Hepatitis in patients receiving cancer chemotherapy

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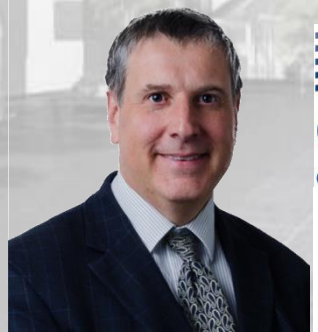

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Disclosure slide

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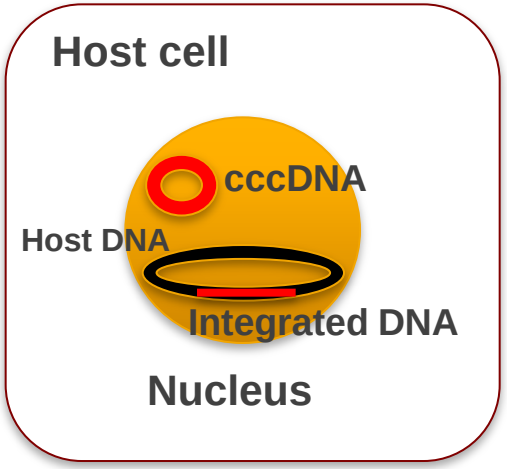
- Financial interest – NO CONFLICT OF INTEREST
- There has been no arrangement, financial or other made with a company whose products are discussed in this presentation

HCV and HBV: Two very different viruses

Hepatitis C

- Hepatitis C serology is simple !
  - HCV Ab is a screening test
  - HCV Ab +ve indicates exposure to HCV
  - Hepatitis C PCR confirms current infection
  - Hepatitis C PCR ≥ 6 months defines Chronic hepatitis C infection

Hepatitis B



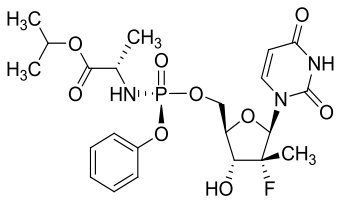
Long-term suppression of viral replication

PEG-IFNα
Nucleos(t)ide analogues
Very few patients 'cured'

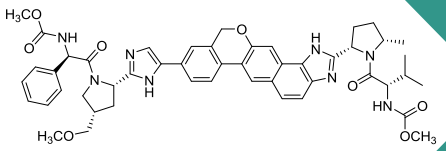
Adapted from 1. Sorriano V, et al. J *Antimicrob Chemother* 2008;62:1-4. 2. Locarnini S and Zoulim F. *Antiviral Therapy* 2010;15

Hepatitis C – now a very curable disease

SOF
Nucleotide polymerase inhibitor



- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet



VEL
NS5A inhibitor

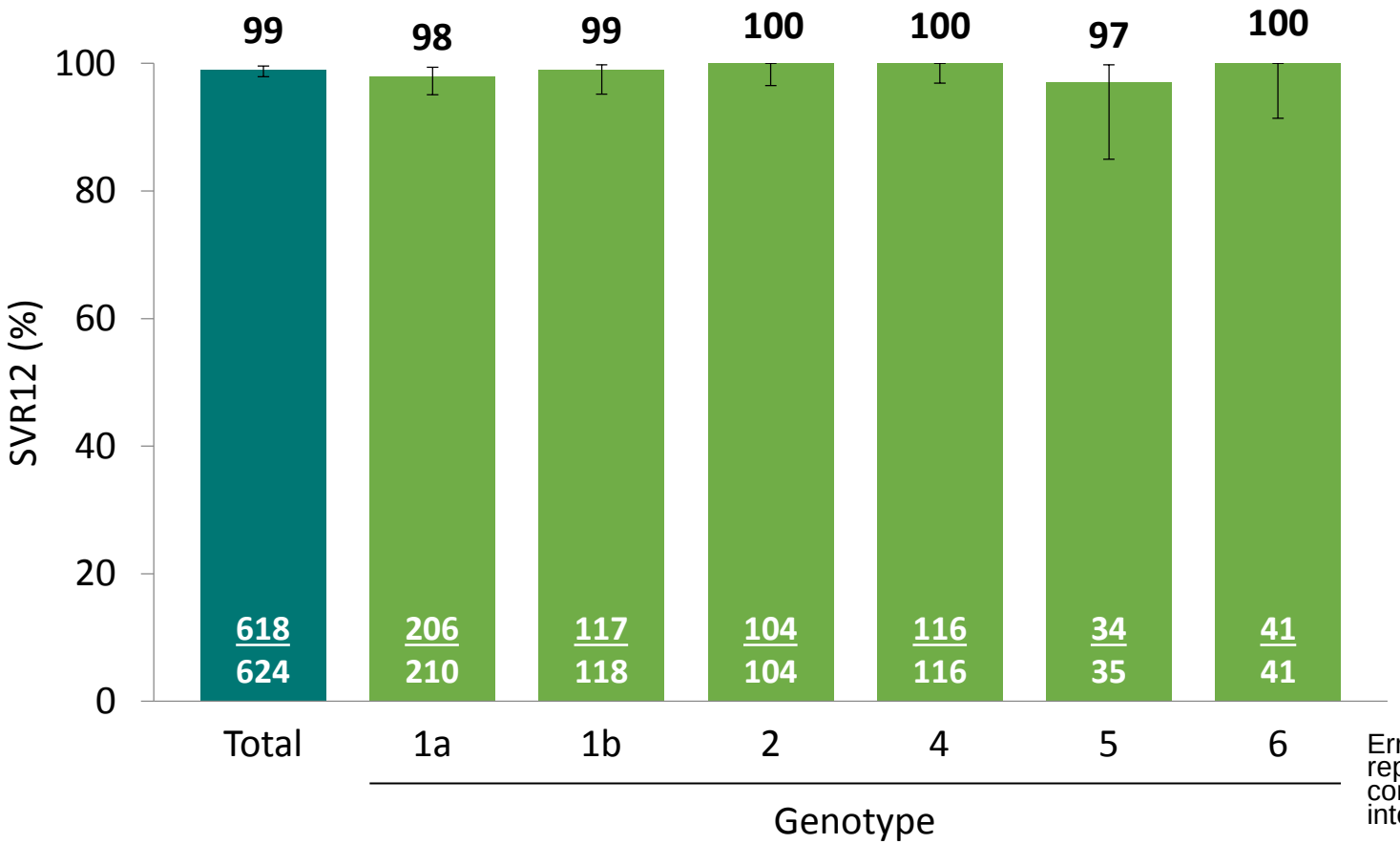
- **Velpatasvir (VEL; GS-5816)[3-5]**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87;
3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195;
5. Lawitz E, et al. J Vir Hep 2015;22:1011-19.

Hepatitis C: Cure by Genotype

ASTRAL-1, SOF/VEL



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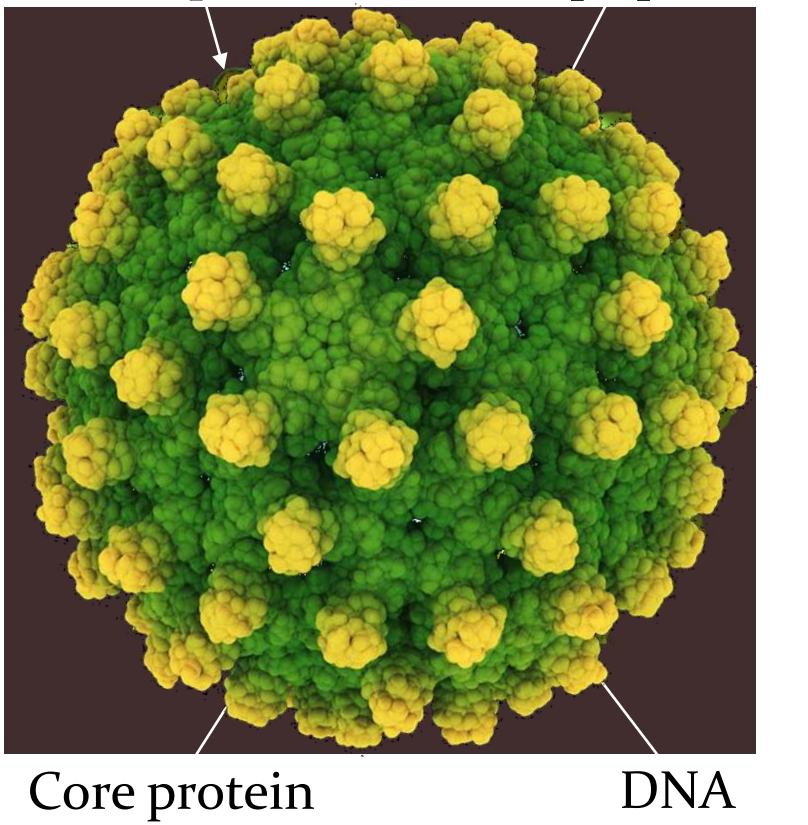
Hepatitis B Virus (HBV)

- Hepa**dna**virus family
- Non-cytopathic
- Capable of reactivation in setting of immunosupression
- Oncogenic (hepatocellular carcinoma)

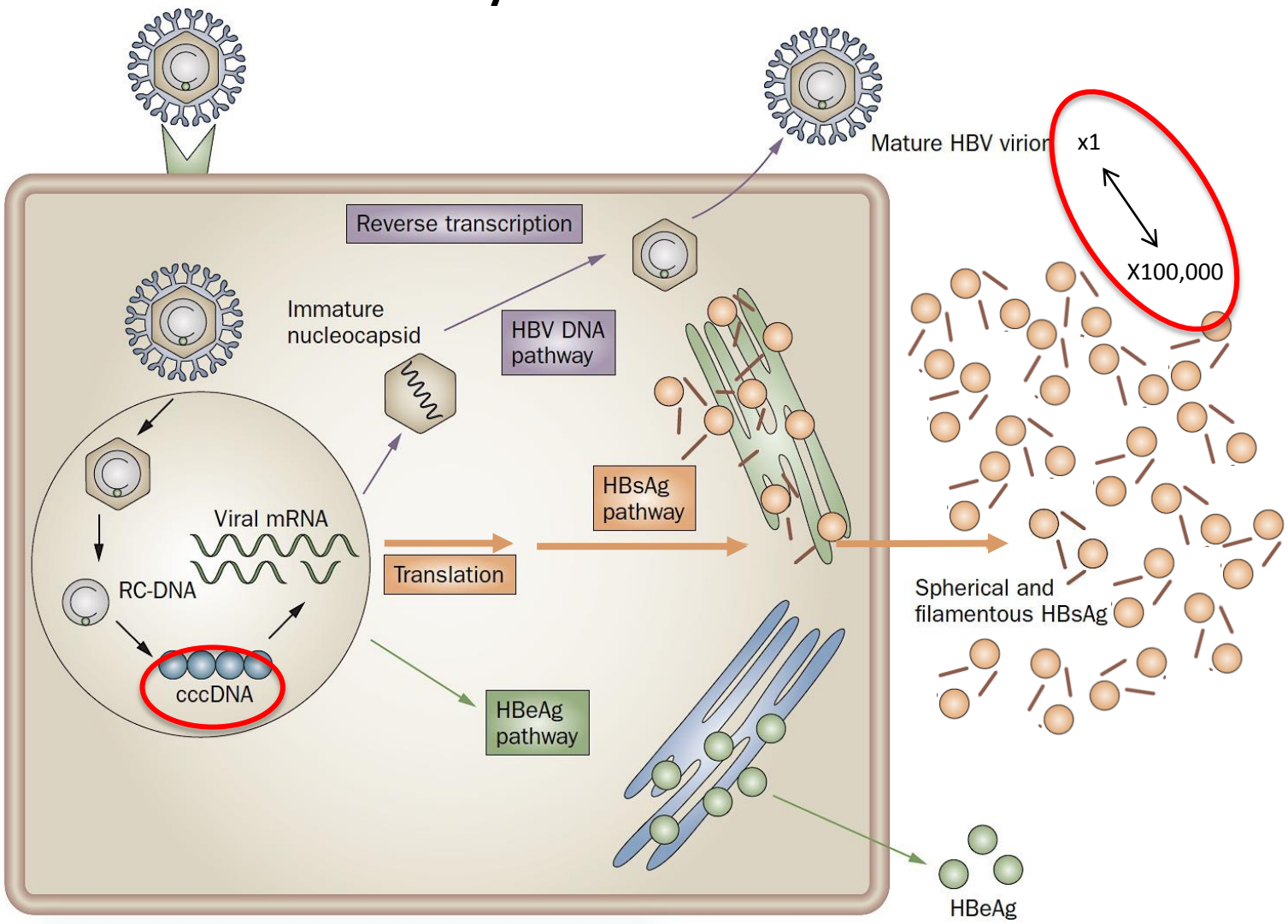


Global burden of hepatitis B

- 2 billion (≈ 1/3 world population) exposed to HBV infection
- > 350-400 million have Chronic HBV
- Total global deaths 1 million per year

World Health Organization (WHO), July 2012

Hepatitis B lifecycle

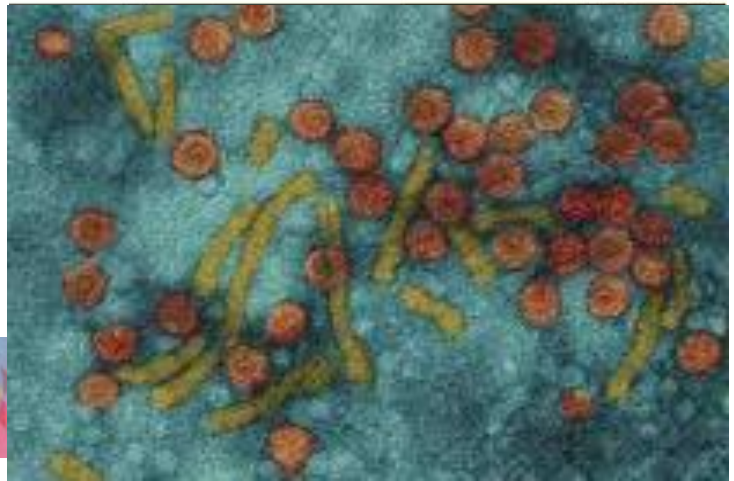


Adapted from Nguyen & Locarnini, Nat. Rev. 2009

Hepatitis B diagnostic panel

- The diagnostic panel for hepatitis B virus (HBV) contains three tests:

Test	Abbreviation
Hepatitis B surface antigen	HBsAg



Towell V & Cowie B. *AFP* 2012;41(4):212–214

Hepatitis B diagnostic panel

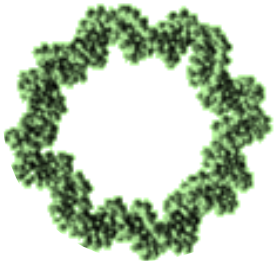
- The diagnostic panel for hepatitis B virus (HBV) contains three tests:

Test	Abbreviation	Allows for determination of
Hepatitis B surface antigen	HBsAg	Active infection (acute or chronic)
Hepatitis B surface antibody	Anti-HBs	Immunity (due to vaccination or past infection)

Towell V & Cowie B. *AFP* 2012;41(4):212–214

Hepatitis B diagnostic panel

- The diagnostic panel for hepatitis B virus (HBV) contains three tests:

Test	Abbreviation	Allows for determination of
		covalently closed circular viral DNA (cccDNA)
Hepatitis B core antibody	Anti-HBc	Any infection (past or active)

Towell V & Cowie B. *AFP* 2012;41(4):212–214

Hepatitis B reactivation

- HBV replication may spontaneously increase and result in hepatitis flares.
- During immune suppression, viral replication may increase considerably
- Following restitution of the host's immune response, T-cell mediated liver injury may occur. (B-cells are also involved in antigen presentation and viral clearance)
- Hepatitis B reactivation or "flares" following chemotherapy can be fatal

Galbraith et al. Lancet 1975; 2: 528–30.

Hepatitis B reactivation - Definitions

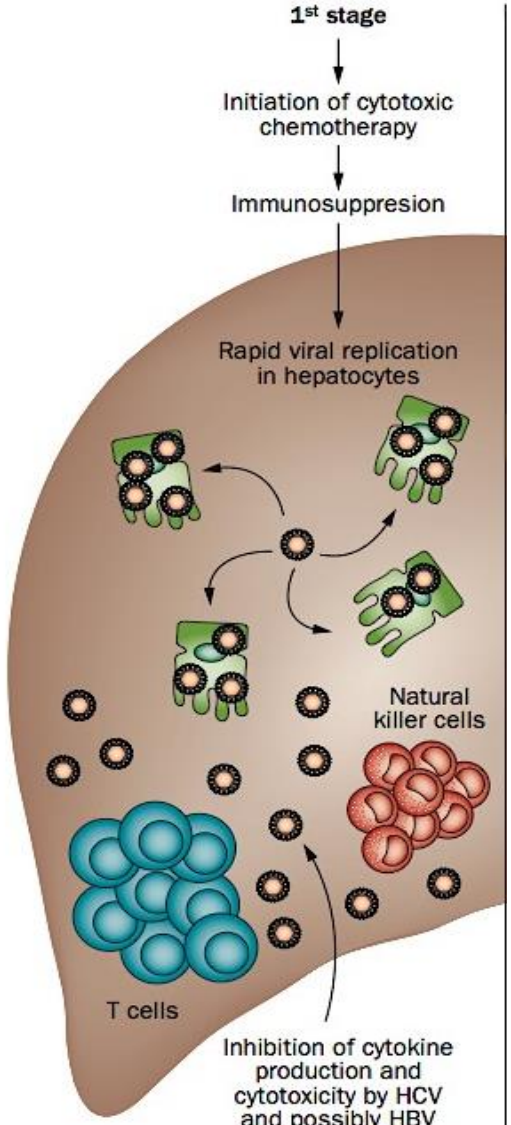
- **New Definition (2013 AASLD):**
  - HBV viral load increase ≥ 100 (≥2 Log 10) fold above baseline

  Or

  New appearance of HBV VL ≥ 100 IU/ml (with previously undetectable)

Mechanisms

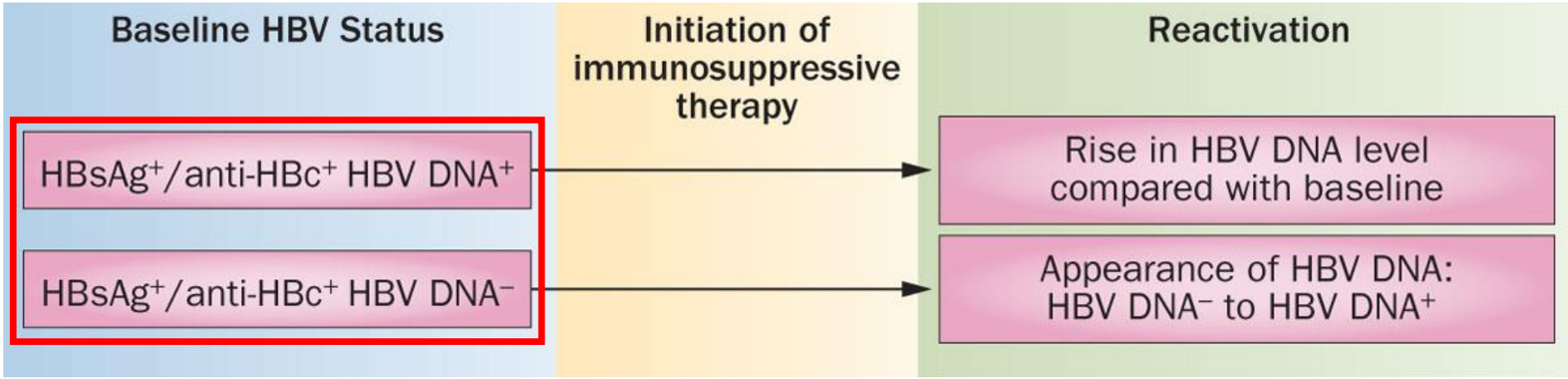
- Indirect through immunosuppression
- Direct through stimulation of glucocorticoid responsive element in the HBV genome
  - leading to upregulation of HBV gene expression
- Inhibition of TNF may also play a role



ALT levels	Normal
Viral load	Increased

Torres et al. Nat.Rev.Clin.Oncol. 156-166 (2012)

Types of HBV reactivation



Hwang & Lok
Nat. Rev. Gastroenterol. Hepatol..2013

Hepatitis B reactivation - Risk

- Chemotherapy regimes:
  - Cytoreductive therapy prior to haematopoietic stem cell transplantation
  - Rituximab (CD20 monoclonal antibody) associated with particularly high risk
  - Steroid containing and anthracycline high risk
- Cancer type:
  - In general, haematological > non-haematological
  - Lymphoma (≈ 50% reactivation if sAg+ve, with mortality of ≈10%)
  - Breast cancer (41-56%)
  - Other solid tumours (14-21%)
- Viral Characteristics:
  - HBsAg +ve, eAg+ve, high HBV viral load
  - In resolved HBV infection (HBcAb +ve) reactivation can still occur
- Patient characteristics:
  - Younger age
  - Male gender

Hepatitis B reactivation

- Complications:
  - Early cessation of chemotherapy
  - Reactivation has broad clinical spectrum;
    - Mild asymptomatic hepatitis ranging to
    - Icteric hepatitis associated with 10-40% mortality
- Management:
  - Screen patients for ‘past’ and current HBV infection
  - Assess risk of reactivation or seroreversion
  - Antiviral prophylaxis prior to chemotherapy
  - Continue prophylaxis for minimum 6-12 months after cessation of chemotherapy

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update

Jessica P. Hwang, Mark R. Somerfield, Devena E. Alston-Johnson, Donna R. Cryer, Jordan J. Feld, Barnett S. Kramer, Anita L. Sabichi, Sandra L. Wong, and Andrew S. Artz

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ABSTRACT

Purpose
This updated provisional clinical opinion presents a revised opinion based on American Society of Clinical Oncology panel consensus in the context of an evolving database.

Context
Despite the 2010 provisional clinical opinion recommendation, there is still evidence of suboptimal hepatitis B virus (HBV) screening among patients at high risk for HBV infection or HBV reactivation after chemotherapy. This updated provisional clinical opinion introduces a risk-adaptive strategy to identify and treat patients with HBV infection to reduce their risk of HBV reactivation.

Provisional Clinical Opinion
Medical providers should screen by testing patients for HBV infection before starting anti-CD20 therapy or hematopoietic cell transplantation. Providers should also screen patients with risk factors for HBV infection. Screening should include both hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc), because reactivation can occur in patients who are HBsAg positive/anti-HBc positive or HBsAg negative/anti-HBc positive. Either total anti-HBc or anti-HBc immunoglobulin G (not immunoglobulin M) test should be used. Clinicians should start antiviral therapy for HBsAg-positive/anti-HBc–positive patients before or contemporaneously with cancer therapy and monitor HBsAg-negative/anti-HBc–positive patients for reactivation with HBV DNA and ALT levels, promptly starting antivirals if reactivation occurs. Clinicians can initiate antivirals for HBsAg-negative/anti-HBc–positive patients anticipating cancer therapies associated with a high risk of reactivation, or they can monitor HBV DNA and ALT levels and initiate on-demand antivirals. For patients who neither have HBV risk factors nor anticipate cancer therapy associated with a high risk of reactivation, current evidence does not support HBV screening before initiation of cancer therapy. Two panel members provided a minority viewpoint, involving a strategy of universal HBsAg and selective anti-HBc testing.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

Clinical Practice Guidelines

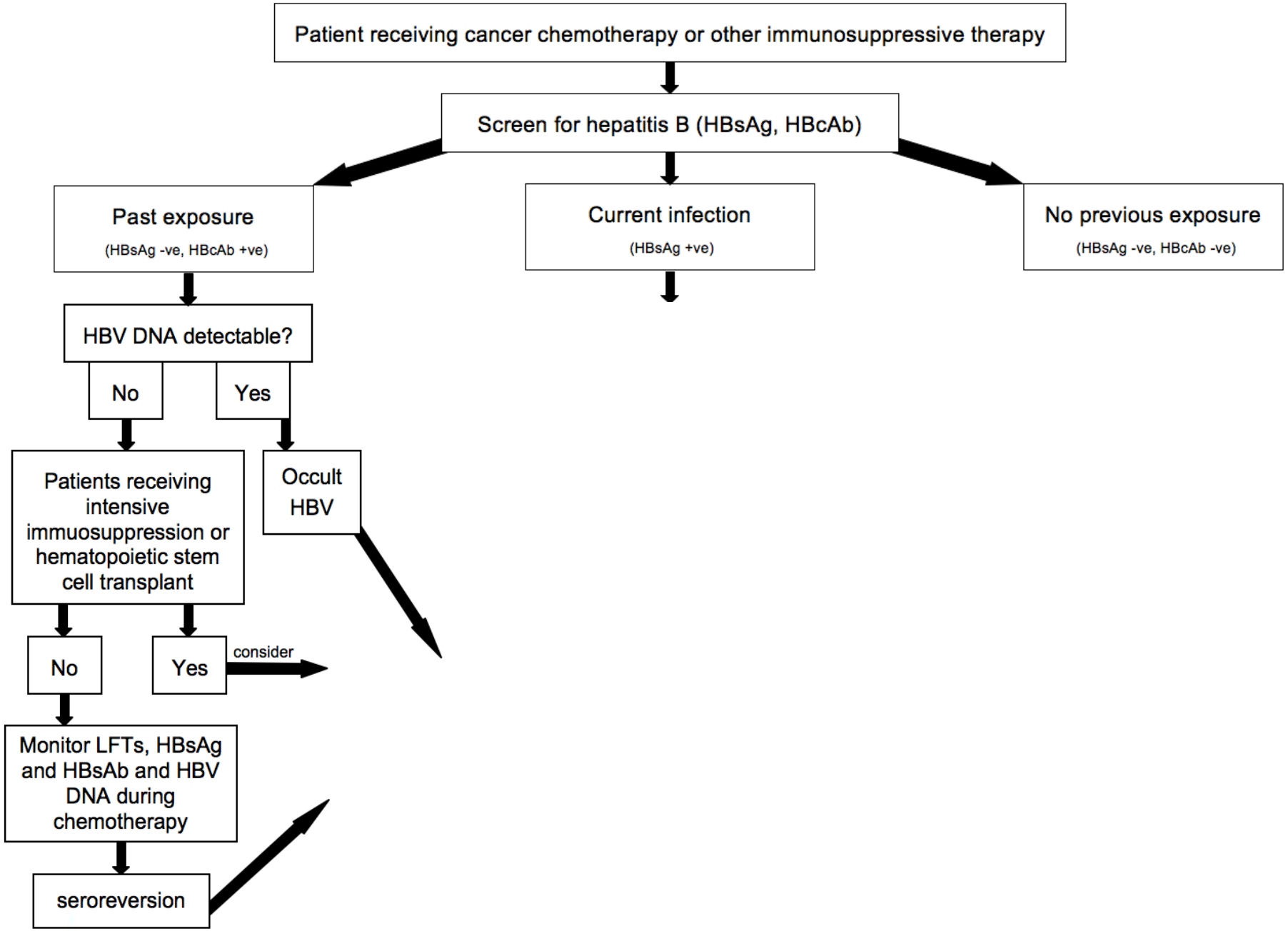
Organisation	HBsAg	HBcAb	HBV DNA	Notes for HBcAb+ve
EASL - 2012	✓	✓	✓	Monitor HBV DNA, treat with antivirals if +ve
CDC -2008	✓	✓		Also recommends sAb
ASCO-2015	✓	✓	+/-	Altered position from 2010
AASLD -2009	✓	✓	✓	If HBV DNA +ve commence antivirals
WGO- 2008	✓	✓	+/-	Monitor “HBV-markers” in occult HBV
APASLD - 2009	✓	✓		If using Rituximab – give prophylaxis
BSH-2008	✓	✓	✓	Use of vaccine in sAb-ve cAb+ve
GESA - 2010	✓	✓	✓	If HBV DNA +ve commence antivirals

European Association for the Study of the Liver (EASL) guidelines 2012

- All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and Anti-HBc prior to initiation of treatment (**A1**)
- HBsAg-positive candidates should receive pre-emptive NA administration during therapy (regardless of HBV DNA levels) and for 12 months after cessation of therapy (**A1**)
  - Low VL (<2000 IU/ml) and limited duration - Lamivudine
  - High VL (>2000 IU/ml) and/or prolonged duration – antiviral with high barrier to resistance, eg entecavir or tenofovir (**C1**)
- Isolated anti-HBc positie patients should have DNA tested
  - DNA positive (occult HBV) treat as HBsAg positive (**C1**)
  - DNA negative, monitor closely (**C1**)

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C

Grading of recommendation	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption	2



Lubel & Angus. J. Gastro. Hep. 2010:25; 864-871

University of Toronto, Canada

Hepatitis B virus screening before adjuvant chemotherapy in patients with early-stage breast cancer: a cost-effectiveness analysis

Table 3 Baseline cost-effectiveness results

Strategy	Cost	QALYs	Versus no screening			Sequential ICER
			ΔCost	ΔQALYs	ICER	
No screening	$53,986	10.4345	–	–	–	–
Screen and treat high-risk only (screen-HR)	$54,120–$54,203	10.4361–10.4361	$134–$217	0.0016–0.0017	$82,188–$130,084	Extendedly dominated[a]
Screen and treat to prevent reactivation (screen-all)	$54,150–$54,252	10.4379–10.4379	$164–$266	0.0034–0.0035	$47,808–$76,527	$47,808–$76,527

QALY quality-adjusted life year, *ICER* incremental cost-effectiveness ratio

[a] Extendedly dominated is the combination of two other alternatives dominated the treatment

HBV screening before adjuvant chemotherapy for breast cancer patients would **prevent a significant number of reactivations**, would likely be **moderately cost-effective**, and **may extend the lives** of breast cancer patients

Wong WWL et al. Breast Cancer Res Treat (2015) 151:639–652

Summary – Key points

- Hepatitis B
  - Screen patients with appropriate serology
    - HBV sAg and cAb
  - Refer for hepatology advice if serology positive
- Hepatitis C
  - Screen patients with HCV Ab, if +ve test PCR
  - Refer for hepatology advice if PCR +ve

THANK YOU

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