

Virus de l'hépatite C: peut-on refermer le livre?

Collège de France, Paris
Infections chroniques et récurrentes
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Place des hépatites dans la mortalité globale

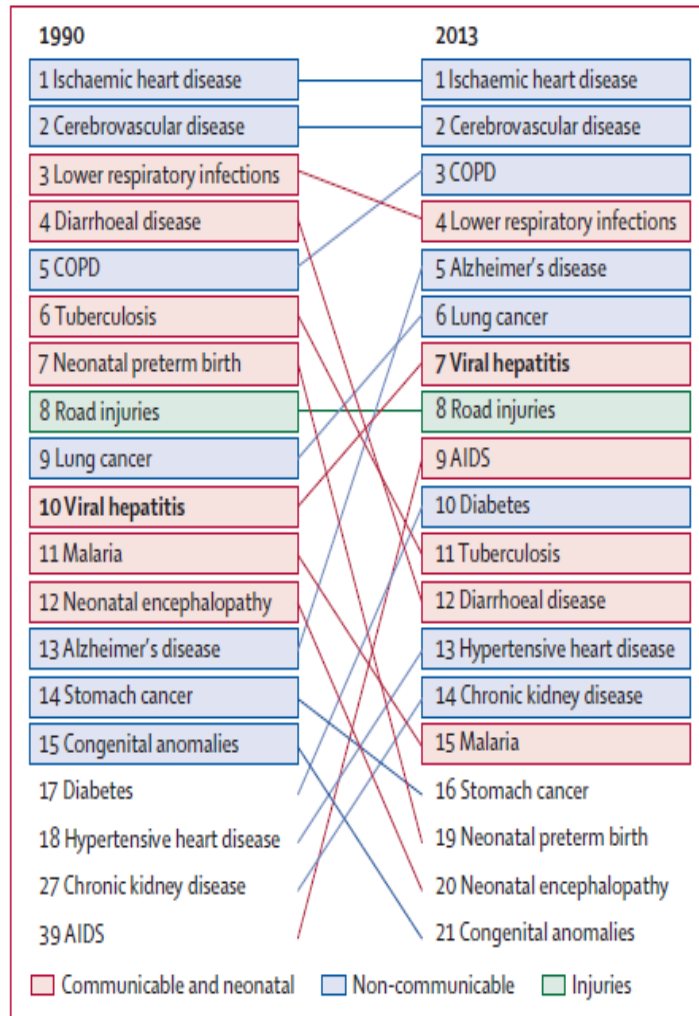
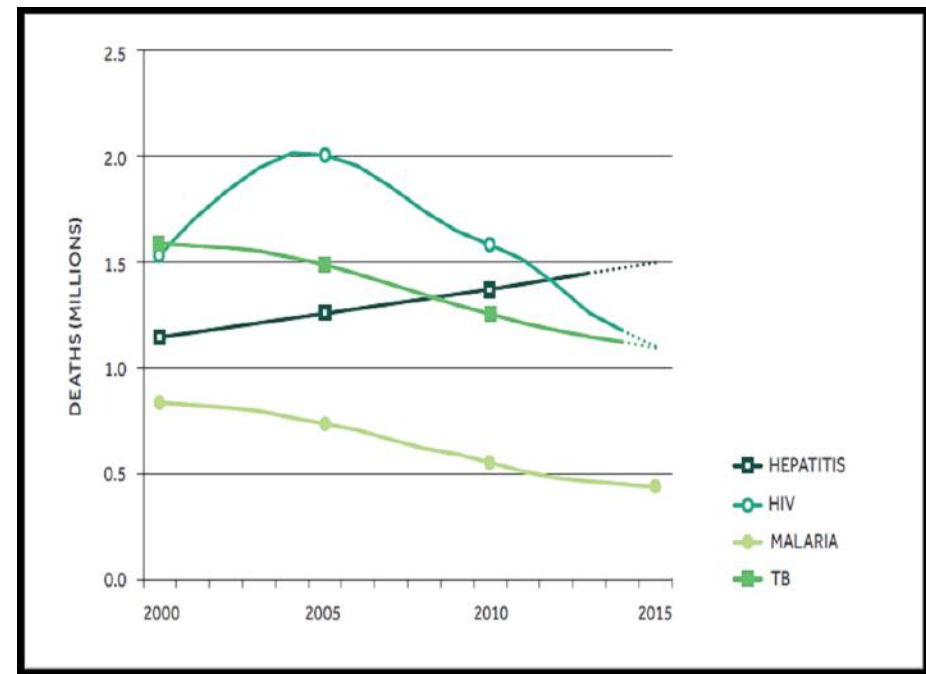
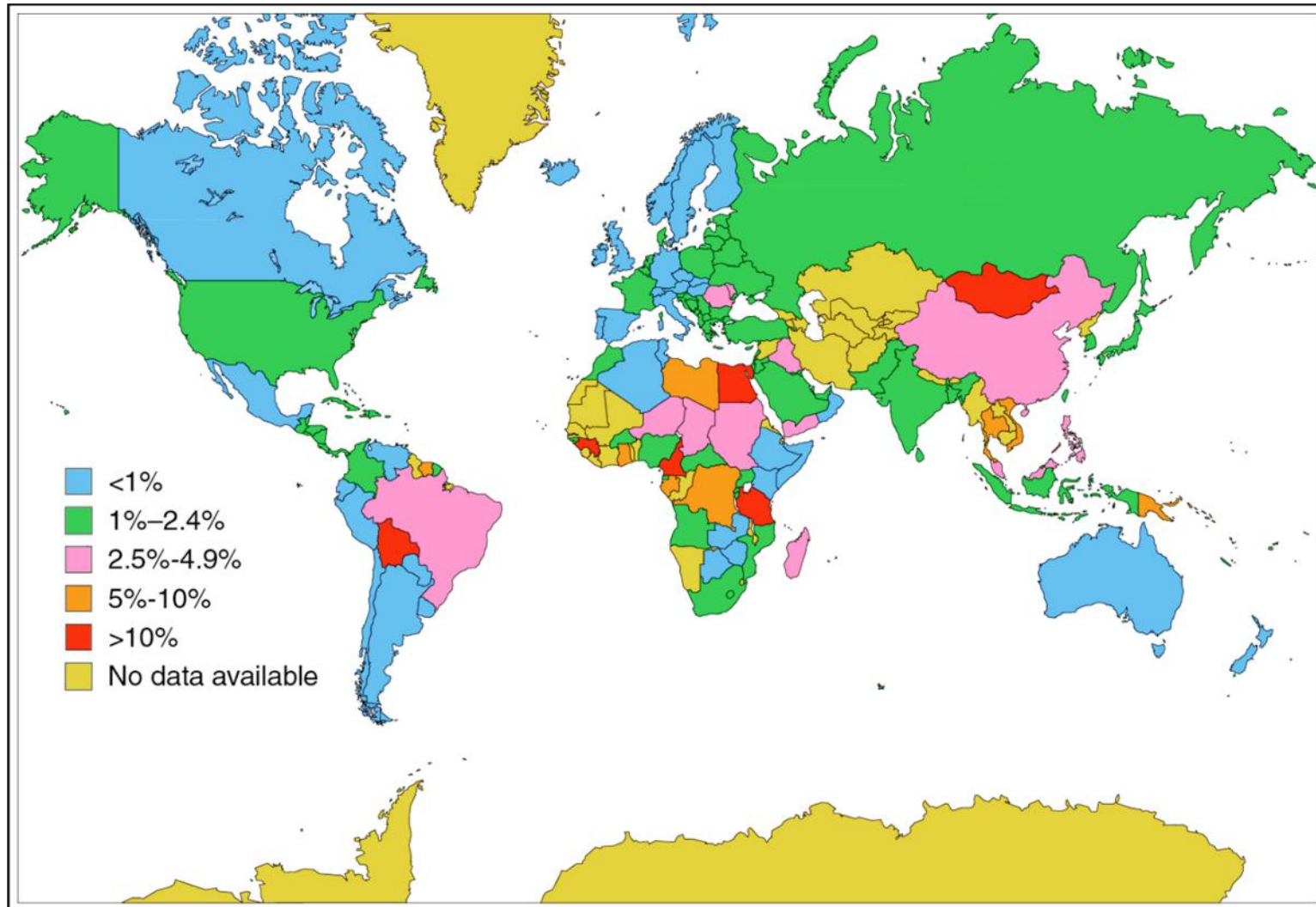


Figure 2: Leading causes of mortality and trends, 1990-2013
 COPD=chronic obstructive pulmonary disease.



Prévalence du VHC

170 millions de porteurs chroniques dans le monde

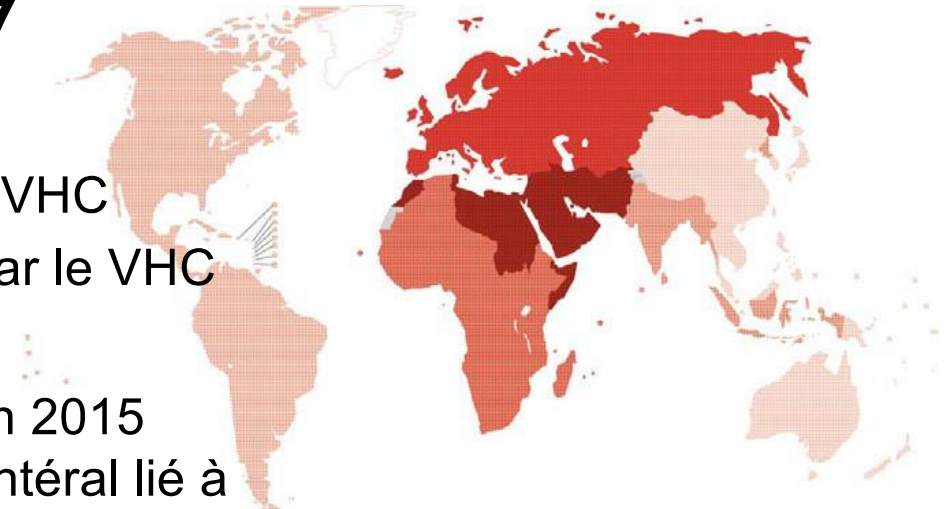


Reprinted from Cohen J. *Science*. 1999;285:26.

Actualisation épidémiologique et perspectives OMS : global Hepatitis report 2017

Actualisation des données épidémiologiques du VHC

- 1 % de la population mondiale infectée par le VHC (71 millions)
- Plus de 1 750 000 nouvelles infections en 2015 (absence d'hémovigilance et risque parentéral lié à l'usage de drogues)
- 2,3 millions de sujets co-infectés VIH/VHC

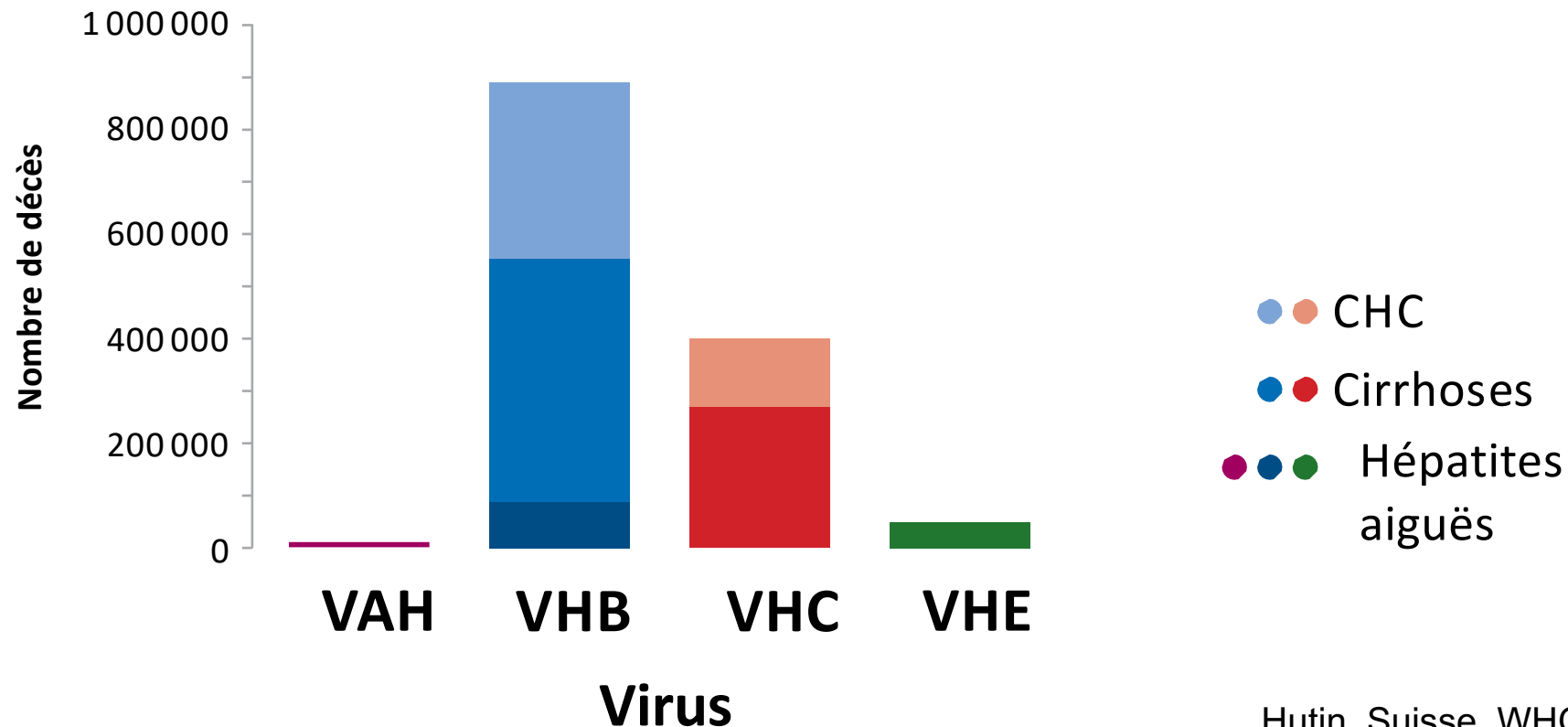


Incidence of HCV infection

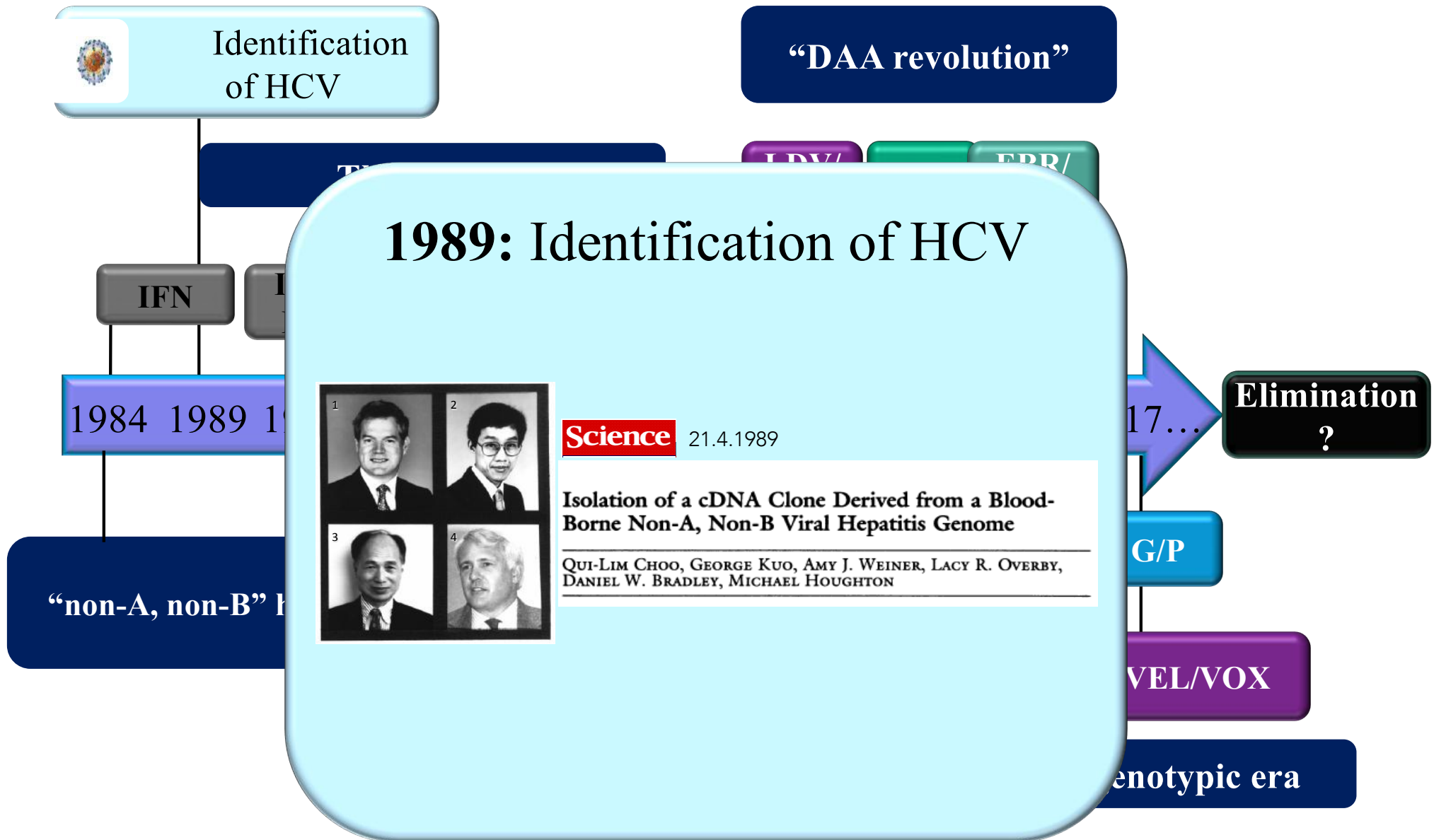
WHO region	Map key	Incidence rate (per 100 000)		Total number (000)	
		Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
Afrique		31,0	22,5–54,4	309	222–544
Amériques		6,4	5,9–7,0	63	59–69
Moyen Orient		62,5	55,6–65,2	409	363–426
Europe		61,8	50,3–66,0	565	460–603
Asie du Sud-Est		14,8	12,5–26,9	287	243–524
Ouest Pacifique		6,0	5,6–6,6	111	104–124
Total		23,7	21,3–28,7	1751	1572–2120

Actualisation épidémiologique et perspectives OMS : global Hepatitis report 2017

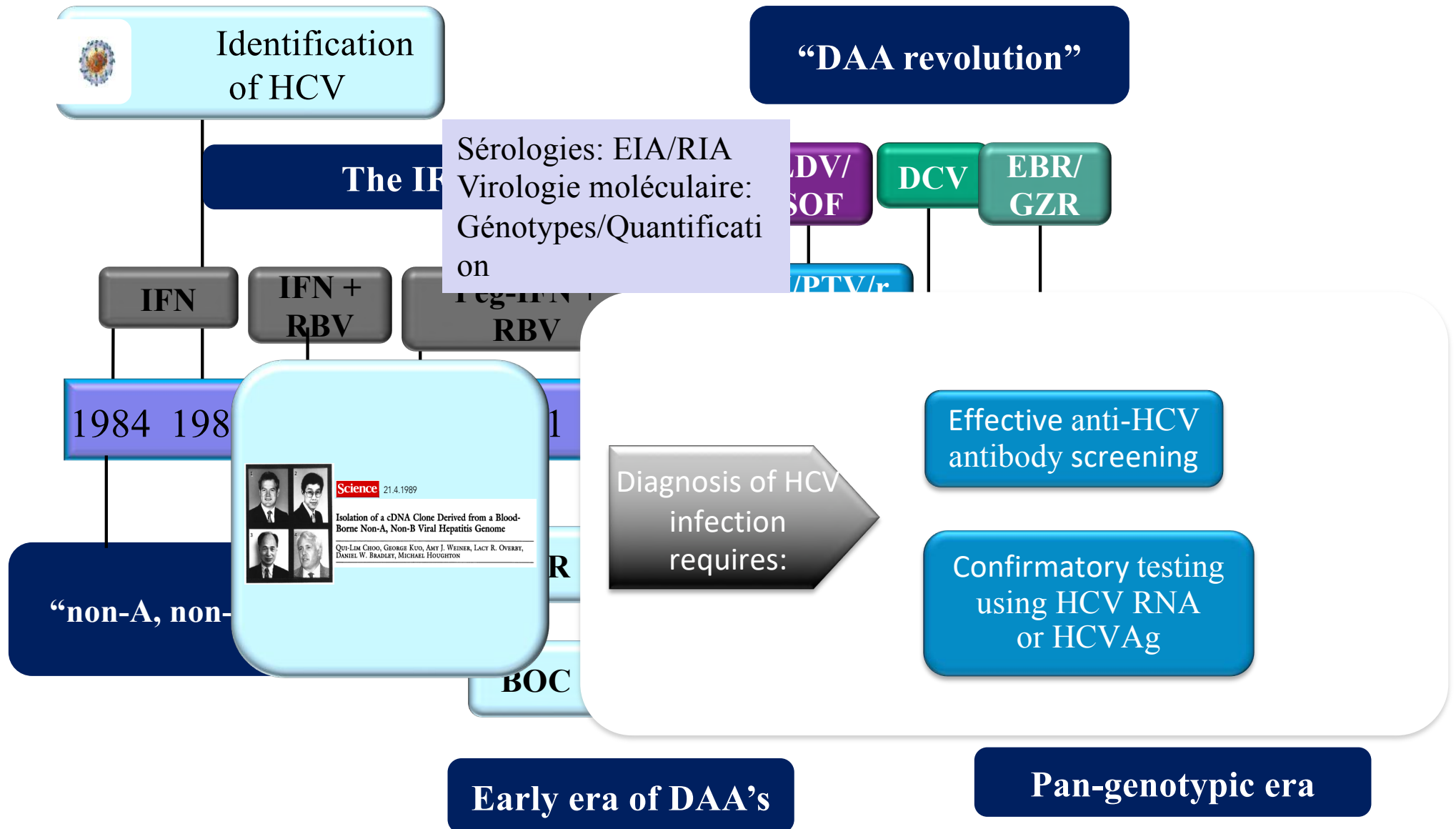
- Mortalité attribuable aux hépatites virales en 2015
- 720 000 décès par cirrhose
- 470 000 décès par carcinome hépatocellulaire
- Augmentation de 22 % depuis 2000



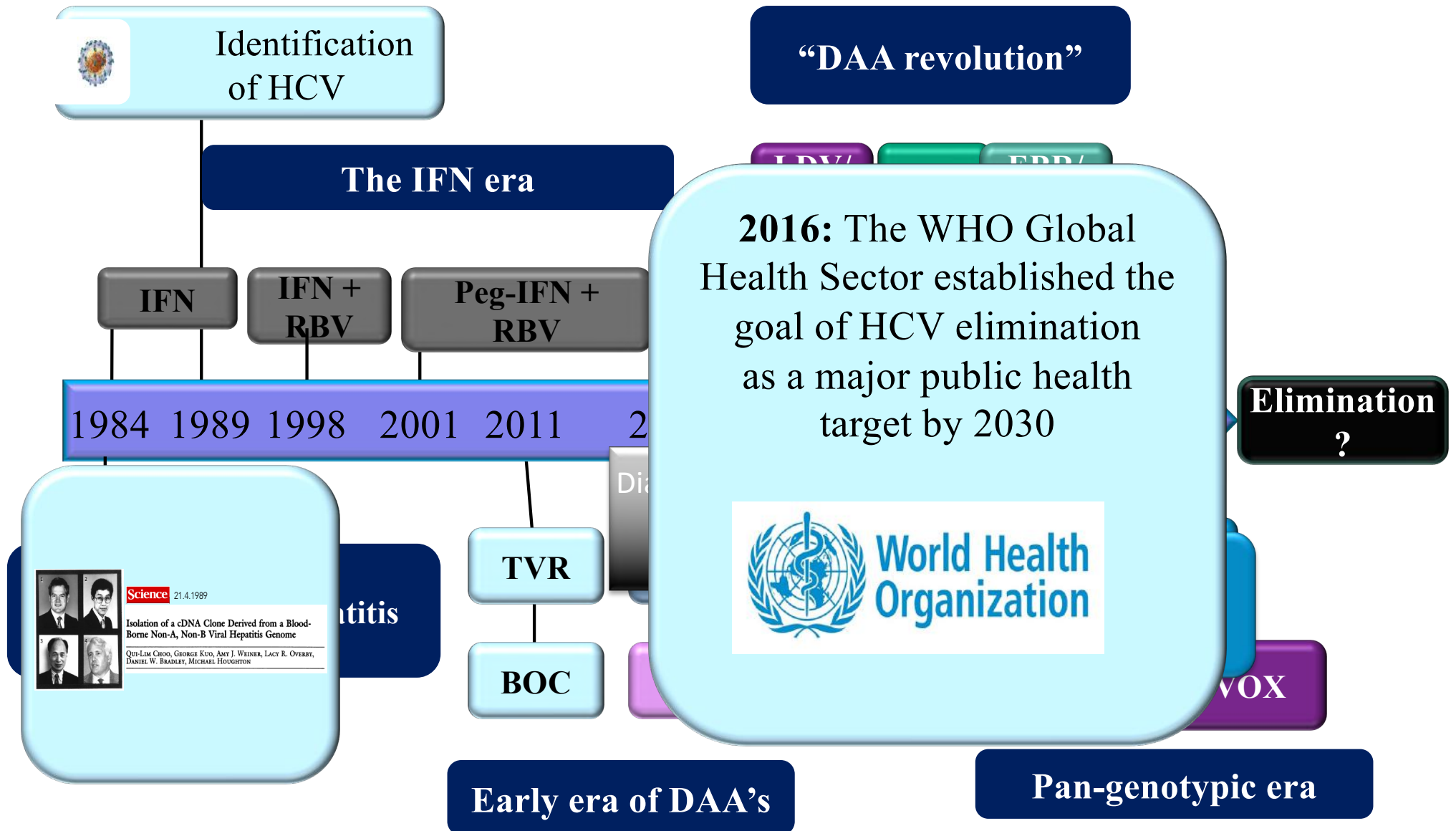
Histoire du VHC



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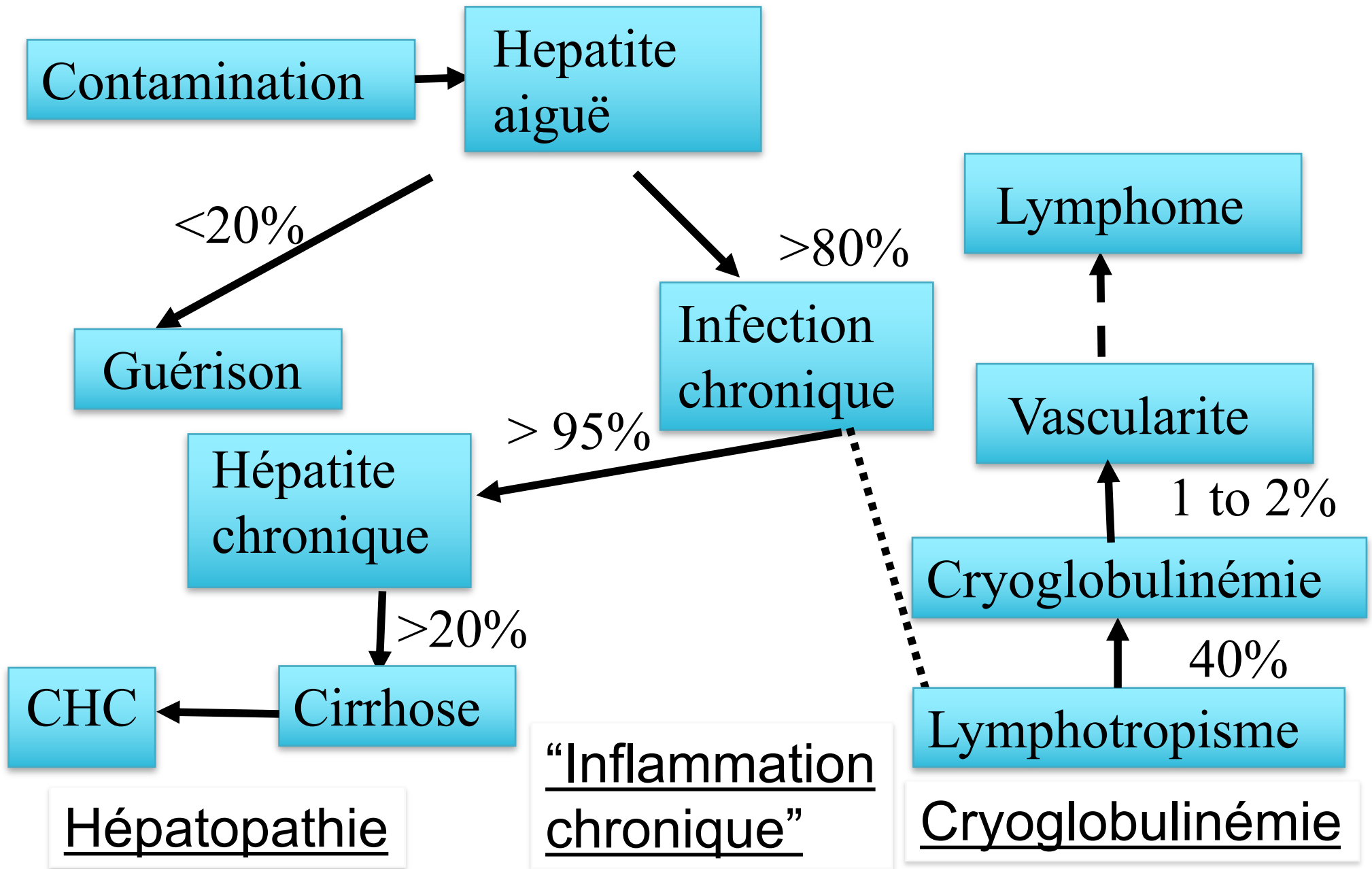
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- Politique d'élimination (OMS)

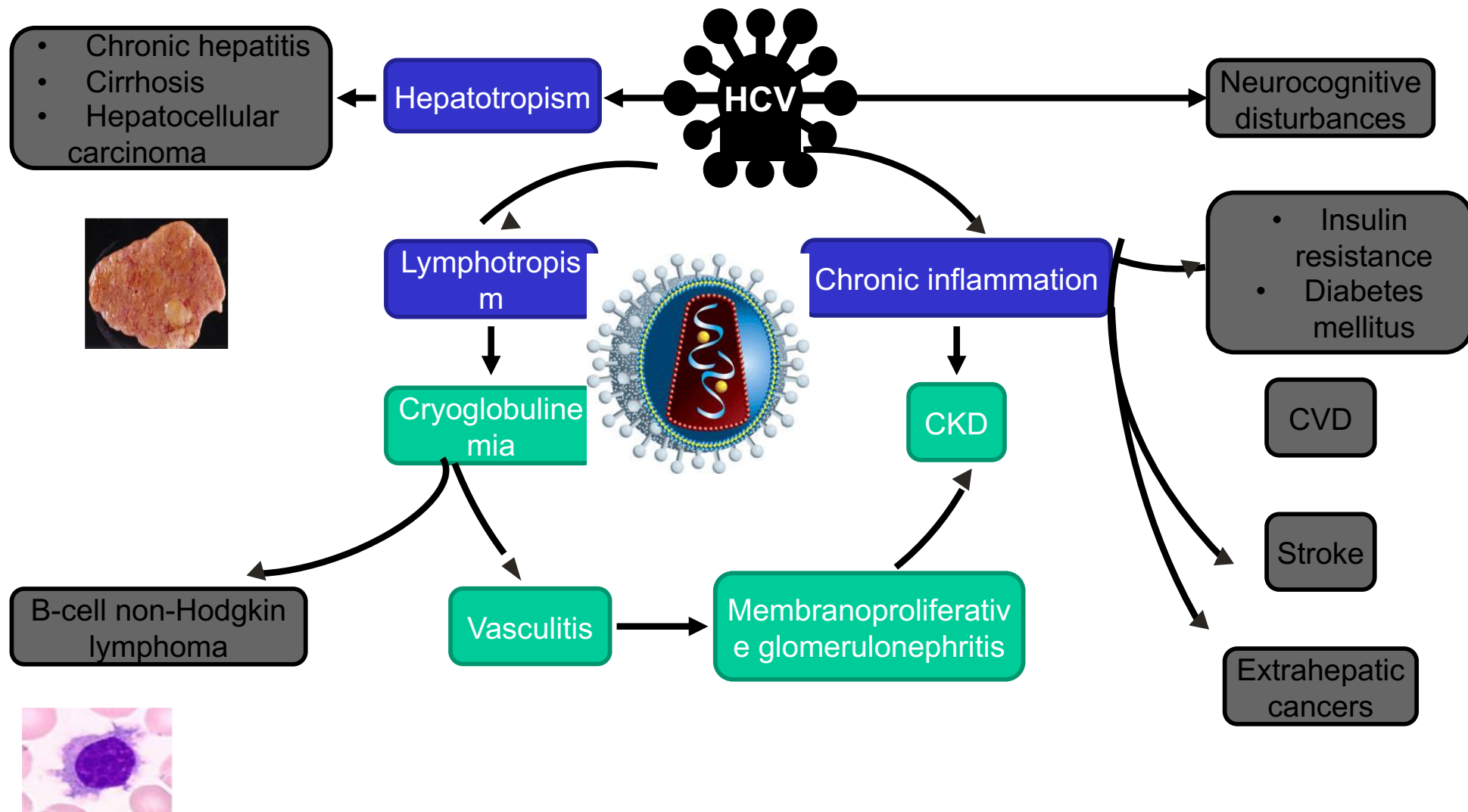
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Histoire naturelle de l'infection virale C



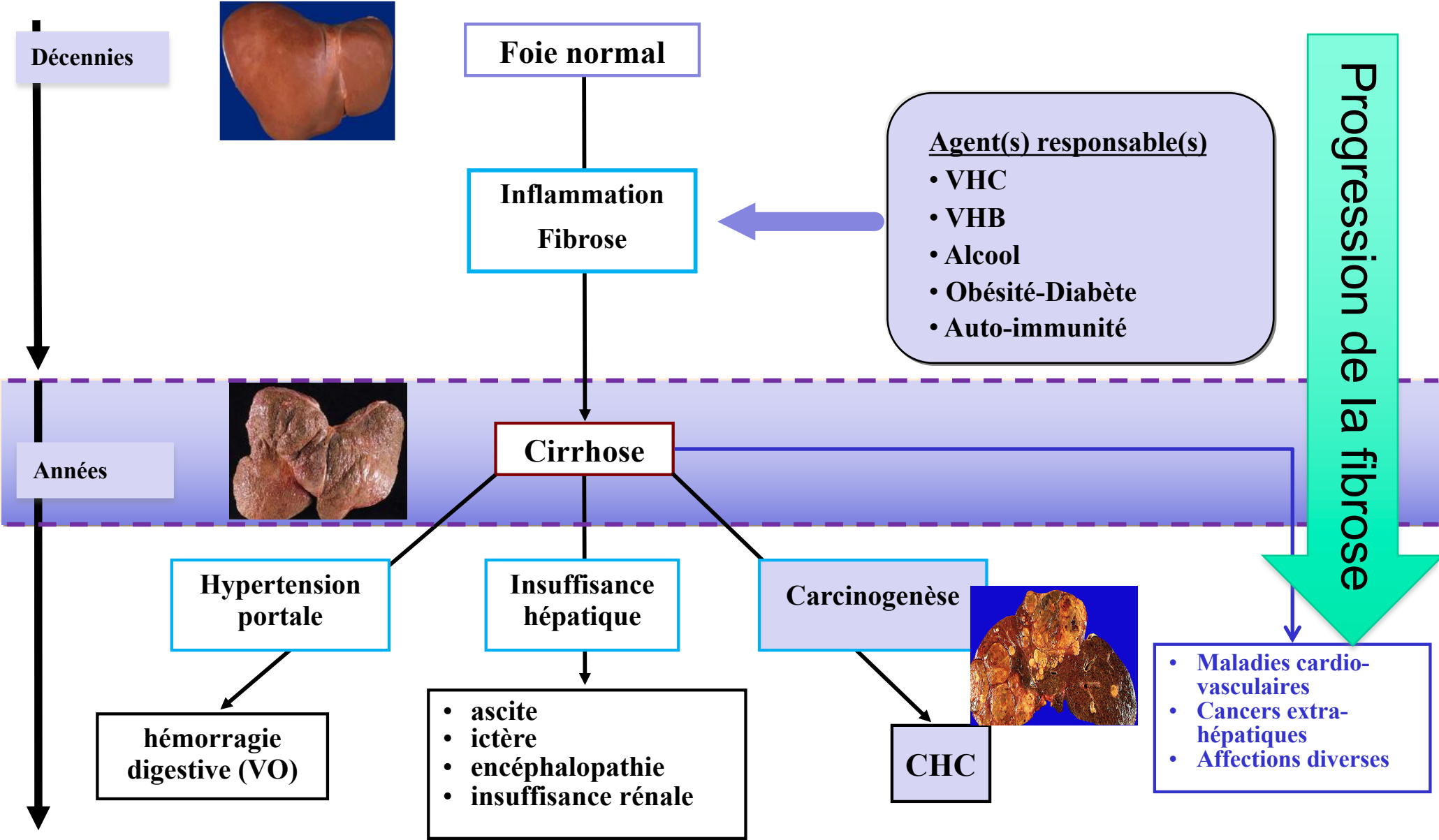
L'infection virale C chronique est une maladie systémique



CKD, chronic kidney disease; CVD, cardiovascular disease

Pol S, et al. Nat Rev Nephrol 2018; doi: 10.1038/s41581-018-0081-8. [Epub ahead of print].

Histoire naturelle des hépatopathies



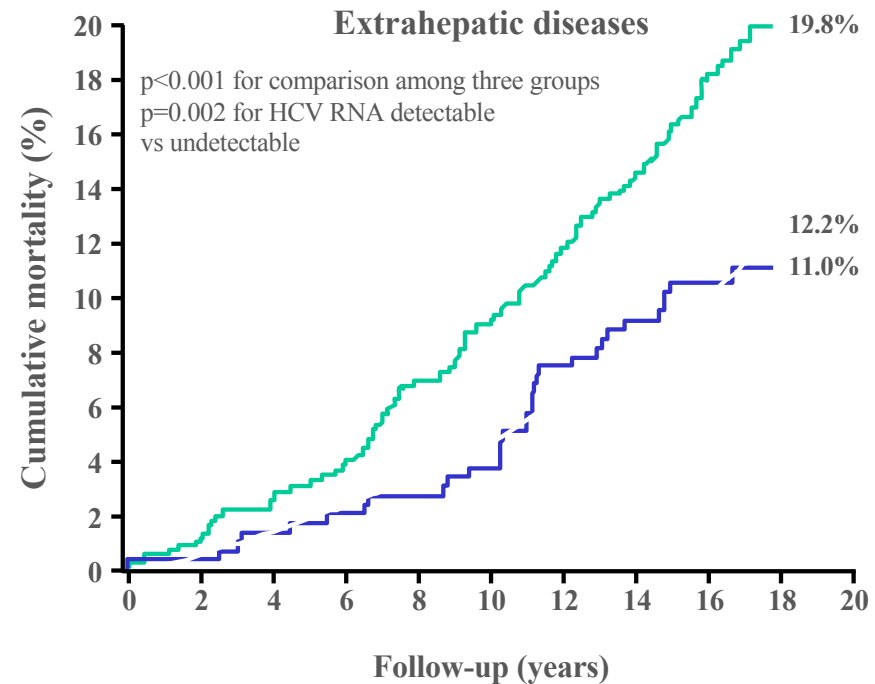
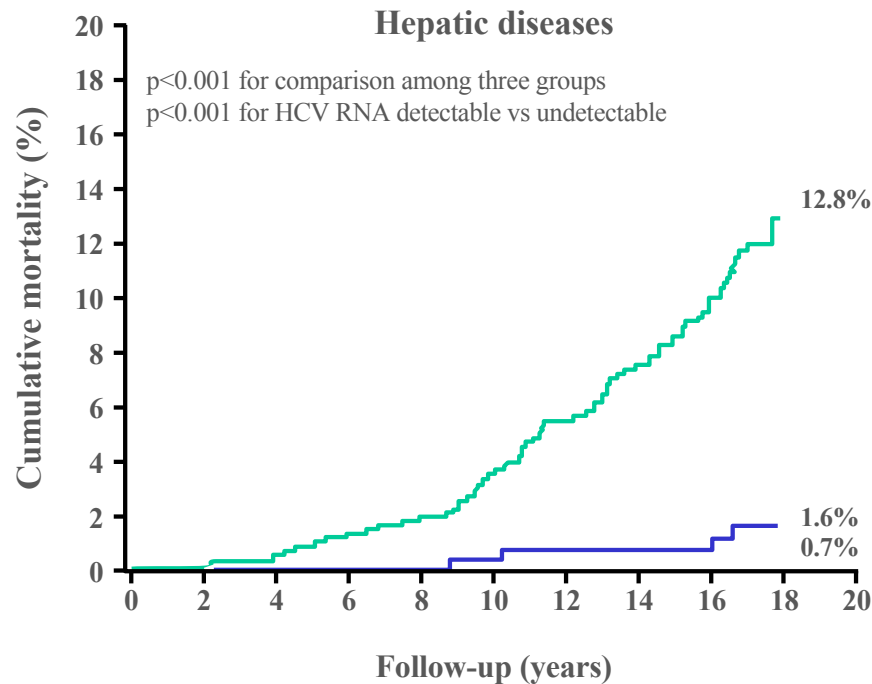
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The REVEAL HCV Cohort Study

23 820 adults, Taiwan

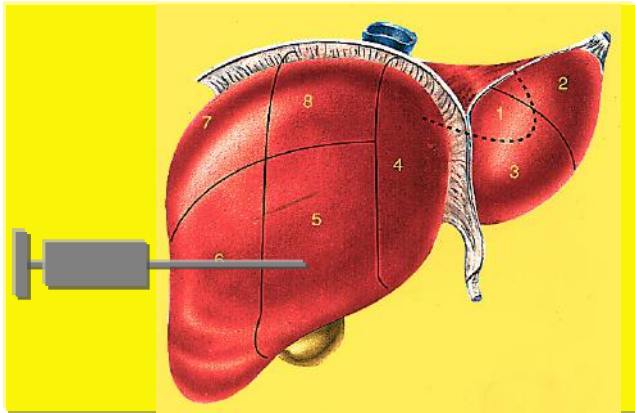
1095 anti-HCV positive; 69.4% with detectable HCV RNA

— HCV seropositive, HCV RNA detectable
— HCV seropositive, HCV RNA undetectable
— HCV seronegative



Evaluation des lésions hépatiques

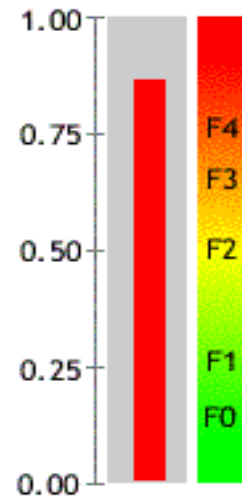
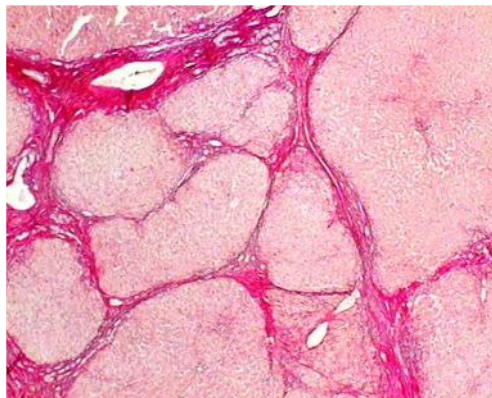
PBH



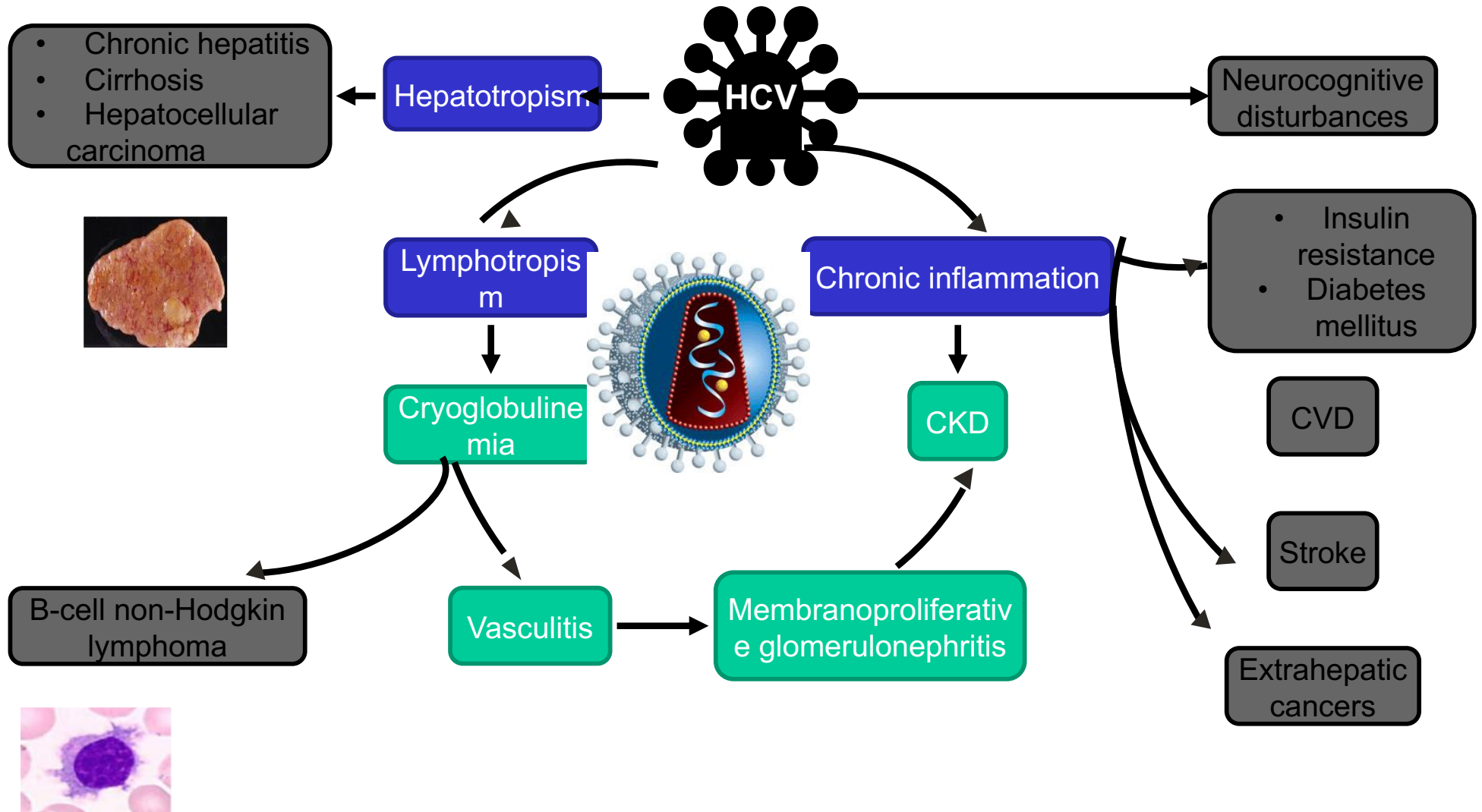
Tests sanguins



Elastométrie



L'infection virale C chronique est une maladie systémique



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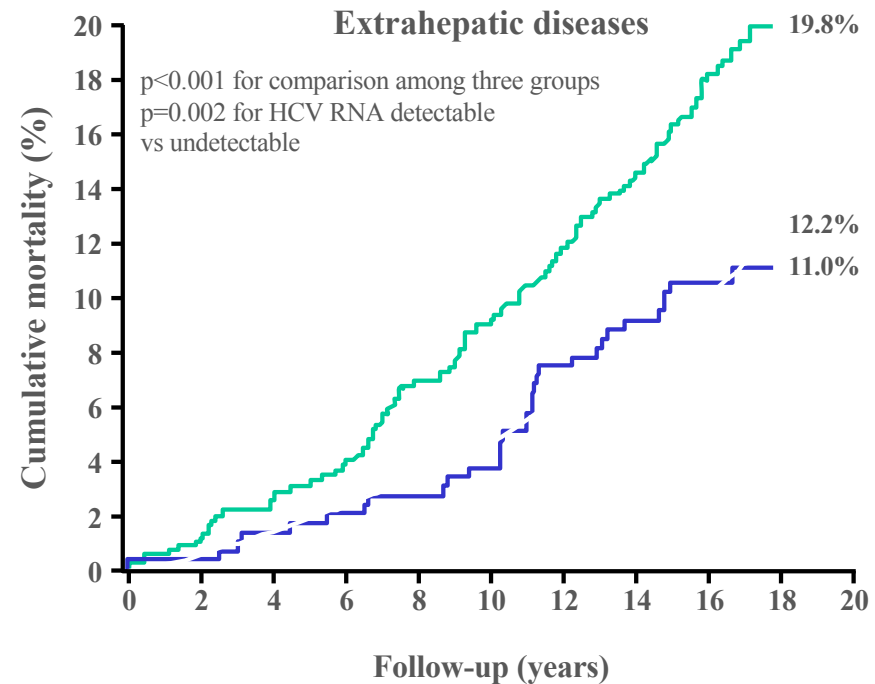
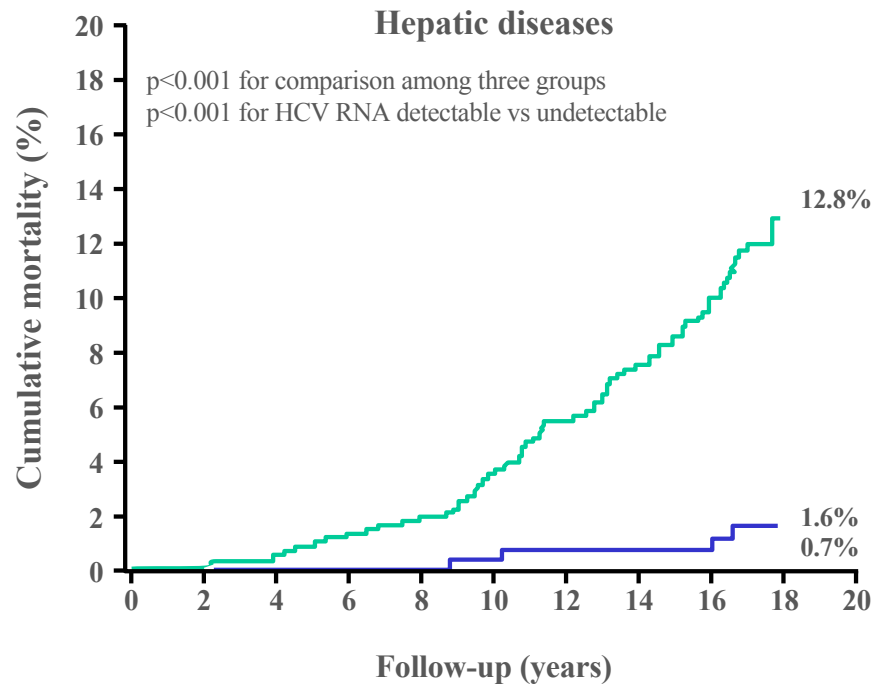
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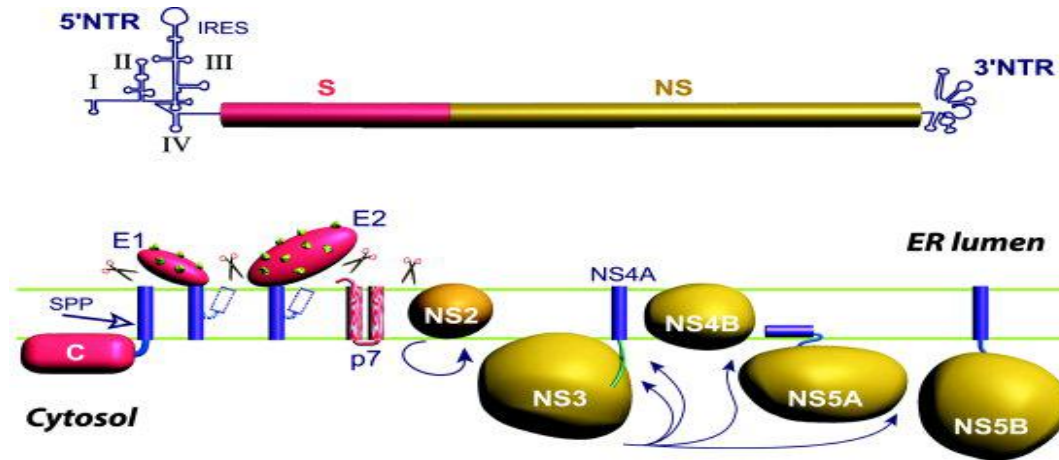


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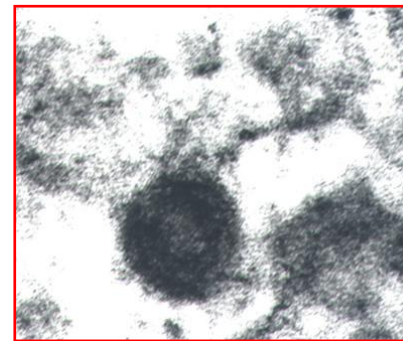
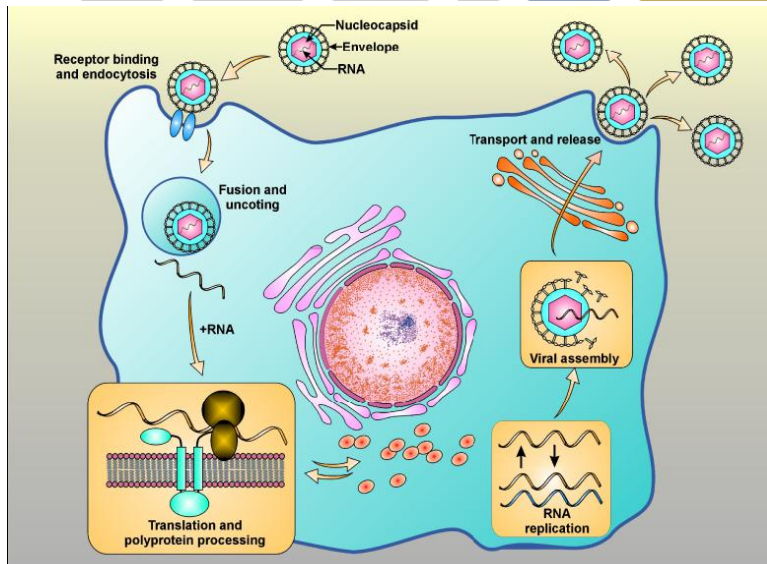
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VHC: une biologie simple sans réservoir ni intégration génomique

ARN VHC

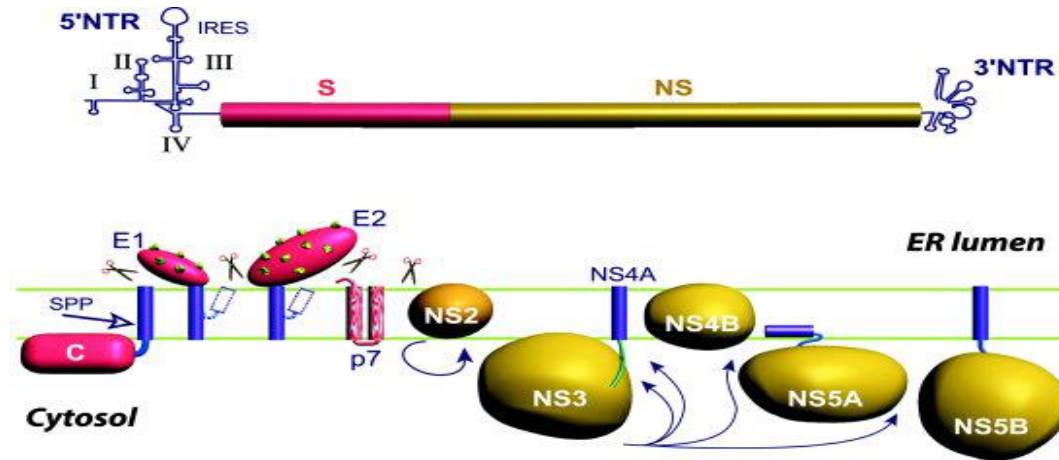


Polyprotéine

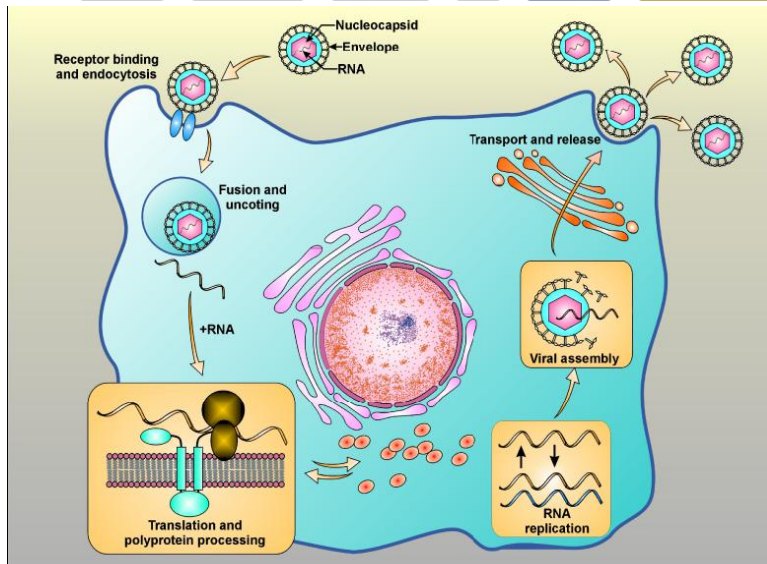


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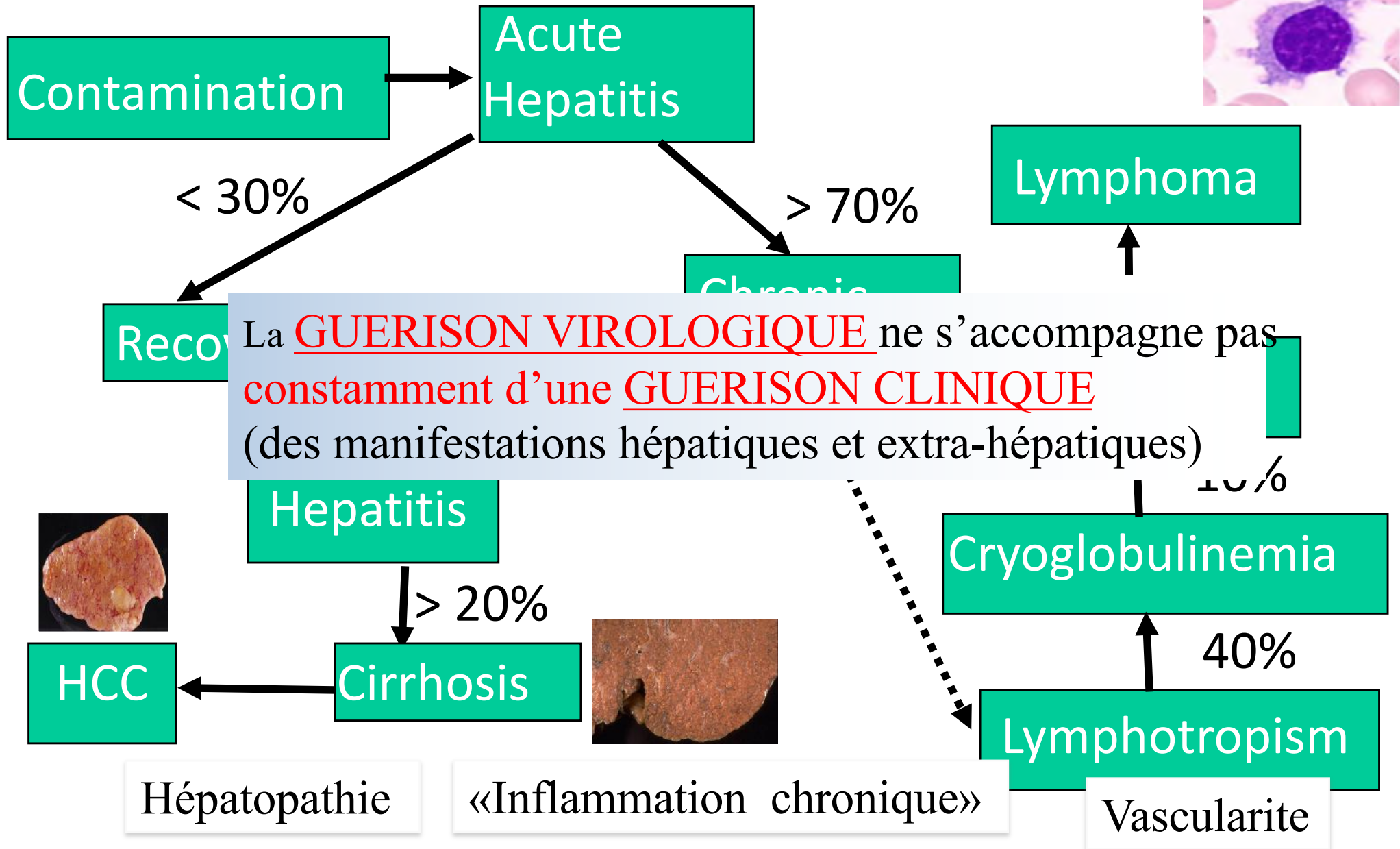


La réponse virologique prolongée (RVP)(ARN VHC indétectable 12 semaines après la fin du traitement) est une **GUERISON VIROLOGIQUE**

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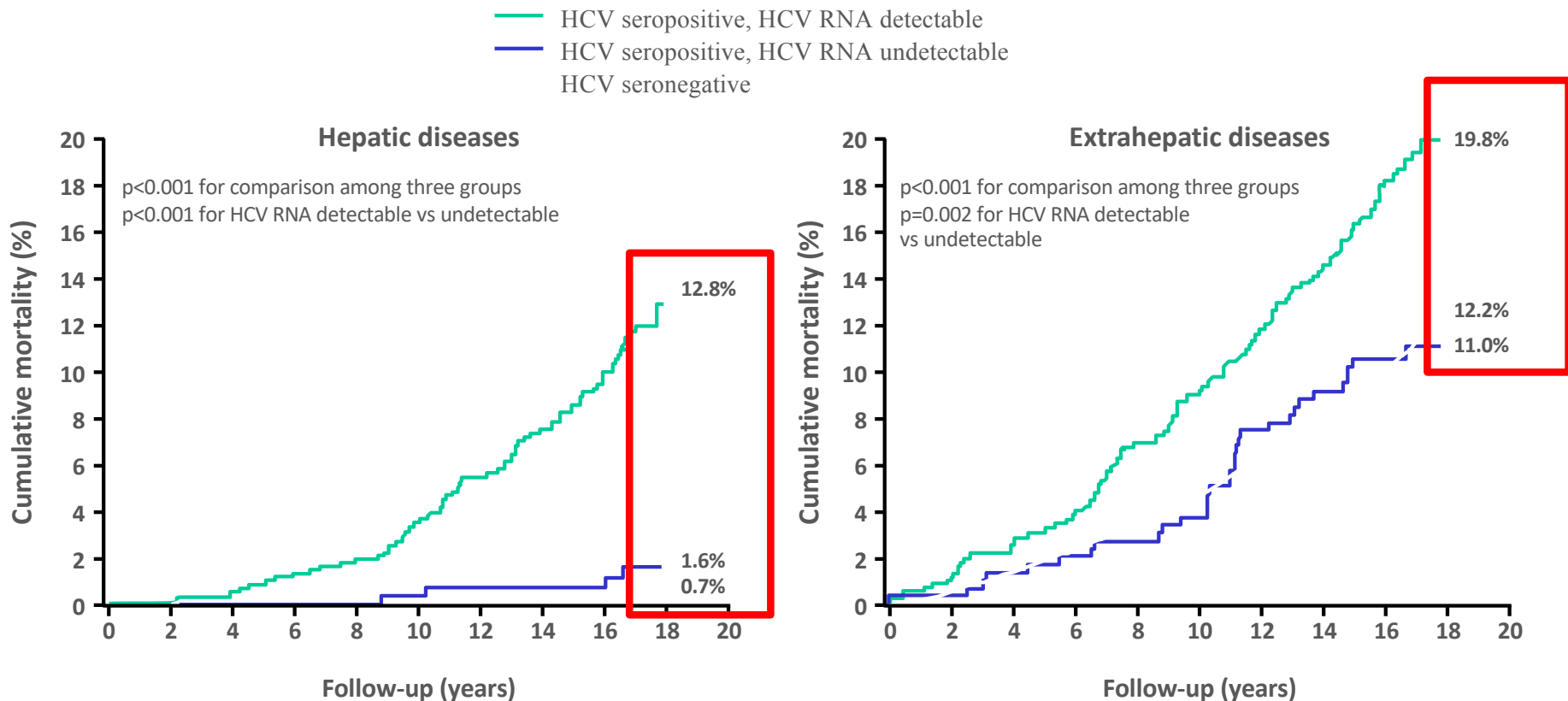


Réduction de la mortalité en l'absence d'infection active par le VHC

The REVEAL HCV Cohort Study

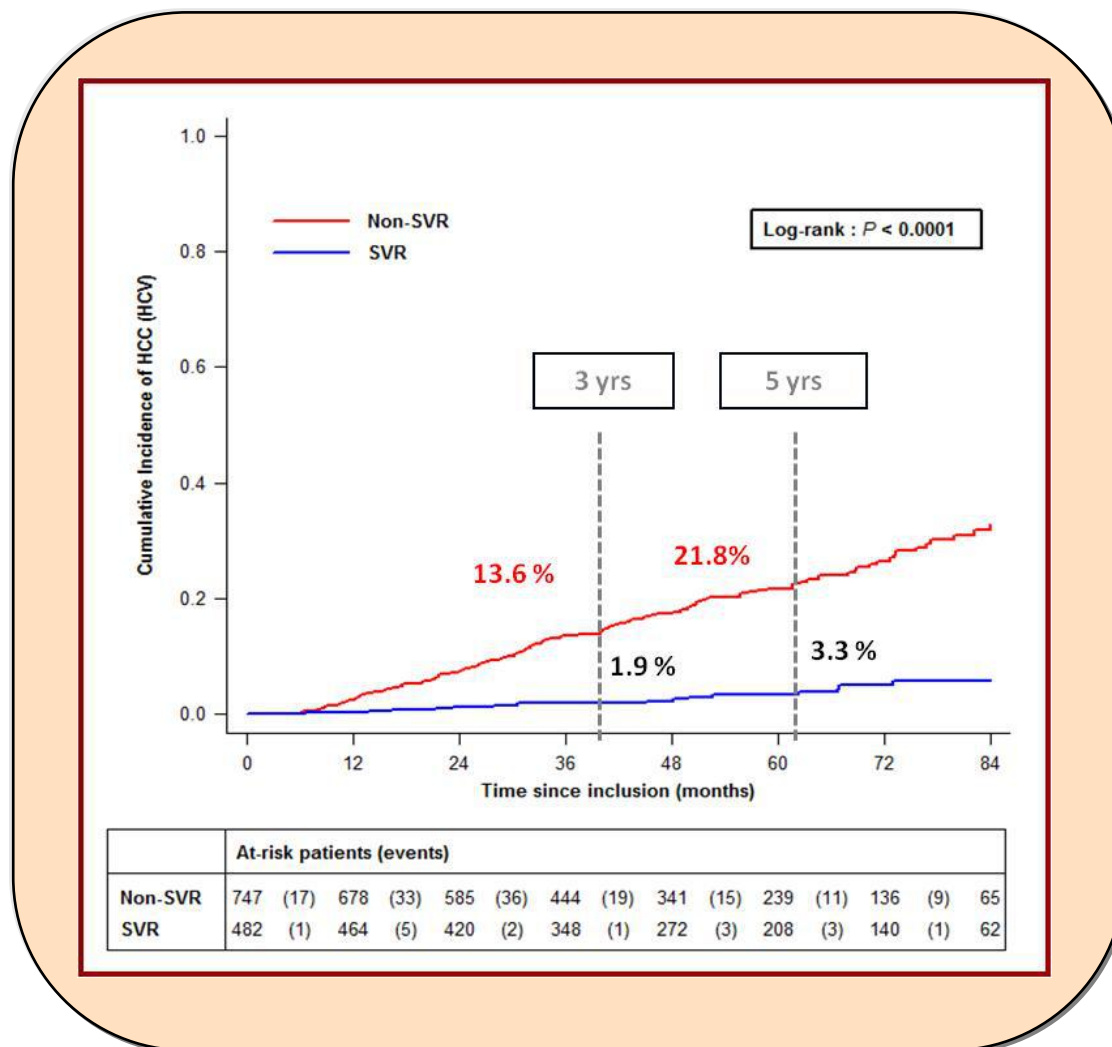
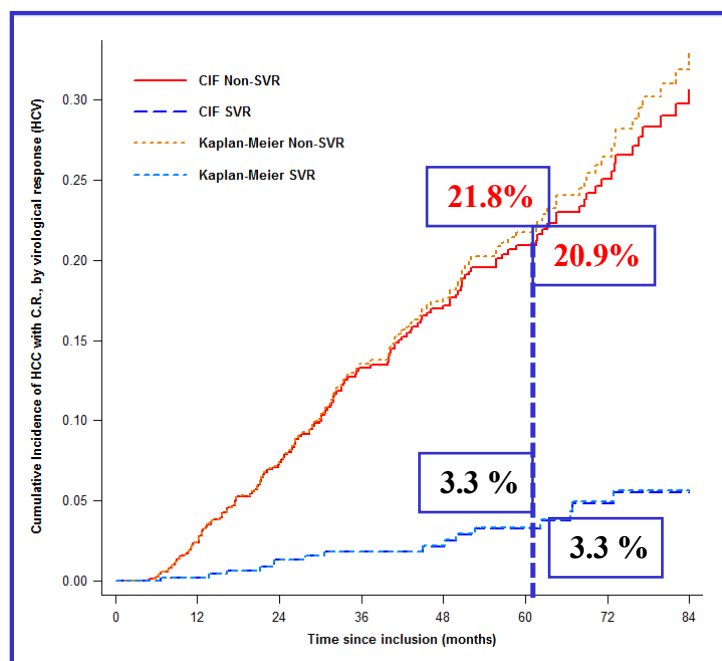
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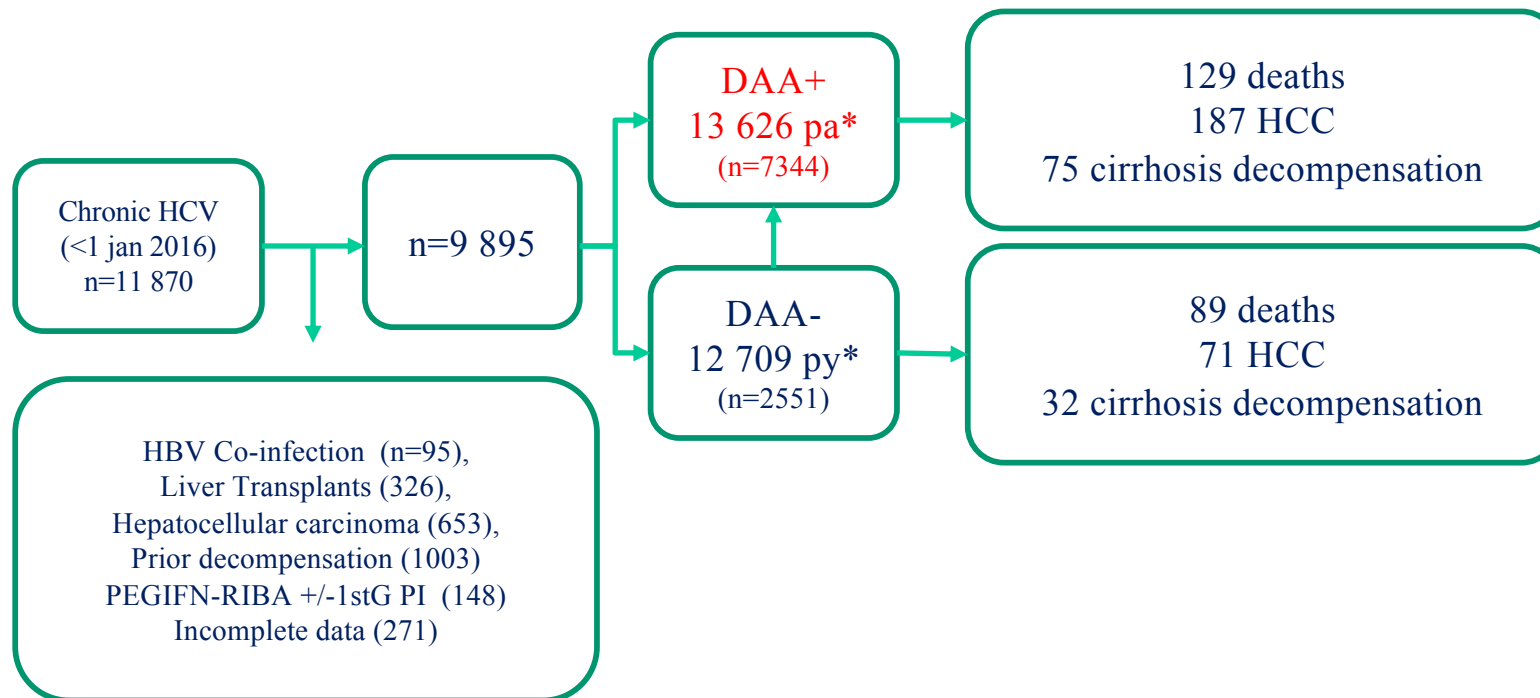
Bénéfices associés aux AVD

Risques compétitifs (Test de Fine and Gray)



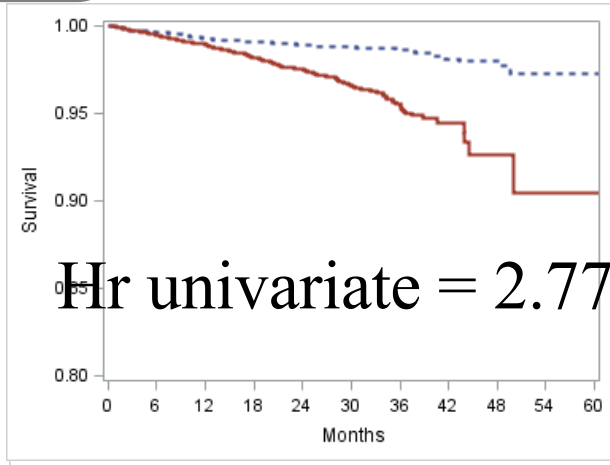
	Pas de RVS	RVS	Total
CHC	143 (19.1)	17 (3.5)	162 (MD: 2)
Décès sans CHC	55 (7.3)	15 (3.1)	87 (MD: 17)

Bénéfices associés à la RVP



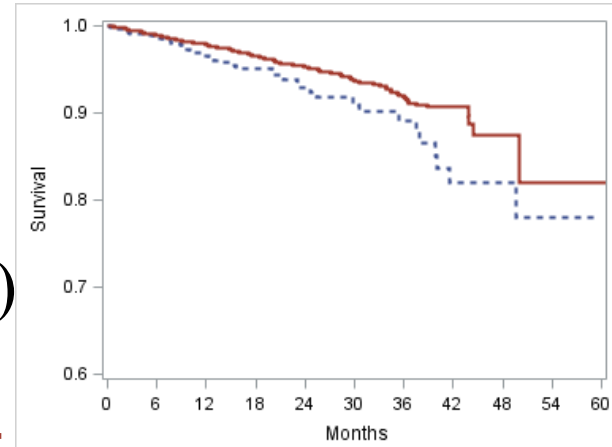
*py = patients-year

Bénéfices associés à la RVP

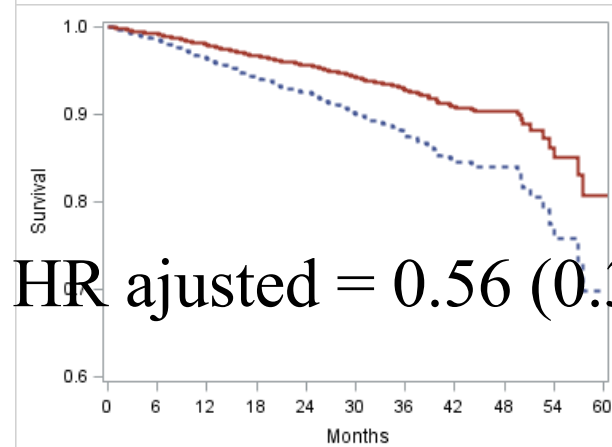


HR univariate = 2.77 (2.07;3.71)

— DAA+
- - - DAA-



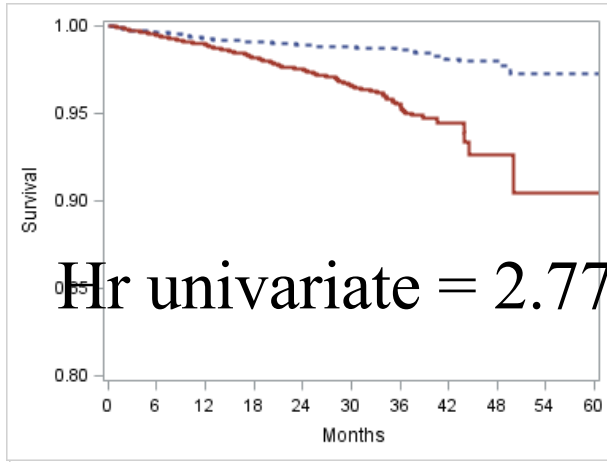
HR adjusted = 0.56 (0.39;0.79)



	Months	0	12	24	36	48	60
N at risk	DAA+	7308	5366	3368	977	57	6
	DAA-	9895	4751	2878	1337	355	10

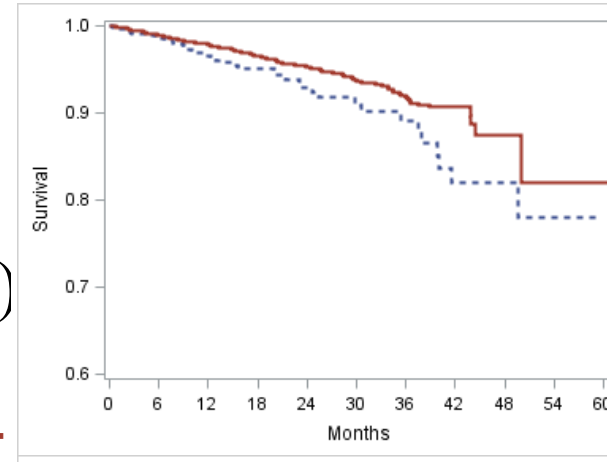
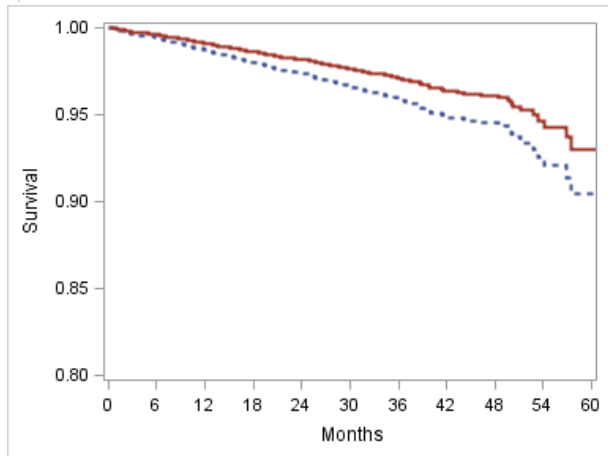
	Months	0	12	24	36	48	60
N at risk	DAA+	2789	2385	1714	574	23	2
	DAA-	3039	542	178	76	33	0

Bénéfices associés à la RVP

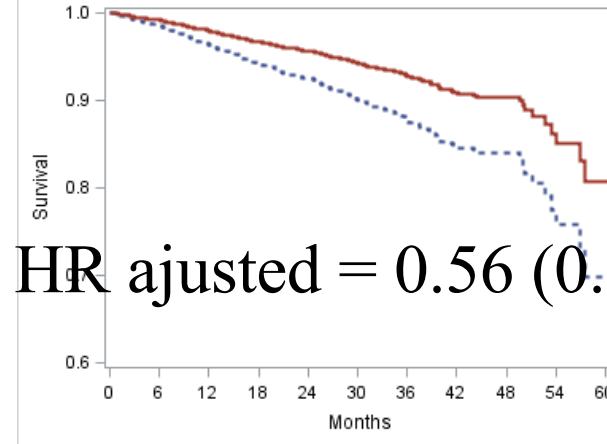


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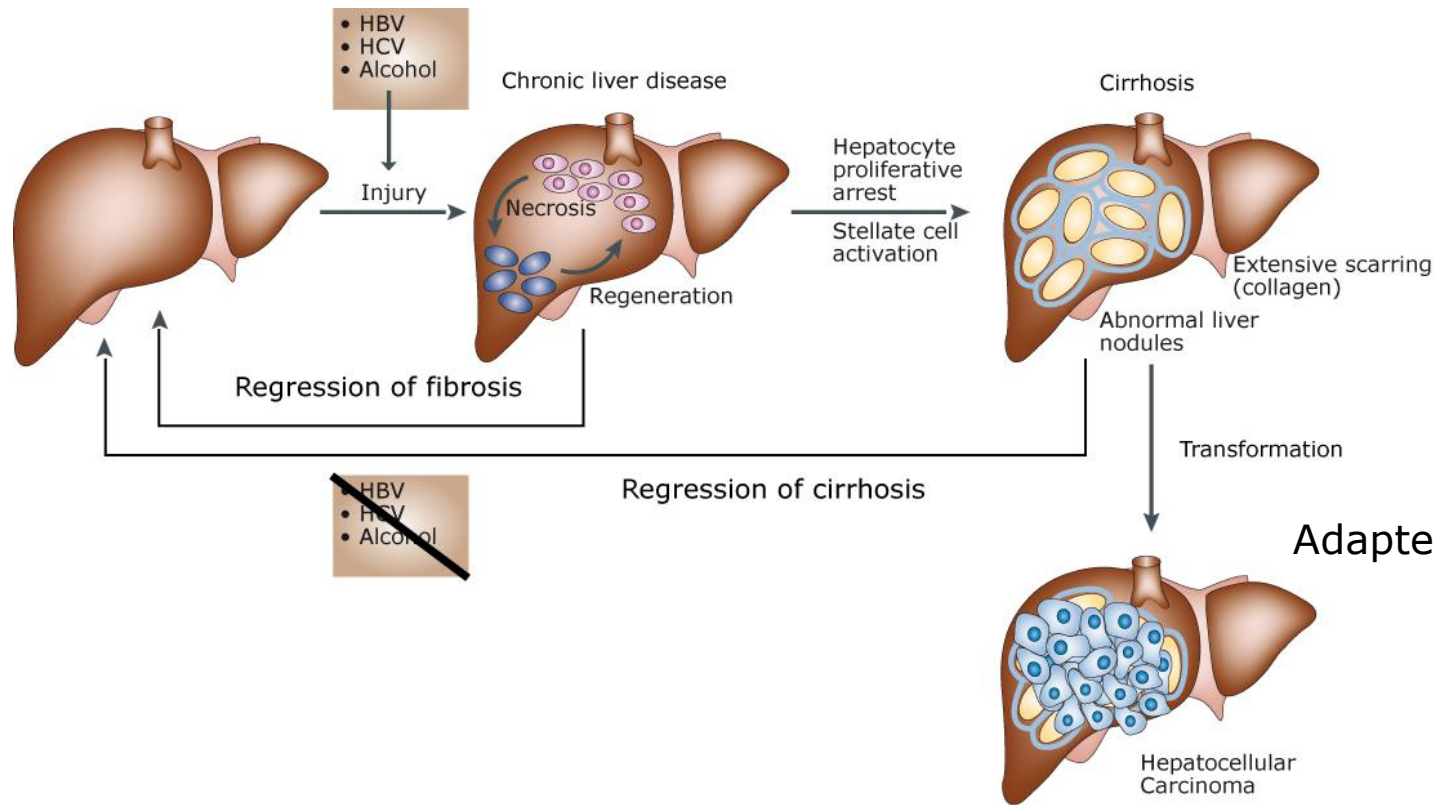
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N at risk	DAA+	7308	5366	3368	977	57	6
	DAA-	9895	4751	2878	1337	355	10

Risk of de novo HCC (all patients (n=9895)

and cirrhotic patients (n=3039))

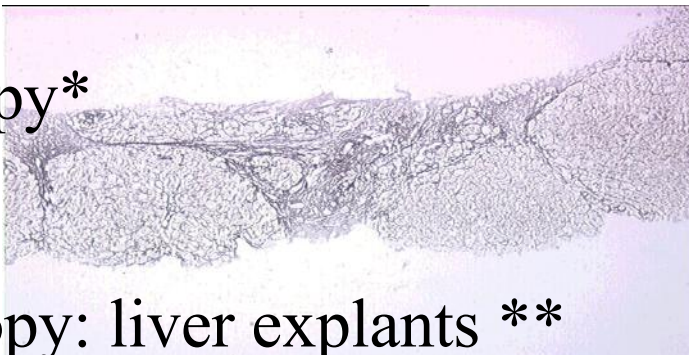
Bénéfices associés à la RVP

Réversibilité de la cirrhose

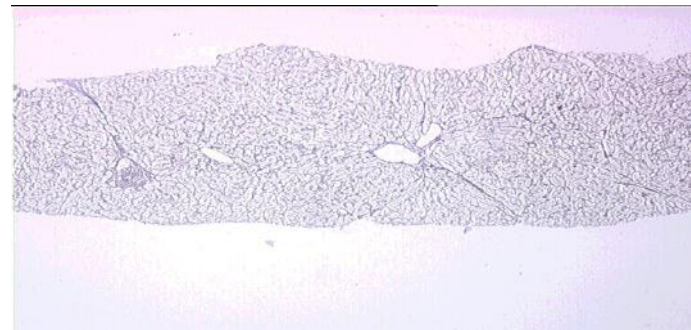


Adapted from Farazi PA et al. 2006

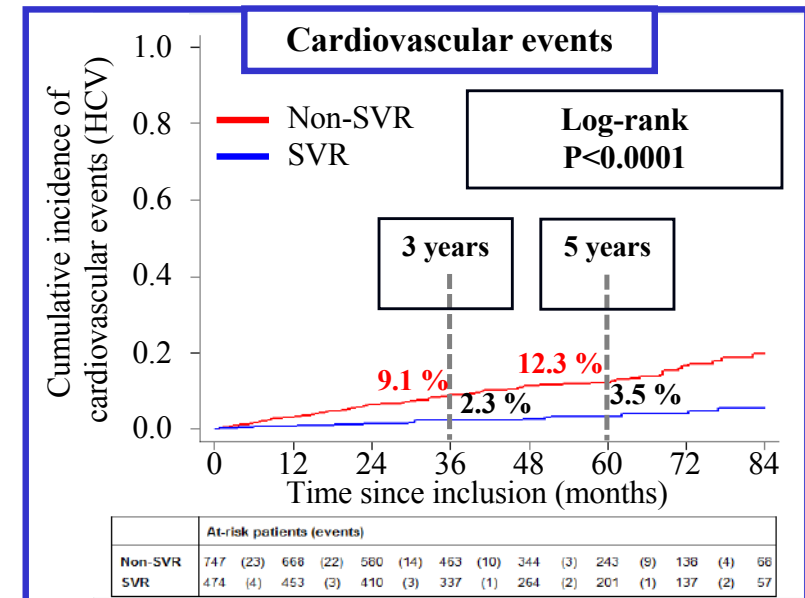
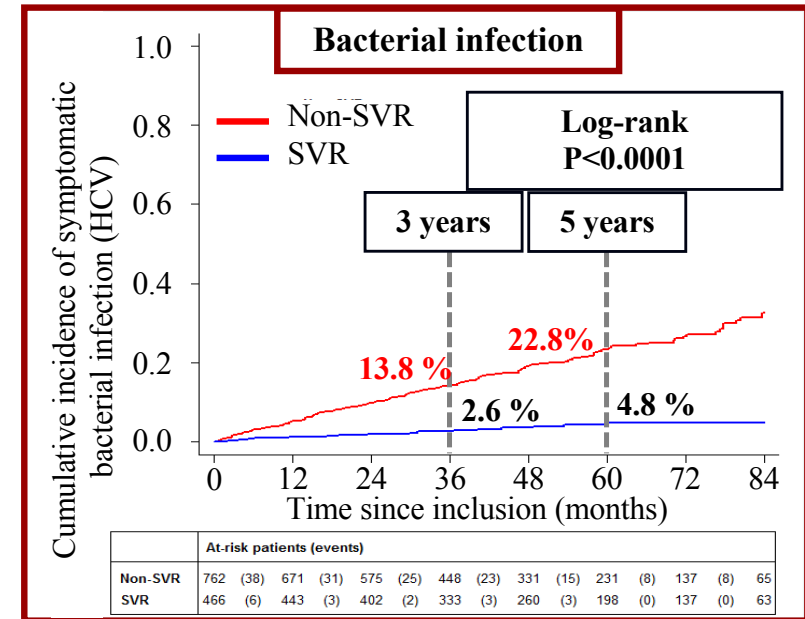
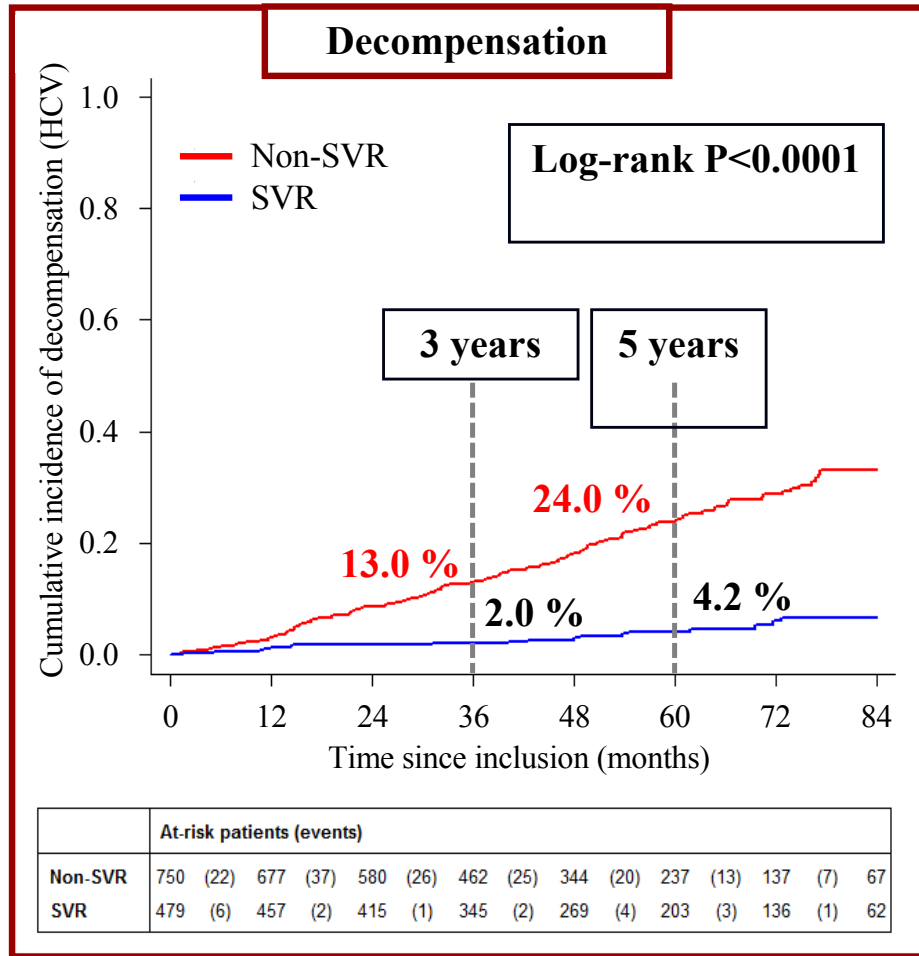
Microscopy*



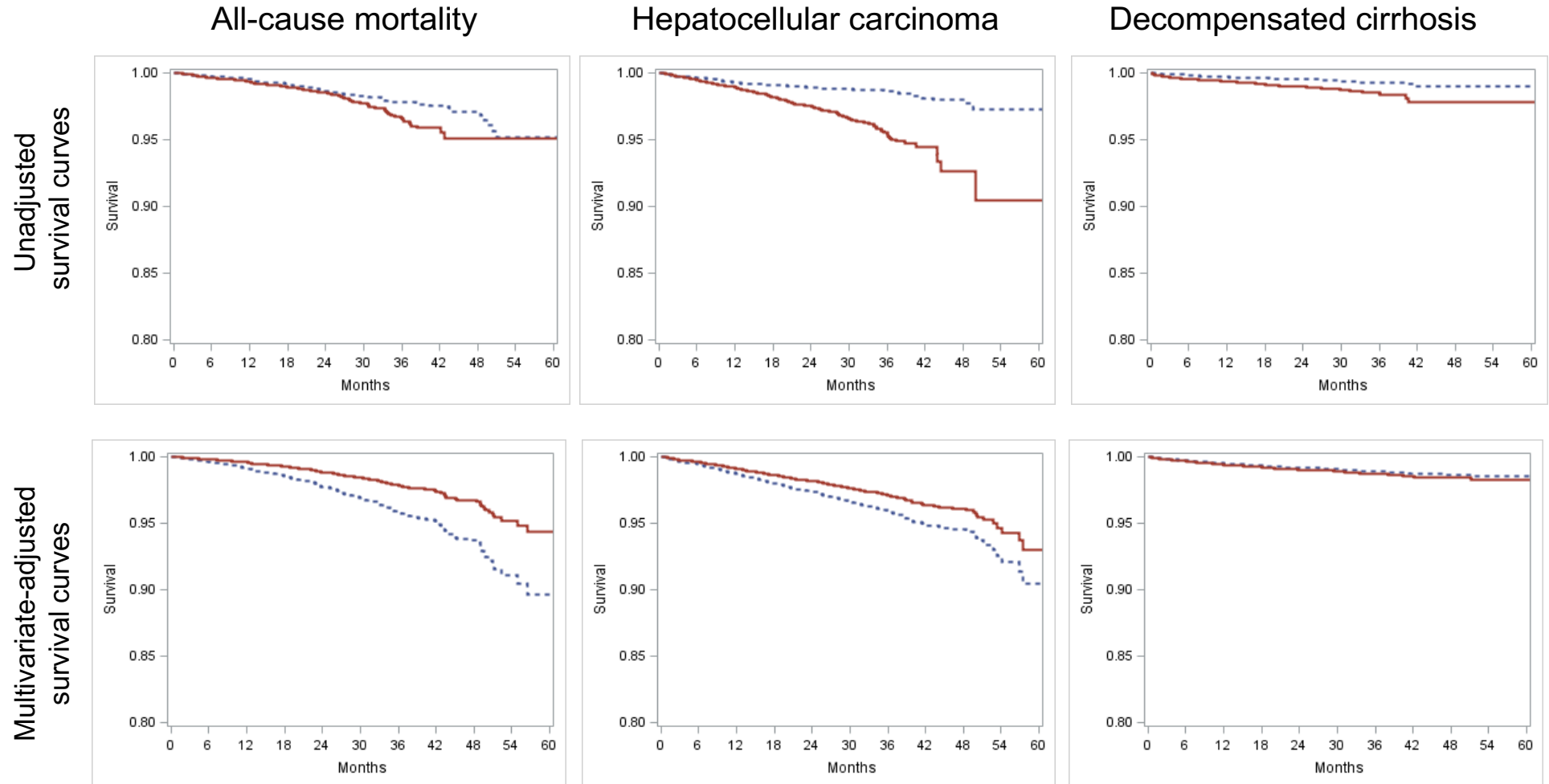
Macroscopy: liver explants **



Bénéfices associés aux AVD



Bénéfices associés à la RVP



	Months	0	12	24	36	48	60
N at risk	DAA+	7344	5448	3469	1012	59	6
	DAA-	9895	4774	2889	1344	360	10

	Months	0	12	24	36	48	60
N at risk	DAA+	7308	5366	3368	977	57	6
	DAA-	9895	4751	2878	1337	355	10

	Months	0	12	24	36	48	60
N at risk	DAA+	7330	5408	3432	996	59	6
	DAA-	9895	4766	2888	1342	360	10

— DAA+ - - - - - DAA-

Traitements par AVD

3 classes d'AVD: Inhibiteurs Protéases, NS5A ou NS5B

(Polymérase)

ATU

Encadrement de la prescription des nouveaux AAD par les RCP

Sofosbuvir
Sovaldi

Simeprevir
Olysio

Daclatasvir
Daklinza

Sofosbuvir
/Ledipasvir
Harvoni

Paritaprevir
Ombitasvir
Viekirax
Dasabuvir
Exviera

Grazoprevir
Elbasvir



AMM

Sofosbuvir
Sovaldi

Simeprevir
Olysio

Sofosbuvir
/ledipasvir
Harvoni

Daclatasvir
Daklinza

Viekirax
Exviera

Grazoprevir
Elbasvir
Zepatier

Restriction initiale du remboursement CPAM aux patients

Fibrose sévère

- F3-F4
- Avant/ après TH

Indépendamment du stade de fibrose

- Cryoglobuline symptomatique
- Lymphome B

Extension des ITR*

- F2 sévère
- VIH F0-F1-F2

Ouverture à tous les patients en Janvier 2017

EASL Recommends Universal Treatment for All People Infected

All patients with HCV infection must be considered for therapy, including treatment-naïve patients and individuals that failed to achieve SVR after prior treatment

Treatment should be considered without delay in patients with:

Significant fibrosis or cirrhosis

Significant EHMs

HCV recurrence after liver transplant

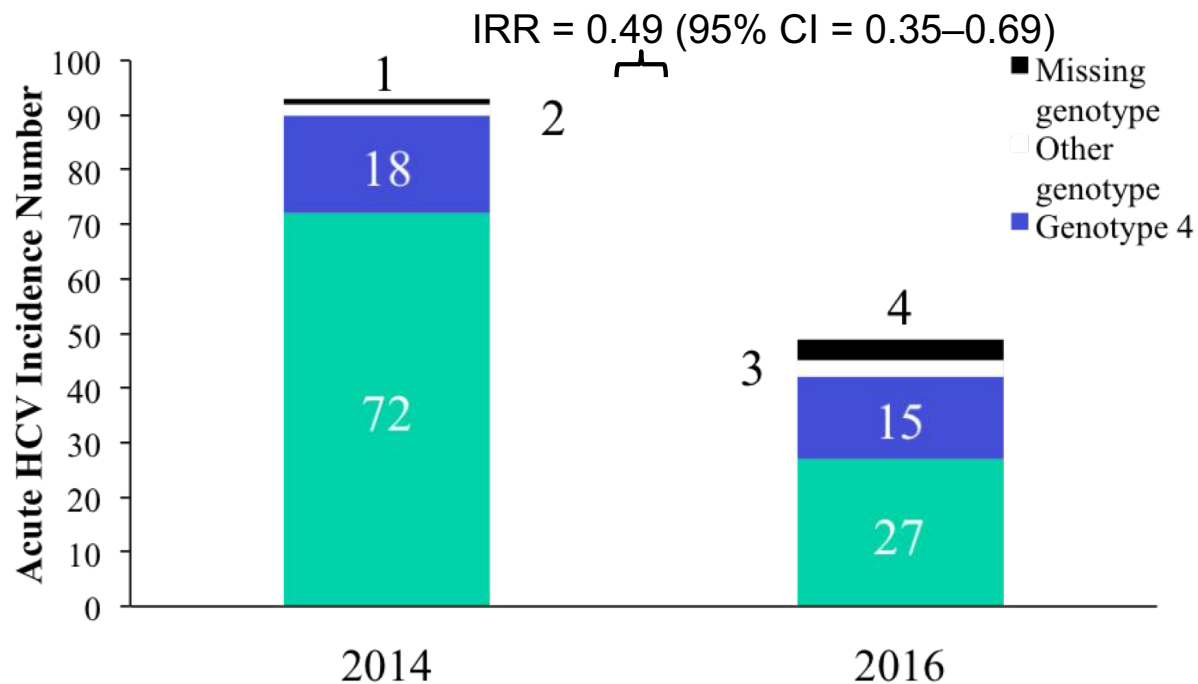
A risk of rapid evolution of liver disease

A risk of infecting others



Decreasing HCV Infection Rate in the Dutch HIV-Positive MSM Population

Retrospective analysis of two prospective studies from the DAHHS to evaluate the effect of introducing interferon-free DAAs for the treatment of chronic HCV in the Netherlands



A 51% decrease in acute HCV infections was observed between 2014 and 2016

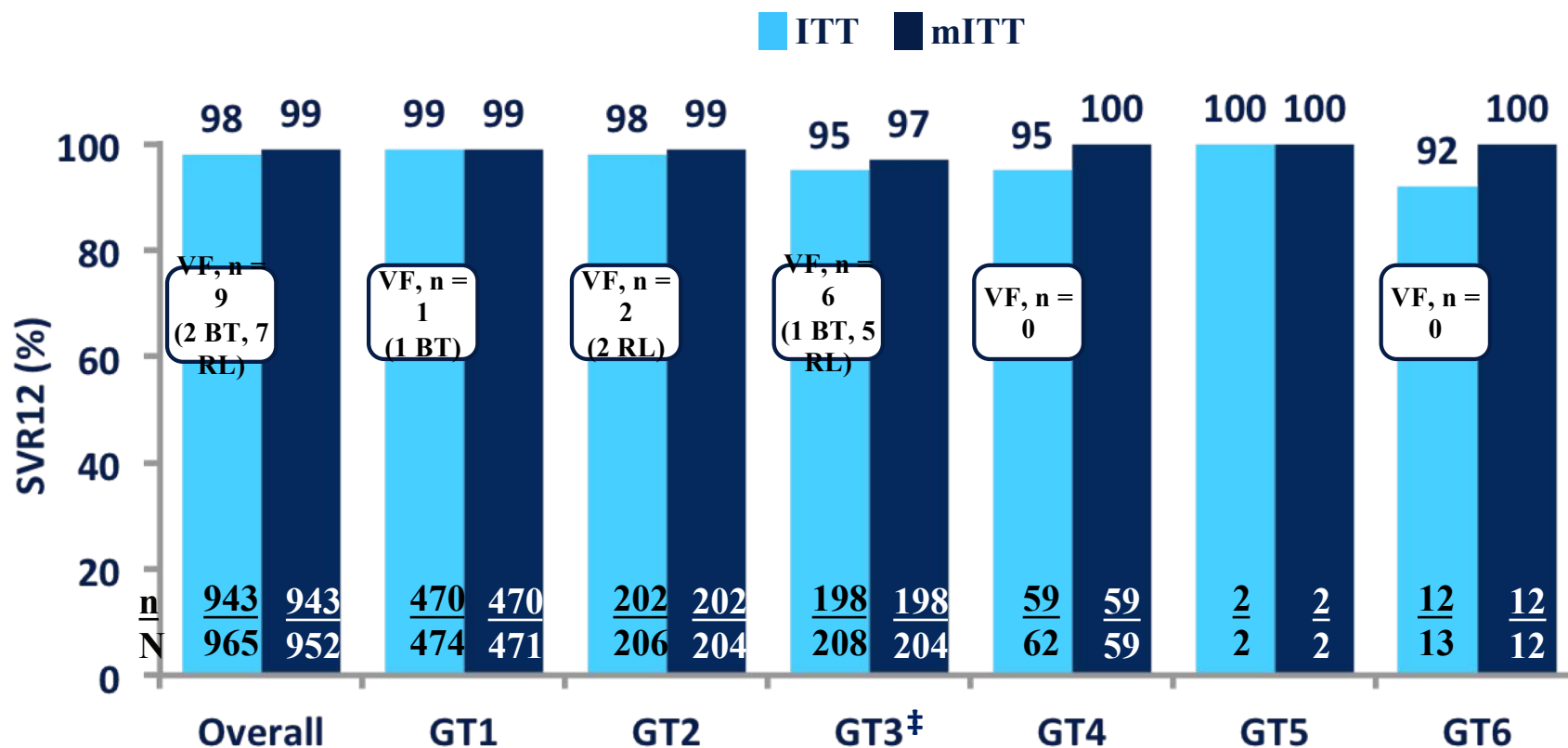
Positive syphilis (from 6.6% to 8.4%, $P = 0.001$) and gonorrhoea (from 16.4% to 19.2%, $P < 0.001$) test results increased from 2014 to 2016

Unrestricted DAA HCV therapy availability has been associated with a decreased HCV infection rate among HIV-positive MSM

DAHHS, Dutch Acute HCV in HIV Studies; IRR, incidence rate ratio; MSM, men who have sex with men.

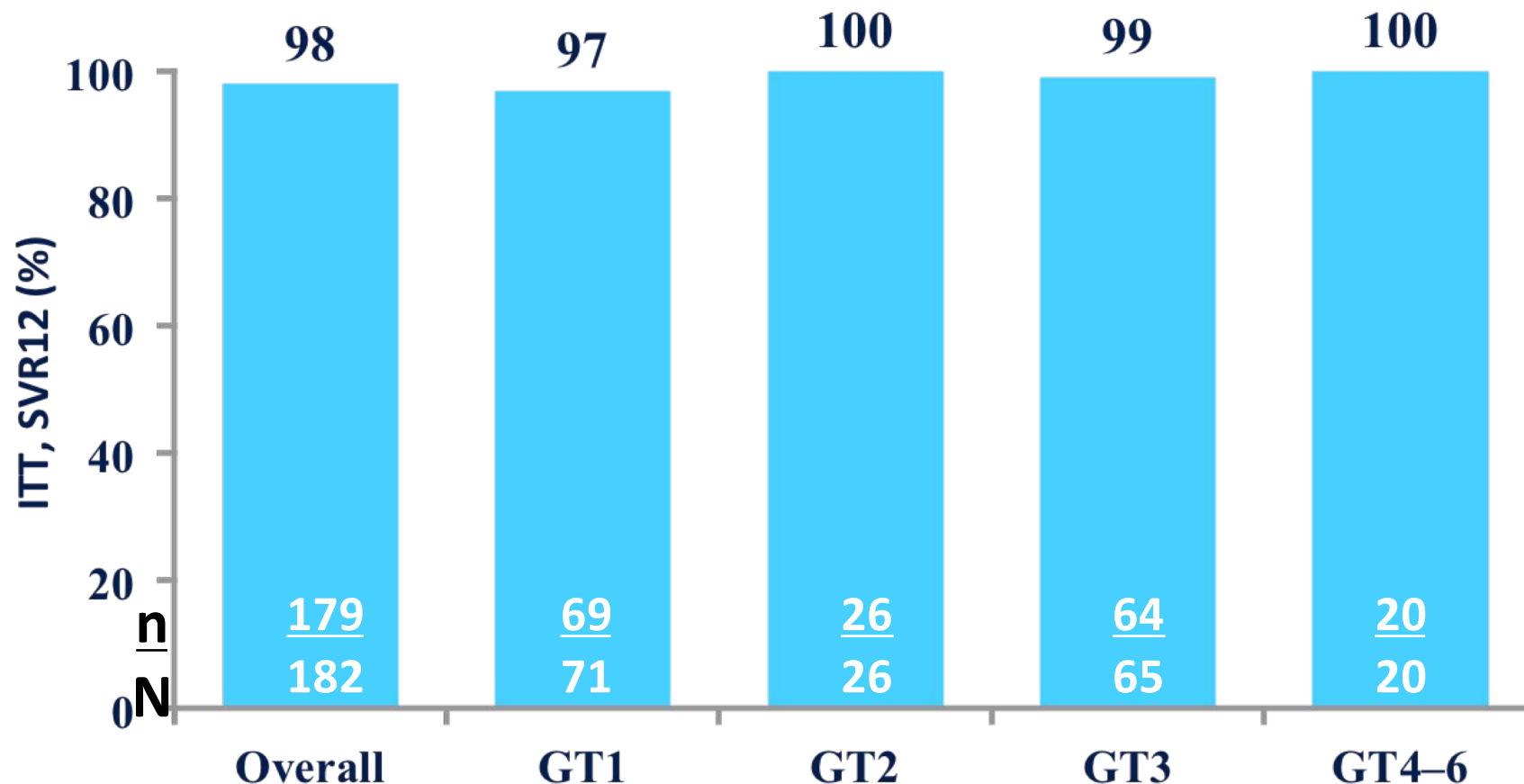
Boerekamps A, et al. *Clin Infect Dis* 2018; **66**:1360–1365.

Glecaprevir/pibrentasvir chez les non cirrhotiques: 8 semaines



* Pooled SVR12 data from arms of nine phase 2 or 3 clinical trials (EXPEDITION-2; EXPEDITION-4; ENDURANCE 1, 2, 3 and 4; SURVEYOR-I Part 2; SURVEYOR-II Parts 1 and 2; and SURVEYOR-II Part 4 studies);
[†] Includes patients with prior SOF use (8-week G/P, n = 10); [‡] All GT3 patients were treatment naive.
 BT, breakthrough; RL, relapse; VF, virologic failure.

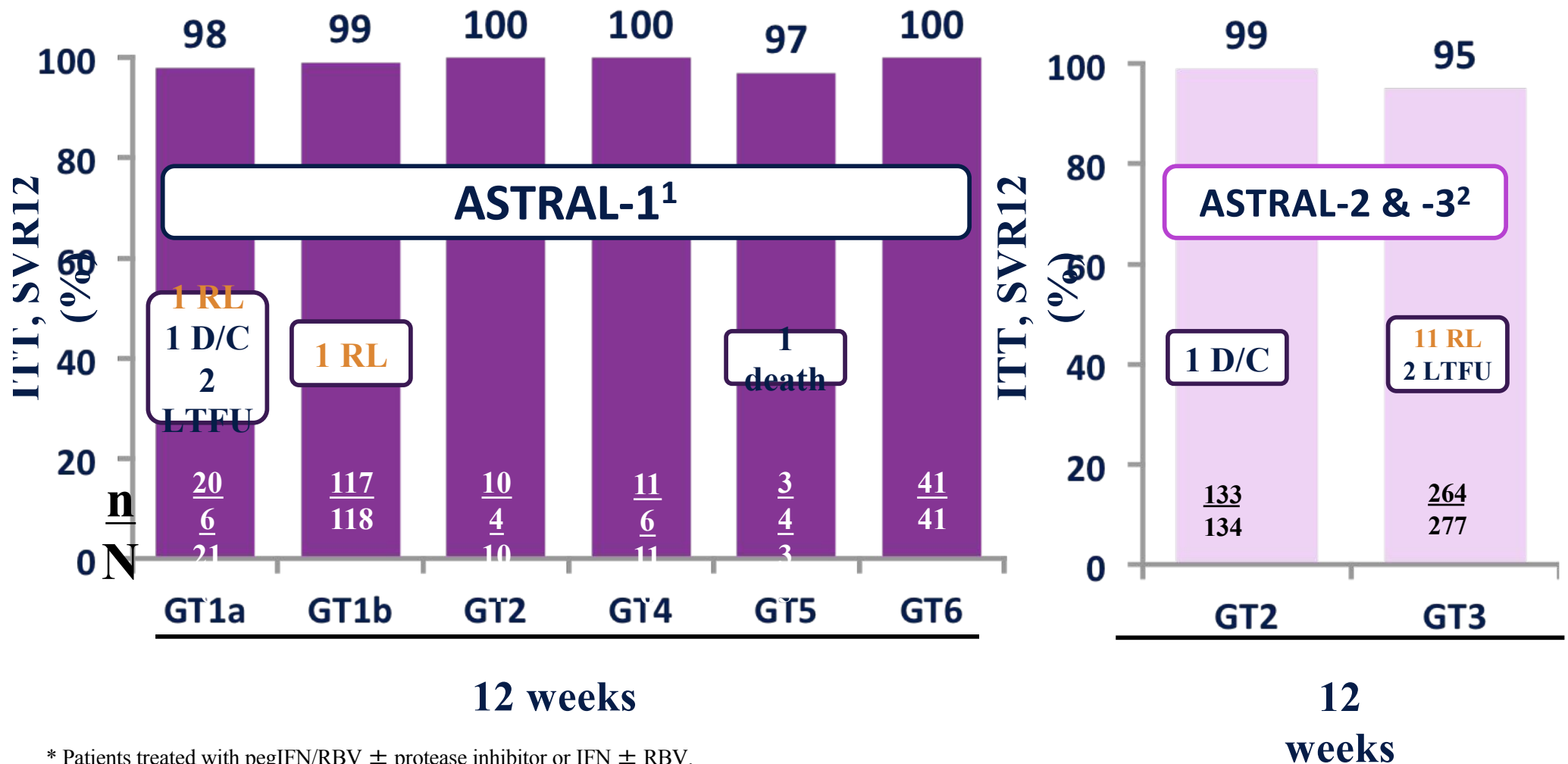
Glecaprevir/pibrentasvir chez les cirrhotiques: 12 semaines



* ITT SVR12 data from the pooled resistance analysis of G/P from phase 2 and 3 clinical studies (SURVEYOR-1 and -2; ENDURANCE-1-4; EXPEDITION-1 and -4).

Krishnan P, *et al. J Hepatol* 2017; **66**(Suppl):S500 (poster presentation FRI-205).

Sofosbuvir/velpatasvir : 12 semaines



* Patients treated with pegIFN/RBV ± protease inhibitor or IFN ± RBV.
D/C, discontinued; LTFU, lost to follow-up.

1. Feld JJ, et al. *N Engl J Med* 2015; **373**:2599–2607; 2. Foster GR, et al. *N Engl J Med* 2015; **373**:2608–2617.

DAA and tolerance

Nb person-year	DAA+ N = 10271	DAA- N = 14233
SAE	1383 (13.5%)	1476 (10.4%)
Arythmia	35 (0.3%)	40 (0.3%)
Cardiac failure	29 (0.3%)	26 (0.2%)
Pulmonary hypertension	3 (0.03%)	2 (0.01%)
Death	151 (1.5%)	228 (1.6%)
SAE of fatal evolution		
Tumors	54	94
Hepato-biliary disease	21	25
Infections	17	33
Cardiac disease	12	17
Others	47	59

DAA and tolerance: brady-arrythmia

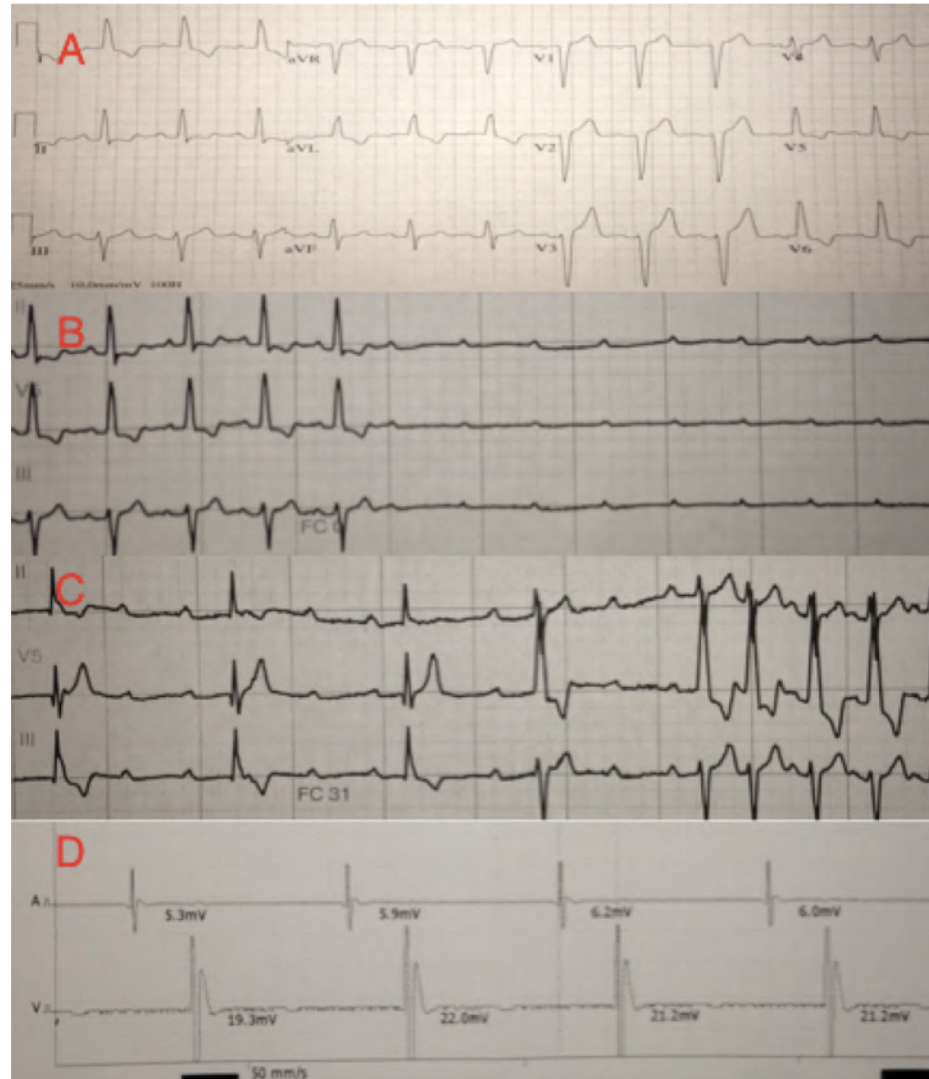
Example 2 : patient 4

D0 : ECG before treatment with sofosbuvir and daclatasvir

D6 : ECG before syncope, 1th degree atrioventricular block

D6 : Intermittent 3rd degree atrioventricular block

Interrogation of pacemaker:
Complete spontaneous resolution of atrioventricular block after treatment discontinuation



EASL Recommendations

Pan-genotypic Regimens

Pan-genotypic regimens (patients <u>without</u> cirrhosis)							
Patients	Prior treatment experience	SOF/VEL (weeks)	GLE/PIB (weeks)	SOF/VEL/VOX (weeks)	LDV/SOF (weeks)	EBR/GZR (weeks)	OBV/PTV/r + DSV (weeks)
GT1a	Treatment-naïve	12	8	No	8-12	12 (HCV RNA \leq 800,000 IU/mL)	No
	Treatment-experienced	12	8	No	No	12 (HCV RNA \leq 800,000 IU/mL)	No
GT1b	Treatment-naïve	12	8	No	8-12	8 (F0-F2) 12 week (F3)	8 week (F0-F2) 12 week (F3)
	Treatment-experienced	12	8	No	12	12	12
GT2	Treatment-naïve	12	8	No	No	No	No
	Treatment-experienced	12	8	No	No	No	No
GT3	Treatment-naïve	12	8	No	No	No	No
	Treatment-experienced	12	12	No	No	No	No
GT4	Treatment-naïve	12	8	No	12	12 (HCV RNA \leq 800,000 IU/mL)	No
	Treatment-experienced	12	8	No	No	No	No
GT5	Treatment-naïve	12	8	No	12	No	No
	Treatment-experienced	12	8	No	No	No	No
GT6	Treatment-naïve	12	8	No	12	No	No
	Treatment-experienced	12	8	No	No	No	No

IFN-free, RBV-free, DAA-based regimens must be used (A1)

* Treatment-experienced to pegIFN + RBV \pm SOF or SOF + RBV.

EASL Recommendations on Treatment of Hepatitis C, 2018. Available at: <http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/easl-recommendations-on-treatment-of-hepatitis-c-2018> (accessed December 2018).

EASL Recommendations

Pan-genotypic Regimens

Pan-genotypic regimens (patients with cirrhosis)							
Patients	Prior treatment experience	SOF/VEL (weeks)	GLE/PIB (weeks)	SOF/VEL/VOX (weeks)	LDV/SOF (weeks)	EBR/GZR (weeks)	OBV/PTV/r + DSV (weeks)
GT1a	Treatment-naïve	12	12	No	12	12 (HCV RNA ≤800,000 IU/mL)	No
	Treatment-experienced	12	12	No	No	12 (HCV RNA ≤800,000 IU/mL)	No
GT1b	Treatment-naïve	12	12	No	12	12	12
	Treatment-experienced	12	12	No	12	12	12
GT2	Treatment-naïve	12	12	No	No	No	No
	Treatment-experienced	12	12	No	No	No	No
GT3	Treatment-naïve	No	12	12	No	No	No
	Treatment-experienced	No	16	12	No	No	No
GT4	Treatment-naïve	12	12	No	12	12 (HCV RNA ≤800,000 IU/mL)	No
	Treatment-experienced	12	12	No	No	No	No
GT5	Treatment-naïve	12	12	No	12	No	No
	Treatment-experienced	12	12	No	No	No	No
GT6	Treatment-naïve	12	12	No	12	No	No
	Treatment-experienced	12	12	No	No	No	No

IFN-free, RBV-free, DAA-based regimens must be used (A1)

* Treatment-experienced to pegIFN + RBV ± SOF or SOF + RBV.

EASL Recommendations on Treatment of Hepatitis C, 2018. Available at: <http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/easl-recommendations-on-treatment-of-hepatitis-c-2018> (accessed December 2018).

EASL Recommendations

Pan-genotypic Regimens

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	Treatment-experienced	12	12	No	No	12 (HCV RNA ≤800,000 IU/mL)	No
GT1b	Treatment-naïve	12	12	No	12	12	12
	Treatment-experienced	12	12	No	12	12	12
GT2	Treatment-naïve	12	12	No	No	No	No
	Treatment-experienced	12	12	No	No	No	No
GT3	Treatment-naïve	No	12	12	No	No	No
	Treatment-experienced	No	16	12	No	No	No
GT4	Treatment-naïve	12	12	No	12	12 (HCV RNA ≤800,000 IU/mL)	No
	Treatment-experienced	12	12	No	No	No	No
GT5	Treatment-naïve	12	12	No	No	No	No
	Treatment-experienced	12	12	No	No	No	No
GT6	Treatment-naïve	12	12	No	12	No	No
	Treatment-experienced	12	12	No	No	No	No

IFN-free, RBV-free, DAA-based regimens must be used (A1)

Ongoing clinical trials seeking to further simplify treatment (e.g. EXPEDITION-8)²

* Treatment-experienced to pegIFN + RBV ± SOF or SOF + RBV.

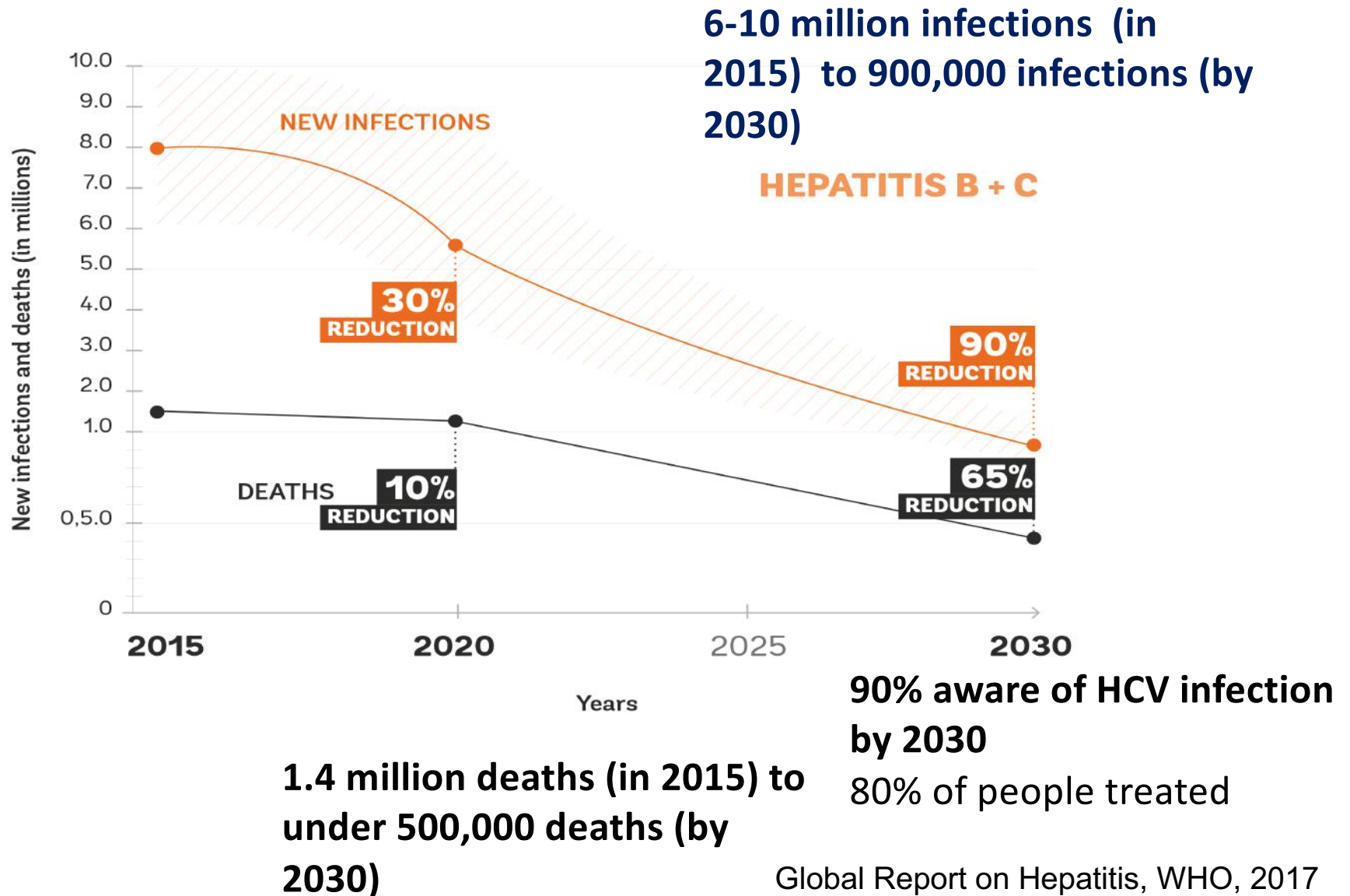
Le VHC : fin du début ou début de la fin?

- Grande efficacité pangénotypique de multiples combinaisons
- Faciles d'usage (8-12 semaines) et bien tolérées
- Bénéfices cliniques avec réversibilité des manifestations clinico-biologiques

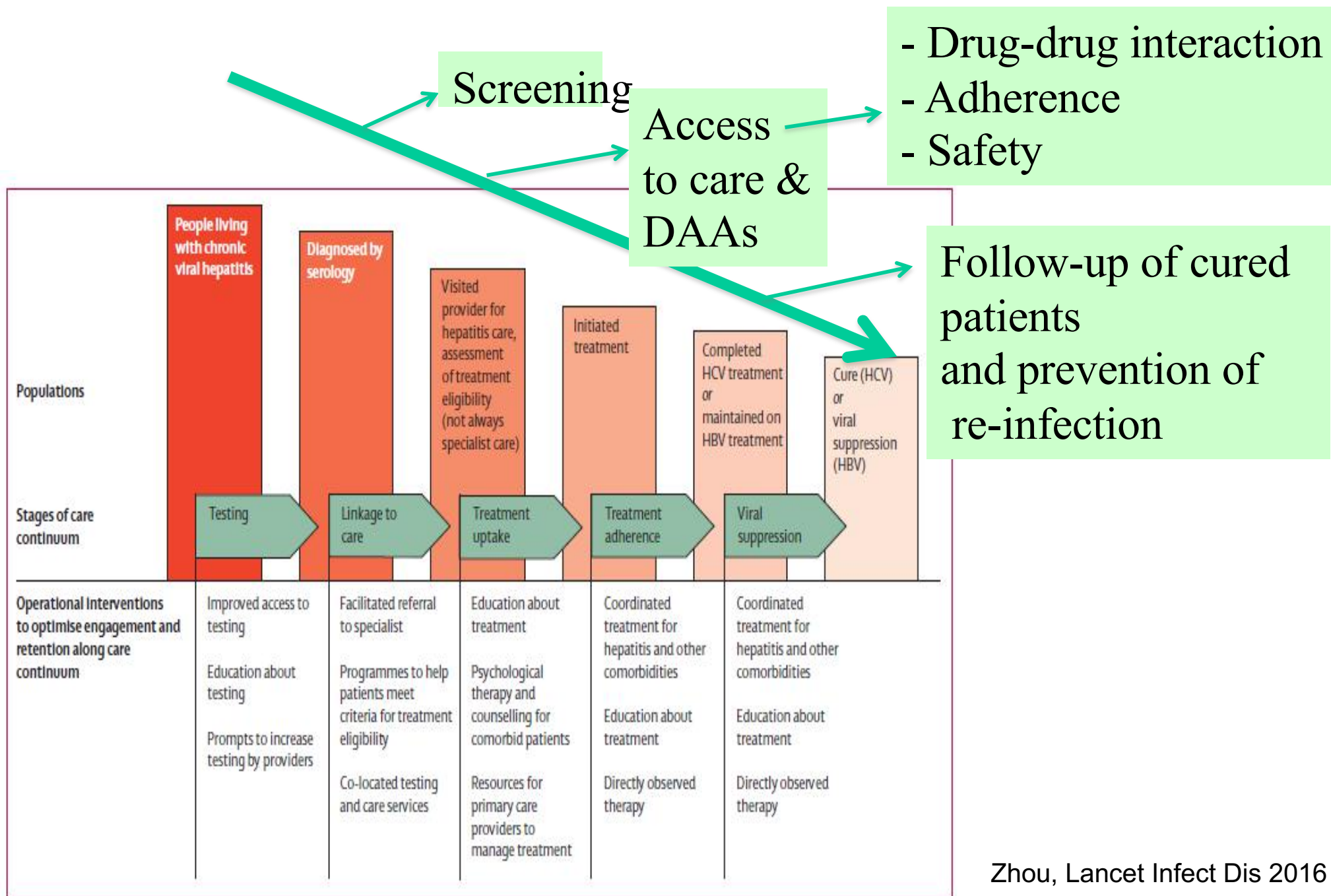
Virus de l'hépatite C: peut-on refermer le livre?

- Infection chronique aux conséquences hépatiques et extra-hépatiques
- La seule infection dont on guérisse (traitements faciles d'usage -8-12 semaines- et bien tolérés)
- Bénéfices cliniques avec réversibilité des manifestations clinico-biologiques
- **Politique d'élimination (OMS)**

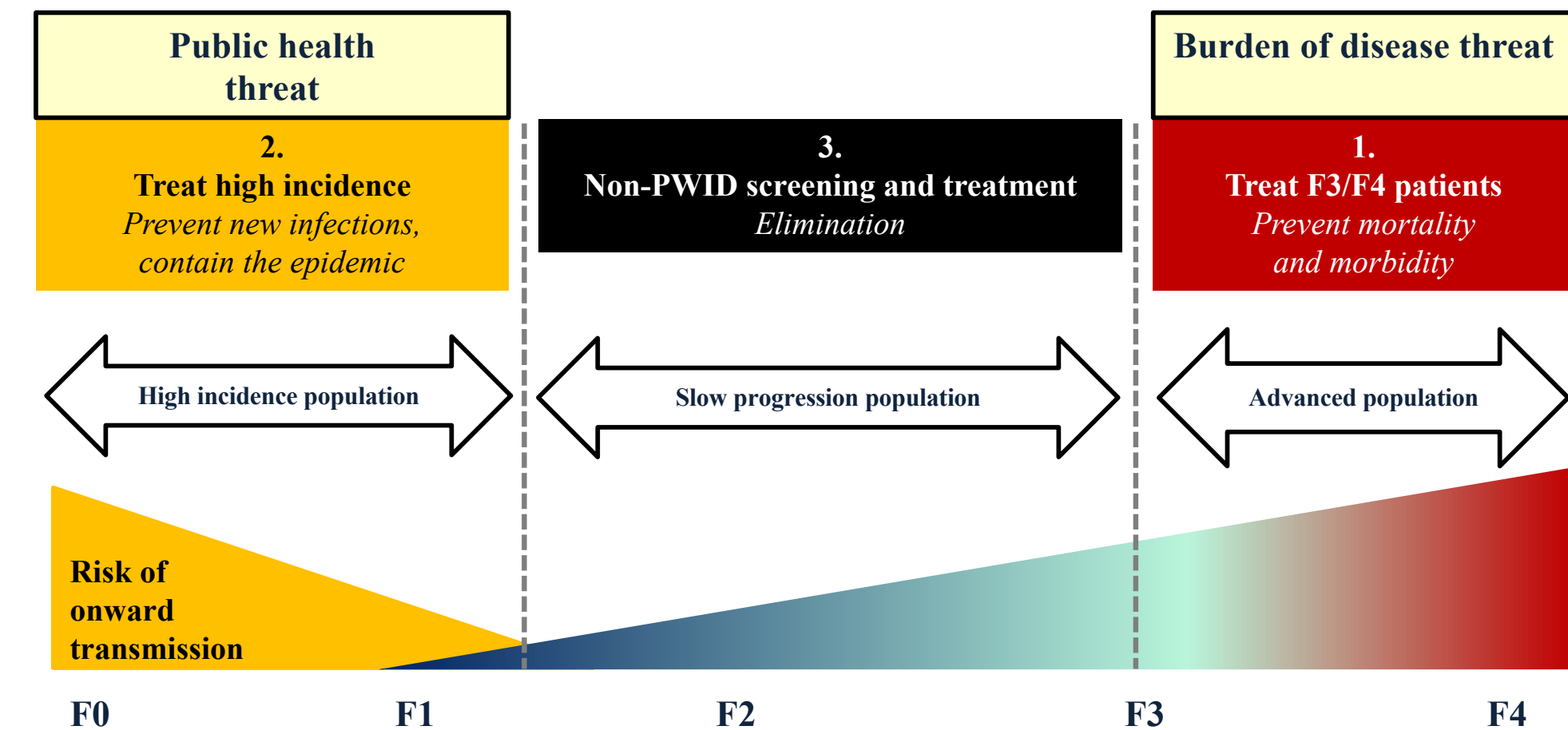
2030 Viral Hepatitis Elimination: one of the WHO sustainable development goals



HCV cascade and Elimination



Politique d'élimination du VHC en France



HCV context in France since 2017



Paris, le 25 mai 2016



Paris, le 25 mai 2016

COMMUNIQUE DE PRESSE

Marisol TOURAINE s'engage pour un accès universel aux traitements innovants contre l'hépatite C

Aujourd'hui, je décide l'accès universel aux traitements de l'hépatite C. Le recours à ce traitement, comme à tout traitement, ne doit dépendre que du choix du patient, éclairé par son médecin, dans le cadre de leur colloque singulier. Le patient doit pouvoir décider en fonction de son appréciation personnelle des avantages et des inconvénients d'être traité, avantages et inconvénients qu'il appartient au médecin d'exposer. Pour permettre cet accès universel, le cadre réglementaire doit être adapté.

Paris, le 31 mars 2017

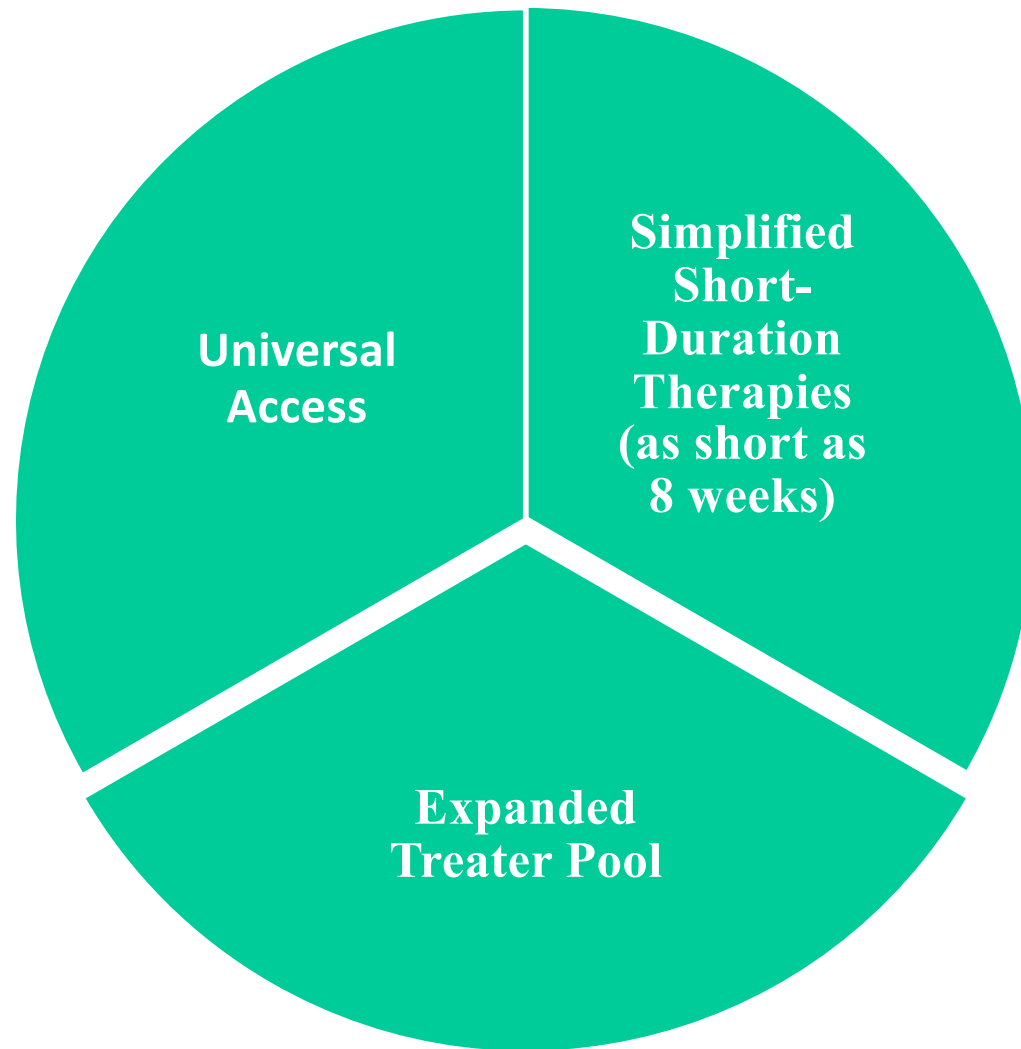
Accès universel aux traitements innovants contre l'hépatite C

Paris, le 26 Mars 2018

L'élimination de l'hépatite C à l'horizon 2025 repose sur 3 actions principales :

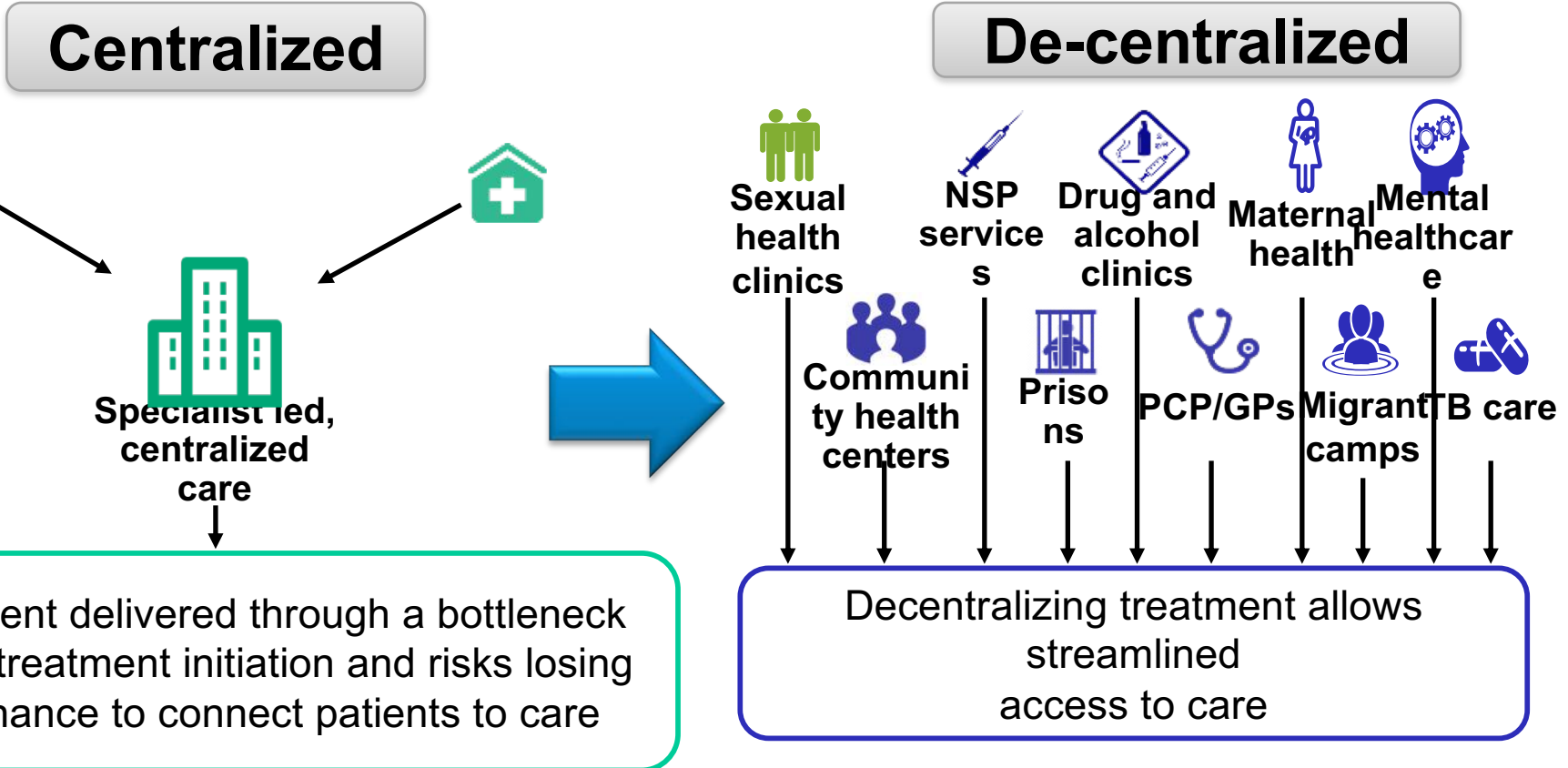
- renforcer l'accessibilité aux traitements de l'hépatite C par l'ouverture à de nouveaux prescripteurs en favorisant les réseaux ville-hôpital ;
- renforcer le dépistage de proximité par test rapide d'orientation diagnostique (TROD) dans une approche combinée du VIH, VHC, VHB ;
- renforcer la prévention par des actions innovantes « d'aller-vers » pour toucher les publics prioritaires et éloignés du système de santé.

How Do We Increase HCV Treatment Uptake?



De-centralizing HCV Management

Patients may face difficulties in accessing testing and treatment facilities. Different populations have differing needs and require specific settings and measures in place to access treatment¹



GP, general practitioner; NSP, needle and syringe program; PWUD, people who use drugs; PCP, primary care practitioner.

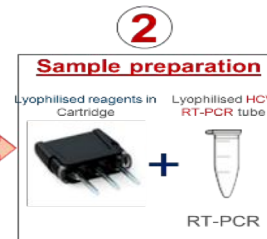
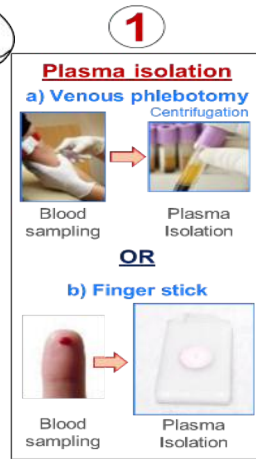
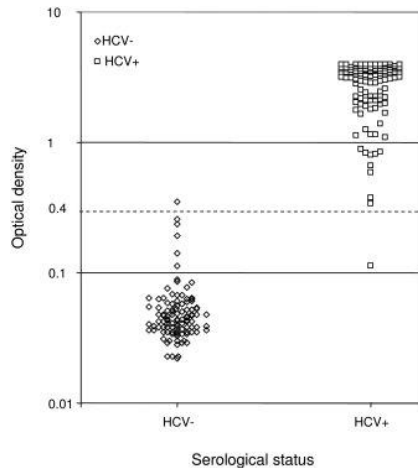
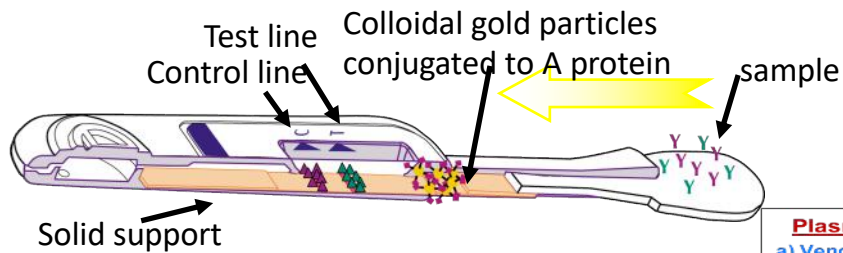
1. EMCDDA Hepatitis C Among Drug Users in Europe. Available at: http://www.emcdda.europa.eu/system/files/publications/2740/att_212353_EN_EMCCDDA_POD_2013_Hep%20C%20treatment.pdf (accessed December 2018).

2. WHO Implementing Comprehensive HIV and HCV Programmes with People Who Inject Drugs. Available at: http://www.who.int/hiv/pub/idu/IDUIT_2017.pdf?ua=1. (accessed December 2018)

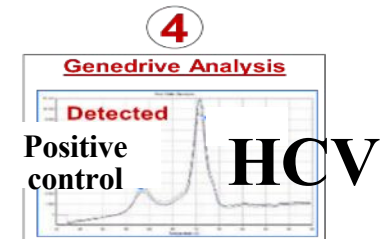
3. WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Available at <https://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2018/en/> (accessed December 2018).

Améliorer le dépistage

Need for easy screening



1. Prevent coagulation and make viral RNA available
2. HCV RT-PCR reagents



Test and treat ?

Llibre A et al, EASL 2017
Submitted

Réduire les coûts

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

150 € 12 weeks fro SOF/DCV in Cambodia



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

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patients
and
their
families

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