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The Effect of HIV Infection, Immunodeficiency and Antiretroviral Therapy on the Risk of Hepatic Dysfunction

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Abstract

Background—Limited data exists regarding the effect of chronic HIV infection on the liver. We sought to characterize the hepatic risks of HIV infection, immunodeficiency and cumulative use of antiretroviral therapy (ART).

Methods—Adult HIV-infected and 10:1 age- and sex-matched HIV-uninfected individuals were followed for incident hepatic dysfunction or hepatic dysfunction-related death. Multivariable Poisson regression models were used to obtain incident rate ratios, adjusting for multiple hepatic risk factors including alcohol/drug abuse, hepatitis B and C, and diabetes.

Results—We identified 20,775 HIV-infected and 215,158 HIV-uninfected individuals. HIV-infected individuals had a significantly greater overall risk compared with HIV-uninfected individuals of both hepatic dysfunction and hepatic dysfunction-related death. The highest risk was seen in patients with low CD4 cell counts not on ART (adjusted rate ratio (aRR) of hepatic dysfunction-related death 59.4; (95% confidence interval [CI]: 39.3–89.7), $P < 0.001$; hepatic dysfunction, aRR 15.7 (95% CI: 11.4–21.6), $P < 0.001$. In an HIV-infected only model, factors that increased risk included low CD4 cell count, high HIV RNA level, alcohol/drug abuse, hepatitis B or C co-infection, and diabetes. Longer cumulative exposure to ART did not increase risk, regardless of therapy class.

Conclusions—HIV-infected individuals have a higher risk of hepatic dysfunction and hepatic dysfunction-related death compared with HIV-uninfected individuals, even with adjustment for known hepatic risk factors. Hepatic outcomes were associated with lower CD4+ T-cell counts, but not with longer cumulative ART exposure. These findings provide indirect evidence supporting early use of ART to reduce the risk for hepatic-related complications.

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Keywords

Hepatic Dysfunction; Hepatic Failure; Liver Failure; Hepatic Dysfunction-Related Death; HIV Infection; Antiretroviral Therapy

INTRODUCTION

The introduction of combination antiretroviral therapy (ART) has dramatically improved the survival of HIV-infected patients in developed countries [1,2,3]. However, as individuals with HIV live longer, long term side effects of HIV are increasingly common, including effects on the liver [4,5,6,7]. Previously reported common etiologies for hepatic dysfunction in the HIV-infected population include co-infection with chronic hepatitis B or C, alcohol and drug abuse, antiretroviral therapy use, diseases such as nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, and opportunistic infections [8,9,10,11]. However, data is lacking on hepatic dysfunction or hepatic dysfunction-related death when compared with HIV-uninfected individuals of similar age and sex. Such data is important in order to assess the effect of chronic HIV infection on the liver.

As an integrated health care system, Kaiser Permanente (KP) provides nearly all care to patients within KP, an environment ideal for conducting such research. In addition, KP maintains a comprehensive HIV registry, facilitating comparative analyses for many outcomes between HIV-infected and HIV-uninfected individuals. The aims of this analysis were to compare the incidence of hepatic dysfunction or hepatic dysfunction-related death between a large cohort of HIV-infected and age- and sex-matched HIV-uninfected individuals, and to examine factors, including degree of immunosuppression, HIV RNA levels, and long-term use of ART, that may affect risk.

METHODS

Study design

We conducted a cohort study from 1996 to 2008 of adult HIV-infected and HIV-uninfected individuals within Kaiser Permanente Southern California (KPSC) and Kaiser Permanente Northern California (KPNC), both of which are large integrated healthcare delivery systems providing comprehensive medical care to more than 6 million members who are demographically representative of all insured Californians [12]. December 2008 was chosen as the endpoint as this represented the latest date that California state mortality data was available at the time of this analysis.

Subjects

HIV-infected individuals were identified from KP-maintained HIV registries, which include all known cases of HIV infection dating back to the early 1980's for KPNC and 2000 for KPSC. HIV-infected individuals are initially identified for inclusion in the registries by a positive HIV antibody test, detectable HIV viral RNA, prescription for an HIV antiretroviral, HIV/AIDS-related diagnosis, or other evidence of HIV infection from electronic sources. Confirmation of cases is done by medical chart review and comparisons of case lists with KP HIV clinics.

The HIV-infected study population consisted of all individuals included in the HIV registries who met the following three inclusion criteria: 1) KP member after January, 1996 in KPNC and after January, 2000 in KPSC (2000 in KPSC represents availability of electronic data required for ascertainment of HIV-infected cases); 2) 18 years of age; and 3) identified as "in-care", defined as having received 1 CD4 test. A total of 4% of eligible

HIV-infected patients were excluded as not being “in care”. The index date for HIV-infected individuals was the earliest date a member meets all 3 criteria.

The eligible HIV-uninfected study population consisted of all individuals meeting the following two inclusion criteria: 1) KP member after January, 1996 in KPNC and after January, 2000 in KPSC; and, 2) 18 years of age. HIV-uninfected individuals were excluded if they were ever included in the HIV registry through 2008. HIV-uninfected individuals were frequency matched 10:1 by age (5-year age groups), sex, KP medical center (to control for socioeconomic factors), and initial year of follow-up for HIV-infected individuals (HIV-uninfected individuals were selected from the pool of active health plan members during the year of initial follow-up of HIV-infected persons). The index date for eligible HIV-uninfected individuals was the earliest date an individual was 18 years of age during the year for which they were selected to be a part of the HIV-uninfected cohort.

To examine the effect of ART class (either protease inhibitor, PI, or non-nucleoside reverse transcriptase inhibitor, NNRTI, based) and cumulative ART duration on the rate of hepatic dysfunction and hepatic dysfunction-related death, a subgroup of HIV-infected individuals was created in which the cumulative duration of medication exposure could be calculated (treatment analysis cohort). For patients in KPNC, previous chart reviews had established a complete antiretroviral history with duration of therapy for all individuals, including the use prior to KP membership; in KPSC such a history was not available and so individuals selected were those who had Kaiser membership for at least 6 months with no ART prescribed. We defined a simultaneous ART regimen among patients as 3 antiretroviral drugs used in combination during the same month; ritonavir at doses 400mg/day was not considered an active drug in the regimen. Total cumulative therapy duration (including for those individuals who received no therapy, who comprised the reference group for this cohort) could thus be calculated in this group of patients by using pharmacy prescription fill and refill data to examine the class-specific, cumulative role of ART on the risk for hepatic dysfunction or hepatic dysfunction-related death.

HIV-infected and matched HIV-uninfected KP individuals were followed until the earliest of death, hepatic-related event, health plan disenrollment, or December 31, 2008.

Data Sources

KP has developed and maintained a large number of administrative and clinical electronic data systems that routinely collect health-related information on its members. Linkage across these systems is feasible since members are assigned a unique lifetime medical record number. The primary data sources for this study were electronic medical records including pharmacy utilization, inpatient and outpatient diagnosis and utilization, laboratory records, administrative files, and mortality databases.

Hepatic Endpoints

We defined hepatic dysfunction as an inpatient or outpatient diagnosis of hepatic failure (ICD-9: 570.xx; ICD-10: K71.1, K72, K72.0, K72.1, K72.9), hepatic encephalopathy (ICD-9: 572.2; ICD-10: included under K72), or esophageal varices with bleeding (ICD-9: 456.0; ICD-10: I85.0). While a formal validation study was not undertaken to assess the accuracy of this method of diagnosing all cases of hepatic failure, it should in fact capture the majority of cases, and any errors should be non differential with regard to HIV status.

In addition we identified hepatic dysfunction by abnormal labs as individuals with an elevated value of aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than 5 times the upper limit of normal AND either an elevated ammonia (greater than the upper limit of normal), or elevated international normalized ratio (INR) greater than the

upper limit of normal (patients were defined by an elevated INR and not by ammonia 91% of the time). All qualifying laboratory tests had to be performed within 7 days of each other. All patients with prevalent hepatic dysfunction events prior to the index date were removed from the analysis (0.6% for the case group and 0.1% for the control group). A hepatic dysfunction-related death was defined as any death preceded within 60 days by a diagnosis of hepatic dysfunction as defined above, and/or hepatic failure listed as the cause of death (underlying or secondary) on the death certificate.

Statistical methods

Initial analyses focused on differences in the incidence of hepatic dysfunction and hepatic dysfunction-related deaths, comparing HIV-infected with HIV-uninfected individuals. We first computed incidence and mortality rates per 100,000 person-years (PY) by HIV infection status. Multivariable Poisson models compared the risk of hepatic dysfunction and hepatic dysfunction-related death by HIV status, with adjustment for age, sex, race/ethnicity, smoking, alcohol abuse diagnosis, drug abuse diagnosis, hepatitis B or C co-infection (obtained by ICD-9 codes and laboratory evidence of infection), hypertension diagnosis, diabetes diagnosis, lipid lowering medication use (given their known hepatic side effects, records from Kaiser pharmacy system) and calendar year. In order to examine factors of HIV disease that may affect risk of hepatic dysfunction, we also compared risk in HIV-uninfected persons with HIV-infected individuals stratified by ART use, CD4+ T-cell counts (200, 201–499, 500 cells/uL), and HIV RNA levels (500, 501–9,999, 10,000–99,999 and 100,000 copies/mL).

Subsequent analyses were restricted to HIV-infected individuals. In order to examine specific risk factors in HIV-infected individuals, multivariable Poisson models were constructed with terms for age, sex, race/ethnicity, CD4 cell count (both recent and lowest KP recorded CD4, framed in 6 month intervals), recent HIV RNA level (framed in 6 month intervals), any use of ART, alcohol or drug abuse diagnoses, smoking, hepatitis B or C co-infection, hypertension, diabetes, and lipid lowering medication usage.

We further examined ART class and cumulative ART duration on the rate of hepatic dysfunction and hepatic dysfunction-related death. To do this, the treatment analysis cohort (as described above) was utilized. Multivariable Poisson models were adjusted with terms for age, sex, race/ethnicity, alcohol or drug abuse diagnoses, smoking, hepatitis B or C co-infection, hypertension, diabetes, lipid lowering medication usage, calendar year and years known HIV infected.

All analyses were performed with SAS (Version 9.1; Cary, North Carolina, USA), using proc GENMOD for Poisson regression. The institutional review boards at KPSC and KPNC approved this study and provided waivers of informed consent.

RESULTS

We identified 20,775 HIV-infected individuals contributing 85,309 person-years (mean 4.4 years per person) and 215,158 HIV-uninfected individuals contributing 1,013,645 person-years (mean 5.3 years per person; Table 1). The HIV-infected group was predominantly male (91%), white (51%), and consisted mostly of men who have sex with men (59%), and had a mean age at start of follow-up of 41 years. Patients in the HIV-uninfected cohort were less likely to be co-infected with hepatitis than those in the HIV-infected cohort. Patients in KPNC and KPSC were demographically similar with the exception of a larger proportion of Hispanic patients in KPSC (data not shown). A total of 12,872 patients were eligible for the treatment analysis cohort; the demographics of this cohort closely mirrored the larger HIV-infected cohort (Table 1).

Among HIV-infected individuals, 437 met the criteria for hepatic dysfunction (491/100,000 person years, CI: 445.3–537.5), compared to 755 in the HIV-uninfected group (67/100,000 person-years, CI: 62.1–71.6), corresponding to an adjusted rate ratio (RR) of 3.5 (95% CI: 3.0–4.0, $P < 0.001$). 170 HIV-infected individuals experienced a hepatic dysfunction-related death (188/100,000 person-years, CI: 159.9–216.5), while 192 HIV-uninfected individuals experienced a hepatic dysfunction-related death (17/100,000 person-years, CI: 14.6–19.4), corresponding to an adjusted RR 5.9 (95% CI: 4.7–7.4, $P < 0.001$). In the 170 cases of hepatic dysfunction-deaths seen in the HIV infected group, only one death was listed as primary hepatic failure related. The most common primary causes noted when hepatic failure was listed as a secondary or underlying cause were HIV/AIDS (69%) or other liver related causes (19%). RRs were similar by sex and geographic location (KPNC vs. KPSC) for both hepatic dysfunction and hepatic dysfunction-related death, as well as when looking at patients only after the year 2000, when both KPNC and KPSC contributed data. Risk was lower in the modern era (2001–2008) than in the earlier era (1996–2000), and remained elevated even when excluding those patients with known hepatitis B or C co-infection (Table 2).

As shown in Table 3, at all levels of immunodeficiency HIV-infected individuals had a greater risk of hepatic dysfunction-related death or hepatic dysfunction compared with HIV-uninfected individuals. The event rates were lowest among those individuals with CD4 500 cells/uL on ART (adjusted RRs for hepatic dysfunction-related death and hepatic dysfunction 1.8 and 1.6, respectively, $P = 0.025$ and $P = 0.002$ compared to HIV-uninfected), while the highest were seen in individuals with CD4 ≤ 200 cells/uL not on ART (adjusted RRs for hepatic dysfunction-related death and hepatic dysfunction 59.4 and 15.7, respectively, $P < 0.001$ for both when compared to HIV-uninfected, Table 3).

Compared with HIV-uninfected individuals, HIV-infected individuals had a higher RR of hepatic dysfunction-related death and hepatic dysfunction with higher levels of HIV RNA ($\geq 100,000$ copies/mL) than lower (≤ 500 copies/mL), with a linear relationship observed between increasing risk and increasing RNA levels. This relationship was consistent whether patients were receiving ART (adjusted RRs for hepatic dysfunction-related death and hepatic dysfunction 3.5 and 2.5 when HIV RNA ≥ 500 copies/mL versus 18.4 and 8.9 when HIV RNA $\leq 100,000$ copies/mL), or not receiving ART (adjusted RRs for hepatic dysfunction-related death and hepatic dysfunction 4.3 and 1.7 when HIV RNA ≥ 500 copies/mL versus 35.7 and 10.0 when HIV RNA $\leq 100,000$ copies/mL), Table 3.

Next, we analyzed our HIV-infected only model that considered ART, CD4 and HIV RNA together, as well as other potential clinical and demographic risk factors for hepatic dysfunction (Table 4). The strongest risk factor for hepatic dysfunction was a history of hepatitis B or C co-infection (adjusted RR 5.3, 95% CI 4.3–6.4, $P < 0.001$). Other risk factors significantly associated with hepatic dysfunction included recent CD4 ≤ 200 versus > 200 , lowest recorded CD4 at KP ≤ 200 versus > 200 , HIV RNA ≥ 500 versus < 500 , alcohol or drug use, and diabetes. Factors not associated with increased risk of hepatic dysfunction included ART use, sex, race/ethnicity, hypertension, and lipid lowering drug use.

Finally, we evaluated the possible effect of cumulative therapy duration of PI- or NNRTI-based ART regimens on the risk for hepatic dysfunction or hepatic dysfunction-related death among individuals with known duration of ART use, using the previously described treatment analysis cohort. A total of 8,449 individuals in this cohort were exposed to simultaneous 3 drug ART (32,368 person-years, mean 3.8 years per person). Total PI exposure was 21,249 person-years among 5,858 people exposed (mean 3.6 years per person); total NNRTI exposure was 15,643 person-years among 5,662 people exposed (mean 2.8 years per person). As was observed in the full HIV-infected cohort, the use of

ART was not associated with an increased risk for hepatic dysfunction, with an adjusted RR per additional year of ART use of 1.02 (95% CI 0.96–1.08, $P=0.49$). The lack of an effect of ART use on hepatic dysfunction was observed for both PI-based ART and NNRTI-based ART (Figure, panel a). For hepatic dysfunction-related death, there was in fact a protective effect of ART, with an adjusted RR per year additional ART use of 0.83 (95% CI 0.72–0.94, $P = 0.004$). As was seen for hepatic dysfunction, the magnitude of this effect was similar by ART class (Figure, panel b).

DISCUSSION

HIV-infected individuals have an increased risk of hepatic dysfunction and hepatic dysfunction-related death compared with HIV-uninfected individuals, even with adjustment for demographic and clinical risk factors. Risk was increased regardless of sex, KP geographic location, or time frame, although risk was slightly reduced in the modern era. Although risk remained elevated for HIV-infected individuals at all levels of immunodeficiency, the greatest risk was observed for those not on ART with CD4 < 200 cells/uL, and the lowest risk was in individuals on ART with CD4 ≥ 500 cells/uL. Risk was also noted to increase with higher levels of HIV RNA. Independent predictors for hepatic dysfunction among HIV-infected individuals included low CD4 cell count (both recent and lowest recorded at KP), high HIV RNA levels, alcohol or drug abuse, hepatitis B or C co-infection, and diabetes. The long term, cumulative use of ART did not increase risk for either hepatic dysfunction or hepatic dysfunction-related death, regardless of class used.

The explanation for the higher observed rate of hepatic dysfunction and hepatic dysfunction-related death was not immediately evident from our study. Although HIV-infected individuals frequently have co-morbidities such as viral hepatitis, these factors were adjusted for in our models and did not completely explain the higher risk for hepatic dysfunction and hepatic dysfunction-related death. Similarly, severe immunosuppression alone was not a sufficient explanation for the excess morbidity and mortality, since even individuals with CD4 cell counts greater than 500 cells/uL had an increased risk, albeit at a lower rate than those with lower CD4 cell counts. And our study results clearly did not point to ART as contributing to risk; in fact risk was reduced with longer duration.

It may be possible that HIV itself is leading to the higher rates of hepatic dysfunction we observed. There have been reports of chronic immune activation in HIV which may lead to chronic stimulation of the inflammatory system [13], and it has been hypothesized that this ongoing activation may lead to many of the long term complications (cardiac, brain) seen in chronically HIV-infected individuals [14]. It is possible that HIV infection leads to activation of the inflammatory cascade in the liver, leading to the greater rate of hepatic dysfunction observed. Such an explanation would be consistent with the observation in our study that patients with high HIV RNA levels had the greatest risk for hepatic dysfunction or hepatic dysfunction-related death. Indeed, other viral infections such as hepatitis C exert their adverse effects on the liver via inflammatory effects leading to liver fibrosis [15,16].

The finding of higher risk for hepatic-related death at lower CD4 cell count has been previously reported [4]. In the EuroSIDA cohort, a 50% increase in CD4 cell count was associated with a RR for hepatic-related death of 0.77 ($P<0.0001$) in a multivariate adjusted model. Similar to the relationship seen in our study, the risk of hepatic-related death decreased with increasing levels of CD4; CD4 cell counts < 50 cells/uL had a death rate of 14.1/1,000 person-years of follow up, compared with 1.6/1,000 person-years of follow up in those patients with CD4 cell counts > 200 cells/uL. However, risk was not compared to a similar HIV-uninfected cohort. And unlike the present study, the EuroSIDA cohort did not examine risk for hepatic dysfunction without death.

Our finding that cumulative ART does not increase risk for hepatic dysfunction or hepatic dysfunction-related death is reassuring, and clinically of great importance in light of calls from the World Health Organization and the United States National HIV/AIDS Strategy to increase the number of HIV-infected individuals on ART [17,18], and the results of the recent HIV Prevention Trials Network 052 study, which demonstrated a reduced rate of sexual transmission of HIV in patients receiving ART [19]. Earlier studies have suggested toxicity with nucleoside reverse transcriptase inhibitor (NRTI) therapy (mitochondrial toxicity) [20], NNRTI therapy [21], and PI therapy [22]. However, unlike our study which measured hepatic dysfunction as defined by impaired hepatic synthetic function or hepatic-related complications such as encephalopathy or esophageal varices, many of these prior studies have used only transaminase elevation as a marker for liver injury. While the lack of an effect on hepatic dysfunction in ART treated patients in our study may reflect that fact that patients are being adequately monitored (and quickly taken off therapy) and hence no effect is observed, it may also be possible that many of the more minor transaminase elevations seen in clinical care may not predispose patients to hepatic failure. And finally, while this project did not break down ART use to specific agents, the difference in risk seen between the 2 eras examined does suggest that newer ARTs may have less effect on the liver than older ones.

We acknowledge certain limitations with our study. As no standard definition based on laboratory values exists for mild to moderate hepatic dysfunction, our definitions were chosen to best represent clinical hepatic synthetic dysfunction. The Model for End-Stage Liver Disease, or MELD score, while accurately predicting mortality from advanced liver failure, is not ideal for quantifying more mild disease [23]. Our definitions were chosen to represent hepatic dysfunction at a level above that seen in simple transaminase elevation, while at a level lower than end-stage liver disease. Moreover, they were equally applied to HIV-infected and –uninfected individuals, and thus any misclassification is anticipated to be non-differential with respect to HIV status. Another limitation was that race/ethnicity was missing for 43% of HIV-uninfected individuals. However, in the HIV-infected cohort we did have data on race for 94% of patients and this factor was not found to be predictive for hepatic dysfunction or hepatic dysfunction-related death. In the HIV-uninfected cohort, it may be possible that hepatitis B, hepatitis C, and HIV may be undiagnosed. Thus we could not verify with certainty that the HIV uninfected group was uninfected; instead patients were presumed uninfected by lack of an HIV diagnosis. We also did not include information on specific hepatitis genotypes or other hepatitis markers in our analysis. Finally, although nucleoside reverse transcriptase inhibitors were not examined as a separate class, over the time period examined this class consistently remained the backbone of ART, with the major difference in treatment being the choice of PI versus NNRTI.

The major strength of our study is the use of a large, well characterized population of HIV-infected and matched HIV-uninfected individuals from the same integrated healthcare system. Our study results have application to those utilizing health care, as data indicates that KP members are very similar to the California statewide population with regards to age, sex and race/ethnicity [12]; moreover, demographics of our HIV-infected population are very similar to reported AIDS cases in California [24].

In summary, we found that when compared with age- and sex-matched HIV-uninfected controls, an increased risk for hepatic dysfunction and hepatic dysfunction-related death exists for HIV-infected individuals. ART use did not increase risk and we found no effect by ART class or cumulative duration of therapy. These findings suggest that early diagnosis of HIV and subsequent initiation of ART prior to significant CD4 cell decline may partially mitigate the risk of hepatic dysfunction or hepatic dysfunction-related death.

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Figure. Effect of cumulative use of protease inhibitor (PI) or non nucleoside based inhibitor (NNRTI) therapy on risk for hepatic dysfunction (panel a) or hepatic dysfunction-related death (panel b)

Squares represent incidence rates by duration PIs, and circles represent incidence rates by duration NNRTIs. Vertical lines are 95% CIs. Corresponding rate ratios for hepatic dysfunction are 1.0 (95% CI 0.9–1.1; $p=0.94$) and 1.1 (95% CI 1.0–1.2; $p=0.07$), per year PI use and NNRTI use, respectively. Corresponding rate ratios for hepatic dysfunction related death are 0.9 (95% CI 0.8–1.0; $p=0.02$) and 0.9 (95% CI 0.8–1.1; $p=0.27$), per year PI use and NNRTI use, respectively. These rate ratios are adjusted for age, sex, race, smoking,

alcohol/drug abuse, hepatitis B/C, hypertension, diabetes, lipid lowering medication use, calendar year, and years known HIV-infected.

Table 1**Study Population**

	HIV-infected	HIV-infected eligible for treatment analysis	HIV-uninfected
<i>n</i>	20,775	12,872	215,158
Mean years follow-up	4.4	4.5	5.3
Mean age, years	41	40	41
Men, %	91	90	90
Race/ethnicity, %			
White	51	51	26
Black	17	19	7
Hispanic	20	19	15
Asian/Pacific Islander	4	4	8
Other	1	1	1
(% unknown)	6	5	43
History of alcohol/drug abuse, ever, %	20	22	8
Tobacco use, ever, %	42	44	28
Known Hepatitis C, %	8	7	1
Known Hepatitis B, %	5	4	1
Diabetes, %	8	7	8
Lipid lowering drug use, %	24	19	18
Hypertension, %	24	22	24
HIV exposure risk, %			
Men who have sex with men	59	62	-
Injection drug use	6	6	-
Heterosexual	13	15	-
Other	2	2	-
(% unknown)	20	16	-
Mean baseline CD4, cells/ μ l	396	364	-
Mean baseline HIV-1 RNA, cp/ml	51,291	74,020	-
ART prior to baseline, %	33	3	-
Years known HIV-infected, mean	3.5	2.75	-
ART exposure, person-years (mean, years)	-	32,368 (3.8)	-
PI exposure, person-years (mean, years)	-	21,249 (3.6)	-
NNRTI exposure, person-years (mean, years)	-	15,643 (2.8)	-

Table 2
Hepatic failure (HF) and hepatic failure-related deaths (HFRD): incidence rates and rate ratios by HIV infection status.

	HIV+			HIV-			Adjusted Rate Ratio [‡]	
	n	rate [‡]	95% CI	n	rate [‡]		RR	(95% CI)
HD								
All pts	437	491	(445.3-537.5)	755	67	(62.1-71.6)	3.5	(3.0-4.0)*
Men	400	499	(450.3-548.1)	697	68	(63.4-73.5)	3.5	(3.0-4.0)*
Women	37	420	(284.9-555.9)	58	52	(38.7-65.6)	3.3	(2.0-5.5)*
Yrs 1996-2000	143	679	(567.4-789.9)	158	57	(48.4-66.3)	5.4	(4.2-7.0)*
Yrs 2001-2008	294	433	(383.7-482.8)	597	70	(64.3-75.5)	4.1	(3.4-5.0)*
KPNC	252	482	(422.4-541.4)	422	61	(55.3-67.0)	3.7	(3.1-4.4)*
KPSC	185	505	(432.2-577.8)	333	76	(67.7-83.9)	3.2	(2.6-3.9)*
Pts index year 2000	240	463	(404.8-522.0)	432	68	(61.9-74.8)	3.1	(2.6-3.7)*
Pts with HCV/HBV	213	1828	(1,582.5-	203	816	(703.6-	2.3	(1.9-2.8)*
Pts without HCV/HBV	224	290	(251.9-327.8)	552	50	(45.8-54.1)	4.4	(3.8-5.2)*
HDRD								
All pts	170	188	(159.9-216.5)	192	17	(14.6-19.4)	5.9	(4.7-7.4)*
Men	158	194	(163.7-224.2)	174	17	(14.5-19.6)	6.0	(4.7-7.6)*
Women	12	135	(58.7-211.6)	18	16	(8.7-23.6)	5.6	(2.4-12.6)*
Yrs 1996-2000	65	305	(230.5-378.6)	37	13	(9.1-17.7)	12.7	(8.1-19.8)*
Yrs 2001-2008	105	152	(123.1-181.3)	155	18	(15.2-20.9)	8.1	(5.8-11.4)*
KPNC	84	158	(124.2-191.7)	87	13	(9.9-15.2)	7.1	(5.1-9.8)*
KPSC	86	232	(182.6-280.4)	105	24	(19.3-28.4)	4.7	(3.4-6.5)*
Pts index year 2000	106	202	(163.6-240.5)	126	20	(16.4-23.4)	5.1	(3.8-6.8)*
Pts with HCV/HBV	87	708	(559.3-856.9)	45	174	(123.2-	4.5	(3.1-6.5)*
Pts without HCV/HBV	83	106	(83.5-129.2)	147	13	(11.1-15.4)	6.5	(4.9-8.6)*

†Cases per 100,000 person-years

‡Reference = HIV-; adjusted for age, sex, race, smoking, alcohol/drug abuse, hepatitis B/C, hypertension, diabetes, lipid lowering medications, calendar year.

* $p < 0.001$ HIV+ vs. HIV

Table 3

Hepatic failure (HF) and hepatic failure-related death rate ratios by CD4 and HIV-1 RNA values

		Hepatic Dysfunction-related Death		Hepatic Dysfunction	
		aRR [‡] (95% CI)	p-value	aRR [‡] (95% CI)	p-value
CD4 500 cells/μL					
ART+	1.8	(1.1–3.1)	0.025	1.6	(1.2–2.1) 0.002
ART–	2.3	(1.0–5.7)	0.066	2.0	(1.3–3.2) 0.002
CD4 201–499 cells/μL					
ART+	3.9	(2.8–5.6)	<.0001	3.2	(2.6–3.8) <.0001
ART–	4.0	(2.1–8.0)	<.0001	2.6	(1.8–3.8) <.0001
CD4 200 cells/μL					
ART+	15.2	(11.2–20.7)	<.0001	7.6	(6.3–9.3) <.0001
ART–	59.4	(39.3–89.7)	<.0001	15.7	(11.4–21.6) <.0001
HIV-1 RNA 500					
ART+	3.5	(2.6–4.8)	<.0001	2.5	(2.1–2.9) <.0001
ART–	4.3	(1.9–9.7)	0.0005	1.7	(0.9–3.1) 0.074
HIV-1 RNA 501–9999					
ART+	7.0	(4.4–11.1)	<.0001	4.5	(3.4–5.9) <.0001
ART–	2.8	(1.0–7.7)	0.041	2.0	(1.1–3.4) 0.017
HIV-1 RNA 10–99,999					
ART+	10.6	(7.1–16.0)	<.0001	6.2	(4.8–7.9) <.0001
ART–	13.7	(9.0–20.8)	<.0001	5.7	(4.3–7.5) <.0001
HIV-1 RNA 100,000					
ART+	18.4	(10.5–32.0)	<.0001	8.9	(6.2–12.9) <.0001
ART–	35.7	(17.3–73.6)	<.0001	10.0	(5.5–18.3) <.0001

[‡]Reference = HIV– individuals.

ART +/-: antiretroviral therapy present/absent

Rate Ratios adjusted for age, sex, race, smoking, alcohol/drug abuse, hepatitis B/C, hypertension, diabetes, lipid lowering medications, calendar year

Table 4

Adjusted rate ratios (RR) for hepatic failure for selected risk factors in HIV-infected patients

	Adjusted RR [‡]	95% CI	P
ART use	0.9	(0.7–1.2)	0.52
Recent CD4 200 vs > 200	2.5	(2.0–2.3)	< 0.001
Lowest KP CD4 200 vs. > 200	1.5	(1.2–2.0)	0.003
HIV RNA 500 vs. < 500	1.7	(1.4–2.1)	< 0.001
Ever alcohol or drug abuse	1.6	(1.3–2.0)	< 0.001
Hepatitis B or C	5.3	(4.3–6.4)	< 0.001
Diabetes	1.9	(1.4–2.5)	< 0.001
Female sex	0.9	(0.6–1.3)	0.46
Black vs. White	1.1	(0.9–1.4)	0.35
Hispanic vs. White	1.6	(0.8–1.4)	0.50
Hypertension	1.1	(0.9–1.4)	0.37
Lipid lowering drug use	1.2	(0.9–1.5)	0.24

[‡]Rate ratios adjusted for all other variables presented.