

Histoire et traitement de l' infection virale C

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Versailles
12.10.2017

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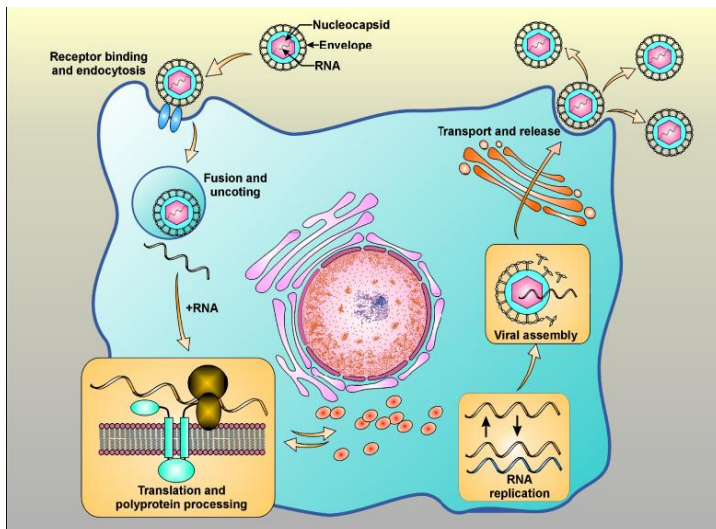
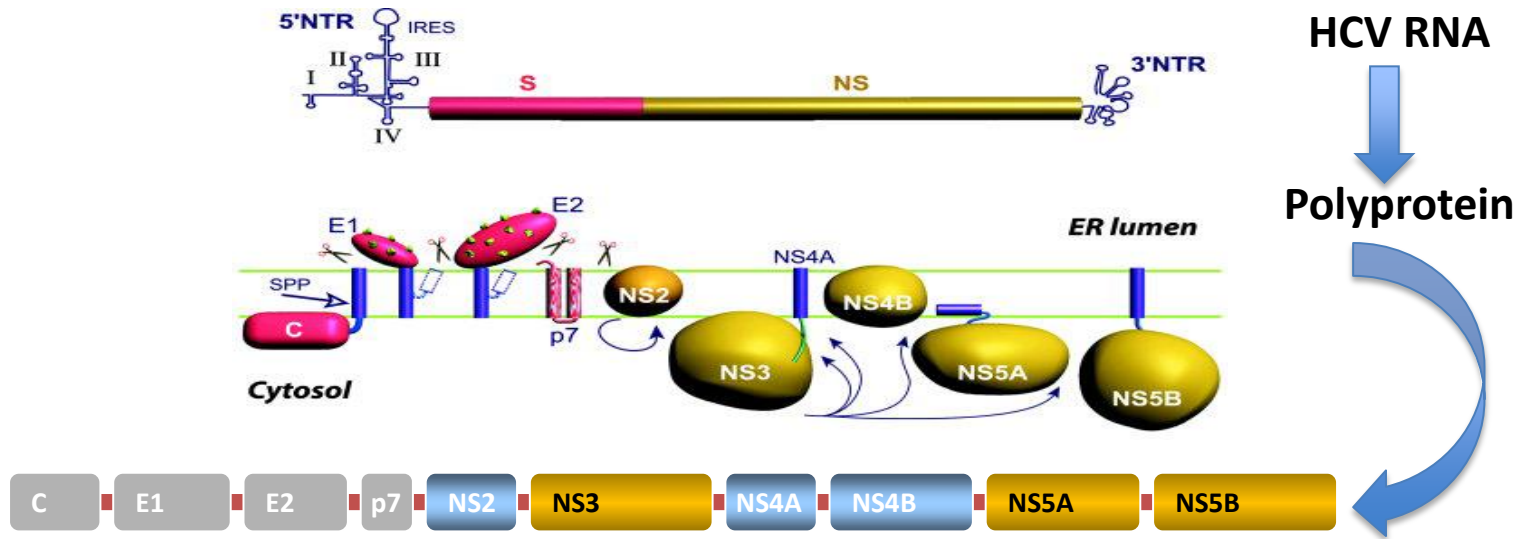
Liens d'intérêts

Speaker : GSK, BMS, Boehringer Ingelheim, Janssen Gilead, Roche, MSD, Sanofi, Novartis, Vertex, Abbvie

Grants : BMS, Gilead, Roche, MSD

Board member : GSK, BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, Abbvie

Non-A non-B: découverte du VHC en 1988



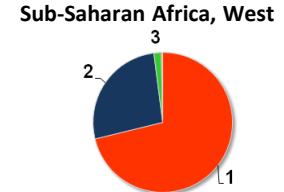
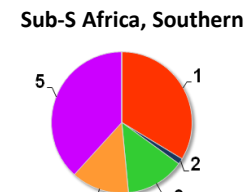
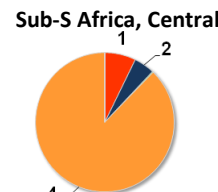
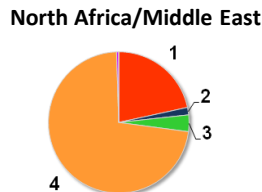
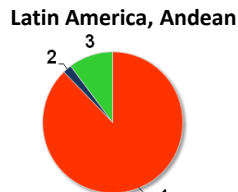
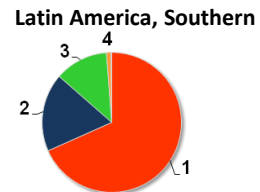
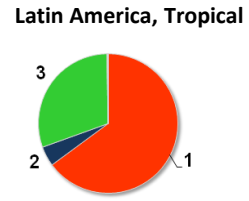
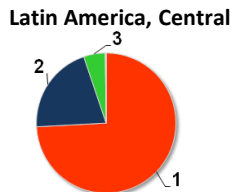
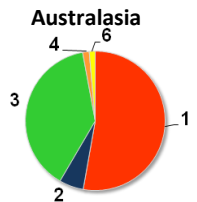
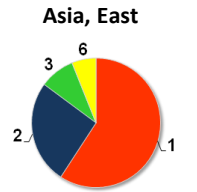
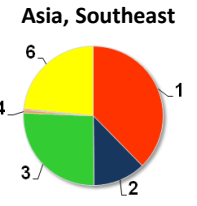
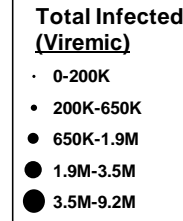
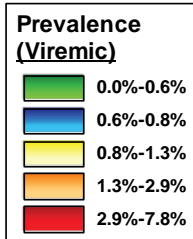
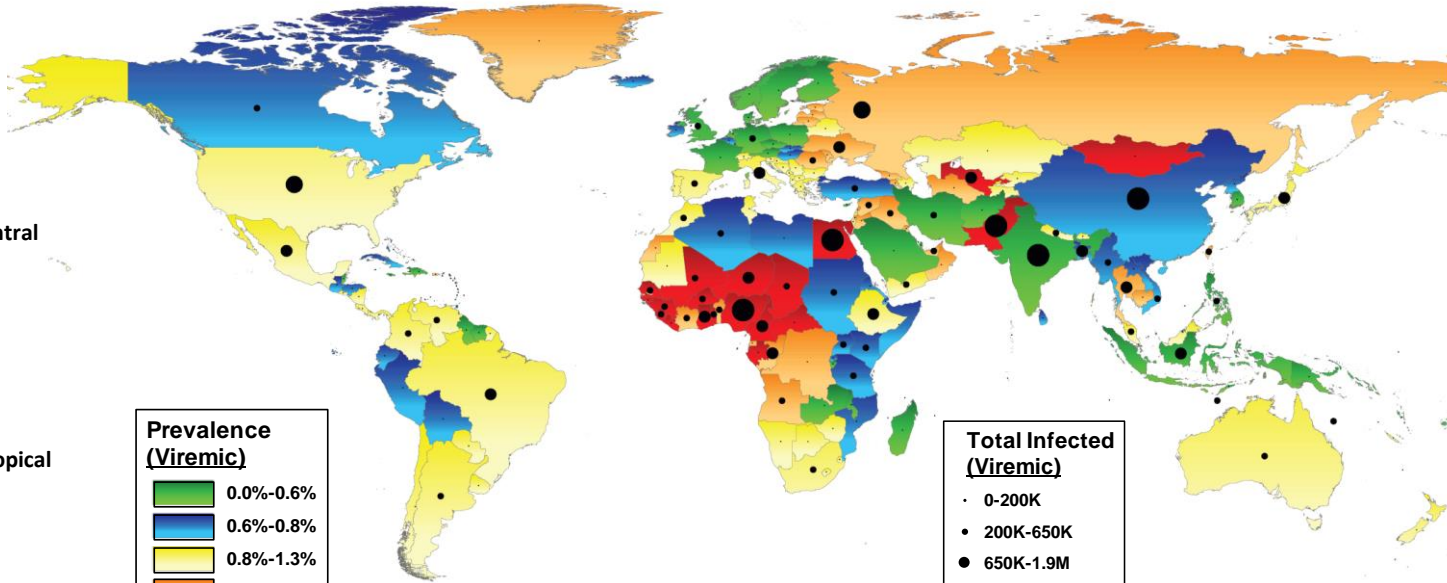
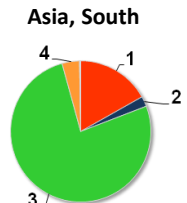
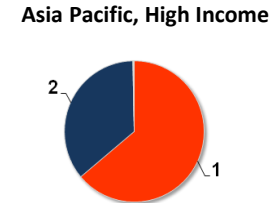
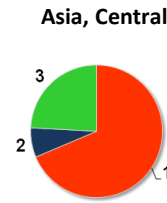
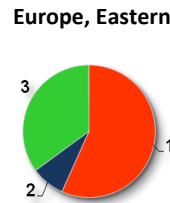
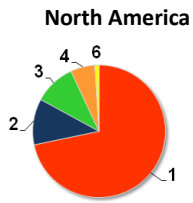
Histoire et traitement de l' infection virale C

- **Pourquoi traiter?**
- **Qui traiter?**

Histoire et traitement de l' infection virale C

- **Pourquoi traiter?**
 - Infection chronique fréquente
 - Manifestations hépatiques et extra-hépatiques: maladie systémique
 - Infection chronique curable
 - Bénéfices associés à la guérison

Prévalence du VHC et distribution génotypique

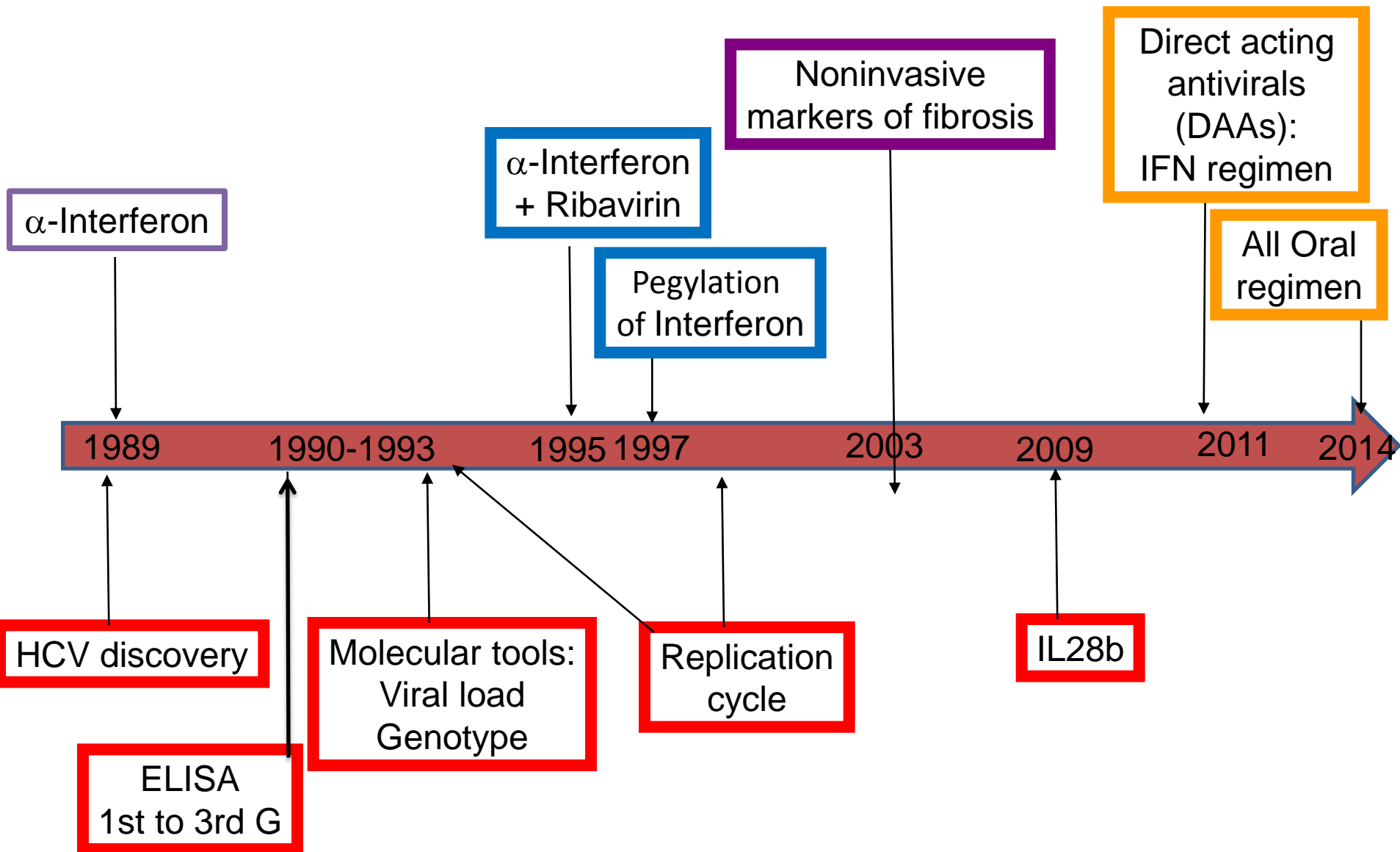


Estimated global prevalence : ~ 3% (71,000,000)

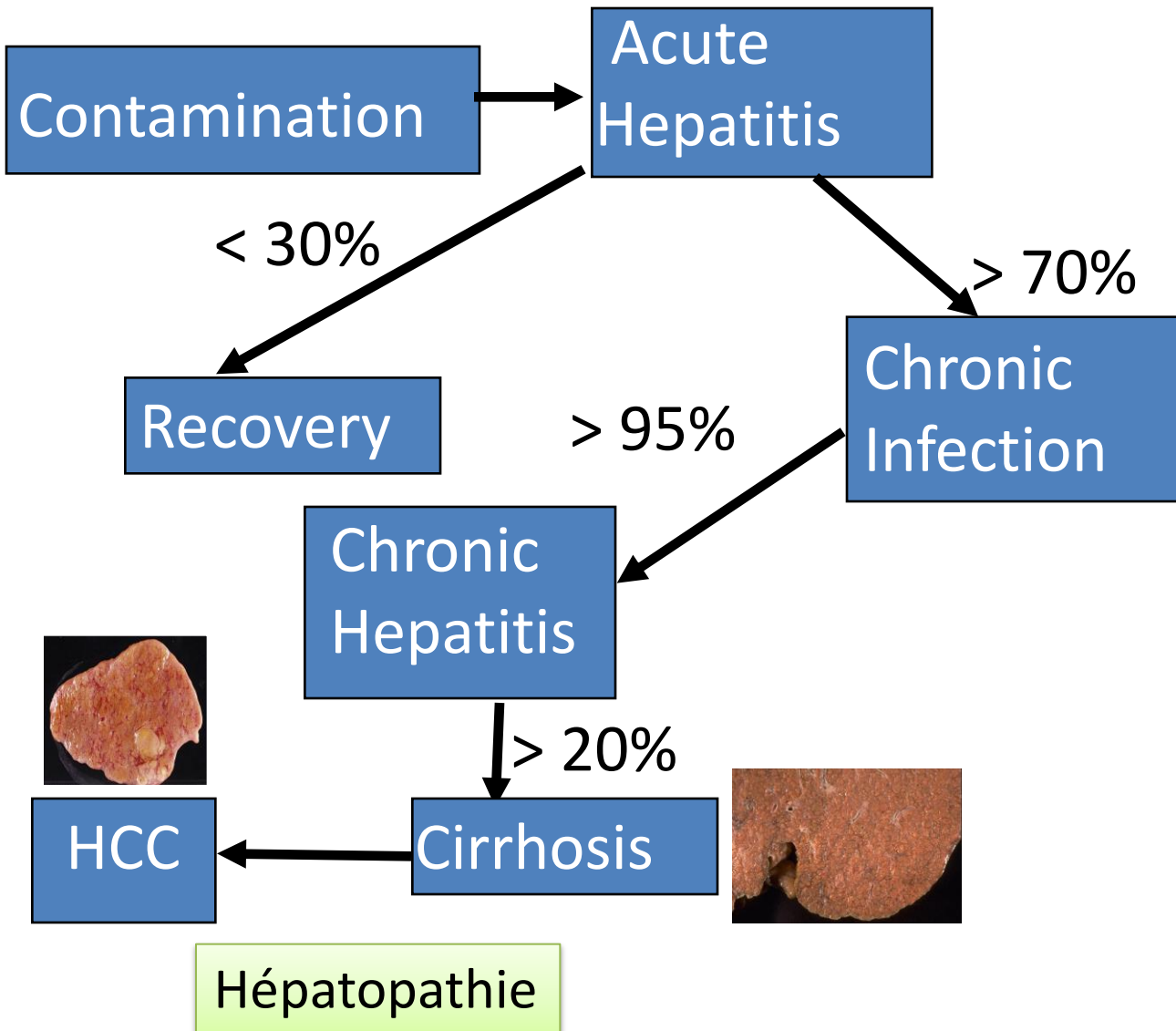
~ 0.3-3 % in EU

7 genotypes GT1 to 7

Histoire du VHC: 25 ans de la découverte à la guérison

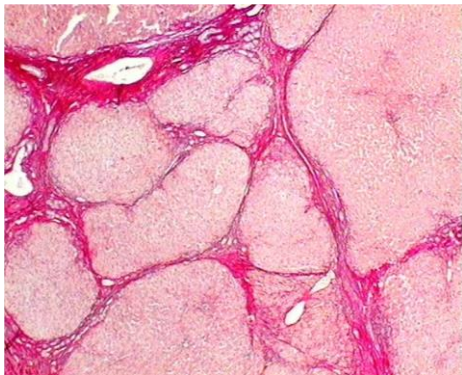
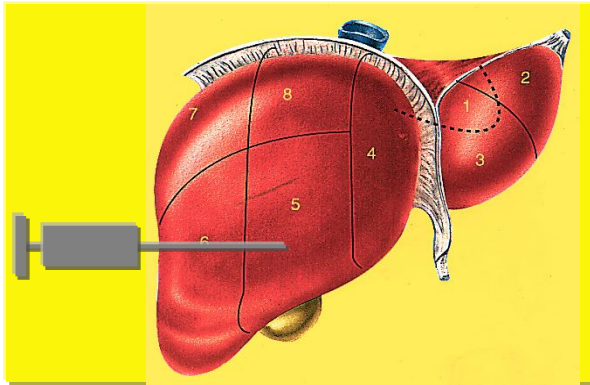


L'infection virale C chronique: une maladie systémique

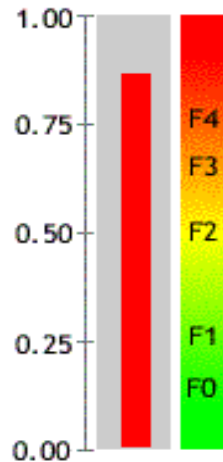


Evaluation de la fibrose: de la biopsie aux tests non invasifs de fibrose

Liver biopsy



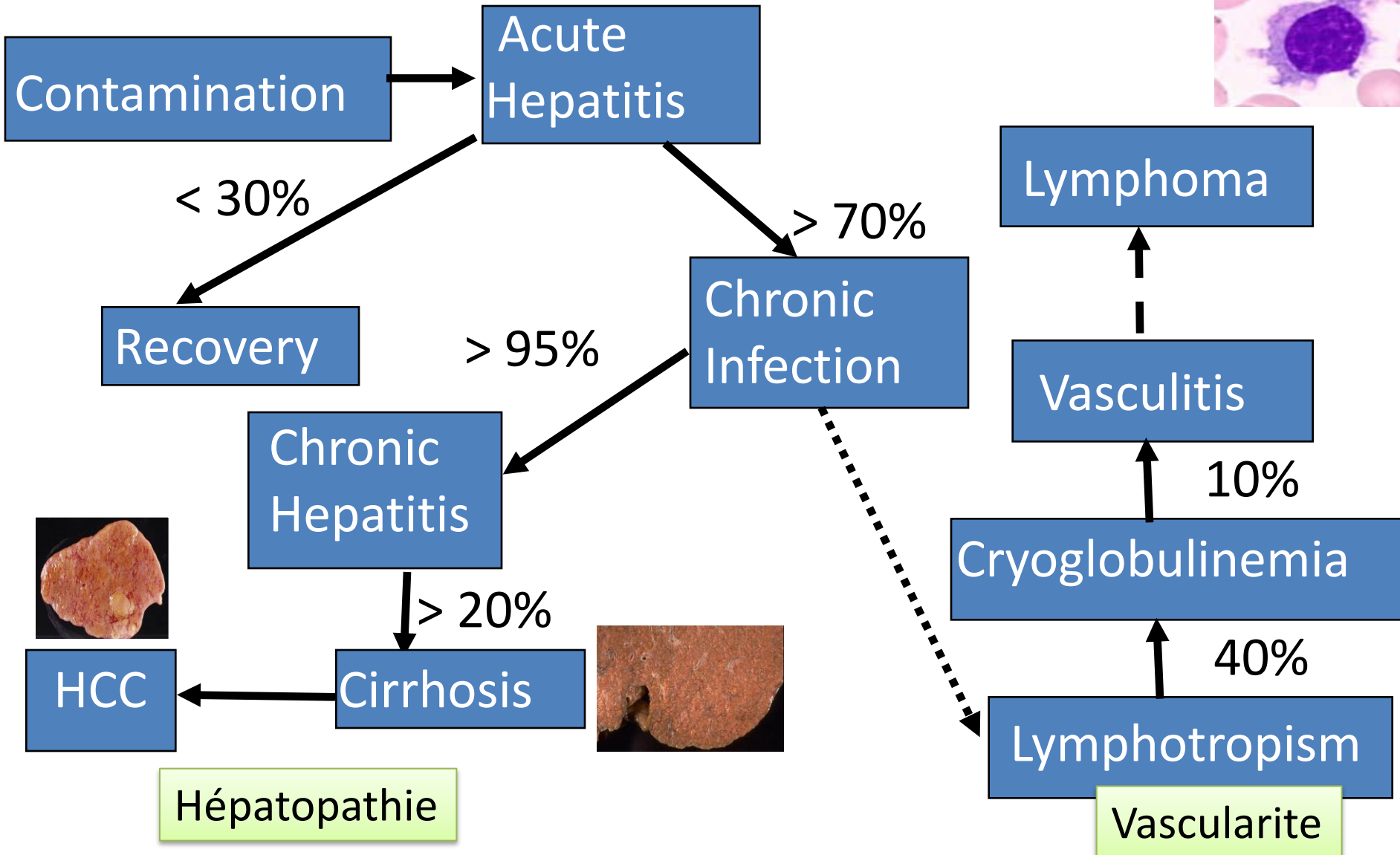
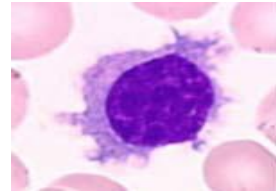
Blood Tests



Fibroscan

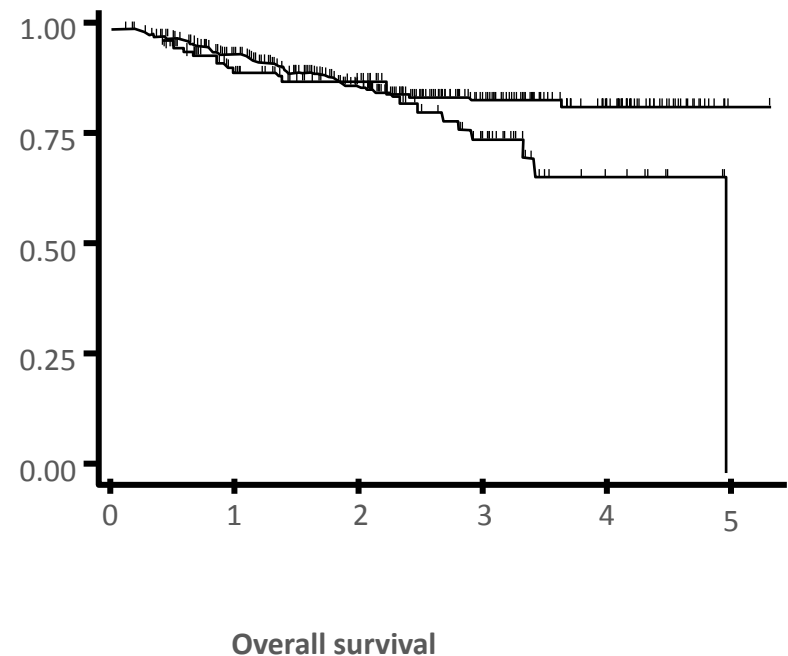
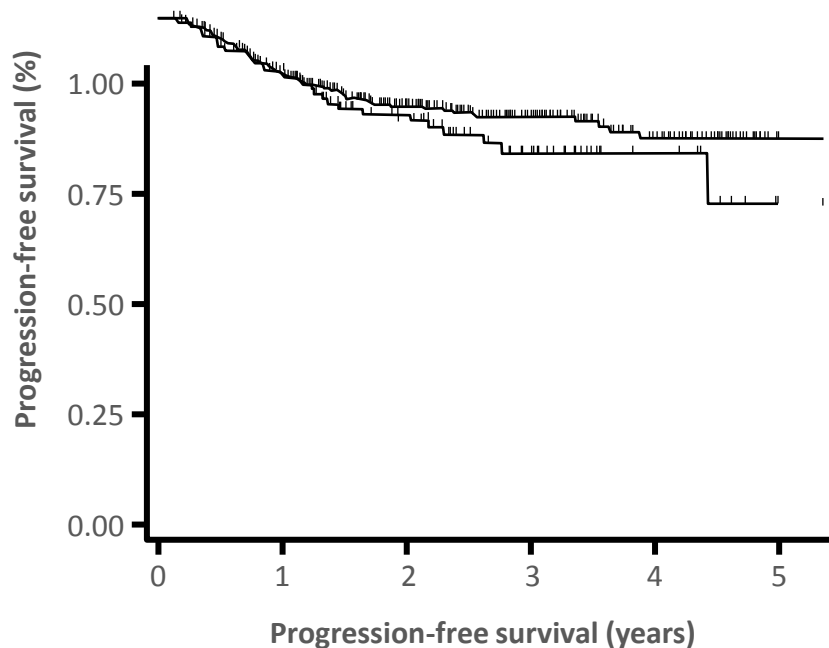


L'infection virale C chronique: une maladie systémique



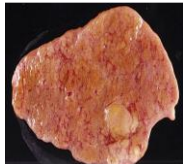
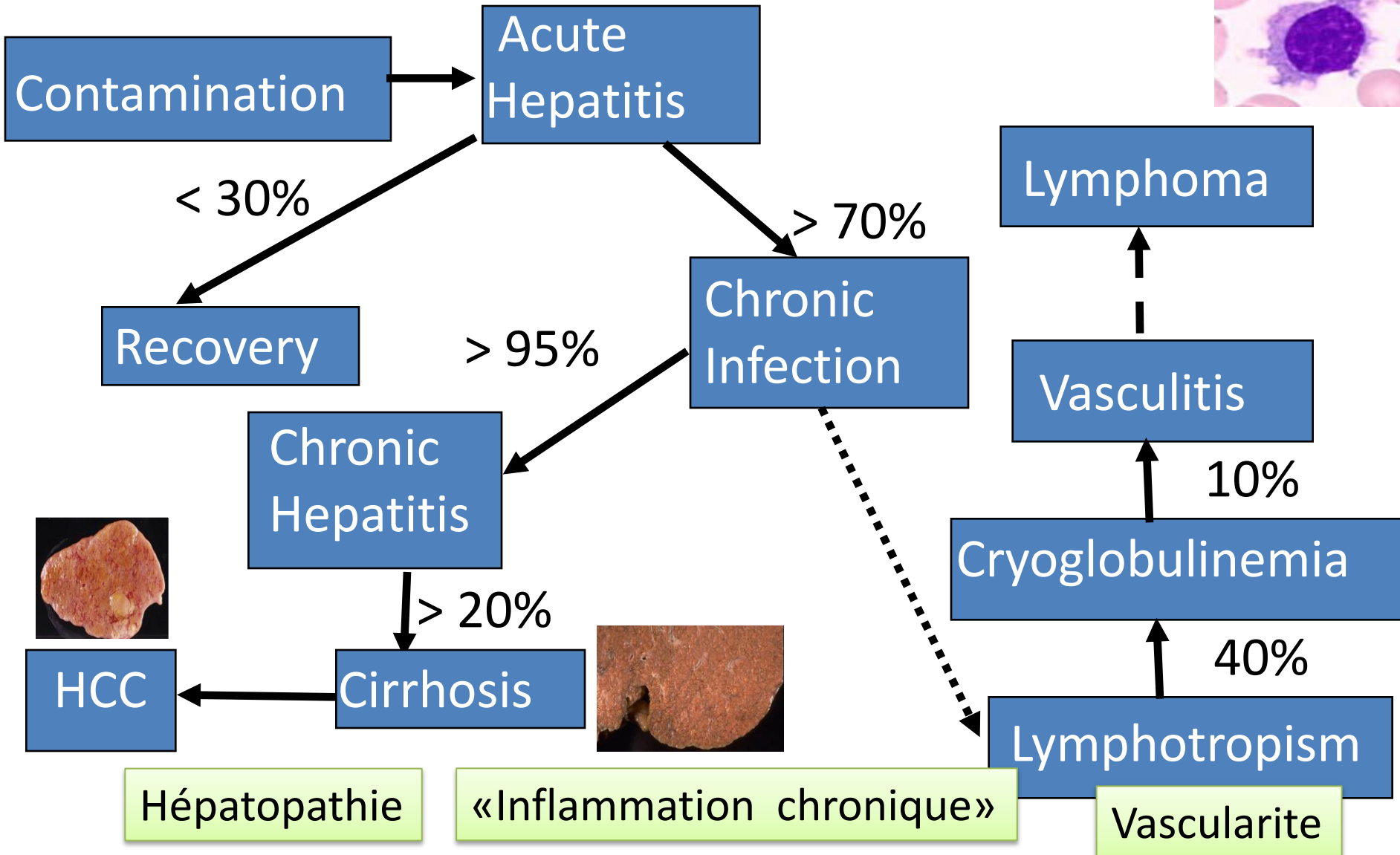
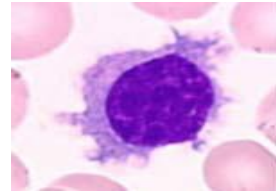
Effets du VHC sur risque et pronostic du LNH diffus

- Japanese patients (n=553) with diffuse large B-cell lymphoma
- 422 HCV negative; 131 HCV positive
- Median follow-up 31–32 months
- Treated with rituximab + multiagent chemotherapy

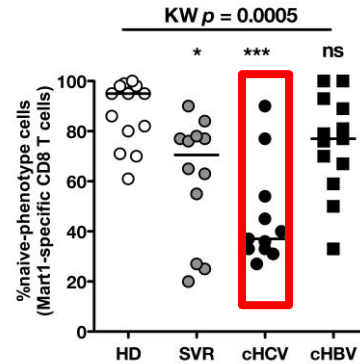
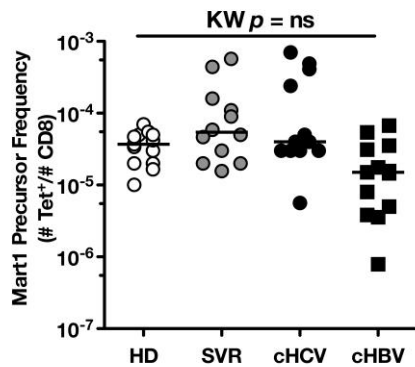


- Tolerability (ALT and AST elevation) was worse in patients with HCV

L'infection virale C chronique: une maladie systémique

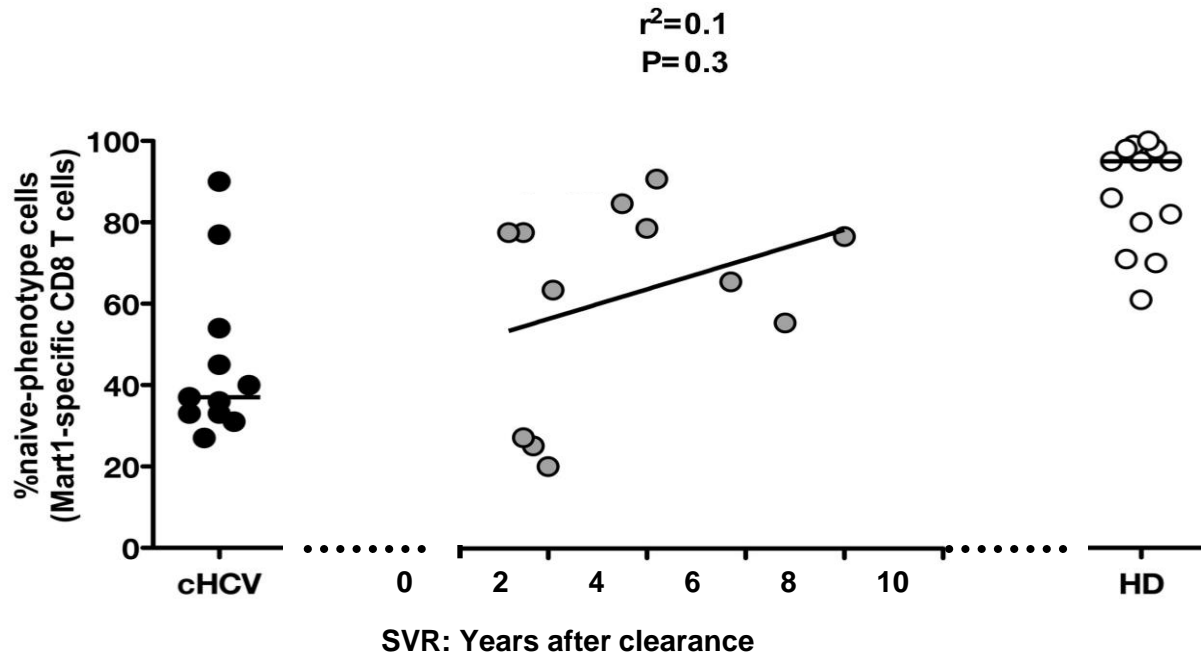


Altérations du répertoire pré-immun et VHC



Antigen-inexperienced CD8 T cell populations show a memory-phenotype

Qualitative alterations of the preimmune repertoire are slowly reversible



VHC et mortalité extra-hépatique

Significant association between HCV and:

- **diabetes** (OR = 1.8)
- **cardio-vascular morbidity** (OR=2.37)
- **cerebro-vascular mortality** (OR= 2.7)
- **renal disease** (HR for ESRD < 59 y= 7.8 vs. 3.2)
- **extra-hepatic cancers**

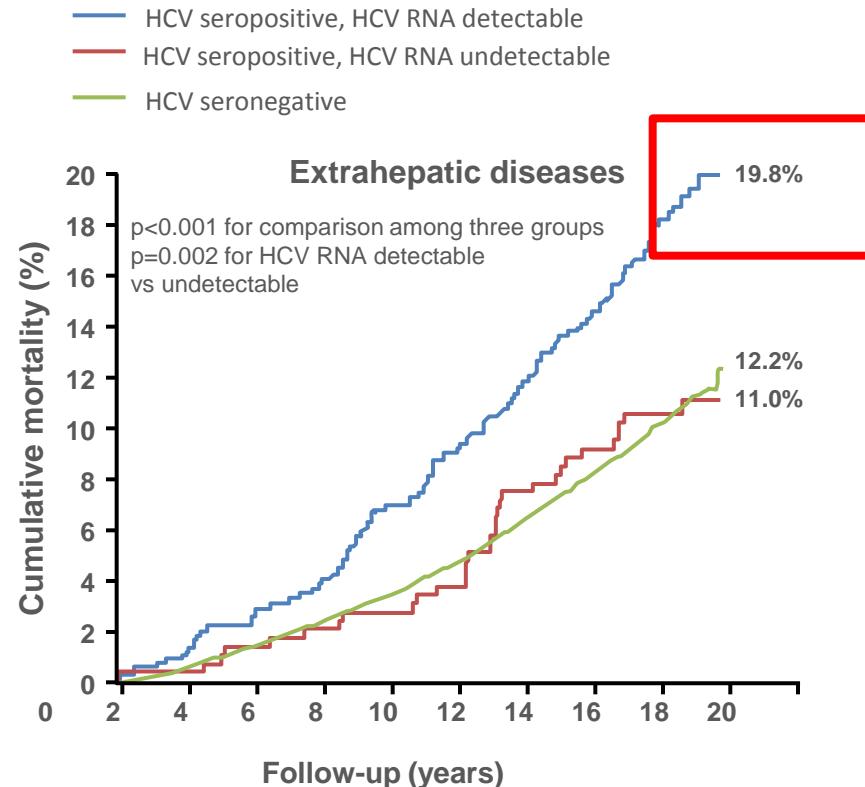
White D et al. J Hepatol 2008;49:831–844

Kakinami L et al. Int J Clin Pract 2013;67:6–13

Lee M-H et al. Stroke 2010;41:2894–2900

Su F-H et al. Am J Kidney Dis 2012;60:553–560

Su F-H et al. BMC Cancer 2011;11:495

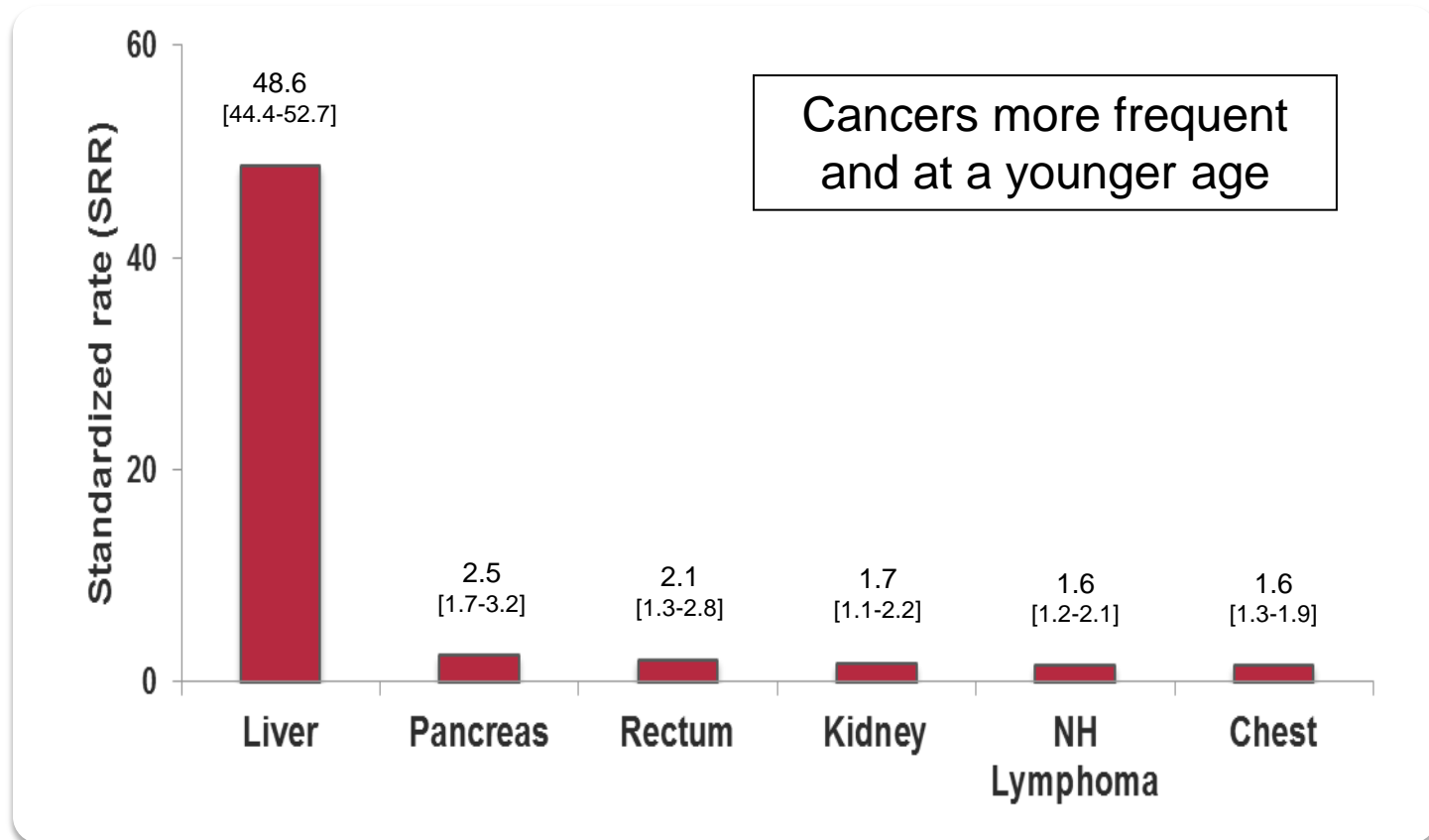


Lee M-H et al, J Infect Dis 2012;206:469–477

VHC & cancer

12,126 HCV+ patients vs. 133,795,000 controls

13 cancer US registries (2006 – 2010)



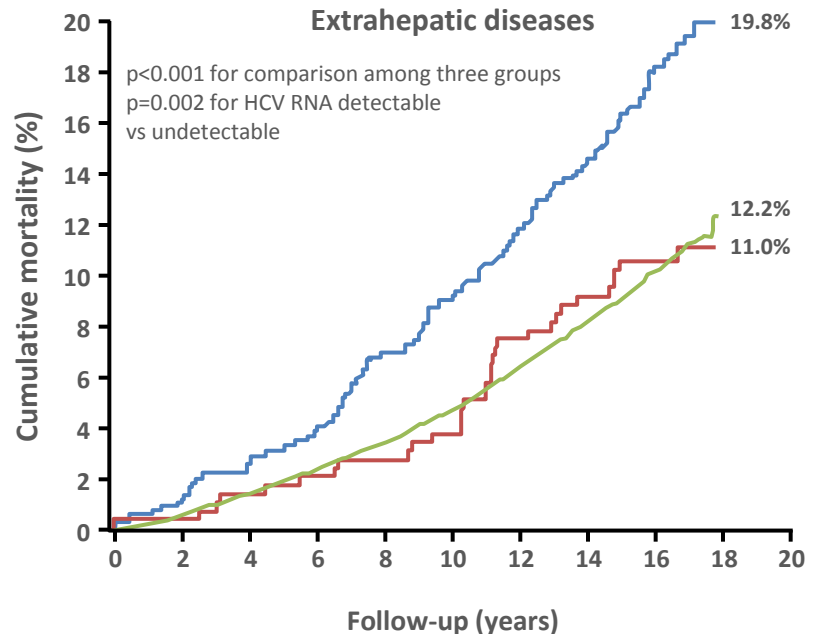
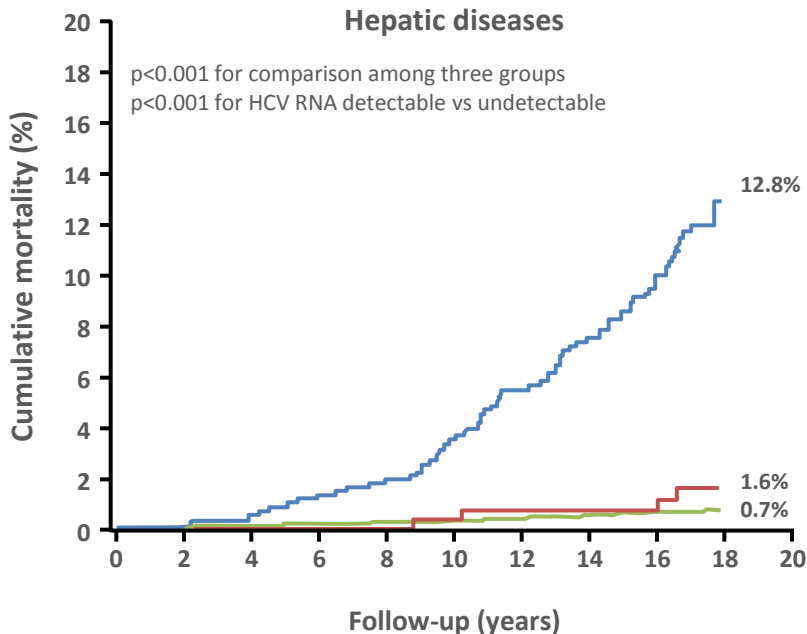
Le VHC augmente la mortalité hépatique et non-hépatique

The REVEAL HCV Cohort Study

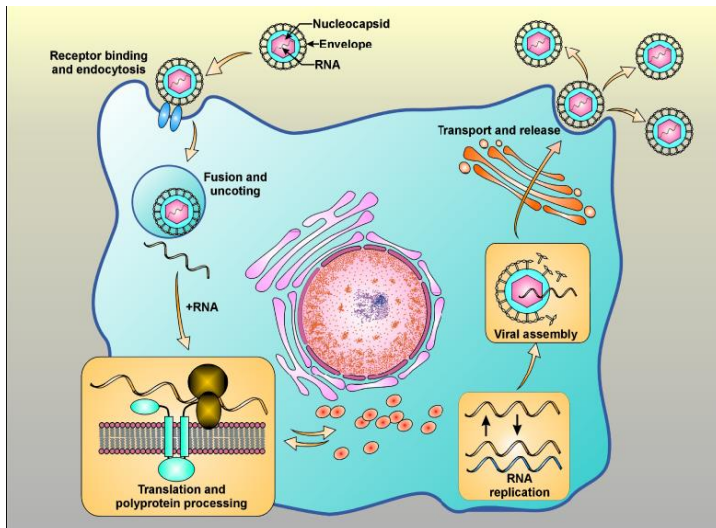
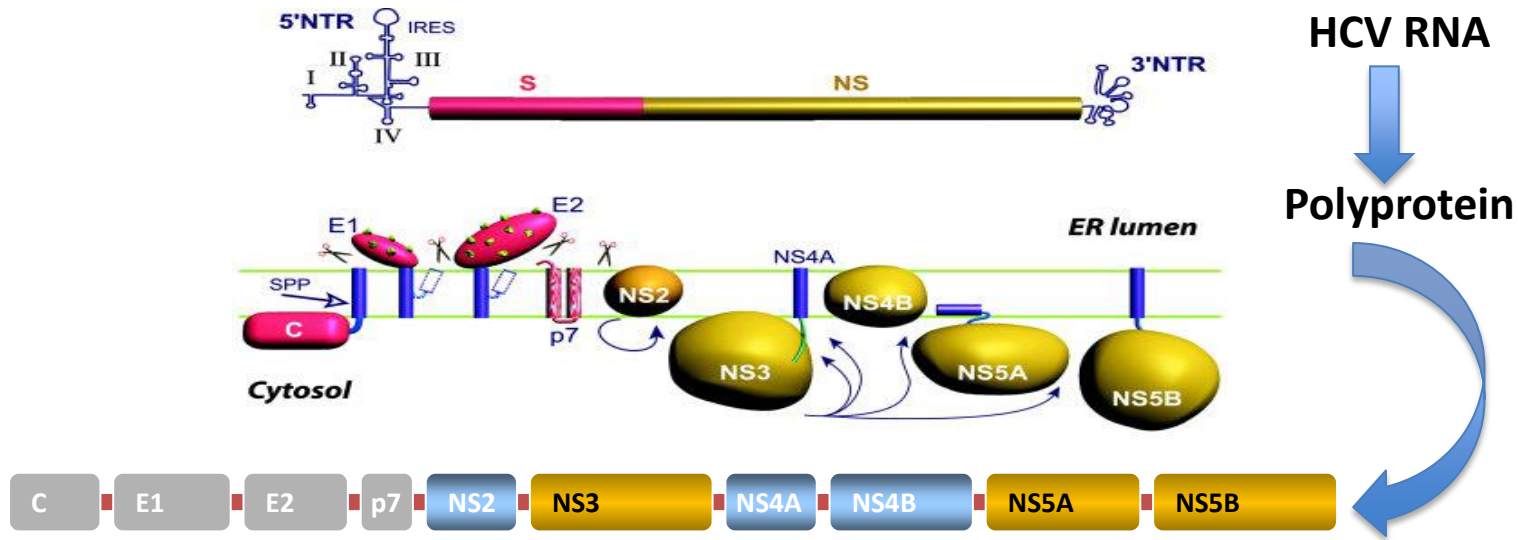
23 820 adults, Taiwan

1095 anti-HCV positive; 69.4% with detectable HCV RNA

- HCV seropositive, HCV RNA detectable
- HCV seropositive, HCV RNA undetectable
- HCV seronegative



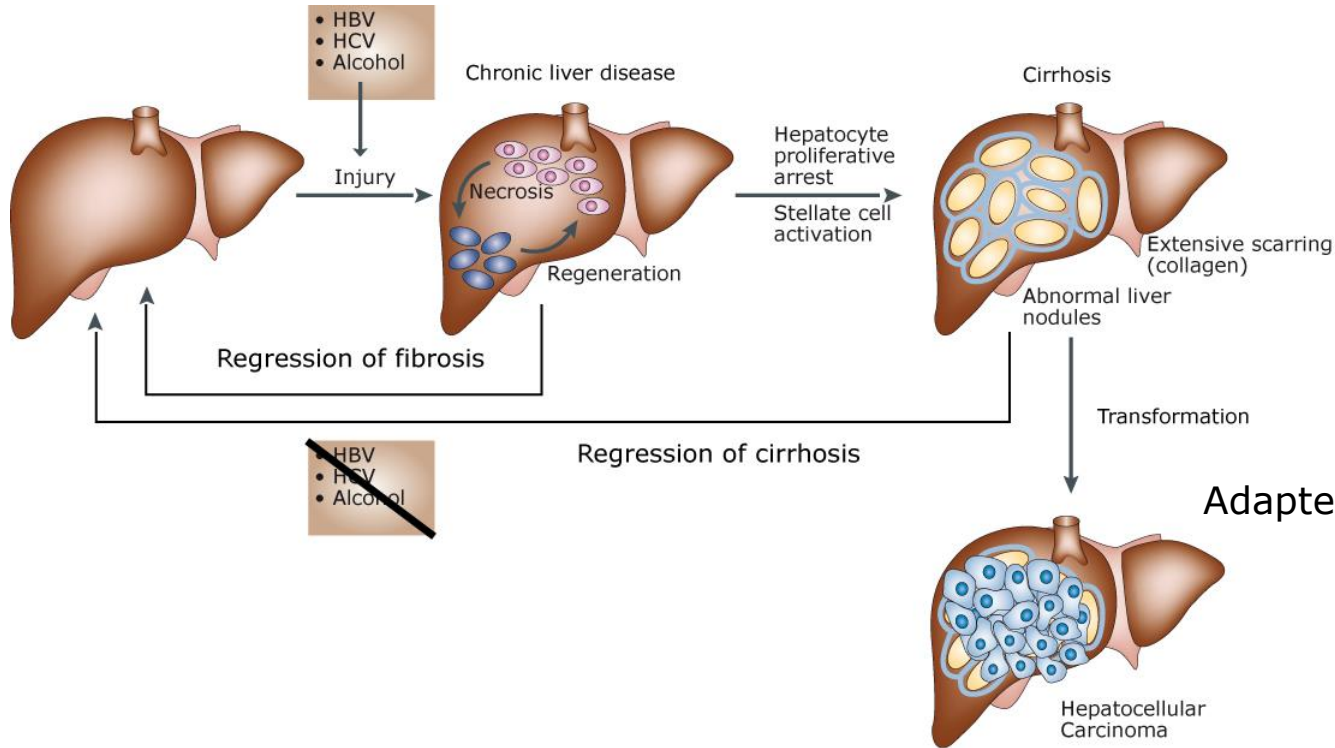
VHC: une biologie simple sans réservoir ni intégration génomique



The sustained virologic response (undetectable HCV RNA 12 weeks after the end of therapy) is a complete cure

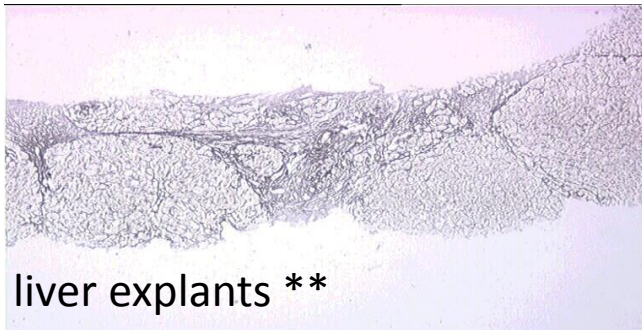
Bénéfices associés à la RVP*

Réversibilité de la cirrhose

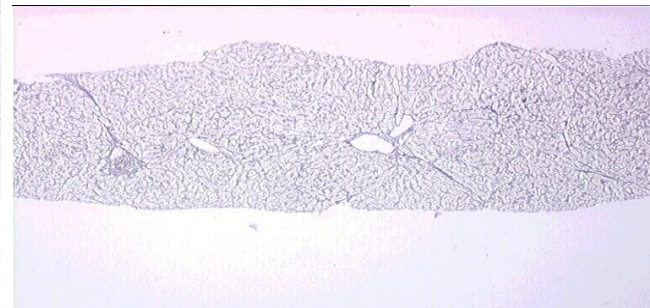


Adapted from Farazi PA et al. 2006

Microscopy*



Macroscopy: liver explants **



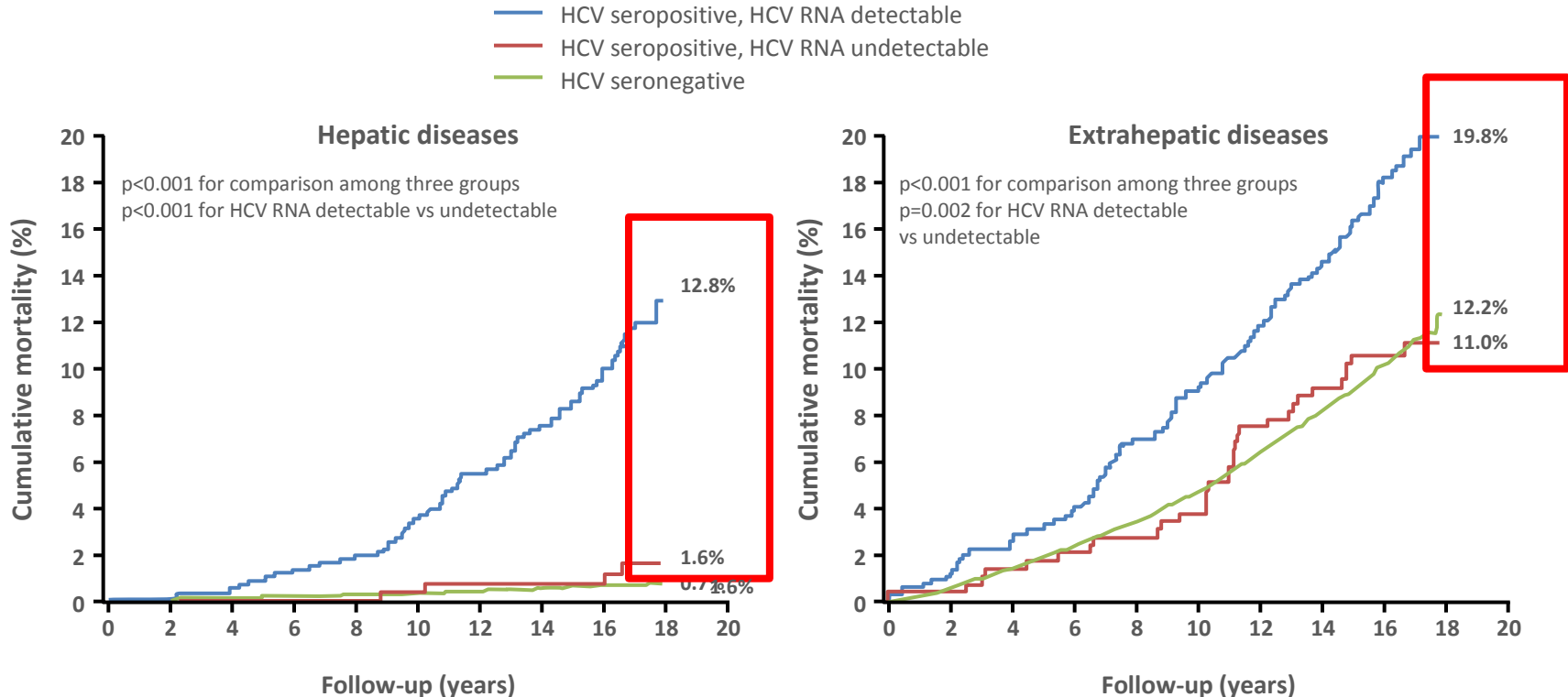
*Pol et al. Human Pathology 2004; **Serpaggi et al. Human Pathology 2007

Le VHC augmente la mortalité hépatique et non-hépatique

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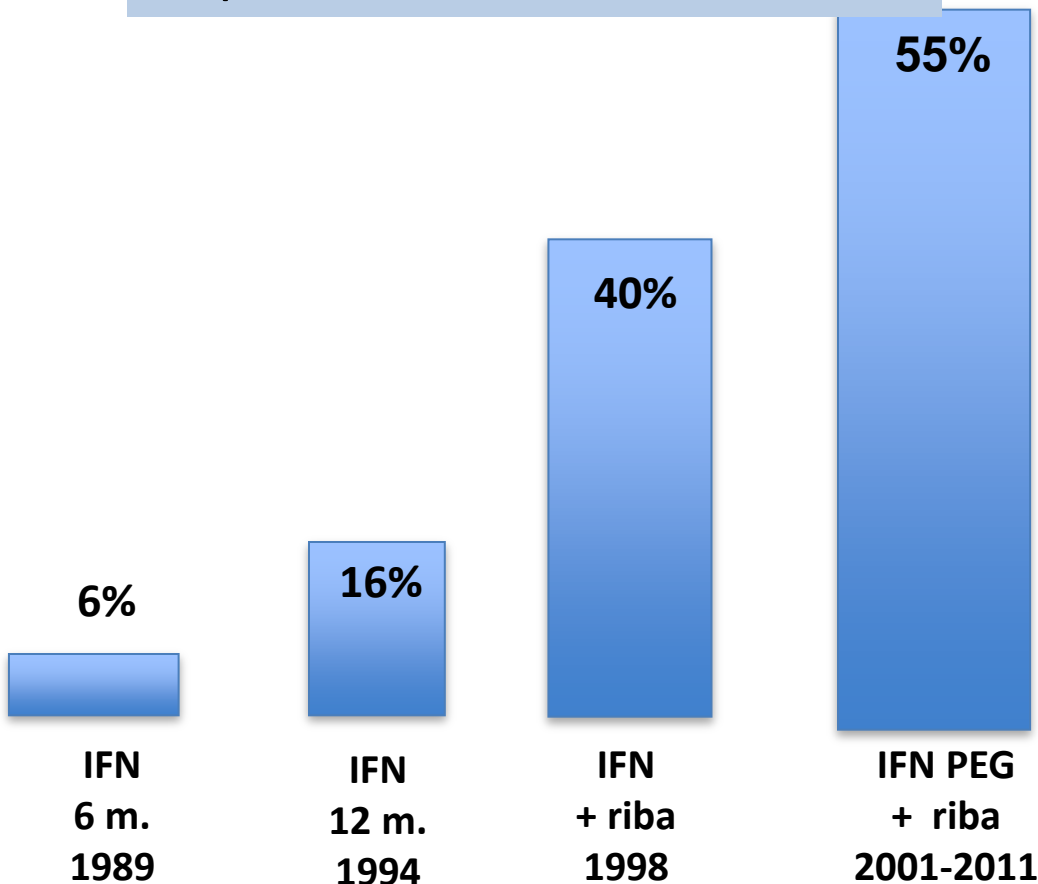


Histoire et traitement de l' infection virale C

- **Pourquoi traiter?**
- **Qui traiter?**

Traitement du VHC chronique : taux de RVP

La pré-histoire de l'Interferon



Predictors of low SVR:

Genotype 1

HIV

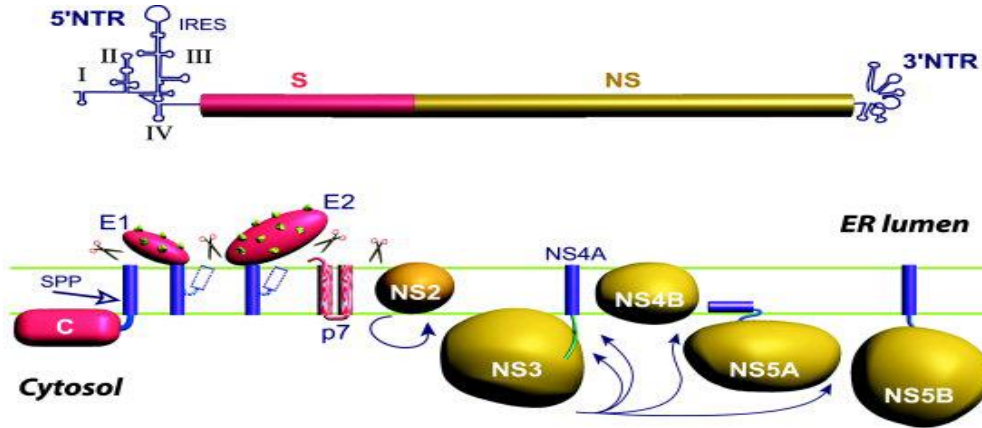
F3/F4

Fatty liver

Metabolic syndrome

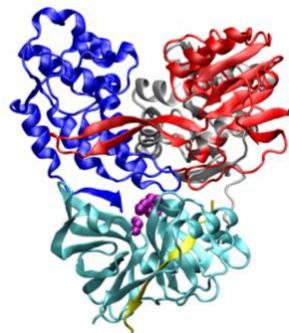
IL28B non CC

Protéines virales du VHC: modélisation des antiviraux directs (AVD)

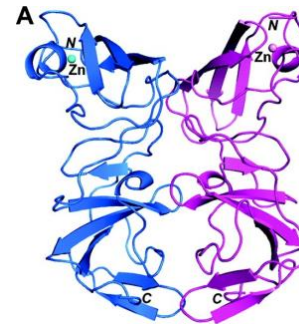


HCV RNA
↓
Polyprotein

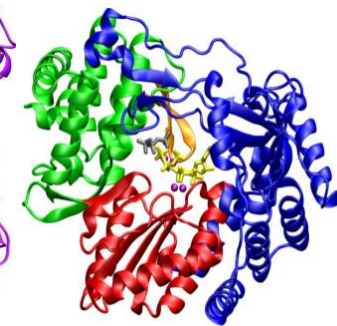
Targets of direct acting antivirals



NS3/4 Protease Inhibitors:
-previr



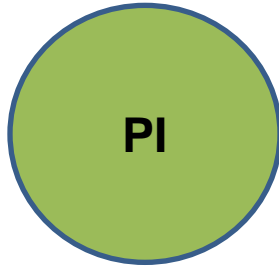
NS5A Replication Complex inhibitors:
-asvir



NS5B Polymerase Inhibitors:
-buvir

AMM des AVD en 2017

IFN-free therapy only



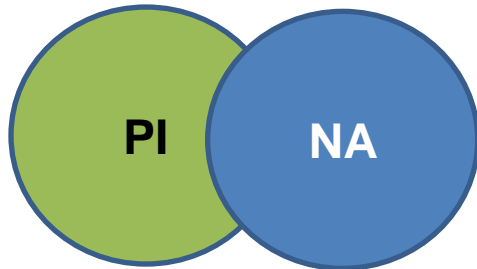
PI
SMV, GZV
GT 1, 4



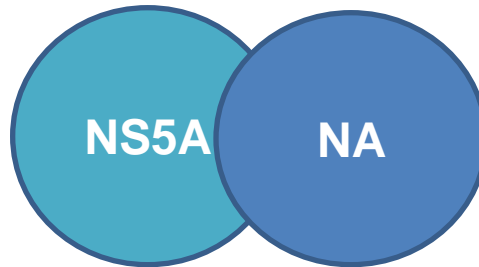
NS5A
DCV, LDV, EBR
GT 1-4



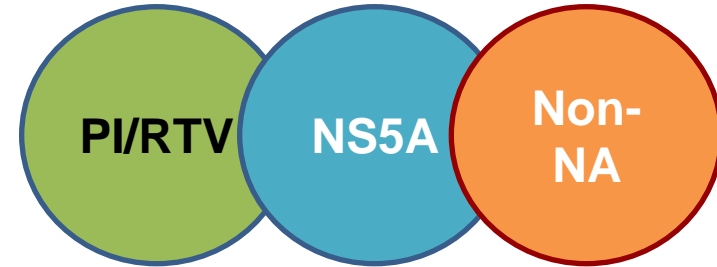
NA
SOF
All GTs



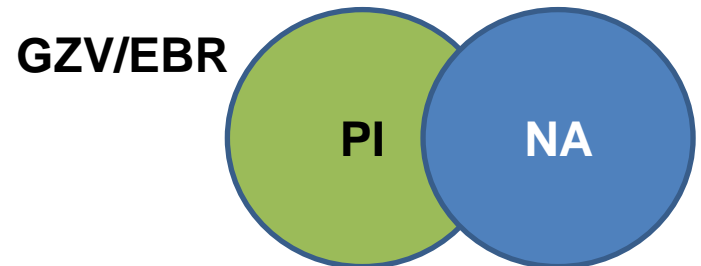
SMV + SOF



LDV/SOF
DCV + SOF
VEL/SOF



OMV/PTV/RTV + DSV

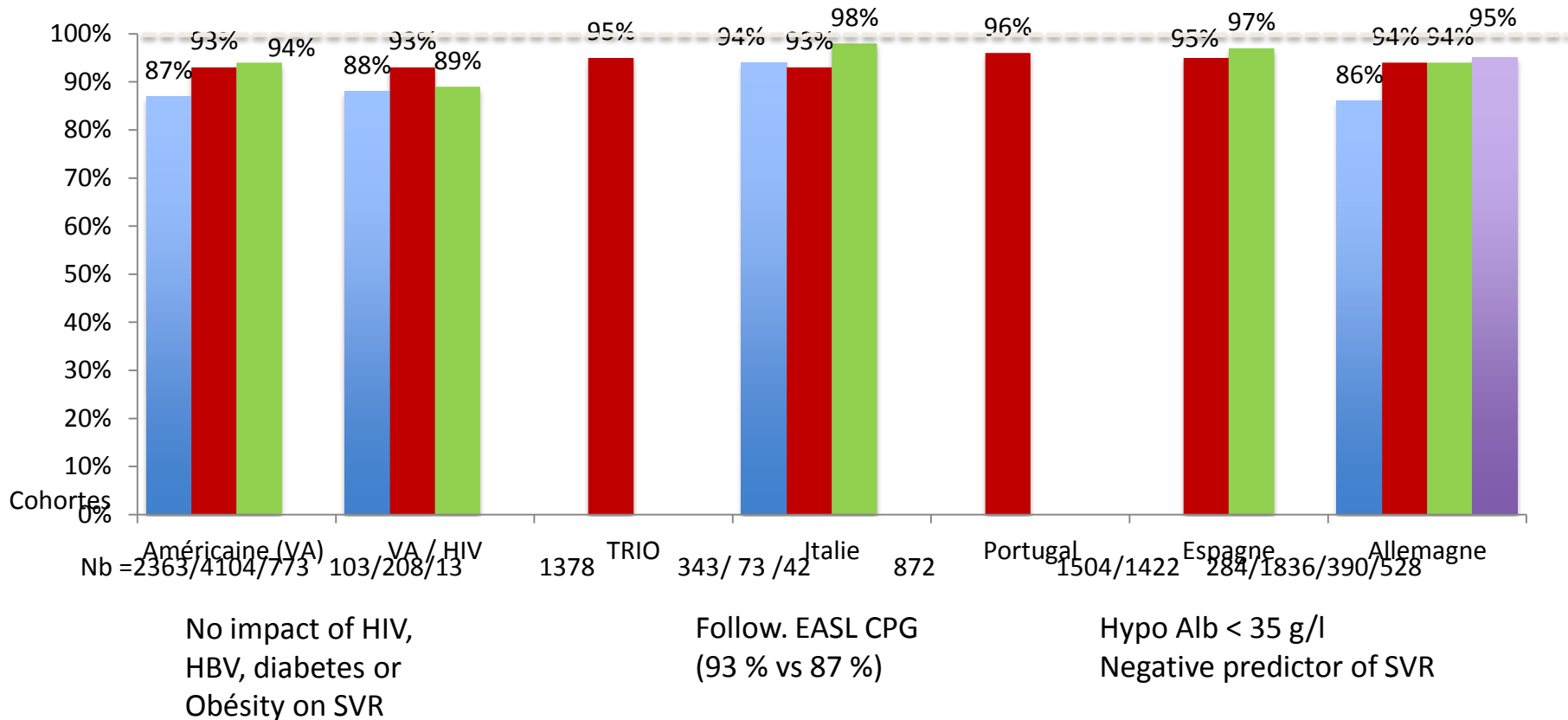


GZV/EBR

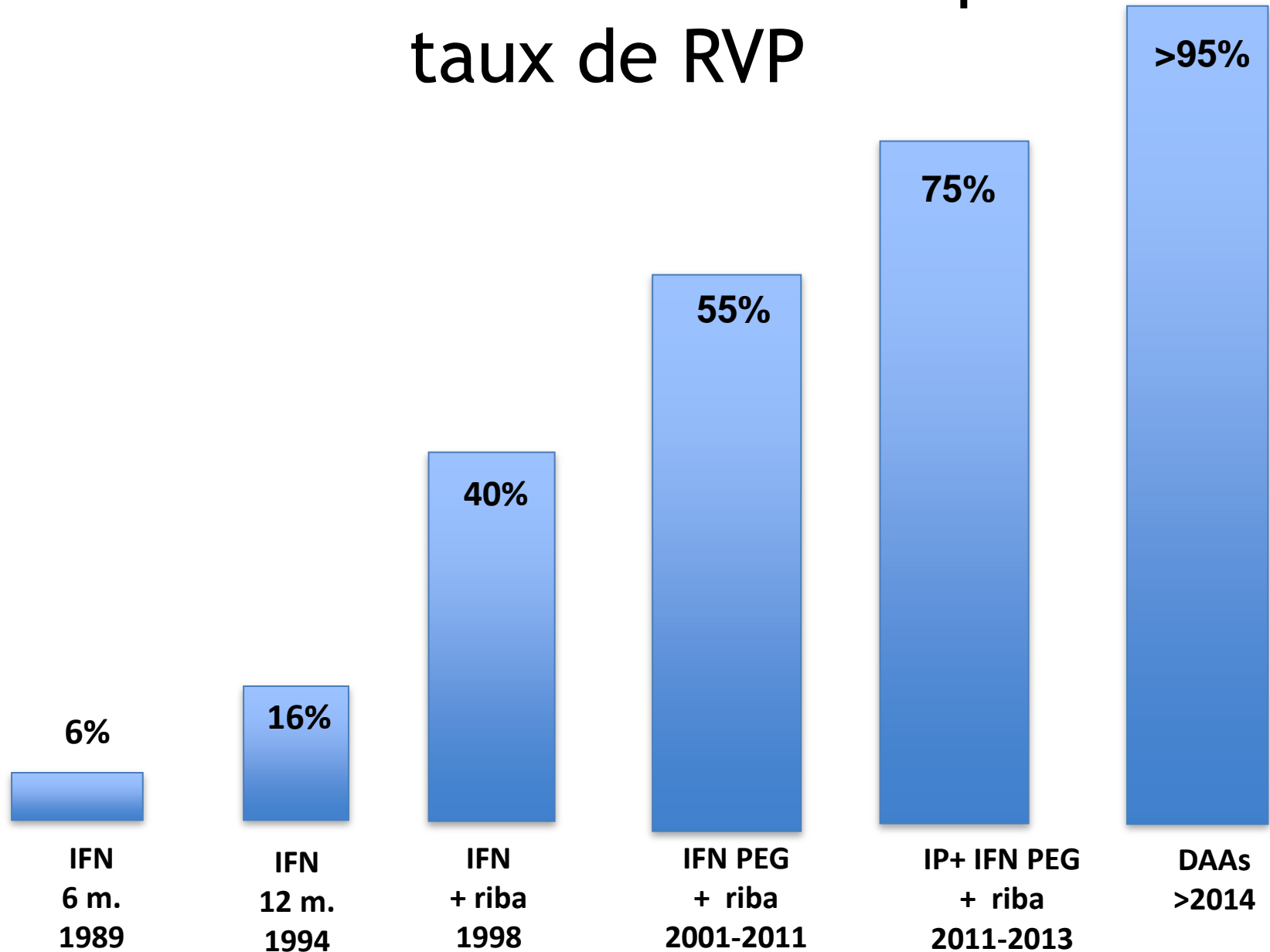
Janssen-Cilag Ltd. OLYSIO[▼] (simeprevir), SmPC, August 2014;
Bristol-Myers Squibb Pharma EEIG. DAKLINZA[▼] (daclatasvir), SmPC, July 2015;
Gilead Sciences Europe Ltd. SOVALDI[▼] (sofosbuvir), SmPC, July 2015;
Gilead Sciences Europe Ltd. HARVONI[▼] (ledipasvir/sofosbuvir), SmPC, July 2015;
AbbVie Ltd. VIEKIRAX[▼] (ombitasvir/paritaprevir/ritonavir), SmPC, January 2015;
AbbVie Ltd. EXVIERA[▼] (dasabuvir), SmPC, January 2015.

Les données de « vraie vie » confirment les essais cliniques: 16 236 patients GT1

■ SIM/SOF ■ SOF/LDV ■ 3D ■ SOF/DCV



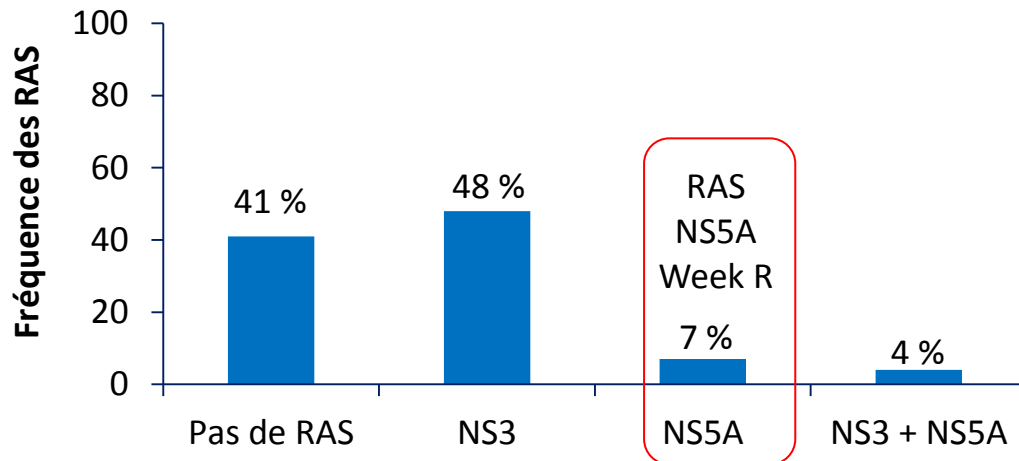
Traitement du VHC chronique : taux de RVP



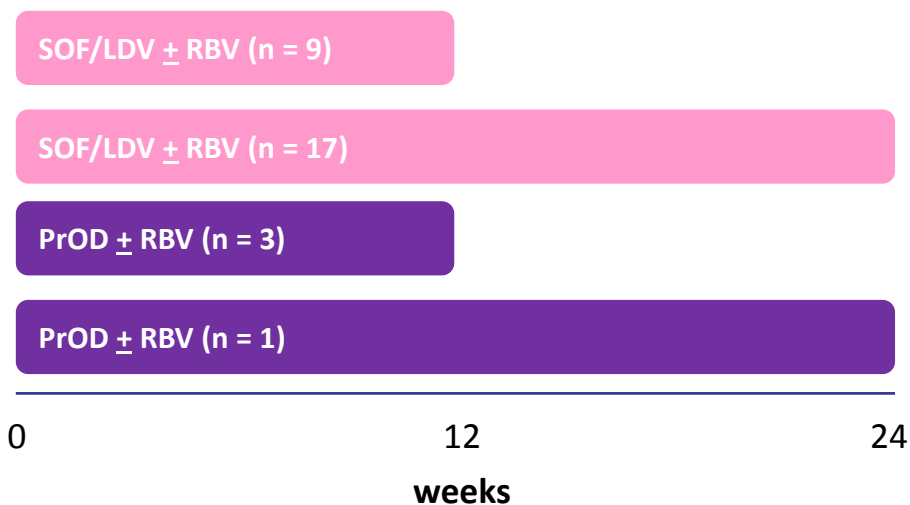
Observatoire de la résistance

Genotype 1

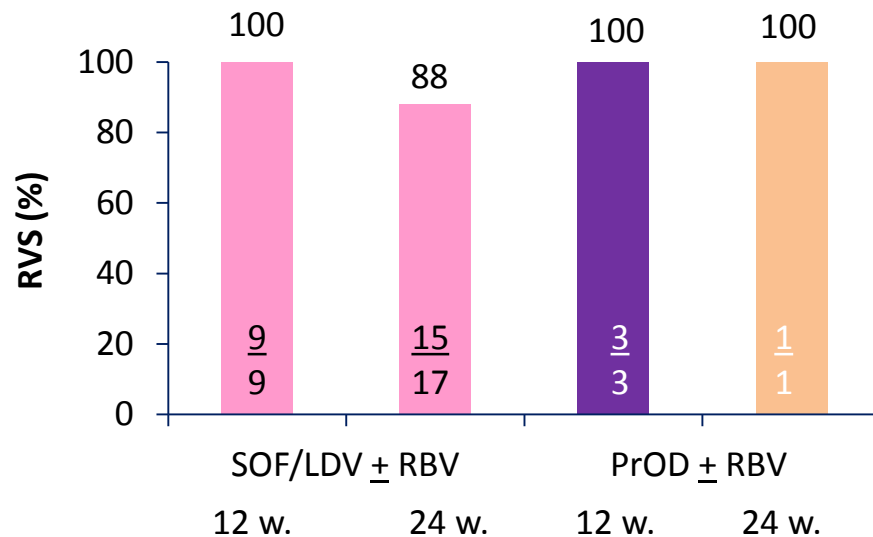
SOF + SMV failure
(n = 31)



Retreatment with NS5A inhibitor containing regimen



Intermediate Analysis : SVR12 = 93,5 % (n = 29/31)

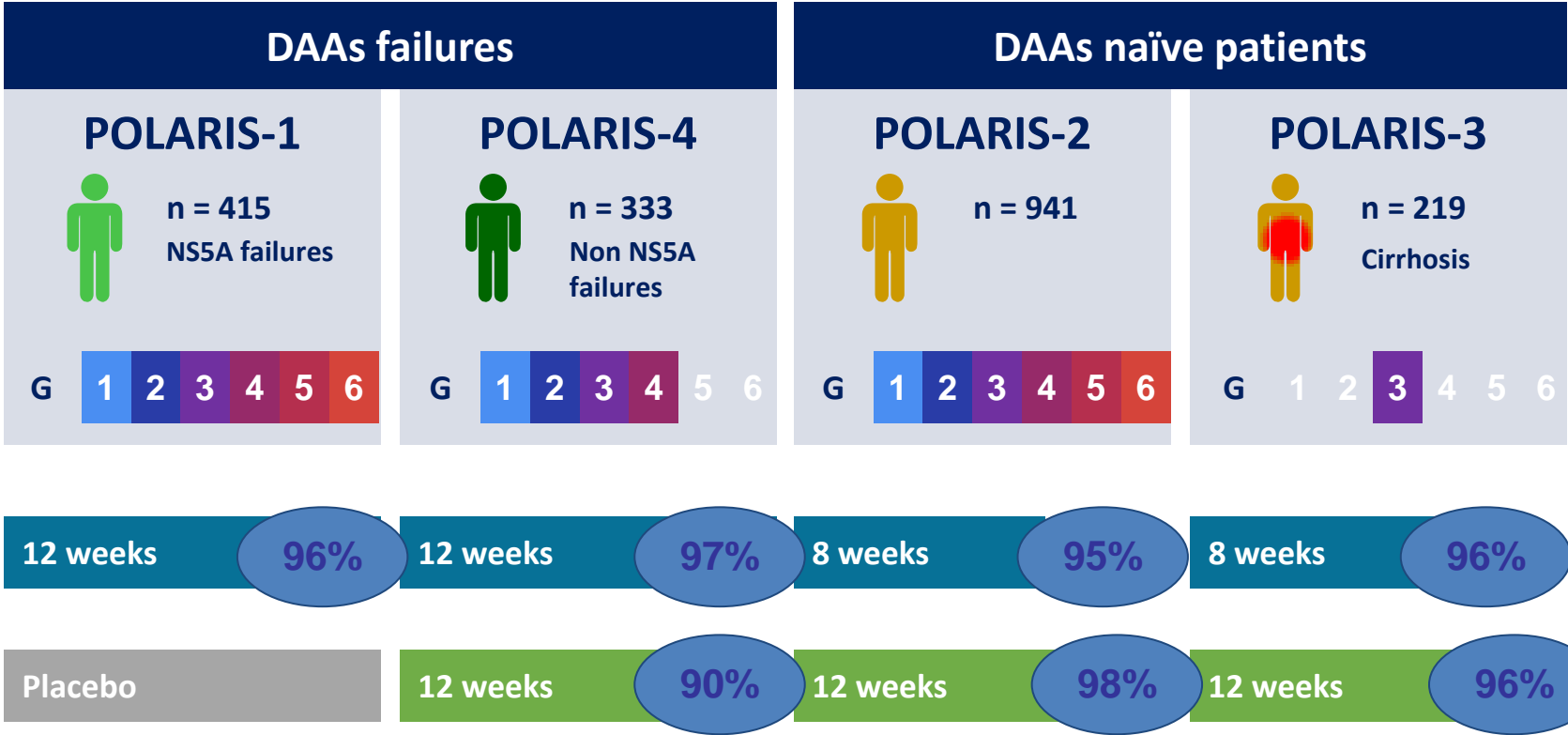


Le VHC : fin du début ou début de la fin?

- Grande efficacité des multiples régimes
- Efficacité pangénotypique
- Faciles/bien tolérés
- Bénéfices cliniques avec réversibilité des manifestations clinico-biologiques

POLARIS: sofosbuvir/velpastasvir/voxilaprevir

Regimen : **SOF/VEL/VOX** **SOF/VEL**



Bourlière M, AASLD 2016, Abs. 194
 Zeuzem S, AASLD 2016, Abs. 109

Jacobson I, AASLD 2016, Abs. LB-12
 Foster G, AASLD 2016, Abs. 258

Glecaprevir/pibrentasvir

ENDURANCE trials

G1 non cirrhotics including HIV
co-infection : 8 vs 12w.

G2 vs placebo : 12 weeks

GT3 : 12 weeks

G4-6 non cirrhotics : 12 weeks

99-100%

MAGELLAN trials

G1/4 DAA failures:

12 vs 16 weeks

SVR 12

EXPEDITION trials

G1, 2, 4-6 cirrhotics

G1-6 CKD4-5

98%

SURVEYOR trials

G2, 4-6 non cirrhotics : 8 weeks

G3 cirrhotics

et/or pretreated : 12 vs 16 weeks

90-100%

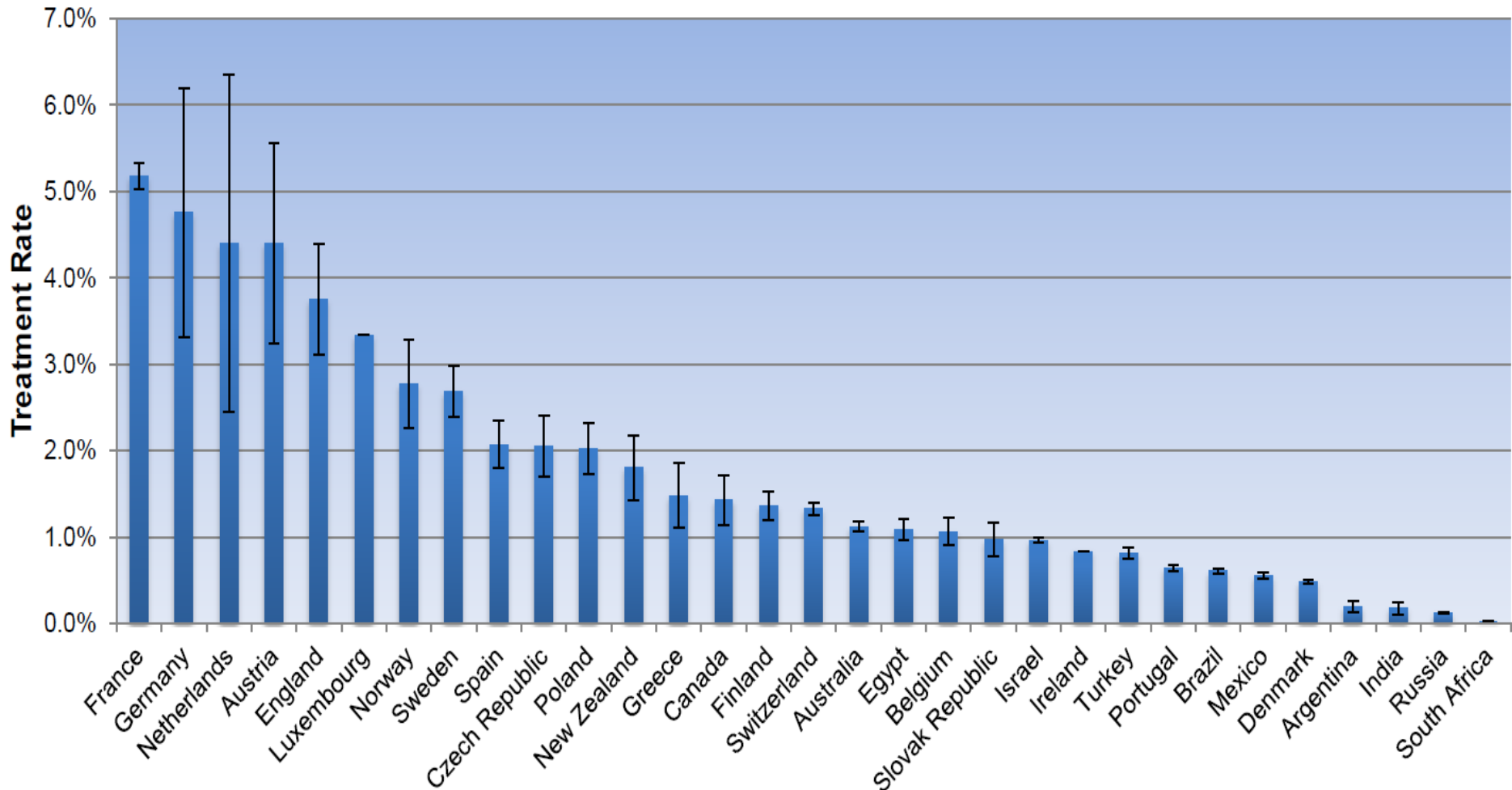
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- Besoins non couverts: amélioration mondiale du
 - dépistage
 - accès aux soins
 - coûts

Diagnostic et accès aux soins avant les AVD (2013)

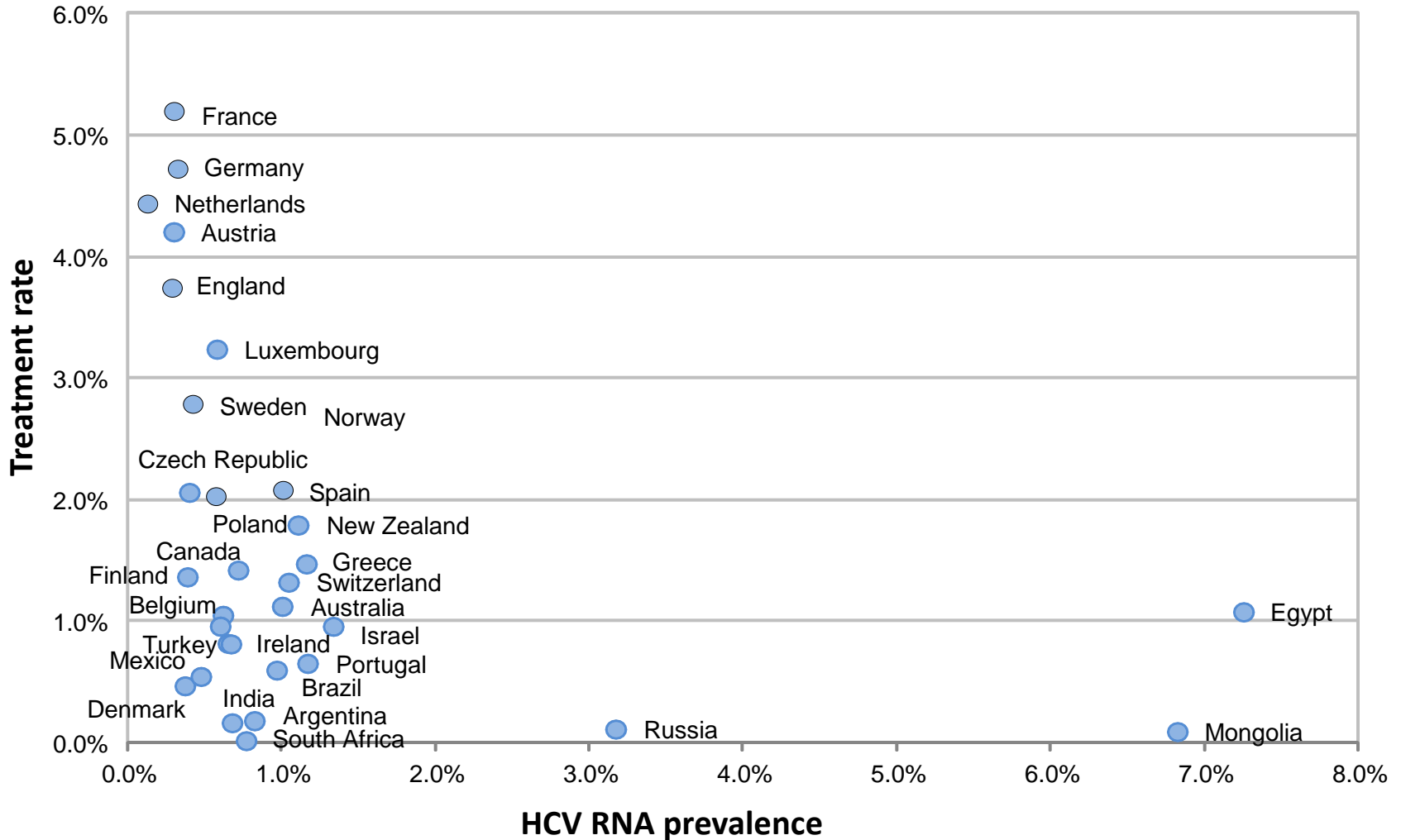
Treatment rate = number of treated annually / estimated total number of viremic



Razavi H et al. J Viral Hepat 2014;21 Suppl 1:34-59.

Hatzakis A et al. J Viral Hepat 2014. Submitted for publication 30 July 2014.

Diagnostic et accès aux soins avant les AVD (2013)



Dore GJ, Ward JW., Thursz. J Viral Hepatitis, 2014, 21, (Suppl. S1), 1–4

Wedemeyer H, Dore GJ, Ward JW. J Viral Hepatitis, 2015, 22, (Suppl. S1), 1–5

Un coût élevé pour la guérison de VHC

Research Article



 **EASL** EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

27,500- 41,000 €

Should we await IFN-free regimens to treat HCV genotype 1 treatment-naïve patients? A cost-effectiveness analysis (ANRS 95141)

Sylvie Deuffic-Burban^{1,2,13,*}, Michaël Schwarzingger^{1,13}, Dorothée Obach^{1,13}, Vincent Mallet^{3,4,5,6}, Stanislas Pol^{3,4,5}, Georges-Philippe Pageaux⁷, Valérie Canva⁸, Pierre Deltenre⁹, Françoise Roudot-Thoraval¹⁰, Dominique Larrey⁷, Daniel Dhumeaux¹¹, Philippe Mathurin^{2,8}, Yazdan Yazdanpanah^{1,12,13}

- But
1. « cost-effective »
 2. for HCV elimination
 3. prize is defined by the « CEPS »
 4. « Licence d'office » is feasible

Accès aux génériques : plusieurs options

Myhep Lvir*

Mylan India Ledipasvir Sofosbuvir Details:

Brand name: MyHep LVIR

Contents : Ledipasvir and Sofosbuvir

Marketed by: Mylan Pharmaceuticals Pvt Ltd.

Form: Tablets

Strength: Lédipasvir 90 mg-Sofosbuvir 400 mg

Packing: Pack of 28 tablets

750 € 12 weeks



*<http://www.indiamart.com/medivacinternational/pharmaceutical-tablets.html>

Elimination du VHC

- New DAAs can achieve SVR in a broad spectrum of patients
- Challenge is how best to apply them in practice for greatest impact

