Non-Hodgkin lymphoma risk in adults living with HIV across five continents: a multicohort study

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Abstract

Objective: To compare non-Hodgkin lymphoma (NHL) incidence rates in adults who started antiretroviral therapy (ART) across the Asia-Pacific, South Africa, Europe, Latin, and North America.

Methods: We included cohort data of adults living with HIV who started ART after 1995 within the framework of the International epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). We used flexible parametric survival models to compare regional NHL rates at 2 years after ART start and to identify risk factors for NHL.

Results: We included 210,898 adults with 1.1 million person-years (pys) of follow-up and 1,552 incident NHL cases (raw overall incidence rate 142/100,000 pys). After adjusting for age at ART start, first-line ART regimen, calendar period of ART start, and especially current CD4 cell count, NHL rates were similar across regions for most population groups. However, South African women remained at increased risk of developing NHL compared with their European counterparts (adjusted hazard ratio [aHR] 1.79, 95% CI 1.19–2.70). In Europe, Latin and North America, NHL risk was highest in men who have sex with men (MSM, aHR 1.30, 95% CI 1.14–1.48), followed by heterosexual men (referent), and women (aHR 0.66, 95% CI 0.57–0.78).

Conclusions: The risk of developing NHL is higher in women in South Africa than in Europe and higher in MSM compared with heterosexual men and women. Reasons for these differences remain unclear. Early ART access and regular patient monitoring to avert low CD4 cell counts remain key for NHL prevention.

Keywords

Non-Hodgkin lymphoma; HIV; antiretroviral therapy; cohort study; incidence rates

Introduction

With the introduction of combination antiretroviral therapy (ART) the risk of developing human immunodeficiency virus (HIV)-related non-Hodgkin lymphoma (NHL) has substantially decreased [1–6]. However, NHL is still one of the most common cancers and a frequent cause of death among adults living with HIV [7–10]. The pathogenesis of HIV-related NHL is not well understood, but HIV-induced immune dysregulation and impaired control of oncogenic viruses seem to play an important role [11]. Epstein Barr virus (EBV), human herpesvirus 8 (HHV-8), and hepatitis C virus (HCV) have been recognized as causative agents of NHL, whereas the role of hepatitis B virus (HBV) in lymphomagenesis is being evaluated [12,13]. Prevalence and average age at acquisition of these viruses differ by population and geographic area. For example, EBV infection is typically delayed in high-income countries compared with low- and middle-income countries [12]. HHV-8 is highly prevalent in HIV-positive men who have sex with men (MSM) in most regions but is also common in heterosexual men and women in sub-Saharan Africa [14]. HCV prevalence is high in persons who inject drugs (PWID) [15], and it is increasing in MSM [16]. Furthermore, access to effective ART also varies across geographic regions. Median CD4 cell count at ART start is considerably lower in sub-Saharan Africa and Latin America than in Central Europe and North America [17]. Nevertheless, studies comparing the risk of developing NHL among adults living with HIV across different geographic regions are not available. We compared NHL incidence rates in adults who had started ART in the Asia-Pacific, South Africa, Europe, Latin America, or North America, and assessed factors associated with regional differences in NHL rates.

Methods

We analyzed cohort data from the International epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. For further information on data collection and merging, see Supplementary Box S1. We included adults (16 years old) living with HIV who started ART after cohort enrollment from 1996 onwards. Incident NHL was defined as NHL diagnosed after ART start. Person-years were measured from ART start to the first occurrence of NHL, last visit, death, or database closure. In a sensitivity analysis, we excluded NHL cases diagnosed within the first six months after ART start. We assumed that adults remained on ART throughout follow-up and did not consider treatment interruptions and terminations. We estimated NHL incidence rates in two different ways: i) by dividing the number of incident NHL cases by person-years (pys) at risk (referred to as raw incidence rates), and ii) using proportional hazard flexible parametric survival models [18]. Flexible parametric survival models allow estimating instantaneous NHL incidence rates at given time points and displaying the change in incidence rates over time graphically. Using these models, we estimated regional crude and adjusted NHL incidence rates over time after ART start and identified risk factors for NHL. We modeled the baseline hazard using restricted cubic splines with four degrees of freedom and allowed for time-dependent region effects with two degrees of freedom. We compared crude and adjusted NHL rates at 2 years after ART start across geographic regions and in a sensitivity analysis, we compared regional NHL rates at 5 years after ART start. We used likelihood ratio tests to test whether the effect

of a risk factor on NHL risk differed across regions. We assessed sex, exposure group (MSM, heterosexual men, women), injection drug use (yes, no), age at ART start (continuous variable), first-line ART regimen (non-nucleoside reverse transcriptase inhibitor [NNRTI]-based, protease inhibitor [PI]-based, other), calendar period of ART start (1996–1998, 1999–2003, 2004–2007, 2008–2014), and current (time-varying) CD4 cell count (continuous variable) in regression analyses. We used the last observation carried forward method for current CD4 cell count, i.e. we assumed that CD4 cell counts remained stable until a new measurement became available. CD4 cell count at ART start and HIV RNA load at ART start were assessed in descriptive analyses.

We used models including region and only one additional covariate with or without its interaction with region (referred to as crude models) to compare the burden of incident NHL across regions. Adjusted models with relevant risk factors and their interaction with region (if necessary) were fit to assess remaining differences in regional NHL rates. Variable selection was not automated, but rather based on clinical and epidemiological reasoning as well as data availability and quality. We derived three adjusted models: model 1 included region, sex and its interaction with region, current CD4 cell count and its interaction with region, age at ART start, first-line ART regimen, and calendar period of ART start. Model 2 was restricted to regions with data on sexual orientation and PWID status (i.e. Europe, Latin and North America), and included region, age at ART start, current CD4 cell count, first-line ART regimen, calendar period of ART start, PWID status, and exposure group. To compare exposure group specific NHL rates across regions, we created model 3 by adding an interaction term between exposure group and region to model 2. To account for differences in HIV-related risk factors across regions, we used the fitted models to predict NHL incidence rates for a chosen set of covariates (including region) and different time points. For men and women (model 1), we used the following covariate profile: start of an NNRTI-based regimen between 2008–2014 at age 40 and current CD4 cell count of 450 cells/μl. For MSM, heterosexual men and women (model 3), we chose the following covariate profile: start of an NNRTI-based regimen between 2008–2014 at age 40, no injection drug use, and current CD4 cell count of 450 cells/μl. We present number and percentages of adults, medians with interquartile ranges (IQR), incidence rates per 100,000 pys, and hazard ratios (HRs) with 95% confidence intervals (CI). All analyses were done in STATA 14 (Stata Corporation, USA), and R (R Foundation, Austria).

Results

Descriptive analyses

We received data for 408,395 adults living with HIV enrolled in 49 eligible cohorts in the Asia-Pacific, Australia, Europe, South Africa, Latin and North America. We excluded 133,420 adults who did not start ART and another 64,077 adults for reasons detailed in Supplement Figure S1. We excluded five cohorts with <100 eligible adults and one region with <500 eligible adults (Australia). In a last step, we excluded 1,792 adults who did not have any CD4 cell count measurement. The Asia-Pacific region with 2,638 adults and 9 incident NHL cases was included for descriptive analyses but excluded from regression models.

The descriptive dataset included 210,898 adults from the Asia-Pacific (n=2,638), South Africa (n=21,656), Latin America (n=8,569), North America (n=16,986) and Europe (n=161,049), see Table 1. Total follow-up was 1.1 million pys with a median of 4.1 years per person (IQR 1.7–7.9); 1,552 adults developed NHL after starting ART (Europe 1,225, North America 204, South Africa 63, Latin America 51, Asia-Pacific 9). Age at ART start was similar across regions with a median of 37.3 years (IQR 31.4–44.4). In the Asia-Pacific, Europe, North, and Latin America about 70% of adults were male, whereas in South Africa 63% were female. In Europe, Latin America, and North America, 40% of adults were MSM in contrast to 23% in the Asia-Pacific. Data on MSM and PWID were not available for South Africa. First-line ART regimens differed by region, with NNRTI used by 90% of adults in South Africa and the Asia-Pacific, and about 40% in Europe and North America. Median CD4 cell count at ART start was highest in Europe (250, IQR 126–368) and lowest in South Africa (107 cells/μL, IQR 43–176). While in South Africa and the Asia-Pacific >95% of adults started ART after 2003, 39% of the European and 63% of the North American study population had started ART before 2004 (Table 1).

In adults who developed NHL, median time from ART start to NHL diagnosis was 1.1 years (IQR 0.3–3.6), see Supplementary Table S1. Fifty-seven (4%) adults diagnosed with incident NHL had a history of Kaposi sarcoma (KS); 39 of them (68%) were MSM. Median CD4 cell count at NHL diagnosis was 220 cells/μL (IQR 96–379); median age at NHL diagnosis was 42.8 years (IQR 36.6–50.6). The raw overall NHL incidence rate was 142/100,000 pys (95% CI 135–150). Raw NHL incidence rates per 100,000 pys were similar in Europe (137, 95% CI 130–145), South Africa (116, 95% CI 91–149), Asia-Pacific (116, 95% CI 60–223), and Latin America (112, 95% CI 85–147), but higher in North America (225, 95% 196–258), see Supplementary Table S2. Incidence rates were particularly high (>1,000/100,000 pys) in adults with current CD4 cell counts <50 cells/μL in North America and Europe (Supplementary Table S3). In contrast, in South Africa, NHL incidence rates were relatively low (150/100,000 pys) in adults with CD4 cell counts <50 cells/μL.

NHL risk factors

In all regions (model 1), NHL incidence rates were highest immediately after starting ART and decreased thereafter (Figure 1), but the decrease was less pronounced in South Africa. The effect of sex on the risk of developing NHL differed across regions (p-value for interaction=0.016). Based on both crude and adjusted analyses, NHL rates were higher among men than among women in Europe, Latin, and North America (Table 2). In South Africa, the risk of developing NHL was similar in women and men (aHR 1.13, 95% CI 0.67–1.91, referent: men).

The effect of current CD4 cell counts on the risk of developing NHL also varied by region (model 1, p=0.004). In Europe, Latin and North America, NHL rates decreased with increasing current CD4 cell counts (Table 2). Per 100 cells/μl increase, NHL rates declined by about one-third in Latin America (aHR 0.66, 95% CI 0.55–0.80), North America (aHR 0.65, 95% CI 0.60–0.71) and Europe (aHR 0.72, 95% CI 0.69–0.74). In contrast, no clear association between current CD4 cell count and the risk of developing NHL was found in South Africa (aHR 0.92, 95% CI 0.78–1.08). The effect of age at ART start, calendar period

of ART start, and first-line regimen did not differ across regions (model 1, Supplementary Table S4). In all regions, NHL rates increased with age (per 10-year increase, aHR 1.29, 95% CI 1.23–1.35). NHL rates decreased from the period 1996–1998 to 1999–2003 and remained stable thereafter. There was no evidence for an association between first-line ART regimen and the risk of developing NHL.

In model 2 without South Africa, we explored the effect of exposure group and injection drug use on NHL risk (Table 3, Supplementary Figure S2). In adjusted analyses, MSM had the highest NHL rates, followed by heterosexual men and women. Compared with heterosexual men, the risk of developing NHL was 30% higher among MSM (aHR 1.30, 95% CI 1.14–1.48), and it was 34% lower in women (aHR 0.66, 95% CI 0.57–0.78). The effect of exposure group on the risk of developing NHL did not differ across Europe, North and Latin America (p=0.330). NHL rates were similar in PWID compared with persons who did not inject drugs in crude (HR 0.98; 95% CI 0.84–1.16) and adjusted analyses (aHR 0.94, 95% CI 0.79–1.12). The effect of injection drug use on NHL rates did not vary by region (p=0.121).

Comparison of NHL rates across geographic regions

The risk of developing NHL was higher in South African women than in European women (aHR 1.79, 95% CI 1.19–2.70, at 2 years after starting ART). In male adults, NHL rates were similar in South Africa and Europe. In crude analyses excluding South Africa, NHL rates at 2 years after ART start were higher in North America than in Europe across all exposure groups, see Table 4. However, after adjustment for HIV-related risk factors – in particular current CD4 cell count – NHL rates among North American women (aHR 0.97, 95% CI 0.64–1.49), heterosexual men (aHR 1.26, 95% CI 0.92–1.74) and MSM (aHR 1.20, 95% CI 0.96–1.49) became more comparable to their European counterparts' rates. In Latin American women, NHL rates at 2 years after starting ART were lower than in European women (aHR 0.26, 95% CI 0.09–0.77). Of note, this estimate was based on only four incident NHL cases in Latin American women. Among heterosexual men (aHR 0.72, 95% CI 0.41–1.27) and MSM (aHR 0.84, 95% CI 0.55–1.27) in Latin America, NHL rates were similar to their European counterparts' rates.

Sensitivity analyses

When we excluded NHL cases diagnosed within the first six months after ART start in sensitivity analyses, raw NHL incidence rates decreased (raw overall NHL incidence rate: 100/100,000 pys, 95% CI 94–106, Supplementary Table S5), but the risk factor analyses (Supplementary Tables S6 and S7) and the regional comparison of NHL rates (Supplementary Table S8) remained similar. When comparing NHL rates at 5 years (instead of 2 years) after ART start, the regional NHL incidence pattern did not change much. Women in South Africa still had considerably higher NHL rates than European women (aHR 2.30, 95% CI 1.34–3.95). After adjustment for HIV-related risk factors, NHL rates in all population groups in North America became more similar to their European counterparts' rates, but they remained elevated (Supplementary Table S9).

Discussion

The overall NHL incidence rate in adults who had started ART was 142/100,000 pys. This exceeds the NHL incidence rates of up to 10/100,000 pys reported for a comparable age group (40–44 years) from the general population in the regions included in our analysis [19]. After adjustment for HIV-related risk factors, NHL rates after starting ART were similar among men in all regions. In contrast, NHL rates were higher in South African than in European women. Across Europe, Latin and North America, the risk of developing NHL was highest in MSM, followed by heterosexual men, and women. In South Africa, NHL rates were similar in men and women. With increasing current CD4 cell counts, the risk of developing NHL decreased among adults in Europe, Latin and North America. However, we did not find an association between current CD4 cell count and the risk of developing NHL in South African adults.

Our analysis is based on a large dataset of adults living with HIV in five continents who had started ART, and it is the first analysis providing a direct comparison of NHL rates in adults living with HIV across geographic regions. We restricted our analysis to adults who had started ART without prior NHL, and we adjusted for current CD4 cell count to account for regional differences in ART provision. The age structures of the included adult populations were similar across regions. We accounted for remaining differences by including age at ART start in the adjusted models. However, NHL ascertainment was not standardized across regions with some cohorts using record linkages with cancer registries and others reviewing medical charts and pathology reports to complement their routine data collection. Variation in the completeness of NHL ascertainment across regions might, therefore, have contributed to regional differences in NHL rates. Information on NHL subtypes was unavailable for most regions and subtype-specific analyses were not possible. However, without standardized protocols for histopathological assessments of NHL across regions, subtype-specific analyses might also be of limited value. For South Africa, reliable cancer data were only available for two urban cohorts that had improved their cancer case recording through record linkages with the National Cancer Registry [20]. These data might not be representative for rural areas of South Africa and for other countries in the Southern African region. We did not take into account ART interruptions and terminations, and not all included adults who had started ART will have remained on ART. Therefore, our NHL incidence rate estimates are not necessarily representative for adults who stayed on ART continuously. HIV RNA data were largely missing in some regions and could not be used to assess ART effectiveness. Data on MSM and PWID were not available for South Africa, but in this region, HIV is mainly spread through heterosexual and vertical transmission. Comprehensive data on ethnicity or region of origin were only available for North America or Europe, respectively, and could not be included in our multiregional analyses. Information on other NHL risk factors including time from HIV infection to ART start and sero-status for potentially relevant co-infections such as EBV, HBV, HCV, and HHV-8 were also mostly missing.

Our study confirms that adults who have started ART remain at considerable risk of developing NHL. The overall incidence rate was 142/100,000 pys which is comparable to incidence rates reported from participating [1,2,4,20–22] and other study groups [5,23–25].

We and others have shown that NHL incidence rates are highest within the first six months after starting ART [1], which might be explained by more frequent NHL diagnoses in this time window due to a closer examination of adults at ART start. Other studies have suggested that immune reconstitution inflammatory syndrome may contribute to the increased number of NHL cases in the first months of ART [26,27]. Our study showed that in most regions men had higher NHL rates than women, which is line with findings from the general population [19] and previous studies in HIV-positive populations [1,2,22,28]. In our study, NHL rates in South Africa were about the same in men and women. Previous studies in this region had not assessed the effect of sex on the risk of developing NHL [20,29]. Across all regions where data on exposure group were available, MSM were at highest risk of developing NHL followed by heterosexual men and women. Similar differences in NHL rates by exposure group have been described before in the Swiss HIV Cohort Study [30], the French Hospital Database on HIV [22] and the COHERE in EuroCoord collaboration [2] – data sources also included in the current analysis. We and others [1,2,22,30] did not observe increased NHL rates in PWID. In line with previous studies, we found that across all regions NHL rates increased with age [1,2,22,28] and declined over calendar periods [1,3–6,31]. As previously reported [2,22,26,28,30,32,33,34], we also observed that in most regions the risk of developing NHL decreased with increasing CD4 cell counts. The lack of an association between current CD4 cell count and NHL rates in South Africa was mainly driven by a small number of NHL cases among adults with low CD4 cell counts in that region. This might be due to selection and detection biases. In settings with limited resources, adults with very low CD4 cell counts might die before an NHL diagnosis can be made. In addition, NHL often presents with non-specific symptoms such as weight loss and night sweats, which might be misdiagnosed as tuberculosis, especially in regions where tuberculosis prevalence is high [35,36].

HIV-associated immunosuppression and co-infection with oncogenic viruses play an important role in the pathogenesis of HIV-related NHL [11]. Early access to HIV care and maintenance of high CD4 cell counts are, therefore, key measures to lower the risk of developing NHL [22,23,37]. In our study, population group specific NHL rates were mostly similar across geographic regions when taking into account differences in HIV-related risk factors in these populations. For example, in crude analyses, NHL rates in all population groups were higher in North America than in Europe, but the rates became similar when we adjusted for age at ART start, first-line regimen, calendar period of ART start, and in particular current CD4 cell counts. However, also in adjusted analyses, MSM had higher NHL rates than heterosexual men and women living with HIV. Furthermore, South African women had a higher risk of developing NHL than European women. It remains unclear why the risk of developing NHL is elevated among those population groups. More frequent clinical assessment in MSM compared with other population groups could lead to a detection bias of NHL in MSM. However, a previous study observed the association between MSM and higher cancer risk specifically for NHL, KS, and anal cancer, but not for other cancers [22]. Co-infection patterns might also contribute to the increased NHL rates in MSM and South African women. Both South African women and MSM are at high risk of co-infection with HHV-8 [14], which has been associated with an increased NHL risk. Yet, HHV-8 has only been associated with two NHL subtypes, i.e. primary effusion lymphoma

(PEL) and HHV-8-associated diffuse large B-cell lymphoma, a form of multicentric Castleman's disease [38], and these NHL subtypes are rare entities. For example, PEL represents <5% of all NHLs in HIV-positive populations [39,40]. Therefore, these HHV-8-related NHL subtypes are unlikely to fully explain the increased NHL risk observed among MSM and South African women. HCV has been associated with NHL development [12,13], and its prevalence is increasing in MSM [16], but we did not find increased NHL rates among PWID, the population group at highest risk for HCV co-infection. The role of co-infections in lymphomagenesis is complex and incompletely understood. Dedicated studies including information on co-infection status of adults living with HIV are needed to clarify whether the increased NHL risk we observed among MSM and South African women can be explained by underlying co-infection patterns.

Conclusion

A better understanding of lymphomagenesis and associated etiologic factors is needed to eventually be able to develop specific preventive measures against NHL in adults living with HIV. In the meantime, early access to ART and regular patient monitoring to avert low current CD4 cell counts remain key for NHL prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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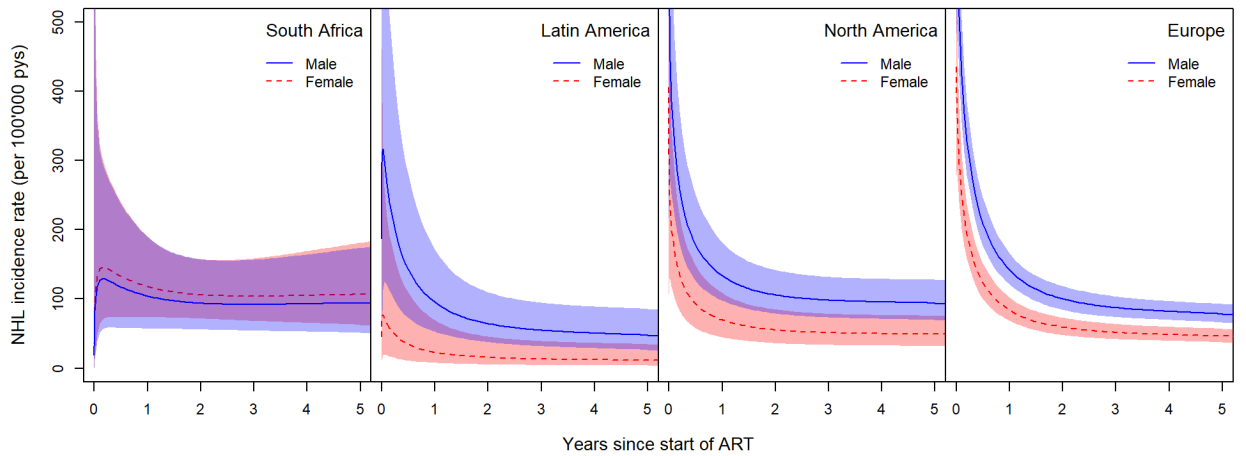**Figure 1: NHL incidence rates by time since ART start in men and women across regions.**
Incidence rates are predicted for adults with a current CD4 cell count of 450 cells/μl who started an NNRTI-based first-line ART regimen between 2008–2014 at the age of 40 years (model 1). ART, antiretroviral therapy; NHL, non-Hodgkin Lymphoma; NNRTI, non-nucleoside reverse-transcriptase inhibitor; pys, person-years.

Table 1:

Patient characteristics at start of ART, stratified by region.

	Asia-Pacific	South Africa	Latin America	North America	Europe
	N (%)	N (%)	N (%)	N (%)	N (%)
All adults	2,638 (100%)	21,656 (100%)	8,569 (100%)	16,986 (100%)	161,049 (100%)
Median follow-up time (IQR) [years]	2.7 (1.7–3.9)	2.0 (0.8–4.0)	4.7 (2.0–8.2)	4.3 (1.7–8.5)	4.5 (1.9–8.5)
Sex / exposure group					
Women	814 (31%)	13,667 (63%)	2,267 (26%)	4,203 (25%)	44,180 (27%)
Men	1,824 (69%)	7,989 (37%)	6,302 (74%)	12,783 (75%)	116,869 (73%)
Heterosexual	1,200 (45%)	6,776 (31%)	1,927 (22%)	3,285 (19%)	45,110 (28%)
MSM	616 (23%)	NR	3,637 (42%)	8,692 (51%)	64,232 (40%)
Missing	8 (<1%)	1,213 (6%)	738 (9%)	806 (5%)	7,527 (5%)
PWID					
Yes	172 (7%)	NR	170 (2%)	2,174 (13%)	17,755 (11%)
No	2,458 (93%)	NR	8,348 (97%)	14,812 (87%)	143,294 (89%)
Missing	8 (<1%)	21,656 (100%)	51 (1%)	0 (0%)	0 (0%)
Median age at ART start (IQR) [years]	36.3 (30.5–43.0)	36.4 (31.0–42.7)	35.6 (29.7–42.9)	39.6 (33.8–46.1)	37.3 (31.4–44.5)
Age at ART start [years]					
16–25	232 (9%)	1,737 (8%)	1,008 (12%)	927 (5%)	13,262 (8%)
26–35	1,055 (40%)	8,643 (40%)	3,426 (40%)	4,838 (28%)	57,975 (36%)
36–45	867 (33%)	7,777 (36%)	2,609 (30%)	6,945 (41%)	55,577 (35%)
46–55	354 (13%)	2,883 (13%)	1,114 (13%)	3,345 (20%)	23,879 (15%)
56	130 (5%)	616 (3%)	412 (5%)	931 (5%)	10,356 (6%)
First line treatment					
NNRTI-based	2,366 (90%)	20,492 (95%)	6,407 (75%)	6,200 (37%)	67,059 (42%)
PI-based	235 (9%)	1,117 (5%)	1,959 (23%)	9,231 (54%)	82,614 (51%)
Other ART	37 (1%)	47 (<1%)	203 (2%)	1,555 (9%)	11,376 (7%)
Calendar year of ART start					
1996–1998	0 (0%)	0 (0%)	109 (1%)	5,466 (32%)	19,216 (12%)
1999–2003	100 (4%)	99 (<1%)	1,969 (23%)	5,228 (31%)	43,675 (27%)
2004–2007	513 (19%)	10,479 (48%)	2,811 (33%)	4,091 (24%)	39,881 (25%)
2008–2014	2,025 (77%)	11,078 (51%)	3,680 (43%)	2,201 (13%)	58,277 (36%)
Median CD4 cell count at ART start (IQR) [cells/µl]	138 (43–234)	107 (43–176)	165 (61–273)	233 (92–378)	250 (126–368)
CD4 cell count at ART start (IQR) [cells/µl]					
<50	677 (26%)	5,507 (25%)	1,527 (18%)	2,652 (16%)	18,051 (11%)
50–99	327 (12%)	3,940 (18%)	1,035 (12%)	1,319 (8%)	11,903 (7%)
100–199	603 (23%)	7,242 (33%)	1,658 (19%)	2,631 (15%)	26,061 (16%)
200–349	735 (28%)	2,626 (12%)	2,151 (25%)	4,205 (25%)	48,356 (30%)
350–499	96 (4%)	398 (2%)	589 (7%)	2,348 (14%)	23,977 (15%)
500–699	16 (1%)	185 (1%)	205 (2%)	1,344 (8%)	11,253 (7%)
700	6 (<1%)	82 (<1%)	81 (1%)	694 (4%)	5,510 (3%)
Missing	178 (7%)	1,676 (8%)	1,323 (15%)	1,793 (11%)	15,938 (10%)

	Asia-Pacific	South Africa	Latin America	North America	Europe
	N (%)	N (%)	N (%)	N (%)	N (%)
Median HIV RNA at ART start (IQR) [log10 copies/ml]	5.0 (4.5–5.4)	4.5 (2.7–5.3)	4.9 (4.3–5.4)	4.5 (3.5–5.2)	4.8 (4.1–5.3)
HIV RNA at ART start (IQR) [log10 copies/ml]					
<2.7	44 (2%)	1,202 (6%)	285 (3%)	2,537 (15%)	13,187 (8%)
2.7–3.9	200 (8%)	596 (3%)	704 (8%)	2,417 (14%)	18,431 (11%)
4.0–4.9	760 (29%)	1,319 (6%)	2,293 (27%)	5,183 (31%)	51,333 (32%)
5.0–5.9	961 (36%)	1,379 (6%)	2,484 (29%)	4,442 (26%)	50,451 (31%)
6.0	78 (3%)	278 (1%)	239 (3%)	122 (1%)	5,078 (3%)
Missing	595 (23%)	16,882 (78%)	2,564 (30%)	2,285 (13%)	22,569 (14%)

ART, antiretroviral therapy; IQR, interquartile range; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NR, not reported; PI, protease-inhibitor; PWID, people who inject drugs; RNA, ribonucleic acid.

Table 2:

Crude and adjusted hazard ratios for the regional effect of sex and current CD4 cell count on the risk of developing NHL in adults who started ART.

	South Africa HR (95% CI)	Latin America HR (95% CI)	North America HR (95% CI)	Europe HR (95% CI)
Sex				
Men	1.00	1.00	1.00	1.00
Women (crude)	1.00 (0.60 – 1.69)	0.23 (0.08 – 0.64)	0.52 (0.36 – 0.75)	0.54 (0.47 – 0.63)
Women (adjusted [*])	1.13 (0.67 – 1.91)	0.24 (0.09 – 0.67)	0.52 (0.36 – 0.76)	0.59 (0.51 – 0.69)
Current CD4 cell count				
Per 100 cells/μl increase (crude)	0.91 (0.77 – 1.07)	0.66 (0.54 – 0.80)	0.66 (0.61 – 0.71)	0.71 (0.69 – 0.73)
Per 100 cells/μl increase (adjusted [**])	0.92 (0.78 – 1.08)	0.66 (0.55 – 0.80)	0.65 (0.60 – 0.71)	0.72 (0.69 – 0.74)

[*] Adjusted for age at ART start, calendar year of ART start, first-line ART regimen, current CD4 cell count and its interaction with region (model 1).

[**] Adjusted for age at ART start, calendar year of ART start, first-line ART regimen, sex and its interaction with region (model 1).

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin lymphoma.

Table 3:

Crude and adjusted hazard ratios for the effect of exposure group and drug use on the risk of developing NHL in adults who started ART, restricted to North America, Latin America, and Europe.

	Crude	Adjusted[*]
	HR (95% CI)	HR (95% CI)
Exposure group		
Women	0.52 (0.44 – 0.61)	0.66 (0.57 – 0.78)
Heterosexual men	1.00	1.00
MSM	0.95 (0.84 – 1.07)	1.30 (1.14 – 1.48)
PWID		
No	1.00	1.00
Yes	0.98 (0.84 – 1.16)	0.94 (0.79 – 1.12)

[*] Adjusted for region, age, calendar year of ART start, first-line ART regimen, current CD4 cell count, and exposure group or PWID, respectively (model 2)

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; MSM, men who have sex with men; NHL, non-Hodgkin lymphoma; PWID, people who inject drugs.

Table 4:

Comparison of NHL rates between different regions and Europe:

Crude and adjusted HRs for being diagnosed with NHL at 2 years after ART start in different population groups.

	Women[1]		All men[1]		Heterosexual men[2]		MSM[2]	
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR** (95% CI)	Crude HR (95% CI)	Adjusted HR** (95% CI)
Region								
Europe	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
North America	1.66 (1.14 – 2.41)	0.97 (0.64 – 1.49)	1.74 (1.45 – 2.08)	1.10 (0.85–1.43)	1.74 (1.26–2.40)	1.26 (0.92–1.74)	1.72 (1.38–2.14)	1.20 (0.96–1.49)
Latin America	0.36 (0.13 – 0.98)	0.26 (0.09 – 0.77)	0.84 (0.59 – 1.22)	0.64 (0.38 – 1.09)	0.80 (0.45–1.43)	0.72 (0.41–1.27)	1.03 (0.68–1.57)	0.84 (0.55–1.27)
South Africa	1.48 (1.03 – 2.14)	1.79 (1.19 – 2.70)	0.80 (0.51 – 1.25)	0.94 (0.56 – 1.58)	–	–	–	–

[1] From models including the variable "sex" and its interaction with region.

[2] From models including the variable "exposure group" and its interaction with region.

* Adjusted for age at ART start, calendar period of ART start, first-line ART regimen, current CD4 cell count and its interaction with region, and sex and its interaction with region (model 1).

** Adjusted for age at ART start, calendar period of ART start, first-line ART regimen, current CD4 cell count, drug use, and exposure group and its interaction with region (model 3).

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin lymphoma.