ORIGINAL ARTICLE

Factors influencing HIV progression in a seroconverter cohort in Madrid from 1985 to 1999

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Objective: To study HIV progression from seroconversion over a 15 year period and measure the population effectiveness of highly active antiretroviral therapy (HAART).
Methods: A cohort study of people with well documented dates of seroconversion. Cumulative risk of AIDS and death were calculated by extended Kaplan-Meier allowing for late entry. Cox proportional hazards models were used to study variables associated with HIV progression. To assess the impact of HAART, calendar time was divided in three periods; before 1992, 1992–6, and 1997–9.
Results: From January 1985 to May 2000, 226 seroconverters were identified. The median seroconversion interval was 11 months, median seroconversion date was March 1993. 202 (89%) were men, 76% of whom were homo/bisexual. A 66% reduction in progression to AIDS was observed in 1997–9 compared to 1992–96 (HR 0.34 95% CI: 0.16 to 0.70). People with primary education appeared to have faster progression to AIDS compared to those with university studies (HR 2.69 95%CI: 1.17 to 6.16). An 82% reduction in mortality from HIV seroconversion was observed in 1997–9 (HR 0.18 95% CI: 0.05 to 0.68) compared to 1992–6. Progression to death for people with primary education was twice as fast as for those with university education (p 0.0007). People without confirmation of an HIV negative test had faster progression (HR 4.47 95% CI: 1.18 to 16.92).
Conclusions: The reduction in progression to AIDS and death from seroconversion from 1992–6 to 1997–9 in Madrid is likely to be attributable to HAART. HIV progression was faster in subjects with primary education; better educational level may be associated with better adherence to medication.

Since the introduction of HAART (highly active antiretroviral therapy) the prognosis for HIV positive patients has improved dramatically in populations with access to these treatments.[1–7] The efficacy of HAART has been well established in clinical trials but these results may not translate well into a given population where the trial conditions are not met. While observational cohorts cannot provide an accurate assessment of individual treatment effectiveness, they can provide a measure of the population effectiveness of these therapies.[3–8] These are essential since they estimate the reduction in HIV progression in a particular setting when those who have indications to be treated are given drugs of proved efficacy. Population effectiveness is heavily determined by other important aspects such as access to health care, prescription practices, drug adherence and level of resistance to antiretroviral drugs, which differ in the various settings HAART is given.[3 7 8]

Spain has been heavily affected by the HIV/AIDS epidemic. HIV/AIDS has been, until recently, the leading cause of death among young adults.[9 10] The autonomous community of Madrid has one of the highest incidences of AIDS in Europe, 110.9 per million inhabitants in 1999, although from 1996, incidence and mortality rates have dropped by 63% and 73% respectively.[11] The median incubation period of AIDS in Spain up to December 1996 was 10 years,[12 13] similar to other European countries.[14–17] HAART has been widely available to all patients in Spain, free of charge, since late 1996.[18] The extent to which HAART contributed to these decreases in AIDS and death and which other factors may have influenced progression rate of HIV in Madrid has not been adequately addressed since data on people with well estimated dates of seroconversion were not available.

We describe the method of assembling a cohort of seroconverters in Madrid, the only seroconverter cohort in Spain whose members are largely homosexual men, study which factors have influenced progression to AIDS and survival from HIV seroconversion over a 15 years period, and measure the population effectiveness of HAART in this setting.

PATIENTS AND METHODS

The definition of a seroconverter was an individual aged 16 years or over who had a negative HIV test within 40 months of the first HIV positive test, or who had a documented acute seroconversion illness with laboratory evidence criteria.[19] Seroconversion was estimated as the mid-point between the last HIV negative and the first HIV positive tests.

Seroconverters were identified at the "Centro Sanitario Sandoval" from 1985 to 2001 and recruitment is ongoing. The Centro Sanitario Sandoval is an ambulatory STD clinic and HIV screening centre whose access is open, free, and anonymous and which has been a pioneering centre in HIV prevention in Madrid. HIV negative subjects are invited to come back after 6 months for follow up HIV tests. If they become HIV positive, patients are followed up every 4 months in the centre until they require antiretroviral treatment and/or hospital admissions. Patients are then referred to various hospitals in Madrid for clinical follow up and antiretroviral treatment.

Complete ascertainment of all seroconverters seen in the recruiting centre was carefully sought. The reconstruction of the cohort was done in 1997, but all people who seroconverted before that date were selected independently from their outcome, since they were identified prospectively from 1985 onwards by recruiting all patients who had a previously documented HIV negative test done either in the recruiting centre

*See Appendix for members of the group.

or elsewhere. If the documentation of the HIV negative test not done in recruiting centre could not be retrieved (as some centres did not provide patients with written documentation of HIV test results), patients had to provide the name of the centre where the test was done, together with the month and the year of the test.

Entry date for the analyses was the estimated date of seroconversion for those seroconverters who had both their last HIV negative result and first HIV positive result in the recruiting centre. For seroconverters who were HIV negative and/or HIV positive in a centre different from recruiting one but who joined the clinic at a later stage, entry date was staggered to the date of the first HIV positive visit to the recruiting centre. Late entry aims to correct the potential "survivor bias" introduced in the analysis by including patients whom might have been identified because they survived long enough, thus excluding rapid progressors.

Follow up information of seroconverters is updated yearly both in the recruiting centre and in the referring hospitals. For patients lost to follow up, crosschecks using name, surname, and date of birth are performed with the data bases from the 12 participating hospitals within the Community of Madrid (see Appendix) and the national AIDS register. Regional AIDS registers report to the National AIDS register and underreporting, 13%, is similar to other European countries.[20] Under-reporting in the autonomous region of Madrid is below 5% for both AIDS cases and deaths among those because of active surveillance for AIDS cases and vital status.[21 22] Mortality data in the national AIDS register are less complete.[22] Update of information from clinic notes and crosschecks with the AIDS register were terminated by 31 July 2001 but analyses were censored by 1 January 2000 to allow for reporting delay. Patients were assumed to be AIDS free by 1 January 2000 if there was no evidence of AIDS in the clinical notes or in the national AIDS register by 31 July 2001. Owing to the characteristics of the recruiting centre, patients could have chosen not to disclose their true names at the time of HIV diagnosis. Therefore, for those seroconverters whose names could not be verified and for the two known to have left the country, censoring date was the last visit to the clinic.

For analyses of time to death, two different censoring strategies were used to allow for the different yield of the mortality information of the national AIDS registry for patients who might have died outside Madrid. The first strategy assumed patients were alive by 1 January 2000 if there was no evidence of death in the clinical notes or in the national AIDS register by 31 July 2001. The second strategy made no assumptions beyond the time they were last seen or reported as AIDS in the national AIDS register.

Statistical analyses

The cumulative risk of AIDS and death (all cause mortality) was calculated by extended Kaplan-Meier estimates allowing for late entry whereby individuals only contribute to the "period at risk" from the time they are identified. The log rank test was used to test differences. Cox proportional hazards models were used to examine the risk of AIDS and death and to assess which variables were associated with progression of disease, also allowing for late entry. The variables tested in univariate analyses were sex, transmission category, age at seroconversion, level of education at first HIV positive visit to the recruiting centre (primary, secondary, university), employment status at first HIV positive visit to the recruiting centre, presence of a documented HIV negative test, being co-infected with hepatitis C virus (HCV), and calendar period under observation (fitted as a time dependent covariate). To assess the impact of new therapies on HIV progression, calendar year at risk was divided in different periods, which reflected the different availability of drugs in our setting. The impact of HAART was tested in various periods and the final classification was as follows; before 1992 where only zidovudine monotherapy was available; 1992–6 where mainly double therapy was available; and 1997–9 where potent antiretroviral therapy and protease inhibitors were introduced.[18] Multivariate analyses were performed to find the best model for developing AIDS and/or dying in people who had been infected for the same length of time.

RESULTS

From January 1985 to May 2000, 226 seroconverters have been identified. The median seroconversion interval was 11 months (interquartile range 7–19 months). The median seroconversion date was March 1993 (interquartile range September 1990 to November 1995).

Three (1%) subjects were identified during acute seroconversion illness and in 26 (11%) documentation of a previous HIV negative test could not be verified. Of the 226 seroconverters; 48 (21%) are being followed up in the recruiting centre, 153 (68%) are being followed in different hospitals, and 25 (11%) are lost to follow up.

Table 1 describes the characteristics of the cohort; 202 (89%) were men, the majority of whom (76%) were infected through sex between men. Of the 24 women, 12 were heterosexual and the rest were current or ex injecting drug user (IDU). Median age at seroconversion was 27 years (range 17–56); 27 years (range 18–56) for men and 25 years for women (range 17–35). Homo/bisexual men were older (median 29 years) than IDUs (median 24 years). There were 26 (12%) individuals born outside Spain, although Spain was the probable country of infection for all subjects. There were statistically significant differences in the educational level of the different transmission categories; a higher proportion of homo/bisexual men (40%) had secondary education and 31% had university education compared to 17% and 6% among IDUs ($p = 0.000$). The majority (81%) was working at the time of seroconversion though this proportion was much lower (64%) among people with primary education compared to those with secondary (83%) and university education (98%). Homosexual men had better qualified jobs compared to other groups (data not shown). People with primary education were 1–2 years younger than the other educational levels ($p=0.050$). There were no statistically significant differences in terms of sex, transmission category, year of seroconversion, employment status, and level of education between cases whose date of HIV negative results was confirmed compared to those in whom it was not, but median age at seroconversion was lower in the former (27.0 years) compared to the other group (31.4 years) ($p=0.029$). Only 149 people had HCV serology available, of which 41 (27%) were co-infected by HCV. Of these, 28 (93%) were IDU, three (20%) heterosexuals, and five (5%) homo/bisexual men.

Figure 1 describes the uptake of different antiretroviral regimens by cohort members over time and how the utilisation of HAART rose sharply from 1997.

Time from seroconversion to AIDS

Forty four (19%) subjects developed AIDS before January 2000. The commonest AIDS defining conditions were tuberculosis (23%) and Kaposi's sarcoma (KS) (16%) followed by oesophageal candidiasis (11%) and *Pneumocystis carinii* pneumonia (9%). There was a marked lengthening of the incubation period of AIDS after 1996. The proportion of people who developed AIDS after 8 years from seroconversion was 43% (95% CI 29% to 60%) in the 1992–6 period compared with 20% (12%–34%) for the 1997–9 period ($p=0.005$) (Fig 2).

Variables associated with progression to AIDS in univariate analyses are shown in table 2. Being co-infected with HCV was not associated with faster progression to AIDS (HR 1.43 95% CI: 0.64 to 3.22). In a multivariate Cox regression model calendar period remained associated with progression to AIDS, and level of education and age at the time of

Table 1 Sociodemographic characteristics of seroconverters (n=226) (100%)

	Educational level at seroconversion					
	Primary (n=72)	Secondary (n=81)	University (n=52)	Unknown (n=21)	Total (n=226)	p Value
Sex						0.147
Female	12	8	2	2	24 (11%)	
Male	60	73	50	19	202 (89%)	
Transmission category						0.000
MSM*	30	61	47	15	153 (68%)	
IDU†	31	8	3	6	48 (21%)	
MSM + IDU	3	5	0	0	8 (3%)	
Heterosexual	7	7	1	0	15 (7%)	
Unknown	1	0	1	0	2 (1%)	
Documentation HIV negative test						0.438
Undocumented	6	12	5	1	24 (11%)	
Documented	66	69	47	20	202 (89%)	
Employment at seroconversion						0.000
Employed	46	67	51	19	183 (81%)	
Unemployed	26	14	1	2	43 (19%)	
Median age at seroconversion	26	28	28	27	27	0.050
Median year of seroconversion	March 1992	August 1993	May 1993	May 1993	March 1993	0.377

*Men who have sex with men.
†Injecting drug user.

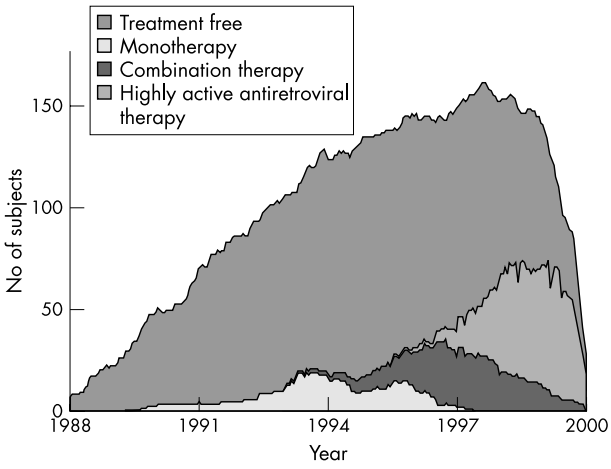

Figure 1 Distribution of the utilisation of different antiretroviral regimens by all HIV+ subjects over time.

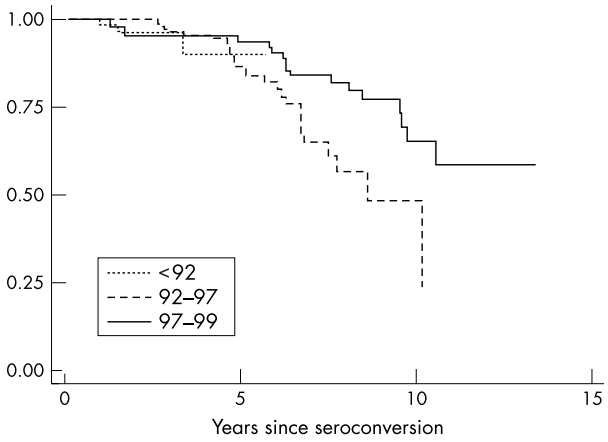

Figure 2 Kaplan-Meier curves of time to AIDS in different calendar periods.

seroconversion had borderline association. There was a strong effect of calendar period under observation with a 66% reduction in progression to AIDS in the 1997–9 period compared to 1992–7 (HR 0.34 (95% CI: 0.16 to 0.70)) (table 3). Progression to AIDS was two and a half times higher among people with primary education compared to those with university education (HR 2.69 (95% CI: 1.17 to 6.16)). This effect was not confounded by category of transmission, which was not itself associated with progression to AIDS. Although there were not enough person years to test for an interaction between the effect of calendar period and level of education, censoring before 1997 and truncating entry at 1997 still revealed an effect of level of education on time to AIDS although it did not reach statistical significance.

Survival from seroconversion

Eighteen (8%) people died before January 2000, of whom two were the result of violent causes (one in a homosexual man and other in an IDU male). Variables associated with survival from seroconversion in univariate analyses are shown in table 4. In multivariate Cox regression, only calendar period, level of education at seroconversion, and not having a negative HIV test confirmed were associated with survival time. The inclusion of age did not improve the fit of the model (Lrtest p=0.255) but was left in the final model as age is established as one of the most important variables influencing HIV progression and there were statistically significant differences in age among different educational levels. No differences in survival were observed from 1986 to 1996, but a marked survival improvement, an 82% reduction in mortality from HIV seroconversion (HR 0.18 (95% CI: 0.05 to 0.68)), was observed for calendar period 1997–9 (table 5). People with primary education at seroconversion progressed to death twice as faster than people with university education (HR 1.97 (95% CI: 0.59 to 6.49)). Although all confidence intervals for the levels of the variable "educational levels" include one, the inclusion of the variable improved the fit of the model (Lrtest p=0.045). There were not enough person years to test for an interaction between the effect of calendar period and level of education but censoring before 1997 and truncating entry at 1997 still revealed an effect of level of education on survival although it did not reach statistical significance.

People who did not have an HIV negative test documented had a progression rate four and half times higher than those in whom an HIV negative test could be verified (HR 4.47 (95% CI: 1.18 to 16.92)).

Repeating these analyses censoring people when last seen did not change the estimates of interest (data not shown).

Table 2 Univariate analyses of variables associated with progression to AIDS

Variable	Univariate HR (95% CI)	p Value
Age*	1.02 (0.97 to 1.07)	0.487
Sex		0.300
Males	1.00	
Females	1.46 (0.71 to 2.94)	
Transmission category		0.909
MSM	1.00	
IDU + MSM/IDU	1.03 (0.57 to 1.87)	
Calendar period		0.023
1986–91	1.36 (0.39 to 4.77)	
1992–6	1.00	
1997–9	0.38 (0.18 to 0.76)	
Educational level at seroconversion		0.175
Primary	2.17 (0.93 to 5.07)	
Secondary	1.15 (0.46 to 2.87)	
University	1.00	
Unknown	1.45 (0.44 to 4.72)	
Employment at seroconversion		0.011
Employed	1.00	
Unemployed	2.18 (1.19 to 3.99)	
Documentation HIV negative		0.192
Undocumented	1.70 (0.76 to 3.78)	
Documented	1.00	

*Per 1 year increase.

Table 3 Multivariate analyses of variables associated with progression to AIDS

Variable	Multivariate HR (95% CI)	p Value
Calendar period		0.0076
1986–91	1.37 (0.39 to 4.86)	
1992–6	1.00	
1997–9	0.34 (0.16 to 0.70)	
Educational level at seroconversion		0.077
Primary	2.69 (1.17 to 6.16)	
Secondary	1.31 (0.52 to 3.26)	
University	1.00	
Unknown	1.56 (0.48 to 5.02)	
Age at seroconversion†	1.03 (0.99 to 1.07)	0.08

*Per 1 year increase.

Table 4 Univariate analyses of variables associated with survival from seroconversion

Variable	Univariate HR (95% CI)	p Value
Age*	1.03 (0.97 to 1.10)	0.295
Sex		0.899
Males	1.00	
Females	0.91 (0.24 to 3.52)	
Transmission category		0.454
MSM	1.00	
IDU + MSM/IDU	1.42 (0.75 to 0.45)	
Calendar period		0.066
1986–91	1.13 (0.09 to 13.60)	
1992–6	1.00	
1997–9	0.21 (0.06 to 0.78)	
Educational level at seroconversion		0.238
Primary	1.67 (0.53 to 5.28)	
Secondary	0.36 (0.06 to 1.99)	
University	1.00	
Unknown	1.21 (0.21 to 6.89)	
Employment at seroconversion		0.033
Employed	1.00	
Unemployed	2.78 (1.08 to 7.13)	
Documentation HIV negative		0.031
Undocumented	3.19 (1.10 to 9.17)	
Documented	1.00	

*Per 1 year increase.

Table 5 Multivariate analyses of variables associated with survival from seroconversion

Variable	Multivariate HR (95% CI)	p Value
Calendar period		0.014
1986–91	1.19 (0.10 to 13.41)	
1992–6	1.00	
1997–9	0.18 (0.05 to 0.68)	
Educational level at seroconversion		0.045
Primary	1.97 (0.59 to 6.49)	
Secondary	0.31 (0.05 to 1.79)	
University	1.00	
Unknown	1.87 (0.29 to 12.10)	
Documentation HIV negative		0.019
Undocumented	4.47 (1.18 to 16.92)	
Documented	1.00	
Age*	1.02 (0.97 to 1.08)	0.255

*Per 1 year increase.

DISCUSSION

A marked reduction in progression to AIDS and death from HIV seroconversion (by 66% and 82% respectively) is observed in 1997–9 compared to 1992–6 in people with similar duration of HIV infection in Madrid. This reduction in HIV progression is likely to be attributable to HAART, which became widely available from 1996 onwards.[18] Since the follow up of the seroconverters identified in the recruiting centre Sandoval has been carried out in the centre as well as in 12 different hospitals, the population effectiveness of HAART measured in this study reflects a wide range of social and medical services.

Important reductions in the risk of death in different calendar periods have been reported by seroconverter cohorts which have looked at the population effectiveness of HAART in different settings; 48% in 1995–7 compared to 1990–3 in the Multicenter AIDS Cohort Study,[3] 50% in the year 1997 using 1983–91 as a reference in the Italian Seroconversion Study,[4] and 64% in 1997–8 compared to 1986–96 in different European countries in the Concerted Action on SeroConversion to AIDS and Death in Europe.[7]

Progression to AIDS and death from HIV seroconversion was faster in subjects with primary education compared to secondary and university education at the time of HIV infection. Better educational level is a marker of higher socioeconomic status which is likely to be associated with better abilities to cope with stressful events, as well as having the knowledge and the capacity to comply better with the increasingly complex antiretroviral regimens. Better educational level has been associated with better adherence to antiretroviral drugs in HIV positive people in our setting.[23] Better adherence, however, does not fully explain the differences in progression found in groups with different educational levels since the effect was also present before HAART because of small numbers, it was not possible to detect statistically significant differences. Few studies have looked at educational level as a covariate in HIV progression and have found no effect.[24] Others have looked at the association between socioeconomic status and HIV progression.[25–27] This association is, however, inconsistent, with some studies reporting no association[25] and others finding faster HIV progression before HAART in groups of lower socioeconomic status.[26] In an Italian study, the effect of socioeconomic status on HIV progression has only been found after the introduction of HAART.[27] Further analyses are being currently undertaken to explain why, in the context of free and universal access to HIV/AIDS care, progression rates of HIV are higher in people with a lower educational level.

Age at HIV seroconversion has been described as one of the most important co-factors in HIV progression.[12–17 28] The magnitude of the effect found in our study is similar to other seroconverter cohorts though it lacked the power to detect statistically significant differences.

Crosschecking with the national AIDS register using different assumptions allows us to minimise losses to follow up without biasing the results. As described by Porter *et al*, the classic approach of censoring people who are event-free at the time they were last seen in cohorts when medical follow up may be outcome dependent may lead to an underestimate of time to AIDS since people doing well are those less likely to attend the clinic.[29] This is particularly relevant in our study since we are more likely to be losing asymptomatic patients rather than cases of AIDS. There is, however, a potential problem with this censoring strategy in that a person who died without AIDS would be missed and survival estimates would be longer. Given that the majority of our population are MSM (in whom pre-AIDS death is uncommon), and that the two censoring strategies used give similar results, it is unlikely that the situation described above may have significantly affected the results.

A potential selection bias may have arisen if patients initially identified as HIV negative in the recruiting centre Sandoval failed to return for an HIV positive test due to causes related to their outcome, such as developing a severe seroconversion illness requiring hospital care. These patients may then choose to be followed up in the hospital rather than in Sandoval, losing a group of patients with potentially faster progression from our cohort.[30] This is, however, a potential bias that will always be encountered when recruiting from ambulatory centres and since the estimate of progression of this cohort before HAART is similar to most other studies, it is unlikely that the scenario described above may have seriously biased the results. Further analyses truncating entry 5 years after seroconversion did not change our overall estimates (data not shown).

People in whom an HIV negative test could not be confirmed had shorter survival from seroconversion. This recall bias has been described in other seroconverter cohorts[29] and underestimates survival times from seroconversion. Since the aims of these analyses were to study which factors influence HIV progression in this cohort and describe its methodology, we decided to leave these 24 people out of current analyses, adjust for its confounding effect, and exclude them from future analyses.

Maintaining the accomplishments achieved in the prognosis of HIV infection will depend on correct patient management, adequate drug adherence, low levels of resistance to antiretroviral drugs, and the absence of competing causes of death not decreased by HAART, such as HCV related severe liver disease and those resulting from the potential complications of antiretroviral treatments. A prevalence of 27% of HIV genotypes with reduced susceptibility to antiretroviral drugs has been detected among a seroconverters identified in the Sandoval centre.[31] The implications this finding will have on response to therapy and HIV progression is uncertain and requires follow up of the cohort, as well as further analyses of why people with a lower educational level have faster HIV progression rates.

APPENDIX

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Key messages

- The reductions in progression to AIDS (by 66%) and death (by 82%) observed in Madrid during 1997–9 in people infected by HIV for the same length of time are attributable to HAART
- In a context of free and universal access to HIV/AIDS care, progression to AIDS and death was faster in subjects with a lower educational level and could reflect worse adherence to medication
- This is the first study assessing the population effectiveness of HAART in Madrid. Determining population effectiveness is essential as it reflects a wide range of social and medical services that may compromise the efficacy shown in clinical trials.

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CONTRIBUTORS

JDR, JdA, CR, MD, VS, and JC initiated this project; AB, JdAJDR, JdA, CR, and SP-H were responsible for data collection; SP-H was responsible for statistical analyses; JdA wrote the first draft of the paper; all authors were involved in the study design and commented interim drafts; all authors have reviewed the final manuscript.

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