Commentary: The changing face of AIDS

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The paper from the CASCADE collaboration\(^1\) is a welcome addition to the growing body of evidence from observational cohort studies showing that the incidence of AIDS-defining diseases has declined dramatically since 1997 when highly active antiretroviral therapy (HAART) was widely introduced. The CASCADE collaboration follows patients with known date of seroconversion and therefore adjustments for duration of HIV infection can be made. The results from the present analyses give rise to several questions. Here I will focus on two issues: firstly, are estimates of disease incidence from seroprevalent cohorts comparable with those from seroincident cohorts? Secondly, what difference is there in the interpretation of a cause-specific and a competing risks model?

The authors state that it is necessary to use a seroincident rather than a seroprevalent cohort to estimate the effect of treatment changes on the incidence of AIDS over time. If we compare the raw incidence rates with the adjusted relative hazards, we can see the importance of adjusting for time since seroconversion. Does this mean that seroprevalent cohorts cannot be used to estimate treatment effects over time because adjustment for time from infection cannot be made? In fact the requirement for an unbiased analysis is for patients at a similar point in the disease process to be compared. An alternative way of characterizing the stage of the infection is to adjust for CD4 cell count and human immunodeficiency virus type 1 (HIV-1) RNA in the analyses, as patients with similar immune suppression and viral load are at a similar risk of AIDS defining diseases. This point was very clearly illustrated in a paper by Tarwater et al.\(^2\) using the Multicenter AIDS Cohort Study (MACS). Gay men were enrolled into the MACS cohort some of whom were seronegative and later converted to seropositive, therefore their dates of seroconversion were well documented. They contrasted two methods of assessing population effectiveness of therapies in HIV cohorts. First, they looked at all patients whose date of infection was known. The relative hazard of AIDS was 1.52 for no therapy, mono therapy was the reference group, 0.91 for dual and 0.30 for triple therapy in the seroincident cohort controlling for duration of infection. In the second method, they used patients whose date of seroconversion was not known and calculated relative hazards adjusting for CD4 cell count and HIV-1 RNA. The corresponding figures for the seroprevalent cohort were 1.52, 1.03 and 0.31. Knowledge of duration of infection did not add significant information beyond that provided by CD4 cell count and levels of HIV-1 RNA. The conclusion was that the two methods worked equally well and that the population effectiveness of drugs could be measured in cohorts that did not have dates of seroconversion.

The diagnosis of AIDS depends on the occurrence of one of many different diseases and each patient can only have one first AIDS event, thus the different diseases can be thought of as competing ‘causes’ of AIDS. The competing risks model is an attempt to model the hypothetical risk of AIDS due to one cause in the absence of other causes.\(^3\) There are two modelling approaches. In the first method we examine the effect of removing other causes. This means we have to decide how the cause we are focussing on will develop in the absence of the removed causes. This is unknown and therefore a standard choice is to assume that the hazard of the cause of interest does not change when the other causes are removed, although this assumption is rarely satisfied. This is the cause-specific model. The second method considers lifetime (or time to AIDS in this case) as a multivariate random variable.\(^4\) Each person has a ‘lifetime’ for each cause and the actual realized lifetime is the minimum of the cause-specific lifetimes. There are conceptual problems with this approach. It implies that for any given person we have a potential observation that he is diagnosed as having AIDS from any cause. Now it is possible to estimate the probability of AIDS due to one cause or another at the end of the follow-up period, but for survivors who are free of AIDS at the end of follow-up the cause of AIDS is indeterminable. This means that we cannot estimate the overall probability of AIDS through a specific cause. Without modelling assumptions such as proportional hazards of cause-specific hazards it is impossible to predict the cause of AIDS for individuals without an AIDS diagnosis at the time of the last observed event. We cannot quantitatively consider the effect on the lifetime of a particular cause of reducing the hazard of some other specific cause.

Where does this leave the interpretation of the CASCADE results? Firstly it is to be noted that there is very little difference between the cause-specific and competing risks models for most diseases. The greatest differences are in the diseases that exhibited the least change in incidence when comparing the pre and post HAART eras. This is to be expected if large reductions in some diseases lead to more patients at risk for progression to AIDS through other causes whose incidence has been less affected by HAART such as the lymphomas. Thus the difference in models is indicating a shift in the type of diseases we might expect to see in HIV patients. However, the quantitative assessment of this shift is not reliably estimated and will in any case be very much a function of time, particularly in this transition period where we have a mixture of long-term survivors who suffered periods of very severe immunosuppression and more recently infected individuals who have never experienced severe immunosuppression.

As HIV patients live longer, other non-AIDS defining diseases will become more common and it is likely that HIV patients will suffer an excess of many diseases over the background population. Some of these may be due to long-term suppression of the immune system, some may be due to co-infection, for example liver disease due to hepatitis C, some possibly due to increased prevalence of other exposures such as smoking, and...
finally some due to side effects of the drugs such as increased rates of heart disease associated with metabolic complications. We might also debate the list of AIDS-defining diseases. The list was enlarged in 1993 and now there seems to be a case for including further diseases such as lip cancer and Hodgkin’s lymphoma where the evidence that they are associated with immune suppression due to HIV infection is strong.\textsuperscript{5,6} The initial list consisted of the most common HIV-related diseases at the time, but now some of these have been almost eliminated by the use of HAART and conversely rarer diseases with longer incubation periods are becoming more evident in the long-term surviving HIV patients.

Acknowledgement

The author would like to thank Matthias Egger for helpful advice.

References