Late Initiation of HAART Among HIV-Infected Patients in Spain Is Frequent and Related to a Higher Rate of Virological Failure but not to Immigrant Status

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Purpose: To determine whether immigrant status is associated with late initiation of highly active antiretroviral treatment (HAART) and/or poor response to antiretrovirals. **Methods:** GESIDA 5808 is a multicenter, retrospective cohort study (inclusion period January 2005 through December 2006) of treatment-naïve patients initiating HAART that compares HIV-infected patients who are immigrants with Spanish-born patients. A late starter (LS) was defined as any patient starting HAART with a CD4+ lymphocyte count <200 cells/μL and/or diagnosis of an AIDS-defining illness before or at the start of therapy. The primary endpoint was time to treatment failure (TTF), defined as virological failure (VF), death, opportunistic infection, treatment discontinuation/switch (D/S), or missing patient. Secondary endpoints were time to treatment failure as observed data (TTO; censoring missing patients) and time to virological failure (TVF; censoring missing patients and D/S not due to VF). **Results:** LS accounted for 56% of the patients. Lower educational and socioeconomic level and intravenous drug use (IVDU) were associated with categorization as LS, but immigrant status was not. Cox regression analysis (hazard ratio [HR]; 95% CI) between LS and non-LS patients showed no differences in TTF (0.97; 0.78–1.20) or TTO (1.18; 0.88–1.58), although it did reveal a difference in TVF (1.97; 1.18–3.29). CD4+ lymphocyte recovery was equivalent for both LS and non-LS patients (159 vs 173). **Conclusions:** In our cohort, immigrant status was not shown to be related to late initiation of HAART. Although LS patients did not have a longer TTF for any reason, TVF was significantly shorter. Despite universal free access to HAART in Spain, measures to ensure early diagnosis and treatment of HIV infection are necessary.
Key words: *HAART, HIV infection, immigrants, late initiation, naive*

Despite advances in the control of HIV infection in industrialized countries during the last 20 years and improved access to diagnosis by means of easy-to-perform, highly sensitive, and often free tests, 30% to 40% of HIV-infected individuals are diagnosed during late phases of the disease.[1–5] Analysis of the factors associated with late diagnosis of HIV has shown that it increases with age and is more common in men, in individuals infected as a result of heterosexual relations, and, in some countries, in immigrants.[2,4–7] Among immigrant populations,

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lack of knowledge of the local language, social exclusion, and cultural and socioeconomic factors can act as barriers to early diagnosis and prompt medical attention.[8,9] Other factors that can affect the response to therapy among immigrants include increased rate of adverse events after initiating antiretroviral therapy,[10] higher rate of treatment discontinuation,[11,12] cultural reluctance to undergoing blood testing,[13] differences in drug metabolism among races,[14] or a differential pattern in resistance mutations of HIV-1 non-B subtypes.[15]

Diagnostic delay is one reason most patients initiate highly active antiretroviral therapy (HAART) with CD4+ lymphocyte counts below recommended levels.[16,17] Late initiation of HAART can have deleterious effects, such as incomplete immunovirological response, higher rates of virological failure, disease progression, concomitant opportunistic infections, and potential drug interactions.[4,18–20] In addition, the higher incidence of AIDS-defining illnesses, hospitalizations, and HAART-related adverse events in HIV-infected patients increases health costs for the community.[2,21]

Our objective was to compare the time to treatment failure between patients who started HAART late and those who started treatment on time in order to determine whether late initiation is associated with a different response to treatment. Furthermore, we hoped to determine whether status as an immigrant is associated with late initiation of HAART and/or a poorer response to antiretroviral therapy compared with the Spanish-born population. In Spain, there are no specific guidelines for HIV testing among immigrants, although immigrants probably undergo testing more frequently than Spanish-born patients because some come from regions where HIV is highly prevalent.

METHODS

We performed a subanalysis of a historical cohort study of HIV-infected individuals attending HIV clinics of 33 Spanish hospitals.[22] Patients were antiretroviral-naïve adults who started HAART between January 2005 and December 2006 and who had at least one follow-up visit any time during the first 6 months of therapy.

The primary objective was to compare the time to treatment failure between patients who started HAART late and those who began on time to determine whether late initiation is associated with a different response to treatment. The 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, or switch/discontinuation of therapy because of toxicity or intolerance. Secondary endpoints were 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). CD4+ cell gain and viral load decrease were calculated as the change during the first year of follow-up from baseline carrying forward the last observation. Late starters were considered to have a CD4+ lymphocyte count <200 cells/μL at the start of therapy, a prior or concomitant diagnosis of AIDS at the start of therapy, or both. We also studied whether immigrant status was associated with late initiation of therapy. Univariate analysis and multivariate analysis were performed to evaluate this association.

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 by graphic methods and Schoenfeld residuals. Cox regression models included the following as covariates: late starter (yes vs no), age, weeks of known HIV infection before starting HAART, gender, incidence of risk behavior for HIV infection, co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), occupational status, and viral load. The adjusted odds ratio between immigrant status and late initiation of therapy was calculated by means of a logistic regression model. SPSS version 15.0 (SPSS Inc, Chicago, Illinois, USA) was used for the statistical analysis.

RESULTS

We identified 1,080 treatment-naïve patients followed for 1,499.31 person years; 606 (56.1%) were late starters and 474 (43.9%) were not (**Table 1**). HAART regimens were similar in both groups. The proportion of patients taking boosted protease inhibitors (34% vs 30.6%; $P = .25$) or non-nucleoside reverse transcriptase inhibitors (66% vs 69.4%; $P = 25$) was equivalent between late and non-late starters, respectively, as was the

Table 1. Baseline characteristics: late starters versus non-late starters

	Non-late starters (n = 474)	Late starters (n = 606)	*P* value
Median age, years (IQR)	36 (31–42)	39 (33–44)	<.001
Male gender, %	66.2	75.6	.003
Immigrants, %	35.2	35.6	.88
Median time since diagnosis of HIV infection, weeks (IQR)	20 (3–36)	12 (1–47)	.019
Risk behavior, %			.01
Heterosexual relations	42.8	32.7	
MSM	32.9	30.4	
Injection drug users	17.5	25.9	
Other	6.8	6.6	
Current drug user, %	4.2	5.0	.84
Active alcohol consumption, %	10.3	11.2	.89
Educational level, %			.017 for trend
No school	10.5	11.0	
Primary	16.5	20.0	
Other	25.8	33.1	
Secondary	30.3	24.2	
University	16.8	11.7	
Occupation, %			.030 for trend
Unemployed	24.7	32.7	
Working 25% to 50% of the time	2.7	2.5	
Working more than >50% of the time	68.1	58.4	
Other	4.5	6.4	
Co-infection with HCV and/or HBV, %			.23
HCV	20.5	24.6	
HBV	4.9	3.6	
HCV+HBV	0.8	1.5	
Not co-infected	63.9	55.8	
Not available	9.9	14.5	
Median CD4+ T-cell count, cells/mm^3 (IQR)	284 (244–342)	91 (36–166)	<.001
Median HIV-1 RNA, $\log_{10}$ copies/mL (IQR)	4.73 (4.2–5.2)	5.01 (4.6–5.6)	<.001

Note: IQR = interquartile range; MSM = men having sex with men; HCV = hepatitis C virus; HBV = hepatitis B virus.

proportion of patients taking abacavir plus lamivudine (ABC+3TC; 11.6 vs 10.8%; *P* = .68) or tenofovir plus emtricitabine/lamivudine (TDF+FTC/3TC; 47.1% vs 45.1%; *P* = .50).

Being a late starter was associated with older age, male gender, less time since diagnosis of HIV infection, lower educational and socioeconomic level, higher incidence of risk behavior, and poorer occupational status. There was no significant association between immigrant status and late initiation of HAART (odds ratio [OR] 1.02; 95% confidence interval [CI], 0.79–1.31). After adjustment for potential confounders (weeks of known HIV infection before starting HAART, incidence of risk behavior for HIV infection, occupational status, and educational level), adjusted OR remains non-significant (OR 1.24; 95% CI, 0.82–1.87). There were no differences in the proportion of late starters within immigrant populations according to geographical origin (sub-Saharan Africa, North

Africa/Middle East, South and Central America, Eastern Europe, and Asia).

The average CD4+ lymphocyte gain (not adjusted for other variables) during the study period was equivalent in both late starters and non-late starters (202 vs 199 cells/mm^3; difference, 3 cells/mm^3; 95% CI, −20.9 to 28.2 cells/mm^3), while the average decrease in HIV-1 $\log_{10}$ viral load was slightly higher in late starters (−3.07 vs −2.80 copies/mL; difference, −0.27 copies/mL; 95% CI, −0.35 to −0.02 copies/mL).

The proportion of virological failure, death, and AIDS-defining illness not due to immune restoration was higher among late starters (**Table 2**). In the univariate analysis, time to treatment failure was similar in both groups (median time 157 weeks for late starters vs 171 weeks for non-late starters; log-rank P = .77), as was the time to treatment failure expressed as observed data (log-rank P = .27). However, time to virological failure was significantly shorter for late starters than for non-late starters (log-rank P = .008) (**Figures 1–3**). The results of Cox regression models, after adjusting for potential confounders, showed the time to treatment failure was not different for late starters and non-late starters (hazard ratio [HR] 0.97; 95% CI, 0.78–1.20). Similarly, there were no differences in time to treatment failure expressed as observed data (HR 1.18; 95% CI, 0.88–1.58). Nevertheless, time to virological failure remained significantly shorter for late starters than for non-late starters (HR 1.97; 95% CI, 1.18–3.29).

DISCUSSION

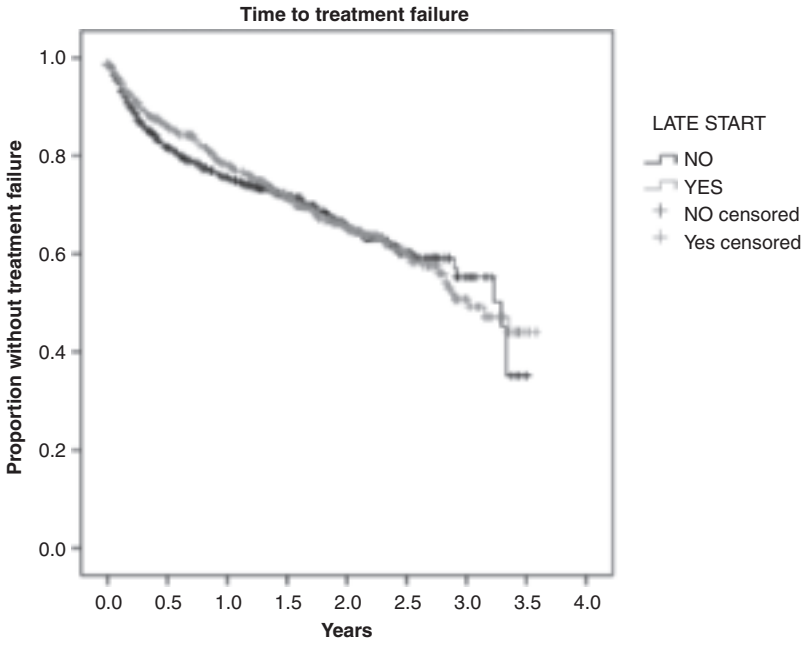
Current guidelines in developed countries recommend starting antiretroviral therapy in patients with <350 CD4+ lymphocytes/μL. Therapy is also recommended in patients with higher T lymphocyte counts and comorbid conditions.[23,24] However, patients frequently (40% to 50%) start therapy with <200 CD4+ lymphocytes/μL.[16,18,25] Consistent with these findings, we observed a high proportion of late starters (56.1%) in non-selected populations comprising all patients attended at the participating hospitals during the study period. Furthermore, late initiation of HAART is frequently a consequence of late diagnosis. In Europe, late diagnosis is currently defined when HIV infection diagnosis is made with <350 CD4+ lymphocytes/μL or symptomatic disease. This definition identifies a higher incidence of late starters than included in this study.[26]

In our cohort, immigrant status was not found to be related to late initiation of HAART, whereas older age, male gender, lower educational and socioeconomic level, higher incidence of risk behavior, and poorer occupational status were. These factors have also been documented in association with late diagnosis or late initiation of therapy in other studies.[2–5] Such information is of great value when identifying high-risk populations in which specific measures aimed at education, prevention, and early diagnosis can be implemented. The lack of association between immigrant status and late initiation of HAART in our study is likely explained by the fact that most HIV-infected immigrants in Spain are from Latin America and, therefore, speak Spanish and are culturally closer to the local population than other immigrant groups.[5] In addition, once the immigrant is legally registered in Spain, access to the health system is much easier. By contrast, in the rest of Europe, HIV infection among immigrants is observed mainly among sub-Saharan Africans.[6,7]

Table 2. Reasons for termination of follow-up

	Non-late starters (n = 474)	Late starters (n = 606)
End of study period	326 (68.8)	410 (67.7)
Loss to follow-up	75 (15.8)	78 (12.9)
Change of therapy due to toxicity	53 (11.2)	63 (10.4)
Virological failure	18 (3.8)	45 (7.4)
Death	2 (0.4)	8 (1.3)
AIDS-defining illness not secondary to immune restoration	0 (0.0)	2 (0.3)

Note: Values are expressed as number of patients (%). χ^2 = 11.72; P = .039.



No. at risk	0	0.5	1	1.5	2.0	2.5	3.0	3.5	4.0
Late starters	606	459	378	296	195	103	34	3	0
Non-late starters	474	340	280	209	134	64	22	3	0

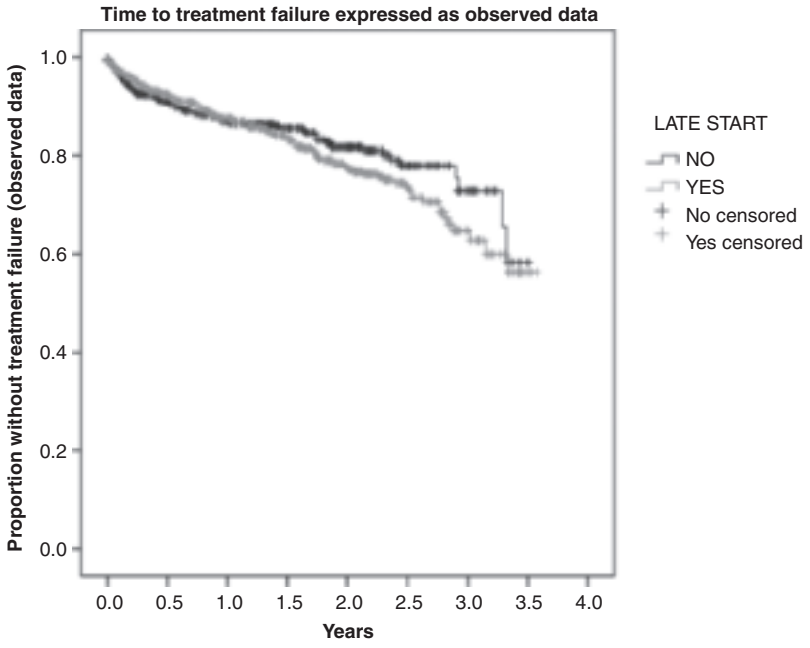
Log-rank test = 0.080; $P = .77$

Figure 1. Time to treatment failure stratified by late start. Curves represent Kaplan-Meier time-to-event analyses.

In the patients observed for this study, late initiation of HAART resulted in an overall increased rate of the compound endpoint of virological failure, opportunistic infections, and death. This negative effect on HIV-related outcomes has been previously documented.[4,18,19] Furthermore, initiation of antiretroviral therapy in patients with advanced HIV disease provides the clinician with additional challenges, such as choosing the optimal time for initiation of antiretroviral therapy in the presence of opportunistic infections, potential drug interactions, or increased incidence of adverse reactions.[20] In our study, the higher rate of virological failure, opportunistic infections, and death among late starters could be explained by a very low median CD4+ cell count at baseline,[18] a higher viral load,[19] and lesser efficacy of some antiretrovirals in patients with low CD4+ cell counts.[27,28] This is not the case for the nucleos(t)ide backbone; even though a poorer response rate has been reported for ABC+3TC with viral loads above 100,000 copies/mL,[29] the proportion of patients who were treated with TDF+FTC/3TC versus ABC+3TC did not differ between late and non-late starters.

Late initiation also has implications for the community in general. When treatment is not initiated early, patients maintain high levels of viremia over long periods, thus increasing the risk of transmission. In addition, health care costs increase due to the greater number of hospital admissions and development of opportunistic infections, antiretroviral toxicity, and complications of HAART such as acute immune reconstitution inflammatory syndrome.[2,21,30]

Our study is limited by the fact that we did not control for some potential confounders such as ethnic group or HIV subtypes. Similarly, because this is not a randomized study, unknown factors could significantly affect the response and may cause imbalance between the 2 populations. The



No. at risk	0	0.5	1	1.5	2.0	2.5	3.0	3.5	4.0
Late starters	606	459	378	296	195	103	34	3	0
Non-late starters	474	340	280	209	134	64	22	3	0

Log-rank test = 1.21; $P = .27$

Figure 2. Time to treatment failure as observed data stratified by late start. Curves represent Kaplan-Meier time-to-event analyses.

rate of losses to follow-up, while not very high, could have hidden small differences between the populations.

CONCLUSIONS

In our cohort, immigrant status was not found to be related to late initiation of HAART late, whereas male gender, older age, intravenous drug use, and lower educational and socioeconomic level were related. Although late starters did not have a longer time to treatment failure for any reason, time to virological failure was significantly shorter. Despite universal free access to HAART in Spain, late initiation of antiretroviral therapy is still very frequent and is observed in more than half of all HIV-infected patients. Patients who are immigrants do not start antiretroviral therapy later than Spain-born patients. It is imperative to implement measures to ensure early diagnosis and the initiation of HAART at an earlier stage, when benefits are higher.

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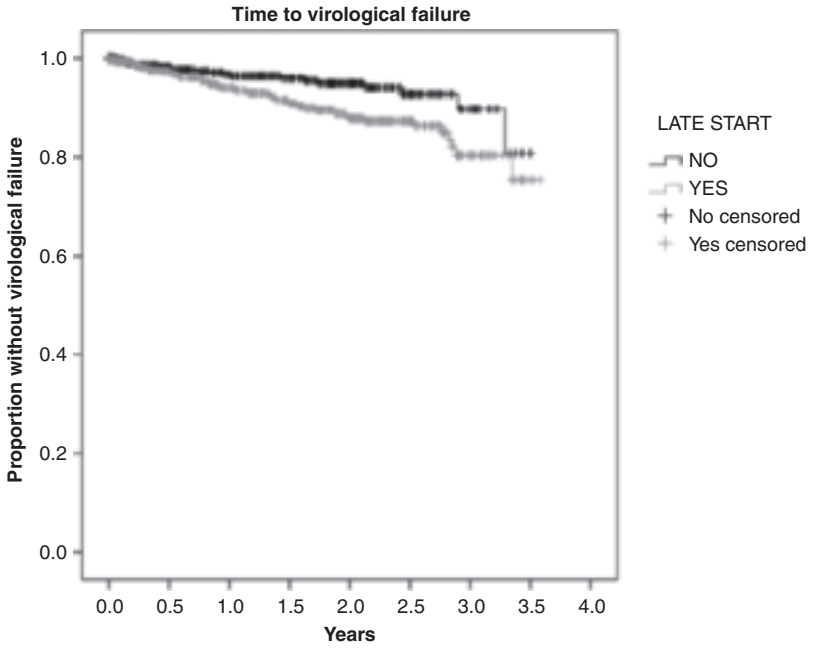

No. at risk	0	0.5	1	1.5	2.0	2.5	3.0	3.5	4.0
Late starters	606	459	378	296	195	103	34	3	0
Non-late starters	474	340	280	209	134	64	22	3	0

Log-rank test = 7.05; $P = .008$

Figure 3. Time to virological failure stratified by late start. Curves represent Kaplan-Meier time-to-event analyses.

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