Annals of Internal Medicine | ARTICLE

Risk for Opportunistic Disease and Death after Reinitiating Continuous Antiretroviral Therapy in Patients with HIV Previously Receiving Episodic Therapy

A Randomized Trial

The SMART Study Group*

Background: Episodic use of antiretroviral therapy guided by $CD4^+$ cell counts is inferior to continuous antiretroviral therapy.

Objective: To determine whether reinitiating continuous antiretroviral therapy in patients who received episodic treatment reduces excess risk for opportunistic disease or death.

Design: Randomized, controlled trial.

Setting: Sites in 33 countries.

Patients: 5472 HIV-infected individuals with $CD4^+$ cell counts greater than 0.350×10^9 cells/L enrolled from January 2002 to January 2006.

Intervention: Episodic or continuous antiretroviral therapy initially, followed by continuous therapy in participants previously assigned to episodic treatment.

Measurements: Opportunistic disease or death was the primary outcome.

Results: Eighteen months after the recommendation to reinitiate continuous therapy, mean $CD4^+$ cell counts were 0.152×10^9 cells/L (95% CI, 0.136 to 0.167×10^9 cells/L) less in participants previously assigned to episodic treatment ($P < 0.001$). The proportion of follow-up time spent with $CD4^+$ cell counts of 0.500×10^9 cells/L or more and HIV RNA levels of 400 copies/mL or less was 29% for participants initially assigned to episodic therapy and 66% for those assigned to continuous therapy. Participants who reinitiated continuous therapy experienced rapid suppression of HIV RNA levels (89.7% with HIV RNA levels ≤400 copies/mL after 6 months), but $CD4^+$ cell counts after 6 months remained 0.140×10^9 cells/L below baseline. The hazard ratio (episodic versus continuous treatment) for opportunistic disease or death decreased after the recommendation to reinitiate continuous therapy (from 2.5 [CI, 1.8 to 3.5] to 1.4 [CI, 1.0 to 2.0]; $P = 0.033$ for difference). The residual excess risk was attributable to failure to reinitiate therapy by some participants and slow recovery of $CD4^+$ cell counts for those who reinitiated therapy.

Limitation: Follow-up was too short to assess the full effect of switching from episodic to continuous antiretroviral therapy.

Conclusion: Reinitiating continuous antiretroviral therapy in patients previously assigned to episodic treatment reduced excess risk for opportunistic disease or death, but excess risk remained. Episodic antiretroviral therapy, as used in the SMART study, should be avoided.

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* For writing group members, see end of article; for investigators in the SMART Study Group, see the **Appendix** (available at www.annals.org).

The SMART (Strategies for Management of Anti-Retroviral Therapy) study was designed to assess whether the risks associated with long-term use of antiretroviral therapy could be reduced through the episodic use of antiretroviral therapy guided by $CD4^+$ cell counts. This treatment interruption strategy (episodic antiretroviral therapy or drug conservation strategy) was compared with the current practice of continuous antiretroviral therapy (viral suppression strategy). As previously reported, the episodic treatment strategy caused an excess risk for opportunistic diseases or death (the primary end point), an excess risk for serious nonopportunistic diseases, and inferior quality of life compared with the continuous antiretroviral therapy strategy (1–4). The excess risk for opportunistic disease or death due to any cause in the drug conservation group was largely attributable to lower $CD4^+$ cell counts and higher HIV RNA levels during follow-up compared with those in the viral suppression group (1, 5). The episodic treatment strategy was discontinued on 11 January 2006, and all participants assigned to the drug conservation group were advised to reinitiate antiretroviral therapy, except for some who had remained antiretroviral therapy–naive. All participants, including those who were still antiretroviral therapy–naive, were then followed for an additional 18 months.

We describe the results of the trial through the end of follow-up and assess the extent to which the excess risk for major clinical outcomes was reduced as a consequence of the recommendation to reinitiate antiretroviral therapy in the drug conservation group.

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Context

Continuous antiretroviral therapy improves outcomes for patients with HIV compared with episodic, $CD4^+$ cell count–guided therapy.

Contribution

This long-term follow-up of clinical trial participants demonstrates that the increased hazard of opportunistic disease and death decreases, but is not eliminated, with resumption of continuous antiretroviral therapy in participants initially assigned to episodic therapy.

Caution

An 18-month follow-up may have been too short to assess true changes in hazard.

Implication

Patients who receive episodic antiretroviral therapy decrease but do not eliminate their excess risk for disease when they resume continuous treatment.

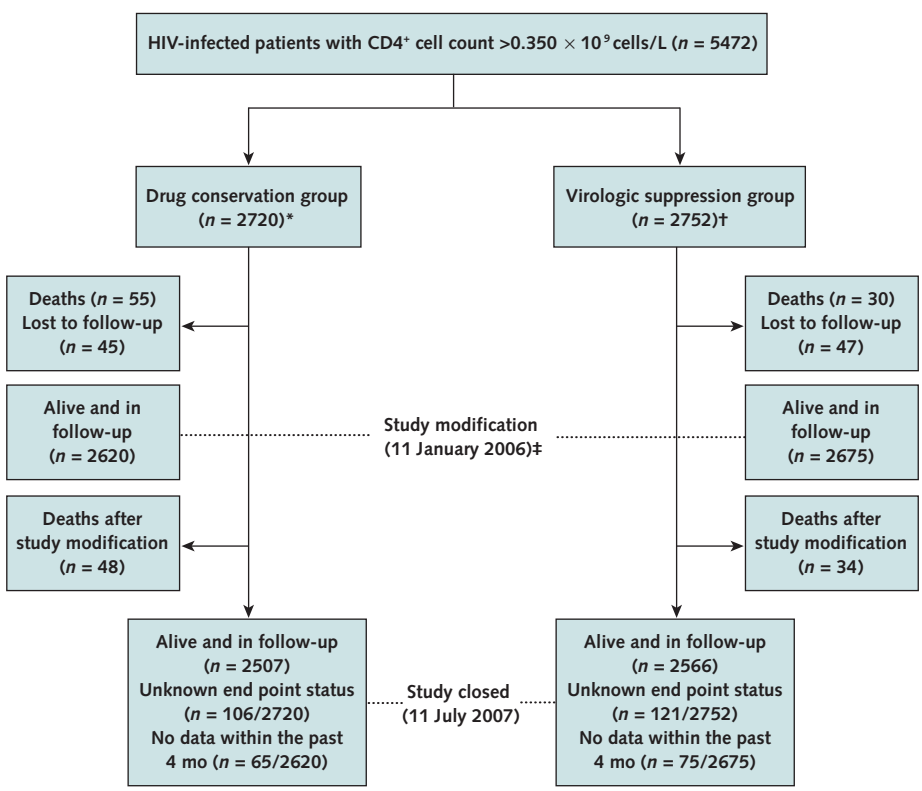
—The Editors

METHODS

Design

The design and data collection methods of the trial have been published (1). In brief, 5472 HIV-infected patients with a $CD4^+$ cell count greater than 0.350×10^9 cells/L were randomly assigned at each clinical site to an episodic antiretroviral therapy strategy (drug conservation group) guided by $CD4^+$ cell counts or to continuous antiretroviral therapy (viral suppression group) (**Figure 1**). The viral suppression strategy aimed to maximally suppress viral replication by continuous use of antiretroviral therapy. The drug conservation strategy entailed episodic use of antiretroviral therapy based on $CD4^+$ cell count thresholds. Therapy was discontinued (or deferred) until $CD4^+$ cell counts decreased to less than 0.250×10^9 cells/L, at which time it was reinitiated and continued until the $CD4^+$ cell count increased to greater than 0.350×10^9 cells/L. On confirmation that the $CD4^+$ cell count was greater than 0.350×10^9 cells/L, antiretroviral therapy was discontinued and resumed again if the $CD4^+$ cell count returned to less than 0.250×10^9 cells/L. During periods of

Figure 1. **Study flow diagram.**



* Discontinues or defers antiretroviral therapy (ART) until $CD4^+$ cell count decreases to $<0.250 \times 10^9$ cells/L, treats to increase $CD4^+$ cell counts $>0.350 \times 10^9$ cells/L, then uses episodic ART based on $CD4^+$ cell count.
† Uses ART to maintain viral load as low as possible, regardless of $CD4^+$ cell count, by changing ART when viral load is not suppressed.
‡ Recommended restarting ART in participants in the drug conservation group unless they are still ART-naive.

antiretroviral therapy, the goal was to achieve maximum viral suppression.

Clinical Outcomes

The primary end point was a composite outcome of new or recurrent opportunistic disease or death from any cause, and the secondary end point was a composite of major cardiovascular, renal, and hepatic diseases (1). At the start of the trial, investigators assumed that the risk for cardiovascular, renal, and hepatic diseases was increased with use of antiretroviral therapy. An end point review committee, blinded to treatment group, reviewed opportunistic diseases; deaths; and cardiovascular, hepatic, and renal disease events by using preestablished criteria. Underlying cause of death was classified by using the Coding of Death in HIV Project system (6).

Modification

After 5472 participants had been enrolled and were in follow-up, the study data safety and monitoring board recommended discontinuing enrollment in the trial because of increased risk for opportunistic disease or death in the drug conservation group. On 11 January 2006, investigators and participants were notified of these findings, enrollment was discontinued, and participants in the drug conservation group who had received antiretroviral therapy were advised to restart it (referred to as "study modification"). Follow-up was continued for all participants through 11 July 2007 (study closure), with the goal of assessing the extent of reduction in the excess risk in the drug conservation group that was achieved as a consequence of the recommendation to reinitiate antiretroviral therapy. Participants in the drug conservation group who were treatment-naive at the time of study modification were included in the analysis. With these additional 18 months of follow-up, the study was powered (80%) to detect a hazard ratio (HR) (drug conservation vs. viral suppression) for opportunistic disease or death of 1.8 or more during follow-up.

Statistical Analysis

The primary analysis was by randomized group. Cox proportional hazard models with a single binary indicator (drug conservation vs. viral suppression) were used to compare the treatment groups for major clinical outcomes through 2 periods: from randomization to study modification on 11 January 2006 and from study modification to study closure on 11 July 2007. Before study modification, comparison of the drug conservation and viral suppression groups for clinical events included all randomly assigned participants. After study modification, comparisons were restricted to participants who had not experienced the event of interest by the study modification in an analysis focused on time to first event. Other outcomes, including the composite of cardiovascular, renal, and liver disease, were considered similarly. Treatment comparisons for time-to-event outcomes were summarized with treatment HRs (drug conservation vs. viral suppression group) and 95% CIs from the Cox models; rates per 100 person-years were also cited. To assess whether the treatment HRs differed between the 2 periods, we included an interaction term between the treatment indicator and period in a Cox model for time to first event from randomization through study closure. We assessed homogeneity of the treatment HRs in the time periods before and after study modification by including a log-time term in the Cox model and testing for interaction with the randomized treatment indicator. In addition, treatment HRs for 6-month intervals before and after study modification were cited.

Plasma HIV RNA levels and $CD4^+$ cell counts were measured every 2 months during the first year after randomization and then every 4 months through study closure on 11 July 2007; $CD4^+$ cell count at antiretroviral therapy initiation was also measured. Mean $CD4^+$ cell count and percentage with an HIV RNA level of 400 copies/mL or less were calculated at baseline and selected study visits before study modification, at study modification, and every 2 months thereafter, and at antiretroviral therapy reinitiation and every month thereafter. Data collection windows were determined by the date of randomization, not by the date of study modification. Therefore, mean $CD4^+$ cell counts at 2 months after study modification (11 March 2006), for example, were estimated by averaging $CD4^+$ cell counts for participants who had a $CD4^+$ cell count within 1 month before or after 11 March 2006. Using these estimates, the percentage with HIV RNA levels of 400 copies/mL or less and average $CD4^+$ cell counts after study modification were compared for drug conservation and viral suppression participants. For comparison, HIV RNA levels and $CD4^+$ cell count at baseline and during the 4 months after randomization were also summarized. Similar methods were used to summarize HIV RNA levels and mean $CD4^+$ cell counts for the drug conservation group after reinitiation of antiretroviral therapy after study modification through study closure.

Person-years accumulated in $CD4^+$ cell count and HIV RNA strata were measured by using time-updated measurements (latest levels). For each stratum, rates of opportunistic disease or death per 100 person-years were computed. Treatment HRs for opportunistic disease or death, adjusted for latest $CD4^+$ cell counts and HIV RNA levels (separately and combined), were estimated by using Cox models with time-updated covariates. Cox models were also used to assess the effect of major clinical events before study modification on risk for death after study modification. Statistical analyses were done by using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). Two-sided *P* values were reported.

Role of the Funding Source

The trial was funded by the National Institute of Allergy and Infectious Disease. As members of the International Network for Strategic Initiative in Global HIV Trials Executive Committee, funding source staff participated

Table 1. **Participant Characteristics at Study Entry, Modification, and Closure, by Treatment Group**

Characteristic	Study Entry		Study Modification, January 2006		Study Closure, July 2007	
	DC Group (n = 2720)	VS Group (n = 2752)	DC Group (n = 2620)	VS Group (n = 2675)	DC Group (n = 2507)	VS Group (n = 2566)
Median age, *y*	43	44	–	–	–	–
Women, %	26.3	28.0	–	–	–	–
Race, %						
Black	28.5	29.8	–	–	–	–
White	56.4	54.8	–	–	–	–
Other	15.1	15.4	–	–	–	–
Mode of infection with HIV, %						
Sexual contact						
Same sex	51.4	48.4	–	–	–	–
Opposite sex	44.4	45.6	–	–	–	–
Injection drug use	9.9	9.6	–	–	–	–
Other or unknown	7.5	8.7	–	–	–	–
Mean $CD4^+$ cell count, $\times 10^9$ *cells/L*	0.658	0.661	0.468	0.682	0.541	0.693
$CD4^+$ cell count $<0.350 \times 10^9$ cells/L, %	0.0	0.0	30.4	5.7	18.0	7.6
Median $CD4^+$ nadir, $\times 10^9$ *cells/L*	0.250	0.250	0.217	0.243	0.208	0.237
HIV RNA level ≤400 copies/mL, %	71.9	71.5	34.5	82.1	73.0	83.6
History of ART						
Current ART use, %	84.2	83.6	35.6	94.4	83.4	95.0
Never used ART, %	4.3	4.8	3.4	0.1	1.8	0.0
Previous AIDS-related illness, %	25.1	23.3	26.5	23.6	–	–

ART = antiretroviral therapy; DC = drug conservation; VS = viral suppression.

in the review of the paper but were not part of the writing group.

Results

Participant Characteristics and Follow-up

From 8 January 2002 to 11 January 2006, 5472 participants were randomly assigned at 318 sites in 33 countries—2720 to the drug conservation group and 2752 to the viral suppression group. During this time, approximately 7300 person-years accrued; after study modification, approximately 7700 additional person-years accrued. In total, participants were followed on average for 2.8 years, of which 1.3 years occurred before study modification.

At study modification, 2620 (96.3%) participants in the drug conservation group and 2675 (97.2%) participants in the viral suppression group were alive and still being followed. At study closure, the primary end point status was unknown (could not be verified within 4 months of the closing date) for 106 (3.9%) and 121 (4.4%) participants in the drug conservation and viral suppression groups, respectively (**Figure 1**).

At baseline, the 2 treatment groups were similar in demographic characteristics (1). At study modification, participants in the drug conservation group were less likely to be prescribed antiretroviral therapy (36% vs. 94%), less likely to have HIV RNA levels of 400 copies/mL or less (35% vs. 82%), and had lower average $CD4^+$ cell counts (0.468 vs. 0.682 $\times 10^9$ cells/L [95% CI for difference, 0.201 $\times 10^9$ cells/L to 0.228 $\times 10^9$ cells/L]). By the end of the study, only 1.8% of drug conservation participants remained antiretroviral therapy–naive (**Table 1**).

Antiretroviral Therapy Use, $CD4^+$ Cell Counts, and HIV RNA Levels after Study Modification

After the recommendation to initiate antiretroviral therapy in the drug conservation group, use of therapy increased from 35.6% at study modification to 74.2% and 83.4% at 6 and 18 months after study modification (study closure), respectively (**Figure 2**). Among drug conservation participants who were not receiving therapy at the time of study modification but had previously received antiretroviral therapy, 77.2% were receiving therapy at study closure. For viral suppression participants, 94% were receiving antiretroviral therapy at study modification and 95% were receiving therapy at study closure.

With the increasing use of antiretroviral therapy in the drug conservation group after study modification, the percentage of these participants with HIV RNA levels of 400 copies/mL or less increased (**Figure 2**, *A*; **Table 2**). At study closure, this percentage was similar to that at baseline (71.9% vs. 73.0%) (**Table 1**). In the viral suppression group, the percentage with HIV RNA levels of 400 copies/mL or less remained stable (**Figure 2**, *A*; **Table 2**). After study modification, the difference between treatment groups in the percentage of participants with HIV RNA levels of 400 copies/mL or less decreased but remained statistically significant at each time point (**Table 2**).

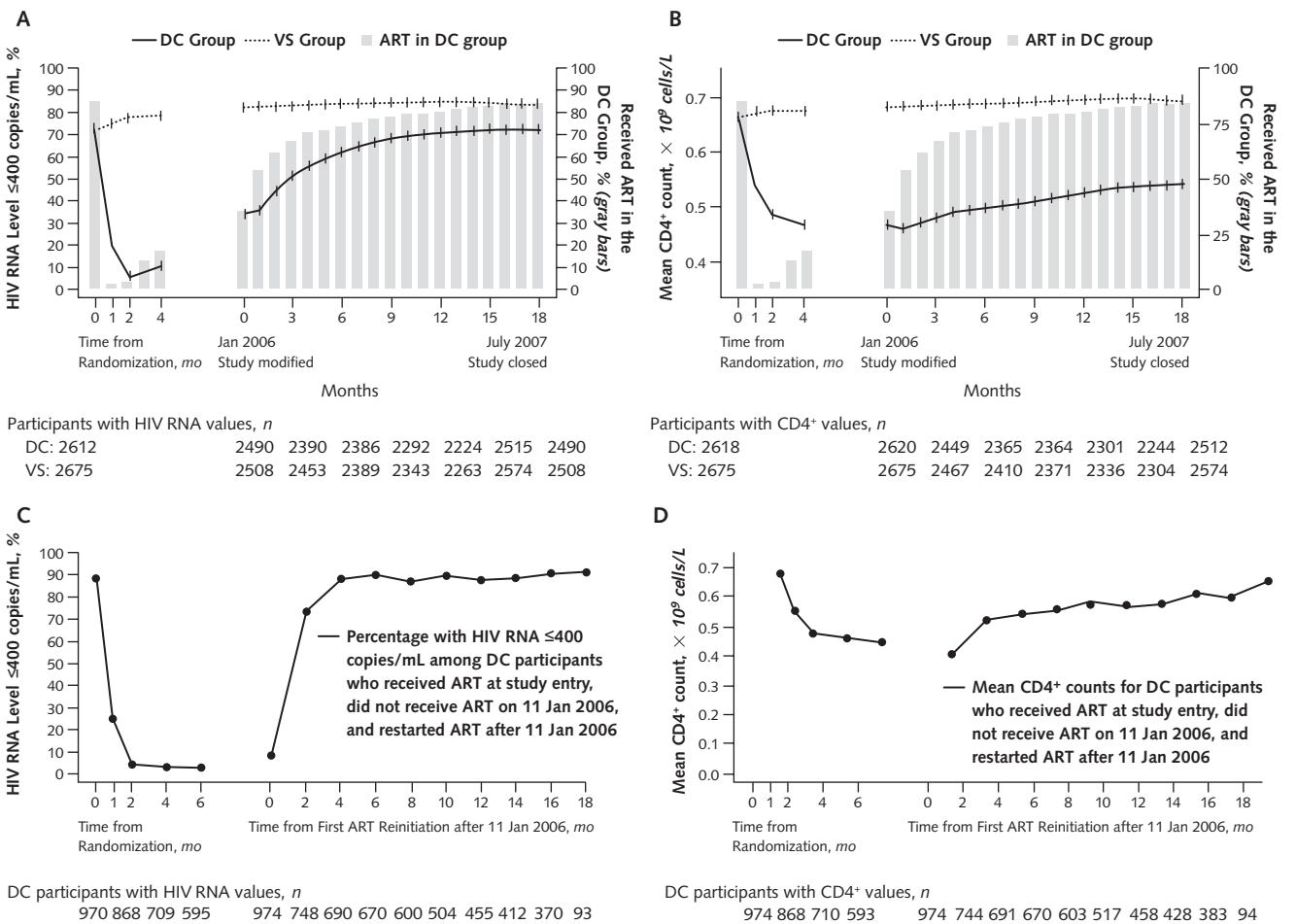
In the drug conservation group, average $CD4^+$ cell count was 0.120 $\times 10^9$ cells/L less at study closure than at baseline (**Table 1**). Average $CD4^+$ cell count increased after study modification for participants in the drug conservation group but remained statistically significantly less than counts for the viral suppression

group throughout the 18-month follow-up (**Figure 2**, *B*; **Table 2**).

We investigated whether the $CD4^+$ cell count differences between treatment groups at study closure were because of differences in use of antiretroviral therapy or incomplete recovery of $CD4^+$ cell count in those who reinitiated antiretroviral therapy. There were 974 participants in the drug conservation group who received antiretroviral therapy at study entry, had not received therapy at study modification, and reinitiated therapy after study modification. These participants reinitiated antiretroviral therapy a median of 41 days after study modification (interquartile range, 16 to 100 days). After antiretroviral therapy reinitiation, the percentage who achieved HIV RNA levels of 400 copies/mL or less increased rapidly (**Figure 2**, *C*). Six months after reinitiating antiretroviral therapy, the percentage with HIV RNA levels of 400 copies/mL or less was similar to baseline, preinterruption levels (89.7% vs. 88.0%). $CD4^+$ cell counts returned to baseline more slowly (**Figure 2**, *D*). Six months after antiretroviral therapy was reinitiated, $CD4^+$ cell count increased an average of 0.151×10^9 cells/L (CI, 0.138 to 0.164×10^9 cells/L); the $CD4^+$ cell count at 6 months after antiretroviral therapy reinitiation, however, remained 0.140×10^9 cells/L (CI, 0.123 to 0.157×10^9 cells/L) below baseline (preinterruption) levels (**Figure 2**, *D*).

Before study modification, participants in the drug conservation group had $CD4^+$ cell counts less than

Figure 2. **Percentages of participants with HIV RNA levels of 400 copies/mL or less and mean $CD4^+$ cell counts through follow-up.**



ART = antiretroviral therapy; DC = drug conservation; VS = viral suppression. **A.** Percentage of participants with HIV RNA levels ≤400 copies/mL, by treatment group from randomization through the first 4 months and from study modification in January 2006 through study closure. Follow-up time before study modification ranged from 0 to 48 months, depending on the date of enrollment. **B.** Mean $CD4^+$ cell counts, by treatment group. The gray bars in panels A and B show the percentage of participants in the DC group who received ART. The percentage increased from 35.6% at study modification to 67.0%, 74.2%, 80.5%, and 83.4% at 3, 6, 12, and 18 months after study modification, respectively. The vertical bars show ±2 SEs. **C.** Percentage with HIV RNA levels ≤ 400 copies/mL among DC participants who received ART at study entry, did not receive ART on 11 January 2006, and restarted ART after study modification. **D.** Mean $CD4^+$ counts for DC group participants who received ART at study entry, did not receive ART on 11 January 2006, and restarted ART after 11 January 2006.

Table 2. **Mean CD4$^+$ Cell Count and Percentage of Participants with HIV RNA Levels ≤400 copies/mL at and after Study Modification, by Treatment Group**

Variable	Mean CD4$^+$ Cell Count, × 10^9 cells/L			HIV RNA Level ≤400 copies/mL, %		
	DC Group	VS Group	Difference (95% CI)*	DC Group	VS Group	Difference (95% CI)*
At study modification	0.468	0.682	−0.214 (−0.228 to −0.201)	34.5	82.1	−47.6 (−49.9 to −45.3)
After study modification						
6 mo	0.503	0.679	−0.177 (−0.194 to −0.160)	62.0	83.9	−21.9 (−24.8 to −19.0)
12 mo	0.530	0.687	−0.157 (−0.176 to −0.138)	70.4	83.9	−13.5 (−16.6 to −10.4)
18 mo	0.541	0.693	−0.152 (−0.167 to −0.136)	73.0	83.6	−10.6 (−12.9 to −8.3)

DC = drug conservation; VS = viral suppression.
* $P < 0.001$ for differences between treatment groups at all time points.

0.350×10^9 cells/L for 31% of the follow-up; after study modification, this percentage decreased to 23%. During both periods, viral suppression participants had CD4$^+$ cell counts less than 0.350×10^9 cells/L for less than 10% of the follow-up. Also, before study modification, participants in the drug conservation group had HIV RNA levels greater than 400 copies/mL for 71% of the follow-up; this decreased to 40% after study modification. For participants in the viral suppression group, this percentage also decreased, from 28% before to 17% after study modification.

Primary End Point and Major Secondary End Points

The rate of first occurrence of opportunistic disease or death decreased by 38% in the drug conservation group after study modification (from 3.4 to 2.1 events per 100 person-years), whereas the rates in the viral suppression group were similar for the 2 periods (1.4 events per 100 person-years) (**Table 3**). The HR for the study's primary outcome decreased from 2.5 (CI, 1.8 to 3.5; $P < 0.001$) before to 1.4 (CI, 1.0 to 2.0; $P = 0.039$) after study modification ($P = 0.033$ for difference) (**Table 3**). These estimates were not substantively altered in an analysis stratified by site (data not shown). Kaplan–Meier curves for the 2 time periods (through the first 18 months after randomization censored at the date of study modification [**Figure 3**, *top*] and through 18 months after study modification [**Figure 3**, *bottom*]) illustrate a decrease in the excess risk in the drug conservation group after study modification. The treatment HR for opportunistic disease or death decreased in the period after study modification, but the trend was not statistically significant ($P = 0.29$) (**Figure 3**, *bottom*).

The decrease in the rate of opportunistic disease or death in the drug conservation group, compared with the rate before study modification, was primarily due to the substantial decrease in the rate of opportunistic disease (2.1 events per 100 person-years before vs. 1.0 event per 100 person-years after) (**Table 3**). The treatment HR for opportunistic disease (fatal or nonfatal) decreased from 3.3 (CI, 2.1 to 5.2; $P < 0.001$) to 1.7 (CI, 1.0 to 2.9; $P = 0.039$) after study modification ($P = 0.100$ for difference). The **Appendix Table** (available at www.annals.org) provides the rates of specific opportunistic diseases experienced by each treatment group before and after study modification.

The treatment HR for all-cause mortality decreased from 1.8 (CI, 1.2 to 2.9; $P = 0.007$) to 1.4 (CI, 0.9 to 2.2; $P = 0.102$) after study modification ($P = 0.44$ for difference) (**Table 3**). Only 7 of the 82 deaths that occurred after study modification were attributed to opportunistic disease, and all 7 occurred among participants in the drug conservation group. The end point review committee classified 9 deaths in the drug conservation group and 11 deaths in the viral suppression group as "unknown cause." Of these deaths with unknown cause, 5 in each group were unwitnessed. For the drug conservation group, the most frequent causes of death were cardiovascular disease ($n = 9$) and opportunistic disease ($n = 7$); for the viral suppression group, the most frequent cause was malignant conditions that were not considered opportunistic ($n = 8$).

Among surviving participants at study modification, 108 in the drug conservation group and 49 in the viral suppression group had experienced an opportunistic disease or a major cardiovascular, renal, or hepatic disease event during the initial follow-up. Participants in both groups with such events were at increased risk for death during the 18 months after study modification. The HR for all-cause mortality for those who experienced at least 1 of these events versus those who did not was 5.8 (CI, 3.2 to 10.7) for both treatment groups combined. With adjustment for the occurrence of an opportunistic disease or a cardiovascular, renal, or hepatic event before study modification, the treatment HR for all-cause mortality after study modification decreased from 1.4 to 1.3 (CI, 0.8 to 2.1).

The rate of cardiovascular, renal, or hepatic disease decreased by 39% for participants in the drug conservation group. The treatment HR for major cardiovascular, renal, or hepatic disease decreased from 1.7 (CI, 1.1 to 2.5; $P = 0.009$) to 1.2 (CI, 0.7 to 1.8; $P = 0.49$) ($P = 0.23$ for difference) (**Table 3**). Findings for the outcomes in **Table 3** were similar for the large subgroup of patients who received antiretroviral therapy at entry (data not shown).

Rate of Primary End Point, by Latest CD4$^+$ Cell Count and HIV RNA Level

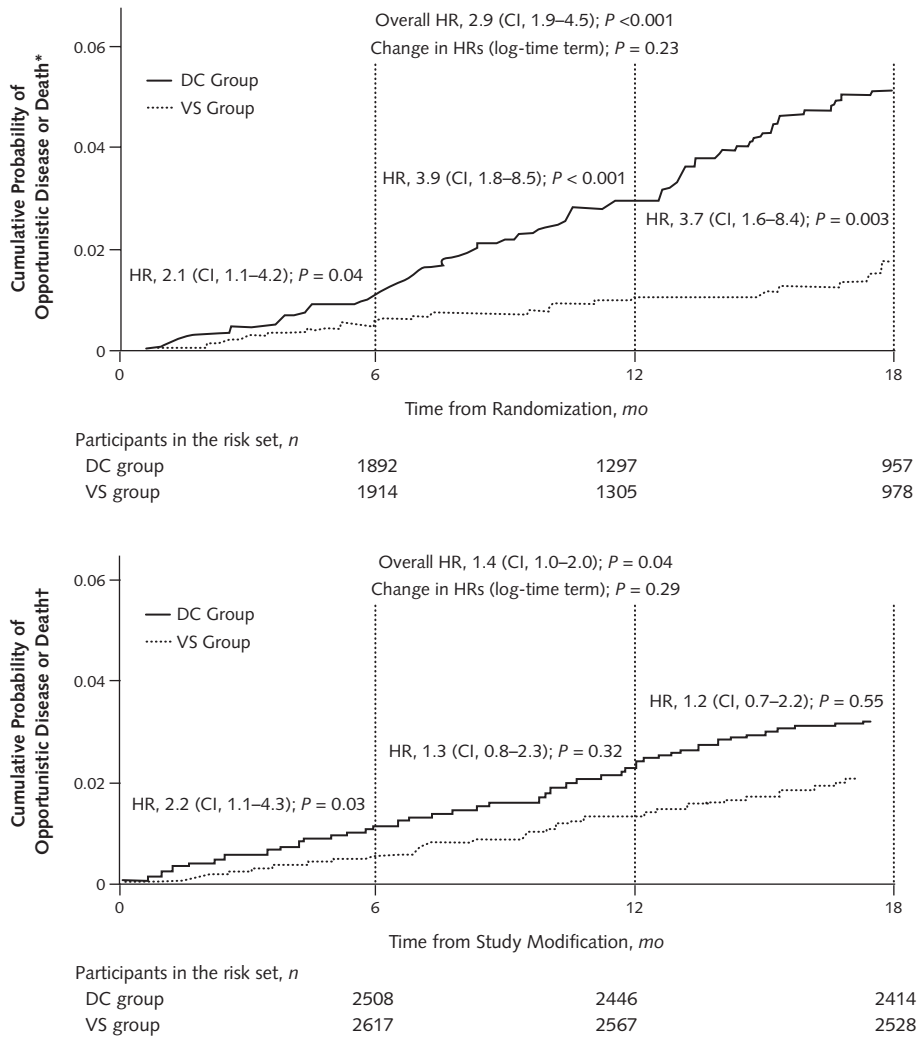
In both treatment groups, rates of opportunistic disease or death were less for patients with higher levels of latest CD4$^+$ cell count and for those with an HIV RNA level of 400 copies/mL or less (**Figure 4**). In an analysis pooling the 2 treatment groups, a 100-cell lower latest CD4$^+$ cell count was associated with a 23% (CI, 12% to 35%) higher risk for opportunistic disease or death. An HIV RNA level greater than 400 compared with 400 copies/mL or less was associated with a 92% (CI, 32% to 177%) higher risk for opportunistic disease or death. When the rates of opportunistic disease or death were considered along with the amount of time in each stratum, drug conservation participants spent less time than viral suppression participants in CD4$^+$ cell count and HIV RNA strata associated with lower risk for opportunistic disease or death. For example, the percentage of follow-up time after study modification in the lowest risk stratum for opportunistic disease or death (CD4$^+$ cell count $\geq 0.500 \times 10^9$ cells/L and HIV RNA levels $\leq$400 copies/mL) (**Figure 4**) was 29% for drug conservation participants and 66% for viral suppression participants. We previously reported that adjustment for differences in latest levels of CD4$^+$ cell count and HIV RNA levels between the drug conservation and viral suppression groups explained a large fraction of the excess risk for opportunistic disease or death in the period before study modification (1, 5). Similar analyses were conducted for the period after study modification. The treatment HR for opportunistic disease or death decreased from 1.4 (CI, 1.0 to 2.0) to 0.9 (CI, 0.6 to 1.3) after adjustment for both latest CD4$^+$ cell count and HIV RNA level.

Table 3. **Occurrence of the Primary End Point and Major Secondary End Points, before and after Study Modification**

End Point	DC Group (n = 2720)			VS Group (n = 2752)			HR (DC vs. VS) (95% CI)	P Value*	P Value for Interaction†
	Participants, n	Participants with Events, n	Event Rate Per 100 PY	Participants, n	Participants with Events, n	Event Rate Per 100 PY			
Primary end point									**0.033**
Premodification	2720	122	3.4	2752	50	1.4	2.5 (1.8–3.5)	<0.001	
Postmodification	2555	76	2.1	2656	55	1.4	1.4 (1.0–2.0)	0.039	
Death from any cause									**0.44**
Premodification	2720	55	1.5	2752	30	0.8	1.8 (1.2–2.9)	0.007	
Postmodification	2620	48	1.3	2675	34	0.9	1.4 (0.9–2.2)	0.102	
Opportunistic disease‡									**0.100**
Premodification	2720	76	2.1	2752	24	0.7	3.3 (2.1–5.2)	<0.001	
Postmodification	2555	38	1.0	2656	23	0.6	1.7 (1.0–2.9)	0.039	
Major cardiovascular, renal, or hepatic disease‡									**0.23**
Premodification	2720	65	1.8	2752	39	1.1	1.7 (1.1–2.5)	0.009	
Postmodification	2574	41	1.1	2645	36	0.9	1.2 (0.7–1.8)	0.49	
Cardiovascular disease‡									**0.32**
Premodification	2720	48	1.3	2752	31	0.8	1.6 (1.0–2.5)	0.051	
Postmodification	2582	35	0.9	2650	32	0.8	1.1 (0.7–1.8)	0.64	
Renal disease‡									**0.014**
Premodification	2720	9	0.2	2752	2	0.1	4.5 (1.0–20.9)	0.054	
Postmodification	2616	1	0.0	2674	6	0.2	0.2 (0.0–1.4)	0.101	
Liver disease‡									**0.175**
Premodification	2720	10	0.3	2752	7	0.2	1.4 (0.6–3.8)	0.46	
Postmodification	2615	7	0.2	2670	1	0.0	7.2 (0.9–58.2)	0.066	

DC = drug conservation; HR = hazard ratio; PY = person-years; VS = viral suppression.
* Tests whether the hazard ratio (DC/VS) = 1, by using separate Cox proportional hazard regression models for each period. Participants who experienced the event of interest before protocol modification were excluded from analyses for the period after study modification.
† For the interaction between period and treatment group in Cox regression; compares the hazard ratios (DC/VS) in the periods before and after study modification.
‡ Fatal or nonfatal.

Figure 3. **Kaplan–Meier curves for the cumulative probability of opportunistic disease or death from any cause before (*top*) and after (*bottom*) study modification.**



Estimated cumulative probabilities of the primary end point for the first 18 months after randomization, censored at study modification (*top*). Cumulative probabilities from study modification to study closure 18 months later; participants who experienced a primary event before study modification were excluded (*bottom*). DC = drug conservation; HR = hazard ratio; VS = viral suppression.

* Censored at the date of study modification.

† After study modification.

Discussion

As a consequence of the recommendation to initiate antiretroviral therapy for treatment-experienced participants in the drug conservation group, excess risk for opportunistic disease or death statistically significantly decreased during the 18 months after study modification compared with the period before study modification. Treatment HRs for other major outcomes also decreased. However, residual excess risk remained at study closure. We attribute the residual excess risk for opportunistic disease or death to lower $CD4^+$ cell counts and higher HIV RNA levels for drug conservation participants compared with viral suppression participants during the post–study modification period.

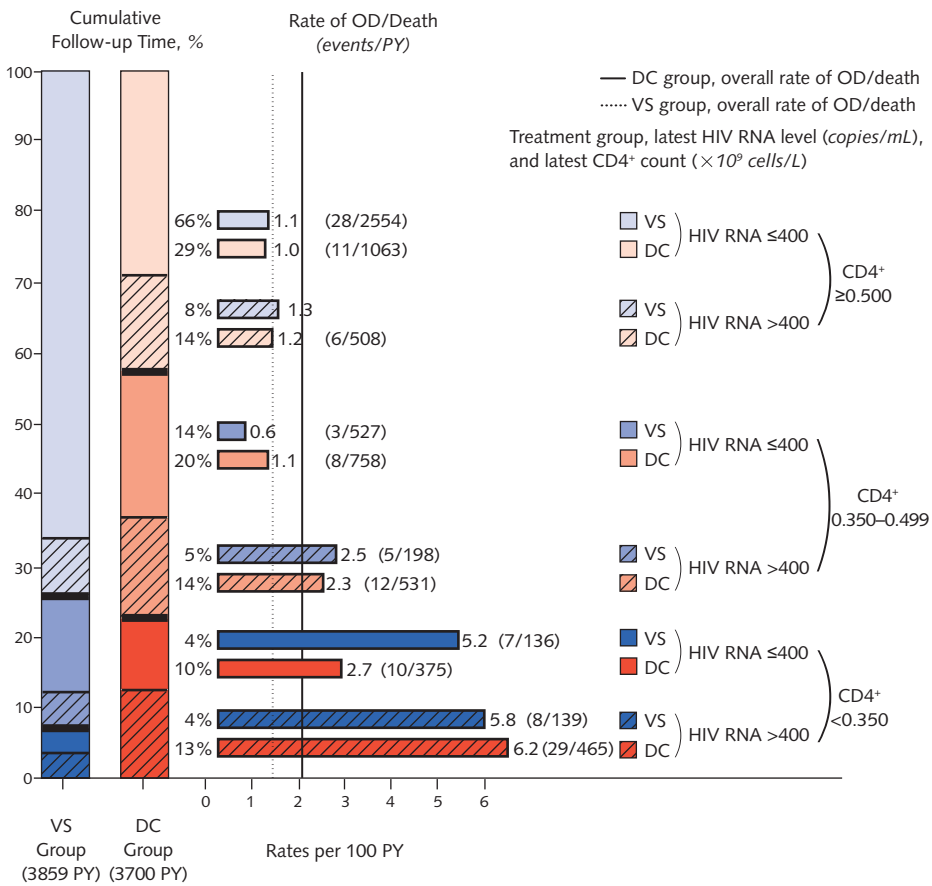
In the post–study modification period, the percentage of follow-up time spent with $CD4^+$ cell counts less than 0.350×10^9 cells/L remained greater for the drug conservation group than the viral suppression group (23% vs. 7%). Similarly, more follow-up time was spent by drug conservation than viral suppression participants with an HIV RNA level greater than 400 copies/mL (40% vs. 17%). Previous trial data before study modification and data from other studies indicate that these differences would be expected to result in a continued higher risk for opportunistic disease or death in the drug conservation group than in the viral suppression group (5, 7–11). Consistent with these observations, adjustment for the latest $CD4^+$ cell counts and HIV RNA levels explains much of

the difference in opportunistic disease or death between the 2 treatment groups. Higher rates of nonopportunistic disease mortality would also be predicted by these $CD4^+$ cell count and HIV RNA level differences (12, 13). The decreasing treatment HR for opportunistic disease or death (**Figure 3**, *bottom*) after study modification is also consistent with the decreasing differences in $CD4^+$ cell count and percentage with HIV RNA levels of 400 copies/mL or less during the 18 months after study modification (**Figure 2**, *A* and *B*; **Table 2**).

We identified 2 reasons for the persistence of lower $CD4^+$ cell counts and higher HIV RNA levels for drug conservation compared with viral suppression participants during the post–study modification period: Not all participants who ever received antiretroviral therapy reinitiated it, and for those who reinitiated therapy, the return to baseline, preinterruption $CD4^+$ levels was incomplete during the 18-month follow-up. Drug conservation participants who did not reinitiate antiretroviral therapy after the study modification had higher nadir, baseline, and study modification $CD4^+$ cell counts (0.400, 0.816, and 0.623×10^9 cells/L, respectively) than did those who reinitiated after study modification (0.262, 0.668, and 0.458×10^9 cells/L, respectively). Perhaps participants and clinicians may have felt that they were "safe" on the basis of their previous and current counts.

Although the percentage of drug conservation participants who achieved HIV RNA levels of 400 copies/mL or less after reinitiating antiretroviral therapy rapidly increased, $CD4^+$ cell counts increased more gradually. Other interruption studies have reported $CD4^+$ cell counts that do not rapidly return to preinterruption levels (14–16). The rate of $CD4^+$ cell count recovery seen over 6 to 18 months (**Figure 2**, *D*) followed a characteristic 2-phase increase within the numeric range reported for HIV-infected patients on initiation of treatment in large antiretroviral therapy–naive cohorts (17–19) and among viral suppres-

Figure 4. **Percentages of follow-up time spent in categories by latest $CD4^+$ cell counts and latest HIV RNA levels and rates of opportunistic disease or death during this time.**



Stacked vertical bars on the left show the percentage of follow-up time spent in each of the 6 categories, by latest $CD4^+$ counts <0.350, 0.350 to 0.499, and ≥0.500 × 10^9 cells/L and latest HIV RNA levels >400 and ≤400 copies/mL for participants in the drug conservation (*DC*) group (*solid line*) and viral suppression (*VS*) group (*dotted line*). Percentage of follow-up time appears to the right of the stacked vertical bars. Horizontal bars show the rates of opportunistic disease (*OD*) or death during follow-up spent at the latest $CD4^+$ and HIV RNA levels in the DC and VS groups. Numbers to the right of the bars are the rates per 100 person-years (*PY*) (number of events, number of PY).

sion participants who initiated antiretroviral therapy after randomization (20). This pattern of $CD4^+$ cell count recovery indicates that more than 18 months, the maximum follow-up time after study modification, would have been required for the average $CD4^+$ cell count to return to preinterruption levels (18, 21).

Before study modification, more drug conservation participants than viral suppression participants experienced opportunistic disease or cardiovascular, renal, or hepatic events. Risk for death after study modification was statistically significantly greater among participants who experienced 1 of these events than among those who did not. These observations may help explain the mortality rate differences between the treatment groups during the 18 months after study modification.

Other factors may have contributed to the residual excess risk in the drug conservation compared with the viral suppression group. We recently reported that antiretroviral therapy interruption resulted in increases in interleukin-6 and D-dimer levels, and these biomarkers were associated with increased risk for all-cause mortality (22). It seems that antiretroviral therapy interruption induced activation of tissue factor pathways, thrombosis, and fibrinolysis, and these changes may have long-term effects.

Our findings emphasize the importance of continued follow-up of participants in trials after identifying deleterious effects of 1 of the interventions and making protocol changes. However, a limitation of our study is that follow-up was too short to assess the full effect of switching from episodic to continuous antiretroviral therapy. As a consequence, although we have good power for confirming a decrease in risk for opportunistic disease or death, power was lower for other outcomes (for example, death and major cardiovascular, renal, or liver diseases), for which fewer events occurred and HRs were not as large before the study modification.

In conclusion, the recommendation to reinitiate antiretroviral therapy resulted in a 38% decrease in the rate of opportunistic disease or death in the drug conservation group. Compared with the viral suppression group, an ongoing though diminished excess risk for opportunistic disease or death remained during the 18 months after this recommendation. Several factors contribute to this excess risk. It seems that our follow-up was too short to observe full reversal of risk, even among those who initiated antiretroviral therapy, as recommended. These findings reinforce the recommendation to avoid use of episodic antiretroviral therapy guided by $CD4^+$ cell counts used in the trial.

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United States (2989 participants): D.I. Abrams, E.A. Acosta, S. Adams, A Adamski, L Andrews, D. Antoniskis, D.R. Aragon, R. Arduino, R. Artz, J. Bailowitz, B.J. Barnett, C. Baroni, M. Barron, J.D. Baxter, D. Beers, M. Beilke, D. Bemenderfer, A. Bernard, C.L. Besch, M.T. Bessesen, J.T. Bethel, S. Blue, J.D. Blum, S. Boarden, R.K. Bolan, J.B. Borgman, I. Brar, B.K. Braxton, U.F. Bredeek, R. Brennan, D.E. Britt, J. Brockelman, S. Brown, V. Bruzzese, D. Bulgin-Coleman, D.E. Bullock, V. Cafaro, B. Campbell, S. Caras, J. Carroll, K.K. Casey, F. Chiang, G. Childress, R.B. Cindrich, C. Clark, M. Climo, C. Cohen, J. Coley, D.V. Condoluci, R. Contreras, J. Corser, J. Cozzolino, L.R. Crane, L. Daley, D. Dandridge, V. D'Antuono, J.G. Darcourt Rizo Patron, J.A. DeHovitz, E. DeJesus, J. DesJardin, M. Diaz-Linares, C. Dietrich, P. Dodson, E. Dolce, K. Elliott, D. Erickson, M. Estes, L.L. Faber, J. Falbo, M.J. Farrough, C.F. Farthing, P. Ferrell-Gonzalez, H. Flynn, C. Frank, M. Frank, K.F. Freeman, N. French, G. Friedland, N. Fujita, L. Gahagan, K. Genther, I. Gilson, M.B. Goetz, E. Goodwin, F. Graziano, C.K. Guity, P. Gulick, E.R. Gunderson, C.M. Hale, K. Hannah, H. Henderson, K. Hennessey, W.K. Henry, D.T. Higgins, S.L. Hodder, H.W. Horowitz, M. Howe-Pittman, J. Hubbard, R. Hudson, H. Hunter, C. Hutelmyer, M.T. Insignares, L. Jackson, L. Jenny, M. John, D.L. Johnson, G. Johnson, J. Johnson, L. Johnson, J. Kaatz, J. Kaczmarski, S. Kagan, C. Kantor, T. Kempner, K. Kieckhaus, N. Kimmel, B.M. Klaus, N. Klimas, J.R. Koeppe, J. Koirala, J. Kopka, J.R. Kostman, M.J. Kozal, A. Kumar, A. Labriola, H. Lampiris, C. Lamprecht, K.M. Lattanzi, J. Lee, J. Leggett, C. Long, A. Loquere, K. Loveless, C.J. Lucasti, R. Luskin-Hawk, M. MacVeigh, L.H. Makohon, S. Mannheimer,

N.P. Markowitz, C. Marks, N. Martinez, C. Martorell, E. McFeaters, B. McGee, D.M. McIntyre, J. McKee, E. McManus, L.G. Melecio, D. Melton, S. Mercado, E. Merrifield, J.A. Mieras, M. Mogyoros, F.M. Moran, K. Murphy, D. Mushatt, S. Mutic, I. Nadeem, R. Nahass, D. Nixon, S. O'Brien, A. Ognjan, M. O'Hearn, K. O'Keefe, P.C. Okhuysen, E. Oldfield, D. Olson, R. Orenstein, R. Ortiz, J. Osterberger, W. Owen, F. Parpart, V. Pastore-Lange, S. Paul, A. Pavlatos, D.D. Pearce, R. Pelz, G. Perez, S. Peterson, G. Pierone Jr, D. Pitrak, S.L. Powers, H.C. Pujet, J.W. Raaum, J. Ravishankar, J. Reeder, N. Regevik, N.A. Reilly, C. Reyelt, J. Riddell IV, D. Rimland, M.L. Robinson, A.E. Rodriguez, M.C. Rodriguez-Barradas, V. Rodriguez Derouen, R. Roland, C. Rosmarin, W.L. Rossen, J.R. Rouff, J.H. Sampson, M. Sands, C. Savini, S. Schrader, M.M. Schulte, C. Scott, R. Scott, H. Seedhom, M. Sension, A. Sheble-Hall, A. Sheridan, J. Shuter, L.N. Slater, R. Slotten, D. Slowinski, M. Smith, S. Snap, C. Somboonwit, D.M. States, M. Stewart, G. Stringer, J. Sullivan, K.K. Summers, K. Swanson, I.B. Sweeton, S. Szabo, E.M. Tedaldi, E.E. Telzak, Z. Temesgen, D. Thomas, M.A. Thompson, S. Thompson, C. Ting Hong Bong, C. Tobin, J. Uy, A. Vaccaro, L.M. Vasco, I. Vecino, G.K. Verlinghieri, F. Visnegarwala, B.H. Wade, V. Watson, S.E. Weis, J.A. Weise, S. Weissman, A.M. Wilkin, L. Williams, J.H. Witter, L. Wojtusic, T.J. Wright, V. Yeh, B. Young, C. Zeana, and J. Zeh.

Uruguay (3 participants): E. Savio and M. Vacarezza.

Appendix Table. **Participants with Specific Opportunistic Disease Events and Rate per 100 Person-Years, before and after Study Modification, by Treatment Group**

Event*	Premodification				Postmodification			
	DC Group Participants with Events, *n*	Event Rate (per 100 PY)	VS Group Participants with Events, *n*	Event Rate (per 100 PY)	DC Group Participants with Events, *n*	Event Rate (per 100 PY)	VS Group Participants with Events, *n*	Event Rate (per 100 PY)
Invasive aspergillosis	0	0.00	1	0.03	0	0.00	0	0.00
Esophageal candidiasis	26	0.70	7	0.19	13	0.34	7	0.18
Bronchi, trachea, or lung candidiasis	2	0.05	0	0.00	0	0.00	0	0.00
Invasive cervical cancer	0	0.00	0	0.00	1	0.03	0	0.03
Cytomegalovirus disease	1	0.03	0	0.00	0	0.00	0	0.00
Chronic intestinal cryptosporidiosis	0	0.00	0	0.00	3	0.08	1	0.03
Extrapulmonary cryptococcosis	1	0.03	0	0.00	1	0.03	0	0.00
HIV-related, stage 2 or higher encephalopathy	1	0.03	0	0.00	1	0.03	0	0.00
Herpes simplex	6	0.16	5	0.13	1	0.03	3	0.08
Herpes zoster	5	0.13	1	0.03	2	0.05	1	0.03
Kaposi sarcoma	7	0.19	2	0.05	5	0.13	2	0.05
Lymphoma	4	0.11	1	0.03	5	0.13	6	0.15
Pulmonary or extrapulmonary tuberculosis	3	0.08	3	0.08	2	0.05	1	0.03
Extrapulmonary *Mycobacterium avium* complex	1	0.03	0	0.00	0	0.00	0	0.00
Pneumocystis (carinii) jiroveci pneumonia	8	0.21	2	0.05	3	0.08	2	0.05
Bacterial pneumonia	8	0.22	3	0.08	2	0.05	1	0.03
Brain toxoplasmosis	1	0.03	0	0.00	0	0.00	0	0.00
The wasting syndrome	4	0.11	0	0.00	0	0.00	0	0.00

DC = drug conservation; PY = person-years; VS = viral suppression.
* Participants could have experienced more than 1 event type; numbers do not sum to the number with the primary end point.