Commentary: Treated HIV infection is a chronic disease: the case against cause of death analyses

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In this issue, Hessamfar-Bonarek et al. studied the cause of death among HIV-infected men and women in France in 2005. The study was based on a national survey in which physicians were asked to report deaths among HIV-infected adults. Each case was documented by a standardized questionnaire. Deaths attributed to conditions included in the Centers for Disease Control and Prevention (CDC) classification of AIDS-defining conditions were categorized as ‘AIDS deaths’; all others were ‘non-AIDS deaths’. More women died of ‘AIDS deaths’ and differences in cause of death by gender were explained by age, substance use (drugs, tobacco and alcohol) and socio-economic precariousness. The authors conclude that socially and economically precarious individuals, particularly women, should be targeted for engagement with health care.

Although their conclusion seems reasonable, cause of death analyses are useful when addressing whether a death is or is not due to a single, unambiguously defined, precipitating event; for example, a violent vs non-violent death. The analyses become, however, increasingly less meaningful as the complexity of the disease increases. Complex chronic disease is present when multiple aetiologies (ageing, disease progression, disease interactions with comorbid conditions and with treatment toxicity) combine to cause progressive loss of physiological reserve with resulting morbidity and mortality. These aetiologies do not act independently, but cumulatively and, at times, synergistically.

Treated HIV infection is a complex chronic disease where multiple aetiologies of morbidity and mortality are the rule rather than the exception. Results from a randomized trial, Strategies for Management of Antiretroviral Therapy (SMART), suggest that many ‘non-AIDS’ conditions (renal disease, liver disease and cardiovascular disease) are caused or exacerbated by HIV disease progression. Based on observational studies, this list of ‘non-AIDS’ conditions associated with HIV disease and mortality continues to grow and includes anaemia, thrombosis, obstructive lung disease, intracranial haemorrhage and several ‘non-AIDS’ cancers. Progression of hepatitis B and C infection is accelerated among those with HIV infection. Further, the association between CDC AIDS-defining conditions and death is highly variable and not uniformly stronger than that for ‘non-AIDS’ conditions.
and death. For example, disseminated herpes simplex disease (an AIDS-defining event) has no association with death, whereas hepatitis C has a strong independent association with mortality and this association is stronger among those co-infected with HIV and hepatitis C. The SMART investigators observed more ‘non-AIDS’ than serious AIDS events and only 8% of the deaths were AIDS-defining. Failing to recognize ‘non-AIDS’ conditions that are caused by multiple aetiologies including HIV infection will cause us to dramatically underestimate the burden of HIV disease. Because the frequency of these ‘non-AIDS’ HIV-associated conditions varies by race/ethnicity, gender, age and health behaviours, cause of death data may lead us to underestimate the effects of HIV among those at greatest risk: the older patients, economically disadvantaged patients, and those who smoke, drink or abuse drugs.

**Causes of death do not tell you about the living**

In the current study, the authors conclude that there are more AIDS-related causes of death among women than among men. This does not prove that there are more AIDS events in women than in men or that mortality from AIDS is higher among women. The HIV epidemic among women is a more recent phenomenon. HIV-infected women who die are younger than HIV-infected men who die. It is likely that younger individuals have fewer competing causes of death. Thus, women may have a lower mortality rate, but a greater proportion of deaths are categorized as AIDS. The study does not include mortality rates among women and men. It is quite possible that age-adjusted rates of mortality from AIDS-defining conditions did not differ by gender—only that a greater proportion of all deaths among younger individuals are from AIDS.

**Cause of death data are inaccurate and susceptible to bias**

The gold standard for cause of death attribution is an autopsy performed by a trained pathologist. Many studies have demonstrated that autopsy results contradict the attending physician. In a recent meta-analysis, 50% of the autopsies produced findings unsuspected by the physician. Even among patients with a clear primary diagnosis (cancer), dying in a highly monitored setting (intensive care unit), there was a 26% discrepancy between pre-mortem diagnosis and post-mortem findings. Expectancy bias is the tendency to see what we expect to see, even when that is not what is there. Expectancy bias can occur when a clinician assigning cause of death has a strong expectation based upon knowledge of the patient’s age, HIV status or health behaviour. For example, expectancy bias occurs when CD4 cell count is used to inform the determination of cause of death or when an individual’s status as a known intravenous drug user influences the determination of whether or not hepatitis C is the cause of death. Imagine two patients, both of whom die at home without autopsy, months after their last clinic visit. At their last visit, Patient A had a CD4 count of 50 and Patient B had a count of 350. We might be tempted to assume that Patient A died of AIDS and Patient B died of ‘unknown causes’, yet this assumption would introduce bias since the same amount of information is available on both patients. Bias is also introduced by informative censoring. Information about death is often missing if the death occurs at home or at a distant location. Since hospital deaths are substantively different from deaths that occur at home, included deaths are different from excluded deaths.

These inaccuracies and biases are problematic because cause of death analyses influence health care policy and research. The motivation is noble: we want to target health conditions that most influence important patient outcomes, most particularly, survival. However, the premise that death is caused by a single process is misguided when applied to those in treatment with HIV infection. Consider an HIV-infected man who smoked heavily for years, has obstructive lung disease and chronic bronchitis. If this patient dies after two episodes of bacterial pneumonia in a 12-month period, his death is an AIDS death. If he dies after a single episode of pneumonia or if he dies of a rapidly progressing lung cancer his death is a non-AIDS death. Yet, in both cases, his death had at least two underlying causes: smoking and HIV infection; both substantially increased his risk of lung disease. Similarly, a patient co-infected with hepatitis C and HIV can expect a substantially different risk of cirrhosis and hepatocellular cancer than a mono-infected patient, yet neither cirrhosis nor hepatocellular cancer are considered AIDS events.

The time has come to phase out cause of death analyses and with it our conception of HIV disease as a single pathological process. A comprehensive conception of HIV infection must recognize the role of multiple pathological processes contributing to chronic inflammation, immune senescence and cumulative depletion of reserve (frailty). We need to study these joint effects—conceptually, statistically, biochemically and operationally. Whereas there remains a role for cause of death when differentiating violent from non-violent death or when no other data are available, it is at best a problematic measure prone to misinterpretation and bias.

**Conflict of interest:** None declared.
References


