

CORRESPONDENCE

Immunosuppression, Timing of Human Herpesvirus 8 Infection, and Risk of Kaposi's Sarcoma among Human Immunodeficiency Virus Type 1–Infected Persons and Transplant Recipients

To the Editor—Jacobson et al. [1] recently provided evidence that, among individuals with human herpesvirus 8 (HHV)–8 infection, Kaposi's sarcoma (KS) is more likely to develop if the infection was acquired after the individual had already become immunocompromised. Their finding confirmed the results of a study showing that the risk of KS is significantly greater if HHV-8 seroconversion (i.e., primary infection with increased virus burden) occurs after infection with human immunodeficiency virus type 1 (HIV-1) [2]. They also showed that the relative hazard of developing KS increased with the duration of HIV-1 infection before HHV-8 seroconversion.

The authors also stated that the fact that HIV-induced immunosuppression facilitates KS disease expression is consistent with the high risk of KS in persons who are immunosuppressed before undergoing organ transplantation. To this regard, they hypothesized that the degree of immunosuppression and the speed at which it is achieved may affect the development of KS, which appears to be faster after transplantation than after acquiring HIV-1 infection.

However, the results of studies conducted on transplant recipients are not completely consistent with the results of the above-mentioned studies conducted among HIV-1–infected cohorts. In particular, an Italian study suggested that individuals who are already infected with HHV-8 before transplantation are at greater risk of developing KS, compared with those who acquire infection after transplantation [3]. In that study, most immunosuppressed transplant recipients had anti-HHV-8 antibodies detectable in their serum before beginning immunosuppressive treatment. These findings are consistent with those of other studies showing that HHV-8 is likely to reactivate after transplantation [4, 5]. Thus, contrary to what has been observed in HIV-1–infected persons, virus reactivation among transplant recipients seems to increase the risk of KS more than does primary infection.

It remains to be determined whether these discrepancies regarding the timing of HHV-8 infection between HIV-1–infected and iatrogenically immunosuppressed individuals are due to the characteristics of the immunosuppression (i.e., severity or length of the induction time) or to HIV-1–related factors (i.e., duration of exposure to HIV-1, Tat-mediated processes).

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Reply

To the Editor—In contrast to studies of Kaposi's sarcoma (KS) among human immunodeficiency virus (HIV)–infected populations, in whom KS is more likely to develop quicker among individuals who become infected with human herpesvirus (HHV)–8 after acquiring HIV-1 than among individuals who become infected with HHV-8 before acquiring HIV-1 [1, 2], Dr. Rezza [3] has brought to our attention a case-control study of post-transplantation KS, in which the overwhelming majority of cases were infected with HHV-8 before becoming immunosuppressed [4]. We do not see the 2 studies as contradictory. As noted in our article [1], we concur that the level of immunosuppression is a key factor in the development of KS, as is, most likely, HHV-8 virus load.

As discussed by Dr. Rezza [3], our supposition that HHV-8 infection after immunosuppression is related to a quicker disease development appears to contradict the results of an Italian study, in which 10 of the 11 people who developed posttransplantation KS, compared with 2 of 17 controls, were HHV-8 seroprevalent. This finding suggests that KS was more likely to develop after reactivation of an existing infection, rather than being the result of acquiring the virus either during or after transplantation [4]. However, this study had a small sample size among a population with a high seroprevalence of HHV-8 [5, 6] and did not compare the hazards of KS according to the timing of infection. In a highly endemic population, reactivation of virus may account for the majority of disease, because

reactivation of virus after transplantation has been shown [7, 8].

In our population, KS also occurred, but at a slower rate, among those who were infected with HHV-8 before acquiring HIV-1, which suggests that reactivation in this population probably also has occurred. Thus, we do not believe that the results of the studies conflict. It will be interesting to compare disease rates among patients undergoing transplantation who are HHV-8 seroprevalent versus those who newly acquire HHV-8. However, this type of cohort study (whether prospective or retrospective) may have to be conducted in a nonendemic population.

It is possible that the timing of reactivation and the HHV-8 viremia produced as a result of reactivation was quite different between the 2 populations. In an endemic population, HHV-8 reactivation due to immunosuppression may be quicker and may result in higher virus loads, compared with primary HHV-8 infection. As we discussed [1], the development of KS may be dependent on the level of HHV-8 virus load, which may be dependent on the level of immunosuppression, as well as on the primary infection. Because the literature on the association of other herpetic infections and the development of disease after immunosuppression indicates that infection during immunosuppression is related to a quicker and more severe outcome, a different mechanism for HHV-8 would be inconsistent for this family of viruses. However, researchers are still in the early stages of understanding the natural history of HHV-8 infection, and we concur that additional research is required to determine the precise role of immunosuppression, including severity and duration, and its interaction with HHV-8 virus load in the development of Kaposi's sarcoma.

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Sensitization to Human Immunodeficiency Virus in Seronegative Exposed Partners

To the Editor—Mazzoli et al. [1] recently presented evidence for the existence of a mucosal immune response in conventionally seronegative sex partners (ELISA/Western blot) of human immunodeficiency virus (HIV)–infected persons [1]. The presence of pathogen-specific IgA in the absence of IgG antibodies is an unprecedented finding in infectious diseases, and underlying mechanisms are obscure. However, the finding suggests the transmission of viral components and is supported by findings of a cellular immune response in partners, health care workers, and vertically exposed persons. Our understanding of this phenomenon will probably depend on future studies of the cellular immune response in exposed subjects. To date, the bulk of evidence for sensitization has been provided by the demonstration of proliferative T cell response to HIV antigens or by studies examining the cytolytic activity of CD8 cells against HIV-infected target cells in exposed partners [2, 3]. Technical sophistication of these classical assays for measuring cellular immunity has, thus far, prevented the widespread study of the phenomenon. Here we report the results of a newly developed flow cytometric method for the detection of HIV-specific CD4 cells in exposed partners [4].

Whole-blood samples from noninfected heterosexual partners were stimulated for 6 h with recombinant HIV p55 *gag* and anti-CD28 costimulator. We added brefeldin during the last 5 h. After intracellular staining of interferon- γ and CD69, gated CD4 lymphocytes positive for both stimulation markers were calculated and were compared with unstimulated controls in a multiparameter flow cytometric detection system. The assay was evaluated in HIV-infected long-term nonprogressors with undetectable HIV RNA (<20 copies/mL) and blood donors. Cytomegalovirus was used as a positive control.

Eight HIV-seronegative heterosexual partners with a >3-month history of sexual exposure were tested. HIV-specific CD4 cells were found in 2 partners at a frequency of 3.4% and 1.4%, compared with 0.5% spontaneously activated CD4 cells in nonstimulated cultures. Both persons had continuous unprotected sex-

ual exposure with the HIV-infected index partner; all other partners had stopped their risky behavior ≥ 3 months before the assessment.

To our knowledge, this is the first demonstration that this rapid technology can be used in exposed persons to detect HIV-specific CD4 cells. The feasibility of the rapid detection method for this purpose will allow for further study of the sensitization observed in exposed persons.

Theoretical considerations suggest that a cellular immune response without a full antibody response, as described by Mazzoli et al. [1], would occur in cases in which HIV is only present intracellularly and not shed in the extracellular compartment. As a consequence, B lymphocytes would be unable to recognize the antigen. T cells, on the other hand, are specialized to detect intracellular antigens on antigen-presenting cells. The observation of a local IgA production in the mucosa in the absence of a systemic humoral immune response might indicate that the viral antigen is confined to the mucosal compartment by a strong cellular immune response. To support this hypothesis, the presence of viral components should be investigated in mucosa-associated lymphatic tissue. The property of this antigenic viral component is not clear but is not necessarily infectious. The lack of a cellular immunity in persons with only remote exposure to HIV, as described in our partner study, speaks against a true infection and favors a temporary presence of viral antigen in the mucosa. This is also supported by a case report of an intermittent cytotoxic T lymphocyte response associated with sexual exposure [5] and by the temporary nature of IgA response, as reported by Clerici et al. [6].

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Reply

To the Editor—Vernazza et al. [1] demonstrate that a rapid and relatively simple flow cytometric technique allows for the detection of exposure to human immunodeficiency virus (HIV) in exposed uninfected (EU) persons. These results are important, because the methods traditionally used to analyze the prevalence of HIV exposure in the absence of overt infection (e.g., antigen-stimulated proliferation and detection of HIV-specific cytotoxic T lymphocytes) are cumbersome and thus far have prevented the study of ample cohorts of study subjects.

Trials for HIV candidate vaccines are planned within the near future in areas of the world where HIV infection is endemic. In these same areas, seronegative exposure to HIV is presumably very high, and scattered data ([2] and authors' unpublished data) suggest that HIV-specific immune responses are detected in $\leq 20\%$ of persons in whom infection does not occur, despite repeated encounters with the virus. The ability of an HIV candidate vaccine to elicit a specific immune response will be a major end point in evaluating vaccine efficacy. Within the populations to be vaccinated, the establishment of the prevalence of an HIV-specific immune response that is secondary to natural exposure to HIV—and not provoked by active immunotherapy—therefore will be of pivotal importance to verify the efficacy of any candidate vaccine.

Vernazza et al. [1] also offer some useful comments in regards to our observation that HIV-specific IgA is detected in the vaginal mucosa of a portion of EU persons. My colleagues and I appreciate these comments and offer additional information. First, we recently showed that HIV-specific IgA (but not IgG) is detectable in the serum of EU persons [3]. Second, serum and mucosal IgA from EU donors can neutralize both T-tropic and M-tropic viruses [3, 4] and can inhibit HIV epithelial transcytosis [5]. In addition, IgA of EU persons recognizes a conformational epitope within gp41 that is distinct from that recognized by the IgA of HIV-infected persons [6]. We do not know why HIV exposure in the absence of apparent infection is associated with the detection of HIV-specific IgA but not of IgG. A simple explanation, which is difficult to prove, is that our results could be biased, because we analyzed EU persons in cross-sectional studies. Hence, it is possible to hypothesize that both HIV-specific IgG and IgA could indeed be present in EU persons for a short time after the first exposure. Particular and yet undefined features of the host response, the

virus itself, or both could favor the preferential maintenance of a prevalent IgA response, a response that, as noted by Vernazza et al., is nevertheless contingent on the fact that HIV exposure is indeed repeated.

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