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HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy

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Abstract

Objective—To evaluate the impact of antiretroviral therapy (ART) on HIV-1 transmission rates among HIV-1 discordant couples in Rakai, Uganda.

Design—Observational cohort study.

Methods—HIV-1 discordant couples were retrospectively identified between 2004 and 2009. Study participants underwent annual screening for HIV-1 and were interviewed to evaluate risk behaviors. Participants were offered voluntary counseling and testing and provided with risk reduction counseling. Free ART was offered to participants with a CD4 cell count of 250 cells/ μ l or less or WHO stage IV disease. HIV-1 incidence and sexual risk behaviors were compared before and after the HIV-1-positive index partners started ART.

Results—Two hundred and fifty HIV-1 discordant couples were followed between 2004 and 2009 and 32 HIV-1-positive partners initiated ART. Forty-two HIV-1 transmissions occurred over 459.4 person-years prior to ART initiation, incidence 9.2/100 person-years [95% confidence interval (CI) 6.59–12.36]. In 32 couples in which the HIV-1 index partners started ART, no HIV-1 transmissions occurred during 53.6 person-years. The 95% CI for the incidence rate difference was –11.91 to –6.38 ($P=0.0097$). Couples reported more consistent condom use during ART use, but there was no significant difference in the number of sexual partners or other risk behaviors. Viral load was markedly reduced in persons on ART.

Conclusion—HIV-1 transmission may be reduced among HIV-1 discordant couples after initiation of ART due to reductions in HIV-1 viral load and increased consistent condom use.

Keywords

antiretroviral; discordant couples; HIV transmission; HIV-1

Introduction

Antiretroviral drugs have proven efficacy in the prevention of mother-to-child transmission of HIV-1 and may play a role in the prevention of HIV-1 transmission in HIV-1 discordant

couples. Viral load is the major determinant governing the risk of sexual transmission in HIV-1 discordant couples and, therefore, effective ART should dramatically reduce transmission rates [1]. Preliminary evidence from observational studies on heterosexual populations and MSM suggests that when ART is taken effectively, the risk of HIV-1 transmission to HIV-1-negative partners is greatly reduced [2,3].

Free ART programs were initiated in Uganda in 2004 coinciding with increased donor resources for HIV/AIDS treatment programs. We began delivering free ART in our rural population in the Rakai district, southwestern Uganda in June 2004 through a decentralized program of 17 mobile clinics. Here we report the rates of HIV-1 transmission among HIV-1 discordant couples in the period prior to ART initiation compared to the period after treatment began.

Methods

HIV-1 discordant couples were identified through the Rakai Community Cohort study (RCCS), which conducts an annual census, health and behavioral survey, and HIV-1 screening among 15 000 individuals aged 15–49 years in 50 villages in rural Rakai district, southwestern Uganda. All RCCS participants provided written informed consent for study participation, including permission to identify married/consensual partners; the RCCS was approved by the western Institutional Review Board (IRB), the Uganda Virus Research Institute Science and Ethics Committee, and the Uganda National Council for Science and Technology. All study participants were offered voluntary HIV-1 testing and individual and couples' counseling. All participants were also counseled on HIV-1 prevention methods through community messages and individual counseling sessions emphasizing abstinence, being faithful, and using condoms, offered by trained HIV-1 counselors.

As of June 2004, the Rakai Program has offered free ART to Rakai district residents, including RCCS participants, who have CD4⁺ T-cell counts of 250 cells/μl or less or WHO stage IV disease. All HIV-1-infected RCCS participants were screened for ART eligibility every 6 months and started on ART if eligible by CD4⁺ cell or clinical criteria. To date, the program has provided ART to over 2100 individuals. For this analysis, we include RCCS data collected in four survey rounds between 2004 and 2009. HIV-1 discordant couples were identified retrospectively for this analysis in which HIV-1 incidence and HIV-1 risk behaviors of the HIV-1-uninfected partners were compared between survey rounds before and after the HIV-1 index partners were started on ART.

Identification of couples

All married participants were identified and retrospectively linked to their spouses, including those in polygamous unions. Couple HIV-1 status was then determined at each visit, and couples were defined as HIV-1 discordant if one member was initially HIV-1-infected and the other uninfected. The first visit at which HIV-1 discordance was determined was classified as the baseline visit for this analysis. At both baseline visit and subsequent follow-up, we linked the HIV-1-positive partner to the Rakai Health Sciences ART service dataset to ascertain whether the HIV-1-positive person was on ART and date of ART initiation. The HIV-1-uninfected person was followed until seroconversion, or censored at the time of marital dissolution due to death, divorce/separation, outmigration, or last survey visit. We estimated person-time of follow-up in years as the duration of time between visits. If seroconversion occurred, we assumed infection occurred in mid-follow-up interval and ascribed half the person-time for this interval. We also estimated person-time exposure for those HIV-1-negative individuals whose HIV-1-positive partners started ART using the date of ART initiation. Such individuals could contribute both periods of exposure time before or

after ART initiation, enabling us to estimate the incidence of HIV-1 transmission among the initially negative partners prior to and after their infected partner was on ART.

Laboratory methods

At each survey round, HIV-1 was ascertained using two different enzyme immunoassays (EIA; Vironostika HIV-1; Organon Teknika, Charlotte, North Carolina, USA, and Cambridge Biotech; Worcester, Massachusetts, USA), with western blot confirmation of all discordant EIAs and of all HIV-1 seroconverters (HIV-1 WB; Bio-Merieux–Vitek, St Louis, Missouri, USA). HIV-1 viral load testing was performed at baseline and at 6 monthly follow-up visits for participants who started on ART using the Roche monitor version 1.5 assay (Roche Diagnostics, Indianapolis, Indiana, USA).

Statistical analysis

We estimated HIV-1 incidence per 100 person-years as the number of new HIV-1 cases divided by the total person-years of follow-up, stratified by ART periods of nonuse and use. We used generalized linear models (GLMs) with a Poisson distribution and a log link function, with robust variance estimates for multiple observations on the same individual, to estimate the incidence rate ratios (IRRs) and the 95% confidence intervals (95% CI) of HIV-1 transmission during ART relative to the non-ART periods. We adjusted for the HIV-1-negative partner's sexual behaviors in a multivariable Poisson regression model. Statistical analyses used STATA software package version 9.2 (College Station, Texas, USA).

Results

In the period between 2004 and 2009, when free ART became available in the Rakai program, 250 HIV-1 discordant couples were identified among whom 32 HIV-1-positive index partners were started on ART. Data from four survey rounds corresponding to 349 observation intervals were included in this analysis. Baseline characteristics of the HIV-1-negative partners in the discordant couple cohort are given in Table 1. Fifty-eight percent (145/250) of couples had a male index positive partner. Consistent condom use with any partner was 4.0%, and alcohol use before sex with any partner was common and reported by 40.4% of HIV-1-negative partners. In 20.0% of couples, HIV-1-negative husbands reported more than one wife (i.e. polygamous unions). The median [interquartile range (IQR)] follow-up time before ART initiation was 1.57 years (1.42–1.72) and median follow-up after ART was 1.54 years (1.00–1.76). During 308 observation intervals before ART exposure, 42 HIV-1 transmissions occurred over 459.3 person-years, with a transmission rate of 9.2/100 person-years [95% CI (6.59–12.36)]. During 41 periods after the 32 HIV-1 index partners received ART, no HIV-1 transmissions occurred over 53.6 person-years. The 95% CI for the incidence rate difference was -11.91 to -6.38 ($P=0.0097$).

There were no statistically significant differences in gender, age, number of sexual partners over the past 12 months, self-reported genital ulcer disease (GUD), or male partner's circumcision status between periods before and after the positive partners started on ART (Table 2). HIV-1-negative partners reported more nonmarital relationships during periods after the positive partner was started on ART, but this was not statistically significant. Consistent condom use with any partner increased significantly from 14.3% prior to ART use to 53.7% after initiation of ART ($P < 0.0001$). Coital frequency declined after ART initiation, although not statistically significant (Table 2, $P=0.081$).

Viral load monitoring was done every 6 months during follow-up for clients started on ART. At 6 months, of 28 partners with an available viral load, 20 (71.4%) were below the limit of

detection (<400 copies/ml) and the remaining eight were below the limit 2000 copies/ml. At 12 months, 85.2% (23/27) had an available viral load less than 400 copies/ml with the remaining four having viral loads ranging from 2293 to 672 513 copies/ml. All 28 clients with an available viral load at 24 months were below the limit of 400 copies/ml.

Discussion

Antiretroviral therapy may have reduced the risk of transmission of HIV-1 among discordant couples in rural Uganda. Although there was a significant increase in consistent condom use following ART initiation (Table 2), the reduction in risk was most likely due to the direct reduction in HIV-1 viral load in the HIV-1-positive partners on ART. The findings are consistent with earlier studies showing that HIV-1 viral load is the most important determinant of HIV-1 transmission risk among discordant couples, with other observational studies reporting a reduction in transmission among HIV-1 discordant couples with ART [1,2,4,5]. These findings add to the growing body of evidence supporting the use of ART for HIV-1 prevention.

This observational study has several limitations. The number of couples started on ART during our study was small, which limited study power. We cannot differentiate between the effects of increased consistent condom use and the effects of ART on HIV viral load, which both occurred during the period of observation. There may have been a component of social desirability in the reported condom use among couples wherein the index positive partner was receiving ART. The lack of randomization of couples in our study could lead to bias due to unmeasured differences between periods before and after index positive partners were started on ART. Finally, adherence counseling and support are key components of the Rakai Health Sciences Program (RHSP) ART program and likely contributed to the good virologic treatment responses observed and the absence of HIV-1 transmission during periods on ART.

Ongoing studies such as the HIV-1 Prevention Trials Network 052 study will test the hypothesis that ART can prevent HIV-1 transmission among HIV-1 discordant couples [6]. Our data provide preliminary evidence to support this hypothesis among rural Ugandans participating in an ongoing cohort study and receiving free ART.

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Table 1

Enrolment characteristics of HIV-1-negative partner in discordant relationship.

	Total		Female HIV-negative (M+F-couples)		Male HIV-negative (M-F+couples)	
	Number	%	Number	%	Number	%
Overall number of couples	250	100.0	145	100.0	105	100.0
Age group						
15-19	13	5.2	13	9.0		0.0
20-24	46	18.4	29	20.0	17	16.2
25-29	72	28.8	50	34.5	22	21.0
30+	119	47.6	53	36.6	66	62.9
Condom use with any partner past 12 months						
Never/no use in 12 months	191	76.4	110	75.9	81	77.1
Inconsistent use	49	19.6	30	20.7	19	18.1
Always	10	4.0	5	3.4	5	4.8
Condom use with marital partner past 12 months						
Never/no use in 12 months	195	78.0	109	75.2	86	81.9
Inconsistent use	47	18.8	31	21.4	16	15.2
Always	8	3.2	5	3.4	3	2.9
Alcohol before sex with any partner						
No alcohol	149	59.6	95	65.5	54	51.4
Yes, had	101	40.4	50	34.5	51	48.6
Alcohol before sex with marital partner						
No alcohol	150	60.0	96	66.2	54	51.4
Yes, had	100	40.0	49	33.8	51	48.6
Male (partner) circumcision status						
Not circumcised	200	80.0	117	80.7	83	79.0
Yes, circumcised	50	20.0	28	19.3	22	21.0
Number of wives in relationship						
Only one	200	80.0	117	80.7	83	79.1
Two or more	50	20.0	28	19.3	22	21.0
Current nonmarital relations						
No, do not have	233	93.2	145	100.0	88	83.8

	Total		Female HIV-negative (M+F-couples)		Male HIV-negative (M-F-couples)	
	Number	%	Number	%	Number	%
Yes, have	17	6.8		0.0	17	16.2
Sexual partners in past 12 months						
Only one	191	76.4	136	93.8	55	52.4
Two/more	59	23.6	9	6.2	50	47.6
Primary occupation						
Home	159	63.6	117	80.7	42	40.0
Government/trade	41	16.4	14	9.7	27	25.7
Fishing/bar worker/trucker	10	4.0	5	3.4	5	4.8
Student/other	40	16.0	9	6.2	31	29.5

Table 2

Sexual behaviors by period and HIV-1-positive partner's antiretroviral therapy status among HIV-1 discordant couples.

Characteristics	Period while positive partner not on ART		Period while positive partner on ART		Fisher's exact test, <i>P</i> value
	Observations	Col %	Observations	Col %	
Total	308	100.0	41	100.0	
Characteristics					
Age group					
15-19	4	1.3	0	0.0	
20-24	31	10.1	1	2.4	0.082
25-29	81	26.3	6	14.6	
30+	192	62.3	34	82.9	
Nonmarital relationships					
None	283	91.9	35	82.4	0.235
Yes	25	8.1	6	14.6	
Sexual partners past 12 months					
None	3	0.98	1	2.4	
One	247	80.5	29	70.7	0.172
2+	57	18.6	11	26.8	
Consistent condom use with any partner					
Never/no use in 12 months	168	54.6	5	12.2	0.000
Inconsistent use	96	31.2	14	34.2	
Always	44	14.3	22	53.7	
Consistent condom use with marital partner					
Never/no use in 12 months	176	57.7	5	12.8	0.000
Inconsistent use	91	29.8	13	33.3	
Always	38	12.5	21	53.9	
Alcohol before sex with any partner					
Did not drink	184	59.7	31	75.6	0.060
Drank	124	40.3	10	24.4	
Alcohol before sex with marital partner					
Did not drink	183	60	29	74.4	0.115
Drank	122	40	10	25.6	

	Period while positive partner not on ART		Period while positive partner on ART		Fisher's exact test, <i>P</i> value
	Observations	Col %	Observations	Col %	
Self-reported GUD					
Did not report	300	97.4	40	97.6	1.000
Reported GUD	8	2.6	1	2.4	
Sexual frequency past 30 days					
<=2	85	32.2	13	37.1	
>2-4	74	28.0	15	42.9	
>4-6	39	14.8	4	11.4	0.081
>6	66	25.0	3	8.6	
Male's circumcision status					
No	213	69.2	25	61.0	0.290
Yes	95	30.8	16	39.0	
HIV incident					
Nonincident	266	86.4	41	100.0	0.008
Incident	42	13.6	0	0.0	
Negative partner					
Female	186	60.4	22	53.7	0.498
Male	122	39.6	19	46.3	

GUD, genital ulcer disease.