

# Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study

E Focà <sup>1,†</sup>, G Cavaglià, <sup>2,†</sup> S Rusconi, <sup>3</sup> A Cascavilla, <sup>4</sup> G Cenderello, <sup>5</sup> A Re, <sup>6</sup> S Casari, <sup>7</sup> L van den Bogaart, <sup>3</sup> PL Zinzani, <sup>4</sup> D Caracciolo, <sup>8</sup> G Di Perri, <sup>2</sup> A Bonito, <sup>2</sup> A Lucchini, <sup>2</sup> G Cassola, <sup>5</sup> P Viale<sup>4</sup> and A Calcagno<sup>2</sup>

<sup>1</sup>Department of Infectious and Tropical Diseases, University of Brescia and Brescia Spedali Civili Hospital, Brescia, Italy,

<sup>2</sup>Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy, <sup>3</sup>Department of Infectious Diseases, Ospedale Luigi Sacco, University of Milan, Milan, Italy, <sup>4</sup>Department of Internal Medicine, Geriatrics and Nephrologic Diseases, Section of Infectious Diseases, S. Orsola-Malpighi Hospital, "Alma Mater Studiorum" University of Bologna, Bologna, Italy, <sup>5</sup>Department of Infectious Diseases, EO Ospedali Galliera, Genova, Italy, <sup>6</sup>Unit of Haematology, Spedali Civili, Brescia, Italy, <sup>7</sup>Unit of Infectious Diseases, Carlo Poma Hospital, Mantova, Italy and <sup>8</sup>Unit of Haematology, Department of Oncology, University of Torino, Torino, Italy

## Objectives

Lymphoproliferative disorders are often observed in HIV-positive patients. Combination antiretroviral treatment (cART) during antineoplastic chemotherapy is beneficial, but little is known about the clinical outcome according to different antiretroviral combinations. The aim of the study was to address this gap in current knowledge.

## Methods

A retrospective study was conducted in five large Italian centres for the period from 1998 to 2015; HIV-positive patients diagnosed with lymphoma were included and demographic, clinical and therapeutic variables were recorded and associated with clinical outcomes. Bivariate and multivariate analyses were performed, including Cox proportional hazard models for survival.

## Results

A total of 399 patients were included in the study. The most common types of lymphoma were diffuse large B-cell lymphoma (DLCLB;  $n = 164$ ), Hodgkin lymphoma (HL;  $n = 99$ ) and Burkitt lymphoma (BL;  $n = 57$ ), followed by plasmablastic lymphoma (PBL;  $n = 38$ ), T-cell lymphoma (TCL;  $n = 17$ ), indolent lymphoma ( $n = 10$ ) and other less common types ( $n = 14$ ). cART was given to 327 (out of 387 evaluable) patients: in 216 subjects it was protease inhibitor (PI)-based, in 73 it was nonnucleoside reverse transcriptase inhibitor (NNRTI)-based and in 18 it was integrase strand transfer inhibitor (INSTI)-based (the remaining 20 individuals received other regimens). The 5-year overall survival was 57.5% (52.8% for DLCLB, 67.8% for HL, 42.3% for BL, 60.6% for PBL and 64.7% for TCL). PI-based ART compared with other compounds was associated with worse survival in non-Hodgkin lymphoma (NHL) and HL patients combined ( $P \leq 0.001$ ) and in NHL patients alone ( $P < 0.001$ ); grade 3–4 haematological toxicities were more commonly observed in PI-treated individuals. Lymphoma diagnosis in recent years, better immunovirological status, lower lymphoma stage and better prognostic indexes were associated with better survival.

## Conclusions

PI-based cART while on chemotherapy was associated with worse overall survival and more frequent haematological complications in HIV-positive patients with lymphoma.

**Keywords:** drug-to-drug interactions, HIV, lymphoma, protease inhibitors, toxicity

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Correspondence: Emanuele Focà, MD PhD, Clinic of Infectious and Tropical Diseases, Department of Clinical and Experimental Sciences, School of Medicine, University of Brescia, Piazzale Spedali Civili 1, Brescia 25136, Italy. Tel: +390303995677; fax: +390303996084; e-mail: emanuele.foca@unibs.it

<sup>†</sup>These two authors contributed equally to the study.

## Introduction

HIV-related lymphomas (HRLs) include a spectrum of different pathological entities, each representing a major complication in the natural history of HIV infection. Their clinical outcome is associated with variables related both to the severity of the neoplastic disease and to the patients' immunovirological status [1,2]. Since the introduction of combination antiretroviral therapy (cART), a remarkable change in HRL incidence and prognosis has been observed. On the one hand, epidemiological data indicate a significant decrease in the absolute incidence of the most aggressive non-Hodgkin lymphoma (NHL) histotypes, and a trend for an increase in the incidence of histotypes with better prognosis such as Hodgkin lymphoma (HL) [3]. On the other hand, a positive direct effect of cART has been suggested, with stronger evidence for an improvement of patients' immunovirological status at lymphoma diagnosis, and more controversial data on cART modulation of chemotherapy-induced immune suppression [4,5]. Combining cART with chemotherapy has been shown to reduce the incidence of chemotherapy- and AIDS-related infectious complications in HRL patients [6]. Moreover, the rate of complete response (CR) to first-line chemotherapy has been shown to be increased by cART in several studies [6–8]; this resulted in an improvement in overall survival (OS) [9,10].

However, there exists a significant potential for pharmacokinetic (PK) interactions between chemotherapy and antitroviral agents, which stems from their shared metabolic pathways involving hepatic cytochromes. Overall, nonnucleoside reverse transcriptase inhibitors (NNRTIs) as a group induce cytochromes essential for metabolism of chemotherapy agents, while protease inhibitors (PIs) tend to inhibit them. Thus, some argue that NNRTIs share the potential to reduce the concentrations, efficacy and adverse effects of chemotherapy agents, while PIs would exert the opposite effect. Nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors (INSTIs) seem to have very few significant drug-to-drug interactions (DDIs). *In vivo* PK studies demonstrated a significant effect of PIs on the area under the curve (AUC) for cyclophosphamide in the Cyclophosphamide, Hydroxydaunorubicin (also called doxorubicin or adramycin), Oncovin (vincristine), Prednisone or Orednisolone (CHOP) regimen [11], and for vinblastine in the Adriamycin (hydroxydaunorubicin/doxorubicin), Bleomycin, Vinblastine, Dacarbazine (ABVD) regimen [12]. For doxorubicin, there is no apparent effect on plasma concentrations, with some authors suggesting an effect on intracellular concentrations [11,13]. In parallel with a beneficial influence of cART on survival and chemotherapy-related infectious complications, some

clinical studies on HRLs have shown an increase in other chemotherapy-related complications, including cytopaenias and neurotoxicity, in patients receiving cART [14,15]. Only a few groups have compared outcomes for patients with HRLs on different cART regimens during chemotherapy [16]. While there is evidence for some influence of the cART subtype on various clinical outcomes, the magnitude of the effect has been found to vary in different studies. A prospective study in NHL patients on the cyclophosphamide, doxorubicin, etoposide (CDE) infusional chemotherapy regimen reported a significant association between PI-based cART and a higher incidence of grade 3–4 infections, grade 4 neutropaenia and lower chemotherapy dose-density [17]. A significantly higher incidence of severe cytopaenias was observed in patients on PI-based cART receiving ABVD chemotherapy for HL [18]. A Korea-based study showed no evidence of an association between PI use and the incidence of febrile neutropaenia in HRL patients [19]. A higher CR rate in HRL patients on PI-based cART was suggested in a retrospective series of 34 patients, but there was an unequal distribution of lymphoma-related prognostic variables among the study groups [20].

The potential for PK interactions seems limited for cART regimens based on the unboosted integrase inhibitor (INI) raltegravir, and observational data show their feasibility and efficacy for HRL patients on chemotherapy [21].

The aim of the study was to analyse the choice of antiretroviral regimens as a prognostic factor and predictor of chemotherapy-associated toxicities in HIV-positive patients diagnosed with lymphomas.

## Methods

We retrospectively identified all consecutive patients diagnosed with HIV-related lymphoma at five Italian institutions between 1998 and 2015. Patients were included if a western blot-confirmed diagnosis of HIV infection and a biopsy-confirmed lymphoma diagnosis were both ascertained. The protocol was approved by each institution's review board and all efforts were made to obtain patients' written consent.

Clinical records were retrospectively reviewed for the following clinical characteristics: age, gender, ethnicity, HIV risk group, hepatitis C virus (HCV) and hepatitis B virus (HBV) infection status, comorbidity burden, duration of HIV infection prior to lymphoma diagnosis and AIDS-defining events (remote or concurrent with lymphoma diagnosis). We divided the study time into three different periods: 1998–2003, 2004–2008 and 2009–2015.

Viro-immunological parameters were CD4 T-cell count and HIV RNA level at different time-points for the CD4 count, the historic CD4 count nadir 'baseline' at lymphoma

diagnosis, the CD4 count 3 months into chemotherapy and that at chemotherapy completion were used.

Patients who received cART were categorized according to whether they were cART experienced or naïve prior to lymphoma diagnosis and according to their baseline cART regimen at the start of chemotherapy.

The characteristics of the lymphoma were recorded as lymphoma histotype, lymphoma staging according to the Ann Arbor system, the number of extranodal sites, the prognostic score (International prognostic index (IPI) and International prognostic score (IPS), respectively, for NHL and HL) and the chemotherapy regimen.

Adverse events were expressed as the presence of significant reductions in dose-density as a result of chemotherapy toxicity, infectious complications, occurrence of haematological toxicity grade 3 or 4 according to the Common Terminology Criteria for Adverse Events (CTCAE) classification, the occurrence of neuropathy, the occurrence of relapse, overall survival, and cause of death.

Prognostic scores were categorized as follows: low (IPI 0–1; IPS 0–1), intermediate (IPI 2–3; IPS 2–4) and high risk (IPI 4–5; IPS 5–7). These categories were analysed according to descriptive statistics.

Comorbidity burden was expressed as an adjusted Charlson comorbidity index, not including AIDS in the calculated score. A significant dose-density reduction was defined as either a delay in chemotherapy completion of more than a third of the scheduled duration, or a > 30% dose reduction for at least one chemotherapy agent, in both cases in response to chemotherapy-related toxicity. Infectious complications were categorized as typical chemotherapy-associated infections (e.g. febrile neutropenia, sepsis, pneumonia or urinary tract infection) or HIV-specific opportunistic infections (e.g. *Candida* oesophagitis, *Pneumocystis jirovecii* pneumonia or tuberculosis). Neuropathy was defined either by Electromyography (EMG) or by obvious clinical features as evident in clinical records.

For univariate analysis,  $\chi^2$ , Kruskall–Wallis tests and Kaplan–Meier models were used. Factors with  $P < 0.10$  in univariate analysis were included in a multivariate model for independence of association. Stepwise selection models were applied to binary logistic regression analysis (dichotomic variables of interest) and to Cox proportional hazard models (survival). Binary logistic regression for identifying variables associated with chemotherapy-related complications was adjusted for baseline CD4 count and cART use (none vs. PI-based vs. other antiretrovirals) and for variables with  $P < 0.10$  in univariate analysis. All statistical calculations were performed with the SPSS program version 23.0 (IBM SPSS Statistics. Armonk, NY, United States).

## Results

### Baseline characteristics

Three hundred and ninety-nine patients were included in the study. They were mostly male (323; 81.1%) and their median age was 43.6 years [interquartile range (IQR) 38.2–50.5 years]. The median baseline CD4 T-cell count and CD4/CD8 ratio were 218 (IQR 102–348) cells/ $\mu$ L and 0.30 (0.15–0.51), respectively. One hundred and twenty subjects were cART-naïve at lymphoma diagnosis [with a median HIV RNA of 4.91 log<sub>10</sub> HIV-1 RNA copies/mL (IQR 4.38–5.48) at lymphoma diagnosis], while 264 were on cART, with 114 (43%) showing plasma HIV RNA < 50 copies/mL. AIDS-related comorbidities were observed in 125 patients (32.6%); 267 individuals (66.9%) had a high general comorbidity burden (Charlson index > 1).

Patients were diagnosed with diffuse large B-cell lymphoma (DLCLB; 164 patients), HL (99 patients), Burkitt lymphoma (BL; 57 patients), plasmablastic lymphoma (PBL; 38 patients), indolent lymphoma (10 patients), T-cell lymphoma (17 patients) and other less common types (four patients). Among the three most prevalent lymphoma histotypes (DLBCL, HL and BL), there were no statistically significant differences in terms of gender, ethnicity, HIV risk group and year of lymphoma diagnosis (Table 1). At the time of lymphoma diagnosis, patients with HL had a higher CD4 percentage (22% vs. 13.4% for DLCLB and 14.8% for BL;  $P < 0.001$ ) and lower HIV RNA levels (44.4% suppressed vs. 30% for DLCLB and 23% for BL;  $P < 0.001$ ) compared with other histologies. Overall, most patients had advanced stage lymphoma (stage 3–4, 283; 70.9%) and intermediate/high prognostic score results (IPI/IPS > 2, 249; 79%). HL patients had a higher incidence of bone marrow involvement (36.0% vs. 20.4% for DLCLB and 27.5% for BL;  $P = 0.034$ ) and a lower risk of extranodal involvement other than bone marrow (21.7% vs. 49.7% for DLCLB and 61.1% for BL;  $P < 0.001$ ).

### Antiretroviral and antineoplastic treatments

Among 387 evaluable patients, 327 (84.5%) received ART after lymphoma diagnosis: PI-based in 216 (55.8%), NNRTI-based in 73 (18.8%), INSTI-based in 18 (4.6%), NRTI-only-based in 12 patients (2.1%) and other combinations in eight individuals (2.1%).

Details of chemotherapy regimens were available in 367 patients; 11 subjects (3.1%) did not start any antineoplastic agent, while 356 patients (89.2%) were treated with chemotherapy or other treatment for lymphoma. Among patients with DLCLB, 109 of 152 evaluable patients received CHOP or CHOP-like regimens (71.7%), 12 CDE (7.9%), 11 M-BACOD (methotrexate with leucovorin,

**Table 1** Patients' characteristics at baseline according to the five main lymphoma histogroups

Variable	DLCLB	HL	BL	PBL	TCL
<i>n</i>	164	99	57	38	17
Age (years)	43 (38–49)	45 (40–53)	42 (35–50)	43 (38–52)	44 (37–55)
Gender (male)	127 (77)	78 (78.8)	50 (87.7)	35 (92.1)	13 (76.5)
Geographical origin					
Europe	141 (92.2)	91 (96.8)	55 (98.2)	35 (92.1)	15 (93.8)
Africa	8 (5.2)	0 (0)	1 (1.8)	2 (5.3)	0 (0)
Asia	2 (1.4)	1 (1.1)	0 (0)	1 (2.6)	1 (6.3)
Other	2 (1.3)	2 (2.1)	0 (0)	0 (0)	0 (0)
Risk factor for HIV acquisition					
IDU	56 (41.8)	32 (39.0)	11 (19.6)	7 (21.9)	7 (46.7)
MSM	23 (15.0)	19 (23.2)	13 (23.2)	13 (40.6)	4 (26.7)
Heterosexual	55 (35.9)	26 (31.7)	23 (41.1)	12 (27.5)	4 (26.7)
Calendar year					
1998–2003	51 (31.3)	28 (28.3)	11 (19.3)	6 (15.8)	10 (58.8)
2004–2008	57 (35.0)	28 (28.3)	26 (45.6)	9 (23.7)	5 (29.4)
2009–2015	55 (33.7)	43 (43.4)	20 (35.1)	23 (60.5)	2 (11.8)
CD4 T lymphocytes (cells/ $\mu$ L)	202 (91–363)	250 (135–348)	208 (115–341)	234 (87–440)	127 (47–306)
Baseline CD4/CD8 ratio	0.26 (0.13–0.40)	0.42 (0.26–0.70)	0.30 (0.12–0.44)	0.30 (0.10–0.50)	0.21 (0.05–0.37)
HIV RNA ( $\log_{10}$ copies/mL)	4.16 (1.69–5.18)	1.69 (< 1.69–4.08)	4.12 (1.69–5.15)	2.01 (1.69–4.76)	3.66 (2.35–4.91)
Plasma HIV RNA < 50 copies/mL	39 (27.5)	46 (53.5)	13 (25.5)	15 (45.5)	2 (12.5)
Time between HIV and lymphoma diagnoses (years)	0.7 (0.1–15.8)	6.9 (2.5–18)	2 (1–9.4)	1.1 (0–4.5)	10.6 (0.6–4.1)
Carlson comorbidity index > 1	114 (69.5)	61 (61.6)	36 (63.2)	25 (65.8)	11 (64.7)
Advanced lymphoma stage (III/IV)	118 (77.1)	64 (74.4)	48 (84.2)	32 (94.1)	9 (64.3)
Bone marrow involvement	29 (20.4)	32 (36)	4 (27.5)	9 (24.3)	3 (21.4)
Extranodal involvement ( $\geq 1$ site apart from bone marrow)	77 (49.7)	18 (21.7)	33 (61.1)	20 (54.1)	7 (46.7)
Prognostic score					
Low risk	32 (29.1)	13 (24.1)	11 (20)	5 (14.7)	2 (18.2)
Intermediate risk	72 (43.9)	26 (48.1)	25 (45.5)	18 (52.9)	7 (63.3)
High risk	41 (28.3)	15 (27.8)	19 (34.5)	11 (32.4)	2 (18.2)

Values are *n* (%) or median (interquartile range).

Prognostic scores: low (IPI 0–1; IPS 0–1), intermediate (IPI 2–3; IPS 2–4) and high risk (IPI 4–5; IPS 5–7).

BL, Burkitt lymphoma; DLCLB, diffuse large B-cell lymphoma; PBL, plasmablastic lymphoma; TCL, T-cell lymphoma; HL, Hodgkin lymphoma; IDU, injecting drug user; MSM, men who have sex with men.

bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) (7.2%), eight ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide cytarabine, bleomycin, vincristine, methotrexate and prednisone) (5.2%), and 10 other chemotherapy regimens. Twenty-four (out of 28 evaluable patients) with PBL received CHOP or CHOP-like regimens (85.7%). Among patients with HL, 44 of 60 evaluable patients received ABVD (73.3%). Thirty of 54 evaluable patients (55.5%) with BL received intensive regimens (containing high-dose methotrexate), and 24 (44.4%) received standard dose chemotherapy (mainly CHOP). Patients with T-cell (T) NHL and low-grade NHL received mainly CHOP. Most DLCLB and BL patients (62% and 70%, respectively) received rituximab treatment and its use increased in more recent years (59% in 2009–2015 vs. 60% in 2004–2008 vs. 33.3% in 1998–2003;  $P < 0.001$ ).

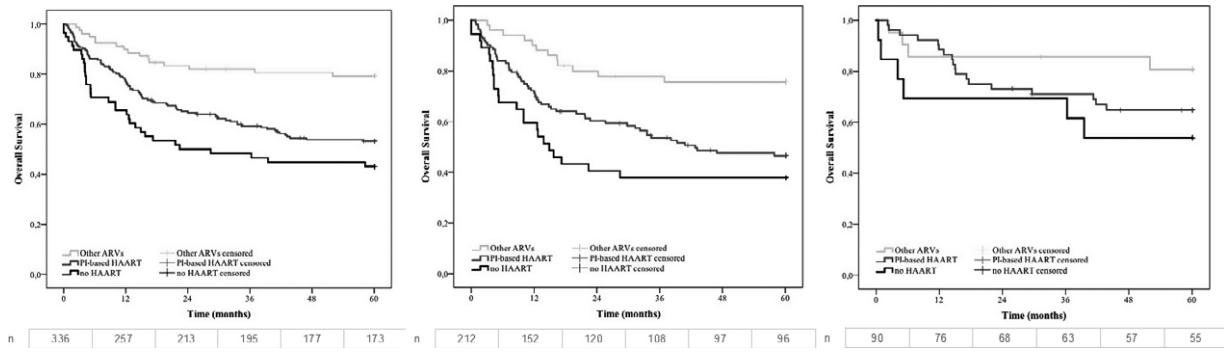
### Survival

Five-year OS was 57.5%; median follow-up was 95 months (average 153 months; IQR 14–275 months). It varied according to histotype as follows: 52.8% (DLCLB),

67.8% (HL), 42.3% (BL), 60.6% (PBL) and 64.7% (T-cell lymphoma; Fig. 1).

For outcome analysis, patients were grouped into three categories: all subjects, patients with NHL (DLCLB, PBL and BL, including rituximab use as a covariate) and those with HL. Results of univariate (log-rank test) and multivariate analysis (Cox proportional hazard model) are shown in Table 2. Survival according to cART choice is depicted in Figure 1. PI coadministration was significantly associated with a higher mortality compared with other antiretrovirals (NNRTI, INSTI and NRTI-only regimens) in all patients (45.6% vs. 20.2%, respectively;  $P \leq 0.001$ ) and in those with NHL (51.8% vs. 23.5%, respectively;  $P < 0.001$ ) but not in those with HL (34.6% vs. 19%, respectively;  $P = 0.211$ ).

In all patients who received a diagnosis in recent years, higher baseline CD4 count and the use of cART avoiding PIs were independently associated with better survival (Table 2). In patients with NHL, younger age, higher baseline CD4 count and the use of cART avoiding PIs were independently associated with better survival. In patients with HL (as a consequence of the smaller sample size),



**Fig. 1** Survival according to highly active antiretroviral therapy (HAART) use in all patients (left), patients with non-Hodgkin lymphoma (middle) and patients with Hodgkin lymphoma (right). Survival of patients with no HAART started (black lines), those on protease inhibitor (PI)-based HAART (grey lines) and those on HAART based on other antiretrovirals (ARVs) (light grey lines) is depicted using Kaplan–Meier curves and compared using log-rank test ( $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.211$  for left, middle and right models respectively).

correlated variables were selected according to the strongest association in univariate analysis. In patients with HL, a diagnosis in recent years and bone marrow noninvolvement were associated with better survival.

#### Dose reductions and toxicity

The prevalence and predictors of chemotherapy-related complications are shown in Table 3. A PI-containing cART was associated with a higher rate (as compared with other antiretrovirals) of grade 3/4 haematological toxicity in all histotypes. In those receiving antiretrovirals ( $n = 323$ ), the prevalence of chemotherapy-associated complications, stratified according to main lymphoma histotypes, is depicted in Figure 2.

#### Discussion

In this large retrospective analysis, we have described the determinants of survival in HIV-positive patients presenting with HL and NHL: a diagnosis performed in recent years, better immunovirological status, lower lymphoma stage, better prognostic indexes and the choice of a non-interacting cART were associated with better survival.

Although heterogeneous, this cohort included several patients with various HIV-associated lymphomas presenting features usually associated with severe immune depression such as extranodal and bone marrow involvement, advanced stage and low prognostic indexes [22]. Approximately 70% of all patients presented comorbidities further complicating the management of the haematological malignancies. HLLs were observed in patients who had higher CD4 cell counts and who were more often on ART, as generally reported [23].

Survival was similar to that previously reported in the literature, with approximately 50% long-term OS in

patients with NHL and 65–70% in patients with HL. Antineoplastic treatments varied by centre and year of diagnosis: the management of HIV-positive subjects improved over time, as demonstrated by the higher survival and the higher use of rituximab in NHL and BL patients in recent years. Conversely, a relatively low number of patients with BL received an infusional intensive antineoplastic regimen (40%): nevertheless, the 5-year survival was comparable to that of other cohorts, including HIV-positive and HIV-negative subjects [24,25].

The selection of cART had an impact on the survival of the included patients. While those who did not start any treatment were possibly those with worse baseline status for whom treatment was considered inappropriate, PI-based regimens were often used in late-presenting patients. The rationale supporting the use of PIs was the need for high genetic barrier drugs and good immunological recovery in patients presenting with very low CD4 counts. PI-associated DDIs and toxicities started to be reported in 2005 and led to the further suggestion to avoid antiretrovirals that may interact with vinca alkaloids [26–29]. Higher vincristine and vinblastine concentrations have been associated with haematological and neurological toxicities, potentially leading to chemotherapy dose reductions or delays and therefore potentially impairing antineoplastic efficacy. We did not observe a significant effect on these outcomes but we did observe an effect on the incidence of haematological toxicities; in patients with HL, although the effect was nonsignificant, chemotherapy dose reductions and infections were more common in patients on PIs. Additionally, specific factors have been associated with complications during antineoplastic treatment, and they include bone marrow involvement, low CD4 count at baseline and rituximab use. HCV infection was associated, independently of lymphoma histotype, with peripheral neuropathy. Chronic HCV

**Table 2** Predictors of 5-year survival in univariate analysis (log-rank test) and multivariate (Cox proportional hazard model) tests

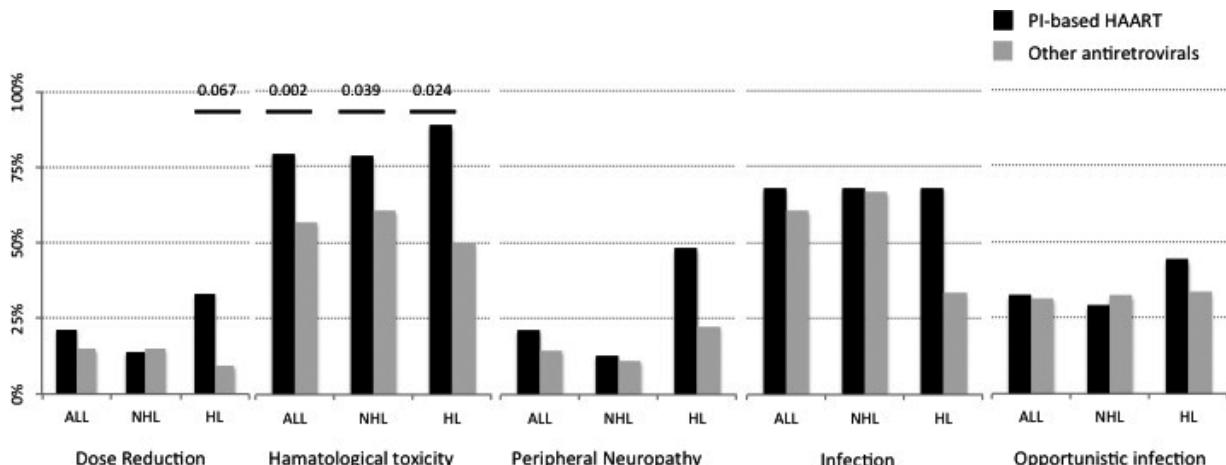
	All			NHLs (DLCBL, PBL and BL)			HL			
	Univariate			Multivariate			Univariate			
	P-value	P-value	aOR	95% CI	P-value	aOR	95% CI	P-value	aOR	95% CI
Calendar year (1998–2003 vs. 2004–2008 vs. 2009–2015)	0.073	0.048	1.292	1.002–1.666	0.140	0.218	—	0.051	0.012	2.008
Male gender	0.444	—	—	—	0.890	—	—	0.051	0.358	—
Age (per 10-year increase)	0.870	—	—	—	0.056	0.002	1.474	1.150–1.889	0.676	—
HCV positivity	0.367	—	—	—	0.260	—	—	0.241	—	—
On HAART at baseline	0.159	—	—	—	0.761	—	—	0.336	—	—
Baseline CD4 (per 100 cells/ $\mu$ L increase)	0.001	0.008	0.812	0.696–0.946	0.010	0.021	0.803	0.667–0.968	0.002	0.197
Baseline HIV RNA < 50 copies/mL	0.025	0.559	—	—	0.724	—	—	—	—	—
HAART regimen (no HAART vs. PI-based vs. other regimens)	< 0.001	1.869	1.320–2.648	< 0.001	0.017	1.507	1.075–2.113	0.021	—*	—*
Baseline AIDS	0.067	0.605	—	—	0.304	—	—	0.007	0.133	—
Carlson index > 1	0.369	—	—	—	0.578	—	—	0.007	0.251	—
Advanced lymphoma stage	0.008	0.140	—	—	0.173	—	—	0.389	—	—
Prognostic scores (high vs. intermediate vs. low risk)	0.213	—	—	—	0.379	—	—	0.035	—*	—*
Bone marrow involvement	< 0.001	0.178	—	—	0.009	0.193	—	0.450	—	—
Rituximab use	NA	NA	NA	NA	0.178	0.827	—	0.005	0.029	2.480
Grade 3/4 haematological toxicity	0.603	—	—	—	0.115	—	—	NA	NA	1.095–5.614
Infections	0.430	—	—	—	0.726	—	—	0.112	—	—
Chemotherapy dose reduction	0.249	—	—	—	0.622	—	—	0.749	—	—
							0.774	—	—	—

BL, Burkitt lymphoma; NHL, non-Hodgkin lymphoma; DLCBL, diffuse large B-cell lymphoma; PBL, plasmablastic lymphoma; HL, Hodgkin lymphoma; aOR, adjusted odds ratio; CI, confidence interval; NA, not applicable because rituximab is not used in patients with HL; —\*, excluded in the final model.

**Table 3** Prevalence and predictors of chemotherapy-associated complications

		All	NHL	HL
Chemotherapy dose reduction	n (%)	55 (17.5)	28 (13.9)	18 (22)
	Predictors in multivariate analysis	None	Female gender Bone marrow involvement Rituximab use	None
Grade 3/4 haematological toxicity	n (%)	149 (68.7)	102 (67.1)	37 (77.1)
	Predictors in multivariate analysis	Baseline AIDS Carlson index > 1 PI-containing cART	Bone marrow involvement Carlson index > 1 PI-containing cART	PI-containing cART
Peripheral neuropathy	n (%)	39 (18.5)	21 (13.8)	15 (33.3)
	Predictors in multivariate analysis	HCV infection	HCV infection	HCV infection
Infection	n (%)	134 (62.3)	100 (64.5)	23 (53.5)
	Predictors in multivariate analysis	Baseline CD4	Baseline CD4	None
Opportunistic infection	n (%)	70 (32.7)	49 (31.8)	15 (34.9)
	Predictors in multivariate analysis	None	High risk (IPI) Rituximab use	None

cART, combination antiretroviral therapy; HCV, hepatitis C virus; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; PI, protease inhibitor.



**Fig. 2** Prevalence of chemotherapy-associated complications according to main lymphoma histotypes and antiretrovirals [protease inhibitors (PIs) vs. non-protease inhibitors] in highly active antiretroviral therapy (HAART) recipients. Significant univariate associations ( $\chi^2$  or Fisher's exact test) are shown above the bars. NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma.

infection may cause peripheral neuropathy but it has not been identified as a risk factor during chemotherapy: higher antineoplastic drug concentrations or pre-existing subclinical neuropathy can explain this finding and warrant caution in HIV/HCV-infected patients presenting with lymphomas.

In the multivariate analysis for survival, different prognostic factors emerged. In NHLs, older age, lower baseline CD4 count and PI use were associated with the risk of death. Prognostic indexes were not retained in the final model, although they were previously validated in other cohorts; the bias of PI administration to patients with a worse clinical status or with late presentation of HIV infection may have affected this finding. In HLs, only earlier year of diagnosis and bone marrow involvement were found to predict

mortality: the smaller sample size was probably insufficient to include all factors in the analysis.

Some limitations of this study should be acknowledged, including the large time-span, the heterogeneous management of patients in different clinical sites, the nonstandardized use of antineoplastic regimens, and the incomplete information on causes of death. Additionally, the relatively small sample size did not allow us to analyse the determinants of death in less common histotypes.

Despite earlier findings of PI-associated toxicities during chemotherapy, no study has reported an association between the use of PIs and survival: our results strengthen the recommendation to avoid such compounds and support the use of noninteracting drugs such as integrase inhibitors. The patients included in this study were

on raltegravir but, given the similar pharmacokinetic pathways, the observed results may reasonably be extended to dolutegravir-containing regimens.

In conclusion, our study demonstrates that, even in recent years, HIV-associated lymphomas have been common in HIV-positive patients and that the choice of a DDI-sparing cART regimen is paramount to enhance survival in this fragile population.

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