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HIV-associated immune dysfunction and viral infection: role in the pathogenesis of AIDS-related lymphoma

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Abstract

HIV infection is associated with a much higher risk for the development of non-Hodgkin lymphoma (AIDS-NHL). The principal causes of lymphomagenesis in HIV-infected individuals are thought to be the loss of immune function seen in HIV infection, which results in the loss of immunoregulation of Epstein–Barr virus-infected B cells, as well as HIV infection-associated immune dysregulation, including chronic B-cell activation. In this review, we discuss recent reports that further support the importance of these factors, and we highlight emerging evidence of different mechanisms that potentially drive lymphomagenesis in HIV-infected individuals.

Keywords

HIV; AIDS; B lymphocyte; Lymphoma; NHL; Activation-induced cytidine deaminase; AID; Cytokines; CXCL13; Germinal center

Introduction

It is well established that HIV-infected individuals develop several cancers more frequently than HIV-negative persons. More specifically, the incidence of non-Hodgkin's lymphoma (NHL) is 70 times greater in HIV-infected individuals than in the general population [1]. In

fact, NHL is seen so frequently in HIV-infected individuals that the presence of NHL is an AIDS-defining criteria [2].

Recently, the World Health Organization (WHO) released a revised classification of HIV-associated lymphomas [3], dividing them into three different categories: (a) lymphomas that also occur in immunocompetent patients, (b) lymphomas that occur more specifically in the setting of HIV infection, and (c) lymphomas occurring in other immunodeficient states (Table 1). Among the first category, lymphomas occurring also in immunocompetent hosts are the following AIDS-NHL subtypes: Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma (HL), mucosa-associated lymphoid tissue (MALT) lymphomas, and rare cases of T cell and natural killer (NK) cell lymphomas. In the second category, lymphoma subtypes that occur in the setting of HIV infection are primary effusion lymphoma (PEL), plasmablastic lymphoma (PL), and lymphoma arising in human herpesvirus type 8 (HHV8)-associated Castleman's disease. Finally, malignancies resembling lymphoid proliferations typical of other immunodeficient states, such as post-transplant-associated lymphoproliferative disease (PTLD), have been seen in a small number of HIV-positive individuals, representing about 5% of HIV-associated lymphomas.

While multiple mechanisms may contribute to lymphomagenesis in HIV-infected persons, there are two major mechanisms that appear to be involved in the development of these cancers: (1) loss of immunoregulatory control of Epstein-Barr virus (EBV) and/or HHV8 and (2) chronic B-cell activation due to the immune dysfunction resulting from HIV infection. As is the case with other cancers, some forms of AIDS-NHL are associated with the infection with oncogenic viruses, EBV, and/or HHV8. EBV infection plays an important role in the pathogenesis of several B-cell malignancies, such as BL, DLBCL, and PTLD in immunosuppressed individuals [4]. EBV plays a unique role in BL, with virtually 100% of endemic African BL tumors being EBV positive, but with less than half of AIDS-associated BL, and a small minority of sporadic BL, being EBV-positive tumors [5, 6]. The role of EBV in the pathogenesis of lymphoma is complex and not completely understood, but most probably has a dual role, with a direct oncogenic role of some of the viral-encoded genes, but with other less direct effects on oncogenesis, perhaps resulting from immune stimulation and inflammation caused by EBV infection.

AIDS-NHL is characterized by the presence of recurrent genetic alterations, which may be due, in part, to errors of normal processes that occur in activated B cells, which involve modification of somatic DNA, such as immunoglobulin gene (*Ig*) class-switch recombination (CSR) and somatic hypermutation (SHM). In BL, the *c-MYC* gene on chromosome 8 undergoes translocation and is juxtaposed to the *Ig* heavy chain (*IgH*) locus on chromosome 14, or to *Ig* light chain loci on chromosomes 2 (*Ig* κ light chain—*Ig* κ), or 22 (*Ig* λ light chain—*Ig* λ), leading to the unregulated up-regulation of *c-MYC* expression. These translocations are believed to occur due to errors in *IgH* CSR and/or SHM and to play a fundamental role in the genesis of BL [7]. By the same token, the DLBCL subtype of AIDS-NHL is associated with *BCL6* oncogene translocation and mutation, which is believed to result from errors in both *IgH* CSR and SHM [8]. Furthermore, Deffenbacher and colleagues recently showed that AIDS-NHL is characterized by recurrent multiple chromosomal alteration, involving not only *MYC* and *BCL6*, but also other potential important pathways, such as FAS, mTOR, RAS, p53, and others [9]. Therefore, changes in HIV infection that result in chronic B-cell hyperactivation [10] have the potential to contribute to the genesis of AIDS-NHL, particularly those forms that are EBV-negative, and are therefore not driven by the expression of EBV-encoded oncogenes.

Activation-induced cytidine deaminase (AID) is a DNA-editing enzyme normally active during B-cell activation and necessary for *Ig* SHM and CSR to occur. It has been shown that

AID promotes *c-MYC/IgH* translocations and is required for the genesis of lymphomas of germinal center (GC) origin [11]. Moreover, AID is able to produce DNA double-strand breaks, not only in Ig genes but also in other loci, causing widespread genome instability, which could contribute to some of the non-Ig related genetic modifications that are present in AIDS-NHL [12]. Notably, *AID* expression is elevated in peripheral blood mononuclear cells (PBMC) of HIV-positive individuals prior to the diagnosis of NHL [13].

Accordingly, multiple mechanisms appear to contribute to the etiology and pathogenesis of HIV-related NHL: on one side, loss of immunoregulation against EBV results in the uncontrolled growth and transformation of infected B cells. On the other side, the enhanced B-cell activation seen in HIV infection, which involves up regulated AID gene expression and activity, results in increased levels of *IgH* CSR and SHM, as well as in potentially oncogenic molecular errors that, helped by other still unknown factors, lead to the development of B-cell lymphoma.

Cytokines and inflammation in AIDS-NHL

As mentioned earlier, B-cell activation is believed to play an important role in the development of AIDS-NHL of the B-cell lineage. In particular, the activation and proliferation of B lymphocytes increases the likelihood of chromosomal translocations and of oncogene mutation, seminal events in lymphomagenesis.

In AIDS-NHL patients, signs of B-cell activation are present years before diagnosis, representing a useful marker of future development of the malignancy, as well as providing insights into the etiology of these cancers. Immunoglobulin levels are known to be elevated in HIV-infected individuals [10], but Landgren and colleagues recently reported that their levels are not different between those HIV-positive individuals that will develop NHL and those who will not. Nevertheless, in the same study, these workers showed that κ and λ free light chains (FLCs) are elevated up to five years before the diagnosis of AIDS-NHL [14], indicating that FLCs are a marker of future NHL development. FLCs are known to be elevated in autoimmune diseases, such as rheumatoid arthritis and Sjögren's syndrome, and their levels correlate with other B-cell activation markers, such as rheumatoid factor, IgG, gammaglobulin and B-cell activating factor (BAFF) [15]. FLCs are also elevated in non-AIDS-related lymphoproliferative disorders [16, 17], confirming their usefulness as marker of future or present B-cell proliferation.

In the past decade, numerous markers associated with B-cell lymphomagenesis in HIV infection have been identified. Whether these molecules are directly involved on the development of the malignancy, are tumor cell products, or are produced by immune cells reacting to the presence of nascent tumors is still not completely clear. Soluble CD27 (sCD27) and soluble CD30 (sCD30) are members of the tumor necrosis factor receptor (TNF-R) superfamily. Both of these molecules have been reported to be elevated in HIV-infected individuals, and in particular, their levels were significantly higher several years before AIDS-NHL diagnosis [18, 19]. Both sCD27 and sCD30 are thought to be markers of B-cell and T-cell activation, and they are also expressed by HIV-negative NHL [20, 21]. Cell surface CD27 is a marker for memory B cells [22]. Widney et al. [19] found that HIV-positive subjects had decreased CD27 expression on circulating B cells, and that this was inversely correlated with serum sCD27 levels [19]. Interestingly, sCD30 levels were seen to correlate with other activation markers (IL10, IL6, sCD23, sCD27, sCD44, CXCL13), and high sCD30 levels were associated with poor survival in AIDS-NHL [18].

Similarly, it has been shown that soluble CD44 (sCD44) is elevated preceding NHL diagnosis [23]. While sCD44 can reflect the state of immune dysregulation that precedes the diagnosis of AIDS-NHL, sCD44 levels also are known to be elevated following NHL

diagnosis [23, 24], suggesting that this may be a product of tumor cells or tumor-reactive cells.

CD23 is the Fc receptor for IgE, which can be cleaved from the B-cell surface to produce its soluble form (sCD23). This molecule has also been shown to be elevated in serum specimens collected from AIDS patients prior to NHL diagnosis [25–27] and may play a more direct etiologic role in the induction of these malignancies. In fact, this marker is directly involved in Interleukin (IL) 4-mediated *IgHCSR* [28, 29], which, as noted earlier, is thought to contribute to lymphomagenesis. In addition to this, sCD23 is able to up-regulate monocyte production of IL6 [30], which is also elevated preceding the diagnosis of certain subtypes of AIDS-NHL [31, 32]. IL6, besides being a marker of immune activation, also contributes to *IgHCSR* in activated B cells [33], thereby having the potential to also contribute to the development of these B-cell malignancies [31].

CXCL13 is a homeostatic B-cell chemokine, known also as B lymphocyte chemo-attractant (BLC). CXCL13 levels are progressively increased in serum of HIV-positive patients and correlate with other inflammatory markers (Inducible Protein (IP)-10, sCD30, sCD27, sCD23), and with HIV viral load [34]. Interestingly, CXCL13 levels significantly decline after initiation of highly active anti-retroviral therapy (HAART) regimen [34]. Furthermore, in HIV-positive individuals, CXCL13 expression on B cells is increased, and CXCL13-bearing B cells are located preferentially in lymph nodes [35], suggesting a possible implication in lymphomagenesis. In a recent study, Widney et al. [36] found that elevated serum levels of CXCL13 preceded AIDS-NHL diagnosis, and also that AIDS-NHL tumors expressed CXCR5, the receptor for CXCL13. This has been recently confirmed and extended in much larger nested case–control studies in the Multicenter AIDS Cohort Study (MACS) and Women’s Interagency HIV Study (WIHS) cohorts, in which it was seen that CXCL13 levels were elevated for several years prior to the diagnosis of AIDS-NHL [37].

In fact, in HIV-negative patients, CXCL13 is associated with CNS lymphoma, with elevated levels of this chemokine found in cerebrospinal fluid of these patients [38]. Furthermore, serum levels of CXCL13 were been seen to be elevated prior to the diagnosis of B cell NHL in immunocompetent HIV-negative persons, in a recent study large nested case–control study done by Levin and co-workers, who found elevated serum CXCL13 levels over several years pre-NHL diagnosis in specimens from the Department of Defence Serum Repository (DoDSR) [39]. These findings suggest that CXCL13, besides being produced at high levels in HIV infection and contributing to AIDS-NHL, may also be involved in the pathogenesis of NHL in HIV-negative populations.

Several studies have examined the association of cytokine genetic signatures and risk for the development of AIDS-NHL. An IL10 genotype associated with relatively higher levels of IL10 production was seen to be associated with increased risk for AIDS-NHL [40]. In a more recent study, it was seen that HIV-positive individuals who carried alleles linked to low IL10 production were seen to be at decreased risk of developing primary CNS lymphoma. [41]. In addition to this, Sasson and colleagues recently showed that IL10 levels were elevated in AIDS-NHL [42]. This finding is consistent with previous studies that show how IL10 levels were elevated up to 36 months prior to the diagnosis of lymphoma and that IL10 expressing genotypes are overrepresented in those who developed AIDS-NHL [40]. Similarly, Aissani and colleagues recently showed that alleles associated with high expression of TNF- α and lymphotoxin (also known as TNF- β) are linked with a higher risk of developing AIDS-NHL [43]. Moreover, TNF- α is known to be able to stimulate proliferation and Ig production in B cells from both HIV-negative and positive individuals [44] and, interestingly, in a recent study was shown to be elevated in AIDS-NHL patients post-diagnosis [42]. This finding, although requiring confirmation in a larger population,

highlights a potential role for TNF- α in the development of this malignancy, highlighting this molecule as a candidate for further analysis. Noticeably, in the same small group of AIDS-NHL patients, IL2 and IL7 levels were also shown to be elevated, compared to controls [42]. No further studies are available regarding these two molecules in the context of AIDS-NHL, but these findings, if confirmed, could add more pieces to the complex picture of AIDS-NHL pathogenesis.

Taken together, all the studies reviewed suggest the association of AIDS-NHL with an immunologic dysregulation. Interestingly, most of the molecules analyzed are produced by, or stimulate the development of, specific subsets of T helper (T_H) cells. In particular, our attention has been caught by the recently described T_H17 subset, which is thought to be involved in autoimmunity and tissue damage [45]. IL6, in concert with TGF- β , stimulates T cells to differentiate toward the T_H17 subset, which itself produces IL6 and TNF- α . Furthermore, recent work from Takagi and colleagues specifically linked CXCL13 with T_H17 cells, which, in contrast to T_H1 and T_H2 , express this molecule [46]. In addition to this, T_H17 cells are present in the tumor microenvironment in multiple types of murine and human tumors [47] and, interestingly, individuals affected by different types of autoimmune disorders have greatly increased risk of developing NHL [48]. This, in addition to the fact that T_H17 is strongly linked with autoimmunity, strengthens the hypothesis that an up-regulation of the T_H17 subset may be involved in the pathogenesis of NHL.

Two of the molecules reviewed here, IL10 and sCD30, are associated with the T_H2 subset [49–51]. This suggests that T_H2 differentiation may also be dysregulated preceding the development of AIDS-NHL. This increased T_H2 activity may also play a role in the T_H17 up-regulation suggested earlier, as T_H2 cells, through the action of IL10, contribute to down-regulation of the T_H1 subset, which is itself an important inhibitor of T_H17 activity [52]. Further support for the role of T_H2 and T_H17 in AIDS-NHL pathogenesis is provided by the fact that *AID* expression is known to be driven by T_H2 or T_H17 type of cytokines, such as IL4, IL13 [51] and CXCL13 ([46] and unpublished results).

However, in contrast to this “ T_H17 hypothesis” is the fact that some studies have shown decreased numbers of T_H17 cells in several tumors, hypothesizing that, instead of contributing to the development of cancer, T_H17 cells could actually contribute to create a sort of “benign” autoimmunity against the tumor cells (reviewed in Ji and Zhang [53]). It is also important to note that some of the markers reviewed here are produced by multiple types of cells. In fact, CXCL13 is also produced by GC follicular T_H cells (T_{FH}) [54] and follicular dendritic cells [55]. Interestingly, T_{FH} also produce IL4, a B-cell-stimulatory cytokine and, considering that they reside specifically in the GC, a preferential location for lymphomagenesis, are potential candidates for the role of “tumor-helper” cells. This role could be played, as well, by tumor associated macrophages, which are known to produce TNF- α , and, as reviewed by Huysentruyt and McGrath [56], are also a viral reservoir, characteristics that would help them promote the genesis and growth of AIDS-NHL.

In conclusion, the role of the cytokines and markers reviewed is not completely understood. We hypothesize that it might represent HIV-driven immune dysregulation resulting in enhanced T_H17 and T_{FH} activity, but this is only one of several possible explanations. Despite incomplete knowledge regarding their origin, these AIDS-NHL biomarkers may certainly be used in the future as lymphoma risk predictors in HIV infection, or implemented as diagnostic or prognostic tools.

Epstein–Barr virus and AIDS-NHL

It has been known for some time that viruses play an important role in the pathogenesis of several cancers. The role of EBV infection in the development of AIDS-NHL is unclear. On

one hand, it is clear that immunosuppression is one risk factor that contributes to the development of B-cell malignancies [57], as it also occurs in patients treated with immunosuppressive drugs after organ transplantation [1, 58, 59]. Similarly, patients with poorly controlled or advanced AIDS may develop lymphoma due to the profound loss of T-cell immune function, which would result in their inability to control EBV + B cells. However, this would account mainly for CNS lymphomas, which are all EBV + and typically develop at low CD4 numbers [60]. On the other hand, the role that EBV plays in the genesis of other types of AIDS-NHL, such as BL or DBLCL, is less clear. These forms of AIDS-NHL develop in HIV-positive persons who have relatively higher CD4 numbers, with a significant minority (30–50%) of these cancers being EBV positive [60]. Immunosuppression does not seem to be the major contributing factor for B-cell lymphoma development in these patients, as the incidence of these forms of AIDS-NHL have not decreased much with HAART [61]. So, it appears that EBV infection can contribute to AIDS-NHL in various ways, but that it is not essential for the development of these cancers.

One unique way by which EBV infection could contribute to the genesis of AIDS-NHL is by promoting DNA-damaging activities, such as *Ig* SHM. It has been observed that tumor cells that are EBV positive present mutations in the variable region (VH) of Ig genes [62–64]. Traditionally, it has been thought that EBV only infects memory B cells, which are post-GC B cells, and would have gone through the SHM and CSR processes and have mutated VH regions in their Ig genes [65, 66]. In this case, EBV would not interfere directly with the SHM process, but rather it would preferentially infect post-GC B cells. However, there is growing evidence that EBV might be infecting/transforming naïve cells (pre-GC cells that have not undergone *Ig* CSR nor SHM). In such a case, the expression of viral genes such as LMP-1 and LMP-2A, which mimic activated CD40 and BCR, respectively, would mimic the GC reaction, where B cells encounter antigen and obtain T cell help through the CD40:CD40L interaction [67–69]. In this case, EBV would be inducing SHM directly upon infection of B cells. Evidence supporting this is the finding that EBV infection induces the expression of *AID* and *POL η* [70], enzymes that are necessary for SHM, through the viral protein LMP-1 [71]. In addition to this, it was seen that EBV infected cells accumulate mutations in their VH genes [72], as well as in protooncogenes such as *BCL-6* and *p53* [70]. BL cells from patients with EBV-negative tumors also were seen to have lower SHM in their VH or their Ig genes than BL cells from patients with EBV-positive tumors [62–64]. There also evidence that EBV further regulates SHM: Tobollik et al. showed that EBNA2 inhibits *AID* expression in latency III, with its effects dominating over those of the induction of *AID* expression mediated by LMP-1 [73].

Another way that EBV might be contributing to the development of AIDS-NHL would be through the direct oncogenic effects of viral proteins such as EBNA-1. EBNA-1 is expressed in all types of latency (I, II, and III) and is expressed in all EBV-associated malignancies, so it seems that it plays an important role in B-cell lymphoma development [67]. EBNA-1 acts as a transcription factor that mediates the expression of viral genes such as EBNA2 and LMP1 and is a necessary factor for B-cell transformation. It can also function as a transcription factor that induces cellular genes that may have oncogenic effects [74].

A third way that EBV may contribute to the development of lymphoma is by regulating the expression of cellular genes by the expression of cellular and viral micro RNAs (miRNA). miRNAs are small non-coding RNA molecules (19–24 nt) that bind to partially complementary sites in mRNA targets. It has been observed that EBV infection has the ability to induce cellular miRNAs, such as mi-155, mi-127, mi-21, and mi-146a [75, 76]. In addition to this EBV itself also encodes for at least 23 viral miRNA, which can regulate cellular genes, such as BHRF1-1,2,3 and BART1,2 [77, 78]. Xia et al. [79] have shown that BHRF1-3 is elevated in EBV-associated AIDS-related DLBCL, and they demonstrated that

it can repress the expression of CXCL11/I-TAC, an interferon-inducible T cell attracting chemokine and a potential regulator of cytotoxic T cells, showing the impact that viral miRNAs can have on immune surveillance. As mentioned earlier, EBV also induces cellular miRNAs. In a recent report Leucci et al. [80] show how EBV induces mi-127, which downregulates the expression of BLIMP-1 and XBP-1, genes that play a crucial role in plasma cell differentiation by regulating *BCL-6* and *c-MYC* expression. mi-127 expression resulted in downregulation of BLIMP-1 and XBP-1, which consequently resulted in the overexpression of BCL-6 and c-MYC at the mRNA and protein level. The upregulation of mi-127 may be a key regulator of lymphomagenesis of EBV-positive tumor cells by blocking the differentiation, stalling B cells at the GC stage.

In summary, in addition to the contribution of EBV lymphomagenesis due to direct transformation of B cells in severely immunosuppressed HIV-positive persons, EBV also has the potential to contribute to the development of AIDS-NHL by inducing B-cell activation, either directly through its viral genes or indirectly by inducing cellular genes. Even though CNS lymphomas driven by the immunosuppression are not as prevalent in the era of HAART, other types of AIDS-NHL that develop at higher CD4 numbers, have either not had their incidence decrease greatly with HAART or, in the case of BL, not shown any decrease in incidence in the HAART era [61]. As nearly half of these lymphomas are EBV positive, it is of great importance to consider the means by which EBV may promote the development of these cancers.

HIV and AIDS-NHL

As mentioned earlier, the two major mechanisms that are believed to lead to the development of AIDS-NHL are chronic B-cell activation due to HIV infection-associated immune dysfunction, and the growth of EBV + transformed B cells due to profound immune suppression. However, one might think that HIV virions themselves might induce B-cell activation, since it has been shown that other viruses such as HPV [81] and HCV [82] can directly activate B cells, thereby inducing *AID* expression, leading to DNA damage that may promote lymphomagenesis. People infected with HPV or HCV are known to be at higher risk of developing lymphoma [83–85]. Additionally, it has been recently shown that the cumulative duration of HIV viremia is predictive of AIDS-NHL development [86], underscoring the potential relevance of the presence of HIV virions in the development of AIDS-NHL.

There is growing evidence that HIV virions can directly contribute to B-cell activation via direct interactions with B cells. Early observations that HIV virions could lead to B-cell activation were first reported by Schnittman et al. [87], but it was unclear how HIV was mediating this activation. Recent reports have shown that HIV gp120 has the capability to induce B-cell activation: CSR, interleukin secretion, and *AID* expression were seen to be induced by exposure to gp120, which interacted with DC-SIGN on B cells [88]. In a similar manner, HIV Tat seems to be involved in lymphomagenesis in mice: Tat expression in lymphoid tissue of transgenic mice was seen to induce the development of B-cell lymphoma, as well as the production of lymphoma-associated cytokines, such as IL6 and IL10 [89]. Also Martin et al. showed that CD40L, which is normally expressed on the surface of activated T cells, was incorporated into HIV virions, and could stimulate B cells via its interactions with CD40, leading to interleukin secretion [90]. In agreement with this, we have recently shown that CD40L incorporated into HIV virions could induce *AID* expression in B cells [91], with the potential to induce *IgH* CSR and SHM, as well as oncogenic changes. More specifically, CD40L expressing HIV virions, and not CD40L-negative virions, induced *AID* expression at the mRNA and protein level. These AID-positive cells also displayed B-cell surface activation markers, such as CD71 and CD10

[91]. This is of great importance, since *AID* is expressed in activated GC B cells, where CSR and SHM occur, and it has been seen that GC cells that express AID also express cell surface CD71 [92]. Hence, CD40L incorporated into HIV virions can directly activate B cells through CD40, inducing AID and CD71 expression, rendering them phenotypically similar to GC B cells. These GC-like B cells can potentially undergo SHM and CSR, and errors in these processes may lead to the development of malignant B-cell clones. In addition to this, we also observed that these B cells not only have an activated phenotype, but they also have the capability to secrete B-cell-activating cytokines, including IL6, IL8, IL10, and GM-CSF [91]. HIV incorporates into its envelope various types of proteins with diverse functions including: adhesion molecules, MHC molecules, B-cell markers, T-cell markers, and macrophage surface proteins [93]. Among this variegate spectrum of molecules, it would be of interest to identify other potential proteins that may be incorporated into HIV virions that may also activate B cells, potentially contributing to lymphomagenesis. An interesting candidate would be CD4, as it has been shown to be present on HIV envelope [94] and CD4-positive virions could potentially bind MHC class II molecules, whose signaling can activate B cells [95, 96]. Other transmembrane proteins potentially involved in this process would be CD80 and CD86 [97]. Both of these molecules interact with CD28, a potent lymphocyte stimulator, normally present in T cells, but also expressed by EBV-positive B-cell lines [98], representing a potential additional pathogenetic mechanism in EBV-induced lymphomagenesis. Clearly, it is of great interest to identify which other proteins might be incorporated in HIV virions, as any B-cell-stimulating transmembrane protein expressed by HIV-infected cells could be incorporated into the HIV envelope and contribute to B-cell activation and to lymphomagenesis.

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Table 1

WHO classification of HIV-associated lymphomas

Lymphomas also occurring in immunocompetent patients	Lymphomas occurring more specifically in HIV-positive patients	Lymphomas occurring in other immunodeficient states
Burkitt lymphoma	Primary effusion lymphoma	Polymorphic B-cell lymphoma (PTLD-like)
Diffuse large B-cell lymphoma	Plasmablastic lymphoma	
Hodgkin lymphoma	Lymphoma arising in HHV8-associated Castleman disease	
Other		
Malt lymphoma		
Peripheral T/NK cell lymphoma		