Faut-il adapter à la coinfection les recommandations de l'AFEF ?

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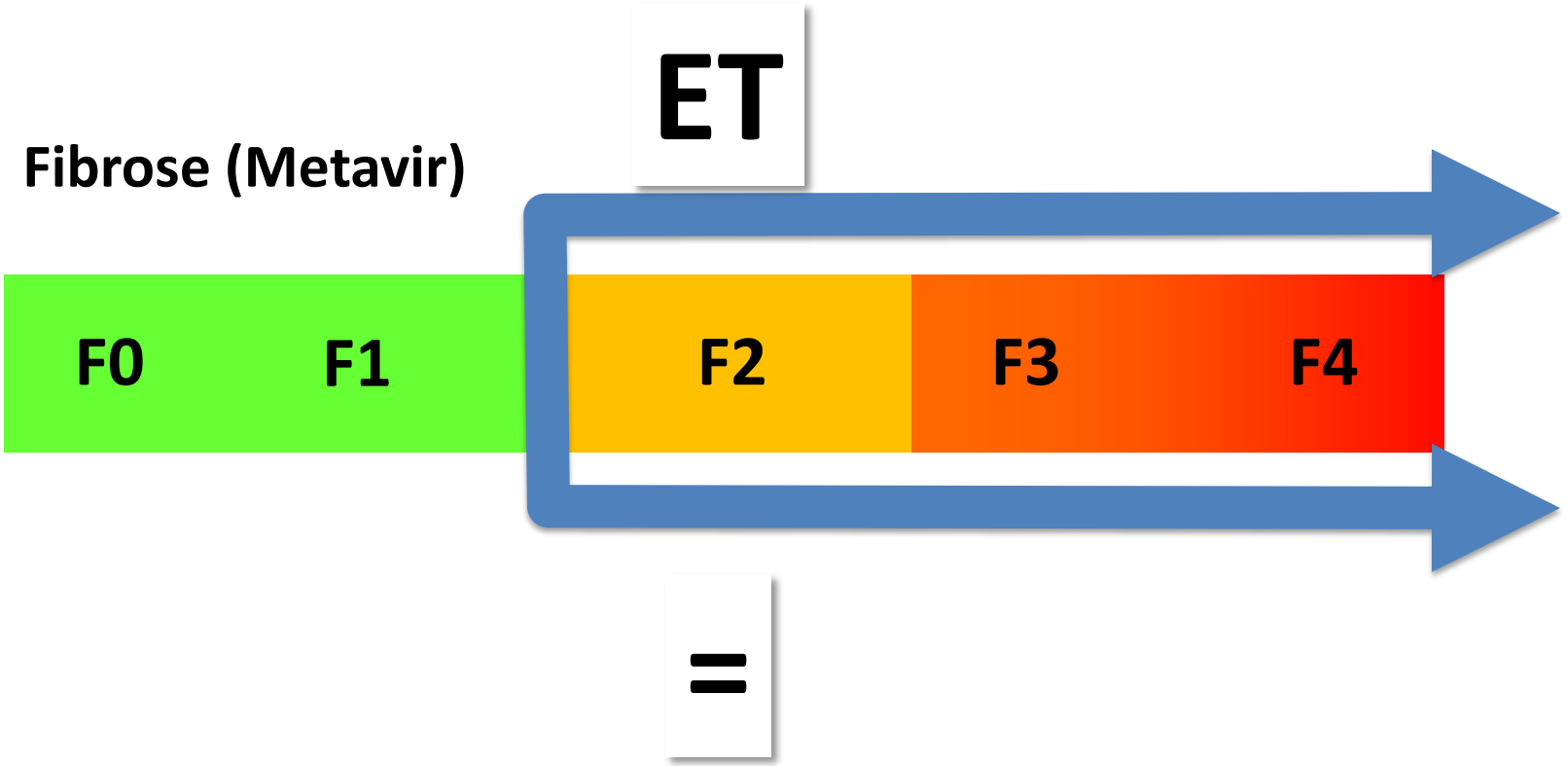
Conflits d’intérêts

- Board français et internationaux, workshop, consulting: Gilead, Bristol-Myers Squibb, MSD, Roche, Janssen, Novartis, Pfizer, Abbott
- Co-investigateur dans des études industrielles : Bristol-Myers Squibb, Roche, Schering-Plough / MSD, Boehringer Ingelheim, Tibotec, Vertex, Janssen, Abbott

Le (near) futur attendu du patient VIH NEG, VHC POS

Recommandations AFEF

PCR VHC POS ± ALT > N



Traitement antiviral
(PR ou PR T/Boc en fonction du génotype)

Des eaux plus calmes sont en vue

Avec des bateaux de compétition…

Recommandations AFEF « actualisées »

PCR VHC POS ± ALT > N

ET

Fibrose (Metavir)

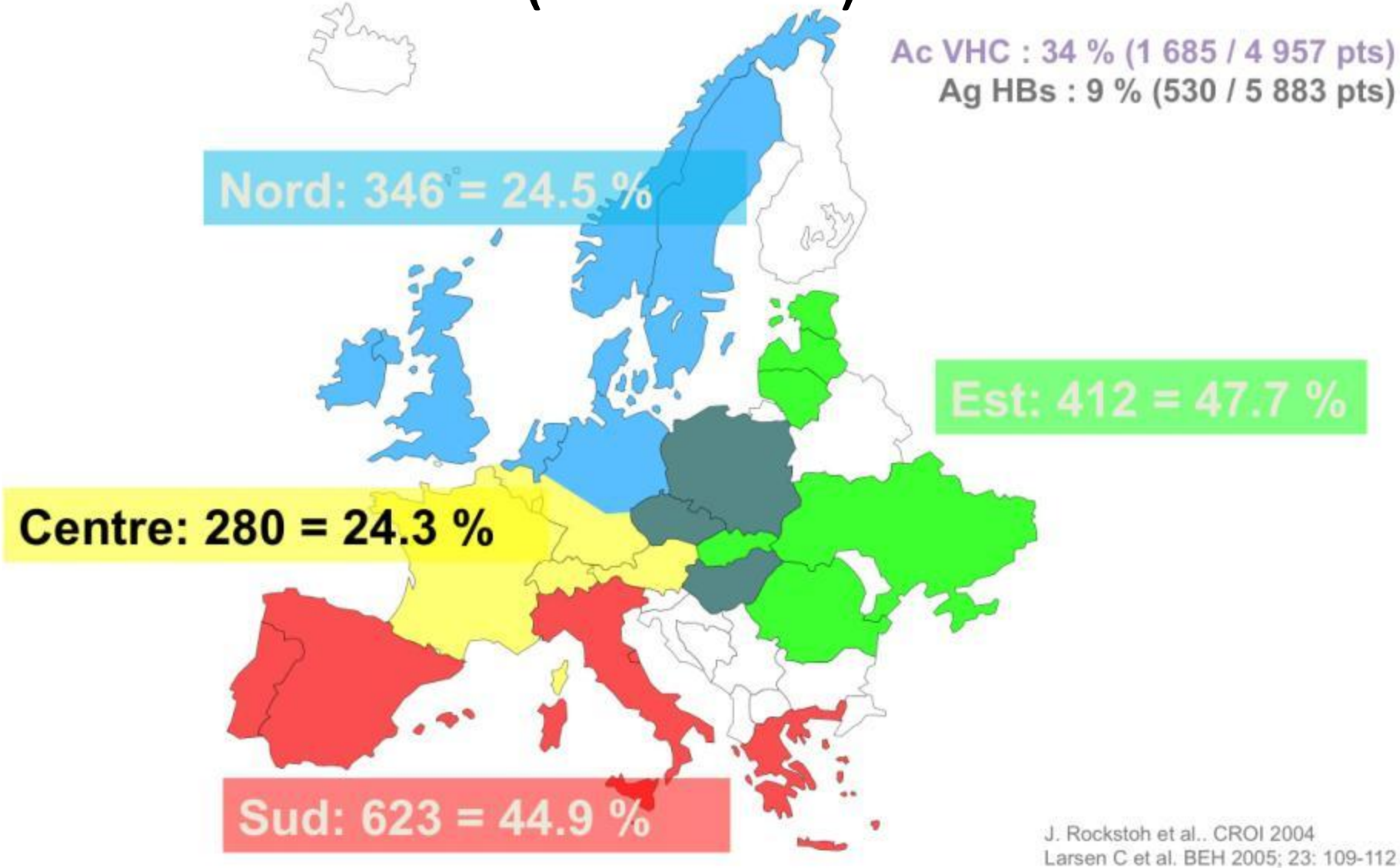
=

Traitement antiviral
(PR ou PR T/Boc en fonction du génotype)

Deuffic-Burban S et al. Soumis

Quid pour les patients VIH/VHC??

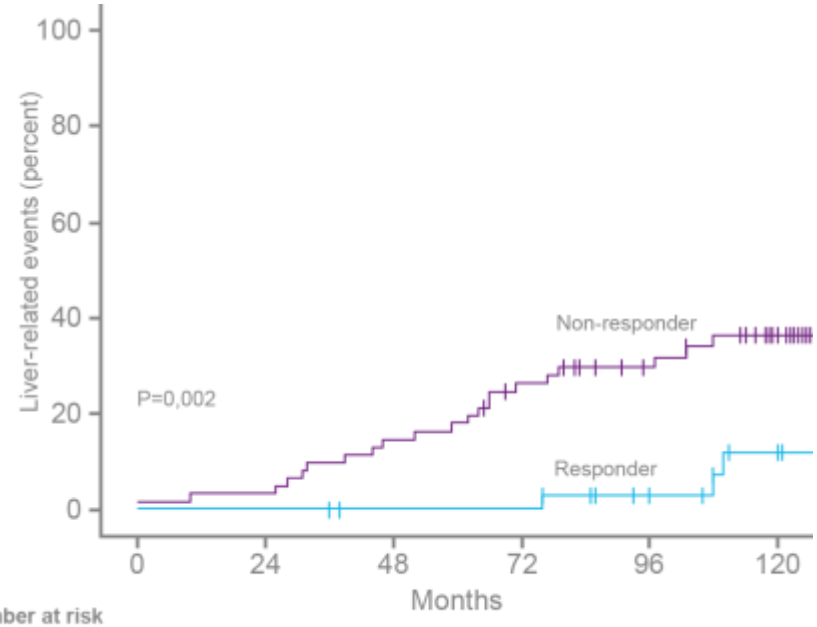
La coinfection en europe (EuroSida)



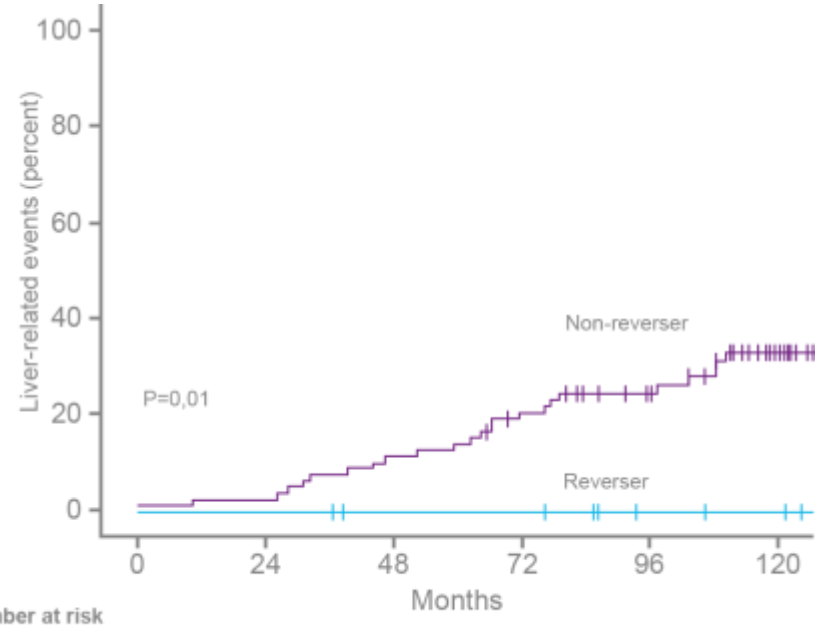
J. Rockstoh et al.. CROI 2004
Larsen C et al. BEH 2005; 23: 109-112

Incidence à 10 ans des événements hépatiques: Patients F3-F4

96 patients VHC
Score METAVIR F3-F4
Médiane de suivi 118 mois; EIQ=86-138 mois



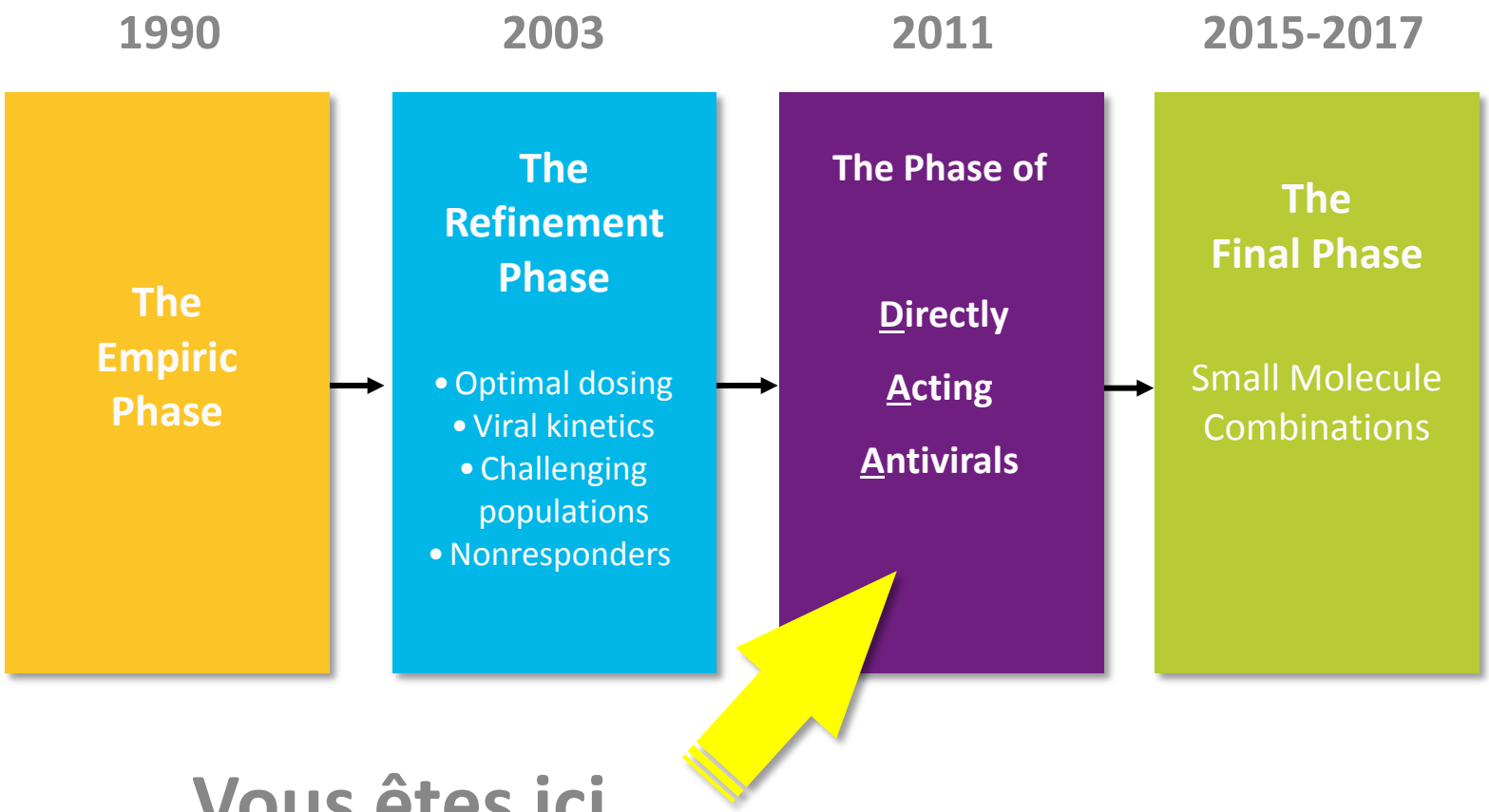
Number at risk						
Non-responder	61	59	52	43	32	22
Responder	35	35	33	33	27	18



Number at risk						
Non-reverser	78	76	69	60	47	30
Reverser	18	18	16	16	12	10

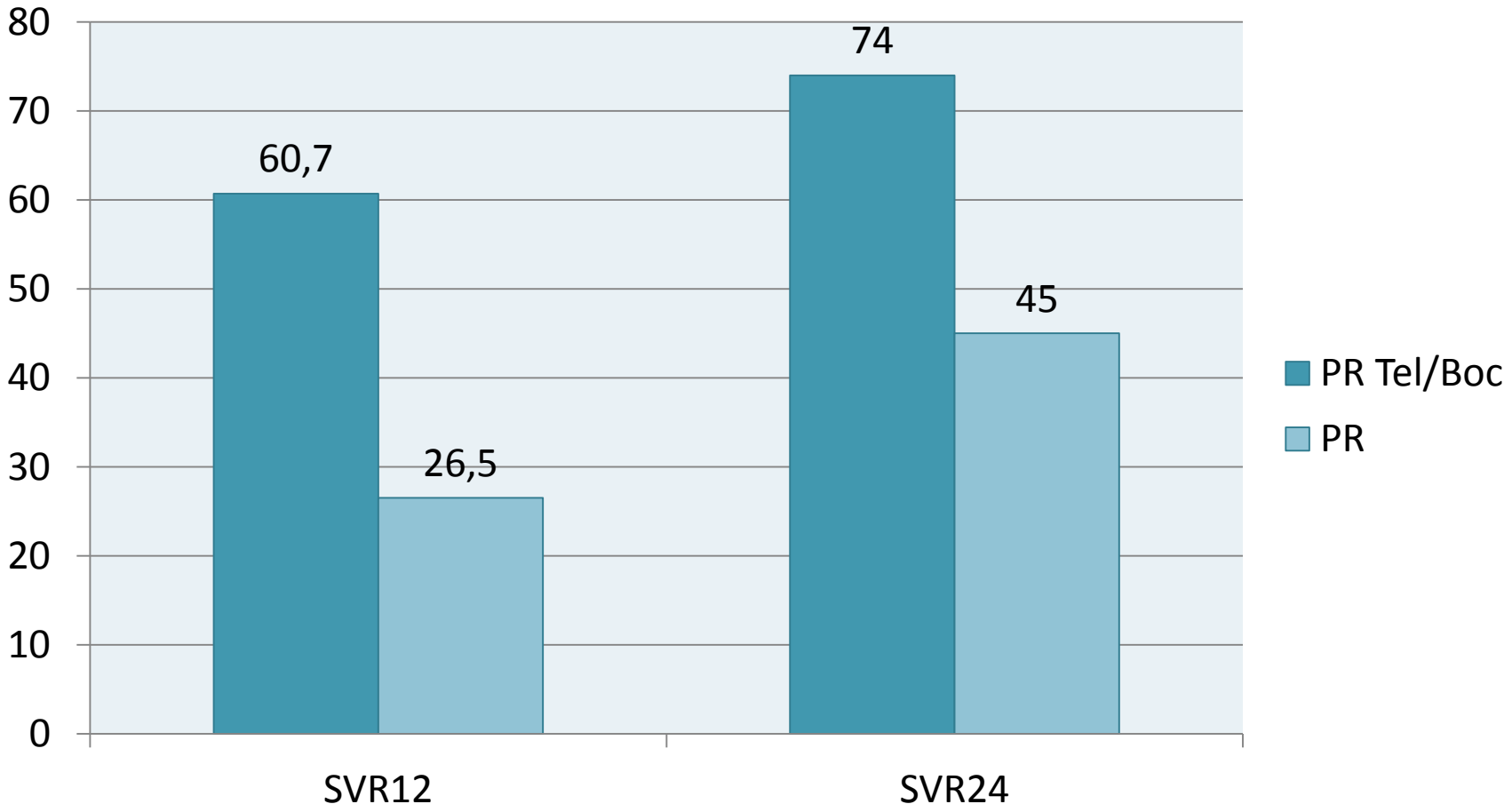
Mallet et al. *Ann Intern Med*. 2008;149(6):399-403

VHC : la révolution thérapeutique en marche



Weisberg IW, et al. Current Hepatitis Reports 2007;6:75-82.

Previr efficacy in HIV/HCV naïve noncirrhotic patients



Mallolas J, EASL 2012; Sulkowski M, USA, AASLD 2012

F0-F1 un jour ≠ F0-F1 toujours (contamination avant 1993)

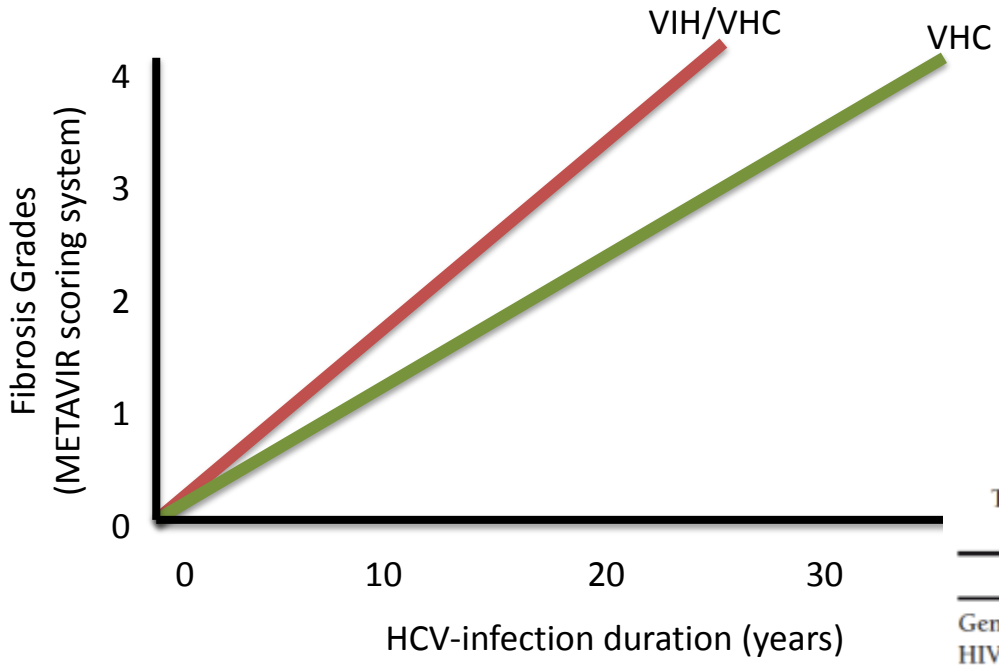


TABLE 2. Risks Factors for Fibrosis Progression in 244 HCV-Infected Patients: Results of the Multivariate Regression Analysis

	β	SE	OR	95% CI OR	P
Gender (men)	0.01	0.049	1.010	0.916-1.113	.7
HIV infection	0.200	0.046	1.221	1.115-1.337	<.0001
Severe immunosuppression*	0.260	0.069	1.296	1.132-1.484	.0002
Age at infection (>25 years old)	0.497	0.054	1.643	1.476-1.829	<.0001
Alcohol consumption (>50 g/d)	0.499	0.048	1.647	1.496-1.812	<.0001

NOTE. Variability of the fibrosis progression rate explained by the model: $r^2 = 0.53$.

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.

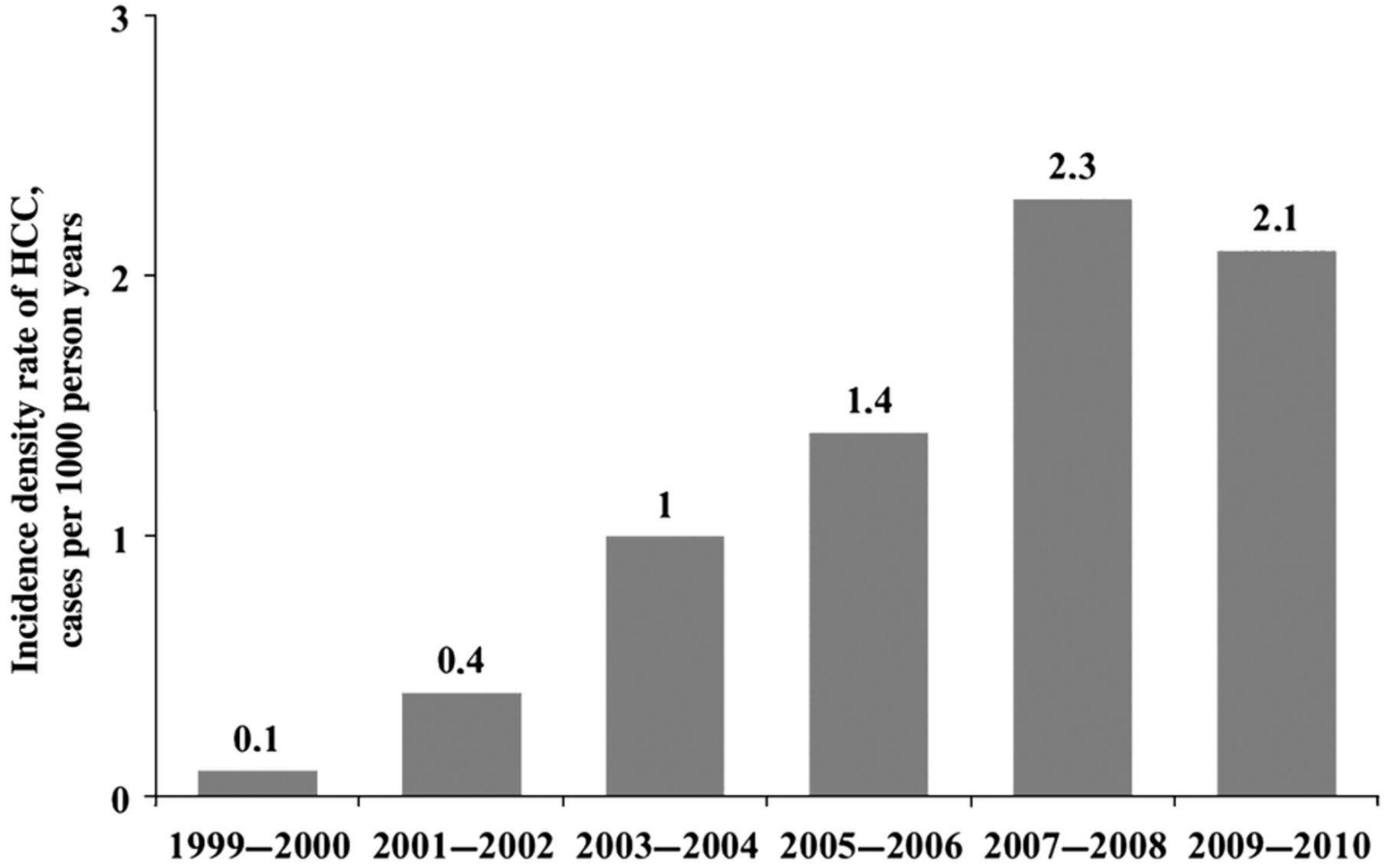
*CD4 ≤200 cell/μL, HIV-seronegative patients were considered to have more than 200 CD4 cells/μL.

Benhamou Y et al. Hepatology 1999

Femme de 51 ans; VIH avant 1987; Pas d'IO; ARV 1997; ATZ/TDF/FTC/RTV 2008; 300-350 CD4 (23%); ARN VIH NEG; Pas de syndrome métabolique; Alcool 30 g/j

- VHC G1, RR (24 semaines) à PR en 2005 (Metavir F2)
- Mars 2011: ALT 3N, PLQ Nl, TP 90%, Bili T 86µmol/L, Alb N, Echo N, FT A3F4 (ATV)
- Octobre 2012: CHC unifocal (5 cm), thrombose portale segmentaire, AFP 4859 UI
- Novembre 2012: Métastases pulmonaires multiples, AFP > 25.000 UI. Prise en charge palliative

Evolution of the incidence density rate of hepatocellular carcinoma in patients coinfected with human immunodeficiency virus and hepatitis C virus during the study period (n = 76).



Merchante N et al. Clin Infect Dis. 2012;cid.cis777

Clinical Infectious Diseases

From: **Relationship of Liver Disease Stage and Antiviral Therapy With Liver-Related Events and Death in Adults Coinfected With HIV/HCV**

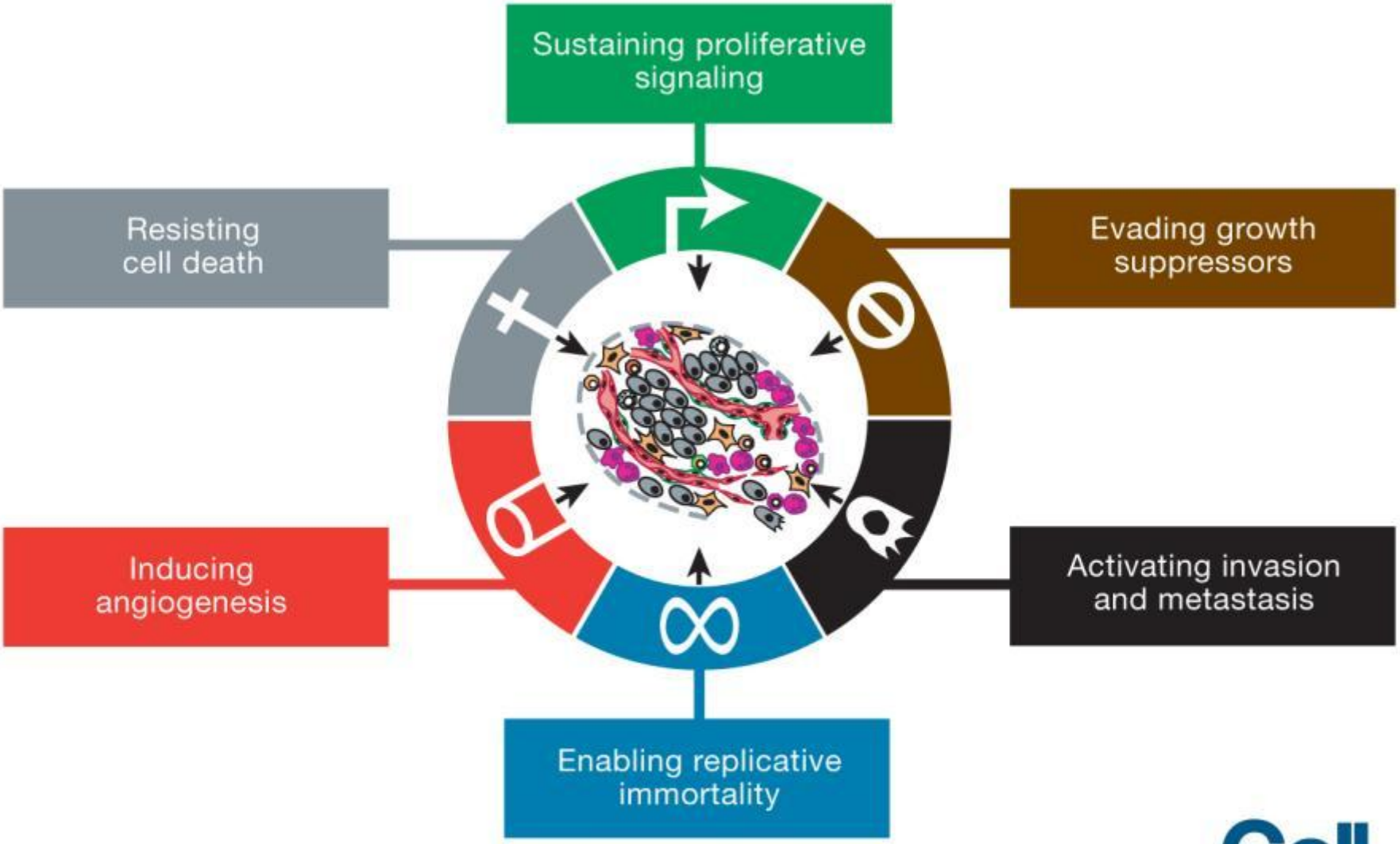
JAMA. 2012;308(4):370-378. doi:10.1001/jama.2012.7844

Figure Legend:

Table 2. Incidence Rates by METAVIR Stage

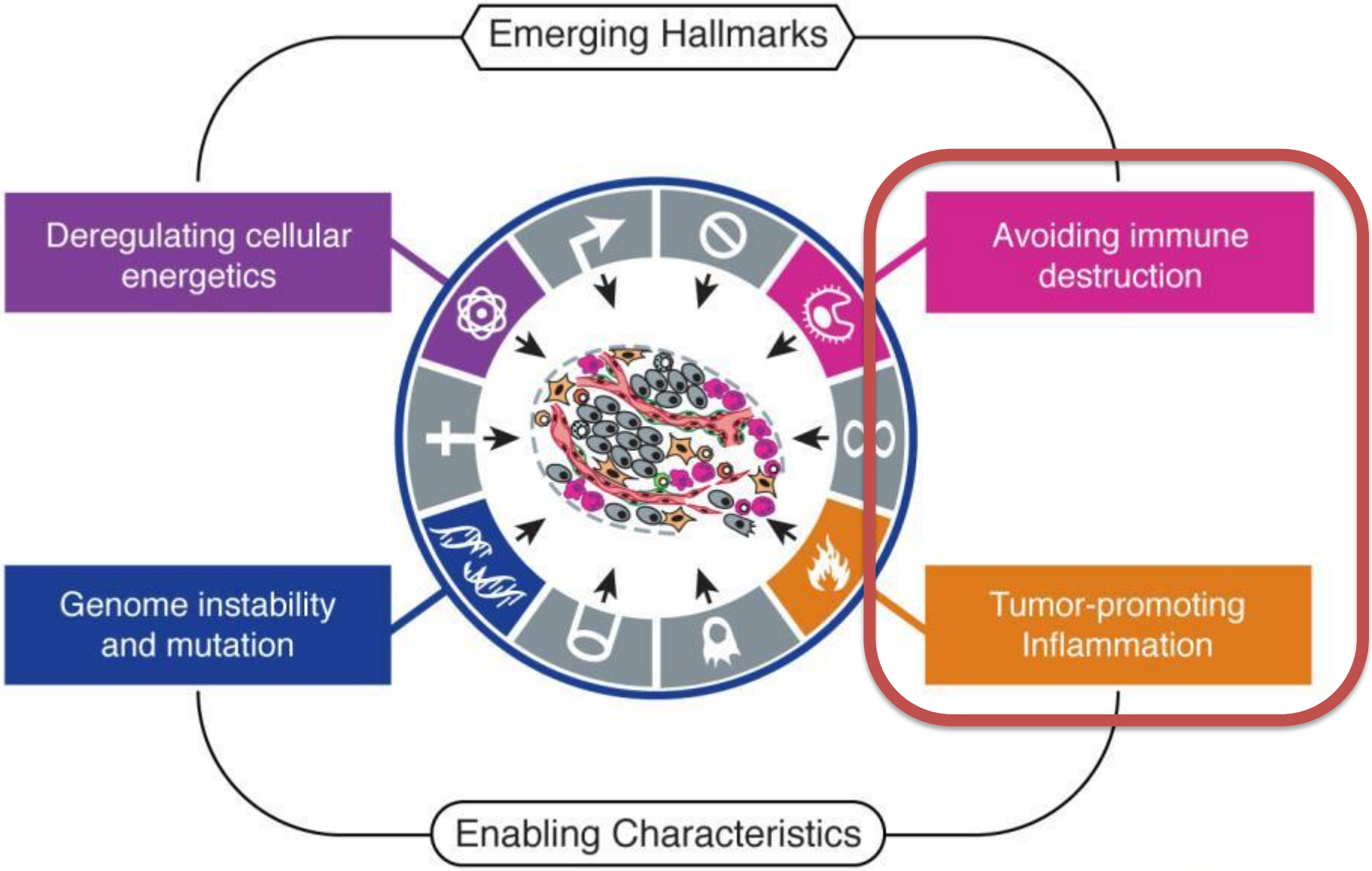
METAVIR Fibrosis Stage[a]	No. of Events	Person-Years[b]	Incidence Rate per 1000 Person-Years (95% CI)[c]
All outcomes: ESLD, HCC, or death			
F0	33	1396.3	23.63 (16.80-33.24)
F1	57	1568.8	36.33 (28.03-47.10)
F2	18	337.1	53.40 (33.65-84.76)
F3	11	195.9	56.14 (31.09-101.38)
F4	31	390.3	79.43 (55.86-112.95)
Total	**150**	**3888.3**	38.58 (32.87-45.27)
Liver-related outcomes: ESLD, HCC, or liver-related death			
F0	4	1396.3	2.86 (1.08-7.63)
F1	16	1568.8	10.20 (6.25-16.65)
F2	9	337.1	26.70 (13.89-51.32)
F3	5	195.9	25.52 (10.62-61.31)
F4	17	390.3	43.56 (27.08-70.07)
Total	**51**	**3888.3**	13.12 (9.97-17.26)

Abbreviations: ESLD, end-stage liver disease; HCC, hepatocellular carcinoma.
[a] METAVIR fibrosis stages: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.
[b] Person-years were calculated from the time of biopsy to the time of event or last follow-up.
[c] Tests for trend were significant for all-cause outcomes ($P < .001$) and liver-related outcomes ($P < .001$).



Hanahan and Weinberg, 2011

Cell PRESS

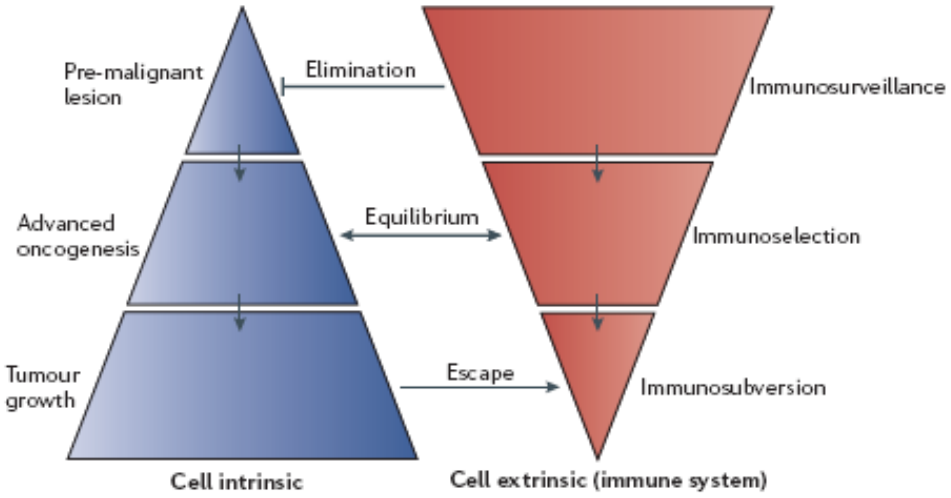


Hanahan and Weinberg, 2011

Cell PRESS

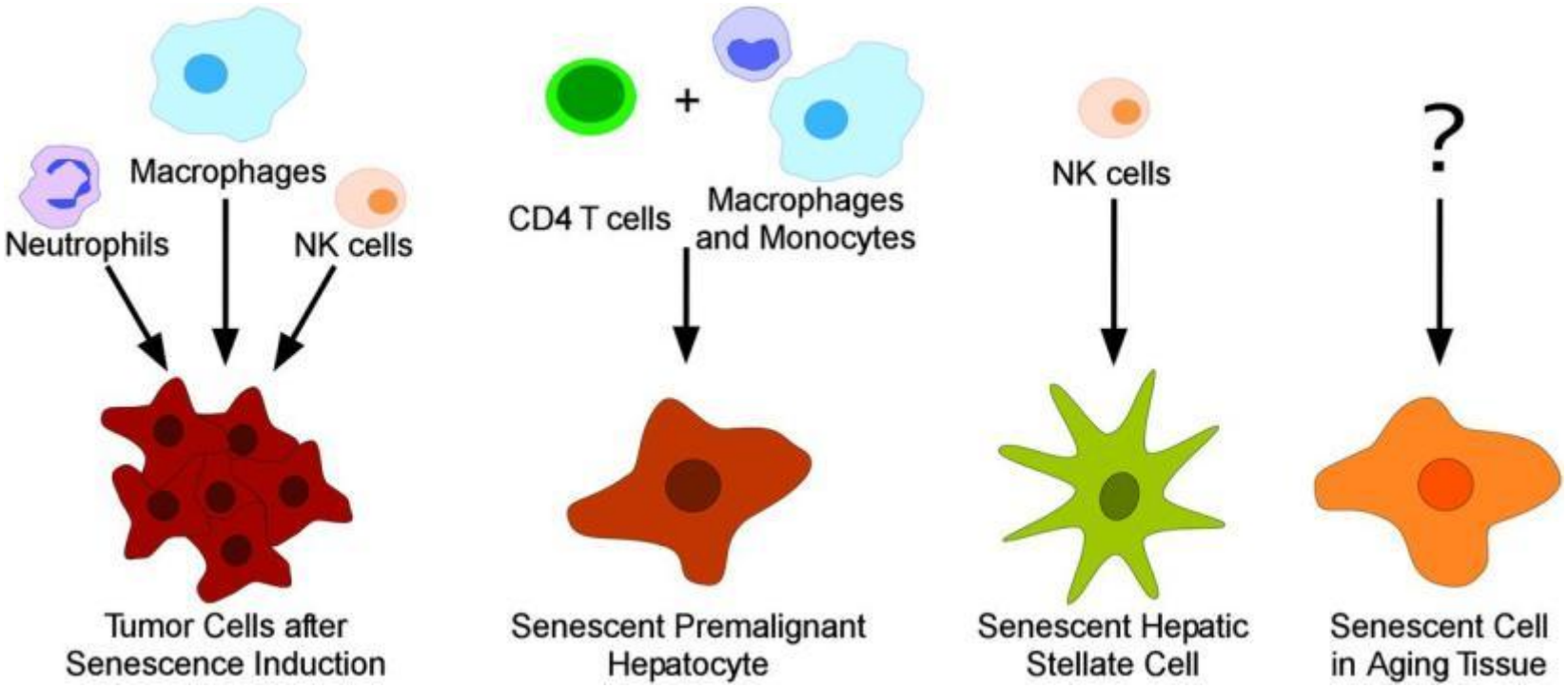
Immunosurveillance

- Le système immunitaire:
  - contrôle le développement des cellules tumorales
  - effectue une sélection darwinienne de clones cellulaires faiblement immunogènes
  - contrôle la phase d'équilibre



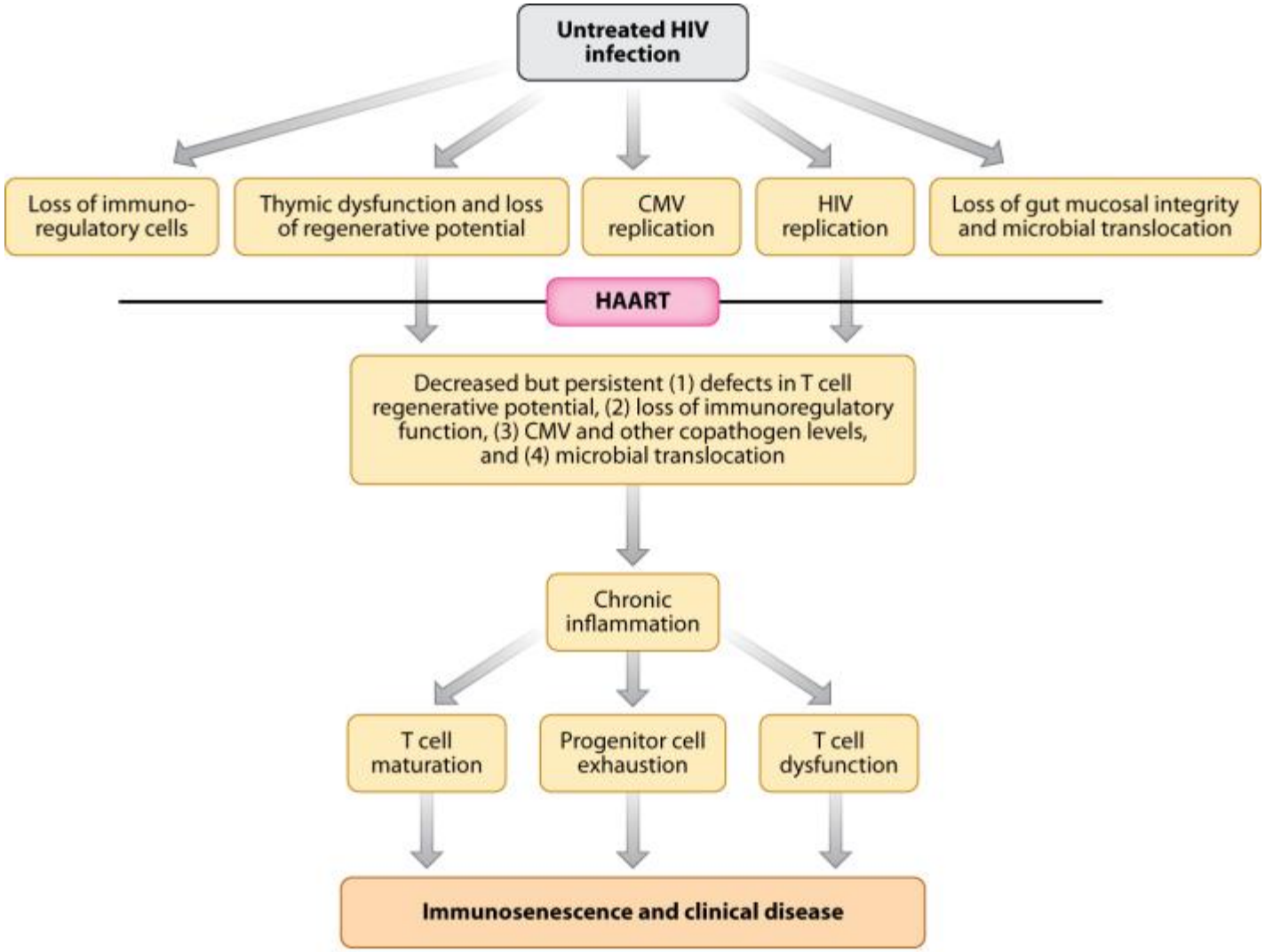
Zitvogel, Tesniere, Kroemer, Nat Rev Immunol 2006

Schematic representation of immune responses against senescent cells in different disease settings.



Hoenicke L , Zender L Carcinogenesis 2012;33:1123-1126

Carcinogenesis



Deeks SG. 2011.
Annu. Rev. Med. 62:141–55

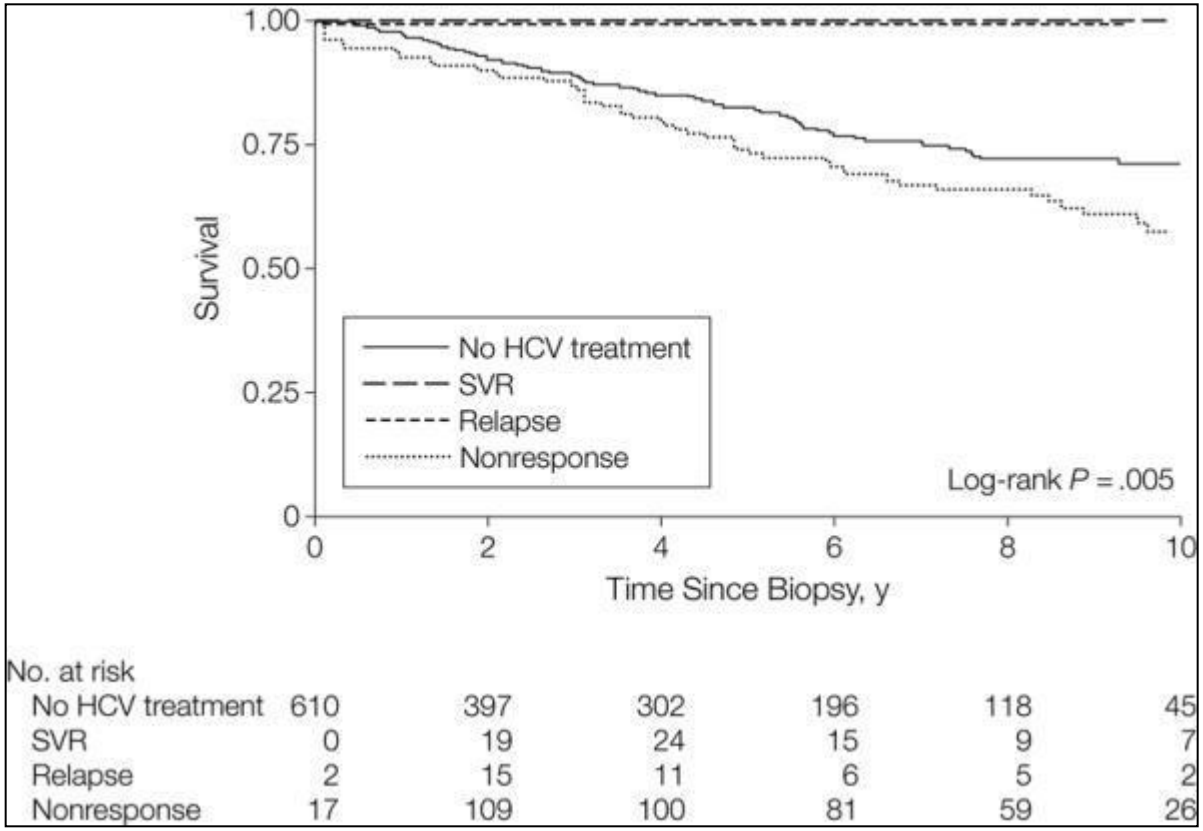
	Hodgkin's lymphoma (n=149)		Lung cancer (n=207)		Liver cancer* (n=119)			
					Model 1		Model 2	
	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
CD4 count (cells per µL)								
≥500	1·0	<0·0001	1·0	<0·0001	1·0	<0·0001	1·0	<0·0001
350–499	1·2 (0·7–2·2)	..	2·2 (1·3–3·6)	..	2·0 (0·9–4·5)	..	1·6 (0·7–3·9)	..
200–349	2·2 (1·3–3·8)	..	3·4 (2·1–5·5)	..	4·1 (2·0–8·2)	..	4·1 (1·9–8·7)	..
100–199	4·8 (2·8–8·3)	..	4·8 (2·8–8·0)	..	7·3 (3·5–15·3)	..	5·9 (2·6–13·3)	..
50–99	7·7 (3·9–15·2)	..	4·9 (2·3–10·2)	..	6·6 (2·4–17·6)	..	5·0 (1·6–15·7)	..
0–49	5·4 (2·4–12·1)	..	8·5 (4·3–16·7)	..	7·6 (2·7–20·8)	..	4·3 (1·1–15·8)	..
Age (years)								
<30	1·0	0·16	1·0	<0·0001	1·0	<0·0001	1·0	<0·0001
30–39	1·5 (0·7–3·0)	..	2·1 (0·5–8·7)	..	2·4 (0·3–18·2)	..	1·5 (0·2–11·8)	..
40–49	1·0 (0·4–2·1)	..	7·0 (1·7–28·2)	..	6·6 (0·9–48·9)	..	4·3 (0·6–31·6)	..
50–59	0·7 (0·3–1·9)	..	14·1 (3·4–57·7)	..	15·6 (2·0–119·3)	..	14·7 (1·9–112·0)	..
≥60	1·2 (0·4–3·4)	..	28·4 (6·9–118·0)	..	26·6 (3·3–212·8)	..	25·2 (3·1–203·6)	..
Sex and exposure group								
MSM	1·0 (0·7–1·6)	<0·0001	0·7 (0·5–1·1)	<0·0001	0·8 (0·5–1·5)	<0·0001	1·0 (0·5–2·0)	<0·0001
IDU	0·8 (0·5–1·3)	..	1·6 (1·1–2·5)	..	3·8 (2·1–6·7)		1·4 (0·7–2·9)	..
Not MSM, not IDU men	1·0	..	1·0	..	1·0		1·0	..
Not IDU women	0·2 (0·1–0·4)	..	0·3 (0·2–0·6)	..	0·2 (0·1–0·5)		0·2 (0·1–0·7)	..
Migration from sub-Saharan Africa	0·7 (0·3–1·4)	0·26	0·4 (0·2–0·9)	0·005	1·8 (0·9–3·6)	0·14	2·0 (0·9–4·0)	0·14
Hepatitis co-infection	..	..	..	..	..	..	14·4 (7·1–29·0)	<0·0001

Age and CD4 cell count are time-varying covariables. Pearson χ^2 was 1·45 (p=0·23) for Hodgkin's lymphoma, 1·57 (p=0·21) for lung cancer, and 1·73 (p=0·19) for liver cancer. RR=rate ratio. MSM=men who have sex with men. IDU=injecting-drug user. *For liver cancer, two multivariable models were studied: without (model 1) or with (model 2) adjustment for hepatitis co-infection.

Table 4: **Multivariable analysis of factors associated with three non-AIDS-defining cancers based on Poisson regression models**

Guiguet M Lancet Oncology 2009

Figure 2.



No. at risk						
No HCV treatment	610	397	302	196	118	45
SVR	0	19	24	15	9	7
Relapse	2	15	11	6	5	2
Nonresponse	17	109	100	81	59	26

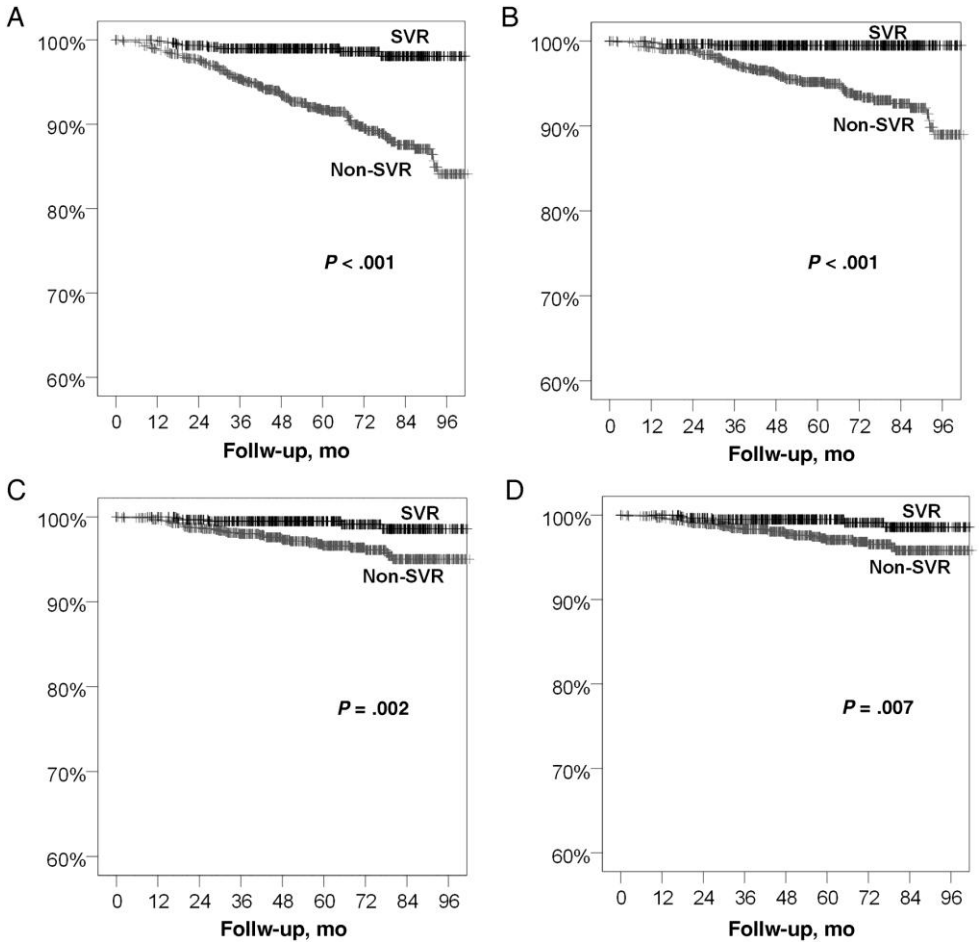
Relationship of Liver Disease Stage and Antiviral Therapy With Liver-Related Events and Death in Adults Coinfected With HIV/HCV.

Limketkai, Berkeley; Mehta, Shruti; Sutcliffe, Catherine; Higgins, Yvonne; MAS, MS; Torbenson, Michael; Brinkley, Sherilyn; MSN, CRNP; Moore, Richard; Thomas, David; MD, MPH; Sulkowski, Mark

JAMA. 308(4):370-378, July 25, 2012.
DOI: 10.1001/jama.2012.7844

Figure 2. Cumulative Survival Free of End-Stage Liver Disease, Hepatocellular Carcinoma, or Death According to Response to Hepatitis C Virus (HCV) Treatment From BaselineHepatitis C virus treatment was considered as a time-varying covariate because individuals could undergo multiple courses of treatment during follow-up with different outcomes. SVR indicates sustained virologic response.

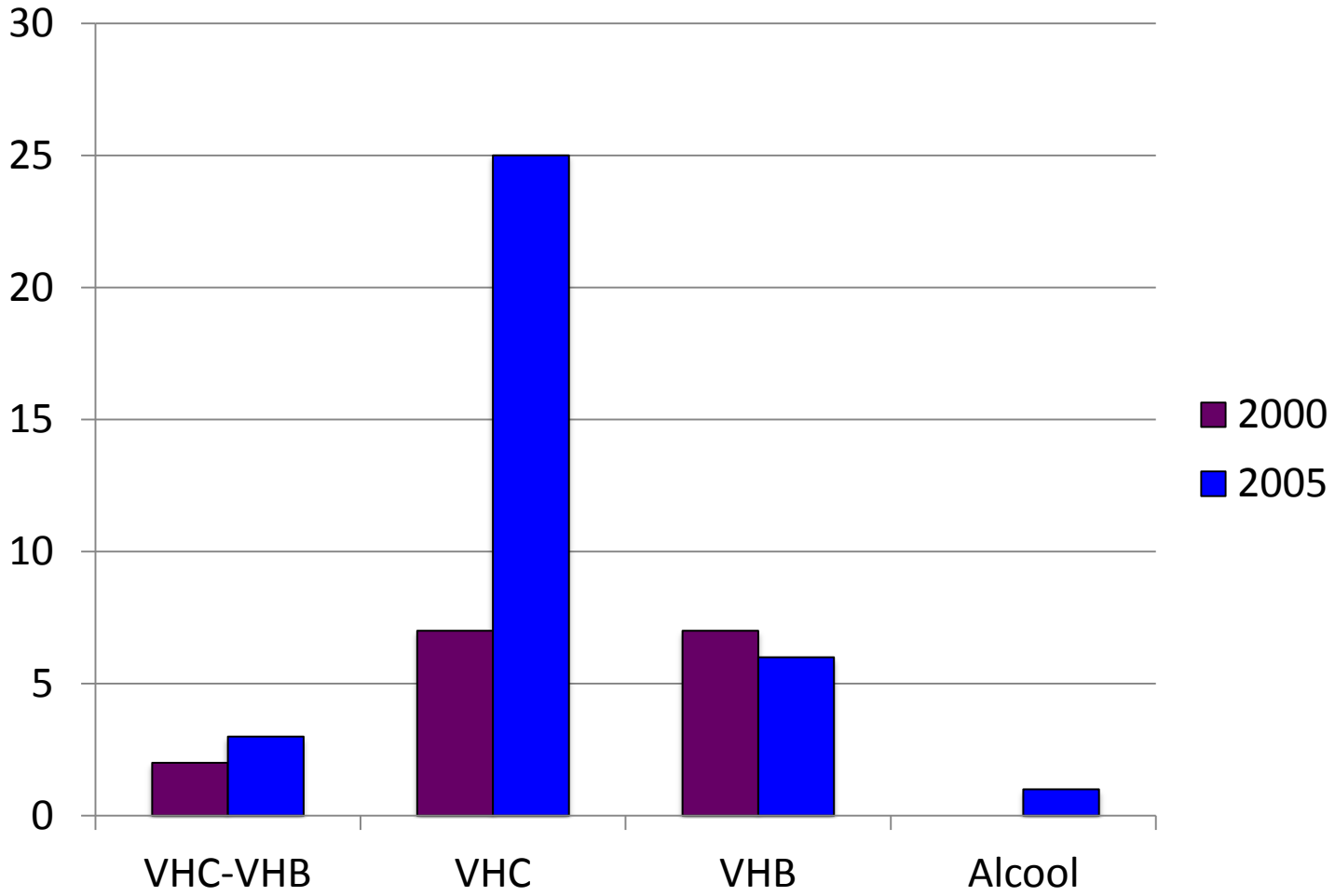
Kaplan-Meier curves showing the occurrence of overall deaths (A), liver-related deaths (B), non–liver related deaths (C), and non–liver-related, non–AIDS-related deaths (D) in 1599 patients coinfected with human immunodeficiency virus and hepatitis C virus, with or without sustained virological response after therapy with interferon plus ribavirin.



Berenguer J et al. Clin Infect Dis. 2012;55:728-736

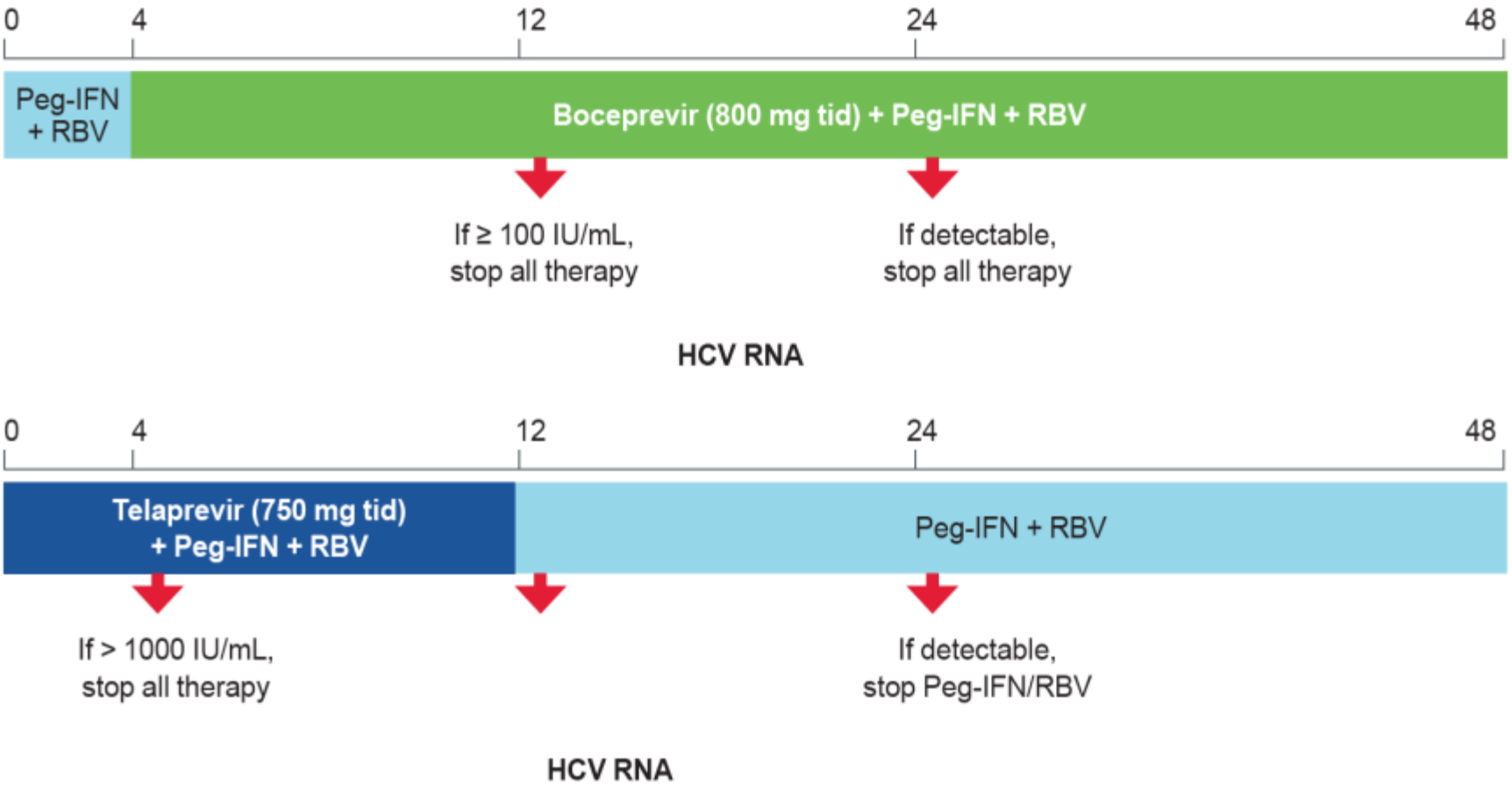
Clinical Infectious Diseases

Nombre de décès rapportés au CHC (cohorte Mortalité 2000-2005)



Salmon D et al. J Hepatol 2009

Use of boceprevir or telaprevir in HIV/HCV-coinfected individuals



Therapy should be stopped if there is a confirmed increase in HCV RNA by 1log10 following a decline at any stage.

EACS Guidelines, novembre 2012
Ingiliz P, Rockstroh J. Liver Int. 2012

Conclusion: il faut traiter vite tous les patients VIH VHC

- Surtout ceux contaminés avant HAART
- VIH avant HAART
  - Sénescence immune prématurée
  - Défaut de contrôle de la tumorigenèse
  - Vitesse de progression de la fibrose accrue
- Poids des comorbidités (alcool) à prendre en compte
- Il faut adapter au VIH les recommandations de l'AFEF