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# Determination of the Underlying Cause of Death in Three Multicenter International HIV Clinical Trials

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## Abstract

**Purpose—**Describe processes and challenges for an Endpoint Review Committee (ERC) in determining and adjudicating underlying causes of death in HIV clinical trials.

**Method—**Three randomized HIV trials (two evaluating interleukin-2 and one treatment interruption) enrolled 11,593 persons from 36 countries during 1999–2008. Three ERC members independently reviewed each death report and supporting source documentation to assign underlying cause of death; differences of opinion were adjudicated.

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**Results—**Of 453 deaths reported through January 14, 2008, underlying causes were as follows: 10% AIDS-defining diseases, 21% non-AIDS malignancies, 9% cardiac diseases, 9% liver disease, 8% non-AIDS-defining infections, 5% suicides, 5% other traumatic events/accidents, 4% drug overdoses/acute intoxications, 11% other causes, and 18% unknown. Major reasons for unknown classification were inadequate clinical information or supporting documentation to determine cause of death. Half (51%) of deaths reviewed by the ERC required follow-up adjudication; consensus was eventually always reached.

**Conclusion—**ERCs can successfully provide blinded, independent, and systematic determinations of underlying cause of death in HIV clinical trials. Committees should include those familiar with AIDS and non-AIDS-defining diseases and have processes for adjudicating differences of opinion. Training for local investigators and procedure manuals should emphasize obtaining maximum possible documentation and follow-up information on all trial deaths.

### Keywords

cause of death; endpoint review committees; clinical trials; HIV; mortality

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For large randomized clinical trials evaluating new treatments or new therapeutic strategies, both overall mortality and cause-specific mortality are important clinical endpoints. Identifying causes of death in HIV-infected patients in the HAART era is critically important for defining the changing epidemiology of HIV disease, understanding potential side effects of antiretroviral therapy (e.g., development of cardiac or liver disease), optimizing HIV clinical management, and designing or interpreting results of clinical trials.[1–13]

Death certificates often classify causes of death as immediate, contributing, and underlying. *Immediate cause of death* is typically defined as the disease or injury directly leading to death, *contributing causes of death* are defined as diseases or injuries that contributed to the fatal outcome, and *underlying cause of death* is defined as the disease or injury that initiated the train of morbid events leading directly to death or the circumstances of the accident or violence that produced the fatal injury. Although many patients have an acute cardiac or respiratory event as the immediate cause of death, underlying cause is typically adopted for tabulation of mortality statistics by organizations including the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).[14,15]

Several analyses have found that endpoint review or clinical event committees may be useful for classifying specific causes of death, especially if such committees review medical records and other documentation.[16–20] Such committees can provide a blinded, objective, and systematic mechanism for evaluating and adjudicating events, including specific causes of death, in clinical trials. Most publications describing use of such committees to classify causes of death have been from cardiovascular or cancer studies, and few reports have described the use of such committees in HIV clinical trials.

In this analysis, we describe how reporting and review of deaths were conducted in three large, multicenter, international HIV clinical trials conducted during 1999–2008, highlight some of the ongoing challenges with classifying cause of death in such studies, and describe the leading underlying causes of death that were evaluated and adjudicated by an Endpoint Review Committee (ERC).

## METHOD

### Studies

Deaths were reported from three multicenter, international randomized HIV clinical trials. The Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) study is

an ongoing open-label trial comparing use of subcutaneous interleukin-2 (IL-2) plus antiretroviral therapy (ART) to ART use alone in participants with baseline CD4+ lymphocyte counts of ≥300 cells/mm$^3$.[21] This study randomized 4,150 patients enrolled during 2000–2003 from 259 international sites. The Subcutaneous Recombinant Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts under Active Antiretroviral Therapy (SILCAAT) study is another ongoing open-label trial comparing use of IL-2 plus ART to ART alone in participants with baseline CD4+ counts of 50–299 cells/mm$^3$.[22] The study randomized 1,971 patients enrolled during 1999–2002 from 139 international sites. The Strategies for Management of Antiretroviral Therapy (SMART) study is a completed study that compared continuous use of ART to episodic use (ART deferred until CD4+ count was <250 cells/mm$^3$ and resumed until CD4+ count was >350 cells/mm$^3$).[4] The study randomized 5,472 patients enrolled during 2002 through January 2006 from 318 international sites.

Of 11,593 HIV-positive persons enrolled from 36 countries in these three studies, 43% were from North America, 34% Europe, 12% South America, 5% Asia, 4% Oceania, and 1% the Middle East or Africa. Twenty-two percent were female and 78% male; 19% were black, 67% Caucasian, and the remainder of other race/ethnicity. The mean age at baseline was between 40 and 41 years for those in ESPRIT and SILCAAT and 44 years for those in SMART. The median baseline CD4+ counts at enrollment were 201 cells/mm$^3$ for SILCAAT, 458 cells/mm$^3$ for ESPRIT, and 597 cells/mm$^3$ for SMART; the median CD4+ nadir counts were 60 cells/mm$^3$ for SILCAAT, 199 cells/mm$^3$ for ESPRIT, and 250 cells/mm$^3$ for SMART.

## Reporting of Death and Pre-Review

All three studies required that deaths be reported within 1 week from the time of site awareness. Death report forms requested information on date of death and a brief narrative description of the death. For one study (SMART), investigators were asked to list in their clinical judgment “what was the primary cause(s) of death”; up to three diagnoses could be listed. For the other two studies, investigators were asked to list on the reporting form “clinical features (cause of death) associated with this event” (up to 4); they were asked to “record a disease or clinical syndrome if established; otherwise record signs or symptoms.” Study sites were asked to provide copies of death certificates, autopsy reports, clinic notes, hospital records, discharge summaries, and any other relevant and available supporting source documentation. Death report forms completed by local site investigators or clinical research nurses were sent with source documentation to the site’s national or regional coordinating center and from there to the study’s data management coordination center. Forms were reviewed at each step to evaluate whether they were filled out completely, supporting source documentation was provided (if referenced), and non-English records were translated. In some cases, study sites were queried for additional documentation or other clinical information. Supporting documentation was reviewed to ensure that participant names and other personal identifiers were redacted, along with any information (including CD4+ count) that may have divulged to which treatment arm the participant had been assigned.

## Endpoint Review Committee and Review Process

Death reports and supporting source documentation were sent to and reviewed by three ERC members who were blinded to treatment allocation. The 14 members of the ERC included two cardiologists and two neurologists; the other 10 reviewers, including the ERC Co-Chairs, were experienced HIV clinicians/investigators. ERC members reflected the geographic diversity of participating sites to help ensure familiarity with regional differences in clinical presentations. Death reviews were typically randomly assigned to ERC members. However, if a reported death was due to suspected neurological or cardiovascular disease, at least one reviewer was a neurologist or cardiologist. A research nurse from the study’s data management center

coordinated the ERC death review process, including communications with reviewers about specific cases.

ERC members reviewed all materials to determine the immediate cause of death, the underlying cause of death, and, if applicable, any contributing causes of death, using standard definitions described previously. Underlying cause of death was specifically defined as the disease or injury that initiated the train of morbid events leading directly to death or the circumstances of the accident or violence that produced the fatal injury.[14] For suicides, accidents, and violent deaths, the ERC policy was for such events to be recorded as both the immediate and underlying causes of death.

Reviews were done without knowledge of randomization assignment and were performed independently by each ERC member. On the death review form, the ERC reviewer recorded the immediate, underlying, and (if applicable) contributing causes of death using the most detailed written terms possible. In addition to this detailed text description, each cause of death was assigned a more general numerical code, adapted from standardized classifications used by the Coding of Death in HIV Project classification system.[23] The underlying cause of death was classified as AIDS-defining if it was a clinical disease in the 1993 CDC revised AIDS surveillance case definition.[24] ERC reviewers could also provide written comments on the review form concerning reasons for their decision. An additional question was subsequently added to the death review forms asking whether the ERC reviewer thought that there was adequate information and supporting documentation provided to make a decision about cause of death. Signed death review forms were returned to the ERC Coordinator.

### Adjudication of Underlying Cause of Death by the ERC

All three reviewers had to agree on the underlying cause of death, including the more specific written term used to describe this cause. If there was an initial difference of opinion between reviewers on underlying cause, there was an adjudication process to reach consensus. The ERC Coordinator sent to all three ERC reviewers the results of the initial reviews, including each reviewer's classification of the underlying cause of death, as well as their written comments concerning this decision. The three ERC members communicated with each other by email (or in a few cases, conference call) until consensus on the underlying cause of death was reached. In some cases, this consensus was to classify the underlying cause of death as unknown.

## RESULTS

### Characteristics of Population

As of January 14, 2008, 453 deaths were reported from the three clinical trials: 213 (47%) persons died during 2004 or earlier, and 240 (53%) during 2005–2007. Of all deaths, 380 (84%) were in males and 73 (16%) in females. The median age at death was 50 years (interquartile range [IQR] 43–57 years). Of 448 persons for whom race/ethnicity was reported, 320 (71%) were Caucasian, 86 (19%) black, and 42 (9%) of other race/ethnicity. Those who died were from 24 different countries; 53% were from North America, 28% from Europe, 10% from South America, 5% from Oceania, 2% from Asia, and 1% from the Middle East or Africa.

### Specific Underlying Causes of Death

For 47 (10%) persons, the underlying cause of death assigned by the ERC was classified as endstage AIDS or an AIDS-defining illness (Table 1); the cause was non-Hodgkin's lymphoma for 24 persons, other AIDS-defining malignancies for 3, an opportunistic infection or recurrent bacterial pneumonia for 13, endstage AIDS (often with multiple co-existing AIDS-defining diseases) for 4, HIV encephalopathy for 2, and HIV wasting syndrome for 1.

For 93 (21%) persons, the cause of death was classified as a non-AIDS-defining malignancy. Of these, 34 were lung cancers, 7 liver cancers, 7 pancreatic cancers, 6 Hodgkin's lymphoma, 6 cancers of the oropharynx (primarily squamous cell), 4 anal cancers, and the remaining 29 various other malignancies. These included cancers of the prostate, bladder, breast, or esophagus; leukemia; melanoma; and metastatic and/or undifferentiated tumors for which the primary site was not identified.

For 40 (9%) persons, the underlying cause of death was classified as due to cardiac disease. These included 26 persons for whom death was specifically attributed by the ERC to myocardial infarction or ischemic/coronary artery heart disease. The other 14 persons included those with hypertensive, valvular, or other cardiac disease (including non-ischemic cardiomyopathy), as well as those with cardiac disease or cardiac arrest in whom the specific etiology of this disease was not further identified or reported.

For 39 (9%) persons, the underlying cause of death was liver disease (excluding liver cancer), including cirrhosis and/or liver failure. Twenty of these were specifically reported as related to hepatitis C virus (HCV) and 10 as related to hepatitis B virus (HBV); the remaining 9 represented other causes of liver disease (such as alcohol) or liver failure/cirrhosis for which the etiology was not reported or identified. For 36 (8%) persons, the cause of death was classified as a non-AIDS-defining infection; these included 19 persons with pulmonary infections including non-recurrent bacterial pneumonia, 13 persons with sepsis or septic shock, and 4 with other infections such as endocarditis or cerebral abscess.

For 22 (5%) persons, the assigned cause of death was suicide. Another 23 (5%) persons died from various other trauma-related or accidental causes, including drowning, head trauma, motor vehicle accidents, and gunshot wounds. For 20 (4%) deaths, the assigned cause was drug overdose and/or acute intoxications. Specific drugs associated with such deaths, if reported, typically were recreational drugs or drugs of abuse, including cocaine, amphetamines, heroin, and other opioids; for some patients, multiple drugs were listed.

Miscellaneous other conditions were classified as the underlying cause of death in another 52 (11%) persons; these included pulmonary emboli, cerebral infarction or hemorrhage, chronic obstructive pulmonary disease, sickle cell and other hematologic diseases, endstage renal failure, chronic pancreatitis, obstetrical complications, and other diseases.

### Unknown Cause of Death

For 81 (18%) deaths, the underlying cause was classified by the ERC as unknown. A small number of these were persons with multiple co-existing illnesses, for whom the underlying cause of death could not be determined among a variety of potential competing causes. Unknown cases included 16 persons who were reported as having been found dead, and another 15 who were reported as suddenly dying with limited details to help identify the underlying etiology, as well as those whose death was first identified through a death notice or after notification by a family member, with no other information provided to the ERC. Of the 81 death reports classified as unknown, 8 (10%) included a copy of a death certificate, 8 (10%) included any clinic note, 2 (2%) included some other information on current medical history, 3 (4%) an autopsy report, 2 (2%) a written summary from the terminal hospitalization, and none included other hospital records from the final month of life. For 62 (77%) of death reports classified as unknown, none of the documentation listed above was supplied. Even when documentation such as a death certificate or clinic note was supplied, it may have shed little light on the underlying cause of death. For 63 unknown cases, ERC reviewers were specifically asked on the death review form about adequacy of information and supporting source documentation; in all 63 (100%) cases, one or more reviewers felt there was inadequate information and documentation provided to make an informed decision about cause of death.

### Adjudication by ERC

For 233 (51%) of the 453 deaths reviewed by the ERC, there was an initial difference of opinion among the three reviewers about underlying cause of death, and assigning a final cause required follow-up discussion (adjudication) among the three reviewers to achieve consensus. Table 2 reports by underlying cause of death the proportion of cases that required this adjudication among reviewers. The causes of death most likely to require follow-up discussion to achieve consensus were drug overdose or acute intoxications (80%), deaths in the "other" category (77%), cardiac disease (75%), and non-AIDS infections (72%); those least likely were suicides (23%), non-AIDS malignancies (25%), and AIDS-defining conditions (26%).

## DISCUSSION

We describe procedures for reporting and review of deaths used in three large multicenter, international HIV clinical trials. Only 10% of deaths were attributed to AIDS-defining illnesses as the underlying cause, with half of such deaths due to non-Hodgkin's lymphoma. For most (72%) deaths, non-AIDS-defining illnesses were assigned as the underlying cause; these included non-AIDS-defining malignancies and infections, liver disease, cardiac disease, suicide, and other trauma. In 18% of cases, the underlying cause of death was classified as unknown, very largely due to insufficient medical history and/or supporting source documentation.

The importance of obtaining adequate information to help correctly determine cause of death cannot be overemphasized. When specifically queried, in all cases where the cause of death was classified as "unknown," one or more ERC reviewers felt there was inadequate information and/or supporting source documentation. In some cases, the cause of death was assigned by the ERC based on limited information that may not have captured the full clinical picture. Information reported by site investigators in clinical trials and/or on death certificates may be inaccurate or incomplete in identifying the specific underlying cause of death.[16–20,25–28] For those patients who die in the hospital, a hospital discharge summary and other hospitalization-related information (including diagnostic study results) may provide essential information. For all patients, including those who die out-of-hospital, clinic notes or records from previous hospitalizations, as well as autopsy reports, may provide similarly valuable information. It is critically important to make maximum efforts to obtain full documentation and clinical information to help most accurately determine cause of death. Investigators who participate in clinical studies should receive training in classification of cause of death, what supporting source documentation to collect in relation to specific events, and the importance of this endeavor.

Clinical event review committees can play a valuable role in both validating study-related endpoints and in helping to more accurately identify cause of death, especially if such committees review medical records and other documentation.[16–20,29–32] Clinicians at individual sites may lack training or expertise in identifying underlying cause of death, have considerable variability in assigning cause of death (especially in large trials with multiple investigators), and be biased by involvement in patient care and (in open-label studies) knowledge of treatment. In contrast, clinical event committees can provide a blinded, objective, independent, and systematic mechanism for evaluating and adjudicating events, including specific causes of death, in clinical trials. Both a smaller number of ERC members (compared to a larger number site investigators from multiple sites) and discussions among ERC members to achieve consensus on cases in which there was initial disagreement served to provide more uniform consistency in classifying underlying cause of death.

Similar to many other endpoint review committees, reviewers in these studies first independently reviewed records for each patient; when they disagreed, the case was discussed

to achieve consensus. In any ERC process with multiple independent reviewers, there should be a process for resolution of differences of opinion.[33,34] Our experience is consistent with other reports that three reviewers/adjudicators for each case is generally a sufficient number in clinical trials.[34] In over half (51%) of reports in this analysis, there were initial differences of opinion among ERC reviewers, reflecting the challenge of assigning a specific text term to underlying cause of death, especially in cases that were complex and/or not clear-cut. Death due to causes such as malignancies and suicides were typically more straightforward and less open to different interpretations among reviewers. On the other hand, deaths due to acute intoxications or cardiac events were often less clear-cut and more commonly adjudicated. For example, in some cases of acute intoxication, the toxicology screen was positive for multiple agents, and the ERC differed on which drug(s) were most likely to have been responsible for death. Another study of death due to cardiovascular events highlighted some of the challenges of identifying precise etiologies as cause of death, such as determining whether a cardiac death was specifically due to ischemic, arrhythmic, left ventricular dysfunction, or other causes.[20] Although the process of adjudication took extra time and effort, in our ERC, through facilitated follow-up discussions among the three reviewers, consensus was eventually always reached.

In planning for assessment of clinical endpoints in HIV clinical trials, it is important to note that our results are consistent with other studies describing the importance of non-AIDS-defining diseases as causes of death among HIV patients in the HAART era.[1–13] The most common causes of death in our analysis were non-AIDS-defining malignancies, present in 21% of cases. Other studies also report non-AIDS-defining malignancies as an important cause of illness and death in HIV-infected persons.[2,6–9,35,36] This likely reflects the contribution of multiple factors, including a reduction in AIDS-related infections as competing causes of mortality, an aging population, and presence of other cancer risk factors. Of interest, lung cancer was the most common non-AIDS malignancy, accounting for almost 8% of all deaths. Studies have reported the risk of lung cancer is greater among persons with HIV/AIDS, even after controlling for smoking history.[36–39] This emphasizes that even though certain malignancies are not AIDS-defining, their development still may be more likely to occur in the HIV-infected patients.

Nine percent of all deaths were due to cardiac-related diseases. Many studies have identified myocardial infarction and other cardiovascular disease as important causes of morbidity and mortality in HIV-infected patients.[1,4,6–9,13,40,41] The development of cardiovascular disease reflects the potential contributions of a variety of interacting factors, including HIV, specific antiretroviral drugs, an aging population, and traditional risk factors such as smoking, diabetes, obesity, and hypertension. One challenge with identifying the true total proportion of deaths due to underlying cardiac disease is that some of the cases classified as unknown were found dead at home or suddenly died, without additional information supplied to the ERC to help identify the underlying cause of death. Some of these unknown cases may have died due to unrecognized or unreported cardiac disease. This emphasizes the importance of sites making thorough efforts to obtain follow-up information on patients who suddenly or unexpectedly die, especially in out-of-hospital settings. Preceding symptoms suggesting myocardial ischemia[42] or a history of recent severe cardiac events can help support a possible cardiac etiology for sudden death.

Nine percent of deaths were due to liver disease, including cirrhosis and endstage liver failure, and another almost 2% to liver cancer. Liver disease as an important cause of death has been well described among those with HIV.[3,6–10,43] Although factors such as alcohol increase the risk of liver disease, decompensated liver disease and liver-related mortality are increased in HIV-infected patients co-infected with HBV or HCV,[44–47] stressing the importance of collecting this information in clinical trials ascertaining liver-related outcomes. Our results

also highlight the potential importance of collecting information about other non-AIDS-defining infections in HIV-positive patients, including bacterial pneumonia and sepsis.[48–51]

Suicide has been reported as the cause of death in other studies of persons with HIV[7,8]; additional evaluations of HIV-infected persons have reported a significant prevalence of suicide ideation.[52,53] Because in our study it was sometimes difficult for the ERC to separate accidental from intentional overdoses as the cause of death, it is possible that the number of suicides was greater than that reported in this analysis. In addition, although suicide was classified as the underlying cause of death, in many cases it was related to depression and other chronic mental health problems, stressing these as important issues for persons with HIV.[54,55] Because detailed information was not routinely collected on the specific circumstances surrounding these suicides, we cannot rule out whether medications, acute illness, or other precipitating factors may have exacerbated depression or other neuropsychiatric disorders.

This article describes the procedures and results from our experience using an ERC to determine underlying cause of death in three large international trials. Our pooled results on cause of death from three studies with different interventions and study populations are not intended to be representative of all HIV-infected patients nor to describe predictors of mortality in certain subpopulations. For example, causes of death will be different for HIV-infected persons from resource-poor countries where co-infections such as tuberculosis are more common.[56,57] In addition, cause of death, although critically important, represents only one measure of the total disease burden due to HIV. However, we believe the methodology and processes we describe, as well as the challenges in determining underlying cause of death, have applicability to HIV clinical trials being conducted in a wide variety of settings.

## CONCLUSION

Our experience highlights a number of issues that must be considered in designing and implementing systems to establish cause of death in HIV clinical trials. We demonstrate that an ERC can be successfully used to provide a blinded, independent, and systematic evaluation and adjudication of specific underlying causes of death in HIV clinical trials. Such committees need to include clinical investigators who are familiar with both AIDS and non-AIDS-related causes of mortality, including those due to non-AIDS malignancies and infections, as well as cardiovascular and liver disease. To most accurately ascertain underlying cause of death by such committees, it is critically important for local sites and investigators to make maximum efforts to obtain full documentation and clinical information. Investigators who participate in clinical studies should receive training in classification of cause of death, what supporting source documentation to collect in relation to specific events, and the importance of this endeavor.

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**Table 1**

Underlying causes of death assigned by endpoint review committee in three HIV clinical trials

| **Cause of death** | ***n*** **(%)** |
|---|---|
| AIDS-defining illness | 47 (10%) |
| Non-AIDS-defining malignancy | 93 (21%) |
| Cardiac disease | 40 (9%) |
| Liver disease (excluding malignancy) | 39 (9%) |
| Non-AIDS-defining infection | 36 (8%) |
| Suicide | 22 (5%) |
| Other trauma-related, accidental | 23 (5%) |
| Drug overdose, acute intoxications | 20 (4%) |
| Other identified causes | 52 (11%) |
| Unknown | 81 (18%) |

**Table 2**

Proportion of cases requiring follow-up discussions (adjudication) by an endpoint review committee (ERC), by underlying causes of death

| | Required adjudication by ERC | |
|---|---|---|
| **Underlying cause of death** | **Yes (*N* = 233)** | **No (*N* = 220)** |
| AIDS-defining illness | 12 (26%) | 35 (74%) |
| Non-AIDS-defining malignancy | 23 (25%) | 70 (75%) |
| Liver disease (excluding malignancy) | 26 (67%) | 13 (33%) |
| Cardiac disease | 30 (75%) | 10 (25%) |
| Non-AIDS-defining infection | 26 (72%) | 10 (28%) |
| Suicide | 5 (23%) | 17 (77%) |
| Other trauma-related, accidental | 7 (30%) | 16 (70%) |
| Drug overdose, acute intoxications | 16 (80%) | 4 (20%) |
| Other identified causes | 40 (77%) | 12 (23%) |
| Unknown | 48 (59%) | 33 (41%) |