

HBV Treatment in HIV

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Rationale to Treat HBV in the HIV-infected Patient

- Increased liver-related morbidity and mortality in coinfecting patients¹
- Risk of HBV-related flares related to the immune reconstitution syndrome (IRIS)²

1. Thio CL, et al. *Lancet*. 2002;360:1921-6.

2. Carr A et al. *Lancet*. 1997;349:995-6.

All Boils Down to...

- ... the need for sustained suppression of HBV DNA
- But... we are unable to use the word “cure”
- ...and low rates of HBeAg loss and/or HBeAg seroconversion in HIV-infected patients infers long-term therapy for the vast majority.

Approach to HBV Therapy in the HIV-infected Patient

- Requires thoughtful clinical decision-making and consideration of whether or not the patient also needs treatment for HIV
- **Drugs with dual HIV/HBV activity:**
 - Lamivudine, emtricitabine, tenofovir, entecavir
- **Drugs that do not induce HIV resistance:**
 - PEG-IFN, adefovir (at 10-mg dose)
 - ?Telbivudine – limited in vitro data only

Limitations in Treatment Data in HIV/HBV Coinfected Patients

- **Few controlled treatment trials in HIV/HBV patients have been published**
- **Much of what is recommended is based on**
 - Large studies in patients with hepatitis B alone
 - Small uncontrolled studies in HIV/HBV coinfecting patients
 - Retrospective analysis of subsets of HIV/HBV coinfecting patients in treatment trials for HIV infection (eg, lamivudine, tenofovir)

Who/When to Treat? What Drug to Use?

*A moving target even in
patients with HBV alone. ...*

AASLD 2007 Guidelines

- Emphasis on ALT abnormalities ($>2\times$ ULN) and specific thresholds of HBV DNA for primary evaluation and treatment
- Definitions of virologic response and virologic failure
- Guidance on possible first-line therapies

HBV DNA and Risk of HCC

Cumulative Incidence of Hepatocellular Carcinoma by HBV DNA Level at Study Entry

Level of HBV DNA, copies/mL	Seronegative for HBeAg, %			
	Cumulative Incidence of Hepatocellular Carcinoma (N=3653)*	Only (n=3088)	Normal ALT Level (n=2966)	Normal ALT Level and No Liver Cirrhosis (n=2925)
<300 (Undetectable)	1.30	1.20	0.98	0.74
300 – 999	1.37	1.21	1.25	0.89
10,000 – 99,999	3.57	3.68	3.42	3.15
100,000 – 999,999	12.17	9.54	8.55	7.96
≥1 million	14.89	17.88	19.51	13.50

ALT=alanine aminotransferase; HBV=hepatitis B virus.

*At the end of the 13th year follow-up.

Chen CJ, et al. *JAMA*. 2006;295:65-73.

HBV DNA and Risk of Cirrhosis

Incidence of Cirrhosis by HBV-DNA Level

Serum HBV-DNA Level, copies/mL	Sample Size	Person-years of Follow-up Evaluation	Cirrhosis Cases	Incidence (per 100,000 person-years)	Adjusted relative Risk (95% confidence interval)
Undetectable	869	10,048.8	34	338.8	Reference
$300 - 9.9 \times 10^3$	1150	13,259.0	57	429.9	1.4 (0.9 - 2.2)
$1.0 - 9.9 \times 10^4$	628	7105.5	55	774.0	2.5 (1.6 - 3.8)
$1.0 - 9.9 \times 10^5$	333	3460.0	65	1878.6	5.9 (3.9 - 9.0)
$\geq 1.0 \times 10^6$	602	6164.3	154	2498.3	9.8 (6.7 - 14.4)

“Roadmap for Management of HBV”

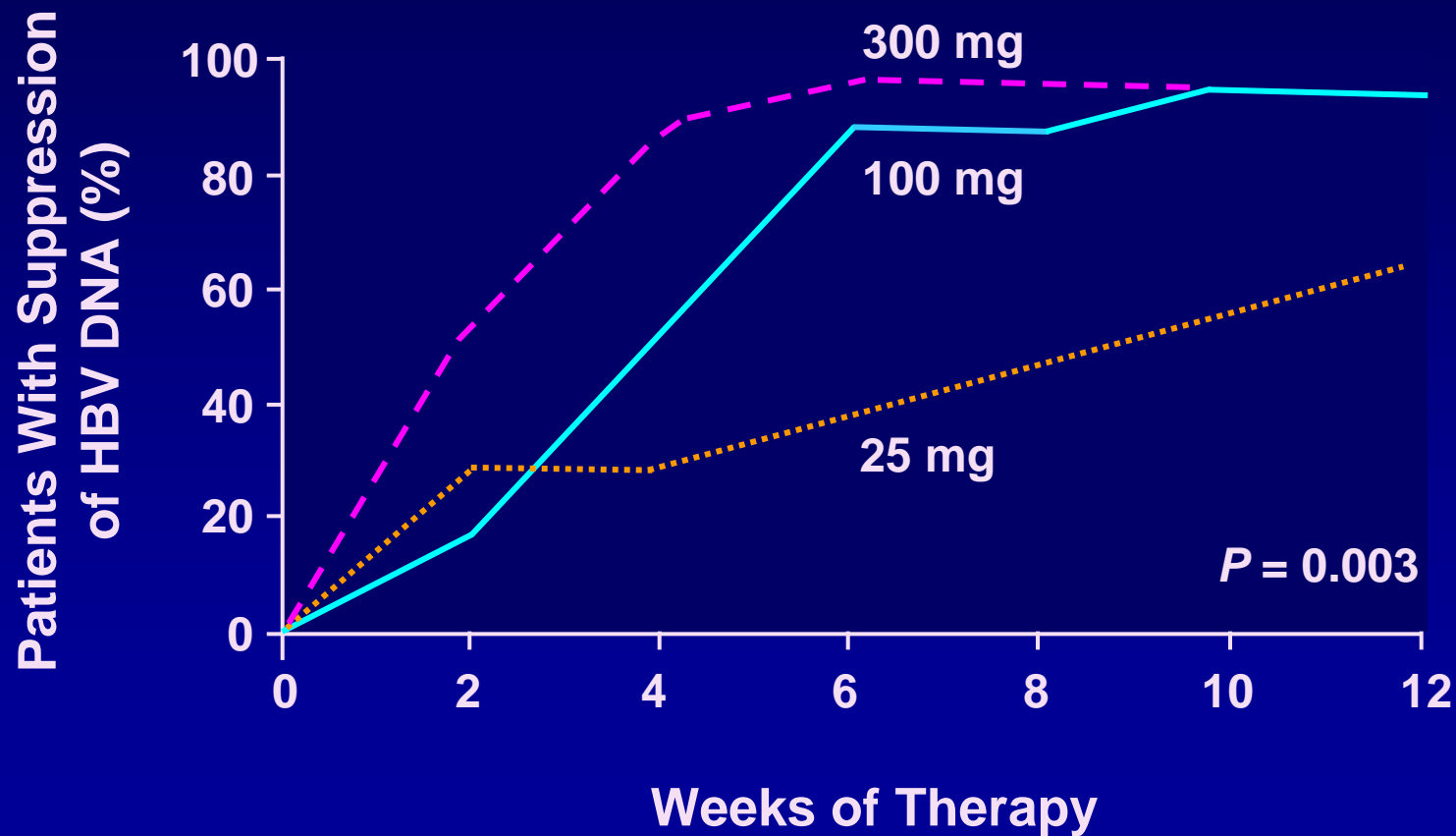
- Emphasis on HBV viral load
- What to do in face of virologic failure?
 - Which drug to add?
 - Which drug to switch to?
- NIH conference pending October 2008

Data on HBV Agents in HIV-infected Patients

Lamivudine

What have we learned?

Suppression of HBV DNA With LAM After 12 Weeks



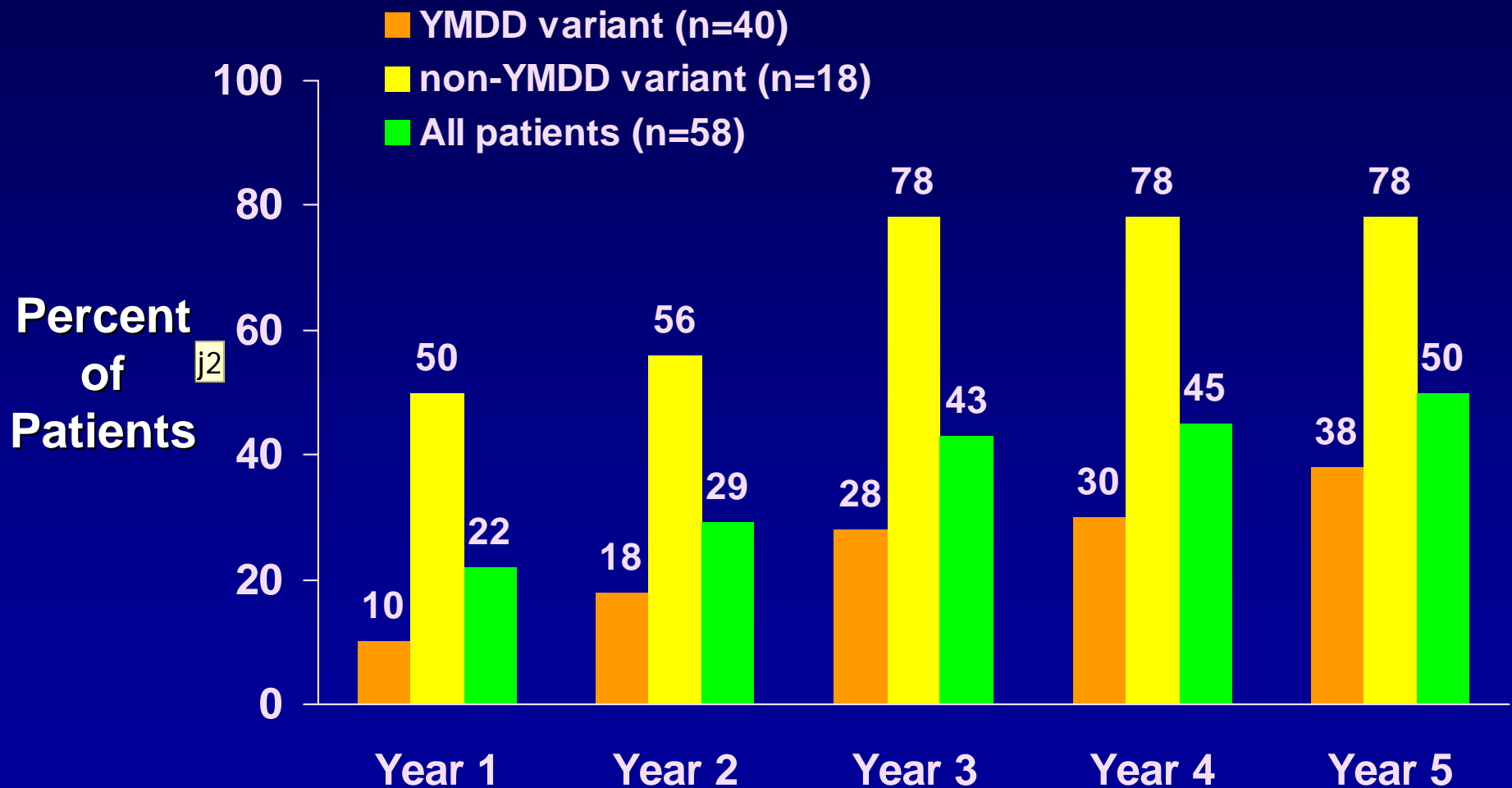
Lamivudine-resistant YMDD Variants in Patients With HBV Alone

Incidence of YMDD Variants

Year	1	2	3	4	5
% of patients	14	30	50	67	69

- LAM-R mutants common (L180M and M204V/I)
- HBV DNA and ALT levels usually below pre-treatment values
- Histologic deterioration after 3 years
- Flares may follow YMDD variant emergence

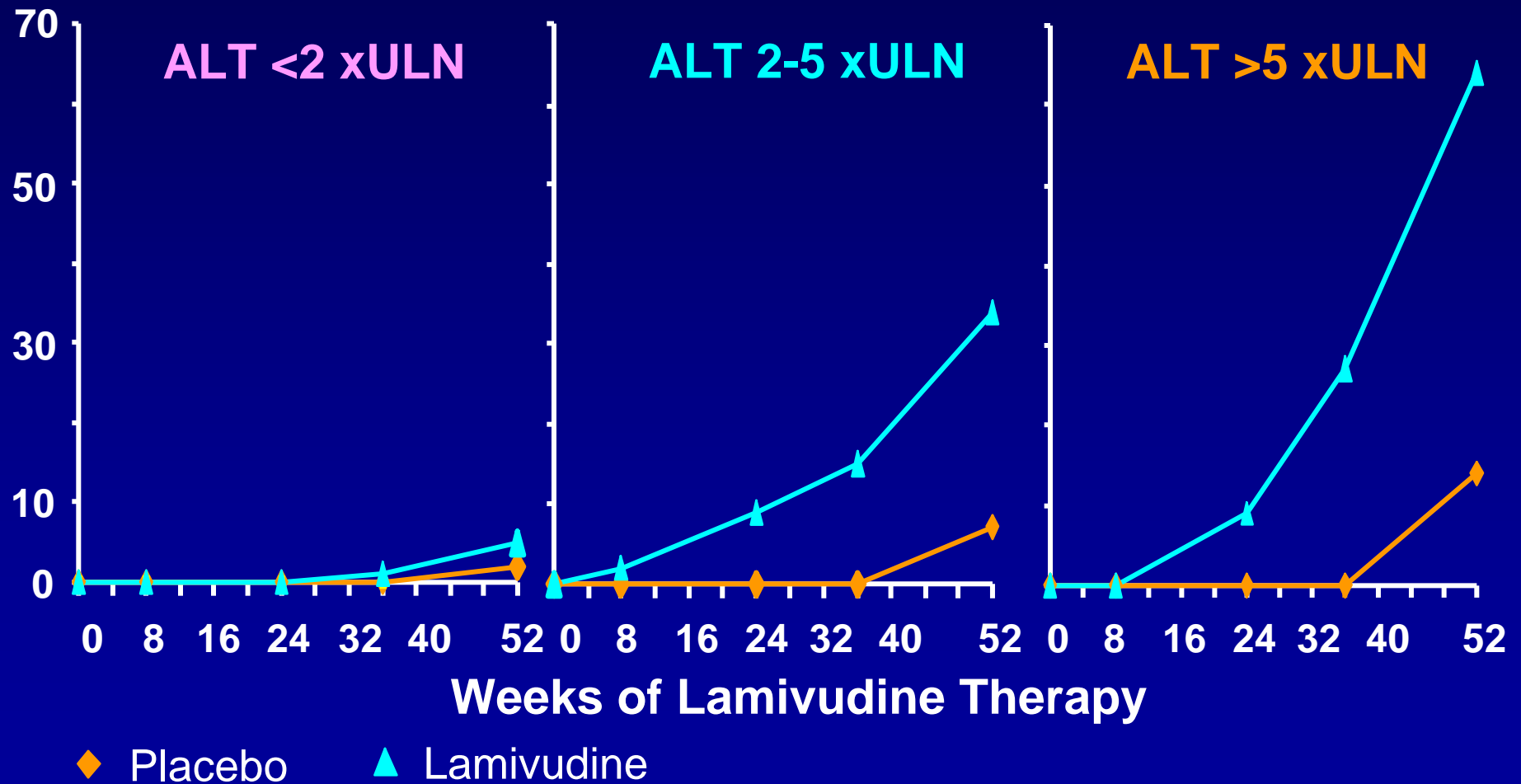
Effect of YMDD-VARIANT on HBeAg Seroconversion Rates



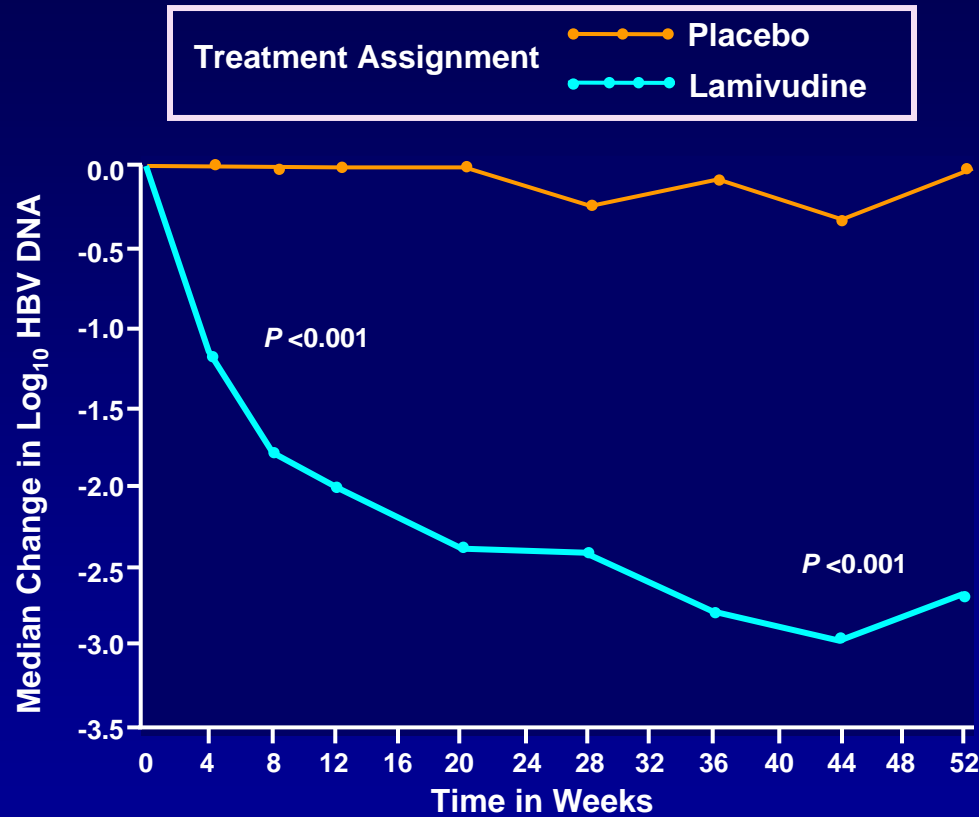
Asian studies – Lai CL, et al. *N Engl J Med.* 1998;339:61-8; Liaw et al, 2000; Leung NW, et al. *Hepatology.* 2001;33:1527-37; Guan R, et al. 2001. Abstract.

HBeAg Seroconversion Relative to Baseline Serum ALT

HBeAg Seroconversion (%)



Lamivudine in HIV/HBV



Week	0	4	8	12	20	28	36	44	52
Placebo (n)	19	17	16	17	14	12	14	10	10
Lamivudine (n)	79	75	72	73	69	60	50	46	38

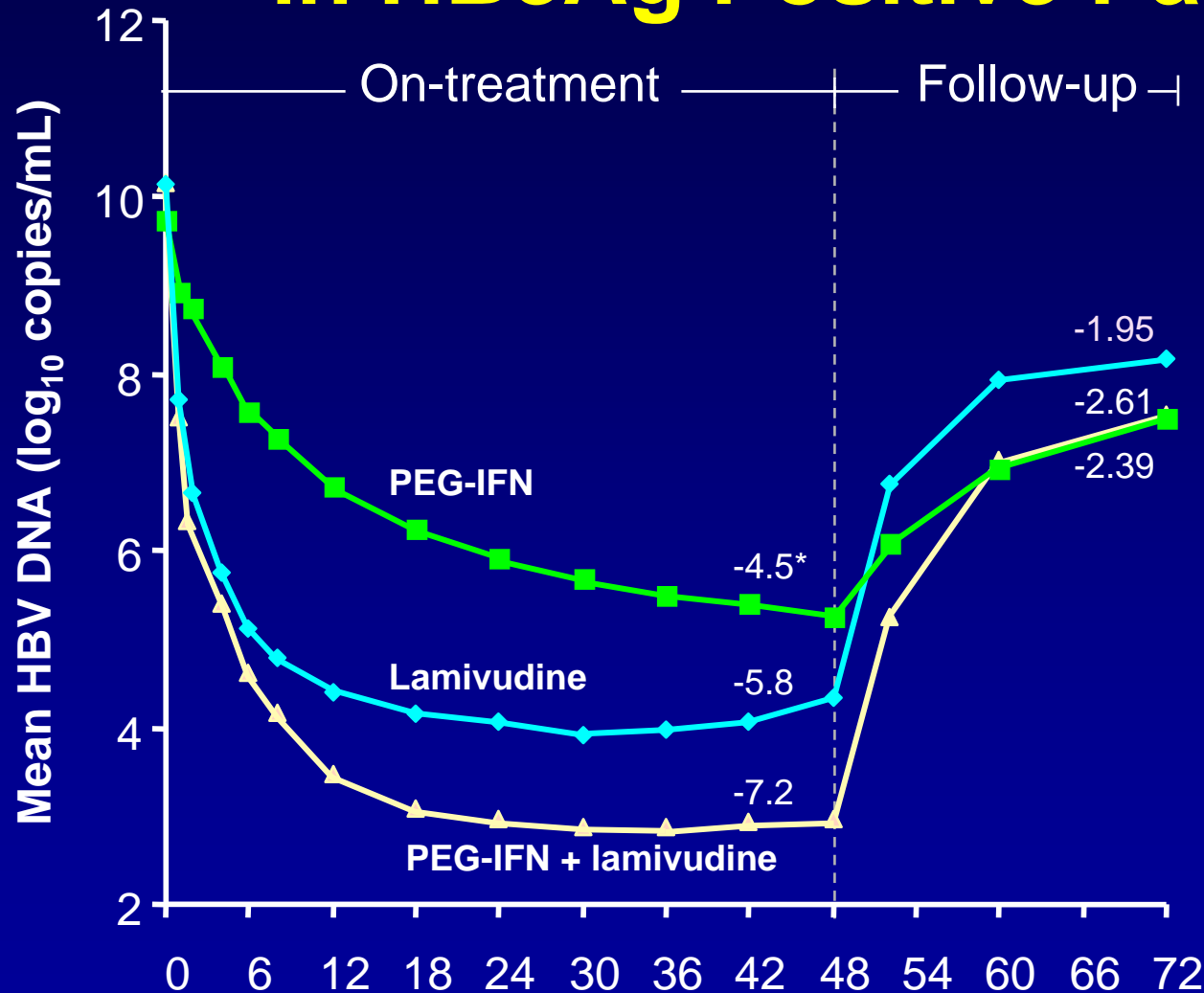
- Efficacy of LAM first inferred from CAESAR trial
- At 52 weeks, HBV DNA declined 2.7 logs in LAM-containing arms
- Low rates of seroconversion

Lamivudine in HIV/HBV (cont)

- Vast majority of patients develop resistance¹
- Low genetic barrier to resistance:
 - M184V for HIV
 - M204I/V and L180M for HBV
- Need to use as part of combination therapy

Pegylated Interferon Alfa2a

On-therapy HBV DNA Suppression in HBeAg Positive Patients



PEG-IFN
HBeAg seroconversion
at EOF = 32%

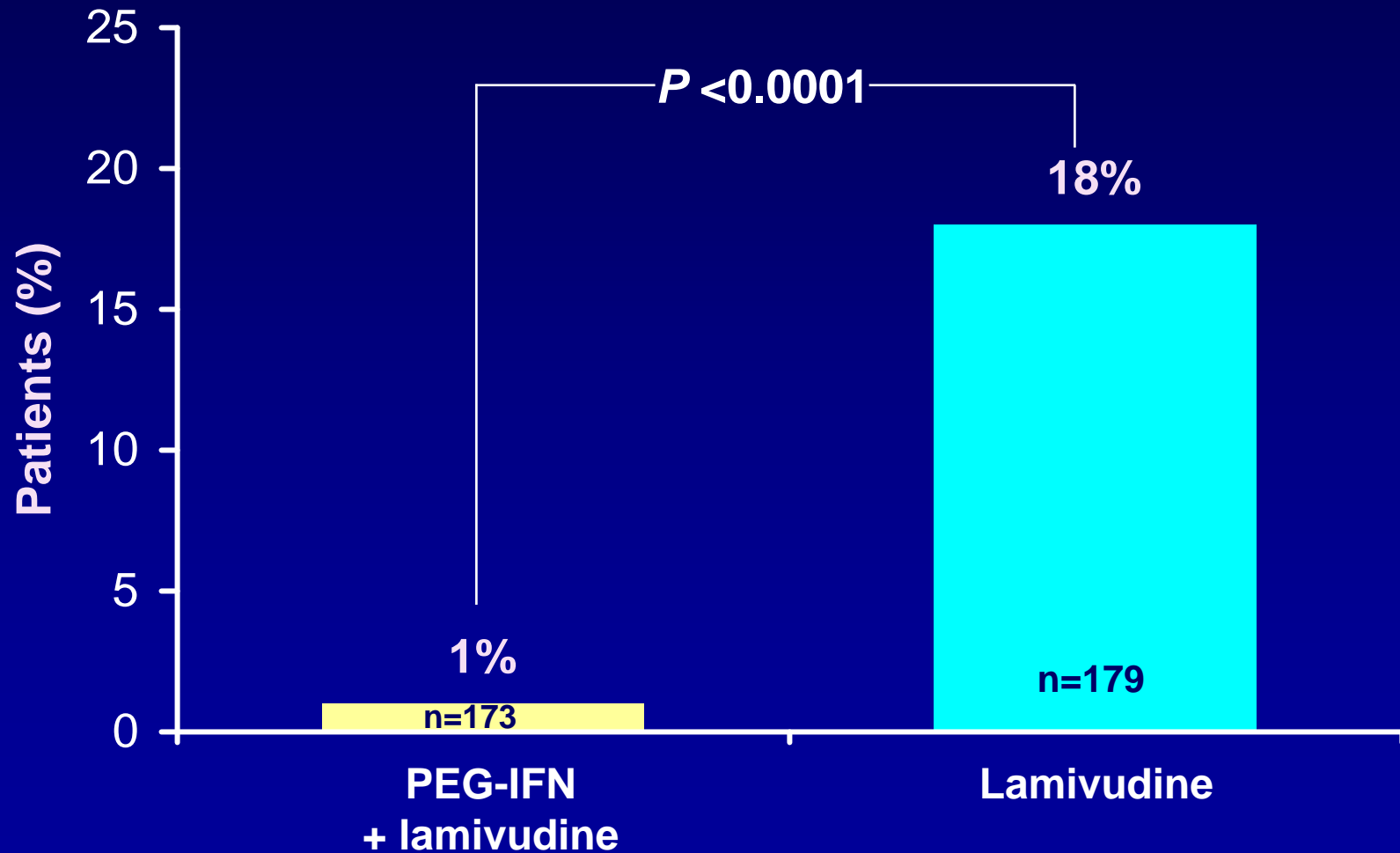
PEG-IFN + LAM
HBeAg seroconversion
at EOF = 27%

LAM
HBeAg seroconversion
at EOF = 19%

*All numbers shown are log₁₀ reduction from baseline.

Lau G, et al. *N Engl J Med.* 2005;352:2682-95.

Decreased Lamivudine Resistance With PEG/LAM than LAM Alone



PEG-IFN in HIV/HBV

- **No data on PEG-IFN in HIV/HBV**

- Poor responses on std IFN reported prior to HAART

- **Advantages**

- PEG-IFN may be considered for HBV treatment regardless of need for ART

- Prefer use in patients with CD4 counts >350 cells, low HBV DNA

- HIV RNA declines on PEG-IFN; however, no evidence of selection for HIV resistance mutations

- ? Role of HBV genotyping

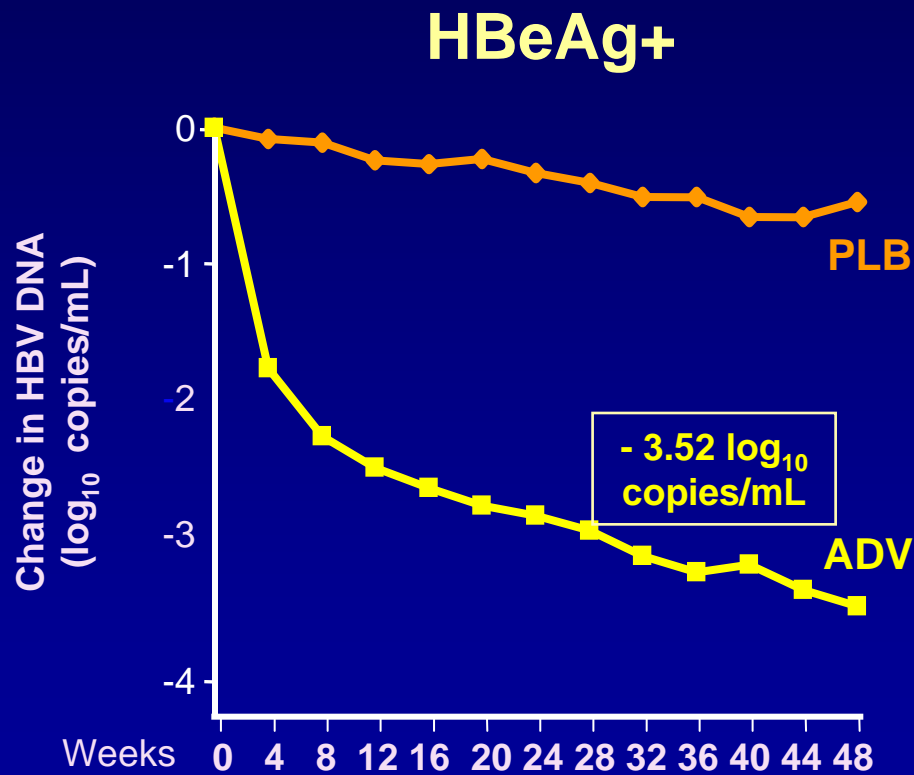
- ? Role in MDR-HBV¹

Adefovir

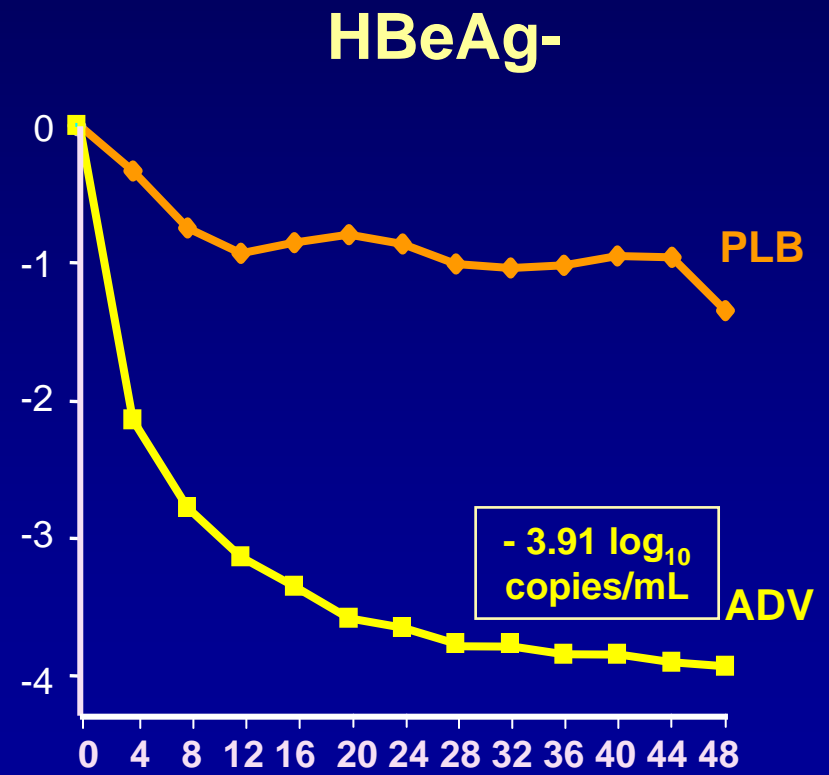
First developed as anti-HIV agent ...

Adefovir Studies

Median Change From Baseline in HBV DNA

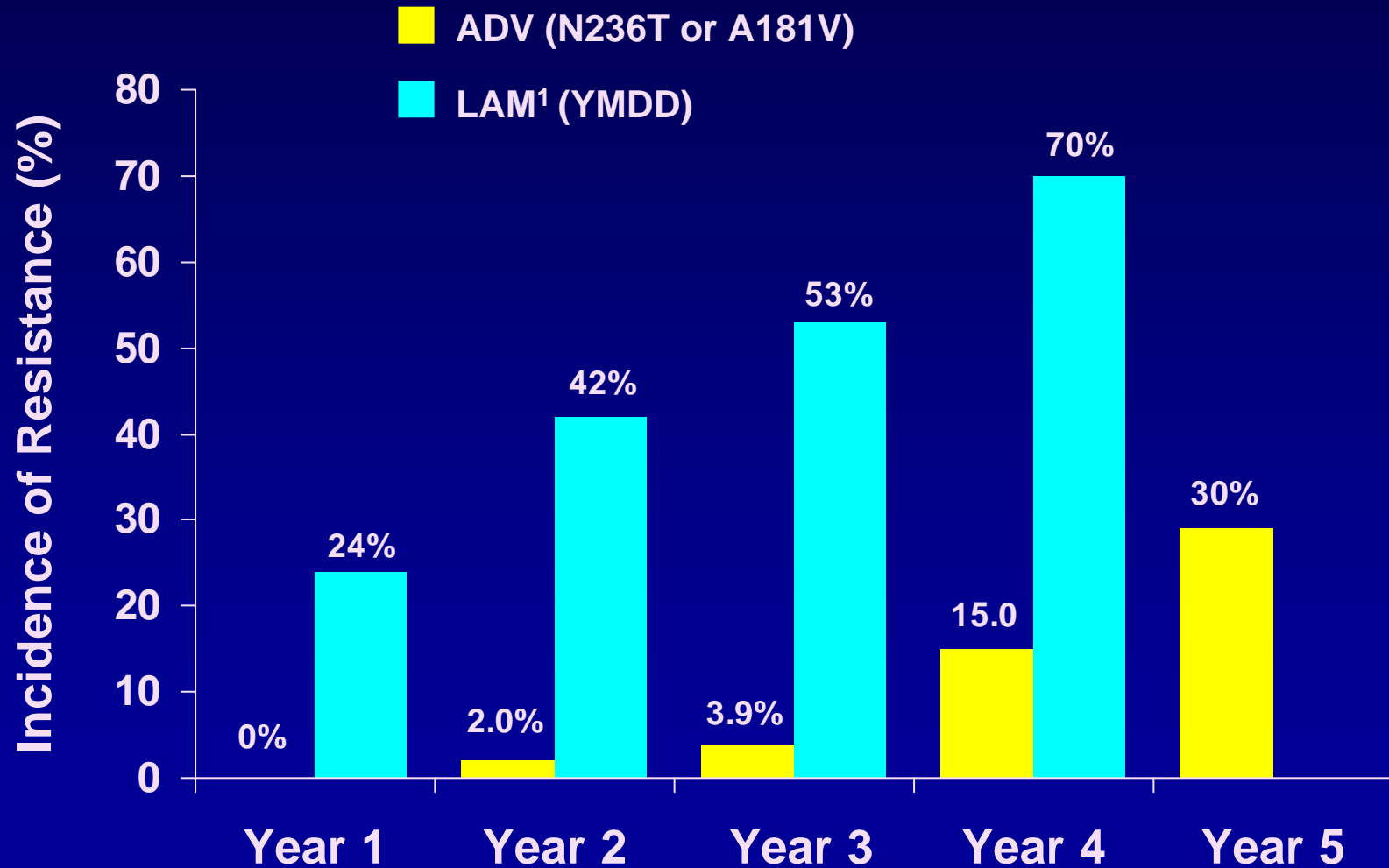


$P < 0.001$



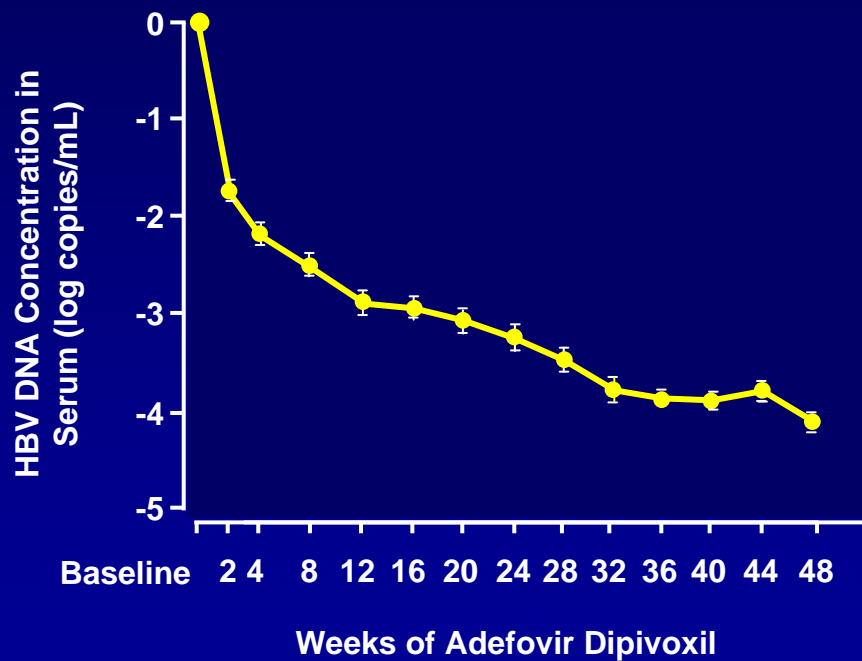
$P < 0.001$

Cumulative Probability of Resistance With LAM vs ADV



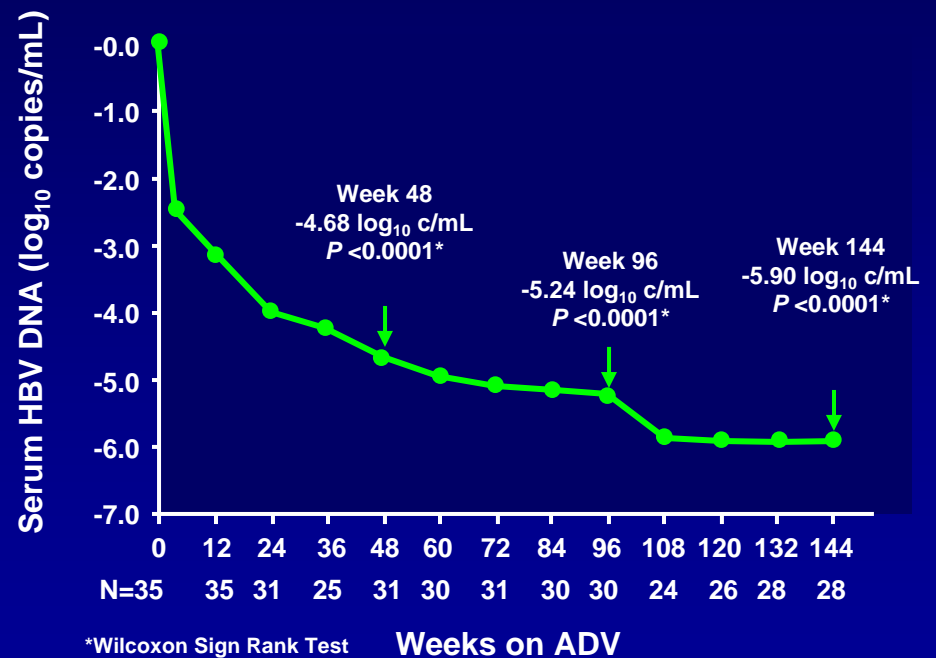
Decline in HBV DNA With ADF in HIV+ Patients With LAM Resistance

48 Weeks of Therapy



Benhamou Y, et al. *Lancet*. 2001;258:718-23.

144 Weeks of Therapy



Benhamou Y, et al. *J Hepatology*. 2006;44:62-7.

Rationale to Treat With ADF and Continue LAM in Face of Resistance

- Some observational data suggest that the risk of developing ADF resistance in patients with pre-existing LAM-resistance appears low when combination therapy is applied

Adefovir in HIV/HBV

- Only 25% achieved HBV suppression¹
- Low rates of HBeAg seroconversion
- No selection of HIV resistance mutations
 - K65R and K70E^{1,2}

1. Benhamou Y, et al. *J Hepatology*. 2006;44:62-7.

2. Sheldon JA, et al. *AIDS*. 2005;19:2036-8.

Can Adefovir Induce HIV Resistance to Tenofovir?

- Study of 13 patients with HIV RNA on Rx¹
- No K65 or 70E mutations found
- **Caveats**
 - Bulk sequencing of PCR products
 - Did prior TAMS decrease emergence of K65R?
- **Subsequent study of 52 HIV/HBV treatment naïve patients²**
 - No K65R developed

Tenofovir

Cousin of adefovir ...

Preliminary Data on Tenofovir versus Adefovir in HBeAg+ Patients

- **Randomized trial of 266 patients demonstrated TDF superior to ADF at wk 48**
 - Viral suppression (76 vs 13%)
 - ALT normalization (69 vs 54%)
- **However, similar results with either drug in:**
 - HBeAg seroconversion (21 vs 18%)
 - Histologic improvement (74 vs 68%)

Tenofovir in HBV Patients With Prior Treatment Experience

- **Study of 101 patients with prior LAM or ADF exposure assigned to TDF**
 - Viral suppression was achieved at 24 and 48 weeks in 72 and 91% of patients, respectively
 - No difference in response based on past treatment or presence of M184V

Tenofovir in HIV/HBV Patients with LAM Resistance

- **Observational cohorts:**

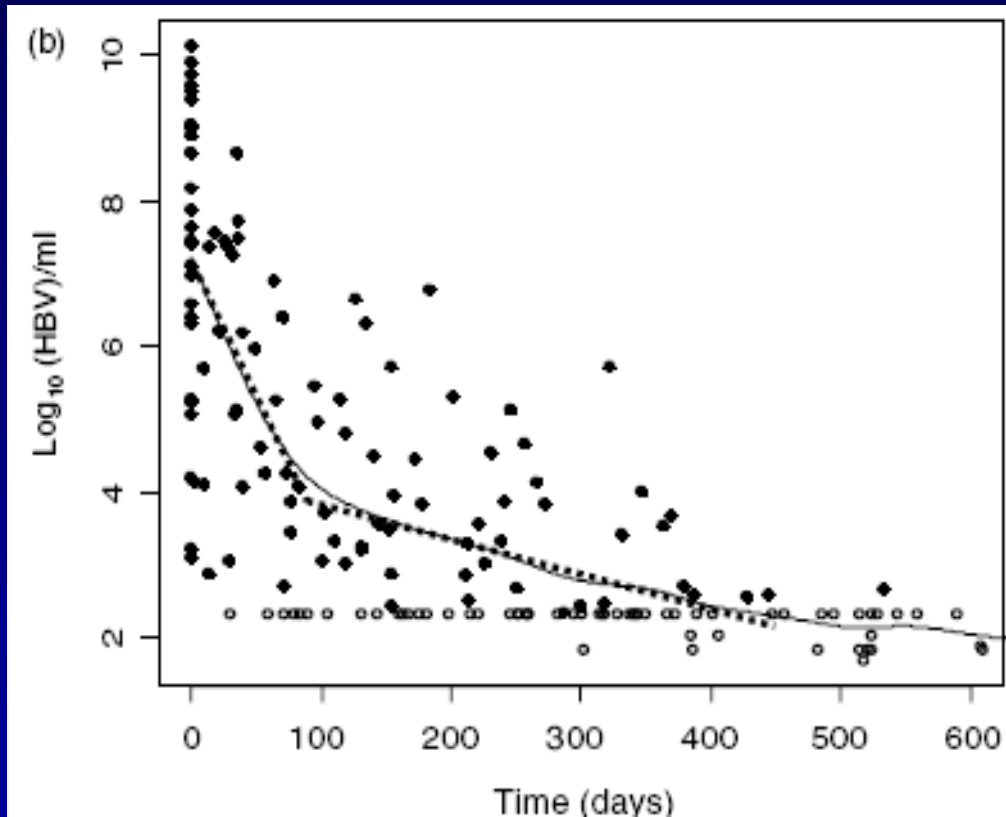
- Treatment with TDF effective in attaining HBV viral suppression
- True in LAM-naive and LAM-resistant patients

Dore GJ, et al. *J Infect Dis.* 2004;189:1185-92.

Nunez M, et al. *AIDS.* 2002;16:2352-4.

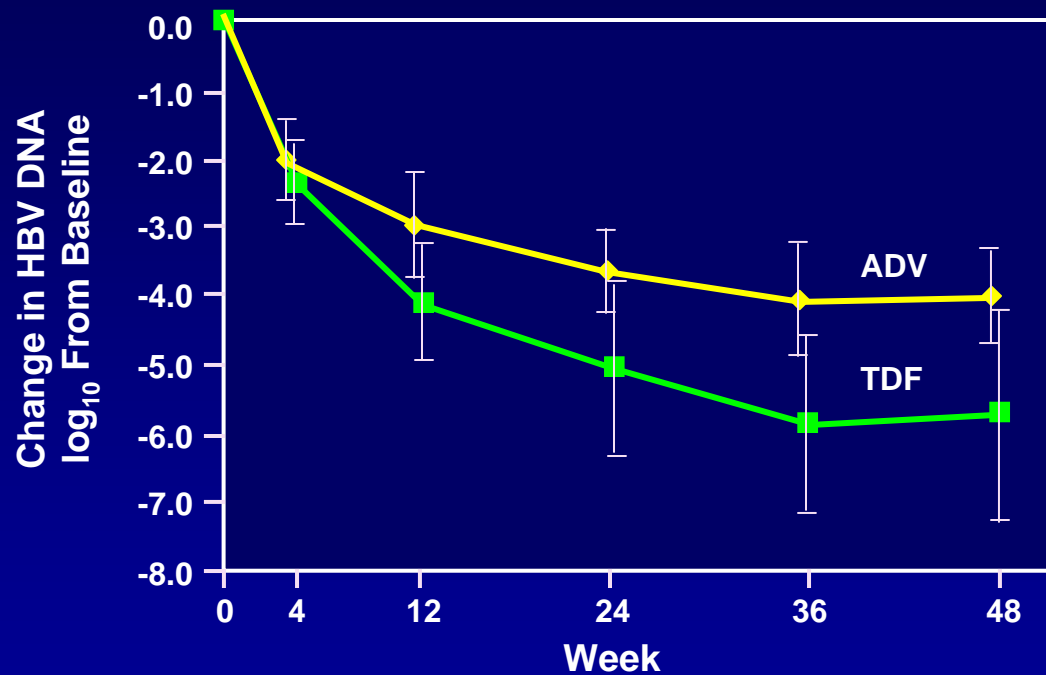
Benhamou Y, et al. *N Engl J Med.* 2003;348:177-8.

Viral Kinetics of HBV DNA



- Prospective cohort of HIV Rx-experienced patients taking TDF or TDF/LAM
- Viral kinetics reflect a biphasic curve regardless of prior LAM exposure

TDF vs ADF in HIV/HBV With LAM Resistance (ACTG A5127)



ADV (n)	25	24	23	20	18	20
TDF (n)	27	26	23	18	17	18

- Prospective randomized, double-blind, placebo controlled trial demonstrated noninferiority of TDF
- Of 35 patients who reached 48 weeks of Rx, 6% on ADF and 20% on TDF had no detectable HBV DNA

Entecavir

Great potency with one major flaw ...

Entecavir vs Lamivudine in HBeAg-positive Patients

- 709 HBeAg+ patients in DB, phase III study
 - Randomized to entecavir (0.5 mg/day) or lamivudine (100 mg/day)

48-Week Results	Entecavir (n=354)	Lamivudine (n=355)	P Value
Histologic improvement, %	72	62	.0085
Median change in HBV DNA from baseline, log ₁₀ copies/mL	-6.9	-5.4	<.0001
HBV DNA <400 copies/mL, %	69	38	<.0001
HBeAg seroconversion, %	21	18	NS

Chang TT, et al. *Hepatology*. 2004;40(suppl 1):193A(70).

FDA Antiviral Drugs Advisory Committee Meeting. March 11, 2005.

Entecavir vs Lamivudine in HBeAg-negative Patients

- 638 HBeAg– nucleoside-naive patients; double-blind, phase III study
 - Randomized to entecavir (0.5 mg/day) or lamivudine (100 mg/day)

48-Week Results	Entecavir (n=325)	Lamivudine (n=313)	P Value
Histologic improvement, %	70	61	.014
Improved Ishak fibrosis score, %	36	38	NS
HBV DNA <400 copies/mL, %	91	73	<.0001
ALT normalization, %	78	71	<.05

Shouval D, et al. *Hepatology*. 2004;40(suppl 1):728A(LB07).
FDA Antiviral Drugs Advisory Committee Meeting. March 11, 2005.

ETV vs LAM in LAM-r HBeAg+ Patients

- 286 patients randomized to ETV (1 mg/day) or lamivudine (100 mg/day)

48-Week Results	Entecavir (n=141)	Lamivudine (n=145)	P Value
Histologic improvement, %	55	28	<.0001
Improved fibrosis, %	34	16	<.01
Undetectable HBV, normal ALT, %	55	4	<.0001
Mean change in HBV DNA, copies/mL (log ₁₀)	-5.1	-0.5	<.0001
Patients with normalized ALT, %	61	15	<.0001
Loss of HBeAg, %	10	3	.028
Seroconversion, %	8	3	.06

Sherman M, et al. *Hepatology*. 2004;40(suppl 1):664A(1152).

FDA Antiviral Drugs Advisory Committee Meeting. March 11, 2005.

Entecavir Resistance in Treatment-naïve Patients

- ETV primary mutations are not seen in treatment-naïve patients
- **ETV-r results from RT substitutions at rtT184, rtS202, or rtM250 in the context of LAM-r virus**
 - For example, rtM204I/V+/-rtL180M
- Susceptibility of ETV is 8-fold lower for LAM-r variants

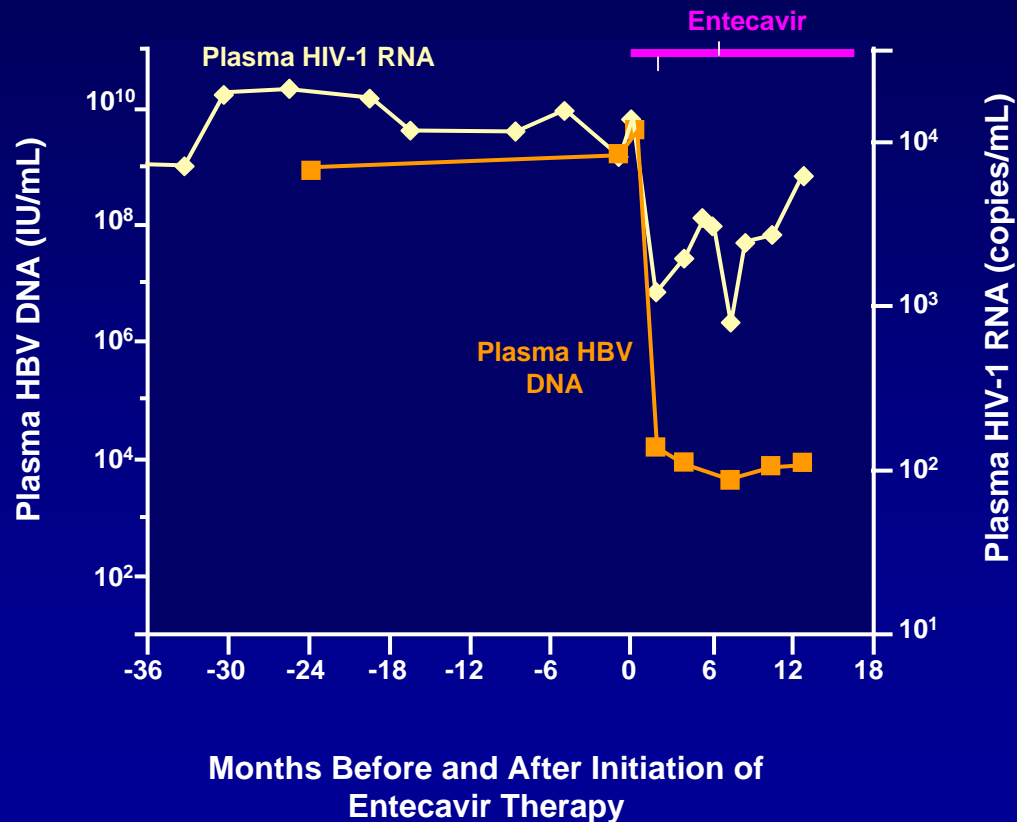
Tenney DJ, et al. *Antimicrob Agents Chemother.* 2004;48:3498-507.

Baldick CJ, et al. *J Hepatol.* 2008;48:895-902.

Entecavir in HIV/HBV Patients

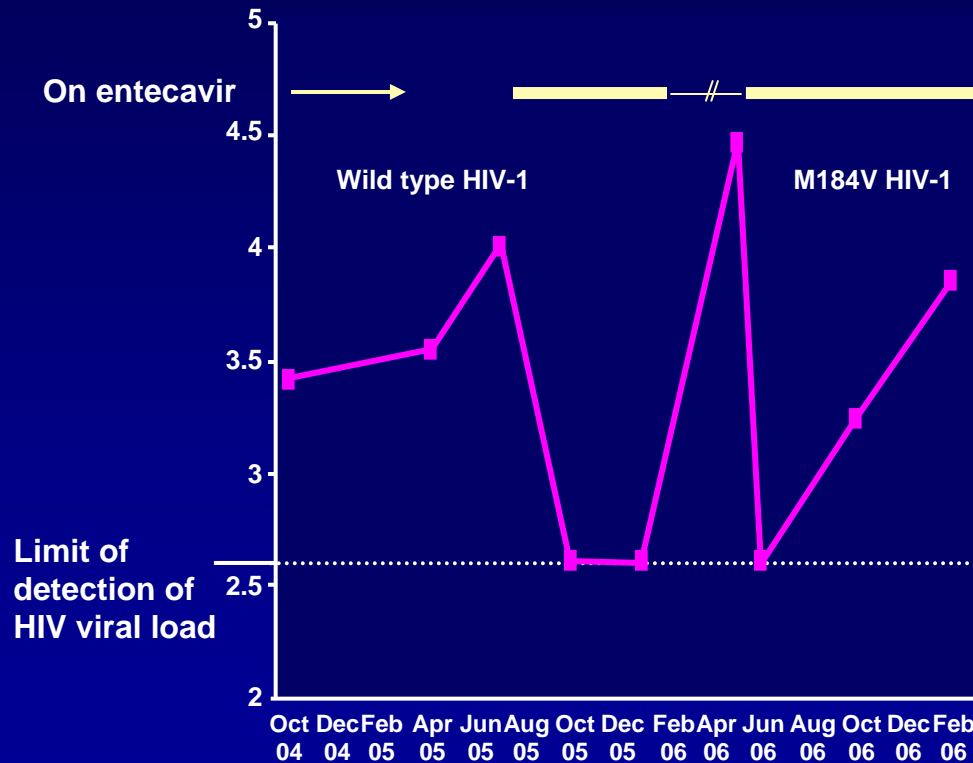
- **Study of 68 patients adding ETV versus placebo to background LAM for 24 weeks**
 - HBV DNA 3.65 log decline with ETV
 - 6% patients achieved HBV suppression with ETV at 24 weeks
 - “No significant changes in HIV RNA or CD4”

ETV is Associated With Declines in HIV Viremia



Report of 3 cases of HIV RNA decline with initiation of ETV

Selection for M184V of HIV-1 by ETV in Treatment-naive Patient



- 51 yo AA MSM
- CD4 877 cells
- HIV RNA 2600 c/mL
- HBeAg+
- HBV DNA 17 million IU/mL
- Changes in HBV DNA associated with drug exposure

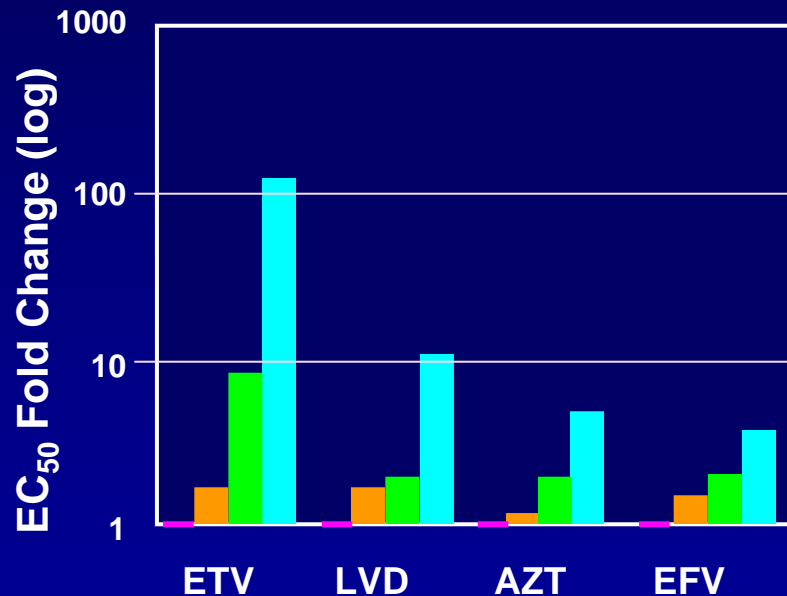
Anti-HIV Activity of ETV in Retrospective Multicenter Study

- Evaluation of HIV RNA and HBV DNA in 10 ART-naïve and 7 ART-experienced patients prior to and during ETV exposure
 - Mean reduction in HIV RNA: 1.2 log
 - No difference based on prior drug experience
 - Emergence of M184V in 6 patients
 - 3 treatment-naïve

FDA: Drug Warning

- [http://www.fda.gov/medwatch/safety/2007/Ba raclude DHCP 02-2007.pdf](http://www.fda.gov/medwatch/safety/2007/Ba-raclude%20DHCP%2002-2007.pdf)
- *Entecavir should not be used as monotherapy for treatment of HBV in HIV coinfecting patients who are not taking ART*

ETV Inhibits HIV In Vitro With Reduced Viral Challenge



- Drug susceptibility at different MOIs¹

2005 package insert

- EC₅₀ 0.026-10 microM
- Lower EC₅₀ values observed with decreased levels of HIV RNA
- ETV selected for M184I at high concentrations
- HIV variants with M184V had lower susceptibility

1. Lin PF, et al. *Antimicrob Agents Chemother.* 2008;52:1759-67.

2. Entecavir [package insert]. Princeton, NJ: Bristol-Myers Squibb;2005.

Telbivudine

Telbivudine

- Similar issues as LAM: excellent tolerance but emergence of resistance over time
- Thus, telbivudine monotherapy is not recommended for HBV-infected patients
- TBV package insert: “No activity against HIV...”
 - $EC_{50} > 100$ microM

NIAID treatment trial

- Open label single arm study of patients not on ART
 - 24 weeks TBV
 - 24 weeks LAM-containing ART
 - Then ART alone...
 - “Study is ongoing but not recruiting...”

**Treatment-naive Patients Who
Are Candidates for ART**

Patients Who Are Candidates for ART

- Excellent rationale for combination therapy (eg, Truvada)
 - Delay onset of **lamivudine** resistance
- Good safety profile
- Low pill burden
- Given with a third agent (eg, PI or NNRTI)

Patients on ART With Detectable HBV DNA

**Options depend on
lamivudine experience**

Treatment of LAM-naive patients on ART

- Substitution of NRTI background with emtricitabine and tenofovir
 - **Switch needs to be based on HIV treatment history and resistance testing**

Patients on LAM-containing ART

- Patients with suppression of HIV but replication of HBV are likely to have LAM-resistance
- Assume cross-resistance to emtricitabine
- Options
 - **Add adefovir**
 - **Change one background NRTI to TDF and continue lamivudine or emtricitabine**
 - **Add pegylated interferon**

Caution When Substituting TDF for Another NRTI

- Need HIV treatment history and past resistance testing to validate strategy of using TDF
- TDF in combination with ddl have been associated with increased rates of virologic failure (HIV)
- Also need to dose reduce ddl if considering this combination

Other Options for LAM-experienced Patient

- **Use of ETV only if HIV RNA is suppressed!**
 - Need 1.0-mg dosing for entecavir
 - Risk of ETV resistance
- Minimal data on pegylated interferon

HIV Patient Who Is NOT A Candidate for ART

- **Entecavir: no longer an option**
- **Pegylated interferon**
 - No risk of HIV or HBV resistance
 - Modest HIV activity
- **Adefovir: low potency**
- **...OR.....**

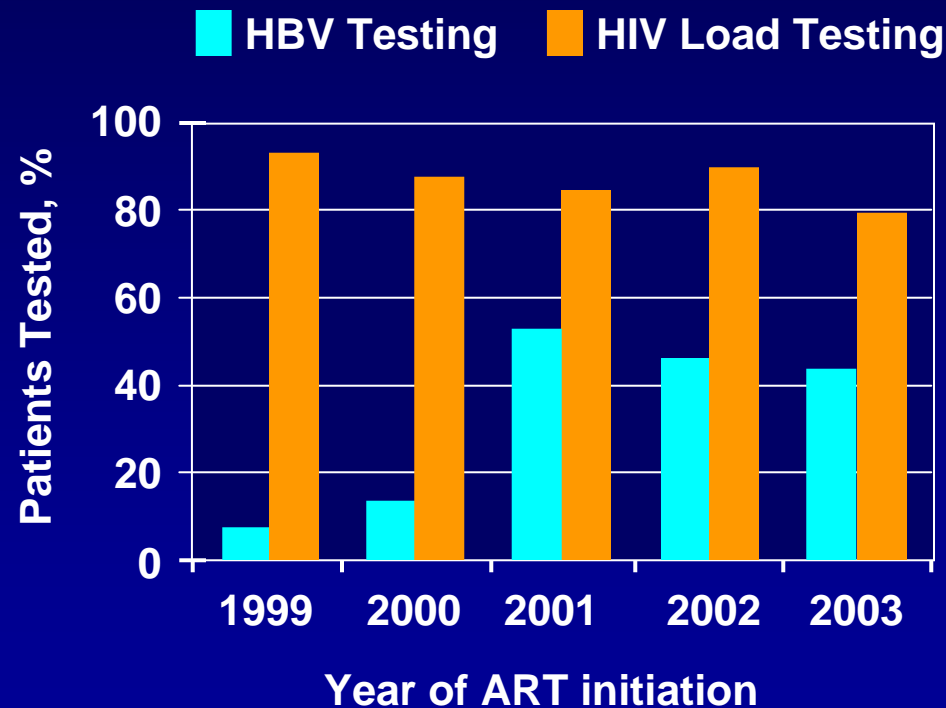
Start ART early...

“Treatment for HIV should be considered at any CD4 cell count. A number of HIV drugs (TDF, FTC, LAM) also are appropriate for HBV therapy and can be used in initial HIV regimens for coinfecting patients.”¹

Diagnostic Confusion Among HIV Providers

- **No discussion in guidelines of diagnosis, staging of disease or monitoring on therapy, or screening for HCC**
- **Limited knowledge among providers regarding chronic HBV infection**
 - Screening
 - Diagnosis
 - Treatment and evaluation of response
 - Monitoring for HCC

Viral Load Monitoring Among HIV Providers in HIV/HBV Patients



- Prior to ART, HBV DNA and HIV RNA testing in 16% and 99%, respectively¹
- Infrequent HBV DNA monitoring during Rx
- Inconsistencies in Rx approach²

1. Jain MK, et al. *Clin Infect Dis*. 2007;44:996-1000.
2. Gaglio PJ, et al. *Clin Infect Dis*. 2007;45:618-23.

Are the guidelines “right on?” ...

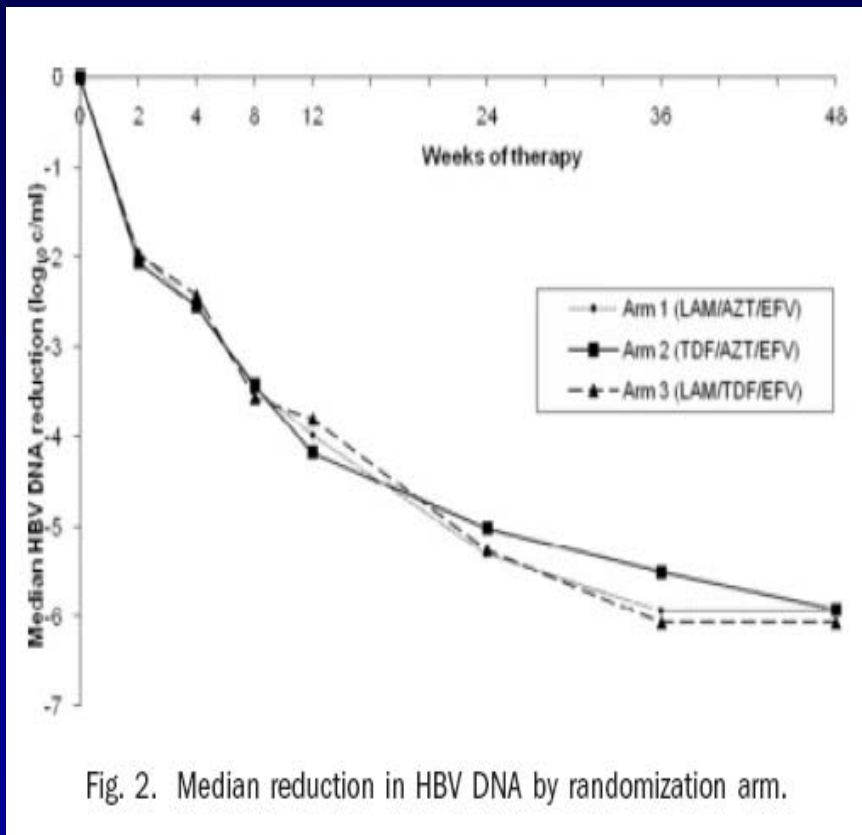
- Pros:

- HBV DNA suppression has been linked to cirrhosis in HCC
- Are we on the verge of a paradigm shift in HBV treatment?
- Long term Rx is usually required

- Cons:

- Will TDF/FTC lead to viral suppression in the majority of patients? Will resistance emerge?
- What to do if seroconversion occurs?
- Are we missing an opportunity to define “best practices” in this patient subset?

LAM vs TDF vs LAM/TDF in HIV/HBV



- 36 HIV/HBV Thai patients
- Randomly assigned to ART containing HBV active agent(s)
- Time-weighted AUC analysis with similar HBV DNA declines
- HBV DNA $<3 \log(10)$ achieved in 46%, 92%, and 91% on LAM, TDF, TDF/LAM respectively.

USPHS Treatment Guidelines

- HBeAg+
 - Abnormal ALT
 - HBV DNA level $>20,000$ IU/mL ($>10^5$ c/mL)
- HBeAg-
 - Abnormal ALT
 - HBV DNA >2000 IU/mL ($>10^4$ c/mL)
- Some experts recommend Rx at any HBV DNA level, particularly those with significant liver disease

USPHS=United States Public Health Service.

**Remain Vigilant When
Initiating HBV Therapy!**

Risk of Immune Reconstitution

- **Risk greatest in those with**
 - Low CD4 at baseline
 - Greatest mean rate change of CD4 with ART
- **Potential for morbidity highest in patients with cirrhosis**
 - Can lead to hepatic decompensation
- **Simultaneous initiation of HIV- and HBV-directed therapy decreases potential risk**
 - Need for appropriate patient counseling

HBV Flares in HIV-infected Patients

- “Drug holidays” or change in HIV regimens can lead to HBV flares when underlying HBV status is not considered
- Flares can be secondary to emergence of drug resistance
- **Flares can be misinterpreted as DILI when ART is changed**

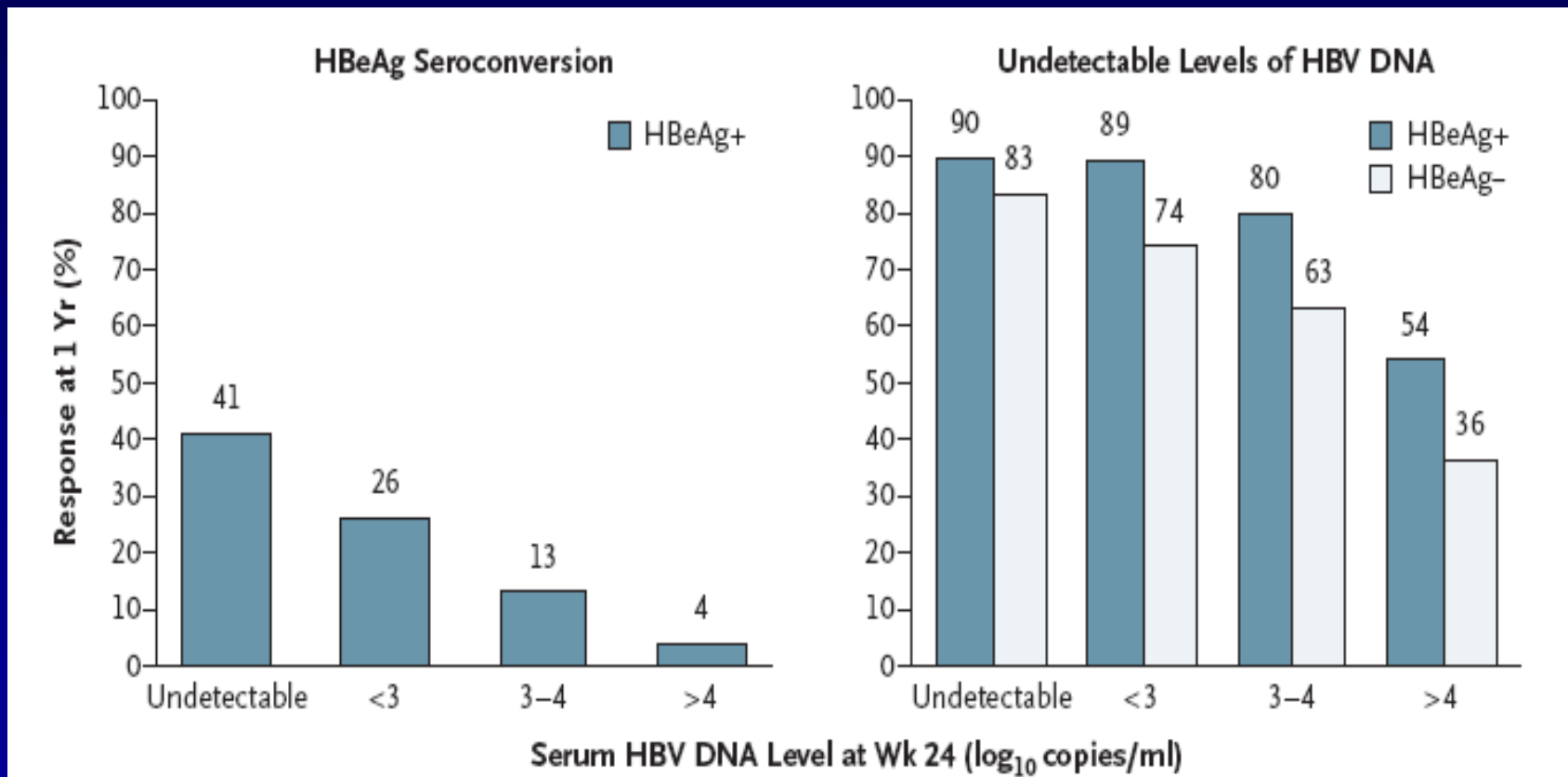
Future Direction

- Opportunity to learn more about combination therapy from our HIV-infected patients (eg, tenofovir/emtricitabine)
- Need for studies of pegylated interferon +/- adefovir in this patient population
- Need for better education of HIV providers regarding HBV

Combination therapy not doctrine yet...

- Rationale
 - Faster attainment of viral suppression – but not always the case...
 - Decrease the risk of resistance
- But...
 - Monotherapy with potent agents like entecavir demonstrates little resistance after four years
 - No greater rates of seroconversion documented
 - Long-term therapy still required
 - No data on “induction/maintenance” approach
 - Still questions on role of PEG + nucleosides/tides...

Outcomes related to HBV DNA levels at week 24 on Telbivudine



Outcomes related to HBV DNA levels at week 24 on Telbivudine

