The Changing Landscape Of Hepatitis C

- Where Do We Go From Here?

DNDi
Drugs for Neglected Diseases *initiative*

July 30, 2015

Shing Chang, PhD

11th Liver Update Meeting, Malaysian Liver Foundation

From Non-A Non-B to DAAs

Science 21 April 1989:
Vol. 244 no. 4902 pp. 359-362
DOI: 10.1126/science.2523562

Science

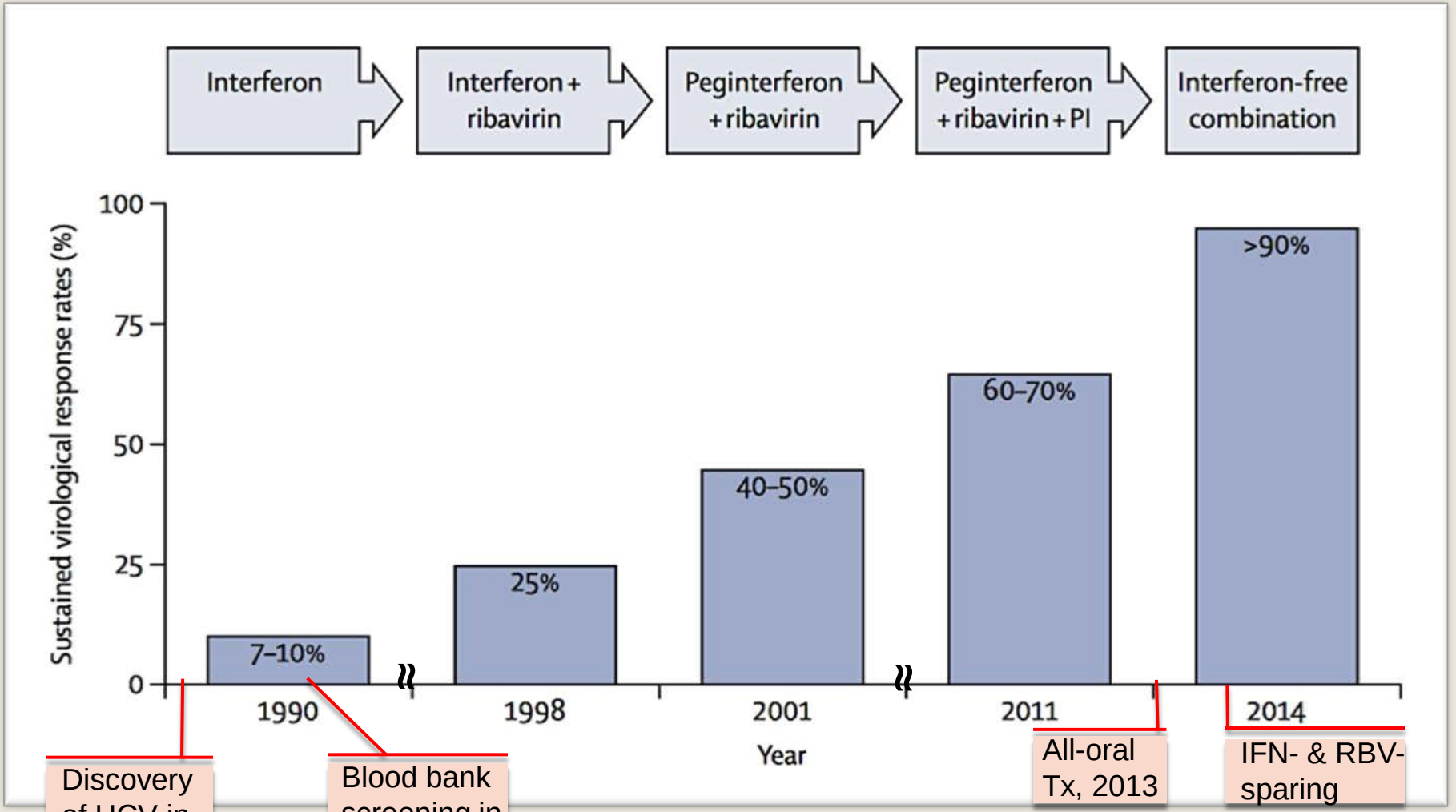
AAAS

REPORTS

Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome

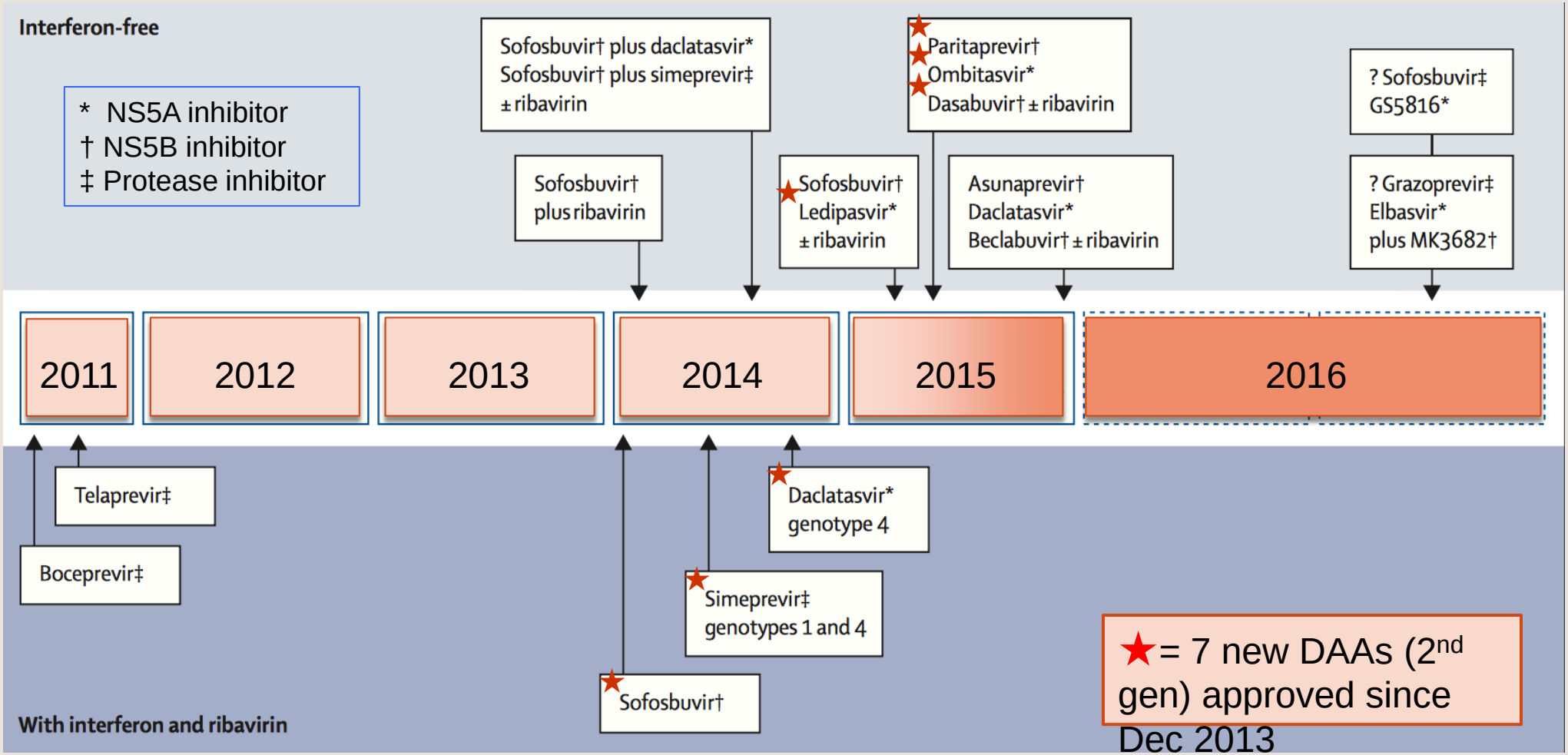
QL Choo, G Kuo, AJ Weiner, LR Overby, DW Bradley, M Houghton

Evolution of diagnostic and therapeutic tools for Hep C



Daniel P Webster, Paul Klenerman, Geoffrey M Dusheiko, The Lancet Volume 385, Issue 9973, P1124-1135 (March 2015) DOI: 10.1016/S0140-6736(14)62401-6

Hep C treatment options – past, present, and future



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Pipeline of new DAAs evolves rapidly

- High SVR
- Well tolerated
- All oral, IFN-sparing, and RBV-sparing
- For most patients, no need for on-treatment monitoring, and treatment duration is 12 weeks
- Price barrier restricts access

The Rich Pipeline of DAAs

Pre-registration stage

Product Name	Company	Notes	Main Territory
OBV+PTV/r	AbbVie	For GT1b patients; priority review	Japan
OBV+PTV/r	AbbVie	Priority review for adults GT4	US
DCV	BMS	Approved in EU	US
DCV	BMS	For GT3 (+ SOF)	US
LDV+SOF	Gilead	For GT1	Japan
GZP+EBV	Merck	Granted FDA Breakthrough Therapy Designations (April 2015) for GT1 with end-stage renal disease on hemodialysis and for people with HCV GT 4. Filed on the FDC on	US +

just approved

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Phase III

Product Name	Company	Notes	Main Territory
OBV	AbbVie		Global
PTV	AbbVie		Global
DCV+ASV+ BCV	BMS	UNITY trial	Global
BCV	BMS		Global
SOF/ GS-5816	Gilead	FDC; pan-GT	Global
MK-3682	Merck	Nucleotide; formerly IDX21437. Initiated in Jan 2015.	
nitazoxanide SR	Romark Laboratories, L.C.	Weak clinical data; low quality, or no, evidence on nitazoxanide for clinically- or patient-relevant outcomes.	Global

Phase II (Part 1 of 2)

Product Name	Company	Notes	Territory
ABT-493	AbbVie	Potential pan-GT	Global
ABT-493 + ABT-530	AbbVie	Pan-GT (99%SVR4 for GT1 in phase 2a)	Global
ABT-530	AbbVie	Potential pan-GT	Global
ACH-3102	Achillion		Global
Sovaprevir	Achillion		Global
ACH-3422	Achillion		Global
AV-4025	Alla Chem, LLC	NS5a Inhibitor. 3-day monotherapy data available. See Endnote.	Global
TT-034	Benitec Biopharma	TT-034 works by producing (in the liver) three silencing short hairpin RNAs (shRNAs), each targeting a different part of the HCV genome. Phase I/IIa on-going as of 5/2015. Some data released at EASL 2015.	Global
BL-8020	BioLineRx, Ltd.	FDC of RBV + hydroxychloroquine for HCV; developed by BioLineRx with Genoscience and Panmed. Phase I/II	Global
BIT225	Biotron Limited	Ion-channel inhibitor.	Global
EDP-239	Enanta	Regained rights from Novartis. May continue clinical development.	Global
EDP-239 + alisporivir	Enanta	Enanta has no rights on alisporivir	Global
GS-9857 + SOF/GS-5816	Gilead	Pan-GT regimen	Global
vedroprevir	Gilead	Not listed in current Gilead Pipeline.	Global
GS-9256	Gilead	Not listed in current Gilead Pipeline	Global
GS-9620	Gilead	TLR-7 agonist (HBV only??)	Global
GS-9669	Gilead	Not listed in current Gilead Pipeline.	Global
velpatasvir (GS-5816)	Gilead	Sofosbuvir, velpatasvir (GS-5816) and GS-9857 triple combo is in phase 2. See Gilead EASL news.	
GS-9857	Gilead	Sofosbuvir, velpatasvir (GS-5816) and GS-9857 triple combo is in phase 2.	
ITX-5061	iTherX, Inc.	Entry inhibitor.	US

Phase II (Part 2 of 2)

Product Name	Company	Notes	Territory
JNJ-56914845	J&J	NS5A inhibitor from GSK	Global
JNJ-42039556	J&J	Studied w SMV; not listed by J&J in 2015 Pipeline.	Global
ALS-2200	J&J (Alios)	Still listed in Clinicaltrials.gov. See note.	
silibinin	Meda AB	Plant extract; iv dosage form. Likely for fibrosis instead of DAA	Global
samatasvir	Merck	IDX-719 NS5A inhibitor– not listed on Merck's pipeline list .	Global
narlaprevir	Merck	SCH 900518 protease inhibitor – not listed on Merck's pipeline list.	Russia
grazoprevir	Merck	See note on Merck studies on GT3.	Global
elbasvir	Merck	See above.	Global
alisporivir	Novartis →Debio	Debiopharm regained full rights.	Global
ravidasvir	Presidio	PPI-668; BI-238630. Out licensed to Pharco. Phase-II/III in Egypt	Egypt
ravidasvir	Presidio	PPI-668; BI-238630. Out licensed to Ascletis.	China
setrobuvir	Roche	Status unknown; listed in Roche's Pipeline Report published in July 2014.	Global
mericitabine	Roche	Status unknown; listed in Roche's Pipeline Report published in July 2014.	
danoprevir	Roche	Mericitabine+danoprevir/r + ribavirin → poor SVR. Phase 2 as listed in Roche's Pipeline 2015	China
miravirsen	Roche (from Santaris)	Phase 2a data reported. Anti miR-122. PK support once monthly or less frequent	Global
furaprevir	TaiGen	(Waiting for partner?)	Global
SCY-635	Waterstone Pharmaceutical, Inc.	Licensed from Scynexis. In discussion with DNDi.	Global

Phase I (Part 1 of 2)

Product Name	Company	Notes	Territory
deldeprevir	Achillion	ACH-2684; phase 1 PoC data available.	Global
ACH-2928	Achillion		
AL-335	Alios Biopharma Inc. (J&J)	Nucleos(t)ide polymerase inhibitor; phase 1 initiated Dec 2014	Global
AVR-560	Alla Chem, LLC	Entry inhibitor.	Global
H-5C	Genecode AS	Anti-sense technology?	Global
GSK-2878175	GlaxoSmith Kline plc	NS5B non-nucleoside polymerase inhibitor.	Global
JNJ-47910382	J&J	NS5A inhibitor; in Phase I since 2012	Global
MK-8408	Merck	Scheduled for April 2014 – June 2015	Global
MK-8876	Merck	Likely a non-nuc NS5B inhibitor	Global
MK-1075	Merck	Could be the Idenix' 2nd nucleotide drug IDX21459. Patient study started April 2015.	Global
MK-2248	Merck	PK/PD study in 2014. Target/class unknown	Global
MK-3682	Merck	IDX21437. Phase 1 / Phase 2; scheduled for completion in April 2015	

Phase I (Part 2 of 2)

Product Name	Company	Notes	Territory
MB-110	Microbio Co., Ltd.	NS5A inhibitor; IND under review by FDA	Global
MBX-700	Microbiotix, Inc.	MBX-700 and MBX-701 (formerly SCH 900942 and SCH 900188), two non-nucleoside inhibitors of the hepatitis C virus NS5B polymerase. Licensed to Merck in 2013.	Global
chlorcyclizine	NIH	BID, +/- RBV	US (NIH)
BZF-961	Novartis AG	No information.	Global
PPI-461	Presidio	NS5A inhibitor	
PPI-383	Presidio	NS5B non-nucleoside inhibitor.	Global
RG-101	Regulus	Phase 2 planned for Q2 2015.	Global
SB-9200	Spring Bank Pharmaceutical, Inc.	Immunomodulator, an Oral Prodrug of the Dinucleotide SB 9000; activating RIG-1 and NOD2. For HBV and HCV. See EASL 2015 news release.	Global
TD-6450	Theravance	NS5A inhibitor. Seeking licensing deal.	Global
ID-12	Intelectual Dialog Ltd.	A Russia-based company. No information on this compound.	Global
ITX-5061	iTherX, Inc.	HCV entry inhibitor. No or limited clinical efficacy	United Kingdom

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Highlight of selected drugs in the pipeline

Product	Company	Class/Stage	Notes
Miravirsen	Roche (from Santaris)	Target: miR-122 Phase IIa	5 weekly sc injections ➔3 log reduction in VL. Some patients had undetectable VL on wk 14.
RG-101	Regulus	Target: miR-122 Phase I	• After single dose of 4 mg/kg, by day 29, all 14 patients showed a mean viral load reduction of 4.8 log (5.8 to 3). • After 57 days, nine of 14 patients had HCV RNA below the limit of quantification (Regulus press release). • Plans to file an IND with the FDA early 2016 • RG-101+simeprevir combination study in H2 2015
chlorcyclizine	NIH	BID, +/- RBV	Entry inhibitor
BIT225	Biotron Limited	Poring inhibitor; Phase II	Clinical conducted with pgIFN+RBV combo. Also claim to have HIV activity. No trial with DAA planned.
alisporivir	Debio	Cyclophilin inhibitor	Future plan unclear
SCY-635	Waterston		Future plan unclear

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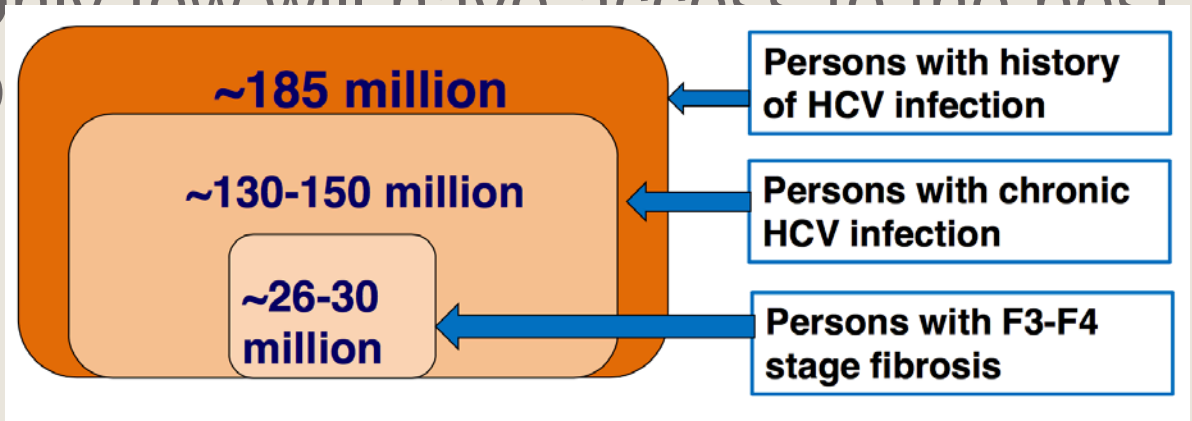
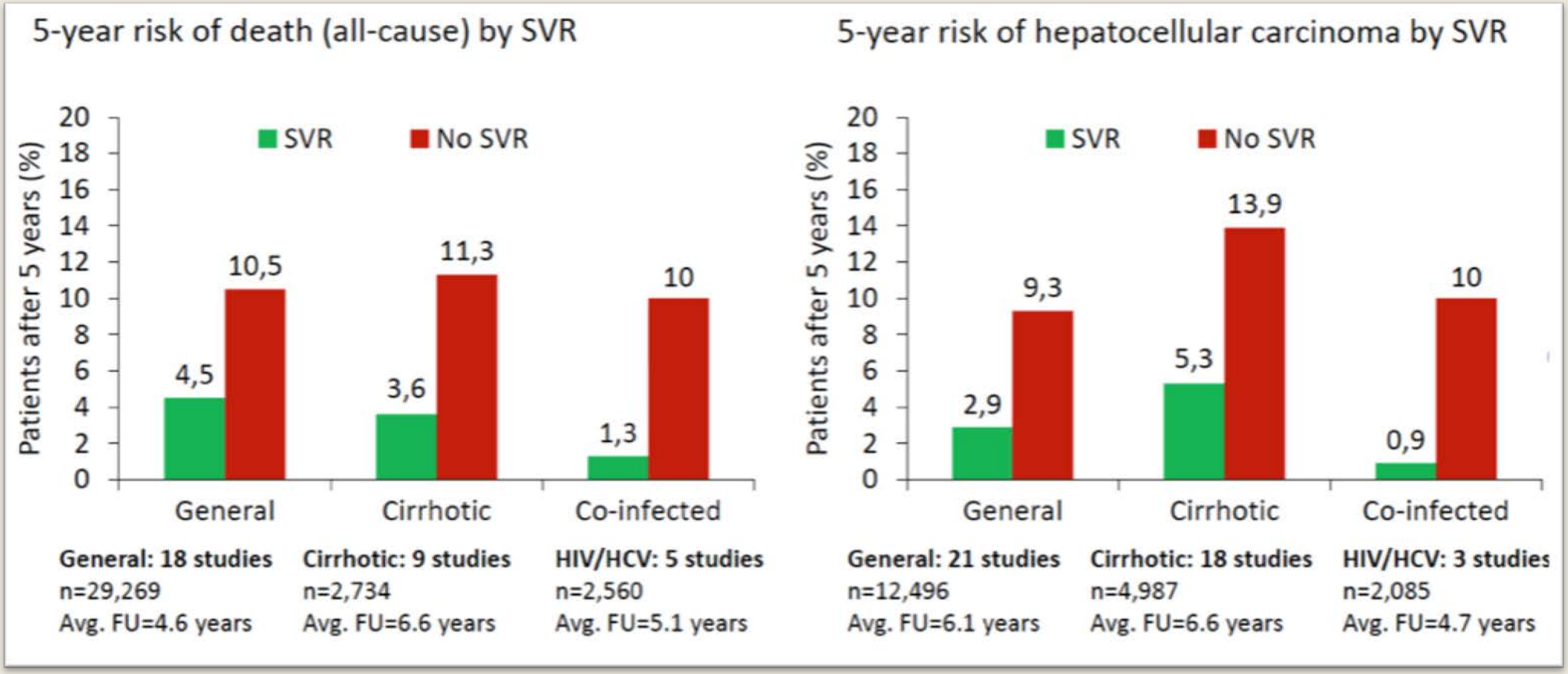
26-30 million people need treatment now.

Only few will have access to the best D



SVR reduces the risk of HCC and death

Meta-analysis of 129 studies of 34,562 patients



Hill A. Clin Inf Dise 2015

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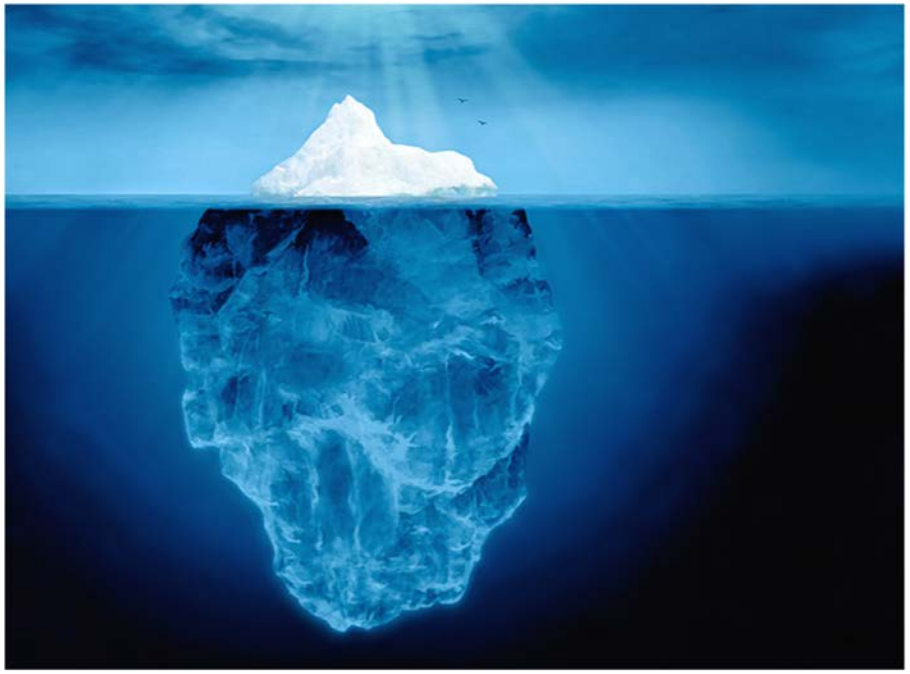
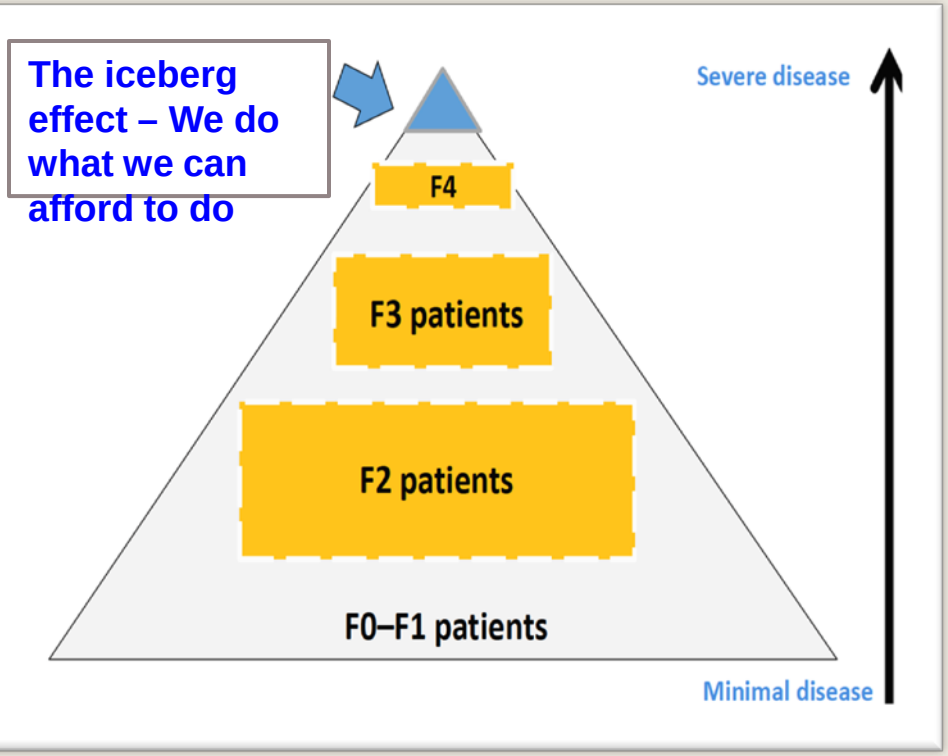
Excellent drugs available, yet we are rationing (thus restricting) treatment, against best clinical judgment





We have to take appropriate and timely steps to control Hep C now.

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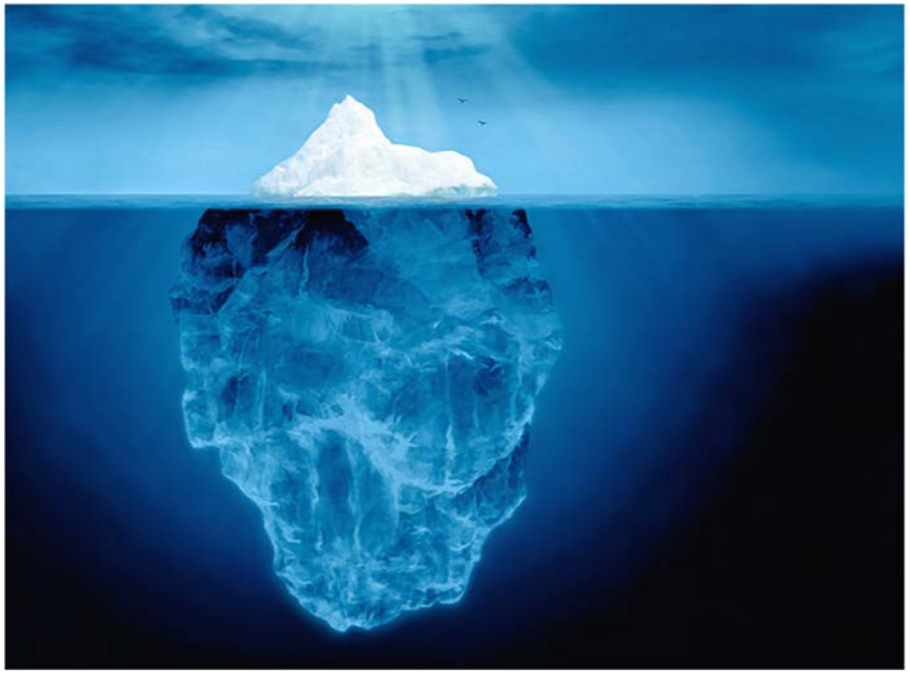

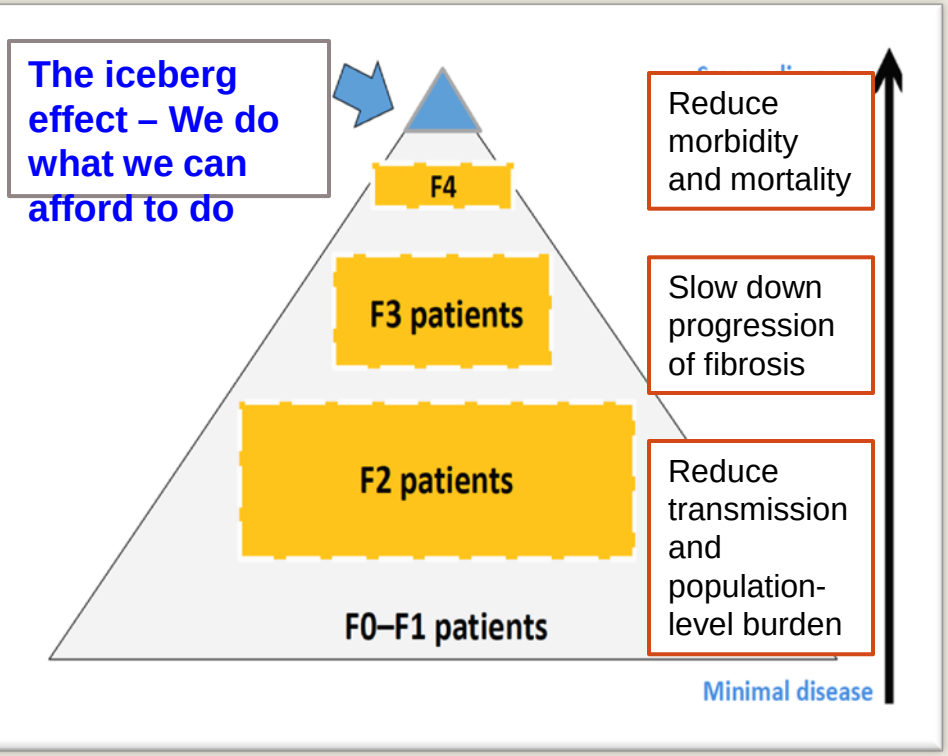

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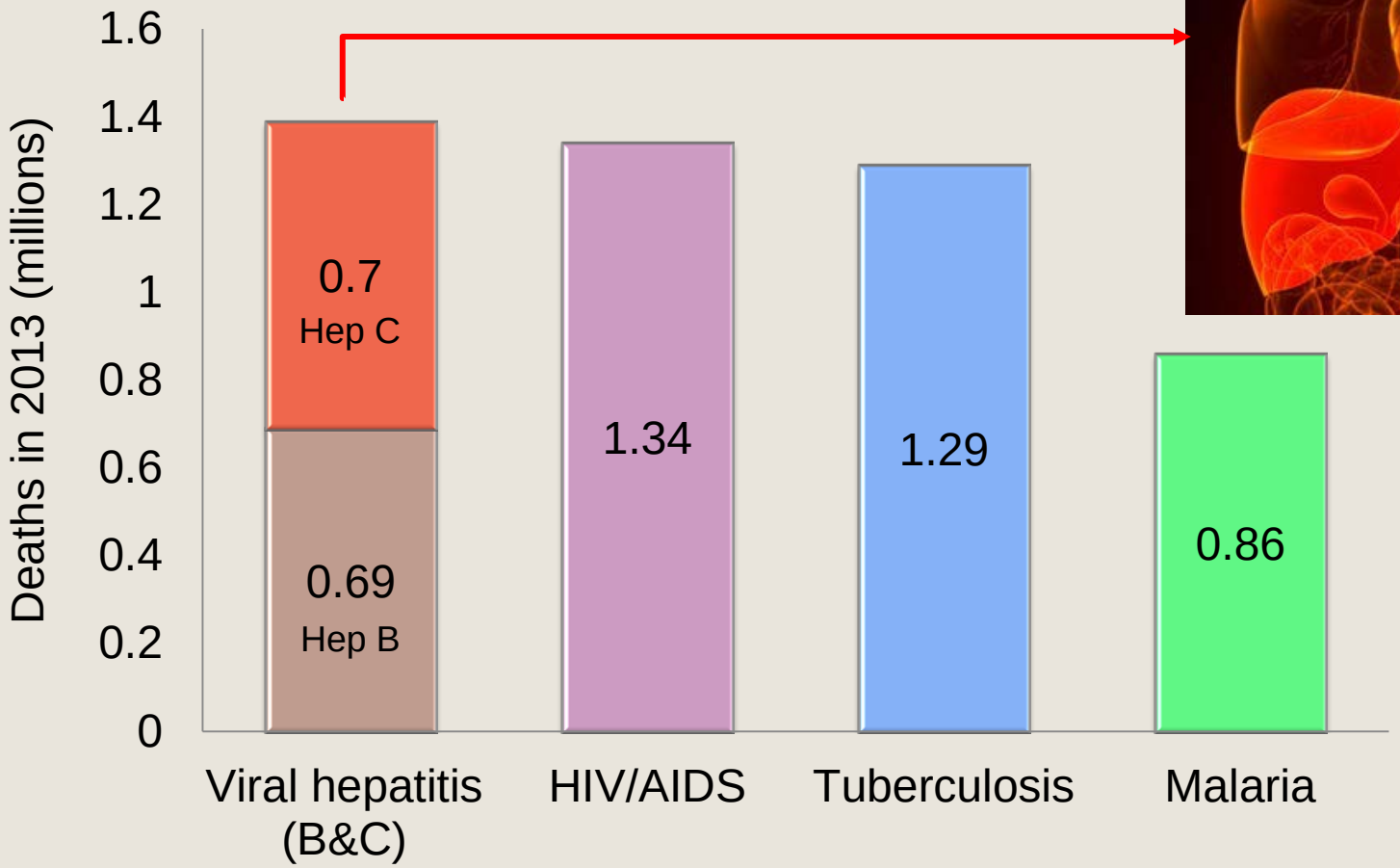
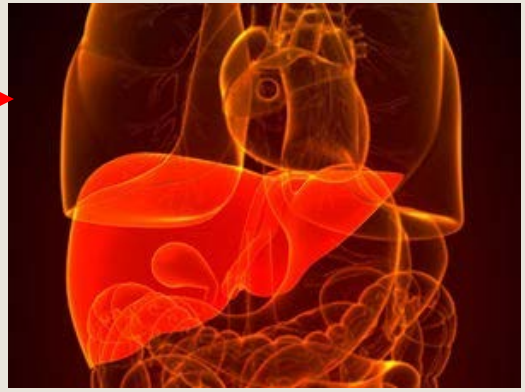
Global mortality due to viral hepatitis (2013)





Naghavi, Mohsen, et al. "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013." *Lancet* 385.9963 (2015): 117-171.

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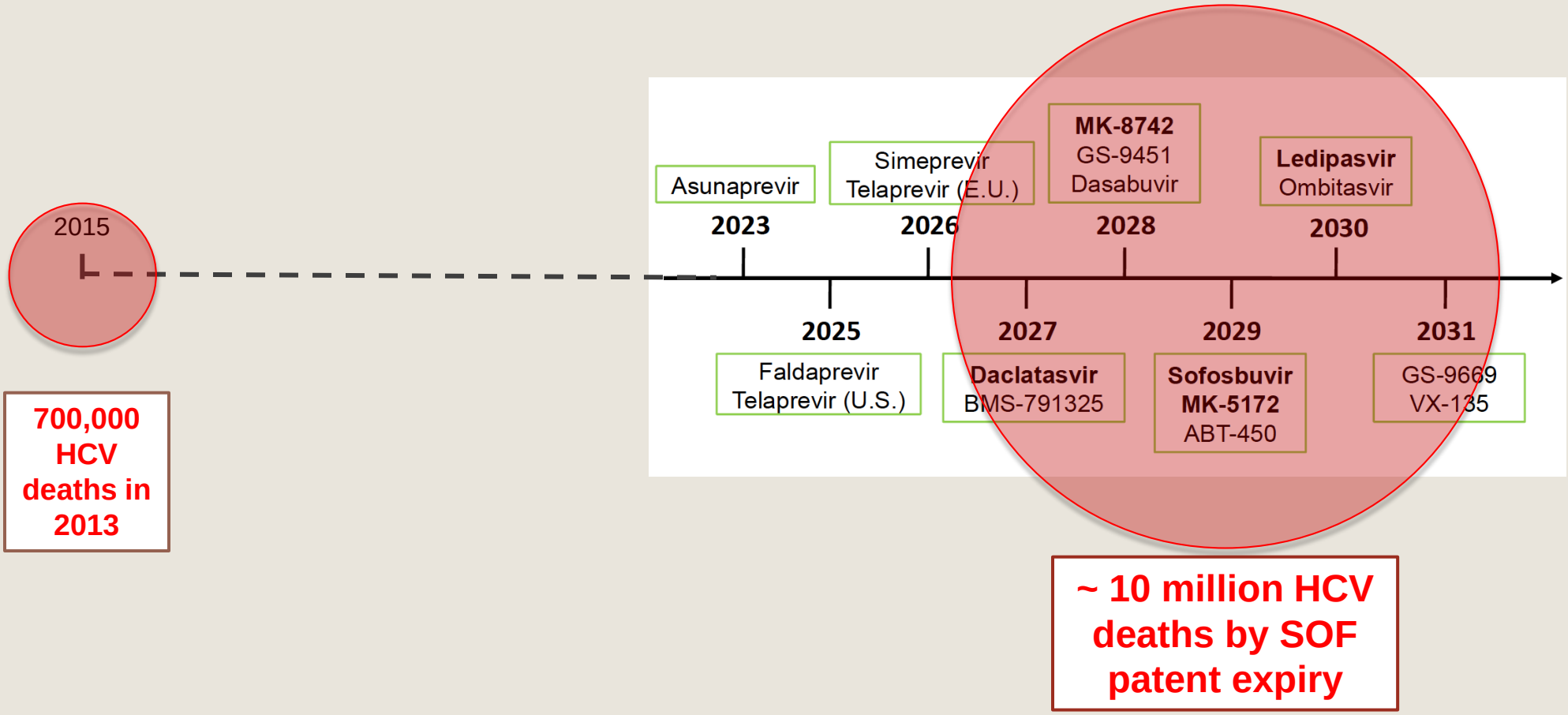
The scientific success exposed our humanitarian failure

- The benefits of, and the need for treatment are obvious
- Yet, the pharmaceutical companies are charging what the market (and the governments) can bear, and more
- Health Systems resort to “rationing” treatment – a decision based on affordability, not on the best medical judgment nor the best public health measure
- Access to essential and life-saving treatment is a fundamental human right
- Millions will die if we wait for affordable drugs based on generics **after** patent expiration

Can we ask patients to wait for patent expiration to access affordable DAAs?



Data from Global Burden of Disease report, 2013. Lancet January 10th 2015, 385: 117-171
FDA Orange Book. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Infographic by TAG.
Modified from Karyn Kaplan, TAG. Bangkok Generics Meting, May 29, 2015

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Can we ask patients to wait for patent expiration to access affordable DAAs?

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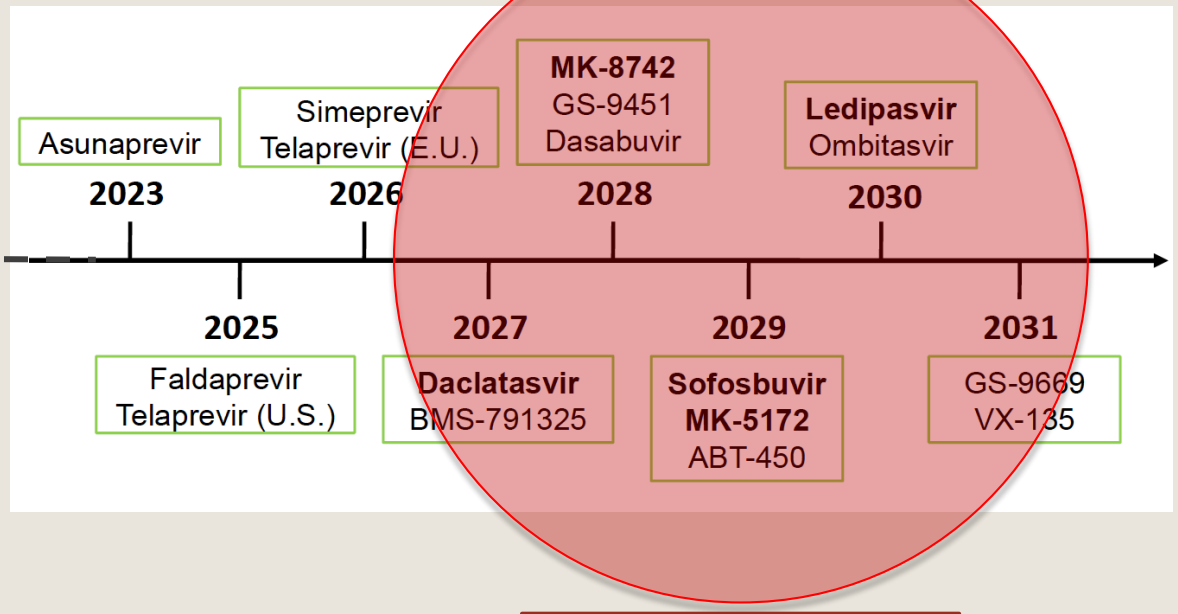
2015

700,000 HCV deaths in 2013



~ 10 million HCV deaths by SOF patent expiry

Data from Global Burden of Disease report, 2013. Lancet January 10th 2015, 385: 117-171
FDA Orange Book. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Infographic by TAG.
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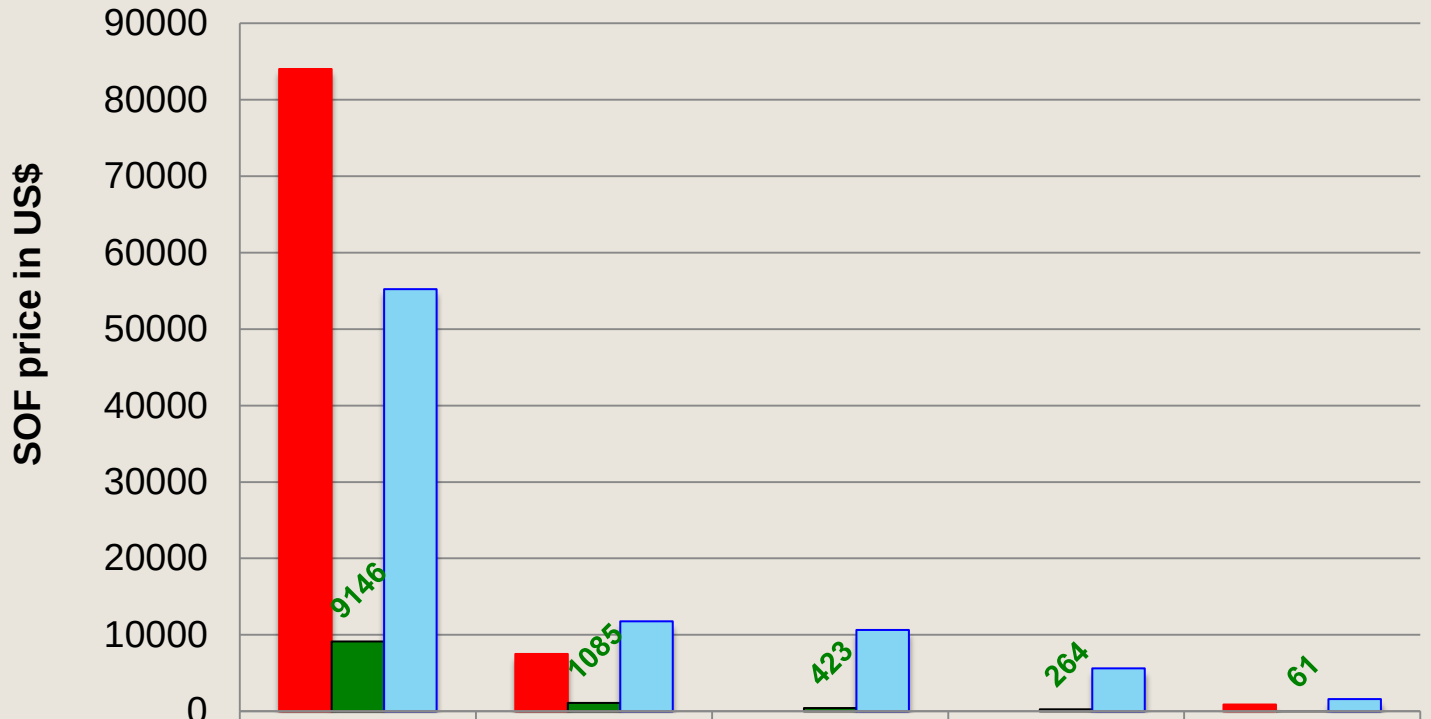
How Are These DAAs Priced?
Why We Cannot Afford Them?

Pricing of sofosbuvir vs. per capita health expenditure and GNI in selected countries

- SOF price is based on 12-wk dosing
- The price for the companion DAA is not included



	US	Brazil	Malaysia	Thailand	India
Price of SOF	84000	7500	?	?	900
Health expenditure per capita	9146	1085	423	264	61
Gross National Income per capita	55200	11760	10660	5610	1610

World Health Organization Global Health Expenditure database from http://data.worldbank.org/indicator/SH.XPD.PCAP
Gross national income (GNI) per capita (formerly GNP per capita) Converted to U.S. dollars using the World Bank Atlas method from http://data.worldbank.org/indicator/NY.GNP.PCAP.CD
Estimated generic cost of production of SOF based on A. Hill Study; CID 58:928-936 (2014)

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Maximizing profit by charging what the market will bear –
Sofosbuvir price is linked to per capita health expenditure and GNI

The Gilead approach to access:

- Voluntary licensing (India)
- Tiered pricing (Brail)

12-wk dosing	US	Brazil	India
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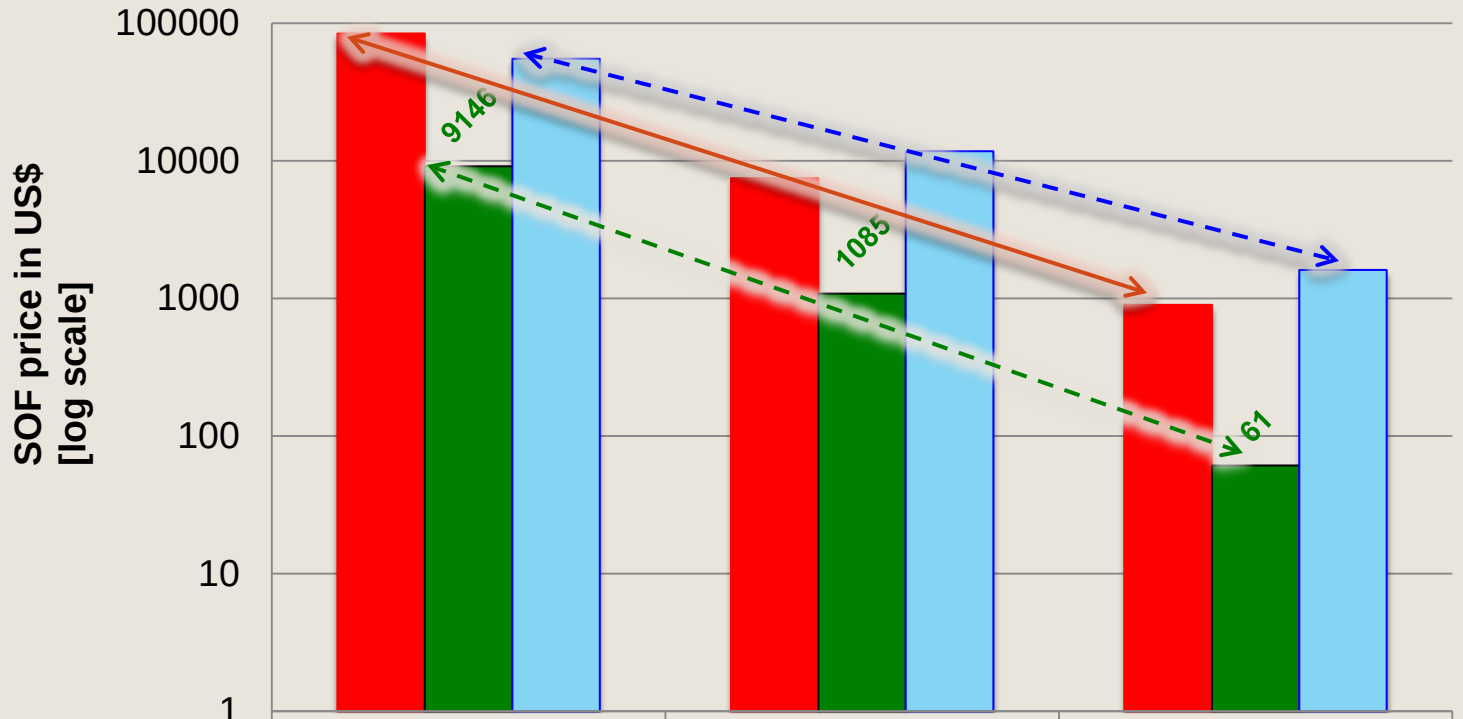
The Gilead approach to access:

- Voluntary licensing
- Tiered pricing
- **Equally unaffordable**
- **Treatment rationing remains**



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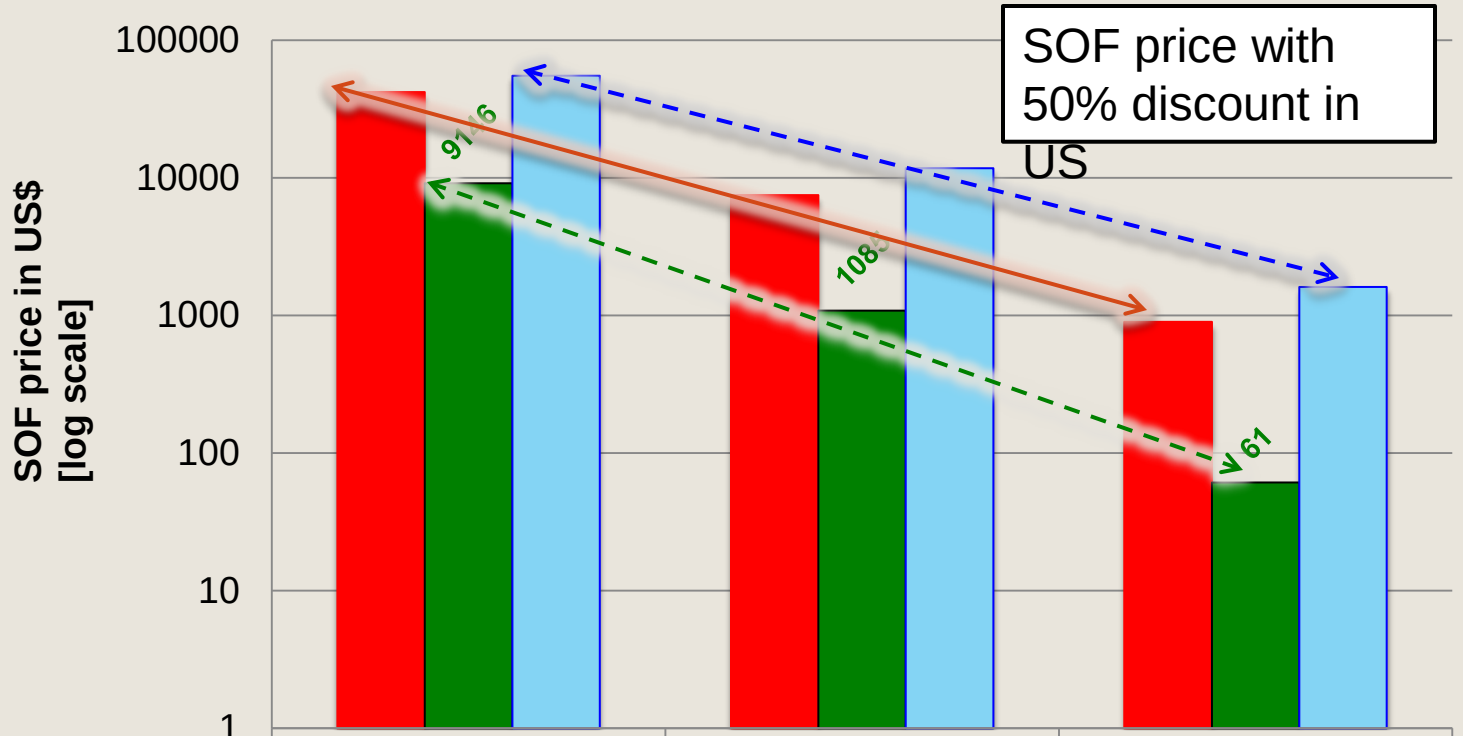

12-wk dosing	US	Brazil	India
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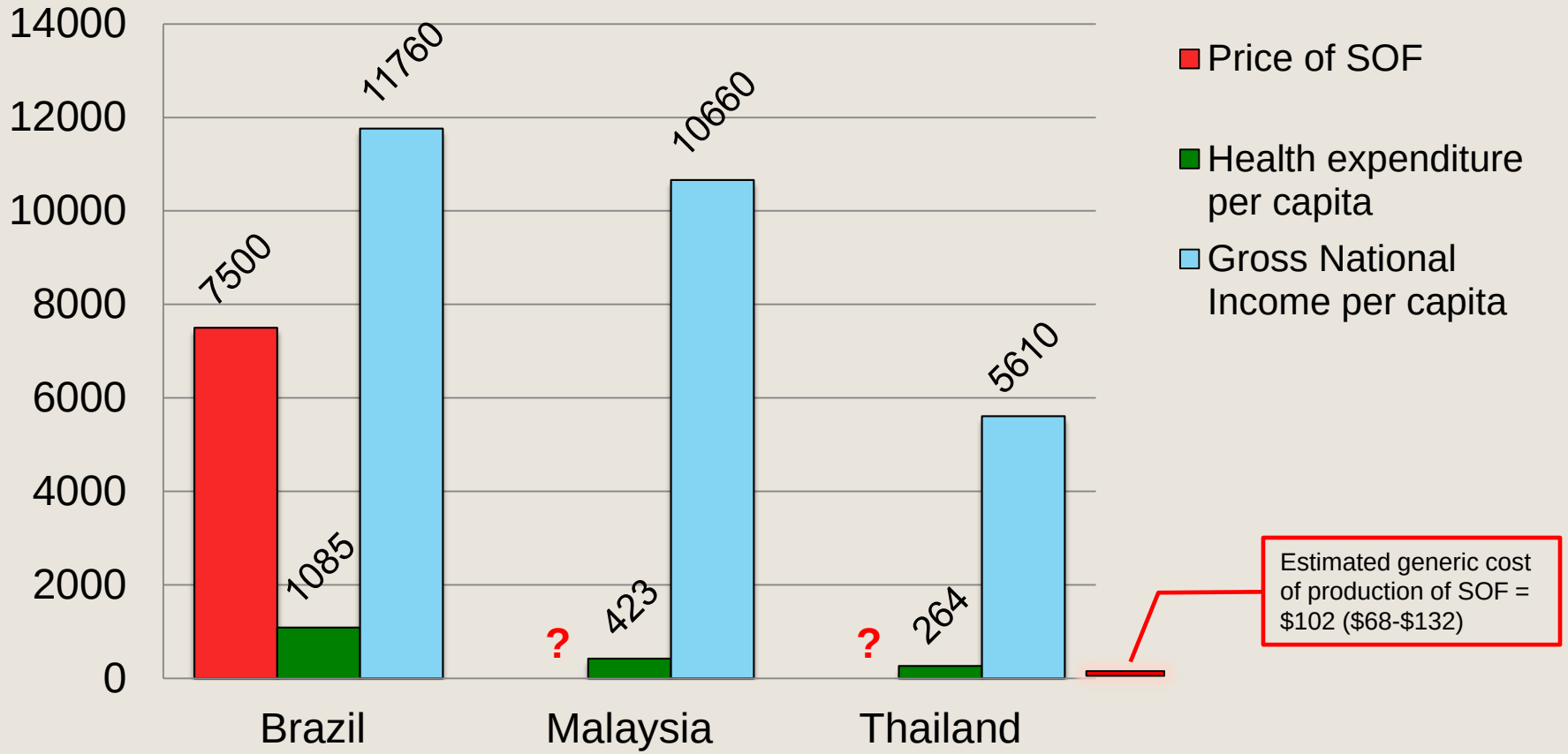
How will SOF be priced in other MICs? – Gilead will price it to maximize profit despite of low cost of production



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Access Of Affordable DAAs

Affordable drugs – several options

- Voluntary licensing and tiered pricing
  - Gilead, facing pressure over the $1,000-a-pill price for SOF before discount, has struck deals with generics makers to provide discounted copies of SOF in 91 developing countries
  - But limiting cheap copies to those countries leaves out certain high-burden MICs where there are over 50 million people with HCV
  - When compared to resources in LICs and MICs, their discounts prices represent simply the strategy of “charge what the market can bear” to maximize profits
- Compulsory licensing
  - An instruments within TRIPS that governments can use to limit the adverse effects of patent protection and thereby ensure a supply of affordable generic drugs to their people. It allows generic manufacturers to produce pharmaceutical products that are currently subject to patent protection
  - Had been used in the past by Canada, Indonesia, Malaysia, Brazil, and Thailand

Access through patent challenge

- I-MAK (Initiative for Medicines, Access & Knowledge) said it had brought legal challenges against Gilead's patents or patent applications in five countries not covered by the agreement: China, Argentina, Brazil, Russia and Ukraine (May 2015).
- India’s Patent Office rejected a key patent on Sovaldi, opening the door for cheap generic copies from domestic drugmakers (Jan 2015). China too in June 2015, following a pre-grant challenge filed by I-MAK.
- Médecins du Monde (MdM) , a global NGO that provides healthcare for vulnerable people, is challenging Gilead’s monopoly on the drug at the European Patent Office (Feb 2015).

Access through government price control of essential medicines

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Drug pricing policy irrational, re-examine it, Supreme Court tells Centre

TNN | Jul 16, 2015, 03.35 AM IST

- All India Drug Action Network, an NGO which challenged the Drug Price Control Order (DPCO) issued by The National Pharmaceutical Pricing Authority (NPPA), Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers
- The Indian Supreme Court on July 15th asked the Ministry to re-examine its drug pricing policy for essential medicines, calling it "unreasonable and irrational"

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We have to change the landscape of the rich hep C pipeline from *for-profit* to *for-patient*

- Many drugs in current pipeline are good, but will not be advanced further
- Stalling in the pipeline is due to the lack of commercial interest and market differentiation (not profitable to invest in them)
- DNDi is in the process of evaluating licensing opportunities
- Ideally, we can develop a “desirable” regimen, by 2020, that fits the target product profile (TPP), for which we will be able to address the patients’ needs without price barrier, and can be scaled up to address the public health needs

Public Health Challenge – Reducing The Disease Burden of Hepatitis C

7 new DAAs approved since Dec 2013 – What are the remaining challenges for *case management* and for *public health*?

Case management

- Fixed-dose combination (more of)
- Shorter treatment durations
- Efficacy in genotypes other than GT1 (global market)
- Efficacy in advanced cirrhotic patients
- Drug-drug interactions
- Resistant HCV variants (naturally occurring and drug induced)

Public health

- Too many infected, too few know their status
- Few countries can afford scale up of testing
- Few countries can afford the drugs to scale up treatment (treatment rationing severely limits the public health impact)
- No prevention in many countries
- No vaccine

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Reduce disease burden – think beyond individual patients

- A major **public health** challenge
- High global disease burden – 130 -150 million people are chronically infected world-wide (WHO). 700,000 died in 2013 (Global Burden of Disease Report, Lancet, 2015). 3-4 million newly infected each year (Modh HK et al., Hepatology, 2013)
- Increasing efficacy of therapy alone with constant numbers of treatments will not have a major impact on HCV-related disease burden.
- 26-30 million need treatment now (WHO 2014)

We should start now with effective and available treatment that is simple to use

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Elimination & eradication – the ultimate goals of public health

THE LANCET

Volume 385, Issue 9973, 21–27 March 2015, Pages 1045

Editorial

Hepatitis C: only a step away from elimination?

The Lancet

Available online 20 March 2015

Liver Int. 2013 February ; 33(0 1): 68–79. doi:10.1111/liv.12063.

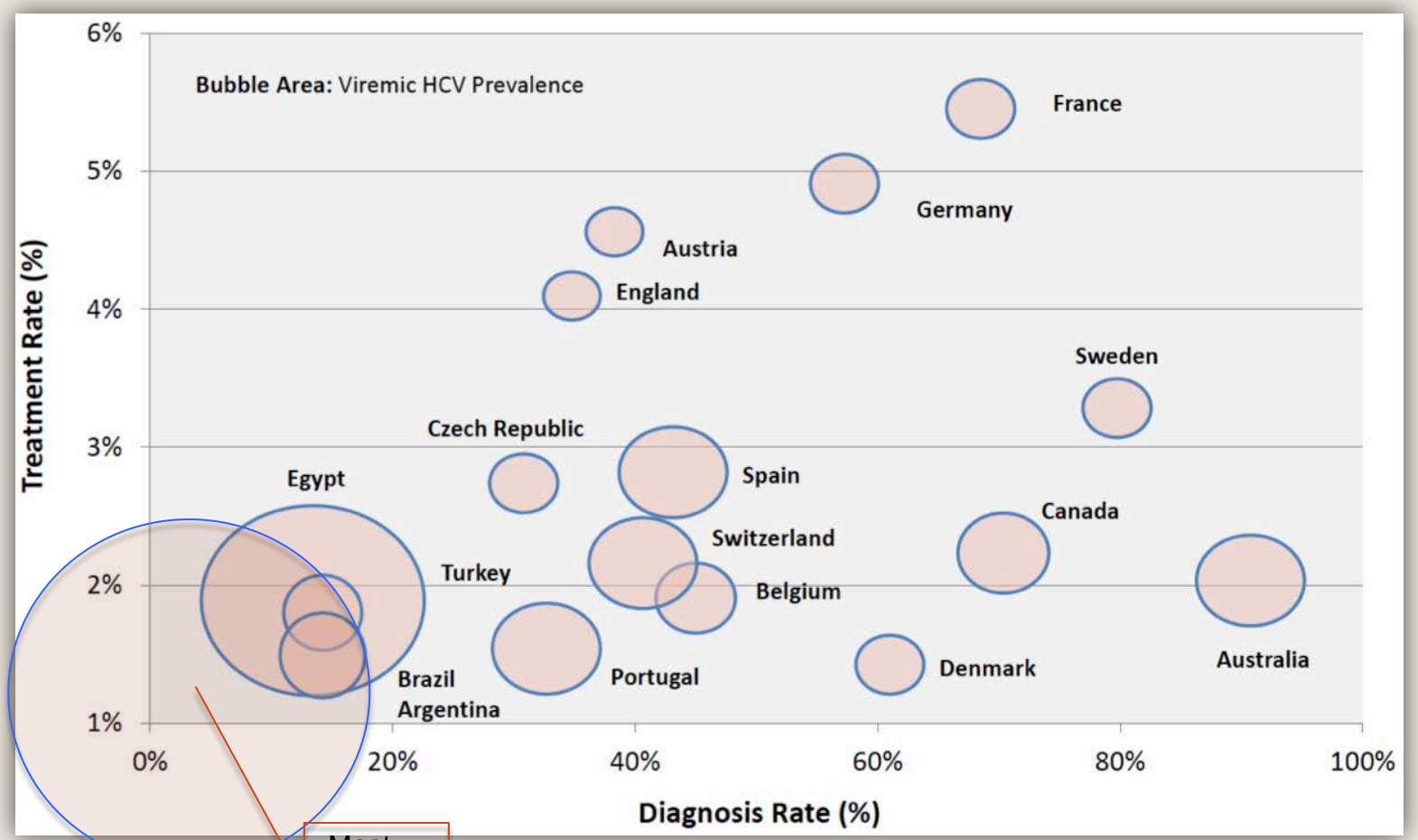
Best strategies for global HCV eradication

Liesl M. Hagan and **Raymond F. Schinazi**
Center for AIDS Research, Emory University School of Medicine and Veterans Affairs Medical Center, Decatur, Georgia 30033, USA

Elimination and eradication start with disease control; disease control starts with affordable treatment

- **Control** as a reduction in the incidence, prevalence, morbidity or mortality of an infectious disease to a locally acceptable level (continued prevention measures are required). Example: diarrheal diseases.
- **Elimination** as reduction to zero of the incidence of disease or infection in a defined geographical area (continued prevention measures are required). Example: measles, poliomyelitis.
- **Eradication** as permanent reduction to zero of the worldwide incidence of infection. Example: smallpox.
- DNDi believes that we can control HCV epidemics if we act now
  - 3 pillars: Availability of effective interventions, practical diagnostic tools, and effective prevention strategy
  - Simplification of effective and well-tolerated treatment is essential to make disease control feasible

Dx and Tx rates vary, and are low in most countries



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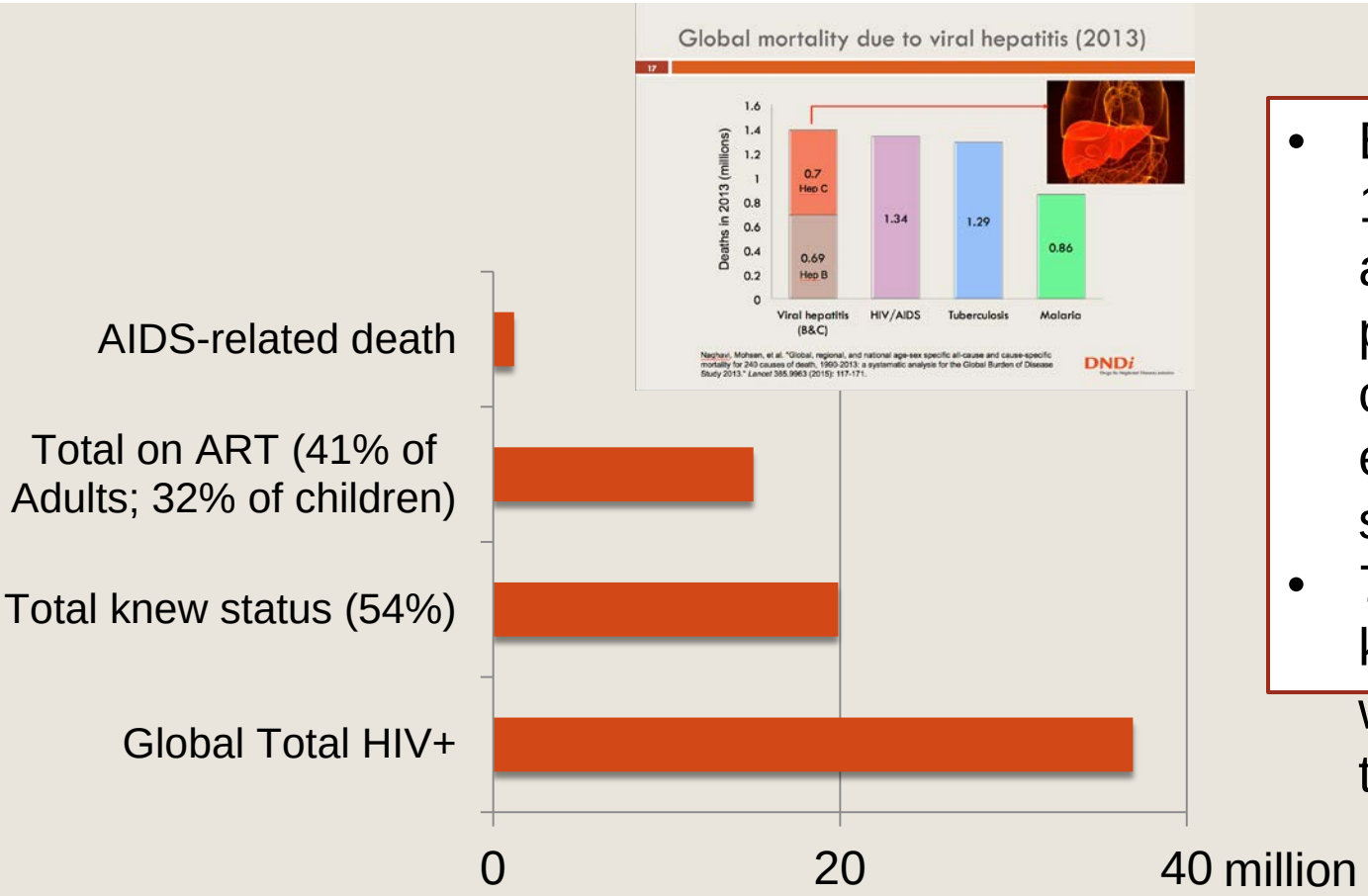
GJ Gore et al., Journal of Viral Hepatitis, 2014, 21 (Suppl. 1), 1–4

Overcoming barriers

- Testing
  - a simple one-size-fits-all Dx, ideally point-of-care
- Treatment
  - a simple one-size-fits-all Tx, at least for all non-cirrhotic patients
- Prevention
  - to effectively reduce the transmission
- Capacities and policies
  - Task shifting, data collection, setting policies, funding/training for scale up, linkage to treatment, prevention measures, ….

Lessen from HIV epidemics – MDG achieved ahead of schedule

MDG: 15 million HIV-positive people on antiretroviral therapy (ART) by 2015



- Ensuring treatment for 15 million people around the world proves that treatment can be scaled up even in resource-poor settings
- 75% of those who knew their status were on ART treatment

UNAIDS Executive Director Michel Sidibé and United Nations Secretary-General Ban Ki-moon announced the achievement and presented the report, *How AIDS Changed Everything -- MDG 6: 15 Years, 15 Lessons of Hope from the AIDS Response*, on July 14, 2015 in Addis Ababa, Ethiopia.

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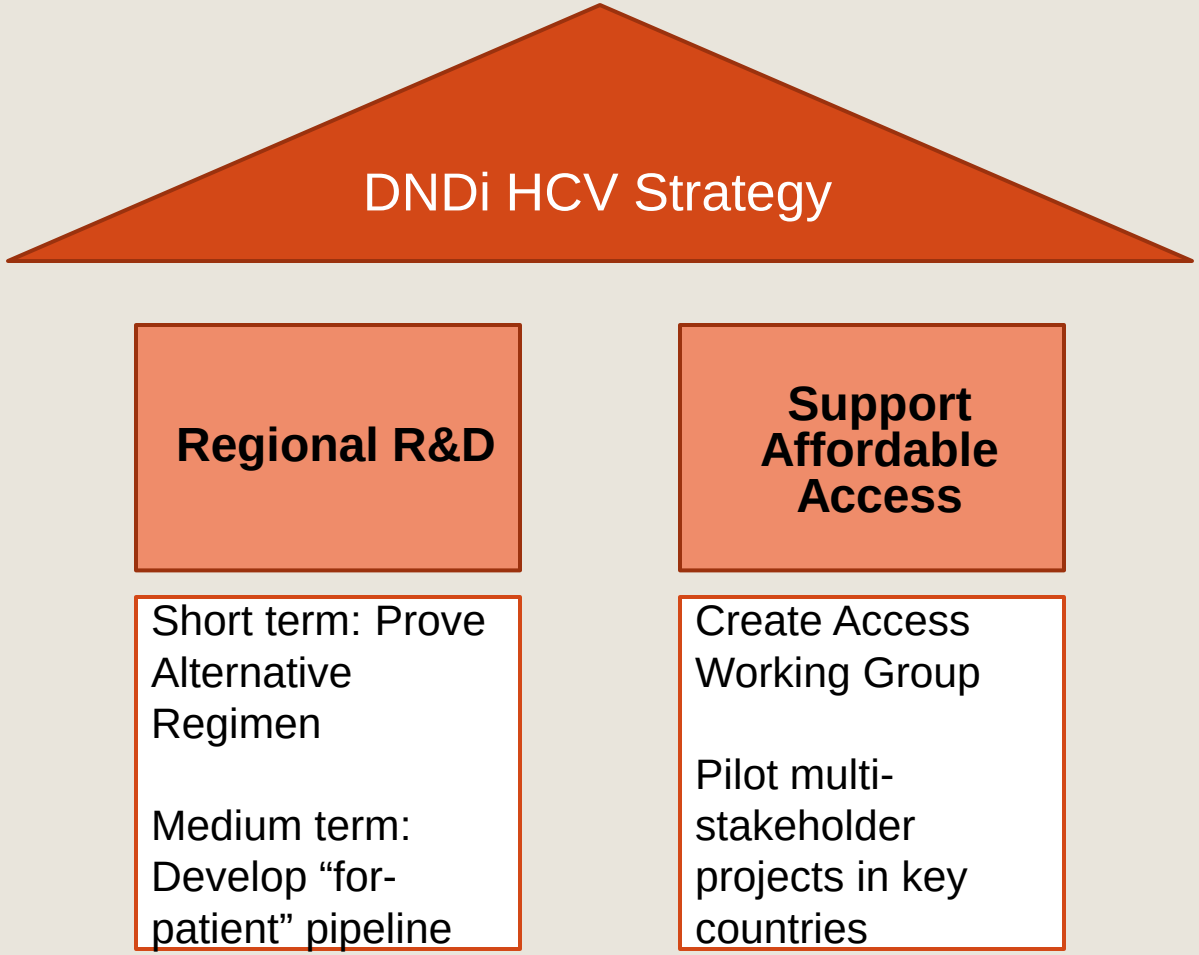
Public health interventions in MICs –

- HCV kills. But HCV infection is curable, and the liver disease is reversible
- We need to reduce the incidence, prevalence, morbidity or mortality of hepatitis C. The time to act is now.
- A comprehensive public health approach requires a concerted effort from multiple stakeholders: governments, manufacturers, civil society/activist groups, IP specialists, key leaders in hepatology and infectious diseases, and public health institutions
- DNDi and partners are prepared to collaborate to address the hepatitis C challenge in Malaysia and Thailand

Public health approaches using DAAs



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Thank You

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