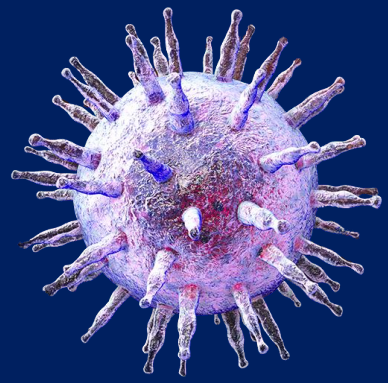
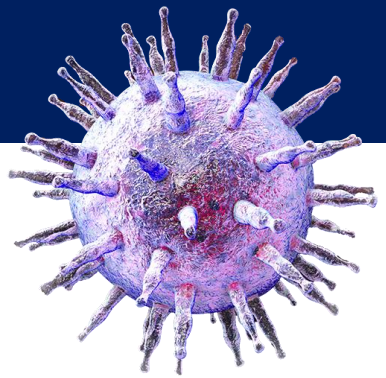


# Epstein-Bar Virus Infection

SHIVA SAMAVAT
Associate Professor of Nephrology
Shahid Labbafinejad Medical Center; SBMU

02.09.2021



# Balanced immune system

Rejection — Infection

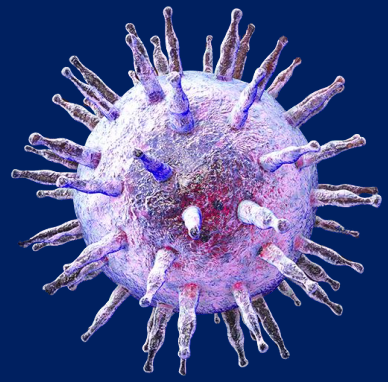
Insufficient immunosuppression

Excessive immunosuppression

BKVN
Nosocomial infections
Latent infections
Community infections
Drug nephrotoxicity

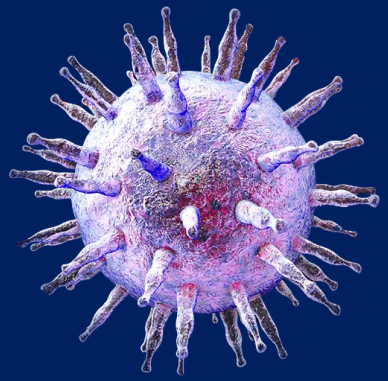
Allograft rejection

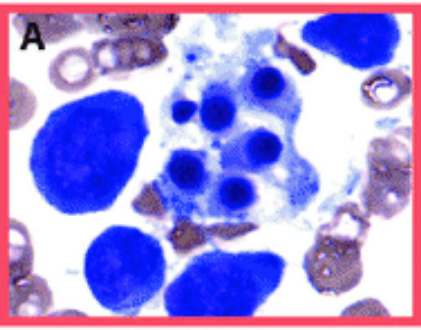
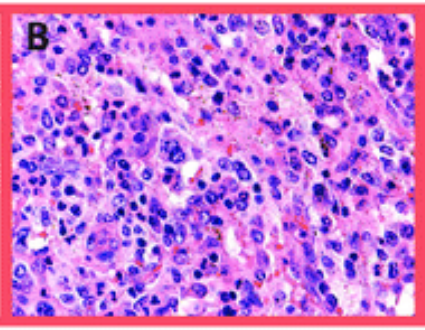
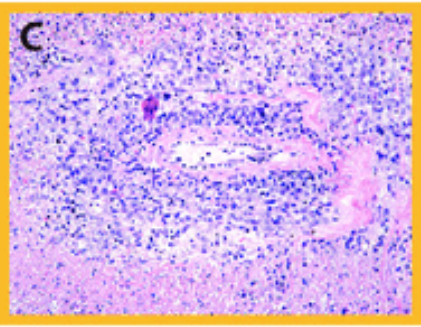
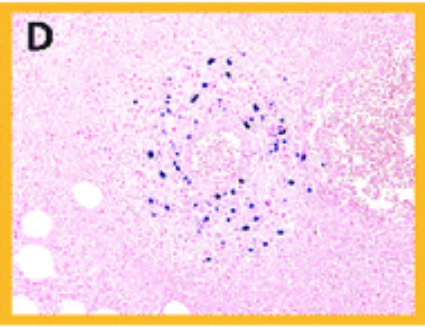
Renal allograft dysfunction

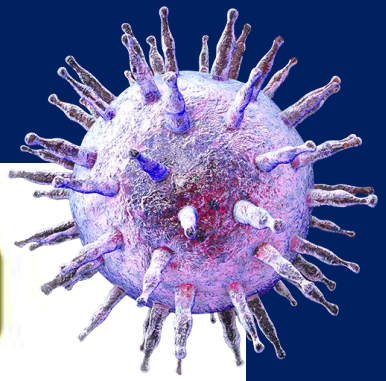


- Epstein–Barr virus (EBV) is a human herpesvirus 4 (HHV-4)
- EBV is a ubiquitous viral pathogen, with a seroprevalence of more than 90% in adults.
- Most primary EBV infections occur during childhood and are asymptomatic.
- Infectious mononucleosis

# Clinical Syndromes



| | | |
|---|---|---|
| Non-neoplastic EBV infections | EBV-associated hemophagocytic lymphohistiocytosis |     |
| Systemic EBV infections | Chronic active EBV infection |     |



# EBV-related human tumors and tumor-like lesions

**Epithelial lesions**

- Nasopharyngeal carcinoma
- Thyroid gland cancer
- Salivary gland cancer
- Gastric carcinoma
- Breast cancer
- Lung cancer
- Colon cancer
- Reanal cancer
- Bladder cancer
- Uterine cervix cancer

**Non-epithelial lesions**

- Burkitt's lymphoma
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Angio-immunoblastic T-cell lymphoma
- T/NK cell lymphoma
- Nasal T/NK cell lymphoma
- Leiomyosarcoma
- Pyothorax-associated lymphoma
- Lymphoproliferative disorders
  - X-linked
  - AIDS-related
  - Post-transplant
  - Drug-related
  - Age-related

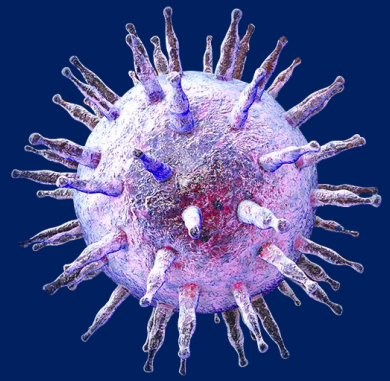
**EBV**

?

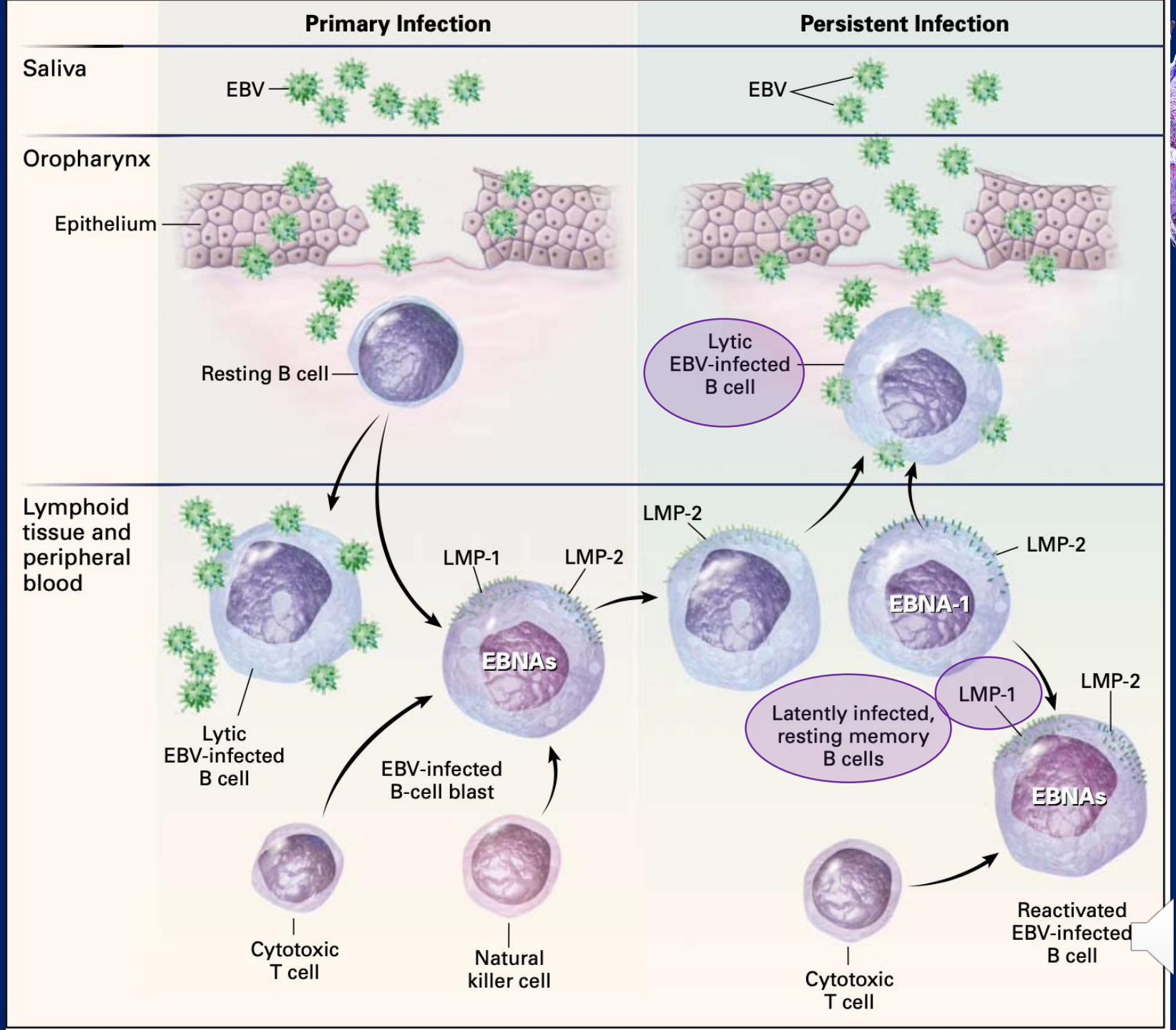
**Oral cavity**

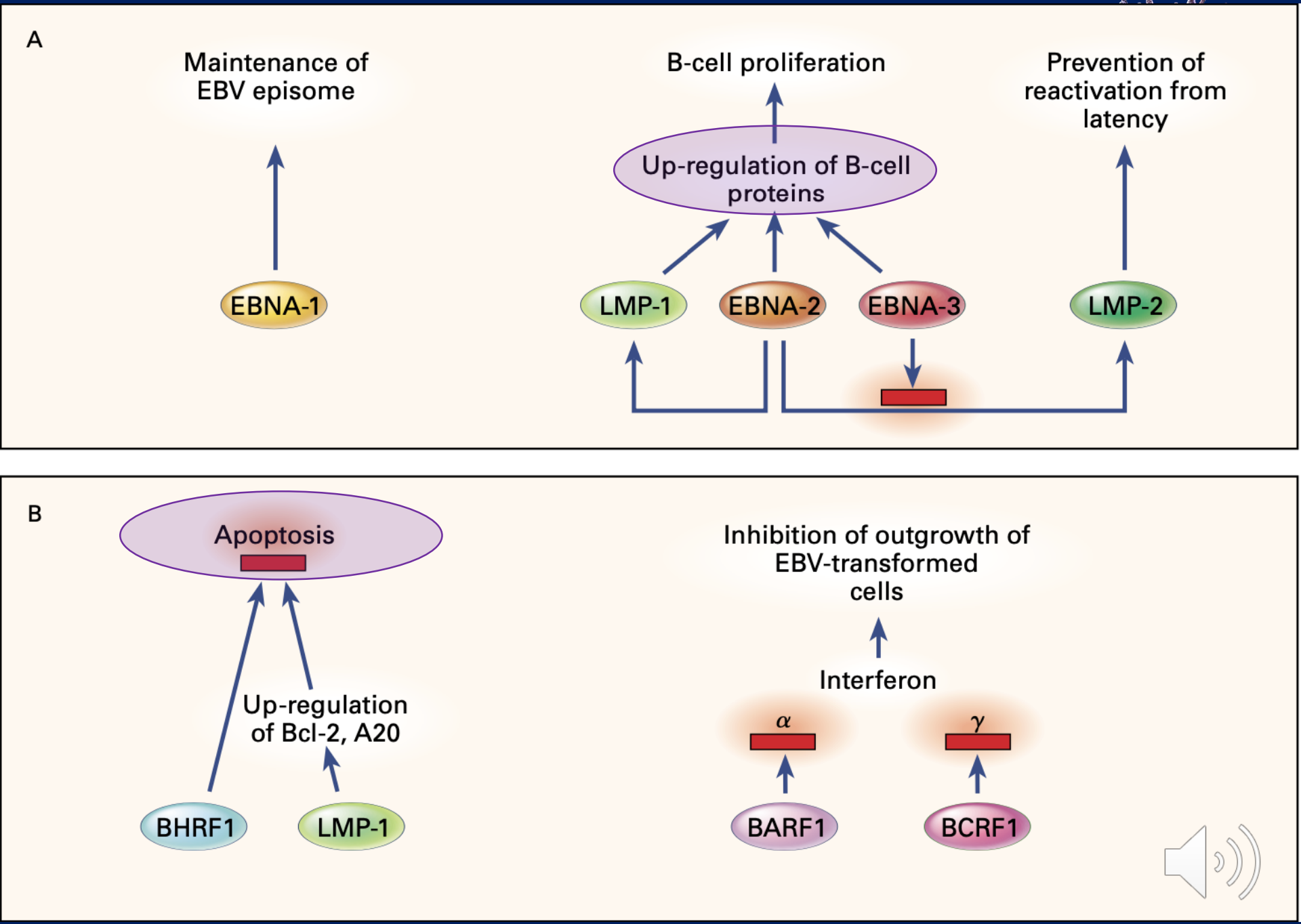
Squamous cell carcinoma

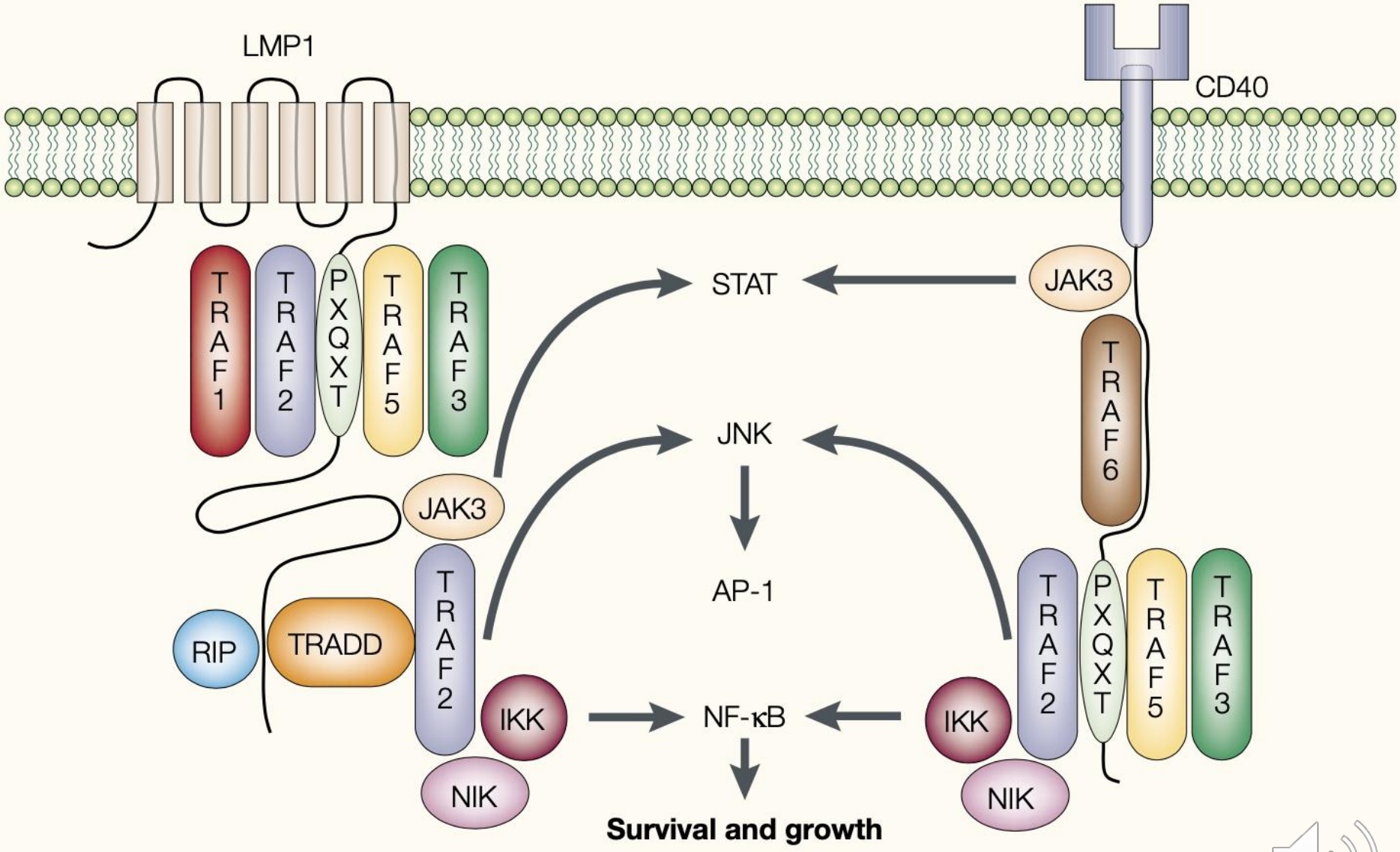
Lymphoproliferative disorders
- Drug-related
- Age-related

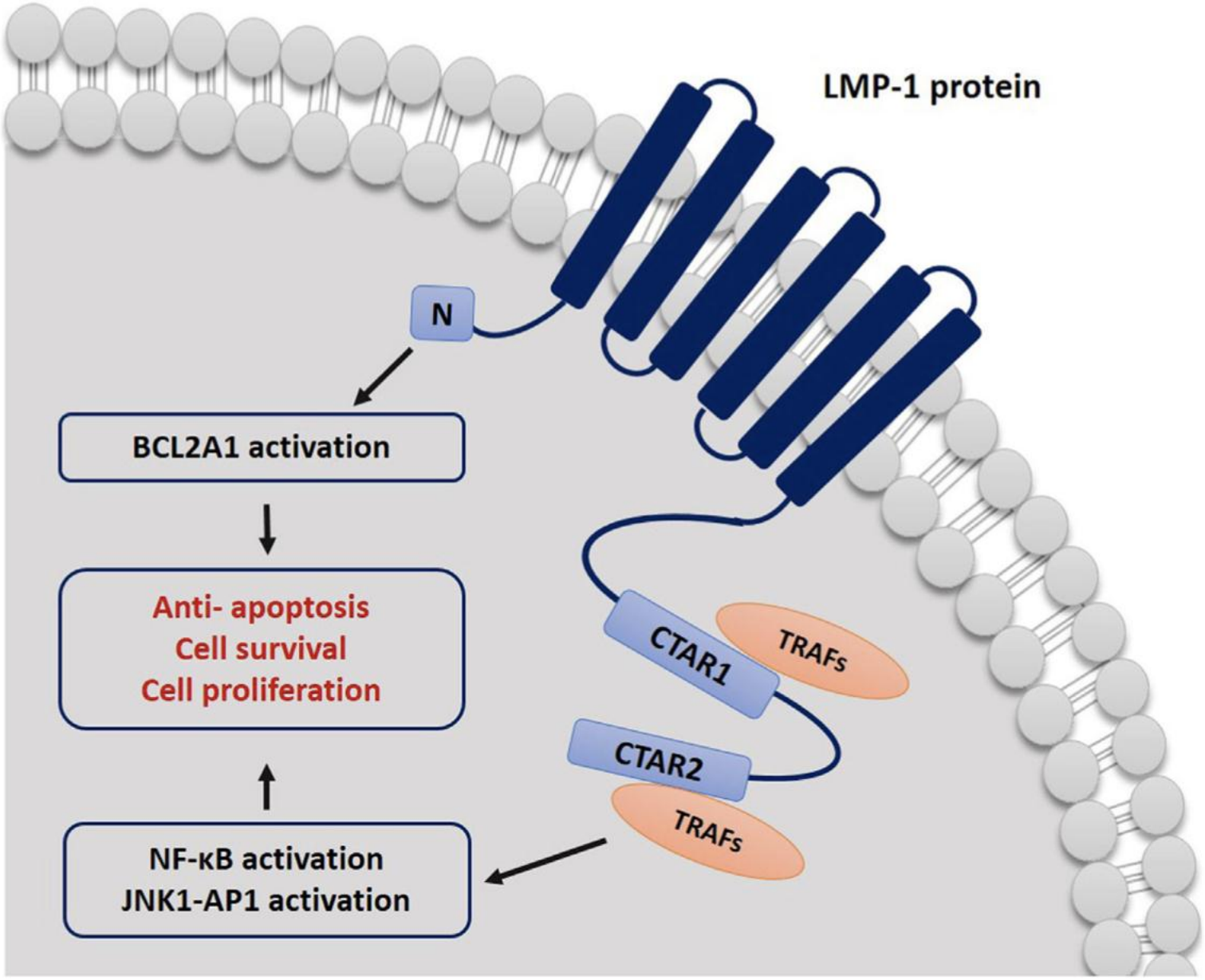


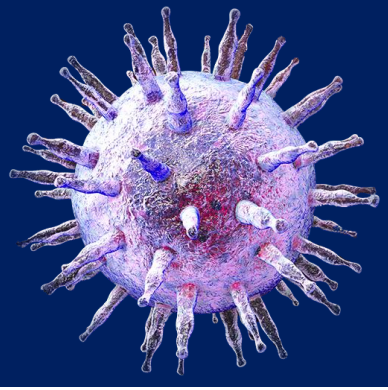
# Pathogenesis of EBV Infection


Primary Infection
Persistent Infection
Saliva
EBV
EBV
Oropharynx
Epithelium
Resting B cell
Lytic EBV-infected B cell
Lymphoid tissue and peripheral blood
LMP-1
LMP-2
EBNAs
LMP-2
LMP-2
EBNA-1
Lytic EBV-infected B cell
EBV-infected B-cell blast
Latently infected, resting memory B cells
LMP-1
LMP-2
EBNAs
Cytotoxic T cell
Natural killer cell
Cytotoxic T cell
Reactivated EBV-infected B cell

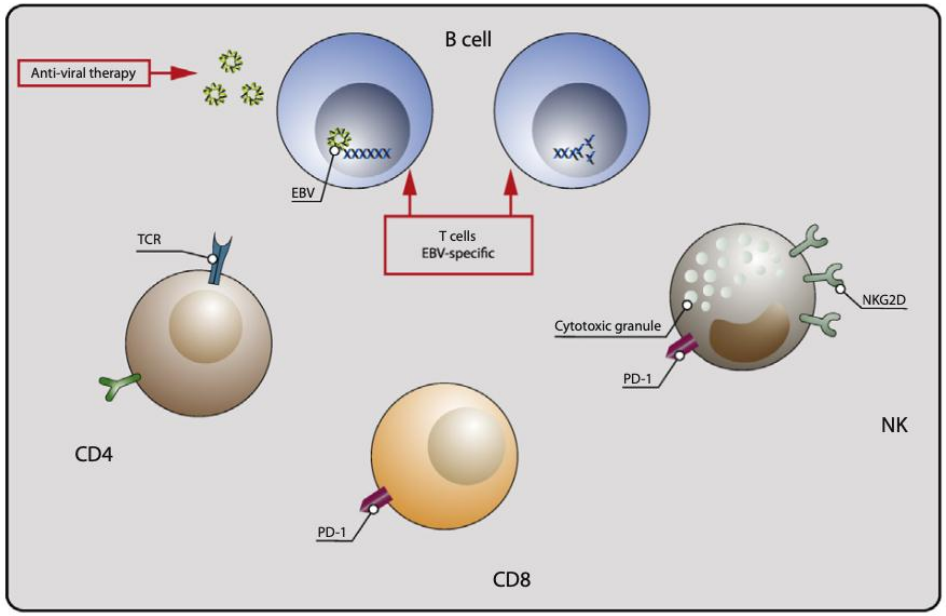

A
Maintenance of EBV episome
EBNA-1
B-cell proliferation
Up-regulation of B-cell proteins
LMP-1
EBNA-2
EBNA-3
Prevention of reactivation from latency
LMP-2
B
Apoptosis
Up-regulation of Bcl-2, A20
BHRF1
LMP-1
Inhibition of outgrowth of EBV-transformed cells
Interferon
α
γ
BARF1
BCRF1


LMP1
CD40
TRAF1
TRAF2
PXQXT
TRAF5
TRAF3
STAT
JAK3
TRAF6
JNK
JAK3
AP-1
RIP
TRADD
TRAF2
IKK
NF-κB
IKK
TRAF2
PXQXT
TRAF5
TRAF3
NIK
NIK
Survival and growth


LMP-1 protein
N
BCL2A1 activation
Anti- apoptosis
Cell survival
Cell proliferation
NF-κB activation
JNK1-AP1 activation
CTAR1
TRAFs
CTAR2
TRAFs

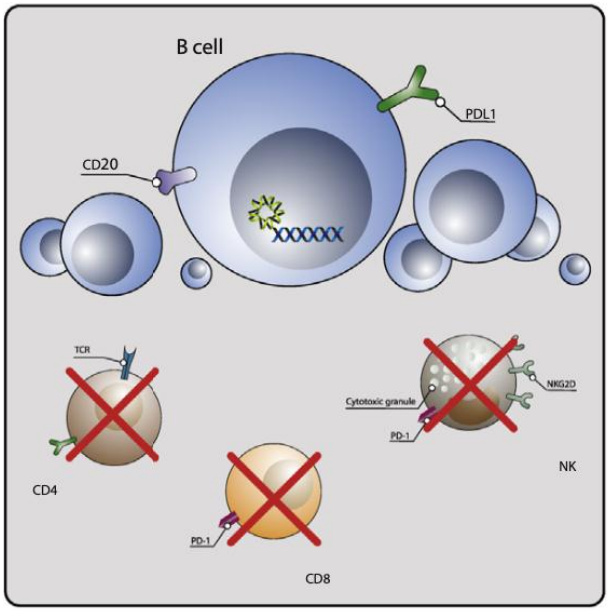


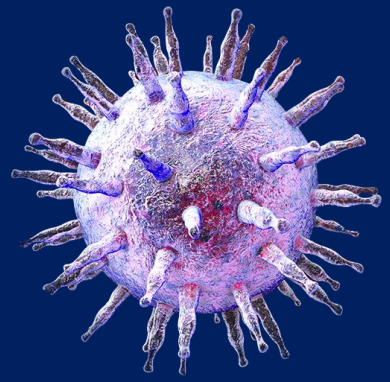
B cell transformation




Introduction of immunosuppression

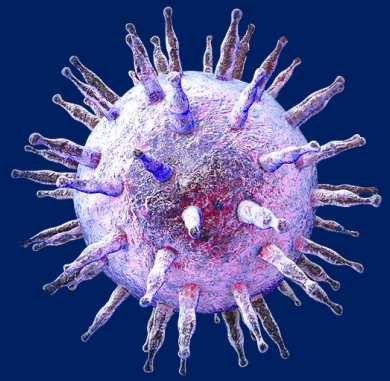
PTLD



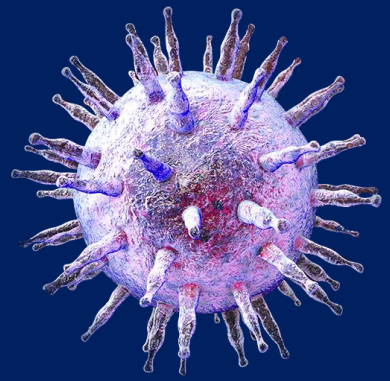


- Lack of cytotoxic T cell response
- $CD4^+$ T cell lymphopenia
- Increased exhausted $CD8^+$ T cells ($PD_1^+$ $CD_8^+$ T cells)
- Viral replication
- B cell Transformation

- Eventually lead to PTLD



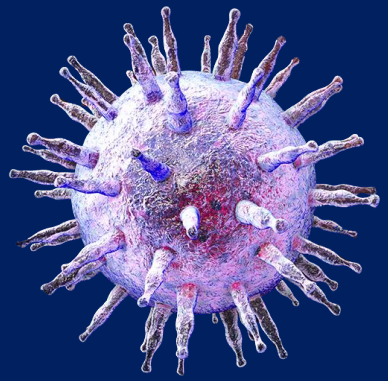
# Risk factors of EBV infection



- EBV sero-mismatch
- Overimmunosuppression:
  - ATG: ATG should be used with caution in EBV D+/R− patients.
  - EBV replication more often in patients receiving belatacept, than it does in those receiving cyclosporine.
  - MMF maintenance has a role in preventing EBV DNAemia.

*American Journal of Transplantation* 2013; 13: 656–562

*Experimental and Clinical Transplantation (2014) 3: 212-219*



# Evaluation and Management of Candidates for Kidney Transplantation

10.5.5 Epstein-Barr virus (EBV)

10.5.5.1: We recommend screening for EBV with EBV viral capsid antigen (VCA) IgG and/or EBV nuclear antigen (EBNA) IgG *(1C)*.

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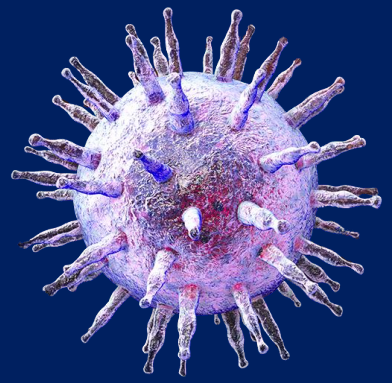
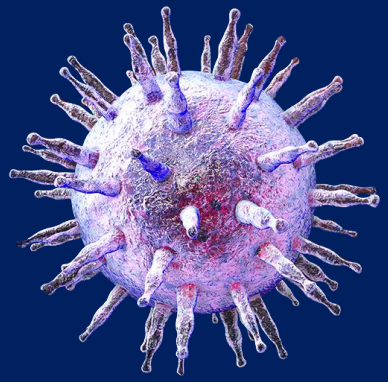


**Recommendations for initial and follow-up screening of viral and non-viral pathogens in kidney transplant candidates.**

| Pathogen | Test | Repeat testing |
|---|---|---|
| **Viral infections** | | |
| HIV | IgG | If negative, repeat annually and at time of transplant |
| HCV | IgG | If negative, repeat annually and at time of transplant |
| HBV | Anti-HBs, Anti-HBc, HBsAg | If negative, repeat annually and at time of transplant |
| CMV | IgG | If negative, repeat at time of transplant |
| EBV | VCA IgG or EBNA IgG | If negative, repeat at time of transplant |
| HSV | IgG | If negative, repeat at time of transplant |
| VZV | IgG | If negative, repeat at time of transplant and 4 weeks post-vaccination |
| Measles, Mumps, Rubella | IgG | If negative, repeat at time of transplant and 4 weeks post-vaccination |
| HTLV | IgG | None unless ongoing risk of exposure |
| **Non-Viral infections** | | |
| Syphilis | IgG with confirmatory testing if IgG positive | None |
| Strongyloides | IgG | None |
| Chagas disease | IgG | None |
| Tuberculosis (in low prevalence areas) | Tuberculin skin test or Interferon-gamma release assay (IGRA) | Annually if ongoing risk of exposure |
| Malaria | Blood smear if clinically indicated | None |



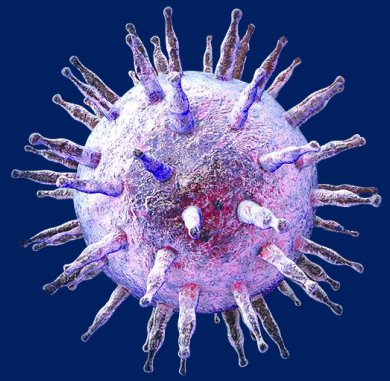
## 13.3: EPSTEIN-BARR VIRUS AND POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

13.3.1: We suggest monitoring high-risk (donor EBV seropositive/recipient seronegative) KTRs for EBV by NAT (*2C*):

- once in the first week after transplantation *(2D)*;
- then at least monthly for the first 3–6 months after transplantation *(2D)*;
- then every 3 months until the end of the first post-transplant year *(2D)*; and
- additionally after treatment for acute rejection. *(2D)*

*Kidney International* advance online publication, 21 October 2009; doi:10.1038/ki.2009.377

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

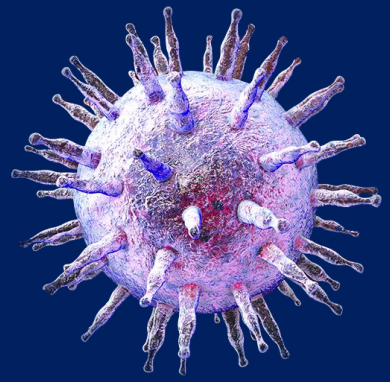


# Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Upton D. Allen[1,2,3] | Jutta K. Preiksaitis[4] | on behalf of the AST Infectious Diseases Community of Practice

*Clinical Transplantation*. 2019;33:e13652.

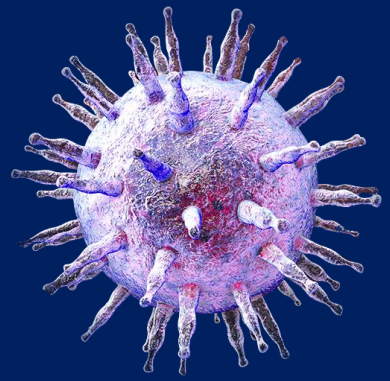
Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research



2. We recommend EBV viral load surveillance and preemptive interventions in patients who are EBV-seronegative pre-transplant (*weak/low*). In patients who receive seropositive donor organs, monitoring should occur weekly to biweekly, when possible over the first post-transplant year until EBV DNAemia is detected. When this occurs, monitoring should occur weekly during initial acute phase of infection, then less frequently by increasing increments until "set point" is achieved (*weak/*

*Clinical Transplantation*. 2019;33:e13652.

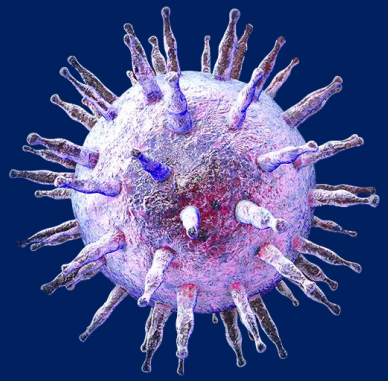
Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research



*very low*). Less frequent initial monitoring (monthly) for community-acquired infection should be considered in seronegative patients who receive seronegative donor organs. Ongoing monitoring beyond the first post-transplant year may be considered in patients who have fluctuating immunosuppression, rejection episodes or have not established a viral "set point."

*Clinical Transplantation*. 2019;33:e13652.

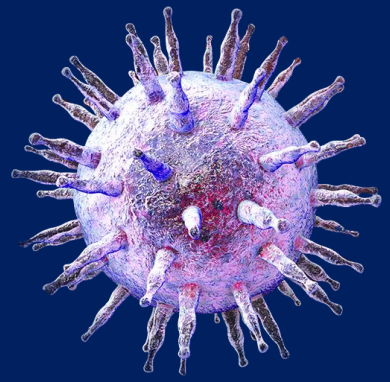
Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research



3. Viral load surveillance and preemptive strategies are not routinely recommended for SOT patients who are EBV seropositive pre-transplant (adults: *strong/low*, children: *weak/low*) with the exception of intestinal transplant recipients (*weak/low*) and in situations where retransplantation occurs following PTLD (*weak/low*).

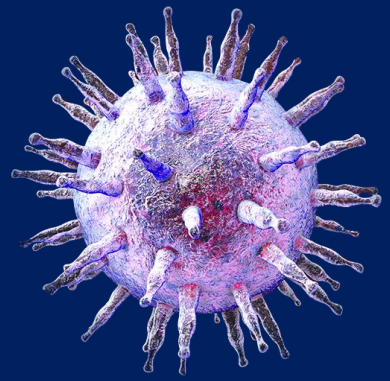
*Clinical Transplantation.* 2019;33:e13652.

# How to monitor?



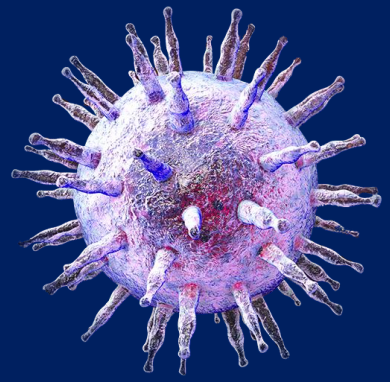
- Whole blood or lymphocyte EBV viral load is higher and becomes detectable earlier than contemporaneously tested plasma.

- Patients should be monitored using the same sample type and the same assay in a single laboratory.



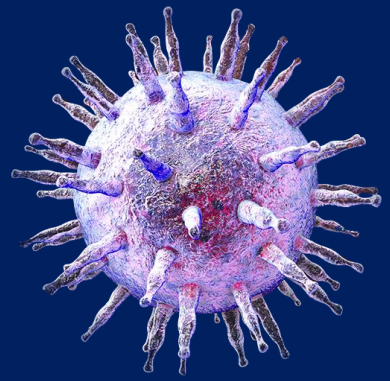
- There are very few natural history studies relating EBV DNAemia levels to PTLD events.

- No specific cut-off.



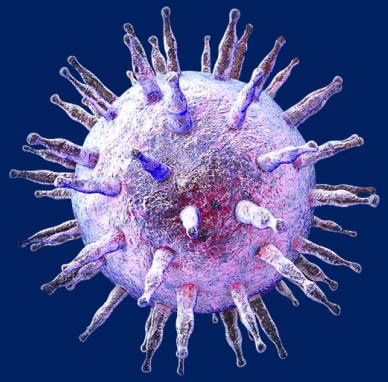
- More useful than a single value might be the trend in viral loads. (rapidly rising count)

- Most centers are more likely to intervene by reducing immunosuppression when loads are serially increasing.



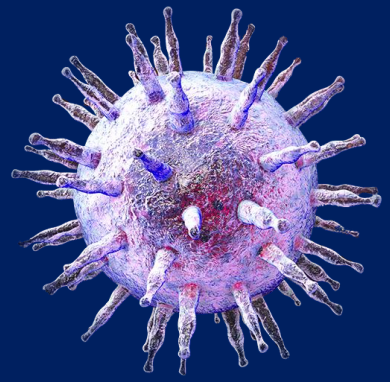
- Adjunctive laboratory testing may improve the specificity of high viral load as a predictor of PTLD:
  - EBV-specific T-cell ELISPOT assays
  - Virus-specific T cell by cytokine flow cytometry
  - CD20 or CD4/CD8/NK cell counts

# Virus-specific T cells



- There is increasing evidence that virus-specific T cells mirror not only the virus-specific but also the general cellular immune defense.

- They may serve as an indicator of the intensity of immunosuppression as well as a prognostic marker for virus-induced diseases after transplantation.



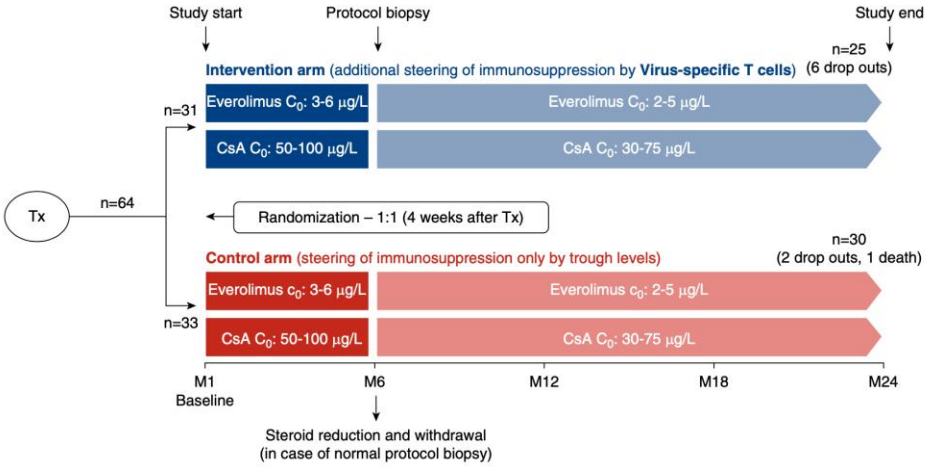
- High levels of EBV-specific CD4 T cells are associated with asymptomatic self-limiting EBV viremia, whereas lack or low levels of EBV-specific CD4 T cells are found in the case of symptomatic, long-term viremia.

- They might be additionally used for steering of the intensity of IS treatment to avoid overimmunosuppression

# Steering of Tx-Immunosuppression by Virus-Specific T Cells (IVIST-Trial)

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

## Methods

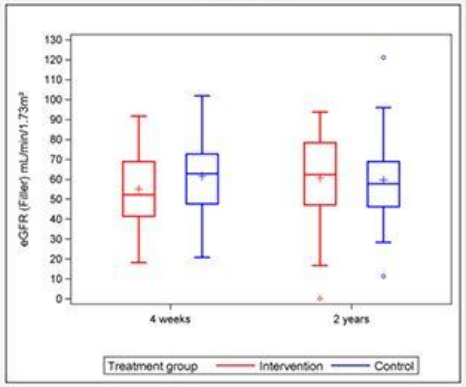



## Conclusion

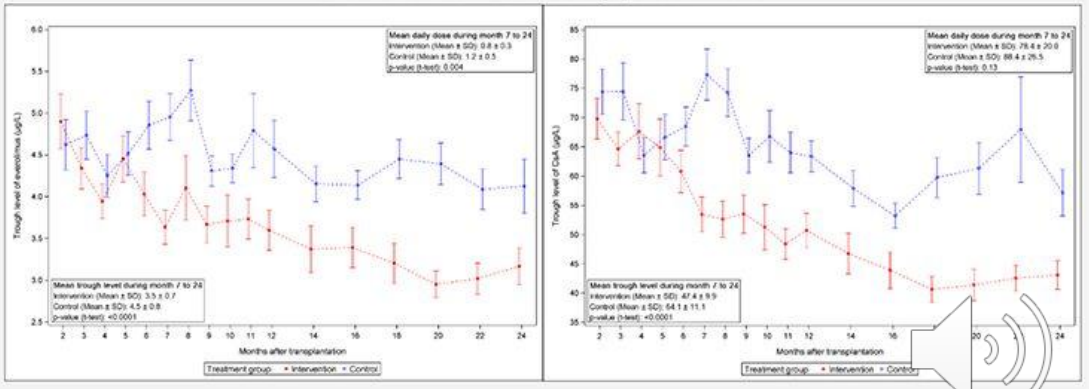
Additional steering of immunosuppressive therapy by Tvis levels is safe, results in a similar GFR and personalizes immunosuppressive therapy by lowering exposure to immunosuppressive drugs leading to economic benefits.

## Outcome

### eGFR

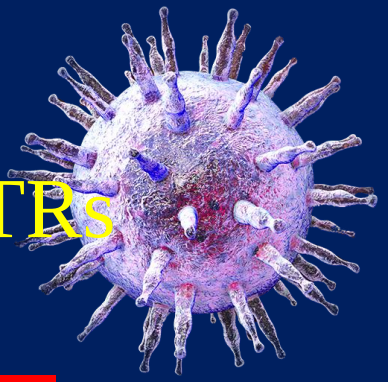



### Dose of Immunosuppressants




doi: 10.1681/ASN.2020050645

# Current approaches for EBV(D+/R–) KTRs



- Antiviral drugs (universal prophylaxis)
- IVIG (universal prophylaxis)
- Monitoring for EBV load by PCR (preemptive prophylaxis):
  - Adjustment of immunosuppression,
  - Antiviral drugs
  - IVIG
  - Infusion of EBV-specific cytotoxic T cells
  - Monoclonal antibody: CD20+ B cells

# The Role of Antiviral Prophylaxis for the Prevention of Epstein–Barr Virus–Associated Posttransplant Lymphoproliferative Disease in Solid Organ Transplant Recipients: A Systematic Review

| Study or Subgroup | prophylaxis Events | Total | no prophylaxis Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **4.2.1 Risk of PTLD with prophylaxis alone** | | | | | | |
| Hocker et al. 2012 | 1 | 20 | 1 | 8 | 2.4% | 0.40 [0.03, 5.65] |
| Kim et al. 2010 | 5 | 26 | 4 | 12 | 12.0% | 0.58 [0.19, 1.77] |
| Kogan et al. 1999 | 0 | 2 | 1 | 1 | 2.4% | 0.22 [0.02, 3.16] |
| Malouf et al. 2002 | 0 | 15 | 1 | 3 | 1.8% | 0.08 [0.00, 1.69] |
| Opelz et al. 2009 | 24 | 882 | 26 | 1345 | 37.2% | 1.41 [0.81, 2.44] |
| Wong et al. 2004 | 4 | 12 | 1 | 4 | 4.6% | 1.33 [0.20, 8.71] |
| Zangwill et al 1998 | 2 | 2 | 10 | 10 | 39.6% | 1.00 [0.59, 1.69] |
| **Subtotal (95% CI)** | | **959** | | **1383** | **100.0%** | **0.97 [0.64, 1.47]** |
| Total events | 36 | | 44 | | | |
| Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 6.85$, df = 6 (P = 0.33); $I^2 = 12\%$ | | | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | | | |
| **4.2.2 Risk of PTLD with antiviral preemptive therapy** | | | | | | |
| Holmes et al. 2002 | 3 | 6 | 0 | 10 | 49.7% | 11.00 [0.66, 182.27] |
| Ozcay et al. 2009 | 0 | 3 | 2 | 5 | 50.3% | 0.30 [0.02, 4.74] |
| **Subtotal (95% CI)** | | **9** | | **15** | **100.0%** | **1.80 [0.05, 62.12]** |
| Total events | 3 | | 2 | | | |
| Heterogeneity: $Tau^2 = 4.51$; $Chi^2 = 3.24$, df = 1 (P = 0.07); $I^2 = 69\%$ | | | | | | |
| Test for overall effect: Z = 0.33 (P = 0.75) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.11$, df = 1 (P = 0.73), $I^2 = 0\%$ | | | | | | |

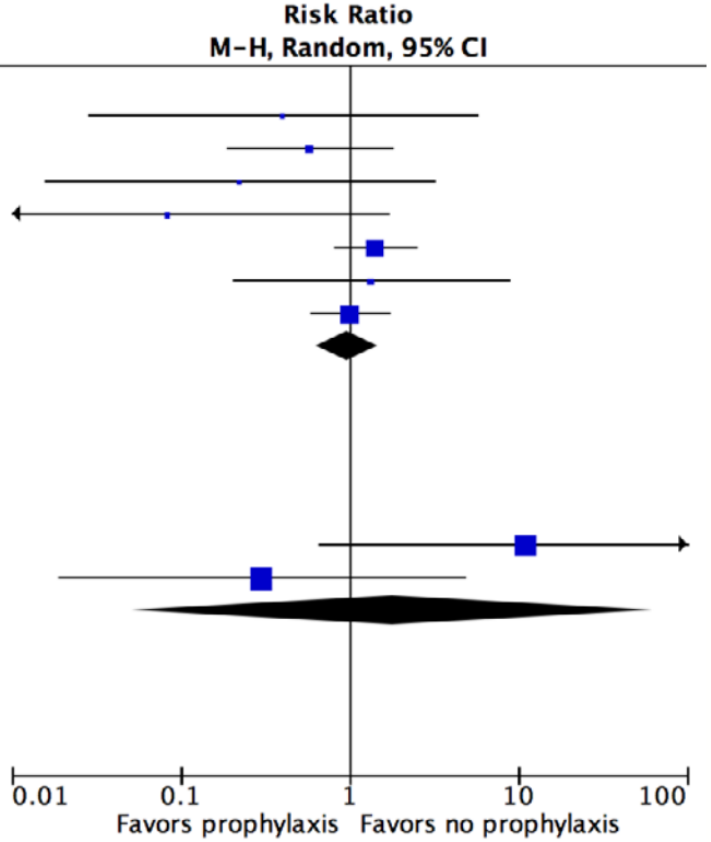
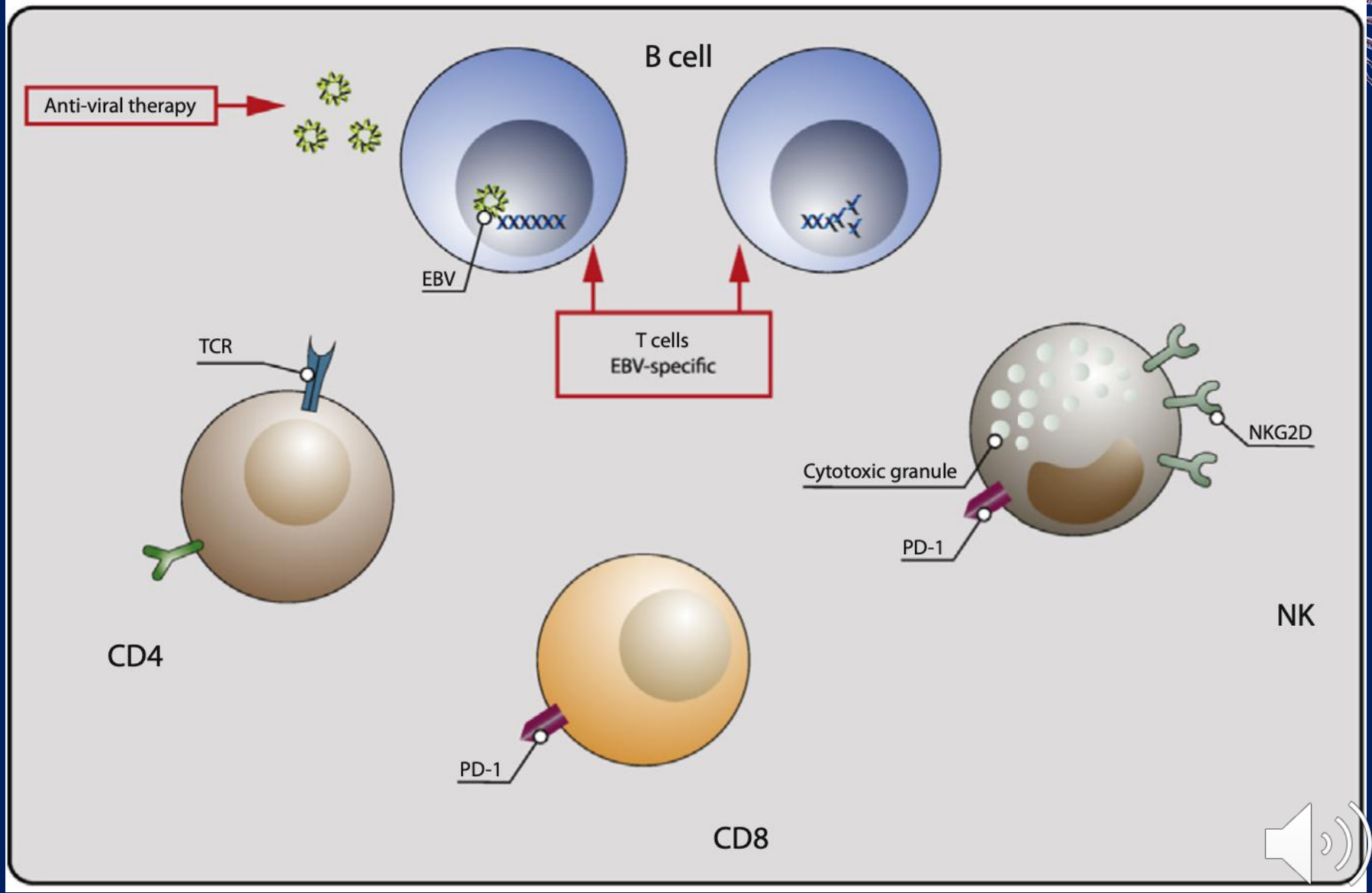
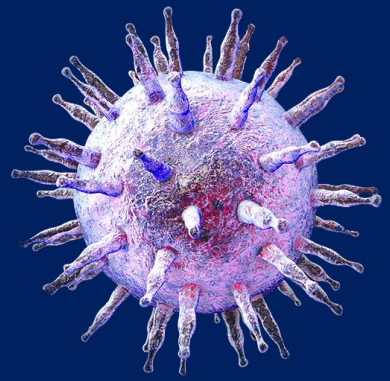



**Figure 4: Effect of antiviral prophylaxis on the incidence of PTLD by subgroups of antivirals given for preempt therapy only and prophylaxis only.** CI, confidence interval; M-H, Mantel-Haenszel; PTLD, posttransplant lymphoproliferative disease.

# B cell transformation



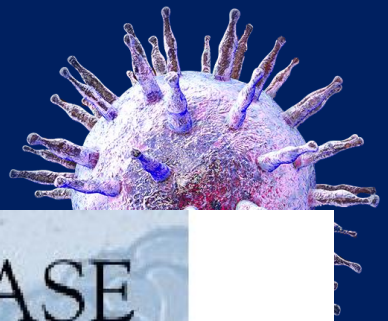
Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research



## Recommendations: prevention

1. The use of antiviral agents, IVIG, and adoptive immunotherapy as universal prophylaxis for early PTLD prevention in EBV-mismatched patients is not recommended (*weak/low*).

*Clinical Transplantation*. 2019;33:e13652.



TRANSPLANT INFECTIOUS DISEASE

Original Article

# Pretransplant prophylactic rituximab to prevent Epstein-Barr virus (EBV) viremia in EBV-seronegative kidney transplant recipients from EBV-seropositive donors: results of a pilot study

Thomas Schachtner ✉, Petra Reinke

First published: 15 September 2016 | https://doi.org/10.1111/tid.12605 | Citations: 16

Prophylactic rituximab given prior to transplantation appears to reduce EBV transmission, EBV viremia, and associated development of PTLD in EBV(D+R–) living KTRs.

Transplant International

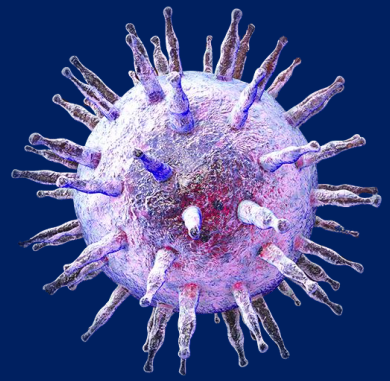
Letter To The Editors

# Multitarget anti-EBV therapy to prevent primary infection in kidney transplant recipients from deceased donor, at risk of post-transplantation lymphoproliferative disorder (EBV D+/R−)

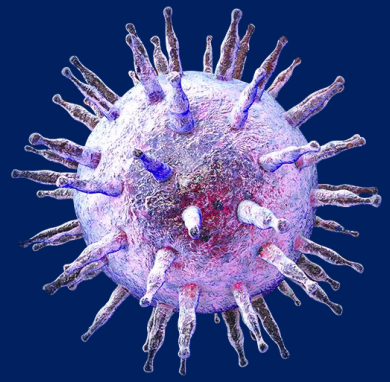
Simon Ville ✉, Jacques Dantal

First published: 17 May 2020 | https://doi.org/10.1111/tri.13652

- 4 KTRs from deceased donors.
- A single dose of rituximab (375 mg/m2 IV, day 0 post-transplantation),
- anti-viral drugs (valganciclovir 450 mg twice daily, 6 months) and IVIG (0,4 g/kg on day 0 and 1).
- Patients received basiliximab as induction therapy, and tacrolimus (though level between 6 and 8 ng/L) combined with acid mycophenolic (720 mg twice a day).
- At the last follow-up ranging from 24 to 36 months, no one has developed PTLD.

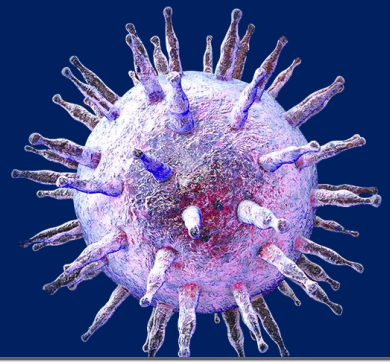


# Posttransplant Lymphoproliferative Disease

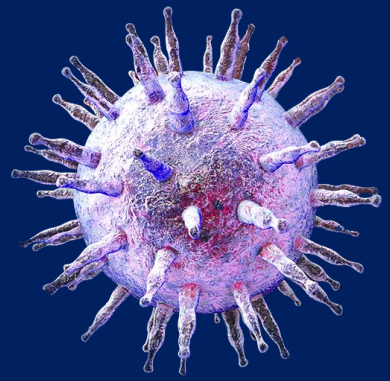


- The overall 5-year PTLD rates in adults ranged from 0.6 to 9%, with a higher rate for intestinal and lung transplantations, but also for seronegative recipients.

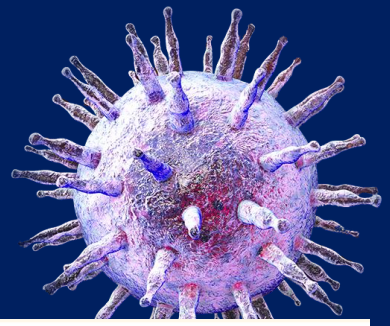
- With highest risk in the first year posttransplant but remaining increased beyond 10 years.



| Variable | Risk after Solid-Organ Transplantation |
|---|---|
| Established risk factors | |
| | Type of transplanted organ, relative risk: multiorgan and intestinal, 239.5; lung, 58.6; pancreas, 34.9; liver, 29.9; heart, 27.6; kidney, 12.6 |
| | EBV mismatch at time of transplantation (recipient EBV-negative, donor EBV-positive); relative risk, 10–75 |
| | |
| | Intensity of induction immunosuppressive therapy and duration of maintenance therapy (including graft-rejection episodes); overall SIR, 10 |

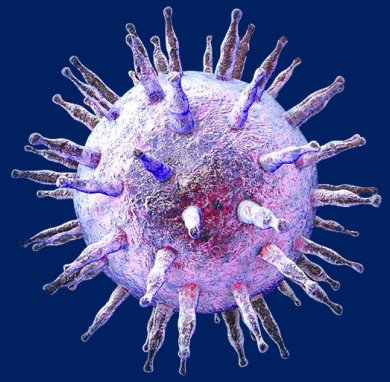


| Strong evidence of risk | |
|---|---|
| | Increased risk associated with ATG, OKT3, tacrolimus, azathioprine, new agents (e.g., belatacept in EBV-negative transplant recipient) |
| | Controversial degree of risk associated with alemtuzumab, cyclosporine, mTOR inhibitors |
| | No increase in risk associated with mycophenolate mofetil, basiliximab, daclizumab |



| Weak evidence of risk | |
|---|---|
| | Underlying disorder (HCV, cystic fibrosis, autoimmune hepatitis) |
| | Race or ethnic group (risk in descending order): white, black, African |
| | |
| | Monoclonal gammopathy of undetermined significance (in recipient) |
| | Non-EBV infection (HCV or CMV infection) |
| | Older donor age and younger recipient age |
| | Cytokine gene polymorphisms |
| | HLA alleles, haplotypes, mismatches, antibodies |

# Clinical Manifestations



- Nonspecific (fever, weight loss, allograft dysfunction, anemia)

- Reflect the site of localization of the mass (lymph node enlargement across one or several different sites externally or internally, symptoms referable to gastrointestinal tract, brain, liver, or kidney).

# A rare presentation of a posttransplant lymphoproliferative disorder

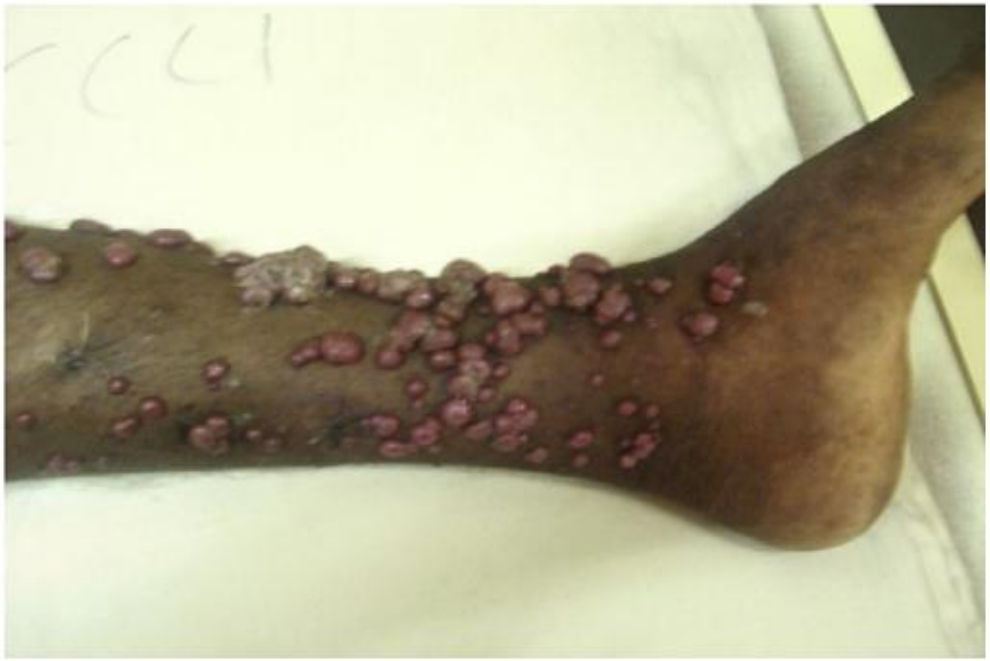
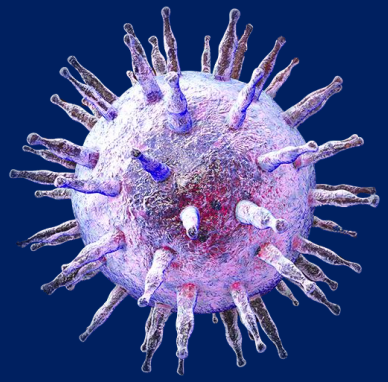


**Figure 1 | Cutaneous plasmacytoma overlying the left shin showing extensive violaceous nodules, some of which have coalesced to form a single mass.**

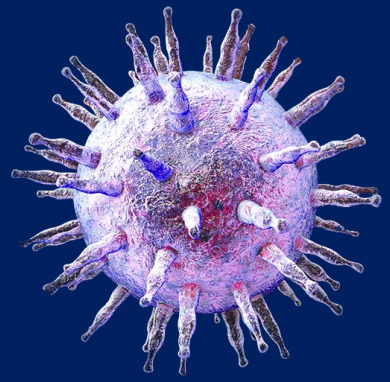
*Kidney International* (2018) **93,** 761; https://doi.org/10.1016/j.kint.2017.10.013

# Early vs late-onset PTLD



- Early-onset PTLD tends to be EBV-driven and often involves the allograft, younger age, extranodal disease, prior treatment of acute rejection, B-cell lymphoma histology, and tumor EBV positivity.

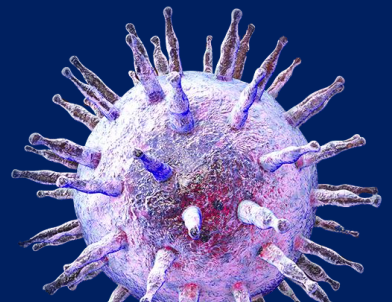
- Burkitt lymphoma and Hodgkin disease were observed only in late PTLDs, which are more likely to present with nodal disease.

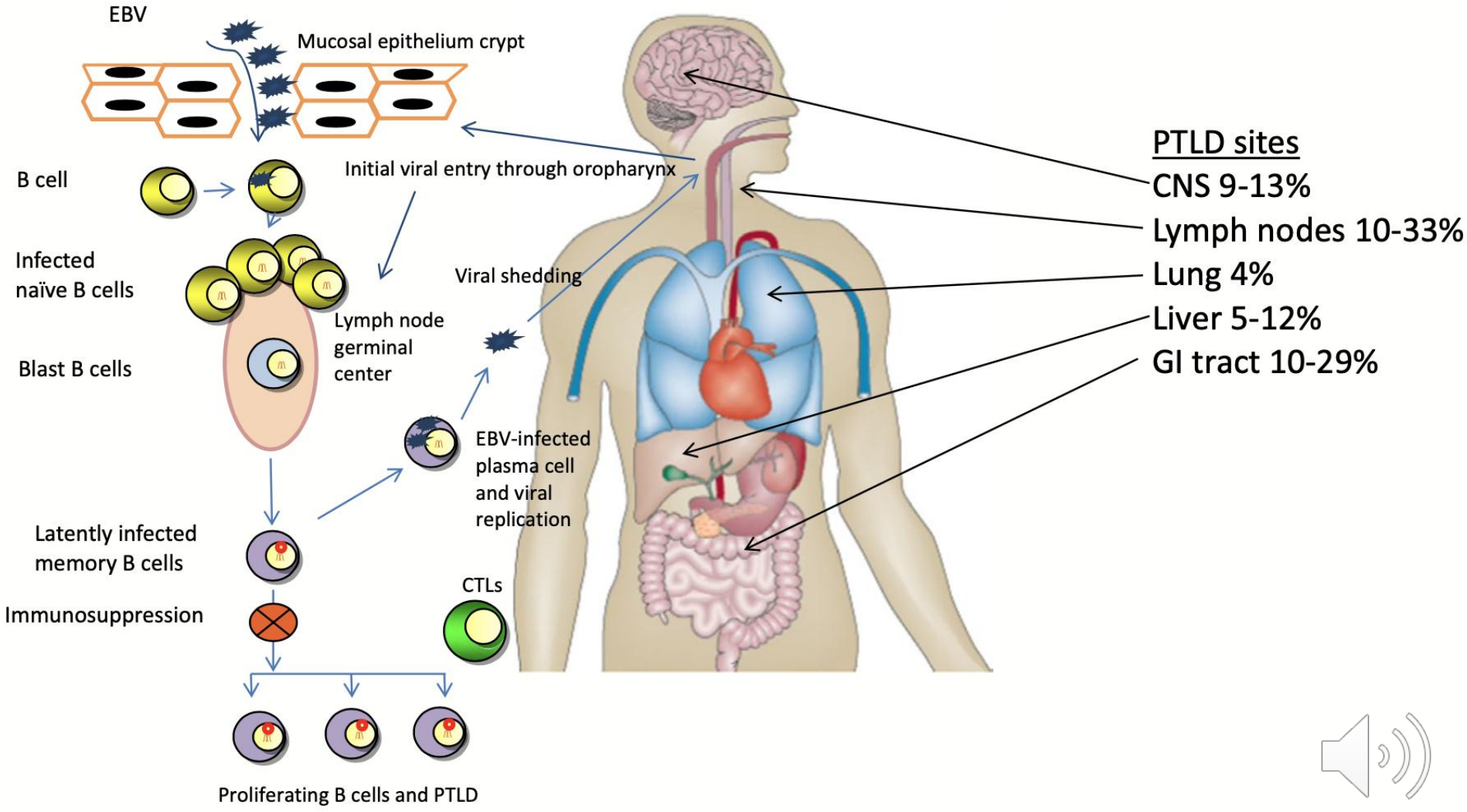


- Although there is a decrease in the risk of early PTLD, the risk of late PTLD is prolonged, possibly as a result of improved survival of KTRs.

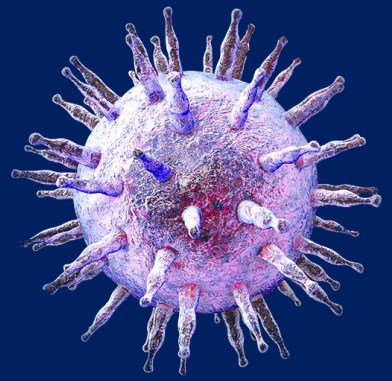
- This is consistent with the fact that higher recipient age is associated with late-onset PTLD.

# Pathogenesis





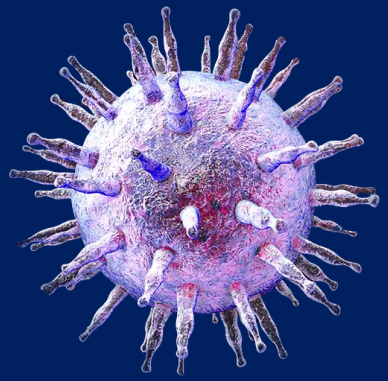
# Classification of PTLD by WHO



| Characteristic | Nondestructive PTLD† | Polymorphic PTLD | Monomorphic PTLD | Hodgkin's Lymphoma–like PTLD |
|---|---|---|---|---|
| Underlying architecture | Nondestructive | Destructive | Destructive | Destructive |
| Composition | Plasma cells, small lymphocytes, immunoblasts | Complete spectrum of B-cell maturation | Fulfills specific WHO criteria for NHL; mantle-cell and follicular NHL are not considered PTLD | Fulfills specific criteria for classic Hodgkin's lymphoma |
| Immunohistochemical features | No diagnostic value | Mixture of B cells and T cells | Monoclonal population 90% DLBCL, mostly CD20+ (majority ABC type) | CD20–, CD30+; most cases CD15+ |
| EBV association | Almost 100% | >90% | Both EBV-positive and EBV-negative | >90% |
| Clonality | No in most cases | Variable | Yes | Yes |
| Molecular genetic findings | None | Variable (BCL6 somatic hypermutations) | Differences between EBV-positive (genomic stable) and EBV-negative (similar to DLBCL in immunocompetent patients) | No information available |
| Clinical features | Mostly early PTLD | Variable | Both early and late PTLD | Possible increase in incidence of late-onset Hodgkin's lymphoma after allogeneic HSCT |

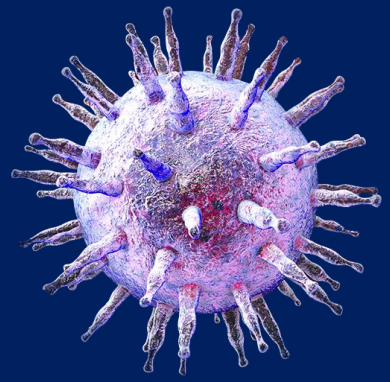
* Information is from Swerdlow et al.[26,27] ABC denotes activated B-cell, DLBCL diffuse large B-cell lymphoma, NHL non-Hodgkin's lymphoma, and WHO World Health Organization.
† Nondestructive PTLD includes plasmacytic hyperplasia PTLD, infectious mononucleosis–like PTLD, and florid follicular hyperplasia PTLD.

# Non-EBV-related tests

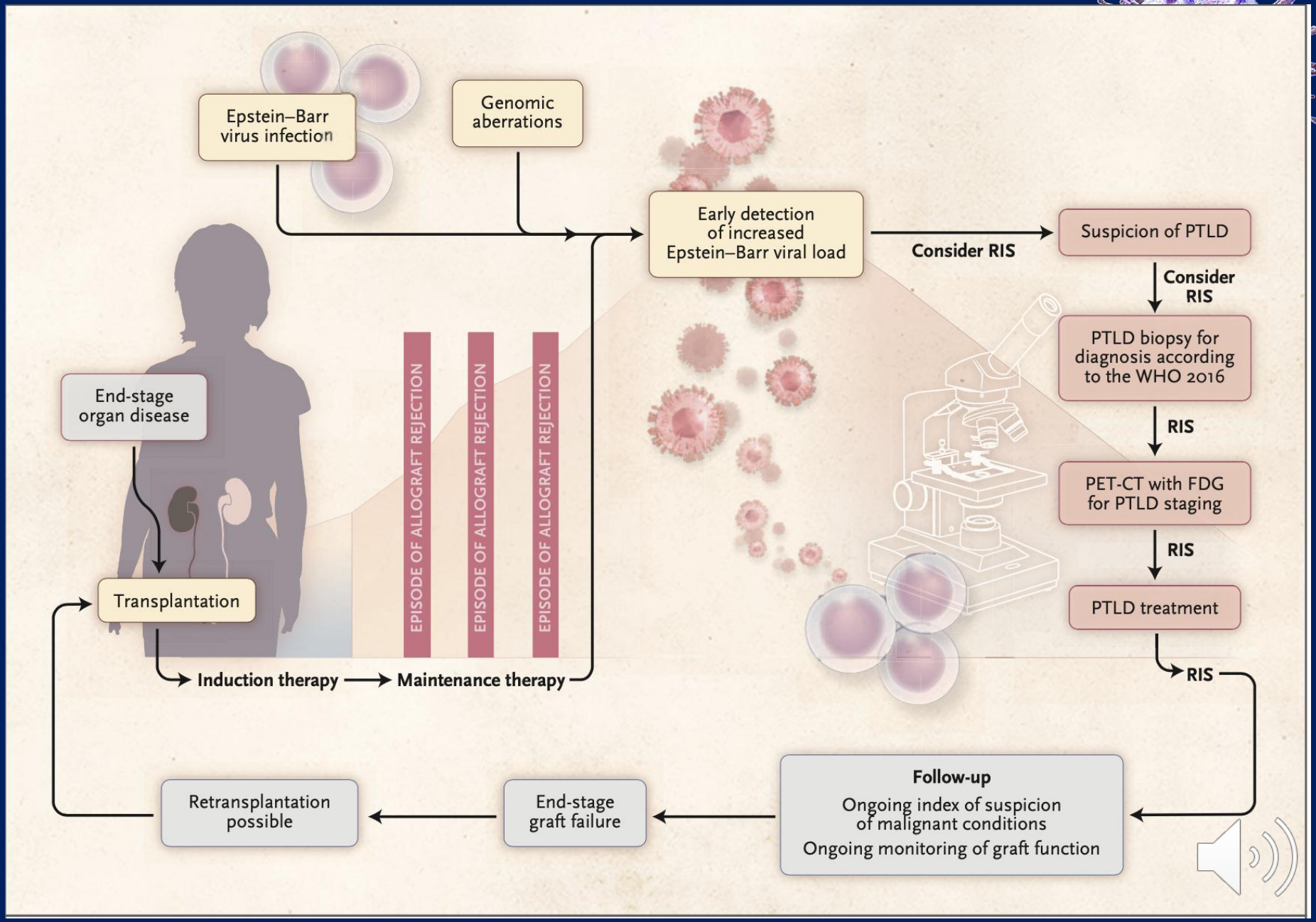


- Lymphopenia
- Anemia
- Disturbed serum electrolytes, liver, and renal function tests.
- Elevations in serum uric acid and LDH
- The presence of concomitant CMV infection should be determined
- Serum IL-6, serum/plasma-free light chains, serum sCD30, serum CXCL13,

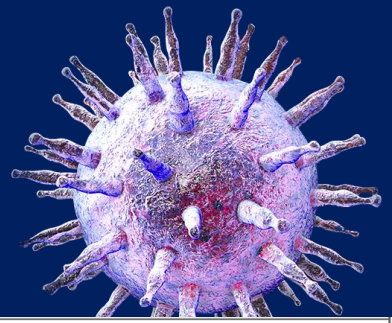
# EBV-related tests



- Anti-VCA IgG and anti-EBNA-1 IgG are serologic tests
- Whole blood or lymphocyte EBV viral load is higher and becomes detectable earlier than contemporaneously tested plasma samples.
- EBV-specific T-cell ELISPOT and tetramer assays, these assays may be more useful for disease occurring early after transplantation.

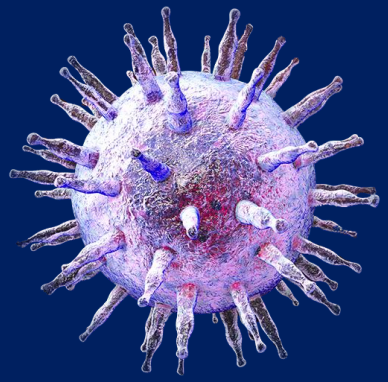

Epstein–Barr virus infection
Genomic aberrations
Early detection of increased Epstein–Barr viral load
Consider RIS
Suspicion of PTLD
Consider RIS
PTLD biopsy for diagnosis according to the WHO 2016
RIS
PET-CT with FDG for PTLD staging
RIS
PTLD treatment
RIS
End-stage organ disease
Transplantation
EPISODE OF ALLOGRAFT REJECTION
EPISODE OF ALLOGRAFT REJECTION
EPISODE OF ALLOGRAFT REJECTION
Induction therapy
Maintenance therapy
Follow-up
Ongoing index of suspicion of malignant conditions
Ongoing monitoring of graft function
End-stage graft failure
Retransplantation possible

# Treatment



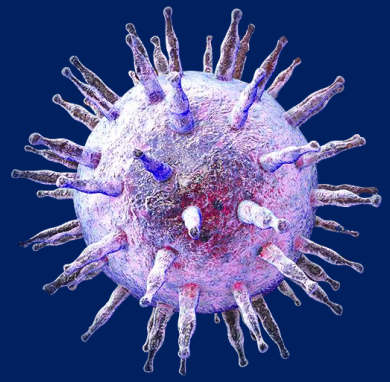
| Treatment | Mechanism of Action | Indications | Considerations |
|---|---|---|---|
| Reduction of immunosuppression | Restoration of T-cell function — in particular, EBV-specific T-cell response | Preemptive therapy in high-risk transplantations; first-line treatment for all PTLD subtypes | High response rates for nondestructive PTLD; responses also observed in EBV-negative cases; takes time, which may not be feasible in very aggressive cases; not indicated as sole up-front therapy for monomorphic non-DLBCL subtypes; risk of organ rejection (can be performed more aggressively with kidney and pancreatic transplants than with other transplant types); less effective after allogeneic HSCT than after SOT |
| Surgery | Reduction of tumoral mass | Limited stage of disease; palliative care | Combined with reduction of immunosuppression; rapid symptom relief |
| Radiotherapy | Reduction of tumoral mass | Limited stage of disease; after chemotherapy in HL; whole-brain radiotherapy in PCNSL if chemotherapy contraindicated; palliative care | Combined with reduction of immunosuppression; rapid symptom relief |
| Chemotherapy | Reduction of tumoral mass | For nondestructive PTLD, polymorphic PTLD, or monomorphic DLBCL in patients who do not have complete remission after reduction of immunosuppression plus rituximab; lymphoma-specific therapy for other (non-DLBCL) monomorphic subtypes | High response rates; risk of infection; reduced treatment-related morbidity and mortality over past two decades |
| Rituximab | Reduction of tumoral mass | First-line treatment (after reduction of immunosuppression) for nondestructive PTLD, polymorphic PTLD, or monomorphic DLBCL; combined with chemotherapy in all non-DLBCL, CD20+ monomorphic subtypes; role in preemptive therapy | Only for CD20+ PTLD; favorable toxic-effects profile; improves performance status before chemotherapy; risk of infection |

# Reduction in Immunosuppression

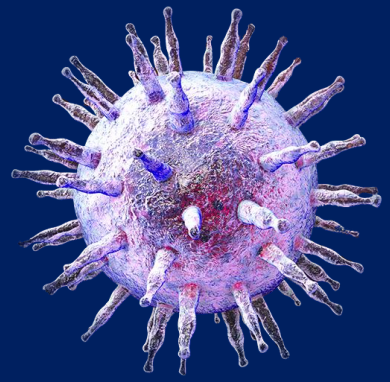


- Reducing CNI dose (targeting 30- 50% reduction of trough levels),
- Discontinuing antimetabolites (AZA, MMF)
- Continuing steroids if possible.

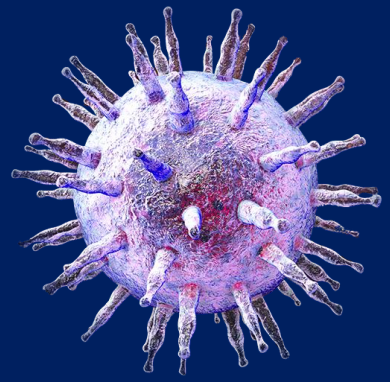
- The time period one should wait before proceeding to alternative therapeutic interventions: within 2-4 weeks?!



- Bulky disease (largest tumor deposit, >7 cm in diameter), an advanced stage (Ann Arbor stage III or IV), and older age (>50 years) are independently associated with a lack of response to reduced immunosuppression.

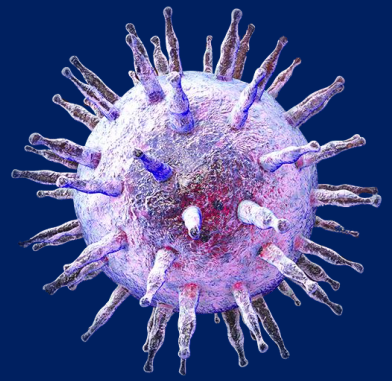


- A case series report described conversion to mTORi (everolimus or sirolimus) and subsequent minimisation or withdrawal of calcineurin inhibitors in 19 renal transplant recipients with PTLD; remission was achieved in 15 patients.



- The use of rituximab as the next step in the treatment of most CD20+ B-cell PTLD when RIS does not result in complete remission.

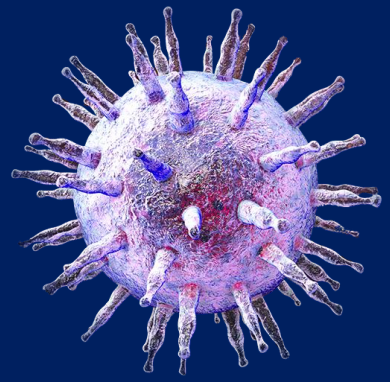
- 4 administrations of rituximab



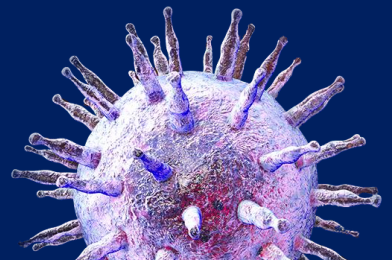
| Treatment | Mechanism of Action | Indications | Considerations |
|---|---|---|---|
| Adoptive immunotherapy (EBV-specific cytotoxic T-cells) | Restoration of EBV-specific T-cell response | Relapsed or refractory PTLD; possible preemptive therapy | Only for EBV-positive cases; time-consuming, high costs, and limited availability; low toxic-effects profile (no risk of GVHD, in contrast to classic donor lymphocyte infusions) |
| Antiviral therapy | Targeting of EBV | Promising role in combination with viral thymidine kinase–inducing agents (e.g., the HDAC inhibitor arginine butyrate), but not further developed | No efficacy as monotherapy (absence of viral thymidine kinase expression in EBV-positive PTLD); only for EBV-positive cases |
| High-dose therapy and autologous HSCT | Reduction of tumoral mass | Relapsed or refractory PTLD | Feasible, but limited experience |

* HDAC denotes histone deacetylase, HL Hodgkin's lymphoma, PCNSL primary central nervous system lymphoma, and SOT solid-organ transplantation.

# EBV-specific CTLs



- EBV-specific CTLs;
  - autologous (solid organ transplantation)
  - donor- derived allogeneic (hematopoietic stem cell transplantation)
  - the use of partially HLA- matched EBV-specific CTLs from healthy donors



ORIGINAL ARTICLE

WILEY

# Cytotoxic T-lymphocyte therapy for post-transplant lymphoproliferative disorder after solid organ transplantation in children

| No. | Age | Primary disease | Graft, age at transplant | Site of PTLD | WHO classification | Prior treatment | No. of EBV-CTL infusions | HLA match between recipient and donor CTL[a] | Response to EBV-CTL |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 11 y | Alpha-1 antitrypsin deficiency | Liver, 2 y | LN | Hodgkin's disease | RIS, IG, antiviral | 4 | 3 of 6 | NR |
| 2 | 4 y | BA | Liver, 10 mo | LN, GI, liver | Polymorphic | RIS, antiviral | 2 | 3 of 6 | CR |
| 3 | 17 mo | Hirschsprung disease | Liver+SB, 9 mo | LN, GI | Monomorphic | RIS, IG, antiviral | 1 | 2 of 6 | CR |
| 4 | 2 y | Congenital intestinal pseudo-obstruction | Liver+SB, 11 mo | GI | Monomorphic | RIS | 4 | 3 of 6 | CR |
| 5 | 12 y | CF-related liver disease | Liver, 11 y | LN, GI, liver | Monomorphic | RIS, antiviral | 4 | 3 of 6 | CR |
| 6 | 12 mo | BA | Liver, 9 mo | LN, GI, tonsil | Monomorphic | RIS, antiviral | 4 | 5 of 6 | CR |
| 7 | 14 mo | BA | Liver, 11 mo | GI | Monomorphic | RIS, rituximab | 4 | 5 of 10 | CR |
| 8 | 4 y | ARPKD and polycystic liver disease | Liver+kidney, 4 y | LN | Monomorphic | RIS, rituximab, IG | 4 | 5 of 10 | CR |
| 9 | 6 y | Malrotation, volvulus | Liver+SB, 2 y | GI | Polymorphic | RIS, rituximab | 4 | 7 of 10 | PR |
| 10 | 21 mo | NEC | Liver+SB, 1 y | GI | Monomorphic | RIS | 4 | 3 of 6 | NR |

*Pediatric Transplantation.* 2018;e13133.

JCI The Journal of Clinical Investigation

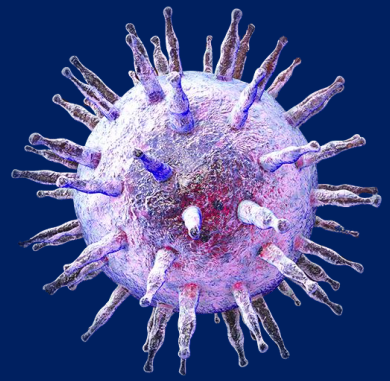
# Off-the-shelf EBV-specific T cell immunotherapy for rituximab-refractory EBV-associated lymphoma following transplantation

Susan Prockop, … , Aisha Hasan, Richard J. O'Reilly

*J Clin Invest.* 2020;130(2):733-747. https://doi.org/10.1172/JCI121127.

**METHODS.** We developed a third-party, allogeneic, off-the-shelf bank of 330 GMP-grade EBV-CTL lines from specifically consented healthy HCT donors. We treated 46 recipients of HCT (*n* = 33) or SOT (*n* = 13) with established EBV-PTLD, who had failed rituximab therapy, with third-party EBV-CTLs. Treatment cycles consisted of 3 weekly infusions of EBV-CTLs and 3 weeks of observation.

**RESULTS.** EBV-CTLs did not induce significant toxicities. One patient developed grade I skin graft-versus-host disease. Complete remission (CR) or sustained partial remission (PR) was achieved in 68% of HCT recipients and 54% of SOT recipients. For patients who achieved CR/PR or stable disease after cycle 1, one year overall survival was 88.9% and 81.8%, respectively. In addition, 3 of 5 recipients with POD after a first cycle who received EBV-CTLs from a different donor achieved CR or durable PR (60%) and survived longer than 1 year. Maximal responses were achieved after a median of 2 cycles.



**ALLELE study: A multicenter, open label, phase III study of tabelecleucel for solid organ or allogeneic hematopoietic cell transplant subjects with Epstein-Barr virus-driven post-transplant lymphoproliferative disease (EBV+ PTLD) after failure of rituximab or rituximab and chemotherapy**

Tabelecleucel is an off-the-shelf, allogeneic EBV-specific T cell therapy.

# Other Therapies???

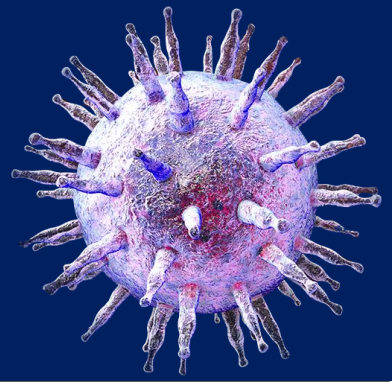
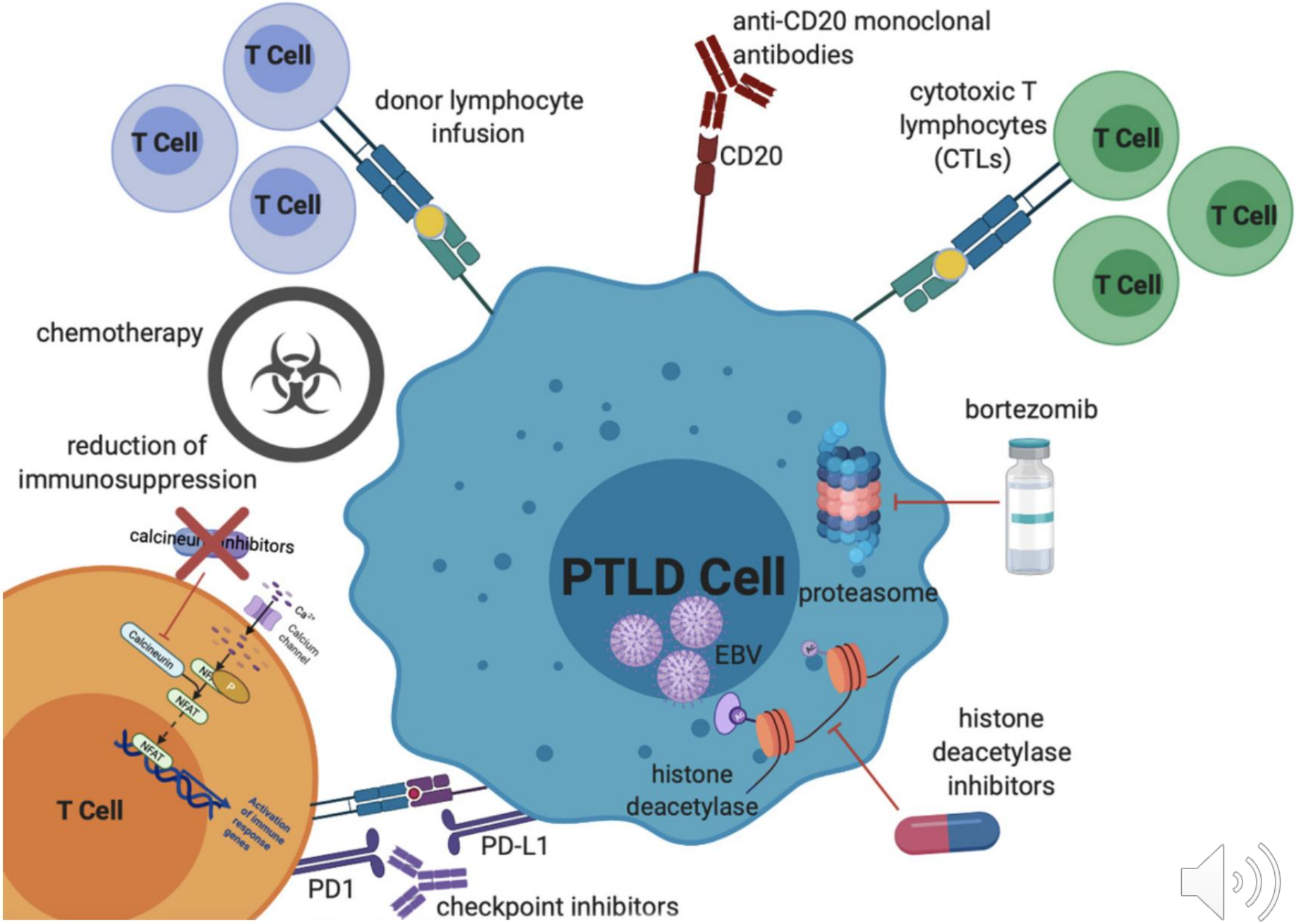


**Table 4. Future Strategies for the Treatment of PTLD.***

| Treatment | Compound | Considerations |
|---|---|---|
| BTK inhibition[78] | Ibrutinib | May also be active in GVHD and graft rejection; promising activity in ABC-type DLBCL |
| Inhibition of PI3K and mTOR[79] | Idelalisib (PI3K inhibitor); sirolimus (rapamycin) and everolimus (mTOR inhibitors) | Strong in vitro evidence of involved pathways; mTOR inhibitors also have strong immunosuppressive activity, but their use in treatment of PTLD is controversial |
| Proteasome inhibition[80] | Bortezomib | In particular, may be useful for early PTLD after allogeneic HSCT |
| Radioimmunotherapy[81] | $^{90}$Y-ibritumomab, tiuxetan | Effective in small pilot trial (SOT) |
| Checkpoint inhibitors[82] | Pembrolizumab, nivolumab | CTLA-4 pathway: contraindication, given high risk of (fatal) acute rejection; PD1 or PDL1 pathway: lower risk of acute rejection; should currently be considered only in clinical trials |
| Anti-CD30 therapy[83] | Brentuximab vedotin | Expression of CD30 in 85% of all PTLD subtypes; responses described in case reports |

* BTK denotes Bruton's tyrosine kinase, CTLA-4 cytotoxic T-lymphocyte–associated antigen 4, PD1 programmed death 1, PDL1 programmed death ligand 1, and PI3K phosphoinositide 3-kinase.


T Cell
T Cell
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donor lymphocyte infusion
anti-CD20 monoclonal antibodies
CD20
cytotoxic T lymphocytes (CTLs)
T Cell
T Cell
T Cell
chemotherapy
reduction of immunosuppression
bortezomib
PTLD Cell
proteasome
EBV
histone deacetylase
histone deacetylase inhibitors
calcineurin inhibitors
Calcium channel
Calcineurin
NFAT
NFAT
T Cell
Activation of immune response genes
PD-L1
PD1
checkpoint inhibitors

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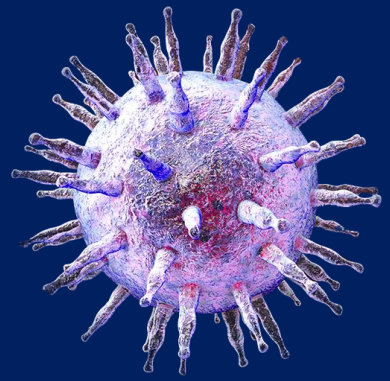
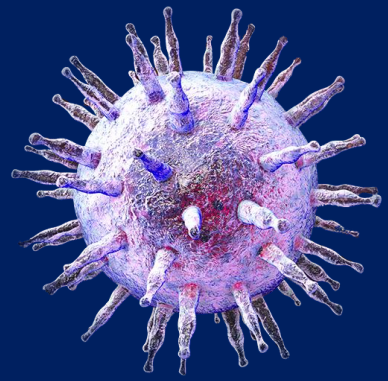


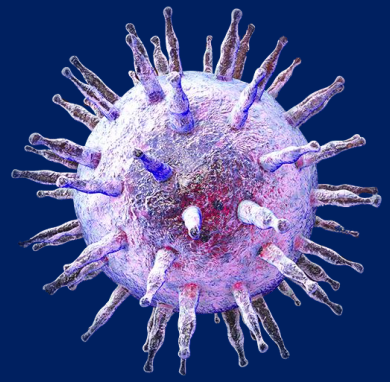
During treatment of PTLD using strategies other than RIS, infection prophylaxis should be reviewed; prophylaxis for *Pneumocystis jirovecii* pneumonia should be reinstituted if it has been discontinued (*strong/high*).

The routine use of EBV viral load monitoring in peripheral blood to monitor treatment response to EBV + PTLD is not recommended (*weak/very low*).

*Clinical Transplantation*. 2019;33:e13652.

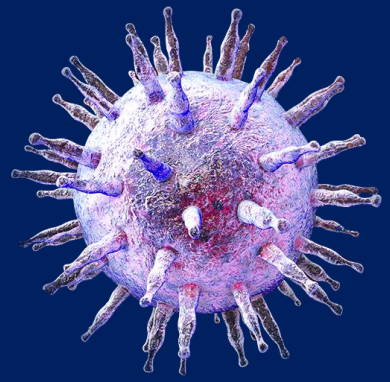


# Transplantation After PTLD



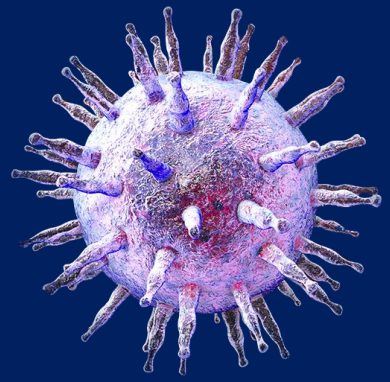
- Recurrence of PTLD in patients having undergone retransplantation as a rare event.

- The ideal time gap between PTLD remission and listing for re-transplantation is not clear.



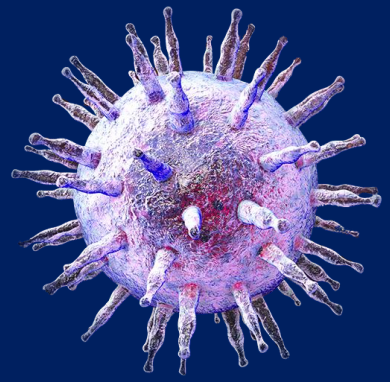
- The British Transplantation Society guidelines recommend a period of at least 1 year from the control of PTLD to retransplantation to minimize the risk of PTLD recurrence

- In the French registry, the median time from PTLD to listing for retransplantation was 65 months and from PTLD to retransplantation was 90 months



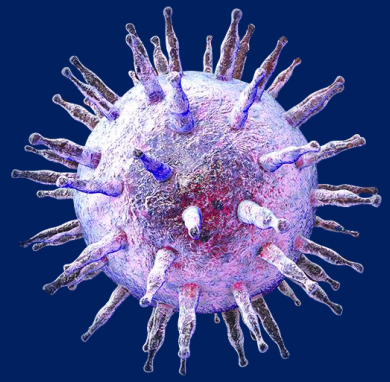
- EBV status at the time of retransplantation is an important predictor of recurrence after retransplantation.

- Patients should present an EBV seroconversion (an EBV IgG seropositive status) before retransplantation and it is advisable that EBV viral load be undetectable at the time of retransplantation.

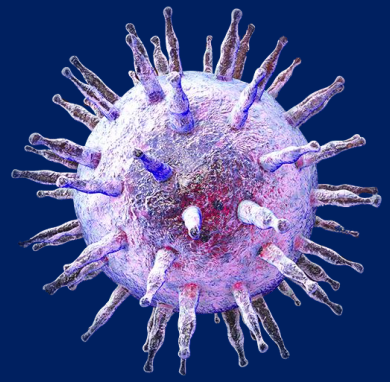


- Patients with low level EBV viremia at the time of retransplantation may benefit from antivirals with intermittent measurements of EBV viral load and subsequent IS adjustments as per the viral load.

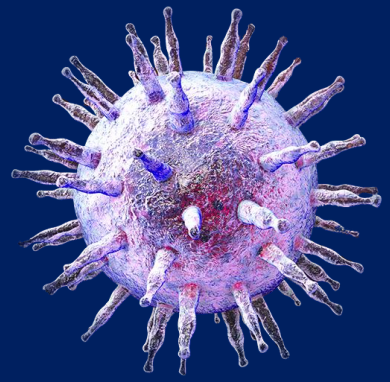
- Rituximab has also been used to prevent EBV viremia in EBV seronegative kidney transplant recipients.



- Rituximab has been used in retransplantations after PTLD both as a desensitisation protocol in high risk sensitised cases and as a prophylaxis for proliferation of EBV in cases with high viral counts



- IL-2R antagonists are the favoured induction agents.
- There is a trend to avoid induction with ATG preparations.
- Maintenance immunosuppression is generally the standard combination of CNI or, MMF and prednisolone
- Low target level



- Mycophenolate sodium is the only agent seen to have a significant protective effect against PTLD and its use is common in most series.

- mTOR inhibitors deserve a special mention in cases of PTLD?


Thank you
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