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Antiretroviral therapy initiation is not associated with risky sexual behavior among heterosexual HIV-infected persons in serodiscordant partnerships

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Abstract

Background—Few prospective studies have assessed whether antiretroviral therapy (ART) use is associated with changes in sexual risk behavior of HIV-infected persons in known HIV-serodiscordant partnerships.

Methods—We conducted a longitudinal analysis of HIV-infected persons with known uninfected partners enrolled in the Partners PrEP Study in Kenya and Uganda. ART use and self-reported sexual behavior were ascertained every 3 months. We assessed the effect of ART on sexual risk behaviors using zero-inflated negative binomial regression. Primary outcomes were condomless vaginal sex acts, pregnancy incidence and new STI diagnoses.

Results—We followed 1817 HIV-infected persons (58% women) for 864 person-years before ART initiation and 771 person-years after ART. Median CD4 and plasma viral load at ART initiation were 277 cells/ μ L and 4.18 log₁₀ copies/mL. ART use was associated with a significant decrease in condomless vaginal sex acts with HIV-uninfected partners (0.65 vs. 0.39 per month; rate ratio [RR] 0.64; 95% CI: 0.55–0.75; $p < 0.001$), but not condomless vaginal sex acts with non-primary partners (1.30 vs. 1.04 per month; RR 0.94; 95% CI: 0.94–1.20; $p = 0.62$). Pregnancy incidence was lower after ART (13.2 vs 8.4 per 100 person-years; HR 0.71, 95% CI: 0.60–0.84, $p < 0.001$). Incident STI diagnoses were similar (OR 1.05, 95% CI: 0.86–1.29; $p = 0.63$).

Conclusions—Substantial risk compensation did not occur following ART initiation among East African HIV-infected persons with known HIV-uninfected partners. These data inform modeling studies of ART for HIV prevention by suggesting that risky sexual behavior did not appear to offset decreased HIV infectiousness in this key population.

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Keywords

HIV; serodiscordant couples; antiretroviral therapy; condomless sex; zero-inflated negative binomial regression

Introduction

Antiretroviral therapy (ART) reduces HIV related morbidity and mortality and prevents HIV transmission (1, 2). ART could have the unintended consequence of increasing sexual risk behavior because of improved physical health and life expectancy, decreased perception of HIV risk (3), and safe sex fatigue in stable partnerships. Risk compensation occurs when individuals who feel protected from a health risk engage in other risk behaviors because of changes in risk perception (4). Risk perception may change because of knowledge that ART-mediated viral suppression reduces HIV transmission risk (reduced-susceptibility optimism), or the belief that ART significantly decreases HIV-related mortality (reduced-severity optimism) (5, 6). Modelling studies suggest that the preventive benefits of expanded ART access could be offset by increased sexual risk behavior (7), because of risk compensation and/or prolonged survival, increasing lifetime duration of infectiousness. The success of ART for HIV prevention is premised on high coverage of HIV testing, linkage of HIV-infected persons to care, early ART initiation regardless of CD4 count, high and sustained ART adherence, and the assumption that sexual risk behavior does not offset decreased HIV infectiousness (3, 8).

Limited data are available regarding sexual risk behavior of ART exposed HIV-infected persons with known uninfected partners in sub-Saharan Africa. Prior studies of unprotected sex with serodiscordant or unknown status partners were cross-sectional and compared HIV-infected persons taking ART versus not, limited by small sample sizes, or had short duration of follow-up limiting assessment of the durable effect of ART on sexual risk behavior (9). We aimed to assess whether ART use is associated with increased frequency of high-risk sexual behavior in a large prospective study of HIV-serodiscordant couples in which the HIV-infected partner initiated ART.

Materials and Methods

Study setting and participants

Between 2008 and 2012, we conducted a prospective study of HIV-serodiscordant couples enrolled in the Partners PrEP Study, a randomized clinical trial of antiretroviral pre-exposure prophylaxis in Kenya and Uganda (10, 11). We previously described sexual behavior of HIV-uninfected members of serodiscordant couples randomized to receive antiretroviral pre-exposure prophylaxis or placebo (12). Here, we describe sexual risk behavior of their HIV-infected partners. At baseline, HIV-infected partners were sexually active and ART naive. HIV-infected women and men were followed for up to 36 months, and received clinical and immunological monitoring for ART eligibility, and referrals to partnering HIV care organizations when eligible for treatment. At each quarterly study visit, data on ART use and sexual behavior within the primary (study) partnership and with other partners (for both

members of the couple) was collected using semi-structured questionnaires. During the study period, national treatment guidelines changed from recommending ART for symptomatic HIV disease or CD4 count <250 cells/ μ L to CD4 count $\geq$ 350 cells/ μ L, in line with evolving World Health Organization guidance. All study participants received HIV prevention services including individual and couple risk-reduction counseling, free condoms, and screening and treatment of sexually transmitted infections.

Institutional review boards at the University of Washington and collaborating institutions at each of the study sites approved the study protocol. All participants provided written informed consent in English or their local language.

Laboratory methods

Blood for CD4 and HIV RNA quantification was collected at enrollment, every six months thereafter, and at study exit. HIV serological testing for HIV-uninfected partners, and urine pregnancy testing for HIV-uninfected women partners were performed monthly. Urine pregnancy testing for HIV-infected women was performed when clinically indicated. For both members of the couple, testing for sexually transmitted infections (STIs) was conducted annually, and when clinically indicated by symptoms and signs suggestive of an STI. Syphilis serology was performed using rapid plasma reagin tests and positive results confirmed using *Treponema pallidum* particle agglutination tests. We tested for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* using APTIMA Combo 2 (Gen-Probe) or COBAS AmpliCor (Roche Diagnostic) assays and for *Trichomonas vaginalis* using APTIMA TV TMA (Gen-Probe) or In Pouch TV (Biomed Diagnostics).

Statistical analysis

The primary outcomes were count of condomless vaginal sex acts (within and outside the primary partnership) and, as markers of condomless vaginal sex, STI diagnoses and pregnancy incidence (including pregnancies in both HIV-infected and uninfected women to capture the partnership nature of the data). Sexual activity was assessed for the prior month, at each quarterly visit. The distribution of sex acts was positively skewed, overdispersed relative to the Poisson distribution (i.e., conditional variance larger than the conditional mean), and zero-inflated. Zero inflation was due to an excess number of zero sex acts, compared to a normal Poisson distribution, which occurred because of abstinence, partnership dissolution or perfect condom use. We evaluated Poisson, negative binomial, and zero-inflated Poisson and negative binomial regression models for best fit. Vuong tests suggested that zero-inflated models provided a better fit than standard regression models (13). Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) indicated that the zero-inflated negative binomial regression (ZINB) model fit the data better than the zero-inflated Poisson model. The ZINB model combines a negative binomial model (for overdispersed count data) and a logistic model (to assess zero inflation). Thus, we report two exponentiated regression coefficients for the association of ART use with sexual behavior: rate ratios from the negative binomial model (for the proportional change in condomless sex acts after ART) and odds ratios from the logistic model (for the relationship between ART use and odds of abstinence, partnership dissolution or perfect condom use). The negative binomial and logistic models were not fit with identical covariates. Potential confounders,

which changed the beta coefficient for ART by more than 10%, were included in adjusted models. We performed sub-group analyses in women, men and younger HIV-infected persons (individuals <30 years may be more likely to desire children). We used robust standard errors in all models to account for within-subject correlation. Pregnancy incidence was compared using the Andersen-Gill extension of the Cox regression model, to account for multiple pregnancies per woman. A binary STI variable was created to indicate diagnosis with gonorrhea, chlamydia, trichomoniasis or syphilis infection; STI incidence was evaluated using logistic regression with generalized estimating equations and robust standard errors to account for multiple observations per person. Statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Enrollment characteristics

Of 4747 HIV-infected women and men enrolled, 1817 initiated ART during the study, of which 1062 (58%) were women. At enrollment, the median age of HIV-infected men and women was 40 years (interquartile range [IQR] 35–45), and 30 years (IQR 25–36), respectively (Table 1). Most (98%) were married and reported a median of 4 sex acts (IQR 2–8) with the primary partner in the prior month. HIV-infected men had longer duration of partnership (13 vs. 6 years; $p<0.001$) and were less likely to report condomless sex in the prior month (21 vs. 29%; $p=0.01$). Nine percent of HIV-infected women were pregnant, and 6% of HIV-infected men reported condomless sex with other partners. *Trichomonas vaginalis* was the most prevalent STI and was identified in 10% of women and 2% of men.

Sexual behavior and ART

The 1817 HIV-infected women and men contributed 10,369 person months of observation before ART initiation and 9,255 person-months after ART. The median duration of follow up after ART initiation was 11.3 months (IQR 5.5–19.4). The median CD4 and plasma HIV RNA concentration at ART initiation were 277 cells/ μ L (IQR 220–355) and 4.18 log₁₀ copies/mL (IQR 3.53–4.73). We observed significant reductions in condomless sex acts with primary partners after ART initiation (0.65 versus 0.39 mean sex acts per month; RR 0.64; 95% CI: 0.55–0.75; $p<0.001$) [Table 2; negative binomial model]. This decline in condomless sex acts was observed in serodiscordant couples in which the HIV-infected partner was female (RR 0.61; 95% CI: 0.51–0.74; $p<0.001$), male (RR 0.68; 95% CI: 0.52–0.89; $p=0.006$) and <30 years (RR 0.57; 95% CI: 0.41–0.79; $p=0.001$). Overall, ART use was associated with lower odds of abstinence, partnership dissolution or perfect condom use (adjusted odds ratio [AOR] 0.75; 95% CI: 0.60–0.94; $p=0.01$) [Table 2; logistic model]. In non-primary partnerships, we observed a non-significant decline in the number of condomless sex acts (1.30 versus 1.04 mean sex acts per month; RR 0.94; 95% CI: 0.73–1.20; $p=0.62$), and a trend towards greater odds of abstinence, partnership dissolution or consistent condom use (AOR 1.35; 95% CI: 0.96–1.91; $p=0.09$).

Pregnancy and STI incidence

The median time from ART initiation to first pregnancy was 7.8 months (IQR 2.7–13.8). The pregnancy incidence rate declined from 13.2 per 100 woman-years (1215 pregnancies; 9191 woman-years) prior to ART initiation to 8.4 per 100 woman-years (174 pregnancies; 2078 woman-years) after ART (HR 0.71; 95% CI: 0.60–0.84; $p<0.001$). Pregnancy incidence decreased in serodiscordant couples with HIV-uninfected women (11.2 vs. 6.4 per 100 woman-years; HR 0.68; 95% CI: 0.50–0.92; $p=0.01$) and HIV-infected women (14.5 vs. 9.8 per 100 woman-years; HR 0.76; 0.62–0.93; $p=0.006$). We diagnosed 462 incident STIs at 5169 visits, including 272 (59%) cases of trichomoniasis, 99 (21%) cases of gonorrhea and 74 (16%) cases of syphilis infection. No significant differences in incident STI diagnoses were observed before versus after ART (8.3 vs. 8.7% of visits; OR 1.05; 95% CI: 0.86–1.29; $p=0.63$). Similar results were obtained when we restricted the analysis to HIV-infected persons who reported sex with other partners (OR 1.01; 95% CI: 0.55–1.83; $p=0.89$).

Discussion

In this prospective study of approximately 1800 East African heterosexual HIV-infected persons with known HIV-uninfected partners who initiated ART during follow-up, ART use was associated with significant reductions in condomless sex acts with primary partners. This decrease in condomless sex acts was observed in HIV-infected women, men, and in participants less than thirty years of age. ART use was also associated with decreased pregnancy incidence, regardless of the woman's HIV status. There was neither a significant increase nor decrease in self-reported condomless sex with non-primary partners or STI incidence.

Our finding that HIV-infected women and men were significantly less likely to self-report condomless sex with primary partners after starting ART, is similar to previous reports (14–24). A meta-analysis of 14 studies of sexual behavior and ART use in sub-Saharan Africa (25) identified only four studies (16, 17, 19, 22) that reported rates of unprotected sex with HIV-uninfected or unknown status partners. ART use was associated with a reduction in unprotected sex (OR 0.55; 95% CI: 0.30–0.99; $p<0.001$) but heterogeneity was significant ($I^2=85.2\%$). In another meta-analysis (9), ART use was associated with decreased unprotected sex with HIV-uninfected or unknown status partners (OR 0.64; 95% CI: 0.46–0.88, $p<0.001$; heterogeneity $I^2=61\%$). Condomless sex decreases after ART initiation in most populations (9), but some sub-populations experience increased condomless sex over time (25, 26). A study from Uganda reported decreased sexual risk behavior in women (OR 0.85 per year of ART) but not men (OR 1.41 per year of ART) (23). In contrast, our results show that ART use was associated with a lower likelihood of sex unprotected by condoms irrespective of the gender of the HIV-infected partner. Unique to this study, all had known HIV-uninfected partners randomized to PrEP or placebo, and both members of the couple were counseled about the efficacy of ART for HIV prevention. The decreased odds of abstinence we observed suggest that the reduction in condomless sex was due to increased condom use with primary partners.

We did not observe significant reductions in condomless sex acts with non-primary partners after ART initiation in our study. Prior work in this setting suggests differences in HIV risk perception lead to risk shifting from the known serodiscordant partnership to outside partners, perhaps due to relationship dissolution and new partnership formation (27). In prior analyses of HIV-uninfected members in this serodiscordant couple cohort, there was no change in the frequency of condomless sex in the primary partnership before and after unblinding of PrEP or placebo assignment (4.9 versus 5.1 sex acts per year; $p=0.25$). Notably, there was a small but significant increase in condomless sex with non-primary partners (6.2 versus 6.8 sex acts per year; $p=0.04$) (12). In contrast, HIV-infected women and men did not report increased condomless sex with non-primary partners in this same cohort. These data suggest no evidence of behavioral risk compensation in HIV-infected persons following ART initiation irrespective of partnership type. Unique to this study, all had known HIV-uninfected partners randomized to PrEP or placebo, and were counseled about the efficacy of ART for HIV prevention.

Pregnancy incidence decreased by 32% among serodiscordant couples with HIV-uninfected women and 24% among couples with HIV-infected women. This decline corroborates the observed decrease in self-reported condomless sex. Decreased pregnancy incidence following ART initiation has been reported in the same setting, but occurred after 24 months of ART (28). In that study, there was no association between self-reported male partner HIV status and pregnancy incidence. In contrast, a large study of 4531 HIV-infected women in 7 sub-Saharan African countries reported a 74% increase in pregnancy incidence after ART (29), as have other studies in the same setting (30, 31). We did not observe significant differences in STI incidence in HIV-infected persons or their HIV-uninfected partners (12), likely because of low STI prevalence in this population of married heterosexual couples.

The success of ‘test and treat’ strategies partly depends on the assumption that the biologic effect of ART in decreasing HIV infectiousness is not offset by behavioral risk compensation (4). Our study found no evidence of increased sexual risk behavior in a cohort in which there were no HIV transmissions on suppressive ART (32). Although the preventive effect of ART does not appear to have been offset in our key population of HIV serodiscordant couples newly initiating ART, HIV transmission persists in other subpopulations with high risk behaviors (33). Future studies should monitor sexual risk behavior trends in high-risk populations on long-term ART.

The strengths of our study include the serodiscordant couple design permitting within-couple analyses, the large sample size providing statistical power to evaluate within-subject comparisons (pre-ART versus post-ART behavior) which are less subject to confounding than comparisons of ART-exposed versus non-exposed persons, and the use of pregnancy and STI incidence as objective markers of condomless sex. Our study has limitations. HIV serodiscordant couples received regular risk reduction counseling which may have reduced the likelihood of risky behavior. Self-report of sexual behavior is subject to recall bias or social desirability, but this was validated by biologic measures of unprotected sex. We did not document specific reasons for self-report of zero condomless sex acts, and are unable to differentiate between perfect condom use and no sex (abstinence or partnership dissolution). We tested for bacterial STIs annually or when clinically indicated and may have

underestimated the true rate of STIs in this population. The short duration of follow up after ART initiation may have limited our ability to detect long term trends in sexual behavior. Nevertheless, studies with longer duration of follow up have reported similar outcomes.

In conclusion, we did not find evidence of increased sexual risk behavior in mutually disclosed HIV serodiscordant couples, which received counseling about ART prevention benefits. These data inform modeling studies of ART for HIV prevention by suggesting that risky sexual behavior did not appear to offset decreased HIV infectiousness in this key population.

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Table 1

Enrollment characteristics of HIV-infected women and men initiating ART

	HIV-infected women (N=1062)	HIV-infected men (N=755)
	Median (IQR) or N (%)	
Demographic characteristics		
Age (years)	30 (25–36)	40 (35–45)
Education (years)	7 (4–7)	7 (4–10)
Monthly income (any)	604 (57)	641 (85)
Couple characteristics		
Married to HIV-uninfected study partner	1033 (97)	748 (99)
Duration of partnership (years)	6 (3–11)	13 (6–19)
Number of children with study partner	2 (0–3)	3 (2–5)
Number of sex acts with study partner, prior month	4 (3–8)	4 (2–6)
Any unprotected sex acts with study partner, prior month	303 (29)	162 (21)
Multiple partners	8 (1)	115 (15)
Any unprotected sex acts with other partners, prior month	2 (<1)	43 (6)
Pregnant (women only)	93 (9)	N/A
Sexually Transmitted Infections		
<i>Trichomonas vaginalis</i>	106 (10)	14 (2)
<i>Neisseria gonorrhoeae</i>	13 (1)	3 (<1)
<i>Chlamydia trachomatis</i>	10 (1)	0 (0)
Syphilis	32 (3)	37 (5)

Table 2

Sexual risk behaviors and associations with ART

Variable	Mean sex acts per month (variance)		Negative Binomial Model ^a		Logistic Model	
	Before ART	After ART	RR* (95% CI)	P	OR** (95% CI)	P
Study partner						
Sex acts	4.40 (21.50)	3.12 (13.91)	0.82 (0.79–0.86)	<0.001	2.89 (2.41–3.46) ^b	<0.001
Condomless sex acts	0.65 (5.72)	0.39 (3.09)	0.64 (0.55–0.75)	<0.001	0.75 (0.60–0.94) ^c	0.01
HIV-infected women	0.79 (7.40)	0.48 (4.14)	0.61 (0.51–0.74)	<0.001	0.81 (0.60–1.11)	0.20
HIV-infected men	0.46 (3.19)	0.27 (1.66)	0.68 (0.52–0.89)	0.006	0.80 (0.56–1.16)	0.24
Age <30 years	0.88 (8.26)	0.52 (4.23)	0.57 (0.41–0.79)	0.001	0.59 (0.30–1.14)	0.12
Other partners						
Sex acts ^d	4.04 (14.14)	3.49 (10.28)	0.98 (0.83–1.14) ^e	0.77	N/A	N/A
Condomless sex acts	1.30 (9.23)	1.04 (6.88)	0.94 (0.73–1.20)	0.62	1.35 (0.96–1.91)	0.09
HIV-infected women	1.22 (4.54)	1.15 (6.84)	1.24 (0.77–2.00)	0.38	1.71 (0.62–4.69)	0.30
HIV-infected men	1.32 (10.20)	1.00 (6.89)	0.84 (0.62–1.13)	0.25	1.28 (0.88–1.88)	0.20
Age <30 years	1.63 (15.22)	1.29 (7.44)	0.64 (0.20–2.02)	0.44	1.09 (0.12–10.7)	0.94

^a all outcomes adjusted for total sex acts or condomless sex acts at enrollment.

^b adjusted for age and gender.

^c adjusted for time-varying age.

^d negative binomial model only (by study design, only non-zero sex acts with other partners were documented).

^e adjusted for gender.

* rate ratios represent the proportional change in condomless sex acts with ART use.

** odds ratios represent the relationship between ART use and abstinence, partnership dissolution or perfect condom use.