Figure 1 (facing page). Phylogenetic Analysis of HIV Quasispecies Isolated from an HIV-Positive Kidney-Transplant Recipient, Showing Two Distinct Viral Lineages.

Panel A shows a neighbor-joining phylogenetic tree that includes a set of the HIV envelope sequences amplified from blood and urine samples obtained from the HIV-positive kidney-transplant recipient (R) before and up to day 16 (D16) after transplantation of a kidney from an HIV-positive donor (D). Two separate viral lineages (lineage 1 and 2) were identified in the recipient after transplantation. Bootstrap values over 80% are indicated. Panel B shows that all the HIV quasispecies in lineage 2 that were amplified from the recipient's urine (solid blue triangles for cell-free viral RNA and green squares for viral DNA associated with renal tubular epithelial [RTE] cells) and plasma (solid orange circles) between 12 hours and 16 days after transplantation are genetically related to the donor viruses and genetically distant from the viral sequences amplified from the recipient's peripheral-blood mononuclear cells (PBMC), plasma, and urine-derived RTE cells before transplantation. Cell-free HIV sequences from both donor urine (before transplantation) and recipient urine (collected 12 hours after transplantation) are closely related to the envelope sequences amplified from the urine-derived RTE cells, which suggests that the viruses that were shed in urine were produced from infected cells within the transplanted kidney. Ten HIV envelope sequences were also amplified from a preimplantation kidney-biopsy sample from the donor (kidney subcluster, labeled D Kidney pre-T). The timing of sample collection is indicated for each of the HIV recipient sequences. Phylogenetic trees with all the amplified HIV envelope sequences are shown in Figure S1A and S1B in the Supplementary Appendix.

This case shows that kidney transplantation from an HIV-positive viremic donor to an HIV-positive recipient can result in the transfer and transient detection of the donor's viral strain in the recipient, even though the recipient is receiving antiretroviral therapy. Since viral sequences provide a clear fingerprint, an analysis of longitudinal samples obtained from the recipient will provide important insights into the viral dynamics, the potential of the kidney to serve as a viral reservoir, and the effect of renal HIV infection on long-term allograft function.

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Inhaled GM-CSF for Pulmonary Alveolar Proteinosis

TO THE EDITOR: In reporting the results of the Pulmonary Alveolar Proteinosis GM-CSF Inhalation Efficacy (PAGE) trial, Tazawa and coworkers (Sept. 5 issue)[1] conclude that there was "a modest salutary effect" on a laboratory outcome but no clinical benefits of inhaled recombinant granulocyte–macrophage colony-stimulating factor (GM-CSF) in patients with autoimmune pulmonary alveolar proteinosis. For 11 years, we have treated a cohort of 28 patients with this condition with only inhaled recombinant GM-CSF, since we do not have access to reliable whole-lung lavage.

In our experience, inhaled recombinant GM-CSF must be used for 1 year or longer in order to achieve both laboratory and clinical effectiveness.[2] Recent data show that patients with high antibody titers may have a poor response.[3] We agree with the proposed approach by Tazawa et al. that to attain remission in such patients, the treatment protocol can be adapted to the patient's condition by increasing the frequency

of administration from alternate days or weeks to continuous administration.[2,4] Did the rigidity of the clinical trial protocol prevent an even greater clinical effectiveness from being realized?

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Dr. Papiris reports receiving fees for participating as a primary investigator, and Dr. Manali, receiving fees for participating as a subinvestigator, in the IMPALA (Efficacy and Safety of Inhaled Molgramostim [rhGM-CSF] in Autoimmune Pulmonary Alveolar Proteinosis [aPAP]) trial. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Our trial was designed to examine the efficacy and safety of inhaled recombinant GM-CSF for 24 weeks in patients with mild-to-moderate autoimmune pulmonary alveolar proteinosis. Our data showed that inhalation of GM-CSF improved oxygenation modestly at the conclusion of the 24-week treatment period; we cannot draw any conclusions about different durations of treatment. However, on the basis of the improved alveolar–arterial oxygen gradient at week 43 in the GM-CSF group in ongoing follow-up, as Papiris et al. pointed out, we can speculate that a longer course of inhaled GM-CSF might lead to better clinical outcomes.

In our trial, of 26 patients in the GM-CSF group who did not have a response and who had an alveolar–arterial oxygen gradient that had decreased by less than 10 mm Hg at week 25, a total of 4 had improvement in the alveolar–arterial oxygen gradient of greater than 10 mm Hg during the subsequent 18-week treatment with inhaled GM-CSF. Since the life span of alveolar macrophages is estimated to be more than 2 to 3 months,[1] longer treatment with inhaled GM-CSF could be favorable. In our trial, baseline levels of antibodies to GM-CSF were not associated with improvement in oxygenation. We agree that data are insufficient to predict which patients would benefit from receiving this agent for longer periods.

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Since publication of their article, the authors report no further potential conflict of interest.

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