

Current Therapy in the Immunocompromised and Transplant Patients

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Immune Compromised Patient Populations

- **HBV-HIV coinfection**
- **Patients undergoing chemotherapy or immunosuppressive therapy**
- **Liver transplant recipients**

HBV-HIV Epidemiology

- **Estimated 4 million HBV-HIV coinfectd worldwide**
- **USA: 5-15% of HIV+ persons HBsAg-positive**
 - 45- 90% of HIV infected subjects have positive HBV serology
 - Aberrant serology may exist (anti-HBc alone)
- **HBV prevalence in HIV+ populations varies by cohort, country**
 - U.S.: IV drug use 7–10%, 9-17% MSM, 4-6% heterosexuals

Impact on HIV on HBV Natural History

- **Increased risk of HBV chronicity after exposure**
- **Increased HBV replication**
 - Viral load affects transmission risk
 - Viral load associated with risk of cirrhosis and HCC
- **Decreased anti-HBe and anti-HBs seroconversion**
- **More frequent finding of “occult” HBV infection**
 - 60-90% anti-HBcAg positive
 - 4- 40% have HBV DNA in serum
- **Increased risk of cirrhosis and hepatoma**

HBV-HIV Coinfection

Who Should be Treated?

1. Persons with elevated HBV DNA levels plus

- **Elevated ALT, AST and/or**
- **Necroinflammation on biopsy (not required but may be useful)**

2. If cirrhosis, regardless of disease activity

3. Controversial areas

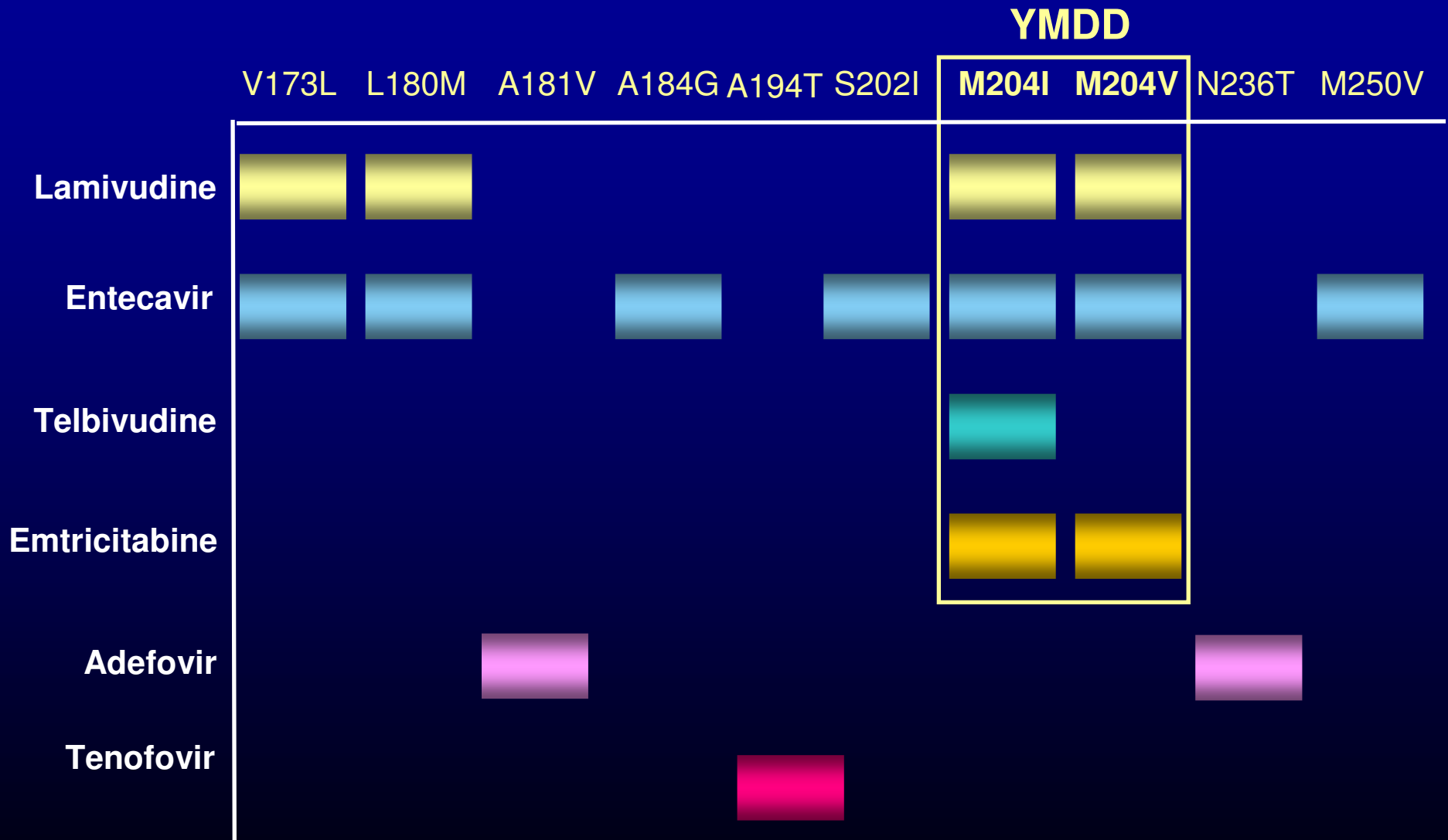
- **Whether anti-HBV treatment must always be initiated when HIV therapy is started**
- **Whether patients with high HBV DNA levels but no indicators of active disease should be treated for HBV**

HBV and HIV Therapies

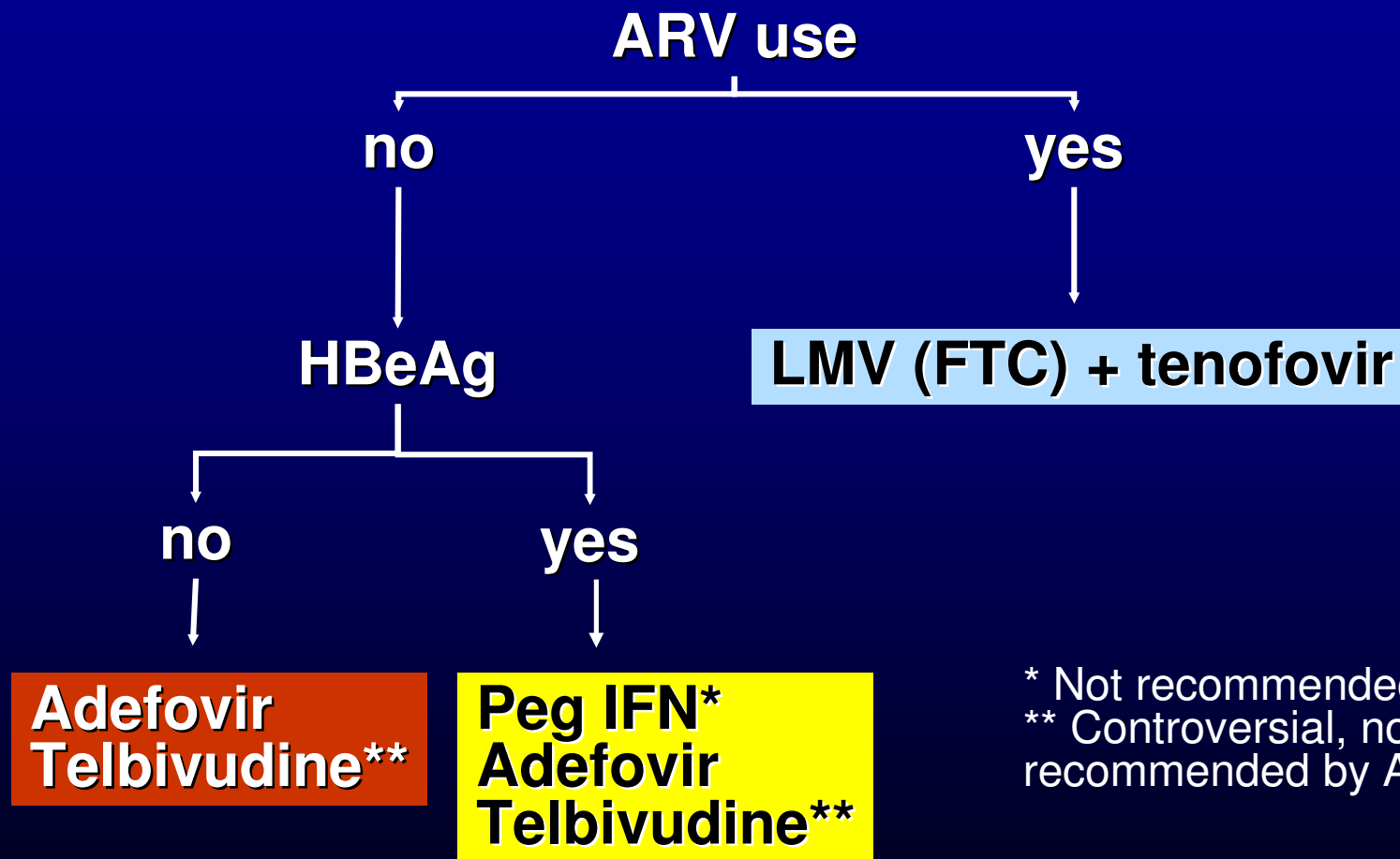
	WT	YMDD	HIV TREAT
Interferon	S	S	N
Lamivudine	S	R	Y
Adefovir	S	S	N
Entecavir	S (0.5)	S (1 mg)	N*§
Telbivudine	S	R	N*
Emtricitabine	S	R	Y
Tenofovir	S	S	Y

* Reports of HIV viral load decline in HIV RNA § Reports of emergence of HIV mutation (M184V)

Cross Resistance with HBV Drugs



Preferred Anti-HBV Agents in Drug-Naive Coinfected Patients

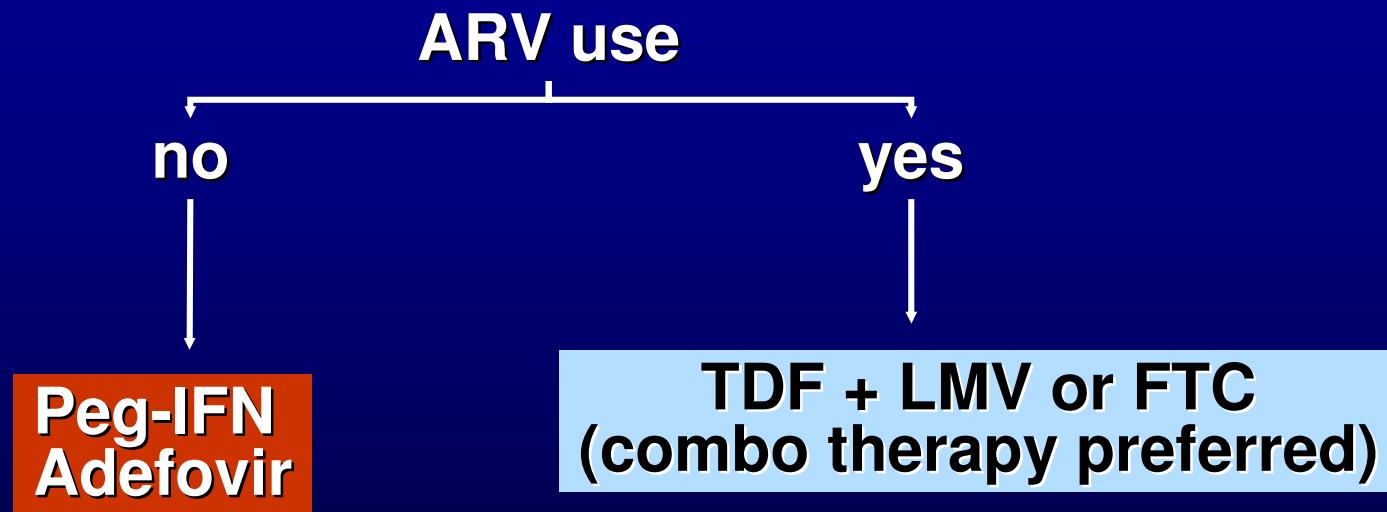


* Not recommended if cirrhosis
** Controversial, not recommended by AASLD

Early HAART Initiation

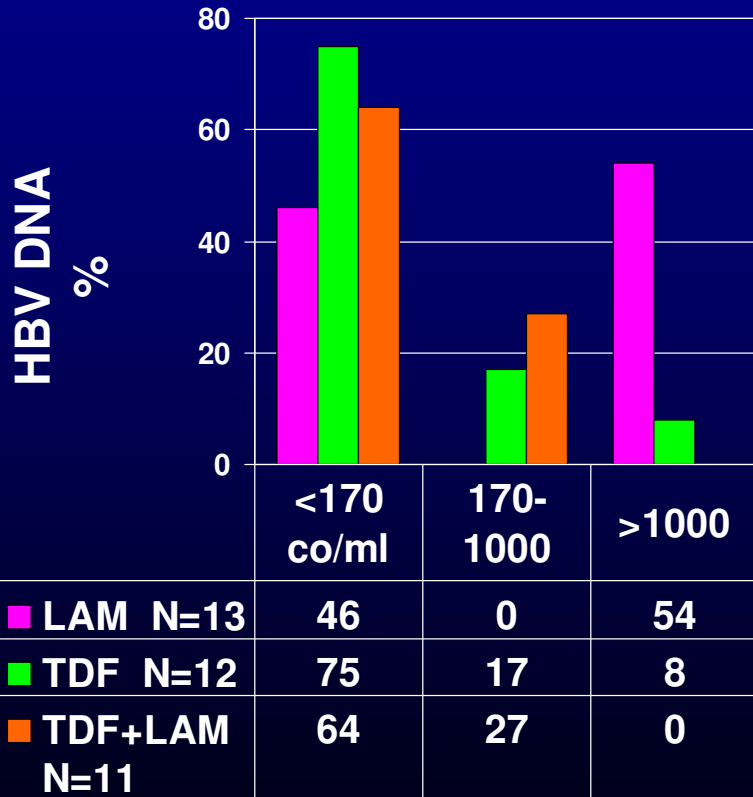
Adapted from
HBV Consensus Conference 2008

Preferred Anti-HBV Agents in Lamivudine-R Coinfected Patients



Combination TDF+LAM vs LAM and TDF Monotherapies

HBV-HIV coinfectd, Rx naïve
48 wk results

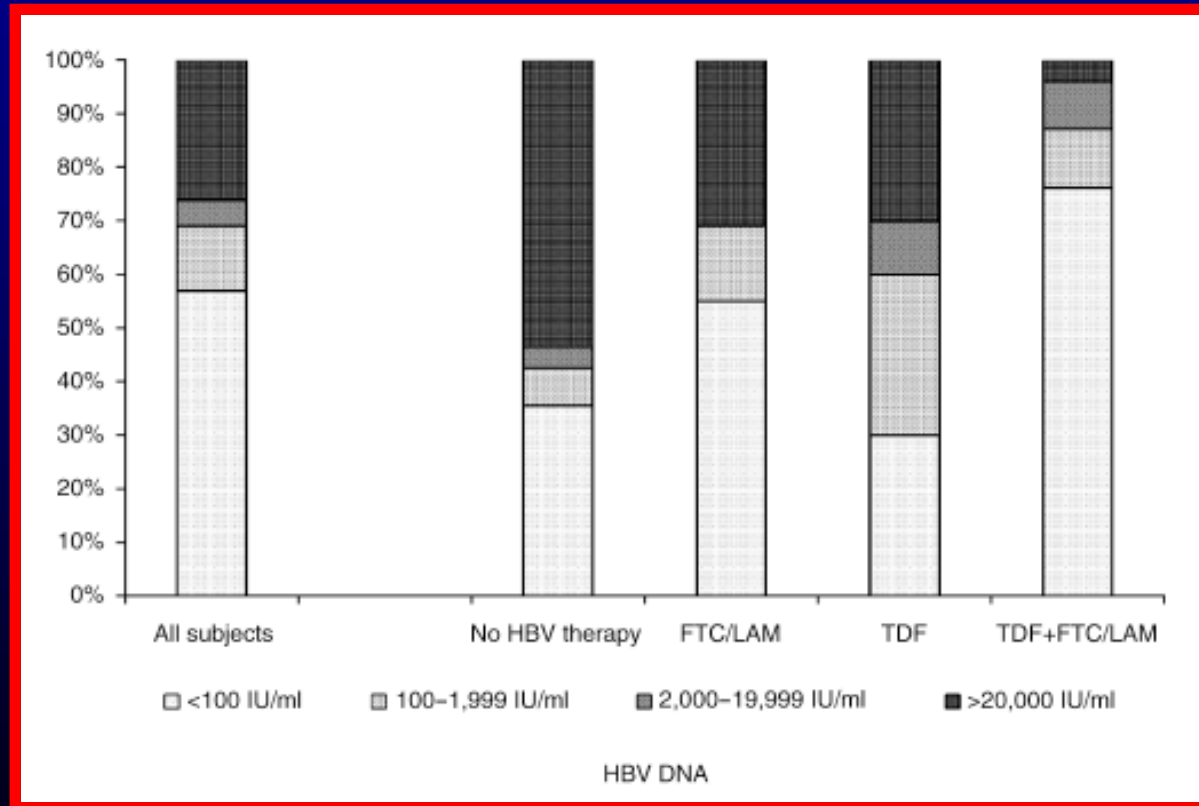


Other Endpoints:

- **HBeAg seroconversion:**
 - LAM = 1/9
 - TDF = 1/6
 - TDF+LAM = 3/7
- **HBsAg loss:**
 - 1 per group
- **Drug resistance**
 - LAM = 17%
 - TDF and TDF/LAM = 0

HBV DNA Suppression Highest in Patients on Combination Therapy

- Cross-sectional study
- 122 US & Australian HIV-HBV coinfecting patients
- 98% LMV experienced



Monitoring on Therapy

- **Flares of ALT during treatment**
 - Occur in up to 20% of patients
 - Generally well-tolerated but may be risk if underlying advanced fibrosis
- **Lack of or suboptimal response at 12-24 weeks**
 - Check for resistance
 - Check compliance
 - Add or change to other drug
- **ART interruptions**
 - Risk of HBV flares if ART therapy interrupted and without provision of alternative HBV drug
 - Alternatives limited - adefovir and possibly telbivudine

Tenofovir and Nephrotoxicity HIV Experience

Review of 27 cases of HIV-infected patients on TDF-containing ART

Characteristic	N=27
Mean Age	45.5 (range, 31–65)
Mean duration of TDF therapy (mos)	11 (range, 1–29)
Mean increase in serum creatinine	0.9–3.9 mg/dL
Mean creatinine level during recovery	1.2 mg/dL

- ARF resolved in 22 of 27 patients after discontinuation of TDF therapy
- No identifiable pattern in terms of pre-existing risk factors for renal dysfunction in these patients other than that they all had HIV
- Frequent monitoring for renal dysfunction is recommended

HBV-HIV Treatment Summary

- **Treat all cirrhotics**
- **Always treat HBV if treating HIV**
- **Always treat HBV if “active” (elevated ALT, or significant histologic disease)**
- **If treating HBV alone:**
 - Pegylated interferon an option for HBeAg+patient without cirrhosis
 - Adefovir for HBeAg-negative patient
- **If treating HBV and HIV:**
 - If wild-type TDF alone is option, but combination recommended if LMV resistant
- **Monitor for renal toxicity if using TDF- containing regimen**

HBV Infection and Chemotherapy

HBV Infection in Patients Receiving Chemotherapy & Immunosuppressives

■ 2008 CDC Guideline for HBV Screening

- Persons needing immunosuppressive therapy (chemotherapy, immunosuppression for rheumatologic or gastroenterologic disorders)

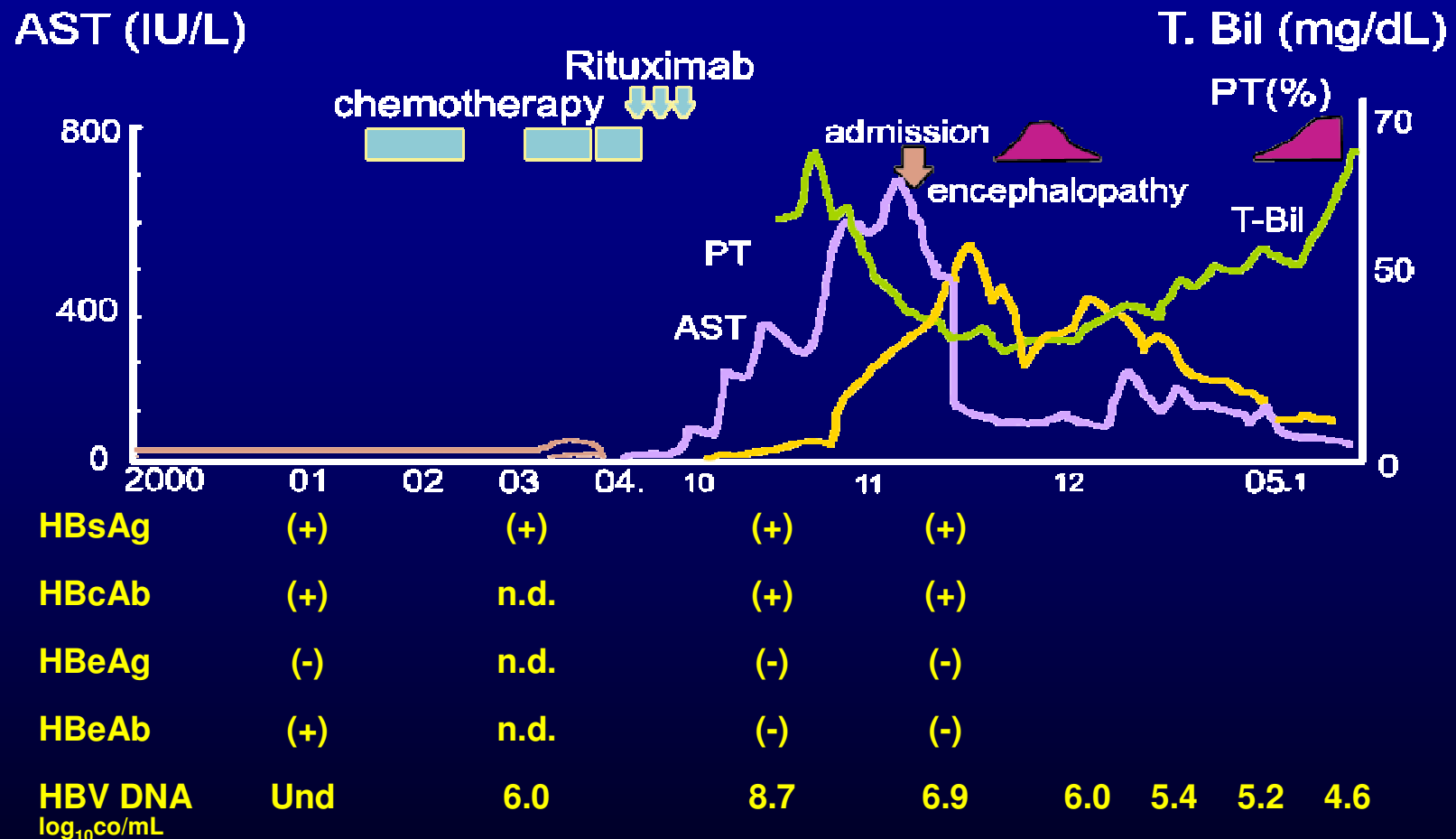
■ Chemotherapy and immunosuppression associated with:

- Aggravate chronic HBV infection: ALT flares
- Reactivate inactive disease
- Can cause fulminant liver failure.... rarely

■ Risk groups:

- HBsAg(+) --> rates of reactivation range from 30-80%
- HBsAg(-) but anti-HBc(+) --> rates of reactivation = 3-4%

Typical Course of HBV Reactivation With Chemotherapy



“Risk” is highest when immune suppressive therapy is withdrawn

Factors Linked with Risk of HBV “Flare” During Chemotherapy

- **HBV DNA levels**
 - Higher risk of flare when serum HBV DNA is detectable
 - High HBV DNA level before chemotherapy predictive in some studies
- **Age, sex, HBeAg concentration, baseline liver enzymes not consistently predictive**
- **Type of chemotherapy**
 - Some suggest rituximab-containing chemotherapy increases the risk
- **Anti-HBs does not affect risk in those HBsAg-negative and anti-HBc positive only**

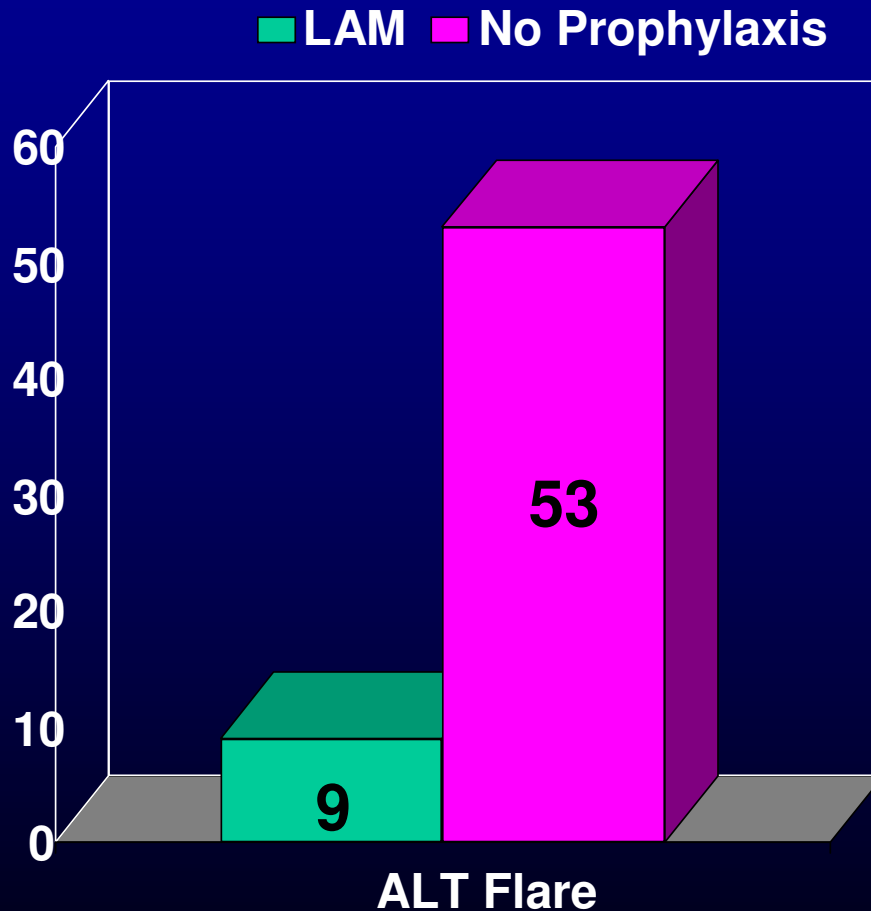
Hui CK, *Gastroenterology* 2006;131:59-68
Millonig et al. *World J Gastroenterol.* 2006;12(6):974-976.
Yeo et al. *Br J Cancer.* 2004;90(7):1306-1311.
Yeo et al. *Clin Oncol.* 2009 Feb 1;27(4):605-11
Lau et al. *Gut.* 2005;54(11):1597-1603.

Prophylactic Antiviral Therapy in Patients Receiving Chemotherapy

- **11 clinical studies, N=173 treated with lamivudine**
 - 1 RCT, 5 prospective studies with historical controls, 5 prospective with no controls
 - 6 hematologic malignancies, 3 breast cancer, 1 nasopharyngeal cancer
- **Lamivudine treatment regimen**
 - 100 mg QD (pediatric: 3 mg/kg)
 - Initiate 1 to 19 days before administering chemotherapy (majority, 7 days)
 - Discontinue 28 to 365 days after last dose of chemotherapy

Efficacy of Lamivudine Prophylaxis

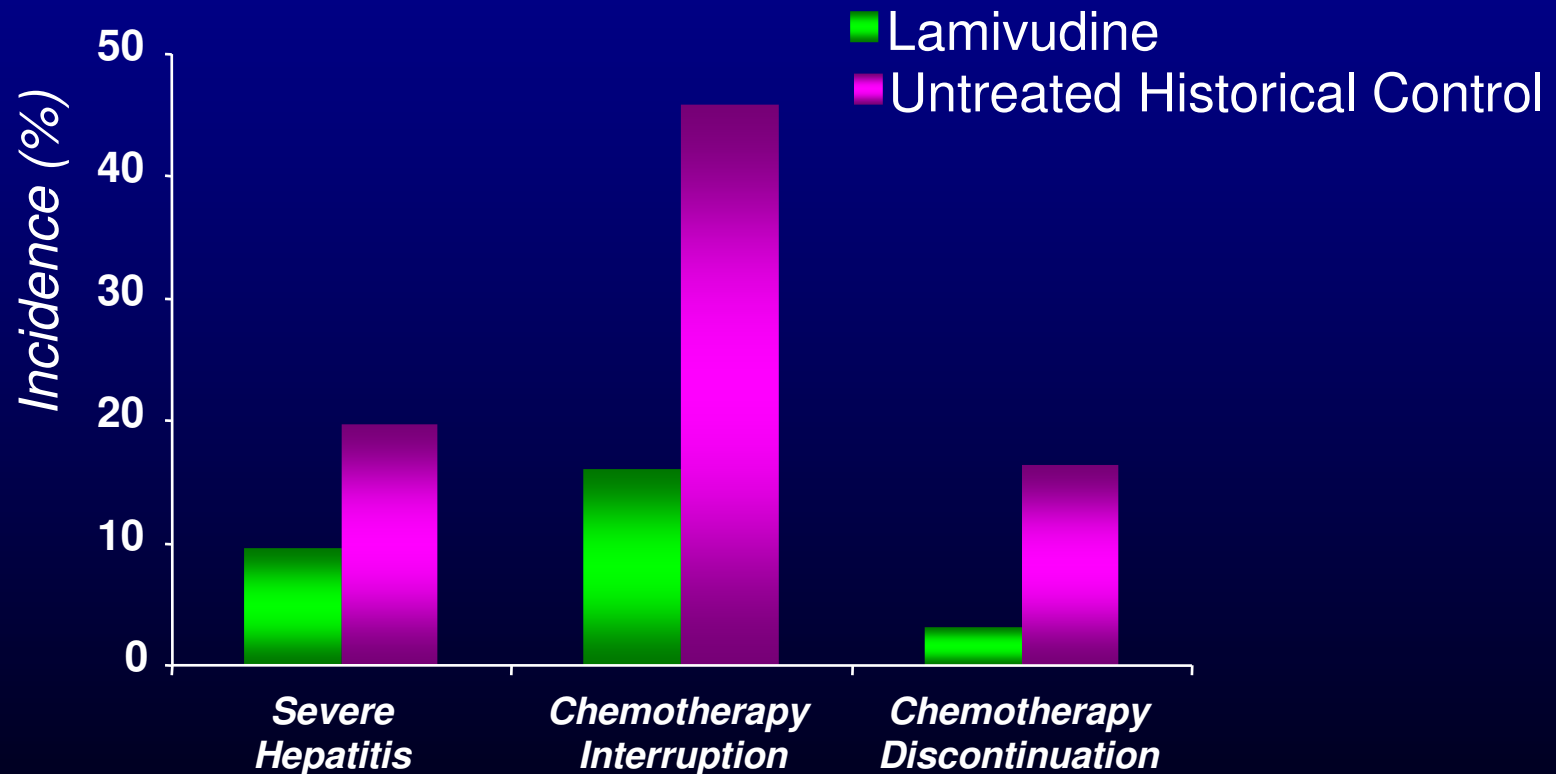
Systematic Review



- **Endpoint = ALT flare defined by ALT increase ≥ 3 -fold**
- **80% reduction in ALT flares in LAM prophylaxis group**
- **Consistent effects across controlled studies**

Other Benefits of Prophylactic Antiviral Therapy

Effect on Chemotherapy Administration



Treatment Recommendations in HBsAg+ Patient

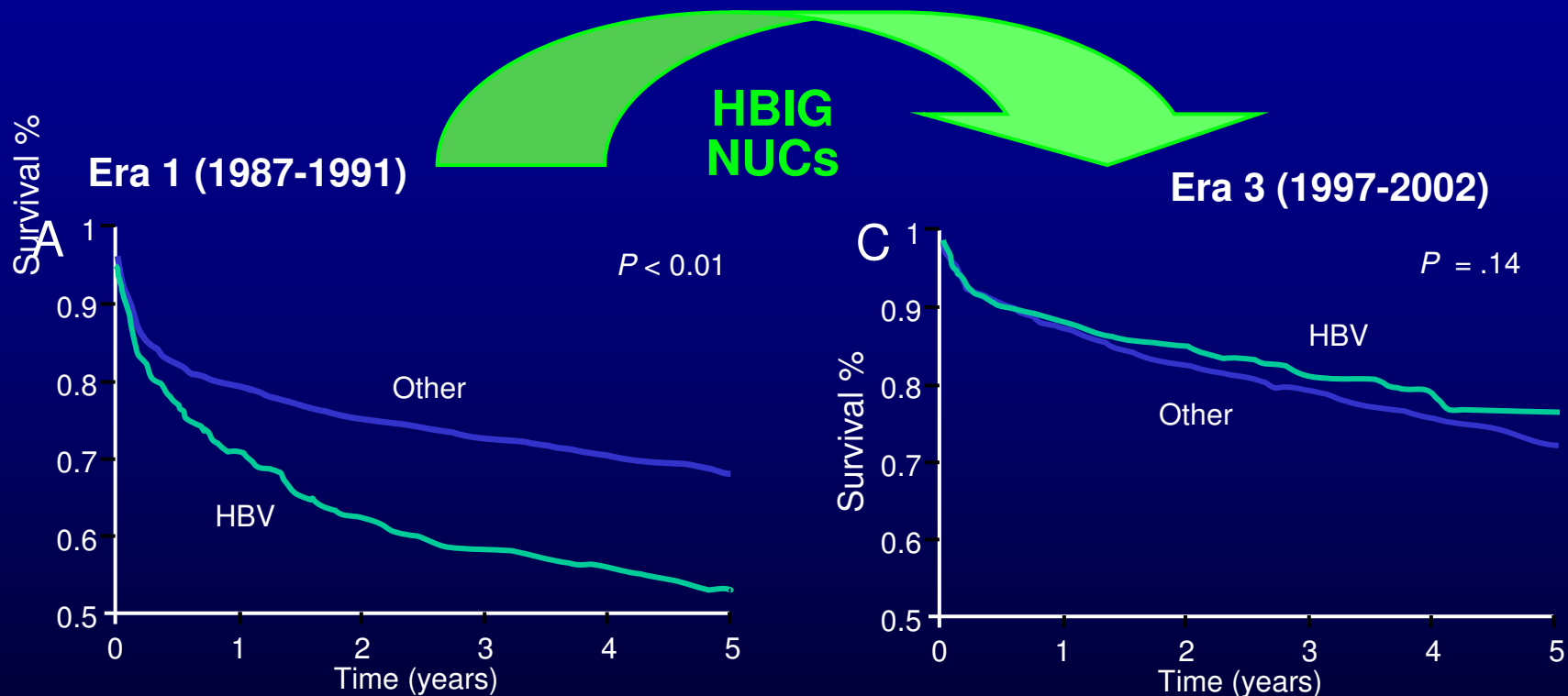
- **What Drugs?**
 - Decision be based on anticipated duration of therapy
 - Choose drug with low likelihood of resistance
 - Previous antiviral history may modify choices
 - Consider NUC toxicities -- rare but if occurs, may limit ability to take chemotherapy, immunosuppression
- **When to Start?**
 - 1 week prior or concomitant with chemo or immune modulatory therapy
- **When to Stop?**
 - If HBV DNA elevated at baseline, longer-term treatment may be indicated (usual treatment endpoints)
 - If HBV DNA low at baseline (<2000 IU/ml), treated for 6-12 months post-chemotherapy

Treatment in Anti-HBc Positive Patient Receiving Chemotherapy

- **Prophylactic antiviral therapy: not routinely recommended as risk of reactivation is low**
 - However, if unable to do close monitoring of HBV DNA levels, prophylaxis safest strategy
- **Preemptive approach:**
 - Monitor HBV DNA levels every 2 to 4 weeks; if \uparrow by $2 \log_{10}$, start antiviral prophylaxis
- **Use same principles for choice of antivirals as HBsAg+ patient**
- **Continue to monitor for at least 6 months after last dose of chemotherapy**

HBV Infection in Transplant Recipients

Liver Transplantation and HBV Progress in Past Decade



- 5-year survival rates ~50%
- Many centers consider HBV to be contraindication for LT

- 5-year survival rates as good or better than for other indications for LT

HBV Prophylaxis in Liver Transplant Recipients

- **HBIG plus antiviral agents is “standard of practice” in most LT programs currently¹**
 - High efficacy ($\geq 90\%$) in preventing HBV recurrence with long-term HBIG plus LAM or ADV therapy ²⁻⁶
 - Large series of prophylaxis using HBIG plus other antivirals are lacking but results predicted to be as good
- **Limitations related to HBIG use:**
 - Need for parenteral administration
 - Cost
 - Availability

¹Terrault, Roche & Samuel, *Liver Transpl* 2005

²Han S, *Liver Transpl* 2003

³Anderson R, *Clin Transpl* 2007

⁴Dickson R, *Liver Transpl* 2006

⁵Marzano A, *Liver Transpl* 2005

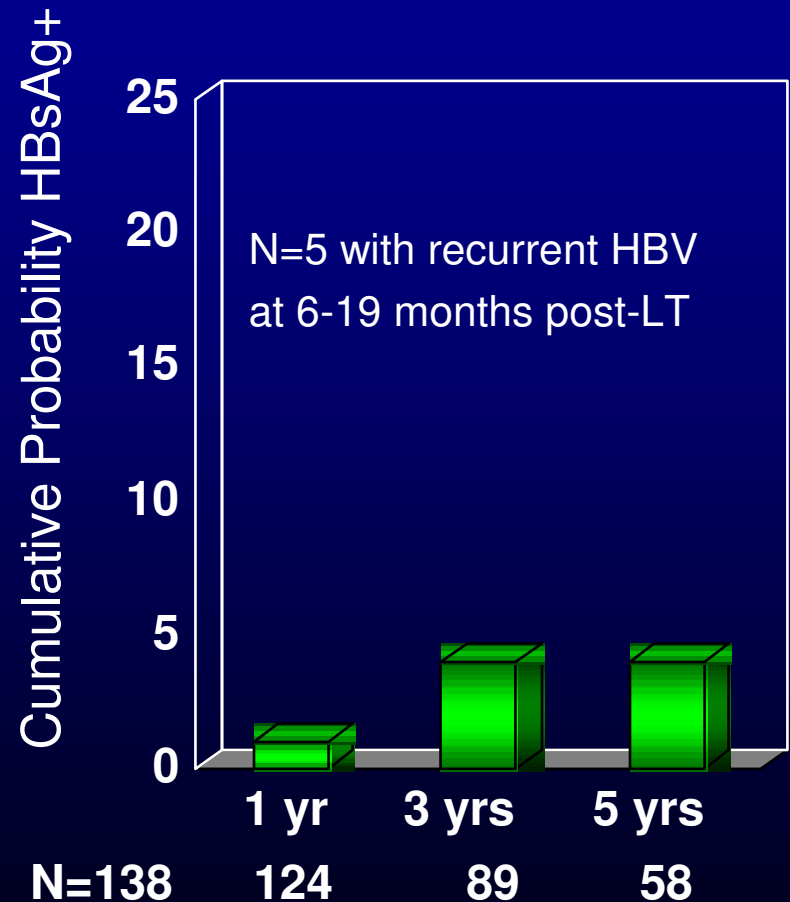
⁶Gane E, *Gastroenterol* 2007

HBIG Minimization Strategies

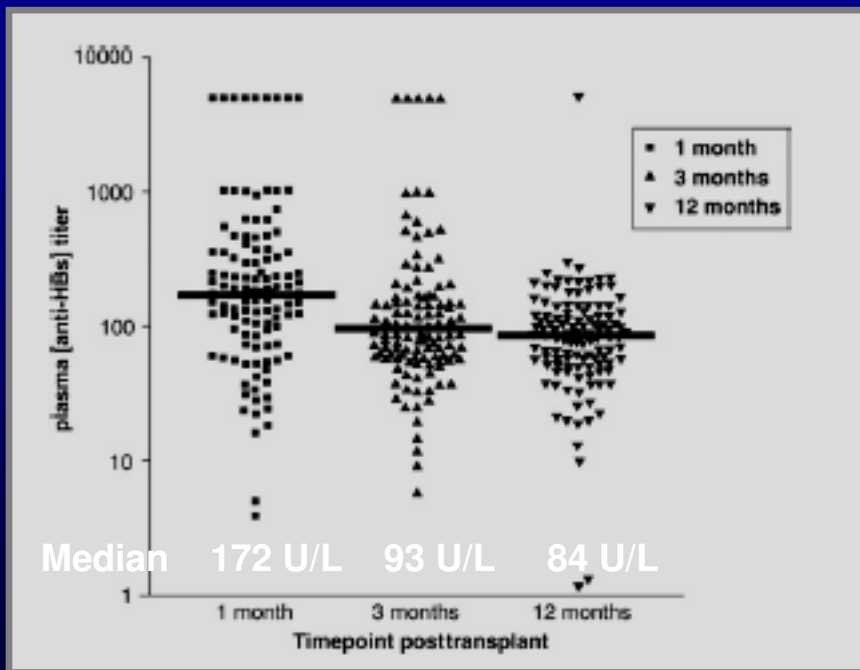
- **Low-dose HBIG and NUC**
 - LMV plus low HBIG highly effective
 - Other NUCs plus low dose HBIG also predicted to be highly effective
- **HBIG discontinuation with continued long-term NUC**
 - Low failure rate is short-term
 - Pre-transplant HBV DNA levels may predict risk
- **HBIG elimination**
 - Use combination NUCs -- no published data yet

Low Dose HBIG and Lamivudine Prophylaxis

- N=147 LT recipients from 1996-2004
- Pre: LAM 100mg daily pre-LT if HBV DNA >100 cop/ml (median 92 d) and continued post-LT
 - 8 LAM-R on combo LAM/ADV
 - Median HBV DNA at LT <300 co/ml (range <300-10⁶)
- Post: LAM + HBIG 800 IM daily X 1 wk, then monthly (except 1 center - 400 IU)
- Median follow-up = 5.1 years



Low Dose HBIG and Lamivudine Prophylaxis



Anti-HBs levels post-LT

Predictors of HBV Recurrence*

- HBV DNA level prior to LAM ($\geq 10^6$ copies/ml)
 - HR = 1.003, p=0.04
- Anti-HBs titer at 12 months (IU/L)
 - HR= 0.975, p=0.06

*Univariate analysis

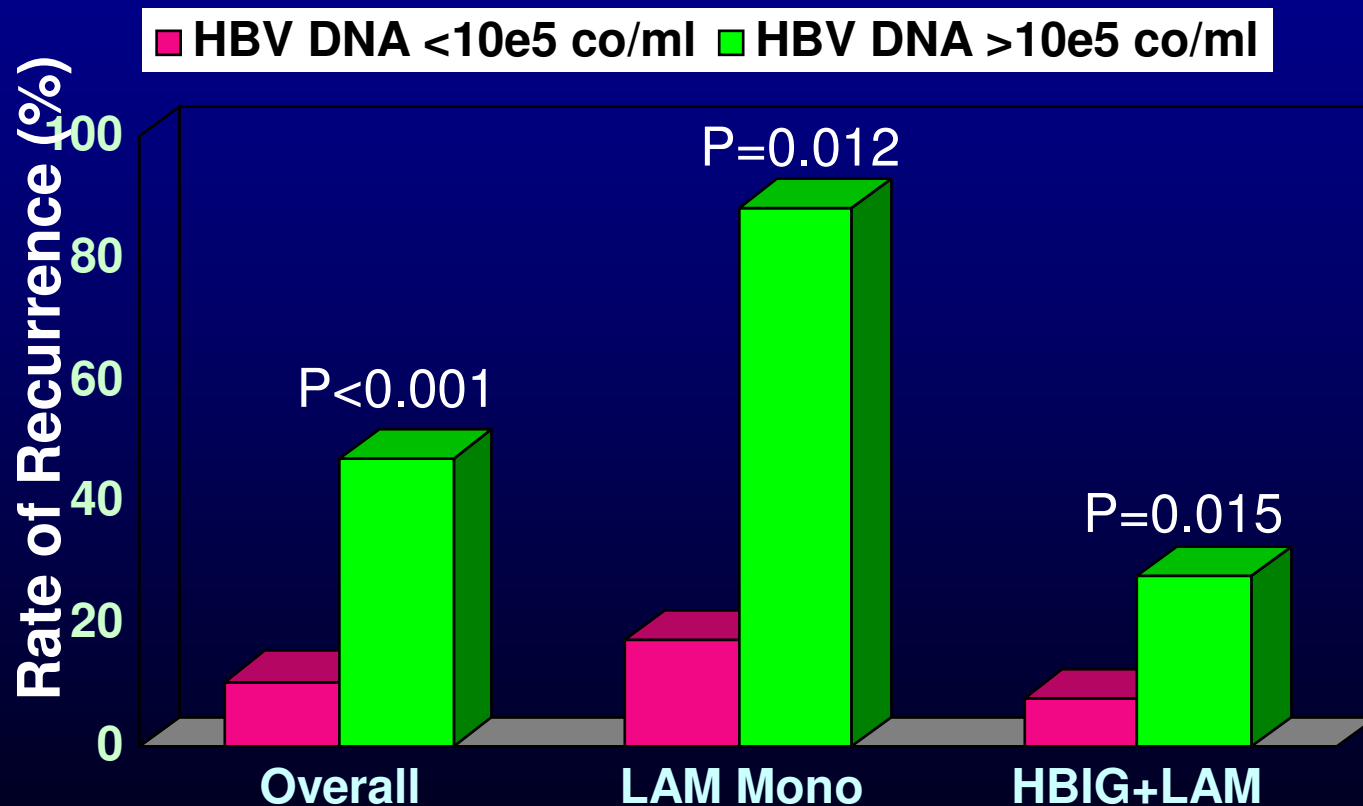
Limited Duration HBIG Plus Long-Term Lamivudine

	N	Duration of HBIG	Median Duration Off HBIG	% with Recurrent HBV	
				1-2 years	3-5 years
Buti Hepatology 2005: A491	14	1 mo	59 mos	0%	14%
Wang Hepatology 2003 A	50	6-12 mos	39 mos	4%	13%
Neff Liver Transpl 2004:10:1372	41	6 mos	64 mos NR 17 mos R	0% NR 13% R	0% (NR) 22% (R)
Wong Liver Transpl 2007:13:374	21	Variable (median 26 mos)	40 mos	0%	9%

Non-replicator = HBV DNA <10⁵ copies/ml

Antivirals versus HBIG + Antivirals Lamivudine

Mean follow-up = 20 mos



LAM mono N=51
Combo N=114

Zheng S et al, Liver Transplant 2006;12:253-8

Factors Associated with Prophylaxis Failure

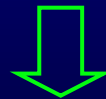
- **HBV DNA levels at time of treatment initiation**
 - HBV DNA levels $>10^5$ copies/ml associated with increased risk of prophylaxis failure
 - Non-replicators (HBV DNA $\leq 10^5$ copies/mL) have low rate of prophylaxis failure regardless of therapy used
- **Presence of drug-resistant HBV**
 - Risk related to uncontrolled drug-resistant viremia at time of LT and availability of alternative drugs with cross-resistance
- **Non-adherence**
 - Poorly quantified but frequently reported among “prophylaxis failures”

Summary

Prophylaxis Tailored to Pre-Transplant Replication Parameters

High Risk

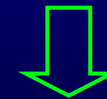
- HBV DNA $\geq 10^4$ IU/ml
- Drug-resistant HBV
- HDV coinfection
- Risks for non-adherence



- Combination HBIG and NUCs long-term
- Include combination NUCs with known efficacy against drug-resistant HBV

Low Risk

- HBV DNA $< 10^4$ IU/ml
- Wild-type HBV
- Compliant



- Candidates for HBIG minimization
- Combination NUCs long-term

Management of Recurrent HBV Disease in Liver Transplant Patients

- **Multi-drug resistant HBV common**
 - Historical use of sequential anti-HBV agents
 - Treatment options for patients with drug resistant HBV disease more limited than for patients without prior drug exposures
- **Disease progression more rapid post-LT**
 - Periods of uncontrolled infection --> greater risk of fibrosis progression
 - Case reports of acute deterioration with emergence of resistance--> surveillance for resistance is important

Prevention better than dealing with recurrent HBV disease