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.1 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 conditions2 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.3 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),4 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,5 thrombosis,6 obstructive lung disease,7 intracranial haemorrhage8 and several ‘non-AIDS’ cancers.9 Progression of hepatitis B and C infection is accelerated among those with HIV infection.10 Further, the association between CDC AIDS-defining conditions and death is highly variable11 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 asso-
ciation is stronger among those co-infected with HIV
and hepatitis C.10

The SMART investigators observed more ‘non-AIDS’
than serious AIDS events and only 8% of the deaths
were AIDS-defining.4 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,1 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 phe-
nomenon. HIV-infected women who die are younger
than HIV-infected men who die. It is likely that youn-
ger 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 con-
tradict the attending physician. In a recent meta-
analysis, 50% of the autopsies produced findings
unsuspected by the physician.12 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.13

Expectancy bias is the tendency to see what we
expect to see, even when that is not what is there.14
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 deter-
mination 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 influ-
ence 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 hepatocel-
lar 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 anal-
yses and with it our conception of HIV disease as a
single pathological process. A comprehensive con-
ception of HIV infection must recognize the role of
multiple pathological processes contributing to
chronic inflammation, immune senescence and cumu-
latve depletion of reserve (frailty). We need to study
these joint effects—conceptually, statistically, bio-
chemically 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.

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References


