

Risk Factors for Liver Enzymes Elevation in HIV-HBV Co-Infected Patients: Focus on Antiretroviral Implication

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Abstract

Background: Transient liver enzyme elevation is frequently described in HIV-infected patients under antiretroviral therapy, especially when there is a concomitant viral hepatitis. However, little is known about the risk factors of acute cytolysis and cholestasis in HIV-HBV co-infected patients. The objective of the present study was to identify such risk factors focusing on the putative implication of antiretroviral drugs.
Methods: Included patients were from a 3-year prospective French multi-center cohort study involving HIV-infected patients with chronic HBV co-infection (HBsAg seropositivity at inclusion). A multivariate Markovian modeling approach was used to describe and to identify independent risk factors of transient severe (ACTG grade 3 or 4) cytolysis and cholestasis in 300 HIV-HBV co-infected patients.
Results: Severe cytolysis and cholestasis incidence were 5.0 (95% CI, 2.5 – 7.5) and 6.7 (95% CI, 3.9 – 9.5) cases for 100 patients-years respectively. Three and two independent risk factors were identified: concurrent chronic hepatitis Delta virus co-infection (HR = 8.35; 95% CI, 1.44 – 48.50), HBV genotype G (HR = 3.87; 95% CI, 1.17 – 12.79) and age (HR = 0.33; 95% CI, 0.12 – 0.88) for severe cytolysis, HBV infection duration longer than 5 years (HR = 3.47; 95% CI, 1.63 – 7.41) and high alcohol consumption (HR = 0.38; 95% CI, 0.21 – 0.70), which seems to slow down cholestasis enzymes' normalization, for severe cholestasis. When focusing on HAART, no pharmacological class was associated with a higher incidence of severe cytolysis, but current use of protease inhibitors appeared to be independently associated with increased rates of severe cholestasis (HR= 2.11; 95% CI, 1.20 – 3.73).
Conclusion: Transient episodes of cytolysis or cholestasis in HIV-HBV co-infected patients were common and associated with patient- and virus-related risk factors rather than antiretroviral classes. These results show that chronic hepatitis B should not preclude the use of any class of antiretrovirals. Patient- and virus-related parameters should be assessed before introducing antiretroviral therapy, and liver enzyme monitoring should be maintained throughout the whole treatment period.

Background

- Roughly 6-9 % of HIV-infected individuals in the Western world are also infected with hepatitis B virus (HBV) and liver-related mortality significantly increases with co-infection¹
- One determinant of liver fibrosis progression towards end stage liver disease is the high frequency of hepatic flares with recurrent liver enzyme elevations in case of HIV-hepatitis co-infection
- The role of putative factors such as excessive alcohol consumption and other potentially liver-damaging medications has been examined.² However, specific characteristics such as hepatitis Delta virus (HDV) co-infection or HBV genetic variability have not yet been investigated
- Antiretroviral drugs have also been reported to induce abnormal liver enzymes levels,³ but their hepatic safety has primarily been evaluated in patients included in well-defined clinical trials or in retrospective studies

Objective

- The objective of the present study was to identify risk factors of severe cytolysis and cholestasis in a large cohort of HIV-HBV co-infected patients. Special attention has been given to the putative role of antiretroviral drugs

Methods

Patients:

- Patients followed-up in the 2002 – 2006 French HIV-HBV Cohort Study (in accordance with the Helsinki declaration) were enrolled in the present study according to the following inclusion criteria:
 - HIV enzyme-linked immunosorbent assay (ELISA) positivity confirmed by a Western blot
 - HBsAg seropositivity at inclusion
 - At least one visit following inclusion

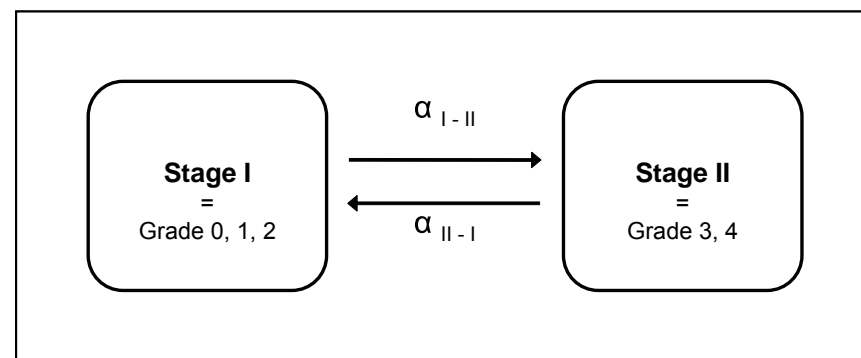
Outcome:

- Variations in serum alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase and total bilirubin were categorized in accordance with the ACTG toxicity grade scale based on changes relative to the upper limit of normal (ULN), enzymes modifications being graded on a scale from 0 to 4. Hepatic enzyme elevations were classified in our analysis in two stages based on this scale: stage I ($\leq 5 \times$ ULN) corresponding to the grades 0, 1 and 2, and stage II ($> 5 \times$ ULN) corresponding to the grades 3 and 4 (considered "severe or life threatening modifications")

Data analysis:

- An homogeneous continuous-time Markov model with both time-independent and time-dependent covariates was used to describe and to identify independent risk factors of transient severe or life threatening modifications

Figure 1.



- Finally, transition probabilities were computed for every six months for the 3 years of follow-up

Table 1. Patients

	All patients (n = 300)	Cytolysis (n = 40)	Cholestasis (n = 54)	Cytolysis + Cholestasis (n = 15)
Demographics				
Age, years (mean, \pm SD)	40.4 (\pm 8.0)	37.9 (\pm 6.4)	43.3 (\pm 7.5)	41.7 (\pm 7.4)
Male (n)	253	37	50	15
HBV prevalence in birth country (n):				
< 2 %	188	29	40	10
[2 – 8] %	28	5	7	4
> 8 %	84	6	7	1
Alcohol dependence (n=289)	62	14	16	6
CDC Stage C (n)	77	16	23	9
HBV infection				
Estimated HBV duration, years (median, Q1-Q3)	6.1 (2.3 – 10.8)	6.1 (3.1 – 10.1)	8.1 (4.6 – 13.1)	8.1 (4.4 – 10.2)
HBV viral load, UI / ml (n):				
< 60 /] 60 – 2.000] /] 2.000 – 20.000] / > 20.000	117/52/20/111	9/6/3/22	19/9/3/23	5/1/0/9
Pre-core region W28 mutation (n)	58 / 200	16 / 32	7 / 37	3 / 10
YMDD mutation (n)	57 / 185	22 / 31	21 / 36	7 / 11
HBV genotype (n=201):				
A / B / D / E / G	134/1/18/23/25	19/0/3/2/9	26/0/5/2/5	6/0/2/0/3
METAVIR fibrosis score (n=97):				
F0 - F2 / F3 - F4	66 / 31	12 / 8	11 / 12	4 / 4
History of acute hepatitis (n = 233)				
Concurrent chronic hepatitis C (n)	27	6	10	4
Concurrent chronic hepatitis D (n)	23	8	6	3
HIV infection				
Estimated HIV duration, years (median, Q1-Q3)	9.9 (3.9 – 14.0)	11.5 (6.9 – 15.1)	14.0 (9.1 – 15.8)	14.5 (12.3 – 15.3)
ARV treatment duration, years (median, Q1-Q3)	5.8 (2.9 – 7.4)	6.2 (4.2 – 7.6)	6.8 (4.7 – 8.9)	7.6 (6.6 – 9.8)
CD4 cell nadir, $\times 10^6$ / l (median, Q1-Q3)	213 (103 – 323)	210 (104 – 389)	167 (90 – 307)	211 (116 – 364)
HIV viral load, copies / ml (n):				
< 50 /] 50 – 10.000] / > 10.000	164/73/63	16/15/9	27/13/14	7/5/3
CD4 cell count, $\times 10^6$ / l (mean, \pm SD)	435.7 (\pm 254.1)	410.5 (\pm 212.8)	398.2 (\pm 245.5)	387.3 (\pm 176.3)
ARV treatment modification during follow-up (n)				
ARV treatment initiation during follow-up (n)	14	2	3	1
Previous exposure to (n):				
Any ARV	273	38	50	14
NRTI	273	38	50	14
NNRTI	145	24	33	9
PI	198	28	39	12
Preinclusion cumulative ARV exposure, years (mean, \pm SD):				
NRTI	9.2 (\pm 6.4)	10.7 (\pm 6.6)	10.7 (\pm 5.7)	12.8 (\pm 5.8)
NNRTI	1.9 (\pm 10.2)	1.1 (\pm 1.3)	1.3 (\pm 1.4)	1.2 (\pm 1.3)
PI	2.4 (\pm 2.7)	3.0 (\pm 3.1)	2.6 (\pm 2.7)	3.2 (\pm 3.1)
Use of potentially hepatotoxic non-ARV drug (n)				
Triglycerides, g/l (mean, \pm SD)	1.7 (\pm 1.2)	1.7 (\pm 0.8)	2.0 (\pm 1.7)	1.9 (\pm 0.8)
Glycemia, mmol/l (mean, \pm SD)	5.0 (\pm 1.0)	4.8 (\pm 0.6)	5.1 (\pm 0.9)	4.9 (\pm 0.6)

Results

Incidence of Severe Cytolysis and Severe Cholestasis:

- Severe cytolysis was seen in 40 of the 300 patients, thus representing an incidence of 5.0 cases for 100 patient-years (95% CI, 2.5 – 7.5)
- Severe cholestasis was seen in 54 of the 300 patients, representing an incidence of 6.7 cases for 100 patient-years (95% CI, 3.9 – 9.5)
- Fifteen patients developed both severe cytolysis and severe cholestasis during the follow-up

Risk factors for Severe Cytolysis:

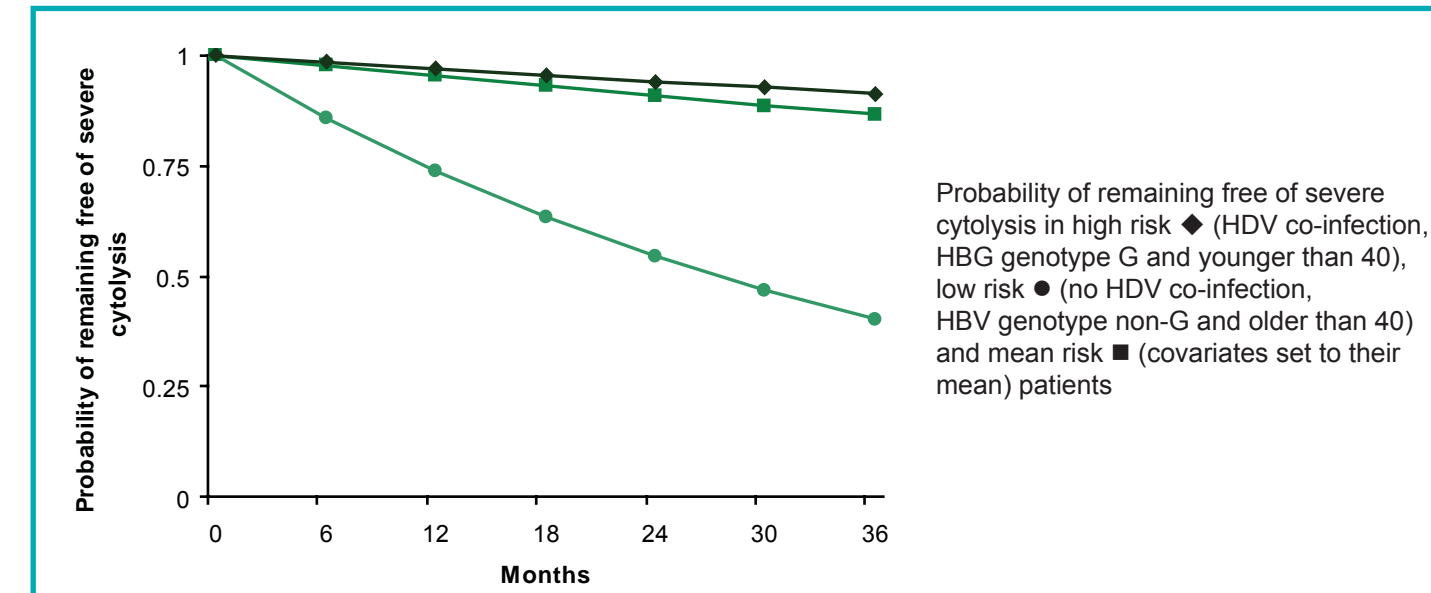
- Three covariates were identified as independent predictive factors for cytolysis stage evolution: HDV co-infection, age older than 40 years, and HBV genotype G

Table 2.

Factor	Transition (I \rightarrow II)			Transition (II \rightarrow I)		
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Concurrent chronic hepatitis D	8.01	2.17	29.62	3.19	0.96	10.56
Age > 40 years	0.27	0.11	0.70	0.23	0.08	0.67
HBV genotype G	4.34	1.50	12.57	1.40	0.48	4.06

- No significant association was found between any current or previous exposure to antiretroviral class and cytolysis stage evolution

Figure 2. Probability of Remaining Free of Severe Cytolysis



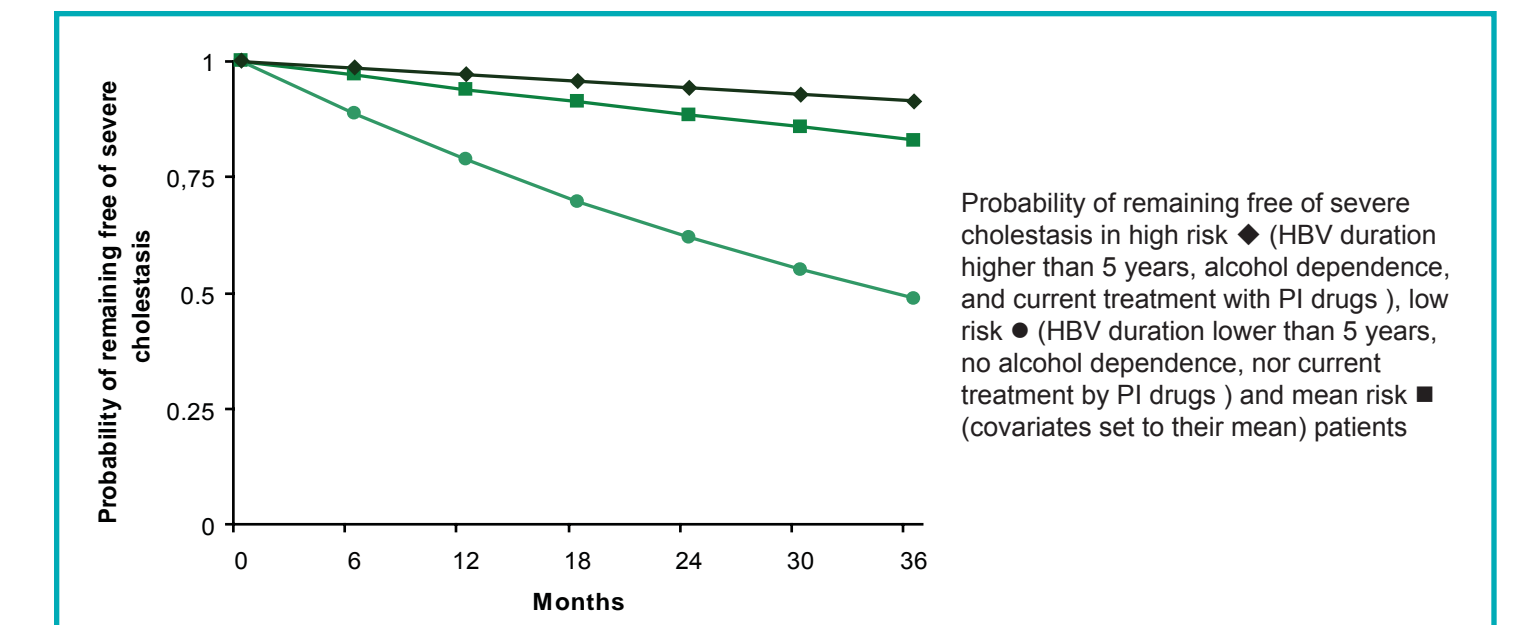
Risk Factors for Severe Cholestasis:

- Three covariates were retained as independent predictive factors for cholestasis stage evolution: an HBV infection duration > 5 years was significantly associated with an increase of progression towards severe cholestasis, whereas alcohol dependence was associated with a decrease of severe cholestasis resolution
- Current use of PI was also identified as independently linked with progression toward severe cholestasis. However, the low number of patients treated by certain PIs prevented us to carry out a specific Markov modeling approach for each drug within this class

Table 3.

Factor	Transition (I \rightarrow II)			Transition (II \rightarrow I)		
	Hazard ratio	95% CI		Hazard ratio	95% CI	
HBV duration > 5 years	3.47	1.63	7.41	1.88	0.88	4.01
Alcohol dependence	1.04	0.57	1.89	0.38	0.21	0.70
Current exposure to NRTI	0.51	0.23	1.11	1.27	0.66	2.44
Current exposure to NNRTI	1.65	0.94	2.91	0.86	0.50	1.46
Current exposure to PI	2.11	1.20	3.73	1.23	0.72	2.11

Figure 3. Probability of Remaining Free of Severe Cholestasis



Conclusions

- In the context of HIV-HBV co-infection:
 - Transient episodes of cytolysis or cholestasis were common
 - These episodes are mostly associated with virus- and patient-related factors
 - The role of protease inhibitors in cholestasis warrants further investigation
 - Chronic hepatitis B should not preclude the use of any class of antiretrovirals
- Patient- and virus-related parameters should be assessed before introducing antiretroviral therapy, and liver enzyme monitoring should be maintained throughout the treatment period

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