# Recommendations for the management of hepatitis C virus infection among people who inject drugs

Geert Robaeys, Jason Grebely, Stefan Mauss, Philip Bruggmann, Joseph Moussalli, Andrea De Gottardi, Tracy Swan, Heiner Stover, Heiner Wedemeyer, Martin Schaefer, Lynn Taylor, Markus Backmund, Maria Prins , Gregory J Dore.

INHSU

# History

- Until recently, HCV treatment guidelines excluded PWID, due to concerns about poor adherence, adverse events and re-infection. Successful HCV treatment studies among PWID challenged this paradigm.
- Despite revised guidelines, few PWID have received HCV treatment.
- The INHSU (International Network on Hepatitis in Substance Users) established an expert panel to develop recommendations to enhance HCV assessment, management and treatment among PWID.

- They presented the recommendations at EASL – ELPA meeting 21th of April, 2012

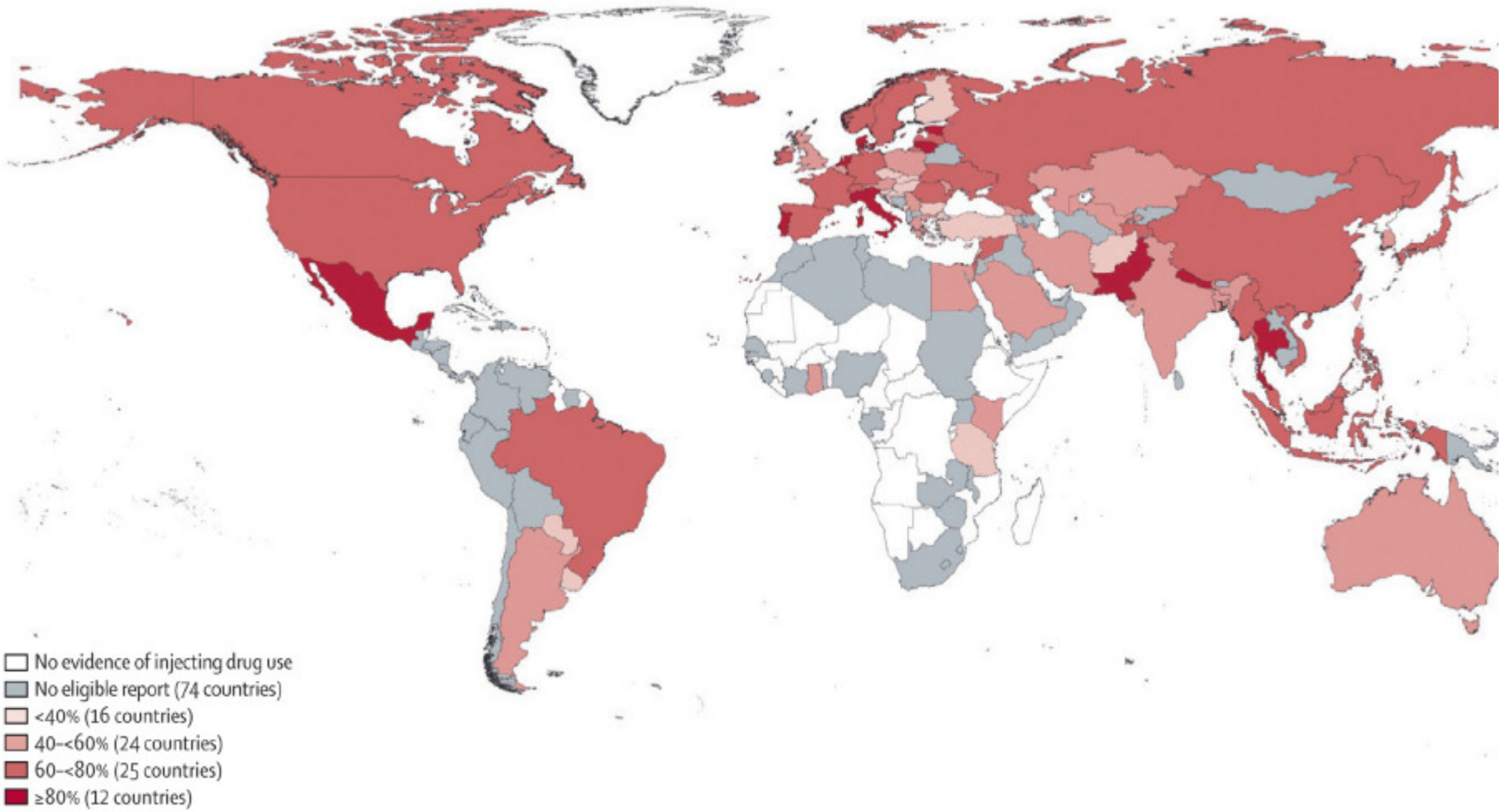
# Evidence grading (adapted from the GRADE system)

| Evidence | | Notes |
|---|---|---|
| **High quality** | Further research is very unlikely to change our confidence in the estimate of effect | A |
| **Moderate quality** | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate | B |
| **Low quality** | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain | C |
| **Recommendation** | | |
| **Strong** | Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost | 1 |
| **Weak** | Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption | 2 |

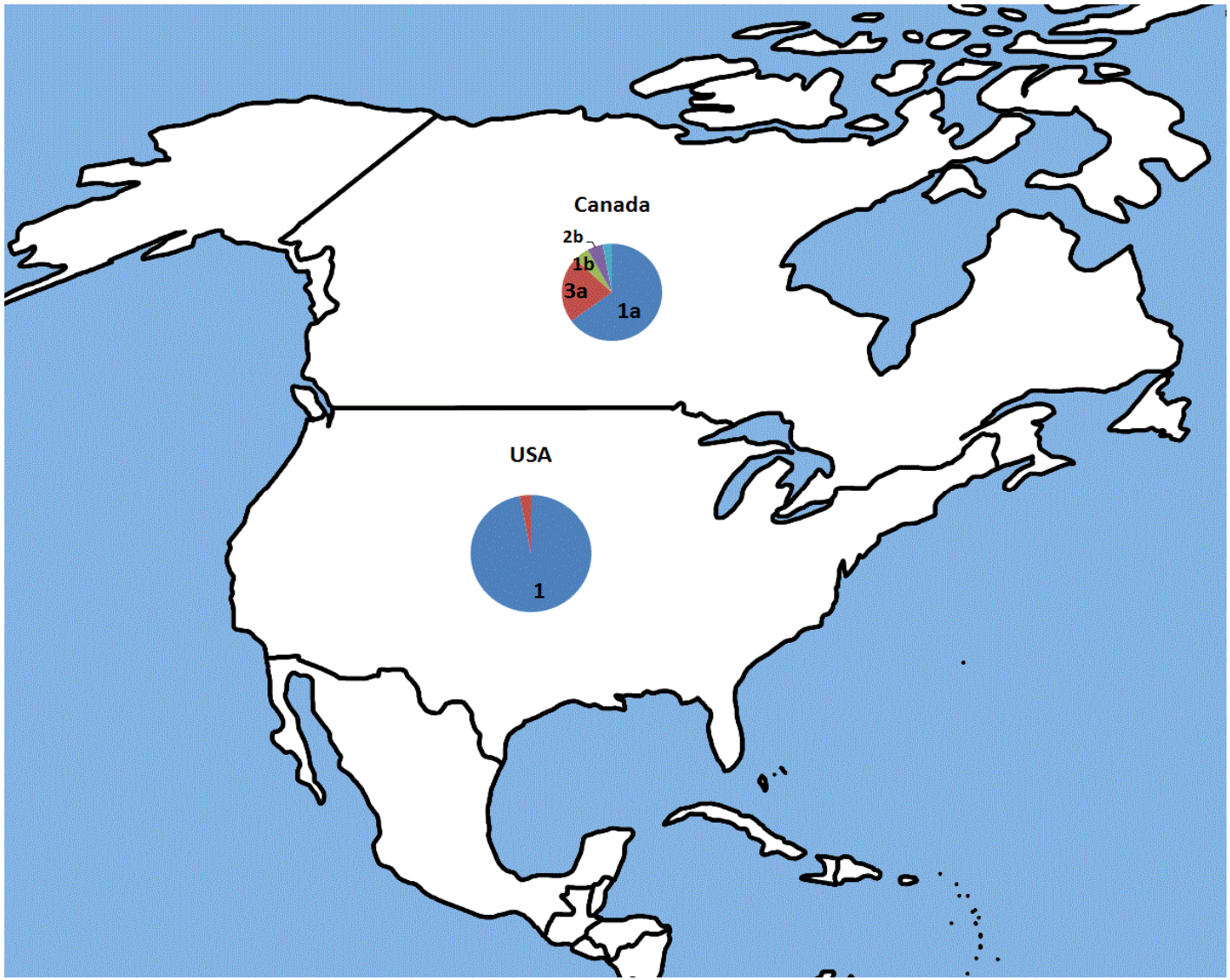
# Epidemiology and prevention of HCV

- PWID should be routinely and voluntarily tested for HCV antibodies/RNA and if negative, every 6-12 months (B1).
- PWID should be provided with
  - clean drug injecting equipment and
  - access to OST
    - as part of widespread comprehensive harm reduction programs,
  - including in prisons (B1).

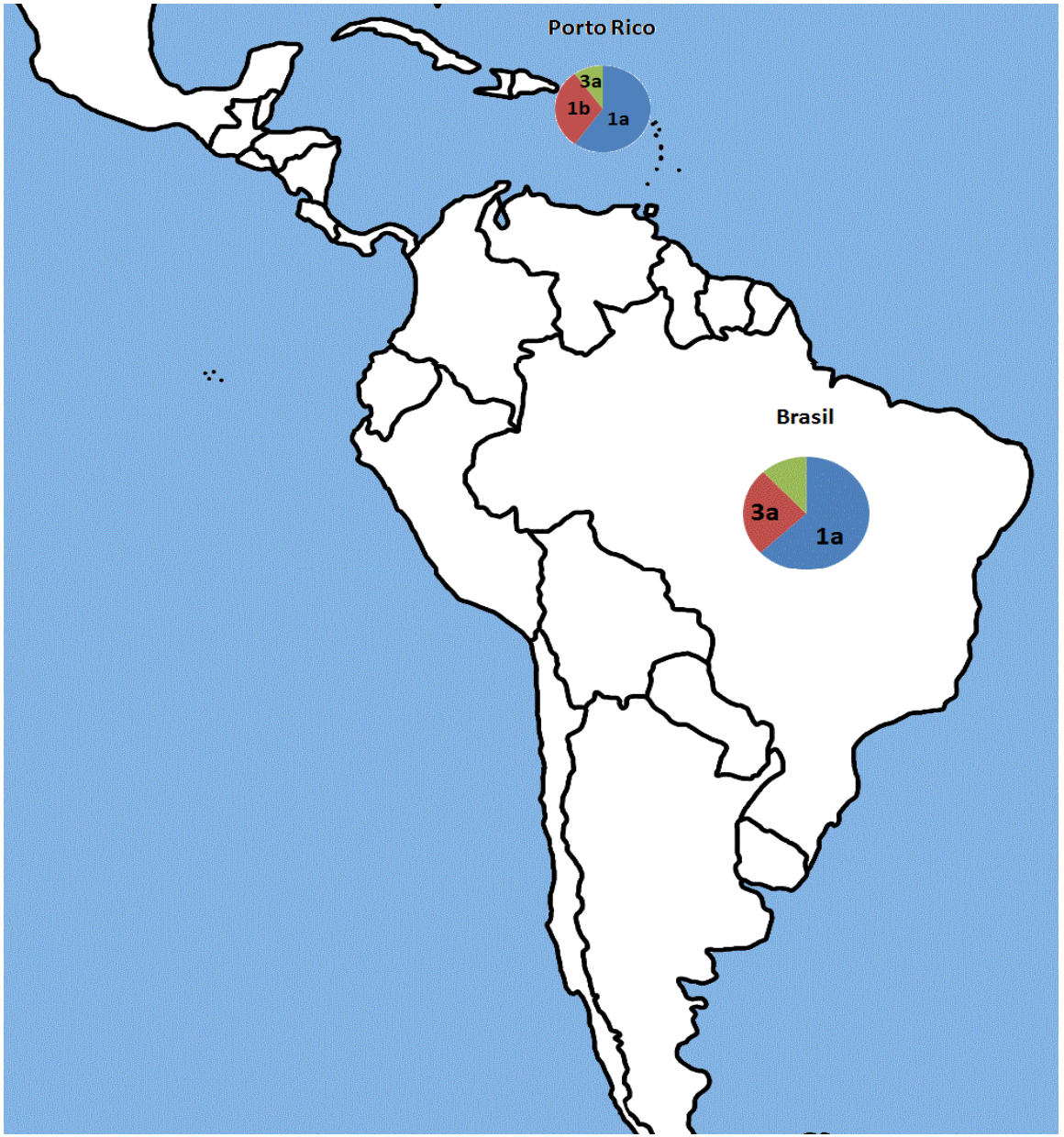
# Prevalence of anti-HCV in people who inject drugs




*Nelson et al, Lancet 2011*




Darush Ghezel Azar, F Nevens, G Robaeys. Increasing prevalence of hepatitis C viral (HCV) infection in drug users in Asia, South-America and Africa makes of it a global problem now. A systematic review. INHSU Brussels, 15-16 9 2011.

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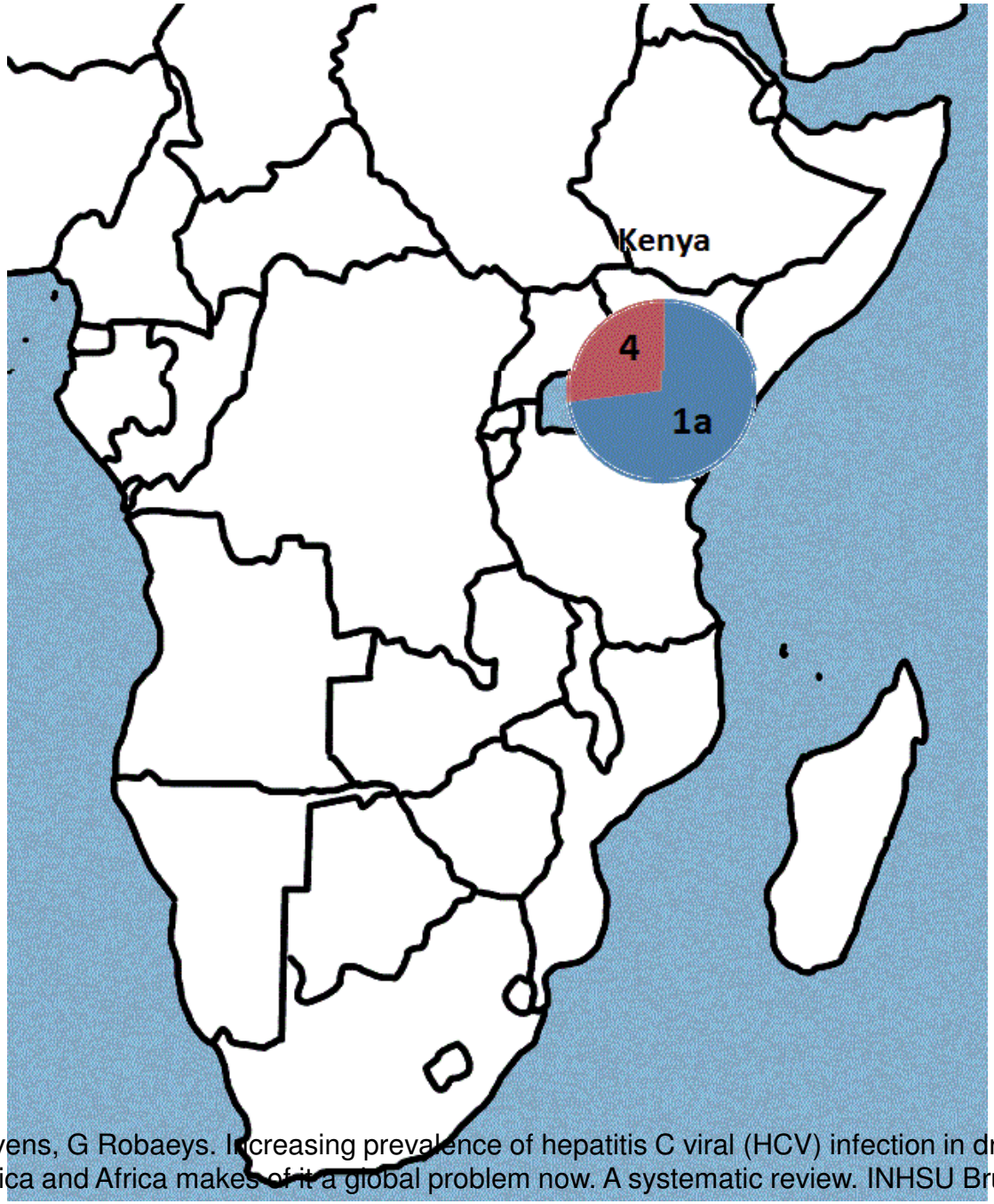


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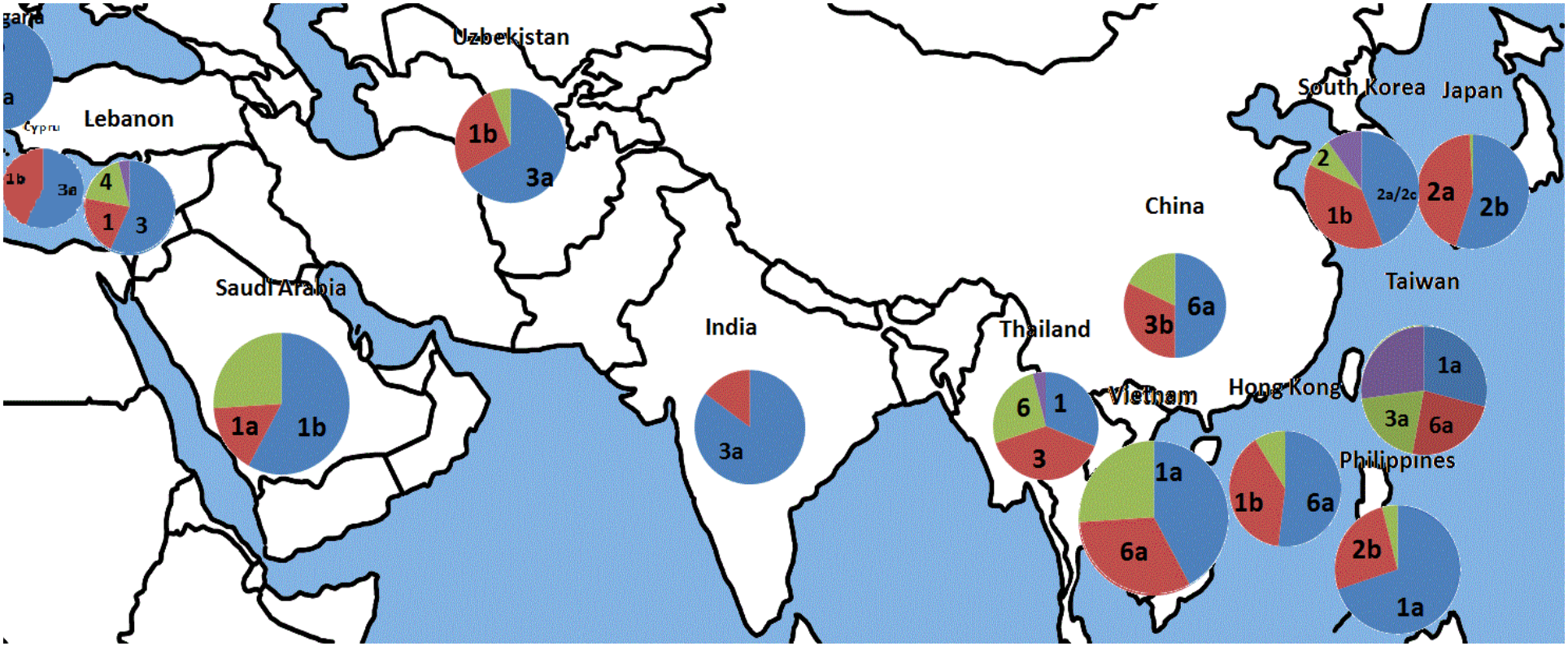


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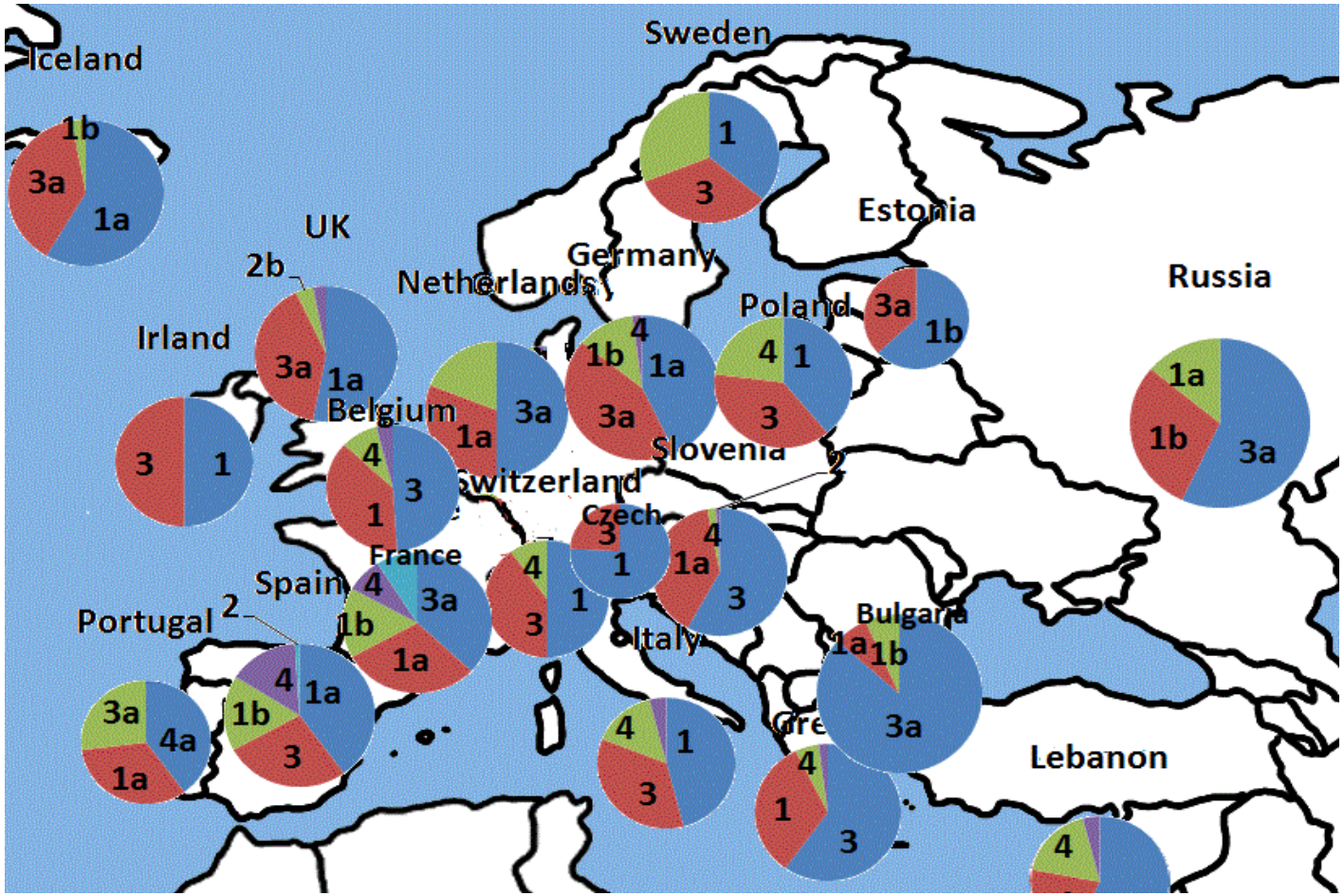
# Genotype HCV in SU

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    - as part of widespread comprehensive harm reduction programs,
  - including in prisons (B1).

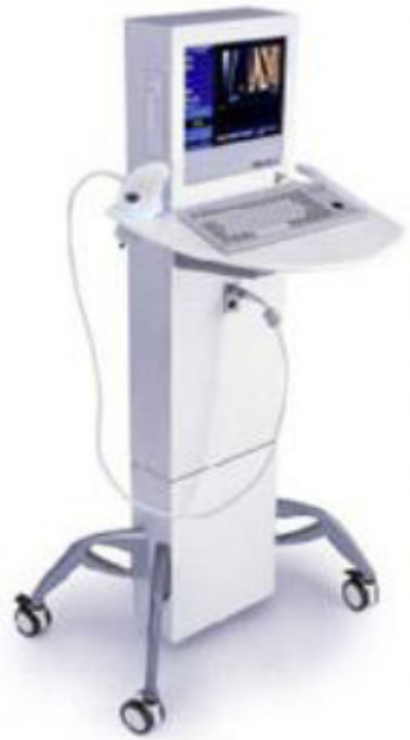
# Natural history of HCV and effects of drugs on the liver

- PWID should be counselled to
  - moderate alcohol intake, or abstain if evidence of advanced liver disease (A1).
  - moderate cannabis use, or abstain if evidence of advanced liver disease (B2).
- Cessation of injecting is not required to limit HCV disease progression (B2).
- The potential impact of drug use on the liver should be discussed with PWID (C2).

# Non-invasive liver fibrosis assessment

- have a reduced risk and greater acceptance than liver biopsy,
  - may enhance HCV screening and disease assessment among PWID, and should be offered, if available (B1).
- Combining multiple non-invasive assessments is recommended, when possible (B1).

# Fibroscan



Fibroscan

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# Saliva tests HCV

- OraQuick HCV®, rapid antibody test et OraQuick advance HIV-1/2 rapid antiboby tests®, OraSure technologies inc.

**Table 2**
Sensitivities and specificities of the OraQuick® HCV Rapid Antibody Test in each specimen type.

| Matrix | Sensitivity[a] | | Specificity[a] | |
|---|---|---|---|---|
| | TP | Proportion (95% CI[b]) | TN | Proportion (95% CI[b]) |
| Serum | 756/757 | 99.9% (99.3%, 100.0%) | 1422/1423 | 99.9% (99.6%, 100.0%) |
| Plasma | 755/756 | 99.9% (99.3%, 100.0%) | 1420/1422 | 99.9% (99.5%, 100.0%) |
| Venipuncture | 753/755 | 99.7% (99.9%, 100.0%) | 1421/1423 | 99.9% (99.5%, 100.0%) |
| Fingerstick | 752/754 | 99.7% (99.0%, 100.0%) | 1421/1422 | 99.9% (99.6%, 100.0%) |
| Oral fluid | 739/753 | 98.1% (96.9%, 99.0%) | 1418/1423 | 99.6% (99.2%, 99.9%) |

*Abbreviations*: TP, true positive; TN, true negative; CI, confidence interval.
[a] Sensitivity and specificity are calculated based on the HCV-infected or not HCV-infected samples with valid OraQuick® Rapid HCV antibody test result.
[b] The two-sided 95% exact CI of sensitivity calculated using the exact method (Clopper–Pearson) by PROC FREQ with options BINOMIAL, EXACT, and ALPHA = 0.05.

Lee et al. Journal of Virological Methods 172 (2011) 27–31

**Sensitivity**
**Serum: 99.9%**
**OF: 98.1%**

**Specificity**
**Serum: 99.9 %**
**OF: 99.6 %**

# Pre-therapeutic assessment

- Pre-therapeutic education should include discussions of
  - HCV transmission
  - risk factors for fibrosis progression
  - treatment
  - reinfection risk
  - harm reduction strategies (B1).
- Pre-therapeutic assessment should include an evaluation of
  - housing
  - education
  - cultural issues
  - social functioning and support
  - finances
  - nutrition
  - drug and alcohol use.

  PWID should be linked into social support services and peer support, if available (A1).

# Peer support

| | Peer groups |
|---|---|
| Visited at least one OASIS HCV group and were enrolled. | 69 % |
| Maintained attendance for at least three HCV groups and initiated buprenorphine | 75 % |

Sylvestre D et al, 2007

# Indications for Treatment

- PWID should receive HCV assessment, with treatment decisions based on an individualised evaluation of
  - Social
  - Lifestyle
  - Clinical factors (B1)
- PWID with absolute contra-indications to SoC should not receive HCV therapy (B1).

# Treatment uptake

- Remains low
- In hospital-based liver clinics: 16%-42%
- In the community, even lower:
  - 1%-16% : WHO
  - 8%: Australia, despite treatment being fully subsidized.
  - 14.5% : USA, treatment rates are declining

Grebely et al, 2011

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Grebely et al, 2011

# SVR in CHC patients in PWID

| Hellard M et al, 2009 | CHC-IDU | Control | Studies | Patients |
|---|---|---|---|---|
| **SVR** | 54.3% (range, 18.1%–94.1%) | 54%–63% | 22 (10 control) | 1268/2520 IVDU/non IVDU |
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| **Prior drug use** | No | | 2 | |
| **Impact of concurrent injection drug use** | 14.8–52.6% nonabstinent IDUs | 34.8–57.0% abstinent IDUs | 3 | 71 nonabstinent IDUs<br>95 abstinent IDUs |

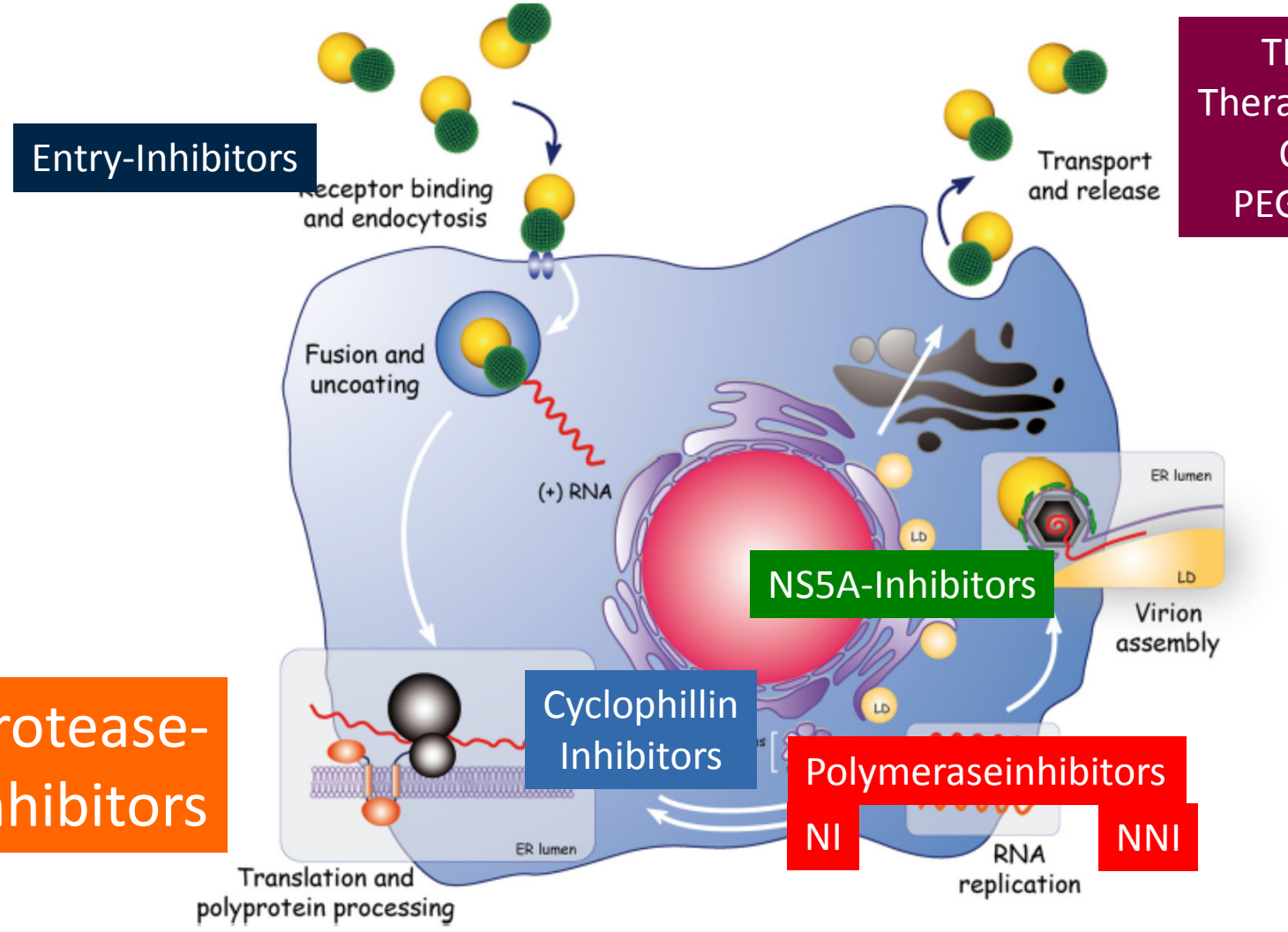
# PEG-IFN and DAA-based treatment: Treatment recommendations

- Telaprevir and boceprevir **can be used** in PWID on OST (B1).
- Evaluation of safety and efficacy of telaprevir and boceprevir, in combination with PEG-IFN/ribavirin, is required *in PWID with chronic HCV genotype 1* (C1).
- Telaprevir and boceprevir therapy does **not require specific methadone and buprenorphine dose adjustment**, but monitoring for signs of opioid toxicity or withdrawal should be undertaken (B1).
- Consideration of telaprevir and boceprevir use in PWID should be undertaken **on an individualized basis**,
- but **those with early liver disease** should generally be advised to await further data and/or potential development of improved DAA-based therapies (B1).

# Antiviral treatment HCV

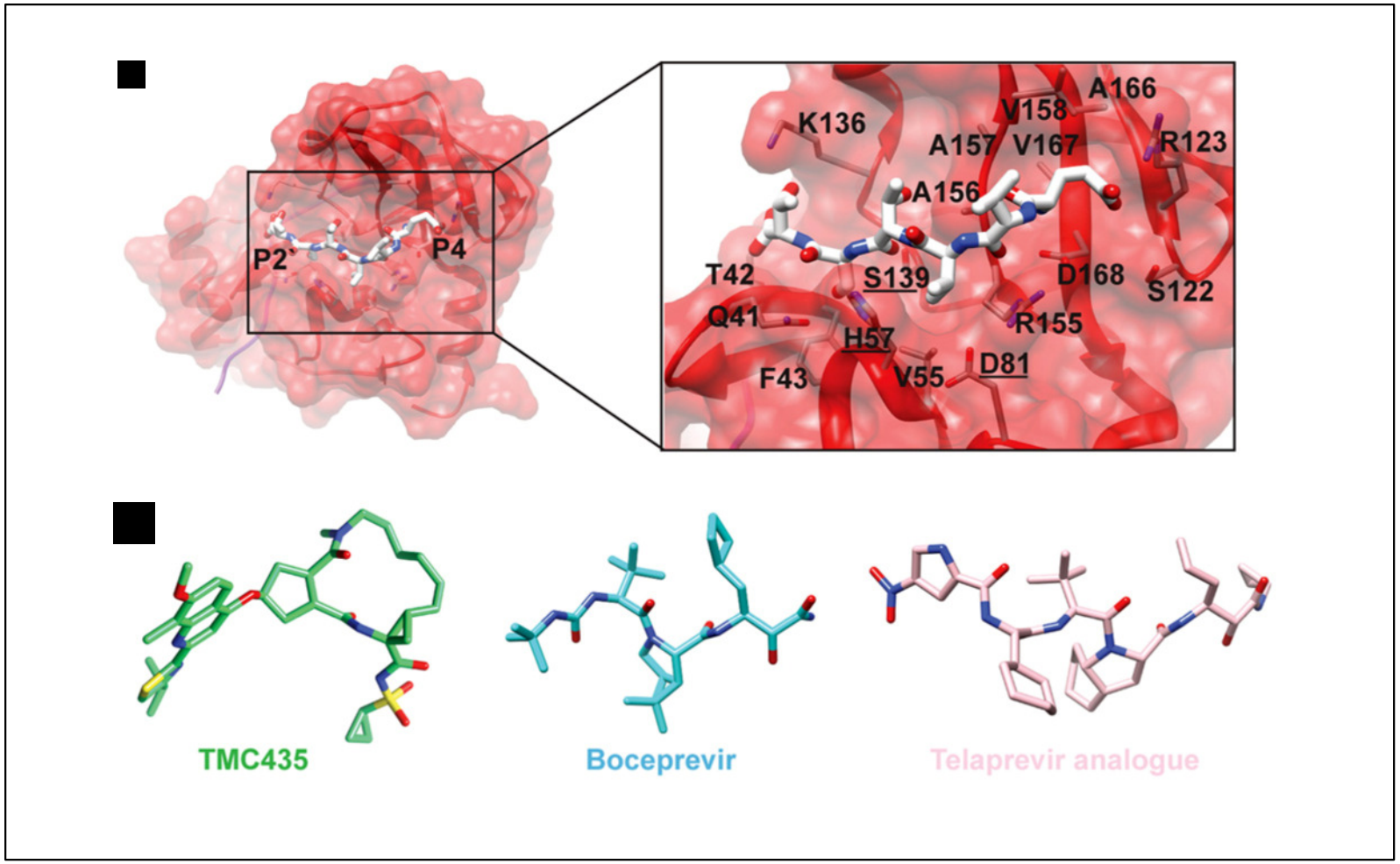
- Peg IFN
  - SC, ½ - 1 y, 1/week
  - Immunomodulatory mechanism
- Ribavirin
  - PO, ½ - 1 y, twice a day
  - Antiviral mechanism
- DAA
  - Boceprevir, telaprevir
  - PO, several times a day
  - Direct antiviral mechanism, NS3 inhibitors
- Outcome
  - SVR 50-80%

# Drug Development against HCV




Popescu C-L & Dubuisson J. *Biol Cell* 2009;102:63-74.

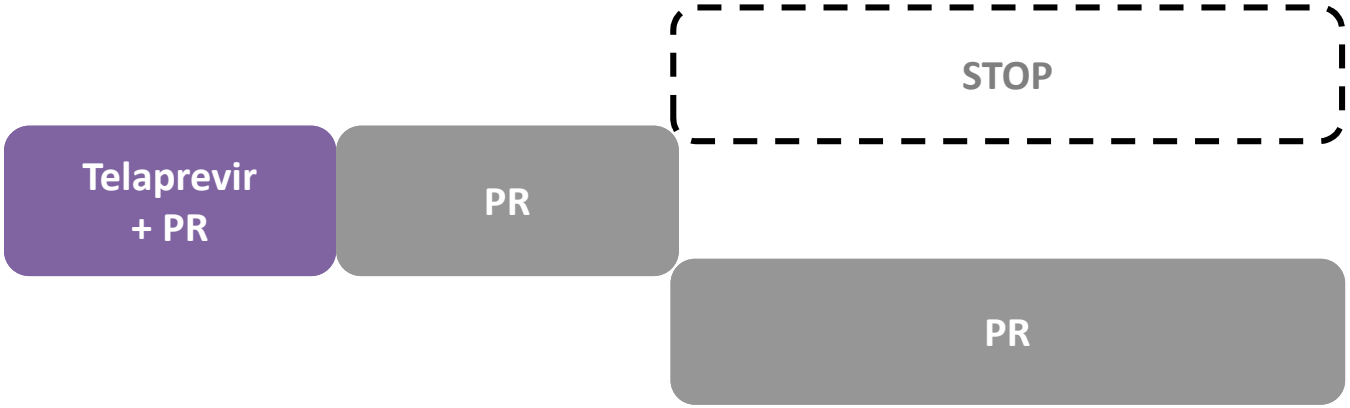
# NS3/4A Protease Inhibitors



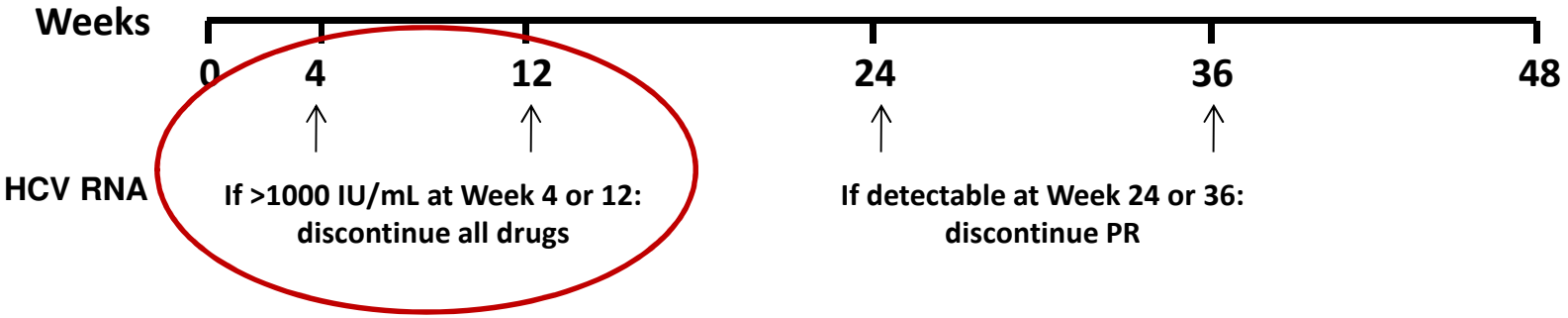

*(Raney et al., J Biol Chem 2010:285:22725-31)*

# Telaprevir regimen in G1 HCV-infected patients

- Non-cirrhotic naïves and relapsers achieving **undetectable HCV RNA at Week 4 and 12 (eRVR)**

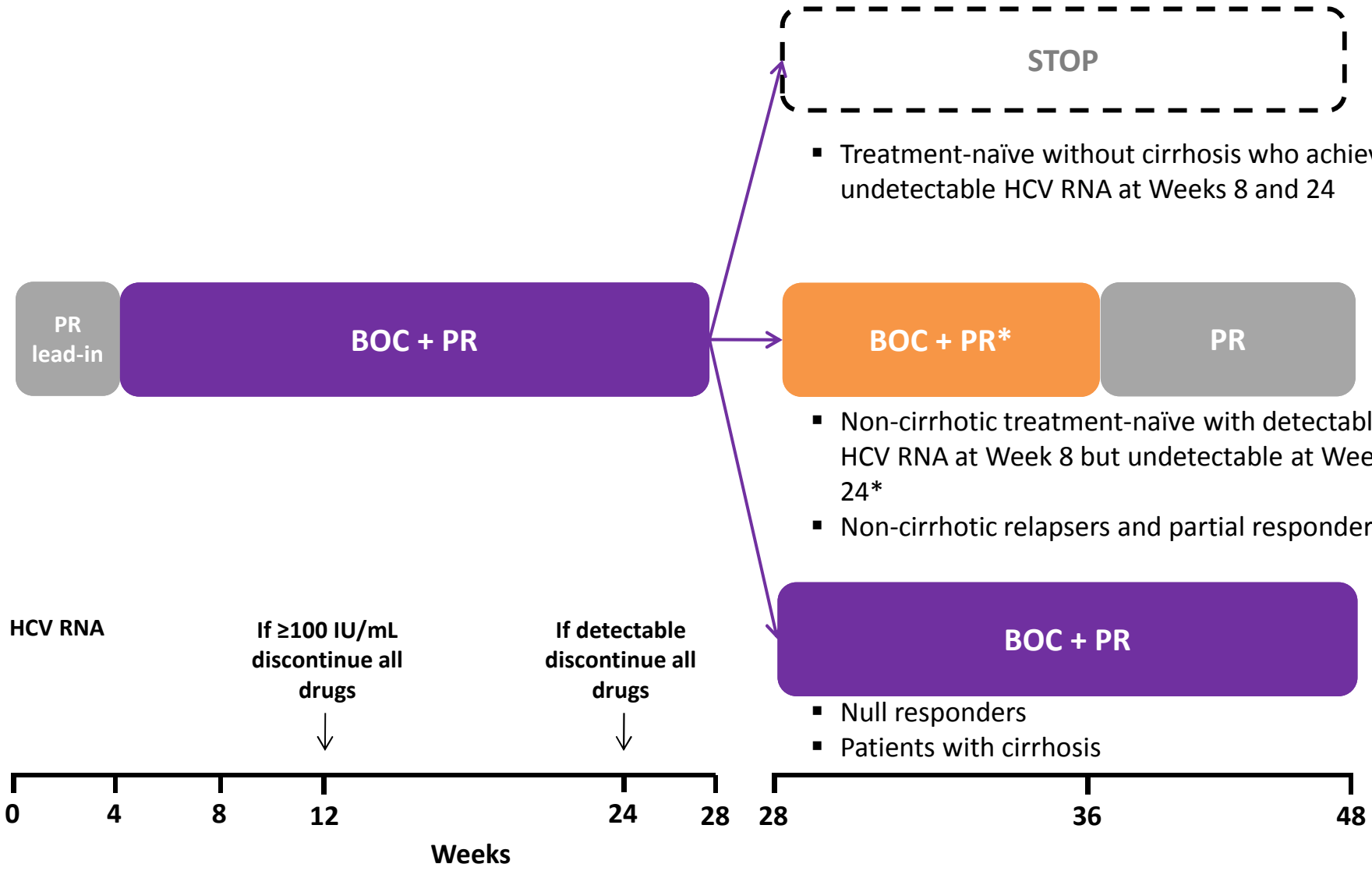



- Non-cirrhotic naïves and relapsers without eRVR
- Partial and null responders
- Patients with cirrhosis




Telaprevir EU SmPC

# Boceprevir regimen in G1 HCV-infected patients




- Treatment-naïve without cirrhosis who achieve undetectable HCV RNA at Weeks 8 and 24
- Non-cirrhotic treatment-naïve with detectable HCV RNA at Week 8 but undetectable at Week 24*
- Non-cirrhotic relapsers and partial responders
- Null responders
- Patients with cirrhosis

*This regimen has only been tested in patients who have failed previous therapy who were late responders

Boceprevir EU SmPC

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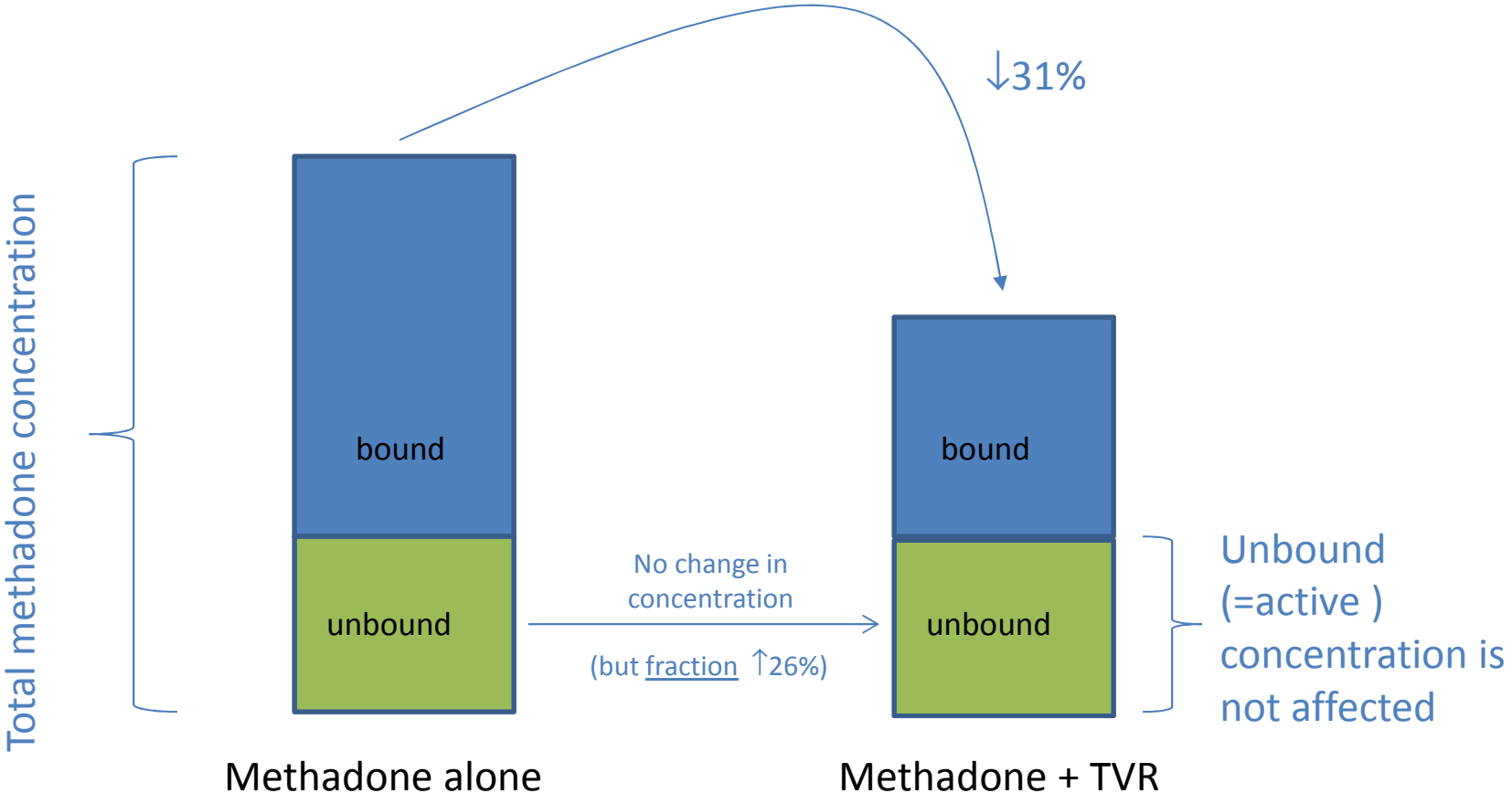
# Effect of Protein Displacement




R van Heeswijk, et al. The Pharmacokinetic Interaction Between Methadone and the HCV Protease Inhibitor Telaprevir. INHSU Brussels, 15-16 9 2011.

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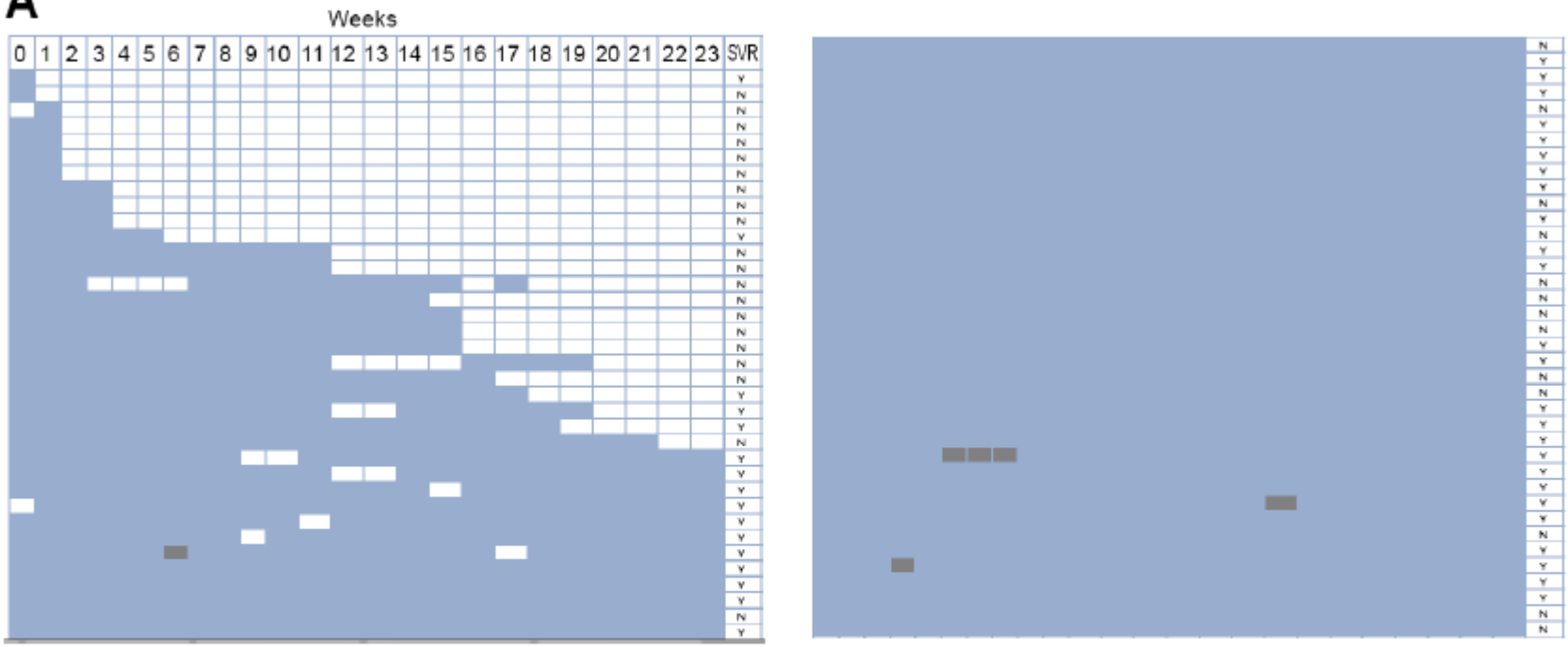
# Impact of drug use on adherence and SVR

- PWID should be counselled on the importance of **adherence** in attaining an SVR (A1).
- Adherence should consider **missed doses and treatment discontinuation** (B1).
- HCV treatment can be considered for PWID, provided they
  - wish to receive treatment and
  - are able and willing to maintain regular appointments (A1).
- **A history of IDU and recent drug use** at treatment initiation are not associated with reduced SVR and decisions to treat must be made on a case-by-case basis (B1).
- PWID with **ongoing social issues, history of psychiatric disease and those with more frequent drug use during therapy** are at risk of lower adherence and SVR and need to be monitored closely during therapy (B1).

# 80/80 non-adherence is driven by treatment discontinuation

**A**




- SVR was higher in those with 80/80 adherence (67% vs. 35%, P=0.007)
- SVR was similar among those with and without missed doses during therapy (73% vs. 60%,P=0.309)
- SVR in those discontinuing therapy between 0-4, 5-19, 20-23 and 24 weeks was 9%, 33%, 43% and 76% (P<0.001).

Grebely J, et al. J Hepatology 2011.

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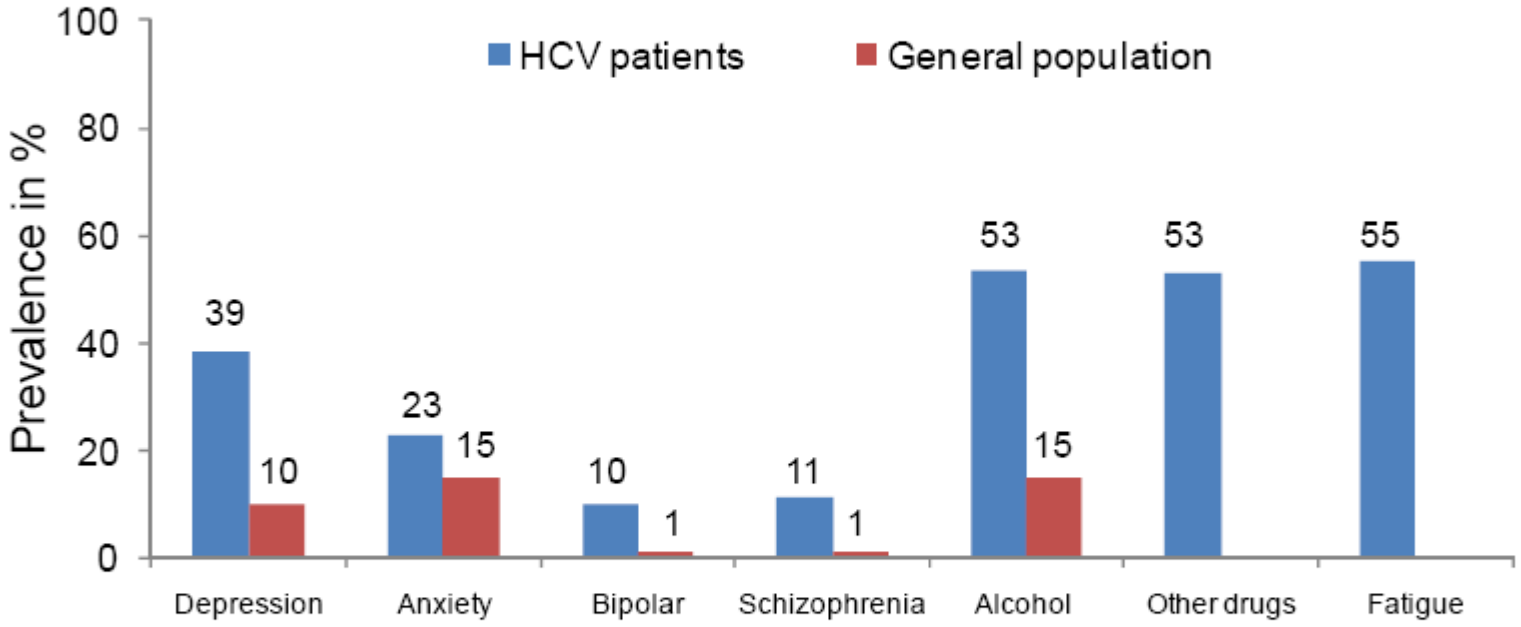
# Impact of mental health on adherence and SVR

- Pre-treatment assessment should **include** an
  - evaluation of previous or current psychiatric illness,
  - engagement with a drug and alcohol counselor or psychiatrist
  - discussions around potential treatment options (A1).
- If psychiatric co-morbidities are present, decisions to treat with PEG-IFN must be made on **a case-by-case basis** (A1).
- In cases of **acute major and uncontrolled psychiatric disorders,** a pre-treatment psychiatric assessment is recommended (C2).
- **Prophylactic antidepressants** are recommended in cases of
  - a history of IFN-induced depression and
  - with depressive symptoms at baseline (B1).

# HCV and Psychiatric comorbidity




1) Nelligan et al., 2008, J Clin Psychiatry 2) Butt et al., 2007, J Vir Hep 3) Butt et al., 2006, J Hepatol 4) Lim et al., 2006, J Clin Gastroenterol 5) Golden et al., 2005, Gen Hosp Psychiatry 6) El-Serag et al., 2002, Gastroenterology 7) Nguyen et al., 2002, Am J Gastroentero 8) Yovtcheva et al., 2001, Psychosomatics 9) Dwight et al., 2000, J Psychosom Res 10) Batista-Nevis et al., 2008, Gen Hosp Psychiatry 11) Lehmann et al., 2002, Am J Gastroenterol 12) Kraus et al., 2001, Psychosomatics 13) Fireman et al., 2005, Clin Infect Dis 14) Cacoub ez al., 2002, J Hepatol 15) Barkhuizen et al., 1999, Am J Gastroenterol 16) Kenny-Walsh et al., 1999, N Engl J Med

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- Drug dependency assessment should be undertaken and OST considered, if applicable (B1).
- Access to harm reduction programmes should be a component of HCV clinical management (B2).
- Peer-based support should be evaluated as a means to improve HCV clinical management (B2).

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# Peer support

| Grebely J et al, 2007 | Peer-support group | |
|---|---|---|
| **Completed therapy** | 66% (12/18) | |
| **EOT** | 67 % (8/12) | **despite ongoing drug use in 75%**<br>- 56 % (n = 10) illicit drug use in 6 months preceding therapy;<br>- 39 % (n=7) actively using illicit drugs at the time of therapy initiation. |

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# Reinfection following successful HCV treatment

- PWID should **not be excluded** from HCV treatment on the basis of perceived risk of reinfection (B1).
- **Harm reduction education and counselling** should be provided for PWID in the context of HCV treatment (B1).
- Following SVR, monitoring for HCV reinfection through **annual HCV RNA** assessment should be undertaken on PWID with ongoing risk behaviour (B2).

# Within appropriate programs, reinfection is low

| Study | Study Population | Median Age | IDU post-treatment | Median Follow-up (years) | New infection | HCV incidence rate |
|---|---|---|---|---|---|---|
| Backmund 2004 | n=18 | 32 | 50% | 2.8 (0.8-5.1) | 11% (2/18) | 4.1/100 py |
| Dalgard 2005 | n=27 | NA | 33% | 5.4 (1.1-6.8) | 4% (1/27) | 0.8/100 py |
| Currie 2008 | n=9 | 46 | 22% | 3.6 (3.2–6.0) | 11% (1/9) | 0.6/100 py |
| Grebely 2010 | n=35 | 44 | 54% | 2.0 (0.4-5.0) | 6% (2/35) | 3.2/100 py |
| Bate 2010 | n=57 | 34 | NA | 3.4 (0.2-11.5) | 9% (5/57) | NA |
| Grady 2011 | n=42 | NA | 21% | 3.0 (2.4-4.1) | 2% (1/42) | 0.8/100py |
| Grebely 2012 | n=87 | 36 | NA | 1.2 (0.1-3.0) | 5% (4/87) | 3.7/100 py |

1) Backmund CID 2004; 2) Dalgard CID 2005; 3) Currie DAD 2008; 4) Grebely J Gastro Hepatol 2010; 5) Bate J Gastroenterol Hepatol 2010; 6) Grebely Hepatology 2012; 7) Grady 2nd *ISHCSU*, Brussels, Belgium 2011.

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# Treatment of acute HCV

- PWID with acute HCV symptoms should be monitored for 12-16 weeks (including HCV RNA levels) to allow potential spontaneous clearance (A1).
- **PEG-IFN mono-therapy for 24 weeks** should be considered for PWID with acute HCV (B1).
- Strategies to optimize adherence should be used in the setting of acute HCV, with consideration of directly observed PEG-IFN therapy (B2).

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# HIV/HCV co-infection

- HIV-infected PWID who are HCV antibody-negative should be **screened annually** for HCV (A1).
- HCV-infected PWID should be screened for HIV (B1).
- The accelerated HCV disease progression in HIV/HCV should be considered in treatment decision-making (B2).
- Potential **drug-drug interactions** between HIV, HCV and OST need to be considered (A1).
- **Early introduction of ART** should be considered (B1).

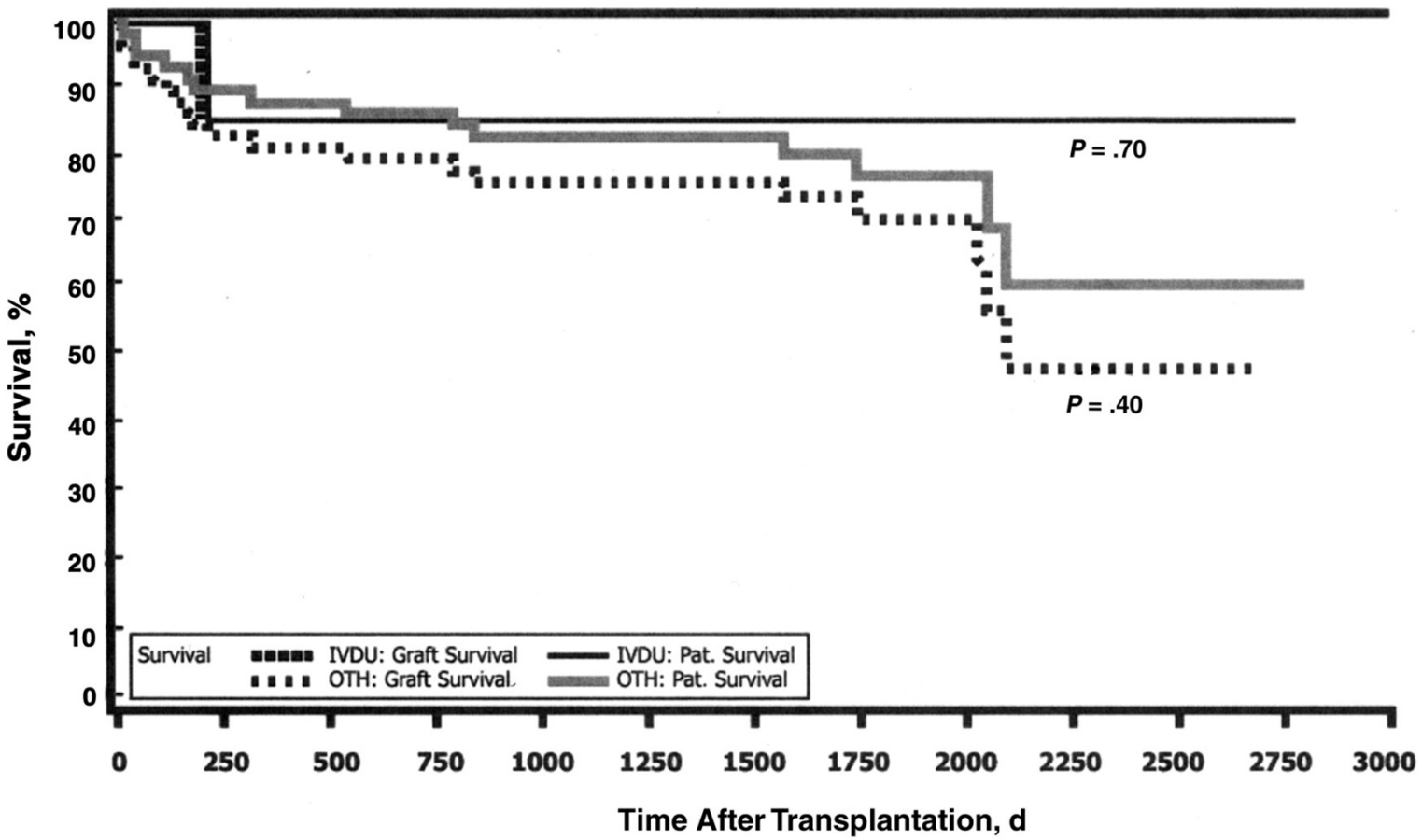
# Management of hepatitis B virus (HBV) co-infection

- PWID should be vaccinated for hepatitis A virus and HBV (A1).
- PWID with HBV/HCV should be considered for PEG-IFN/ribavirin therapy (B1).

# Liver transplantation

- Awareness should be raised that liver transplant **is a therapeutic option** in those with a
  - history of IDU
  - illicit drug abstinence for > 6 months (B2).
- **OST is not a contraindication** for liver transplantation and individuals on OST should not be advised to reduce or stop therapy (A1).
- **Psychiatric evaluation and follow-up** should be offered to PWID undergoing liver transplantation (B1).

# Outcome




Robaeys et al. Transplantation Proceedings. 2009

# Liver transplantation

- Awareness should be raised that liver transplant **is a therapeutic option** in those with a
  - history of IDU
  - illicit drug abstinence for > 6 months (B2).
- **OST is not a contraindication** for liver transplantation and individuals on OST should not be advised to reduce or stop therapy (A1).
- **Psychiatric evaluation and follow-up** should be offered to PWID undergoing liver transplantation (B1).

Thank you for your attention