

# Effectiveness of highly active antiretroviral therapy in Spanish cohorts of HIV seroconverters: differences by transmission category

Santiago Pérez-Hoyos<sup>a</sup>, Julia del Amo<sup>b,d</sup>, Roberto Muga<sup>e</sup>,  
Jorge del Romero<sup>c</sup>, Patricia García de Olalla<sup>f</sup>, Rafael Guerrero<sup>g</sup>,  
Ildefonso Hernández-Aguado<sup>d</sup> and GEMES\*

**Objective:** To evaluate the population effectiveness of highly active antiretroviral therapy (HAART) in HIV progression and determine the heterogeneity of the effect of HAART in GEMES (Spanish multicenter study of seroconverters).

**Design:** Multicenter cohort study.

**Methods:** Data from 1091 persons with well-documented HIV seroconversion dates from 1980s to January 2000 were analysed. Risk of AIDS and death in subjects with same duration of HIV infection were compared in different calendar periods; before 1992, 1992–1995 (reference), 1996–1997, 1998 and 1999 with Kaplan–Meier methods and Cox proportional hazards models, allowing for late entry, fitting calendar period as time-dependent covariate and adjusting for transmission category, age and gender.

**Results:** Statistically significant reductions in the risk of AIDS were first observed in 1998 [hazard ratio (HR), 0.59; 95% confidence interval (CI), 0.35–1.01] becoming more pronounced in 1999 (HR, 0.45; 95% CI, 0.24–0.84). Reduction in the risk of death was seen in 1997, though only reached borderline significance in 1999 (HR, 0.53; 95% CI, 0.26–1.07). Progression to AIDS and death was slower in women (HR, 0.68; 95% CI, 0.46–0.99 and HR, 0.53; 95% CI, 0.33–0.87, respectively). Compared with men who have sex with men (MSM), intravenous drug users (IDU) had lower reductions in the risk of AIDS and death.

**Conclusions:** Reductions in incidence of AIDS and death in GEMES are seen after 1998 and 1999, respectively, compared with 1992–1995, being more pronounced in MSM compared with IDU, the commonest category in Spain.

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From <sup>a</sup>EVES (Valencian School for Health Studies), Valencia, <sup>b</sup>Plan Nacional del SIDA, Ministry of Health and Consumption and <sup>c</sup>Centre for Health, Sandoval, Madrid, <sup>d</sup>Department of Public Health, University Miguel Hernández, Alicante, <sup>e</sup>Hospital Germans Trias i Pujol, <sup>f</sup>IMSP (Municipal Institute of Public Health), and <sup>g</sup>Red Penitentiary of Catalonia, Barcelona, Spain. \*See the Appendix for members of GEMES.

Requests for reprints to: S. Pérez Hoyos, Epidemiology and Statistics Unit, Valencian School for Health Studies (EVES), C/Juan de Garay 21, 46017 Valencia, Spain.

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## Introduction

Important reductions in HIV progression to both AIDS and death have been observed since the introduction of highly active antiretroviral treatments (HAART) in settings where these can be delivered. This evidence, first shown in clinical trials [1,2], has also been reproduced in observational cohort studies of incident and prevalent cases introducing individual treatment as a covariate in the analyses, measuring the individual effectiveness [3–9]. Some of these results may, however, be confounded by the selection bias introduced by the patients who receive treatment, since these tend to be subjects infected for longer periods of time and with more advanced immunosuppression [10,11].

Since the introduction and the uptake of HAART in different groups within the same population has not been homogeneous over time, analyses that compare progression in persons infected for the same length of time (or with similar progression markers at the time treatment is introduced) in different calendar periods are necessary. These analyses measure the population effectiveness of the different therapies and allow for better control of the survivorship bias. Population effectiveness complements the information derived from clinical trials by providing an indirect measure of accessibility and utilization of services as well as of compliance with the medication [10,11]. The population effectiveness of HAART has been described in seroconverter cohorts such as the MACS [12,13] in the United States and the CASCADE collaboration [14] in Europe, showing important reductions in the incidence of AIDS and death following the introduction of HAART.

Spain has one of the highest incidences of AIDS in Western Europe and most of its cases have occurred among intravenous drug users (IDU) [15]. As in other European countries, the number of AIDS cases declined after the introduction of HAART in late 1996, though this decline in Spain had already started in 1994 as a result of changes in the AIDS case definition [15,16]. Despite the fact that the Spanish national health service offers free antiretroviral treatment to all HIV-positive patients, the social exclusion of the most numerous group of patients, IDU, could impair both access and compliance with these treatments, thus compromising its population effectiveness. It is, therefore, essential to measure the population effectiveness of HAART in different settings with different epidemiological characteristics since, unlike efficacy, it is expected to be very heterogeneous. GEMES, the Spanish Multicenter Study Group of Seroconverters, has provided information of the incubation period of AIDS in Spain up to 1996 [17]. The objectives of this study are to evaluate the effectiveness of HAART in individuals with the same duration of infection after

controlling for potential confounders, and to determine the heterogeneity of the effect of HAART in different subgroups of the population.

## Patients and methods

Data from 1091 persons with well-documented HIV seroconversion dates from five established seroconverter cohorts included in GEMES were analysed. The cohorts within GEMES have identified HIV seroconverters either retrospective or prospectively from the 1980s to current date and follow them up over time. All subjects who fulfilled the criteria of seroconverter were included in the study. A seroconverter was defined as an individual who had had an HIV-negative test previous to the first HIV-positive one. Seroconversion was estimated as the mid-point between the last HIV negative and the first HIV positive tests.

The current analyses have used data from five cohorts within GEMES: the cohort from the CIPS (Centres for AIDS Information and Prevention) within the Valencian Community, the cohort from the Municipal Institute for Public Health (IMSP) of Barcelona recruited at CAS (Centres for care and monitoring drug addicts of Barcelona), the cohort from a hospital detoxification unit at the Hospital Germans Tras i Pujol in Badalona, the cohort of seroconverters from prisons of the Autonomous Community of Catalonia and the cohort of Sandoval (Centre for Sexually Transmitted Diseases and HIV Counseling and Testing in Madrid). More information on the characteristics of these cohorts can be obtained from individual publications [18–22].

Information on sociodemographic characteristics, age, gender and transmission category [IDU, men who have sex with men (MSM), heterosexuals], as well as clinical and immunological data (number and type of AIDS events, antiretroviral treatments prescribed, CD4 lymphocyte cell counts, HIV RNA viral load and vital status) is collected. Follow-up information of seroconverters is up-dated yearly. Each of the cohorts within GEMES follows its seroconverters at the recruiting centres and referral hospitals and performs cross-checks with local and/or National AIDS Registers and mortality registers. Regional AIDS Registers in Spain report to the National AIDS Register and under-reporting, 13%, is similar to that in other European countries [23,24].

## Statistical analyses

Progression to AIDS and death from HIV seroconversion was analysed, allowing for late entry to the date of the first HIV-positive test. For these analyses, individuals who were AIDS free and alive by January 2000

were censored. Individuals with pre-AIDS mortality were censored as AIDS free at the moment of death for time to AIDS analysis. They were treated as dead for time to death analysis.

Since the objective of these analyses was to measure the effectiveness of HAART at the population level, calendar year at risk was divided in different periods, which reflected changes in the availability of antiretroviral drugs in Spain. The reference period chosen was 1992–1995, and this was compared with time before 1992, when only zidovudine monotherapy was available, and with years 1996–1997, 1998 and 1999, when potent antiretroviral therapy and protease inhibitors were being prescribed [25]. Calendar period was modelled as a time-dependent covariate so each individual contributed to the analyses with as many registers of ‘time periods’ he/she has been at risk. Each of these registers has the duration of HIV infection the seroconverter had at the beginning and at the exit of that calendar period, and what was the outcome in terms of AIDS and death.

The cumulative risk of AIDS and death (all cause mortality) was calculated by extended Kaplan–Meier estimates allowing for late entry to allow comparison of subjects infected for the same length of time in different calendar periods.

Cox proportional hazards models were used to examine the risk of AIDS and death in the previously described calendar periods, allowing for late entry. The resulting relative hazard should be interpreted as the excess or the absence in the risk of AIDS and death had the conditions in each period been constant in subjects infected for the same length of time. Analyses were adjusted for age at seroconversion, gender and transmission category. In order to determine the modifying effect of these demographic variables on the effectiveness of HAART, interaction terms were included in the regression models.

Analyses were performed in Stata 7.0 (StataCorp., College Station, Texas, USA) using robust methods to estimate confidence intervals

## Results

Table 1 shows the sociodemographic characteristics of the 1091 seroconverters from all cohorts: 80.9% were men and the majority were IDU, except for the Madrid–Sandoval cohort where 69% were MSM. Median age at seroconversion ranged from 22.6 years in the IDU cohort of Badalona to 27.6 years in the Sandoval–Madrid cohort. The IDU cohort of Badalona had showed the earliest seroconversion dates and,

**Table 1. Descriptive statistics of cohorts integrating GEMES.**

	All cohorts	CIPS Valencia	Sandoval–Madrid	Badalona cohort	IMSP–Barcelona	Prisons–Barcelona
Total No. subjects	1091	275	254	143	167	252
Men (%)	867 (80.9)	199 (72.4)	228 (89.8)	114 (79.7)	122 (73.0)	204 (80.9)
Men who have sex with men (%)	174 (15.9)	—	174 (68.5)	—	—	—
Intravenous drug users (%)	830 (76.1)	275 (100)	53 (20.9)	143 (100)	146 (87.4)	213 (84.5)
Others categories of transmission (%)	87 (8.0)	—	27 (10.6)	—	21 (12.6)	39 (15.5)
Age at seroconversion (median)	25.5	24.7	27.6	22.6	25.9	25.9
Year of seroconversion (median)	April 1993	January 1992	May 1993	November 1986	August 1994	September 1995
Years of follow up (median)	4.55	6.10	3.42	7.08	3.17	3.43
Ever received antiretroviral treatment (%)	348 (31.9)	130 (42.3)	122 (48.0)	46 (32.2)	26 (15.6)	24 (9.5)
Subjects contributing time alive in each calendar period						
Before 92	304	89	75	118	4	18
1992–1995	735	225	162	106	103	109
1996–1997	800	257	162	76	147	158
1998	729	241	160	57	104	167
1999	694	233	147	51	84	179
AIDS (%)	203 (18.6)	54 (19.6)	46 (18.1)	58 (40.6)	26 (15.6)	19 (7.5)
AIDS incidence per 100 person-year	4.63	4.73	4.97	6.39	5.18	2.09
Deaths (%)	147 (13.5)	44 (16.0)	19 (7.5)	51 (35.7)	25 (15.0)	8 (3.2)
Death rate per 100 person-year	2.80	2.63	1.89	4.91	4.42	0.83
Pre-AIDS deaths (% of total deaths)	54 (36.7)	15 (34.1)	3 (15.8)	15 (29.4)	15 (60.0)	6 (75.0)

therefore, had the longest follow-up (median 7.08 years). The latest seroconversion time corresponded to seroconverters identified in prisons.

The incidence of AIDS was 4.63/100 person-years (203 cases) and was higher in the more mature cohorts. There were 147 deaths, with a death rate of 2.80/100 person-years. The percentage of pre-AIDS deaths (proportion of total number of deaths) was high, 36.7%, rising up to 60% and 75% in the less-mature cohorts (IMSP-Barcelona and prison cohorts, respectively); the lowest was in Sandoval-Madrid cohort, 15.8%. All women were IDU; pre-AIDS death was 37.5% in women and 35.3% in male IDU.

Overall, 31.9% had ever received any antiretroviral treatment; the highest treatment rate, 48%, was in the Sandoval-Madrid cohort, where 69% were MSM. IDU and those recruited in prison showed lower rates of treatment, ranging from 9.5% to 42.5%. The proportion of women receiving antiretroviral treatment was 37.7%, higher than the 27.4% of the male IDU. Figure 1 describes the proportion of persons receiving antiretroviral treatment over different calendar periods and how this proportion increased from 1997 onwards, peaking at 30% by January 2000.

**Time to AIDS**

Time to AIDS in different calendar periods in persons infected for the same length of time is shown in the Kaplan-Meier curves in Fig. 2. Compared with the period 1992-1995, reductions in the proportion of persons developing AIDS are observed in 1998 and more pronouncedly in 1999.

Multivariate analyses show that statistically significant reductions in progression to AIDS were first observed in 1998, by 41% [hazard ratio (HR), 0.59; 95% confidence interval (CI), 0.35-1.01], increasing up to 55% (HR 0.45; 95% CI, 0.24-0.84) in 1999 (Table 2).

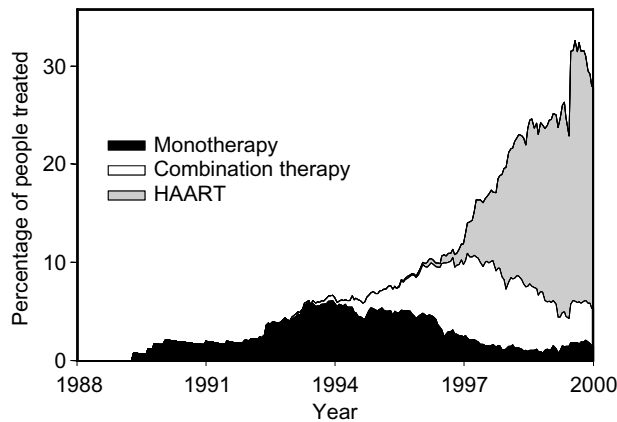


Fig. 1. Distribution of treatments over time for GEMES cohorts (HAART, highly active antiretroviral therapy).

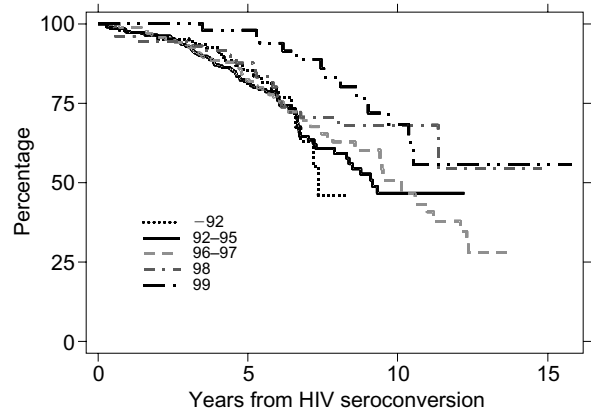


Fig. 2. Time to AIDS for GEMES cohorts according to calendar year.

Progression to AIDS was significantly slower in women (HR, 0.68; 95% CI, 0.46-0.99) though no interaction between calendar period and gender was found ( $P = 0.7747$ ) (Table 2). Transmission category modified the effect of calendar period on time to AIDS ( $P = 0.08$ ); MSM had a more pronounced reduction in the risk of AIDS compared with IDU (Table 3).

**Time to death**

Time to death in different calendar periods in persons infected for the same length of time are shown in the Kaplan-Meier curves in Fig. 3. Reductions in the proportion of persons dying were observed from 1997 onwards.

Multivariate analyses show that reductions in the risk of death were seen from 1997 onwards, though they only reach borderline statistical significance in 1999 (HR, 0.53; 95% CI, 0.26-1.07). Progression to death, as with AIDS, was also significantly slower in women (HR, 0.53; 95% CI, 0.33-0.87) (Table 2). No interaction with gender was found ( $P = 0.1329$ ). Transmission category also modified the effect of calendar period on time to AIDS ( $P = 0.05$ ). While MSM had reductions in the risks of death from 1996-1997 onwards, these were of smaller magnitude in IDU and were only observed by 1998-1999 (Table 3).

**Discussion**

This study shows substantial reductions in the risk of AIDS and death in Spain, starting in 1998. These are the first analyses that have measured the population effectiveness of HAART in different transmission categories. Although HAART has been available since late 1996, its population impact was not apparent until 1998 and has been smaller in IDU than in MSM.

A significant slower progression to both AIDS and

**Table 2. Effect of calendar period on time from seroconversion to AIDS and death.**

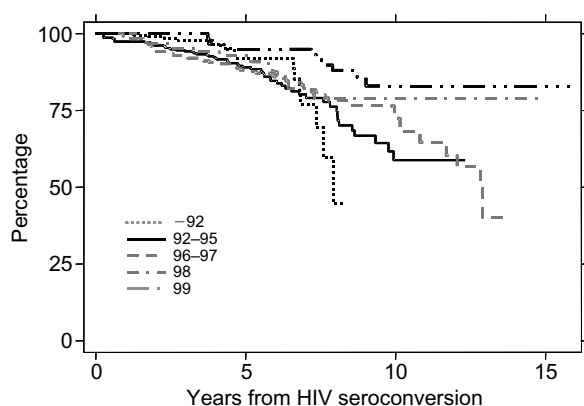
	Time to AIDS		Time to death	
	Relative risk (95% CI)	<i>P</i> value	Relative risk (95% CI)	<i>P</i> value
Calendar period				
Before 1992	1.08 (0.63–1.87)	0.776	0.75 (0.34–1.64)	0.469
1992–1995	1	–	1	–
1996–1997	0.94 (0.66–1.33)	0.741	1.03 (0.66–1.60)	0.899
1998	0.59 (0.35–1.01)	0.056	0.83 (0.46–1.51)	0.547
1999	0.45 (0.24–0.84)	0.012	0.53 (0.26–1.07)	0.079
Sex				
Men	1	–	1	–
Women	0.68 (0.46–0.99)	0.046	0.53 (0.33–0.87)	0.012
Age (per year increase in age)	1.01 (0.98–1.04)	0.460	1.03 (0.99–1.06)	0.101

CI, confidence interval.

**Table 3. Effect of calendar period on time from seroconversion to AIDS and death for men who have sex with men (MSM) and for intravenous drug users (IDU).**

	Time to AIDS		Time to death	
	IDU, RR (95% CI)	MSM, RR (95% CI)	IDU, RR (95% CI)	MSM, RR (95% CI)
Calendar period				
Before 1992	1.03 (0.57–1.85)	1.38 (0.37–5.1)	0.89 (0.49–1.61)	0.47 (0.06–3.56)
1992–1995	1	1	1	1
1996–1997	1.07 (0.73–1.58)	0.61 (0.26–1.48)	1.05 (0.67–1.62)	0.12 (0.01–0.98)
1998–1999	0.72 (0.44–1.16)	0.11 (0.02–0.49)	0.57 (0.33–0.96)	0.26 (0.05–1.22)
Sex				
Men	1	–	1	–
Women	0.67 (0.46–0.99)	–	0.55 (0.34–0.90)	–
Age (per year increase in age)	1.01 (0.97–1.04)	1.01 (0.97–1.04)	1.03 (0.99–1.07)	1.03 (0.99–1.07)

RR, relative risk; CI, confidence interval.

**Fig. 3. Time to death for GEMES cohorts according to calendar year.**

death has been observed in women, all of whom were IDU and had a higher uptake of antiretroviral therapy compared with male IDU. Women within GEMES had also slower progression to AIDS before the availability of HAART [17], a finding only reported by the SEROCO cohort from France and not found by most other seroconverter studies [26–28]. In spite of the reported differences in the prognostic value of viral

load and lymphocyte CD4 cell counts [29,30], no translation in terms of poorer long-term clinical outcome have been reported in women after HAART [31,32]. Antiretroviral therapy has proven to be highly effective in improving HIV-related morbidity and mortality rates in both women and men [28,31,32] but in some settings, women may be less likely than men to use these therapies. The Italian Seroconversion Study found a decreased population effectiveness of HAART in females by 1997 [27] but we have not detected a differential effect of the population effectiveness of HAART by gender. It is important to monitor the effectiveness of HAART by gender in different settings as the social characteristics of the HIV epidemic may affect how HAART will impact on disease progression in men and women. Further analyses to explore the gender differences in HIV progression detected within GEMES are currently being conducted.

The reductions in progression to death found in this study were less marked in IDU than in MSM, though no differences were detected in time to AIDS. This is likely to be because of the higher proportion of non-HIV-related deaths among IDU as well as the better

uptake and compliance with various health interventions by MSM. A higher pre-AIDS mortality in IDU had been described before HAART [33] since IDU in our setting are exposed to competing causes of death that are not decreased by HAART, such as drug-related deaths [34] and hepatitis C end-stage liver disease [35]. Unfortunately, cause of death was not available in most of GEMES cohort members. Pre-AIDS mortality in some IDU cohorts accounts for a third of all deaths, though the short follow-up in some cohorts may account partly for this high proportion. The uptake of antiretroviral treatment was also lower in IDU compared with MSM, as has been reported by other groups in Europe [36,37] which did not, however, lead to differences in clinical progression.

The methodology used to assess the population impact of HAART in these cohorts allows a public health indicator of the evolution of HIV progression trends in different calendar periods to be obtained, provided the date of seroconversion is well documented [10,11,38]. This is particularly useful for cohorts with difficult follow-up, such as those containing IDU, where regular lymphocyte CD4 cell counts and HIV viral load measurements are not easily available. The irregular follow-up of IDU may underestimate the proportion receiving HAART and this bias has to be taken into account when correlating an apparently low use of HAART with high population effectiveness. Although the external validity of the information from seroconverter cohorts with regards to trends in the general HIV-positive population has some limitations [38], the heterogeneity of GEMES cohorts, recruited from very different settings such as outpatients prevention centres, hospital-based clinics and prisons from different regions of Spain, allows generalization of the results from GEMES to HIV progression in Spain.

The population effectiveness of HAART measured in GEMES became statistically significant in years 1998 and 1999 for AIDS and death, respectively, compared with 1992–1995, while the reduction in HIV progression in cohorts from the United States [12] and Europe [14,27,36] became apparent earlier. Detels *et al.* [12] found a 48% reduction in the risk of death in 1995–1997 compared with 1990–1993 in the United States. In Europe, Dorrucci *et al.* [27] estimated a 46% reduction in the risk of death in 1997 compared with that before 1991 and the CASCADE collaboration [14,28] found a 64% reduction in the risk of death in 1997–1998 period compared with that in 1986–1996. None of these studies reported differences in progression by transmission category though subanalyses from the Italian cohort suggested that the reductions in AIDS and death appeared to be smaller in IDU and heterosexuals [27]. In the CASCADE study, IDU were less likely to start HAART but, up to 1999, this finding had no translation in terms of clinical progression [36].

The overall use of HAART for GEMES members was only 25% by 1999 but was twice as common in MSM than in IDU, accounting for the differential population effectiveness of HAART in different subgroups of the population. Although the proportion of IDU receiving HAART may be underestimated for the reasons discussed above, these results highlight the fact that HAART is under-utilized in IDU. Given that IDU account for 60% of the Spanish AIDS epidemic, the delayed population effectiveness of HAART has profound public health implications. It is essential to develop and sustain interventions that improve access and compliance with HAART, to reduce competing causes of death and to continue monitoring the population effectiveness HAART in our setting.

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## Appendix

The membership of GEMES includes Centre of GEMES Data Analysis, Valencian School for Health Studies (EVES): Santiago Pérez-Hoyos, Inmaculada Ferreros; Centres for AIDS Attention and Prevention (CAPS) of Barcelona: Joan Caylá, Patricia Garcia de Olalla, Teresa Brugal; Valencian Centres for AIDS Information and Prevention (CIPS): Ildefonso Hernández Aguado, Manoli Garcia de la Hera, Isabel Hurtado, Julian González-Aracil, M José Aviñó; Hospital Germans Trias i Pujol, Badalona: Robert Muga, Arantza Sanvicens, Bonaventura Clotet, Jordi Tor; Sandoval-Madrid: Jorge del Romero, Carmen Rodríguez, Mercedes Díez, Soledad García, Vicente Soriano (for the Grupo de Seroconvertidos de la Comunidad de Madrid): Catalanian Prisons: Rafael Guerrero, Andrés Marco; Hospital La Paz: Manolo Quintana, Alicia Barrasa, Julia del Amo; Hospital Vall d'Hebron: Isabel Ruiz, Joan Tussell; Hospital Virgen del Rocío de Sevilla: Rosario Perez y José Miguel Cisneros; National AIDS Register: Jesús Castilla.