

Hepatitis C 2014: New Successes, New Challenges

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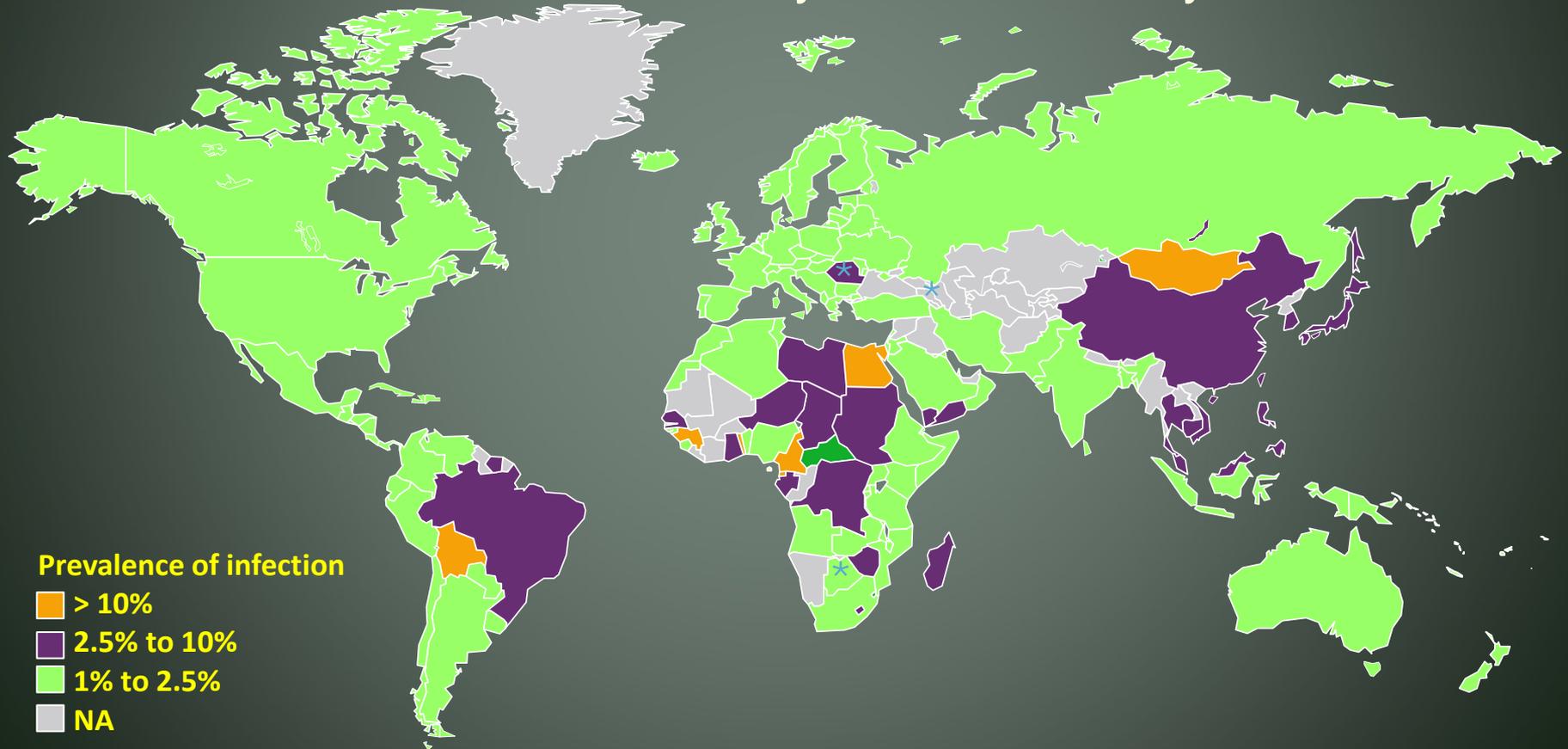
St. Joseph's Hospital and Medical Center

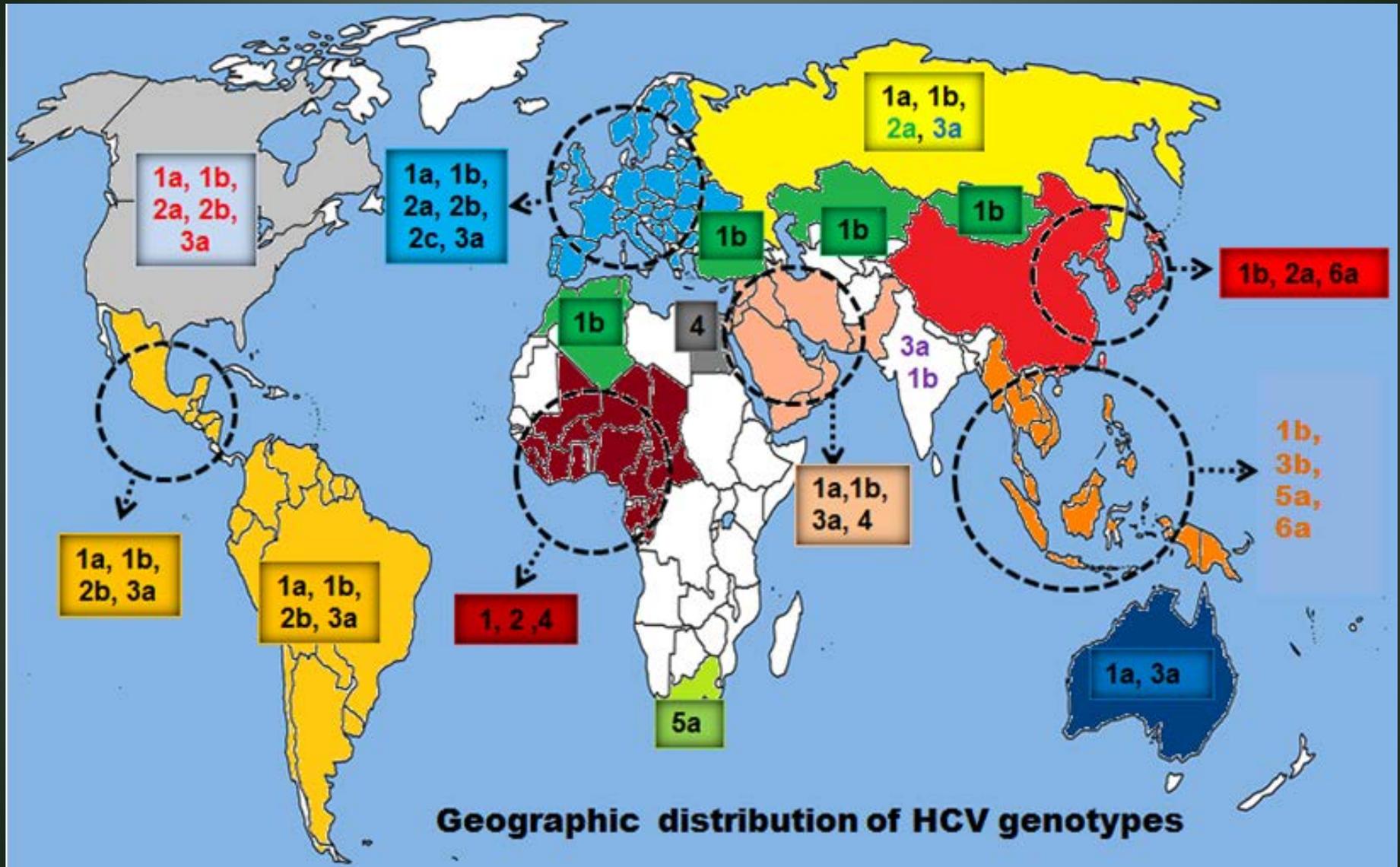
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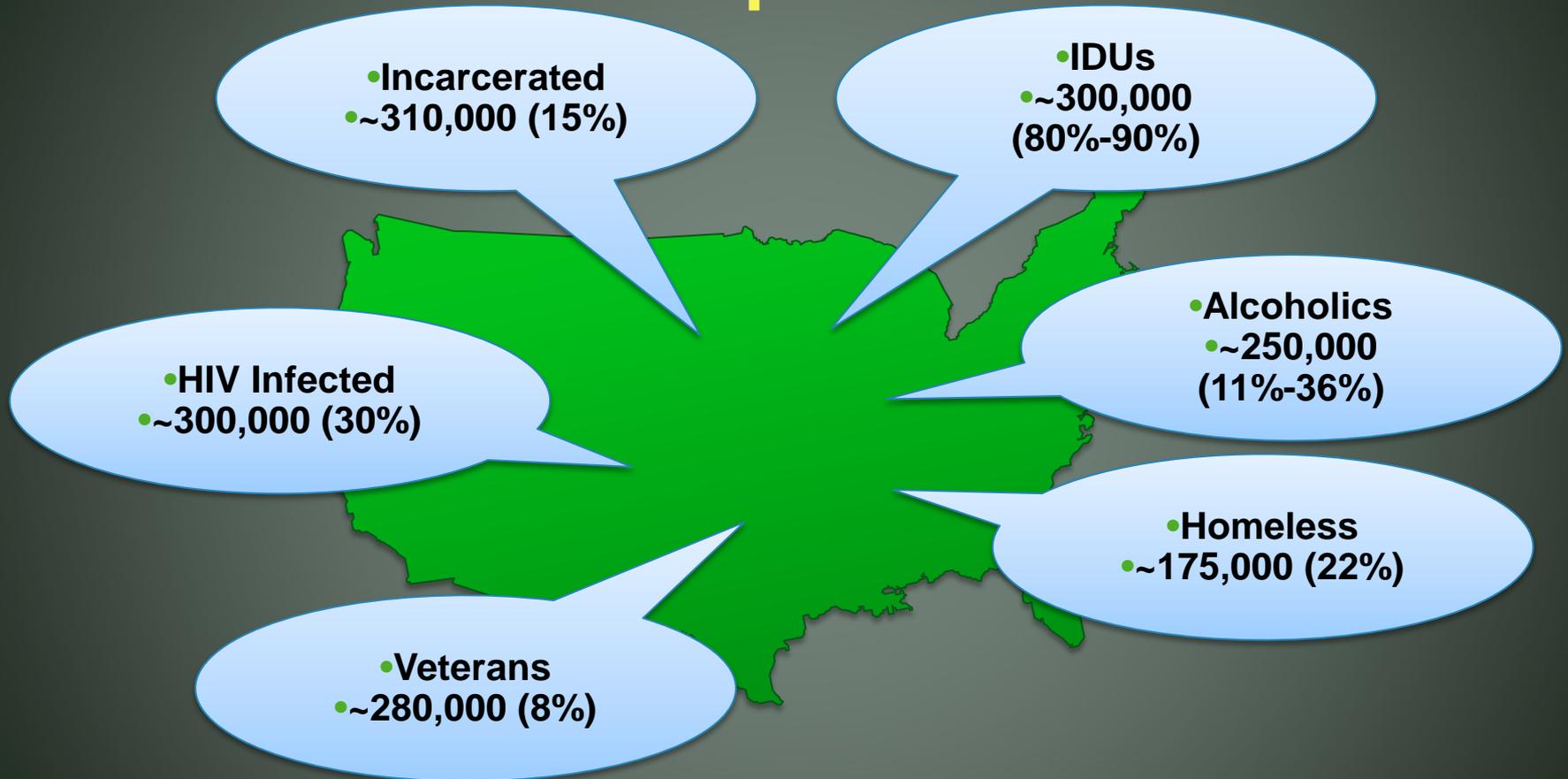
HCV Infection Worldwide

- 170 million persons with HCV
- 3-4 million newly infected each year

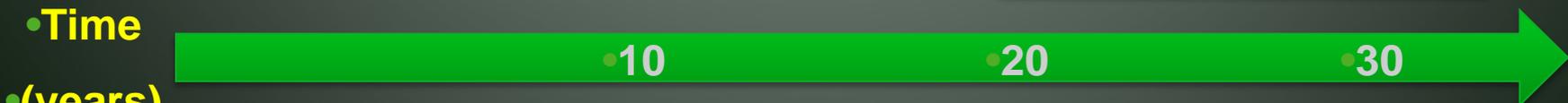
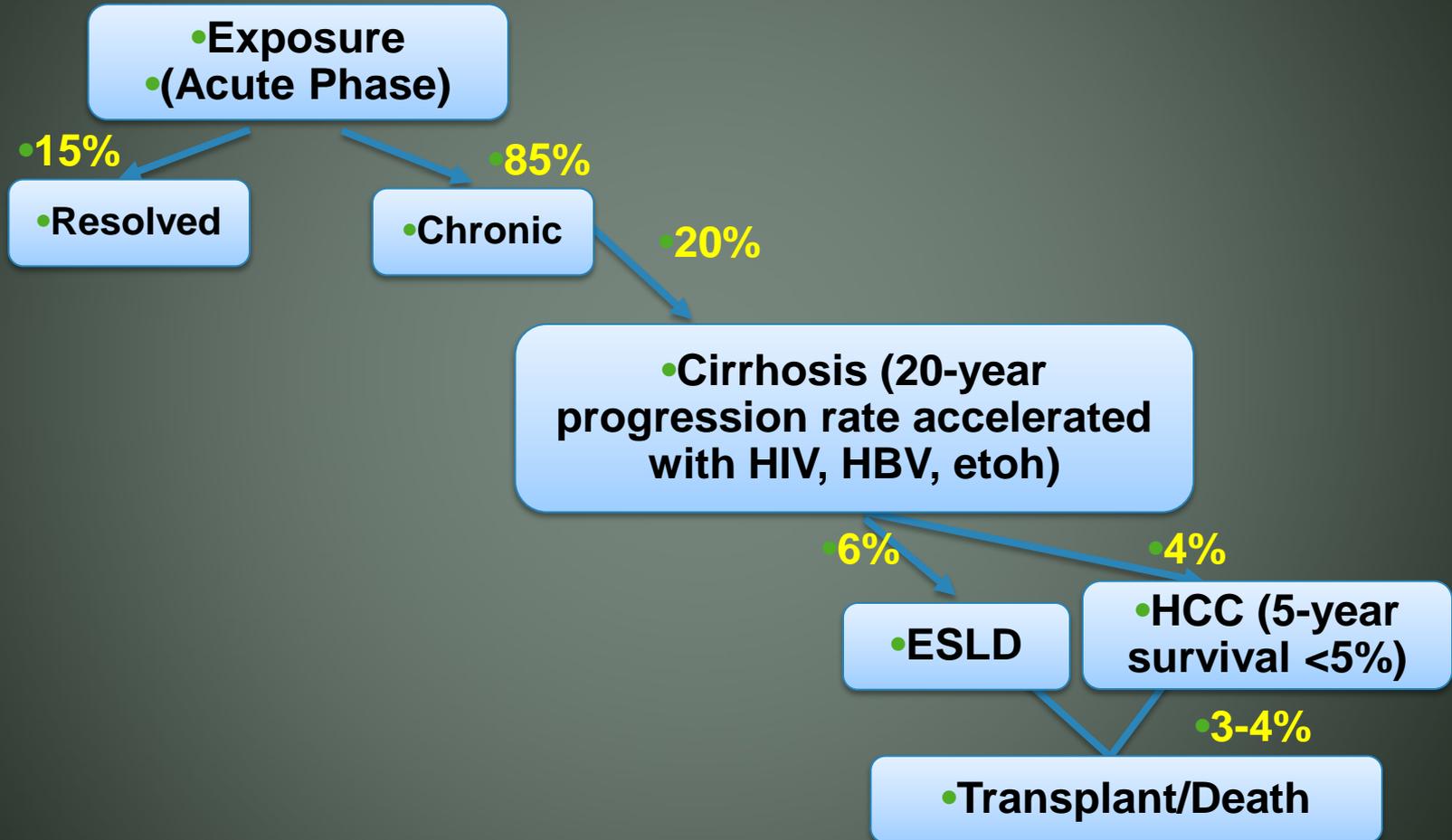




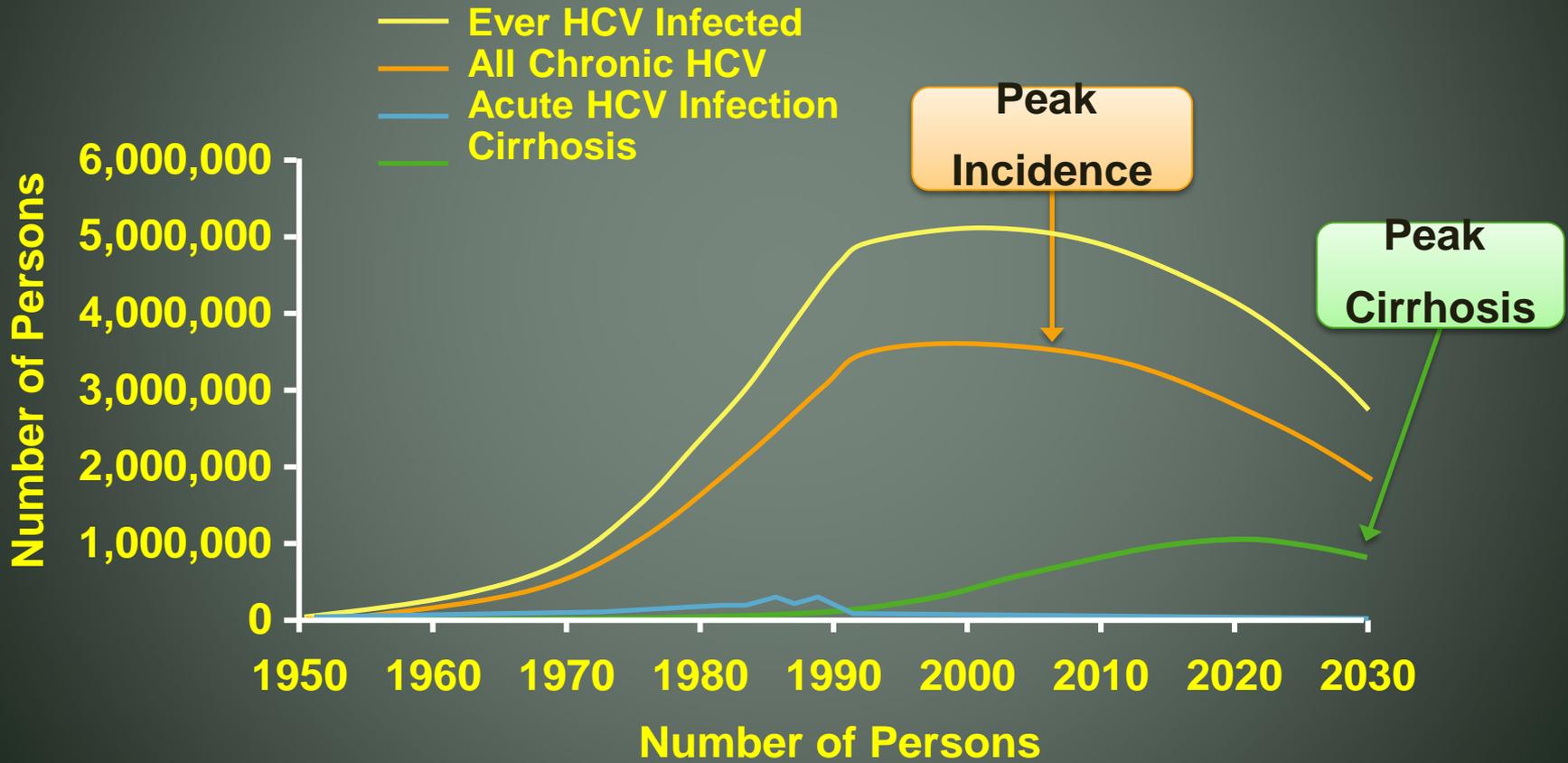
HCV Prevalence in High-Risk US Populations



HCV Infection: Natural Disease Progression



The Changing Face of HCV in the US



1998 – 2012: HCV Testing Recommendations in United States

- **CDC recommendations (1998)**
 - Ever injected illegal drugs
 - Received clotting factors made before 1987
 - Received blood/organs before July 1992
 - Ever on chronic hemodialysis
 - Evidence of liver disease (elevated ALT)
 - Infants born to HCV infected mothers
 - HIV infection

National Hepatitis C Prevention Strategy

2001



SAFER • HEALTHIER • PEOPLE™

Rationale for Birth Cohort Screening

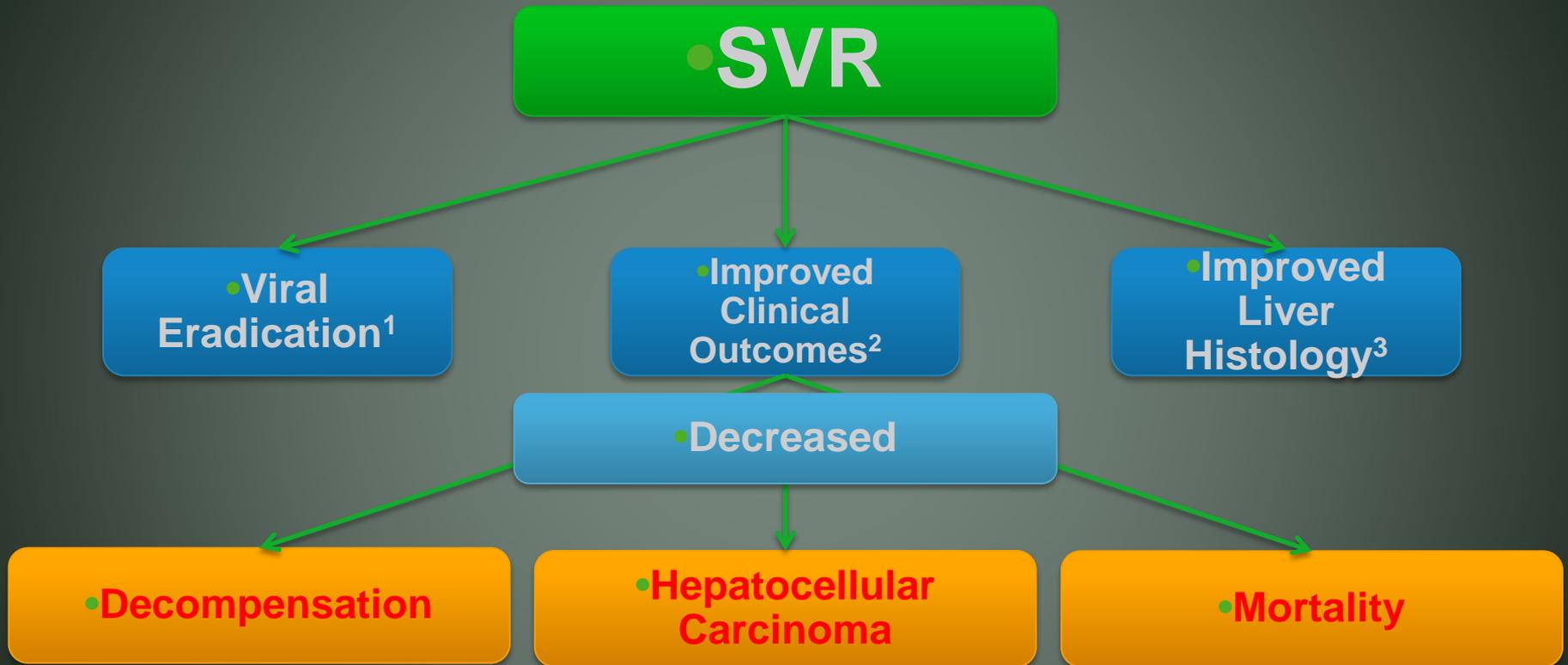
- Chronic HCV prevalence, US (all persons)
 - 1.3% (3.2 million)
- 65.6% of all infected persons in the U.S. were born between 1945-1964
 - Overall prevalence, 4.3%
 - Men 6.2%
 - Black Americans, 9.4%
 - Black American men, 13.6%



CDC 2012: Recommendation of HCV Screening and Linkage to Care

- Summer, 2012: Revise CDC guidelines to promote early detection
 - Confirm active HCV infection (HCV PCR, core antigen)
 - Routine and periodic testing of persons with transmission risks (e.g. IDU)
 - Routine one-time testing of subpopulations of high prevalence (e.g., birth cohort 1946-1964) of HCV disease
 - Integrate HCV and HIV screening in STD clinics, drug outreach, prisons
- Improve training of clinicians in viral hepatitis screening, management, and care
- Support models and standards of care that promote linkage of HCV screening with medical management and treatment services (ECHO)

Sustained Virologic Response (SVR) Leads to Improved Outcome

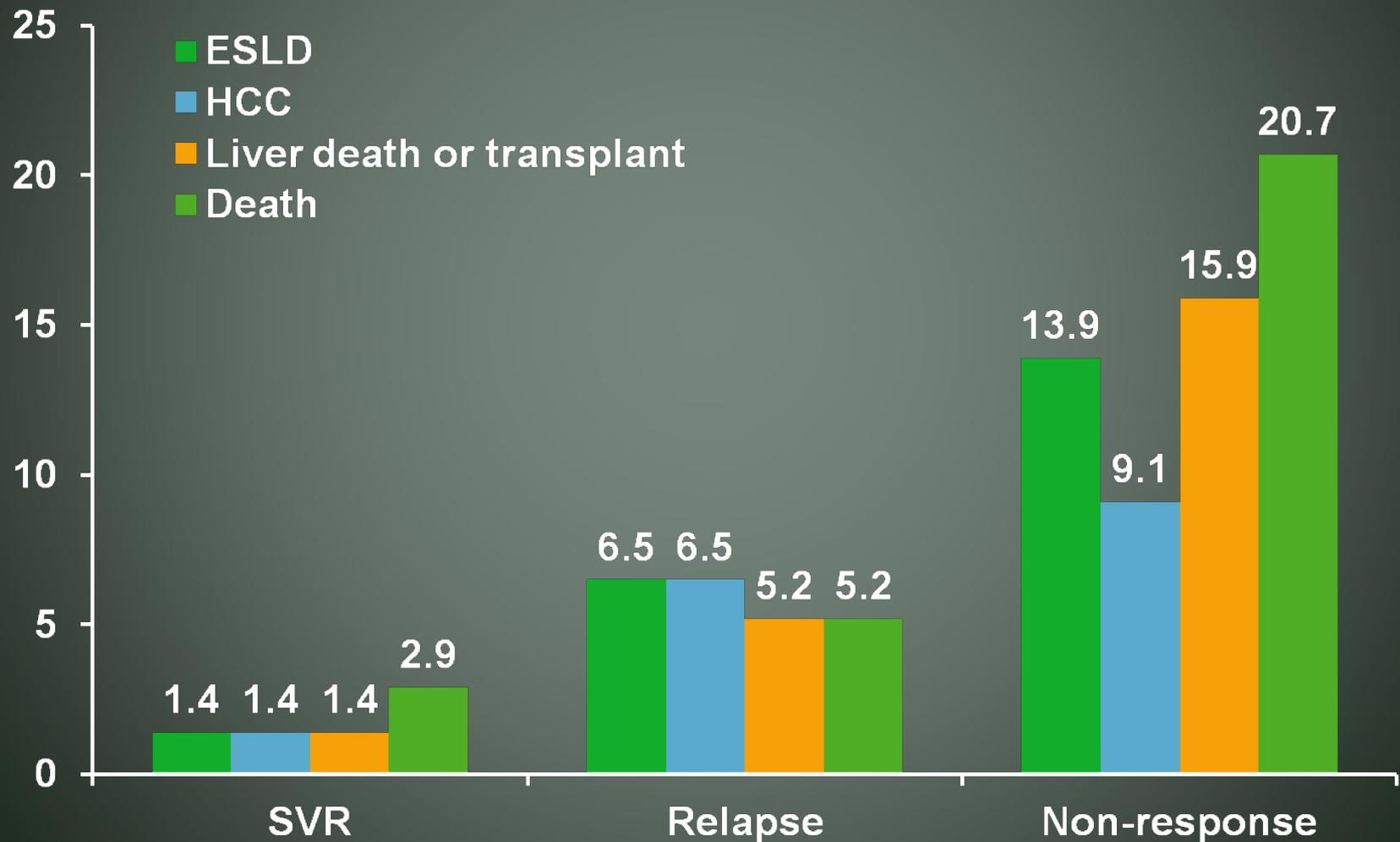


•1. Maylin S, et al. Gastroenterology. 2008;135:821-829.

•2. Poynard T, et al. Gastroenterology. 2002;122:1303-1313.

•3. Veldt BJ, et al. Ann Intern Med. 2007;147:677-684.

SVR Is Associated with Lower Incidence of ESLD, HCC or Death: Results from the HALT-C Trial



Telaprevir or Boceprevir + PegIFN/RBV SVR in Treatment Naïve HCV G1 “1st Gen Protease Inhibitors”

	TVR (ADVANCE)		BOC (SPRINT-2)	
	TVR12/PR RGT 750 mg q8h	PEG/R	BOC/PR RGT (non-AA/AA) 800 mg tid	PEG/R (non-AA/AA)
SVR	75%	44%	67/42%	40/23%

Jacobson I et al, NEJM 2011; 364:2405-2416
Poordad F et al, NEJM 2011; 364:1195-1206

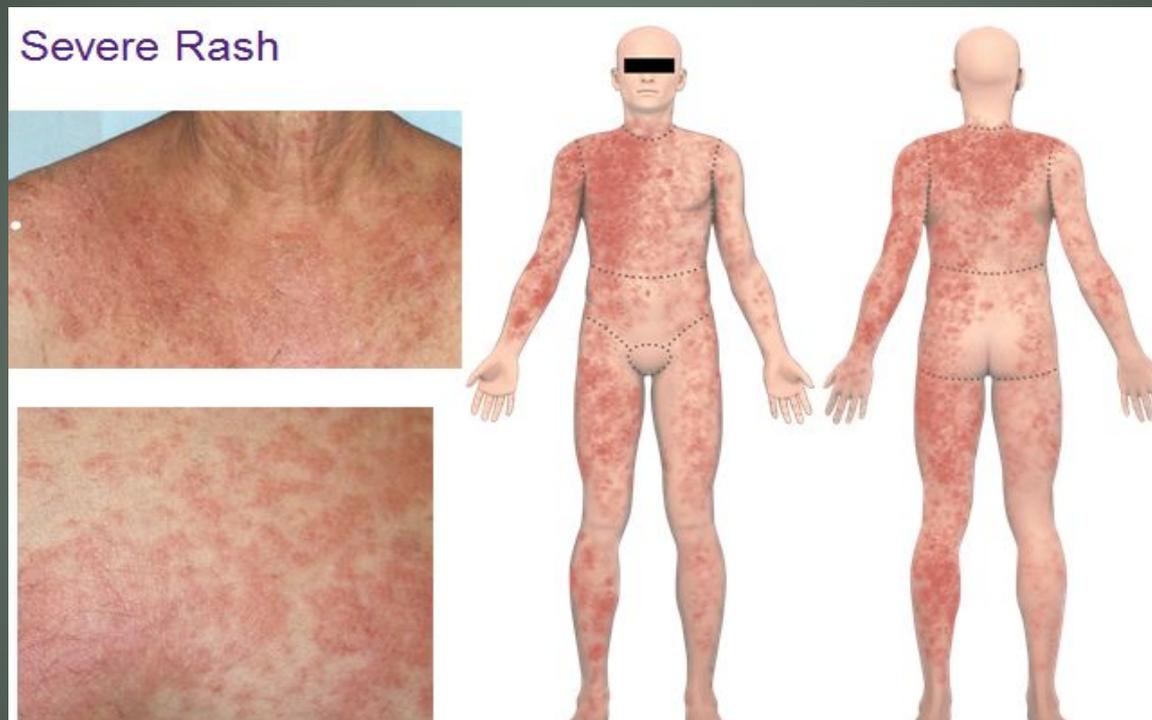
Issues with 1st Generation PIs: Toxicities

(genotype 1 only; given with PEG and ribavirin)

	ADVANCE (TVR)		SPRINT-2 (BOC)	
	TVR12/PR	PR	BOC-RGT	PR
D/C for AEs	10%	7%	12%	16%
D/C for rash	7%	1%	--	--
Anemia (<10/<8.5 g/dL)	36%/9%	14%/2%	45%/5%	26%/4%

The 1st generation PI's significantly increased SVR rates for genotype 1 patients but...

Telaprevir: Severe Rash



- Generalized rash, or rash with vesicles, bullae, or ulcerations
- No Stevens-Johnson Syndrome/DRESS
- Stop telaprevir, if no improvement in 7 days, stop PegIFN + RBV
- Do not reintroduce telaprevir
- If no improvement, refer to Dermatologist

Stevens-Johnson Syndrome (SJS)/Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

- SJS: Fever, target lesions, mucosal erosions/ulcerations
- Drug rash with eosinophilia and systemic symptoms
 - Rash, fever, facial edema, internal organ involvement
 - \pm Eosinophilia
- Urgent Dermatology referral



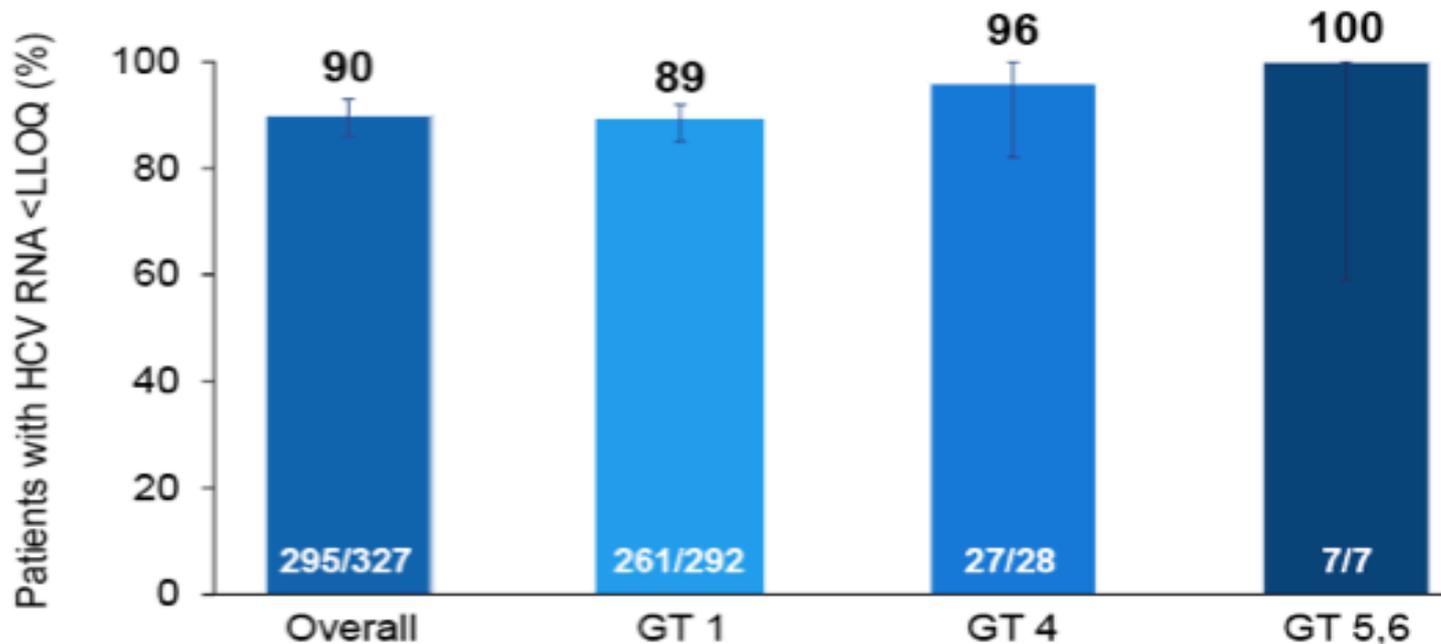
“Real world” experience with boceprevir or telaprevir + PegIFN/RBV in an observational cohort at academic and community sites: HCV-TARGET

Main issues: Severe anemias and rashes

	Boceprevir (n=262)	Telaprevir (n=838)
Male sex	60.3%	60.7%
Median age, years (range)	56 (20-76)	56 (18-75)
Black race	15.7%	15.9%
Genotype 1, no subtype	22.1%	22.3%
Cirrhosis	29.8%	45%
SVR, Treatment-naïve patients	58%	61%
Premature Discontinuations	41.6%	34.7%
Epoetin alfa use	41%	38%
Transfusion	10%	10%
Skin Rash	32%	63%
Serious Adverse Events (SAE)	15%	11%

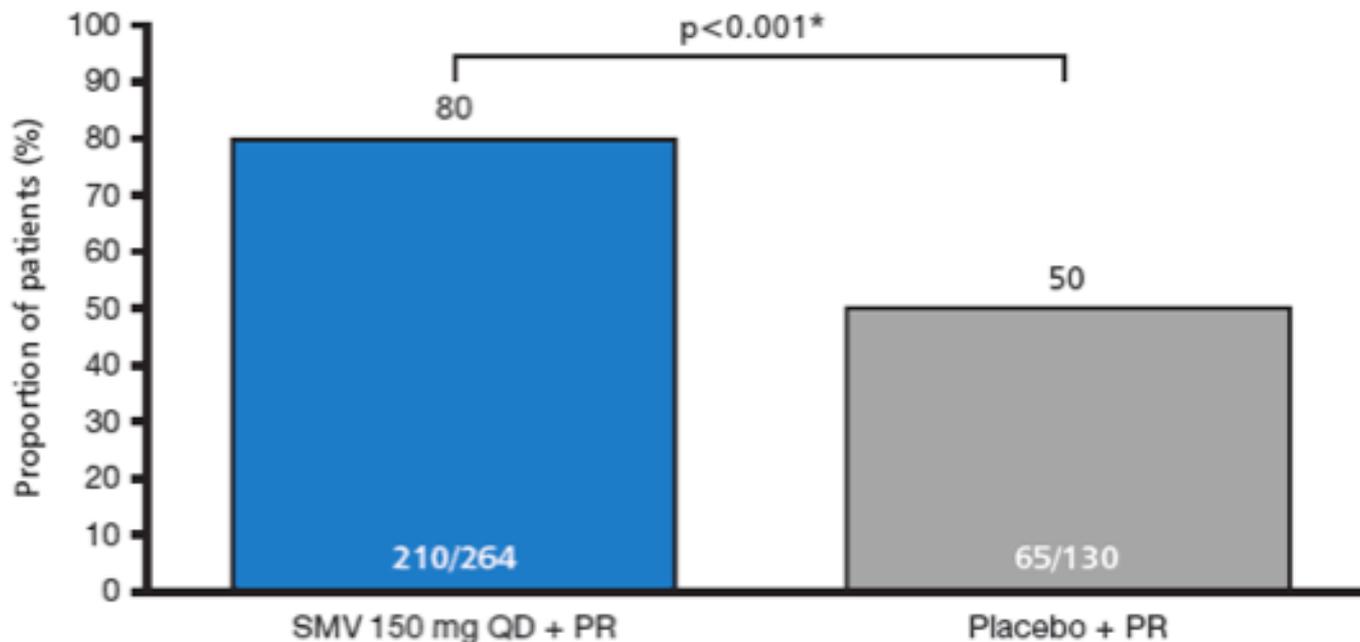
NEUTRINO Study: Sofosbuvir + PegIFN/RBV for 12 Weeks: 90% SVR₁₂ in Treatment-Naïve HCV Genotypes 1, 4, 5, and 6

Results: SVR12 by HCV Genotype



QUEST-1 (Phase III) Study: Simeprevir (TMC435) + PegIFN/RBV HCV G1 Treatment-Naïve Patients

FIGURE 2: Sustained virological response (SVR12).

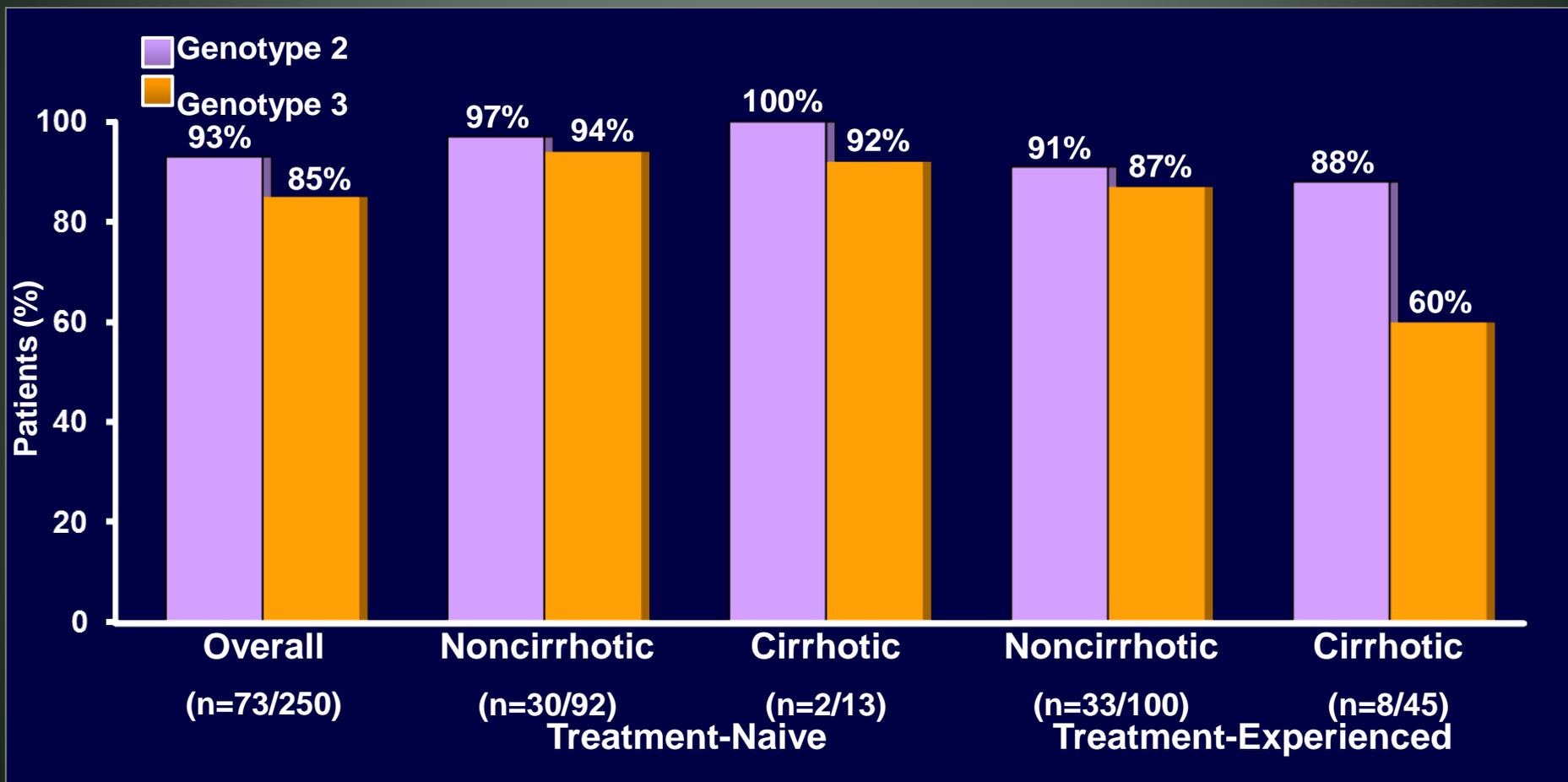


*controlling for stratification factors.

PR, peginterferon α -2a + ribavirin; SVR12, sustained virological response (HCV RNA undetectable) 12 weeks after planned treatment end.

Interferon-Free Regimens

VALENCE Trial: SVR12 Rates in HCV Genotype 2 or 3 Sofosbuvir + ribavirin 12/24 weeks



No resistance detected in patients with relapse.

Zeuzem S, et al. *Hepatology*. 2013;58(suppl 1):733A-734A. Abstract 1085.

HIGHLIGHTS OF PRESCRIBING INFORMATION FOR SOFOSBUVIR:

- One 400 mg tablet taken once daily with or without food.
- Sofosbuvir efficacy has been established in genotype 1, 2, 3 or 4 infection, including those with HCC meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1.
- HCV Mono-infected and HCV/HIV-1 Treatment Duration:
 - Genotype 1 or 4 Sofosbuvir + P/R X 12 weeks
 - Genotype 2 Sofosbuvir + ribavirin 12 weeks
 - Genotype 3 Sofosbuvir + ribavirin 24 weeks
- Sofosbuvir in combination with ribavirin for 24 weeks can be considered for genotype 1 who are interferon ineligible.
- A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease.

HIGHLIGHTS OF PRESCRIBING INFORMATION FOR SIMEPREVIR:

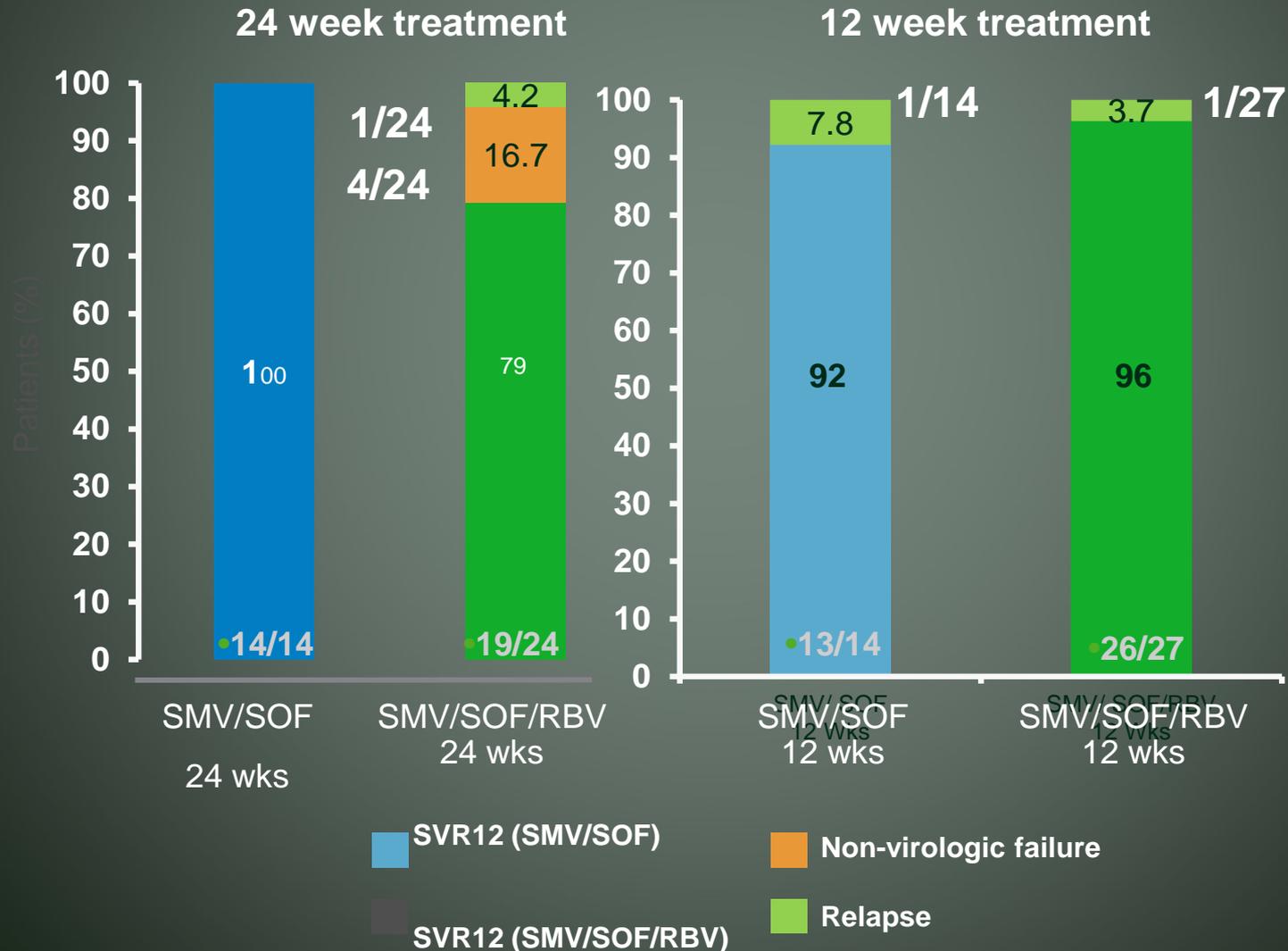
- One 150 mg capsule taken once daily with food.
- TN+TR (incl cirrhosis): S+P+R X12 weeks then 12 weeks P+R
- Partial+Nulls (incl cirr): S+P+RX 12 weeks then 36 weeks P+R
- Screen genotype 1a for the NS3 Q80K polymorphism at baseline .
- Treatment Week 4, 12 and 24 $>$ or $=$ 25 IU/mL, D/C S+P+R
- Use sun protection measures and limit sun exposure
- ***BUT...Most utilization so far is with sofosbuvir and NOT with this FDA approved interferon – based regimen***

SVR results of a once-daily regimen of **simeprevir** (TMC435) plus **sofosbuvir** (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The **COSMOS** study

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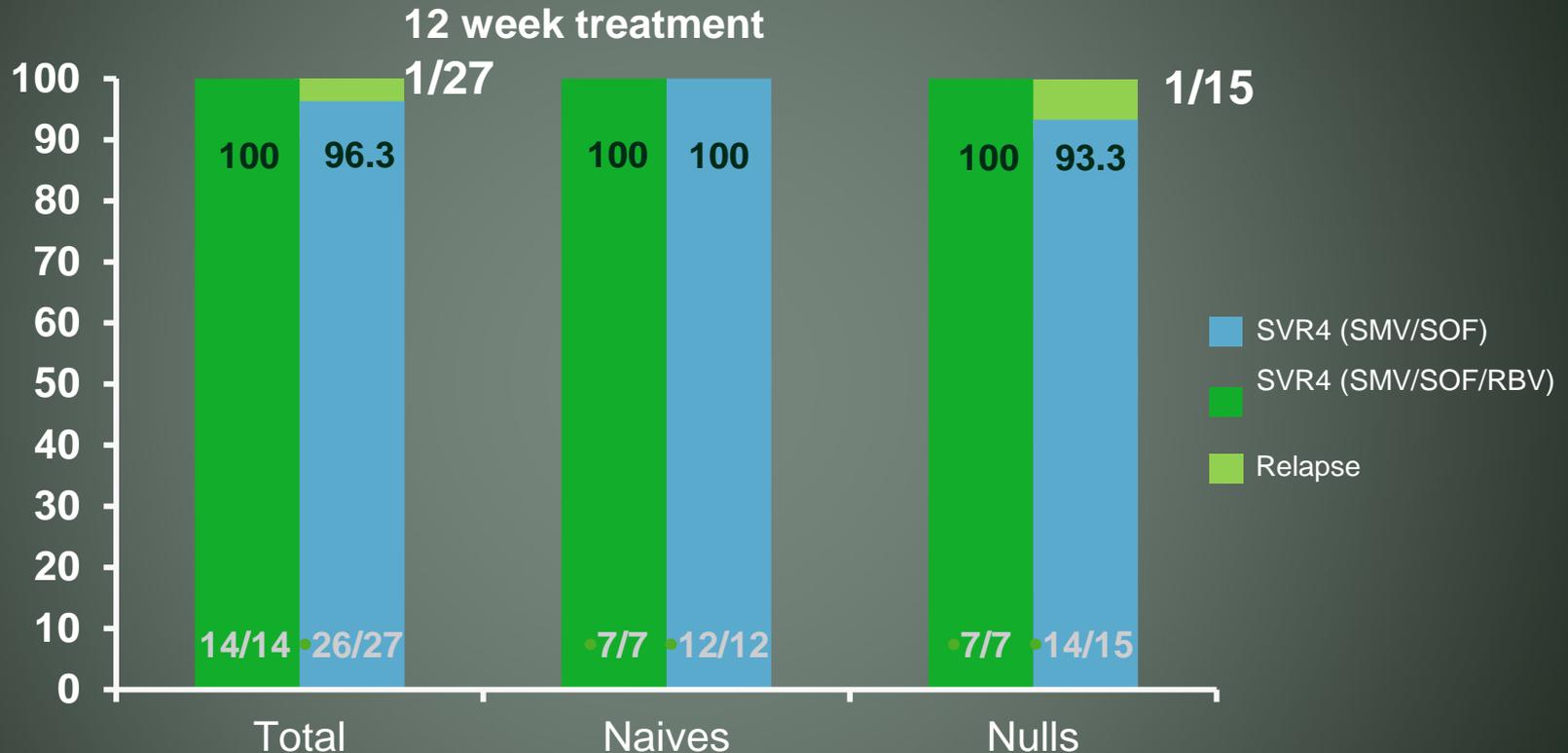
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Cohort 1: Null responders (F0-2)*



*ITT population

Cohort 2: Naïve and prior null responders (F3-4): Interim analysis, SVR4



There were 9 naïve and 9 null responders METAVIR F4 patients
 The only relapser was a F4 prior null responder

**HCV Treatment Guidelines
AASLD
2014**

Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection or Who Experienced Relapse after Prior PEG/RBV Therapy, by HCV Genotype

Genotype	Recommended	Alternative	NOT Recommended
1	<p>IFN eligible: SOF + PEG/RBV x 12 weeks</p> <p>IFN ineligible [1]: SOF + SMV ± RBV x 12 weeks</p>	<p>IFN eligible: SMV x 12 weeks + PEG/RBV x 24 weeks*</p> <p>IFN ineligible [1]: SOF + RBV x 24 weeks</p>	<p>TVR + PEG/RBV x 24 or 48 weeks (RGT)</p> <p>BOC + PEG/RBV x 28 or 48 weeks (RGT)</p> <p>PEG/RBV x 48 weeks</p> <p>Monotherapy with PEG, RBV, or a DAA Do not treat <u>decompensated cirrhosis</u> [2] with PEG or SMV</p>
2	SOF + RBV x 12 weeks	None	<p>PEG/RBV x 24 weeks</p> <p>Monotherapy with PEG, RBV, or a DAA</p> <p>Any regimen with TVR, BOC, or SMV</p>
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	<p>PEG/RBV x 24-48 weeks</p> <p>Monotherapy with PEG, RBV, or a DAA</p> <p>Any regimen with TVR, BOC, or SMV</p>
4	<p>IFN eligible: SOF + PEG/RBV x 12 weeks</p> <p>IFN ineligible [1]: SOF + RBV x 24 weeks</p>	SMV x 12 weeks + PEG/RBV x 24-48 weeks	<p>PEG/RBV x 48 weeks</p> <p>Monotherapy with PEG, RBV, or a DAA</p> <p>Any regimen with TVR or BOC</p>
5 or 6	SOF + PEG/RBV x 12 weeks	PEG/RBV x 48 weeks	<p>Monotherapy with PEG, RBV, or a DAA</p> <p>Any regimen with TVR or BOC</p>

For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.



NDC 61950-1501-1 28 tablets

Sovaldi™
(sofosbuvir) Tablets
400 mg

Note to pharmacist:
Do not cover ALLIANT box with pharmacy label.

**ALLIANT. Find out about medications that
should NOT be taken with Sovaldi™.**



Launch trajectories (vs Incivek)

- ISI \$5Bn scenario
- Incivek
- - Est. Incivek + Victrelis
- Sovaldi TRx



Genotype 1 FDA Approved & IFN-free regimens in development – actual study data linked to below the table

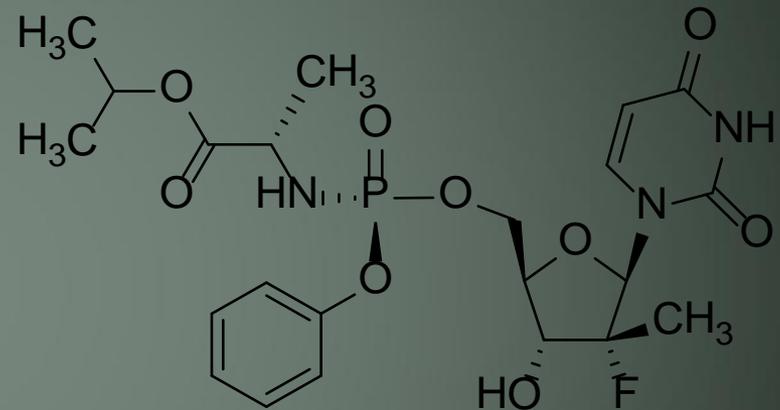
Gilead	Sofosbuvir+Ledipasvir	Phase 3	93-99%	12-24 weeks
	Sofosbuvir+Ledipasvir	Phase 3	95%	8 weeks
	Sofosbuvir+Ribavirin	FDA approved Dec/13 for mono & coinfectd	72% Overall - SVR 76% (HIV-coinfectd PHOTON Study) - 50-84% (monoinfectd) several small studies-links below	24 weeks 12 weeks
	Sofosbuvir+PegINF/Rbv (Mono & HIV coinfectd)	FDA approved Dec/13 for mono & coinfectd	89% overall - 80% for patients with cirrhosis - 92% for patients without cirrhosis	12 weeks
Abbvie	ABT-450+ABT-267+ABT-333+Rbv	Phase 3	92-99%	12 weeks
Janssen	Sofosbuvir+Simeprevir	Phase 2	96-100%	12 weeks
BMS	Daclatasvir+Sofosbuvir (treatment-naives & protease experienced)	Phase 2 results In phase 3 now	100%	12-24 weeks
BMS	Daclatasvir+Asunaprevir+BMS325 (with & without Rbv in phase 3)	Phase 2 results In phase 3 now	94%	12 weeks
Merck	MK-5172+MK8742	Phase 2	100%	12 weeks
GT1b BMS	Daclatasvir + Asunaprevir	Phase 3 results	84-87% SVR	24 weeks
Gt1b Abbvie	ABT-450/r + ABT-267	Phase 2 results	95% SVR treat-naives (n=40) 90% SVR prior null responders (n=40)	12 weeks 12 weeks

The “Ideal” HCV Antiviral

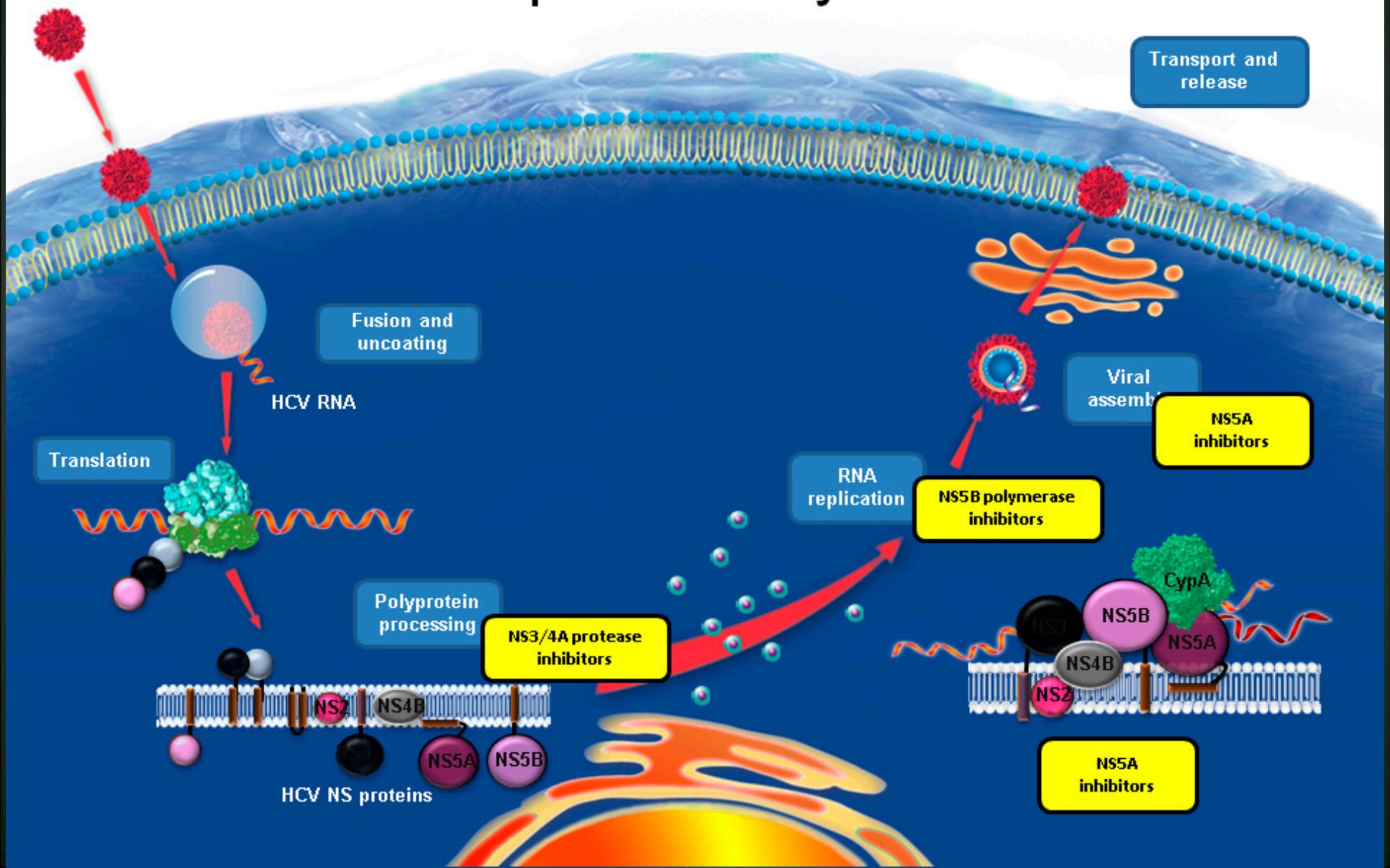
- High Antiviral Activity
- Activity against all genotypes
- High barrier to resistance
- Simple application (few pills, QD dosing)
- Highly favorable safety profile
- No Drug-Drug interactions
- Short and finite duration of therapy
- Efficacious in all patient populations
- Cure (very high SVR rates)
- High value

Sofosbuvir

- HCV-specific nucleotide polymerase inhibitor (chain terminator)
- Antiviral activity and clinical efficacy in HCV GT 1–6
- ◆ High barrier to resistance
- ◆ Once-daily, oral, 400-mg tablet
- Approved for use in combination with other agents for the treatment of chronic HCV
- Safety established in >3000 patients including patients with compensated cirrhosis



Potential Therapeutic Targets in the HCV Replication Cycle



Direct Acting Antivirals

- Simeprevir NS3/4A Protease Inhibitor
- Asunaprevir NS3/4A Protease Inhibitor
- ABT-450 NS3/4A Protease Inhibitor
- MK-5172 NS3/4A Protease Inhibitor
- MK-8742 NS5A Inhibitor
- Ledipasvir NS5A Inhibitor
- Daclatasvir NS5A Inhibitor
- Ombitasvir (ABT-267) NS5A Inhibitor
- GS-5816 NS5A inhibitor
- Dasabuvir (ABT-333) NS5B Non-nucleoside Polymerase Inhibitor
- Sofosbuvir NS5B Nucleotide Polymerase Inhibitor

Gilead Files for U.S. Approval of Ledipasvir/Sofosbuvir Fixed-Dose Combination Tablet for Genotype 1 Hepatitis C

-- If Approved, Fixed-Dose Combination Would be First Oral Treatment Regimen for Patients with Genotype 1 HCV Infection, Eliminating Need for Both Interferon and Ribavirin –

FOSTER CITY, Calif.--(BUSINESS WIRE)--Feb. 10, 2014-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the company has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for a once-daily fixed-dose combination of the NS5A inhibitor ledipasvir (LDV) 90 mg and the nucleotide analog polymerase inhibitor sofosbuvir (SOF) 400 mg for the treatment of chronic hepatitis C genotype 1 infection in adults. The data submitted in the NDA support the use of LDV/SOF in patients with genotype 1 hepatitis C virus (HCV) infection, with a treatment duration of eight or 12 weeks depending on prior treatment history and whether they have cirrhosis. Approximately 75 percent of people infected with HCV in the United States have the genotype 1 strain of the virus.

“Today’s filing brings us one step closer to our goal of offering all patients with hepatitis C a simple, safe and highly effective all-oral treatment regimen,” said Norbert Bischofberger, PhD, Executive Vice President of Research and Development and Chief Scientific Officer. “Based on the data from the Phase 3 ION studies, the LDV/SOF combination may have the potential to cure HCV in genotype 1 patients in as little as eight weeks and without the need for interferon injections or ribavirin.”

The FDA has assigned LDV/SOF a Breakthrough Therapy designation, which is granted to investigational medicines that may offer major advances in treatment over existing options. The NDA for LDV/SOF is supported by three Phase 3 studies, ION-1, ION-2 and ION-3, in which nearly 2,000 genotype 1 HCV patients were randomized to receive the fixed-dose combination, with or without RBV, for treatment durations of eight, 12 or 24 weeks. Trial participants included patients who were treatment-naïve or who had failed previous treatment, including protease inhibitor-based regimens, and also included patients with compensated cirrhosis.

Gilead plans to file for regulatory approval of LDV/SOF in other geographies, including the European Union, in the first quarter of 2014. Gilead has submitted an application to the European Medicines Agency (EMA) for accelerated assessment of LDV/SOF, a designation that is granted to new therapies and medicines of major public health interest. If accepted, accelerated assessment could shorten the EMA’s review time of LDV/SOF by two months, although it does not guarantee a positive opinion from the Committee for Medicinal Products for Human Use or approval by the European Commission.

Interferon ineligible...

Thrombocytopenia

Hypoalbuminemia

Autoimmune Diseases

Psychiatric Diseases

Anemia

Eye diseases

Skin diseases

Previous Interferon Treatment Failure

HCV/HIV Coinfection

The issue will be setting the thresholds

Payer Considerations

What constitutes “interferon ineligible”?

Will interferon even matter by 2015?

Is there any valid medical reason to delay HCV therapy when safe, well-tolerated therapies with >95% cure rates are available today?

Should an effort be made to restrict the prescribing of HCV treatment only to certain providers or specialists?

Does the degree of fibrosis, assessed either by biopsy or elastography, matter any more?

Will patients accept that their insurance simply cannot afford to treat them?

What has changed?

- Mainstream HCV therapy of past two years now not recommended, being removed from formularies
- Side effect management now negligible
- Compliance /adherence now paramount
- Cost has eclipsed efficacy in the discussion
- The value equation:

$$\text{Value} = \frac{\text{quality or efficacy}}{\text{cost}}$$

New Hepatitis Drug Worth \$1,000 per Pill Questioned by Democrats

By [Julie S](#) | Mar 22, 2014 10:22 AM EDT

Democratic members of the Congress have issued a letter to the makers of a drug used to cure hepatitis C to question its very expensive price.

The letter was sent by Henry Waxman of California, Frank Pallone Jr. of New Jersey and Diana DeGette of Colorado. It was addressed to Gilead Sciences, the maker of the drug referred to as Sovaldi.

“Our concern is that a treatment will not cure patients if they cannot afford it,” the congressmen wrote in their letter, as reported by the [New York Times](#).

On the other hand, Gilead Sciences explained that the price for Sovaldi is the fairest price that they could offer for the drug. The company’s executive vice president for corporate and medical affairs, Gregg Alton, expressed that they are willing to meet with the members of the Congress to settle the issue.

“We think the price is fair,” he said in an interview with the *N.Y Times*. “It will save the system money long term.”

It is estimated that three to four million Americans are suffering from hepatitis C. If left untreated, it could lead to more serious infections such as cirrhosis and liver cancer. Sovaldi was approved by the Food and Drug Administration in December 2013 and could cure 80 percent of hepatitis C cases in a matter of 12 weeks. This is a higher cure rate using the least amount of time possible. Treatment using Sovaldi was also noted to induce the least cases of side effects.

However, insurers argue that a 12-week treatment with Sovaldi can cost \$1000 a pill, and this is very expensive.

“It’s unprecedented that we have a drug that is this expensive that this many patients can benefit from,” Dr. Steve Miller told *N.Y Times*. Miller is the chief medical officer for Express Scripts, the largest pharmacy benefits manager. “You have a drug that has the potential to break a lot of the payers.”

- **Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 HCV in interferon ineligible/intolerant individuals**

Hepatology March 28 2014 Accepted Unedited

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Abstract

Background: Treatment guidance for chronic hepatitis C (CHC) released by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) offer two options for interferon-ineligible/intolerant individuals with genotype 1 infection: sofosbuvir/ribavirin (SOF/RBV) for 24 weeks, or sofosbuvir/simeprevir (SOF/SMV) for 12 weeks. A 24-week course of SOF/RBV costs approximately US\$169,000, with sustained virologic response (SVR) rates ranging from 52-84%; 12 weeks of SOF/SMV costs approximately \$150,000, with SVR between 89% and 100%. Because SOF/SMV is currently used off-label, debate exists among physicians and payers about whether it should be prescribed and covered. This paper presents a cost-effectiveness analysis of these two treatment regimens accounting for costs of drugs, treatment-related medical care, re-treatment for individuals who do not achieve SVR, and natural history of continued HCV infection after failed re-treatment. The model uses a lifetime horizon and a societal perspective.

Results: In the base case scenario, SOF/SMV dominated SOF/RBV in a modeled 50-year-old cohort of treatment-naïve and treatment-experienced subjects, excluding those who failed prior therapy with telaprevir or boceprevir. SOF/SMV yielded lower costs and more quality-adjusted life years (QALYs) for the average subject compared to SOF/RBV (\$165,336 and 14.69 QALYs vs. \$243,586 and 14.45 QALYs, respectively). In base case cost-analysis, the SOF/SMV treatment strategy saved \$91,590 per SVR compared to SOF/RBV. Under all one-way sensitivity scenarios, SOF/SMV remained dominant and resulted in cost savings.

Conclusions: These results suggest that a 12-week course of SOF/SMV is a more cost-effective treatment for genotype 1 CHC than 24 weeks of SOF/RBV among interferon-ineligible/intolerant individuals, supporting the AASLD/IDSA guidance and offering implications for both clinical and regulatory decision-making as well as pharmaceutical pricing.

Status of HCV Therapy as of July 2014

No strategy yet for treat now vs. waiting

First generation PI's now obsolete

Interferon becoming obsolete

Biopsy usually unnecessary

Costs are a major challenge

No one wants interferon

No one wants to wait

AASLD vs. FDA?

A moving target

*“We want to treat patients with
what we ourselves would take if we had HCV”*

Where do we go from here...

“The availability of new DAAs will provide unprecedented opportunities for off-label HCV therapies in many patients. These patients will include those who are unwilling to take, or intolerant of, IFN and those in need of HCV therapy with no other treatment options. For many, this will ultimately be tempered by FDA-approved all-oral options, but until that time, patients, prescribers, and payers will struggle in an environment where more questions exist than answers. There are no rules, and thus there will be little consistency. Historical precedent only serves as proof of concept. Hepatitis C therapy is not offered under the Ryan White CARE Act rules, and as a consequence, HCV treatment will certainly become polarized. No standard for the minimal amount of safety and efficacy data exists, and in many cases, providers will make treatment decisions without the support of the FDA or treatment guidelines. Patient communication, critical evaluation of available evidence, and meticulous management of off-label treatment recipients will be of paramount importance as we enter into the next era of on- and off-label DAA therapy.”

Aronsohn, Reau, Jensen; Hepatology, March 1, 2014