Table 1 JC viraemia in five patients with human immunodeficiency virus who developed progressive multifocal leukoencephalopathy (PML)

Patient number	Time (months) before diagnosis (all patients free from neurological symptoms)								At diagnosis
	8	7	6	5	4	3	2	1	Presence of PML symptoms
1	—	ND	ND	ND	—	ND	ND	ND	+ (1.02×10^3 copies/ml)
2	—	ND	ND	—	—	ND	ND	ND	ND
3	ND	ND	ND	—	—	—	ND	—	ND
4	—	—	—	+ (1×10^3 copies/ml)	ND	—	—	—	+ (3.2×10^2 copies/ml)
5	ND	ND	ND	ND	ND	ND	—	—	ND

ND, no data; —, negative JC viraemia; +, positive quantitative JC viraemia (limits of detection 1.08×10^2 to 1.08×10^{11} copies per ml in blood).

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Authors' response

We have read with interest the letter by Pineton de Chambrun and colleagues. The letter reflected on our prospective study of JC viral loads in immunosuppressed patients with Crohn's disease and in controls. We thank the colleagues from Lille for their interest in our work and for further exploring this difficult issue, which will be crucial for the further development of anti-integrin therapies to treat inflammatory disorders. In the five patients with human immunodeficiency virus (HIV) diagnosed with progressive multifocal leukoencephalopathy (PML), the authors could not detect JC viraemia in the months preceding the clinical diagnosis. This finding is in contrast with the case of PML we reported in a patient treated with the anti- α_4 integrin monoclonal antibody natalizumab.¹ However, the authors correctly state that the data available in the literature on the occurrence of JC viraemia before the development of symptomatic PML are inconsistent.²

We would like to respond to some of the issues raised by the authors. First, the diagnosis of PML in the five patients described appears sound and adds to the value of exploring JC virus replication. However, in contrast to our prospective trial incorporating 331 patients and controls, this small retrospective study has inherent limitations. First, blood sampling was not planned ahead of time and varied substantially

between patients. Stored serum was available at the time of diagnosis in only two of the five patients and both these two patients had positive JC viraemia. In the months before the clinical diagnosis of PML sampling was highly variable and this generates an important risk for sampling bias and for missing transient viraemia. Second, it is unknown when these PML cases occurred, how rapidly the samples were frozen and how many thawing cycles they were subjected to. Given the relatively low JC viral loads found in the positive patients (3.0×10^2 to 1.0×10^3 copies/ml) it is possible that in some of the samples the viral DNA degraded and JC viral loads fell below the limit of detection (1.1×10^2 copies/ml). Third, the state of immunosuppression induced by HIV-AIDS is clearly more profound and different from the medical immunosuppression associated with the use of steroids, azathioprine or anti-tumour necrosis factor (TNF) agents. The pathways by which JC virus travels to and reactivates in the brain may be similar for all types of immunosuppression, but there are no data to support that hypothesis. Therefore, we believe that specific studies in immunosuppressed patients with inflammatory bowel disease (IBD) are needed and that we cannot extrapolate data from patients with HIV-AIDS or haematological malignancies. Finally, even if JC viral loads in the cerebrospinal fluid (CSF) correlate better with PML, spinal taps are too invasive for regular screening. Furthermore, the appearance of JC virus in the CSF is probably a late phenomenon when irreversible encephalopathy has already started.

Optimising the long-term benefit to risk ratio is of paramount importance in the treatment of chronic immune disorders such as Crohn's disease. The medical need for biological agents other than anti-TNF agents and the promising results with anti-integrin therapies in IBD, are inevitably being weighed against the limited but real risk of PML. We agree with the colleagues in Lille, that any attempt to develop a non-invasive screening strategy for early detection of JC virus

replication relevant to the development of the devastating and irreversible damage PML causes in the brain, should be fostered.

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CORRECTIONS

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