Montefiore Einstein
Center for Transplantation

A Hepatitis C Primer for Non-Treaters

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HCV infection: it's personal

CEDARS-SINAI

Achilles A. Demetriou, MD, PhD, Former Chair of Cedars-Sinai Department of Surgery, 1946-2013: Internationally Recognized Liver Surgical Scientist Dies After Fight with Liver Cancer

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Newswise — LOS ANGELES — June 27, 2013 – Achilles A. Demetriou, MD, PhD, an internationally distinguished surgical scientist who spent nearly four decades investigating and treating liver disease, and who led Cedars-Sinai's Department of Surgery to national distinction, has died. He was 67.

MEDIA CONTACT

Available for logged-in reporters only

CHANNELS

Recently Deceased

KEYWORDS

Bioartificial Liver, Liver Disease, Demetriou, Liver Failure

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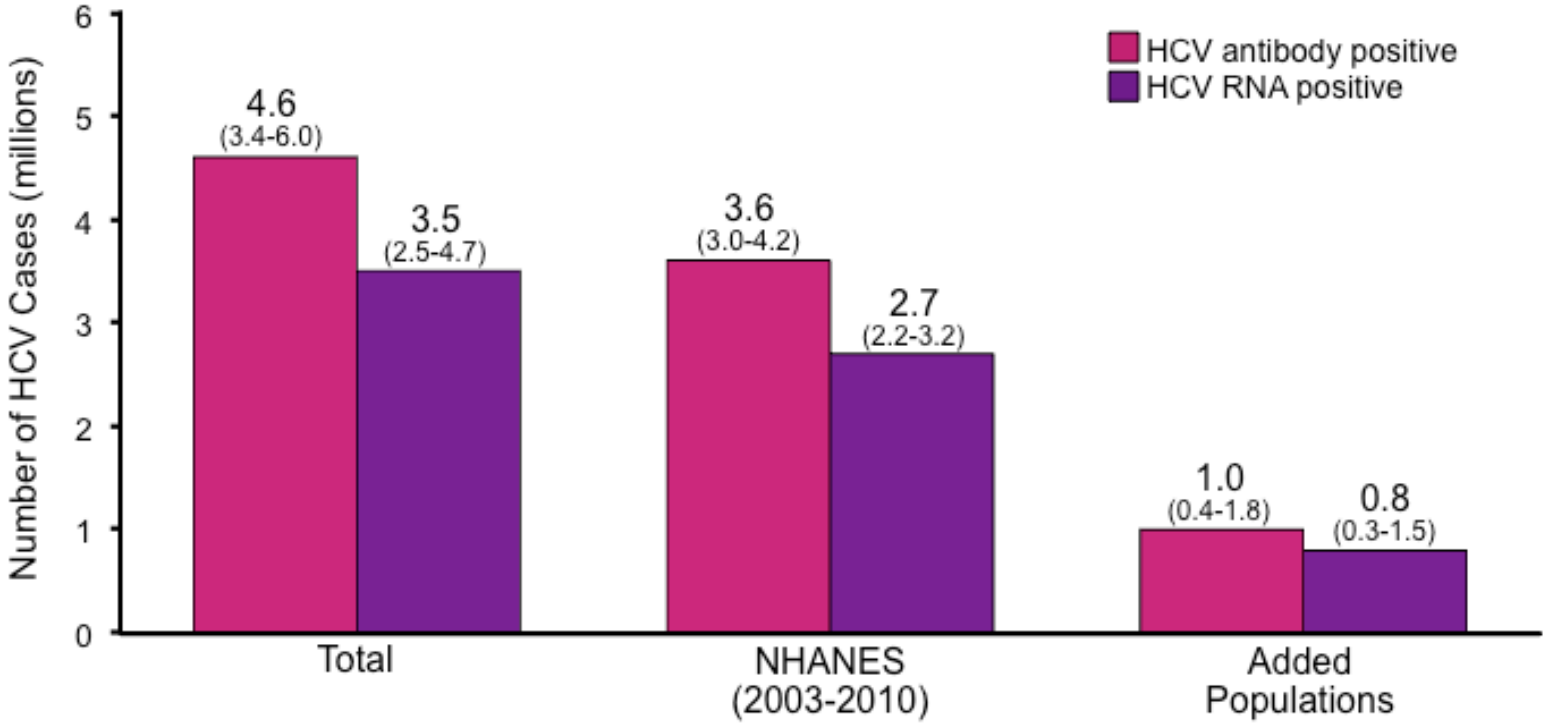
Risk factors for HCV infection

Infection requires viral passage through protective anatomic barriers

- Parenteral and intranasal drug use
- Transfusion of infected blood and blood products (before 1992)
- Other needle sticks: (amateur) tattoo; health-care workers (surgeons); dialysis
- Anal intercourse

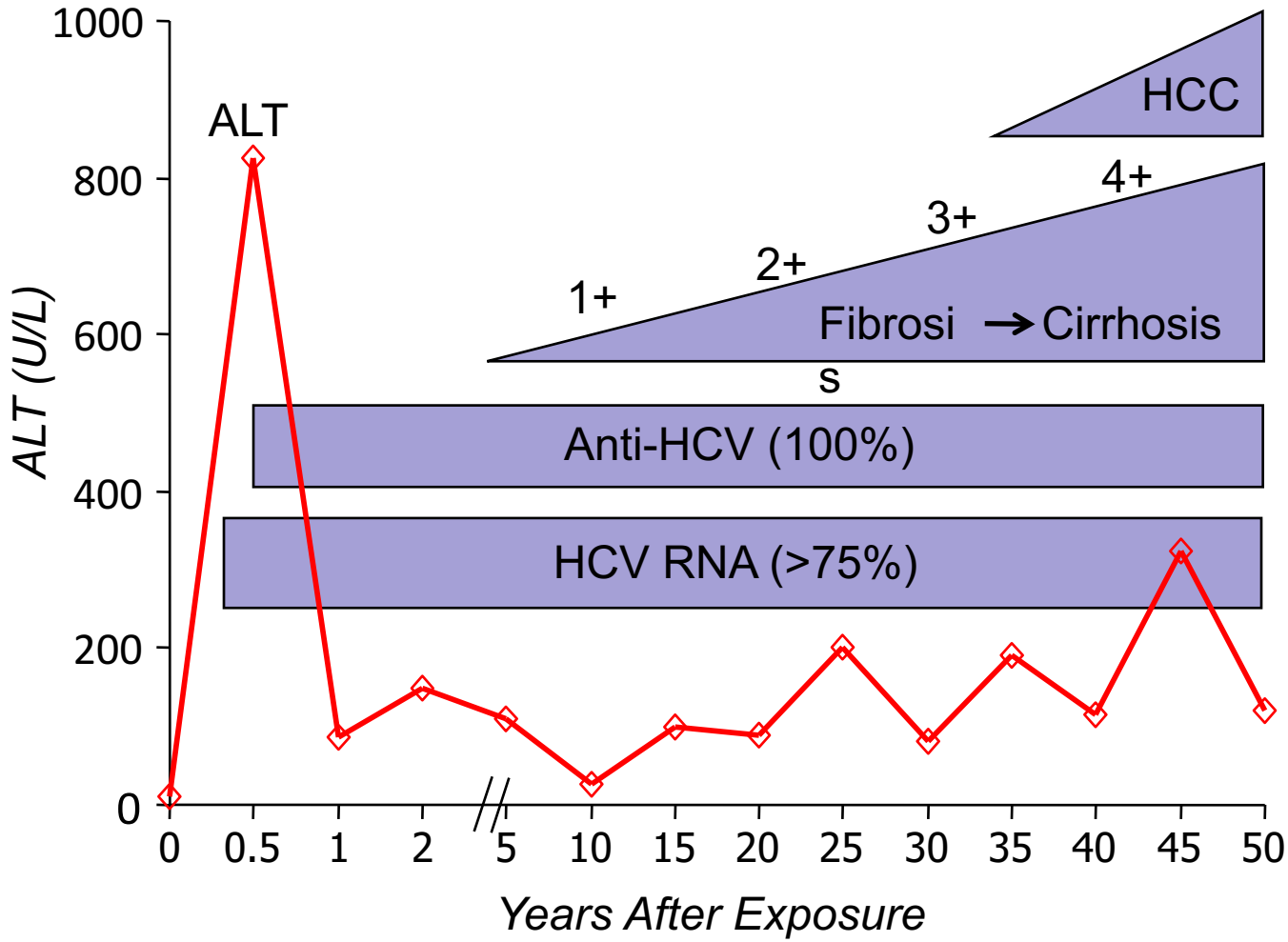
Prevalence of hepatitis C: NHANES

Denniston MM. Ann Intern Med. 2014;160:293-300



Time course of disease progression

Hoofnagle JH. Hepatology. 2002;36:S21-S29.



Annual HCV disease progression

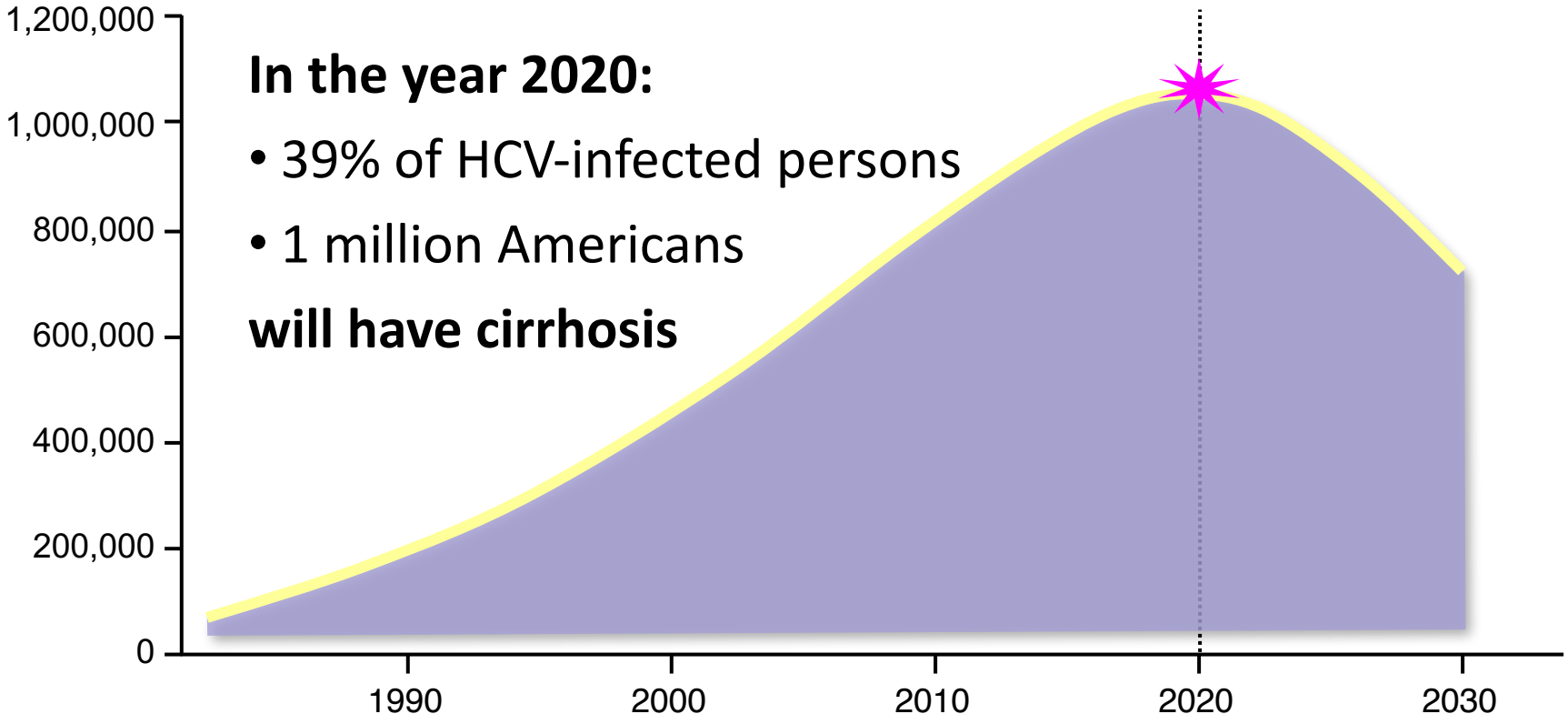
Davis et al. Liver Transpl, 2003;9:331-338

Hornberger et al. J Viral Hepat, 2006;13:377-386

- Compensated cirrhosis, years 1-13: 0.6%
- Compensated cirrhosis, year 14+: 2.3%
- Decompensation: 4.0%
- Cirrhosis to HCC: 4-8%
- Transplantation: 4.3%

Estimated prevalence of cirrhosis

Davis et al. Liver Transpl, 2003;9:331-338



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AASLD & IDSA treatment guidelines

www.hcvguidelines.org

Recommendations for when and in whom to initiate treatment

Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions.

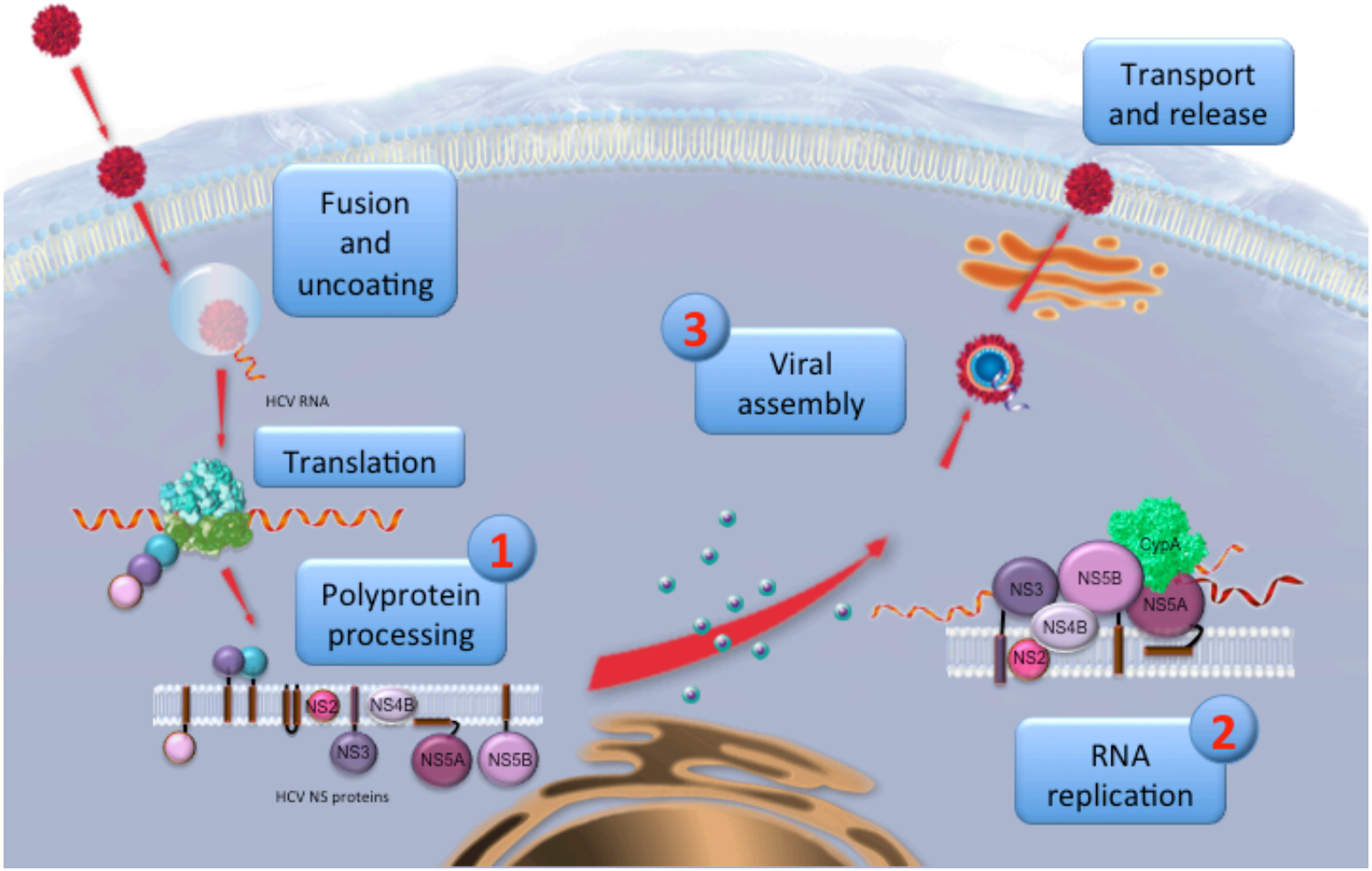
Rating: Class I, Level A

Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir stage F3), those with compensated cirrhosis (Metavir stage F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.

Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications are given high priority.

Ratings: See tables

Hepatitis C virus life cycle



Generic-drug naming conventions

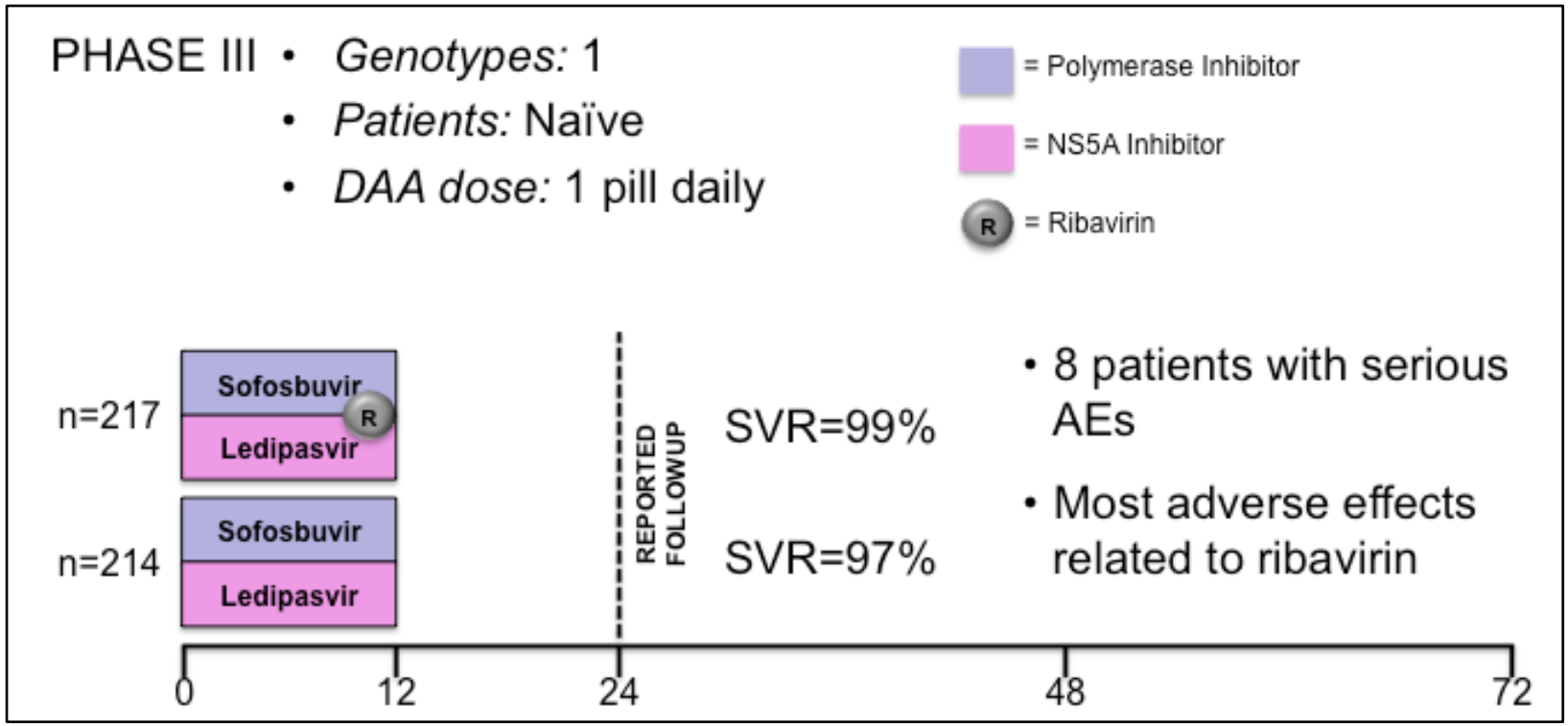
1. *Protease inhibitors:* names end with "PREvir," e.g. simePREvir, paritaPREvir, grazoPREvir
2. *Polymerase inhibitors:* names end with "BUvir," e.g. sofosBUvir, dasaBUvir
3. *NS5A inhibitors:* names end with "ASvir," e.g. ledipASvir, velpatASvir, daclatASvir

FDA-approved all-oral treatment regimens for hepatitis C

1. Epclusa™: *sofosbuvir/velpatasvir*
2. Harvoni™: *sofosbuvir/ledipasvir*
3. Mavyret™: *glecaprevir/pibrentasvir*
4. Technivie™: *paritaprevir/ombitasvir*
5. Viekira Pak™: *paritaprevir/dasabuvir/ombitasvir*
6. Vosevi™: *voxilaprevir/sofosbuvir/velpatasvir*
7. Zepatier™: *grazoprevir/elbasvir*

Phase-3 trial: sofosbuvir/ledipasvir

Afdhal, et al. NEJM, 2014;370:1889



Factors affecting treatment choice

- Insurance approval
- Viral genotype
- Renal function
- Presence of cirrhosis, decompensation
- Treatment history = resistance profile
- Potential drug-drug interactions

AASLD & IDSA treatment guidelines

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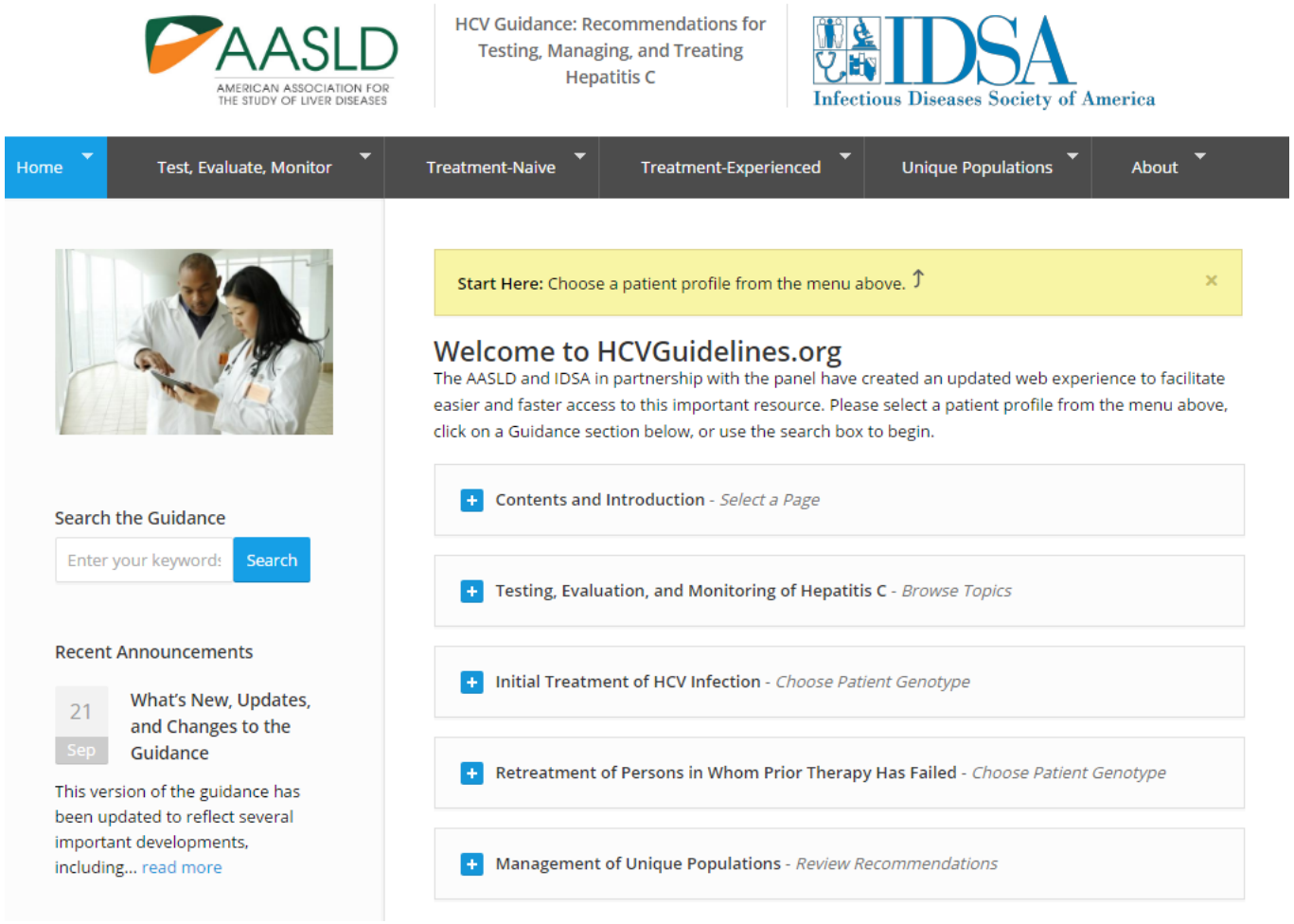

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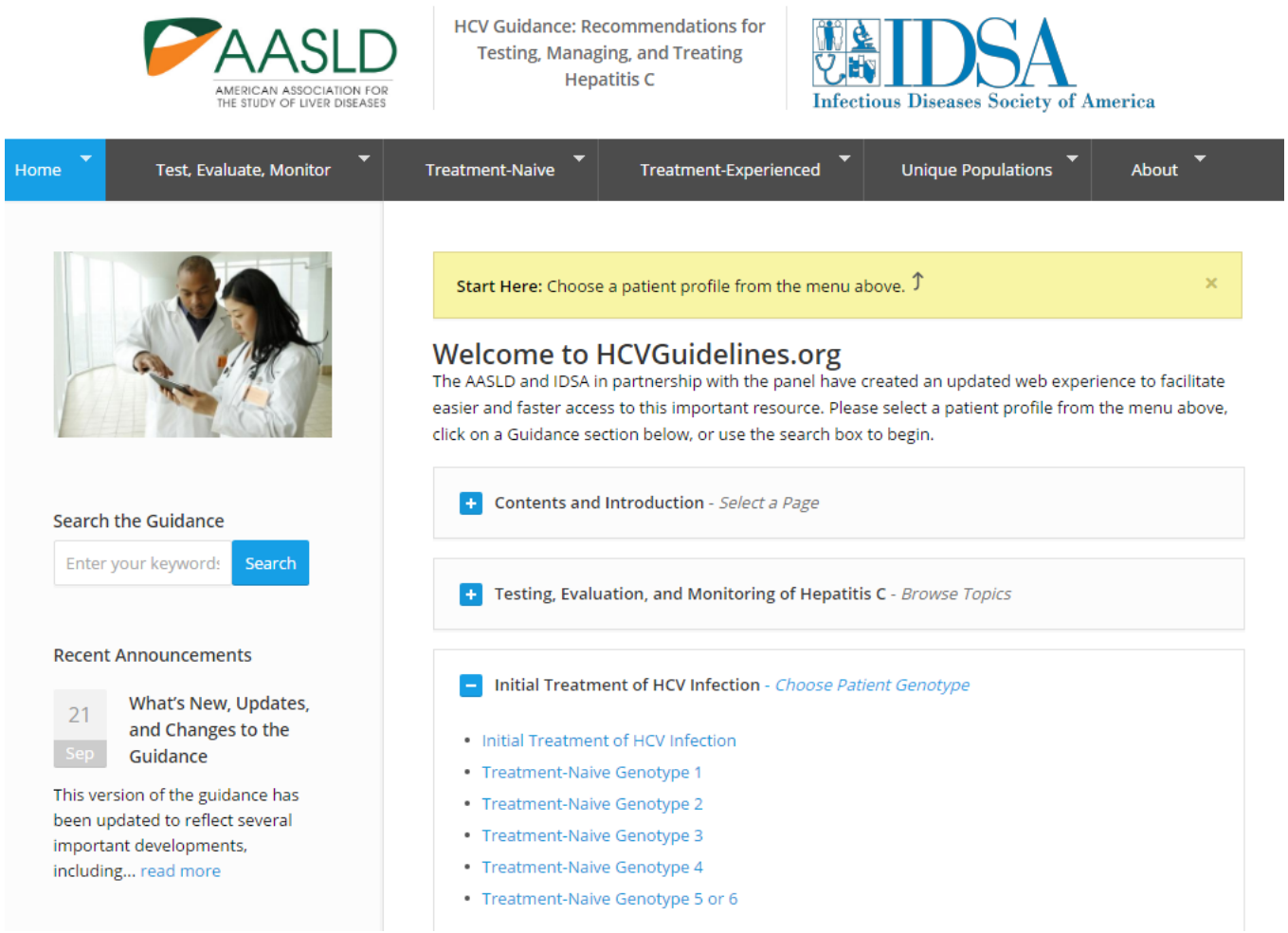

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AASLD & IDSA treatment guidelines

www.hcvguidelines.org

Recommended and alternative regimens listed by evidence level and alphabetically for: **Treatment-Naive Genotype 1a Patients Without Cirrhosis**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

[c] The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Drug-drug interactions:

Bioavailability of drugs is dependent on factors that alter their metabolism and intracellular concentration through:

- *Induction or inhibition* of CYP3A4 (metabolizes > 50% of FDA-approved drugs including many DAAs)
- *Induction or inhibition* of membrane transporters [OATP, BCRP (ABCG2), P-gp (ABCB1, MDR1)] responsible for cellular uptake and elimination of organic compounds

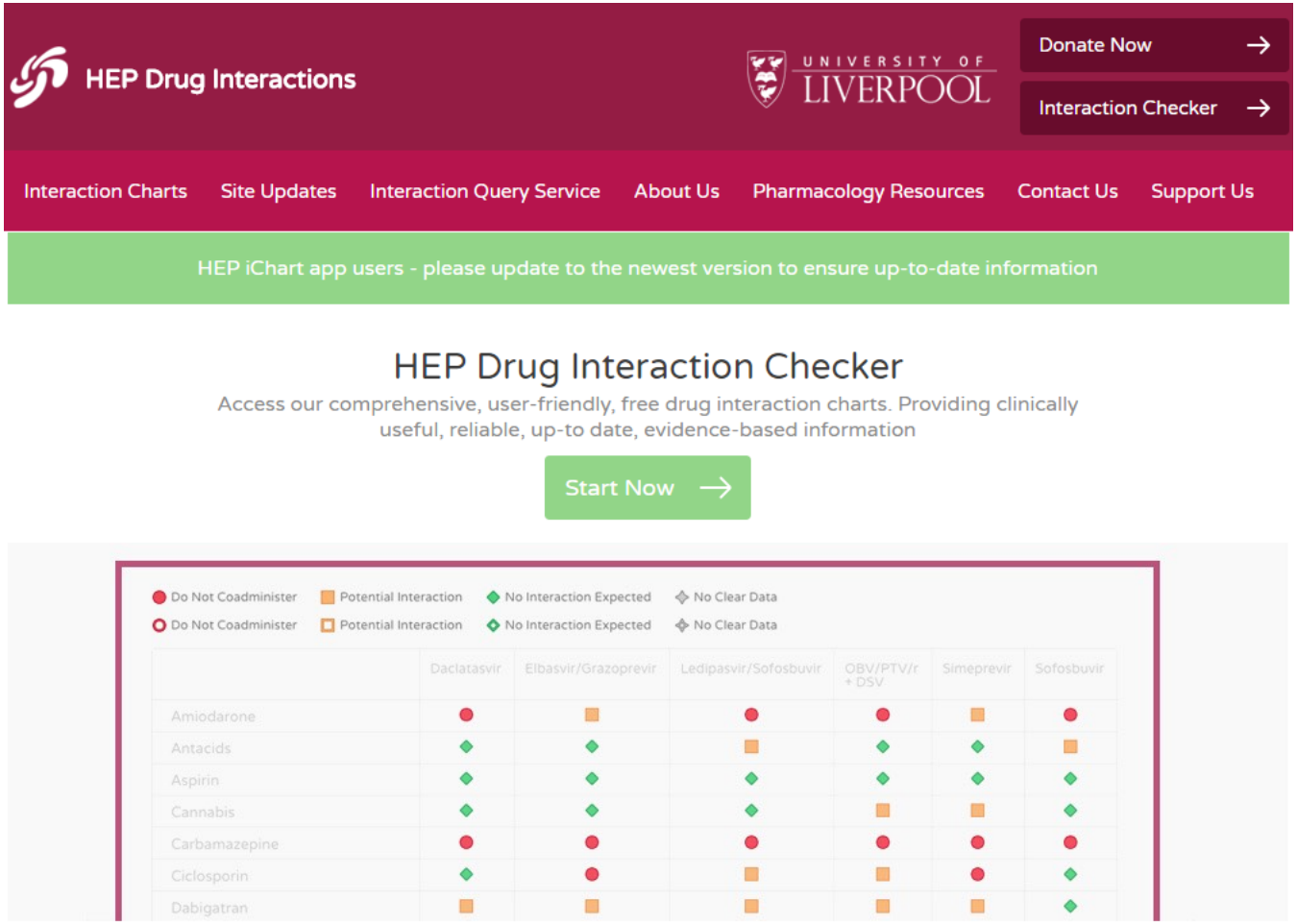
This is a mutual effect of drugs on each other: victims and perpetrators

Drug-drug interactions: Viekira Pak™ (steps 1-3)

Component	Role	Enzymes	Transporters
Paritaprevir (ritonavir-boosted)	**Victim**	Substrate of CYP3A4	Substrate of P-gp, BCRP and OATP1B1
	Perpetrator	Inhibits multiple enzymes	Inhibits P-gp, BCRP and OATP1B1/3
Ombitasvir	**Victim**	Substrate of CYP3A4	Substrate of P-gp
	Perpetrator	Inhibits multiple enzymes	
Dasabuvir	**Victim**	Substrate of CYP3A4 and others	Substrate of P-gp
	Perpetrator	Inhibits UGT1A1	Inhibits BCRP

Hepatitis C drug interactions

www.hep-druginteractions.org



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Hepatitis C therapy: conclusions

- Simple
- Well tolerated
- Multiple options
- Highly effective

Diagnose and treat patients before they develop end-stage liver disease and liver cancer