Clinical Presentation and Outcome of Hepatocellular Carcinoma in HIV Infected Patients

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Background

- HCC risk factors exposure higher in HIV+ than in general population
- Enhanced hepatocarcinogenesis in Tat transgenic mice (Vogel 91, Cavallini 93, Altavilla 01)
- SIR of HCC in HIV+: 11 (Serraino 00)
- 25% liver related mortality in HIV+ in France due to HCC
- More severe presentations of HCC in HIV+ in small case series (Soriano 01, Bruno 02)

Aims

- To identify clinical characteristics of HCC in HIV+ and to compare them with those observed in HIV- control groups

Methods 1

- **Design of the study :**
  - Retrospective observational case-control study
- **Recruitment of cases**
  - Questionnaire and CRF sent to all centers collaborating with Gruppo Italiano Cooperativo AIDS e Tumori (GICAT) and to 2 Spanish centers collaborating with a tumor registry in HIV → notification all observed cases of HCC

Methods 2

- **Case definition:**
  - Diagnosis of HCC according to EASL guidelines
  - Anti HIV reactivity confirmed by WB
  - Caucasian pts.
  - Retrospective data collection by standardized CRF
- **Comparison with:**
  - Data obtained "prospectively" with the same CRF from 384 patients with first diagnosis of HCC aged less than 76 residing in the province of Brescia and recruited prospectively from 1995 to 1998 in the two hospital of the town by the Brescia HCC study group.
  - Data obtained from 701 pts. included in the Cancer of the Liver Italian Project (CLIP) HCC registry

GICAT STUDY ON HCC IN HIV

Chronological and geographic distribution

Year	N of cases
1989:	1
1997:	2
1998:	2
1999:	2
2000:	6
2001:	18
1- 6 2002:	10
All:	41

Demographics

Variable	HIV+	HIV-	
N.	41	384 BHSG	701 CLIP
Gender: Male	40 (98%)°	315 (82%)	528 (75%)
Median Age years (IQR)	42 (40-46)*	65 (60-70)	64 (59-70)
HIV Risk factors:			
IDU	35	-	
Blood products	1	-	
Promiscuous Heter.	1	-	
Homosex.	3	-	
Unknown	1		

* P < 0.001 Kruskal Wallis test; ° p= < 0.05 Fisher exact test

Characteristics – HIV related

Variable	HIV+
Median time from first parenteral exposure (IQR) years	22 (18,5-25)
Previous diagnosis of AIDS n. (%)	9 (24%)
Median CD4 cells/mmc (IQR)	267 (180-341)
CD4 level: n (%) ≥500 200-500 < 200	 3 (7%) 22 (54%) 16 (39%)
Assuming HAART n. (%)	31 (77%)
HIVRNA cp/ml: ≥10.000 Detectable < 10.0000 Undetectable	 4 (10%) 18 (47%) 16 (42%)

Characteristics – Liver disease

Variable	HIV+	HIV-	
		BHSG	CLIP
Child class:		*	§
A n. (%)	11 (27%)	158 (41%)	306 (44%)
B n. (%)	16 (39%)	101 (26%)	299 (43%)
C n. (%)	12 (29%)	70 (18%)	97 (14%)
Not assessed	2 (5%)	55 (14%)	
HBsAg+ n (%)	12 (29%)	94 (24%)	148 (21%)
HCVAb+ n. (%)	36 (88%)§	156 (41%)§	532 (75%)*
Alcohol abuse: (>80 g/day for more than 5 yrs)	13 (32%)§	242 (63%)§	Not ass.
Etiology		*	
HBV	4 (10%)	42 (11%)	
HCV	22 (54%)	87 (23%)	
Alcohol abuse	1 (2%)	119 (31%)	
Mixed	14 (34%)	108 (28%)	

Characteristics - Tumour

Variable	HIV+	HIV-	
		BHSG	CLIP
AFP > 400 ng/dL (%)	14 (35%)	70 (20%)	200 (28%)
Morphology %: Multiple nodule or Infiltrating	26 (63%)	212 (45%) *	363 (52%)
Tumour diameter % (nodular type) < 2 cm 2-5 cm > 5 cm	 5 (25%) 10 (50%) 5 (25%)	 73 (22%) 181 (55%) 76 (23%)	
Pts. with Extra-hepatic extra-nodal metastasis at 1st diagn. n. %	6 (15%)	19 (5%)*	18 (2,6%)§
Portal vein invasion n. %	13 (32%)	81 (21%)	99 (15%)§

* $p < 0.05$; § $p < 0.01$ chi square test; or Fisher's exact test

Clinical feature associated with HIV infection in HCC: logistic regression models adjusted for age, gender and Child's class

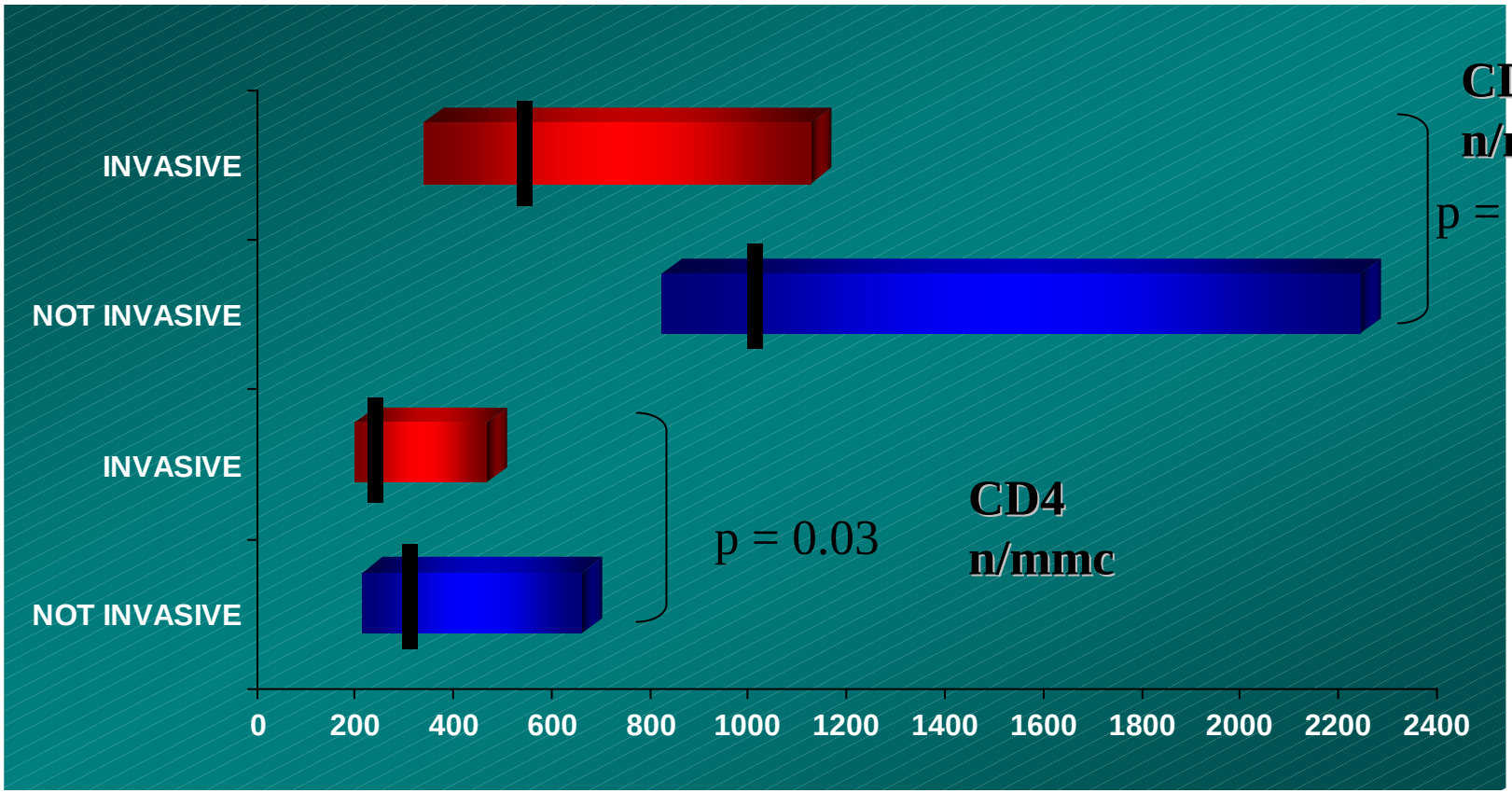
Feature	HIV+	HIV- Brescia HCC study group	Multivariate analysis OR (95%CI)
Number	41	384	
HCVAb+ n(%)	36 (88%)	156 (41%)	11,4 (2,1-62,1)
Infiltrating tumour and extranodal metastasis	22 (54%)	63 (16%)	11,8 (2,8-49)

Clinical feature associated with HIV infection in HCC:logistic regression models adjusted for age, gender and Child's class

Feature	HIV+	CLIP database	Multivariate analysis OR (95%CI)
Number	41	701	
HCVAb+ n (%)	36 (88%)	532 (75%)	9 (1,9-42,9)
Extrahepatic-extranodal metastasis	6 (15%)	18 (3%)	17,3 (3-99)

Median and IQR of CD4 and CD8 counts in HIV + with HCC stratified according to invasiveness

INVASIVE: Infiltrative with vascular invasion and/or extrahepatic extra-nodal metastasis



No difference: demographical, clinical, etiological characteristics

Screening for HCC in HIV+

- 22/41 cirrhosis Child A or B
- 8/22 included in screening program for HCC
- Larger Diameter > 5 cm:
  - **5/8 screened**
  - **6/14 unscreened**

Follow up

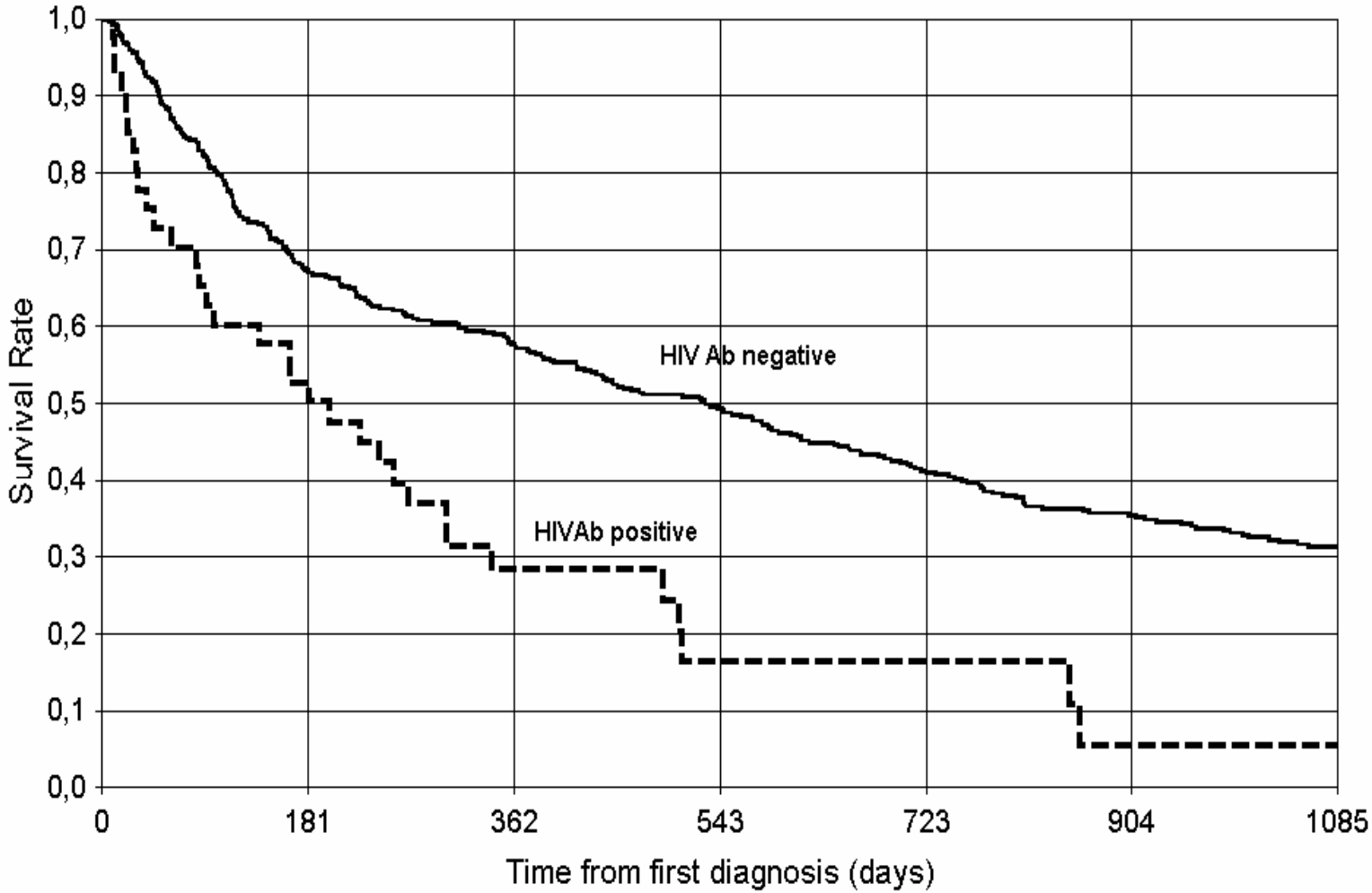
median duration 182 days; IQR 43-303; range 10-1431 days

Variable	HIV+	HIV-	
		BHSG	CLIP
Treatment§:			
Surgery (hepatic resection or OLT)	2 (5%)	54 (14%)	99 (17%)
Locoregional treatment	14 (35%)	180 (47%)	301 (43%)
Medical or no treatment	25 (60%)	150 (38%)*	301 (43%)*

* $p < 0.05$; § $p < 0.01$ chi square test; or Fisher's exact test

Locoregional treatment: PEI, TACE, RFA etc.

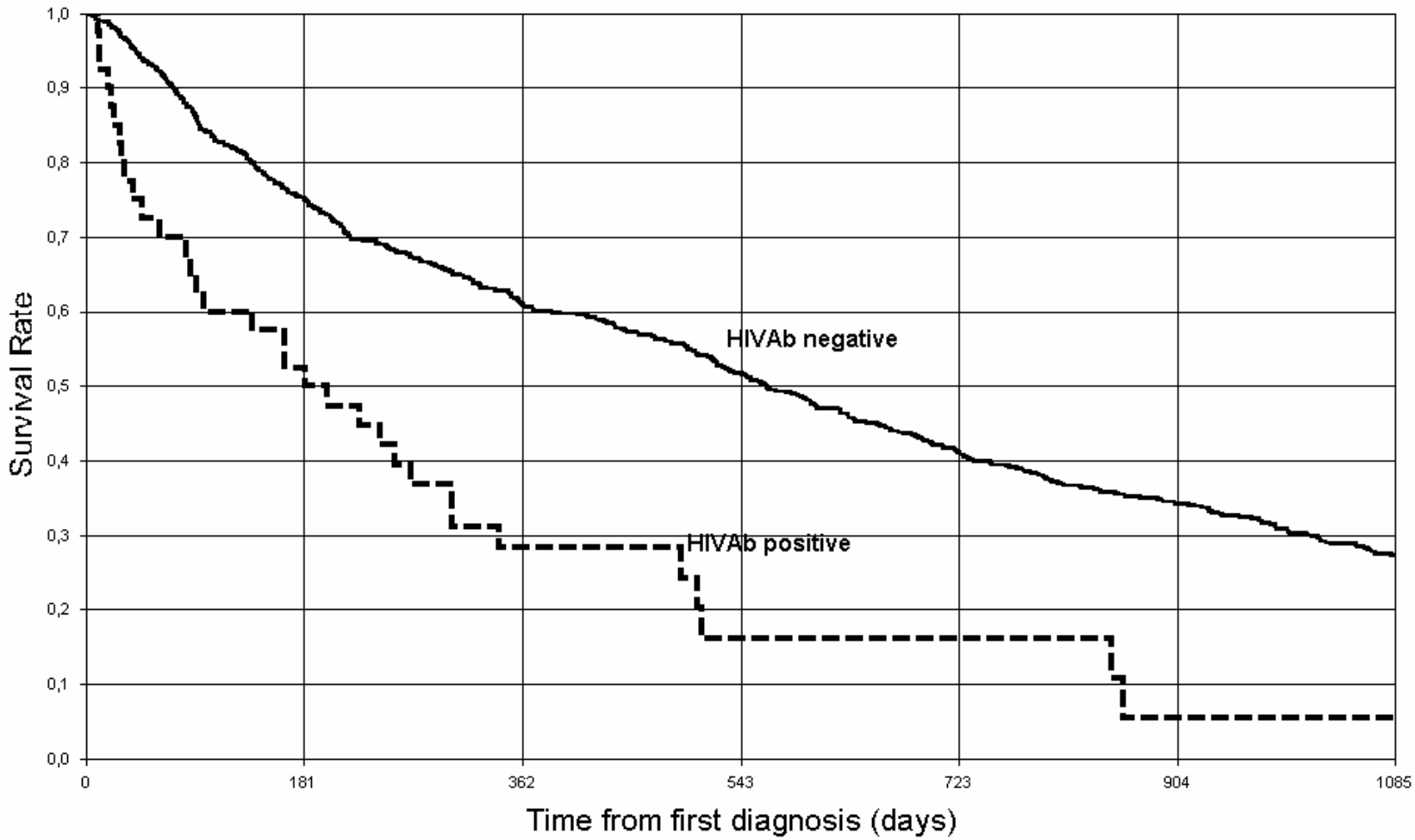
Comparison between Kaplan Meier survival curves of the 41 anti HIV positive patients with HCC from GICAT registry and the 384 anti HIV negative patients from Brescia HCC study group database.



Multivariate analysis of clinical, biochemical and pathologic variables significantly associated with survival of 425 patients with Hepatocellular carcinoma: 41 HIV infected patients from GICAT data base and 384 HIV uninfected patients from the Brescia HCC study group data base

Variables and categories	HR	95% CI	P value
Child B	1,68	1,25-2,26	<0.001
Child C	2,09	1,49-2,94	<0.001
Portal Vein invasion	1,43	1,01 - 2,04	0,05
diameter (cm) >5 cm	1,49	1,08-2,07	0,015
Serum AFP (ng/dL) ≥ 400	1,49	1,01-2,04	0,012
Treatment: None or medical treatment	3,27	1,37-4,51	<0,001
Anti HIV reactivity: Positive	1,63	1,10 - 2,40	0,015

Comparison between Kaplan Meier survival curves of the 41 anti HIV positive patients with HCC from GICAT registry and: the 701 anti HIV negative patients from CLIP database.

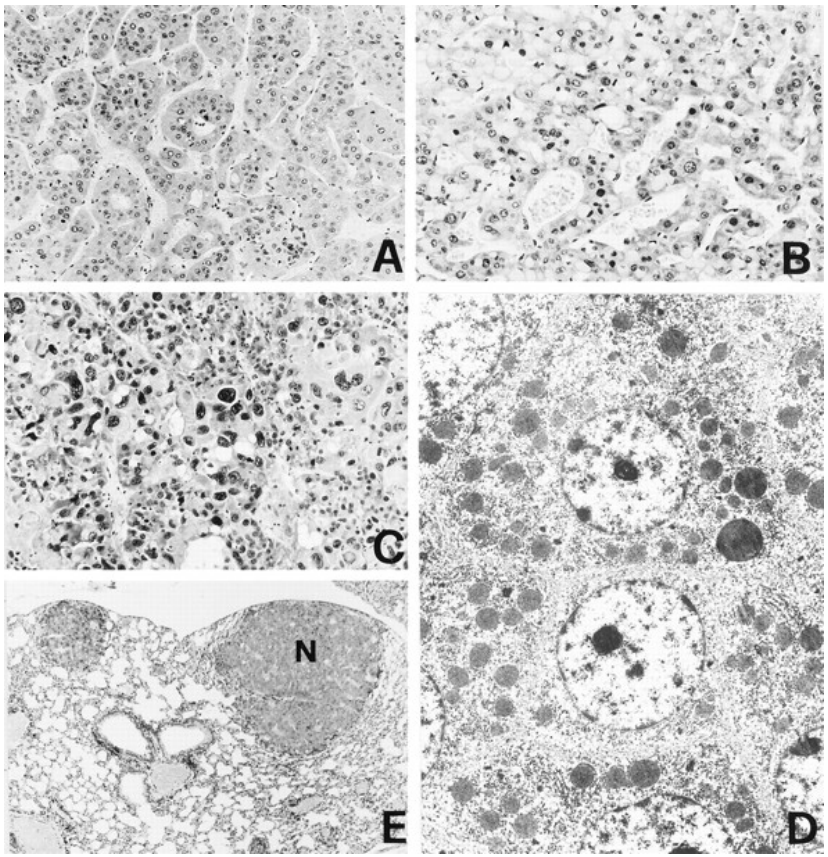


Multivariate analysis of clinical, biochemical and pathologic variables significantly associated with survival of 742 patients with Hepatocellular carcinoma: 41 HIV infected patients from GICAT data base and 701 HIV uninfected patients from the CLIP data base

Variables and categories	HR	95% CI	P value
Child B Child C	1,5 2,29	1,25-1,82 1,77-2,96	<0.001
Portal Vein invasion	1,32	1,04 – 1,69	0,024
diameter (cm) >5 cm	1,92	1,52-2,41	<0,001
Serum AFP (ng/dL) ≥ 400	1,42	1,17-1,73	<0,001
Treatment: None or medical treatment	2,12	1,74 - 2,59	<0,001
Anti HIV reactivity: Positive	1,63	1,02 - 2,61	0,045

Conclusions

- Most cases in pts. with controlled and stable HIV disease
  - HCC determinant of prognosis
- Young age and short “incubation period”
  - Hepatocarcinogenesis more rapid in HIV+? Increasing number of cases in the next years?
- HCV is the main risk factor
  - Treatment of HCV co-infection could prevent HCC and reduce the expected increase in HCC related mortality in HIV+
- More severe clinical presentation
- Lower chance for cure
- Lower susrvival
  - Need for prevention strategies and different screening strategies



We now report that transgenic mice carrying the HIV tat gene develop a high incidence of hepatocellular carcinoma after a long latency and that these changes in the liver are likely to be initiated by extrahepatic growth signals from the tat expressing cells in these mice. We predict that as acquired immunodeficiency syndrome patients begin to respond to therapy and show prolonged survival, such "secondary" malignancies induced by HIV will become increasingly prevalent.

Vogel et al Cancer Res 1991

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