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I have financial relationships within the last 12 months relevant
to my presentation with:

Research Grant Support: Bristol-Myers Squibb, Gilead Sciences,
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AND

My presentation does include discussion of off-label or
investigational use

Emtricitabine for the treatment of HBV

Two Year Tenofovir Disoproxil Fumarate (TDF) Treatment and Adefovir Dipivoxil (ADV) Switch Data in HBeAg-Positive Patients With Chronic Hepatitis B (Study 103)

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Background

- Tenofovir DF (TDF) is a nucleotide analog and obligate chain terminator
- Approved for HIV-1 in 2001: ~ 2 million patient-years of experience
- Approved for chronic hepatitis B (CHB) in 2008
- Week 48 Phase 3 data¹ showed TDF superior to adefovir dipivoxil (ADV) in HBeAg-positive patients:
 - 76% of TDF-treated patients versus 13% ADV-treated patients had HBV DNA <400 copies/mL

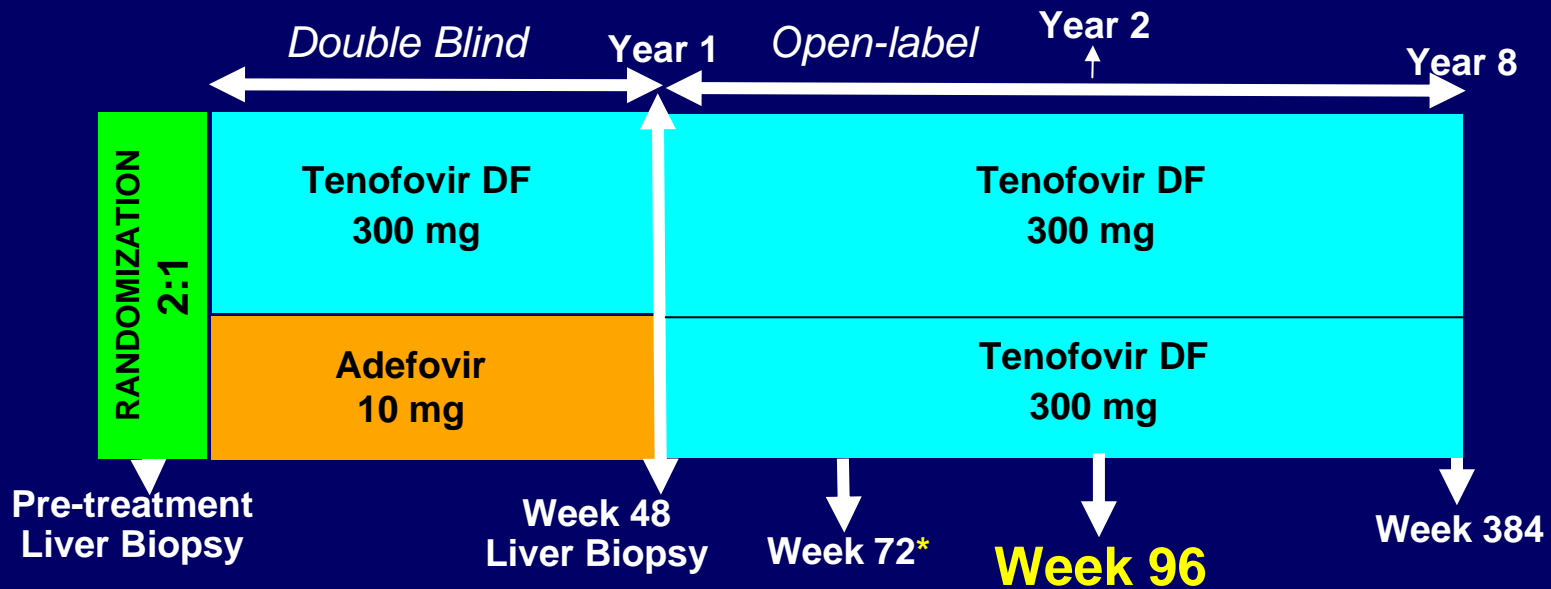
¹Marcellin, Heathcote et al 2008 NEJM 359:2442-55

Aim

To evaluate the safety and efficacy of:

- 2 years of TDF therapy
- Switch from ADV to TDF

HBeAg Positive Study 103 Design



Patients (on study) N=

TDF → TDF	176	154	145
TDF → FTC/TDF		(15)*	
ADV → TDF	90	84	83
ADV → TDF → FTC/TDF		(13)*	

86% retention

*Week 72 HBV DNA \geq 400 copies/mL option to add emtricitabine (FTC) to TDF in a fixed dose tablet

Key Eligibility Criteria

Key eligibility criteria

- HBeAg+ patients
- Age 18-69 years
- Compensated liver disease
- Nucleos(t)ide naive
- HBV DNA $> 10^6$ copies/mL
- ALT $\geq 2 \times$ ULN and $<10 \times$ ULN
- Knodell necroinflammatory score ≥ 3
- HIV-1, HDV, HCV seronegative

Methods

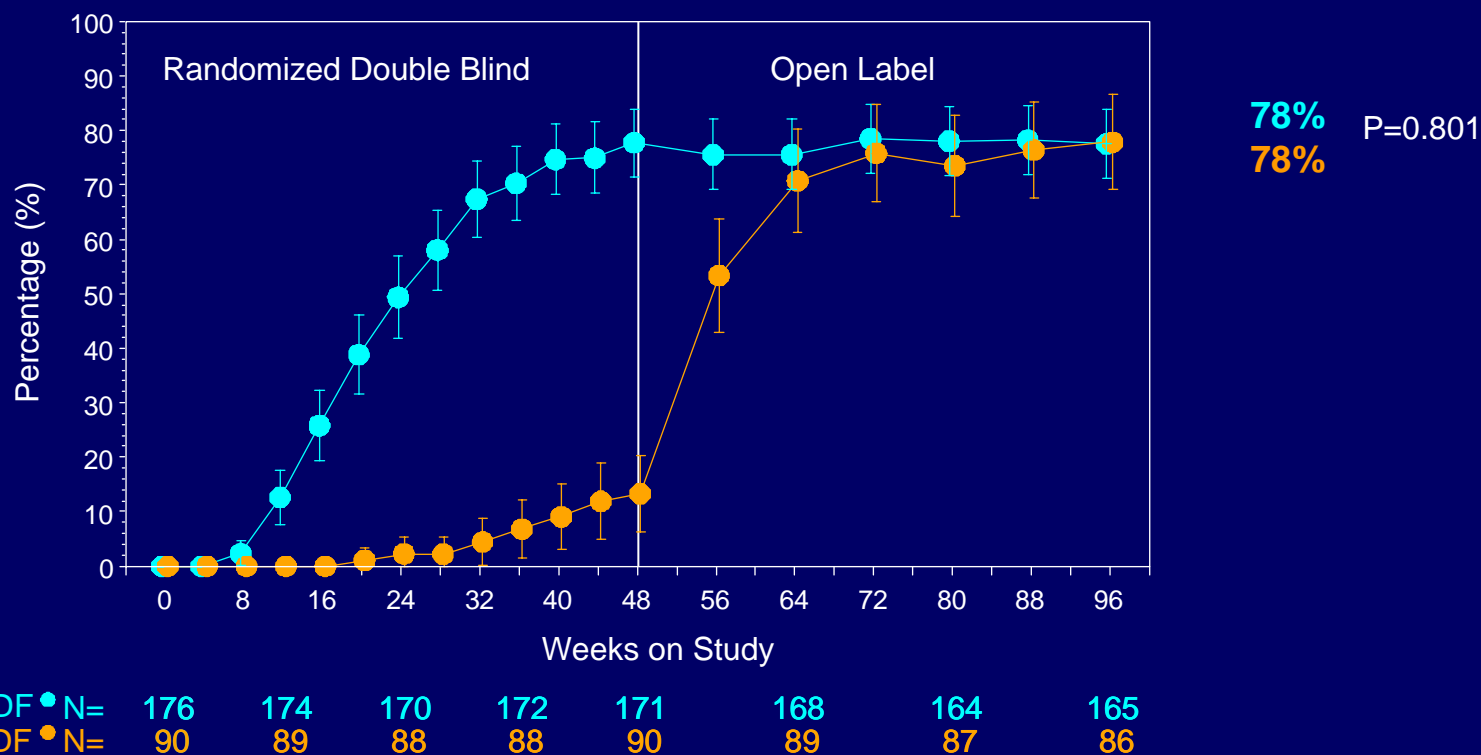
Monitoring During Year 2 (after Week 48 through Week 96)

- HBV DNA and laboratory analyses every 8 weeks
- HBeAg and HBsAg every 16 weeks
- Resistance surveillance: patients with HBV DNA ≥ 400 copies/mL (69 IU/mL)

Baseline Disease and Demographic Characteristics

	TDF (N=176)	ADV (N=90)
Mean Age (years)	34	34
Race		
Caucasian	52%	51%
Asian	36%	36%
Male	68%	71%
Mean HBV DNA (log₁₀ copies/mL)	8.64	8.88
Mean ALT (U/L)	142	155
Mean Knodell necroinflammatory score	8.3	8.5
Knodell fibrosis score = 4 (cirrhosis)	20%	21%
Viral Genotype		
A	24%	21%
B	15%	11%
C	25%	30%
D	32%	35%

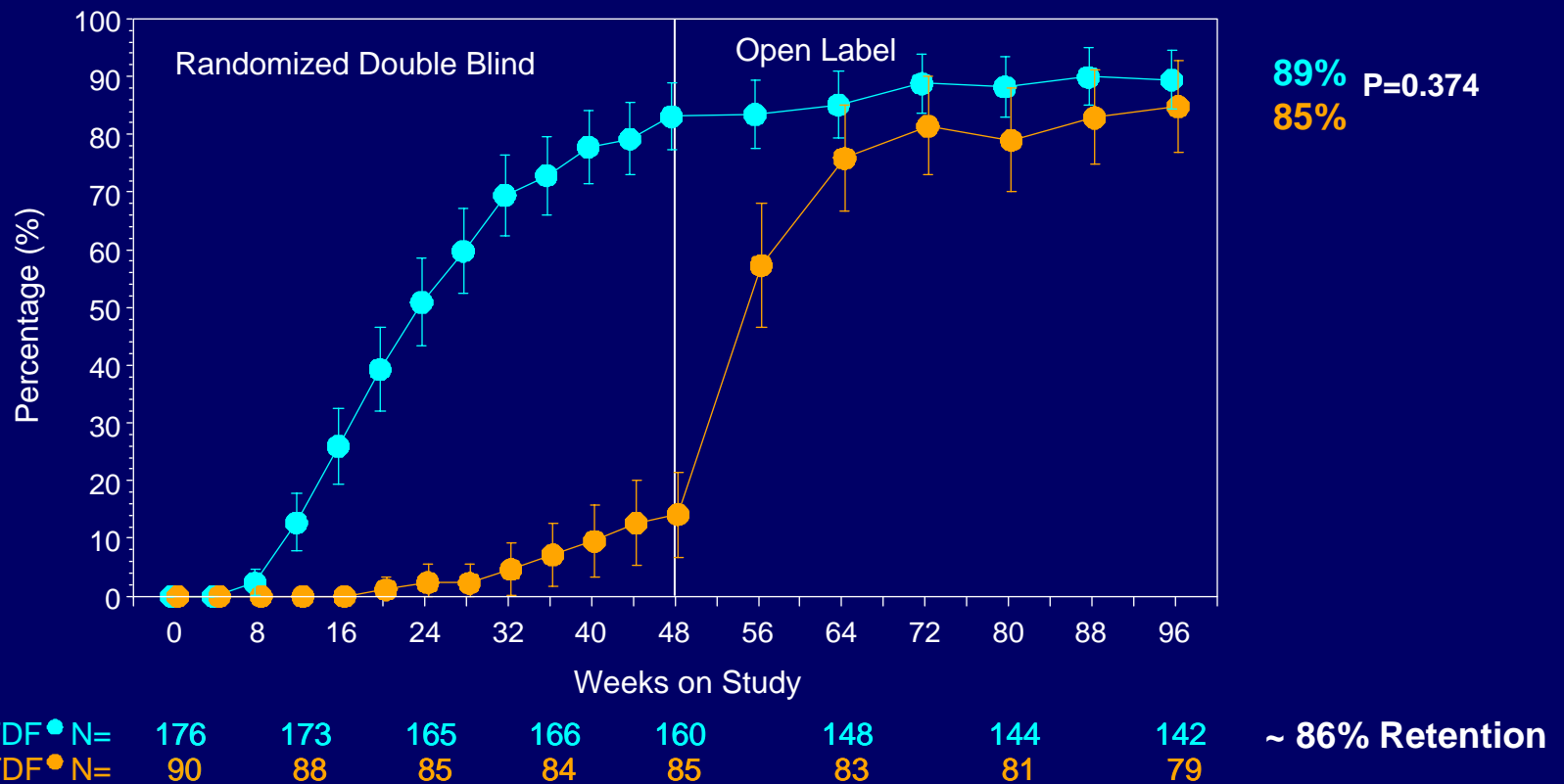
% Patients with HBV DNA < 400 copies/mL (95% CI) (ITT)



Includes 5 patients who had HBV DNA <400 copies/mL at week 96 on FTC + TDF

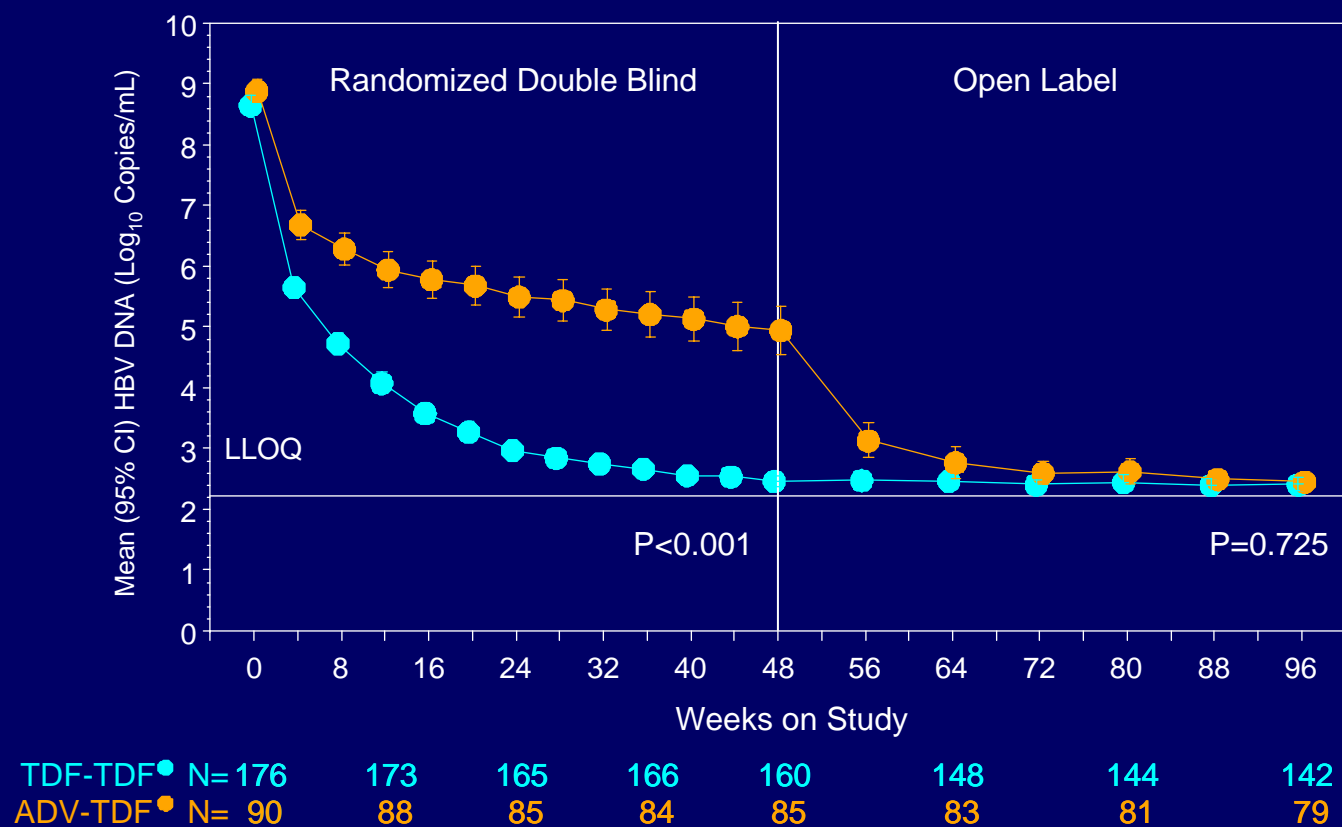
Long Term Evaluation-ITT Analysis: Patients who discontinued for administrative reasons with HBV DNA <400 copies/mL were excluded for visits after discontinuation (N=8). At week 96, 7 patients were missing data at random.

% Patients with HBV DNA < 400 copies/mL (95% CI) (On-Treatment Analysis)



Includes 5 patients who had HBV DNA <400 copies/mL at week 96 on FTC + TDF

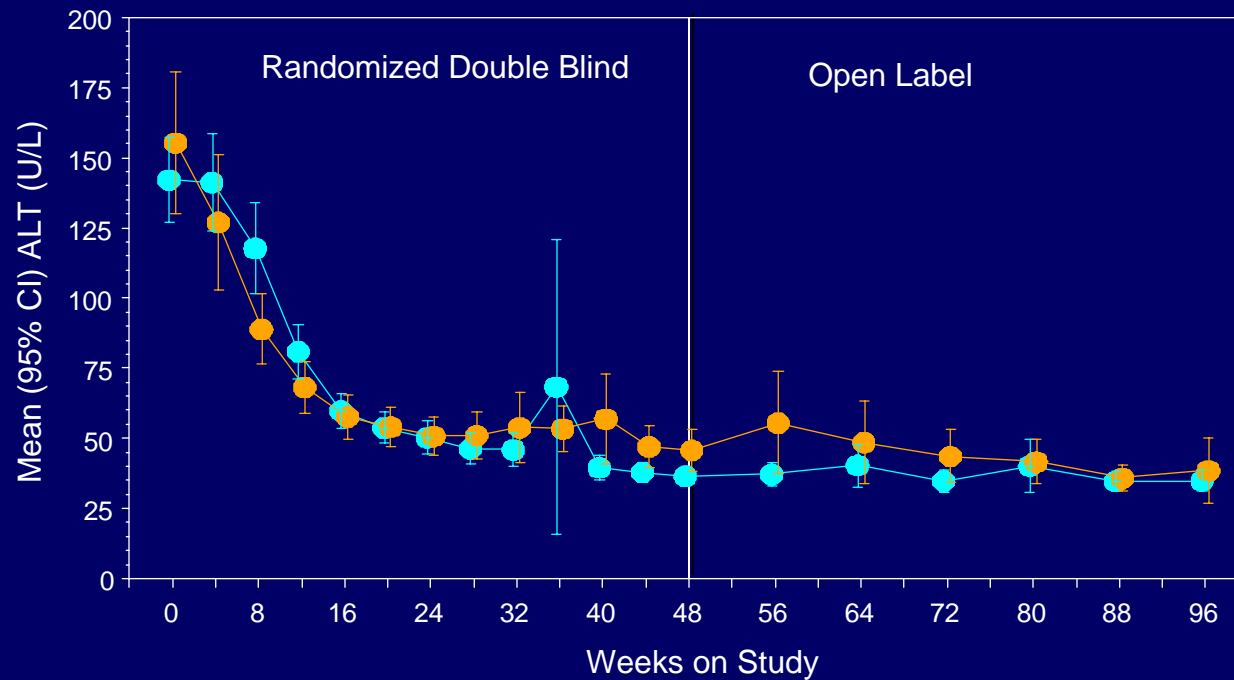
Mean HBV DNA (\log_{10} copies/mL) (95% CI)



ADV Switch Patients

- Viral suppression (below 400 copies/mL) was maintained in 100% (12/12) of patients who were responders on ADV
- Viral suppression at Week 96 was achieved in 82% (55/67) of patients who were viremic at Week 48

Mean ALT (U/L) (95% CI)



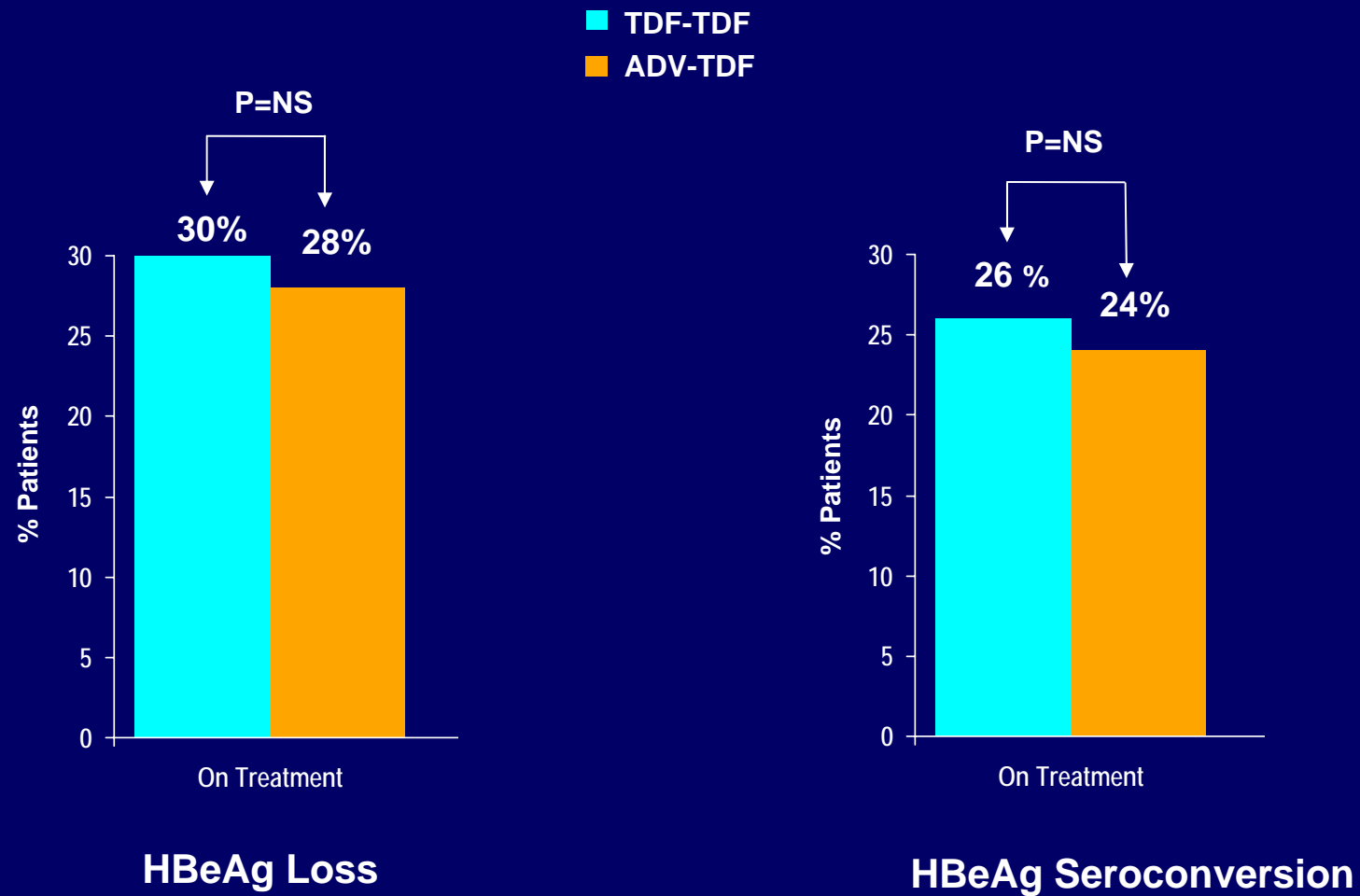
35 U/L
39 U/L

P= 0.765

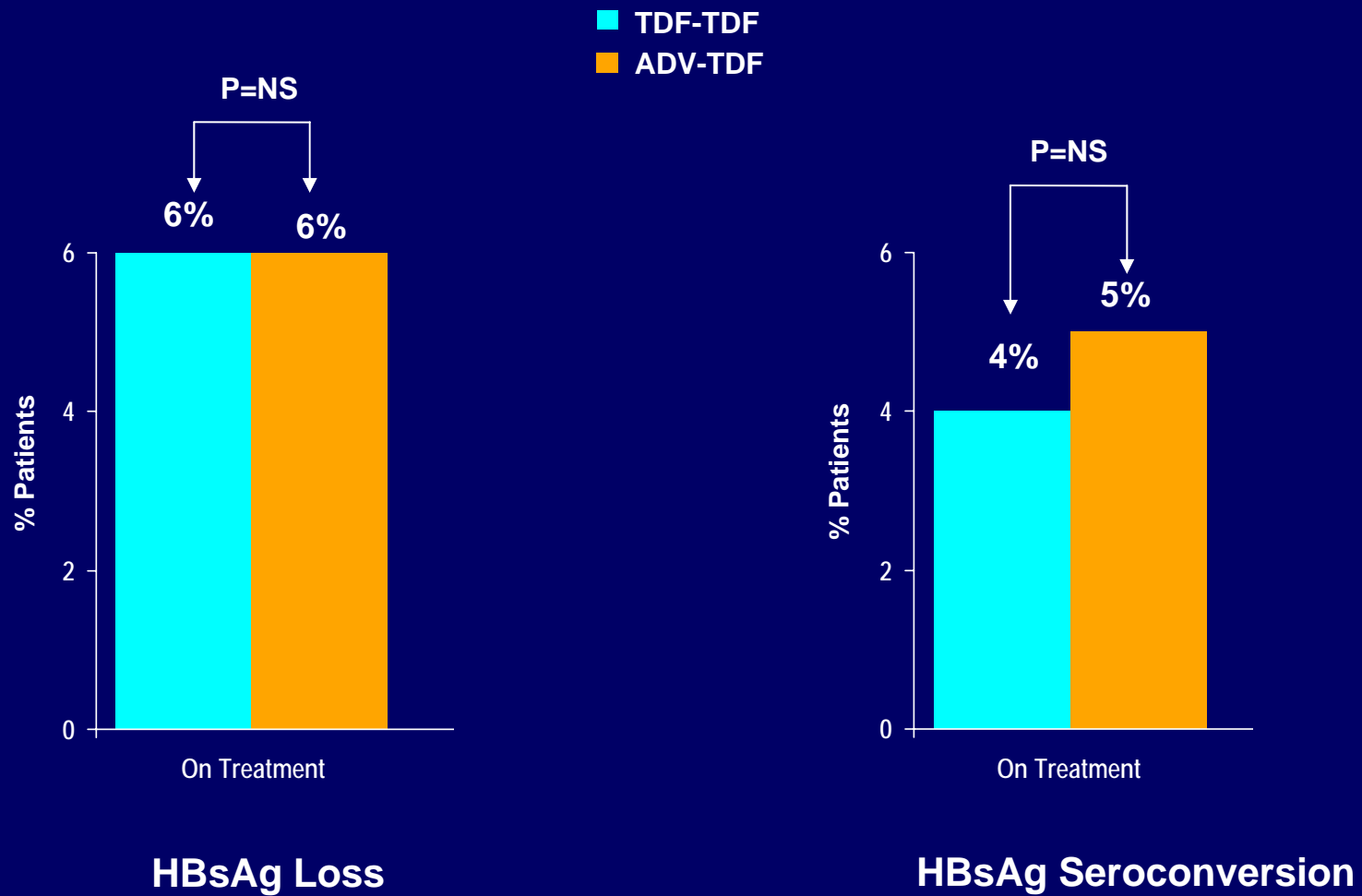
TDF-TDF ● N= 176 174 165 164 160 148 145 140
 ADV-TDF ● N= 90 87 85 84 84 84 79 80

ULN for females=34 U/L
 ULN for males=43 U/L

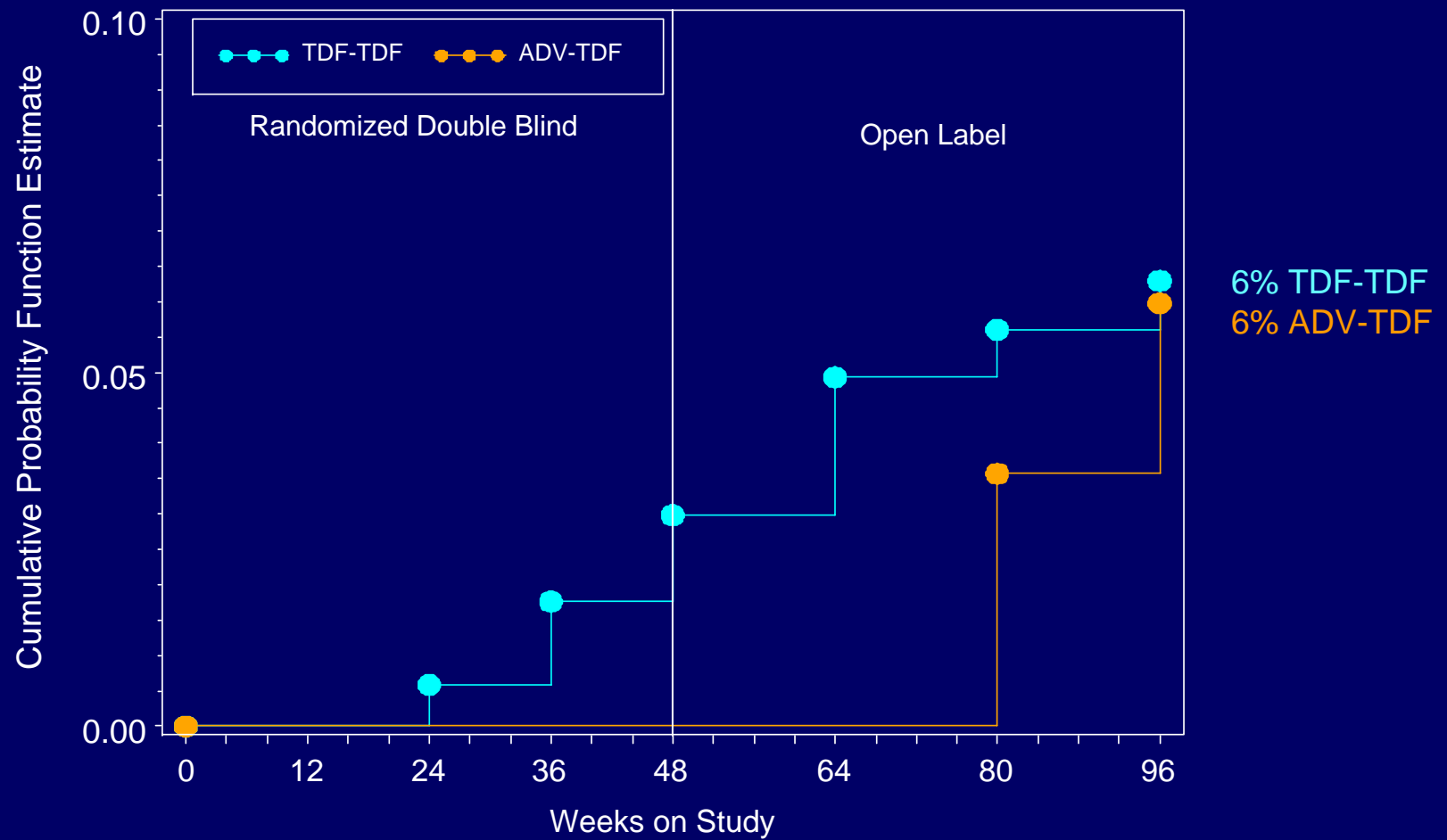
% Patients with HBeAg Loss and Seroconversion Week 96



% Patients with HBsAg Loss and Seroconversion Week 96



Cumulative Probability* of HBsAg Loss



*Kaplan-Meier

FTC added to TDF for HBV DNA ≥ 400 copies/mL

28 patients added FTC to TDF prior to week 96:

- 15 TDF-TDF and 13 ADV-TDF
- Mean time on FTC+TDF: 16 weeks (0, 27 weeks)
- Mean HBV (min, max) DNA at time of addition: 4.36 \log_{10} copies/mL (2.23, 9.07)

At Week 96:

- Mean (min, max) HBV DNA: 3.57 \log_{10} copies/mL (2.23, 8.26)
- 5 patients had HBV DNA <400 copies/mL

Resistance Surveillance

Genotyping
(HBV pol / RT)



Phenotyping
(HBV pol / RT)

All patients :

- at baseline
- yearly if ≥ 400 copies/mL (≥ 69 IU/mL)
- at discontinuation of TDF mono-therapy if ≥ 400 copies/mL

Any patient post-baseline with:

- conserved site changes in pol/RT
- virologic breakthrough
- polymorphic site changes (> 1 patient)

Resistance Surveillance Results

No resistance up to 2 years of TDF monotherapy

- No HBV pol/RT amino acid substitutions associated with TDF resistance were detected through 96 weeks of TDF monotherapy

Week 96 TDF Resistance Surveillance...

A Snow-Lampart et al. Oral #156 “Antiviral Resistance and HBV” March 22, 3:50-4:05 pm (Maryland A)

Summary of Safety Data during Open Label TDF Week 96

	TDF-TDF (N=154)	ADV-TDF (N=84)
Study Drug-Related SAE	1 (<1%)	2 (2%)
Deaths	0	0
G3 or G4 Laboratory	11 (7%)	8 (10%)
Discontinued due to an AE creatinine ↑	1 (<1%) 1	0 0
Confirmed phosphorus < 2mg/dL	0	1 (1%)
Confirmed 0.5 mg/dL ↑ in creatinine	0	2 (2%)
Confirmed creatinine clearance <50 mL/min	0	0

Conclusions Study 103

Week 96

- 88% of patients on therapy had HBV DNA <400 copies/mL
- 6% achieved HBsAg loss
- No resistance detected up to 2 years on TDF monotherapy
- Patients can safely and effectively switch from ADV to TDF treatment
- TDF was well tolerated through Week 96
- TDF demonstrated durable, potent antiviral activity through Week 96