Prescribing and Adverse Event reporting information

Dovato
dolutegravir/lamivudine

POWER REIMAGINED

AN INNOVATIVE, GUIDELINE-RECOMMENDED REGIMEN FOR YOUR PATIENTS LIVING WITH HIV

POWERFUL, DURABLE EFFICACY[1,2]

HIGH BARRIER TO RESISTANCE[1,2]

TDF, TAF AND ABC FREE[3]

DOVATO is indicated for the treatment of HIV-1 in adults and adolescents above 12 years weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

DTG 50 mg + 3TC 300 mg used in the GEMINI studies.

gemini 1 gemini 2

METABOLIC PARAMETERS AT 96 WEEKS

DOVATO vs DTG + TDF/FTC in treatment-naïve patients[1]

	Changes in bone turnover biomarkers significantly favour DOVATO vs DTG + TDF/FTC[1] The GEMINI studies did not determine whether these changes translate to clinical differences.
	Changes in renal function biomarkers significantly favour DOVATO vs DTG + TDF/FTC[1] The GEMINI studies did not determine whether these changes translate to clinical differences. AEs due to renal and urinary disorders were comparable across both arms (~5%).[4]
	Improvements in TC/HDL ratio occurred in both arms, with a statistically greater reduction in the DTG + TDF/FTC arm[1]
	Overall mean weight change from baseline was +3.1 kg in the DOVATO arm and +2.1 kg in the DTG + TDF/FTC arm[1]

TANGO

CHANGES IN METABOLIC PARAMETERS AT 48 WEEKS AFTER SWITCHING FROM TAF-CONTAINING REGIMENS

DOVATO vs TAF-containing regimens in virologically suppressed patients[2,5]

	INSULIN RESISTANCE SIGNIFICANTLY FEWER patients with insulin resistance* after switching to DOVATO from a TAF-containing regimen[5]
	LIPIDS SIGNIFICANT IMPROVEMENTS in most lipid parameters in the DOVATO arm vs TAF-containing regimens arm, including TC/HDL ratio[2]
	WEIGHT GAIN AND METABOLIC SYNDROME OBSERVED SIMILAR[5†]: • Small increases in mean weight (≈0.8 kg) in both arms • Increases in metabolic syndrome‡ • Median changes in fasting glucose and HbA_{1c}

*Defined as homeostatic model assessment of insulin resistance (HOMA-IR) ≥2.[5]
†Longer-term data required to determine clinical impact of switching to DOVATO from TAF-containing regimens.
‡Defined by the International Diabetes Federation as a combination of risk factors for cardiovascular disease.[6]

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ORIGINAL RESEARCH

The extent of B-cell activation and dysfunction preceding lymphoma development in HIV-positive people‡

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Objectives

B-cell dysfunction and activation are thought to contribute to lymphoma development in HIV-positive people; however, the mechanisms are not well understood. We investigated levels of several markers of B-cell dysfunction [free light chain (FLC)-κ, FLC-λ, immunoglobulin G (IgG), IgA, IgM and IgD] prior to lymphoma diagnosis in HIV-positive people.

Methods

A nested matched case–control study was carried out within the EuroSIDA cohort, including 73 HIV-positive people with lymphoma and 143 HIV-positive lymphoma-free controls. Markers of B-cell dysfunction were measured in prospectively stored serial plasma samples collected before the diagnosis of lymphoma (or selection date in controls). Marker levels $\leq$ 2 and $>$ 2 years prior to diagnosis were investigated.

Results

Two-fold higher levels of FLC-κ [odds ratio (OR) 1.84; 95% confidence interval (CI) 1.19, 2.84], FLC-λ (OR 2.15; 95% CI 1.34, 3.46), IgG (OR 3.05; 95% CI 1.41, 6.59) and IgM (OR 1.46; 95% CI 1.01, 2.11) were associated with increased risk of lymphoma $>$ 2 years prior to diagnosis, but not $\leq$ 2 years prior. Despite significant associations $>$ 2 years prior to diagnosis, the predictive accuracy of each marker was poor, with FLC-λ emerging as the strongest candidate with a c-statistic of 0.67 (95% CI 0.58, 0.76).

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‡This work was presented as a Thistle Presentation (poster + 7-min speed presentation) at HIV Drug Therapy, Glasgow, UK, October 2016 (P189)

*on behalf of EuroSIDA in EuroCOORD members are in Appendix.

Conclusions

FLC-κ, FLC-λ and IgG levels were higher > 2 years before lymphoma diagnosis, suggesting that B-cell dysfunction occurs many years prior to lymphoma development. However, the predictive value of each marker was low and they are unlikely candidates for risk assessment for targeted intervention.

Keywords: B-cell dysfunction, biomarkers, free light chains, HIV, immunoglobulins, lymphoma

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Introduction

HIV-positive persons are known to have higher rates of infection-related malignancies as a result of increased immune deficiency [1–4]. The Epstein–Barr virus (EBV) has been associated with almost all cases of Hodgkin's lymphoma (HL) and between 30 and 100% of cases of non-Hodgkin's lymphoma (NHL) occurring in the setting of HIV infection. Effective combination antiretroviral treatment (cART) has led to a significant decline in the incidence of all subtypes of NHL (except Burkitt) [5–12]. Despite this, NHL still accounts for approximately half of all AIDS-related malignancies and its incidence remains around 10-fold higher in HIV-positive than in HIV-negative people. Conversely, HL incidence has remained stable or even increased in HIV-positive people since the introduction of cART, and is estimated to be 11-fold higher (with estimates ranging from 5- to 15-fold) than in the HIV-negative population.

Despite lymphomas being common cancers in HIV-positive populations, the mechanisms driving their pathogenesis in the HIV-positive setting are poorly understood. Untreated HIV infection causes disruption to the immune system, characterized by hypergammaglobulinaemia, immune deficiency, immune dysfunction, senescence, chronic immune activation (or T-cell activation) and inflammation, several of which are thought to be drivers of the development of B-cell malignancies [4,13–17]. Increased B-cell activation and proliferation also lead to increased synthesis of antibodies [18], which consist of two light chain immunoglobulins (Igs) bound to two heavy-chain immunoglobulins (IgG, IgA, IgM, IgD or IgE). During immunoglobulin production, more light chains are produced than heavy chains, and excess unbound light chains [known as free light chains (FLCs)] enter the circulation, where both immunoglobulins and FLCs can be detected in serum [19]. There are two types of FLC, kappa (FLC-κ) and lambda (FLC-λ) [20], which are markers of nonspecific polyclonal B-cell activation and hypergammaglobulinaemia, both of which have been linked to HIV disease severity and lymphoma development [19,21–24].

While HIV-associated immune deficiency, B-cell dysfunction, B-cell activation, and reactivation of latent EBV infection all play a role in lymphoma development, it is unclear whether HIV-related factors facilitate B-cell proliferation which promotes EBV expansion or if ongoing EBV replication directly causes immune activation prior to lymphoma development, or there is a combination of both. This study aimed to investigate the relationship between B-cell activation, as demonstrated by increased levels of immunoglobulins and FLCs, and the subsequent risk of lymphoma development in HIV-positive people.

Methods

The EuroSIDA study

EuroSIDA is a prospective, observational, open cohort study of more than 22 000 HIV-positive people aged > 16 years in 107 centres across 35 European countries, Israel and Argentina recruited since May 1994 (details at www.cphiv.dk). Informed consent was obtained from all patients. Basic demographic, clinical and laboratory data are collected every 6 months, including all CD4 counts and HIV RNA viral loads measured since last follow-up, starting and stopping dates of all antiretroviral drugs, and dates of AIDS-defining diagnoses [using the 1993 Centers for Disease Control and Prevention (CDC) clinical definition, including AIDS-defining malignancies (ADM)]. All new non-AIDS-defining diagnoses (including HL) [25] have been collected since 2001. All reported malignancies were source verified against case notes at the sites by members of the coordinating office to ensure data accuracy. Loss to follow-up in EuroSIDA is < 5% per 100 person-years of follow-up (PYFU) and is consistent over time [26]. EuroSIDA has an established biobank, where prospective plasma samples have been collected at approximate 6-monthly intervals. This sample repository currently holds more than 78 000 plasma samples from 8300 patients.

Nested case–control study

A 1:2 nested case–control study was performed within the EuroSIDA cohort utilizing stored plasma samples to investigate the kinetics and predictive value of several markers of immune activation: FLC-κ, FLC-λ, IgG, IgA, IgM and IgD. Both cases and controls were selected from

HIV-positive people enrolled in EuroSIDA with prospective follow-up after 1 January 2001. Eligible people with a primary diagnosis of lymphoma after 1 January 2001 were considered as cases. For each case, two matched controls (where available) were selected from eligible people with no history of NHL or HL at the time of diagnosis for each case (referred to as the "selection date" of the matched controls). Both cases and controls were required to have at least one plasma sample available prior to the diagnosis date (or selection date in controls). Cases and controls were matched on region of Europe, gender, date of earliest plasma sample (± 2 years), date of latest plasma sample (± 2 years), age at earliest plasma sample (± 5 years), and CD4 cell count at earliest plasma sample (± 200 cells/μL). The windows used for matching were selected to allow suitable identification of controls while ensuring as few cases as possible were excluded from analyses. All available serial samples for cases and controls prior to the date of lymphoma diagnosis or selection date in controls were considered for inclusion. Where more than one plasma sample was available during the same calendar year, one plasma sample was randomly selected. The date of the earliest plasma sample was considered as baseline. We initially selected 73 cases and 143 controls (three cases had only one suitable control available) with 600 samples for inclusion. However, six samples were not available and 594 samples were analysed.

Laboratory markers

Serial samples for cases and controls were analysed for FLC-κ, FLC-λ, IgG, IgA, IgM and IgD. All biomarkers were centrally measured by a technician blinded to case/control status on frozen stored plasma at the Department of Clinical Biochemistry at Rigshospitalet. FLC (the κ and λ Freelite® turbidimetric/nephelometric immunoassay The Binding Site Group Ltd (Birmingham, UK); product codes: LK016.S and KL018.S), IgG (NK004.S), IgA (NK010.S), IgM (NK012.S) and IgD (LK013.S) concentrations were measured on plasma in all patients using the Immunoassay from Binding Site Group Ltd (Birmingham, UK) on the SPAPLUS® (The Binding Site Group Ltd).

Statistical analysis

We considered the relationship between FLC-κ, FLC-λ, the ratio of FLC-κ to FLC-λ (FLC-κ/λ), the sum of FLC-κ and λ (FLC-κ+λ), IgG, IgA, IgM and IgD and lymphoma development.

Unadjusted conditional logistic regression models were used to investigate the association between the odds of developing lymphoma and a higher level of each marker using samples that were collected ≤ 2 and > 2 years prior to lymphoma diagnosis or selection date in controls. In the case where more than one sample was available within the same time period, one was randomly selected. Many other studies have used the upper limit of normal to identify high marker levels; however, it was decided not to use this approach as these limits have been validated in the HIV-negative population only. Instead, marker levels were investigated on the $\log_2$ scale, giving an odds ratio (OR) which corresponded to a 2-fold increase (or a doubling) of each marker level. Polyclonal elevations in FLCs refer to proportionately elevated levels of FLC-κ and FLC-λ, defined as FLC-κ > 19.4 mg/L and FLC-λ > 26.3 mg/L and FLC-κ/λ between 0.26 and 1.65. Monoclonal elevations in FLCs refer to a disproportionately higher level of one FLC, defined as FLC-κ > 19.4 mg/L or FLC-λ > 26.3 mg/L and FLC-κ/λ not between 0.26 and 1.65.

The area under the receiver–operator curve statistic (c-statistic) was calculated to determine the predictive value of each marker. Predictive ability was classified as follows: c-statistic 0.51–0.6, poor; 0.61–0.7, poor–moderate; 0.71–0.8, moderate; 0.81–0.9, good; 0.9–1, excellent. This calculation was performed for each marker using plasma samples collected ≤ 2 and > 2 years prior to lymphoma diagnosis or selection date in controls.

The percentage change for each marker over calendar time (% change per year) in the period prior to diagnosis or selection date in controls was investigated using mixed models with random slopes and intercepts (accounting for multiple measurements within each person).

Patient factors associated with higher B-cell activation marker levels were assessed using mixed models. In order to minimize bias resulting from our nested case–control study design (leading to a nonrepresentative patient population where 1 in 3 develop a lymphoma), this analysis of factors was restricted to controls only. Factors investigated included current age, gender, region of Europe, current use of cART (defined as at least three antiretroviral drugs), current and nadir CD4 cell counts, current HIV viral load (HIV-VL), and area under the curve (AUC) of HIV-VL. AUC of HIV-VL is a measure of accumulated exposure to replicating HIV [27]. All statistical tests were two-sided with a type I error rate of 5%. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of cases and controls

Characteristics of cases (n = 73; 52 with NHL and 21 with HL) and controls (n = 143) are shown in Table 1. There

Table 1 Baseline characteristics of cases and controls

Factor	Overall (n = 216) n (%)	Cases (n = 73) n (%)	Controls (n = 143) n (%)	P-value
Categorical variables				
Male gender†	193 (89.4)	65 (89.0)	128 (89.5)	NA
Risk group				
Homosexual	114 (52.8)	41 (56.2)	73 (51.0)	0.39
Other	102 (47.2)	32 (43.8)	70 (49.0)	
White race	180 (83.3)	56 (76.7)	124 (86.7)	0.06
Region of Europe†				
South‡	46 (21.3)	16 (21.9)	30 (21.0)	NA
West–central	75 (34.7)	25 (34.2)	50 (35.0)	
North	72 (33.3)	24 (32.9)	48 (33.6)	
East–central	21 (9.7)	7 (9.6)	14 (9.8)	
East	2 (0.9)	1 (1.4)	1 (0.7)	
Prior AIDS-defining event (excluding NHL) [1]	60 (27.8)	23 (31.5)	37 (25.9)	0.33
Prior non-AIDS-defining event (excluding HL) [2]	5 (2.3)	2 (2.7)	3 (1.4)	0.88
Hepatitis C				
Positive	46 (21.3)	7 (9.6)	39 (27.3)	0.02
Negative	128 (59.3)	50 (68.5)	78 (54.5)	
Unknown	42 (19.4)	16 (21.9)	26 (18.2)	
Hepatitis B				
Positive	17 (7.9)	8 (11)	9 (6.3)	0.22
Negative	171 (79.2)	53 (72.6)	118 (82.5)	
Unknown	28 (13.0)	12 (16.4)	16 (11.2)	
On cART	158 (73.1)	46 (63.0)	112 (78.3)	0.02

Numerical variables	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	P-value
Age (years)†	216	42.2 (36.9, 49.7)	73	42.6 (37.0, 50.5)	143	41.8 (36.6, 49.3)	0.47
CD4 (cells/μL)†	216	317.5 (208.0, 477.0)	73	316.0 (180.0, 500.0)	143	319.0 (213.0, 461.0)	0.06
First sample date†	216	11DEC1999 (20JUL1998, 09OCT2004)	73	15NOV1999 (24JAN1998, 16JUL2004)	143	25JAN2000 (28JUL1998, 14OCT2004)	0.67
eGFR	53	97.1 (77.2, 104.4)	19	98.6 (61.9, 107.4)	34	95.4 (79.9, 104.1)	0.82
Nadir CD4 count (cells/mm^3)	216	120.0 (44.0, 228.0)	73	179.0 (55.0, 280.0)	143	101.0 (40.0, 200.0)	0.37
AUC of CD4 count (cells x year/mm^3)	216	1092 (477.7, 1943)	73	860.7 (395.3, 1585.9)	143	1181.1 (573.9, 2284.5)	0.08
HIV viral load (copies/mL)	206	215.0 (< 50, 2100)	68	671.5 (79.5, 10993.5)	138	140.0 (< 40, 848.0)	< 0.01
AUC of HIV viral load (copies × year/mL)	206	18269 (3671, 11×10^4)	68	35983.7 (4255.5, 130491.8)	138	15212.8 (3442.2, 100042.1)	0.51
Duration of time on cART (years)	216	1.4 (0.2, 3.1)	73	0.9 (0.0, 2.5)	143	1.7 (0.4, 3.3)	< 0.01
Marker levels							
Baseline FLC-κ (mg/L)	213	32.0 (23.4, 50.5)	71	39.9 (28.1, 62.1)	142	29.4 (20.8, 41.0)	< 0.01
Latest FLC-κ (mg/L)	213	34.9 (21.3, 55.1)	71	36.7 (24.5, 57.0)	142	33.1 (20.1, 54.8)	0.68
Baseline FLC-λ (mg/L)	214	21.8 (14.5, 31.4)	72	27.7 (19.2, 45.0)	142	18.6 (13.7, 27.2)	< 0.01
Latest FLC-λ (mg/L)	214	21.8 (13.7, 34.3)	72	24.5 (17.2, 40.1)	142	21.3 (12.9, 31.7)	0.87
Baseline FLC-κ (mg/L)	213	1.6 (1.2, 2.0)	71	1.6 (1.2, 2.0)	142	1.6 (1.2, 2.1)	0.12
Latest FLC-κ (mg/L)	214	1.6 (1.3, 2.1)	72	1.6 (1.2, 2.0)	142	1.7 (1.3, 2.2)	0.81
Baseline FLC(mg/L)	213	53.4 (39.3, 80.8)	71	69.6 (49.6, 99.5)	142	48.2 (36.7, 67.6)	< 0.01
Latest FLC(mg/L)	214	56.9 (38.3, 90.3)	72	63.5 (41.1, 92.0)	142	53.9 (35.5, 84.9)	0.75
Baseline IgG (g/L)	214	14.3 (11.1, 17.8)	72	15.8 (12.5, 19.6)	142	13.2 (10.3, 16.9)	< 0.01
Latest IgG (g/L)	214	13.0 (10.5, 17.1)	72	14.4 (11.5, 18.2)	142	12.8 (10.1, 16.4)	0.18
Baseline IgA (g/L)	214	2.2 (1.5, 3.6)	72	2.7 (1.5, 3.8)	142	2.2 (1.6, 3.3)	0.34
Latest IgA (g/L)	214	2.3 (1.4, 3.4)	72	2.5 (1.3, 3.5)	142	2.2 (1.5, 3.4)	0.28
Baseline IgM (g/L)	214	0.8 (0.5, 1.3)	72	1.1 (0.7, 1.7)	142	0.8 (0.5, 1.1)	0.02
Latest IgM (g/L)	214	0.8 (0.5, 1.3)	72	0.8 (0.5, 1.5)	142	0.8 (0.5, 1.2)	0.86
Baseline IgD (g/L)	214	28.5 (6.7, 58.9)	72	39.2 (9.0, 60.3)	142	26.0 (6.7, 58.2)	0.12
Latest IgD (g/L)	214	21.9 (7.2, 59.8)	72	24.5 (10.7, 87.1)	142	21.0 (6.7, 53.9)	0.29

AUC, area under the curve; cART, combination antiretroviral therapy; eGFR, estimated glomerular filtration rate; FLC, free light chain; HL, Hodgkin's lymphoma; Ig, immunoglobulin; IQR, interquartile range; NHL, non-Hodgkin's lymphoma.
†Matching variable.
‡Includes Israel and Argentina.

was a median of 2.0 years [interquartile range (IQR) 0.4, 3.1 years] between the first and last plasma samples [cases: 2.1 years (IQR 0.6, 4.4 years); controls: 1.8 years (IQR 0.0, 4.3 years); P = 0.72] and a median of 1.3 years (IQR 0.3, 2.9 years) between the last sample and the date of lymphoma diagnosis in cases. Cases differed from

controls according to HIV-related factors, including HIV-VL and treatment. Median HIV-VL was higher in cases than controls and a lower proportion of cases than controls were on cART at baseline (63.0 *vs.* 78.3%, respectively). The median duration of cART was also lower in cases (0.9 years; IQR 0.0, 2.5 years) than in controls (1.7 years; IQR 0.4, 3.3 years). At the earliest sample, median levels of FLC-κ, FLC-λ and FLC-κ+λ were elevated in cases relative to controls; however, the median FLC-κ/λ ratio was similar. Levels of IgG and IgM were also elevated in cases; however, levels of IgA and IgD were similar in cases and controls. In addition, a lower proportion of cases were hepatitis C virus (HCV) positive compared with controls (9.6 *vs.* 27.3%, respectively). Cases and controls were well balanced in terms of other nonmatched demographic characteristics. There was no difference in the levels of any B-cell markers at the latest sample (all $P > 0.05$).

OR of developing a lymphoma during prospective follow-up

The OR of developing lymphoma for a 2-fold higher marker level both ≤ 2 and > 2 years before lymphoma diagnosis or selection date in controls is shown in Figure 1. Two-fold higher levels of FLC-κ [OR 1.84; 95% confidence interval (CI) 1.19, 2.84], FLC-λ (OR 2.15; 95% CI 1.34, 3.46), IgG (OR 3.05; 95% CI 1.41, 6.59) and IgM (OR 1.46; 95% CI 1.01, 2.11) were predictive of lymphoma development > 2 years prior to diagnosis. However, associations were not evident ≤ 2 years prior to diagnosis. No association was found for 2-fold higher IgA or IgD (although the *P*-value was close to 0.05 for the association > 2 years prior for IgD) at either time-point. FLC-κ+λ (OR 2.08; 95% CI 1.30, 3.35) was predictive > 2 years but not ≤ 2 years prior to lymphoma diagnosis. The ratio of FLC-κ/λ was not predictive at either > 2 years or ≤ 2 years prior to diagnosis. Proportionately high levels of both FLC-κ and FLC-λ were associated with lymphoma > 2 years prior to diagnosis (OR 4.74; 95% CI 1.71, 27.56), but not ≤ 2 years prior (OR 1.62; 95% CI 0.54, 5.05). Having a disproportionately high level of one FLC was not associated with lymphoma at either time-point.

Of the HIV-related markers, HIV-VL AUC was associated with a higher risk in samples obtained ≤ 2 years prior to diagnosis; however, HIV-VL was predictive > 2 years prior. In those who had HIV-VL measured, a 10-fold higher HIV-VL was predictive of lymphoma development > 2 years prior to development (OR 1.51; 95% CI 1.1, 2.08), but not ≤ 2 years prior (OR 1.31; 95% CI 0.99, 1.75), whereas for a 10-fold higher AUC of HIV-VL, there was no association > 2 years prior to diagnosis (OR 1.25; 95% CI 0.93, 1.67), but a 1.68-fold higher odds of lymphoma ≤ 2 years prior to diagnosis (95% CI 1.08, 2.62).

Predictive value of B-cell markers

The marker with the best predictability > 2 years prior to lymphoma diagnosis was FLC-λ (Table 2). This marker predicted lymphoma diagnosis with better accuracy than chance alone ($P < 0.01$); however, the c-statistic of 0.67 suggests only poor–moderate classification power. The following markers also had some predictive power (all $P < 0.05$); however, prediction was poor to moderate at best: FLC-κ+λ (c-statistic 0.67; poor–moderate prediction), and IgG (c-statistic 0.64; poor–moderate). Only FLC-λ (c-statistic 0.61) predicted lymphoma ≤ 2 years prior to diagnosis; however, accuracy was poor. No other markers were predictive (all $P > 0.05$).

Trajectories of B-cell markers prior to lymphoma diagnosis

The trajectories of each marker in the cases and controls and unadjusted per cent change per year for each marker in the time leading up to diagnosis or selection date in controls are shown in Figure 2. In unadjusted analysis, the largest difference was observed for IgM, which was declining in cases by 6.42% (95% CI 3.12, 9.61%) per year, but levels were stable in controls (per cent change per year 0.40%; 95% CI −2.09, 2.95%). The difference in the rate of change per year between cases and controls was statistically significant (*P* for interaction < 0.01). Levels of IgG were also declining in cases, but were stable in controls, which was a borderline significant difference in the rate of change per year (*P* for interaction = 0.10). Although levels of FLC-κ were stable in cases but increasing in controls, the difference in the rate of change per year between cases and controls was non-significant (*P* for interaction = 0.20). The ratio of FLC-κ/λ was increasing in cases, but was stable in controls, and, conversely, FLC-κ+λ was increasing in controls but stable in cases; however, the differences in the rate of change per year between cases and controls were not significant (*P* for interaction = 0.44 and 0.16, respectively). Levels of FLC-λ, IgA, and IgD did not change over time in either cases or controls. In those who had an HIV-VL measured ($n = 586$ samples in 214 people), HIV-VL levels were high many years prior to diagnosis (Figure 2), and significantly declined in cases in the time leading up to diagnosis, whereas levels were stable in controls; however, this difference was not significant ($P = 0.11$). The level of current CD4 cell count was stable in both cases and controls. The results were similar after adjustment for

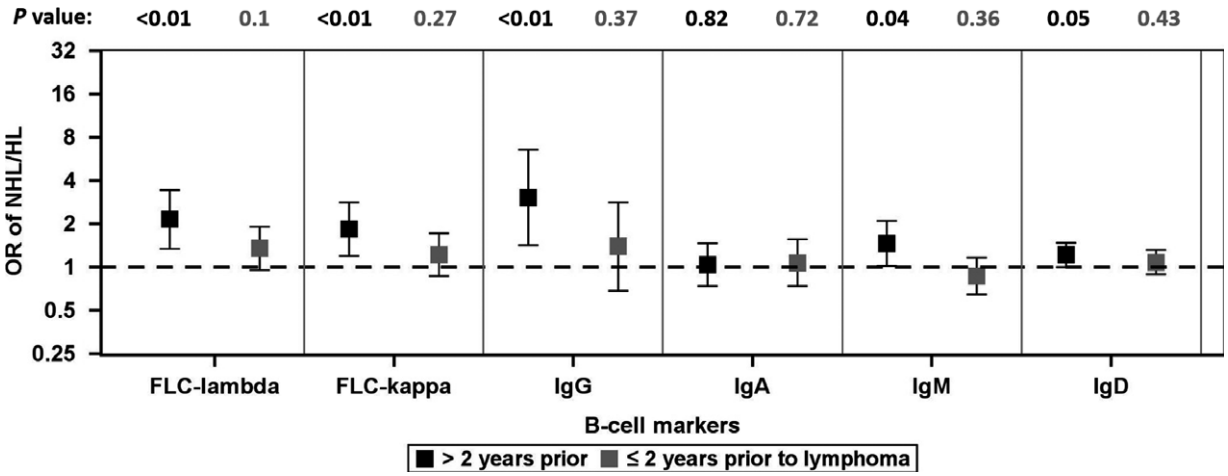

Figure 1 Odds ratio (OR) of lymphoma associated with a 2-fold increase in B-cell markers, ≤ 2 and > 2 years prior to diagnosis. FLC, free light chain; HL, Hodgkin's lymphoma; Ig, immunoglobulin; NHL, non-Hodgkin's lymphoma.

matching variables (data not shown). Further adjustment for current CD4, age and HIV treatment variables also produced consistent results (data not shown).

Patient factors associated with higher B-cell activation marker levels in controls

Demographic and HIV-related factors that were associated with B-cell marker levels in the control population are shown in Table 3. For each factor, the adjusted fold change in marker level is presented. For example, those from southern Europe had on average a 1.46-fold higher marker level compared with those from west–central Europe. Higher levels of FLC-κ, FLC-λ, and IgG were associated with HIV transmission modes other than men who acquired HIV through sex between men (MSM), lower current CD4 cell count, higher current HIV-VL, and not being on cART (borderline for FLC-λ). FLC-κ and FLC-λ levels also increased with older age. Higher IgA level was associated with lower CD4 cell count and higher AUC of HIV-VL. Higher IgM level was associated with higher HIV-VL, not being on cART, and HIV transmission mode other than MSM. Higher IgD level was associated with higher AUC of HIV-VL only.

Discussion

This study investigated the trajectories of FLC-κ, FLC-λ, IgG, IgA, IgM, and IgD over time prior to lymphoma diagnosis. We have shown that the strength of the association diminished consistently with time leading up to diagnosis. Levels of FLC-κ, FLC-λ, and IgG were associated with lymphoma development in HIV-positive people > 2 years prior to lymphoma development. However, the magnitude of the associations was moderate, and poorly predicted lymphoma development. The markers investigated in this study, therefore, are unlikely to be strong candidates for risk assessment for targeted interventions.

Table 2 c-statistics for prediction of lymphoma diagnosis for each marker, stratified by < 2 years prior to diagnosis and ≤ 2 years prior to diagnosis

	≥ 2 years		< 2 years	
B-cell markers	c-Statistic	*P**	c-Statistic	*P**
FLC-κ	0.65 (0.56, 0.74)	0.29	0.56 (0.45, 0.66)	0.29
FLC-λ	0.67 (0.58, 0.76)	< 0.01	0.61 (0.51, 0.71)	0.04
Ratio FLC-κ/λ	0.53 (0.43, 0.62)	0.60	0.54 (0.43, 0.64)	0.48
Sum FLC-$\kappa+\lambda$	0.67 (0.58, 0.76)	< 0.01	0.58 (0.47, 0.68)	0.15
IgG	0.64 (0.55, 0.73)	< 0.01	0.55 (0.45, 0.65)	0.32
IgA	0.52 (0.42, 0.62)	0.65	0.50 (0.40, 0.61)	0.94
IgM	0.59 (0.49, 0.69)	0.09	0.52 (0.41, 0.63)	0.70
IgD	0.58 (0.49, 0.68)	0.10	0.54 (0.44, 0.64)	0.43

FLC, free light chain; Ig, immunoglobulin.
**P* compares the c-statistic for each marker to 0.5 (i.e. prediction is no better than chance).

Proportionately higher levels of both FLC-κ and FLC-λ (indicating polyclonal expansion) were associated with lymphoma > 2 years prior to diagnosis. Two main studies have also demonstrated that elevated levels of FLC-κ and FLC-λ are associated with a higher likelihood of lymphoma in HIV-positive people [23,24]. The study by Landgren *et al.* [24] found that elevated FLC-κ and FLC-λ were associated with NHL 2–5 years prior to diagnosis; conversely, only FLC-λ was associated with NHL 0–2 years prior to diagnosis [24]. However, a later study by the same group found FLC-κ and FLC-λ levels to be

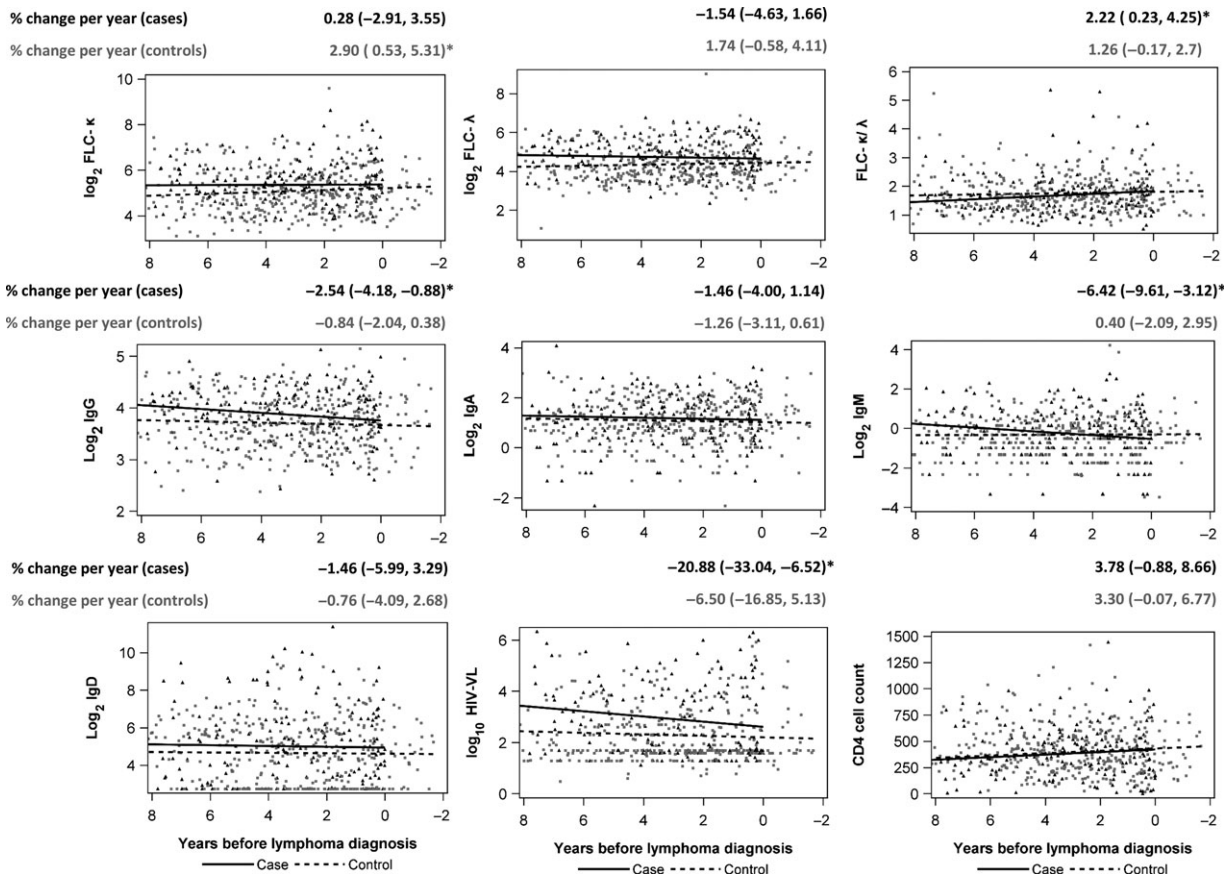

Figure 2 Trajectories of free light chain (FLC)-κ and FLC-λ, FLC-κ/λ, immunoglobulin G (IgG), IgA, IgM, IgD, current HIV viral load (HIV-VL) and CD4 count prior to the Selection date. The unadjusted percentage change per year in each marker per year (i.e. the slope) in the time leading up to diagnosis is shown at the top of each panel. **P* for change < 0.05: this is testing whether there is a significant increase or decline in the markers over time. *P* for interaction: this tests whether the per cent change per year is different in cases and controls. FLC-κ: 0.2; FLC-λ: 0.1; ratio FLC-κ/λ: 0.44; IgG: 0.10; IgA: 0.90; IgM: < 0.01; IgD: 0.81; current HIV-VL: 0.11; current CD4 cell count: 0.87.

similarly predictive of all AIDS-defining events and not specifically NHL [22]. Results were consistent in the more recent study by Bibas *et al.* (2012), who found FLC-κ and FLC-λ to be predictive of both NHL and HL independently of CD4 cell count and HIV-VL. Our findings that FLC-κ and FLC-λ are predictive of lymphoma in the long term are somewhat consistent with those of Landgren *et al.* and Bibas *et al.*; however, we did not find an association with FLC-λ closer to diagnosis. Furthermore, our finding that polyclonal FLC elevations preceded lymphoma development is also consistent with those of both studies [23,24].

Our results demonstrated an association between IgG and IgM > 2 years prior to the date of lymphoma diagnosis (although the association with IgM was borderline), which attenuated closer to this date. This was driven by a faster decline in levels in cases while controls remained stable. Studies have found mixed associations between immunoglobulins and lymphoma in HIV infection. For example, an Australian study found that high levels of serum globulin, mainly IgG, were predictive of NHL [28]. However, other studies found no association between serum globulin, immunoglobulins and NHL [24,29,30].

The attenuation of associations between markers of B-cell activation ≤ 2 years prior to diagnosis and lymphoma may simply be reflecting a 2-year lag period for an increase in B-cell activity to manifest as a clinically detectable lymphoma [23]. However, it is more likely that the observed trends are signifying the concurrent, but very different, immune consequences induced by HIV infection and lymphoma development and disentangling this relationship is not straightforward. HIV-related immune dysfunction is associated with elevated serum levels of immunoglobulins, mainly IgG but also IgA and

Table 3 Multivariate analysis of the fold change in marker levels associated with patient factors

	Fold change in FLC-κ (95% CI)	*P*	Fold change in FLC- λ (95% CI)	*P*	Fold change in IgG (95% CI)	*P*	Fold change in IgA (95% CI)	*P*	Fold change in IgM (95% CI)	*P*	Fold change in IgD (95% CI)	*P*
Age (1 year older)	1.25 (1.13, 1.38)	< 0.01	1.14 (1.03, 1.26)	0.01	1.00 (0.94, 1.05)	0.89	0.96 (0.87, 1.06)	0.47	1.06 (0.95, 1.17)	0.29	0.84 (0.70, 1.02)	0.08
Region												
South	1.46 (1.10, 1.95)	0.01	1.45 (1.08, 1.95)	0.01	1.31 (1.12, 1.52)	< 0.01	0.98 (0.74, 1.30)	0.91	1.24 (0.92, 1.67)	0.15	1.06 (0.61, 1.84)	0.85
North	1.20 (0.95, 1.52)	0.12	1.25 (0.98, 1.59)	0.07	1.20 (1.06, 1.37)	< 0.01	1.16 (0.92, 1.46)	0.22	1.12 (0.88, 1.44)	0.35	1.01 (0.64, 1.59)	0.98
East and east–central	1.11 (0.77, 1.59)	0.58	0.99 (0.69, 1.44)	0.98	1.15 (0.95, 1.40)	0.14	1.11 (0.78, 1.59)	0.55	1.66 (1.15, 2.41)	< 0.01	0.53 (0.26, 1.07)	0.08
West–central	Reference		Reference		Reference		Reference		Reference		Reference	
Female gender	1.03 (0.73, 1.46)	0.87	0.88 (0.61, 1.25)	0.47	0.97 (0.81, 1.17)	0.76	0.90 (0.64, 1.27)	0.55	1.17 (0.81, 1.67)	0.41	1.14 (0.58, 2.23)	0.71
Non-white ethnicity	0.90 (0.65, 1.23)	0.5	0.92 (0.66, 1.27)	0.6	1.06 (0.89, 1.26)	0.51	0.74 (0.54, 1.02)	0.07	0.84 (0.60, 1.17)	0.3	0.87 (0.47, 1.61)	0.65
Non-MSM transmission mode	1.33 (1.07, 1.66)	0.01	1.36 (1.09, 1.70)	< 0.01	1.19 (1.06, 1.34)	< 0.01	0.87 (0.70, 1.07)	0.19	1.34 (1.07, 1.68)	0.01	0.99 (0.65, 1.50)	0.95
Current CD4 count (2-fold higher)	0.91 (0.86, 0.97)	< 0.01	0.91 (0.86, 0.96)	< 0.01	0.97 (0.94, 0.99)	0.02	0.92 (0.88, 0.97)	< 0.01	0.96 (0.90, 1.02)	0.15	0.93 (0.85, 1.02)	0.13
Nadir CD4 count (2-fold higher)	1.00 (0.95, 1.06)	0.92	1.01 (0.96, 1.08)	0.63	0.99 (0.96, 1.02)	0.68	0.98 (0.93, 1.04)	0.53	1.06 (1.00, 1.13)	0.05	0.99 (0.88, 1.10)	0.82
Current HIV-VL												
Missing	1.39 (0.76, 2.53)	0.29	1.54 (0.88, 2.68)	0.13	1.15 (0.85, 1.55)	0.37	0.99 (0.59, 1.66)	0.97	1.36 (0.75, 2.49)	0.31	1.13 (0.43, 2.99)	0.8
Low: < 500 copies/mL	0.86 (0.78, 0.94)	< 0.01	0.86 (0.79, 0.94)	< 0.01	0.92 (0.88, 0.96)	< 0.01	1.02 (0.94, 1.11)	0.63	0.72 (0.66, 0.80)	< 0.01	1.09 (0.94, 1.27)	0.25
High: ≥ 500 copies/mL	Reference		Reference		Reference		Reference		Reference		Reference	
AUC of HIV-VL												
Missing	0.81 (0.48, 1.36)	0.42	0.73 (0.45, 1.19)	0.21	0.82 (0.63, 1.07)	0.15	0.82 (0.52, 1.28)	0.38	0.66 (0.39, 1.11)	0.12	0.67 (0.29, 1.59)	0.37
Low: < 50%	0.91 (0.78, 1.05)	0.2	0.96 (0.83, 1.10)	0.53	0.95 (0.88, 1.02)	0.16	0.85 (0.74, 0.97)	0.02	0.88 (0.76, 1.02)	0.09	0.75 (0.59, 0.97)	0.03
High: ≥ 50%	Reference		Reference		Reference		Reference		Reference		Reference	
Not on cART	1.25 (1.07, 1.47)	< 0.01	1.16 (0.99, 1.35)	0.06	1.15 (1.06, 1.25)	< 0.01	0.98 (0.85, 1.14)	0.83	1.29 (1.09, 1.52)	< 0.01	0.98 (0.75, 1.28)	0.88

Models were adjusted for all variables listed in the table.
MSM, men who have sex with men; AUC, area under the curve; cART, combination antiretroviral therapy; CI, confidence interval; FLC, free light chain; Ig, immunoglobulin; VL, viral load.

IgD [16]. Conversely, studies in the general population have found lower levels of IgM, IgA and IgG prior to lymphoma diagnosis [31], and levels declined with more advanced disease [32], which was speculated to be driven by the developing lymphoma. Additionally, transformed B cells may have compromised immunoglobulin production and levels may not reflect the immune environment in which the lymphoma was initiated [32]. Therefore, it is possible that the decline in marker levels ≤ 2 years prior to diagnosis may be a consequence of early undiagnosed lymphoma. A similar phenomenon has been reported for undiagnosed HL and declining CD4 cell counts within 1–2 years prior to diagnosis [33,34].

Current HIV-VL was found to be a strong predictor of lymphoma risk > 2 years prior to diagnosis; however, AUC of HIV-VL was a predictor ≤ 2 years prior to diagnosis. Our results support the strong association between cumulative HIV-VL and AIDS-related lymphoma identified in previous studies [35]. Furthermore, elevated levels of FLC-λ, FLC-κ, and IgG were associated with higher current HIV-VL and lower current CD4 count in controls, which is consistent with other studies [23,36]. This may indicate that a history of uncontrolled HIV-VL plays an integral role in lymphoma development, and elevated FLCs reflect HIV-specific B-cell dysfunction [37] occurring long before diagnosis. Furthermore, HIV-specific B-cell dysfunction may contribute to lymphoma development by facilitating the reactivation of latent EBV, resulting in the long-term stimulation and proliferation of impaired B cells [38].

The major strength of our study is the availability of serial plasma samples collected prior to and independently of lymphoma diagnosis, as well as the inclusion of a comparatively large number of lymphomas from contemporary HIV-positive individuals. However, the limitations need to be considered. Firstly, it is possible that changes in FLCs and immunoglobulins reflect undiagnosed or late diagnosed cancer rather than preceding cancer development. In this study, we grouped NHL and HL together as we did not have the numbers to investigate them separately. Furthermore, FLCs are excreted from the kidneys and therefore levels are possibly affected by renal function [39]. Measurements of estimated glomerular filtration rate (eGFR) were only available for one-third of samples (175 of 592; prospective collection of serum creatinine measurements to calculate eGFR started in 2004); however, in people with eGFR measurements available, there was no evidence of a difference in eGFR between cases and controls at baseline. Cases were less likely to be on treatment than controls and a lower proportion were HCV-positive. HCV infection is associated with several B-cell disorders, including cryoglobulinaemia and B-cell NHL, and elevated levels of FLC-κ and an abnormal FLC ratio have been associated with the severity of B-cell dysfunction in HCV-positive people [40,41]. Therefore, the higher HCV prevalence in the control group may result in an underestimation of the effects. Further adjustment for potential confounders was not possible, although no other significant imbalances were evident at baseline. Baseline CD4 count was included as a matching factor in order to investigate the independent associations between B-cell activation and lymphoma development; however, it should be kept in mind that this may result in an underestimate of the association between markers of B-cell activation and lymphoma development.

In conclusion, FLC-λ, FLC-λ and IgG were higher > 2 years before lymphoma diagnosis, but the difference diminished nearer diagnosis. B-cell dysfunction, as demonstrated by polyclonal hyperglobulinaemia, occurs many years prior to lymphoma development. The trajectories of FLC-κ, FLC-λ, IgG, IgA, IgM and IgD over time prior to lymphoma diagnosis show that the strength of association diminishes consistently with time leading up to diagnosis. The magnitude of the associations was moderate at best, and poorly predicted lymphoma development. The markers investigated are unlikely to be strong candidates for risk assessment for targeted interventions.

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Appendix 1: EuroSIDA in EuroCOORD

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