The simplification of hepatitis B care.

MARGARET HELLARD AM

The simplification of hepatitis B care.

Why this is important.

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The simplification of hepatitis B care.

Why not?

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The simplification of hepatitis B care.

Why it is important to achieve hepatitis elimination globally.

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The simplification of hepatitis B care.

Why it is important for our patients.

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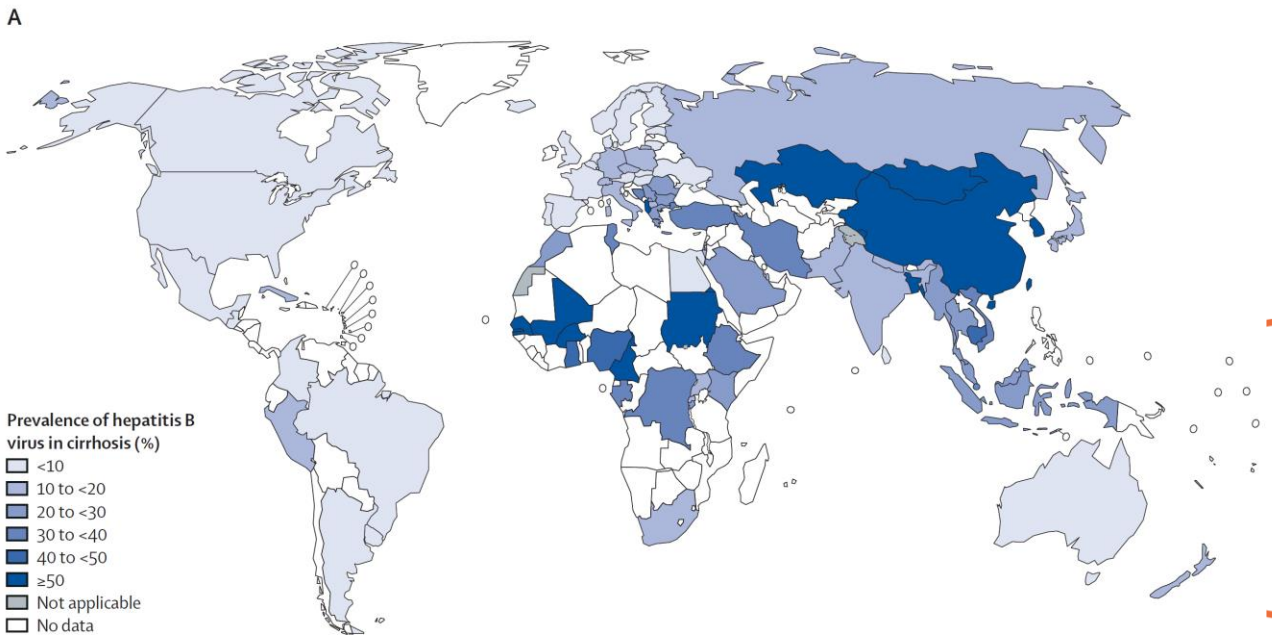
Hepatitis B – why should we care

~296 million people were living with chronic hepatitis B infection in 2019

1.5 million new infections each year

In 2019- an estimated 820 000 deaths, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).



WHO hepatitis B 2030 elimination targets

Reduce new infections by 90%

Reduce deaths by 65% (<1 per 100,000 death rate)

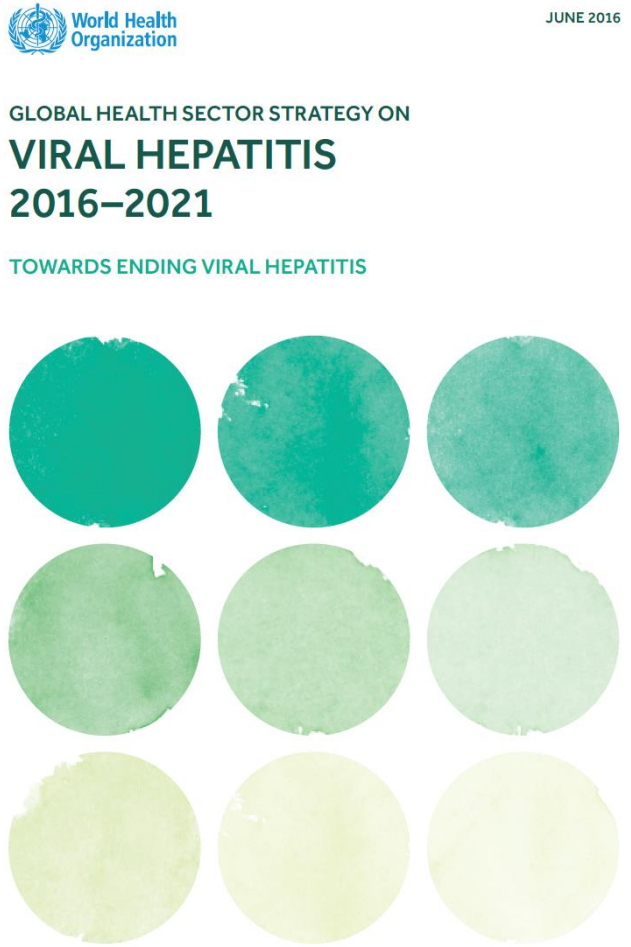
90% diagnosed

90% linked to care

15% on treatment (80% of those eligible)

Without meeting WHO elimination 2030 targets:

- 63 million avoidable new infections
- 17 million preventable deaths



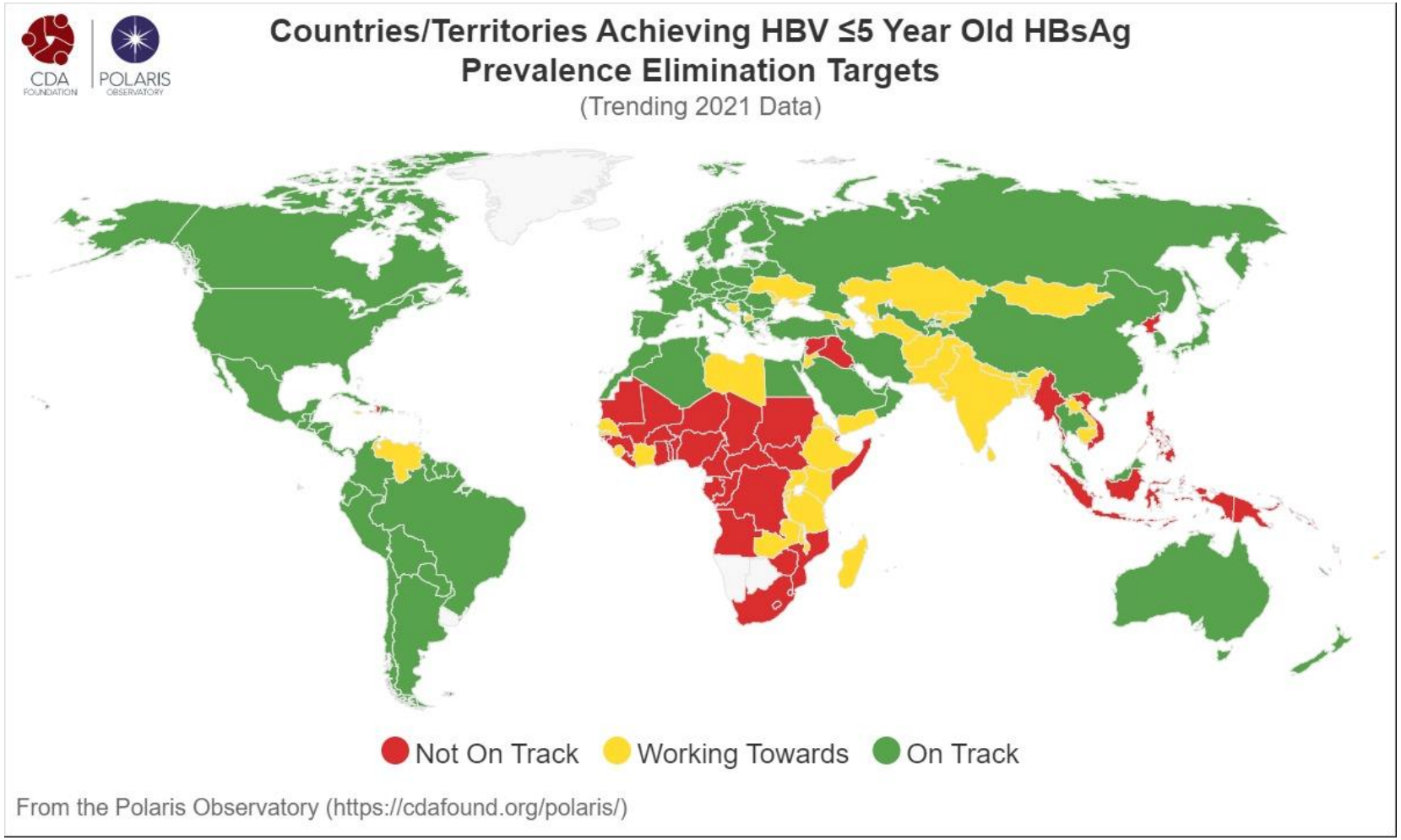
Why we can achieve elimination

- We have a fanstatic, highly effective vaccine which can stop people getting infected
- Critically – the most cases of new infections globally occur due to mother to child transmission at/near childbirth.
- Giving birthdose vaccines could stop new infections but in many countries in the world this is not happening

Why we can achieve elimination

- We have tests to detect hepatitis B and monitor its progress
- We have highly effective treatments that stop people getting sick and dying from hepatitis B
- However most people in the world remain undiagnosed and untreated

Progress has stalled



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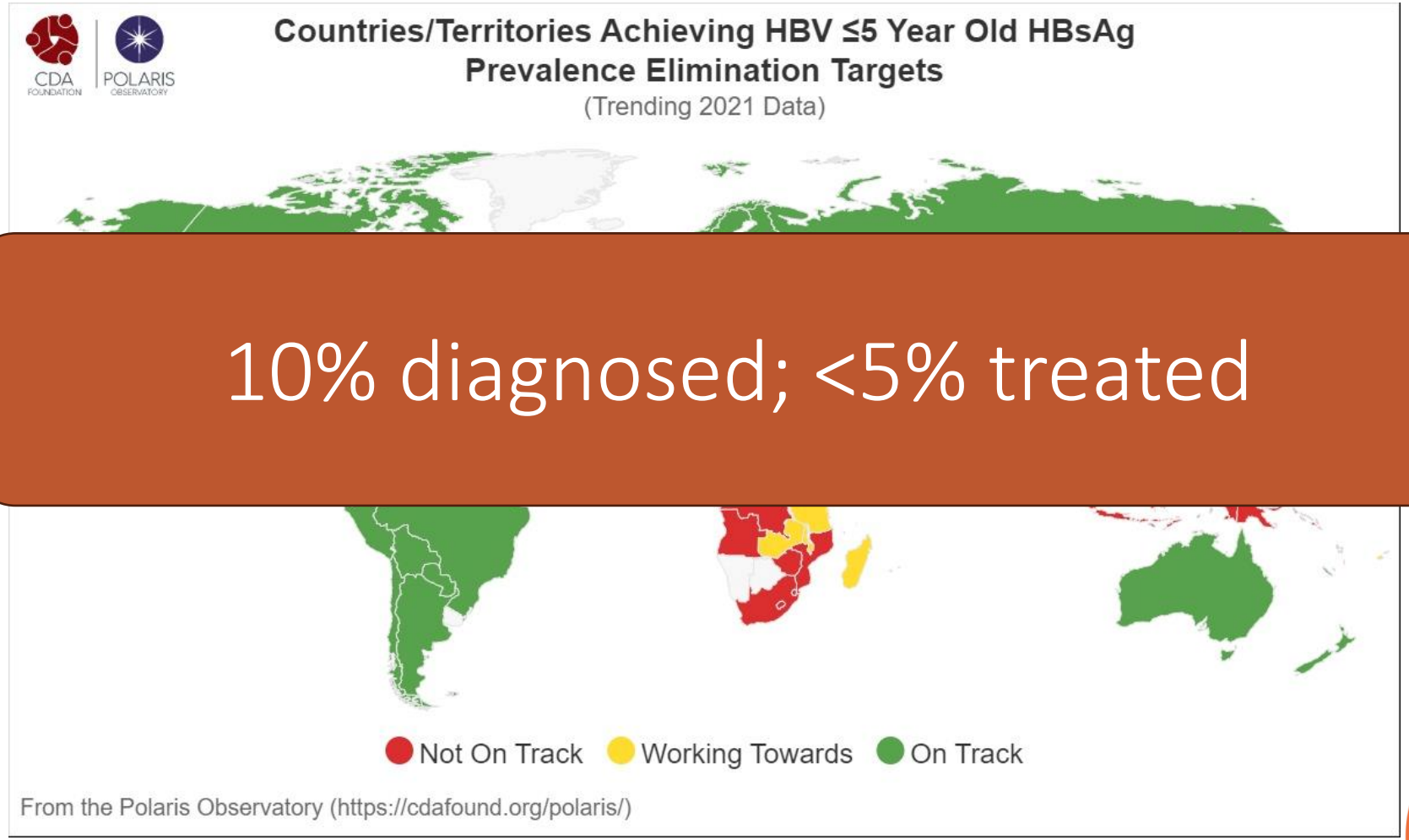

10% diagnosed; <5% treated

Global hepatitis B vaccination coverage

46% Birth dose

87% 3x doses

13% HBIg

<1% TDF in T3

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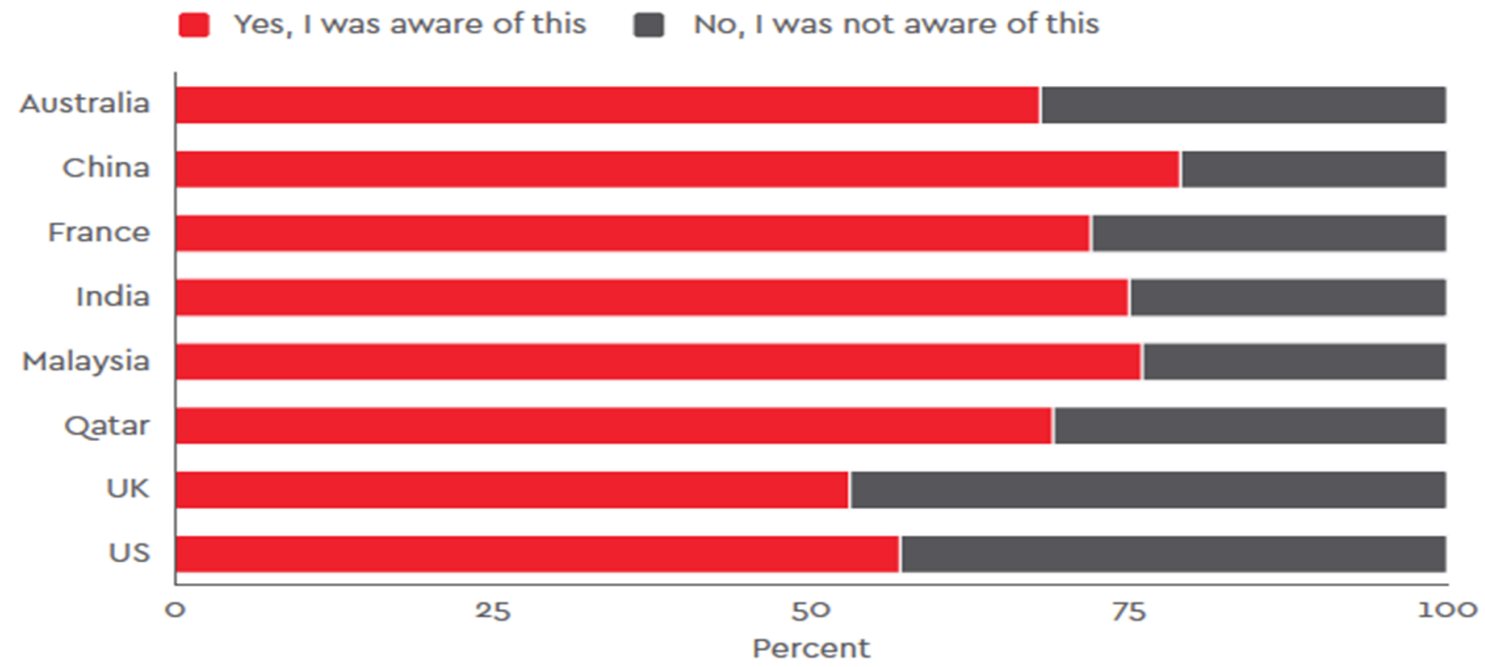
Why are we failing?

Lack of awareness about a hepatitis B vaccine



Source: YouGov

Confusion about treatment

HBV Treatment Recommendation Based on Major Organization Guidelines

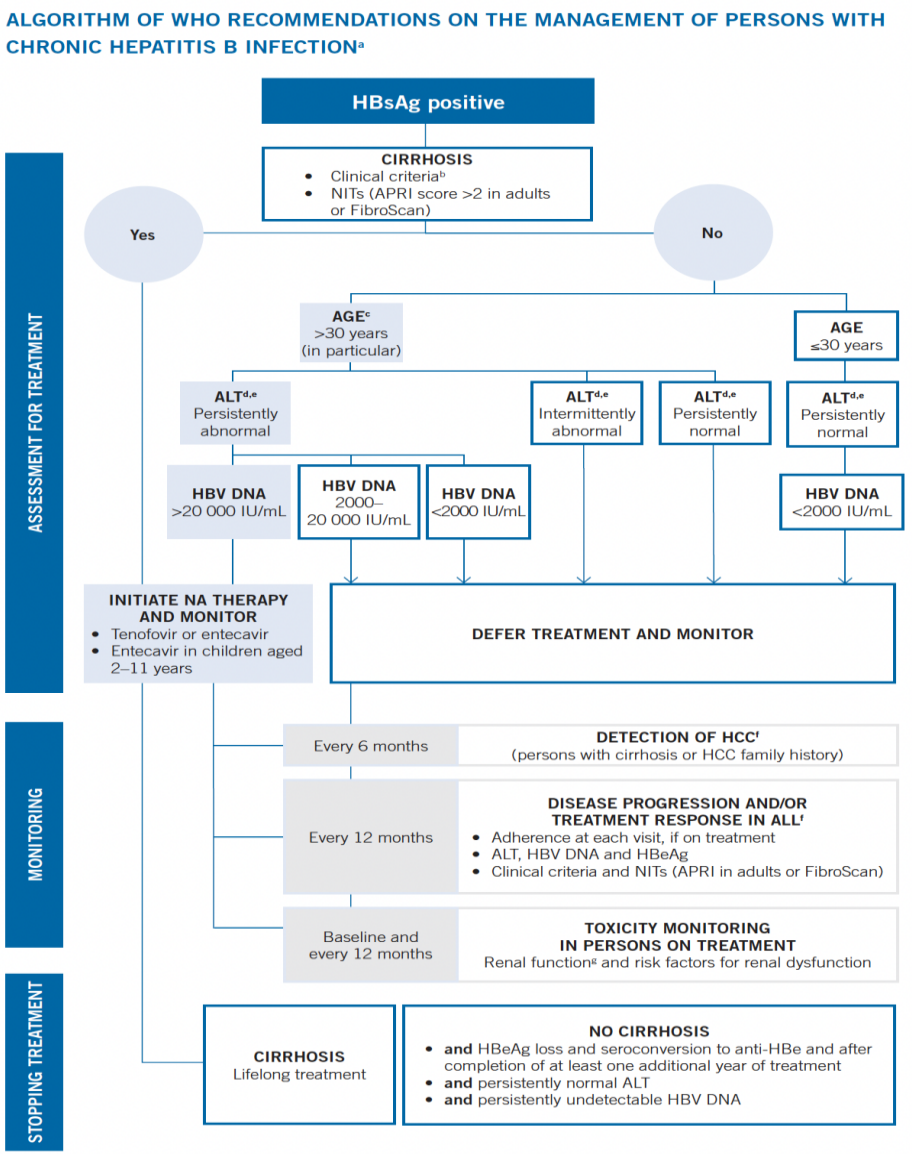
Indication	AASLD 2018	APASL 2015	EASL 2017
Decompensated Cirrhosis	• Treat all[1] *and* • Refer for liver transplantation	• Treat all[1]	• Treat all[1]
Compensated Cirrhosis	• Treat all[1]	• Treat if: - HBV DNA >2,000 IU/mL *or* - ALT elevated	
Without Cirrhosis	• Treat if: - ALT elevation (≥2x ULN[2]) *or* - Significant histologic disease[4] *and* HBeAg-positive	• Treat if: - ALT elevation (>2x ULN[3]) *or* - Significant histologic disease[4] *and* HBeAg-positive	• Treat if: - ALT >40 IU/L, HBV DNA >2000 IU/mL, and biopsy evidence of at least moderate necroinflammation (or at least moderate fibrosis) *or* - HBV DNA >20,000 IU/mL and ALT > 2x ULN[3] regardless of degree of fibrosis

[1] Regardless of HBV DNA, ALT, or HBeAg status; [2] Upper limit of normal, defined as ALT 35 for men, 25 for women; [3] Defined as ALT 40 for both men and women; [4] Defined as at least moderate necroinflammation or at least moderate fibrosis according to histopathologic grading/staging.

Figure 4 - Guidelines for the Treatment of Chronic Hepatitis B

Current treatment guidelines are a bit complicated!

WHO – 2015 recommendations



Some countries are trying to make it simpler - Ethiopia.

	Treatment criteria
I	Clinically diagnosed cirrhosis
II	APRI >0·7
III	ALT >40 U/L and HBV viral load >2000 IU/mL
IV	HCC in first-degree relative and HBV viral load >2000 IU/mL

APRI=aspartate aminotransferase to platelet ratio index. ALT=alanine aminotransferase. HBV=hepatitis B virus. HCC=hepatocellular carcinoma.

Table: **Treatment eligibility criteria in the hepatitis B scale-up programme, Ethiopia**

THE LANCET , MARCH 2022

Ethiopia – getting simpler

	Treatment criteria
I	Clinically diagnosed cirrhosis
II	APRI >0·7

But for many low and middle income countries the cost of testing is still way too expensive

APRI=aspartate aminotransferase to platelet ratio index. ALT=alanine aminotransferase. HBV=hepatitis B virus. HCC=hepatocellular carcinoma.

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HBV DNA test - 14000 Birr (> 220 SF)
Average monthly salary in Ethiopia – 8000 - 10000 Birr

Table: Treatment eligibility criteria in the hepatitis B scale-up programme, Ethiopia

THE LANCET , MARCH 2022

There is a lot of confusion, and we are doing badly
Current HBV epidemic

	HIV[1,2,3]	HBV[4,5]	HCV[6,5]
Estimated Prevalence	38.4 million	296 million	58 million
Percentage Diagnosed	85%	10.5%	21%
Percentage Treated	75%	2.3%	13%
Deaths per year	650,000	820,000	290,000
Treatment cost per person	$50/year	$29/year	$60/cure

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So why not just offer treatment to everyone?

Yes – I did say just offer treatment to everyone

- The medications (tenofovir and entecavir) are excellent – effective, minimal side effects
- Resistance – doesn't seem to be an issue
- Lowers cancer risk
- Reduces progression to CLD
- Stops/reduces transmission - mother to child transmission, other- reduces infectiousness.
- Undetectable – is nearly untransmissible – so people can reduce their risk of accidently transmitting infection to others.
- Psychosocial benefit – the person on treatment gets to control their environment.

Wouldn’t it be good to do a trial first?

HCC takes decades to develop

Required sample size and time of follow up impractical, costly

Drugs off patent- Pharma not keen

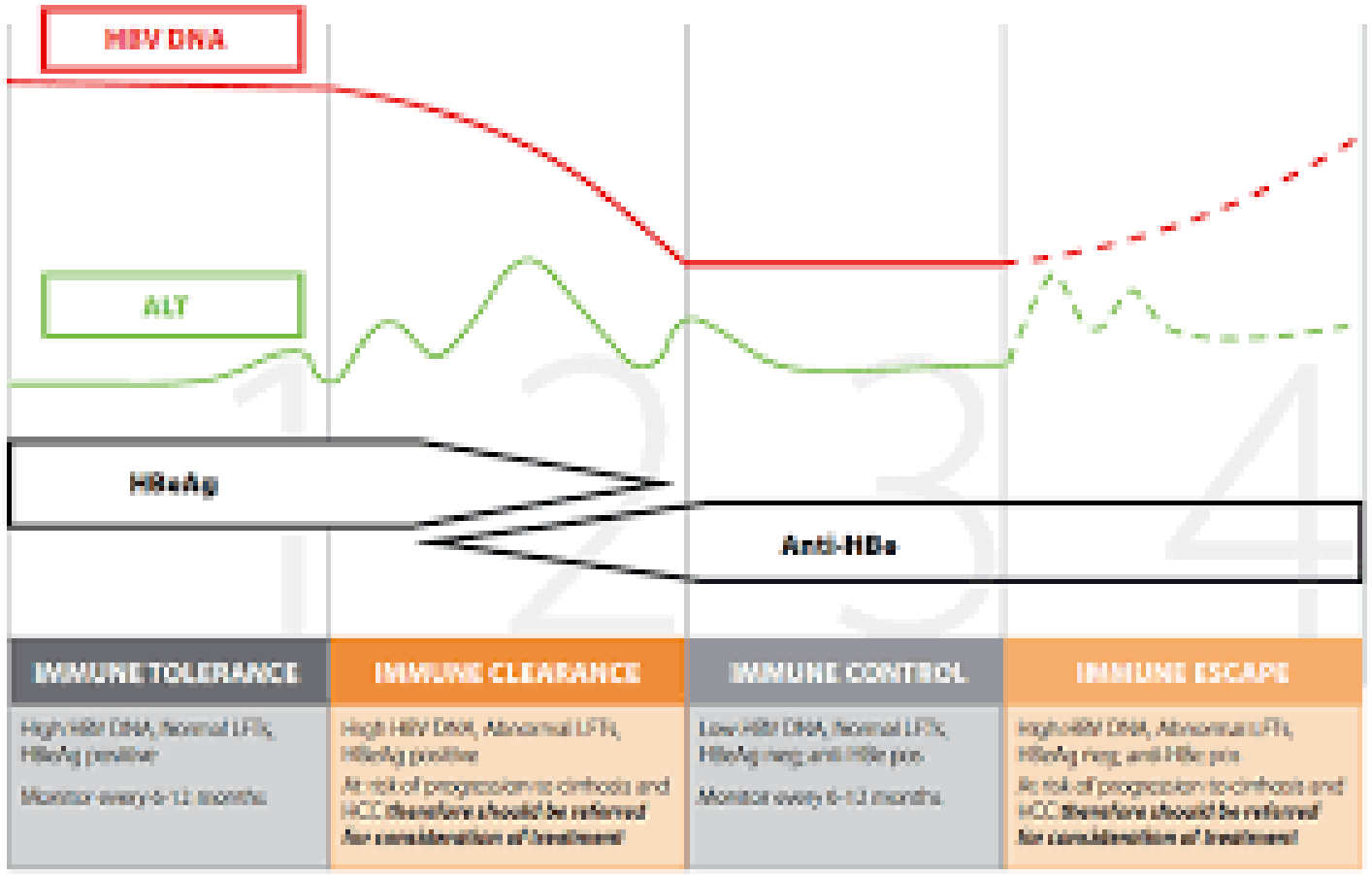
Some data sources can help

- Scientific studies of early carcinogenesis
- High quality longitudinal cohort studies
- Modelling studies

So, what to do when the evidence is not clear and never going to be clear?

So lets look at some of the information we have available to us. What do we know?

The phases of hepatitis B infection



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1. Carcinogenesis begins early in HBV infection

HBV DNA integration in the host genome is a pivotal step in HCC

- Clonal expansion of hepatocytes, dysregulated immune signalling, gene mutations

Integration events - proportional to viral load

Frequency of integration sites is associated with high risk-HCC and death

Highest in HBeAg positive patients

- **Often do not currently fulfill treatment criteria**

Zhao LH, Nat Comm 2016
You SL, Annal Med 2004
Chen CJ, JAMA 2006
Iloeje UH, Gastroenterology 2006
Mason WS, Gastroenterology 2016

Immune tolerant (IT) phase - Not so benign?

Cumulative incidence of HCC, death or transplant is higher in IT than immune active (sometimes called immune clearance) (IA)on NAs

4535 HBeAg positive without cirrhosi

- Median follow up 5 years
- Median HBV DNA 8 log
- Median ALT 19IU/mL

Untreated IT phase had

2-3 times higher liver events than IA phase on Rx

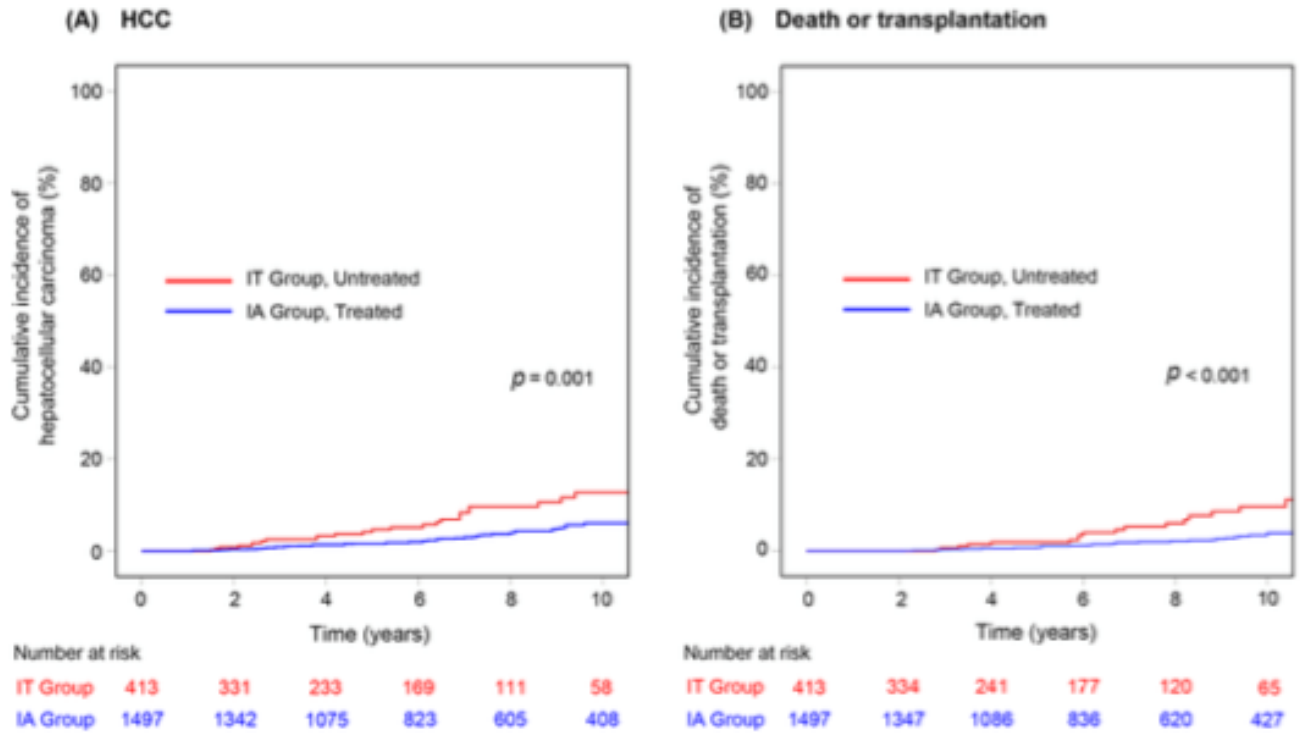


Figure 2 Cumulative incidences of HCC and death or transplantation in the IT-phase vs IA-phase patients. (A) Cumulative incidence of HCC. (B) Cumulative incidence of death or transplantation. HCC, hepatocellular carcinoma; IA, immune-active; IT, immune-tolerant.

Kim G-A, *et al*. *Gut* 2017;**0**:945–952. doi:10.1136/gutjnl-2017-314

Why people die from hepatitis B infection?

Without treatment,
1 in every 5 people with CHB develops cirrhosis over 5 years

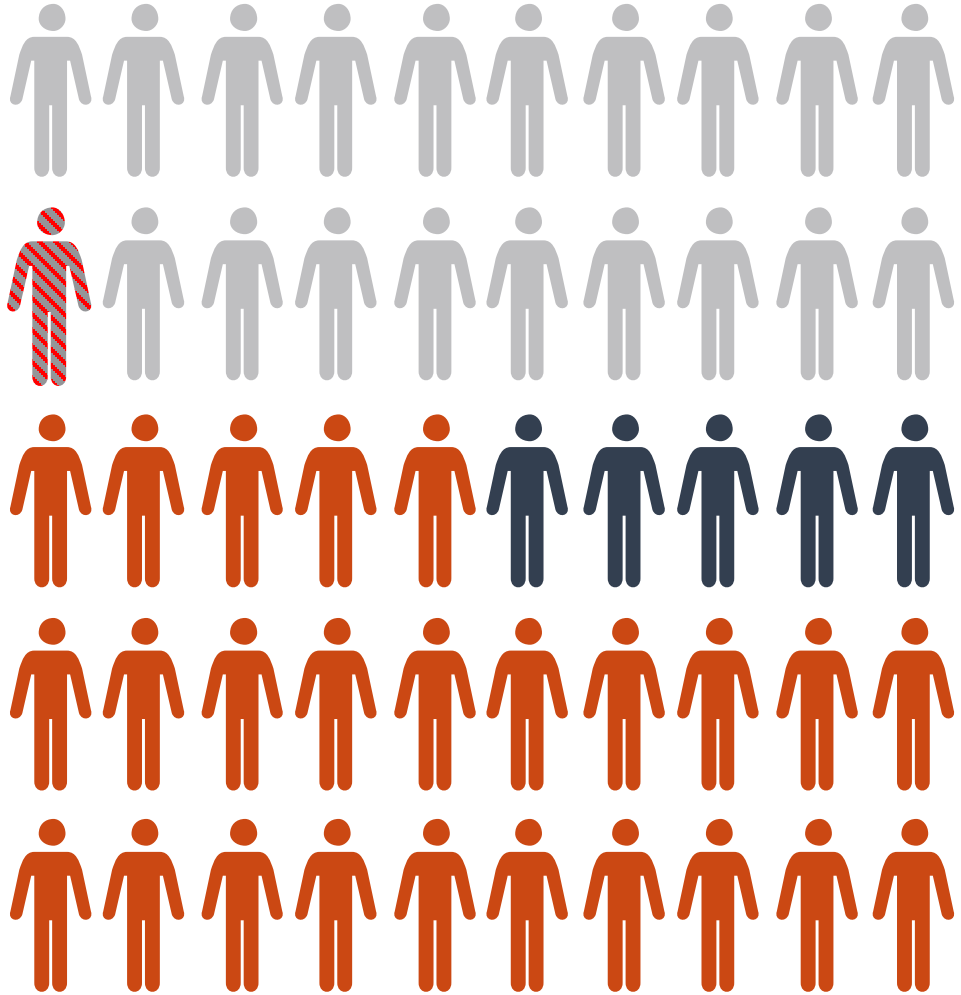
Why people die from hepatitis B infection?

Without treatment,
5 in every 100 people
with CHB develop HCC
per year

1-2 of those will be in
patients WITHOUT
cirrhosis

Does our current HBV treatment strategy reduce deaths from cirrhosis and HCC?

Using current guidelines, ~20% of CHB patients are eligible for treatment



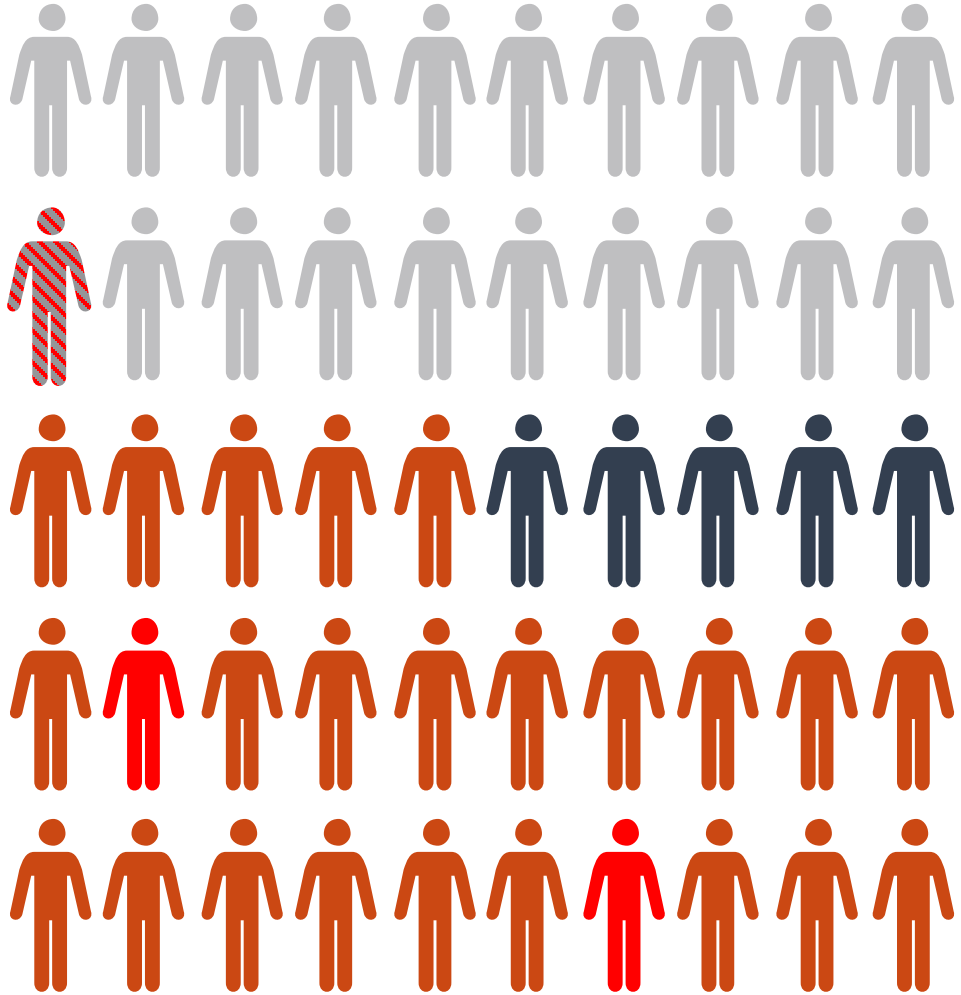
NA prevents cirrhosis and reduces HCC risk

TREATED, *cirrhosis*:
2-7% risk HCC

TREATED, *no cirrhosis*:
0.1-1% risk of HCC

Papatheodoridis GV; J Hepatol 2015

Will the current HBV treatment strategy reduce deaths from cirrhosis and HCC?



NA treatment prevents cirrhosis and reduces the risk of HCC

TREATED, no cirrhosis:
0.1-1% risk of HCC

TREATED, cirrhosis:
2-7% risk HCC

1-2% risk of HCC among those who do not fulfil treatment criteria

Papatheodoridis GV; J Hepatol 2015

Lower cancer risk

Observational Study

Medicine®

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Lower liver cancer risk with antiviral therapy in chronic hepatitis B patients with normal to minimally elevated ALT and no cirrhosis

Joseph K. Hoang, BS[a], Hwai-I Yang, PhD[b,c,*], An Le, BA[a], Nghia H. Nguyen, MD[a,e], Derek Lin, MD[f], Vinh D. Vu, BS[a], Kevin Chaung, BS[a], Vincent Nguyen, MD[a], Huy N. Trinh, MD[g], Jiayi Li, MD[h], Jian Q. Zhang, DNP[i], Chien-Jen Chen, PhD[b,j], Mindie H. Nguyen, MD[a,d,*]

Abstract

For chronic hepatitis B (CHB), alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN) is often used as a major criteria to initiate treatment in absence of cirrhosis, though patients with lower ALT may not be free from future risk of hepatocellular carcinoma (HCC). We aimed to examine the effect of antiviral therapy on HCC incidence based on ALT levels.

We performed a retrospective study on 3665 patients consisting of United States and Taiwanese REVEAL-HBV cohort who were consecutive, treatment-naïve, noncirrhotic CHB patients aged ≥40 years. Patients were categorized by ALT cutoffs (≥2 × ULN vs <2 × ULN) and subgrouped by treatment status. Kaplan–Meier and Cox proportional hazards models were used to calculate cumulative incidence and hazard ratio (HR) of HCC adjusting for REACH-B scores.

A total of 202 patients developed HCC. Antiviral treatment significantly reduced HCC risk: HR 0.24, 95% confidence interval 0.10–0.58; $P = 0.001$. HCC incidence per 100,000 person-years was significantly higher in untreated versus treated patients, even for those with ALT < 2 × ULN: 314.46 versus 0 per 100,000 person-years, $P = 0.0042$. For patients with Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) ≥ 2000 IU/mL, the number-needed-to-treat (NNT) were 15 and 14 to prevent 1 incident HCC at year 10 for patients with ALT < 2 × ULN and ≥2 × ULN, respectively.

After adjustment by REACH-B score, antiviral treatment significantly decreased HCC incidence even in patients with ALT < 2 × ULN. NNT to prevent 1 incident HCC after 10 years of therapy was low (14–15) in patients with mildly elevated HBV DNA ≥ 2000 IU/mL regardless of ALT levels.

Abbreviations: AASLD = American Association for the Study of Liver Diseases, ALT = aminiotransferase, CHB = chronic hepatitis B, CI = confidence intervals, CT = computed tomography, ESLD = end-stage liver disease, HBeAg = hepatitis B e antigen, HCC = hepatocellular carcinoma, HR = hazard ratio, MRI = magnetic resonance imaging, NNT = number-needed-to-treat, ULN = upper limit of normal.

Keywords: ALT, antivirals, HBV DNA, hepatocellular carcinoma, REACH-B

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EASL CONGRESS 2023
Vienna, Austria
21–24 June

Risk of developing cancer - comparison of HBV, HCV, and smoking

H. Razavi [1], C. Estes [1], D. Razavi-Shearer [1], S. Blach [1], I. Gamkrelidze [1], K. Razavi-Shearer [1], A. Voeller [1]
[1] CDA Foundation, Lafayette, Colorado, United States

CDA FOUNDATION POLARIS OBSERVATORY

Introduction

Hepatitis B and C viruses (HBV & HCV) are the most common chronic viral infections in the world accounting for 316 million infections globally.[1,2] HBV and HCV were responsible for 932,000 new hepatocellular carcinoma (HCC) cases in 2022 which is projected to increase to 1,076,000 annual cases by 2030 at current trends.[1,2] The two viral infections also accounted for 1.2 million liver related deaths (HCC and cirrhosis) in 2022 and are projected to increase to 1.4 million annual deaths by 2030.[1,2] Reducing the number of new HCC cases associated with HBV & HCV infections should be a key goal of national viral hepatitis elimination programs.

Aim

HBV and HCV are oncoviruses, but the risk of developing cancer is often stated in an annual rate which is difficult to interpret by patients and healthcare workers. The objective of this work was to quantify the risk of cancer from viral hepatitis as compared to a known cancer-causing risk factor – smoking

Method

- A PubMed literature search was conducted to find longitudinal studies that reported the adjusted hazard ratio and odds ratio of developing hepatocellular carcinoma (HCC) among HBV/HCV infected individuals and cancer among active smokers.
- 236 articles were found.
- Full abstracts were reviewed by two epidemiologists to remove non-relevant studies.
- Full articles were reviewed to remove all studies in special populations, specific age groups, small sample size, and treated cohorts.
- Robust articles reporting relative risk were found for HBV and HCV cohorts but not cohorts of smokers. They were excluded from this analysis.

Conclusions

- Hepatitis B and C viruses are highly oncogenic leading to cancers in multiple organs/ sites.
- HBV & HCV infected individuals have a similar or significantly higher risk of developing cancer than someone who actively smokes one pack of cigarettes per day.
- Currently, most international testing and treatment guidelines focus on treating HBV and HCV infections as a liver disease.
- HBV and HCV should be considered as cancer causing infections and international guidelines should be reconsidered accordingly.

Acknowledgements

This work was funded by the Polaris Observatory which received funding from John C. Martin Foundation, EndHep2030, Zeshan Foundation, Gilead Sciences and AbbVie

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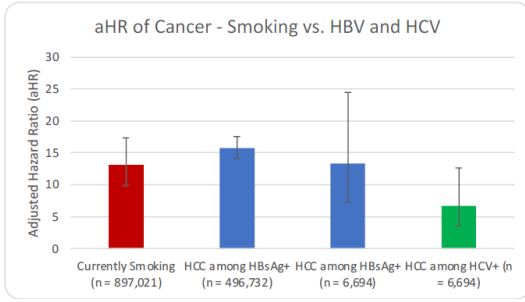
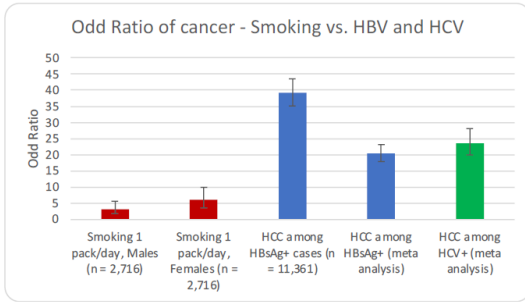
Results

- *Fourteen studies were found that had comparable data for HBV, HCV, and smoking allowing comparison across risk factors.*
- *Adjusted hazard ratio (which takes into account discontinuation and deaths) of developing HCC for individuals infected with HBV [3,4] or HCV [4] was comparable to the risk of developing cancer for someone who is an active smoker.[5,6]*
- *The odds ratio of developing HCC from HBV/HCV infection was 4-8 times higher than someone who actively smokes one pack of cigarettes per day.[7-9]*
- *Cancers associated with HBV infections include:*
  - *HCC (aOR – 39.11) [7]*
  - *Leukemia (aOR = 11.48) [7]*
  - *Intrahepatic bile duct (aOR = 3.83) [7]*
  - *Pancreas (aOR = 1.37) [7]*
  - *Stomach (aHR – 1.41) [3]*
  - *Colorectal (aHR = 1.42) [3]*
- *Cancers associated with HCV infections include:*
  - *Liver, cervix, pancreas, and skin [10]*
  - *Oropharyngeal, non-Hodgkin lymphoma, peritoneum and unspecified, mediastinum, and kidney [11]*





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Lowers cancer risk

Observational Study

Medicine®

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Lower liver cancer risk with antiviral therapy in chronic hepatitis B patients with normal to minimally elevated ALT and no cirrhosis

Joseph K. Hoang, BS[a], Hwai-I Yang, PhD[b,c,*], An Le, BA[a], Nghia H. Nguyen, MD[a,e], Derek Lin, MD[f], Vinh D. Vu, BS[a], Kevin Chaung, BS[a], Vincent Nguyen, MD[a], Huy N. Trinh, MD[g], Jiayi Li, MD[h], Jian Q. Zhang, DNP[i], Chien-Jen Chen, PhD[b,j], Mindie H. Nguyen, MD[a,d,*]

Abstract

For chronic hepatitis B (CHB), alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN) is often used as a major criteria to initiate treatment in absence of cirrhosis, though patients with lower ALT may not be free from future risk of hepatocellular carcinoma (HCC). We aimed to examine the effect of antiviral therapy on HCC incidence based on ALT levels.

We performed a retrospective study on 3665 patients consisting of United States and Taiwanese REVEAL-HBV cohort who were consecutive, treatment-naïve, noncirrhotic CHB patients aged ≥40 years. Patients were categorized by ALT cutoffs (≥2 × ULN vs <2 × ULN) and subgrouped by treatment status. Kaplan–Meier and Cox proportional hazards models were used to calculate cumulative incidence and hazard ratio (HR) of HCC adjusting for REACH-B scores.

A total of 202 patients developed HCC. Antiviral treatment significantly reduced HCC risk: HR 0.24, 95% confidence interval 0.10–0.58; $P = 0.001$. HCC incidence per 100,000 person-years was significantly higher in untreated versus treated patients, even for those with ALT < 2 × ULN: 314.46 versus 0 per 100,000 person-years, $P = 0.0042$. For patients with Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) ≥ 2000 IU/mL, the number-needed-to-treat (NNT) were 15 and 14 to prevent 1 incident HCC at year 10 for patients with ALT < 2 × ULN and ≥2 × ULN, respectively.

After adjustment by REACH-B score, antiviral treatment significantly decreased HCC incidence even in patients with ALT < 2 × ULN. NNT to prevent 1 incident HCC after 10 years of therapy was low (14–15) in patients with mildly elevated HBV DNA ≥ 2000 IU/mL regardless of ALT levels.

Abbreviations: AASLD = American Association for the Study of Liver Diseases, ALT = aminiotransferase, CHB = chronic hepatitis B, CI = confidence intervals, CT = computed tomography, ESLD = end-stage liver disease, HBeAg = hepatitis B e antigen, HCC = hepatocellular carcinoma, HR = hazard ratio, MRI = magnetic resonance imaging, NNT = number-needed-to-treat, ULN = upper limit of normal.

Keywords: ALT, antivirals, HBV DNA, hepatocellular carcinoma, REACH-B

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After adjustment by REACH-B score, antiviral treatment significantly decreased HCC incidence even in patients with ALT $<2\times$ ULN. NNT to prevent 1 incident HCC after 10 years of therapy was low (14–15) in patients with mildly elevated HBV DNA ≥ 2000 IU/mL regardless of ALT levels.

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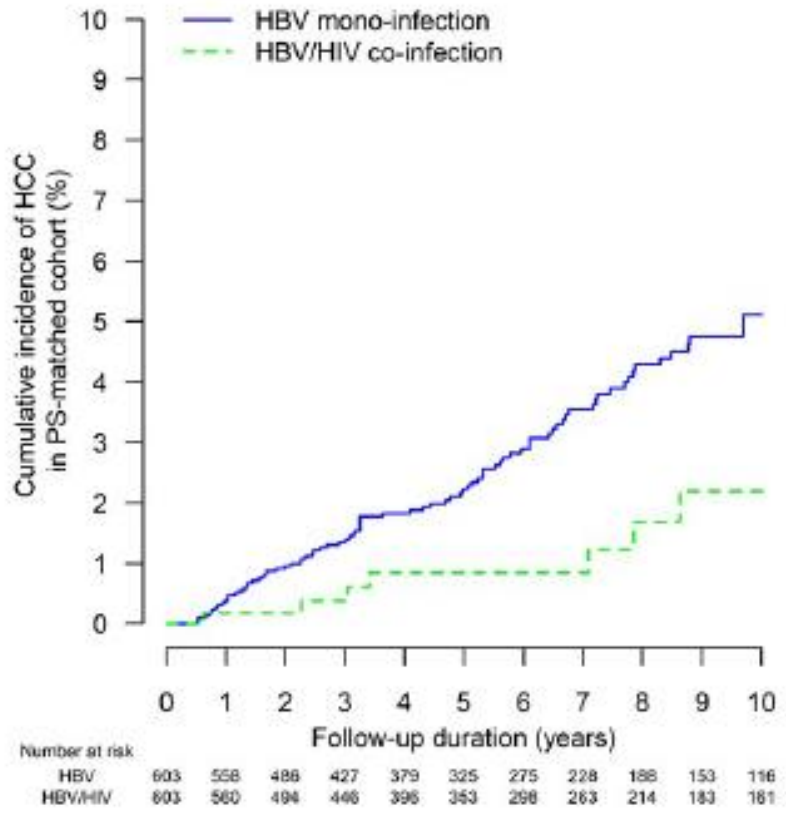
HBV/HIV compared to HBV mono-infection

ure 2. Kaplan Meier curves showing incidence of hepatocellular carcinoma in HBV/HIV co-infected and HBV mono-infected patients



Disclosures. **All authors:** No reported disclosures.

Lui et al 2017


Treatment can stop transmission

Prevents HBV transmission

TA-PROHM study:

Single arm multicentre in Cambodia

1 urban centre (BD), 4 regional centres (no BD)

TDF and vaccination, *with or without HBIg*

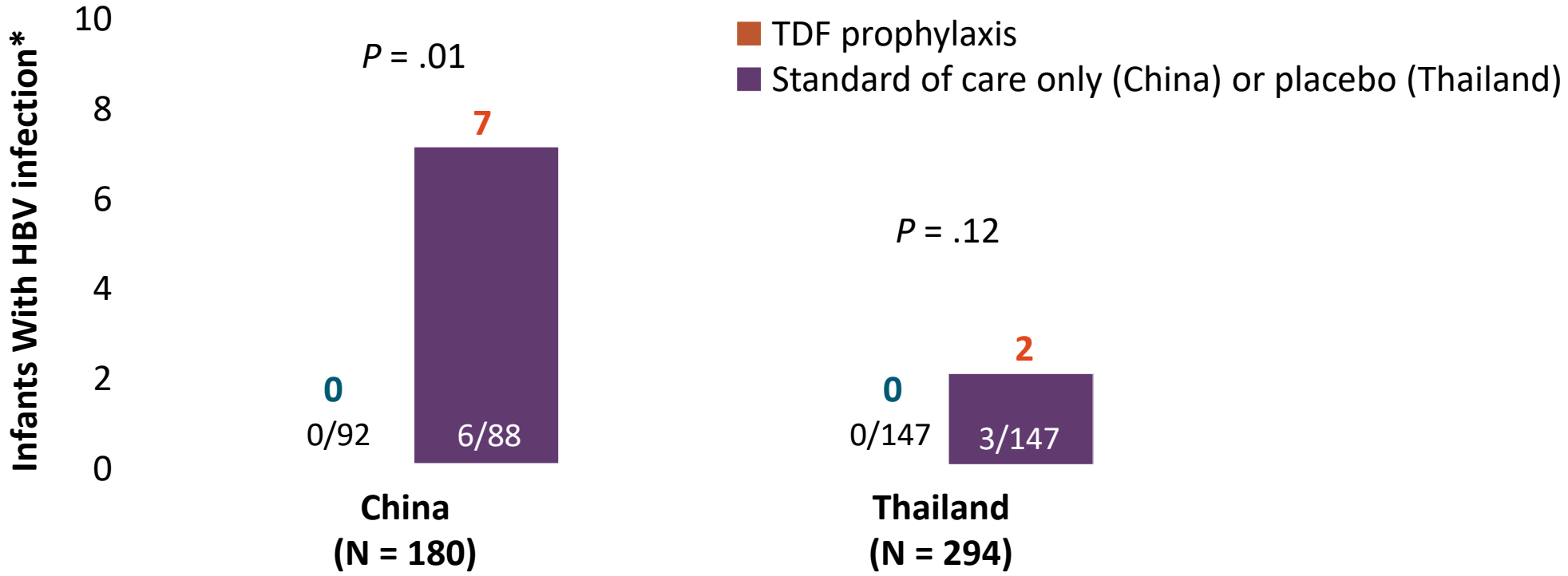
IF eAg pos OR ALT > 40IU/L

> 4 wks TDF prevented MTCT as well as HBIg

- 0% where > 4wks TDF, 1% where < 4 wks TDF

TDF Prophylaxis to Prevent Mother-to-Child HBV Transmission During Pregnancy

No cases of transmission with TDF prophylaxis during third trimester of gestation in randomised controlled trials in Asia[1,2]



*At Wk 28 following delivery in China and 6 mos following delivery in Thailand.

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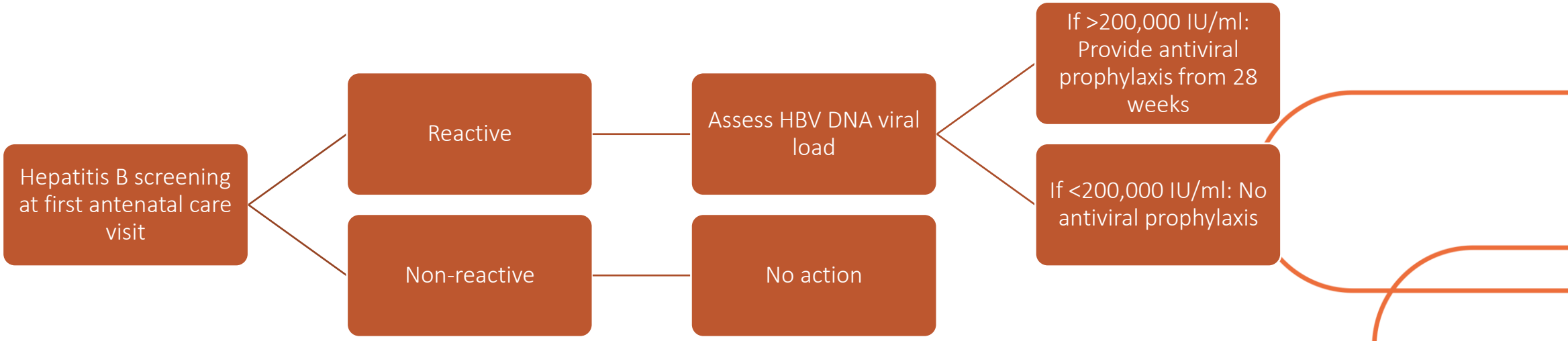
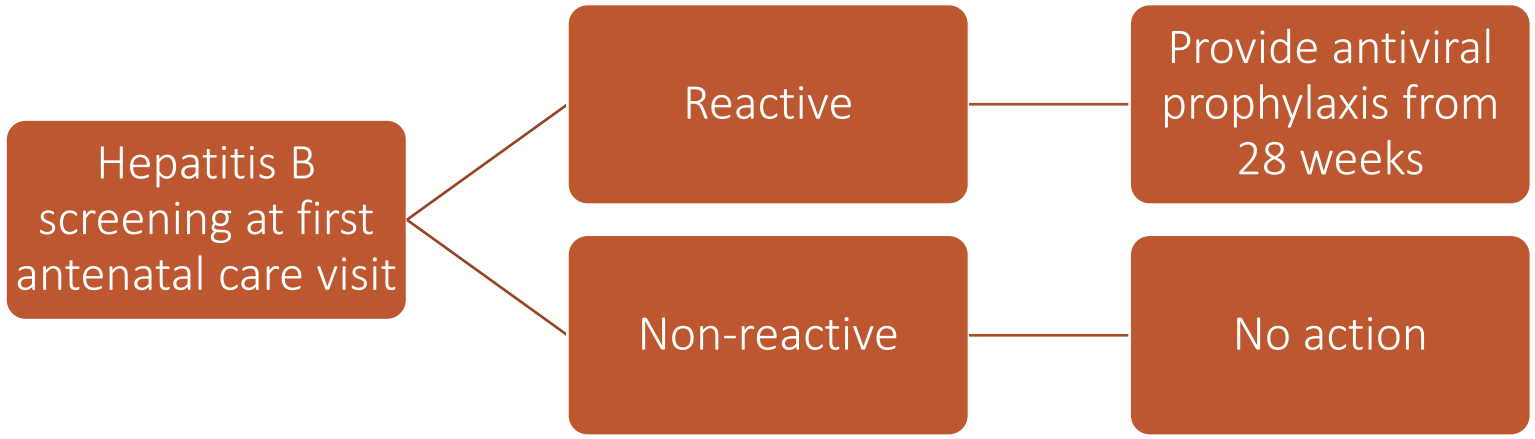
Guideline-based care approach: WHO recommendations for antiviral prophylaxis



New study in Vanuatu- treat all HBsAg-positive pregnant women



Reasons to not take treatment.

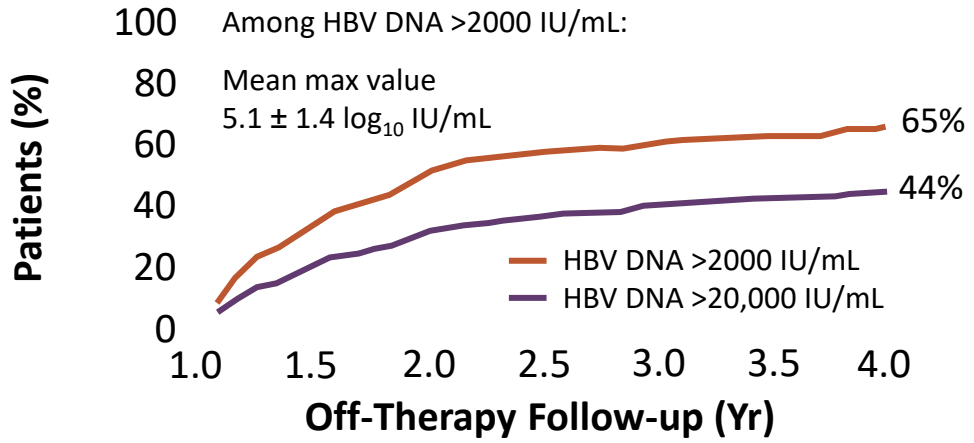
- Drugs have costs
- You don’t get cured – if you come off treatment the virus comes back
- Drugs have side effects
- If stop taking medication – at risk of a flare
- Drugs – reminds you that you have the disease/infection

Treatment is not curative for all people – relapse if stop

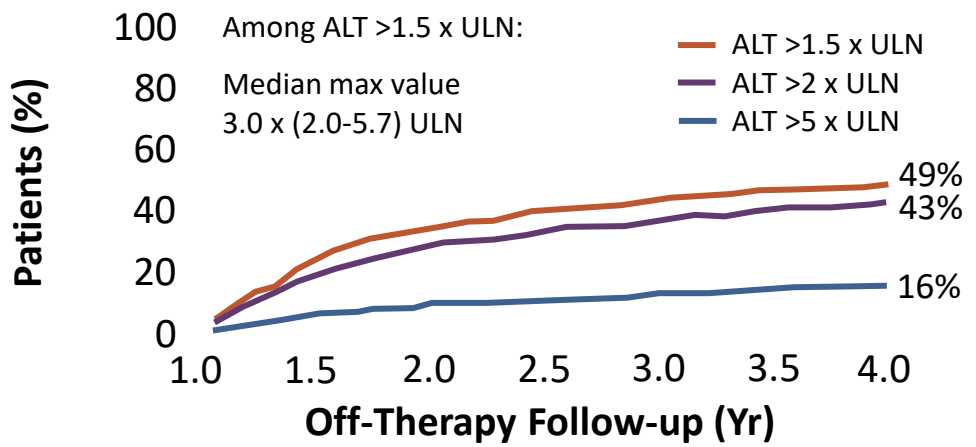
AIDS 2022

RETRACT-B: Relapse and Retreatment Over 4 Yr

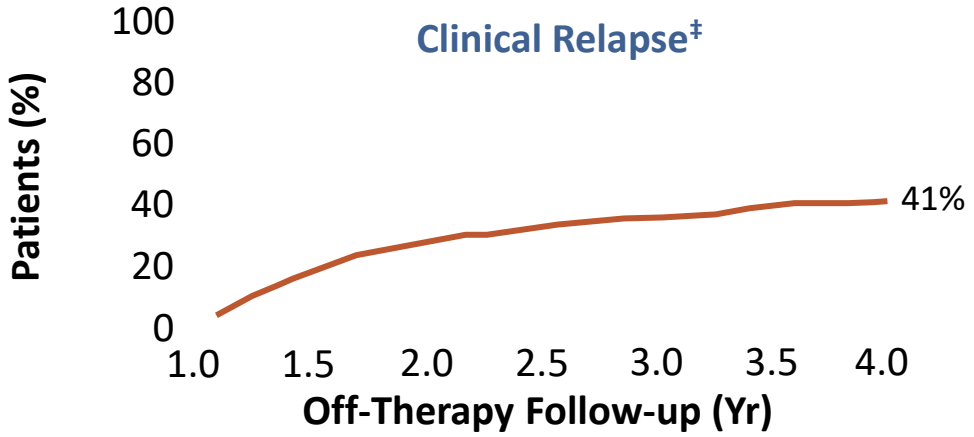
Virologic Relapse*



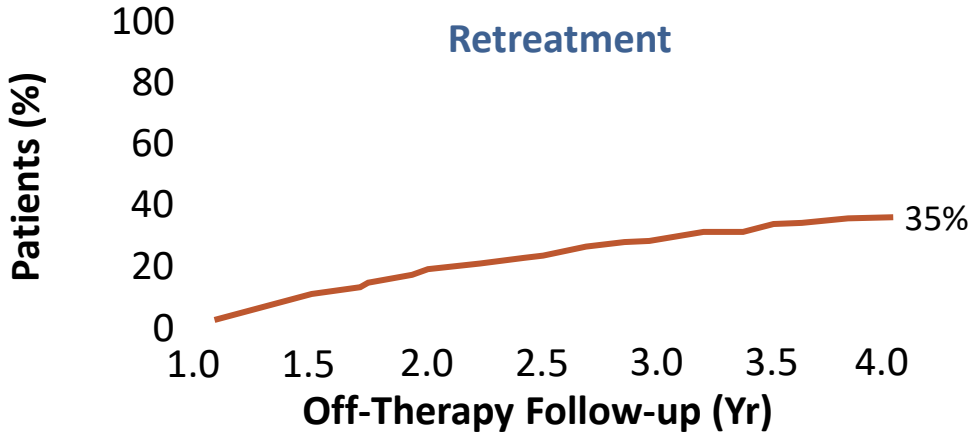
Biochemical Relapse†



Clinical Relapse‡



Retreatment



*Virologic relapse: HBV DNA >2000 IU/mL. †Biochemical relapse: ALT >1.5 x ULN. ‡Clinical relapse: HBV DNA >2000 IU/mL and ALT >1.5 x ULN.

Hirode. AASLD 2021. Abstr OA22. Reproduced with permission.

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RETRACT-B: Relapse and Retreatment Over 4 Yr

So what!

We treat lots of other non-curative diseases – after assessing risk and benefit

- HIV
- Diabetes
- Hypertension
- Raised cholesterol
- Cardiac disease
- Arthritis
- The list goes on and on.

Side effects and flares

Side effects

People have been taking tenofovir lifelong for their HIV as part of their ART

Yes – side effects occur – but need to balance risk.

Flares

Flares occur when people stop treatment

Stopping nucleot(s)ide analogues in non-cirrhotic HBeAg-negative chronic hepatitis B patients: HBsAg loss at 96 weeks is associated with low baseline HBsAg levels

Samuel A. L. Hall[1,2] | Gareth S. Burns[1,2] | Despina Anagnostou[1] | Sara Vogrin[2] | Vijaya Sundararajan[2,3] | Dilip Ratnam[4,5] | Miriam T. Levy[6] | John S. Lubel[7,8] | Amanda J. Nicoll[9] | Simone I. Strasser[10,11] | William Sievert[4,5] | Paul V. Desmond[1] | Meng C. Ngu[12] | Peter Angus[13,14] | Marie Sinclair[13] | Christopher Meredith[15] | Gail Matthews[16] | Peter A. Revill[17] | Kathy Jackson[17] | Margaret Littlejohn[17] | D. Scott Bowden[17] | Stephen A. Locarnini[17] | Kumar Visvanathan[1,2] | Alexander J. Thompson[1,2]

[1]Gastroenterology Department of St Vincent's Hospital Melbourne, Melbourne, Australia

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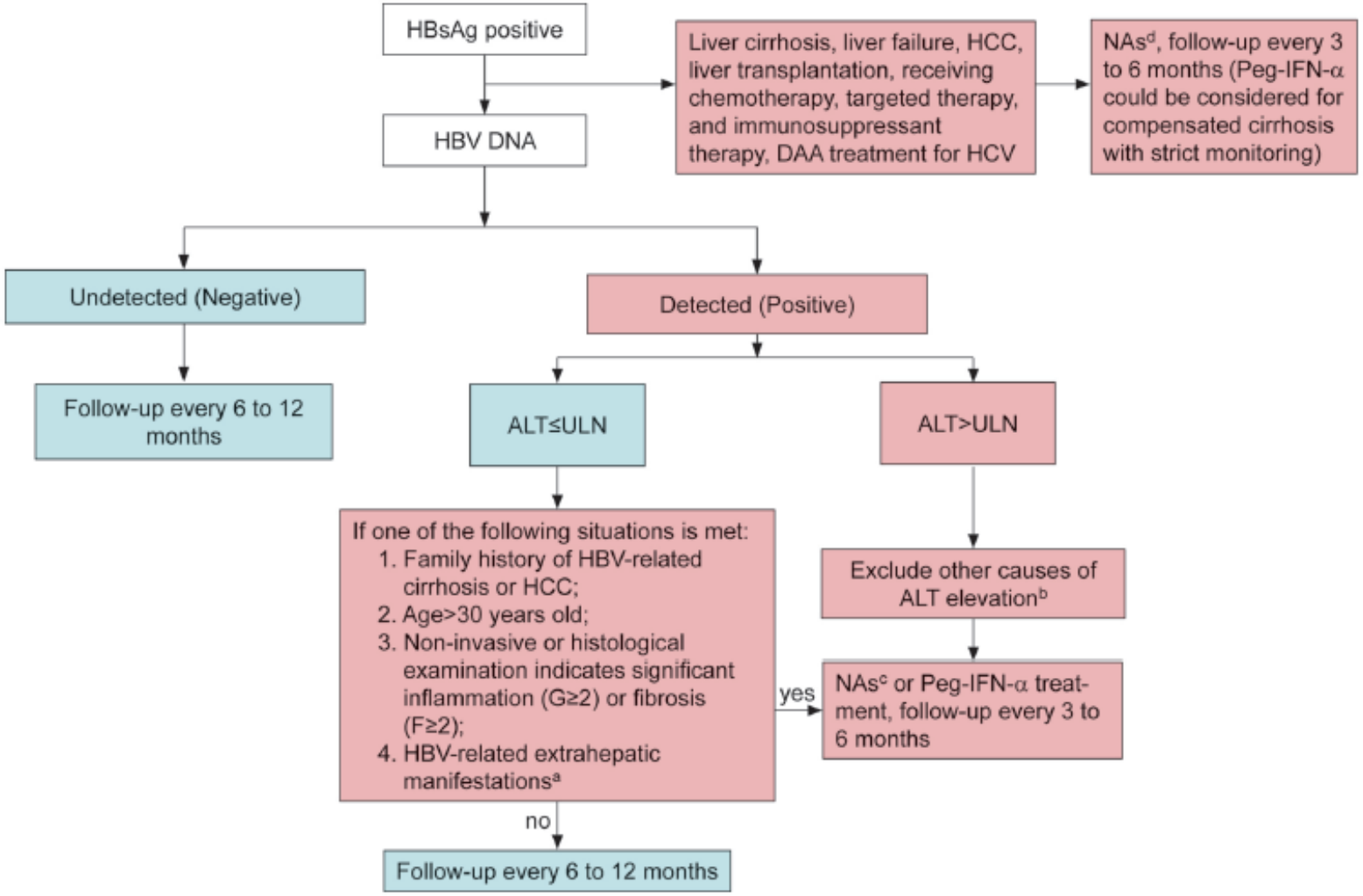
3.4 | Safety

There were no unexpected safety issues through 96 weeks of follow-up. In five patients, bilirubin rose >2× ULN in the context of an ALT flare, but this settled rapidly as the ALT dropped. Three of these patients were started on NA therapy; in two patients the ALT flare settled spontaneously under observation. There were no liver decompensation events (INR >1.5, hepatic encephalopathy, ascites) in these non-cirrhotic patients, and no cases of HCC or development of cirrhosis during the follow-up period.

So where to from here?

New Chinese National HBV Guidelines

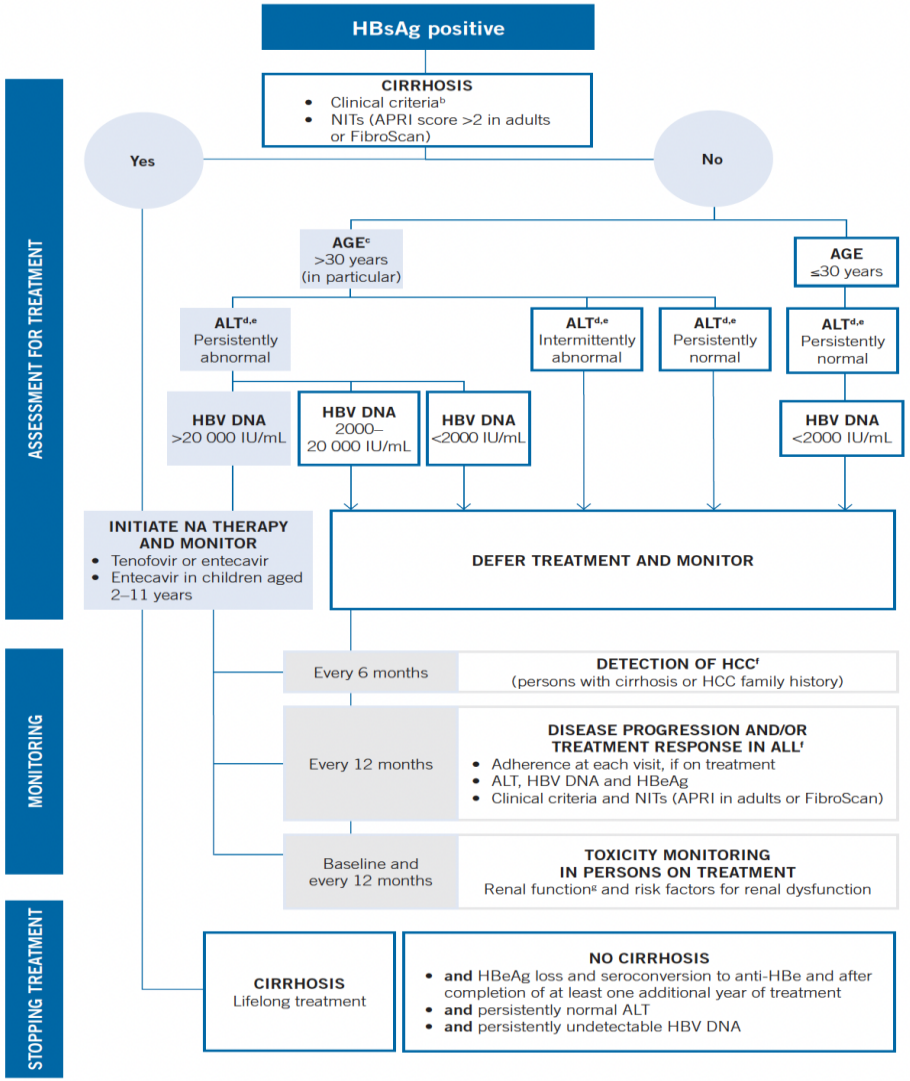
- Treat all HBsAg positive if:
- Cirrhosis, *OR*
- Detectable HBV DNA, AND
  - Age > 30 yrs, *OR*
  - FHx HCC or cirrhosis, *OR*
  - F2 or A2, *OR*
  - Extra-hepatic Cx



You H, J Clin Transl Hep 2023

2015

ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]



2023

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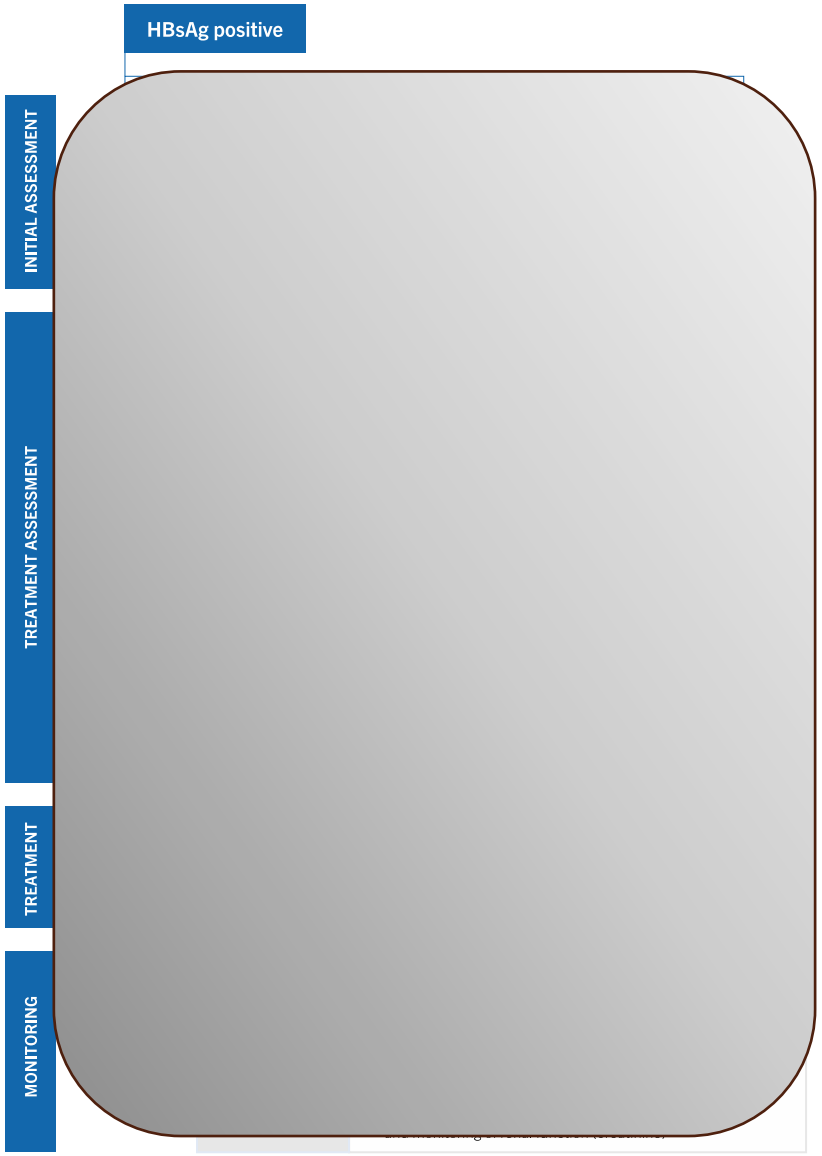

Who should decide?

- The person with hepatitis B
- They should be provided with the information – the pros and cons
- Government regulation should not stop their choice
- Clinicians should provide support and guidance to help them choose – not restrict their choice.

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- Many others

Burnet
reach for the many

Thank you

PROFESSOR MARGARET HELLARD

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