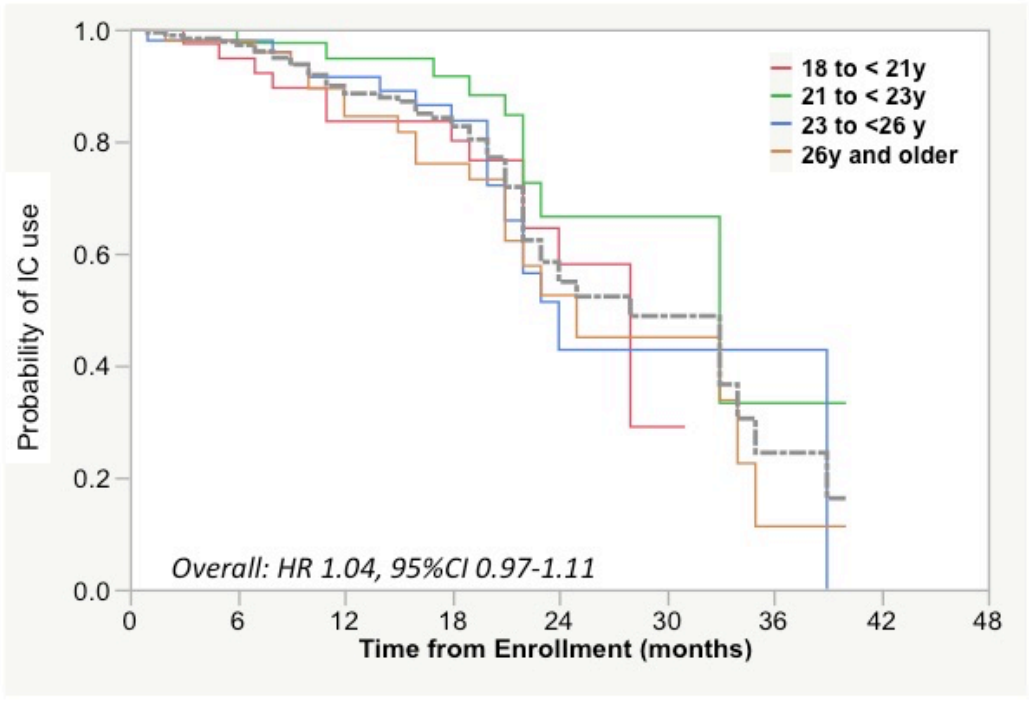
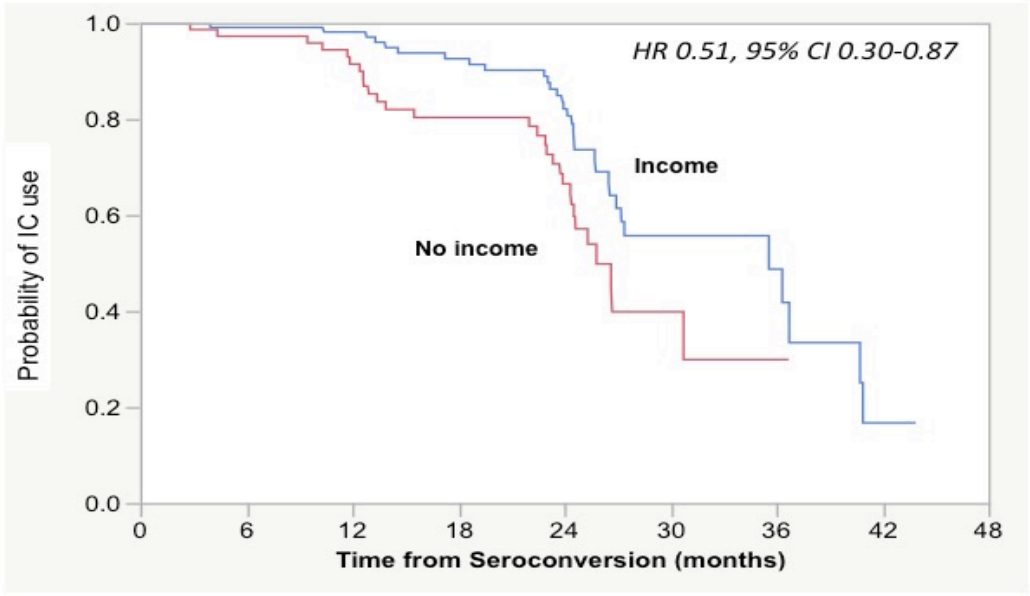


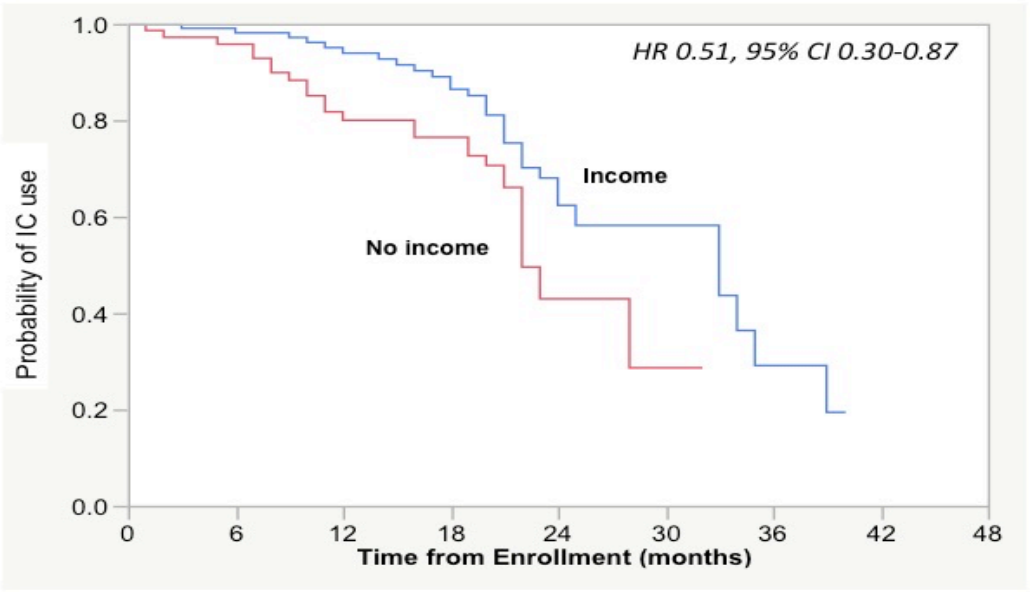
Figure 4. KM survival curves for IC use grouped by earning personal income (blue) and no personal income (red) over time from A) seroconversion or B) MTN-015 enrollment.

A.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
Income	**109**	**106**	**101**	**79**	**60**	**15**	**8**	**3**	**0**
(Percent of baseline)		97%	93%	72%	55%	14%	7%	3%	0%
No income	**72**	**71**	**63**	**47**	**33**	**5**	**2**	**0**	**0**
(Percent of baseline)		99%	88%	65%	46%	7%	3%	0%	0%

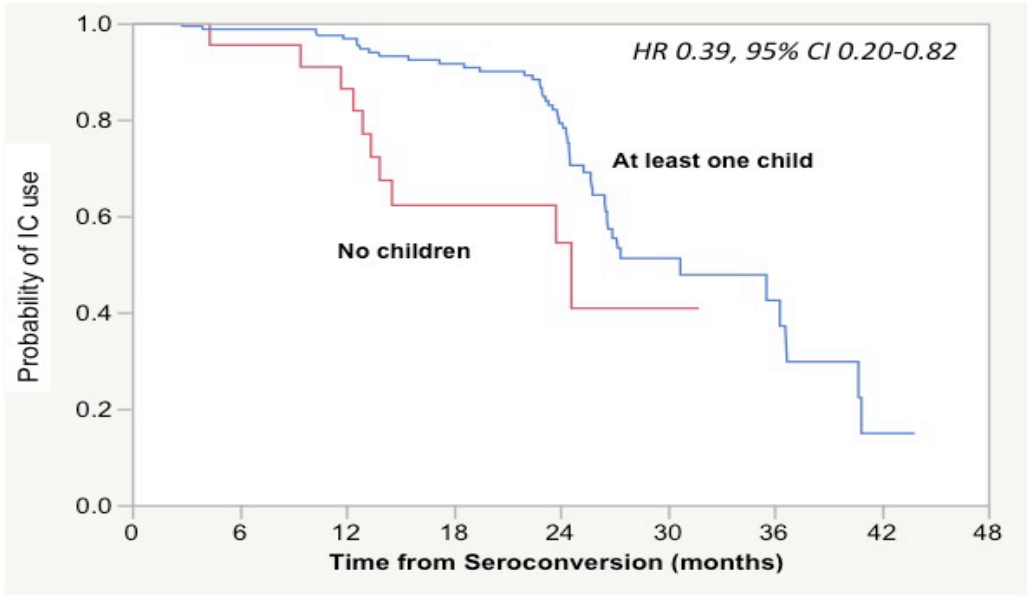
B.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
Income	**109**	**105**	**83**	**69**	**24**	**11**	**5**	**0**	**0**
(Percent of baseline)		96%	76%	63%	22%	10%	5%	0%	0%
No income	**72**	**66**	**47**	**41**	**9**	**3**	**0**	**0**	**0**
(Percent of baseline)		92%	65%	57%	13%	4%	0%	0%	0%

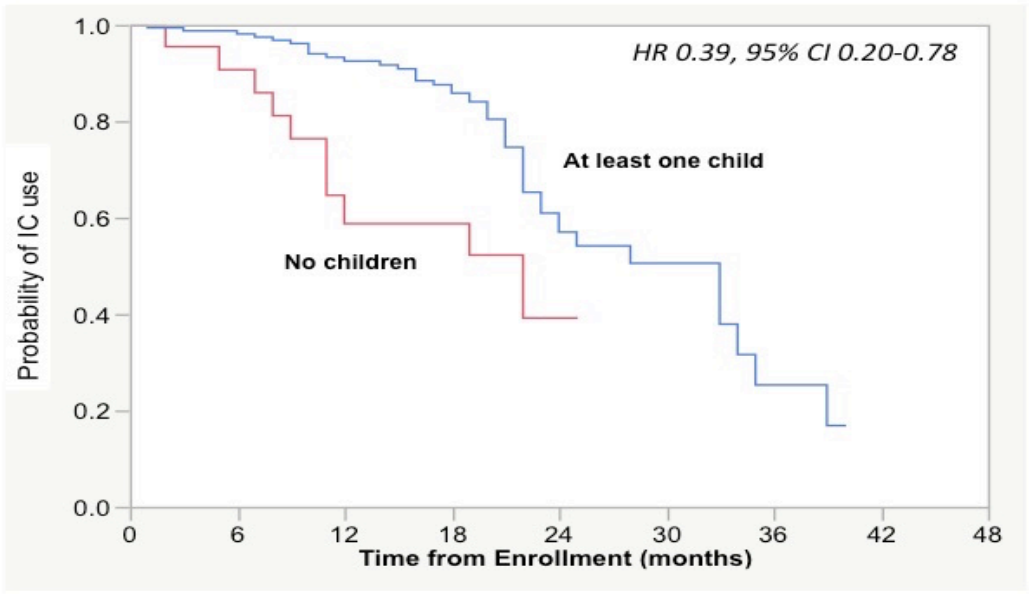
Figure 5. KM survival curves for IC use grouped by having had at least one child (blue) and not having any children (red) at baseline over time from A) seroconversion or B) MTN-015 enrollment.

A.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
At least one child	160	156	145	116	85	18	9	3	0
(Percent of baseline)		98%	91%	73%	53%	11%	6%	2%	0%
No children	22	22	20	11	8	2	0	0	0
(Percent of baseline)		100%	91%	50%	36%	9%	0%	0%	0%

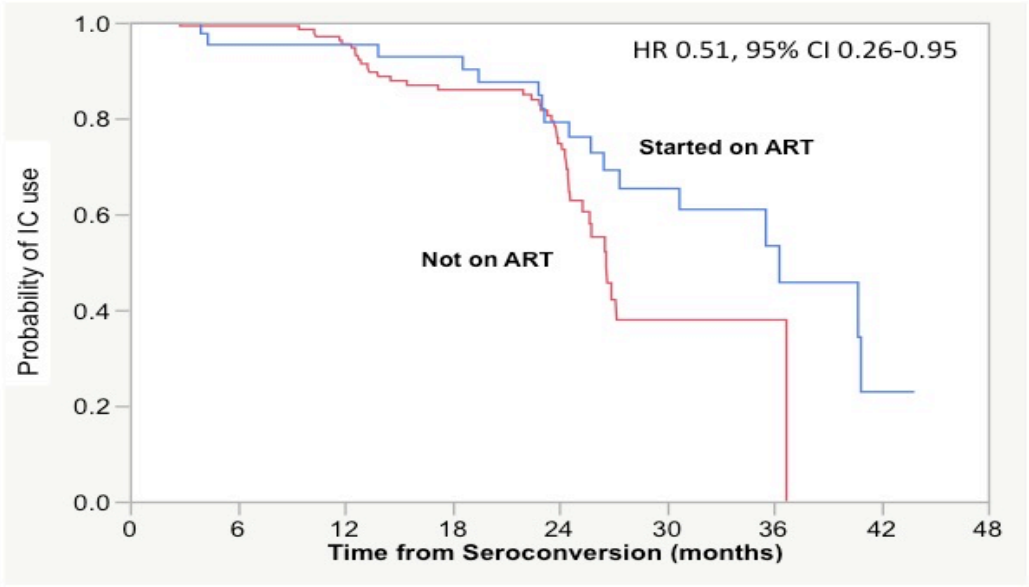
B.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
At least one child	160	153	120	101	31	13	5	2	0
(Percent baseline)		95%	75%	63%	19%	8%	3%	1%	0%
No children	22	20	11	10	2	0	0	0	0
(Percent of baseline)		91%	50%	9%	1%	0%	0%	0%	0%

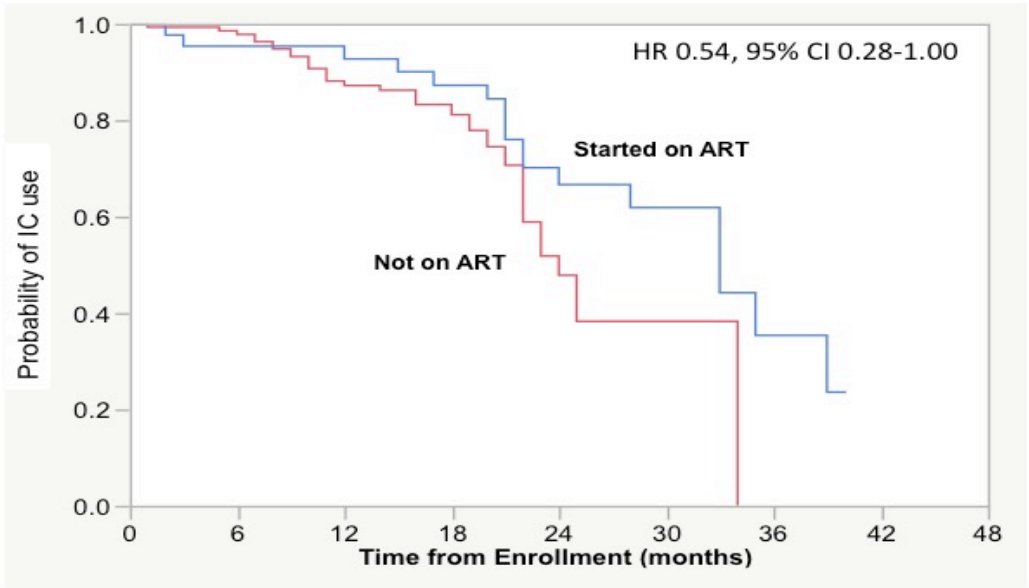
Figure 6. KM survival curves for IC use grouped by starting on ART during follow-up and not starting on ART during follow-up over time from A) seroconversion or B) MTN-015 enrollment.

A.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
Started on ART	43	42	41	36	29	18	8	3	0
(Percent of baseline)		98%	95%	84%	67%	42%	19%	7%	0%
Not on ART	139	136	124	91	64	2	0	0	0
(Percent of baseline)		98%	89%	65%	46%	1%	0%	0%	0%

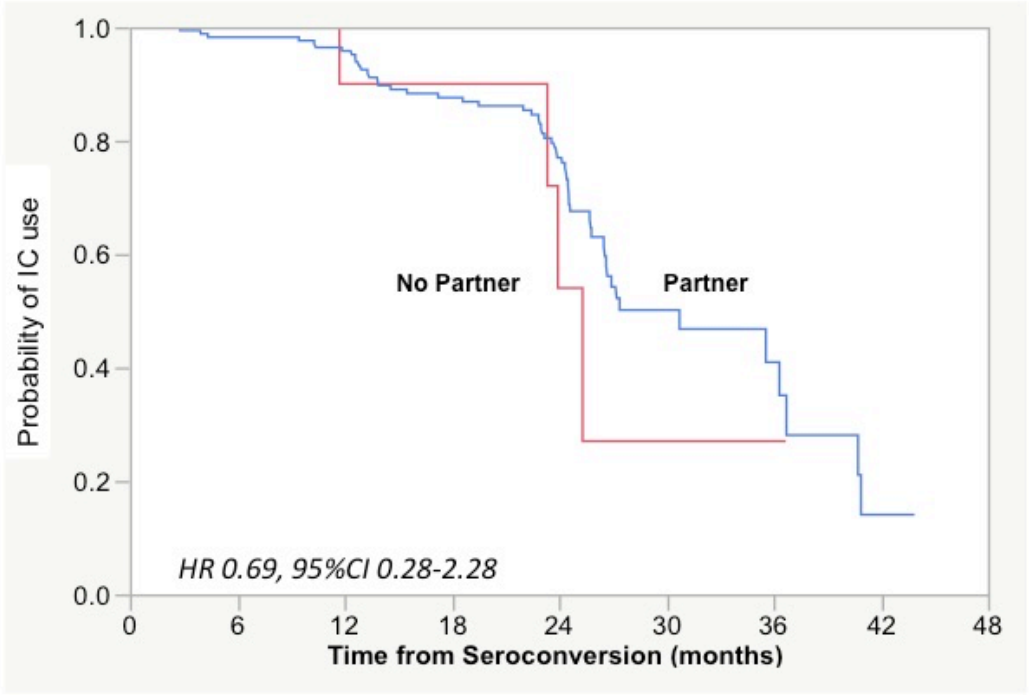
B.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
Started on ART	43	41	36	32	20	12	5	0	0
(Percent of baseline)		95%	84%	74%	47%	28%	12%	0%	0%
Not on ART	139	132	95	79	13	5	0	0	0
(Percent of baseline)		95%	68%	57%	9%	4%	0%	0%	0%

Figure 7. KM survival curves for IC use grouped by having had at least one partner in last 3 months (blue) and not having a partner in last 3 months (red) during follow-up over time from A) seroconversion or B) MTN-015 enrollment

A.



B.

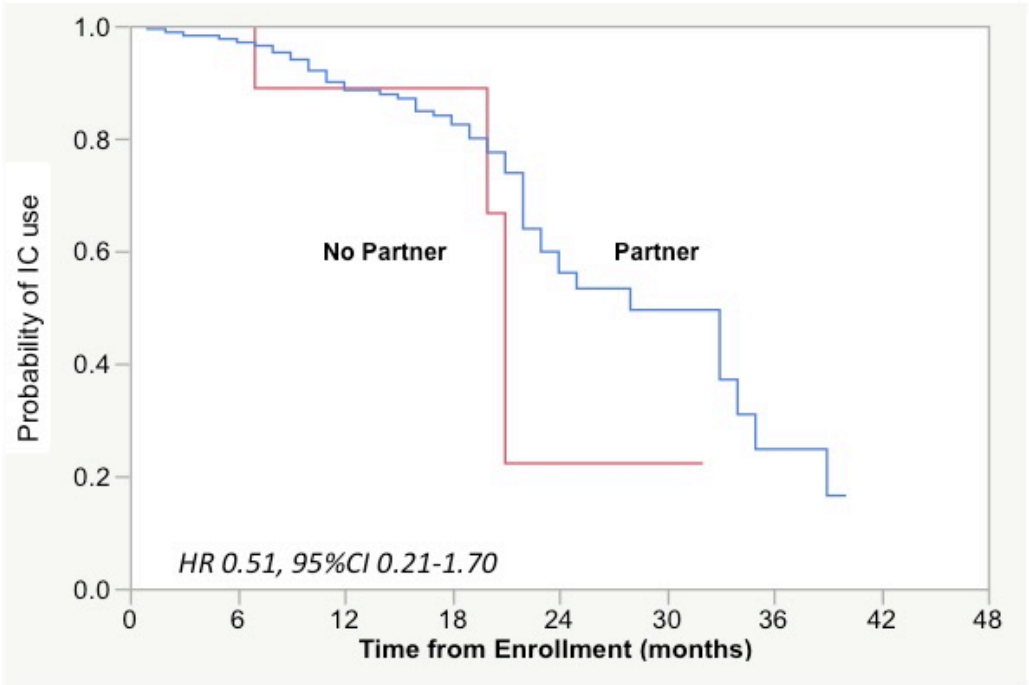
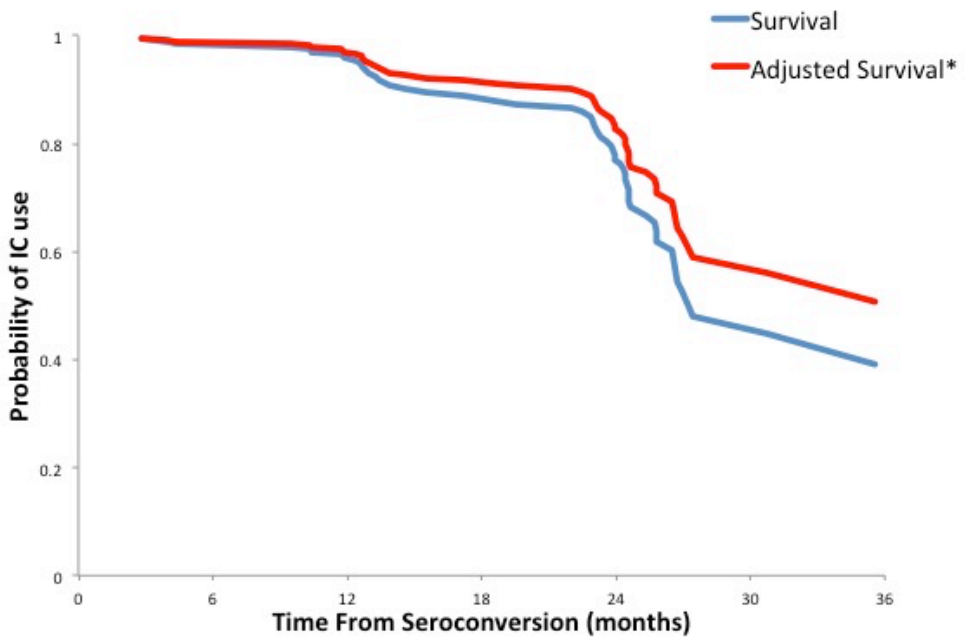


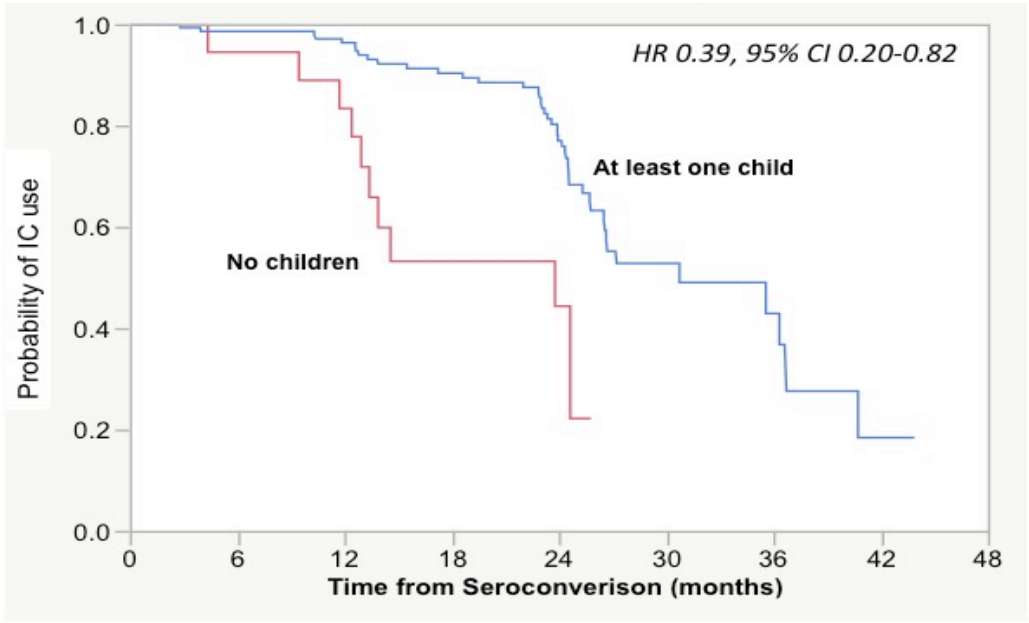
Figure 8. KM survival curves for IC use over time from seroconversion among participants overall (blue) and adjusted for having at least one child and earning personal income (red).



*Adjusted by mean of covariates method for baseline variables of having at least one child and earning personal income

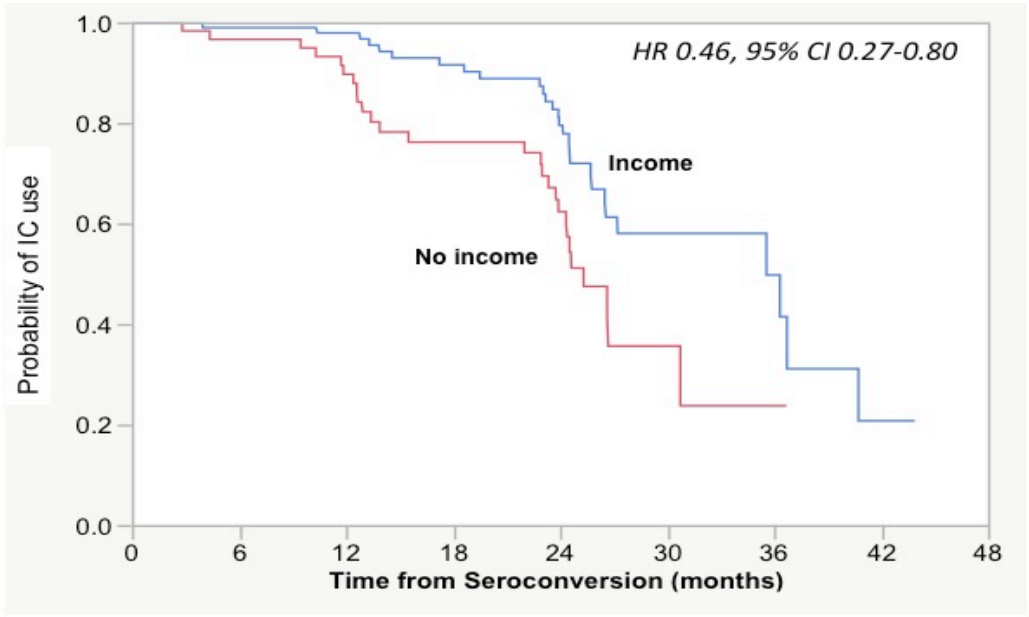
Figure 9. Sensitivity analyses excluding women with prolonged time to MTN-015 entry of greater than 6 months (m) for baseline characteristics of A) having at least one child or B) earning personal income (*n = 158*).

A.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
At least one child	**140**	**136**	**127**	**99**	**72**	**16**	**7**	**3**	**0**
(Percent of baseline)		97%	91%	71%	51%	11%	5%	2%	0%
No children	**18**	**18**	**16**	**9**	**6**	**0**	**0**	**0**	**0**
(Percent of baseline)		100%	89%	50%	33%	0%	0%	0%	0%

B.



Number at risk	Baseline	6m	12m	18m	24m	30m	36m	42m	48m
Income	**98**	**95**	**90**	**68**	**51**	**13**	**7**	**3**	**0**
(Percent of baseline)		97%	92%	69%	52%	13%	7%	3%	0%
No income	**59**	**58**	**52**	**39**	**27**	**4**	**2**	**0**	**0**
(Percent of baseline)		98%	88%	66%	46%	7%	3%	0%	0%

CHAPTER TWO: STATISTICAL APPENDIX

Survival C statistic: Gönen and Heller

In order to assess outcomes discrimination for the Cox proportional hazard models, survival C-statistics were calculated using the 'CPE' package in R version 3.1.2 (www.r-project.org), which implements the G**ö**nen & Heller concordance probability estimate (CPE).[36] This concordance index is relatively unaffected by independent censoring and aims to predict survival based on the linear predictors or event probabilities from the Cox model.[37]

The C statistic for each variable in association with time from HIV seroconversion to IC discontinuation is shown for the univariate models in Table 3 below. Additional variables demonstrating higher values of C statistic (greater than 0.525) that were not statistically significant by Cox-proportional hazard modeling (at $p<0.05$) were older age of partner at last vaginal sex as reported at baseline, having an HIV positive partner, and baseline CD4 count (absolute and percentage). Notably, the highest C statistic 0.57 was for earning personal income, and none were greater than 0.6, suggesting a relatively low discriminating power of predicting whom will discontinue using IC based on univariate analyses.

The C statistic was calculated for the multivariate model (Multivariate 1) that was selected in the primary analysis as shown in Table 4. The addition of multiple variables increased the discriminatory power of the model. For comparison, an alternative multivariate model (Multivariate 2) was assessed taking into account reported condom use at last vaginal sex in place of the variable having at least one partner in the last three months. The two variables (condom use at last vaginal sex and at least one partner in the last 3 months) were not included in the same model due to multicollinearity: during the study, participants who reported not

having a partner in the last months were not subsequently asked behavioral questions regarding last vaginal sex as they were assumed not to be sexually active.

Overall the C statistics were not highly informative in this analysis.

Table 3. Survival C statistics associated with each variable and time from seroconversion to IC discontinuation (Row color denotes high (green) to low (red) values).

Variable^	Univariate models
	C-statistic
Age, y	0.532
Parity: At least one child	0.547
Earns Personal Income	0.577
Follow-up at least 1 partner last 3m	0.511
Follow-up condom use at last vaginal sex	0.539
Education: Secondary school	0.501
Owns a home	0.514
Married	0.505
Male sexual partner	0.508
Partner age, y	0.512
Baseline older partner age at last vaginal sex	0.555
Cohabitation at baseline	0.509
Partner financial support	0.525
Partner with >1 other partner	0.512
Intimate partner violence in last 12 m	0.525
Known HIV status of partner	0.501
HIV positive partner	0.529
Baseline Partners in last 3months	0.505
Baseline transactional sex in last 3m	0.509
HIV status disclosure anyone	0.512
HIV status disclosure to partner	0.509
HIV status Immediate disclosure	0.525
Changed partner during follow-up	0.511
HIV viral load, log copies/mL	0.571
Baseline CD4 count, absolute, cell/mm3	0.531
Baseline CD4 count, percentage	0.537
Started ART during follow-up	0.558

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

Table 4. Survival C statistics associated with multivariate models in predicting IC discontinuation (Row color denotes high (green) to low (red) values).

Variables^	Univariate C-statistic	Multivariate 1 C-statistic	Multivariate 2 C-statistic
Age, y	0.532	**0.620**	0.636
At least one child	0.547		
Earns Personal Income	0.577		
Follow-up at least 1 partner last 3 months	0.511		XX
Follow-up condom use at last vaginal sex	0.539	XX	

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

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