The Use of Hepatitis B or Hepatitis C Infected Organs in Transplantation

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Outline

- Hepatitis B
- Hepatitis C
- Use of viremic organs
- Our center’s experience

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5 Types of Viral Hepatitis

	Hep A	Hep B	Hep C	Hep D	Hep E
Type of virus	RNA	**DNA**	**RNA**	RNA	RNA
Possible chronic infection	No	**Yes**	**Yes**	Yes	Yes
Transmission route	Fecal-oral	**Blood and other body fluids**	**Blood and other body fluids**	Blood and other body fluids	Fecal-oral
Incubation time	14-28 days	**30-180 days**	**14-180 days**	HDV requires HBV for replication	14-70 days
Treatment	No	**Yes**	**Yes**	Yes	No
Cure	Yes	**No**	**Yes**	No	Yes
Vaccine	Yes	**Yes**	**No**	No	Yes (China only)

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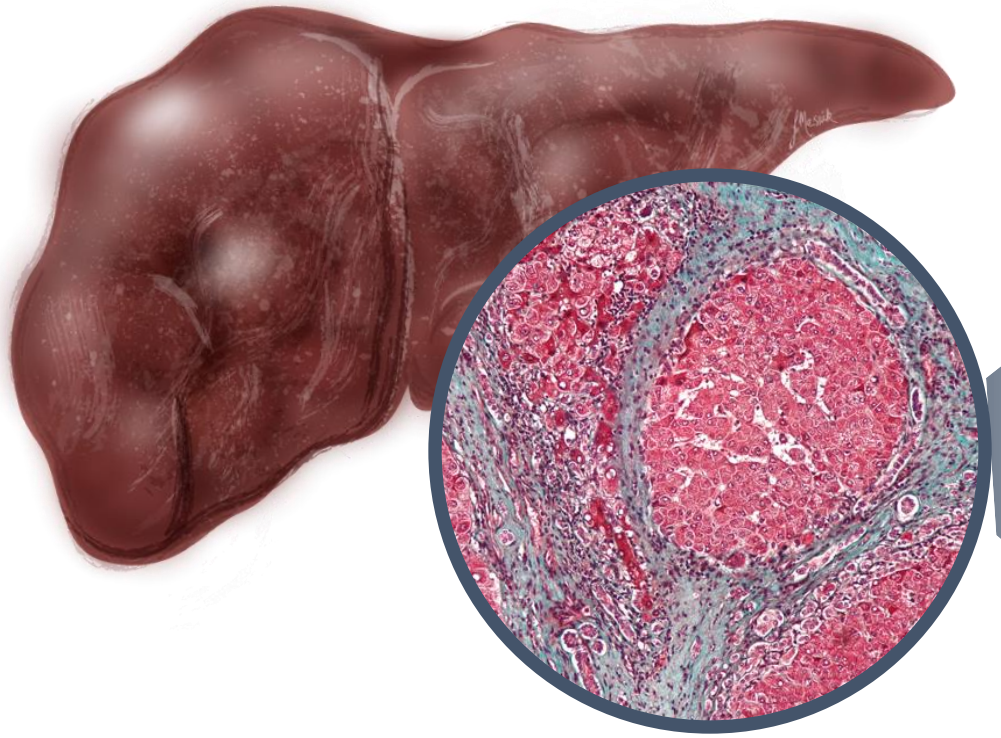
End stage liver disease is the final pathway for most chronic liver diseases, including HBV and HCV chronic infection



Accumulation of collagen deposition= fibrosis → cirrhosis

Decompensation/liver failure

Hepatocellular carcinoma

Liver transplantation

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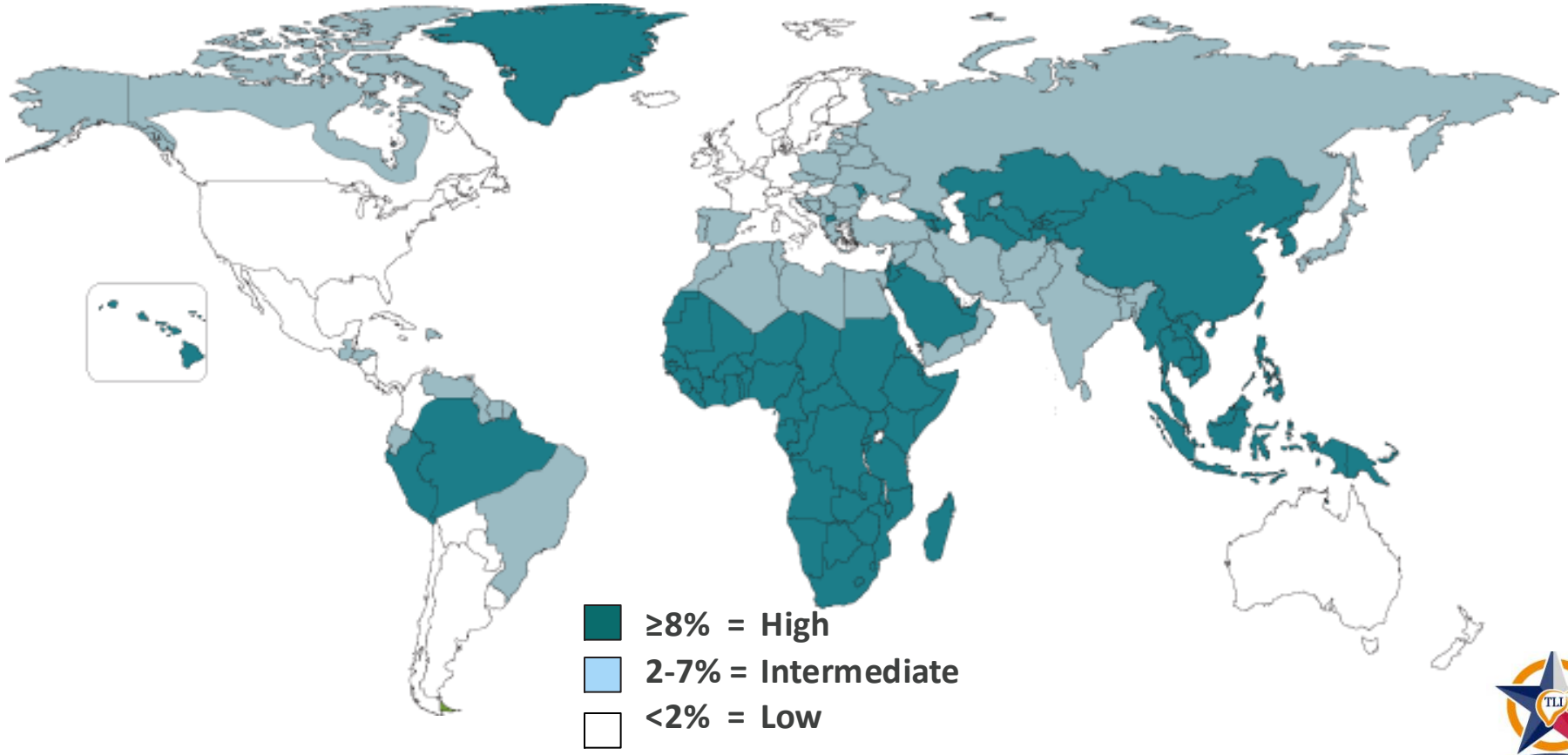
Ge PS, Runyon BA. *N Engl J Med*. 2016;375:767-777.

Hepatitis B

Hepatitis B

- DNA virus. Hepadnavirus family
- Global epidemic: 350 million people worldwide have CHB



WHO. Hepatitis B Fact Sheet.

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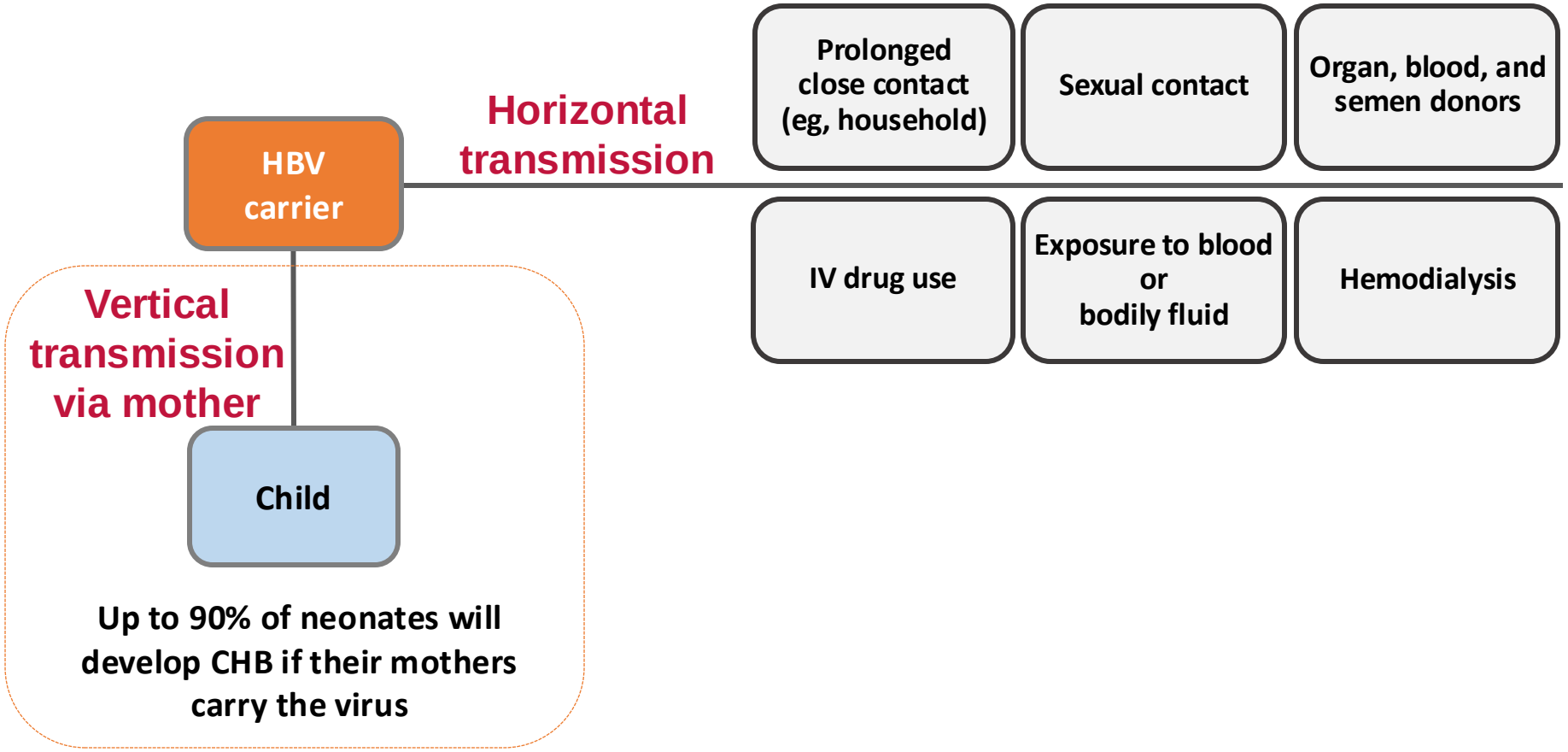
Modes of HBV Transmission



CDC. Morb Mortal Wkly Rep. 2008;57:1-20; CDC. Morb Mortal Wkly Rep. 2005;54:1-31.

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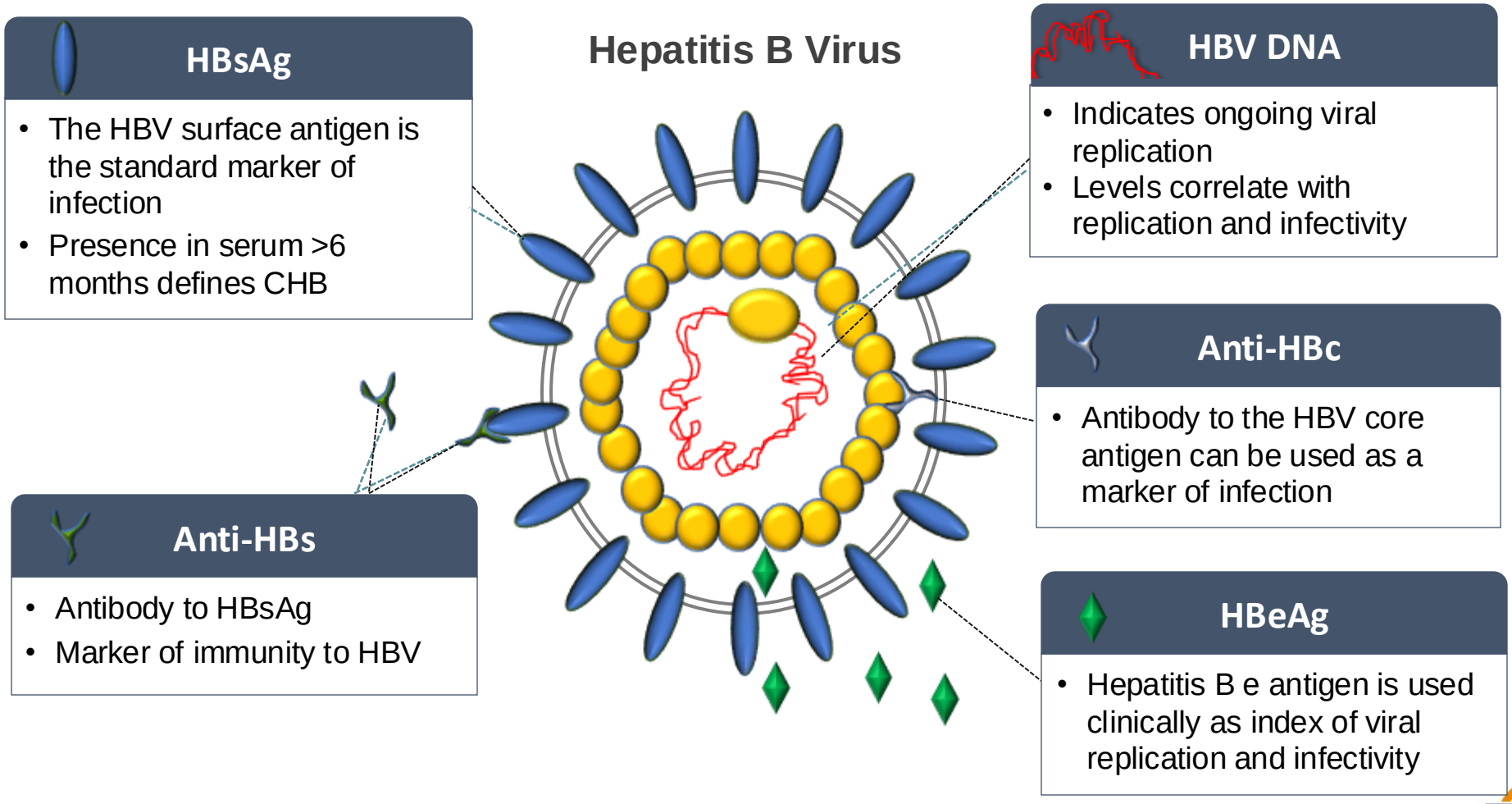
Serologic Markers in HBV Infection



Dienstag JL. *N Engl J Med*. 2008;359:1486-1500

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Hepatitis B Serology

HBsAg	Anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
+	+	-	-	Chronic infection
+	+	+	-	Acute or reactivated infection
-	-	-	+	Immune due to vaccination
-	+	-	+	“Immune” due to resolved infection
-	+	-	-	1. Resolved infection (most common) 2. False-positive anti-HBc (rare) 3. "Low level" chronic infection 4. Resolving acute infection

cdc.gov

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Hepatitis C

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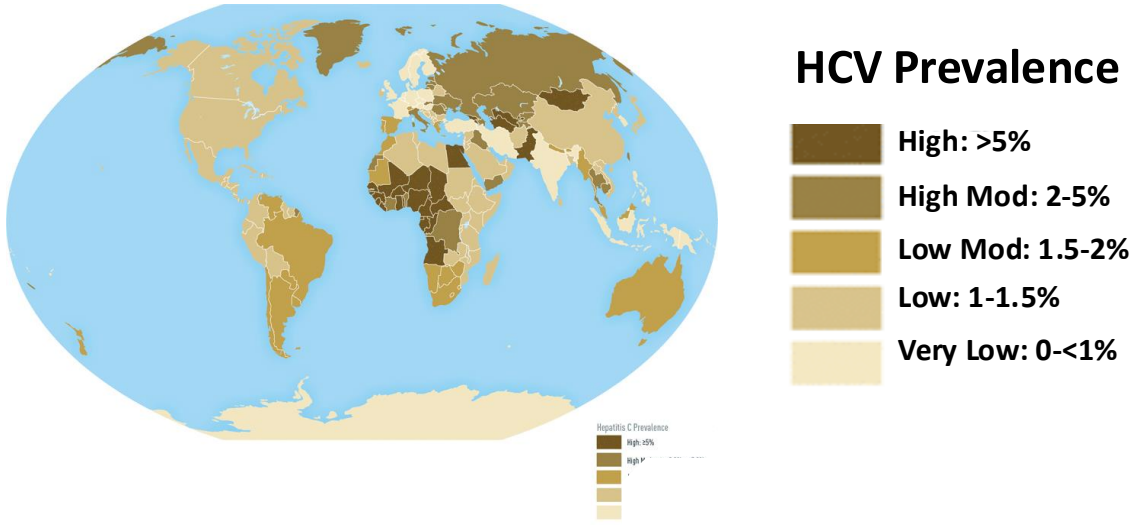
Hepatitis C: Worldwide Presence

- Worldwide prevalence: 130-150 million
  - Viral hepatitis causes >50% of cirrhosis and >70% of HCC
- US prevalence: 3.5 million
  - Most common indication for liver transplantation



www.cdc.gov; Denniston MM et al. *Annals Int Med*. 2014; Holmberg SD et al. *NEJM*. 2013.

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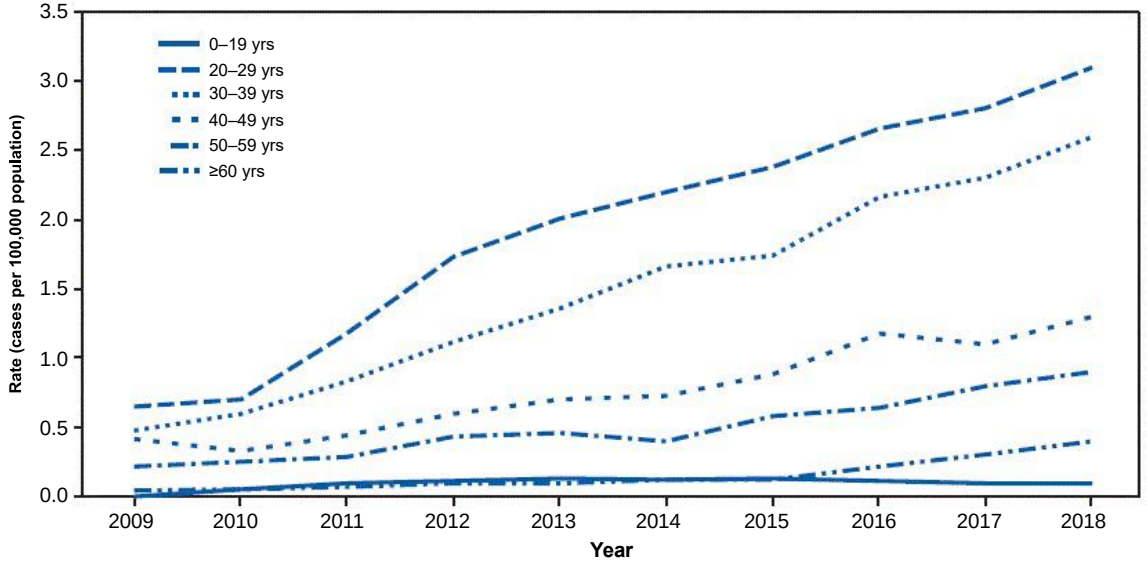
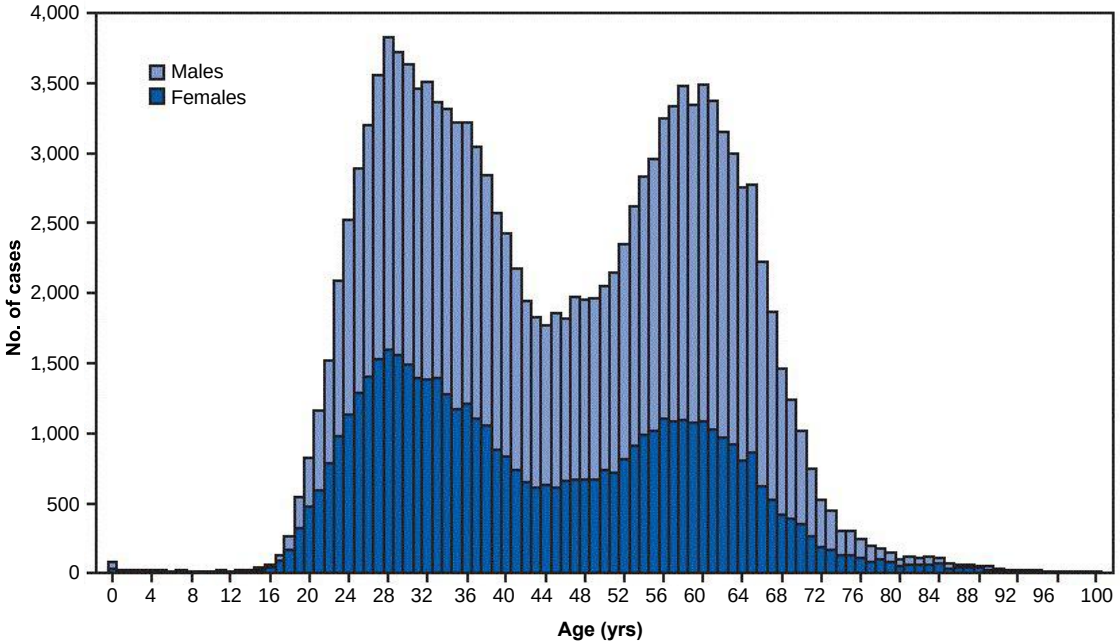
Acute and Chronic Hepatitis C Cases – US, 2009–2018

Rate of reported acute HCV cases, by year and age group



Number of newly reported chronic HCV cases, by sex and age



Alpha (born after 2012), 1.0 cases/100,000 person
Generation Z (born 1997–2012), 6.1
Millennial (born 1981–1996), 89.7
Generation X (born 1966–1980), 66.7
Baby boomers (born 1945–1965), 79.8
Silent (born 1928–1944)
Greatest (born 1901–1927)

Ryerson AB et al. *MMWR Morb Mortal Wkly Rep*. 2020;69:399–404.

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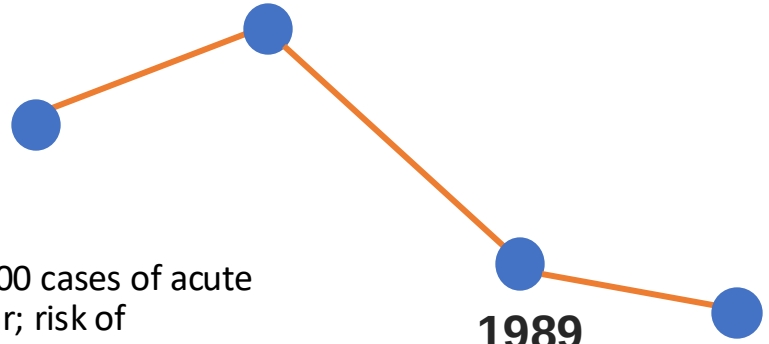
Populations at Risk

Baby Boomers (born 1945-1965)

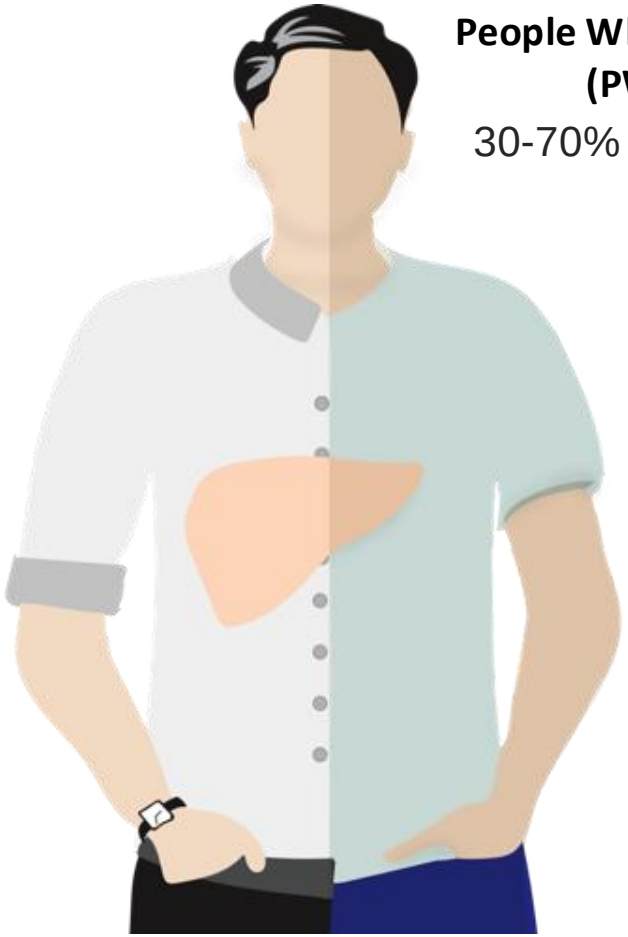
1970s
Volunteer donor system reduces risk of exposure via blood transfusion



1960s
Up to 300,000 cases of acute HCV per year; risk of exposure via blood transfusion up to 33%

1989
HCV discovered

1992
Widespread introduction of HCV antibody testing



People Who Use Drugs (PWUD)
30-70% prevalence

Alter HJ. Nat Med. 2000;6:1082-1086.

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EVERY ADULT

At least once

EVERYONE WITH RISK FACTORS

Regularly

- Persons who inject drugs and share needles, syringes, or other drug preparation equipment
- Persons receiving maintenance hemodialysis
- Persons with abnormal liver tests or liver disease (persistently abnormal ALT levels)
- Children born to mothers with HCV infection

EVERY PREGNANT WOMAN

Every pregnancy

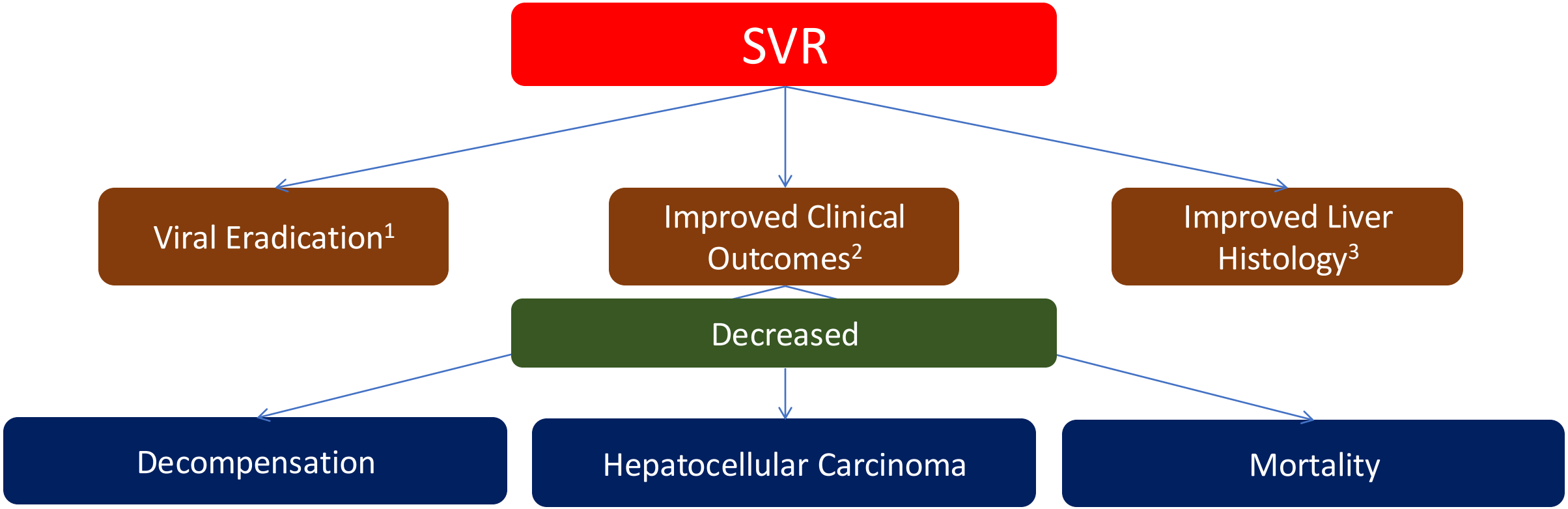
CDC Recommendations for Hepatitis C Screening, MMWR, April 2020

Sustained Virologic Response (SVR) = Cure

- Unlike HIV and HBV infection, HCV infection is a curable disease
  - HCV does not archive its genome in the nucleus and does not integrate in the host DNA
- What does cure mean
  - Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
  - SVR12 is almost invariably durable
- What it doesn't mean
  - Patients who continue risk behaviors may ultimately become reinfected (no immunity from prior exposure)

Ghany MG, et al. *Hepatology*. 2009;49(4):1335-1374.

SVR Leads to Improved Outcomes



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.

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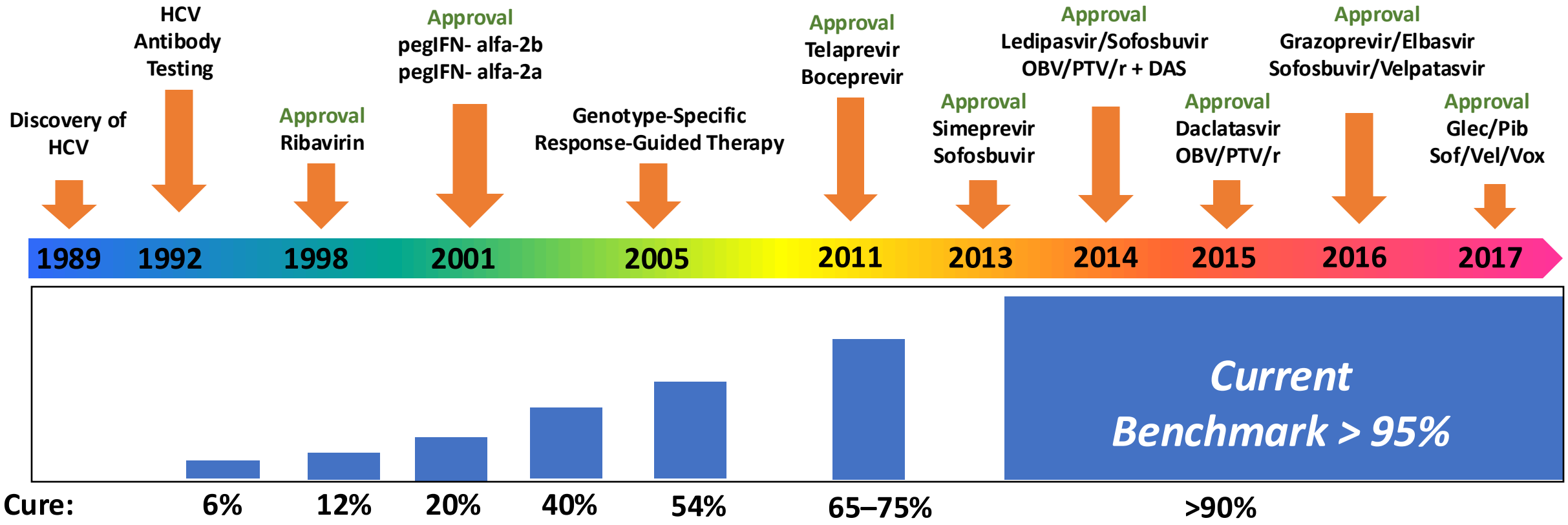
Discovery of Direct Acting Antivirals (DAAs) Revolutionized HCV Therapy



- Patients can be cured in 8-12 weeks
- Therapy with oral DAAs have very few adverse events
- Interferon and ribavirin rarely used

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Use of Viremic Organs

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HBV #1 Case Question

A 58-year-old man with a past medical history of decompensated alcohol-related cirrhosis and MELD score of 38 is currently undergoing orthotopic liver transplant. The transplant surgery team consults you for recommendations regarding hepatitis B core positivity in the donor organ.

Recipient profile: **HBsAg negative, HBsAb positive, HBcAb negative, HBV DNA negative.**
Donor profile: **HBsAg negative, HBsAb negative, HBcAb positive, HBV NAT negative.**

What is the best next step in management?

A. Administer hepatitis B immune globulin immediately after transplant
B. Check HBV DNA and HBsAg every 3 months and start treatment if either is detectable
C. Administer hepatitis B immune globulin immediately after transplant and start prophylactic tenofovir
D. Start prophylactic tenofovir after transplant
E. No prophylaxis needed

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HBV Case #1: Start Prophylactic Tenofovir After Transplant

- In recipients who are not HBcAb+ and HBsAb+ that receive isolated HBcAb+ donor organs, prophylaxis with antiviral therapy should be given
- Consider withdrawal after 1 year if HBsAb titer is greater than 10 IU/ml (not typically done)

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HBV Case Question #2

A 58-year-old man with a past medical history of decompensated alcohol-related cirrhosis and MELD score of 38 is currently undergoing orthotopic liver transplant. The transplant surgery team consults you for recommendations regarding hepatitis B core positivity in the donor organ.

Recipient profile: **HBsAg negative, HBsAb positive, HBcAb positive, HBV DNA negative**
Donor profile: **HBsAg negative, HBsAb positive, HBcAb negative, HBV NAT negative**

What is the best next step in management?

A. Administer hepatitis B immune globulin immediately after transplant
B. Check HBV DNA and HBsAg every 3 months and start treatment if either is detectable
C. Administer hepatitis B immune globulin immediately after transplant and start prophylactic tenofovir
D. Start prophylactic tenofovir after transplant and consider withdrawal after 1 year if HBsAb titer is greater than 10 IU/ml
E. No prophylaxis needed

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HBV Case #2: No Prophylaxis Needed

Hep B Viremic Donors: Management in LT Recipients

Donor status	Pre-LT considerations	Management of recipient infected with same virus	Management of recipient uninfected pre-LT	Additional precautions
HBsAg-negative, anti-HBc positive	Assess severity in fibrosis in donor liver Assess anti-HBs status of recipient	Antiviral therapy from time of LT HBIG may be considered	Antiviral therapy from time of LT No role for HBIG	Antivirals of choice – tenofovir or entecavir (high barrier to resistance)
HBsAg positive	Assess severity in fibrosis in donor liver	Antiviral therapy from time of LT No role for HBIG	Antiviral therapy from time of LT No role for HBIG	Antivirals of choice – tenofovir or entecavir (high barrier to resistance) **Avoid in recipient with HCC as indication** **Consider HCC surveillance post-LT**

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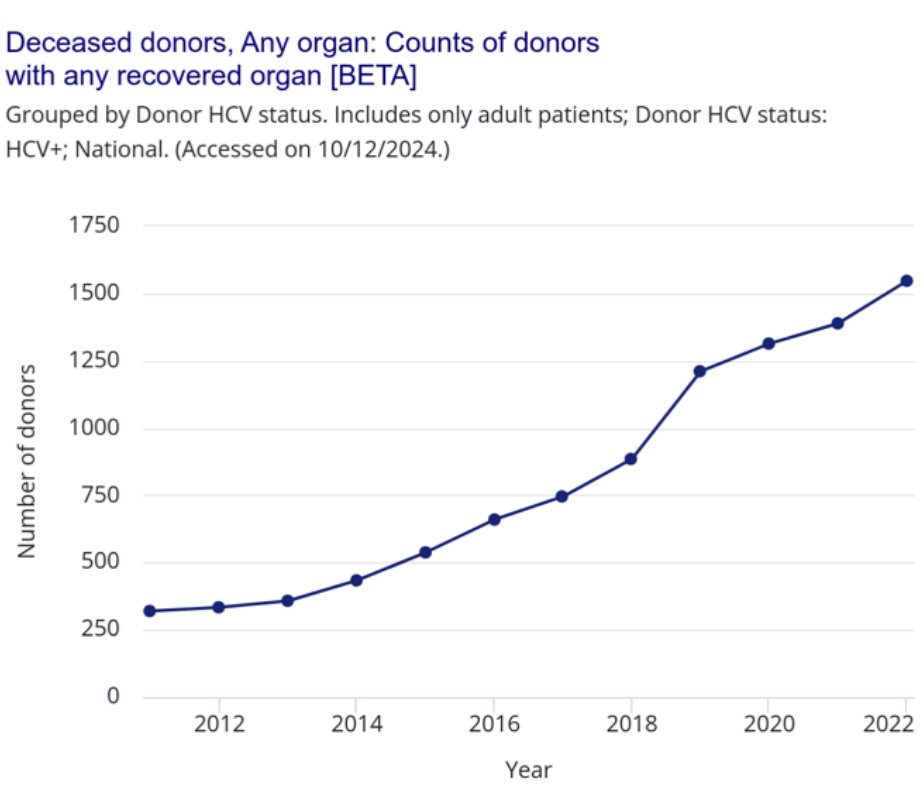
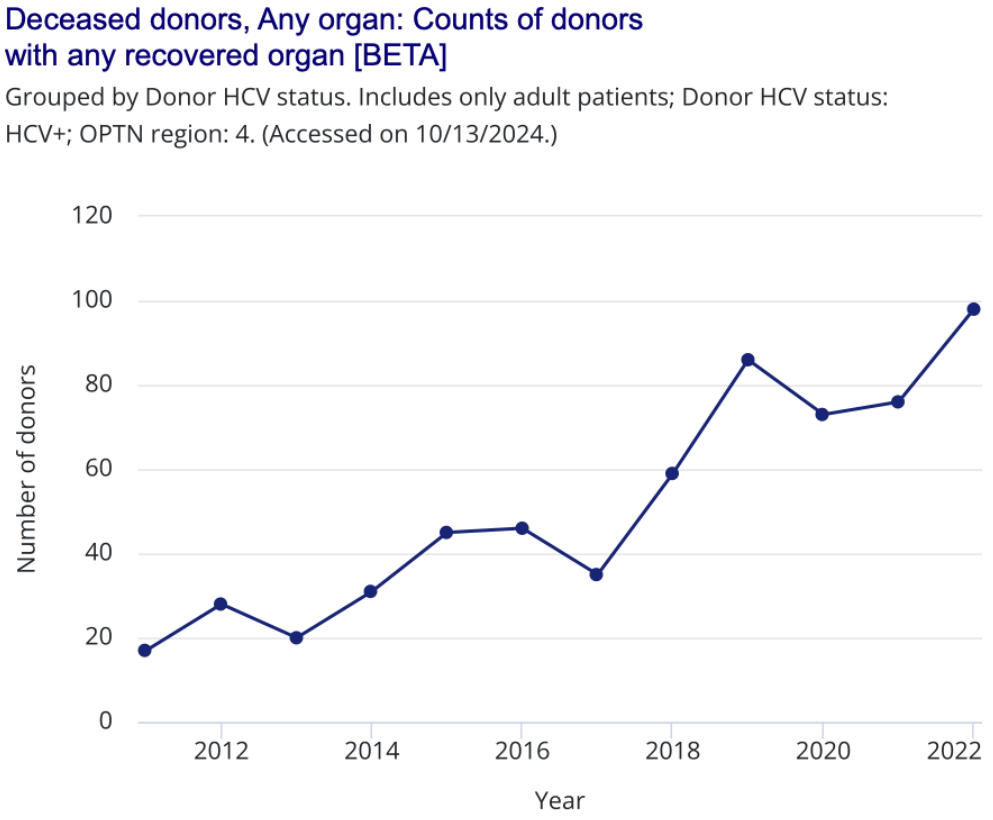
Count of HCV+ Deceased Donors (2012-2022)

National



OPTN Region 4



srtr.ogr

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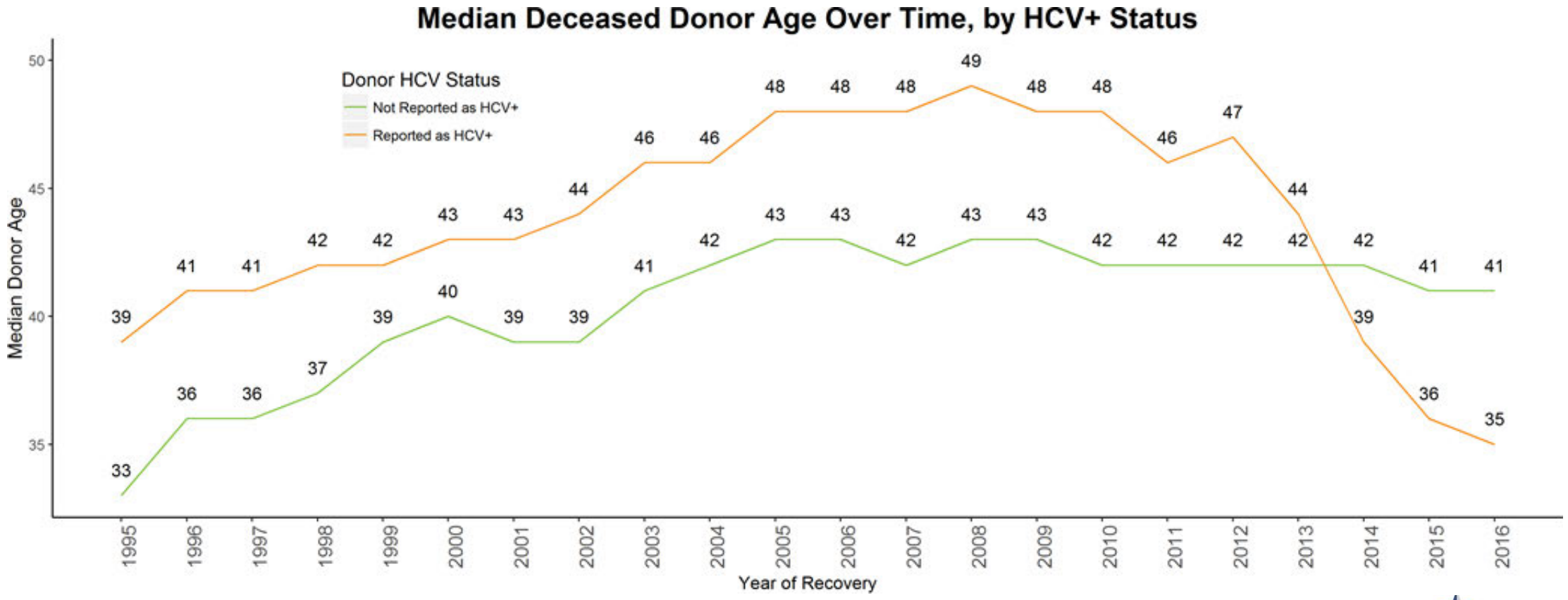
Median Deceased Donor Age Over Time (by Reported HCV Serostatus)



Levitsky J, Formica RN, Bloom RD et al., *American Journal of Transplantation* 2017; 17: 2790-2802.

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HCV Infection Post-Transplant

- Persistence of HCV infection after transplant results in a variable clinical course ranging from mild fibrosis to severe graft damage.
- Progressive centrilobular ballooning degeneration, bridging fibrosis, and cholestasis seen in 20%-40% of post-transplant patients with untreated HCV infection.[1]
- Advanced fibrosis can occur in up to 45% of post-transplant patients, and graft cirrhosis can develop within as little as 5 years post-transplant.[2,3]
- 5-10% of post-transplant patients will develop severe progressive cholestatic hepatitis leading to liver failure.[4,5]

[1]Dickson RC et al., *Transplantation* 1996; 61(5): 701-705; [2]Berenguer M et al., *Hepatology* 2000; 32(4): 852-858; [3]Firpi et al., *Liver Transpl* 2009; 15(9): 1063-1071; [4]Schluger LK et al, *Hepatology* 1996; 23(5): 971-976; [5]Yilmaz N et al., *Liver Transpl* 2007; 13(7): 975-984.

Nucleic Acid Testing (NAT) Assay

- Detects HCV virus RNA in the donor's blood.

- NAT tests reduced the time between HCV infection and detection from 70 days to 3–5 days.
  - The advent of NAT has led to a redefinition of the phrase "HCV-positive donor" by the American Society of Transplantation (ASTS).

Treatment of HCV Post-Transplant

- HCV viremia in the recipient is quantifiable in blood within the first 1 to 2 days
- Elevation of serum aminotransferase levels occur within the first few weeks, with cases of fibrosing cholestatic hepatitis reported
- Treatment immediately or shortly after transplantation
- Standard duration of 12 weeks of therapy
- Efficacy is high with DAAs, with sustained virologic responses reported in >95% with the first course of treatment

Drug Interactions Between Immunosuppressive Agent and DAAs

	Tacrolimus	Cyclosporine	Sirolimus	Everolimus	Azathioprine	Mycophenolate mofetil
Glecaprevir-pibrentasvir	Monitor levels*	If cyclosporine dose >100 mg/day, not recommended	Monitor levels¶	Monitor levels△	✓	✓
Sofosbuvir-velpatasvir	Monitor levels*	Monitor levels◇	Monitor levels¶	Monitor levels△	✓	✓
Ledipasvir-sofosbuvir	Monitor levels*	✓	Monitor levels¶	Monitor levels△	✓	✓
Sofosbuvir-velpatasvir-voxilaprevir	Monitor levels*	Not recommended	Monitor levels¶	Monitor levels△	✓	✓

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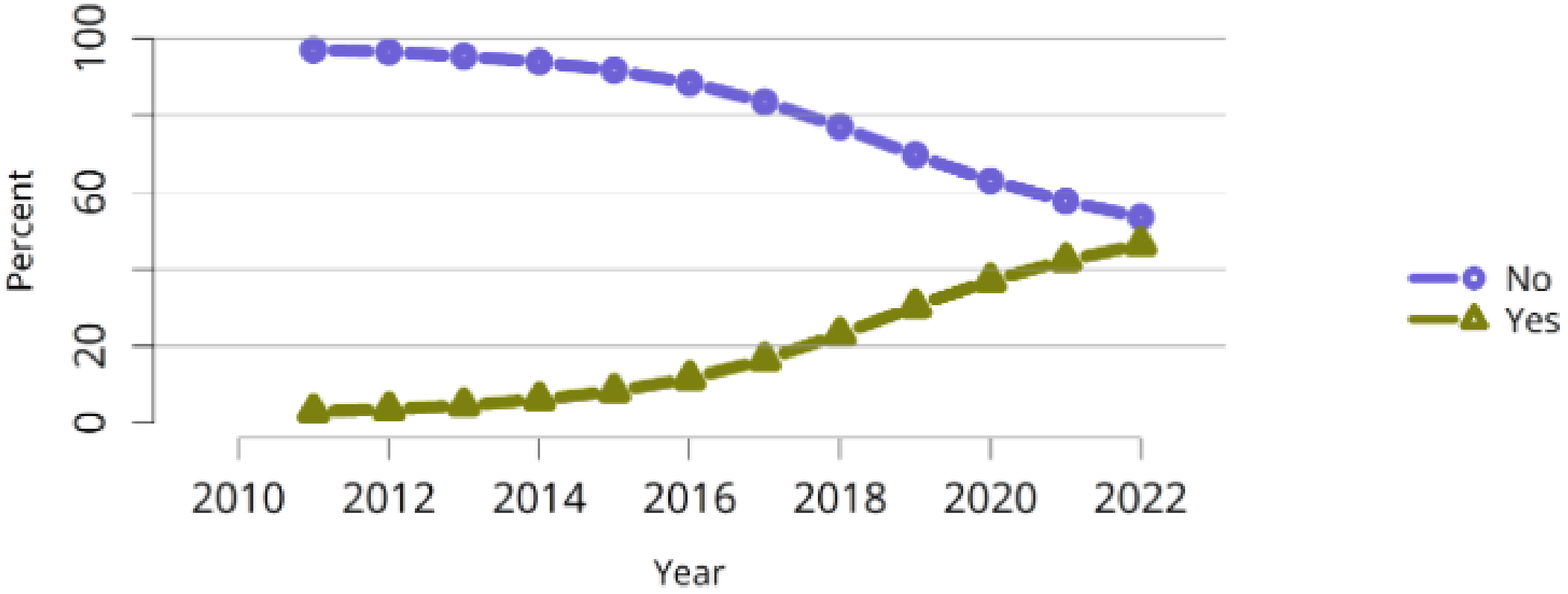
Adults Willing to Accept Kidney from HCV+ Donor



Lentine KL et al., OPTN/SRTR 2022 Annual Data Report: Kidney

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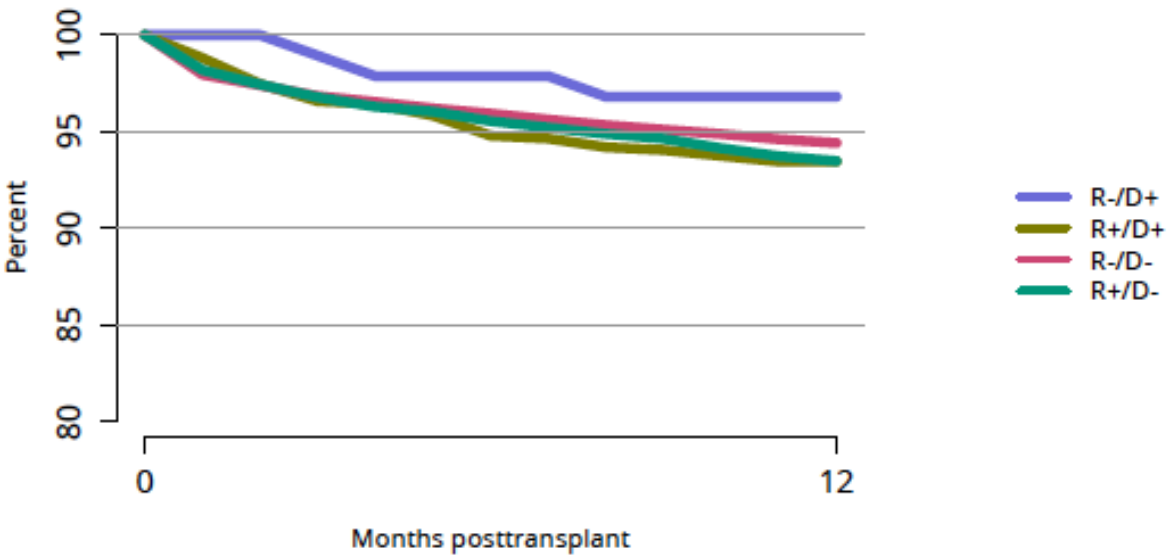
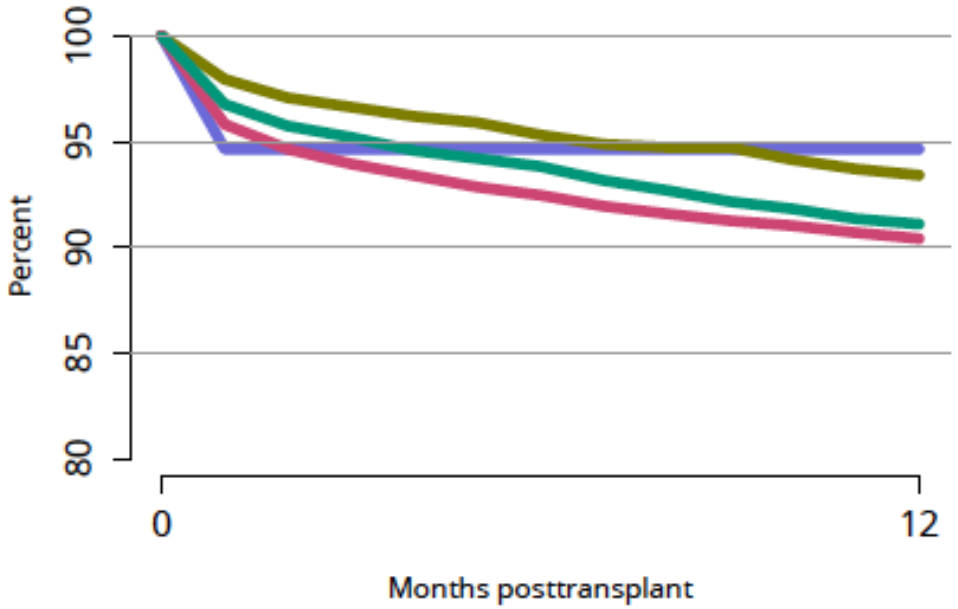
Graft Survival Among Transplant Recipients

Kidney transplant recipients, 2016-2017, by donor HCV NAT and recipient HCV Ab status.



Liver transplant recipients, 2016-2017, by donor HCV NAT and recipient HCV Ab status.



Wang JH et al., OPTN/SRTR 2018 Annual Data Report: Hepatitis C

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Our Center’s Experience

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Patient Demographics and Baseline Characteristics

Age (years) (mean, range)	59.5 (26-78)
Gender	
Male	59 (69.4%)
Female	26 (30.6%)
Ethnicity	
Hispanic/Latino	61 (71.8%)
Non-Hispanic/Non-Latino	24 (28.2%)
Race	
Caucasian	78 (91.8%)
African American	3 (3.5%)
Asian	2 (2.4%)
Multiracial	1 (1.2%)
Transplanted Organ	
Liver	37 (43.5%)
Kidney	45 (52.9%)
Liver + Kidney	3 (3.5%)
HCV Genotype (n=66)*	
GT1a	42 (63.6%)
GT1b	5 (7.6%)
GT2	9 (13.6%)
GT3	8 (12.1%)
GT4	2 (3.0%)

- The patient population was predominantly Caucasian middle-aged men of Hispanic descent.
- HCV genotype 1a (63.6%) was the most common followed by genotype 2 (13.6%) and genotype 3 (12.1%).
- **98.8% of patients achieved sustained virologic response (SVR) after DAA treatment.**

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Conclusions

- Organ transplantation in the US is negatively impacted by long waitlist times and high waitlist mortality.
- Prior to direct-acting antiviral (DAA) therapy against the hepatitis C virus (HCV), organs from deceased donors infected with HCV were rarely transplanted due to the risk of transmission of the virus through the allograft.
- HCV infection of the allograft occurs in most recipients of HCV+ organs; however, treatment with DAAs results in >95% cure and these regimens can be safely administered post-transplant.