Viral Hepatitis:

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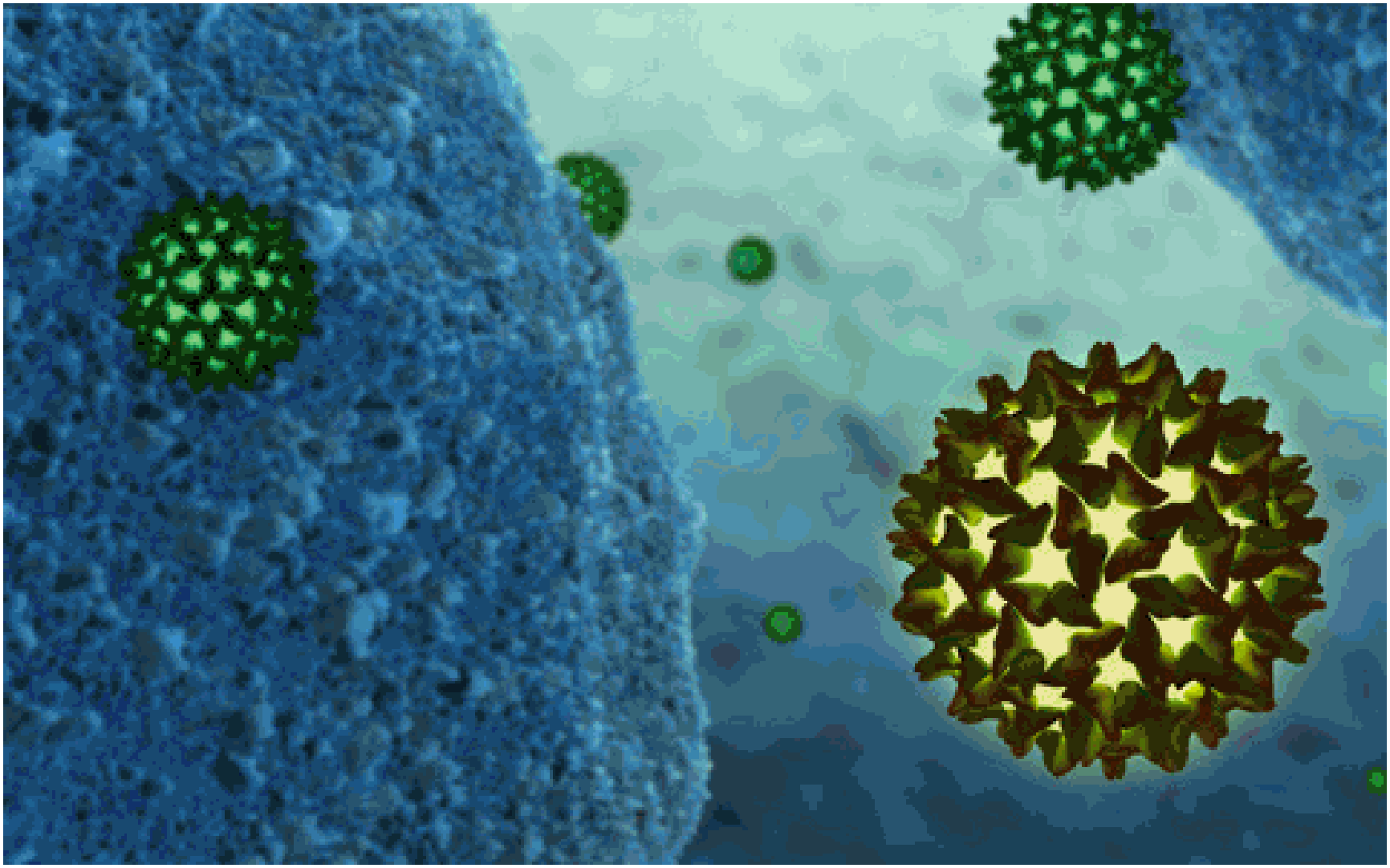
General and Infectious Diseases Physician

Outline:

- Virology

- HBV + pregnancy
- HCV + ‘new’ treatments

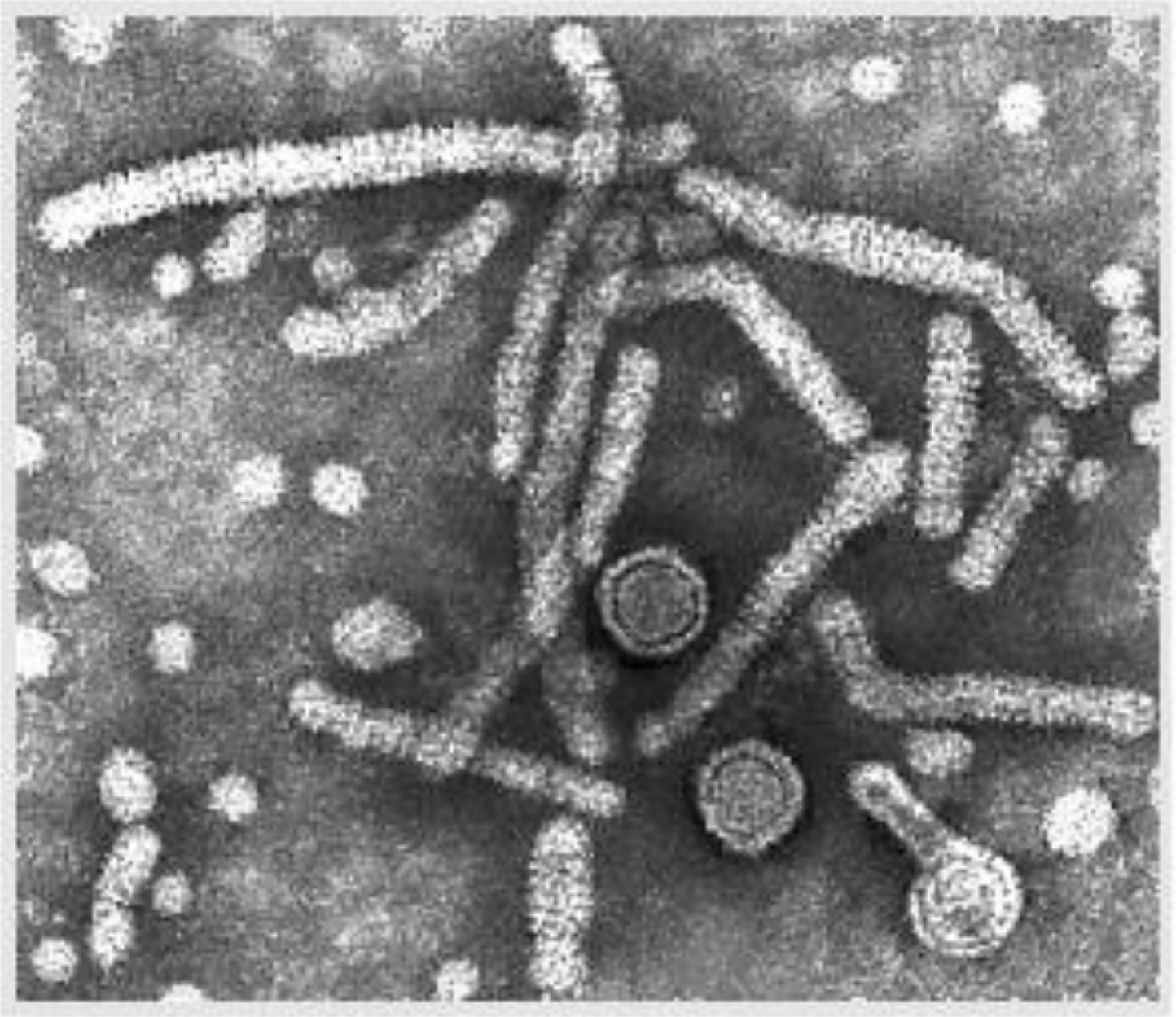
- Cases
- Hepatitis Foundation



HBV: virus

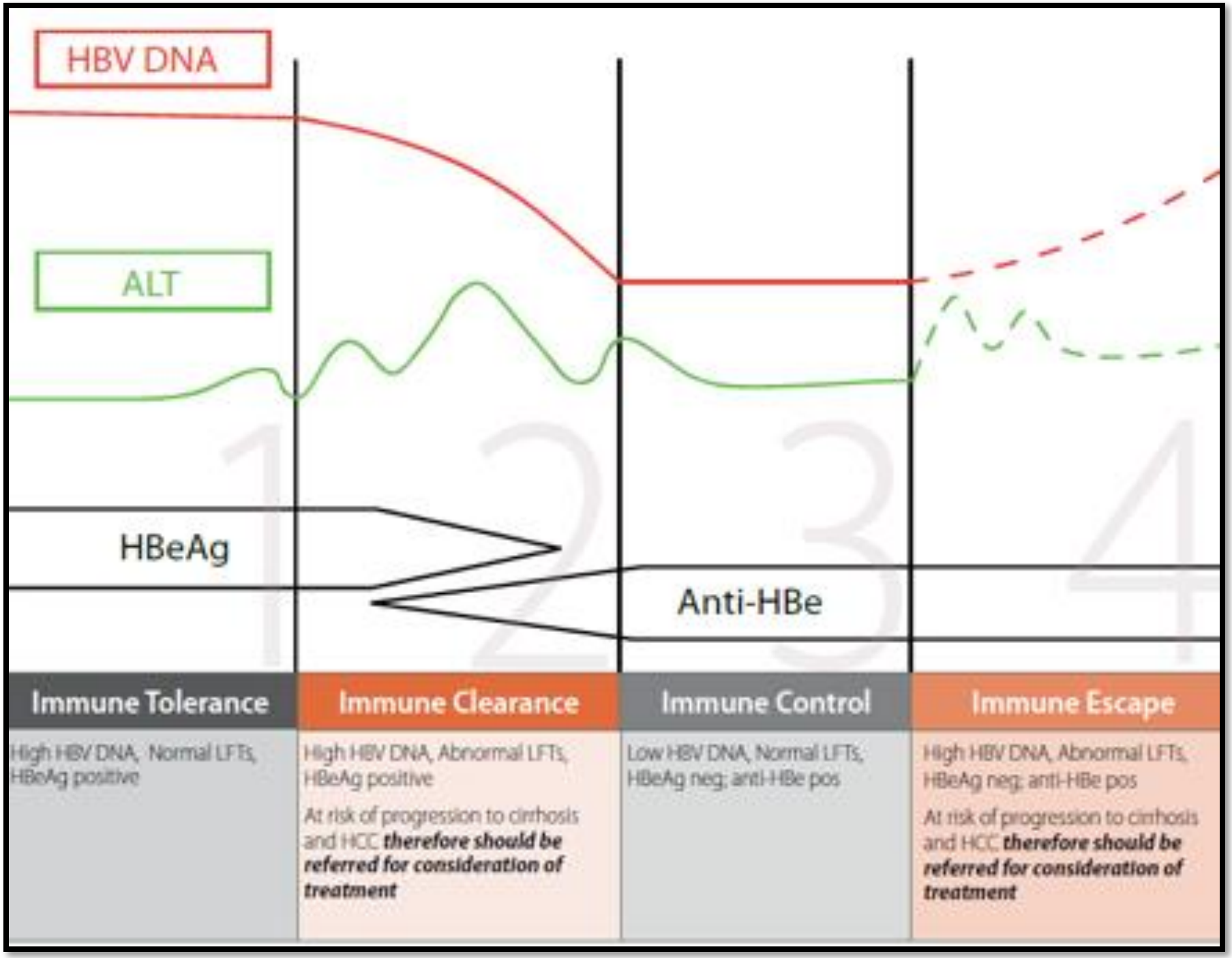
- HBsAg far in excess of complete virions, 1000:1!
- Anti-HBs or HBsAg, not both
  - Immune or infected
- HBeAg and antiHBe, not both
  - immune recognition leads to replication control
- Overlapping reading frames
  - Circular, Compact DNA
- ‘similar’ retro-viruses, reverse transcriptase
  - Lamivudine, Tenofovir – HIV, HBV – RNA to DNA

HBV:



Treatment targets:

- ***Separate to*** transcription of proteins
  - core Ag, surface Ag, ‘e’ Ag, enzymes
  - ready for packaging
- ***RNA -> DNA*** replication interrupted
- Importantly HBsAg levels do not drop
  - HDV!
  - Different enzyme, so not treated by HBV drugs


HBV DNA
ALT
HBeAg
Anti-HBe
1
2
3
4
Immune Tolerance
High HBV DNA, Normal LFTs, HBeAg positive
Immune Clearance
High HBV DNA, Abnormal LFTs, HBeAg positive
At risk of progression to cirrhosis and HCC therefore should be referred for consideration of treatment
Immune Control
Low HBV DNA, Normal LFTs, HBeAg neg; anti-HBe pos
Immune Escape
High HBV DNA, Abnormal LFTs, HBeAg neg; anti-HBe pos
At risk of progression to cirrhosis and HCC therefore should be referred for consideration of treatment

Staging and Assessment:

- Transmission:
  - Duration, vertical, horizontal
  - Anyone still at risk – household members
  - Family members affected, ?HCC
- (Alcohol, IVDU, other viruses ..)

Staging and Assessment:

- Serology, DNA, ALT
  - Stage 1, 2, 3, 4
- Imaging / Fibroscan: F0 – F1

- Treatment decision

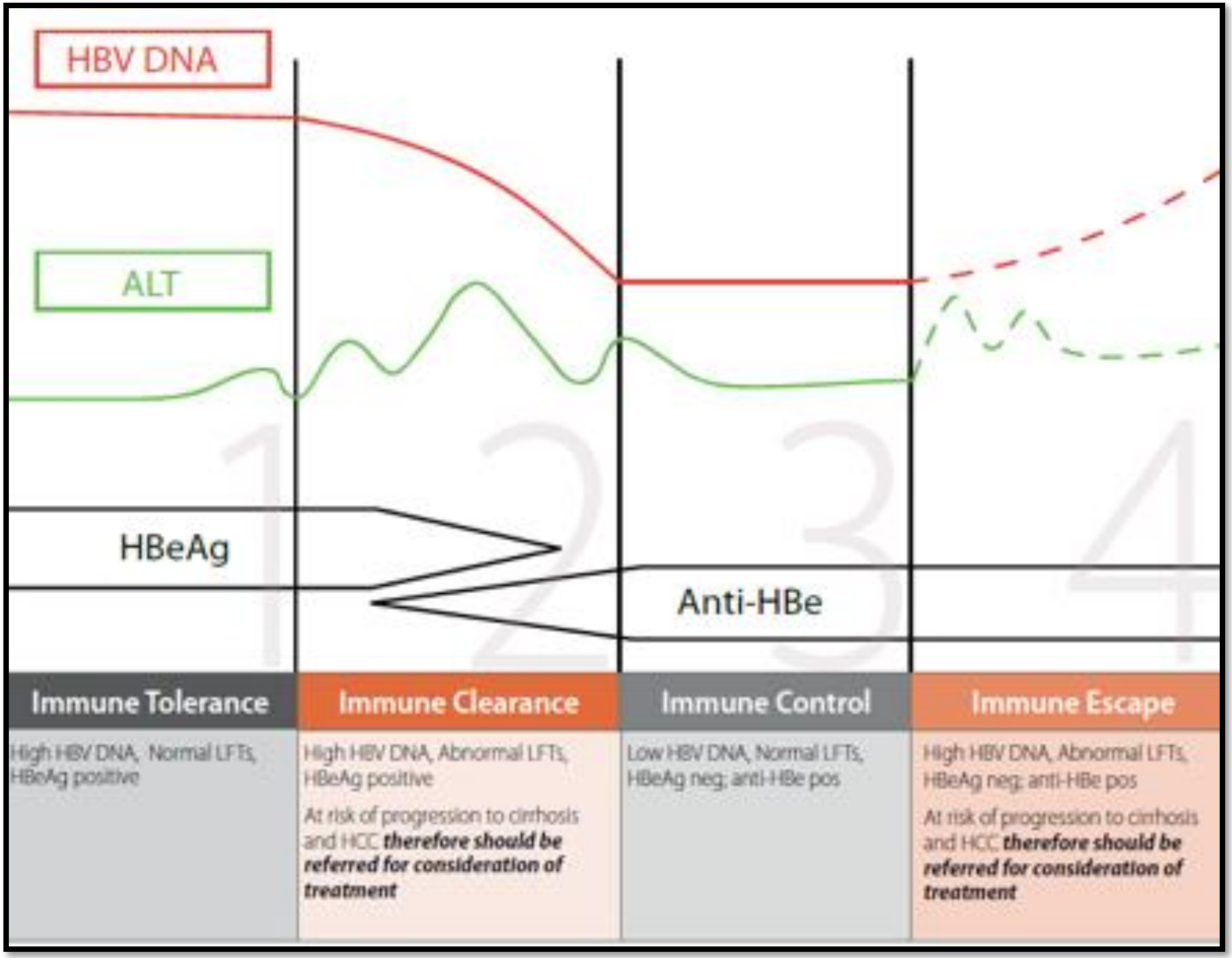
Cases - serology:

- Any HBsAg positive is Hep B positive
- Any viral load positive is Hep B positive

- Anti-HBc = core, infection, but persistent
  - IgM or IgG, not reliable
- Anti-HBs = surface, immunity, past infection or vaccine
  - Present EARLY infection, cannot detect

Cases 1: 46M, Maori

- ref with ALT 2-3x ULN x2yrs
- Viral load 38,000, now 2.2 mil IU/mL
- HBsAg pos, antiHBc pos, HBeAg pos
  - HAV immune, HCV neg, HIV neg
  - No alcohol
  - High R AKA secondary trauma
  - Diabetic – HbA1c = 50mmol/mol, ACR normal
  - Fibroscan = 5.0kPa, c/w F0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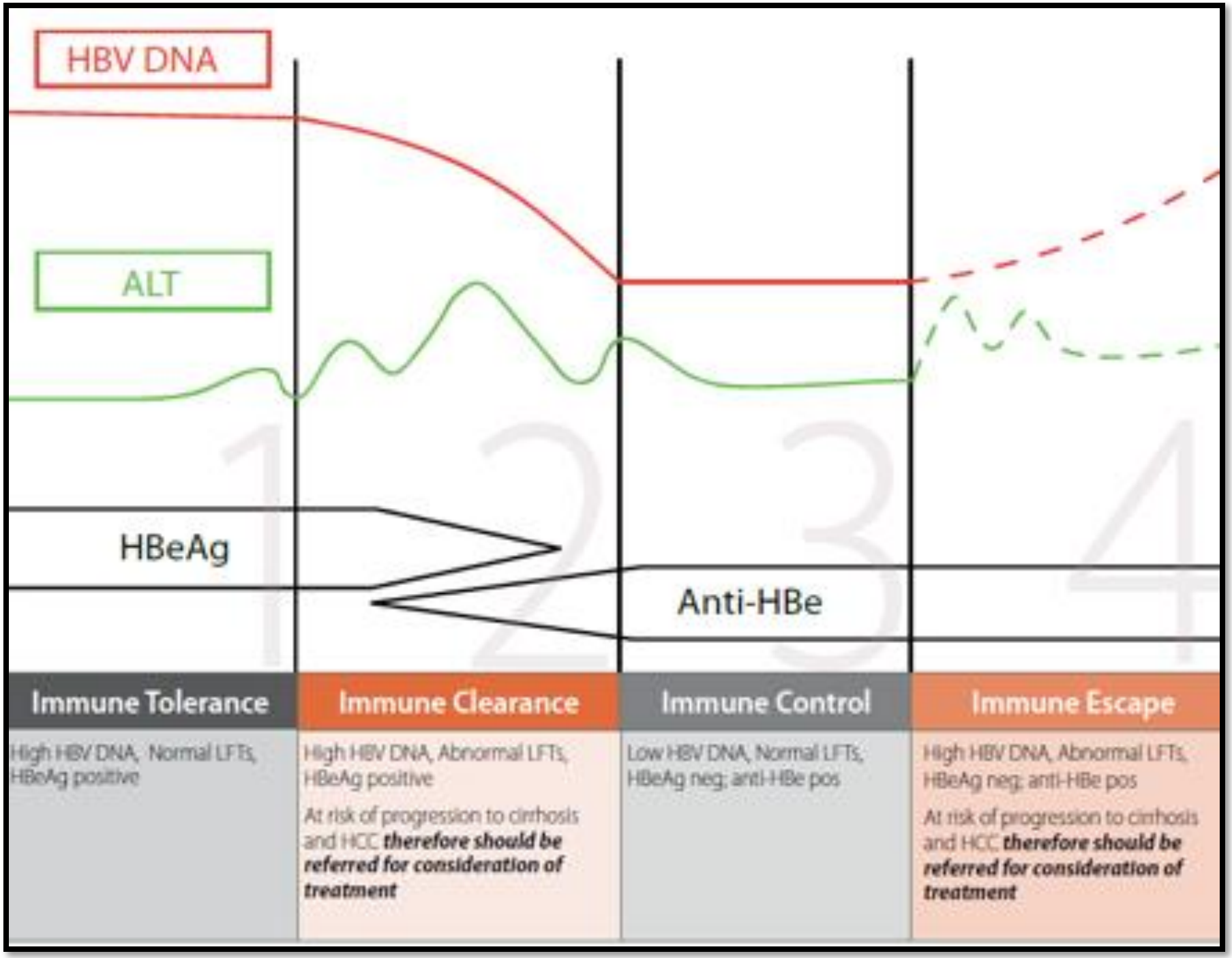
Case 2: 33M, Caucasian

- Ref, unwell diarrhoea and fatigue, ?unrelated
- HBV since childhood, Kawerau
- ALT 4-5x ULN, 8mths
- Viral load 126,861 IU/mL

- HBsAg pos, antiHBc pos, antiHBe pos
- Fibroscan 10.2 kPa, IQR 2.6, success rate 100%
  - Consistent with F3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Fibroscan:

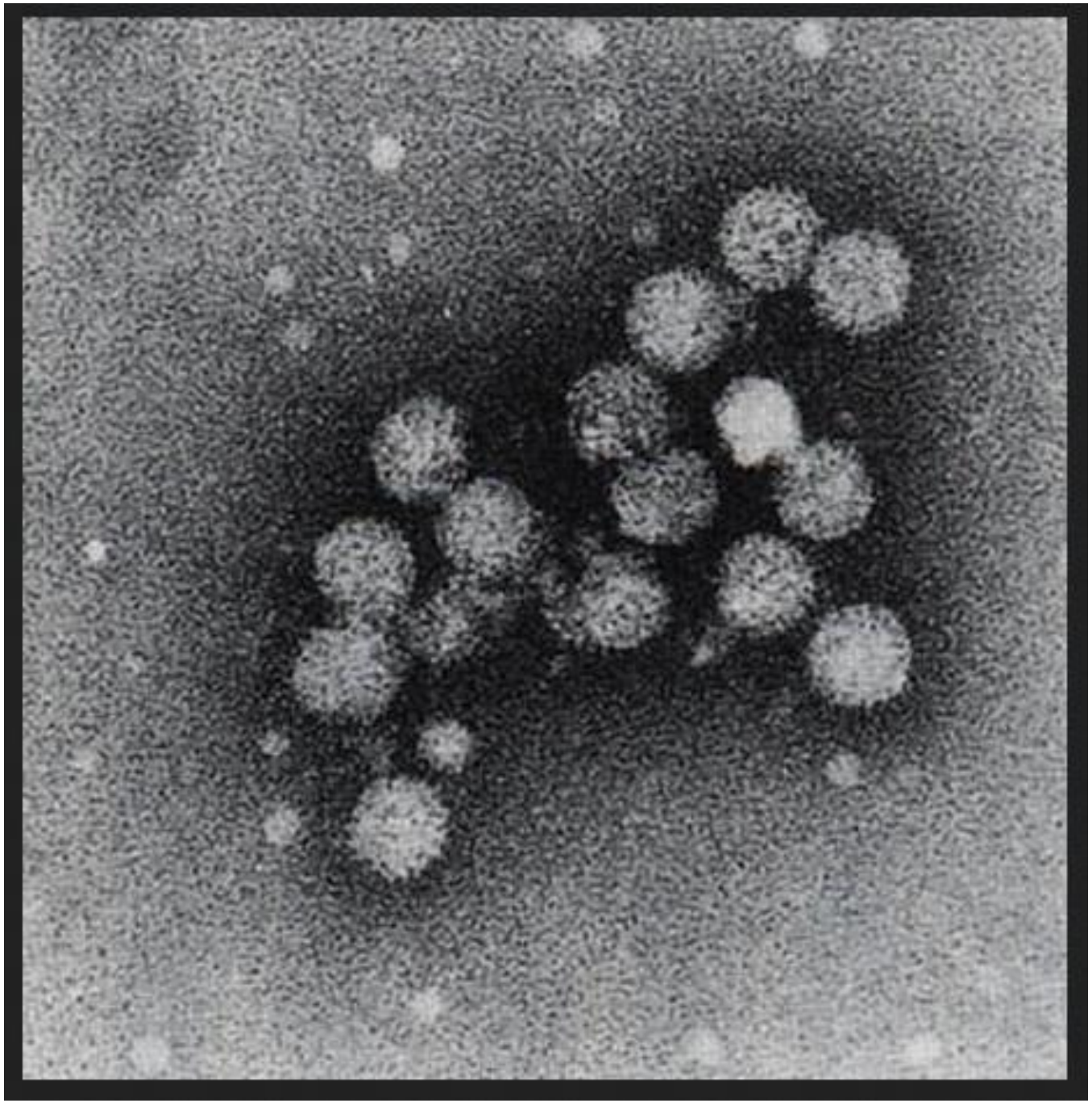
HBV and Pregnancy:

- Antenatal screens n= 99.8% Waikato
  - 50% GP, 50% midwife
- Comment from lab: “obtain VL, refer”
  - Not happening ..
- Usual care –
  - HBIG and extra vaccine dose at birth
  - Can breast feed
- We need to improve ?better targeting

Pregnancy Treatment:

- Pharmac – tenofovir 4/12
- HBeAg pos HBV >10e8 IU/mL
  - Australian data approx 7-8%
  - Pharmac submission >30%!
  - International 10-15% ..
- Why?
  - Highly dependent on the viral load
  - Highly dependent on quality O&G care
  - Somewhat dependent on genotype/ genetics

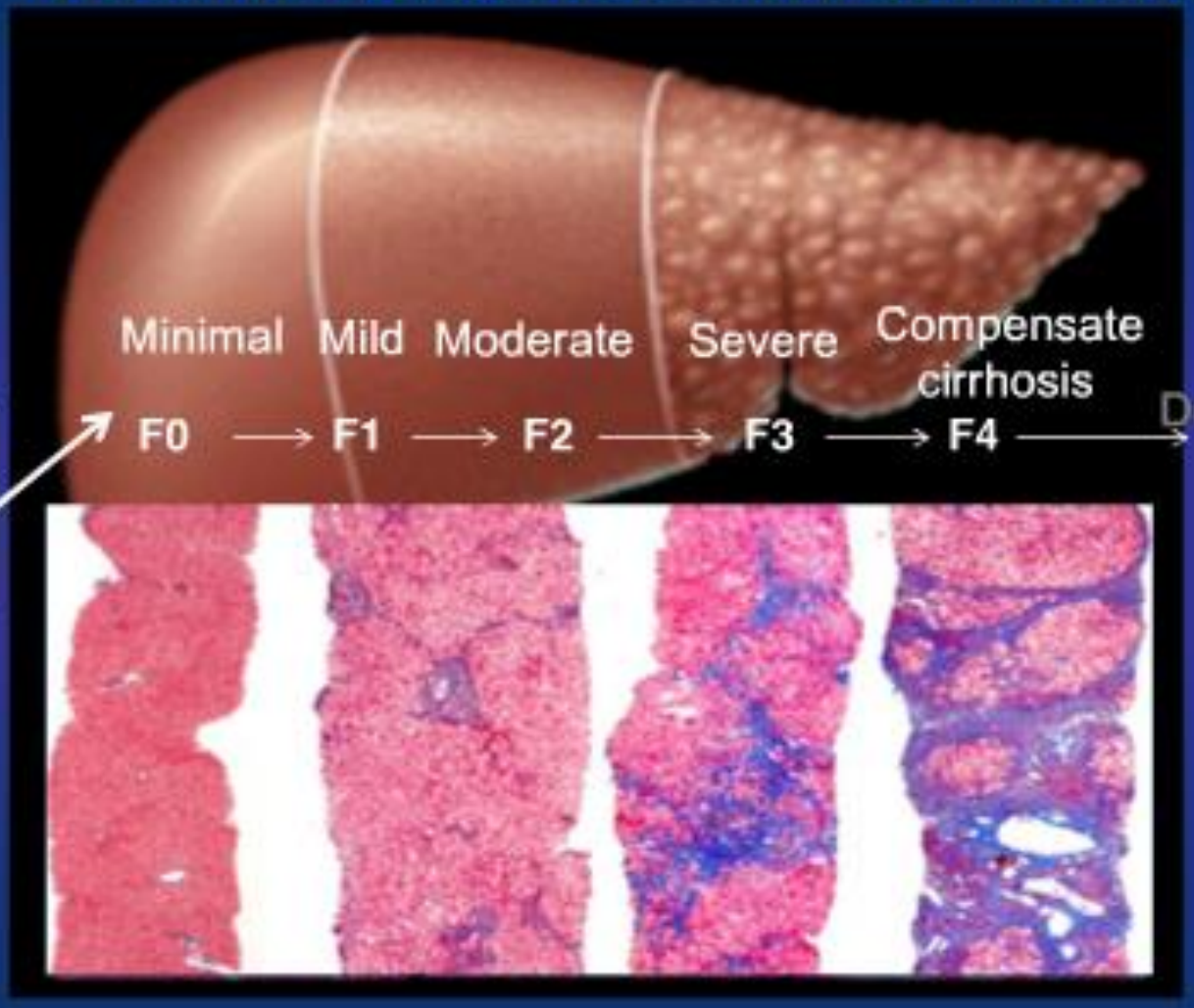
HCV:



HCV: virus

- ‘simple’ by comparison
- BUT RNA with very high turn-over
- multiple quasi-species, ie high variation
- Genotypes 1-6, accumulated variation
  - NZ: G1 and G3
- Enzyme targets – vs Peg-Interferon / RBV
  - Polymerase inhibitors, nucs, non-nucs, NS5B
  - Inhibitor of polymerase replication complex, NS5A
  - Protease inhibitors, NS3/4A

FROM INFECTION TO COMPENSATED CIRRHOSIS



PROGRESSION TO ADVANCED FIBROSIS 2-4%/yr 5-8%/yr 10-20%/yrs

Staging and Assessment:

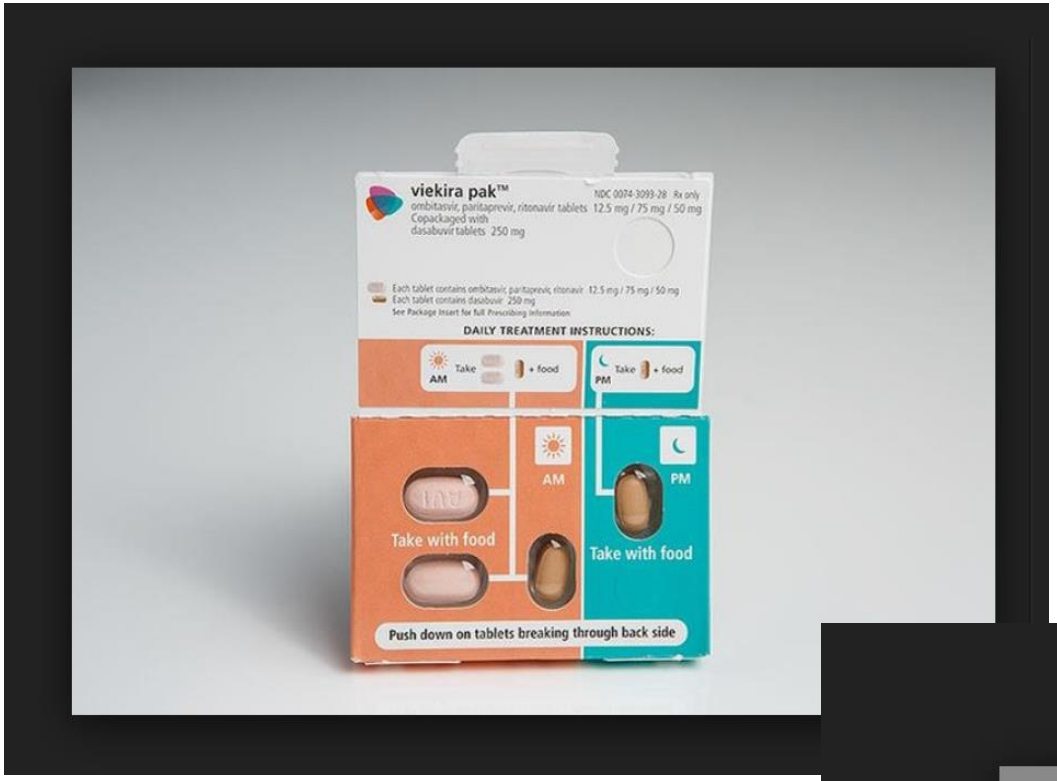
- Hx: acquisition, alcohol, IVDU
- Confirm HCV Ag or PCR, genotype
- Level of fibrosis?
- Cirrhotics, HCC screening

- Delay treatment, most
- Trials unit ..
  - Largely finished

Exhibit 1: HepC Phase 3 data summary

		% cirrhosis	Treatment	n	Duration	SVR12
GILD	ION-1	16%	Harvoni	214	12wks	98%
	Treatment naive		Harvoni + RBV	217	12wks	97%
	genotype 1					
	ION-2	20%	Harvoni	109	12wks	94%
	Treatment experienced		Harvoni + RBV	111	12wks	96%
	genotype 1		Harvoni	109	24wks	99%
			Harvoni + RBV	111	24wks	99%
	ION-3	0%	Harvoni	215	8wks	94%
	Treatment naive		Harvoni + RBV	216	8wks	93%
	genotype 1		Harvoni	215	12wks	95%
ABBV	PEARL-II	0%	Viekira Pak +RBV	88	12wks	97%
	Treatment experienced		Viekira Pak	91	12wks	100%
	genotype 1b					
	PEARL-III	0%	Viekira Pak +RBV	210	12wks	99%
	Treatment naive		Viekira Pak	209	12wks	99%
	genotype 1b					
	PEAR-IV	0%	Viekira Pak +RBV	100	12wks	97%
	Treatment naive		Viekira Pak	205	12wks	90%
	genotype 1a					
	TURQUOISE	100%	Viekira Pak +RBV	208	12wks	92%
	Treatment experience &		Viekira Pak +RBV	172	24wks	96%
	naïve, genotype1					
	SAPPHIRE-I	0%	Viekira Pak +RBV	473	12wks	96%
	Treatment naive					
	genotype 1					
	SAPPHIRE-II	0%	Viekira Pak +RBV	297	12wks	96%
	Treatment experienced					
	genotype 1					
MRK	C-EDGE TN	22%	MK-5172/MK-8742	316	12wks	95%
	Treatment naive					
	genotype 1a		MK-5172/MK-8742	157	12wks	92%
	genotype 1b		MK-5172/MK-8742	131	12wks	99%
	genotype 4		MK-5172/MK-8742	18	12wks	100%
	genotype 6		MK-5172/MK-8742	10	12wks	80%
	C-EDGE TE	35%	MK-5172/MK-8742	105	12wks	92%
	Treatment experienced	34%	MK-5172/MK-8742 + RBV	104	12wks	94%
	genotype 1, 4 and 6	36%	MK-5172/MK-8742	105	16wks	92%
		35%	MK-5172/MK-8742 + RBV	106	16wks	97%

Around 93-99%



Viekira Pak

Harvoni

Classes:

RNA replication :	Genotype	Potency	Barrier to resistance	Side effects	Examples
NS3/4A Protease Inhibitors	G1	High	Low	Many BD-TDS	Bocepravir, telepravir, Simepravir - Q80K Paritaprevir
NS5A replication complex inhibitor	multiple	High	Low	Few OD	Ledipasvir
NS5B Non-Nuc polymerase inhibitor	G1	Int	Low	Drug-drug interactions ++	Dasabuvir
NS5B Nuc Polymerase inhibitor	Pan-genotypic	High	High	Few OD	Sofosbuvir G1/2 >G3

New agents:

- Much higher SVRs
- Multiple low barrier R, or incl 1 high barrier R
- Pan-genotypic: sofosbuvir, daclatasvir, ledipasvir
- G3 becomes harder
- Traditionally harder to treat, now easier
  - Cirrhotics, treatment experienced, null responders
  - HIV co-infection, only consideration is DDIs, duration
  - Renal failure, still need RBV

New HCV agents:

- Health economics
- 30-50,000 pos in NZ
  - 50% diagnosed and 50% undiagnosed
- 4 billion to ‘cure in one generation’
  - n=100 treated/yr PegIFN-RBV +/- BOC = 68K
  - Sofosbuvir/ Ledipasvir (Harvoni) = 75K
- Likely funding:
  - transplant, decompensated cirrhotics only?
  - Won’t impact HCC or transplant listings


The Hepatitis Foundation of New Zealand
www.hepatitisfoundation.org.nz

Hepatitis Foundation:

- HBV, all HBV pos can be referred
  - 6/12 bloods, referral algorithm Specialist Care
  - Education, family testing
- HCV Pilot: BOP / Wgtn, Roll-out across NZ
  - 50/50 funding with HF and PHOs
  - Re-issue all ‘old’ HCV pos results to GP, starting high case load, refer HF
  - HF: fibroscan, refer cirrhotics Specialist care
  - GP: follow-up non-cirrhotics

Summary:

- HBV:
  - Every HBV should be diagnosed and monitored lifelong
  - Pregnancy – add viral load in all and treat high viral loads
- HCV:
  - Few treatment indications currently!
  - New agents – not funded
- Hepatitis foundation:
  - HBV, education, monitoring, referral algorithm
  - HCV, pilot, fibroscan, non-cirrhotics GP, cirrhotics Spec care, treatment ?will be in GP