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**The influence of the patients' educational levels on socioeconomic, clinical, immunological and virological end-points**

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The influence of the patients' educational levels on socioeconomic, clinical, immunological and virological end-points.

For Peer Review Only

**Abstract**

To analyse the influence of educational levels on diverse baseline and follow-up characteristics and outcomes of HIV-infected patients, we sequentially evaluated 1352 individuals with known educational levels, who initiated a nelfinavir-based regimen. Higher educational degrees were associated with better baseline clinical ( $P=0.03$ ) and immunological ( $P=0.003$ ) conditions, not related to transmission categories, which were also observed during follow-up ( $P=0.003$ ). However, these differences were only found in antiretroviral-experienced patients ( $P=0.002$ ), while naïve patients had very similar values ( $P=0.8$ ). Overall, there were different CD4 responses ( $P=0.06$ ), but not viral load responses ( $P=0.6$ ), to antiretroviral therapy according to the educational level, but these differences were more marked in the last 6 months of follow-up ( $P=0.008$ ). Patients with higher educational degrees had higher rates of adherence to medical appointments both before ( $P=0.0003$ ) and during the study period ( $P=0.01$ ), as well as to antiretroviral therapy in univariate ( $P=0.003$ ) and multivariate analyses ( $P=0.007$ ). Similarly, baseline CD4 counts proved to be independently associated with education after adjustment for other variables ( $P=0.0006$ ). The educational groups also differed in diverse socioeconomic parameters and certain beliefs about HIV infection ( $P<0.0001$  for each). We conclude that the patient's educational level influences clinical and immunological outcomes of HIV infection. This impact is probably mediated through differences in the long-term effects of treatment, as a result of adherence to antiretroviral therapy and to medical indications. The evaluation of social aspects such as the patient's education should be incorporated into routine clinical practice to improve the results of treatment.

Key words: Education, socioeconomic factors, antiretroviral therapy, CD4, viral load, outcomes

## INTRODUCTION

Besides highly active antiretroviral therapy (HAART), some demographic and epidemiological features, such as age, gender and transmission categories, have been found to be associated with clinical, and viroimmunological outcomes (Collazos, Asensi & Carton, 2007; Dray-Spira & Lert, 2003; Fardet et al, 2006, Grabar et al, 2004; Perez & Moore, 2003; Rodriguez-Arenas et al, 2006; Umeh & Currier, 2005; von Oberbeck et al, 1994;). On the other hand, the socioeconomic status, including the educational level, has also been associated with survival in studies carried out in the general population (Huisman et al 2005; Lundberg, 1993; Steenland, Henley & Thun, 2002) and in intravenous drug users (IDU) (Davoli et al, 1993; Hembree et al, 2005), usually showing poorer outcomes for patients with lower socioeconomic status.

Regarding HIV infection, few studies have evaluated the role of the socioeconomic and educational status in certain important end points, mainly survival. Moreover, most of these studies analysed data or were carried out before the introduction or generalization of HAART (del Amo et al, 2002; Katz et al, 1998; Piketty et al, 1999; Schechter et al, 1994), evaluated socioeconomic aspects different from education (Antunes, Waldman & Borrell, 2005; Katz et al, 1998; McFarland et al, 2003; Piketty et al, 1999; Rapiti et al, 2000; Wallace, 2003; Wood et al, 2002), focused on specific populations such as IDU (Jarrin et al, 2007; Piketty et al, 1999) or homosexual men (Schechter et al, 1994), studied only specific aspects such as adherence to HAART (Gordillo et al, 1999; Nemes, Carvalho & Souza, 2004) or concentrated on the different access to HAART in diverse socioeconomic categories (Junghans et al, 1999; McFarland et al, 2003). Finally, the studies conducted in the HAART era did not disclose which patients were receiving or not HAART or the antiretroviral regimens used (Borrell et al, 2006; Caro-Murillo et al, 2007; Jarrin et al, 2007; Junghans et al, 1999; Saraceni et al, 2005). Consequently, it is surprising the lack of reliable data regarding the possible influence of educational levels on diverse outcomes of HIV infection in patients receiving HAART.

Therefore, this study was carried out to analyse the specific role of the educational level in important baseline and follow-up parameters and outcomes of HIV-infected patients receiving a relatively similar HAART. To this aim, a large sample of patients was extracted from a large, multicenter cohort who initiated a nelfinavir-based regimen.

## METHODS

The data for this study were extracted from the Grupo Español para el Estudio Multifactorial de la Adherencia (GEEMA) cohort. This prospective, multicenter, nationwide cohort was composed of more than 3000 patients recruited from 69 hospitals of Spain (see appendix). All patients, older than 18 years, initiated nelfinavir therapy in combination with other antiretroviral drugs and were followed-up during 12 months. The inclusion period extended from January 1998 to December 1999 and evaluations took place at baseline and at the 3<sup>rd</sup>, 6<sup>th</sup> and 12<sup>th</sup> month after the onset of nelfinavir therapy. Diverse demographic, therapeutical, clinical and laboratory data were recorded for each patient at each evaluation. Approximately half of the patients underwent a particular evaluation that included social aspects such as educational level, beliefs about HIV infection, social support and a specific evaluation of adherence to antiretroviral therapy. No specific criteria were used for the selection of these patients, but it depended on the availability at each hospital of the adherence counselor described below.

For the purpose of this study only patients for whom data about their educational backgrounds were available were selected. Patients were grouped into one of three educational levels: None or basic, secondary or university studies. None or basic studies included patients who did not complete or had completed, respectively, a basic education of about 8 years of primary schooling. Secondary studies implied to have completed a basic education as well as an additional 3 or 4 year period of secondary education. University studies implied to have reached a university degree, which was obtained after an average of 5 years of specialised studies initiated after the completion of secondary studies.

CD4 counts were measured by flow-cytometry and viral load by either branched DNA or RNA-PCR assays. The lower detection limit was established at 200 copies/ml. Adherence in the entire cohort was evaluated using a validated simplified questionnaire administered by the clinician at different time points (Knobel et al, 2002). However, in addition to this questionnaire, the subset of patients included in this study completed another more detailed questionnaire with the help of a nurse or pharmacist collaborator (treatment adherence counsellor). Patients were considered fully adherents if showed good adherence at all evaluations. If adherence was suboptimal at any evaluation, patients were considered as non-adherents, regardless of the adherence observed at other time points.

*Statistical analysis.* Categorical variables were compared with the Chi-square test or the Fisher exact tests as appropriate. The Kruskal-Wallis test was used for the comparison of

quantitative parameters between the three educational groups, and the Friedman test for evaluating the changes over time of CD4 counts and viral load in the same patient. The independent associations of diverse parameters with CD4 counts and viral load were assessed with stepwise multiple linear regressions. Stepwise logistic regressions were used for identifying explanatory parameters for dichotomous variables. The losses to follow-up were evaluated by Kaplan-Meier analysis and log-rank test. The comparisons of CD4 and viral load response-curves to HAART during the follow-up period in the three educational groups were carried out with a general linear model repeated measures procedure. The limit of statistical significance was established at  $P < 0.05$  for a two-sided test. SPSS software v. 15.0 was used for statistical analysis.

## **RESULTS**

The study group was composed of 1352 patients (median age 35 years, IQ range 31-39, 74% men, 82% antiretroviral-experienced). None or basic studies were reported by 924 patients (68.3%), secondary studies by 317 (23.5%) and university studies by 111 (8.2%). The median CD4 counts at the study onset was 259/ $\mu$ l (IQ range 140-432), and the mean viral load 3.90 log copies/ml (SD 1.29).

Table 1 shows the baseline characteristics of the patients grouped according to their respective educational levels. Interestingly, there were statistically significant differences in the baseline CD4 counts and rates of AIDS diagnosis; patients with more advanced studies had better immunological status and lower rates of AIDS. This trend was also observed in each of the HIV transmission categories (data not shown). However, these differences corresponded only to antiretroviral-experienced patients, as antiretroviral-naïve patients had similar values in the different educational categories.

Figure 1 depicts the course of CD4 counts over time. Patients who completed university studies had higher CD4 counts over time than the remainder patients. However, this was due to the subset of patients with prior antiretroviral experience, because in naïve patients the curves followed a similar course, particularly during the initial months of therapy. All three educational groups showed highly significant increases in their CD4 counts over time, both in antiretroviral-naïve and experienced patients ( $P < 0.0001$ ).

A general linear model repeated measures procedure, using interaction tests for prior antiretroviral therapy, revealed that the slope of the CD4 curves over time were different among

the three educational groups, with a P value close to the significance level ( $P=0.06$ ). The lack of statistical significance may be attributed to the considerable reduction in the sample size associated with the general linear model, as patients lacking any of the four CD4 determinations were excluded from the analysis (only 607 patients had all four determinations). The university group experienced better responses to HAART than the secondary and none/basic educational level groups ( $P=0.05$ , and  $P=0.1$ , respectively, Scheffe test). Regarding the three follow-up intervals, the slopes of the curves according to the general linear model were similar in the baseline to 3<sup>rd</sup> month ( $P=0.8$ ) and in the 3<sup>rd</sup> to 6<sup>th</sup> month periods ( $P=0.6$ ), but significantly different in the 6<sup>th</sup> to 12<sup>th</sup> month interval ( $P=0.008$ ). This could mean that late, but not early, immunological responses to HAART were different among the three educational groups.

Figure 2 shows the course of viral load and viral suppression over time. All three educational categories experienced marked decreases in viral load ( $P<0.0001$ ). There were no significant differences among the educational groups at baseline, or in the slopes of the viral response-curves during follow-up ( $P=0.6$ ). Table 2 shows the prevalence of some events or characteristics during follow-up. There were no statistically significant differences among the groups regarding clinical progression or death, although there was a clear trend towards better clinical outcomes in patients with higher educational levels. This trend was also observed in each of the transmission categories (data not shown). Similarly, higher educational groups had higher rates of adherence, trend that was also present in each of the transmission categories (data not shown). Kaplan-Meier analysis revealed that patients with higher degrees of education experienced fewer and later dropouts during follow-up ( $P=0.01$ , log-rank test).

Following medical evaluation, the treatment adherence counsellor asked patients for the degree of resolution of their doubts about antiretroviral treatment. There were no significant differences between those who considered their doubts quite or fully resolved and those who reported none or poor resolution (none/basic studies 83.3%, secondary 88.8%, university 85.6%,  $P=0.06$ ). On the contrary, there were highly significant differences ( $P<0.0001$ ) regarding the patients' opinion about the main objective pursued with antiretroviral treatment. Patients with higher degrees of education were more prone to believe that the aim was to improve viroimmunological parameters (university 81.4%, secondary 49.8%, none/basic 40.6%), and less prone to believe that it was to prolong life (15.1%, 34.2% and 36.8%, respectively) or cure the infection (1.2%, 9.9% and 17.1%, respectively).



Multiple regression analyses revealed that, after adjusting for diverse baseline parameters (gender, age, educational degree, transmission categories, prior antiretroviral experience, CD4 counts and viral load), baseline CD4 counts were independently associated with educational degree ( $P=0.0006$ ), baseline viral load ( $P<0.0001$ ), and age ( $P=0.02$ ). On the contrary, education was not significantly associated with baseline viral load ( $P=0.8$ ), or with final CD4 counts ( $P=0.6$ ) or viral load ( $P=0.5$ ).

Logistic regression analyses showed that, after adjusting for baseline parameters, adherence to antiretroviral therapy was independently predicted by the educational level ( $P=0.007$ ), increasing age ( $P<0.0001$ ), absence of prior antiretroviral experience ( $P=0.0008$ ), and transmission categories ( $P=0.006$ ). Among the latter, IDU showed lower adherence than men who have sex with men (OR 0.66, 95% CI 0.43-0.995,  $P=0.047$ ), heterosexual (OR 0.68, 95% CI 0.48-0.97,  $P=0.03$ ) and other transmission categories (OR 0.34, 95 CI 0.15-0.74,  $P=0.007$ ). Regarding the different degrees of education, adherence was lower in patients with none/basic studies than in those with secondary (OR 0.62, 95% CI 0.45-0.84,  $P=0.002$ ) or university studies (OR 0.68, 95% CI 0.40-1.14,  $P=0.1$ ), the latter not being statistically significant very probably because of the limited sample size. On the contrary, clinical progression or death was not significantly predicted by education, but by lower baseline CD4 ( $P=0.001$ ), poorer adherence ( $P=0.02$ ) and prior antiretroviral experience ( $P=0.03$ ).

## **DISCUSSION**

We have evaluated several major parameters of HIV infection in diverse educational categories. Overall, most patients reported none or basic studies and a minority of them completed university studies. This fact may clearly be attributed to socioepidemiological reasons, as almost three-fourths of the patients had acquired the infection through intravenous drug use, a population usually associated with lower educational degrees (Caro-Murillo et al, 2007; del Amo et al, 2002). In fact, the educational level of the study population was lower than that of the general population for this age group in our country .

Few studies in the HAART era have analysed clinical progression or death in different educational levels (Borrell et al, 2006; Jarrin et al, 2007; Junghans et al, 1999; Saraceni et al, 2005). In addition to the reduced number of these reports, their design, methodology, setting, source of data, population evaluated, educational groups and parameters analysed were different, limiting furthermore the drawing of definitive conclusions. Besides, these studies did

not focus on the effects or type of HAART, reported the outcomes of the patients actually receiving HAART (as many patients were not treated or were not HIV-infected), or analysed other important variables such as viroimmunological parameters, adherence or prior history of antiretroviral treatment. In fact, to our knowledge, this is the first study that comprehensively evaluates all these important aspects.

Similarly to some of these studies (Borrell et al, 2006; Jarrin et al, 2007; Saraceni et al, 2005) we found an inverse relationship between mortality and educational level, with differences so marked as a two-fold higher mortality in patients with none or basic education than in those with university degrees. However, these differences were not statistically significant, which may be attributed to the reduced number of adverse clinical outcomes observed in our series, clearly related to a relatively short follow-up period for patients receiving HAART. These different outcomes could also be ascribed to unequal access to HAART or medical care in patients with different socioeconomic development (Borrell et al, 2006; Dray-Spira & Lert, 2003; Jarrin et al, 2007; McFarland et al, 2003; Rapiti et al, 2000). However, some authors did not find different outcomes despite unequal access to care (Junghans et al, 1999), and our study suggests that the poorer outcomes of patients with lower educational levels were due to factors other than access to medical care and therapy, as all patients were attending specialised clinics and were receiving HAART at no cost.

In fact, we found that higher educational groups had better clinical and immunological conditions at baseline, not related to transmission categories, which were also maintained during follow-up. Interestingly, these differences were only observed in antiretroviral-experienced patients, as naïve patients had very similar values regardless of their educational level. This observation suggests that these differences resulted from the long-term effects of antiretroviral therapy. In this regard, differences in the slope of the CD4 curves were more evident in the last 6 months of follow-up, and patients with higher educational degrees had higher rates of adherence to HAART, which proved to be independently associated with education. Furthermore, patients with higher educational levels were also more prone to fulfill medical appointments both before and during the study period. The lack of differences in viral load among the educational groups could be related to the short follow-up period, as longer periods should evidence virological failures in less adherent patients.

On the other hand there were highly significant differences in the patients' opinion about the main objective pursued with treatment. Patients with higher degrees of education were

much more prone to believe that the aim was to improve viroimmunological parameters and much less prone that it was to cure the infection.

All these data considered altogether suggest that the best clinical and immunological results observed in patients with higher educational categories were not due to different access to antiretroviral therapy or medical care, but to their educational background and related socioeconomic and psychosocial issues. Presumably more educated patients may develop better abilities to cope with the adverse consequences of a chronic illness, to comply better with its complex treatment and to follow medical indications. In fact, demographic and psychosocial factors are associated with the degree of adherence (Dray-Spira & Lert, 2003), and adherence is essential for obtaining optimal clinical and viroimmunological results.

Our study has some valuable points that support the validity of our observations. First, we analysed a large number of patients recruited all across our country, minimizing therefore bias related to local disparities in the educational background or in HIV management strategies. In addition, about 90% of our patients were Caucasian individuals from Spain, minimizing also the possible interactions of racial or ethnic factors on the medical care and course of HIV infection (Anastos et al, 2000; Hellinger & Fleishman, 2001), and the variability of educational patterns in different countries. In addition, all patients were treated with HAART and were attending specialised HIV clinics, both aspects provided cost-free in our country, reducing therefore the variability in access to medical care reported in other countries (Dray-Spira & Lert, 2003; Davidson et al, 1998; Fleishman et al, 2005). On the other hand, whereas other studies on this topic mixed treated and untreated patients, and the treatment regimens for those receiving HAART were unknown, all patients in our study received a therapy based on the same protease inhibitor. In addition, our separate analysis of antiretroviral-naïve and experienced patients allowed us to evaluate the course of therapy in these two clearly different populations, as evidenced by our results. Finally, data were recorded prospectively, as opposed to studies based on population registries and surveillance databases in which the exactitude of the gathered data is expectedly lower.

Limitations to our study include a relatively short follow-up period for evaluating clinical outcomes, although the results we found after one year of follow-up fully agreed with those of other studies (Borrell et al, 2006; Jarrin et al, 2007; Saraceni et al, 2005). On the other hand, other newer, potent antiretroviral regimens might obtain better clinical or viroimmunological outcomes. However, this fact would not invalidate our findings, as all patients received a similar

regimen. Finally, extrapolation of our results to other countries and settings should be made with caution, as factors such as race, ethnicity, and inequalities in the access to care, which may be present in other settings, were not controlled for in our study given our homogenous population.

We conclude that the educational level has an impact on clinical and immunological outcomes of HIV infection. This effect is probably mediated through a better understanding of and coping with the infection and its consequences, mainly adherence to antiretroviral therapy and to medical indications. Our results suggest that the evaluation of some social aspects, such as the patient's educational status, should be incorporated into routine clinical practice. This evaluation would allow paying particular attention to the patients belonging to the lower social strata, to improve their understanding of the HIV infection and their adherence to factors necessary to control it, mainly HAART. Similarly, educational aspects should also be considered in the implementation of treatment strategies and in the design and interpretation of clinical trials, because extrapolation of the results to different sociocultural settings may be difficult.

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**Legend to figures.**

Figure 1. Course of CD4 counts over time, in all patients and in antiretroviral-naïve and experienced patients, according to the three educational levels: None or basic (circles, thick line), secondary (triangles, discontinuous line) and university (squares, thin line). The values represent the median of all measurements available at each time point, and the P values the comparisons among them (Kruskal-Wallis test).

Figure 2. Course of viral load (left panel) and rates of suppressed viral load (right panel) over time according to the three educational levels: None or basic (circles, thick line), secondary (triangles, discontinuous line) and university (squares, thin line). P values represent the comparisons of the values available at each time point (Kruskal-Wallis and Chi-square tests for viral load and rates of viral suppression, respectively).

Table 1. Baseline characteristics of the patients

		None or basic n (%)	Secondary n (%)	University n (%)	P value
<b>Gender</b>	Men	659 (73.9%)	223 (73.1%)	84 (77.8%)	0.6 <sup>a</sup>
<b>Age</b>	Median age [IQ range] (years)	34 [31-38]	35 [32-39]	38 [33-44]	<0.0001 <sup>b</sup>
<b>HIV transmission categories</b>	Intravenous drug use	621 (70.6%)	170 (55.9%)	30 (28.6%)	<0.0001 <sup>a</sup>
	Men who have sex with men	64 (7.3%)	69 (22.7%)	55 (52.4%)	
	Heterosexual	167 (19.0%)	58 (19.1%)	16 (15.2%)	
	Others	27 (3.1%)	7 (2.3%)	4 (3.8%)	
<b>Clinical and immunological CDC stages</b>	A	319 (37.7%)	118 (42.6%)	43 (44.8%)	0.4 <sup>a</sup>
	B	227 (26.8%)	75 (27.1%)	24 (25.0%)	
	C	300 (35.5%)	84 (30.3%)	29 (30.2%)	
	1	61 (6.9%)	21 (7.3%)	8 (8.1%)	0.5 <sup>a</sup>
	2	291 (32.9%)	99 (34.3%)	41 (41.4%)	
	3	533 (60.2%)	169 (58.5%)	50 (50.5%)	
		Prior AIDS diagnosis (clinical or immunological)	584 (66.9%)	177 (61.9%)	54 (55.1%)
	Prior AIDS diagnosis (only naïve patients)	96 (61.5%)	27 (60.0%)	14 (70.0%)	0.7 <sup>a</sup>
	Prior AIDS diagnosis (only experienced patients)	487 (68.0%)	150 (62.2%)	40 (51.3%)	0.006 <sup>a</sup>
<b>Adherence to scheduled medical appointments prior to inclusion</b>	Missing of at least one appointment during the preceding year	158 (35.3%)	29 (20.6%)	7 (15.2%)	0.0003 <sup>a</sup>
<b>Socioeconomic characteristics</b>	Living alone at home	58 (6.3%)	43 (13.7%)	30 (27.3%)	<0.0001 <sup>a</sup>
	Having a job at the time of inclusion	253 (27.8%)	152 (48.4%)	67 (60.9%)	<0.0001 <sup>a</sup>
	Patients' notification of HIV infection to family members or friends	820 (93.7%)	262 (91.3%)	73 (79.3%)	<0.0001 <sup>a</sup>
	Support received from family members or friends	697 (95.0%)	207 (92.4%)	59 (93.7%)	0.3 <sup>a</sup>
<b>Antiretroviral therapy</b>	Prior antiretroviral therapy	739 (81.2%)	263 (84.6%)	89 (80.9%)	0.4 <sup>a</sup>
	Prior protease inhibitor therapy	585 (63.3%)	227 (71.6%)	71 (64.0%)	0.03 <sup>a</sup>
	Median time on antiretrovirals in experienced [IQ range] (months)	15.7 [8.4-28.9]	12.5 [8.2-22.3]	18.4 [10.1-33.0]	0.07 <sup>b</sup>
<b>Immunological parameters</b>	Median CD4 counts all patients [IQ range] (cells/ $\mu$ l)	249 [130-416.3]	280 [161-447]	334 [182.5-492.5]	0.003 <sup>b</sup>
	Median CD4 counts naïves [IQ range] (cells/ $\mu$ l)	203 [56-408]	190.5 [88.3-360.8]	195 [132-425.5]	0.8 <sup>b</sup>
	Median CD4 counts experienced [IQ range] (cells/ $\mu$ l)	254 [143-423.3]	296 [173-462]	346 [210.8-515.8]	0.002 <sup>b</sup>
<b>Virological parameters</b>	Undetectable viral load	179 (21.0%)	62 (20.9%)	27 (25.7%)	0.5 <sup>a</sup>
	Mean viral load all patients [SD] (log copies/ml)	3.93 [1.30]	3.83 [1.23]	3.87 [1.34]	0.4 <sup>b</sup>
	Mean viral load naïves [SD] (log copies/ml)	4.64 [1.01]	4.82 [1.10]	4.65 [1.12]	0.2 <sup>b</sup>
	Mean viral load experienced [SD] (log copies/ml)	3.76 [1.30]	3.65 [1.17]	3.68 [1.33]	0.4 <sup>b</sup>

Percentages have been calculated considering only patients for whom data are available

<sup>a</sup> Chi-square test

<sup>b</sup> Kruskal-Wallis test

Table 2. Frequency of diverse events or characteristics according to the educational levels

	None or basic	Secondary	University	P value
	n (%)	n (%)	n (%)	
Adverse events due to HAART	65 (12.5)	36 (17.4)	6 (8.1)	0.08
Clinical progression or death	41 (9.2)	12 (7.1)	3 (4.8)	0.4
Undetectable viral load at 12 <sup>th</sup> month	294 (59.2)	101 (53.4)	39 (56.5)	0.4
Methadone use (all patients)	168 (19.7)	21 (6.8)	5 (4.8)	<0.0001
Methadone use (only patients infected through intravenous drug use)	151 (27.1)	18 (11.0)	3 (12.5)	<0.0001
Patients who received only NRTIs in addition to nelfinavir	681 (75.8)	213 (68.9)	78 (71.6)	0.05
Full adherence to HAART	283 (39.0)	134 (50.0)	50 (56.2)	0.003
Never miss an antiretroviral dose	192 (28.1)	71 (27.3)	36 (41.4)	0.03
If missed, do not take later the forgotten dose	304 (44.4)	111 (42.7)	23 (26.4)	0.006
Symptoms of malaise or discomfort	355 (51.5)	137 (53.1)	43 (48.3)	0.7
Failure to comply with the 12 <sup>th</sup> month evaluation	294 (33.5)	82 (27.0)	25 (23.8)	0.02

Percentages have been calculated considering only patients for whom data are available

P values have been calculated by the Chi-square test

HAART denotes highly active antiretroviral therapy and NRTIs, nucleoside reverse transcriptase inhibitors



