Consequently, an investigation of seroprevalence rates in our cohort provides us with the natural history of loss of antibody rather than information on infection rates in these individuals.

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Coinfection with Human T Lymphotropic Virus Type I and Human Immunodeficiency Virus

To the Editor—Harrison et al. [1] report an interesting study on the effect of coinfection with human T lymphotropic virus type I (HTLV-I) on human immunodeficiency virus (HIV) viral load in vivo. The extent of the immunomodulatory effect of HTLV-I on HIV-infected patients is a significant unresolved problem, and study of the effect of coinfection on rates of HIV replication is an important approach to this problem. This study, however, neither resolves the question of the effect nor furthers our understanding of the natural history of coinfection.

The conclusions of the study are weakened by an inappropriate assumption, by the choice of controls, and by a confusing statistical analysis. The problematic assumption is that HIV viral load is an equally good surrogate marker for clinical disease progression in people coinfected as it is in people infected with HIV alone. The authors correctly state that “coinfection with HTLV-I and HIV is associated with a dissociation of CD4 lymphocyte count and HIV clinical stage” [2–5], and so it is surprising that they accept the validity of HIV viral load as a surrogate marker of HIV clinical disease for use in coinfected patients before this assumption is validated. (It is ironic that this claim appears in the same volume as the paper by De Gruttola et al. [6], which explicitly reminds us of the danger of relying on a surrogate marker before it is validated.) It is possible that an effect on natural history could be mediated by some mechanism other than an effect on HIV replication, and so a study that fails to show an effect of coinfection on HIV viral load does not demonstrate that “there is no biologic basis for the hypothesis that HTLV-I accelerates the progression of HIV infection.”

A demonstration of no effect may not be conclusive evidence against a significant biologic and clinical interaction, but it would be important; however, the authors do not demonstrate this. They express reservations about the small sample size, but their choice of controls is more problematic. The authors did not match by stage of disease and so could not control for the significant effect this factor has on viral load [7]. They do claim to have adjusted for CD4 lymphocyte count, but details are not provided, the analysis was presumably not performed on paired cases and controls (see below), and (as mentioned above) the CD4 cell count appears to be a poor surrogate marker in coinfected patients. It would be difficult to define an adequate matching criterion for stage, but a preliminary approach could have been to use the World Health Organization (WHO) staging system.

The approach the authors used to compare viral loads between cases and controls is also puzzling. They chose to compare the means of the 2 groups (cases vs. controls) rather than to do a paired analysis of cases and their individual controls. This is an inappropriate analysis without first demonstrating similar variances in the distribution of viral loads in the 2 populations, eliminates much of the value of performing a case-control study, and could easily hide significant associations. This is especially concerning given the logarithmic nature of viral loads, since a single high value could dramatically effect the mean.

Finally, there are two interesting findings in this study that the authors fail to discuss. First, they report a significantly higher mean CD4 cell count for cases compared with controls (394 vs. 276/mm³, P = .06). Interpretation of the CD4 cell counts alone would be confounded by the lack of paired analysis mentioned previously, but the juxtaposition of higher CD4 cell counts with more advanced disease is consistent with a dissociation between CD4 cell counts and clinical disease, similar to that observed by others. Second, the observation that there is a “trend toward a higher viral load in late HIV infection among subjects with single infection compared with those with coinfection” deserves speculation. Might this not be a first hint that HIV viral load, like CD4 cell count, might be a less-informative surrogate marker in those coinfected with HTLV-I?

That there is an immunomodulatory effect of HTLV-I in patients coinfected with HIV is likely. Only after the nature and extent of this effect has been defined with natural history and epidemiology studies will we be able to define the validity of surrogate markers and attempt to understand the underlying biology. Studies of effects of coinfection on HIV replication are important, but negative
studies will not be adequate to exclude a potentially significant effect on natural history.

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6. De Gruttola V, Fleming T, Lin DY, Coombs R. Perspective validating and a high frequency of myelopathy, further evidence of an approach and study designs. Our study, although unable to define the geometric mean viral load than subjects with coinfection (P = .91). Similar results were obtained following adjustment for World Health Organization HIV stage.

Marsh points out that we failed to discuss the finding of a “dissociation between CD4 cell counts and clinical disease similar to that observed by others.” To the best of our knowledge, our previous study was the first to report this phenomenon in association with coinfection [7]. This issue, with a reference to that study, is mentioned in the introduction of our paper [4]. We also recently reported an association between coinfection and a high frequency of myelopathy, further evidence of an interaction between these two viruses [8]. We agree with Marsh that his statement on the use of HIV viral load in HTLV-I coinfection is speculative.

HTLV-II coinfection is an interesting example of how erroneous hypotheses are generated by limited data. The original studies that reported that HTLV-II accelerated the progression of HIV infection were based on seroprevalent cases for which the date of HIV seroconversion was not known [9–11]. The concern with these studies was that HTLV-II infection could simply have been a marker for longer duration of HIV infection [12]. In fact, a recent study using seroincident HIV cases for which the time of HIV seroconversion was known demonstrated no effect, validating the concern about the earlier studies [13].

HTLV-I coinfection is less common in the United States than HTLV-II coinfection, making it less likely that a similar natural history study using seroincident cases will be performed. Therefore, an examination of this issue will require a variety of approaches and study designs. Our study, although unable to definitively answer the question, adds one piece to the puzzle and suggests that HTLV-I may not accelerate the progression of HIV infection.

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