HEPATITIS B: WHO AND WHEN TO TREAT?

George V. Papatheodoridis

Professor in Medicine & Gastroenterology

Medical School of
National & Kapodistrian University of Athens

Director of Academic Department of Gastroenterology,
Laiko General Hospital,
Athens, Greece

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Conflicts of interest

- Advisor: Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Glaxo-Smith Kleine, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisc, Roche

- Lecturer: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Novartis, Roche

- Research grants: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Roche

- Clinical trials: Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Idenix, Merck Sharp & Dohme, Novartis, Novo Nordisc, Regulus, Roche

- Data Safety Management Board: Gilead

CHRONIC HBV INFECTION

- To treat or not to treat?

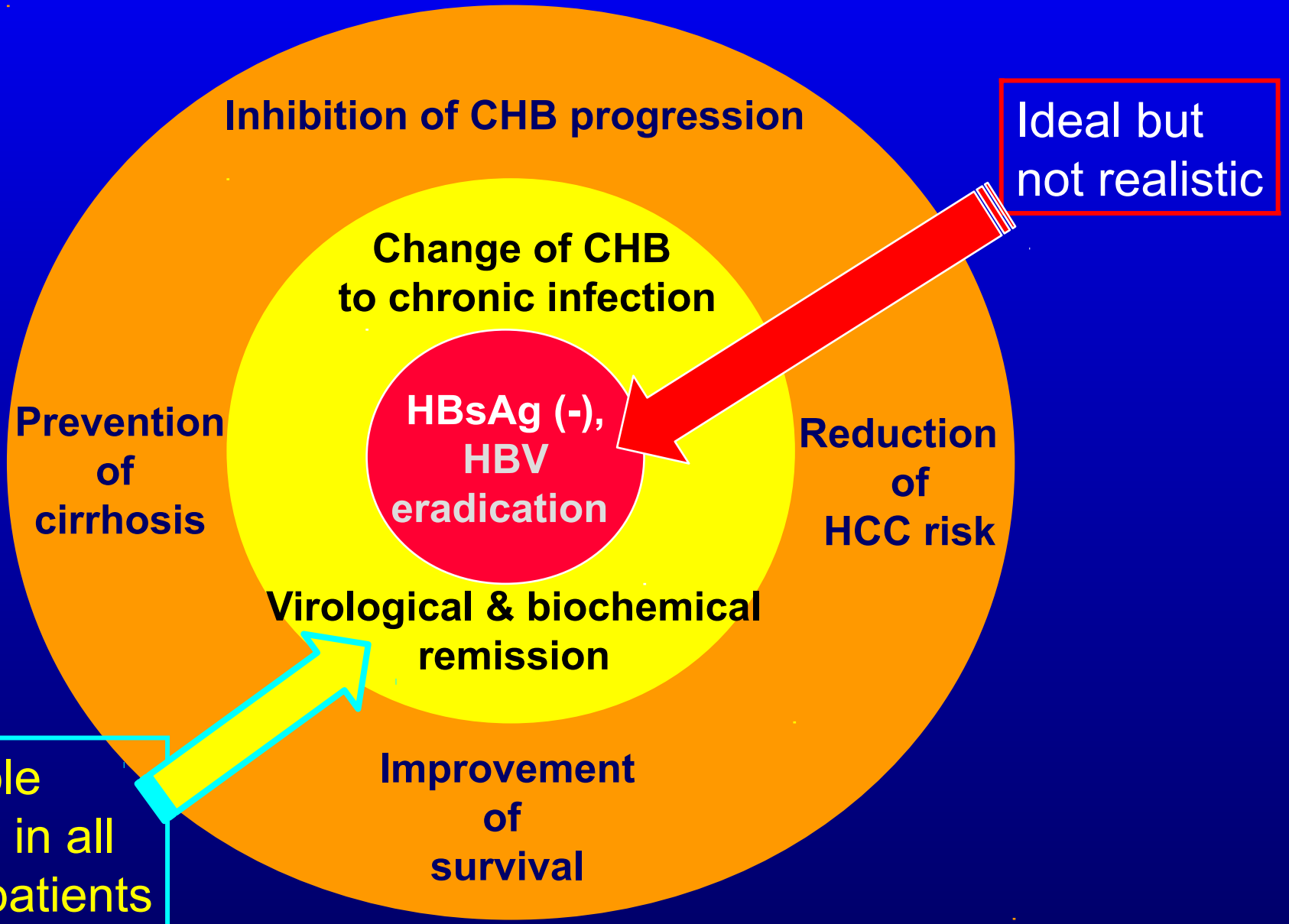
- To treat the right patient at the right time (who and when to treat)

Who and when to treat (indications for treatment) in patients with chronic HBV infection

Depend on

- Natural history of disease
- Goals of therapy
- Available drugs
  - efficacy
  - safety, tolerability
  - contraindications
  - *cost*

Therapeutic goals in CHB



Endpoints of therapy

Recommendations:

1)The induction of **long-term suppression of HBV DNA** levels represents the **main endpoint** of all current treatment strategies
(Evidence level I, grade of recommendation 1)

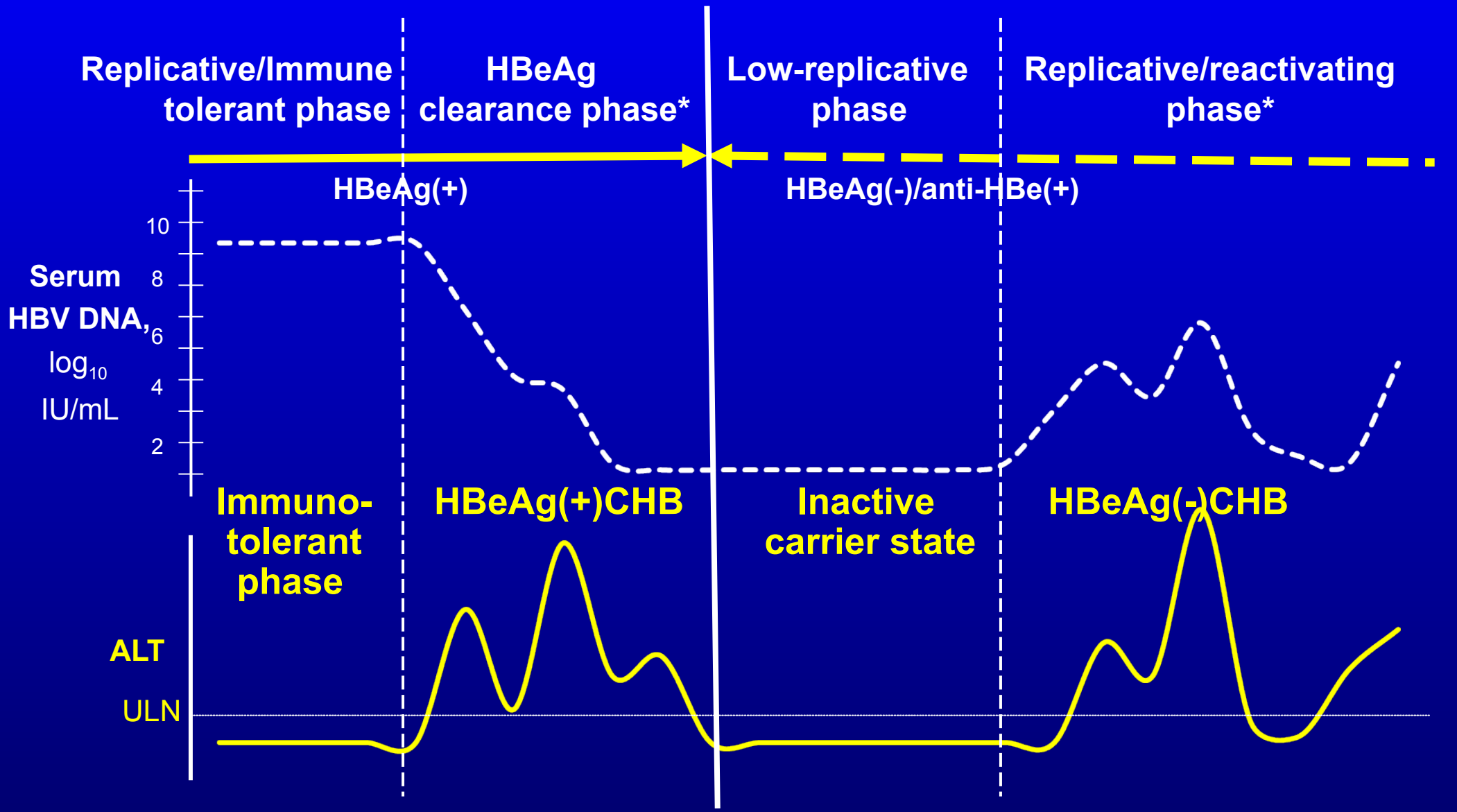
2)The induction of **HBeAg loss,** with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a **valuable endpoint,** ….
(Evidence level II-1, grade of recommendation 1)

3)A biochemical response defined as **ALT normalization** should be considered as an **additional endpoint,** …... *(Evidence level II-1, grade of recommendation 1)*

4)HBsAg loss, with or without anti-HBs seroconversion, is an **optimal endpoint**, ….. *(Evidence level II-1, grade of recommendation 1)*

EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

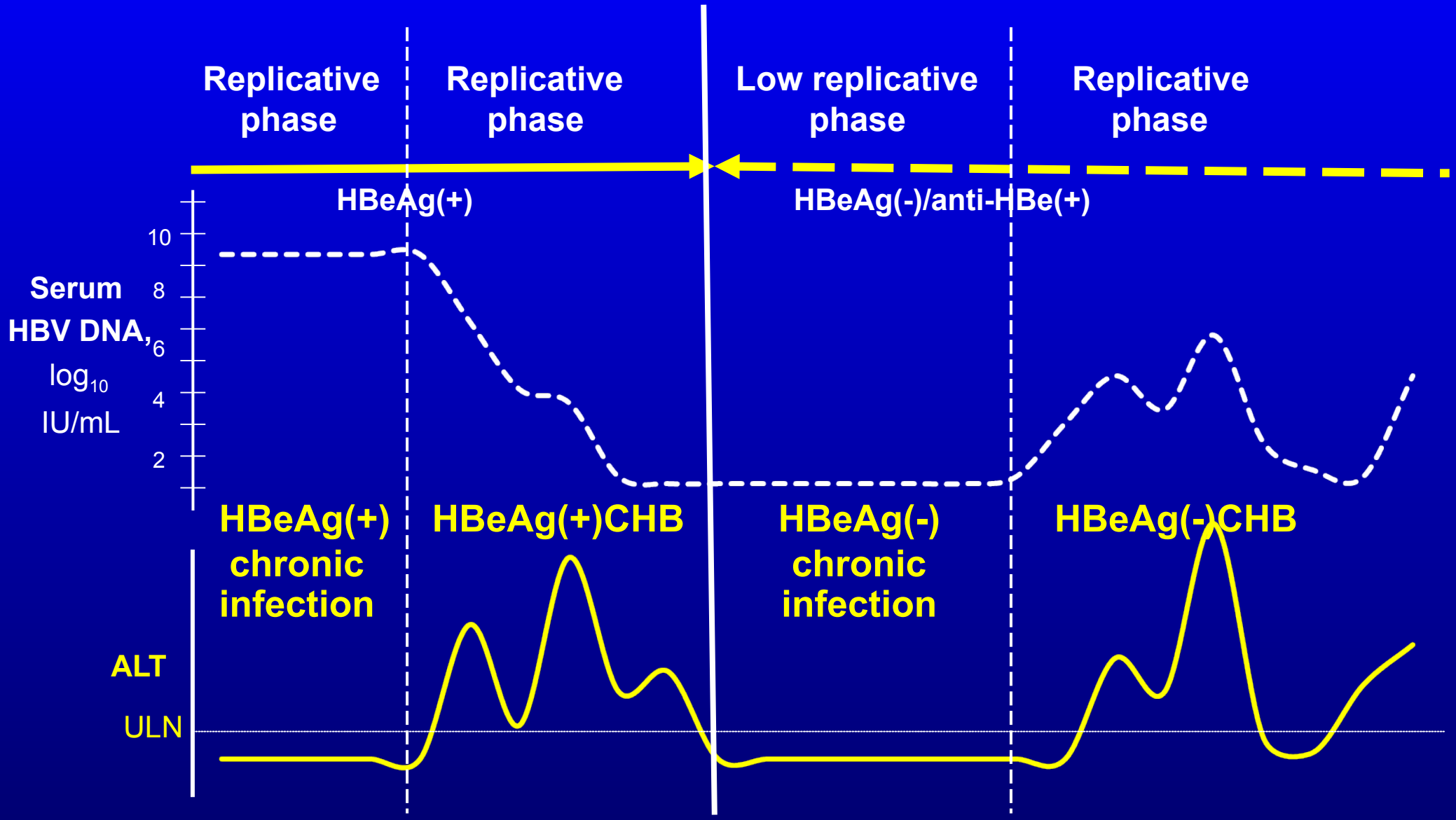
Natural History of Chronic HBV Infection



*Immune reactive phases

Papatheodoridis GV et al. Lancet Infect Dis 2008; 8: 167-78.

Natural History of Chronic HBV Infection



EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

Treatment indications in CHB

EASL[1] (2017) HBeAg (+/-)	AASLD[2] (2015) HBeAg (+/-)	APASL[3] (2015) HBeAg (+/-)
ALT >2xULN (40 IU/L) and HBV DNA >20,000 or Cirrhosis and HBV DNA+:	ALT ≥2xULN (30/19 IU/L for M/F) and HBV DNA >20,000/2,000 for HBeAg+/- : Therapy	ALT ≥2xULN (40 IU/L) and HBV DNA >20,000/2,000 for HBeAg+/- : Therapy
ALT >1-2xULN and/or HBV DNA ≤20,000 Elastography* or Biopsy*	ALT <2xULN and HBV DNA >2,000: Therapy if significant histology	ALT <2xULN and /or HBV DNA ≤20,000/2,000 for HBeAg+/-: Follow-up &
Fo… & age >30 or advanced disease or specific indications (eg immunosuppression etc)	…specific indications (perhaps age>40, HCC family history, immunos. etc)	…st – …is, age>35, family history of HCC/Ci

EASL/APASL - ALT traditional ULN: ~40 IU/L

EASL - Liver stiffness >9 or 12 kPa if ALT ≤ULN or >ULN (<5xULN): severe fibrosis or cirrhosis

*Therapy if stiffness >9/12 kPa for ALT≤/>ULN or biopsy shows ≥ moderate histol. lesions

1. EASL HBV CPGs 2017. J Hepatol 2017;67:370-398. 2. Terrault NA et al. Hepatology 2016;63:261-73.
3. SK Sarin et al. Hepatol Intern 2016;10:1-98

HBV DNA in IU/mL

Indications for treatment

Recommendations:

1)All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, **should be treated**. *(Evidence level I, grade of recommendation 1)*

2)Patients with compensated or decompensated **cirrhosis need treatment**, with any detectable HBV DNA level and regardless of ALT levels
(Evidence level I, grade of recommendation 1)

3)Patients with **HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis**. *(Evidence level II-2, grade of recommendation 1)*

4)Patients with HBeAg-positive or HBeAg-negative **chronic HBV infection** and family history of HCC or cirrhosis and extrahepatic manifestations **can be treated** even if typical treatment indications are not fulfilled *(Evidence level III, grade of recommendation 2)*

EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

Chronic HBV cases with grey-zone treatment indications

- Female, 28 years old, HBeAg+

  HBV DNA 35,000,000 IU/ml

  ALT 28, 50, 33 IU/L on 3 occasions

  within last year Liver stiffness 6 kPa

Should we treat without a liver biopsy? Most probably no

Should we recommend a liver biopsy?

- Male, 45 years old, HBeAg-/anti-HBe+

  HBV DNA 6,500 IU/ml

  ALT 45, 34, 38 IU/L on 3 occasions

  within last year Liver stiffness 8.2 kPa

Which is the probability of ≥moderate histological lesions?

Antiviral therapy in HBeAg(+) patients with PNALT?

- Maintenance of high HBV replication: increasing numbers of infected hepatocytes, risk of progression of liver lesions, increasing HCC risk
- High risk of HBV transmission

- Usually minimal histological lesions
- Low probability of anti-HBe seroconversion after Peg-IFN/NAs
- (Peg-)IFNa: not effective - NAs: inhibition of HBV replication
- Probably life-long therapy in young patients:
  long-term safety, family planning?

Do I treat my HBV immunotolerant patients?

No

Except for a few

GV Papatheodoridis, 9th Paris Hepatitis Conference 2016
J Vlachogiannakos & G Papatheodoridis. Liver Intern 2016; 36 (Suppl 1):93-9.

Management of HBeAg-positive patients with high HBV DNA (>20,000 IU/mL) and PNALT

- **Age >40 years**: treatment
- **Age 30-40 years**: decisions individualised - liver biopsy
- **Age <30 years**: follow-up (ALT /3-6 mos, HBeAg/anti-HBe /6-12 mos)
- **Positive family history for HCC**: reduce the age limit for treatment initiation
- **Clinical or laboratory indications of advanced liver lesions**

  (eg low PLT, high g-globulins, splenomegaly, spiders, palmar erythema, high stiffness on Fibroscan etc): liver biopsy even in patients <30 years

Potential additional treatment indications

- Professional reasons
- Last trimester of pregnancy

Management of HBeAg-positive patients with high HBV DNA (>20,000 IU/mL) and PNALT

- **Age ≥30 years**: may be treatment
- **Age <30 years**: follow-up (ALT /3-6 mos, HBeAg/anti-HBe /6-12 mos)
- **Liver stiffness >9 kPa:** can be treated
- **Positive family history for HCC**: can be treated
- **Clinical or laboratory indications of advanced liver lesions**

  (eg low PLT, high g-globulins, splenomegaly, spiders, palmar erythema):

  can be treated

Potential additional treatment indications

- Professional reasons
- Last trimester of pregnancy

EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

HBeAg(-) chronic HBV

HBeAg-negative chronic infection (inactive carriers)

(good long-term outcome – variable risk of progression to HBeAg-neg. CHB)

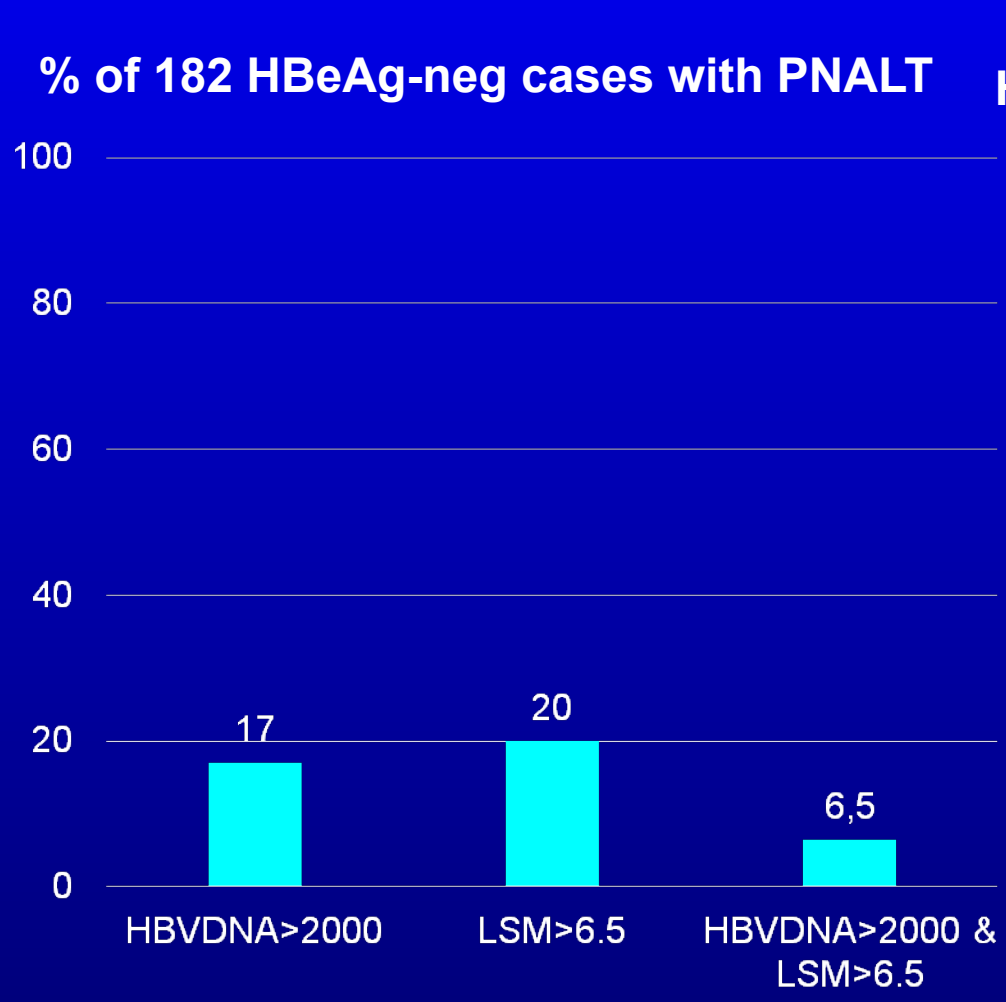
Differential diagnosis and follow-up based on ALT, HBV DNA, liver biopsy – emerging role of elastography and HBsAg levels

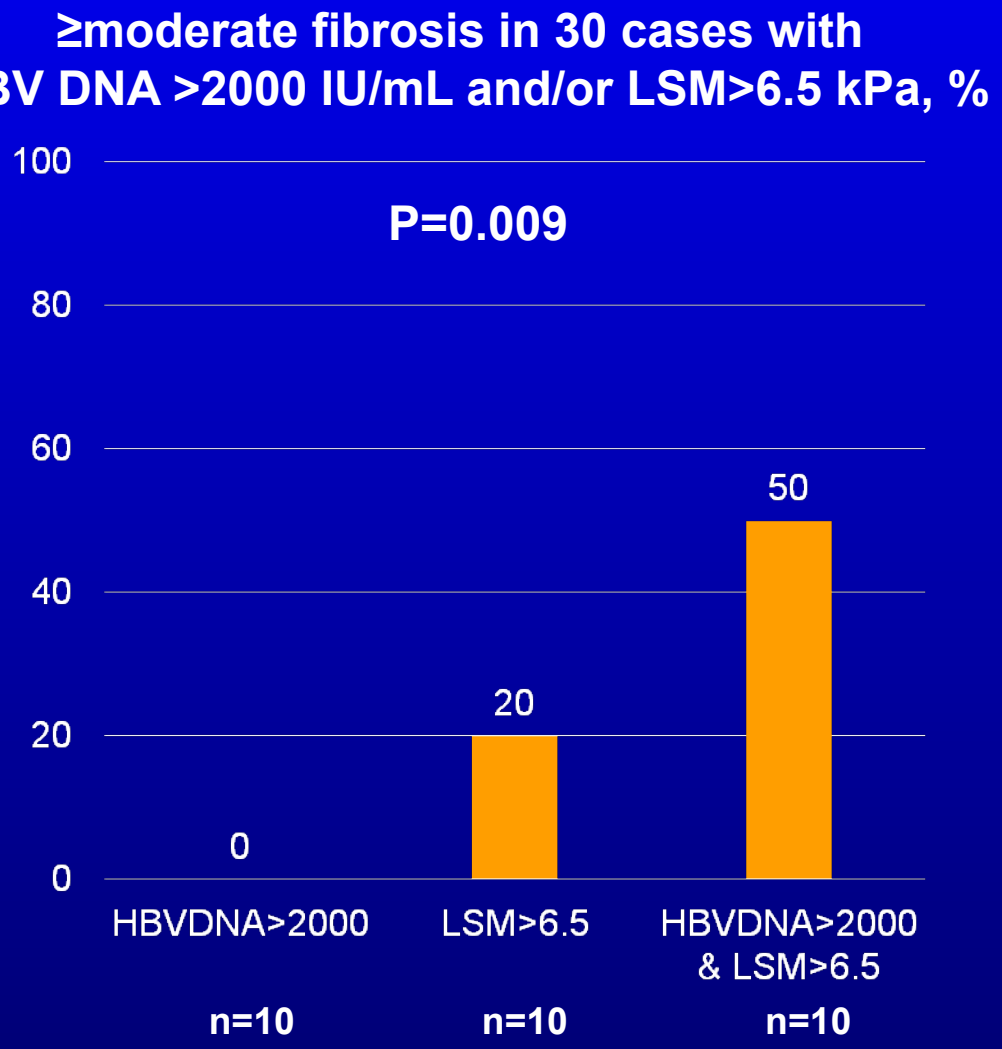
Don't treat – Follow-up for life

Patients with HBeAg-negative CHB

(progressive liver disease)

HBV DNA, Elastographic (LSM) and histological findings in 182 HBeAg-negative patients with PNALT & HBV DNA <20,000

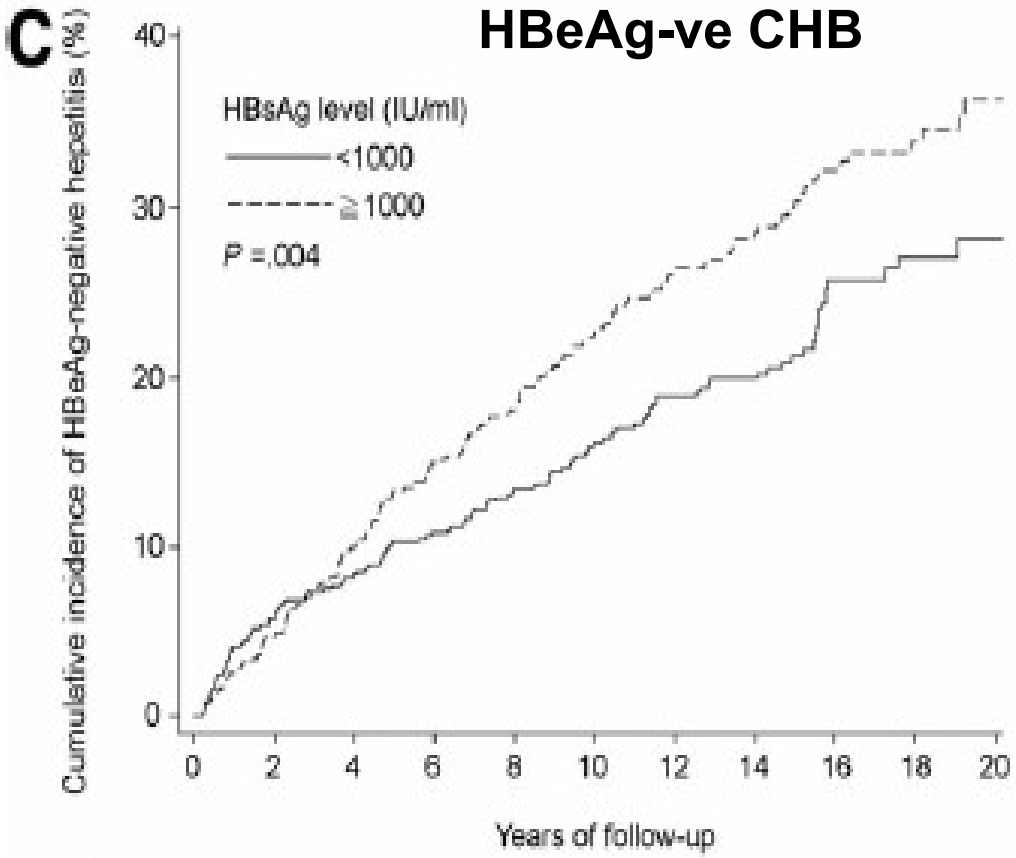




LSM: liver stiffness measurements, PNALT: persistently normal ALT

GV Papatheodoridis et al. J Viral Hepat 2014 ;21:517-24.

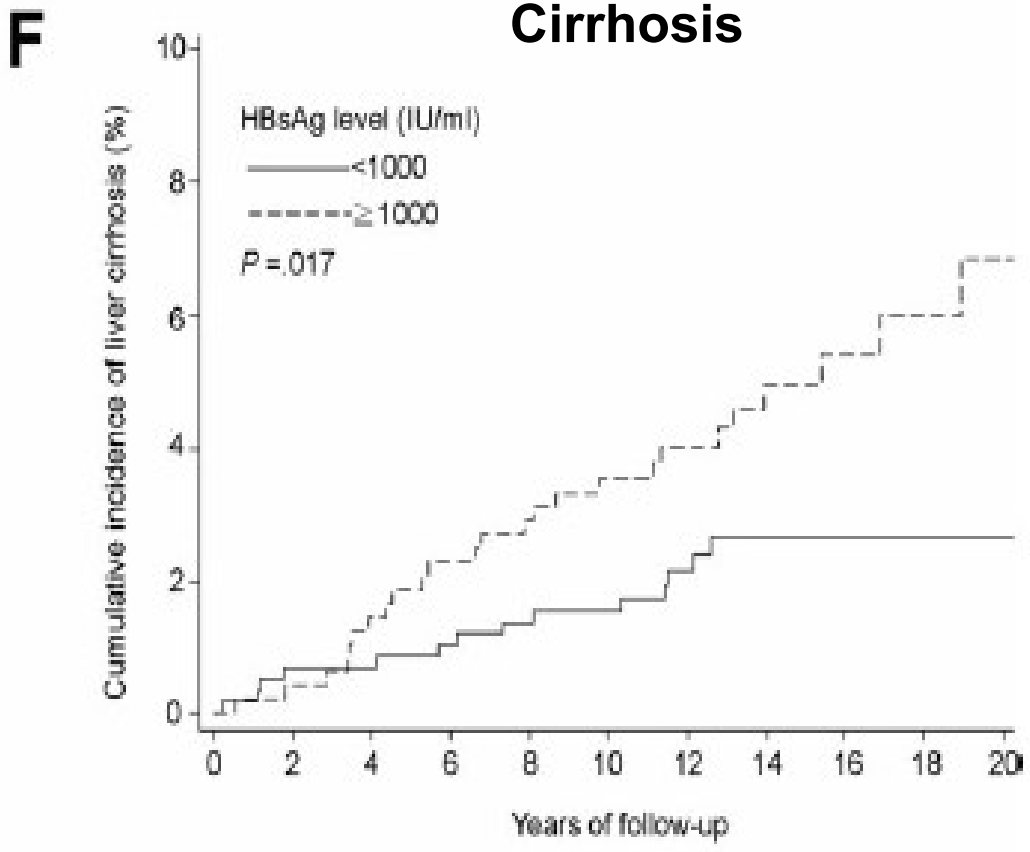
Disease progression in HBeAg-ve patients with HBV DNA<2000 IU/mL



Number at risk

Serum HBsAg levels at baseline (IU/ml)

<1000	585	551	536	521	503	454	357	265	146	90	58
≥1000	483	460	435	410	394	350	288	210	132	100	57



Number at risk

Serum HBsAg levels at baseline (IU/ml)

<1000	585	581	581	578	573	532	432	315	182	111	71
≥1000	483	481	476	471	466	436	373	276	182	131	81

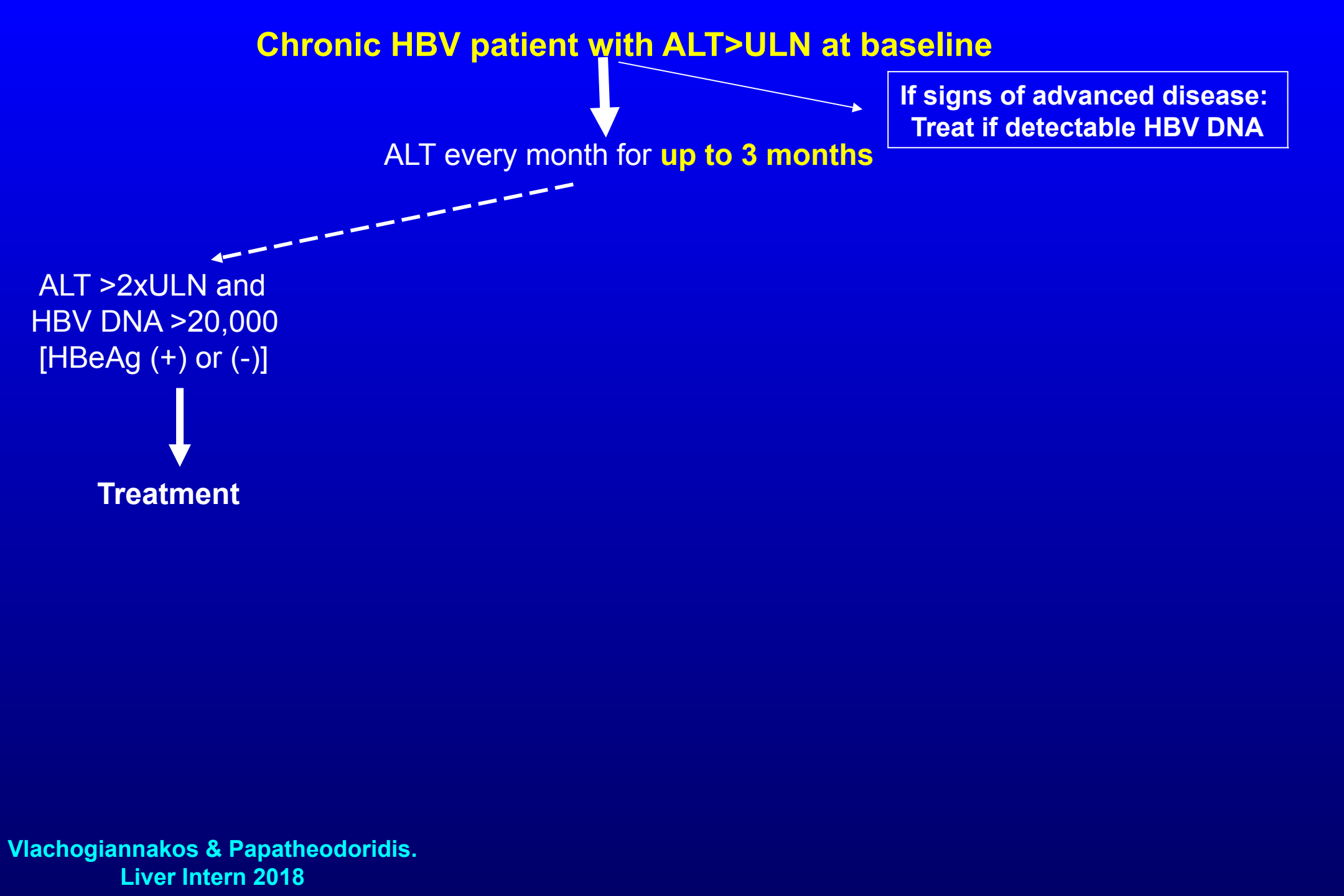
Tseng TC et al. Hepatology 2013;57:441-50

Chronic HBV patient with ALT>ULN at baseline

ALT every month for **up to 3 months**

If signs of advanced disease:
Treat if detectable HBV DNA

Vlachogiannakos & Papatheodoridis.
Liver Intern 2018



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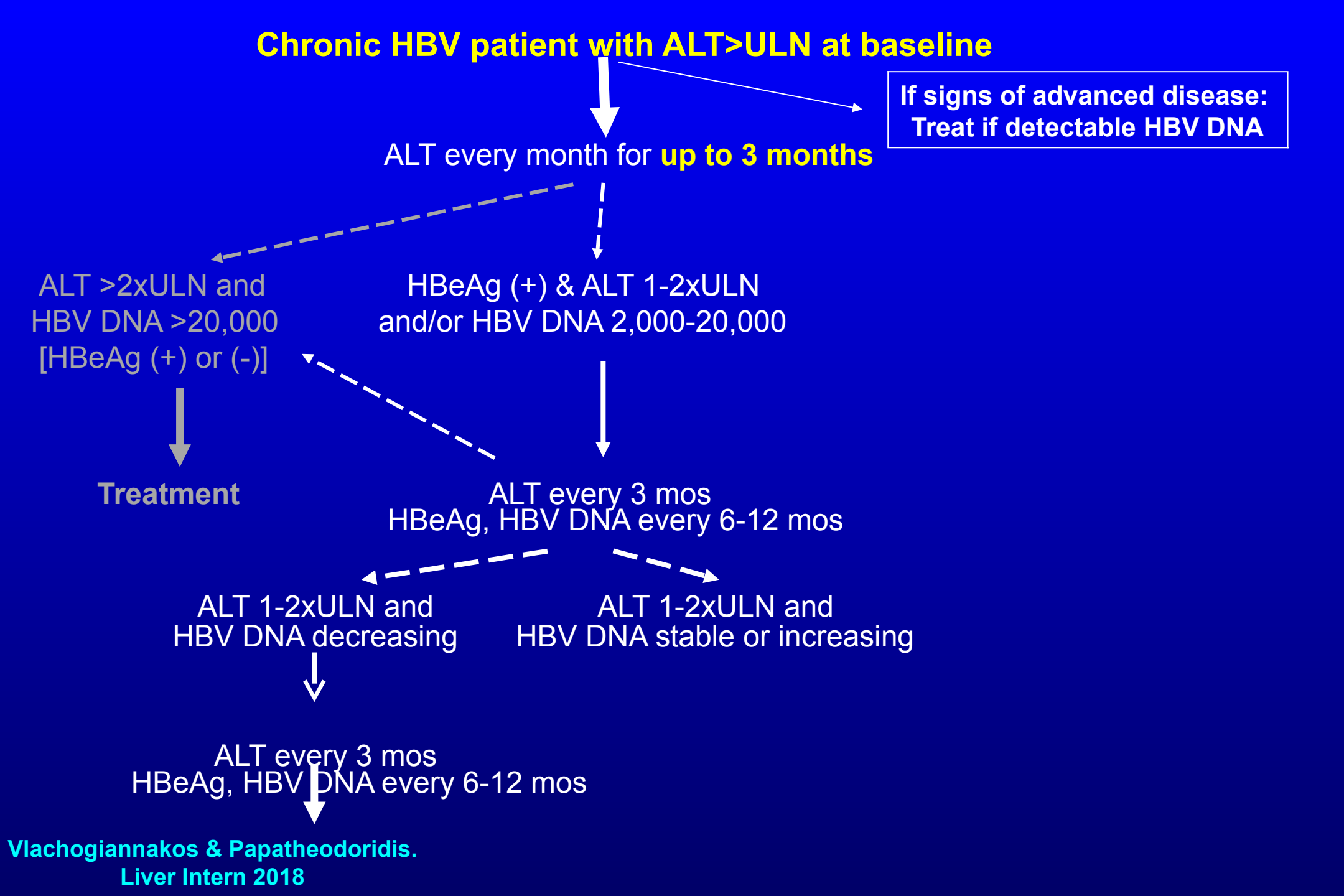
Chronic HBV patient with ALT>ULN at baseline
If signs of advanced disease:
Treat if detectable HBV DNA
ALT every month for up to 3 months
ALT >2xULN and
HBV DNA >20,000
[HBeAg (+) or (-)]
HBeAg (+) & ALT 1-2xULN
and/or HBV DNA 2,000-20,000
Treatment
ALT every 3 mos
HBeAg, HBV DNA every 6-12 mos
ALT 1-2xULN and
HBV DNA decreasing
ALT 1-2xULN and
HBV DNA stable or increasing
ALT every 3 mos
HBeAg, HBV DNA every 6-12 mos
Vlachogiannakos & Papatheodoridis.
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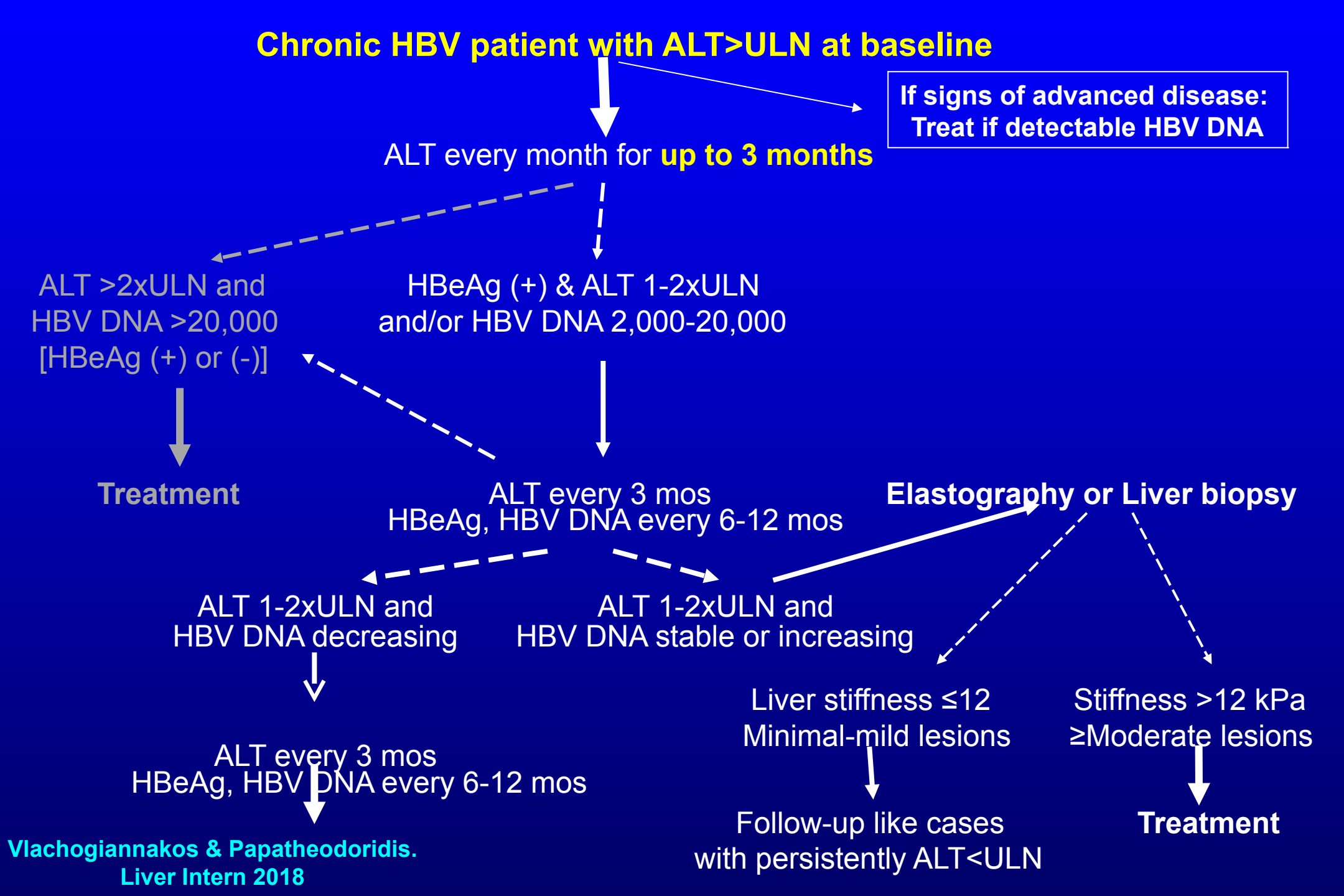
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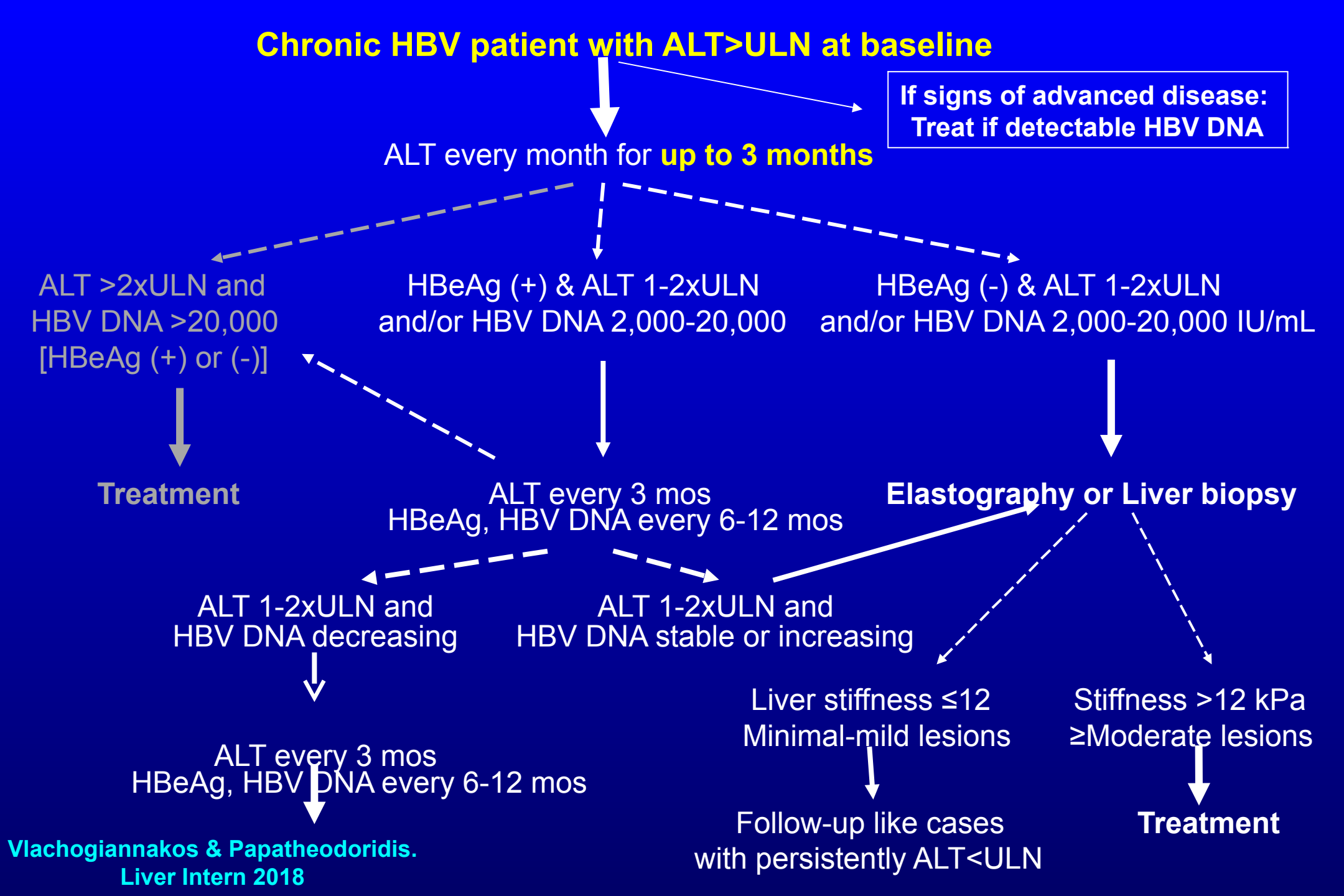
ALT every 3 mos
HBeAg, HBV DNA every 6-12 mos
Elastography or Liver biopsy
ALT 1-2xULN and
HBV DNA decreasing
ALT 1-2xULN and
HBV DNA stable or increasing
ALT every 3 mos
HBeAg, HBV DNA every 6-12 mos
Liver stiffness ≤12
Minimal-mild lesions
Stiffness >12 kPa
≥Moderate lesions
Follow-up like cases
with persistently ALT<ULN
Treatment
Vlachogiannakos & Papatheodoridis.
Liver Intern 2018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If signs of advanced disease:
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and/or HBV DNA 2,000-20,000
HBeAg (-) & ALT 1-2xULN
and/or HBV DNA 2,000-20,000 IU/mL
Treatment
ALT every 3 mos
HBeAg, HBV DNA every 6-12 mos
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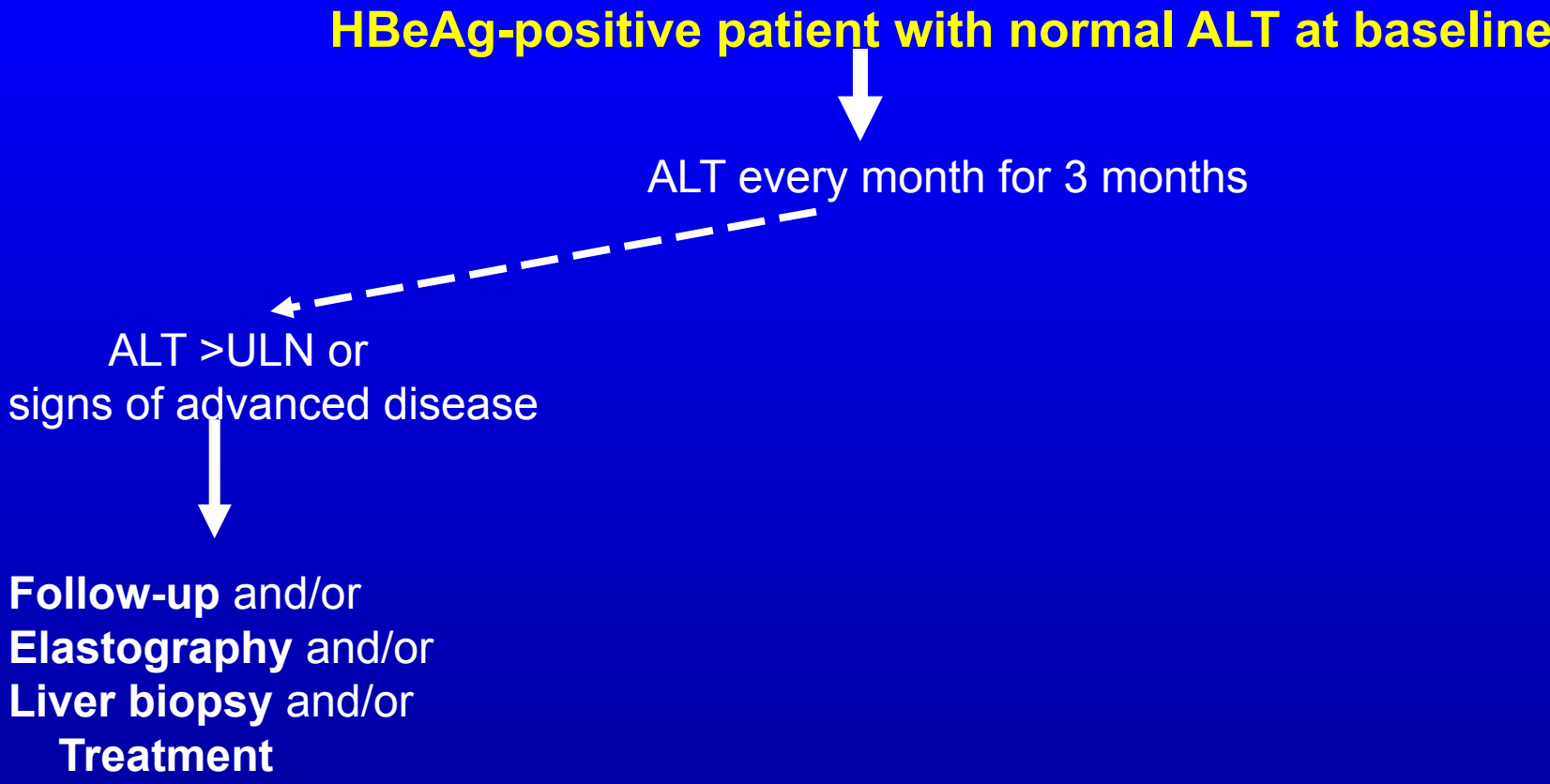

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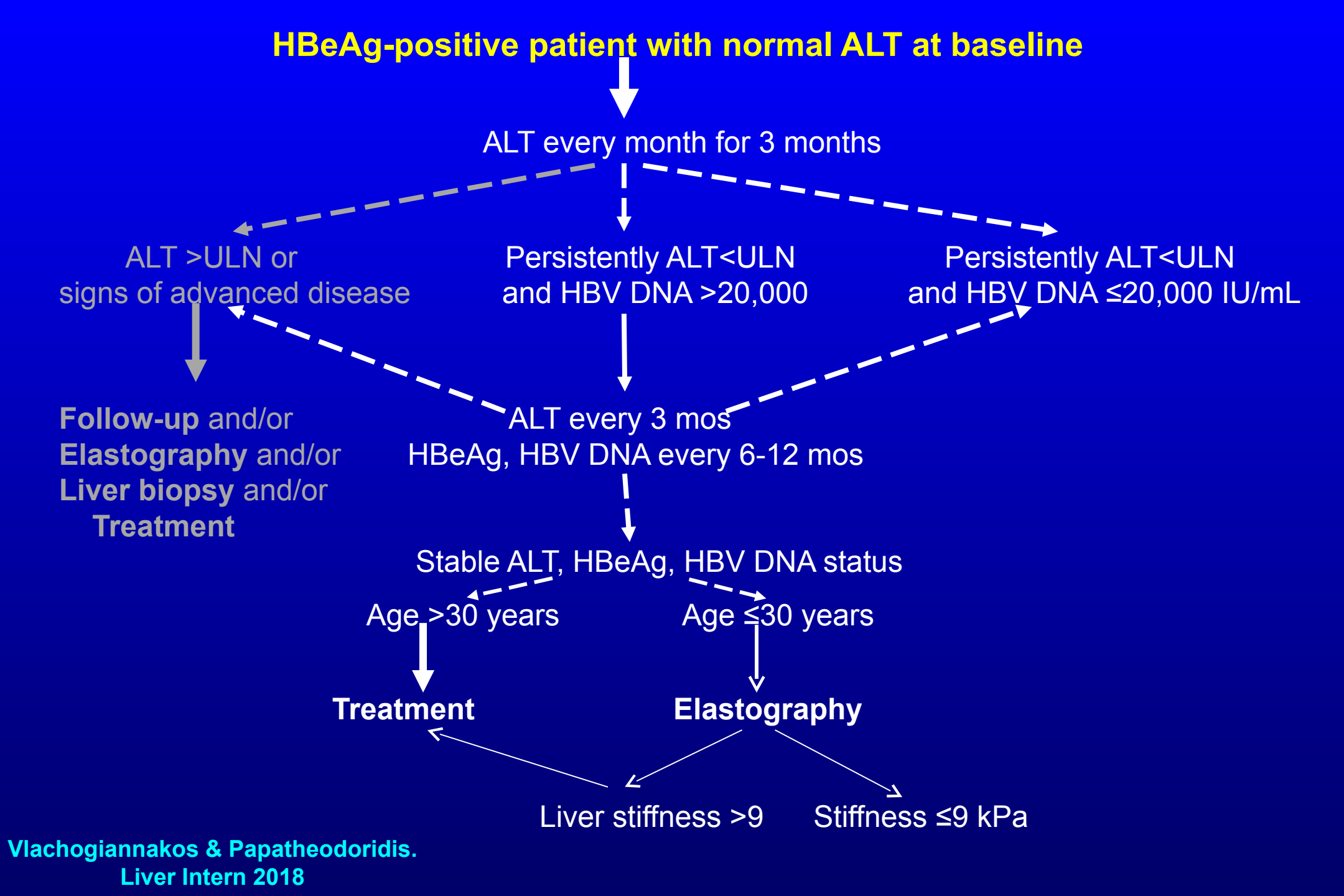
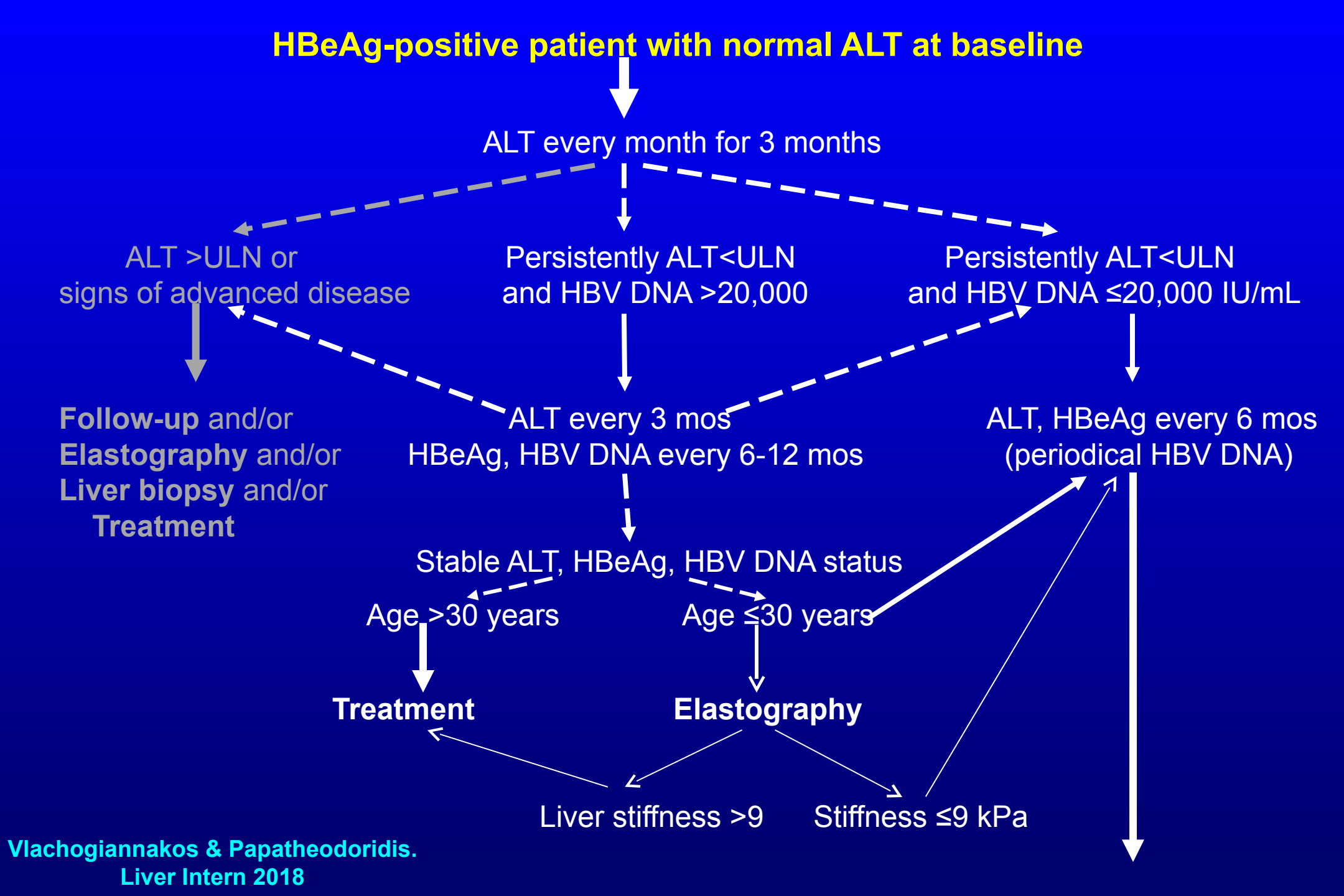

HBeAg-positive patient with normal ALT at baseline
ALT every month for 3 months
ALT >ULN or signs of advanced disease
Persistently ALT<ULN and HBV DNA >20,000
Persistently ALT<ULN and HBV DNA ≤20,000 IU/mL
Follow-up and/or Elastography and/or Liver biopsy and/or Treatment
ALT every 3 mos HBeAg, HBV DNA every 6-12 mos
Stable ALT, HBeAg, HBV DNA status
Age >30 years
Age ≤30 years
Treatment
Elastography
Liver stiffness >9
Stiffness ≤9 kPa
Vlachogiannakos & Papatheodoridis. Liver Intern 2018


HBeAg-positive patient with normal ALT at baseline
ALT every month for 3 months
ALT >ULN or signs of advanced disease
Persistently ALT<ULN and HBV DNA >20,000
Persistently ALT<ULN and HBV DNA ≤20,000 IU/mL
Follow-up and/or Elastography and/or Liver biopsy and/or Treatment
ALT every 3 mos HBeAg, HBV DNA every 6-12 mos
ALT, HBeAg every 6 mos (periodical HBV DNA)
Stable ALT, HBeAg, HBV DNA status
Age >30 years
Age ≤30 years
Treatment
Elastography
Liver stiffness >9
Stiffness ≤9 kPa
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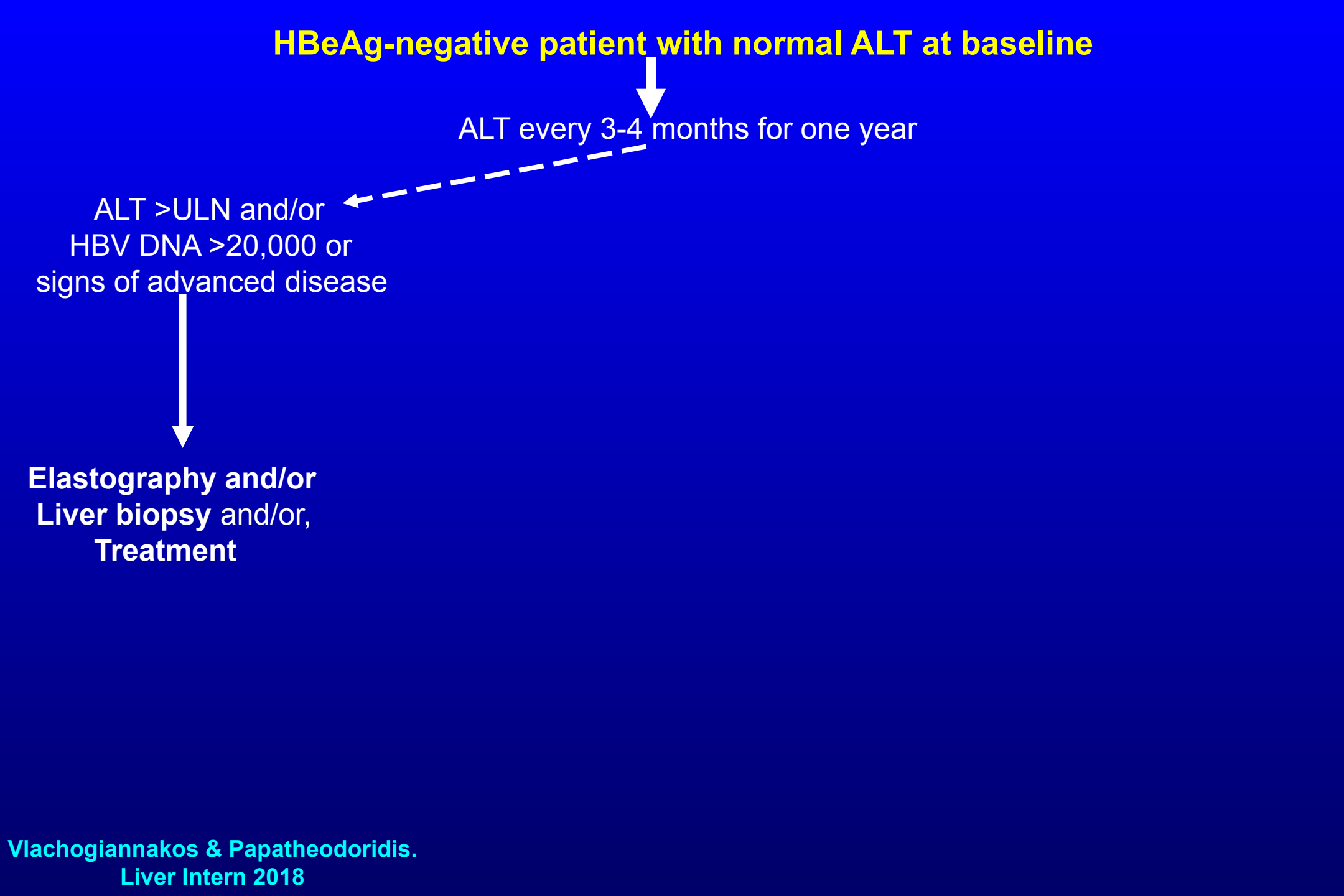

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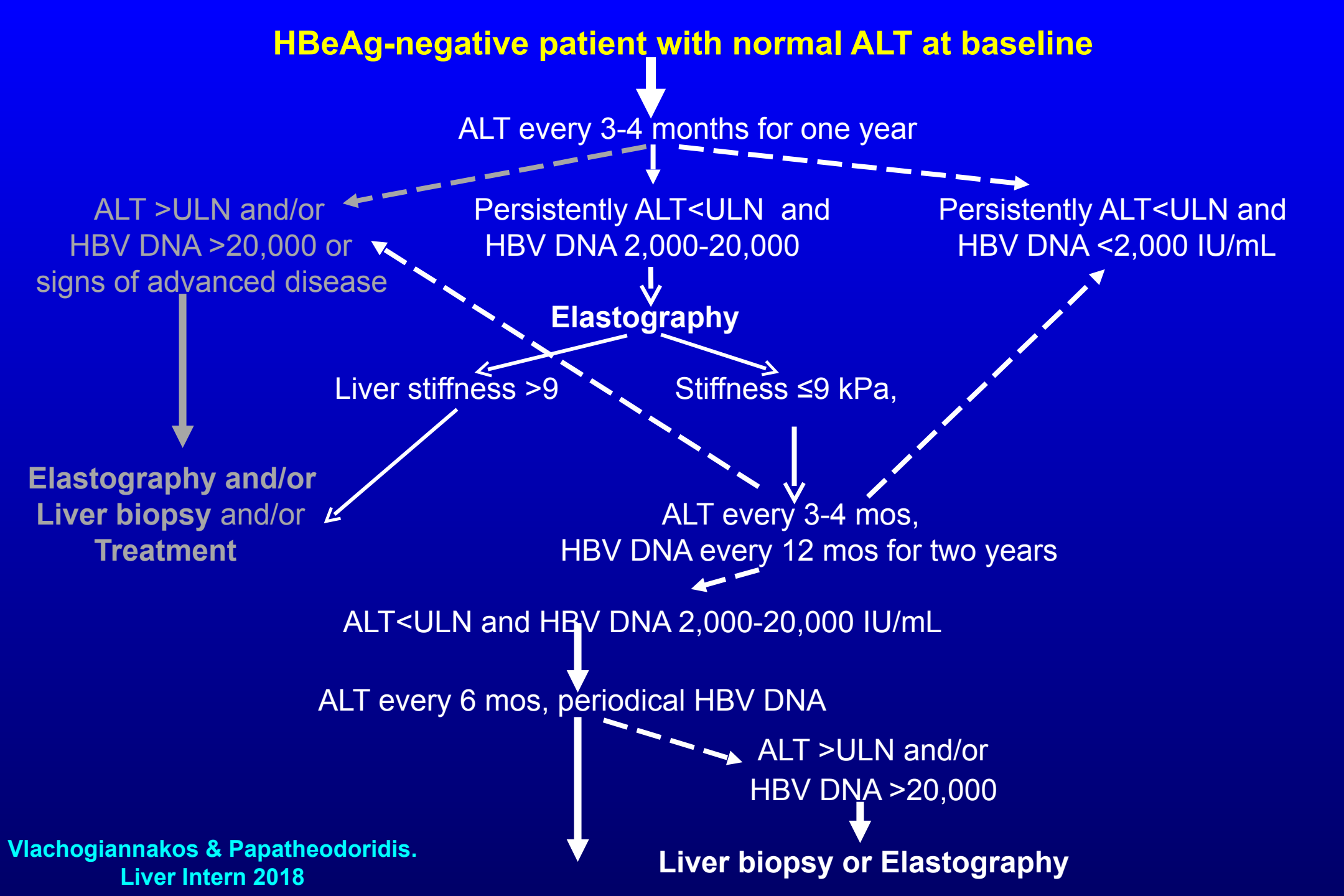
HBeAg-negative patient with normal ALT at baseline
ALT every 3-4 months for one year
ALT >ULN and/or
HBV DNA >20,000 or
signs of advanced disease
Persistently ALT<ULN and
HBV DNA 2,000-20,000
Persistently ALT<ULN and
HBV DNA <2,000 IU/mL
Elastography
Liver stiffness >9
Stiffness ≤9 kPa,
Elastography and/or
Liver biopsy and/or
Treatment
ALT every 3-4 mos,
HBV DNA every 12 mos for two years
ALT<ULN and HBV DNA 2,000-20,000 IU/mL
ALT every 6 mos, periodical HBV DNA
ALT >ULN and/or
HBV DNA >20,000
Liver biopsy or Elastography
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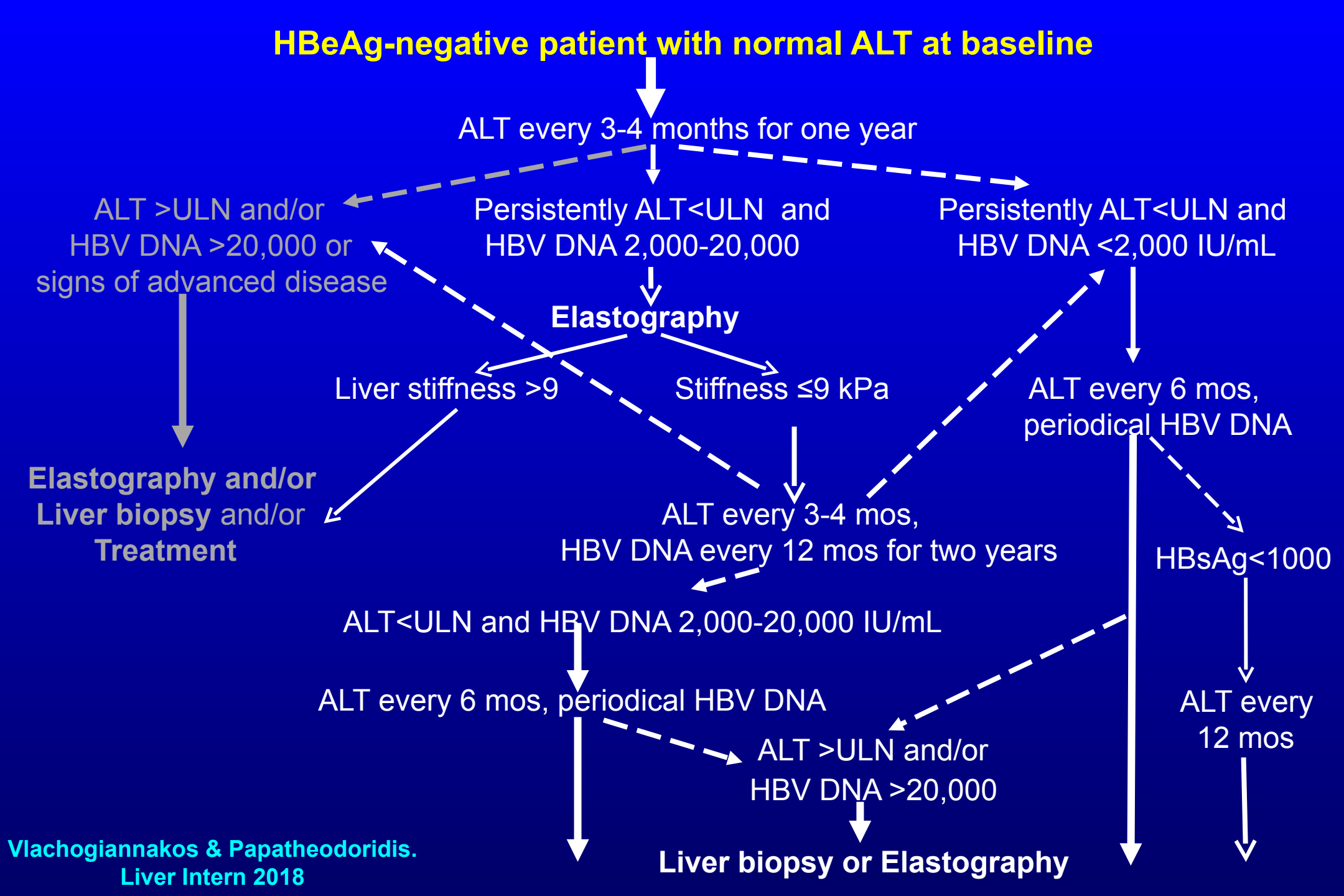
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ALT every 3-4 months for one year
ALT >ULN and/or
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Persistently ALT<ULN and
HBV DNA 2,000-20,000
Persistently ALT<ULN and
HBV DNA <2,000 IU/mL
Elastography
Liver stiffness >9
Stiffness ≤9 kPa
Elastography and/or
Liver biopsy and/or
Treatment
ALT every 3-4 mos,
HBV DNA every 12 mos for two years
ALT every 6 mos,
periodical HBV DNA
HBsAg<1000
ALT<ULN and HBV DNA 2,000-20,000 IU/mL
ALT every 6 mos, periodical HBV DNA
ALT >ULN and/or
HBV DNA >20,000
ALT every
12 mos
Liver biopsy or Elastography
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Additional indications of treatment/prophylaxis for chronic HBV patients

- Liver transplantation (NA ±HBIG)
- HBV-HIV co-infection
- HDV-HBV co-infection with ongoing HBV replication
- HBV-HCV co-infection during and for 12 weeks after DAAs
- Last trimester of pregnancy and up to 12 weeks after delivery if HBV DNA >200,000 IU/ml or HBsAg >4 $\log_{10}$ IU/ml
- During and for 12 months after immunosuppressive therapy or chemotherapy
- Healthcare workers performing exposure prone procedures with serum HBV DNA >200 IU/ml
- Extrahepatic manifestations and replicative HBV infection

Thank you!