Factors associated with delayed linkage to care following HIV diagnosis in the WHO European Region

Concise title: Delayed linkage to care in WHO European Region

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ABSTRACT

Objectives: To describe linkage to HIV care following diagnosis in Europe and to identify factors associated with delayed linkage

Methods: We analysed data of adults (aged ≥15yrs) diagnosed with HIV from 2010-2014 in 31 European countries. Linkage to care was calculated using the time between HIV diagnosis and first CD4 count. Linkage was considered delayed if the CD4 count was taken more than three months after diagnosis. Logistic regression was used to determine factors for delayed linkage.

Results: Of the 120,129 adults diagnosed from 2010-2014, 4,560 were previously diagnosed elsewhere, 808 died within three months of diagnosis and 54,731 people were missing CD4 count and/or date information. Among the 60,030 people included, linkage to care within three months was 96%. A lower bound (LB) for this was 55%, when those missing CD4 data were assumed not to be linked. Prompt linkage varied significantly by region (Western: 97% (LB: 65%); Central: 90% (LB: 65%); Eastern: 91% (LB: 11%)) and risk group. In multivariable analysis, delayed linkage to care was associated with: acquiring HIV through injecting drug use/heterosexual contact, being diagnosed in Central/Eastern Europe and having a first CD4 count >200 cells/mm^3. People of older age at diagnosis and those diagnosed after 2011 were more likely to be linked promptly. Associations differed by region.

Conclusions: Among those with CD4 data available, linkage to care is prompt. However, HIV surveillance must be strengthened and data quality improved, particularly in Eastern Europe. Our findings highlight disparities in care access and significant differences between regions.

INTRODUCTION

Prompt linkage to specialist care following diagnosis with HIV is crucial to optimise patient outcomes and reduce ongoing transmission.(1) Delayed linkage to HIV care and access to treatment can result in faster disease progression and increased mortality.(2) Current World Health Organization (WHO) HIV testing guidelines promote timely linkage to care for all people living with HIV through interventions aimed at reducing the time between diagnosis and engagement, such as peer support, integrated prevention, testing and care services and intensified post-test counselling by community health workers.(3)

However, evidence suggests a number of barriers to accessing HIV medical care exist that might lead to delayed access. Data from the Stigma Index survey, conducted in a number of countries across Europe in 2009, highlighted that women in particular delay care due to concerns about anticipated stigma.(4) While stigma was also an issue for men, they also reported more physical barriers to accessing HIV care including affordability and incarceration. Both men and women reported delaying care due to not feeling ready to deal with their HIV infection. Qualitative studies have identified additional barriers including concerns over confidentiality and HIV status disclosure, language, poor treatment infrastructure and access and dissatisfaction with the quality of services and medical staff.(5, 6) The existence of such barriers highlights the need for routine public health monitoring of entry into HIV care after diagnosis.

Established in its current form in 2008, The European Surveillance System (TESSy) provides a unique opportunity to assess linkage to care across Europe.(7) The 53 countries in the WHO European Region report new HIV cases annually to the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe.(7) Information is collected on demographic and clinical characteristics at diagnosis, including first CD4 count. In these analyses, we utilise TESSy data to describe linkage to care following diagnosis and identify factors associated with delayed linkage, using the date of first CD4 count as a proxy for care entry, assuming that baseline laboratory tests such as CD4 count are conducted on all newly diagnosed persons at the first visit as per WHO guidelines.(8)

METHODS

Data sources

Analyses were carried out using surveillance data of laboratory-confirmed new diagnoses of HIV. Data were submitted in September 2015 via TESSy to the ECDC and the WHO

Regional Office for Europe. To be included, countries must have used the 2015 submission template to report data (n=33/53),(9) as this was the first year that first CD4 date was collected. The full list of fields reported in the 2015 TESSy submission template can be found in Supplementary Table 1. Data from two countries were excluded, one with errors identified in CD4 reporting and one in which CD4 were only reported for patients with AIDS-defining illnesses. Of the 31 countries that met the inclusion criteria, 26 reported data retrospectively for all years (2010-2014) and 5 partial years.

Population

Analyses were restricted to adults (aged ≥15 years) diagnosed from 2010-2014. People were excluded if they had been previously diagnosed with HIV, previously attended for HIV care (CD4 more than 14 days prior to diagnosis date) or died within three months of diagnosis. In addition, individuals for whom the time it took to link to care could not be calculated were excluded – those that had no CD4 data reported, only the year of diagnosis/CD4 count reported or a CD4 count reported with no date.

All partial dates, where the only month/quarter and year were provided, were defaulted to the middle of the month/quarter.

Definitions

People testing positive for HIV were considered linked if they attended for specialist HIV care after diagnosis. Linkage to care was calculated as the time between HIV diagnosis and the date of the first CD4 cell count measure, which was used as a proxy for care entry. CD4 counts were included up to 14 days prior to diagnosis to account for potential errors in date reporting.

Linkage was considered prompt if the patient was seen for HIV care (had a CD4 count taken) in the three months (≤91 days) following diagnosis (10) and delayed if a patient was seen for HIV care more than three months after diagnosis.

Analyses

All analyses were carried out using STATA v13 (College Station, Texas, USA). In descriptive analyses, prompt linkage to care was presented by demographic and diagnosis characteristics for Europe overall and by region. We also included lower bounds, assuming that those without a CD4 count were not linked to care, to better understand the impact of missing data. All country-level estimates were anonymised.

Logistic regression was used to determine risk factors for delayed linkage. Factors found to be significant (p<0.05) in univariable analysis were included in multivariable analysis. The final model was fitted to the regional data to explore geographical variation. We carried out sensitivity analysis of the logistic regression excluding countries missing data for any of the five years to determine the impact on the model.

RESULTS

A total of 120,129 adults were diagnosed in the 31 countries between 2010 and 2014 and reported through the revised template (Supplementary Table 2). Of these individuals, 3,793 had evidence of a previous positive HIV test, 767 were reported as being previously in HIV care and 808 died within three months of diagnosis, with a limited opportunity to be linked. A further 44,766 people had no CD4 data available, 4,203 had incomplete CD4 or diagnosis dates (year only) and 5,762 had a CD4 count reported but no date. People without a CD4 count or with incomplete CD4 information (n=52,187) were more likely to be women, infected through heterosexual contact, originating from the reporting country and diagnosed in Eastern Europe (p<0.001) (Supplementary Table 3).

Of the 60,030 adults from 23 countries with available CD4 data, prompt linkage within three months of diagnosis was 96% (n=57,565). Overall, prompt linkage was high (≥90%) across all population sub-groups (Figure 1; Supplementary Table 4). However, there was distinct regional variation (Western Europe: 97% (50,804/52,571); Central Europe: 90% (4,469/4,950); Eastern Europe: 91% (2,292/2,509)), with the lowest levels of linkage seen in people acquiring their HIV through injecting drug use (IDU) in Central (85%; 748/875) and Eastern Europe (84%; 452/535). Linkage ranged by country from 82-100% (Supplementary Table 5).

Given the high proportion of missing CD4 data, we estimated lower bounds of linkage to care within three months of diagnosis (Figure 1; Supplementary Tables 4 and 5). When the 44,766 adults without a CD4 count were categorised as not linked to care and added to the denominator, prompt linkage across the WHO European Region dropped to 55%. Again there was significant variation across regions (Western Europe: 64% (50,804/77,975); Central Europe: 65% (4,469/6,858); Eastern Europe: 11% (2,292/19,963)). CD4 data reporting was poorest for countries from Eastern Europe and among people who acquired their infection through IDU.

After adjustment in multivariable analysis (Table 1), delayed linkage to care was associated with: acquiring HIV though IDU (adjusted odds ratio (adjOR) 2.14; 95% confidence interval

(CI): 1.82-2.52), heterosexual transmission (adjOR 1.34; 95%CI: 1.18-1.52)) or other infection routes (adjOR 2.75; 95%CI: 1.84-4.10), being diagnosed in Central (adjOR 2.82; 95%CI: 2.47-3.23) or Eastern Europe (adjOR 2.62; 95%CI: 2.19-3.13) and having a first CD4 count >200 cells/mm^3 (200-349: adjOR 1.26 (95%CI: 1.09-1.45); 350-499: adjOR 1.39 (95%CI: 1.21-1.60); ≥500: adjOR 1.56 (95%CI: 1.37-1.77)). Older age at diagnosis (≥35 years) and being diagnosed after 2011 were associated with faster linkage to care. Sex and region of origin were not associated with linkage delays.

In a regression sensitivity analysis, when countries with data for partial years were excluded, there was no difference in which factors were significant in multivariable analysis (data not shown).

When the data were stratified by region of diagnosis (Supplementary Table 6), people who acquired HIV through IDU remained significantly more likely to delay linkage compared to other exposure groups in all regions. Also, people diagnosed in more recent years were more likely to link to care promptly across Europe. Sex was not associated with delayed linkage in any region. While younger age was significant predictor of delayed linkage in Western and Eastern Europe, it was not associated with the outcome in Central Europe. Region of origin was only significant in Central and Eastern Europe and first CD4 count after diagnosis was only significant in Western Europe.

DISCUSSION

In this study, we explore linkage to specialist care following diagnosis with HIV in Europe. Our findings using available CD4 data as proxy to indicate that linkage is timely, with over 95% of adults accessing care in the three months following diagnosis. However, there is considerable heterogeneity across regions of Europe and vulnerable subpopulations exist at higher risk of delayed entry into care.

Consistent with the literature, our results indicate delayed linkage to HIV care among people who inject drugs (PWID).(11) People who use illicit drugs can face a variety of complex challenges, such as homelessness, unemployment, psycho-social instability, other addictions and a lack of family or social support which may affect their use of medical services.(12) Other barriers to health service utilisation for drug users include stigma, discrimination by medical staff, ill-health including depression and withdrawal, fear of incarceration and a lack of service integration.(13)

People acquiring their HIV infection through heterosexual transmission and other routes also delayed linkage to care compared to men who have sex with men (MSM). However, high

rates of engagement and retention in HIV care services are well documented among MSM in Western Europe.(14, 15) MSM are also more likely than other transmission risk groups to be diagnosed in sexual health clinics which have faster referral pathways to care.(15)

Delayed access to care was found to be associated with higher CD4 counts at diagnosis; these patients are more likely to be asymptomatic and feel well. "Not feeling ill" is a known predictor of postponing access to medical care.(16) The association between younger age and delayed linkage to care has also been documented.(17)

Encouragingly, in the overall model, sex and migrant status, assigned using information on region of origin, had no impact on the timeliness of linkage to care. However, there was significant geographical variation in predictors of delayed linkage. The association between delayed linkage and region of origin, first CD4 count after diagnosis and age at diagnosis differed across European regions. These disparities may be reflective of the diverse health systems across Europe and the varying country-level legal and regulatory barriers that exist.(18) Laws criminalising certain sexual behaviours or key populations can deter people from services and may inhibit disclosure of risk behaviours.(19) In a number of European countries, access to free HIV care and treatment is also restricted for certain groups such as undocumented migrants.(18, 19) As such, regional associations should not be applied at a country-level. Regional variation can also be explained by differences epidemiological data collection mechanisms. Many national public health agencies have difficulty collecting any longitudinal patient data on care after HIV diagnosis.(20, 21) Collaboration between surveillance organisations and nationally representative HIV clinical cohorts has been shown to help address gaps in data availability.(22)

There are a number of limitations to these analyses. Firstly, the generalisability of our study is limited by the extent of missing CD4 data in TESSy. Information on care entry was only available for ~50% of people newly diagnosed with HIV in Europe. It was not known whether CD4 data were missing because the individuals were not linked to care or if there were issues with data collection or reporting. Reasons for missing data may differ by country. When people without CD4 data were considered not linked, representing a lower bound, prompt linkage was only 55%. Lower bound estimates demonstrate the vast regional variation in data completeness, with particularly limited CD4 reporting by countries in Eastern Europe. Furthermore, there were 20 countries that did not submit any CD4 data to TESSy and were completely excluded from these analyses. As such, we are unable to make any conclusions as to the quality of their HIV care provision.

A second limitation of these analyses was that due to the retrospective nature of this study, we were restricted to the basic demographic data available through the European surveillance of HIV. Other factors known to be associated with delayed linkage to care were not able to be captured such as education,(16, 17) HIV diagnosis setting,(16) stigma and discrimination(16) and individual resource limitations.(16)

Reporting delay and underreporting may have also impacted the results. The extent to which these issues affect the data have been described previously.(7) Mortality may have been underestimated as few countries are able to link to their national mortality register which may partially explain why some people had missing CD4 information.(23)

Finally, our analysis relied on first CD4 date as a proxy for care entry as the date the patient first attended for HIV care is not collected at a European level. This may have underestimated the time it took patients to link to care in countries where CD4 count testing is done on diagnostic samples and may have overestimated the time to link in countries where CD4 counts are not taken at the first clinic appointment. However, CD4 count has been well-established as a proxy of linkage (24) and it is recommended to be taken as part of a baseline assessment in most countries in Europe.(8)

Our findings draw attention to disparities in linkage to care across Europe. To ensure prompt access to HIV care after diagnosis and ultimately optimise outcomes for all people diagnosed with HIV, testing facilities should adopt a proactive approach and facilitate linkage to care, providing support and assistance in the organisation of the first appointment at HIV clinics. These analyses demonstrate that the TESSy dataset is useful in monitoring linkage to HIV care following diagnosis in Europe. However, national HIV surveillance programmes must be strengthened and data completeness significantly improved, particularly in Eastern Europe, to better understand groups most at risk of delaying linkage and monitor the performance of health services programmes.

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Table 1: Factors associated with delayed linkage to care in the WHO European Region, 2010-2014

Variables		Unadjusted odds ratio			Adjusted odds ratio		
		OR	95% CI	p value*	OR	95% CI	p value*
Sex	Men	1.00	-	-	1.00	-	-
	Women	1.15	1.05 - 1.26	0.003	0.95	0.84 - 1.08	0.427
Age at diagnosis	15-24	1.00	-	-	1.00	-	-
	25-34	0.81	0.72 - 0.91		0.89	0.77 - 1.02	
	35-44	0.65	0.58 - 0.74		0.85	0.73 - 0.98	
	45-54	0.60	0.52 - 0.70		0.86	0.73 - 1.02	
	55-64	0.43	0.35 - 0.54		0.68	0.53 - 0.87	
	≥65	0.40	0.27 - 0.58	<0.001	0.50	0.31 - 0.82	0.005
Diagnosis year	2010	1.00	-	-	1.00	-	-
	2011	1.11	0.98 - 1.26		1.03	0.90 - 1.19	
	2012	0.93	0.82 - 1.06		0.84	0.72 - 0.97	
	2013	0.78	0.68 - 0.89		0.68	0.58 - 0.79	
	2014	0.98	0.86 - 1.11	<0.001	0.83	0.71 - 0.96	<0.001
Region of diagnosis	Western Europe	1.00	-	-	1.00	-	-
	Central Europe	3.09	2.78 - 3.44		2.82	2.47 - 3.23	
	Eastern Europe	2.72	2.35 - 3.15	<0.001	2.62	2.19 - 3.13	<0.001
Exposure	Sex between men	1.00	-	-	1.00	-	-
	Heterosexual contact	1.30	1.19 - 1.42		1.34	1.18 - 1.52	
	Injecting drug use	3.42	2.99 - 3.92		2.14	1.82 - 2.52	
	Other	2.95	2.09 - 4.17	<0.001	2.75	1.84 - 4.10	<0.001
Region of origin	Reporting country	1.00	-	-	1.00	-	-
	Other Europe	1.07	0.94 - 1.21		1.10	0.95 - 1.25	
	Elsewhere	0.82	0.74 - 0.91	<0.001	1.10	0.97 - 1.25	0.204
First CD4 after diagnosis (cells/mm^3)	<200	1.00	-	-	1.00	-	-
	200-349	1.26	1.11 - 1.43		1.26	1.09 - 1.45	
	350-499	1.28	1.13 - 1.44		1.39	1.21 - 1.60	
	≥500	1.41	1.27 - 1.58	<0.001	1.56	1.37 - 1.77	<0.001

*Likelihood ratio test

Figure 1: Prompt linkage to care after diagnosis in: (a) WHO European Region, (b) Western Europe, (c) Central Europe and (d) Eastern Europe, 2010-2014
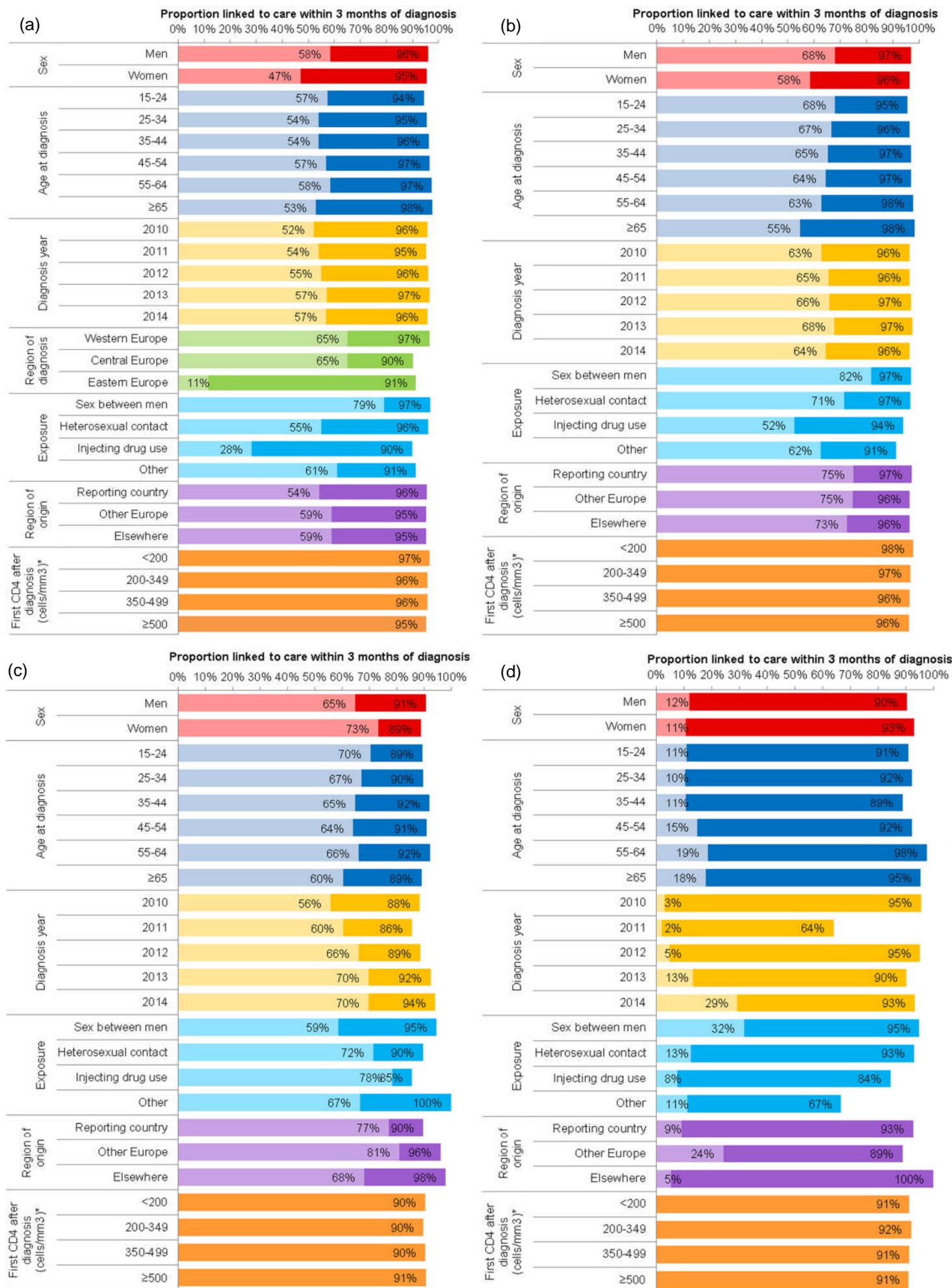
*Lower bound calculation not possible as CD4 required for breakdown