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CD4+ Count–Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group*

ABSTRACT

BACKGROUND

Despite declines in morbidity and mortality with the use of combination antiretroviral therapy, its effectiveness is limited by adverse events, problems with adherence, and resistance of the human immunodeficiency virus (HIV).

METHODS

We randomly assigned persons infected with HIV who had a CD4+ cell count of more than 350 per cubic millimeter to the continuous use of antiretroviral therapy (the viral suppression group) or the episodic use of antiretroviral therapy (the drug conservation group). Episodic use involved the deferral of therapy until the CD4+ count decreased to less than 250 per cubic millimeter and then the use of therapy until the CD4+ count increased to more than 350 per cubic millimeter. The primary end point was the development of an opportunistic disease or death from any cause. An important secondary end point was major cardiovascular, renal, or hepatic disease.

RESULTS

A total of 5472 participants (2720 assigned to drug conservation and 2752 to viral suppression) were followed for an average of 16 months before the protocol was modified for the drug conservation group. At baseline, the median and nadir CD4+ counts were 597 per cubic millimeter and 250 per cubic millimeter, respectively, and 71.7% of participants had plasma HIV RNA levels of 400 copies or less per milliliter. Opportunistic disease or death from any cause occurred in 120 participants (3.3 events per 100 person-years) in the drug conservation group and 47 participants (1.3 per 100 person-years) in the viral suppression group (hazard ratio for the drug conservation group vs. the viral suppression group, 2.6; 95% confidence interval [CI], 1.9 to 3.7; P<0.001). Hazard ratios for death from any cause and for major cardiovascular, renal, and hepatic disease were 1.8 (95% CI, 1.2 to 2.9; P=0.007) and 1.7 (95% CI, 1.1 to 2.5; P=0.009), respectively. Adjustment for the latest CD4+ count and HIV RNA level (as time-updated covariates) reduced the hazard ratio for the primary end point from 2.6 to 1.5 (95% CI, 1.0 to 2.1).

CONCLUSIONS

Episodic antiretroviral therapy guided by the CD4+ count, as used in our study, significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy, largely as a consequence of lowering the CD4+ cell count and increasing the viral load. Episodic antiretroviral therapy does not reduce the risk of adverse events that have been associated with antiretroviral therapy. (ClinicalTrials.gov number, NCT00027352.)

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With the advent of potent combination antiretroviral therapy came the hope that such therapy might lead to the eradication of infection with the human immunodeficiency virus (HIV).[1] It was soon recognized, however, that this goal was unlikely to be achieved owing to the existence of latent reservoirs; people infected with HIV would need to receive antiretroviral therapy for many years, if not for life.[2,3] Potent antiretroviral therapy is associated with substantial benefits with regard to morbidity and mortality.[4-6] However, the therapy is also associated with both short-term and long-term adverse events.[7,8] Major metabolic and cardiovascular complications have been a particular concern.[9,10] In addition, HIV can become resistant to available antiretroviral therapy, particularly if adherence is poor, which can lead to cross-resistance within a class of drugs and, ultimately, to multidrug resistance.[11] Prolonged use of antiretroviral therapy is also expensive.[12]

The inherent risks and problems associated with lifelong antiretroviral therapy have led to the study of treatment-sparing strategies that might provide the benefits of antiretroviral therapy while minimizing the risk of adverse events and other risks associated with long-term use. We conducted the Strategies for Management of Antiretroviral Therapy (SMART) trial in order to compare a treatment strategy of episodic use of antiretroviral therapy according to the CD4+ count with the current practice of continuous antiretroviral therapy.

METHODS

The SMART study was initiated by the Terry Beirn Community Programs for Clinical Research on the Acquired Immunodeficiency Syndrome (AIDS) and implemented in collaboration with regional coordinating centers in Copenhagen (the Copenhagen HIV Programme), London (the Clinical Trials Unit of the Medical Research Council), and Sydney (the National Centre in HIV Epidemiology and Clinical Research). Some members of the SMART writing group developed the study protocol with the sponsor, the Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID). The writing group takes full responsibility for the completeness and veracity of the data, data analyses, and this article. Drugs used in the study were purchased by patients either directly or through insurance, Social Security, or public access programs.

PARTICIPANTS

Persons infected with HIV who were older than 13 years and were not pregnant or breast-feeding were eligible for the study if their CD4+ count exceeded 350 cells per cubic millimeter and they were willing to initiate, modify, or stop antiretroviral therapy according to study guidelines. Participants were eligible whether or not they had received or were currently receiving antiretroviral therapy. The study was approved by the institutional review board at each site, and written informed consent was obtained from all participants.

STUDY DESIGN

The SMART study is a randomized trial comparing two antiretroviral treatment strategies. Investigators and participants were aware of the treatment assignments. The viral suppression strategy, which was the control strategy, was defined to be consistent with the 2003 guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents[13]: available antiretroviral regimens were to be used in an uninterrupted manner with the goal of maximal and continuous suppression of HIV replication. The experimental drug conservation strategy entailed the episodic use of antiretroviral therapy according to CD4+ count thresholds: the use of antiretroviral therapy was deferred until the CD4+ count decreased to less than 250 cells per cubic millimeter, at which time antiretroviral therapy was to be initiated (or reinitiated) and continued until the CD4+ count increased to more than 350 cells per cubic millimeter. The protocol also permitted antiretroviral therapy to be initiated (or reinitiated) if symptoms of disease from HIV infection (e.g., oral thrush) developed or the percentage of CD4+ lymphocytes (CD4+ percentage) was less than 15%. On confirmation that the CD4+ count was more than 350 cells per cubic millimeter, antiretroviral therapy was to be stopped and then resumed when the CD4+ count was less than 250 cells per cubic millimeter. During periods of antiretroviral therapy, the goal was to achieve maximal viral suppression. The CD4+ count thresholds for stopping and starting antiretroviral therapy were chosen on the basis of reported associations between CD4+ counts and the risks of opportunistic diseases and death.[13-16]

The primary end point was new or recurrent opportunistic disease or death from any cause. Qualifying clinical events included those in the revised case definition for AIDS of the Centers for

Disease Control and Prevention,[17] as well as additional conditions related to immunodeficiency (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Important secondary end points included death from any cause; serious opportunistic disease[18]; major cardiovascular, renal, or hepatic disease (see the Supplementary Appendix); and grade 4 adverse events (not including opportunistic disease) or death from any cause. Grade 4 adverse events were defined as potentially life-threatening symptomatic events requiring medical intervention, according to the toxicity table of the Division of AIDS of the NIAID. Data on lower-grade toxic effects were not collected.

Using preestablished criteria, an end-point review committee that was unaware of the treatment assignments reviewed the events classified as opportunistic disease, death from any cause, or major cardiovascular, hepatic, or renal disease. The end-point review committee classified the underlying cause of death using the Coding of Death in HIV (CoDe) project system.[19] Opportunistic disease and major cardiovascular, renal, or hepatic diseases classified as confirmed or probable by the end-point review committee were considered end points, as were all deaths, irrespective of the cause.

We calculated that 6000 patients would need to be enrolled for the study to have a statistical power of 80% to detect a 17% relative reduction in the rate of opportunistic disease or death from any cause in the drug conservation group as compared with the viral suppression group, with a two-sided alpha level of 0.05. Follow-up was to continue until 910 primary end points had occurred (estimated to be at least 6 years for each participant), assuming an event rate in the viral suppression group of 1.3% in each of the first 2 years and 2.6% per year thereafter.[20] Randomization was stratified according to clinical site with the use of permuted blocks of random sizes.

DATA COLLECTION AND FOLLOW-UP

Before randomization, participants' antiretroviral therapy history and medical history were obtained, as were the nadir CD4+ count; the highest recorded plasma HIV RNA level; the CD4+ count, CD4+ percentage, and HIV RNA level at baseline; and the three most recent CD4+ counts, CD4+ percentages, and HIV RNA levels before baseline. Follow-up visits were scheduled at 1 month and 2 months, every 2 months thereafter for the first year, and every 4 months in the second and subsequent years. At each visit, a history was taken and an examination conducted, and the CD4+ count and HIV RNA level were measured. More frequent assessments could be carried out if clinical care was required. At baseline and at each annual visit, a 12-lead electrocardiogram was obtained; the data were electronically transmitted to a reading center for detection of any changes indicative of a silent myocardial infarction.[21-23]

INTERIM MONITORING OF SAFETY AND EFFICACY

An independent data and safety monitoring board reviewed interim analyses from the SMART study at least annually. According to protocol guidelines, the board was to consider early termination of the study or modification of the protocol if findings concerning the primary end point (opportunistic disease or death from any cause) and the secondary end point of major cardiovascular, renal, or hepatic disease were consistent — both favoring the same treatment group — and there was clear and substantial evidence of benefit or harm. An O'Brien–Fleming boundary and the Lan–DeMets spending function were used to control the type I error with regard to the primary end point.[24,25]

On January 10, 2006, at its sixth meeting, the board recommended stopping enrollment in the SMART trial because of a safety risk in the drug conservation group and because it appeared to be very unlikely that superiority of the drug conservation treatment would be shown. On January 11, 2006, investigators and participants were notified of these findings, enrollment was stopped, and participants in the drug conservation group were advised to restart antiretroviral therapy. All participants continued in follow-up. This article describes findings through the closure of enrollment.

STATISTICAL ANALYSIS

The drug conservation and viral suppression groups were compared according to the intention-to-treat principle. Time-to-event methods (Kaplan–Meier survival curves and Cox proportional-hazards models) were used to compare the drug conservation group and the viral suppression group with respect to event rates for opportunistic disease or death from any cause; death from any cause; serious and nonserious opportunistic disease; major cardiovascular, renal, or hepatic disease; and grade 4 events.[26] Follow-up data were censored

Table 1. Baseline Characteristics of Study Participants.*

Characteristic	Drug Conservation Group (N=2720)	Viral Suppression Group (N=2752)	All (N=5472)
Age (yr)			
Median	43	44	43
Interquartile range			38–50
Female sex (%)	26.3	28.0	27.2
Race (%)†			
Black	28.5	29.8	29.1
White	56.4	54.8	55.6
Other	15.1	15.4	15.3
Mode of infection with HIV (%)‡			
Sexual contact			
With person of same sex	51.4	48.5	49.9
With person of opposite sex	44.4	45.6	45.0
Injection-drug use	9.8	9.5	9.7
Other or unknown	7.5	8.7	8.1
CD4+ count (cells/mm^3)			
Median	597	597	597
Interquartile range			466–790
CD4+ nadir (cells/mm^3)			
Median	250	250	250
Interquartile range			155–359
HIV RNA ≤400 copies/ml (%)	71.8	71.5	71.7
Prior recorded highest HIV RNA level (log copies/ml)			
Median	4.8	4.8	4.8
Interquartile range			4.2–5.3
Cardiovascular risk factor			
Current smoker (%)	41.3	39.6	40.5
Diabetes (%)	7.0	7.1	7.0
Prior cardiovascular disease (%)	6.7	6.1	6.4
Blood pressure–lowering drugs (%)	19.2	18.1	18.6
Lipid-lowering drugs (%)	15.7	15.6	15.6
Total cholesterol (mg/dl)			
Median	191	189	190
Interquartile range			163–220
High-density lipoprotein cholesterol (mg/dl)			
Median	40	41	40
Interquartile range			33–50

either when participants were lost to follow-up before January 11, 2006, or on that date.

The hazard ratios for the comparison of the drug conservation group with the viral suppression group were estimated from Cox models with a single binary treatment group indicator. We tested the proportional-hazards assumption by including an interaction term between the treat-

Table 1. (Continued.)

Characteristic	Drug Conservation Group (N = 2720)	Viral Suppression Group (N = 2752)	All (N = 5472)
History of ART (%)			
Never received ART	4.4	4.8	4.6
Previous PI use	69.5	67.7	68.6
Previous NNRTI use	64.7	63.9	64.3
Use of ART at baseline	84.3	83.6	83.9
Time since first ART (yr)			
Median	6	6	6
Interquartile range			3–8
Type of ART at baseline (% of patients receiving ART)			
PI	45.1	45.2	45.2
NNRTI	50.0	47.9	49.0
PI and NNRTI	6.3	5.3	5.8
Most common drug combinations			
Zidovudine, lamivudine, efavirenz	10.3	9.9	10.0
Zidovudine, lamivudine, nevirapine	7.4	7.7	7.5
Zidovudine, lamivudine, abacavir	6.5	7.1	6.8
Zidovudine, lamivudine, nelfinavir	4.6	3.9	4.3
Prior AIDS-related illness (%)	24.7	23.1	23.9
Hepatitis B (%)	2.4	2.2	2.3
Hepatitis C (%)	15.3	14.4	14.8

* None of the characteristics differed significantly between treatment groups. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. Percentages may not total 100 because of rounding. ART denotes antiretroviral therapy, PI protease inhibitor, and NNRTI nonnucleoside reverse-transcriptase inhibitor.
† Race was self-reported.
‡ Mode of infection was self-reported. Percentages do not total 100 because some participants reported more than one mode.

ment indicator and the log-transformed follow-up time.[26]

The primary end point was summarized for selected subgroups that were predefined according to baseline characteristics. The heterogeneity of hazard ratio estimates for subgroups was assessed by including an interaction term between treatment and subgroup in expanded Cox models.

Cox proportional-hazards models were used to assess the effects of CD4+ counts and HIV RNA levels as time-dependent covariates during follow-up on the hazard ratios for opportunistic disease or death from any cause. Statistical analyses were performed with the use of SAS software, version 8.2. All reported P values are two-sided and have not been adjusted for multiple examinations of the data.

RESULTS

BASELINE CHARACTERISTICS

Between January 8, 2002, and January 11, 2006, 5472 participants were randomly assigned to treatment groups (2720 to the drug conservation group and 2752 to the viral suppression group). Participants were enrolled at 318 sites in 33 countries. Table 1 summarizes key baseline characteristics. The treatment groups were well balanced at entry.

FOLLOW-UP

Total follow-up time was approximately 3700 person-years in each group, with a mean follow-up time of 16 months. Approximately 26% of participants were followed for more than 2 years. Participants attended 96.5% of follow-up visits in

the drug conservation group and 94.8% of follow-up visits in the viral suppression group. On January 11, 2006, the status with regard to the primary end point was unknown for 32 participants (1.2%) in the drug conservation group and 41 participants (1.5%) in the viral suppression group (Fig. I in the Supplementary Appendix).

USE OF ANTIRETROVIRAL THERAPY AND CHANGES IN CD4+ AND HIV RNA LEVELS

After randomization, the median duration of the first period of interruption of antiretroviral therapy for participants in the drug conservation group was 16.8 months (interquartile range, 5.7 to 42.3) (Fig. IIA in the Supplementary Appendix shows the percentage of participants who received antiretroviral therapy through follow-up). A total of 343 participants stopped antiretroviral therapy a second time, and 62 participants stopped three or more times. The average CD4+ count decreased by 87 cells per cubic millimeter per month during the first 2 months after randomization among participants in the drug conservation group (Fig. IIB in the Supplementary Appendix); thereafter, it continued to decline but at a lower rate. On average, throughout follow-up, the CD4+ count was 206 cells per cubic millimeter lower in the drug conservation group than in the viral suppression group. HIV RNA levels also changed rapidly in the drug conservation group after randomization: within 2 months, the percentage of participants with HIV RNA levels of 400 copies per milliliter or less decreased from 71.8% to 6.0% (Fig. IIC in the Supplementary Appendix). After reinitiation of antiretroviral therapy in the drug conservation group, the median time to an HIV RNA level of 400 copies per milliliter or less was 3.1 months (Fig. IIIA in the Supplementary Appendix); the CD4+ count increased by an average of 166 cells per cubic millimeter within 8 months (Fig. IIIB in the Supplementary Appendix).

On average, participants in the drug conservation group and the viral suppression group received antiretroviral therapy during 33.4% and 93.7% of the follow-up time, respectively. Participants in both groups had CD4+ counts of 350 cells per cubic millimeter or more during the majority of the follow-up time (67.9% of the time in the drug conservation group and 92.7% of the time in the viral suppression group) (Fig. 1). Participants in the drug conservation group had CD4+ counts of less than 250 cells per cubic millimeter during 8.6% of the follow-up time, as compared with 1.8% of the time in the viral suppression group. The percentage of follow-up time during which participants had HIV RNA levels

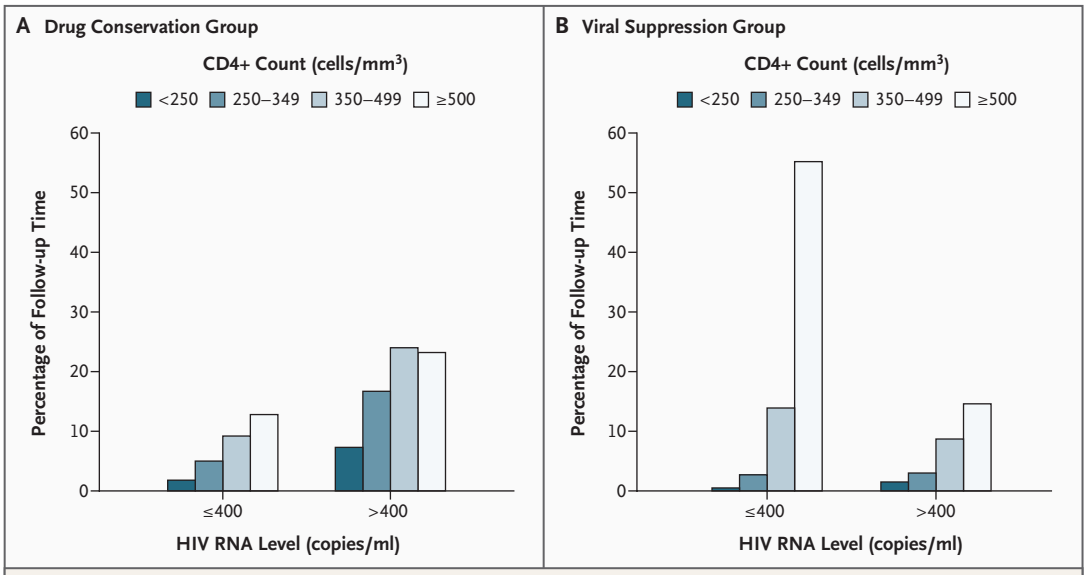


Figure 1. Percentage of Follow-up Time during Which Participants Had a Specified CD4+ Count and HIV RNA Level.
For 28.8% of the 3666 person-years of follow-up in the drug conservation group (Panel A), the HIV RNA level was 400 copies per milliliter or less. Patients received antiretroviral therapy during 33% of the follow-up time. For 72.3% of the 3701 person-years of follow-up in the viral suppression group (Panel B), the HIV RNA level was 400 copies per milliliter or less. Patients received antiretroviral therapy during 94% of the follow-up time.

of 400 copies per milliliter or less was substantially greater in the viral suppression group than in the drug conservation group (72.3% and 28.8%, respectively).

PRIMARY END POINT AND ITS COMPONENTS

There were 120 participants in the drug conservation group and 47 in the viral suppression group who had an opportunistic disease or died from any cause (Table 2). The cumulative probabilities of opportunistic disease or death from any cause after 12, 24, and 36 months were 0.030, 0.067, and 0.091 in the drug conservation group and 0.010, 0.021, and 0.042 in the viral suppression group, respectively (Fig. 2A).

The estimated hazard ratio for opportunistic disease or death from any cause was 2.6 (95% confidence interval [CI], 1.9 to 3.7; P<0.001) (Table 2 and Fig. 2A), and it did not vary significantly over the follow-up period (P=0.78 for proportional hazards). Among patients in the drug conservation group who reached the primary end point, death from any cause was the most common individual event (39.2%), followed by esophageal candidiasis (20.0%) and pneumonia from *Pneumocystis jiroveci* infection (6.7%). Among patients in the viral suppression group who reached the primary end point, the most common event was death from any cause (57.4%), followed by esophageal candidiasis (14.9%) (Table I in the Supplementary Appendix).

The estimated hazard ratio for serious opportunistic disease, a component of the primary end point, was 6.6 (95% CI, 1.5 to 29.1; P=0.01); the hazard ratio for nonserious events associated with opportunistic disease was 3.6 (95% CI, 2.1 to 6.1; P<0.001); and the hazard ratio for death from any cause was 1.8 (95% CI, 1.2 to 2.9; P=0.007) (Table 2 and Fig. 2B).

Only 8% of deaths were due to opportunistic disease. The most common underlying causes of death were cancers other than those considered to be opportunistic disease (in 11 participants in the drug conservation group and 5 participants in the viral suppression group); cardiovascular disease (7 participants and 4 participants, respectively); substance abuse (3 participants and 5 participants, respectively); accident, violence, or suicide (3 participants and 4 participants, respectively); and infection other than that considered to be

Table 2. Primary and Major Secondary End Points.*

End Point	Drug Conservation Group (N=2720)		Viral Suppression Group (N=2752)		Hazard Ratio for Drug Conservation Group vs. Viral Suppression Group (95% CI)	P Value
	No. of Participants with Event	Event Rate (per 100 Person-Yr)	No. of Participants with Event	Event Rate (per 100 Person-Yr)		
Primary end point	120	3.3	47	1.3	2.6 (1.9–3.7)	<0.001
Death from any cause	55	1.5	30	0.8	1.8 (1.2–2.9)	0.007
Opportunistic disease						
Serious	13	0.4	2	0.1	6.6 (1.5–29.1)	0.01
Nonserious	63	1.7	18	0.5	3.6 (2.1–6.1)	<0.001
Major cardiovascular, renal, or hepatic disease	65	1.8	39	1.1	1.7 (1.1–2.5)	0.009
Fatal or nonfatal cardiovascular disease	48	1.3	31	0.8	1.6 (1.0–2.5)	0.05
Fatal or nonfatal renal disease	9	0.2	2	0.1	4.5 (1.0–20.9)	0.05
Fatal or nonfatal liver disease	10	0.3	7	0.2	1.4 (0.6–3.8)	0.46
Grade 4 event	173	5.0	148	4.2	1.2 (1.0–1.5)	0.13
Grade 4 event or death from any cause	205	5.9	164	4.7	1.3 (1.0–1.6)	0.03

* Numbers of individual events of each type do not sum to the total number because some participants had more than one event. End-point definitions are listed in the Supplementary Appendix. Grade 4 events were determined on the basis of toxicity grades developed by the Division of AIDS of the NIAID. CI denotes confidence interval.

an opportunistic disease (3 participants and 1 participant, respectively). For 18 participants who died (15 in the drug conservation group and 3 in the viral suppression group), the underlying cause of death could not be determined (Table II in the Supplementary Appendix).

We examined the robustness of the primary end-point findings by considering three additional outcomes: opportunistic diseases (restricted to those that were new [nonrecurrent]) or death from any cause; fatal and nonfatal cases of opportunistic disease (excluding deaths from causes other than opportunistic disease); and all reported cases of opportunistic diseases and deaths irrespective of the classification after review by the end-point review committee. The estimated hazard ratios for these three outcomes in the drug conservation group versus the viral suppression group were 2.6 (95% CI, 1.8 to 3.7; P<0.001), 3.6 (95% CI, 2.2 to 5.9; P<0.001), and 2.5 (95% CI, 1.9 to 3.3; P<0.001), respectively.

MAJOR CARDIOVASCULAR, RENAL, AND HEPATIC DISEASE

Among the participants in the drug conservation group, 65 had at least one episode of major cardiovascular, renal, or hepatic disease, as did 39 participants in the viral suppression group (hazard ratio, 1.7; 95% CI, 1.1 to 2.5; P=0.009) (Table 2 and Fig. 2C). Estimated hazard ratios for each type of disease were all greater than 1.0, favoring the viral suppression group.

GRADE 4 EVENTS

Grade 4 adverse symptomatic events occurred in 173 participants in the drug conservation group and 148 participants in the viral suppression group (hazard ratio, 1.2; 95% CI, 1.0 to 1.5; P=0.13) (Table 2 and Fig. 2D, and Table III in the Supplementary Appendix). The hazard ratio for the composite outcome of a grade 4 event or death from any cause was 1.3 (95% CI, 1.0 to 1.6; P=0.03).

PRIMARY END POINT ACCORDING TO SUBGROUP

Estimated hazard ratios varied significantly according to race, baseline HIV RNA level, and baseline CD4+ cell count (Fig. 3). Among participants who were receiving antiretroviral therapy at baseline, for those with an HIV RNA level of 400 copies per milliliter or less at baseline, the hazard ratio for opportunistic disease or death from any cause was 4.0, whereas those with levels of more than 400 copies per milliliter had a hazard ratio of 1.2 (P<0.001). This significant difference was due to different rates of opportunistic disease or death from any cause in the viral suppression group between the subgroups with HIV RNA levels of 400 copies per milliliter or less and those with HIV RNA levels of more than 400 copies per milliliter (0.8 and 2.6 events per 100 person-years, respectively), in contrast to similar rates for those subgroups in the drug conservation group (3.2 and 3.1, respectively).

Figure 2 (facing page). Cumulative Probability of the Primary End Point (Panel A); Death from Any Cause (Panel B); Major Cardiovascular, Renal, or Hepatic Disease (Panel C); and Grade 4 Adverse Events (Panel D).

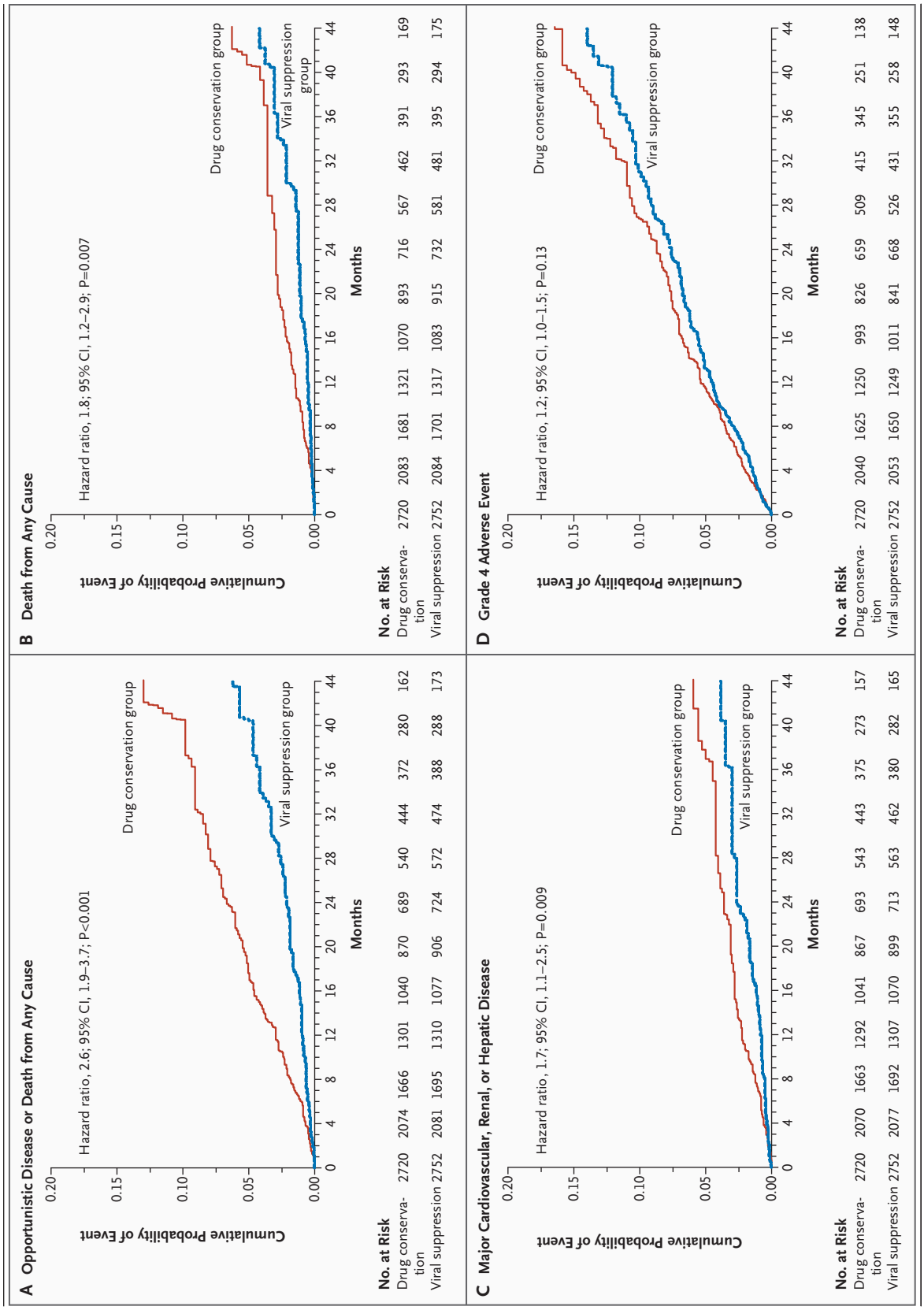
Grade 4 adverse events were determined on the basis of toxicity grades developed by the Division of AIDS of the NIAID. End-point definitions are listed in the Supplementary Appendix.

ADJUSTMENT FOR LATEST CD4+ COUNT AND HIV RNA LEVEL

Proportional-hazards models were used to assess the effects of time-dependent covariates corresponding to the latest CD4+ counts and latest HIV RNA levels, considered separately and together, on the hazard ratio (Fig. 4). The hazard ratio for opportunistic disease or death from any cause was reduced from 2.6 to 1.7 (95% CI, 1.2 to 2.5) after adjustment for the latest CD4+ count; it was further reduced to 1.5 (95% CI, 1.0 to 2.1) after adjustment for both the latest HIV RNA level and the latest CD4+ count. Adjusted for both the latest HIV RNA level and the latest CD4+ count, the hazard ratios for opportunistic disease and for death from causes other than opportunistic disease were 1.7 (95% CI, 1.0 to 2.9) and 1.2 (95% CI, 0.7 to 2.2), respectively; unadjusted, these hazard ratios were 3.6 (95% CI, 2.2 to 5.9) for opportunistic disease and 1.8 (95% CI, 1.1 to 2.9) for death from causes other than opportunistic disease, respectively.

DISCUSSION

Our data demonstrate that continuous use of antiretroviral therapy is superior to its episodic use as guided by the CD4+ count, with antiretroviral therapy deferred until the CD4+ count is less than 250 cells per cubic millimeter. The superiority of the viral suppression strategy, designed to achieve



Subgroup	Drug Conservation	Viral Suppression	Hazard Ratio	P Value for Interaction
	No. of participants with events (rate per 100 person-yr)			
Age				0.67
≤45 yr	47 (2.3)	19 (0.9)	2.5	
>45 yr	73 (4.7)	28 (1.7)	2.7	
Sex				0.44
Male	86 (3.1)	34 (1.3)	2.5	
Female	34 (4.0)	13 (1.3)	3.1	
Race				0.02
Black	55 (4.5)	17 (1.2)	3.7	
Other	65 (2.8)	30 (1.3)	2.1	
Baseline HIV RNA level				<0.001
≤400 copies/ml	72 (3.2)	18 (0.8)	4.0	
>400 copies/ml	22 (3.1)	19 (2.6)	1.2	
Baseline CD4+ count				0.02
350–449 cells/mm^3	24 (3.2)	18 (2.2)	1.5	
450–549 cells/mm^3	27 (3.7)	7 (0.9)	4.1	
550–649 cells/mm^3	19 (3.5)	7 (1.3)	2.8	
≥650 cells/mm^3	50 (3.2)	15 (1.0)	3.2	
Nadir CD4+ count				0.57
<50 cells/mm^3	13 (3.8)	6 (1.6)	2.3	
50–99 cells/mm^3	7 (2.9)	2 (0.8)	3.4	
100–199 cells/mm^3	24 (3.5)	11 (1.8)	2.0	
200–299 cells/mm^3	30 (3.6)	11 (1.2)	3.1	
300–399 cells/mm^3	30 (4.1)	11 (1.5)	2.6	
≥400 cells/mm^3	16 (2.1)	6 (0.8)	2.7	
Duration of ART				0.16
0 to <3 yr	23 (2.8)	7 (0.8)	3.6	
3 to <5 yr	30 (2.7)	8 (1.1)	3.5	
5 to <7 yr	27 (3.1)	15 (1.7)	1.8	
≥7 yr	40 (3.6)	17 (1.5)	2.5	
History of ART at baseline				0.56
Never received ART	4 (2.7)	1 (0.5)	5.2	
Previous use of ART but no use at baseline	22 (4.4)	9 (1.7)	2.6	
Use of ART at baseline	41 (2.6)	19 (1.2)		
1 or 2 Classes	53 (3.9)	18 (1.4)	2.2	
3 Classes			2.9	

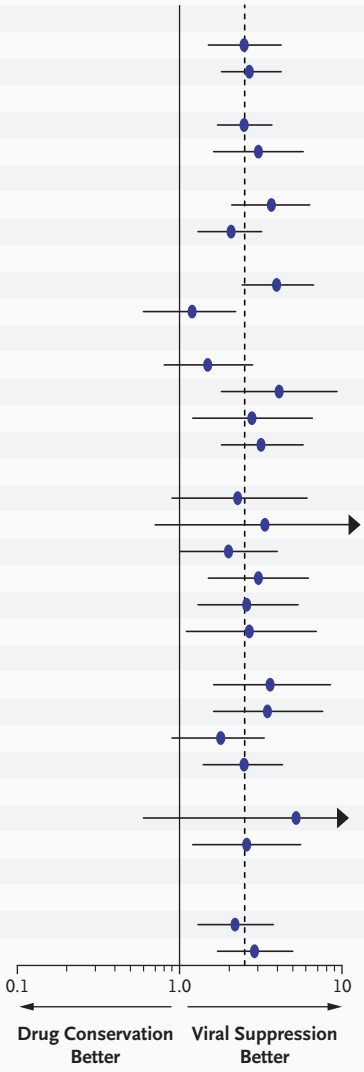


Figure 3. Hazard Ratios for Opportunistic Disease or Death from Any Cause.

The dashed line represents the overall hazard ratio (drug conservation group vs. viral suppression group) of 2.6. Horizontal lines indicate 95% CIs. Subgroup data for HIV RNA levels were restricted to participants who were receiving antiretroviral therapy at baseline. Race was self-reported. ART denotes antiretroviral therapy.

maximal and continuous suppression of HIV replication with the use of antiretroviral therapy, was evident with regard to the primary end point (opportunistic disease or death from any cause), as well as death from any cause, serious opportunistic disease, and an important secondary end point, major cardiovascular, renal, or hepatic disease.

Interruption of antiretroviral therapy has been advocated as a treatment strategy to enhance the quality of life, limit adverse events, and allow for the emergence of the predominant wild-type virus in patients infected with multidrug-resistant HIV.[27,28] Two randomized studies have used higher CD4+ count thresholds than those used in our study for the initiation of antiretroviral therapy, but they involved only 69 patients[29] and 74 pa-

tients[30,31] and were therefore too small to allow for the reliable assessment of effects of treatment interruption on clinical outcomes.

More recently, the findings of two other larger, randomized trials were reported. In the Staccato study, in which the primary end point was virologic suppression and the amount of exposure to antiretroviral drugs, 284 patients were randomly assigned to receive antiretroviral therapy guided by the CD4+ count (with therapy deferred until the CD4+ count was less than 350 cells per cubic millimeter and then used until the CD4+ count was more than 350 cells per cubic millimeter) and 146 patients were randomly assigned to receive continuous antiretroviral therapy.[32] After approximately 2 years of follow-up, diarrhea and neuropathy were more common among those receiving continuous therapy, and oral and vaginal candidiasis were more common among those receiving episodic therapy. In the Trivacan study, 216 patients were randomly assigned to episodic therapy with the same CD4+ count thresholds as those in our study, and 110 patients were randomly assigned to continuous antiretroviral therapy.[33] An increased risk of bacterial infections and other complications were noted in the episodic treatment group.

When we began our study, data indicated that the risk of AIDS was low among patients who had never received antiretroviral therapy and among those who had received it but who also had CD4+ counts of more than 200 cells per cubic millimeter.[14-16] Consequently, we chose to use a CD4+ count threshold of 250 cells per cubic millimeter for initiation (or reinitiation) of antiretroviral therapy in the drug conservation group, and CD4+ counts and symptoms were monitored closely. Data also indicated that complications and deaths among patients with higher CD4+ levels were largely due to grade 4 adverse events and deaths from causes other than opportunistic disease that were either associated with antiretroviral therapy or attributable to non-HIV causes.[8] Thus, we expected the risk of death from causes other than opportunistic disease to decrease with the interruption of antiretroviral therapy, rather than to increase.

In our study, deaths represented a large percentage of the primary events (44.3%) and, as in other reports, deaths from causes other than opportunistic disease were common.[8,34-36] The excess of deaths from causes other than opportunistic disease in the drug conservation group was surprising. Furthermore, contrary to available data and to the assumptions underlying our study design, participants in the drug conservation group had a higher rate of major cardiovascular, renal, or hepatic disease than did those in the viral suppression group. On the basis of prior findings, and as a consequence of less exposure to antiretroviral therapy in the drug conservation group,[10,37] we expected the rate of cardiovascular disease to be 15% lower in the drug conservation group than in the viral suppression group.

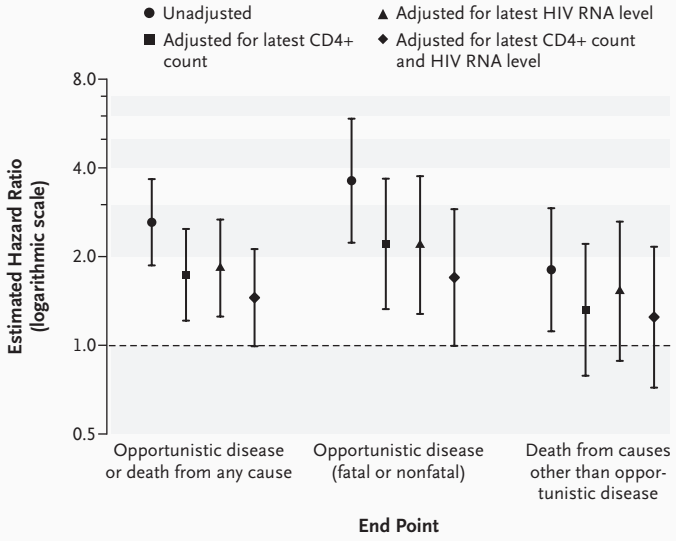


Figure 4. Estimated Unadjusted and Adjusted Hazard Ratios (Drug Conservation Group vs. Viral Suppression Group) for Opportunistic Disease or Death from Any Cause, Opportunistic Disease (Fatal or Nonfatal), and Death from Causes Other Than Opportunistic Disease.

End-point definitions are listed in the Supplementary Appendix. I bars denote the 95% CIs.

There were fewer occurrences of major hepatic or renal disease than of cardiovascular disease in our study, but hepatic or renal disease was still more frequent in the drug conservation group than in the viral suppression group. Some antiretroviral drugs have been associated with adverse hepatic and renal events,[7,38,39] but recent findings indicate that these events are also related to the level of immunodeficiency[40,41] and that antiretroviral therapy improves these outcomes either directly by inhibiting viral replication or indirectly by improving immune function.[39] Our data support these findings. Adjustment for the latest CD4+ count reduced the hazard ratio in the drug conservation group versus the viral suppression

group for death from causes other than opportunistic disease, confirming that immunosuppression increases the risk of death among patients with diseases not traditionally believed to be opportunistic in nature. Much, but not all, of the difference in the rates of opportunistic disease or death from any cause between the drug conservation group and the viral suppression group was explained by differences in the CD4+ count and HIV RNA level during follow-up. The hazard ratio for opportunistic disease or death from any cause in the drug conservation group versus the viral suppression group was reduced from 2.6 to 1.5 after adjustment for the latest CD4+ count and the latest HIV RNA level. The reasons for the remaining excess risk are not clear.

Although our findings indicate that the interruption of antiretroviral therapy with the use of higher CD4+ count thresholds than those used in our study may result in lower risks of opportunistic disease or death from any cause, the lack of benefit of our interruption strategy on major adverse events associated with antiretroviral therapy suggests that such strategies should be viewed as carrying a net clinical risk unless proven otherwise in appropriately powered studies.

In summary, our findings provide clear and compelling evidence that the episodic antiretroviral strategy, guided by the CD4+ count, used in the SMART study is deleterious. Our results indicate that some of the excess risk of opportunistic disease or death from any cause in the drug conservation group appears to be attributable to the longer period during which participants had reduced CD4+ counts. Further research is needed to evaluate the effect of interrupting antiretroviral therapy on immune function, inflammation, and other markers.

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APPENDIX

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REFERENCES

1. Perelson AS, Essunger P, Cao Y, et al. Decay characteristics of HIV-1 infected compartments during combination therapy. Nature 1997;387:188-91.

2. Chun TW, Fauci AS. Latent reservoirs of HIV: obstacles to the eradication of virus. Proc Natl Acad Sci U S A 1999;96:10958-61.

3. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat Med 1999;5:512-7.

4. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced immunodeficiency virus infection. N Engl J Med 1998;338:853-60.

5. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. Lancet 1998;352:1725-30.

6. d'Arminio Monforte A, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly antiretroviral therapy. Arch Intern Med 2005;165:416-23. [Erratum, Arch Intern Med 2005;165:1200.]

7. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet 2000;356:1423-30.

8. Reisler RB, Han C, Burman WJ, Tedaldi EM, Neaton JD. Grade 4 events

are as important as AIDS events in the era of HAART. J Acquir Immune Defic Syndr 2003;34:379-86.
9. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study. Lancet 1999; 353:2093-9.
10. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and risk of myocardial infarction. N Engl J Med 2003;349:1993-2003. [Erratum, N Engl J Med 2004;350:955.]
11. Clavel F, Hance AJ. HIV drug resistance. N Engl J Med 2004;350:1023-35.
12. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS unified budget and workplan, 2006–2007. (Accessed November 2, 2006, at http://data.unaids.org/publications/irc-pub06/JC1147-UBW_en.pdf.)
13. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. July 2003. (Accessed November 2, 2006, at http://AIDSinfo.nih.gov/ContentFiles/AdultandAdolescentGL.1102003004.pdf.)
14. Phair JP, Mellors JW, Detels R, Margolick JB, Munoz A. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. AIDS 2002;16:2455-9.
15. Mocroft A, Katalama C, Johnson AM, et al. AIDS across Europe, 1994-1998: the EuroSIDA study. Lancet 2000;356:291-6.
16. Strategies for management of antiretroviral therapy (SMART) protocol. Bethesda, MD: National Institutes of Health. (Accessed November 2, 2006, at http://www.smart-trial.org.)
17. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41:No. RR-17:1-19.
18. Neaton JD, Wentworth DN, Rhame F, Hogan C, Abrams DI, Deyton L. Considerations in choice of a clinical endpoint for AIDS clinical trials (CPCRA). Stat Med 1994;13:2107-25.
19. Copenhagen HIV Programme (CHIP) home page. (Accessed November 2, 2006, at http://www.cphiv.dk.)
20. Shih JH. Sample size calculation for complex clinical trials with survival endpoints. Control Clin Trials 1995;16:395-407.
21. Crow RS, Prineas RJ, Jacobs DR Jr, Blackburn H. A new epidemiologic classification system for interim myocardial infarction from serial electrocardiographic changes. Am J Cardiol 1989;64:454-61.
22. Crow RS, Prineas RJ, Hannan PJ, Grandits G, Blackburn H. Prognostic associations of Minnesota Code serial electrocardiographic change classification with coronary heart disease mortality in the Multiple Risk Factor Intervention Trial. Am J Cardiol 1997;80:138-44.
23. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code manual of electrocardiographic findings. Littleton, MA: John Wright–PSG, 1982.
24. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
25. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
26. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. 2nd ed. New York: John Wiley, 2002.
27. Lori F, Lisziewicz J. Structured treatment interruptions for the management of HIV infection. JAMA 2001;286:2981-7.
28. Hogg RS, Havlir D, Miller V, Montaner JSG. To stop or not to stop: that is the question, but what is the answer? AIDS 2002;16:787-9.
29. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callagaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective study. AIDS 2004; 18:439-46.
30. Cardiello PG, Hassink E, Ananworanich J, et al. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. Clin Infect Dis 2005;40:594-600.
31. Ananworanich J, Siangphoe U, Hill A, et al. Highly active antiretroviral therapy (HAART) retreatment in patients on CD4-guided therapy achieved similar virologic suppression compared with patients on continuous HAART. J Acquir Immune Defic Syndr 2005;39:523-9.
32. Ananworanich J, Gayet-Ageron A, Le Braz M, et al. CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. Lancet 2006;368:459-65.
33. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. Lancet 2006;367:1981-9.
34. Selik RM, Byers RH Jr, Dworkin MS. Trends in diseases reported on U.S. death certificates that mentioned HIV infection, 1987-1999. J Acquir Immune Defic Syndr 2002;29:378-87.
35. Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol 2005;34:121-30.
36. Crum NF, Riffenburgh RH, Wegner S, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. J Acquir Immune Defic Syndr 2006;41:194-200.
37. d'Arminio A, Sabin CA, Phillips AN, et al. Cardio- and cerebrovascular events in HIV-infected persons. AIDS 2004;18: 1811-7.
38. Gonzalez de Requena D, Nunez M, Jimenez-Nacher I, Soriano V. Liver toxicity caused by nevirapine. AIDS 2002;16: 290-1.
39. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2005;40: 1559-85.
40. Qurishi N, Kreuzberg C, Lüchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet 2003;362:1708-13.
41. Mocroft A, Soriano V, Rockstroh J, et al. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? AIDS 2005;19:2117-25.