Should all genotype 1 patients be started on triple therapy in Asia-Pacific?

3rd APASL STC on HCC
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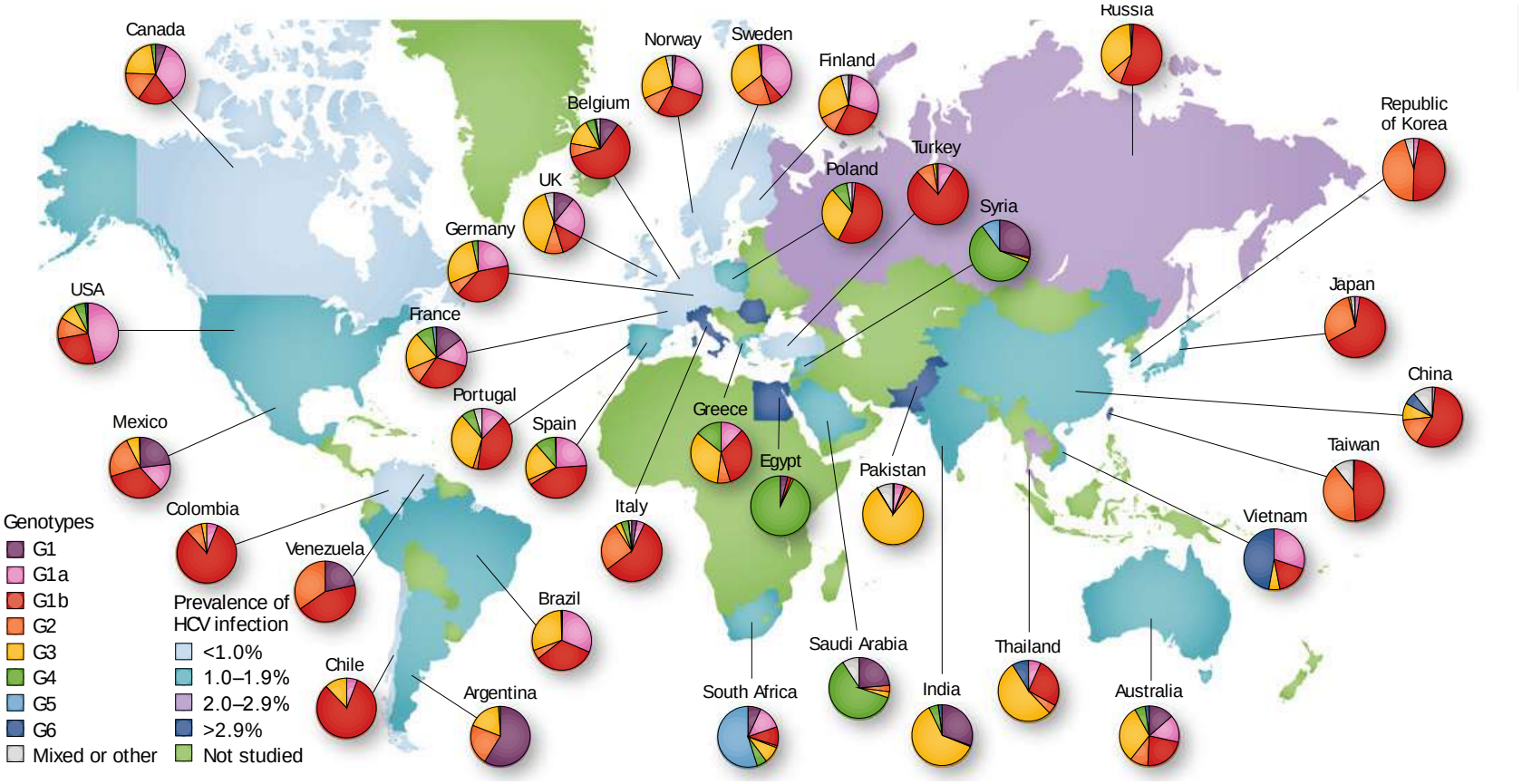
Humanity & Health

At least half of the people in the world who are infected with HCV reside in Asia-Pacific region

Countries	Absolute number of HCV-infected individuals
China	29.8 million
India	18.2 million
Egypt	11.8 million
Pakistan	9.4 million
Indonesia	9.4 million

Hajarizadeh, B. et al. Nat. Rev. Gastroenterol. Hepatol. 10, 553–562 (2013)

The estimated prevalence of HCV infection and the distribution of HCV genotypes across the world



Center for Disease Analysis, http://c4da.com/HepC/HepMap.html

Two Protease Inhibitors Approved for GT1 HCV Infection Combined With PR

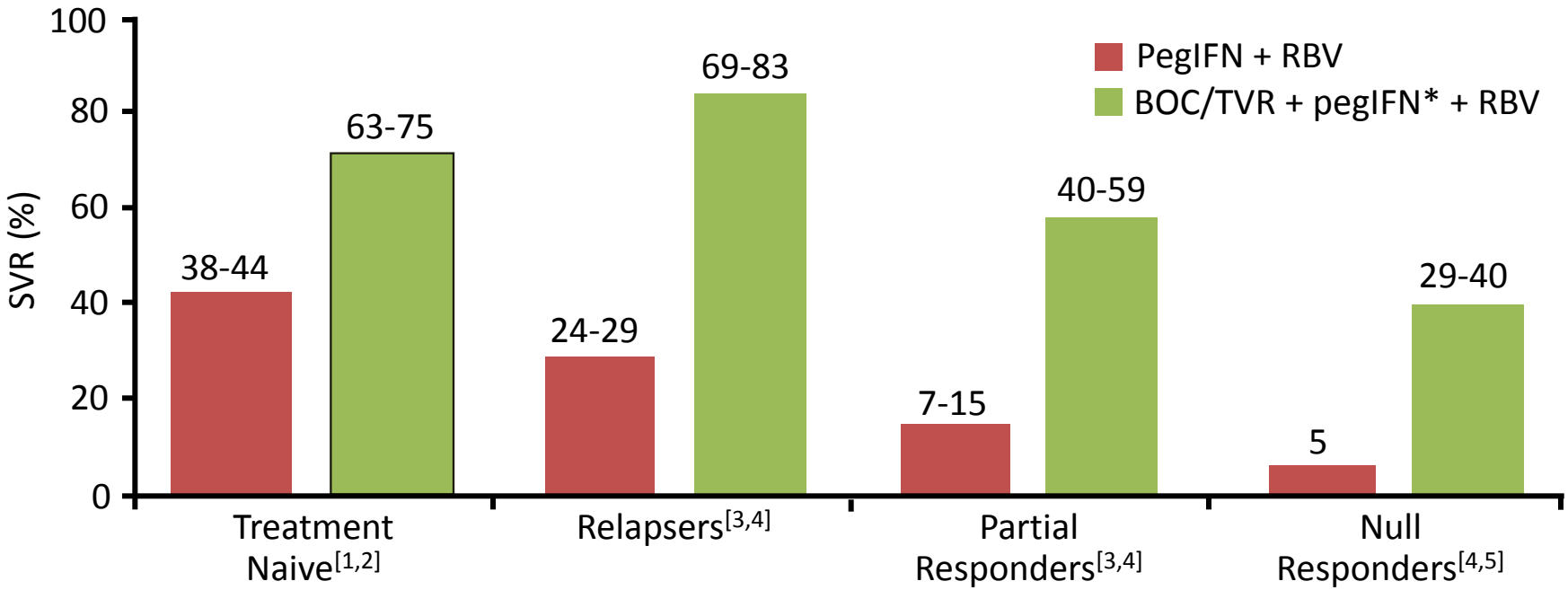
Protease Inhibitor	Recommendations	Administration
Boceprevir 800 mg TID (every 7-9 hrs)[1,2]	▪ Naive to previous therapy ▪ Previous treatment failure ▪ Compensated cirrhosis ▪ Response-guided therapy ▪ Take with food	▪ All patients initiate therapy with **4-wk pegIFN/RBV lead-in phase** ▪ After completion of lead-in phase, **boceprevir should be added to continued pegIFN/RBV for 24-44 wks**
Telaprevir 750 mg TID (every 7-9 hrs)[2,3]	▪ Naive to previous therapy ▪ Previous treatment failure ▪ Compensated cirrhosis ▪ Response-guided therapy ▪ Take with food (not low fat)	▪ All patients initiate therapy with **12-wk period of triple therapy** with telaprevir plus pegIFN/RBV ▪ Followed by **12-36 wks of pegIFN/RBV**

Practical concern on the use of triple therapy

- Efficacy
- Adverse events
- Drug-drug interaction
- **Costs and Availability**

Efficacy

Triple Therapy Improves SVR in GT 1 Patients

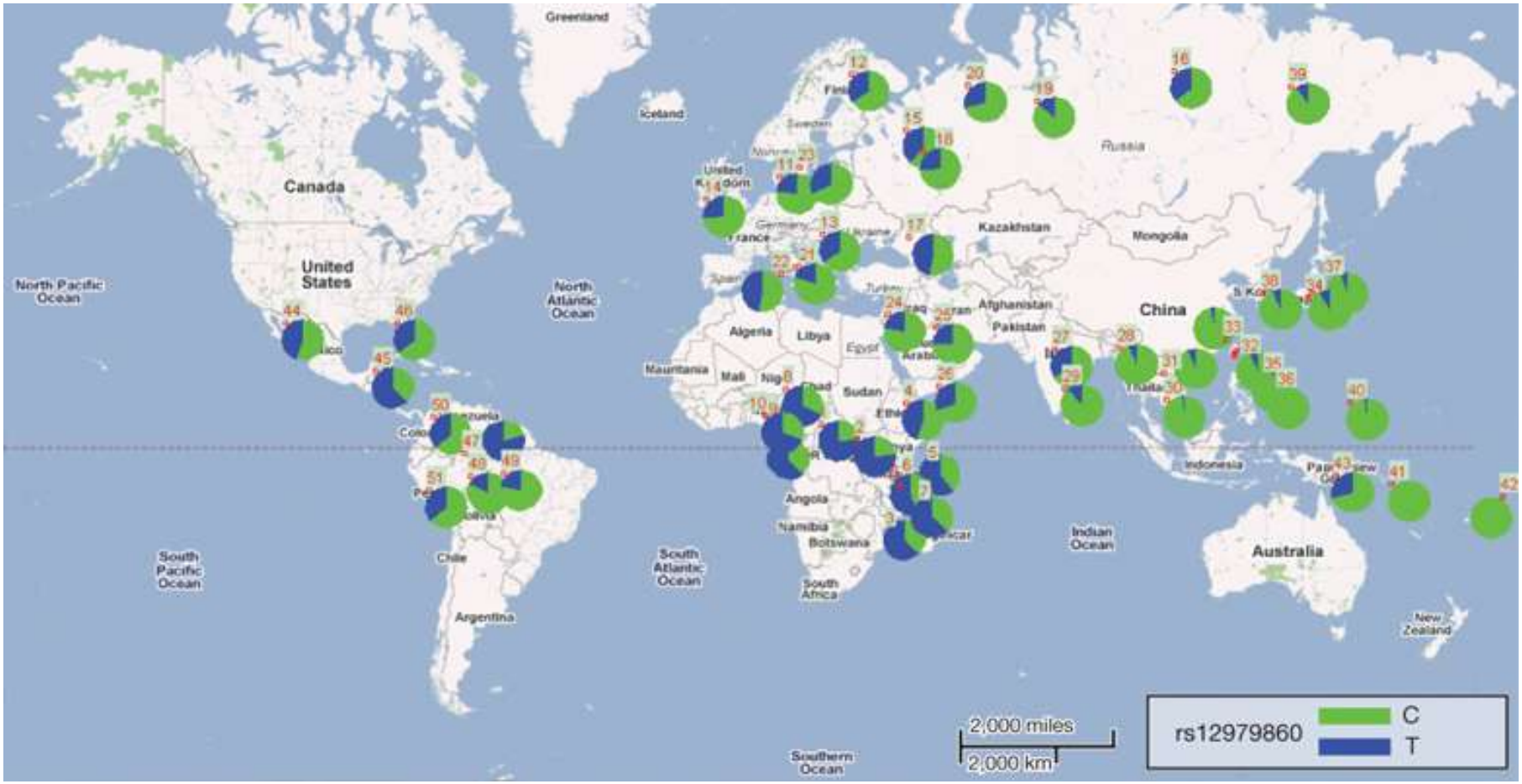


*BOC was administered with pegIFN-α2b; TVR was administered with pegIFN-α2a in these trials.

1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 2. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.
3. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 4. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428.
5. Bronowicki JP, et al. EASL 2012. Abstract 11.

Regional Distribution of *IL28B* rs12979860 CC Genotype

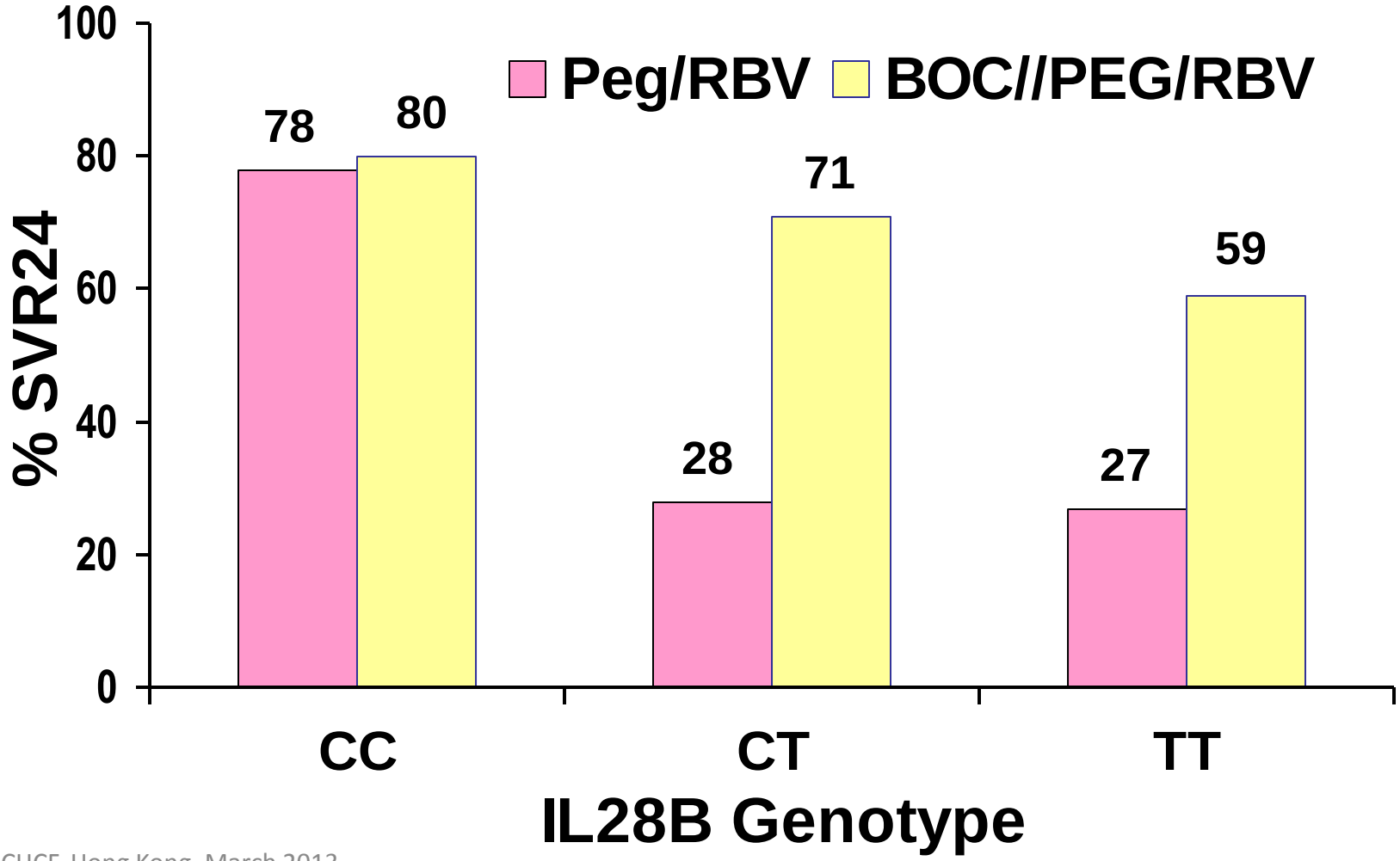
Explain higher SVR rates with PR in Asian patients than in Western patients (70 vs 50%)



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

Protease inhibitors in Treatment-naïve Asians

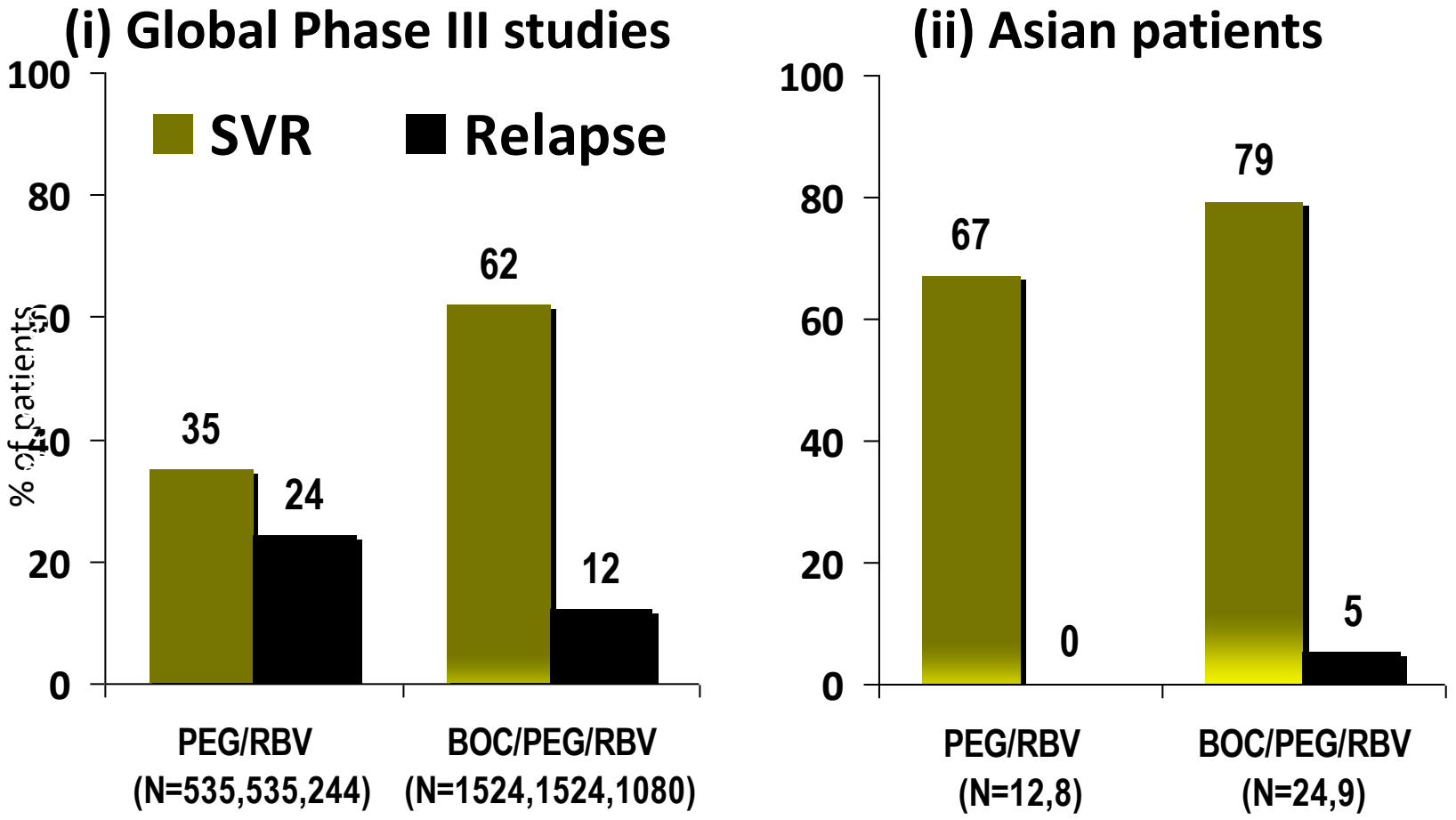
Benefit reduced in Favorable CC Genotype



Poordad F, et al. *N Engl J* 2011; 364: 1195-206

Protease inhibitors in treatment-naïve patients

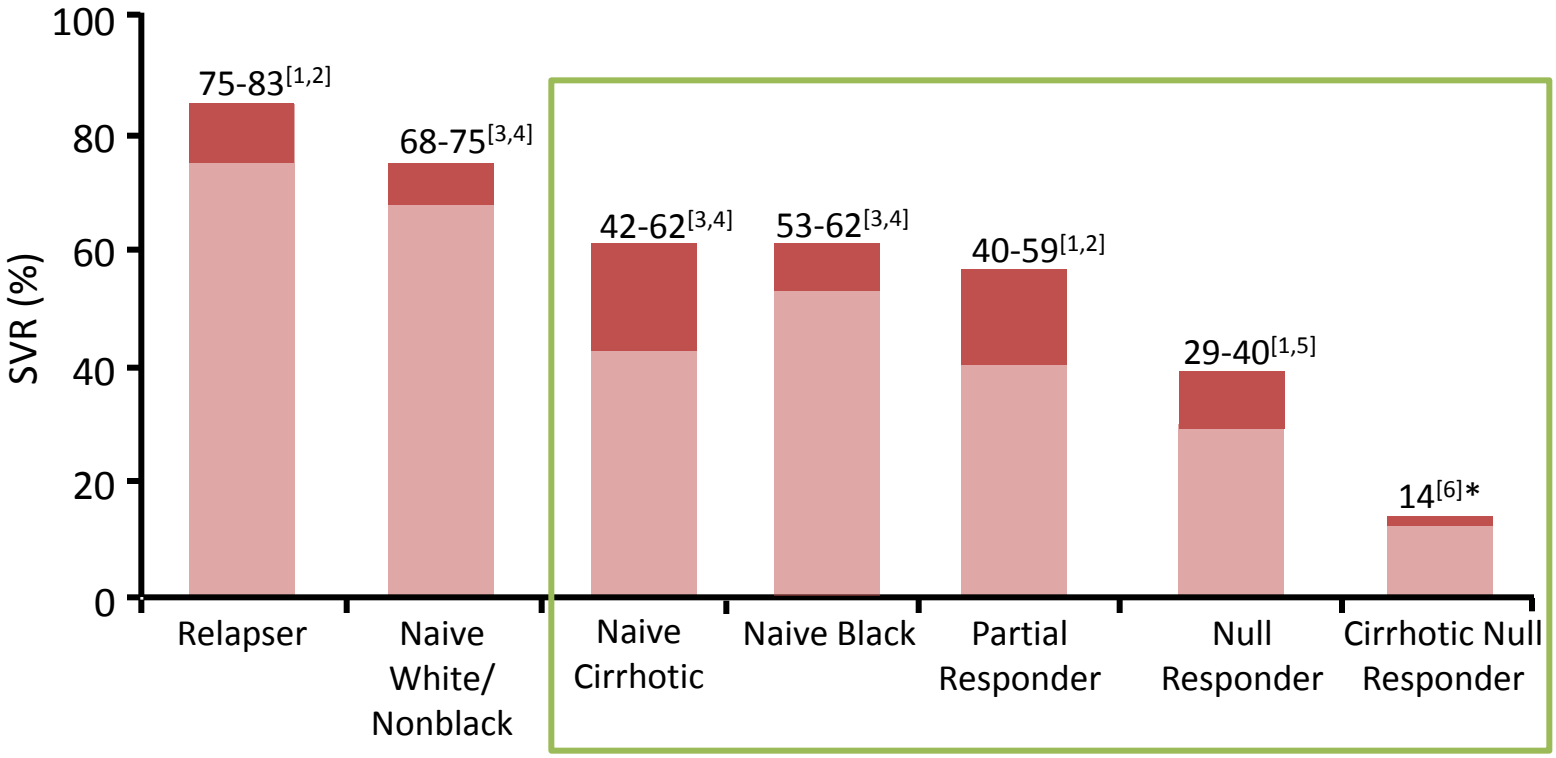
Sustained Virologic Responses



Poordad F, et al. *N Engl J* 2011; 364: 1195-206

Hu KQ, et al. *Hepatol Int* 2012.

Limited Efficacy With Telaprevir and Boceprevir in Some Patient Groups



1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 5. Bronowicki J, et al. EASL 2012. Abstract 11. 6. Zeuzem S, et al. EASL 2011. Abstract 5.

Adverse events

Telaprevir for untreated chronic hepatitis C virus infection [193]

Adverse event	With telaprevir (%)	Without telaprevir (%)
Gastrointestinal disorders		
Nausea	40–43	31
Diarrhea	28–32	22
Skin disorders		
Pruritus	45–50	36
Rash	35–37	24
Anemia	37–39	19

Boceprevir for untreated chronic hepatitis C virus infection [192]

Adverse event	With boceprevir (%)	Without boceprevir (%)
Anemia	49	29
Dysgeusia	37–43	18
Neutropenia ($500–750/mm^3$)	24–25	14
Resistance-associated variants	15–17	–

Poynard T et al. Gastroenterology 2099; 136:1618–1628; Bacon BR et al. Hepatology 2009;49: 1838–1846

Safety Concerns Increased in Patients With More Advanced Disease

- CUPIC trial
  - Early access program with telaprevir and boceprevir from France enrolling treatment-experienced patients with cirrhosis
    - Wk 16 interim analysis of 497 patients
  - High rate of serious adverse events: 33% to 45%
    - Anemia
    - Grade 2: 19% to 23%
    - Grade 3/4: 4% to 12%
  - High rate of premature discontinuation: 23% to 26%

Hezode C, et al. AASLD 2012. Abstract 51.

Higher Discontinuation Rates in Real-World Settings Than in Clinical Trials

- 2 centers in Dallas and Miami with 12-wk follow-up[1]
- Exclusions: transplantation, dialysis, or HIV coinfected
- Of 498 patients identified
  - 18% began triple therapy
  - 21% discontinued triple therapy before Wk 12

- Mount Sinai Medical Center and Montefiore with 12-wk follow-up[2]
- Of 174 patients who initiated TVR-based triple therapy
  - 33% discontinued TVR prematurely
  - 21% discontinued treatment due to adverse events

1. Chen EY, et al. AASLD 2012. Abstract 133. 2. Bichoupan K, et al. AASLD 2012. Abstract 1755.

Data lacking in Asia

Drug-drug interaction

Both BOC and TVR Have Potential for Many Drug–Drug Interactions

- BOC
  - Strong inhibitor of CYP3A4/5
  - Partly metabolized by CYP3A4/5
  - Potential inhibitor of and substrate for P-gp
- TVR
  - Substrate of CYP3A
  - Inhibitor of CYP3A
  - Substrate and inhibitor of P-gp

Challenges With Adherence to Complex Regimens

- Triple therapy regimens are complex, presenting challenges to medication adherence[1,2]
  - TID dosing
  - Food requirements
- Data show pegIFN/RBV adherence decreases over time[3]
  - Addition of PIs may exacerbate this trend

1. Telaprevir [package insert]. October 2012. 2. Boceprevir [package insert]. November 2012.
3. Lo Re V 3rd, et al. Ann Intern Med. 2011;155:353-360.

APASL consensus statements and management algorithms for hepatitis C virus infection

- PR48 is the current standard treatment, especially for patients infected with HCV genotype 1

- Triple therapy with DAAs should be the standard therapy for retreating CHC patients who fail to respond to SOC

Omata et al Hepatol Int 2012; 6:409–435

Costs and Availability

Median cost estimates and 95% credible intervals from the primary (Bayesian Markov) budget impact analysis for response-guided therapy

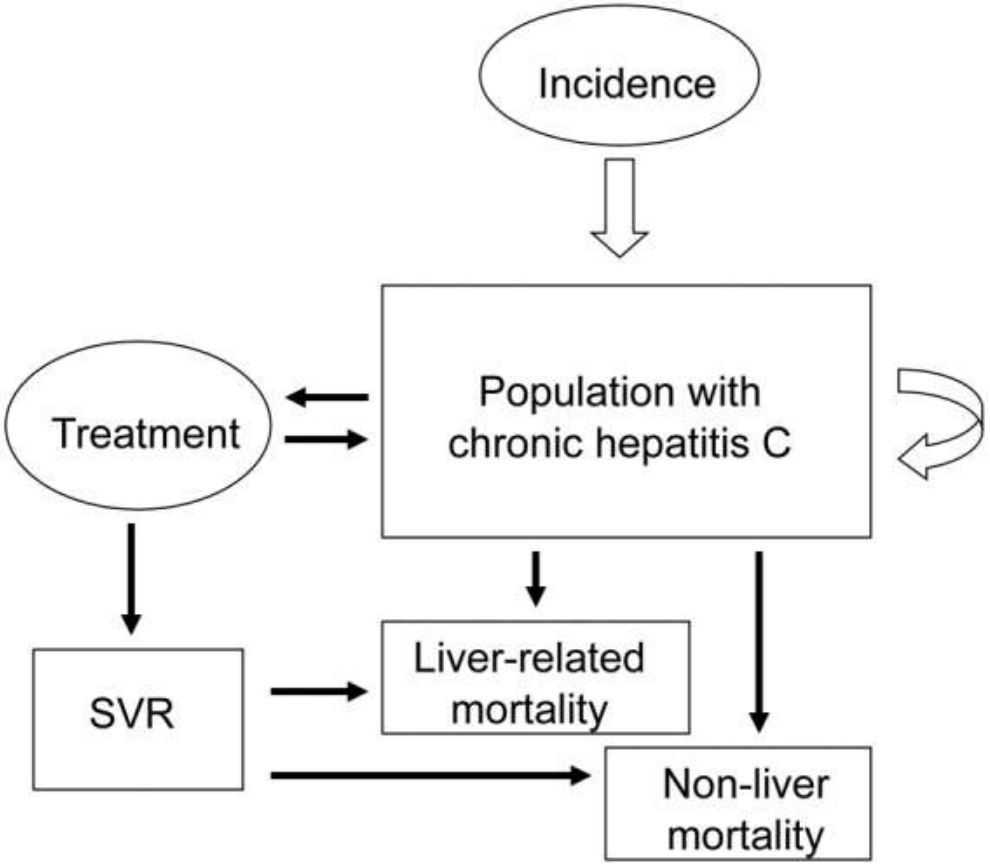
	Treatment-naïve	Treatment-naïve: early responder	Treatment-naïve: late responder	Treatment-experienced	Treatment-experienced: early responder	Treatment-experienced: late responder
Boceprevir + standard of care						
Standard of care	£5866 (£5753–5990)	£5549 (£5439–5651)	£6648 (£6363–6951)	£6475 (£6275–6633)	£6225 (£6026–6423)	£7022 (£6639–7405)
Boceprevir	£15,080 (£14,780–15,390)	£14,560 (£14,220–14,870)	£16,380 (£15,710–17,030)	£16,680 (£16,160–17,180)	£16,680 (£16,060–17,290)	£16,680 (£15,730–17,630)
Clinical monitoring	£1569 (£1509–1629)	£1525 (£1449–1600)	£1678 (£1593–1766)	£1652 (£1589–1714)	£1619 (£1539–1698)	£1731 (£1640–1824)
AE management	£326 (£303–349)	£325 (£298–352)	£328 (£287–372)	£274 (£252–296)	£274 (£248–300)	£274 (£234–316)
Total cost	£22,850 (£22,400–23,300)	£21,960 (£21,490–22,390)	£25,030 (£24,030–26,030)	£25,060 (£24,320–25,770)	£24,790 (£23,940–25,640)	£25,710 (£24,300–27,090)
Assumed SVR	–	97%	68%	–	97%	68%
Cost per SVR	£26,748 (£25,978–27,489)	£22,639 (£22,155–23,082)	£36,809 (£35,338–38,279)	£29,110 (£27,886–30,320)	£25,557 (£24,680–26,443)	£37,809 (£35,735–39,838)
Telaprevir + standard of care						
SOC	£6470 (£6279–6624)	£5986 (£5899–6069)	£7385 (£6929–7770)	£7744 (£7593–7902)	£7814 (£7713–7901)	£7615 (£7230–8032)
Telaprevir	£21,450 (£21,230–21,650)	£21,970 (£21,780–22,130)	£20,480 (£19,980–20,930)	£21,610 (£21,420–21,800)	£22,140 (£21,990–22,260)	£20,630 (£20,160–21,060)
Clinical monitoring	£1654 (£1591–1714)	£1586 (£1507–1662)	£1780 (£1684–1876)	£1831 (£1768–1897)	£1841 (£1758–1926)	£1814 (£1721–1908)
AE management	£359 (£335–382)	£355 (£328–383)	£365 (£224–408)	£357 (£334–379)	£374 (£347–402)	£324 (£287–362)
Total cost	£29,930 (£29,560–30,280)	£29,890 (£29,560–30,380)	£30,010 (£29,050–30,850)	£31,880 (£31,200–31,880)	£32,170 (£31,900–32,400)	£30,380 (£29,540–31,220)
Assumed SVR	–	97%	68%	–	97%	68%
Cost per SVR	£35,536 (£34,760–36,237)	£30,907 (£30,474–31,320)	£44,132 (£42,721–45,368)	£37,194 (£36,581–37,781)	£33,165 (£32,887–33,402)	£44,676 (£43,441–45,912)

Abbreviations: AE, adverse event; SOC, standard of care; SVR, sustained virological response

SOC (PR48)	Treatment-Naive	Treatment-experienced
Cost per SVR	£25, 740 (£24, 670–26, 860)	£28,040 (£27,540–28,540)

Thorlund et al. ClinicoEconomics and Outcomes Research 2012:4 349–359.

Structure of the Markov model representing the population infected with hepatitis C



Cost-effectiveness modeling studies

- Based on the estimate
  - Incidence of liver complications
  - Costs
  - Quality-adjusted life years (QALYs)
    - number of years of life that would be added by the Rx
  - Incremental cost-effectiveness ratios (ICERs)
    - **ICER = (C1 – C2) / (E1 – E2)**
- Generally support the use of response-guided triple therapy, versus dual therapy

Base-case cost-effectiveness results (per patient): discounted lifetime costs, QALYs and incremental cost- effectiveness ratios of BOC/RGT vs. PR48 and BOC/PR48 vs. PR48

	PR48	BOC/RGT	BOC/PR48
Costs (2010 US$):			
AV Therapy Drug Costs	29,573	47,582	69,928
EPO for treatment-related anemia	3,637	5,050	8,493
Monitoring Costs	2,110	1,796	2,380
SVR	0	0	0
F0-F3	7,538	4,786	4,461
Compensated Cirrhosis, F4	3,749	2,266	2,100
Decompensated Cirrhosis	4,223	2,677	2,505
Hepatocellular Carcinoma	5,043	3,128	2,915
Liver Transplantation	1,067	669	624
Post-Liver Transplant	1,822	1,155	1,081
Total Costs	**58,761**	**69,110**	**94,488**
Total QALYs	**14.55**	**15.17**	**15.20**
ICER		16,792/QALY	55,162/QALY

Ferrante et al. BMC Infectious Diseases 2013, 13:190

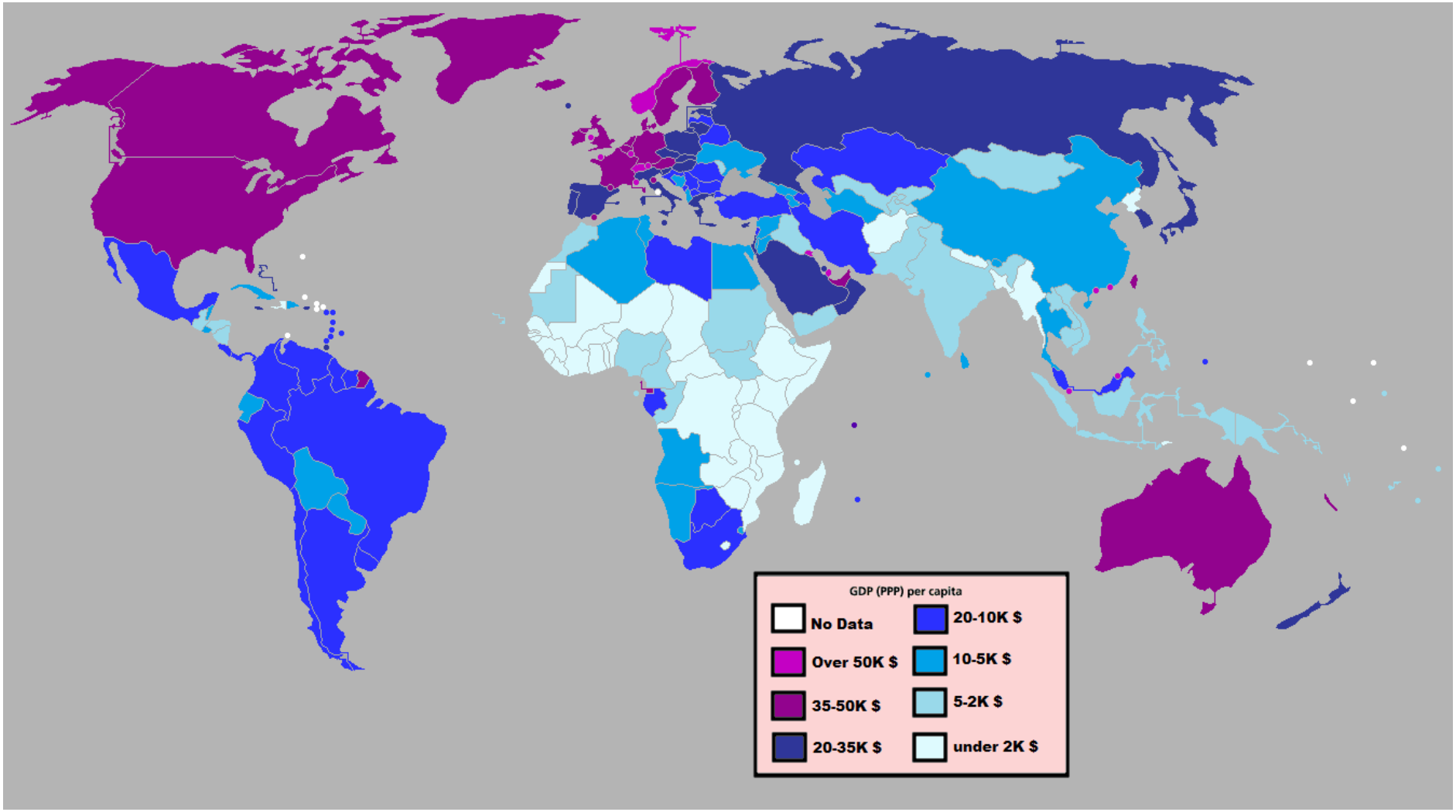
Major limitations of the published cost-effectiveness modeling studies

- Most of the patients included in these studies are Westerners and whether these clinical data can be transposed to Asian, need to be determined

- Factors
  - Economic
    - GDP
    - Cost of health care
    - Generic availability
  - Disease
    - Host responsiveness to therapy-IL28B
    - HCV genotype variability
  - Cultural
    - Form of therapy
    - Side effects
    - Traditional therapy
    - Myths
  - Pharmaceutical marketing strategy
  - Government and public health care
  - Availability of protease inhibitors

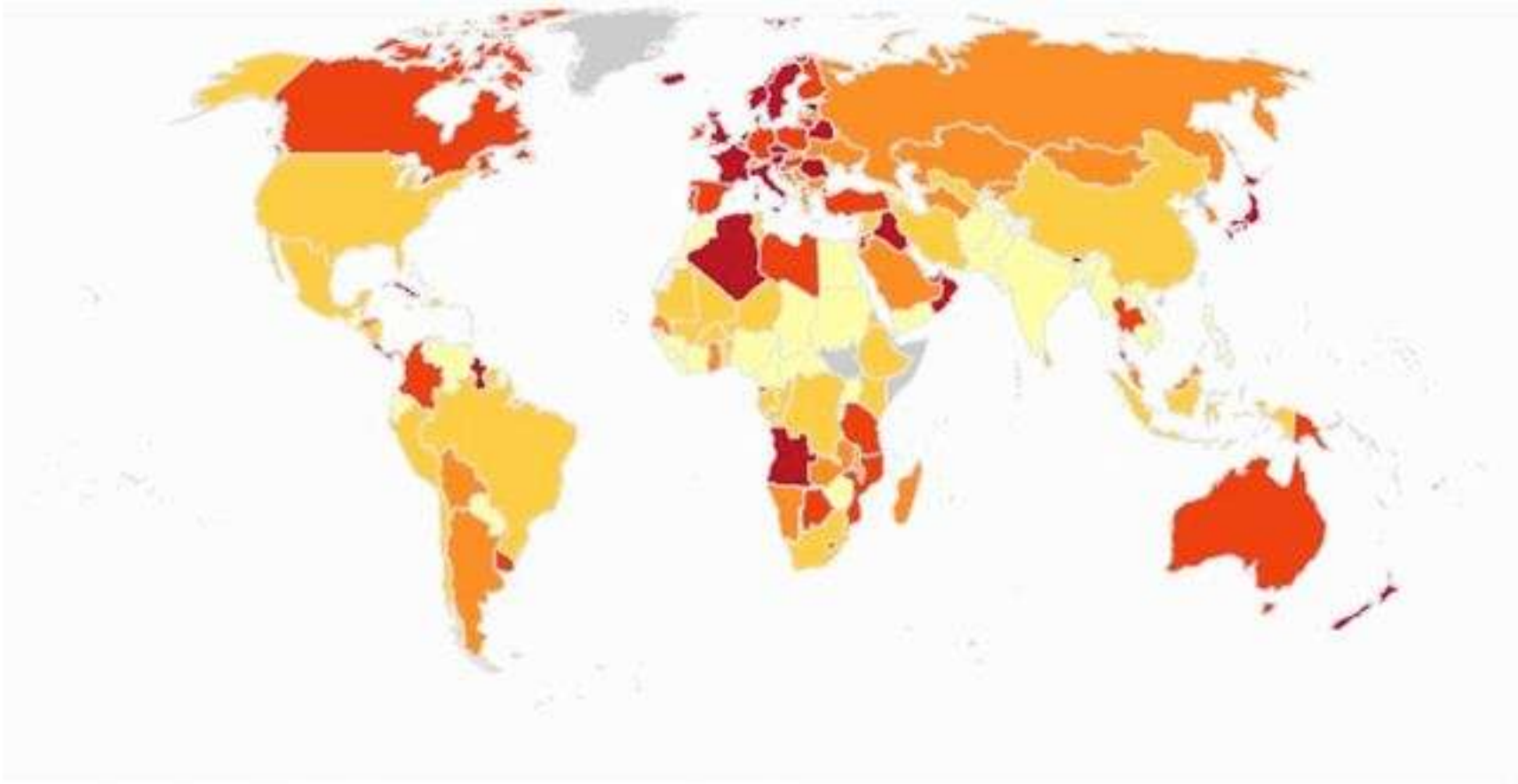
Countries by 2011 GDP (PPP) per capita

Gross domestic product at purchasing power parity per capita= the value of all final goods and services produced within a country in a given year, divided by the average (or mid-year) population of the same year



Based on World Bank figures; if no IMF/World Bank figure was available for a country, the CIA figure was used

Figure 1: Public Expenditure on Health as Percentage of Total Health Expenditure, 2011



Asia countries with PIs registered

Country	Boceprevir	Telaprevir
Australia	✔	✔
Hong Kong	✔	
Indonesia	✔	
Japan		✔
Kazakhstan	✔	
Malaysia	✔	
New Zealand	✔	✔
Philippines	✔	
Singapore	✔	
Turkey	✔	
Turkmenistan	✔	
Uzbekistan	✔	

National Health Insurance system (Asia-Pacific region)

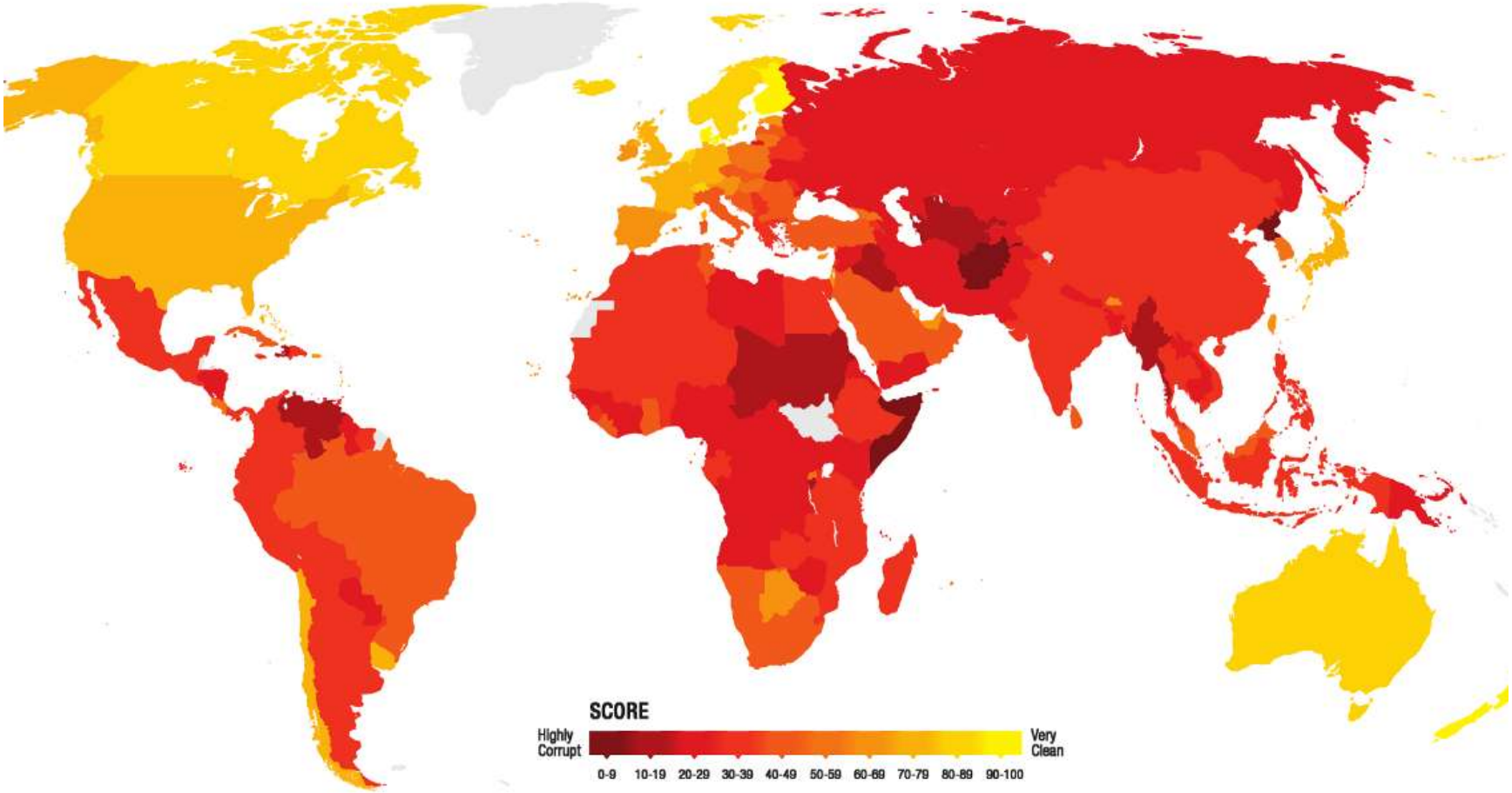
- Australia, Japan, New Zealand, China, Mongolia, Philippine, Vietnam, Korea, Taiwan

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

Political corruption

The use of power by government officials for illegitimate private gain. An illegal act by an officeholder constitutes political corruption only if the act is directly related to their official duties, is done under color of law or involves trading in influence.



Marketing strategy of Pharmaceutical Giants

South China Morning Post
INSIGHT & OPINION
WED Nov 20, 2013 Updated: 5:42pm

COMMENT · INSIGHT & OPINION

Integrity and transparency needed to cure corruption in business

Yury Fedotov says private-sector wrongdoing needs to be tackled head-on

Yury Fedotov

PUBLISHED : Wednesday, 20 November, 2013, 5:37pm
UPDATED : Wednesday, 20 November, 2013, 5:37pm

A GlaxoSmithKline office in Shanghai. Photo: Reuters

Conclusions

- Addition of 1st generation Pis (Telaprevir and Boceprevir) to PR48 has significantly improved sustained virological response rates in patients infected with HCV GT1

- Both PIs drugs are as yet not registered in the majority of Asian countries, and therefore not accessible to Asian patients

- Cost remains one big factor that deters wider registration and use of these drugs in Asia

Conclusions

- Much of Asia has a favorable CC IL28B genotype which confers better interferon sensitivity.

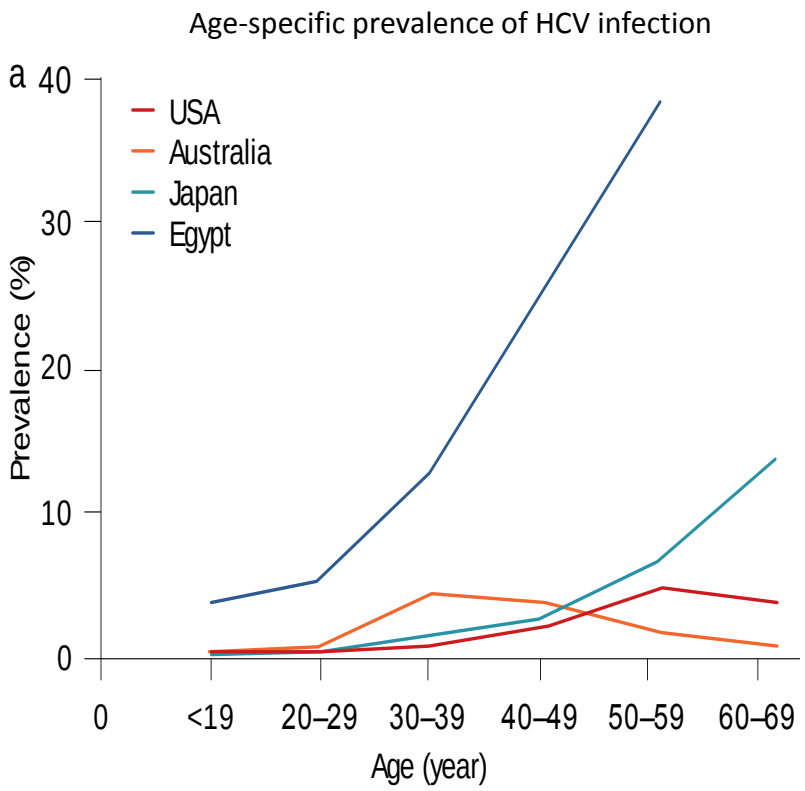
- Consensus recommendations of APASL 2012
  - consider PR48 as first line therapy for many patients with HCV GT1

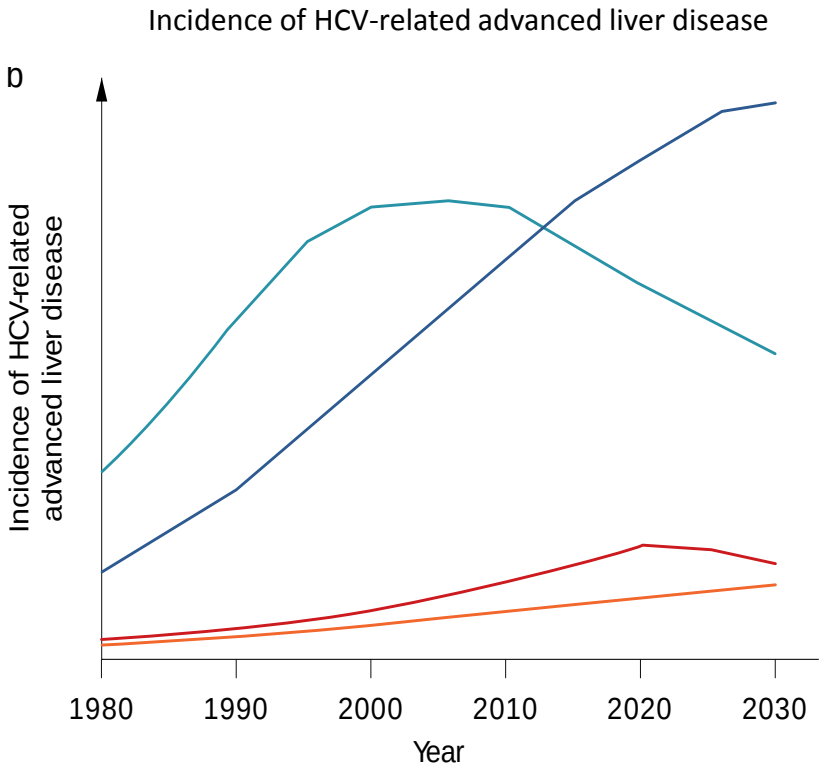
- If triple therapy is to become wide spread in Asia, generous patient assistance programs and dramatic cost reductions would be needed

Who should be started with triple therapy?

The Ford class aircraft carriers will be the mainstay of the US Navy's force projection capability

Chronic hepatitis C infection- a growing health problem in Asia-Pacific region





Escalations in HCV-related cirrhosis and hepatocellular carcinoma- Asia-Pacific region in the next twenty years

2nd Chinternational Hepatitis C Forum

15th – 16th February 2014

Guangzhou, China