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Hormonal contraception, pregnancy, breastfeeding and risk of HIV disease progression among Zambian women

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Abstract

Background—Some studies suggest hormonal contraception, pregnancy, and/or breastfeeding may influence rates of HIV disease progression.

Methods—From 1994-2012, HIV discordant couples recruited at couples' voluntary HIV counseling and testing centers in Lusaka were followed 3-monthly. Multivariate survival analyses explored associations between time-varying contraception, pregnancy, and breastfeeding and two outcomes among HIV-positive women: 1) time-to-death and 2) time-to-antiretroviral treatment (ART) initiation.

Results—Among 1,656 female seropositive, male seronegative couples followed for 3,359 person years (PY), 224 women died (6.7/100PY;95%CI:5.8-7.6). After 2003, 290 women initiated ART (14.5/100PY;95%CI:12.9-16.2). In a multivariate model of time-to-death, hormonal implant (aHR=0.30;95%CI:0.10-0.98) and injectable (aHR=0.59;95%CI:0.36-0.97) were significantly protective relative to non-hormonal method use while OCP use was not (aHR=1.08;95%CI: 0.74-1.57) controlling for baseline HIV disease stage, time-varying pregnancy, time-varying breastfeeding, and year of enrollment. In a multivariate model of time-to-ART initiation, implant

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was significantly protective (aHR=0.54;95%CI:0.31-0.95) while OCP (aHR=0.70;95%CI: 0.44-1.10) and injectable (aHR=0.85;95%CI:0.55-1.32) were not relative to non-hormonal method use controlling for variables above, woman's age, and literacy. Pregnancy was not significantly associated with death (aHR=1.07;95%CI:0.68-1.66) or ART initiation (aHR=1.24;95%CI: 0.83-1.86) while breastfeeding was protective for death (aHR=0.34;95%CI:0.19-0.62) and ART initiation (aHR=0.49;95%CI:0.29-0.85).

Conclusions—Hormonal implants and injectables significantly predicted lower mortality; implants were protective for ART initiation. OCPs and pregnancy were not associated with death or ART initiation, while breastfeeding was protective for both. Findings from this 18-year cohort study suggest 1) HIV-positive women desiring pregnancy can be counseled to do so and breastfeed, and 2) all effective contraceptive methods including injectables and implants should be promoted to prevent unintended pregnancy.

Keywords

breastfeeding; HIV disease progression; hormonal contraception; longitudinal cohort; pregnancy; Zambia

Introduction

Hormonal contraceptive method use is associated with decreased maternal-child mortality, reduced unintended pregnancy, and improved reproductive autonomy for women [1]. Hormonal methods are also a mainstay of Prong II (prevention of unintended pregnancy) of the WHO's four-pronged prevention of mother-to-child transmission (PMTCT) strategy [2]. However, conflicting evidence exists as to whether hormonal method use increases HIV disease progression in infected women [3]. A systematic review by Phillips et al [4] found that ten of eleven observational studies showed no increased risk for HIV disease progression for hormonal versus non-hormonal method users. However, a randomized controlled trial (RCT) in which Zambian women were randomized to receive either the copper intrauterine device (IUD) or hormonal contraception (depot medroxyprogesterone acetate (DMPA) injectables or oral contraceptive pills (OCPs)) found in an intention-to-treat analysis that OCP use and DMPA use were associated with 1) CD4 <200 cells/mm^3 or ART initiation and 2) death or CD4 <200 cells/mm^3 or ART initiation compared to women using the copper IUD [5]. Though an RCT, this study suffered from high rates of method stopping and switching [3]. Current WHO Medical Eligibility Criteria (MEC) recommendations, developed after reviewing this literature, place no restriction on use of hormonal contraceptive methods by women based on HIV status [3].

The alternative to contraception is often pregnancy, and the relationship between pregnancy and associated hormonal changes and HIV disease progression has been studied for over two decades [6,7] also with mixed findings. A recent systematic review and meta-analysis [7] synthesized findings from several observational studies. Of four studies meeting inclusion criteria [8-11], pregnancy was marginally though not significantly associated with low CD4 among ART naïve women; the only study from an Africa cohort (Uganda) also did not find an association between pregnancy and time-to-CD4 <200 cells/mm^3 [10]. Conversely, in five studies meeting inclusion criteria [12-15], pregnancy was significantly associated with HIV-

related death; the only study from an African cohort (Rwanda) did not find an association with time-to-HIV-related death[12]. Three other recent observational studies (with the primary objective of assessing the relationship between hormonal contraception and HIV disease progression) also reported measures of effect for time-varying pregnancy with conflicting findings. A study of 2,269 chronically HIV infected women from seven East and Southern African countries found that pregnancy was significantly associated with first occurrence of CD4 <200 cells/mm^3, ART initiation, or non-traumatic death[16]. Conversely, another study among 303 recently HIV infected women from Uganda and Zimbabwe found no significant association between pregnancy and time-to-clinical AIDS, death, or ART initiation[17]. Finally, a study among 625 Ugandan women also found no significant association between pregnancy and time-to-AIDS or death [18].

Finally, as pregnancy is often followed by breastfeeding which is also associated with hormonal changes, researchers have undertaken studies of the relationship between breastfeeding and HIV disease progression again with mixed findings. An RCT in Kenya showed that mortality among women randomized to breastfeeding increased three fold [19], while studies in Tanzania, Zambia, South Africa, Zimbabwe, and Malawi have not observed associations between breastfeeding and death or decreased CD4 count [20-24].

With a growing population of HIV-infected women in sub-Saharan Africa, evaluating factors that may predict disease progression is imperative to improve health outcomes. In this study, we identify factors associated with HIV disease progression in HIV-positive women in Zambia and specifically evaluate the impact of contraceptive use, pregnancy, and breastfeeding on disease progression.

Methods

Ethics

Approvals by the Office for Human Research Protections-registered Institutional Review Boards at Emory University and in Zambia were obtained. All participating couples provided written informed consent.

Participants

Study recruitment, eligibility, follow-up, and data collection methods employed by the Rwanda Zambia HIV Research Group (RZHRG) have been reported previously [25-28]. Briefly, we recruited cohabiting couples in Lusaka, Zambia via community promotions [29-31] to receive couples' voluntary HIV counseling and testing (CVCT) services [32]. HIV discordant couples were enrolled in 3-monthly longitudinal follow-up between 1994-2012. This analysis considers only couples in which the woman was HIV-positive at enrollment; women were censored if the couple separated, their male partner seroconverted, or if either partner was lost to follow-up. HIV testing using rapid serologic tests was conducted at baseline (and three-monthly visits for negative partners)[33]. The primary objective of this cohort study was to determine predictors of heterosexual HIV-1 transmission, and censoring criteria were selected based on that primary objective.

Exposures of interest

Time-varying contraceptive method, pregnancy, and breastfeeding were the exposures of interest. Contraceptive methods were provided at the research site at each 3-monthly follow-up visit [34,35] categorized as: condoms alone, OCPs were typically combination estrogen and progesterone; progesterone-only pills were prescribed to breastfeeding women until children were six months old), DMPA injectables (150mg IM dosage), copper IUD, contraceptive implant (Norplant or Jadelle levonorgestrel implant), or permanent methods (hysterectomy, tubal ligation, or vasectomy)). Contraceptive methods were categorized as implant, injectable, or OCP versus non-hormonal contraception control (including condoms alone, copper IUD, or permanent methods). Time-varying pregnancy was determined via pregnancy test or visual confirmation by a nurse counselor. Time-varying breastfeeding included intervals in which women self-reported breastfeeding and all intervals that were up to six months post-partum without infant death.

Covariates

As previously reported, baseline and time-varying demographic, family planning, behavioral, sexual history, and clinical data are collected from each couple [28]. In this analysis, we considered covariates known or hypothesized to be related to disease progression including baseline measures of women's year of study enrollment, age (continuous and categorical measures considered), monthly household income (US Dollar equivalent, adjusted for exchange rate, continuous and categorical measures considered), literacy in Nyanja (the most common local language), and stage of HIV. We used the Modified Kigali combined HIV staging system, which incorporates clinical stage with erythrocyte sedimentation rate (ESR), hematocrit, and body mass index (BMI)[32,36].

Outcomes

Primary outcomes of interest are time-to-1) all cause-death among female partners (>90% of which were HIV related) or 2) ART initiation (not including short-course for PMTCT) among female partners. Since ART was not readily available in Zambia before 2003 and the first ART initiation occurred in November of 2003, analysis of ART initiation is restricted to November 2003-2012. Date of death among women was reported by male study partners or other family members. Time of ART initiation was obtained by self-report or plasma ART levels. Since we censor at ART initiation, no ART users are included in the time-to-death analysis.

Data analysis

Analyses were conducted with SAS v9.4 (Cary, NC). Outcome rates were calculated as the number of outcomes per woman-year of follow-up, stratified by time-varying contraceptive method exposure, pregnancy, and breastfeeding. Event rates were compared to reference groups using univariate Cox models. Outcome rates were also calculated stratified by other demographic and clinical covariates. Associations between these covariates and the outcomes of interest were evaluated using univariate Cox models. Crude hazard ratios (HRs), 95% confidence intervals (CIs), and associated p-values are presented.

Multivariate Cox models accounting for repeated observations estimated the effect of time-varying contraceptive methods and covariates on the outcomes of interest. Covariates included in the models were those that were significantly associated with the outcome of interest in univariate analyses using Bonferroni corrected p-values (p=0.006) and which changed point estimates for any exposures of interest by +/- 10%. Multi-collinearity was assessed; if any two variables were collinear, the variable with the weakest association with the outcome was removed. The proportional hazards assumption was confirmed for time-independent covariates.

Sensitivity analyses

Sensitivity analyses explored the effects of running models using censoring during pregnancy intervals and, for time-to-death, we additionally ran a model including women's baseline viral load which was a significant predictor of death but only available from 1999 onwards. We also built multivariate models assessing the effect of progestin-only and combined OCPs separately, and removing IUDs from the reference group. Finally, we varied the assumed duration of breastfeeding from 4-months to 1-year postpartum.

Results

Outcome rates overall and by contraceptive methods, unadjusted (Table 1)

Among 1,656 M-F+ couples followed for 3,359 person-years (PY), 224 women died (6.7/100PY;95%CI:5.8-7.6). Compared to women using non-hormonal methods, women using implants (HR=0.32, p=0.051) and injectables (HR=0.60, p=0.040) experienced lower rates of death while women using OCPs did not (HR=1.19, p=0.340). Compared to women who were not pregnant, women who were currently pregnant did not experience significantly increased rates of death (HR=1.32, p=0.211) while women who were currently breastfeeding (HR=0.32, p<0.001) experienced lower rates of death.

The first ART initiation occurred in November of 2003. Between November 2003-2012, 290 women initiated ART (14.5/100PY;95%CI:12.9-16.2). Compared to women using non-hormonal methods, women using implants (HR=0.45, p=0.004) and OCPs (HR=0.65, p=0.044) experienced significantly lower rates of ART initiation in univariate analyses, as did women using injectables though this was not significant (HR=0.71, p=0.098). Compared to women who were not pregnant, women who were currently pregnant experienced non-statistically significantly increased rates of ART initiation (HR=1.28, p=0.217) while women who were currently breastfeeding (HR=0.45, p=0.003) experienced significantly lower rates of ART initiation.

Outcome rates by covariates, unadjusted (Table 2)

Covariates significantly (Bonferroni p<0.006) associated with time-to-death included enrolling in the study at any time before 2007 (HR between 2.12- 3.02) versus after 2007, and having stage III (HR=2.15) or stage IV (HR=2.91) HIV disease versus stage I at enrollment, and increasing viral load (HR=2.43).

Covariates associated (Bonferroni p<0.006) with time-to-ART initiation included enrolling in the study before 2007 (HR between 0.21-0.42) versus any time after 2007, increasing woman's age (HR=1.06), being literate in Nyanja (HR=1.43), and having stage III (HR=1.90) or stage IV (HR=3.09) HIV disease versus stage I at enrollment.

Multivariate models and sensitivity analyses: time-to-death (Table 3)

In a multivariate model of time-to-death (Model 1), hormonal implant (aHR=0.30) and injectable (aHR=0.59) were significantly protective relative to non-hormonal method use while OCP use was not (aHR=1.08, NS) controlling for baseline HIV disease stage, time-varying pregnancy, breastfeeding, and year of study enrollment. Pregnancy was not significantly associated with death (aHR=1.07, NS) while breastfeeding significantly delayed death (aHR=0.34) in multivariate analyses. In the model censoring for pregnancy intervals (Model 2), implant use (p=0.040), injectable use (p=0.032), and breastfeeding (p<0.001) reached significance for their protective effects on time-to-death. In both Models 1 and 2, having stage III (aHR=2.00-2.01) or stage IV (aHR=2.66-2.95) HIV disease versus stage I at enrollment was significantly associated with time-to-death.

In a multivariate model additionally controlling for baseline log viral load (VL), though VL was significantly associated with time-to-death (aHR=2.66;95%CI:1.99-3.53, p<0.0001), the addition of VL did not change the point estimates for the exposures of interests by +/- 10% and was therefore not considered a confounder of the associations of interest. Running models among those with VL measures (collected after 1999) but without the VL covariate showed similar results (data not shown).

Multivariate models and sensitivity analyses: time-to-ART initiation (Table 4)

Multivariate models and sensitivity analyses: time-to-ART initiation (Table 4). In a multivariate model of time-to-ART initiation post-November 2003 (Model 1), implant was significantly protective (aHR=0.54) while OCP (aHR=0.70, NS) and injectable (aHR=0.85, NS) use were not significantly protective relative to non-hormonal method use controlling for woman’s baseline age, literacy, HIV disease stage, time-varying pregnancy, time-varying breastfeeding, and year of study enrollment. Pregnancy was not significantly associated with ART initiation (aHR=1.24, NS) while breastfeeding was significantly protective for ART initiation (aHR=0.49) in multivariate analyses. In the model censoring for pregnancy intervals (Model 2), implant use (p=0.048) and breastfeeding (p=0.013) reached significance for their protective effects on time-to-ART initiation while injectable (p=0.393) and OCP use (p=0.162) were non-significantly protective. In both Models 1 and 2, increasing age (aHR=1.05), being literate in Nyanja (aHR=1.39-1.41), and having stage III (aHR=2.13-2.15) or stage IV (aHR=3.62-3.82) HIV disease versus stage I at enrollment were significantly associated with time-to-ART initiation.

Sensitivity analyses (data not shown)

Multivariate models assessing the effect of progestin-only and combined OCPs separately did not change our findings related to OCPs (i.e., the point estimates for OCPs in multivariate models did not change in magnitude by +/-10%, direction, or statistical significance). For example, in multivariate model 1 of time-to-ART initiation, the HR for

combined OCPs was 0.69;95%CI:0.42-1.12 and for progestin-only OCPs was 0.78;95%CI: 0.19-3.20. Excluding IUDs from the referent group leads to similar findings (i.e., the point estimates for contraceptive methods in multivariate models did not change in magnitude by +/-10%, direction, or statistical significance). We do not have the power to look at IUD users individually (only 1.5% of all intervals were IUD using intervals). Assuming breastfeeding of 4-months up to 1-year did not change our findings (i.e., the point estimates for breastfeeding in multivariate models did not change in magnitude by +/-10%, direction, or statistical significance).

Discussion

In this prospective cohort of HIV-positive Zambian women in discordant couples, we found injectable hormonal contraception and hormonal implant associated with significantly lower mortality rates when adjusted for pregnancy, breastfeeding and demographic and clinical covariates. We did not observe this association with OCP. In an analogous analysis of time-to-ART initiation, only the protective effect of the hormonal implant was statistically significant. Time dependent measures of pregnancy were not significantly associated with either death or ART initiation while breastfeeding was significantly protective for both.

The majority of published observational studies have found no increased HIV disease progression among women using hormonal methods [4]. Our study shows a protective effect of hormonal implant and injectable contraception. These findings are similar to Allen et al [35], which found a borderline protective effect for time varying injectable (p=0.09) and OCP (p=0.08) use and time-to-HIV-related death in Rwandan women in multivariate models. Similarly, Heffron et al [16] found that rates of disease progression (using a composite outcome of CD4 decline to less than 200 cells/mm^3, initiation of ART, or death) were significantly lower for women using hormonal contraceptives versus non-hormonal contraceptive methods in a prospective cohort of women from seven East and southern African countries.

We also did not find that time-varying measures of pregnancy were significantly associated with either HIV disease progression outcome, similar to findings from several meta-analyses and individual studies which do not indicate a deleterious effect of pregnancy on HIV disease progression [6,7,17,18,35,37] and in contrast to the relatively few studies which have seen this association [7,16]. The finding that breastfeeding was strongly associated with a delay in both death and ART initiation was somewhat surprising given an RCT in Kenya which showed that mortality among women randomized to breastfeeding was three times higher than the corresponding rate among bottle-feeding women [19]. However, subsequent studies in Tanzania, Zambia, South Africa, Zimbabwe, and Malawi have not seen an association between breastfeeding and death or decreased CD4 count [20-24]. We may be observing the result of the “healthy pregnant woman” bias, since women who are able to get pregnant (and then breastfeed a child who survives) are healthier.

The association between women who experience pregnancy or breastfeeding (not necessarily those who are currently pregnant or breastfeeding) is also of interest. In the time-to-ART initiation analysis, cumulative prior pregnancies and associated breastfeeding

reported at enrollment were collinear with age. We retained age in the model (which was a significant risk factor); replacing age with cumulative prior pregnancy gave a non-significant protective effect for that variable (aHR=0.99;95%CI:0.94-1.05, p=0.75). Neither age nor cumulative prior pregnancies and associated breastfeeding were associated with death in univariate or multivariate analyses.

Though findings from the START trial suggest ART should now be offered at time of diagnosis [38], we feel that use of ART initiation as a proxy outcome for disease progression remains relevant given that ART rationing is a current front-line reality in many locations [39,40]. Despite the lowering of initiation criteria by WHO over the years, a review of 56 articles from 2002-2013 showed that CD4 counts at ART presentation in sub-Saharan Africa have not increased over the past ten years [41]. However, it is possible that changes in national guidelines may lead to increased median CD4 counts at ART initiation, as it has in Rwanda [42] and if economic conditions improve so that initiation upon diagnosis becomes a reality, ART as a proxy outcome for disease progression may become less relevant.

It was not surprising that viral load and HIV staging were predictive of mortality and that HIV staging was predictive of ART initiation. The staging system combining clinical and laboratory criteria employed here has been shown to reflect a range of HIV-related outcomes including death and have prognostic significance among HIV-positive women in Rwanda [32] and Zambia [36]. This further supports the use of the modified Kigali combined staging system (using hematocrit and ESR in lieu of CD4, including pulmonary tuberculosis in stage 4, and substituting low BMI for weight loss, among other less impactful adaptations) for predicting HIV-related disease outcomes among adults in circumstances that do not allow systematic CD4 screening.

Our findings also suggest that illiteracy may be a barrier to ART initiation. Similarly, recent systematic review using data from South Africa suggests that people with low education attainment have lower access to ART [43]. In our study, though staff provided ART referrals and assisted patients in accessing ART services in government clinics to the extent possible if obstacles were reported, low literacy may have impeded patient willingness or their ability to follow through on referrals and prescriptions. This hypothesized role of socioeconomic disparities in health warrants further exploration among Zambian women.

Our study has limitations, including that we began following women after they were already HIV-infected and therefore cannot measure time-to-event since HIV infection; however we do not expect any bias introduced by not knowing the duration of infection to be differential. Similarly, we did not follow women from the time they initiated contraception prior to study start, but again we do not expect this bias to be differential -- and in fact, most women (77.2%) were not using any method of contraception at baseline. Deaths were reported by family members who provided verbal autopsies, and many ART initiations were self-reported, but again we do not expect any information bias to be differential by the exposure of interest. Women who chose certain contraceptive methods may be different from those who chose others by unmeasured confounders. Additionally, as we censor couples at seroconversion of the HIV-negative male partner, we may be limiting our follow-up of more vulnerable woman-person-years. Loss to follow-up among M-F+ couples, which we have

reported in our cohorts to be associated with residence far from the clinic, younger age, and younger women's age at first intercourse, no income, fewer lifetime sex partners, no history of genital abnormalities in women, and male partners having a recent concurrent partner [26] may also limit the generalizability of our findings. Finally, three-monthly study visits included assessments of HIV disease and referrals to government clinics where ART was available, so our clients were likely to initiate ART sooner than people in the general population also limiting generalizability.

Our study has several strengths. We are able to reliably assess contraceptive method use and rates of stopping/switching by providing the methods at the research site every three months; this overcomes limitations with self-reported method use commonly reported in other studies. As the outcomes of interest were also assessed often, at least 3-monthly, we are able to more accurately assess when outcomes occurred. We also have relatively more power than previous studies to disaggregate the effects of implant use (73% power for the time-to-death analysis and 55% power for the ART initiation analysis for implant use) on disease progression. Finally, we measure and control for several fixed and time-varying covariates associated with disease progression.

Conclusions

Hormonal contraceptive implants and injectable contraception were associated with significantly lower mortality rates among HIV infected women. Hormonal implants were also protective for ART initiation. OCPs and pregnancy were not associated with death or ART initiation, while breastfeeding was protective for both. These findings add to a relatively small, inconclusive literature and suggest that HIV-positive women desiring pregnancy can be counseled to do so and to breastfeed without concerns about deleterious health related to pregnancy or breastfeeding.

For HIV-positive women who wish to delay fertility, our findings support the conclusion that hormonal implants and injectables can be used without concerns about deleterious health effects and with possible health benefits. Given high rates of unintended pregnancy and associated maternal-child mortality among HIV-positive women in sub-Saharan Africa, as well as the cost-effectiveness of prevention of unintended pregnancy for PMTCT strategy [44], we recommend increasing the contraceptive method mix for all women with and at-risk of HIV with a focus on long-acting reversible contraceptive (LARC) methods, both hormonal and non-hormonal, which are highly effective and may be associated with better health outcomes among HIV-positive women but remain inaccessible in much of Africa. Further study is needed of the copper IUD, a non-hormonal LARC method that is highly cost-effective in preventing unplanned pregnancy and may have health benefits for HIV-positive women. Finally, as we have shown previously that contraception uptake increases, especially LARC methods, after couples' HIV and family planning counseling with fertility intention assessment [45], we recommend that HIV and family planning services in Africa be integrated with a focus on couples.

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Table 1

Disease progression outcome rates and univariate associations with time-varying contraceptive methods, pregnancy status, and breastfeeding (N = 1656 HIV-positive women in discordant relationships, Lusaka, Zambia)

	1995-2012							Nov 2003-2012						
	PY at risk	Deaths	Outcome / 100 PY	HR	95% CI		p-value	PY at risk	ART initiations	Outcome / 100 PY	HR	95% CI		p-value
Total outcomes:	**3358.5**	**224**	**6.7**					**2001.9**	**290**	**14.5**				
Time-varying exposures														
Contraceptive method														
Non-hormonal*	2319.4	161	6.9	ref				1306.7	226	17.3	ref			
Implant	166.9	3	1.8	0.32	0.10	1.00	0.051	144.4	14	9.7	0.45	0.26	0.77	0.004
Injectables	416.9	19	4.6	0.60	0.37	0.98	0.040	276.2	26	9.4	0.71	0.47	1.07	0.098
OCPs	455.3	41	9.0	1.19	0.84	1.68	0.340	274.6	24	8.7	0.65	0.42	0.99	0.044
Pregnant														
No	2771.6	185	6.7	ref				1632.6	245	15.0	ref			
Yes	265.3	23	8.7	1.32	0.86	2.04	0.211	149.4	29	19.4	1.28	0.87	1.88	0.217
Breastfeeding														
No	2896.2	212	7.3	ref				1812.0	276	15.2	ref			
Yes	471.0	12	2.5	0.32	0.18	0.57	<.001	198.6	14	7.1	0.45	0.26	0.77	0.003

* Intrauterine device, none/condoms alone, permanent methods

HR: hazard ratios from univariate Cox models; PY: person-years; CI: confidence interval; ART: antiretroviral treatment; OCP: oral contraceptive pills

p-values are 2-tailed from univariate Cox models

Table 2

Disease progression outcome rates and univariate associations with baseline covariates (N = 1656 HIV-positive women in discordant relationships, Lusaka, Zambia)

	1995-2012							Nov 2003-2012						
	PY at risk	Deaths	Outcome / 100 PY	HR	95% CI		p-value	PY at risk	ART initiations	Outcome / 100 PY	HR	95% CI		p-value
Baseline measures														
Date of enrollment														
1995-1998	1288.6	104	8.1	2.12	1.25	3.62	0.006	181.2	16	8.8	0.36	0.22	0.61	<0.001
1999-Nov 28, 2003	871.1	62	7.1	3.02	1.74	5.25	<.0001	622.0	30	4.8	0.21	0.14	0.30	<.0001
Nov 29, 2003-2006	651.7	42	6.4	2.57	1.44	4.58	0.001	651.7	71	10.9	0.42	0.32	0.55	<.0001
2007-2012	555.8	16	2.9	ref				555.8	173	31.1	ref			
Age (per year increase)				1.01	0.99	1.03	0.340				1.06	1.04	1.08	<.0001
Age (years)														
<25	1082.4	71	6.6	ref				530.2	45	8.5	ref			
25-34	1655.2	108	6.5	1.07	0.79	1.46	0.644	1077.6	156	14.5	1.70	1.22	2.37	0.002
≥35	629.7	45	7.1	1.17	0.80	1.70	0.416	402.8	89	22.1	2.72	1.90	3.90	<.0001
Monthly family income (USD)														
0-30	958.8	79	8.2	ref				451.5	48	10.6	ref			
31-90	1503.6	97	6.5	0.86	0.64	1.16	0.322	875.9	114	13.0	1.05	0.75	1.47	0.795
≥91	869.4	47	5.4	0.87	0.60	1.27	0.503	665.2	126	18.9	1.16	0.83	1.64	0.387
Reads Nyanja														
With difficulty/not at all	2487.9	172	6.9	ref				1479.0	194	13.1	ref			
Yes, easily	809.2	48	5.9	0.87	0.63	1.20	0.406	489.3	94	19.2	1.43	1.12	1.83	0.005
HIV stage														
Stage I	1374.3	61	4.4	ref				932.6	125	13.4	ref			
Stage II	1056.1	53	5.0	1.03	0.71	1.49	0.887	598.9	75	12.5	1.16	0.87	1.55	0.304
Stage III	777.0	86	11.1	2.15	1.54	3.00	<.0001	393.6	69	17.5	1.90	1.40	2.57	<.0001
Stage IV	159.7	24	15.0	2.91	1.80	4.68	<.0001	85.4	21	24.6	3.09	1.92	4.95	<.0001
Log viral load (per log10 copies/ml increase) *				2.43	1.85	3.19	<.0001				1.09	0.84	1.41	0.522

HR: hazard ratios from univariate Cox models; PY: person-years; CI: confidence interval; ART: antiretroviral treatment; USD: United States Dollar

p-values are 2-tailed from univariate Cox models

* Viral load collected from 1999 onwards

Table 3

Multivariate Cox models of time to death (N = 1656 HIV-positive women in discordant relationships, Lusaka, Zambia, 1995-2012)

	Model 1				Model 2 (censoring pregnant intervals)			
	aHR^	95%CI		p-value	aHR^	95%CI		p-value
Contraceptive method (time-varying)								
Non-hormonal*	ref				ref			
Implant	0.30	0.10	0.98	0.045	0.29	0.09	0.95	0.040
Injectables	0.59	0.36	0.97	0.038	0.58	0.35	0.95	0.032
OCPs	1.08	0.74	1.57	0.694	1.06	0.72	1.57	0.755
Pregnant (time-varying)								
No	ref							
Yes	1.07	0.68	1.66	0.781				
Breastfeeding (time-varying)								
No	ref				ref			
Yes	0.34	0.19	0.62	<.001	0.33	0.18	0.60	<.001
HIV stage (baseline)								
Stage I	ref				ref			
Stage II	1.04	0.71	1.53	0.833	1.12	0.74	1.67	0.599
Stage III	2.00	1.41	2.83	<.001	2.01	1.38	2.93	<.001
Stage IV	2.66	1.60	4.42	<.001	2.95	1.74	5.01	<.0001

aHR: adjusted hazard ratios from multivariate Cox models; CI: confidence interval; ART: antiretroviral treatment; OCP: oral contraceptive pills

p-values are 2-tailed

* Intrauterine device, none/condoms alone, permanent methods

^ Controlling for date of enrollment

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Table 4

Multivariate Cox models of time to ART initiation (N = 1656 HIV-positive women in discordant relationships, Lusaka, Zambia, November 2003-2012)

	Model 1				Model 2 (censoring pregnant intervals)			
	aHR^	95%CI		p-value	aHR^	95%CI		p-value
Contraceptive method (time-varying)								
Non-hormonal*	ref				ref			
Implant	0.54	0.31	0.95	0.032	0.57	0.32	1.00	0.048
Injectables	0.85	0.55	1.32	0.466	0.83	0.53	1.28	0.393
OCPs	0.70	0.44	1.10	0.123	0.72	0.45	1.14	0.162
Pregnant (time-varying)								
No	ref							
Yes	1.24	0.83	1.86	0.295				
Breastfeeding (time-varying)								
No	ref				ref			
Yes	0.49	0.29	0.85	0.012	0.50	0.29	0.86	0.013
Age (baseline, per year increase)	1.05	1.04	1.07	<.0001	1.05	1.03	1.07	<.0001
Reads Nyanja (baseline)								
With difficulty/not at all	ref				ref			
Yes, easily	1.41	1.09	1.82	0.009	1.39	1.06	1.83	0.018
HIV stage (baseline)								
Stage I	ref				ref			
Stage II	1.21	0.89	1.65	0.220	1.26	0.91	1.74	0.161
Stage III	2.15	1.56	2.96	<.0001	2.13	1.51	2.99	<.0001
Stage IV	3.62	2.20	5.97	<.0001	3.82	2.31	6.34	<.0001

aHR: adjusted hazard ratios from multivariate Cox models; ART: antiretroviral treatment; OCP: oral contraceptive pills

p-values are 2-tailed

* Intrauterine device, none/condoms alone, permanent method

^ Controlling for date of enrollment