

Management of Hepatitis B & HIV Coinfection: A Clinical Update



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In patients with HIV/HBV co-infection who are HBcoreAb(IgG + IgM) positive only, with negative HBsAg and negative HBsAb, all of the following are true except:

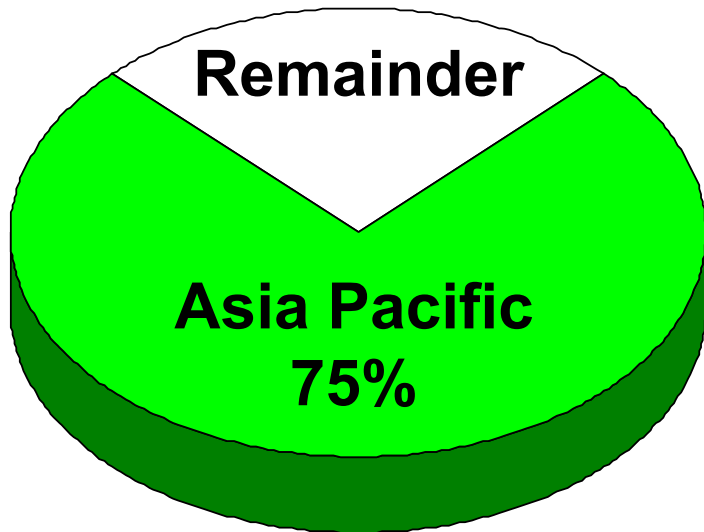
- a) Some of these patients have chronic hepatitis B.**
- b) Some of the patients are candidates for vaccination against hepatitis B.**
- c) Most of these patients have been naturally infected with hepatitis B.**
- d) These patients are immune to hepatitis B.**
- e) Some of these patients will have detectable hepatitis B DNA by viral load testing.**
- f) I do not know, I'm coming to learn.**



Objectives

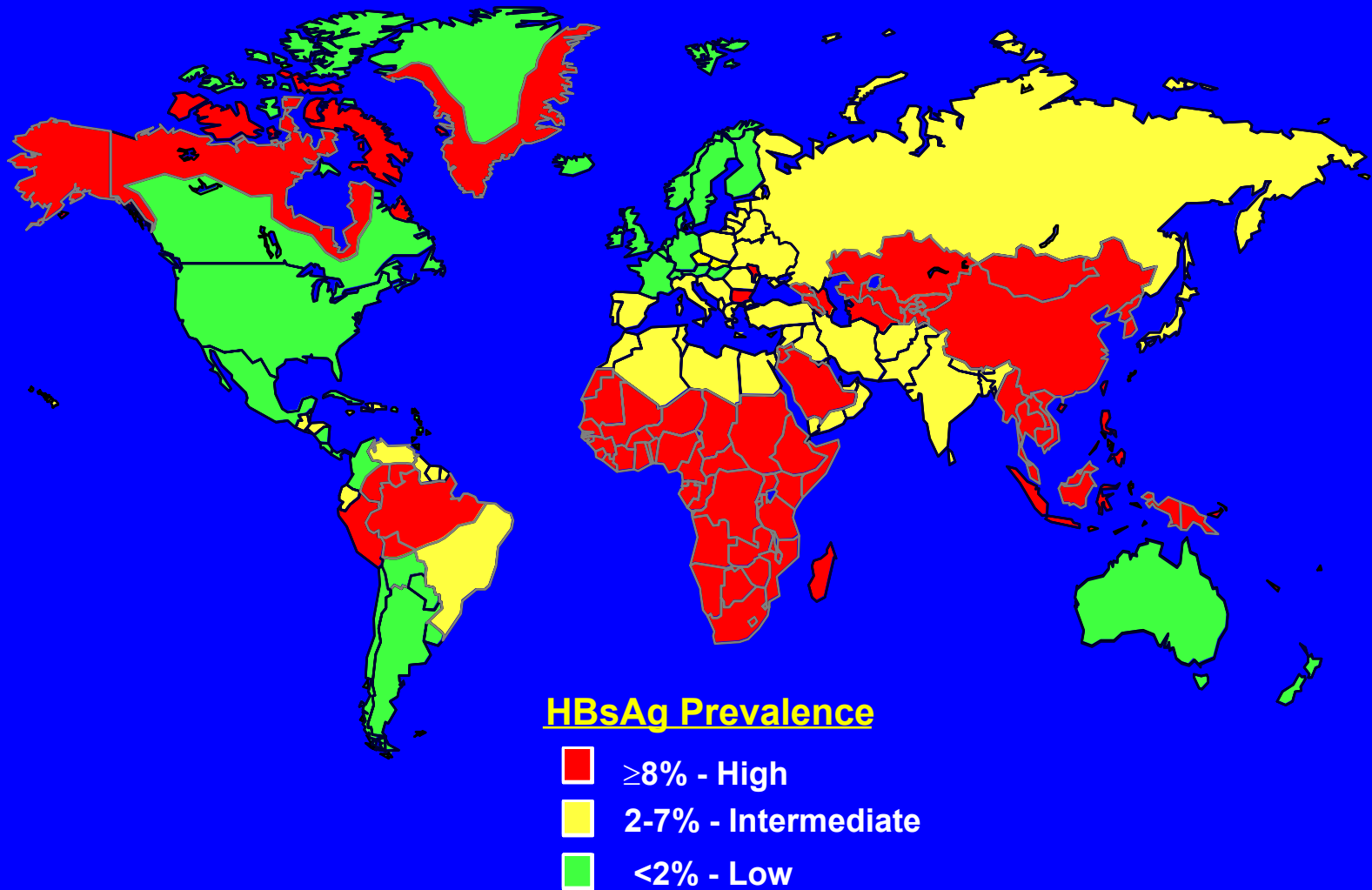
- **Epidemiology & transmission**
- Review serologic evaluation of hepatitis
- Review the work-up for chronic hepatitis B
- Treatment of hepatitis B in patients with HIV
- Prevention

Hepatitis B: A Global Healthcare Challenge



- **350 million** chronic HBsAg carriers worldwide
- **1.25 million** in US with chronic HBV
- 25-40% will die due to hepatitis B, or HBV related complications
- Up to **2 million** die each year from HBV infection, making it the 10th leading cause of death

Geographic Distribution of Chronic HBV Infection



HBV Modes of Transmission

- Sexual



- Parenteral

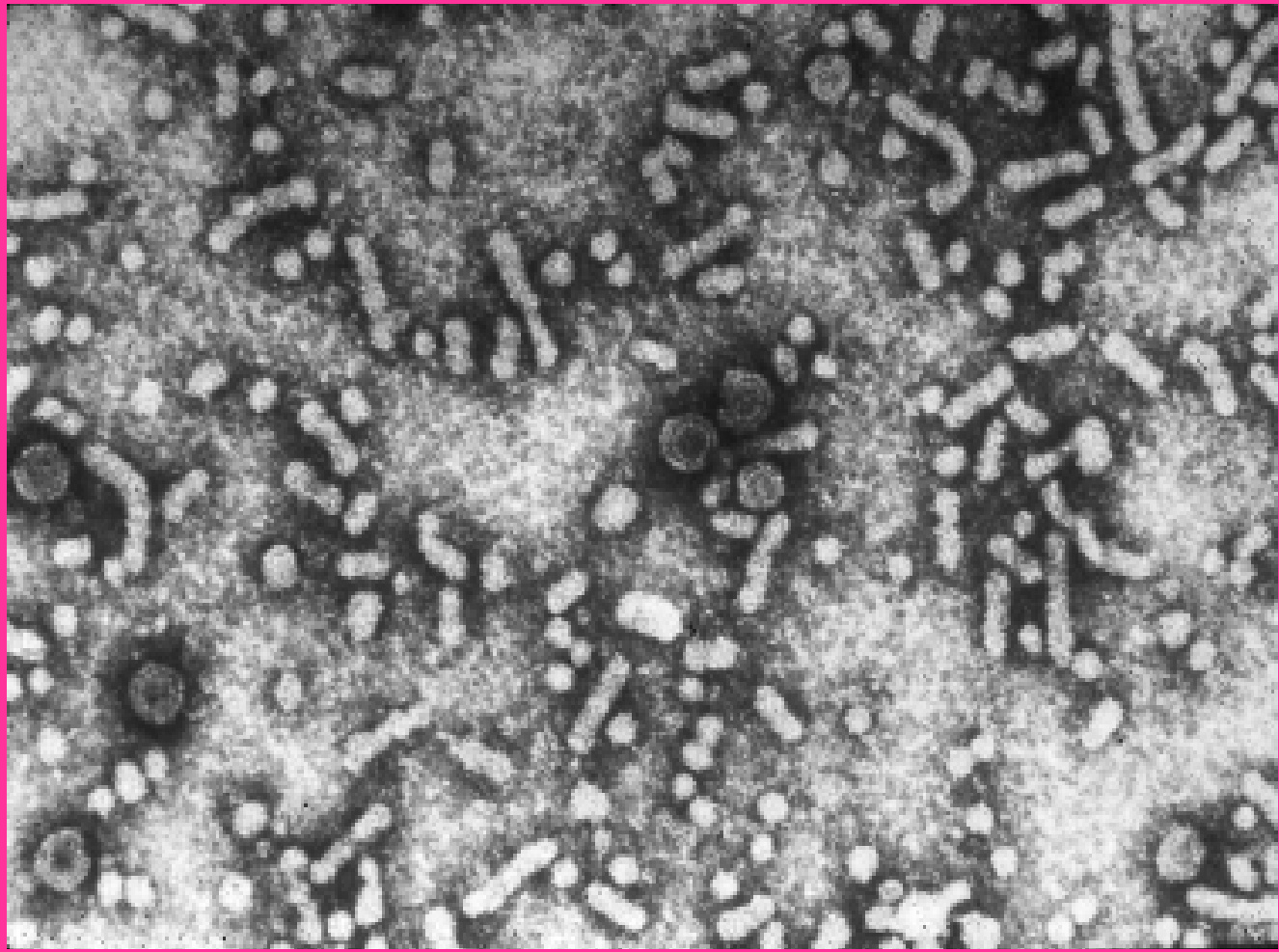
- Perinatal



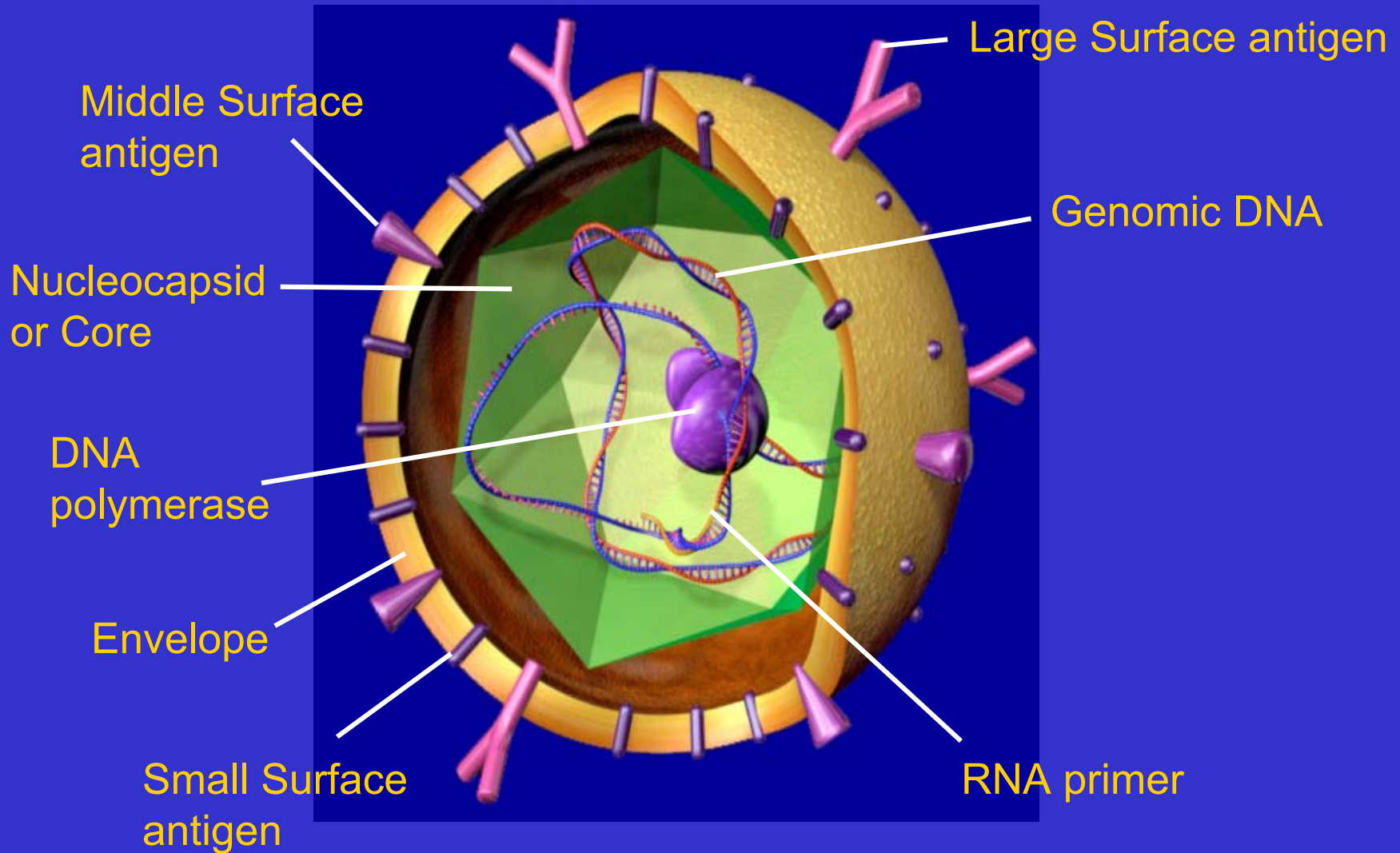
Concentration of HBV in Various Body Fluids

High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breast milk

Hepatitis B Virus



Hepatitis B Virus

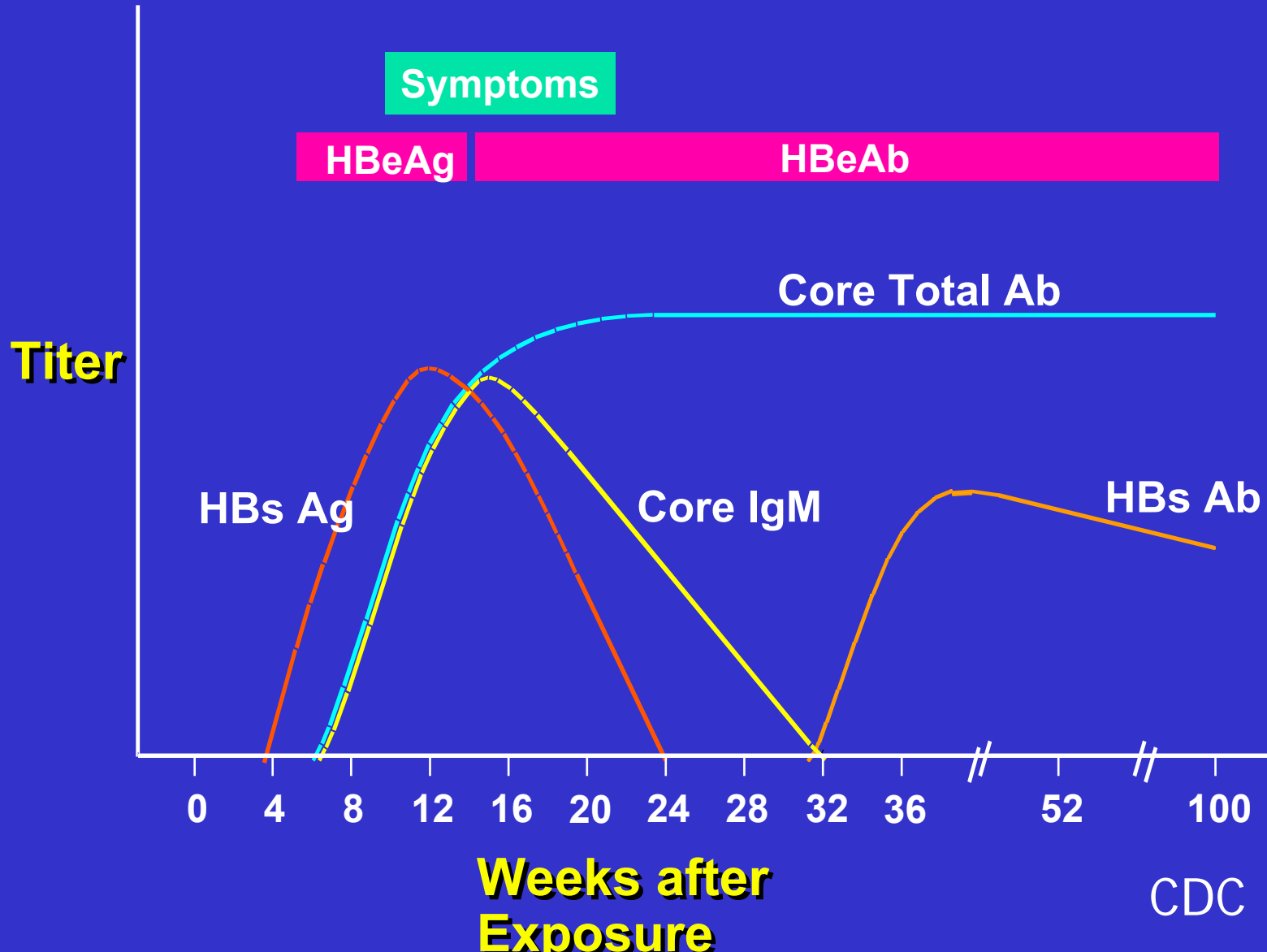




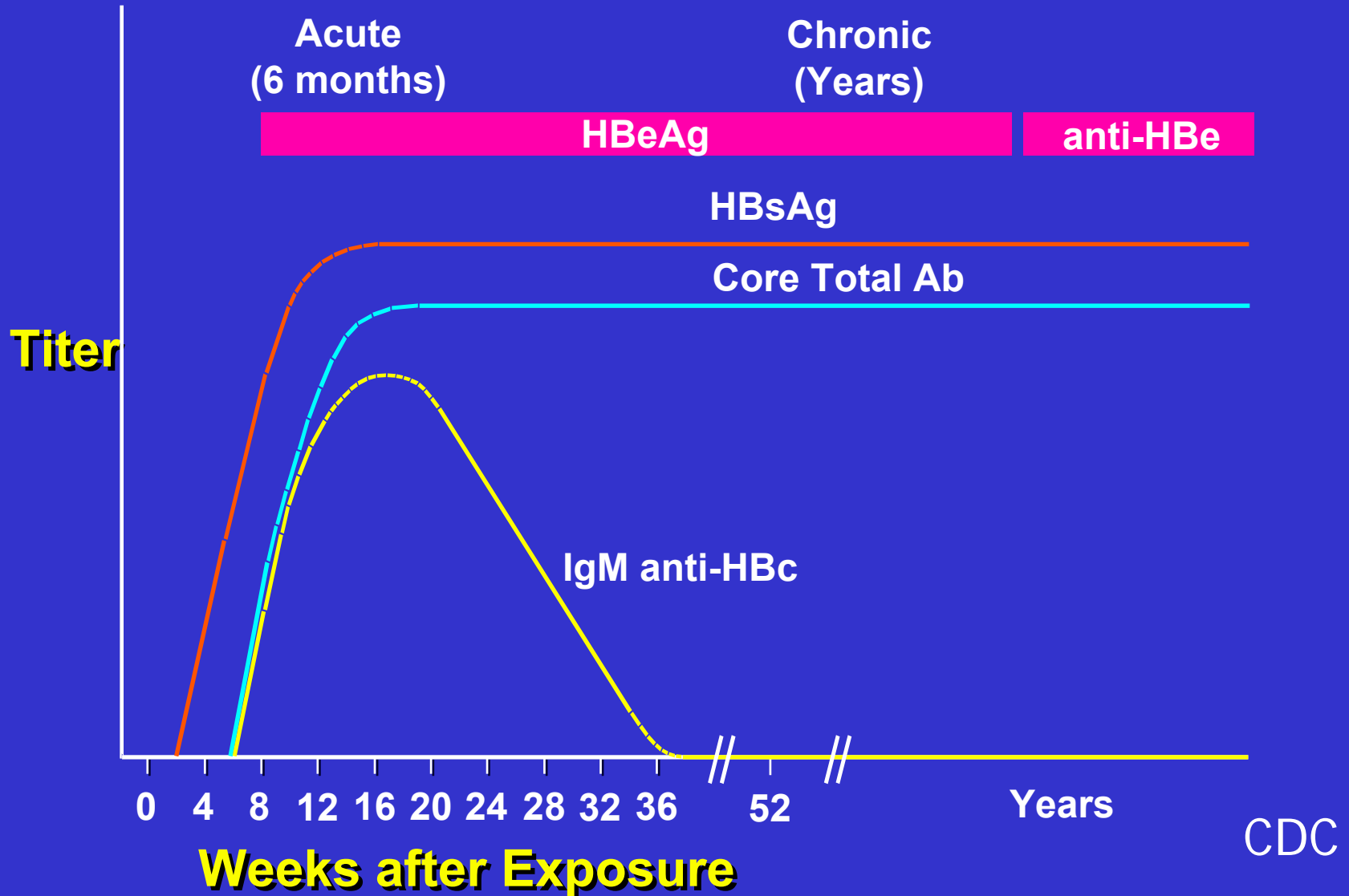
Hepatitis B

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Acute Hepatitis B Virus Infection RECOVERY



Chronic Hepatitis B Virus Infection

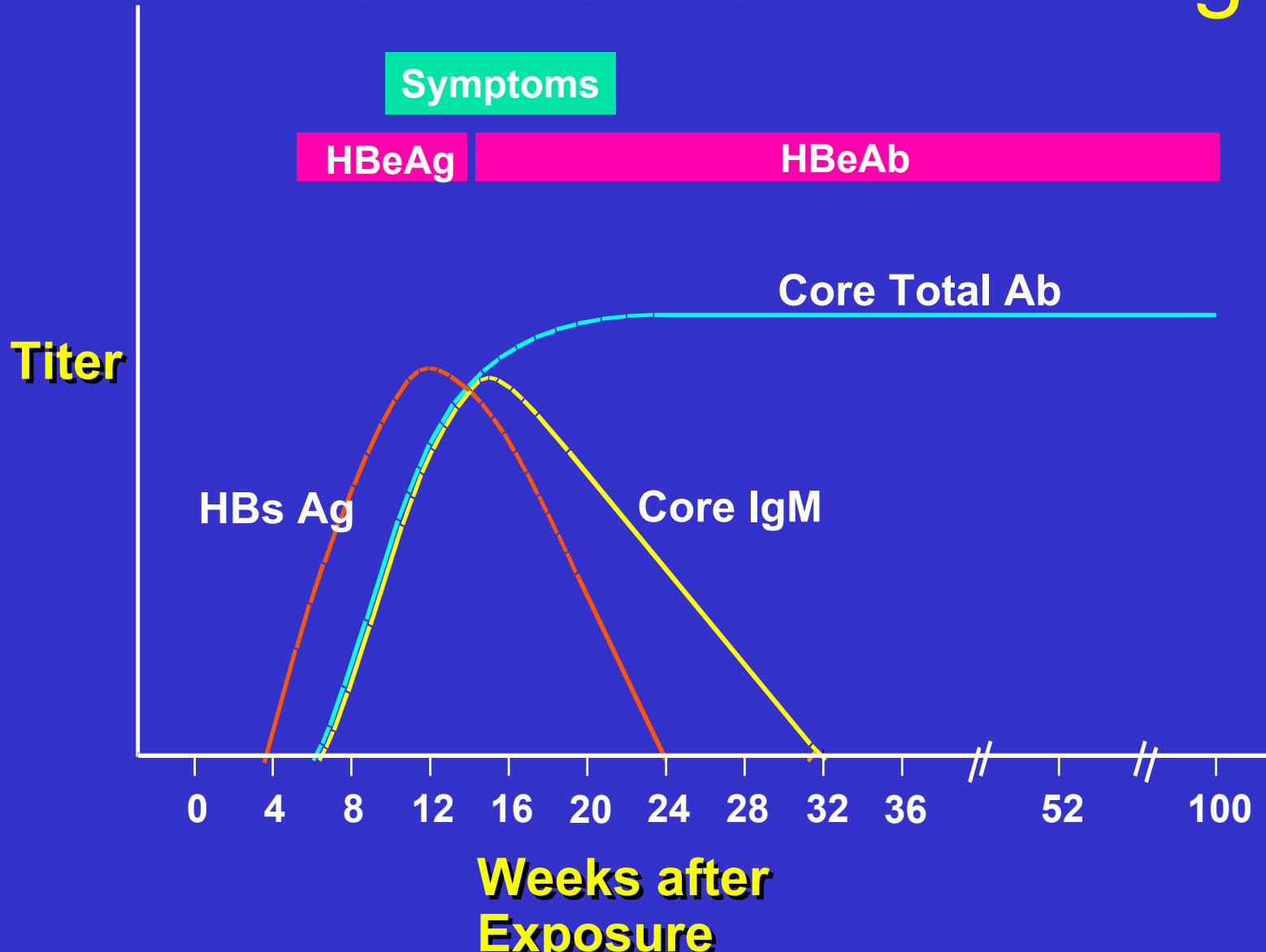




Only HBcore Ab Positive (Total IgG + IgM)

- HBs antigen and HBs antibody negative
- Common with HIV coinfection
- IgM component negative with chronic disease
- May be carrier (chronically infected), despite negative HBsAg
 - Can distinguish by hepatitis B DNA testing

Chronic Hepatitis B Virus Infection without Persistent HBsAg





Only HBcore Ab Positive (Total IgG + IgM)

- Could also be a false positive result
 - HBe Ab can distinguish natural infection from a false positive
- New York State revised guidelines
 - Consider vaccination of these patients if HBV DNA testing negative
 - www.HIVguidelines.org



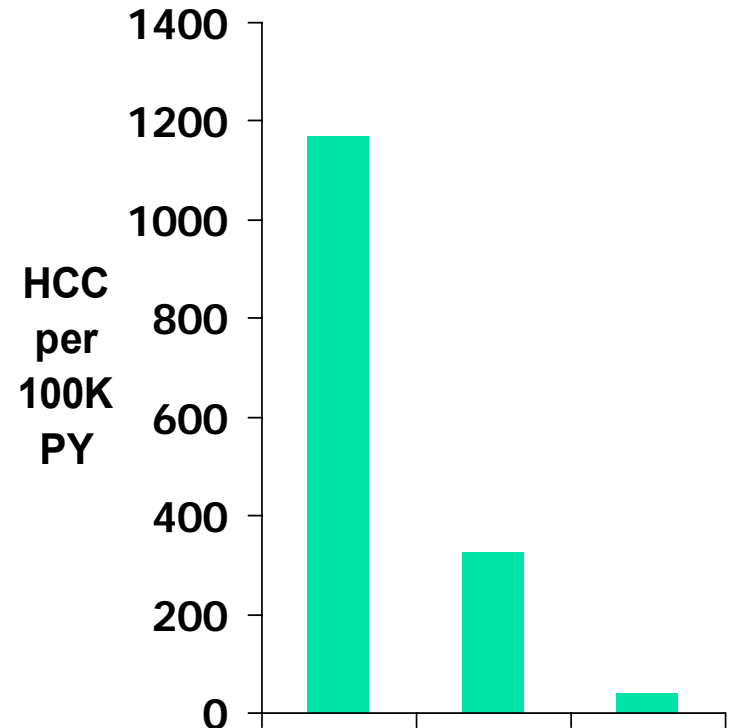
Hepatitis B and HIV Coinfection

- Higher HBV DNA viral loads than with HBV alone
- Higher mortality with HIV coinfection
- Less hepatic damage with uncontrolled HIV
- Immune reconstitution increases hepatic injury due to inflammatory response

■ Peters M 9th CROI Seattle, 2002

HBeAg and Risk of Hepatocellular Carcinoma

- 11,893 men in Taiwan
- 1991-92 enrolled
- HBeAg, HBsAg testing
- HCC by link with cancer registry



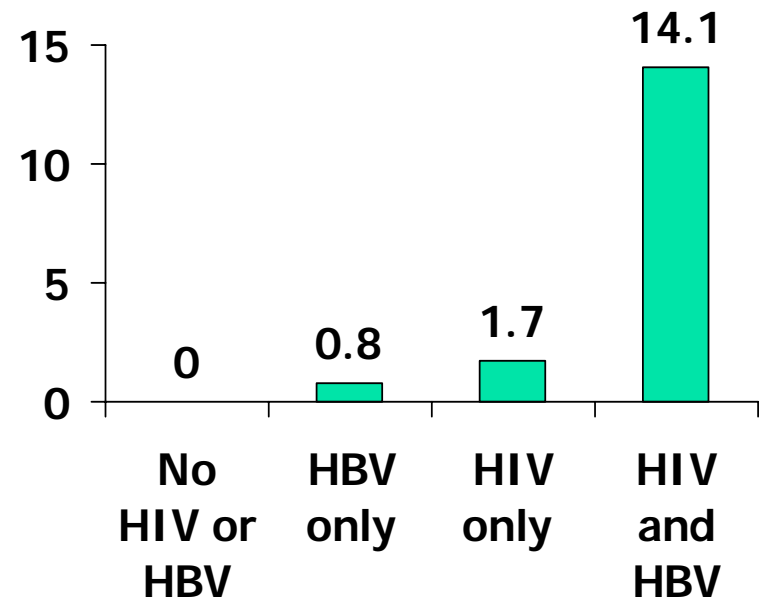
HBeAg

HBsAg

HIV Coinfection Increases the Risk of ESLD due to HBV

- MACS 4,967 men
 - HIV+ 47%
 - HBV+ 6% (n=326)
 - HIV/HBV 4.3% (n=213)
- HIV/HBV: 17-fold higher risk of liver death compared to HBV alone
 - Alcohol
 - Low CD4
 - Increased risk after 1996

Liver Mortality by HIV and HBV Status





Hepatitis B

- Epidemiology & transmission
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- **Review the work-up for chronic hepatitis B**
- Treatment of hepatitis B in patients with HIV
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Chronic Hepatitis B Work-up

- Serologies
 - Also screen for A, C and Delta
- Liver enzymes
- Viral load for HBV DNA by PCR
- Alpha fetoprotein monitoring q 6 months
- Hepatic imaging – US or CT scan
- Liver biopsy



Hepatitis B

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Criteria for Treatment

- American Association for the Study of Liver Diseases
 - AST/ALT > 2 times ULN
 - HBV DNA PCR > 100,000 c/mL
 - Liver histology showing moderate or severe inflammation

Chronic Hepatitis B

Treatment: FDA-approved

- Alfa interferon; pegylated interferon alfa 2a
- Lamivudine (Epivir HB)
 - HBV rebound possible if lamivudine stopped
- Adefovir (Hepsera) - active against lamivudine-resistant HBV; pilot study
 - N = 35; 5.15 \log_{10} decrease in viral load
 - Mean CD4+ 423 cells/cmm
 - Benhamou *Lancet* 2001:358
- Entecavir (Baraclude)
 - Active against lamivudine-resistant HBV
- Telbivudine



Dual Hepatitis B/HIV Coinfection Therapies

- Lamivudine (Epivir)
- Off-label uses
 - Emtricitabine (Emtriva)
 - Tenofovir DF (Viread) – active against lamivudine-resistant HBV
 - Emtricitabine/tenofovir (Truvada)



Rebound Hepatitis

- Associated with removal of hepatitis B therapy
- Could occur inadvertently with change in HIV therapy for virologic failure
 - Should maintain HIV drugs with activity against HBV when changing HAART

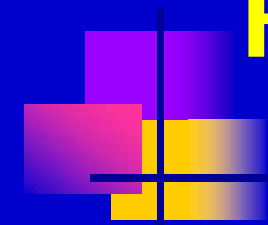


Interferon for Chronic Hepatitis B

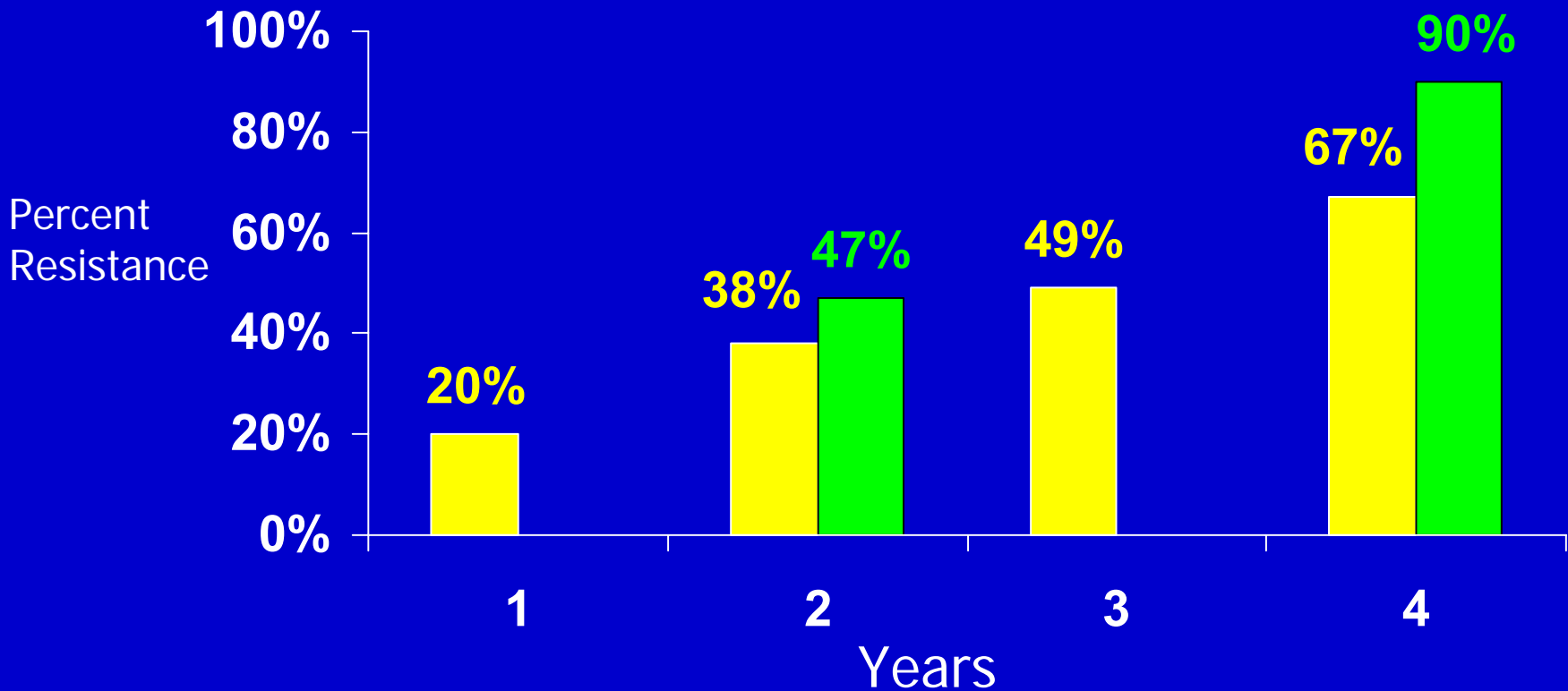
- Immune modulator and antiviral activity
- Subcutaneous injection of 30-35 million units/week for 16 weeks¹ if HBeAg+
 - 1 year for HBeAg- & HBeAb+ patients
- Lasting response (HBeAg loss) in about 20-40% of patients treated
- Poorer response in Asians, long-term infection, more advanced disease²

1. Intron A. *Physicians' Desk Reference*. © Montvale, NJ: Medical Economics; 1998:2637-2645.
2. Wong DK, et al. *Ann Intern Med*. 1993;119:312-323.

Incidence of LAM Resistance in HBV and HBV/HIV Patients



■ HIV negative ■ HIV positive



Benhamou et al., *Hepatology*, 1999.

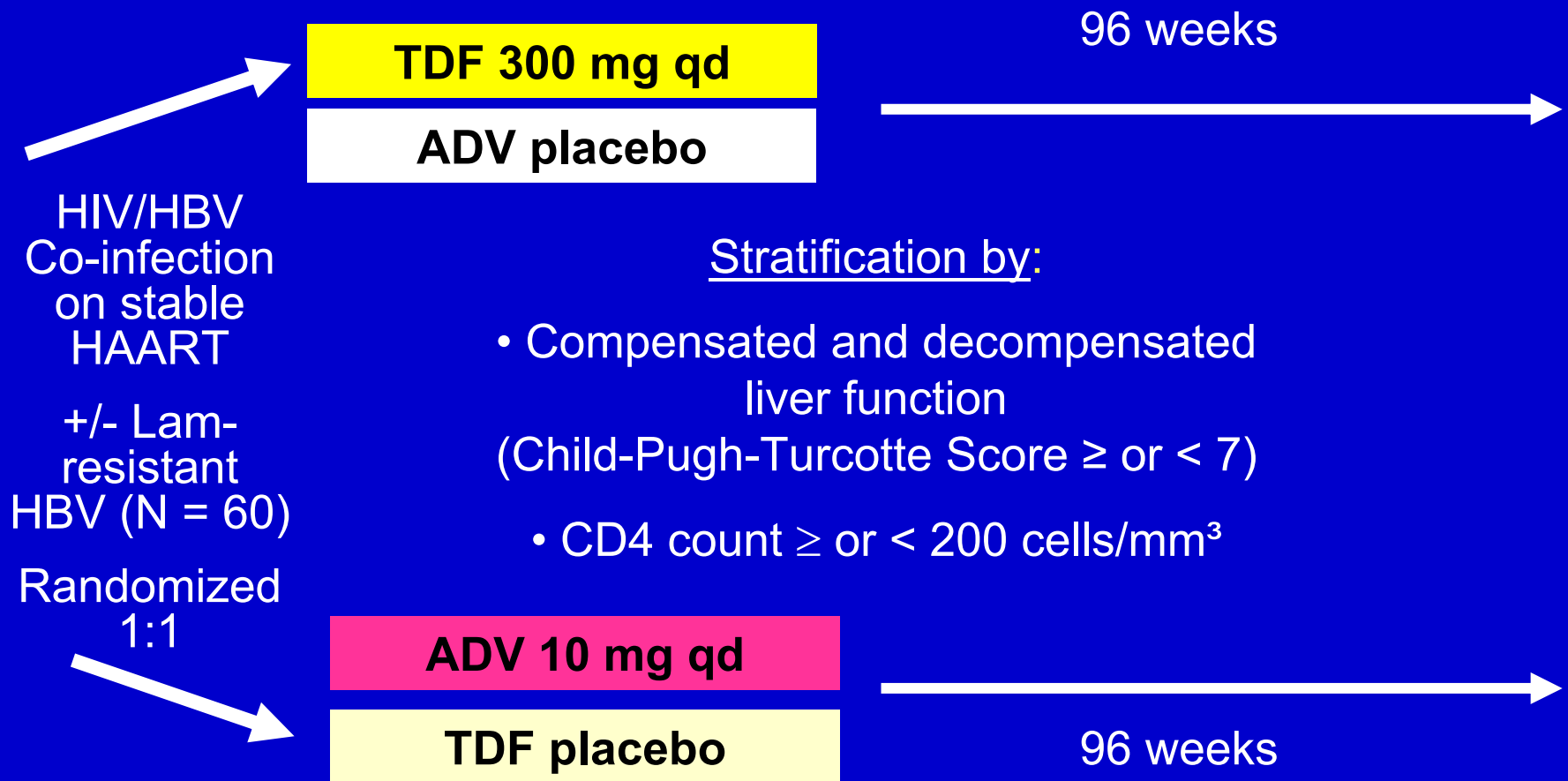
TDF + LMV May be More Efficacious than LMV Alone in Anti-retroviral Naïve Patients

Study design: Tenofovir vs stavudine with efavirenz and lamivudine

Substudy Of GS 903 – naïve to HBV therapy

Week 48	TDF + LMV	LMV
	N=5	N=6
ΔHBV DNA (log₁₀ copies/ml), mean	-4.70	-2.95
HBV DNA <1000	4	1
YMDD	0/1	4/5
Anti-HBe+	1	1
ΔALT, mean	-55	-22

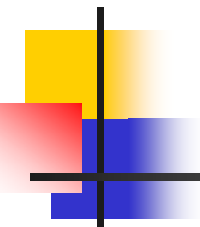
TDF vs ADV for HIV/HBV Coinfection (AACTG 5127)



Noninferiority trial



Baseline Demographic Characteristics



	ADV (n=25)	TDF (n=27)
Median age (years)	47	40*
Male	96 %	89 %
Caucasian	56 %	56 %
Black	32 %	33 %
Hispanic	4 %	11 %
Asian	4 %	0 %
IDU	4 %	22 % [#]
Median CD4 cells/mm ³	486	422
HIV RNA < 400 c/mL	80%	70%

* p=0.001; # p=0.10

Baseline HBV and HIV Disease Characteristics

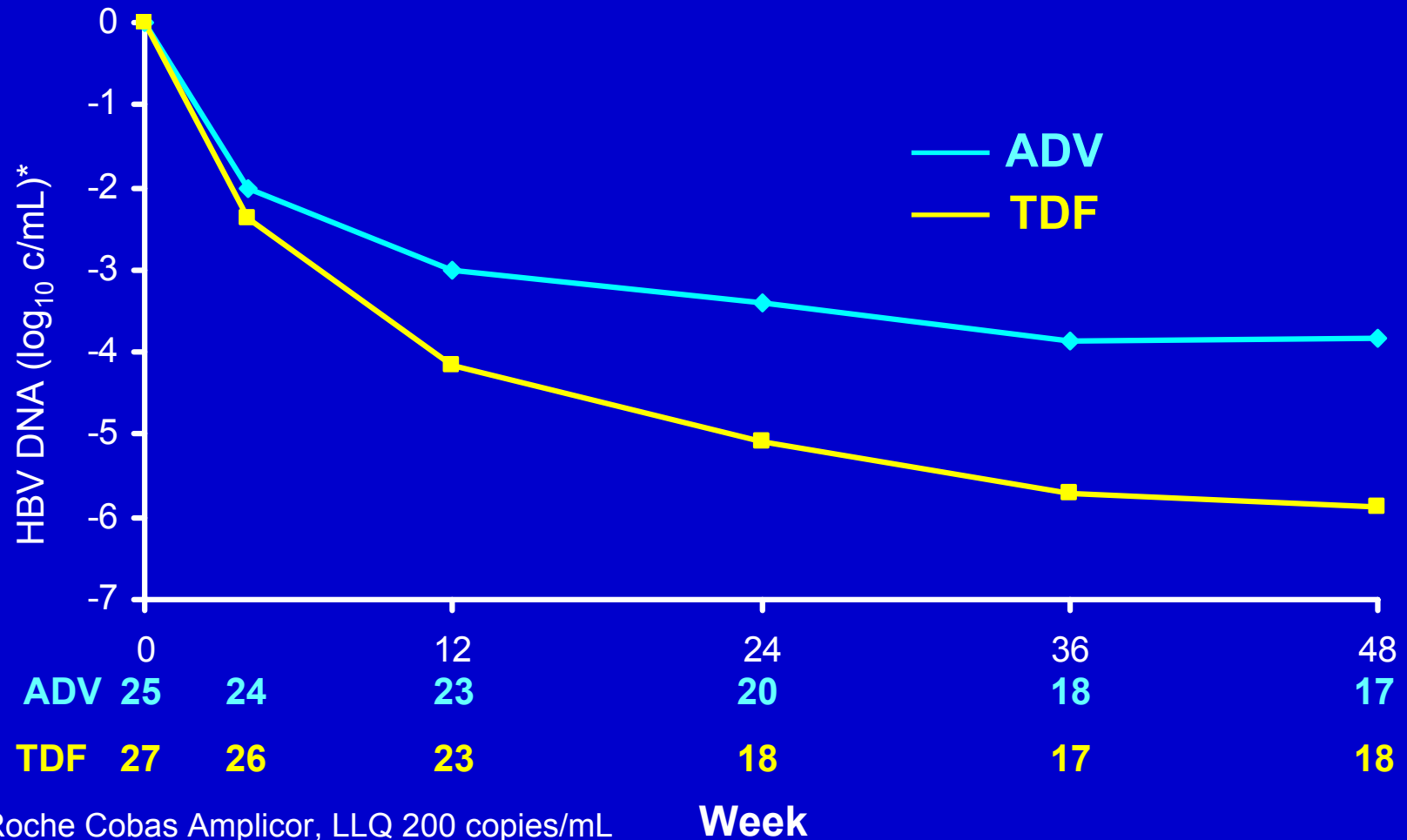
ADV*

TDF*

Mean HBV DNA log ₁₀ c/mL	8.8 ± 1.9	9.5 ± 1.1
CPT < 7	100%	96%
ALT ≤ ULN	60%	67%
Mean ALT (IU/L)	66 ± 33	70 ± 92
HBeAg positive	82%	92%
3TC/ LAM experienced	80%	74%

*Normal CBC, creatinine, albumin, bilirubin (88%)

Mean Change from Baseline in HBV DNA





Adverse Events

2 deaths: one HCC at week 49 on ADV
 one TDF at 57 weeks cause unknown

<u>Lab Abnormality</u>	ADV	TDF
Chemistry	8/25	8/27
Liver	14/25	13/27
↑amylase/ lipase	4/25	8/27
Pancreatitis	2/25	1/27
	(ddI)	(AZT/3TC/NVP)
Abnormal protime	0/25	1/27
Creatinine ≥grade 2	0/25	0/27

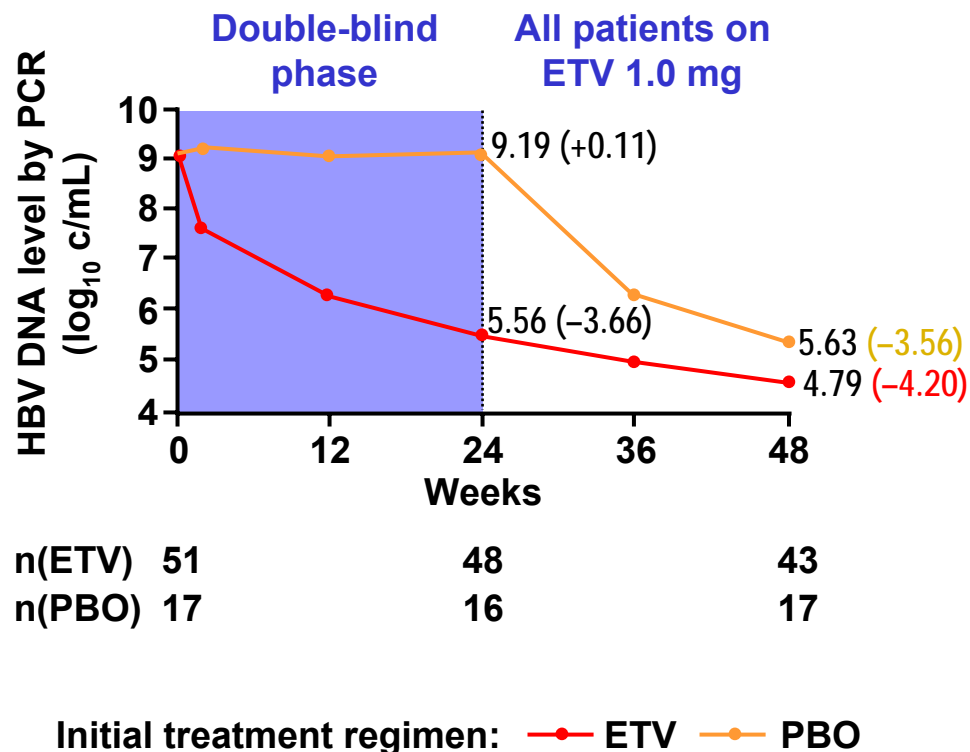


Entecavir (Baraclude)

- Potent selective inhibitor of HBV DNA polymerase
- “No anti-HIV activity”
- No mitochondrial toxicity
- No impact on cytochrome P450
- Oral therapy
 - 0.5 mg and 1 mg doses

Entecavir (ETV) in HIV/HBV Coinfection: 48-week Results

- Double-blind, placebo-controlled trial in HIV/HBV coinfection; $n=68$
- Entry criteria: ≥ 24 weeks prior 3TC or evidence of resistance (YMDD)
- Randomized 1:3 to placebo ($n=17$) or ETV ($n=51$)
- No DC due to AE up to Week 48
- 42/51 (82%) at Week 48 in the ETV arm had HBV DNA < 300 c/mL





Entecavir: HIV Activity?

- Study evaluating ETV in HIV
 - ETV potently inhibits HIV *in vitro* at an IC_{50} between 0.1 and 1 nM
 - 3 HIV/HBV pts treated with ETV had significant decline in HIV RNA of $\sim 1-3 \log_{10}$ copies/mL
 - 1 pt had emergence of M184V mutation while samples for other 2 pts not available
 - At start of ETV, and at 4 and 6 months following start, 0%, 61% and 100% of HIV clones harbored M184V
- ETV may have some anti-HIV activity and use of it in HIV/HBV co-infected patients not on HAART may lead to HIV resistance

Indications for Initiating ART: Chronic Infection

Clinical Category and/or CD4 Count	Recommendation
<ul style="list-style-type: none">■ History of AIDS-defining illness■ CD4 < 350 cells/mm³■ Pregnant women■ HIV-associated nephropathy■ Hepatitis B coinfection, when HBV treatment is indicated*	Initiate ART

*Treatment with fully suppressive drugs active against both HIV and HBV is recommended.



Telbivudine (Tyzeka)

- Once daily, oral nucleoside analog
 - FDA-approved Oct. 25, 2006
- Inhibits 2nd strand DNA synthesis
- GLOBE international trial: n = 1367
 - Superior to lamivudine in HBeAg+ pts (75% vs 67%) at 52 weeks ($p < 0.05$) & 104 wks
 - Similar to lamivudine in HBeAg- pts (75% vs 77%) at 52 weeks; superior at 104 wks
 - Transient increases in CK seen more frequently in TBV pts vs lamivudine pts

Press Release: Idenix/Novartis Nov 14, 2005.

Lai CL *et al.* *Hepatology* 2006;44:222A. Abst 91



Liver Transplantation for HBV-infected Patients

- 35 coinfecting patients referred to UCSF for evaluation, 2000 – 2002.
 - 10 died – median follow-up of 7.5 months
 - 4 underwent liver transplantation
 - All survived and are without evidence of HBV recurrence



Hepatitis Delta (D)

- Defective RNA virus that uses HBsAg for its structural protein shell
- Most common in IVDU, hemophiliacs
- Incubation: 30 – 180 days
- High prevalence in Amazon basin, Central Africa, southern Italy, and Middle East
- Simultaneous coinfection – concomitant with acute HBV
- Superinfection – in patients with chronic HBV



Hepatitis Delta (D)

- Simultaneous coinfection
 - <5% result in chronic infection
 - HDV is cleared as HBsAg is cleared
 - Severe illness, with 2 - 20% mortality



Hepatitis Delta (D)

- Superinfection
 - > 70% result in chronic infection, as HBsAg is persisting
 - Worse than HBV or HCV alone
 - High titers of anti-HDV (>1:100)
 - Progression to cirrhosis in 10 - 15 years



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Hepatitis B Vaccination

- MSM or multiple sexual partners
- Chronic hepatitis/liver disease (non-HBV)
- Injection drug users
- Inmates/staff; staff for mentally disabled
- Health care workers, including laboratory staff
- Household contacts of carriers
- Hemophiliacs; dialysis patients
- Infants/children



Post-exposure Prophylaxis

- Hepatitis B Immune Globulin
 - Best if administered in 1st 24 hours, but can be given up to 7 days after percutaneous or permucosal exposure
 - Within 14 days for post-sexual exposure
- Hepatitis B vaccine series



The Future for HBV Therapy

- More data coming with HIV-infected population
- Chronic therapy beyond 1-2 years
- Combination therapies for HBV
- Investigational agents
- Liver transplantation for fulminant hepatitis or advanced cirrhosis



Summary – Chronic Hepatitis B

- Check serologies for hepatitis A, B & C for all HIV-infected patients
- Vaccinate for A & B if non-immune
- Options exist for simultaneous treatment of HIV and HBV
- If HBV needs treated, treat for both HIV and HBV at the same time.



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- b) Some of the patients are candidates for vaccination against hepatitis B.**
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- f) I'm sorry, I did not learn.**



Web Addresses/ Phone Numbers

- www.HIVguidelines.org
- www.aidsetc.org
- www.hivandhepatitis.com
- www.aidsinfo.nih.gov
- www.cdc.gov
- AMC Division of HIV Medicine
 - 518-262-4043
 - E-mail: Fishd@mail.amc.edu