with anti-CD25 monoclonal antibody basiliximab 20 mg intravenously on posttransplant days 1 and 4. In HCV-infected patients, antiviral therapy with pegylated interferon and ribavirin for 6–12 months was given for fibrosis stage 2 or higher; in HBV-infected patients, anti-HBV immunoglobulins plus lamivudine 100 mg/day was administered. Forty healthy blood donors served as a control group. DNA extracted from 200 μL of plasma samples was examined for TTV presence and loads by using single-step universal TaqMan real-time polymerase chain reaction with a sensitivity of 2.0 log_{10} DNA copies/mL of plasma, as previously described [7].

No statistically significant difference was found in mean recipient or donor age, sex, or baseline liver disorder across the 3 experimental groups. All recipients tested positive for TTV viremia on the pretransplant serum sample. Figure 1 summarizes the kinetics of TTV viremia in the 4 experimental arms (1 prospective and 3 retrospective). The low-CNI + ECP protocol was associated with the lowest increase in TTV viremia compared with the other 2 different immunosuppressive protocols used in the historical arms of the study throughout the first posttransplant year (CNI vs low-CNI + ECP, P < .01; CNI + AZA/MMF vs low-CNI + ECP, P < .01), thus establishing a continuous direct relationship between intensity of iatrogenic maintenance immunosuppression and increases in TTV viremia.

These findings are not entirely unexpected, as it was already known from studies in hematological patients treated with high-dose chemotherapy that TTV viremia has a fast and sustained dose-response effect [10] that might eventually be exploited to tailor iatrogenic immunosuppression. Because there is a growing need for tailor-made maintenance immunosuppressant dosing to minimize side effects (opportunistic infections, viral reactivations, and secondary cancers) while maximizing graft survival, we propose that TTV could be a cheap surrogate marker of functional immune competence. Larger prospective studies with a longer follow-up will be needed to confirm this, including in other kinds of solid organ transplants.

### Notes

**Author contributions.** D. F. designed the study and wrote the manuscript. L. M. performed laboratory testing for TTV titers. F. M. analyzed the data and wrote the manuscript. M. P. provided scientific supervision of the entire project and manuscript.

**Potential conflicts of interest.** All authors: No reported conflicts.

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### Torque Teno Virus Load as a Biomarker of Immunosuppression? New Hopes and Insights

**To the Editor**—We thank Focosi and colleagues for their comments [1] concerning our article [2]. The results presented in their letter are of major interest and the conclusions are attractive.

We want to emphasize that, similar to studies in adults, our results confirmed that a clear correlation between torque teno virus (TTV) load and the intensity of immunosuppression was shown in pediatric liver transplant recipients. This was related to the number of immunosuppressive drugs. As it has been clearly established that TTV is ubiquitous but has a variable prevalence [3], we also believe that TTV infection should be evaluated mainly on the basis of the viral load, and not on the prevalence, in healthy individuals as well as in patients with chronic conditions.

Focosi et al [1] suggested that a continuous relationship can be established between intensity of iatrogenic maintenance immunosuppression and increase in TTV viremia in hepatitis B virus.
(HBV)/hepatitis C virus (HCV)–related patients with cirrhosis undergoing orthotopic liver transplantation (OLT). Similar data were reported in patients with oncological conditions [4], in HCV-infected patients [5], and after OLT [6]. However, other factors must be taken into consideration by which viral load can decrease in transplant patients, even when administered immunosuppression is high.

As physicians involved in the follow-up of immunosuppressed patients (solid organ or tissue transplant, cancer, inflammatory bowel diseases, etc), we need to develop reliable and inexpensive markers of immune system function. The results of Focosi et al. [1] contribute to this. However, we need to further elucidate some remaining questions:

- What is the influence of hepatotropic viral agents such as HBV, HCV, or hepatitis E virus (HEV) on TTV load? We found that TTV load decreases when a hepatotropic virus, such as HEV, infects immunosuppressed patients [2]. Previously, we also reported a high prevalence of chronic HEV infection in such patients [7]. Correlation between recent HEV infection and lower TTV load could result from 2 phenomena: (1) competitive use of the replication machinery, as TTV and HEV can both replicate in hepatocytes [8]; or (2) HEV-triggered liver inflammation that nonspecifically impairs TTV through hepatocyte death and increased interferon secretion. Concordant with this hypothesis, TTV is susceptible to the effects of interferon [9]. Altogether, these results suggest that, in contrast to the cooperation between TTV and some viral agents such as Epstein-Barr virus [10], TTV and HEV do not act as cofactors, and that liver inflammatory activity could impair TTV replication in the liver. The relationship with HBV, HCV, and other hepatotropic viruses needs to be further analyzed in larger studies.

- Viral load can decrease in patients with rejection or chronic hepatitis, as the liver is one of the sites of TTV replication. We found a lower viral load in patients with chronic hepatitis after OLT than in those with a normal histology [2]. This finding in pediatric liver transplant recipients needs further evaluation in patients receiving other organs.

- If we are to use TTV viremia as “biomarker,” what “range” levels should be considered normal?

- The difficulties of standardization of such a tool may also be highly dependent on the specific condition of the patient. An interesting population is the bone marrow recipient, since these patients are transitorily immunosuppressed following chemotherapy or in the event of treatment of graft-vs-host disease. We should also take into consideration that patients after kidney transplant have significantly different immunosuppressive regimens compared with immunocompromised patients with Crohn’s disease treated with biologics or immunomodulators. Therefore, individualized management of this “biomarker,” based on each specific patient, seems necessary, making standardization difficult.

- It has been reported that the prevalence of TTV is geographically variable. Even if we suppose that prevalence is not an indicator of pathogenicity, could such a large variability in prevalence influence the behavior of the infection at an individual level? When TTV prevalence is almost 100% of the general population in a particular area, could the chronic exposure to this virus be a source of repetitive pathogenicity for immunosuppressed patients? Although this is purely speculative, it should be studied with large comparative and prospective studies.

Altogether, we are encouraged to see that major observations are being published concerning the role of TTV viremia in patients with chronic immunosuppressive conditions. The letter by Focosi et al. [1] is clinically relevant and represents an important contribution to the long-term management of immunocompromised patients.

**Note**

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