Risk, predictors, and mortality associated with non-AIDS events in newly diagnosed HIV-infected patients: role of antiretroviral therapy

Mar Masiá[a,b], Sergio Padilla[a,b], Débora Álvarez[c], Juan C. López[d], Ignacio Santos[e], Vicente Soriano[f], José Hernández-Quero[g], Jesús Santos[h], Cristina Tural[i], Julia del Amo[c], Félix Gutiérrez[a,b], CoRIS*

Objective: We aimed to characterize non-AIDS events (NAEs) occurring in newly diagnosed HIV-infected patients in a contemporary cohort.

Methods: The Cohort of the AIDS Research Network (CoRIS) is a prospective, multicenter cohort of HIV-infected adults antiretroviral naive at entry, established in 2004. We evaluated the incidence of and the mortality due to NAEs and AIDS events through October 2010. Poisson regression was used to investigate factors associated with a higher incidence of NAEs.

Results: Overall, 5185 patients (13.306 person-years of follow-up), median age (interquartile range) 36 (29–43) years, participated in the study. A total of 86.5% patients had been diagnosed in 2004 or later. The incidence rate of NAEs was 28.93 per 1000 person-years [95% confidence interval (CI) 26.15–32.07], and of AIDS-defining events 25.23 per 1000 person-years (95% CI 22.60–28.16). The most common NAEs were psychiatric, hepatic, malignant, renal, and cardiovascular related. After adjustment, age, higher HIV-viral load, and lower CD4 cell count at cohort entry were associated with the occurrence of NAEs, whereas likelihood significantly decreased with sexual transmission and higher educational level. Additionally, antiretroviral therapy was inversely associated with the development of some NAEs, specifically of psychiatric [incidence rate ratio (95% CI) 0.54 (0.30–0.96)] and renal-related [incidence rate ratio (95% CI) 0.31 (0.13–0.72)] events. One hundred and seventy-three (3.33%) patients died during the study period. NAEs contributed to 28.9% of all deaths, with an incidence rate (95% CI) of 3.75 (2.84–4.94) per 1000 person-years.

Conclusion: In patients newly diagnosed with HIV infection, NAEs are a significant cause of morbidity and mortality. Our results suggest a protective effect of antiretroviral therapy in the occurrence of NAEs, in particular of psychiatric and renal-related events.

AIDS 2013, **27**:181–189

Keywords: antiretroviral therapy, clinical events, cohort, comorbidity, complications, mortality

[a]Infectious Diseases Unit, Hospital General Universitario de Elche, [b]Clinical Medicine Department, Universidad Miguel Hernández, Elche, [c]Centro Nacional de Epidemiología, Instituto de Salud Carlos III, [d]Hospital Universitario Gregorio Marañón, [e]Hospital Universitario La Princesa, [f]Hospital Carlos III, Madrid, [g]Hospital Universitario San Cecilio, Granada, [h]Hospital Universitario Virgen de la Victoria, Málaga, and [i]Hospital Universitario Germans Trias i Pujol, Badalona, Spain.

Correspondence to Mar Masiá, MD, Clinical Medicine Department, Infectious Diseases Unit, Hospital General Universitario de Elche, Universidad Miguel Hernández, Elche, Spain.

Tel: +34 96 667 91 54; fax: +34 96 667 91 56; e-mail: marmasiac@gmail.com

* See Supplemental Data.

Received: 24 June 2012; revised: 3 September 2012; accepted: 4 September 2012.

DOI:10.1097/QAD.0b013e32835a1156

Introduction

The advent of combination antiretroviral therapy (cART) has shifted patterns of morbidity and mortality in HIV-infected persons from AIDS-defining diseases, consisting of immunodeficiency-related opportunistic infections and malignancies, to the so-called non-AIDS events (NAEs) [1,2]. The cause of NAEs is probably multifactorial; they have been related to cART-associated toxicity [3,4], older age [5–9], low CD4 cell counts [6,8–10], immune activation in spite of effective ART [11], and lifestyle issues [6,9,12].

Most studies dealing with the epidemiology of NAEs have focused on severe NAEs [2], non-AIDS-defining deaths [2,8], or on specific events, such as neoplasms or cardiovascular diseases [12,13–16], but very few have addressed the occurrence of the overall spectrum of NAEs. Moreover, these latter studies involve cohorts in which follow-up started in the pre or peri-cART period [6,7,10], when antiretroviral regimens included drugs with higher metabolic toxicity and patients reached higher levels of immune deficiency. Whether the frequency, spectrum, and risk factors for NAEs are the same in patients diagnosed in the current era, characterized by an increasing trend to earlier cART initiation, a growing use of the less toxic new antiretrovirals, and a change in some lifestyle factors, such as a decreasing smoking habit, is unknown.

We investigated the incidence, risk factors, and mortality associated with the occurrence of NAEs in newly diagnosed HIV-infected patients from a contemporary cohort.

Methods

The cohort of adults with HIV infection of the AIDS Research Network (CoRIS) is an open, prospective, multicenter cohort of adult participants with confirmed HIV infection, naive to ART at study entry, who are recruited in HIV care units of the Spanish Public Health System [17]. CoRIS was launched in 2004. Currently, 28 sites – 27 public hospitals and one HIV/STD clinic – from 13 of the 17 autonomous communities that make up Spain participate in the cohort. Each center recruits into the cohort all individuals seen for the first time in the center who meet the following criteria: over 13 years of age, confirmed HIV diagnosis, and naive to ART. Written informed consent is obtained from all the patients. Patient information is collected using two structured questionnaires, one at cohort entry and the other for follow-up visits. Demographic, clinical, laboratory, microbiological, and treatment information is recorded. Among clinical data, all AIDS-defining diseases occurred since the HIV diagnosis and during follow-up are registered. cART is documented in detail, with the beginning and ending dates for each drug. Data are collected at baseline and prospectively updated and sent to the coordinating center every 6 months until 2008, and annually since then. Patient follow-up ends when the patient dies or transfers follow-up care to another center that is not CoRIS and cannot provide follow-up. In the coordinating center, all information is transformed into a standardized format and merged into a central dataset in a software application designed for the study.

All centers were invited in February 2008 to provide the following incident NAEs: cardiovascular-related (acute myocardial infarction, angina, congestive heart failure, stroke, transient ischemic attack, silent cerebrovascular disease, peripheral arterial disease, coronary-related death), non-AIDS-defining malignancies, renal-related (acute renal failure, chronic kidney disease, renal tubulopathy/Fanconi syndrome, permanent dialysis, kidney biopsy), liver-related (ascites, hepatic encephalopathy, variceal hemorrhage, hepatic transplant, hepatocellular carcinoma, liver insufficiency/cirrhosis), psychiatric (depression requiring drug therapy, suicide attempt, psychosis), bone-related (nontraumatic vertebral and nonvertebral fractures, avascular necrosis of the bone), and metabolic (diabetes, lactic acidosis). Centers were asked to collect retrospectively all of the above NAEs occurring from the day of entry in the cohort to February 2008 (including patients who had died or were lost to follow-up prior to data collection) and to report them prospectively since then. Additionally, all deaths occurring from the day of inclusion in the cohort in which the main cause was attributed to any of the above NAEs were included among NAEs.

Centers were provided with a structured event reporting form containing the list of events to be reported and the precise definition of each NAE required for the inclusion (see Supplemental Data Files, http://links.lww.com/QAD/A261). Investigators also had to fill a specific event form for each particular NAE with additional data detailing the event. AIDS events were diagnosed using the clinical definition from the Centers for Disease Control and Prevention (CDC) [18].

Death due to an AIDS-defining event was defined as death attributable to a category C disease listed by the CDCs [18]. Death due to a NAE was classified according to a revised version of the 'Coding Death in HIV' (CoDe) classification system [19,20].

Statistical analyses

Descriptive analyses were used to summarize the incidence rates of each of the NAEs or AIDS events, and the characteristics of the patients developing them. Incidence rates of clinical events were calculated as the number of new events divided by the number of

person-years of follow-up. Follow-up for the analysis of incident NAEs and AIDS events accrued from the day of inclusion in the cohort to the date of the development of a NAE or AIDS event, respectively. Only events occurring after cohort entry were included in analyses. Follow-up of patients not developing events accrued from the day of inclusion in the cohort to the date of last visit or death. Data were abstracted from the study database on February 2011 and follow-up of patients was administratively censored after the last cohort merging on 31 October 2010. As the number of subsequent events developing in the same patient was low, for simplicity, analyses for the overall spectrum of NAEs and AIDS events were based only on the first event that occurred during follow-up. Poisson regression models were used to determine the demographic, clinical, and treatment-related factors associated with the development of a new NAE or AIDS event. cART exposure was included in the model as time-dependent covariate. In patients on cART, we measured time from the start of cART until the diagnosis of the event or the last follow-up visit. We used an intent-to-treat approach and, thus, ignored subsequent changes in treatment, including treatment interruptions and terminations. Multivariable models were adjusted for the effect of all the variables included in univariate analyses. All analyses were stratified by center. Independent-adjusted models were developed to assess factors associated with the occurrence of any first NAE, and with the occurrence of each specific NAE category; for this last analysis, all events occurring in the same person belonging to different categories were included. Incidence rate ratios (IRRs) for death were estimated using Poisson regression. All the analyses were conducted using Stata software (V.11.2; Stata Corporation, College Station, Texas, USA).

Results

Baseline characteristics

Overall, 5185 patients, with 13.306 person-years of follow-up, were analyzed. Demographic and clinical characteristics of the patients are provided in Table 1. Median time since HIV diagnosis was 0.11 years [interquartile range (IQR) 0.03–0.51 years], and 86.5% of the patients had been diagnosed in 2004 or later. Median CD4 cell count at inclusion in the cohort was 342 cells/μl (IQR 163–546 cells/μl).

A total of 3522 (67.92%) patients started cART during follow-up with a median total treatment duration of 1.71 years (IQR 0.57–3.30 years). The most frequent antiretroviral regimens at the last cohort visit or just

Table 1. Baseline characteristics of the patients.

	All	AIDS event	Non-AIDS event
Patients [*n* (%)]	5185 (100)	318 (100)	367 (100)
Women [*n* (%)]	1069 (20.62)	45 (14.15)	77 (20.98)
Age at cohort entry [years, median (IQR)]	36 (29–43)	40 (28–46)	41 (34–47)
Educational level			
None/primary	1799 (34.70)	143 (44.97)	167 (45.50)
Secondary/university	2407 (46.42)	107 (33.65)	106 (28.88)
Unknown	979 (18.88)	68 (21.38)	94 (25.61)
HIV transmission groups [*n* (%)]			
IDU	698 (13.46)	73 (22.96)	107 (29.16)
MSM	2465 (47.54)	112 (35.22)	104 (28.34)
Heterosexual	1828 (35.26)	116 (36.48)	142 (38.69)
Other/unknown	194 (3.74)	17 (5.35)	14 (3.81)
Prior clinical AIDS [*n* (%)][a]	663 (12.79)	0	83 (22.62)
CD4 cell count at cohort entry [cells/μl, median (IQR)]	342 (163–546)	109 (109–242)	230 (61–454)
HIV RNA at cohort entry (copies/ml)			
$<10^5$ [*n* (%)]	3503 (67.56)	140 (44.03)	206 (56.13)
$>10^5$ [*n* (%)]	1523 (29.37)	162 (50.94)	141 (38.42)
Unknown	159 (3.07)	16 (5.03)	20 (5.45)
Hepatitis C virus coinfection [*n* (%)]	612 (11.80)	49 (15.41)	84 (22.89)
Hepatitis B virus coinfection [*n* (%)]	189 (3.65)	13 (4.09)	21 (5.72)
Endpoints [*n* (IR; 95% CI)]			
Non-AIDS-defining event	367 (28.93; 26.15–32.07)		
Psychiatric	122 (9.62; 8.06–11.49)		
Liver-associated event	57 (4.49; 3.47–5.83)		
Non-AIDS-defining malignancy	54 (4.26; 3.26–5.56)		
Kidney-associated event	42 (3.39; 2.51–4.57)		
Cardiovascular	34 (2.68; 1.91–3.75)		
Metabolic	30 (2.28; 1.59–3.29)		
Bone	28 (2.21; 1.52–3.20)		
AIDS-defining event	318 (25.23; 22.60–28.16)		
Deaths	173 (13.00; 11.20–15.09)		

CI, confidence interval; IDU, injection drug user; IQR, interquartile range; IR, incidence rate.
[a]Prior clinical AIDS means AIDS diagnosis before cohort entry.

before the clinical event were based on nonnucleoside reverse transcriptase inhibitors (NNRTIs; 1718 patients; 51.4%; of them, 83.7% were receiving efavirenz), followed by protease inhibitor-based regimens (1157 patients; 34.6%; of them, 29% were receiving atazanavir or atazanavir/r, and 18.8% darunavir/r). Tenofovir was the most frequent nucleoside reverse transcriptase inhibitor, received by 74.4% of the patients. There were 6.3% patients treated with any of the newest antiretrovirals (raltegravir, maraviroc, or etravirine).

Incidence of non-AIDS events and AIDS events

Median (IQR) follow-up of the patients was 2.09 (0.84–3.68) years. A total of 367 patients developed 423 incident NAEs during the follow-up period (12 669 person-years until event or last visit), with an incidence rate of 28.93 cases per 1000 person-years [95% confidence interval (CI) 26.15–32.07 cases per 1000 person-years]. Three hundred and eighteen patients developed an AIDS-defining event (12 602 person-years follow-up until event or last visit), with an incidence rate of 25.23 cases per 1000 person-years (95% CI 22.60–28.16 cases per 1000 person-years). Eighty-eight percent of all AIDS patients had been diagnosed at cohort entry or during the first 3 months after inclusion, and 44.7% of the 318 incident AIDS events occurred within the first 3 months after the diagnosis of HIV infection. Three hundred and twenty one (6.19%) patients developed one NAE, and 46 (0.88%) patients developed at least two NAEs during follow-up. The most common NAEs were psychiatric (122 events), followed by hepatic (57 events), malignant (54 events), renal (42 events), and cardiovascular-related events (34 events; Fig. 1). The incidence rates for each specific NAE are shown in Table 1. Depression requiring drug therapy was the most frequent psychiatric-related event in 70.49% cases, followed by suicide attempt in 15.57%. Among malignancies, lung cancer (11 patients, 20%) was the most common followed by Hodgkin lymphoma (eight patients, 14%), head and neck cancer (seven patients, 12%), and hepatocellular carcinoma and anal cancer (five patients each, 9.2%; Fig. 1). Acute renal failure was the first cause of renal-related events (60.4%), followed by

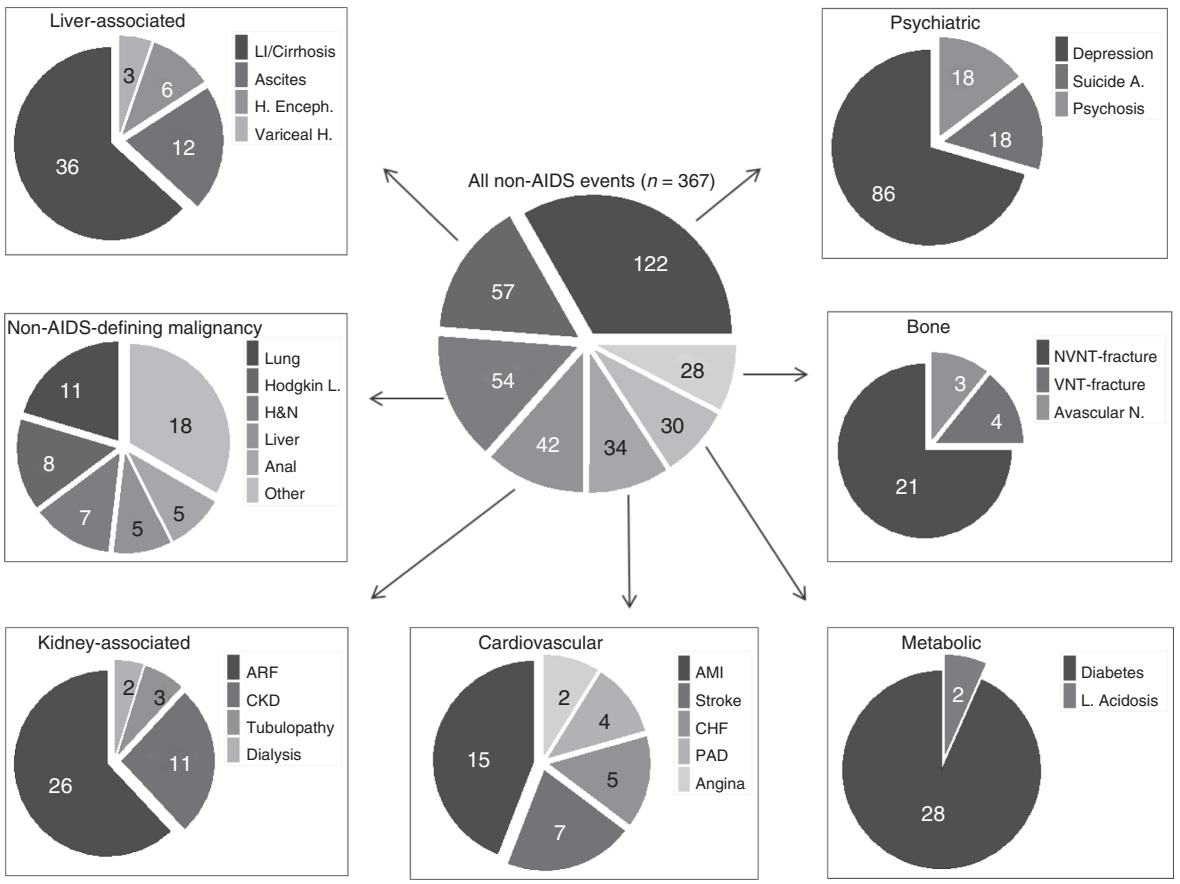

Fig. 1. Frequency of non-AIDS events. AMI, acute myocardial infarction; ARF, acute renal failure; Avascular N., avascular necrosis of the bone; CHF, congestive heart failure; CKD, chronic kidney disease; H. Enceph., hepatic encephalopathy; Hodgkin L., Hodgkin lymphoma; H&N, head and neck; L. Acidosis, lactic acidosis; LI/Cirrhosis, liver insufficiency/cirrhosis; NVNT fracture, nonvertebral nontraumatic fracture; PAD, peripheral arterial disease; Suicide A., suicide attempt; Variceal H., variceal hemorrhage; VNT fracture, vertebral nontraumatic fracture.

chronic kidney disease (25.5%). The most frequent causes of AIDS diagnosis were tuberculosis in 72 (22.6%) patients (39 pulmonary and 33 extrapulmonary or disseminated), *Pneumocystis jiroveci* pneumonia in 63 (19.8%), and Kaposi's sarcoma in 30 (9.4%).

Incidence rate of any first NAE decreased over calendar time, from 35.26 (95% CI 30.19–41.19) cases per 1000 person-years in the period 2004–2007 to 25.40 (95% CI 22.17–29.10) cases per 1000 person-years in the period 2008–2010 ($P = 0.001$; Fig. 2). The mean (SD) CD4 cell count at which cART was initiated increased steadily throughout the observation period; 147 (IQR 56–271) cells/μl in 2004 to 278 (IQR 168–357) cells/μl in 2010 ($P < 0.001$, test for linear trend). Accordingly, there was also a decrease in the number of AIDS events over calendar time during the same period (Fig. 2). The proportion of patients included in the cohort developing incident AIDS events within the first 3 months after the diagnosis of HIV infection was 2.92% during 2004–2007 and 2.53% during 2008–2010 ($P = 0.399$).

Risk factors for the development of non-AIDS events

Factors associated with the occurrence of any first NAE are shown in Fig. 3 and Supplemental Data, http://links.lww.com/QAD/A261. In unadjusted analysis, there was an increased IRR for the occurrence of any NAE with increasing age, hepatitis C virus (HCV) coinfection, prior clinical AIDS, lower CD4 cell count at cohort entry with a gradient effect, and higher HIV-viral load. Factors inversely associated with the development of NAEs were HIV transmission categories MSM and heterosexual, and secondary or higher educational level. After adjustment (Fig. 3 and Supplemental Data, http://links.lww.com/QAD/A261), the occurrence of a first NAE remained inversely associated with initiation of cART, sexual transmission of HIV infection and higher educational level, whereas the likelihood significantly increased with age, with a gradient effect (highest likelihood in those with age >50 years), higher viral load, and CD4 cell counts less than 200 cells/μl at cohort entry. An exploratory analysis including subsequent events occurring in the same patient showed similar results (data not shown).

The IRR for each specific NAE category adjusted for age, prior clinical AIDS, exposure to cART, and CD4 cell count at cohort entry are shown in Fig. 4 and Supplemental Data, http://links.lww.com/QAD/A261. Older participants showed higher IRRs for all NAE categories. Initiation of cART was inversely associated with the incidence of psychiatric and kidney-related NAEs.

Mortality associated with non-AIDS events and AIDS events

One hundred and seventy-three (3.33%) patients died during the study period; in 50 (28.90% of all deaths) of them, the cause of death was a NAE. The incidence rate (95% CI) for death in the cohort was 13.00 (11.20–15.09) per 1000 person-years. The incidence rate (95% CI) for NAE-related death was 3.75 (2.84–4.94) per 1000 person-years, and for AIDS-related death 5.93 (4.76–7.40) per 1000 person-years. Malignancy [incidence rate (95% CI) 1.57 (1.02–2.42) per 1000 person-years] and liver-related disease [incidence rate (95% CI) 1.35 (0.85–2.14) per 1000 person-years] were the most frequent causes of NAE-related deaths.

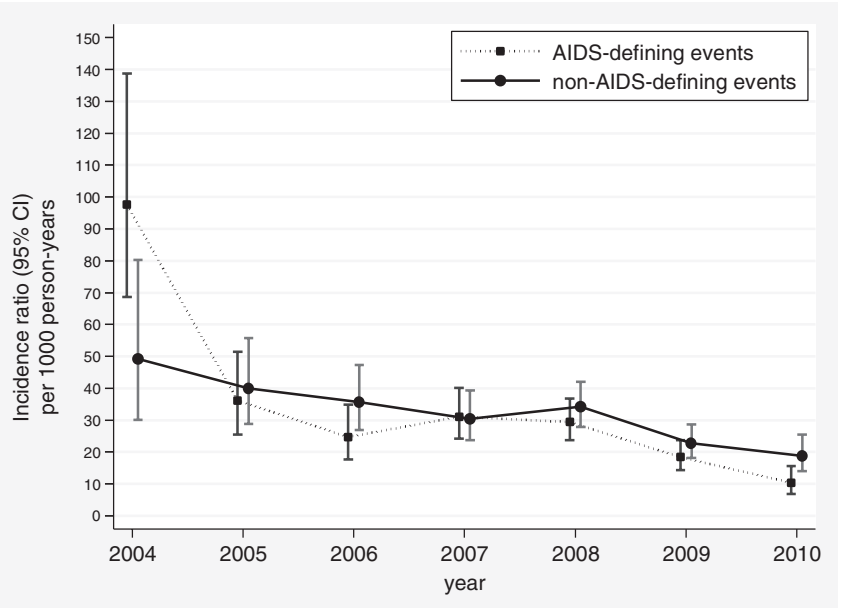

Fig. 2. Incidence rates of non-AIDS and AIDS events by calendar year of follow-up.

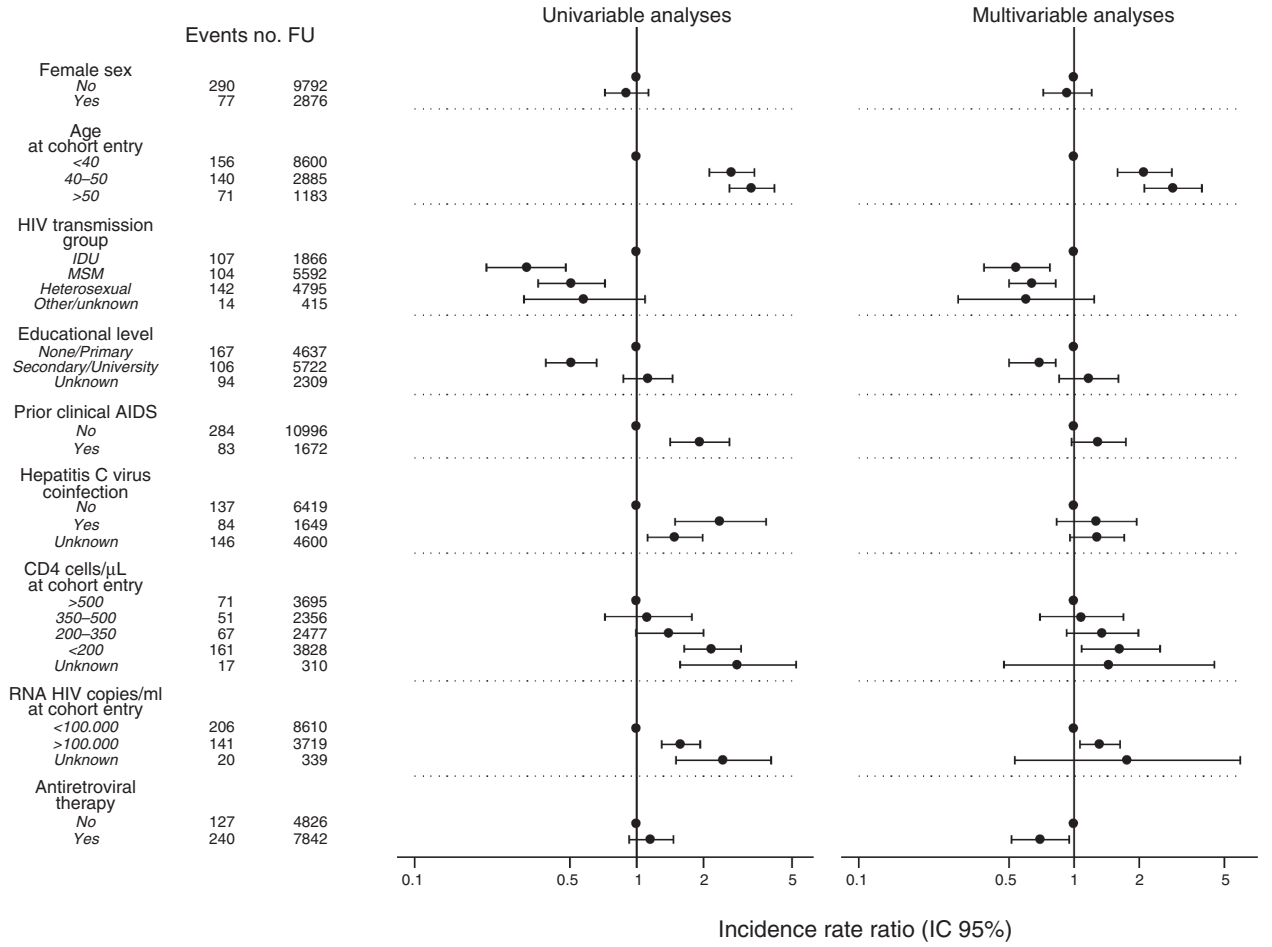

Fig. 3. Unadjusted and adjusted incidence rate ratios for the occurrence of non-AIDS events. Multivariable models were adjusted for sex, age, HIV transmission group, educational level, prior AIDS, hepatitis C coinfection, CD4 cells, and HIV viral load at cohort entry, and antiretroviral therapy initiation. CI, confidence interval; FU, follow-up in patient-years; IDU, injection drug user; IRR, incidence rate ratio.

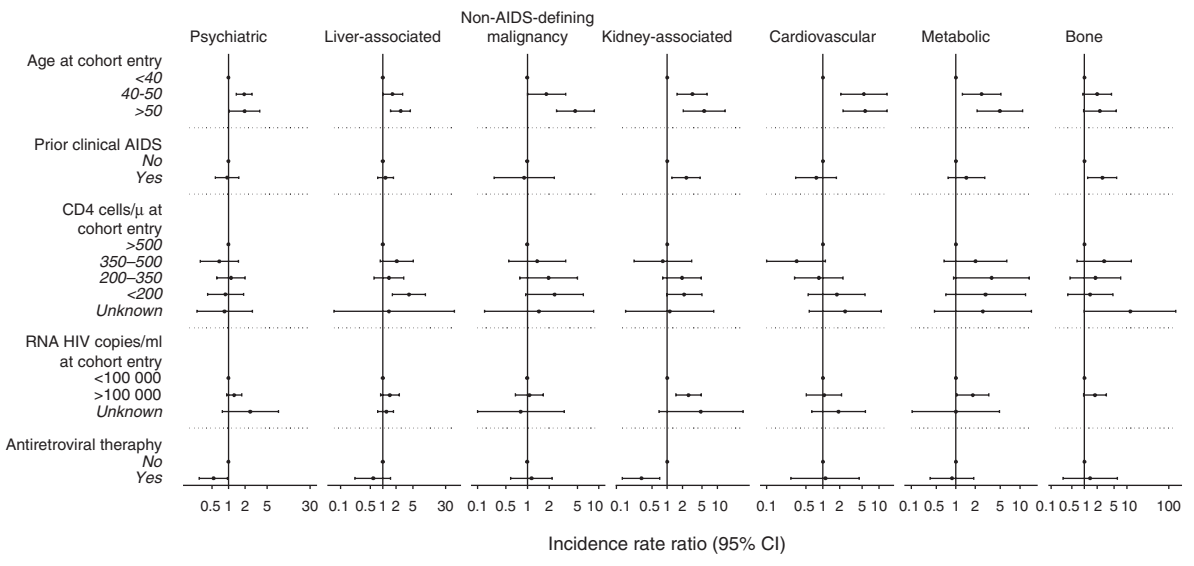

Fig. 4. Adjusted incidence rate ratios for each specific category of non-AIDS events. Multivariable models were adjusted for sex, age, HIV transmission group, educational level, prior AIDS, hepatitis C coinfection, CD4 cells and HIV viral load at cohort entry, and antiretroviral therapy initiation. CI, confidence interval.

Discussion

This is the first large study addressing the occurrence of NAEs in recently diagnosed HIV-infected patients in the current era, when relatively nontoxic antiretroviral agents are available for treatment. We have found that the spectrum of NAEs developing in these patients includes psychiatric, hepatic, and malignant diseases among the three most frequent causes. The associated mortality is significant, because NAEs accounted for nearly one-third of all deaths occurring in the patients. We have also identified several predictors for the development of NAEs, and one of them was cART, which showed an inverse association with NAEs, particularly with renal and psychiatric events. Finally, our results suggest a decrease in the occurrence of NAEs over time in parallel to a documented earlier initiation of cART.

According to our data, clinicians should be aware that during the initial follow-up after HIV diagnosis, NAEs do occur and, as expected, older patients and those presenting with lower CD4 cell counts and higher viral load are at increased risk for their occurrence [6–10]. Additionally, we found novel sociodemographic factors to be inversely associated with NAEs, including a higher educational level and sexual transmission. A recent study has revealed an association between lower educational level and both, delayed HIV diagnosis and higher mortality rates [21], the two conditions potentially linked with a higher occurrence of NAEs. Also consistent with our results, sexual transmission has been related to earlier HIV diagnosis and lower mortality when compared to injection drug use, the alternative major HIV transmission route [21,22]. However, one of the most relevant findings from this contemporary study is the lower incidence of NAEs associated with exposure to cART, and the inverse relationship of cART with renal and psychiatric events. To the best of our knowledge, no beneficial effect of cART on different NAE categories had been demonstrated in cohort studies besides the Strategies for Management of Antiretroviral Therapy (SMART) trial [23], in which structured interruptions of therapy were associated with a higher incidence of several NAEs compared to continuous therapy.

Renal-related events were significantly less frequent among patients receiving cART. Whereas in previous cohorts reporting on incidence of NAEs, only end-stage renal disease/severe nephropathy [6,7], or chronic kidney disease [24] comprised this NAE category, we included a broader spectrum of renal disease, among which acute renal failure was the most common event. This probably contributes to explain the higher incidence of renal events found in our cohort in comparison with previous ones. Our findings support an overall beneficial effect of cART on renal complications of HIV disease that might well extend beyond HIV-associated nephropathy [25]. This study is also the first to show an inverse relationship between cART and psychiatric events occurrence in a prospective cohort. This was an unexpected finding, especially when the most common antiretroviral regimens in our cohort were based on efavirenz, an antiretroviral drug linked with central nervous system toxicity [26]. Data from experimental studies suggest that HIV *per se* and/or the associated inflammation may play an important role in HIV-associated depression [27], which turned out to be the most frequent psychiatric event in our cohort. Most investigations have focused on potential mechanisms linking inflammation-induced depression to tryptophan metabolism, as a reduction in the bioavailability of tryptophan could affect serotonergic neurotransmission in the brain leading to depressive symptoms [28]. As cART may downregulate the immune system in HIV-infected patients, it might also be expected to reduce the risk of depression.

The most common NAEs developing in the patients were psychiatric, hepatic, and neoplastic events. This is in contrast to earlier cohorts in which, apart from bacterial infections, the most frequent NAEs were malignancies and cardiovascular events [6,7,10]. Factors partially contributing to explain such differences might be the lower CD4 nadir achieved by the patients in the past, the higher toxicity of older antiretrovirals, both associated with the occurrence of malignancies and cardiovascular events, respectively [5,12,13,15,29,30], and the shorter follow-up period. Nevertheless, the comparison of the incidence of NAEs between different studies is complex due to the heterogeneous composition of each NAE class, differences in the definitions of the specific events, and even the absence of a consensus about the categories to be included under the term of NAE. Psychiatric events, the most frequent event category in our cohort, have scarcely been included among NAEs [2,6,9,31], although it was one of the causes of death in our patients. The second most frequent category was hepatic-related events, in spite of the lower prevalence of HCV infection in this cohort compared with older Spanish studies [32–34]. This is in agreement with the increase in the proportion of patients with HCV who develop cirrhosis, and in the cirrhosis-associated mortality described in recent years [35]. Likewise, an increase of HCV cirrhosis and its complications is projected to occur through the next decade [36]. A smaller percentage of patients were infected with hepatitis B virus, which might also have contributed to the liver-associated events. By contrast, cardiovascular events were visibly less frequent in our patients than in previous cohorts. Apart from the above mentioned factors, other issues probably contributing to this lower incidence were the younger age of the patients, the shorter follow-up compared with other cohorts, and the lower incidence of coronary heart disease in southern Europe compared with other western countries [37].

Although differences in data collection during the two periods preclude any conclusion to be drawn, we

observed that the incidence rate of NAEs during the last follow-up period (2008–2010) was lower than the incidence during the years following cohort initiation, a remarkable finding considering the prospective collection of events in recent years. Apart from reporting delay as one of the contributing factors, this may support the inverse relationship between NAEs and cART which, as we documented, was initiated earlier throughout the observation period. Accordingly, there was a concomitant decrease in AIDS events during the study. It is noteworthy the relatively elevated incidence rate of AIDS despite the contemporary nature of the cohort. Many AIDS events occurred within the first 3 months after the diagnosis of HIV infection, suggesting that they were late HIV diagnoses, a current prevalent and concerning issue [22,38,39] that has been particularly common in our cohort [40]. No differences were found in the proportion of 'late diagnoses', according to the above definition, between the periods 2004–2007 and 2008–2010.

Mortality among patients developing NAEs was significant, as it contributed to one-third of all deaths. Malignancies and liver-related were the most frequent NAEs-related death categories. Of concern, both were among the three most frequent NAEs occurring in the patients. This may suggest that, apart from the cART, additional strategies should be adopted during the initial care to contribute to reducing mortality in recently diagnosed HIV-infected patients, including a more exhaustive intervention on HCV, papillomavirus, and smoking habit among others.

Limitations of the study are the mentioned retrospective collection of NAEs until February 2008. Second, the observational nature of the study does not allow establishing a causal relationship between ART and the occurrence of NAEs with the statistical methods used herein. Marginal structural models constitute the methodological approach of choice to determine the effect of cART on the occurrence of NAEs for this cohort studies [41]. Additionally, no data were available of additional risk factors for the development of NAEs, such as cardiovascular risk factors or lifestyle issues, and the low number of events in some categories and the differences in their pathogenesis (i.e. in the non-AIDS-defining malignancies category) might not allow detecting some existing associations. The strengths are the contemporary nature of the cohort, with a majority of recently diagnosed patients, naive at entry, with comparable criteria for cART initiation as those currently used, and with most of the newest and less toxic antiretrovirals available. The high number of both, ART-naive patients and modern antiretroviral regimens, allowed us to show the association of cART with the incidence of NAEs in the current ART era. Additional strengths are the country representativeness of the cohort, the inclusion of a great majority of clinically overt events, the homogeneity of the NAEs included, with prespecified and precise diagnostic criteria followed by all the centers, and the inclusion of psychiatric events, which turned out to be the main cause of NAEs and had an inverse association with cART, hence warranting their inclusion from now among NAEs categories.

Conclusion

In conclusion, in patients newly diagnosed with HIV infection in the current era, NAEs are a frequent cause of morbidity and mortality during the initial follow-up, with a predominance of psychiatric, hepatic, malignant, and renal-related diseases. Our results suggest a beneficial effect of cART in the occurrence of NAEs, especially in psychiatric and renal related NAEs.

Acknowledgements

The present study would not have been possible without the collaboration of all the patients, medical and nursing staff, and data managers who have taken part in the project.

All authors contributed to preparation of the article. In addition, individual authors had the following contributions to the study: Study design was done by F.G., M.M., and J.A.; data entry and cleaning was done by D.A.; data analysis was done by S.P.; drafting of the article was done by M.M. and F.G. All authors reviewed and approved the final version of the article.

The authors would like to thank Inmaculada Jarrín for her help in the statistical analyses of data.

This work has been supported in part by Red Temática de Investigación Cooperativa en VIH/SIDA-Instituto de Salud Carlos III-RETIC RD06/0027, and Instituto de Salud Carlos III-FIS (PI081893).

Conflicts of interest

There are no conflicts of interest.

References

1. Deeks SG, Phillips AN. **HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity.** *BMJ* 2009; **338**:a3172; doi: 10.1136/bmj.a3172.
2. Neuhaus J, Angus B, Kowalska JD, La Rosa A, Sampson J, Wentworth D, *et al*. **Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV.** *AIDS* 2010; **24**:697–706.
3. Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, *et al*. **Class of antiretroviral drugs and the risk of myocardial infarction.** *N Engl J Med* 2007; **356**:1723–1735.
4. Obel N, Thomsen HF, Kronborg G, Larsen CS, Hildebrandt PR, Sorensen HT, *et al*. **Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study.** *Clin Infect Dis* 2007; **44**:1625–1631.
5. Crum-Cianflone N, Hullsiek KH, Marconi V, Weintrob A, Ganesan A, Barthel RV, *et al*. **Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study.** *AIDS* 2009; **23**:41–50.

6. Mocroft A, Reiss P, Gasiorowski J, Kowalska J, Chiesi A, Gatell J, *et al*. **Serious fatal and nonfatal non-AIDS-defining illnesses in Europe.** *J Acquir Immune Defic Syndr* 2010; **55**:262–270.
7. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, *et al*. **Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study.** *Clin Infect Dis* 2011; **53**:1130–1139.
8. Marin B, Thiébaut R, Bucher HC, Rondeau V, Costagliola D, Dorrucci M, *et al*. **Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy.** *AIDS* 2009; **23**:1743–1753.
9. Moore RD, Gebo KA, Lucas GM, Keruly JC. **Rate of comorbidities not related to HIV infection or AIDS among HIV-infected patients, by CD4 cell count and HAART use status.** *Clin Infect Dis* 2008; **47**:1102–1104.
10. Ferry T, Raffi F, Collin-Filleul F, Dellamonica P, Waldner A, Strady C, *et al*. **Uncontrolled viral replication as a risk factor for non-AIDS severe clinical events in HIV-infected patients on long-term antiretroviral therapy: APROCO/COPILOTE (ANRS CO8) cohort study.** *J Acquir Immune Defic Syndr* 2009; **51**:407–415.
11. Kaplan RC, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ, *et al*. **T cell activation and senescence predict subclinical carotid artery disease in HIV-infected women.** *J Infect Dis* 2011; **203**:452–463.
12. Krishnan S, Schouten JT, Jacobson DL, Benson CA, Collier AC, Koletar SL, *et al*. **Incidence of non-AIDS-defining cancer in antiretroviral treatment-naïve subjects after antiretroviral treatment initiation: an ACTG longitudinal linked randomized trials analysis.** *Oncology* 2011; **80**:42–49.
13. Kesselring A, Gras L, Smit C, van Twillert G, Verbon A, de Wolf F, *et al*. **Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy.** *Clin Infect Dis* 2011; **52**:1458–1465.
14. Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, *et al*. **Combination antiretroviral therapy and the risk of myocardial infarction.** *N Engl J Med* 2003; **349**:1993–2003.
15. Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simon A, *et al*. **Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4.** *Arch Intern Med* 2010; **170**:1228–1238.
16. Freiberg M, McGinnis K, Butt A, Goetz MB, Brown S, Oursler KA, *et al.* **HIV is associated with clinically confirmed myocardial infarction after adjustment for smoking and other risk factors** [abstract 809]. *Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections*; 2 March 2011; Boston, Massachusetts.
17. Caro-Murillo AM, Castilla J, Pérez-Hoyos S, Miró JM, Podzamczer D, Rubio R, *et al*. **Spanish cohort of naïve HIV-infected patients (CoRIS): rationale, organization and initial results.** *Enferm Infecc Microbiol Clin* 2007; **25**:23–31.
18. **1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.** *MMWR Recomm Rep* 1992; **41**:1–19.
19. Antiretroviral Therapy Cohort Collaboration. **Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies.** *Clin Infect Dis* 2010; **50**:1387–1396.
20. Hernando V, Sobrino-Vegas P, Burriel MC, Berenguer J, Navarro G, Santos I, *et al.* **Differences in the causes of death of HIV-positive subjects in a cohort study by data sources and coding algorithms**. *AIDS* 2012; **26**:1829–1834.
21. Sobrino-Vegas P, Rodríguez-Urrego J, Berenguer J, Caro-Murillo AM, Blanco JR, Viciana P, *et al*. **Educational gradient in HIV diagnosis delay, mortality, antiretroviral treatment initiation and response in a country with universal healthcare.** *Antivir Ther* 2012; **17**:1–8.
22. Grigoryan A, Hall HI, Durant T, Wei X. **Late HIV diagnosis and determinants of progression to AIDS or death after HIV diagnosis among injection drug users, 33 US States, 1996–2004.** *PLoS One* 2009; **4**:e4445.
23. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al*. **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006; **355**:2283–2296.
24. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, *et al*. **Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients.** *AIDS* 2010; **24**:1667–1678.
25. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. **Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study.** *AIDS* 2004; **18**:541–546.
26. Gutiérrez F, Navarro A, Padilla S, Antón R, Masiá M, Borrás J, *et al*. **Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring.** *Clin Infect Dis* 2005; **41**:1648–1653.
27. Lawson MA, Kelley KW, Dantzer R. **Intracerebroventricular administration of HIV-1 Tat induces brain cytokine and indoleamine 2,3-dioxygenase expression: a possible mechanism for AIDS comorbid depression.** *Brain Behav Immun* 2011; **25**:1569–1575.
28. Widner B, Laich A, Sperner-Unterweger B, Ledochowski M, Fuchs D. **Neopterin production tryptophan degradation and mental depression: what is the link?** *Brain Behav Immun* 2002; **16**:590–595.
29. Guiguet M, Boué F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. **Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study.** *Lancet Oncol* 2009; **10**:1152–1159.
30. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, *et al*. **Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study.** *J Infect Dis* 2010; **201**:318–330.
31. Wester CW, Koethe JR, Shepherd BE, Stinnette SE, Rebeiro PF, Kipp AM, *et al*. **Non-AIDS-defining events among HIV-1-infected adults receiving combination antiretroviral therapy in resource-replete versus resource-limited urban setting.** *AIDS* 2011; **25**:1471–1479.
32. Pérez Cachafeiro S, Del Amo J, Iribarren JA, Salavert M, Gutiérrez F, Moreno A, *et al*. **Decrease in serial prevalence of coinfection with hepatitis C virus among HIV-infected patients in Spain, 1997–2006.** *Clin Infect Dis* 2009; **48**:1467–1470.
33. Roca B, Suarez I, Gonzalez J, Garrido M, de la Fuente B, Teira R, *et al*. **Hepatitis C virus and human immunodeficiency virus coinfection in Spain.** *J Infect* 2003; **47**:117–124.
34. Gutiérrez F, Padilla S, Masiá M, Iribarren JA, Moreno S, Viciana P, *et al*. **Patients' characteristics and clinical implications of suboptimal CD4 T-cell gains after 1 year of successful antiretroviral therapy.** *Curr HIV Res* 2008; **6**:100–107.
35. Kanwal F, Hoang T, Kramer JR, Asch SM, Goetz MB, Zeringue A, *et al*. **Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection.** *Gastroenterology* 2011; **140**:1182–1188.
36. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. **Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression.** *Gastroenterology* 2010; **138**:513–521.
37. Marín A, Medrano MJ, González J, Pintado H, Compaired V, Bárcena M, *et al*. **Risk of ischaemic heart disease and acute myocardial infarction in a Spanish population: observational prospective study in a primary-care setting.** *BMC Public Health* 2006; **6**:38.
38. Johnson M, Sabin C, Girardi E. **Definition and epidemiology of late presentation in Europe.** *Antivir Ther* 2010; **15 (Suppl 1)**: 3–8.
39. Girardi E, Sabin CA, Monforte AD. **Late diagnosis of HIV infection: epidemiological features, consequences and strategies to encourage earlier testing.** *J Acquir Immune Defic Syndr* 2007; **46 (Suppl 1)**:S3–8.
40. Sobrino-Vegas P, García-San Miguel L, Caro-Murillo AM, Miró JM, Viciana P, Tural C, *et al*. **Delayed diagnosis of HIV infection in a multicenter cohort: prevalence, risk factors, response to HAART and impact on mortality.** *Curr HIV Res* 2009; **7**:224–230.
41. Cole SR, Hernán MA, Robins JM, Anastos K, Chmiel J, Detels R, *et al*. **Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models.** *Am J Epidemiol* 2003; **158**:687–694.