The Incidence and Risk Factors Associated with Chronic Liver Enzyme Elevation (cLEE) in HIV-Monoinfected Persons

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Abstract

Background: Chronic liver-associated enzyme elevations (cLEE) are common in persons with HIV; however, the significance in patients without hepatitis B or C co-infection remains unclear. The aims of this study were to evaluate the incidence and risk factors associated with cLEE in HIV-monoinfected subjects enrolled in the US Military HIV Natural History Study (NHS).

Methods: We included NHS subjects who were HBV and HCV seronegative with follow-up after 1996. cLEE was defined as alanine amino transferase (ALT) levels ≥ 1.25 x the upper limit of normal recorded at ≥ 2 visits spanning a period of 6 months within 2 years. Baseline characteristics between patients with and without cLEE were compared. Percentages are presented for categorical variables with medians and interquartile ranges presented for continuous variables. Multivariate Cox proportional hazards models were used to examine risk factors for cLEE.

Results: Of 3,163 included patients, 367 (11.7%) met criteria for cLEE. The incidence of cLEE was 1.4/100 person years of follow-up (1.2-1.5) with a period prevalence of 35%. Significant differences in baseline characteristics between groups are tabulated below. The median time from HIV diagnosis to cLEE was 5 years (3-8) with the majority of ALT elevations categorized as grade 1 (40%). BMI was significantly associated with cLEE only in the unadjusted model. In an adjusted model, male gender (HR 1.7 [1.0-2.8]) and Hispanic/Other race (compared with Caucasians: HR 1.8 [1.3-2.5]) were associated with cLEE while African American race was protective (compared with Caucasians: HR 0.75 [0.58 – 0.98]). Use of antiretroviral therapy [ART] (HR 1.9 [1.2-3.0]) and non-ART antiretrovirals (HR 2.0 [1.1-3.4]) were also associated with cLEE.

Conclusion: cLEE is common in the NHS, although the incidence rate is lower than that reported in other cohorts. ART use was associated with cLEE emphasizing the need for surveillance of liver enzymes in patients on ART. The association between race and cLEE needs further evaluation

Variable	Total		no cLEE		cLEE		P-Value
Year of HIV dx	2000	(1992,2008)	2001	(1993,2008)	1994	(1988,2002)	<.0001
Years on ART	3.7	(1.8,6.3)	3.7	(0.9,2.7)	4.1	(2.0,6.5)	<.0001
Nadir CD4 count	312	(216,420)	320	(225,431)	257	(134,362)	<.0001
BMI	25	(23,28)	25	(23.0,27.45)	26	(24,29)	0.0021

Background

- Liver enzyme abnormalities are common in persons with HIV, occurring in approximately 40-60% of patients on ART (Sterling et al, 2008).
- Available literature has largely focused on liver enzyme abnormalities in patients with hepatitis B or hepatitis C co-infection or severe liver enzyme elevations alone (Kovari et al, 2016).
- As a result, the significance of chronic liver enzyme elevation (cLEE) in HIV-monoinfected persons remains unclear.
- The aims of this study were to evaluate the incidence of and risk factors associated with cLEE in HIV-monoinfected subjects enrolled in the US Military HIV Natural History Study (NHS).

Study Population

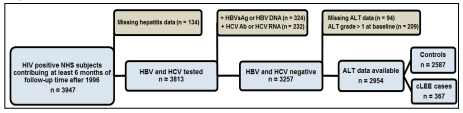
- The US Military Natural History Study (NHS), is a prospective observational cohort of consenting HIV-infected military personnel and beneficiaries.
- Approximately once every 6 months, NHS subjects meet with an HIV specialist at a participating Military Treatment Facility (MTF).
- During NHS visits, subjects undergo lab draws for testing (to include liver associated enzymes), examination by a physician and medical records are abstracted to capture clinical information.

Methods

Inclusion criteria:

- HIV positive NHS subjects contributing at least 6 months of follow-up time after 1996
- HCV and HBV negative
- Baseline ALT grade 0

Figure 1. Flow Chart of included Subjects



Case Definition - Chronic liver enzyme elevation (cLEE) was defined as ALT grade 1 or higher recorded at ≥ 2 visits spanning a period of 6 months within 2 years.

Alanine aminotransferase (ALT) grades:

- Grade 0: < 1.25 x ULN
- Grade 1: 1.25 – 2.5 x ULN
- Grade 2: 2.6 – 5.0 x ULN
- Grade 3: 5.1 – 10 x ULN
- Grade 4: > 10 x ULN

Figure 2.

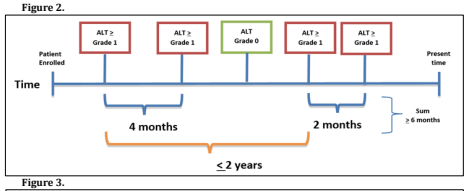
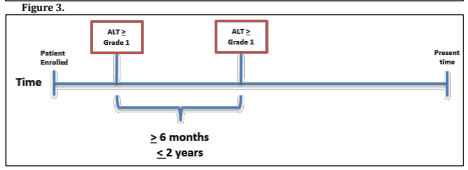


Figure 3.



Statistical Methods:

Baseline characteristics between patients with and without incidence cLEE were compared utilizing chisq for categorical and Wilcoxon Mann U test for continuous variable. Incidence rates with 95% CI were plotted by year. Univariate and multivariate Cox proportional hazards models were used to examine risk factors for cLEE.

Results

Table: 1 Baseline Characteristics of Cohort Comparing Patients with cLEE to patients without cLEE

Variable List	Total	Non- cLEE Cases	cLEE Cases	P-Value
Participants	N = 2954	N = 2587	N = 367	
Age	27.82 (23.75,33.83)	27.58 (23.65,33.63)	29.38 (25.26,35.40)	**0.0001**
Year of HIV, dx	2000 (1992,2008)	2001 (1993,2008)	1994 (1988,2002)	**<.0001**
BMI (continuous)+	25.2 (23.0,27.6)	25.1 (22.9,27.4)	26.3 (23.6,28.7)	**0.0016**
ALT FU Time, Years	5.57 (2.46,10.22)	5.94 (2.61,11.27)	3.75 (1.25,6.61)	**<.0001**
Race				**<.0001**
African American	1315 44.52	1189 45.96	126 (34.33)	
Caucasian	1189 40.25	1026 39.66	163 (44.41)	
Hispanic/Other	450 15.23	372 14.38	78 (21.25)	
Gender				0.1298
Female	218 7.38	198 7.66	20 (5.45)	
Male	2734 92.62	2387 92.34	347 (94.55)	
BMI at HIV dx				**0.0141**
<20	61 4.39	58 4.64	3 (2.13)	
20-25	558 42.30	543 43.47	45 (31.91)	
25-30	596 42.88	522 41.79	74 (52.48)	
30+	145 10.43	126 10.09	19 (13.48)	
Time to ART from HIV dx, yrs +	0.66 (0.15,2.84)	0.66 (0.15,2.84)	0.79 (0.15,3.00)	0.8188
Time on ART, yrs +	5.17 (2.38,10.07)	5.49 (2.44,10.90)	4.07 (2.04,6.51)	**<.0001**
Nadir CD4 count	296 (189,469)	307 (203,422)	216 (99,317)	**<.0001**
Peak log VL	11.01 (9.96,11.97)	10.96 (9.09,11.85)	11.38 (10.38,12.53)	**<.0001**
Treatment Regimen at time of first ALT +				**<.0001**
Not on ARVs	1416 47.95	1241 47.97	175 47.81	
On non-HAART ARVs	388 13.14	301 11.64	87 23.77	
D4/DDI/DDC	101 4.42	87 3.36	14 3.83	
Other HAART	1048 35.49	958 37.03	90 24.59	
Hyperlipidemia				0.4720
No	1825 61.78	1592 61.54	233 (63.49)	
Yes	1129 38.22	995 38.46	134 (36.51)	
Hypertension				0.0847
No	2261 76.54	1967 76.03	294 (80.11)	
Yes	693 23.46	620 23.97	73 (19.89)	
Diabetes				0.9435
No	2815 95.29	2465 95.28	350 95.37	
Yes	139 4.71	122 4.72	17 4.63	

Continuous variables are expressed as medians with interquartile ranges
Categorical variables are expressed as frequencies with percentages in parenthesis
+denotes missing variables [BMI n = 1799, Time from diagnosis to initiation of ART = 2627, Time on Art n=2615, Treatment regimen at first ALT n = 2953]

Incidence Cases	Follow-up Time	Rate/100 P-Y	95% CI low	95% CI high
367	240037.34	1.53	1.38	1.69

Period Prevalence	Total Population	Prevalence
434	3163	13.72%

Figure 4. Rates of cLEE per year with 95% confidence intervals

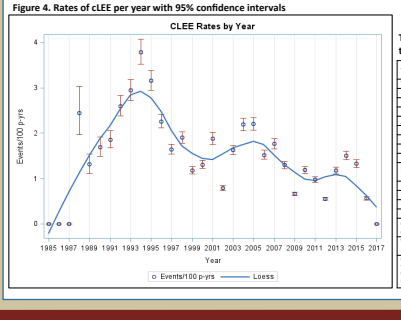


Table 2. Characteristics at time of cLEE diagnosis

Variables	cLEE cases (n = 367)
Year	
1988-1996	98 (26.70)
1997-2006	165 (44.96)
2007-2016	104 (28.34)
ALT grade	
Grade 1	148 (40.33)
Grade 2	146 (39.78)
Grade 3	53 (14.44)
Grade 4	20 (5.45)
HIV RNA level (copies/ml)	
<400	157 (57.51)
400-1000	71 (26.01)
1,000-50,000	12 (4.40)
50,000+	33 (12.09)
CD4 count (100 cells/mm^3)	449.5 (276, 670)
Time since HIV dx (yrs)	5.34 (2.81, 8.32)

Categorical variables are expressed as frequencies with percentage
Continuous variables are show as medians with interquartile ranges

Results (cont.)

Table: 3 Adjusted and Unadjusted Hazard Ratios (HR)

	Unadjusted HR	95% Confidence Interval		p-value	Adjusted HR	95% Confidence Interval		p-value
		Lower	Upper			Lower	Upper	
Age	1.009	0.996	1.021	0.1662	1.000	0.985	1.015	0.9793
Year of HIV Diagnosis	0.976	0.963	0.990	**0.0007**	0.975	0.955	0.996	**0.0179**
Race								
Caucasian	Ref							
African-American	0.725	0.574	0.915	**0.0069**	0.747	0.571	0.978	**0.0336**
Hispanic/Other	1.670	1.270	2.195	**0.0002**	1.800	1.313	2.468	**0.0003**
Gender								
Female	Ref							
Male	1.631	1.039	2.560	**0.0336**	1.655	0.995	2.754	0.0525
On ARVs/HAART								
Not on ARVs	Ref							
On non-HAART ARVs	3.635	2.490	5.307	**<.0001**	1.942	1.135	3.325	**0.0155**
D4/DDI/DDC HAART	2.104	1.098	4.032	**0.0251**	1.843	0.926	3.667	0.0818
Other HAART	2.039	1.427	2.913	**<.0001**	1.898	1.230	2.930	**0.0038**
BMI Category								
BMI <20	Ref							
BMI 20-25	0.713	0.523	0.972	**0.0323**	0.606	0.418	0.880	**0.0084**
BMI 25-30	1.090	0.837	1.420	0.5226	0.997	0.719	1.382	0.9854
BMI 30+	1.449	1.054	1.992	**0.0223**	1.367	0.933	2.004	**0.1089**
CD4 cell count, 100 cells/mm^{3*}	0.921	0.884	0.960	**<.0001**	1.000	0.999	1.000	**0.4905**
Log_{10} HIV RNA level, copies/ml*	1.088	0.992	1.193	0.0731	1.073	0.957	1.204	0.2267

Conclusions

- cLEE is common in the NHS with an incidence of 1.41/100 PY. Although this is lower than that reported in other cohorts, we suspect this is a reflection of the young age of our participants. Reduced rates of IVDU and medical comorbidities associated with LFT abnormalities (i.e. metabolic syndrome) may have also contributed to reduced incidence in this group.
- The majority of ALT grades at time of cLEE diagnosis were grade 1 highlighting the importance of further investigating the clinical significance of these low level elevations over time.
- ART use was associated with cLEE emphasizing the need to monitor liver enyzmes in patients on ART. However, further analyses are required to elucidate specific ART regimens.
- Although the strongest association with ART was in persons taking older regimens, an association still existed when accounting for known hepatotoxic HAART agents and warrants further evaluation.
- The association between race and cLEE needs further evaluation.

Acknowledgments

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