Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of HBV or HCV co-infection. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study

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Abstract: Background. Liver diseases are leading causes of death in HIV-positive persons since the widespread use of combination antiretroviral treatment (ART). Most of these deaths are due to hepatitis C (HCV) or B (HBV) virus co-infections. Little is known about other causes. Prolonged exposure to some antiretroviral drugs might increase hepatic mortality.Methods. All patients of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study without HCV or HBV co-infection 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 co-infection for 114,478 person-years. There were 12 liver-related deaths (incidence, 0.10/1000 person-years); 7 because of severe alcohol use and 5 due to established ART-related toxicity. The rate of ART-related deaths in treatment-experienced persons was 0.04 (95% CI 0.01, 0.10) per 1000 person-years.Conclusions. We found a low incidence of liver-related deaths in HIV-infected persons without HCV or HBV co-infection. Liver-related mortality because of ART-related toxicity was rare.

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Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of HBV or HCV co-infection. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study

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summary:

In a large prospective multicohort study 22,910 HIV-positive participants without HBV or HCV co-infection were followed for 114,478 patient-years. The incidence of liver-related death was low at 0.10 per 1000 patient-years. Liver-related mortality due to antiretroviral drug-related toxicity was rare.

ABSTRACT

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

Methods: All patients of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study without HCV or HBV co-infection 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 co-infection for 114,478 person-years. There were 12 liver-related deaths (incidence, 0.10/1000 person-years); 7 because of severe alcohol use and 5 due to established ART-related toxicity. The rate of ART-related deaths in treatment-experienced persons was 0.04 (95% CI 0.01, 0.10) per 1000 person-years.

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

INTRODUCTION

Liver diseases are among the most frequent causes of non-AIDS-related deaths in HIV-positive persons [1-4]. Most of these deaths are the consequence of hepatitis C (HCV) or hepatitis B virus (HBV) co-infections, or alcohol use; little is known about other causes [5]. Results of two 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, including many HCV-coinfected persons, found an increased rate of liver-related deaths per year of ART in multivariable analyses also adjusted for latest CD4 cell counts [1], and the EuroSIDA observational cohort showed similar results [6].

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 ALT (reported as adverse events to antiretrovirals) was associated with a higher mortality, independent of chronic hepatitis virus co-infections [7]. In contrast, mortality was not increased in participants with chronic ALT elevation and without viral hepatitis in another SHCS analysis, but the observation period was shorter and the patient number smaller [8]. Recently, new hepatic syndromes related to ART have emerged in HIV-infected persons. Non-cirrhotic portal hypertension, a potentially life-threatening liver disease, has been linked to didanosine use [9, 10]. Furthermore, 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 (i) to assess liver-related mortality in HIV-positive persons without chronic viral hepatitis in the D:A:D cohort, and (ii) to provide comprehensive clinical details of these events. The role of ART and death was of particular interest.

METHODS

Study design

The D:A:D Study, founded in 1999, is a prospective observational study of 11 previously established cohorts as described in detail [14]. Currently, 49,737 HIV-positive individuals (33,308 from the original two recruitments with an additional 16,429 newly included in the cohort from 2009) are followed at 212 clinics in Europe, the United States, and Australia. The primary end point was myocardial infarction with other endpoints (including deaths) 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 collection forms are completed, including sociodemographic, clinical, laboratory, and treatment information. 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 causes of death have 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 the etiology. Other categories were 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 the clinical charts were retrospectively reviewed by local investigators of participating institutions 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, non-cirrhotic portal hypertension, 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 sero-positive 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 or 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 >40g/d and in male >60g/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 (six months after the patient's last clinic visit), or the end of study follow-up (1st 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 to 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's 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. 4703 (9%) participants were excluded because they belonged to cohorts not responding to 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 (see 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 percent. 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%) were liver-related. Thus, the incidence of liver-related deaths in persons not co-infected with HCV or HBV was 0.10 per 1000 person-years (95% CI 0.05, 0.18).

Description of patients who died from liver disease

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

Liver biopsies were performed only in two patients and autopsy in one, confirming the diagnosis of alcoholic liver disease, respectively showing histological findings consistent with non-cirrhotic portal hypertension [10, 16]. No patient was treated with transjugular intrahepatic portal systemic shunting and none received a liver transplant.

Comparison of patients with liver-related death with patients without liver-related death

Participants who died from all causes compared to 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 higher, and more frequently had a history of previous clinical AIDS (data not shown).

Patients with liver-related death compared to 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 significantly longer exposed to ART at

baseline. 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 co-infection, followed for 114,478 patient-years, the incidence of liver-related deaths was very low at 0.10 per 1000 patient-years. Among the 12 persons who died from liver-related causes, seven died because of alcohol use, and five most probably as a consequence of ART-related hepatotoxicity.

Liver-related mortality in the large population-based NHANES III study in the United states, in HCV antibody negative adults was 0.16 (95% CI, 0.10-0.25) per 1000 person years and thus very similar to our findings of 0.10 (0.05-0.18) among HIV positive individuals without HCV or HBV. In persons with chronic HCV infection, however, mortality in the NHANES III study 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% were attributable to chronic viral hepatitis. Severe alcohol consumption was reported in nearly half of the patients, and only three of 48 persons were HCV/HBV-negative [3]. In a recent collaborative analysis of 13 HIV cohorts, 113 of 1876 deaths (7%) were assigned 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 sero-status 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 re-

investigation showed that chronic hepatitis virus infection was frequent in the group without HCV or HBV documentation.

We found that non-cirrhotic portal hypertension was the cause for only two liver-related deaths. In the last years, several case series and case reports on the disease have been published [10, 16, 19-22]. The pathogenesis is multi-factorial 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 is high [10]. Fortunately, current data indicate that it is indeed a rare disease with a lower mortality than previously suspected. We found two liver-related deaths attributable to severe hyperlactataemia. In both cases, regimens included stavudine and didanosine. Exposure to nucleoside reverse transcriptase inhibitors (NRTI), particularly to the dideoxynucleosides didanosine, stavudine and zalcitabine, is associated with the inhibition of mitochondrial DNA γ-polymerase leading to severe hyperlactataemia. Lactic acidosis is rarely observed, but its mortality rate is high [23, 24], which is the reason that these drugs are no longer recommended. Non-nucleoside reverse transcriptase inhibitors (NNRTI), 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 co-infected 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 deaths due to alcoholic liver disease, probably explained by the exclusion of many at-risk patients such as injecting drug users. This patient group who is at risk for multiple substance

dependence syndrome, including alcohol [30], had to almost completely be 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 were longer exposed to ART and longer known to be HIV-infected, both of which might indicate a longer exposure to older and more hepatotoxic antiretrovirals, also in patients with alcoholic liver disease, in whom the cause of death might have been multi-factorial. But 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. Furthermore, the endpoint, 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 (e.g. 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 which might be more common for patients with alcoholic liver disease. However, as 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, as 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

which limited a multivariable analysis of predictors of these liver-related deaths, it was not possible to perform a formal competing risks analysis to take account of individuals who died of other causes prior to the clinical manifestation of liver disease.

In conclusion, this is the first large study assessing liver-related deaths in HCV or HBV sero-negative 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 the general HCV-negative population in the United States. This is good news in times in which 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 co-medication - potentially leading to drug-drug interactions and hepatotoxicity - will be necessary in this aging and multi-morbid person group. Therefore, ongoing monitoring of liver-related mortality and its contributors in HIV-positive persons will remain important.

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Aquitaine	**CPCRA**	**NICE Cohort**
France	**USA**	**France**
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The Netherlands	**Europe**	**Switzerland**
AHOD	**HIV-BIVUS**	**St.Pierre Brussels Cohort**
Australia	**Sweden**	**Belgium**
BASS	**The ICONA Foundation**	
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Table 1: Characteristics of D:A:D study participants without HCV or HBV co-infection at study entry.

Total of participants	**n**	**22,910**
Male gender	n (%)	**16737 (73.1)**
Age (years)	median (IQR)	**38 (32, 46)**
Period of D:A:D cohort registration, n (%)	≤2002	**11896 (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	**10827 (47.3)**
	black	**1762 (7.7)**
	other	**499 (2.2)**
	unknown	**9817 (42.9)**
Mode of HIV transmission, n (%)	heterosexual	**9472 (41.3)**
	homosexual	**11430 (49.9)**
	IDU	**404 (1.8)**
	other/unknown	**1604 (7.0)**
Year of first HIV diagnosis	median (IQR)	**1999 (1994, 2004)**
BMI (kg/m2), n (%)	<18	**621 (2.7)**
	>18, <26	**13228 (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 (years)	median (IQR)	**0.9 (0.0, 3.5)**
Cumulative NRTI exposure (years)	median (IQR)	**0.8 (0.0, 3.5)**
Cumulative PI exposure (years)	median (IQR)	**0.0 (0.0, 2.1)**
Cumulative NNRTI exposure (years)	median (IQR)	**0.0 (0.0, 0.3)**
Treatment status, n (%)	naïve	**8724 (38.1)**
	interruption	**1072 (4.7)**
	on ART	**13114 (57.2)**

Table 2: Clinical description of HIV-positive patients without HCV or HBV 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*		CDC stage C	Exposure to ART (years)		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	nor 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

* Log10 copies/ml or below 50 HIV RNA copies/ml

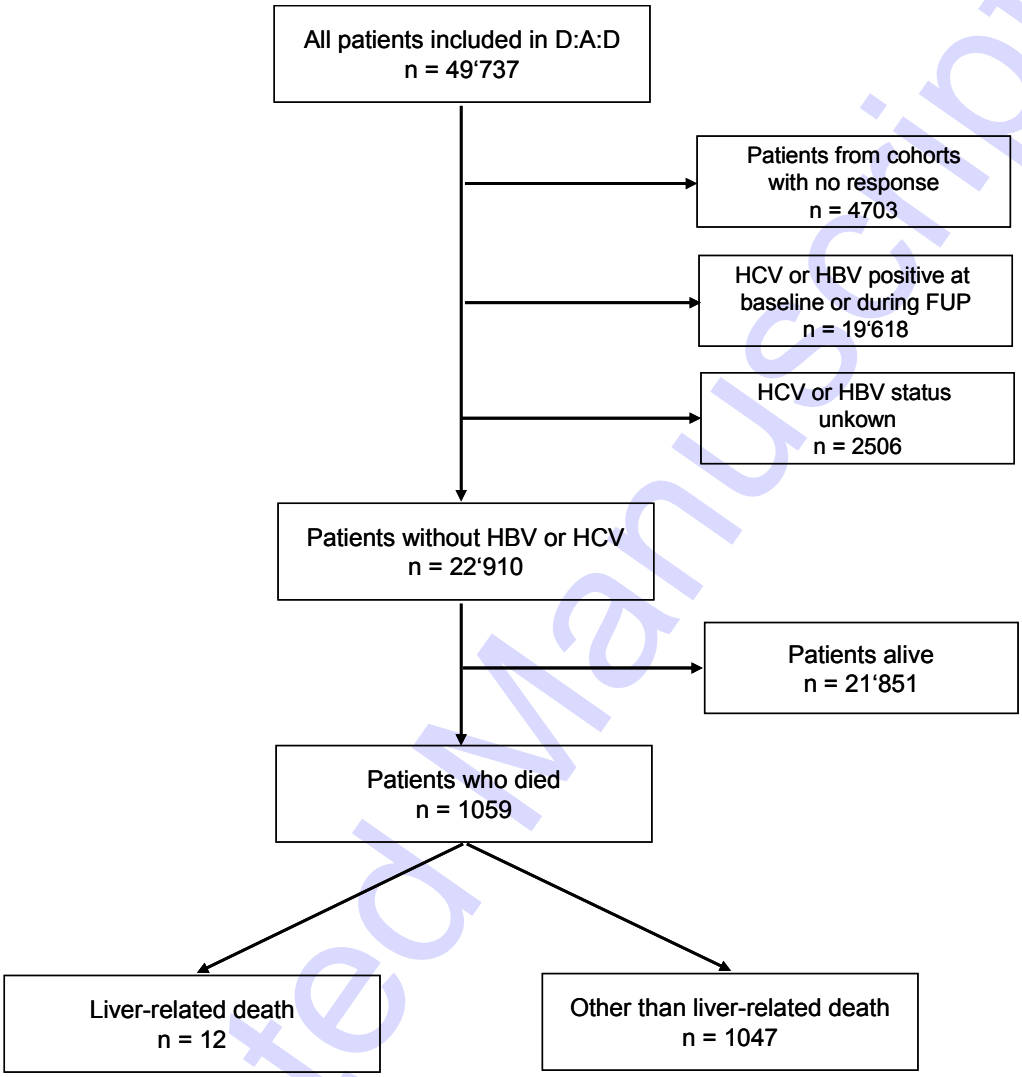
Abbreviations: ART, antiretroviral therapy. BL, baseline. ddI, didanosine. D4T, stavudine. EFV, efavirenz. F, female. HCC, hepatocellular carcinoma. Hypersens, hypersensitivity reaction. M, male. NCPH, non-cirrhotic portal hypertension. NVP, nevirapine.

Table 3: Comparison of characteristics of HCV- and HBV-seronegative patients with liver-related death with HCV- and HBV-seronegative patients dying from other causes.

		Liver-related death	Death from other causes*	P value
No. of patients (%)		12 (100)	1047 (100)	
Male gender	n (%)	10 (83.3)	876 (83.7)	1.00
Age (years)	median (IQR)	45 (36, 55)	47 (38, 57)	0.74
Year of first HIV diagnosis	median (IQR)	92 (89, 94)	95 (90, 00)	0.05
Date of D:A:D cohort registration,	<2002	12 (100.0)	793 (75.7)	0.15
	2003-2006	0	216 (20.6)	
	2007-2009	0	38 (3.6)	
At baseline				
Exposure to ART, years	median (IQR)	5.5 (4.1, 6.6)	2.8 (0.1, 5.2)	0.008
Treatment status, n(%)	naive	1 (8.3)	238 (22.7)	0.23
	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)	0.50
Peak HIV-1 RNA (log10copies/ml)	median (IQR)	5.2 (4.9, 5.6)	5.3 (4.7, 5.8)	0.45
Previous clinical AIDS	n (%)	6 (50.0)	688 (65.7)	0.40
Cumulative ART exposure				
Any, years	median (IQR)	7.9 (5.2, 10.0)	5.6 (1.5, 8.9)	0.14
NRTIs, years	median (IQR)	7.9 (5.2, 10.0)	5.4 (1.5, 8.6)	0.11
NNRTIs, years	median (IQR)	0.9 (0.0, 1.6)	0.6 (0.0, 2.2)	0.98
PIs, years	median (IQR)	3.5 (0.2, 6.8)	2.7 (0.3, 5.1)	0.68
Current treatment status, n (%)	naive	1 (8.3)	66 (6.3)	0.75
	interruption	3 (25.0)	370 (35.3)	
	on ART	8 (66.7)	611 (58.4)	

*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).
Abbreviations: ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Figure 1: Patient Flowchart



Abbreviations: FUP, follow-up; HBV, hepatitis B virus; HCV, hepatitis C virus.