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Hepatic Safety and Tolerability of Raltegravir among HIV Patients Coinfected with Hepatitis B and/or C

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Abstract

Background—Potential liver toxicity is an important consideration for antiretroviral selection among patients coinfected with HIV and viral hepatitis (B and/or C). We sought to describe the hepatic safety profile of raltegravir in this population.

Methods—Using data from HIV clinical cohorts at Johns Hopkins University and the University of North Carolina at Chapel Hill, we evaluated factors associated with liver enzyme elevations (LEEs) and calculated adverse event incidence rates for patients initiated on raltegravir-containing regimens prior to January 1, 2010. LEEs were graded according to Division of AIDS definitions.

Results—During the study period, 456 patients received raltegravir – of whom 36% were hepatitis-coinfected (138 HCV, 17 HBV, 11 HBV+HCV). Coinfected patients were more likely to have baseline abnormal LEEs, and developed severe (grade 3–4) LEEs at a rate 3.4 times that of HIV-monoinfected patients (95% confidence interval (CI), 1.28, 9.61). Among all participants, the incidence rate for first occurrence of severe LEEs was 5 per 100 person-years (95% CI, 3, 7). In adjusted analyses, coinfected patients had a 2.7-fold increased hazard of severe LEEs (95% CI, 1.03, 7.04). Sixty percent of severe abnormalities occurred within 6 months after starting raltegravir; the drug was discontinued in 3 coinfected patients (1.3%) and 18 monoinfected patients (6.2%).

Conclusions—Compared to HIV-monoinfected patients, those with HIV-hepatitis coinfection are at increased hazard of developing LEEs on raltegravir, at a level similar to other

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antiretrovirals. Severe events were uncommon, rarely leading to raltegravir discontinuation. With appropriate monitoring, raltegravir-based therapy is safe in hepatitis-coinfected patients.

Keywords

integrase strand transfer inhibitors; hepatotoxicity; clinical cohort; United States

Introduction

Raltegravir, the first HIV integrase strand-transfer inhibitor in clinical use, demonstrated a generally favorable safety and tolerability profile in early-phase clinical trials (1, 2) and phase III studies among treatment-experienced (3–5) and antiretroviral (ARV)-naïve (6–8) patients. In the BENCHMRK trials of raltegravir versus placebo with an optimized background regimen among ARV-experienced patients, the incidence of drug-related adverse events was lower for patients treated with raltegravir than with placebo (32.8 vs. 51.6 cases per 100 person-years (PY), respectively). (5) Liver enzyme elevations (LEEs) were infrequent and similar to placebo, with grade 3 increases in aspartate aminotransferase (AST) occurring at a rate of 2.4 cases per 100 PY on raltegravir and 2.2 cases per 100 PY on placebo. Incident grade 4 AST abnormalities were rarely observed and were less frequent on raltegravir (0.4 cases versus 1.1 cases per 100 PY on placebo). (5) In the STARTMRK study of raltegravir versus efavirenz, paired with tenofovir/emtricitabine among treatment-naïve patients, grade 3 and 4 AST abnormalities were not significantly different between raltegravir (3.2%) and efavirenz (2.9%). (8)

Notably, patients with viral hepatitis coinfection were underrepresented in the BENCHMRK (n=113, 16%) (3) and STARTMRK (n=34, 6%) (8) trials. Compared with HIV-monoinfected patients, greater proportions of those with viral hepatitis developed transaminase elevations in these studies, though the absolute number of patients experiencing hepatotoxicity was small. No significant differences in the frequency or severity of hepatotoxicity were observed between patients receiving raltegravir and those randomized to control groups, though the precision of these estimates was low. (9)

Given the paucity of data on raltegravir among patients with chronic viral hepatitis and the apparently favorable hepatotoxicity profile of the drug, we used data from two large clinical cohorts to determine the safety and tolerability of raltegravir among patients with HIV-viral hepatitis coinfection.

Patients and methods

Study Population

All patients were enrolled in either of the HIV clinical cohorts at Johns Hopkins University (JHHCC) or the University of North Carolina (UCHCC), both described previously. (10, 11) Each cohort collects comprehensive demographic, clinical and laboratory data from institutional electronic records and standardized medical record reviews. For this study, we included all HIV-1 infected patients at least 18 years of age who initiated raltegravir prior to January 1, 2010, with alanine aminotransferase (ALT) and AST levels available at

raltegravir initiation and at least once while on raltegravir. Institutional review board approval was obtained at each of the participating institutions.

Measures

Patients were classified as either HIV-monoinfected or hepatitis-coinfected (with HBV, HCV, or both). We defined HBV infection as having any history of surface antigenemia or detectable HBV DNA. HCV infection was defined as positive HCV antibody or detectable HCV RNA. Laboratory markers of liver function included AST, ALT and total bilirubin. Using the August 2009 clarification of the Division of AIDS (DAIDS) adverse event tables as a guide, (12) we defined the primary endpoint ("any LEE") as the first occurrence of an abnormality in AST or ALT of any severity (DAIDS grade 1 or higher) that was at least one grade greater than at raltegravir initiation. Secondary endpoints included the occurrence of severe LEEs (DAIDS grade 3 or 4) if at least one grade greater than at raltegravir initiation, and raltegravir discontinuation.

Statistical Analysis

Patients contributed person-time to the analysis from the first date of raltegravir initiation until a primary endpoint was reached, raltegravir was discontinued, or January 1, 2010 – whichever occurred first. Differences in demographic and clinical characteristics at baseline (raltegravir initiation) were tested using the Wilcoxon-Mann-Whitney test for continuous variables, and Pearson's χ^2 test for categorical variables. We calculated incidence rates (IR) and incidence rate ratios (IRR) with corresponding 95% confidence intervals (CI) using an exact Poisson distribution. Kaplan-Meier curves and the log-rank test were used to describe time to primary and secondary endpoints. Multivariable Cox proportional hazards regression was used to identify factors associated with the time to first new DAIDS hepatic event and raltegravir discontinuation. All analyses were done in SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Of the 456 HIV-infected patients who initiated raltegravir, 30% were HCV-coinfected, 4% had HBV, and 2% had both hepatitis viruses. The median age was 48 years (range: 19–78), and two-thirds of patients were male (68%) and Black (66%) (Table 1). Twenty-nine percent of patients had a history of injection drug use (IDU). The vast majority of patients had extensive prior ARV exposure; only 21 patients (5%) were ARV-naïve at raltegravir initiation. The median time from first ARV initiation to starting raltegravir was 11 years (interquartile range [IQR]: 6–13); 74% had prior NNRTI use and 89% prior PI use.

Raltegravir was initiated in calendar years 2007 (n=56), 2008 (n=297) and 2009 (n=103). In addition to raltegravir, 58% of patients also received a PI (primarily a ritonavir-boosted PI, 94%), 10% an NNRTI, and 17% both a PI and an NNRTI, as part of the index regimen. At raltegravir initiation the median CD4 cell count was approximately 300 cells/μL; 38% and 54% had HIV RNA <50 and <400 copies/mL, respectively (Table 1).

Patients coinfected with HBV and/or HCV were slightly older and more likely to be Black than patients without hepatitis coinfection (Table 1). Hepatitis-coinfected patients were

significantly more likely to have a history of IDU, in comparison to uninfected patients (65% versus 9%, P<0.01 respectively). We observed some slight differences in the class of ARVs provided in addition to raltegravir, with hepatitis-coinfected patients more likely to receive a PI, and uninfected patients more likely to receive only NRTIs or an NNRTI (with or with NRTI). CD4 cell counts and HIV RNA levels were comparable by hepatitis coinfection status; however, coinfected patients had higher baseline values of liver function tests.

At raltegravir initiation, grade 1, 2, 3 and 4 transaminase abnormalities were noted in 20%, 8%, 1% and 0% of patients, respectively. Compared with HIV-monoinfected patients, those with hepatitis coinfection were more likely to have grade 1 (34% versus 11%), grade 2 (13% versus 5%), or grade 3 (2% versus 0%) abnormalities at baseline (P<0.01). The median time from raltegravir initiation to discontinuation or end of follow-up was 12 months (interquartile range, IQR: 6–17). Patients had a median of four ALT and four AST measurements available (IQR for both: 2, 7) and the median was four in the monoinfected and coinfected groups with similar interquartile ranges. During observed time on raltegravir, 124 (27%) patients developed at least a one grade elevation in ALT or AST from baseline, including 64 (14%), 40 (9%), 12 (3%), and 8 (2%) progressing to grade 1, 2, 3 and 4 abnormality during follow-up. Of the 20 patients (4.4%) who developed grade 3–4 abnormalities, 12 (60%) were hepatitis-coinfected. The overall incidence rate (IR) for first occurrence of at least a one-grade LEE was 39 per 100 PY (95% CI: 32, 46), and hepatitis-coinfected patients experienced a 3-fold greater rate in comparison to uninfected patients (IRR 2.99, 95% CI: 2.06, 4.32).

The IR for first occurrence of severe LEEs (DAIDS grade 3 or 4) was 5 per 100 PY (95% CI: 3, 7) among all patients, and nearly 3.5 times greater among hepatitis-coinfected patients (IRR=3.41, 95% CI: 1.28, 9.61). The vast majority of any grade and severe grade LEEs occurred within the first 6 months of raltegravir initiation (77% and 60%, respectively), regardless of coinfection status. Hepatitis-coinfected patients were consistently at greater risk of experiencing LEEs of any grade and grade 3–4 across time from raltegravir initiation (Figures 1A and 1B, respectively, P<0.01).

The unadjusted hazard ratio (HR) for time to first LEE of any grade for hepatitis-coinfected versus HIV-monoinfected patients was 2.48 (95% CI: 1.73, 3.54), decreasing only slightly to 2.17 (95% CI: 1.50, 3.16) after adjustment for baseline ALT or AST elevation of any grade, cohort site, and frequency of ALT and AST measurements (Table 2). In unadjusted analyses, having at least a grade 1 elevation in either ALT or AST at raltegravir initiation was associated with a 1.91-fold greater hazard of experiencing LEEs during follow-up (95% CI: 1.28, 2.87). No other factors were associated with having LEEs of any grade.

The strongest association with a severe-grade LEE was HBV/HCV coinfection, with an HR of 2.69 (95%CI: 1.03, 7.04) after adjusting for elevated baseline transaminase level, cohort site, frequency of ALT and AST measurements and baseline CD4 cell count (Table 2). Any grade ALT or AST abnormality at raltegravir initiation was associated with developing severe hepatoxicity in unadjusted analyses, but did not remain statistically significantly associated in multivariable models. Higher CD4 cell count at raltegravir initiation was

associated with a lower hazard of experiencing a severe grade laboratory abnormality in ALT or AST during follow-up in both unadjusted and adjusted analyses – an effect that was independent of co-infection status. As with any-grade toxicity, no other patient demographic or clinical characteristics were associated with experiencing a severe-grade LEE.

Eighteen monoinfected patients (6.2%) and 3 coinfected patients (1.3%) discontinued raltegravir at a median of 7 months after initiation (IQR: 2, 8). Time to discontinuation of raltegravir among coinfected patients was longer (HR 0.48, 95% CI: 0.14, 1.64) (Table 3), although the estimate was imprecise. Among the patients reaching grade 3–4 LEEs, 3 of 8 monoinfected patients discontinued raltegravir, compared to only 1 of 12 coinfected patients (P=0.26). After adjusting for baseline HIV RNA viral load and transaminase level, patients with higher CD4 counts were less likely to discontinue raltegravir, while those who developed grade 3–4 abnormalities in AST and/or ALT were more likely to have the drug stopped. No other factors were identified which predicted earlier raltegravir discontinuation.

Discussion

In this study of 456 patients in clinical care treated with raltegravir, those with hepatitis B and/or C were at greater risk for developing LEEs, but the absolute number of hepatitis-coinfected patients experiencing severe abnormalities was small (n=12, 2.6% overall). Three hepatitis-coinfected patients discontinued raltegravir during the study period, only one of whom had severe transaminase elevations. The majority of abnormalities declared themselves within the first 6 months after initiating raltegravir, which is similar to other analyses of ARV-related LEEs. (13) Our findings are concordant with those of several recent, smaller European cohort studies. Vispo *et al*. conducted a prospective, observational study of 126 monoinfected and 92 HIV/HCV coinfected patients initiating raltegravir between 2006–2009, in Madrid, Spain. (14) Compared to monoinfected patients, those with HCV coinfection had 3.1 times the risk of an LEE elevation of any severity. Severe hepatotoxicity was observed in only 3 patients, all of whom were coinfected – but the authors attributed the LEEs to causes other than raltegravir exposure. In another study from Spain, Macías *et al.* used retrospective cohort data to examine severe LEEs among 108 HIV/HCV coinfected patients during their first 12 months of raltegravir exposure. (15) Ten patients developed grade 3–4 transaminase abnormalities, but no patients discontinued raltegravir due to hepatoxic events, leading the authors to conclude that raltegravir is safe in this population. Finally, Weimer *et al.* examined data from a nationwide observational study of raltegravir recipients in Italy to study the impact of HBV or HCV coinfection on responses to “salvage” ARV regimens. (16) Data from 168 monoinfected and 107 coinfected patients were analyzed, revealing similar immunologic and virologic responses, regardless of coinfection status. Though the hazard of grade 3–4 LEEs was 1.8 times higher among coinfected patients, there was no difference in the rate of raltegravir discontinuation between the two groups.

Ninety-five percent of patients in our study were treatment-experienced, with a median of 11 years from the time of first ARV exposure to raltegravir initiation. Over half of patients were virologically suppressed (HIV RNA <400 copies/mL) at baseline, suggesting that raltegravir was often initiated for regimen simplification or tolerability issues, rather than

suspected treatment failure. Plasma HIV RNA suppression at baseline was not associated with a lower risk of transaminase elevation (Table 2). A greater proportion of hepatitis-coinfected patients received a PI as the companion to raltegravir compared with HIV-monoinfected individuals, which may reflect clinicians' perception that NNRTI may be more hepatotoxic NNRTIs (17, 18) in this population.

Hepatitis coinfection and abnormal AST and/or ALT levels at baseline are frequently identified as predictors of severe ARV-related hepatotoxicity, (19) yet our cumulative incidence of grade 3–4 hepatotoxicity (4.4%) was lower than that seen in other cohort studies with similar proportions of coinfected participants (6–18%). (20–22) Servoss *et al.* found that 824 of 8,851 AIDS Clinical Trials Group patients (8.7%) developed severe LEEs after initiating new regimens. (13) More recent studies have focused on the hepatotoxicity of newer ARV regimens. Among 745 HIV/HCV coinfected patients in a multicenter observational cohort, Macías, *et al*. found that grade 3–4 LEEs were less common among patients receiving efavirenz (6%) compared with nevirapine (11%) or a ritonavir-boosted PI (10.5%). (23) Therapy was discontinued most often among nevirapine recipients (13%). Neukam, *et al*. assessed the frequency of severe LEEs among 76 Spanish patients initiating an efavirenz-containing regimen and 186 initiating a boosted PI. (24) There was no difference in the proportion developing grade 3–4 LEEs between the two groups (efavirenz, 6.6%; boosted PI, 8.1%, P=0.681). Indeed, in two recent reviews of the hepatotoxicity of ARVs among all HIV-infected patients (25) and among HIV/HCV-coinfected individuals (26), the hepatic safety profile of newer agents appears significantly improved compared to agents used in the late 1990s and early 2000s.

Patients with lower CD4 cell counts at raltegravir initiation were more likely to develop severe-grade AST and/or ALT abnormalities, though this was not more prominent among coinfected patients. This observation could implicate antiretroviral-related liver injury, rather than hepatitis virus-related immune reconstitution phenomena. Correlations between peak transaminase levels and the extent of CD4 cell count increase above baseline have been described previously among patients initiating combination ARV therapy. (27) Sulkowski *et al.* found CD4 gains of >50 cells/μL and baseline counts <200 cells/μL were each associated with severe-grade hepatotoxicity after initiating ARVs. (28)

Given that 90% of our coinfected patients had HCV, our findings should provide additional reassurance about the use of raltegravir in patients living with HIV/HCV coinfection. Raltegravir may assume an important role in HCV management over the next several years, as a variety of highly efficacious direct-acting antiviral (DAA) treatment options become available clinically and we learn more about their individual pharmacokinetic profiles. The first approved DAAs, boceprevir and telaprevir, are NS3/4A HCV protease inhibitors that have a variety of drug-drug interactions with ARVs – especially NNRTIs and PIs. (29) This necessitates either modification of the ARV regimen to avoid interactions prior to pursuing HCV treatment or, in the case of telaprevir, sometimes dose modification of the DAA itself. Raltegravir lacks clinically significant drug-drug interactions with boceprevir, (30) telaprevir (31), and another NS3/4A inhibitor, simeprevir (32), which was recently approved by the U.S. Food and Drug Administration (FDA). (33) Pharmacokinetic studies show a

similarly favorable profile with sofosbuvir (34), a nucleotide analogue inhibitor of HCV polymerase (NS5B) – also recently FDA-approved. (35)

Our study has several specific strengths and limitations. Because all data come from participants in two large HIV clinical cohort studies, our findings are more generalizable to clinical care settings than are data from clinical trials. The size of our sample is large, compared to other recent cohort studies of raltegravir in hepatitis-coinfected populations [14–16]. Since patients were being followed for clinical care purposes rather than in a clinical trial setting, liver enzyme measurements were obtained per routine rather than according to a fixed study protocol. Similarly, coinfection status was assessed using data available at any point prior to raltegravir initiation and a specific assessment of HBV DNA or HCV RNA in co-infected patients at the time of initiation was not available. Finally, we did not extract data on hepatitis treatment status for this study, so the influence of controlled HBV or previously treated HCV cannot be determined from these data.

In summary, though we found a nearly 3.5-fold increased rate of severe LEEs among hepatitis-coinfected patients treated with raltegravir, the development of grade 3–4 transaminitis was a rare event overall, occurring in only 5 cases per 100 person-years of follow-up. Our overall cumulative incidence of grade 3–4 LEEs was generally lower than that reported in other studies of ARVs, reflecting the hepatic safety of raltegravir in comparison to other drugs in other classes. Given its safety, tolerability, and the favorability of its pharmacokinetics with available DAAs and those in development, the benefits of using raltegravir in the management of HIV/HCV coinfected patients seem to clearly outweigh any risks.

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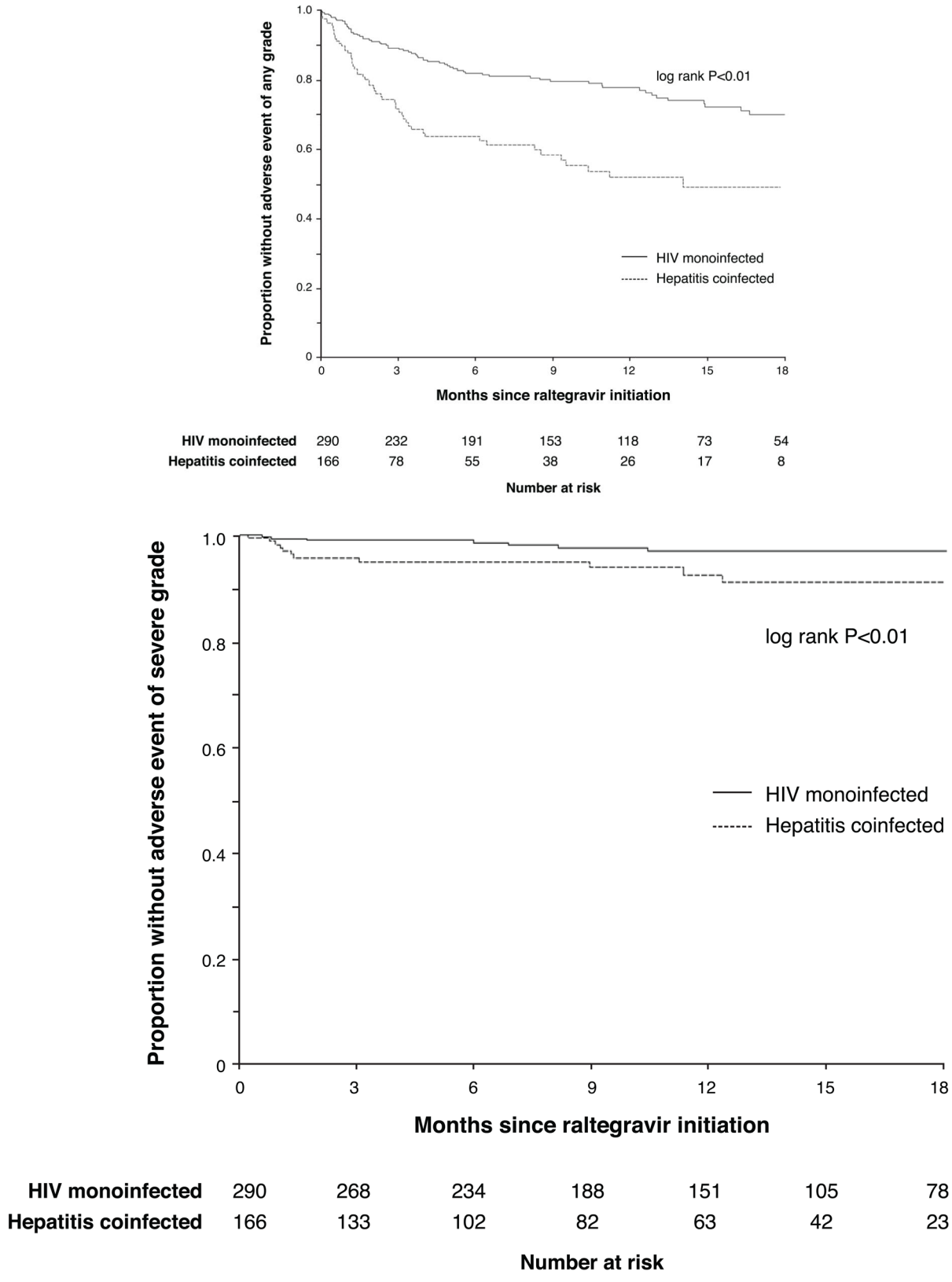

Figure 1.

Figure 1A. Time to first hepatotoxic adverse event of any grade (DAIDS grade 1–4)
Figure 1B. Time to first hepatotoxic adverse event of severe grade (DAIDS grade 3–4)

Table 1

Patient demographic and clinical characteristics at raltegravir initiation, stratified by hepatitis coinfection

Characteristic[a,b]	All (n=456)	HBV ± HCV coinfection (n=166)[c]	HIV monoinfection (n=290)	P
Site[d]				
JHHCC	320 (70)	135 (81)	185 (64)	<0.01
UCHCC	136 (30)	31 (19)	105 (36)	
Age (years)	48 (43–53)	50 (46–55)	47 (42–53)	<0.01
Women	144 (32)	51 (31)	93 (32)	0.77
Black	300 (66)	131 (79)	169 (58)	<0.01
MSM	158 (35)	31 (19)	127 (44)	<0.01
IDU	134 (29)	108 (65)	26 (9)	<0.01
Prior ARV exposure				
NNRTI	337 (74)	120 (72)	217 (75)	0.55
PI	407 (89)	143 (86)	264 (91)	0.10
None (ARV naïve)	21 (5)	7 (4)	14 (5)	0.76
Raltegravir regimen				
NRTI	67 (15)	16 (10)	51 (18)	<0.01
NNRTI	46 (10)	11 (7)	35 (12)	
PI	266 (58)	115 (69)	151 (52)	
NNRTI and PI	77 (17)	24 (14)	53 (18)	
CD4 cell count (cells/mm^3)	330 (147, 514)	312 (142, 490)	342 (148, 519)	0.63
HIV RNA level (copies/mL)	271 (<50, 36,497)	181 (<50, 29,100)	295 (<50, 44,614)	0.89
<400 copies/mL	247 (54%)	156 (54%)	91 (55%)	0.83
<50 copies/mL	174 (38%)	113 (39%)	61 (37%)	0.64
ALT (U/L)	29 (20, 45)	31 (23, 60)	26 (18, 38)	<0.01
AST (U/L)	31 (24, 29)	46 (30, 66)	27 (22, 37)	<0.01
Albumin (g/dL)	4.1 (3.8, 4.4)	3.9 (3.5, 4.3)	4.2 (3.9, 4.5)	<0.01
Total bilirubin (mg/dL)	0.4 (0.3, 0.7)	0.5 (0.3, 1.0)	0.4 (0.3, 0.6)	0.02

[a] Characteristics are either n (%), or median (interquartile range)

[b] ALT, alanine aminotransferase; ARV, antiretroviral; AST, aspartate aminotransferase; IDU, injection drug use; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor;

[c] Hepatitis C, n= 138; hepatitis B, n= 17; both hepatitis viruses, n= 11

[d] JHHCC, Johns Hopkins HIV Clinical Cohort, UCHCC, University of North Carolina Center for AIDS Research HIV Clinical Cohort

Table 2

Associations with time from raltegravir initiation to first elevated alanine and aspartate aminotransferase levels of any grade (DAIDS grades 1–4) and severe grade (DAIDS grades 3–4)

	Hazard Ratio (95% Confidence Interval)[a]			
	Any Grade		Severe Grade	
Characteristic [b]	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
HBV/HCV coinfection [c]	2.48 (1.73, 3.54)	2.17 (1.50, 3.16)	3.28 (1.33, 8.09)	2.69 (1.03, 7.04)
Age (per 10 year increase)	1.00 (0.82, 1.21)		1.16 (0.71, 1.92)	
Women	1.10 (0.75, 1.61)		1.60 (0.65, 3.91)	
CD4 cell count (per 100 cell/μL increase)	0.98 (0.91, 1.04)		0.77 (0.61, 0.95)	0.78 (0.62, 0.97)
HIV RNA >50 copies/mL	0.93 (0.65, 1.33)		2.02 (0.73, 5.56)	
Elevated ALT or AST [d]	1.91 (1.28, 2.87)	1.50 (0.98, 2.29)	2.90 (1.20, 6.96)	1.87 (0.73, 4.77)

[a] All adjusted estimates based on Cox proportional hazards regression models adjusted for characteristics listed in table, as well as, site and frequency of ALT/AST measurements.

[b] All characteristics measured at raltegravir initiation.

[c] HBV/HCV, HIV-infected patients coinfected with hepatitis B and/or hepatitis C; ALT, alanine aminotransferase; AST, aspartate aminotransferase

[d] Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) based on a DAIDS grade 1–4 elevation measured at raltegravir initiation

Table 3

Patient demographic and clinical characteristics associated with raltegravir discontinuation

	Hazard Ratio (95% Confidence Interval)	
Characteristic[a,b]	**Unadjusted**	**Adjusted**
HBV/HCV coinfection [c]	0.48 (0.14, 1.64)	
CD4 cell count (per 100 cell/mm^3 increase)	0.67 (0.51, 0.86)	0.71 (0.55, 0.92)
HIV RNA >50 copies/mL	0.64 (0.25, 1.65)	
Elevated ALT or AST [d]	0.93 (0.31, 2.78)	
ALT/AST DAIDS grade 1–4	1.28 (0.49, 3.31)	
ALT/AST DAIDS grade 3–4	4.64 (1.56, 13.81)	3.53 (1.10, 11.37)

[a] All adjusted estimates based on Cox proportional hazards regression models adjusted for characteristics listed in table, as well as site.

[b] All characteristics measured at raltegravir initiation, except alanine aminotransferase (ALT) or aspartate aminotransferase (AST) DAIDS grade 1–4 and 3–4 elevations.

[c] HBV/HCV, HIV-infected patients coinfected with hepatitis B and/or hepatitis C

[d] Elevated ALT or AST based on a DAIDS grade 1–4 elevation measured at raltegravir initiation.