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Abstract

Background: Whether by HAART, viral hepatitis, or alcohol, transaminitis (elevated ALT and AST) is common among those with HIV infection. We used data from VACS 3 and CHORUS to determine the importance of transaminitis in predicting survival after adjusting for CD4 count and HIV-1 RNA.

Methods: The VACS 3 and CHORUS cohorts have been described in detail. At the time of analysis, VACS 3 has data on CD4, viral load (VL), ALT (SGPT), and AST (SGOT) on 773 patients, 56 have died. VACS 3 patients are predominantly male (99%), African-American (55%), and contracted HIV via IV drug use or heterosexual exposure (53%). CHORUS has data on 4946 patients, 280 have died. CHORUS subjects are predominantly male (91%), white (75%), and men who have sex with men (87%). Variables were transformed to approximate normal distributions (table). Cox proportional hazards survival models were used to measure variable importance. ROC area (C statistic) was used to compare discrimination of the models. Linear regression was used to determine whether hepatitis C infection mediates transaminitis.

Results: In unadjusted analyses, CD4, VL, and AST were significant predictors of survival in both cohorts ($P < 0.001$). ALT was significant only in CHORUS ($P < 0.001$). A model restricted to CD4 and VL demonstrated discrimination in both CHORUS and VACS 3 (ROC: 0.78, 0.63). A model restricted to AST and ALT also demonstrated discrimination in both (ROC: 0.70, 0.62). The full model was superior (ROC: 0.82, 0.71):

Variable	Transformation	CHORUS		VACS 3	
		HR	P	HR	P
CD4 Count	Square root	0.89	<0.001	0.94	.009
Viral Load	Log ₁₀	1.37	<0.001	1.35	.008
AST	Natural Log	3.21	<0.001	2.59	<.001
ALT	Natural Log	0.49	<0.001	0.44	.002

In both, hepatitis C was associated with increased AST ($P < 0.001$) and ALT ($P < 0.001$), but not with survival.

Conclusions: An important strength of this result is consistency across two diverse cohorts. Transaminitis is a major determinant of survival and should be carefully considered in all phases of HIV therapy.

Introduction

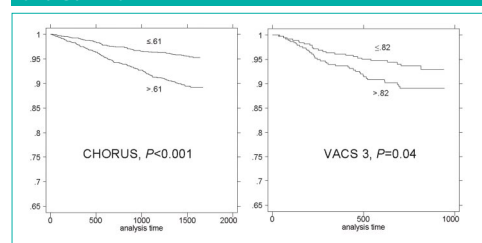
As a result of successful treatment with multidrug, multiclass antiretroviral medications, patients with HIV infection are living longer and are increasingly at risk of death from non-HIV comorbid conditions (Fusco GP, IAC poster #5584). A primary cause of death due to comorbid disease may be death from liver failure or cirrhosis (Fusco GP, IAC poster #5584). Further, anemia has long been known to be associated with survival in HIV infection¹ and may be an even stronger predictor in the post HAART era.² It is not known whether anemia and transaminitis independently contribute to risk of mortality in HIV. In an effort to better define the role of these common abnormalities in determining survival in the post-HAART era, we conducted parallel and combined analyses of two multi-site observational studies: one based in a community setting and one based in the Veterans Administration Healthcare System.

The Collaborations in HIV Outcomes Research – US (CHORUS) Study is a community-based observational cohort following nearly 6000 patients at four sites (Comprehensive Care Center, Nashville, TN; Liberty Medical Group, New York, NY; Pacific Horizon, San Francisco, CA; Pacific Oaks, Los Angeles, CA). The Veterans Aging Cohort 3 Site Study (VACS 3) is a Veterans Administration clinic-based cohort of 881 patients served by three VA facilities (Houston, TX; Manhattan, NY; and Cleveland, OH). Parallel and combined analyses in two large and diverse cohorts of patients with HIV were performed to assess if transaminitis or anemia were associated with poorer survival. We also asked whether mild to moderate levels of transaminitis and anemia were associated with poorer survival.

Methods

All consented patients with minimum laboratory data and follow up were included in the analysis. Transaminitis was defined as an elevation above the upper limit of laboratory normal in either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in plasma. ALT and AST were strongly correlated (CHORUS 0.89, VACS 0.79, P for both <0.001). AST was selected for further evaluation because it was more strongly associated with survival (Figure 1). AST values were standardized to the normal range. AST results above the normal range were assigned a score greater than 1. Results at the top of normal were assigned a score of 1 and results within the normal range were assigned a score of less than 1.

Figure 1 • Kaplan-Meier Curves of Median AST and Survival



Alcohol use was defined as a diagnosis of alcohol abuse. Hepatitis B and C status were based on laboratory serologies. Current medications were determined by prescription record (CHORUS) or pharmacy fill data (VACS 3). Anemia was defined as an elevation above the upper limit of normal in hemoglobin. For all variables, the value closest to enrollment was selected for modeling.

We first evaluated the relationship of AST with survival in each cohort separately and simply cut the sample at the median value for the cohort. These were then illustrated using Kaplan-Meier curves. After testing to insure that an indicator for study cohort was not significant in a Cox model of survival adjusted for AST, hemoglobin, CD4 cell count, and viral load, we combined the two samples to improve our ability to evaluate important cutpoints in AST and hemoglobin. Finally, linear regression was used to evaluate mediators of hemoglobin and AST. Because these varied some by cohort, this analysis is presented in parallel.

Results

As of May 6, 2002, CHORUS had enrolled 5985 patients and observed 400 deaths. The VACS 3 database included 881 patients and 71 deaths. A substantial proportion of both cohorts (CHORUS 21% and VACS 3 31%) had an AST value at enrollment greater than top normal.

In both cohorts, AST, ALT, and hemoglobin demonstrated an independent association with survival after adjustment for CD4 cell count, HIV-1 RNA, and age (Table 1).

Table 1 • Multivariable Analyses: Hazard Ratios and P Values for Variables Associated with Survival*

Variable	CHORUS		VACS 3	
	HR	P	HR	P
Hemoglobin	0.80	<0.001	0.75	<0.001
Hepatitis C	1.25	0.2	1.07	0.8
Chronic hepatitis B	0.84	0.2	0.82	0.7
AST/Top Normal	1.35	<0.001	1.47	0.001
ALT/Top Normal	0.83	0.005	0.61	0.04
SORT (CD4)	0.91	<0.001	0.97	0.1
Log (HIV-1 RNA)	1.40	<0.001	1.54	<0.001
Age	1.04	<0.001	1.05	<0.001

*Proportional Hazards, C Statistic for Models: 0.83, 0.78, respectively.

In an assessment of cutpoints, AST values were divided into normal (<5 top normal), mild (.5-1 top normal), moderate (1-2-fold top normal), and severe (>2-fold normal). There was little difference between mild and moderate elevation in AST. Therefore, we combined these two levels to yield three levels of AST elevation (Figure 2). Similarly, when hemoglobin cutpoints were considered, three levels of anemia; normal (>13 mg/dL), moderate (11-13 mg/dL), and severe (<11 mg/dL) were most meaningful (Figure 3).

Figure 2 • Kaplan-Meier Curves of AST (Combined Cohorts)

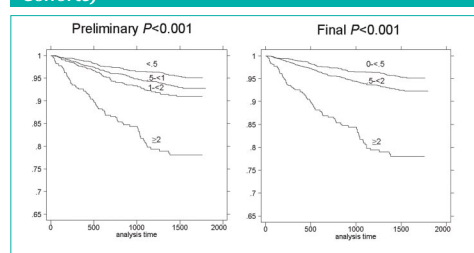
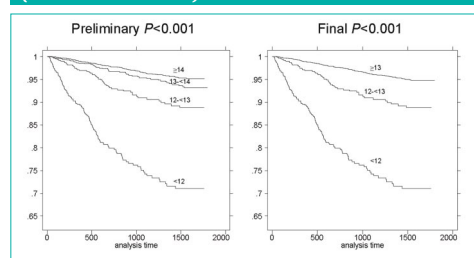
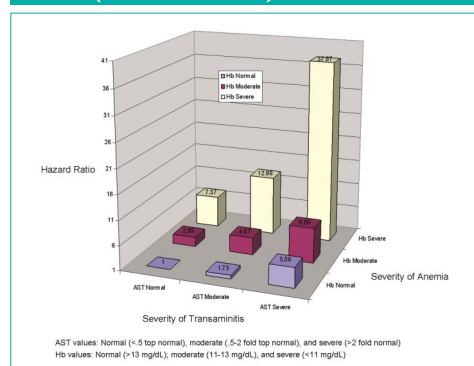


Figure 3 • Kaplan-Meier Curves of Hemoglobin (Combined Cohorts)



Additionally, we considered eight combinations of transaminitis and anemia (eg, normal AST, moderate anemia; moderate AST, normal anemia; etc.) to a comparison group of normal AST and normal hemoglobin. Each level of transaminitis and anemia was independently associated with survival and having both transaminitis and anemia of any level of severity resulted in a poorer survival than having only one of the conditions (Figure 4).

Figure 4 • Combined Effect of Transaminitis and Anemia (Combined Cohorts)



Finally, the etiology of transaminitis was explored (Table 2). In a linear regression model, AST elevation was associated in both cohorts with hepatitis C, chronic hepatitis B, and increasing age. In addition, AST elevation was also significantly associated with a diagnosis of alcohol abuse or dependence, CD4 cell count, and HIV-1 RNA viral load in CHORUS. Alcohol use as reported by the patient was associated with AST elevation in VACS 3 (data not otherwise shown). Of note, neither cumulative dose of any non-nucleoside reverse transcriptase inhibitor nor cumulative dose of zidovudine was associated with AST elevation.

Table 2 • Mediators of Transaminitis: Multivariable Analyses of AST*

Variable	CHORUS		VACS 3	
	β^*	P	β^*	P
Hepatitis C	15.4	<0.001	6.4	<0.001
Chronic hepatitis B	4.3	<0.001	3.7	<0.001
Alcohol Abuse Diagnosis	3.2	0.001	-1.2	0.2
Age	2.3	0.02	-2.0	0.05
SORT (CD4)	-7.7	<0.001	-1.4	0.2
Log (HIV-1 RNA)	ns	ns	ns	ns
NNRTI Cumulative Exposure	ns	ns	ns	ns
RTV Cumulative Exposure	ns	ns	ns	ns

*Linear Regression, R^2 for Model: 0.07, 0.08. HR standardized by dividing it by SE, reflects statistical weight of variable in model.

Discussion

- This analysis of two large and diverse HIV populations is likely to be highly generalizable.
- Combining data from the two samples allowed sufficient events to consider multiple etiologies and cutpoints.
- The relationship with alcohol and AST was somewhat variable suggesting that better measures of alcohol consumption are needed.
- Next steps include exploring optimal clinical interventions.

Conclusions

- ◆ AST and hemoglobin are associated with HIV disease severity and age.
- ◆ AST and hemoglobin predict survival independently of CD4, HIV-1 RNA, and age.
- ◆ Even mild to moderate transaminitis and anemia are associated with survival.
- ◆ Hepatitis C and chronic hepatitis B are strongly associated with transaminitis but not directly associated with survival.
- ◆ Alcohol use is associated with transaminitis.
- ◆ Management of transaminitis and anemia deserve clinical attention.

References

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