« Peut-on éradiquer l'hépatite C ? »

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Equipe ATIP/Avenir INSERM (U1137) : "Modélisation, Aide à la Décision, et Coût-Efficacité en Maladies Infectieuses"

Université Paris Diderot: site Bichat

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
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Inserm

lame UMR 1137
Infection • Antimicrobiens • Modélisation • Evolution

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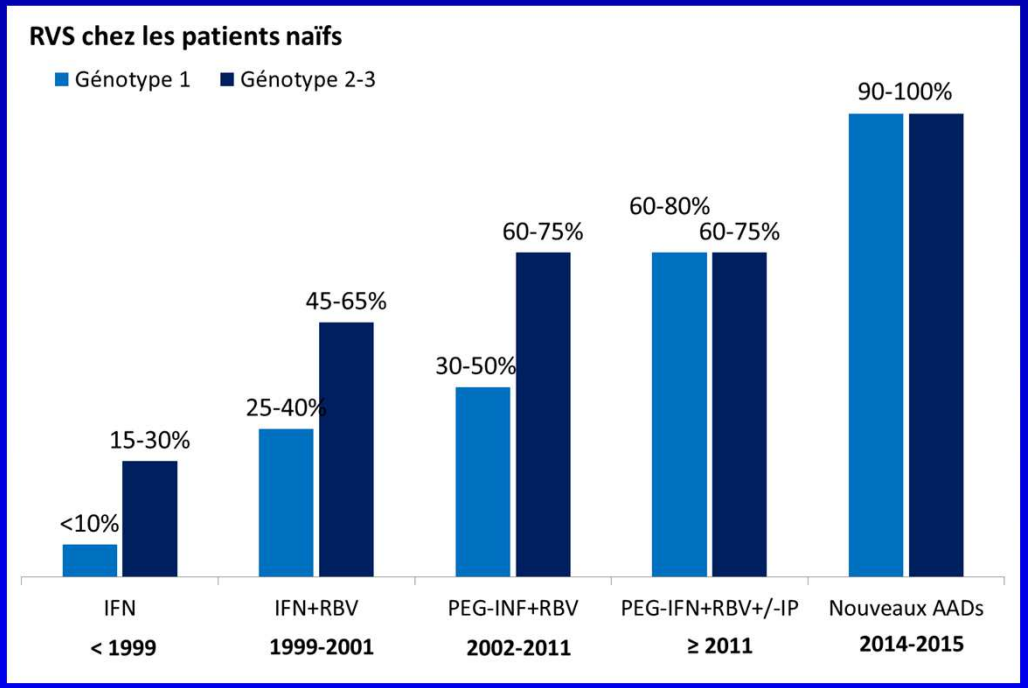
Contexte

- Progrès thérapeutiques considérables
  - Efficacité
  - Durée
  - Tolérance



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/688227/2014
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Exviera
dasabuvir

On 20 November 2014, the Committee for Medicinal Products for Human Use (CHMP) a
positive opinion, recommending the granting of a marketing authorisation for the medi
Exviera, 250 mg film-coated tablets intended for the treatment of chronic hepatitis C in
combination with other medicinal products. The applicant for this medicinal product is A
They may request a re-examination of any CHMP opinion, provided they notify the Euro
Agency in writing of their intention within 15 days of receipt of the opinion.

The active substance of Exviera is dasabuvir sodium, a non-nucleoside inhibitor of the h
dependent RNA polymerase encoded by the NS5B gene.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/688255/2014
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Viekirax
ombitasvir / paritaprevir / ritonavir

On 20 November 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Viekirax (12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir), film-coated tablets intended for the treatment of chronic hepatitis C in adults in combination with other medicinal products. The applicant for this medicinal product is AbbVie Ltd. They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The active substances of Viekirax are ombitasvir, an inhibitor of HCV non-structural protein NS5A, which is essential for the viral replication, paritaprevir, an inhibitor of the nonstructural protein NS3/4A protease, also essential for the viral replication, and ritonavir, a potent cytochrome P450 3A4 inhibitor used as a pharmacokinetic enhancer.

FOR IMMEDIATE RELEASE

EUROPEAN COMMISSION GRANTS MARKETING AUTHORIZATION FOR GILEAD'S HARVONI®▼ (LEDIPASVIR/SOFOSBUVIR), THE FIRST SINGLE TABLET REGIMEN TO TREAT THE MAJORITY OF CHRONIC HEPATITIS C PATIENTS WITH GENOTYPE 1 AND 4

-- Once-Daily Single Tablet Regimen Eliminates the Need for Interferon and Ribavirin for Patients with Genotype 1 and 4 Hepatitis C without Cirrhosis or with Compensated Cirrhosis --

Harvoni is indicated for the treatment of chronic hepatitis C virus (HCV) in adults and is recommended in treatment-naïve and treatment-experienced cirrhotic and non-cirrhotic genotype 1 and 4 patients with a treatment duration of 12 or 24 weeks depending on prior treatment history and cirrhosis status. Eight weeks of treatment with Harvoni may be considered in non-cirrhotic treatment-naïve genotype 1 patients. In genotype 1 and 4 patients with decompensated cirrhosis, and genotype 3 patients with cirrhosis and/or prior treatment failure, Harvoni should be used in combination with ribavirin for 24 weeks. Harvoni is also indicated for patients with HCV who have HIV co-infection.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 15, 2014 VOL. 370 NO. 20

Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis

Kris V. Kowdley, M.D., Stuart C. Gordon, M.D., K. Rajender Reddy, M.D., Lorenzo Rossaro, M.D., David E. Bernstein, M.D., Eric Lawitz, M.D., Mitchell L. Shiffman, M.D., Eugene Schiff, M.D., Reem Ghalib, M.D., Michael Ryan, M.D., Vinod Rustgi, M.D., Mario Chojkier, M.D., Robert Herring, M.D., Adrian M. Di Bisceglie, M.D., Paul J. Pockros, M.D., G. Mani Subramanian, M.D., Ph.D., Di An, Ph.D., Evguenia Svarovskaia, Ph.D., Robert H. Hyland, D.Phil., Phillip S. Pang, M.D., Ph.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Andrew J. Muir, M.D., David Pound, M.D., and Michael W. Fried, M.D., for the ION-3 Investigators*

Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial

Mark Sulkowski, Christophe Hezode, Jan Gerstoft, John M Vierling, Josep Mallolas, Stanislas Pol, Marcelo Kugelmas, Abel Murillo, Nina Weis, Ronald Nahass, Oren Shibolet, Lawrence Serfaty, Marc Bourliere, Edwin DeJesus, Eli Zuckerman, Frank Dutko, Melissa Shaughnessy, Peggy Hwang, Anita Y M Howe, Janice Wahl, Michael Robertson, Eliav Barr, Barbara Haber

Lancet 2015

Le traitement a un double impact :

- Individuel : guérison du malade
- Collectif : la transmission

$\rightarrow$ Patients non-virémiques : ne transmettent pas l'infection

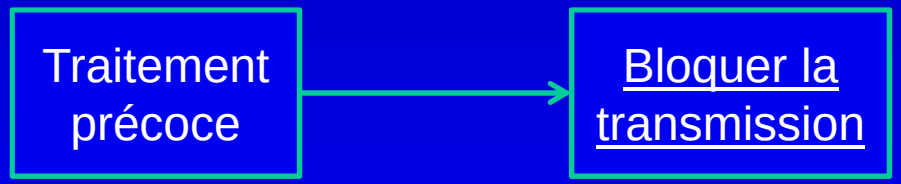
Table 1. Analysis of risk factors for hepatitis C virus (HCV) seroconversion in health care workers who did (case patients) or did not (matched control subjects) experience HCV seroconversion after occupational exposure to HCV.

Variable	Case patients (n = 60)	Matched control subjects (n = 204)	Unadjusted matched OR (95% CI)	P
HCV load[b]				
≤4 $\log_{10}$ copies/mL	1 (1.7)	11 (5.4)	1.0	
>4 to 6 $\log_{10}$ copies/mL	5 (8.3)	10 (4.9)	5.5 (0.6–55.5)	.15
>6 $\log_{10}$ copies/mL	6 (10.0)	6 (2.9)	11.0 (1.1–114.1)	.04

Yazdanpanah; Clin Infect Dis 2005

Test and Treat hépatite C

Traitements plus efficaces : « TasP » notamment dans les populations des UD



Test and Treat hépatite C

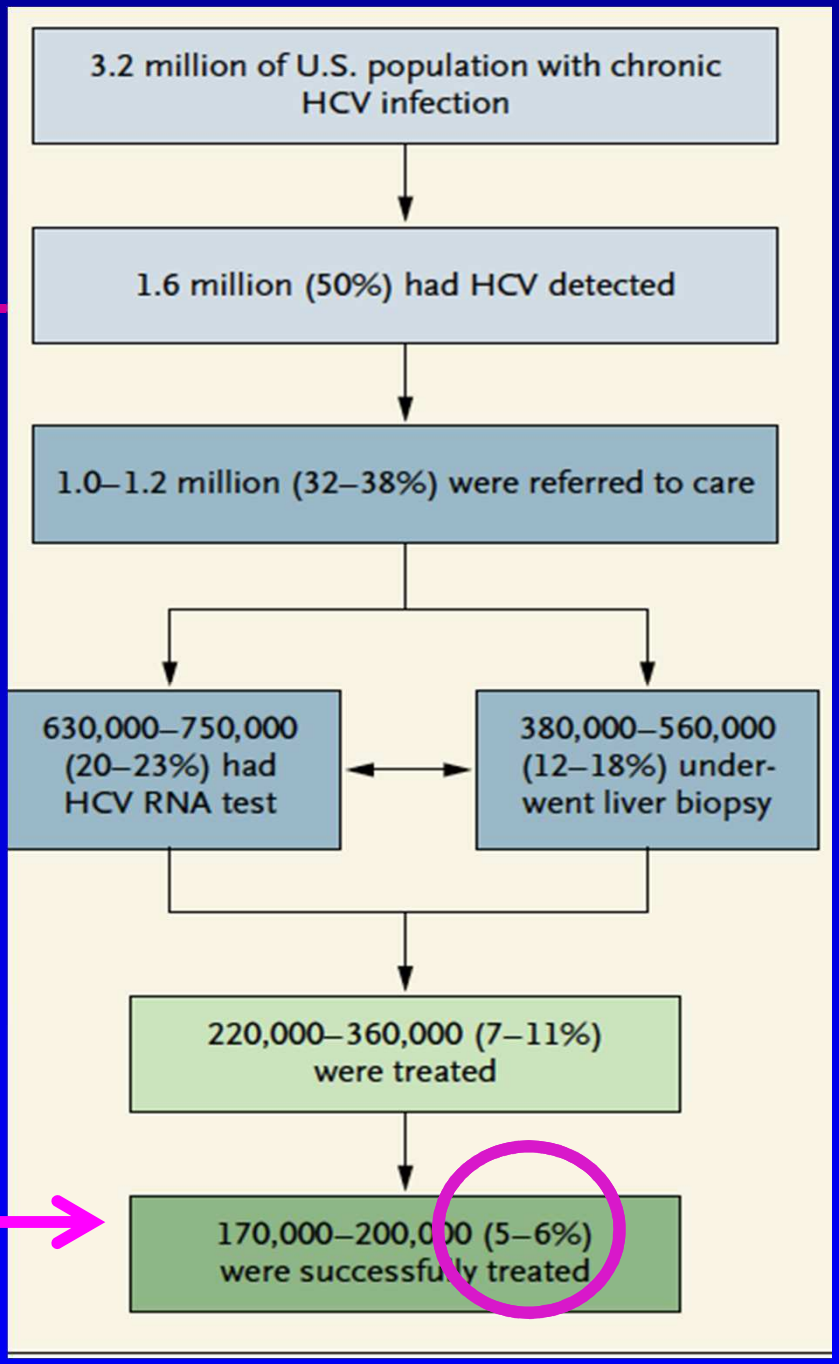
Efficacité : dépend de plusieurs facteurs :

- Efficacité des traitements
- Articulation avec les structures de soin
- Adhérence au traitement

Dépistage efficace à deux niveaux :

- couverture de la population : diagnostiquer le plus grand nombre d'infectés
- rapidité : délais infection→diagnostic le plus court possible

Cascade of care in the United States



The proportion of patients successfuly treated in the US

Holmberg SD, et al. NEJM 2013;368(20):1859-61.

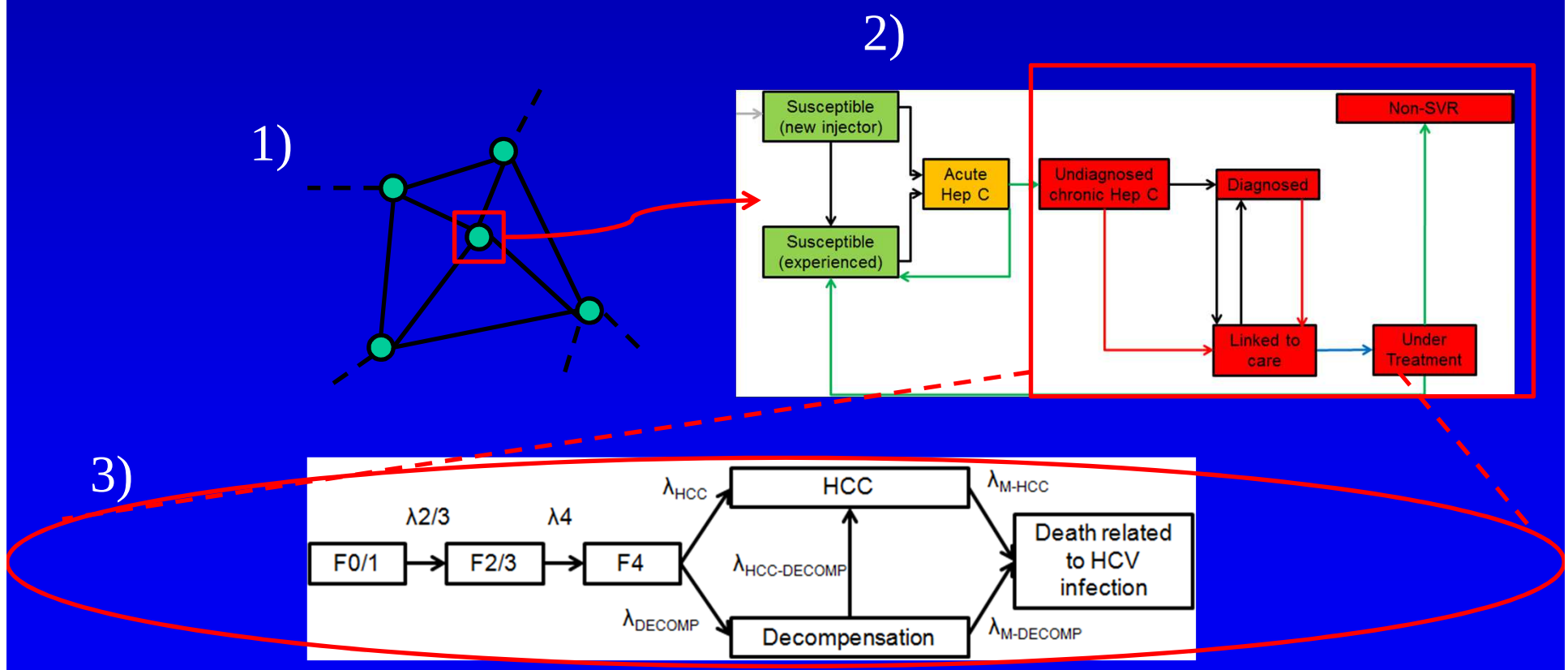
Impact of new DAA-containing regimens on HCV transmission among people who inject drugs (PWID): a model-based analysis (ANRS 95146)

Anthony Cousien, Viet Chi Tran, Marie Jauffret-Roustide, Sylvie Deuffic-Burban, Jean-Stéphane Dhersin, Yazdan Yazdanpanah

Cousien et al. Hepatology 2015

Methods

1) Network model for the infectious contacts in the population
2) Individual-based model for HCV infection and care
3) Natural history model for chronic hepatitis C
+ mortality, and cessation of drug use



Cousien et al. Hepatology 2015

Scenarios

Scenario	Testing (active / inactive PWID) Time to diagnosis (mean)	Time to linkage to care (mean)	Lost to follow-up (%/y)	Treatment initiation criteria	%SVR (genotype 1 / 2,3)
1 (ref)	1.25 y / 1.45 y	2.1 y	14%/y	F2 →F4	81.3%

Incoming DAAs regimens

Cousien et al. Hepatology 2015

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Current treatment standards

Cousien et al. Hepatology 2015

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Cousien et al. Hepatology 2015

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3	1.25 y / 1.45 y	**6 months**	**5%/y**	F2 →F4	81.3%

Cousien et al. Hepatology 2015

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Cousien et al. Hepatology 2015

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Cousien et al. Hepatology 2015

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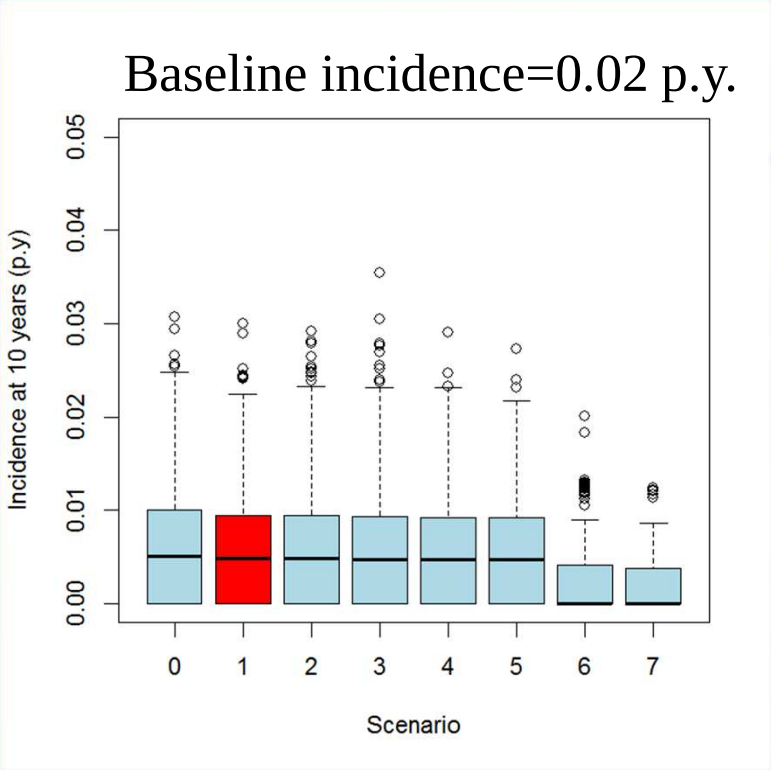
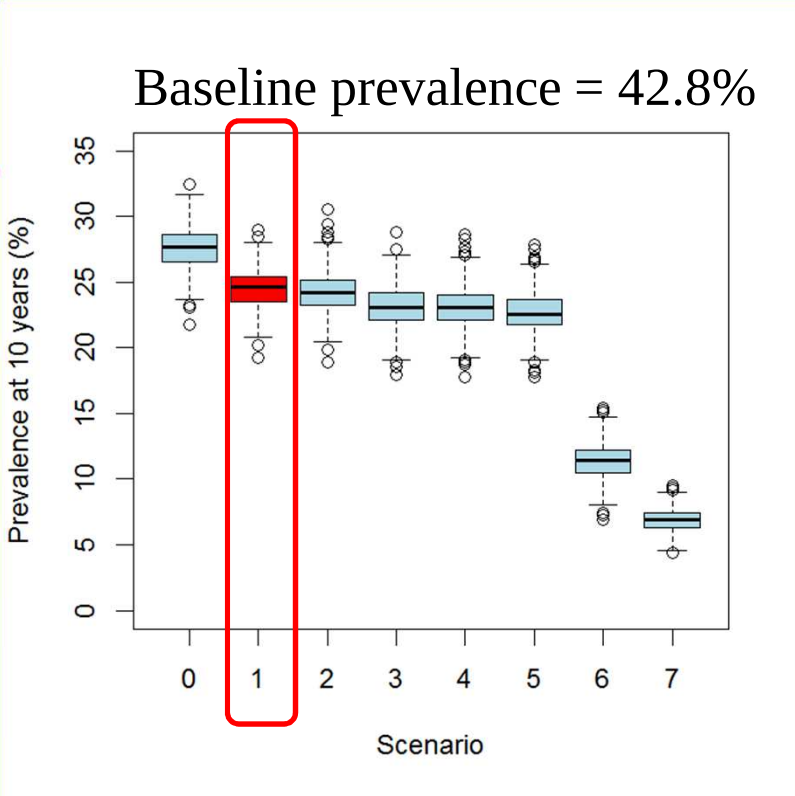
Cousien et al. Hepatology 2015

Results: HCV transmission (10 years)





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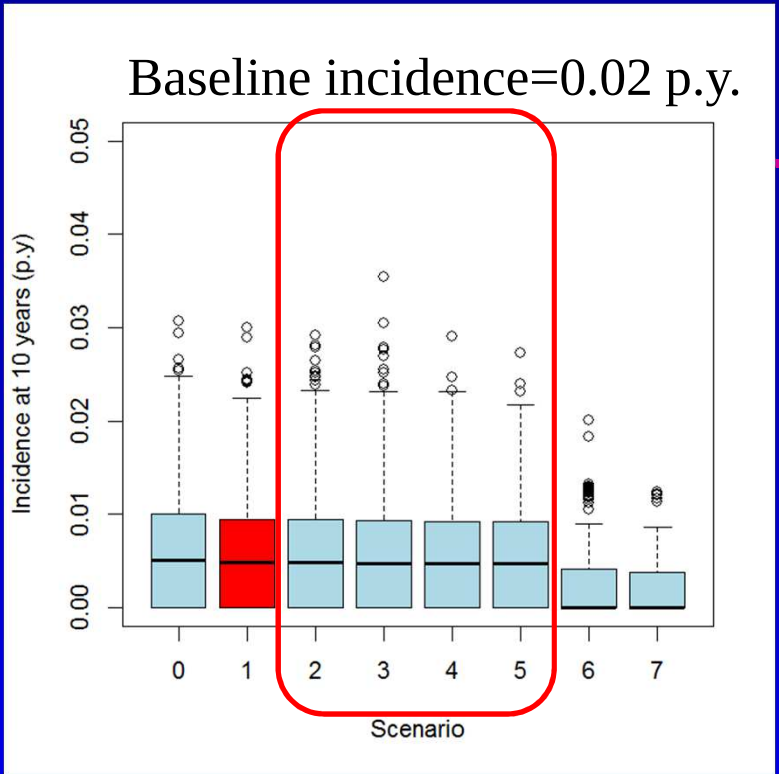

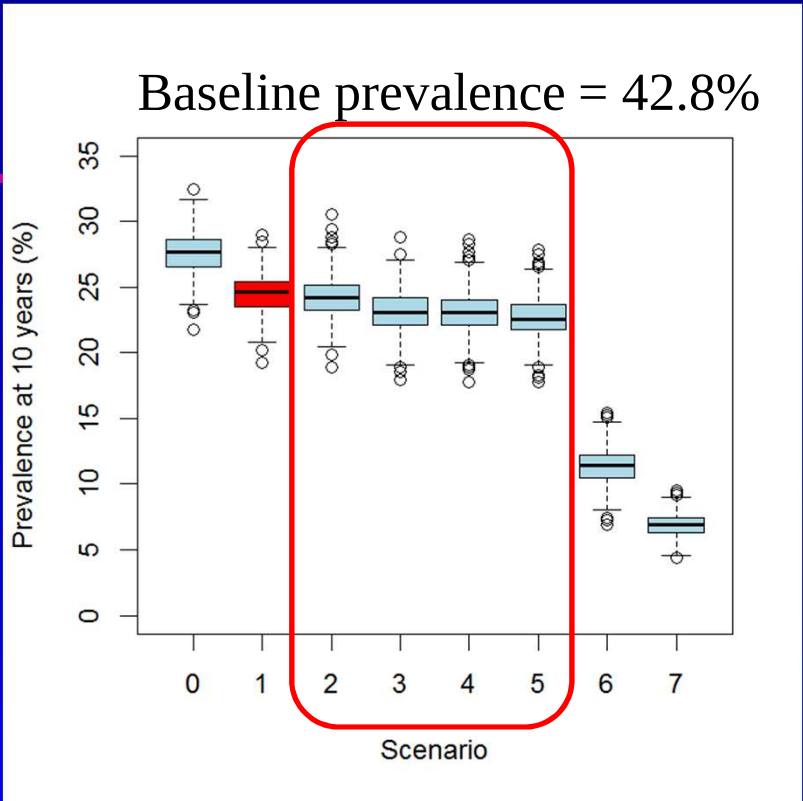

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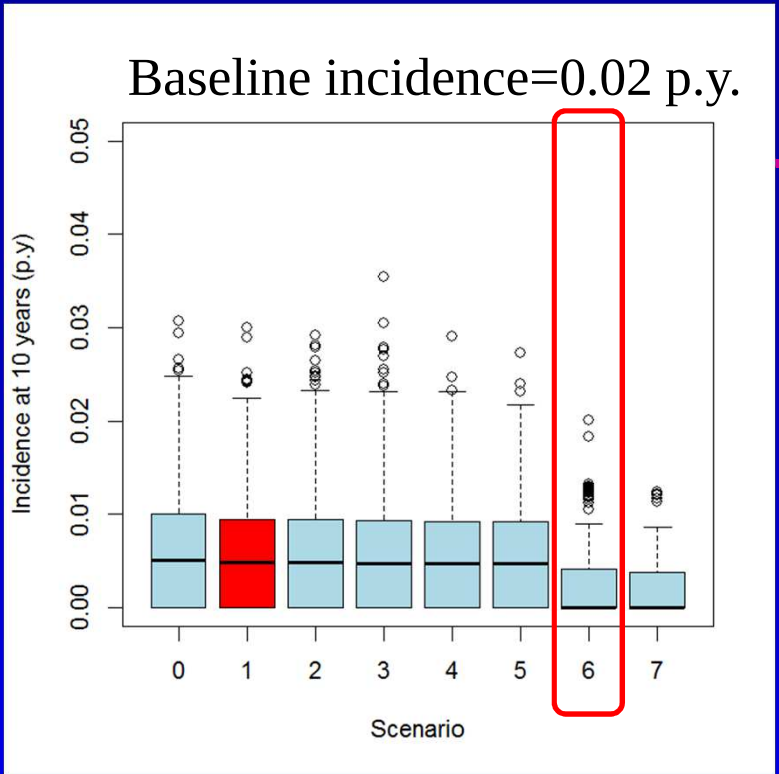

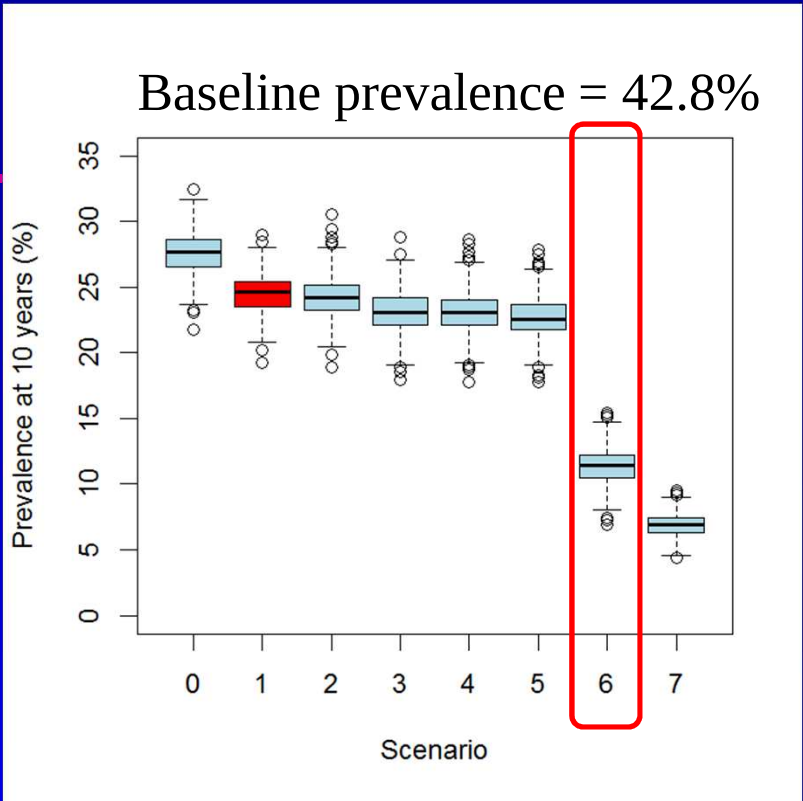

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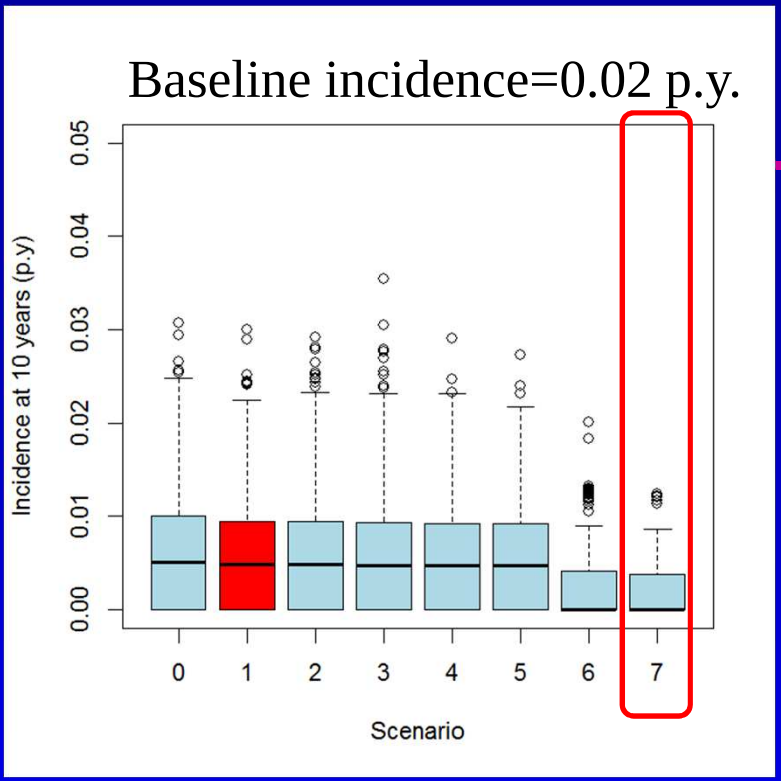
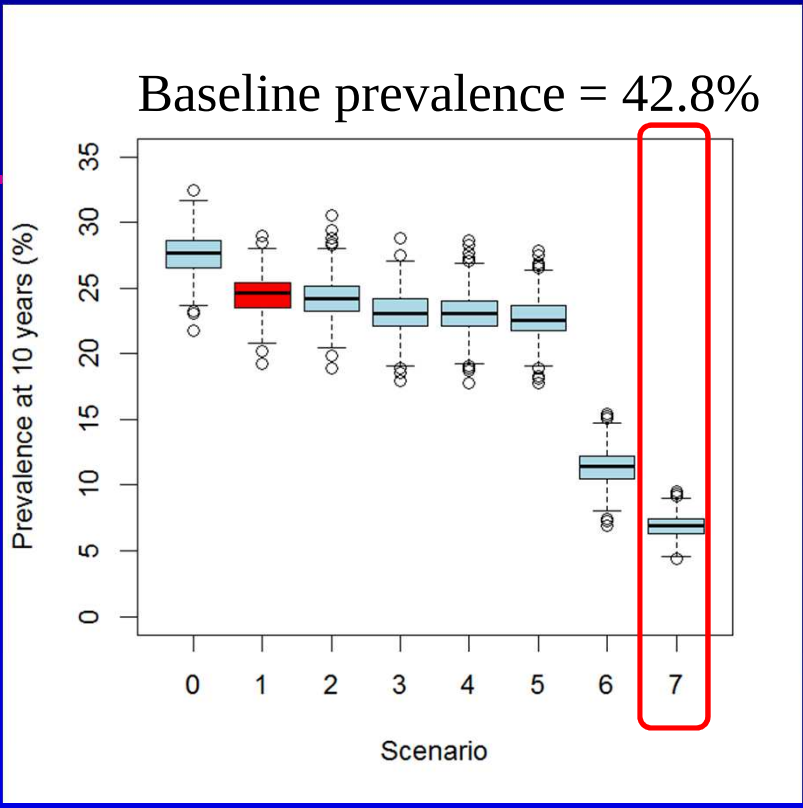
Results: HCV transmission (10 years)

Baseline incidence=0.02 p.y.



Baseline prevalence = 42.8%



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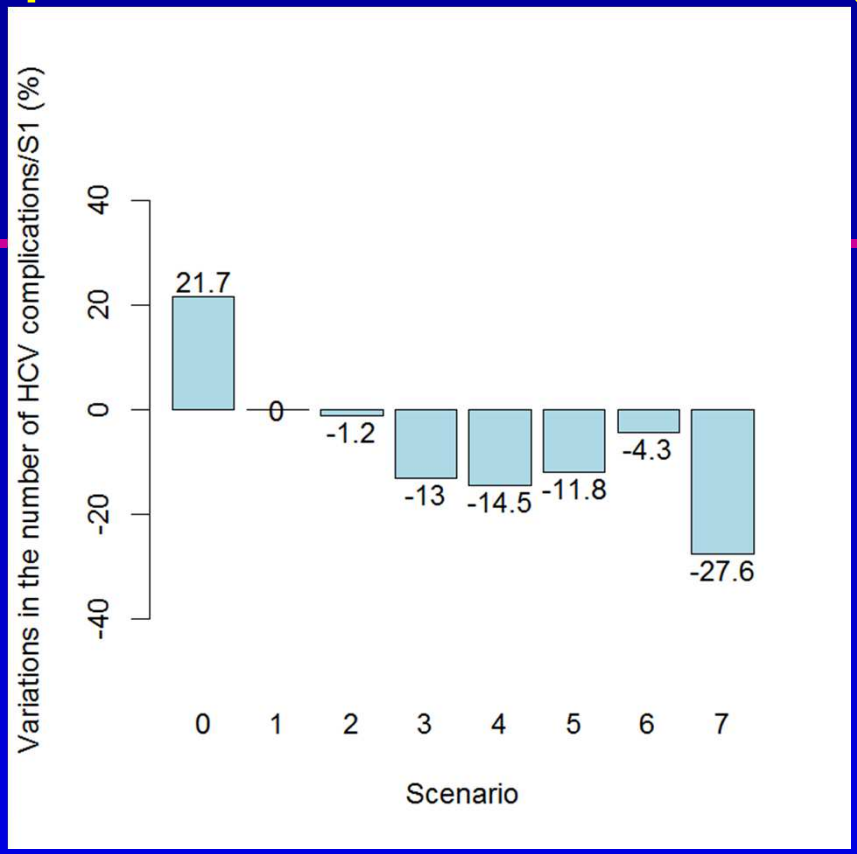
Results: complications of cirrhosis (40 years)



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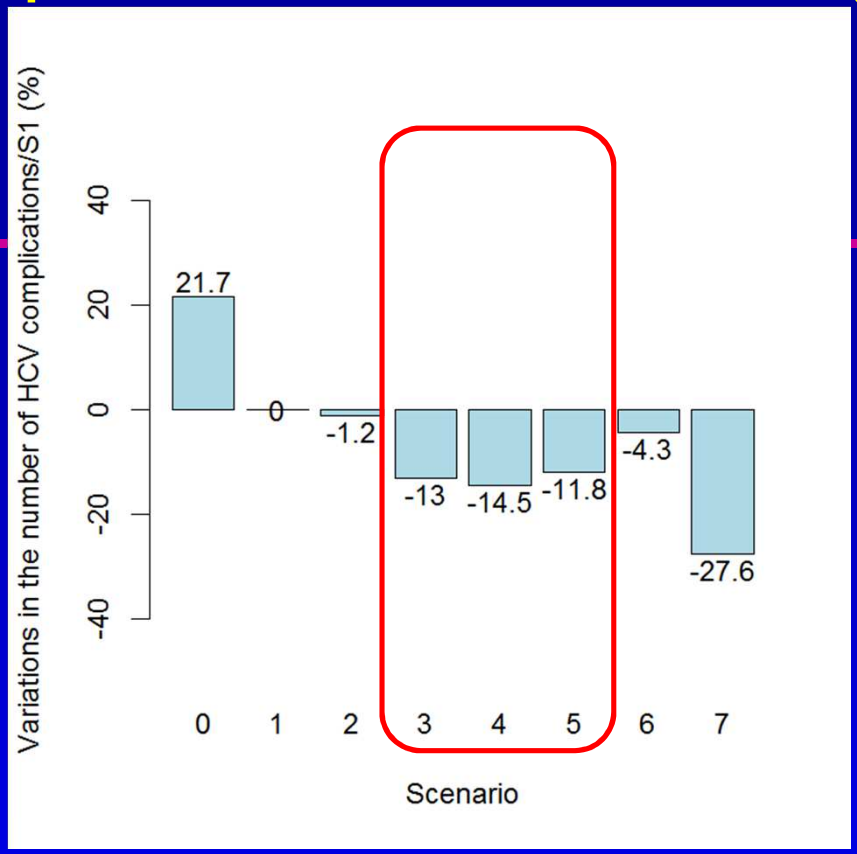

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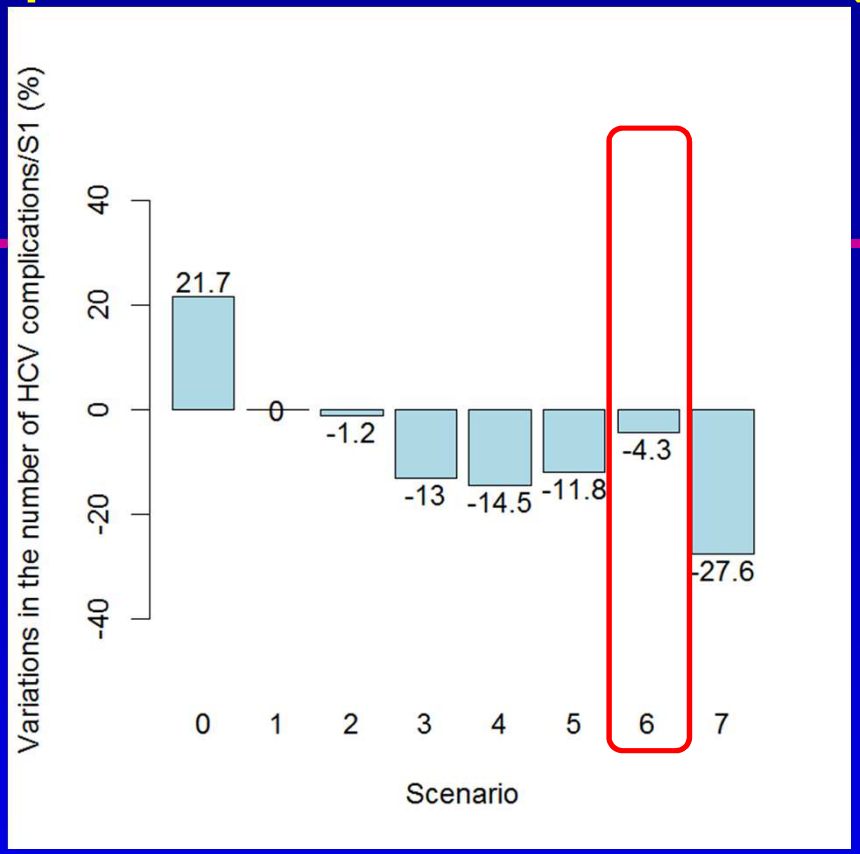

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Améliorer le dépistage

- Prévalence
  - Ac anti-VHC = 0,84 %

- Proportion de sujets ne connaissant pas leur séropositivité
  - VHC : 43 % (2004)
    - **100 868 personnes** (IC 95 % : 58 534-143 202).

VHC en France (données 2004)
Meffre J Med Virol 2010

Améliorer le dépistage

Proportion de sujets connaissant leur séropositivité

- 2004 57%
  - No transfusion, not IDU 25,6%
  - IDU 93,2%
  - Transfusion before 1992 66,5%

Dubois Hepatology 1997
Meffre J Med Virol 2010

Outils et Acteurs du Dépistage

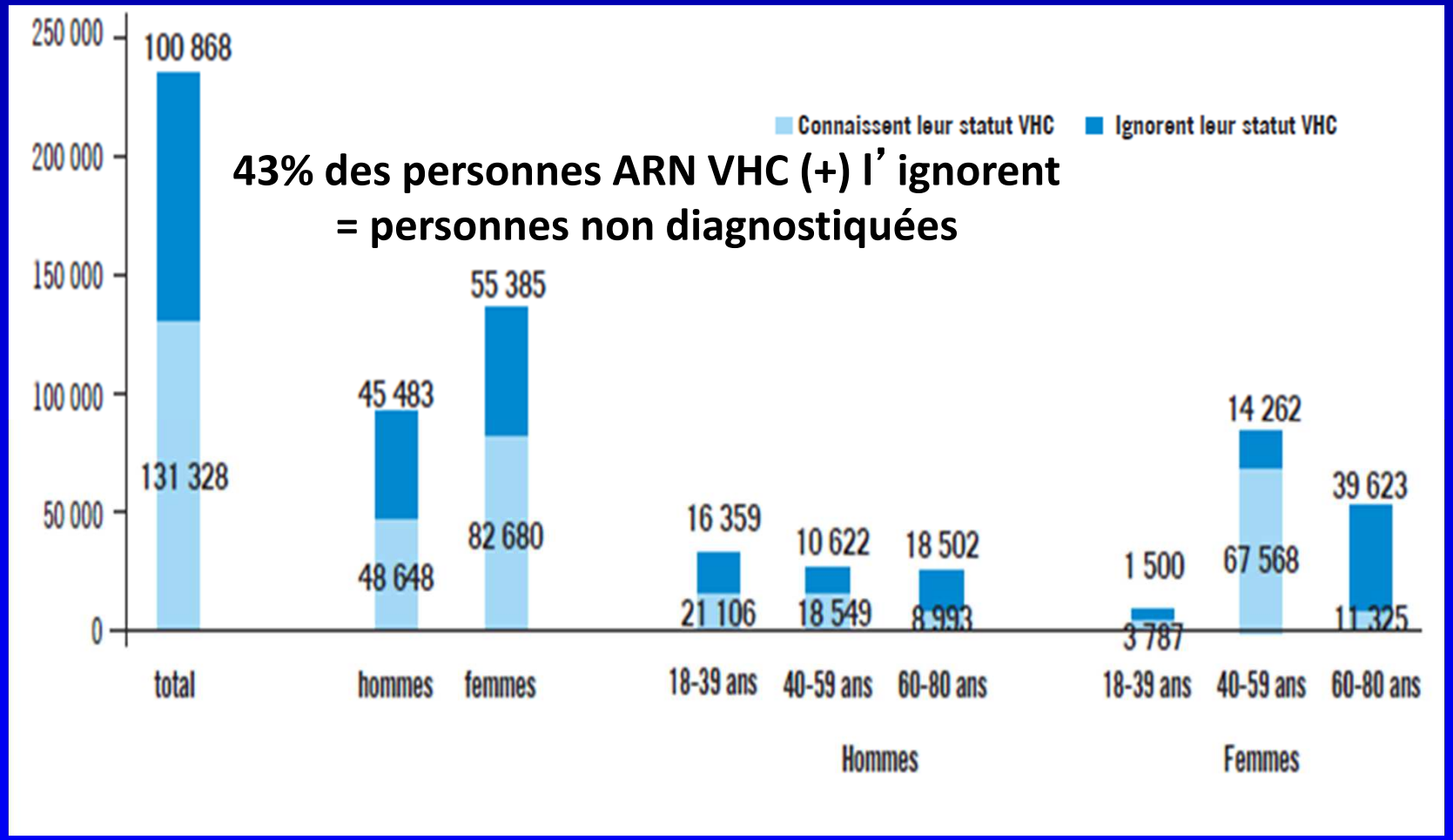
- Tests rapides d'orientation diagnostique (TROD):
  - –Sang capillaire ou liquide craviculaire
  - –Faciles à réaliser, rapides, utilisables hors des structures de soins habituelles mais sensibilité plus faible
  - –Recommandations HAS: validation pour le VHC
- Acteurs actuels: médecins généralistes, CDAG, CSAPA, CIDDIST : amélioration possible (CeDIGG)
  - acteurs médicaux et non-médicaux

Dépistage

- Les recommandations de dépistage de l'infection par le VHC:
  - en France: datent de 2001:
    - dépistage ciblé sur des facteurs de risque.
  - En Amérique du Nord (2012):
    - dépistage systématique d'une génération (1945-65 [USA], 1945-75 [Canada])

Dépistage Infection VHC

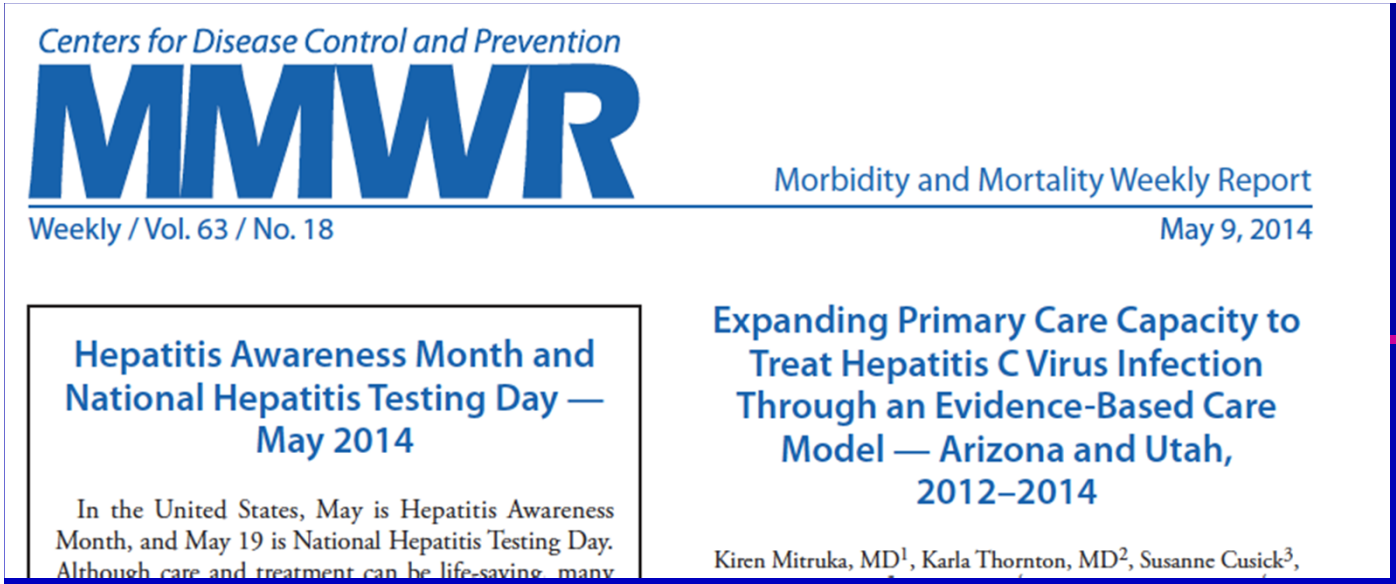
Patients ARN + (InVS 2004)



- **Les hommes**
- **Les viroses chroniques (VHB, VHC, VIH) +++**

Améliorer le lien avec les structures de soins

- Consultations avancées
  - Dans le cadre de réseaux ville-hôpital
  - CDAG/CIDDIST (CeDIGG),
  - Structures d'addictologie (CSAPA) ou de réduction des risques (CAARUD),
- Microstructures médicales (réseaux de ville multidisciplinaires incluant les travailleurs sociaux),
- « Maison du patient »



Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 63 / No. 18

May 9, 2014

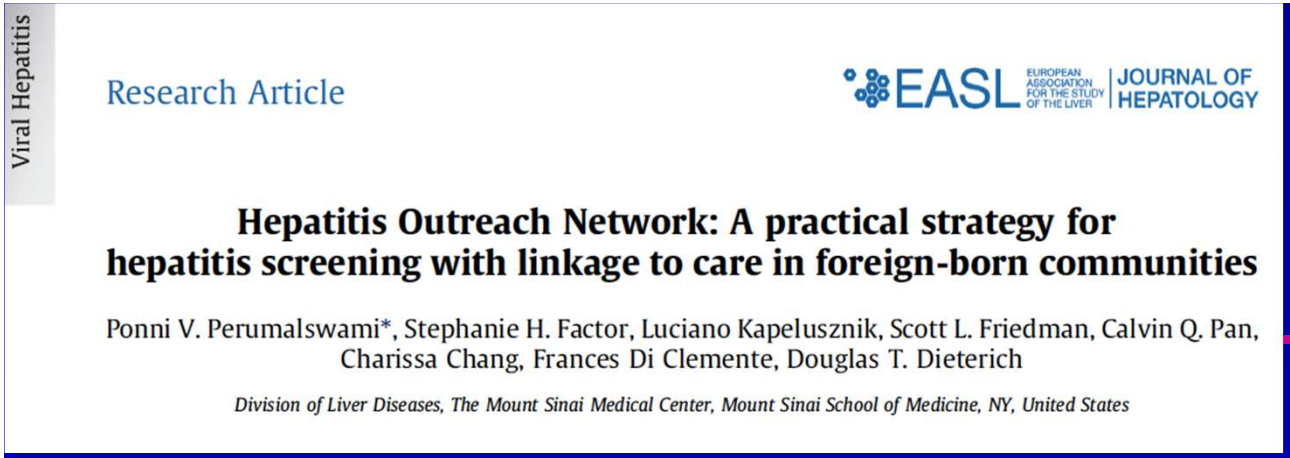
Hepatitis Awareness Month and National Hepatitis Testing Day — May 2014

In the United States, May is Hepatitis Awareness Month, and May 19 is National Hepatitis Testing Day. Although care and treatment can be life-saving, many

Expanding Primary Care Capacity to Treat Hepatitis C Virus Infection Through an Evidence-Based Care Model — Arizona and Utah, 2012–2014

Kiren Mitruka, MD[1], Karla Thornton, MD[2], Susanne Cusick[3],

- To build primary care capacity to treat diseases among rural, underserved populations through videoconferencing and case-based learning in “teleECHO” clinics.
  - 66 primary care clinicians, predominantly from rural settings.
  - 93% of the clinicians had no prior experience in care and treatment of HCV infection.
  - 129 (46%) of HCV-infected patients seen in teleECHO clinics received antiviral treatment, more than doubling the proportion of patients expected to receive treatment



Viral Hepatitis

Research Article

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

Hepatitis Outreach Network: A practical strategy for hepatitis screening with linkage to care in foreign-born communities

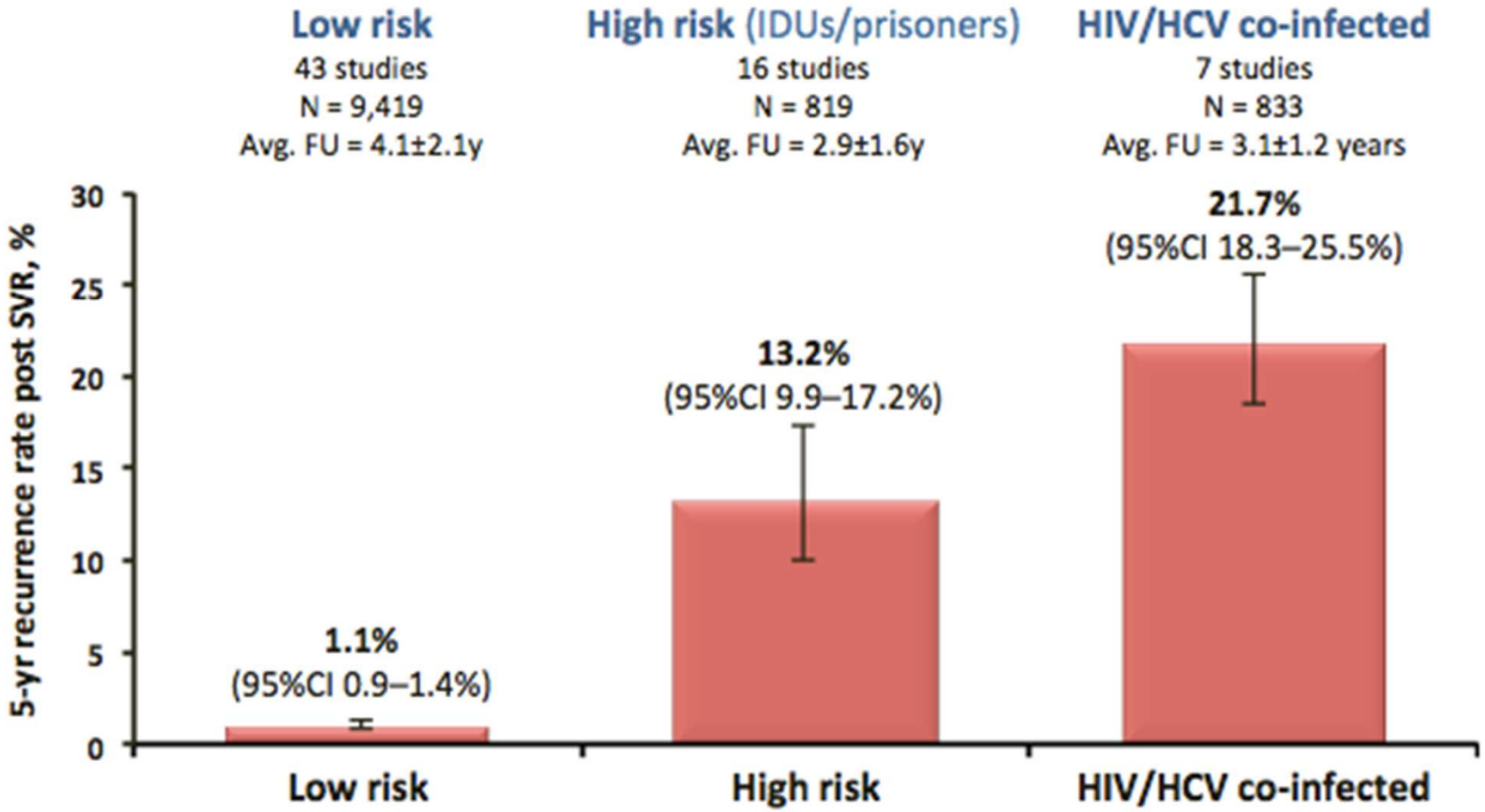
Ponni V. Perumalswami*, Stephanie H. Factor, Luciano Kapelusznik, Scott L. Friedman, Calvin Q. Pan, Charissa Chang, Frances Di Clemente, Douglas T. Dieterich

Division of Liver Diseases, The Mount Sinai Medical Center, Mount Sinai School of Medicine, NY, United States

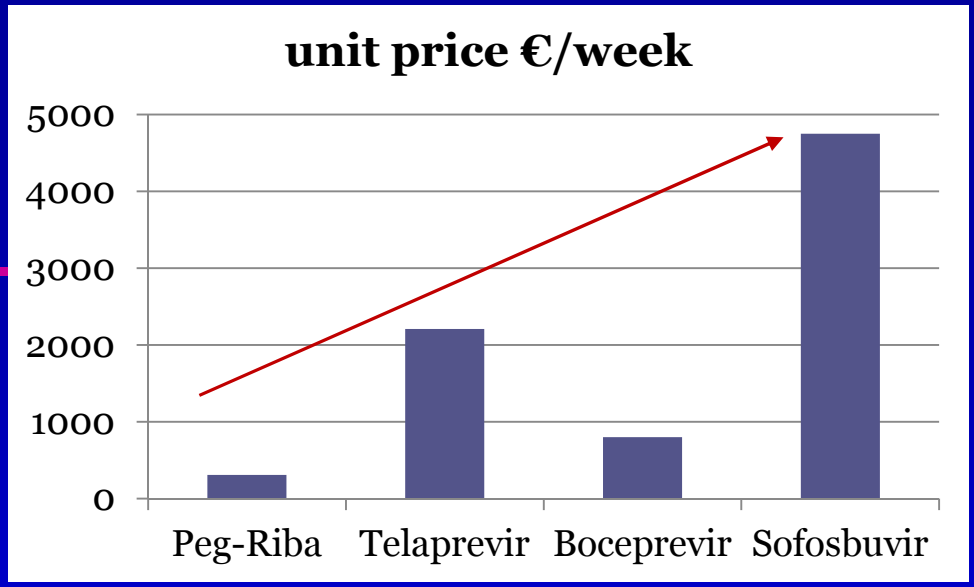
- Trained patient navigators based in the community-based organizations
  - encouraged patients to receive a full medical evaluation from a health care provider (make phone calls; free full medical evaluations offered)
  - encouraged adherence to follow-up care by scheduling visits, providing reminders via telephone and postcards, and meeting the patient on the appointment day and escorting them throughout their visit at the medical center
  - Participants reimbursed for transportation.

Risk of late relapse or re-infection with Hepatitis C after Sustained Virological Response: meta-analysis of 66 studies in 11,071 patients

Five-year rate (95%CI) of recurrence post-SVR, by risk group



Hill A *et al*, Abstract 654, CROI Seattle 2015



Des progrès thérapeutiques révolutionnaires mais aussi une augmentation des couts

1,000€ for 12-week RBV

41,000€ for 12-week SOF

48,000€ for 12-week SOF+LDV

41,400€ Viekirax

3,600€ Exviera

35,000€ for 12- or 24-week DCV

35,000€ for 12-week SIM

Septembre 2015

EFFECTIVENESS AND COST-EFFECTIVENESS OF IMPROVEMENTS IN HARM REDUCTION INTERVENTIONS, A BETTER CASCADE OF CARE, AND TREAT AS PREVENTION OF CHRONIC HEPATITIS C IN PEOPLE WHO INJECT DRUGS (PWID) IN FRANCE (ANRS 95146)

Anthony Cousien[1,2], Viet Chi Tran[3], Sylvie Deuffic-Burban[1,2,4], Marie Jauffret-Roustide[5,6], Guillaume Mabileau[1,2], Jean-Stéphane Dhersin[7], Yazdan Yazdanpanah[1,2,8]

[1]IAME, UMR 1137, INSERM, F-75018 Paris, France; [2]IAME, UMR 1137, Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France; [3]Laboratoire Paul Painlevé UMR CNRS 8524, UFR de Mathématiques, Université des Sciences et Technologies Lille 1, Cité Scientifique, Villeneuve d'Ascq, France; [4]inserm, LIRIC UMR995, F-59000 Lille, France; Univ Lille, F-59000 Lille, France; [5]CERMES3: Centre de Recherche Médecine, Sciences, Santé, Santé Mentale et Société, (INSERM U988/UMR CNRS8211/Université Paris Descartes, École des Hautes Etudes en Sciences Sociales), Paris, France; [6]Institut de Veille Sanitaire, Saint-Maurice, France; [7]Université Paris 13, Sorbonne Paris Cité, LAGA, CNRS, UMR 7539, F-93430, Villetaneuse, France; [8]Service des Maladies Infectieuses et Tropicales, Hôpital Bichat Claude Bernard, Paris, France

contact: anthony.cousien@inserm.fr / Université Paris 7, UFR de Médecine - Site Bichat ; Inserm UMR1137, IAME; 16 rue Henri Huchard - 75018 Paris - France

Evaluer, dans une population de 10 000 UDI en Île-de-France, l'efficacité et le coût-efficacité

- D'améliorations des mesures de réductions des risques (substitution, accès au matériel d'injection)
- D'amélioration du dépistage, du lien aux soins, de l'adhérence au traitement
- D'un changement du critère d'initiation du traitement

Cousien et al, AASLD 2015

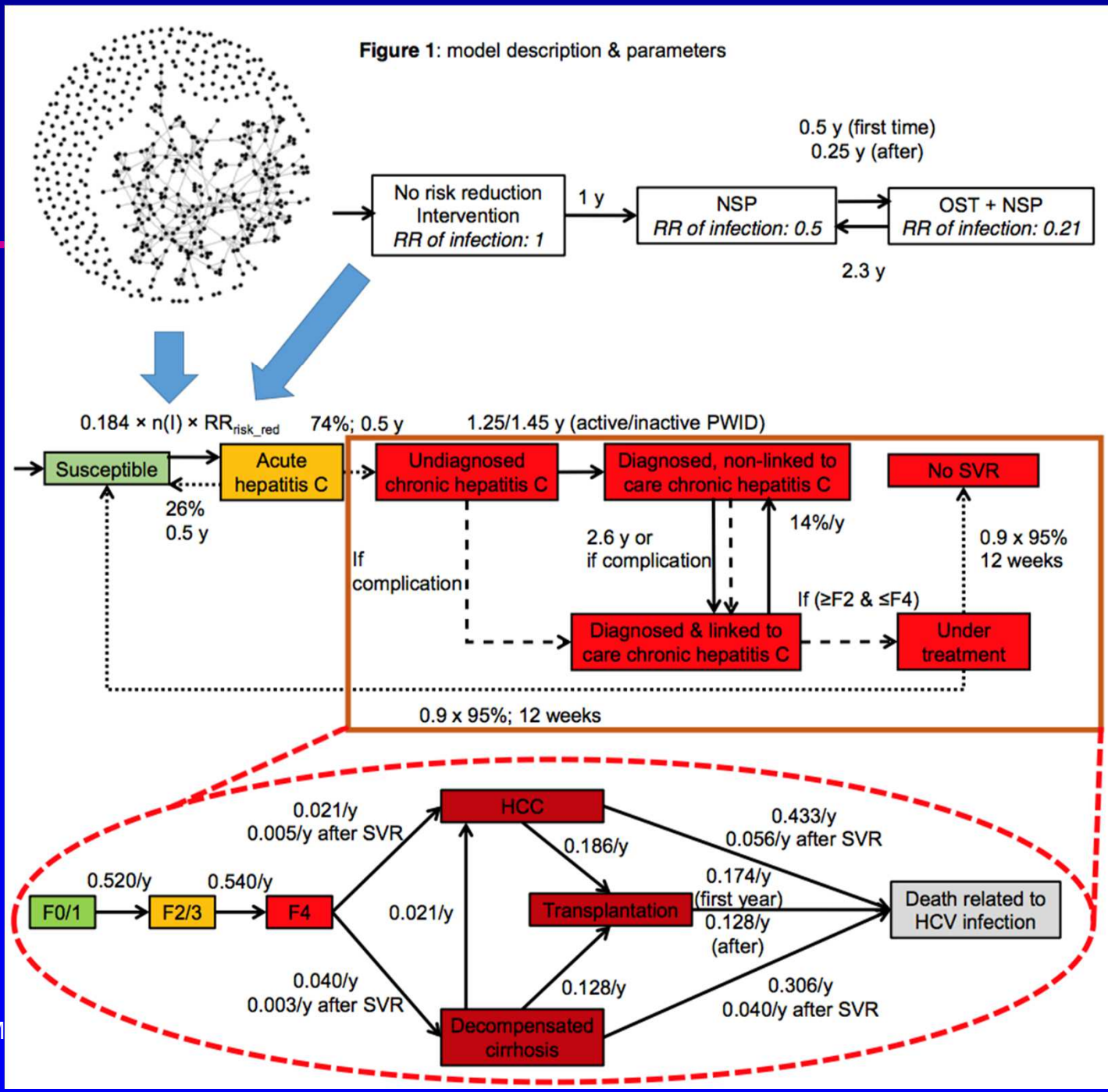


Figure 1: model description & parameters
0.5 y (first time)
0.25 y (after)
No risk reduction Intervention
RR of infection: 1
1 y
NSP
RR of infection: 0.5
OST + NSP
RR of infection: 0.21
2.3 y
0.184 × n(I) × RR risk_red
74%; 0.5 y
1.25/1.45 y (active/inactive PWID)
Susceptible
Acute hepatitis C
26%
0.5 y
Undiagnosed chronic hepatitis C
Diagnosed, non-linked to care chronic hepatitis C
No SVR
14%/y
2.6 y or if complication
If complication
0.9 x 95% 12 weeks
If (≥F2 & ≤F4)
Diagnosed & linked to care chronic hepatitis C
Under treatment
0.9 x 95%; 12 weeks
HCC
0.021/y
0.005/y after SVR
0.186/y
0.433/y
0.056/y after SVR
0.520/y
0.540/y
F0/1
F2/3
F4
0.021/y
Transplantation
0.174/y
(first year)
0.128/y
(after)
Death related to HCV infection
0.040/y
0.003/y after SVR
0.128/y
0.306/y
0.040/y after SVR
Decompensated cirrhosis

Résultats

Scénario	Coût moyen sur la durée de vie (€)	Espérance de vie ajustée (QALY)	Nombre moyen d'infections nouvelles	Nombre moyen de reinfections	ICER (€/QALY)
S1 – Référence (pratique actuelle)	25 598	16.57	3 271	872	
S2 – Améliorer la reduction des risques	25 682	16.58	3 254	868	Dominance étendue par S4
S4 – Améliorer la cascade de soins	26 745	16.81	3 341	1 140	4 715
S5 – Combiner S3 & S4	**31 437**	**17.02**	**2 008**	**972**	**22 859**
S6 – Combiner S2 &S3 &S4	31 523	17.02	2 007	972	Dominé par S5
S3 – Initiation du traitement : Fibrose ≥ F0	31 885	16.72	3 218	1 430	Dominé par S5

Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2012.03932.x

Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings

Peter Vickerman[1,2], Natasha Martin[1,2], Katy Turner[2] & Matthew Hickman[2]

London School of Hygiene and Tropical Medicine, London, UK[1] and University of Bristol, Bristol, UK[2]

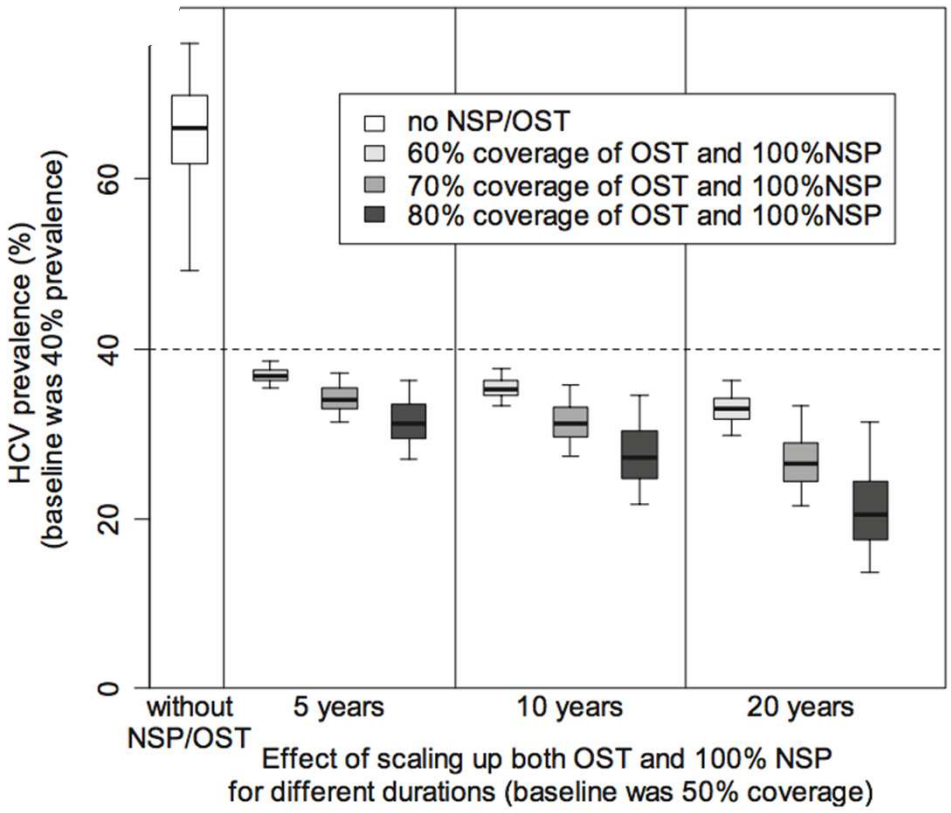


Figure 4 Impact of changing coverage of opiate substitution therapy (OST) and high coverage needle and syringe programmes (NSP) (100%NSP) from 50% for each to 0, 60, 70 and 80% for a UK setting with a stable 36–44% baseline chronic hepatitis C virus

Inserm, IAME U1137, Team DeSCID : « Decision Sciences in Infectious Diseases: Prevention, Control and Care »

Intervention Packages against HIV and HCV infections for People Who Inject Drug in Eastern Europe and Central Asia: A Modeling and Cost-Effectiveness Study

Guillaume MABILEAU (Inserm), Otilia SCUTELNICIUC (UNAIDS), Aliya BOKAZHANOVA (UNAIDS), Vinay SALDANHA (UNAIDS), Elena LOSINA (Harvard Medical School), Manoela MANOVA (UNAIDS), Jean-Elie MALKIN (GAHSC), Yazdan YAZDANPANAH (Inserm)

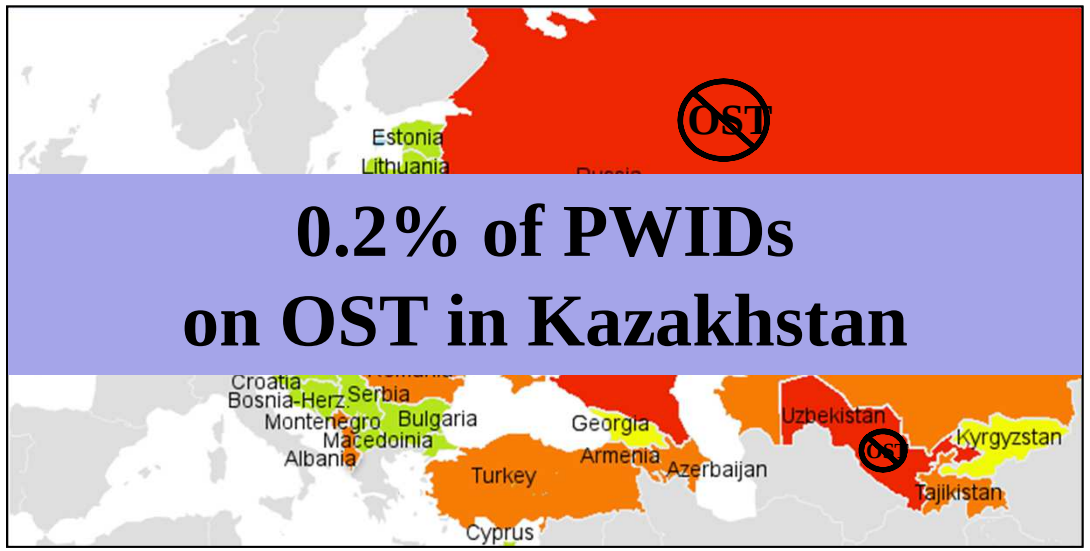
September, 2015

➢ Background

Programs have been initiated to **reduce** the incidence of these infections among PWIDs:

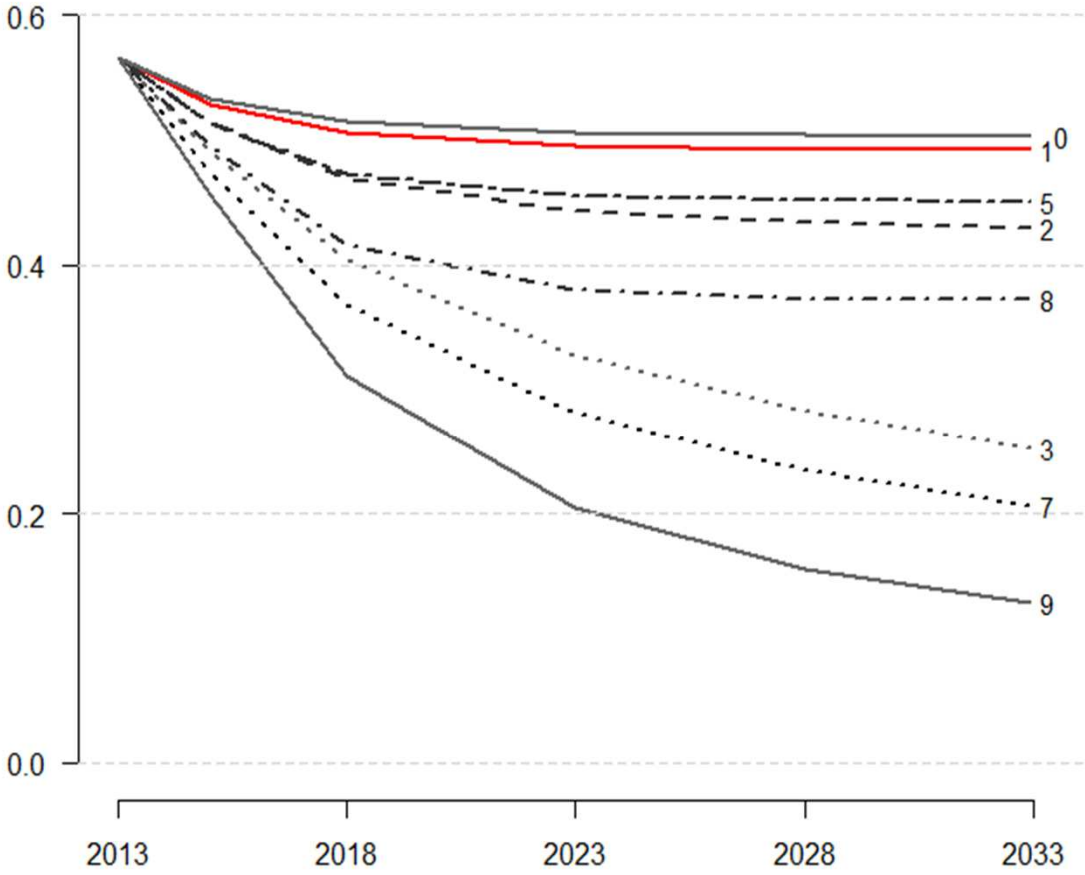
- ➢ **Needle-Syringe** programs (NSP)
- ➢ Access to **antiretroviral** treatments (ART)
- ➢ **Screening** and linkage to care
- ➢ Access to **opioid substitution** therapies (OST)
- ➢ **Access to HCV treatment** to care

Coverages remain **limited**



Results on effectiveness

HCV prevalence among PWIDs in Kazakhstan (parameters at baseline)

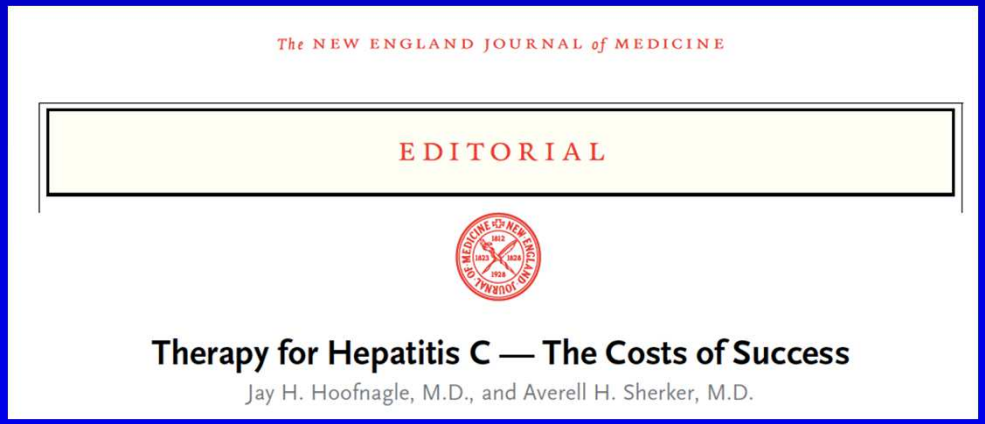


1) Baseline
2) Increase of **NSP** (60 vs. 37% at baseline)
3) Increase of **NSP**, **OST** (20 vs. 0.2%)
5) Increase of **anti-HCV** (50 vs. 0.001%)
7) Increase of **NSP**, **OST**, **anti-HCV**
8) Increase of **anti-HCV**, **DIAG HCV** (75 vs. 27%)
9) Increase of **NSP**, **OST**, **anti-HCV**, **DIAG HCV**
0) Alternative scenario with 2005 coverages

NSP + OST ++++
Then in addition HCV diagnosis + HCV TRT +++

« Coût-efficace » ≠ « pas chère »

Impact budgétaire



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Therapy for Hepatitis C — The Costs of Success

Jay H. Hoofnagle, M.D., and Averell H. Sherker, M.D.

‘With the present estimates of costs, treating even half the HCV-infected persons in the United States would add billions of dollars to an already overburdened medical care system. Costs alone cast a pall over the stunning success in achieving the long-hoped-for goal of a safe and effective therapy for hepatitis C.’

Hoofnagle JH, and Sherker AH. N Engl J Med 2014; 370:1552–53.

Impact budgétaire Etats Unis

- Over 5 years
- Only drug costs ($/week)
  - Peg-RBV=$587
  - RBV=$309
  - BOC=$1100
  - TVR=$4100
  - SOF=$7000
  - LDV=$875

⇨**$136 billion** = $85,000 / pts

- Assumptions
  - 1.32 million treatment-naive and 450,000 treatment-experience persons aware of their HCV disease
  - 510,000 diagnosed in the 5 years

Chhatwal et al, Ann Intern Med 2015

Impact budgétaire France

- Over 3 years
- Only drug costs
  - 87€ for RBV
  - 41,000€ for 12-week SOF
  - 48,000€ for 12-week SOF+LDV
  - 35,000€ for 12- or 24-week DCV
- Assumptions
  - Treating if ≥ F2 with priority to ≥ F3
  - ≤ 20,000 patients treated/year
  - Scenarios
    1. Limited to 18-70 years old
    2. ≥ 18 without age limit

1ère année : 80% des F3-F4, 50% des F2

2ème année : 100% des F3-F4, 80% des F2

3ème année : 100% des F2-F4

⇨38,200 treated patients =1.8-2.3 billion €

Deuffic-Burban et al, AASLD 2014

- Coût des traitements contre l’hépatite C ++++

Inserm, Avenir team « Decision Sciences in Infectious Disease Prevention, Control and Care »

Inserm
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de la santé et de la recherche médicale

anrs France REcherche Nord & sud Sida-hiv Hépatites
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