



### TOPICS

- Signs & Symptoms
- Incidence & Survival
- Impact on Patients' Lives
- Treatment
- Potential Barriers to Treatment
- Potential Barriers & Solutions
- Policy Considerations

**P**atients with rare diseases often struggle to get a timely diagnosis and proper treatment. By definition, rare diseases are infrequent, with fewer than 200,000 people affected. Between a lack of specialized knowledge and a focus on more common conditions, rare diseases are simply not top of mind for most clinicians.

One such disease is Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disorder. Known as EBV+ PTLD, the condition is an ultra-rare and highly aggressive form of lymphoma that can emerge after certain transplants.

Only a few hundred cases of EBV+ PTLD are diagnosed in the United States each year. Undereducation, delayed diagnosis and barriers within a patient's health plan can complicate a situation that's already life-or-death. Treatment options are available for patients, and the first medication designed specifically for EBV+ PTLD will be up for FDA approval soon.

That fact offers hope to patients and providers alike. For potential treatments to be accessible, however, a few obstacles must first be addressed.



### ABOUT EBV+ PTLD

Following a transplant, there is a risk that a patient's body rejects the new organ or tissue. Medication that suppresses the immune system helps to prevent serious complications. It also, however, increases patients' risk of developing infections. A small minority of patients may develop post-transplant complications such as EBV+ PTLD.

An ultra-rare cancer, EBV+ PTLD is related to the Epstein-Barr virus. Also known as EBV, the virus is one of the most common, with an estimated 90% of adults carrying a dormant form of EBV. While dormant, the virus is inactive and doesn't actively harm the patient. Its presence can, however, lead to EBV+ PTLD.



EBV+ PTLD can develop after a solid organ transplant or a hematopoietic cell transplant, such as a bone marrow transplant or a stem cell transplant. EBV+ PTLD may develop if:

**+** A patient is already positive for EBV and his or her immunosuppressants allow the dormant virus to become active.

**+** A patient originally is negative for EBV but comes into contact with it and, because of immunosuppressant medications, cannot fight off the virus.

Risk varies by age, type of transplant, and mode and type of immune suppression. Another factor is whether the donor or the transplant recipient is EBV positive or EBV negative prior to transplant.

EBV+ PTLD is a potentially deadly, unpredictable and often fast-moving lymphoma. That's why early diagnosis and prompt treatment are crucial.<sup>1</sup>

Staying connected to the latest scientific information, treatment guidelines and current resources will offer clinicians and their patients the best chances for successful treatment.<sup>2</sup>



## SIGNS & SYMPTOMS

The symptoms and severity of EBV+ PTLD can vary greatly from one person to another.

Several factors play a role, including the type of EBV+ PTLD and the area of the body that's affected. Patients may develop vague and nonspecific symptoms that are common to any number of other conditions.

About half of all cases are early onset, occurring during the first year after transplant. For patient survival, it's critical to monitor patients' EBV levels. By testing patients' EBV viral loads, health care providers can work to detect early evidence of a threat. Given how rapid onset cases can be, many patients require frequent viral load testing and active monitoring to stay ahead of complications.

### SIGNS & SYMPTOMS MAY INCLUDE:



**Abdominal Pain**



**Bowel Perforation**



**Chronic Sinus Congestion & Discomfort**



**Fever or Night Sweats**



**Gastrointestinal Bleeding**



**Malaise & Lethargy**



**Nausea & Vomiting**



**Sore Throat**



**Swollen Lymph Glands**



**Weight Loss<sup>3</sup>**



## INCIDENCE & SURVIVAL

The incidence of EBV+ PTLD varies by the type of transplant. For example, solid organ transplant patients are diagnosed with EBV+ PTLD at different rates:

- Intestinal and multi-organ transplants (5%-20%)
- Lung and heart transplants (2%-10%)
- Renal and liver transplants (1%-5%)<sup>4</sup>

Rates of EBV+ PTLD are higher in pediatric patients than in adults, largely because pediatric patients are more likely to be EBV- at the time of transplant.<sup>5</sup> Among cases of EBV+ PTLD in the United States and Europe, 80% are from patients who were EBV- at the time of transplant.<sup>6</sup>

Only a few hundred patients are impacted by EBV+ PTLD every year. But for those who do receive a diagnosis, the survival rates are devastating. For hematopoietic cell transplant patients whose condition has not responded to initial therapies, the median survival time is approximately three weeks. Solid

organ transplant patients who have failed other therapeutic options have a median survival time of just over four months.<sup>7</sup>



## IMPACT ON PATIENTS' LIVES

The long and difficult journey of a transplant recipient starts far before the transplant itself.

Solid organ transplant patients may undergo years of treatments, hospitalizations or surgeries to treat organ failure. Some patients have already failed numerous treatments by the time they have opted to undergo the high-risk transplant procedure as a last resort. This journey continues even after they are added to the waitlist for an organ. It may take years to receive, if received at all.

For patients and families, a diagnosis of EBV+ PTLD is an unexpected shock. After the long journey to a transplant, patients expect to reclaim their lives. But this additional diagnosis is devastating, especially considering its survival rate and the lack of available FDA-approved treatments.<sup>8</sup>



*"The understanding, outcomes and prognosis for patients with EBV+ PTLD have come a long way as solid organ transplant has evolved over time."*

Thomas Habermann, MD



## TREATMENT

While there are no treatments specifically approved for EBV+PTLD, treatment options are available and include some of the same agents that are used regularly in the treatment of lymphoma. There is a long history of treatment with EBV specific T cells for these lymphomas and a current trial of this approach with the goal of FDA approval is ongoing.

Therapeutic options, primarily existing lymphoma treatments, are curative for many patients, though with potential complications. For example, one common response to this cancer in solid organ transplant recipients is initial treatment with anti-CD20 monotherapy, followed by chemotherapy when necessary.<sup>9,10</sup>

While there are no FDA-approved therapies yet, T-cell therapy development over the past 20 years has paved the way for a new option. A new therapy, known as tabellecleucel, may provide patients and providers with treatment that can help. This immunotherapy provides healthy donor T cells to the patient that can effectively fight the EBV+ cells in the patient.

Tabellecleucel is in Phase 3 clinical trials and has been granted

breakthrough therapy designation by the FDA. If approved, it will be the first FDA-approved treatment for EBV+ PTLD.



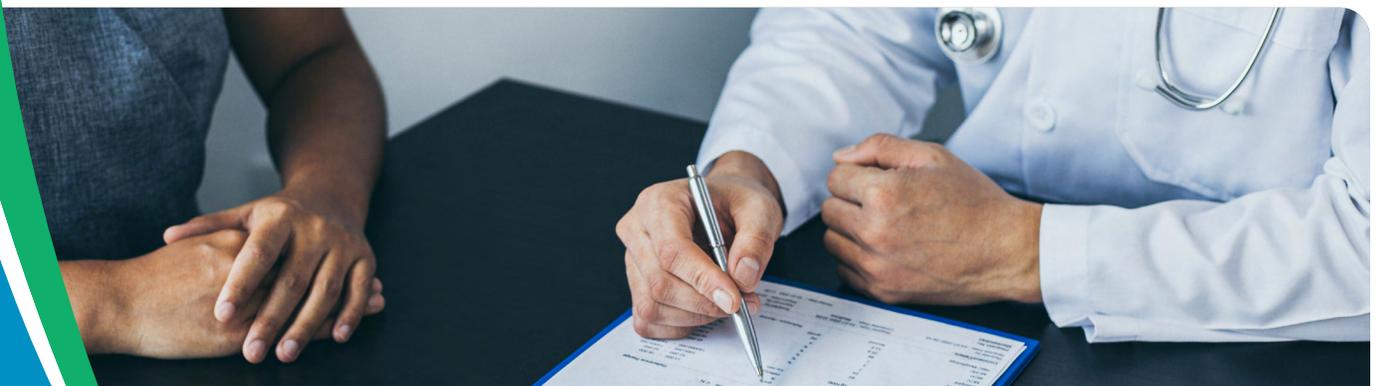
## POTENTIAL BARRIERS TO TREATMENT

Medical breakthroughs can save lives – but only if patients have access to them. Providers have expressed concern about the potentially problematic payment models that health plans may use to cover the new treatment.

### *Prior Authorization*

The greatest challenge that EBV+ PTLD patients and clinicians may face in accessing breakthrough medications is prior authorization. Because timely treatment for this condition and many others is imperative, prior authorization can delay life-saving care.

Prior authorization is a process wherein insurance companies must review prescribed treatments before a patient can receive coverage. Health care providers must fill out the required paperwork and submit it to insurers for patients to access the treatment they need. But seeking approval can take time, and there's no guarantee that a request will be approved.



The rarity of EBV+ PTLD may increase the burden posed by prior authorization. While most providers are familiar with routine prior authorization forms for more common treatments, EBV+ PTLD forms may be complicated and rarely used. Recalling the details of the process, completing the paperwork swiftly and accurately, and then receiving timely approval could pose a serious challenge. And when treatment for EBV+ PTLD is a race against time, patients and providers shouldn't be forced to wait when there is a life-saving treatment available.

EBV+ PTLD patients have already faced a life-threatening condition, a transplant and now a severe cancer. Ensuring that they can access treatments quickly and without unnecessary utilization management could be the difference between life and death.

Adequate Medicare reimbursement is also paramount to ensuring access. For hospitals to allow access to a new, potentially lifesaving treatment, CMS must first ensure proper coding for reimbursement.

Providers must be ready to advocate for their patients and serve as expert voices to health boards and decision-making bodies to encourage timely access.

### **Cost Sharing for Patients**

Other threats include cost-sharing, which can burden patients with high out-of-pocket expenses.

If patients' costs are exorbitant, patients may be priced out of treatment. Orphan drugs are often expensive because of the extensive research put into them and the small audience the medication serves. Affordability for patients, and policies that allow for co-pay assistance, are necessary given the potential costs of treatment.

Patients should not have to choose between living in bankruptcy or dying untreated.

And while these treatments may be expensive for patients, they also place a heavy burden on the health care system. By the time they are diagnosed with EBV+ PTLD, patients have already generated significant costs for transplantation and transplant maintenance.



***“These patients have already gone through the harrowing experience of failure of an organ, then the joy of getting an organ transplant, followed by the shock of knowing they now have a cancer. Along their medical journey, many patients and families have incurred enormous health care costs.”***

Vikas Dharnidharka, MD, MPH



## POTENTIAL BARRIERS & SOLUTIONS

### *Uniform Coding*

Upon FDA approval, new therapies need prompt uniform coding to ensure efficient reimbursement. Without proper coding, even an approved medication may be met with coverage questions that could delay treatment. With coverage for an ultra-rare condition like EBV+ PTLD, integration into coding and billing systems could take even longer and could cost patients time they don't have.<sup>11</sup>

While acquiring various codes can be challenging, especially for lesser-known treatments for rare conditions, tabelecleucel has been fortunate enough to receive an administration code. Other coding issues, however, may present barriers moving forward.

### *Clear Guidelines*

Guidelines for the use of EBV+ PTLD treatment may pose another serious challenge. Both hospitals and insurers will need to implement clear guidelines for tabelecleucel.

But the rarity of EBV+ PTLD means that even when tabelecleucel is

approved, many organizations may lack the necessary pathways to authorize treatment and limit the dangers of prior authorization.

When cases of EBV+ PTLD do arise, the lack of guidelines may lead to mismanaged requests and added delays. Lack of a streamlined process for patient considerations and expedited appeals could impact patients' health, treatment and lifespan.

### *Clinician Engagement*

Clinician engagement will be important as health plans and insurers work to understand the severity and rapid progression of EBV+ PTLD. Experts must be willing to lend their expertise to health plans, conveying the urgency behind timely approval processes and rapid treatment. The prior authorization process must include specialists in peer-to-peer meetings to provide a practical voice for patients. Understanding that new ground is being broken will help clinicians remember that their voices are essential to advocating for new medicines, treatments and their patients.

### *Patient Education*

After spending years in hospitals and in the medical system, patients faced with post-transplant complications can be their own best advocate and must be educated on signs and symptoms of complications. While providers watch patients closely, educated patients must be part of the equation.

### *Awareness*

For both patients and providers, awareness also presents a common challenge. As a rare disease, many transplant patients aren't aware of this condition at all. And even among clinicians in the field, the odds of EBV+ PTLD are so slim that many aren't familiar with this form of cancer.

Not every oncologist is equipped to handle EBV+ PTLD. But while they may not have the tools to adequately treat EBV+ PTLD, they still need to be aware of this condition and be able to refer patients to providers who can aid patients. Improving awareness for patients and providers has the potential to drastically improve patients' survival rate by allowing EBV+ PTLD to be caught earlier.

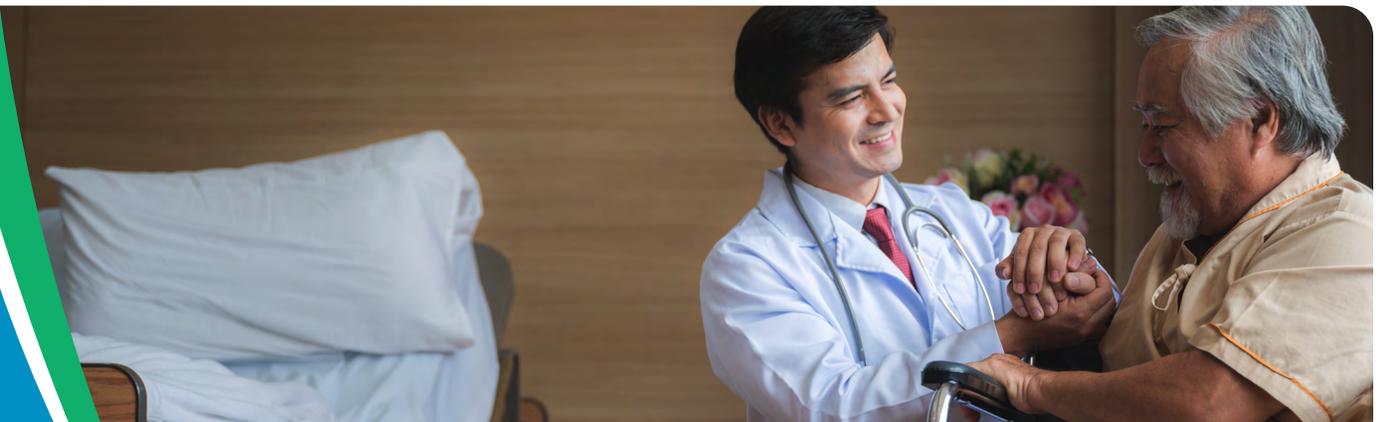


### **POLICY CONSIDERATIONS**

Given how time sensitive treatment of EBV+ PTLD is, it is crucial that restrictions do not go beyond the label. Options to address prior authorization include federal and state legislation that would streamline the FDA and health plan authorization process for orphan drugs or breakthrough treatments.

Viable treatment options may need to be considered under “gold card” legislation, which would allow select physicians with proven track records and expertise in their field, long-standing approvals to bypass arduous prior authorization processes.<sup>12</sup>

When transplant specialists encounter EBV+ PTLD, policies like these will ensure their experience is accounted for in delivering treatment and will support patients during the crucial time available to combat the disease. A recent study by the American Medical Association found that only 11% of health plans offered exemptions from prior authorization.<sup>13</sup>



A photograph showing a group of healthcare professionals in a meeting. A man in a white lab coat with a stethoscope around his neck is standing and gesturing while speaking to a group of people seated around a table. The seated individuals, including a man in blue scrubs and several women in white lab coats, are listening attentively. On the table are a laptop, papers, and a whiteboard with medical diagrams. The background shows a modern clinical setting with large windows and medical equipment.

## CONCLUSION

Clinicians must be equipped and prepared to advocate for their patients' access to groundbreaking new drugs. This is especially true for EBV+ PTLD, a serious rare cancer resulting from a life-changing transplant.

New treatments have the potential to save lives, and once they are approved patients will need speedy access. Patients should not have to suffer life-threatening bureaucratic delays, and providers should be able to focus on treating their patients, not endless piles of paperwork.

EBV+ PTLD moves fast. Ensuring a timely response to prior authorization requests, generating awareness among transplant patients, and informing providers and preparing them for the likely fight for their patients should be policy priorities in the months and years ahead.

## REFERENCES

1. National Organization of Rare Disorders. Rare Disease Database. "Post-Transplant Lymphoproliferative Disease." 2018. <https://rarediseases.org/rare-diseases/posttransplant-lymphoproliferative-disorders/>
2. Atara Biotherapeutics. EBVPTLD homepage. 2022. <https://www.ebvptld.com/>
3. Atara Biotherapeutics. Risk Factors. 2022. <https://www.ebvptld.com/monitoring-and-evaluation/#anchor-risk-factors>
4. Shahid S, Prockop SE. Epstein-Barr Virus-Associated Post-Transplant Lymphoproliferative Disorders: Beyond Chemotherapy Treatment. *Cancer Drug Resist* 2021; 4:646-64. DOI: 10.20517/cdr.2021.34. <https://cdrjournal.com/article/view/4094#B14>
5. National Center for Biotechnology Information. National Institute of Health. National Library of Medicine. Impact of Epstein-Barr Virus Donor and Recipient Serostatus on the Incidence of Post-Transplant Lymphoproliferative Disorder in Kidney Transplant Recipients. <https://pubmed.ncbi.nlm.nih.gov/22273720/>
6. Parker A, Bowles K, et al. Haemato-oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society. Diagnosis of Post-Transplant Lymphoproliferative Disorder in Solid Organ Transplant Recipients—BCSH and BTS Guidelines. *Br J Haematol*. 2010 Jun; 149(5):675-92. DOI: 10.1111/j.1365-2141.2010.08161. PMID: 20408847. <https://pubmed.ncbi.nlm.nih.gov/20408847/>
7. Atara Biotherapeutics. Pipeline Medications. 2022. <https://www.atarabio.com/pipeline/tabelecleucel/>
8. Atara Biotherapeutics. Patient Impact. 2022. <https://www.ebvptld.com/about-ebvptld/#anchor-patient-impact>
9. Allen UD, Preiksaitis JK. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13652.
10. Styczynski J, van der Velden W, Fox CP, et al. Management of Epstein-Barr virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. *Haematologica*. 2016;101(7):803-811.
11. Alliance for Patient Access. [https://admin.allianceforpatientaccess.org/wp-content/uploads/2022/04/AfPA\\_EBV-PTLD-Initiative\\_RD-Working-Group-Meeting-Summary\\_Apr-2022.pdf](https://admin.allianceforpatientaccess.org/wp-content/uploads/2022/04/AfPA_EBV-PTLD-Initiative_RD-Working-Group-Meeting-Summary_Apr-2022.pdf)
12. Alliance for Patient Access. [https://admin.allianceforpatientaccess.org/wp-content/uploads/2022/04/AfPA\\_EBV-PTLD-Initiative\\_RD-Working-Group-Meeting-Summary\\_Apr-2022.pdf](https://admin.allianceforpatientaccess.org/wp-content/uploads/2022/04/AfPA_EBV-PTLD-Initiative_RD-Working-Group-Meeting-Summary_Apr-2022.pdf)
13. American Medical Association. PA Reform. <https://www.ama-assn.org/system/files/2021-05/prior-authorization-reform-progress-update.pdf>

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## ABOUT THE RARE DISEASES WORKING GROUP

*The Alliance for Patient Access' Rare Diseases Working Group is a network of policy-minded health care providers who advocate for patient-centered care.*

*To learn more, visit [allianceforpatientaccess.org/rare-diseases](https://allianceforpatientaccess.org/rare-diseases)*



**Rare Diseases**  
Working Group

## EBV+ PTLD INITIATIVE MEMBERS

Vikas Dharnidharka, MD, MPH • Neel Gupta, MD

Thomas Habermann, MD • Susan Prockop, MD

*Please note that the views expressed in this document do not necessarily reflect those of the institutions with which working group members are affiliated.*