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| Complete List of Authors: | Reyes-Urueña, Juliana; Centre d'Estudis Epidemiològics sobre les ITS i Sida de Catalunya (CEEISCAT)<br>Campbell, Colin; Public Health England, Tuberculosis Section, Centre for Infectious Disease Surveillance and Control, National Infection Service<br>Vives, Nuria; Centre d'Estudis Epidemiològics sobre les ITS i Sida de Catalunya (CEEISCAT)<br>Esteve, Anna; Centre d'Estudis Epidemiològics sobre les ITS i Sida de Catalunya (CEEISCAT)<br>AMBROSIONI, Juan ; Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer<br>Tural , Cristina; Hospital Universitari Germans Trias i Pujol<br>Ferrer, Elena; Hospital Universitari de Bellvitge<br>Navarro, Gemma; Hospital Parc Tauli,<br>Force, Luis; Hospital de Mataro<br>García, Isabel; Hospital General d'Hospitalet<br>MASABEU, Àngels ; Hospital de Palamós<br>Vilaró, Josep ; Consorci Hospitalari de Vic<br>Garcia de Olalla, Patricia; Agencia de Salut Pública de Barcelona,<br>Caylà, Joan; CIBER de Epidemiología y Salud Pública (CIBERESP), ; Public Health Agency of Barcelona, Epidemiology Service<br>Miro, Josep; Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer<br>Casabona, Jordi; Hospital Universitari Germans Trias i Pujol, Centre for Epidemiological Studies on HIV/STI in Catalonia (CEEISCAT); Instituto de Salud Carlos III, Biomedical Research Consortium of Epidemiology and Public Health (CIBERSP) |
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**Research report**

# Estimating the HIV undiagnosed population in Catalonia, Spain: The first step in the cascade of care for key groups

Juliana REYES-URUEÑA[*1,2,3,4], Colin NJ CAMPBELL[5], Núria VIVES[1,2,3,4], Anna ESTEVE[1,2,3,4], Juan AMBROSIONI[6], Cristina TURAL[7], Elena FERRER[8], Gemma NAVARRO[9], Lluis FORCE[10], Isabel GARCÍA[11], Àngels MASABEU[12], Josep VILARÓ[13], Patricia GARCÍA DE OLALLA[2,14], Joan A. CAYLÀ[2,14], Josep M. MIRÓ[6], Jordi CASABONA[1,2,3,4] and PISCIS investigators.

[1] Centre Estudis Epidemiologics sobre les Infeccions de Transmissio Sexual i Sida de Catalunya (CEEISCAT), Dept Salut, Generalitat de Catalunya, Spain.
[2] CIBER Epidemiologia y Salud Pública (CIBERESP), Spain.
[3] Institut d'Investigació Germans Trias i Pujol (IGTP), Spain.
[4] Departament de Pediatria, d'Obstetricia i Ginecologia i de Medicina Preventiva i de Salut Publica, Universitat Autònoma de Barcelona, Bellaterra, Spain.
[5] Tuberculosis Section, Centre for Infectious Disease Surveillance and Control, National Infection Service, Public Health England, London, United Kingdom.
[6] Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Spain.
[7] Hospital Universitari Germans Trias i Pujol, Badalona, Spain.
[8] Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain.
[9] Corporació Sanitària i Universitària Parc Taulí, Sabadell, Spain.
[10] Hospital de Mataró, Mataró, Spain.
[11] Hospital General d'Hospitalet, Barcelona, Spain.
[12] Hospital de Palamós, Spain,
[13] Consorci Hospitalari de Vic, Barcelona, Spain
[14] Agencia de Salud Pública de Barcelona, Spain.

***Corresponding author***
Juliana Reyes-Urueña
Centre Estudis Epidemiologics sobre les Infeccions de Transmissio Sexual i Sida de Catalunya (CEEISCAT), Dept Salut, Generalitat de Catalunya, Spain.
Email: jmreyes@iconcologia.net
Phone number: +34 934978931

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**Abstract**

**Objective**: Undiagnosed HIV continues to be a hindrance to efforts aimed at reducing incidence of HIV. The objective of this study was to provide an estimate of the undiagnosed HIV population in Catalonia.

**Methods**: To estimate HIV incidence, time between infection and diagnosis, and the undiagnosed population stratified by CD4 count, we used the ECDC HIV Modelling Tool version 1.2.2. This model uses data on new HIV and AIDS diagnoses from the Catalan HIV/AIDS surveillance system from 2001 to 2013. Data used to estimate the proportion of people enrolled, on ART and virally suppressed in the HIV care cascade were derived from the PISCIS cohort.

**Results**: The total number of people living with HIV in Catalonia in 2013 was 34,729 (32,740-36,827), with 12.3% (11.8-18.1) of whom were undiagnosed. By 2013, there were 8,458 (8,101, 9,079) Spanish-born MSM and 2,538 (2,334-2,918) migrant MSM living with HIV in Catalonia. A greater proportion of migrant MSM than local MSM was undiagnosed (32% vs. 16%). In the subsequent steps of the HIV care cascade, migrants MSM experience greater losses that the Spanish-born MSM; in retention in care (74% vs. 55%), in the proportion on cART (70% vs. 50%) and virally suppressed (65% vs. 46%).

**Conclusions**: By the end of 2013, there were an estimated 34,729 people living with HIV in Catalonia, of whom 4,271 were still undiagnosed. This study shows that the Catalan epidemic of HIV has continued to expand with the key group sustaining HIV transmission being MSM living with undiagnosed HIV.

**Key words:** HIV surveillance; HIV undiagnosed infection; Continuum of care; Migrant; MSM; cascade

**Strengths and limitations of this study**

- The use of regular surveillance and cohort data gives high consistency of local estimates.
- The use of the HIV Modelling Tool allowed calculating the first step of the HIV care cascade by region of origin and among MSM in Catalonia.
- The various subgroup analyses completed for this study may not necessarily explain complex differences in global HIV epidemic dynamics among migrants and MSM, but they do demonstrate that the key group sustaining HIV transmission is MSM living with undiagnosed HIV.
- Linking surveillance and cohort dataset to population migration and death registries is weak in Catalonia; therefore this information is poorly crossed between datasets; which can lead to misclassification of vital status or out-migration that might over-estimate the number still alive and living in Catalonia.

## Introduction

Undiagnosed HIV continues to be a hindrance to efforts aimed at reducing incidence of HIV. People who remain unaware of their HIV status for a long time have an increased risk of transmitting the virus to others [1]. Some studies have shown that undiagnosed individuals may give rise to most new HIV transmissions [1,2], due to higher infectiousness because of elevated viral load at the time of HIV seroconversion [3] or poor decisions related to their risk behaviours [4]. Furthermore, undiagnosed individuals are also at risk of delayed diagnosis as they do not benefit from timely initiation of combination antiretroviral treatment (cART), experience higher HIV-related morbidity and higher mortality, being 11 times more likely to die within a year of being tested than if they had been tested after they were first exposed [5].

In 2015, it was estimated that around 15-16% (122,000/810,000) of people living with HIV (PLHIV) were unaware of their infection in the European Union and the European Economic Area (EU/EEA) [6,7], with proportions ranging from 10% in Sweden [8], 12% in both the Netherlands and Italy [9,10], 17% in UK [11] to 34% in France [12]. Numbers reported from the US are similar to those in Western Europe, with 16.4% of the HIV-infected individuals being undiagnosed in 2013 [13]. In previous work on the Catalan HIV care cascade, we were not in the position to estimate this step, relying on average European estimates [14]. The availability of the ECDC model [15] means we now have a tool that is readily available and uses routinely available surveillance data to estimate undiagnosed HIV, time from infection to diagnosis and estimated annual incidence.

Estimates of the number of people in a country or region who have undiagnosed HIV are of paramount importance for understanding the burden of HIV, stimulating the early identification and treatment such people, and informing strategic plans for the future delivery of cART [16]. Therefore the objective of this study was to provide an estimate of the undiagnosed HIV population in Catalonia, taking into account both men who have sex with men (MSM) and region of origin, using an ECDC model that uses routinely available surveillance data.

## Methods

We undertook descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born populations. Migrants were defined as individuals born in a country other than Spain.

The primary data source was the unified Catalan HIV/AIDS surveillance system from 2001 to 2013 [17]. We extracted information on the date of HIV diagnosis, sex, age, transmission mode (people who inject drugs (PWID), heterosexual men, heterosexual women and MSM), CD4+ cell count and clinical stage at diagnosis (presentation with late and/or advanced HIV disease). Data used to calculate the number of PLHIV, the number of undiagnosed and diagnosed population and the time between infection and diagnosis, were the annual number of new HIV diagnoses by CD4+ count stratum adjusted for delay in reporting and under-notification, the annual number of new AIDS cases, and the annual number of concurrent HIV/AIDS diagnoses (an AIDS diagnosis within 6 weeks of HIV diagnosis).

Data used to estimate the proportion of people enrolled, on ART and virally suppressed in the HIV care cascade were derived from the PISCIS Cohort, which includes data on over 17000 HIV-positive people seen for follow-up (coverage around 80%) in all of the participating centres in Catalonia and is fully described elsewhere [18]. Each of these steps were analysed by region of origin and by MSM who were under active follow-up on the cohort.

Written informed consent and ethical approval was not obtained, as the data used were aggregate anonymized surveillance and HIV care information.

### Statistical analysis

Differences in the distribution of sex, age, transmission mode and presentation with late and/or advanced HIV disease, were assessed by region of origin, using Pearson's chi-squared test for categorical variables and Student's T test for continuous variables.

To estimate HIV incidence, time between infection and diagnosis, and the undiagnosed population by CD4 count strata and its 95% confidence intervals (CI), we used the ECDC HIV Modelling Tool version 1.2.2 [15], which is based on a multi-state back-calculation model that uses surveillance data on new HIV and AIDS diagnoses and that models the HIV incidence curve by cubic splines. The model is described in detail elsewhere [16,19]. We considered five distinct historical periods for which CD4 stratum-specific diagnosis rates were estimated: (1) 1980-1984, during which the first AIDS cases were diagnosed; (2) 1985–1998, when serological testing for HIV became widely available; (3) 1999–2001, the start of the era of combination antiretroviral therapy (cART); (4) 2002-2013. Annual numbers of HIV diagnoses were available from 2001 onwards. The CD4 count at the time of diagnosis was defined as the first CD4 count after diagnosis and before start of treatment. Overall, 81.6% of the patients diagnosed from 2001 onwards had a CD4 count available at the time of diagnosis. The estimated annual numbers of diagnoses by CD4 count stratum were then fitted to the observed numbers. The number of HIV-infected who were still alive by the end of 2013 was estimated by subtracting the cumulative number of people who died from the cumulative number of HIV infections. The number of deaths among diagnosed people was taken from the Catalan HIV Surveillance System from 2001-2013.

The subsequent step of linked to care was calculated by applying to the preceding stage a proportion estimated from surveillance data. The proportions retained in care, on cART and virally suppressed were derived from the PISCIS cohort. A fuller description of the methods used has been published elsewhere [14]. The level of significance was set at p value <0.05. Data analysis was performed using Stata 12. CollegeStation,TX:StataCorpLP.

## Results

There were 10,150 new HIV diagnoses in adults (>18 years of age) reported to the Catalan National Surveillance System from 2001 to 2013, 60% of the cases were Spanish-born, 80.2% were men, and the median age was 35 years old. The epidemiological profile of migrants was different to that of the Spanish-born population; there was a higher proportion of women (24.6% and 16.7%, respectively) and were younger at diagnosis (median age of 33 vs. 37, respectively). In both migrants and the Spanish-born groups, the most frequent at-risk population was MSM (40% and 43%, respectively). Supplemental File.

Between 1980 and 2013, a cumulative number of 41,364 (CI=35,299, 44,990) infections in the Catalan population were estimated to have occurred. The number of new HIV infections peaked around 1988 with 3,124 (CI=3,031, 3,159) (figure 1A), declining nearly sevenfold, from 2,674 (CI=2,388, 2,663) in 1990 to 391 (CI=188, 372) in 1999. From 2011 the number of new infections stared to peak up again reaching levels comparable with those in the mid-1990s, with the highest number in 2013, 1,120 (CI=461, 1,324). In 2013, the number of new infections among the Spanish-born population reached a number of 744 (CI=546, 934) (Figure 2A), while among the migrants was 376 new infections (CI=281, 471) (Figure 2C). Finally among MSM, in both Spanish-born and migrants there was a clear stepping increase in the number of new infections from 2001, reaching the highest number in 2013, with 404 (CI=322, 480) and with 227 (CI=163, 310), respectively (Table 1).

The mean time between infection and diagnosis if diagnosis rates remain the same as in the year of infection is shown in Figure 1B. Between 1980 and 1983, when HIV could only be diagnosed once AIDS symptoms appeared, the average time between infection and HIV diagnosis for people infected in this period, were conditions to have remained as they were in this period, would have been 11.6 years. This decreased to 4.7 years (CI=4.4, 5.0) in the period 1984–1998. From 2000 onwards, the time to HIV diagnosis steadily decreased to 3.9 (CI=3.6, 4.6) years on average for the whole population in 2013. By region of origin, in both Spanish-born people and migrants, there was a

similar decreasing trend in the average time from infection to diagnosis until it reached 3.6 years (CI=3.4, 3.8) and 4.7 years (CI=4.6, 5.01), respectively in 2013.

Figure 1C shows the estimated total number of PLHIV in Catalonia from 1980 to 2013, including those not yet diagnosed. Overall, there was an increasing trend throughout the time period, reaching the highest number of people in 2013, a total of 34,729 (CI=32,740, 36,827) PLHIV in Catalonia. Of these, 4,271 (CI=3,737, 6252) were undiagnosed, a proportion of 12.3% (CI=11.8, 18.1). Comparing the trend in the number of PLHIV between migrant and Spanish-born groups (Figure 2B and Figure 2D), it was observed that among locals there was a progressive but not very pronounced rise from 1991 to reach the highest number in 2013 with 27,648 (CI=25,365, 29,379) PLHIV, just 5.8% (CI=5.8, 6.6) of whom were undiagnosed (1,603, CI= 1,421, 1,819). Conversely, among migrants the number of PLHIV rose steeply since the beginning of the epidemic, also reaching a peak in 2013 with 7,081 (CI=6,492, 7,616), but with four times the undiagnosed population (23.4%, CI=22.7, 25.1) compared to the local population. Among (Figures 3A and 3B) both local and migrant MSM there has been a large increase in the number of MSM living with HIV in the last 10 years, with a higher increasing slope among migrant MSM. By 2013, there were 8,458 (CI=8,101, 9,079) Spanish-born MSM and 2,538 (CI=2,334, 2,918) migrant MSM living with HIV in Catalonia, with 16.4% (CI=14.2, 17.7) and 32.3% (CI=28.4, 34.4) undiagnosed, respectively.

Finally, figure 4 shows the differences in the HIV care cascade in MSM by origin. As a percentage of the total PLHIV, migrant MSM have a greater proportion undiagnosed (32% vs. 16%) that local MSM. In subsequent steps in the HIV care cascade, migrant MSM experience greater losses due to the big different in the proportion of undiagnosed, when compared to the Spanish-born MSM, with lower proportion retained in care (74% vs. 55%), on cART (70% vs. 50%) and virally suppressed (65% vs. 46%).

## Discussion

Our study estimates that by the end of 2013, there were an estimated number of 34,729 people living with HIV in Catalonia, Spain, of whom 4,271 were still undiagnosed. This study also shows that migrants had a very high proportion of undiagnosed compared to Spanish-born population, and as it has been described by other sources of information from Catalonia [17], this study found that the Catalan epidemic of HIV has continued to expand during the past decade with the key group sustaining HIV transmission being MSM living with undiagnosed HIV and in the asymptomatic stage, especially migrants MSM.

The estimated overall prevalence of undiagnosed HIV-infected people in Catalonia (12.3%) is within the range of those recently obtained in other countries by 2013: 10% in Italy, 12% in Austria, 16% in Belgium and France, 17% in Germany, 18% in Spain and 19% in United Kingdom [7]. Nevertheless we think that some underestimation may have occurred due to two facts; first, that the method that we applied uses data on case reports, which may be subject to underreporting, which can be ranged between 10% to 40% [20,21], and can lead to underestimates HIV incidence and may also affect estimates of diagnosis rates, and thus lower the percent undiagnosed; and second, by the fact that we could not feed the model with migration data. As Catalan epidemic is highly influence by migration we believe that this lower the estimates of the annual number of new HIV infections and therefore undiagnosed HIV-infected individuals.

In line with our results, other studies also had identified among migrants a great proportion of undiagnosed [22,23]. In Catalonia this could be explained by the fact that migrants experienced a higher number of barriers to access HIV testing services than the Spanish-born population and that these needs might be driven primarily by shared risk factors [24]. This also can be due to the fact that migrants face cultural and linguistic barriers, as well as, legal and administrative impediments to accessing health services and thus HIV testing facilities [25]. In Europe the HIV testing uptake among migrants range from 23% to 64% [25]. This difference can differ by sex, as higher proportion of migrant women have been tested for HIV compared with men; this is

partially owing to women's acceptance of routine HIV screening during antenatal care. However, beyond this, several studies support a gender difference in HIV testing uptake, with migrant men being not only less exposed to HIV testing but also less willing to be tested [25]. However, this lower rate of HIV testing among migrant men might be more representative of migrant heterosexual men that MSM migrants, as these later perceive themselves as being at higher risk for HIV, and thus being more likely to have ever been tested for HIV than the local MSM [26,27]. Although, it has been found that untested migrant MSM are particularly hard to reach [27], which in line with our estimates.

Our results suggest that the Catalan HIV epidemic has been sustained by the HIV transmission among undiagnosed MSM, as it has been described in other studies in Catalonia [28,29]. Consistent with this, in the United Kingdom, using the same model it has been estimated that around two in three new infections were attributable to MSM living with undiagnosed HIV [30], and in Switzerland that around 82% of new cases among MSM were acquired from HIV undiagnosed men [31]. This finding can be explained by an increase in risky sexual behaviours [32,33], including high prevalence of unprotected anal intercourse and increasing numbers of sexual partners [34]. This is also supported by a recent survey that reported that 37% of MSM recruited in gay venues had not tested for HIV in the past 12 months [32]. It has also been described that a great proportion of undiagnosed MSM have acquired the infection recently, which made them to be most infectious and the maintenance group of the HIV epidemic [34]. The risky sexual conducts among migrant MSM have been also described, with higher prevalence of unprotected anal intercourse than Spanish-born MSM [35,36] and specifically among Latin American MSM, high HIV prevalence rates among those diagnosed with syphilis and gonorrhoea, as well as, with high prevalence and incidence rates of STIs in those newly diagnosed with HIV [35]. While limited resources should be allocated primarily to promote testing in high-activity MSM, as they are the key group sustaining the epidemic, there is also a case for encouraging all MSM including migrants MSM to test regularly for HIV, this includes design long term

sustainable outreach-based HIV interventions to reach as many MSM as we could for HIV testing.

Biomedical and behavioural interventions, targeting both HIV-infected and HIV-uninfected MSM, should be used. In this regard, it will be essential to use interventions with proven efficacy , such as treatment as prevention, test and treat interventions, in combination with pre-exposure prophylaxis in highly adherent people, and to implement effective behavioural interventions that prevent an increase in risky behaviours, all of these intervention must be integrated in a well-designed strategy of combination prevention, as it has been described in other studies [37]. Besides, in order to reduce the fraction of undiagnosed should be considered implementing and scaling up innovative approaches to promote greater access to and uptake of HIV testing by those most at risk, including community-based testing, home sampling, as well as indicator-condition- guided testing.

These results must be interpreted in light of several key methodological limitations. The use of the HIV Modelling Tool facilitated the standardisation of estimates for PLHIV, however available information is partial and not representative of the different subpopulations of migrants and MSM across all Catalonia. Despite this limitation, this analysis allowed us to calculate the first step of the HIV care cascade by region of origin and among MSM in Catalonia. The various subgroup analyses completed for this study may not necessarily explain complex differences in global HIV epidemic dynamics among migrants and MSM, but they do demonstrate that the key group sustaining HIV transmission is MSM living with undiagnosed HIV and that among migrants testing coverage will need to be intensify and increase to find those undiagnosed. Although the use of PISCIS cohort data improved the consistency of the estimates, we are unable to link surveillance and cohort datasets to maximise internal consistency, therefore we are unable to distinguish between those diagnosed and those linked to care (enrolled in the cohort), although linkage to care is expected to be high given the Catalan healthcare system characteristics and the high cohort coverage. Additionally, using a single VL measurement may also over-estimate durable viral suppression,

however, they provide a snapshot of the continuum in 2013 which is simple to interpret and communicate to policy-makers, as it has been described by other authors [7,38]. Finally, linking surveillance and cohort dataset to population migration and death registries is weak in Catalonia; therefore this information is poorly crossed between datasets; which it can lead to misclassification of vital status or out- migration that might over-estimate the number still alive and living in Catalonia. Also, lack of reliable in-migration data complicated modelling of HIV incidence and the separation of earlier infections from new infections occurring after arrival within Catalonia. This demonstrates the urgent need to systematically incorporate longitudinal linked data across the different registries in the HIV information system aimed at monitoring and evaluate the HIV epidemic and its response at the local level.

In conclusion, our study suggests that about 4,271 individuals living with HIV remained undiagnosed in Catalonia in 2013, with the greatest proportion among migrants and MSM from abroad and local. New screening strategies to further increase the offer and uptake of HIV testing and to reach out undiagnosed individuals are needed in order to reduce HIV transmission, targeting key population like migrants and MSM to ensure timely access to HIV care, to finally achieve global 90-90-90 targets to reduce HIV incidence and the number of persons remaining undiagnosed in Catalonia.

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**Conflict of interest**

The authors have no conflicts of interest to disclose.

**Authors' contributions**

CNJC and JRU developed the concept of the manuscript. CNJC and JRU carried out the modelling analysis and JRU and NV the remaining analysis. AE has calculated the adjustment for delayed reporting. JRU wrote the first draft and responded to reviewers comments. All authors have read and approved the final manuscript.

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**Data sharing**

Extra data is available by emailing jmreyes@iconcologia.net

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**Table 1.** Estimated annual number of new HIV infections and estimated average time from infection to HIV diagnosis by year of infection by origin in men who have sex with men, Catalonia, 2001-2013.

| | Incidence | | | |
|---|---|---|---|---|
| | Spanish born MSM | | Migrants MSM | |
| Year | N | IC95% | N | IC95% |
| 2001 | 134 | (108-159) | 52 | (39-69) |
| 2002 | 151 | (127-172) | 74 | (63-90) |
| 2003 | 163 | (138-181) | 99 | (87-113) |
| 2004 | 172 | (156-188) | 126 | (113-141) |
| 2005 | 181 | (164-196) | 152 | (137-167) |
| 2006 | 191 | (174-210) | 176 | (159-192) |
| 2007 | 204 | (190-222) | 195 | (178-212) |
| 2008 | 222 | (209-238) | 209 | (195-225) |
| 2009 | 245 | (231-260) | 219 | (205-237) |
| 2010 | 274 | (255-296) | 225 | (204-249) |
| 2011 | 310 | (275-347) | 228 | (196-261) |
| 2012 | 353 | (298-408) | 228 | (183-283) |
| 2013 | 404 | (322-480) | 227 | (163-310) |

**MSM**: men who have sex with men; **IC95%:** Confidence interval

**Figure 1.** Model outcomes for the total population in Catalonia, 1980-2013. **A.** Annual number of new HIV infections, **B.** Average time from HIV infection to diagnosis by year of infection. **C.** Total number of people living with VIH, including diagnosed and undiagnosed HIV infections.

**C.** Total number of people living with VIH, including diagnosed and undiagnosed HIV infections:
- Total number of people living with HIV in Catalonia
- Total number of people diagnosed with HIV in Catalonia
- Total number of people undiagnosed with HIV in Catalonia

**Figure 2.** Model outcomes by region origin in Catalonia, 1980-2013. **A.** Annual number of new HIV infections among Spanish born-population **B.** Total number of Spanish born people living with VIH, including diagnosed and undiagnosed HIV infections. **C.** Annual number of new HIV infections among migrants. **D.** Total number of migrants living with HIV, including diagnosed and undiagnosed HIV infections.

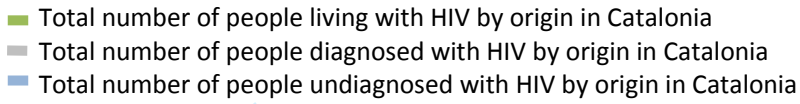


**Figure 3.** Model outcomes for the men who have sex with men by origin in Catalonia, 1980-2013. **A.** Total number of Spanish born men who have sex with men living with VIH, including diagnosed and undiagnosed HIV infections. **B.** Total number of migrant men who have sex with men living with VIH, including diagnosed and undiagnosed HIV infections.

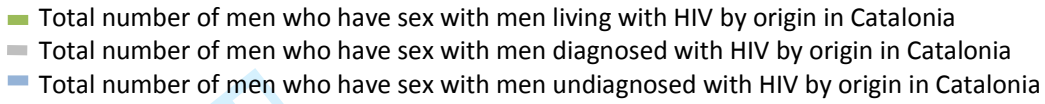
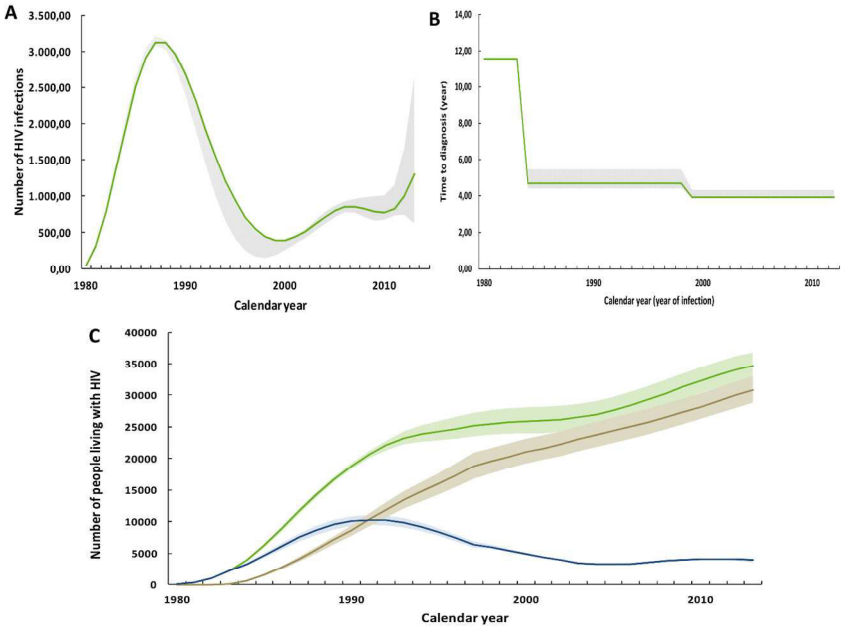


**Figure 4.** Cascade of HIV care of men who have sex with men by region of origin in Catalonia, 2013. **A**. Spanish-born men who have sex with men **B.** Migrants men who have sex with men.

**PLHIV:** People living with HIV; **cART:** combined antiretroviral therapy; **VL:** Viral load.

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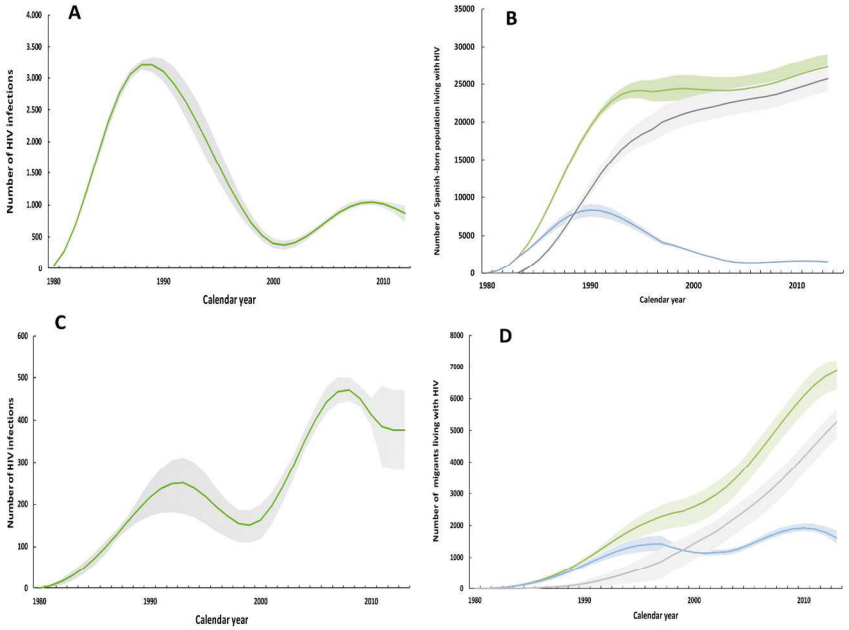


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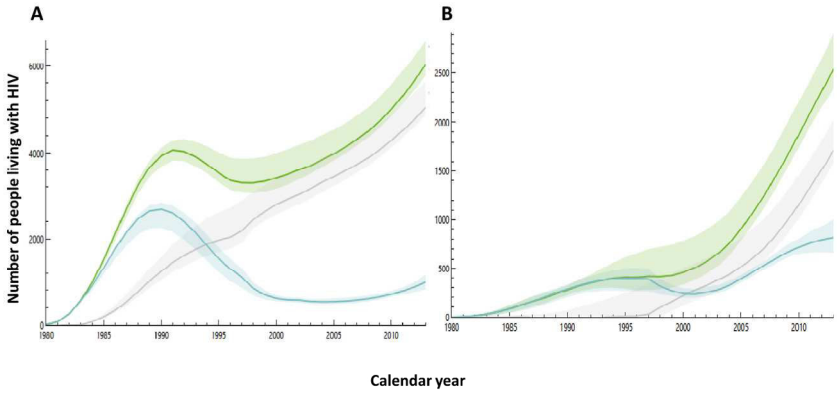


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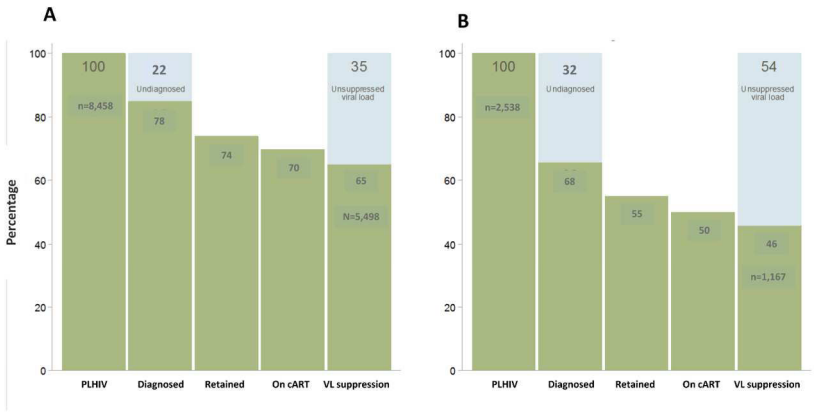


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**Table 1.** Baseline epidemiological characteristics of people aware of their HIV status notified to the surveillance system by origin, Catalonia, 2001-2013.

| | Spanish-born population n (%) | Migrants n (%) | Total n (%) | P value[a] |
|---|---|---|---|---|
| **HIV cases** | 6089 (59.9) | 4061 (40.0) | 10150 (100) | <0.001 |
| **Sex** | | | | <0.001 |
| Men | 5072 (83.3) | 3061 (75.4) | 7879 (80.2) | |
| Women | 1016 (16.7) | 999 (24.6) | 1950 (19.8) | |
| **Age** (median) | 37,00 | 33,00 | 35,00 | <0.001[b] |
| **Age group** | | | | <0.001 |
| <20 | 79 (1.3) | 81 (2.0) | 160 (1.6) | |
| 20-39 | 3586 (58.9) | 3058 (75.3) | 6644 (65.4) | |
| 40-49 | 1443 (23.7) | 703 (17.3) | 2146 (21.2) | |
| >=50 | 980 (16.10) | 219 (5.4) | 1200 (11.9) | |
| **Risk population** | | | | <0.001 |
| PWID | 986 (16.2) | 276 (6.8) | 1263 (12.5) | |
| Heterosexual men | 1206(19.8) | 926 (22.8) | 2132 (21.0) | |
| MSM | 2618 (43.0) | 1624 (40.0) | 4243 (41.8) | |
| Heterosexual women | 737 (12.1) | 849 (20.9) | 1586 (15.6) | |
| Unknown | 542 (8.9) | 386 (9.5) | 928 (9.1) | |
| **Late diagnosis** | 3069 (50.4) | 2193 (54.0) | 5262 (51.8) | <0.001 |
| **Advanced HIV** | 2003 (32.9) | 1336 (32.9) | 3339 (32.9) | 0.933 |

**PWID:** people who inject drugs; **MSM**: men who have sex with men

[a] Pearson's chi-squared test.

[b] Student's t–test.

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) **X (Page 1)** |
| | | (*b*) **X Page -2** |
| **Introduction** | | |
| Background/rationale | 2 | **X Page 4** |
| Objectives | 3 | **X Page 4** |
| **Methods** | | |
| Study design | 4 | **X Page 5** |
| Setting | 5 | **X Page 5** |
| Participants | 6 | *Cohort study*—**X Page 5**<br>*Cross-sectional study*—**X Page 5** |
| Variables | 7 | **X Page 5** |
| Data sources/ measurement | 8* | **X Page 6** |
| Bias | 9 | |
| Study size | 10 | |
| Quantitative variables | 11 | **X Page 6** |
| Statistical methods | 12 | (*a*) **X Page 6** |
| | | (*b*) **X Page 6** |
| | | (*c*) **X Page 6** |
| | | (*d*) |
| | | (*e*) **X Page 6** |

Continued on next page

| | | |
|---|---|---|
| **Results** | | |
| Participants | 13* | (a) Page 7 |
| | | **(b)** |
| | | **(c)** |
| Descriptive data | 14* | (a) **X Page 7** |
| | | (b) **X** |
| | | (c) *Cohort study* |
| Outcome data | 15* | *Cohort study*—**X Page 8** |
| | | *Cross-sectional study*—**X Page 7** |
| Main results | 16 | (*a*) **X Pages 7-8** |
| | | (*b*) |
| | | (*c*) |
| Other analyses | 17 | |
| **Discussion** | | |
| Key results | 18 | **X Page 9** |
| Limitations | 19 | **X Page 11** |
| Interpretation | 20 | **X Page 10** |
| Generalisability | 21 | **X Page 12** |
| **Other information** | | |
| Funding | 22 | **X Page 13** |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Estimating the HIV undiagnosed population in Catalonia, Spain: Descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born population.



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**Research report**

# Estimating the HIV undiagnosed population in Catalonia, Spain: Descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born population.

Juliana REYES-URUEÑA[*1,2,3,4], Colin NJ CAMPBELL[5], Núria VIVES[1,2,3,4], Anna ESTEVE[1,2,3,4], Juan AMBROSIONI[6], Cristina TURAL[7], Elena FERRER[8], Gemma NAVARRO[9], Lluis FORCE[10], Isabel GARCÍA[11], Àngels MASABEU[12], Josep VILARÓ[13], Patricia GARCÍA DE OLALLA[2,14], Joan A. CAYLÀ[2,14], Josep M. MIRÓ[6], Jordi CASABONA[1,2,3,4] and PISCIS investigators.

[1] Centre Estudis Epidemiologics sobre les Infeccions de Transmissio Sexual i Sida de Catalunya (CEEISCAT), Dept Salut, Generalitat de Catalunya, Spain.
[2] CIBER Epidemiologia y Salud Pública (CIBERESP), Spain.
[3] Institut d'Investigació Germans Trias i Pujol (IGTP), Spain.
[4] Departament de Pediatria, d'Obstetricia i Ginecologia i de Medicina Preventiva i de Salut Publica, Universitat Autònoma de Barcelona, Bellaterra, Spain.
[5] Tuberculosis Section, Centre for Infectious Disease Surveillance and Control, National Infection Service, Public Health England, London, United Kingdom.
[6] Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Spain.
[7] Hospital Universitari Germans Trias i Pujol, Badalona, Spain.
[8] Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain.
[9] Corporació Sanitària i Universitària Parc Taulí, Sabadell, Spain.
[10] Hospital de Mataró, Mataró, Spain.
[11] Hospital General d'Hospitalet, Barcelona, Spain.
[12] Hospital de Palamós, Spain,
[13] Consorci Hospitalari de Vic, Barcelona, Spain
[14] Agencia de Salud Pública de Barcelona, Spain.

***Corresponding author***
Juliana Reyes-Urueña
Centre Estudis Epidemiologics sobre les Infeccions de Transmissio Sexual i Sida de Catalunya (CEEISCAT), Dept Salut, Generalitat de Catalunya, Spain.
Email: jmreyes@iconcologia.net
Phone number: +34 934978931

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## Abstract

**Objective**: Undiagnosed HIV continues to be a hindrance to efforts aimed at reducing incidence of HIV. The objective of this study was to provide an estimate of the undiagnosed HIV population in Catalonia, and compare the HIV care cascade with this step included between high-risk populations.

**Methods**: To estimate HIV incidence, time between infection and diagnosis, and the undiagnosed population stratified by CD4 count, we used the ECDC HIV Modelling Tool version 1.2.2. This model uses data on new HIV and AIDS diagnoses from the Catalan HIV/AIDS surveillance system from 2001 to 2013. Data used to estimate the proportion of people enrolled, on ART and virally suppressed in the HIV care cascade were derived from the PISCIS cohort.

**Results**: The total number of people living with HIV in Catalonia in 2013 was 34,729 (32,740-36,827), with 12.3% (11.8-18.1) of whom were undiagnosed. By 2013, there were 8,458 (8,101, 9,079) Spanish-born MSM and 2,538 (2,334-2,918) migrant MSM living with HIV in Catalonia. A greater proportion of migrant MSM than local MSM was undiagnosed (32% vs. 22%). In the subsequent steps of the HIV care cascade, migrants MSM experience greater losses that the Spanish-born MSM; in retention in care (74% vs. 55%), in the proportion on cART (70% vs. 50%) and virally suppressed (65% vs. 46%).

**Conclusions**: By the end of 2013, there were an estimated 34,729 people living with HIV in Catalonia, of whom 4,271 were still undiagnosed. This study shows that the Catalan epidemic of HIV has continued to expand with the key group sustaining HIV transmission being MSM living with undiagnosed HIV.


**Key words:** HIV surveillance; HIV undiagnosed infection; Continuum of care; Migrant; MSM; cascade

**Strengths and limitations of this study**

- The use of regular surveillance and cohort data gives high consistency of local estimates.
- The use of the HIV Modelling Tool allowed calculating the first step of the HIV care cascade by region of origin and among MSM in Catalonia.
- The various subgroup analyses completed for this study may not necessarily explain complex differences in global HIV epidemic dynamics among migrants and MSM, but they do demonstrate that the key group sustaining HIV transmission is MSM living with undiagnosed HIV.
- Linking surveillance and cohort dataset to population migration and death registries is weak in Catalonia; therefore this information is poorly crossed between datasets; which can lead to misclassification of vital status or out-migration that might over-estimate the number still alive and living in Catalonia.

## Introduction

Undiagnosed HIV continues to be a hindrance to efforts aimed at reducing incidence of HIV. People who remain unaware of their HIV status for a long time have an increased risk of transmitting the virus to others [1]. Some studies have shown that undiagnosed individuals may give rise to most new HIV transmissions [1,2], due to higher infectiousness because of elevated viral load at the time of HIV seroconversion [3] or poor decisions related to their risk behaviours [4]. Furthermore, undiagnosed individuals are also at risk of delayed diagnosis as they do not benefit from timely initiation of combination antiretroviral treatment (cART), experience higher HIV-related morbidity and higher mortality, being 11 times more likely to die within a year of being tested than if they had been tested after they were first exposed [5].

In 2015, it was estimated that around 15-16% (122,000/810,000) of people living with HIV (PLHIV) were unaware of their infection in the European Union and the European Economic Area (EU/EEA) [6,7], with proportions ranging from 10% in Sweden [8], 12% in both the Netherlands and Italy [9,10], 17% in UK [11] to 34% in France [12]. Numbers reported from the US are similar to those in Western Europe, with 16.4% of the HIV-infected individuals being undiagnosed in 2013 [13]. In previous work on the Catalan HIV care cascade, we were not in the position to estimate this step, relying on average European estimates [14]. The availability of the ECDC model [15] means we now have a tool that is readily available and uses routinely available surveillance data to estimate undiagnosed HIV, time from infection to diagnosis and estimated annual incidence.

Estimates of the number of people in a country or region who have undiagnosed HIV are of paramount importance for understanding the burden of HIV, stimulating the early identification and treatment such people, and informing strategic plans for the future delivery of cART [16]. Therefore the objective of this study was to provide an estimate of the undiagnosed HIV population in Catalonia, taking into account both men who have sex with men (MSM) and region of origin, using an ECDC model that

uses routinely available surveillance data, and compare the HIV care cascade with this step included between these two high-risk populations.

## Methods

We undertook descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born populations. Migrants were defined as individuals born in a country other than Spain.

The primary data source was the unified Catalan HIV/AIDS surveillance system from 2001 to 2013 [17]. We extracted information on the date of HIV diagnosis, sex, age, transmission mode (people who inject drugs (PWID), heterosexual men, heterosexual women and MSM), CD4+ cell count and clinical stage at diagnosis. Late diagnosis and advanced HIV infection were defined as a CD4 cell count below 350 cells/ml or AIDS and CD4 cell count below 200 cells/ml or AIDS at the time of HIV diagnosis, respectively. Data used to calculate the number of PLHIV, the number of undiagnosed and diagnosed population and the time between infection and diagnosis, were the annual number of new HIV diagnoses by CD4+ count stratum adjusted for delay in reporting and under-notification, the annual number of new AIDS cases, and the annual number of concurrent HIV/AIDS diagnoses (an AIDS diagnosis within 6 weeks of HIV diagnosis).

Data used to estimate the proportion of people enrolled, on ART and virally suppressed in the HIV care cascade were derived from the PISCIS Cohort, which includes data on over 17000 HIV-positive people seen for follow-up from 1998 (coverage around 80%) in all of the participating centres in Catalonia and is fully described elsewhere [18]. The first two steps of the HIV care cascade (PLWHIV and diagnosed and proportion of undiagnosed population) were derived from the estimates calculated with the ECDC tool, whereas the last three were derived from the PISCIS cohort. Each of these steps were analysed by region of origin and by MSM.

Written informed consent and ethical approval was not obtained, as the data used were aggregate anonymized surveillance and HIV care information.

## Statistical analysis

Differences in the distribution of sex, age, transmission mode and presentation with late and/or advanced HIV disease, were assessed by region of origin, using Pearson's chi-squared test for categorical variables and Student's T test for continuous variables.

To estimate HIV incidence, time between infection and diagnosis, and the undiagnosed population by CD4 count strata and its 95% confidence intervals (CI), we used the ECDC HIV Modelling Tool version 1.2.2 [15], which is based on a multi-state back-calculation model that uses surveillance data on new HIV and AIDS diagnoses and that models the HIV incidence curve by cubic splines. The model is described in detail elsewhere [16,19]. We considered four distinct historical periods for which CD4 stratum-specific diagnosis rates were estimated: (1) 1980-1984, during which the first AIDS cases were diagnosed; (2) 1985–1998, when serological testing for HIV became widely available; (3) 1999–2001, the start of the era of combination antiretroviral therapy (cART); (4) 2002-2013, the start of the HIV notification in Catalonia. Annual numbers of HIV diagnoses were available from 2001 onwards. The CD4 count at the time of diagnosis was defined as the first CD4 count after diagnosis and before start of treatment. Overall, 81.6% of the patients diagnosed from 2001 onwards had a CD4 count available at the time of diagnosis. The estimated annual numbers of diagnoses by CD4 count stratum were then fitted to the observed numbers. The number of HIV-infected who were still alive by the end of 2013 was estimated by subtracting the cumulative number of people who died from the cumulative number of HIV infections. The number of deaths among diagnosed people was taken from the Catalan HIV Surveillance System from 2001-2013.

The subsequent step of linked to care was calculated by applying to the preceding stage a proportion estimated from surveillance data. The proportions retained in care, on cART and virally suppressed were derived from the PISCIS cohort. A fuller description of the methods used has been published elsewhere [14]. The level of significance was set at p value <0.05. Data analysis was performed using Stata 12. CollegeStation,TX:StataCorpLP.

**Results**

There were 10,150 new HIV diagnoses in adults (>18 years of age) reported to the Catalan National Surveillance System from 2001 to 2013, 60% of the cases were Spanish-born, 80.2% were men, and the median age was 35 years old. The epidemiological profile of migrants was different to that of the Spanish-born population; there was a higher proportion of women (24.6% and 16.7%, respectively) and were younger at diagnosis (median age of 33 vs. 37, respectively). In both migrants and the Spanish-born groups, the most frequent at-risk population was MSM (40% and 43%, respectively). Supplemental File Table A.

Between 1980 and 2013, a cumulative number of 41,364 (CI=35,299, 44,990) infections in the Catalan population were estimated to have occurred. The estimated number of new HIV infections peaked around 1988 with 3,124 (CI=3,031, 3,159) (figure 1A), declining nearly sevenfold, from 2,674 (CI=2,388, 2,663) in 1990 to 391 (CI=188, 372) in 1999. From 2011 the estimated number of new infections stared to peak up again reaching levels comparable with those in the mid-1990s, with the highest estimated number in 2013, 1,120 (CI=461, 1,324). The estimated mean time between infection and diagnosis if diagnosis rates remain the same as in the year of infection is shown in Figure 1B. Between 1980 and 1983, when HIV could only be diagnosed once AIDS symptoms appeared, the estimated average time between infection and HIV diagnosis for people infected in this period, were conditions to have remained as they were in this period, would have been 11.6 years. This decreased to 4.7 years (CI=4.4, 5.0) in the period 1984–1998. From 2000 onwards, the estimated time to HIV diagnosis steadily decreased to 3.9 (CI=3.6, 4.6) years on average for the whole population in 2013. By region of origin, in both Spanish-born people and migrants, there was a similar decreasing trend in the estimated average time from infection to diagnosis until it reached 3.6 years (CI=3.4, 3.8) and 4.7 years (CI=4.6, 5.01), respectively in 2013. Figure 1C shows the estimated total number of PLHIV in Catalonia from 1980 to 2013, including those not yet diagnosed. Overall, there was an increasing trend throughout the time period, reaching the highest estimated number of people in 2013, a total of

34,729 (CI=32,740, 36,827) PLHIV in Catalonia. Of these, 4,271 (CI=3,737, 6252) were undiagnosed, a proportion of 12.3% (CI=11.8, 18.1).

In 2013, the estimated number of new infections among the Spanish-born population reached a number of 744 (CI=546, 934) (Figure 2A), while among the migrants was 376 new infections (CI=281, 471). Finally among MSM, in both Spanish-born and migrants there was a clear stepping increase in the estimated number of new infections from 2001, reaching the highest number in 2013, with 404 (CI=322, 480) and with 227 (CI=163, 310), respectively (Table 1).

The estimated total number of PLHIV comparing the trend in the number of PLHIV between migrant and Spanish-born groups (Figure 2B and Figure 2D), it was observed that among locals there was a progressive but not very pronounced rise from 1991 to reach the highest estimated number in 2013 with 27,648 (CI=25,365, 29,379) PLHIV, just 5.8% (CI=5.8, 6.6) of whom were undiagnosed (1,603, CI= 1,421, 1,819). Conversely, among migrants the estimated number of PLHIV rose steeply since the beginning of the epidemic, also reaching a peak in 2013 with 7,081 (CI=6,492, 7,616), but with four times the estimated undiagnosed population (23.4%, CI=22.7, 25.1) compared to the local population. Among (Figures 3A and 3B) both local and migrant MSM there has been a large increase in the estimated number of MSM living with HIV in the last 10 years, with a higher increasing slope among migrant MSM. By 2013, there were 8,458 (CI=8,101, 9,079) Spanish-born MSM and 2,538 (CI=2,334, 2,918) migrant MSM living with HIV in Catalonia, with 16.4% (CI=14.2, 17.7) and 32.3% (CI=28.4, 34.4) undiagnosed, respectively.

Data from the PISCIS cohort is available on Supplemental File Table B. Finally, figure 4 shows the differences in the HIV care cascade in MSM by origin. As a percentage of the total PLHIV, migrant MSM have a greater proportion undiagnosed (32% vs. 16%) that local MSM. In subsequent steps in the HIV care cascade, migrant MSM experience greater losses due to the big different in the proportion of undiagnosed, when compared to the Spanish-born MSM, with lower proportion retained in care (74% vs. 55%), on cART (70% vs. 50%) and virally suppressed (65% vs. 46%).

## Discussion

Our study estimates that by the end of 2013, there were an estimated number of 34,729 people living with HIV in Catalonia, Spain, of whom 4,271 were still undiagnosed. This study also shows that migrants had a very high proportion of undiagnosed compared to Spanish-born population, and as it has been described by other sources of information from Catalonia [17], this study found that the Catalan epidemic of HIV has continued to expand during the past decade with the key group sustaining HIV transmission being MSM living with undiagnosed HIV and in the asymptomatic stage, especially migrants MSM.

The estimated overall prevalence of undiagnosed HIV-infected people in Catalonia (12.3%) is within the range of those recently obtained in other countries by 2013: 10% in Italy, 12% in Austria, 16% in Belgium and France, 17% in Germany, 18% in Spain and 19% in United Kingdom [7]. Nevertheless we think that some underestimation may have occurred due to two facts; first, that the method that we applied uses data on case reports, which may be subject to underreporting, which can be ranged between 10% to 40% [20,21], and can lead to underestimates HIV incidence and may also affect estimates of diagnosis rates, and thus lower the percent undiagnosed; and second, by the fact that we could not feed the model with migration data. As Catalan epidemic is highly influence by migration we believe that this lower the estimates of the annual number of new HIV infections and therefore undiagnosed HIV-infected individuals.

In line with our results, other studies also had identified among migrants a great proportion of undiagnosed [22,23]. In Catalonia this could be explained by the fact that migrants experienced a higher number of barriers to access HIV testing services than the Spanish-born population and that these needs might be driven primarily by shared risk factors [24]. This also can be due to the fact that migrants face cultural and linguistic barriers, as well as, legal and administrative impediments to accessing health services and thus HIV testing facilities [25]. In Europe the HIV testing uptake among migrants range from 23% to 64% [25]. This difference can differ by sex, as higher proportion of migrant women have been tested for HIV compared with men; this is

partially owing to women's acceptance of routine HIV screening during antenatal care. However, beyond this, several studies support a gender difference in HIV testing uptake, with migrant men being not only less exposed to HIV testing but also less willing to be tested [25]. However, this lower rate of HIV testing among migrant men might be more representative of migrant heterosexual men that MSM migrants, as these later perceive themselves as being at higher risk for HIV, and thus being more likely to have ever been tested for HIV than the local MSM [26,27]. Although, it has been found that untested migrant MSM are particularly hard to reach [27], which in line with our estimates.

Our results suggest that the Catalan HIV epidemic has been sustained by the HIV transmission among undiagnosed MSM, as it has been described in other studies in Catalonia [28,29]. Consistent with this, in the United Kingdom, using the same model it has been estimated that around two in three new infections were attributable to MSM living with undiagnosed HIV [30], and in Switzerland that around 82% of new cases among MSM were acquired from HIV undiagnosed men [31]. This finding can be explained by an increase in risky sexual behaviours [32,33], including high prevalence of unprotected anal intercourse and increasing numbers of sexual partners [34]. This is also supported by a recent survey that reported that 37% of MSM recruited in gay venues had not tested for HIV in the past 12 months [32]. It has also been described that a great proportion of undiagnosed MSM have acquired the infection recently, which made them to be most infectious and the maintenance group of the HIV epidemic [34]. The risky sexual conducts among migrant MSM have been also described, with higher prevalence of unprotected anal intercourse than Spanish-born MSM [35,36] and specifically among Latin American MSM, high HIV prevalence rates among those diagnosed with syphilis and gonorrhoea, as well as, with high prevalence and incidence rates of STIs in those newly diagnosed with HIV [35]. Resources should be allocated primarily to promote testing in high-activity MSM, as they are the key group sustaining the epidemic, but also for encouraging all MSM including migrants MSM to test regularly for HIV, this includes design long-term sustainable outreach-based HIV interventions to reach as many MSM as we could for HIV testing.

Biomedical and behavioural interventions, targeting both HIV-infected and HIV-uninfected MSM, should be used. In this regard, it will be essential to use interventions with proven efficacy , such as treatment as prevention, test and treat interventions, in combination with pre-exposure prophylaxis in highly adherent people, and to implement effective behavioural interventions that prevent an increase in risky behaviours, all of these intervention must be integrated in a well-designed strategy of combination prevention, as it has been described in other studies [37]. Besides, in order to reduce the fraction of undiagnosed should be considered implementing and scaling up innovative approaches to promote greater access to and uptake of HIV testing by those most at risk, including community-based testing, home sampling, as well as indicator-condition- guided testing.

These results must be interpreted in light of several key methodological limitations. The use of the HIV Modelling Tool facilitated the standardisation of estimates for PLHIV, however available information is partial and not representative of the different subpopulations of migrants and MSM across all Catalonia. Despite this limitation, this analysis allowed us to calculate the first step of the HIV care cascade by region of origin and among MSM in Catalonia. The various subgroup analyses completed for this study may not necessarily explain complex differences in global HIV epidemic dynamics among migrants and MSM, but they do demonstrate that the key group sustaining HIV transmission is MSM living with undiagnosed HIV and that among migrants testing coverage will need to be intensify and increase to find those undiagnosed. Although the use of PISCIS cohort data improved the consistency of the estimates, we are unable to link surveillance and cohort datasets to maximise internal consistency, therefore we are unable to distinguish between those diagnosed and those linked to care (enrolled in the cohort), although linkage to care is expected to be high given the Catalan healthcare system characteristics and the high cohort coverage. Additionally, using a single VL measurement may also over-estimate durable viral suppression, however, they provide a snapshot of the continuum in 2013 which is simple to interpret and communicate to policy-makers, as it has been described by other authors [7,38]. Finally, linking surveillance and cohort dataset to population migration and

death registries is weak in Catalonia; therefore this information is poorly crossed between datasets; which it can lead to misclassification of vital status or out- migration that might over-estimate the number still alive and living in Catalonia. Also, lack of reliable in-migration data complicated modelling of HIV incidence and the separation of earlier infections from new infections occurring after arrival within Catalonia. This demonstrates the urgent need to systematically incorporate longitudinal linked data across the different registries in the HIV information system aimed at monitoring and evaluate the HIV epidemic and its response at the local level.

In conclusion, our study suggests that about 4,271 individuals living with HIV remained undiagnosed in Catalonia in 2013, with the greatest proportion among migrants and MSM from abroad and local. New screening strategies to further increase the offer and uptake of HIV testing and to reach out undiagnosed individuals are needed in order to reduce HIV transmission, targeting key population like migrants and MSM to ensure timely access to HIV care, to finally achieve global 90-90-90 targets to reduce HIV incidence and the number of persons remaining undiagnosed in Catalonia.

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**Conflict of interest**

The authors have no conflicts of interest to disclose.

**Authors' contributions**

CNJC and JRU developed the concept of the manuscript. CNJC and JRU carried out the modelling analysis and JRU and NV the remaining analysis. AE has calculated the adjustment for delayed reporting. JRU wrote the first draft and responded to reviewers comments. All authors have read and approved the final manuscript.

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**Data sharing**

Extra data is available by emailing jmreyes@iconcologia.net

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**Table 1.** Estimated annual number of new HIV infections and new HIV, HIV/AIDS and AIDS diagnoses reported to the Catalan surveillance system, by year of infection and origin in men who have sex with men, Catalonia, 2001-2013.

| | Estimated new HIV infection | | | | New HIV diagnoses reported to the Catalan surveillance system | | New HIV /AIDS diagnoses reported to the Catalan surveillance system | | New AIDS diagnoses reported to the Catalan surveillance system | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Spanish born MSM | | Migrants MSM | | Spanish born MSM | Migrants MSM | Spanish born MSM | Migrants MSM | Spanish born MSM | Migrants MSM |
| Year | N | IC95% | N | IC95% | N | N | N | N | N | N |
| 2001 | 134 | (108-159) | 52 | (39-69) | 152 | 47 | 45 | 10 | 68 | 16 |
| 2002 | 151 | (127-172) | 74 | (63-90) | 175 | 62 | 41 | 16 | 55 | 19 |
| 2003 | 163 | (138-181) | 99 | (87-113) | 158 | 59 | 44 | 20 | 70 | 23 |
| 2004 | 172 | (156-188) | 126 | (113-141) | 185 | 89 | 28 | 14 | 52 | 23 |
| 2005 | 181 | (164-196) | 152 | (137-167) | 181 | 91 | 27 | 11 | 36 | 20 |
| 2006 | 191 | (174-210) | 176 | (159-192) | 187 | 109 | 26 | 18 | 52 | 16 |
| 2007 | 204 | (190-222) | 195 | (178-212) | 207 | 125 | 26 | 19 | 39 | 34 |
| 2008 | 222 | (209-238) | 209 | (195-225) | 183 | 133 | 19 | 17 | 35 | 27 |
| 2009 | 245 | (231-260) | 219 | (205-237) | 191 | 115 | 26 | 13 | 40 | 20 |
| 2010 | 274 | (255-296) | 225 | (204-249) | 224 | 175 | 24 | 22 | 34 | 38 |
| 2011 | 310 | (275-347) | 228 | (196-261) | 193 | 243 | 14 | 18 | 27 | 25 |
| 2012 | 353 | (298-408) | 228 | (183-283) | 282 | 189 | 19 | 10 | 35 | 22 |
| 2013 | 404 | (322-480) | 227 | (163-310) | 291 | 185 | 19 | 19 | 32 | 28 |

**MSM**: men who have sex with men; **IC95%:** Confidence interval

**Figure 1.** Model outcomes for the total population in Catalonia, 1980-2013. A. Estimated annual number of new HIV infections, B. Estimated average time from HIV infection to diagnosis by year of infection. C. Estimated total number of people living with HIV, including diagnosed and undiagnosed HIV infections.

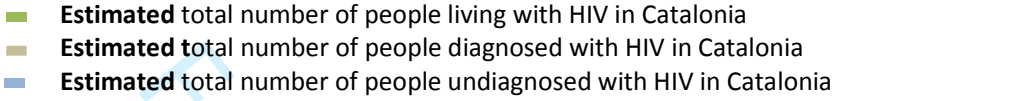

**Figure 2.** Model outcomes by region origin in Catalonia, 1980-2013. A. Estimated annual number of new HIV infections among Spanish born-population B. Estimated total number of Spanish born people living with HIV, including diagnosed and undiagnosed HIV infections. C. Estimated annual number of new HIV infections among migrants. D. Estimated total number of migrants living with HIV, including diagnosed and undiagnosed HIV infections.

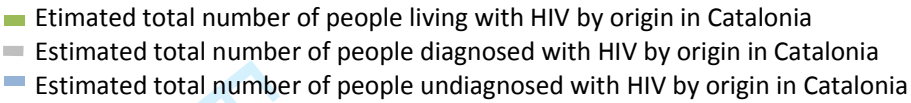

**Figure 3.** Model outcomes for the men who have sex with men by origin in Catalonia, 1980-2013. A. Estimated total number of Spanish born men who have sex with men living with HIV, including diagnosed and undiagnosed HIV infections. B. Estimated total number of migrant men who have sex with men living with HIV, including diagnosed and undiagnosed HIV infections.

**Estimated** total number of men who have sex with men living with HIV by origin in Catalonia
**Estimated** total number of men who have sex with men diagnosed with HIV by origin in Catalonia
**Estimated** total number of men who have sex with men undiagnosed with HIV by origin in Catalonia

**Figure 4.** Cascade of HIV care of men who have sex with men by region of origin in Catalonia, 2013. **A**. Spanish-born men who have sex with men **B.** Migrants men who have sex with men.

**PLHIV:** People living with HIV; **cART:** combined antiretroviral therapy; **VL:** Viral load.

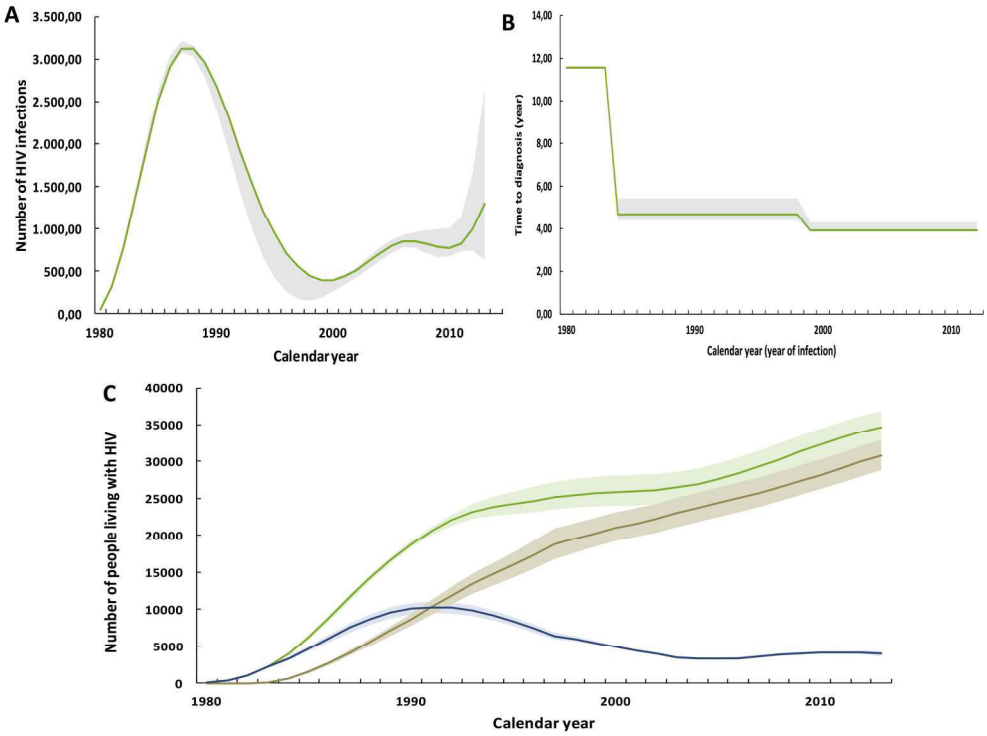


Figure 1

190x142mm (300 x 300 DPI)

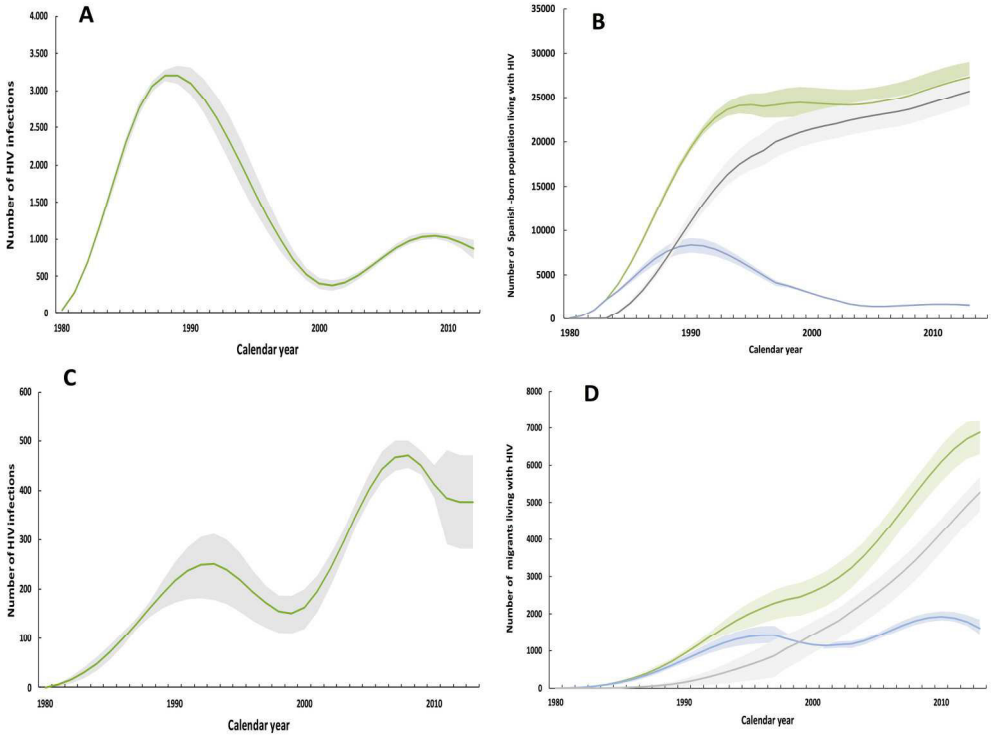


Figure 2

190x142mm (300 x 300 DPI)

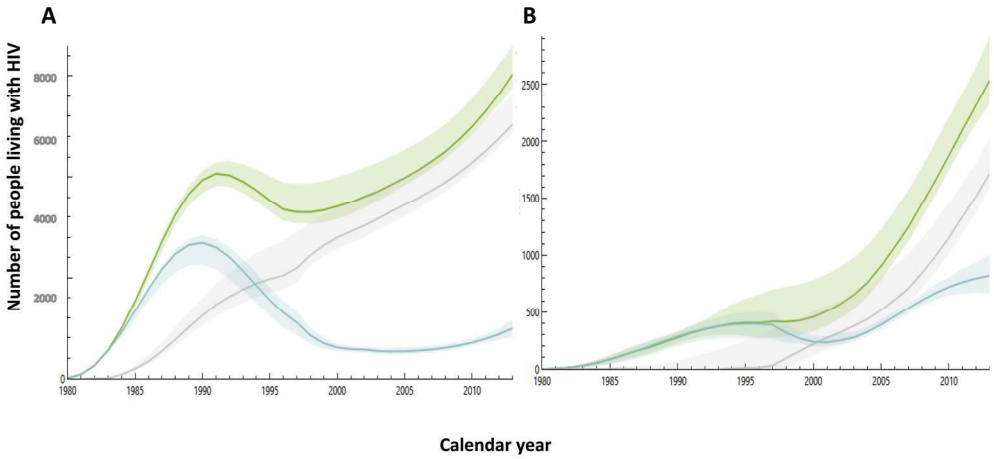


Figure 3

190x142mm (300 x 300 DPI)

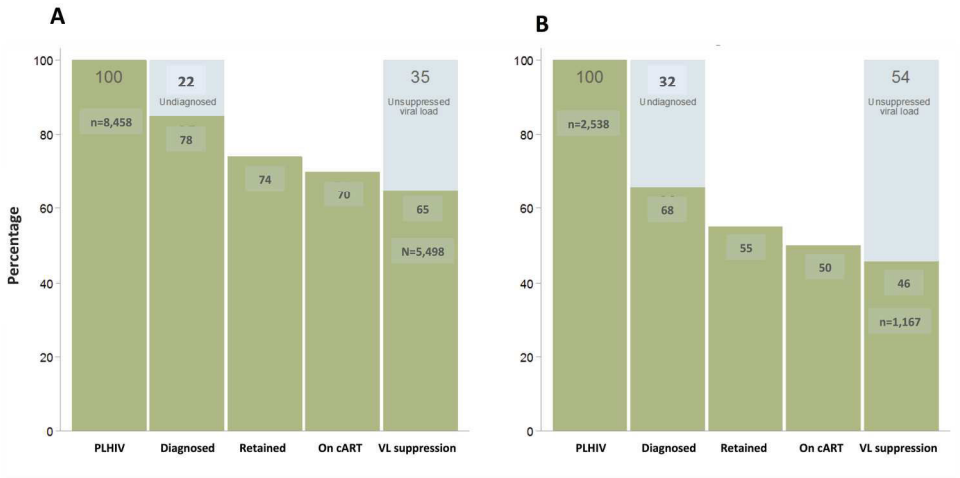


Figure 4

190x142mm (300 x 300 DPI)

**Table A.** Baseline epidemiological characteristics of people aware of their HIV status notified to the surveillance system by origin, Catalonia, 2001-2013.

| | Spanish-born population | Migrants | Total | P value[a] |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | |
| **HIV cases** | 6089 (59.9) | 4061 (40.0) | 10150 (100) | <0.001 |
| **Sex** | | | | <0.001 |
| Men | 5073 (83.3) | 3062 (75.4) | 8135 (80.2) | |
| Women | 1016 (16.7) | 999 (24.6) | 2015 (19.8) | |
| **Age** (median) | 37,00 | 33,00 | 35,00 | <0.001[b] |
| **Age group** | | | | <0.001 |
| <20 | 79 (1.3) | 81 (2.0) | 160 (1.6) | |
| 20-39 | 3586 (58.9) | 3058 (75.3) | 6644 (65.4) | |
| 40-49 | 1443 (23.7) | 703 (17.3) | 2146 (21.2) | |
| >=50 | 980 (16.10) | 219 (5.4) | 1200 (11.9) | |
| **Risk population** | | | | <0.001 |
| PWID | 986 (16.2) | 276 (6.8) | 1263 (12.5) | |
| Heterosexual men | 1206(19.8) | 926 (22.8) | 2132 (21.0) | |
| MSM | 2618 (43.0) | 1624 (40.0) | 4243 (41.8) | |
| Heterosexual women | 737 (12.1) | 849 (20.9) | 1586 (15.6) | |
| Unknown | 542 (8.9) | 386 (9.5) | 928 (9.1) | |
| **Late diagnosis** | 3069 (50.4) | 2193 (54.0) | 5262 (51.8) | <0.001 |
| **Advanced HIV** | 2003 (32.9) | 1336 (32.9) | 3339 (32.9) | 0.933 |

**PWID:** people who inject drugs; **MSM**: men who have sex with men

[a] Pearson's chi-squared test.

[b] Student's t–test.

**Table B**. Comparison of socio-demographic characteristics and clinical features of people enrolled in HIV care (PISCIS cohort), by place and region of origin, Catalonia - Spain, 1998-2013.

| | Spanish-born population | Migrants | Total | |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | P value[a] |
| **Total** | 4194 (69.6) | 1828 (30.4) | 6022 (100) | |
| **Sex** | | | | |
| Men | 3363 (80.2) | 1466 (80.2) | 4829 (80.2) | 1.000 |
| Women | 831 (19.8) | 362 (19.8) | 1193 (19.8) | |
| **Age** median (IQR)[b] | 37 (31-44) | 34 (29-40) | 36 (30-43) | <0.001 |
| **Risk population*** | | | | |
| PWID | 1034 (24.7) | 87 (4.8) | 1121 (18.6) | <0.001 |
| MSM | 1786 (42.6) | 1026 (56.1) | 2812 (46.7) | |
| Heterosexual women and men | 1075 (25.6) | 624 (34.1) | 1699 (28.2) | |
| Others | 297 (7.1) | 91 (5.0) | 388 (6.4) | |
| **Educational level** | | | | |
| Primary education or less | 1215 (29.0) | 435 (23.8) | 1650 (27.4) | <0.001 |
| Secondary education | 795 (19.0) | 571 (31.2) | 1366 (22.7) | |
| Undergraduate education | 491 (11.7) | 412 (22.5) | 903 (15.0) | |
| Unknown | 1693 (40.4) | 410 (22.4) | 2103 (34.9) | |
| **Years on follow up median (IQR)** | 5.5 (2.7-9.4) | 3.5 (1.5-6.2) | 5.4(2.5-9.5) | <0.001 |
| **Number of people on ART** | 3931 (93.7) | 1659 (90.8) | 5590 (92.8) | <0.001 |
| **Number of people with suppressed VL** | 3655 (87.2) | 1515 (82.9) | 5170 (85.8) | <0.001 |

**PWID:** people who inject drugs; **MSM**: men who have sex with men.
*Only 2 had an unknown risk group
[a]Chi-Cuadrado
[b]Student's t–test.

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Pg 1 | |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Pg 2 | |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Pg 4 | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Pg 4 | |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | Pg 6 | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Pg 6 | |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Pg 6 | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pg 6 - 7 | |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Pg 6 | |
| Bias | 9 | Describe any efforts to address potential sources of bias | | |
| Study size | 10 | Explain how the study size was arrived at | | |

Continued on next page

| | | | |
|---|---|---|---|
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Pg 5-6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Pg 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | Pg 6 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Pg 8 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Pg 8 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Pg 6 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | Pg 8 |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | Pg 8-9 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (*b*) Report category boundaries when continuous variables were categorized | Pg 8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |

Continued on next page

| | | | |
|---|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Pg 10 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Pg 12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Pg 11 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Pg 12 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Pg 14 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Estimating the HIV undiagnosed population in Catalonia, Spain: Descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born population.



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**Research report**

# Estimating the HIV undiagnosed population in Catalonia, Spain: Descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born population.

Juliana REYES-URUEÑA[*1,2,3,4], Colin NJ CAMPBELL[5], Núria VIVES[1,2,3,4], Anna ESTEVE[1,2,3,4], Juan AMBROSIONI[6], Cristina TURAL[7], Elena FERRER[8], Gemma NAVARRO[9], Lluis FORCE[10], Isabel GARCÍA[11], Àngels MASABEU[12], Josep VILARÓ[13], Patricia GARCÍA DE OLALLA[2,14], Joan A. CAYLÀ[2,14], Josep M. MIRÓ[6], Jordi CASABONA[1,2,3,4] and PISCIS investigators.

[1] Centre Estudis Epidemiologics sobre les Infeccions de Transmissio Sexual i Sida de Catalunya (CEEISCAT), Dept Salut, Generalitat de Catalunya, Spain.
[2] CIBER Epidemiologia y Salud Pública (CIBERESP), Spain.
[3] Institut d'Investigació Germans Trias i Pujol (IGTP), Spain.
[4] Departament de Pediatria, d'Obstetricia i Ginecologia i de Medicina Preventiva i de Salut Publica, Universitat Autònoma de Barcelona, Bellaterra, Spain.
[5] Tuberculosis Section, Centre for Infectious Disease Surveillance and Control, National Infection Service, Public Health England, London, United Kingdom.
[6] Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Spain.
[7] Hospital Universitari Germans Trias i Pujol, Badalona, Spain.
[8] Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain.
[9] Corporació Sanitària i Universitària Parc Taulí, Sabadell, Spain.
[10] Hospital de Mataró, Mataró, Spain.
[11] Hospital General d'Hospitalet, Barcelona, Spain.
[12] Hospital de Palamós, Spain,
[13] Consorci Hospitalari de Vic, Barcelona, Spain
[14] Agencia de Salud Pública de Barcelona, Spain.

***Corresponding author***
Juliana Reyes-Urueña
Centre Estudis Epidemiologics sobre les Infeccions de Transmissio Sexual i Sida de Catalunya (CEEISCAT), Dept Salut, Generalitat de Catalunya, Spain.
Email: jmreyes@iconcologia.net
Phone number: +34 934978931

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## Abstract

**Objective**: Undiagnosed HIV continues to be a hindrance to efforts aimed at reducing incidence of HIV. The objective of this study was to provide an estimate of the undiagnosed HIV population in Catalonia, and compare the HIV care cascade with this step included between high-risk populations.

**Methods**: To estimate HIV incidence, time between infection and diagnosis, and the undiagnosed population stratified by CD4 count, we used the ECDC HIV Modelling Tool version 1.2.2. This model uses data on new HIV and AIDS diagnoses from the Catalan HIV/AIDS surveillance system from 2001 to 2013. Data used to estimate the proportion of people enrolled, on ART and virally suppressed in the HIV care cascade were derived from the PISCIS cohort.

**Results**: The total number of people living with HIV in Catalonia in 2013 was 34,729 (32,740-36,827), with 12.3% (11.8-18.1) of whom were undiagnosed. By 2013, there were 8,458 (8,101, 9,079) Spanish-born MSM and 2,538 (2,334-2,918) migrant MSM living with HIV in Catalonia. A greater proportion of migrant MSM than local MSM was undiagnosed (32% vs. 22%). In the subsequent steps of the HIV care cascade, migrants MSM experience greater losses that the Spanish-born MSM; in retention in care (74% vs. 55%), in the proportion on cART (70% vs. 50%) and virally suppressed (65% vs. 46%).

**Conclusions**: By the end of 2013, there were an estimated 34,729 people living with HIV in Catalonia, of whom 4,271 were still undiagnosed. This study shows that the Catalan epidemic of HIV has continued to expand with the key group sustaining HIV transmission being MSM living with undiagnosed HIV.


**Key words:** HIV surveillance; HIV undiagnosed infection; Continuum of care; Migrant; MSM; cascade

**Strengths and limitations of this study**

- The use of regular surveillance and cohort data gives high consistency of local estimates.
- The use of the HIV Modelling Tool allowed calculating the first step of the HIV care cascade by region of origin and among MSM in Catalonia.
- The various subgroup analyses completed for this study may not necessarily explain complex differences in global HIV epidemic dynamics among migrants and MSM, but they do demonstrate that the key group sustaining HIV transmission is MSM living with undiagnosed HIV.
- Linking surveillance and cohort dataset to population migration and death registries is weak in Catalonia; therefore this information is poorly crossed between datasets; which can lead to misclassification of vital status or out-migration that might over-estimate the number still alive and living in Catalonia.

## Introduction

Undiagnosed HIV continues to be a hindrance to efforts aimed at reducing incidence of HIV. People who remain unaware of their HIV status for a long time have an increased risk of transmitting the virus to others [1]. Some studies have shown that undiagnosed individuals may give rise to most new HIV transmissions [1,2], due to higher infectiousness because of elevated viral load at the time of HIV seroconversion [3] or poor decisions related to their risk behaviours [4]. Furthermore, undiagnosed individuals are also at risk of delayed diagnosis as they do not benefit from timely initiation of combination antiretroviral treatment (cART), experience higher HIV-related morbidity and higher mortality, being 11 times more likely to die within a year of being tested than if they had been tested after they were first exposed [5].

In 2015, it was estimated that around 15-16% (122,000/810,000) of people living with HIV (PLHIV) were unaware of their infection in the European Union and the European Economic Area (EU/EEA) [6,7], with proportions ranging from 10% in Sweden [8], 12% in both the Netherlands and Italy [9,10], 17% in UK [11] to 34% in France [12]. Numbers reported from the US are similar to those in Western Europe, with 16.4% of the HIV-infected individuals being undiagnosed in 2013 [13]. In previous work on the Catalan HIV care cascade, we were not in the position to estimate this step, relying on average European estimates [14]. The availability of the ECDC model [15] means we now have a tool that is readily available and uses routinely available surveillance data to estimate undiagnosed HIV, time from infection to diagnosis and estimated annual incidence.

Estimates of the number of people in a country or region who have undiagnosed HIV are of paramount importance for understanding the burden of HIV, stimulating the early identification and treatment such people, and informing strategic plans for the future delivery of cART [16]. In the other hand, the use of the HIV treatment cascade as a straightforward guide to quantify population-level estimates of successive steps from diagnosis to viral suppression will facilitate measurement, monitoring, and provision of HIV care. Therefore the objective of this study was to provide an estimate

of the undiagnosed HIV population in Catalonia, taking into account both men who have sex with men (MSM) and region of origin, using an ECDC model that uses routinely available surveillance data, and compare the HIV care cascade with this step included between these two high-risk populations.

## Methods

We undertook descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born populations. Migrants were defined as individuals born in a country other than Spain.

The primary data source was the unified Catalan HIV/AIDS surveillance system from 2001 to 2013 [17]. We extracted information on the date of HIV diagnosis, sex, age, transmission mode (people who inject drugs (PWID), heterosexual men, heterosexual women and MSM), CD4+ cell count and clinical stage at diagnosis. Late diagnosis and advanced HIV infection were defined as a CD4 cell count below 350 cells/ml or AIDS and CD4 cell count below 200 cells/ml or AIDS at the time of HIV diagnosis, respectively. Data used to calculate the number of PLHIV, the number of undiagnosed and diagnosed population and the time between infection and diagnosis, were the annual number of new HIV diagnoses by CD4+ count stratum adjusted for delay in reporting and under-notification, the annual number of new AIDS cases, and the annual number of concurrent HIV/AIDS diagnoses (an AIDS diagnosis within 6 weeks of HIV diagnosis).

Data used to estimate the proportion of people enrolled, on ART and virally suppressed in the HIV care cascade were derived from the PISCIS Cohort, which includes data on over 17000 HIV-positive people seen for follow-up from 1998 (coverage around 80%) in all of the participating centres in Catalonia and is fully described elsewhere [18]. The first two steps of the HIV care cascade (PLWHIV and diagnosed and proportion of undiagnosed population) were derived from the estimates calculated with the ECDC tool, whereas the last three were derived from the PISCIS cohort. Each of these steps were analysed by region of origin and by MSM.

Written informed consent and ethical approval was not obtained, as the data used were aggregate anonymized surveillance and HIV care information.

## Statistical analysis

Differences in the distribution of sex, age, transmission mode and presentation with late and/or advanced HIV disease, were assessed by region of origin, using Pearson's chi-squared test for categorical variables and Student's T test for continuous variables.

To estimate HIV incidence, time between infection and diagnosis, and the undiagnosed population by CD4 count strata and its 95% confidence intervals (CI), we used the ECDC HIV Modelling Tool version 1.2.2 [15], which is based on a multi-state back-calculation model that uses surveillance data on new HIV and AIDS diagnoses and that models the HIV incidence curve by cubic splines. The model is described in detail elsewhere [16,19]. We considered four distinct historical periods for which CD4 stratum-specific diagnosis rates were estimated: (1) 1980-1984, during which the first AIDS cases were diagnosed; (2) 1985–1998, when serological testing for HIV became widely available; (3) 1999–2001, the start of the era of combination antiretroviral therapy (cART); (4) 2002-2013, the start of the HIV notification in Catalonia. Annual numbers of HIV diagnoses were available from 2001 onwards. The CD4 count at the time of diagnosis was defined as the first CD4 count after diagnosis and before start of treatment. Overall, 81.6% of the patients diagnosed from 2001 onwards had a CD4 count available at the time of diagnosis. The estimated annual numbers of diagnoses by CD4 count stratum were then fitted to the observed numbers. The number of HIV-infected who were still alive by the end of 2013 was estimated by subtracting the cumulative number of people who died from the cumulative number of HIV infections. The number of deaths among diagnosed people was taken from the Catalan HIV Surveillance System from 2001-2013.

The subsequent step of linked to care was calculated by applying to the preceding stage a proportion estimated from surveillance data. The proportions retained in care, on cART and virally suppressed were derived from the PISCIS cohort. A fuller description of the methods used has been published elsewhere [14]. The level of significance was set at p value <0.05. Data analysis was performed using Stata 12. CollegeStation,TX:StataCorpLP.

**Results**

There were 10,150 new HIV diagnoses in adults (>18 years of age) reported to the Catalan National Surveillance System from 2001 to 2013, 60% of the cases were Spanish-born, 80.2% were men, and the median age was 35 years old. The epidemiological profile of migrants was different to that of the Spanish-born population; there was a higher proportion of women (24.6% and 16.7%, respectively) and were younger at diagnosis (median age of 33 vs. 37, respectively). In both migrants and the Spanish-born groups, the most frequent at-risk population was MSM (40% and 43%, respectively). Supplemental File Table A.

Between 1980 and 2013, a cumulative number of 41,364 (CI=35,299, 44,990) infections in the Catalan population were estimated to have occurred. The estimated number of new HIV infections peaked around 1988 with 3,124 (CI=3,031, 3,159) (figure 1A), declining nearly sevenfold, from 2,674 (CI=2,388, 2,663) in 1990 to 391 (CI=188, 372) in 1999. From 2011 the estimated number of new infections stared to peak up again reaching levels comparable with those in the mid-1990s, with the highest estimated number in 2013, 1,120 (CI=461, 1,324). The estimated mean time between infection and diagnosis if diagnosis rates remain the same as in the year of infection is shown in Figure 1B. Between 1980 and 1983, when HIV could only be diagnosed once AIDS symptoms appeared, the estimated average time between infection and HIV diagnosis for people infected in this period, were conditions to have remained as they were in this period, would have been 11.6 years. This decreased to 4.7 years (CI=4.4, 5.0) in the period 1984–1998. From 2000 onwards, the estimated time to HIV diagnosis steadily decreased to 3.9 (CI=3.6, 4.6) years on average for the whole population in 2013. By region of origin, in both Spanish-born people and migrants, there was a similar decreasing trend in the estimated average time from infection to diagnosis until it reached 3.6 years (CI=3.4, 3.8) and 4.7 years (CI=4.6, 5.01), respectively in 2013. Figure 1C shows the estimated total number of PLHIV in Catalonia from 1980 to 2013, including those not yet diagnosed. Overall, there was an increasing trend throughout the time period, reaching the highest estimated number of people in 2013, a total of

34,729 (CI=32,740, 36,827) PLHIV in Catalonia. Of these, 4,271 (CI=3,737, 6252) were undiagnosed, a proportion of 12.3% (CI=11.8, 18.1).

In 2013, the estimated number of new infections among the Spanish-born population reached a number of 744 (CI=546, 934) (Figure 2A), while among the migrants was 376 new infections (CI=281, 471). Finally among MSM, in both Spanish-born and migrants there was a clear stepping increase in the estimated number of new infections from 2001, reaching the highest number in 2013, with 404 (CI=322, 480) and with 227 (CI=163, 310), respectively (Table 1 and Figure 2B).

The estimated total number of PLHIV comparing the trend in the number of PLHIV between migrant and Spanish-born groups, it was observed that among locals there was a progressive but not very pronounced rise from 1991 to reach the highest estimated number in 2013 with 27,648 (CI=25,365, 29,379) PLHIV, just 5.8% (CI=5.8, 6.6) of whom were undiagnosed (1,603, CI= 1,421, 1,819) (Figure 2C and Figure 2D). Conversely, among migrants the estimated number of PLHIV rose steeply since the beginning of the epidemic, also reaching a peak in 2013 with 7,081 (CI=6,492, 7,616), but with four times the estimated undiagnosed population (23.4%, CI=22.7, 25.1) compared to the local population. Among (Figures 3A and 3B) both local and migrant MSM there has been a large increase in the estimated number of MSM living with HIV in the last 10 years, with a higher increasing slope among migrant MSM. By 2013, there were 8,458 (CI=8,101, 9,079) Spanish-born MSM and 2,538 (CI=2,334, 2,918) migrant MSM living with HIV in Catalonia, with 16.4% (CI=14.2, 17.7) and 32.3% (CI=28.4, 34.4) undiagnosed, respectively.

Data from the PISCIS cohort is available on Supplemental File Table B. Finally, figure 4A and 4B shows the differences in the HIV care cascade in MSM by origin. As a percentage of the total PLHIV, migrant MSM have a greater proportion undiagnosed (32% vs. 16%) that local MSM. In subsequent steps in the HIV care cascade, migrant MSM experience greater losses due to the big different in the proportion of undiagnosed, when compared to the Spanish-born MSM, with lower proportion

retained in care (74% vs. 55%), on cART (70% vs. 50%) and virally suppressed (65% vs. 46%).

## Discussion

Our study estimates that by the end of 2013, there were an estimated number of 34,729 people living with HIV in Catalonia, Spain, of whom 4,271 were still undiagnosed. This study also shows that migrants had a very high proportion of undiagnosed compared to Spanish-born population, and as it has been described by other sources of information from Catalonia [17], this study found that the Catalan epidemic of HIV has continued to expand during the past decade with the key group sustaining HIV transmission being MSM living with undiagnosed HIV and in the asymptomatic stage, especially migrants MSM.

The estimated overall prevalence of undiagnosed HIV-infected people in Catalonia (12.3%) is within the range of those recently obtained in other countries by 2013: 10% in Italy, 12% in Austria, 16% in Belgium and France, 17% in Germany, 18% in Spain and 19% in United Kingdom [7]. Nevertheless we think that some underestimation may have occurred due to two facts; first, that the method that we applied uses data on case reports, which may be subject to underreporting, which can be ranged between 10% to 40% [20,21], and can lead to underestimates HIV incidence and may also affect estimates of diagnosis rates, and thus lower the percent undiagnosed; and second, by the fact that we could not feed the model with migration data. As Catalan epidemic is highly influence by migration we believe that this lower the estimates of the annual number of new HIV infections and therefore undiagnosed HIV-infected individuals.

In line with our results, other studies also had identified among migrants a great proportion of undiagnosed [22,23]. In Catalonia this could be explained by the fact that migrants experienced a higher number of barriers to access HIV testing services than the Spanish-born population and that these needs might be driven primarily by shared risk factors [24]. This also can be due to the fact that migrants face cultural and linguistic barriers, as well as, legal and administrative impediments to accessing health services and thus HIV testing facilities [25]. In Europe the HIV testing uptake among migrants range from 23% to 64% [25]. This difference can differ by sex, as higher proportion of migrant women have been tested for HIV compared with men; this is

partially owing to women's acceptance of routine HIV screening during antenatal care. However, beyond this, several studies support a gender difference in HIV testing uptake, with migrant men being not only less exposed to HIV testing but also less willing to be tested [25]. However, this lower rate of HIV testing among migrant men might be more representative of migrant heterosexual men that MSM migrants, as these later perceive themselves as being at higher risk for HIV, and thus being more likely to have ever been tested for HIV than the local MSM [26,27]. Although, it has been found that untested migrant MSM are particularly hard to reach [27], which in line with our estimates.

Our results suggest that the Catalan HIV epidemic has been sustained by the HIV transmission among undiagnosed MSM, as it has been described in other studies in Catalonia [28,29]. Consistent with this, in the United Kingdom, using the same model it has been estimated that around two in three new infections were attributable to MSM living with undiagnosed HIV [30], and in Switzerland that around 82% of new cases among MSM were acquired from HIV undiagnosed men [31]. This finding can be explained by an increase in risky sexual behaviours [32,33], including high prevalence of unprotected anal intercourse and increasing numbers of sexual partners [34]. This is also supported by a recent survey that reported that 37% of MSM recruited in gay venues had not tested for HIV in the past 12 months [32]. It has also been described that a great proportion of undiagnosed MSM have acquired the infection recently, which made them to be most infectious and the maintenance group of the HIV epidemic [34]. The risky sexual conducts among migrant MSM have been also described, with higher prevalence of unprotected anal intercourse than Spanish-born MSM [35,36] and specifically among Latin American MSM, high HIV prevalence rates among those diagnosed with syphilis and gonorrhoea, as well as, with high prevalence and incidence rates of STIs in those newly diagnosed with HIV [35]. Resources should be allocated primarily to promote testing in high-activity MSM, as they are the key group sustaining the epidemic, but also for encouraging all MSM including migrants MSM to test regularly for HIV, this includes design long-term sustainable outreach-based HIV interventions to reach as many MSM as we could for HIV testing.

Biomedical and behavioural interventions, targeting both HIV-infected and HIV-uninfected MSM, should be used. In this regard, it will be essential to use interventions with proven efficacy , such as treatment as prevention, test and treat interventions, in combination with pre-exposure prophylaxis in highly adherent people, and to implement effective behavioural interventions that prevent an increase in risky behaviours, all of these intervention must be integrated in a well-designed strategy of combination prevention, as it has been described in other studies [37]. Besides, in order to reduce the fraction of undiagnosed should be considered implementing and scaling up innovative approaches to promote greater access to and uptake of HIV testing by those most at risk, including community-based testing, home sampling, as well as indicator-condition- guided testing.

These results must be interpreted in light of several key methodological limitations. The use of the HIV Modelling Tool facilitated the standardisation of estimates for PLHIV, however available information is partial and not representative of the different subpopulations of migrants and MSM across all Catalonia. Despite this limitation, this analysis allowed us to calculate the first step of the HIV care cascade by region of origin and among MSM in Catalonia. The various subgroup analyses completed for this study may not necessarily explain complex differences in global HIV epidemic dynamics among migrants and MSM, but they do demonstrate that the key group sustaining HIV transmission is MSM living with undiagnosed HIV and that among migrants testing coverage will need to be intensify and increase to find those undiagnosed. Although the use of PISCIS cohort data improved the consistency of the estimates, we are unable to link surveillance and cohort datasets to maximise internal consistency, therefore we are unable to distinguish between those diagnosed and those linked to care (enrolled in the cohort), although linkage to care is expected to be high given the Catalan healthcare system characteristics and the high cohort coverage. Additionally, using a single VL measurement may also over-estimate durable viral suppression, however, they provide a snapshot of the continuum in 2013 which is simple to interpret and communicate to policy-makers, as it has been described by other authors [7,38]. Finally, linking surveillance and cohort dataset to population migration and

death registries is weak in Catalonia; therefore this information is poorly crossed between datasets; which it can lead to misclassification of vital status or out- migration that might over-estimate the number still alive and living in Catalonia. Also, lack of reliable in-migration data complicated modelling of HIV incidence and the separation of earlier infections from new infections occurring after arrival within Catalonia. This demonstrates the urgent need to systematically incorporate longitudinal linked data across the different registries in the HIV information system aimed at monitoring and evaluate the HIV epidemic and its response at the local level.

In conclusion, our study suggests that about 4,271 individuals living with HIV remained undiagnosed in Catalonia in 2013, with the greatest proportion among migrants and MSM from abroad and local. New screening strategies to further increase the offer and uptake of HIV testing and to reach out undiagnosed individuals are needed in order to reduce HIV transmission, targeting key population like migrants and MSM to ensure timely access to HIV care, to finally achieve global 90-90-90 targets to reduce HIV incidence and the number of persons remaining undiagnosed in Catalonia.

**Acknowledgements**

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**Conflict of interest**

The authors have no conflicts of interest to disclose.

**Authors' contributions**

CNJC and JRU developed the concept of the manuscript. CNJC and JRU carried out the modelling analysis and JRU and NV the remaining analysis. AE has calculated the adjustment for delayed reporting. JRU drafted the manuscript and integrated critical feedback from JA, CT, EF, GN, LF, IG, AM, JV, PGO, JAC, JMM and JC. All authors read and approved the final version of the manuscript.

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**Data sharing**

Extra data is available by emailing jmreyes@iconcologia.net

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**Table 1.** Estimated annual number of new HIV infections and new HIV, HIV/AIDS and AIDS diagnoses reported to the Catalan surveillance system, by year of infection and origin in men who have sex with men, Catalonia, 2001-2013.

| | Estimated new HIV infection | | | | New HIV diagnoses reported to the Catalan surveillance system | | New HIV /AIDS diagnoses reported to the Catalan surveillance system | | New AIDS diagnoses reported to the Catalan surveillance system | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Spanish born MSM | | Migrants MSM | | Spanish born MSM | Migrants MSM | Spanish born MSM | Migrants MSM | Spanish born MSM | Migrants MSM |
| Year | N | IC95% | N | IC95% | N | N | N | N | N | N |
| 2001 | 134 | (108-159) | 52 | (39-69) | 152 | 47 | 45 | 10 | 68 | 16 |
| 2002 | 151 | (127-172) | 74 | (63-90) | 175 | 62 | 41 | 16 | 55 | 19 |
| 2003 | 163 | (138-181) | 99 | (87-113) | 158 | 59 | 44 | 20 | 70 | 23 |
| 2004 | 172 | (156-188) | 126 | (113-141) | 185 | 89 | 28 | 14 | 52 | 23 |
| 2005 | 181 | (164-196) | 152 | (137-167) | 181 | 91 | 27 | 11 | 36 | 20 |
| 2006 | 191 | (174-210) | 176 | (159-192) | 187 | 109 | 26 | 18 | 52 | 16 |
| 2007 | 204 | (190-222) | 195 | (178-212) | 207 | 125 | 26 | 19 | 39 | 34 |
| 2008 | 222 | (209-238) | 209 | (195-225) | 183 | 133 | 19 | 17 | 35 | 27 |
| 2009 | 245 | (231-260) | 219 | (205-237) | 191 | 115 | 26 | 13 | 40 | 20 |
| 2010 | 274 | (255-296) | 225 | (204-249) | 224 | 175 | 24 | 22 | 34 | 38 |
| 2011 | 310 | (275-347) | 228 | (196-261) | 193 | 243 | 14 | 18 | 27 | 25 |
| 2012 | 353 | (298-408) | 228 | (183-283) | 282 | 189 | 19 | 10 | 35 | 22 |
| 2013 | 404 | (322-480) | 227 | (163-310) | 291 | 185 | 19 | 19 | 32 | 28 |

**MSM**: men who have sex with men; **IC95%:** Confidence interval

**Figure 1.** Model outcomes for the total population in Catalonia, 1980-2013. A. Estimated annual number of new HIV infections, B. Estimated average time from HIV infection to diagnosis by year of infection. C. Estimated total number of people living with HIV, including diagnosed and undiagnosed HIV infections.

**C. Estimated** total number of people living with **HIV**, including diagnosed and undiagnosed HIV infections:

- **Estimated** total number of people living with HIV in Catalonia
- **Estimated** total number of people diagnosed with HIV in Catalonia
- **Estimated** total number of people undiagnosed with HIV in Catalonia

**Figure 2.** Model outcomes by region origin in Catalonia, 1980-2013. A. Estimated annual number of new HIV infections among Spanish born-population B. Estimated annual number of new HIV infections among migrants. C. Estimated total number of Spanish born people living with HIV, including diagnosed and undiagnosed HIV infections. D. Estimated total number of migrants living with HIV, including diagnosed and undiagnosed HIV infections.

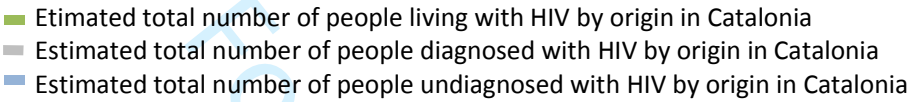

**Figure 3.** Model outcomes for the men who have sex with men by origin in Catalonia, 1980-2013. A. Estimated total number of Spanish born men who have sex with men living with HIV, including diagnosed and undiagnosed HIV infections. B. Estimated total number of migrant men who have sex with men living with HIV, including diagnosed and undiagnosed HIV infections.

**Estimated** total number of men who have sex with men living with HIV by origin in Catalonia
**Estimated** total number of men who have sex with men diagnosed with HIV by origin in Catalonia
**Estimated** total number of men who have sex with men undiagnosed with HIV by origin in Catalonia

**Figure 4.** Cascade of HIV care of men who have sex with men by region of origin in Catalonia, 2013. **A**. Spanish-born men who have sex with men **B.** Migrants men who have sex with men.

**PLHIV:** People living with HIV; **cART:** combined antiretroviral therapy; **VL:** Viral load.

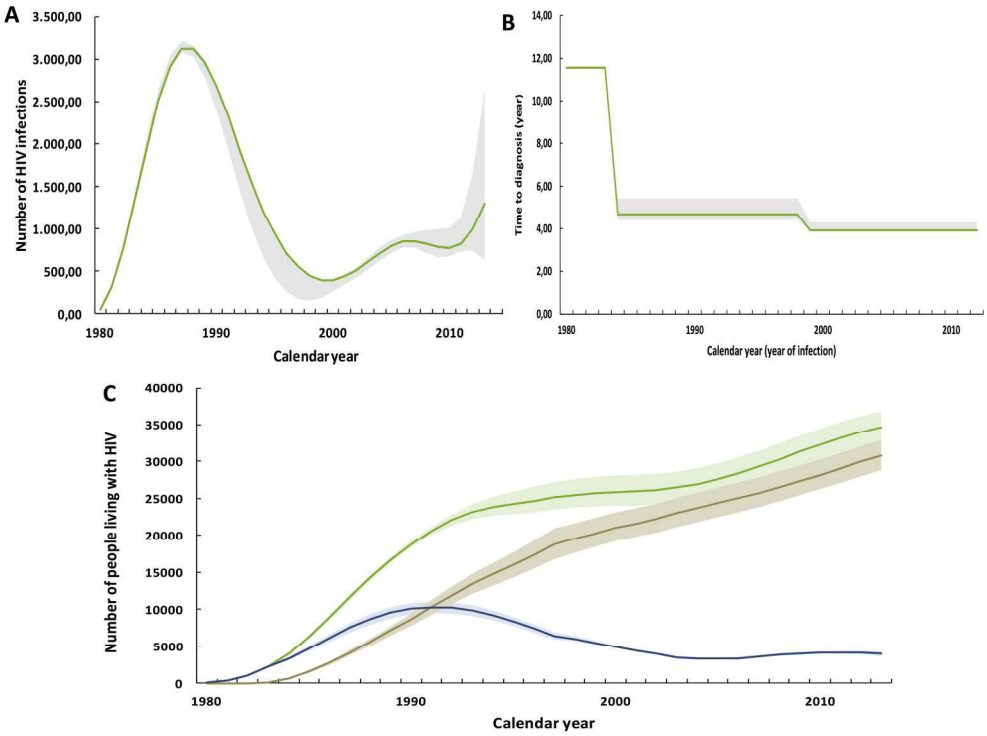


Figure 1

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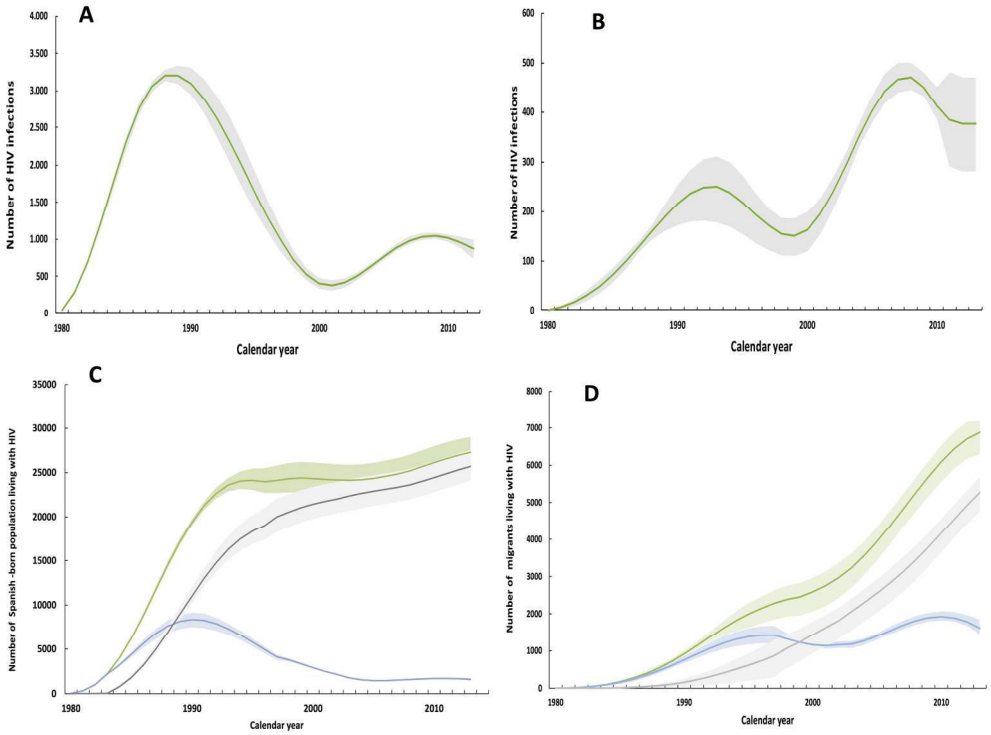


Figure 2.

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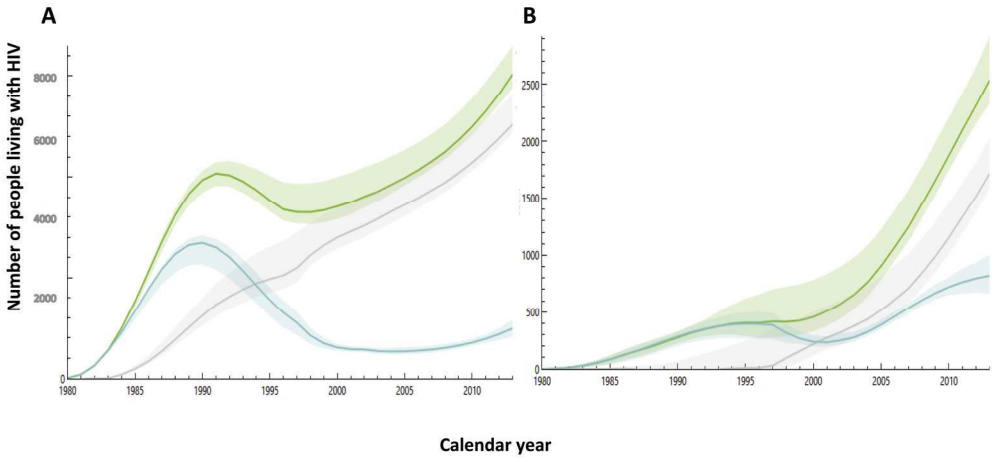


Figure 3

190x142mm (300 x 300 DPI)

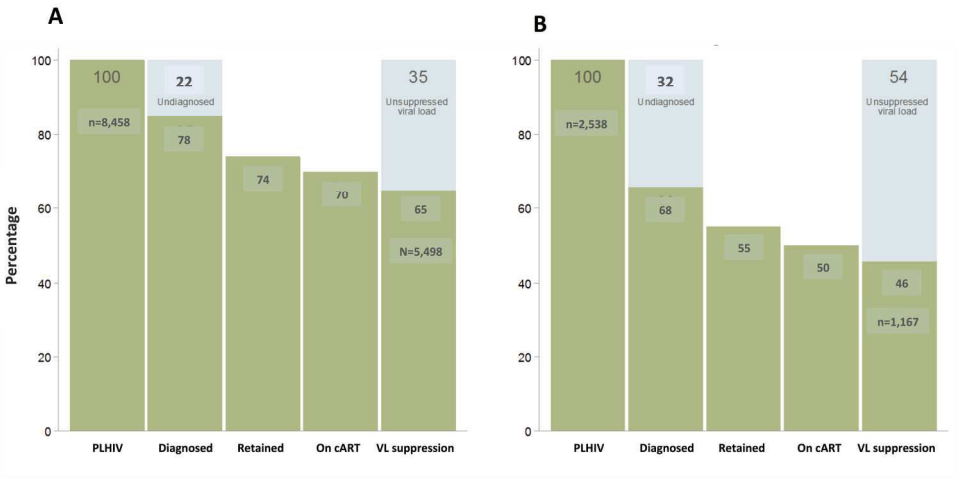


Figure 4

190x142mm (300 x 300 DPI)

**Table A.** Baseline epidemiological characteristics of people aware of their HIV status notified to the surveillance system by origin, Catalonia, 2001-2013.

| | Spanish-born population | Migrants | Total | P value[a] |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | |
| **HIV cases** | 6089 (59.9) | 4061 (40.0) | 10150 (100) | <0.001 |
| **Sex** | | | | <0.001 |
| Men | 5073 (83.3) | 3062 (75.4) | 8135 (80.2) | |
| Women | 1016 (16.7) | 999 (24.6) | 2015 (19.8) | |
| **Age** (median) | 37,00 | 33,00 | 35,00 | <0.001[b] |
| **Age group** | | | | <0.001 |
| <20 | 79 (1.3) | 81 (2.0) | 160 (1.6) | |
| 20-39 | 3586 (58.9) | 3058 (75.3) | 6644 (65.4) | |
| 40-49 | 1443 (23.7) | 703 (17.3) | 2146 (21.2) | |
| >=50 | 980 (16.10) | 219 (5.4) | 1200 (11.9) | |
| **Risk population** | | | | <0.001 |
| PWID | 986 (16.2) | 276 (6.8) | 1263 (12.5) | |
| Heterosexual men | 1206(19.8) | 926 (22.8) | 2132 (21.0) | |
| MSM | 2618 (43.0) | 1624 (40.0) | 4243 (41.8) | |
| Heterosexual women | 737 (12.1) | 849 (20.9) | 1586 (15.6) | |
| Unknown | 542 (8.9) | 386 (9.5) | 928 (9.1) | |
| **Late diagnosis** | 3069 (50.4) | 2193 (54.0) | 5262 (51.8) | <0.001 |
| **Advanced HIV** | 2003 (32.9) | 1336 (32.9) | 3339 (32.9) | 0.933 |

**PWID:** people who inject drugs; **MSM**: men who have sex with men

[a] Pearson's chi-squared test.

[b] Student's t–test.

**Table B**. Comparison of socio-demographic characteristics and clinical features of people enrolled in HIV care (PISCIS cohort), by place and region of origin, Catalonia - Spain, 1998-2013.

| | Spanish-born population | Migrants | Total | |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | P value[a] |
| **Total** | 4194 (69.6) | 1828 (30.4) | 6022 (100) | |
| **Sex** | | | | |
| Men | 3363 (80.2) | 1466 (80.2) | 4829 (80.2) | 1.000 |
| Women | 831 (19.8) | 362 (19.8) | 1193 (19.8) | |
| **Age** median (IQR)[b] | 37 (31-44) | 34 (29-40) | 36 (30-43) | <0.001 |
| **Risk population*** | | | | |
| PWID | 1034 (24.7) | 87 (4.8) | 1121 (18.6) | <0.001 |
| MSM | 1786 (42.6) | 1026 (56.1) | 2812 (46.7) | |
| Heterosexual women and men | 1075 (25.6) | 624 (34.1) | 1699 (28.2) | |
| Others | 297 (7.1) | 91 (5.0) | 388 (6.4) | |
| **Educational level** | | | | |
| Primary education or less | 1215 (29.0) | 435 (23.8) | 1650 (27.4) | <0.001 |
| Secondary education | 795 (19.0) | 571 (31.2) | 1366 (22.7) | |
| Undergraduate education | 491 (11.7) | 412 (22.5) | 903 (15.0) | |
| Unknown | 1693 (40.4) | 410 (22.4) | 2103 (34.9) | |
| **Years on follow up median (IQR)** | 5.5 (2.7-9.4) | 3.5 (1.5-6.2) | 5.4(2.5-9.5) | <0.001 |
| **Number of people on ART** | 3931 (93.7) | 1659 (90.8) | 5590 (92.8) | <0.001 |
| **Number of people with suppressed VL** | 3655 (87.2) | 1515 (82.9) | 5170 (85.8) | <0.001 |

**PWID:** people who inject drugs; **MSM**: men who have sex with men.
*Only 2 had an unknown risk group
[a] Pearson's chi-squared test
[b]Student's t–test.

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No. | Recommendation | Page No. | Relevant text from manuscript |
|---|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Pg 1 | |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Pg 2 | |
| **Introduction** | | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Pg 4 | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Pg 4 | |
| **Methods** | | | | |
| Study design | 4 | Present key elements of study design early in the paper | Pg 6 | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Pg 6 | |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | Pg 6 | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pg 6 - 7 | |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Pg 6 | |
| Bias | 9 | Describe any efforts to address potential sources of bias | | |
| Study size | 10 | Explain how the study size was arrived at | | |

Continued on next page

| | | | |
|---|---|---|---|
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Pg 5-6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Pg 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | Pg 6 |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Pg 8 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Pg 8 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Pg 6 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | Pg 8 |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | Pg 8-9 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (*b*) Report category boundaries when continuous variables were categorized | Pg 8 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |

Continued on next page

| | | | |
|---|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Pg 10 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Pg 12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Pg 11 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Pg 12 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Pg 14 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.