# Treatment guidelines for viral hepatitis in Luxembourg

Vic Arendt
Service National de Maladies Infectieuses
CHL

Brussels, VHPB meeting 8 november 2017

# Disclosures:

- Research grants and educational grants from Gilead and AbbVie

# Luxembourg hepatitis treatment guidelines

- Luxembourg does not have treatment guidelines for hepatitis B or C
- CNS (caisse nationale de santé) does not give recommandations and does not impose restrictions on the use of antivirals for HBV or HCV
- DAA have to be prescribed by a specialist in GI, ID or internal medicine and delivered through a hospital pharmacy

# LUX tt. guidelines

- SLG (société luxembourgeoise de gastroentérologie) informal position: why would we impose restrictions on ourselves, if we are free to prescribe as we like
- National Hepatitis Action Plan: recommands to follow the EASL guidelines
- EASL guidelines for HCV and HBV exist and are updated on a regular basis

# We didn’t want to re-invent the wheel!

SEPTEMBER 2016

EASL | JOURNAL OF HEPATOLOGY

## EASL Recommendations on Treatment of Hepatitis C 2016

Clinical Practice Guidelines

CrossMark

EASL | JOURNAL OF HEPATOLOGY

## EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

# HBV: indications for treatment, EASL 2017

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).
- Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).
- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).

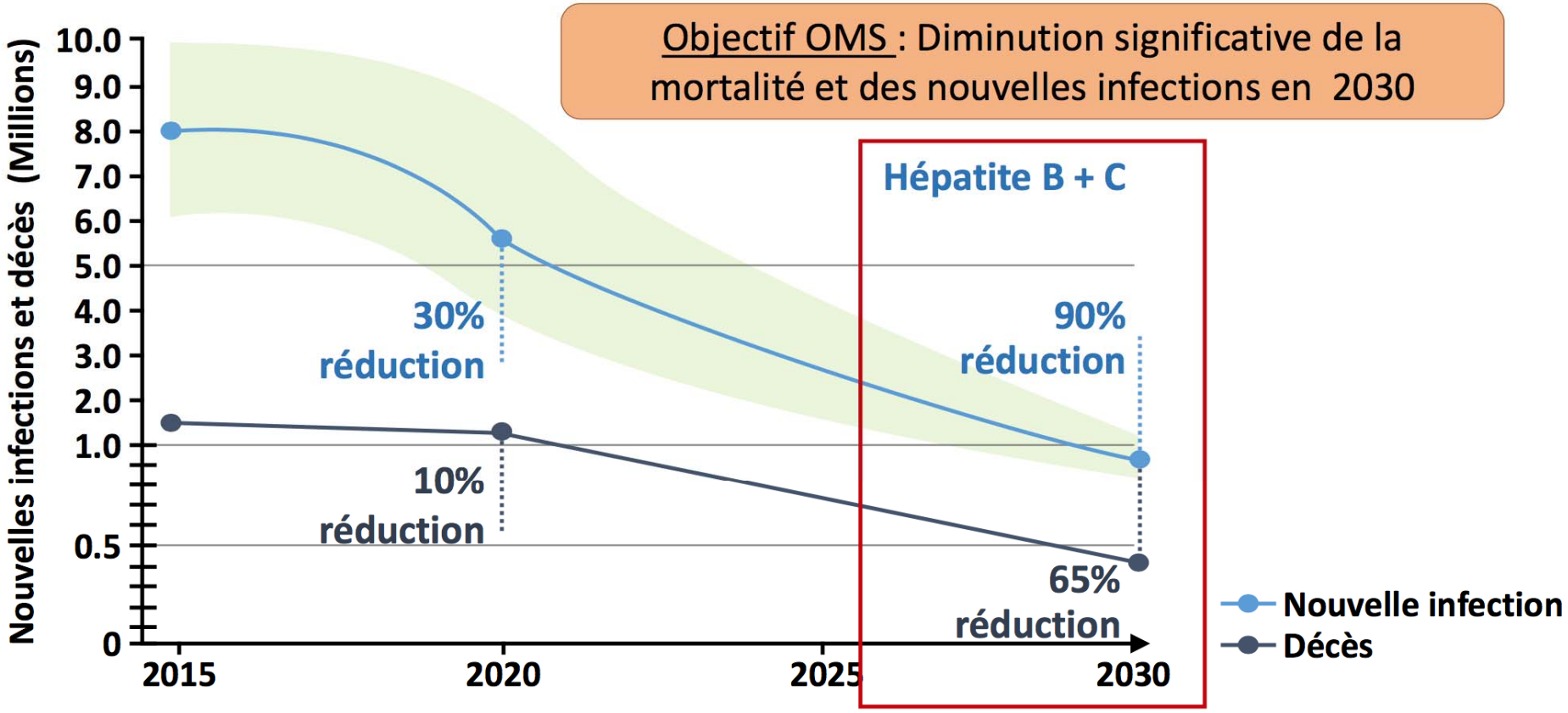
- **Indications for HCV treatment: who should be treated?**

- **All** treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must **be considered for therapy (A1).**

- Treatment should be considered **without delay** in patients with significant brosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis,
- in patients with clinically signicant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), in patients with HCV recurrence after liver transplantation, and
- in **individuals at risk of transmitting HCV** (active injection drug users, men who have sex with men with high- risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals) (**A1**).
- Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score ≥18-20 should be transplanted rst and treated after transplantation. If the waiting time is more than 6 months, these patients can be treated before transplantation (**B1**).
- Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities (**B2**).
- National elimination plans require the development of economic partnerships and planning to expedite unrestricted access to treatment (**B1**).

# Objectif OMS 2030

Objectif OMS : Diminution significative de la mortalité et des nouvelles infections en 2030



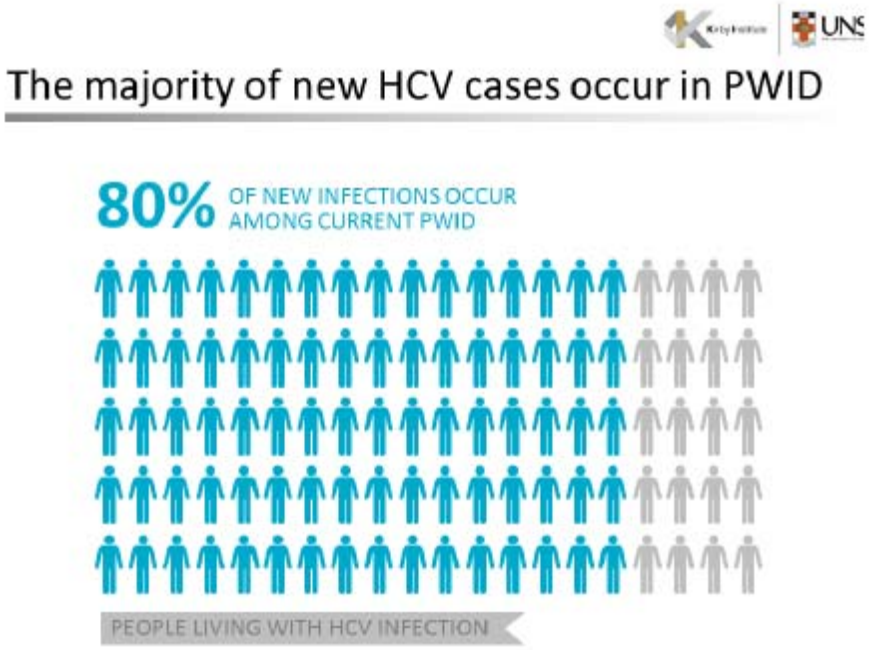

WHO Global Health Sector strategy on viral hepatitis 2016–2021. Available at: www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ (accessed June 2017).

# Discussion points

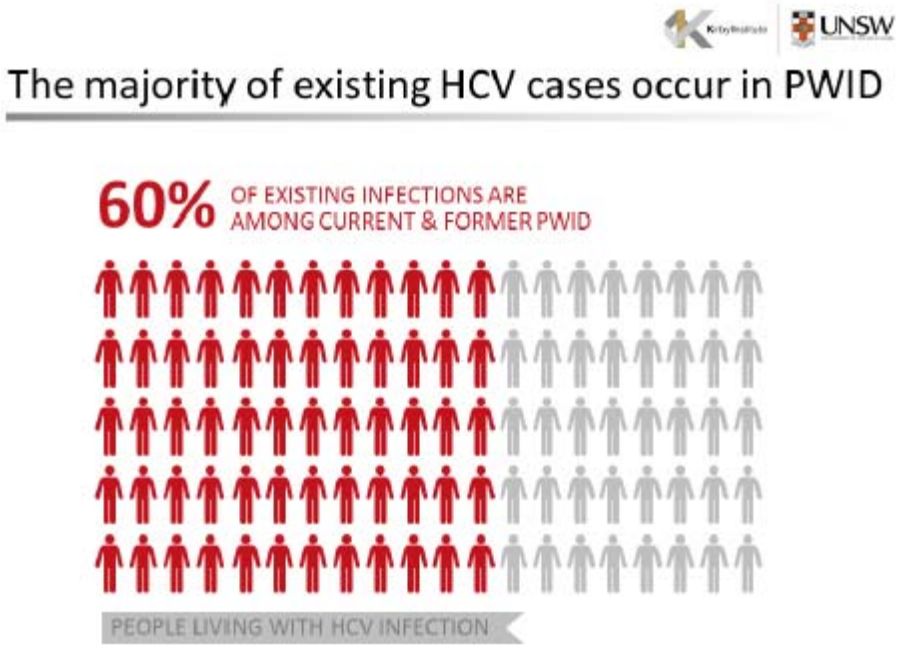
- Little discussion about hepatitis B guidelines
  - In case of doubt, usually discussed w/ GI colleagues

- WHO targets for 2030 and how they apply to an epidemic mostly limited to PWIDs
  - EASL recommandation: treat preferentially patients at high risk of transmission, e.g. active PWIDs
- In practice, attitude may be different:
  - How about active PWIDs? Concerns about re-infection and adherence
  - How about patients eager to be treated , even without fibrosis;
    - those extremely stressed by the presence of the disease, who don't dare having a glass of champagne for NewYear's eve?
    - Those with debilitating fatigue?

# 1. Epidémiologie de l'hépatite C: Les UDI sont LA population à risque!




1) Hajarizadeh B, et al. *Nature Rev Gastroenterol Hepatol* 2013. 2) Grebely J and Dore GJ *Antiviral Research* 2014.




1) Hajarizadeh B, et al. *Nature Rev Gastroenterol Hepatol* 2013. 2) Grebely J and Dore GJ *Antiviral Research* 2014.

>=70% de prévalence chez les PWIDs au Luxembourg

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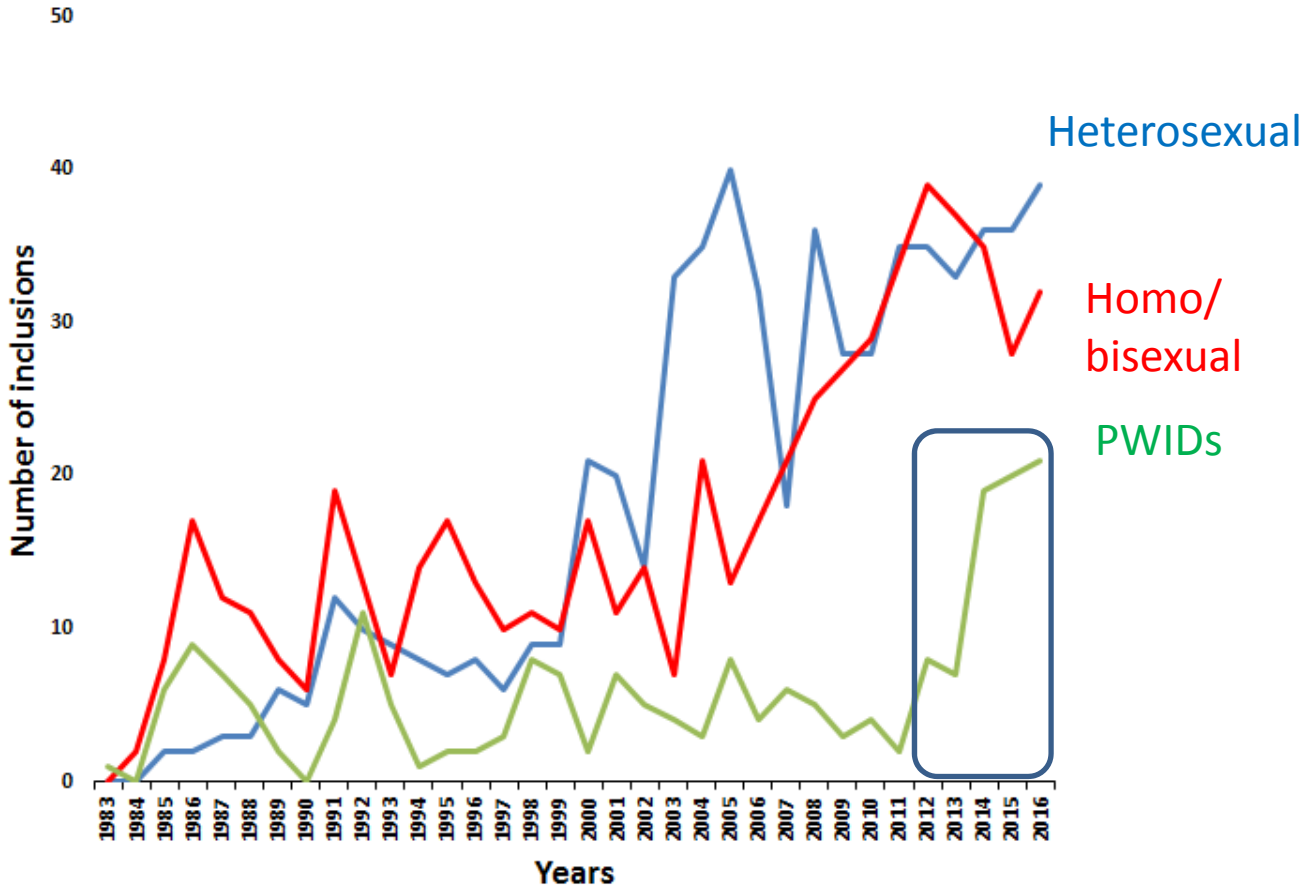
# HIV outbreak in PWIDs

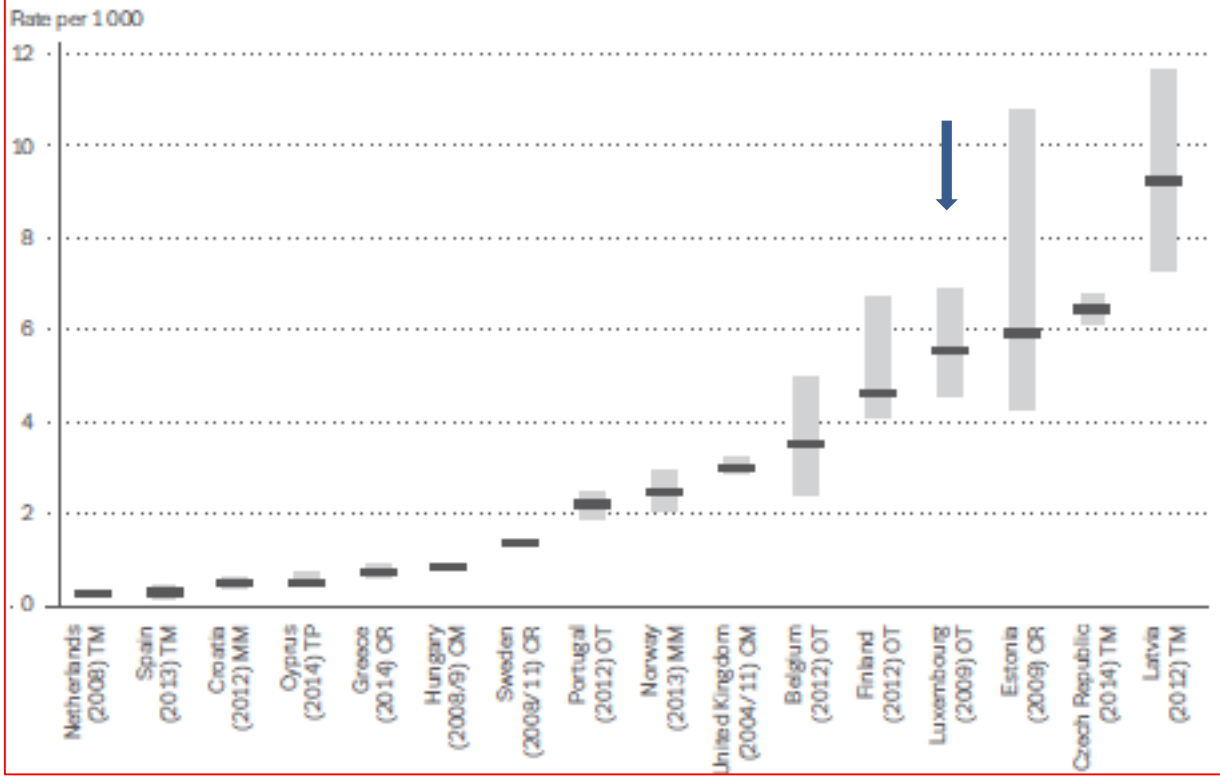



- 2013-2016: 67 new PWIDs cases included in the HIV cohort at the National Service of Infectious Diseases
- 8 PWIDs included in 2017 (increased treatment access, reinforcement of awereness and prevention measures).

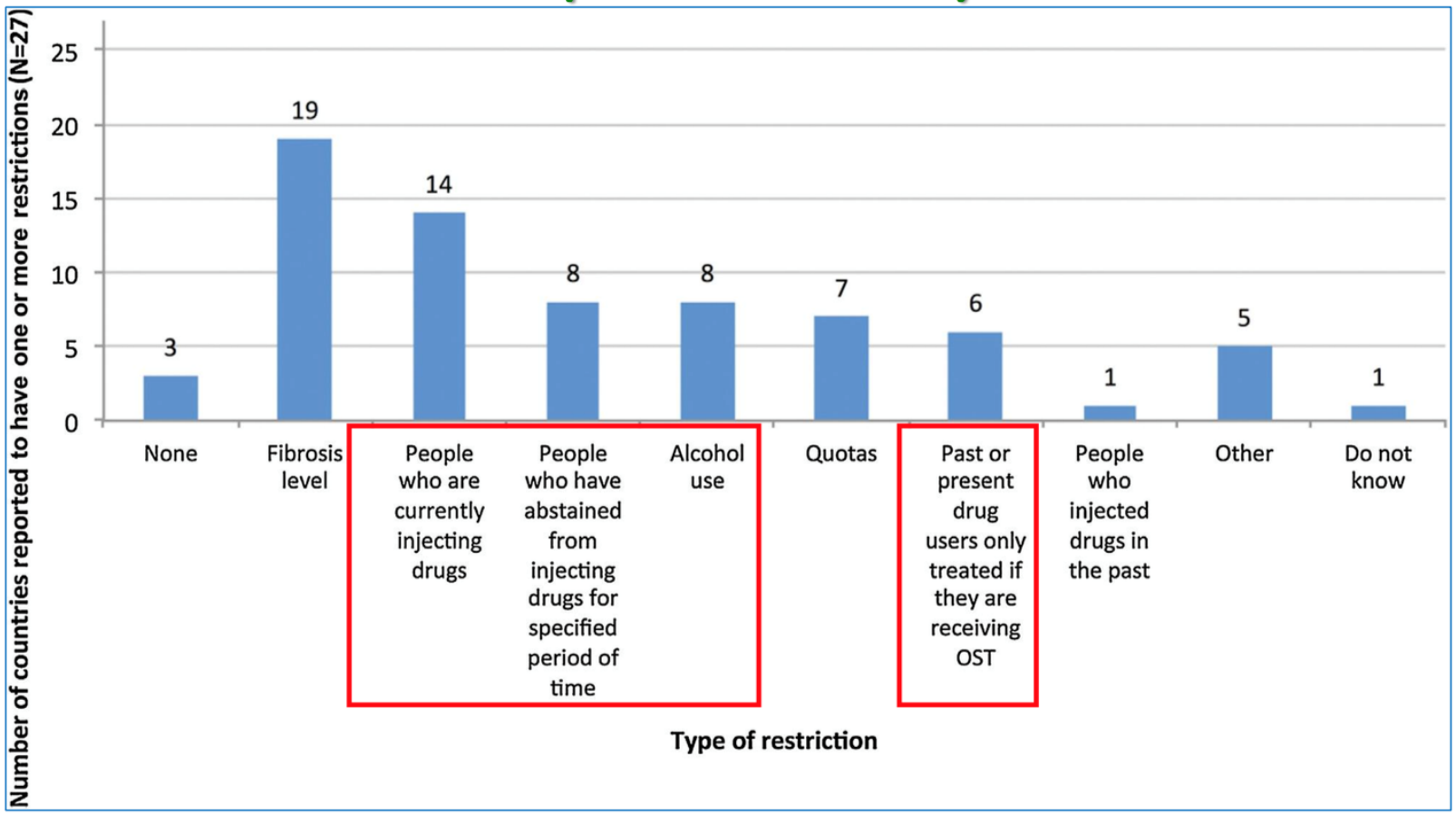
# Prévalence UDIs en Europe

FIGURE 1.7

**Estimates of the prevalence of injecting drug use (rate per 1 000 population aged 15–64), 2007–14 data collection (last study available)**



# 3. Raisons de restriction de l'accès aux antiviraux dans 27 pays Hep-CORE Study

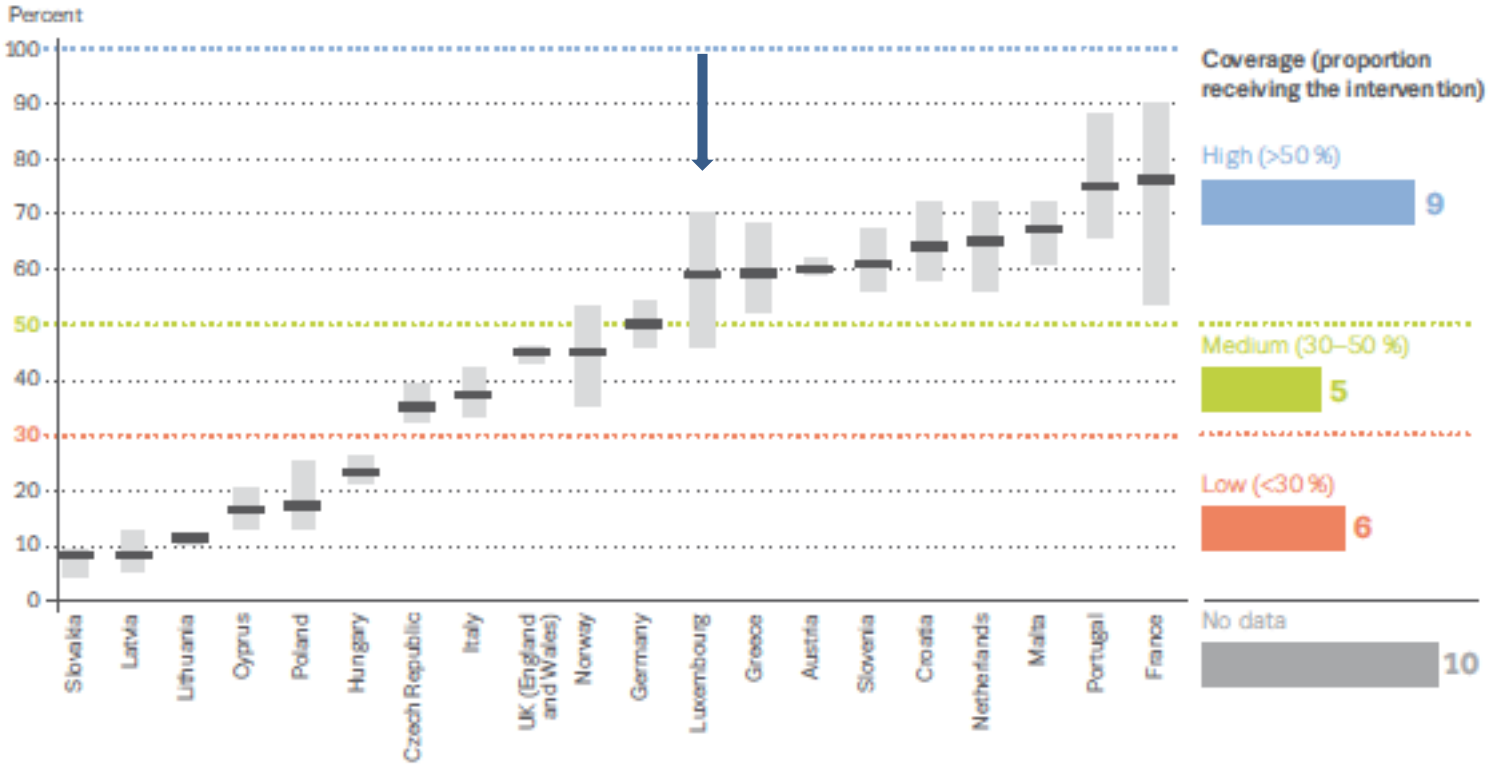



J.V. Lazarus, et al., Restrictions on access to direct-acting antivirals for people who inject drugs: International Journal of Drug Policy (2017)

# OST- Methadone ou Suboxone

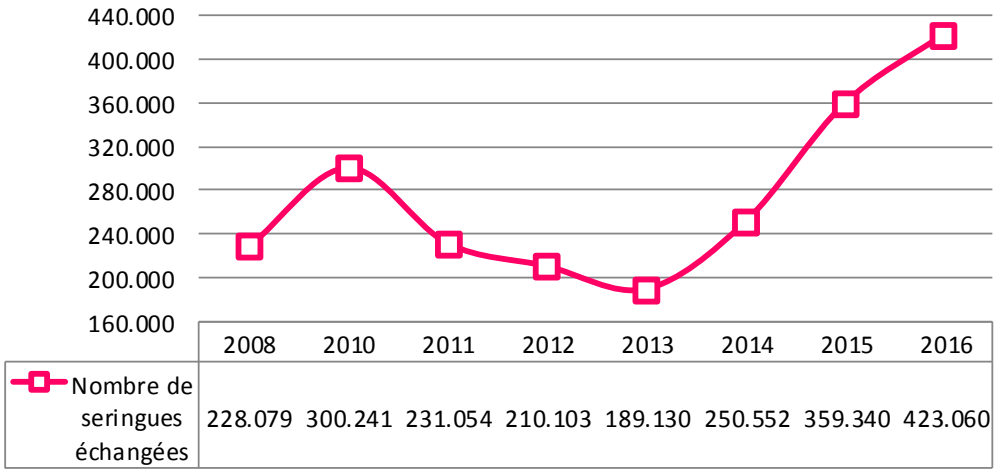
FIGURE 1.9

**Percentage of the estimated population of high-risk opioid users receiving substitution treatment in 2014**



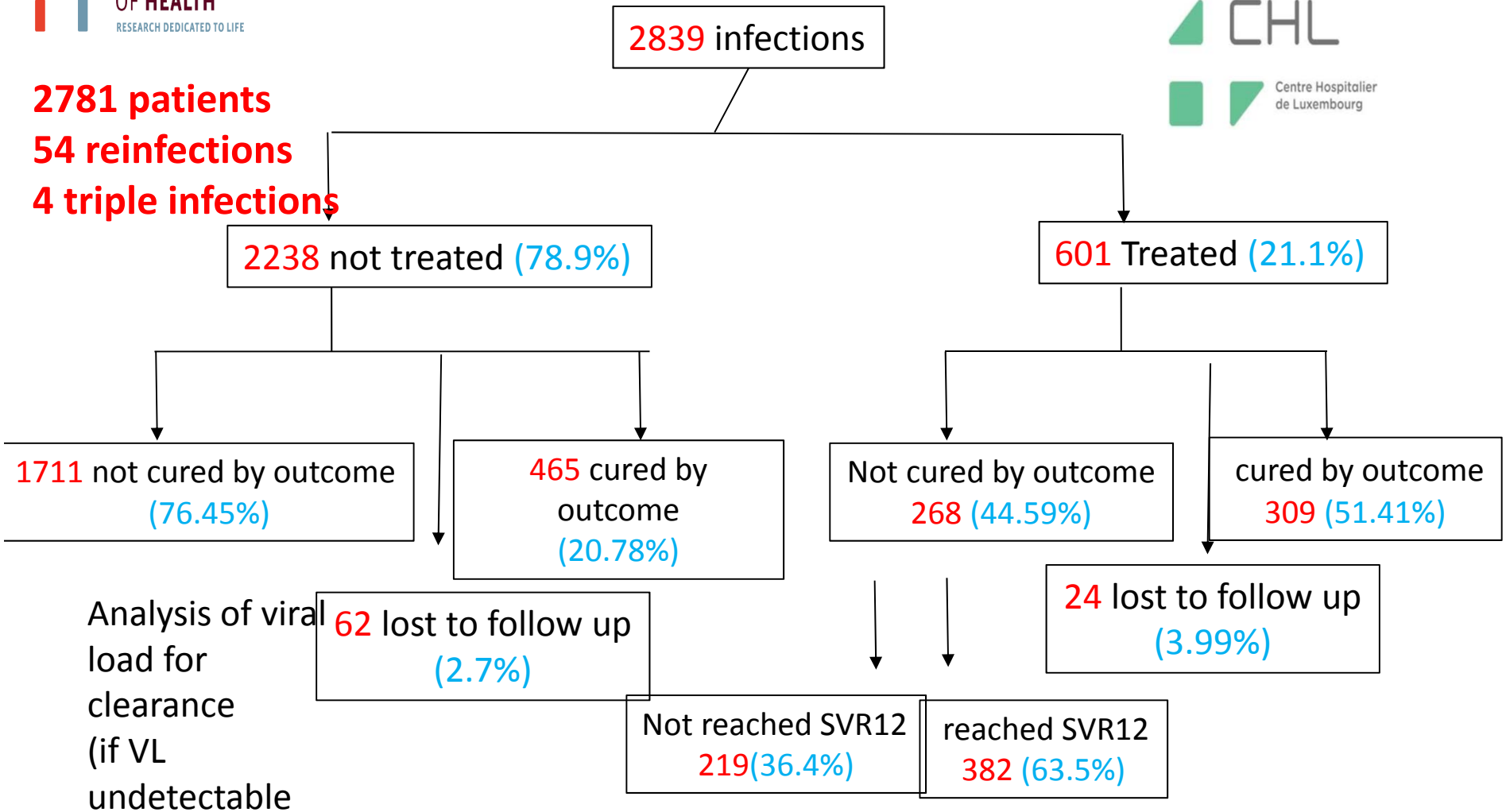
# Échange de seringues UDIs, Luxembourg

## en 2016, > 200 seringues par UDI actif



# Analysis of IFN/RBV outcome

**2781 patients**
**54 reinfections**
**4 triple infections**




Analysis of viral load for clearance (if VL undetectable after 6 months)

**Nicolas Sauvageot, CCMS**

SVR12 : sustained virological response viral load undetectablef ater 12 weeks of treatment,

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# Treatment in the DAA area in Luxembourg (+/- 550.000 habitants)

2015: 168 patients

2016: +/- 280 patients

Thus a rather high treatment coverage

+/-10% of estimated viremic patients per year

# Traitements des Hépatites C au CPL de Schrassig de 2003-2013

- En intention de traiter, 122/204 (59.8%) détenus ont atteint une SVR12. Parmi eux 21 patients guéris ont été réinfectés pendant la période de suivi entre 2003 et 2013, ce qui conduit à un taux de réinfection de 17,2%.

- D'autre part 44/204 patients (21.5%) ont présenté un échec au traitement et 21.07% (43/204) d'individus ont été perdus de vue.

# Traitements des Hépatites C au CPL de Schrassig de 2003-2013

- Les patients non réinfectés en Décembre 2013 ont été ensuite suivis jusqu'en Décembre 2015, et 9 patients supplémentaires ont été réinfectés. Au total depuis 2003, 30 patients guéris ont eu une autre charge virale détectable, donnant un taux de réinfection de 24.5% (30/122 patients).
- 15/30 réinfections ont été confirmées par un changement de génotype.

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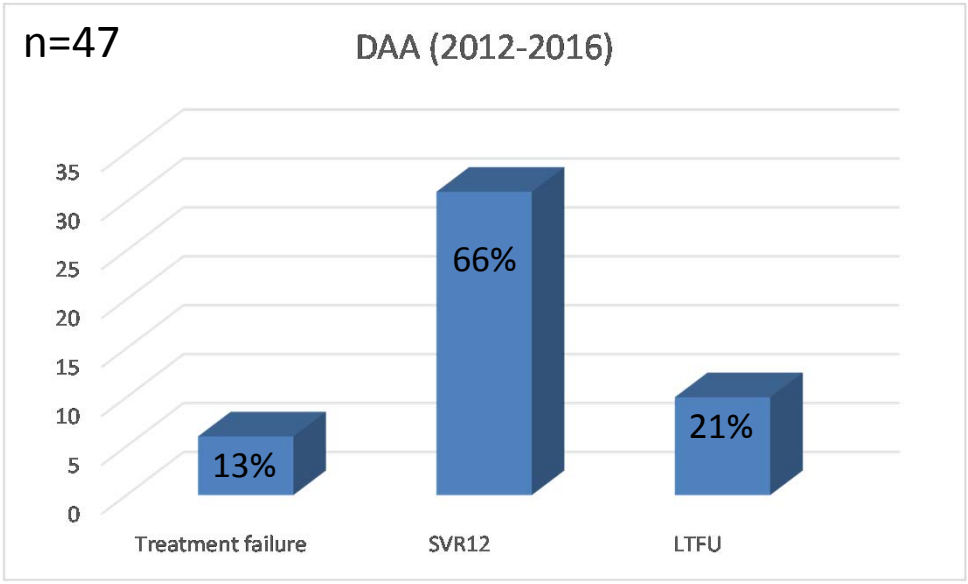
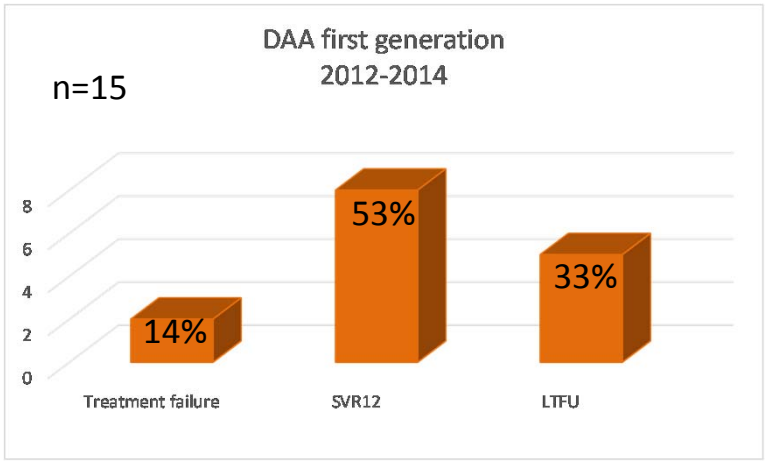
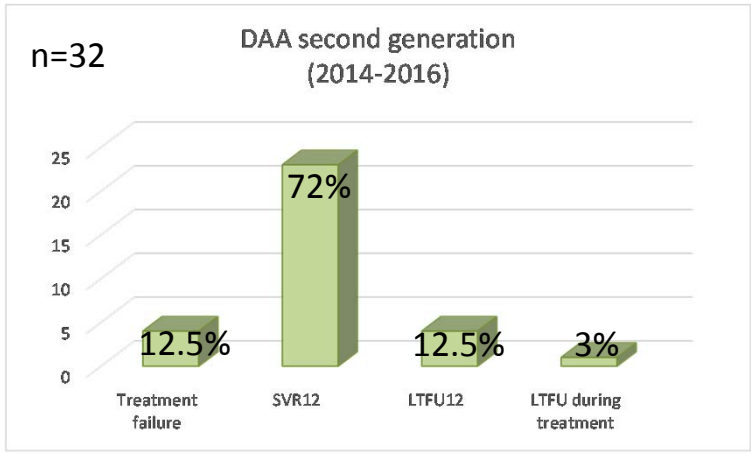
# Treatment effectiveness with DAA in prison



Cochrane Library

Cochrane Database of Systematic Reviews

# Direct-acting antivirals for chronic hepatitis C (Review)

Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, Poropat G, Djurisic S, Weiss KH, Bjelakovic M, Bjelakovic G, Klingenberg SL, Liu JP, Nikolova D, Koretz RL, Gluud C

# EASL RELEASES EDITORIAL RESPONSE TO COCHRANE REVIEW OF DAAS IN HCV

BY EASL JUNE 28,2017  THEME HEPATITIS C

EASL raises serious concerns over Cochrane systematic review and questions conclusions in an Editorial published today in the Journal of Hepatology

GENEVA, Switzerland 28 June 2017 – The European Association for the Study of the Liver (EASL) expresses its serious concerns with the recent publication by the Cochrane Group Review entitled “Direct acting antivirals for chronic hepatitis C” by Jakobsen et al. in which the authors conclude that: “DAAs on the market or under development do not seem to have any effects on risk of serious adverse events [but] we could neither confirm nor reject that DAAs had any clinical effects.”

## Mortalité chez les patients atteints d'hépatite C chronique en Suède

- Régistre national suédois (+/- 9 millions de personnes)
- En 2003, 0,36% atteints d'hépatite C chronique. Mortalité 5,8 x plus élevée que dans la population générale.
- EASL 2016 (K. Büsch et al): 1997-2013, 44.413 patients HCV+ appareillés 1:5 avec des patients contrôles.
- Durant cette période les mortalités étaient respectivement de 28 /1000 personnes-années (HCV+) et 6/1000 personnes-années (population contrôle)
- 27% des décès étaient liés à des causes hépatiques (cirrhose et cancer du foie)
- Conclusion: mortalité presque 5x plus élevée que dans la population générale; 27%, de cause hépatique.

# De quoi meurent les usagers de drogues?

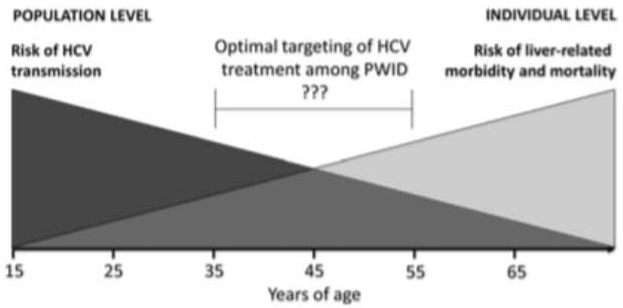
- Méta-analyse (>50 publis de pays « riches »): OMS
- CMR 2,3/100PY
  - Overdose
  - HIV
  - Sexe: H>F; mais les femmes UDI meurent 16x plus que des femmes non UDI du même âge
  - Morts violentes : homicides, accidents, suicides
  - Liver-related death
  - Autres co-morbidités: endocardites, abcès, TVP/embolies…

# Qu'en est-il du toxicomane jeune?

- Vancouver: factors associated with premature mortality among young (<30) IDU Harm Reduction Journal,2007
  - F: homicide; H. suicides et overdoses
- Vancouver, Am J Epidemiol 2016: idem; excess mortality < HIV in women persists!
- Vancouver: predictors of liver-related death among people who inject drugs in Vancouver: 15-year prospective cohort J Int AIDS Soc 2014(1996-2011)
  - :2279 UDI; liver-related mortality 2,1 par 1000 personnes-années; pas de corrélation entre HCV+ et mortalité mais bien entre HCV+/HIV+ et mortalité
- San Francisco: Young IDU cohort, 10 year follow-up (Am J Epidemiol, 2012) 9,1 décès/1000PA; overdose 57%; suicide 13%; accidents 10,5%; IDU-related medical conditions 13%

Prioritarisation for HCV treatment?

# 4.Patients différents, besoins différents

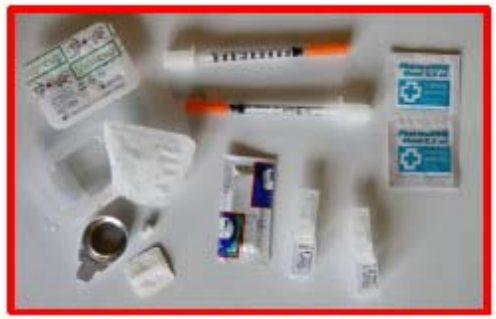


Bénéfice: Collectivité > Individu
Besoins: Psycho-social > Médical
Objectifs: Réductions pratiques à risques (NSP) > Rétention en soins (OST) > DAA
Motivation au traitement faible donc utilisation d'incitatifs +++

Bénéfice: Individu > Collectivité
Besoins: Médical, gestion des comorbidités, suivi fibrose
Objectifs: Accès et choix du traitement DAA selon génotype, stade fibrose et DDI, diminution comportementale facteurs fibrogènes
Suivi adhérence minimale

# To what extend is TasP effective for HCV?

## 2. VHC chez UDI: Moyens de préventions



Programmes d'échange de seringues (NSP)


Traitement DAA

Incidence⬇ : vers éradication?

PEOPLE LIVING WITH HCV INFECTION

Substitution opioïdes (OST)

Vaccin

*Curr Opin Infect Dis*. 2015 December ; 28(6): 576–582. doi:10.1097/QCO.0000000000000216.

Review paper

# HCV Treatment as Prevention in People Who Inject Drugs – testing the evidence

**Matthew Hickman**[1], **Daniela De Angelis**[2], **Peter Vickerman**[1], **Sharon Hutchinson**[3], and **Natasha Martin**[1,4]

However, there is to date no empirical evidence from trials or observational studies that test the model projections and "prevention benefit" hypothesis

**Summary—Eliminating HCV through scaling up treatment is a theoretical possibility. But empirical data are required to demonstrate that HCV treatment can reduce HCV transmission which will require an improved evidence base and analytic framework for measuring PWID and HCV prevalence.**

J.Gastroenterol.Hepatol.2016**Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia.** Scott N[1,2]et al.

- **AIM:** determine the cost-effectiveness of treating PWID with interferon-free direct-acting antiviral therapy in Australia.

- **METHODS:**

•Using a deterministic model of HCV treatment and liver disease progression, **including a fixed rate of re-infection**, the expected healthcare costs and quality-adjusted life years (QALYs) of a cohort of newly HCV-infected PWID were calculated for: no treatment; treatment after initial infection ("early-treatment"); and treatment prior to developing compensated cirrhosis ("late-treatment"). Incremental cost-effectiveness ratios (ICERs) were used to compare scenarios.

- **RESULTS:**

Late-treatment was cost-effective compared to no treatment, +/- 3 QALY gain per person; 5078$/QALY

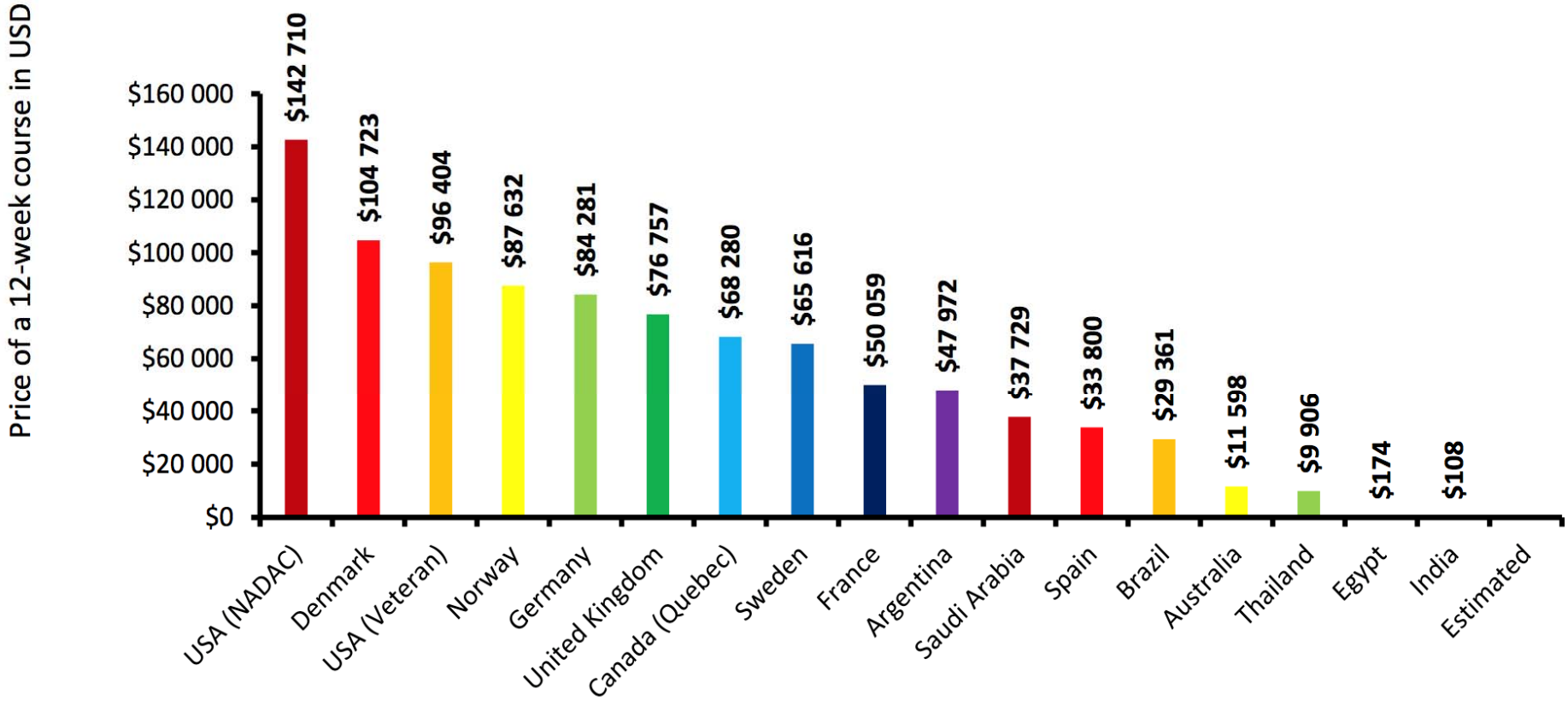
Compared to late-treatment, early-treatment gained a further 2.27 QALY, at $17,090/QALY

- **CONCLUSIONS:**

- **Late-treatment more cost-effective than early treatment**

- **Calculations based on the Australian model**

# Combien coute une cure de 12 semaines de SOF/DCV?



Research Article

JOURNAL OF HEPATOLOGY

# Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation

Natasha K. Martin[1,2,*], Peter Vickerman[2], Gregory J. Dore[3], Jason Grebely[3], Alec Miners[4], John Cairns[4], Graham R. Foster[5], Sharon J. Hutchinson[6,7], David J. Goldberg[6,7], Thomas C.S. Martin[8], Mary Ramsay[9], the STOP-HCV Consortium, Matthew Hickman[2]

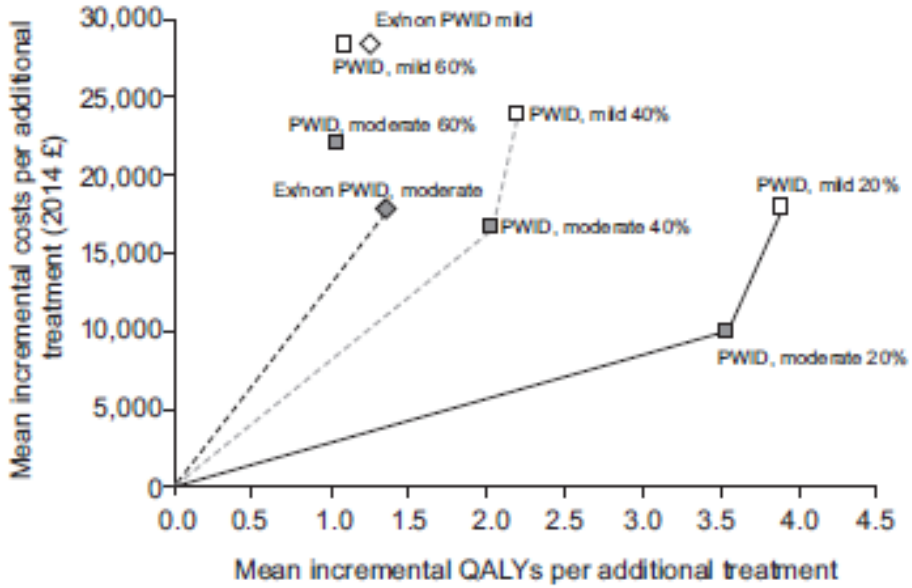



**Fig. 1. Results on the incremental cost-effectiveness plane showing the efficient frontiers for 20% (solid line), 40% (dashed grey line), and 60% (dashed black line) chronic prevalence scenarios for the 'Future IFN-free DAA' treatment scenario.** Results shown for treatment of PWID populations (squares)

By contrast, at 60% chronic prevalence (Table 3, Fig. 1, Supplementary Table 1), targeting moderate ex/non-PWID was the only cost-effective option compared to delaying treatment. In this setting, due to the very high risk of reinfection, treatment of PWID was not cost-effective compared to delay.

In Luxembourg, only treating former PWIDs >=F2 would be considered cost-effective inthis model

Grebely J et al. *Journal of the International AIDS Society* 2017, **20**:22146
http://www.jiasociety.org/index.php/jias/article/view/22146 | http://dx.doi.org/10.7448/IAS.20.1.22146

JIAS Journal of the International AIDS Society

Commentary

# Elimination of HCV as a public health concern among people who inject drugs by 2030 – What will it take to get there?

Jason Grebely[§1,2], Gregory J. Dore[1,2], Sébastien Morin[3], Jürgen K. Rockstroh[4,5] and Marina B. Klein[5,6]

[§]**Corresponding author:** Jason Grebely, The Kirby Institute, UNSW Sydney, Sydney 2052, Australia. (jgrebely@kirby.unsw.edu.au)

Key recommendations for action to eliminate HCV infection as a global health threat among PWID by 2030:

1. Reforming drug policies – Countries must consider drug policy reforms. This includes the decriminalization of drug use and/or possession, or providing alternatives to emprisonment for PWID
2. Scaling up harm reduction services
3. Making health services accessible for PWID- Universal Health Coverage (see SDGs)
4. Supporting community empowerment and community-based programmes
5. Improving access to affordable diagnostics and medicines – Advocates, researchers, healthcare providers, policy makers, and the affected community must work together to negotiate better prices
6. Eliminating stigma, discrimination, and violence

Grebely J et al. *Journal of the International AIDS Society* 2017, **20**:22146
http://www.jiasociety.org/index.php/jias/article/view/22146 | http://dx.doi.org/10.7448/IAS.20.1.22146


Commentary

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[§]**Corresponding author:** Jason Grebely, The Kirby Institute, UNSW Sydney, Sydney 2052, Australia. (jgrebely@kirby.unsw.edu.au)

## Competing interests

•JG is a consultant/advisor and has received research grants from Abbvie, Cepheid, Bristol Myers Squibb, Gilead Sciences and Merck/MSD.
•GD is a consultant/advisor and has received research grants from Abbvie, Bristol Myers Squibb, Gilead, Merck, Janssen and Roche.
•JKR has received honoraria for consulting or speaking at educational events from Abbott, Abbvie, Bionor, BMS, Cipla, Gilead, Janssen, Merck and ViiV.
•MBK received research grants for investigator initiated trials from Merck and ViiV Healthcare; consulting fees from ViiV Healthcare, Bristol-Meyers Squibb, Merck, Gilead and AbbVie


•More expensive than gold!
•Production cost is less than 0,5% of the price
Un bon médicament ne sert à rien si les patients qui en ont besoin
ne peuvent y accéder
SOFOSBUVIR
MEDECINS SANS FRONTIERES
LES MÉDICAMENTS NE DEVRAIENT PAS ÊTRE UN LUXE

# CNS, 2015, medicines delivered by hospital pharmacies for outpatients

**Tableau 3**

| Indication principale | Monta | Patients | Montant/patient |
|---|---|---|---|
| Hépatite C | 10.422.614,72 | 168 | 62.039,37 |
| Cancer | 8.767.302,68 | 386 | 22.713,22 |
| VIH | 5.882.452,18 | 752 | 7.822,41 |
| SEP | 2.068.885,10 | 115 | 17.990,31 |
| HTAP | 1.661.036,78 | 76 | 21.855,75 |
| Polyneuropathie associée à l'ATTR | 913.109,05 | 9 | 101.456,5 |
| Thrombopénie | 480.013,39 | 29 | 16 |
| Fibrose pulmonaire | 407.449,77 | 20 | |
| Maladie de Pompe | 407.449,44 | 1 | |
| Asthme | 388.411,78 | 67 | |
| Myélofibrose / Maladie de Vaquez | 339.731,07 | | |
| Parkinson | 319.058,55 | | 0,95 |

TOP 12 par indication principale en 2015 : Nombre de patients [illegible] de montants

OST programme: 600.000
NSP pg.:400.000
Total plan to fight drug addiction:
10 mio/yr

# Conclusion

- Luxembourg recommands to follow the EASL guidelines for treatment of Hepatitis B and C
- For HCV, PWIDs represent currently the bulk of the epidemic
- Treatment coverage is relatively high
- Real-world data for TasP in HCV in a setting as ours (>70% prevalence) are lacking
- Cost of drugs is a barrier to access to treatment or at least to TasP against HCV