People living with undiagnosed HIV infection and a low CD4 count: estimates from surveillance data, Italy, 2012 to 2014

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Background and aims: Late HIV diagnosis is associated with onward HIV transmission, higher morbidity, mortality and healthcare costs. In Italy, more than half of people living with HIV were diagnosed late during the last decade, with a CD4 count < 350 cells/mm³ at diagnosis. We aimed to determine the number and characteristics of people living with undiagnosed HIV infection and low CD4 counts in Italy. Methods: Data on newly reported HIV diagnoses from 2012 –2014 were obtained from the national HIV surveillance system. We used the European Centre for Disease Prevention and Control HIV modelling tool to calculate the undiagnosed prevalence and yearly diagnosed fraction (YDF) in people with low CD4 count. Results: The estimated annual number undiagnosed HIV infections with low CD4 count was on average 6,028 (95% confidence interval (CI): 4,954–8,043) from 2012–2014. In 2014, most of the undiagnosed people with low CD4 count were men (82.8%), a third acquired HIV through sex between men (MSM) (35.0%), and heterosexual transmission (33.4%), respectively. The prevalence of undiagnosed HIV infection was 11.3 (95% CI: 9.3–14.9) per 100,000 residents ranging from 0.7 to 20.8 between Italian regions. Nationally the prevalence rate was 280.4 (95% CI: 173.3–450.2) per 100,000 MSM, 8.3 (95% CI: 4.9–13.6) per 100,000 heterosexual men, and 3.0 (95% CI: 1.4–5.6) per 100,000 women. The YDF was highest among heterosexual women (27.1%; 95% CI: 16.9–45.2%). Conclusions: These findings highlight the importance of improving efforts to identify undiagnosed HIV infections primarily among men, both MSM and heterosexual men.

Introduction
Late diagnosis of HIV remains a major public health concern worldwide [1-3]. In 2015, close to half (48%) of people newly diagnosed with HIV in European countries were late presenters, with CD4 counts below 350 cells/mm³ at diagnosis, including 28% with advanced HIV infection (CD4 < 200 cells/mm³) [1]. In Italy, despite HIV testing and healthcare being free of cost for the individual, more than half of the ca 4,000 people diagnosed with HIV annually are diagnosed with a CD4 count < 350 cells/mm³, and ca 40% are at the symptomatic stage of infection when diagnosed [4,5]. The late diagnosis of HIV infection has negative consequences, both at the individual and population levels. People presenting late respond insufficiently to antiretroviral therapy (ART) and treating them is often complex and costly. Individuals who are in an advanced stage of immunosuppression due to HIV are at high risk of clinical events and death [6,7]. At population level, those diagnosed late are a potential source of HIV transmission for a considerable period [8]. Low CD4 count and high viral load contribute significantly to the risk of sexual transmission [9].

Given the prevalence of late diagnoses, it is likely that a considerable number of people with low CD4 counts remain undiagnosed in Italy. Mammone et al. estimated that there are 12,000–18,000 undiagnosed people living with HIV in Italy [10], although no estimate of those undiagnosed with a low CD4 count was calculated. Knowing the numbers of people living with undiagnosed HIV and with a low CD4 count could be useful in predicting the prevalence of late HIV presentation and its consequences of poor prognosis and onward transmission. Being aware of the overall numbers of those who are undiagnosed and of the respective numbers in relevant subpopulations can support the monitoring of national and local HIV prevention strategies, the
**Figure 1**
Prevalence rates of people living with undiagnosed HIV and with low CD4 cell count\(^a\) by HIV exposure group\(^b\) and region\(^c\), Italy, 2014

A. Total population

- **<4 per 100,000**
- **4–8 per 100,000**
- **8–12 per 100,000**
- **12–16 per 100,000**
- **≥16 per 100,000**

B. Heterosexual women

- **<4 per 100,000**
- **4–8 per 100,000**
- **8–12 per 100,000**
- **12–16 per 100,000**
- **≥16 per 100,000**

C. Men who have sex with men

- **<4 per 100,000**
- **4–8 per 100,000**
- **8–12 per 100,000**
- **12–16 per 100,000**
- **≥16 per 100,000**

D. Heterosexual men

- **<4 per 100,000**
- **4–8 per 100,000**
- **8–12 per 100,000**
- **12–16 per 100,000**
- **≥16 per 100,000**

MSM: men who have sex with men.

\(^a\) CD4 count < 350 cells/mm\(^3\)

\(^b\) The undiagnosed rates were calculated as follows: total population (panel A) – number of all undiagnosed with CD4 < 350 cells/mm\(^3\) divided by the number of residents in each region, multiplied by 100,000; Italian average: 11.3 (95%CI: 9.3-14.9) per 100,000 residents. Heterosexual women (panel B) – number of undiagnosed heterosexual women with CD4 < 350 cells/mm\(^3\) divided by the number of women resident in each region, multiplied by 100,000; Italian average: 3.0 (95%CI: 1.4-5.6) per 100,000 heterosexual women residents. MSM (panel C) – number of undiagnosed MSM with CD4 counts < 350 cells/mm\(^3\) divided by the number of MSM (3% of men) resident in each region, multiplied by 100,000; Italian average: 280.4 (95%CI: 173.3–450.2) per 100,000 MSM residents. Heterosexual men (panel D) – number of undiagnosed heterosexual men with CD4 counts < 350 cells/mm\(^3\) divided by the number of heterosexual men (97% of men), resident in each region, multiplied by 100,000; Italian average: 8.3 (95%CI: 4.9-13.6) per 100,000 heterosexual men residents.

\(^c\) For regions (one in the Central area and one in the North area) that did not collect data on the clinical stage and CD4 count, the number of undiagnosed was estimated assuming the distribution of clinical stage and CD4 count observed at national level (Table 2).
revision of health policies and the allocation of economic resources to prevention and control efforts [11]. The aim of this study was to estimate the number of people living with undiagnosed HIV and a low CD4 count in Italy, to analyse the characteristics of this population and to evaluate the prevalence of undiagnosed HIV infection in the general population.

**Methods**

To estimate the number of people living with undiagnosed HIV and a low CD4 count, we applied the model proposed by Lodwick et al. [12]. This model is part of the European Centre for Disease Prevention and Control (ECDC) HIV modelling tool. The tool uses routine surveillance data to calculate estimates of the number of people living with HIV as well as of those not yet diagnosed. It does not depend on historical data, i.e. it can be used even with limited years of available data [13]. Of the two models included we choose the London model as it applies to the way HIV data was collected through the Italian HIV surveillance system effective as of 2012.

**Data source**

We obtained data from the Italian National HIV Surveillance system (INHS) on people aged > 15 years who were diagnosed with HIV between 2012 and 2014 and reported to the INHS by June 2015 [5].

In Italy, the reporting of new HIV diagnoses is mandatory since July 2008 for all clinicians [14]. There are 173 Infectious Diseases Centers (IDC) in Italy that offer free monitoring and health management to all HIV-positive persons, including non-nationals and undocumented migrants [15]. Most people who test HIV-positive are diagnosed at IDCs directly and those who are tested in other health facilities are further referred to an IDC for confirmatory testing and diagnosis.

Data on new diagnoses are collected by regional surveillance systems and sent annually to the INHS coordinated by the Italian national institute of health in Rome. While the surveillance did not cover all regions previously, since 2012 there was 100% geographical coverage with all regions reporting data to the INHS [5].

The INHS collects the following data on an annual basis: (i) demographic data (age, sex, nationality, geographical area of diagnosis, and geographical area of residence), (ii) clinical information (clinical stage, CD4 counts, and viral load) and (iii) HIV exposure group data (people who inject drugs (PWID), heterosexual

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* CD4 count < 350 cells/mm³
women, heterosexual men, men who have sex with men (MSM), and other/not available) [5].

Residences in Italy were grouped into three areas based on the of Italian National Bureau of Statistics (ISTAT) classification: (i) North (Piemonte, Valle d’Aosta, Liguria, Lombardia, Trentino–Alto Adige, Friuli–Venezia Giulia, Veneto and Emilia Romagna); (ii) Central (Toscana, Marche, Lazio, and Umbria); and (iii) South (Abruzzo, Molise, Campania, Puglia, Calabria, Basilicata, Sicilia, and Sardegna) [16]. For non-Italian citizens without residence in Italy, we assigned the place of diagnosis as residence.

**Description of the model**

The model proposed by Lodwick et al. [12] is based on back-calculation principles. In brief, the method assumes that people living with undiagnosed HIV develop AIDS or other HIV-related symptoms of sufficient severity, or symptoms which are sufficiently specific to HIV, and will seek care and, as a result, be diagnosed with HIV. It uses information derived from people newly diagnosed at an advanced stage of HIV infection (clinical stage B or clinical stage C) with CD4 counts < 350 cells/mm³, stratified into eight groups based on CD4 counts at HIV diagnosis (< 20 cells/mm³, 20–49, 50–99, 100–149, 150–199, 200–249, 250–299, 300–350). Specifically, for each CD4 count stratum the number of those undiagnosed is obtained by dividing the number of symptomatic diagnoses by the CD4-specific rate of HIV symptoms estimated in cohort studies. The total number of undiagnosed people with HIV with a CD4 count < 200 cells/mm³ (advanced HIV infection) was obtained summing the specific stratum estimates, from the first (< 20 cells/mm³) to the fifth (150–199 cells/mm³) stratum. Similarly, the total number of undiagnosed people with HIV with a CD4 count < 350 cells/mm³ (late presenters) was obtained summing the eight specific stratum estimates.

The ECDC HIV modelling tool version 1.2.1 [13] was used to calculate the estimates stratified by main demographic characteristics (age, sex, nationality, geographical area of residence) and HIV exposure groups (PWID, heterosexual women, heterosexual men, MSM, and other/not available). The tool permits the estimation of undiagnosed people living with HIV according to the different characteristics.

**Adjustment for missing values and reporting delay**

The estimates obtained from the model were adjusted for reporting delays or underreporting of HIV diagnoses with HIV-related symptoms as proposed in the original publication [12]. As information on clinical stage and CD4 count were missing in around 30% of the INHS records, the missing values were adjusted under the assumption that the distribution of clinical stage and CD4 count among diagnosed cases with missing data was similar to that of diagnosed cases with available data [17]. In brief, the estimates obtained from the London method were divided by the proportion of all diagnoses with symptoms, where the CD4 count was known.

The following steps were used for the adjustment: first, the proportion of missing data was calculated relative to the clinical stage and CD4 count for each characteristic of the new diagnoses. Second, the estimates of undiagnosed people living with HIV were multiplied by the inverse of the missing proportion according to each characteristic. Last, the reporting delay to the INHS was considered, with the adjusting of the annual estimates by a reporting delay of 5%, introduced for each year of the 3 years, given that all new HIV diagnoses were notified to the surveillance system within 3 years after diagnosis [5]. In other words, it was assumed that in 2015 the INHS data were all complete for 2012 (100%), and almost complete for 2013 (95%) and 2014 (90%). Therefore, for each characteristic we adjusted the estimates multiplying them by the following:

\[
\text{Adjustment factor} = \frac{1}{(1 - \text{proportion of missing} - \text{annual reporting delay})}
\]

Table 1 shows the proportion of missing data (of CD4 count and/or clinical stage) with the respective ‘adjustment factors’ applied to undiagnosed people living with HIV estimates by main characteristics. As an example, when estimating the undiagnosed number of women, missing CD4 count and clinical stage accounted for 27% in 2012, 29% in 2013, and 26% in 2014 of the cases. The adjustment factors for women were: \(1/(1 - 0.27) = 1.37\); \(1/(1 - 0.29 - 0.05) = 1.52\) and \(1/(1 - 0.26 - 0.05 - 0.05) = 1.56\) in the 3 years, respectively. Of note, there was a direct relationship between the proportions of missing data and the value of the adjustment factors: the higher the adjustment factor, the higher the proportion of missing data (Table 1).

**Characteristics of people undiagnosed and newly diagnosed with HIV and with low CD4 count in 2014**

The characteristics of both people undiagnosed and newly diagnosed with HIV and a low CD4 count were described for the year 2014 to compare characteristics of those undiagnosed with low CD4 count with new HIV diagnoses with a low CD4 count.

The yearly diagnosed fraction (YDF) in people with a low CD4 count (CD4 < 350 cells/mm³ or CD4 < 200 cells/mm³) was calculated according to main characteristics for the year 2014. YDF has been recently proposed by Sasse et al. [18] to evaluate the ratio of new diagnoses among people living with HIV who can be diagnosed in a given year. In our study, YDF was calculated among people with HIV and with a low CD4 count according to the following formula:

\[
\text{YDF} = \frac{\text{Number of new diagnoses}}{(\text{Number of new diagnoses} + \text{Estimated number of undiagnosed HIV})} \times 100
\]
Prevalence of undiagnosed HIV infection with low CD4 count in 2014

To evaluate the prevalence of undiagnosed people living with HIV and a low CD4 count for the year 2014, the rate expressed was calculated as follows:

$$\text{Estimated number of undiagnosed people living with HIV with a CD4 < 350 cells/mm}^3 \times 100,000 \approx \frac{\text{Number of people aged 15–74 years}}{\text{Person years of exposure}}$$

As a denominator, the population aged > 15 years up to 75 years estimated by the ISTAT was used [16]. The described undiagnosed prevalence of HIV infection was also calculated by region of residence and by HIV exposure group. As denominator, the female population for heterosexual women and the male population for men was used. For MSM, a proportion of 3% of the adult male population was assumed, given that published data reveals estimates of MSM ranging from 2% to 4% of the male population in Italy [19–21]. Thus, for heterosexual men the remaining 97% of male population was used.

Results

National HIV surveillance system data

About 4,000 new HIV diagnoses were notified to the INHS annually during the period 2012–2014 (Table 2). Clinical stage at HIV diagnosis was reported for 70% of people, 39% of them were diagnosed at clinical advanced stage (clinical stage B or C). Table 2, shows the distribution of new HIV diagnoses by main characteristics; these were similar during the 3 years: the majority were men, more than half aged between 25 and 44 years, and more than one third were MSM. More than half were diagnosed late, namely with CD4 count < 350 cells/mm³.

Estimates of people living with undiagnosed HIV and a low CD4 count

Using the described model, the estimated number of people living with undiagnosed HIV infection and with CD4 count < 350 cells/mm³ in Italy was 6,028 (95% CI: 4,882–7,826) in 2012, 6,156 (95% CI: 4,882–7,786) in 2013, and 5,090 (95% CI: 4,042–6,784) in 2014. Table 3, shows the estimated number of undiagnosed people living with HIV and CD4 count < 350 cells/mm³ by demographic information, and by geographical area of residence. The highest estimated numbers in 2014 were in men (4,893; 95% CI: 3,992–6,568), both MSM (2,115; 95% CI: 1,292–3,395) and heterosexual men (2,017; 95% CI: 1,183–3,301) as well as in people living in the North (2,475; 95% CI: 1,651–3,783).

The estimated number of people living with undiagnosed HIV infection and CD4 count < 200 cells/mm³ in Italy was 2,467 (95% CI: 2,052–3,145) in 2012, 2,456 (95% CI: 2,027–3,151) in 2013, and 2,524 (95% CI: 2,075–3,246) in 2014 (Table 3). Also for the undiagnosed people with CD4 count < 200 cells/mm³, the highest estimates were in men, those living in the North and in MSM.

Among the undiagnosed people living with HIV and with low CD4 count, the proportion of those with CD4 count < 200 cells/mm³ was 40.9% in 2012, 39.9% in 2013, and 42.8% in 2014. These proportions were similar according to all characteristics from 2012 to 2014.

Characteristics of people undiagnosed and newly diagnosed with HIV and with low CD4 count in 2014

In Table 4, for the year 2014, main characteristics of people undiagnosed and newly diagnosed with HIV and with a low CD4 count are compared. The characteristics of those newly diagnosed and with a low CD4 count were similar to those of people with undiagnosed HIV and with a low CD4 count.

Many people undiagnosed and with CD4 count < 350 cells/mm³ were men and older than 35 years, while a third were MSM and, another third were heterosexual men. About a third were born abroad and nearly half resided in the North of Italy. Similarly, men (MSM and heterosexual men), people older than 35 years, and those living in the North were among those most represented among undiagnosed people with HIV and with CD4 count < 200 cells/mm³ (Table 4).

In Table 4 also shows the YDFs by main characteristics and CD4 count. The YDF was 20.6% (95% CI: 16.4–23.8%) among people with CD4 count < 350 cells/mm³; the highest proportion was observed among heterosexual women (27.1%; 95% CI: 16.9–45.2%) and among people living in the North (26.6%; 95% CI: 19.1–35.2%). The YDF among people with CD4 count < 200 cells/mm³ was 28.3% (95% CI: 23.5–32.5%); once again, the highest proportion was observed among heterosexual women (36.1%; 95% CI: 26.0–49.9%). Similar results for the previous years (2012 and 2013) were observed (data not shown).

Prevalence of people living with undiagnosed HIV and with low CD4 cell count in 2014

Figure 1 shows the prevalence of people with undiagnosed HIV and with CD4 count < 350 cells/mm³, calculated as a rate per 100,000 adult residents. Overall, this rate was 11.3 (95% CI: 9.3–14.9) per 100,000 residents older than 15 years. The prevalence of people with undiagnosed HIV varied between the different Italian regions from 0.7 per 100,000 (Calabria) to 20.8 per 100,000 adults (Liguria); North and Central areas showed higher rates of those undiagnosed with a low CD4 count (Figure 1A).

Figure 1 (Panel B–D) shows the regional prevalence rates of undiagnosed people with HIV and with low CD4 cell count by HIV exposure groups. For heterosexual women the prevalence rate was 3.0 (95% CI: 1.4–5.6) per 100,000 women; the regional rates ranged from 0.1 (Friuli) to 15.6 (Trentino Alto Adige). Most of the Italian regions (15 regions) had prevalence rates ranging from 2.0 to 4.0 per 100,000 women (Figure 1B). For MSM the rate at national level was 280.4 (95% CI: 173.3

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– 450.2) per 100,000 MSM, for heterosexual men it was 8.3 (95% CI: 4.9–13.6) per 100,000 heterosexual men. The prevalence rates among MSM ranged from 6.2 (Basilicata, Molise, and Valle d’Aosta) to 450.6 (Liguria); almost all regions showed rates higher than 16 per 100,000 (Figure 1C), in particular five regions showed a regional rate higher than 300.0 per 100,000 MSM (Umbria, Sicilia, Toscana, Lombardia, and Liguria) (results not shown in the figure). The regional rates varied for heterosexual men from 0.4 (Basilicata, and Friuli) to 16.1 (Valle d’Aosta) per 100,000 heterosexual men; almost half of the Italian regions (nine regions) had an estimated prevalence rate higher than 8.0 per 100,000 heterosexual men (Figure 1D).

The annual rate of new diagnoses in Italy was 6.1 per 100,000 adult residents in 2014, ranging from 2.0 (Calabria region) to 11.1 (Lazio region) [5] (data not shown).

Figure 2 shows the relationship between the prevalence rate of undiagnosed HIV infection with CD4 count < 350 cells/mm³, and the rate of new HIV diagnoses in the 20 Italian regions. A positive correlation (ρ Spearman = 0.66; p value = 0.002) showed that regions with higher rate of new diagnoses also were the regions with a higher rate of undiagnosed people.
Discussion

Estimating the number of people living with undiagnosed HIV and with a low CD4 count enables the identification of determinants for a delayed access to care. We estimated the number of people with HIV and with a low CD4 count in Italy who are not yet diagnosed using an easy, reproducible, and validated model [13]. The strength of this study is that it provided estimates of demographic characteristics of undiagnosed people with HIV. The average yearly number of people living with undiagnosed HIV infection and CD4<350 cells/mm³ was 6,000 over the period 2012 to 2014, with a similar pattern across the years. The estimate of people with low CD4 count corresponded to 40% of the total number of people (including asymptomatic) with undiagnosed HIV infection in Italy (i.e. 15,000) [10]. The same proportion of people (40%) with CD4 count <350 cells/mm³ was found in France for the estimated undiagnosed people with HIV in 2010 [22]. Our numbers indicate there are a substantial number of people with undiagnosed HIV in Italy who need to be treated immediately. Failure to diagnose these individuals will result in greater morbidity and mortality for them, risk
| Table 3 | Estimated number of people living with undiagnosed HIV with CD4 < 350 cells/mm³ or CD4 < 200 cells/mm³, by main characteristics and year, Italy, 2012–2014 |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | **2012** | **2013** | **2014** |
|         | Point estimate (n) | 95% CI | Point estimate (n) | 95% CI | Point estimate (n) | 95% CI |
| **Undiagnosed with CD4 < 350 cells/mm³** | | | | | | |
| Total population | 6,028 | 5,090–7,826 | 6,156 | 4,891–8,517 | 5,899 | 4,882–7,786 |
| **Sex** | | | | | | |
| Women | 1,230 | 1,021–1,690 | 1,200 | 650–2,051 | 1,017 | 499–1,790 |
| Men | 4,799 | 3,998–6,323 | 4,961 | 3,874–7,085 | 4,893 | 3,992–6,568 |
| **Age group (years)** | | | | | | |
| 15–24 | 148 | 29–349 | 267 | 40–589 | 218 | 32–500 |
| 25–34 | 1,483 | 811–2,510 | 1,593 | 849–2,749 | 1,283 | 671–2,171 |
| 35–44 | 1,963 | 1,255–3,074 | 1,935 | 1,224–3,095 | 1,798 | 1,047–2,958 |
| 45–54 | 1,393 | 828–2,262 | 1,354 | 750–2,316 | 1,294 | 672–2,277 |
| ≥ 55 | 932 | 459–1,670 | 965 | 458–1,752 | 1,233 | 640–2,149 |
| **HIV exposure group** | | | | | | |
| PWID | 413 | 132–688 | 304 | 104–603 | 213 | 55–457 |
| Heterosexual women | 1,039 | 539–1,787 | 952 | 480–1,689 | 827 | 374–1,514 |
| Heterosexual men | 1,863 | 1,177–3,322 | 2,018 | 1,242–3,263 | 2,017 | 1,183–3,301 |
| MSM | 1,860 | 1,164–2,937 | 2,050 | 1,255–3,279 | 2,115 | 1,292–3,395 |
| Other/NA | 835 | 376–1,554 | 1,037 | 273–2,268 | 868 | 306–1,701 |
| **Nationality** | | | | | | |
| Italian | 4,386 | 3,382–6,101 | 4,703 | 3,617–6,617 | 4,178 | 3,128–5,922 |
| Non-Italian | 1,644 | 960–2,668 | 1,441 | 781–2,497 | 1,738 | 972–2,926 |
| **Geographical area** | | | | | | |
| North | 3,063 | 2,030–4,462 | 2,924 | 2,025–4,414 | 2,475 | 1,651–3,783 |
| Central | 1,899 | 947–3,310 | 2,027 | 963–3,836 | 1,838 | 943–3,109 |
| South | 1,212 | 728–1,948 | 1,320 | 763–2,194 | 1,555 | 940–2,511 |
| **Undiagnosed with CD4 < 200 cells/mm³** | | | | | | |
| Total population | 2,467 | 2,052–3,145 | 2,456 | 2,027–3,151 | 2,524 | 2,075–3,246 |
| **Sex** | | | | | | |
| Women | 457 | 326–644 | 553 | 341–860 | 416 | 247–656 |
| Men | 2,012 | 1,650–2,590 | 1,903 | 1,544–2,472 | 2,114 | 1,714–2,755 |
| **Age group (years)** | | | | | | |
| 15–24 | 96 | 27–203 | 81 | 18–178 | 65 | 8–155 |
| 25–34 | 461 | 272–731 | 442 | 251–709 | 358 | 196–587 |
| 35–44 | 810 | 546–1,215 | 826 | 547–1,247 | 812 | 530–1,236 |
| 45–54 | 638 | 423–952 | 654 | 421–1,002 | 667 | 421–1,033 |
| ≥ 55 | 406 | 238–645 | 419 | 251–664 | 569 | 345–896 |
| **HIV exposure group** | | | | | | |
| PWID | 149 | 58–283 | 122 | 47–232 | 133 | 42–265 |
| Heterosexual women | 378 | 219–602 | 415 | 241–663 | 345 | 196–554 |
| Heterosexual men | 808 | 550–1,123 | 859 | 578–1,290 | 889 | 585–1,354 |
| MSM | 761 | 514–1,123 | 734 | 485–1,103 | 787 | 523–1,183 |
| Other/NA | 371 | 188–657 | 403 | 156–760 | 503 | 232–892 |
| **Nationality** | | | | | | |
| Italian | 1,770 | 1,446–2,285 | 1,794 | 1,655–2,334 | 1,920 | 1,558–2,494 |
| Non-Italian | 701 | 452–1,070 | 674 | 417–1,047 | 590 | 350–942 |
| **Geographical area** | | | | | | |
| North | 1,349 | 1,053–1,817 | 1,214 | 921–1,674 | 1,194 | 899–1,652 |
| Central | 531 | 284–877 | 729 | 417–1,171 | 768 | 421–1,254 |
| South | 517 | 341–777 | 520 | 335–795 | 568 | 369–866 |

CI: confidence interval; MSM: men who have sex with men; NA: not available; PWID: people who inject drugs.

*: Estimates adjusted for reporting delays and missing values.
of onward transmission and greater costs accrued for the health system.

Focusing on the most recent year analysed, the prevalence of undiagnosed HIV infections was 11.3 per 100,000 adults in the resident population in 2014, ranging from 0.7 to 20.8 for different regions. Differences in regional prevalence could be attributed to factors, such as (i) different spread of HIV infection [5,15], (ii) different levels of HIV risk awareness [23,24], and (iii) the risk groups prevalent in each region.

This is in line with a cross-sectional study [20] that indicated a higher prevalence of people diagnosed and linked to care in northern Italy. Moreover, despite IDCs being well distributed throughout Italy, surveillance data indicates higher numbers of new diagnoses of HIV infection and AIDS, as well as of HIV-positive people under treatment, in the North [5,15].

Different levels of HIV risk awareness were confirmed in a respective study, which showed that people living in the North were less aware of HIV risk factors compared with those in the Centre and South of Italy [23]. Furthermore, a study showed that regional differences of HIV risk awareness seem to be correlated with different socioeconomic factors and lifestyles existent in North and South Italy (unpublished data).

Differences in regional prevalences of undiagnosed HIV infection were very similar to those observed among HIV-positive people diagnosed that were linked to care

### Table 4

Proportions of new HIV diagnoses, undiagnosed and yearly diagnosed fraction among people living with HIV and with low CD4 count by main characteristics, Italy, 2014

| HIV exposure group | New diagnoses with CD4 < 350 cells/mm³ | Undiagnosed people with CD4 < 350 cells/mm³ | YDF in people with CD4 < 350 cells/mm³ | New diagnoses with CD4 < 200 cells/mm³ | Undiagnosed people with CD4 < 200 cells/mm³ | YDF in people with CD4 < 200 cells/mm³ |
|--------------------|-------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------|----------------------------------------|-------------------------------------|
| Total population   | 1,529                               | 5,899                                  | 20.6                                | 998                                 | 2,524                                  | 28.3                                |
| Sex                |                                     |                                        |                                      |                                     |                                        |                                      |
| Women              | 344                                 | 1,017                                  | 25.3                                | 216                                 | 416                                    | 34.2                                |
| Men                | 1,185                               | 4,893                                  | 19.5                                | 782                                 | 2,114                                  | 27.0                                |
| Age group (years)  |                                     |                                        |                                      |                                     |                                        |                                      |
| 15–24              | 76                                  | 218                                    | 25.9                                | 36                                  | 65                                     | 35.6                                |
| 25–34              | 326                                 | 1,283                                  | 20.3                                | 163                                 | 358                                    | 31.3                                |
| 35–44              | 501                                 | 1,798                                  | 21.8                                | 328                                 | 812                                    | 28.8                                |
| 45–54              | 380                                 | 1,294                                  | 22.7                                | 294                                 | 667                                    | 30.6                                |
| ≥ 55               | 246                                 | 1,233                                  | 21.2                                | 177                                 | 569                                    | 23.7                                |
| HIV exposure group |                                     |                                        |                                      |                                     |                                        |                                      |
| PWID               | 65                                  | 213                                    | 23.4                                | 48                                  | 133                                    | 26.5                                |
| Heterosexual women | 308                                 | 827                                    | 27.1                                | 195                                 | 345                                    | 36.1                                |
| Heterosexual men   | 486                                 | 2,017                                  | 19.4                                | 347                                 | 889                                    | 28.1                                |
| MSM                | 539                                 | 2,115                                  | 20.3                                | 306                                 | 787                                    | 28.0                                |
| Other/NA           | 131                                 | 868                                    | 14.4                                | 102                                 | 503                                    | 16.9                                |
| Nationality        |                                     |                                        |                                      |                                     |                                        |                                      |
| Italian            | 1,105                               | 4,178                                  | 20.9                                | 738                                 | 1,920                                  | 27.8                                |
| Non-Italian        | 418                                 | 1,738                                  | 19.4                                | 255                                 | 590                                    | 23.5                                |
| Geographical area  |                                     |                                        |                                      |                                     |                                        |                                      |
| North              | 895                                 | 2,425                                  | 26.6                                | 570                                 | 1,194                                  | 23.2                                |
| Central            | 230                                 | 1,838                                  | 15.1                                | 156                                 | 768                                    | 16.9                                |
| South              | 404                                 | 1,555                                  | 20.6                                | 272                                 | 568                                    | 22.5                                |

MSM: men who have sex with men; NA: not available; PWID: people who inject drugs; YDF: yearly diagnosed fraction.

*a Defined as CD4 < 350 cells/mm³ and CD4 < 200 cells/mm³.

*b Data in this table are underestimated, as in the Central area new diagnoses with missing CD4 count was at 60%.

The YDF is expressed as the yearly number of new diagnoses / (yearly number of new diagnoses + estimated number of undiagnosed people living with HIV).
[15] as well as to differences observed among new HIV diagnoses across the Italian regions [5]. These findings confirm that, at least in Italy, regions with high rates of new diagnoses also encompass a high proportion of both diagnosed and undiagnosed people [5,15]. This highlights the importance of the regional differences in the spread of HIV infection that can be observed at a wider level across European countries as well as within the United States [25,26].

In addition, the highest prevalence of undiagnosed HIV infection was observed among MSM in whom it was 280 per 100,000 MSM, whereas among heterosexual men it was 8 per 100,000 heterosexual men, and among heterosexual women it was 3 per 100,000 female residents, with large differences across the Italian regions. Even though MSM have been reported to have high HIV testing rates compared with other key populations in high-income countries [24,27-29], as well as, the highest perception of the risk of HIV infection [23,24], the study findings show that they account for the highest number (2,115) and the highest proportion (35%) of undiagnosed people with a low CD4 count in 2014. MSM in Italy are also the subgroup most represented (nearly 50%) among the total population of undiagnosed HIV people (including asymptomatic), as estimated by Mammone et al. [10]. This could be attributed to a high rate of new infections in this group during the most recent years [1,30-32] combined with a large number of undiagnosed people who contribute to ongoing transmission [10,22,33]. In addition, a high HIV prevalence and a high proportion of MSM with undiagnosed HIV could be attributed to high levels of sexual activity and to some risk behaviours for sexual transmission of HIV [34]. Therefore, test-seeking behaviour should be encouraged and voluntary counselling and testing made more accessible in Italy, a country where the stigma against HIV and homosexuality may still be prevalent [20,35].

Focusing on the most recent year in our analysis, a high proportion of undiagnosed people with low CD4 count was reported among heterosexual men (33.4%), whereas in other Italian studies this population accounted for a quarter of the total undiagnosed (including those asymptomatic [10]), and a quarter of new diagnoses reported to the INHS [5]. The higher proportion of heterosexual men among undiagnosed with a low CD4 count could depend, partly, on the fact that heterosexuals were more likely to have a longer undiagnosed interval (time lag from infection to HIV diagnosis) as shown in other studies worldwide [8,36-38]. In Italy, Mammone et al. [37] estimated that heterosexuals had a far longer lag from infection to HIV diagnosis compared with MSM (7.7 vs 3.7 years).

We found a YDF of 20.6% which was similar to that reported recently by Sasse [18] on the total HIV population in the European countries. Among heterosexual women the YDF was the highest (27.1%) compared to the other groups, suggesting a more frequent access to HIV testing, likely facilitated from routine screening during pregnancy in this population [5,39]. This result may mean a certain degree of success with regard to testing in this group. The highest YDF (26.6%) among people living in the North compared to the other areas may be an indicator of the wider availability of IDCs and HIV testing services in this area [40]. A higher detection could represent a more efficient and therefore better surveillance system.

This study has some limitations. First, we assumed that people with HIV who develop AIDS, or other HIV-related symptoms, will almost certainly present for care, and as consequence, will be all diagnosed with HIV and notified to the surveillance system (assumption of London method) [12,13]. However, the assumption of the London method can be considered acceptable for our study, as HIV testing and access to care are free in all IDCs and the proportion of people living with HIV who do not attend the IDCs should be reasonably low. Another limitation was the assumption that CD4 counts in those where the information was not available was the same as in those with available information. This assumption was supported by other studies conducted on the Italian HIV Surveillance data [10]. The missing CD4 count information, in the Italian national HIV surveillance data, mainly in the Central regions, may make the estimates less robust. However, in the remaining areas the proportion of missing data were lower than 10%.

In terms of the reporting delay we assumed a constant decrease over the 3 years. This had a small impact on the estimates as it was sufficiently low. Other limitations which may have a considerable impact on the eventual estimates include the effect of new testing strategies, the changes over time in the reporting of data, and the different quality of data in the surveillance systems of all the regions.

Conclusions
About 6,000 HIV-positive people with low CD4 counts, remained annually undiagnosed between 2012 and 2014 in Italy. This indicates that ca 40% of the 15,000 total undiagnosed people living with HIV in Italy were in immediate need of diagnosis, linkage to care and antiretroviral treatment in order to avert high HIV-related morbidity, mortality and healthcare costs.

The majority of those with undiagnosed HIV and with low CD4 counts were MSM and heterosexual men, and there were large differences in prevalence of undiagnosed HIV infections with low CD4 across the Italian regions. These findings highlight the importance of improving HIV testing availability, with a focus on men, in order to diagnose and provide treatment to those living with undiagnosed HIV in Italy.
Regional representatives of the National HIV Surveillance System

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1. European Centre for Disease Prevention and Control (ECDC) / World Health Organization Regional Office for Europe (WHO). HIV/AIDS surveillance in Europe 2015. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/HIV-AIDS-surveillance-Europe-2015.pdf
2. The late presenters working group in COHERE in EuroCoord. Late presentation for HIV care across Europe: update from the Collaboration of Observational National HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013. Euro Surveill. 2015;20(47):30070.
3. Centers for Disease Control and Prevention (CDC). HIV Surveillance Report, 2014; vol. 26. Atlanta: CDC; Nov 2015. Available from: https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html
4. Camoni L, Raimondo M, Regine V, Salfa MC, Suligoi Regional representatives of the HIV Surveillance System. Late presenters among persons with a new HIV diagnosis in Italy, 2010-2011. BMC Public Health. 2013;13(1):281. https://doi.org/10.1186/1471-2458-13-281 PMID: 23537210
5. Raimondo M, Borsos S, Regine V, Pugliese L, Santequiliani M, Ferri M, et al. Assessing the impact of early HIV detection on new HIV diagnoses and global AIDS incidence in Italy 2013. AIDS. 2016;30(9) Suppl 1, Italian. Available from: http://www.iss.it/publ/index.php?lang=1&id=3003&tipo=4
6. Girardi E, Sabin CA, Montforte AD. Late diagnosis of HIV infection: epidemiological features, consequences and strategies to encourage earlier testing. [Acquir Immune Defic Syndr. 2007;46(Suppl 1):S3-8. https://doi.org/10.1097/01.qai.0000286597.57066.2b PMID: 17713423
7. Platten M, Linnemann R, Kümmerle T, Jung N, Wyen C, Ehren K, et al. Clinical course and quality of care in ART-naive patients newly presenting in a HIV outpatient clinic. Infection. 2014;42(5):849-57. https://doi.org/10.1007/s15010-014-0664-9 PMID: 24966163
8. Wong NS, Wong KL, Lee MP, Tsang OTY, Chen DHCP, Lee SS. Estimation of the undiagnosed intervals of HIV-infected people by a modified back-calculation method for reconstructing the epidemic curves. PLoS One. 2016;11(7):e0159021. https://doi.org/10.1371/journal.pone.0159021 PMID: 27403882
9. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Rakai Project Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med. 2000;342(13):921-9. https://doi.org/10.1056/NEJM200003303421303 PMID: 10738050
10. Mammonne A, Pezzotti P, Regine V, Camoni L, Puro V, Ippolito G, et al. How many people are living with undiagnosed HIV infection? An estimate for Italy, based on surveillance data. AIDS. 2016;30(7):1131-6. https://doi.org/10.1097/QAD.0000000000001034 PMID: 26807973
11. Op de Coul EL, Schreuder I, Conti S, van Sighem A, Xiridou M, Van Veen MG, et al. Changing Patterns of Undiagnosed HIV Infection in the Netherlands: Who Benefits Most from Intensified HIV Test and Treat Policies? PLoS One. 2015;10(7):e0133232. doi: https://doi.org/10.1371/journal.pone.0133232. eCollection 2015.
12. Lodwick RK, Nakagawa F, van Sighem A, Phillips AN. Use of surveillance data on HIV diagnoses with HIV-related symptoms to estimate the number of people living with undiagnosed HIV in need of antiretroviral therapy. PLoS One. 2015;10(3):e0121992. https://doi.org/10.1371/journal.pone.0121992 PMID: 26578925
13. European Centre for Disease Prevention and Control (ECDC). HIV modelling tool. Stockholm: ECDC; 14 Sep 2015. Available from: https://ecdc.europa.eu/en/publications-data/hiv-modelling-tool
14. Italian Ministry of Health. Decreto Ministeriale 31 marzo 2008. istituzione del sistema di sorveglianza delle nuove diagnosi di infezioni da HIV. [Establishment of the surveillance system for new diagnoses of HIV infection]. Gazzetta Ufficiale n. 175, 28 July 2008. Italian. Available from: http://old.iss.it/binary/coa/cont7/DECRETO_31_marzo_2008.pdf
15. Camoni L, Raimondo M, Dorucci M, Regine V, Salfa MC, Suligoi BCARPHA Study Group. Estimating minimum adult HIV prevalence: a cross-sectional study to assess the characteristics of people living with HIV in Italy. AIDS Res Hum Retroviruses. 2015;31(3):282-7. https://doi.org/10.1089/aid.2014.0154 PMID: 25432098
16. Istituto Nazionale di Statistica (ISTAT). Demografia in Cifre. [Demography in figures]. Rome: ISTAT. [Accessed 28 Jun 2017]. Italian. Available from: http://www.demo.istat.it/
17. Little RJA, Rubin DB. Statistical Analysis with Missing Data. 2nd ed. New York: Wiley; 2002.
18. Sasse A. Letter to the editor: New metrics to monitor progress towards global HIV targets: using the estimated number of undiagnosed HIV-infected people as denominator. Euro Surveill. 2016 Dec 15;21(50). pii: 30424. doi: https://doi.org/10.2807/1560-7917.ES.2016.21.50.30424
19. Marcus U, Hickson F, Weatherburn P, Schmidt AJEMIS Network. Estimating the size of the MSM populations for 38 European countries by calculating the survey-surveillance discrepancies (SSD) between self-reported new HIV diagnoses from the European MSM internet survey (EMIS) and surveillance-reported HIV diagnoses among MSM in 2009. BMC Public Health. 2013;13(1):99. https://doi.org/10.1186/1471-2458-13-99 PMID: 24208818

20. Istituto Nazionale di Statistica (ISTAT). [The homosexual population in Italian society]. Statistiche. Report Anno 2011. Italian. Available from: http://www.istat.it/it/archivio/62168

21. Grazzini G, Raimondo M, Facco G, Regine V, Pugliese L, Kaus C, et al. A cross-sectional study among blood donors on sexual risk behaviors for HIV infection. Vox Sang. 2015;109(Suppl. 1):228-9.

22. Supervie V, Ndwazin JD, Lodi S, Costagliola D. The undiagnosed HIV epidemic in France and its implications for HIV screening strategies. AIDS. 2014;28(12):1797-804. https://doi.org/10.1097/QAD.0000000000000270 PMID: 24681416

23. Giannini E, Regine V, Pezzotti P, Suligoi B, Mammea A, Girardi E. “Stima della proporzione di insospevoli del rischio di HIV in Italia: analisi dei dati del sistema di sorveglianza HIV”. Approfondimenti in: Regine V, Pugliese L, Boros S, Santiaguliani M, Ferris M, Suligoi B. Aggiornamento delle nuove diagnosi di infeczione da HIV e dei casi di AIDS in Italia al 31 dicembre 2016. Not Ist Super Sanità. 2017; 30(9) Suppl 1:17-18. Available from: http://old.iss.it/publ/index.php?lang=it&id=3087&tipo=4

24. Clifton S, Nardone A, Field N, Mercer CH, Tanton C, Macdowall W, et al. Continuous increase in HIV-1 incidence after the year 2000 among men who have sex with men in Rome: insights from a 25-year retrospective cohort study. Euro Surveill. 2013;18(33):20694. https://doi.org/10.2807/1560-7917.ES2013.18.33.20694 PMID: 24266528

25. Hall HI, An Q, Tang T, Song R, Chen M, Green TA, et al. Population-based HIV-1 incidence in France, 2003-08: a modelling analysis. Lancet Infect Dis. 2010;10(10):682-9. https://doi.org/10.1016/S1473-3099(10)70167-5 PMID: 20832367

26. Meireles P, Lucas R, Carvalho C, Fuertes R, Brito J, Campos M, et al. Incident risk factors as predictors of HIV seroconversion in the Lisbon cohort of men who have sex with men: first results, 2011-2014. Euro Surveill. 2015;20(41):21093. https://doi.org/10.2807/1560-7917.ES2015.20.41.21093 PMID: 25884151

27. Yin Z, Brown AE, Hughes G, Nardone A, Gill ON, Delpech VC, et al. HIV in the United Kingdom 2014 Report: data to end 2013. London: Public Health England, Nov 2014. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf

28. Ferrer L, Furegato M, Foschia JP, Folch C, González V, Ramarli D, et al. Undiagnosed HIV infection in a population of MSM from six European cities: results from the Sialon project. Eur J Public Health. 2015;25(3):494-500. https://doi.org/10.1093/eurpub/ckw139 PMID: 25161202

29. Miranda M, Gios L, Joanna Davis R, Furegato M, Breveglieri M, Folch C, et al. Socio-demographic factors predicting HIV test seeking behaviour among MSM in 6 EU cities. Eur J Public Health. 2017;27(2):313-8. https://doi.org/10.1093/eurpub/ckw144 PMID: 27657534

30. Ndwazin JD, Costaglola D, Supervie V. New method for estimating HIV incidence and time from infection to diagnosis using HIV surveillance data: results for France. AIDS. 2011;25(35):3905-13. https://doi.org/10.1097/QAD.0b013e3283f50669 PMID: 21811147

31. Mammea A, Pezzotti P, Camoni L, Raimondo M, Dorruchi M, et al. Time from infection with HIV to diagnosis in Italy: an estimate using surveillance data. Oral presentation. Proceedings of the 8th Italian Conference on AIDS and antiviral research (ICAR); 2016 Jun 6-8; Milan, Italy.

32. Song R, Hall HI, Green TA, Szarwarkow CL, Pantazis N. Using CD4 Data to Estimate HIV Incidence, Prevalence, and Percent of Undiagnosed Infections in the United States. J Acquir Immune Defic Syndr. 2017;74(1):3-9. https://doi.org/10.1097/QAI.0000000000001151 PMID: 27509244

33. European Centre for Disease Prevention and Control. Antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility in the EU/EEA, Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/antenatal-screening-HIV-hepatitis-B-syphilis-rubella-EU.pdf

34. Mirandola M, Gios L, Joanna Davis R, Furegato M, Breveglieri M, Folch C, et al. [People living with HIV in Italy: data from the second census]. Not Ist Super Sanità. 2017; 30(1). Italian. Available from: http://www.iss.it/binary/publ/cont/ONLINE_GENNAIO.pdf

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