

Impact of HIV on HBV

Does it make a difference?



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Impact of HIV on viral hepatitis

Topics

- Epidemiology
- Progression of hepatitis-related liver disease
- Co-morbidities
- Treatment

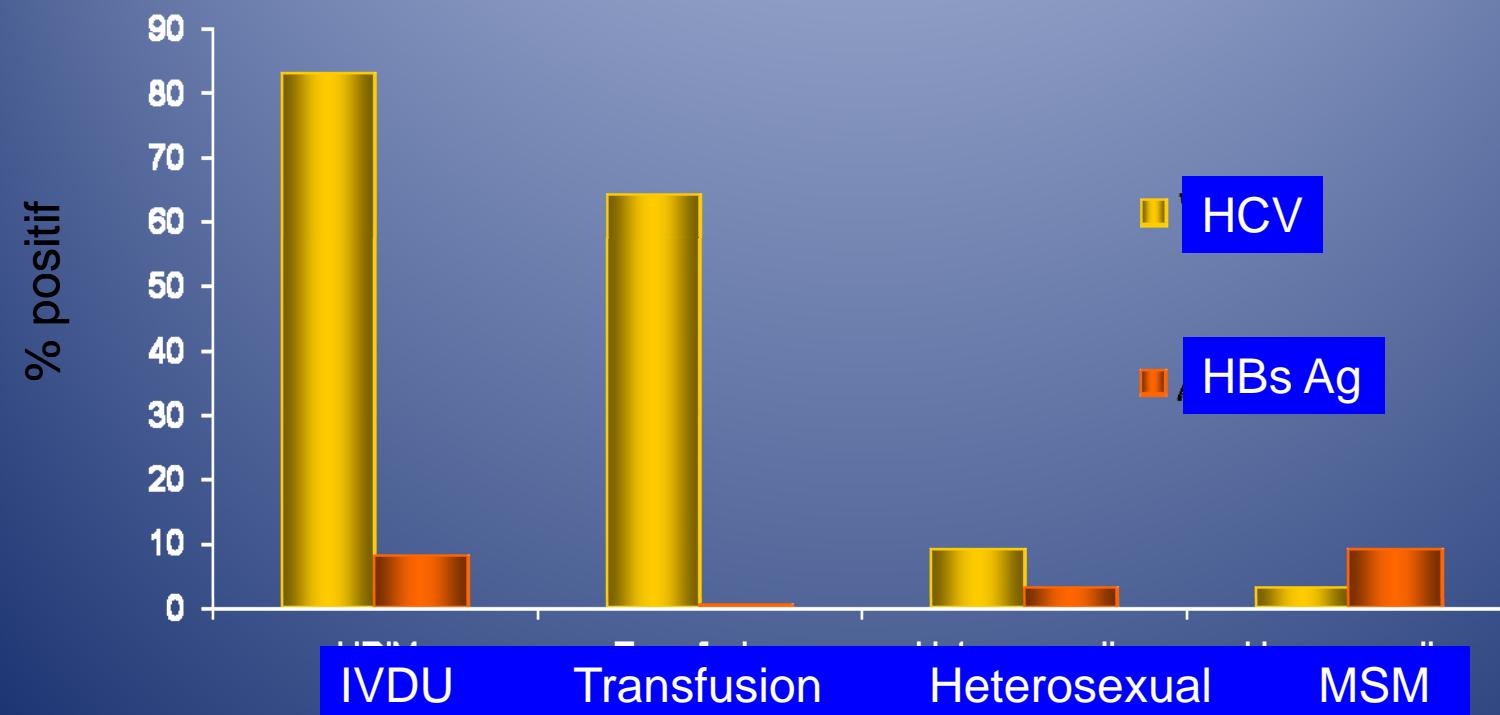
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Prevalence of HBs Ag (and HCV) in HIV infection according to the risk factor

HBs Ag: 7% in HIV+ vs. 0.7% in the general population



Salmon-Céron D et al, Med Mal Infect 2003 ; Denis F et al, PatholBiol 1997 ;
Sherman et al, CID 2002 ; Kellerman JID 2003

Impact of HIV on viral hepatitis

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- Epidemiology: viral hepatitis are 4- to 10-fold more frequent in HIV-infected patients
- Progression of hepatitis-related liver disease
- Co-morbidities
- Treatment

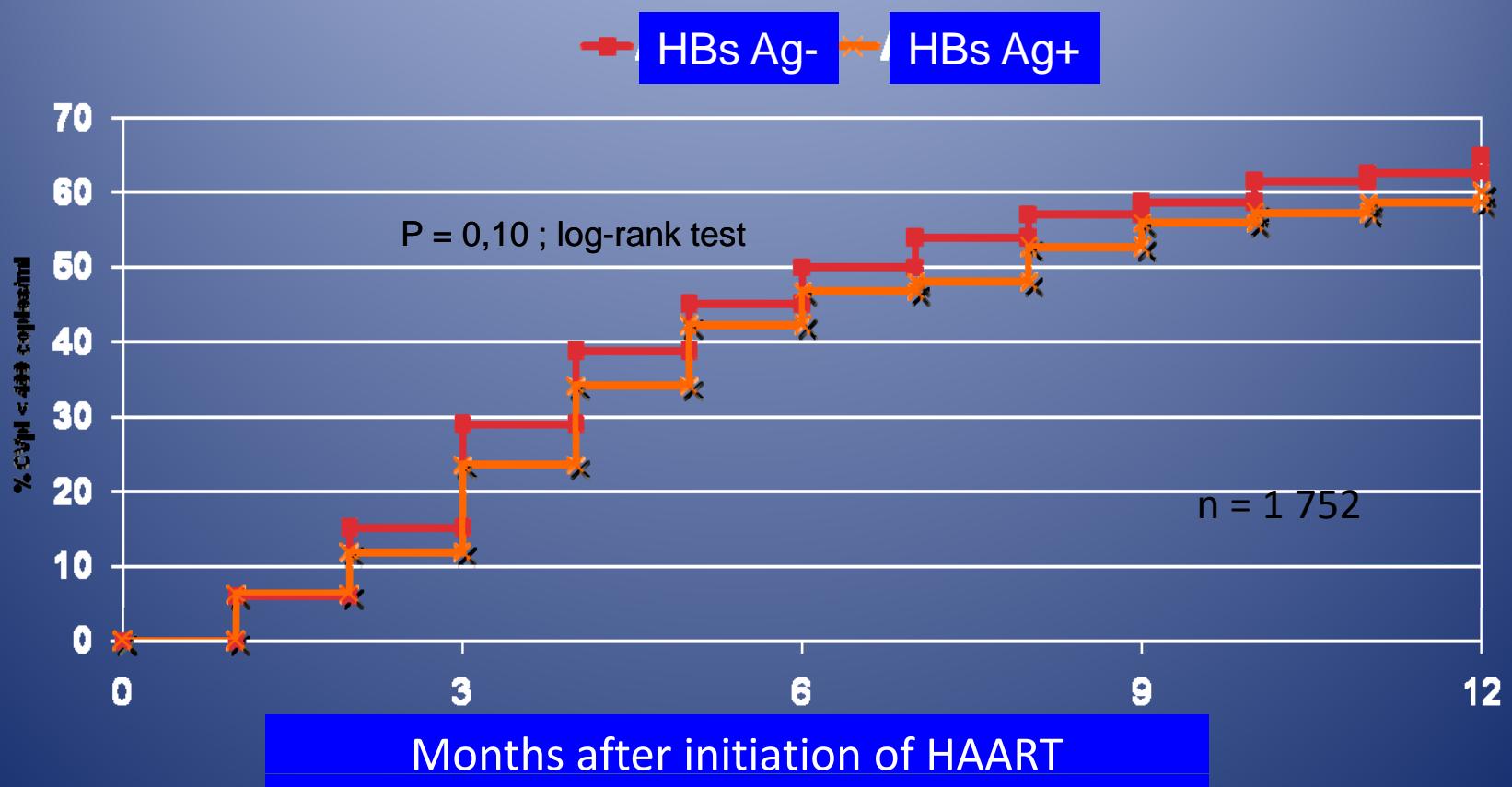
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No impact of HBV on HIV

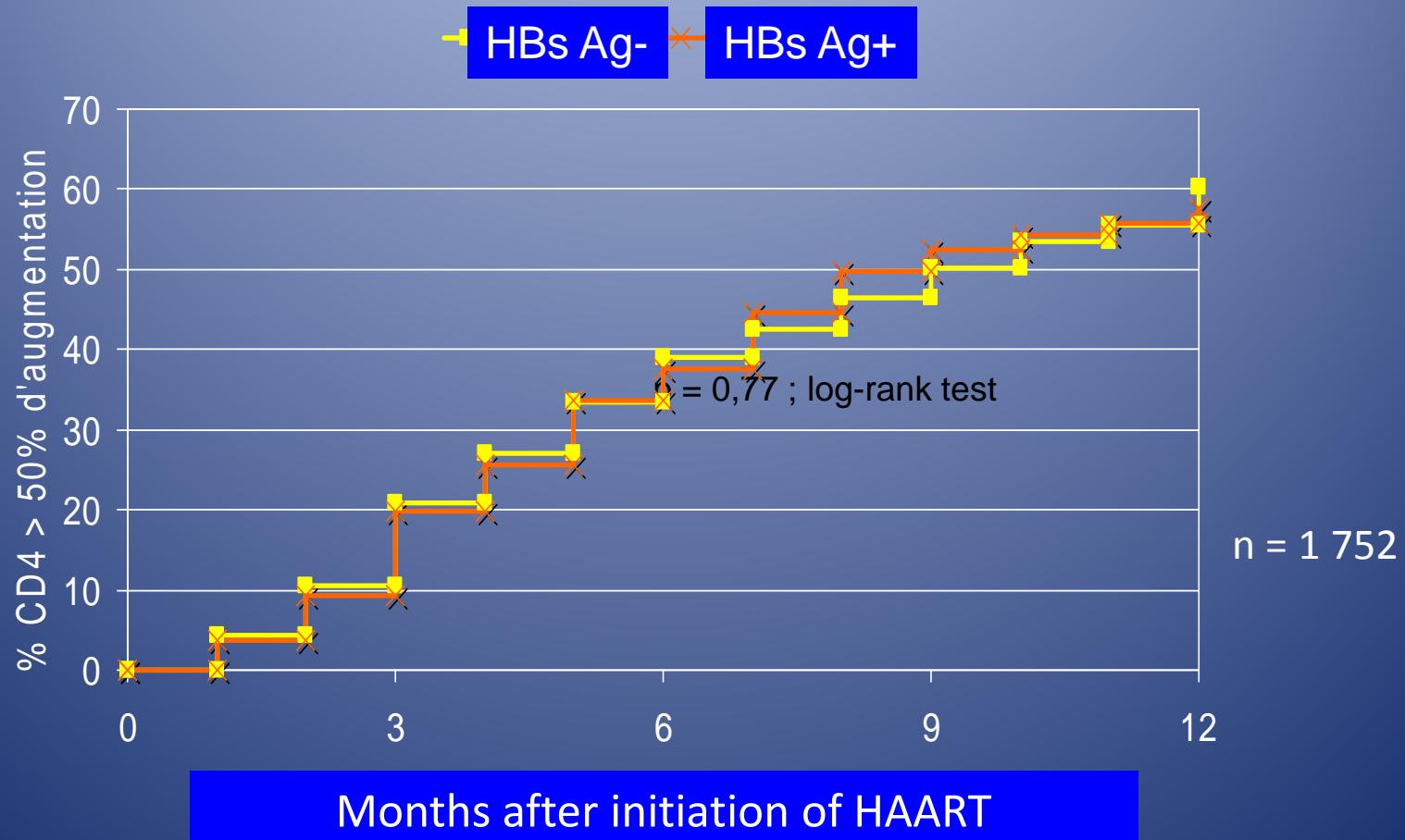
Immune restoration under HAART:
Median delay for VL < 400 copies/ml : 6 vs. 7 months



Konopnicki et al, AIDS 2005

No impact of HBV on HIV

Immune restoration under HAART:
Median delay for CD4 increase > 50%: 9 vs. 8 months



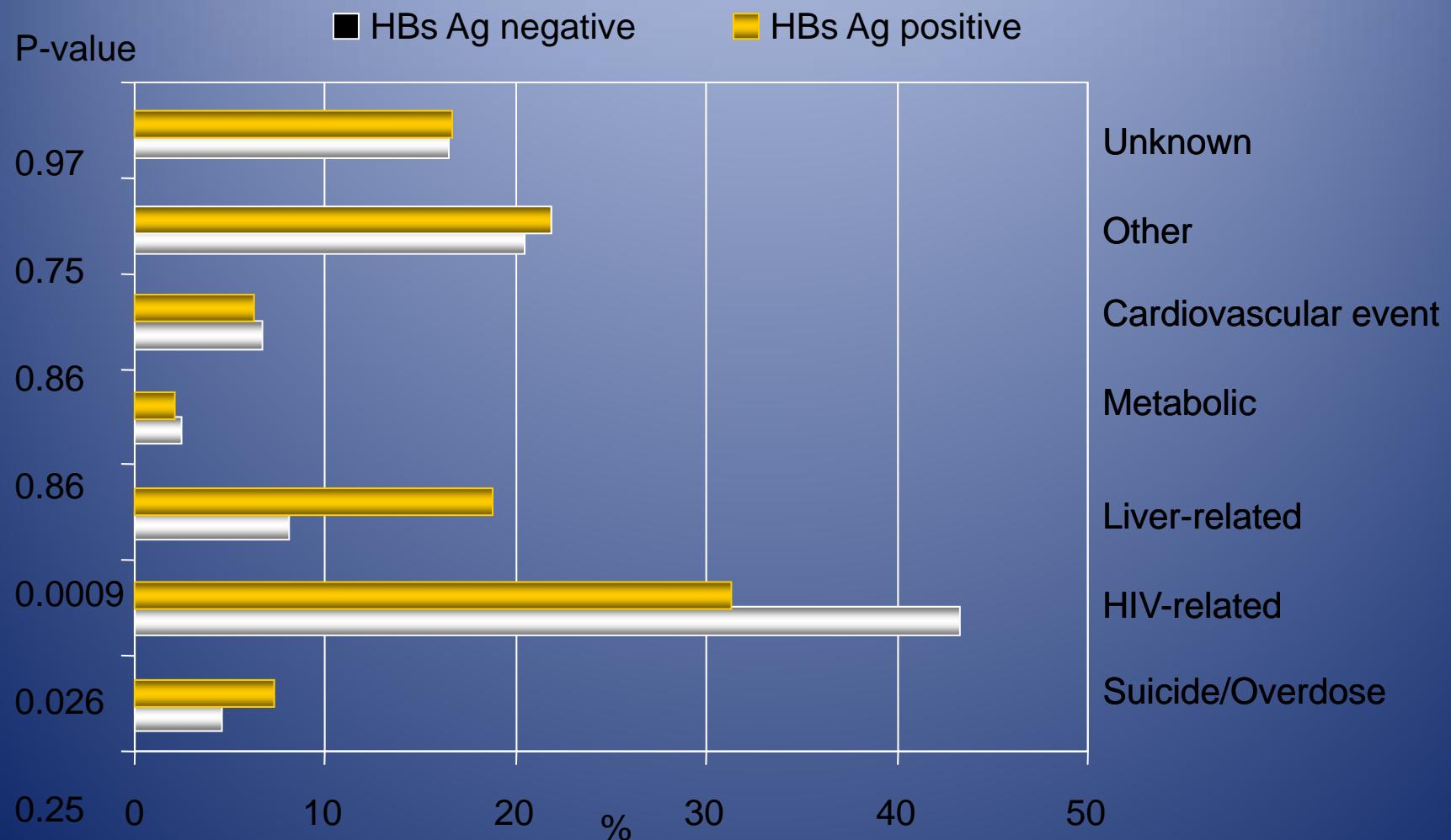
Konopnicki et al, AIDS 2005

Deleterious impact of HIV on HBV (Before 1998)

- Increased risk of chronic infection
- Increased HBV replication
- Decreased rate of anti-HBe and of anti-HBs seroconversion
- Increased progression of liver fibrosis
- Increased risks of cirrhosis, HCC, decompensation and liver-related mortality

Impact of HIV on HBV (after 1998)

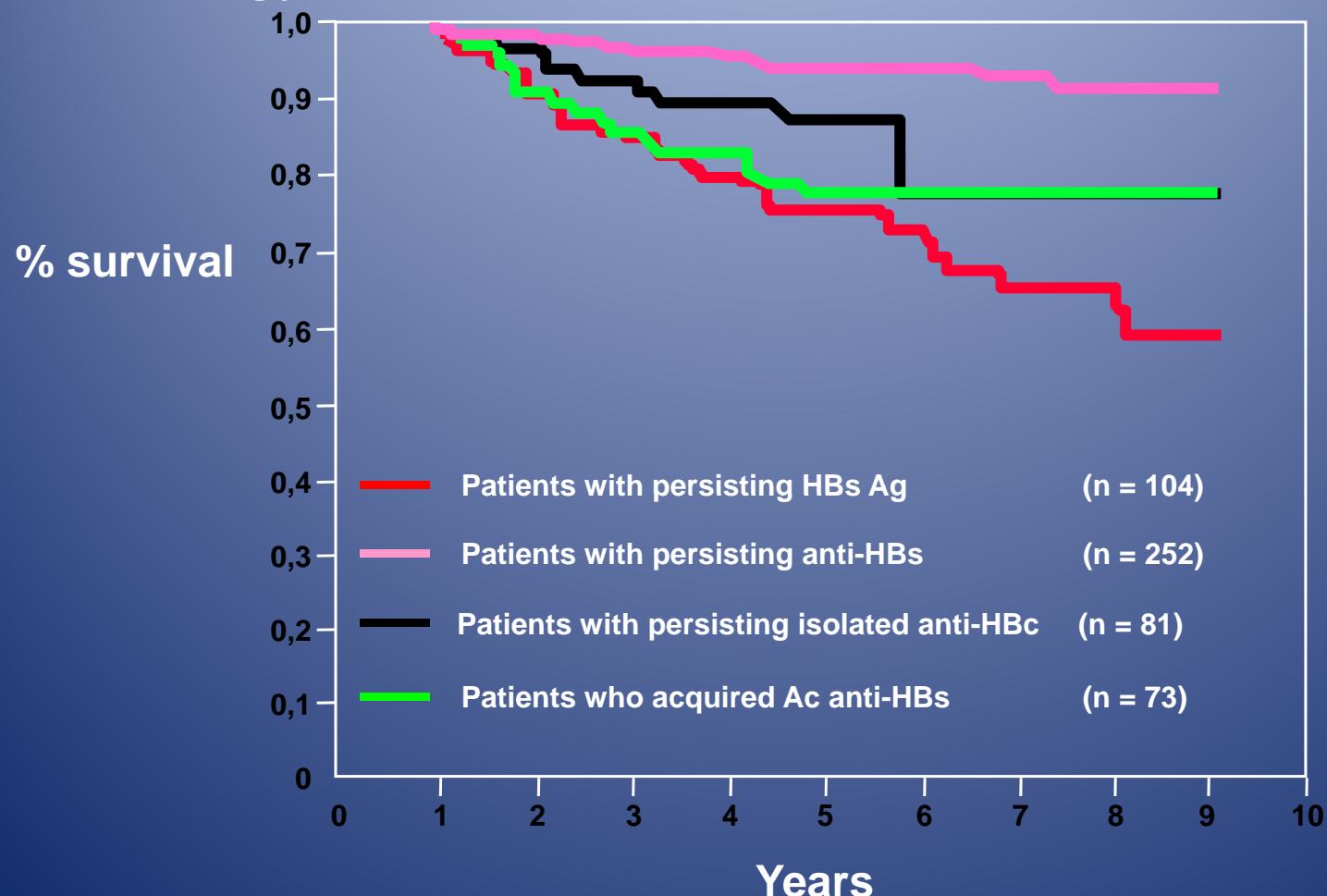
Causes of deaths in HIV+



Konopnicki D for the EuroSIDA group, AIDS 2005

Impact of HIV on HBV (after 1998)

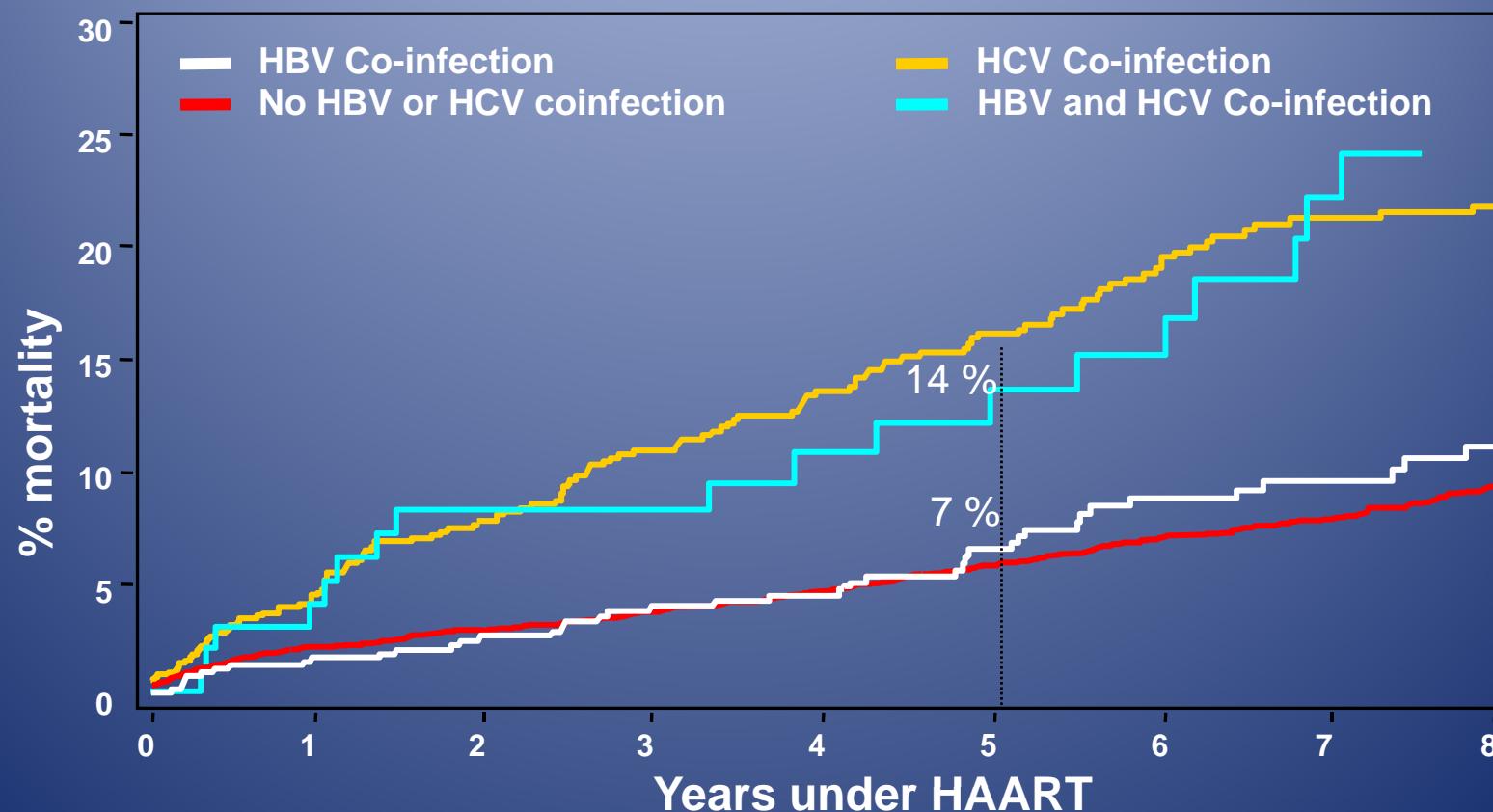
Prospective follow-up of 633 patients (mean 5 years) according to HBV serology



Sheng WH, CID 2007,

Impact of HIV on HBV (after 1998)

1 129 HCV/HIV and 815 HIV/HBV co-infected patients from the ATHENA cohort (85 % under HAART) /follow up from 2001 to 2006



Impact of HIV on HBV (after 1998)

EPIB 2008 = To compare HIV+ and HIV- patients with HBV

	HIV+	HIV-	p
	n = 246	n = 205	
Age	45 ± 9	42 ± 13	< 0.0001
% Male gender	78.5	62.0	<0.0001
% HDV+	12.4	5.9	0.04
% HCV+	12.6	2.9	0.0002

Years of HBV diagnosis

HBV transmission route

HBV genotype

} < 0.0001

Impact of HIV on HBV (after 1998)

EPIB 2008 = To compare HIV+ and HIV- patients with HBV

	HIV+	HIV-	p
	n = 246	n = 205	
1st HBV DNA (log IU/mL)	3.9 ± 2.6	4.8 ± 2.5	0.002
% 1st HBeAg+	46.4	32.8	0.01
% HBV therapy	92.7	57.1	< 0.0001
% last HBV DNA < 2000 IU/mL	86.6	77.7	0.02
% last HBV DNA < LOQ	71.0	44.1	<0.0001
% HBe Ag loss	36.1	44.4	0.36
% HBsAg loss	10.1	1.6	0.02
% HBsseroconversion	7.5	1.6	0.02
Last fibrosis score	1.9 ± 1.4	1.4. ± 1.1	0.002
% cirrhosis	14.4	6.4	0.02
% HCC	1.3	1.1	



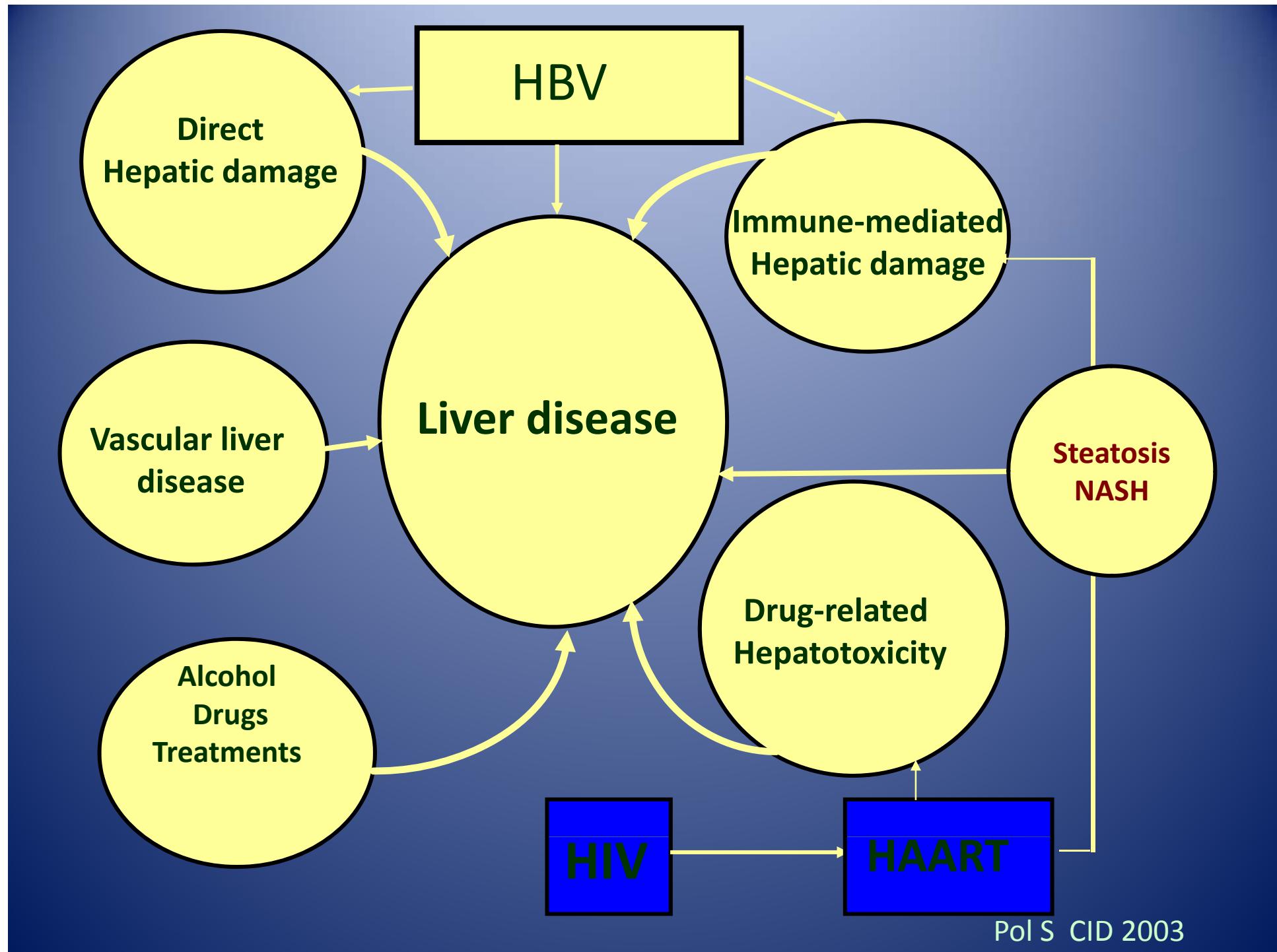
HIV infection has no negative impact on likelihood of HBV therapeutic success

Piroth L et al. J Hepatol 2010

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HIV/HBV: anti-HBV therapy

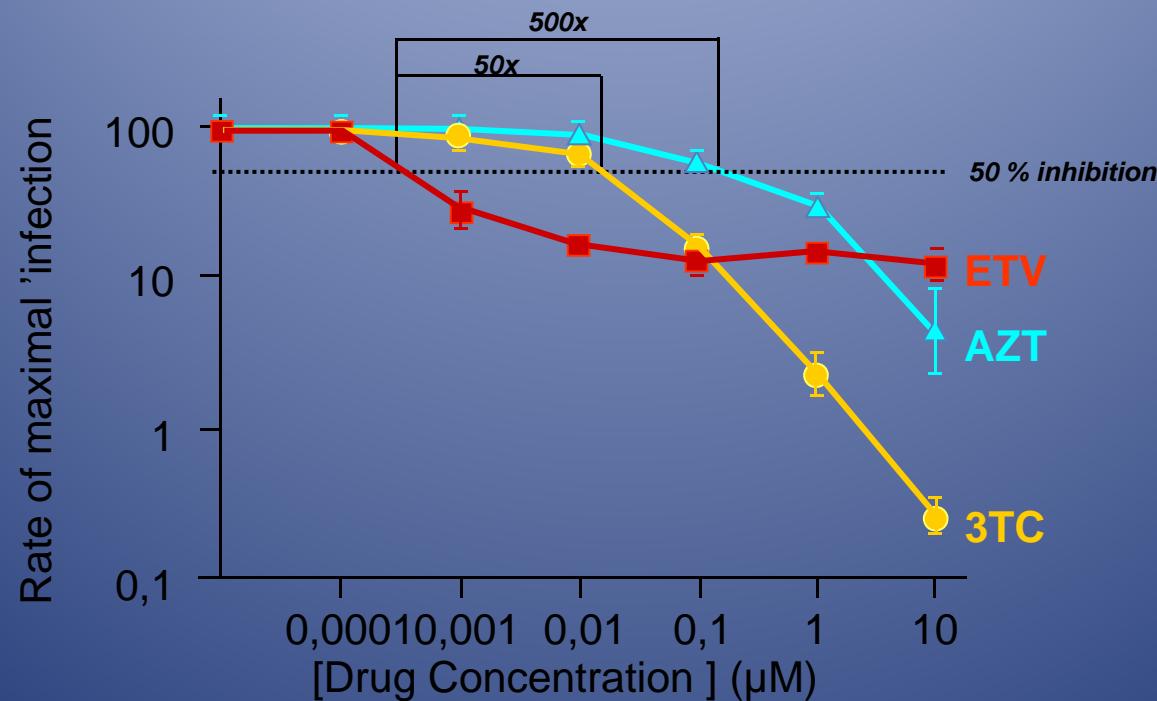
	IFN	LAM	ETV*	FTC	TDF*	ADV*
No. of patients	87	215	51	33	200	35
Duration (weeks)	12-24	48	24	48	24-48	48-144
Anti-HBV activity	wt, preC	wt, preC	wt, preC, LAM-R	wt, preC	wt, preC LAM-R	wt, preC, LAM-R
HBV DNA decline (log cp/ml)	26%**	2.7	3.6	3	4.4	4 - 5.4
Hbe seroconv.	9%	11%	?	?	4%	7%
ALT response	12-20%	30-50%	49%	?	?	35-66%
Histological improvement	?	?	?	?	?	33-50%

* Added to LMV in the majority of the cases. ** < 6log copies/ml

Wong DK et al. Gastroenterology 1995. Di Martino V et al. Gastroenterology 2002. Dore GJ et al. J Infect Dis 1999. Benhamou Y et al. Hepatology. 1996 Pessoa W et al. CROI 2005. Raffi F et al. 2003 IAS. Peter M et al. CROI 2005. Ristig MB et al. J Infect Dis. .2002 Benhamou Y et al. N Engl J Med. 2003. Benhamou Y et al. Lancet 2001 and AASLD, 2003

Impact of entecavir on replication and selection of HIV1 resistances

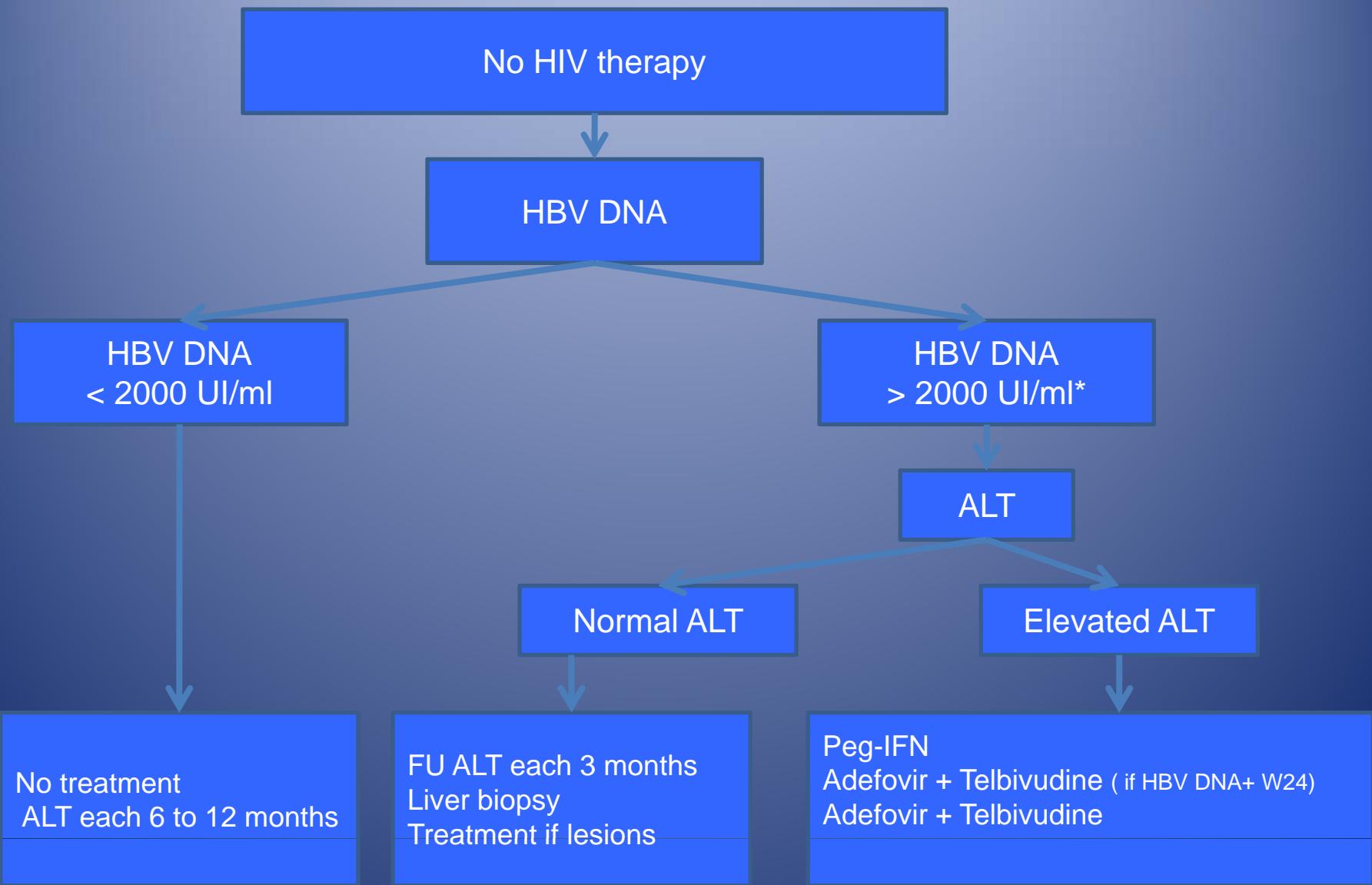
- Entecavir : No significant anti-HIV activity



Impact of entecavir on replication and selection of HIV1 resistances

- Entecavir : No significant anti-HIV activity
- 3 anecdotal reports of HIV decline >1 log under entecavir
- Study of clonal populations of one of 3 HIV/HBV co-infected patients under entecavir monotherapy :
 - No M184V mutation at D0
 - Vs. 61 % and 96 % at M4 and M6

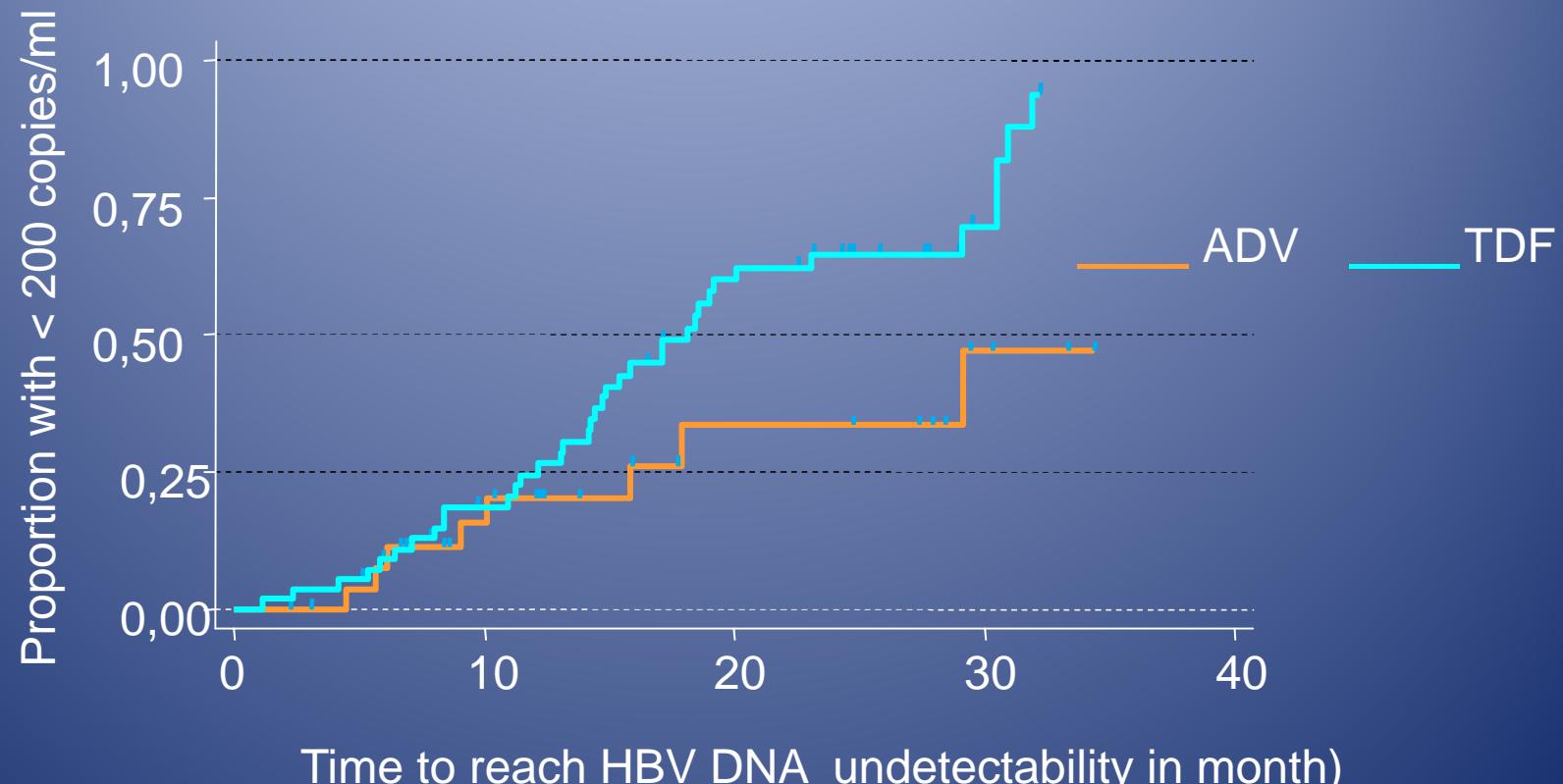
HBV therapy of HIV-infected patient



Expert Report (Rapport Yeni 2008)

Higher efficacy of tenofovir vs. Adefovir in co-infected

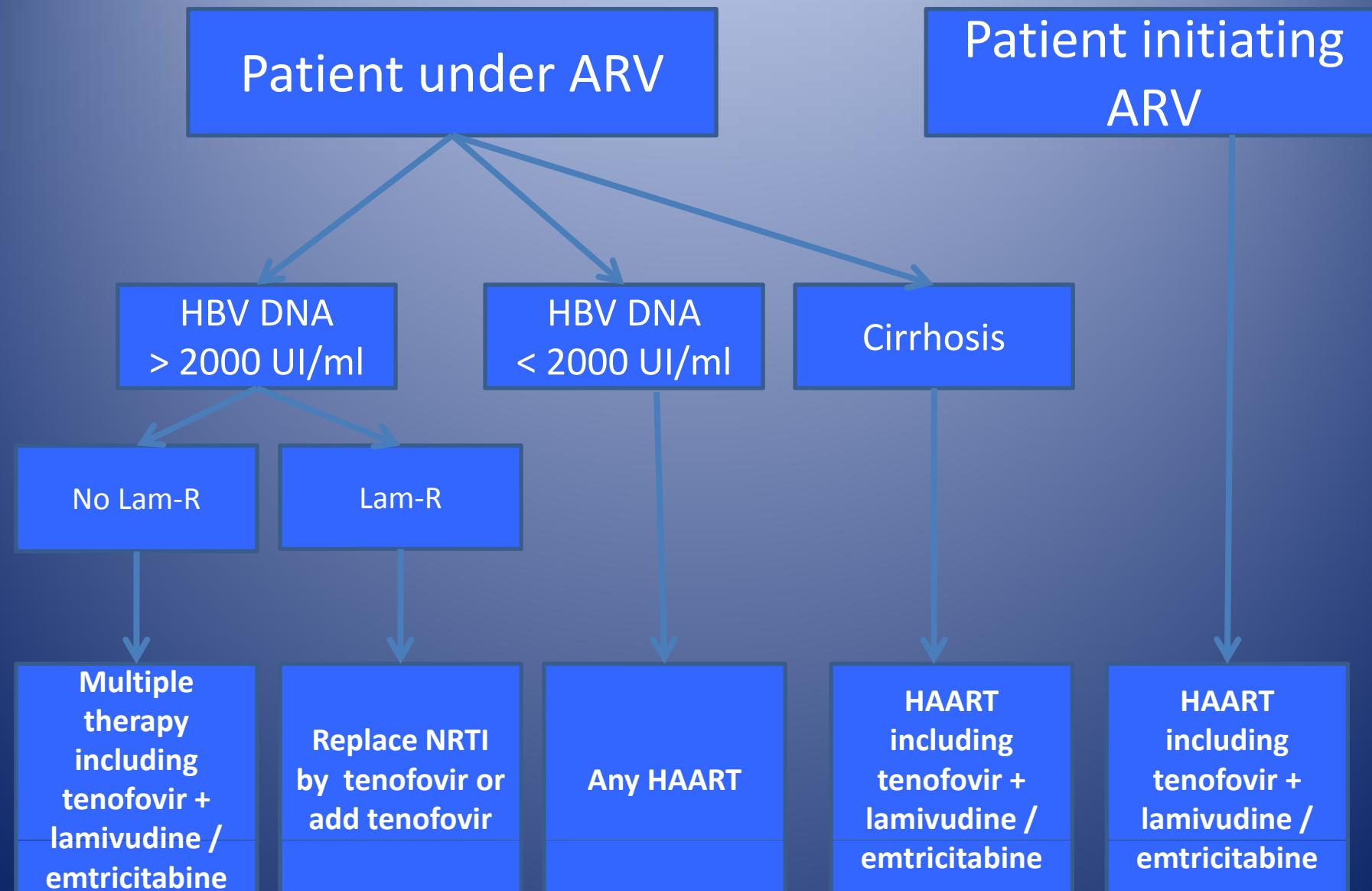
85 patients (56 under tenofovir TDF, 29 under adefovir ADV)



(HR = 2.8 ; IC95% 1.1-6.8 ; p = 0.025)

Lacombe K, Antiviral Therapy 2008

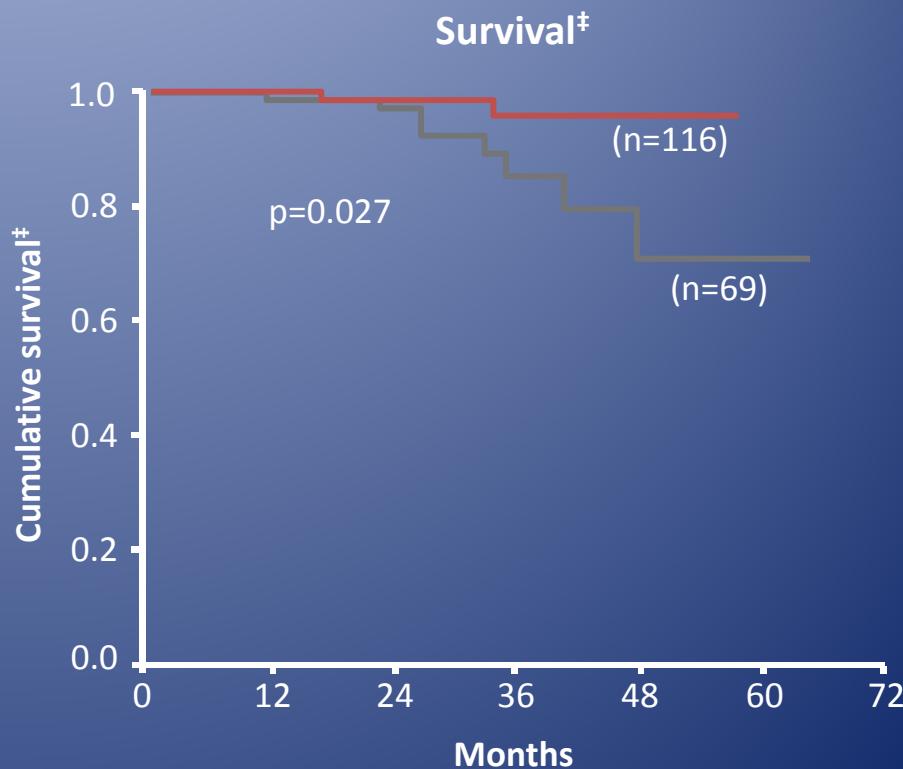
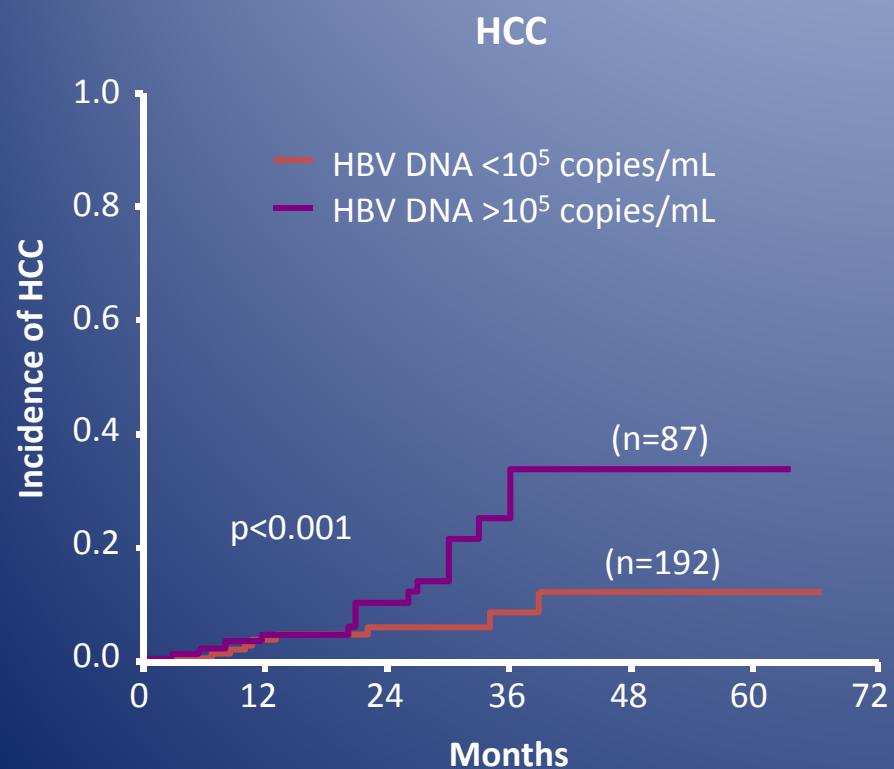
HBV therapy of HIV-infected patient



Expert Report (Rapport Yeni 2008)

Clinical benefits associated with viral suppression

On-treatment with LVD (100 mg OD)[†]



*Virologic response = HBV DNA <10⁵ copies/mL;

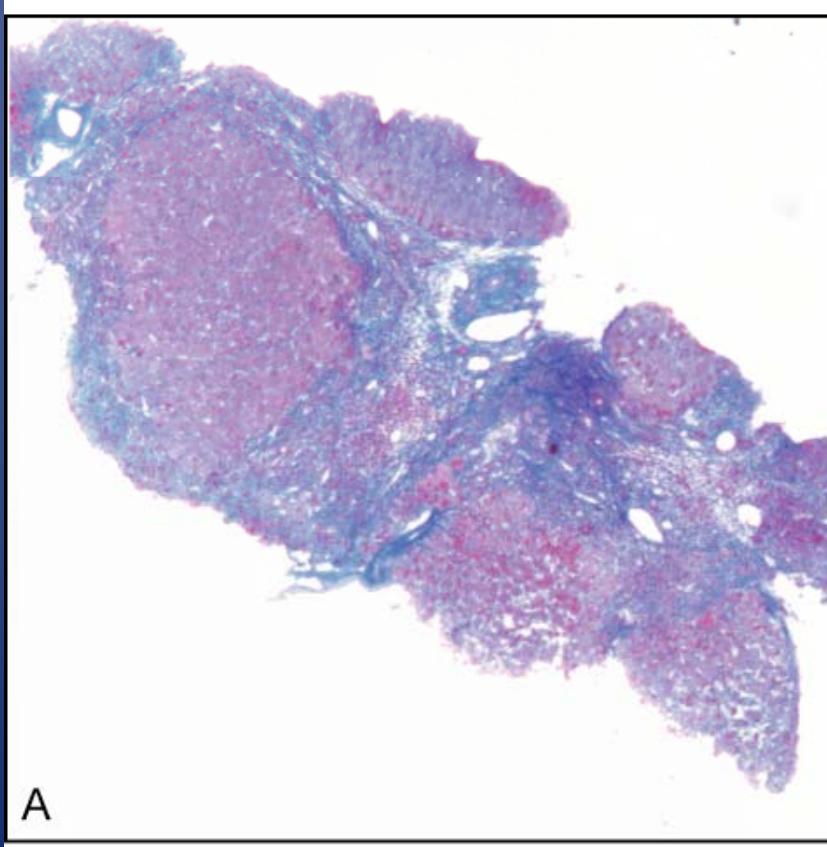
[†]Minority of patients received LVD 150 mg OD;

[‡]Patients with Child-Turcotte-Pugh A cirrhosis

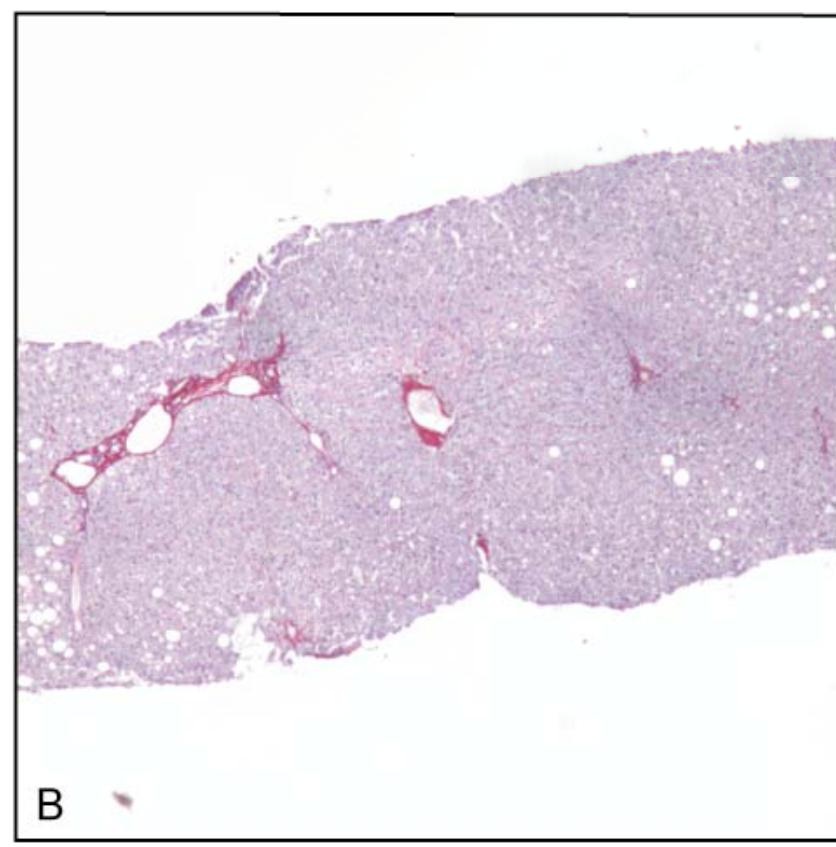
Di Marco V, Hepatology 2004

Clinical benefits associated with viral suppression

HBV cirrhosis reversal



A2 F4



A1F1

Mallet V, Antiviral Therapy 2007

HBV infection in HIV

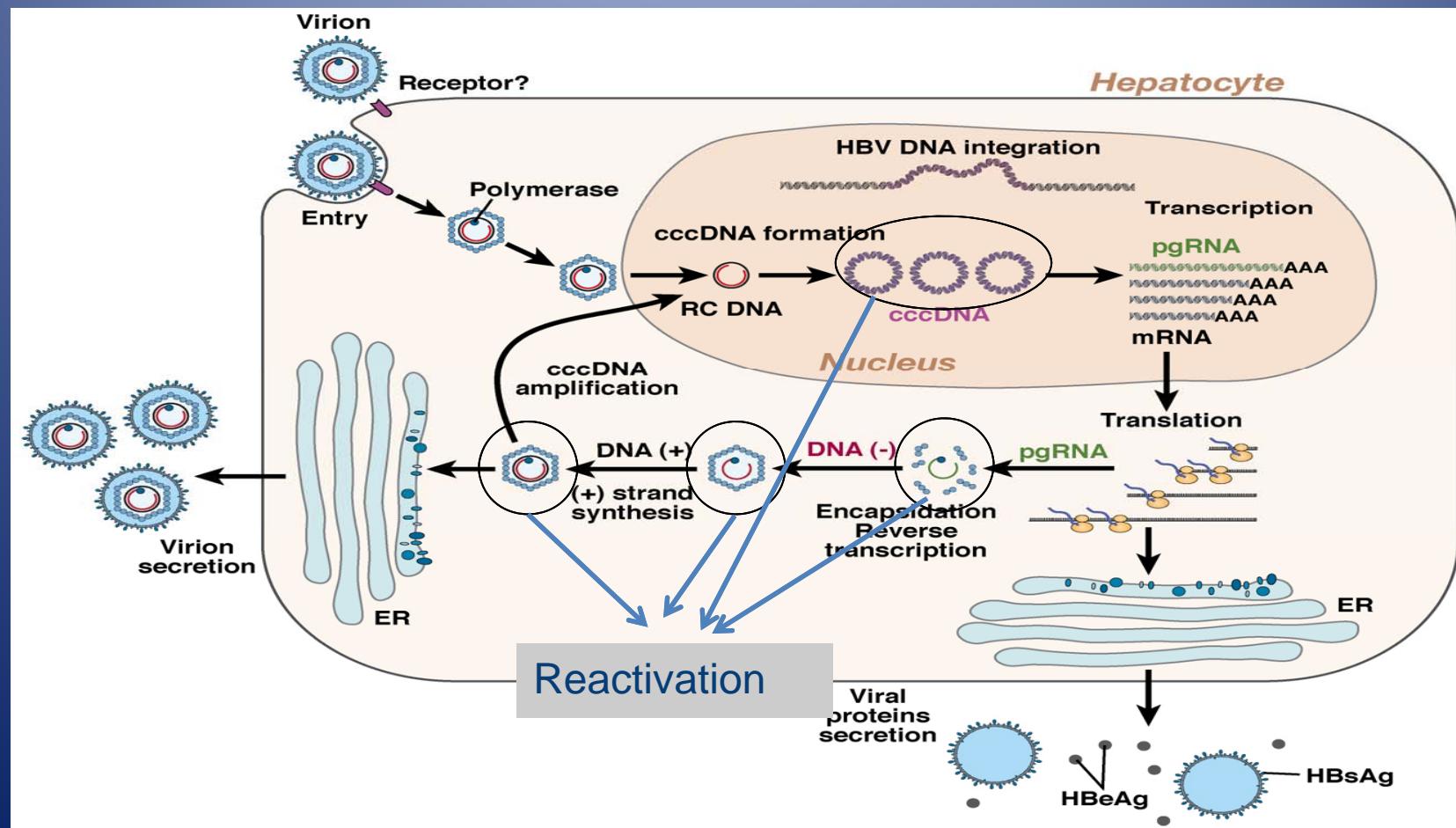
The 2 remaining problems

- Reactivation:

HBV infection in HIV

The 2 remaining problems

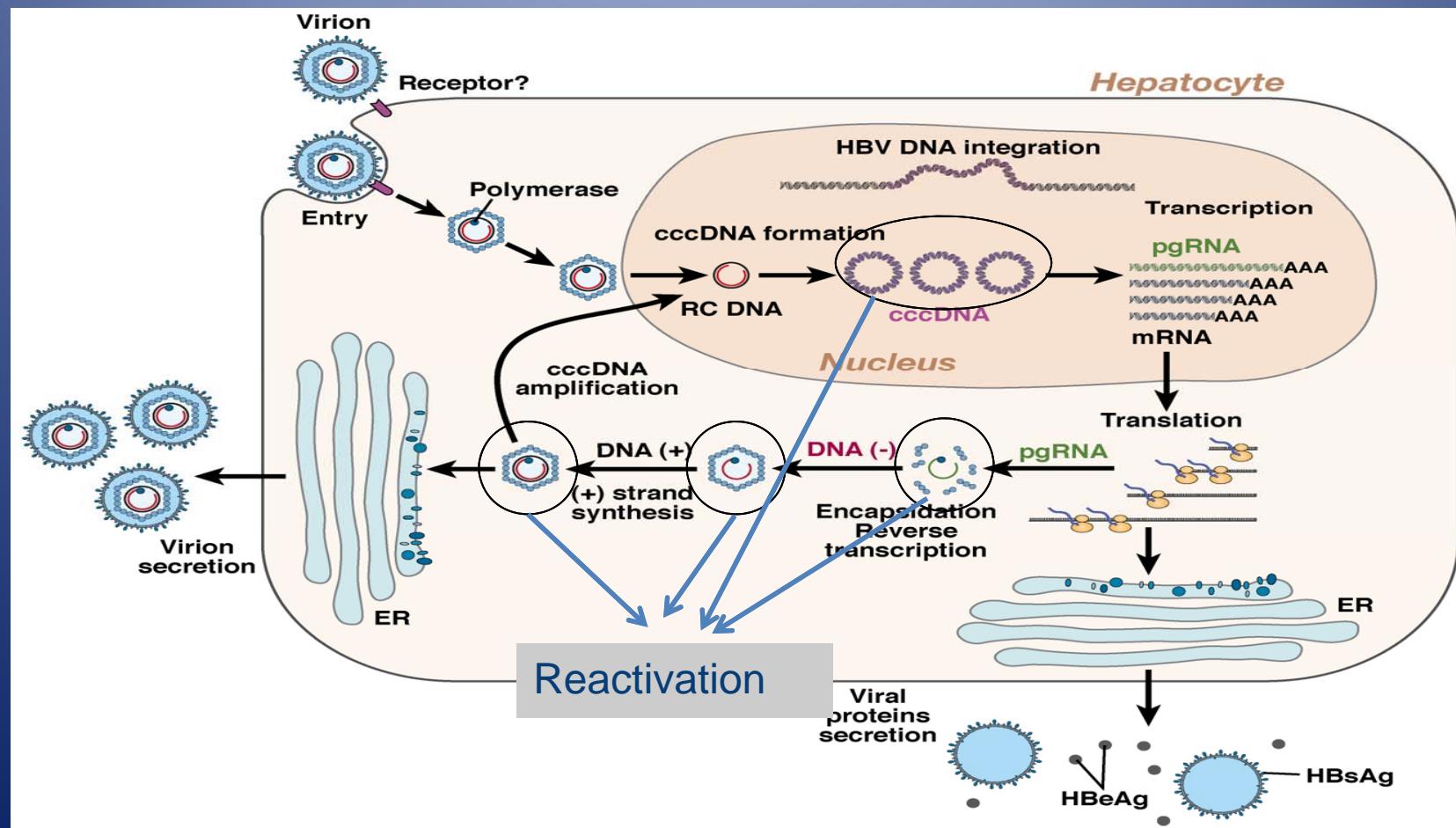
- Reactivation:



HBV infection in HIV

The 2 remaining problems

- Reactivation: No HBV drug discontinuation



HBV infection in HIV

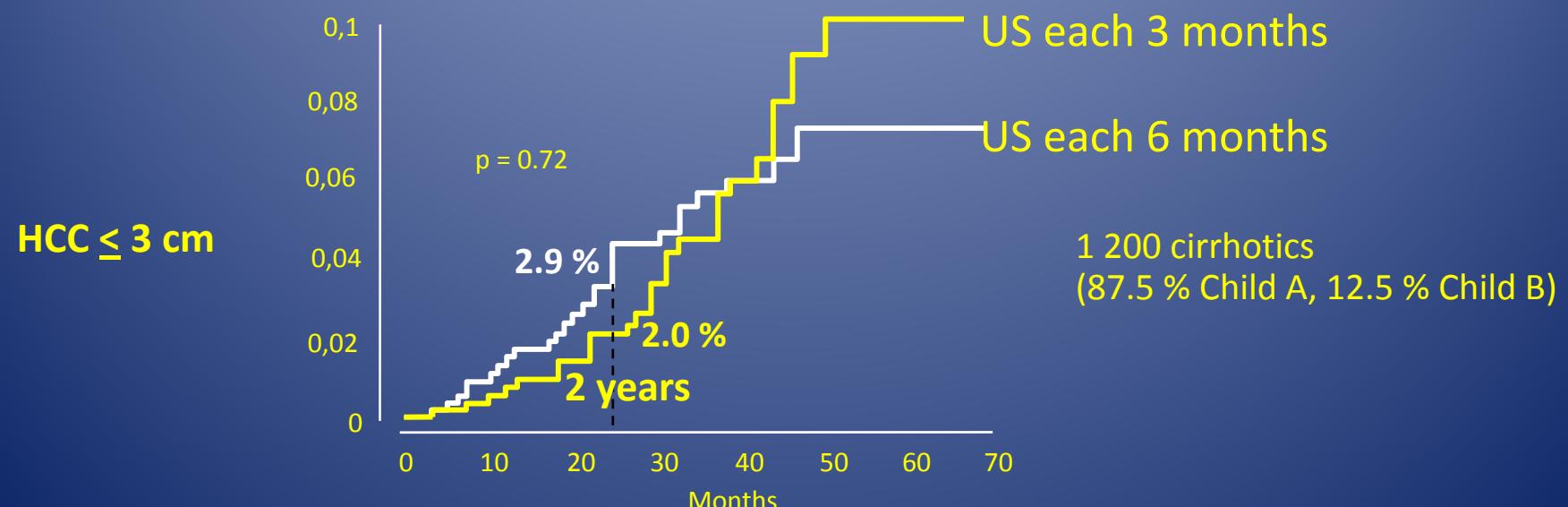
The 2 remaining problems

- Reactivation: No HBV drug discontinuation
- Hepatocellular carcinoma: to maintain US screening

HBV infection in HIV

The 2 remaining problems

- Reactivation: No HBV drug discontinuation
- Hepatocellular carcinoma: to maintain US screening



HBV infection in HIV

The 2 remaining problems

- Reactivation: No HBV drug discontinuation
- Hepatocellular carcinoma: to maintain US screening each 4 months



The physician (and patient) responsibility

HBV infection in HIV

The 2 hopes

- To improve vaccine efficacy
- To avoid post-transplantation problems by efficient pre-Tx viral suppression and post-Tx prophylaxis

Anti-HBV vaccination in HIV+ : Interest of double doses

- Prospective re-vaccination of 144 patients with 40 ug at M0, M1, M2
- Response rate: 51 % 1 month after 1st injection
- Predictors: young age, gender, undetectable HIV RNA

Anti-VHB vaccination in HIV+ : Interest of double doses

Figure 2: Percentage of responders and high responders at week 28 (intent-to-treat analysis).

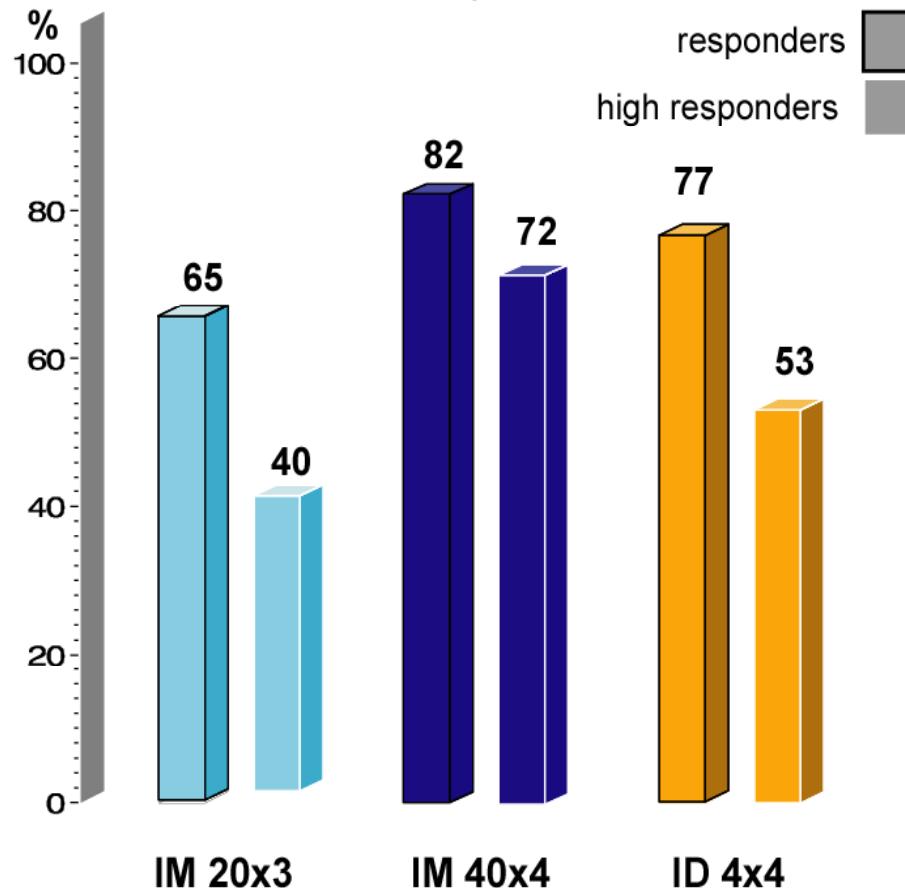
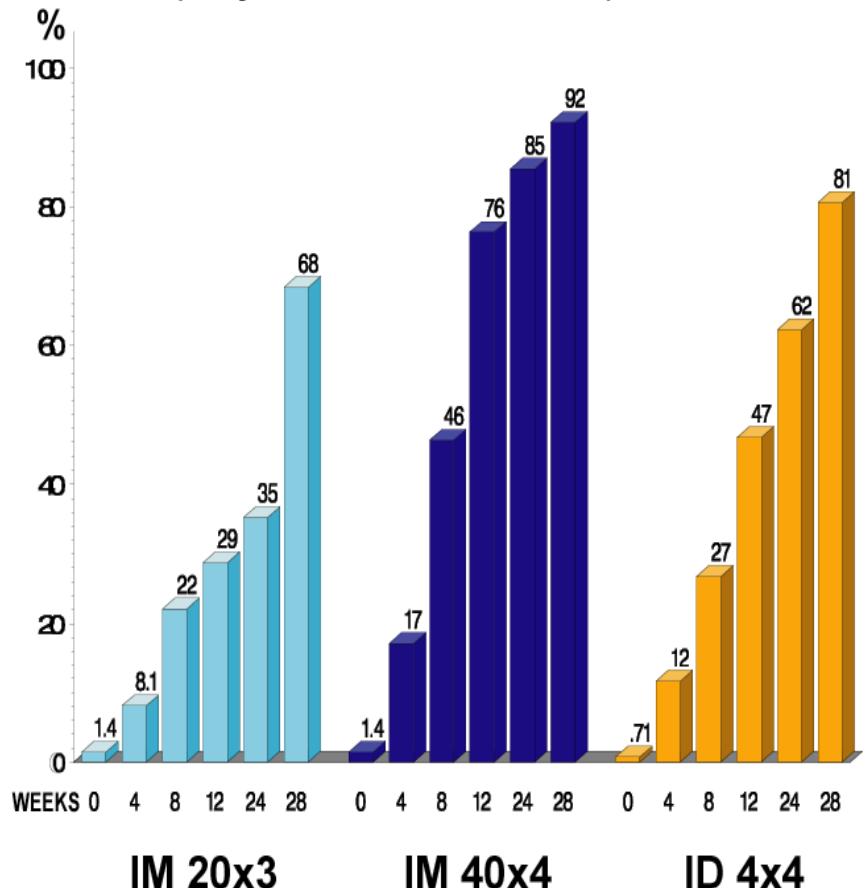


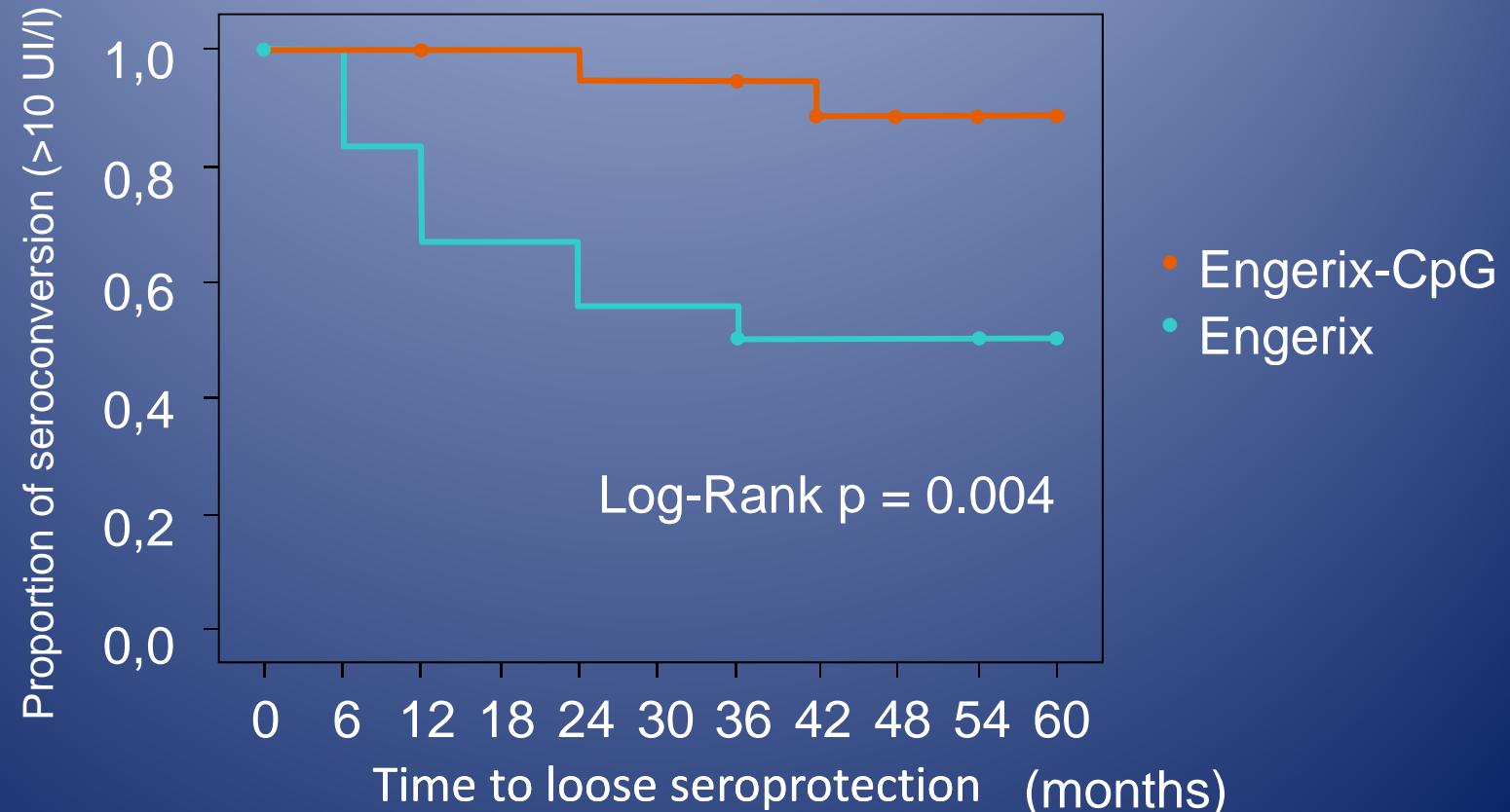
Figure 3: Evolution of seroconversion rate (subjects with available sera).



ANRS trial. By courtesy of O. Launay

Anti-VHB vaccination in HIV+ non responders: Interest of adjuvants

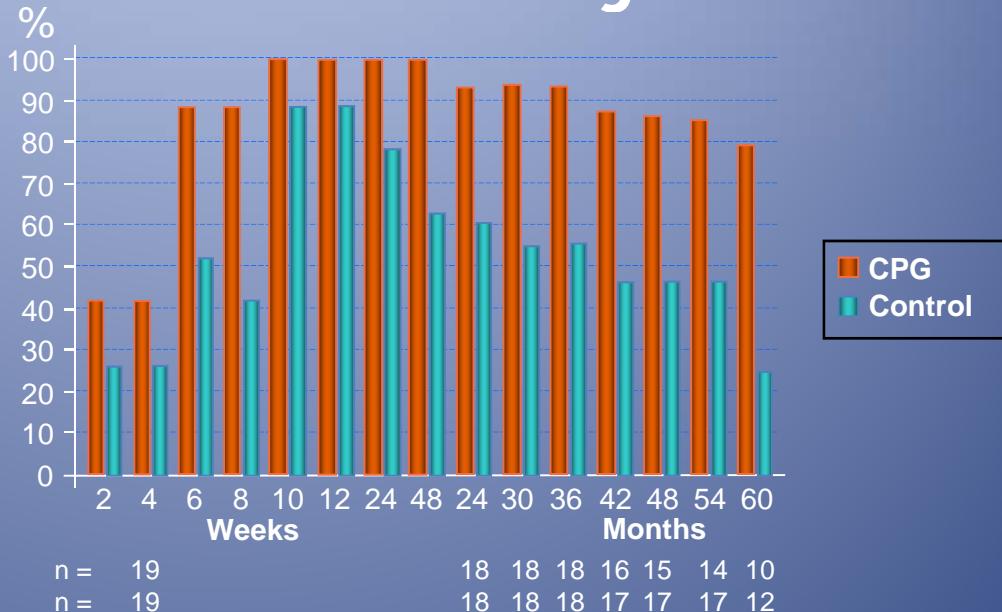
Double-blind randomized trial in 36 patients including 18 non responders : double dose (40 ug) at M0, M1 and M2 +/- 1 mg CPG7909 (B lymphocytic immunostimulant CpG)



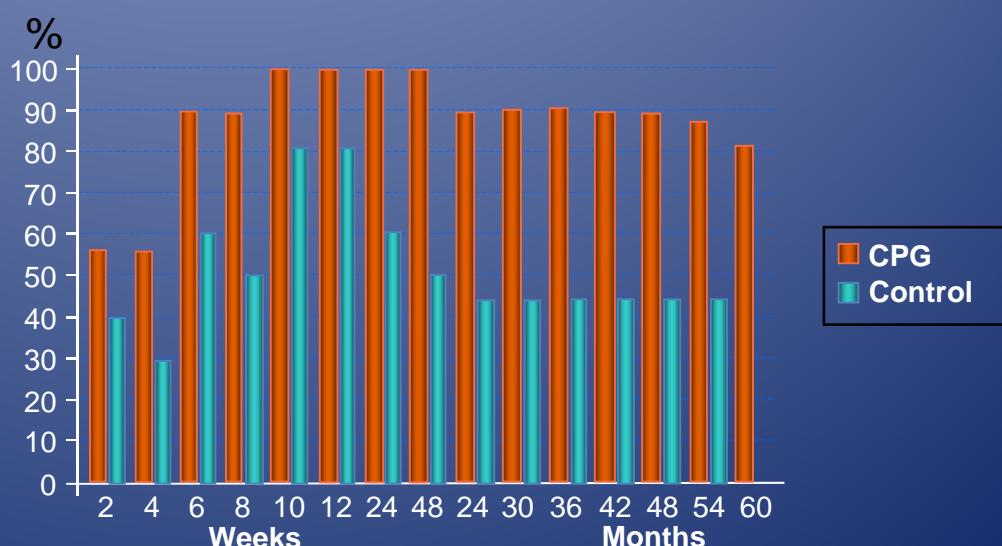
Cooper CL, CID 2008

Anti-VHB vaccination in HIV+ non responders: Interest of adjuvants

- Rate of anti-HBs > 10 UI/l
 - All the patients



- Rate of anti-HBs > 10 UI/l
 - Non responders to 1st vaccination



Conclusions

- HBV: more frequent but no negative impact after 2005
- Follow up and treatment guidelines in co-infected patients ~ HBV mono-infected
- Objectives of therapy: undetectable HBV DNA (>95%)
 - To reduce disease progression
 - To reduce viral resistance (not reported in HIV/HBV)
- Sustained anti-HBV therapy
 - Long term tolerability
 - Long term adherence
 - Long term resistance