Antiretroviral Drug-Related Liver Mortality Among HIV-Positive Persons in the Absence of Hepatitis B or C Virus Coinfection: The Data Collection on Adverse Events of Anti-HIV Drugs Study

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Background. Liver diseases are the leading causes of death in human immunodeficiency virus (HIV)–positive persons since the widespread use of combination antiretroviral treatment (cART). Most of these deaths are due to hepatitis C (HCV) or B (HBV) virus coinfections. Little is known about other causes. Prolonged exposure to some antiretroviral drugs might increase hepatic mortality.

Methods. All patients in the Data Collection on Adverse Events of Anti-HIV Drugs study without HCV or HBV coinfection were prospectively followed from date of entry until death or last follow-up. In patients with liver-related death, clinical charts were reviewed using a structured questionnaire.

Results. We followed 22 910 participants without hepatitis virus coinfection for 114 478 person-years. There were 12 liver-related deaths (incidence, 0.10/1000 person-years); 7 due to severe alcohol use and 5 due to established ART-related toxicity. The rate of ART-related deaths in treatment-experienced persons was 0.04/1000 person-years (95% confidence interval, .01, .10).

Conclusions. We found a low incidence of liver-related deaths in HIV-infected persons without HCV or HBV coinfection. Liver-related mortality because of ART-related toxicity was rare.

Keywords. liver-related mortality; drug toxicity; antiretroviral therapy; HIV infection; cohort study.

Liver diseases are among the most frequent causes of non-AIDS–related deaths in human immunodeficiency virus (HIV)-positive persons [1–4]. Most deaths result from hepatitis C (HCV) or hepatitis B virus (HBV) coinfections or alcohol use; little is known about other causes [5]. Results of 2 prospective observational cohorts suggest that prolonged exposure to antiretroviral therapy (ART) may increase the risk for fatal liver failure. The Data Collection on Adverse Events of Anti-HIV Drug (D:A:D) cohort, which includes many HCV-coinfected persons, found an increased rate of liver-related deaths per year of ART in multivariable analyses that were also adjusted for the latest CD4 cell counts [1]. The EuroSIDA observational cohort showed similar results [6].

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The role of ART in liver-related mortality in patients without chronic viral hepatitis is less well defined. In the Swiss HIV Cohort Study (SHCS), elevated alanin aminotransferase (ALT; reported as adverse events to antiretrovirals), was associated with a higher mortality, independent of chronic hepatitis virus coinfections [7]. In contrast, mortality was not increased in participants with chronic ALT elevation and without viral hepatitis in another SHCS analysis; however, the observation period was shorter and the patient number smaller [8]. Recently, new hepatic syndromes related to ART have emerged in HIV-infected persons. Noncirrhotic portal hypertension, a potentially life-threatening liver disease, has been linked to didanosine use [9, 10]. In addition, steatosis and steatohepatitis are common in HIV-positive persons with and without chronic viral hepatitis [11, 12] and are associated with advanced liver fibrosis and cirrhosis [13]; ART as a risk factor has been discussed.

The aims of this study were to (1) assess liver-related mortality in HIV-positive persons without chronic viral hepatitis in the D:A:D cohort and (2) provide comprehensive clinical details of these events. The role of ART in death was of particular interest.

METHODS

Study Design

The D:A:D study, which was founded in 1999, is a prospective observational study of 11 previously established cohorts, as described previously [14]. Currently, 49 737 HIV-positive individuals (33 308 from the original 2 recruitments with 16 429 added to the cohort from 2009) are followed at 212 clinics in Europe, the United States, and Australia. The study's primary endpoint is myocardial infarction, with other events (including death) as secondary endpoints.

Data Collection

All participants were under active follow-up in their individual cohorts at the time of enrollment in the D:A:D study. At enrollment and at least every 8 months thereafter, standardized data forms, which are used to collect information on sociodemographic, clinical, laboratory, and treatment information, are completed. Data on HBV and HCV antibody status and hepatitis viral load assessments, if available, have been collected since January 2004. Previously collected HBV or HCV results by the participating cohorts were included. Information on cause of death has been prospectively collected using the Cause of Death (CoDe) in HIV protocol, which is specifically designed for classifying causes of death in HIV-positive persons [15].

For the present analysis, deaths were classified as liver related if the underlying cause was recorded as liver failure, regardless of etiology. Other categories include AIDS, cardiovascular disease (CVD), non-AIDS malignancy (excluding AIDS-defining and hepatitis virus-associated malignancies), and other/unknown.

In all persons with liver-related death and negative HCV or HBV status, local investigators of participating institutions retrospectively reviewed the clinical charts using a structured questionnaire. This chart review ascertained that inclusion criteria were met and provided additional information on the cause of liver-related death (including severe alcohol use, nonalcoholic fatty liver disease, medical treatment, noncirrhotic portal hypertension, and other disorders), liver-related symptoms, laboratory and histology results, and interventions, including liver transplantation. In unclear circumstances of liver-related death, a brief narrative was given.

Definitions

HCV infection was defined as present in persons who were seropositive for HCV or who had test results positive for HCV RNA. HBV infection was defined as present in persons who were positive for hepatitis B surface antigen, hepatitis B e antigen, or hepatitis B core antibodies or who had detectable HBV DNA during the study period. Thus, patients with chronic and previous HCV infections and chronic, active, and previous HBV infections were excluded. Patients with unknown HBV or HCV status were also excluded. Severe alcohol use was defined according to the WHO definition as alcohol consumption in female >40 g/d and in male >60 g/d.

Statistical Analyses

All D:A:D study participants with negative HCV and HBV status were included. Participants were followed from the date of entry into the D:A:D study until the date of death, the date of loss to follow-up (6 months after the patient's last clinic visit), or the end of study follow-up (1 February 2010), whichever occurred first. The incidence of liver-related deaths was defined as the number of such deaths divided by the total person-years of follow-up. HCV- or HBV-negative participants with liver-related death were compared with participants without chronic viral hepatitis who died from causes that were not liver related using data at baseline and data from the last clinic visit before death. *P* values were calculated using Fisher exact tests and Mann-Whitney *U* tests, as appropriate. Due to the small number of endpoints, multivariable analyses were not feasible. Analyses were performed using SAS version 9.1.

RESULTS

Baseline Characteristics

Of 49 737 participants followed between 1 December 1999 and 1 February 2010, 19 618 (40%) were HCV or HBV positive at baseline or during follow-up and 2506 (5%) had unknown HCV or HBV status. A total of 4703 (9%)

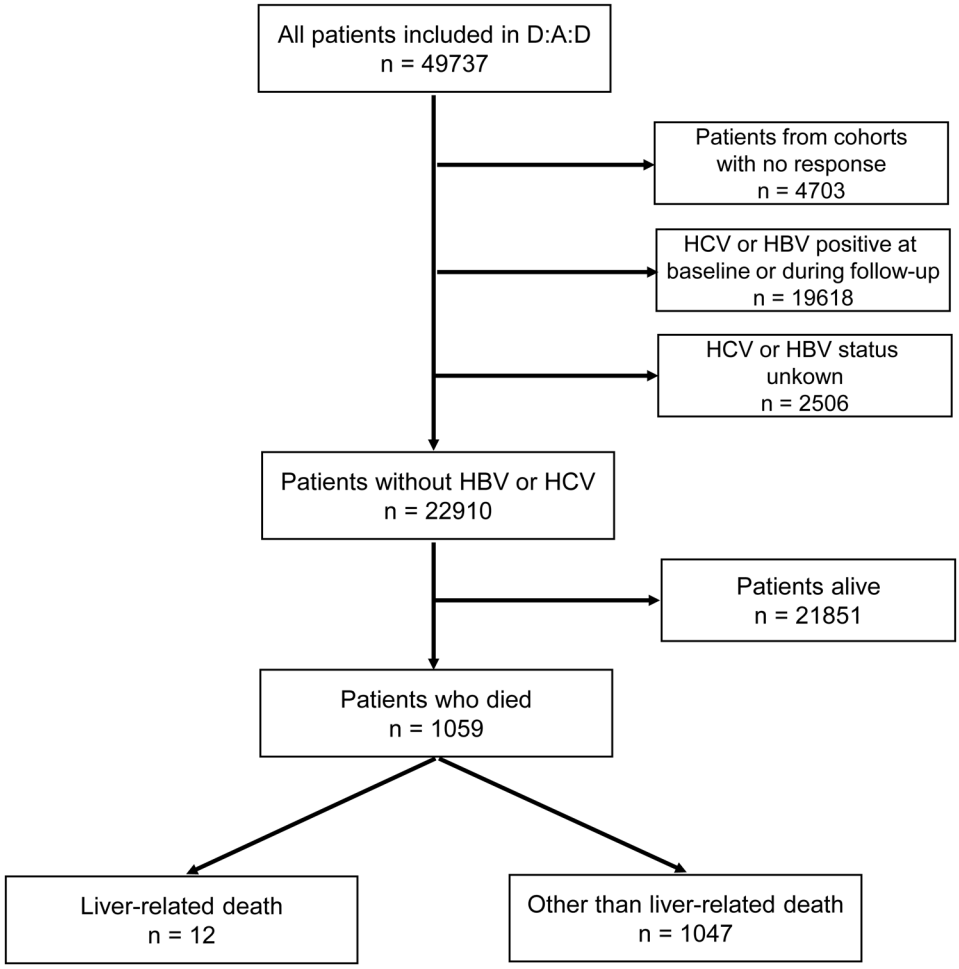

Figure 1. Patient flowchart. Abbreviations: D:A:D, Data Collection on Adverse Events of Anti-HIV Drug; HBV, hepatitis B virus; HCV, hepatitis C virus.

participants were excluded because they belonged to cohorts that did not provide the requested information for this study. Thus, 22 910 (46%) HCV- and HBV-negative participants who were followed for 114 478 patient-years were included in these analyses (Figure 1). Over the years, the percentage of patients with documentation gaps of more than 1 year remained low and varied between 3% and 6%. The baseline characteristics of the study participants are shown in Table 1.

A total of 1059 (4.6%) of the patients died; 12 (0.05%) deaths were liver related. Thus, the incidence of liver-related deaths in persons not coinfected with HCV or HBV was 0.10/1000 person-years (95% confidence interval [CI], .05, .18).

Description of Patients Who Died From Liver Disease

Clinical data are summarized in Table 2. Five participants died due to ART toxicity. Of these, 2 patients experienced acute liver failure with lactic acidosis on regimens that included didanosine and stavudine, with 1 patient also receiving metformin. A third patient developed fatal liver failure because of a hypersensitivity reaction to nevirapine. Two patients died of noncirrhotic portal hypertension; both had been exposed to didanosine. The rate of ART-related death in treatment-experienced individuals was 0.04 (95% CI, 0.01, 0.10), with 5 events over 1000 person-years. Seven liver-related deaths were due to severe alcohol use, including 1 patient with an additional diagnosis of hemochromatosis.

Histopathological findings (2 biopsies and 1 autopsy) confirmed the clinical diagnosis of alcoholic liver disease and noncirrhotic portal hypertension. (Signs of alcoholic liver disease were found in 1 biopsy and in the autopsy of 2 patients with alcoholic liver disease, and 1 biopsy of a patient with noncirrhotic portal hypertension showed histopathological findings consistent with noncirrhotic portal hypertension) [10, 16]. No patient was treated with transjugular intrahepatic portal systemic shunting and none received a liver transplant.

Table 1. Characteristics of Data Collection on Adverse Events of Anti-HIV Drug Study Participants Without Hepatitis C Virus or Hepatitis B Virus Coinfection at Study Entry

Total of Participants	n	22 910
Male gender	n (%)	16 737 (73.1)
Age (y)	Median (IQR)	38 (32, 46)
Period of D:A:D cohort registration, n (%)	≤2002	11 896 (51.9)
	2003–2006	7060 (30.8)
	2007–2009	3954 (17.3)
Duration of D:A:D cohort follow-up	Median (IQR)	4.9 (2.2, 8.3)
Ethnicity, n (%)	White	10 827 (47.3)
	Black	1762 (7.7)
	Other	499 (2.2)
	Unknown	9817 (42.9)
Mode of HIV transmission, n (%)	Heterosexual	9472 (41.3)
	Homosexual	11 430 (49.9)
	IDU	404 (1.8)
	Other/ unknown	1604 (7.0)
Year of first HIV diagnosis	Median (IQR)	1999 (1994, 2004)
BMI (kg/m^2), n (%)	<18	621 (2.7)
	≥18, ≤26	13 228 (57.7)
	>26, ≤30	2618 (11.4)
	>30	902 (3.9)
	Unknown	5541 (24.2)
Diabetes mellitus	n (%)	597 (2.6)
Smoking status, n (%)	Current	7014 (30.6)
	Former	4715 (20.6)
	Never	6788 (29.6)
	Unknown	4393 (19.2)
CD4 cells/μL	Median (IQR)	410 (250, 595)
	n (%) <200	3837 (17.9)
Previous clinical AIDS	n (%)	5176 (22.6)
Cumulative ART exposure (y)	Median (IQR)	0.9 (0.0, 3.5)
Cumulative NRTI exposure (y)	Median (IQR)	0.8 (0.0, 3.5)
Cumulative PI exposure (y)	Median (IQR)	0.0 (0.0, 2.1)
Cumulative NNRTI exposure (y)	Median (IQR)	0.0 (0.0, 0.3)
Treatment status, n (%)	Naïve	8724 (38.1)
	Interruption	1072 (4.7)
	on ART	13 114 (57.2)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; D:A:D, Data Collection on Adverse Events of Anti-HIV Drug; HIV, human immunodeficiency virus; IDU, intravenous drug use; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Comparison of Patients Who Died From Liver-Related Death With Patients Who Did Not Die From Liver-Related Death

Participants who died from all causes compared with patients who remained alive were more often male and were older. Their first HIV diagnosis was earlier, their nadir and baseline CD4 cell counts were lower, maximum HIV-1 RNA levels were higher, and a history of previous clinical AIDS was more frequent (data not shown).

Patients who died from liver-related causes compared with patients who died from other causes (AIDS 376 [35.9%], CVD 116 [11.1%], non-AIDS malignancies 149 [14.2%], other causes 315 [30.1%], unknown causes 91 [8.7%]) were exposed to ART at baseline for a significantly longer period of time. Time of first HIV diagnosis was earlier and enrollment in the D:A:D study was earlier, probably reflecting longer duration of HIV infection (Table 3).

DISCUSSION

In this large prospective cohort of 22 910 HIV-positive participants without hepatitis coinfection who were followed for 114 478 patient-years, the incidence of liver-related deaths was very low at 0.10/1000 patient-years. Among the 12 persons who died from liver-related causes, 7 died because of alcohol use and 5 most probably as a consequence of ART-related hepatotoxicity.

In the large population-based National Health and Nutrition Examination Survey (NHANES) III study in the United States, liver-related mortality in adults who were HCV antibody negative was 0.16 (95% CI, .10–.25) per 1000 person-years; this is very similar to our finding of 0.10 (0.05–0.18) per 1000 person-years among HIV-positive individuals without HCV or HBV. However, in the NHANES III study, mortality of persons with chronic HCV infection was 4.4 (1.5–12.9) per 1000 person-years [17].

In HIV-positive persons without HCV or HBV coinfection, limited data are available on liver-related mortality. In the French Mortavic study, 48 of 287 deaths (17%) in HIV-positive individuals in 2005 were related to end-stage liver disease, of which 94% of deaths were attributable to chronic viral hepatitis. Severe alcohol use was reported in nearly half of the patients, and only 3 of 48 persons were HCV/HBV-negative [3]. In a recent collaborative analysis of 13 HIV cohorts, 113 of 1876 deaths (7%) were related to liver diseases. In 50 patients (44%), hepatitis viruses were not the cause of liver-related death. However, information on the proportion of patients with positive or unknown HCV/HBV serostatus was missing [18]. A previous analysis of the D:A:D study group found 341 of 2482 deaths (14%) to be liver related; 56 patients (2.3%) with liver failure had no documentation of chronic viral hepatitis [4]. However, our current reinvestigation showed that chronic hepatitis virus infection was frequent in the group without HCV or HBV documentation.

We found that noncirrhotic portal hypertension was the cause of only 2 liver-related deaths. Several case series and case reports on the disease have been published recently [10,

Table 2. Clinical Description of Human Immunodeficiency Virus–Positive Patients Without Hepatitis C Virus or Hepatitis B Virus Infection and Liver-Related Death

Patient	Cause of Death	Date of Death	Clinical Manifestations	Sex	Age at BL	First HIV Diagnosis	CD4 Cell Count/μL		HIV RNA[a]		CDC Stage C	Exposure to ART (y)		Comments
							BL	Last	BL	Last		BL	Last	
1	Alcohol	2003	Esophageal varices, ascites	M	55	1984	420	350	<50	5.37	yes	5.7	7.4	
2	Alcohol	2005	Not reported	M	38	1988	322	137	<50	4.08	yes	6.9	11.9	
3	Alcohol	2005	Splenomegaly	M	34	1991	174	236	3.45	<50	yes	6.3	11.7	Hemochromatosis
4	Alcohol	2001	Ascites, encephalopathy, HCC	M	57	1991	640	350	<50	<50	yes	3.8	4.3	
5	Alcohol	2003	Not reported	M	40	1986	297	242	4.20	5.00	no	8.5	10.9	
6	Alcohol	2007	Splenomegaly, ascites	M	35	1995	375	311	3.40	4.11	no	4.4	8.6	
7	Alcohol	2004	Splenomegaly, esophageal varices, varicel bleeding, ascites	F	34	2000	405	247	4.18	5.62	no	0	0	
8	NCPH	2000	Splenomegaly, esophageal varices, ascites	M	56	1990	114	114	<50	1.70	no	8.0	8.4	NCPH, ddI
9	ART	2001	Splenomegaly, encephalopathy	M	82	1994	437	437	1.94	1.99	no	5.6	6.1	Lactic acidosis: ddI, d4T
10	ART	2000	Ascites	F	46	1993	1080	1080	<50	<50	yes	3.4	3.5	Hypersens: NVP
11	ART	2006	Splenomegaly, esophageal varices, ascites, encephalopathy	M	44	1996	309	327	3.73	4.66	yes	5.4	9.1	Lactic acidosis: ddI, D4T, metformin
12	NCPH	2001	Splenomegaly, esophageal varices, portal vein thrombosis	M	54	1993	175	339	3.63	3.48	no	5.5	6.6	NCPH, ddI

Abbreviations: ART, antiretroviral therapy; BL, baseline; ddI, didanosine; D4T, stavudine; EFV, efavirenz; F, female; HCC, hepatocellular carcinoma; hypersens, hypersensitivity reaction; M, male; NCPH, noncirrhotic portal hypertension; NVP, nevirapine.

[a]Log10 copies/mL or below 50 HIV RNA copies/mL.

Table 3. Comparison of Characteristics of Hepatitis C Virus (HCV)– and Hepatitis B Virus (HBV)–Seronegative Patients With Liver-related Death With HCV- and HBV-seronegative Patients Dying From Other Causes

Characteristic	Liver-Related Death	Death From Other Causes[a]	*P* Value
No. of patients (%)	12 (100)	1047 (100)	
Male gender,			
n (%)	10 (83.3)	876 (83.7)	1.00
Age (y)			
Median (IQR)	45 (36, 55)	47 (38, 57)	.74
Year of first HIV diagnosis			
Median (IQR)	92 (89, 94)	95 (90, 00)	.05
Date of D:A:D cohort registration			
≤2002	12 (100.0)	793 (75.7)	.15
2003–2006	0	216 (20.6)	
2007–2009	0	38 (3.6)	
At baseline			
Exposure to ART, y			
Median (IQR)	5.5 (4.1, 6.6)	2.8 (0.1, 5.2)	.008
Treatment status, n(%)			
Naive	1 (8.3)	238 (22.7)	.23
Interruption	0 (-)	84 (8.0)	
On ART	11 (91.7)	725 (69.3)	
At last visit			
Nadir CD4 cells/μL			
Median (IQR)	97 (56, 171)	70 (16, 165)	.50
Peak HIV-1 RNA (log10 copies/mL)			
Median (IQR)	5.2 (4.9, 5.6)	5.3 (4.7, 5.8)	.45
Previous clinical AIDS,			
n (%)	6 (50.0)	688 (65.7)	.40
Cumulative ART exposure			
Any, y			
Median (IQR)	7.9 (5.2, 10.0)	5.6 (1.5, 8.9)	.14
NRTIs, y			
Median (IQR)	7.9 (5.2, 10.0)	5.4 (1.5, 8.6)	.11
NNRTIs, y			
Median (IQR)	0.9 (0.0, 1.6)	0.6 (0.0, 2.2)	.98
PIs, y			
Median (IQR)	3.5 (0.2, 6.8)	2.7 (0.3, 5.1)	.68
Current treatment status, n (%)			
Naive	1 (8.3)	66 (6.3)	.75
Interruption	3 (25.0)	370 (35.3)	
On ART	8 (66.7)	611 (58.4)	

Abbreviations: ART, antiretroviral therapy; D:A:D, Data Collection on Adverse Events of Anti-HIV Drug; HIV, hummunodecifiency virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] Death from other causes, n (%): AIDS, 376 (35.9); cardiovascular disease, 116 (11.1); non-AIDS malignancies, 149 (14.2); other causes, 315 (30.1); unknown causes, 91 (8.7).

16, 19–22]. The pathogenesis was found to be multifactorial, with didanosine exposure as an important risk factor. Patients present with esophageal varices, ascites, splenomegaly, portal vein thrombosis, variceal hemorrhage, or liver failure as severe and life-threatening complications. Mortality in advanced stages of disease is high [10]. Fortunately, current data indicate that it is indeed a rare disease with a lower mortality than previously suspected.

We found 2 liver-related deaths attributable to severe hyperlactataemia. In both cases, regimens included stavudine and

didanosine. Exposure to nucleoside reverse transcriptase inhibitors, particularly to the dideoxynucleosides (didanosine, stavudine, and zalcitabine), is associated with the inhibition of mitochondrial DNA γ-polymerase, leading to severe hyperlactatemia. Lactic acidosis is rarely observed; however, the mortality rate is high [23, 24], which is the reason that these drugs are no longer recommended. Nonnucleoside reverse transcriptase inhibitors, especially nevirapine, are associated with an increased risk of acute hepatotoxicity, typically due to hypersensitivity reactions. In line with our study findings, such adverse events are rare [25, 26].

We expected that liver-related deaths in persons not coinfected with hepatitis viruses were frequently due to severe alcohol consumption. Among HIV-positive persons, the reported prevalence of severe alcohol use ranges from 2.8% to 35%, depending on the observed population [27–30]. However, we found a low rate of death to be due to alcoholic liver disease, which is probably explained by the exclusion of many at-risk patients such as injection-drug users. Those in this patient group, who are at risk for multiple substance-dependence syndromes including alcohol [30], were almost completely excluded from analyses because of chronic viral hepatitis.

In agreement with other investigations, older age, male gender, lower CD4 cell counts, high HIV-1 viral load, and previous clinical AIDS were associated with death from all causes [18, 31]. We found that patients with liver-related death had been exposed to ART for a longer period of time and were known to be HIV-infected for a longer period of time. Both of these conditions might indicate a longer exposure to older and more hepatotoxic antiretrovirals. This is also true for patients with alcoholic liver disease, in whom the cause of death might have been multifactorial. However, this remains speculative because of the low number of endpoints.

The strength of this study is its large size and the long-term prospective observation. Additionally, the endpoint, that is, liver-related cause of death, was prospectively collected and centrally adjudicated using the CoDe system. Limitations are that multivariable analyses to identify associated risk factors were not possible because of the rare occurrence of endpoints under investigation; information on severe alcohol use was available only in case patients; and liver-related deaths were retrospectively reevaluated. We cannot rule out some underreporting of liver-related deaths. First, liver-related deaths might be difficult to capture because of multiple potential contributing factors (eg, sepsis or renal dysfunction). Central adjudication by several experienced clinicians, however, should have minimized such misclassifications. Second, some patients may have experienced liver-related death after being lost to follow-up, a scenario that might be more common in patients with alcoholic liver disease. However, because patients totally lost from HIV care are unlikely to be on ART, these missed events are unlikely to contribute to rates of ART-related liver mortality. Furthermore, because follow-up on such patients is right-censored on the date of loss to follow-up, our rate estimates should not be substantially biased by the exclusion of these events. Finally, given the very small number of events that limited a multivariable analysis of predictors of these liver-related deaths, it was not possible to perform a formal competing risks analysis to account for individuals who died of other causes prior to the clinical manifestation of liver disease.

In conclusion, this is the first large study to assess liver-related deaths in HCV or HBV seronegative patients. The incidence of liver-related deaths unrelated to chronic viral hepatitis, in particular life-threatening hepatotoxic side effects due to antiretrovirals, was very low and comparable to that of the general HCV-negative population in the United States. This is good news in times when HIV infection has evolved into a chronic disease, lifelong ART remains a necessity, earlier therapy for all HIV-positive persons is a matter of debate, and more comedication—potentially leading to drug–drug interactions and hepatotoxicity—will be necessary in this aging and multimorbid population. Therefore, ongoing monitoring of liver-related mortality and its contributors in HIV-positive persons will remain important.

Notes

Acknowledgments. D:A:D Participating Cohorts[colcnt = 3].

D:A:D steering committee: In the following sections, all persons marked with * are on the D:A:D steering committee. Persons marked with # are chairpersons. Members of the D:A:D steering committee from the oversight committee: S. Collins, N. Shortman, D. Butcher, R. Rode, W. Powderly. **D:A:D central coordination:** S.W. Worm, C.A. Sabin,* D. Kamara, L. Ryom, M. Ellefson, C. Smith, J. Tverland, J. Nielsen, J.D. Lundgren.# **D:A:D data managers:** R. Salbøl Brandt (coordinator), M. Rickenbach, L. Fanti, E. Krum, M. Hillebregt, S. Geffard, A. Sundström, M. Delforge, E. Fontas, F. Torres, H. McManus, S. Wright, J. Kjær. **Verification of endpoints:** A. Sjøl (cardiovascular disease, primary endpoint), P. Meidahl (oncology, new endpoint), J. Helweg-Larsen (hematology, new endpoint), J. Schmidt Iversen (nephrology, new endpoint)

Members of the 11 cohorts are as follows:

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Aquitaine, France
ATHENA, Netherlands
BASS, Spain
CPCRA, United States
EuroSIDA, Europe
HIV-BIVUS, Sweden
ICONA Foundation, Italy
NICE, France
SHCS, Switzerland
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References

1. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med **2006**; 166:1632–41.
2. Lewden C, May T, Rosenthal E, et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalite 2000 and 2005" surveys (ANRS EN19 and Mortavic). J Acquir Immune Defic Syndr **2008**; 48:590–8.
3. Rosenthal E, Salmon-Ceron D, Lewden C, et al. Liver-related deaths in HIV-infected patients between 1995 and 2005 in the French GERMIVIC Joint Study Group Network (Mortavic 2005 study in collaboration with the Mortalite 2005 survey, ANRS EN19). HIV Med **2009**; 10:282–9.
4. Smith C. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. AIDS **2010**; 24:1537–48.
5. Kovari H, Weber R. Influence of antiretroviral therapy on liver disease. Curr Opin HIV AIDS **2011**; 6:272–7.
6. Mocroft A, Soriano V, Rockstroh J, et al. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? AIDS **2005**; 19:2117–25.
7. Keiser O, Fellay J, Opravil M, et al. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: effect on mortality and treatment modification. Antivir Ther **2007**; 12:1157–64.
8. Kovari H, Ledergerber B, Battegay M, et al. Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis b or c virus co-infection. Clin Infect Dis **2010**; 50:502–11.
9. Maida I, Nuñez M, Rios MJ, et al. Severe liver disease associated with prolonged exposure to antiretroviral drugs. J Acquir Immune Defic Syndr **2006**; 42:177–82.
10. Kovari H, Ledergerber B, Peter U, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. Clin Infect Dis **2009**; 49:626–35.
11. McGovern BH, Ditelberg JS, Taylor LE, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. Clin Infect Dis **2006**; 43:365–72.
12. Guaraldi G, Squillace N, Stentarelli C, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis **2008**; 47:250–7.
13. Ingiliz P, Valantin MA, Duvivier C, et al. Liver damage underlying unexplained transaminase elevation in human immunodeficiency virus-1 mono-infected patients on antiretroviral therapy. Hepatology **2009**; 49:436–42.
14. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med **2003**; 349:1993–2003.
15. Kowalska JD, Friis-Moller N, Kirk O, et al. The Coding Causes of Death in HIV (CoDe) Project: initial results and evaluation of methodology. Epidemiology **2011**; 22:516–23.
16. Vispo E, Moreno A, Maida I, et al. Noncirrhotic portal hypertension in HIV-infected patients: unique clinical and pathological findings. AIDS **2010**; 24:1171–6.
17. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. Clin Infect Dis **2011**; 53:150–7.
18. 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**; 50:1387–96.
19. Mallet V, Blanchard P, Verkarre V, et al. Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients. AIDS **2007**; 21:187–92.
20. Schiano TD, Kotler DP, Ferran E, Fiel MI. Hepatoportal sclerosis as a cause of noncirrhotic portal hypertension in patients with HIV. Am J Gastroenterol **2007**; 102:2536–40.
21. Saifee S, Joelson D, Braude J, et al. Noncirrhotic portal hypertension in patients with human immunodeficiency virus-1 infection. Clin Gastroenterol Hepatol **2008**; 6:1167–9.
22. Chang PE, Miquel R, Blanco JL, et al. Idiopathic portal hypertension in patients with HIV infection treated with highly active antiretroviral therapy. Am J Gastroenterol **2009**; 104:1707–14.
23. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. Clin Infect Dis **2002**; 34:838–46.
24. Arenas-Pinto A, Grant A, Bhaskaran K, et al. Risk factors for fatality in HIV-infected patients with dideoxynucleoside-induced severe hyperlactataemia or lactic acidosis. Antivir Ther **2011**; 16: 219–26.
25. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. J Infect Dis **2005**; 191:825–9.
26. Chu KM, Boulle AM, Ford N, et al. Nevirapine-associated early hepatotoxicity: incidence, risk factors, and associated mortality in a primary care ART programme in South Africa. PLoS One **2010**; 5: e9183.
27. Chander G, Lau B, Moore RD. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. J Acquir Immune Defic Syndr **2006**; 43:411–7.
28. Justice AC, Lasky E, McGinnis KA, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: a comparison of disease measurement strategies. Med Care **2006**; 44: S52–60.
29. Samet JH, Cheng DM, Libman H, et al. Alcohol consumption and HIV disease progression. J Acquir Immune Defic Syndr **2007**; 46:194–9.
30. Conen A, Fehr J, Glass TR, et al. Self-reported alcohol consumption and its association with adherence and outcome of antiretroviral therapy in the Swiss HIV Cohort Study. Antivir Ther **2009**; 14:349–57.
31. Marin B, Thiebaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. AIDS **2009**; 23:1743–53.