



# Liver Function Tests Independently Predict HIV Survival

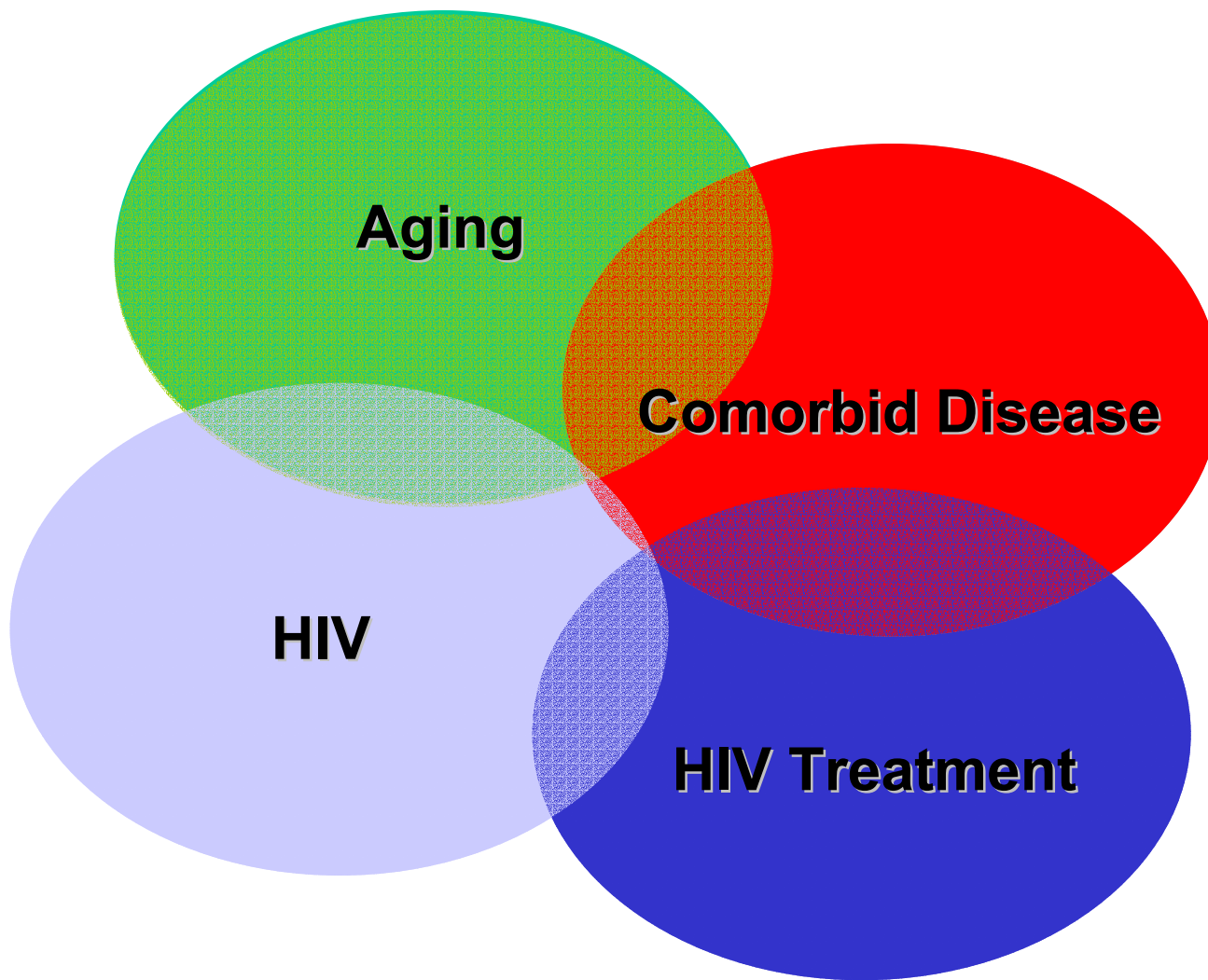
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for the CHORUS and VACS 3 Project Teams



# HIV Outcomes in 2002





# Liver “Function” Tests

- Aminotransferases (hepatocellular injury )
  - Alanine (ALT): only in cytosol of liver
  - Aspartate (AST): liver, cardiac and skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes and erythrocytes
    - Mitochondria and cytosol
    - 80% of AST in liver is mitochondrial
  - Elevations less than twice top normal ignored



# Anemia

- Measured using hemoglobin
- Common complication of HIV and treatment
- Predicts survival
- Mild to moderate anemia ignored



# Aminotransferase Elevation: Clinical Questions

- What causes it?
- Does it predict survival?
  - Independent of CD4 cell count and HIV-1 RNA?
  - Independent of age and anemia?
- What are important survival cut points and are these additive with cut points for anemia?



# Subjects



	<b>CHORUS</b>	<b>VACS 3</b>
Prospective Consent	Yes	Yes
EMR Data & Surveys	+ Scripts	+ Pharmacy
Enrollment	97-present	99-00
Patients Enrolled	5985	881
Deaths	400	71
Sites	4	3
Age (median years)	39	49
Predominant Race	White	African American
Predominant Risk	MSM	IVDU, Heterosexual
Women (n)	563	11



# Data

- Laboratory values closest to date of enrollment
  - AST and ALT were standardized to laboratory normal
    - $>1$  mean value above normal
    - $=1$  are top normal
    - $<1$  normal
  - CD4 and HIV-1 RNA transformed
  - Hemoglobin did not require transformation
- Alcohol based on diagnostic codes
- Hepatitis B and C status based on lab data



# ALT, AST, and Survival

Variable	CHORUS		VACS 3	
	HR*	p	HR*	p
AST/Top Normal	6.98	<0.001	2.29	0.02
ALT/Top Normal	3.15	0.002	0.18	0.9
AST/ALT	6.48	<0.001	3.20	0.001

\* ALT and AST were highly correlated in both cohorts. In CHORUS the correlation was 0.89, in VACS it was 0.79,  $p < 0.0001$ . HR adjusted for CD4 and HIV-1 RNA. Proportional Hazards, HR standardized by dividing it by standard error, reflects statistical weight of variable in model.



# Survival: Multivariable Analyses\*



Variable	CHORUS		VACS 3	
	HR*	p	HR*	p
AST/Top Normal	6.40	<0.001	2.62	0.09
AST/ALT	3.08	0.002	1.50	0.1
Hemoglobin	-6.40	<0.001	-3.91	<0.001
Hepatitis C	1.53	0.1	0.24	0.8
Chronic hepatitis B	-1.35	0.2	-0.33	0.7
SQRT (CD4)	-9.22	<0.001	-1.46	0.1
Log (HIV-1 RNA)	5.82	<0.001	3.71	<0.001
Age	5.77	<0.001	3.67	<0.001

\* Proportional Hazards, HR standardized by dividing it by standard error, reflects statistical weight of variable in model. C Statistic for Models: 0.83, 0.78 respectively.



# AST: Multivariable Analyses\*

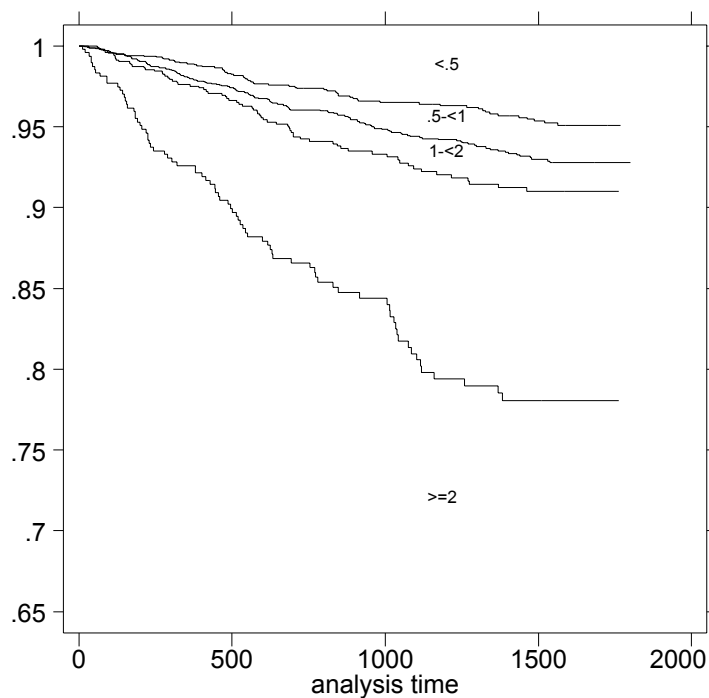


Variable	CHORUS		VACS 3	
	$\beta^*$	p	$\beta^*$	p
Hepatitis C	15.4	<0.001	6.1	<0.001
Chronic Hepatitis B	4.3	<0.001	3.7	<0.001
Alcohol Abuse Diagnosis	3.0	0.002	0.2	0.9
Age	2.8	0.005	-1.8	0.08
SQRT (CD4)	-5.5	<0.001	-1.5	0.1
Log (HIV-1 RNA)	3.1	0.002	0.4	0.7
NNRTI Cumulative Exposure	-0.6	0.5	-0.4	0.7
RTV Cumulative Exposure	1.0	0.3	0.2	0.9

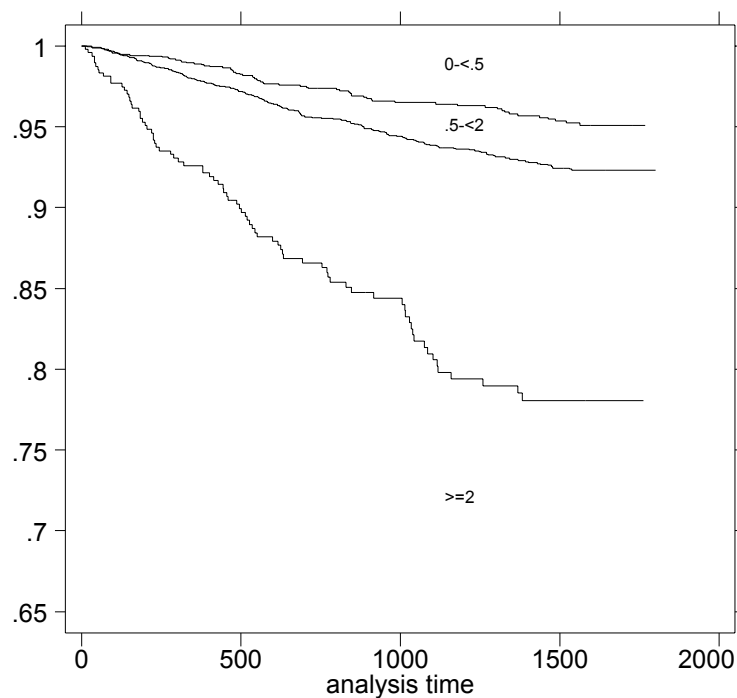
\*Linear Regression,  $R^2$  for Model: 0.07, 0.08. Beta standardized by dividing it by standard error, reflects statistical weight of variable in model

# KM Curves: AST (Combined Cohorts)

Preliminary  $p < 0.001$



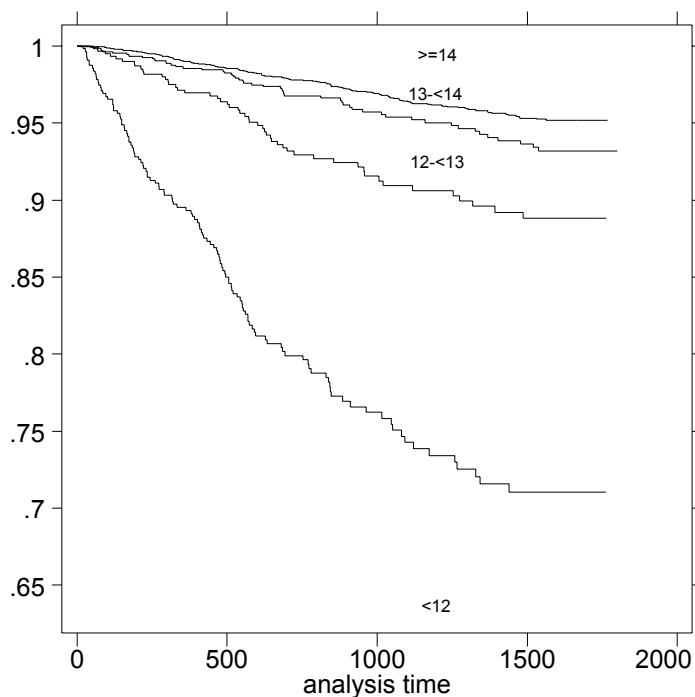
Final  $p < 0.001$



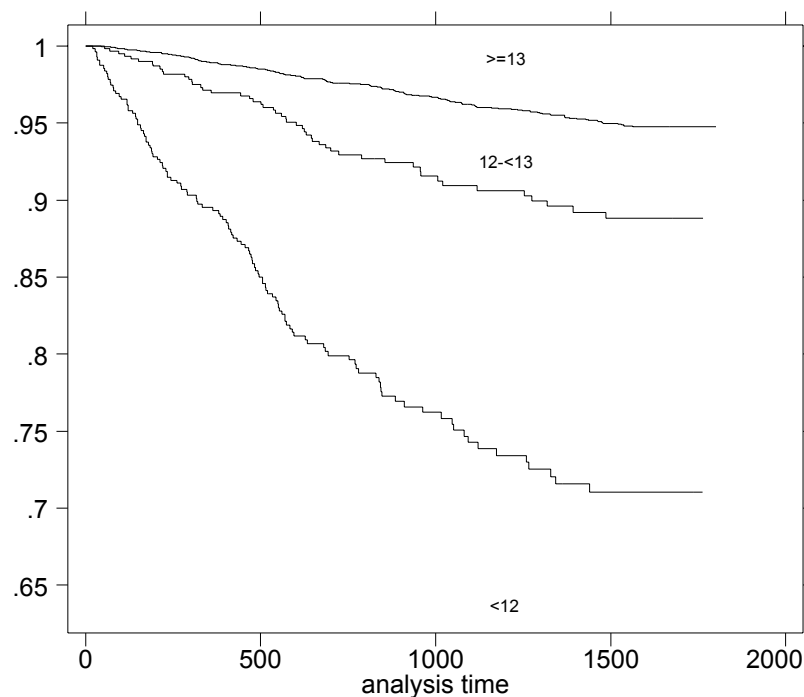


# KM Curves: Hemoglobin (Combined Cohorts)

Preliminary  $p < 0.001$



Final  $p < 0.001$

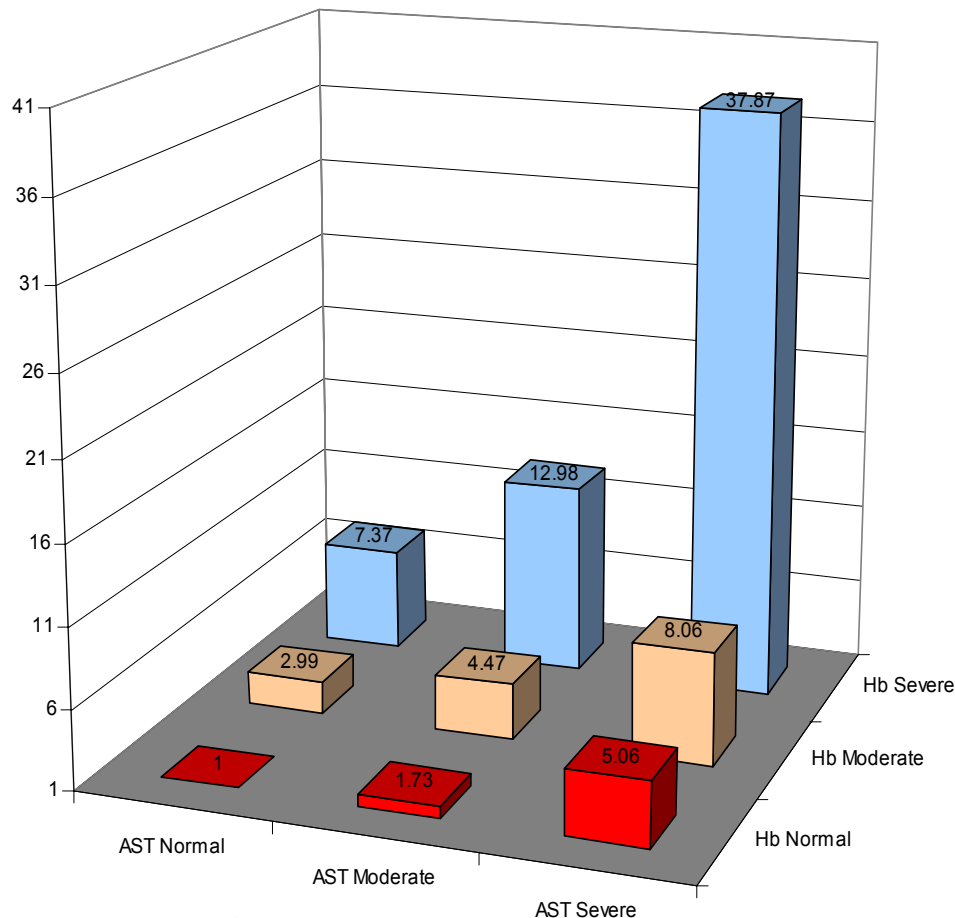




# Severity of AST Elevation and Anemia (Combined Cohorts)



Hazard Ratio



Severity of Anemia

Severity of AST Elevation

AST values: Normal (<.5 top normal), moderate (.5-2 fold top normal), and severe (>2 fold normal)

Hb values: Normal (>13 mg/dl); moderate (11-13 mg/dl), and severe (<11 mg/dl)



# Discussion

- **Strengths**

- Two cohorts
- Large samples, many events
- Clinical data
- Evaluate cut points, etiologies

- **Limitations**

- AST and ALT covariance
- Unable to characterize proportion of AST
  - From hepatocytes
  - From mitochondria
- Measure of alcohol use



# Conclusions



- AST elevation
  - Is associated with, in order of importance:
    - Hepatitis C and chronic B
    - Decreasing CD4 cell count and increasing HIV-1 RNA
    - Alcohol abuse
    - Increasing age
  - Predicts poorer survival after adjustment for
    - CD4 cell count and HIV-1 RNA
    - Age and hemoglobin
- Effects of AST elevation and anemia are additive
- Even mild AST elevations and anemia deserve attention