TITEL PAGE

TITLE: Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons

RUNNING HEAD: End-stage liver disease, HCC and ART

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ETHICS COMMITTEE APPROVAL

This analysis was conducted in accordance with the Declaration of Helsinki and approved by national ethical committee where necessary.

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ABSTRACT (246, max 250 words)

OBJECTIVES: Whilst several antiretroviral drugs (ARVs), including the d-drugs stavudine (d4T) and didanosine (ddI), may cause biomarker-defined hepatotoxicity, their association with clinically defined end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) remains unknown.

DESIGN: Prospective cohort study

METHODS: D:A:D participants were followed until the first of ESLD (variceal bleeding, hepatic encephalopathy, hepatorenal syndrome or liver transplantation), HCC (histology or alpha-fetoprotein plus imaging), death, 6 months after last visit or 1/2/2014. Associations between ESLD/HCC and cumulative use of individual ARVs were investigated using Poisson regression adjusting for potential confounders.

RESULTS: During a median follow-up of 8.4 years, 319 ESLD/HCC cases occurred (incidence 1.01/1000 person-years [95%CI 0.90-1.12]) with a 62.6% one-year mortality rate. After adjustment, cumulative (per 5 years) exposure to d4T (relative rate 1.46 [95%CI 1.20-1.77]), ddI (1.32 [1.07-1.63]), tenofovir (TDF, 1.46 [1.11-1.93]) and (fos)amprenavir (APV, 1.47 [1.01-2.15]) was associated with increased ESLD/HCC rates. Longer exposure to emtricitabine (0.51 [0.32-0.83]) and nevirapine (0.76 [0.58-0.98]) were associated with lower ESLD/HCC rates. The ddI/d4T-associated increased ESLD/HCC rate only started to decline 6 years after cessation.

CONCLUSION: Cumulative use of d4T, ddI, TDF and APV were independently associated with increased ESLD/HCC rates, and intensified monitoring of liver function should hence be considered amongst all individuals exposed for longer time-periods. The use of d-drugs should furthermore be avoided, where there are alternatives

available and focus should be put on those with longer-term d-drugs exposure who remain at increased ESLD/HCC risk. The unexpected, and viral hepatitis independent, TDF association calls for further investigations.

KEY WORDS; end-stage liver disease, hepatocellular carcinoma, hepatotoxicity, HIV, d-drugs, (fos)amprenavir, tenofovir

TEXT (3.495 words, max 3500)

Introduction

The majority of the antiretroviral (ARV) drug classes used for the treatment of HIV have an intrinsic potential to cause hepatotoxicity, which may be induced through various mechanisms [1-4]. Previous studies have estimated that up to 30% of all HIV-positive persons will experience some form of hepatotoxicity associated with ARV treatment (ART) [1-3]. Studies that have investigated adverse ART-liver effects have commonly been based on changes in liver-related biomarkers such as transaminases [3, 5-9], fibrosis markers (e.g. hyaluronic acid) [10], imaging modalities or biopsy findings [11-17]. Furthermore, most studies have been of a relatively modest size or of a cross-sectional nature, making assessments of the time course between exposure and outcomes difficult [13-19]. Studies have also been conducted primarily among individuals who are co-infected with HIV and viral hepatitis, in whom the incidence of adverse hepatic impairment is elevated compared to HIV mono-infected individuals [5, 14, 18, 20, 21]. Indeed, a previous D:A:D analysis in participant without viral hepatitis found that deaths related to liver failure are rare in HIV-positive individuals without viral hepatitis B (HBV) or C (HCV) [20].

The adverse effects of ART on development of liver impairment have been debated for years [20, 22-25]. The diverse study outcomes are, however, not surprising as these will naturally depend on the individual ARV investigated. ART is known to have an overall beneficial effect on liver-related outcomes, largely due to attenuating liver disease progression in viral hepatitis co-infected individuals by improvements in

immune function [22, 24], and the direct antiviral effect on HBV by certain individual ARVs such as tenofovir (TDF), lamivudine (3TC) and emtricitabine (FTC). Conversely, other ARVs, such as tipranavir (TPV), have a known direct hepatotoxic effect [4]. Furthermore, an excess risk of liver-related death with cumulative ART use has been observed after accounting for improvements in the CD4 cell count [24, 26].

Among the individual ARVs, dideoxynucleoside analogues or 'd-drugs' and, in particular, didanosine (ddI) and stavudine (d4T), have commonly been associated with alterations in liver function and severe steatosis/fibrosis development [11, 13, 16, 17, 27-31]. Moreover, ddI use has been linked with development of non-cirrhotic portal hypertension [32, 33]. Use of d-drugs is now rare in most high-income countries due to their serious adverse effects including neuropathy and lipodystrophy [4]. D-drug use was, however, common in the past, and previous exposure may also impact on subsequent liver function [34]. In 2010 the WHO launched an initiative aiming to reduce the use of d4T. However, many individuals in resource-limited settings continue to use d-drugs due to their widespread availability and low cost; as such, an estimated 1.1 million individuals still initiated a d4T-based first-line ARV regimen in 2011 [35, 36].

 Of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), in particular nevirapine (NVP) has been linked to hepatotoxicity as part of a systemic hypersensitivity reaction [1, 26, 37-39]. Compared to the suspected liver steatosis/fibrosis effect of d-drugs and other nucleoside reverse transcriptase inhibitors (NRTIs), the NNRTI class effect on the liver is of a hepatitis-like nature [1, 4, 26, 37-39].

Among the protease inhibitors (PIs), particular atazanavir (ATV) may cause

hyperbilirubinemia and cholecystolithiasis, whilst TPV-related hepatitis is expected in

10% of recipients [4, 40, 41]. Co-infection with viral hepatitis has been associated with

increased plasma levels of PIs, but the clinical impact of co-infection on ARV-related

hepatotoxicity is unknown [42].

Whilst most ARV-related adverse liver effects are reported to be acute, mild and

asymptomatic [3], prospective investigations of long-term ARV use and clinical

manifestations of end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC)

have not, as yet, been conducted in a large heterogeneous cohort setting. This analysis

aimed to describe incidence rates (IRs), predictors and survival after ESLD/HCC with

focus on the potential association with cumulative use of individual ARVs, and in

particular d-drugs, due to their high susceptibility to induce fibrosis.

Methods

Study population

The Data Collection on Adverse events of Anti-HIV Drugs Study (D:A:D) is a prospective

cohort collaboration established in 1999 which follows more than 49,000 HIV-1-

positive persons in Europe, the United States and Australia; details have been

published previously [17]. Data on clinical events including ESLD, cancers, myocardial

infarction, stroke, invasive cardiovascular procedures and death are collected in real-

time during routine clinical care. Events are validated centrally and monitored

regularly. In addition, information on demographic factors, ART, viral hepatitis,

laboratory test results, cardiovascular risk factors and AIDS events is collected

electronically at enrolment and every six months.

Endpoint definition

From 1/2/2004 onwards systematic collection of ESLD and cancer events (including

HCC) was initiated in D:A:D. A designated ESLD event form was developed to collect

detailed information on the clinical symptoms defining ESLD: bleeding from

endoscopically verified gastric or oesophageal varices; stage III-IV hepatic

encephalopathy; hepatorenal syndrome; or liver transplantation (more information at

www.chip.dk). In addition, pathology reports and transient elastographies results are

collected. Information on HCC, including histology findings or the combination of

elevated alpha-fetoprotein and HCC specific imaging findings, is collected on a

designated cancer form. Where a diagnosis of ESLD/HCC was reported only on a fatal

case reporting form (Coding Causes of deaths in HIV, CoDe, more information at

www.chip.dk) [43], the death was only considered to be an ESLD or HCC event if

information was provided on the clinical symptoms and histology/imaging findings.

Statistical methods

D:A:D participants were followed from the date of enrolment in the study or 1/2/2004,

if this was later (baseline), until the first of an ESLD/HCC event, death, six months after

last visit or 1/2/2014. Only the first ESLD or HCC event reported for each individual

during prospective follow-up was included in the analysis. IRs were calculated per 1000

person years of follow-up (PYFU). Kaplan-Meier estimation was used to describe the

risk of mortality following a diagnosis of ESLD/HCC. Poisson regression models were

used to quantify the relationship between ESLD/HCC and cumulative ARV use.

Potential confounders considered for adjusted models were calendar year [categorised as before 2008, 2008/2009 and after 2009], demographic variables (gender, age [<35 or >35 years], ethnicity [Caucasian vs. other], participating cohort, smoking status [current, previous, never, unknown]), HIV-related factors (route of HIV acquisition [IDU vs. other], previous AIDS diagnosis) and HBV and HCV co-infection status [negative, positive, unknown]), with variables retained in multivariable models if they were significantly associated (p<0.05) with the outcome in univariate models.

Subsequent models also considered adjustment for the latest viral load [VL, fitted categorically] and CD4 count, both as time-updated covariates; these covariates were purposely not included in our primary analyses of ARV associations, as they may lie on the causal pathway between ARV exposure and ESLD/HCC.

ARV exposure was fitted cumulatively (per 5 years) as it was hypothesised that the risk of any adverse liver events would increase with longer exposure [44]. All ARV exposures were considered, regardless of when they accrued– thus, individuals may already have accrued several years of exposure to some of the ARVs prior to baseline; exposure then continued to accrue after baseline if the individuals continued to receive the drugs (or restarted them at a later point in time).

An investigation of the association between time since d-drug discontinuation and ESLD/HCC rates was conducted adjusting for cumulative exposure to each drug and other potential confounders. This allowed us to assess the potential for any increased risk of ESLD/HCC to be reversed after cessation of the drug.

All statistical analyses were carried out using SAS version 9.3 (Statistical Analysis Software, Cary, NC, USA).

Results

Characteristics

A total of 45,544 individuals were followed in D:A:D from 1/1/2004 and were included in the analysis; these individuals were predominantly Caucasian (49.6%), male (73.5%) and had acquired HIV through sex between men, MSM (44.5%) (Table 1). The median age was 40 (interquartile range [IQR] 34-46) years at baseline and the median CD4 count 434 (IQR 282-621) cells/mm^3. During a median FU of 8.4 (IQR 5.5-12.6) years a total of 319 ESLD/HCC events occurred (IR 1.01/1000 PYFU, 95% confidence interval [CI] 0.90-1.12) of which 209 were ESLD and 110 HCC events. Overall, 157 (49.2%) of the ESLD/HCC events were identified through an ESLD form, 88 (27.6%) through a cancer form, and the remaining 74 (23.2%) through a death form. The most common clinical manifestation of ESLD was hepatic encephalopathy grade III-IV (43.3%), followed by endoscopically verified variceal bleeding (27.4%), hepatorenal syndrome (14.6%) and liver transplantation (5.1%), while 9.6% had more than one manifestation at the same event date. The median age of individuals experiencing ESLD/HCC (at the time of the event) was 47 (IQR 42-52) years, the most common mode of HIV acquisition was injection drug use (IDU, 53.6%), the median CD4 cell count was 266 (IQR 153- 448) cells/mm^3 and 72.4% were confirmed HCV positive and 39.9% HBV positive (Table 1). As 82.8% of all events occurred in individuals co-infected with viral hepatitis the ESLD/HCC IR was low in individuals without HCV or HBV evidence (0.19/1000 PYFU

[95% CI 0.13- 0.26]) (Table 2). Whilst the ESLD/HCC IR was similar for individuals with HIV/HCV and HIV/HBV co-infection the number of individuals with HIV/HCV/HBV was limited (data not shown).

Prognosis

The 319 individuals with ESLD/HCC were followed for a median of 0.23 (IQR 0.01-1.88) years after diagnosis, over which time 241 (75.6%) died. The median survival after an ESLD/HCC diagnosis was 0.27 years, while the one-year mortality rate (Kaplan-Meier estimate) was 62.6%. After exclusion of 52 individuals diagnosed with ESLD/HCC at time of death, the median survival after an ESLD/HCC event was 0.66 years and the one-year mortality rate 55.0%.

Associations between ARV exposure and ESLD/HCC

Associations between individual ARVs and ESLD/HCC were initially explored without adjustment for calendar year, demographics, HIV-related factors and viral hepatitis status (but with adjustment for other ARVs in the regimen) (Figure 1).

Among the NRTIs, a linear and similar cumulative effect of ddI and d4T was observed (d4T 1.80/5 years [1.42-2.27] and ddI 1.55/5 years [1.25-1.92]). Increased exposure to 3TC (1.31/5 years [1.07-1.60]) and TDF (1.55/5 years [1.17-2.04]) were unexpectedly also associated with increased rates of ESLD/HCC. In contrast, a reduced rate of ESLD/HCC was seen in individuals with longer exposure to FTC (0.54/5 years [0.34-0.86]). After adjustment for potential confounders, significant associations remained with cumulative use of d4T (1.46/5 years [1.20-1.77]), ddI (1.32/5 years [1.07- 1.63]),

TDF (1.46/5 years [1.11-1.93]) and FTC (0.51/5 years [0.32-0.83]), while the association

with 3TC no longer remained significant (Figure 1).

Among the NNRTIs use of NVP was surprisingly associated with a reduced rate of

ESLD/HCC in both unadjusted (0.56/5 years [0.43-0.74]) and adjusted (0.76/5 years

[0.58-0.98]) analyses.

(Fos)amprenavir (APV) was the only PI associated with ESLD/HCC in unadjusted models

(1.82/5 years [1.16-2.85]) and this association remained significant in the fully adjusted

multivariate model (1.47/5 years [1.01-2.15]).

A sensitivity analysis stratified according to viral hepatitis status reached consistent

associations for all ARVs, including TDF, although the number of events was low in

those without evidence of HBV/HCV (data not shown).

The associations with ddI and d4T were explored in more detail, as determined *a priori*

due to the potential long terms effects on liver function after ceased use. When

exposure to ddI was considered without any d4T exposure, the association between

ddI and ESLD/HCC was reduced slightly (1.28/5 years [0.98-1.66]) as was d4T exposure

when used without ddI (1.43/5 years [1.16-1.77]). When used concomitantly the

association with ESLD/HCC was strengthened (2.03/5 years [1.44-2.85]), however, only

to the extent that would be expected on the basis of combining the effects of each

drug when used separately, as there was no evidence of synergy between the two

drugs in this model. There was no strong evidence to indicate that the associations

between the two d-drugs and ESLD/HCC differed between individuals with and without

viral hepatitis co-infection (p=0.50 for interaction between d4T and any hepatitis, p=0.09 for ddI and any hepatitis), although due to the small number of events in those without co-infection, the power to detect a significant interaction was extremely low.

Of the 18,676 persons on d4T or ddI, 91.4% stopped their use at least once during follow-up, with only 18.4% of the PYFU in those exposed to d-drugs being current users. Those having previously stopped d-drugs had higher ESLD/HCC rates than those currently on d-drugs, an effect that only started to wane slightly after more than six years after cessation (Table 3).

Discussion

This is the first large, prospective and long-term analysis to investigate incidence, outcomes and risk factors for clinically defined liver failure and cancer in HIV-positive persons with focus on the contribution of individual ARVs.

We observed a relatively low overall IR of ESLD/HCC in this large heterogeneous cohort of both HIV mono- and viral hepatitis co-infected persons. In comparison, a recent retrospective analysis from the VA cohort found that among ARV-treated HIV/HCV co-infected persons, 7.4 % experienced hepatic decompensation at 10 years [45]. This higher rate may, however, be explained by the conservative ESLD/HCC criteria in D:A:D, and by the inclusion of ascites in the definition of hepatic decompensation, which was not originally included in the D:A:D definition as it may also be seen in other non-cirrhotic liver disease-related conditions [46].

The prognosis following ESLD/HCC was poor with a median one-year survival of only 0.27 years. This observation calls for an increased awareness of ESLD/HCC risk factors and management. The recent introduction of effective direct acting agents (DAAs) for treatment of HCV will likely change the ESLD/HCC incidence and survival over the years to follow.

ARV risk factors of ESLD/HCC

We identified cumulative use of ddI, d4T, TDF and APV to be independently associated with an increased rate of ESLD/HCC development, while use of FTC and NVP were associated with decreased rates.

The association between cumulative ddI and d4T use and excess ESLD/HCCIR builds on the observations of a number of relatively small studies of HIV- mono and viral hepatitis co-infected individuals using various biomarkers of liver failure [5, 14, 18]. A recent retrospective study among 146 HIV/HCV co-infected persons found that each additional year of use of these drugs was associated with a 50% increase in the odds of progressing one or more grades on the Brunt score [15]. Likewise, a subanalysis among 205 HIV/HCV co-infected persons randomised to two types of anti-HCV treatment found that ddI use was associated with three-fold higher odds of histologically verified fibrosis [16], and a European cross-sectional study of 671 HIV/HCV co-infected persons found that a median use of ddI exceeding 5 months increased the odds of severe liver fibrosis by 70% [13].

The IR of ESLD/HCC among those who had been exposed to ddI and/or d4T was higher among individuals who had discontinued the drugs, than among those currently receiving them. This may reflect the fact that those at highest underlying risk of ESLD/HCC may be most likely to stop the d-drugs. Several mechanisms have been suggested for d-drug hepatotoxicity including inhibition of the mitochondrial DNA polymerase gamma and the mitochondrial respiratory chain with resulting oxidative damages and lactic acidosis [3, 16, 47, 48], hepatic steatosis (micro- and macrovascular), hepatocellular damage and ultimately development of cirrhosis [13, 15].

The observed higher incidence of ESLD/HCC did not begin to decrease until six years after cessation of ddI and d4T, suggesting that exposure to the drugs may have caused irreversible tissue damage. This finding is in accordance with work from Scourfield et al. who found that the adverse liver effects of ddI developed late and after use of the drug was discontinued [34]. These observations hence have important implications for the clinical management of all HIV-positive persons with current or prior d-drug use. Use of d-drugs should therefore be avoided if possible, in particular in individuals with high underlying risk of ESLD/HCC such as those with viral hepatitis. Due to the long-lasting adverse effects of d-drugs also after their use have been discontinued one might further consider intensifying monitoring with liver-biomarkers, and if abnormal, by transient elastography or liver biopsy among individuals with long-term prior d-drug use to better identify individuals at increased ESLD/HCC risk.

In contrast to the associations seen with ddI and d4T, the observed association between ESLD/HCC and TDF was unexpected. As TDF may be used preferentially among those with HBV co-infection, it may not be surprising that we see an increased rate of hepatotoxicity in those exposed to this drug [1, 49]. Importantly, however, the TDF association remained unchanged after stratifying according to and adjusting for viral hepatitis status, suggesting the association is not dependent on HBV and is not simply explained by an increased ESLD/HCC risk among individuals co-infected with HBV and preferentially treated with TDF. Furthermore a recent D:A:D analysis which investigated predictors of chronic liver enzyme elevation among individuals without viral hepatitis, also confirmed the positive association with cumulative TDF use, supporting this observation [50]. Finally 3TC, which is also used to treat HBV-infection, although less often due to a lower genetic resistance barrier, did not remain statistically significantly associated with ESLD/HCC in adjusted models. Use of FTC, which is commonly co-prescribed with TDF (68% of those currently on TDF were also on FTC) was further independently associated with a lower ESLD/HCC risk and further argues against the hypothesis that our observed TDF association simply reflects a higher rate of unreported HBV infection. Outside the D:A:D study, only a few studies, predominantly smaller case reports, have reported a positive association between liver impairment and TDF [49, 51, 52]. This TDF association does, however, seem to be robust in D:A:D and is related to several liver outcomes, calling for confirmation in other large studies. No biological mechanism is currently known for TDF to cause ESLD/HCC, but the effect may relate to the development of mitochondrial toxicity in hepatocytes as described in renal tubular cells [53], and steatosis is described in the

TDF product information [54]. Our results call for further investigations in mechanistic studies.

Based on the literature, if anything, one would have expected use of NVP to be associated with increased risk of ESLD/HCC [1, 26, 37-39]. Instead, we observed a lower rate of ESLD/HCC associated with cumulative NVP use. This may reflect the fact that NVP may only contribute to acute, but not more advanced and chronic stages of liver disease, but may also reflect some degree of confounding by indication with NVP not being prescribed to high risk individuals, or being discontinued in those who experience liver enzyme elevations after starting the drug.

Elevated levels of transaminases are a common adverse effect of APV, although a recent small study did not identify a safety concern with long term use [55, 56]. A recent mechanistic study further found some evidence to support an anti-HCC effect of APV [57]. APV may, due to its use in calculating dose recommendations for various levels of liver impairment, preferably have been used in individuals with liver impairment and use is currently limited[58]. No other statistically significant associations were observed for cumulative use of other PIs including ATV. This suggests that from a clinical liver endpoint perspective the commonly used PIs can be safely used in HIV-positive individuals over longer periods of time, a finding that is in accordance with other recent studies using biomarker-defined hepatotoxicity. Of note, use of TPV and darunavir are still too limited to allow for robust statistical analyses in D:A:D. Furthermore, our analysis did not consider any impact of DAAs for treatment of

HCV, where there are known drug-drug interactions with PIs, as the use of DAAs in D:A:D is still extremely low.

Limitations

The limitations of this analysis should be acknowledged and include the lack of a systematic collection on information on alcohol consumption. However, the associations observed with use of ddI, d4T, TDF, APV, NVP and FTC are unlikely to be confounded by alcohol usage, as the choice of ART including these ARVs is unlikely to be modified by the clinician's knowledge of the individuals alcohol consumption. A high number of ARVs were included in the analysis, hence we cannot rule out that findings may be a result of multiple testing and the possibility of false positive error. Confounding by indication cannot be ruled out for a number of the included ARVs, in particular APV and NVP. Finally, non-ARV hepatotoxic treatment such as anti-TB treatment with isoniazid and rifampicin, or sulphonamides used to treat PCP may represent unmeasured confounding although adjustment for previous AIDS events did not change any of the observed ARV associations.

Conclusion

Whilst the ESLD/HCC incidence was relatively low in this large heterogeneous cohort, and predominantly seen in individuals with viral hepatitis co-infection the prognosis following a diagnosis was very poor. Cumulative use of ddI, d4T, TDF and APV was independently associated with increased rates of ESLD/HCC, while use of NVP and FTC was associated with lower rates. There was no evidence for reversibility of ESLD/HCC risk upon cessation of d-drugs, and intensified monitoring of liver function and

avoidance of hepatotoxic compounds should hence be considered amongst all with

longer-term current or prior d-drug exposure. The unexpected and viral hepatitis

independent, TDF association calls for further investigations, whilst use of d-drugs

should be avoided, where there are alternatives available.

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CONFLICTS OF INTEREST

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Table 1. Characteristics of persons included in analysis

at baseline and at the time of ESLD/HCC

		All eligible participants at baseline	At the time of an ESLD/HCC event
Number of participants		45,544 (100.0)	319 (100.0)
Gender	Male	33,465 (73.5)	254 (79.6)
	Female	12,079 (26.5)	65 (20.4)
Age (years)	Median (IQR)	40 (34-46)	47 (42-52)
Mode of acquisition	MSM	20,284 (44.5)	64 (20.1)
	IDU	6,396 (14.0)	171 (53.6)
	Heterosexual	15,316 (33.6)	67 (21.0)
	Other/unknown	3,548 (7.8)	17 (5.3)
Ethnicity	Caucasian	22,609 (49.6)	180 (56.4)
	Black African	4,263 (9.4)	12 (3.8)
	Other	1,265 (2.8)	1 (0.3)
	Unknown	17,407 (38.2)	126 (39.5)
CD4 count (cells/mm³)	Median (IQR)	434 (282-621)	266 (153-448)

HIV RNA (log$_{10}$ copies/mL)	Median (IQR)	2.3 (1.7-4.3)	1.7 (1.7-2.6)
HCV status*	Negative	29,002 (63.7)	71 (22.3)
	Positive	8,259 (18.1)	231 (72.4)
	Unknown	8,283 (18.2)	17 (5.3)
HBV status**	Negative	30,690 (67.5)	174 (54.6)
	Positive active	2,074 (4.6)	63 (19.8)
	Positive inactive	6,021 (13.2)	64 (20.1)
	Unknown	6,759 (14.8)	18 (5.6)
Smoking status	Current smoker	17,443 (38.7)	180 (56.4)
	Ex smoker	7,682 (17.0)	84 (26.3)
	Never smoker	11,909 (26.4)	43 (13.5)
	Not known	8,089 (17.9)	12 (3.8)
Previous AIDS		10,846 (23.8)	155 (48.6)

* HCV status (Negative: seronegative, or seropositive but HCV-RNA negative. Positive: seropositive and HCV-RNA positive or HCV-RNA unknown or not tested)

** HBV status (positive: active infection [HB surface antigen, HB e antigen, or HBV DNA positive]; positive: inactive infection [HB surface antigen positive, anti-HB e antibody positive, or HBV DNA negative])

Tabel 2. Incidence of ESLD/HCC (per 1000 PYFU) stratified by viral hepatitis status

Factor		Number of events	PYFU	Rate	(95% CI)
Overall		319	315,368	1.01	(0.90-1.12)
HCV status*	Negative	72	229,434	0.31	(0.24-0.39)
	Positive	229	63,786	3.59	(3.13-4.06)
	Unknown	18	22,148	0.81	(0.48-1.28)
HBV status*	Negative	175	242,901	0.72	(0.61-0.83)
	Positive-active	59	12,907	4.57	(3.40-5.74)
	Positive-inactive	65	42,016	1.55	(1.17-1.92)
	Unknown	20	17,545	1.14	(0.64-1.64)

* HCV status (Negative: seronegative, or seropositive but HCV-RNA negative. Positive: seropositive and HCV-RNA positive or HCV-RNA unknown or not tested)

** HBV status (positive: active infection [HB surface antigen, HB e antigen, or HBV DNA positive]; positive: inactive infection [HB surface antigen positive, anti-HB e antibody positive, or HBV DNA negative])

Figure 1. Association between cumulative (per 5 year) ARV exposure and ESLD/HCC

Table 3. Associations between current, cumulative and past exposure to d-drugs (ddI and d4T) and rates of ESLD/HCC

	Rate of ESLD/HCC (per 1000 PYFU[a], 95% CI[a])	Adjusted for:		
		No other factor	Exposure to other NRTIs, PIs and NNRTIs	Exposure to other NRTIs, PIs and NNRTIs and potential confounders[c]
		Relative rate[b] (95% CI)	Relative rate (95% CI)	Relative rate (95% CI)
Never received d-drugs	0.50 (0.40, 0.61)	0.60 (0.37, 0.98)	0.65 (0.40, 1.05)	1.03 (0.60, 1.73)
Currently on d-drugs	1.30 (0.87, 1.76)	Ref.	Ref.	Ref.
Stopped d-drugs and off for:				
≥0, <2 years	1.89 (1.32, 2.45)	1.70 (1.07, 2.69)	1.72 (1.08, 2.72)	1.64 (1.03, 2.60)
≥2, <4 years	1.85 (1.30, 2.41)	1.60 (1.01, 2.52)	1.65 (1.04, 2.61)	1.59 (1.00, 2.52)
≥4, <6 years	1.93 (1.36, 2.50)	1.63 (1.04, 2.56)	1.72 (1.09, 2.73)	1.63 (1.03, 2.59)
≥6, <8 years	1.56 (1.00, 2.12)	1.34 (0.81, 2.20)	1.48 (0.89, 2.46)	1.48 (0.89, 2.47)

>8 years	1.40 (0.95, 1.85)	1.25 (0.78, 2.01)	1.44 (0.88, 2.36)	1.49 (0.90, 2.47)
Cumulative exposure (/year) to d-drugs	n/a	1.07 (1.03, 1.11)	1.07 (1.03, 1.12)	1.06 (1.01, 1.10)

[a]PYFU: person-years of follow-up; CI: confidence interval; [b] adjusted for time since stopping d-drug and cumulative exposure to d-drug; [c]Age, gender, injection drug use as mode of HIV acquisition, previous AIDS diagnosis, viral hepatitis B/C co-infection, calendar period, time since stopping d-drug and cumulative exposure to d-drugs