

Three Years of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg-Positive Patients (HBeAg+) With Chronic Hepatitis B (Study 103)

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Background

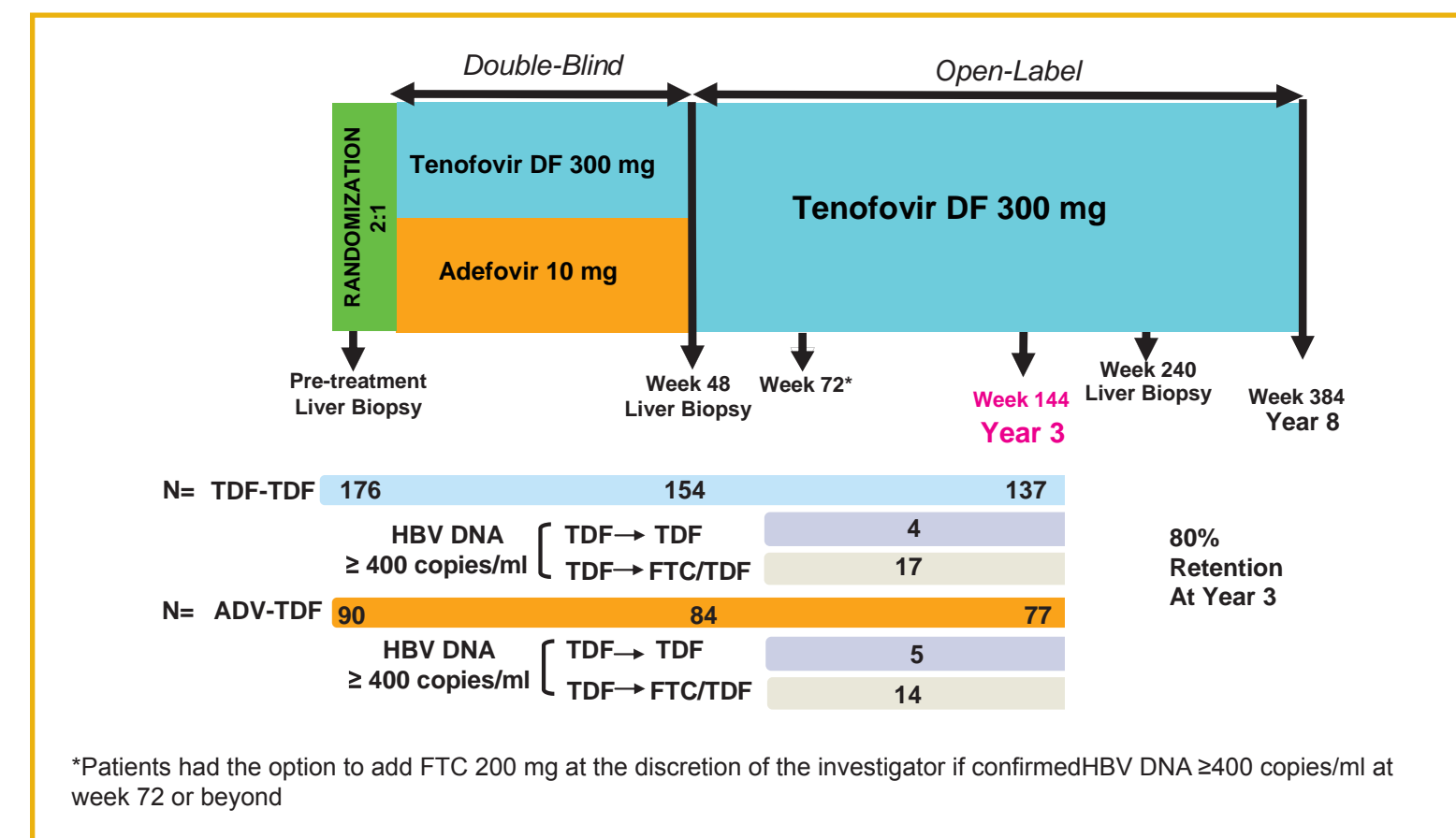
- Tenofovir DF (TDF) was approved for HIV-1 in 2001 and chronic hepatitis B (CHB) in 2008: ~ 2.4 million patient-years of experience
- Week 48 Phase 3 data showed TDF superior to adefovir dipivoxil (ADV):
 - 76% of HBeAg-positive TDF-treated patients (versus 13% ADV-treated patients) had HBV DNA <400 copies/mL
- TDF treatment in HBeAg-positive patients beyond Week 48 showed:
 - Both stable and viremic patients on ADV can effectively switch to TDF and achieve or maintain viral suppression (HBV DNA < 400 copies/mL), normal ALT and increasing HBeAg and HBsAg loss at Week 96
 - TDF patients treated for 96 weeks maintained HBV DNA < 400 copies/mL, normal ALT levels and experienced increasing HBeAg and HBsAg loss

Objective

- Evaluate the safety and efficacy of up to 3 years of TDF therapy

Methods

Figure 1. HBeAg Positive Study 103 Design



Key Eligibility Criteria

- HBeAg-positive patients
- Age 18-69 years
- Compensated liver disease
- Nucleos(t)ide naive
- HBV DNA > 10⁶ copies/mL
- ALT ≥ 2 x ULN and <10 x ULN (females ULN=34 U/L; males ULN=43)
- Knodell necroinflammatory score ≥ 3
- HIV-1, HDV, HCV seronegative

Assessments During Year 3

- HBV DNA and laboratory data every 12 weeks
- HBeAg and HBsAg every 12 weeks
- Resistance surveillance: patients with HBV DNA ≥ 400 copies/mL (69 IU/mL)

Statistical Methods

Long-Term Evaluation, TDF only analysis [LTE-TDF]

- Patients discontinuing the study early and missing data due to death; safety, tolerability, or efficacy; loss to follow-up; or for any other reason who were failures for the endpoint or had an ongoing AE at the last on-study visit were considered failures.
- Patients missing data at random or who discontinued for administrative reasons with HBV DNA <400 copies/mL with no ongoing AEs were excluded for visits after discontinuation.
- Patients with HBsAg loss who discontinued the study for any reason and met the endpoint criteria at the last on-study visit had the last value carried forward (LOCF) and were included in the analysis as a success.
- Patients who added emtricitabine were considered failures at all time points following the addition of emtricitabine

Open-Label Extension, TDF only analysis [OLE-TDF]

- Includes only those patients who entered the open label extension
- Employs an intent-to-treat missing=failure approach
- Patients who added emtricitabine were considered failures at all time points following the addition of emtricitabine

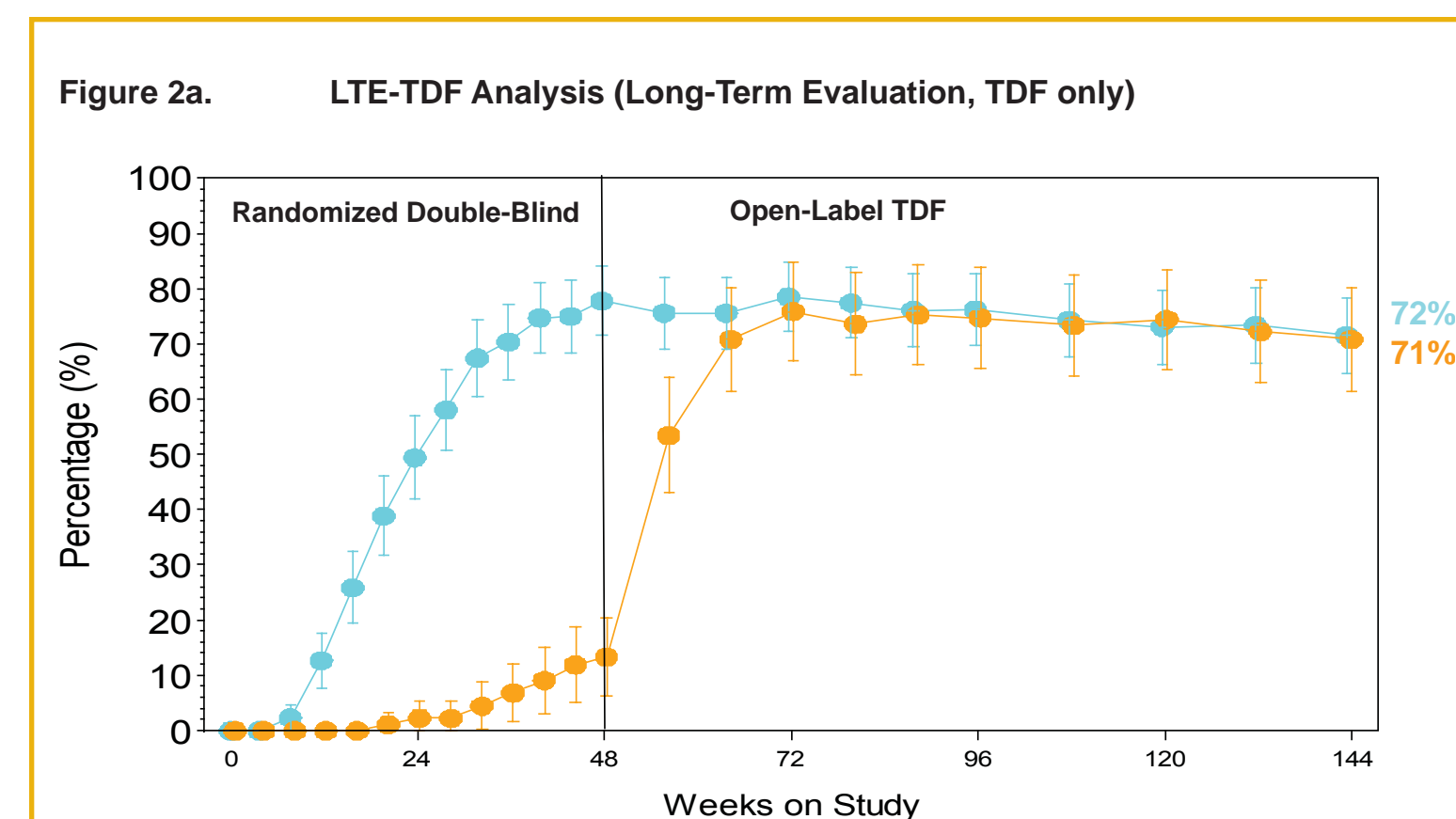
On-Treatment Analysis [observed data, missing=excluded]

- Excludes patients with missing data from both the numerator and denominator at each applicable time point for the analyses of HBV DNA, ALT, and HBeAg loss and seroconversion

Table 1. Baseline Characteristics of Patients Entering Year 3 Similar to Patients Randomized

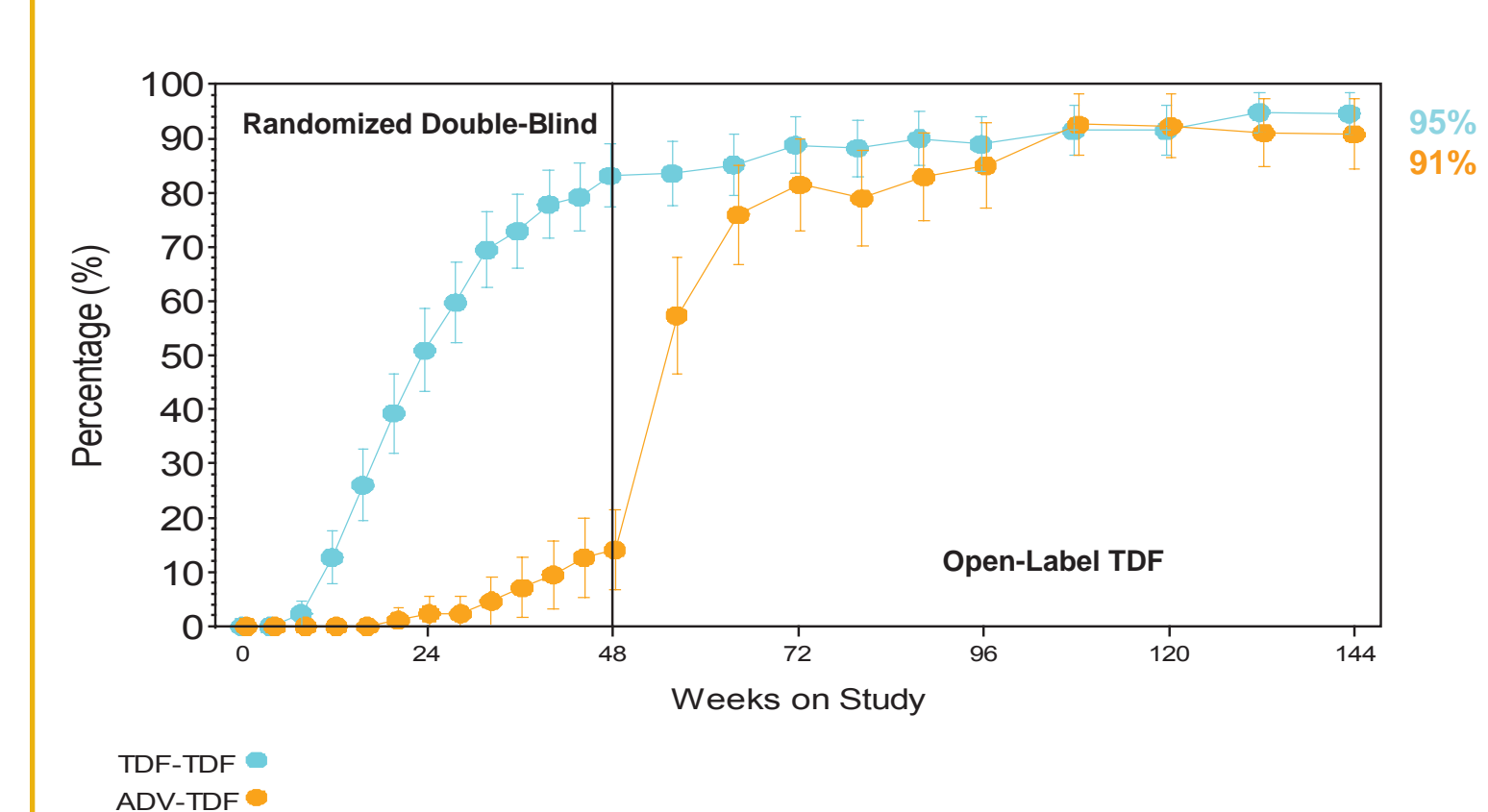
	Randomized Treatment		Patients Entering Year 3	
	TDF (N=176)	ADV (N=90)	TDF-TDF (N=141)	ADV-TDF (N=82)
Mean Age (years)	34	34	35	35
Race				
Caucasian	52%	51%	55%	54%
Asian	36%	36%	34%	34%
Male	68%	71%	72%	72%
Mean HBV DNA (log ₁₀ copies/mL)	8.64	8.88	8.66	8.84
Mean ALT (U/L)	142	155	142	159
Mean Knodell necroinflammatory score	8.3	8.3	8.2	8.5
Mean Knodell fibrosis Score	2.3	2.4	2.3	2.5
Knodell fibrosis score = 4 (cirrhosis)	20%	20%	22%	20%
Viral Genotype				
A	23%	21%	25%	21%
B	15%	11%	13%	8%
C	25%	30%	24%	31%
D	31%	35%	33%	36%

Figure 2. HBV DNA Remains Suppressed with up to 3 Years of TDF Treatment (% Patients with HBV DNA < 400 copies/mL)



- OLE-TDF Analysis: % Patients with HBV DNA <400 copies/mL was 75% TDF-TDF and 74% ADV-TDF

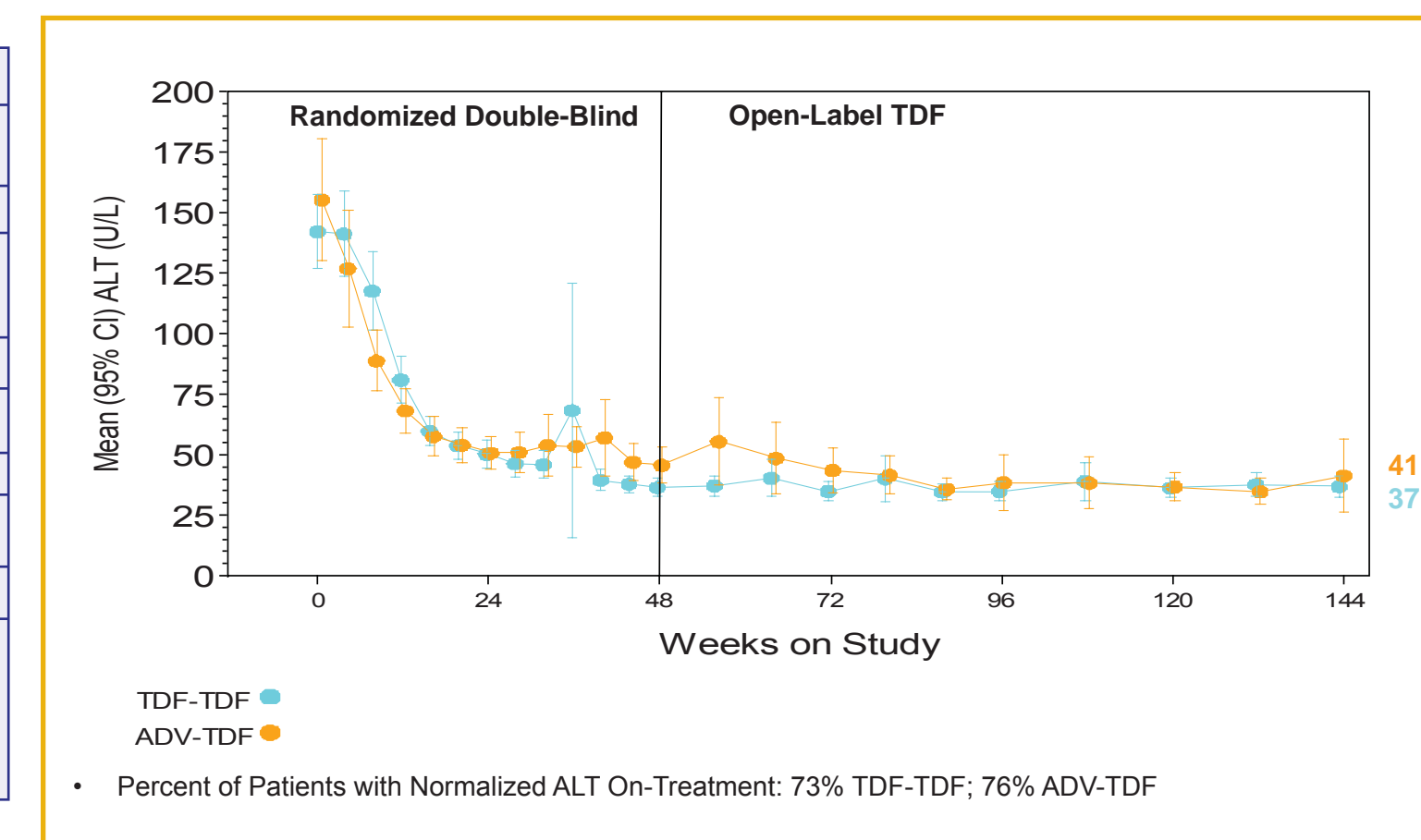
Figure 2b. On-Treatment Analysis



- Includes 17 patients across both treatment groups who had HBV DNA <400 copies/mL at week 144 on FTC + TDF

Results

Figure 3. ALT (U/L) Over Time



- Percent of Patients with Normalized ALT On-Treatment: 73% TDF-TDF; 76% ADV-TDF

Surveillance for Resistance Results

Overall HBV DNA from 18 viremic patients were genotypically evaluated and 5 patients had amino acid substitutions in conserved site region:

Patients originally randomized to TDF:
TDF: rR51K
FTC + TDF: rR192H
FTC + TDF: rL180L/M ± rM204M/V ± rT181T

Patients originally randomized to ADV:
ADV-TDF: rN236N/T ± rR274Q/R
ADV-TDF: rG152E

Phenotypically these conserved site changes were evaluated in vitro in HepG2 cells. No HBV pol/RT amino acid substitutions associated with TDF resistance developed through 144 weeks of treatment

For complete details see Poster # 480 by Snow-Lampart et al. Resistance Surveillance for up to 144 Weeks in HBeAg+ and HBeAg- Hepatitis B Patients Treated with Tenofovir DF Showed No Relationship Between Virologic Breakthrough and Emergence of Genotypic Changes in HBV Polymerase

Table 2. Summary of Cumulative Open Label Safety Data Through Week 144

	TDF-TDF (N=154) ^a	ADV-TDF (N=84) ^a
Study Drug-Related SAE	2 (1.3%)	2 (2.4%)
Deaths	0	0
Grade 3 or Grade 4 Laboratory Abnormality	19 (12.3%)	13 (15.5%)
Discontinued due to an AE	1 (<1%)	0
creatinine increase	1 (<1%)	0
Confirmed phosphorus < 2mg/dL	0	1 (1%)
Confirmed 0.5 mg/dL increase from baseline in creatinine	0	2 (2%)
Confirmed creatinine clearance < 50 mL/min	0	0

a. N's reflect the number of patients who entered the open-label extension

Figure 6. Creatinine Over Time

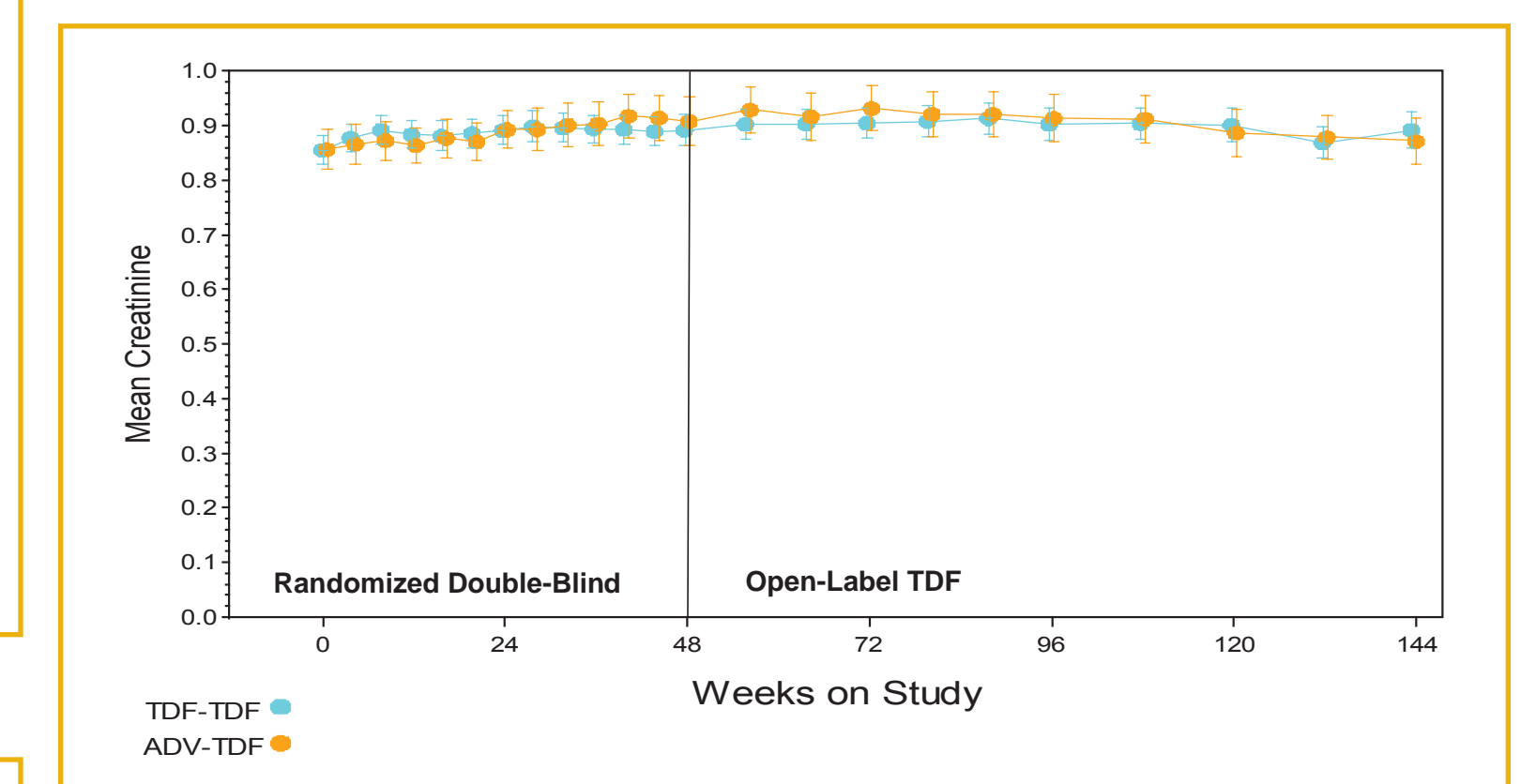


Figure 4. On-Treatment of Patients Initially Randomized to TDF with HBeAg Loss and Seroconversion at Years 1, 2 and 3

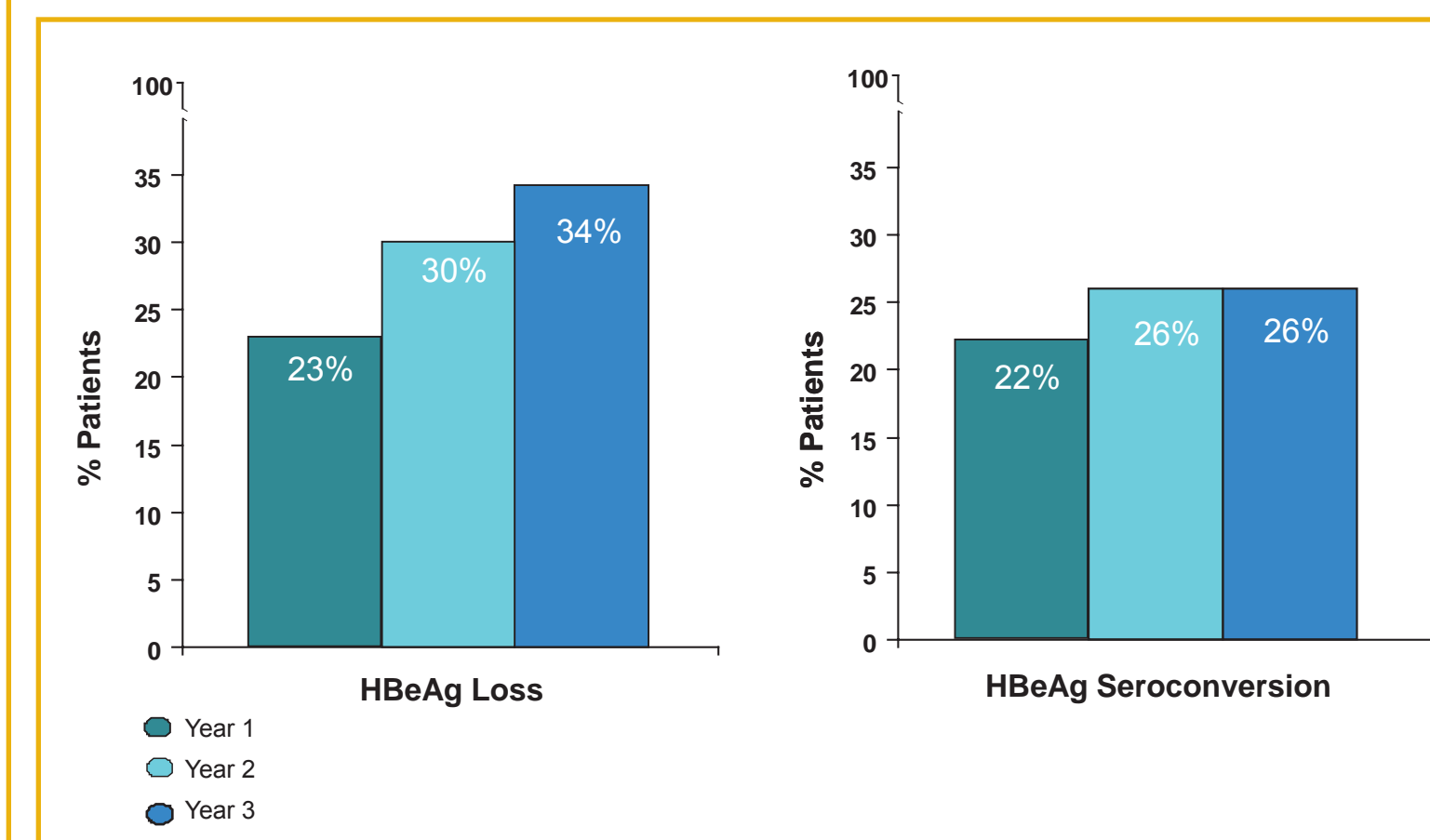
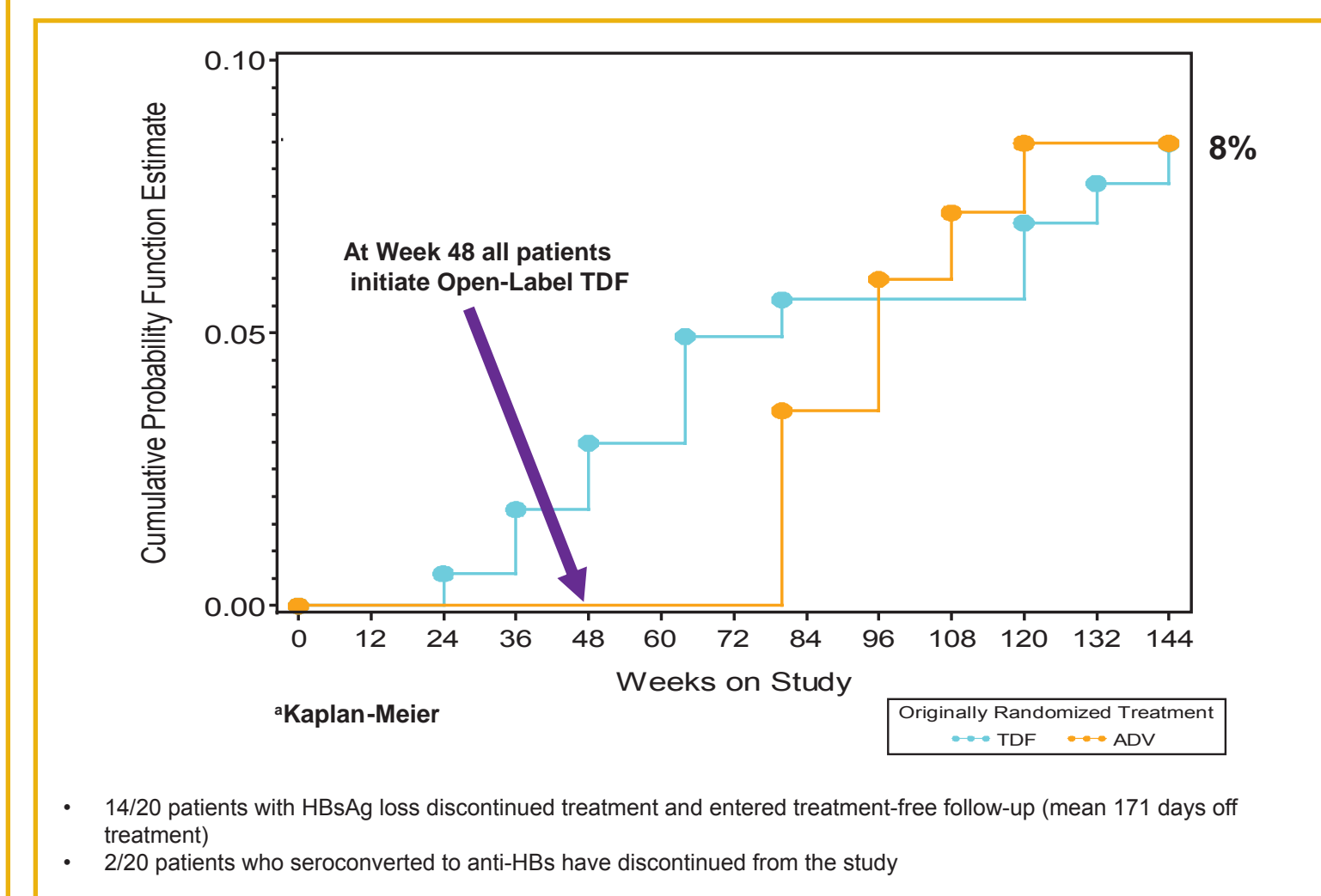


Figure 5. Cumulative Probability* of HBsAg Loss



- 14/20 patients with HBsAg loss discontinued treatment and entered treatment-free follow-up (mean 171 days off treatment)
- 2/20 patients who seroconverted to anti-HBs have discontinued from the study

Conclusions

At Year 3, 80% of patients remained on treatment demonstrating

- durable and potent antiviral activity, i.e., 93% of patients had HBV DNA <400 copies/mL
- an 8% cumulative probability of HBsAg loss
- no resistance to TDF
- a favorable tolerability profile

Acknowledgements

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