CONCISE COMMUNICATION

How many people are living with undiagnosed HIV infection? An estimate for Italy, based on surveillance data

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Objective: To estimate the size and characteristics of the undiagnosed HIV population in Italy in 2012 applying a method that does not require surveillance data from the beginning of the HIV epidemic.

Methods: We adapted the method known as 'London method 2'; the undiagnosed population is estimated as the ratio between the estimated annual number of simultaneous HIV/clinical AIDS diagnoses and the expected annual progression rate to clinical AIDS in the undiagnosed HIV population; the latter is estimated using the $CD4^+$ cell count distribution of asymptomatic patients reported to surveillance. Under-reporting/ascertainment of new diagnoses was also considered. Also, the total number of people living with HIV was estimated.

Results: The undiagnosed HIV population in 2012 was 13 729 (95% confidence interval: 12 152–15 592), 15 102 (13 366–17 151) and 16 475 (14 581–18 710), assuming no under-reporting/ascertainment, 10 and 20% of under-reporting/ascertainment, respectively. The percentage of undiagnosed cases was higher among HIV people aged below 25 years (25–28%), MSM (16–19%) and people born abroad (16–19%), whereas it was small among injection drug users (3%).

Conclusion: The estimate of people in Italy with undiagnosed HIV in 2012 was in a plausible range of 12 000–18 000 cases, corresponding to 11–13% of the overall prevalence. The method is straightforward to implement only requiring annual information from the HIV surveillance system about $CD4^+$ cell count and clinical stage at HIV diagnosis. Thus, it could be used to monitor if a certain prevention initiative lead to the reduction of the undiagnosed HIV population over time. It can also be easily implemented in other countries collecting the same basic information from the HIV surveillance system.

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Keywords: back-calculation, $CD4^+$ cell count, HIV surveillance, HIV undiagnosed infections, prevalence

Introduction

To control the HIV epidemic, it is necessary to develop, plan and implement innovative strategies to find undiagnosed persons and engage them in care and treatment. A preliminary step to reach this objective is to regularly monitor the size and characteristics of the undiagnosed population and properly address interventions, i.e. according to age, sex and sexual behavior.

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Broadly, three approaches have been used to estimate the number of people with undiagnosed HIV: prevalence surveys [1], extended back-calculation on HIV and AIDS data [2,3], and other statistical models based on the synthesis of various data sources [4,5]. All methods are quite complex and demand surveillance systems that have been in place for a long time, along with population-based or community-based surveys.

In Italy, national surveillance of new HIV diagnoses was only established in 2008, and prevalence surveys are not routinely carried out; thus, given the available data, it is necessary to consider alternative methods to estimate the undiagnosed population.

The objective of this study was to provide an estimate of the undiagnosed HIV population in Italy in 2012, also stratified by sex, HIV exposure category, age group, and country of birth, using a simple approach of combining routine surveillance data with estimates of progression to AIDS before HAART introduction. An estimate of the overall prevalence of persons living with HIV in Italy in 2012 was also provided.

Methods

The method is a modification of the 'London method 2' [6–8] and it does not require surveillance data from the beginning of the HIV epidemic. Very briefly, the undiagnosed HIV population is estimated as the ratio between the estimated annual number of simultaneous HIV/clinical AIDS diagnoses and the expected annual progression rate to AIDS in the undiagnosed population. This progression rate was estimated considering the annual AIDS incidence by $CD4^+$ cell count in untreated patients before the introduction of HAART (as derived from by cohort studies, [9]) and the $CD4^+$ cell count distribution of newly diagnosed asymptomatic HIV reported to surveillance.

Thus, the annual number of cases with undiagnosed HIV, n, can be estimated by:

$$n = \frac{S}{\sum_{i=1}^{k} p_i * r_i}$$

where S is the estimate of simultaneous HIV/clinical AIDS diagnoses, p_i is the proportion of patients in $CD4^+$-stratum i among asymptomatic, r_i is the annual AIDS rate in $CD4^+$-stratum i, k is the number of $CD4^+$ cell count classes considered (see http://links.lww.com/QAD/A872).

We considered new HIV diagnoses in 2012, reported by June 2014, to the Italian HIV surveillance system [10]. Available information were date of birth, sex, nationality, date of diagnosis, reasons for testing, HIV exposure category, $CD4^+$ cell count and clinical stage at HIV diagnosis (i.e. asymptomatic stage, symptomatic non-AIDS stage, AIDS stage).

Also, different scenarios about under-reporting/ascertainment of HIV/AIDS were considered to estimate the undiagnosed population.

We estimated the overall HIV prevalence in Italy in 2012 through several steps: the number of people diagnosed and in care in 2012 was retrieved from a national survey [11]. The total number of people diagnosed was obtained considering the estimated percentage of people not retained in care according to a survey performed in three Italian infectious disease clinics [12]. Finally, the number of people living with HIV was obtained by adding the estimates of undiagnosed HIV cases to the estimates of diagnosed.

Analyses were performed using R software 3.1.0 [13]; multiple imputation was implemented through mi R-package [14].

Results

There were 4082 new HIV diagnoses in adults (≥15 years of age) reported to the Italian National Surveillance System by July 2014 with an HIV test date in the year 2012. In total 13.8% of the cases had an unknown HIV exposure category, 21.6 and 28.4% had a missing $CD4^+$ cell count and clinical stage respectively (Supplementary Table 1, http://links.lww.com/QAD/A872).

Table 1 shows the distribution of new HIV diagnosis by clinical stage and $CD4^+$ cell count at diagnosis and estimated annual rate to clinical AIDS in people with undiagnosed HIV (0.076 and 0.078 for raw and imputed data, respectively). This means that 7.6–7.8% of undiagnosed HIV positive cases would progress to AIDS, unless they were diagnosed with HIV before the end of the year.

Table 2 shows the estimates of simultaneous HIV/clinical AIDS diagnoses, the number expected to progress to AIDS in that year unless they were diagnosed before, and the number of undiagnosed HIV cases in Italy in 2012 considering three different scenarios about under-reporting. Estimates are stratified according to HIV exposure category, sex, nationality and age group.

The median estimates of the number of undiagnosed cases vary between 13 729 [95% confidence interval (CI): 12 152–15 592] and 16 475 (95%CI: 14 581–18 710) under the hypothesis of no under-reporting

Table 1. Distribution of new HIV diagnosis by clinical stage and CD4$^+$ cell count at diagnosis and estimated annual rate to clinical AIDS in people with undiagnosed HIV, Italy, 2012.

	Original data								Imputed data[b]										
CD4$^+$ cell count	Asymptomatic		Symptomatic non-AIDS		AIDS		Missing	Total	Asymptomatic		Symptomatic non-AIDS		AIDS		Total	AIDS annual rate (r_i)[a]	SE (r_i)[a]	p_i*r_i (from original data)	p_i*r_i (from imputed data)
	N	% (p_i)	*N*	%	*N*	%	*N*	*N*	*N*	% (p_i)	*N*	%	*N*	%	*N*				
<20	16	0.893	41	8.577	162	25.352	18	213	22	0.862	51	7.692	214	24.683	287	2.01517	0.41135	0.018	0.017
20–49	36	2.010	47	9.833	171	26.761	5	254	45	1.763	58	8.748	203	23.414	306	0.72072	0.11849	0.014	0.013
50–99	71	3.964	64	13.389	118	18.466	20	253	98	3.840	87	13.122	160	18.454	345	0.43625	0.05728	0.017	0.017
100–149	70	3.908	57	11.925	66	10.329	16	193	105	4.114	79	11.916	94	10.842	278	0.21992	0.03079	0.009	0.009
150–199	104	5.807	44	9.205	45	7.042	13	193	143	5.603	63	9.502	65	7.497	271	0.10771	0.01523	0.006	0.006
200–349	372	20.771	114	23.849	40	6.260	57	526	534	20.925	162	24.434	74	8.535	770	0.03318	0.00282	0.007	0.007
350–499	437	24.400	65	13.598	13	2.034	60	515	599	23.472	93	14.027	26	2.999	718	0.01563	0.0016	0.004	0.004
≥500	685	38.247	46	9.623	24	3.756	102	755	1006	39.420	70	10.558	31	3.576	1107	0.00779	0.00094	0.003	0.003
Total (*N*)	1791	100	478	100	639	100	291	3199	2552	100	663	100	867	100	4082			$\sum p_i r_i$=0.078	$\sum p_i r_i$=0.076
Missing	9	–	0	–	7	–	867	883	0		0		0		0				
Total	1800	–	478	–	646	–	1158	4082	2552		663		867		4082				

$\sum p_i r_i$, estimated mean annual progression rate to AIDS for the undiagnosed HIV population; $p_i = n_i$/N*100, percentage of patients in CD4$^+$ stratum *i* among newly diagnosed asymptomatic HIV; r_i, annual AIDS rate in CD4$^+$ stratum *i*; SE, standard error.

[a]From Cascade collaboration (Guiget *et al.* Open AIDS J. 2008, and Professor K. Porter, personal communication).

[b]Mean values based on 1000 imputed datasets.

Table 2. Estimated number (95%CI) of people living with undiagnosed HIV infection in Italy in 2012, in total, and by HIV exposure category, sex, country of birth and age.

	$\sum r_i * p_i$	Simultaneous HIV/clinical AIDS	Prevented clinical AIDS	Estimated number of undiagnosed HIV+		
				No under-reporting	10% under-reporting	20% under-reporting
Total	0.076 (0.065–0.086)	867 (842–893)	170 (152–187)	13 729 (12 152–15 592)	15 102 (13 366–17 151)	16 475 (14 581–18 710)
HET-F	0.085 (0.072–0.103)	169 (157–181)	36 (32–41)	2411 (2000–2832)	2652 (2220–3115)	2893 (2400–3398)
HET-M	0.105 (0.087–0.128)	347 (330–367)	59 (51–67)	3880 (3178–4609)	4267 (3496–5071)	4656 (3813–5532)
IDU	0.088 (0.068–0.121)	67 (60–75)	11.5 (9–14)	895 (653–1136)	984 (719–1251)	1074 (784–1364)
MSM	0.054 (0.046–0.064)	284 (266–303)	62 (55–70)	6382 (5406–7368)	7020 (5947–8105)	7659 (6487–8841)
Women	0.087 (0.075–0.106)	180.5 (168–193)	38 (34–44)	2500 (2087–2919)	2750 (2295–3210)	3000 (2504–3502)
Men	0.072 (0.062–0.084)	687 (665–711)	131 (117–144)	11 352 (9866–12 870)	12 488 (10 852–14 157)	13 623 (11 839–15 444)
Italy	0.070 (0.060–0.08)	604 (585–625)	121 (108–133)	10 416 (9177–11 803)	11 457 (10 095–12 984)	12 499 (11 013–14 165)
Abroad	0.093 (0.077–0.112)	263 (247–279)	49 (43–55)	3358 (2798–3963)	3694 (3078–4360)	4030 (3358–4756)
15–24	0.038 (0.028–0.056)	39 (32–46)	7 (5–9)	1189 (812–1667)	1309 (894–1834)	1428 (975–2000)
25–34	0.072 (0.060–0.087)	183 (169–197)	49 (44–56)	3240 (2714–3800)	3564 (2986–4180)	3888 (3258–4500)
35–44	0.078 (0.066–0.092)	272 (259–285)	54 (47–60)	4192 (3578–4863)	4611 (3936–5348)	5031 (4294–5834)
45–54	0.097 (0.081–0.118)	230 (219–242)	43 (37–47)	2815 (2336–3294)	3097 (2570–3623)	3378 (2804–3952)
>54	0.08 (0.064–0.105)	143 (134–152)	17 (15–20)	2013 (1528–2492)	2215 (1681–2742)	2416 (1834–2991)

and under-reporting of 20%, respectively; estimates stratified by HIV exposure category evidenced that MSM had the highest estimate of undiagnosed cases whereas the injection drug users (IDU) was the category with the lowest estimate; regarding sex, estimates of undiagnosed HIV+ men were around 4.5 times more than those for women; three times higher for people born in Italy than for those born abroad; regarding age, the highest estimate of undiagnosed cases was for the 35–44 years old group.

Finally, we estimated that the undiagnosed HIV population in Italy was around 11–13% for an overall prevalence of about 125 000–130 000 cases; regarding the exposure category, it is of note that the estimated percentage of undiagnosed HIV among IDU was around 3% whereas the estimated percentage among MSM accounted for about 16–19%; regarding sex, the estimated percentage was about 7–8% in women compared with 13–15% in men; with respect to the country of birth, the estimated percentage of undiagnosed cases was higher in those born abroad (16–19%) than those born in Italy (10–12%); regarding age groups, the percentage of undiagnosed cases was particularly high among those aged below 25 years old (25–28%) whereas the lowest percentage was among those aged 50–59 years old (Supplementary Table 2, http://links.lww.com/QAD/A872).

Discussion

The magnitude and characteristics of the undiagnosed HIV population is important for focusing intervention strategies and prevention initiatives. Reducing the prevalence of undiagnosed HIV infection and increasing the proportion of HIV-infected individuals who are aware of their status are important for HIV prevention, as the transmission rate from the unaware group was estimated to be 3.5 times higher than the aware group [15] and that persons who are undiagnosed accounted for almost one-third of transmissions [16]. Also, it was estimated that about eight transmissions would be averted per 100 persons newly aware of their infection [17].

Thus, increasing the number of HIV-infected persons who are diagnosed and linked with effective care and prevention programs may have the potential to significantly reduce new HIV infections over time. In addition, diagnosed persons can benefit from clinical treatments to prevent immune system damage and opportunistic infections.

Using routine surveillance data, we estimated that there were about 12 000–18 000 people in Italy with undiagnosed HIV, corresponding to 11–13% of the overall prevalent population with HIV. This estimate is lower than that obtained (19%) from routine HIV testing among persons attending clinics for sexually transmitted

infections (STI), in 2013 [18]. This estimate could be over-biased because of possible nondisclosure of HIV status due to convenience and discomfort in disclosing risky sexual behavior to healthcare professionals [19,20].

The percentage of undiagnosed cases was lower for IDU (around 3.0%) and higher for MSM (16–19%); the low percentage among IDU is likely attributable to routine HIV testing for all people attending drug treatment services since the 1980s, and to the decreasing incidence of new HIV infections in this group [21]. Stratified estimates also evidenced a higher percentage of undiagnosed men compared with women, in people born abroad compared with those born in Italy, and in people below 25 years old compared with the other age groups.

The approach we used is simpler than other statistical methods requiring historical data about new HIV/AIDS diagnoses; in particular, only annual routine surveillance data for new HIV diagnoses such as $CD4^+$ cell count, presence/absence of HIV/AIDS-related symptoms are needed to implement the method. Thus, it could be used for example to evaluate if a particular strategy (e.g. expanded HIV testing in men older than 45, opt-out testing in specific health facilities, rapid-test testing among young people) leads to a reduction of the undiagnosed population from one year to another. A similar approach, (although with different assumptions) the so-called 'London 1 method', was recently proposed [22] to estimate the number of undiagnosed in the lower $CD4^+$ cell count range (i.e. <200 or <350 cells/μl).

The estimated overall prevalence of undiagnosed HIV-infected people in Italy are in line with those recently obtained in other countries using statistical/mathematical models: 16–18% in 2009–2010 in United States [23,24], 20% in 2010 in France [25], 17% in United Kingdom in 2014 [26], 9.4% in Australia in 2013 [27]. For MSM these percentage were 15% in 2011 in the Netherlands [28], 13% in Switzerland in 2010 [29], 22% in England and Wales in 2010 [30].

Some issues should be considered. The method mainly relies on the assumption that the $CD4^+$ cell count distribution in the undiagnosed population is similar to that of newly diagnosed asymptomatic people. This assumption cannot be verified, although the distribution of $CD4^+$ cell count in asymptomatic people we used was not particularly different from the $CD4^+$ cell count distribution estimated in undiagnosed [26,28], whereas it appeared to be different from that reported in [30] (Supplementary Table 3, http://links.lww.com/QAD/A872). To evaluate the impact of the assumption on the estimates we performed some simulations assuming that the undiagnosed HIV people had $\pm$ 5%, $\pm$ 10% and $\pm$ 15% $CD4^+$ cell counts, compared with the new asymptomatic HIV diagnoses; the estimates varied up to $\pm$ 2500 cases, corresponding up to $\pm$ 2% on the overall prevalence.

Another issue is also the possible under-reporting/ascertainment of both AIDS and HIV diagnoses. Assuming that under-reporting/diagnosis was not different by clinical stage, $CD4^+$ at diagnosis and the other characteristics considered, a 10% (20%) increase of under-reporting/diagnosis results in about 1% (2%) increase in prevalence of undiagnosed infections (Supplementary Table 2, http://links.lww.com/QAD/A872).

We assumed that the progression rates depend only on $CD4^+$ cell count and that the estimates before introduction of HAART could be similar to current AIDS progression rates among the undiagnosed. Our method did not consider age [31] as determinant of progression before introduction of HAART, although such a development could be incorporated to refine the estimates.

Finally, to estimate the overall prevalence of people living with HIV, we also considered the percentage of those not retained in care. This percentage was considered equal in all subgroups evaluated.

In conclusion, the estimated undiagnosed HIV population in Italy is in a plausible range of 12 000–18 000 cases, corresponding to 11–13% of the overall prevalence. The approach described can also be easily implemented in other countries where HIV surveillance systems have routinely been collecting data on $CD4^+$ cell count and clinical stage at diagnosis.

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A.M., P.P., and E.G. conceived the initial idea and the study design; A.M. and P.P. implemented the model and drafted the manuscript; V.R. and L.C. managed the database of National Surveillance System and extracted the data; B.S. coordinated the National Surveillance System and contributed to data interpretation; V.P. and G.I. contributed to data interpretation; A.M. and P.P. revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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