# Title: HODGKIN LYMPHOMA IN PEOPLE LIVING WITH HIV

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## ABSTRACT

Despite widespread use of combined antiretroviral therapy (cART) and increased life expectancy in people living with HIV (PLWH), HIV-related lymphomas (HRL) remain a leading cause of cancer morbidity and mortality in PLWH, even in patients optimally treated with cART. While incidence of aggressive forms of non-Hodgkin lymphoma decreased after cART advent, incidence of Hodgkin lymphoma (HL) has increased among PLWH in recent decades. The co-infection of Epstein Barr virus plays a crucial role in the pathogenesis of HL in the HIV setting. Currently, PLWH with HRL, including HL, are treated similarly to HIV-negative patients and, importantly, the prognosis of HL in PLWH is approaching to that of the general population. In this regard, effective cART during chemotherapy is strongly recommended since it has been shown to improve survival rates in all lymphoma subtypes, including HL. As a consequence, interdisciplinary collaboration between HIV specialists and hemato-oncologists for the management of potential drug-drug interactions and overlapping toxicities between antiretroviral and antineoplastic drugs is crucial for the optimal treatment of PLWH with HL. In this article the authors review and update the epidemiological, clinical and biological aspects of HL presenting in PLWH with special emphasis in the improvement on prognosis and the factors that have contributed to it.

**Keywords:** HIV; Hodgkin lymphoma; antiretroviral therapy, prognosis

## INTRODUCTION

Since the introduction of combination antiretroviral therapy (cART) the incidence of opportunistic infections and AIDS defining cancers, such as Kaposi sarcoma (KS), aggressive non-Hodgkin lymphoma (NHL) and cervical cancer, has decreased in people living with HIV (PLWH)(1,2). However, lymphoma is the second most frequent AIDS-defining cancer in developed countries and is still one of the most frequent neoplastic causes of death among HIV-infected individuals. The most common HIV-related lymphomas are diffuse large B-cell lymphoma (DLBCL), which includes primary CNS lymphoma (PCNSL), and Burkitt lymphoma (BL). Primary effusion lymphoma (PEL), and plasmablastic lymphoma (PL) are less frequent, although they occur with preference in HIV-positive patients. Hodgkin lymphoma (HL) is a non-AIDS defining cancer but PLWH have between 5 and 26-fold higher risk of developing it than the general population. Unlike the dramatic decrease observed in the incidence of NHL among PLWH with the introduction of ART, the risk of HL initially increased but, eventually has remained stable or decreased(2–4).

Classical HL (cHL) is the type that has been linked to PLWH. The most common histologic subtype is mixed cellularity followed by nodular sclerosis and lymphocyte-depleted(5–8). Unlike cHL affecting the general population, around 90% of cases of PLWH-related are associated with Epstein-Barr virus (EBV) infection of the tumoral cells, which are the Hodgkin Reed-Sternberg cells (HRS)(9). The etiopathogenesis of HIV-related cHL is not yet fully understood. However, there are evidences indicating a crucial role for EBV infection of pre-apoptotic B-cells, together with a cooperation with HIV, for triggering the lymphomagenic process(10,11). Interactions between the tumoral cells and the microenvironment will eventually contribute to maintain the proliferation and scape from the immune responses(10,12).

Although presenting with more aggressive characteristics, PLWH with cHL have similar response rates and survival than HIV-negative patients, when they are treated with the same standard therapies(8,13). Early and effective cART during chemotherapy has been shown to increase survival rates. Hence, initiation or maintenance of cART is highly recommended for PLWH patients with any type of lymphoma, including cHL (14–16). As a consequence, it is currently very important to take into account the potential drug-drug interactions between antiretrovirals and drugs administered for the treatment of HL.

In this article the authors review and update the epidemiological, clinical and biological aspects of HL presenting in PLWH with special emphasis in the improvement on prognosis and the factors that have contributed to it.

## EPIDEMIOLOGY

The relative risk of HL in PLWH is 5 to 26-fold higher than in the general population with an estimated incidence of around 50 cases per 100,000 person-years(3,17). The subtype characteristically linked to HIV infection is cHL. Some studies show that PLWH at cHL diagnosis are older than that of the general population, such as one from the French ANRS-CO16 Lymphovir cohort (median of 44 vs 29 years) (18) and other from the UK (median of 41 vs 31 years)(13). With the advent of cART, an increase in the incidence of HL was observed in the first years. However, after the increment observed in the first decade, the incidence of HL eventually seems to remain stable in the last years(3,19,20). In a collaborative work, including 33 observational cohort studies of adult and pediatric HIV-infected patients in 30 European countries, PLWH who develop HL had lower CD4 counts than controls (PLWH without lymphoma) (17). However, at cHL diagnosis patients usually have a moderate decrease of CD4+ lymphocytes (between 150 and 260 cells/µL(21,22). It has been speculated that this fact could be explained because a certain number of CD4-positive lymphocyte counts are needed to facilitate the micro-environment development and the proliferation of HRS cells(23,24). In turn, HRS cells produce many cytokines and chemokines, resulting in an influx of activated CD4 cells, histiocytes, and other cells. On the other hand, very low CD4 counts would lead to an impairment of these mechanisms and, hence, to a worse condition for the development of HL in severely immunosuppressed PLWH(22,25,26). This hypothesis would explain the observation that the increase in the incidence of HL in the cART era has been observed mainly in those HIV-infected individuals with moderate immune suppression. On the other hand, the most immune suppressed individuals would be at lower risk of developing HL, but higher than those with CD4 counts above $0.5x10^9$/L, who have a similar risk than the general population(22). Of note, some studies reported that HIV-infected individuals are at higher risk of developing HL in the first 6 months after initiation of ART(27,28).

## ETIOPATHOGENESIS

In cHL, the malignant HRS are scarce among an extensive and complex microenvironment. They are B-cells because carry immunoglobulin (Ig) heavy and light chain V gene rearrangements (29). Their specific origin appears to be, in the majority of cases, pre-apoptotic germinal center (GC) B cell because destructive somatic mutations in the rearranged immunoglobulin (Ig) genes have been observed, leading to the loss of the capacity to express a B-cell receptor (BCR)(23). The sequence of events during malignant transformation of pre-apoptotic GC B cells toward HRS cells is poorly understood but, escape from programmed cell death, seems to be an early and essential event(30). Nearly all cases of cHL with destructive Ig gene mutations eliminating BCR expression (e.g. nonsense mutations) are EBV-positive, suggesting that EBV-encoded genes have a particular function to prevent apoptosis of HRS-cell precursors that acquire these crippling mutations(31).

Virtually all cases of cHL in PLWH are EBV associated and show type II latency pattern. They express viral proteins such as EBV nuclear antigen-1 (EBNA1), latent membrane protein 1 (LMP1), and LMP2, as well as EBERs and BARTs RNAs (32–36,36). There are some evidences indicating a pathogenic role for EBV in the early stages of lymphomagenesis in EBV-positive cHL cases(10). The protein EBNA1 is mandatory for the replication of the viral genome(23). The expression of LMP1 and LMP2A (one of the two proteins encoded by *LMP2*), seems to play a crucial role in the development of EBV-related cHL(37,38). LMP1 promotes B-cell activation and proliferation by activating NF-κB, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3-K), IRF7, and STAT pathways(39). This function is mainly produced because LMP1 mimics CD40 receptor (34,40,41). Interestingly, HIV virions from CD4+ cells harbor a CD40 ligand (CD40L) that might complement the effects induced by LMP1(42–44). On the other hand, LMP2A prevents apoptosis via mimicking B-cell receptor (BCR) signaling(45,46). In addition, EBV induces the overexpression of PD-L1 in a subset of cHL cases, leading to immune scape response and contributing all together to EBV-infected HRS proliferation and tumor progression(47).

The implication of EBV seems to be higher influencing the microenvironment of cHL as EBV-positive cHL tissues are enriched in genes characteristic of T-cell and antiviral responses. The cellular microenvironment of EBV-positive cHL cells is largely composed of immune cells that are probably attempting to eliminate EBV-positive HRS cells, together with inflammatory cells that contribute to the growth of the neoplastic component(10,12). Cytotoxic T lymphocytes have been isolated from cHL patients and have been shown to specifically kill LMP1 and LMP2 expressing targets *ex vivo* (48,49). Moreover, high numbers of CD4+ CD25+ regulatory T cells (Tregs) have been detected in the peripheral blood and tumor tissues of cHL patients(48–52). The proteins EBNA1 and LMP1 have been demonstrated to play a role in attracting Tregs to the cHL tissue(53,54). Additionally, high numbers of CD8+ and natural killer cells have been identified in tissues of cHL cases (46). Therefore, it seems that, in EBV-positive cHL, activated CD8+ T cells, probably specific for viral epitopes, and Treg cells coexist in the microenvironment(10).

Compared to EBV-negative cases, EBV-related cHL have higher infiltration by macrophages, mainly of type M1, which promote Th1 responses and kill tumor cells(55–58). There are some evidences indicating that this macrophage infiltrating pattern is also predominant in cHL in the HIV setting (59,60). A differential characteristic of the HIV-related cHL microenvironment is the paucity of CD4+ cells in the infiltrate surrounding HRS cells(61,62). This is likely due to the reduced CD4+ lymphocyte count present in PLWH at cHL diagnosis. Moreover, a significant reduction of CD56+ cells (functional NK cells), CD57+ cells (terminally differentiated T lymphocytes and mature NK), CD123+ plasmocytoid dendritic cells, and B cells, have been observed(62). These findings show the differences between the microenvironment of cHL in PLWH and that of the general population and could contribute to the increased incidence of cHL among HIV-infected people(62). On the other hand, the absolute number of CD8+ T lymphocytes is preserved in these cases, although a decrease in infiltrating GrB+ cells (activated cytotoxic cells) and an increase in infiltrating TIA+ T cells (mainly non-activated cytotoxic cells) are observed(59,61). It has been speculated that these differences in the cellular components of the microenvironment could be due to the specific cytokine/chemokine profile of HIV-related cHL(10).

A cooperation between HIV and EBV has been speculated to take part in lymphomagenesis, trough interactions mediated by cellular dysregulation/immunodeficiency and/or chronic antigenic stimulation/inflammation(11). Regarding this, some HIV-encoded proteins and this virus itself, promote B-cell proliferation and activation by chronic antigenic stimulation(63–65). This would lead to an oligoclonal dysregulated B-cell expansion that would be at risk of acquiring genetic alterations finally leading to lymphoma development(10). The hyperactivated B cells, induced either directly or indirectly by HIV stimuli, may express activation-induced cytidine deaminase (AID), a DNA editing enzyme that mediates immunoglobulin class switch recombination, somatic hypermutation and the development of chromosomal translocations(66,67).

In summary, the lymphomagenesis of cHL in PLWH seems to be the result of interactions between pre-apoptotic B-cells and the microenvironment, and the cooperation of both viruses, EBV and HIV; along with the presence of inherent genetic abnormalities. These mechanisms might trigger the lymphomagenesis by activating cell signaling pathways. The interactions between HRS cells and the microenvironment will eventually develop and maintain the malignant cell growth.

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## PATHOLOGICAL AND CLINICAL CHARACTERISTICS

The WHO classification of tumours of hematopoietic and lymphoid tissues considers two types of HL with different pathological characteristics; Nodular lymphocyte predominant HL and classical HL (cHL), which is the type associated to HIV infection(68). From the 4 histological cHL subtypes, the most frequent among PLWH is mixed cellularity followed by nodular sclerosis(5,8,69).

Pathology findings are similar in HIV-positive and HIV-negative patients. In both settings, HRS are characteristically observed on a heterogeneous background of lymphocytes, eosinophils, neutrophils, macrophages, and plasma cells. Neoplastic cells show the usual HRS phenotype (PAX5+, CD30+, CD15+), rarely express CD20 and usually are CD45 negative. The frequency of mixed cellularity subtype increases along with the decrease of CD4 + lymphocytes(22). Coinfection with EBV occurs in 90-100%of cases compared to 30-40% in HIV-negative patients (10,23,68). The HRS cells express EBNA1, LMP1 and are EBER positive. Figure 1 shows a typical case of mixed cellularity in an HIV-positive case.

Characteristic pathological finding in HIV-related cHL is a higher amount of HRS cells, compared with cHL in HIV-negative patients(10). The presence of large confluent areas of necrosis underlying the presence of a pro-inflammatory activity has been also described, with a “sarcomatoid pattern”, attributed to the increased quantity of CD163 spindle shaped macrophages (59). The most typical feature of HIV-related cHL probably is the scarce number of CD4+ T cells present in the microenvironment and an inverted CD4/CD8 T-cell ratio resulting in a predominance of CD8+ T lymphocytes in the background(59,61,62).

Regarding the clinical features, the proportion of males is higher than in HIV-negative subjects and some studies have shown that the age at diagnosis is higher in PLWH (13,20). Among PLWH, cHL often presents with unfavorable features at diagnosis, such as poorer performance status, advanced-stage, extranodal disease, and bone marrow involvement(8,13,18). The presence of B symptoms is also more frequent than in the general population(13) and exclusive extranodal presentation has been reported in some sites such as bone marrow and liver(70,71). In the cART era the median CD4 count at HL diagnosis is between 120 and 385 x $10^9$/L (5,8,13) (Table 1).

## TREATMENT AND PROGNOSIS

Before starting the treatment, a staging procedure, including the same tests as in HIV-negative patients, should be performed. A basal PET-CT scan is mandatory in all cases but, bone marrow biopsy can be avoided in most cases due to the reliability of PET-CT in diagnosing infiltration by cHL in this site.

With the introduction of cART, the prognosis of PLWH and cHL has been steadily improving until patients have reached almost the same outcomes as cHL in the general population when applying the same treatments (5,8,13,72). Some studies, performed in the cART era, have shown that response rates and survival of cHL in PLWA are similar to those in HIV-negative patients, although HIV-patients presented more aggressive characteristics (8,13,18,73,74).

For this reason, the recommendations for the treatment of cHL in PLWH should not differ from those in the general population. Standard regimens such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), BEACOPP (bleomycin, etoposide, doxorubicine, cyclophosphamide, vincristine, procarbazine, prednisone) baseline and Stanford V have been demonstrated to be highly effective in HIV-infected patients(5,8,13,72,75,76). In a retrospective study comparing PLWH and HIV-negative individuals treated with ABVD, the complete response (CR) rates were 74% and 79%, respectively, and five-year overall survival (OS) was 81% and 88% for HIV-positive and HIV-negative patients, respectively (13). Results from the French cohort reported again no differences between HIV-negative and HIV-positive patients(18) In a similar study, patients with advanced cHL treated with ABVD, had similar CR rates, (89% in HIV-positive vs. 91% in HIV-negative) and survival (Figure 2)(8). In all this studies, HIV-positive patients received cART concomitantly with ABVD. Moreover, Yotsumoto and colleagues, compared only EBV positive HL cases, most of them treated with ABVD (with or without radiotherapy) and did not find significant differences in the CR rate, OS and progression-free survival (PFS) between EBV+ HIV-positive and EBV+ HIV negative instances. However, in this study whether HIV-positive patients received cART along with chemotherapy was not reported(73).

As in HIV-negative patients, the treatment can be tailored taking into account the risk factors and stratifying the patients aiming less toxicity and high efficacy. In this sense, Hentrich et al reported a study administering different treatment to patients with early-stage with favorable risk HL (2 cycles of ABVD followed by 20 Gy of involved-field radiotherapy) than to those with early unfavorable (4 cycles of BEACOPP baseline followed by 30 Gy of involved-field radiotherapy)(72). In this study, advanced stage patients received 6-8 cycles of BEACOPP baseline. The results of these approaches showed similar outcomes to those reported in the general population. However some patients with advanced disease died because of neutropenic infections related to treatment toxicity, meaning that this regimen should be given with caution in PLWH(72). On the other hand, due to the lack of prospective studies, there are scarce reliable information on toxicity of ABVD in PLWH. However, based on the available information, this regimen seems to be safe with acceptable toxicity in the HIV-setting (5,13). Table 1 summarizes the results of front-line treatment of cHL in PLWH of the main studies performed in the cART era.

Interim PET-CT after two or three cycles can be used to decide if less chemotherapy can be given according to the to the metabolic response. A study by Lawal et al showed the usefulness of fluorine-18-fluorodeoxyglucose PET (FDG-PET) to stratify PLWH and cHL, without differences in metabolic parameters between HIV-positive and HIV-negative patients(77). A study by Okosun et al demonstrated the utility of an interim FDC-PET to predict outcomes in PLWH with advanced stage cHL(78). Other studies have shown the feasibility of stage-adapted approach treatments in the HIV-setting based on an interim PET(79).

Brentuximab vedotin (BV) is an anti-CD30 antibody drug conjugate potently active in Hodgkin lymphoma approved by the Food and Drug Administration and the European Medicines Agency for frontline treatment of HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD-BV). However, as usual, trials excluded HIV-infected patients and the usefulness of BV in PLWH with cHL is still under investigation. A phase I trial demonstrated the combination AVD-BV was well tolerated with 100% CR, in the absence of strong CYP3A4 inhibitors as part of cART, and a phase II trial is ongoing(80).

Relapses in HIV-infected patients with cHL can be treated with the same strategies as HIV-negative patients including autologous stem cell transplantation. Several studies have reported similar outcomes in HIV-infected and general population treated with salvage therapy followed by autologous stem cell transplantation(81–83). Moreover, 2 patients with cHL have been reported in a prospective clinical trial of allogeneic bone marrow transplantation for patients with HIV and hematological malignancies(84).

The new immunomodulatory treatments such as checkpoint inhibition with anti-PDL1 drugs have been used in some patients and are currently under investigation in a clinical trial combining Nivolumab and Ipilimumab, a monoclonal antibody against CTLA-4 (NCT02408861)(85,86).

**Additional measures and supportive care**

In addition to specific lymphoma treatment, there are other issues to take into account in the management of HIV-related lymphomas. Antimicrobial systematic prophylaxis is a matter of controversy. Some groups are in favor of using fluoroquinolones, but this practice is not generally recommended, because of the concern of generating bacterial resistances to antibiotics and side effects(14,87). However, primary infectious prophylaxis using colony-stimulating factors such as G-CSF given after every cycle of chemotherapy, is highly recommended(14,16,88). Prophylaxis against *Pneumocystis jirovecii* should be given to all PLWH who receive chemotherapy or radiotherapy as these treatments have demonstrated to decrease CD4+ lymphocyte counts(89–91).The most recommended is cotrimoxazole, that could have the additional benefits of preventing from bacterial infections and toxoplasmosis. *Mycobacterium avium* complex should also be prevented in patients with CD4+ lymphocytes lower than 50/µL, using oral azithromycin(88,92).

## MANAGEMENT OF cART IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA

### Initiation / maintenance of cART

Whether combining cART with chemotherapy outweighs potential risk of increased toxicity has remained controversial. The risk of overlapping toxicities and the potential for difficult-to-manage drug-drug interactions have been reasons to justify postponement or interruption of cART during chemotherapy by some authors(92,93). However, effective cART during chemotherapy has been shown to improve survival in PLWH with lymphoma(94–99). Gopal and colleagues reported a 35% increase in mortality 5 years after lymphoma diagnosis for each log10 increase in plasma HIV RNA load within the 6 months after lymphoma diagnosis(97). In addition, interruption of cART has been associated with higher risk of death, AIDS, and serious non-AIDS morbidity(100). Consequently, initiation or maintenance of cART is currently recommended for PLWH with cancer, including cHL (101). One possible exception to this statement would be the case of patients with a very poor prognosis. In such patients it may be reasonable to forego cART since they are unlikely to have either HIV-related symptoms or a survival benefit from the addition of cART.

### Drugs interactions between cART and chemotherapy

Currently approved antiretroviral drugs include nucleos(t)ide and non-nucleoside reverse-transcriptase inhibitors (NRTIs and NNRTIs, respectively), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors (102). Management of PLWH with cHL remains challenging due to potential drug-drug interactions among antineoplastics, co-medications and antiretroviral drugs.

Despite the lack of controlled studies, clinically significant interactions between chemotherapy regimens and cART have been reported. The risk for interactions is highest with antiretroviral regimens that include ritonavir or cobicistat (commonly known as “boosters”). The use of boosters aims to increase concentrations in plasma of other antiretrovirals including PIs or the INSTI elvitegravir to attain therapeutic concentrations over 24 hours. However, ritonavir and cobicistat are potent inhibitors of cytochrome P450 enzymes and drug transporters which are involved in the disposition of numerous drugs, leading to marked increases in drug exposure(103,104). Specifically in PWLH with lymphoma, the use of boosters have been associated with a higher probability of dose-reduction and treatment delay as well as with worse OS(105,106). Specifically, the use of ritonavir was shown to raise the risk of both hematologic and nonhematologic adverse events in PLWH treated with cyclophosphamide, doxorubicin and etoposide(107,108). Similarly, Leveque et al described increased autonomic neurotoxicity in one patient receiving lopinavir/ritonavir and vincristine(109). All these limitations together with current availability of other cART options with similar efficacy and better tolerability mean that unboosted regimens should be considered for PLWH undergoing chemotherapy for lymphoma.

In patients with lymphoma unboosted INSTIs may be particularly recommended due to their favorable interaction profile with antineoplastic drugs. Raltegravir, dolutegravir or bictegravir do not exert inducer or inhibitor effects on P450 enzymes or drug transporters, minimizing their potential for drug interactions (110–112). Conversely, elvitegravir needs to be co-administered with cobicistat. For this reason, the use of elvitegravir-based cART in PLWH receiving chemotherapy shares most of the limitations of boosted PIs, and its use in this setting should be discouraged.

On the contrary to ritonavir or cobicistat, some NNRTIs (i.e nevirapine, efavirenz, etravirine) are moderate to potent inducers of cytochrome P450 enzymes, and could potentially reduce exposure, and thus efficacy, of certain chemotherapy drugs (113). Rilpivirine and doravirine are second-generation NNRTIs that do not induce the P450 system limiting their potential for interactions with chemotherapy(114,115).

Nucleoside analogues reverse transcriptase inhibitors are still considered the backbone of cART (102). Although no pharmacokinetic interactions between NRTIs and chemotherapy are expected, their concomitant use with chemotherapy may be limited by pharmacodynamic interactions with overlapping toxicity. Tenofovir may be associated with renal toxicity (116). Thus, if the patient is receiving tenofovir disoproxil fumarate with other potentially nephrotoxic drugs (i.e., methotrexate, cisplatin, etc). the use of tenofovir alafenamide may be preferred. Similarly, zidovudine may cause anemia, myelosuppression, fatigue and nausea; and patients treated with didanosine or stavudine may develop peripheral neuropathy, which can be worsened by chemotherapy (102).

Beside causing drug interactions, antiretroviral drugs may also be victims of interactions caused by co-medications commonly used in patients with lymphoma. For example, omeprazole and other proton pump inhibitors may reduce oral bioavailability of rilpivirine, and co-administration may result in loss of therapeutic effect of rilpivirine(114). Antiacids or multivitamins containing divalent cations may decrease oral absorption of INTIs if they are taken at the same time, and dose staggering should be recommended(117,118).

**Clinical approach to management of patients on cART and Hodgkin lymphoma**

Since standard dosing algorithms do not exist for managing interactions between cART and chemotherapy, increased monitoring for safety and efficacy is strongly recommended in PLWH undergoing chemotherapy for cHL. In addition, the risk of specific drug-drug interactions between antiretroviral and antineoplastic or supportive drugs should be addressed. In this regard, we recommend consulting specific web pages on this topic, such as www.hiv-druginteractions.org (119) or www.hivclinic.ca/main/drugs_interact.html (120)(Table2).

A stable antiretroviral regimen can be modified before chemotherapy to avoid drug-drug interactions, reduce toxicity, and improve adherence and tolerability. As abovementioned, discontinuation of ritonavir or cobicistat-containing regimens in favour of unboosted INSTIs should be encouraged. However, the discontinuation of a single drug in the antiretroviral regimen thought to interact with chemotherapy must be avoided, as this may decrease the efficacy of cART and promote the development of viral resistance to the other antiretrovirals that are to be continued. Therefore, interdisciplinary collaboration is mandatory for the optimal treatment of the oncologic process and HIV infection(21,121,122). Changes in cART should be made in consultation with an HIV specialist, since knowledge of the patient's complete treatment history, including resistance data is crucial when designing alternative cART options.

## CONCLUSIONS

The widespread use of cART produced initially an increase in the incidence of cHL in PLWH. The etiopathogenesis of this lymphoma in the HIV-setting has some differential characteristics due to HIV and EBV cooperation and the different composition of the microenvironment compared to non-HIV patients. Although more aggressive clinical features are still present in HL affecting PLWH, the prognosis has improved and is currently similar to that of HIV-negative patients. The therapeutic approach for HIV-related cHL should not differ from that for the general population. The standard strategies used in the general population to treat cHL have been shown to be equally effective among PLWH. Patients with HIV-related cHL should be placed or maintained on cART during treatment. However, the concomitant administration of chemotherapy with cART may be challenging due to drug-drug interactions and overlapping toxicity. Thus, interdisciplinary collaboration between hemato-oncologists and HIV specialists is crucial for the optimal treatment of both lymphoma and HIV infection while minimizing the risk of adverse outcomes for the patient.

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**Table 1. Results of front-line treatment of the main studies performed on cHL in PLWH since the introduction of cART**

| Author | Chemotherapy Regimen | N | Median age (range) | Stage | CD4+ count/µL Median (range) | CR (%) | Survival (%) | Overall Survival (%) |
|---|---|---|---|---|---|---|---|---|
| Spina et al(75) | Stanford V | 59 | 38 (28-64) | I-IV | 238 (32-1038) | 81 | 68 (3-yr DFS) | 51 (3-yr) |
| Hartmann et al(76) | BEACOPP | 12 | 33 (22-49) | III-IV | 205 (110-1020) | 100 | 70 (5-yr DFS) | 70 (5-yr) |
| Xicoy et al(5) | ABVD | 51 | 37 (24-61) | II-IV | 129 (5-1209) | 87 | 95 (5-yr EFS) | 76 (5-yr) |
| Montoto et al(13) | ABVD | 93 | 41 (26-73) | I-IV | NA | 74 | 59 (5-yr EFS) | 81 (5-yr) |
| Hentrich et al(72)[1] | BEACOPP or ABVD[2] Stage-adapted | 71/108 | 44 (27-70)[3] | III-IV | 240 (7-967)[3] | 86[1] | 87.5 (2-yr PFS)[1] | 87 (2-yr)[1] |
| Castillo et al(74) | ABVD | 229 | NA | III-IV | NA | 83 | 69 (5-yr PFS) | 78 (5-yr) |
| Besson et al(18) | ABVD (96%) | 68 | 44 (38-48) | I-IV | 387 (151-540) | NA | 89 (2-yr PFS | 94 (2-yr) |

[1] Treatment results refer only to advanced stage cases (III-IV, N=78), [2] ABVD was given in advanced stage if CD4 < 50/µl, [3]results refer to the whole series (N=108); ABVD: adriamycin-bleomycin-vinblastine-dacarbazine BEACOPP: bleomycin-etoposide-doxorubicin (adryamicine)-cyclophosphamide-vincristine (oncovin)-procarbacine-prednisone; CR: complete response; DFS: disease free-survival, EFS: event-free survival, NA: not available.

**Table 2. Main drug-drug interactions (DDI) between drugs for the treatment of Hodgkin lymphoma and antiretroviral agents** (www.hiv-druginteractions.org; www.hivclinic.ca/main/drugs_interact.html)*

| | DRV/r DRV/c | ATV/r ATV/c | LPV/r | NVP | EFV | ETR | RPV | DOR | RAL | EVG/c | DTG | BIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cyclophosphamide (CYC)** | Monitor CYC toxicity | Monitor CYC toxicity | Monitor CYC toxicity | Monitor CYC efficacy / toxicity | Monitor CYC efficacy / toxicity | Monitor CYC efficacy / toxicity | No DDI expected | No DDI expected | No DDI expected | Monitor CYC toxicity | No DDI expected | No DDI expected |
| **Doxorubicin (DOX)** | No DDI expected | Monitor ECG | Monitor ECG | No DDI expected | No DDI expected | No DDI expected | Monitor ECG | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected |
| **Vincristine / Vinblastine (VIN)** | Increased VIN toxicity | Increased VIN toxicity | Increased VIN toxicity | Monitor VIN efficacy | Monitor VIN efficacy | Monitor VIN efficacy | No DDI expected | No DDI expected | No DDI expected | Increased VIN toxicity | No DDI expected | No DDI expected |
| **Prednisone (PRE)** | Monitor PRE toxicity | Monitor PRE toxicity | Monitor PRE toxicity | Monitor PRE efficacy | Monitor PRE efficacy | Monitor PRE efficacy | No DDI expected | No DDI expected | No DDI expected | Monitor PRE toxicity | No DDI expected | No DDI expected |
| **Etoposide (ETO)** | Monitor ETO toxicity | Monitor ETO toxicity | Monitor ETO toxicity | Monitor ETO efficacy | Monitor ETO efficacy | Monitor ETO efficacy | No DDI expected | No DDI expected | No DDI expected | Monitor ETO toxicity | No DDI expected | No DDI expected |
| **Bleomycin (BLE)** | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected |
| **Brentuximab (BRE)** | Monitor BRE | Monitor BRE | Monitor BRE | No DDI expecte | No DDI expecte | No DDI expecte | No DDI expecte | No DDI expecte | No DDI expecte | Monitor BRE | No DDI expecte | No DDI expecte |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | toxicity | toxicity | toxicity | d | d | d | d | d | d | toxicity | d | d |
| **Dacarbazine (DAC)** | Monitor DAC toxicity | Monitor DAC toxicity | Monitor DAC toxicity | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected |
| **Nivolumab (NIV)** | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected |
| **Pembrolizumab (PEM)** | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected |
| **Procarbazine (PRO)** | Monitor PRO efficacy | Monitor PRO efficacy | Monitor PRO efficacy | Monitor PRO efficacy | Monitor PRO efficacy | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected |
| **Rituximab (RIT)** | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected | No DDI expected |

DRV/r: darunavir/ritonavir; DRV/c: darunavir/cobicistat; ATV/r: atazanavir/ritonavir; ATV/c: atazanavir/cobicistat;LPV/r: lopinavir/ritonavir; NVP: nevirapine; EFV: Efavirenz; ETR: etravirine; RPV: rilpivirine; DOR: doravirine; RAL: raltegravir; EVG/c: elvitegravir/cobicistat; DTG: dolutegravir; BIC: bictegravir.

* Co-administration of most of these drugs has not been studied. Potential DDI are based on theoretical data.

** Monitor QT interval in the ECG with lopinavir/ritonavir, atazanavir and rilpivirine.

## LEGENDS FOR FIGURES

**Figure 1.** Classical Hodgkin Lymphoma, Mixed Cellularity. The lymph node architecture is effaced by a mixed population of lymphocytes, plasma cells, eosinophils, histiocytes and Reed-Sternberg (RS) cells (A and B, Hematoxilin & eosin, 100x and 400x). RS cells are weakly positive for PAX5 (C, 200X), and Epstein-Barr encoded RNA (EBERs) can be detected (D, 200X). CD30 and CD15 are strongly positive in RS cells (E and F respectively, 200x).

**Figure 2** Comparison of disease-free survival (DFS) and Overall survival (OS) between HIV-infected and HIV-uninfected patients with cHL treated with ABVD. The curves show that HIV condition has not influence on survival(8).

Footnotes. CR1: first complete response; DFS: disease-free survival; OS: overall survival.

Figure 1

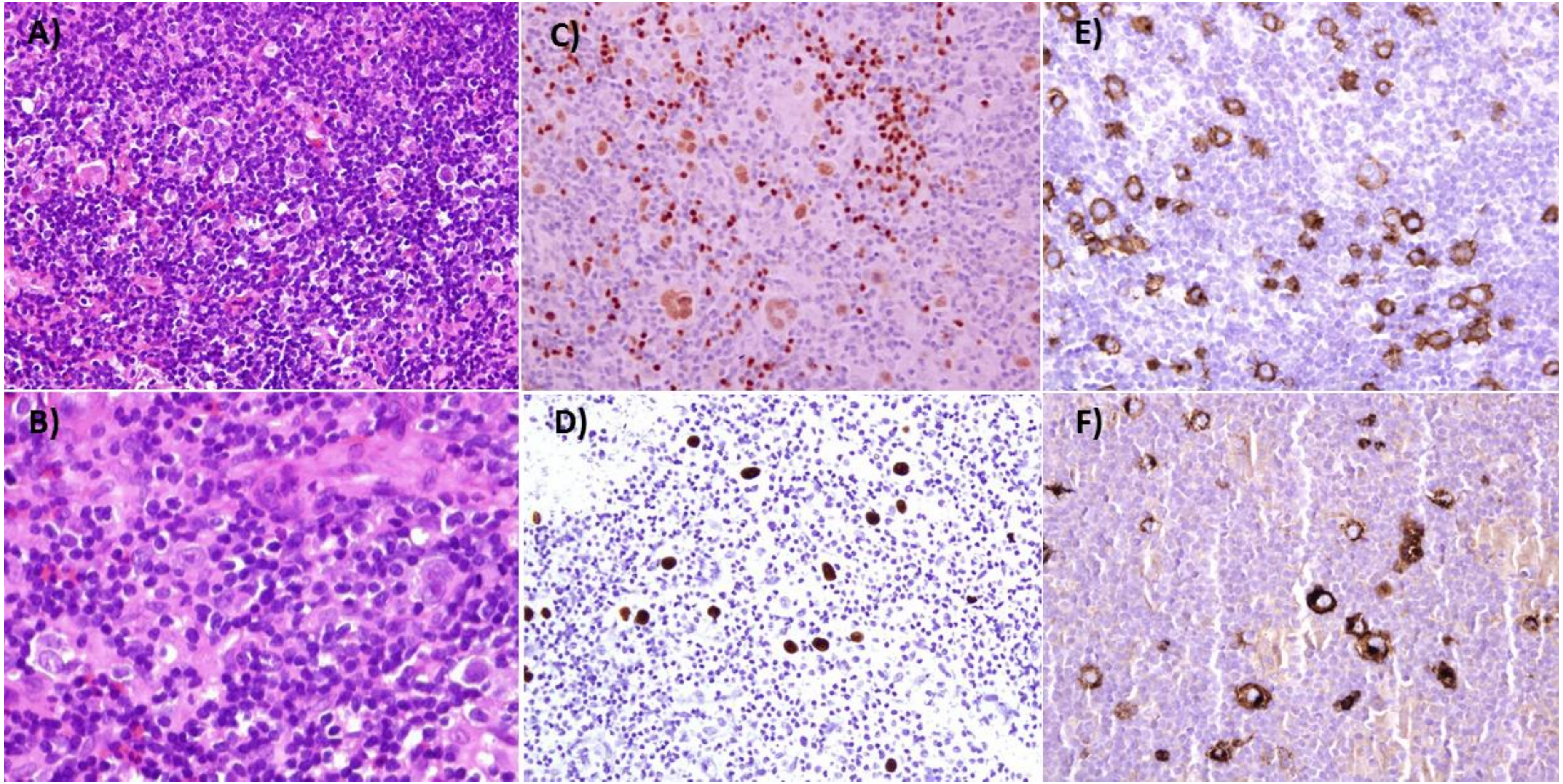


**Figure 2A**

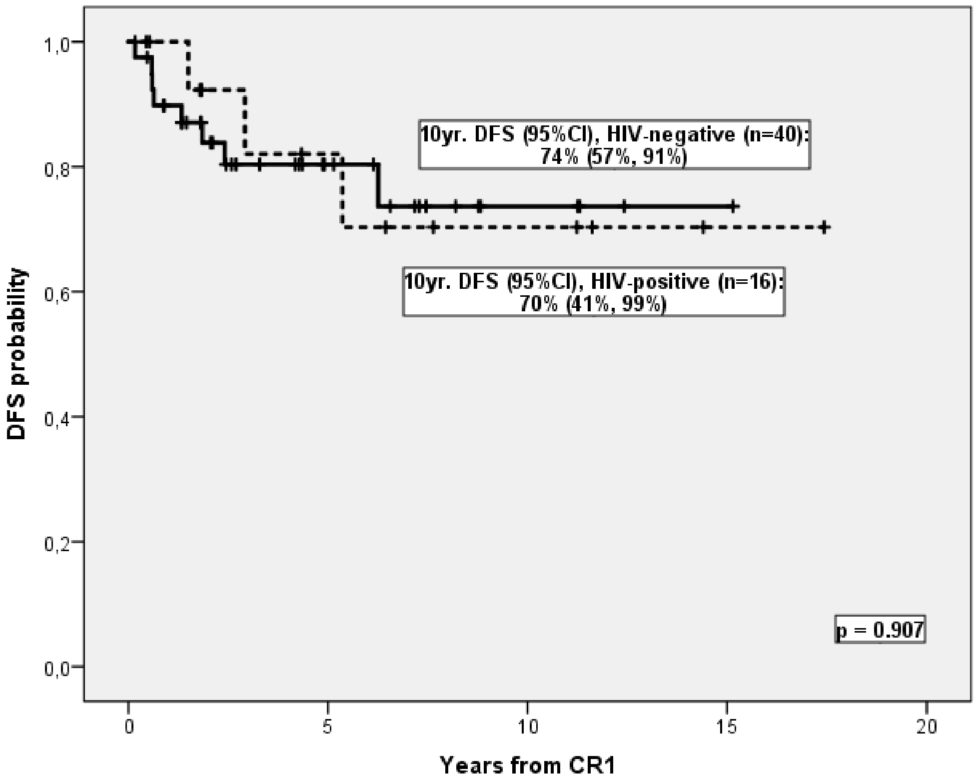
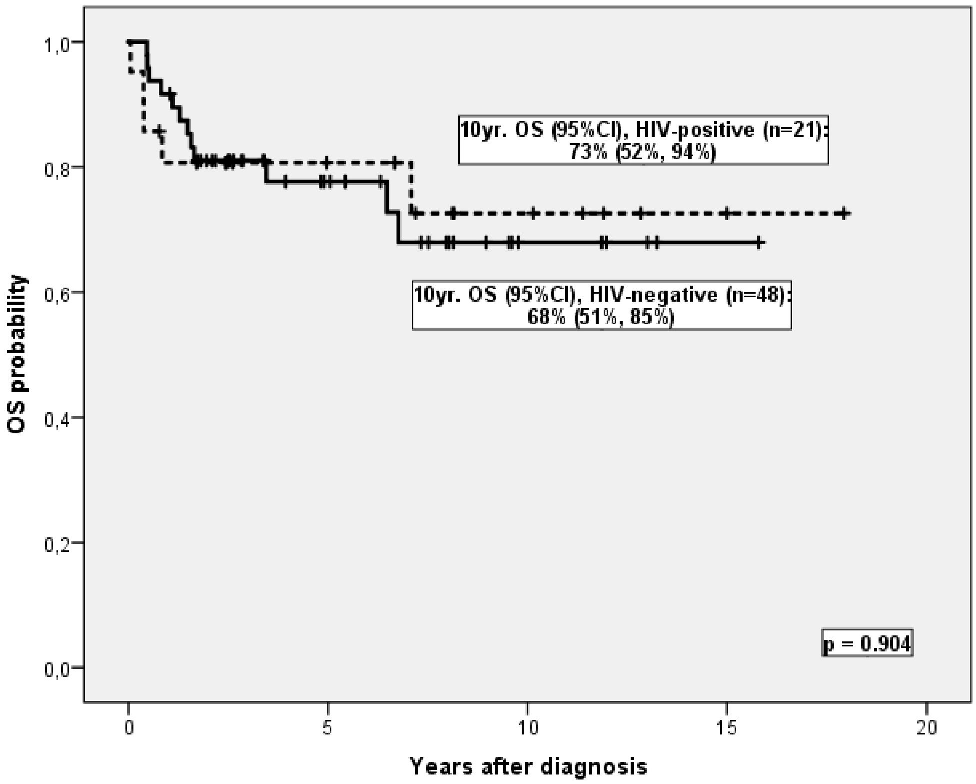



**Figure 2B**




CR1: first complete response; DFS: disease-free survival; OS: overall survival.