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Risk of All-cause Mortality Associated with Non-fatal AIDS and Serious Non-AIDS Events among Adults Infected with HIV

Jacqueline NEUHAUS[1], **Brian ANGUS**[2], **Justyna D. KOWALSKA**[3], **Alberto LA ROSA**[4], **Jim SAMPSON**[5], **Deborah WENTWORTH**[1], and **Amanda MOCROFT**[6] **for the INSIGHT SMART and ESPRIT Study Groups**

[1] University of Minnesota, Minneapolis, MN, USA

[2] Nuffield Department of Medicine, Univeristy of Oxford, Oxford, UK

[3] Copenhagen HIV Programme, Copenhagen, Denmark

[4] Asociacion Civil IMPACTA Salud y Educacion, Lima, Peru

[5] The Research and Education Group, Portland, OR, USA

[6] University College London Medical School, Royal Free Campus, London, UK

Abstract

Objectives—Among patients with HIV, the risk of death associated with different AIDS events has been quantified, but the risk of death associated with non-AIDS events has not been examined. We compared the risk of all-cause mortality following AIDS versus serious non-AIDS (SNA) events in SMART and ESPRIT.

Design—Data from 9,583 HIV-infected participants, 5,472 with CD4+ >350 cells/mm^3 enrolled in SMART and 4,111 with CD4+ ≥300 cells/mm^3 enrolled in ESPRIT were analyzed.

Methods—Cumulative mortality 6 months after AIDS and SNA (cardiovascular, renal, hepatic disease and malignancies) was estimated using the Kaplan-Meier method. Cox models were used to estimate hazard ratios (HRs) associated with AIDS and SNA on the risk of death overall and by treatment group within study.

Results—AIDS and SNA occurred in 286 and 435 participants with 47 (16%) and 115 (26%) subsequent deaths, respectively. Six-month cumulative mortality was 4.7% (95%CI:2.8–8.0) after experiencing an AIDS event and 13.4% (95%CI:10.5–17.0) after experiencing an SNA event. The adjusted HR for all-cause mortality for those who experienced AIDS versus those who did not was 4.9 (95%CI:3.6–6.8). The corresponding HR for SNA was 11.4 (95%CI:9.0–14.5) ($p<0.001$ for difference in HRs). Findings were similar for both treatment groups in SMART and both treatment groups in ESPRIT.

Conclusions—Among HIV-infected persons with higher CD4+ counts, SNA events occur more frequently and are associated with a greater risk of death than AIDS events. Future research should

Correspondence: Jacqueline Neuhaus, MS, Division of Biostatistics, School of Public Health, University of Minnesota; 2221 University Ave SE, Suite 200, Minneapolis, MN 55414; jacquie@ccbr.umn.edu.

Contribution of authors

Jacqueline Neuhaus performed statistical analyses and drafted the manuscript, Brian Agnus, Justyna D. Kowalska, Alberto La Rosa and Jim Sampson provided input into analyses and contributed to the interpretation of data and to writing the manuscript. Deborah Wentworth supported statistical analyses and provided input into the analyses and interpretation of data. Amanda Mocroft contributed to the development of the project, provided input into the analyses and interpretation of data, and contributed to writing the manuscript. All authors have approved the final version.

be aimed at comparing strategies to reduce morbidity and mortality associated with SNA events for HIV-infected persons.

Keywords

HIV; cardiovascular disease; renal disease; hepatic disease; malignancies; mortality

Introduction

There is emerging evidence that HIV increases the risk of serious events other than AIDS, such as cardiovascular, renal and hepatic events and malignancies,[1] and the incidence of these events appears higher than that of AIDS events at higher CD4+ cell counts.[2,3]

While several studies have examined the risk of death following different AIDS-related events,[4–9] the risk of death following different serious non-AIDS events in HIV-infected persons has not been studied, nor has the relative impact of AIDS and non-AIDS events in terms of subsequent mortality been reported. Such information would be useful for targeting specific interventions and for prioritizing future research.

We used data from two large international randomized clinical trials in HIV-infected patients with high CD4+ counts, the Strategies for Management of Anti-Retroviral Therapy (SMART) trial and the Evaluation of Subcutaneous Proleukin® in a Randomized International Trial (ESPRIT) to examine the risk of all-cause mortality after experiencing AIDS and serious non-AIDS events. AIDS events were further categorized as serious and non-serious based on earlier work[4]; non-AIDS events were subdivided as cardiovascular, renal, hepatic or malignancies. We hypothesized that the risk of death differed following AIDS versus non-AIDS events and that this risk also varied by type of AIDS and non-AIDS events.

Methods

Study Population

The design, methods and results of the SMART study have been published.[10,11] A total of 5472 participants with CD4+ count >350 cells/mm^3 were randomized to either CD4+ guided episodic use of antiretroviral therapy (ART) (DC group) or to continuous use of ART (VS group). Median (IQR) follow-up was 2.4 (1.8–3.5) years.

The design, methods and results of ESPRIT have also been reported.[12,13] A total of 4,111 participants with a CD4+ count ≥300/mm^3 were included in the analysis cohort and were randomized to interleukin-2 (IL-2) plus continuous ART or to continuous ART alone. Median (IQR) follow-up was 6.8 (5.7–7.6) years.

In both SMART and ESPRIT local practice guidelines were consulted for use of preventive treatments for opportunistic diseases and for serious non-AIDS conditions. Likewise, the treatment of these conditions was not directed by either protocol and were managed according to local clinical guidelines.

Events

A medical history was obtained prior to randomization for participants in both SMART and ESPRIT. A history of AIDS events, hepatic events, and cardiovascular disease (CVD) events was collected in both studies. History of non-AIDS cancers and renal disease was only available for SMART participants. Due to the use of IL-2, Inclusion and exclusion criteria were more restrictive in ESPRIT than SMART with respect to past events. For example, in ESPRIT, patients were required to not have evidence of active clinical disease for at least one year for

any AIDS condition. In addition, patients with malignancies who were taking cytoxic chemotherapy were not eligible.

AIDS events (henceforth called AIDS) were defined in SMART[10] and ESPRIT[13] according to the revised clinical case definition for AIDS published by the Centers for Disease Control and Prevention[14], as well as additional conditions related to immunodeficiency. Serious AIDS events that were pre-specified in each protocol were progressive multifocal leukoencephalopathy, lymphoma, visceral Kaposi's sarcoma, AIDS dementia complex, toxoplasmosis, histoplasmosis, cryptococcosis, Mycobacterium Avium Complex disease, wasting syndrome, and cytomegalovirus disease.[4]

Serious non-AIDS events (henceforth called SNA) included: 1) major cardiovascular disease (CVD) events: myocardial infarction (MI), stroke, or coronary artery disease (CAD) requiring an invasive procedure; 2) end stage renal disease (ESRD); 3) decompensated cirrhosis; and 4) all non-AIDS defining malignancies, excluding non-melanomatous skin cancers.

Multiple events of a given type were not included. AIDS and SNA events were considered if the participant survived at least 1 day after diagnosis. One fatal (survival < 1 day) AIDS and 11 fatal non-AIDS events occurred and were not included in the AIDS and SNA event categories. For both studies, all AIDS and SNA events and deaths were reviewed by a Clinical Events Committee, blinded to treatment group. Underlying cause of death was classified using the system of the Coding of Death in HIV Project.[15]

Statistical Analysis

Cox proportional hazards models, stratified by study and treatment group, were used to examine predictors for AIDS and SNA events including the following covariates: age, gender, race, body mass index (BMI), blood-pressure medication, lipid-lowering medication, hepatitis co-infection, nadir CD4+, prior SNA, prior AIDS, and time-updated CD4+ count and HIV-RNA (≤500 versus >500 copies/ml).

Cox models for survival (with date of randomization as time zero) that included an indicator for the event of interest as a time-updated covariate were used to assess the effect of AIDS or SNA on the risk of death. For example, when assessing the risk of an AIDS event on subsequent mortality, a variable representing AIDS took a value of 0 before the event and 1 thereafter for participants who experienced an AIDS event; participants who did not experience an AIDS event took a value of 0 throughout follow-up. These models were stratified by study and treatment group. Adjusted Cox models included age, gender, race, baseline CD4+ count, nadir CD4+count, baseline HIV-RNA (≤500 versus >500 copies/ml) and time-updated CD4+ count and HIV-RNA (≤500 versus >500 copies/ml). To examine whether the risk of death following an AIDS or SNA event varied by study or treatment group within study, expanded Cox models were considered with interaction terms. To assess whether the increased risk of death for SNA versus AIDS varied by time period after the event, hazard ratios for death associated with SNA and AIDS were calculated for the first 6 months and for after 6 months following the diagnosis of the event by including time-updated covariates for the two time periods. Selected analyses were also considered after excluding those with a history of AIDS or SNA at study entry.

Among those who experienced AIDS and SNA events, Kaplan-Meier estimates of the cumulative percent dead at 6 and 12 months after AIDS and SNA events were determined. The time from the first AIDS and SNA event until death was depicted using a Kaplan-Meier plot. Predictors of mortality following an event were examined using Cox models (with the date of the event as time zero) stratified by study and treatment group. Covariates considered for mortality following an AIDS event were age, gender, race, BMI, nadir CD4+ count, AIDS or non-AIDS event prior to study entry, and CD4+ count and HIV-RNA prior to non-fatal event.

An additional multivariate model was assessed adding an indicator for whether or not the AIDS event met the serious definition. For mortality following SNA, baseline diabetes, hepatitis B or C co-infection, use of lipid-lowering medication and use of blood-pressure medication were considered in addition to the covariates considered for AIDS. Smoking status was available for SMART participants, but not for ESPRIT participants. Thus, an analysis examining predictors for mortality following SNA events for only SMART participants, including smoking status in addition to the covariates listed above, was also carried out.

Statistical analyses were performed using SAS, Version 9.1 (Cary, NC, USA). All reported p-values are two-sided.

Role of the Funding Source

SMART and ESPRIT were funded by the National Institute of Allergy and Infections Disease. As members of the International Network for Strategic Initiative in Global HIV Trials Executive Committee, funding source staff participated in the review of the paper but were not part of the writing group.

Results

Demographic and HIV Disease Characteristics

As previously reported,[10,13] median CD4+ levels at study entry for SMART and ESPRIT were 597 and 457, respectively. The percent with HIV-RNA ≤500 was 72.6 for SMART and 79.7 for ESPRIT. Eighty-four percent of participants in SMART were on ART at study entry and all ESPRIT participants were required to be on or initiating ART at the time of randomization. Median time since first taking ART was 6.0 years for SMART and 4.2 years for ESPRIT.

Overall, twelve percent of participants had BMI levels of 30 kg/m^2 or greater. Forty percent of SMART participants were current smokers and 42% had cholesterol levels of 200 or greater at study entry (these data were not collected in ESPRIT).

Table 1 shows baseline characteristics and latest CD4+ and HIV-RNA levels by non-fatal event status. AIDS events occurred in 286 participants (158 in SMART and 128 in ESPRIT) at a rate of 0.7 per 100 person-years. SNA events occurred in 435 participants (205 in SMART and 230 in ESPRIT) at a rate of 1.0 per 100 person-years. Median (IQR) months from randomization to AIDS was 20 (8–32) for SMART and 36 (20–62) for ESPRIT for those who experienced an event. Median (IQR) months from randomization to SNA was 17 (9–31) for SMART and 45 (23–65) for ESPRIT. Median (IQR) follow-up time following AIDS and SNA was 17 (7–28) months for SMART and 31 (11–57) months for ESPRIT. Independent predictors for AIDS events included older age (p=0.0007), history of AIDS (p<0.0001), lower latest CD4+ (p<0.0001) and latest HIV-RNA >500 (p<0.0001). Independent predictors associated with SNA included older age (p<0.0001), male gender (p=0.0006), use of blood-pressure medication (p=0.009), use of lipid-lowering medication (p=0.02), nadir CD4+ (p=0.05), history of SNA (p=0.03) and latest HIV-RNA >500 (p=0.03).

Twenty-eight percent of participants experiencing an AIDS event had latest CD4+ levels <250 $cells/mm^3$ compared to 9% for those with a SNA event. Median (IQR) days from latest CD4 + to event was 43 (20–77) for AIDS and 48 (22–74) for SNA. Participants who experienced an AIDS event, an SNA event and no event spent 12%, 4% and 2% of follow-up time with CD4+ levels <250 and 55%, 76% and 76% of follow-up time with HIV-RNA levels ≤500, respectively.

Mortality associated with Non-fatal AIDS and SNA Events

Overall, there were 167 deaths (rate= 1.1 per 100 person years; 95%CI: 0.9 to 1.3) in SMART and 223 deaths (rate = 0.8 per 100 person years; 95%CI: 0.7 to 0.9) in ESPRIT. In SMART, but not ESRPIT, death rates differed by treatment group. Rates were 1.4 (per 100 person-years; 95%CI: 1.1 to 1.6) for the DC group and 0.8 (per 100 person-years; 95%CI: 0.6 to 1.0) for the VS group.

Forty-seven participants (16%) who experienced AIDS and 115 participants (26%) who experienced SNA subsequently died. In those who died, median (IQR) months from the event to death was 9 (6–21) for AIDS and 6 (2–19) for SNA. Twenty-six of the 47 deaths (55%) occurring after a non-fatal AIDS event were due to AIDS-related causes and 87 of the 115 deaths (76%) after a SNA event were due to SNA-related causes, including 60 cancer-related, 14 CVD-related and 13 hepatic-related deaths. Twenty-five participants experienced both an AIDS and SNA event and are included in both event categories; 8 of these participants died.

Six and 12-month cumulative mortality after experiencing an AIDS event were 4.7% (95% CI: 2.8 to 8.0) and 11.1% (95%CI: 7.9 to 15.7), respectively. These percentages were greater after experiencing an SNA event; 13.4% (95%CI: 10.5 to 17.0) and 19.0% (95% CI: 15.5 to 23.2) for 6 and 12 month estimates (Table 2 and Figure 1), respectively. Mortality following SNA was highest for hepatic events, renal events and malignancies with 12 month estimates of 39.7%, 32.7% and 29.5 %, respectively (Table 2). The most common non-AIDS malignancy was lung cancer for which 12 month mortality was 61.2%. The Kaplan-Meier plot (Figure 1) shows a significantly higher risk of death following SNA events in comparison to the risk following AIDS events (log rank 11.86, p=0.0006).

The univariate HR for all-cause mortality for those who experienced an AIDS event vs. those who did not was 7.4 (95% CI: 5.4 to 10.1). The corresponding unadjusted HR for SNA was 17.6 (95%CI: 14.0 to 22.2). After adjusting for baseline covariates and latest CD4+ count and HIV-RNA, HRs for death for those who experienced AIDS and SNA were 4.9 (95% CI: 3.6 to 6.8) and 11.4 (95% CI: 9.0 to 14.5), respectively ($p<0.001$ for difference in HRs) (Figures 2a and 2b). Results were consistent across studies and p-values for tests for homogeneity across treatment groups for SMART, ESPRIT and SMART/ESPRIT combined were 0.77, 0.57 and 0.93 for AIDS events and 0.49, 0.10 and 0.25 for SNA events, respectively. Risk of death was greater in the early follow-up period after SNA events. For example, in the first 2 months following an SNA event, the risk of death was 40.8 (95% CI: 27.0–61.5). By 6 months this HR was 27.6 (95%CI: 20.3 to 37.5)), and after 6 months it was 7.1 (95%CI: 5.3 to 9.6)). The HRs for death in the first 6 months following AIDS and afterwards were 5.8 (95%CI: 3.3 to 10.2) and 4.6 (95% CI: 3.2 to 6.7), respectively. During the first 6 months following a non-fatal event, the risk of death was significantly greater for SNA than AIDS ($p<0.0001$). This difference was not seen after the first 6 months (p=0.49).

Adjusted HRs for all-cause mortality associated with the different types of SNA events were 3.0 (95%CI: 2.0 to 4.6) for CVD events, 16.8 (95%CI: 7.3 to 38.7) for renal events, 19.5 (95% CI: 11.4 to 33.4) for hepatic events and 14.6 (95%CI: 11.1 to 19.3) for non-AIDS malignancies (Figure 3). The adjusted HR for death associated with lung cancer was 22.9 (95%CI: 13.8 to 37.8). Risk of death also varied according to type of AIDS events. The adjusted HR for death following serious AIDS events was 10.8 (95%CI: 7.3 to 16.1); for all other AIDS events it was 3.1 (95%CI: 2.0 to 4.7).

Results were similar when excluding participants with a history of AIDS or SNA events prior to randomization. When excluding participants with a history of an AIDS event, the adjusted HR for death associated with AIDS events during follow-up was 6.0 (95% CI: 4.0 to 8.9). Similarly, when excluding participants with a history of an SNA event, the adjusted HRs for

death associated with SNA events during follow-up in SMART (patients with a history of CVD, non-AIDS cancer, cirrhosis and ESRD excluded) and ESPRIT (patients with a history of CVD or cirrhosis excluded) were 15.4 (95% CI: 10.1 to 23.3) and 11.3 (95% CI: 8.1 to 15.8), respectively.

Predictors for Mortality following AIDS or SNA Events

In a multivariate analysis, older age (HR per 10 years older=1.4 (95%CI: 1.0 to 1.9), p=0.04) and lower CD4+ count prior to the non-fatal event (HR per 100 cells higher=0.9 (95%CI: 0.7 to 1.0), p=0.04) were associated with death following an AIDS event. When adding an indicator for whether or not the AIDS event met the serious definition, age and latest CD4+ remained significant and experiencing a serious AIDS event was associated with an increased risk of death (HR=6.3 (95%CI: 3.2 to 12.4), p<0.0001). Predictors associated with death following an SNA event were older age (HR per 10 years older=1.4 (95%CI: 1.1 to 1.8), p=0.002), viral hepatitis (B and/or C) co-infection (HR=2.0 (95%CI: 1.2 to 3.3), p=0.007) and diabetes (HR=1.7 (95%CI: 1.0–3.0), p=0.05). In an analysis of only SMART patients, smoking status was not an independent predictor of mortality following a SNA event (HR=1.6 (95%CI: 0.8 to 3.1), p=0.14).

Discussion

The number of participants who experienced SNA events in the SMART and ESPRIT studies exceeded those who experienced AIDS events by almost 50% (435 versus 286 events). As compared to participants who did not develop such an event, the risk of death following SNA events was twice as high compared to AIDS events. This difference in mortality risk for the different types of events was apparent early on and was maintained throughout the follow-up period.

This is consistent with other studies that have shown that, in the era of combination antiretroviral therapy, SNA events dominate morbidity at high CD4+ counts[2,16,17] and may even occur more frequently than AIDS events in individuals with advanced HIV.[18] Additionally, the majority of deaths in HIV-infected persons are now due to non-AIDS causes.[19–21] In this study, the median CD4+ cell counts prior to AIDS and SNA events were 356 cells/mL (IQR: 227–540) and 518 cells/mL (IQR: 360–727), respectively.

As noted in other studies[9], we found that not all AIDS events were associated with the same risk of death. The HR for death following serious AIDS events, events which were associated with a higher risk of death before the availability of HAART,[4] was 10.8 compared to 3.1 for all other AIDS events. Recent studies have reported that the risk of death following non-Hodgkin's lymphoma is particularly high.[9,22] In our study, 64% of the serious AIDS events were lymphomas (of any type) which resulted in a HR for death of 9.5.

SNA events were shown to be not only more frequent, but also related to significantly higher mortality than AIDS events. Most of the SNA events in SMART and ESPRIT were CVD and cancer, with substantially fewer renal and hepatic events. Preventing SNA events in some patients may be clinically possible.[23] Prevention of CVD is important as it remains the most common SNA event and contributes significantly to all cause mortality. Decreasing modifiable CVD risk factors could thus have an impact on mortality in HIV-infected individuals. Additionally, it has been shown that HIV-infected patients are as likely to achieve conventional risk factor treatment goals, such as normalizing blood pressure or lipid levels, as HIV-uninfected patients.[24] The risk of death after experiencing a CVD event did not increase substantially after the first six months following the event. This is similar to reports in the general population in which the risk of death following CVD events was greatest in the early time period after hospitalization with such an event.[25,26]

Along with CVD, malignancies were the other most common type of SNA events in this analysis and contributed substantially to all-cause mortality. It has been shown that for some non-AIDS defining malignancies there might be a benefit in routine screening.[27] Despite this, HIV-infected patients are not always undergoing the same routine cancer screening tests as the general population.[28] In addition, there are major risk factors, such as HCV and HBV infection, tobacco smoking or heavy alcohol consumption, which may contribute to specific non-AIDS malignances and can be addressed in clinical practice.[29] In our study, lung cancer and prostate cancer were the most common cancers and for these cancers mortality risk varied considerably, consistent with data from the general population.[25,26,30–32]

In our study, older age, diabetes and co-infection with hepatitis B or C were independent predictors for death following a non-AIDS event. This finding, along with prior information that patients with diabetes are at an increased risk of death following MI[33] and cancer[34] events in the general population, emphasizes the importance of identifying and properly managing patients with diabetes and other risk factors in order to prevent the occurrence of non-fatal events as well as to increase survival following these events. In contradiction to the findings with AIDS events, latest CD4+ was not an independent predictor for death following a non-AIDS event in our study. This may be due to the fact that these events occurred at higher CD4 + cell counts and that most of the follow-up time was spent at relatively high CD4+ counts.

Excluding participants with a history of non-fatal events at enrollment into SMART and ESPRIT did not change our results. Both studies enrolled relatively healthy participants with high CD4+ levels and patients were not permitted to enroll in ESPRIT if there was any evidence of active clinical disease within the year prior to randomization. AIDS and SNA events experienced prior to enrollment most likely occurred long enough before enrollment into SMART and ESPRIT to allow participants to recover from the non-fatal event attenuating the impact of any disease that occurred prior to enrollment.

The prevalence of risk factors, such as smoking, obesity, and elevated cholesterol levels, for the development of SNA events is high in our cohort and this has been noted in other HIV studies.[35] A recent report found that mortality among patients who start ART, survive the first 6 months, and achieve an HIV-RNA level $\leq$ 500 copies/mL and CD4+ count $\geq$ 350 cells/mm^3 is modestly higher than in the general population.[36] The higher mortality may be due to these other risk factors. This highlights the importance of smoking cessation and the management of other modifiable risk factors.

There are some limitations to this study. We studied HIV-infected participants with higher CD4+ counts who met eligibility criteria for the randomized trials. While both trials had broad inclusion criteria, participants who developed events may have been healthier than a random sample of HIV-infected participants. Another limitation was that smoking status was not collected in ESPRIT and hepatitis status and use of lipid lowering and blood-pressure lowering drugs was not available for all ESPRIT participants.

In summary, we have shown by pooling results form 2 large studies in nearly 10,000 HIV-infected patients with carefully documented and adjudicated AIDS and SNA events, that the risk of death is greater following SNA than AIDS events. This finding is important given the much greater frequency of SNA than AIDS events. Further, the risk of death varies by type of AIDS and SNA event. These results have implications for defining major outcomes in clinical studies and for setting priorities for the development and evaluation of interventions to reduce morbidity and mortality among patients infected with HIV.

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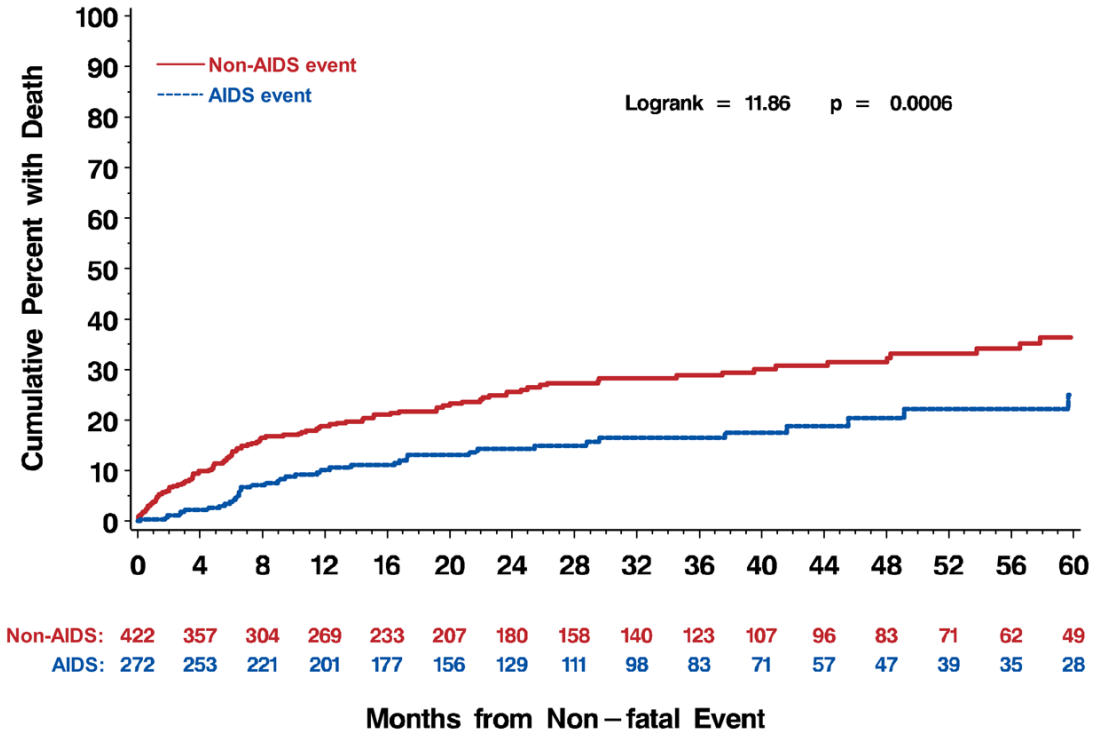

Figure 1.
Time from AIDS or SNA event to death. SMART and ESPRIT combined.

Figure 2a.

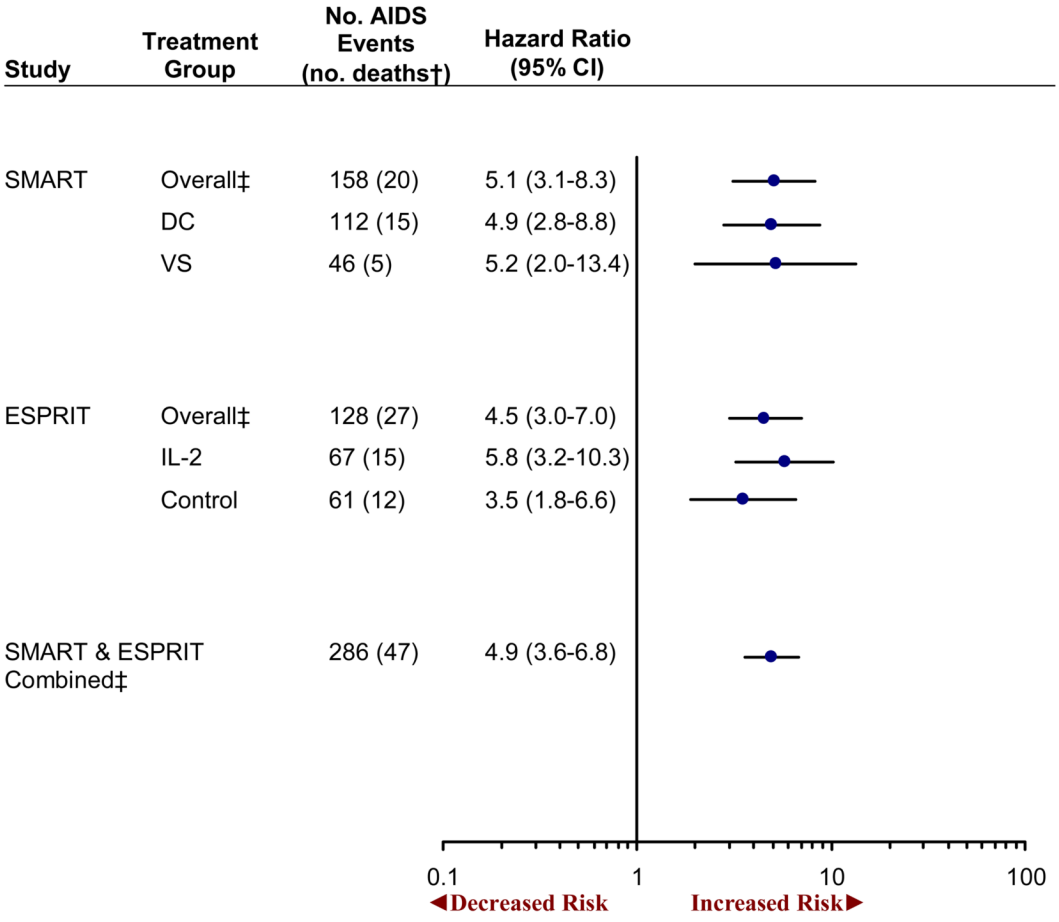

Figure 2b.

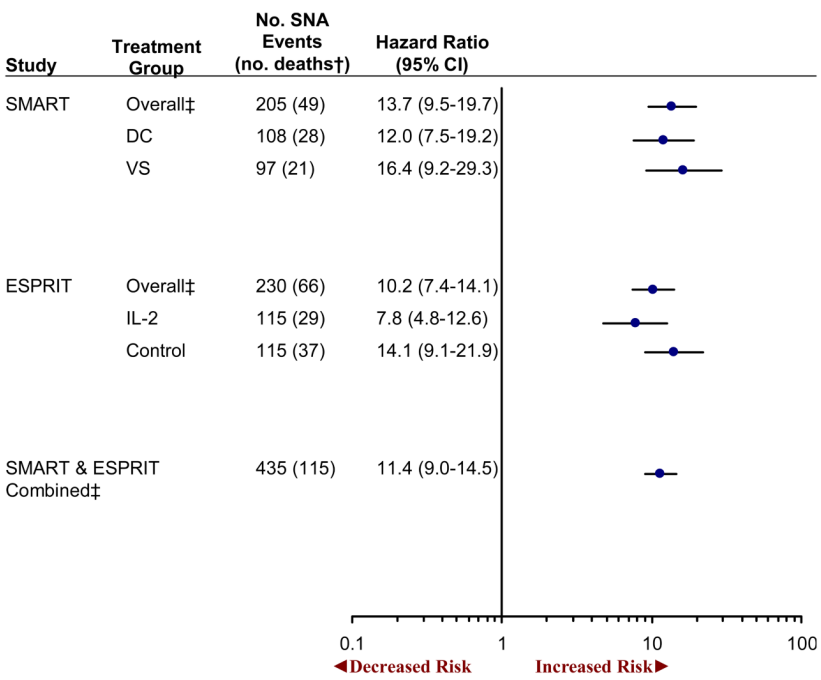

Figure 2.

Figure 2a. Adjusted* hazard ratios for death associated with AIDS events during follow-up. Interaction p-values across treatment groups for SMART, ESPRIT and combined are 0.77, 0.57, 0.93 respectively.

Figure 2b. Adjusted* hazard ratios for death associated with SNA events during follow-up. Interaction p-values across treatment groups for SMART, ESPRIT and combined are 0.49, 0.10, 0.25 respectively.

*Adjusted for age, gender, black race, baseline CD4, baseline HIV-RNA (> 500 copies), nadir CD4, and latest CD4 and HIV-RNA (> 500 copies)

†Deaths occurring after AIDS event

‡Stratified by treatment group and study

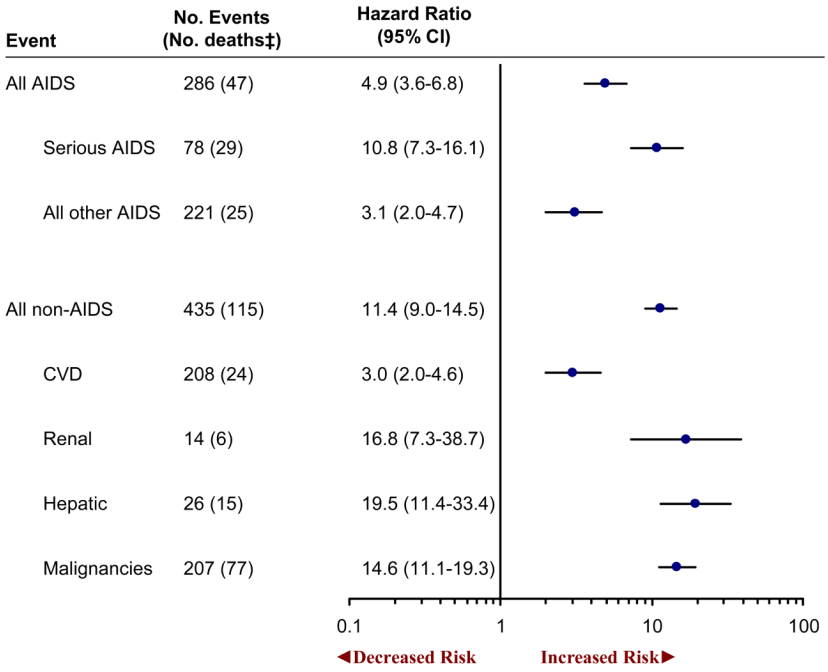

Figure 3.

Adjusted* hazard ratios† for death associated with types of AIDS and SNA events during follow-up. SMART and ESPRIT combined.

*Adjusted for age, gender, black race, baseline CD4, baseline HIV-RNA (> 500 copies), nadir CD4, and latest CD4 and HIV-RNA (> 500 copies)

†Stratified by treatment group and study

‡Deaths occurring after AIDS or SNA event

Table 1

Characteristics of SMART and ESPRIT Participants with and without AIDS or SNA Events*

	SMART			ESPRIT			SMART and ESPRIT Combined		
	No Event	AIDS	Serious Non-AIDS	No Event	AIDS	Serious Non-AIDS	No Event	AIDS	Serious Non-AIDS
N (DC/VS or IL2/ Control)	5122 (2509/2613)	158 (112/46)	205 (108/97)	3765 (1897/1868)	128 (67/61)	230 (115/115)	8887	286	435
Age at baseline (median; IQR)	43 (37, 50)	45 (40, 52)	50 (44, 57)	39 (34, 46)	43 (36, 48)	49 (41, 55)	42 (36, 48)	43 (38, 51)	49 (43, 56)
Gender (% female)	27.4	28.5	18.5	19.3	18.8	6.1	24.0	24.1	12.0
Race (% black)	28.6	35.4	39.5	9.4	7.0	6.1	20.5	22.7	21.9
BMI at baseline (median; IQR)	24.9 (22.4, 28.0)	25.0 (22.6, 28.3)	25.1 (22.3, 28.4)	23.7 (21.9, 25.9)	24.3 (21.9, 26.6)	24.0 (22.0, 26.4)	24.4(22.1, 27.1)	24.7 (22.1, 27.9)	24.4 (22.1, 27.3)
BP-lowering drug use at baseline (%)	15.3	23.4	38.0	4.7	2.9	15.3	12.8	15.3	27.1
Lipid-lowering drug use at baseline (%)	17.9	17.7	29.3	9.5	10.7	20.0	13.1	14.9	24.8
Hepatitis B or C co-infected (%)	16.6	25.9	22.0	21.9	20.0	23.0	18.6	23.6	22.5
Nadir CD4+ (median; IQR)	250 (157, 359)	234 (140, 348)	230 (108, 303)	199 (92, 308)	168 (70, 285)	180 (80, 274)	230 (125, 342)	208 (110, 311)	200 (94, 300
Baseline CD4+ (median; IQR)	598 (467, 792)	556 (456, 728)	575 (449, 780)	457 (372, 583)	415 (346, 572)	474 (386, 590)	528 (416, 704)	495 (390, 655)	512 (415, 671)
Baseline HIV-RNA $\leq$ 500 copies/ mL (%)	73.2	55.7	70.6	80.5	56.7	80.9	76.3	56.1	76.0
History of AIDS at baseline (%)	23.5	41.1	29.8	25.6	31.3	28.3	24.4	36.7	29.0
History of CVD at baseline (%)	3.4	3.2	9.8	0.8	0.8	4.4	2.3	2.1	6.9
History of cirrhosis at baseline (%)	0.4	0.6	2.0	0.3	0.9	1.1	0.4	0.7	1.5
History of non-AIDS cancer at baseline	2.2	6.3	6.3	NA	NA	NA	--	--	--
History of ESRD at baseline (%)	0.1	0.6	0	NA	NA	NA	--	--	--
Latest CD4+ prior to event (median; IQR)†	570 (429, 756)	343 (243, 505)	485 (360, 657)	608 (443, 825)	373 (209, 586)	568 (365, 816)	586 (435, 786)	356 (227, 540)	518 (360, 727)

	SMART			ESPRIT			SMART and ESPRIT Combined		
	No Event	AIDS	Serious Non-AIDS	No Event	AIDS	Serious Non-AIDS	No Event	AIDS	Serious Non-AIDS
Latest HIV-RNA prior to event ≤ 500 (%)†	77.1	29.1	58.5	88.4	51.6	80.4	81.9	39.2	70.1
Number (%) of subsequent deaths	103 (2.0)	20 (12.7)	49 (23.9)	133 (3.5)	27 (21.1)	66 (28.7)	236 (2.7)	47 (16.4)	115 (26.4)

*13 SMART and 12 ESPRIT participants experienced both an AIDS and SNA event, 5 and 3 subsequently died, respectively.

†Latest levels are levels prior to event for participants with events and last follow-up measurement for participants without events.

DC=DC group; VS=VS group; NA=not available

Table 2

Risk of death after experiencing an AIDS or SNA event during SMART or ESPRIT

			Estimated Mortality (Cumulative Percent and 95% CI)	
Non-fatal Event	**No. with event**	**No. (%) deaths**	**6 month KM estimate**	**12 month KM estimate**
AIDS	**286**	**47 (16.4)**	**4.7 (2.8–8.0)**	**11.1 (7.9–15.7)**
-Serious AIDS*	78	29 (37.2)	8.1 (3.7–17.1)	29.0 (19.8–41.4)
-All other AIDS†	221	25 (11.3)	5.2 (2.9–9.1)	7.2 (4.4–11.7)
Serious non-AIDS	**435**	**115 (26.4)**	**13.4 (10.5–17.0)**	**19.0 (15.5–23.2)**
-CVD	208	24 (11.5)	4.9 (2.7–8.9)	6.1 (3.5–10.5)
- MI	93	7 (7.5)	4.3 (1.6–11.1)	4.3 (1.6–11.1)
- Stroke	40	8 (20.0)	13.2 (5.7–28.9)	16.3 (7.6–32.8)
- CAD	133	11 (8.3)	1.5 (0.4–5.9)	2.4 (0.8–7.2)
-Renal	14	6 (42.9)	21.4 (7.5–52.8)	32.7 (13.1–67.0)
-Hepatic	26	15 (57.7)	35.7 (20.4–57.4)	39.7 (23.7–61.2)
-Malignancies‡	207	77 (37.2)	19.8 (14.9–26.1)	29.5 (23.5–36.6)
- Lung	44	30 (68.2)	41.6 (28.2–58.2)	61.2 (46.1–76.6)
- Prostate§	25	2 (8.0)	4.3 (0.6–27.1)	4.3 (0.6–27.1)
- Anal	29	4 (13.8)	7.0 (1.8–25.3)	11.1 (3.7–30.6)
AIDS or serious non- AIDS	**696**	**154 (22.1)**	**9.5 (7.6–12.0)**	**15.5 (12.9–18.6)**

*PML (n=1), lymphoma (n=50), visceral KS (n=0), AIDS dementia complex (n=5), toxoplasmosis (n=3), histoplasmosis (n=1), cryptococcosis (n=6), MAC (n=1), wasting syndrome (n=8), and cytomegalovirus disease (n=3).

†Most common events were esophageal candidiasis (n=70), PCP (n=34), TB (n=23), mucocutaneous KS (n=22) and bacterial pneumonia (n=22).

‡Most common types of cancer were lung (n=44), prostate (n=25) and anal (n=29).

§Out of 7,331 males.