it is intuitively more appealing in such a situation to use co-infection as the origin from which time to KS is measured, a complete analysis that uses both origins (i.e., HHV-8 infection and coinfection) provides the elements to fully characterize how HHV-8, HIV, and HIV-related immunosuppression interact for the development of KS.

In our publication [2], we presented both analyses and showed that HHV-8 alone carried a negligible risk for KS and that, after dual infection, those who acquired HHV-8 after HIV had an elevated hazard for KS (relative hazard = 1.75). Although this association did not reach nominal statistical significance, it confirmed the finding of Renwick et al. [4] but did not correspond to the simplistic example of the 2 persons whose experience demonstrates a relative hazard of 1, as provided by Cannon and Pellett [1]. Of more importance, the elevated relative hazard of persons infected with HHV-8 after HIV is reinforced by the effect of measures of immunosuppression (CD4 cell count) and viral replication (HIV RNA) on the risk of KS, as we documented [2].

We welcome the consensus of Cannon and Pellett on our primary inference; however, we believe that, for prevention of KS, the most important aspect is not to become infected with HIV if one is infected with HHV-8. If one does, it is imperative to treat the HIV infection and to maintain a competent immune system.

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Viral Diversity in Some Immunodominant Epitopes: Possible Implications for Retroviral Immunopathogenesis

To the Editor—The work by Furukawa et al. [1] shows that tax gene diversity and genetic background, such as the presence of HLA-A*02 haplotype, are independently associated with human T cell lymphotropic virus (HTLV)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) development. Furukawa et al. noted that the taxA subgroup, which has nucleotide TTAC sequence modifications, compared with the prototype strain ATK, had a 2-fold greater frequency among patients with HAM/TSP than in HTLV type I (HTLV-I)-infected healthy carriers or patients with adult T cell leukemia. These findings are intriguing, and one possible explanation is that genetic substitutions in the tax gene lead to modifications in its activity, since this region is responsible for immune activation during HTLV-I infection. The observation that viral genetic diversity may result in different clinical outcomes is not unique to HTLV infection.

One variant of human immunodeficiency virus (HIV) subtype B that cocirculates in Brazil has a tryptophan that replaces proline at the V3 loop of gp120 in the virus envelope. More recently, we and others have observed that this strain, which is found almost exclusively in Brazil, may result in less risk for AIDS development than the US/European HIV B strain in the antiretroviral treatment scenario [2] (authors’ unpublished data).

Therefore, a few amino acid modifications may implicate a different cell tropism for the coreceptor usage or escape mechanisms for the neutralizing antibodies or T cell–mediated lysis.

The HTLV-I nucleotide substitutions in the taxA subgroup possibly is related to increased activity in the transactivation process, which leads to a higher interleukin (IL)–2 and IL-2R induction and not just a higher DNA virus load. Another attractive possibility is that the lower tax activity seen in HTLV-II–infected carriers may explain the lower risk for disease development [3]. This hypothesis could be tested by using the luciferase assay to determine whether tax activity is responsible for this outcome. Furthermore, what the HIV-1 V3 loop region and HTLV-I tax protein may have in common is that both are responsible for immune activation during HTLV-I infection. The observation that viral genetic diversity may result in different clinical outcomes is not unique to HTLV infection.

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Reply

To the Editor—In our report, we showed that phylogenetic subgroups in human T lymphotropic virus type I (HTLV-I) \textit{tax} gene are associated with different risks for HTLV-I–associated myelopathy/tropical spastic paraparesis \cite{1}. Casseb \cite{2} suggests possible different risks for AIDS development in variant human immunodeficiency type I infection.

In HTLV-I, there are 4 nucleotide alterations between \textit{tax} subgroup A and subgroup B, and 2 are nonsynonymous substitutions. As we discussed elsewhere \cite{1} and as suggested by Casseb \cite{2}, there are several possible explanations for the different risks. First, \textit{tax} itself could be responsible. Renjifo et al. \cite{3} showed different transactivation activity among naturally existing \textit{tax} sequences; however, Nakane et al. \cite{4} found no differences. We are testing to determine whether transactivation activity is different between 2 \textit{tax} subgroups on 3 enhancers, such as the HTLV-I 21-bp enhancer \cite{5}, the NF-xB enhancer \cite{6}, and the c-fos enhancer \cite{7}. It is also possible that the cytotoxic T lymphocyte (CTL) response to Tax peptides, including the altered amino acids between 2 \textit{tax} subgroups, may elicit different CTL responses. We also are testing the biologic difference between peripheral blood mononuclear cells infected with 2 HTLV-I subgroups. Second, because \textit{tax} subgroups are tightly associated with the HTLV-I subgroups based on the long-terminal repeat (LTR) gene, it also is possible that another part of HTLV-I is responsible for the different risks. As far as we sequenced the LTR in 4 HTLV-I with \textit{taxA} and 3 with \textit{taxB}, the second and third 21-bp enhancer sequences \cite{5} were identical. However, sequence differences in another part of the LTR might influence the integration site. It is also possible that differences in other HTLV-I genes, such as \textit{env}, may influence the migration of HTLV-I–infected cells. We hope that these studies will clarify whether \textit{tax} itself or other factors related to the HTLV-I subgroups are responsible for the different risks for HTLV-I infection outcome.

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Misleading Negative Findings in a Field Trial of Killed, Oral Cholera Vaccine in Peru

To the Editor—The recent paper by Taylor et al. \cite{1} discusses whether a 2-dose primary regimen of recombinant B subunit–killed whole cell oral cholera vaccine protected against El Tor cholera in a field trial done in Pampas, Peru. This is an important public health issue, because a 2-dose regimen may be financially and logistically feasible for developing countries. The authors conclude that a 2-dose regimen was not effective, although boosting with a third dose conferred protection. Unfortunately, there are several reasons to question the conclusion about a lack of protection by a 2-dose primary series of the vaccine.

As shown in table 1, 3 placebo-controlled, randomized trials