Episodic Antiretroviral Therapy Increases HIV Transmission Risk Compared With Continuous Therapy: Results of a Randomized Controlled Trial

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Objective: To compare the HIV transmission risk among patients randomized to episodic versus continuous antiretroviral therapy.

Design: This was a substudy of the Strategies of Management of Antiretroviral Therapy study, in which patients were randomized to continuous versus $CD4^+$-guided episodic antiretroviral therapy. Participants were surveyed about sexual activity and needle sharing and had laboratory testing for gonorrhea, chlamydia, and syphilis.

Results: A total of 883 patients were enrolled in this study, the mean age of the patients was 45 years, 25% were women, and 78% were on antiretroviral therapy. At baseline, 136 participants (15.4%) had high-risk behavior (vaginal or anal sex without a condom, needle sharing, or incident bacterial sexually transmitted infection). After randomization, the proportion of participants reporting high-risk behavior was stable and did not differ by randomized arm ($P = 0.39$). Among participants off therapy at baseline, high-risk behavior was less common 4 months after randomization among those who were randomized to start antiretroviral therapy ($P = 0.03$). HIV transmission risk (high-risk behavior while HIV RNA level >1500 copies/mL) with partners perceived to be HIV uninfected was higher in the episodic therapy arm ($P = 0.02$).

Conclusions: Patients on episodic antiretroviral therapy did not decrease high-risk behavior, and because HIV RNA levels were higher, this strategy may result in increased HIV transmission.

Key Words: antiretroviral therapy, HIV transmission risk, high-risk behavior, randomized trial

(*J Acquir Immune Defic Syndr* 2008;49:142–150)

INTRODUCTION

Episodic antiretroviral therapy was suggested as a way of retaining the benefits of combination antiretroviral therapy while minimizing adverse effects of antiretroviral drugs.[1,2] However, interruption of antiretroviral therapy results in viral rebound, and plasma HIV RNA levels are closely associated with the risk of perinatal and heterosexual transmission of HIV.[3–5] Therefore, one of the concerns about episodic antiretroviral therapy is the possibility of increased risk of HIV transmission to sexual and needle-sharing partners.[6]

The overall effect of the use of antiretroviral therapy on HIV transmission risk may include factors other than its effect on HIV RNA level. Previous studies have suggested that the availability of antiretroviral therapy might result in increased risk behavior. Among gay men in the United States and Western Europe, rates of unprotected anal sex increased in the years after introduction of potent combination antiretroviral therapy.[7,8] At the same time, rates of gonorrhea and syphilis increased among populations at risk of HIV infection.[8] Furthermore, patients with previously diagnosed HIV infection were a prominent group in many of the recently reported outbreaks of syphilis, an infection that is both an indicator of risk behavior and a factor that increases the probability of HIV transmission.[9,10] Thus, based on these population and surveillance studies, it was hypothesized that availability of antiretroviral therapy led to increased sexual risk behavior among both HIV-infected and HIV-uninfected patients, perhaps because of a decreased perception of risk of HIV transmission while on treatment and/or a general improvement in health and well-being. If the use of antiretroviral therapy is associated with an increase in risk behavior, this would partly negate the beneficial effect of antiretroviral therapy on genital viral load.[11] A limitation of previous observational studies of the effect of antiretroviral therapy on HIV transmission risk behaviors is that the use of antiretroviral therapy was not randomized, making it difficult to adjust for possible confounding factors.

The Strategies for Management of Antiretroviral Therapy (SMART) study was a large, randomized clinical trial comparing episodic $CD4^+$-guided antiretroviral therapy versus

Received for publication January 10, 2008; accepted June 13, 2008.

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This study was presented in part at the 14th Conference on Retroviruses and Opportunistic Infections, February 2007, Los Angeles, CA.

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continuous antiretroviral therapy. Enrollment in the SMART study and the episodic antiretroviral treatment were stopped early (January 11, 2006) because of an excess risk of death, opportunistic disease, and serious cardiovascular and metabolic events among participants on the episodic therapy arm.[12] We report the results of a substudy comparing HIV transmission risk behavior among patients randomized to episodic therapy versus continuous antiretroviral therapy in the SMART study. Among patients who entered the study on antiretroviral therapy, this randomized comparison allows the assessment of the effect of stopping versus continuing antiretroviral therapy on transmission risk behavior. On the other hand, among those who entered the study off antiretrovirals, the comparison is between (re)starting versus deferring therapy.

METHODS

Study Population

Between January 2002 and January 2006, 5472 participants in 33 countries were enrolled in the SMART trial. A subset of geographically diverse sites in the United States (New York City, Richmond, Washington, DC, Denver, Portland, San Francisco, Detroit, Philadelphia, and southern New Jersey) coenrolled participants in this substudy on HIV transmission risk. Eligibility criteria for the SMART trial included a $CD4^+$ lymphocyte count >350 cells per cubic millimeter and willingness to start or discontinue antiretroviral therapy according to randomization assignment. At enrollment, participants could be antiretroviral naive, off antiretroviral therapy, but with a history of therapy, or on antiretroviral therapy.[12] The study was reviewed by institutional review boards at each site, and informed consent was obtained from each participant.

Study Design

Study participants were randomized 1:1 to continuous antiretroviral therapy with the goal of maximal viral suppression [viral suppression (VS) strategy] versus $CD4^+$-guided episodic therapy with the threshold to stop therapy at $CD4^+$ lymphocyte count >350 cells per cubic millimeter and the threshold to (re)start therapy at <250 cells per cubic millimeter [drug conservation (DC) strategy]. The primary endpoint of the SMART study was the occurrence of a new opportunistic disease or death, and the initial results of the study have been previously reported.[12] During the informed consent process, patients were informed that HIV RNA levels would be higher among patients randomized to the episodic therapy (either because of treatment interruption or because of deferral of therapy) and that this might increase the risk of HIV transmission to partners.

Data Collection

This study assessed risk behavior known to result in HIV transmission and performed laboratory testing for bacterial sexually transmitted infections, as a second measure of risk behavior. Substudy-specific visits were at baseline, 4 months, 12 months, and annually thereafter. At each substudy visit, blood and urine specimens were collected, and patients completed a brief confidential survey of sexual and needle-sharing behavior, modeled after a set of questions suggested for HIV/sexually transmitted disease behavioral surveillance by a workgroup for the Centers for Disease Control and Prevention.[13] To minimize recall bias, the survey asked about sexual and needle-sharing behavior for the previous 2 months. Participants reported the number of sexual partners but not the number of times they had sex with each partner. The type of sex (oral, anal, vaginal), condom use, and perceived HIV serostatus were reported for the last episode of sex with the main partner and, if applicable, occasional partner(s).

Laboratory testing for bacterial sexually transmitted infections included urine DNA amplification testing (using any licensed test) for *Neisseria gonorrhea* and *Chlamydia trachomatis* and serological testing for syphilis [screening rapid plasma reagin test (RPR) with testing for specific treponemal antibody (eg, Fluorescent Treponemal Antibody Absorbed [FTA-ABS] test) for those with a positive RPR]. Laboratory testing was performed at accredited local laboratories. In addition, patients also had $CD4^+$ lymphocyte and HIV RNA levels determined at each study visit. Genotypic resistance testing using the TRUGENE HIV-1 kit (Visible Genetics Inc., Toronto, Canada) was performed at a central laboratory for baseline samples with an HIV RNA level >1000 copies per milliliter.

Outcome Measures

The primary endpoint of this study was *high-risk behavior*, defined as any of the following: self-reported anal or vaginal sex without a condom; self-reported needle sharing; or a new diagnosis of gonorrhea, chlamydia, or syphilis. Incident syphilis was defined as newly positive nontreponemal test (RPR) confirmed by a treponemal test (FTA-ABS) or a greater than 4-fold increase in RPR titer among patients with a positive RPR and FTA-ABS at baseline.

Participants were considered to have *HIV transmission risk* if they engaged in high-risk behavior as defined above while having an HIV RNA level >1500 copies per milliliter. This threshold for HIV RNA levels was chosen because there were no cases of heterosexual transmission of HIV in the Rakai study of discordant couples when the infected partner had a plasma HIV RNA level <1500 copies per milliliter.[4] Participants were considered to have *transmission risk to HIV negative patients or those with unknown serostatus* if they engaged in high-risk behavior with such partners while their HIV RNA level was >1500 copies per milliliter. Participants were considered *at risk of transmitting drug-resistant HIV* if their baseline sample had at least 1 major resistance mutation[14] and they had high-risk behavior as defined above while their HIV RNA level was >1500 copies per milliliter.

Statistical Methods

Sample Size Calculation

We hypothesized that participants randomized to continuous antiretroviral therapy would more often have high-risk behavior than participants randomized to episodic antiretroviral therapy. Based on prior observational cohort studies,[15–18] we hypothesized that approximately 20% of patients in the continuous therapy arm would have high-risk behavior. This study was powered to detect a 2-fold difference in high-risk behavior (10% vs. 20%). When an interim analysis showed

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that the proportion of patients with high-risk behavior at baseline was lower than postulated (15%), the sample size was increased from 600 to 1010 participants.

Data Analysis

Data were censored on January 11, 2006, the date when the $CD4^+$-guided episodic antiretroviral therapy strategy was modified. All comparisons between treatment arms were by intention to treat.

At baseline, the association between risk factors and high-risk behavior was assessed with Pearson χ^2-test for independence and logistic regression. We used generalized estimating equations (GEEs) to compare the 2 randomized treatment arms longitudinally for proportions of patients with high-risk behavior (primary endpoint) and other endpoints. The treatment effect is presented as the ratio, between the 2 treatment groups, of the follow-up versus baseline odds ratios (comparing relative change from baseline). Subgroups of patients were compared for differential treatment effect by testing for interaction between treatment, follow-up, and subgroup indicators in the GEE models. Within treatment groups, changes in proportions over time were also assessed using GEE models.

When the survey and all laboratory tests were missing, the patient visit was excluded from the analyses. Partially missing information was imputed as "no risk" because prevalence of high-risk behavior was low. As sensitivity analysis, the primary endpoint analyses were repeated excluding all patient visits where any information needed to ascertain the primary endpoint was missing. Analyses were performed with SAS version 9.1.

RESULTS

Participant's Characteristics

Of the 995 patients enrolled in the SMART study at participating sites, 883 (89%) coenrolled in this substudy of transmission risk behavior between January 2002 and January 2006. Compared with participants who enrolled in the SMART study at participating sites but did not participate in this substudy, those who enrolled in the substudy were more often female (25% vs. 14%, $P = 0.01$), more often reported heterosexual contact as their risk for HIV acquisition (47% vs. 31%, $P = 0.002$), and more often had an HIV RNA level >400 copies per milliliter (36% vs. 34%, $P = 0.01$) at baseline. Of the 883 substudy participants, 440 were randomized to episodic therapy and 443 to continuous antiretroviral therapy. The randomized groups were well balanced for demographic and clinical characteristics (Table 1).

Baseline Risk Behavior

Of the 875 participants who completed the baseline risk behavior survey, 20 (2%) reported having used injection drugs within the past 2 months, 2 of whom reported sharing needles (Table 2). A total of 504 (58%) participants reported having sex within the past 2 months, with an average of 2 sexual partners. Sex with partners perceived to be HIV uninfected or of unknown HIV serostatus was common. Of the entire study population, 18% reported anal or vaginal sex with a main partner who was perceived to be HIV uninfected or of unknown HIV status. Among those who reported being sexually active, 60% of episodes of anal or vaginal sex with main partners and 66% of episodes of anal or vaginal sex with occasional partners were with partners perceived to be HIV uninfected or of unknown HIV status. Condoms were used more frequently for sex with partners perceived to be HIV uninfected or of unknown HIV status than for sex with HIV-infected partners (Table 2). One (0.1%) patient had a positive urine test for gonorrhea at baseline, and 11 (1%) had a positive test for chlamydia.

Factors Associated With High-Risk Behavior at Baseline

At baseline, 136 (15.4%) participants engaged in high-risk behavior. Factors associated with high-risk behavior included age less than 45 years, black or white (compared with Hispanics), male–male sex or male–male sex plus injection drug use as HIV acquisition risk factors, higher educational levels, and being off antiretroviral therapy (Table 3). At baseline, self-reported high-risk behavior was borderline associated with a diagnosis of gonorrhea or chlamydia (odds ratio: 3.4, 95% confidence interval: 1.0 to 11.7, $P = 0.06$).

Follow-Up

The mean follow-up time was 25.5 months, and 54% of the participants were followed-up for at least 2 years. Sixteen (1.8%) participants were lost to follow-up. Behavioral surveys were available from 94.8% of the scheduled substudy visits, and full laboratory testing results were available from 90.4% of those visits; neither differed by randomized arm. In accordance with the SMART study design, participants in the episodic therapy arm received antiretroviral therapy for much less of the follow-up time than those in the continuous therapy arm (39% vs. 91% of follow-up time, respectively, $P < 0.001$), and the difference in antiretroviral therapy usage was greatest in the first year after randomization (24% vs. 94% of time). The median time to first (re)initiation of antiretroviral therapy in the episodic therapy arm was 16 months.

Changes in Sexual Activity and Injection Drug Use

The proportion of participants reporting any sexual activity within the 2 months before study visits was similar in both treatment arms. Sexual activity appeared to decrease slightly in the first 4 months after study entry and thereafter remained stable at approximately 55%. Similarly, there were no differences between the 2 randomized arms in the average number of sexual partners, perceived HIV status of partners, the proportion reported having main or occasional partners, or reported condom use with main or occasional partners (data not shown). Injection drug use was infrequently reported (approximately 2%) and did not differ by randomized arm.

Changes in High-Risk Behavior

The proportion of participants reporting high-risk behavior (anal or vaginal sex without a condom, needle sharing, or laboratory diagnosis of incident chlamydia, gonorrhea, or syphilis) was similar in both study arms (Fig. 1A; $P = 0.39$ for treatment difference through follow-up). In the continuous

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TABLE 1. Baseline Characteristics by Treatment Group and Overall

	Episodic ART (DC Group) (n = 440)	Continuous ART (VS Group) (n = 443)	Total (N = 883)
Demographics			
Age (yrs), mean (SD)	45.4	44.4	44.9 (8.8)
Gender (% female)	25.7	24.8	25.3
Race			
Hispanic (%)	13.6	15.6	14.6
Black (%)	44.5	46.3	45.4
White (%)	40.5	34.8	37.6
Other (%)	1.4	3.4	2.4
HIV acquisition risk factor (CDC classification)			
MSM (%)	49.1	45.1	47.1
MSM/IDU (%)	3.6	5.2	4.4
IDU (%)	12.7	9.9	11.3
Heterosexual (%)	32.3	35.2	33.7
Other/unknown (%)	2.3	4.5	3.4
Education level			
Less than high school (%)	19.8	20.8	20.3
High school or GED (%)	29.3	28.2	28.8
Some college (%)	34.3	35.2	34.8
Completed college (%)	9.8	10.4	10.1
Any postgraduate (%)	6.8	5.4	6.1
$CD4^+$(cells/mm^3), median (IQR)	567	549	555 (437, 733)
$CD4^+$nadir (cells/mm^3), median (IQR)	276	245	260 (150, 372)
HIV RNA ≤400 copies per milliliter (%)	53.2	53.7	53.5
Prior recorded highest log HIV RNA (log copies/mL) median (IQR)	4.7	4.8	4.8 (4.1, 5.3)
ART history			
Antiretroviral naive (%)	6.4	8.1	7.2
PI experienced (%)	70.2	66.4	68.3
NNRTI experienced (%)	62.7	59.6	61.2
On ART at baseline (%)	77.7	77.7	77.7
Time since first prescribed ART (yrs) median, (IQR)	6	6	6 (3, 9)
Prior AIDS-related illnesses (%)	26.6	30.9	28.8
Hepatitis B (%)	3.4	1.8	2.6
Hepatitis C (%)	21.6	21.4	21.5

ART, antiretroviral therapy; DC, drug conservation; GED, general education degree; IDU, injection drug use; IQR, interquartile range; PI, protease inhibitor; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; SD, standard deviation; VS, viral suppression.

therapy group, high-risk behavior declined from 15.6% at baseline to 10.4% at month 4 ($P = 0.005$) and then returned closer to the baseline value. However, high-risk behavior appeared to decline somewhat in the episodic treatment group as well, and there was no evidence for a difference in high-risk behavior during the first 4 months in the episodic versus continuous therapy arms ($P = 0.15$).

As sensitivity analyses, we compared treatment groups for high-risk behavior after excluding all visits where information for assessing this endpoint was partially missing and found similar results.

Incident bacterial sexually transmitted infections were diagnosed at 37 follow-up visits, 1.8% of the 2024 visits at which testing was performed. There were no differences in the incidence of bacterial sexually transmitted infections between the 2 treatment arms. Of the 38 incident infections diagnosed during follow-up, there were 13 cases of chlamydia, 5 cases of gonorrhea, and 20 cases of syphilis.

Subgroup Analyses

We evaluated whether baseline factors influenced the difference in high-risk behavior between the 2 randomized arms. There was no treatment difference in high-risk behavior within subgroups of participants defined by gender, sexual preference, race, and age, and no evidence for differential treatment effects across these subgroups.

For participants on antiretroviral therapy at baseline, for whom the randomization was to interrupt versus continue antiretroviral therapy, high-risk behavior remained stable over follow-up, and was very similar in the 2 arms (Fig. 1B). However, among participants not on antiretroviral therapy at baseline, there was a significant decrease in transmission risk behavior among those randomized to start antiretroviral therapy (from 20% at baseline to 10% at 4 months, $P = 0.05$; Fig. 1C). In contrast, among those randomized to defer therapy, the proportion with high-risk behavior remained stable. For participants not on antiretroviral therapy at

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TABLE 2. Baseline Sexual and Needle-Sharing Behavior

	Population, n (%)*	Subset, n (%)†
Self-reported risk behavior (last 2 mo)	875	
Injected drugs	20 (2.3)	
Shared needles		2 (10.0)
Had sex with another person (oral, anal, or vaginal)	504 (57.6)	
Number of sex partners		
1		314 (62.3)
2		82 (16.3)
3 or more		95 (18.8)
Not answered		13 (2.6)
Had sex with main partner		346 (68.7)
Not answered		1 (0.2)
Had sex with occasional partner		199 (39.5)
Not answered		1 (0.2)
Last episode of sex with the main partner was anal or vaginal	263 (30.1)	
Perceived HIV status of main partner and condom use at the last episode (anal or vaginal sex)		
HIV+, condom used		47 (17.9)
HIV+, condom not used		57 (21.7)
HIV−, condom used		116 (44.1)
HIV−, condom not used		23 (8.7)
Unknown HIV status, condom used		9 (3.4)
Unknown HIV status, condom not used		10 (3.8)
Not answered		1 (0.4)
Last episode of sex with an occasional partner was anal or vaginal	131 (15.0)	
Perceived HIV status of the last occasional partner and condom use at the last episode (anal or vaginal sex)		
HIV+, condom used		21 (16.0)
HIV+, condom not used		20 (15.3)
HIV−, condom used		31 (23.7)
HIV−, condom not used		5 (3.8)
Unknown HIV status, condom used		31 (23.7)
Unknown HIV status, condom not used		19 (14.5)
Not answered		4 (3.1)
High-risk behavior (self-reported anal or vaginal sex without condom or shared needles or laboratory evidence of STD)	136 (15.4)‡	
Self-reported high-risk behavior (anal or vaginal sex without condom or shared needles in past 2 months)	126 (14.4)	
Self-reported high-risk sexual behavior with a partner who was HIV− or of unknown HIV serostatus (anal or vaginal sex without condom)	54 (6.2)	

STD, sexually transmitted disease.
*Percent relative to number of participants with surveys, n = 875, unless otherwise noted.
†Percent relative to subsets defined by the bolded subheadings
‡Percent relative to number of participants with surveys or tests for STD, n = 882. This includes 36 participants with partially missing information; of these, 7 have high-risk behavior, and for 29 the endpoint was imputed as "no risk behavior." Survey and laboratory tests were missing for 1 participant (excluded).

baseline, the difference in high-risk behavior between the 2 treatment arms was significant at 4 months ($P = 0.02$) but not over the entire follow-up period ($P = 0.11$).

Changes in HIV Transmission Risk

Because of the large difference in antiretroviral therapy usage by treatment arm during follow-up, participants in the episodic therapy arm had HIV RNA levels greater than 1500 copies/mL much more often than participants in the continuous therapy arm (63% of follow-up time versus 25%, respectively, $P < 0.001$). As a result of higher HIV RNA levels and the lack of difference in high-risk behavior by treatment arm during follow-up, the proportion of participants with HIV transmission risk (high-risk behavior while having an HIV RNA level >1500 copies/mL) was higher in the episodic than in the continuous therapy arms ($P < 0.001$ for treatment difference; Fig. 2). Similarly, transmission risk to a partner perceived to be HIV uninfected or of unknown HIV serostatus was substantially higher in the episodic treatment arm ($P = 0.02$; Fig. 2).

Finally, we evaluated the risk of transmitting drug-resistant HIV by treatment arm. At baseline, approximately 19% of participants had HIV RNA level >1000 copies per milliliter and an HIV strain with at least 1 major resistance

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TABLE 3. Factors Associated With High-Risk Behavior At Baseline

Factor	Number in Subgroup	Number With High-Risk Behavior (%)	OR	95% CI	*P**
Gender					0.73
Male	659	100 (15.2)	0.9	0.6 to 1.4	
Female	223	36 (16.1)	1.0		
Age (yrs)					0.03
<45	442	80 (18.1)	1.5	1.0 to 2.2	
≥45	440	56 (12.7)	1.0		
Race/ethnicity					0.04
Hispanic	129	10 (7.8)	0.4	0.2 to 0.8	
Black	400	64 (16.0)	0.9	0.6 to 1.3	
White	332	60 (18.1)	1.0		
Other	21	2 (9.5)	0.5	0.1 to 2.1	
HIV acquisition risk factor†					0.01
MSM	415	80 (19.3)	1.0		
MSM/IDU	39	8 (20.5)	1.1	0.5 to 2.4	
IDU	100	9 (9.0)	0.4	0.2 to 0.9	
Heterosexual	298	34 (11.4)	0.5	0.3 to 0.8	
Other/unknown	30	5 (16.7)	0.8	0.3 to 2.3	
Educational level					0.004
Less than high school	179	12 (6.7)	1.0		
High school or GED	253	38 (15.0)	2.5	1.2 to 4.9	
Some college	307	60 (19.5)	3.4	1.8 to 6.5	
Completed college	89	15 (16.9)	2.8	1.3 to 6.3	
Any postgraduate	54	11 (20.4)	3.6	1.5 to 8.6	
Antiretroviral use at baseline					0.05
On antiretroviral therapy	686	97 (14.1)	0.7	0.4 to 1.0	
Off antiretroviral therapy	196	39 (19.9)	1.0		

CI, confidence interval; GED, general education degree; IDU, injection drug use; MSM, men who have sex with men; OR, odds ratio.
*χ^2 test for association between baseline high-risk behavior and subgroup factor.
†CDC classification system.

mutation. Among those, the proportion with high-risk behavior remained stable and was similar in both treatment arms. However, due to the higher HIV RNA levels in the episodic treatment arm, the proportion of patients at risk of transmitting a resistant strain was also higher in this treatment arm ($P = 0.04$; Fig. 2).

DISCUSSION

This is the first randomized study to evaluate the effect of antiretroviral therapy on transmission risk behavior. Episodic use of antiretroviral therapy did not decrease high-risk sexual or needle-sharing behavior that may result in HIV transmission, compared with continuous therapy use. Because HIV RNA levels were higher among participants on episodic therapy, whereas high-risk behavior remained similar to that in the continuous therapy arm, patients randomized to episodic therapy had a higher risk of transmitting HIV infection, including drug-resistant HIV. Additionally, among participants entering the study off antiretroviral therapy, high-risk behavior decreased initially among participants randomized to start antiretroviral therapy, compared with those randomized to defer therapy.

A number of cross-sectional studies have evaluated the association between antiretroviral therapy and sexual risk behavior. The results of individual studies differ, but a meta-analysis showed no association between antiretroviral therapy use and risk behavior.[19] Longitudinal cohort studies have also had disparate results, with some showing an increase in risk behavior after starting combination antiretroviral therapy,[20] and others showing stable or decreased risk behavior after starting.[21,22] Other studies suggested a more complex effect of starting antiretroviral therapy on risk behavior; women reported a decrease in number of sexual partners, but an increase in episodes of unprotected vaginal intercourse.[23] Our study, the first to evaluate the effect of antiretroviral therapy in a randomized manner, found no evidence for a disinhibitory effect of being on antiretroviral therapy, as overall risk behavior was not affected by randomization to episodic versus continuous antiretroviral therapy.

We enrolled a population with demographic characteristics representative of those of patients in HIV care in the United States.[24] A cross-sectional analysis of baseline risk behavior showed that participants who were on antiretroviral therapy reported less high-risk behavior. Starting antiretroviral therapy was followed by a significant decrease in high-risk

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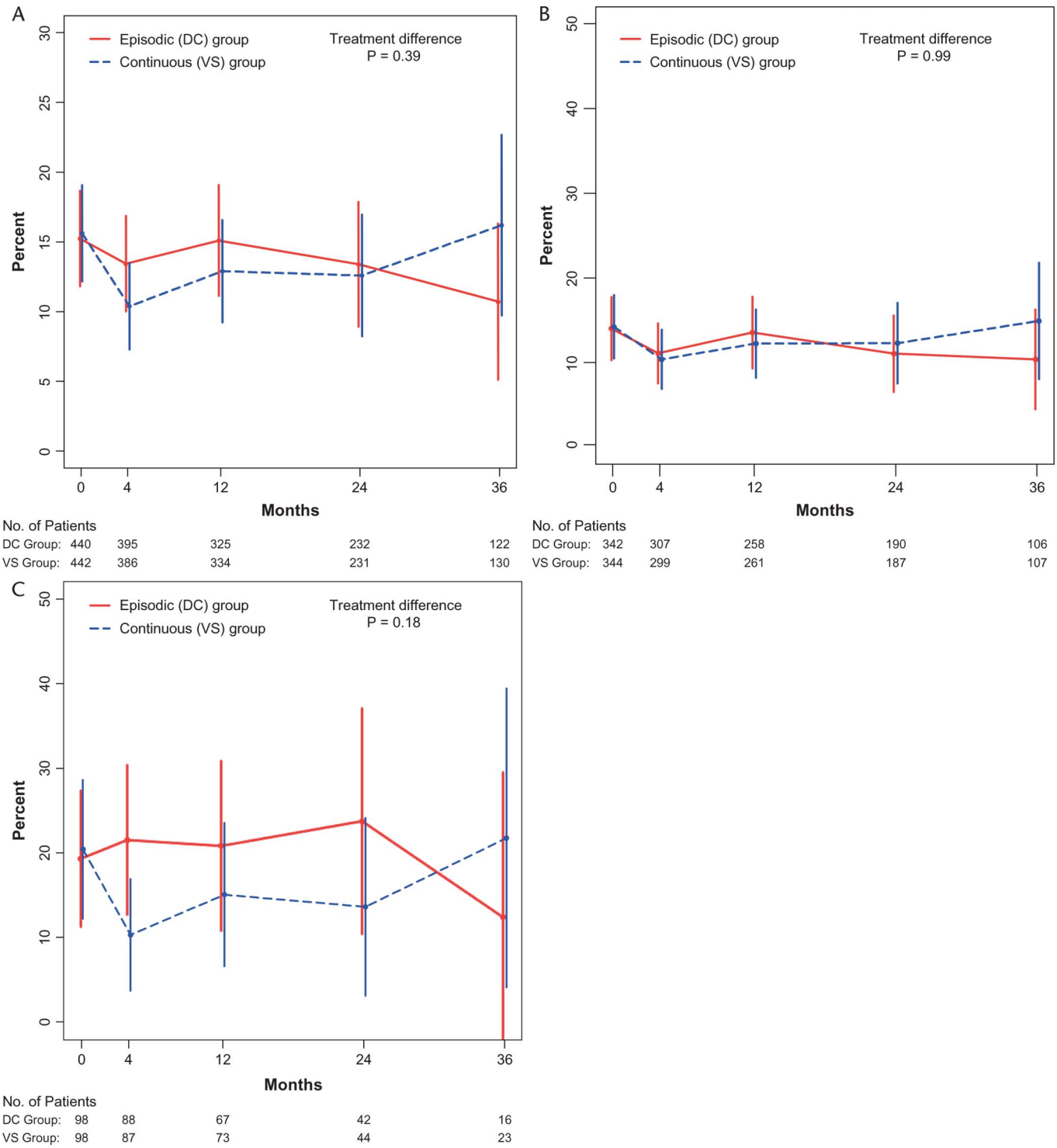

FIGURE 1. Proportion of patients with high-risk behavior, by treatment group, for all patients (A), among those who entered the study on antiretroviral therapy (B), and among those who entered the study off antiretroviral therapy (C). Error bars show ±2 SEs.

behavior, to approximately the level observed among participants who were on antiretroviral therapy at enrollment. These findings have potential importance in the question of the optimal timing of initiation of antiretroviral therapy. If starting antiretroviral therapy is associated with decreases in both genital viral load and high-risk behavior, as we have demonstrated, then initiation of antiretroviral therapy may prove to be an important strategy for the prevention of HIV transmission.

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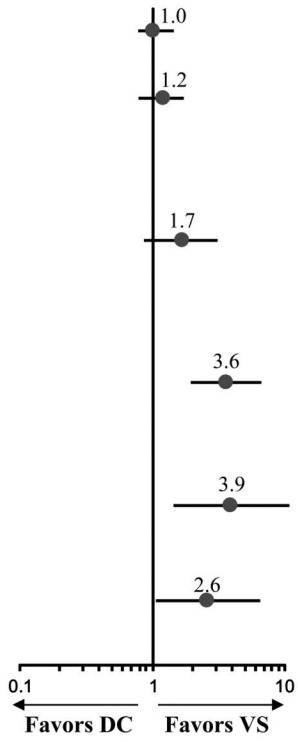
Endpoint	Treatment Group	Pct. with endpoint at baseline	Average pct. with endpoint through follow-up[a]	Treatment Effect[b] Ratio of change[c] (DC/VS) and 95% Confidence Interval	p-value
Anal or vaginal sex in the past 2 months	Episodic (DC)	38.4	34.1	1.0	0.73
	Continuous (VS)	42.2	36.1		
High-risk behavior *(anal or vaginal sex without a condom or needle-sharing or an incident bacterial sexually-transmitted infection)*	Episodic (DC)	15.2	13.6	1.2	0.39
	Continuous (VS)	15.6	12.3		
High-risk behavior with a HIV-negative or unknown sero-status partner *(anal or vaginal sex without a condom)*	Episodic (DC)	5.7	5.4	1.7	0.09
	Continuous (VS)	6.6	4.3		
HIV transmission risk, any partner *(high-risk behavior while having an HIV-RNA level > 1500 copies/mL)*	Episodic (DC)	5.7	10.1	3.6	<0.001
	Continuous (VS)	6.8	3.5		
HIV transmission risk to partners who are HIV-uninfected or of unknown sero-status	Episodic (DC)	2.1	4.4	3.9	0.02
	Continuous (VS)	2.3	1.4		
Risk of drug-resistant HIV *(HIV transmission risk and presence of at least one major mutation on baseline genotypic test)*	Episodic (DC)	2.5	2.5	2.6	0.04
	Continuous (VS)	3.4	1.2		



[a] Percent of patient-visits with endpoint
[b] Estimated using GEE for longitudinal binary data
[c] Ratio of odds ratios of follow-up versus baseline proportions, in the DC and VS treatment groups, comparing relative change from baseline

FIGURE 2. Treatment effect [episodic (drug conservation) versus continuous (viral suppression) antiretroviral therapy] on high-risk behavior and other outcomes, comparing change in proportions from baseline through follow-up between the 2 treatment groups. DC, drug conservation; VS, viral suppression.

Our study has at least 6 limitations. First, substudy participants had slightly different demographics from those who were eligible but did not coenroll; however, the substudy population closely resembles the SMART study population at participating clinical sites because 89% of SMART participants at these sites coenrolled in the substudy. Second, the power of this substudy to detect differences in risk behavior by randomized arm was lower than planned because enrollment in the SMART study was stopped early and the follow-up time was curtailed. However, this study was originally powered to detect a 2-fold difference between treatment arms, and there was no trend suggesting any such difference. Third, we did not directly assess HIV transmission but used the prevalence of high-risk behavior at elevated HIV RNA levels as a surrogate for HIV transmission. Fourth, our survey was brief so that it would fit easily into study visits for a large clinical trial that assessed many other outcomes. As a result, the survey did not provide detailed information about the number and type of sexual encounters. Fifth, we may have underestimated the incidence of bacterial sexually transmitted infections, both because of infrequent sampling and because we did not test for anal or pharyngeal gonorrhea and chlamydia.[25] Finally, the risk of transmitting HIV resistant strains was likely underestimated because genotypic testing was done only at baseline and only for patients with HIV RNA >1000 copies per milliliter.

In summary, episodic use of antiretroviral therapy did not affect high-risk sexual and needle-sharing behavior, compared with continuous therapy. Because episodic therapy resulted in higher HIV RNA levels, the unchanged high-risk behavior increased the risk of HIV transmission, including the transmission of drug-resistant strains. Randomization to start antiretroviral therapy was associated with a trend toward decreased high-risk behavior, which may augment the effect of viral load reduction in decreasing HIV transmission.

ACKNOWLEDGMENTS

We gratefully acknowledge the commitment of all the participants in the Transmission Risk Behavior substudy of the SMART study and the many investigators and clinical staff. Birgit Grund had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. None of the authors have financial conflicts of interest. Grant support provided by

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NIAD, NIH grants U01AI042170 and U01AI46362. Participating clinical sites (number of participants enrolled) and investigators are listed below.

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