Original Article

A NATIONAL COHORT OF HIV-INFECTED PATIENTS IN BELGIUM: DESIGN AND MAIN CHARACTERISTICS

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ABSTRACT

In Belgium, individual laboratory and treatment data of all HIV-infected patients seen in the 9 AIDS Reference Centres and 7 AIDS Reference Laboratories are collected prospectively since 2006. We present here an analysis of patients recorded in the cohort database between 1st of January 2006 and 31st of December 2008. During that period, 11982 patients were under medical follow-up in Belgium. Sixty-one percent of the patients were male and the median age was 39.8 at the time of first recorded viral load. Among the patients whose nationality or probable mode of transmission was recorded, nearly half (48.0%) were Belgian and 38.3% originated from Sub-Saharan Africa; heterosexual contacts were reported in the majority of cases (56.0%) followed by homosexual contacts (35.3%). A total of 145 deaths were reported. Around three quarters of the patients were on ART. The median CD4 cell count rose from 470 cells/mm^3 in 2006 to 501 cells/mm^3 in 2008. This cohort enabled us to obtain comprehensive information on the numbers and characteristics of HIV-infected patients currently being followed up in Belgium, and on trends in antiretroviral therapy and biological results. This will serve for planning purposes, evaluation of access to care and as a source of information for further studies.

Key words: HIV, cohort studies, AIDS, Belgium, epidemiology

Appendix 1:
Members of the Belgian HIV Cohort Study Group: Revalidatiecentrum UZBrussel: Lacor P; Revalidatiecentrum Instituut voor Tropische Geneeskunde / Universitair Ziekenhuis Antwerpen: Florence E; Specifiek Revalidatiecentrum inwendige ziekten van de Universitaire Ziekenhuizen van de KULeuven: Van Wijngaerden E; «Centre de Prise en charge», Cliniques Universitaires Saint-Luc, Bruxelles: Vandercam B; «Unité de Traitement des Immunodéficiences», Hôpital Erasme, Bruxelles: Goffard JC; Referentiecentrum van het Universitair Ziekenhuis Gent: Vogelaers D and Vandekerckhove L; Centre de Référence de l'Université de Liège: Moutschen M; «Centre Arthur Rimbaud», CHU Charleroi: Legrand JC; «Centre de Traitement de l'Immunodéficience», CHU St-Pierre, Bruxelles: De Wit S; LRS Unité de Microbiologie, UCL, Bruxelles: Goubau P; ARL Laboratorium voor Virologie, KULeuven: Van Ranst M; LRS Laboratoire de Virologie, Hôpital Erasme, Bruxelles: Liesnard C; ARL Laboratorium voor Microbiologie, ITG, Antwerpen: Fransen K; ARL Laboratorium voor Bacteriologie en Virologie, UZ Gent: Plum J; ARL Universitair Ziekenhuis Brussel: Pierard D; LRS Centre de Transfusion sanguine, Université de Liège: Gothot A; ARL Universitair Medisch Centrum Sint-Pieter: Van den Wijngaert S.

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) and the human immunodeficiency virus (HIV) infection are under epidemiological surveillance in Belgium since 1985. The Scientific Institute of Public Health (IPH) collects notifications of new HIV diagnoses from the AIDS Reference Laboratories and of new AIDS cases from clinicians (1-3). This comprehensive surveillance system was implemented soon after the first AIDS cases were reported in Belgium in 1983 and has been providing important information on the spread, the demographics and other characteristics including risk factors of the HIV epidemic in Belgium. This surveillance system does not

allow monitoring of outcomes of HIV infected patients. There is however a need for such information as the size of the HIV-infected population is steadily increasing since the introduction of antiretroviral therapy and the resulting increase in life expectancy (4).

In several European countries, cohorts of HIV infected patients have already been set up. These cohorts are valuable sources of clinical, epidemiological and public health information and have improved our understanding of the natural course of the disease and associated risk factors, as well as our knowledge of the effects of antiretroviral therapy. Some cohorts include all patients seen for care in the country (5) whilst others focus on patients seen in specific centres only (6-9). Consequently, national coverage of the HIV patient population and representativity of the patients included vary between cohorts.

In this context, the Belgian HIV Cohort was initiated in 2006 to obtain a more comprehensive picture of the HIV epidemic in Belgium. It consists of a prospective multicenter data collection from all seven AIDS Reference Laboratories (ARL) and all nine AIDS Reference Centres (ARC) in Belgium. The aim of this cohort is to acquire and share information on the characteristics of the HIV population under medical follow-up and the evolution of these characteristics. The implementation of such a cohort will hopefully contribute to improve the management of the People Living with HIV/AIDS (PLWHA) in Belgium. More specifically, the objectives of the cohort are to estimate the number of HIV patients in follow-up and their demographic profile, to monitor outcomes in terms of death and lost to follow-up and to assess immunological (CD4) and virological (VL) changes over time, as well as antiretroviral therapy (ART) uptake.

In this article we describe the design features of the Belgian HIV Cohort and present selected demographic, laboratory and treatment characteristics of the HIV patients under medical follow-up in Belgium from 2006 to 2008.

METHODS

National surveillance of HIV diagnoses

Screening HIV tests can be performed in any clinical biology laboratory in Belgium.

However, samples that test positive have to be sent for confirmation to one of the 7 ARLs that will perform further screening tests and immunoblots. These ARLs are officially recognised by the Belgian social security body, the National Institute of Sickness and Invalidity Insurance (INAMI/RIZIV). In case of a new confirmed diagnosis of HIV infection, data on age, sex, nationality, residence, sexual orientation, probable mode of HIV transmission and CD4 cell count at the time of HIV diagnosis are collected from the treating physician. These data are then sent by the ARLs to the IPH and included in the database of HIV diagnoses.

HIV patients care system in Belgium

The INAMI/RIZIV also officially recognizes nine ARCs that are specialised in the management of HIV infected patients, which includes clinical care and psychosocial support. HIV-positive patients can either attend one of the ARCs, other clinics specialised in HIV care or be seen by a general practitioner.

Only ARLs are mandated to carry out viral load measurements and resistance tests necessary for the medical monitoring of the HIV infected patients. Therefore, the number of patients with VL measurements reported by the ARLs provides a reliable estimate of the total number of HIV patients in current follow-up in Belgium.

Data collection of HIV patients in follow-up

The IPH started collecting individual routine data on HIV patients in follow-up from the 7 ARLs on 1st of January 2006 and from the 9 ARCs on 1st of April 2006 (Figure 1). Data of all patients with at least one viral load measurement performed in an ARL and/or at least one medical contact in an ARC since 2006 are recorded in the cohort. Once a year, all ARLs and ARCs transmit their data covering the period 1st of January - 31st of December in a standardised electronic format to the IPH.

The following information is collected: viral loads, CD4 cell counts, antiretroviral therapy (as of 31st of December), date of last medical visit during the year and death notifications.

The same coding system is used as that in the IPH's database of HIV diagnoses. In that way, demographic data and dates of HIV diagnosis from that database can be linked to the data of patients in follow-up.

Follow-up data are checked at the IPH for out-of-range and missing values which are reported back to the centres and laboratories for correction. Biological data of patients reported by more than one ARC or ARL during a given year are merged.

Statistical analysis

All patients in follow-up in the database between 1st January 2006 and 31st December 2008 were included in the present analysis. We defined the total population under follow-up as the patients with at least 1 VL measurement recorded during the study period. Analyses of antiretroviral therapy and biological data were performed on all the patients seen in the ARCs between April 2006 and December 2008. For each year, antiretroviral therapy was defined as the treatment regimen on the 31st of December. Patients below 15 years of age were excluded from the analyses of biological data.

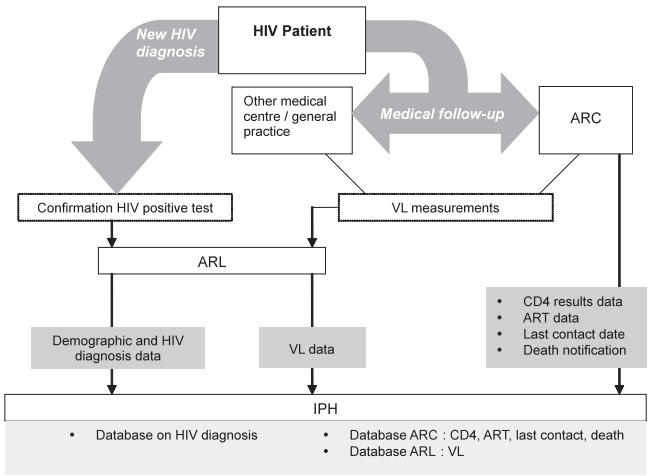

Figure 1: *Data collection flow for HIV patients in Belgium.*

Proportions or medians with interquartile ranges were calculated for all variables. Comparisons between the patients lost to follow-up and the others were made with chi-square and Kruskal-Wallis tests. P-values of less than 0.05 were considered statistically significant. Analyses were performed with Stata version 10 (StataCorp, College Station, Texas, USA).

RESULTS

Population characteristics

Since 1985 up to the 31st of December 2008, 22243 persons were diagnosed with HIV infection in Belgium.

Between January 2006 and December 2008, a total of 11982 patients were under medical follow-up. The number of patients increased from 8583 patients in 2006 to 9351 in 2007 and 10071 in 2008. Sixty-one percent of the 11982 patients were male. The median (IQR) age at the first recorded VL after the 1st of January 2006 was 41.4 (34.2-48.2) years for men and 37.2 (30.4-44.1) years for women (Figure 2). Two percent of the patients were less than 15 years old.

Of the patients whose nationality was recorded, nearly half (48.0%) had the Belgian nationality and 38.3% were from Sub-Saharan Africa (Table 1). Among those with available data on probable mode of transmission, heterosexual contact was reported in the majority of cases (56.0%) while sexual intercourse between men was the probable mode of transmission in 35.3% of cases; intravenous drug use (IDU) was reported by 3.3% of patients only. More than half of the patients (63.7%) were diagnosed with HIV from 2000 onwards, 30.0% between 1990 and 1999 and 6.3% before 1990.

Out of the 11982 patients in care, 9071 (75.7%) HIV patients were followed up in the nine ARCs. Among these patients, 145 deaths were reported.

Antiretroviral therapy

Nearly three quarters of the patients were on ART (Table 2). Among them more than 97% were receiving at least 3 different ARV drugs. The proportion receiving nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) remained stable over the years. The proportion of patients on non-nucleoside reverse transcriptase inhibitors (NNRTI) decreased slightly, whereas the proportion on protease inhibitors (PI) increased, particularly those on lopinavir/ritonavir (20.9% in 2007 and 23.2% in 2008).

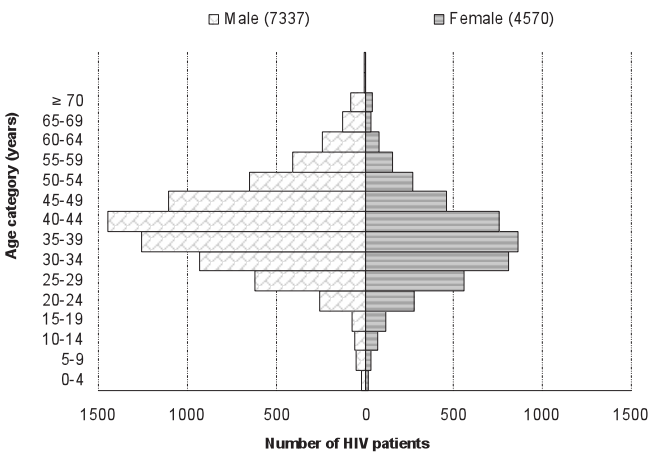

Figure 2: *Age and gender distribution of the HIV patients in medical follow-up in Belgium, 2006-2008.*

Table 1: Characteristics of the HIV patients in medical follow-up in Belgium, 2006-2008

	n	%
Gender	(n = 11907)	
Male	7337	61.6
Female	4570	38.4
Age at entry: median (range)	39.8	(0-88)
Nationality	(n = 7321)	
Belgium	3515	48.0
Europe, excluding Belg.	585	8.0
Sub-Saharan Africa	2805	38.3
North Africa	117	1.6
Other	299	4.1
Transmission risk group	(n = 6871)	
Heterosexual	3845	56.0
Homosexual	2424	35.3
Intravenous drug use (IDU)	228	3.3
Mother-to-child	126	1.8
Other [a]	219	3.2
Homosexual + IDU	29	0.4
Year of HIV diagnosis	(n = 9086)	
< 1985	5	0.1
1985-89	569	6.3
1990-94	1104	12.2
1995-99	1622	17.9
2000-04	2709	29.8
2005-08	3077	33.9

[a] Other: transfusion recipients and persons with haemophilia.

Biological results

The latest CD4 cell counts and VL measurements in each year of follow-up are presented in Table 3. Around 80% of the patients had at least 2 CD4 cell counts and 2 VL measurements per year. Median CD4 count rose over the years (470 cells/mm^3 in 2006 to 501 cells/mm^3 in 2008) and the proportion of patients with CD4 counts < 200 cells/mm^3 decreased from 9.3% in 2006 to 6.2% in 2008. At the same time, the proportion of patients with VL > 1.7 log copies/ml decreased from 41.2% in 2006 to 34.5% in 2008. For both parameters, the changes were particularly pronounced among those on ART. Some of

Table 2: Exposure to different classes of ARV drugs among HIV patients of the Belgian ARCs, 2006-2008

	2006	2007	2008
Population *	**6651**	**7063**	**7730**
ART status:			
on ART: n (%)	4744 (71.3%)	5186 (73.4%)	5835 (75.5%)
not on ART: n (%)	1744 (26.2%)	1728 (24.5%)	1878 (24.3%)
unknown: n (%)	163 (2.5%)	149 (2.1%)	17 (0.2%)
≥ 3 ARV drugs: %	97.4%	97.3%	97.8%
NRTI: %	98.5%	98.2%	98.1%
PI: %	49.4%	53.0%	54.1%
NNRTI: %	47.6%	46.6%	46.9%

* Excluding patients followed in more than one ARC or deceased.

Table 3: CD4 counts and viral loads among HIV patients of the Belgian ARCs, 2006-2008

	2006	2007	2008
CD4 counts			
% with > 1 CD4 count per year			
in patients not on ART	N/A	71.4%	71.8%
in patients on ART	N/A	87.8%	86.7%
in all patients	N/A	82.8%	82.9%
Latest CD4 count value in year			
Median [IQR] cells/mm^3			
in patients not on ART	478 [360-640]	478 [370-633]	486 [370-642]
in patients on ART	469 [317-660]	493 [342-680]	506 [356-686]
in all patients	470 [332-655]	486 [350-667]	501 [360-675]
Proportion < 200 cells/mm^3			
in patients not on ART	5.3%	3.2%	3.7%
in patients on ART	10.6%	8.0%	7.1%
in all patients	9.3%	7.0%	6.2%
VL measurements			
% with > 1 VL measurement per year			
in patients not on ART	N/A	65.3%	72.7%
in patients on ART	N/A	83.9%	91.2%
in all patients	N/A	78.0%	86.6%
Latest VL result in year			
Proportion > 1.7 log copies/ml			
in patients not on ART	90.7%	94.5%	92.3%
in patients on ART	24.5%	16.2%	16.0%
in all patients	41.2%	35.4%	34.5%

N/A: not available.

the patients may have had their treatment modified between the time of last laboratory measurement and the time of treatment recording at the end of the year.

DISCUSSION

Nearly 12000 HIV-infected patients were in medical follow-up in Belgium between 2006 and 2008. This number increased every year.

Compared to HIV patients followed in neighbouring countries (6, 10,11) patients in the Belgian cohort are characterised by a large proportion of women and a large proportion of patients from sub-Saharan Africa. This is reflected in the main mode of transmission which is sexual intercourse between men and women. These features are similar to the characteristics of the new diagnoses of HIV infection in Belgium (2): they show a predominance of the heterosexual mode of transmission and a high proportion of migrants from sub-Saharan Africa. However, the proportion of MSM among the newly diagnosed individuals has sharply increased over the last years (from 23.2% in 2002 to 45.9% in 2008) (12). Consequently a slight increase in the number of MSM patients in follow-up (28.4% in 2006 and 29.8% in 2008) is observed.

A large majority of the patients were seen in ARCs. Nearly three quarters of them were on treatment with at least 3 different antiretroviral drugs. In 2 other cohorts in the Netherlands and Switzerland (10, 11), around 80% of the patients were reported to be on ART. The proportion of patients on ART is influenced by the characteristics of the patients included in each cohort such as disease stage. For instance the Swiss HIV Cohort Study reported that AIDS patients were better represented in the cohort than in the patients reported by the Federal Office of Public Health (13).

An increase in the use of PIs, particularly lopinavir/ritonavir, was observed during the study period. Both PIs or NNRTIs in combination with 2 NRTIs are recommended by the European AIDS Clinical Society as first line therapy in treatment naïve HIV-infected patients (14). The observed increase could be due to the preference for PI-based regimens for therapy initiation in some cases using the argument of their higher genetic barrier to resistance. The proportion of patients on second line therapy with regimens including a PI may also have increased, seeing the aging of the HIV-infected population and the need to switch therapy for various reasons at some point in the 'treatment life' of a patient. Other factors such as drug characteristics may have influenced the choice of ART by clinicians (15). For instance, availability of lopinavir/ritonavir in combination tablets, the fact that it could be kept outside the refrigerator and the small number of pills can probably explain its preferential use among the available PIs at the time. The choice of antiretroviral drug can also be influenced by drug availability and reimbursement conditions in Belgium; these are constantly evolving and will surely influence the antiretroviral drugs used in the following years.

More than 80% of patients had at least 2 laboratory follow-up measurements performed per year. In the coming years, we may see a decrease in the number of VLs per year for patients on a stable and fully suppressive combination antiretroviral therapy, as suggested in a recent article by Reekie et al (16). But this may be balanced out by the more frequent VLs asked for patients more virologically unstable or just starting on ART.

Several determinants could explain the observed increase in median CD4 values of the patients over the years. Firstly, an evolution towards earlier diagnosis of HIV-infection with higher CD4 counts at diagnosis has been observed in Belgium (2). Secondly, ART initiation may take place at higher levels of CD4 counts, following the recent treatment recommendations towards earlier therapy initiation (14, 17-19). Changes in guidelines have indeed been described to have an influence on the timing of ART initiation (20). Thirdly, a better adherence to treatment thanks to better tolerated, easier to use and more potent drugs could also have had an impact on CD4 values. A corresponding decreasing trend in the proportion of patients with CD4 cells below 200 cells/mm^3 - patients at higher risk of death - was observed between 2006 and 2008.

One of the strengths of this cohort is that the general characteristics of the HIV patients presented here are representative of all HIV patients in Belgium. Indeed all viral load assays are performed in the ARLs, with the exception of a few patients enrolled in some pharmaceutical trials or whose biological analyses are performed abroad. On the other hand, information on ARV treatments and CD4 cell counts was collected only from the ARCs and VL data were analysed only for those patients.

Patients followed in other medical centres than the ARCs tend to be slightly younger, more likely to be of non-Belgian nationality and to be more recently diagnosed with HIV than ARC patients. Given that these differences could have an impact on therapy and biological results, we cannot generalise the information on ART nor apply our biological findings to all the Belgian HIV patients. Nevertheless the patients seen in ARCs do represent ¾ of all HIV-infected patients under follow-up.

In conclusion, the implementation of this cohort has enabled us to obtain comprehensive data on the number and characteristics of HIV-infected patients currently being followed up in Belgium. It provided us with information on trends in antiretroviral therapy and biological results for more than three quarters of the seropositive patients under care. Such data should be of help for planning future needs in terms of treatment and laboratory follow-up. It could also prove useful to evaluate access to care of HIV-infected patients. Finally, the cohort will be a valuable source of data to support other specific studies.

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CONFLICT OF INTEREST: None.

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