ORIGINAL RESEARCH

Analysis of serious non-AIDS events among HIV-infected adults at Latin American sites

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Objective

Acquired immune deficiency appears to be associated with serious non-AIDS (SNA)-defining conditions such as cardiovascular disease, liver and renal insufficiency and non-AIDS-related malignancies. We analysed the incidence of, and factors associated with, several SNA events in the LATINA retrospective cohort.

Materials and methods

Cases of SNA events were recorded among cohort patients. Three controls were selected for each case from cohort members at risk. Conditional logistic models were fitted to estimate the effect of traditional risk factors as well as HIV-associated factors on non-AIDS-defining conditions.

Results

Among 6007 patients in follow-up, 130 had an SNA event (0.86 events/100 person-years of follow-up) and were defined as cases (40 with cardiovascular events, 54 with serious liver failure, 35 with non-AIDS-defining malignancies and two with renal insufficiency). Risk factors such as diabetes, hepatitis B and C virus coinfections and alcohol abuse showed an association with events, as expected. The last recorded CD4 T-cell count prior to index date ($P = 0.0056$, with an average difference of more than 100 cells/μL) and area under the CD4 cell curve in the year previous to index date ($P = 0.0081$) were significantly lower in cases than in controls. CD4 cell count at index date was significantly associated with the outcome after adjusting for risk factors.

Conclusions

The incidence and type of SNA events found in this Latin American cohort are similar to those reported in other regions. We found a significant association between immune deficiency and the risk of SNA events, even in patients under antiretroviral treatment.

Introduction

The use of combination antiretroviral therapy (cART) has dramatically changed the clinical course and prognosis of HIV infection [1–4]. There is increasing recognition of the contribution of serious conditions not classically recog-

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nized as AIDS-related to the morbidity and mortality of HIV-infected individuals. Among those conditions, cardiovascular disease (including stroke), liver and renal insufficiency and non-AIDS-defining cancer are of particular relevance because of their high prevalence. In contrast to the classical HIV-related events, which are usually seen at low CD4 T-cell counts, the so-called serious non-AIDS (SNA) events can be seen over a broad range of CD4 cell counts. Congruent data from cohorts and clinical

trials have shown a reduction in the risk of SNA events with the current use of cART, even at CD4 cell counts above the current thresholds for treatment initiation [5–14]. This fact is of particular relevance in the discussion of when to start antiretroviral therapy, as morbidity and mortality among patients with CD4 cell counts >350 cells/μL are largely driven by non-AIDS-defining conditions [15–16].

Large cohort studies such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) collaboration and CASCADE showed that the rates of death from all causes, from hepatic causes and from non-AIDS-defining malignancies were higher in patients with lower CD4 cell counts [8,11,12].

In the SMART trial, a greater number of SNA events were observed in patients interrupting antiretroviral treatment and having, on average, lower CD4 cell counts [13]. Similarly, in the FIRST study, an increased risk of SNA events was observed in patients with more pronounced immunodeficiency under stable cART [17].

Many Latin American countries share a longstanding history of provision of care and antiretroviral treatment to people in need, and the availability of information regarding the characteristics of clinical events in HIV-infected patients is crucial for the future optimization and expansion of these policies, in particular considering that some of the currently used antiretrovirals have toxicities whose clinical manifestation resemble immunodeficiency driven SNA events [18–20]. However, the problem of late diagnosis may be associated with an increased prevalence of SNA events as many patients obtain access to care and treatment with low CD4 cell counts.

This study describes the frequency and type of SNA events in patients with HIV infection followed at the Latin American sites participating in the LATINA cohort, and investigates the specific factors associated with the risk of these events.

Materials and methods

The LATINA retrospective cohort

The LATINA cohort is a multinational initiative, the aim of which is to provide direct information about the clinical characteristics of the HIV/AIDS epidemics within the Latin American region. Although a wide range of epidemiological data has been collected regularly by national AIDS programmes, there is almost no previous experience in systematic collection of clinical features and therapeutic results for HIV-infected patients in Latin America [21]. A retrospective cohort study was designed for the present project. Inclusion criteria were as follows: the patient had their first medical visit to a participating cohort site between 1 January 1997 and 31 December 2007, had attended at least two clinical visits at the site, and was at least 16 years old at the baseline visit. By February 2008, LATINA included patients from one site in Brazil (1030 patients), one site in Mexico (1297 patients), one site in Peru (231 patients) and five sites in Argentina (3449 patients).

Through full review of patient medical charts, all incident cases of SNA events were identified as being any of the following: acute myocardial infarction (MI), cardiovascular disease requiring an invasive procedure (coronary artery bypass graft, angioplasty, stent placement or endarterectomy), stroke, terminal liver failure or cirrhosis, renal insufficiency requiring dialysis or kidney transplant and non-AIDS-defining malignancies. Each site sent a checklist of supporting evidence for each SNA and the diagnostic certainty was established centrally through a set of standardized diagnostic criteria (see Appendix A1). A case was defined as any patient with an SNA event while in follow-up at any of the network sites and who did not have a history of this type of event before the baseline visit. The 'index date' for a case was defined as the work-up date of the first SNA event. Two analyses were considered; one including both confirmed and probable cases and another considering only confirmed cases.

For each case, corresponding controls with no previous history of SNA events were randomly selected, without replacement, from cohort members at risk at the case 'index date' using an incidence density sampling scheme [22]. Each case was matched with three controls of the same site, gender and age-group stratum (age at index date <30 years, between 30 and 39 years, between 40 and 49 years, and ≥ 50 years).

Retrospective data were collected for both cases and controls using standardized case report forms. Data included mode of transmission, race, history of opportunistic infections and SNAs, comorbidities occurring at any time since HIV diagnosis (diabetes mellitus, smoking, hyperlipidaemia, alcohol abuse, hepatitis B and hepatitis C), antiretroviral treatments, and laboratory data (CD4 cell counts and HIV viral load).

Diabetes mellitus was defined by antidiabetic drug use, at least two glucose values of >126 mg/dL or an abnormal glucose tolerance test; hyperlipidaemia was defined by: 1) use of lipid lowering agents or at least two total cholesterol values >240 mg/dl, or 2) at least two low-density lipoprotein (LDL) cholesterol values >160 mg/dl, or 3) at least two high-density lipoprotein (HDL) cholesterol values <40 mg/dl; alcohol abuse was defined as a history of admission because of alcohol-related conditions or a history of alcohol consumption that compromises daily activities; hepatitis B and C virus (HBV and HCV) infections

were defined as the presence of positive confirmation serologies or viral load.

Exposure was assessed for the controls and the case at the same point in time relative to baseline (i.e. controls were assigned 'index dates' similar to those of the corresponding cases), and within 1 year before the index date. Different laboratory markers were analysed at the index date; for example, the latest recorded viral load and CD4 cell count values; the rate of change in CD4 cell counts, defined as the difference in the two latest recorded CD4 cell counts divided by the time elapsed between them, and the area under the CD4 cell count curve during the last year prior to the index date. Additionally, the history of AIDS events prior to the index date was captured in the following variables: having had opportunistic infections ever, years from last AIDS event to index date and incidence of AIDS events since HIV diagnosis to index date (1/person-years of follow-up).

Exposure to antiretroviral treatment by the index date was summarized using different variables in order to capture the history of antiretroviral treatments: ever received antiretroviral treatment, on treatment at index date, ever received abacavir during the prior 6 months, time elapsed since treatment initiation (in months), percentage of time off treatment since starting antiretroviral treatment, and maximum period (in months) off antiretroviral treatment. The patient's cumulative exposure to specific antiretroviral drugs was defined as: number of months receiving nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), abacavir or stavudine.

Both the retrospective cohort and the current project were approved by corresponding Institutional Review Boards.

Statistical analysis

Four different outcomes were analysed: all SNA cases, cardiovascular events, terminal liver failure or cirrhosis and non-AIDS-defining malignancies. Conditional logistic regression models (univariate and multivariate) were fitted to investigate the relationship between the risk of an SNA event and the recorded factors (PHREG procedure, SAS, version 9.1; SAS Institute, Cary, NC, USA). Under the sampling scheme used to select controls, the proportional hazards model has been shown to produce consistent estimates of the relative risks [23,24].

Results are presented as odds ratios (OR) and 95% confidence interval (CI) estimates. Stepwise forward selection was used to select independent predictors of the event occurrence, with 0.50 and 0.15 as P-values for entry into the model and being retained in the model, respectively. Known recorded risk factors for the SNA

events were forced into the model [25]. Thus, smoking status, diabetes mellitus and hyperlipidaemia were forced into the cardiovascular events model; hyperlipidaemia, HBV and HBC coinfections and alcohol abuse were forced into the model for terminal liver conditions; and smoking status was forced into the non-AIDS malignancies model. All of the former factors were forced into the model that estimated risk for SNA as a composite outcome. In addition, the indicator of ever received antiretroviral treatment was always forced into the models because all the variables associated with antiretroviral treatment were defined as interactions; i.e. 0 or missing if never treated. The following variables were considered as potential predictors: race, mode of transmission, HIV infection history, immunological factors and exposure to antiretroviral treatment. Although age and gender are known to be associated with most non-AIDS events, they were not included in the models because they were used as matching variables.

Results

As of February 2008, 6007 patients had been included in the LATINA retrospective cohort, with a mean of 3.2 years and a median of 2.5 years of follow-up. Of the 6007 patients, 30% were women and 21% had a history of AIDS-defining conditions before the baseline visit. The incidence of AIDS events was 4.7 per 100 person-years of follow-up.

A total of 130 patients had an SNA event (94 confirmed and 36 probable) and were defined as cases, with an incidence rate of 8.6 events per 1000 person-years (95% CI 7.2, 10.0).

Twenty-eight of these patients (21%) were female. Forty patients (30.7%) had a cardiovascular condition [11 had an MI (five confirmed), 13 had cardiovascular disease requiring an invasive procedure and 16 had a stroke (nine confirmed); incidence of cardiovascular events: 2.2 events per 1000 person-years (95% CI 1.5, 2.9)]; 54 patients (41.5%) had liver failure/cirrhosis (34 confirmed) [incidence: 2.9 events per 1000 person-years (95% CI 2.1, 3.7)]; 35 patients (27%) had a non-AIDS-defining malignancy (34 confirmed) [incidence 1.9 events per 1000 person-years (95% CI 1.2, 2.5)] and two (1.5%) had terminal renal insufficiency (both confirmed). One patient experienced simultaneously a liver failure and a cardiovascular disease. The median time of follow-up until the index date for cases and controls was 1.42 and 2.45 years, respectively (P = 0.12; univariate conditional logistic regression).

Univariate analyses

Table 1 compares the general characteristics of all cases and controls. The frequency of injecting drug use was

significantly higher in the cases ($P = 0.001$), as were the frequencies of histories of some traditional risk factors such as HCV coinfection ($P < 0.001$), HBV coinfection ($P = 0.017$), diabetes ($P = 0.001$) and alcohol abuse ($P = 0.016$). The frequencies of indicators of immunological status at index date were significantly lower in the cases. Last recorded CD4 cell count prior to index date ($P = 0.0056$, with an average difference of > 100 cells/μL; not shown) and area under the CD4 cell curve in the year previous to the index date ($P = 0.0081$) were significantly different between cases and controls. The distribution of CD4 cell counts at the index date showed significant differences between cases and controls.

Table 2 shows a similar univariate analysis considering cases of cardiovascular disease. As expected, diabetes mellitus was more frequent among the cases (OR = 13.1; $P = 0.001$). In this pathology group, HIV history, measured as either a history of AIDS (OR = 2.35, $P = 0.051$) or the AIDS event incidence per year since HIV diagnosis (OR = 1.57, $P = 0.052$), and recent abacavir use (OR = 3.0, $P = 0.052$) were associated

Table 1 Characteristics of the cases ($n = 130$) and controls ($n = 390$)

Variable*	Cases	Controls	OR[†]	95% CI	P-value
Categorical variables					
Mode of transmission[‡] [n (%)]					
Heterosexual	65 (50)	189 (48.5)			
Homosexual/bisexual	41 (31.5)	165 (42.3)	0.64	(0.38, 1.08)	0.095
Parenteral	19 (14.6)	17 (4.4)	3.86	(1.72, 8.66)	0.001
Unknown/other	5 (3.9)	19 (4.9)	0.67	(0.23, 1.97)	0.470
Risk factor [n (%)]					
HBV coinfection	36 (27.7)	71 (18.2)	1.81	(1.11, 2.95)	0.017
HCV coinfection	39 (30.0)	33 (8.5)	7.01	(3.61, 13.6)	<0.001
Drug abuse	22 (16.9)	51 (13.1)	1.38	(0.79, 2.41)	0.264
Alcohol abuse	30 (23.1)	56 (14.4)	1.93	(1.13, 3.29)	0.016
Current smoker	36 (27.7)	95 (24.4)	1.21	(0.76, 1.94)	0.427
Diabetes	15 (11.5)	13 (3.3)	4.02	(1.79, 9.03)	0.001
Hyperlipidaemia	38 (29.2)	85 (21.8)	1.51	(0.95, 2.39)	0.080
HIV history [n (%)]					
Ever history of AIDS	48 (36.9)	121 (31.0)	1.34	(0.86, 2.07)	0.193
Immune status					
CD4 cell count at index date [n (%)]					
> 500 cells/μL	23 (17.7)	140 (35.9)			
350–500 cells/μL	29 (22.3)	82 (21.0)	2.48	(1.31, 4.69)	0.005
200–349 cells/μL	31 (23.8)	101 (25.9)	2.20	(1.18, 4.08)	0.013
< 200 cells/μL	47 (36.2)	67 (17.2)	5.78	(2.99, 11.2)	<0.0001
ARV treatment [n (%)]					
Ever ARV treatment	105 (80.8)	311 (79.7)	1.07	(0.64, 1.80)	0.793
ARV treatment at index date	88 (67.7)	270 (69.2)	0.93	(0.60, 1.43)	0.739
Recent abacavir use (last 6 months)	18 (13.8)	39 (10.0)	1.47	(0.79, 2.71)	0.218
Numerical variables [mean (SD)]					
Years since HIV diagnosis	5.82 (4.60)	5.19 (4.21)	1.04	(0.99, 1.09)	0.125
HIV history					
Years since last AIDS event[§]	1.27 (2.55)	1.07 (2.10)	1.04	(0.95, 1.13)	0.376
AIDS event incidence/person-years follow-up	0.27 (0.91)	0.21 (0.75)	1.08	(0.85, 1.37)	0.509
Last recorded VL log	2.89 (1.40)	2.80 (1.29)	1.06	(0.90, 1.26)	0.469
Immune status					
CD4 cell area under the curve (last year)[1]	320 (233)	428 (246)	0.77	(0.68, 0.86)	<0.001
CD4 cell count at ARV start (cells/μL)[¶1]	202 (162)	248 (206)	0.85	(0.68, 1.05)	0.137
ARV treatment					
Months since ARV treatment start[¶2]	42.7 (38.0)	38.2 (34.0)	1.04	(0.94, 1.14)	0.448
% time off ARV treatment[¶]	8.4 (21.4)	6.5 (17.6)	1.01	(0.99, 1.02)	0.414
Months on stavudine[¶2]	14.4 (25.6)	10.3 (19.9)	1.09	(0.97, 1.21)	0.129
Months on NNRTI[¶2]	14.1 (21.9)	14.4 (21.1)	0.97	(0.84, 1.11)	0.665
Months on PI[¶2]	19.7 (28.1)	16.2 (24.1)	1.05	(0.95, 1.17)	0.326

*All variables defined until index date.
[†]Crude (nonadjusted) OR estimated under a conditional logistic model.
[‡]OR estimated using heterosexual as the reference category.
[§]Among those who had a previous AIDS event.
[¶]Among those who started antiretroviral treatment.
[1]OR for 100 CD4 count cells/μL.
[2]OR for 1 year change.
ARV, antiretroviral; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; VL, viral load.

Table 2 Characteristics of the cases ($n = 40$) and controls ($n = 120$) who experienced cardiovascular events

Variable*	Cases	Controls	OR[†]	95% CI	P-value
Categorical variables					
Mode of transmission[‡] [n (%)]					
Heterosexual	19 (47.5)	61 (50.8)			
Homosexual/bisexual	17 (42.5)	48 (40)	1.22	(0.49, 3.03)	0.670
Parenteral	2 (5.0)	3 (2.5)	3.77	(0.28, 49.9)	0.314
Unknown/other	2 (5.0)	8 (6.7)	0.70	(0.12, 4.23)	0.701
Risk factors [n (%)]					
HBV coinfection	7 (17.5)	17 (14.2)	1.29	(0.49, 3.42)	0.606
HCV coinfection	4 (10)	5 (4.2)	2.64	(0.65, 10.8)	0.177
Drug abuse	3 (7.5)	9 (7.5)	1.00	(0.24, 4.18)	1.000
Alcohol abuse	3 (7.5)	8 (6.7)	1.14	(0.27, 4.75)	0.853
Current smoker	10 (25)	28 (23.3)	1.12	(0.44, 2.84)	0.811
Diabetes	10 (25)	4 (3.3)	13.14	(2.85, 60.6)	0.001
Hyperlipidaemia	15 (37.5)	28 (23.3)	2.17	(0.93, 5.04)	0.073
HIV history [n (%)]					
Ever history of AIDS	17 (42.5)	33 (27.5)	2.35	(1.00, 5.54)	0.051
Immune status					
CD4 cell count at index date [n (%)]					
> 500 cells/μL	8 (20.0)	47 (39.2)			
350–500 cells/μL	7 (17.5)	24 (20.0)	1.83	(0.60, 5.54)	0.286
200–350 cells/μL	12 (30.0)	32 (26.7)	2.84	(0.99, 8.09)	0.051
< 200 cells/μL	13 (32.5)	17 (14.2)	6.47	(1.94, 21.5)	0.002
ARV treatment [n (%)]					
Ever ARV treatment	35 (87.5)	96 (80)	1.85	(0.61, 5.62)	0.278
ARV treatment at index date	28 (70)	85 (70.8)	0.96	(0.44, 2.10)	0.920
Recent abacavir use (last 6 months)	7 (17.5)	8 (6.7)	3.00	(1.00, 9.09)	0.052
Numerical variables [mean (SD)]					
Years since HIV diagnosis	4.8 (3.9)	5.1 (4.2)	0.98	(0.89, 1.08)	0.658
HIV history					
Years since last AIDS event[§]	1.50 (2.96)	1.02 (2.19)	1.08	(0.94, 1.23)	0.292
AIDS event incidence/person-years follow-up	0.58 (1.53)	0.17 (0.61)	1.57	(1.00, 2.48)	0.052
Last recorded VL log	2.59 (1.33)	2.72 (1.34)	0.96	(0.70, 1.31)	0.796
Immune status					
CD4 cell area under the curve (last year)[1]	345 (226)	449 (243)	0.75	(0.61, 0.93)	0.008
CD4 cell count at ARV start (cells/μL)[¶1]	202 (158)	273 (225)	0.84	(0.58, 1.23)	0.377
ARV treatment					
Months since ARV treatment start[¶2]	42.5 (40.4)	37.4 (34.9)	0.98	(0.83, 1.14)	0.764
% time off ARV treatment[¶]	8.7 (23.2)	4.2 (14.4)	1.01	(0.99, 1.03)	0.243
Months on stavudine[¶2]	16.8 (28.9)	8.9 (19.0)	1.13	(0.94, 1.35)	0.187
Months on NNRTI[¶2]	12.0 (17.3)	16.0 (25.1)	0.84	(0.65, 1.07)	0.157
Months on PI[¶2]	25.1 (34.2)	16.7 (25.6)	1.05	(0.90, 1.23)	0.512

*All variables defined until index date.
[†]Crude (nonadjusted) OR estimated under a conditional logistic model.
[‡]OR estimated using heterosexual as the reference category.
[§]Among those who had a previous AIDS event.
[¶]Among those who started ARV treatment.
[1]OR for 100 CD4 count cells/μL.
[2]OR for 1 year change.
ARV, antiretroviral; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; VL, viral load.

with the outcome. Immunological variables showed the same pattern as found in the analysis of all the cases.

Table 3 shows the univariate approach for the liver disease outcome. Known risk factors such as HBV coinfection (OR = 2.5, $P = 0.011$), HCV coinfection (OR = 16.6, $P < 0.001$), alcohol abuse (OR = 2.9, $P = 0.003$) and parenteral mode of transmission (OR = 4.6, $P = 0.003$) were significantly associated with the risk of a severe liver condition. Again, significantly lower CD4 cell counts were observed in the cases. As expected, HCV and HBV

coinfections were both strongly associated with parenteral mode of transmission (data not shown).

Finally, the same analytical approach for the subgroup of non-AIDS-related malignancies (depicted in Table 4) showed that no variable was significantly associated with the outcome, although immune-related variables showed the same pattern as described above.

In addition, some other variables were considered in either the general or the particular analysis (e.g. race, undetectable viral load at index date, abacavir use and

Table 3 Characteristics of the cases ($n = 54$) and controls ($n = 162$) with terminal liver failure or cirrhosis

Variable*	Cases	Controls	OR[‡]	95% CI	P-value
Categorical variables					
Mode of transmission[‡] [n (%)]					
Heterosexual	25 (46.3)	77 (47.5)			
Homosexual/bisexual	12 (22.2)	70 (43.2)	0.39	(0.15, 1.03)	0.057
Parenteral	1 (1.9)	4 (2.5)	4.56	(1.66, 12.5)	0.003
Unknown/other	16 (29.6)	11 (6.8)	0.51	(0.04, 6.52)	0.601
Risk factors [n (%)]					
HBV coinfection	23 (42.6)	40 (24.7)	2.48	(1.23, 4.97)	0.011
HCV coinfection	32 (59.3)	22 (13.6)	16.60	(5.81, 47.8)	<.001
Drug abuse	17 (31.5)	33 (20.4)	1.78	(0.89, 3.52)	0.101
Alcohol abuse	21 (38.9)	29 (17.9)	2.89	(1.45, 5.76)	0.003
Current smoker	18 (33.3)	39 (24.1)	1.60	(0.81, 3.17)	0.176
Diabetes	3 (5.6)	6 (3.7)	1.56	(0.36, 6.67)	0.551
Hyperlipidaemia	12 (22.2)	37 (22.8)	0.96	(0.45, 2.07)	0.923
HIV history [n (%)]					
Ever history of AIDS	33 (61.1)	51 (31.5)	1.41	(0.73, 2.74)	0.305
Immune status					
CD4 cell count at index date [n (%)]					
> 500 cells/μL	7 (13.0)	59 (36.4)			
350–500 cells/μL	15 (27.8)	32 (19.8)	5.74	(1.87, 17.6)	0.002
200–350 cells/μL	11 (20.4)	45 (27.8)	2.57	(0.87, 7.58)	0.086
< 200 cells/μL	21 (38.9)	26 (16)	11.81	(3.66, 38.1)	<.0001
ARV treatment [n (%)]					
Ever ARV treatment	44 (81.5)	127 (78.4)	1.26	(0.53, 2.94)	0.601
ARV treatment at index date	36 (66.7)	107 (66.0)	1.03	(0.53, 2.02)	0.932
Recent abacavir use (last 6 months)	4 (7.4)	16 (9.9)	0.74	(0.24, 2.27)	0.594
Numerical variables [mean (SD)]					
Years since HIV diagnosis	6.52 (4.91)	5.37 (4.38)	1.07	(0.99, 1.15)	0.084
HIV history[§]					
Years since last AIDS event[§]	1.11 (2.11)	1.23 (2.27)	0.97	(0.84, 1.13)	0.717
AIDS event incidence/person-years follow-up	0.16 (0.39)	0.20 (0.79)	0.92	(0.56, 1.51)	0.735
Last recorded VL log	3.12 (1.44)	2.78 (1.26)	1.21	(0.93, 1.56)	0.152
Immune status					
CD4 cell area under the curve (last year)[1]	300 (231)	422 (232)	0.70	(0.57, 0.86)	0.001
CD4 cell count at ARV start (cells/μL)[¶1]	211 (209)	235 (210)	0.89	(0.65, 1.21)	0.452
ARV treatment	42.8 (33.6)	39.0 (33.8)	1.01	(0.86, 1.18)	0.902
Months since ARV treatment start[¶2]	42.8 (33.6)	39.0 (33.8)	1.01	(0.86, 1.18)	0.902
% time off ARV treatment[¶]	11.3 (24.9)	7.7 (17.6)	1.01	(0.99, 1.02)	0.419
Months on stavudine[¶2]	13.7 (24.3)	11.5 (21.7)	1.05	(0.88, 1.23)	0.588
Months on NNRTI[¶2]	17.4 (25.1)	14.3 (20.0)	1.06	(0.86, 1.30)	0.607
Months on PI[¶2]	17.7 (24.8)	16.9 (23.9)	1.02	(0.85, 1.20)	0.879

*All variables defined until index date.
[†]Crude (nonadjusted) OR estimated under a conditional logistic model.
[‡]OR estimated using heterosexual as the reference category.
[§]Among those who had a previous AIDS event.
[¶]Among those who started ARV treatment.
[1]OR for 100 CD4 count cells/μL.
[2]OR for 1 year change.
ARV, antiretroviral; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; VL, viral load

maximum time off antiretroviral treatment) and showed no statistically significant differences between groups (data not shown).

Multivariate analyses

To determine the independent predictive value of the selected variables for the analysed outcomes, stepwise variable selection under a conditional logistic regression model was performed. Measured traditional risk factors for the SNA events were forced into the models. Table 5a presents the final model for the risk of any type of non-AIDS event. After adjusting for smoking status, diabetes mellitus, hyperlipidaemia, HCV and HBV coinfection and alcohol abuse, only the last recorded CD4 cell count prior to the index date was found to be an independent predictor of risk ($P < 0.0001$). A 100 cell/μL lower CD4 cell count at the index date produced a 30% increase in the odds of SNA

Table 4 Characteristics of the cases ($n = 35$) and controls ($n = 105$) with non-AIDS-defining malignancies

Variables*	Cases	Controls	OR[†]	95% CI	*P*-value
Categorical variables					
Mode of transmission[‡] [*n* (%)]					
Heterosexual	20 (57.1)	49 (46.7)			
Homosexual/bisexual	12 (34.3)	46 (43.8)	0.59	(0.24, 1.43)	0.242
Parenteral	2 (5.7)	7 (6.7)	0.82	(0.08, 8.05)	0.863
Unknown/other	1 (2.9)	3 (2.9)	0.70	(0.14, 3.49)	0.665
Risk factors [*n* (%)]					
HBV coinfection	7 (20)	15 (14.3)	1.55	(0.55, 4.37)	0.408
HCV coinfection	3 (8.6)	7 (6.7)	1.34	(0.31, 5.85)	0.696
Drug abuse	2 (5.7)	8 (7.6)	0.74	(0.15, 3.63)	0.707
Alcohol abuse	5 (14.3)	18 (17.1)	0.75	(0.21, 2.60)	0.648
Current smoker	8 (22.9)	29 (27.6)	0.77	(0.30, 1.93)	0.575
Diabetes	2 (5.7)	3 (2.9)	2.00	(0.33, 11.9)	0.448
Hyperlipidaemia	10 (28.6)	22 (21)	1.46	(0.63, 3.35)	0.373
HIV history [*n* (%)]					
Ever history of AIDS	9 (25.7)	38 (36.2)	0.60	(0.25, 1.43)	0.252
Immune status					
CD4 cell count at index date [*n* (%)]					
> 500 cells/μL	8 (22.9)	34 (32.4)			
350–500 cells/μL	6 (17.1)	25 (23.8)	1.05	(0.30, 3.68)	0.934
200–350 cells/μL	8 (22.9)	22 (21.0)	1.57	(0.51, 4.82)	0.436
< 200 cells/μL	13 (37.1)	24 (22.9)	2.54	(0.84, 7.67)	0.098
ARV treatment [*n* (%)]					
Ever ARV treatment	25 (71.4)	85 (81.0)	0.60	(0.25, 1.43)	0.249
ARV treatment at index date	23 (65.7)	75 (71.4)	0.77	(0.34, 1.74)	0.523
Recent abacavir use (last 6 months)	6 (17.1)	11 (10.5)	1.83	(0.59, 5.65)	0.292
Numerical variables [mean (SD)]					
Years since HIV diagnosis	5.7 (4.8)	5.1 (4.2)	1.03	(0.94, 1.13)	0.477
HIV history					
Years since last AIDS event[§]	0.92 (2.22)	0.97 (1.79)	0.99	(0.81, 1.21)	0.897
AIDS event incidence/person-years follow-up	0.09 (0.19)	0.29 (0.83)	0.39	(0.08, 1.71)	0.212
Last recorded VL log	2.89 (1.38)	2.94 (1.29)	1.00	(0.71, 1.41)	0.998
Immune status					
CD4 cell area under the curve (last year)[1]	325 (255)	414 (272)	0.86	(0.72, 1.02)	0.086
CD4 cell count at ARV start (cells/μL)[¶1]	206 (91)	222 (175)	0.85	(0.48, 1.48)	0.563
ARV treatment					
Months since ARV treatment start[¶2]	39.3 (41.4)	37.4 (33.7)	1.10	(0.92, 1.32)	0.294
% time off ARV treatment[¶]	4.1 (11.3)	6.6 (20.1)	0.99	(0.96, 1.02)	0.555
Months on stavudine[¶2]	9.6 (18.3)	9.7 (17.7)	1.00	(0.76, 1.31)	0.989
Months on NNRTI[¶2]	12.2 (21.6)	14.2 (19.6)	1.02	(0.75, 1.38)	0.926
Months on PI[¶2]	15.0 (24.7)	14.1 (22.5)	1.09	(0.86, 1.37)	0.487

*All variables defined until index date.
[†]Crude (nonadjusted) OR estimated under a conditional logistic model.
[‡]OR estimated using heterosexual as the reference category.
[§]Among those who had a previous AIDS event.
[¶]Among those who started ARV treatment.
[1]OR for 100 CD4 count cells/μL.
[2]OR for 1 year change.
ARV, antiretroviral; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; SD, standard deviation; VL, viral load.

events. The only other covariate that marginally increased the risk of SNAs was time on stavudine.

We also assessed whether the same factors were independent predictors of risk for each of the subgroups of SNA pathologies. Table 5b shows the final model of the conditional logistic regression analysis for cases of cardiovascular events. After adjusting for smoking status, diabetes mellitus and hyperlipidaemia, CD4 cell count at the index date remained as an independent predictor of risk

($P = 0.006$). Cumulative exposure to stavudine increased the risk of cardiovascular events (OR = 1.04, $P = 0.006$); i.e. 1 more month on stavudine increased the odds of a cardiovascular event by 4%. In addition, the percentage of time off treatment once antiretroviral treatment had started increased the risk of a cardiovascular event (OR = 1.02, $P = 0.049$). Years since HIV diagnosis appeared to have a protective effect, probably indicating a selection bias in the sense that patients with higher risk of these events or

Table 5 Conditional logistic regression selected model. (a) All cases; (b) those with cardiovascular events; (c) those with liver disease; (d) those with non-AIDS malignancies

Variable	OR*	(95% CI)	P-value
(a)			
Ever ARV treatment	0.88	(0.48, 1.62)	0.688
Current smoker	0.98	(0.56, 1.72)	0.947
Diabetes	3.79	(1.54, 9.32)	0.004
Hyperlipidaemia	1.90	(1.10, 3.27)	0.021
HCV coinfection	6.41	(3.04, 13.5)	<0.0001
HBV coinfection	1.43	(0.79, 2.58)	0.242
Alcohol abuse	1.33	(0.71, 2.48)	0.376
Months on stavudine[†]	1.11	(0.97, 1.26)	0.114
Last recorded CD4 cell value[‡]	0.77	(0.69, 0.87)	<0.0001
(b)			
Ever ARV treatment	1.20	(0.32, 4.49)	0.785
Current smoker	1.47	(0.45, 4.81)	0.521
Diabetes	20.2	(3.4, 119.9)	0.001
Hyperlipidaemia	3.09	(1.00, 9.55)	0.050
Years since HIV diagnosis	0.82	(0.68, 0.98)	0.031
Months on stavudine[†]	1.60	(1.16, 2.21)	0.004
% time off ARV treatment	1.02	(1,00, 1.04)	0.049
Last recorded CD4 cell value[‡]	0.72	(0.57, 0.91)	0.006
(c)			
Ever ARV treatment	0.91	(0.29, 2.83)	0.876
Hyperlipidaemia	1.01	(0.37, 2.79)	0.981
HBV coinfection	1.37	(0.53, 3.50)	0.508
HCV coinfection	16.7	(4.95, 56.2)	<0.0001
Alcohol abuse	1.86	(0.75, 4.62)	0.183
Last recorded CD4 cell value[‡]	0.68	(0.53, 0.87)	0.003
(d)			
Ever ARV treatment	0.69	(0.25, 1.83)	0.455
Current smoker	0.39	(0.11, 1.30)	0.124
Hyperlipidaemia	2.49	(0.94, 6.57)	0.066
HBV coinfection	3.22	(0.82, 12.6)	0.094
Ever history of AIDS	0.43	(0.16, 1.16)	0.094
Last recorded CD4 cell value[‡]	0.78	(0.63, 0.96)	0.020

*Adjusted OR.
[†]OR per 1-year increment.
[‡]OR per CD4 cell count 100 cells/µL increment.
ARV, antiretroviral; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.

longer follow-up times are those who are followed. Table 5c shows the final selected model for the subgroup of patients who had severe liver diseases and their controls. After adjusting for hyperlipidaemia, HBV and HCV coinfection and alcohol abuse, the only prognostic factor of the outcome was CD4 cell count prior to the index date (OR = 0.996, P = 0.003). Finally, the outcome of non-AIDS-related malignancy was not clearly associated with any of the potential prognostic factors selected (Table 5d), and again CD4 cell count was associated with the outcome. OR estimates were similar when we considered models excluding factors not significantly associated with the outcome (results not shown).

A second analysis was performed considering only the 94 confirmed cases and their corresponding 282 controls (results not shown), and this yielded essentially the same conclusions as described above.

Discussion

The overall findings of this study of the LATINA cohort confirm previous published data from the Northern Hemisphere regarding the impact of SNA events on morbidity in HIV-infected subjects and the existence of a significant association of SNA events with the severity of immune deficiency. The prevalence of AIDS-defining events in this cohort reflects the advanced stage of the HIV-infected patients followed at many Latin American sites. Although the somewhat higher frequency of terminal liver disease may warrant further confirmation and study, the overall distribution of SNA events was similar to that previously reported [15,16]. While traditional risk factors for these types of events showed an expected behaviour, we also found a significant association between the CD4 cell count and outcome.

We found a significant association between SNA events and the CD4 cell count closest to the index date and also the area under the curve of CD4 cell counts within the year prior to the time of the event, which provided an additional perspective on the immunological status of the patients.

SNA events were studied as a composite outcome as it has been hypothesized that they may all be similarly affected by HIV-induced immune deficiency. However, each SNA event has different risk factors and pathogenesis, and thus we also performed an exploratory analysis of different types of events.

In a similar way, immunological status remained significantly associated with cardiovascular events, advanced liver disease and non-AIDS-related malignancies in adjusted models. For cardiovascular disease, diabetes mellitus showed an expected significant association with the outcome, as did immunological status and cumulative use of stavudine in the multivariate model. Recent use of abacavir prior to the index date showed an association only in the univariate analysis, but low numbers of patients on this drug and the overall number of cardiovascular events may have precluded the finding of further significant results for this variable.

HIV disease itself has been related to HDL-cholesterol depletion, inflammation and endothelial dysfunction, among other pro-atherogenic conditions [26,27]. Although several of these changes may be at least partially reversed by cART, some antiretroviral drugs do themselves have a negative impact on cardiovascular risk [28–30]. Known risk factors for liver disease, such as HBV or HCV coinfection and alcohol abuse, appeared to be associated with the outcome in the univariate analysis, and HCV coinfection remained in the multivariate model along with immunological status. Immune deficiency has previously been shown to be associated with more rapid progression of liver fibrosis in hepatitis B and C [31–33].

In the analysis of non-AIDS malignancies, only immune deficiency was shown to be associated with the outcome, which may reflect the diversity of types of cancer that were gathered together in this category (e.g. lung, breast, gastric, larynx, thyroid and basocellular skin cancer).

The association between risk of SNA events and immune deficiency in HIV-infected subjects has been already reported in North American and European cohorts and multinational trials but, to our knowledge, this is the first report of data from the Latin American region. Overall we found that the frequency and type of events were similar to those previously reported in other regions.

It is thought that cART may lower the risk of many non-AIDS events as it does with AIDS-defining conditions, although it is unclear whether the effect is of similar strength. However, cohort data such as those from D:A:D indicate that the risk of cardiovascular events increases with the use of some specific antiretroviral drugs [34]. Current evidence suggests that the rates of many non-AIDS events are higher in patients with low CD4 cell counts. Data from the Hopkins cohort show that the incidence rate of these comorbidities is highest when the CD4 count is <350 cells/μL, especially in patients not receiving cART [35]. In this regard, the increased risk of SNA events could be interpreted as one of the consequences of slower or incomplete immune restoration in patients starting cART at lower CD4 cell counts.

This finding could be of particular relevance in our settings, where cART is usually not initiated until the CD4 cell count is <250–300 cells/μL, despite local guideline recommendations to consider treatment at earlier stages [36]. In addition, data from the SMART trial indicate that episodic use of antiretroviral therapy according to CD4 cell count is associated with increased risk of SNA events, a finding that appeared consistently across a broad range of CD4 cell counts [17].

Several limitations apply to the present study. Above all, the retrospective nature of these data (even with the data verification process that took place within the cohort) and the limited number of potential predisposing variables that we were able to analyse mean that caution is required in the interpretation of the results. Ascertainment bias should be addressed in the discussion of retrospective data. Nevertheless, given the nature and relevance of the clinical events analysed and the systematic revision of the clinical charts that was performed at all participant sites, we believe that there was a very low chance of missing or misinterpreting the identified cases. In addition, each of the sites acted as the primary provider for medical care of the patients, so the risk of missing these kinds of events was probably very low. A relatively low number of SNA events were identified in this cohort, and thus only strong associations were likely to be identified, and analysis of different types of events should be regarded as exploratory. In addition, as few sites have participated in this first project of the LATINA cohort, these results should not be used to extrapolate the situation to the entire Latin American region.

We focused the analysis on the influence of immune deficiency on SNA events, and thus we believe that the results obtained for cART-associated variables should be interpreted with caution, as CD4 cell count is in the causal path between treatment and outcome. Nevertheless, we believe that these findings contribute to growing knowledge regarding the relevance of SNA events as a global problem, providing information on a region for which little information has been published to date.

In summary, we found that SNA events are prevalent among HIV-infected subjects in Latin America and we found significant evidence supporting an association between immune deficiency and the risk of SNA events, when events were considered either together or separately according to type. These results contribute to a large body of evidence that supports the need to better understand the potential benefit of earlier use of cART. Randomized trials will probably be needed to enable definitive conclusions to be drawn about the impact of these findings on current antiretroviral treatment recommendations.

Acknowledgements

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Appendix (Supplemental Digital Content)

Table A1 Criteria for diagnosis of serious non-AIDS (SNA) events

Diagnosis	Criteria
Acute myocardial infarction	(A) (*Probable*): Acute clinical symptoms compatible with myocardial ischemia plus persistent changes in the ST segment of the ECG. (B) (*Confirmed*): Acute clinical symptoms compatible with myocardial ischemia plus Q wave appearance OR acute clinical symptoms compatible with myocardial ischemia plus increase in CPK-MB to at least $2 \times$ upper normal values and/OR increase in troponin levels OR diagnosis of myocardial infarction in autopsy.
Coronary artery disease requiring invasive procedure	Written medical report of the procedure.
Stroke	(A) (*Probable*): Acute onset of neurological deficit of at least 24-h duration in the absence of other demonstrable causes. (B) (*Confirmed*): A criteria plus imaging study (CT OR MRI) showing ischaemic OR haemorrhagic lesion compatible with clinical symptoms OR diagnosis of stroke in autopsy.
Terminal liver disease OR cirrhosis	A (*Probable*): Compatible clinical findings (ascites, hepatic encephalopathy, gastric OR oesophageal varices, spontaneous bacterial peritonitis, etc.) plus at least one of the following laboratory abnormalities: platelets $< 150\,000$ cells/µL, AST $>$ ALT, prothrombin time abnormality plus albumin < 3 g/dL OR fibroscan OR elastogram compatible with fibrosis OR imaging study compatible with cirrhosis. B (*Confirmed*): Histological evidence of cirrhosis in biopsy OR autopsy.
Terminal renal failure	Documentation of peritoneal dialysis OR haemodialysis for at least 3 months OR documented renal transplant procedure.
Non AIDS-defining malignancies	(A) (*Probable*): Diagnosis of malignancy other than Kaposi sarcoma, invasive cervical cancer OR non-Hodgkin's lymphoma in medical note OR medical chart. (B) (*Confirmed*): Diagnosis of malignancy other than Kaposi sarcoma, invasive cervical cancer OR non-Hodgkin's lymphoma in pathology report OR autopsy report.
Pulmonary thromboembolism	(A) (*Probable*): Compatible signs and symptoms plus elevated D dimer OR echocardiographic OR ECG signs of right ventricular dysfunction. (B) (*Confirmed*): Compatible signs and symptoms plus positive VQ scan OR angio-MRI OR pulmonary angiography OR helicoidal CT scan with contrast.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; OR, odd ratios.