

Response to Combined Antiretroviral Therapy According to Gender and Origin in a Cohort of Naïve HIV-Infected Patients: GESIDA-5808 Study

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Background: We analyzed differences in response to combined antiretroviral therapy (cART) according to sex and geographic origin in a retrospective comparative study of Spanish-born and immigrant patients initiating cART. **Methods:** The primary endpoint was time to treatment failure (TTF), defined as virological failure, death, opportunistic infection, interruption of cART, or loss to follow-up. Late diagnosis was defined as a CD4+ cell count ≤ 200 cells/mm³ and/or AIDS at initiation of cART. Survival was analyzed using Kaplan-Meier analysis and Cox regression. **Results:** We followed 1,090 patients, of whom 318 were women (45.6% immigrant women [IW]). At initiation of treatment, women had a higher CD4+ count than men (217 vs 190 cells/mm³), a lower viral load (4.7 vs 5 log), and fewer were late starters (49% vs 59%). The adjusted risk of TTF between women and men was not significantly different (hazard ratio [HR], 1.10; 95% CI, 0.79-1.53). TTF was shorter among IW than Spanish-born women (124 weeks [95% CI, 64-183] vs 151 [95% CI, 127-174]) and loss to follow-up was double that of Spanish-born women (25.5% vs 11.6%). **Conclusions:** Although response to cART was similar for both sexes, men started treatment later. IW were more frequently lost to follow-up and switched treatment. Measures to improve medical follow-up after initiation of cART should be promoted among this minority group. **Key words:** cART, HIV infection, immigrants, naïve, women

Both the impact of the HIV/AIDS epidemic and the effect of combined antiretroviral therapy (cART) can vary with sex, although study results are contradictory: some show better outcomes for women in terms of clinical, virological, and immunological response,¹⁻⁴ whereas others show no differences.⁵⁻⁷ 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.⁸ The proportion of infected individuals varies depending on the region, although global epidemiologic data indicate that the HIV epidemic increasingly

affects women.⁹ At present, women make up half of the world's HIV-infected population.⁹ Additionally, the choice of antiretroviral regimen may be conditioned by pregnancy or the desire to become pregnant.

HIV-infected women in Western Europe make up a diverse population. Many are immigrants^{10,11} who face significant barriers to HIV care.¹²

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HIV Clin Trials 2012;13(3):131-141
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www.thomasland.com

doi: 10.1310/hct1303-131

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Furthermore, immigrant women (IW) may be at increased risk of late presentation and delayed access to care.^{10,11} Approximately one-third of immigrants to Europe are from Sub-Saharan Africa,¹³ and 62.3% are women. These patients are likely to face specific cultural barriers to contraception and HIV care.^{12,14}

In Spain, half of the women undergoing HIV testing are immigrants, and up to 25% of AIDS cases among women are diagnosed in IW from Sub-Saharan Africa and Latin America.^{15,16} IW are at higher risk for HIV infection than nonimmigrant women.^{10,11} Very little information is available on IW, who may experience additional difficulties for HIV care, such as marginalization, cultural differences, communication problems, or reduced access to health services and specialized gynecologic care.

The primary objective of this study was to investigate differences in treatment response according to sex and geographic origin in an HIV-infected cohort comprising Spanish-born and immigrant patients initiating antiretroviral therapy. The study also analyzed whether IW in particular are at greater risk of treatment failure.

METHODS

The present study is a subanalysis of GES-5808, a retrospective observational and longitudinal cohort study performed in 33 Spanish hospitals.¹⁷ The sample comprises both immigrant and Spanish-born HIV-infected antiretroviral-naïve patients who started treatment between January 2005 and December 2006. Follow-up was censored in September 2008. 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 an ad hoc database.

Our primary objective was to compare the time to treatment failure (TTF) between men and women who started cART to determine whether sex is associated with a different response to treatment. The analysis was performed on an intention-to-treat basis, and failure was defined as any of the following: (a) an increase in HIV-1 RNA levels above the limit of quantitation (LOQ) in 2 consecutive determinations during follow-up after an initial response (only one determination was required if the physician changed therapy after the

first viral load above the LOQ, or when this determination corresponded to the last visit available); (b) not reaching an HIV-1 RNA level <50 copies/mL during the first 24 weeks; (c) no decrease in HIV-1 RNA level of $2 \log_{10}$ at weeks 12-16, if no other visit was available; (d) loss to follow-up; (e) new HIV-related opportunistic infection not due to immune reconstitution; (f) death; and (g) switch or discontinuation of therapy. TTF was counted from baseline to failure and was considered as "0" for those patients with no virological response (HIV-1 RNA levels never reached <50 copies/mL); when 2 viral loads above the LOQ were available, TTF was considered the time to the first viral load.

Secondary endpoints were TTF expressed as observed data (TTF-OD; same endpoints as TTF but with missing patients censored) and time to virological failure (TVF; same endpoints as TTF but with missing patients and treatment discontinuations not due to virological failure censored). We also compared TTF between IW and Spanish-born women (SBW) and described the reasons for termination of follow-up.

Decrease in viral load and CD4+ cell recovery were calculated as the change after the first year of follow-up compared with baseline, carrying forward the last observation. Late initiation of cART was defined as the presence of a CD4+ lymphocyte count below 200 cells/mm³ at initiation, the presence of AIDS before or at initiation of cART, or both.

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. The requirements of the Cox analysis were checked using graphic methods and Schoenfeld residuals. Cox regression models included the following as covariates: sex, age, time since HIV diagnosis, origin (IW vs SBW), risk practice, coinfection by HBV/HCV, occupational status, viral load, educational level, and the interaction between occupational status and sex. Variables were included in the model according to their significance in the univariate analysis and to the importance given to each variable, regardless of whether or not it was clearly significant in this analysis. The variable "sex" (women vs men) was forced into a nonautomatic backward elimination strategy aimed at providing a valid estimate in such a way that the variable with the highest *P* value that was not a

confounder was excluded at every step. Variables were considered to be confounders if the estimate of the coefficient of the variable “sex” changed by more than 10% when that variable was removed from the maximal model. SPSS version 15.0 (SPSS Inc, Chicago, Illinois, USA) was used for the statistical analysis.

RESULTS

We identified 1,090 treatment-naïve patients followed for 1,386.3 person-years; 318 (29.2%) were women. Sociodemographic characteristics and HIV stage are shown in **Table 1**. Origin differed significantly according to sex, as the proportion of women was greater in immigrants than in the Spanish-born population (37.5% vs 24.6%; $P < .001$). One-third (34.5%) of IW came from Sub-Saharan Africa; the remainder were 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 intravenous drug use (IVDU; 18.6%), while the most common risk practices among men were having sex with other men (41.1%), followed by heterosexual relations (27.6%). It is noteworthy that risk practices varied significantly ($P < .001$) according to origin, for both women and men. Infection through sexual relations was more frequent in IW than in SBW (79.3% vs 69.4%), whereas IVDU was documented more often in SBW (28.3% vs 5.5%). Heterosexual relations was a more common risk practice in immigrant men (IM) than in Spanish-born men (SBM) (42.6% vs 20.8%), in contrast with IVDU (6.2% for IM vs 31.9% SBM).

Overall, 56% of patients initiated cART late; this was less common among women than among men (49% vs 59%). At initiation of treatment, women had a higher CD4+ lymphocyte count (217 vs 190 cells/mm³) and lower viral load (4.7 vs 5 log), and fewer women had a category C disease (21.2% vs 29%). No significant differences were observed in the median CD4+ lymphocyte gain during the study period (not adjusted for other variables) between women or men (185 vs 205 cells/mm³, difference -20 cells/mm³; 95% CI, -46.4 to 6.2 cells/mm³), while reduction in plasma viral load was slightly higher in men (2.33 vs 2.59

log₁₀ decrease, difference 0.26 log₁₀; 95% CI, 0.07-0.44 log₁₀). Similarly, no significant differences in variations in other laboratory parameters (cholesterol, triglycerides, high-density lipoprotein [HDL], low-density lipoprotein [LDL], aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, and gamma-glutamyl transferase [GGT]) were observed between men and women during the study period.

When we analyzed the reasons for termination of follow-up, we did not find significant differences between women and men, although losses to follow-up and treatment switches seemed more common in women (**Table 2**). In fact, when failure due to any cause was analyzed (excluding termination of study follow-up because of end of study), treatment failed more often in women (37.1% vs 29.4%; $P = .013$). In the univariate analysis, TTF was significantly shorter in women (median, 147 weeks; 95% CI, 122-171 weeks) than in men (median, 171 weeks; 95% CI, 156-185 weeks) (log-rank $< .001$) (**Figure 1**). TTF-OD was also significantly shorter for women (log-rank $P = .034$) (**Figure 2A**). However, TVF was no different between women and men (log-rank $P = .50$) (**Figure 2B**). After adjustment for potential confounders, Cox regression models showed that TTF was no different for women or men (hazard ratio [HR], 1.101; 95% CI, 0.79-1.53) (**Table 3**).

When we analyzed the women's cohort (145 IW and 173 SBW), we found no baseline differences for immunological and virological status or proportion of late initiation of cART (52.8% in IW vs 45.9% in SBW), whereas IVDU and coinfection with hepatotropic viruses were more common among SBW. Reasons for termination of follow-up were not homogeneously distributed between IW and SBW: excessive loss to follow-up was observed among IW (double that of SBW), as was an increase in the number of treatment switches (**Table 4**). Recovery of CD4+ lymphocyte count was significantly poorer in IW (137 vs 170 CD4+ cells/mm³; $P = .023$), as was reduction in viral load (2.38 vs 2.91 log₁₀; $P < .001$). TTF was significantly shorter in IW (median, 124 weeks; 95% CI, 64-183 weeks) than in SBW (median, 151 weeks; 95% CI, 127-174 weeks) (log-rank $P = .012$) (**Figure 3**). The HR of failure for IW versus SBW was 1.58 (95% CI, 1.10-2.27).

When we analyzed the men's cohort, there were no significant differences in TTF between

Table 1. Baseline characteristics

Variable	Women (n=318)		Men (n=772)		P value for the comparison between sexes
	N	%	N	%	
Cohort					.001
Immigrant	145	45.6	242	31.3	
Spanish-born	173	54.4	530	68.7	
Median (IQR) in years	35 (29-41)		39 (33-44)		.001
Median (IQR) CD4+ cells/mm ³	217 (113-300)		190 (69-280)		.002
Median (IQR) viral load, copies/mL	4.7 (4.2-5.2)		5.0 (4.5-5.4)		.001
Median (IQR) time in months since HIV diagnosis ^a	15 (2-43)		16 (2-49)		.55
Risk practice					.001
Heterosexual relations	242	76.1	213	27.6	
Relations between MSM	0	0	317	41.1	
Other	17	5.3	58	7.5	
IVDU	59	18.6	184	23.8	
Alcohol consumption					.001
No	160	92.5	323	75.5	
Yes	13	7.5	105	24.5	
Active drug consumption					.89
No	153	91.6	361	91	
Yes	14	8.4	36	9.0	
Chronic HBV or HCV infection					.32
HBVsAg+	9	2.8	38	4.9	
HBVsAg+/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					.001
No schooling	41	18.2	41	7.6	
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					.001
Unemployed	110	44.9	137	22.5	
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					.006
A	194	62.2	389	51.7	
B	52	16.7	146	19.4	
C	66	21.2	218	29.0	
Late initiation ^b					.003
No	160	51.0	314	41.0	
Yes	154	49.0	452	59.0	

Note: CDC = Centers for Disease Control and Prevention; HBV = hepatitis B virus; HCV = hepatitis C virus; IQR = interquartile range; IVDU = intravenous drug use; MSM = men who have sex with men.

^aMonths since the diagnosis of HIV infection until initiation of treatment.

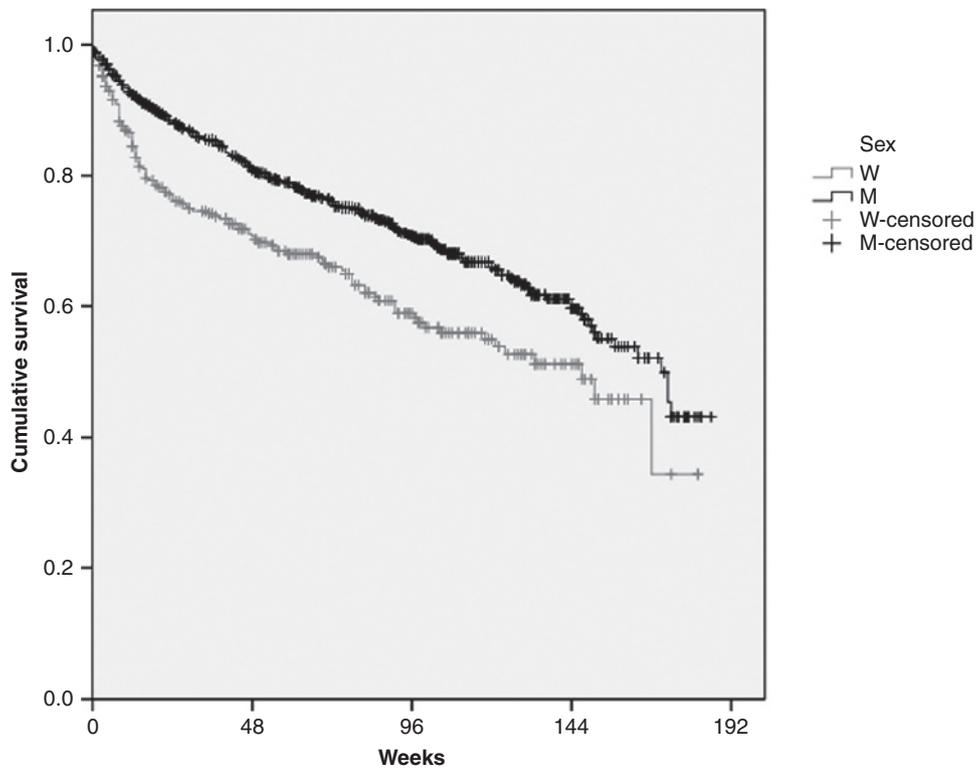
^bLate start: initiation of combination antiretroviral therapy (cART) with <200 CD4+ lymphocytes, diagnosis of previous AIDS, or AIDS at initiation of cART.

Table 2. Reasons for termination of follow-up

	Women		Men	
	N	%	N	%
Virological 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 ^a	0	0.0	2	0.3
Switch of cART	40	12.6	76	9.8
End of study	200	62.9	545	70.6

Note: $\chi^2=9.65$; $P = .086$. cART = combination antiretroviral therapy.

^aOpportunistic infection not attributable to immune restoration.



No. at risk	Week 0	Week 48	Week 96	Week 144	Week 192
Women	318	171	85	26	0
Men	772	513	296	82	0

Log-rank test: 14.13 ($P < .001$)

Figure 1. Time to treatment failure (women vs men). W = women; M = men.

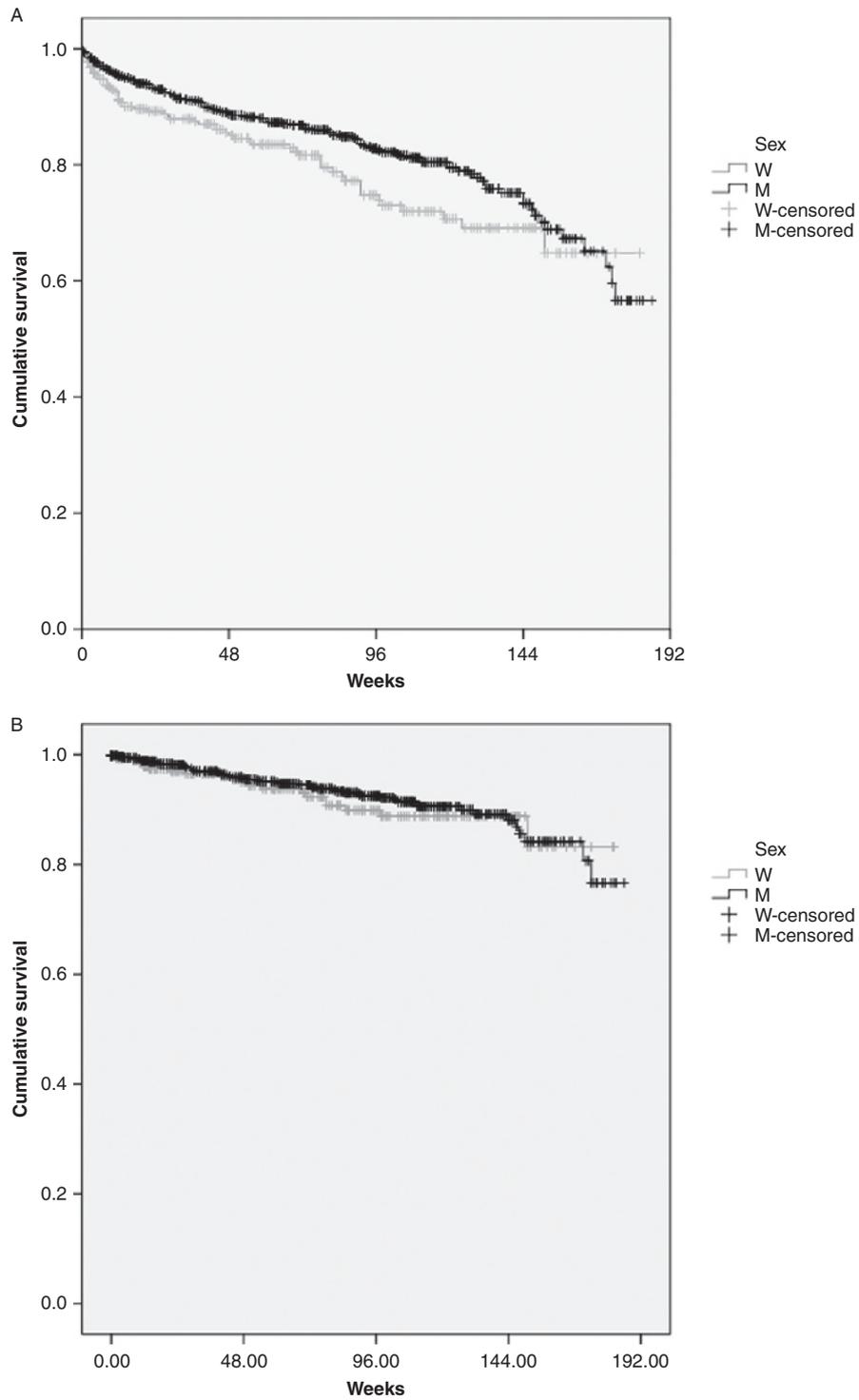


Figure 2. Time to treatment failure according to observed data (A) and time to virological failure (B) (women vs men). For (A), log-rank test: 4.49 ($P = .034$). For (B), log-rank test: 0.44 ($P = .50$). W = women; M = men.

Table 3. Risk of treatment failure according to sex (women vs men)

	B	Standard error	P value	HR	95% CI for HR	
					Lower	Upper
Sex	.096	.167	.564	1.101	.794	1.527
Risk practice (ref. heterosexual relations)			.218			
Relations between MSM	-.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

Note: The maximum model included the interaction Occupational Status x Sex and the following variables: sex, age, time since infection, origin (immigrant vs Spanish-born), risk practice, coinfection by HBV/HCV, occupational status, educational level, and viral load. B = coefficient of regression; CI = confidence interval; HR = hazard ratio; IVDU = intravenous drug use; MSM = men who have sex with men.

Table 4. Reasons for termination of follow-up

Reason for failure	Women's cohort		Total
	Immigrants (n=145)	Spanish-born (n=173)	
Virological failure	6 (4.1%)	11 (6.4%)	17 (5.3%)
Loss to follow-up	37 (25.5%)	20 (11.6%)	57 (17.9%)
Death related to HIV infection	1 (0.7%)	3 (1.7%)	4 (1.3%)
Switch of therapy	20 (13.8%)	20 (11.6%)	40 (12.6%)
End of study	81 (55.9%)	119 (68.8%)	200 (62.9%)

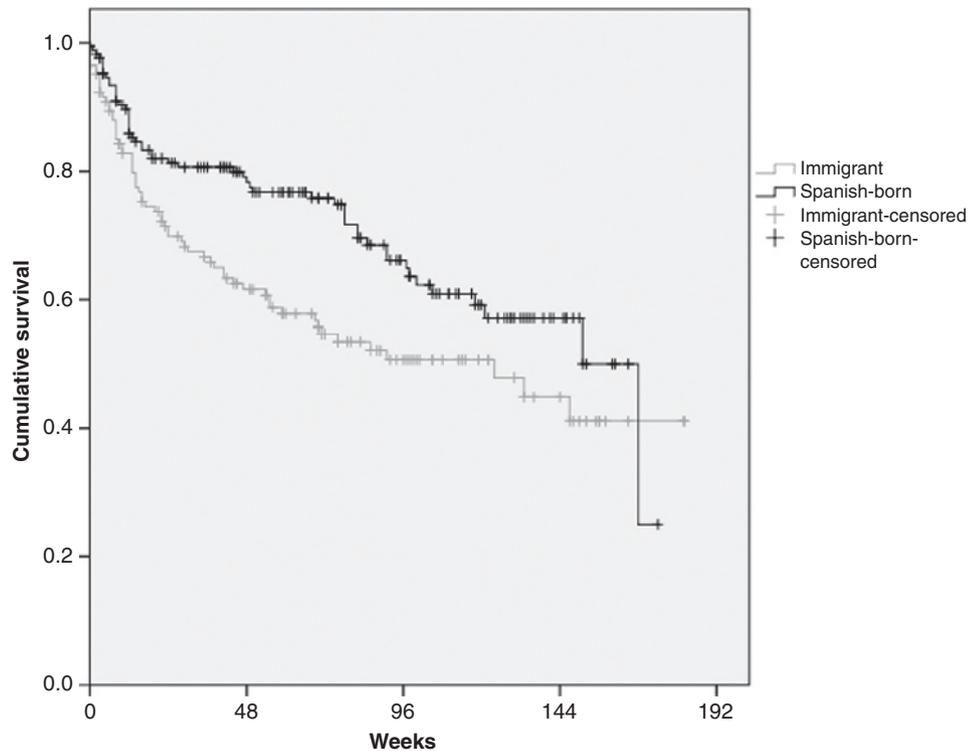
Note: $\chi^2 = 12.4$; $P = .015$.

immigrant and Spanish-born men (data not shown).

DISCUSSION

Response to cART in terms of TTF was similar in both sexes after adjustment for potential confounding factors. Men were older and more frequently started therapy late, while loss to follow-up and treatment switches were more common in women. Indeed, for IW, this scenario was even worse, as the proportion of dropouts doubled that of SBW, shortening TTF and leading to a poorer immunovirological response.

Data on whether immunovirological or clinical outcomes after cART differ significantly between women and men are not consistent. In a systematic review published in 2007, Nicastrì et al⁶ found little evidence of sex differences in response to antiretroviral therapy. However, the authors highlighted the limited follow-up in a number of studies (6-12 months) and the fact that most of these studies were insufficiently powered to detect sex differences.⁶ Similarly, subsequent findings have not demonstrated differences in immunovirological response, progression to AIDS, or death in mostly pretreated and naïve patients.^{3,18} More recent data have not clarified this issue, thus



No. at risk	Week 0	Week 48	Week 96	Week 144	Week 192
Immigrant	145	70	33	13	0
Spanish-born	173	101	52	12	0

Log-rank test: 6.3 ($P = .012$)

Figure 3. Time to treatment failure (immigrant women vs Spanish-born women).

perpetuating the ongoing debate. In a prospective observational study (66% women) carried out in Tanzania, poorer treatment outcomes were documented for men¹⁹; however, this finding cannot be fully explained by nonadherence and advanced baseline immunodeficiency. In the sex substudy of the CASTLE clinical trial, the intention-to-treat analysis showed lower virological response rates for women in the boosted atazanavir and lopinavir arms.²⁰ Although no major clinical trials explore response to cART according to sex in naïve patients, one recent trial (the GRACE study) compares response to cART according to sex in experienced patients.²¹ In the GRACE study, the primary objective was to evaluate sex-based differences

in virologic response rate (HIV RNA <50 copies/mL; intention-to-treat population) at 48 weeks. The primary analysis was established in terms of noninferiority assuming a maximum allowable absolute difference for women versus men of $\leq 15\%$. The authors could not demonstrate statistically significant differences in virological response rates according to gender, but the 95% confidence interval went beyond the established limit for noninferiority (absolute difference, -9.6% ; 95% CI, -19.9 to 0.7 ; $P = .067$). However, when patients who withdrew for reasons other than virological failure were censored, response rates were similar for women and men (absolute difference, -3.9% ; 95% CI, -13.9 to 6 ; $P = .44$). The authors attributed

these differences in virological response to a higher discontinuation rate among women.

Our multivariate analysis showed no differences by sex in risk for treatment failure (HR for women vs men, 1.101; 95% CI, 0.794-1.527). Nevertheless, Kaplan-Meier plots disclosed a significantly shorter TTF and TTF-OD for women, although this was not the case for TVF, where missing patients and treatment discontinuations not due to virological failure (both more frequent among women) were censored. This increased rate of discontinuation in women is well established in previous studies.^{6,8,20,21} The reported reasons for treatment interruption included pregnancy,²⁰ suboptimal adherence,²⁰ differences in tolerability,²¹ greater toxicity,⁷ drug interactions,^{22,23} body weight or self-perceived body changes,^{24,25} and pharmacokinetic issues.²⁶⁻²⁸

Some of the factors mentioned above mainly affect IW. We found excessive loss to follow-up in IW (double that of SBW) and more frequent treatment switches (although these may not be clinically significant), even when there were no baseline differences in immunological and virological status or number of patients starting therapy late. Moreover, IVDU and coinfection with hepatotropic viruses were more common among SBW. Similarly, the results from the Swiss cohort study²⁹ show that Sub-Saharan African migrants (65% of whom were women) had double the risk of viral failure on cART, worse adherence, and more frequent loss to follow-up than autochthonous patients. Other reasons for poor adherence and follow-up include the high number of sex workers among HIV-infected IW in Spain,^{30,31} greater difficulty in attending scheduled check-ups owing to work responsibilities, a low educational level,³² the stigma associated with HIV infection (which often affects women more intensely), cultural and language barriers, and poorer socioeconomic status, which in turn makes access to health services and treatment adherence more difficult.³³⁻³⁵

Losses to follow-up were not necessarily those patients who were no longer attended by the national health service, given that they could restart medical care at another hospital. However hospital databases are not connected, with the results that patients moving from one hospital to another could be considered as lost to follow-up. In Spain, access to treatment for HIV infection is

universal and free through the national health service. Irrespective of their financial situation, all patients with a medical card receive health care from the national health system or through collaboration with different nongovernmental organizations. Thus, characteristics of the health system would not seem to affect the differential dropout rate observed between IW and SBW.

The proportion of women with HIV infection is increasing, and there is a pressing need for sex-specific information on antiretroviral therapy outcomes. It would be desirable to implement clinical trials in which the main comparison is of outcome of cART by sex, in order to accurately assess the efficacy of antiretroviral therapy in men and women. This approach would also illustrate which factors are related to adherence and follow-up and how these could affect both sexes. In the case of migrants, and specifically IW, improving information about available health services, production of culturally adapted health information materials, and involvement of intercultural mediators and translators to improve patient-physician communication could be of great value. Our results show that the factors preventing patients from obtaining the maximum benefit from cART differ according to sex. Men would benefit more from an early diagnosis to promote earlier initiation of cART. IW would benefit from additional measures allowing them to continue medical follow-up after initiation.

ACKNOWLEDGMENTS

This work was supported by a grant from Bristol-Myers Squibb to the Fundación SEIMC-GESIDA. The authors declare no conflicts of interest.

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