Professor Norbert Bräu

James J Peters VA Medical Center, New York, USA

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Prof Norbert Bräu	None
Date	**November 2013**

British HIV Association – BASL – BVHG

6th Annual Conference for the Management of HIV / Hepatitis Co-infection

Hepatocellular Carcinoma in HIV-infected Patients

Wednesday, 13 November 2013

Norbert Bräu, MD, MBA

Professor of Medicine,
Icahn School of Medicine at Mount Sinai, New York NY

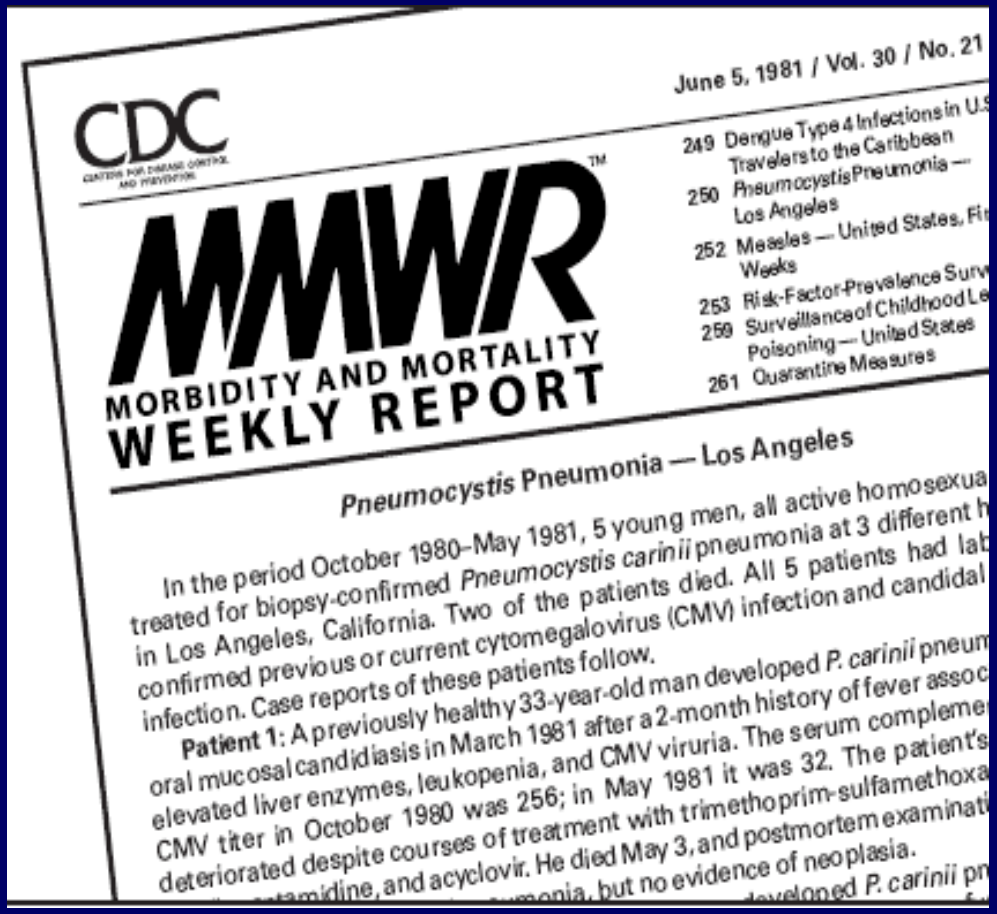
Director, Viral Hepatitis Program
JJ Peters VA Medical Center, Bronx NY

JJ Peters VA Medical Center

Mount Sinai School of Medicine

32 ½ years ago …

5 June 1981



CDC

June 5, 1981 / Vol. 30 / No. 21

MMWR™

MORBIDITY AND MORTALITY
WEEKLY REPORT

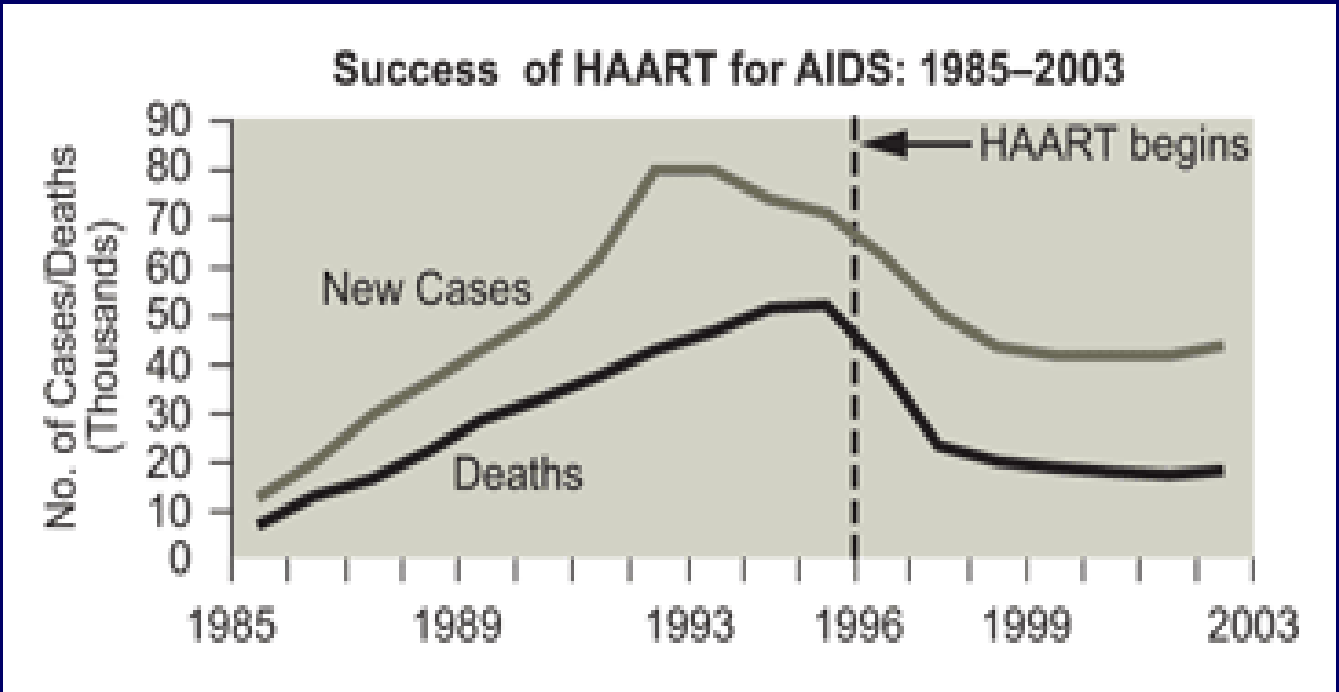
Pneumocystis Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active homosexual, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole, pentamidine, and acyclovir. He died May 3, and postmortem examination revealed pneumonia, but no evidence of neoplasia.

developed *P. carinii* pn

Effect of HAART on Survival



Rising rate of liver-related deaths and of HCC

France: Mortalité 2000 & 2005

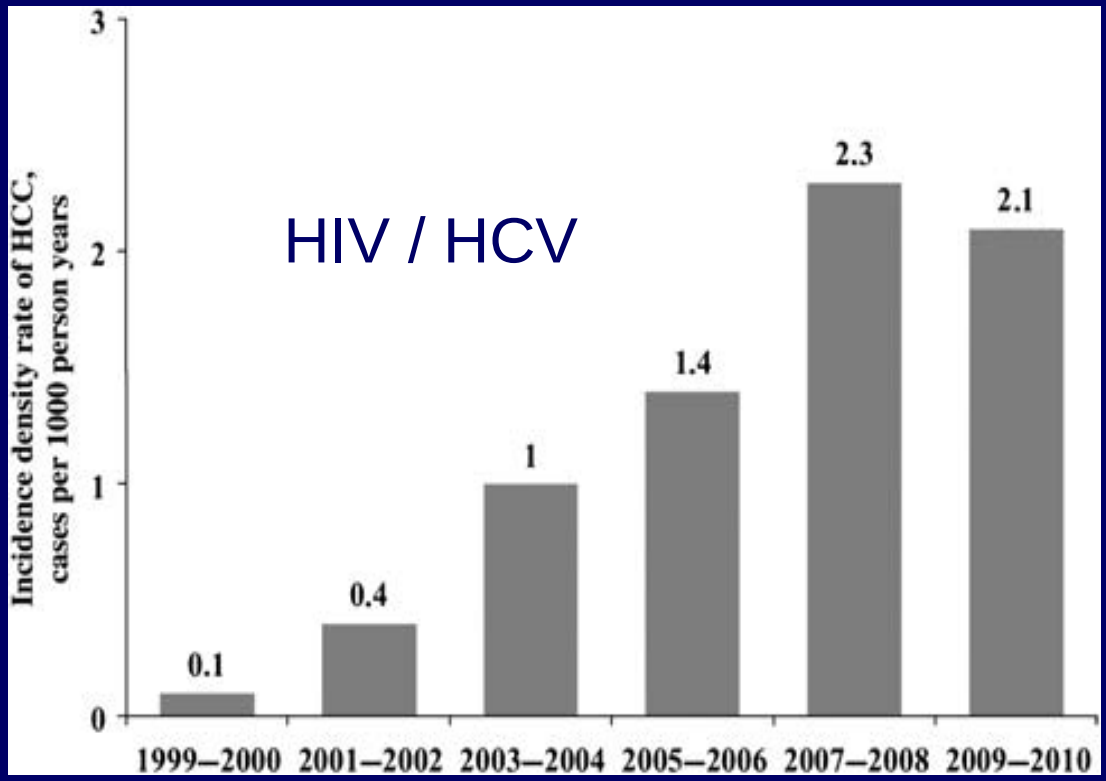
	2000	2005	
N HIV+ patients	~64,000	78,000	
Deaths	964 (1.5%)	1,042 (1.3%)	
Liver deaths:	13.4%	15.4%	
→ HCC deaths:	15%	25%	p=0.03

Salmon-Ceron D, J Hepatol, April 2009

HCC in HIV – Rising Incidence

Andalucia (Spain) 1999 – 2010

n = 14,300 (2010)



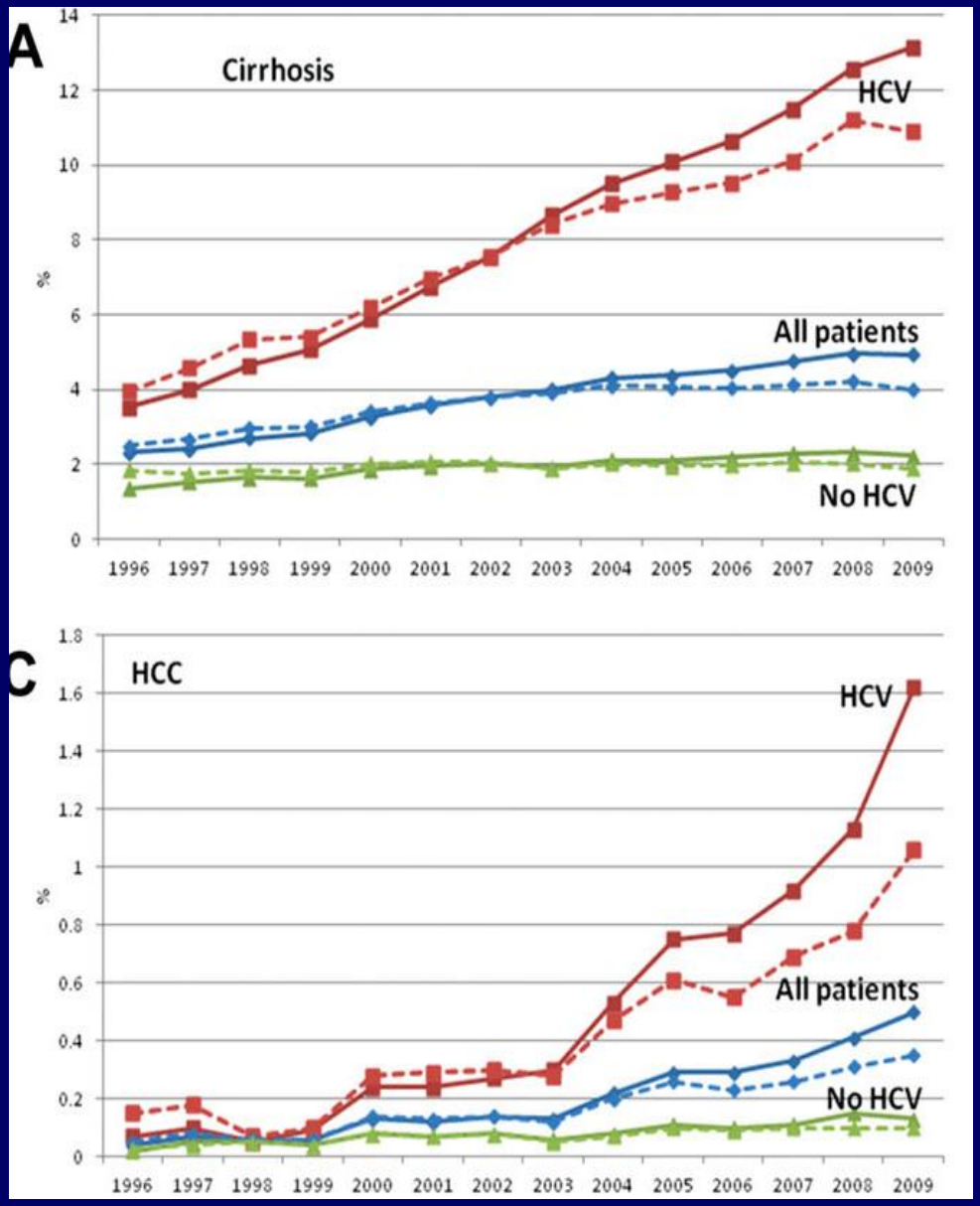
All HIV patients	0.1	0.2	0.5	0.7	1.0	0.9

Merchante N. et al., Clin Infect Dis, Jan 2013

HCC in HIV – Rising Prevalence

VA System (USA)
1996 – 2009

n = 24,000 (2009)



Ioannou GN. et al., Hepatology, Jan 2013

HIV and HCV or HBV coinfection
Epidemiology

HCV or HBV within HIV+ pts:

HCV strongly depends on mode of transmission of HIV itself:

Anti-HCV[+], total	42.5%
IDU	91 %
blood transfusion	71 %
sexual transmission	7.1 %

HBV less pronounced

HBsAg[+], total	6.9%
MSM 11.0%; IDU 6.4%; blood Tx 2.5%	

N=1,935

Saillour F et al., Brit Med J, 1996

HCC Incidence in HIV / HCV vs. HCV

VA System (USA) 1991 – 2000

	HIV/HCV n = 4,760	**HCV** n = 26,600	IRR	adj. HR*
Incid. /1000 PY	**1.3**	**2.0**	**0.67**	**1.04**
		p	0.046	0.87

* Adjusted for age, race, sex, HBV, DM, alcohol, drug use

Kramer JR et al., Am J Gastroenterol, 2005

HCC Incidence in HIV - HCV – alcohol

VA System (USA) 1997 – 2004

	HIV(+)	**HIV(-)**
matched 1:2	n = 14,018	n = 28,036

	Model 1		Model 2	
	IRR	95% CI	IRR	95% CI
HIV	**1.68**	1.02 - 2.77	0.96	0.56 - 1.63
HCV	—	—	**12.54**	6.46 - 24.35
Alcohol ab.	—	—	**1.85**	1.03 - 3.35
Age	**1.05**	1.03 - 1.06	**1.08**	1.05 - 1.10

McGinnis KA et al., J Clin Oncol, 2006

HCC in HIV - Outcome

Case Series

2001 n= 7 García-Samaniego J et al. (Madrid), *Am J Gastro*

HCC in HIV - Outcome

Case Series

2001	n= 7	García-Samaniego J et al. (Madrid), *Am J Gastro*
2004	n=41	Puoti M et al. (Italy), *AIDS*
2007	n=63	North American Liver Cancer in HIV Study Group
		Bräu N et al., *J Hepatol*
2011	n=102	Berretta M et al. (Italy), *Oncologist*

HCC in HIV - Outcome

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		Bräu N et al., *J Hepatol*
2011	n=102	Berretta M et al. (Italy), *Oncologist*
2012	n=26	Yopp AC et al. (Dallas), *Clin Gastroent Hepatol*
2012	n=23	Lim C at al. (Paris), *JAIDS*
2013	n=48	Pavoni M et al. (Bologna, Italy), *Dig Liver Dis*

HCC in HIV - Outcome

1st Italian HCC in HIV study (2004)

Median survival:

HIV-pos. (**n=41**) **5.9 mo**

HIV-neg. (n=701) **18.0 mo**

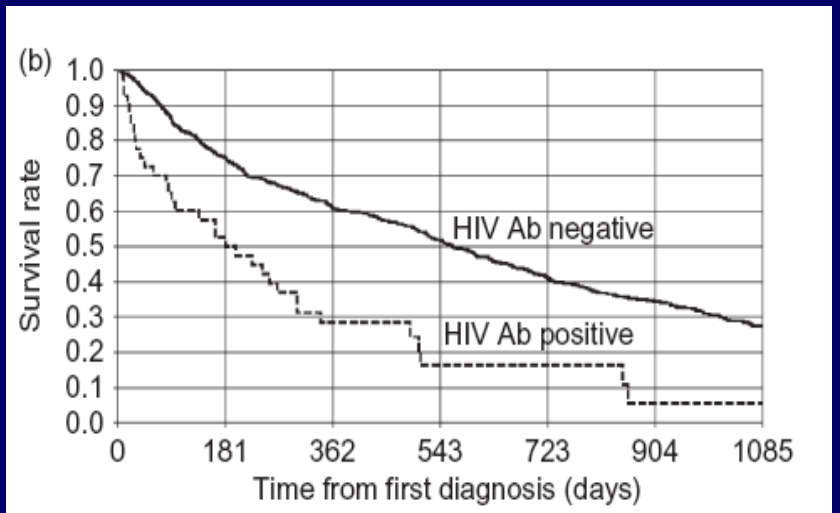


Fig. 1. Comparison between Kaplan–Meier survival curves in 41 HIV-positive patients with HCC and (a) 385 HIV-negative patients from the Brescia HCC Study Group database, and (b) 701 HIV-negative patients from the CLIP database. Ab, Antibody.

Puoti M et al., AIDS, Nov-2004

1st Italian HCC in HIV study (2004)

Table 4. Multivariate analysis of clinical, biochemical and pathologic variables significantly associated with survival in 742 patients with hepatocellular carcinoma (41 HIV-infected patients and 701 HIV-uninfected patients from the CLIP database).

Variables and categories	Hazard ratio	95% confidence interval	*P*
Liver function status			
Child–Pugh class A	1.0		
Child–Pugh class B	1.5	1.25–1.82	
Child–Pugh class C	2.29	1.77–2.96	< 0.0001
Portal Vein invasion			
No	1.0		0.024
Yes	1.32	1.04–1.69	
Lesion morphology [diameter (cm)]			
< 5 cm	1.0		< 0.0001
> 5 cm	1.92	1.52–2.41	
Serum alfafetoprotein (ng/dL)			
< 400	1.0		< 0.0001
≥ 400	1.42	1.17–1.73	
Treatment:			
Any type	1.0		< 0.0001
None or medical treatment	2.12	1.74–2.59	
Anti HIV reactivity			
Negative	1.0		0.045
Positive	1.63	1.02–2.61	

Puoti M et al., AIDS, Nov-2004

North American Liver Cancer in HIV Study Group

* 12 sites (US, Canada) HIV-pos. HCC (n=63)
* 4 sites HIV-pos. + HIV–neg. HCC (n=226)

Bräu N et al., J Hepatol, Oct 2007

N American HCC in HIV Study: Patient Characteristics

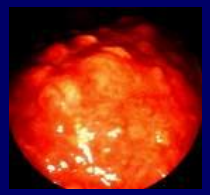
	HIV-positive n=63	HIV-negative n=226	P
Age, mean (years)	**52**	**64**	**<0.001**
Etiology of HCC (%)			**<0.001**
Viral Hepatitis	**97%**	**71%**	
HCV	**72%**	**67%**	
HBV	25%	4%	
Non-viral	**3%**	**29%**	
Alcohol	**2%**	**17%**	
Iron Overload	0%	2%	
Unknown	2%	10%	

Bräu N et al., J Hepatol, Oct 2007

N American HCC in HIV Study: Patient Characteristics

	HIV-positive n=63	HIV-negative n=226	P
Initial Presentation			
Liver Mass on Imaging (Screening)	32%	51%	
Elevated AFP (Screening)	18%	11%	**0.048**
Symptoms	**51%**	**38%**	
Abdominal Pain, Weight Loss, Abdominal Distension			
Extrahepatic Metastases	13%	8%	0.25
Skeletal, Lungs, Inferior Vena Cava, Heart, Adrenal, Gall Bladder, Lymph Nodes, Multiple Sites			

Bräu N et al., J Hepatol, Oct 2007

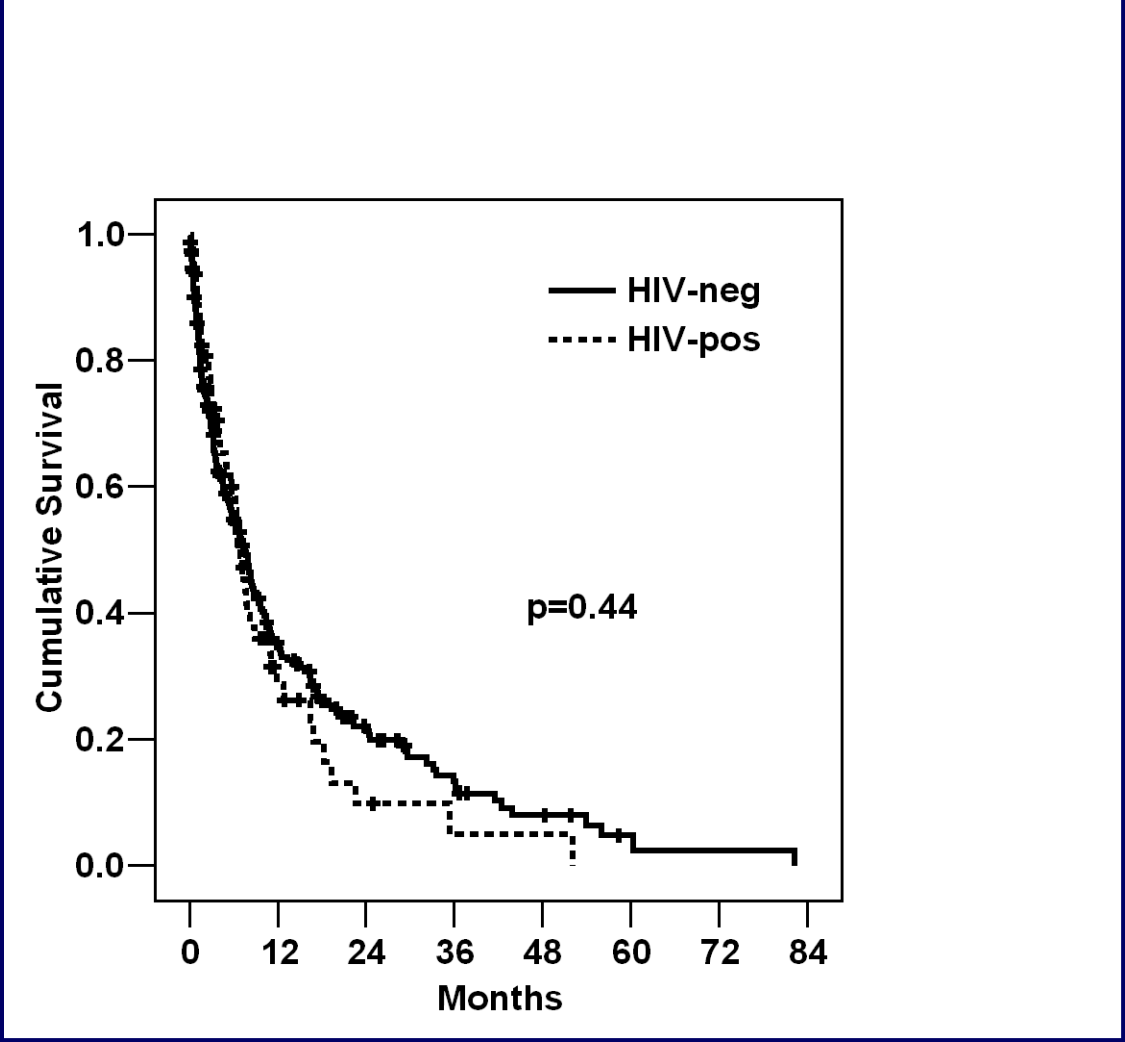


N American HCC in HIV Study: Tumor Staging

	HIV-positive n=63	HIV-negative n=226	P
Barcelona Clinic Liver Cancer (BCLC) Stage, %	n=62	n=214	
A	26%	21%	
B	24%	21%	0.47
C	**39%**	**40%**	
D	**11%**	**18%**	
Advanced BCLC Stage (C+D)	***50%***	***58%***	

Bräu N et al., J Hepatol, Oct 2007

N American HCC in HIV Study: Survival All Patients



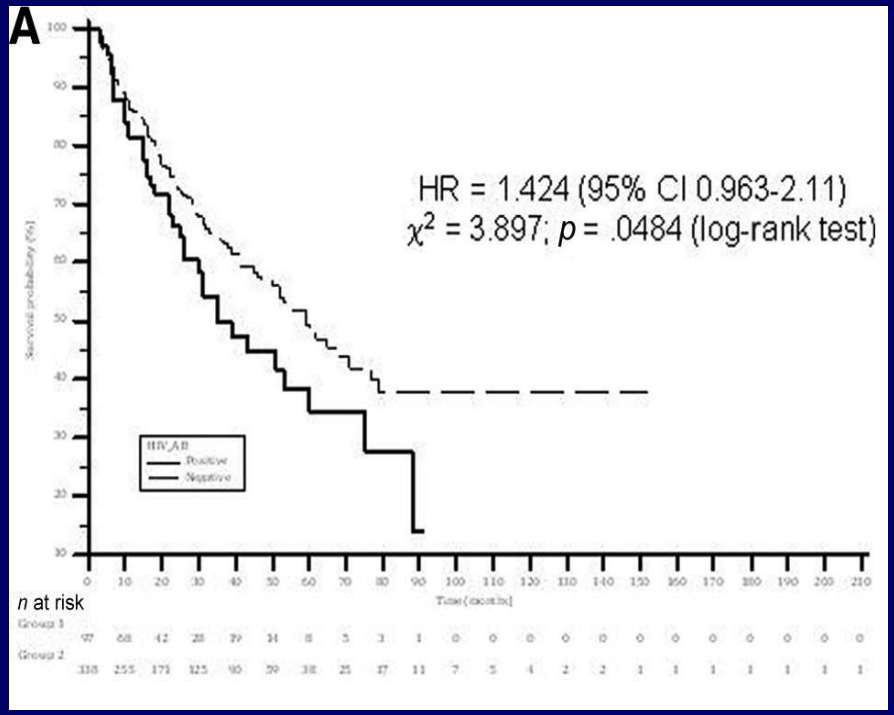
At risk HIV[-]	226	64	29	14	7	2	1	**median survival: 7.5 mo**
At risk HIV[+]	63	11	3	1	1	0	0	**median survival: 6.9 mo**

2nd Italian HCC in HIV study (2011)

Median survival:

HIV-pos. **35 mo**

HIV-neg. **59 mo**



Berretta M et al., Oncologist, 2011

Comparison Survival HIV(+) vs. HIV(-)

	N		Median survival (mo)		
Study	**HIV(+)**	**HIV(-)**	**HIV(+)**	**HIV(-)**	**p**
Italy (2004)	41	701	5.9	18.0	**0.045**
North America (2007)	63	226	6.9	7.5	0.44
Italy (2011)	104	484	35	59	**0.048**
Dallas (2012)	26	164	9.6	5.2	0.85
Paris (2012)	23	46	18	26	0.2
Bologna (2013)	48	234	16	30	**0.035**

HCC in HIV - Therapy

Sorafenib

Italian cohort (2007 – 2010)	**HIV(+) N=27**	HIV(-) in SHARP trial N=299 *Llovet JM, NEJM, 2007*
Overall Survival (median)	**12.8 mo**	10.7 mo
Time to Progression	**5.1 mo**	5.5 mo
Grade 3-4 toxicity		
Diarrhea	4 (15%)	8%
Hand & Foot Skin Reaction	4 (15%)	8%
Hypertension	3 (11%)	2%

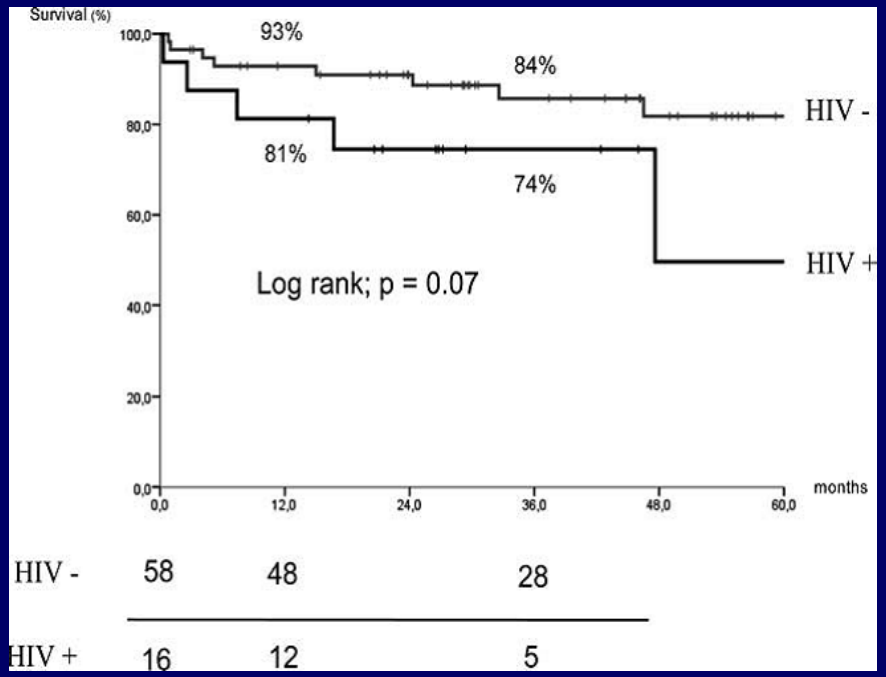
Berretta M et al., Anticancer Drugs, Feb-2013

HCC in HIV - Therapy

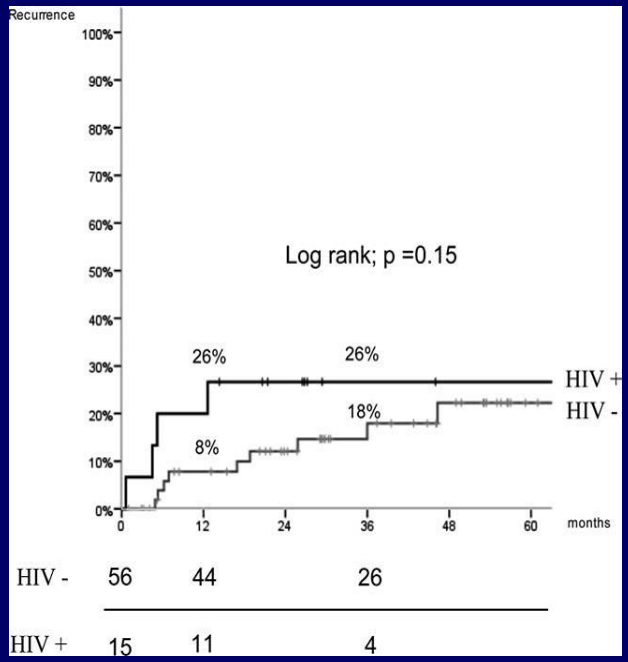
Transplantation

Single center, Paris **HIV(+) 21 → 16 OLT** HIV(-) 65 → 58 OLT

Survival



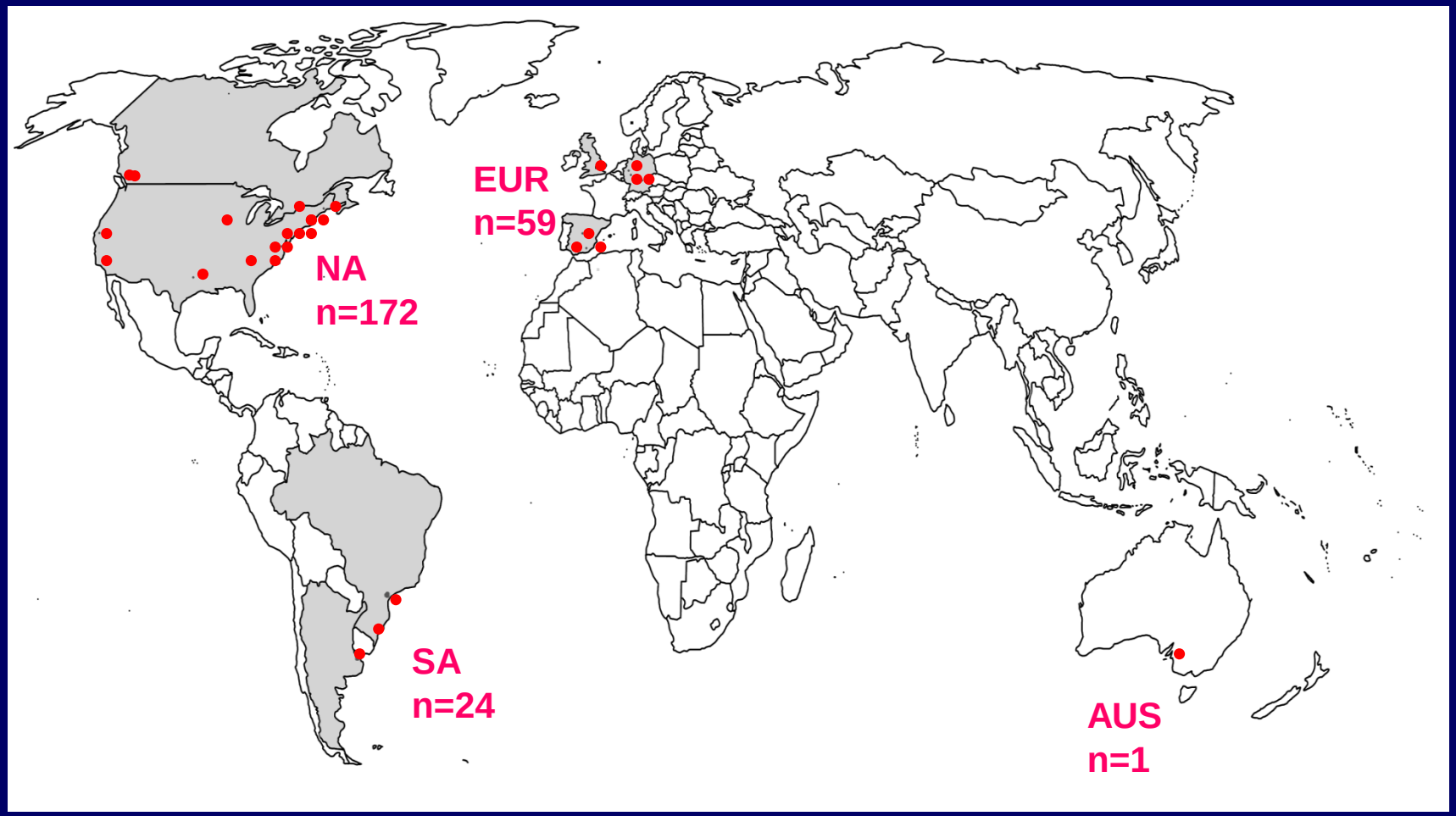
HCC Recurrence



Vibert E et al., Hepatology, Feb 2011

Liver Cancer in HIV Study Group

N=256 as of 15-Sep-2013



Does Screening for HCC in HIV/HCV Patients Improve Survival ?

Method:

N=167 HIV/HCV patients with HCC

Diagnosis of HCC via Screening vs. Symptoms

Compare:

- *** Staging**
- *** Therapy**
- *** Survival** **(adjust for lead-time bias)**

Screening for HCC in HIV/HCV Patients

Patient Characteristics

	Screened n=117 (59%)	Not Screened n=81 (41%)	P
Age (yrs), Mean	**52**	**54**	**0.082**
Female Sex	4%	10%	0.162
Alcohol abuse	**30%**	**50%**	**0.003**
CTP Score:	**6.6**	**7.7**	**<0.001**
HIV parameters			
Median CD4+ cells (per mm3)	**344**	**274**	**0.027**
HIV RNA <400 copies/mL	**79%**	**54%**	**<0.001**

Fox RK, AASLD, Washington DC, Nov 2013

Screening for HCC in HIV/HCV Patients

Tumor Characteristics

	Screened n=117	Not Screened n=81	P
Hepatic Lesions			
Single Tumor	55%	40%	0.035
Multiple Tumors	42%	58%	
Median Size Largest Tumor (cm)	3.0	5.2	<0.001
Portal Vein Thrombosis	12%	31%	0.001
Extrahepatic Metastases	9%	28%	<0.001
Meets Milan criteria for OLT	64%	29%	<0.001

HCC Tumor Staging

	Screened n=117	Not Screened n=81	P
BCLC Stage, n (%)			
A	44%	7%	
B	17%	20%	<0.001
C } Advanced,	27%	43%	
D } Incurable	11%	30%	
BCLC Stages C and D	39%	73%	<0.001

Fox RK, AASLD, Washington DC, Nov 2013

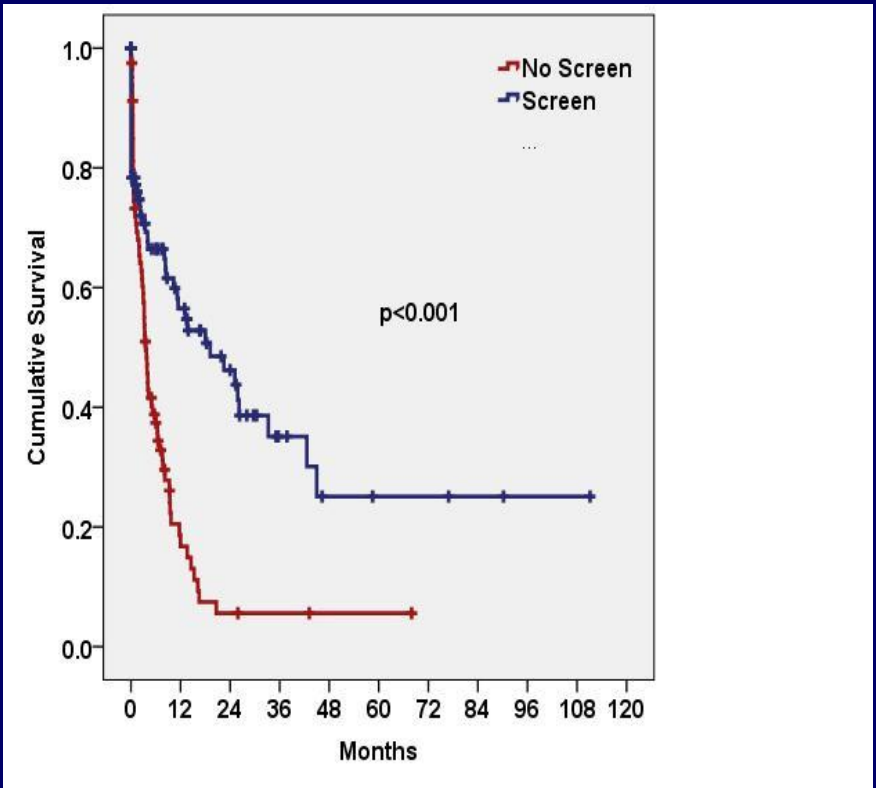
Screening for HCC in HIV/HCV Patients

HCC Therapy

	Screened n=117	Unscreened n=81	P
Potentially Curative, n (%)	**53 (46%)**	**10 (12%)**	**<0.001**
Radiofrequency Ablation	19	5	
Percutaneous Ethanol Injection	8	2	
Surgical Resection	17	2	
Liver Transplantation	9	1	
Effective, Non-Curative, n (%)	**35 (30%)**	**17 (21%)**	
Chemoembolization	28	14	
Sorafenib	4	3	
Sorafenib & Chemoembolization	3	0	
No Therapy, n (%)	**28 (24%)**	**54 (67%)**	
Any HCC Therapy	**88 (76%)**	**27 (33%)**	

Fox RK, AASLD, Washington DC, Nov 2013

Screening for HCC in HIV/HCV Patients
Survival – adjusted for lead-time bias (8.6 mo)



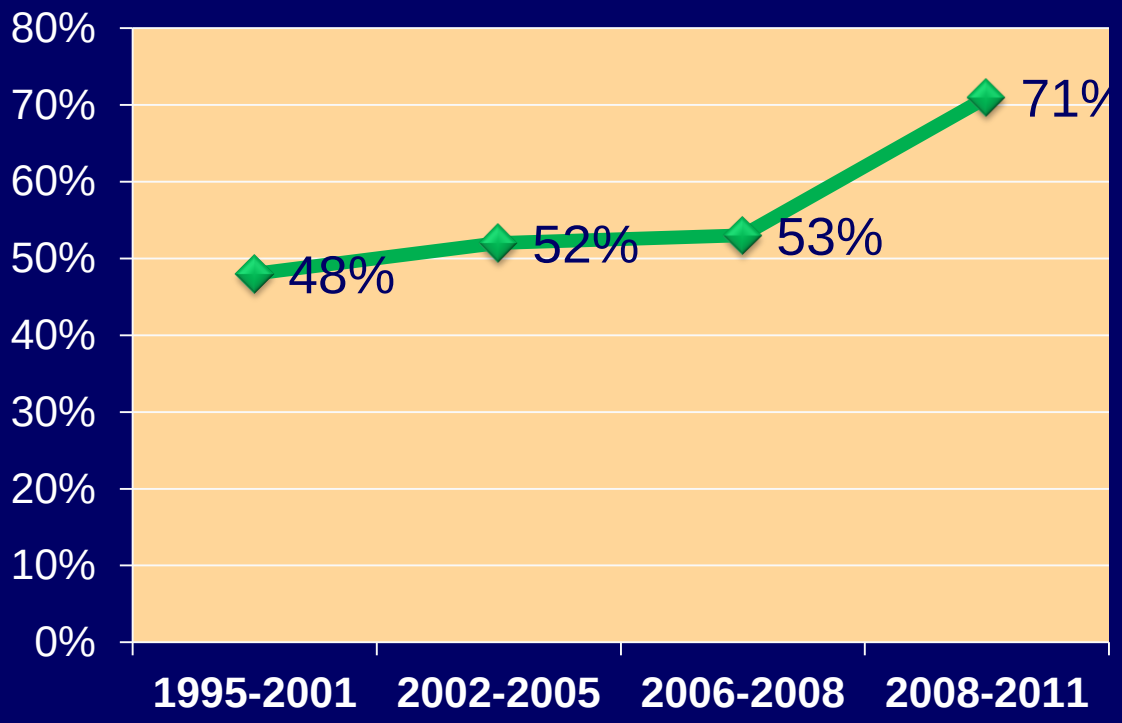
Median survival

Screened **19.2 mo**

Unscreened **3.5 mo**

Fox RK, AASLD, Washington DC, Nov 2013

Screening for HCC in HIV/HCV Patients
Screening over Time



Fox RK, AASLD, Washington DC, Nov 2013

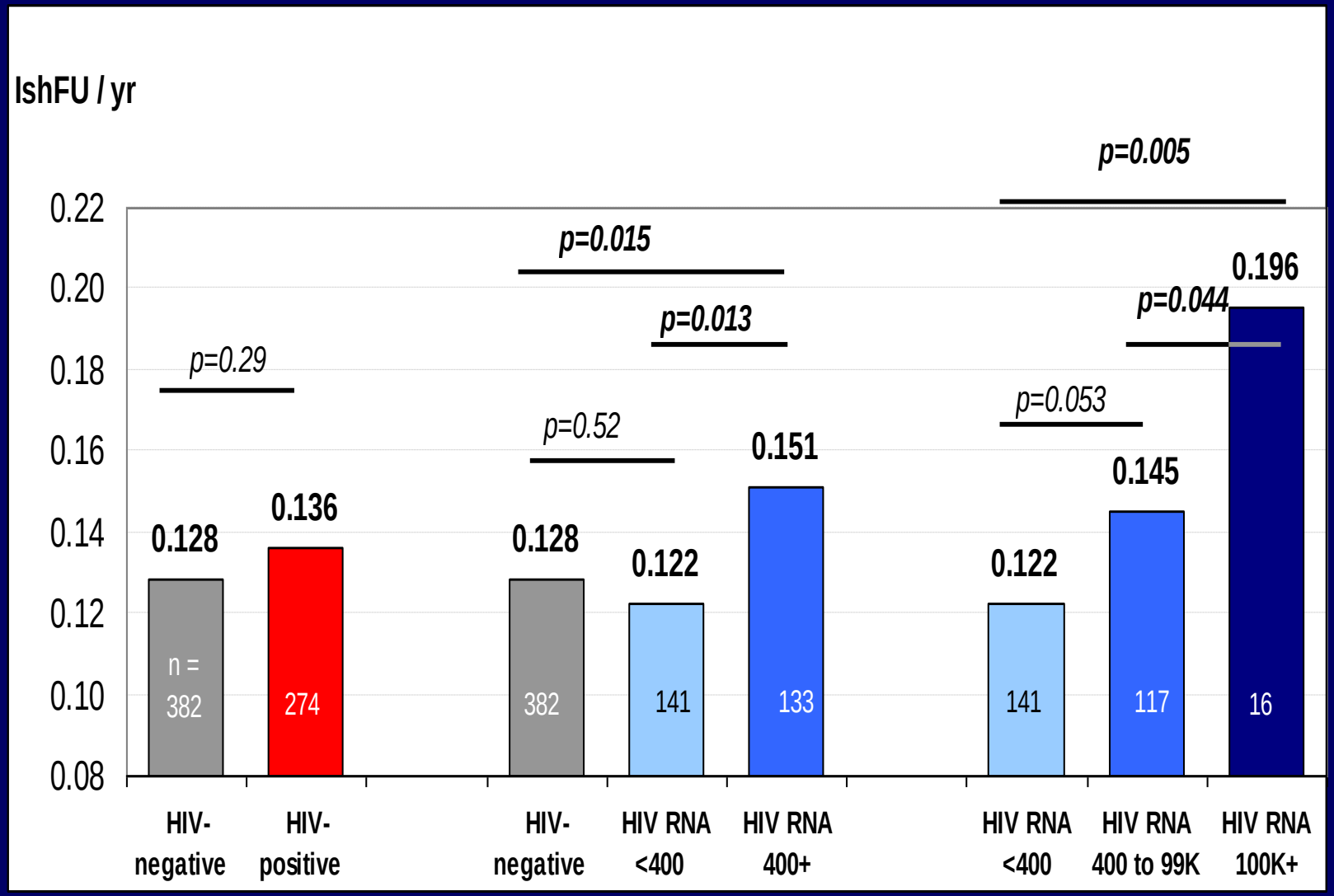
HIV Viral Load & Natural History of HCC

Hypothesis:

HIV viremia negatively influences course of HCC

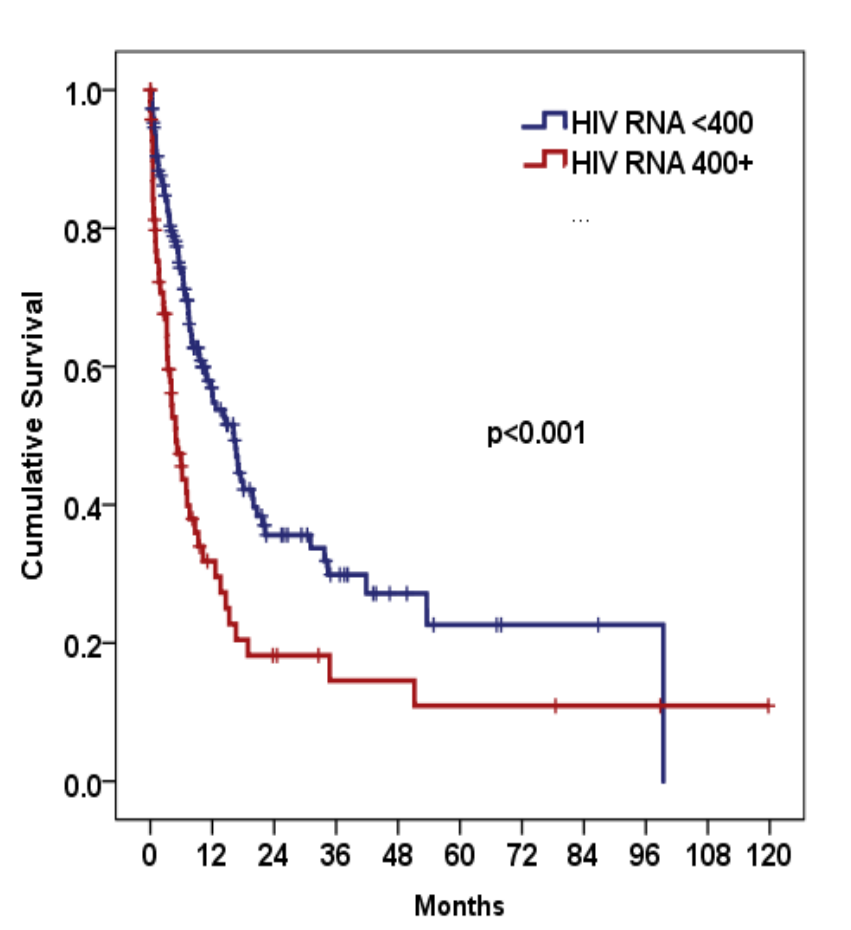
In HIV/HCV: More rapid progression of hepatic fibrosis with HIV RNA 400+ Copies/ml

Fibrosis Progression Rate by HIV Viral Load in chronic hepatitis C



Bräu N, J Hepatol, Jan 2006

HIV Viremia: Influence on HCC Survival



Median survival

HIV RNA <400 c/ml 16.2 months
HIV RNA 400+ c/ml 5.0 months

Chen TY, EASL 2013, Amsterdam, NL

HIV Viremia: Influence on HCC Survival

Multi-Variable Cox Regression Analysis

Factor	Hazard Ratio	Univariate P	Multi-variable Hazard Ratio	95% Conf. Interval	Multi-var. P
Initial Presentation through Screening	4.90	<0.01	2.56	1.64-4.00	<0.01
Effective HCC Therapy	6.80	<0.01	2.86	1.82-4.55	<0.01
BCLC stages C&D vs. A&B	0.37	<0.01	0.55	0.35-0.86	0.01
HIV RNA Level (per log10 copies/ml)	0.74	<0.01	0.85	0.72-0.99	0.03
ALT/AST ≥ 1.5	0.42	<0.01	0.53	0.35-0.80	<0.01
AFP ≥ 200	0.26	<0.01	0.33	0.22-0.50	<0.01
Age (per year)	0.97	0.01	0.97	0.94-0.99	<0.01
CD4+ Cells (per 100/mm3)	1.12	0.01			

Chen TY, EASL 2013, Amsterdam, NL

HCC in HIV – Future Investigations

- Comparison of BCLC staging and MESIAH score as predictors of survival
- Continental differences
- Trends of HCC in HIV over time (1992 – 2013)

- Does HIV increase incidence of HCC in cirrhosis? (VACS cohort)

Summary: HCC in HIV

- HIV-positive patients: liver disease & HCC increasing as cause of death
- Rise in prevalence and incidence of HCC
  - driven by HCV coinfection

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  - smaller tumors, earlier BCLC stages, more frequent HCC therapy,
  - better survival (14 vs. 4 mo)

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- Please send us your cases of HCC in HIV patients: www.HCCinHIV.org
  norbert.brau@va.gov

Thank you for your kind attention