

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283-96.

Web-Only Appendix

This appendix includes additional information on the definition of key outcomes. In addition, 3 web-only figures and 3 web-only tables are included in this appendix.

Endpoint Definitions

Opportunistic diseases (OD) included in the primary endpoint (see Table 2 and web-table I) were: Aspergillosis, bartonellosis, esophageal candidiasis, candidiasis of bronchi, trachea, or lungs, invasive cervical cancer, Chagas disease of the central nervous system (CNS), cytomegalovirus virus (CMV) disease, CMV retinitis, extrapulmonary coccidioidomycosis, cryptosporidiosis, extrapulmonary cryptococcosis, HIV-related encephalopathy, persistent Herpes simplex, disseminated Herpes zoster, extrapulmonary histoplasmosis, isosporiasis, Kaposi's sarcoma, leishmaniasis, Burkitt's lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, primary lymphoma of the brain, tuberculosis, microsporidiosis, Mycobacterium avium complex (MAC), other non-tuberculous species or unidentified species Mycobacterium, nocardiosis, penicilliosis, extrapulmonary Pneumocystis jiroveci, Pneumocystis jiroveci pneumonia, bacterial pneumonia (2 episodes within 12 months), progressive multifocal leukoencephalopathy, Rhodococcus equi disease, Salmonella septicemia (2 episodes within 12 months), toxoplasmosis of brain, wasting syndrome due to HIV.

Serious OD, a subset of OD events, include: Progressive multifocal leukoencephalopathy, lymphoma, visceral Kaposi's sarcoma, HIV-related encephalopathy (AIDS dementia complex), toxoplasmosis, histoplasmosis, cryptococcosis, MAC, wasting syndrome, and CMV disease. These events have been associated with a greater risk of subsequent mortality than other OD events (see reference 18).

An Endpoint Review Committee reviewed all OD events, CVD, renal and hepatic events and deaths blinded to treatment group.

Major cardiovascular, renal and hepatic disease outcomes include: non-fatal myocardial infarction (MI) requiring hospitalization or diagnosed by serial Q-wave change on electrocardiogram (ECG) (silent MI), non-fatal stroke, coronary artery disease requiring surgery, death from CVD, non-fatal or fatal kidney failure, non-fatal or fatal cirrhosis.

A confirmed diagnosis of hospitalization for MI required the following: A plus B, A plus C or B plus C:

- (A) Symptoms (such as chest pain) of at least 20 minutes duration compatible with myocardial ischemic pain.
- (B) ECG changes compatible with an acute MI, such as new persistent ST segment elevation of ≥ 0.1 mV or new pathologic Q waves (QRS >0.04 sec), each in contiguous leads.
- (C) A serum biochemical marker compatible with an acute MI, such as:

- 1) Total CK at least twice the upper limit of normal with an MB fraction of >5% of total CK, or
- 2) Troponin >2 times the upper limit of normal, or
- 3) LDH1/LDH2 ratio ≥ 1 .

Silent MI required the appearance of significant new Q waves with or without significant change in repolarization STT wave morphology as determined by Minnesota Code comparison of baseline and follow-up ECGs. The rules for significant change are listed in reference 21. All such changes indicated by the computer program measurements were overread by MD electrocardiographers for confirmation. ECGs were read blinded to treatment group. For further information on the definition of silent MI see references 21-23.

For coronary artery disease requiring surgery the following was counted: 1) coronary artery bypass graft; 2) coronary artery stent implant; 3) coronary artherectomy; or 4) percutaneous transluminal angioplasty.

A confirmed diagnosis of a non-fatal stroke required A plus B plus C or D or E.

- (A) Unequivocal objective findings or a localizing neurologic deficit (with or without recent onset of severe headache and loss of consciousness)
- (B) Duration longer than 24 hours.
- (C) Absence of another disease process causing neurologic deficit, such as neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder.

- (D) Diagnosis of stroke based on abnormality demonstrated by CT or MRI consistent with current neurologic signs or symptoms.
- (E) Positive lumbar puncture (for subarachnoid hemorrhage).

For non-fatal renal disease either 1) dialysis or kidney transplant required to preserve life or 2) supporting documentation indicating the results of the procedure(s) giving rise to the diagnosis of end stage renal disease (ESRD) were counted.

For non-fatal cirrhosis A or B plus C plus D or E was required.

- (A) Histologic evidence obtained by liver biopsy or autopsy.
- (B) Clinical evidence of cirrhosis (at least one of the following must be present: ascites, hepatic encephalopathy, or gastric or esophageal varices).
- (C) Increased PT or INR.
- (D) Albumin <3.0 g/dL or < 30 g/L.
- (E) Imaging consistent with cirrhosis in the radiologist's opinion.

Web Table I. Number of Patients with Specific Opportunistic Disease (OD) Events and Rate per 100 Person Years by Treatment Group

Event ^a	DC Group		VS Group	
	N	Rate	N	Rate
Aspergillosis, invasive	0	0.00	1	0.03
Candidiasis, esophageal	24	0.65	7	0.19
Candidiasis of bronchi, trachea, or lungs	2	0.05	0	0.00
CMV disease	1	0.03	0	0.00
Cryptococcosis, extrapulmonary	1	0.03	0	0.00
Encephalopathy, HIV-related, stage 2 or higher	1	0.03	0	0.00
Herpes simplex	6	0.16	3	0.08
Herpes zoster	5	0.13	1	0.03
Kaposi's sarcoma	7	0.19	1	0.03
Lymphoma	4	0.11	1	0.03
Tuberculosis, pulmonary or Extrapulmonary	3	0.08	2	0.05
Mycobacterium avium complex, Extrapulmonary	1	0.03	1	0.03
PCP	8	0.21	2	0.05
Bacterial pneumonia	8	0.21	2	0.05
Toxoplasmosis of brain	1	0.03	0	0.00
Wasting syndrome	4	0.11	0	0.00

^a Other OD events included in the primary endpoint were not reported for either treatment group.

Web Table II. Underlying Cause of Death by Treatment Group

Cause of Death	DC Group		VS Group	
	N	%	N	%
OD	4	7.3	3	10.0
Cancer, excluding OD cancers	11	20.0	5	16.7
Cardiovascular complications	7	12.7	4	13.3
Infection	3	5.5	1	3.3
Hepatic complications	1	1.8	2	6.7
Renal complications	3	5.5	0	0.0
Chronic obstructive lung disease	1	1.8	1	3.3
Hematological disease	2	3.6	0	0.0
Digestive system disease	1	1.8	1	3.3
CNS disease	1	1.8	0	0.0
Respiratory disease	0	0.0	1	3.3
Substance abuse	3	5.5	5	16.7
Accident/violent/suicide	3	5.5	4	13.3
Cause unknown	15	27.3	3	10.0
Total	55	100.0	30	100.0

Web Table III: Number of Patients Experiencing Grade 4 Adverse Events and Rate per 100 Person Years by Body System and Treatment Group

Body System	DC Group		VS Group	
	N	Rate	N	Rate
Systemic	43	1.19	33	0.90
Heart	26	0.72	17	0.46
Circulatory	21	0.58	14	0.38
Trauma	7	0.19	7	0.19
Anemia	5	0.14	1	0.03
Upper GI	10	0.27	9	0.24
Thrombocytopenia	4	0.12	0	0.00
Lower GI	17	0.47	16	0.43
Renal	8	0.22	13	0.35
Liver, Gall Bladder	10	0.27	10	0.27
Musculoskeletal	11	0.30	15	0.41
Neurological	23	0.63	21	0.57
Respiratory	34	0.94	11	0.30
Reproductive	6	0.16	7	0.19
Skin	14	0.38	4	0.11
Psychological	24	0.66	21	0.57
Metabolic, Nutrition	24	0.66	10	0.27

Web Figure Legends

Figure I: SMART Study Design and CONSORT Flow Diagram.

Figure IIa: Percent of Participants Prescribed ART by Month of Follow-up and Treatment Group.

Figure IIb: Change in CD4+ Cell Count from Baseline by Month of Follow-up and Treatment

Group. In the DC group, the average CD4+ count decreased by 87 cells/mm³ per month during the first 2 months following randomization; thereafter, it continued to decline at a lower rate.

Among those taking ART at entry, the drop in CD4+ count in these first 2 months was greater for those with lower nadir CD4+ counts (a decrease of 26 CD4+ cells per 100 cells lower nadir CD4+) and for those with higher baseline counts (a decrease of 30 CD4+ cells per 100 cells higher baseline CD4+) ($P < 0.001$ for both in multiple regression analysis). On average through follow-up, the CD4+ count was 206 cells/mm³ lower for the DC compared to the VS group.

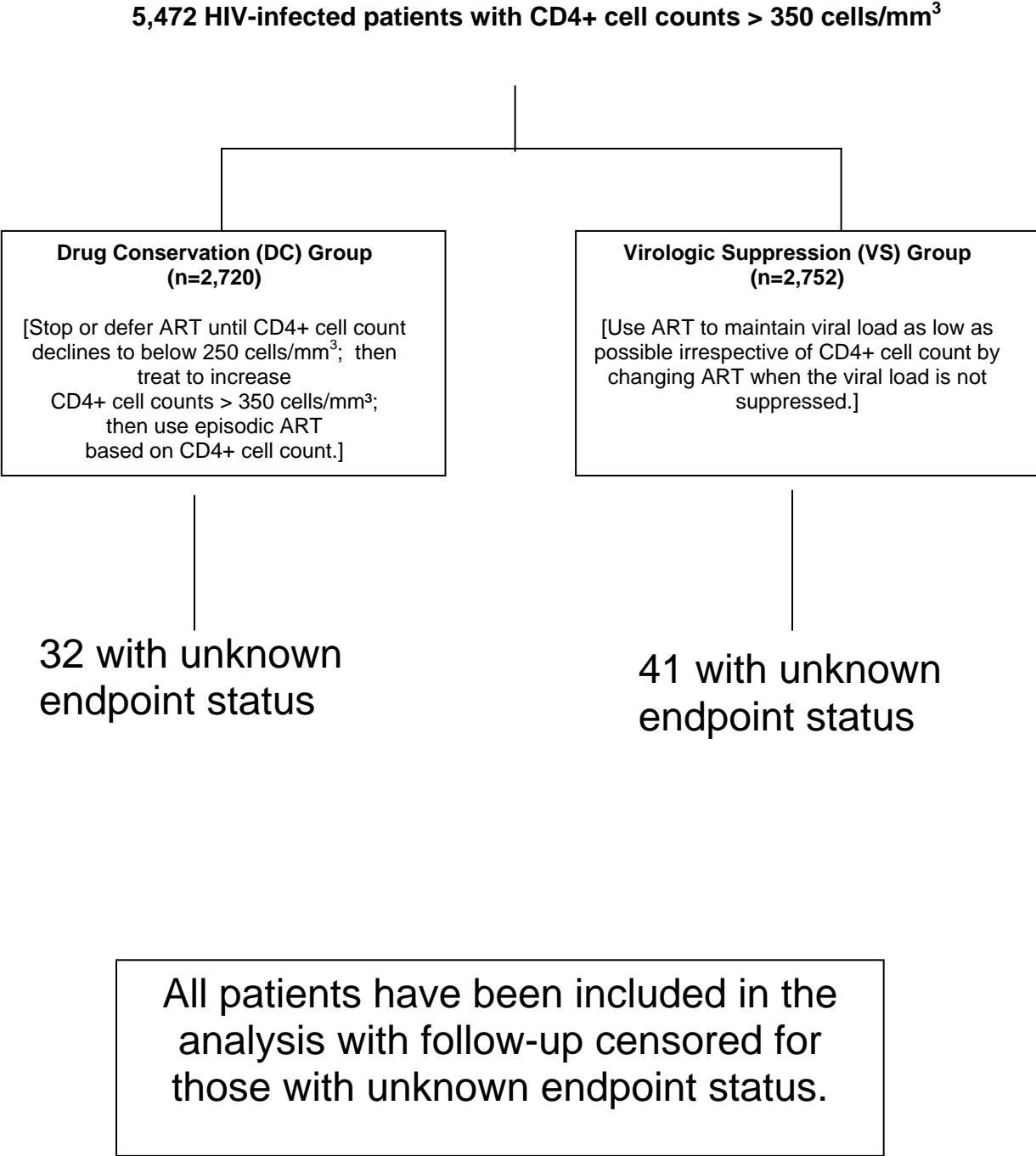
Figure IIc: Percent of Participants with HIV-RNA Level ≤ 400 Copies/mL by Month of Follow-up and Treatment Group. The percent with HIV-RNA ≤ 400 copies/mL in the DC group decreased sharply during the first 2 months, from 72% at baseline to 6% at 2 months. Afterwards, that percentage increased as DC participants (re-)initiated ART per study guidelines, to 28% and 48% at 12 and 36 months, respectively. In the VS group, the percent of participants with HIV-RNA ≤ 400 copies/mL increased initially from 72% at baseline to 78% at 2 months as some participants initiated ART, and then slowly decreased to baseline levels.

Figure IIIa: Cumulative Probability ($\times 100$) of DC Participants with HIV-RNA Level ≤ 400 Copies/mL Following (Re-)Initiation of Antiretroviral Treatment after the First Treatment Interruption by Baseline HIV RNA Level. Follow-up is censored when participants stop ART. Among 1,109 DC participants who re-initiated ART, the median time to an HIV-RNA ≤ 400 copies/mL was 3.1 months. The percent achieving an HIV-RNA level ≤ 400 copies/mL within 8

months after ART had been (re-)initiated were 88.0% and 65.7%, respectively, for those with ≤ 400 and >400 copies/mL at baseline.

Figure IIIb: Change in CD4+ Cell Count Following Re-Initiation of ART After the First Treatment Interruption for Participants in the DC Group. Follow-up is censored when participants stop ART. CD4+ count increased rapidly following re-initiation of ART with an average increase of 166 cells/mm³ by 8 months.

Figure I. SMART study design and CONSORT flow diagram



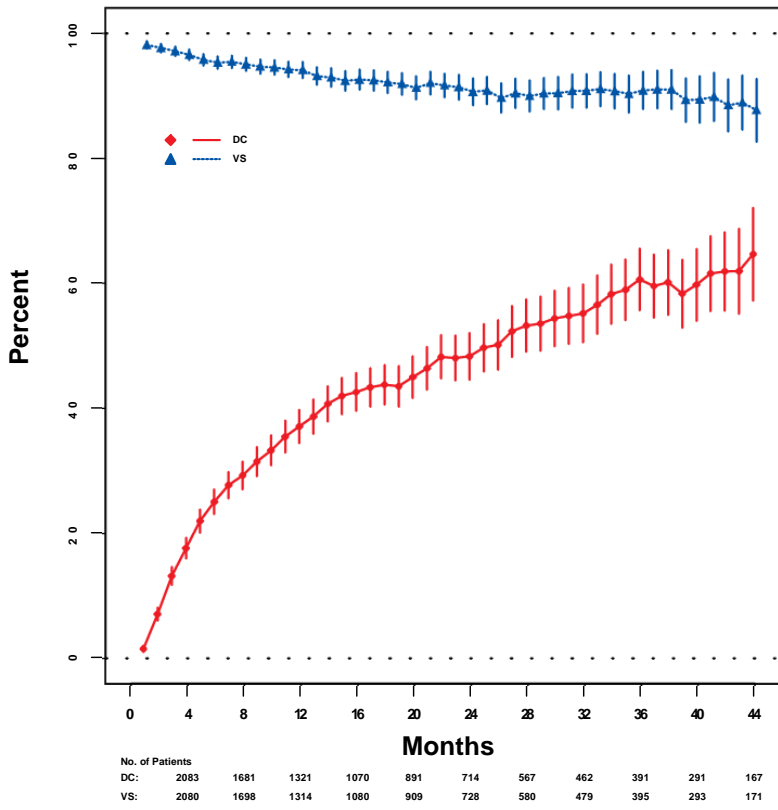


Figure IIa

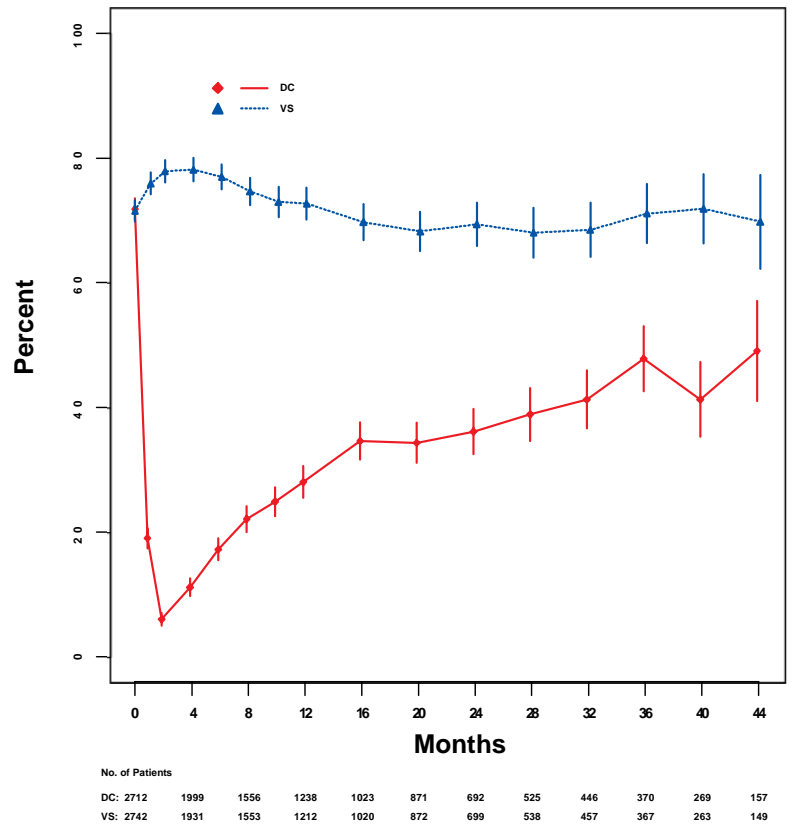


Figure IIc

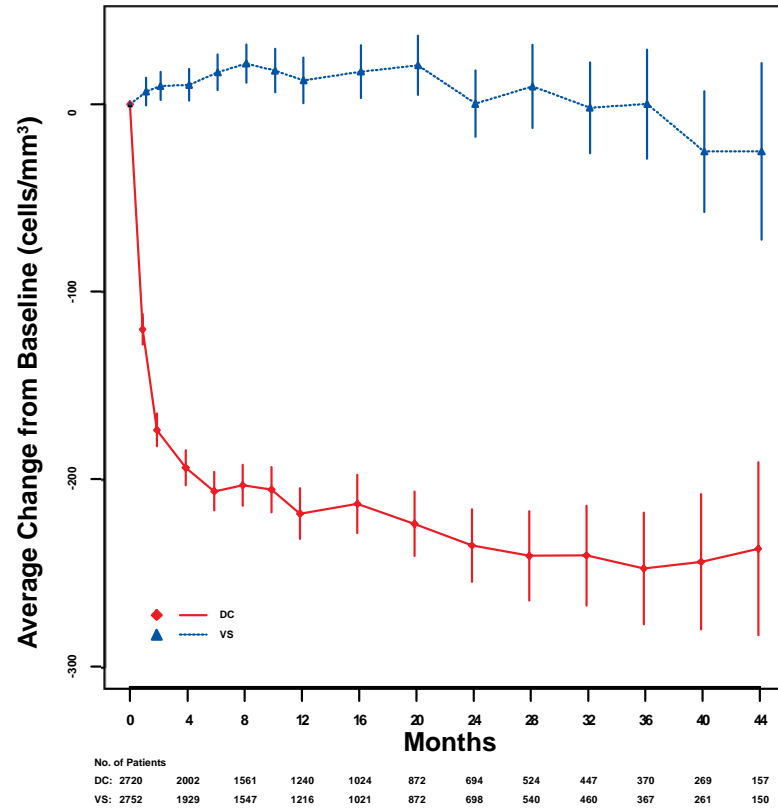


Figure IIb

