Effect of Order of Infection with Human Immunodeficiency Virus and Human Herpesvirus 8 on the Incidence of Kaposi's Sarcoma

To the Editor—In an important study of human herpesvirus 8 (HHV-8) in a large cohort of homosexual men, Jacobson et al. [1] examined the effect of temporal order of infection with human immunodeficiency virus (HIV) and HHV-8 on the risk of developing Kaposi's sarcoma (KS). Their main conclusion was that men who became infected with HIV before HHV-8 seroconversion had a higher risk of KS than did those initially infected with HHV-8. The conclusion is attractive in its neat linkage between immune status and opportunistic disease. However, the effect of order of infection on KS risk was overestimated, because, in some analyses, time at risk for KS was incorrectly measured. With correct measurements, order of infection had only a modest influence on KS risk, particularly in comparison with other factors, such as CD4 cell count and HIV load.

Because KS risk is negligible before infection with both HIV and HHV-8, time to KS should be measured starting at the time of dual infection. However, in most of their analyses, the authors measured time from HHV-8 seroconversion to KS. Thus, for men infected first with HHV-8, time to KS was inflated, because it included time during which the men had negligible risk of KS. The problem with measuring time to KS beginning with HHV-8 seroconversion is illustrated in the following example. Suppose one man acquires HIV infection at year 0, HHV-8 infection at year 1, and KS at year 2, and a second man acquires HHV-8 infection at year 0, HIV infection at year 1, and KS at year 2. For the first man, time from HHV-8 seroconversion to KS is 1 year, and for the second man it is 2 years. By using the authors’ metric of time from HHV-8 seroconversion to KS, the first man appears to have a greater risk of KS, even though both men have the same time from dual infection to disease.

As the example demonstrates, measuring time from HHV-8 seroconversion to KS exaggerates the effect of order of infection. Two critical observations were made in analyses based on this metric: first, men who seroconverted to HHV-8 after HIV infection had a higher risk of KS than did men who seroconverted to HHV-8 before HIV infection (hazard ratio = 2.55; \( P = .036 \)); and second, the risk of KS in HHV-8–infected men increased for each year of HIV infection (hazard ratio = 1.6, \( P < .001 \)). From these observations, the authors concluded, “...[T]he risk of disease is significantly increased if HHV-8 seroconversion occurs after being infected with HIV-1, confirming the work by Renwick et al.” [1, p. 1945, 2]. However, in the authors’ analyses that used the correct metric (time from dual infection to KS), the risk increase was half as large (hazard ratios of 1.75 and 1.276, respectively) and not statistically significant (\( P = .194 \) and \( P = .267 \), respectively). The study by Renwick et al. [2], which used the correct metric, found a similar increased risk due to order of infection (hazard ratio = 1.6, \( P = .04 \)). Thus, when the correct metric was used, both studies found the effect of order of infection to be modest and of marginal statistical significance.

Although order of infection may be associated with KS risk, other factors are likely to play a larger role in development of KS. In the study by Jacobson et al., when results with the correct metric are taken into account, CD4 cell count and HIV load appear to be more important determinants of KS than is order of infection. These findings support the conclusion that KS development is a multifactorial process in which order of infection plays only a modest part.

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References

Reply

To the Editor—We are pleased that Cannon and Pellett [1] subscribe to our inferences [2] that the development of human immunodeficiency virus (HIV)–associated Kaposi’s sarcoma (KS) is a multifactorial process. As we noted [2], the influences of immunosuppression, represented by CD4 cell count and HIV RNA, outweigh the importance of timing of infections. Further evidence for the association of KS with immunosuppression is the dramatic decrease in KS incidence in the current era of highly active antiretroviral therapy [3].

We respectfully disagree with their supposition that our analysis, in which we used human herpesvirus 8 (HHV-8) infection as the origin for examining time to KS, was incorrect. Because HHV-8 is the causative agent of KS, infection with HHV-8 places persons at risk for the disease. The risk is not necessarily the same at all times after HHV-8 infection and, indeed, could be negligible in the absence of immunosuppression. Although