

HBV Resistance and Safety 2010

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**SCSG 2010
Post-AASLD
Symposium**

SOUTHERN
CALIFORNIA
SOCIETY OF
GASTROENTEROLOGY

Objectives

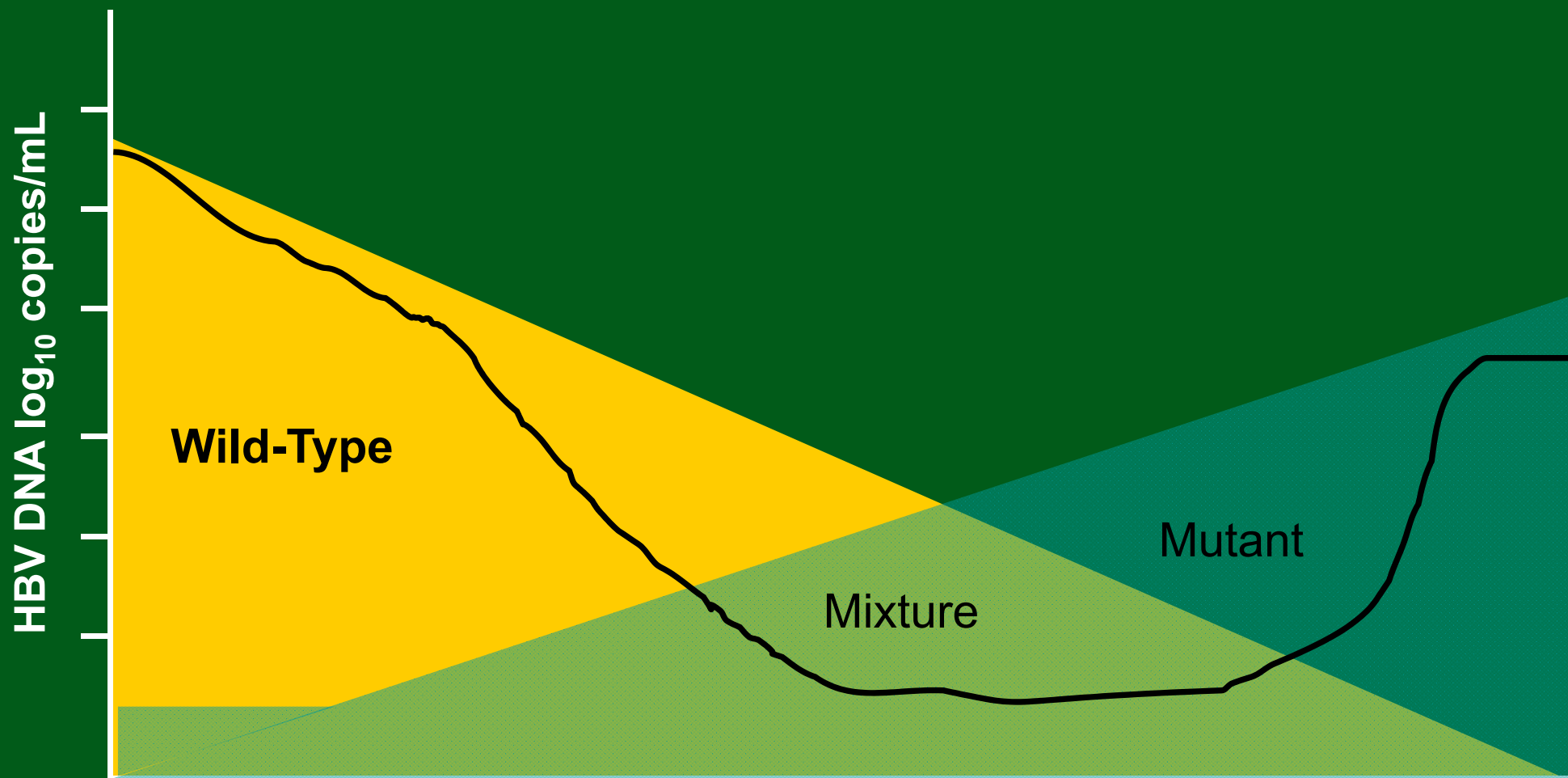
- Review safety concerns with long term nucleos(t)ide use
- Discuss treatment options with drug induced resistance

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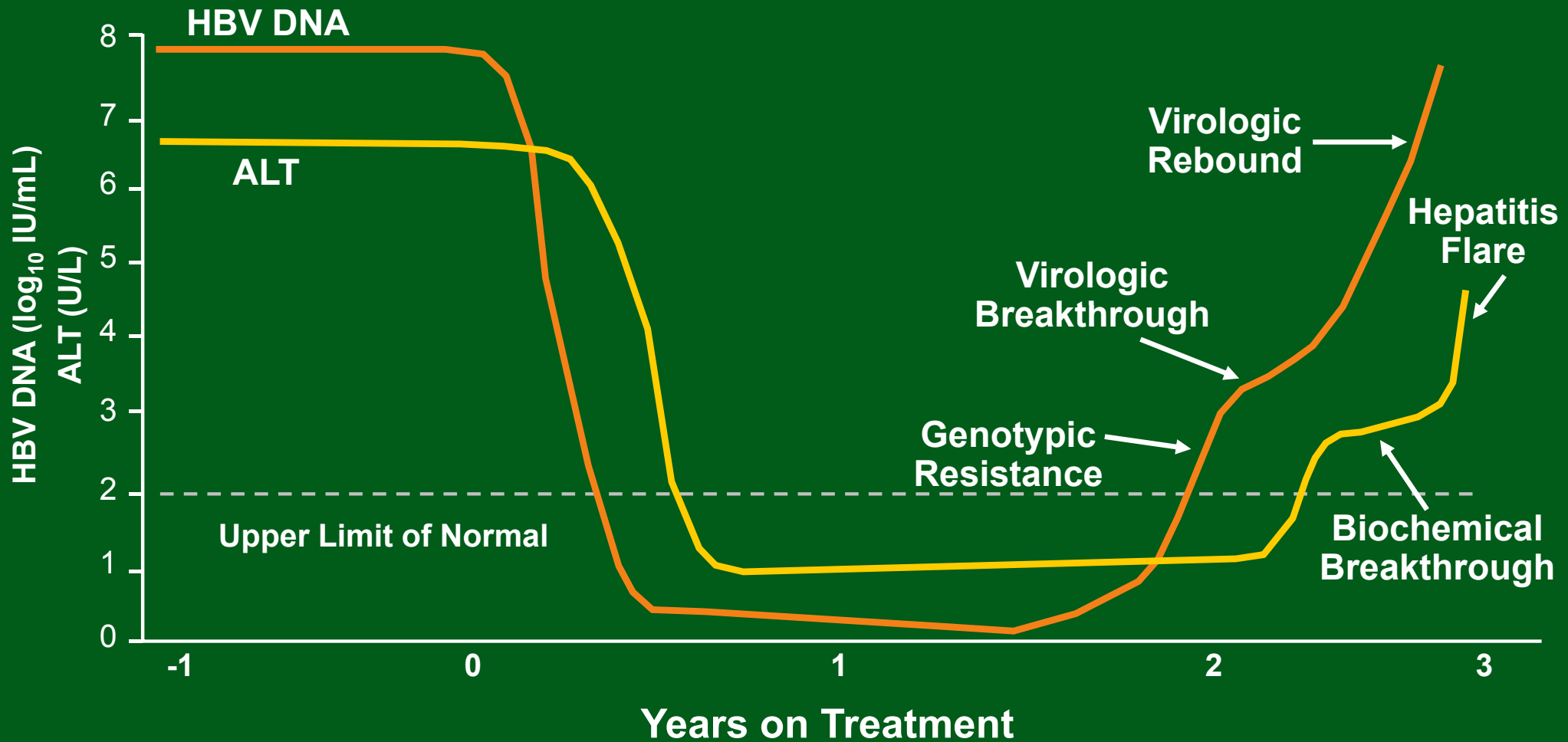
Duration of HBV Treatment

- HBeAg-positive
 - An additional 12 months after HBeAg seroconversion to reduce relapse rate (non-cirrhotics)
- HBeAg-negative
 - Relapse common after cessation of therapy
 - Long-term treatment currently recommended
- Cirrhosis
 - Long-term therapy required or until HBsAg loss
 - Combination therapy may be considered

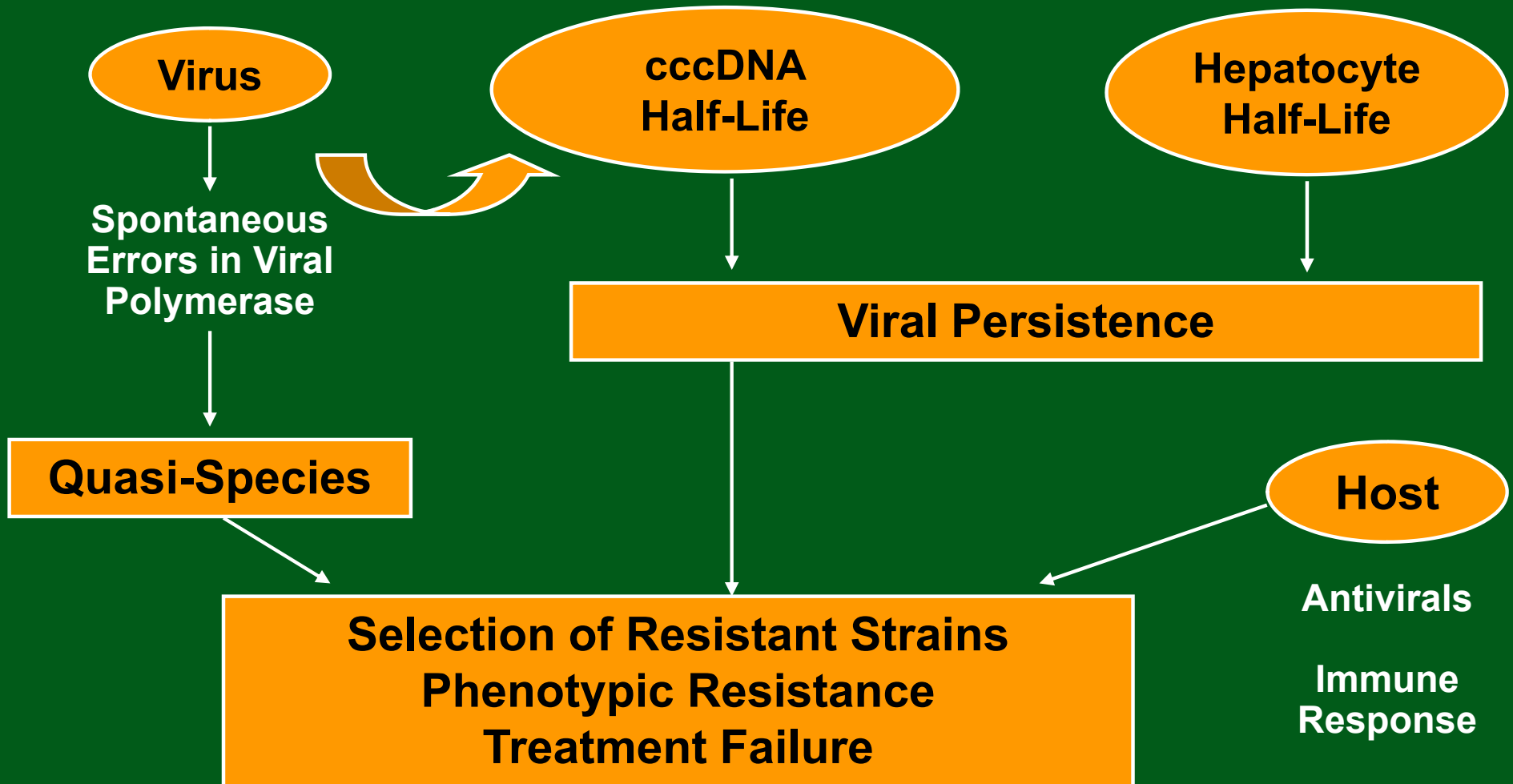
Appearance of Resistance-Related Mutations Is Associated With Virologic Breakthrough



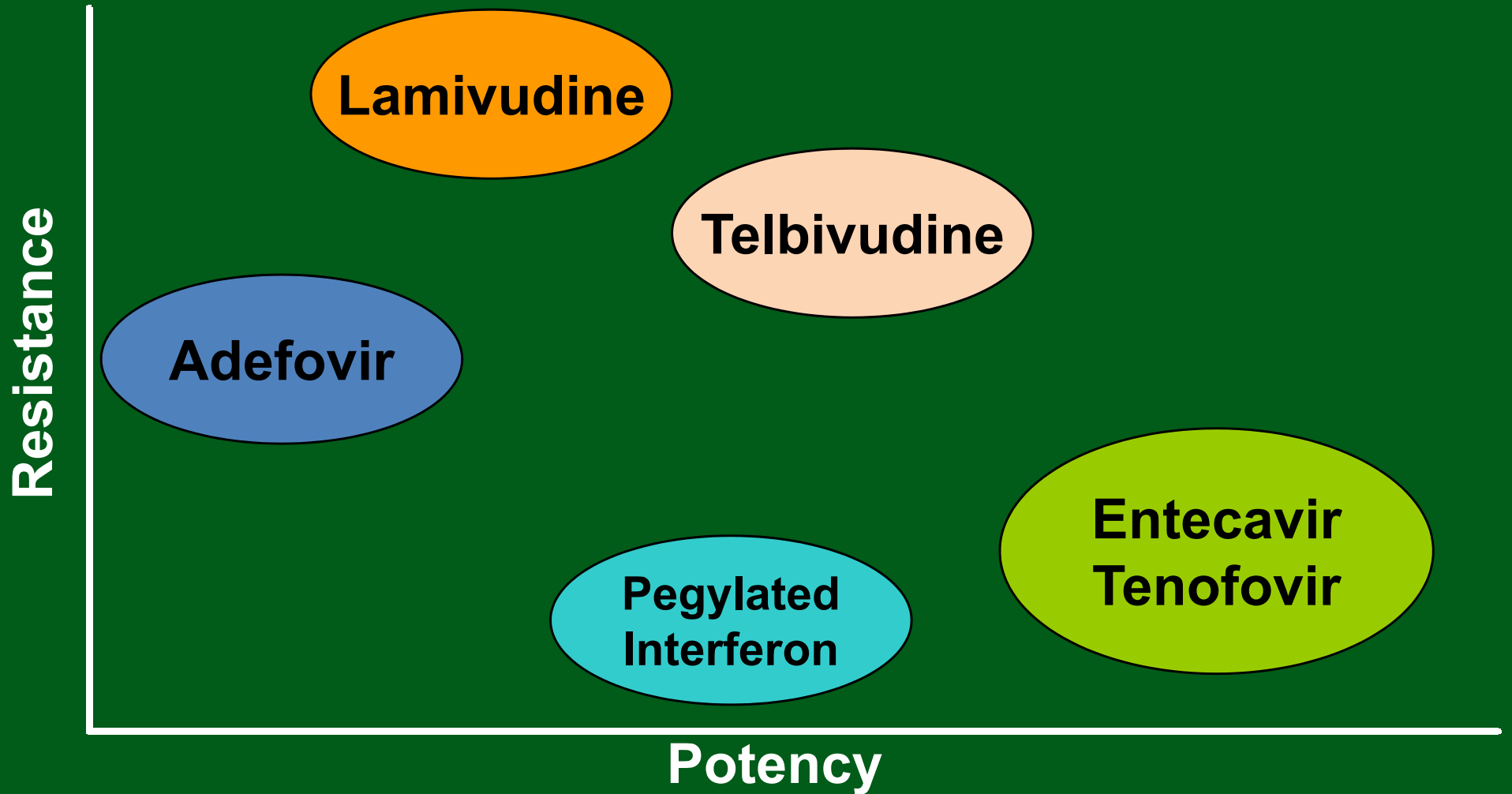
Manifestations of Antiviral Resistance



Viral Persistence and Mechanism for Selection of Mutant HBV Strains



Resistance-Potency Schematic of Available HBV Agents



Emergence of Hepatitis B Resistant Variants

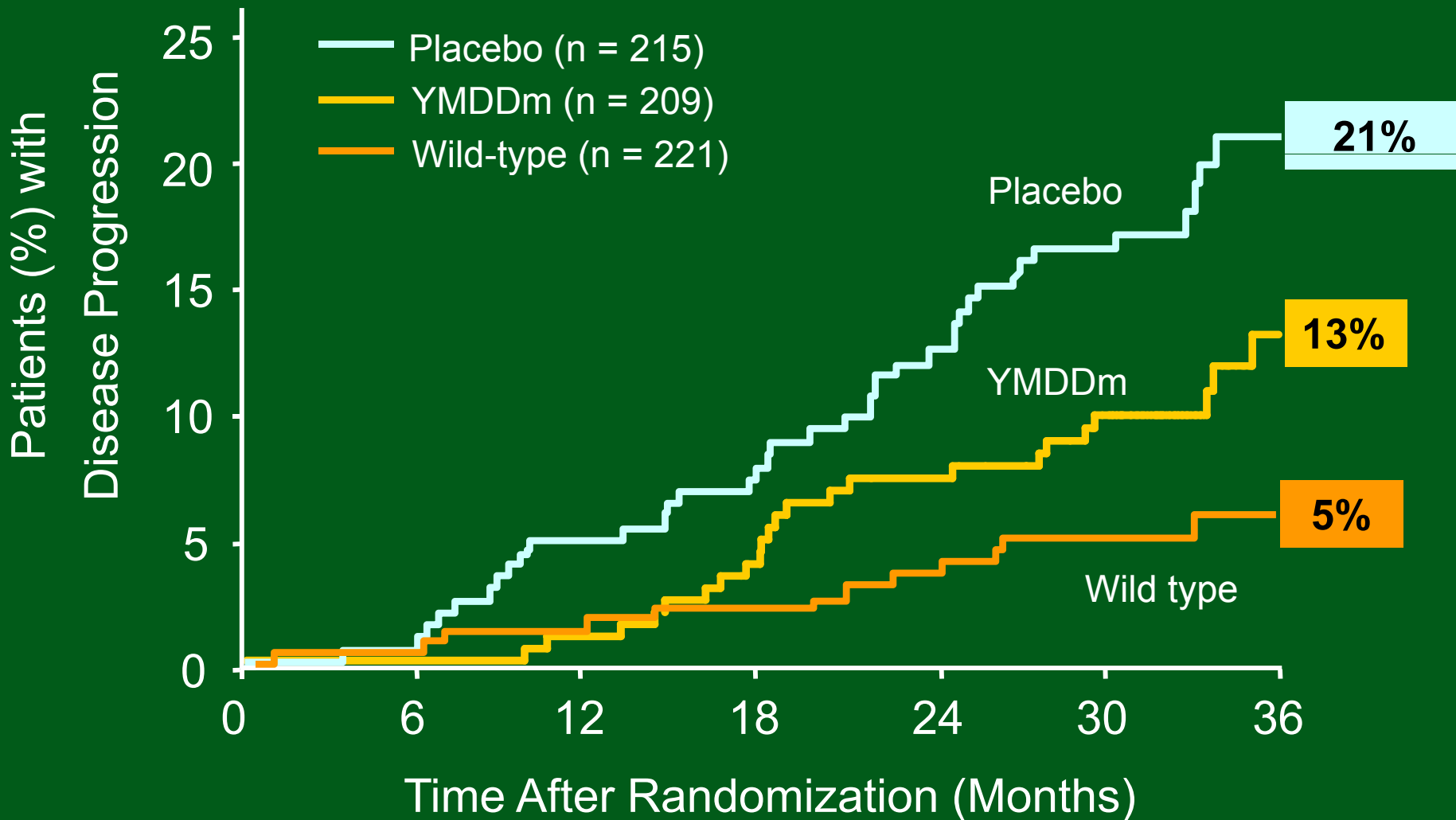
	HBV Resistance at Year of Therapy (% patients)				
	1	2	3	4	5
Lamivudine	23	46	55	71	90
Adefovir					
Naïve HBeAg-negative	0	3	11	18	29
Lamivudine resistant	18	--	--	--	--
Entecavir					
Naïve	0.1	0.4	1.2	1.2	1.2
Lamivudine resistant	6	14	32	40	--
Emtricitabine	9-16	19-37	--	--	--
Telbivudine					
HBeAg-positive	4.4	21.6	--	--	--
HBeAg-negative	2.7	8.6	--	--	--
Tenofovir DF					
Naïve	0	0	0	--	--
Lamivudine resistant	0	0	0	--	--

Thio C, et al. *AIDS Rev.* 2007; Benhamou Y. *JAIDS.* 2007; Colonno R, et al. *EASL.* 2007. Abstract 781.
 Heathcote EJ, et al. *Hepatology.* 2009; Abstract 483; Marcellin P, et al. *Hepatology.* 2009; Abstract 481.
 Tenney DJ, et al. *APASL.* 2008. Abstract PL02.

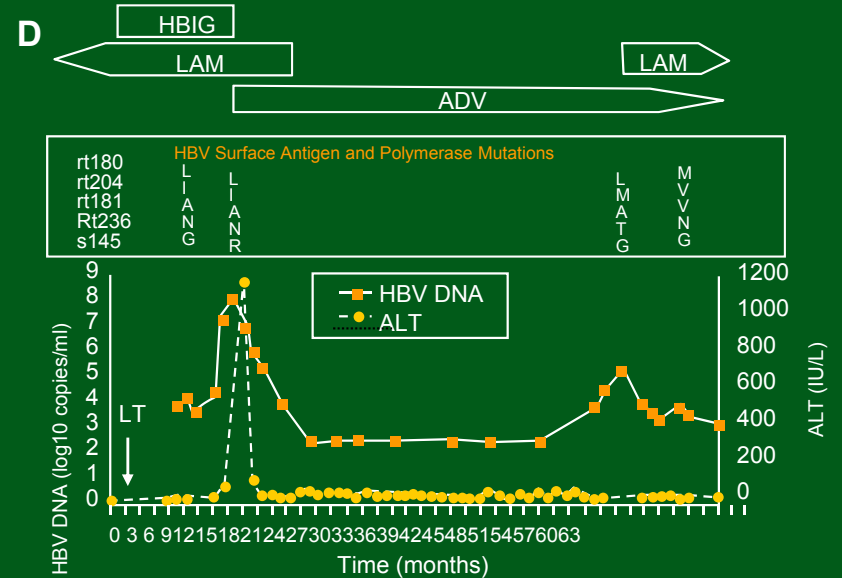
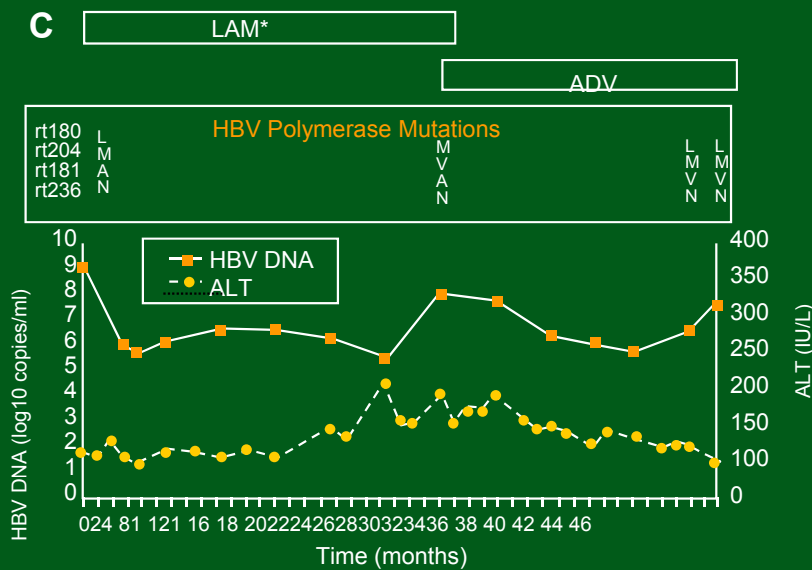
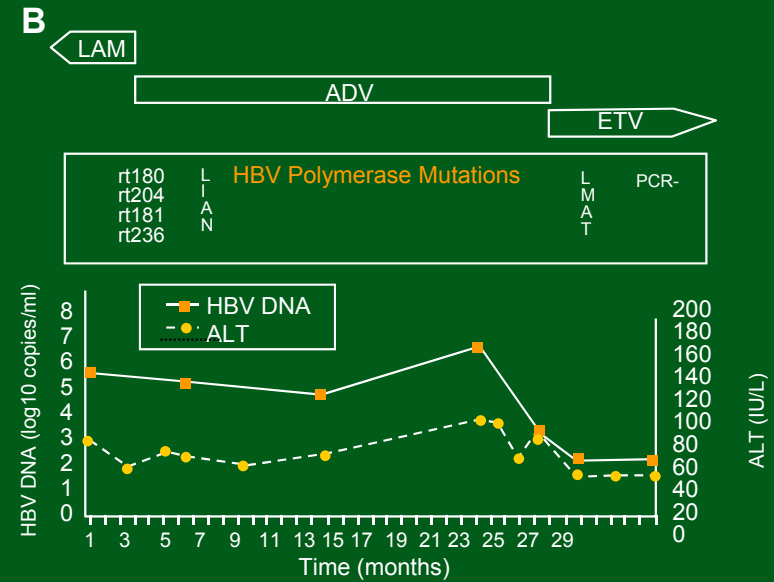
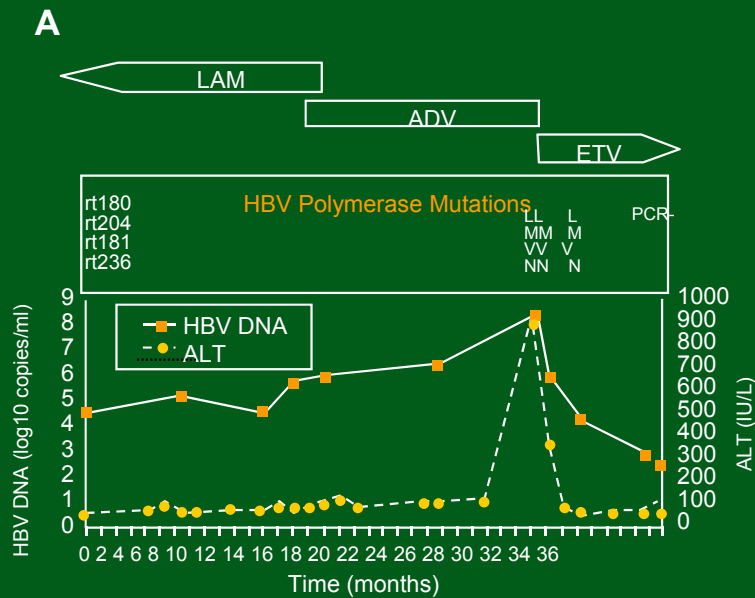
Implications of Resistance to HBV Therapies

- Loss of clinical benefits
 - Loss of initial HBV DNA response with rebound
 - ALT increase and eventual reversion of histologic improvement
 - Progressive liver disease
 - Decompensation in patients with cirrhosis,
- Development of multidrug resistance
 - Cross resistance
 - New resistance mutations
- Transmission of resistant virus

Lamivudine in HBeAg+/- CHB Time to Disease Progression by YMDD Status



Adefovir resistance associated with viral rebound and hepatic decompensation



Objectives

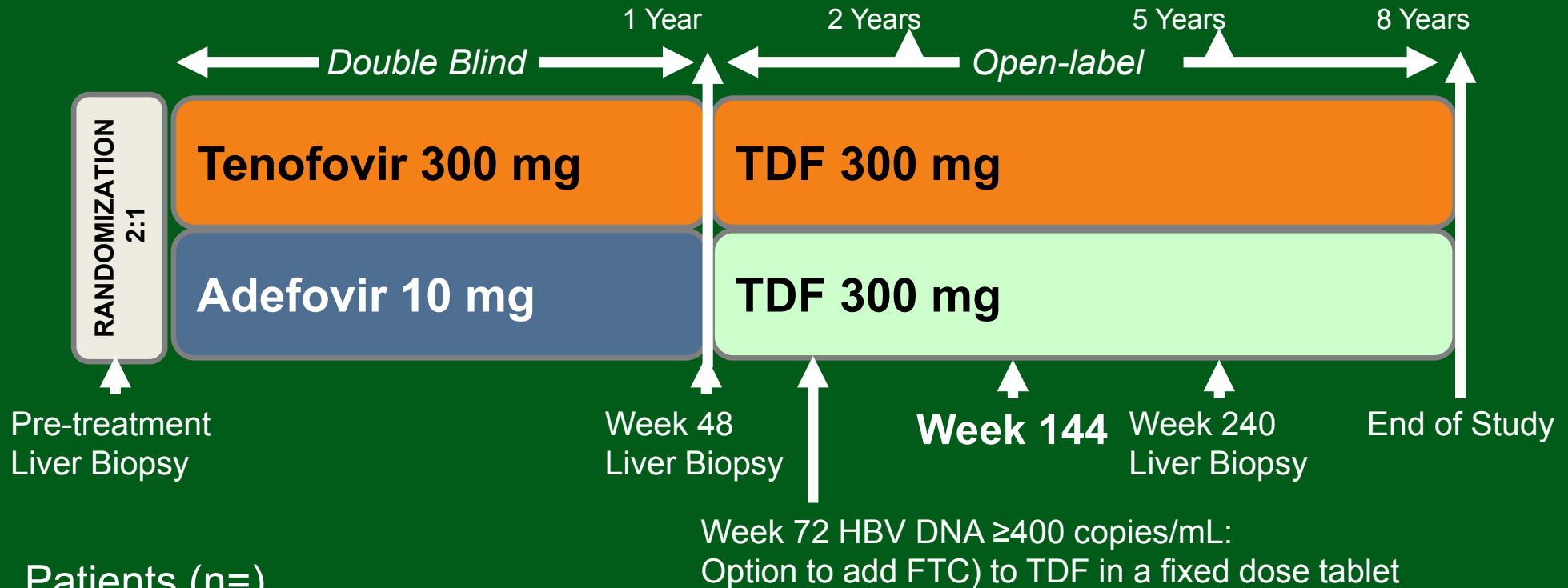
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Abstracts on Long-term Nucleos(t)ides

Studies GS-102 and GS-103: Safety and Tolerability of TDF in Patients with CHB

Randomized, Double-Blind, Comparison of TDF vs. ADV for CHB



Patients (n=)

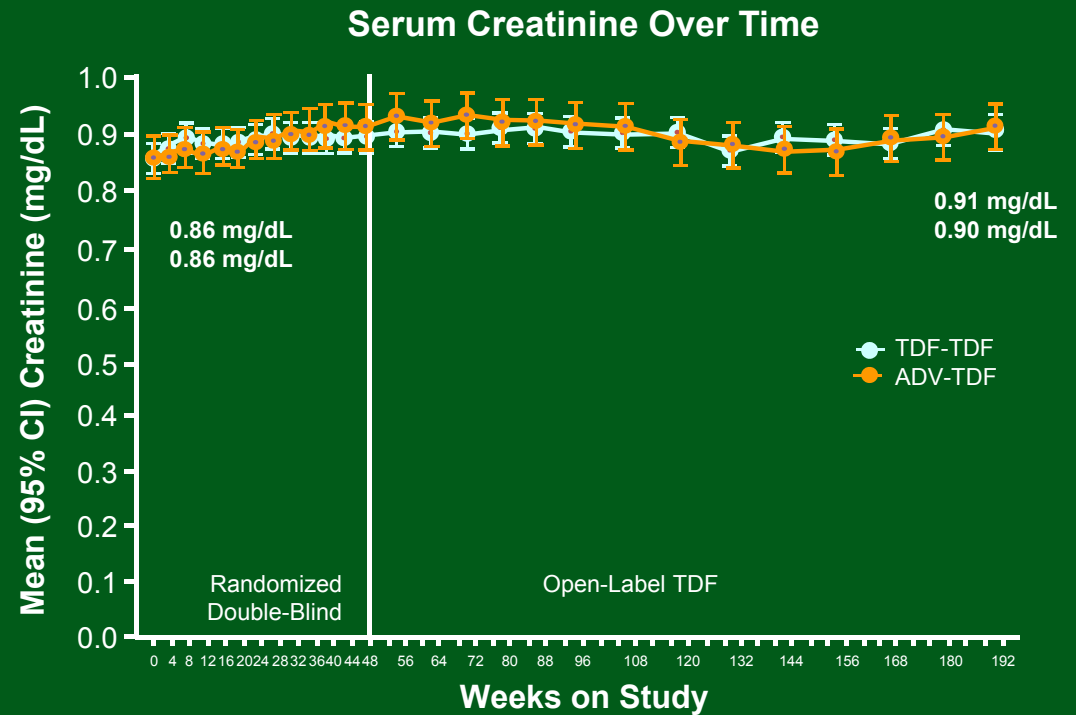
HBeAg- (GS-102)	TDF → TDF (n=250)
	ADV → TDF (n=125)
HBeAg+ (GS-103)	TDF → TDF (n=176)
	ADV → TDF (n=90)

Studies GS-102/103: Four-Year Tenofovir Renal Safety in HBeAg(-) and (+) Patients

Summary of Cumulative Open-Label Renal Safety (Weeks 48 to 192)

Study 102: HBeAg(-)	TDF-TDF (n=235)	ADV-TDF (n=112)
Confirmed ↓ Phosphorus <2 mg/dL	1%	2%
Confirmed ≥0.5 mg/dL Creatinine	1%	<1%
Confirmed Creatinine Clearance <50 mL/min	0	<1%

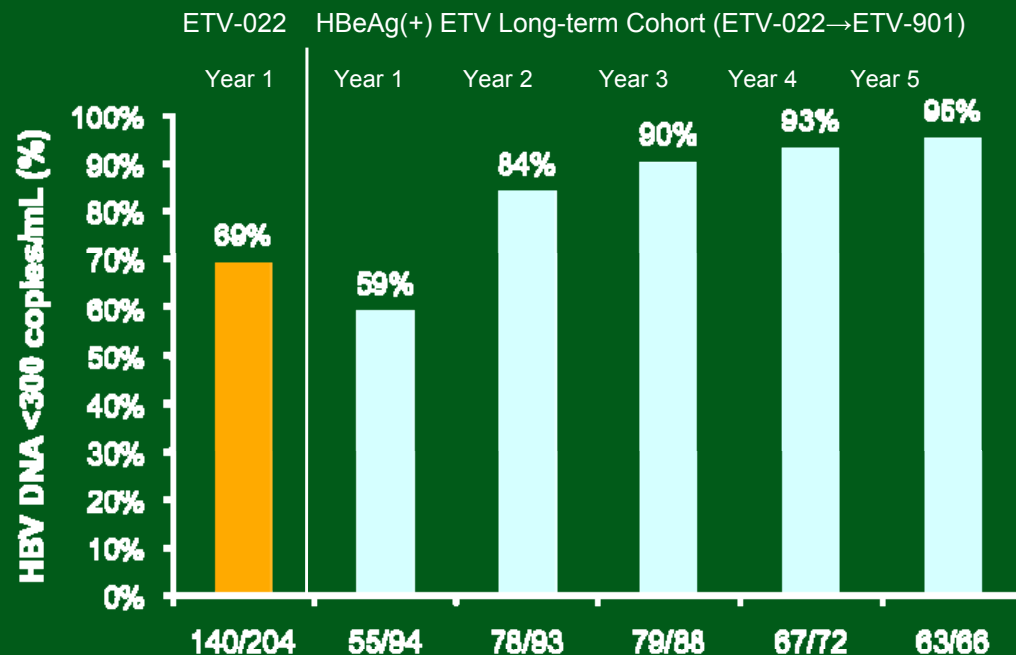
Study 103: HBeAg(+)	TDF-TDF (n=154)	ADV-TDF (n=84)
Confirmed ↓ Phosphorus <2 mg/dL	<1%	1%
Confirmed ≥0.5 mg/dL creatinine	<1%	2%
Confirmed Creatinine Clearance <50 mL/min	0	0



Five Years of Entecavir in Asian Patients

- Follow-up study (ETV-901) of 94 HBeAg(+) patients from the parent study (ETV-022)
- ETV 1 mg/day
- HBeAg status at 5 years
 - Loss: 26/65 (40%)
 - Seroconversion: 12/65 (18%)
- No safety issues detected

Proportion Achieving HBV DNA <300 copies/mL Through 5 Years



Long-term Entecavir Treatment for up to 5 Years in Asians with HBeAg positive Nucleos(t)ide naive Chronic Hepatitis B: Results from ETV-022 and -901.

- 94 Asian patients
- Cumulative rate of HBeAg loss at week 240 was 40%
- Cumulative rate of HBeAg seroconversion was 18%.
- No entecavir resistance detected at 5 years.
- No discontinuation of drug for adverse effects

Long Term Asian study cohort		
Week	HBV DNA < 300 copies/mL	ALT \leq 1 x upper limit of normal
48	59%	63%
96	84%	75%
144	90%	73%
192	93%	87%
240	95%	76%

Prevalence of renal alterations indicative for proximal tubular damage in patients with hepatitis B during long-term tenofovir treatment

- Mean treatment duration – 28.9 months
- N = 61
- Patients had comorbidities

proximal tubular damage ~
1) Glycosuria
2) Phosphate loss
3) Alpha1-microglobulinuria

Mean GFR	102ml/min
GFR decline	58%
TRP reduction <82%	10%
TmPO4/GFR reduction	30%

High prevalence of reduced bone mineral density in patients with chronic hepatitis B under nucleot(s)ides analogues treatment

N=319 consecutive patients with hepatitis B

75% men, 63 years, 57% cirrhosis

- Tenofovir/adefovir lamivudine n=239
- Lamivudine n= 20
- Entecavir n=60

Results: Osteoporosis found in 60 (19%) and osteopenia in 157 (49%)

Multivariate Analysis

Variable	Odds Ratio (Confidence interval)
Male gender	0.48 (0.25-0.91)
Older age	1.03 (1-1.05)
Nucleotide treatment	0.57 (.32-.99)

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Overall and Multi-Drug HBV Resistance

- **Method:**

- 7,922 Chinese patients collected (2007-2010)
- Direct PCR sequencing used to screen HBV reverse-transcriptase region
- Clonal sequencing performed to identify MDR HBV strains

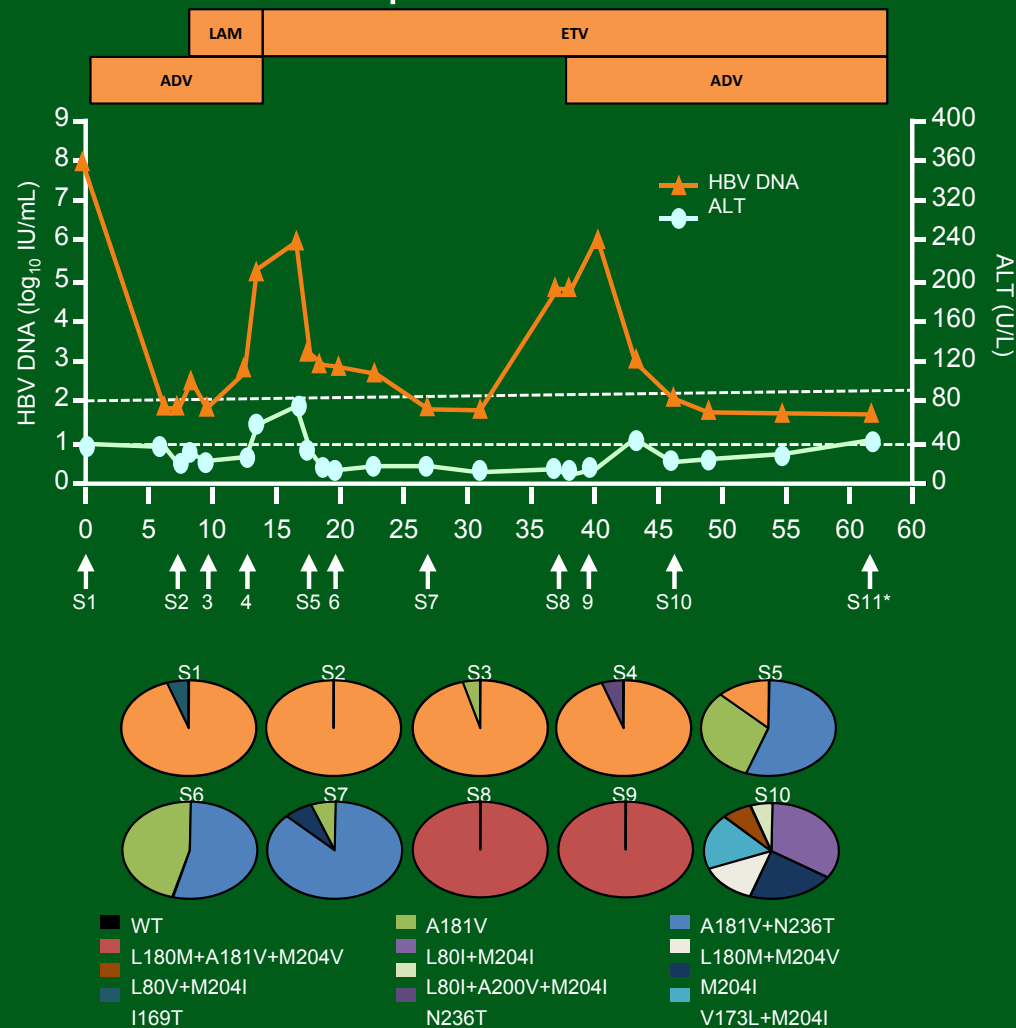
- **Results:**

- Drug-resistance mutations detected in 30.3% of samples
- MDR HBV strains were detected alone or together with other mutant/wild-type HBV strains in 11 patients

Characteristics of MDR Hepatitis B and Viral Suppression

- All patients harboring MDR HBV had received long-term sequential NA therapies
- MDR strains suppressible by combination therapy with ADV and ETV or LAM
- HBV MDR Conclusions:
 - Associated with sequential use of antiviral drugs
 - Combination of ADV and ETV or LAM option if TDF not available

Evolution and Suppression of HBV MDR in Representative Strain



*Clonal sequencing for S11 failed because of undetectable viral load

Prevalence and Impact of Antiviral Resistance in Naïve CHB Patients

- Study to determine prevalence of antiviral drug resistance mutations in naïve CHB patients and impact of mutations on response to NA treatment
- **Methods:**
 - 203 NA-naïve CHB patients (2000-2010)
 - Antiviral drug resistance tested by direct sequencing
 - Polymerase gene sequences compared to consensus sequence of respective HBV genotype using HBV database

	No-Treatment (n=121)	Subsequent Treatment (n=82)	<i>P</i>
Age	39	44	0.005
Male	55%	73%	0.007
Race			
Caucasian	19%	34%	0.11
Asian	70%	56%	
African American	7%	6%	
Other	3%	4%	
ALT (U/L)	58 ± 110	136 ± 199	0.002
HBeAg Positive	26%	59%	<0.001
HBV DNA (log ₁₀ IU/mL)	4.5 ± 1.9	6.7 ± 1.8	<0.001

Impact of Antiviral Resistance on Treatment of Naïve CHB Patients

CHB Patients with Subsequent HBV Treatment (n=82)

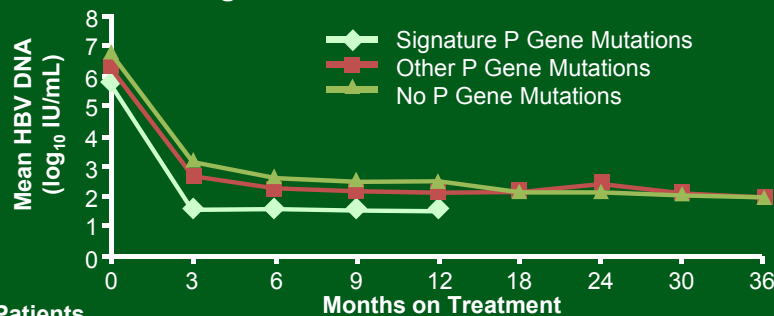
	Pre-existing P Gene Mutations			
	Signature	Other	No	P value
Number of Patients	3	8	71	
Medications				
Lamivudine	0	2	13	0.94
Adefovir	1	1	6	
Entecavir	2	4	34	
Tenofovir		1	14	
Telbivudine	0	0	1	
Other	0	0	3	

Conclusions:

- Prevalence of antiviral resistance HBV mutations In NA-naïve patients is low

- Pre-existing mutations (as minor variant) do not impact response to NA treatment

Effect of Preexisting P Gene Mutations on Treatment Outcomes



Number of Patients

Evaluated	Signature P Gene Mutations	Other P Gene Mutations	No P Gene Mutations
3	8	71	
	3	54	29
	0	29	13
	0	3	13

- Data support current recommendation that resistance testing not needed prior to start of NA in CHB

Abstracts on Lamivudine Resistance

Comparison of Three Rescue Strategies for LAM-resistant CHB

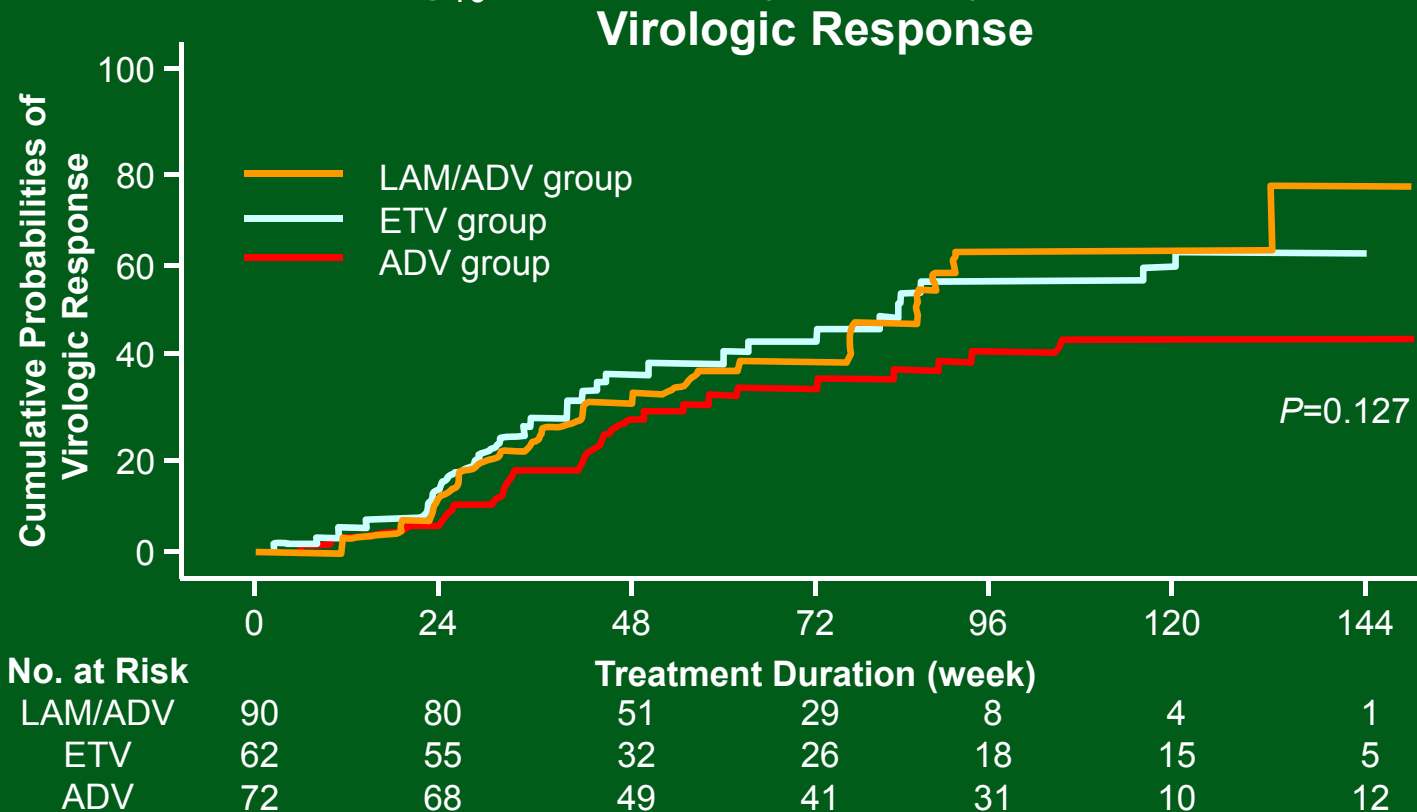
- Treatment options for LAM-resistant CHB, before availability of TDF included:
 - LAM + ADV
 - ADV
 - ETV (1 mg/day)
- Objective: Compare the efficacy and genotypic resistance of these 3 options
- Methods: Consecutive patients (N=224) treated for LAM-R CHB at Seoul National University Hospital, Seoul, Korea (2005-2009)

Baseline Characteristics

Variable	LAM/ADV (n=90)	ETV (n=62)	ADV (n=72)	<i>p</i>
Mean Age (year)	48	48	48	0.768
Male	75.6%	74.2%	72.2%	0.891
Liver Cirrhosis	42.2%	38.7%	43.1%	0.865
HBeAg-positive	74.2%	66.7%	62.2%	0.304
Median HBV DNA (Log ₁₀ copies/mL)	7.97	7.69	7.57	0.215
ALT >2x ULN	70.0%	80.6%	80.6%	0.121
LAM-resistant Mutation				0.528
rtM204I/V/S	36.7%	37.1%	29.2%	
rtM204I/V/S+rtL180M/V	63.3%	62.9%	70.8%	
Median F/U (weeks)	70.0	121.2	124.2	<0.001

Rescue Strategies for LAM-Resistant CHB: Virologic Results

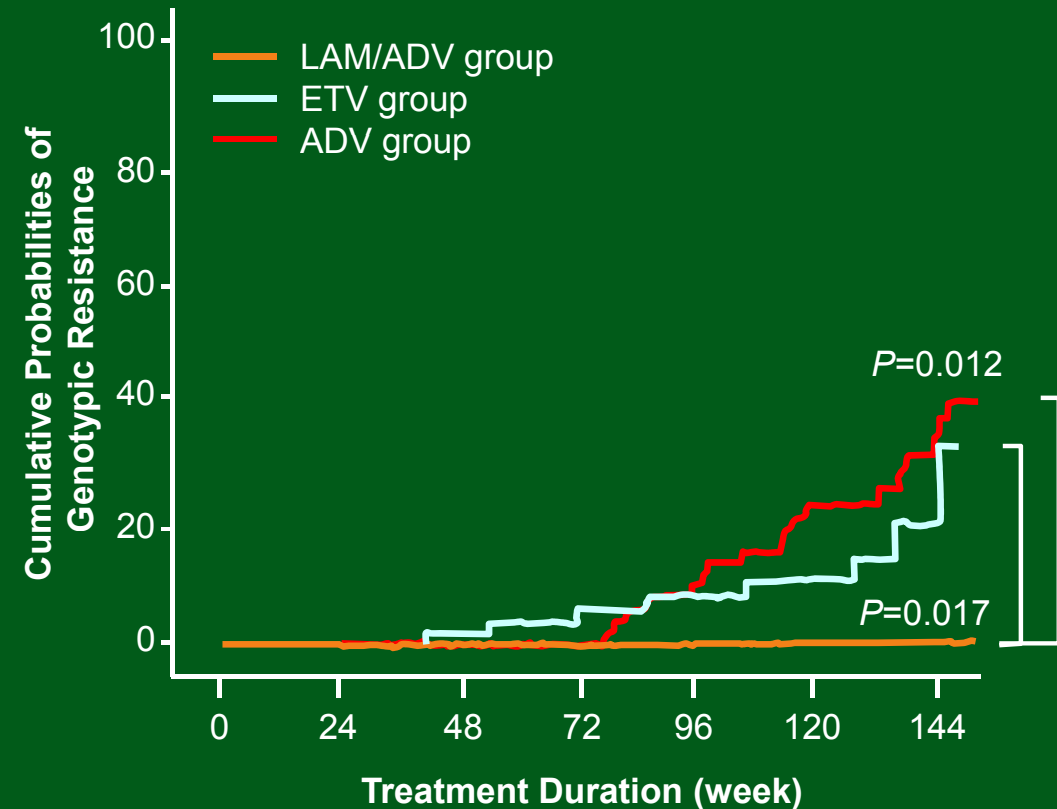
- Mean treatment duration of 74.5 weeks
- At week 48, mean decrease in HBV DNA similar among three groups:
 - LAM/ADV: $4.38 \pm 1.88 \log_{10}$ copies/mL
 - ETV: $4.05 \pm 1.95 \log_{10}$ copies/mL
 - ADV: $3.57 \pm 2.50 \log_{10}$ copies/mL ($P=0.112$)



Rescue Strategies for LAM-Resistant CHB: Resistance Results

- Higher rates of virologic breakthrough in ADV group ($P=0.02$)
- Emergence of genotypic resistance to ETV or ADV was significantly less frequent with LAM/ADV
- No patient achieving undetectable HBV DNA within 48 weeks developed genotypic resistance during treatment
- Conclusions:
 - LAM/ADV superior to ETV or ADV monotherapy
 - ETV or ADV monotherapy should be continued only in patients who achieve undetectable HBV DNA within 48 weeks

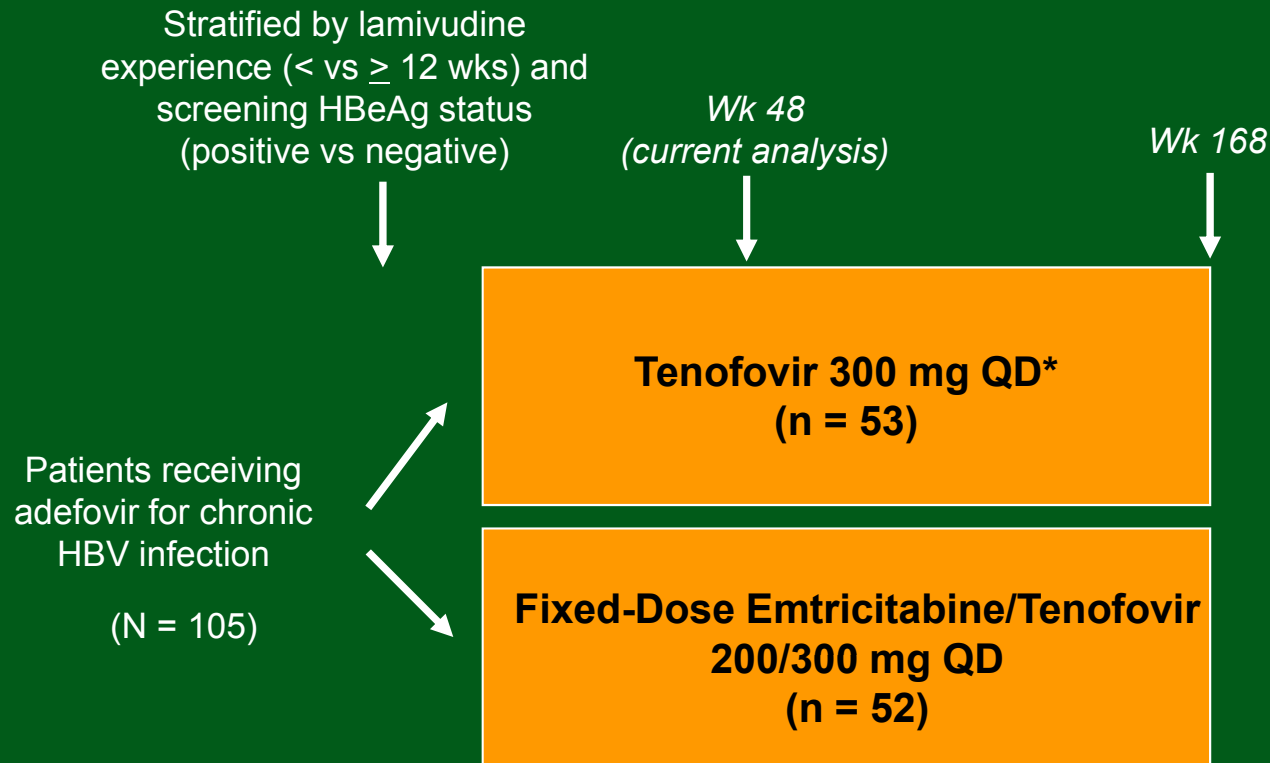
Genotypic Resistance



No. at Risk		Treatment Duration (week)						
		0	24	48	72	96	120	144
LAM/ADV	90	90	90	70	42	18	8	4
ETV	62	62	62	52	45	41	32	7
ADV	72	72	72	64	61	52	37	23

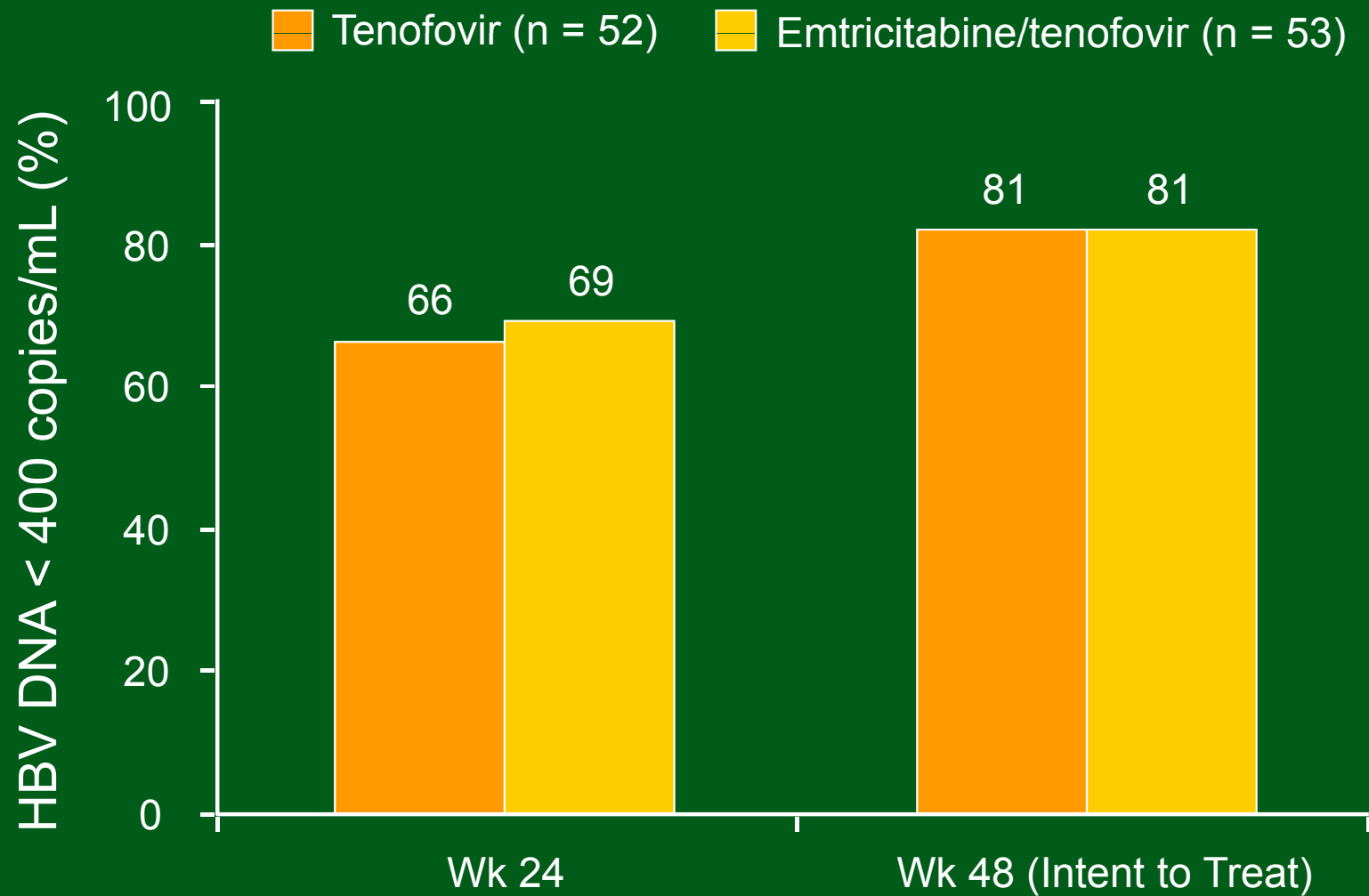
Abstracts on Adefovir Suboptimal Response and Resistance

Efficacy of Tenofovir for the Treatment of Chronic HBV Infection in Adefovir Nonresponders

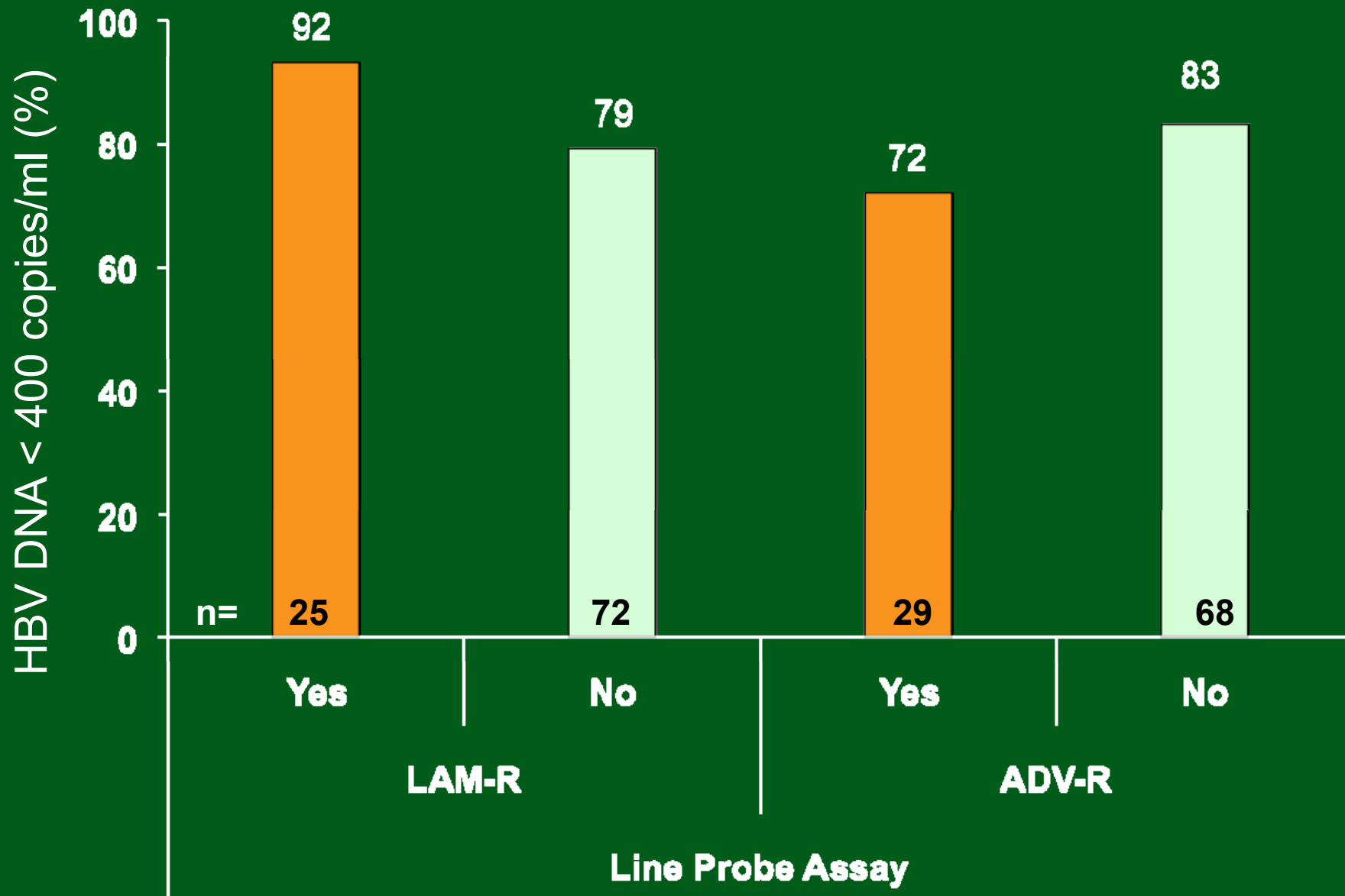


*If HBV DNA \geq 400 copies/mL at or after Wk 24, patients could add emtricitabine (as open-label, fixed-dose emtricitabine/tenofovir) for \geq 12 wks or discontinue study and start commercially available HBV treatment.

Efficacy of Tenofovir for the Treatment of Chronic HBV Infection in Adefovir Nonresponders



Efficacy of Tenofovir for the Treatment of Chronic HBV Infection in Adefovir Nonresponders



Use of Tenofovir in Patients with Lamivudine and Adefovir Resistance

- Virologic response to tenofovir not affected by presence of lamivudine resistance mutations but significantly decreased when adefovir resistance mutations present
 - HBV DNA < 400 copies/mL for patients with vs without adefovir resistance
 - Overall: 52% vs 100%
- At Mo 12: 33% vs 90%

Mean HBV DNA, log ₁₀ copies/mL (SD)	Wild Type (n = 22)	Lamivudine Resistance (n = 70)	Adefovir Resistance (n = 21)	Log Rank P Value
Baseline	8.3 (8.9)	8.3 (8.8)	8.4 (8.7)	.92
Mo 12	2.9 (3.3)	3.0 (3.4)	5.6 (6.2)	.001

Comparison of LAM + ADV vs. ETV Alone in ADV-resistant CHB Patients

- Study to compare treatment response between LAM + ADV and ETV in ADV-resistant patients
- 46 patients with ADV-R prospectively analyzed
 - ADV naïve: 6
 - ADV + LAM-R: 40*
- Treatment:
 - 24 LAM + ADV
 - 22 ETV (8: 0.5 mg; 14: 1 mg)

Patient Baseline Characteristics

	LAM + ADV (n=24)	ETV (n=22)	P
Age (years)	48.4	53.4	0.13
Male	21	22	0.24
ALT (IU/L)	165.7	199	0.67
Total Bilirubin (mg/dL)	1.1	1.3	0.19
HBeAg(+)	58.3%	54.5%	0.56
Liver Cirrhosis	70.8%	77.3%	0.74
HBV Genotype B:C	13:11	9:13	0.37
HBV DNA (log ₁₀ copies/mL)	5.6	5.8	0.75
ADV Naïve	4	2	0.25
rtA181T/V±rtN236T	15	15	0.67

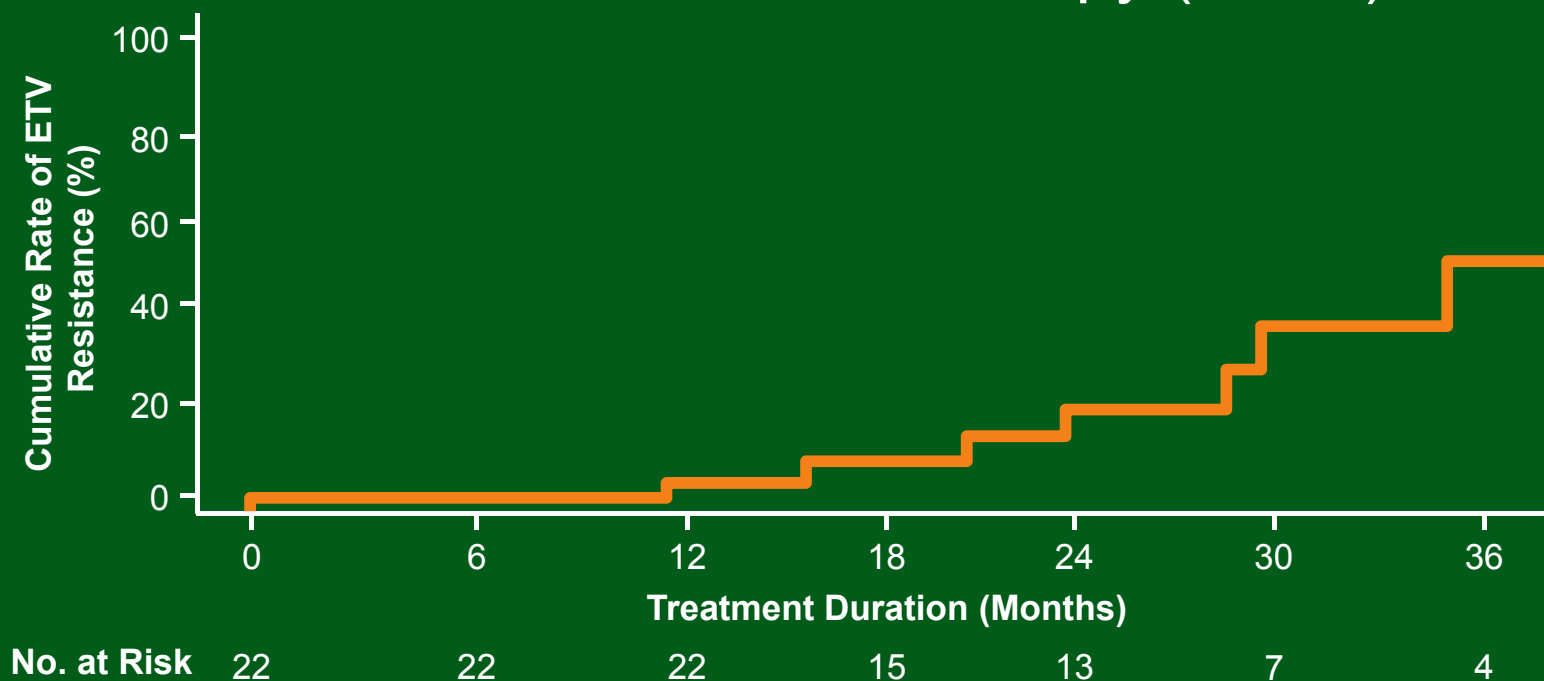
Comparisons of Baseline Factors between Patients with rtN236T and rtA181T/V ± rtN236T Resistance

	rtN236T (n=16)	rt181T/V ± rtN236T (n=30)	P
Age (years)	55.3	48.4	0.046
Male	16	27	0.19
ALT (IU/L)	186.4	179.0	0.93
Total Bilirubin (mg/dL)	1.2	1.1	0.60
HBeAg(+)	2	22	<0.001
Liver Cirrhosis	14	20	0.17
HBV Genotype B:C	15:1	9:21	<0.001
HBV DNA (log copies/mL)	5.5	5.8	0.6

*rtN236T:16; rtA181T: 6; rt181V:9; rt181V+rtN236T: 12; rt181T+rt236V:3

LAM Plus ADV vs. ETV Monotherapy in ADV-resistant CHB Patients: Results

Cumulative Rate of ETV-R in ADV-R Patients Treated with ETV monotherapy (N=22)



- Combined LAM and ADV treatment was less effective in rtA181T/V \pm rtN236T than single rtN236T ADV resistant mutation
- Incidence of ETV resistance was high in LAM/ADV-resistant patients treated with ETV monotherapy

Abstracts on Entecavir Suboptimal Response and Resistance

Treatment of CHB Patients after Partial Response to Entecavir

- Retrospective analysis of treatment of Asian patients with partial response to ETV at 6-12 months (N=42)
 - No mutation and/or virologic breakthrough of >1 log IU/mL from nadir
- Treatment ETV + ADV (12%), ETV + TDF (74%) or TDF (14%)
- Endpoint: Complete viral suppression (HBV DNA <60 IU/mL)

Baseline Patient Characteristics

Characteristic	Baseline Prior to Any Antiviral
Age at ETV Treatment	36
Male	57%
Ethnicity	
Vietnamese	85%
Other Asian	15%
Serology	
Genotype B	63%
Genotype C	37%
HBeAg(+)	95%
Dosage	
0.5 mg Entecavir	64%
1.0 mg Entecavir	36%
Treatment Experienced	
Lamivudine	7%
Adefovir	7%

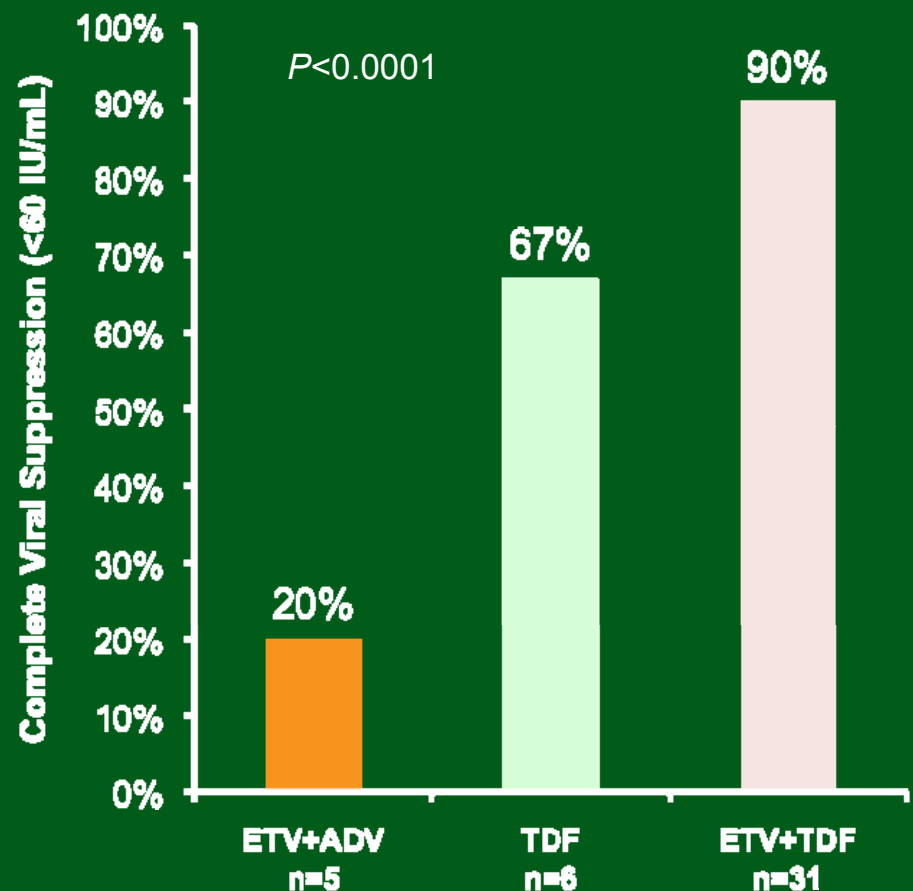
Patient Characteristics Prior to Antiviral Therapy and at Switch

Characteristic	Prior to Any Antiviral	At Switch (Prior to New Therapy)
HBV DNA (\log_{10} IU/mL)	8.2	3.4
ALT (U/L)	40	32
Treatment Duration (mos.)	25	14

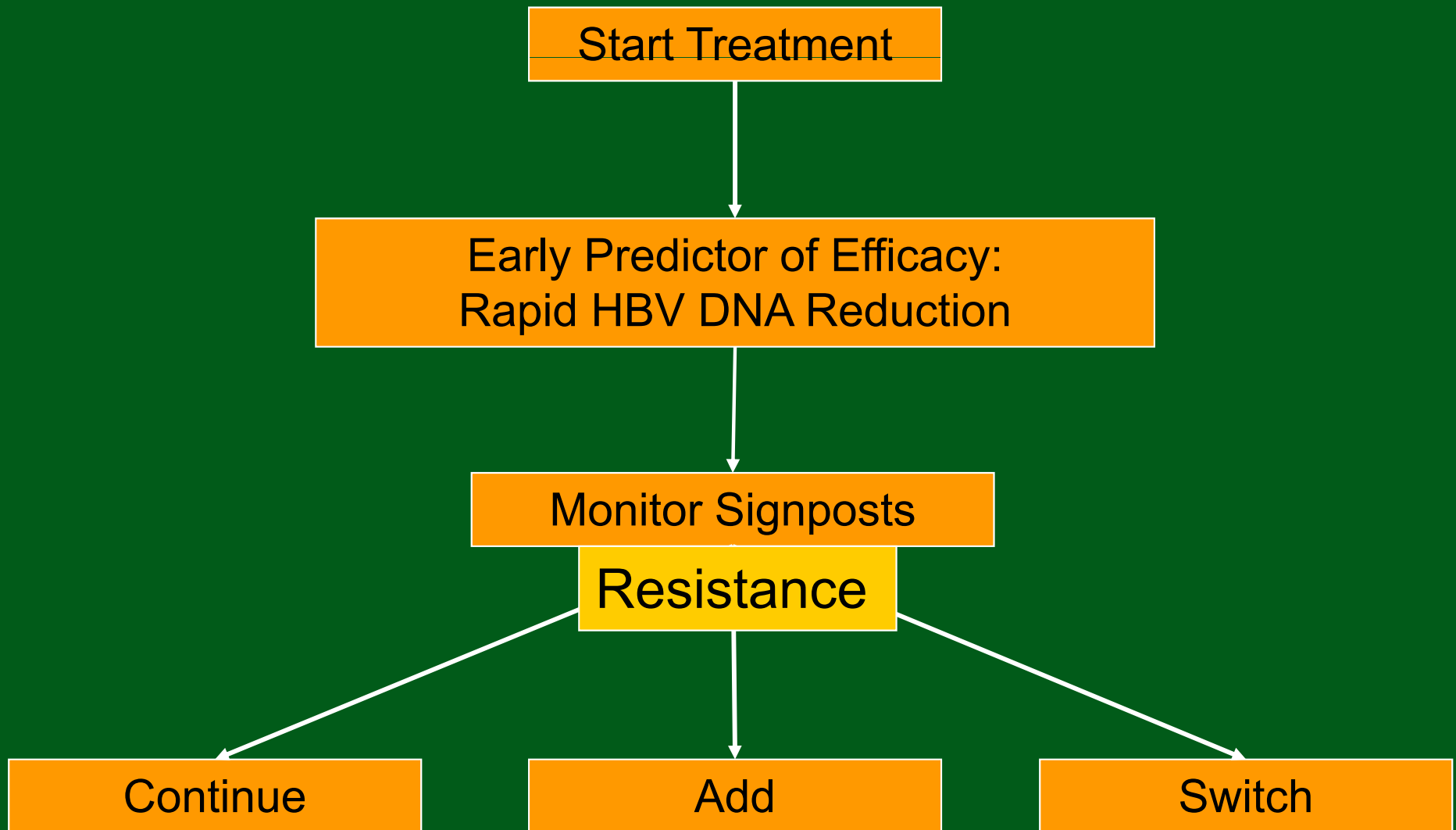
Response Rates Higher with ETV + TDF After Partial Response to Entecavir

- ETV + TDF and TDF alone achieved higher rates of complete viral suppression
- One patient achieved HBeAg loss on ETV + TDF, but no patient achieved HBeAg seroconversion
- All patients with persistently elevated HBV DNA on ETV + ADV achieved CVS 6 months after switching to ETV + TDF

Complete Viral Suppression Rates after 6 Months of New Therapies



Possible Approaches to Resistance



Summary: AASLD Guidelines for Management of Antiviral-Resistant Hepatitis B

Resistance

Rescue Therapy

Lamivudine Add adefovir or tenofovir DF
Stop lamivudine, switch to emtricitabine/tenofovir DF

Adefovir Add lamivudine
Stop adefovir, switch to:
 Emtricitabine/tenofovir DF
Switch to or add entecavir (if no prior lamivudine resistance)

Entecavir Switch to tenofovir DF or emtricitabine/tenofovir DF

Telbivudine Add adefovir or tenofovir DF
Stop telbivudine, switch to emtricitabine/tenofovir DF

Thank you