Association of Noncirrhotic Portal Hypertension in HIV-Infected Persons and Antiretroviral Therapy with Didanosine: A Nested Case-Control Study

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Background. Noncirrhotic portal hypertension (NCPH) is a newly described life-threatening liver disease of unknown cause in human immunodeficiency virus (HIV)–infected persons. Postulated pathogenesis includes prolonged exposure to antiretroviral therapy, particularly didanosine.

Methods. We performed a nested case-control study including 15 patients with NCPH and 75 matched control subjects of the Swiss HIV Cohort Study to investigate risk factors for the development of NCPH. Matching criteria were similar duration of HIV infection, absence of viral hepatitis, and follow-up to at least the date of NCPH diagnosis in the respective case.

Results. All 15 case patients had endoscopically documented esophageal varices and absence of liver cirrhosis on biopsies; 4 died because of hepatic complications. At NCPH diagnosis, case patients and control subjects were similar concerning sex; race; Centers for Disease Control and Prevention stage; HIV-RNA level; CD4 cell count nadir; and lipids and lipodystrophy. Differences were found in age (conditional logistic regression odds ratio [OR] for 10 years older, 2.9; 95% confidence interval [CI], 1.4–6.1); homosexuality (OR, 4.5; 95% CI, 1.2–17); current CD4 cell count <200 cells/μL (OR, 34.3; 95% CI, 4.3–277); diabetes mellitus (OR, 8.8; 95% CI, 1.6–49); alanine aminotransferase level higher than normal (OR, 13.0; 95% CI, 2.7–63); alkaline phosphatase higher than normal (OR, 18.3; 95% CI, 4.0–85); and platelets lower than normal (OR, 20.5; 95% CI, 2.4–178). Cumulative exposure to antiretroviral therapy (OR per year, 1.3; 95% CI, 1.0–1.6), nucleoside reverse-transcriptase inhibitor (OR, 1.3; 95% CI, 1.1–1.7), didanosine (OR, 3.4; 95% CI, 1.5–8.1), ritonavir (OR, 1.4; 95% CI, 1.0–1.9), and nelfinavir (OR, 1.4; 95% CI, 1.0–1.9) were longer in case patients. Exposure to nonnucleoside reverse-transcriptase inhibitor and other protease inhibitors were not different between groups. In bivariable models, only the association of NCPH with didanosine exposure was robust; other covariables were not independent risk factors.

Conclusions. We found a strong association between prolonged exposure to didanosine and the development of NCPH.

Mortality and morbidity from AIDS-defining diseases has decreased dramatically since the introduction of combination antiretroviral therapy (ART) [1, 2]. As persons infected with human immunodeficiency virus (HIV) live longer, serious non–AIDS-defining diseases become increasingly important, and novel clinical manifestations or disease entities may emerge. Liver-related morbidity and mortality are major problems among HIV-infected patients [3]. Main causes of chronic liver disease are infection due to hepatitis C virus and hepatitis B virus, alcohol abuse, nonalcoholic fatty liver disease, and drug-induced toxicity [4]. Prolonged exposure to some antiretroviral drugs might increase hepatic mortality [3].

Recently, several reports of HIV-infected persons with symptomatic noncirrhotic portal hypertension (NCPH) were published [5–13] (table 1). Patients presented with esophageal varices, variceal bleeding, ascites, splenomegaly, and rarely, encephalopathy. In

Received 20 January 2009; accepted 12 April 2009; electronically published 9 July 2009.

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Clinical Infectious Diseases 2009; 49:626–35

1058-4838/2009/4904-0021$15.00
DOI: 10.1086/603559

Table 1. Literature Review on Noncirrhotic Portal Hypertension (NCPH) in HIV-Infected Persons

Author, year of publication	Case definition	Study design	No. of patients	Liver biopsy findings	Proposed risk factors for NCPH or elevated liver enzymes
Maida et al, 2006 [5]	Elevated liver enzymes of unknown origin	Case-control (1:1; matched by age, sex, CD4 cell count)	17 with elevated liver enzymes; suspected NCPH in 9 of 17	Biopsy in only 5 of 17: microvesicular steatosis in 5 of 5, mild fibrosis in 3 of 5, cirrhosis in 2 of 5	Prolonged DDI exposure
Mallet et al, 2007 [6]	Abnormal liver function tests or symptomatic PH of unknown origin	Case series	8	NRH in 7 of 8, sinusoidal dilatation in 1 of 8	DDI exposure (DDI in 8 of 8)
Arey et al, 2007 [7] (letter)		Case report	1	NRH	NVP (but patient with former DDI exposure)
Sandrine et al, 2007 [8] (letter)		Case report	1	NRH	Exposure to DDI and NVP
Garvey et al, 2007 [9] (letter)		Case series	6	NRH in 2 of 6, venous outflow obstruction in 3 of 6, normal in 1 of 6	DDI (in 5 of 6), coagulopathy (in 4 of 6)
Schiano et al, 2007 [10]	NCPH with variceal bleeding; HPS in biopsy; no etiology	Case series	4	HPS in 4 of 4	NVP (current therapy in 3 of 4); ART history not described
Maida et al, 2008 [11]	Elevated liver enzymes of unknown origin	Case series	32 with elevated liver enzymes; esophageal or gastric varices in 13 of 32	Biopsy in only 12 of 32: unspecific liver fibrosis in 3 of 12, NRH in 2 of 12, periportal fibrosis in 3 of 12	Prolonged DDI exposure, homosexual transmission modus
Tateo et al, 2008 [12]	Liver transplantation due to NCPH	Case series	3	NRH in 3 of 3	…
Saifee et al, 2008 [13]	NRH in wedge biopsies	Case series	11	NRH in 11 of 11	DDI in 11 of 11, coagulopathy in 8 of 10

NOTE. ART, antiretroviral therapy; DDI, didanosine; HIV, human immunodeficiency virus; HPS, hepatoportal sclerosis; NRH, nodular regenerative hyperplasia; NVP, nevirapine; PH, portal hypertension.

many cases, portal thrombosis was noted. Some patients developed severe complications that required liver transplantation. Liver biopsies revealed no cirrhosis, and in a great part, nodular regenerative hyperplasia was found. Histological changes were usually very subtle and often were not detected using routine stains. The etiology of this new disease in HIV-infected patients remains obscure. Besides a prothrombotic state and HIV itself, ART, particularly didanosine (DDI), has been postulated as a cause. However, implicating which medication might cause NCPH in ART-experienced patients is difficult, because patients usually have an ART history with numerous different drugs.

The methodology of those reports, however, does not allow for clear-cut conclusions on the association of NCPH with the use of antiretrovirals. Besides 2 case reports and 6 case series, only 1 case-control study was published (table 1). That case-control study assessed HIV-infected patients with elevated liver enzymes of unknown origin; only a subset of case patients (9 of 17 case patients) had portal hypertension. Liver biopsy was performed in 5 patients, of whom 2 had cirrhosis [5–13]. In the Swiss HIV Cohort Study, we have encountered a number of patients with unexplained NCPH. The purpose of this study was to identify risk factors for this newly described disease by means of a nested case-control design and strict criteria for the diagnosis of NCPH.

METHODS

Study population. The Swiss HIV Cohort Study is an ongoing, prospective cohort study that was established in 1988 and that continually enrolls and observes HIV-infected individuals aged ⩾16 years at 5 university outpatient clinics, 2 large district hospitals, affiliated regional hospitals, and private practices [14]. Information and laboratory values are collected in accordance with defined criteria at registration and at follow-up visits every 6 months. The study was approved by local ethical review boards, and written informed consent was obtained from all participants.

Patients with idiopathic NCPH were retrospectively identified by patient charts. A review of medical charts of all case patients was performed, and data were extracted using a standardized data-collection form. Inclusion criteria were the presence of endoscopically documented esophageal varices or hepatic venous pressure gradient ⩾10 mm Hg, absence of hepatic cirrhosis on liver biopsy, and no common cause of liver disease, such as hepatitis C virus or active hepatitis B virus infection, elevated alcohol consumption, hemochromatosis, Wilson disease, α1-antitrypsin deficiency, autoimmune hepatitis, nonalcoholic fatty liver disease, and hepatotoxic drugs. Hepatitis C virus infection was defined as present in patients who were seropositive for hepatitis C virus or who had test results positive for hepatitis C virus RNA. Active hepatitis B virus infection was defined as present in patients who were seropositive for hepatitis B surface antigen or hepatitis B e antigen or who had detectable hepatitis B virus DNA. Time of diagnosis of portal hypertension was defined by the time of confirmation of esophageal varices. For patients without a known date of seroconversion, we assessed the date of HIV infection in accordance with a back calculation model [15].

For each case patient, we selected 5 control subjects from the Swiss HIV Cohort Study without viral hepatitis, with a similar date of HIV infection ($\pm$6 months), and with a follow-up to at least the date of diagnosis of NCPH in the corresponding case patient.

Statistical analysis. Associations between NCPH and the following factors were assessed by univariable and bivariable conditional logistic regression: demographic characteristics (age, sex, mode of HIV acquisition, and race); presence of diabetes mellitus; current values for body mass index, blood pressure, lipodystrophy, total and high-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, and alkaline phosphatase; current and nadir CD4 cell count; current and maximum HIV-1 viral load; previous clinical AIDS events; and exposure to different drug classes, different nucleoside reverse-transcriptase inhibitor (NRTI) backbone-combinations, and individual antiretroviral drugs. Central obesity was defined in accordance with the new worldwide definition [16], with sex- and ethnicity-specific waist circumference cut-off values as follows: Europeans and sub-Saharan Africans, ⩾94 cm for males and ⩾80 cm for females; south Asians, Chinese, and south and central Americans, ⩾90 cm for males and ⩾80 cm for females; and Japanese, ⩾85 cm for males and ⩾90 cm for females. A full multivariable model was not possible because of the limited number of case patients. Variables with significant associations in the univariable analysis were used as covariables in bivariable models together with DDI exposure per year. We considered only cumulative drug exposure for univariable and bivariable models because of potential reverse causality problems with current use. A Kaplan-Meier survival analysis of matched HIV-infected control subjects and patients with NCPH was made. For statistical analysis, we used Stata software, version 10.1 (StataCorp).

RESULTS

Description of case patients. From September 2000 through May 2007, we observed 15 patients with unexplained NCPH. First symptoms that prompted investigations of the portal system were elevated liver enzymes, hematemesis, or ascites. The majority were male (13 [87%]) and had acquired HIV through homosexual intercourse (11 [73%]). The median age at time of diagnosis was 52 years (interquartile range [IQR], 47–59 years). All 15 case patients were ART experienced. At time of diagnosis, 11 (73%) were receiving ART and 4 (27%) had in-

terrupted ART because of suspected hepatotoxicity. In 9 case patients (60%), viral load was undetectable; in another 2, viral load was <100 copies/mL. Mean time from diagnosis of HIV to diagnosis of NCPH was 14.6 years (IQR, 10.8–18.2 years). All 15 case patients had endoscopically documented esophageal varices; 7 developed recurrent episodes of variceal bleeding. Thirteen case patients were found to have splenomegaly (in 2, the size of the spleen was not documented). Ascites was recorded in 8 case patients and hepatic encephalopathy in 2. At time of diagnosis, portal vein thrombosis was present in 3 case patients; during follow-up, it was present in 2. Alkaline phosphatase and liver enzymes were mostly only mildly and intermittently elevated. Markers for liver synthesis were usually normal, and platelets were often slightly less than the normal limit. At least 1 liver biopsy, either transabdominal or transjugular, was performed in all patients. None of the liver biopsies showed cirrhosis. Histology did reveal a variety of lesions often occurring together, such as periportal fibrosis in 10 case patients (67%), perisinusoidal fibrosis in 1 (7%), sinusoidal dilatation in 1 (7%), low grade portal and lobular inflammation in 7 (47%), ductopenia and ductular proliferation in 4 (27%), macrovacuolar and/or microvesicular steatosis in 6 (40%), and hepatocellular necrosis in 4 (27%). Nodular regenerative hyperplasia was seen in the biopsy of one patient (7%) and normal liver appearance in the biopsy of another one (7%).

Treatment was symptomatic following the same protocol as in cirrhosis, including β-blocker, variceal banding, and diuretics. One patient was treated with transjugular intrahepatic portal systemic shunting for refractory symptoms; no one received a liver transplant.

Comparison of demographic and clinical characteristics of case patients and control subjects. The comparison of 15 case patients and 75 control subjects as well as the results of univariable conditional logistic regression analysis are summarized in table 2. In univariable analysis, at time of diagnosis of NCPH, no differences between case patients and control subjects were found in median HIV infection date (December 1989 vs March 1990), median cohort registration date (July 1995 vs December 1995), and median duration of cohort follow-up (11.9 vs 12.0 years), reflecting proper selection of control subjects. Sex and race did not differ between the 2 groups. Patients with NCPH were significantly older than their matched control subjects (52 vs 43 years; odds ratio [OR] per 10 years older, 2.9; 95% confidence interval [CI], 1.4–6.1), and HIV was transmitted more often through homosexual intercourse (OR, 4.5; 95% CI, 1.2–17). At time of diagnosis, median CD4 cell count was substantially lower (165 vs 522 cells/μL) and more often <200 cells/μL (53% vs 4%; $P = .001$) in individuals with NCPH. Nadir CD4 cell count was also lower (103 vs 164 cells/μL) but without statistical significance. Spleen sequestration with lymphopenia cannot explain the low absolute CD4 cell count in NCPH patients, because of concomitant lower CD4 cell percentage (19% vs 27%; $P < .001$). No differences were found in HIV-1–RNA levels at time of diagnosis, maximum HIV-1–RNA levels, and clinical Centers for Disease Control and Prevention disease stage. Alanine aminotransferase levels were more often elevated above normal value ($P = .001$), alkaline phosphatase were more often elevated above normal value ($P < .001$), and blood platelets were more often reduced below normal value ($P < .006$) in NCPH patients. Most of the risk factors for nonalcoholic fatty liver disease [17, 18], including dyslipidemia, high blood pressure (data not shown), central obesity, and lipodystrophy, did not differ between case patients and control subjects. However, diabetes mellitus was overrepresented in NCPH patients (27% vs 4%; $P = .013$). We attributed a significantly lower body mass index in the NCPH group to weight loss in the context of progressive liver disease.

Association of antiretroviral treatment and NCPH. The antiretroviral treatment history of patients with NCPH and control subjects is shown in table 3. Individuals with NCPH started ART more frequently with monotherapy (40% vs 27%) or dual therapy (33% vs 15%), compared with control subjects, who initiated more often with combination ART (27% vs 48%). In univariable analysis, exposure to any ART was significantly longer in NCPH patients (OR per year exposure, 1.31; 95% CI, 1.04–1.65). They were significantly longer exposed to NRTI (OR 1.33; 95% CI, 1.06–1.66), whereas exposure to protease inhibitors and nonnucleoside reverse-transcriptase inhibitor did not differ. Because in the published literature an association between DDI and NCPH is postulated, we analyzed different NRTI backbones with and without DDI. DDI with stavudine (OR, 2.06; 95% CI, 1.36–3.13) and DDI with other NRTI (not zidovudine and not stavudine; OR, 2.13; 95% CI, 1.35–3.37) showed a significant association with NCPH, whereas the effect for the combination of DDI and zidovudine was attenuated (OR, 1.59; 95% CI, 0.88–2.89; $P = .13$). Backbones without DDI were conversely associated with the development of NCPH (OR, 0.82; 95% CI, 0.70–0.96). Among individual antiretroviral drugs, DDI exposure was clearly standing out in NCPH patients (OR, 3.44; 95% CI, 1.46–8.14). All case patients had a treatment history with DDI (100% vs 35%; $P < .001$). Cumulative exposure to ritonavir (therapeutic dose; OR, 1.42; 95% CI, 1.04–1.94) and to nelfinavir (OR, 1.39; 95% CI, 1.04–1.86) was also increased in patients with NCPH. In contrast, use of lamivudine was significantly higher in the control group (OR, 0.67; 95% CI, 0.49–0.91).

The final bivariable model is presented in table 4. A full multivariable model was not possible because of the low case number. After adjustment for the different covariables, only exposure to DDI remained a highly significant risk factor for the development of NCPH.

Outcome. Mortality after diagnosis of NCPH differed from

Table 2. Comparison of Characteristics of Patients with Noncirrhotic Portal Hypertension and Matched Control Subjects

Characteristic	Case patients (n = 15)	Control subjects (n = 75)	Odds ratio (OR) (95% CI)	P[a]
Date of HIV infection, median (IQR)	December 1989 (November 1985–August 1992)	March 1990 (January 1986–July 1992)	…	.96[b]
Date of cohort registration, median (IQR)	July 1995 (January 1989–July 1997)	December 1995 (October 1991–March 2000)	…	.10[b]
Duration of cohort follow-up, median years (IQR)	11.9 (9.1–18.4)	12.0 (7.8–16.5)	…	.47[b]
Sex				.12
Female	2 (13.3)	26 (34.7)	0.29 (0.06–1.40)	
Male	13 (86.7)	49 (65.3)	1	
Age, years				
Median (IQR)	52 (47–59)	43 (38–49)	2.93 (1.4–6.1)[c]	.004
<45	3 (20.0)	44 (58.7)	1	.013
⩾45	12 (80.0)	31 (41.3)	7.23 (1.52–34.33)	
Mode of HIV infection				.046
Heterosexual	4 (26.7)	43 (57.3)	1	
Homosexual	11 (73.3)	30 (40.0)	4.3 (1.12–16.5)	
Injecting drug use	0 (0)	2 (2.7)	NC	
Race				.89
White	13 (86.7)	64 (85.3)	1.12 (0.21–5.88)	
Other	2 (13.3)	11 (14.7)	1	
Current CD4 cell count, cells/μL				.001
Median (IQR)	165 (114–312)	522 (364–740)	…	
Below 200	8 (53.3)	3 (4.0)	34.33 (4.25–277.11)	
Nadir CD4 cell count, cells/μL				.19
Median (IQR)	103 (27–184)	164 (83–335)	…	
Below 100	7 (46.7)	21 (28.0)	2.10 (0.69–6.42)	
HIV-1–RNA copies/mL log				.5
Median (IQR)	0 (0–1.99)	0 (0–2.23)	…	
<Level of detection	9 (60.0)	38 (50.7)	1.51 (0.46–4.93)	
Peak HIV-1–RNA, copies/mL log, median (IQR)	5.08 (4.77–5.45)	5.00 (4.25–5.52)	…	.58
Previous clinical AIDS	3 (20.0)	16 (21.3)	0.92 (0.22–3.84)	.90

BMI,[d] kg/m^2				.003[e]
Median (IQR)	20.8 (18.6–22.3)	23.7 (21.8–26.0)	…	
<25.0	14 (100)	40 (60.6)	13.11 (2.03–∞)	
⩾25.0	0 (0)	26 (39.4)	1	
Central obesity[f]	4 (26.7)	34 (45.3)	0.39 (0.10–1.4)	.15
Diabetes mellitus	4 (26.7)	3 (4.0)	8.78 (1.58–48.74)	.013
Lipodystrophy[g]				
Atrophy	8 (57.1)	24 (35.3)	2.2 (0.73–6.63)	.16
Fat accumulation	4 (28.6)	19 (27.9)	1.0 (0.25–3.92)	>.99
ALT, IU/L			13.0 (2.67–62.97)	.001
Median (IQR)	51 (34–65)	26 (17–36)	…	
Higher than normal value[h]	9 (60.0)	12 (16.0)	…	
AP, IU/L			18.3 (3.95–84.81)	<.001
Median (IQR)	175 (149–362)	85 (70–104)	…	
Higher than normal value[h]	11 (73.3)	10 (13.3)	…	
Platelets/μL			20.52 (2.36–178.19)	.006
Median (IQR)	166 (116–228)	242 (196–284)	…	
Lower than normal value[h]	5 (33.3)	1 (1.3)	…	
Antiretroviral therapy				
Naive	0 (0)	8 (10.7)	1	.10
Currently interrupted	4 (26.7)	9 (12.0)	NC	
On treatment	11 (73.3)	58 (77.3)	NC	

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; AP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; NC, not computable.

[a] All *P* values are from conditional logistic regression, unless otherwise indicated.
[b] From Wilcoxon rank-sum test.
[c] OR per 10 years older.
[d] Data about BMI were available for 14 case patients and 66 control subjects only.
[e] From exact conditional regression analysis.
[f] For central obesity definition, see "Statistical analysis."
[g] Data about lipodystrophy were available for 14 case patients and 68 control subjects only.
[h] Normal values: ALT, female ⩽35 IU/L, male ⩽50 IU/L; alkaline phosphatase, female ⩽104 IU/L, male ⩽129 IU/L; platelets ⩽143 × 10^3 cells/μL.

Table 3. Comparison of Antiretroviral Therapy (ART) History of Patients with Noncirrhotic Portal Hypertension and Matched Control Subjects at Time of Diagnosis

ART or individual antiretroviral drugs	Cumulative median years (IQR)		Odds ratio (95% CI) per year exposure	P[a]
	For case patients (n = 15)	For control subjects (n = 75)		
Any ART	8 (5–11)	6 (3–8)	1.31 (1.04–1.65)	.022
Combination ART	6 (3–9)	4 (1–7)	1.17 (0.96–1.43)	.13
NRTIs	8 (5–11)	6 (3–8)	1.33 (1.06–1.66)	.015
NNRTIs	1 (0–5)	0 (0–3)	1.12 (0.89–1.40)	.33
PIs unboosted	3 (1–5)	1 (0–3)	1.18 (0.96–1.46)	.12
PIs boosted	0 (0–4)	0 (0–2)	1.19 (0.93–1.52)	.16
Didanosine plus stavudine	2 (0–4)	0 (0–0)	2.06 (1.36–3.13)	.001
Didanosine plus zidovudine	0 (0–0)	0 (0–0)	1.59 (0.88–2.89)	.13
Didanosine plus another (not zidovudine, not stavudine)	1 (0–3)	0 (0–0)	2.13 (1.35–3.37)	.001
Backbone without didanosine	4 (1–7)	8 (4–11)	0.82 (0.70–0.96)	.015
Zidovudine	1 (0–3)	2 (0–5)	0.91 (0.73–1.12)	.36
Zalcitabine	0 (0–0)	0 (0–0)	0.96 (0.50–1.87)	.91
Didanosine	5 (4–6)	0 (0–1)	3.44 (1.46–8.14)	.005
Stavudine	3 (2–5)	1 (0–3)	1.24 (0.99–1.55)	.06
Lamivudine	0 (0–2)	3 (0–6)	0.67 (0.49–0.91)	.01
Abacavir	0 (0–1)	0 (0–2)	0.91 (0.67–1.24)	.54
Tenofovir	0 (0–1)	0 (0–0)	1.44 (0.88–2.37)	.15
Efavirenz	0 (0–5)	0 (0–2)	1.24 (0.96–1.61)	.10
Nevirapine	0 (0–0)	0 (0–0)	0.81 (0.39–1.68)	.57
Saquinavir	0 (0–1)	0 (0–0)	1.19 (0.77–1.83)	.44
Ritonavir (full dose)	1 (0–3)	0 (0–1)	1.42 (1.04–1.94)	.029
Indinavir	0 (0–2)	0 (0–1)	0.95 (0.69–1.31)	.76
Nelfinavir	0 (0–5)	0 (0–1)	1.39 (1.04–1.86)	.028
Lopinavir/r	0 (0–0)	0 (0–0)	0.81 (0.40–1.62)	.55
Amprenavir	0 (0–0)	0 (0–0)	2.62 (0.74–9.27)	.14
Atazanavir	0 (0–0)	0 (0–0)	0.80 (0.29–2.21)	.67

NOTE. For the drugs fosamprenavir, tipranavir, and darunavir, the number of exposed patients was too small for calculations. CI, confidence interval; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] From conditional logistic regression.

that of the matched control subjects. Whereas none of the control subjects died during the median follow-up of 12 years (IQR, 8–17 years), 4 patients with NCPH (27%) died of liver disease during the same follow-up time (median interval, 12 years; IQR, 9–18 years); among these 4 patients, 2 died of variceal hemorrhage and 2 of liver failure.

DISCUSSION

In this nested case-control study, prolonged exposure to DDI was the only independent risk factor for NCPH in HIV-infected patients. Significant associations for NCPH in univariable analysis such as age, homosexual transmission category, low CD4 cell count, diabetes mellitus, low body mass index, and exposure to NRTI, ritonavir, and nelfinavir did not remain stable in bivariable models. This is in agreement with the recently published case reports and case series on NCPH in HIV-infected persons, in which DDI was suspected to play a major role in the pathogenesis of NCPH (table 1). Some studies have implicated nevirapine as a causative agent [7, 8, 10], but we did not find any evidence for that.

Idiopathic NCPH is a poorly understood condition attributed to obstructive portal venopathy [19, 20]. Pathologically, 2 types of lesions have been described: alterations in small vessels, regarded as the initial lesions, and changes in liver architecture consisting of fibrosis and/or nodule formation, regarded as secondary [21]. Histological findings are very heterogeneous and include periportal and perisinusoidal fibrosis, hepatoportal sclerosis, nodular regenerative hyperplasia, and incomplete septal cirrhosis [19, 20, 22]. These histological differences might reflect chronologic progression of a single dis-

Table 4. Bivariable Odds Ratios (ORs) for the Effect of Didanosine (DDI) on Noncirrhotic Portal Hypertension and ORs for the Covariables Before and After Adjustment for DDI

	Unadjusted covariable	Covariable adjusted for DDI		DDI adjusted for covariable	
Covariable	OR (95% CI)	OR (95% CI)	*P*	OR (95% CI)[a]	*P*
Age, per 10 years older	2.57 (1.29–5.13)	3.69 (0.54–25.0)	.18	4.93 (1.21–20.1)	.026
Homosexual transmission category	4.52 (1.19–17.2)	133.6 (0.13–1.3 × 10^5)	.17	5.57 (1.24–25.1)	.025
CD4 cell count, <200 cells/μL	34.3 (4.25–277)	359.4 (0.04–3.6 × 10^6)	.21	4.68 (1.01–21.7)	.049
Diabetes mellitus	8.78 (1.58–48.7)	1.57 (0.02–108)	.83	3.37 (1.40–8.15)	.007
Therapy, per year					
NRTI (not DDI)	0.80 (0.67–0.97)	1.18 (0.77–1.81)	.45	4.79 (1.18–19.5)	.029
NNRTI	1.12 (0.89–1.40)	1.44 (0.88–2.37)	.15	4.47 (1.26–15.8)	.02
Protease inhibitor	1.18 (0.96–1.46)	1.21 (0.72–2.02)	.47	3.91 (1.33–11.5)	.013
Lamivudine	0.67 (0.49–0.91)	0.81 (0.46–1.42)	.46	2.94 (1.29–6.67)	.01
Ritonavir	1.42 (1.04–1.94)	1.17 (0.74–1.82)	.50	3.37 (1.38–8.22)	.008
Nelfinavir	1.39 (1.04–1.86)	1.61 (0.88–2.93)	.12	4.23 (1.32–13.5)	.015

NOTE. CI, confidence interval; NNRTI nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

[a] The unadjusted OR for DDI was 3.44 (95% CI, 1.46–8.14; $P = .005$).

ease. Vascular alterations result in hepatic venoocclusive disease and lead to the syndrome of NCPH [19, 23]. In HIV-positive patients with symptomatic NCPH, the most common histological finding was nodular regenerative hyperplasia; Schiano et al [10] described hepatoportal sclerosis, and Maida et al [5, 11] described microvesicular steatosis, unspecific liver fibrosis, and periportal fibrosis (table 1). Liver biopsies of our NCPH patients mainly showed periportal fibrosis.

Idiopathic NCPH has been associated with certain drugs and systemic diseases, including hypercoagulability, autoimmune disorders, and myeloproliferative or lymphoproliferative disorders [24]. Most of these diseases are known to cause vascular damage. The pathomechanism of DDI causing NCPH remains hypothetical. Prolonged DDI exposure might lead to a mitochondrial damage [25, 26], injuring endothelial cells. 6-thioguanine, another nucleoside analogue used for the treatment of leukemia, has been described to cause hepatic venoocclusive disease resulting in NCPH [27]. In the Data Collection on Adverse Events for Anti-HIV Drugs (D:A:D study), a significant increased risk of myocardial infarction associated with recent use of DDI was observed [28]. This finding, however, could not be confirmed in the Strategies for Management of Antiretroviral Therapy (SMART) study, in which no association of DDI use was found with either altered risk of cardiovascular disease or altered levels of inflammatory and coagulation markers [29].

The pathogenesis of NCPH in HIV infection is probably multifactorial. Besides ART, a prothrombotic state was postulated to be an important causative factor leading to microthrombosis and vascular obstruction. Several reports have noted thrombophilic abnormality in affected patients [9, 13, 30]. HIV might predispose to hypercoagulability and small vessel thrombosis [31, 32]. Furthermore, HIV is thought to trigger HIV-associated pulmonary hypertension by direct endothelial toxicity [33]. A similar mechanism could occur in the liver. The patients with NCPH in our study did not have signs or symptoms of a prothrombotic state, pulmonary hypertension, or a disturbed endothelial function.

Univariable results of our study showed an association of age and homosexual transmission category. In a population not infected with HIV, NCPH with nodular regenerative hyperplasia seems to be more prevalent in the elderly. An autopsy study found a >7-fold higher prevalence in patients aged >80 years, compared with patients aged <60 years [21]. This might reflect the higher prevalence of systemic diseases such as lymphoproliferative and myeloproliferative disorders in an elderly population. Systemic diseases were excluded in case patients of our study. Maida et al [5, 11] reported an overrepresentation of the homosexual transmission category in NCPH and HIV. In the case series by Mallet et al [6], sex was equally distributed, and in the other case series [9, 10, 13], distribution of HIV transmission was not mentioned. Diabetes mellitus was more common in our NCPH patients ($P = .013$ in univariable analysis). However, diabetes mellitus is not known to cause NCPH, either in a general population or in HIV-infected persons.

The strength of this study is its case-control design. To our knowledge, this is the only case-control study to investigate risk factors for the development of NCPH. In addition, case patients met well-defined criteria for the diagnosis of NCPH: endoscopically confirmed esophageal varices as a sign of portal hypertension, exclusion of cirrhosis in biopsies, and absence of known causes for liver disease. Limitations include the relatively small sample size due to the rarity of symptomatic NCPH. Therefore, type 1 errors cannot be excluded. We could evaluate

only information and laboratory values collected within the protocol of the Swiss HIV Cohort Study. We retrospectively could not search for coagulopathies as a possible cofactor in the pathogenesis of NCPH. Case patients were identified by physicians remembering affected patients. Less severe cases might have escaped detection. We cannot rule out the possibility that some of our control subjects had asymptomatic NCPH.

An important finding of this study is that long-term toxicity of antiretroviral drugs might emerge only after decades. As persons with HIV infection in industrialized countries live longer and ART exposure is prolonged, we need to be alert for novel clinical manifestations attributable to drug-related adverse events.

In summary, we described a case series of 15 HIV infected patients with NCPH and assessed associated risk factors in a nested case-control analysis. We found a strong correlation between the exposure to DDI and the development of NCPH. Because NCPH may result in dramatic complications with increased mortality, a high index of suspicion is needed in DDI-exposed patients with clinical signs of liver disease, and rapid evaluation is warranted. Besides symptomatic treatment of portal hypertension, DDI needs to be withdrawn.

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Acknowledgments

Financial support. The Swiss HIV Cohort Study, supported by the Swiss National Science Foundation.

Potential conflicts of interest. H.K. has received travel grants from Abbott. B.L. has received travel grants, grants, or honoraria from Abbott, Aventis, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Roche, and Tibotec. M.F. has received travel grants or speaker's honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche, and Tibotec. J.J. has received travel grants from Bristol-Myers Squibb, Gilead, and Pfizer. N.J.M. has received grants from Novartis and Roche. R.W. has received travel grants or speaker's honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, LaRoche, TRB Chemedica, and Tibotec. All other authors: no conflicts.

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