Inferior Clinical Outcome of the CD4⁺ Cell Count–Guided Antiretroviral Treatment Interruption Strategy in the SMART Study: Role of CD4⁺ Cell Counts and HIV RNA Levels during Follow-up

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

**Background and methods.** The SMART study compared 2 strategies for using antiretroviral therapy—drug conservation (DC) and viral suppression (VS)—in 5472 human immunodeficiency virus (HIV)–infected patients with CD4⁺ cell counts >350 cells/μL. Rates and predictors of opportunistic disease or death (OD/death) and the relative risk (RR) in DC versus VS groups according to the latest CD4⁺ cell count and HIV RNA level are reported.

**Results.** During a mean of 16 months of follow-up, DC patients spent more time with a latest CD4⁺ cell count <350 cells/μL (for DC vs. VS, 31% vs. 8%) and with a latest HIV RNA level >400 copies/mL (71% vs. 28%) and had a higher rate of OD/death (3.4 vs. 1.3/100 person-years) than VS patients. For periods of follow-up with a CD4⁺ cell count <350 cells/μL, rates of OD/death were increased but similar in the 2 groups (5.7 vs. 4.6/100 person-years), whereas the rates were higher in DC versus VS patients (2.3 vs. 1.0/00 person-years; RR, 2.3 [95% confidence interval, 1.5–3.4]) for periods with the latest CD4⁺ cell count ≥350 cells/μL—an increase explained by the higher HIV RNA levels in the DC group.

**Conclusions.** The higher risk of OD/death in DC patients was associated with (1) spending more follow-up time with relative immunodeficiency and (2) living longer with uncontrolled HIV replication even at higher CD4⁺ cell counts. Ongoing HIV replication at a given CD4⁺ cell count places patients at an excess risk of OD/death.

**Trial registration.** ClinicalTrials.gov identifier: NCT00027352.

There has been a growing recognition that short- and long-term adverse events [1, 2], difficulties with maintaining high rates of adherence [3, 4], the development of resistance [5], and cost could all affect the ability to sustain the positive effects of antiretroviral therapy (ART). Thus, it is critical that research be conducted to optimize strategies for use of available drugs. One potential strategy is to delay or interrupt ART while the CD4⁺ cell count remains above a certain threshold (so-called CD4⁺ cell count–guided interruptions). Recently, 3 randomized, controlled trials (SMART [6], Trivacan [7], and DART [8]) were prematurely halted on the recommendation of the data and safety monitoring boards because of a >2-fold excess risk of predefined diseases associated with chronic HIV infection (opportunistic diseases [ODs]) in the group allocated to treatment interruption. Consistent with these results, in a fourth study (Staccato), an excess risk of OD in the CD4⁺ cell count–guided interruption arm was also observed [9]. In SMART, there was also a difference in the risk of serious ODs and all-cause mortality [6].

In the report of the primary results of SMART [6], much, but not all, of the excess risk of the primary end point, OD or death (OD/death), associated with the
CD4+ cell count–guided interruption of ART was related to lower CD4+ cell counts and higher HIV RNA levels during follow-up, compared with those in the continuous ART group. Here, we further explore the reasons for the higher-than-expected rates of OD/death (and of OD and death analyzed separately) in the ART-interruption group. An improved understanding of the underlying reasons for the higher rates of nonfatal or fatal OD events and of death from causes other than OD (non-OD death), particularly at higher CD4+ cell counts, could provide insights into the risks of uncontrolled viral replication and help to determine whether the CD4+ cell count can be relied on as the primary marker of HIV-induced immunodeficiency.

METHODS

Study design and conduct. The SMART study was a randomized trial conducted by 318 clinical sites in 33 countries comparing 2 ART strategies in HIV-infected adults with CD4+ cell counts >350 cells/µL. Details of the design and conduct of SMART have been published elsewhere [6]. Briefly, the viral suppression (VS) strategy involves continuous use of ART with the goal of maximal suppression of HIV replication, whereas the CD4+ cell count–guided interruption-of-ART strategy (drug conservation [DC]) involves stopping ART when CD4+ cell counts are >350 cells/µL and reinstituting ART when CD4+ cell counts fall to <250 cells/µL. On 11 January 2006, enrollment was stopped and the DC strategy discontinued, because of the increased risk of OD (see the primary report [6] for a list of ODs) or death from any cause in comparison to the VS strategy.

In the present article, the influence of CD4+ cell count and HIV RNA level on 3 clinical outcomes is assessed: (1) OD/death, the primary end point of SMART; (2) fatal or nonfatal OD; and (3) non-OD death.

Statistical analyses. For each treatment group, the overall median follow-up CD4+ cell count was determined as the median of counts at months 2, 4, 8, and every 4 months thereafter from the time of randomization for all patients, censored at the time of OD/death. Overall HIV RNA levels, CD4+ cell percentages, and CD4+ cell count slopes were determined similarly. Throughout follow-up, the latest CD4+ cell count slope was calculated using the latest CD4+ cell count and the count preceding it (unit, cells/µL/month). Postrandomization HIV RNA levels and CD4+ cell counts were summarized in a scatter plot using contour lines that identified where 25%, 50%, and 75% of the pairs of CD4+ cell counts and HIV RNA levels resided; the contour lines were estimated nonparametrically [10], on the basis of the CD4+ cell counts and HIV RNA levels at months 2, 4, 8, and every 4 months thereafter.

Cox proportional hazards models were used to assess the effects of time-dependent covariates (latest measurements for CD4+ cell count, CD4+ cell percentage, HIV RNA level, and CD4+ cell count slope) and fixed covariates (defined at baseline) on the hazard ratios (HRs) of the 3 outcomes in the 2 treatment groups. For these analyses, HIV RNA levels were categorized into 3 strata. Follow-up time was defined as the period from randomization to the first occurrence of the outcome of interest, death, loss to follow-up, or 11 January 2006.

Person-years at specific CD4+ cell counts or HIV RNA levels were counted using the latest measured value during follow-up. In these follow-up time strata determined by latest CD4+ cell count and HIV RNA level, the relative risk (RR) for the DC group versus the VS group (hereafter, “RR[DC/VS]”—was estimated by Poisson regression. For the DC group, event rates were also estimated during follow-up for the first period of not receiving ART (from randomization to ART [re]initiation), the first subsequent period of receiving ART (censored at ART discontinuation), and the remaining later follow-up time.

All P values are 2-sided. Analyses were performed using SAS (version 9.1). Figure 1 was generated using R (available at: http://www.r-project.org/).

RESULTS

The SMART study. Between 8 January 2002 and 11 January 2006, 5472 patients with entry CD4+ cell counts >350 cells/µL were randomized—2720 to the DC group and 2752 to the VS group. The mean follow-up time was 16 months. The percentage of follow-up time when participants were receiving ART differed markedly between the DC and VS groups (34% vs. 94%). The majority of follow-up time (61%) in the DC group accrued in patients undergoing their first cycle of ART interruption. As intended by the study design, the median CD4+ cell count during follow-up was 206 cells/µL lower in the DC group than the VS group. The majority of follow-up time was spent with CD4+ cell counts ≥350 cells/µL in both groups (69% vs. 92%), whereas the duration of follow-up time with HIV RNA levels >400 copies/mL was substantially higher for the DC group than the VS group (71% vs. 28%), reflecting less use of ART in the former group.

A total of 121 patients in the DC group and 48 patients in the VS group experienced at least 1 OD/death event, giving rates for this outcome of 3.4 and 1.3/100 persons-years, respectively (HR, 2.6 [95% confidence interval [CI], 1.9–3.6]). In patients with at least 1 event, 75 (62%) in the DC group and 22 (46%) in the VS group were ODs (fatal or nonfatal). Non-OD deaths occurred in 51 (42%) and 27 (56%) patients, respectively.

Laboratory markers during follow-up. Figure 1 shows a scatter plot for pairs of CD4+ cell counts and HIV RNA levels observed during follow-up in the DC and VS groups. The contour lines circumscribe the areas of highest density for 25%, 50%, and 75% of the pairs in the DC (red) and VS (blue) groups. The figure also shows box plots for the distributions of CD4+ cell
counts and HIV RNA levels, both overall (red, DC; blue, VS) and just before the occurrence of OD/death events (gray).

The median latest CD4+ cell counts before OD/death events were 342 and 530 cells/µL for the DC and VS groups, respectively (figure 1, vertical dashed lines), compared with the overall medians of 417 and 617 cells/µL for the entire DC and VS groups, respectively (vertical dotted lines). Thus, for both strategies, patients who experienced an OD/death event had a median latest CD4+ cell count before the event that was 75–87 cells/µL lower than the median follow-up counts in their respective treatment group. The situation for HIV RNA level was similar, with higher values just before the occurrence of events relative to the median values during follow-up for each group.

Risk factors for clinical outcome. For patients in the DC and VS groups, a 100 cell/µL higher latest CD4+ cell count was associated with a 25% (95% CI, 14%–35%) and 15% (−1% to 29%) reduced risk of OD/death, respectively (table 1). In the DC group, the latest CD4+ cell count appeared to be a stronger predictor of OD (fatal and nonfatal) than of non-OD death. Evaluation of the CD4+ cell percentage rather than the absolute CD4+ cell count yielded comparable findings.

The latest HIV RNA level was predictive of OD/death, OD (fatal or nonfatal), and non-OD death in the VS group but not in the DC group, after adjustment for latest CD4+ cell count (table 1). When the analyses were repeated including only events that occurred at a latest CD4+ cell count ≥350 cells/µL, the same general pattern emerged (data not shown).

The unadjusted HR of DC versus VS for OD/death was 2.6 (95% CI, 1.9–3.6), and, after adjustment for the covariates shown in table 1, it fell to 1.3. Likewise, the HR of DC versus VS declined from 3.5 (95% CI, 2.2–5.6) to 1.4 for fatal and nonfatal OD and from 1.9 (95% CI, 1.2–3.0) to 1.3 for non-OD death after adjustment.

Risk of clinical disease in laboratory-defined subgroups. The rates of OD/death—and the rates of OD (fatal and nonfatal) and non-OD deaths—in the 2 follow-up strata with the lowest

![Figure 1](http://jid.oxfordjournals.org/)

Figure 1. Scatter plot of pairs of follow-up CD4+ cell counts and HIV RNA levels obtained at months 2, 4, 8, and every 4 months thereafter, summarized by red and blue contour lines that circumscribe the regions of highest density for 25%, 50% and 75% of the CD4+ cell count/HIV RNA level pairs in the drug conservation (DC; red) group and the viral suppression (VS; blue) group. Red (DC) and blue (VS) box plots show separately the distributions of CD4+ cell counts (horizontal plots; median, interquartile range, and range) and HIV RNA levels (vertical plots). The gray box plots show the latest CD4+ cell counts and HIV RNA levels before opportunistic disease or death (OD/death) for the 121 DC and 48 VS patients with such an event. Vertical and horizontal lines mark the median CD4+ cell count and HIV RNA level for the entire treatment group (dotted) and the medians of the latest values before OD/death (dashed). Gray shading highlights HIV RNA levels ≤400 copies/mL.
Table 1. Hazard ratios for the effect of latest CD4+ cell count, latest HIV RNA level, age, prior AIDS, and CD4+ cell percentage on opportunistic disease or death (OD/death), OD (fatal or nonfatal), and death from causes other than OD (non-OD death), for the continuous antiretroviral therapy (ART) (viral suppression [VS]) group, the ART interruption (drug conservation [DC]) group, and both groups combined.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard ratio (95% CI)</th>
<th></th>
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<th>Hazard ratio (95% CI)</th>
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<th></th>
<th>Hazard ratio (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>DC</td>
<td>VS</td>
<td>Allb</td>
<td>DC</td>
<td>VS</td>
<td>Allb</td>
<td>DC</td>
<td>VS</td>
<td>Allb</td>
</tr>
<tr>
<td>Latest CD4+ cell count, per 100 cells/mL higher</td>
<td>0.75 (0.65–0.86)</td>
<td>0.85 (0.71–1.01)</td>
<td>0.78 (0.70–0.87)</td>
<td>0.69 (0.57–0.83)</td>
<td>0.81 (0.63–1.03)</td>
<td>0.73 (0.63–0.84)</td>
<td>0.90 (0.74–1.09)</td>
<td>0.88 (0.69–1.11)</td>
<td>0.87 (0.75–1.01)</td>
</tr>
<tr>
<td>Latest HIV RNA level</td>
<td>0.89 (0.49–1.60)</td>
<td>2.31 (1.08–4.94)</td>
<td>1.37 (0.86–2.19)</td>
<td>1.14 (0.50–2.60)</td>
<td>1.83 (0.57–5.89)</td>
<td>1.43 (0.73–2.79)</td>
<td>0.81 (0.36–1.80)</td>
<td>2.77 (1.02–7.50)</td>
<td>1.39 (0.73–2.64)</td>
</tr>
<tr>
<td>Age at entry, per 10 years older</td>
<td>1.17 (0.71–1.90)</td>
<td>4.10 (1.80–9.34)</td>
<td>1.82 (1.19–2.80)</td>
<td>1.77 (0.90–3.45)</td>
<td>3.45 (1.05–11.32)</td>
<td>2.28 (1.27–4.09)</td>
<td>0.77 (0.37–1.59)</td>
<td>4.86 (1.58–14.94)</td>
<td>1.54 (0.82–2.88)</td>
</tr>
<tr>
<td>AIDS diagnosis before entry, yes vs. no</td>
<td>1.52 (1.26–1.84)</td>
<td>1.67 (1.23–2.28)</td>
<td>1.56 (1.33–1.83)</td>
<td>1.27 (0.99–1.63)</td>
<td>1.33 (0.84–2.12)</td>
<td>1.28 (1.03–1.60)</td>
<td>1.92 (1.46–2.53)</td>
<td>1.92 (1.28–2.88)</td>
<td>1.93 (1.54–2.41)</td>
</tr>
<tr>
<td>DC vs. VS</td>
<td>1.38 (0.92–2.05)</td>
<td>1.79 (0.97–3.31)</td>
<td>1.50 (1.07–2.10)</td>
<td>1.45 (0.87–2.41)</td>
<td>3.02 (1.23–7.39)</td>
<td>1.75 (1.13–2.71)</td>
<td>1.35 (0.73–2.50)</td>
<td>1.02 (0.43–2.43)</td>
<td>1.28 (0.78–2.12)</td>
</tr>
<tr>
<td>Alternate model: latest CD4+ cell percentage, per 1% higher</td>
<td>0.95 (0.93–0.98)</td>
<td>0.98 (0.94–1.01)</td>
<td>0.96 (0.94–0.98)</td>
<td>0.93 (0.90–0.96)</td>
<td>0.95 (0.90–1.00)</td>
<td>0.93 (0.91–0.96)</td>
<td>0.98 (0.94–1.01)</td>
<td>1.00 (0.95–1.05)</td>
<td>0.98 (0.95–1.01)</td>
</tr>
</tbody>
</table>

**NOTE.** Hazard ratios and 95% confidence intervals (CIs) were estimated by multiple Cox proportional hazards regression. Hazard ratio estimates are adjusted for all variables listed in the table plus baseline and nadir CD4+ cell count, baseline HIV RNA level, and latest CD4+ cell count slope (none of these additional factors contributed independently to the risk of OD/death). Factors significantly associated with risk are shown in boldface.

* Additionally adjusted for treatment group.

** In the global comparison of all 3 strata, HIV RNA level was a statistically significant predictor of the risk of OD (fatal or nonfatal) in the DC group (P = .02).

* Results of the same models with CD4+ cell percentage included instead of CD4+ cell count; in these models, the prognostic information for HIV RNA level, age, and prior diagnosis of AIDS was comparable to the findings in this table for the absolute CD4+ cell count (data not shown).
latest CD4+ cell counts (<250 and 250–349 cells/μL) were comparable for the DC and VS groups (figure 2A). However, as a consequence of the DC strategy, patients in this group spent almost 4-fold more of the follow-up time with their latest CD4+ cell counts being >350 cells/μL; hence, these patients experienced many more OD/death events (63 events during 1096 person-years [5.7 events/100 person-years]) than did the VS patients (13 events during 280 person-years [4.6 events/100 person-years]), resulting in an RR(DC/VS) of 1.2 (95% CI, 0.7–2.3). When the latest CD4+ cell counts were ≥350 cells/μL, the
Table 2. Events by latest CD4+ cell count and HIV RNA level throughout follow-up and, for the drug conservation (DC) group, during the first period of not receiving antiretroviral therapy (ART) (from randomization to ART [re]initiation), the first subsequent period of receiving ART, and the remaining later follow-up time.

<table>
<thead>
<tr>
<th>Event, latest CD4+ cell count, latest HIV RNA level</th>
<th>DC group</th>
<th>VS group</th>
<th>RR(DC/VS)</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD/death ≤350 cells/µL</td>
<td>5.9 (14/237)</td>
<td>1.7 (2/120)</td>
<td>3.6</td>
<td>0.8–15.6</td>
<td>.09</td>
</tr>
<tr>
<td>OD/death &gt;400 copies/mL</td>
<td>5.7 (49/859)</td>
<td>6.9 (11/160)</td>
<td>0.8</td>
<td>0.4–1.6</td>
<td>.57</td>
</tr>
<tr>
<td>OD/death &gt;350 cells/µL</td>
<td>1.9 (15/790)</td>
<td>0.7 (17/2545)</td>
<td>2.8</td>
<td>1.4–5.7</td>
<td>.003</td>
</tr>
<tr>
<td>OD/death &gt;400 copies/mL</td>
<td>2.5 (43/1709)</td>
<td>2.1 (18/856)</td>
<td>1.2</td>
<td>0.7–2.1</td>
<td>.52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DC group, period</th>
<th>First not receiving ART</th>
<th>First receiving ART</th>
<th>Later follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD (fatal or nonfatal) ≤350 cells/µL</td>
<td>3.0 (7/237)</td>
<td>0 (0/120)</td>
<td>9.7 (1/10)</td>
</tr>
<tr>
<td>OD (fatal or nonfatal) &gt;400 copies/mL</td>
<td>4.2 (36/859)</td>
<td>3.8 (6/160)</td>
<td>3.9 (19/489)</td>
</tr>
<tr>
<td>OD (fatal or nonfatal) &gt;350 cells/µL</td>
<td>0.9 (7/970)</td>
<td>0.3 (8/2545)</td>
<td>0.4 (1/281)</td>
</tr>
<tr>
<td>OD (fatal or nonfatal) &gt;400 copies/mL</td>
<td>1.5 (25/1709)</td>
<td>0.9 (8/856)</td>
<td>1.2 (17/1444)</td>
</tr>
</tbody>
</table>

| Non-OD death ≤350 cells/µL                        | 2.8 (7/248)             | 1.7 (2/121)         | 0.0 (0/10)      |
| Non-OD death >400 copies/mL                       | 1.7 (15/881)            | 3.7 (6/164)         | 1.2 (6/493)     |
| Non-OD death >350 cells/µL                        | 1.1 (9/808)             | 0.4 (9/2555)        | 0.4 (1/281)     |
| Non-OD death >400 copies/mL                       | 1.2 (20/1729)           | 1.2 (10/865)        | 1.0 (14/1450)   |

| NOTE. Data are the rate per 100 PY (no. of events/no. of PY). CI, confidence interval; non-OD death, death from causes other than OD; OD, opportunistic disease; OD/death, OD or death; PY, person-years; RR(DC/VS), relative risk for DC vs. VS; VS, viral suppression. |
| a Obtained by Poisson regression. |

The rate of OD/death was approximately twice as high in the DC group than the VS group (58 events during 2499 persons-years [23 events/100 persons-years] and 35 events during 342 persons-years [1.0 events/100 persons-years], respectively), with an RR(DC/VS) of 2.8 (95% CI, 1.4–5.7). In the DC group, OD/deaths were higher in the DC group than the VS group; in the 3 strata with higher latest HIV RNA levels, the differences in rates between the 2 groups were not statistically significant (figure 2B).

To further explore the findings displayed in figures 2A and 2B, time spent with the latest CD4+ cell count ≥350 cells/µL was further broken down into time spent with the latest HIV RNA level ≤400 and >400 copies/mL (table 2). In both the DC and VS group, event rates at a latest CD4+ cell count ≥350 cells/µL were highest when the HIV RNA level was >400 copies/mL. The greater risk at a latest CD4+ cell count ≥350 cells/µL in the DC group than the VS group is explained in large part by the longer time spent with a HIV RNA level >400 copies/mL, allowing for more events to occur (43 OD/deaths during 1709 person-years at a latest CD4+ cell count ≥350 cells/µL and a latest HIV RNA level >400 copies/mL in the DC group, vs. 18 during 856 person-years in the VS group).

Most of the follow-up for the VS patients was spent at CD4+ cell counts ≥350 and HIV RNA levels ≤400 copies/mL (69% of follow-up time), and the rate of OD/death was very low (0.7/100 person-years). The RR(DC/VS) of OD/death at these latest levels was 2.8 (95% CI, 1.4–5.7). In the DC group, OD/deaths at a latest CD4+ cell count ≥350 cells/µL and a latest HIV RNA level ≤400 occurred predominantly while receiving ART (rate of 2.1 during the first period of receiving ART, compared with 0.7 during the first period of not receiving ART). Additionally, person-years while receiving ART and having a CD4+ cell count ≥350 cells/L and an HIV RNA level ≤400 copies/mL were mostly accumulated after the first (re)initiation of ART (509/790 person-years) (table 2) by patients with short initial periods of not receiving ART (median, 4.5 months) and a less favorable risk profile (at baseline, a median CD4+ cell count of 565 cells/µL, a nadir CD4+ cell count of 188 copies/µL, and a prior AIDS rate of 34%, compared with 646 cells/µL, 286 cells/µL, and 19%, respectively, for DC patients who did not [re]initiate ART before 11 January 2006; P < .001 for all 3 variables).
ART and risk of clinical outcome in the DC arm. To
determine whether ART interruption per se was associated with
an increased risk of OD/death in the DC group, analyses accord-
ing to use of ART at entry were done. Overall, OD/death rates for
DC patients were similar for those receiving (3.2/100 person-
years) and not receiving ART (4.0/100 person-years) at entry.
Rates of events during the first period of not receiving ART and
the first subsequent period of receiving ART were also similar for
DC patients who were taking ART at entry (i.e., those who dis-
continued ART) and those who were not (i.e., those who de-
ferred initiation of ART). For example, in the stratum with a
CD4+ cell count ≥350 cells/μL and an HIV RNA level >400
copies/mL, during the first period of not receiving ART, rates
were 1.9 and 2.5/100 person-years for DC patients taking and
not taking ART at entry, respectively. For this same stratum,
during the first period of on ART during follow-up, rates were
6.4 and 4.5/100 person-years, for DC patients taking and not
taking ART at entry.

Analyses were also done for DC patients to determine whether
rates of OD/death were higher immediately after (re)initiating
ART and then declined, which would be consistent with clinical
disease induced by restoration of immune function once ART
was (re)initiated. Rates of OD/death events for DC patients dur-
ing their first period of receiving ART, which started at the first
(re)initiation of ART after the initial deferral or discontinua-
tion of ART at study entry, were 5.2, 4.3, and 5.1/100 person-years
during months 0–4, 4–8, and 8–12 after (re)initiating ART,
respectively. The median CD4+ cell count among those patients
who continued to receive ART increased slightly across the 3
indicated time intervals (369 [interquartile range, 284–492],
401 [322–530], and 411 [323–532] cells/μL, respectively).

DISCUSSION

The SMART study demonstrated that continuous use of ART
was superior to a CD4+ cell count–guided episodic ART strategy
in terms of delaying OD/death [6]. Continuous ART reduced
HIV RNA levels and increased CD4+ cell counts, whereas inter-
ruption of ART resulted in opposite trends. Figure 1 shows that
follow-up CD4+ cell counts tended to be higher and HIV RNA
levels tended to be lower in the continuous ART group (VS) than
in the ART interruption group (DC), as was anticipated per the
design of the SMART study. We previously reported that differ-
ences in CD4+ cell count and HIV RNA level during follow-up
explained most, but not all, of the excess risk of OD, OD/death,
and non-OD death for the DC group compared with the VS
group [6]. The more-detailed analyses conducted here indicated
that the excess risk of OD/death in the DC group compared with
the VS group is likely to be due to 2 factors: (1) DC patients spent
a much greater percentage of follow-up time with CD4+ cell
counts <350 cells/μL than do VS patients, and the risk of OD/
death was substantially greater at those levels than at ≥350 cells/
μL; and (2) DC patients had HIV RNA levels >400 copies/mL
for most of the follow-up time when their CD4+ cell counts were
≥350 cells/μL, and this uncontrolled viral replication even at
these higher CD4+ cell counts was associated with an increased
risk of OD/death.

Although the risk of OD/death was also elevated in DC pa-
tients with a CD4+ cell count ≥350 cells/μL and an HIV RNA
level ≤400 copies/mL, we believe that this can be largely attrib-
uted to clinicians being more likely to have patients in the DC
group at high risk of clinical events continue ART for longer
periods of time while their CD4+ cell counts were ≥350 cells/μL
rather than interrupt ART as per study guidelines. This may have
resulted in these patients spending more time with an HIV RNA
level ≤400 copies/mL than DC patients at less risk of events.
Such selection could have resulted from the study recommenda-
tion to (re)initiate ART early (i.e., before CD4+ cell counts
reached the threshold of <250 cells/μL) on the basis of detection
of symptoms or evidence of a rapid decline in CD4+ cell count.
In support of this explanation, there is evidence that those who
(re)initiated ART were, as a group, already at a higher risk of
clinical disease at baseline. Moreover, decisions to restart ART at
a CD4+ cell count ≥250 cells/μL could have been based on sub-
tle signs of impending clinical disease that a clinician had dis-
cerned but that were not captured in our data. Also, when the
DC strategy was terminated on 11 January 2006, 49% of the
patients were still in their first period of not receiving ART and
had an HIV RNA level >400 copies/mL, which would be ex-
pected to amplify the overrepresentation of high-risk patients
with respect to person-time with an HIV RNA level ≤400 cop-
ies/mL. This selection of DC patients with a higher risk of OD/
death to (re)initiate ART may also explain why the RR of OD/
death associated with the latest HIV RNA levels was weaker in
the DC group. Those who comprised the “denominator” in
these analyses (i.e., those with an HIV RNA level ≤400 copies/
ML) already had a high rate of the outcome.

The inferiority noted with the DC strategy in terms of the 3
clinical events described above was similar in patients who were
taking and not taking ART at study entry, which argues against
treatment interruption per se as the explanation, although it is
important to keep in mind that the number of patients were not
taking ART at entry was relatively small (n = 880).

We also considered the possibility that the occurrence of
higher rates of OD/death in the DC group may be due to se-
quele of (re)initiation of ART as, for example, immune-
restoration disease. However, our data do not appear to support
this hypothesis. This syndrome is also most likely to occur in
patients with more-advanced immunodeficiency [11, 12] than
that observed in this study. Although the rate of OD/death after
ART (re)initiation and while having a HIV RNA level ≤400 cop-
ies/mL in the DC group was higher than the overall rate of OD/
death in the VS group, at least some of these events were ex-
pected to occur because of the lower CD4+ cell count at the time

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when ART was (re)initiated (median, 235 cells/μL) and because of the assumed tendency of clinicians to preferentially admini-
ster ART to patients with emerging symptoms before the event was diagnosed, as discussed above.

The observed association between higher latest CD4+ cell counts and a lower risk of OD in both the DC and VS groups, despite the generally relatively high CD4+ cell counts throughout follow-up, corroborates the findings of a recent study [13] and suggests that the incidence of ODs becomes progressively lower with higher CD4+ cell counts, even for those counts above the current threshold for initiation of ART.

The increased risk in the DC group compared with the VS group when latest CD4+ cell counts were ≥350 cells/μL appears to be explained by the increase in viral replication after cessation of ART. DC patients had much higher HIV RNA levels than did VS patients during the time when CD4+ cell counts were ≥350 cells/μL. The detrimental effect of higher levels of HIV RNA even at high CD4+ cell counts may be due to the impairment of immune function via mechanisms that are not entirely reflected by the number of CD4+ cells in peripheral blood, comparable to reports for primary HIV infection [14–17]. Furthermore, risk of OD is also known to be predicted by markers of immune activation, independently of HIV RNA level and CD4+ cell count [18, 19]. It may be, for example, that HIV RNA level is also acting as a measure of immune activation, in the absence of more-direct measures. Additionally, some organ pathologies may be directly caused by HIV replication [20, 21].

The risk of death from causes other than OD was significantly higher in the DC group than in the VS group, and there was a suggestion that these deaths were also inversely associated with latest CD4+ cell count (table 1), although the association was weaker than that for OD and did not achieve statistical significance. The influence of latest CD4+ cell count is further supported by the reduction in the RR (DC/VS) for non-OD death once adjustment was made for latest CD4+ cell count. These findings confirm recent reports suggesting a detrimental effect of immunosuppression on the risk of fatal outcomes of diseases not traditionally believed to be opportunistic in nature, for example, deaths from liver failure [22–24]. This finding affirms the importance of using combined outcomes (such as OD and all-cause mortality) for assessment of outcomes of HIV-treatment strategies (as was done in SMART), rather than focusing solely on OD and death due to OD as clinical outcomes of interest. Because deaths from causes other than OD dominate among patients receiving ART [22, 25–30], the SMART study finding, along with recent data from observational studies, support consideration of initiating ART before even moderate levels of immunodeficiency develop. However, definitive information to guide such an approach awaits the conduct of a randomized trial approaching the scale of SMART.

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