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Hepatitis Delta in Sub-Saharan Africa

With expert speaker:

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Associate Professor
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Have a Question?

Questions? Submit questions in the chat box at anytime throughout the webinar.

Hepatitis D Virus in Sub-saharan Africa

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Consultant-Gastroenterologist/Hepatologist
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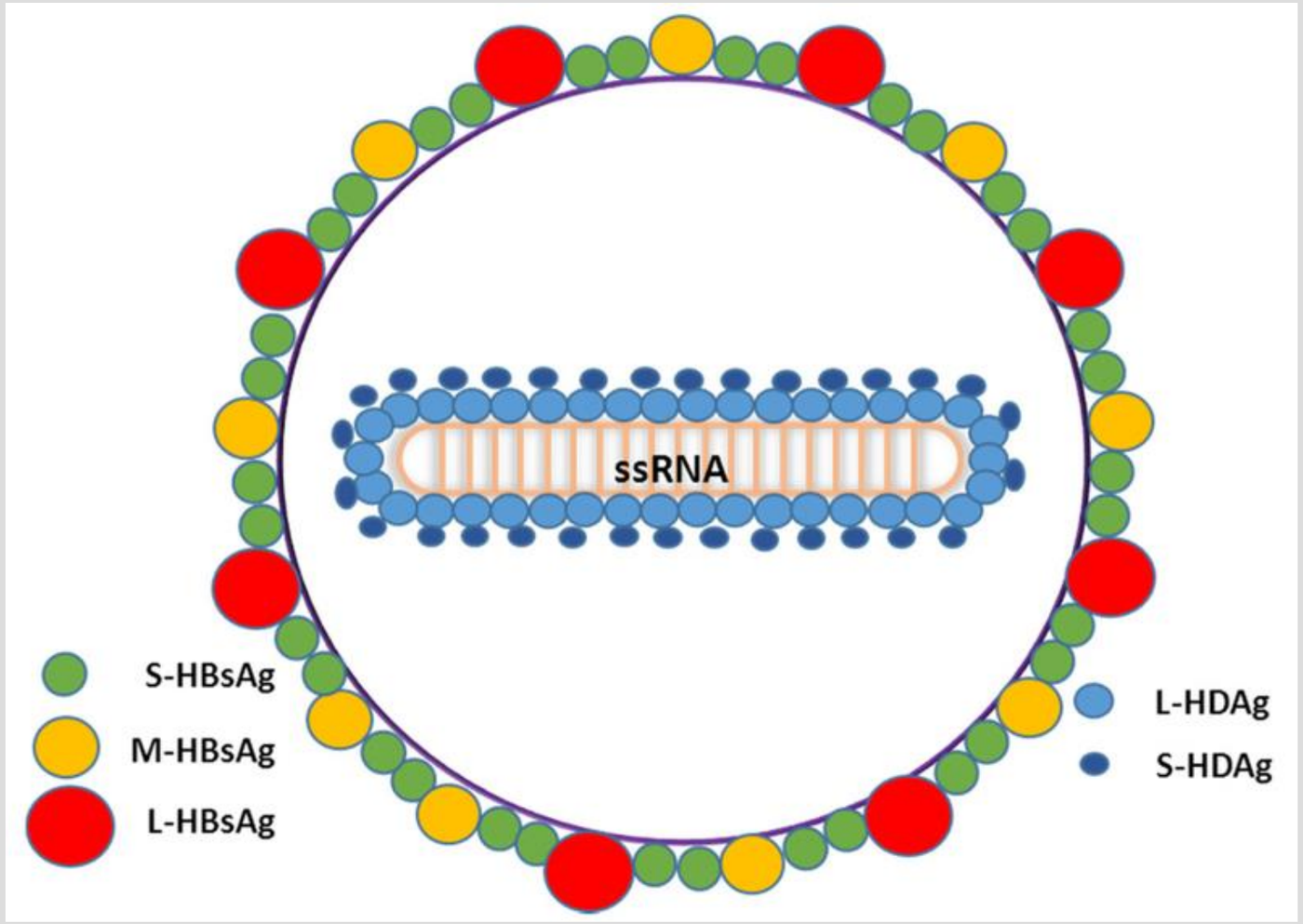
Webinar, June 6, 2019

Outline

* Introduction
* Epidemiology
* Ethiopian Experience
* Challenges
* Future perspectives
* Summary

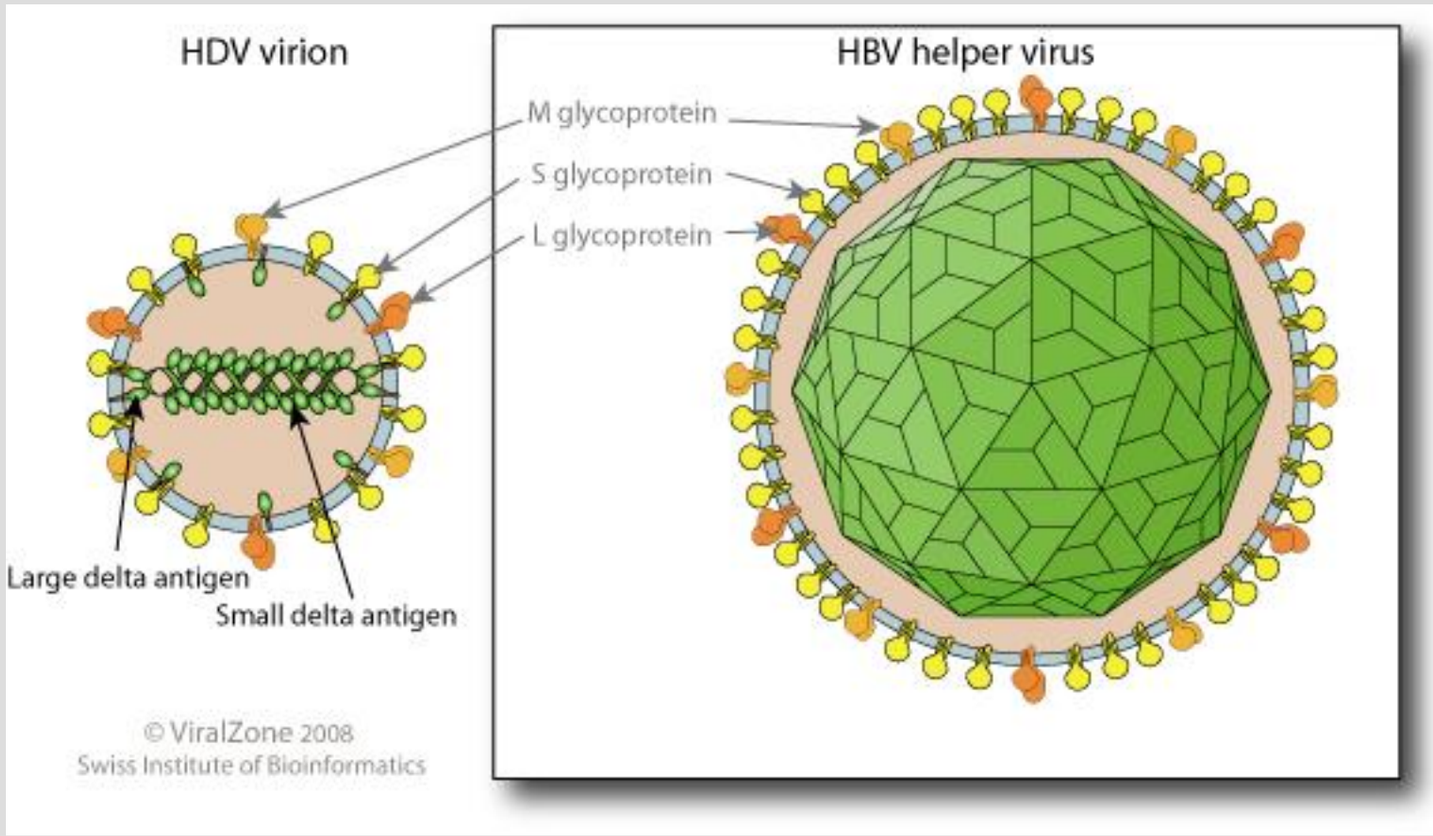


Hepatitis D Virus

- Defective virus
- 35 nm diameter consisting

small delta Ag surrounded by

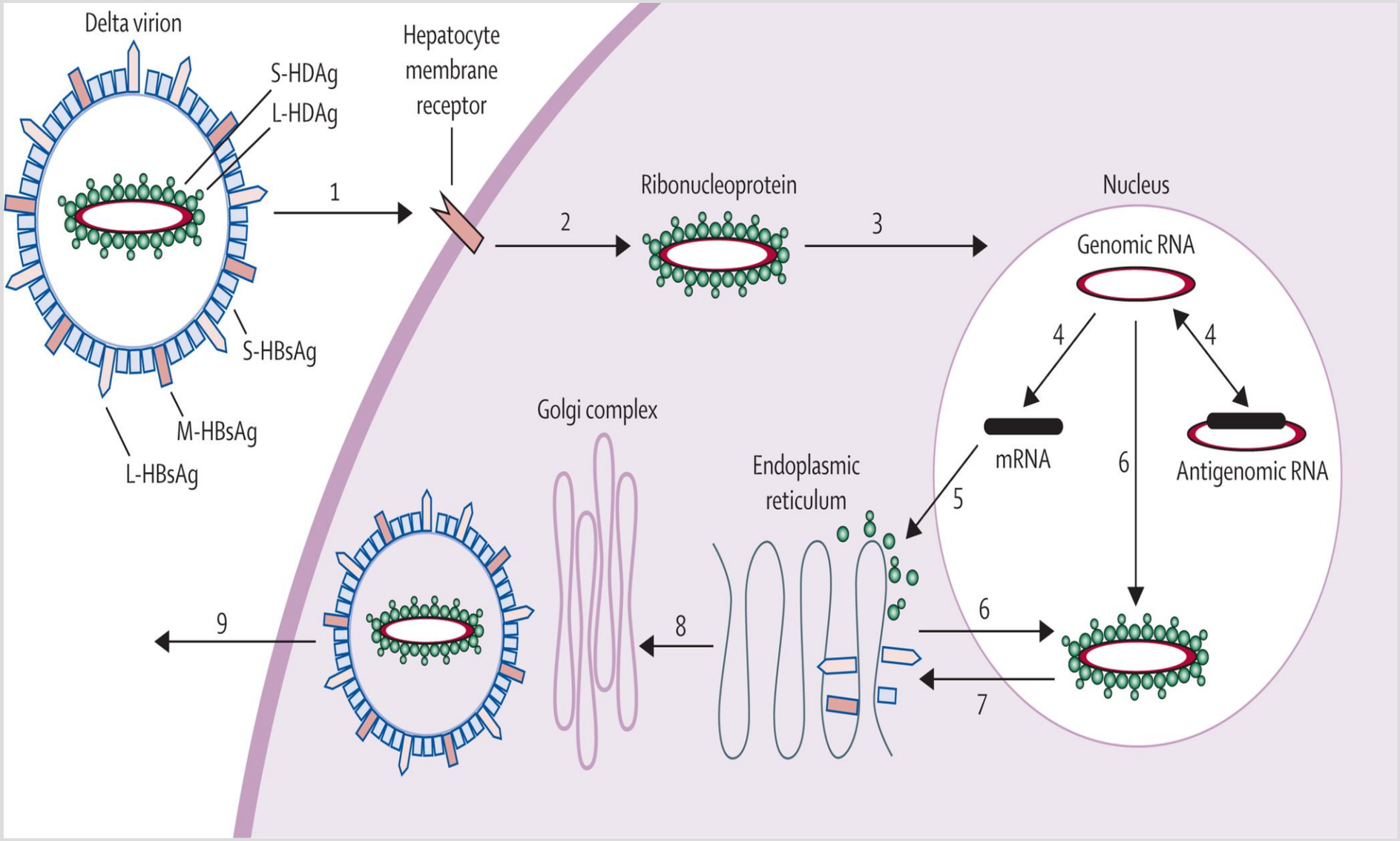
outer coat of HBsAg



- Very small genome - ssRNA, negative sense (1,700 nucleotides)

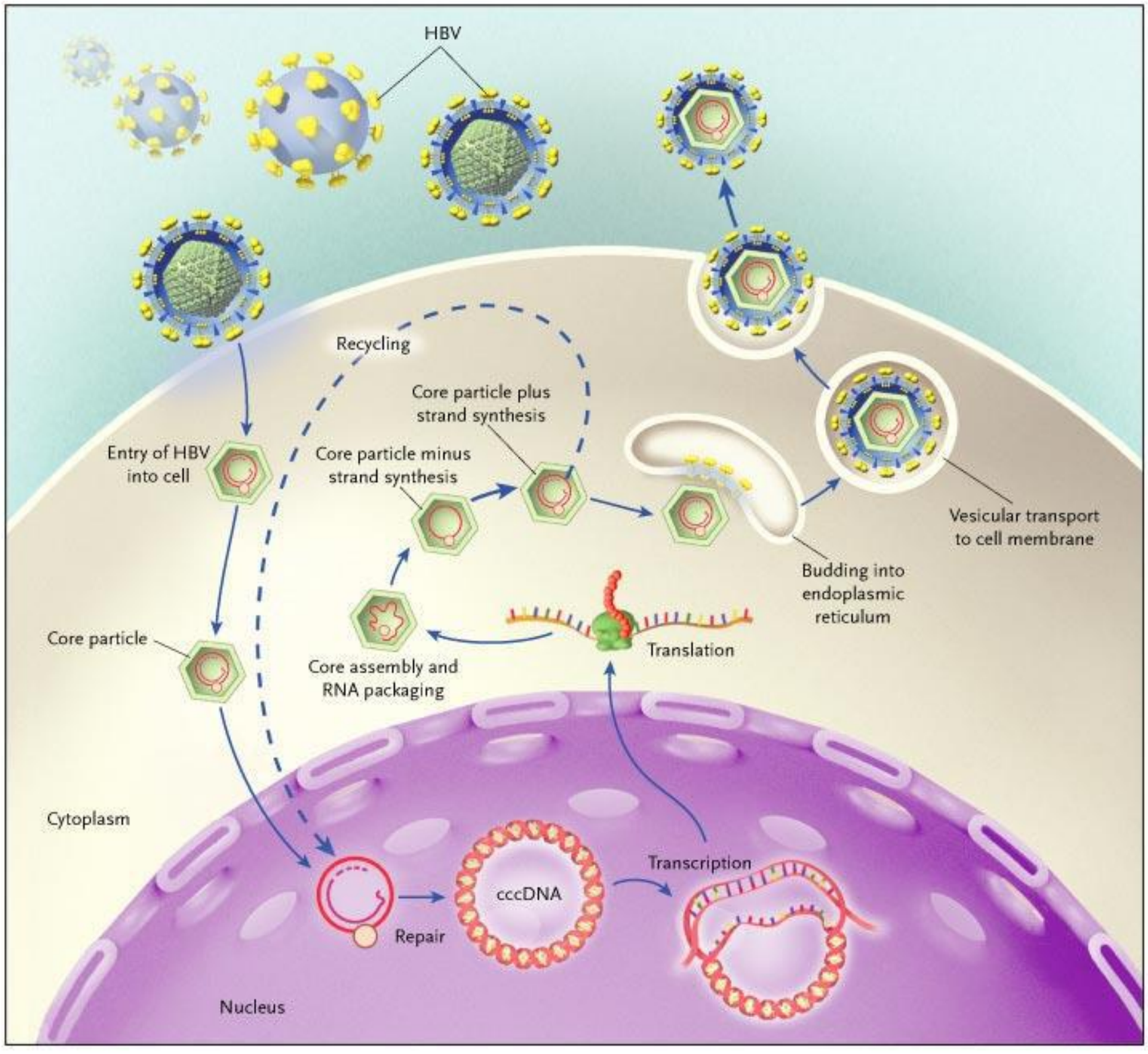
Wang et al.; 1986 -Ryu et al,; 1993

Replication of HDV



Hughes et al., Lancet 2011; 378;9785, 73-85

Replication of HBV



Ganem& Prince, NEJM 2004

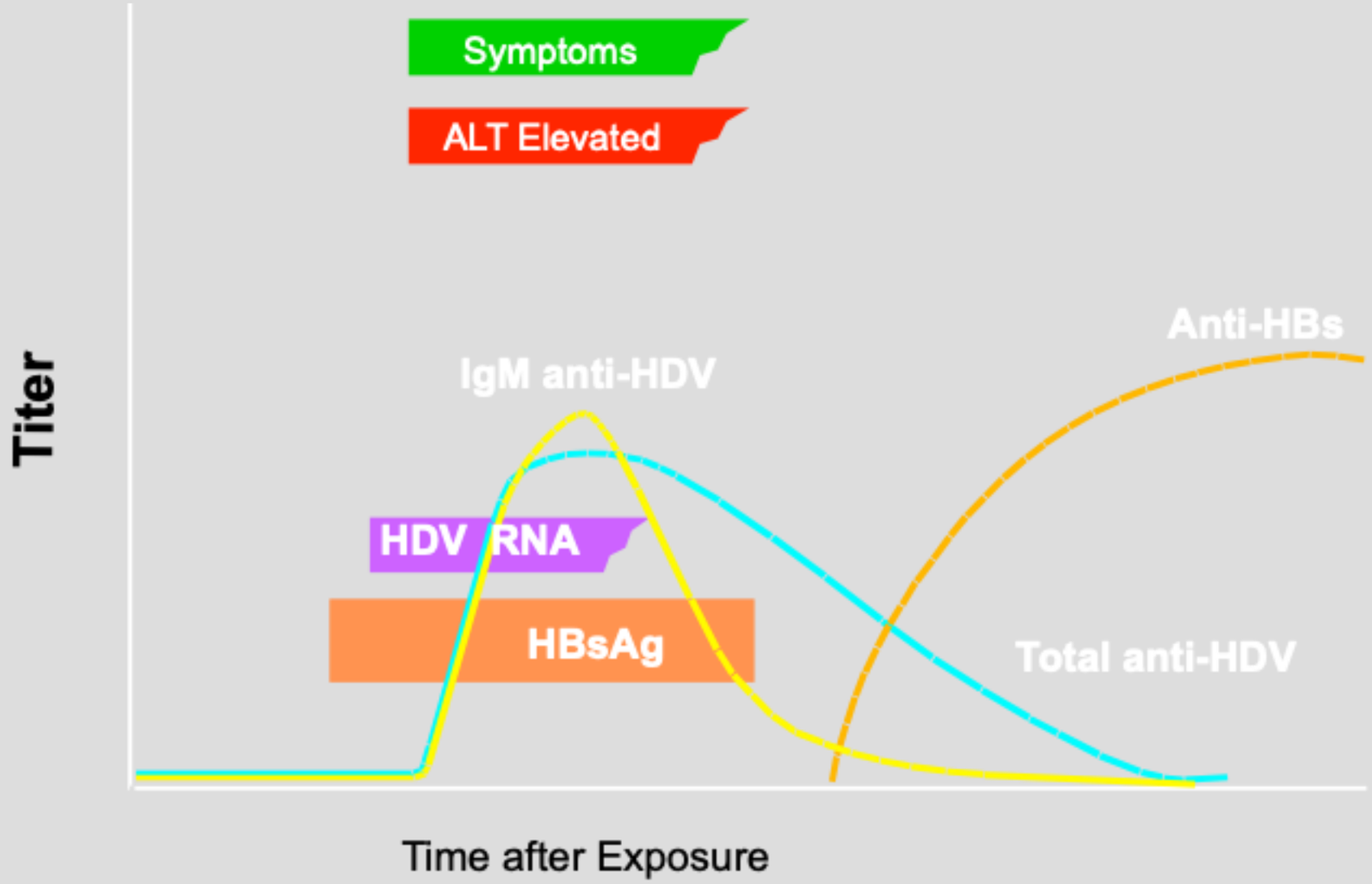
Modes of Transmission

- Requires presence of HBsAg
- Similar modes of transmission to HBV
- Vertical transmission of HDV - rare
- Infection during early childhood
- Sexual transmission
- Percutaneous exposure, scarification
- Special risk groups:- IV drug users, Dialysis, HIV +, Hemophilia
- Blood transfusion, unsterile syringes …

Hepatitis D Virus

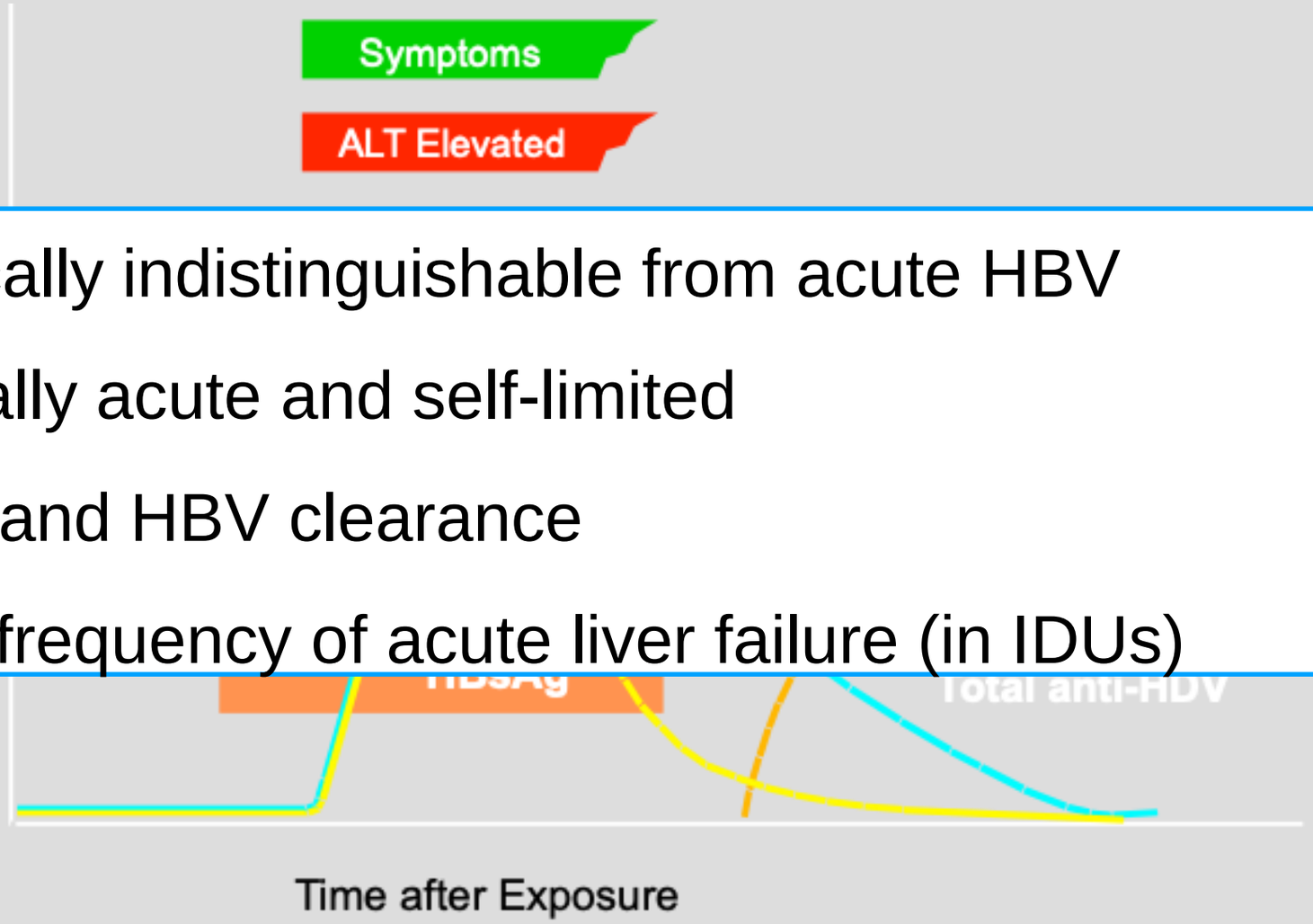
- Immune mediated liver injury
  - Superinfection in a patient with CHB
  - Coinfection

HBV-HDV coinfection
Typical serological course



CDC

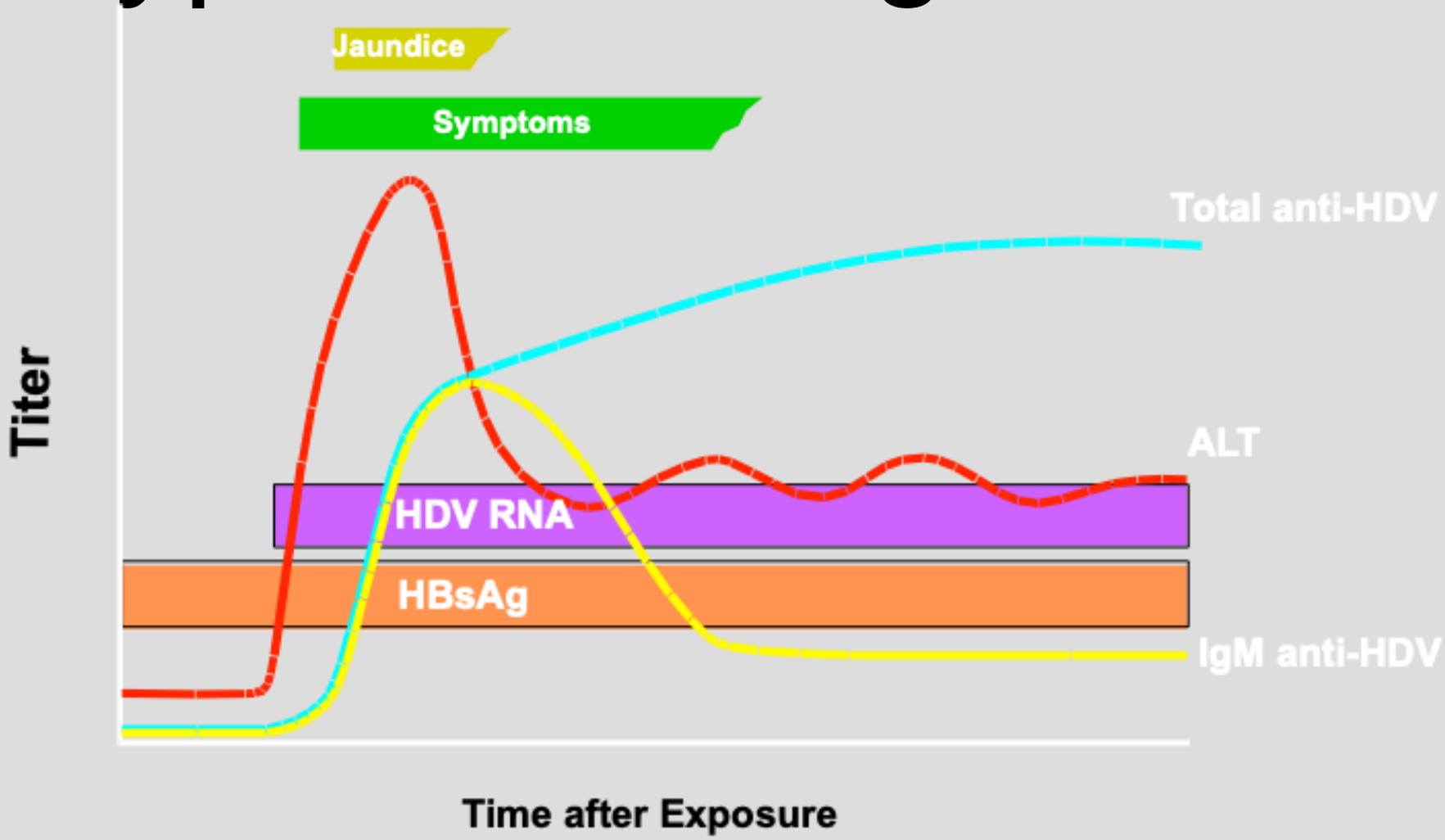
HBV-HDV coinfection
Typical serological course



- Clinically indistinguishable from acute HBV
- Usually acute and self-limited
- HDV and HBV clearance
- High frequency of acute liver failure (in IDUs)

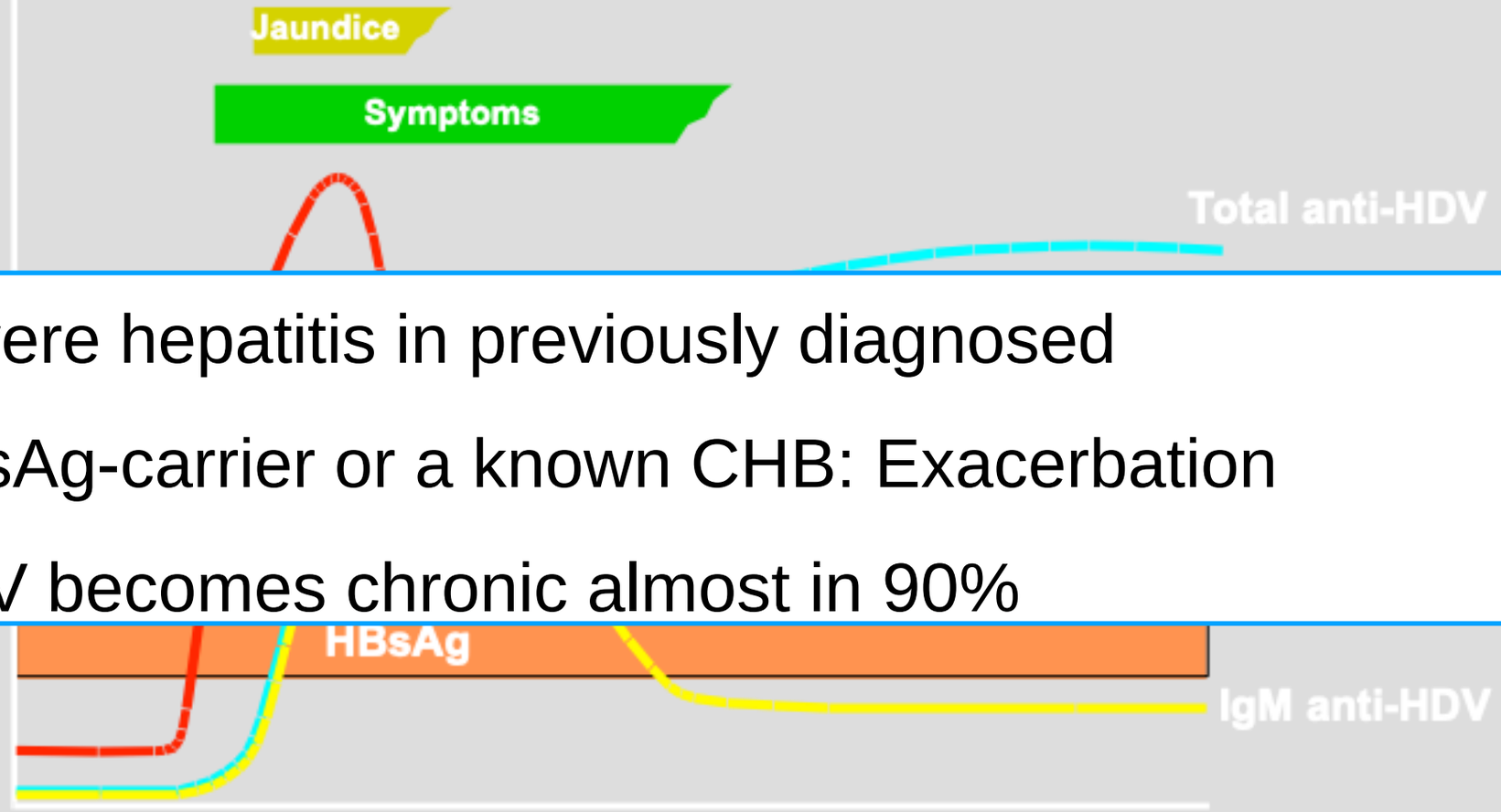
CDC

HBV-HDV Super-infection
Typical serologic course



CDC

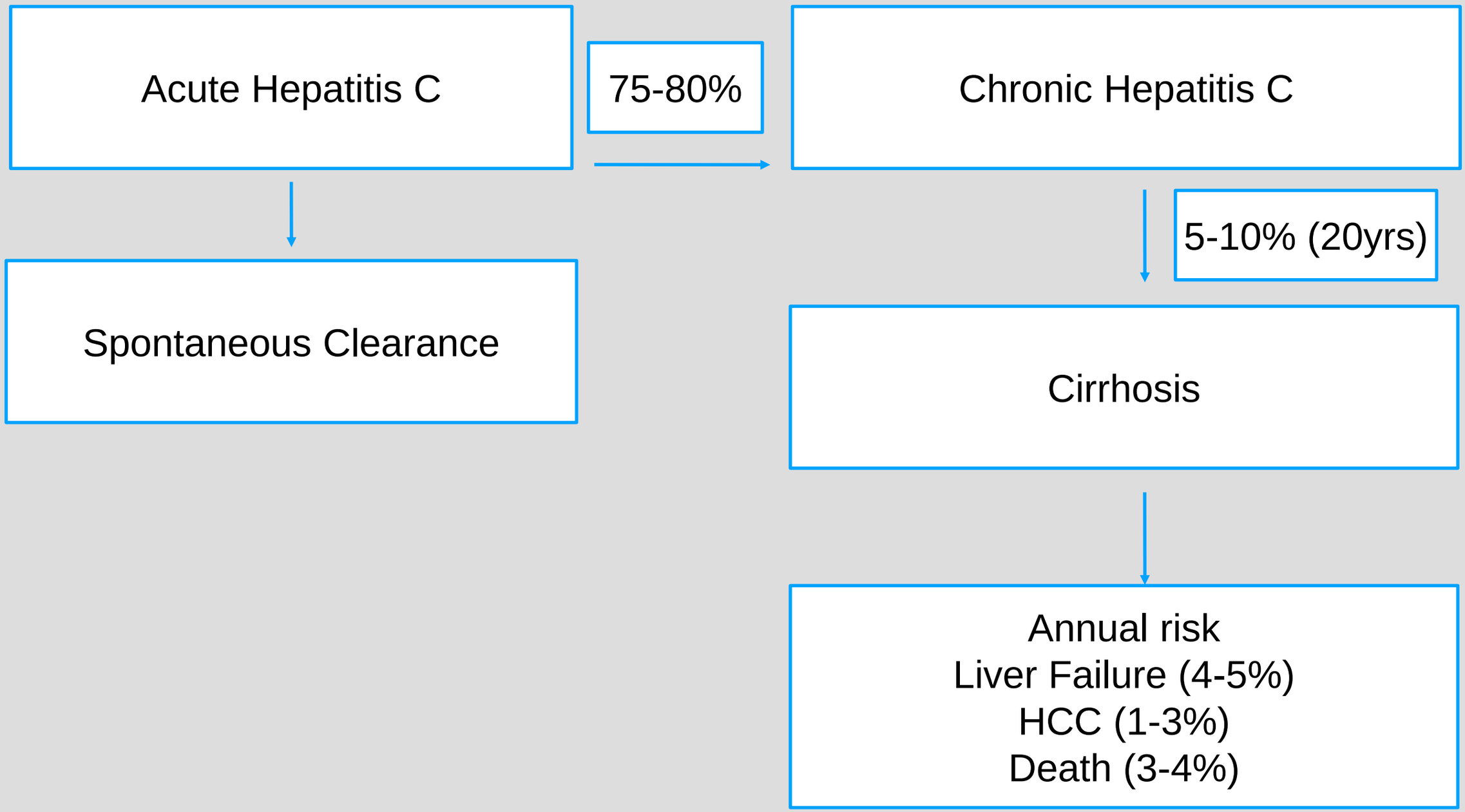
HBV-HDV Super-infection
Typical serologic course



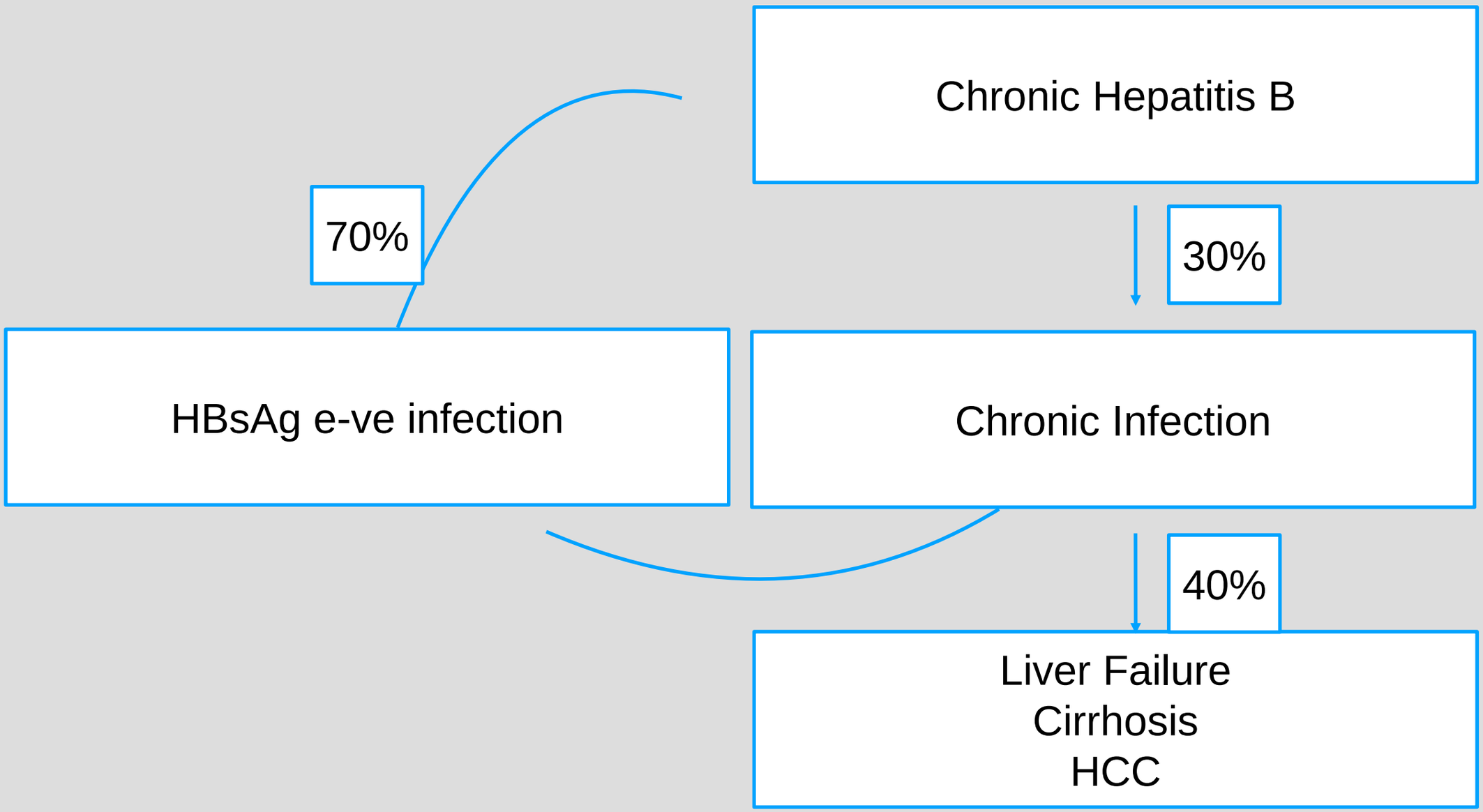
- Severe hepatitis in previously diagnosed
- HBsAg-carrier or a known CHB: Exacerbation
- HDV becomes chronic almost in 90%

CDC

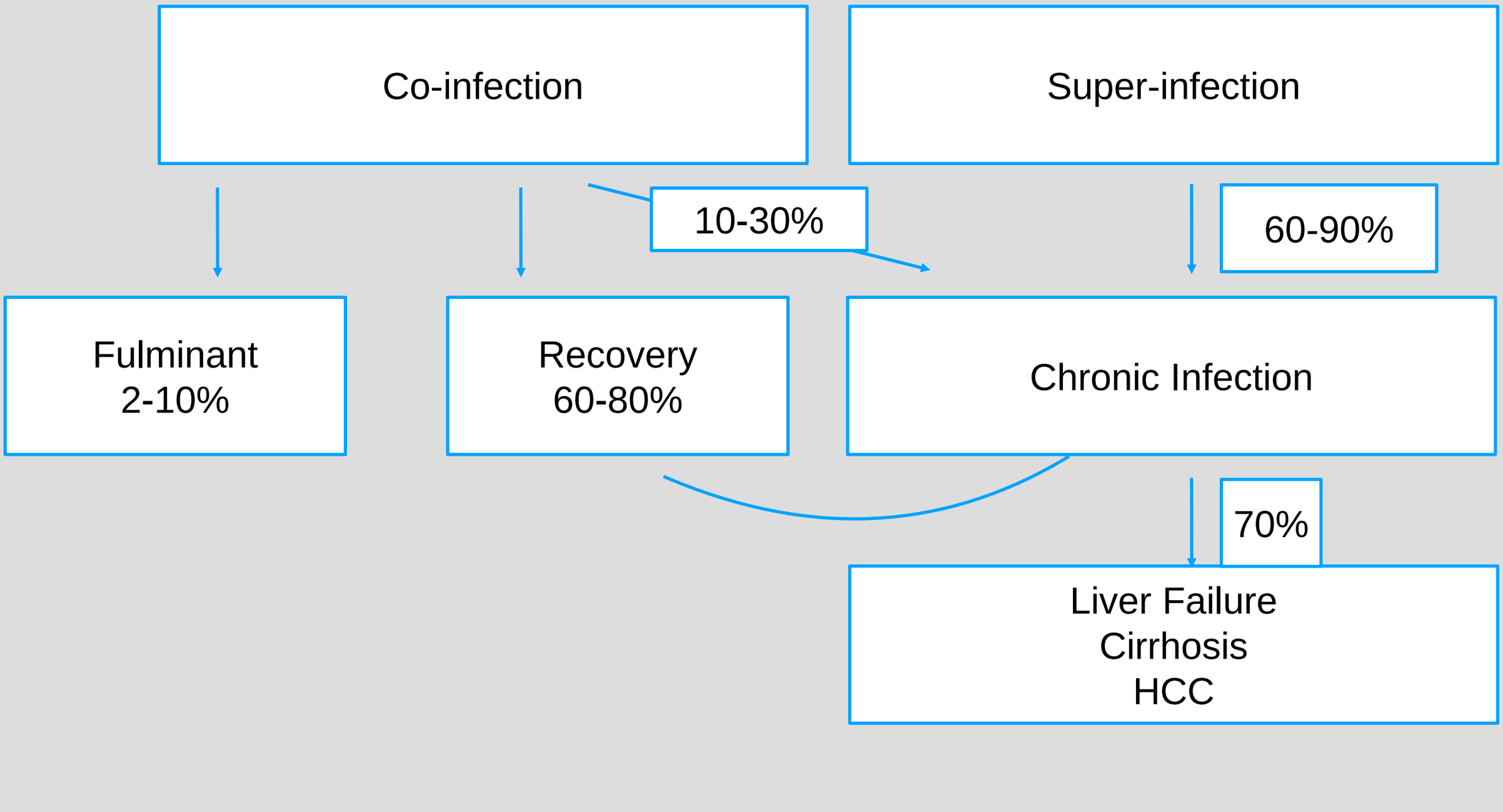
Natural history of HCV



Natural history of HBV



Natural history of HDV



- Responsible for most severe and difficult to treat hepatitis
- Severe/fulminant acute hepatitis
- Rapid progression to cirrhosis and HCC
- Annual rate of cirrhosis (4%), HCC (2.8%)
- * Screen for HDV in all carriers once when initiating and when worsening

Viral Dominance

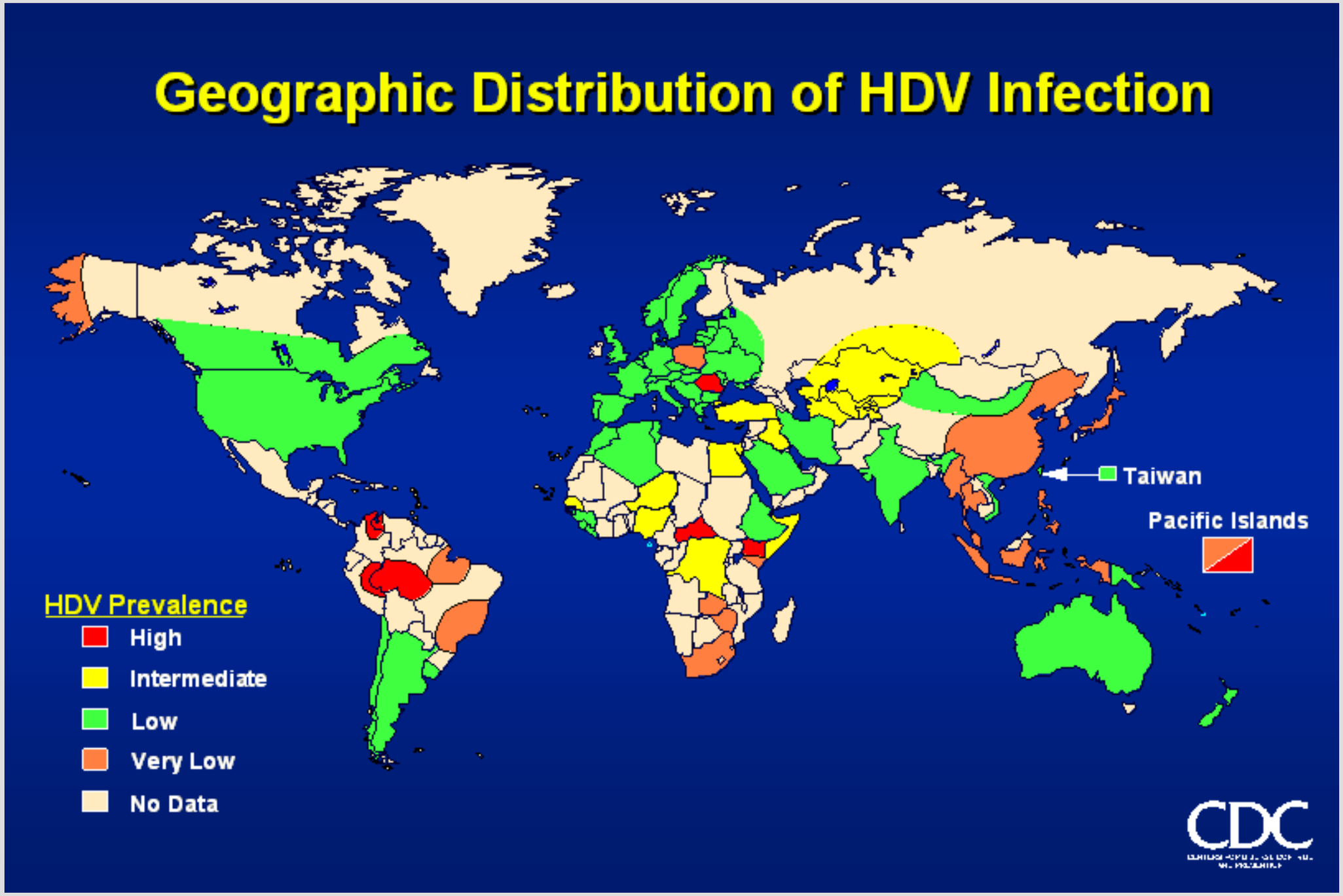
Typical

- HBV DNA suppressed
- High HDV RNA
- ALT elevated
- Advanced fibrosis
- HBeAg-ve, HBeAb+

Atypical

- HBV DNA high
- ALT levels fluctuate
- Progressive
- HCC

Epidemiology



- 15-20 million worldwide infection
- Large geographic variations
- High - Eastern Europe, the Middle East, Central Asia, northern South America and certain countries in sub-Saharan Africa
- Scarcity of data from Africa
- **Potentially major problem considering the data on HBV**

Prevalence of Anti-HDV antibodies in Africa

Central Africa:

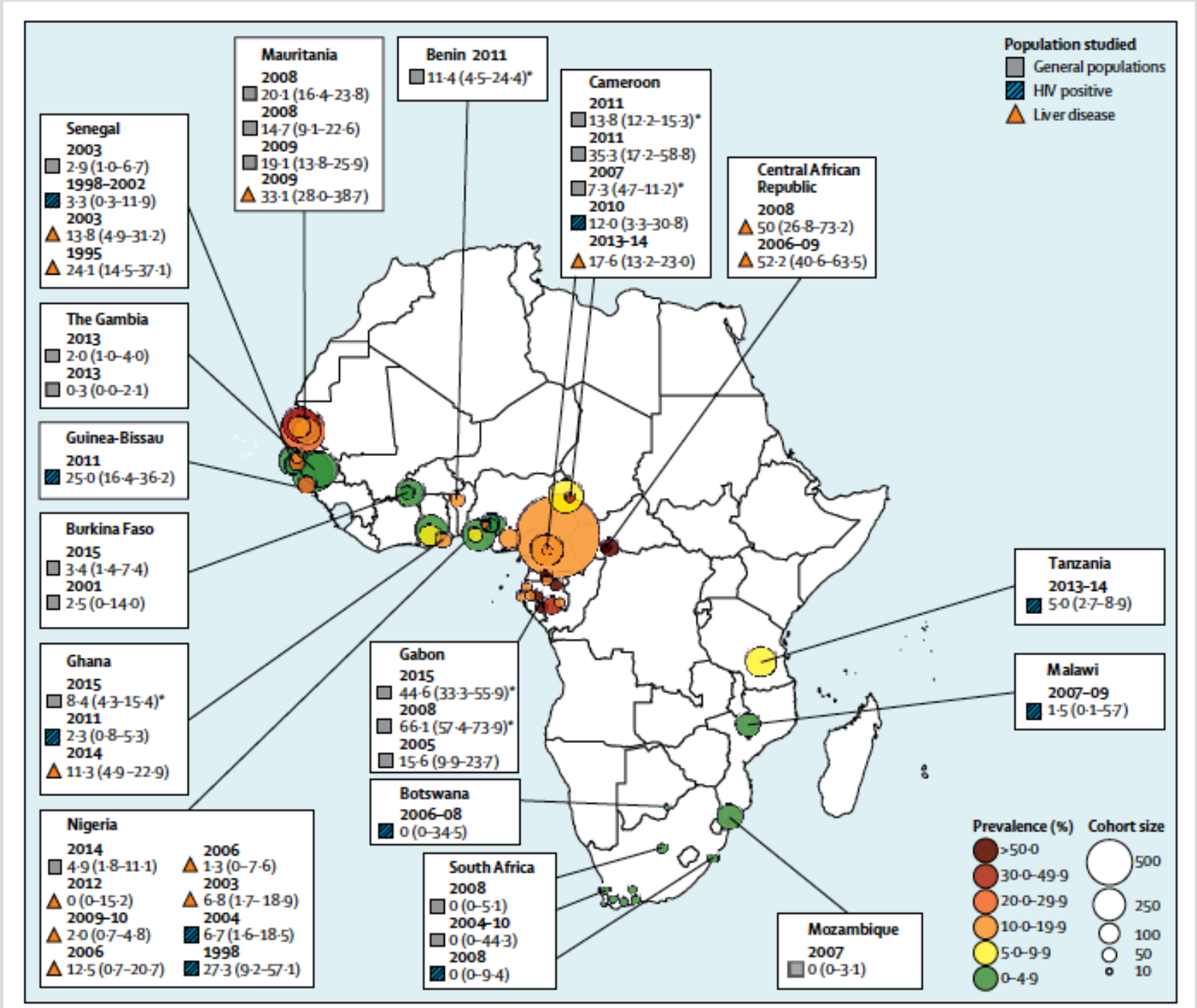
- Gen. Pop: 25.64%(12.09-42)
- HCC:37.77%(12.13-67.54)

West Africa:

- Gen. Pop:7.33% (3.55-12.20)
- HCC:9.57%(2.31-20.43)

East and South Africa:

- Gen.Pop: 0.05%(0.00-1.78)

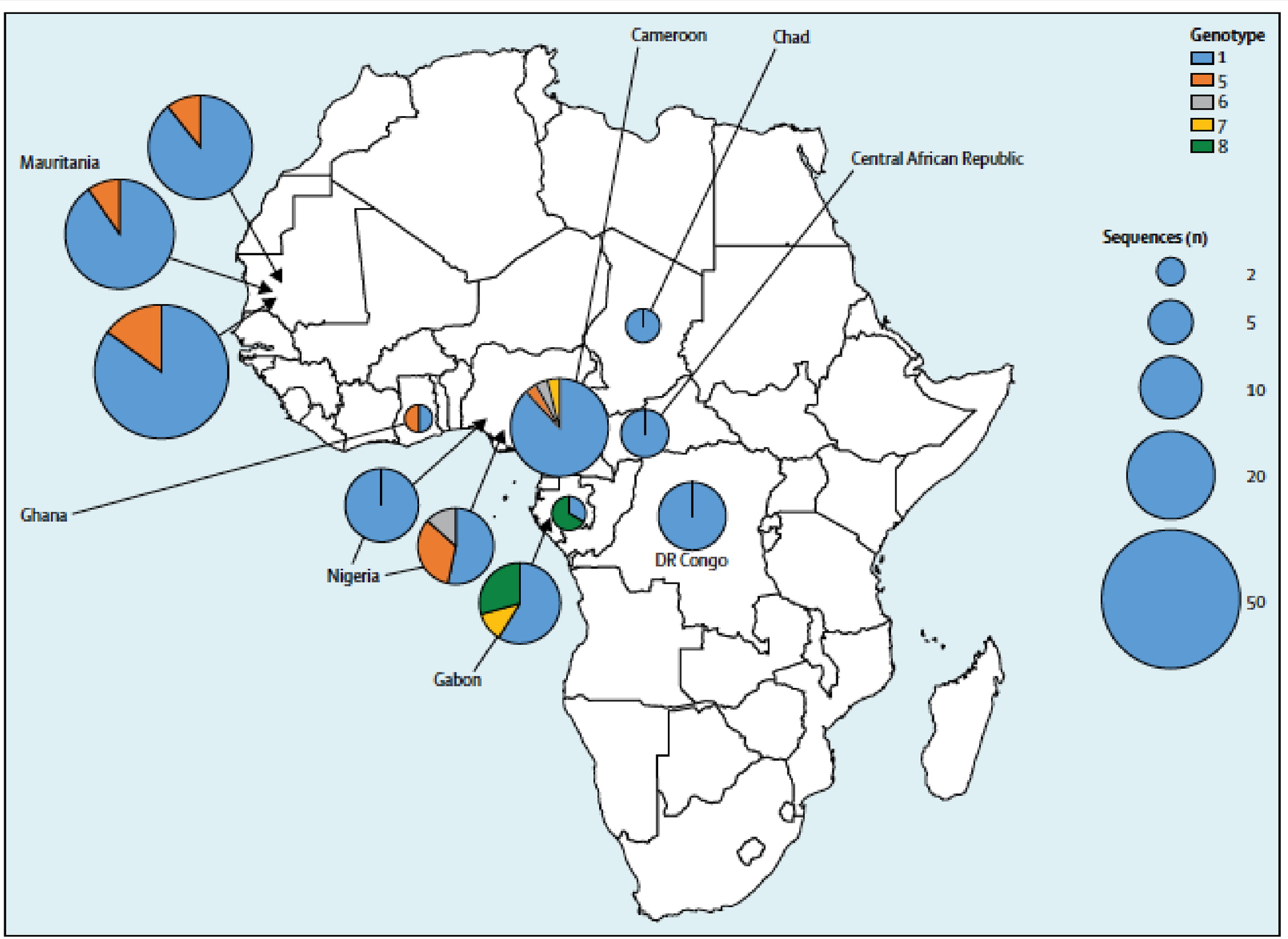


Pooled overall seroprevalence of hepatitis D virus was 8.39%

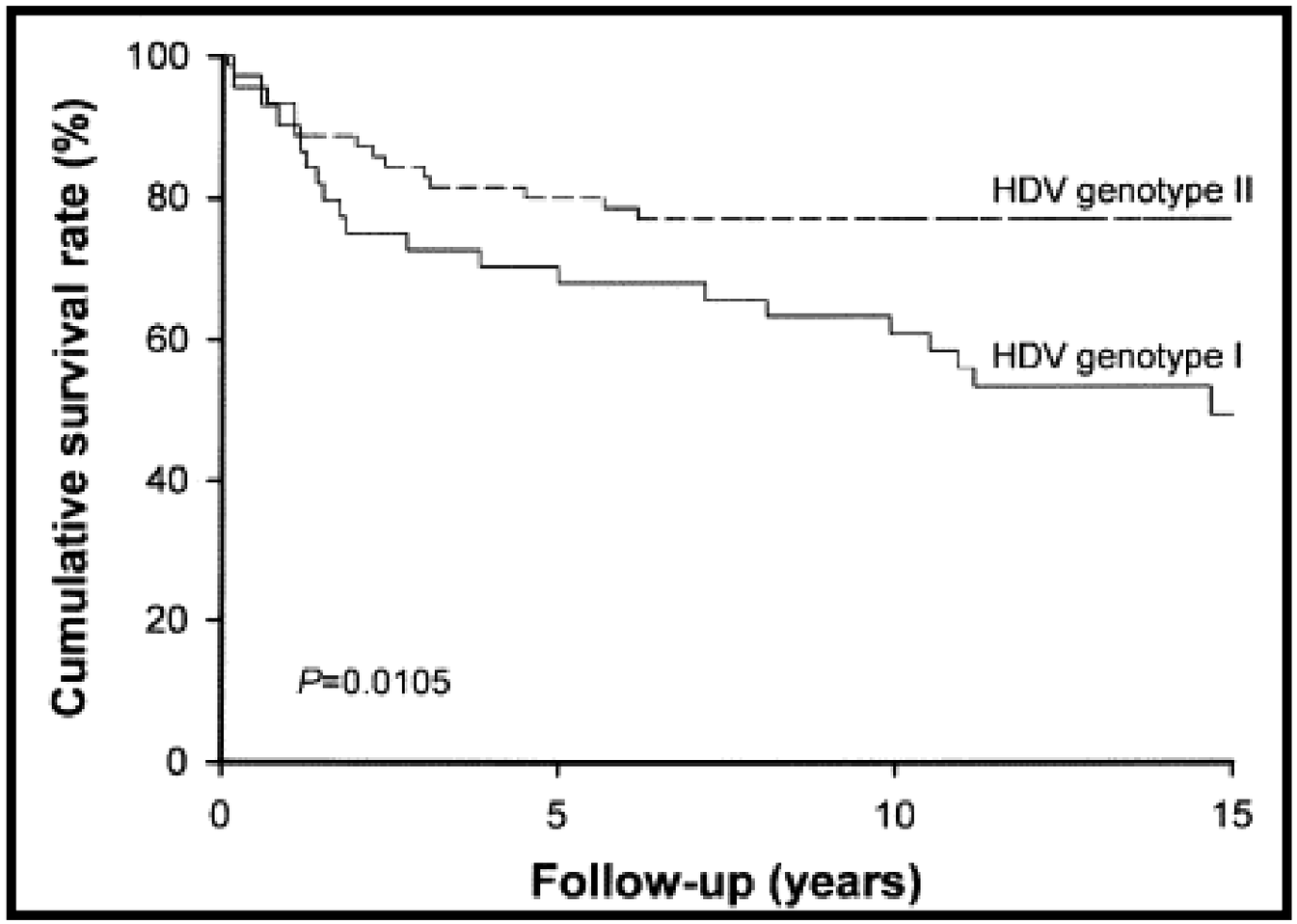
Anti-HDV in CLD Vs Asymptomatic
OR 5·24 (95% CI 2·74–10·01; p<0·0001)

Alexander J Stockdale, et al. Lancet Glob health 2017

HDV genotype distribution in Sub-Saharan Africa



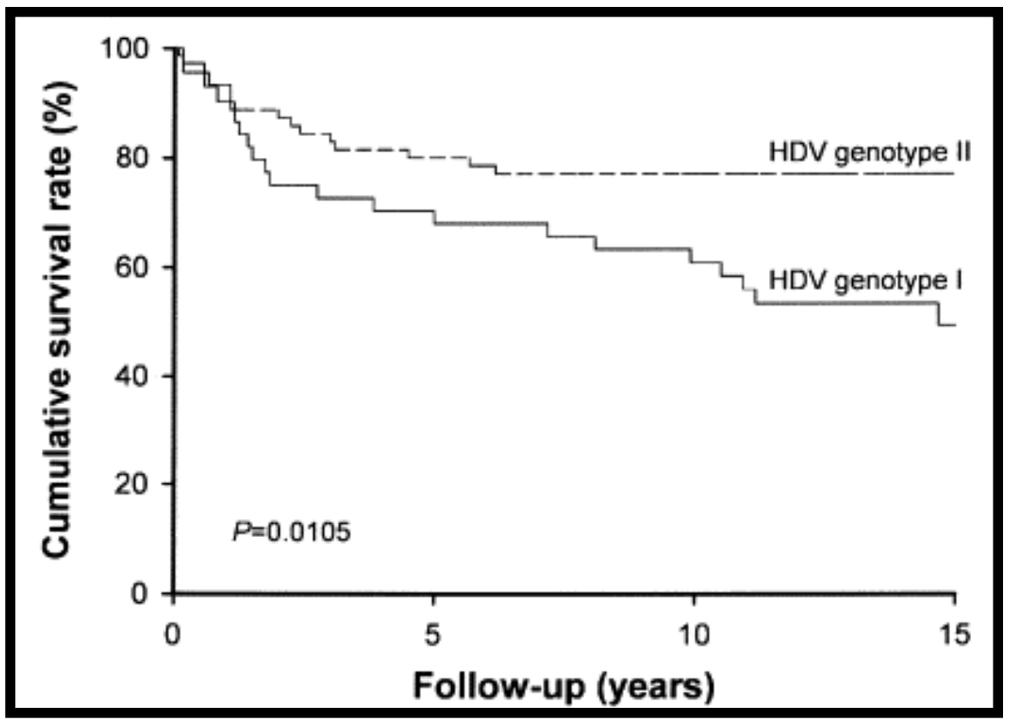
Outcomes



Patients at risk			
HDV genotype 1:46	29	25	10
HDV genotype 2:72	55	49	27

Su et al. Gastroenterol 2006;

Outcomes



Genotype 1 HDV in acute hepatitis

- Increased risk of fulminant failure

Genotype 1 HDV in chronic hepatitis

- Rapid progression to cirrhosis
- Risk of HCC 3X higher
- Mortality 2X higher

Su et al. Gastroenterol 2006

Guidelines

World Health Organization

WHO response

WHO does not have specific recommendation on hepatitis D,

APASL,2015

- Less common

AASLD,2018

- Testing at risk
- Periodic retesting
- HBV DNA low, high ALT
- Uncertainty
- Anti-HDV —- HDV RNA,
- HBV DNA
- Peg IFN-alpha 12 months

EASL,2017

- Treatment in persistent HDV replication (PEG-IFN)
- HDV RNA level
- RX >/ 1 year

AASLD- High risk groups

Persons born in regions with reported high HDV endemicity*
- Africa (West Africa, horn of Africa)
- Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)
- Pacific Islands (Kiribati, Nauru)
- Middle East (all countries)
- Eastern Europe (Eastern Mediterranean regions, Turkey)
- South America (Amazonian basin)
- Other (Greenland)

Persons who have ever injected drugs

Men who have sex with men

Individuals infected with HCV or HIV

Persons with multiple sexual partners or any history of sexually transmitted disease

Individuals with elevated ALT or AST with low or undetectable HBV DNA

AASLD, 2018

Ethiopia

- East Africa

- The current population of **Ethiopia** is **109,907,625** as of Monday, June 3, 2019, based on the latest United Nations estimates.

- Estimated HBV prevalence 10%

Previous Studies

- 2.7% among patients with viral Hepatitis

Gebreselassie L et. al IARC Sci Publ. 1984

- 5.8% of military recruits with chronic HBV infection

Rapicetta et al. Eur J Epidemiol. 1988;4:185-188

- Hospital based study (249 cases) from 1986-90; 24% anti-HDV positive in cirrhotic patients

CLD in Ethiopia: Identification of common causes. E. Tsega


ORIGINAL ARTICLE

WILEY Liver INTERNATIONAL

Hepatitis delta virus infection in a large cohort of chronic hepatitis B patients in Ethiopia

Hanna Aberra[1] | Emmanuel Gordien[2] | Hailemichael Desalegn[1] | Nega Berhe[3,4] | Girmay Medhin[3] | Bitsatab Mekasha[1] | Svein G. Gundersen[5,6] | Athenaïs Gerber[2] | Kathrine Stene-Johansen[7] | Joakim Øverbø[8] | Asgeir Johannessen[4]

- A treatment program at St. Paul's Hospital MMC
- Advanced analysis from 1267 patients

- HDV serology - ELISA
- HBV viral load
- HDV RNA detection
- HDV genotype

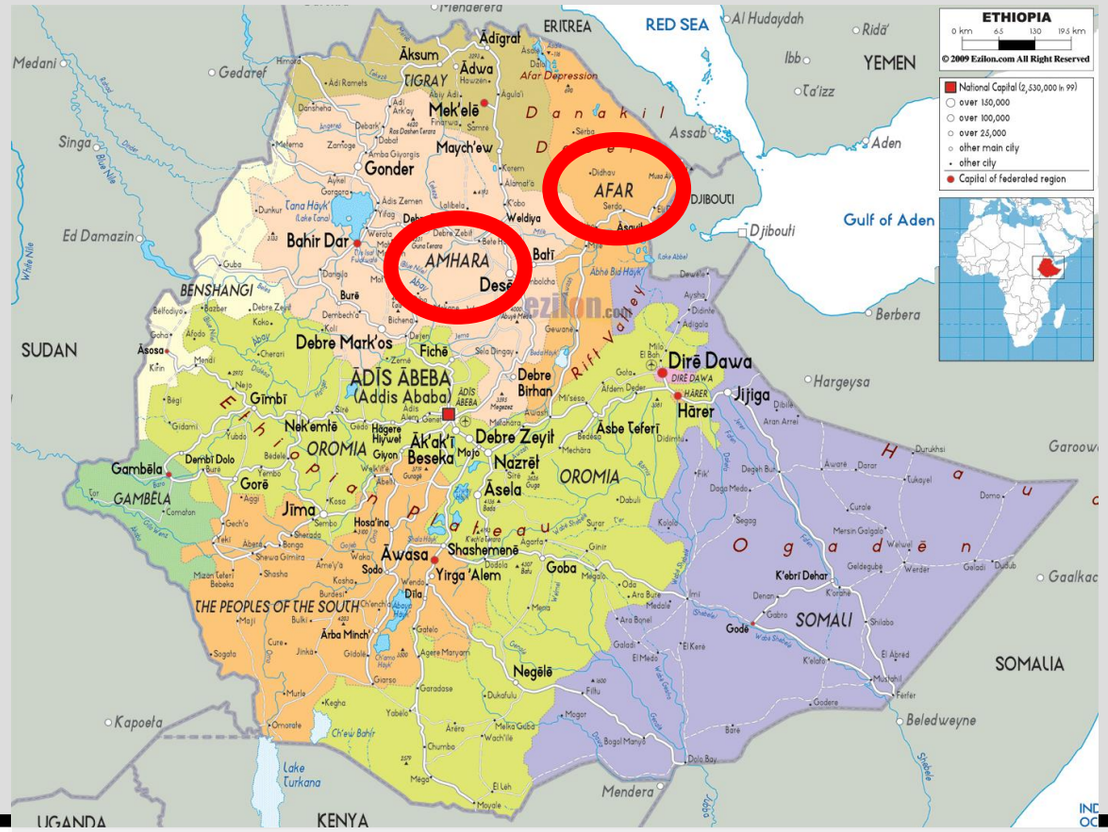
Centre national de référence des hépatites B, C et Delta,

Hôpitaux Universitaires de Paris-Seine- Saint- Denis, Bobigny, France

- Fibroscan - Echosens 402

Baseline characteristics in HDV RNA-positive vs HDV RNA-negative patients, Ethiopia

Characteristics	HDV RNA-negative (n = 1255) n (%)	HDV RNA-positive (n = 12) n (%)	P
Sex			
Male	740 (59.0)	8 (66.7)	.771
Female	515 (41.0)	4 (33.3)	
Age group (y)			
18-25	271 (21.6)	3 (25.0)	.223
26-35	532 (42.4)	3 (25.0)	
36-45	280 (22.3)	2 (16.7)	
>45	172 (13.7)	4 (33.3)	
Marital status			
Married	766 (61.0)	10 (83.3)	.143
Single/divorced/widowed	489 (39.0)	2 (16.7)	
Occupation			
Civil servant	312 (24.9)	3 (25.0)	.163
Private	555 (44.2)	2 (16.7)	
Housewife	134 (10.7)	2 (16.7)	
Other	254 (20.2)	5 (41.7)	
Address			
Addis Ababa	852 (67.9)	2 (16.7)	<0.001
Oromia	196 (15.6)	1 (8.3)	
SNNPR	60 (4.8)	1 (8.3)	
Amhara	70 (5.6)	4 (33.3)	
Tigray	39 (3.1)	1 (8.3)	
Afar	13 (1.0)	3 (25.0)	
Other	25 (2.0)	0 (0.0)	



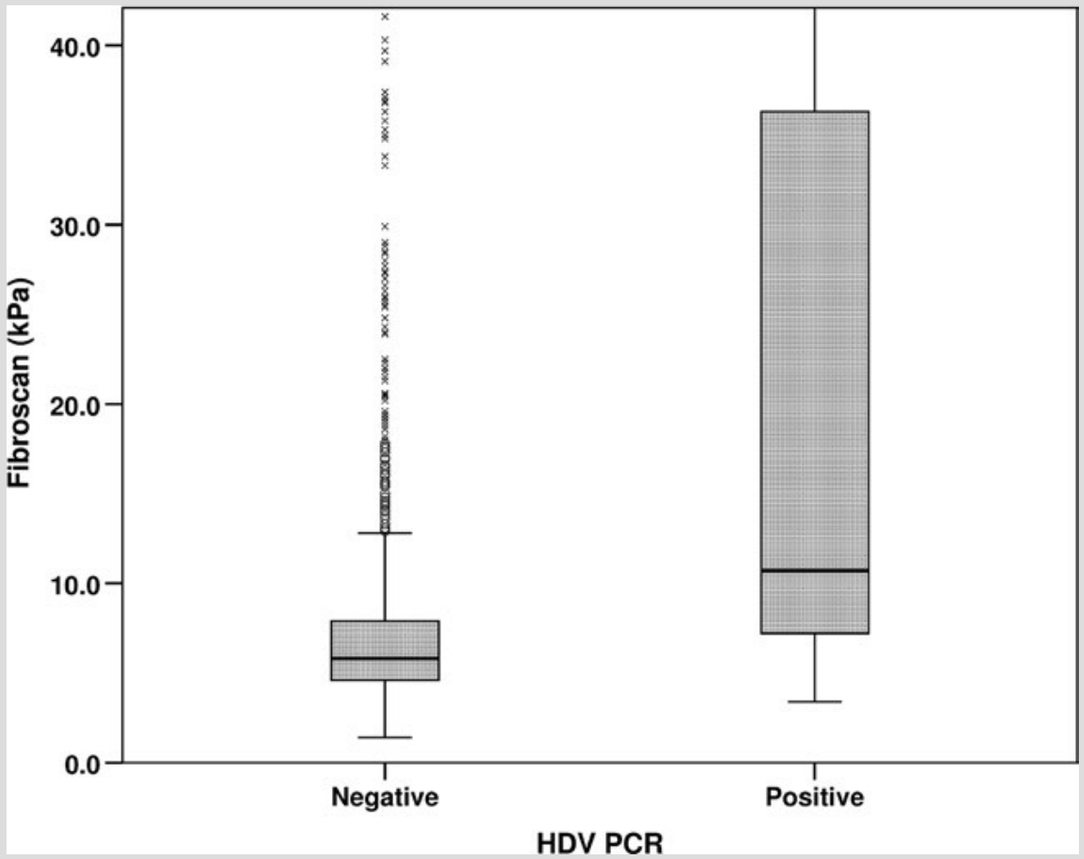
Alcohol abuse			
Yes	44 (3.5)	0 (0.0)	1.000
No	1211 (96.5)	12 (100)	
Fasting TE value (kPa)[a]			
≤7.9	923 (75.3)	4 (36.4)	0.011
8.0-11.7	102 (8.3)	2 (18.2)	
>11.7	201 (16.4)	5 (45.5)	
ALT (U/L)			
≤40	1011 (80.6)	8 (66.7)	.192
41-80	179 (14.3)	2 (16.7)	
>80	65 (5.2)	2 (16.7)	
HBV viral load (IU/mL)[b]			
<2000	702 (56.5)	6 (50.0)	.717
2000-20 000	250 (20.1)	2 (16.7)	
≥20 000	290 (23.3)	4 (33.3)	
HCV serostatus[c]			
Positive	27 (2.5)	1 (9.1)	.249
Negative	1057 (97.5)	10 (90.9)	

HDV Prevalence

- 25 samples - positive or indeterminate for HDV antibodies with the Diasorin assay,
- 19 were confirmed positive with the Dia. Pro assay
- Overall HDV prevalence of **1.5% (19 of 1267)**.
- Using a sensitive HDV RNA RT-PCR assay , **0.9%**
- 2/3 rd has active infection

Association with Liver Injury

- ALT levels 40 U/L (IQR 29-57) compared to 25 U/L (IQR 18-36), P =0.031



- Median fibroscan

(10.7 kPa [IQR 6.8-36.8] vs 5.8 kPa [IQR 4.6-7.9], P = .014)

Association with Mortality

No.	Sex	Age	Address	HDV viral load (IU/mL)	HBV viral load (IU/mL)	HCV serosta-tus	Fibroscan (kPa)	ALT (U/L)	TDF therapy	Outcome
1	M	28	SNNPR	<100	320	Pos	34.3	57	Y	In care
2	M	49	Afar	200	21	Neg	6.8	40	N	In care
3	F	27	Tigray	160 000	89	Neg	10.7	38	Y	In care
4	F	22	Amhara	440 000 000	18 000 000	Neg	7.6	102	Y	In care
5	M	50	Addis Ababa	1 100 000	10 000	Neg	75.0	110	Y	HCC
6	M	48	Addis Ababa	<100	510	Neg	3.4	28	N	In care
7	M	44	Amhara	1 500 000	26 000 000	Neg	61.6	56	Y	In care
8	M	40	Oromia	685 000	49	Neg	36.8	32	Y	Died
9	M	20	Afar	2 700 000	9700	Neg	35.8	40	Y	LFU
10	F	50	Amhara	6 600 000	16	Neg	6.7	40	N	In care
11	F	22	Amhara	770 000	>100 000 000	Neg	8.2	22	Y	Died
12	M	26	Afar	3 400 000 000	55 000	N/A	N/A	23	N	

Mortality was significantly associated with active HDV infection at univariable analysis (crude odds ratio 5.3; 95% confidence interval 1.1-24.7; P = .035).

HDV genotypes

- All HDV-infected strains belonged to genotype 1
- These strains clustered together (2 clusters considering R0 sequences and one for full-length genome sequence) and with ancient previously described HDV-1 sequences from Somalia and Ethiopia, and together with sequences from Central and Eastern Africa
- The strains also shared the Serine 202 African marker in the HDV-1 L-HDAg

Phylogenic trees - using R0 / whole-genome sequences

At least two studies shows clade homogeneity (Clade I)

Phylogenetic trees of Ethiopian strains, using (A) R0 or (B) whole-genome sequences.

Belyhun et al. Virology Journal (2017) 14:176

Sub-Summary

- HDV prevalence was 1.5% - 2/3rd active infection
- Associated with raised ALT, fibroscan values
- Though small sample size, it is associated with high mortality
- Screen for HDV at initiating treatment for HDV and during worsening

Acknowledgement
EthNoHep Group

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- Hanna Aberra
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- **Asgeir Johannessen**

Case-control study to assess the impact of HDV

Viral Marker	**Blood donors**	**Patient controls (free from liver diseases)**	**CLD**	**HCC**	**Total**
HDV-Ab	03/98 **(3.1%)**	04/82 **(4.9%)**	13/63 **(20.6%)**	11/49 **(22.4%)**	31 Anti-HDV +

- **Among 180 HBsAg positive Healthy controls 7 (7/180) positive for anti HDV antibody (3.8%)**

- **Among 112 HBsAg positive CLD patients 24 (24/112) positive for anti HDV antibody (21.4%)**

Unpublished data, Ongoing, 2019

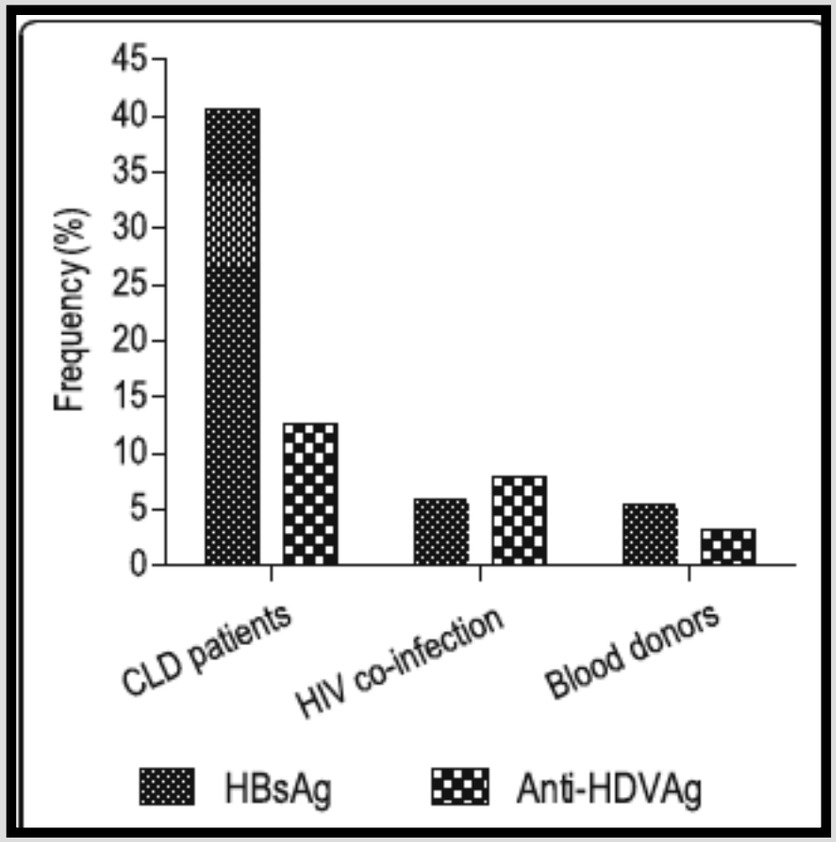
Patient/client specific clinical and virological characteristics of those with HDV full genome sequenced (n = 6)

Study groups	Lab. Code	Age/sex	Virological characteristics							Clinical characteristics
			Anti-HCV	HIV status	HBV viral load	HBeAg	HBV genotype	HDV viral load	HDV genotype	
HIV co-infected	**ETH3790**	**34/M**	**Neg**	**Pos**	**3.62**	**Neg[a]**	**A1**	**9.67×10^6**	**I**	**WHO stage I**
	ETH2170	**36/F**	**Pos**	**Pos**	**Un**	**Pos**	**–**	**2.27×10^5**	**I**	**WHO stage IV**
	ETH2280	**33/M**	**Neg**	**Pos**	**Un**	**Neg**	**–**	**7.08×10^7**	**I**	**WHO stage I**
CLD patients	**ETH4060**	**60/M**	**Neg**	**Neg**	**6.34**	**Neg**	**A1**	**3.01×10^5**	**I**	**Liver cirrhosis**
	ETH4100	**33/M**	**Neg**	**Neg**	**3.15**	**Neg**	**A1**	**2.28×10^5**	**I**	**HCC**
	ETH3020	21/F	Neg	Pos	6.90	Pos	A1			
Blood donors	**ETH2056**	**47/M**	**Neg**	**Neg**	**8.39**	**Neg**	**D2**	**6.55×10^5**	**I**	**–**
	ETH5660	55/M	Neg	Neg	0.79	Neg[a]				

Belyhun et al. Virology Journal (2017) 14:176

	Blood Donors	HIV co-infection	CLD	HIV YM(I)DD	Total
Anti-HDAg	3.2%	8%	12.7%	None	321 patients
HDV Viremia rate	33.3%	30.0%	23.1%		

- All were genotype 1
- serine at amino acid position 202



Belyhun et al. Virology Journal (2017) 14:176

How HDV dominance impaired?

- Immune escape HBsAg mutations Q164A and sE164D
- Concomitant rtV173L
- HBV drug resistant mutations (rtM204V/I)

- More than 80% anti-HDV Ab positive high HBV DNA
- Certain amino acid sequences in the C-terminal domain of the surface protein are essential for assembly of HDV particles
- HBV drug resistant mutations (rtM204V/I) 29.3% in HIV infected

Belyhun et al. Virology Journal (2017) 14:176

Kenya

- Anti-HDV 31% in health individuals- Northern Kenya
- Around 1% (2/202) in the southern part of kenya

Greenfield C et. al. Am J Epidemiol.1986

Treatment

- No effective cure
- Peg. Interferon - 25% viral clearance
- Frequent relapse - SVR is replaced with MVR
- FHF - Liver transplant
- LT - Best outcome

Drug	Mechanism	Clinical Trial phase	
Lonafarnib	Prenylation Inhibitor	III	
Myrcludex B (Bulevirtide)	Entry Inhibitor	III	
Lambda (PEG INT)	Immune response stimulator	II	
Ezetimibe	NTCP inhibitor	II	
Additional 4 drugs in Pre-clinical trial			

Drug Watch chart updated March 2019.

Hepatitis in Sub-saharanAfrica

- Prevalence of HBV 8-10% in most countries

  (100 million HBV in Africa ; **5** million HDV infection)

- Generalized epidemic - Not confined to specific segment or high risk groups

- Biological and molecular tests are unacceptably expensive in SSA and sent abroad

- HBV patients get free drug only if they have HIV infection

- Left with following natural course of the disease - many end up in Hospitalization

Hepatitis in Sub-saharanAfrica; Challenges

Epidemiology Data

Prevention

Awareness - Campaigns, civil society — extremely low

Birth dose vaccine, HBIG — <10% in SSA

No birth dose vaccine under national program; HBIG not available

HBsAg - 35 USD

HBIG - >100 USD

HBV vaccination prevents from HDV infection

Hepatitis in Sub-saharanAfrica

Diagnosis	HDAg, HDV RNA	HDAg(IgM) :- 80 USD HDVRNA :- 202 USD

Biological and molecular tests are unacceptably expensive in SSA and sent abroad

Hepatitis in Sub-saharanAfrica

Drug Therapy

Accessibility

Only 1% chronic carriers are able to access treatment

HBV patients get free drug only if they have HIV infection

HDV is more worse
One year cost of PEG interferon is around 15,600 USD

Hepatitis in Sub-saharanAfrica

Chronic lack of funding of viral hepatitis programs

Care during hospitalization

Decompensation management, Liver Transplant

Cancer Management

Hospice care is not widely available

Many end up in Hospitalization - affect entire family emotionally and financially

Health care system

- Out-of-pocket payment for health services
- Most laboratories do not have advanced investigation set-ups
- Proper protection means for health professionals- Vaccination, Personal protections (Gloves,..) , Sterilizing materials
- **Lack of political will and commitment in Viral Hepatitis**
- Lack of programs by the MOH -

Needs/Opportunities for improvement

- Awareness campaigns
- Availability of literature , websites for health care providers- Hepatitis B foundation, Hepatitis Delta network
- Some improvement on data from African studies
- Many lessons should be drawn from HIV
- Training on HDV tests for African professionals
- Involvement in Research
- Strengthening HBV birth-dose, HBIG

Recommendations

- Universal protection of health care workers - Hospital safety
- Vaccinate for hepatitis at birth instead of starting at six weeks
- Drug availability - Pharmaceuticals
- Collaboration;- Clinicians, associations, advocate to government
- Unacceptable global inequalities - Scientific and Medical collaboration from developed countries
- Across SSA, hepatitis does not receive the attention that HIV did in 2000 from NGO and civil society - NGO, Civil Society involvement
- Governments:- **Prioritization of the health agenda** - Safety for Health workers the environment, prioritizing lab reagents and drugs

Conclusion

- HDV is overlooked - not routinely reported, underestimated
- Clade homogeneity in the Ethiopian studies - 1
- Severe form of viral hepatitis with rapid progression to HCC
- More data is needed from the Eastern Africa to - support from HDIN
- Current therapy - Interferon, emerging oral therapies
- Prevention;
- Super;- Educate to reduce risk behaviors
- Coinfection;- Pre or post-exposure prophylaxis (HBIG and/or HB vaccine)

“Countries must invest in programs that keep people healthy & out of hospitals.

Prevention is not only better than cure - it’s cheaper”

WHO Director #WHA72

THANK YOU

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Q & A

Please submit questions in the chat box!

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