Use of cohort data to estimate national prevalence of transmitted drug resistance to antiretroviral drugs in Spain (2007–2012)

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Abstract

Prevalence of transmitted drug resistance (pTDR) to antiretroviral drugs in Spain (2007–2012) was estimated using the CoRIS cohort, adjusting its territorial distribution and transmission route to the reference population from the Spanish Information System on New human immunodeficiency virus diagnoses. A total of 2702 patients from ten autonomous communities and with naive FASTA sequence within 6 months of human immunodeficiency virus diagnosis were selected. Weighted pTDR, estimated using the inverse probability of selection in the sample by autonomous communities and transmission group, was 8.12% (95% CI 6.44–9.80), not significantly different from unweighted pTDR. We illustrate how proportional weighting can maximize representativeness of cohort-based data, and its value to monitor pTDR at country level.

Keywords: Antiretroviral agents, cohort studies, drug resistance, epidemiological monitoring, human immunodeficiency virus

Epidemiological surveillance of human immunodeficiency virus (HIV) infection provides an invaluable input for public health policy development and programme planning and evaluation. In Spain, there is a national surveillance system for new HIV and AIDS diagnoses but no system has been established for surveillance of transmitted drug resistance (TDR) in newly diagnosed HIV-infected patients. TDR due to transmitted mutations in reverse transcriptase and protease regions has been associated with a higher risk of virological failure to first-line antiretroviral therapy [1], so this information is of great value for informing national recommendations.

The cohort of the Spanish AIDS Research Network (CoRIS) is an open, multicentre, prospective cohort of HIV-positive, antiretroviral-naive subjects over 13 years of age. It started recruiting in 2004; 31 HIV units from 13 of the 17 autonomous communities of Spain participate. Descriptions of the cohort have been previously published [2,3]. However, territorial distribution of cases varies according to number and size of hospitals contributing to CoRIS and is misbalanced compared with the Spanish Information System on New HIV-diagnoses (SINIVIH) [4]. CoRIS collects FASTA sequences encoding the HIV reverse transcriptase and protease, if available, from routine resistance testing. Previous studies on TDR have been published for data between 2004 and 2011 [5–7]. As of December 2012, 29 sites from ten autonomous communities were contributing FASTA sequences.

This study used FASTA sequences available in the CoRIS cohort to estimate the national prevalence of TDR and estimated phenotypic resistance to antiretroviral drugs in patients diagnosed in the period 2007–2012 in Spain, adjusting its territorial distribution and transmission route to the corresponding surveillance data.

We selected the first sequence for each patient available while naive to antiretroviral therapy and within the first 6 months after the first HIV diagnosis [8,9]. TDR-associated

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mutations were evaluated following the WHO surveillance drug resistance mutation list updated in 2009 by Bennett et al. [10]. Phenotypic resistance to antiretroviral drugs making part of recommended initial regimens was predicted using the Stanford HIVdb v6.3.2 algorithm [11,12].

Considering CoRIS as a sample of the cases notified in the SINIVIH, weights were calculated as the inverse probability of being selected, multiplied by total patients for a constant sample size. The selection probability was derived by dividing the number in each autonomous community infected though a particular route in CoRIS by the total number of persons in those categories in the SINIVIH. Weighted prevalences and their 95% CI were calculated.

Of 5773 patients in CoRIS, 2702 fulfilled inclusion criteria. Included patients had a higher proportion of males (89.4% versus 85.6%), men who have sex with men (MSM; 72.4% versus 64.6%), Spanish (71.5% versus 68.0%) and were younger (median of 33.7 versus 34.4 years); all differences significant at $p < 0.01$. Median CD4 count was also higher (419; interquartile range 256–612 versus 400; 230–600; $p < 0.01$). Compared with the SINIVIH and before weighting, we similarly found an over-representation of younger males, MSM and Spanish. After weighting, the profile became more similar to SINIVIH, although an infra-representation of foreigners persisted (Table 1). Weights are shown in Table 2.

Results were not significantly different in weighted and unweighted models (all $p > 0.10$), probably indicating that the CoRIS cohort is highly representative of the current Spanish epidemic. Weighted prevalence of TDR and weighted predicted phenotypic resistance were, respectively: 8.12% (95% CI 6.44–9.80) and 10.67% (9.51–11.84) globally; 3.62% (2.52–4.74) and 2.29% (1.53–3.06) for nucleoside reverse transcriptase inhibitors; 3.37% (2.28–4.46) and 8.53% (7.04–10.01) for non-nucleoside reverse transcriptase inhibitors; and 2.17% (1.23–3.11) and 0.74% (0.31–1.16) for protease inhibitors. The incorporation of E138A as a mutation for rilpivirine in the Stanford algorithm was responsible for the higher predicted resistance to non-nucleoside reverse transcriptase inhibitors. E138A is a frequently detected mutation in antiretroviral-naive patients as a singleton, but there is no evidence so far on its real impact; the exact role of this and other singletons in this codon merits further study.

Surveillance of TDR in newly diagnosed patients is of outmost importance for monitoring the emergence and spread of resistant variants in a population, and has direct implications in HIV management policies and recommendations [13,14]. Our analysis illustrates how proportional weighting can be used to maximize representativeness of cohort-based data. In a similar way, Hofstra et al. and Vercauteren et al. estimated the

TABLE 1. Characteristics of the cohort of the Spanish AIDS Research Network (CoRIS) sample: non-weighted and weighted proportions; comparison with characteristics of the Spanish Information System on New HIV-diagnoses (SINIVIH; 2007–2012 aggregated)

	CoRIS (n = 2702)			SINIVIH (n = 21210)	
	Non-weighted		Weighted[a]		
	n	(%)	(%)	*n*	(%)
Transmission category					
IDU	85	(3.1)	(6.6)	1397	(6.6)
MSM	1955	(72.4)	(50.2)	10 640	(50.2)
HET	595	(22.0)	(32.5)	6890	(32.5)
Other	23	(0.9)	(10.8)	2283	(10.8)
Unknown	44	(1.6)			
Sex					
Men	2421	(89.6)	(82.7)	17 204	(81.1)
Women	281	(10.4)	(17.3)	4006	(18.9)
Age (years)					
15–19	36	(1.3)	(1.3)	316	(1.5)
20–24	341	(12.6)	(10.6)	2004	(9.4)
25–29	542	(20.1)	(15.9)	3681	(17.4)
30–39	1019	(37.7)	(37.6)	7816	(36.8)
40–49	511	(18.9)	(21.3)	4858	(22.9)
≥50	253	(9.4)	(13.3)	2535	(12.0)
Region of origin					
Spain	1933	(71.5)	(73.0)	12 974	(61.2)
Western Europe	92	(3.4)	(3.2)	910	(4.3)
Eastern Europe	55	(2.0)	(2.6)	697	(3.3)
Sub-Saharan Africa	81	(3.0)	(3.7)	1829	(8.6)
Northern Africa	27	(1.0)	(1.1)	268	(1.3)
Latin America	498	(18.4)	(15.8)	4337	(20.4)
Other/Unknown	16	(0.6)	(0.6)	195	(0.9)
CD4 count (cells/mm^3)					
<200	475	(17.6)	(22.8)	6213	(29.3)
200–349	545	(20.2)	(21.3)	3950	(18.6)
>349	1643	(60.8)	(52.6)	11 047	(52.1)
Unknown	39	(1.4)	(3.3)		(12.4)

Abbreviations: IDU, injecting drug user; MSM, men who have sex with men; HTX, heterosexual exposure.
[a]Weighted sample: inverse weights for the probability of being selected in the sample according to Autonomous Community and Transmission category.

TABLE 2. Sample size by autonomous community in the Spanish Information System on New HIV-diagnoses (SINIVIH) and in the non-weighted cohort of the Spanish AIDS Research Network (CoRIS) sample and calculated weights by autonomous communities and transmission group

	Sample size by AC				Calculated weights			
	SINIVIH		CoRIS Sample					
Autonomous community	*n*	(%)	*n*	(%)	IDU	MSM	HTX	OTH/UNK
Andalusia	3546[a]	(16.72)	717	(26.54)	1.35	0.43	0.95	4.42
Balearic Islands	1034	(4.88)	62	(2.29)	2.04	1.71	2.45	8.41
Basque Country	1114	(5.25)	119	(4.40)	2.22	0.79	1.52	3.54
Canary Islands	1562	(7.39)	69	(2.55)	10.70	2.21	5.03	6.88
Catalonia	4423	(20.85)	200	(7.40)	5.72	2.17	3.11	9.68
Galicia	1216	(5.73)	88	(3.26)	4.18	1.40	1.73	4.40
La Rioja	129	(0.61)	44	(1.63)	1.02	0.14	0.47	0.45
Navarre	195	(0.92)	42	(1.55)	1.53	0.59	0.57	0.51
Madrid	6042	(28.49)	1233	(45.63)	1.37	0.47	1.15	2.08
Valencian Community	1943[a]	(9.16)	128	(4.74)	1.00	1.14	1.85	10.79

Abbreviations: AC, autonomous community; IDU, injecting drug user; MSM, men who have sex with men; HTX, heterosexual exposure; OTH/UNK, other or unknown route of transmission.
[a]Estimated parameter, official estimates from the National Surveillance System, SINIVIH.