Towards the update of the KDIGO guidelines on hepatitis C in CKD

Professor Michel Jadoul

Dept of Nephrology

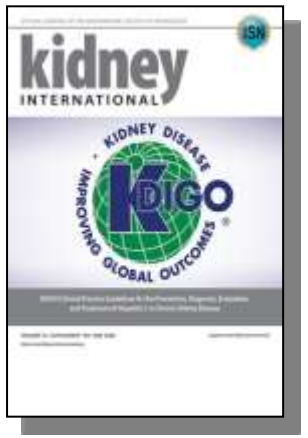
Cliniques universitaires Saint-Luc

Université catholique de Louvain

Brussels , Belgium

First Global Guideline in Nephrology

- Published in April 2008 (Supplement of Kidney International)
- Available on the KDIGO website (www.kdigo.org)
  - Complete guideline document in English
  - Executive Summary with recommendations in Arabic, Chinese, French, Italian, Japanese, Russian, Spanish, and Turkish



KDIGO
Практическое руководство
по предотвращению, диагностике,
обследованию и лечению гепатита С
у больных ХБП

Руководство 3: Профилактика гепатита С в отделении гемодиализа

3.1 Отделение гемодиализа дожно собдюдать строгие меры профилактики инфекций, передающихся парентеральным путем, включая гепатит С (Высокий)

- Изоляция пациентов, инфицированных вирусом гепатита С, не замещает строгого собдюдения мер профилактики по предотвращению кровяных инфекций. (Низкий)
- **Использование диализных машин, предназначенных только для инфицированых вирусом гепатита С пациентов, не рекомендуется (Средний)**
- Если невозможно избежать повторного использования диализатора, можно использовать диализатор от инфицированного вирусом гепатита С пациента повторно только после процедуры дезинфекции в строгом соответствии с мерами по предотвращению кровяных инфекций. (Низкий)

Guideline Topics (Chapters)

1. Detection and evaluation of HCV in CKD
2. Treating HCV infection in CKD
3. Preventing HCV transmission in hemodialysis units
4. Management of HCV before and after kidney transplantation
5. Diagnosis and management of kidney diseases associated with HCV infection

Guideline Topics (Chapters)

1. Detection and evaluation of HCV in CKD
2. Treating HCV infection in CKD
3. Preventing HCV transmission in hemodialysis units
4. Management of HCV before and after kidney transplantation
5. Diagnosis and management of kidney diseases associated with HCV infection

HCV testing for patients on HD: how?

Enz.Imm. Assay *vs* **Nucleic Acid Testing**

EIA **NAT (PCR, TMA,..)**

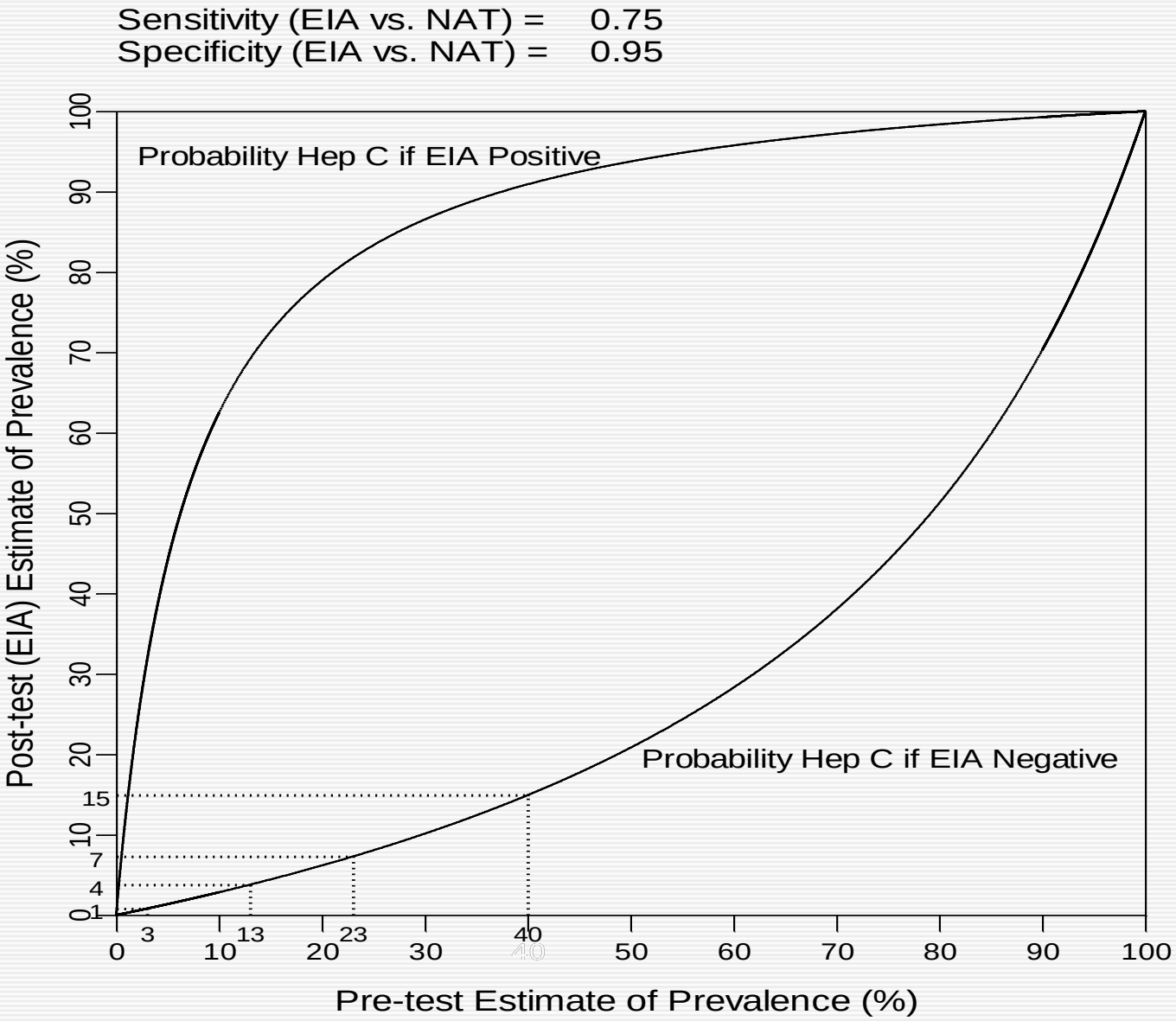
easy, inexpensive complex, expensive

- **What about sensitivity/specificity in CKD 5D?**

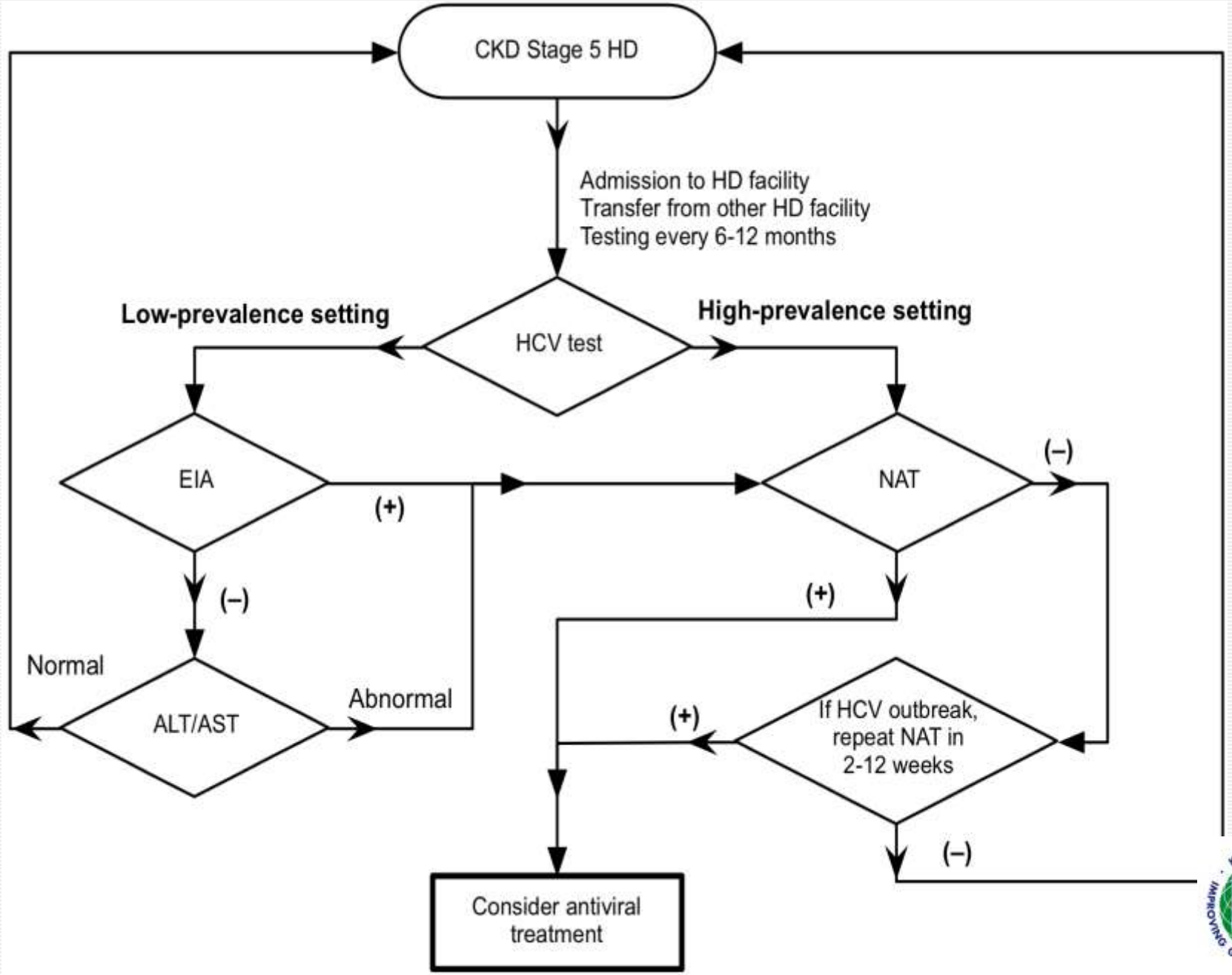
Meta-analysis of studies comparing EIA vs NAT

- **13 studies available, over 10 000 HD patients**
- **gold standard Nucleic acid testing (PCR)**
- **EIA 3: sensitivity around 75%, specificity around 95%**

Testing for HCV: how?



Diagnosis of HCV in CKD Stage 5 on HD



Diagnosis of HCV infection

- If HCV linked to CKD, independently of other CKD classical risk factors, this might be a good reason to recommend broader testing of CKD patients for HCV

  WG will review cohort studies
- HCV antigen and HCV core-specific antibodies : some recent data, to be reviewed by WG

Guideline Topics (Chapters)

1. Detection and evaluation of HCV in CKD
2. Treating HCV infection in CKD
3. Preventing HCV transmission in hemodialysis units
4. Management of HCV before and after kidney transplantation
5. Diagnosis and management of kidney diseases associated with HCV infection

Treating HCV infection in ESRD classical view

- While on HD , (Peg) IFN + Ribavirin if very careful monitoring possible (preferably in clinical studies)
- Sustained Viral Response rates : around 35-40% in dialyzed pts

  Drop out rate : 35%
- (Peg) IFN contraindicated after TP: high risk of loss of graft (rejection)

UPDATE

Nephrology

Ann J Nephrol 2013;38:405–412
DOI: 10.1159/000355615

Received: August 2, 2013
Accepted: September 16, 2013
Published online: October 29, 2013

Hepatitis C Infection Is Very Rarely Treated among Hemodialysis Patients

David A. Goodkin[a] Brian Bieber[a] Brenda Gillespie[b] Bruce M. Robinson[a]
Michel Jadoul[c]

[a]Arbor Research Collaborative for Health, Ann Arbor, Mich., USA; [b]University of Michigan, Ann Arbor, Mich., USA; [c]Cliniques Universitaires St-Luc, Université catholique de Louvain, Brussels, Belgium

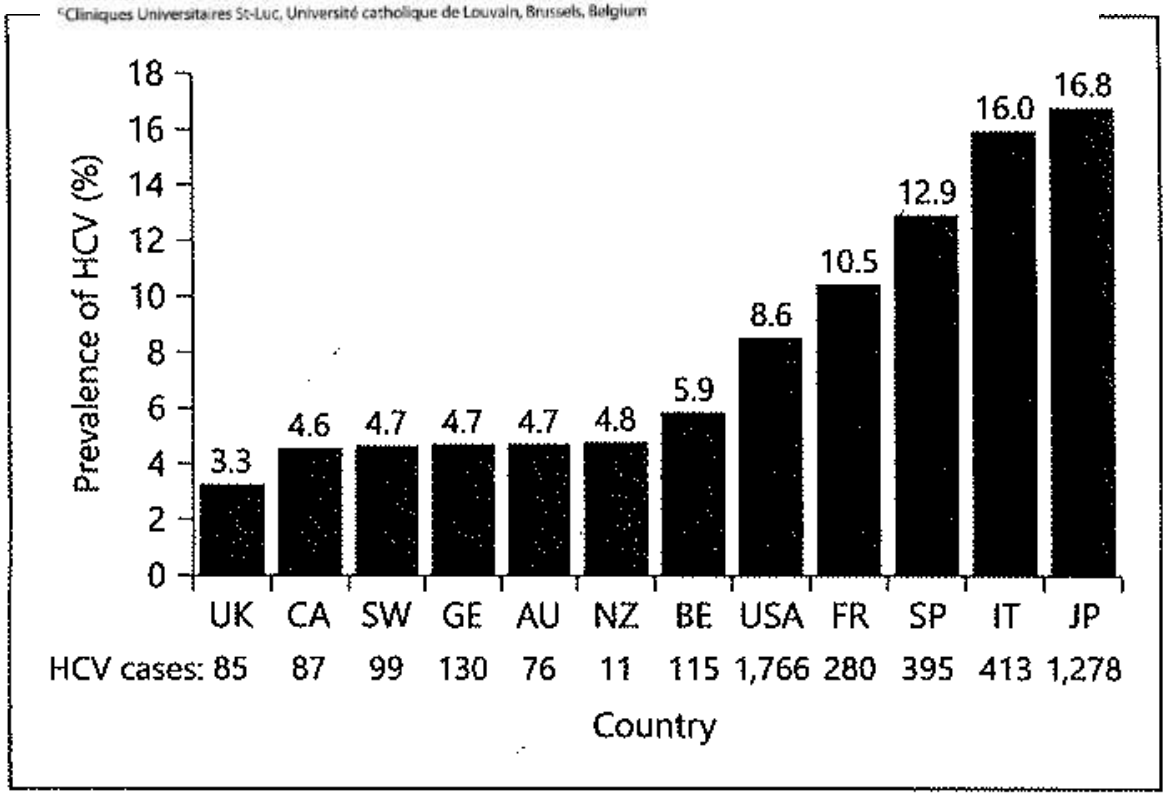
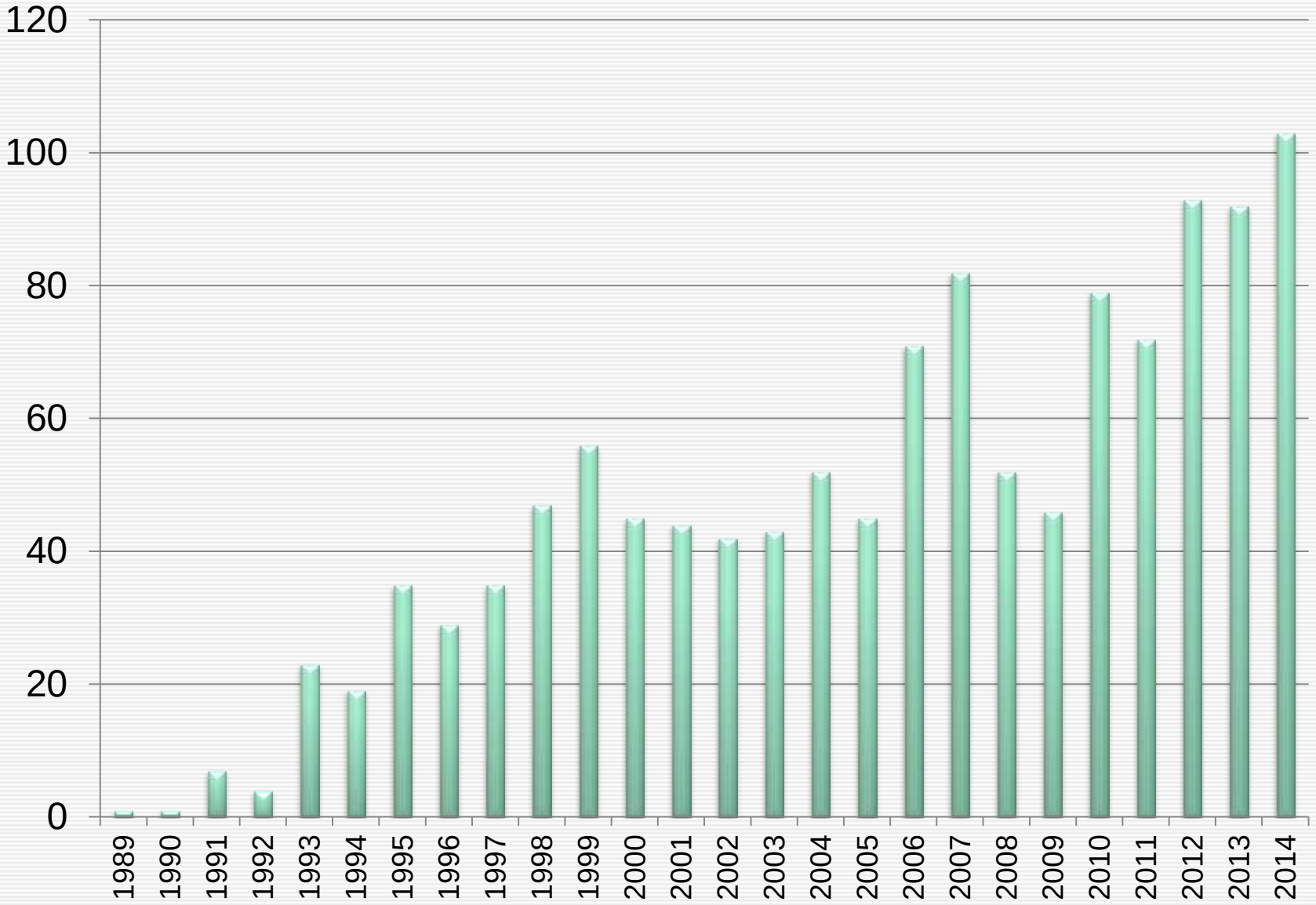


Fig. 3. Prevalence of HCV infection in HD patients, by country. Overall prevalence 9.5% (4,735 of 49,767 patients). CA = Canada; SW = Sweden; GE = Germany; AU = Australia; NZ = New Zealand; BE = Belgium; FR = France; SP = Spain; IT = Italy; JP = Japan.

UPDATE

RCT and HCV - number of citations/year



Treating HCV infection in ESRD new developments

- Many new antiHCV drugs
  - several NS3-4A protease inhibitors
  - NS5B (non)-nucleos(t)ide inhibitors
  - NS5A inhibitors
  - hosttargeting antiviral agents

- Sustained viral response rates 80- 100%, even without interferon
- Shorter regimens (3 months in some)
- Many drugs not eliminated by the kidney but metabolized by liver microsomes (CYP3 A4,…) : drug interactions with CNI,….

UPDATE

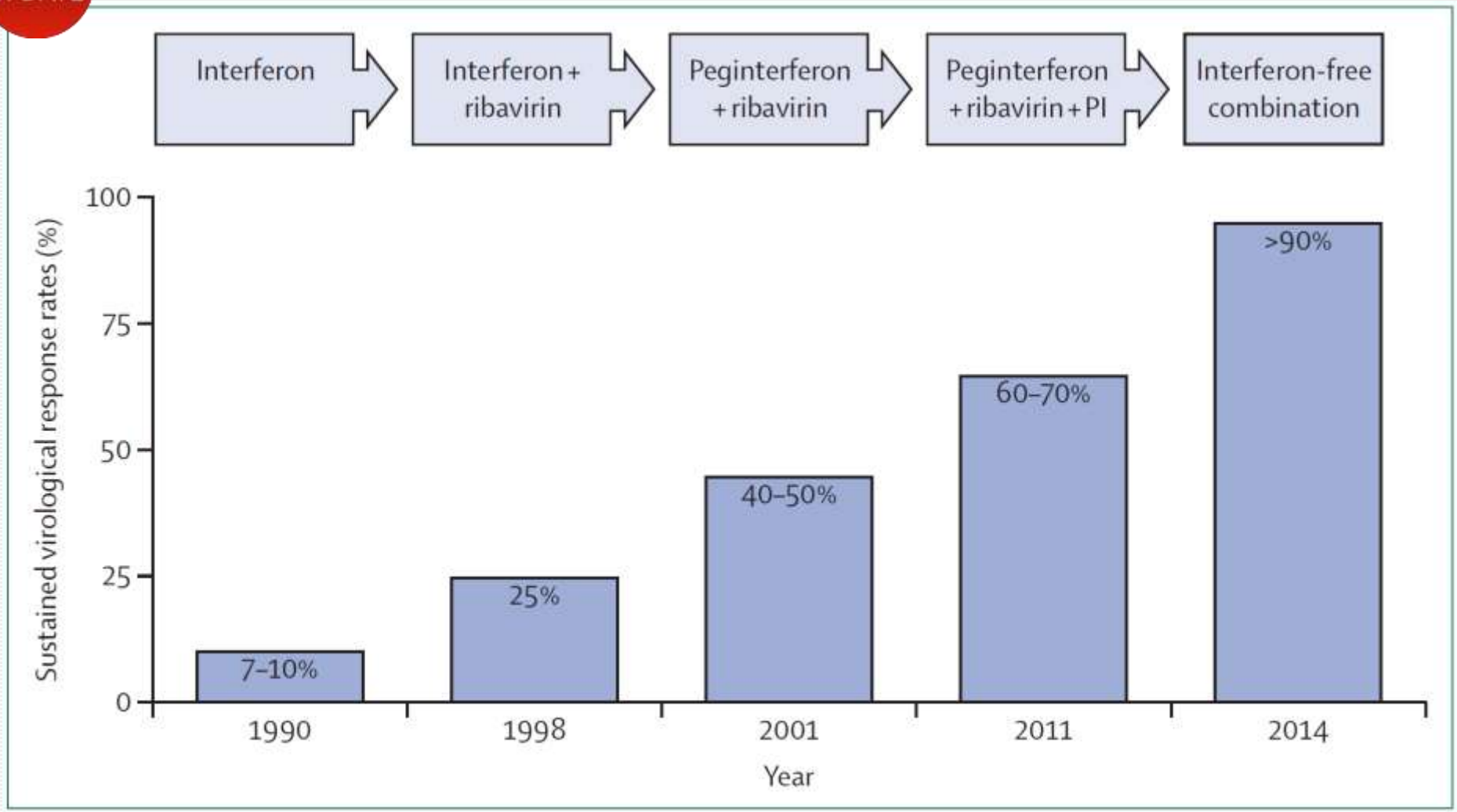


Figure 1: **Changes in standard of care for HCV, and improvements in numbers of sustained virological responses**
Data from references 9–12. PI=protease inhibitor.

Hepatitis C

Daniel P Webster, Paul Klenerman, Geoffrey M Dusheiko

Lancet 2015; 385: 1124–35

UPDATE

Response Guided Treatment with Telaprevir or Boceprevir in End Stage Renal Disease Patients with Hepatitis C Genotype 1

Anish Patel, Seth Sclair, Omer Junaidi, Violet Copado, Cynthia Levy, Paul Martin, Madhavi Rudraraju, Kalyan R Bhamidimarri

Journal of GHR 2014 November 21 3(11): 1335-1339

UPDATE

All patients received pegylated interferon alpha 2a (P), ribavirin (R) and either boceprevir (BPR) 800 mg every eight hours or telaprevir (TPR) 750 mg every eight hours. All patients treated with BPR received 1-month lead-in, P 180 mcg weekly and R 200 mg three times weekly whereas those treated with TPR received no lead-in, P 135 mcg weekly and R 200 mg daily, twice weekly or three times weekly at the discretion of the clinician (based on baseline hemoglobin).

Journal of GHR 2014 November 21 3(11): 1335-1339

UPDATE

Table 2 Review of treatment characteristics and results of therapy in both cohorts.

Treatment Characteristics and Responses	Telaprevir Cohort	Boceprevir Cohort
Number of patients	9	7
Genotype		
1a	6 (67)	4 (57)
1b	3 (33)	3 (43)
Treatment History		
Naive	6 (67)	5 (72)
Prior Relapse	2 (22)	1 (14)
Prior Non-Responder	1 (11)	0
Unknown	0	1 (14)
IL28b Genotype		
CT	4 (44)	2 (29)
TT	4 (44)	2 (29)
Unknown	1 (12)	3 (42)
Stage of Liver Disease		
0	3 (33)	1 (14)
1	3 (33)	1 (14)
2	0	0
3	0	2 (29)
4	3 (33)	3 (43)
eRVR	5 (56)	1 (14)
EOT response	4 (44)	6 (86)
SVR (12 weeks post)	3 (33)	4 (57)

Categorical variables are described as *n* (%); IL28b: interleukin 28b; eRVR: extended rapid virologic response; EOT: end of treatment; SVR: sustained virologic response.

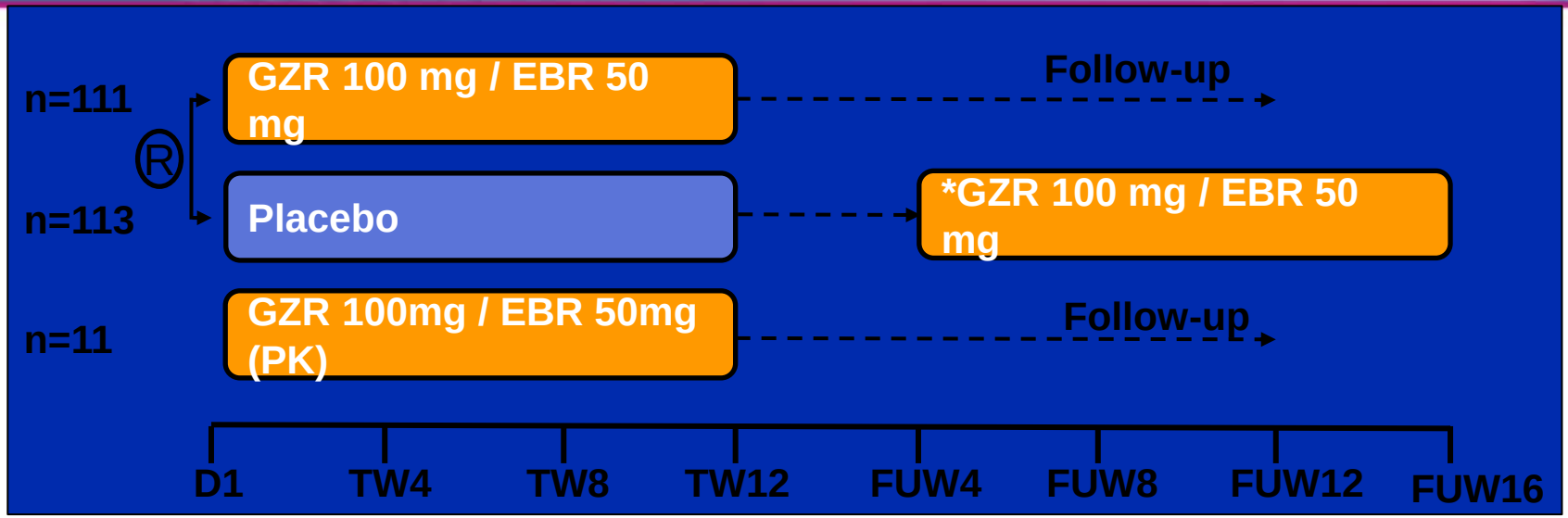
UPDATE

Table 3 Review of treatment complications with both cohorts.

Safety Characteristics and Management	Telaprevir Group	Boceprevir Group
RBV dose reduction	0	2 (29)
IFN dose reduction	1 (11)	1 (14)
Neupogen therapy	2	1
Thrombocytopenia	1 (11)	0
Promacta therapy	1	0
Anemia Management		
EPO	7 (78)	5 (71)
Blood Transfusion	2 (22)	1 (14)
Miscellaneous Complications		
Hepatic Decompensation	1 (11)	0
Non-Compliance	1 (11)	0
Pneumonia	0	1 (14)
Dehydration	1 (11)	0
Fistula Infection	1 (11)	0

Categorical variables are described as *n* (%); RBV: ribavirin; IFN: pegylated interferon-alpha2a; EPO: erythropoietin.

C-SURFER: STUDY DESIGN



- Randomized, parallel-group, multi-site, placebo-controlled trial
- Stratification by diabetes (yes/no) and hemodialysis status (HD/non-HD)
- 224 patients randomized to immediate treatment with GZR/EBR or deferred treatment where patients received placebo for 12 weeks then open-label GZR/EBR starting at FUW4
- 11 patients in open-label GZR/EBR arm underwent intensive pharmacokinetic sampling

*Deferred open-label treatment arm (all randomized patients remained blinded to treatment until FW4)
GZR and EBR were administered as separate entities in the immediate and PK arms, and as a fixed dose-combination in the deferred arm. CKD = chronic kidney disease; GT = genotype; HD = hemodialysis; R = randomized

From: Roth D. ILC 2015, #LP02

C-SURFER: KEY INCLUSION/EXCLUSION CRITERIA

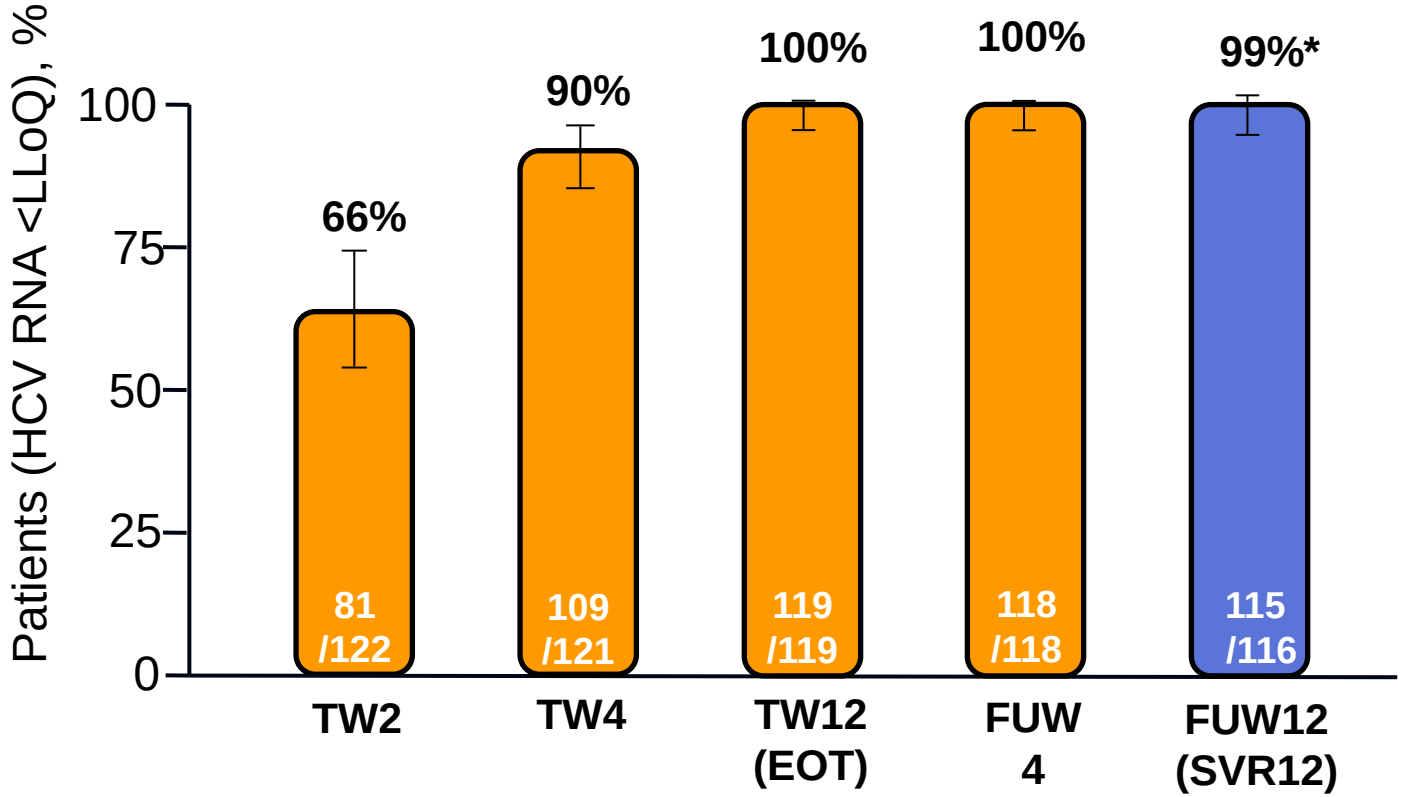
- HCV GT1 infection
- Treatment-naive and treatment-experienced patients
- CKD stage 4/5 (± hemodialysis dependence)
  - CKD stage 4: eGFR 15-29 mL/min/1.73m^2
  - CKD stage 5: eGFR <15 mL/min/1.73m^2 or on dialysis
  - target 20% non-hemodialysis patients
- Compensated cirrhosis allowed
  - Liver staging was based on biopsy within 24 months of enrolment; Fibroscan within 12 months of enrolment; or a combination of Fibrotest score of >0.75 and an AST:platelet ratio index of >2
  - Patients with presence or history of ascites, gastric or variceal bleeding, hepatic encephalopathy, or other signs/symptoms of advanced liver disease were excluded
- HBV and HIV negative

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

From: Roth D. ILC 2015, #LP02

C-SURFER: ON-TREATMENT VIROLOGIC RESPONSE (ITG)

1 noncirrhotic patient with HCV GT1b infection relapsed at FW12



*Efficacy is presented for the modified full analysis set population (mFAS). Full Analysis set: patients with SVR12 94%

6 patients were excluded from the per protocol: lost to follow-up (n=2), n=1 each for death, non-compliance, withdrawal by subject, and withdrawal by physician (due to violent behavior)

From: Roth D. ILC 2015, #LP02

C-SURFER: ADVERSE EVENT SUMMARY (≥ 10%)

	GZR / EBR (ITG) (n=111)	Placebo (DTG) (n=113)	Difference in % Estimate (95% CI)
Adverse events*, n (%)	84 (75.7)	95 (84.1)	-8.3 (-18.9, 2.2)
Headache	19 (17.1)	19 (16.8)	0.3 (-9.6, 10.4)
Nausea	17 (15.3)	18 (15.9)	-0.6 (-10.3, 9.1)
Fatigue	11 (9.9)	17 (15.0)	-5.1 (-14.1, 3.7)
Insomnia	7 (6.3)	12 (10.6)	-4.3 (-12.2, 3.2)
Dizziness	6 (5.4)	18 (15.9)	-10.5 (-19.1, -2.6)
Diarrhea	6 (5.4)	15 (13.3)	-7.8 (-16.1, -0.2)
Serious AEs, n (%)	16† (14.4)	19 (16.8)	-1.5 (11.2, 8.1)
Discon due to an AE, n (%)	0 (0)	5 (4.4)	-4.4 (10.0, -1.0)
Deaths‡, n (%)	1 (0.9)	3 (2.7)	-1.8 (-6.7, 2.5)

*Reported in ≥10% of patients in either treatment group (ASaT)
†One SAE in the ITG was considered drug-related (elevated lipase)
‡One ITG patient died from cardiac arrest and 3 DTG patients died from aortic aneurysm, pneumonia, and unknown cause
AE = adverse event; DTG = deferred treatment group; ITG = immediate treatment group; SAE = serious adverse event

From: Roth D. ILC 2015, #LP02

C-SURFER: CONCLUSIONS

- Once daily GZR/EBR for 12 weeks was highly effective for treatment of HCV GT1 infection among patients with CKD stage 4/5
- Efficacy is consistent across different subpopulations:
  - GT1a and 1b
  - Diabetes
  - Hemodialysis
- Failure to achieve SVR12 is rare
  - One patient relapsed
- Once daily GZR/EBR for 12 weeks was generally well-tolerated in this study population of patients with advanced kidney disease

From: Roth D. ILC 2015, #LP02

Cost issues !

Editorial

The main drawback of these new agents is the huge price tag, which will make treatment out of reach for people in the developed and developing world. Indeed, current treatment uptake is also impeded by cost. One 12 week course of sofosbuvir will cost US$84 000, even though the scientist involved in formulating sofosbuvir, Raymond Schinazi, estimates costs at just $1400. An even lower price was shown by Andrew Hill and colleagues in a recent study. Based on the fact that the new hepatitis C treatments are comparable in molecular structure and chemistry to HIV antiretrovirals, the authors used the same market dynamics to determine the minimum cost to manufacture them, which was $100–250 per 12 week treatment course; they concluded that at these low prices, widespread access to these new medicines is feasible within 15 years. Although manufacturers are likely to offer low-income countries steep discounts, around 75% of people with hepatitis C live in middle-income countries regarded as emerging markets by companies, and so are unlikely to benefit from the kind of discounts needed to make treatment available.

Therapy for Hepatitis C — The Costs of Success

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

Unfortunately, not all barriers to treatment will be lifted. The major limitation remaining will be economic. The current cost of a 12-week regimen of sofosbuvir alone is $84,000, or $1,000 per tablet.[11] The addition of ledipasvir will add to the costs, and these estimates do not include expenses for diagnostic assays, monitoring, and physician visits.

The predicted costs of the new oral antiviral agents are as breathtaking as their effectiveness.

This article was published on April 12, 2014, at NEJM.org.

http://www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/

WHO | WHO moves to imp...

Sign up for WHO updates

عربي 中文 English Français Русский Español

World Health Organization

Health topics Data Media centre Publications Countries Programmes Governance About WHO Search

Media centre

Media centre
News
News releases
Pr
Stat
Note
Event
Fact s
Featu
Comm
Multim
Conta

WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers

Share Print

News release

Treatments for hepatitis C are evolving rapidly, with several new, highly effective and safe medicines on the market and many in the development pipeline," said Dr Marie-Paule Kieny, WHO Assistant Director-General for Health Systems and Innovation. **"While some efforts have been made to reduce their price for low-income countries, without uniform strategies to make these medicines more affordable globally the potential for public health gains will be reduced considerably."**

May 2015

professions. This year, the Committee underscored the urgent need to take action to promote equitable access and use of several new highly effective medicines, some of which are currently too costly even for high-income countries.

New medicines to treat Hepatitis C

These included new medicines to treat hepatitis C, which affects about 150 million people globally, killing approximately half a million people each year, when chronic infection develops into liver cirrhosis or liver cancer. The disease is present in high- and lower-income countries alike, with higher concentrations in several middle- and

Direct-acting agents			
NS3/NS4A inhibitors	NS5A inhibitors	NS5B inhibitors (nucleoside)	NS5B inhibitors (non-nucleoside)
Telaprevir*	Daclatasvir (BMS-790052)	Sofosbuvir (GS-7977)*	Setrobuvir (ANA598)
Boceprevir*	Ombitasvir (ABT-267)	Mericitabine (RG-7128)	Tegobuvir (GS-9190)
Danoprevir (RG-7227)	Ledipasvir (GS-5885)	Valopicitabine	Filibuvir (PF-868554)
Faldaprevir (BI201335)*	Samatasvir (IDX 719)	MK-3682	Dasabuvir (ABT-333)
Vaniprevir (MK-7009)	Elbasvir (MK-8742)		Deleobuvir (BI 207127)
Sovaprevir (ACH-1625)	GS-5816		Beclabuvir (BMS-791325)
Simeprevir (TMC435)*	ACH-3102		ABT-072
Asunaprevir (BMS−650032)			GS-9669
Paritaprevir (ABT-450)			VX-222
Grazoprevir (MK−5172)			
Vedroprevir (GS−9451)			
Host-targeting agents (host target)			
Alisporivir aka DEB025 (cyclophilin A)			
Miravirsen aka SPC3649 (miR-122)			
SCY-635 (cyclophilin A)			

UPDATE

CURRENT OPINION

New hepatitis C virus therapies: drug classes and metabolism, drug interactions relevant in the transplant settings, drug options in decompensated cirrhosis, and drug options in end-stage renal disease

Paul Y. Kwo[a] *and Maaz B. Badshah*[b]

Table 1. Drug interactions with currently available direct acting antiviral agent

	SOF	SOF/LDV	SIM	PTV/OMB DSV	DCV
Tacrolimus	NI	NI	NI	I, reduce TAC to 0.5 1–2 weeks	NI
Cyclosporine	NI	NI	I, C	I, reduce CYA to 20%	NI
Sirolimus/everolimus	NI	NI	NI	I, no data	NI
Mycophenolate/mycophenolic acid	NI	NI	NI	I, reduce MMF by 50%	NI
Azathioprine	NI	NI	NI	NI	NI

C, contraindicated; CYA, cyclosporin; I, interaction; NI, no interaction demonstrated or expected; LDV, ledipasvir; MMF, mycophenolate mofetil; PTV/OMB DSB, paritaprevir/ombitasvir, Dasabuvir; SIM, simeprevir; SOF, sofosbuvir; TAC, tacrolimus.

Curr Opin Organ Transplant 2015, 20:235–241

UPDATE

CURRENT OPINION

New hepatitis C virus therapies: drug classes and metabolism, drug interactions relevant in the transplant settings, drug options in decompensated cirrhosis, and drug options in end-stage renal disease

Paul Y. Kwo[a] *and Maaz B. Badshah*[b]

Table 3. Direct acting antiviral agent use in renal disease

Stage of CKD	SOF	SOF/LDV	SIM	PTV/OMB DSB	DAC
Stage 1 GFR > 90 ml/min	Y	Y	Y	Y	Y
Stage 2 (mild) GFR 60–89 ml/min	Y	Y	Y	Y	Y
Stage 3 (moderate) GFR 30–59 ml/min	Y	Y	Y	Y	Y
Stage 4 (severe) GFR 15–29 ml/min	N	N	Y	Y	Y
Stage 5 (renal failure) GFR < 15 ml/min or dialysis	N	N	N	N	Y

CKD, chronic kidney disease; LDV, ledipasvir; SOF, sofosbuvir.

UPDATE

Annals of Internal Medicine | Review

Screening for Hepatocellular Carcinoma in Chronic Liver Disease

A Systematic Review

Devan Kansagara, MD, MCR; Joel Papak, MD; Amirala S. Pasha, DO, MS; Maya O'Neil, PhD; Michele Freeman, MPH; Rose Relevo, MLIS, MS; Ana Quiñones, PhD; Makalapua Motu'apuaka, BS; and Janice H. Jou, MD, MHS

Mortality	2 RCTs of patients with HBV-related disease (total n = 19 200) 18 NRCSs (1 of patients with HBV-related disease, 3 of patients with HCV-related disease, 7 of patients with HBV/HCV–related disease, and 7 of patients with HBV/HCV/alcohol–related disease) (total n = 12 887) 1 meta-analysis of 36 NRCSs (total n = 13 361)	In 1 trial of ultrasonography with high risk of bias, the RR for death due to HCC was 0.63 (95% CI, 0.41–0.98). In 1 trial of α-fetoprotein with unclear risk of bias, all-cause mortality per 100 person-years was 1.84 vs. 1.79 (P = NS) in the intervention and usual care groups, respectively. The combined OR of 3-y survival in the meta-analysis of 36 observational studies was 1.90 (CI, 1.67–2.17).	Very low	Trials were limited by selective outcome reporting, allocation concealment, and other analytic issues. Observational studies were limited by selection, lead-time, and length-time biases. Screening consistently diagnosed HCC at an earlier stage, but the effect on overall mortality is unclear.

Conclusion: There is very-low-strength evidence about the effects of HCC screening on mortality in patients with chronic liver disease. Screening tests can identify early-stage HCC, but whether systematic screening leads to a survival advantage over clinical diagnosis is uncertain.

Guideline Topics (Chapters)

1. Detection and evaluation of HCV in CKD
2. Treating HCV infection in CKD
3. **Preventing HCV transmission in hemodialysis units**
4. Management of HCV before and after kidney transplantation
5. Diagnosis and management of kidney diseases associated with HCV infection

HCV KDIGO Guideline 3: preventing HCV transmission in HD
evidence based?

- No Randomized Controlled Trial for prevention
- « old » high quality evidence supporting hygienic precautions (WHO, CDC,….)
- A few large good quality observational studies

Nosocomial transmission of HCV: which routes?

Based on molecular virology combined with epidemiology, the vast majority of transmission events occur at same time /other monitors

- External surfaces
- Hands of staff
- Multidose vials or contaminated injectable drugs

Isolation of HCV (+) patients ?

- Two large prospective observational studies: no protective impact of isolation

  Italy: Petrosillo et al. AJKD 2001

  DOPPS: Fissell et al. Kidney Int 2004

update of DOPPS data is ongoing with more countries, 15 years instead of 3-5 years F Up ….

Guideline 3.1: Hemodialysis units should ensure implementation of, and adherence to, strict infection-control procedures designed to prevent transmission of blood-borne pathogens, including HCV. (Strong)

- *Isolation of HCV-infected patients is not recommended as an alternative to strict infection-control procedures for preventing transmission of blood-borne pathogens. (Weak)*
- The use of dedicated dialysis machines for HCV-infected patients is not recommended. (Moderate)
- *Where dialyzer reuse is unavoidable, it is suggested that the dialyzers of HCV-infected patients can be reused provided there is implementation of, and adherence to, strict infection-control procedures. (Weak)*

Key elements for the prevention of nosocomial HCV transmission

- Hand Hygiene (hydroalcoolic solution) before contact with patient and after gloves withdrawal
- Wear gloves, to be changed between patients/stations
- Prepare drugs in clean area

Key elements for the prevention of nosocomial HCV transmission (II)

- Dedicate small items (tourniquet, tape, ….) to a single patient (if not, disinfect between patients)
- Do not return unused material from contaminated to clean area
- Clean/disinfect surfaces of HD environment before next session

Guideline Topics (Chapters)

1. Detection and evaluation of HCV in CKD
2. Treating HCV infection in CKD
3. Preventing HCV transmission in hemodialysis units
4. Management of HCV before and after kidney transplantation
5. Diagnosis and management of kidney diseases associated with HCV infection

UPDATE

G4: Management of the wait-listed pretransplant candidate

- is a liver biopsy still mandatory to assess the extent of fibrosis ?
  - non invasive algorithms : AST/platelet ratio
    Fibrotest
  - transient elastography (Fibroscan)
- Reduced need for combined liver kidney TP?
- New questions related to HCV-HIV co-infection
  - HIV + no longer contraindication for kidney TP
  - Sequential / combined treatement ?
  - drug interactions !!

Guideline Topics (Chapters)

1. Detection and evaluation of HCV in CKD
2. Treating HCV infection in CKD
3. Preventing HCV transmission in hemodialysis units
4. Management of HCV before and after kidney transplantation
5. Diagnosis and management of kidney diseases associated with HCV infection

UPDATE

Guideline 5

- many new antiHCV drugs (DAAs) : impact on cryo-induced/MP GN?
- Many new biologic agents : place in management of HCV-related GN with or without DAAs

Summary

- Perfect time to update the 2008 KDIGO HCV Guidelines
- Many new developments

  - diagnosis

  - management

  - treatment

- The draft updated guideline will be available for public review ; register at www.kdigo.org

Back up slides

Table 1: Summary of current direct-acting antivirals and use in renal impairment

Drug	Elimination	Level of Evidence	Dosage Adjustment for Severe Renal Impairment (eGFR 15-29 mL/min)	Dosage Adjustment for ESRD and HD (eGFR <15 mL/min)
Simeprevir 150mg daily	Feces 91%; Urine <1%	Weak	Not required • PK data	Likely not required • PK data • Clinical trials required
Sofosbuvir 400mg daily	Urine 81%; Feces 15%	Moderate	Likely not required • PK data • Case series • Prospective cohort	Limited data available • Clinical trials required
Ledipasvir 90mg daily	Feces 86%; Urine 1%	Weak	Not required • PK data	Likely not required. • Clinical trials required.
3D Regimen: Ombitasvir 25mg/ paritaprevir 150mg/ ritonavir 100mg, and dasabuvir 500mg daily	Feces>86%; Urine <11%	Moderate	Not required • Clinical Trial results pending	Not required • Clinical Trial results pending
Daclatasvir 60mg daily	Feces 88%; Urine 7%	Weak	Not required • PK data	Not required • PK data

Table 2: Summary of future direct-acting antivirals and use in renal impairment

Drug	Elimination	Level of Evidence	Dosage Adjustment for Severe Renal Impairment (eGFR 15-29 mL/min)	Dosage Adjustment for ESRD and HD (eGFR <15 mL/min)
Grazoprevir/Elbasvir 100/50mg daily	Urine <1%	Strong	Not required • RCT	Not required • RCT

Weak level of evidence=Single/steady state pharmacokinetic studies, case series, open-label phase 2 trial
Moderate level of evidence=Longitudinal observational study, multi-centre open label phase 3 trial
Strong level of evidence= Randomized un-blinded multi-centre controlled trial

Table 3: Summary of the current American Association for the study of liver diseases treatment recommendations in CKD stage 4 and 5 for each HCV genotype

Genotype	AASLD Treatment Recommendations	AASLD/IDSA Recommendations in CKD Stage 4	AASLD/IDSA Recommendations in CKD Stage 5
1a	SOF+SMV ± RBV LDV-SOF ± RBV OBV-PTV/r + DSB + RBV	SOF+SMV ± RBV (Consult expert for SOF use) OBV-PTV/r + DSB + RBV	OBV-PTV/r + DSB + RBV
1b	SOF+SMV ± RBV LDV-SOF ± RBV OBV-PTV/r + DSB	SOF+SMV ± RBV (Consult expert for SOF use) OBV-PTV/r + DSB	OBV-PTV/r + DSB
2	SOF+RBV	SOF+RBV (Consult expert for SOF use)	None provided
3	SOF+RBV	SOF+RBV (Consult expert for SOF use)	None provided
4	LDV-SOF OBV-PTV/r + DSB +RBV SOF+RBV SOF+SMV ± RBV	OBV-PTV/r + DSB + RBV SOF+RBV (Consult expert for SOF use) SOF+SMV ± RBV (Consult expert for SOF use)	OBV-PTV/r + DSB + RBV
5 & 6	LDV-SOF SOF+RBV	SOF+RBV (Consult expert for SOF use)	None provided

DSB= dasabuvir, LED=ledipasvir, OBV=ombitasvir, PTV=paritaprevir, r=ritonavir, RBV=ribavirin, SIM=simeprevir, and SOF=sofosbuvir

In press