Hepatitis B Update

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Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

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GUIDELINES

Asian-Pacific clinical practice guidelines of hepatitis B: a 2015 update

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Update on Prevention, Diagnosis, an Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

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Hepatitis B in New Zealand

- 100,000 people infected with hepatitis B in NZ
- Ethnic prevalences
  - Pacific Islanders 3-13%
  - Chinese 9%
  - South East Asian 9%
  - Maori 6%
  - NZ European 1%

Recent changes

- Removal of Pharmac prescribing restrictions
  - No longer needs Special Authority
  - Any doctor / NP can prescribe
  - Removal of requirements to have defined level of fibrosis
- Pharmac switch to generic anti-viral medications
  - Now ~$50/month compared with ~$300-500/month for ETV, TDF

Risk factors for progression / complications

- Male
- eAntigen positive status
- Higher viral load
- Co-infection: HDV, HCV, HIV
- Alcohol, smoking
- FHx HCC

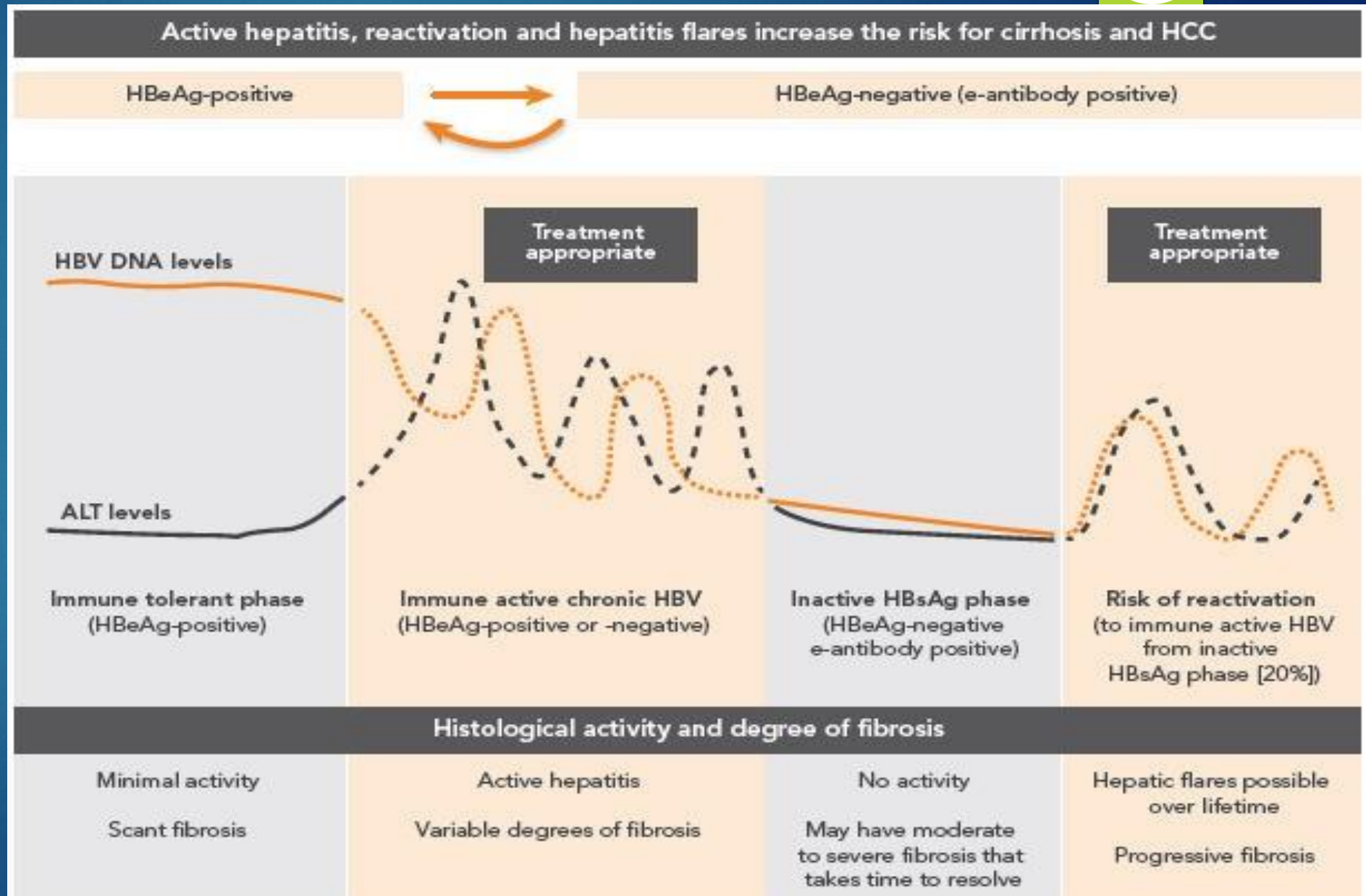
Serology

- HBsAg +: virus present, indicates current infection
- HBcAb +: past or current exposure to virus. If HBsAg –ve = immune.
- HBsAb +: past or current exposure to virus or vaccine.
  If HBsAg negative = immune
- HBeAg +: more active form of the virus, usually high replicative state
- HBeAg –ve: less active form of the virus, damage can still occur.

Definitions

- eAg + infection
  - AKA "Immune tolerant"
  - HBV DNA high, eAg positive, persistently normal ALT, no evidence of liver injury.
- eAg -ve infection:
  - Low replicative state,
  - AKA: "inactive carrier", "inactive chronic hepatitis B infection"
  - Avoid "inactive carrier" as falsely suggests no potential for complications.
  - HBV DNA <2,000, eAg negative, persistently normal ALT, no evidence of liver injury.

Natural History

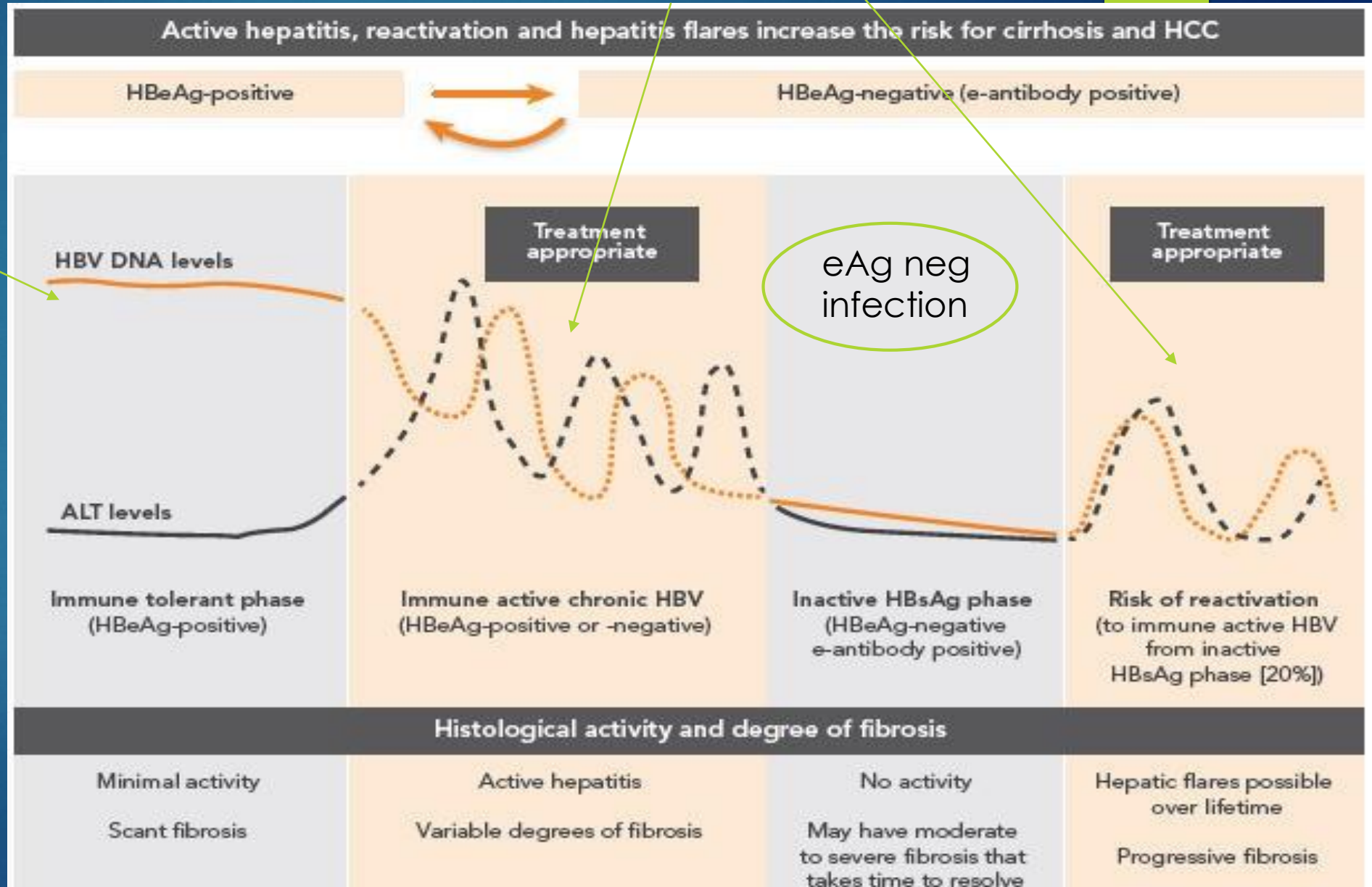


Natural History

Chronic active hepatitis

eAg pos infection

eAg neg infection



ALT Reference Range

- APASL:
  - ALT M <30
  - ALT F <19
  - or both <40 as little evidence that treating borderline elevation makes a difference.
- AASLD
  - M <35
  - F <25
- EASL – not defined.

eAntigen positive

- Treat
- Monitor
- Grey zone

eAntigen positive - Treat

- Active hepatitis: ALT >2xULN
- Persistent over a period of time (without eAg seroconversion)
- HBV DNA > 20,000
- Regardless of fibrosis stage

- HBV DNA 2,000–20,000: may be seroconverting, observe for a period of time.

- Annual rate of spontaneous HBeAg clearance during this phase is 3-12% [APASL pg 8]
- HBeAg seroconversion on treatment ~30% after a few years.

eAg positive - monitor

- ALT < ULN
- HBV DNA >20,000.
- Truly immune tolerant, infection with no active hepatitis very low risk of progression. Taiwan 240pts, mean age 27, over 10yrs: <5% cirrhosis and no HCC.
- TDF +/- emtrictabine in eAg + immune tolerant (normal ALT): successful suppression of HBV DNA, but only 5% eAg seroconversion after 3.7yrs.
- Therefore treatment not recommended unless evidence of significant fibrosis or cirrhosis or in a trial [APASL, pg23].

eAg positive - monitor

- 2 studies (Korean, Indian) show that 28-40% of people eAg +ve with persistently normal ALT had significant fibrosis and
- HBV DNA level did not predict level of fibrosis.
- Need to assess fibrosis stage at some age point: 35/40, especially if ALT borderline normal or slightly elevated.

eAg positive monitoring

- What tests and how often
- Secondary care v community
- Cost
- ALT 3-6 monthly.
- HBV DNA (Guidelines) 6-12 monthly or “more frequently” if ALT rises.
- eAg 6-12 monthly.
- Pragmatic:
  - ALT, eAg 6 monthly,
  - HBV DNA 3 yearly if stable in pattern of infection / immune tolerant. Fluctuations in HBV DNA in this context is not going to change management.
  - Fibrosis assessment 3-5 yearly over age 35/40.

eAg positive – further assessment…

- Age >35/40
- ALT: >ULN - <2xULN
- HBV DNA >20,000 (2,000 – 20,000 – may be seroconverting).

- Exclude other causes,
- Assess fibrosis stage
- APASL: biopsy if non-invasive tests suggest significant fibrosis.
- Treat if ≥F2 and elevation persists esp if age > 35/40

eAntigen negative

- Treat
- Monitor
- Grey zone

eAg negative – case – Dr C

- 46yr M, health professional.
- Chinese, vertical transmission.
- No FHx HCC.
- No significant alcohol.
- Recalls he had eAg seroconverted before first assessment as teenager in country of origin.

eAg negative - case

	2008-09			
Age	36			
ALT	27~36			

- What next?

eAg negative - case

	2008-09			
Age	36			
ALT	27~36			
HBV DNA	21,000			

- What next?
- Frequency of HBV DNA monitoring?

Frequency of HBV DNA monitoring – eAg neg.

- HBV DNA <2,000 & normal ALT – no need to treat: Monitor
  - ALT 3-6 monthly.
  - HBV DNA (Guidelines): 6-12 monthly, or just if ALT rises (AASLD *contradicts itself*).
  - Pragmatic: annually initially then decrease frequency.
- HBV DNA >2,000 & normal ALT or <2x ULN*:
  - ALT 3 monthly (for the 1st yr and 6 monthly thereafter).
  - HBV DNA (Guidelines): "regularly"
  - Pragmatic: every year for 3 years...
  - Fibrosis assessment

eAg negative - case

	2008-09 -10	2011-13		
Age	36	~40		
ALT	27~36	~30		
HBV DNA	21,000	-		

eAg negative - case

	2008-09 -10	2011-13	2015-18	
Age	36	~40	46	
ALT	27~36	~30	32~46	
HBV DNA	21,000	-	6,000 (April '18)	

- Fibroscan (May 2018): 5.5kPa (BMI 26.6)

- Would you recommend treatment?
- Would you do anything else?

eAntigen negative - Treat

- Chronic active hepatitis: HBV DNA >20,000 & ALT > 2xULN then Rx regardless of fibrosis stage.
- HBV DNA >2,000 & ALT > ULN* &/or at least moderate/severe inflammation or significant fibrosis
- Guidelines continue to put forward role of liver biopsy, especially if age >40 and early acquisition.
- Treat if FHx HCC even if active inflammation criteria not meet.

eAg negative - case

	2008-09 -10	2011-13	2015-18	Nov 2018
Age	36	~40	~43	46
ALT	27~36	~30	32~46	46
HBV DNA	21,000	-	6,000 (Apr '18)	12,000

- Fibroscan (May 2018): 5.5kPa (BMI 26.6)
- Abdo US: steatosis otherwise nad.

- Would you treat or monitor?
- Would you do a liver biopsy?
- Would you commence HCC surveillance?

Low viral load – to treat or not

- Level of evidence – expert opinion:
- If there is significant fibrosis, but normal / minimally elevated ALT and HBV DNA levels below cut-offs (eAg pos <20,000, eAg neg <2,000):
- Treatment recommended in order to prevent further progression of fibrosis. Rx may stabilize disease or even lead to regression in fibrosis. [APASL]

Hepatitis Foundation of New Zealand – community based monitoring – 26,000

- Historically:
  - LFTs, AFP, HBsAg, HBeAg 6 monthly with FBC annually age>40.
  - HBV DNA only requested if HBeAg neg and persistent elevated LFTs.
  - Only referred to secondary care if Pharmac criteria meet.
- Now
  - Increased frequency of HBV DNA testing ($)
  - Lower threshold to consider treatment
  - More referrals to secondary care for assessment and discussion around pros and cons of commencing long term anti-virals.
  - Inform HFNZ once treatment commenced. We can continue blood monitoring for you.

Cost of increased HBV DNA frequency

- 14,000 age >35
- 3,500 have already had at least one HBV DNA
- 10,500 x $220* = 2.3million initially
- ~ 1million annually thereafter.
- DHB / laboratory budgets.

HFNZ – Systems and Processes

- Massive IT system modernisation
- Modern client management system and national registry all in one.
- Allows advanced interoperability between HFNZ and 3rd parties
- Linkage to care from the community through to secondary care when needed
- Macro: interoperability with statistics NZ & mesh block data to identify areas of suspected high prevalence for increased case finding.
- Increased efficiency in back office processes
- Better monitoring & care of the patients registered with us
- Advanced data analysis will enable accurate evaluation of progress

US HCC surveillance (HFNZ)

- Cirrhosis
- FHx HCC 1st degree relative, from age 30
- Co-infection with HDV, HCV, HIV, regardless of fibrosis stage
- After HBsAg serconversion continue US surveillance
  - Cirrhosis
  - FHx HCC 1st degree relative.
- To be defined / may be different in secondary care:
  - Ethnic and age based cut-offs
  - Fibrosis stage based cut-offs.
  - Risk predictor score based cut-offs, eg/ REACH-B,

Role of Primary Care

- GPs can now be first prescribers of ETV/TDF
- Don't have the knowledge base, not as straight forward as treating Hep C.
- Don't want to muddy the waters when we really want them engaged with Hep C.
- In conjunction with HFNZ / Secondary care advice and support treatment initiation by GPs useful in reducing barriers to care for people who have difficulty accessing secondary care clinics
  - Rural,
  - Previous DNAs
  - Language

For the next session…

- Occupational Health
  - Health Professionals – Exposure Prone Procedures
  - Professional Council requirements re BBV.
  - Police
  - Food handling, meat works…
- Stopping rules
- Use of HBsAg titres
- Defining the HCC surveillance cut-offs for New Zealand

Take home points

- Treat:
  - All cases with cirrhosis or severe liver disease with any detectable HBV DNA
  - HBeAg pos pts with persistent ALT >2xULN
  - HBeAg neg pts with persistent ALT >2xULN & HBV DNA >2,000
- Monitor:
  - HBeAg pos age <35 with normal ALT*
  - HBeAg neg with normal ALT* and HBV DNA <2000
- Further consideration:
  - HBeAg pos pts age >35
  - HBeAg neg with normal ALT or <2xULN & HBV DNA >2000
  - HBeAg neg with raised ALT and HBV DNA <2000.

Context – WHO Hepatitis Elimination Targets

- Prevention:
  - 90% of infants receiving 3 doses of vaccine — 90% ✓
  - Prevention of vertical transmission with birth dose vaccine — 90% ✓
  - Blood safety – screening of donated blood products — 100% ✓
- Treatment
  - Diagnose — 90%
  - Treat — 80% of eligible
- Incidence of infection
  - Reduction of new infections by — 90% ✓
- Mortality
  - Reduction of HBV related mortality by — 65%