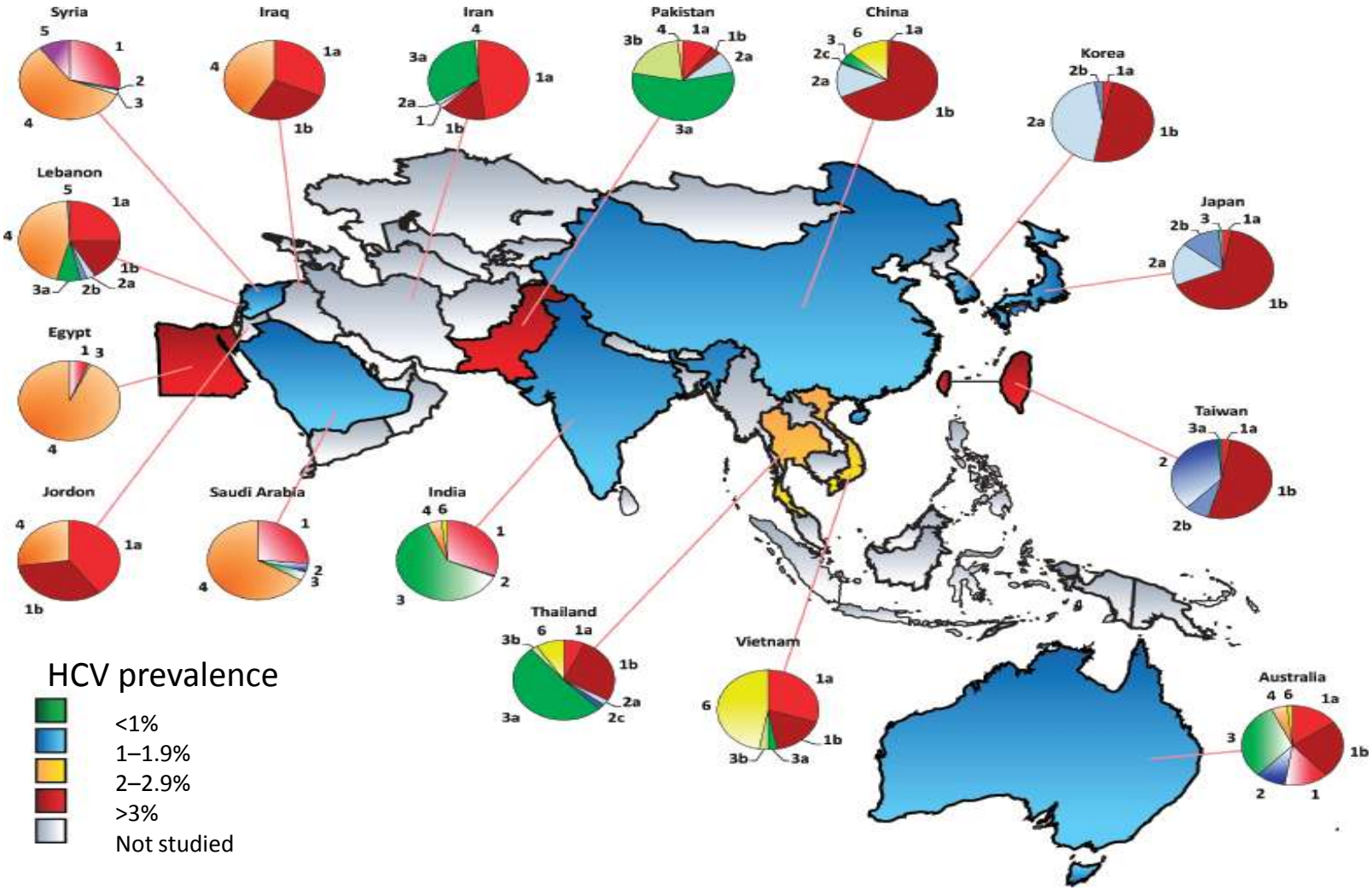
Optimal Therapy for Genotype non-1 in Asia Pacific?

Dr Saeed Hamid
Professor & Chair
Department of Medicine
Aga Khan University, Karachi

A systematic review of HCV epidemiology in Asia



Sievert, Liver Int 2011

1>3>2>4>6

Distribution Of HCV Genotypes in Pakistan

Genotype	Frequency	Percentage
1a	24	2.98
1b	29	3.60
2	12	1.49
3a	642	79.65
3b	66	8.19
4h, 4k	5	0.62
5a, 6a	15	1.86
10a	4	0.5
Non-typeable	9	1.12

N= 806

Moatter, Hamid et al, Intl. J. Inf. Dis. 2002

Distribution Of HCV Genotypes in Pakistan

Genotype	Frequency	Percentage
1a	24	2.98
1b	29	3.60
2	12	1.49
3a	642	79.65
3b	66	8.19
4h, 4k	5	0.62
5a, 6a	15	1.86
10a	4	0.5
Non-typeable	9	1.12

The difficult to Treat Genotype?

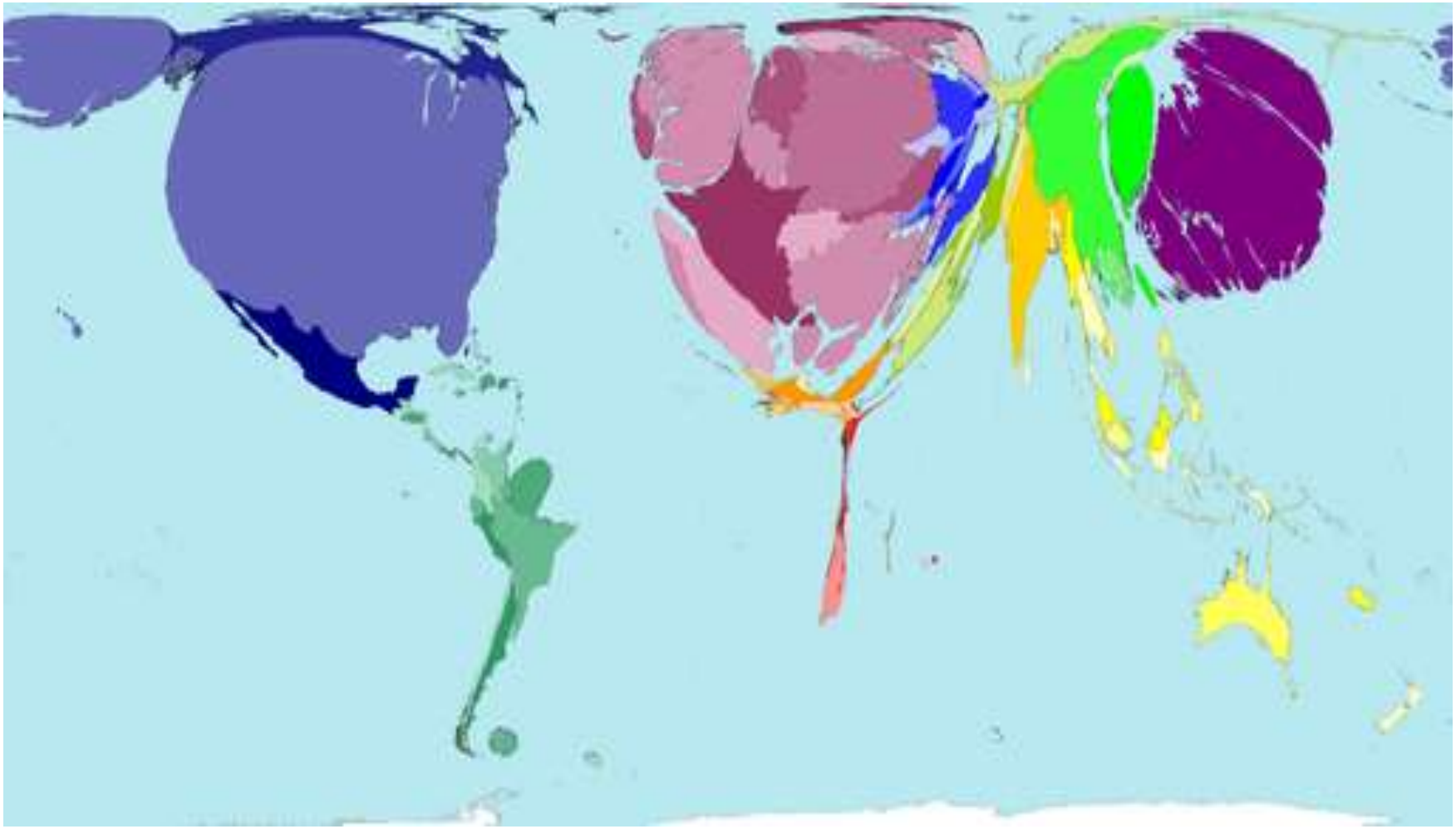
N= 806

Moatter, Hamid et al, Intl. J. Inf. Dis. 2002

Regional Distribution of *IL28B* rs12979860 CC Genotype

Thomas DL, et al. Nature. 2009;461:798-801.

The World based on Gross National Income & Public Health Spending



www.worldmapper

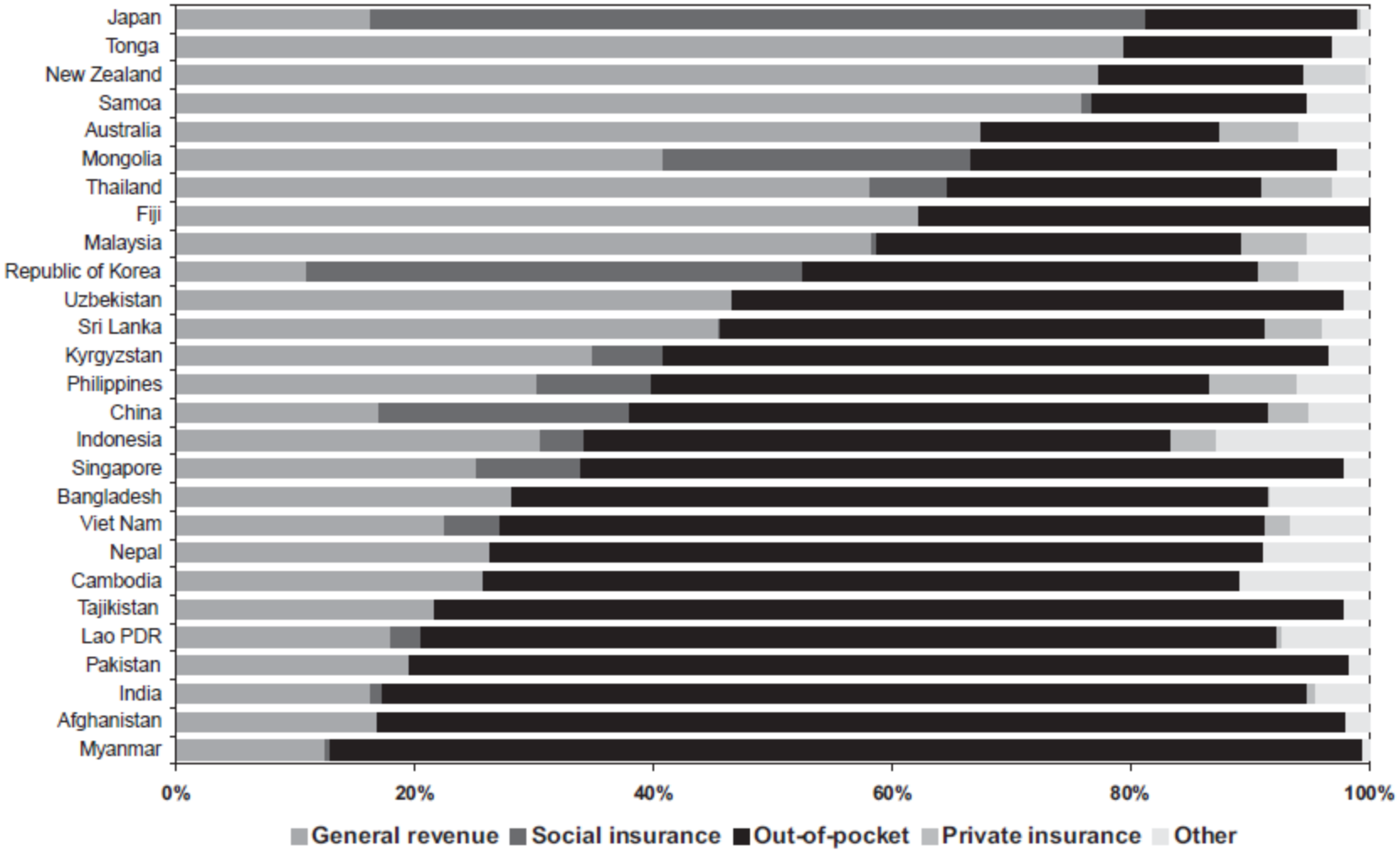
National Health Insurance system (Asia-Pacific region)

- Australia, Japan, New Zealand, China, Mongolia, Philippine, Vietnam, Korea, Taiwan

Countries with fully developed systems of social security	**Countries with partially developed systems of social security**
Australia, Japan, New Zealand	China, Mongolia, Philippines, Vietnam, Korea, Taiwan, Thailand

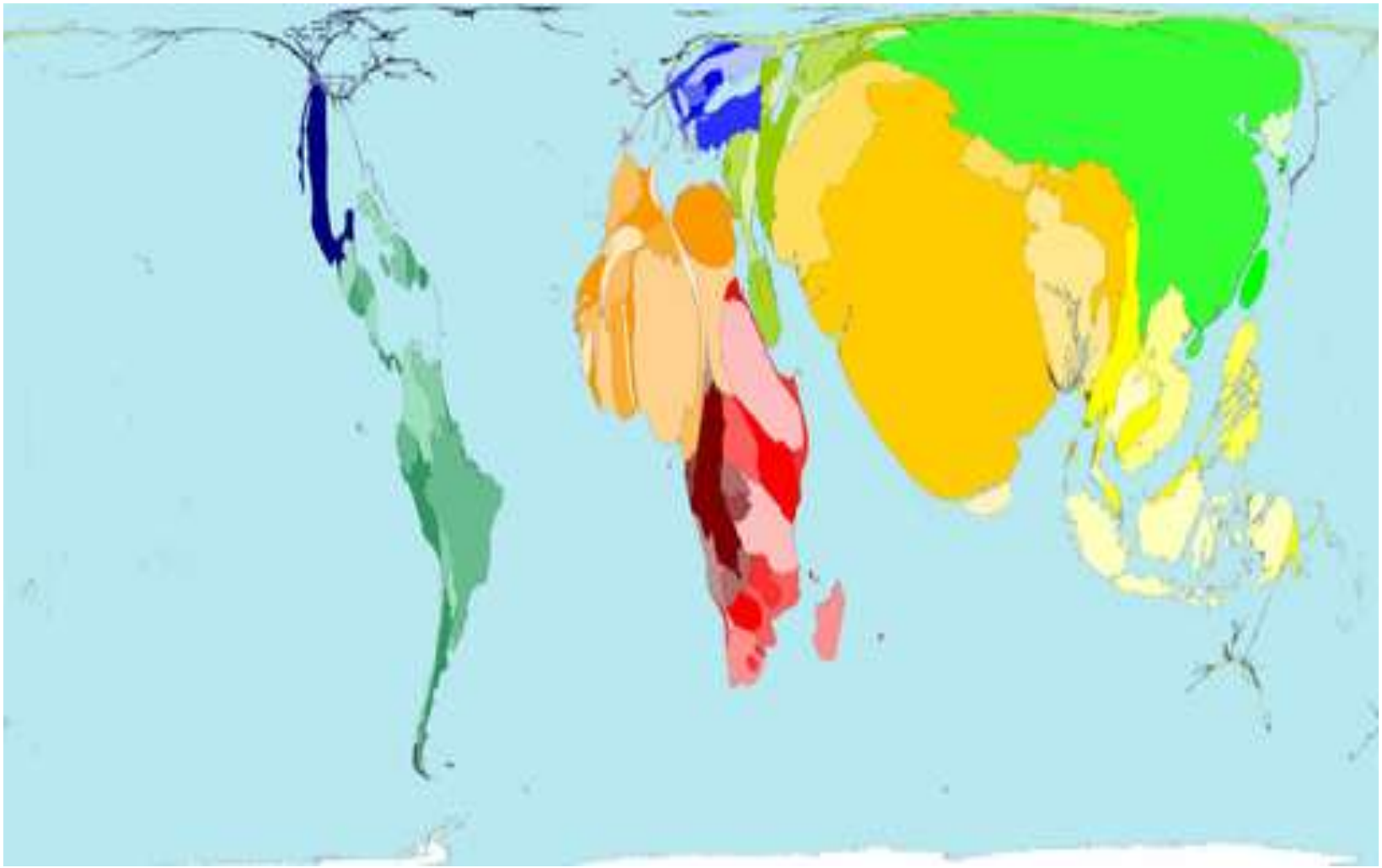
Source: ILO (2013). Social Security in the Asia and Pacific Region - An Overview. Global Extension of Social Security accessed on 3/20/2013 from: http://www.social-protection.org/gimi/gess/ShowRegionProfile.do?rid=11

Sources of health-care financing in selected Asia-Pacific countries, 2004



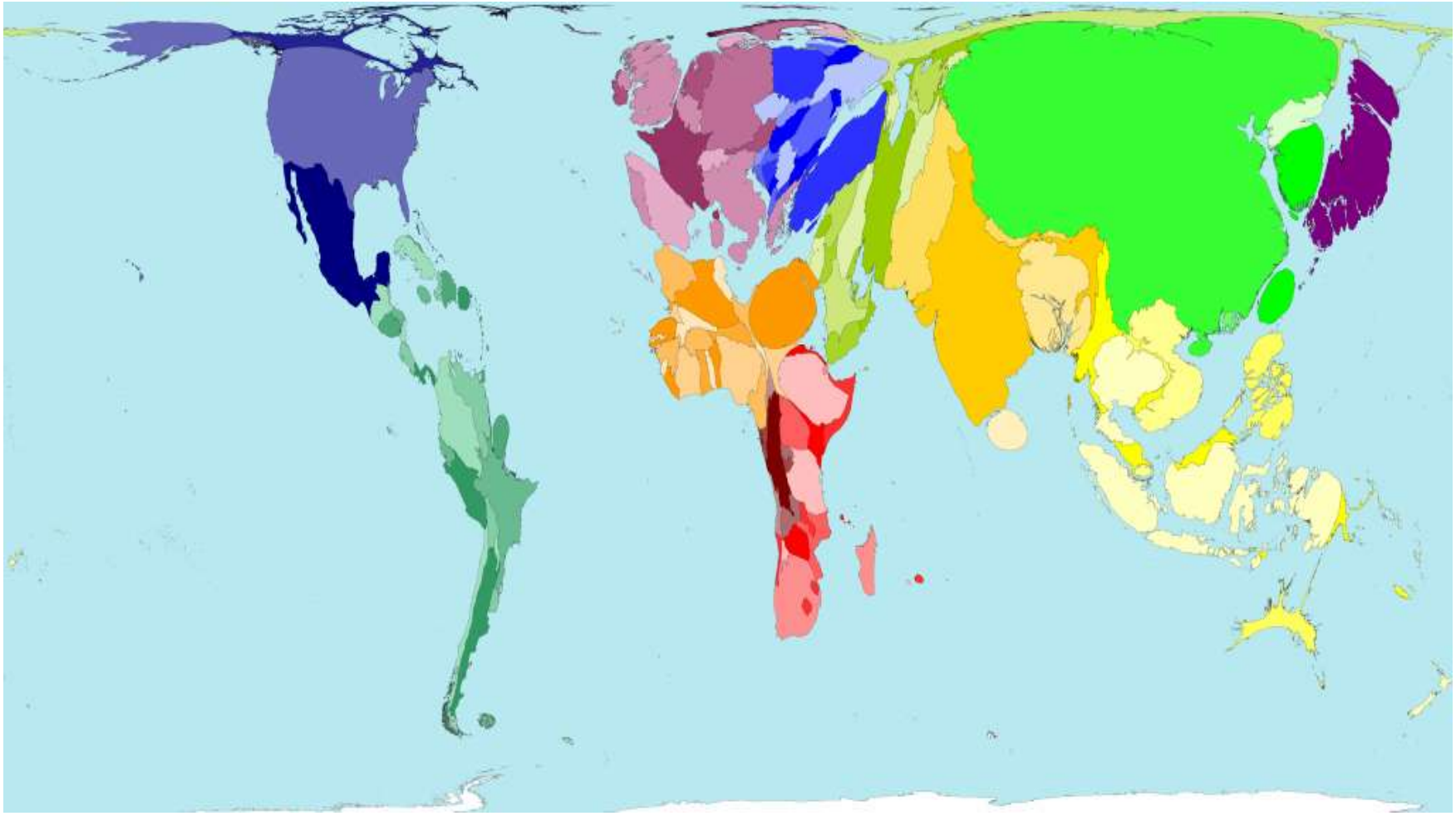
Note: Countries are listed in descending order of reliance on public financing (general revenue plus social insurance).
Source: WHO (2007).

Proportion of people living on US 10$ Purchasing Power Parity



www.woldmapper

Access to essential and affordable medicines : Use of traditionals and generics



www.worldmappers

APASL consensus statements and management algorithms for hepatitis C virus infection

Masao Omata · Tatsuo Kanda · Ming-Lung Yu · Osamu Yokosuka · Seng-Gee Lim · Wasim Jafri · Ryosuke Tateishi · Saeed S. Hamid · Wan-Long Chuang · Anuchit Chutaputti · Lai Wei · Jose Sollano · Shiv Kumar Sarin · Jia-Horng Kao · Geoffrey W. McCaughan

Hepatol Int (2012) 6:409–435

- Patients with HCV genotype 2 and 3 can be treated regardless of the stage of the disease (III).

In chronic HCV G/T 2 / 3 infection, the following apply: (I)

- Treatment with either conventional interferon alfa plus ribavirin or peg-IFN alfa with or without ribavirin for 24 weeks is recommended
- Peg-IFN plus ribavirin might be more effective in patients with cirrhosis.
- There is some evidence that shortening duration of therapy to 16 weeks in HCV genotype 2 infection provides equal SVR to 24 weeks treatment.

Response to Peg-interferon + Ribavirin for Chronic HCV in Asia

Patient population	Treatment regimen	Asian studies		
		Country	Reference	SVR rate
Genotype 1:	PegIFN plus SD RBV for 48 weeks	China	Yu *et al.*[67]	44%
		Japan	Kuboki *et al.*[46]	61%
		Korea	Lee *et al.*[56]	70%
		Taiwan	Liu *et al.*[60]	76%
		Taiwan	Liu *et al.*[59]	77%
		Taiwan	Yu *et al.*[61]	79%
Genotype 1, LVL, and RVR	PegIFN plus SD RBV for 24 weeks	Taiwan	Liu *et al.*[60]	94%
		Taiwan	Yu *et al.*[61]	96%
Genotype 2/3	PegIFN plus LD RBV for 24 weeks	China	Yu *et al.*[67]	75%
		Taiwan	Liu *et al.*[107]	84%
		Korea	Lee *et al.*[56]	94%
	PegIFN plus SD RBV for 24 weeks	Taiwan	Yu *et al.*[63]	95%
Genotype 2/3 and RVR	PegIFN plus SD RBV for 16 weeks	Taiwan	Yu *et al.*[63]	100%
Genotype 4	PegIFN plus SD RBV for 48 weeks	Kuwait	Hasan *et al.*[53]	68%
Genotype 6	PegIFN plus SD RBV for 48 weeks	Hong Kong	Fung *et al.*[15]	86%

LD RBV, lower dose of ribavirin, 800 mg/day; LVL, low baseline viral loads; PegIFN, peginterferon; RVR, rapid virological response; SD RBV, standard dose of ribavirin, 1000–1200 mg/day; SVR, sustained virological response.

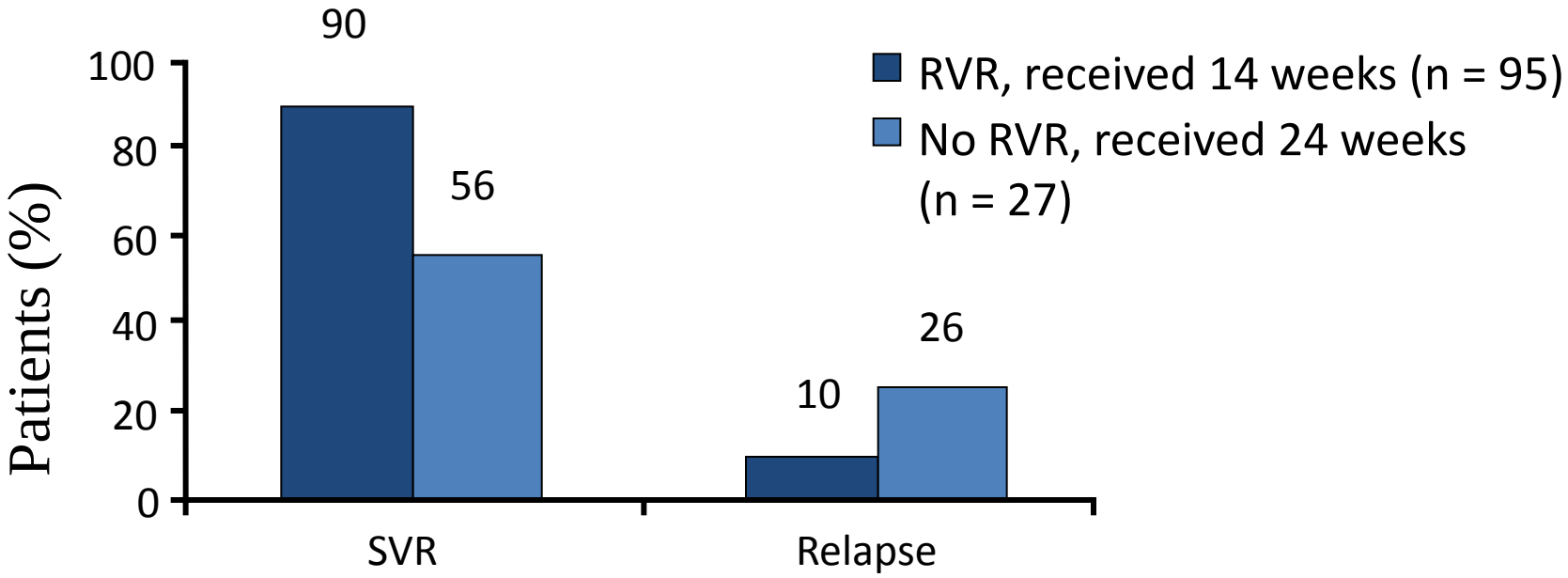
Ming-Lung Yu, Journal of Gastroenterology and Hepatology **24** (2009)

Genotype 2 and 3 Short Term Treatment

	n	Treatment	Treatment Duration	RVR	SVR
Von Wagner	153	Peg-IFN alpha-2a and RBV 800-1200	16 wks vs 24 wks	46%	16 wks: 82% 24 wks: 80%
Dalgard	122	Peg-IFN alpha-2b and RBV 800-1400	14 wks vs 24 wks	78%	14 wks: 90% 24 wks: 56% (if no RVR)
Mangia	283	Peg-IFN alpha-2b and RBV 1000-1200	12 wks vs 24 wks	62%	12 wks: 85% 24 wks: 64%

Shorter Treatment in Genotype 2/3 Patients Achieving RVR

- PegIFN alfa-2b + weight-based RBV
  - 14 weeks for patients with RVR; 24 weeks for patients without RVR



Dalgard O, et al. Hepatology. 2004;40:1260-1265.

Short Vs Standard Course Conventional Interferon Treatment in Patients with Genotype 3 Chronic HCV Infection. (STAR TRIAL: NCT 00502970)

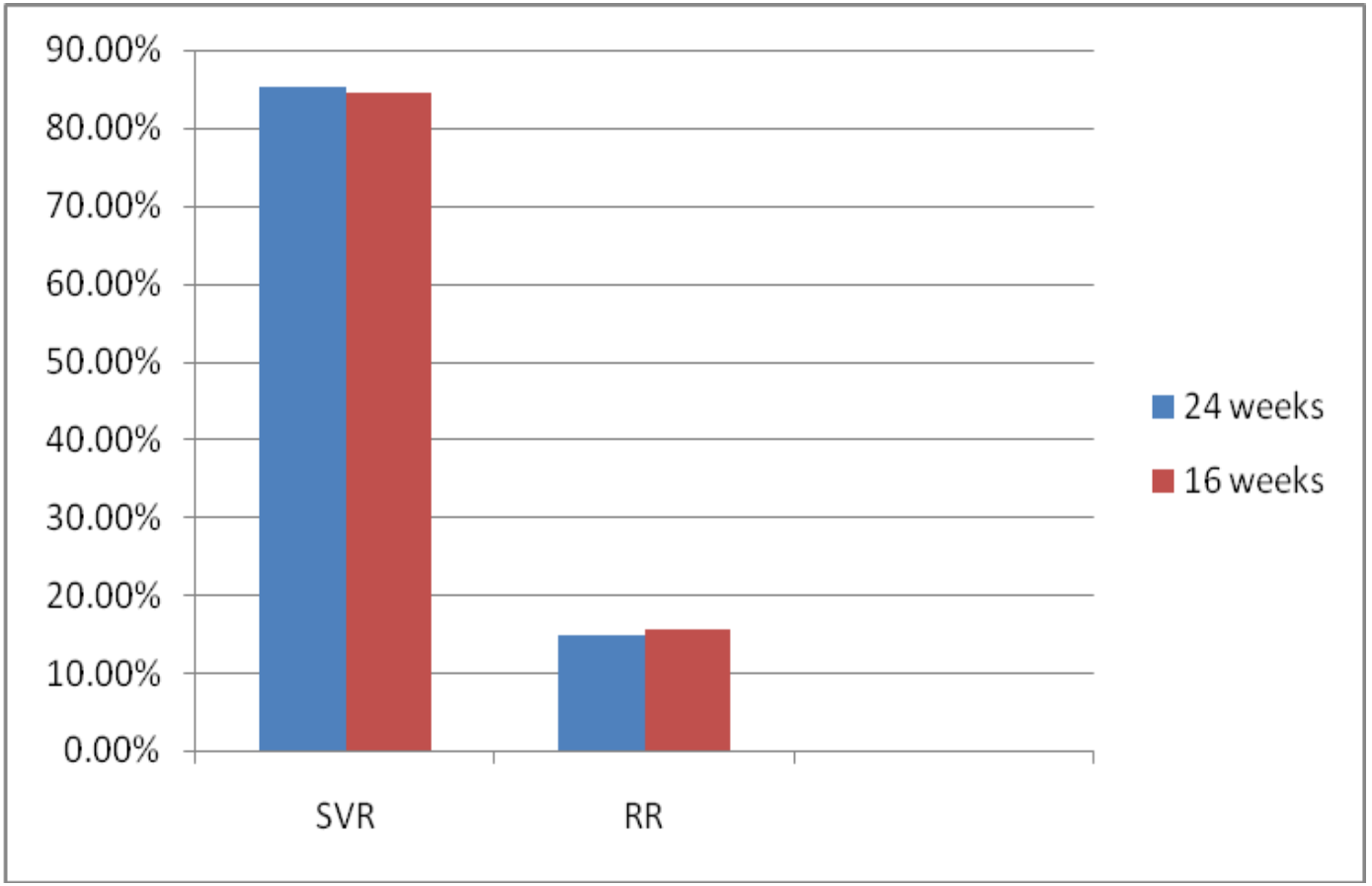


Fig 2: The primary outcome measures i.e. SVR in the 24 vs. 16 weeks treatment (ITT analysis). Reported p-values are one-sided.

Short treatment in HCV Genotype 2 or 3

1469 treatment naïve patients with GT2 or 3, elevated ALT, HCV RNA >600 IU/mL, and compensated disease

Peg-IFN α-2a 180 μg/wk
+ RBV 800 mg/d

Randomized

Treated x 24 wk

Treated x 16 wk

SVR 76%

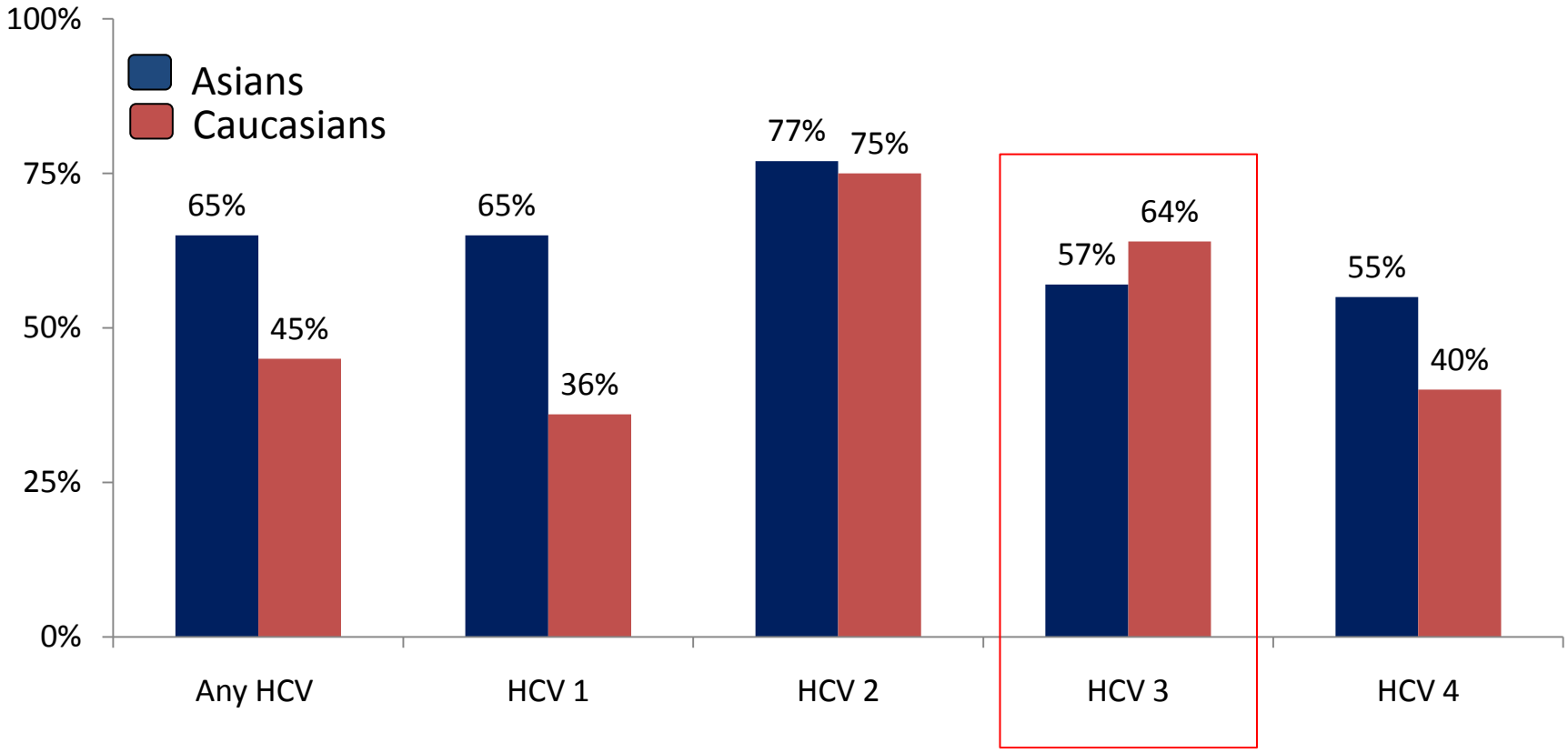
P<0.001

SVR 65%

"The decline in SVR associated with the shorter duration of therapy was the result of a higher relapse rate."

Shiffman ML, *N Engl J Med* 2007;357:124-134.

Racial differences in SVRs for Peg IFN + Riba therapy



Missiha S, C. Am. J. Gastroenterol. 2007; 102: 2181–8.

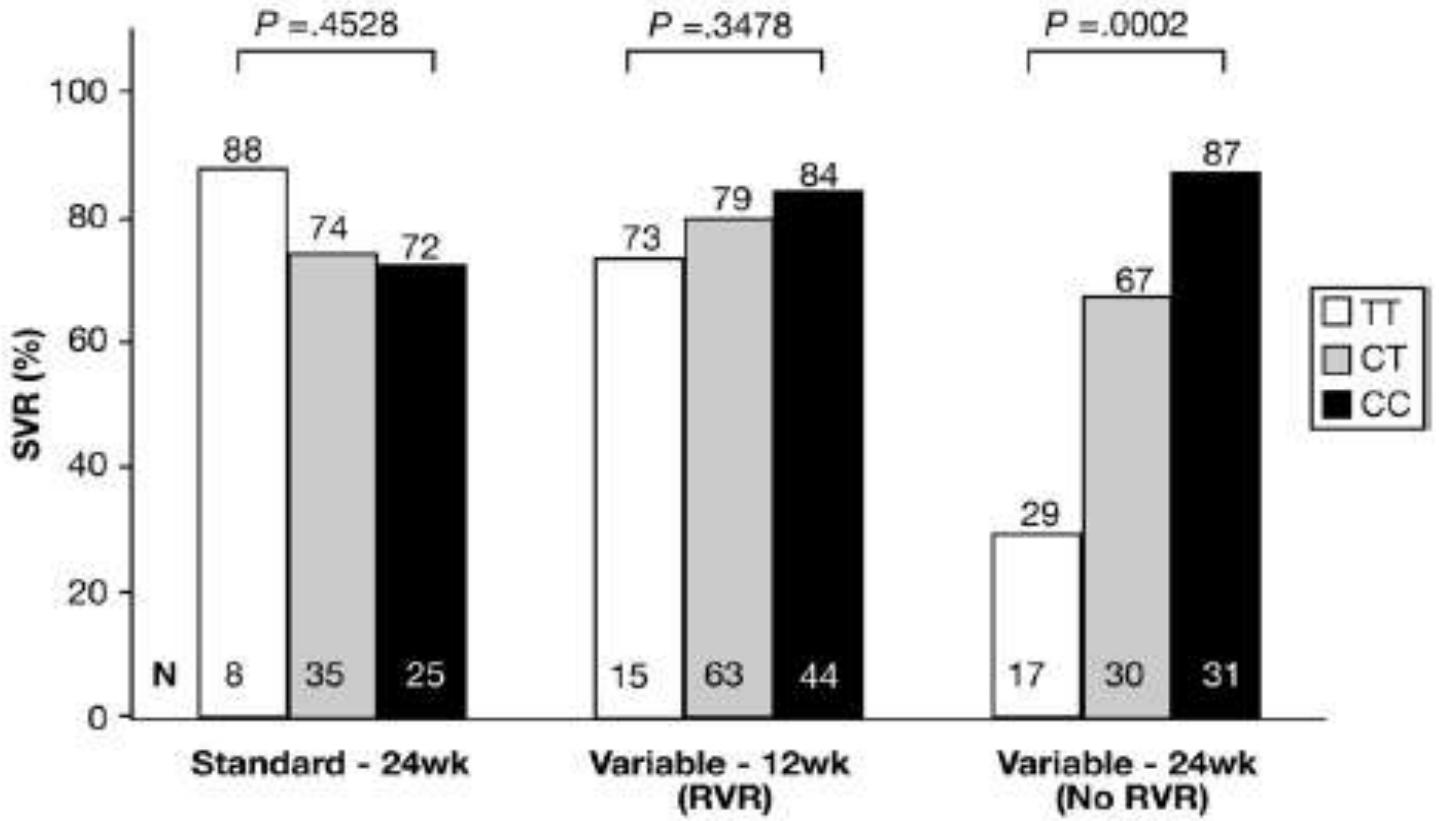
Roulot D, J. Viral Hepat. 2007; 14: 460–7.

HCV: Response to treatment at AKU

- Genotype-3 is found in 708/805 (87.8%) patients.
- The SVR to combination therapy (Interferon + Ribavirin) was achieved in 130/208 (62.5%)
- Patients of <35 years of age showed an SVR in 72%.
- The maximum SVR was achieved in patients aged 15-30 years (27/33, 81.8%)

Mumtaz et al, Saudi Med J 2008

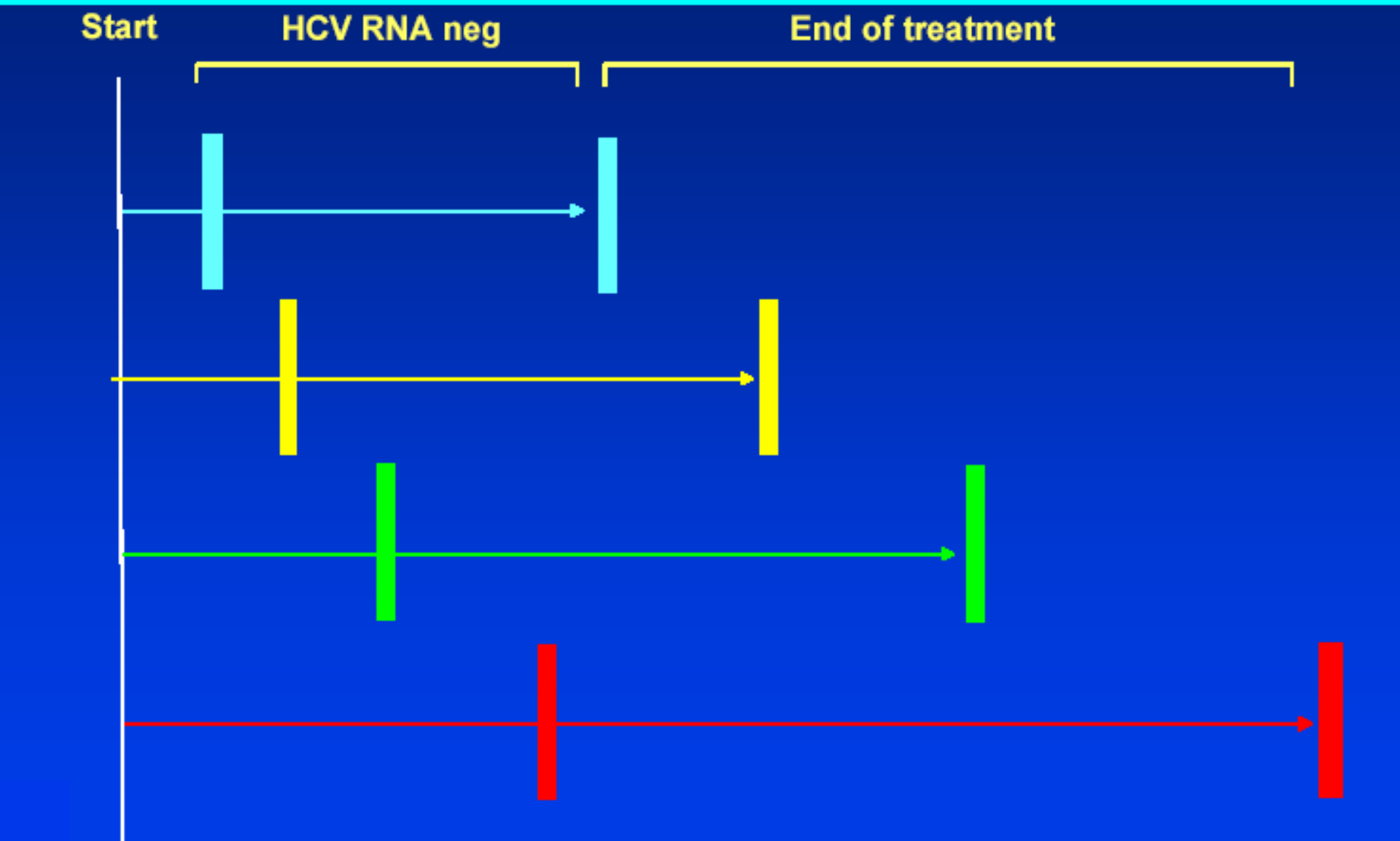
IL28B Polymorphism and response to treatment in GT 2/3



Mangia, Gastro 2010

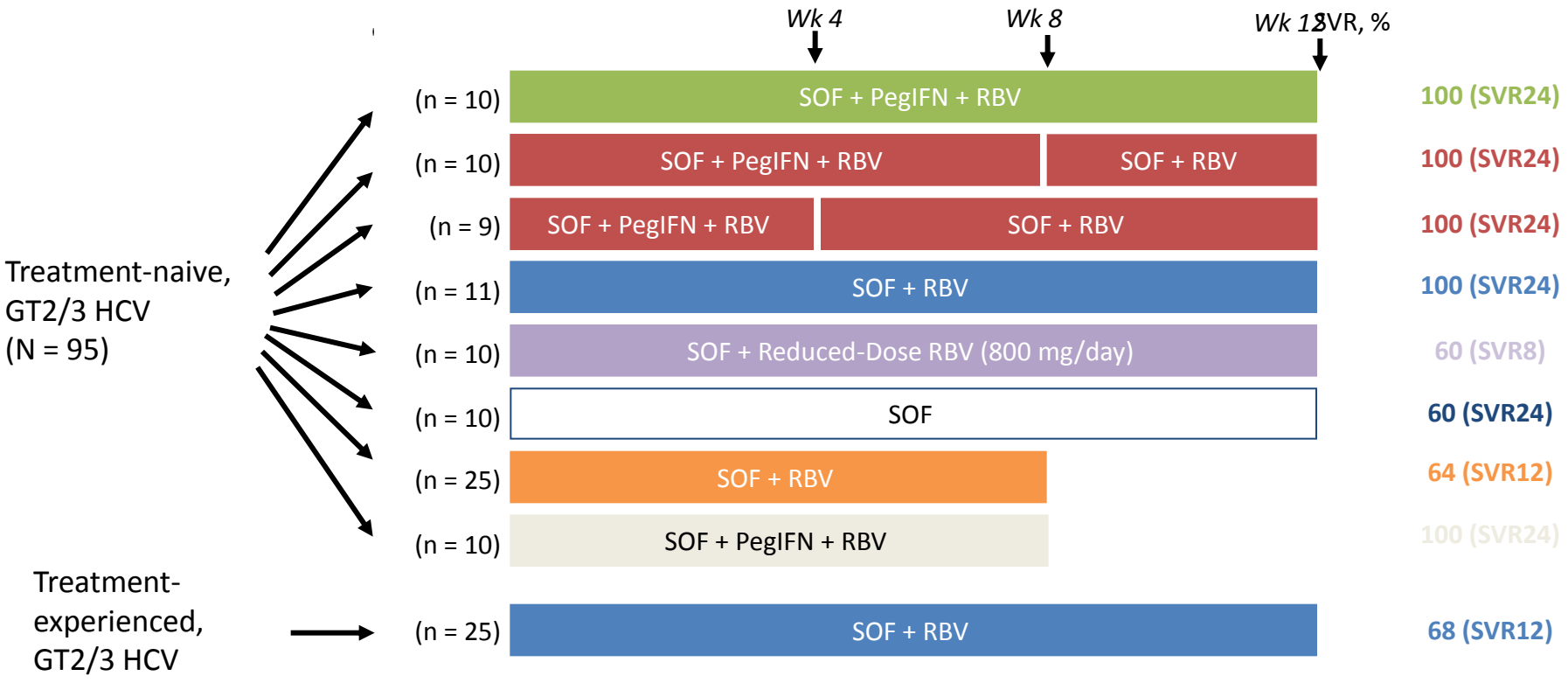
The "Accordion" Effect in HCV Therapy

The Earlier HCV RNA Clears, The Shorter The Treatment Required



Sofosbuvir in Patients With GT2/3 HCV

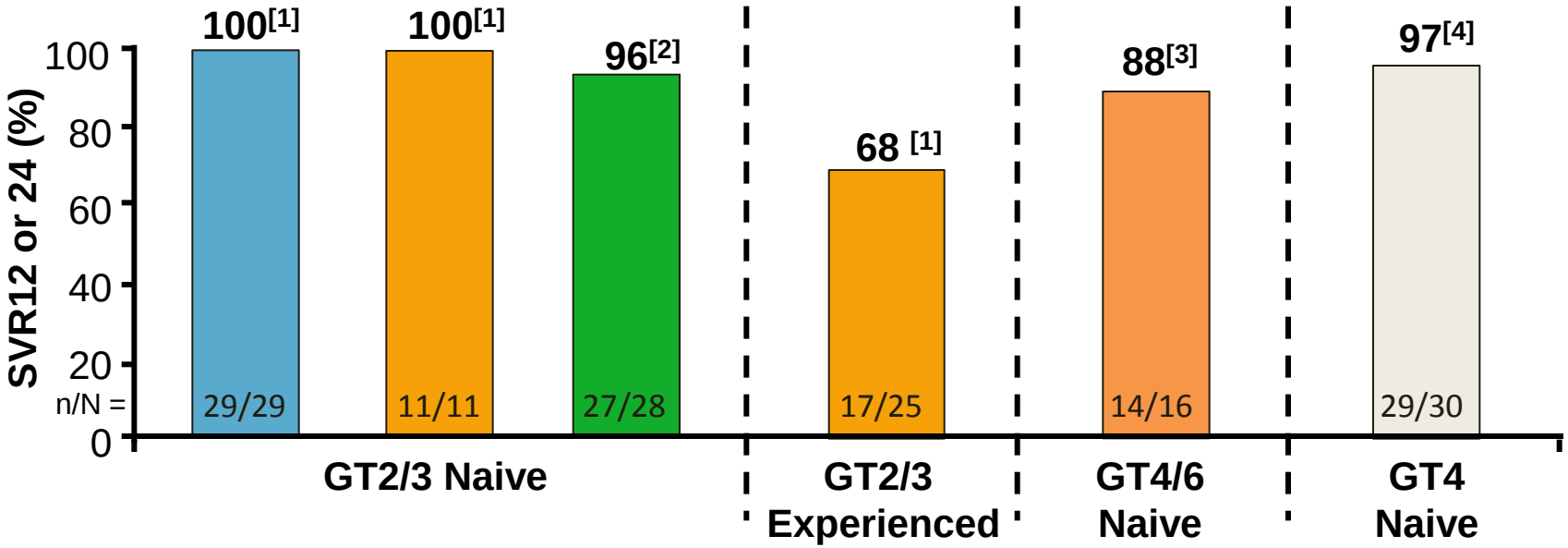
- Interim analysis of nonrandomized phase II study with SOF (nucleoside polymerase inhibitor) ± GS-5885 (NS5A inhibitor)



Gane EJ, et al. AASLD 2012.

Polymerase Inhibitors Efficacy in Non–GT 1 Patients

- Sofosbuvir (nuc) + RBV x 12 wks + pegIFN x 4-12 wks
- Sofosbuvir (nuc) + RBV x 12 wks
- Sofosbuvir (nuc) + daclatasvir (NS5A) ± RBV x 24 wks
- Sofosbuvir (nuc) + pegIFN + RBV x 24 wks
- Danoprevir (PI)/ritonavir + pegIFN + RBV x 12-24 wks



1. Gane EJ, et al. AASLD 2012. Abstract 229. 2. Sulkowski M, et al. AASLD 2012. Abstract LB-2.
3. Hassanein T, et al. AASLD 2012. Abstract 230. 4. Hezode C, et al. AASLD 2012. Abstract 760.

Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection

FISSION:

- Sofosbuvir plus ribavirin in patients with HCV genotype 2 or 3 infection.
- 12 weeks of sofosbuvir plus ribavirin or 24 weeks of peginterferon alfa-2a plus ribavirin.
- SVR of 56% in GT 3 for Sof+Rib vs 63% for Peg+Riba
- SVR in patients with cirrhosis 47% for sofosbuvir + ribavirin vs 38% for peginterferon–ribavirin.
- Possible that response rates in patients with genotype 3 infection can be improved by adding peginterferon to sofosbuvir

and ribavirin or by extending the duration of treatment with sofosbuvir and ribavirin.

Lawitz, NEJM 2013

Sofosbuvir for Hepatitis C Genotype 2 or 3 in Patients without Treatment Options

POSITRON:

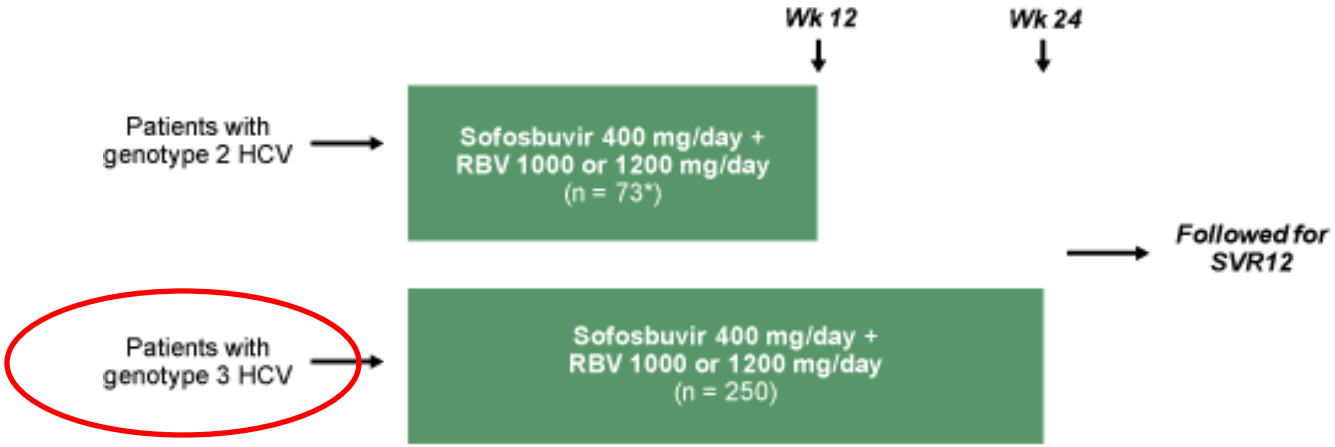
- 12 weeks of Sofosbuvir + Ribavirin vs placebo in patients who had previously discontinued interferon therapy.
- SVR 12= 61% for GT 3, 21% in cirrhotics

FUSION:

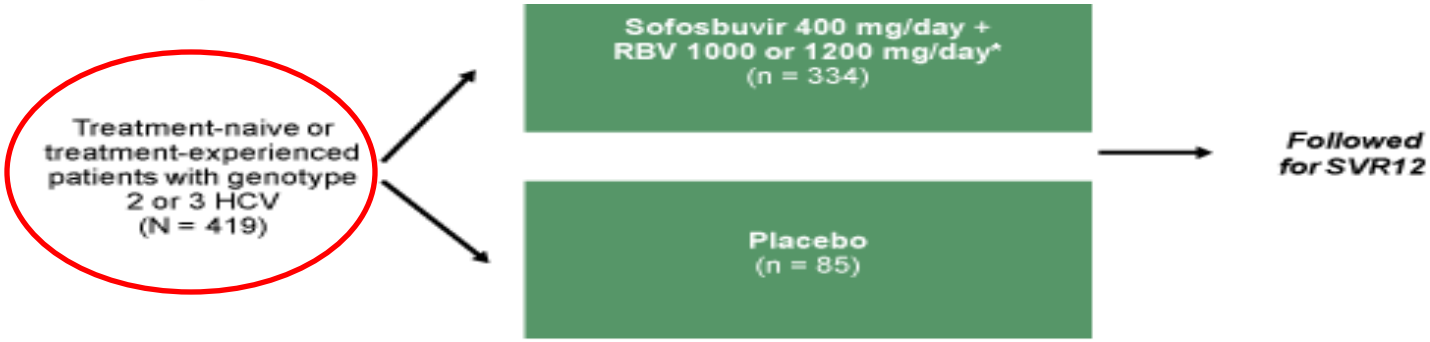
- Non-responders to prior PEG-IFN+Riba
- 12 or 16 weeks of Sofosbuvir + Ribavirin
- SVR 12= 30% and 62% respectively, among patients with HCV genotype 3 infection

Jacobson, NEJM 2013

VALENCE: Sofosbuvir/RBV for 24 Weeks in Patients Infected With Genotype 3 HCV



*11 additional patients with genotype 3 completed treatment before the protocol was amended. These patients were included with genotype 2 patients for safety analysis and analyzed separately for efficacy.



*RBV dosing by baseline weight: 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg.

VALENCE: Main Findings

- High overall SVR12 rates in both arms
  - 12-week treatment for genotype 2 HCV: 93% (68/73)
  - 24-week treatment for genotype 3 HCV: 85% (212/250)
- High SVR12 rates in patients with genotype 2 HCV regardless of previous treatment status and cirrhosis status (88-100%)
- SVR12 rates in genotype 3 HCV
  - Naive, non-cirrhotic: 94% (86/92)
  - Naive, cirrhotic: 92% (12/13)
  - Experienced, non-cirrhotic: 87% (87/100)
  - Experienced, cirrhotic: 60% (27/45)
- Sofosbuvir/RBV for 12 or 24 weeks was safe, well tolerated

Economic Burden of the HCV Epidemic

- Few countries have conducted studies to estimate
  HCV-related costs
  - Most studies have unreliable estimates
- In the US, total medical costs from HCV infection expected to increase from $30 billion in 2009 to > $85 billion in 2024
  - Estimate based on pegIFN/RBV treatment; potential impact of DAAs not reflected

Milliman, Inc. Consequences of HCV: costs of a baby boomer epidemic, 2009.

The Role of Distributive Justice

- With expected high demands for DAA based all oral therapy, how will providers decide who gets treated first?
  - First-come, first-served approach?
  - Need-based allocation system?
- Distributive justice principle
  - Fair, equitable, and appropriate distribution of limited resources
  - Must balance equality with relative medical need when applying principle to scarce medical resource

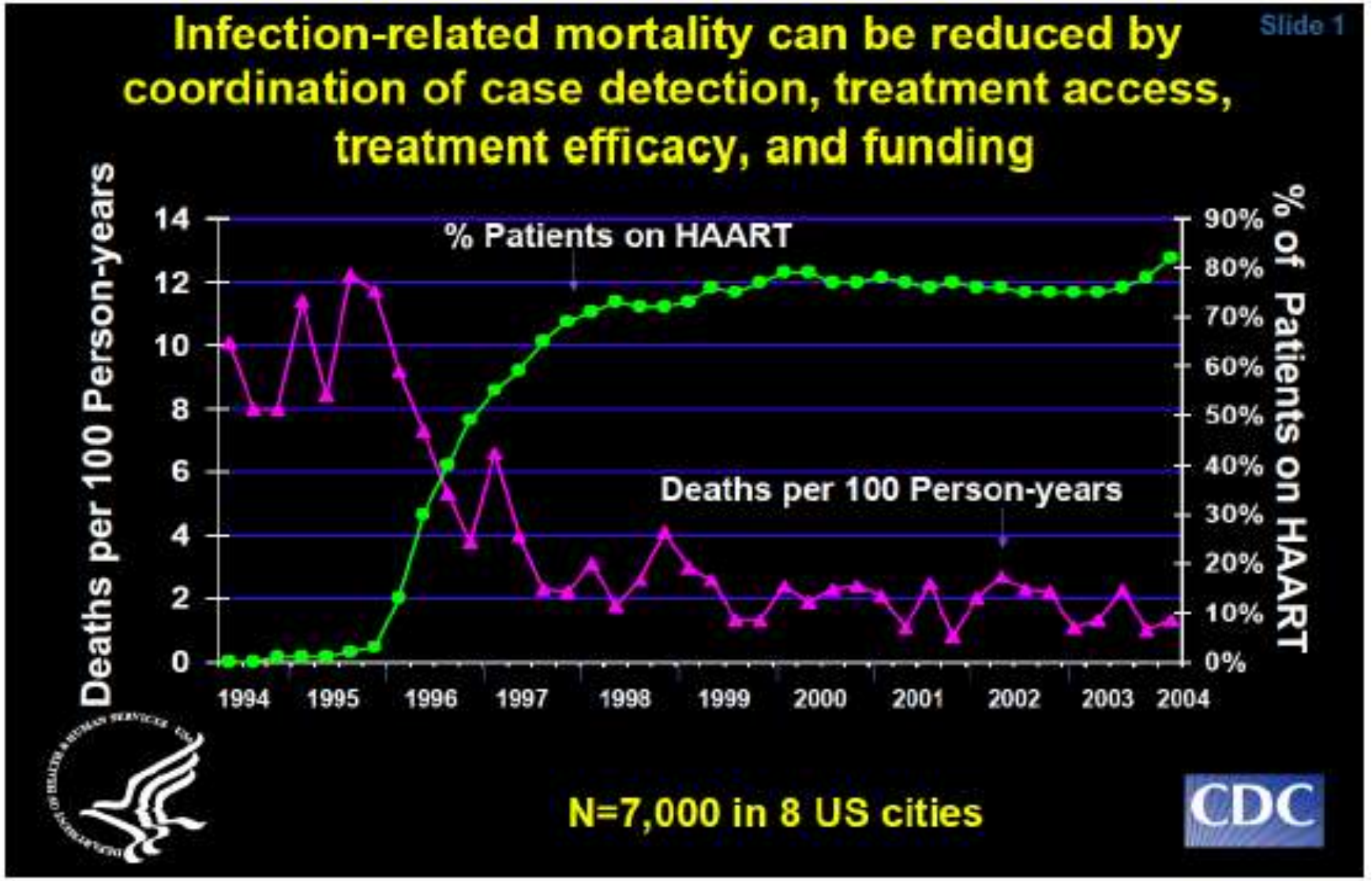
Aronsohn A, et al. Hepatology. 2011;53:1789-1791.

Possible Solutions for Medication access: The HIV Paradigm

- Government purchases either directly or though UN support
- Drug supplied to “Certified Centers” in public and private sector that are accredited for treatment
- Drug is not available in market pharmacies:

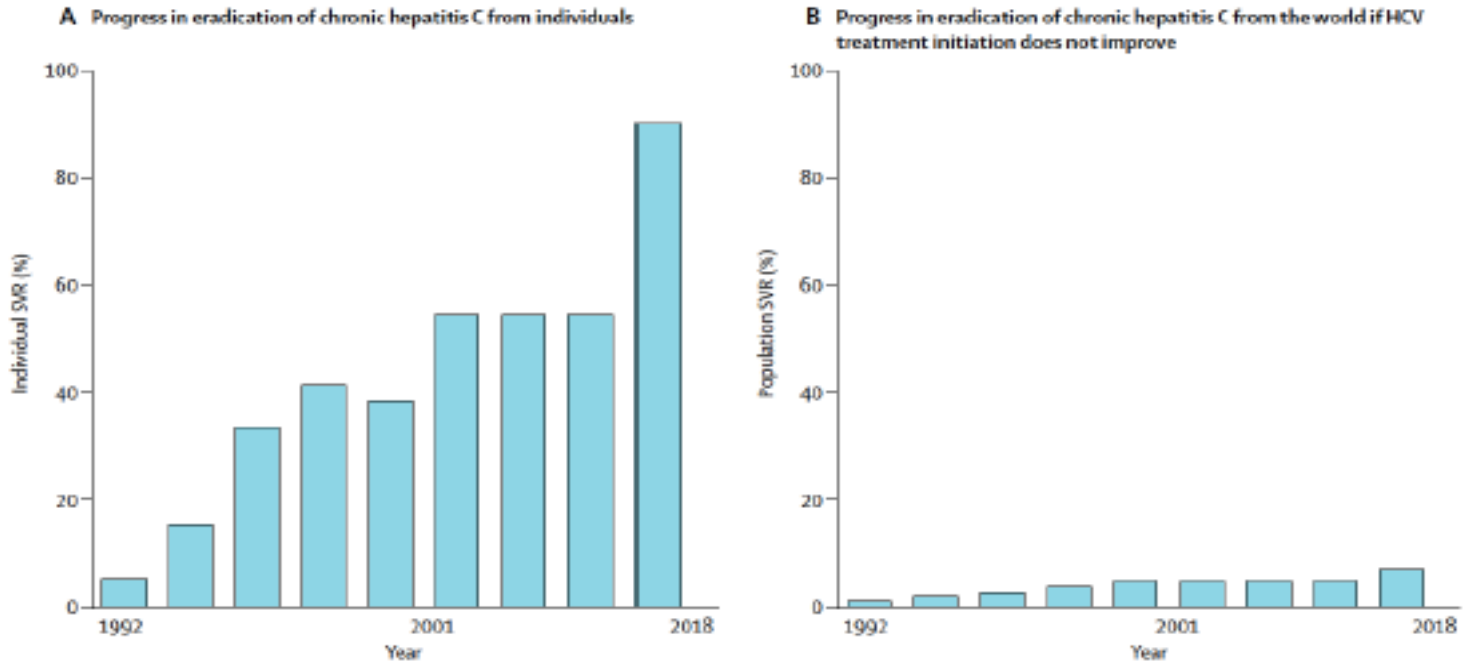
  e.g. Rwanda

Lessons from the HIV World



Lessons for the HCV World

Even highly efficacious treatments are don't help if they aren't given



Thomas Lancet 2010

Conclusions

- HCV genotype 3 is the predominant genotype after 1 in Asia.
- Interferon + Ribavirin combination therapy remains the mainstay of treatment of non-1 Genotype infection in Asia.
- HCV 3 responds heterogeneously to IFN/RIB therefore treatment has to be individualized.
- Well selected HCV 3 show excellent IFN responsiveness
- HCV 3 infection is likely to be the first to witness all oral DAA therapies.
- When that happens, much of Asia-Pacific will struggle with the cost of therapy.
- This however is also an opportunity to make a real difference to control HCV infection in this region.

APASL STC on HCV
Pakistan, October 17-19, 2014