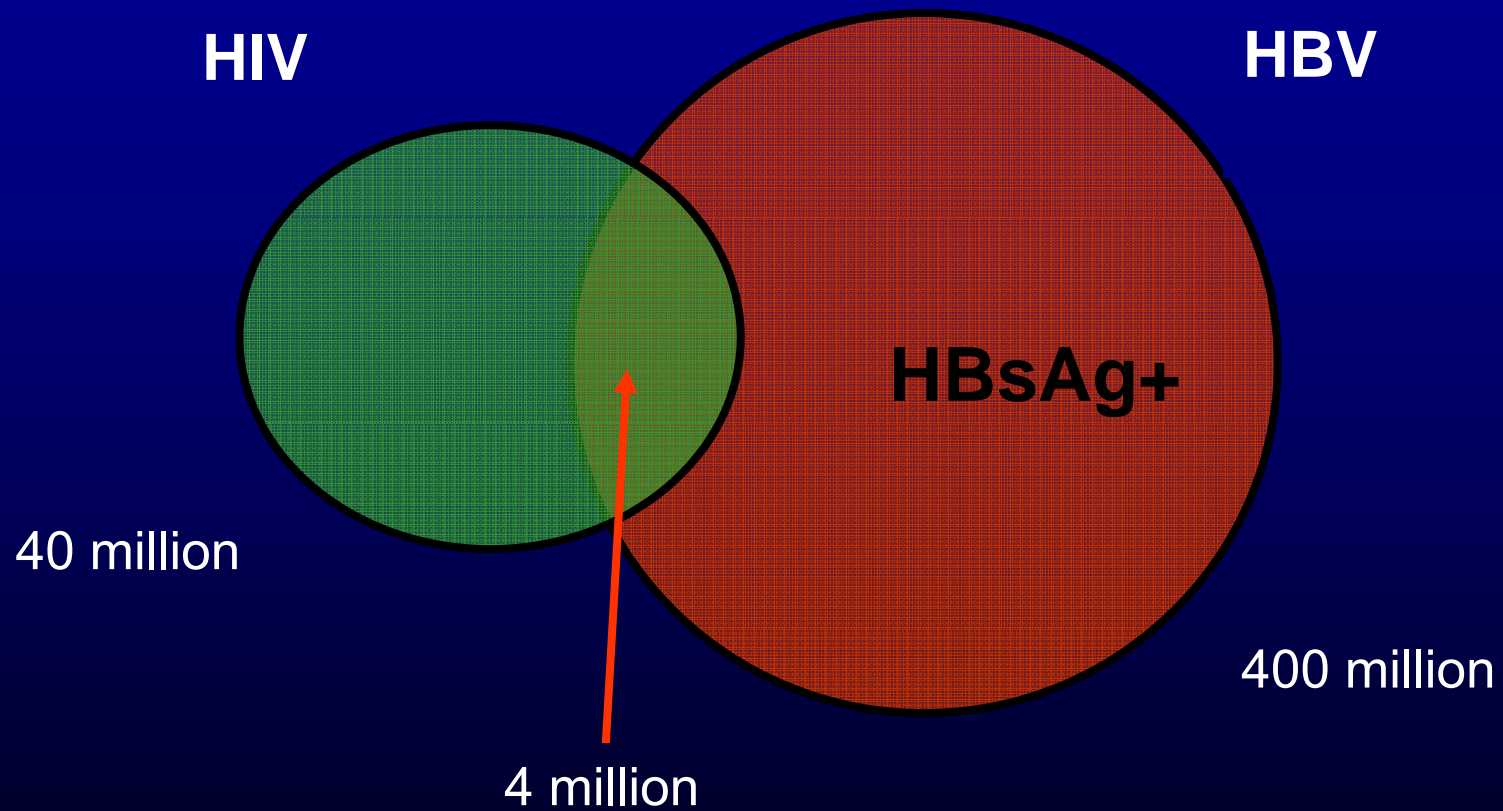


Treatment of HIV/HBV Coinfections

Marion Peters MD
University of California
San Francisco
2007

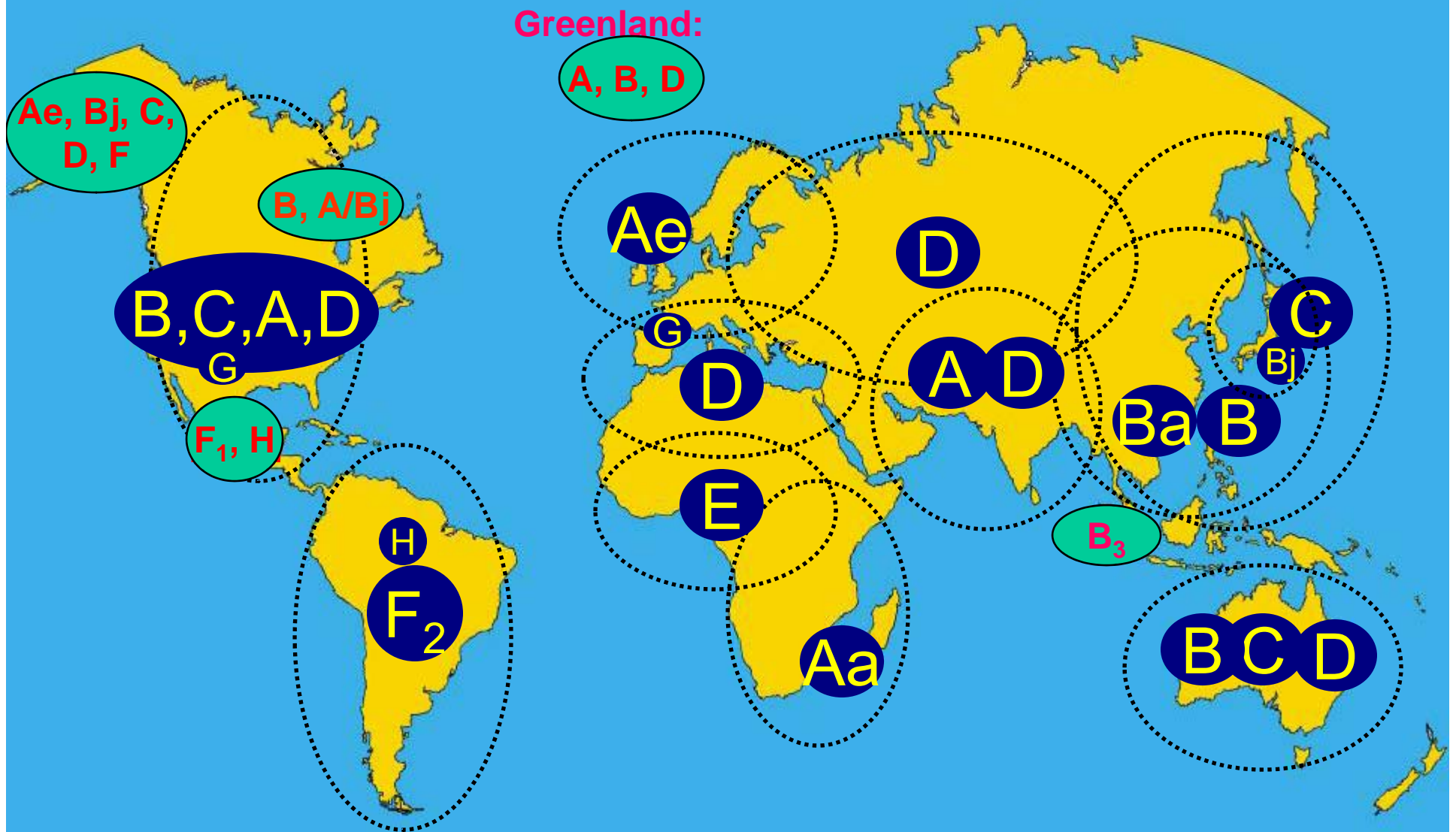
Overlapping HIV and HBV Epidemics



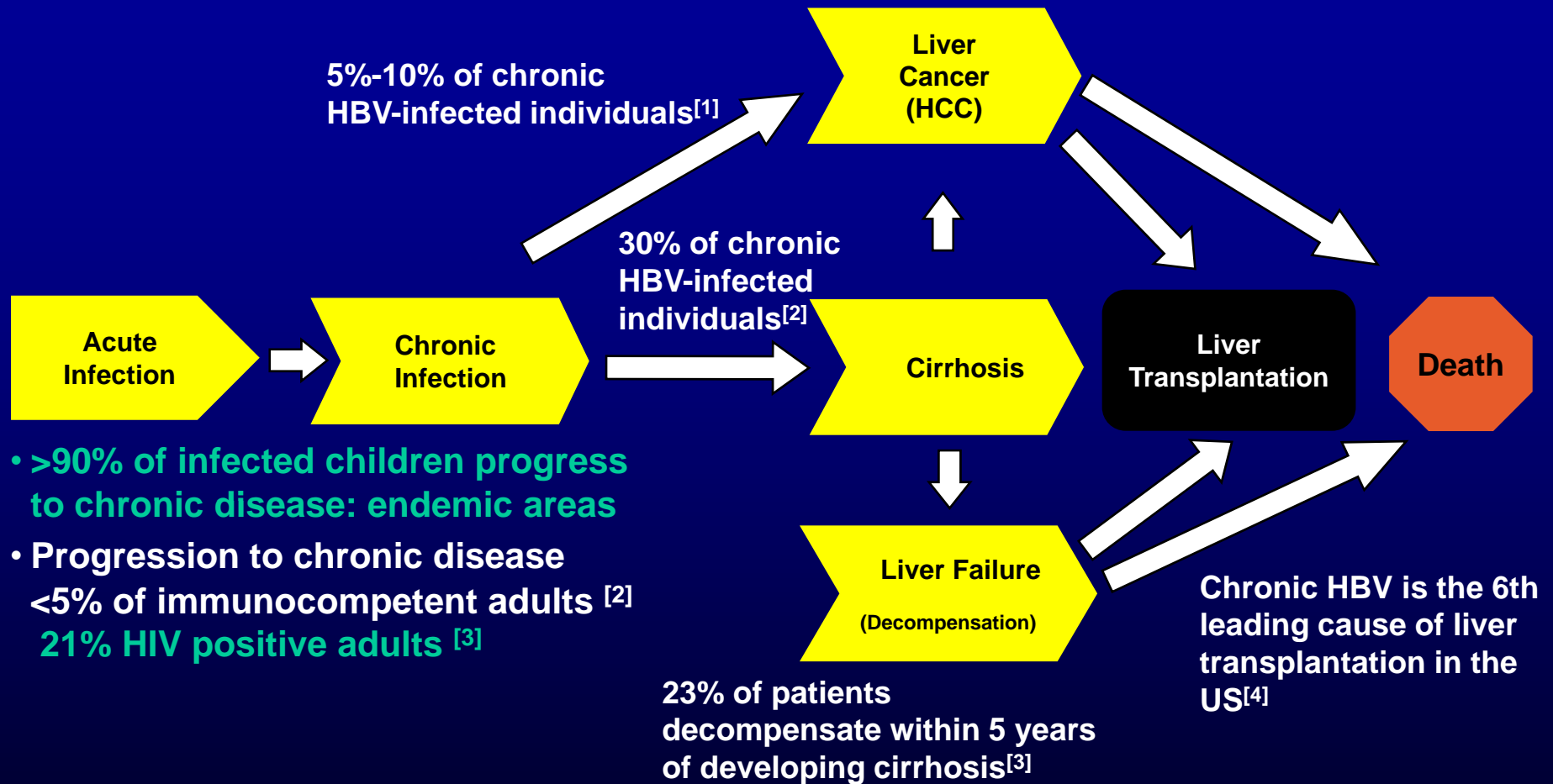
HBV Epidemiology

- 300-400 million infected worldwide
- HIV 5%-30+% depending upon cohort, country
- Adult sexual or parenteral: genotype A>>G
 - IV drug use 5%–10%
 - US 9-10%
 - EuroSIDA 8.7% HBsAg
- Vertical or childhood:
 - Uganda 73% (n = 64)
 - Tanzania 9% (n = 66), Malawi 16.9% (n = 279)
 - Nigeria 25.9%

Geographic Distribution of HBV Genotypes



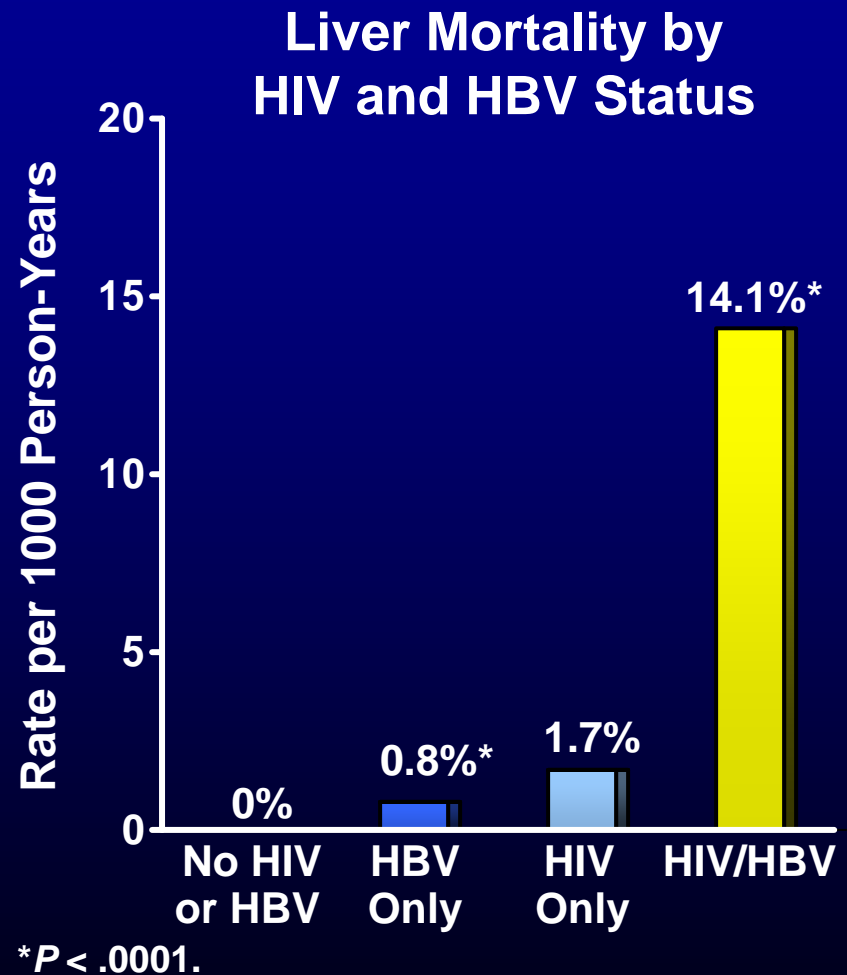
Hepatitis B Disease Progression



1. Torresi J, et al. Gastroenterology. 2000;118(2 suppl 1):S83-S103. 2. Fattovich G, et al. Hepatology. 1995;21:77-82. 3. Moyer LA, et al. Am J Prev Med. 1994;10(suppl):45-55. 4. Perrillo R, et al. Hepatology. 2001;33:424-432. 3 Hadler SC, et al. J Infect Dis. 1991;163:454-459

HIV Coinfection Increases the Risk of ESLD Due to HBV

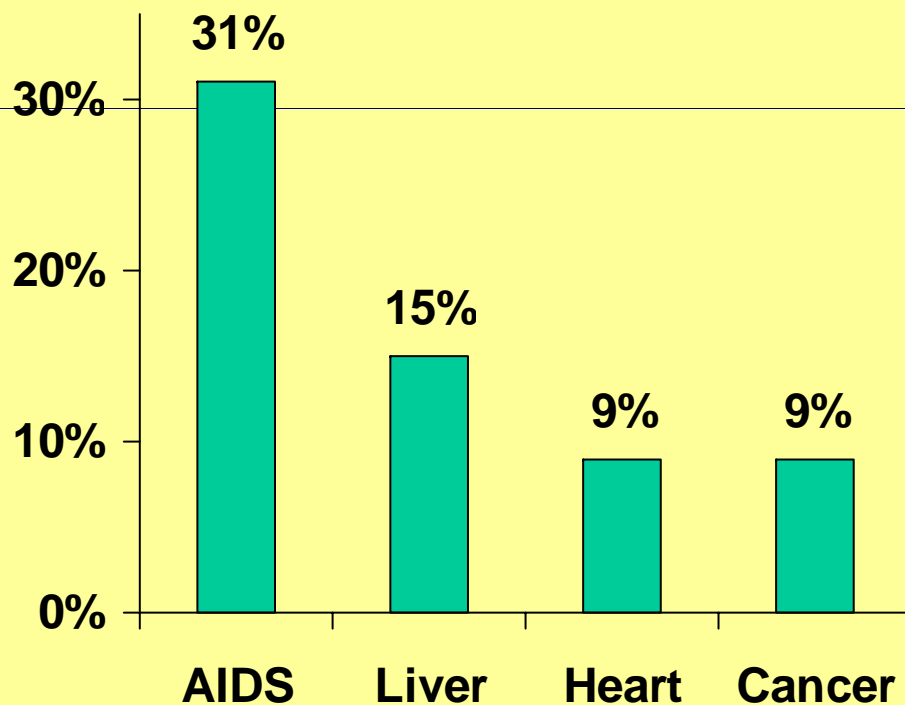
- Multicenter Cohort Study
 - 4967 HBsAG negative MSM
 - HIV: 47% (n=2346)
 - 326 HBsAG positive
 - HIV: 65% (n=213)
- HIV/HBV coinfection
 - 19-fold higher risk of liver death compared with HBV monoinfection
 - Risk of liver-related mortality increased with:
 - Alcohol consumption
 - Low nadir CD4+ cell counts
 - Antiretroviral therapy



Thio CL, et al. Lancet. 2002;360:1921-1926.

The Causes of Death Among HIV+ Persons with Access to ARVs

D.A.D: Cause of Death^[1]



Multivariate model for liver death:

HCV 6.7 (3.9 – 11.2)

HBV 3.7 (2.4 – 5.9)

HCC 82/10,000

Low CD4 1.23 (1.2 – 1.3)

IDU 2.0 (1.2 – 3.4)

Older age 1.3 (1.2 – 1.5)

1. Weber S, Arch Intern Med. 2006;166:1632-1641

Initial Evaluation of a Person With HIV Infection

- Screen for HBsAg, HBc total, HBsAb
 - If negative: vaccinate
 - If anti-HBc alone check HBV DNA
- Screen for hepatitis A
 - If anti-HAV negative vaccinate
 - Not Twinrix (need higher HBV vaccine dose)

HBV- HIV Co-infection

- Atypical serological results occur
 - Anti-HBcAg (core) alone in 57 HIV + patients
 - Sole marker for 31 mos in 98% (1/3 bx CHB)
 - ACTG: 10% anti-HBc have HBV DNA
 - WIHS: <2% women with anti-HBc had low HBV DNA
 - Higher prevalence in HCV-HIV tri-infected subjects
- If HBcAb pos, HBsAg neg, HBsAb neg
 - Test HBV DNA
 - If positive, treat as HBV
 - If negative, vaccinate

Initial Evaluation of a Person With HBV and HIV Infection

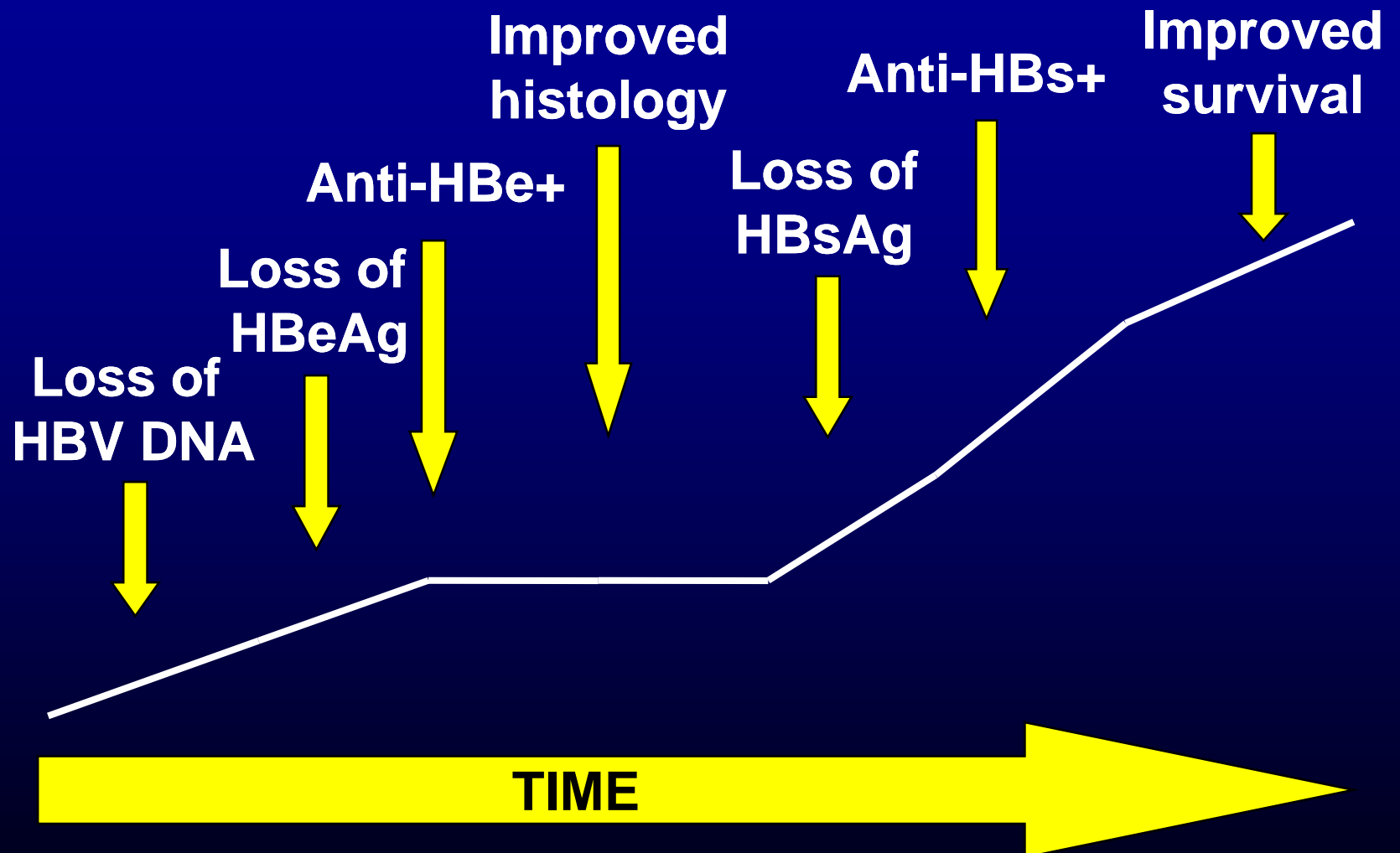
- Screen and vaccinate household / sexual contacts
- History and physical examination
- Biochemistry tests
 - Complete liver panel, CBC, INR
 - HBeAg, anti-HBe, HBV DNA
 - AFP
 - HDV in endemic areas and IDU
- Baseline liver ultrasound

HBV Vaccine Response Rate

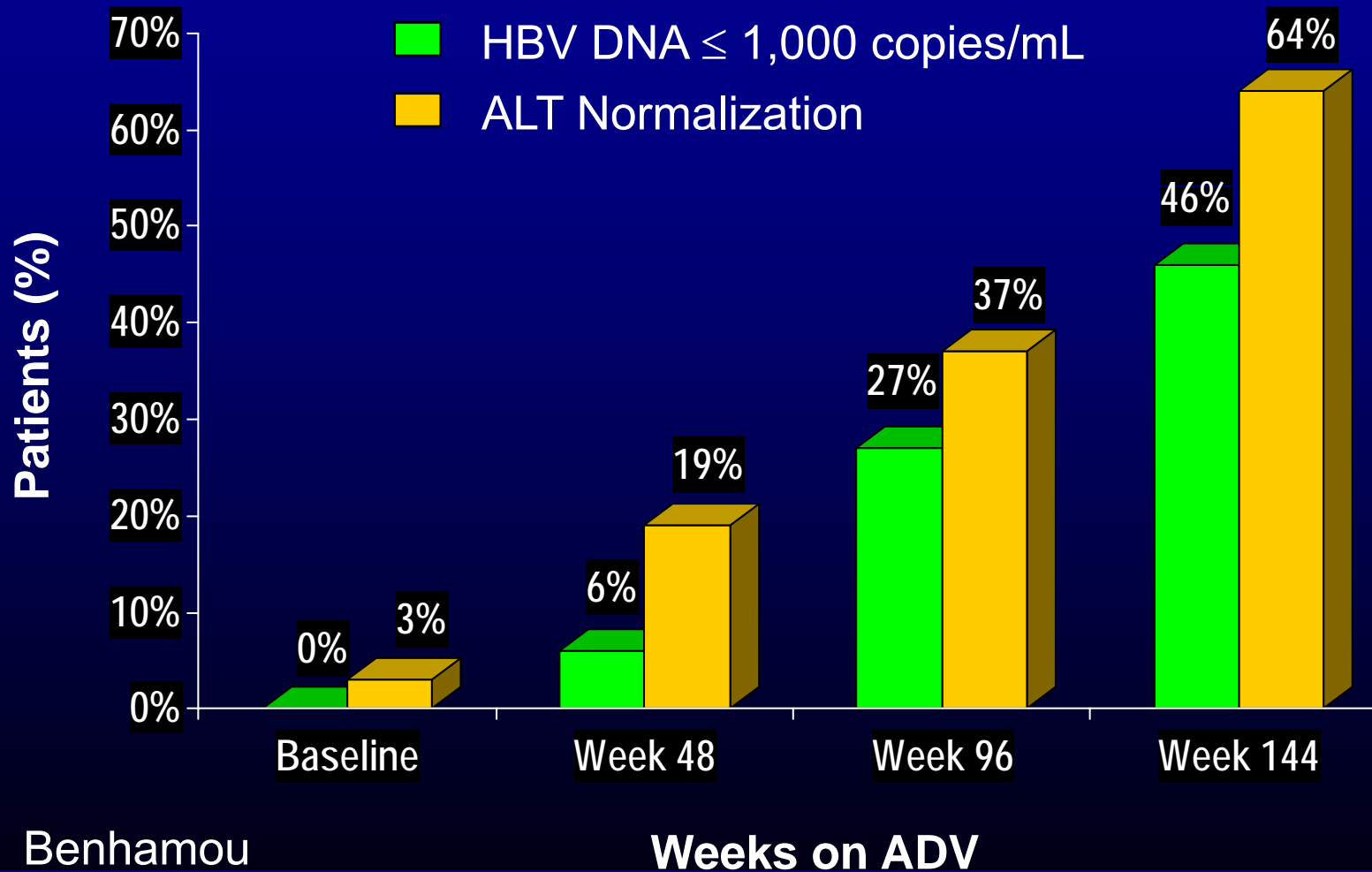
- HIV-positive patients respond less well to the HBV vaccine especially if the CD4+ cell count is < 500 cells/mm³ and lose protective antibodies faster
 - RR $> 87\%$ in HIV+ if CD4 count > 500 cells/mm³
 - RR 33% in HIV+ if CD4 count is between 200- 500 cells/mm³
- Check anti-HBs; non responders- repeat vaccination; poorly successful with double dose
- Use of adjuvants (e.g. GM-CSF- ACTG) being studied

Keet 1992; Rey 2000; Fonseca 2005;
BHIVA guidelines HIV/HBV Coinfection 2004. Available at: <http://www.bhiva.org/files/file1001581.pdf>

Therapeutic endpoints over time



HBV HIV Serum HBV DNA and ALT



Benhamou

Weeks on ADV

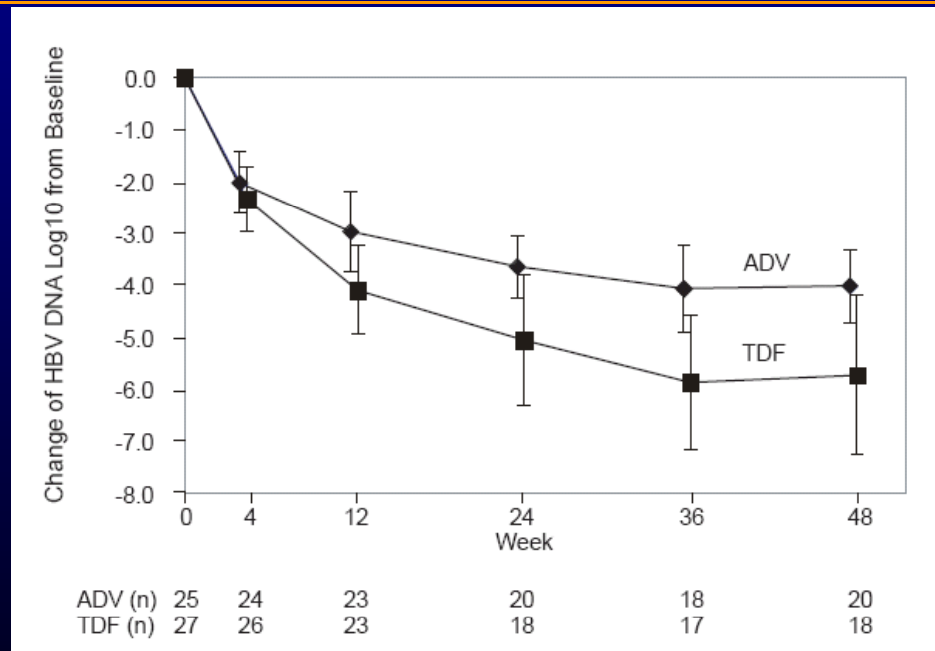
TDF vs adefovir for HBV in HIV coinfection ACTG A5127-OLD

- Double-blind, placebo-controlled study of ADF (10 mg) vs TDF (300 mg)
- Patients on stable HAART; $n=52$
- HBV DNA $>100,000$ c/mL
- HIV RNA $<10,000$ c/mL
- Early termination when endpoints met
- Genotype A \gg G
- 80% HBeAg pos

Serum HBV DNA DAVG₄₈ (log₁₀ c/mL)

	<i>n</i>	ADF	TDF	Diff	Lower CI
ITT	52	-3.12	-4.03	0.91	-0.498
Mod. ITT	47	-3.35	-4.46	1.11	-0.090
AT	41	-3.48	-4.76	1.28	0.180

Mean change in HBV
DNA from BL



Peters Hepatology 2006

Peters M, et al. 72th CROI, Boston 2006, #124

DAVG: time-weighted average change from baseline

DHHS Guidelines for HIV HBV Patients

HIV Treatment	HBV Treatment	Recommendation
Required	Not required	<ul style="list-style-type: none"> • Backbone: TDF/FTC or TDF + 3TC • Avoid use 3TC, TDF, or FTC as single HBV-active agents*
Required	Required	<ul style="list-style-type: none"> • Backbone: TDF + 3TC or TDF/FTC • Entecavir or ADV • Do not use 3TC, TDF, or FTC as single HBV-active agents*
Not required	Required	<ul style="list-style-type: none"> • Early ART • Pegylated interferon alfa does not lead to HIV or HBV resistance and may be considered • ADV may be considered but presents a theoretical risk of development of HIV resistance to TDF • Avoid use of FTC, 3TC, TDF, ETV without HAART as HIV resistance may emerge

* to avoid development of HBV-resistant mutants

DHHS Guidelines. 2007 www.aidsinfo.gov-UPDATED FOR ETV.

Agents With Activity Against HIV and HBV

HBV	WT	YMDD	HIV TREAT
Lam	S	R	Y
ADV	S	S	N
ETV	S (0.5)	S (1 mg)	N*
FTC	S	R	Y
LdT	S	R	N
TDF	S	S	Y

* FDA warning in patients not on ART

R, resistant; S, sensitive.

Entecavir

- ETV HIV/ HBV study was in patients stable HIV on ART-2004
- 2007-report of cases with ETV alone in HIV patients
 - 0.5 log₁₀ drop in HIV RNA
 - emergence of HIV mutation (M184V)
 - ETV 5'-triphos substrate for HIV-1 RT, ↓ susceptibility to M184V mutant
- More cases of M184V mutant noted, including in HIV patients never on ART or anti-HBV drug
- FDA Black Box Warning: Caution using in those not receiving ART, especially in those with 3TC experience

Thio C.NEJM 2007; Domaoal , Schinazzi and Anderson J Biol Chem 2007

HIV / HBV Treatment: Choices

HBV with ART

- Treat HBV regardless of HBV DNA level
- Nucleoside + nucleotide analogues:
 - 3TC/ FTC/ ETV + TDF/ADV (*DHHS FTC + TDF*)
 - Use in combination
- Do not stop therapy as flare will occur which can be life threatening
 - STACCATO: 5/6 STI with HBV HIV “flared”, 1 severe

Sherman, McGovern, Nguyen, Peters 2007 DHHS IDSA guidelines, AIDS 2008

Causes of Abnormal LFTs in HIV/HBV

1. Spontaneous HBV clearance (rare in HIV)
2. Reactivation of HBV with improved immune response
 - Immune reconstitution- continue therapy
 - HAART without anti-HBV therapy- add anti-HBV
 - HAART holiday: continue HBV therapy
3. Hepatotoxicity
4. Development of drug resistance e.g. lamivudine after 4 yrs 90%- use combination therapy
5. Other liver disease- e.g acute Hep A or C, NAFLD

HIV / HBV Treatment: Choices HBV alone

- consider ART therapy early
- consider ART therapy early
- consider ART therapy early

HIV / HBV Treatment: Choices HBV alone

- consider ART therapy early
- Use standard HBV monotherapy guidelines
 - HBeAg pos HBV DNA levels > 20,000 IU/mL (>10⁵ c/ml)
 - HBeAg neg HBV DNA levels > 2,000 IU/mL (>10⁴ c/ml)
 - significant fibrosis on biopsy
- Nucleoside + nucleotide analogues long term
- Combination ideal for long-term therapy
- Pegylated Interferon may be useful with high CD4+ counts (>350), high ALT, and lower HBV DNA (rare)

Sherman, McGovern, Nguyen, Peters 2007 DHHS IDSA guidelines

HIV / HBV Treatment: Choices- resource limited settings

- In HIV patients, HBV not tested prior to therapy in many settings e.g. Africa, SE Asia
- Most studies contain 3TC, d4T or ddl
- Limited (20%) use of TDF-containing regimens e.g. ACTG

New HBV drugs

- Telbivudine
 - No HIV activity
 - Studies in HIV/HBV underway
 - Not efficacious in YMDD mutants
- Clevudine
 - Licensed in Korea for monotherapy
 - Not efficacious in YMDD mutants

? Anti-HIV effect if used without ART

GLOBE: Early HBV DNA Levels and Year 1 Outcomes With Telbivudine

Year 1 outcomes linked to viral load at weeks 12 and 24

93% of HBV DNA $>3 \log_{10}$ c/mL at week 24 failed to seroconvert by year 1

Week 52 Outcome	Week 24 HBV DNA Levels, copies/mL			
	Undetectable	300 to $<3 \log_{10}$	3-4 \log_{10}	$>4 \log_{10}$
HBV DNA negative				
• HBeAg(+)	91	69	30	5
• HBeAg(-)	94	67	40	10
Normal ALT levels				
• HBeAg(+)	88	89	79	53
• HBeAg(-)	81	68	60	41
Virologic breakthrough				
• HBeAg(+)	1	4	9	14
• HBeAg(-)	0	7	17	44
HBeAg seroconversion	41	26	13	4

Monitor on therapy

- HBV and HIV genotyping with resistance at baseline
- Initiate therapy
- If no response at 12-24 weeks
- Check resistance
- Check compliance
- Add or change to other drug

Should We Treat HBV infected Pregnant Women?

- HBV monoinfected:
 - Determine if patient has active disease
 - if yes treat
- If immunotolerant (high viral load $> 10^{7-8}$) consider treating in third trimester to decrease vertical transmission
- Lamivudine has long-term safety data

Treatment of Pregnant Women with HBV and HIV

- HIV Therapy varies between countries: US:
 - All pregnant women tested for HBsAg and HIV
 - ART to prevent mother to child transmission including 2 anti-HBV drugs started asap usually Truvada and efavirenz
 - Continued until after delivery or after breast feeding if ART not indicated

Treatment of Pregnant Women with HIV and HBV

Resource limited settings:

- HBsAg not tested in many countries
- Treatment of HIV varies from
 - Combivir (3TC + AZT) and NVP (intl recs) w28 till birth
 - EFV alone at birth
- Problems: If HBV positive and no anti-HBV drugs can reactivate inactive disease with ART, increase chance of PMTC
- HBIG and HBV vaccine not given in all countries as SOC

DHHS IDSA guidelines 2007

HDV with HIV and HBV

- Rare: in 423 HIV + patients 4.7% had multiple viruses HIV, HBV, HCV, HDV- all in IDU
- most common multiple hepatitis was triple BCD
- BCD had higher cirrhosis, negative serum HBeAg and HCV PCR compared to patients with single HBV or HCV
- Patients with chronic hepatitis D showed uniform suppression of HBV and HCV replication markers

HDV HIV and HBV

HIV HBV and	26 + HDV	78 no HDV
• IDU	7.7%	1.3%
• HBV DNA (median)	4.04	5.75 log ₁₀ c/mL;
• hepatitis flares	57.7%	23.1%
• hyperbilirubinemia	34.6%	14.1%
• liver cirrhosis	26.9%	5.1%
• hepatic decomp	23.1%	5.1%
• LAM R	0%	57.1%
• death (adj HR)	5.41; (CI 1.39–23.85)	

CID 2007 Sheng

HBV HDV HCV coinfection in HIV

- HBV - HCV in 3% to 5% of HIV-individuals
 - “viral interference” seen
- Consider need for ART first
- If ART is not required, interferon therapies, which suppress both HCV and HBV, should be considered
- If IFN-based therapy for HCV has failed, treat HBV with nucleoside and nucleotide analogs

Soriano 2007

HBV-HIV Summary

- ALT does not well predict liver damage in HIV
- Many HIV medications are hepatotoxic but there are other causes of ALT elevations
- More patients have ESLD with HIV
- Atypical serology may occur
- Immune response predict outcome
- Treat if HBV viremic even if decompensated
- Always treat HBV if treating HIV
- Seroconversion to HBeAb, HBsAb rare
- Treatment of HBV alone remains a challenge