

Chapman University
Chapman University Digital Commons

Pharmacy Faculty Articles and Research

School of Pharmacy

9-23-2016

Does Persistent HIV Replication Explain Continued Lymphoma Incidence in the Era of Effective Antiretroviral Therapy?

Jennifer Totonchy

Chapman University, totonchy@chapman.edu

Ethel Cesarman

Weill Cornell Medical College

Follow this and additional works at: http://digitalcommons.chapman.edu/pharmacy_articles



Part of the [Cancer Biology Commons](#), and the [Virus Diseases Commons](#)

Recommended Citation

Totonchy J, Cesarman E. Does persistent HIV replication explain continued lymphoma incidence in the era of effective antiretroviral therapy? *Curr Opin Virol*. 2016;20:71-77. doi: 10.1016/j.coviro.2016.09.001

This Article is brought to you for free and open access by the School of Pharmacy at Chapman University Digital Commons. It has been accepted for inclusion in Pharmacy Faculty Articles and Research by an authorized administrator of Chapman University Digital Commons. For more information, please contact laughtin@chapman.edu.

Does Persistent HIV Replication Explain Continued Lymphoma Incidence in the Era of Effective Antiretroviral Therapy?

Comments

NOTICE: this is the author's version of a work that was accepted for publication in *Current Opinion in Virology*. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in *Current Opinion in Virology*, volume 20, in 2016. DOI: [10.1016/j.coviro.2016.09.001](https://doi.org/10.1016/j.coviro.2016.09.001)

The Creative Commons license below applies only to this version of the article.

Creative Commons License



This work is licensed under a [Creative Commons Attribution-NonCommercial-No Derivative Works 4.0 License](https://creativecommons.org/licenses/by-nc-nd/4.0/).

Copyright

Elsevier

Does persistent HIV replication explain continued lymphoma incidence in the era of effective antiretroviral therapy?

Jennifer Totonchy¹ and Ethel Cesarman¹

¹ Weill Cornell Medicine, Department of Pathology and Laboratory Medicine

Corresponding author:

Ethel Cesarman

Weill Cornell Medicine

1300 York Avenue, C-410B

New York, NY 10065.

Phone: 212-746-8838.

Fax: 212-746-4416.

E-mail: ecesarm@med.cornell.edu

Running title: Lymphoma and HIV suppressive therapy

Highlights

- * Control of HIV with cART fails to reduce the incidence of many lymphomas.
- * Replication of HIV in lymph nodes may affect lymphoma risk during therapy.
- * Replication of HIV in adipose tissue may create a lymphoma-promoting metabolic state.
- * HIV pathology in reservoirs may inform mechanisms of cART-resistant lymphoma risk.

Abstract

Non-Hodgkin lymphomas are highly increased in incidence in individuals infected with HIV, and this continues to be the case in spite of highly effective combined antiretroviral therapy (cART). New evidence has demonstrated that while successful virtual recovery of CD4 counts and elimination of HIV from peripheral blood can be achieved with cART, viral replication can still occur in lymphoid tissues. In addition, recent studies have suggested that adipose tissue provides an additional reservoir for HIV-infected macrophages and T lymphocytes even in the context of successful cART therapy. In this review article, we discuss possible mechanisms leading to the development of lymphoma in the cART era.

Introduction

The incidence of Kaposi Sarcoma (KS) and other AIDS-defining cancers has decreased significantly since combined antiretroviral therapy (cART) became widely available [1], but overall cancer incidence is increasing in patients living with HIV (PLWH) [2]. Indeed, the D:A:D study recently concluded that malignancy is now the leading cause of non-AIDS-related mortality in the PLWH [3]. Although some studies attribute this trend to increased survival rates in the cART era producing an aging HIV-infected population [4], standardized incidence ratios for several cancers including anal, liver, and lung malignancies are demonstrably higher in the HIV-positive population compared to the general population [5]. Importantly, the incidence of malignancy in this cohort can be correlated with lower CD4+ T cell count at cART initiation [5], suggesting that HIV-mediated immunosuppression predisposes patients to malignancy even when HIV disease is later controlled. Malignant lymphoproliferation is common in HIV positive patients regardless of treatment status [6], and non-Hodgkin lymphomas (NHL) are still considered an AIDS-defining cancer. Although incidence of some types of NHL have decreased in the cART era, other manifestations of NHL are increasing and NHL remains a significant source of mortality in HIV-infected individuals [7,8]. In fact, lymphomas have become the most common AIDS-related cancer in the developed world, constituting over 50% of all AIDS defining cancers and the most common cause of cancer-related death in HIV-infected individuals [9]. Interestingly, KSHV co-infection further increases the risk of NHL in HIV positive patients [10], and rates of KSHV-associated PEL and MCD remain rare but are unaffected by the widespread use of cART [5,11]. Similarly, incidence of EBV-associated lymphomas including Burkitt lymphoma and classical Hodgkin's Lymphoma (cHL) remains high. Moreover, aggressive histological subtypes of cHL occur more frequently in PLWH and these cases are often characterized by increased numbers of pathogenic Reed-Sternberg cells that are EBV infected, suggesting that EBV has an

unusual role in cHL pathogenesis in the context of HIV infection [6,12]. Taken together, these data suggest that (1) HIV infection predisposes patients to malignant lymphoproliferation in general and (2) cART-mediated immune reconstitution is not always sufficient to prevent disease progression in PLWH. In this review, we will highlight some of the recent reports which may shed light on the persistence of lymphoma in PLWH in the context of successful cART treatment.

Persistent replication of HIV in lymph node reservoirs

Despite the success of cART at preventing the progression of HIV infection to AIDS, it is now apparent that more subtle HIV-mediated pathology, including increased susceptibility to malignancy, persists even in well-controlled patients with high CD4 counts and undetectable levels of circulating HIV. The concept that latent reservoirs of HIV infected cells persist in anatomical sites where penetration of cART drugs is low has received considerable attention in recent years as a significant barrier to achieving an HIV cure [13,14]. Indeed, viral persistence in lymph nodes and gut-associated lymphoid tissues (GALT) under cART therapy has been documented in both HIV [15] and SIV [16,17] infection. However, the definition of these reservoirs as “latent” has recently been challenged in an elegant study by Lorenzo-Redondo et al, which demonstrates that HIV continues to replicate in lymphoid tissue and traffics between the lymph nodes and blood even in the context of effective cART-mediated suppression of plasma viremia. Moreover, the authors posit that viral evolution in these protected niches may be independent of selective pressure from cART therapy [18]. This provides us with a theoretical context in which the persistent immune dysfunction found in PLWH successfully treated with cART may be due to residual viral pathogenesis restricted to the lymph nodes rather than aberrations caused by dysregulated immune reconstitution. Indeed, recent evidence suggests that germinal center resident follicular helper T lymphocytes (Tfh) may be a site

of HIV persistence [17,19,20] and that the lack of CD8+ T cell surveillance of the germinal center [21] may contribute to the escape of HIV-infected T cells from elimination by CTL in this niche. Moreover, these results create a framework in which we can hypothesize HIV-infected T lymphocytes in germinal centers contribute to the development of lymphoma in PLWH and that this pathology persists during cART.

Contribution of HIV to a lymphomagenic microenvironment during cART

Given the novel finding that HIV continues to replicate in lymph nodes during cART therapy, and that germinal center-resident Tfh cells are a particularly critical cell type for HIV persistence, we will now consider possible mechanisms, other than the obvious possibility of chronic antigenic stimulation, by which HIV might contribute to lymphoma risk in this context.

Effects of follicular T cell subsets in the germinal center

Recent findings suggest that Tfh from HIV-infected individuals are phenotypically [20] and functionally [22] distinct from those of uninfected controls, raising the possibility that the significant aberrations in B cell development and function observed during chronic HIV infection [23,24] might stem from effects of HIV-infected Tfh on the germinal center reaction. Appropriate Tfh function is also critical to the control of chronic viral infection [25,26], suggesting that HIV-mediated dysfunction in this cell type may also play a role in lymphoma pathogenesis driven by viral co-pathogens such as EBV and KSHV.

Interestingly, Cubas et al demonstrated that Tfh from HIV-infected subjects displayed increased IL-21 production after *ex vivo* stimulation [22]. Given the well-documented effects of IL-21 on EBV latency and LMP1 expression [27-29], it is interesting to speculate that HIV-driven changes in Tfh function might enhance B cell transformation by EBV.

Similarly, it was recently shown that expanded Tfh cell populations in individuals chronically infected with HIV are associated with an increase in germinal center B cells

and plasma cells, decrease of memory B cells and IgG1 hypersecretion [30]. Moreover, the expansion of T follicular regulatory cells (Tfr) in HIV disease adds a layer of complexity to this milieu [31]. Taken together, the expansion of both Tfh and Tfr would have the expected outcome of diminishing B cell activation. Instead, these expansions are coincident with excessive B lymphocyte activation [32] and hypergammaglobulinemia [33], underscoring the fact that, although follicular T lymphocyte subsets increase in frequency, their normal lymph node functions are perturbed in the context of chronic HIV infection leading to poorly-understood alterations in B cell physiology (Figure 1). Certainly, additional mechanisms underlying lymphoma development in this context will continue to evolve along with our understanding of the normal and pathological role of follicular T cell subsets in the germinal center reaction.

Chronic B cell stimulation

It is well known that HIV-induces chronic B cell stimulation, which may be critical for the development of lymphoma [32,34,35]. In particular germinal center expansion, as seen as a florid follicular hyperplasia at the early stages of AIDS, is thought to contribute to lymphomagenesis. This is the site where B cell receptor rearrangements occur (i.e class switching) and also somatic hypermutation through the effects of activation-induced cytidine deaminase (AID), and these events can result in mistakes involving oncogenic genetic alterations. In addition, lymphomas in HIV-infected patients are most frequently of germinal center cell origin (including Burkitt lymphoma and GC-subtype of diffuse large B cell lymphoma). These B cell abnormalities were still present in cART-treated patients, albeit somewhat diminished when compared to untreated patients. This indicates that even in the context of good peripheral HIV control through cART, there are B cell abnormalities that could play a role in lymphoma development.

Direct effects of HIV virions and proteins on lymphomagenesis

If HIV maintains active replication in lymph nodes during cART treatment, we must consider that direct functions of HIV virions and/or HIV proteins on B cell functionality may also persist even if HIV does not directly infect the B cells that give rise to lymphomas. A number of potential mechanisms by which HIV proteins might directly contribute to lymphoma have previously been characterized [1,36], and specifically a number of these may contribute to B cell hyperplasia, including Tat [37], Nef [38,39], Env gp120 [40], Env gp130 and Gag p17 [41]. Tat has inhibitory effects on DNA repair mechanisms in B cells [42], and can activate DNMT1 resulting in aberrant hypermethylation of target genes [43]. HIV viral proteins have been shown to interact with other oncogenic herpesviral proteins, even if expressed in different cells, through secretion or transmission of HIV proteins by structures like nanotubules or exosomes (reviewed in [44,45]). Two studies have documented interactions between HIV Nef and KSHV: (1) Nef could synergize with KSHV vIL-6 and activate the AKT pathway, which lead to angiogenesis and tumor formation in a model of Kaposi sarcoma [46] and (2) Nef was shown to regulate KSHV latency by inducing cellular miRNA 1258 (hsa-miR-1258) that directly targets a seed sequence in the 3' untranslated region of the mRNA encoding the major lytic switch protein of KSHV (RTA) [47]. HIV Nef was shown to be secreted in exosomes [48] and to penetrate bystander, uninfected B cells [38]. Thus, it may have an effect in maintaining latency of EBV or KSHV-infected B cells that eventually become transformed. Transgenic mice expressing the HIV protein Tat develop B cell lymphoma, a phenotype that might be linked to the ability of Tat to induce production of IL-6 and IL-10. Using another transgenic mouse model, Curreli et. al. recently described the association of pre-lymphoma lymphadenopathy associated with increased expression of the HIV proteins p17 and gp120 [49]. Indeed, high levels of p17 persist in lymph nodes of PLWH, even under the influence of cART [50,51]. Working from these observations, Dolcetti and colleagues recently demonstrated that particular p17 sequence variants are expressed in HIV patients

presenting with NHL, and that these altered p17 proteins have direct effects on B cell proliferation and signaling to Akt and PTEN [52]. It is particularly interesting to consider that these lymphomagenic p17 variants may arise during HIV sequence evolution in lymph nodes during cART, thus providing a source of lymphoma risk independent of treatment status. A different mechanism by which HIV itself may affect lymphoma development is suggested by the observation that host-derived CD40L can be incorporated into virions and the binding of these virions to B lymphocytes can potentiate activation and proliferation mimicking the endogenous CD40-CD40L interaction [40].

Adipose tissue reservoirs and implications for lymphoma

An increasing number of population studies are linking both infection and cART treatment with increased incidence of obesity in PLWH [53,54]. Although there is no consensus in the clinical literature as to whether there is a direct association between obesity and risk of NHL in the general population [55], recent studies suggest that in the context of HIV infection in general, and PLWH on cART specifically, obesity coupled with specific defects in adipose tissue metabolism could provide a context in which lymphoma risk is increased. In particular, recent studies demonstrate that adipose tissue provides an additional reservoir for HIV-infected immune cells (macrophages and T lymphocytes) even in the context of successful cART therapy [56,57], and studies using SIV infection of non-human primates (NHP) conclusively demonstrate that HIV infection of adipose tissue contributes to metabolic abnormalities and systemic inflammation during chronic infection [56,58], similar to what is observed in PLWH. Moreover, a significant proportion of PLWH on cART therapy have lipodystrophy, characterized by a loss of subcutaneous adipose tissue coupled with an increase in visceral adipose tissue [59-61] and these modifications are associated with chronic inflammation and, specifically, increased levels of serum leptin and IL-6 [62]. Increased expression and circulation of leptin was also reported in chronic SIV infection in NHP [58]. Aside from the obvious contribution of chronic inflammation in

lipodystrophy to lymphoma risk, a number of recent studies specifically link leptin signaling to pathogenesis in lymphoma via induction of PI3K/Akt signaling [63-66]. Thus, it seems that adipose-specific metabolic defects in PLWH undergoing cART treatment could directly contribute to lymphoma risk via increases in circulating leptin. Moreover, a number of direct effects of HIV accessory proteins on adipocyte functions have been described in animal models [67,68] and human cells [69-71] many of which could contribute to the induction of a lymphoma-promoting chronic inflammatory state.

Conclusions

A great deal of progress has been made controlling HIV infection and preventing the progress to full-blown AIDS. This has led to a marked decrease of some AIDS defining malignancies like Kaposi sarcoma, but surprisingly not their disappearance and some cancers may even be rising in incidence as people with HIV infection are living longer. Of note, lymphomas are occurring in people with controlled HIV infection and no overt immunodeficiency. While lymphoma is considered an “AIDS defining condition”, these individuals may not have other evidence of AIDS, such as opportunistic infections, and respond to lymphoma treatment with survival comparable to that of HIV-negative individuals. Thus, one could argue that lymphoma should no longer be considered an “AIDS-defining cancer”, but rather an “HIV-associated malignancy”.

HIV is considered an oncogenic pathogen, although it does not directly infect the cancer cells [1], and an indirect role related to inflammation and HIV proteins that may be secreted has been implicated for some time. However, control of HIV should have eliminated these factors responsible for lymphoma development. A possible explanation has been that HIV infection results in upregulation of AID, which induces gene rearrangements and somatic hypermutation in B cells and could induce aberrant genetic alterations resulting in permanent damage that leads to lymphoma down the road,

regardless of subsequent control of HIV. However, this phenomenon has not been formally demonstrated experimentally. The recent evidence demonstrating that HIV continues to replicate in lymph node reservoirs even in the context of successful cART suppression of plasma viremia creates a new scenario wherein the effects of HIV on follicular T cell subsets as well as direct effects of HIV proteins may induce lymphoma development, even in when HIV disease is well-controlled, and may explain the continued prevalence of HIV-associated lymphomas in the era of effective antiretroviral therapy.

Grants

EC is funded by NIH/NCI grants 1R01CA154228 and R01-CA103646 and JT is funded by NIDCR grant 5K99 DE024969-01.

Bibliography

1. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, Ghissassi El F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, et al.: **A review of human carcinogens-- Part B: biological agents.** *Lancet Oncol* 2009, **10**:321–322.
2. Bonnet F, Lewden C, May T, Heripret L, Jouglu E, Bevilacqua S, Costagliola D, Salmon D, Ch ne GV, Morlat P: **Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy.** *Cancer* 2004, **101**:317–324.
- *3. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, Kowalska JD, de Wit S, Law M, Sadr el W, et al.: **Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration.** *Lancet* 2014, **384**:241–248. **Latest comprehensive multicohort study showing marked increase in mortality from non-AIDS cancers in the HIV positive population during cART era.**
4. Yanik EL, Napravnik S, Cole SR, Achenbach CJ, Gopal S, Olshan A, Dittmer DP, Kitahata MM, Mugavero MJ, Saag M, et al.: **Incidence and Timing of Cancer in HIV-Infected Individuals Following Initiation of Combination Antiretroviral Therapy.** *CLIN INFECT DIS* 2013, **57**:756–764.
5. Powles T, Robinson D, Stebbing J, Shamash J, Nelson M, Gazzard B, Mandelia S, Moller H, Bower M: **Highly Active Antiretroviral Therapy and the Incidence of Non-AIDS-Defining Cancers in People With HIV Infection.** *Journal of Clinical Oncology* 2009, **27**:884–890.
6. Carbone A, Vaccher E, Gloghini A, Pantanowitz L, Abayomi A, De Paoli P, Franceschi S: **Diagnosis and management of lymphomas and other cancers in**

HIV-infected patients. *Nat Rev Clin Oncol* 2014, **11**:223–238.

7. Breen EC, Hussain SK, Magpantay L, Jacobson LP, Detels R, Rabkin CS, Kaslow RA, Variakojis D, Bream JH, Rinaldo CR, et al.: **B-Cell Stimulatory Cytokines and Markers of Immune Activation Are Elevated Several Years Prior to the Diagnosis of Systemic AIDS-Associated Non-Hodgkin B-Cell Lymphoma.** *Cancer Epidemiology Biomarkers & Prevention* 2011, **20**:1303–1314.
8. Seaberg EC, Wiley D, Martínez-Maza O, Chmiel JS, Kingsley L, Tang Y, Margolick JB, Jacobson LP, Multicenter AIDS Cohort Study (MACS): **Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007.** *Cancer* 2010, **116**:5507–5516.
9. Simard EP, Engels EA: **Cancer as a cause of death among people with AIDS in the United States.** *CLIN INFECT DIS* 2010, **51**:957–962.
10. Burbelo PD, Kovacs JA, Wagner J, Bayat A, Rhodes CS, De Souza Y, Greenspan JS, Iadarola MJ: **The Cancer-Associated Virus Landscape in HIV Patients with Oral Hairy Leukoplakia, Kaposi's Sarcoma, and Non-Hodgkin Lymphoma.** *AIDS Research and Treatment* 2012, **2012**:1–10.
11. Bhutani M, Polizzotto MN, Uldrick TS, Yarchoan R: **Kaposi Sarcoma–Associated Herpesvirus-Associated Malignancies_ Epidemiology, Pathogenesis, and Advances in Treatment.** *Seminars in Oncology* 2015, **42**:223–246.
12. Brugnaro P, Morelli E, Cattelan F, Petrucci A, Panese S, Esemè F, Cavinato F, Barelli A, Rauseo E: **Non-AIDS defining malignancies among human immunodeficiency virus-positive subjects: Epidemiology and outcome after two decades of HAART era.** *World J Virol* 2015, **4**:209–218.
13. Barton K, Winckelmann A, Palmer S: **HIV-1 Reservoirs During Suppressive Therapy.** *Trends Microbiol.* 2016, **24**:345–355.
14. Licht A, Alter G: **A Drug-Free Zone-Lymph Nodes as a Safe Haven for HIV.** *Cell Host and Microbe* 2016, **19**:275–276.
15. Stockenström von S, Odevall L, Lee E, Sinclair E, Bacchetti P, Killian M, Epling L, Shao W, Hoh R, Ho T, et al.: **Longitudinal Genetic Characterization Reveals That Cell Proliferation Maintains a Persistent HIV Type 1 DNA Pool During Effective HIV Therapy.** *J. Infect. Dis.* 2015, **212**:596–607.
- *16. Santangelo PJ, Rogers KA, Zurla C, Blanchard EL, Gumber S, Strait K, Connor-Stroud F, Schuster DM, Amancha PK, Hong JJ, et al.: **Whole-body immunoPET reveals active SIV dynamics in viremic and antiretroviral therapy-treated macaques.** *Nat. Methods* 2015, **12**:427–432. **Novel imaging study demonstrating residual SIV in GALT and isolated lymph nodes in primates under cART.**
- *17. Fukazawa Y, Lum R, Okoye AA, Park H, Matsuda K, Bae JY, Hagen SI, Shoemaker R, Deleage C, Lucero C, et al.: **B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers.** *Nat Med* 2015, **21**:132–139. **Establishes that specific persistence of SIV infection in Tfh is due to exclusion of CD8 T cells from B cell follicles, providing an immune-privileged reservoir.**

- **18. Lorenzo-Redondo R, Fryer HR, Bedford T, Kim E-Y, Archer J, Kosakovsky Pond SL, Chung Y-S, Penugonda S, Chipman JG, Fletcher CV, et al.: **Persistent HIV-1 replication maintains the tissue reservoir during therapy.** *Nature* 2016, **530**:51–56. **Important study showing that HIV replication and evolution continues in reservoirs during cART, challenging the definition of these reservoirs as “latent”.**
19. Perreau M, Savoye A-L, De Crignis E, Corpataux J-M, Cubas R, Haddad EK, De Leval L, Graziosi C, Pantaleo G: **Follicular helper T cells serve as the major CD4 T cell compartment for HIV-1 infection, replication, and production.** *J Exp Med* 2013, **210**:143–156.
- **20. Kohler SL, Pham MN, Folkvord JM, Arends T, Miller SM, Miles B, Meditz AL, McCarter M, Levy DN, Connick E: **Germinal Center T Follicular Helper Cells Are Highly Permissive to HIV-1 and Alter Their Phenotype during Virus Replication.** *J Immunol* 2016, **196**:2711–2722. **Demonstrates that germinal center Tfh are an important source of HIV persistence and that infection alters Tfh function, potentially underlying immune dysregulation during successful HIV therapy.**
21. Connick E, Mattila T, Folkvord JM, Schlichtemeier R, Meditz AL, Ray MG, McCarter MD, Mawhinney S, Hage A, White C, et al.: **CTL fail to accumulate at sites of HIV-1 replication in lymphoid tissue.** *The Journal of Immunology* 2007, **178**:6975–6983.
- **22. Cubas RA, Mudd JC, Savoye A-L, Perreau M, van Grevenynghe J, Metcalf T, Connick E, Meditz A, Freeman GJ, Abesada-Terk G, et al.: **Inadequate T follicular cell help impairs B cell immunity during HIV infection.** *Nat Med* 2013, **19**:494–499. **Important study linking HIV infection of follicular Tfh cells to decreased B cell survival and antibody production.**
23. van Grevenynghe J, Cubas RA, Noto A, DaFonseca S, He Z, Peretz Y, Filali-Mouhim A, Dupuy FP, Procopio FA, Chomont N, et al.: **Loss of memory B cells during chronic HIV infection is driven by Foxo3a- and TRAIL-mediated apoptosis.** *J Clin Invest* 2011, **121**:3877–3888.
24. Moir S, Fauci AS: **Insights into B cells and HIV-specific B-cell responses in HIV-infected individuals.** *Immunological Reviews* 2013, **254**:207–224.
25. Fahey LM, Wilson EB, Elsaesser H, Fistonich CD, McGavern DB, Brooks DG: **Viral persistence redirects CD4 T cell differentiation toward T follicular helper cells.** *J Exp Med* 2011, **208**:987–999.
26. Harker JA, Lewis GM, Mack L, Zuniga EI: **Late interleukin-6 escalates T follicular helper cell responses and controls a chronic viral infection.** *Science* 2011, **334**:825–829.
27. Kis LL, Salamon D, Persson EK, Nagy N, Scheeren FA, Spits H, Klein G, Klein E: **IL-21 imposes a type II EBV gene expression on type III and type I B cells by the repression of C- and activation of LMP-1-promoter.** *Proc Natl Acad Sci USA* 2010, **107**:872–877.
28. Konforte D, Simard N, Paige CJ: **Interleukin-21 regulates expression of key Epstein-Barr virus oncoproteins, EBNA2 and LMP1, in infected human B cells.**

Virology 2008, **374**:100–113.

- **29. Wu L, Ehlin-Henriksson B, Zhu H, Ernberg I, Klein G: **EBV counteracts IL-21-induced apoptosis in an EBV-positive diffuse large B-cell lymphoma cell line.** *Int J Cancer* 2013, **133**:766–770. **Important study linking HIV infection of follicular Tfh cells to decreased B cell survival and antibody production.**
30. Lindqvist M, van Lunzen J, Soghoian DZ, Kuhl BD, Ranasinghe S, Kranias G, Flanders MD, Cutler S, Yudanin N, Muller MI, et al.: **Expansion of HIV-specific T follicular helper cells in chronic HIV infection.** *J Clin Invest* 2012, **122**:3271–3280.
31. Miles B, Miller SM, Folkvord JM, Kimball A, Chamanian M, Meditz AL, Arends T, McCarter MD, Levy DN, Rakasz EG, et al.: **Follicular regulatory T cells impair follicular T helper cells in HIV and SIV infection.** *Nat Commun* 2015, **6**:8608.
32. Martínez-Maza O, Breen EC: **B-cell activation and lymphoma in patients with HIV.** *Curr Opin Oncol* 2002, **14**:528–532.
33. De Milito A, Nilsson A, Titanji K, Thorstensson R, Reizenstein E, Narita M, Grutzmeier S, Sönnnerborg A, Chiodi F: **Mechanisms of hypergammaglobulinemia and impaired antigen-specific humoral immunity in HIV-1 infection.** *Blood* 2004, **103**:2180–2186.
34. Przybylski GK, Goldman J, Ng VL, McGrath MS, Herndier BG, Schenkein DP, Monroe JG, Silberstein LE: **Evidence for early B-cell activation preceding the development of Epstein-Barr virus-negative acquired immunodeficiency syndrome-related lymphoma.** *Blood* 1996, **88**:4620–4629.
35. Pelicci PG, Knowles DM, Arlin ZA, Wieczorek R, Luciw P, Dina D, Basilico C, Dalla-Favera R: **Multiple monoclonal B cell expansions and c-myc oncogene rearrangements in acquired immune deficiency syndrome-related lymphoproliferative disorders. Implications for lymphomagenesis.** *J Exp Med* 1986, **164**:2049–2060.
36. Cesarman E: **How do viruses trick B cells into becoming lymphomas?** *Curr. Opin. Hematol.* 2014, **21**:358–368.
37. Lefevre EA, Krzysiek R, Loret EP, Galanaud P, Richard Y: **Cutting edge: HIV-1 Tat protein differentially modulates the B cell response of naive, memory, and germinal center B cells.** *The Journal of Immunology* 1999, **163**:1119–1122.
38. Qiao X, He B, Chiu A, Knowles DM, Chadburn A, Cerutti A: **Human immunodeficiency virus 1 Nef suppresses CD40-dependent immunoglobulin class switching in bystander B cells.** *Nat Immunol* 2006, **7**:302–310.
39. Swingler S, Brichacek B, Jacque J-M, Ulich C, Zhou J, Stevenson M: **HIV-1 Nef intersects the macrophage CD40L signalling pathway to promote resting-cell infection.** *Nature* 2003, **424**:213–219.
40. He B, Qiao X, Klasse PJ, Chiu A, Chadburn A, Knowles DM, Moore JP, Cerutti A: **HIV-1 envelope triggers polyclonal Ig class switch recombination through a CD40-independent mechanism involving BAFF and C-type lectin receptors.** *The Journal of Immunology* 2006, **176**:3931–3941.

41. Giagulli C, Marsico S, Magiera AK, Bruno R, Caccuri F, Barone I, Fiorentini S, Andò S, Caruso A: **Opposite effects of HIV-1 p17 variants on PTEN activation and cell growth in B cells.** *PLoS ONE* 2011, **6**:e17831.
42. Nunnari G, Smith JA, Daniel R: **HIV-1 Tat and AIDS-associated cancer: targeting the cellular anti-cancer barrier?** *J. Exp. Clin. Cancer Res.* 2008, **27**:3.
43. Luzzi A, Morettini F, Gazaneo S, Mundo L, Onnis A, Mannucci S, Rogena EA, Bellan C, Leoncini L, De Falco G: **HIV-1 Tat induces DNMT over-expression through microRNA dysregulation in HIV-related non Hodgkin lymphomas.** *Infectious Agents and Cancer* 2014, **9**:41.
44. Teow S-Y, Nordin AC, Ali SA, Khoo AS-B: **Exosomes in Human Immunodeficiency Virus Type I Pathogenesis: Threat or Opportunity?** *Adv Virol* 2016, **2016**:9852494–8.
45. Zaccard CR, Rinaldo CR, Mailliard RB: **Linked in: immunologic membrane nanotube networks.** *J Leukoc Biol* 2016, **100**:81–94.
46. Zhu X, Guo Y, Yao S, Yan Q, Xue M, Hao T, Zhou F, Zhu J, Qin D, Lu C: **Synergy between Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6 and HIV-1 Nef protein in promotion of angiogenesis and oncogenesis: role of the AKT signaling pathway.** *Oncogene* 2014, **33**:1986–1996.
47. Yan Q, Ma X, Shen C, Cao X, Feng N, Qin D, Zeng Y, Zhu J, Gao S-J, Lu C: **Inhibition of Kaposi's sarcoma-associated herpesvirus lytic replication by HIV-1 Nef and cellular microRNA hsa-miR-1258.** *J Virol* 2014, **88**:4987–5000.
48. Lenassi M, Cagney G, Liao M, Vaupotic T, Bartholomeeusen K, Cheng Y, Krogan NJ, Plemenitas A, Peterlin BM: **HIV Nef is secreted in exosomes and triggers apoptosis in bystander CD4+ T cells.** *Traffic* 2010, **11**:110–122.
49. Curreli S, Krishnan S, Reitz M, Lunardi-Iskandar Y, Lafferty MK, Garzino-Demo A, Zella D, Gallo RC, Bryant J: **B cell lymphoma in HIV transgenic mice.** *Retrovirology* 2013, **10**:92.
50. Dolcetti R, Gloghini A, Caruso A, Carbone A: **A lymphomagenic role for HIV beyond immune suppression?** *Blood* 2016, **127**:1403–1409.
51. Popovic M, Tenner-Racz K, Pelsler C, Stellbrink H-J, van Lunzen J, Lewis G, Kalyanaraman VS, Gallo RC, Racz P: **Persistence of HIV-1 structural proteins and glycoproteins in lymph nodes of patients under highly active antiretroviral therapy.** *Proc Natl Acad Sci USA* 2005, **102**:14807–14812.
- **52. Dolcetti R, Giagulli C, He W, Selleri M, Caccuri F, Eyzaguirre LM, Mazzuca P, Corbellini S, Campilongo F, Marsico S, et al.: **Role of HIV-1 matrix protein p17 variants in lymphoma pathogenesis. Demonstrates that specific HIV p17 isoforms are associated with HIV lymphoma and that extracellular p17 accumulation in lymph nodes can contribute to the development of lymphoma.** *Proc Natl Acad Sci USA* 2015, **112**:14331–14336.
53. Erlandson KM, Lake JE: **Fat Matters: Understanding the Role of Adipose Tissue in Health in HIV Infection.** *Curr HIV/AIDS Rep* 2016, **13**:20–30.

54. Crum-Cianflone N, Roediger MP, Eberly L, Headd M, Marconi V, Ganesan A, Weintrob A, Barthel RV, Fraser S, Agan BK, et al.: **Increasing rates of obesity among HIV-infected persons during the HIV epidemic.** *PLoS ONE* 2010, **5**:e10106.
55. Sarkozy C, Camus V, Tilly H, Salles G, Jardin F: **Body mass index and other anthropometric parameters in patients with diffuse large B-cell lymphoma: physiopathological significance and predictive value in the immunochemotherapy era.** *Leuk. Lymphoma* 2015, **56**:1959–1968.
- *56. Damouche A, Lazure T, Avettand-Fènoël V, Huot N, Dejuq-Rainsford N, Satie A-P, Mélard A, David L, Gommet C, Ghosn J, et al.: **Adipose Tissue Is a Neglected Viral Reservoir and an Inflammatory Site during Chronic HIV and SIV Infection.** *PLoS Pathog.* 2015, **11**:e1005153. **Identifies adipose tissue as an important reservoir for SIV infection and that the adipose reservoir contributes to a chronic inflammatory state.**
- *57. Couturier J, Suliburk JW, Brown JM, Luke DJ, Agarwal N, Yu X, Nguyen C, Iyer D, Kozinetz CA, Overbeek PA, et al.: **Human adipose tissue as a reservoir for memory CD4+ T cells and HIV.** *AIDS* 2015, **29**:667–674. **Demonstrates that HIV-infected CD4+ T cells are resident in adipose tissue in cART-treated patients and that adipocyte-derived soluble factors can enhance HIV production and T cell survival.**
- **58. Couturier J, Agarwal N, Nehete PN, Baze WB, Barry MA, Sastry KJ, Balasubramanyam A, Lewis DE: **Infectious SIV resides in adipose tissue and induces metabolic defects in chronically infected rhesus macaques.** *Retrovirology* 2016, doi:10.1186/s12977-016-0260-2. **Important study correlating SIV infection of adipose-resident T cells with metabolic defects, including adipocyte defects and systemic dyslipidemia, contributing to a pro-inflammatory metabolic state.**
59. Carr A, Law M, HIV Lipodystrophy Case Definition Study Group: **An objective lipodystrophy severity grading scale derived from the lipodystrophy case definition score.** *J. Acquir. Immune Defic. Syndr.* 2003, **33**:571–576.
60. Nguyen A, Calmy A, Schiffer V, Bernasconi E, Battegay M, Opravil M, Evison J-M, Tarr PE, Schmid P, Perneger T, et al.: **Lipodystrophy and weight changes: data from the Swiss HIV Cohort Study, 2000-2006.** *HIV Med.* 2008, **9**:142–150.
61. Andany N, Raboud JM, Walmsley S, Diong C, Rourke SB, Rueda S, Rachlis A, Wobeser W, Macarthur RD, Binder L, et al.: **Ethnicity and gender differences in lipodystrophy of HIV-positive individuals taking antiretroviral therapy in Ontario, Canada.** *HIV Clin Trials* 2011, **12**:89–103.
62. Langkilde A, Petersen J, Henriksen JH, Jensen FK, Gerstoft J, Eugen-Olsen J, Andersen O: **Leptin, IL-6, and suPAR reflect distinct inflammatory changes associated with adiposity, lipodystrophy and low muscle mass in HIV-infected patients and controls.** *Immun Ageing* 2015, **12**:9.
63. Lin S, YuJun L, XiaoMing X, WenWen R: **Expression and significance of leptin receptor, p-STAT3 and p-AKT in diffuse large B-cell lymphoma.** *Acta Histochem.* 2014, **116**:126–130.

64. Uddin S, Mohammad RM: **Role of leptin and leptin receptors in hematological malignancies.** *Leuk. Lymphoma* 2016, **57**:10–16.
65. Mouzaki A, Panagoulas I, Dervilli Z, Zolota V, Spadidea P, Rodi M, Panitsas FP, Lagadinou E, de Lastic A-L, Georgakopoulos T: **Expression patterns of leptin receptor (OB-R) isoforms and direct in vitro effects of recombinant leptin on OB-R, leptin expression and cytokine secretion by human hematopoietic malignant cells.** *Cytokine* 2009, **48**:203–211.
66. Uddin S, Bu R, Ahmed M, Hussain AR, Ajarim D, Al-Dayel F, Bavi P, Al-kuraya KS: **Leptin receptor expression and its association with PI3K/AKT signaling pathway in diffuse large B-cell lymphoma.** *Leuk. Lymphoma* 2010, **51**:1305–1314.
67. Balasubramanyam A, Mersmann H, Jahoor F, Phillips TM, Sekhar RV, Schubert U, Brar B, Iyer D, Smith EO, Takahashi H, et al.: **Effects of transgenic expression of HIV-1 Vpr on lipid and energy metabolism in mice.** *Am. J. Physiol. Endocrinol. Metab.* 2007, **292**:E40–8.
68. Asztalos BF, Mujawar Z, Morrow MP, Grant A, Pushkarsky T, Wanke C, Shannon R, Geyer M, Kirchhoff F, Sviridov D, et al.: **Circulating Nef induces dyslipidemia in simian immunodeficiency virus-infected macaques by suppressing cholesterol efflux.** *J. Infect. Dis.* 2010, **202**:614–623.
69. Agarwal N, Iyer D, Patel SG, Sekhar RV, Phillips TM, Schubert U, Oplt T, Buras ED, Samson SL, Couturier J, et al.: **HIV-1 Vpr induces adipose dysfunction in vivo through reciprocal effects on PPAR/GR co-regulation.** *Sci Transl Med* 2013, **5**:213ra164–213ra164.
70. Cheney L, Hou JC, Morrison S, Pessin J, Steigbigel RT: **Nef inhibits glucose uptake in adipocytes and contributes to insulin resistance in human immunodeficiency virus type I infection.** *J. Infect. Dis.* 2011, **203**:1824–1831.
71. Díaz-Delfín J, Domingo P, Wabitsch M, Giralt M, Villarroya F: **HIV-1 Tat protein impairs adipogenesis and induces the expression and secretion of proinflammatory cytokines in human SGBS adipocytes.** *Antivir. Ther. (Lond.)* 2012, **17**:529–540.

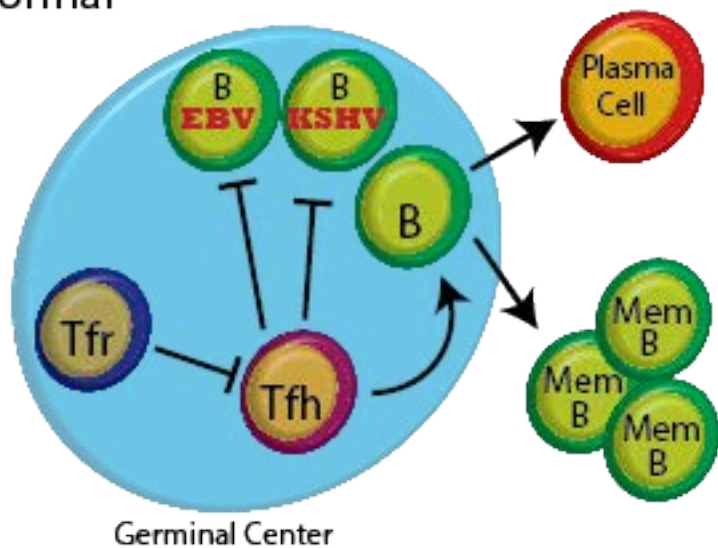
Figure Legend

Figure 1: Model of intra-follicular dysfunction leading to lymphoma in chronic HIV infection.

(A) In normal lymph nodes, Tfr regulate the proliferation and function of Tfh, which, in turn, suppress replication of lymphotropic pathogens KSHV and EBV and regulate the germinal center reaction and production of memory B lymphocytes and plasma cells. (B) HIV infection results in expansion of both Tfr and Tfh subsets, but dysregulates their

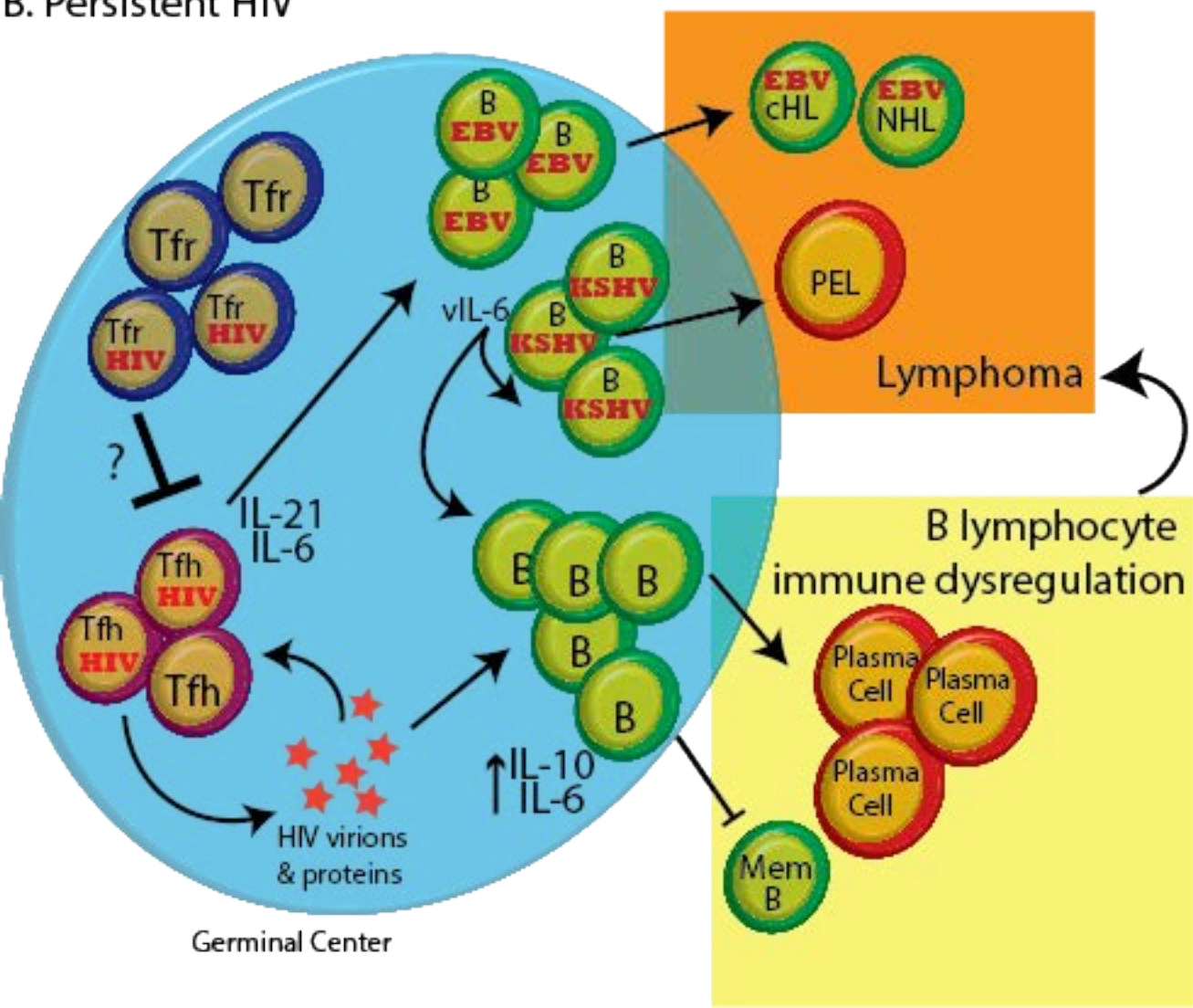
interaction as well as the ability of Tfh to provide appropriate help to B cells, creating a decrease in memory B cell production and dysregulation of plasma cell differentiation. Suppression of Tfh function could allow proliferation of lymphotropic pathogens KSHV and EBV and allow direct lymphomagenesis by viral mechanisms. Additionally, HIV gene products and virions accumulating in lymph nodes contribute directly to both B cell dysfunction and viral lymphomagenesis.

A. Normal



Germinal Center

B. Persistent HIV



Germinal Center