PE 7.9/2

A retrospective cohort study to determine the epidemiology of and factors associated with HIV-related outcomes among immigrants starting antiretroviral therapy in Spain. The HIVIS Study (GESIDA 5808)

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12th European AIDS Conference. November 11-14, 2009. Cologne, Germany

INTRODUCTION

- Migration is a growing social phenomenon with a well-recognized impact on the epidemiology of infectious diseases.
- Today, 11.3% of the Spanish population is foreign-born and a third of newly diagnosed HIV-infected patients are immigrants.
- HIV infection in immigrants can present origin-related characteristics such as a higher prevalence of non-B subtypes, different reference ranges for laboratory tests, imported infections, different patterns of HBV/HCV infection, and different abilities to tolerate the adverse effects of antiretroviral drugs.
- In addition, communication difficulties, social exclusion, and cultural factors may act as barriers to health care in this population.
- Although several studies have addressed diverse health care–related issues of the immigrant population in Spain, there are no data on treatment and outcome.

METHODS

Study population

- Historical cohort study of HIV-infected individuals attending the HIV clinics of 33 Spanish hospitals.
- Patients: Antiretroviral-naïve adults who started HAART between January 2005 and December 2006, and who had at least one follow-up visit during the following six months were classified as autochthonous or immigrant.

Objectives and endpoints

- The primary objective was to compare the **time to treatment failure** between autochthonous and immigrant patients in order to know whether being an immigrant is associated with a different prognosis of HIV infection. Analysis was performed on an intention-to-treat (ITT) basis and failure was defined as virological failure, loss to follow-up, new HIV-related opportunistic infection not due to immune reconstitution, death, and switch or discontinuation of therapy because of toxicity/intolerance.
- Secondary endpoints: **time to treatment failure expressed as observed data** (same endpoints as time to treatment failure, but missing patients were censored) and time to virological failure (same endpoints as **time to treatment failure**, but missing patients and treatment discontinuations not due to virological failure were censored).
- Late initiation of HAART was defined as a CD4 lymphocyte count <200/μgL at the start of therapy, a prior or concomitant diagnosis of AIDS at the start of therapy, or both.

Statistical analyses

- Survival was calculated using Kaplan-Meier plots and differences were evaluated using the log-rank test.
- A Cox regression model was used to control for confounders. For primary and secondary endpoints, an "explicative" strategy was followed, including, in all models, the variable "Immigrant vs autochthonous patients".

RESULTS

Demographic data

- We identified a total of 1090 treatment-naive patients (387 immigrants and 703 autochthonous) (Table1).
- The immigrant population was younger, with a higher proportion of women, and heterosexual relations were more frequently a route of infection. Among immigrants, the period between diagnosis of HIV infection and initiation of treatment was shorter, and there were fewer intravenous drug users and patients coinfected by HCV.
- AIDS-defining conditions were identified in 89 immigrants and 143 autochthonous patients (Table 2).
- The immigrants were from South and Central America and the Caribbean (31%), Sub- Saharan Africa (28.3%), Western Europe and the United States (12.2%), North Africa (7.7%), Asia (7.4%), Eastern Europe (6.3%), the Middle East (6.1%), and other regions (4.4%).
- For the sake of the comparison between the different regions of origin, those from Western Europe and the United States were excluded as was the group of immigrants from other regions (there were few cases and the origins were very diverse), and those from North Africa and the Middle East were grouped together (Table 3).

Laboratory parameters

- At baseline there were no significant differences between immigrants and autochthonous patients in (median) CD4 cells/μgL (193.5 vs. 201.5) and HIV-1 Log_{10} viral load (4.95 vs. 4.98).
- CD4 lymphocyte gain during the study period was similar in both immigrants and autochthonous patients (162 vs. 168; difference –6.0; 95% CI, –39 to 20), while HIV-1 Log_{10} viral load decrease was slightly lower (–2.63 vs. –3.01; difference 0.37; 95% CI, – 0.20 to –0.55).

Effectiveness

- The proportion of virological failure was similar between the cohorts, although losses to follow-up and switches in treatment due to intolerance or toxicity were more frequent in the immigrant cohort (Table 4).
- Time to treatment failure was significantly shorter for immigrants than for autochthonous patients (median time, 147 weeks vs. 168 weeks; log-rank, p=0.014) (Figure 1).
- Time to treatment failure expressed as observed data (p=0.33) and time to virological failure did not differ between the cohorts (p=0.77).
- The median time to treatment failure was significantly shorter for women than for men (147 weeks vs. 171; p<0.001). Nevertheless, when time to treatment failure was stratified by cohort, the difference was significantly shorter for immigrant women (124 weeks vs. 171; p<0.001), but not for autochthonous women (151 weeks vs. 173; p=0.14).
- Cox regression models included the following as covariates: cohort (immigrant vs. autochthonous), age, weeks of known HIV infection before initiation of HAART, gender, risk behaviour for HIV infection, co-infection with HBV or HCV, occupational status, and the interaction between occupational status and cohort.
- After adjusting for these variables, the time to treatment failure was no different between immigrants and autochthonous patients (hazard ratio [HR]=0.88; 95% confidence interval [CI], 0.66-1.20). Similarly, there were no differences in time to treatment failure expressed as observed data (HR, 0.95; 95% CI, 0.66-1.36) or time to virological failure (HR 1.005, 95% CI, 0.57-1.78).
- Time to treatment failure was significantly shorter for Sub-Saharan African immigrants than for the other groups (log-rank, p=0.003) (Figure 2) (Table 5).

RESULTS (CONT.)

TABLE 1. Baseline characteristics (values expressed as percentages unless otherwise indicated).

	Immigrants (n=387)	Autochthonous (n=703)	p value
Age years, median (IQR)	34 (29-40)	39 (34-45)	<0.001
Gender, female	37.5	24.6	<0.001
Risk behaviour			<0.001
Heterosexual relations	56.3	32.7	
MSM	29.2	30.4	
Injection drug users	5.9	31.0	
Other	8.5	5.8	
Current drug user	1.8	6.1	<0.001
Active alcohol consumption	8.3	12.2	0.044
Educational level			0.15
No school	13.8	9.0	
Primary	19.8	17.6	
Other	25.7	32.0	
Secondary	26.1	27.6	
University	14.6	13.8	
Occupation			0.002
Unemployed	29.0	28.9	
Working 25-50% of the time	4.3	1.8	
Working >50% of the time	64.7	61.9	
Other	2.0	7.4	
Co-infection with HCV and/or HBV			<0.001
HCV	7.0	31.3	
HBV	5.4	3.7	
HCV+HBV	1.3	1.1	
Not co-infected	74.4	50.9	
Not available	11.9	12.9	
Previous AIDS	25.9	27.1	0.69
CD4+T-cell count cells/mm³, median (IQR)	193.5 (77-280)	201.5 (78-289)	0.51
HIV-1 RNA log_{10} copies/mL, median (IQR)	4.95 (4.29-5.44)	4.98 (4.50-5.35)	0.22
Time until initiation of HAART weeks, median (IQR)	8.0 (2-27)	21 (3-71)	<0.001
Late initiation of HAART	56.4	56.0	0.88
Antiretroviral therapy			0.78
2 NUCs+ATV/r	3.6	4.6	
2 NUCs+EFV	60.6	55.0	
2 NUCs+FPV/r	2.6	3.0	
2 NUCS+LPV/r	17.9	20.8	
2 NUCs+NVP	6.5	6.4	
2 NUCs+SQV/r	3.1	3.9	
3-4 NUCs	2.1	2.7	
Other*	3.6	3.6	

* Generally quadruple regimens with 3 NUCs plus either a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor, or both. ATV, atazanavir; EFV, efavirenz; FPV, fosamprenavir; IQR, interquartile range; LPV, lopinavir; MSM, men who have sex with men; NUCs, nucleos(t)ides; NVP, nevirapine; SQV, saquinavir.

TABLE 2. AIDS-defining conditions prior to or at the moment of starting HAART (values expressed as percentages).

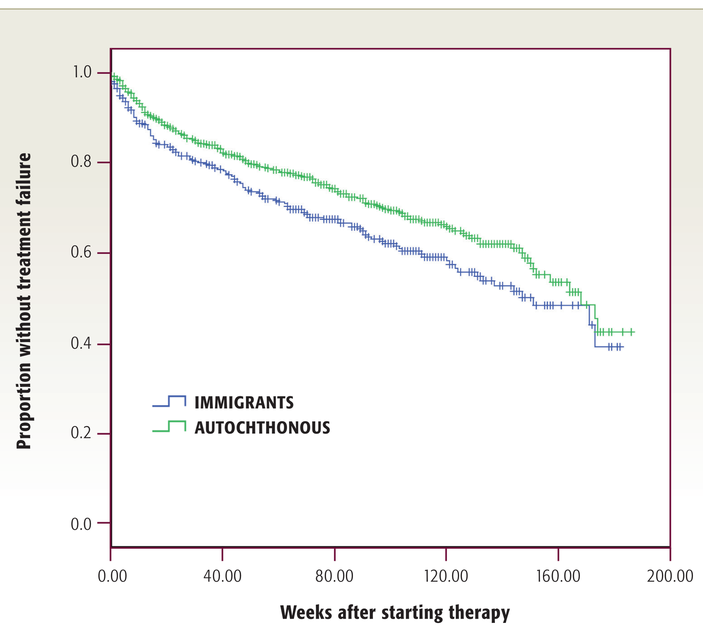
Diagnosis	Immigrants (n=89)	Autochthonous (n=143)	Total
P. jiroveci pneumonia	14.6	25.2	21.1
Pulmonary tuberculosis	19.1	11.9	14.7
Extrapulmonary tuberculosis	20.2	10.5	14.2
Kaposi sarcoma	7.9	10.5	9.5
Oesophageal candidiasis	5.6	11.2	9.1
Cerebral toxoplasmosis	5.6	5.6	5.6
CMV disease	5.6	5.6	5.6
Wasting syndrome	7.9	2.8	4.7
Non-Hodgkin lymphoma	4.5	3.5	3.9
Cryptosporidium species diarrhoea	3.4	2.1	2.6
Progressive multifocal leukoencephalopathy	0.0	4.2	2.6
Recurrent pneumonia	0.0	2.8	1.7
Extrapulmonary cryptococcosis	1.1	1.4	1.3
HIV-related encephalopathy	0.0	2.1	1.3
Chronic intestinal isosporiasis	3.4	0.0	1.3
Recurrent *Salmonella* species bacteraemia	0.0	0.7	0.4
Disseminated histoplasmosis	1.1	0.0	0.4

χ^2=29.41; p=0.021

TABLE 3. Baseline characteristics: immigrant cohort by region of origin (values expressed as percentages unless otherwise indicated).

	South and Central America (n=117)	Sub-Saharan Africa (n=107)	North Africa-Middle East (n=52)	Asia (n=28)	Eastern Europe (n=24)	p value
Age years, median (IQR)	33 (28-39)	35 (29-42)	31 (28-36)	36 (28-40)	32 (29-35)	0.052
Gender, female	30.8	45.8	57.7	21.4	37.5	0.002
Risk behaviour						<0.001
Heterosexual relations	47.9	77.6	75.0	39.3	33.3	
MSM	45.3	13.1	13.5	42.9	37.5	
Injection drug users	2.6	1.9	3.8	0.0	12.6	
Other	4.3	7.5	7.7	17.9	16.7	
Current drug user	1.7	0.9	0.0	0.0	8.3	0.041
Educational level						<0.001
No school	4.8	26.0	20.9	12.0	6.7	
Primary	40.3	27.4	7.0	0.0	6.7	
Other	11.3	19.2	46.5	32.0	13.3	
Secondary	27.4	16.4	20.9	40.0	33.3	
University	16.1	11.0	4.7	16.0	40.0	
Occupation						0.001
Unemployed	14.9	44.7	34.8	22.2	25.0	
Working 25-50% of the time	4.1	7.1	0.0	0.0	12.5	
Working >50% of the time	78.4	48.2	58.7	77.8	62.5	
Other	2.7	0.0	6.5	0.0	0.0	
Co-infection with HCV and/or HBV						0.51
Yes	10.3	13.5	10.9	3.7	19.0	
Previous AIDS	25.0	21.0	25.5	23.1	39.1	0.51
Late initiation of HAART	56.5	56.1	50.0	60.7	56.5	0.90
Reasons for discontinuation of antiretroviral therapy						0.001
End of study period	63.2	45.8	73.1	85.7	75.0	
Loss to follow-up	8.5	29.9	17.3	7.1	12.5	
Change of therapy due to toxicity	21.4	14.0	5.8	0.0	4.2	
Virological failure	4.3	9.3	3.8	7.1	8.3	
Death	1.7	0.0	0.0	0.0	0.0	
AIDS-defining illness not secondary to immune restoration	0.9	0.9	0.0	0.0	0.0	

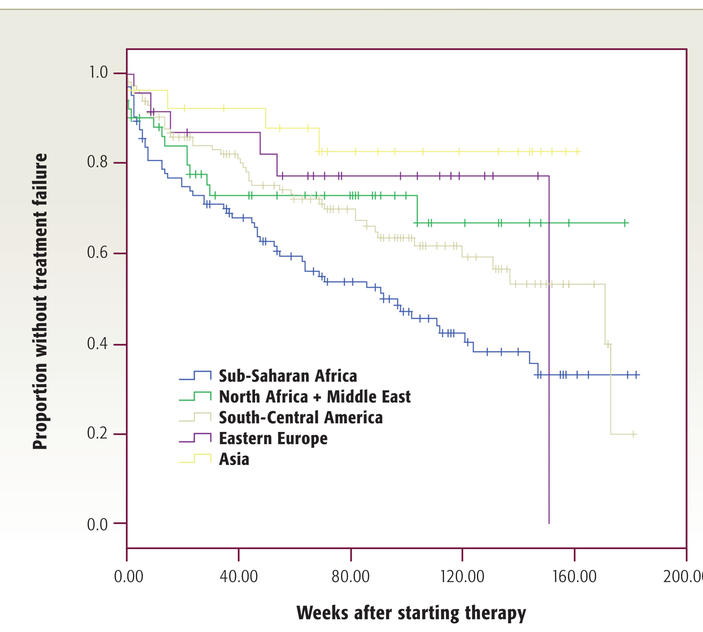
FIGURE 1. Time to treatment failure by cohort group. Curves represent Kaplan-Meier time-to-event analyses.



No at Risk					
Immigrants	387	255	166	72	15
Autochthonous	703	480	325	139	27

Log-rank test: 6.06 (p=0.014)

FIGURE 2. Time to treatment failure for immigrants by region of origin. Curves represent Kaplan-Meier time-to-event analyses.



No at Risk					
Sub-Saharan Africa	107	66	44	21	8
North Africa-Middle East	52	30	22	8	1
South-Central America	117	78	55	25	5
Eastern Europe	24	18	9	4	0
Asia	28	21	13	8	1

Log-rank test: 16.1 (p=0.003)

TABLE 4. Reasons for discontinuation of antiretroviral therapy.

	Immigrants (n=387)	Autochthonous (n=703)	Total
End of study period	245 (63.3)	500 (71.1)	745 (68.3)
Lost to follow-up	69 (17.8)	85 (12.1)	154 (14.1)
Change of therapy due to toxicity	48 (12.4)	68 (9.7)	116 (10.6)
Virological failure	21 (5.4)	42 (6.0)	63 (5.8)
Death	2 (0.5)	8 (1.1)	10 (0.9)
AIDS-defining illness not secondary to immune restoration	2 (0.5)	0 (0.0)	2 (0.2)

χ^2=14.61; p=0.012. Values are expressed as number of patients (%).

TABLE 5. Hazard ratio for failure according to region of origin.

Region of origin (Ref Sub-Saharan Africa)	HR	95% CI	
		Lower	Upper
North Africa + Middle East	0.53	0.30	0.96
Latin America	0.62	0.42	0.93
Eastern Europe	0.43	0.19	1.00
Asia	0.23	0.08	0.65

p=0.005

CONCLUSIONS

- Response to antiretroviral therapy seems to be similar in HIV-infected immigrants living in Spain and HIV-infected autochthonous patients.
- Late initiation of HAART is still very frequent in HIV-infected patients in Spain.
- Specific measures may be required to remove the barriers hindering antiviral efficacy in Sub-Saharan Africans and immigrant women.

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