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Response to HAART According to Sex and Origin (Immigrant vs. Spanish-born) in a Cohort of Naive HIV-infected Patients Starting Antiretroviral Therapy (GESIDA-5808 Study).

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INTRODUCTION

- At present, women make up half of the world's HIV-infected population. The proportion of infected individuals varies depending on the region, although global epidemiologic data indicate that the epidemic increasingly affects women. The impact of HIV/AIDS and HAART varies with sex. Available information on potential differences focuses on the natural history of the disease, access to treatment, the pharmacokinetic or safety profile of antiretroviral drugs, adherence, and response to treatment. Fertility and pregnancy must also be taken into consideration.
- Very little information is available on immigrant women (IW), who may experience additional difficulties such as marginalization, cultural differences, communication problems, or reduced access to health services and specialized gynecologic care.
- The primary objective of the subanalysis by sex of the HIVIS study is to investigate differences in an HIV-infected cohort treated in Spain. This cohort comprises Spanish-born and immigrant patients. Baseline characteristics were examined, as was the response to treatment according to sex. The study also analyzes whether IW in particular are at greater risk.

METHODS

Study population

The present study is a subanalysis of GES-5808, a retrospective observational and longitudinal cohort study performed in 33 Spanish hospitals. The sample comprises both immigrant and Spanish-born HIV-infected antiretroviral-naive patients who started treatment between January 2005 and December 2006. Follow-up was censored in September 2008. In order to rule out selection bias, all patients attending the participating hospitals were included if they had at least one follow-up visit. Demographic and clinical data were entered into a database.

Endpoints

- Primary endpoint: *Time to treatment failure*. Failure was defined as virologic failure, death, opportunistic infection, interruption of HAART, or loss to follow-up.
- Secondary endpoints: *Time to treatment failure expressed as observed data* (losses were censored) and *time to virologic failure* (losses and switches were censored). The proportions and counts of sociodemographic and clinical variables were compared and reported using graphs, tables, and measures of central tendency.
- Late initiation of HAART: Late initiation was defined as the presence of a CD4 lymphocyte count ≤200 cells/μL at initiation of HAART, the presence of AIDS before or at initiation of HAART, or both.

Time was counted from initiation of the treatment regimen until treatment failure. For those patients who did not present a response, time to treatment failure was considered to be "0". The increase in CD4 lymphocyte count and the reduction in viral load were analyzed during the first year of follow-up, carrying forward the last observation in the case of missing data.

Statistical analysis

Time to treatment failure was analyzed using Kaplan-Meier curves and the log-rank test to compare curves. Multivariate analysis was performed using a Cox proportional hazards model to control for confounders. The assumptions of the Cox analysis were verified using graphic methods and Schoenfield residuals. An explanatory modeling strategy was used, including the variables selected in the maximum model and any significant interactions. An elimination strategy was applied (non-automated "backward" method). A colinearity analysis was also performed.

RESULTS

Demographics

- Of the 1,090 patients included in the analysis, 318 (29.2%) were women. Sociodemographic characteristics and HIV stage are shown in Tables 1 and 2. The main differences observed were as follows:
- Origin differed significantly according to sex: the proportion of women was greater in immigrants than in the Spanish-born population.
  - One-third (34.5%) of IW came from Sub-Saharan Africa. The remainder was from Central-South America/Caribbean (25.4%), the Middle East (12.7%), North Africa (8.5%), Western Europe/USA (7.7%), Eastern Europe (6.3%), and other regions (4.9%).
  - Women were younger than men (35 vs. 39 years).
  - The most common risk practice among women was sexual relations (76.1%), followed by IVDU (18.6%); among men, the most common risk practices were homosexual relations (41.1%), followed by heterosexual relations (27.6%).
  - Risk practice varied according to origin, as follows:
    - Women (*P*<.001): sexual relations (IW 79.3% vs. Spanish-born women [SBW] 69.4%), IVDU (IW 5.5% vs. SBW 28.3%), and other/unknown (IW 15.2% vs. SBW 2.3%).
    - Men (*P*<.001): heterosexual relations (IM 42.6% vs. SBM 20.8%), homosexual relations (IM 43.0% vs. SBM 40.2%), IVDU (IM 6.2% vs. SBM 31.9%) and other/unknown (IM 8.2% vs. SBM 7.1%).
  - Women consumed less alcohol (4.1% vs. 13.6%), whereas active drug consumption was equivalent between men and women (4.4% vs. 4.7%).
  - Educational level was lower among women than among men, as was occupational status.
- Overall, 56% of patients initiated HAART late; this was less common among women than among men (49% vs. 59%). Fewer women had a category C disease at the start of treatment (21.2% vs. 29%). Women had a higher CD4 lymphocyte count (217 vs. 190 cells/mm^3) and lower viral load (4.7 vs. 5 log).
- No significant differences were observed in the median CD4 lymphocyte gain during the study period: women 185 vs. men 205 (*P*=.13; 95% CI, –46.4 to 6.2).

Outcomes

- Log_{10} reduction in viral load was slightly higher in men: 2.33 vs. 2.59 (*P*=.006; 95% CI, 0-07-0.44).
- No significant differences were recorded in variations in other laboratory parameters: cholesterol, triglycerides, HDL, LDL, AST, ALT, bilirubin, and GGT.
- Overall, no significant differences were observed in the reasons for treatment failure, although loss to follow-up and treatment switch was more common in women (Table 3). When the proportion of failures was analyzed, taking all the reasons together, treatment failed more often in women: 37.1% vs. 29.4% (*P*=.013).
- Time to treatment failure was significantly shorter in women (median 147 weeks; 95% CI, 122-171) than in men (median 171 weeks; 95% CI, 156-185) (Figure 1).
- Time to treatment failure according to observed data was also significantly shorter for women (*P*=.034) (Figure 2); time to virological failure was not (*P*=.50) (Figure 3).
- A multivariate Cox model was constructed for the primary endpoint to compare the risk of treatment failure between women and men. When the model was controlled for potential confounders, no greater risk of failure was observed in women (Table 4).
- Analysis of the women's cohort revealed the risk of treatment failure to be significantly greater in IW than SBW (Figure 4):
  - Median weeks to failure: IW 124 (95% CI, 64-183) vs. SBW 151 (95% CI, 127-174).
  - The HR of failure for IW vs. SBW was 1.58 (95% CI, 1.10-2.27).
  - Most IW were from Sub-Saharan Africa and Central-South America/Caribbean. At baseline, both groups presented an equivalent immunological and virological status. Late initiation of HAART was similar in both groups (IW 52.8% vs. SBW 45.9%). IVDU and coinfection with hepatotropic viruses was more common among SBW.
  - Excessive loss to follow-up was observed among IW (double that of SBW) (Table 5).
  - Recovery of CD4 lymphocyte count (IW 137 vs. SBW 170; *P*=.023) was significantly poorer in IW, and viral load reduction was lower (IW 2.38 vs. SBW 2.91; *P*<.001).

RESULTS (CONT.)

Table 1. Baseline characteristics

Variable (*P* value for the comparison between sexes)		Sex: Women N	Women %	Men N	Men %
Cohort	Immigrant	145	45.6	242	31.3
(*P*<.001)	Spanish-born	173	54.4	530	68.7
Median (IQR) age, y (*P*<.001)		35 (29-41)		39 (33-44)	
Median (IQR) CD4, cells/μL (*P*=.002)		217 (113-300)		190 (69-280)	
Median (IQR) viral load, copies/mL *P*=.001		4.7 (4.2-5.2)		5.0 (4.5-5.4)	
Median (IQR) time since infection* *P*=.55		15 (2-43)		16 (2-49)	
Risk practice	Heterosexual	242	76.1	213	27.6
(*P*<.001)	Homosexual	0	0	317	41.1
	Other	17	5.3	58	7.5
	IVDU	59	18.6	184	23.8
Alcohol consumption	No	160	92.5	323	75.5
(*P*<.001)	Yes	13	7.5	105	24.5
Active drug consumption	No	153	91.6	361	91
(*P*=.89)	Yes	14	8.4	36	9.0
HBV or HCV infection	HBsAg+	9	2.8	38	4.9
(*P*=.32)	HBsAg/HCV+	5	1.6	8	1.0
	No	200	62.9	446	57.8
	Not available	38	11.9	99	12.8
	HCV+	66	20.8	181	23.4
Educational level	No schooling	41	18.2	41	7.6
(*P*<.001)	Primary	50	22.2	91	16.8
	Other	74	32.9	155	28.5
	Secondary	40	17.8	168	30.9
	Tertiary	20	8.9	88	16.2
Occupational status	Unemployed	110	44.9	137	22.5
(*P*<.001)	Working 25-50%	9	3.7	14	2.3
	Working >75%	112	45.7	425	69.8
	Other	14	5.7	33	5.4
CDC stage	A	194	62.2	389	51.7
(*P*=.006)	B	52	16.7	146	19.4
	C	66	21.2	218	29.0
Late initiation**	No	160	51.0	314	41.0
(*P*=.003)	Yes	154	49.0	452	59.0

* Time since infection: months since the diagnosis of HIV infection until initiation of treatment.
** Late start: initiation of HAART with <200 CD4 lymphocytes, diagnosis of previous AIDS, or AIDS at initiation of HAART.

Table 2. Geographic origin

			Sex: Women (n=315)	Men (n=766)	Total
Region	Sub-Saharan Africa	No.	49	58	107
		%	**15.6%**	**7.6%**	**9.9%**
	North Africa	No.	12	17	29
		%	**3.8%**	**2.2%**	**2.7%**
	Central-South America/Caribbean	No.	36	81	117
		%	**11.4%**	**10.6%**	**10.8%**
	Eastern Europe	No.	9	15	24
		%	**2.9%**	**2.0%**	**2.2%**
	Western Europe/USA	No.	184	565	749
		%	**58.4%**	**73.8%**	**69.3%**
	Asia	No.	6	22	28
		%	**1.9%**	**2.9%**	**2.6%**
	Middle East	No.	18	5	23
		%	**5.7%**	**.7%**	**2.1%**
	Other	No.	1	3	4
		%	**.3%**	**.4%**	**.4%**

χ^2=52.74; *P*<.001

Table 3. Reason for termination of follow-up

Variable	Sex: Women N	Women %	Men N	Men %
Virologic failure	17	5.3	46	6.0
Loss to follow-up	57	17.9	97	12.6
Related death	4	1.3	6	0.8
Opportunistic infection*	0	0.0	2	0.3
Switch of HAART	40	12.6	76	9.8
End of study	200	62.9	545	70.6

χ^2=9.65; *P*=.086. * Opportunistic infection not attributable to immune restoration.

Table 4. Risk of treatment failure by sex (women vs. men)

	B	ET	*P* Value	HR	95% CI for HR: Lower	Upper
Sex	**.096**	**.167**	**.564**	**1.101**	**.794**	**1.527**
Risk practice (Ref. hetero)			.218			
Homosexual	-.295	.185	.110	.744	.518	1.069
IVDU	-.005	.175	.976	.995	.706	1.401
Occupational status (Ref. unemployed)			<.001			
Working 25-50%	.296	.309	.338	1.345	.734	2.464
Working >75%	-.520	.150	.001	.595	.443	.798

The maximum model included the interaction, occupational status, *sex, and the following variables: sex, age, time since infection, origin (immigrant vs. Spanish-born), risk practice, coinfection by HBV/HCV, occupational status, viral load.

Table 5. Reasons for termination of follow-up (women's cohort)

			Women: Immigrants	Women: Spanish-born	Total
Reason for failure	Virologic failure	No.	6	11	17
		%	**4.1%**	**6.4%**	**5.3%**
	Loss to follow-up	No.	37	20	57
		%	**25.5%**	**11.6%**	**17.9%**
	Death related to HIV infection	No.	1	3	4
		%	**.7%**	**1.7%**	**1.3%**
	Switch of therapy	No.	20	20	40
		%	**13.8%**	**11.6%**	**12.6%**
	Censorship	No.	81	119	200
		%	**55.9%**	**68.8%**	**62.9%**
Total		No.	145	173	318
		%	**100,0%**	**100.0%**	**100.0%**

χ^2=12.4; *P*=.015

Figure 1. Time to treatment failure (women vs. men)

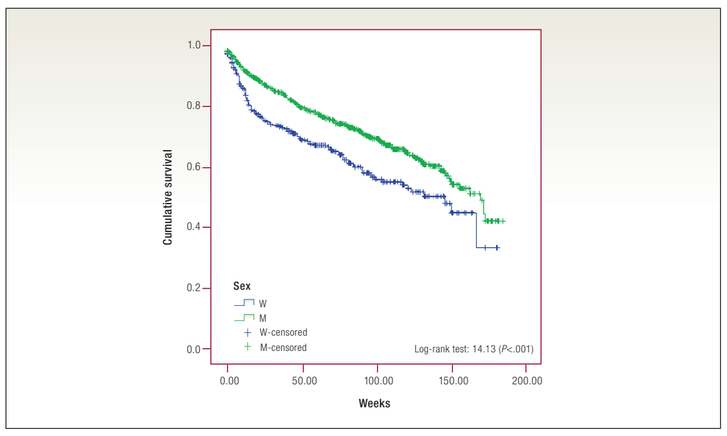


Figure 2. Time to treatment failure according to observed data (women vs. men)

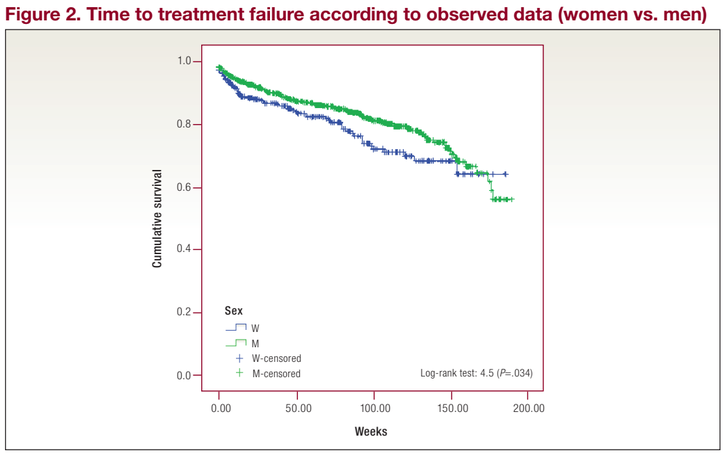


Figure 3. Time to virological failure (women vs. men)

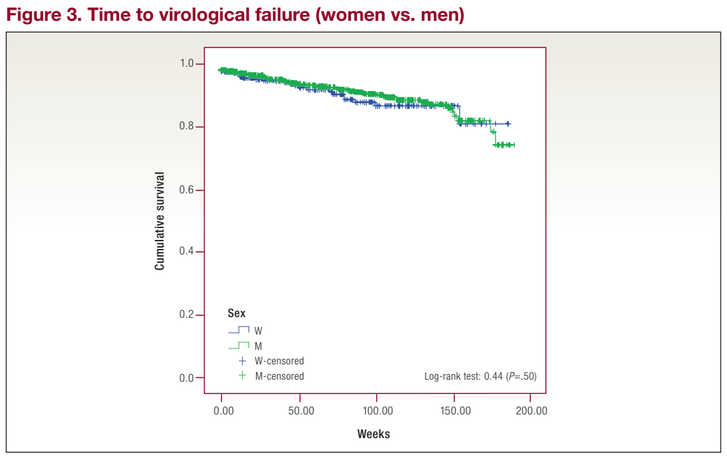
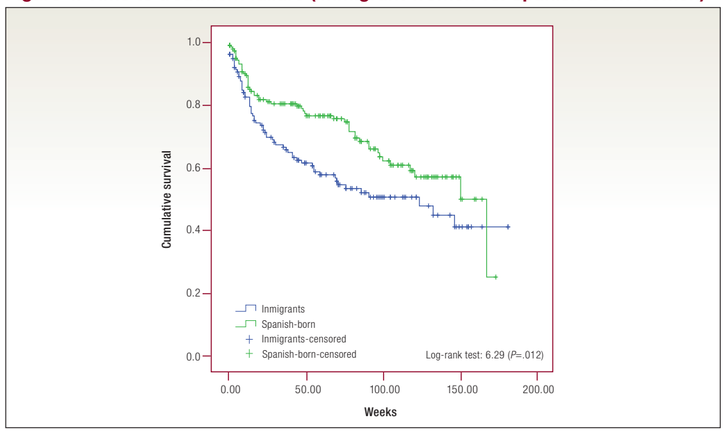


Figure 4. Time to treatment failure (immigrant women vs. Spanish-born women)



CONCLUSIONS

- **The route of acquisition of HIV varied with the origin and sex of the patients: acquisition was mostly sexual in women (almost exclusively among IW) and in men (the proportion of heterosexual acquisition was higher in IM). IVDU was always more common in Spanish-born patients.**
- **The response to HAART was similar between men and women.**
- **Although men started HAART later and experienced more opportunistic diseases, a larger proportion of losses to follow-up and switches in therapy was observed in women.**
- **This situation was worse in IW: the proportion of dropouts was double that of SBW, with a shorter time to treatment failure, a lower CD4 gain, and a lower viral load reduction.**
- **Our results show that the factors preventing patients from obtaining the maximum benefit from HAART differ according to sex. Men would benefit more from an early diagnosis to promote earlier initiation of HAART. Women—especially IW—would benefit from additional measures allowing them to continue medical follow-up after initiation.**

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