

**Incidence and risk factors of HIV-related non-Hodgkin lymphoma in
the era of combination antiretroviral therapy:
European multi-cohort study**

The Collaboration of Observational HIV Epidemiological Research Europe
(COHERE) study group*

* Members of writing committee and collaboration are listed at the end of the
article

Running head:

HIV-related non-Hodgkin lymphoma in the era of antiretroviral therapy

Correspondence:

Dr. Julia Bohlius

Institute of Social and Preventive Medicine (ISPM)

University of Bern

Finkenhubelweg 11, CH-3012 Bern, Switzerland.

jbohlius@ispm.unibe.ch, Tel +41 31 631 35 10, Fax +41 31 631 35 20

Abstract 249 words, main text 2861 words, 4 tables, 3 figures, 44 references

Abstract

Background: Incidence and risk factors of HIV-associated non-Hodgkin lymphoma (NHL) are not well defined in the era of combination antiretroviral therapy (cART).

Methods: 56,305 adult HIV-1 infected patients who started cART in one of 22 prospective studies in Europe were included. Weibull random-effects models were used to estimate hazard ratios (HRs) for developing systemic NHL, including CD4 cell counts and viral load as time-updated variables.

Results: During 212,042 person-years of follow-up, 521 patients were diagnosed with systemic NHL and 62 with primary brain lymphoma (PBL). The incidence rate of systemic NHL was 463 per 100,000 person-years not on cART and 205 per 100,000 person-years in treated patients, for a rate ratio of 0.44 (95% confidence interval [CI] 0.37 to 0.53). The corresponding incidence rates of PBL were 57 and 24 per 100,000 person-years (rate ratio 0.43; 95% CI 0.25 to 0.73). Suppression of HIV-1 replication on cART (HR 0.60, 95% CI 0.44-0.81, comparing ≤ 500 with 10,000-99,999 viral copies/ml) and increases in CD4 counts (HR 0.30, 0.22-0.42, comparing ≥ 350 with 100-199 cells/ μL) were protective; a history of Kaposi sarcoma (HR 1.70, 1.08-2.68, compared to no history of AIDS), transmission through sex between men (HR 1.57, 1.19-2.08, compared to heterosexual transmission) and older age (HR 3.72, 2.38-5.82, comparing ≥ 50 with 16-29 years) were risk factors for systemic NHL.

Conclusions: The incidence rates of both systemic NHL and PBL are substantially reduced in patients on cART. Timely initiation of therapy is key to the prevention of NHL in the era of cART.

Keywords: non-Hodgkin lymphoma; cohort studies; antiretroviral therapy; Kaposi sarcoma; immunodeficiency; viral load; Europe

Introduction

Human immunodeficiency virus (HIV)-infected patients are at increased risk of developing non-Hodgkin Lymphoma (NHL) when compared to the general population [1, 2]. In the 1980s the risk of NHL within three years of an AIDS diagnosis was increased 165-fold when compared to people without AIDS [3]. Following its introduction in 1996, combination antiretroviral therapy (cART) has led to a substantial reduction in HIV-associated morbidity and mortality; however, cohort studies have shown that the decline in the incidence of NHL in the cART era was less pronounced than that observed for Kaposi's Sarcoma (KS) or opportunistic infections [4-7]. Consequently NHL has become one of the most frequent AIDS-defining events in recent years [8] and the most common cancer associated with HIV in the USA [7]. In HIV-infected patients NHL poses particular therapeutic challenges [9] and continues to be an important cause of death in the era of cART [10].

Previous studies showed that the risk of NHL in HIV-infected persons is increased in older patients [11-14], in patients with more advanced immunodeficiency [11-15] and patients with high HIV-1 viral loads [11, 14]. Many of these studies were, however, from the pre-cART era or lacked information on cART at the patient level [16]. Only a few, relatively small studies specifically addressed risk factors for NHL in patients receiving cART [11, 13, 14].

We analyzed the database of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) to examine the incidence and risk factors of NHL in the cART era.

Methods

COHERE is a collaboration of 33 observational cohort studies in 30 European countries [17]. COHERE was established in 2005 with the objective of conducting hypothesis-driven research on the prognosis and outcome of HIV-infected individuals across Europe. All cohorts have been approved by local ethics committees or institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least once every 6 months. Each cohort submits information using the standardized HIV Collaboration Data Exchange Protocol (HICDEP) [18] to co-ordinating centres at the Copenhagen HIV Program (CHIP), Copenhagen, Denmark, or the Institut de Santé Publique d'Épidémiologie et de Développement (ISPED), Bordeaux, France. Data collected include information on patient demographics, use of cART, CD4 cell counts and percentages, HIV-1 RNA concentrations (viral loads), AIDS and deaths. Further information is given at <http://www.chip.dk/COHERE/tabid/295/Default.aspx> and <http://etudes.isped.u-bordeaux2.fr/cohere/>. Twenty-two cohorts from ten countries contributed data to the present analyses.

Inclusion criteria and definitions

We included all adult (aged 16 years or older) antiretroviral treatment-naïve HIV-infected patients enrolled in COHERE cohorts who started cART at some point after 1 January 1998, at a time when cART had become well established and widely used in Europe. All patients had to have at least one CD4

cell measurement after enrolment and before starting cART. In patients developing NHL, the CD4 count had to be measured before the diagnosis of NHL. Baseline CD4 cell count was defined as the first CD4 count measured during a visit after 1 January 1998. The baseline HIV-1 RNA was taken as the measurement closest to the baseline CD4 cell count, within a window of plus or minus 30 days not on cART. The nadir CD4 cell count was defined as the lowest ever measured CD4 cell count up to seven days after starting cART. In patients who developed NHL before starting cART, the nadir CD4 count had to be measured before the diagnosis of NHL. We defined cART as a regimen with at least 3 antiretroviral drugs from any drug class, including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and fusion inhibitors. Data were merged on 31 July 2006.

The diagnosis of NHL was made on the basis of the 1993 CDC (Centers for Disease Control and Prevention) histology criteria [19]. Burkitt's lymphoma, immunoblastic lymphoma and primary brain lymphoma (PBL) are included in the CDC definition. We included all subtypes of NHL including unspecified and other types in our analysis. However, information on subtypes was incomplete in many cohorts, except for the distinction between PBL and systemic NHL. We therefore restricted the analysis to comparisons between PBL and systemic NHL. For patients in clinical CDC stage C (AIDS) at baseline we distinguished between patients with a history of Kaposi Sarcoma and patients with a history of another

AIDS-defining illness: Kaposi Sarcoma may be associated with an increased risk of some subtypes of NHL in HIV-infected patients [20-22].

Statistical analysis

The incidence rate of systemic NHL and PBL was calculated by dividing the number of patients developing the disease by the number of person-years at risk. In patients not on cART we measured time from the date of the first visit with a CD4 cell count after 1 January 1998 (baseline) until the date of NHL diagnosis, start of cART or the last follow-up visit, whichever came first. In patients on cART we measured time from the start of cART until the diagnosis of NHL or the last follow-up visit. We used an intent-to-continue-treatment approach and thus ignored subsequent changes to treatment, including treatment interruptions and terminations. Prevalent cases, i.e. patients with NHL at baseline, were excluded.

We identified risk factors for developing systemic NHL using Weibull models, with random-effects to account for heterogeneity between cohort studies. The number of PBL cases was too small to allow meaningful analyses. Multivariable models included age and CDC clinical stage (at baseline or at start of cART), sex, transmission risk group, and nadir CD4 counts. Variables were included in the model based on biological and statistical reasoning; no automated selection procedure was applied. The effect of changes in CD4 cell counts and plasma HIV-1 RNA load over time were explored in time-updated models. Results are presented as medians with interquartile ranges (IQR), incidence rates per 100,000 person-years with 95% confidence intervals (CIs), Kaplan-Meier estimates of the cumulative incidence of NHL and crude and adjusted

hazard ratios (HRs) with 95% CIs. All statistical analyses were done in Stata (version 10, StataCorp, College Station, Texas).

Results

Characteristics of cohorts and patients

The database included a total of 67,659 patients, including 1,176 patients who had been diagnosed with NHL. Of note, among patients with NHL, 660 (56.1%) had been diagnosed while not on cART. A total of 11,354 (16.8%) patients were excluded from the analysis for the reasons detailed in [Figure 1](#). The most important reasons for exclusion were missing CD4 counts between 01.01.1998 and the start of cART or the diagnosis of NHL. Of note, this group included many patients who were diagnosed with NHL and enrolled in the cohort around the same time, i.e. patients with prevalent NHL. Patients not diagnosed with NHL and excluded because of missing CD4 counts were more likely to have a history of intravenous drug use (27% versus 17%) and of AIDS compared to included patients (26% versus 18%); patients were similar with respect to age and gender. Among patients with NHL those who were excluded had more often been diagnosed with AIDS before developing NHL compared to included patients (22% versus 14%), but they were similar with respect to age, gender and risk group.

A total of 56,305 patients (83%) were included in analyses. The median date of the last follow up was June 1, 2005 (IQR May 11, 2004 to December 21, 2005). The characteristics of the included patients are shown in [Table 1](#). Median age was 36.1 years, and most patients were male (n=40,350, 72%). Overall, heterosexual contacts were the most frequent risk factor for HIV transmission, followed by sex between men and injection drug use. The median baseline CD4

cell count was 192 cells/ μ L and the median plasma HIV-1 RNA load 75,001 copies/mL. Overall 10,382 (18%) of patients were in CDC clinical stage C at baseline. Among 1,186 patients with a history of KS, 747 (63%) were men who had sex with men (MSM).

During 212,042 person-years of follow-up, 583 patients were diagnosed with NHL, including 62 (11%) cases of PBL and 521 cases (89%) of systemic NHL. Among the latter, 382 (73%) lymphomas were classified as not specified and 36 (7%) as other; 60 patients (12%) were diagnosed with a Burkitt's lymphoma and 43 (8%) with a diffuse large cell lymphoma. Twenty-nine patients had a KS diagnosed prior to the diagnosis of NHL. The median time between the diagnosis of KS and NHL was 293 days (IQR 65 to 679 days). Compared to patients who did not develop NHL, patients diagnosed with NHL were older, more likely to be male, and more likely to be in more advanced stages of the infection, with lower CD4 cell counts and higher plasma HIV-1 RNA loads at baseline ([Table 1](#)). Patients on cART at the time of systemic NHL diagnosis were more often in advanced clinical stage (26% versus 12% in CDC clinical stage C) and had lower CD4 cell counts (median 164 cells/ μ L versus 187 cells/ μ L) compared to cART naïve patients. As expected, patients who had not been on cART had higher HIV-1 RNA viral loads ([Table 4](#)).

Incidence of NHL while not on cART and on cART

A total of 155 systemic NHL were diagnosed while not on cART and 366 were diagnosed on cART. The incidence rate was 462.6 (95% CI 395.3 to 541.5) per 100,000 person-years not on cART and 205.1 (95% CI 185.1 to 227.2) per

100,000 person-years in treated patients, for a rate ratio of 0.44 (95% CI 0.37 to 0.53). There were 19 diagnoses of PBL in patients not on cART and 43 diagnoses of PBL on cART. The incidence rate was 56.7 (95% CI 36.2 to 88.9) per 100,000 person-years not on cART and 24.1 (95% CI 17.9 to 32.5) per 100,000 person-years on cART, for a rate ratio of 0.43 (95% CI 0.25 to 0.73). Overall the median time from the start of observation to the diagnosis was 81 days (IQR 18 to 707 days) while not on cART, and 287 days (IQR 82-860 days) while on cART. In sensitivity analyses incidence rates were similar when including the patients with missing CD4 counts, but excluding prevalent cases. Figure 2 shows that incidence rates for any type of NHL declined with increasing nadir CD4 counts and decreasing baseline HIV-1 RNA viral load. These trends were particularly pronounced in patients not on cART. Figure 3 shows the cumulative incidence of any NHL (systemic NHL and PBL) after start of cART by nadir CD4 cell count. Overall 1.21% (95% CI 1.09% – 1.34%) of patients had developed a systemic NHL or PBL at five years after starting cART. The cumulative incidence at five years was higher in patients with nadir CD4 cell counts <50 cells/ μ L (1.86%, 95% CI 1.53% – 2.25%) compared to patients with nadir CD \geq 350 cells/ μ L (0.43%, 95% CI 0.29% – 0.63%).

Risk factors for systemic NHL while not on cART and on cART

In univariable analysis the incidence rate while not on cART was higher in men than in women, higher in men who have sex with men than in other transmission groups (i.e. injection-drug use and heterosexual contacts) and higher among patients aged 50 years or older, patients with a history of KS,

patients with nadir CD4 cell counts below 100 cells/ μ L and patients with baseline HIV-RNA plasma loads of 100,000 copies/mL or greater (Table 2). Differences in the same direction were observed in patients developing NHL on cART.

In multivariable analyses treating CD4 counts and HIV-1 viral load as time-updated variables (Table 3) associations with age, CD4 cell count and HIV-1 viral load remained both for systemic NHL diagnosed while not on cART and for systemic NHL diagnosed on cART. A history of KS and transmission group men who have sex with men were additional risk factors in patients on cART. There was little evidence for a difference in risk across cART regimens (PI-based, NNRTI-based or NRTIs only).

Discussion

The incidence of HIV-associated NHL in patients receiving cART was lower than in patients not on cART, with reductions in incidence rate of over 50% both for systemic NHL and PBL. A history of advanced immunodeficiency and older age were associated with an increased risk of systemic NHL both in patients receiving and not receiving cART. In patients on cART, a prior diagnosis of KS and transmission through sex between men was also associated with NHL. Exposure to high plasma HIV-1 RNA concentrations and low CD4 cell counts were risk factors in patients not receiving cART. Conversely, suppression of HIV-1 replication and immune recovery were protective factors in patients receiving cART. Our results thus support the notion that both immunodeficiency and replication of HIV-1 play a role in the development of NHL [13, 14, 23].

Our study has several limitations. The analysis was restricted to patients with CD4 cell counts available before the start of cART and prior to the diagnosis of NHL. This meant that some patients were excluded from the analysis, although incidence rates were similar when they were included in sensitivity analyses. In the majority of cases the histological subtype was not specified and we could therefore only distinguish between systemic NHL and PBL. The number of patients developing PBL was small even in this large collaborative study. Finally, cART naïve patients who developed NHL and died before starting cART were not included in the present data set. This may have lead to an underestimation of the incidence rate of NHL in patients not on cART. On the other hand, our analysis of patients on cART may have included periods where

cART was interrupted, leading to overestimation of the incidence rate of NHL on cART.

Previous studies have shown a decline in the incidence of HIV-related NHL when comparing the pre-cART and cART eras [15, 24]. The interpretation of these comparisons is, however, not straightforward because the treatment status of the individual patient was not known [15, 24]. As our study shows, the availability of cART does not mean that all patients actually receive cART: in our study about 50% of patients (before exclusions) were not on cART when diagnosed with NHL. Similar data were reported both in other cohort studies [25-27] and clinical trials [28].

Our data confirm that exposure to low CD4 cell counts is the main risk factor for developing NHL [11-15] but within categories of similar CD4 cell nadirs, cART treated patients had a lower risk of NHL compared to patients not on cART. Of note, a diagnosis of AIDS was not associated with an increased risk of NHL after adjusting for nadir CD4 cells count. However, we found that a history of KS was a significant risk factor in patients on cART, after adjusting for transmission group and other risk factors in multivariable analysis.

Pathways that may be involved in the development of lymphoma in HIV-infected patients include immunosuppression, chronic B- cell stimulation and transformation caused by other co-infecting viruses, such as Epstein Barr virus (EBV) and human herpes virus 8 (HHV-8) [29-32]. The association between HHV-8 and KS, and the rare multicentric Castleman disease and primary effusion lymphoma is well established while a possible association with other

lymphoproliferative disorders is a matter of ongoing debate [32-37]. Results from previous studies suggested an increased risk of specific subtypes of NHL in HIV-infected patients diagnosed with KS [20, 21, 38-41]. Our results provide some support for the hypothesis that HHV-8 may contribute to the development of NHL. However, patients with a malignant disease are generally at increased risk of developing secondary NHL and other malignancies, which may be related to exposure to chemotherapy and genetic factors [42]. Further studies are needed to clarify a possible role of HHV-8 and specific subtypes of HIV-associated NHL.

The CD4 cell count at which cART should be initiated is a central but unresolved issue in the care of HIV-1 infected patients. The results of our study are relevant to this debate: the strong relationship between exposure to low CD4 cell counts and the risk of NHL, and the protective effect of suppressing HIV-1 replication supports the move towards earlier initiation of cART. In the SMART randomized controlled trial the incidence of malignancies was higher in the drug conservation arm in which cART was stopped if the CD4 cell count exceeded 350 cells/ μ L and restarted if it fell to less than 250 cells/ μ L, compared to the viral suppression arm utilizing continuous cART [43]. The International AIDS Society USA Panel recommends that antiretroviral therapy is started in individuals whose CD4 count drops below 350 cells/ μ L, and that the decision should be individualized in patients with CD4 counts above 350 cells/ μ L [44]. Of note, in our analysis the risk of NHL was higher in patients with nadir CD4 counts in the range of 200 to 349 cells/ μ L compared to patients with nadir counts above 350

cells cells/ μ L. This might be particularly important in patients aged 50 years or older, given their increased risk of NHL, and slower immune recovery.

In conclusion, the risk of HIV-related NHL is more than halved in patients on cART. Timely initiation of cART followed by suppression of HIV replication and immune recovery are key factors to prevent NHL in the era of cART. The association with Kaposi Sarcoma suggests a role of HHV-8 in HIV-associated NHL, which needs further investigation.

Acknowledgements

We are grateful to all patients, doctors and study nurses who were involved in the participating cohorts. This project was funded by a Swiss Bridge Award to Matthias Egger. The COHERE study group is funded by grants from the French Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS), the Dutch HIV Monitoring Foundation and the Danish Augustinus Foundation. The study was supported in part by the Spanish Network for AIDS Research (RIS; ISCIII-RETIC RD06/006).

Appendix: The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group

Writing group for the study of lymphoma

Julia Bohlius,¹ Kurt Schmidlin,¹ Dominique Costagliola,² Gerd Fätkenheuer,³ Margaret May,⁴ Ana Maria Caro-Murillo,⁵ Amanda Mocroft,⁶ Fabrice Bonnet,⁷ Gary Clifford,⁸ Anastasia Karafoulidou,⁹ Jose M. Miro,¹⁰ Jens Lundgren,¹¹ Genevieve Chene,¹² Matthias Egger.¹

- 1) Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland
- 2) Inserm, U720 UPMC Université Paris 06, France
- 3) Universitätsklinik Köln, Cologne, Germany
- 4) Department of Social Medicine, University of Bristol, UK
- 5) Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, España
- 6) University College London Medical School, London, UK
- 7) Centre d'Information et de Soins de l'Immunodéficience Humaine (CISIH), CHU de Bordeaux, France
- 8) International Agency for Research on Cancer (IARC), Lyon, France
- 9) 2nd Blood Transfusion and Hemophilia Center, Laikon General Hospital, Athens, Greece

10) Infectious Diseases Service, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain

11) Copenhagen HIV Programme, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark

12) INSERM, U897 Epidemiology and Biostatistics, Université Victor Segalen Bordeaux 2, Bordeaux, France.

Cohort representatives for lymphoma project

Andrea Antinori (ICONA), Fabrice Bonnet (AQUITAINE), Francois Boué (FHDH), Norbert Brockmeyer (KOMPNET), Jordi Casabona (PISCIS), Fabrice Bonnet (AQUITAINE), Dominique Costagliola (FHDH), Fernando Dronda (CoRIS), Niels Obel (Danish HIV Cohort), Gerd Fätkenheuer (Cologne-Bonn), Martin Fischer (CHIC), Silvia Franceschi (SHCS), Diana Gibb (CHIPS), Vincent Le Moing (COPILOTE), Amanda Mocroft (EUROSIDA), David Nadal (SHCS), Giota Touloumi (AMACS), Maria Prins (CASCADE), François Raffi (COPILOTE), Bernardino Roca (VACH), Annelies Verbon (ATHENA), Timo Wolf (Frankfurt HIV-Cohort), Claudia Fortuny (HIV-MIP).

Methodologists and project staff for lymphoma project

Julia Bohlius, Rana Chakraborty, Gary Clifford, Matthias Egger, Silvia Franceschi, Margaret May, Christoph Minder, Jonathan Sterne, Marcel Zwahlen

Staff at the Regional Coordinating Centers

Michelle Ellefson, Jesper Kjaer (CHIP, Copenhagen), Fidéline Collin, Céline Colin (ISPED, Bordeaux)

COHERE Steering Committee

Executive Committee: Ian Weller (Chair, University College London), Dominique Costagliola (Vice-chair, FHDH), Bruno Ledergerber (Vice-chair, SHCS), Jens Lundgren (Head, Copenhagen Regional Co-ordinating Center), Genevieve Chene (Head, Bordeaux Regional Co-ordinating Center).

Cohort representatives: Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Cecile Goujard (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Frank de Wolf (ATHENA), Peter Reiss (ATHENA), Kholoud Porter (CASCADE), Maria Dorrucchi (CASCADE), Caroline Sabin (UK CHIC), Diana Gibb (CHIPS), Julia Del Amo (Co-RIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Schlomo Staszewski (Frankfurt), Santiago Perez-Hoyos (GEMES-Haemo), Jesus Almeda (HIV-MIP), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA, IMIT), Maurizio de Martino (ITLR), Norbert Brockmeyer (KOMPNET), Gerd Fatkenheuer (Cologne-Bonn), Jose Ramos (Madrid Cohort), Manuel Battegay (MoCHIV, Swiss HIV Cohort Study), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M Miro (PISCIS), Antonella Castagna (San Raffaele), Stephane de Wit (St. Pierre Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH); European AIDS Treatment Group: Nikos Dedes; *Project Leaders:* Caroline Sabin, Andrew Phillips, Hansjakob Furrer, Ole Kirk, Matthias Egger, François Dabis, Marie- Louise Newell, Jonathan Sterne, Amalio Telenti.

COHERE data managers

Nikos Pantazis (AMACS), Jérôme Lechenadec (ANRS CO1/CO10 EPF), Faroudy Boufassa, Laurent Tran (ANRS CO2 SEROCO, ANRS CO6 PRIMO), Eric Balestre (ANRS CO3 AQUITAINE), Emilie Lanoy (ANRS CO4 FHDH), Françoise Couturier (ANRS CO8 COPILOTE), Theo Rispens, Luuk A.J. Gras (ATHENA), Krishnan Bhaskaran (CASCADE), Caroline Sabin, Teresa Hill (CHIC), Ali Judd, Trinh Duong (CHIPS), Paz Sobrino (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Jesper Kjær (EuroSIDA), Beverley Jennings (Frankfurt), Santiago Pérez-Hoyos (GEMES Haemo), Jesus Almeda (HIV-MIP), Sandro Bonfigli (ICC), Alessandro Cozzi-Lepri (ICONA), Stefano Corvasce, Fulvio Adorni, Anna Lisa Ridolfo (IMIT), Giuseppe Paraninfo (Italian Master Cohort), Jose T. Ramos (Madrid Cohort), Olivia Keiser (MoCHIV), Vanni

Borghi (Modena Cohort), Janet Masters (NSHPC), Berta Ortiga (PISCIS),
Salpietro Stefania (San Raffaele), Martin Rickenbach (Swiss HIV Cohort Study),
Benedicte Poll (St. Pierre Cohort), Myriam Garrido (VACH).

Table 1: Patient characteristics at baseline

	Patients diagnosed with NHL (n=583)	Patients not diagnosed with NHL (n=55,722)	P
Type of NHL			
Systemic NHL	521 (89%)	-	
PBL	62 (11%)	-	
Age (years) at baseline			<0.0001
Median (IQR)	39.3 (34.0 to 47.5)	36.1 (30.9 to 42.4)	
16-29	62 (11%)	11,818 (21%)	
30-39	240 (41%)	25,606 (46%)	
40-49	160 (27%)	12,061 (22%)	
≥ 50	121 (21%)	6,237 (11%)	
Sex			<0.0001
Women	109 (19%)	15,846 (28%)	
Men	474 (81%)	39,876 (72%)	
Transmission risk group			<0.0001
Injection-drug use	89 (15%)	9,377 (17%)	
MSM	242 (42%)	18,249 (33%)	
Heterosexual	196 (34%)	22,707 (41%)	
Other / unknown	56 (10%)	5,389 (10%)	
CDC clinical stage			<0.0001
Stage A / B	446 (77%)	45,477 (82%)	
Stage C without KS	108 (19%)	9,088 (16%)	
Stage C with KS	29 (5%)	1,157 (2%)	
Nadir CD4 cell count (cells/μ L)			<0.0001
Median (IQR)	111 (43 to 217)	193 (82 to 308)	
< 50	161 (28%)	9,678 (17%)	
50-99	103 (18%)	6,249 (11%)	
100-199	149 (26%)	12,705 (23%)	
200-349	118 (20%)	16,424 (29%)	
≥ 350	52 (9%)	10,666 (19%)	
Plasma HIV-1 RNA (copies/mL)			<0.0001
Median (IQR)	109,900 (30,550 to 327,000)	75,000 (19,800 to 230,000)	
≥500,000	88 (15%)	6,131 (11%)	
100,000-499,999	175 (30%)	14,568 (26%)	
10,000-99,999	181 (31%)	19,000 (34%)	
501-9,999	51 (9%)	7,117 (13%)	
≤ 500	2 (0.3%)	490 (1%)	
Missing	86 (15%)	8,416 (15%)	

NHL, Non Hodgkin Lymphoma; PBL, Primary Brain Lymphoma; KS, Kaposi Sarcoma; baseline relates to the first examination after 1.1.1998. P-values from chi-squared tests.

Table 2: Incidence rate of systemic non-Hodgkin lymphoma overall and stratified by potential risk factors

	Not on cART			On cART		
	No. of NHL	Person-years at risk	Incidence rate per 100,000 person-years (95% CI)	No. of NHL	Person-years at risk	Incidence rate per 100,000 person-years (95% CI)
All	155	33,503	462.6 (395.3 to 541.5)	366	178,475	205.1 (185.1 to 227.2)
Age (years)						
16-29	23	8,436	272.6 (181.2 to 410.3)	28	33,163	84.4 (58.3 to 122.3)
30-39	53	16,091	329.4 (251.6 to 431.2)	159	85,139	186.8 (159.9 to 218.2)
40-49	48	6,358	754.9 (568.9 to 1,001.8)	100	39,550	252.8 (207.8 to 307.6)
≥ 50	31	2,618	1,183.9 (832.6 to 1,683.5)	79	20,622	383.1 (307.3 to 477.6)
Sex						
Women	31	9,759	317.6 (223.4 to 451.7)	64	48,389	132.3 (103.5 to 169.0)
Men	124	23,743	522.3 (438.0 to 622.8)	302	130,085	232.2 (207.4 to 259.9)
Transmission risk group						
Injection-drug use	22	7,029	313.0 (206.1 to 475.3)	63	34,850	180.8 (141.2 to 231.4)
MSM	65	12,103	537.0 (421.1 to 684.8)	149	57,575	258.8 (220.4 to 303.9)
Heterosexual	49	11,641	420.9 (318.1 to 556.9)	121	70,274	172.2 (144.1 to 205.8)
Other / unknown	19	2,730	696.1 (444.0 to 1,091.3)	33	15,776	209.2 (148.7 to 294.2)
CDC clinical stage						
Stage A/B	136	31,517	431.5 (364.8 to 510.5)	271	144,738	187.2 (166.2 to 210.9)
Stage C without KS	16	1,819	879.7 (538.9 to 1,435.9)	73	29,752	245.4 (195.1 to 308.6)
Stage C with KS	3	167	1,797.4 (579.7 to 5,573.0)	22	3,985	552.1 (363.5 to 838.5)
Nadir CD4 count (cells/μ L)						
< 50	29	2,576	1,125.9 (782.4 to 1,620.2)	100	31,338	319.1 (262.3 to 388.2)
50-99	31	2,572	1,205.4 (847.7 to 1,714.0)	65	19,821	327.9 (257.2 to 418.2)
100-199	32	9,193	348.1 (246.2 to 492.2)	101	37,866	266.7 (219.5 to 324.2)
200-349	40	13,948	286.8 (210.4 to 391.0)	73	49,849	146.4 (116.4 to 184.2)
≥ 350	23	5,214	441.1 (293.1 to 663.8)	27	39,601	68.2 (46.8 to 99.4)
HIV-1 RNA (copies/mL)						
≥ 500,000	15	1,044	1,436.9 (866.2 to 2,383.4)	68	21,085	322.5 (254.3 to 409.0)
100,000-499,999	42	4,163	1,009.0 (745.6 to 1,365.3)	119	51,190	232.5 (194.2 to 278.2)
10,000-99,999	51	12,789	398.8 (303.1 to 524.7)	99	61,130	161.9 (133.0 to 197.2)
501-9,999	23	9,253	248.6 (165.2 to 374.1)	26	18,595	139.8 (95.2 to 205.4)
≤ 500	0	-	-	7	3,502	199.9 (95.3 to 419.3)

cART, combination antiretroviral therapy; NHL, Non Hodgkin Lymphoma; KS Kaposi Sarcoma. Incidence rates from Poisson regression models.

All variables except nadir CD4 count were measured at baseline for the analysis of patients not on cART and at the start of cART for the analysis of patients on cART.

Table 3: Adjusted hazard ratios for systemic non-Hodgkin lymphoma from multivariable models

	Not on cART	On cART
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Age at start cART (years)		
16-29	1	1
30-39	0.97 (0.59 to 1.61)	1.98 (1.31 to 2.99)
40-49	1.94 (1.16 to 3.25)	2.35 (1.52 to 3.62)
≥ 50	2.84 (1.61 to 4.99)	3.72 (2.38 to 5.82)
Sex		
Women	1	1
Men	1.12 (0.70 to 1.80)	1.17 (0.86 to 1.59)
Transmission risk group		
Injection-drug use	0.82 (0.45 to 1.48)	1.10 (0.77 to 1.55)
MSM	1.23 (0.79 to 1.92)	1.57 (1.19 to 2.08)
Heterosexual	1	1
Other/unknown	1.49 (0.85 to 2.63)	1.01 (0.67 to 1.51)
CDC clinical stage		
Stage A/B	1	1
Stage C without KS	0.78 (0.43 to 1.43)	0.86 (0.65 to 1.13)
Stage C with KS	1.00 (0.24 to 4.14)	1.70 (1.08 to 2.68)
CD4 count (cells/ μ L)		
< 50	1.15 (0.53 to 2.48)	1.76 (1.20 to 2.58)
50-99	2.72 (1.46 to 5.04)	1.48 (1.02 to 2.15)
100-199	1	1
200-349	0.70 (0.41 to 1.22)	0.60 (0.44 to 0.81)
≥ 350	0.42 (0.24 to 0.74)	0.30 (0.22 to 0.42)
HIV-1 RNA (copies/mL)		
≥ 500,000	2.16 (1.21 to 3.87)	1.55 (0.96 to 2.49)
100,000-499,999	1.75 (1.16 to 2.65)	0.99 (0.66 to 1.48)
10,000-99,999	1	1
501-9,999	1.05 (0.64 to 1.72)	1.11 (0.77 to 1.60)
≤ 500	-	0.60 (0.44 to 0.83)

HR, hazard ratio; CI, confidence interval; cART, combination antiretroviral therapy; KS Kaposi Sarcoma.

Models included CD4 count and HIV-1 RNA as time-updated variables and age, sex, transmission risk group and CDC clinical stage at baseline or start cART.

Table 4: Characteristics of patients with systemic non-Hodgkin lymphoma on cART and not on cART at diagnosis

	Not on cART	On cART	P
Number of patients	155	366	
Age (years) at NHL diagnosis			0.043
Median (IQR)	41.1 (34.3 to 48.9)	41.3 (36.1 to 49.3)	
16-29	18 (12%)	19 (5%)	
30-39	49 (32%)	143 (39%)	
40-49	53 (34%)	118 (32%)	
≥ 50	35 (23%)	86 (24%)	
Sex			0.497
Women	31 (20%)	64 (17%)	
Men	124 (80%)	302 (83%)	
Transmission risk group			0.601
Injection-drug use	22 (14%)	63 (17%)	
MSM	65 (42%)	149 (41%)	
Heterosexual	49 (32%)	121 (33%)	
Other / unknown	19 (12%)	36 (9%)	
CDC clinical stage at baseline			0.002
Stage A / B	136 (88%)	271 (74%)	
Stage C without KS	16 (10%)	73 (20%)	
Stage C with KS	3 (2%)	22 (6%)	
CD4 cell count (cells/μ L) at NHL diagnosis			0.002
Median (IQR)	187 (70 to 320)	164 (80 to 280)	
< 50	20 (13%)	38 (10%)	
50-99	25 (16%)	36 (10%)	
100-199	20 (13%)	69 (19%)	
200-349	32 (21%)	54 (15%)	
≥ 350	28 (18%)	43 (12%)	
Missing	30 (19%)	126 (34%)	
Plasma HIV-1 RNA (copies/mL) at NHL diagnosis			<0.0001
Median (IQR)	99,150 (16,450 to 315,650)	400 (50 to 12,048)	
≥500,000	18 (12%)	12 (3%)	
100,000-499,999	38 (25%)	19 (5%)	
10,000-99,999	36 (23%)	28 (8%)	
501-9,999	17 (11%)	45 (12%)	
≤ 500	3 (2%)	115 (31%)	
Missing	43 (28%)	147 (40%)	

NHL, Non Hodgkin Lymphoma, KS, Kaposi Sarcoma; baseline relates to the first examination after 1.1.1998. P-values from chi-squared tests.

Figure 1 – Identification of study population

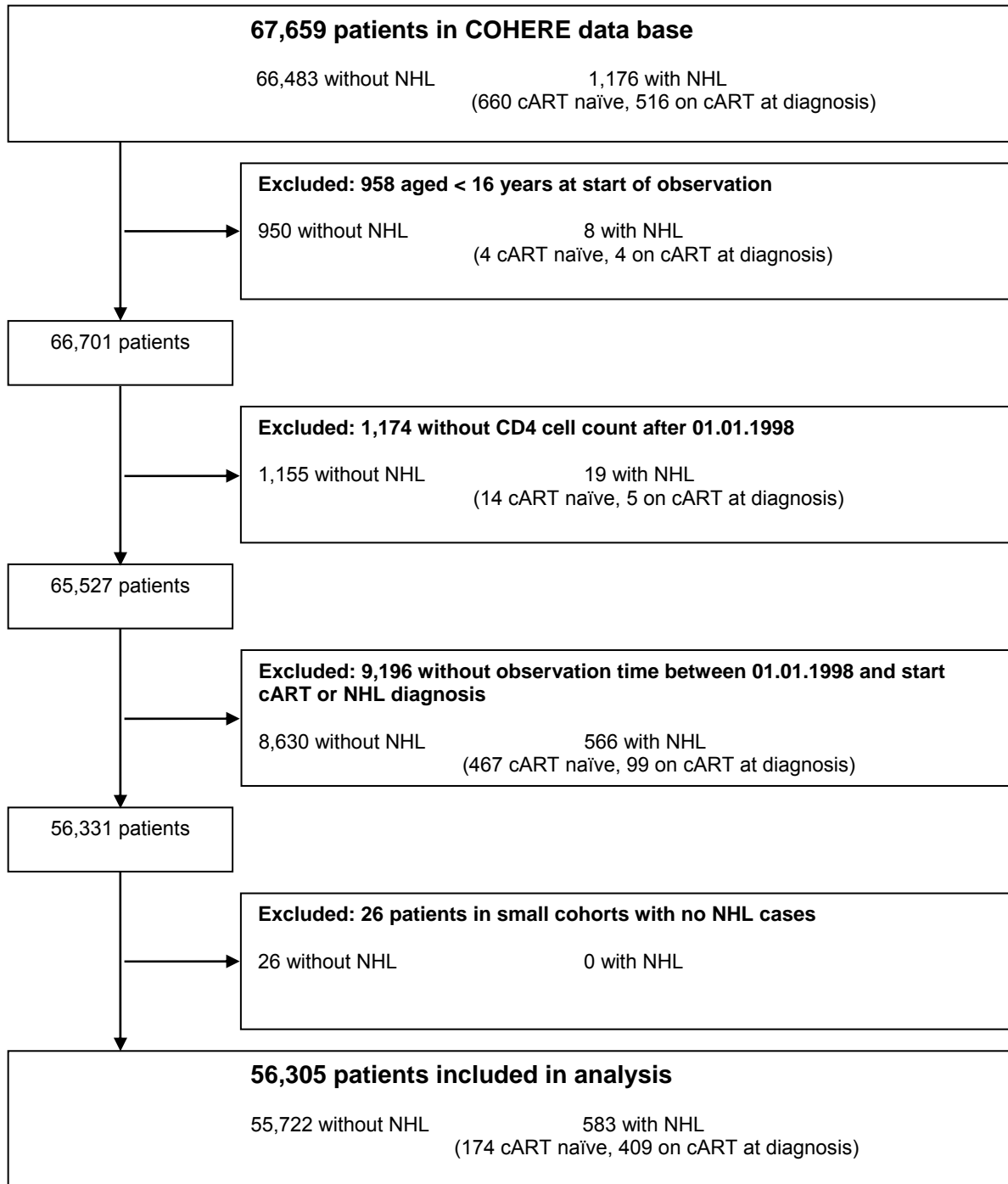
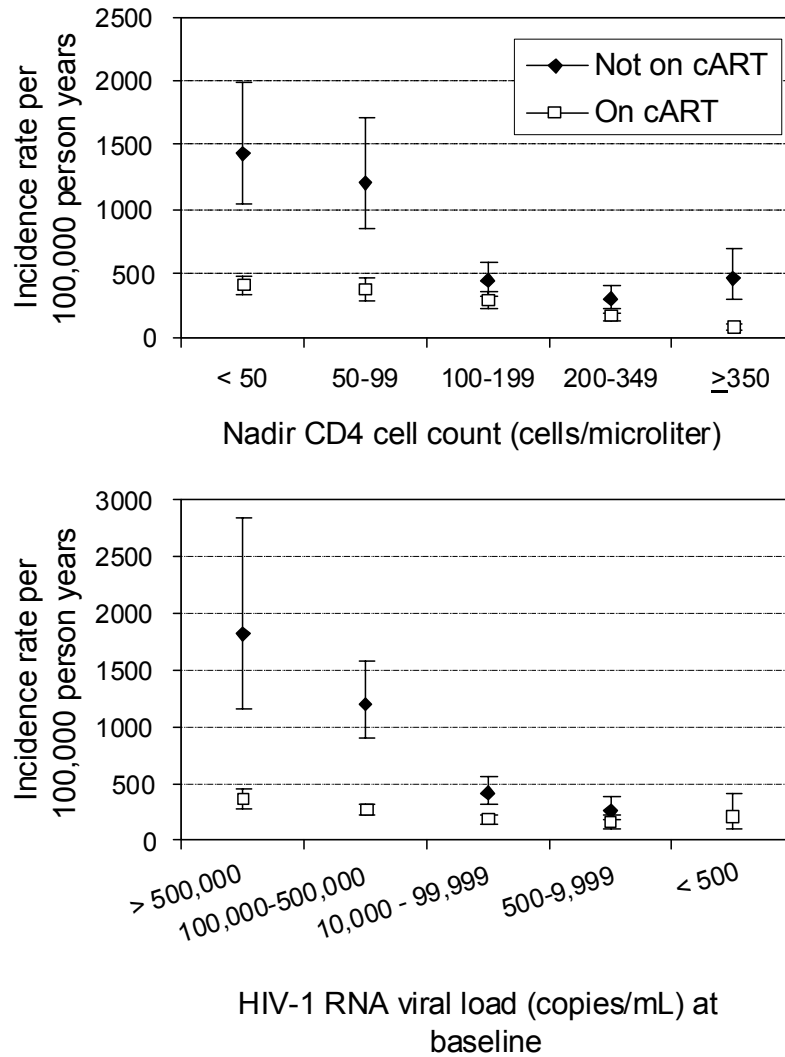
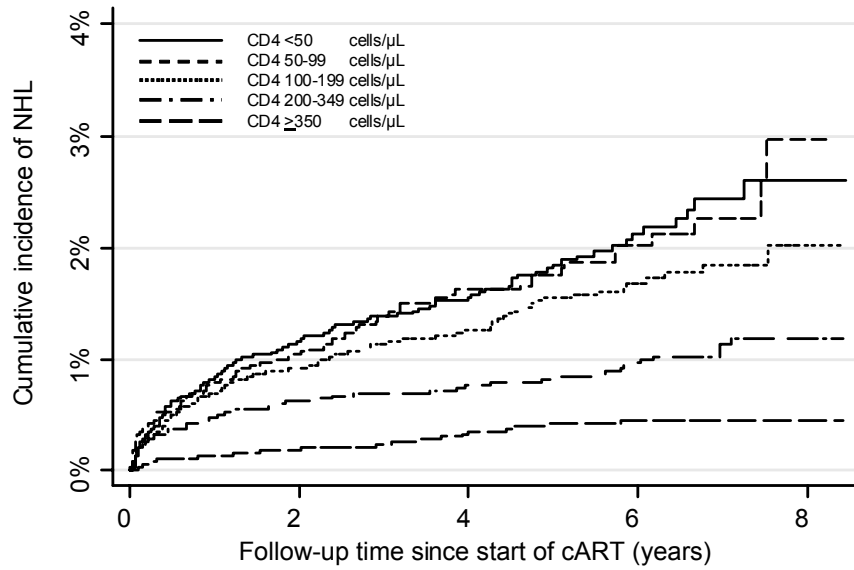


Figure 2 - Incidence rate of any type of non-Hodgkin lymphoma (systemic NHL and PBL) across categories of baseline CD4 cell count (upper panel) and HIV-1 viral load (lower panel) in patients on cART and not on cART



inserm-00394577, version 1 - 12 Jun 2009

Figure 3 - Cumulative incidence of any type of non-Hodgkin lymphoma (systemic NHL and PBL) in patients on cART by nadir CD4 cell count



Number at risk

CD4 <50 cells/μL	2631	6113	3846	1746	72
CD4 50-99 cells/μL	1551	3848	2496	1147	57
CD4 100-199 cells/μL	2514	7287	5039	2477	109
CD4 200-349 cells/μL	3027	9646	6911	3632	211
CD4 ≥350 cells/μL	3190	7428	5462	3010	181

References

1. Dal Maso L, Franceschi S. Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in people with AIDS. *Lancet Oncol* 2003; **4**:110-119.
2. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001; **285**:1736-1745.
3. Cote TR, Biggar RJ, Rosenberg PS, et al. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. *Int J Cancer* 1997; **73**:645-650.
4. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* 1999; **282**:2220-2226.
5. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008; **123**:187-194.
6. Crum-Cianflone N, Hullsiek KH, Marconi V, et al. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study. *AIDS* 2009;**23**:41-50.
7. Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. *AIDS* 2008; **22**:489-496.
8. d'Arminio MA, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. *Arch Intern Med* 2005; **165**:416-423.
9. Spano JP, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D. AIDS-related malignancies: state of the art and therapeutic challenges. *J Clin Oncol* 2008; **26**:4834-4842.
10. Bonnet F, Burty C, Lewden C, et al. Changes in cancer mortality among HIV-infected patients: the Mortalite 2005 Survey. *Clin Infect Dis* 2009; **48**:633-639.
11. Kirk O, Pedersen C, Cozzi-Lepri A, et al. Non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy. *Blood* 2001; **98**:3406-3412.
12. Stebbing J, Gazzard B, Mandalia S, et al. Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol* 2004; **22**:2177-2183.
13. Polesel J, Clifford GM, Rickenbach M, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *AIDS* 2008; **22**:301-306.

14. Zoufaly A, Stellbrink H, an der Heide M, et al. Insufficient Virus Suppression during HAART Is a Strong Predictor for the Development of AIDS-related Lymphoma: German CLINSURV Cohort. 2008.
15. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst* 2007; **99**:962-972.
16. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008; **123**:187-194.
17. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group. Response to combination antiretroviral therapy: variation by age. *AIDS* 2008; **22**:1463-1473.
18. Kjaer J, Ledergerber B. HIV cohort collaborations: proposal for harmonization of data exchange. *Antivir Ther* 2004; **9**:631-633.
19. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992; **41**:1-19.
20. Engels EA, Rosenberg PS, Frisch M, Goedert JJ. Cancers associated with Kaposi's sarcoma (KS) in AIDS: a link between KS herpesvirus and immunoblastic lymphoma. *Br J Cancer* 2001; **85**:1298-1303.
21. Deloose ST, Smit LA, Pals FT, Kersten MJ, van Noesel CJ, Pals ST. High incidence of Kaposi sarcoma-associated herpesvirus infection in HIV-related solid immunoblastic/plasmablastic diffuse large B-cell lymphoma. *Leukemia* 2005; **19**:851-855.
22. Chadburn A, Hyjek E, Mathew S, Cesarman E, Said J, Knowles DM. KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. *Am J Surg Pathol* 2004; **28**:1401-1416.
23. Bonnet F, Balestre E, Thiebaut R, et al. Factors associated with the occurrence of AIDS-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: Aquitaine Cohort, France. *Clin Infect Dis* 2006; **42**:411-417.
24. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* 2000; **92**:1823-1830.
25. Hoffmann C, Wolf E, Fatkenheuer G, et al. Response to highly active antiretroviral therapy strongly predicts outcome in patients with AIDS-related lymphoma. *AIDS* 2003; **17**:1521-1529.
26. Antinori A, Cingolani A, Alba L, et al. Better response to chemotherapy and prolonged survival in AIDS-related lymphomas responding to highly active antiretroviral therapy. *AIDS* 2001; **15**:1483-1491.

27. Simcock M, Blasko M, Karrer U, et al. Treatment and prognosis of AIDS-related lymphoma in the era of highly active antiretroviral therapy: findings from the Swiss HIV Cohort Study. *Antivir Ther* 2007; **12**:931-939.
28. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol* 2006; **24**:4123-4128.
29. Grulich AE, Wan X, Law MG, et al. B-cell stimulation and prolonged immune deficiency are risk factors for non-Hodgkin's lymphoma in people with AIDS. *AIDS* 2000; **14**:133-140.
30. Lim ST, Levine AM. Recent advances in acquired immunodeficiency syndrome (AIDS)-related lymphoma. *CA Cancer J Clin* 2005; **55**:229-241.
31. Sullivan RJ, Pantanowitz L, Casper C, Stebbing J, Dezube BJ. HIV/AIDS: epidemiology, pathophysiology, and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castlemann disease. *Clin Infect Dis* 2008; **47**:1209-1215.
32. Carbone A, Cesarman E, Spina M, Gloghini A, Schulz TF. HIV-associated lymphomas and gamma-herpesviruses. *Blood* 2008.
33. Du MQ, Bacon CM, Isaacson PG. Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 and lymphoproliferative disorders. *J Clin Pathol* 2007; **60**:1350-1357.
34. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castlemann disease. *Blood* 2002; **99**:2331-2236.
35. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; **266**:1865-1869.
36. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med* 1995; **332**:1186-1191.
37. Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. *J Intern Med* 2008; **264**:537-548.
38. Ridolfo AL, Santambrogio S, Mainini F, et al. High frequency of non-Hodgkin's lymphoma in patients with HIV-associated Kaposi's sarcoma. *AIDS* 1996; **10**:181-185.
39. Biggar RJ, Curtis RE, Cote TR, Rabkin CS, Melbye M. Risk of other cancers following Kaposi's sarcoma: relation to acquired immunodeficiency syndrome. *Am J Epidemiol* 1994; **139**:362-368.

40. Engels EA, Pittaluga S, Whitby D, et al. Immunoblastic lymphoma in persons with AIDS-associated Kaposi's sarcoma: a role for Kaposi's sarcoma-associated herpesvirus. *Mod Pathol* 2003; **16**:424-429.
41. Martin-Carbonero L, Palacios R, Valencia E, et al. Long-term prognosis of HIV-infected patients with Kaposi sarcoma treated with pegylated liposomal doxorubicin. *Clin Infect Dis* 2008; **47**:410-417.
42. Krishnan B, Morgan GJ. Non-Hodgkin lymphoma secondary to cancer chemotherapy. *Cancer Epidemiol Biomarkers Prev* 2007; **16**:377-380.
43. Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS* 2007; **21**:1957-1963.
44. Hammer SM, Eron JJ, Jr., Reiss P, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *JAMA* 2008; **300**:555-570.