haematologica
Journal of the Ferrata Storti Foundation

Epstein-Barr virus reactivation and post-transplant lymphoproliferative disease risk deserve a place in the JAK inhibitor toxicity profile. Comment on: "Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications"

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Received: September 1, 2026.
Accepted: September 10, 2026.

Citation: Tang-Her Jaing and Yi-Lun Wang. Epstein-Barr virus reactivation and post-transplant lymphoproliferative disease risk deserve a place in the JAK inhibitor toxicity profile. Comment on: "Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications".
Haematologica. 2026 Sept 17. doi: 10.3324/haematol.2026.301889 [Epub ahead of print]

Subject: Cover letter – Comment submission: EBV Reactivation and PTLD Risk in JAK Inhibitor Toxicity

Dear Editor,

We would like to submit the enclosed Comment, titled "EBV Reactivation and PTLD Risk Deserve a Place in the JAK Inhibitor Toxicity Profile. Comment on: ‘Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications’," for consideration in Haematologica.

This Comment responds to the recently published review by Unkenholz et al, "Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications" (Haematologica, Early View, published August 13, 2026; doi:10.3324/haematol.2026.301214). We highlight a gap in the review's infectious-complications discussion: despite a well-supported mechanistic rationale, Epstein-Barr virus (EBV) reactivation and post-transplant lymphoproliferative disease (PTLD) risk are omitted from the toxicity profile, a gap with particular relevance for pediatric hematopoietic cell transplantation recipients. We support this argument with published evidence spanning adult pharmacovigilance data, the pediatric REACH4/REACH5 trials, a first-line low-dose ruxolitinib study, and a single-center pediatric safety series.

The manuscript is submitted as a Comment: main text of approximately 515 words, 8 references, no figures or tables, and two authors, consistent with the journal's requirements for this type of article.

This work has not been published and is not under consideration elsewhere.

AI-assisted technology disclosure: During the preparation of this Comment, the authors used Claude (Anthropic) to assist with literature synthesis, drafting, and formatting compliance with journal guidelines. The authors reviewed and edited all AI-assisted content and took full responsibility for the content of this article.

Thank you for your consideration. We look forward to your response.

Sincerely,

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Epstein-Barr virus reactivation and post-transplant lymphoproliferative disease risk deserve a place in the JAK inhibitor toxicity profile. Comment on: "Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications"

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Word count: main text approximately 515 words; 8 references; no figures or tables, per Comments format.

Author Contributions: Tang-Her Jaing conceived the response, performed the literature review, and drafted the manuscript. Yi-Lun Wang critically reviewed and revised the manuscript for important intellectual content. Both authors approved the final version for submission.

Disclosures: The authors declare no relevant financial or non-financial competing interests related to this work.

We read with interest the review by Unkenholz et al on the evolving role of Janus kinase (JAK) inhibitors in lymphoid malignancies and their immune-mediated complications[1]. The authors provide a comprehensive account of JAK inhibitor efficacy across B- and T-cell lymphomas, hemophagocytic lymphohistiocytosis, and graft-versus-host disease (GVHD), together with a mechanistically grounded discussion of hematologic, infectious, and cardiovascular toxicity. We wish to draw attention to a gap in the infectious complications section that we believe merits correction, particularly for readers caring for pediatric hematopoietic cell transplantation (HCT) recipients.

The review correctly identifies that JAK inhibitors impair host defense by blocking signaling downstream of the common gamma-chain cytokines IL-2, IL-7, IL-15, and IL-21, and names cytomegalovirus (CMV) reactivation, Pneumocystis jirovecii pneumonia, and invasive fungal infection as the clinically relevant consequences[1]. Epstein-Barr virus (EBV) reactivation and post-transplant lymphoproliferative disease (PTLD) are notably absent from this list, despite the fact that IL-15-dependent NK- and CD8+ T-cell surveillance is a principal mechanism by which EBV-infected B cells are normally controlled. The mechanistic argument the authors use to justify CMV and fungal risk applies with equal force to EBV.

This omission is not merely theoretical. A pharmacovigilance analysis of 57 ruxolitinib-treated GVHD patients found ruxolitinib initiation to be a significant adverse prognostic factor for EBV reactivation (hazard ratio 2.657, 95% CI 1.82–3.87), in addition to CMV reactivation[2]. The randomized REACH2 and REACH3 trials that the review cites as establishing ruxolitinib as standard of care for steroid-refractory acute and chronic GVHD were conducted exclusively in patients aged 12 years and older[3,4]. Pediatric-specific data have since emerged: the phase 1/2 REACH4 study in treatment-naive and steroid-refractory pediatric acute GVHD and the phase 2

REACH5 study in pediatric chronic GVHD, together with several single-center pediatric cohorts, none of which appear in the review despite being directly relevant to its subject matter[5,6]. The risk is not confined to steroid-refractory salvage use: a study of low-dose ruxolitinib added to first-line corticosteroid therapy for newly diagnosed acute GVHD reported a higher rate of EBV reactivation than corticosteroids alone (82.9% vs 70.2%; hazard ratio 1.43, 95% CI 1.03–1.97), though without a corresponding increase in EBV-related PTLD[7]. A single-center pediatric series similarly reported viral reactivation in 56% of ruxolitinib-treated patients, including one case of EBV-related central nervous system PTLD that necessitated drug discontinuation[8].

We raise this because pediatric HCT recipients already undergo intensified EBV surveillance protocols in many centers, given the well-established elevated PTLD risk associated with T-cell-depleted and haploidentical grafts, and because no graft-versus-leukemia effect offsets this infectious risk when GVHD is treated in the non-malignant or minimal-residual-disease setting. Extending JAK inhibitor use into younger children, as REACH4 and REACH5 now support, and into first-line settings, as the low-dose combination data now suggest, changes the risk-benefit calculus in ways that an EBV-blind toxicity framework does not capture.

We would encourage the authors, and clinicians applying this review's toxicity model in practice, to add EBV DNAemia to the recommended monitoring alongside CMV in ruxolitinib-treated GVHD patients, and to include the pediatric-specific and first-line safety data now available when counselling families and designing viral surveillance protocols in this population.

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