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Reply to Torre

To the Editor—We appreciate the comments from Torre [1] in response to our report on the role of interleukin (IL)-18 in early HIV-1 infection [2]. Torre points out the interaction between IL-18 and IL-12, in which IL-12 induces the expression of IL-18 receptors and enhances IL-18 activity. Defective in vitro IL-12 production in peripheral blood mononuclear cells (PBMCs) of HIV-1-infected patients is mentioned as a possible mechanism of reduced HIV-1 immunity. We agree that interactions between IL-18 and IL-12 might be important contributors to HIV-1 control. However, there are situations in which IL-12 might not be required for IL-18 activity. For example, IL-18 increases HIV-1 production in chronically infected monocytic U1 cells and in lymphocytic ACH2 cells in vitro, with no demonstrated role played by IL-12 in these cells [3, 4]. Therefore, IL-18 might affect HIV-1-infected cells independently of IL-12.

Torre et al. [5] have shown elevations in IL-18 levels during symptomatic but not asymptomatic stages of HIV-1 infection. We demonstrated elevated IL-18 levels in persons with precisely defined acute or recent (very early) infection, at a time when the viral set point is being established [2]. We believe that it is important to study antiretroviral immunity soon after infection, when a robust host response can control viral replication [6]. Therefore, our results showing elevated IL-18 levels during early infection might indicate an antiretroviral role of IL-18 during a pivotal time in the host-pathogen interaction. Torre speculates that unsuccessful long-term HIV-1 control might be due to mechanisms other than the inability of IL-18 to enhance Th1-type immunity, such as reduced production of IL-12, IL-2, or interferon (IFN)-γ; we agree. Torre further speculates that elevations in IL-18 levels during the later stages of HIV-1 infection are associated with reductions in IL-12 and IFN-γ levels and that this might result in IL-18 enhancement of Th2-type immunity and increased HIV-1 replication. Contrary to this hypothesis, increased IL-18 levels during the later stages of the disease might represent a compensatory measure to drive a degraded immune system.

Torre notes that, in an animal model of simian immunodeficiency virus infection, increased viremia and declining CD4 cell counts were associated with elevated IL-18 levels, which suggests that IL-18 is not antiviral during early infection. We interpret these observations differently. IL-18 might in fact be antiviral, but suppression is incomplete and results in increases in both viral load and IL-18 levels. If the biological effect of IL-18 had been blocked in these animal studies, viremia might have increased and revealed an antiviral role for IL-18. Torre references a publication by his group showing IL-18–induced HIV-1 synthesis in promonocytic cells (actually a chronically infected T cell line) as a demonstration of IL-18 proviral effects. Our group was the first to demonstrate a proviral effect of IL-18 in a human monocytic cell line infected with HIV-1 [4]. However, the activity of IL-18 in chronically infected monocytic and lymphocytic cell lines might not reflect the effects of IL-18 in vivo. For example, we have shown that IL-18 inhibited HIV-1 production in primary human PBMCs infected with HIV-1 [7]. Primary human PBMCs infected with virus more closely reflect in vivo conditions, and these results support an antiviral role for IL-18. It appears that IL-18 possesses proviral or antiretroviral effects depending on cell type, cytokine microenvironment, or stage of disease.

Torre points out that HIV-1 replication results in a blunted cytokine response and reduced Th1-type immunity. HIV-1–induced damage to the immune system is uncontested, and we believe that escalating immune dysfunction might explain increases in IL-18 levels during disease progression. Because the failing immune system becomes less responsive to IL-18, IL-18 levels rise in an attempt to drive Th1-type immunity. Torre notes that proinflammatory cytokines are important for an effective antiretroviral host response and that there is no guarantee that administration of a single molecule (such as IL-18) will enhance immunity in patients. Although proof that IL-18 enhances Th1 immunity and is antiretroviral in infected patients must await clinical study, several observations suggest that this strategy has merit. First, IL-18 enhances both Th1 immunity and inflammation. Therefore, IL-18 can augment the antiretroviral host defense, increase IFN-γ (IL-18 is also known to be an IFN-γ-inducing factor), enhance IL-12 function (because IL-12 increases IL-18 receptor expression), and increase the production of proinflammatory cytokines that Torre notes might be important for HIV-1 suppression. Second, IL-18 has demonstrated antiviral activity in several animal models [8–10].

We agree with Torre that the precise role of IL-18 in HIV-1 infection is not settled and can only be determined by continued in vitro and in vivo study. An important step in determining a proviral or antiretroviral role of IL-18 will be taken by specifically blocking IL-18 in infected patients and observing the effect on viral loads.

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Persistence of Cell-Mediated Immunity to Vaccinia Virus

To the Editor—We read with interest the article by Sivapalasingam et al. [1] about immunological memory after smallpox vaccination. They reported that “at >20 years after vaccination, 9 (14%) of 66 vaccinates tested had detectable IFN-γ–producing lymphocytes…, but 29 (97%) of 30 vaccinates had a neutralizing-antibody titer ≥1:20.” (p. 1153). This finding is in line with our previous report that, a few decades after smallpox vaccination, the immediate neutralizing-antibody-producing effector-memory response was positive in only 15% of patients (6/39) but that the neutralizing antibody titer persisted [2]. As discussed elsewhere [2, 3], we thought that the enzyme-linked immunospot (ELISPOT) assay might not be sensitive enough to detect low frequencies of vaccinia-specific T cells. Recently, we developed a simple and reliable intradermal skin test that uses inactivated vaccinia virus for the assessment of cell-mediated immunity (CMI) to vaccinia virus [3]. We showed that this intradermal skin test correlated better with residual immunity to vaccinia virus than an in vitro ELISPOT assay [3]. We thus examined the levels and durations of CMI against vaccinia virus by use of the intradermal skin test in individuals who had received smallpox vaccination ≥2 decades earlier. We compared it with CMI in unvaccinated individuals and recently vaccinated individuals.

Eighty-three healthy adults between 19 and 51 years of age were recruited. Those who had never received a smallpox vaccination and had no typical vaccinia scar were classified as vaccine-naive persons (n = 20). The remaining persons (n = 63) were classified as remotely vaccinated persons. In addition, 6 individuals who had received Lancy-Vaxinia smallpox vaccine 2–3 years previously were recruited and classified as recently vaccinated persons. The intradermal skin test was done as described elsewhere [3]. On the basis of results from 20 vaccinia-naive individuals, a positive cutoff of the intradermal skin test was determined as ≥4 mm: the mean ± SD induration size was 2.0 ± 1.4 mm in 20 vaccinia-naive individuals, and the induration size was ≤3 mm in 19 of 20 vaccinia-naive individuals.

The induration size of intradermal skin test according to years after smallpox vaccination is shown in figure 1. The positive response rate to the intradermal skin test was 63% (40/63) in individuals vaccinated ≥20 years earlier, 64% (34/53) in those vaccinated ≥30 years earlier, and 65% (11/17) in those vaccinated ≥40 years earlier. However, the size of induration started to shrink a few decades after vaccination (r = −0.6; P < .001).

Previous epidemiologic estimates for smallpox outbreaks showed that smallpox vaccination confers protection against...