*REVIEW*

# Lymphoproliferative disorders in inflammatory bowel disease patients on immunosuppression: Lessons from other inflammatory disorders

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## Abstract

Immunosuppressive agents, such as thiopurines, methotrexate, and biologics, have revolutionized the treatment of inflammatory bowel disease (IBD). However, a number of case reports, case control studies and retrospective studies over the last decade have identified a concerning link between immunosuppression and lymphoproliferative disorders (LPDs), the onco-logical phenomenon whereby lymphocytes divide uncontrollably. These LPDs have been associated with Epstein-Barr virus (EBV) infection in which the virus provides the impetus for malignant transformation while immunosuppression hampers the immune system's ability to detect and clear these malignant cells. As such, the use of immunosuppressive agents may come at the cost of increased risk of developing LPD. While little is known about the LPD risk in IBD, more is known about immunosuppression in the post-transplantation setting and the development of EBV associated post-transplantation lymphoproliferative disorders (PTLD). In review of the PTLD literature, evidence is available to demonstrate that certain immune suppressants such as cyclosporine and T-lymphocyte modulators in particular are associated with an increased risk of PTLD development. As well, high doses of immunosuppressive agents and multiple immunosuppressive agent use are also linked to increased PTLD development. Here,

we discuss these findings in context of IBD and what future studies can be taken to understand and reduce the risk of EBV-associated LPD development from immunosuppression use in IBD.

**Key words:** Epstein-Barr virus; Immunosuppression; Post-transplantation lymphoproliferative disorders; Lymphoproliferative disorders; Inflammatory bowel disease

**Core tip:** Immunosuppressive agents, such as thiopurines, methotrexate, and biologics, have revolutionized the treatment and maintenance therapy of inflammatory bowel disease (IBD). However, their use may come at the cost of increased risk of developing lymphoproliferative disorders (LPD). While little is known about this risk in IBD, more is known about immunosuppression risk in the fields of rheumatoid arthritis and post-transplantation with regards to the development of Epstein-Barr virus (EBV) associated LPD. Here, we attempt to review lymphoma risk in the setting of immunosuppression use in various medical conditions, discuss what lessons may be translatable to the IBD field and what future directions can be taken to reduce the risk of EBV-associated LPD from immunosuppression use in IBD.

## INTRODUCTION

Inflammatory bowel disease (IBD) is a term that describes a collection of autoimmune gastrointestinal conditions, most notably Crohn's disease (CD) and ulcerative colitis (UC). While UC is confined to the colon, CD can involve the entire digestive tract from mouth to anus. The pathogenesis of IBD is currently thought to be the result of a combination of host/genetic, environmental and microbial factors that perpetuate chronic and inappropriate inflammation of the gastrointestinal tract[1]. IBD has a bimodal age distribution with first diagnoses occurring between 15 to 40 years of age or 50 to 80 years of age[2]. In addition to age, a range of other risk factors have been linked to the development of IBD including gender, ethnicity, smoking, gut microbiome and medications[3]. One concerning consequence of IBD, and its treatment, is the increased incidence of lymphoproliferative diseases (LPD). LPDs include B- and T-cell lymphoma, the development of which can be the result of Epstein-Barr virus (EBV) mediated malignant

transformation of normal B- and T- lymphocytes to divide uncontrollably. Other pathogens, such as other human T-cell lymphotropic virus-1, human herpesvirus-8, hepatitis B and C, human papilloma virus, Kaposi's sarcoma-associated herpesvirus, Merkel cell polyomavirus and *Helicobacter pylori* have also been implicated in malignant transformation of the infected host[4,5]. LPD encompasses a diverse group of hematological malignancies that can either be acute or chronic in nature; either leukemic or lymphoid in morphology. One unique group of LPD includes the post-transplantation lymphoproliferative disorders (PTLD), which can develop due to both primary and secondary immunosuppression[6]. IBD itself, even independent of immunosuppressive treatment, is thought to be associated with either no or a slight increase in the risk of LPD development[7-10]. However, an increase in rates of LPD development in those with IBD who are on immunosuppressive therapy has been noted by different groups worldwide, documented in a variety of population-based, retrospective and case control studies[8,11,12]. Collectively, these studies point to the possibility that increased malignancy rates may be due the use of particular immunosuppressive therapies that inhibit normal host immunity and exposure to EBV, which in an immunosuppressed host, can infect host cells and result in malignant transformation. While limited data is available in the IBD population, there is a wealth of studies conducted on PTLD and rheumatoid arthritis patients. The development of PTLD primarily involves either reactivation of latent EBV infection or new EBV infection and as such, the development of PTLD is screened for in the most high-risk population (EBV negative recipient matched with EBV positive donor) by monitoring EBV viral load. In the rheumatoid arthritis population, the use of methotrexate is well described to confer a significant risk of lymphoma development. In this review, we first describe the well-established causal relationship between EBV infection and LPD development. Second, we explore the effect of immunosuppression, including biologics, in the post-transplantation and rheumatoid arthritis populations on EBV-associated LPD development. Third, we examine what is known currently about the risk of EBV-associated LPD development in patients treated with immune suppressants in IBD. Lastly, we discuss what can be translated from the post-transplantation literature to IBD to manage risks of EBV-associated LPD while on immune suppressants.

## EBV CAUSES LPD

EBV is a double-stranded DNA virus belonging to the herpesvirus family that is ubiquitously found worldwide in roughly 90%-95% of adults[13]. The peak incidence by age is bimodal as roughly half of children under five years of age in developed countries acquire this relatively benign infection, often passing as a constellation of unremarkable upper respiratory tract infection symptom

while the second peak of infections occurs in the 15 to 24 years old group[13]. EBV spreads *via* oral secretions and blood, capable of triggering B-lymphocyte and epithelial cell uptake[13]. Once intracellular, EBV initiates the lytic phase of infection, resulting in the lysis of the cellular host and subsequent release of viral progenies. In an immunocompetent host, cell-mediated immunity is activated as cytotoxic T lymphocytes (CTLs) target viral infected cells for apoptosis[13]. A proportion of EBV infected B-lymphocytes escape CTLs detection and continues on to become long-lived infected memory B-lymphocytes where the virus persists in the latent phase of its life cycle[13].

In latent phase, viral proteins are capable of initiating host malignant transformation in a subset of individuals, resulting in uncontrolled memory B-lymphocytes pro-liferation, or a LPD. A number of prospective and case-control studies worldwide have identified EBV infection as a risk factor to the development of LPDs such as Hodgkin lymphoma, Burkitt's lymphoma, and a subset of aggressive non-Hodgkin lymphomas[14,15]. Hodgkin lymphoma has been the best studied and remains the lymphoma with the strongest association between EBV[16]. A causal relationship has been established in *in vitro* studies where EBV infection of human B-lymphocytes results in the uncontrolled proliferation of infected cells[17]. One study suggests that the rate of malignant transformation in EBV infected individuals occurs at a rate of 1:1000 over the span of four years from infection to Hodgkin lymphoma detection[14].

Certain risk factors have been associated with higher rates of LPDs. A case-control study from England revealed that the age of first infection is associated with a higher odds-ratio of developing Hodgkin's lymphoma with the highest odds-ratio in the 16-24 years of age group[18]. Immune deficient patients have increased susceptibility to LPD development in part due to an inability to mount an EBV-specific immune response. Those with compromised immunity[19] or those receiving immunosuppressive therapies[20,21] have been found to have an altered humoral immunity against EBV. As such, increased rates of EBV-associated LPD have been documented in patients with human immune-deficiency virus[22] those with inherited immune-deficiencies[23] and in post-transplanted patients receiving immuno-suppressive therapy[24].

## EFFECT OF POST-TRANSPLANTATION IMMUNOSUPPRESSION ON EBV-ASSOCIATED LPD DEVELOPMENT

EBV is thought to be responsible for the majority of cases of PTLD, defined as uncontrolled lymphoid or plasma cell proliferation post solid organ or hematologic transplantation in the setting of immunosuppressive agents[25]. PTLDs include a range of subtypes. Early lesions, which include plasmacytic hyperplasia and infectious mononucleosis, and polymorphic PTLD typically involve EBV and occur within the first year post trans-plant. On the other hand, monomorphic PTLDs, which are histologically identical to B- or T-cell derived non-transplant malignant lymphomas, tend to occur late post transplant, involve EBV less often, and are clinically more aggressive. Hodgkin lymphoma type PTLD is the least common subtype[26-30]. Similar to the risk factors for development of LPDs in immunocompetent patients infected with EBV, studies of post-transplant patients revealed the key risk factors for developing PTLD include the degree of T-lymphocyte immunosuppression and the EBV serostatus[31,32]. The risk of PTLD in renal transplant patients is thought to be 6-20 times higher than the general population while those receiving heart transplants have an estimated 200 times higher risk due to the relatively intensive immunosuppression that thoracic transplant recipients receive[29]. A number of multi-national retrospective database review studies revealed the greatest yearly incidence rate was seen in the first year post transplantation with the number of new cases steadily declining over the five years of study[32,33], suggesting that the degree of immuno-suppression, which typically is highest during the first year post-transplantation, may increase the risk for PTLD development[29]. Studies with longer follow-up, however, show a second peak in incidence at around 8 years post-transplant, suggesting that prolonged high doses of immunosuppression are also associated with increased rates of PTLD development[30,34].

Different immune-suppressive induction agents have been hypothesized to confer different risk for developing PTLD[29,35,36]. In addition, combination therapy, while most successful at preventing rejection, is associated with greater risk of PTLD development in one pediatric population[37]. Agents that suppress CTLs, such as belatacept and efalizumab[38-40], and T-lymphocytes in general, such as OKT3 and thymoglobulin[36,38], were suggested to have a greater role in inducing PTLD than those that mediate general immunosuppression. Given that viral infected cells are cleared by activated CTLs, agents that hamper CTLs is thought to be permissive for viral infection and later malignant transformation of the infected host. The rates of PTLD were found to increase dramatically as well with the initial use of cyclosporine[41,42]. Fortunately, by implementing drug-level monitoring and dose reduction, rates of PTLD have dropped since the early days of cyclosporine use. Certain agents, such as mycophenolate mofetil, have not been associated with any increased risk of PTLD[38,43].

In addition to the degree and type of immuno-suppression, EBV seronegativity is an independent risk factor for the development of PTLD. The risk of PTLD is greater in EBV seronegative patients who become infected while immune suppressed than in seropositive recipients reactivating latent EBV infection post-transplantation[24]. Numerous studies have identified EBV seroconversion after either solid organ or hemato-logical transplantation as a risk factor for PTLD develop-ment[37,44-48]. EBV naïve patients receiving immune

suppressants were found to be at a higher risk of developing PTLD compared to EBV positive patients in one landmark University of Alberta retrospective study[49]. Since then, others in different centers have likewise identified EBV seronegativity in the pre-transplantation individual as a significant risk factor for developing PTLD post transplantation[44,45,50]. EBV seronegativity has a stronger impact on the risk of PTLD that occurs early (*i.e.*, within 1 year) as opposed to late post transplant[30,34]. As such, EBV seronegative patients are subjected to monitoring during the first year post-transplantation to detect PTLD development (discussed in the "PTLD Prevention" section).

### PTLD prevention
To address the increased risk of malignant trans-formation of PTLD in context of immunosuppression and EBV infection, some have recommended that routine monitoring of EBV viral load be undertaken in the post-transplant settings. Rising viral load raises the suspicion of PTLD development since a high EBV viral load has been documented in some studies to precede the development of EBV-mediated PTLD[51-55]. As such, the absolute viral load has been proposed as prognostic of PTLD development[47,53]. However, in part due to a number of technical challenges of the EBV viral load assay, including a lack of standardized reference ranges for instrument calibration across multiple assay platforms, the positive predictive value of this assay remains low as an elevated viral load has high sensitivity but lacks specificity for PTLD development[56-61]. Thus, the utility of EBV viral load monitoring in a seropositive patient remains highly controversial[62-64]. On the other hand, serial EBV viral load monitoring in the seronegative recipient is an effective tool to identify those at clear risk of developing PTLD[65,66]. By routine monitoring of EBV viral load in the seronegative recipient, pre-emptive interventions, such as anti-viral treatment and rituximab therapy, may be undertaken to prevent PTLD development when rising EBV viral load is detected[55,65,67-71].

## EBV-ASSOCIATED LPD DEVELOPMENT IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH IMMUNE SUPPRESSANTS
Several large-scale population studies have demonstrated a mildly elevated risk of LPD and EBV-associated LPD in those with rheumatoid arthritis (RA) and an even higher risk in patients being actively immunosuppressed compared to the healthy population[72-74]. Mechanistically, patients with RA have been shown to have defective EBV-specific T cell function, resulting in a greater number of infected lymphocytes and as such are at a higher risk than the general population for development of LPD[75]. The addition of an immunosuppressive agent further elevates the risk of EBV-associated LPD,

increasing the relative risk for LPD development from 2.5 (RA without immunosuppression) to 10 (RA with immunosuppression)[76]. The highest incidence of LPD development typically occurs within the first year post treatment[77,78]. Various immune suppressive agents have been linked to an increased risk of malignancies. The best-studied immune suppressant in context of RA and LPD development is methotrexate (MTX). This immunosuppressive agent has such a strong association with LPD development that the 2008 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues recognized MTX-associated LPD as in independent entity[79]. MTX-associated LPD is commonly characterized by the presence of EBV virus in the lymphoma tissue and that discontinuation of MTX in results in regression of LPD in many but not all patients[80,81]. Furthermore, this risk of MTX-associated LPD increases with higher treatment doses[82]. Thus, it has been proposed that should MTX treated RA patients develop LPD, they should then receive EBV serologic screening to determine if MTX should be discontinued[83] as the likelihood of regression post MTX discontinuation appear to be linked to EBV status[80].

Anti-tumor necrosis factor (TNF)α antibody therapy has also been shown to increase rates of LPD in RA patients compared to healthy controls in a systematic meta-analysis[84]. In one head to head comparison of anti-TNFα (infliximab) against MTX treatment, anti-TNFα agents were associated with higher rates of LPD than MTX[85]. The risk of LPD development is likewise correlated with higher doses of anti-TNFα (either infliximab or adalimumab)[84]. One recent report has even linked adalimumab to EBV-associated lymphoproliferative disorder development after two years of treatment[86].

## EBV-ASSOCIATED LPD DEVELOPMENT IN IBD PATIENTS TREATED WITH IMMUNE SUPPRESSANTS
### EBV and IBD
Given the extensive data from the post-transplantation and RA literature that shows the risk of EBV-associated LPD increases with immunosuppression, one logical question to ask is whether similar immunosuppression in other disease states, such as IBD, is also associated with increased rates of LPD. Furthermore, given that IBD patients are often diagnosed and initiate treatment younger than 30 years of age (an age demographic with many unexposed to EBV), concern for LPD risk in EBV seronegative patients may be raised.

Even without treatment, IBD patients have higher rates of infections such as non-antibiotic associated *Clostridium difficile* colitis[87], cytomegalovirus[87,88], and infectious colitis[88]. It is unclear why IBD is associated with higher rates of these specific infections. Regardless, it is clear is that with the addition of immunosuppressive agents, this infectious risk increases substantially[88-91]. However, with respect to EBV, Reijasse *et al*[92] did not

find a relationship between EBV viral load and severity of CD activity or the type of immunosuppression (infliximab infusion, corticosteroids, azathioprine and cyclosporine) used. Similarly, Fernandez Salazar *et al*[93] found that EBV seropositive CD patients in remission maintained on either no immunosuppression, azathioprine and/or infliximab did not have any significant changes to the viral load. However, interestingly patients with the most severe uncontrolled CD activity were found to have transient dramatic spikes in EBV viral load[92,94] with EBV DNA detected in colonic mucosal B-lymphocytes[94].

### EBV-associated LPD and IBD
The link between EBV-associated LPD and IBD remains somewhat controversial as there have been a number of conflicting major studies done to date. The majority of large population-based studies have failed to find a significant association between IBD and LPD[95-100]. On the other hand, studies based in tertiary referral centers, which may have an inherent a referral bias towards those with more severe disease, showed that after factoring in the type and dose of immune suppressants used, IBD by itself does confer a slightly elevated risk for LPD[7,101]. In addition, when subgroup analysis was undertaken in one population-based study from the University of Manitoba, an increased risk of LPD in male patients with CD was found[102]. The difficulty in large population studies is that a number of factors, such as IBD disease severity and immune suppressant usage, are often not accounted for. Thus, it remains unclear how much IBD by itself, without the influence of immune suppressants, contributes to LPD development.

While the influence of IBD on EBV-associated LPD development has not been independently determined, analysis of IBD patients on immunosuppressive therapy demonstrates a clear risk for the development of EBV-associated LPD. An estimated 50% of IBD patients on immunosuppressive therapy with LPD were EBV seropositive[8,103] with a number of case reports identifying EBV DNA present in LPDs that developed post immunosuppression in IBD patients[104-107]. In reviewing the post-transplantation literature, a major risk for the development of PTLD is EBV seroconversion or EBV naivety while on immune suppressants and those who were EBV seropositive prior to transplantation habouring a latent infection represents a minor risk factor[44,45,49,50]. Currently, only a handful of case reports have documented the link between EBV seroconversion and LPD development in context of IBD and immunosuppression. Van Biervliet *et al*[108] reported the case of a young EBV seronegative CD patient who developed LPD shortly after treatment with azathioprine. Similarly, a 16-year-old CD patient who became seropositive while on therapy of mesalamine, azathioprine and infliximab infusion consequently developed EBV-associated LPD[109]. Lastly, a 25-year-old CD patient develops LPD after undergoing EBV seroconversion while on azathioprine[110]. Taken together, these reports may indicate a risk of LPD development from EBV seroconversion while on immune suppressants in IBD patients on immune suppressants. Perhaps an argument can thus be made for EBV serological monitoring in the EBV naïve IBD population. However, more research is needed to determine the effectiveness and utility of such an approach.

### Role of immune suppressants on EBV-associated LPD development in IBD
Medical therapy for IBD is often individualized and there are nuanced differences between the management of CD and UC[111]. Regardless, typical immunosuppressive regimens may include prednisone, mesalazine, cyclosporine, thiopurines, such as azathioprine (AZA) and 6-mercaptopurine (6-MP), and infliximab[111]. (MTX is also used in IBD treatment, though much less frequently than in RA management and thus scant safety data is available in the IBD population). These therapies have been examined for a correlation with EBV-associated LPD development. Mechanistically, it is theorized that increased cancer risk may be conferred with a disturbed mucosal barrier and increased inflammation resulting in an accumulation of genetic mutations provides the opportunity for EBV-mediated malignant transformation. Immunosuppressive agents hamper the innate and adaptive responses for tumor surveillance and clearance[95].

The best studied of all IBD treatment agents, AZA and 6-MP, were associated with an increased risk of LPD when standard dosing (AZA 2.5 mg/kg per day; 6-MP 1.5 mg/kg per day) were used[8,10-12]. Dayharsh *et al*[112] found in a retrospective study that thiopurine use dramatically increased the rates of EBV-associated LPD in their IBD population (17% increase to 50%). Similarly, thiopurine treatment in a French nationwide prospective observational cohort study (CESAME) was associated with increased EBV-associated lymphomas[113]. A recent review of the Kaiser Permanente Cancer Registry of 16023 IBD patients revealed an increased incidence of lymphomas in thiopurine treated patients[9]. Finally, in a recent meta-analysis[114] and a retrospective cohort study of the United States Veteran Affairs database[11], both publications demonstrated a 4-fold increased risk of lymphoma in AZA or 6-MP treated IBD patients compared with the general population[11,114]. The meta-analysis found the lymphoma development risk increased with duration of immunosuppression and decrease with discontinuation of therapy[114]. In fact, one case report described lymphoma regression upon withdrawal of thiopurine[115]. Thus, given the higher risk of EBV-associated LPD development in young male IBD patients, some groups have proposed the avoidance of thiopurine use in this particular population altogether[116,117].

In addition to thiopurine, other IBD treatment agents have been studied, albeit to a lesser extent. MTX is one such agent. There has been scant data on MTX and EBV-associated LPD development in the IBD population. Kandiel *et al*[11] found that 2 of the 4 cases of lymphoma development in IBD patients involved treatment with MTX (31 patients of the 782 person study

received MTX in total). While studies in IBD are lacking, studies involving patients with rheumatoid arthritis found MTX treatment to be associated with increased risk of lymphoma development[118,119]. One case report documented the development of EBV-associated LPD in a patient with rheumatoid arthritis receiving MTX with lymphoma regression upon discontinuation of MTX use[120].

Another commonly used class of IBD agents is the anti-TNFα antibody, including both adalimumab and infliximab[12]. Adalimumab has been linked to Hodgkin Lymphoma development[121] or recurrence[122]. However, the largest trial to date involving adalimumab use found no increased incidences of T-cell non Hodgkin Lymphoma development over control[123]. This study, however, did find increased risk of T-cell non Hodgkin Lymphoma development in those treated with anti-TNFα agents (either adalimumab or infliximab) in combination with a thiopurine[123]. The link between infliximab and LPD is likewise controversial. There are a number of trials that have identified a small but significant risk of lymphoma development in IBD patients on infliximab. In the ACCENT I maintenance infliximab infusion randomized placebo-controlled trial, two cases of EBV-associated non-Hodgkin lymphoma were found out of 573 patients (all participants had a score of at least 220 on the CD activity index)[124]. A second study based at the Mayo Clinic found one case of EBV-associated lymphoma out of 500 patients[11]. A third smaller randomized, double-blinded placebo controlled trial of 73 IBD patients who were either refractory to conventional treatments or responded sub-optimally to treatment were initiated on a course of four infliximab infusions every 8 wk[125]. One patient developed B-cell lymphoma 9.5 mo post initial infusion[125]. A large retrospective chart review of the Kaiser Permanente Cancer Registry revealed an increased standardized incidence rate ratio (5.5 for past use; 4.4 for current use) of lymphoma development over nearly 6-year span in the IBD population treated with infliximab over those without[9]. Finally, a recent meta-analysis of 26 publications found, in subgroup analysis, an increased risk of non-Hodgkin's lymphoma development in anti-TNFα agent treated IBD male patients aged 20-54 years of age[12]. On the other hand, a number of studies have failed to find evidence of increased LPD risk from infliximab use. The large Crohn's Therapy Resource, Evaluation, and Assessment Tool registry found no increased risk of lymphoma in IBD patients treated with infliximab over control population[126]. A selective small meta-analysis of randomized controlled trials failed to find an increased risk of lymphoma associated with infliximab over those that did not receive any anti-TNFα agents. Finally, a recent study of long-term safety of infliximab use found no increase LPD risk conferred by infliximab over control over the span of 14 years[127].

There are several inherent difficulties in establishing a role for infliximab in EBV-associated LPD development in IBD. First, most studies do not stratify the data based on disease severity. It may be reasonable to suspect that those requiring treatment with an anti-TNFα agent is associated with more refractory or severe disease as biologics are typically prescribed after other immune suppressants have failed. As such, more severe inflammatory disease may independently confer a higher LPD risk. Second, it maybe challenging to show the effect of anti-TNFα therapy alone in the development of LPD as the control group typically has received some form of immunosuppressive therapy. Third, very few patients will have received only anti-TNFα therapy without prior exposure to any other immunosuppressive agents. As such, there may be an accumulated risk from multiple agent use. This raises the hypothesis that it may not be any specific immunosuppressive agent that may be the culprit for LPD development, but rather the combination or addition of the third or the fourth agent that statistically increases LPD risk[128]. One observation that supports this theory is the increasing rates of hepatosplenic T-cell lymphoma (HSTCL) where the majority of reported cases involve young male patients (average age mid-twenties) receiving either prolonged thiopurine therapy (more than two years) or combination immunosuppression therapy of thiopurine and anti-TNF therapy[129,130]. As such, some have proposed that male patients under 35 years of age on prolonged thiopurine treatment or combination therapy should be monitored carefully for signs of HSTCL[129,130].

In summary, EBV-associated LPD may not be elevated in IBD from a population perspective but appears to occur more frequently in the younger male population, possibly due to the fact that significant EBV exposure occurs during this time. What might be behind the gender differences is currently unclear. In addition, regardless of patient demographics, thiopurines appear to confer the greatest risk of EBV-associated LPD development when compared to the methotrexate or biologics.

## LESSONS FROM IMMUNE SUPPRESSION USE: FUTURE DIRECTIONS FOR IBD RESEARCH

Attempting to interpret findings from one field and apply them to another must be done with caution, as the dosing and treatment regimens of immune suppressants used in IBD are different than those used post-transplantation or in RA. Furthermore, the pathophysiology of these diseases, although incompletely elucidated, are likely quite different. However, given the sparse data available in the IBD field surrounding the risks of immune suppressants, complications from their use in the context of other inflammatory diseases should also not be overlooked. Currently, there is a trend amongst IBD physicians to move towards increased use of MTX for the purposes of both primary immunosuppression and also for suppression of anti-biologics antibody production. As the data linking lymphoma risk in MTX use in RA is mounting, the role of MTX in lymphoma development
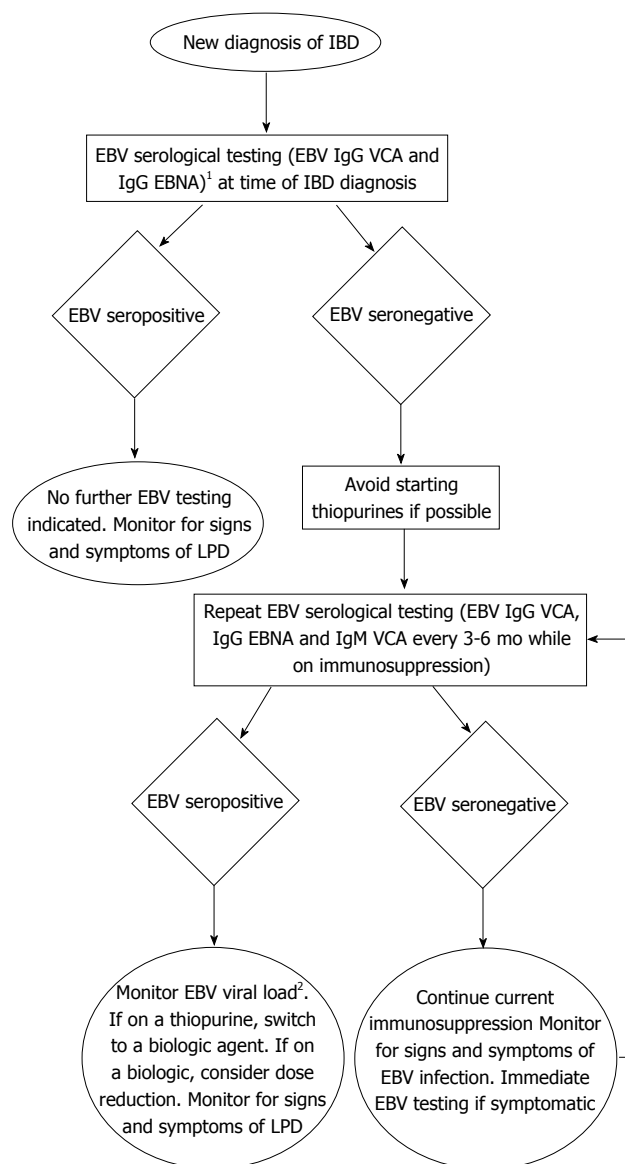
**Figure 1  Proposed algorithm for treatment management of inflammatory bowel disease patients who are either Epstein-Barr virus seropositive or negative.** [1]EBV monospot or EBV IgM have not been shown to be helpful in in determining serostatus; [2]EBV viral load should be done by polymerase chain reaction in whole blood in EDTA collection tube. EBV: Epstein-Barr virus; IBD: Inflammatory bowel disease; EBNA: Epstein-Barr virus-determined nuclear antigen; LPD: Lymphoproliferative disorders; VCA: Viral-capsid antigen; EDTA: Ethylenediaminetetraacetic acid.

in IBD should be examined more closely. Furthermore, it remains largely unclear what effect the dose, the combination and the duration of IBD immunosuppressive therapy has on EBV-associated LPD development. In review of the available data, more questions remain than answers. Is there a role for EBV serological screening as in the post-transplantation field and if so, who should be screened and for how long? The younger male population appears to have a higher risk of LPD development while on immune suppressants and given the second peak of EBV seroconversion is within the same age range, should males between the ages of 18 to 30 be selected for routine EBV viral load screening while on therapy? Are there certain combinations of drugs

or specific therapies that should be avoided or dose adjusted to minimize the risk of EBV-associated LPD? Should withdrawal of immunosuppressive therapy be initiated as soon as metrics of early remission is achieved to minimize LPD risk? How should this be balanced with the risk of disease flare or risk of subsequent surgery? The benefit of immunosuppressive therapies in IBD, much like in RA, is unequivocal but the risk of LPD development is a cost that while relatively small is one which not all patients are comfortable with. Many questions surrounding how best to utilize and discontinue these powerful immunosuppressive agents remain. As such, the development of an early screening tool to further minimize the risk of LPD may invaluable to all IBD patients on immunosuppressive treatment (Figure 1).

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