Hepatitis Delta Virus: Evaluation & Treatment

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Disclosures

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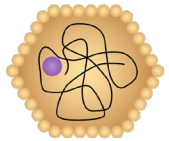
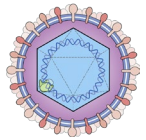
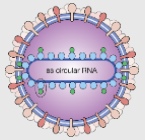
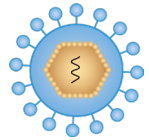
HDV Is the Most Severe Form of Viral Hepatitis

	HEPATITIS A[1]	HEPATITIS B[2]	HEPATITIS C[3]	HEPATITIS D[4]	HEPATITIS E[5]
					
RISK FOR PROGRESSION TO CHRONIC HEPATITIS	No, but can cause fatal fulminant hepatitis in a very small proportion	Adults: 5% Children: 90%	55%-85%	76%	Can occur rarely in immunosuppressed individuals
RISK FOR CIRRHOSIS/HCC	No, as infection is generally short-lived	20%-30% (lifetime)	15%-30% (20 years)	Cirrhosis within 5 years; HCC within 10 years	No, as virus does not result in chronic infection

1. WHO. July 27, 2021. Accessed September 30, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-a 2. WHO. July 27, 2021. Accessed September 30, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
3. WHO. July 27, 2021. Accessed September 30, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c 4. Miao Z, et al. *J Infect Dis*. 2020;221(10):1677-1687. 5. WHO. July 27, 2021. Accessed September 30, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-e

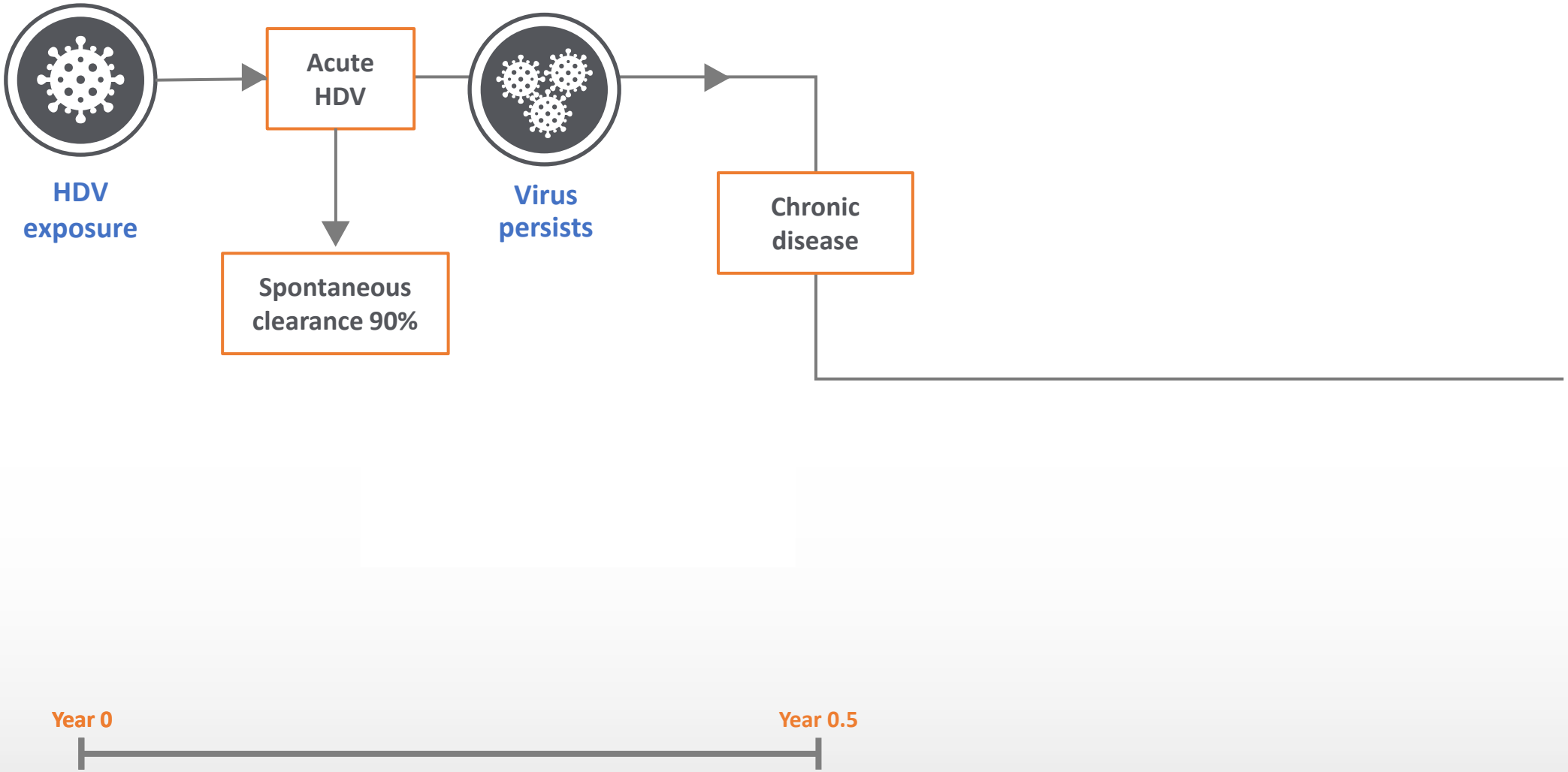
Etiology of HDV[1,2]

 **CAUSE**	**Infection with HDV**	Only patients infected with HBV can contract HDV – HDV is acquired simultaneously (coinfection) or as a superinfection in those already infected with HBV
 **TRANSMISSION**	**Via percutaneous or mucosal contact with infectious blood or body fluids**	**Common routes of transmission**: contaminated needles or transfusion, sexual transmission, sharing razors and toothbrushes **Not as common routes**: Vertical transmission from mother-to-baby, and mucosal contact with infectious blood or body fluids
 **SYMPTOMS**	**Often asymptomatic**	No particular symptoms related specifically to HDV. Individuals with chronic infection are at high risk for developing severe liver disease, including cirrhosis and HCC
 **COURSE OF INFECTION**	**Acute or chronic**	*Acute:* occurs suddenly, may cause severe symptoms, resolves within 6 months. Can clear spontaneously; however, can lead to acute liver failure *Chronic:* long-term consequence of infection associated with high risk for liver disease
 **CONSEQUENCES OF INFECTION**	**Increased risk for cirrhosis and HCC than HBV alone**	HDV is the most severe form of chronic viral hepatitis due to more rapid progression to liver-related death and HCC than the other viruses

CDC. Updated March 9, 2020. Accessed March 2021. https://www.cdc.gov/hepatitis/hdv/hdvfaq.htm#section1 2. WHO. July 28, 2021. Accessed September 26, 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d

Clinical Course of HDV

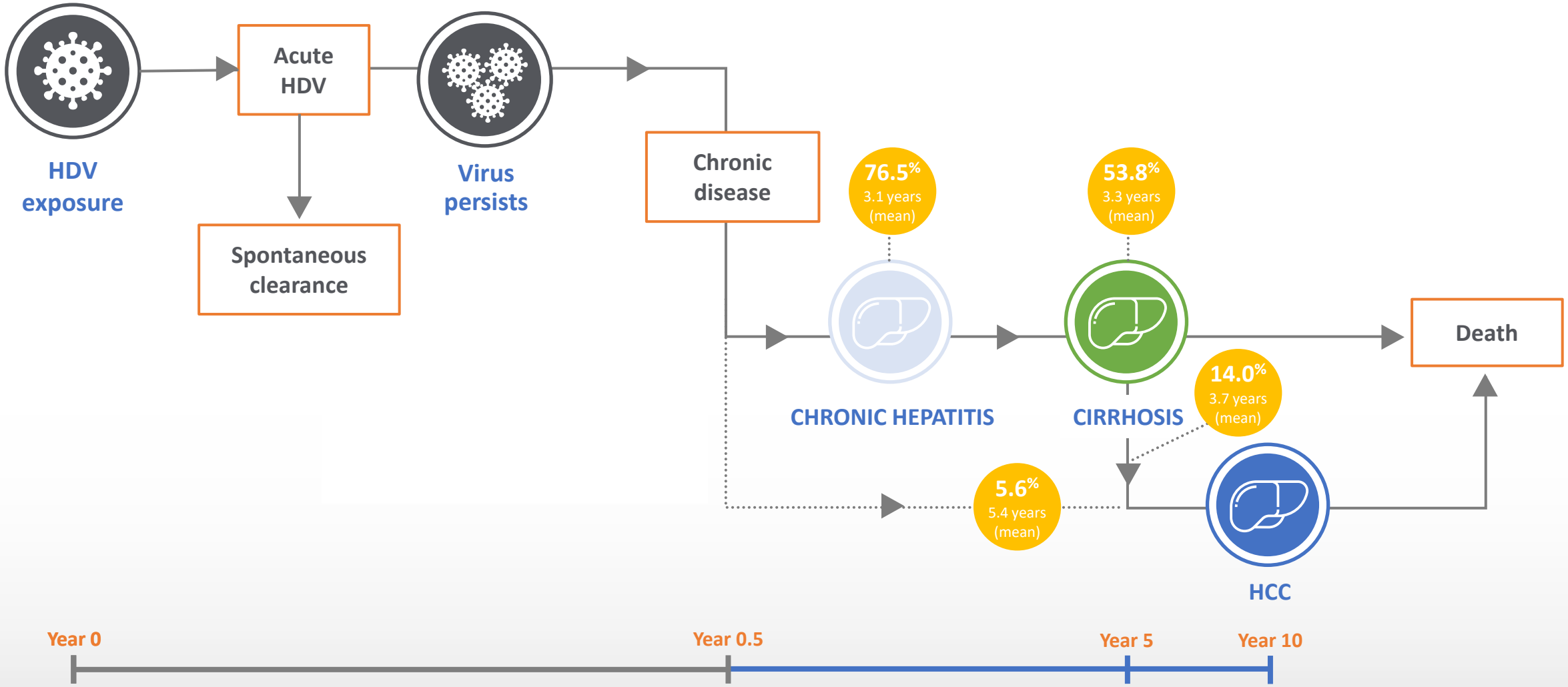
HBV/HDV coinfection often leads to rapid progression to cirrhosis and HCC



Miao Z, et al. *J Infect Dis.* 2020;221(10):1677-1687.

Clinical Course of HDV

Chronic HBV/HDV infection often leads to rapid progression to cirrhosis and HCC



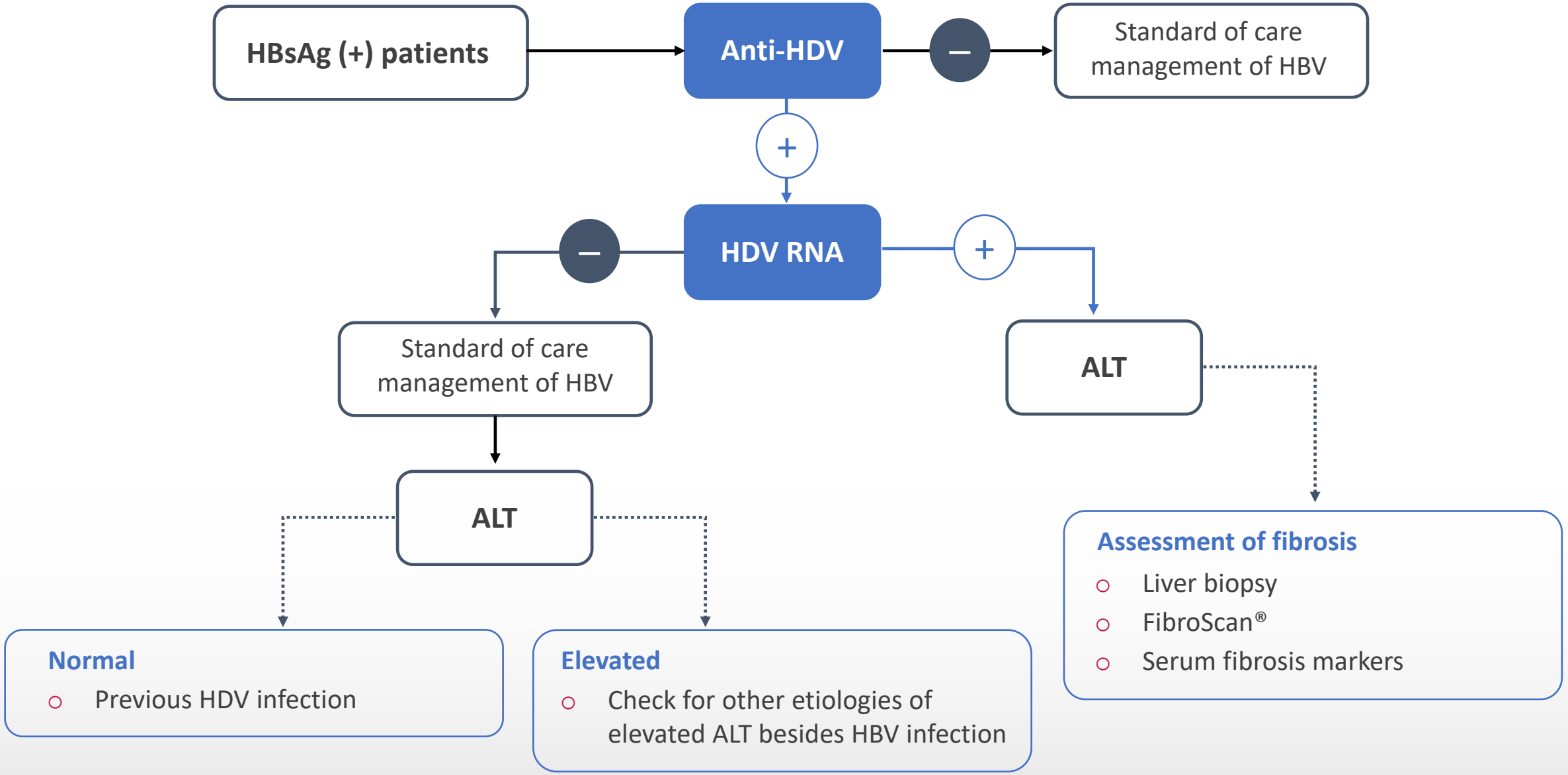
Miao Z, et al. *J Infect Dis.* 2020;221(10):1677-1687.

Diagnosis of Different Stages of HDV Infection[1-4]

Diagnostic Marker	Acute HDV/HBV Coinfection	Acute HDV Superinfection	Chronic HDV Infection
HBsAg	+	+	+
Anti-HBc, IgM	+	–	–
Serum HDAg (by EIA/RIA)	Early and short-lived, and frequently missed	Early and transient, and frequently missed	Transient and may not be detected
Serum HDV RNA (by RT-PCR)	+	+	+
Anti-HDV, total	Late, low titers	Rapidly increasing titers	High titers
Anti-HDV, IgM	+	Rapidly increasing and persistent titers	Variable titers, usually high titers

Note: HDV genotyping is not done routinely in clinical practice.
EIA=enzyme immunoassay; HBc=hepatitis B core; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HDAg=hepatitis delta antigen; HDV=hepatitis delta virus; IgM=immunoglobulin M; RIA=radio immunoassay; RNA=ribonucleic acid; RT-PCR=reverse transcription polymerase chain reaction.
1. Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599. 2. Sarin SK, et al. *Hepatol Int*. 2016;10(1):1-98. 3. WHO. March 2015. Accessed March 30, 2021. https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1 4. Cheung A, Kwo P. *Clin Liver Dis*. 2020;24(3):405-419.

Algorithm for the Evaluation of HDV



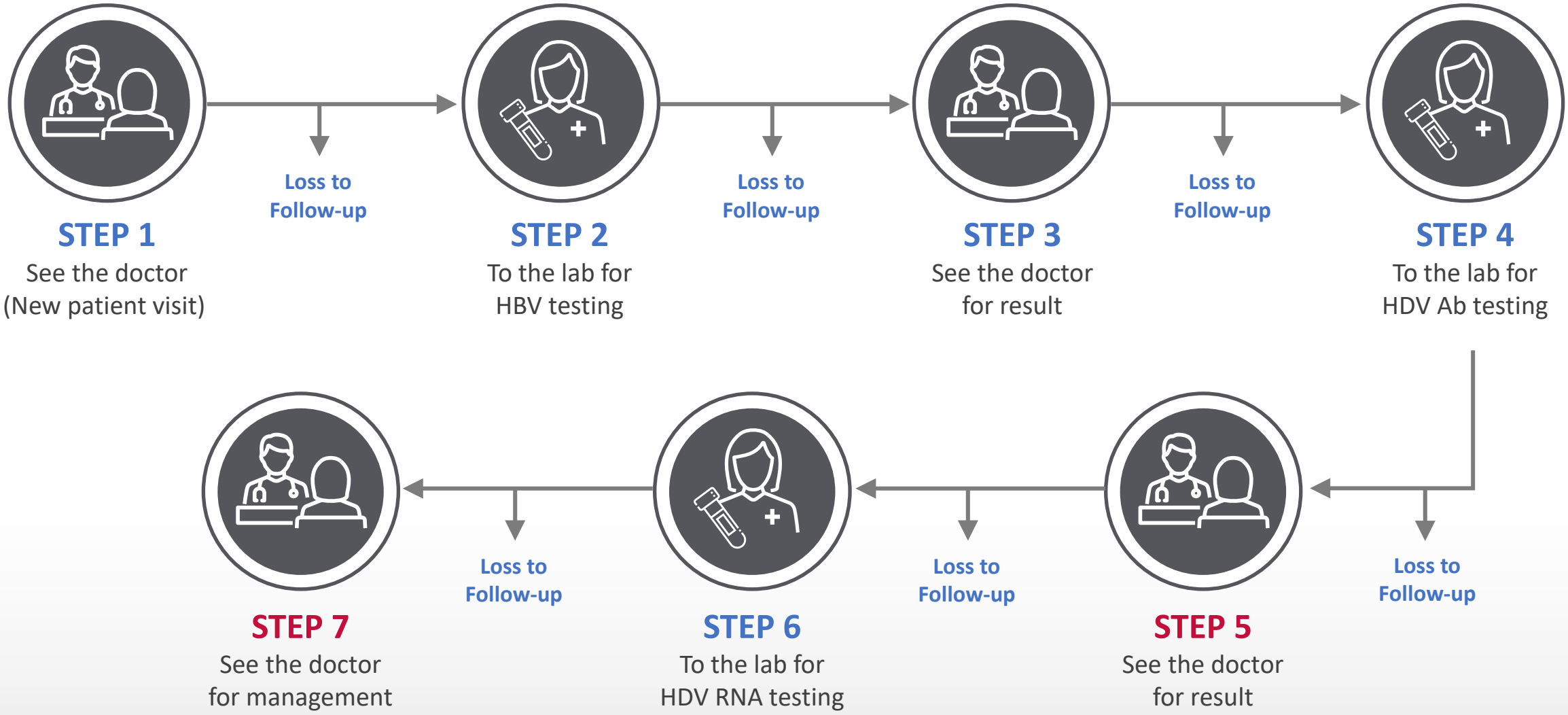
Adapted from: Shah PA, et al. *Gastroenterol Rep (Oxf)*. 2019;7(6):396-402.

Test Name	Test Code	Reference Lab	CPT Code
HDV Antibody, Total	4990	Quest Diagnostics	86692
	20799	ARUP Laboratories	
	20799	Mayo Clinic Laboratories	
	99202	Viracor Eurofins	
HDV Antibody, IgM	20799	BioAgilytix	
	35664	Quest Diagnostics	
	30336	Viracor Eurofins	
	98507	ARUP Laboratories	
HDV RNA, Quantitative	37889	Quest Diagnostics	87799
	2013881	ARUP Laboratories	
HDV RNA, Qualitative	34469	Quest Diagnostics	87798
	3900	Viracor Eurofins	
	1844	Bioreference Laboratories	
HDV Antigen	2006450	ARUP Laboratories	87380
	-	BioAgilytix	
HDV Genotyping and NAT	CDC-10328	CDC	Not CLIA approved

This may not be a comprehensive list of all available codes and labs offering HDV testing. This is for your information only. Each provider must make an individual decision for each patient's needs. Gilead does not guarantee the coverage or reimbursement of any item or service through the use of these codes

https://testdirectory.questdiagnostics.com/test/home accessed Feb 8, 2022; https://www.aruplab.com/testing accessed Feb 8, 2022; https://www.mayocliniclabs.com/test-catalog/search?q=hepatitis+delta accessed Feb 15, 2022; https://www.eurofins-viracor.com/clinical/test-menu/?search_field=HDV accessed Feb 15, 2022; https://www.bioagilytix.com/bioagilytix-diagnostics/ accessed Feb 15, 2022, https://www.bioreference.com/physicians/resources/test-directory/?type=by_test&test_id=1840 accessed Feb 15, 2022

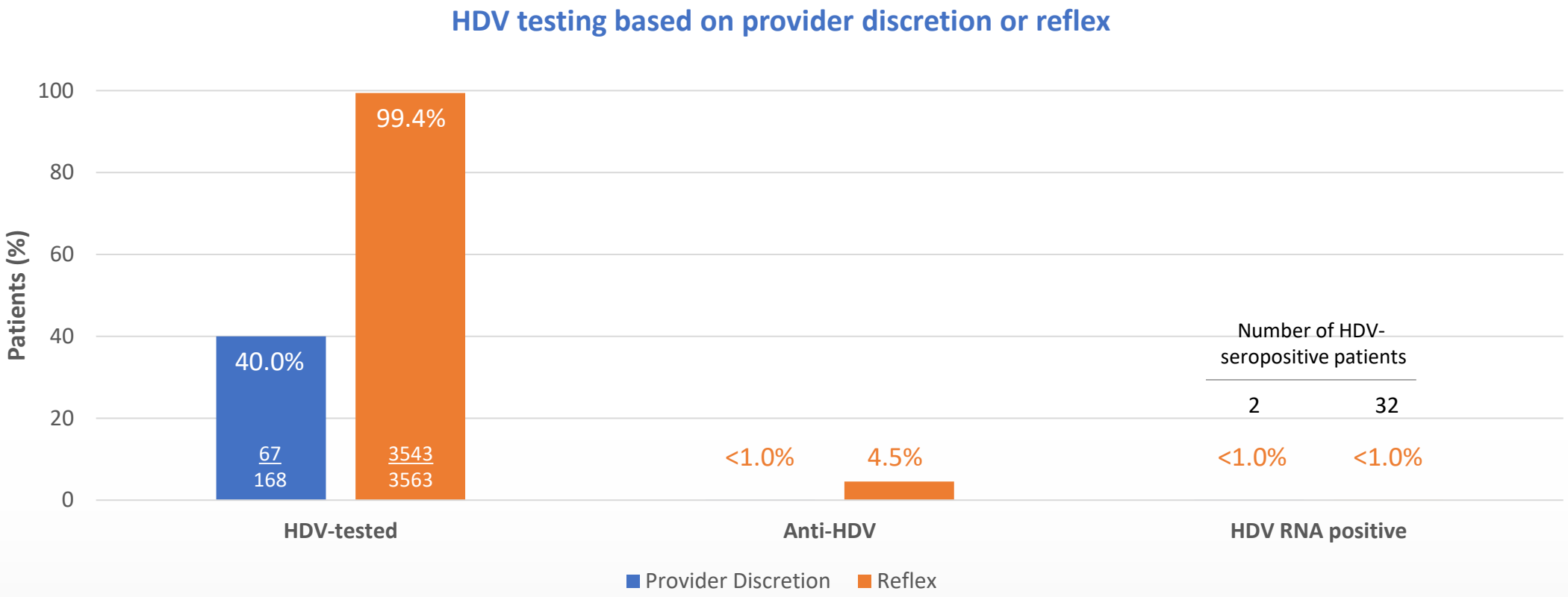
Current HDV Testing: Impact on Follow-up



Adapted from: Feld JJ. *Clin Liv Dis*. 2018;12(5):125-129.

HBsAg-positive Reflex to Anti-HDV: 2 London Centers

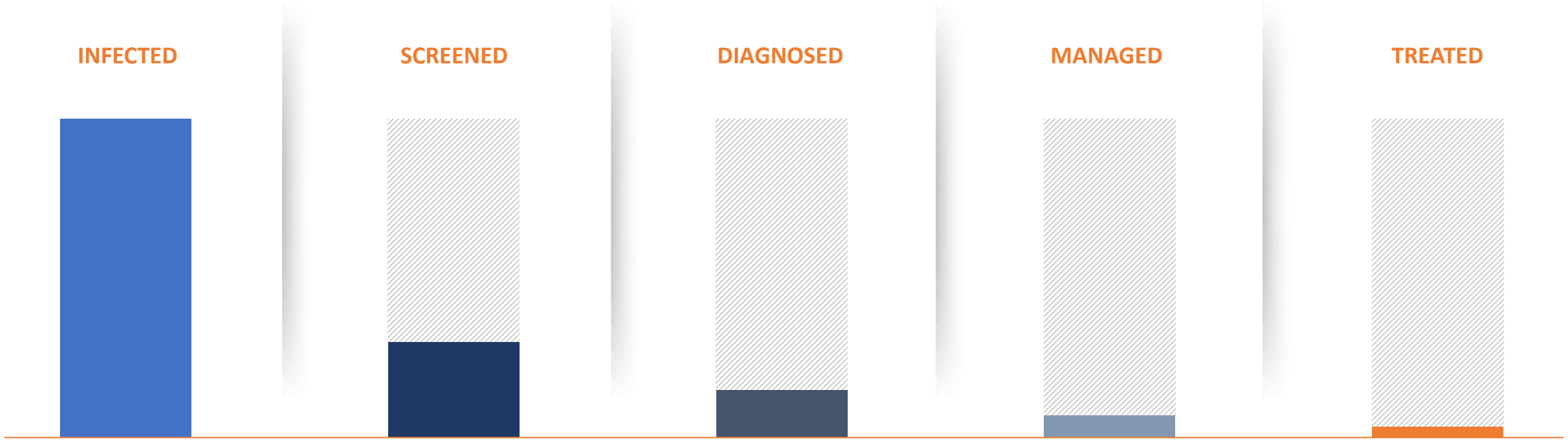
Cross-sectional analysis of HDV testing among HBsAg-positive patients at 2 London Centers, 2005-2012



The center with a reflex laboratory algorithm achieved anti-HDV testing of almost all first HBsAg-positive samples over a 12-year period

El Bouzidi K, et al. *J Clin Virol*. 2015;66:33-37.

There Are Unmet Needs Across the HDV Cascade of Care[1-3]



- Lack of robust data
- Number of patients with HDV unknown

- Test availability
- Standardized screening tests needed
- Standardized screening policies needed

- Protocol for testing HDV in HBsAg-positive patients needed
- Protocol for HDV confirmation in HBsAg-positive patients needed

- Surveillance protocols to detect rapid disease progression needed

- Lack of effective and specific treatment options
- Clarity on which stage of disease to treat patients needed

1. Stockdale AJ, et al. *J Hepatol*. 2020;73(3):523-532. 2. Miao Z, et al. *J Infect Dis*. 2020;221(10):1677-1687. 3. Shah PA, et al. *Gastroenterol Rep (Oxf)*. 2019;7(6):396-402.

Testing Recommendations for HDV

	WHOM TO TEST?	HOW TO TEST?
AASLD[1] (2018)	○ HBsAg+ patients with HDV risk factors ○ Low/undetectable HBV DNA and high ALT	○ Anti-HDV ○ HDV RNA
EASL[2] (2017)	○ All patients infected with HBV	NO RECOMMENDATION
APASL[3] (2016)	○ Patients with chronic HBV and chronic liver disease	○ HDAg or Anti-HDV ○ HDV RNA
WHO[4] (2015)	NO RECOMMENDATION	○ Anti-HDV ○ HDV RNA

AASLD=American Association for the Study of Liver Diseases; APASL=Asian Pacific Association for the Study of the Liver.

1. Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599. 2. EASL. *J Hepatol*. 2017;67(2):370-398. 3. Sarin SK, et al. *Hepatol Int.* 2016;10(1):1-98. 4. WHO. March 2015. Accessed March 30, 2021. https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1

Barriers to HDV Screening

DIAGNOSTIC CHALLENGES[1-3]

Not widely available recently in some countries and potentially inconclusive HDV antibody tests

Lack of routine screening of patients with HBsAg

Lack of standardization of HDV RNA tests (although newer assays are better standardized)

LACK OF SCREENING

EDUCATION CHALLENGES[4-6]

Limited and conflicting guidance on HDV screening (national and international guidelines)

Limited HCP education/ awareness of HDV

Reduced motivation to screen due to no approved treatment options until recently[a]

[a]No approved therapy exists in the United States.

1. Wedemeyer H, Negro F. *Gut*. 2019;68(3):381-382. 2. Safaie P, et al. *Virus Res*. 2018;250:114-117. 3. EASL. *J Hepatol*. 2017;67(2):370-398. 4. Terrault NA, et al. *Hepatology*. 2018;67(4):1560-1599. 5. Sarin SK, et al. *Hepatol Int*. 2016;10(1):1-98. 6. WHO. March 2015. Accessed March 30, 2021. https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1

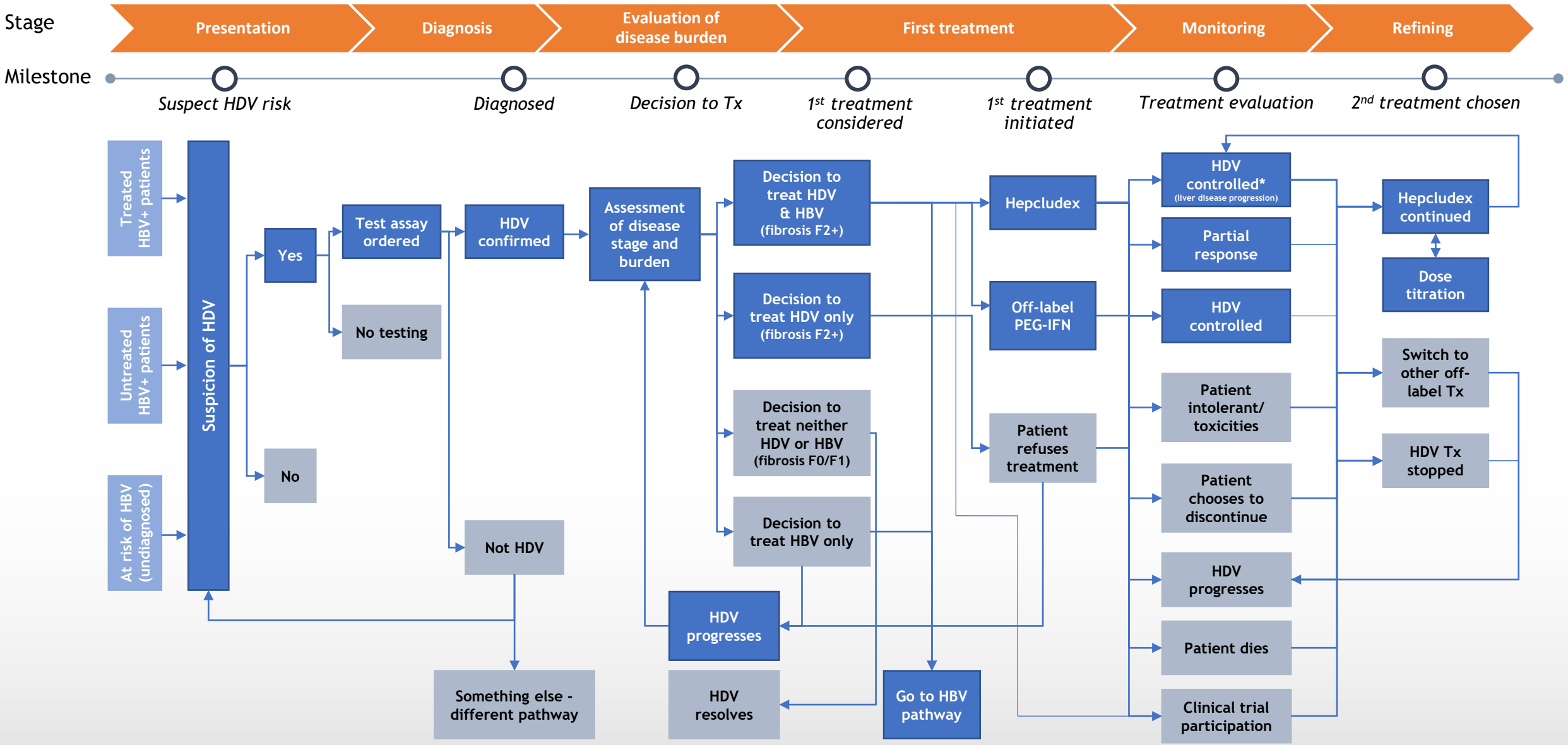
Guideline recommendations for management of HDV - treatment

	Treatment options	Treatment endpoint	Management
AASLD[1] (2018)	• PEG-IFNα for 1 year • Patients with elevated HDV RNA and ALT elevation	• Undetectable HDV RNA • ALT normalisation/ improved histology	• Test for HDV relapse if ALT increases • Manage in specialist centres
APASL[2] (2016)	• PEG-IFNα for ≥1 year • Optimal duration of therapy not well defined	• Undetectable HDV RNA	• Monitor for ≥6 months post-treatment
EASL[3] (2017)	• PEG-IFNα for ≥48 weeks • HDV/HBV patients with compensated liver disease	• Undetectable HDV RNA	• Long-term HDV RNA monitoring required
WHO[4] (2015)	• PEG-IFNα for ≥1 year	• Undetectable HDV RNA	No recommendation

1. Terrault N, et al. Hepatology 2018;67:1560-99; 2. Sarin SK, et al. Hepatol Int 2016;10:1-98;
3. European Association for the Study of the Liver. J Hepatol 2017;67:370-98;
4. WHO HBV guidelines. March 2015. Available at: https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1 (Accessed March 2021).

NOTE: Treatment of HDV with PEG-IFNα is off-label.
AASLD: American Association for the Study of Liver Diseases; ALT: alanine aminotransferase; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HDV: hepatitis D virus; PEG-IFN: pegylated interferon; RNA: ribonucleic acid; WHO: World Health Organization.

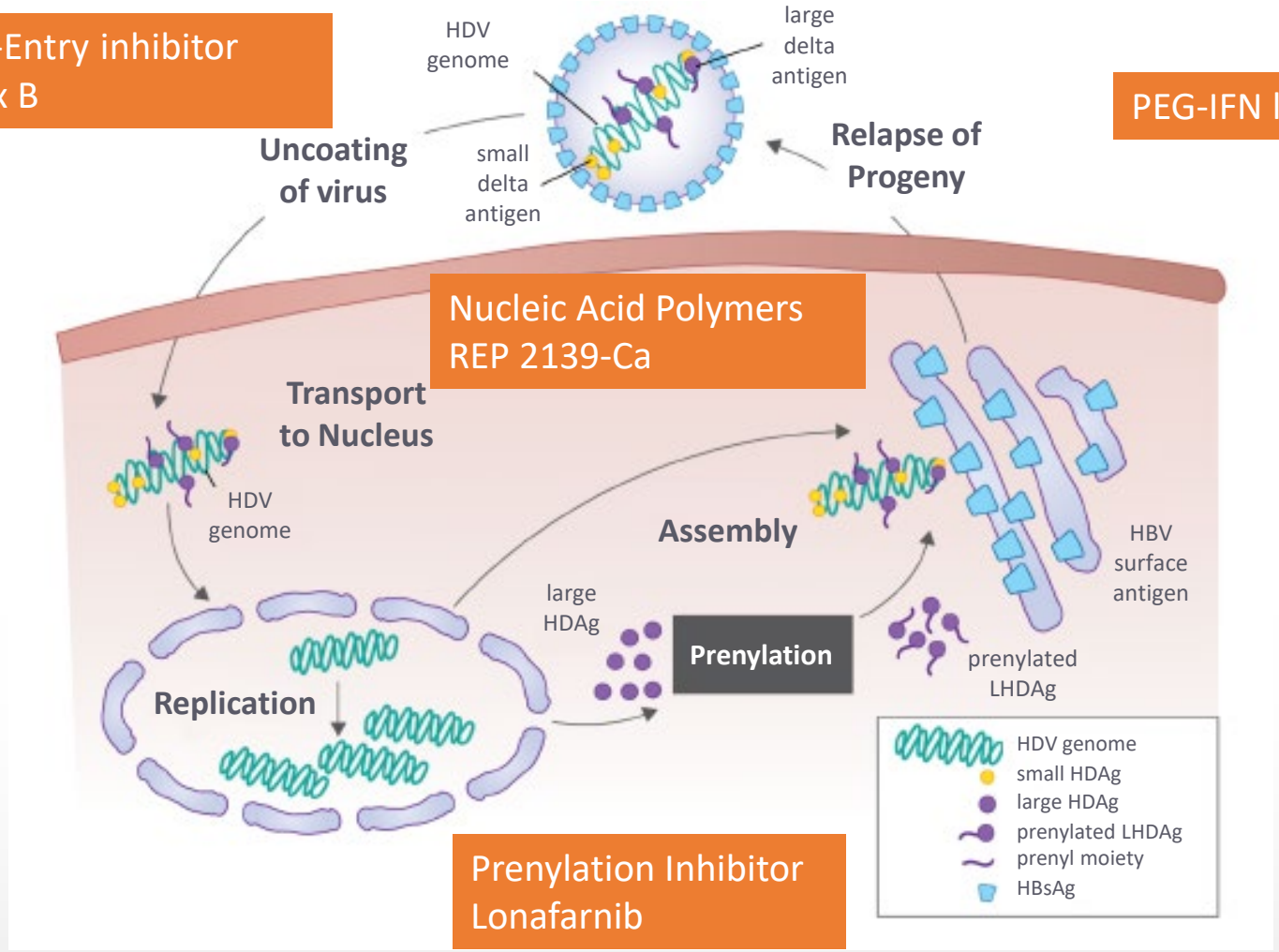
Identification and management of chronic HDV



Hepatitis Delta: New Therapies

HBV/HDV-Entry inhibitor
Myrcludex B

PEG-IFN lambda



Nucleic Acid Polymers
REP 2139-Ca

Prenylation Inhibitor
Lonafarnib

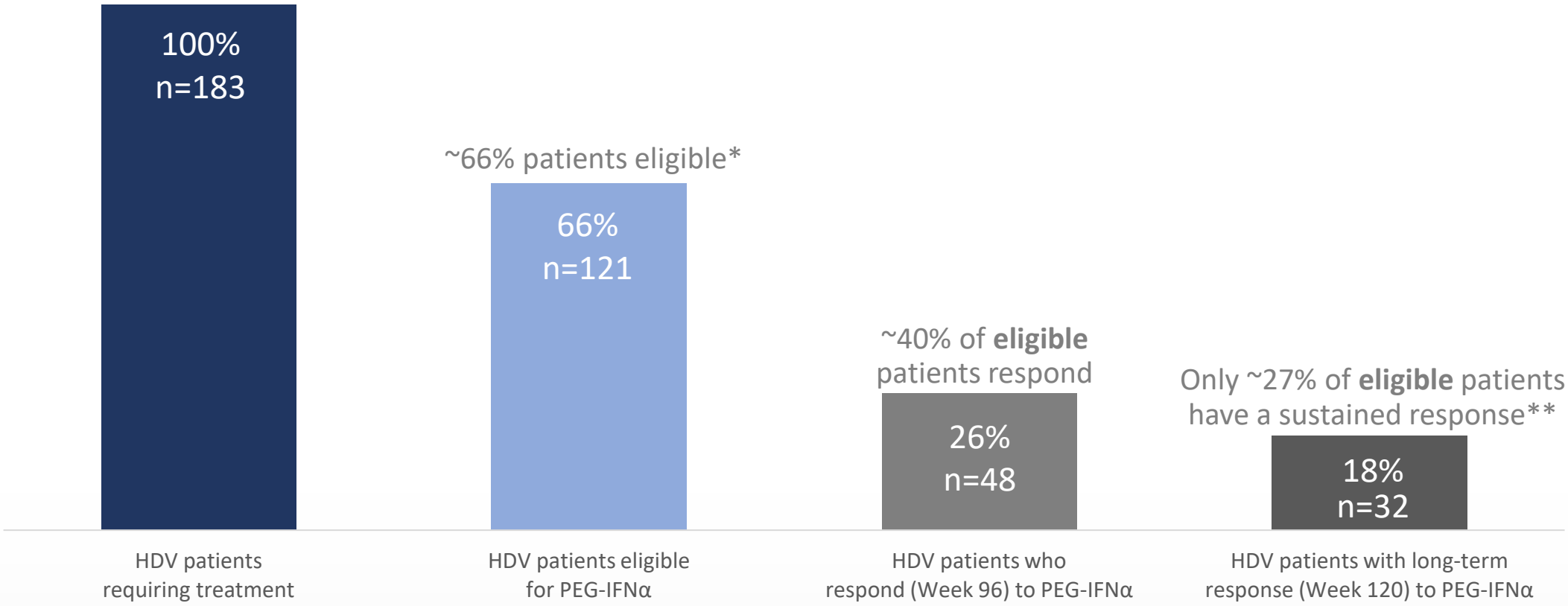
Regulatory and guideline efficacy endpoints

	Chronic On-Therapy Endpoint	Cure Off-Therapy Endpoint
 Draft Guidance November 2019	*"…a **greater than or equal to 2-log$_{10}$ decline in HDV RNA and ALT normalization** on-treatment could be considered an acceptable surrogate endpoint"*	*"The proportion of trial patients with **undetectable serum HDV RNA** (defined as less than the lower limit of quantification (LLOQ), target not detected (TND)) and **ALT normalization**."*
  2019 EASL-AASLD HBV Treatment Endpoints Conference October 2019	*"…a **2-log reduction in HDV RNA might suffice**."*	*"…**undetectable serum HDV RNA 6 months after stopping treatment** as the endpoint …Normalisation of ALT is also desired"*

1. FDA. https://www.fda.gov/media/132137/download. Accessed February 2021; 2. Cornberg M, et al. J Hepatol. 2020 Mar;72:539-57. doi: 10.1016/j.jhep.2019.11.003. Epub 2019 Nov 12.

ALT: alanine aminotransferase; HBV: hepatitis B virus; HDV, hepatitis D virus; RNA: ribonucleic acid.

Response to PEG-IFNα treatment

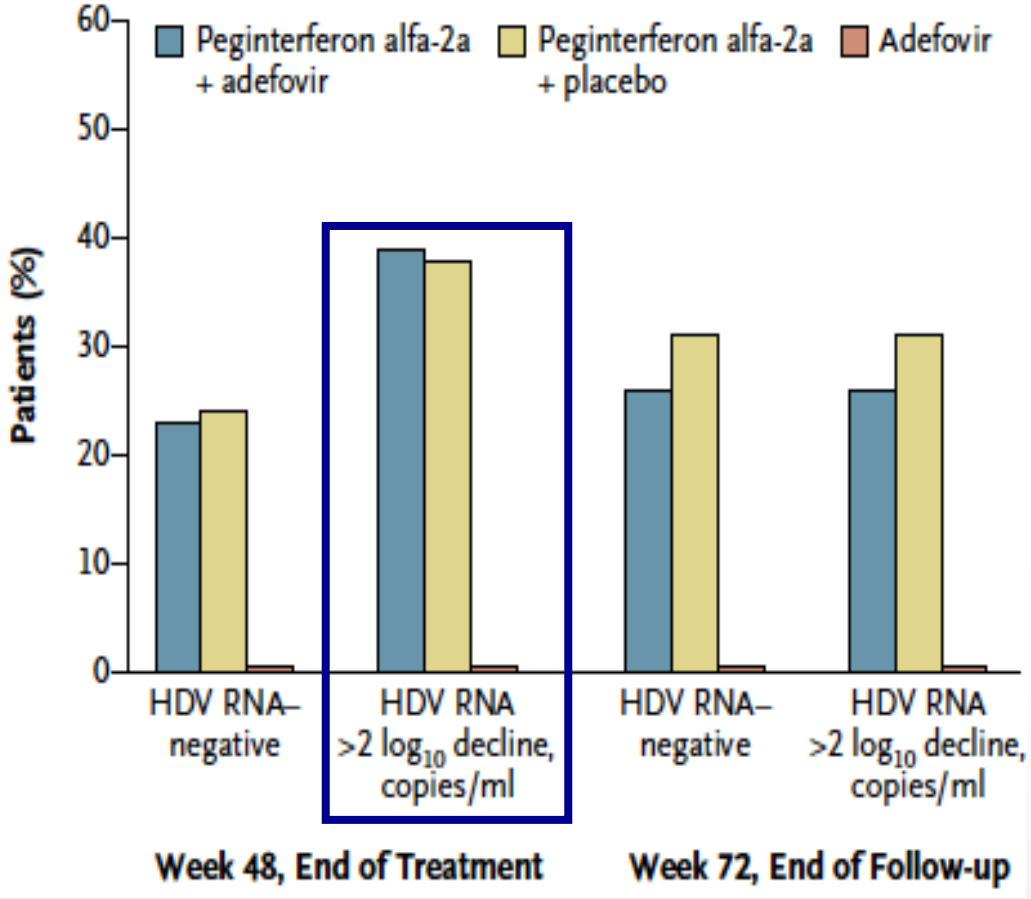


Only a subset of patients are treated with PEG-IFNα, of which a small proportion respond to treatment

*Ineligibility based on contraindications, intolerance and presence of advanced liver disease in HIDIT-II (62 of 183 screened did not meet inclusion criteria or met exclusion criteria);
**Response defined as undetectable HDV RNA after 120 weeks of treatment.
HDV: hepatitis D virus; PEG-IFNα: pegylated interferon alpha.

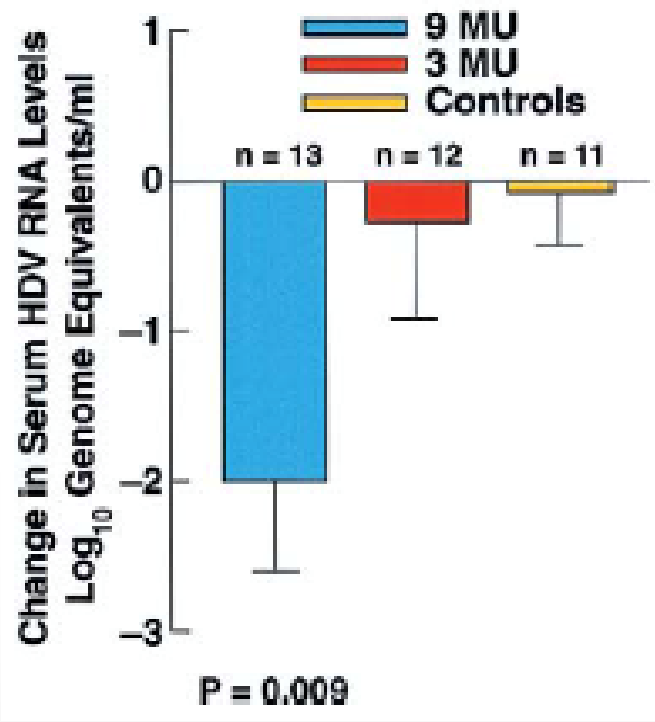
Wedemeyer H, et al. Lancet Infect Dis 2019;19:275-86.

EOT HDV RNA ≥ 2 Log Decline Improves Survival



Wedemeyer, Yurdaydin et al, NEJM 2011

Of 17 pts with post-tx week 24 HDV RNA negativity, 9 were HDV RNA (+) at EOT



Farci et al, Gastro 2004

HEPCLUDEX (Bulevirtide) EMA Indication

Indication	• Treatment of chronic hepatitis delta virus (HDV) infection in HDV RNA-positive adult patients with compensated liver disease
Administration	• Administered at 2 mg once daily (every 24 hours ± 4 hours) by subcutaneous injection • Monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying HBV infection
Instructions for Use	• Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection • Optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit

Reference: Summary of Product Characteristics, available at www.eua.europa.eu

Bulevirtide monotherapy at low and high dose in patients with chronic hepatitis delta: 24 weeks interim data of the phase 3 MYR301 study

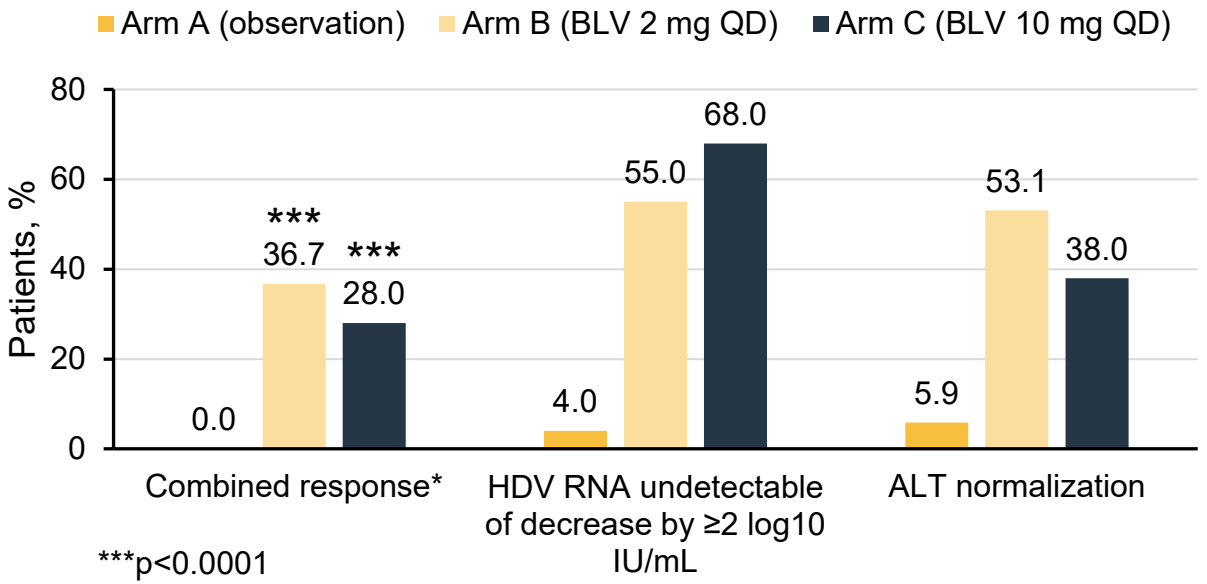
RESULTS

- *Baseline demographics*:
  - 57.3% of patients were male, 82.7% white, and the mean age was 41.8 years
  - HDV RNA levels were 5.05 $\log_{10}$ IU/mL and ALT mean levels were 110.9 U/L
  - 47.3% of patients had compensated liver cirrhosis
- *Safety*: BLV was well tolerated during the first 24 weeks

TEAE (patient n)	Arm A (Observation; n=51)	Arm B (BLV 2 mg QD; n=49)	Arm C (BLV 10 mg QD; n=50)
Any	55 (26)	121 (32)	245 (36)
Grade 3–4 AE	2 (4)	2 (4)	1 (2)
Serious TEAE	1	0	0

- *Efficacy*: after 24 weeks, significantly more patients treated with BLV (2 mg or 10 mg) vs no antiviral treatment achieved:
  - A combined virological and biochemical response*
  - An HDV RNA decrease by ≥2 log10 IU/mL
  - ALT normalization

Efficacy endpoints



CONCLUSION

- These interim data from the phase 3 trial confirm that 24 weeks of BLV monotherapy was associated with significant HDV RNA decline and improvement in biochemical disease activity
- BLV is well tolerated in patients with compensated HDV infection
- These findings further support the conditional approval of 2 mg BLV in the EU

*Undetectable HDV RNA (<LoD) or decrease by ≥2 log10 IU/mL and ALT normalization.

Wedemeyer, et al. ILC 2021; LBP-2730

EASL™ The Home of Hepatology

Beyond cATU: Bulevirtide ± PegIFNα-2a for Chronic HDV Infection: Virologic Efficacy

Time	HDV RNA Undetectable or Decrease by ≥2 log_{10} From Baseline,*† % (n/N)	
	Bulevirtide (n = 77)	Bulevirtide + PegIFNα-2a (n = 68)
Day 0	0	0
Mo 1	1.5 (1/66)	22.0 (11/50)
Mo 2	14.8 (8/54)	48.8 (20/41)
Mo 3	28.2 (20/71)	68.6 (35/51)
Mo 6	52.3 (34/65)	84.4 (38.45)
Mo 9	59.2 (29/49)	89.5 (34/38)
Mo 12	68.3 (28/41)	93.9 (31/33)

*Missing does not equal failure. †Study not powered to compare bulevirtide vs bulevirtide + pegIFNα-2a.

De Ledinghen. AASLD 2021. Abstr OA21.

Slide credit: clinicaloptions.com

‡

Other Drug classes by therapeutic target in clinical development

	HBsAg secretion inhibitors	Prenylation inhibitors	Immune modulators
Therapies in development (Company)	• REP2139 **(Replicor)**	• Lonafarnib (Eiger Biopharmaceuticals)	• PEG-IFNλ (Eiger Biopharmaceuticals)
Stage of replication cycle affected	• Broad-spectrum antiviral activity	• Inhibits L-HDAg prenylation	• Induces IFN-stimulated genes and activates JAK and STAT
Consequence(s)	• Inhibits export of HBsAg to serum • HDV virions cannot be formed without HBsAg	• Essential for interaction with HBsAg • Lack of prenylation prevents HDV virion formation	• General broad antiviral response
Progress	• Phase 2 trials	• Phase 3 trials*	• Phase 2 trials

*Lonafarnib is boosted with ritonavir.

HBsAg: hepatitis B surface antigen; HDV: hepatitis D virus; IFN: interferon; JAK-STAT: Janus-kinase-signal transducer and activator of transcription; L-HDAg: large hepatitis D antigen; PEG-IFN: pegylated interferon.

Gilman C, et al. World J Gastroenterol 2019;25:4580-97;
Koh C, et al. Gastroenterology 2019;156:461-6.

Do we need HDV cure in the era of HBV cure?

- HDV is the most severe form of hepatitis
- 15 – 20 Million chronically infected, presumably more
- Lack of global epidemiology data
- HDV requires only small amounts of HBsAg to complete viral packaging
- Only sterilizing HBV cure will obviate a need for an HDV cure
- Functional HBV cure: Maybe, but when ? Sufficient for HDV cure/control ?
- Sterilizing HBV cure: Not in sight, seems necessary for HDV cure !
- **Do we need HDV cure: YES !**

HDV Treatments Are Needed – HDV Cure is the Objective!

- HDV is the most severe form of hepatitis
- HDV requires only small amounts of HBsAg to complete viral packaging
- Theoretically, Sterilizing HBV cure is the only way to obviate a need for an HDV cure
- **Sterilizing HBV cure**: Nowhere in sight, remove all cccDNA and all integrants
- **Functional HBV cure:** Can it be discovered, developed and approved in our lifetime?
  - I expect 30% Functional Cure with 4 drug combination therapies, 60% Sustained HBV DNA Suppression and 10% Relapse < 4 years

HDV treatments:
In Phase 3; on track to be approved within the next 2-3 years!

Thank you!

Acknowledgements: