HEPATITIS B ONLINE

Hepatitis B Medications

Tenofovir DF (*Viread*)

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Tenofovir DF (TDF)
Summary of Key Studies

- Phase 3 Trials
  - Study 102: TDF versus Adefovir in HBeAg-Negative
  - Study 103: TDF versus Adefovir in HBeAg-Positive
  - Study 108: TDF versus TAF in HBeAg-Negative
  - Study 110: TDF versus TAF in HBeAg-Positive

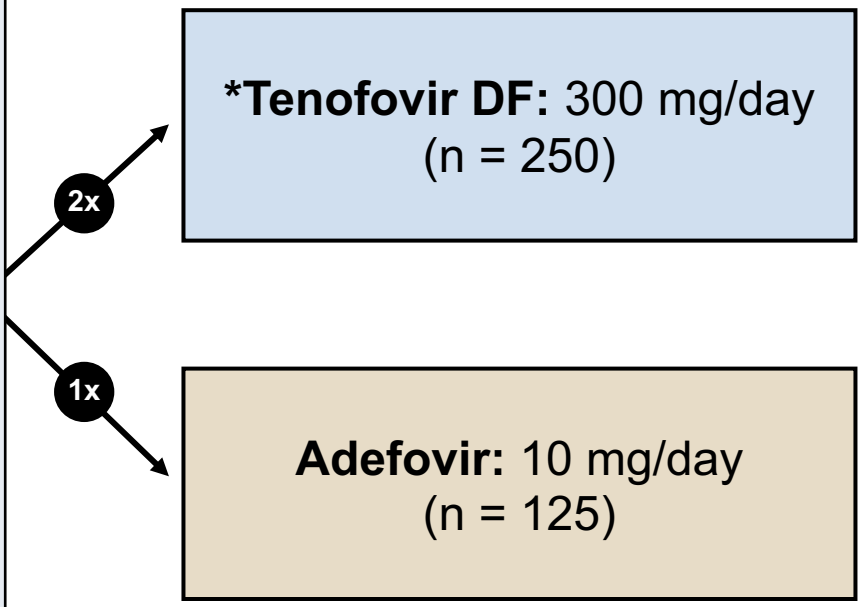
Tenofovir DF versus Adefovir in Chronic HBV
*Study 102: HBeAg-Negative

*Published in tandem with Study 103

Tenofovir DF versus Adefovir HBeAg-NEGATIVE Participants: Study 102 Design

102: Study Design

- **Background**: Randomized, double-blind, controlled, phase 3 study to compare tenofovir DF versus adefovir for the treatment of HBeAg-negative adults with chronic HBV
- **Key Inclusion Criteria**
  - Age 18-69 years
  - HBeAg-negative
  - ALT 1-10 x ULN
  - HBV DNA >100,000 copies/mL
  - CrCl ≥70 mL/min
  - Knodell necroinflammation score ≥3
  - Compensated liver disease



*Stratified by 1:1 by prior lamivudine or emtricitabine exposure (<12 weeks versus ≥12 weeks)

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF versus Adefovir
Study 102: HBeAg-Negative Participants

Baseline Characteristic	Tenofovir DF (n = 250)	Adefovir (n = 125)
Age, mean (±SD), years	44 ±10.6	43 ±10.0
Male, no. (%)	193 (77)	97 (78)
Race, no. (%)		
White	161 (64)	81 (65)
Asian	63 (25)	30 (24)
Black	8 (3)	4 (3)
Other	18 (7)	10 (8)
Knodell inflammatory score, mean (±SD)	7.8 ±2.44	7.9 ±2.18
Knodell fibrosis score, mean (±SD)	2.3 ±1.21	2.4 ±1.23
Mean HBV DNA, $\log_{10}$ IU/mL (±SD)	6.86 ±1.31	6.98 ±1.27
Prior treatment with lamivudine or emtricitabine, no. (%)	43 (17)	23 (18)

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

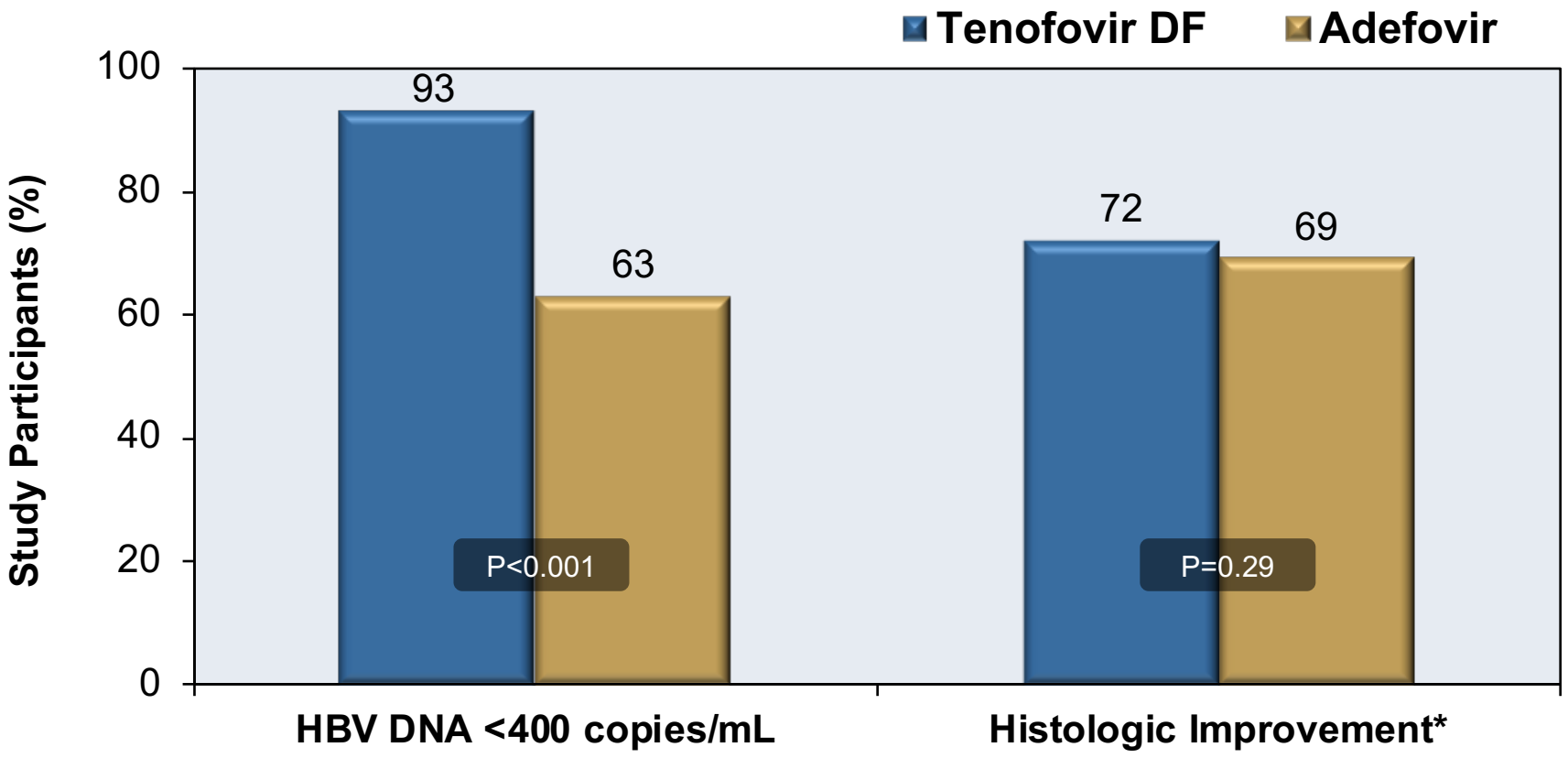
Tenofovir DF versus Adefovir Study 102: HBeAg-Negative

Baseline Characteristic	Tenofovir DF (n = 250)	Adefovir (n = 125)
Alanine aminotransferase, no. (%)		
<2 x upper limit of normal	95 (38)	38 (30)
2 to <5 x upper limit of normal	117 (47)	54 (43)
≥5 x upper limit of normal	38 (15)	33 (26)
Previous treatment with interferon, no. (%)	42 (17)	23 (18)
HBV genotype, no. (%)		
A	28 (12)	14 (11)
B	22 (9)	17 (14)
C	29 (12)	12 (10)
D	156 (64)	79 (63)
E, F, G, H	8 (3)	3 (2)
Other or unknown	7 (3)	0

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF versus Adefovir
Study 102: HBeAg-Negative Participants

HBeAg-Negative Participants: Week 48 Treatment Response



*Reduction of ≥2 points in the Knodell necroinflammatory score without an increase in fibrosis

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Safety and Adverse Events
Study 102 (HBeAg-Negative) & 103 (HBeAg-Positive)

Conclusions: “Among patients with chronic HBV infection, tenofovir DF at a daily dose of 300 mg had superior antiviral efficacy with a similar safety profile as compared with adefovir dipivoxil at a daily dose of 10 mg through week 48.”

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

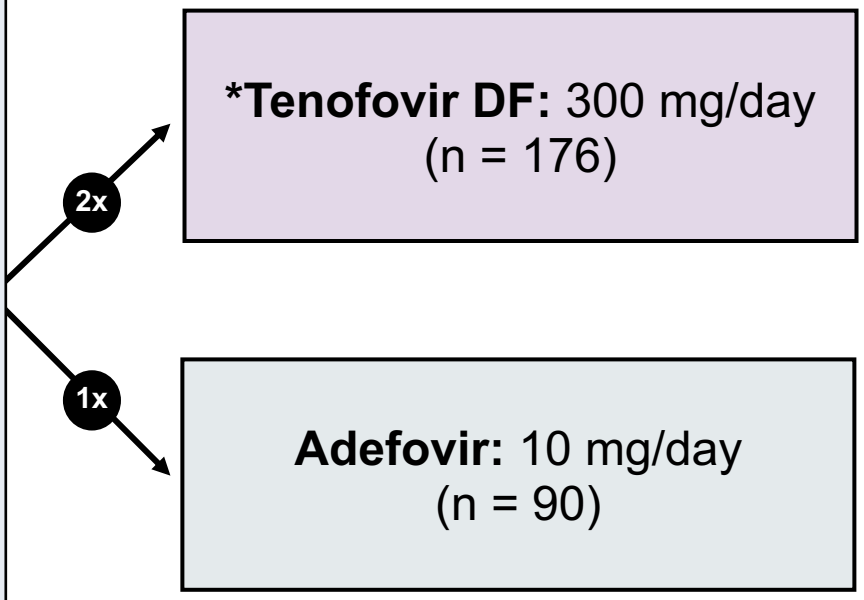
Tenofovir DF versus Adefovir in Chronic HBV Study 103: HBeAg-Positive

*Published in tandem with Study 102

Tenofovir DF versus Adefovir HBeAg-POSITIVE Participants: Study 103 Design

103: Study Design

- **Background**: Randomized, double-blind, controlled, phase 3 study to compare tenofovir DF versus adefovir for the treatment of HBeAg-positive adults with chronic HBV
- **Key Inclusion Criteria**
  - Age 18-69 years
  - HBeAg-positive (≥6 months)
  - ALT 2-10 x upper limit of normal
  - HBV DNA >1 million copies/mL
  - CrCl ≥70 mL/min
  - Knodell necroinflammation score ≥3
  - Compensated liver disease



*Stratified by 1:1 by ALT elevation (<4X ULN versus ≥4X ULN)

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF versus Adefovir Study 103: HBeAg-Positive

Baseline Characteristic	Tenofovir DF (n = 176)	Adefovir (n = 90)
Age, mean (±SD), years	34 ±11	34 ±12
Male, no. (%)	119 (68)	64 (71)
Race, no. (%)		
White	92 (52)	46 (51)
Asian	64 (36)	32 (36)
Black	13 (7)	5 (6)
Other	7 (4)	7 (8)
Knodell inflammatory score, mean (±SD)	8.3 ±2.14	8.3 ±2.27
Knodell fibrosis score, mean (±SD)	2.3 ±1.23	2.4 ±1.19
Mean HBV DNA, $\log_{10}$ IU/mL (±SD)	8.64 ±1.076	8.88 ±0.930
Prior treatment with lamivudine or emtricitabine, no. (%)	8 (5)	1 (1)

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

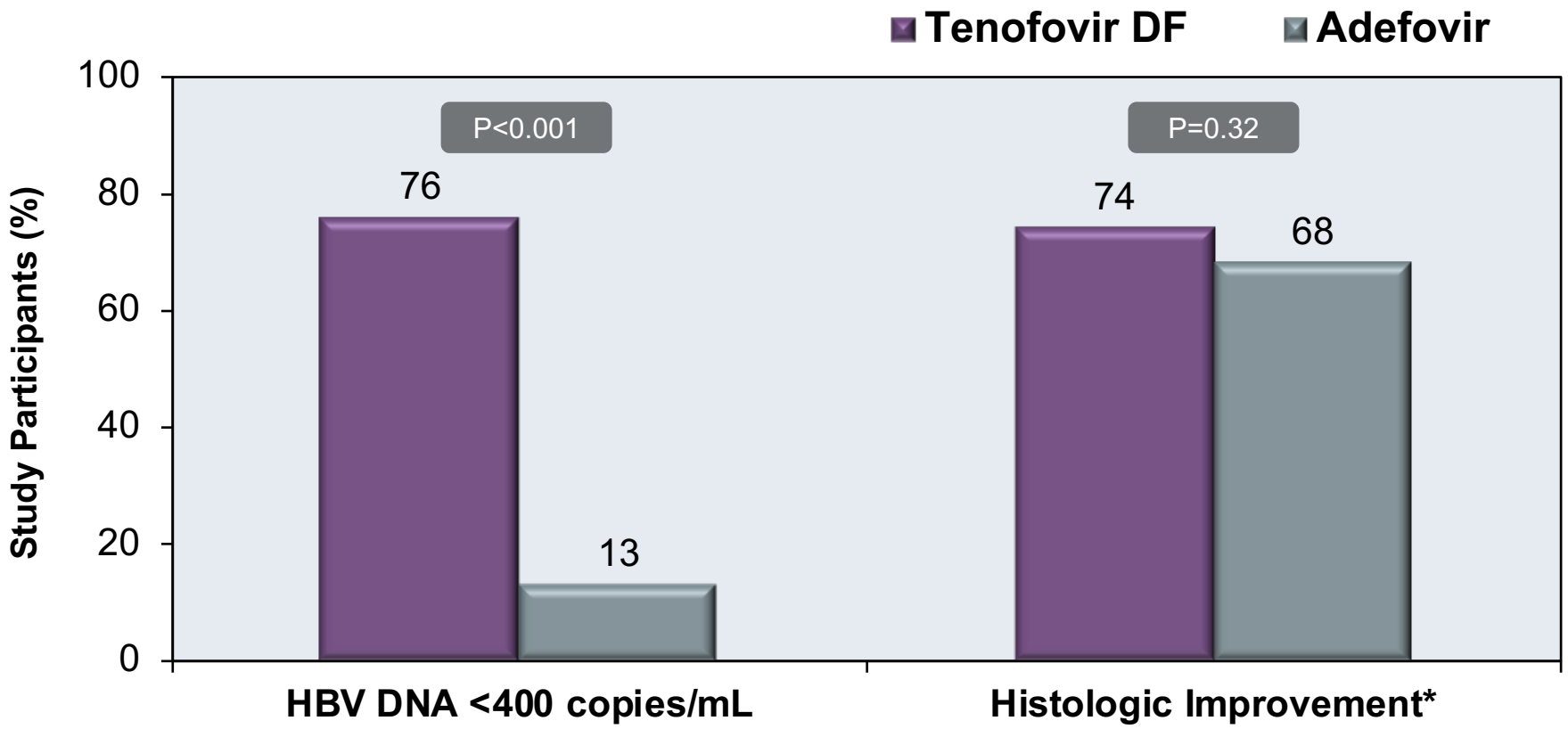
Tenofovir DF versus Adefovir Study 103: HBeAg-Positive

Baseline Characteristic	Tenofovir (n = 176)	Adefovir (n = 90)
Alanine aminotransferase, no. (%)		
<2 x upper limit of normal	39 (22)	16 (18)
2 to <5 x upper limit of normal	105 (60)	55 (61)
≥5 x upper limit of normal	32 (18)	19 (21)
Previous treatment with interferon, no. (%)	30 (17)	13 (14)
HBV genotype, no. (%)		
A	41 (24)	18 (20)
B	25 (14)	10 (11)
C	43 (25)	26 (30)
D	55 (32)	31 (35)
E, F, G, H	9 (5)	3 (3)
Other or unknown	3 (2)	2 (2)

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF versus Adefovir
Study 103: HBeAg-Positive Results

HBeAg-Positive Participants: Week 48 Treatment Response

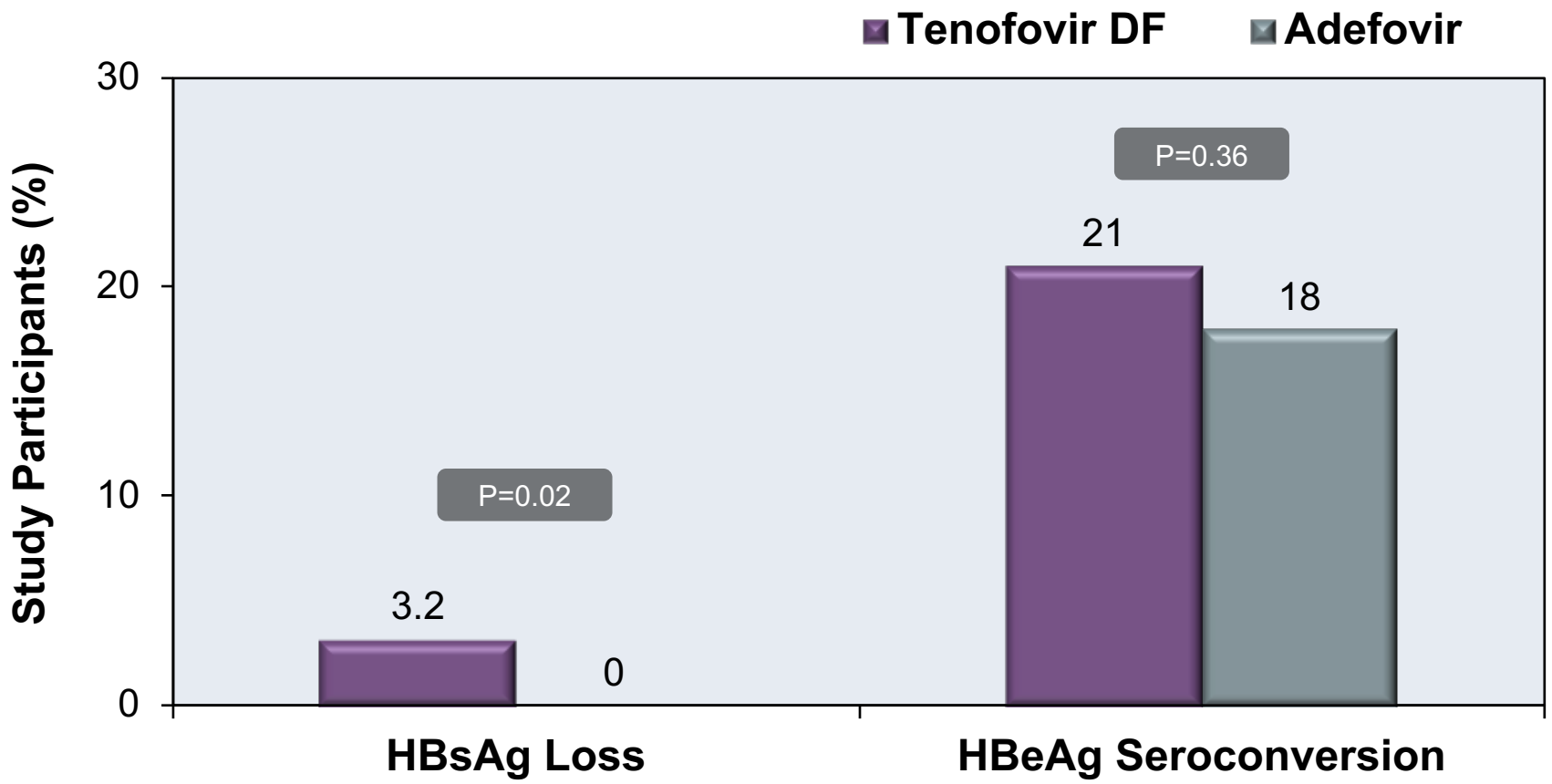


*Reduction of ≥2 points in the Knodell necroinflammatory score without an increase in fibrosis

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF versus Adefovir
Study 103 Serologic Responses

HBeAg-Positive Participants: Week 48 Treatment Response



Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Safety and Adverse Events
Study 102 (HBeAg-Negative) & 103 (HBeAg-Positive)

Conclusions: “Among patients with chronic HBV infection, tenofovir DF at a daily dose of 300 mg had superior antiviral efficacy with a similar safety profile as compared with adefovir dipivoxil at a daily dose of 10 mg through week 48.”

Source: Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF versus Adefovir in Chronic HBV
Study 102 and 103: Combined Data Analysis

*Published in tandem with Study 102

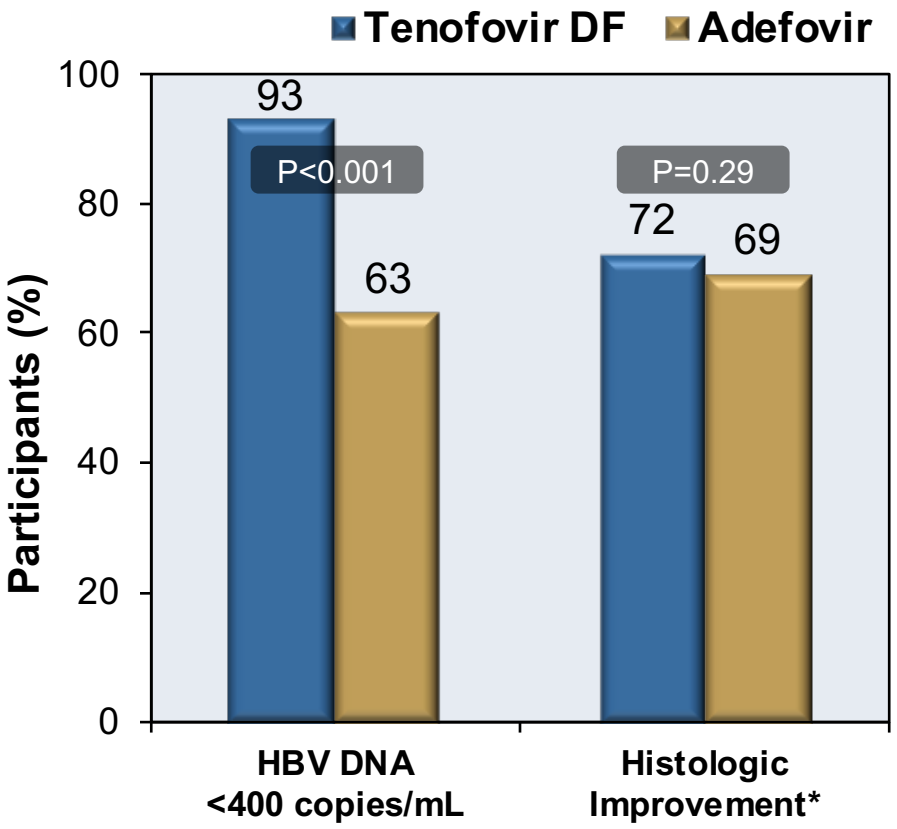
Tenofovir DF versus Adefovir Study Design: 102 and 103

- **Background**
  - Two phase 3, randomized double-blind controlled trials
  - 106 center sites: Europe (60), Asian-Pacific (15), N. America (31)
- **Subjects**
  - Study 102: Chronic HBeAg-negative with ALT >1 and <10x ULN
  - Study 103: Chronic HBeAg-positive with ALT >2 and <10x ULN
  - Exclusions: decompensated liver disease; HIV, HCV, or delta infection; HCC; CrCl <70 mL/min, Hgb <8 mg/dL, or ANC <1,000/mm^3
- **End-Points**
  - Primary: HBV DNA to <400 copies/mL & histologic improvement (≥2 point drop in Knodell score without increased fibrosis)
  - Secondary: HBV DNA and ALT levels over time, HBeAg and HBsAg loss and seroconversion

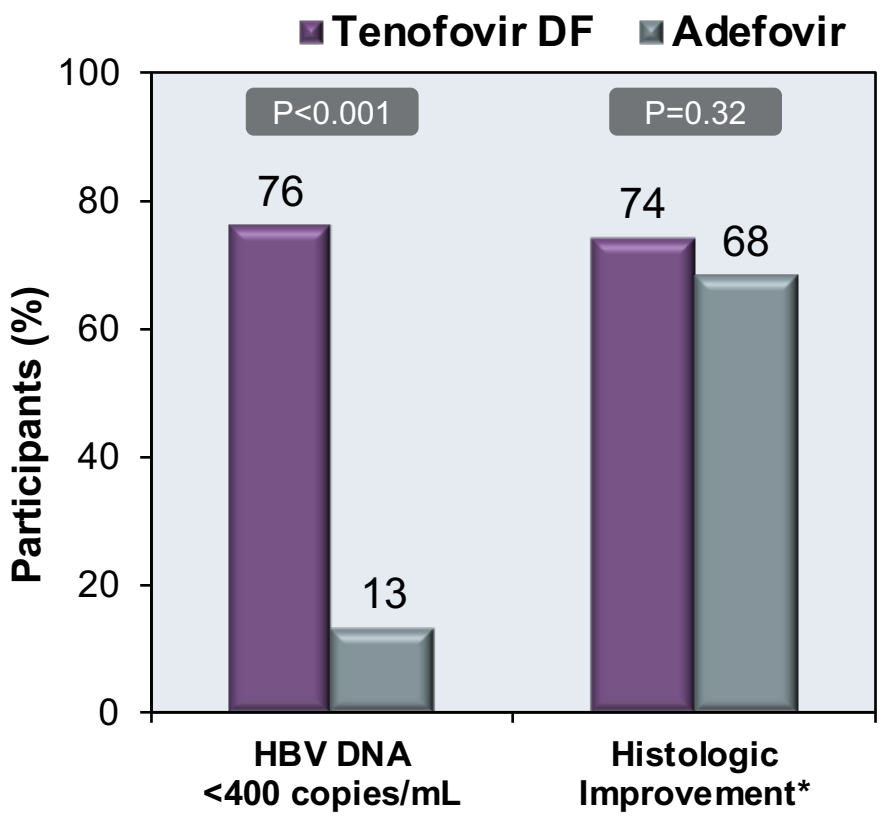
Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF versus Adefovir
Study 102 and 103: 48 Week Treatment Response

Study 102: HBeAg-Negative Patients



Study 103: HBeAg-Positive Patients

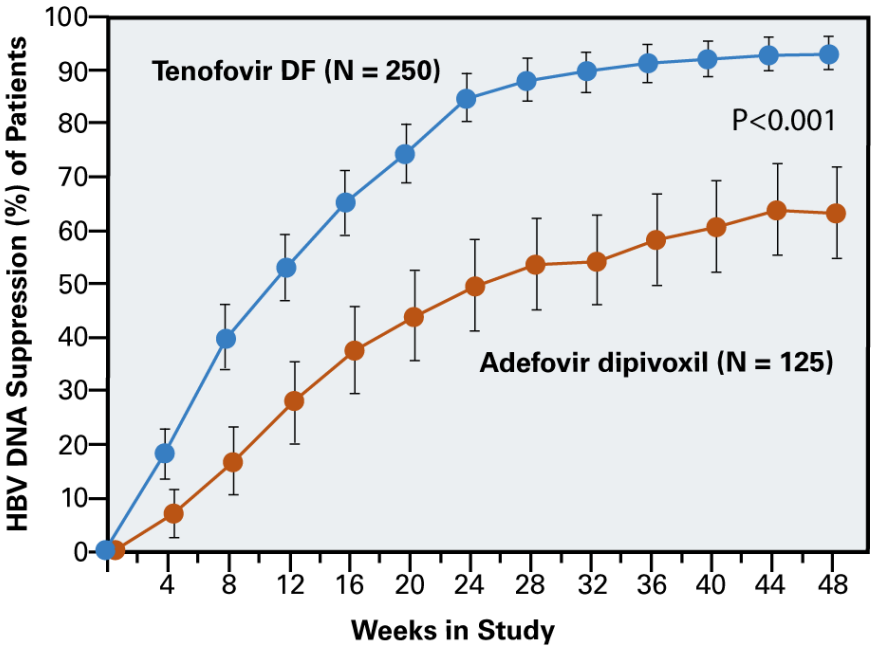


*Reduction of ≥2 points in the Knodell necroinflammatory score without an increase in fibrosis

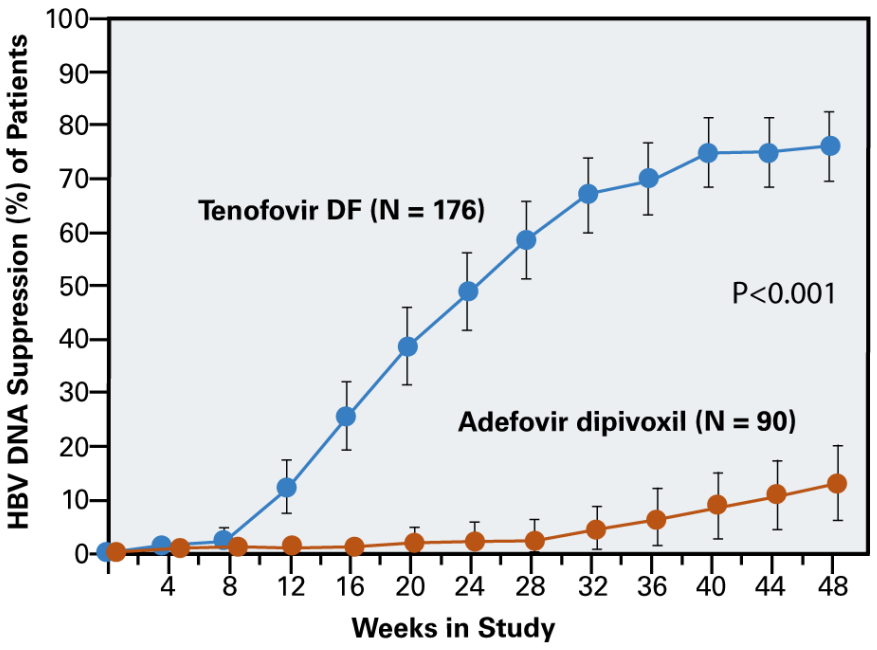
Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF in Patients with Chronic HBV
Study 102 and 103: 48 Week Treatment Response

Study 102: HBeAg-Negative Patients



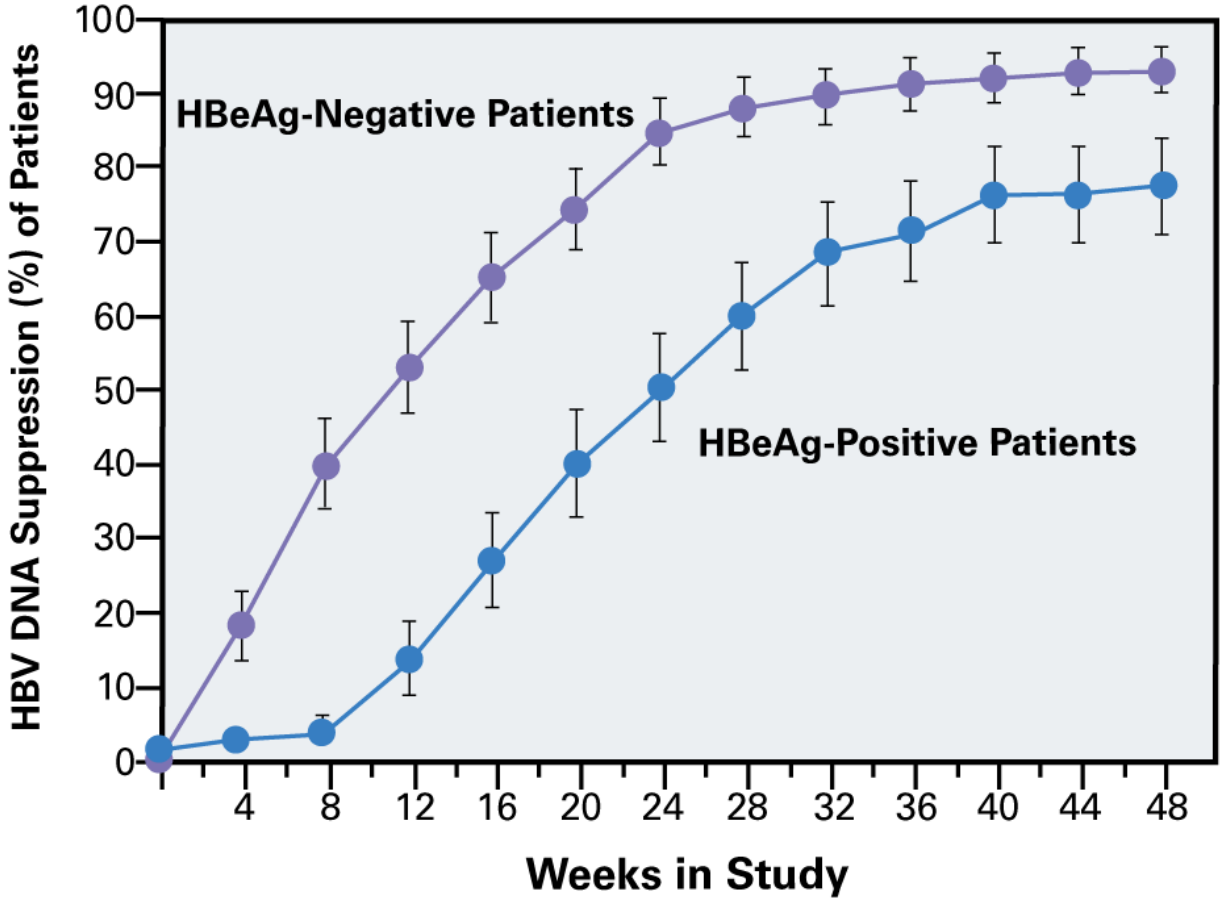
Study 103: HBeAg-Positive Patients



*HBV DNA suppression defined as <400 copies/mL

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Tenofovir DF in Patients with Chronic HBV
Combined Data from Studies 102 and 103



*HBV DNA suppression defined as <400 copies/mL

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Safety and Adverse Events
Study 102 and 103: HBeAg-Negative and HBeAg-Positive

Baseline Characteristic	Tenofovir DF (n = 426)	Adefovir (n = 215)
Any adverse event ≥10%, no. (%)		
Headache	39 (22)	16 (18)
Nasopharyngitis	105 (60)	55 (61)
Nausea	32 (18)	19 (21)
Serious adverse event, no. (%)	27 (6)	14 (7)
Adverse event leading to discontinuation, no. (%)	5 (1)	3 (1)
Lab abnormalities, no. (%)		
Grade 3 ALT (>5-10x ULN) and 2x baseline	13 (3)	2 (1)
Grade 4 ALT (>10x ULN) and 2x baseline	11 (3)	4 (2)
Confirmed serum Cr increase ≥0.5 mg/dL	0	1 (<1)
Confirmed creatinine clearance <50 mL/min	0	0

UNL = upper limit of normal

Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Safety and Adverse Events
Study 102 (HBeAg-Negative) & 103 (HBeAg-Positive)

Conclusions: “Among patients with chronic HBV infection, tenofovir DF at a daily dose of 300 mg had superior antiviral efficacy with a similar safety profile as compared with adefovir dipivoxil at a daily dose of 10 mg through week 48.”

Source: Source: Marcellin P, et al. N Engl J Med. 2008;359:2442-55.

Impact of Tenofovir DF on Fibrosis and Cirrhosis
Studies 102 and 103: 5-Year Follow-Up

Impact of Tenofovir DF on Fibrosis and Cirrhosis
Study 102 and 103: 5-Year Follow-Up Design

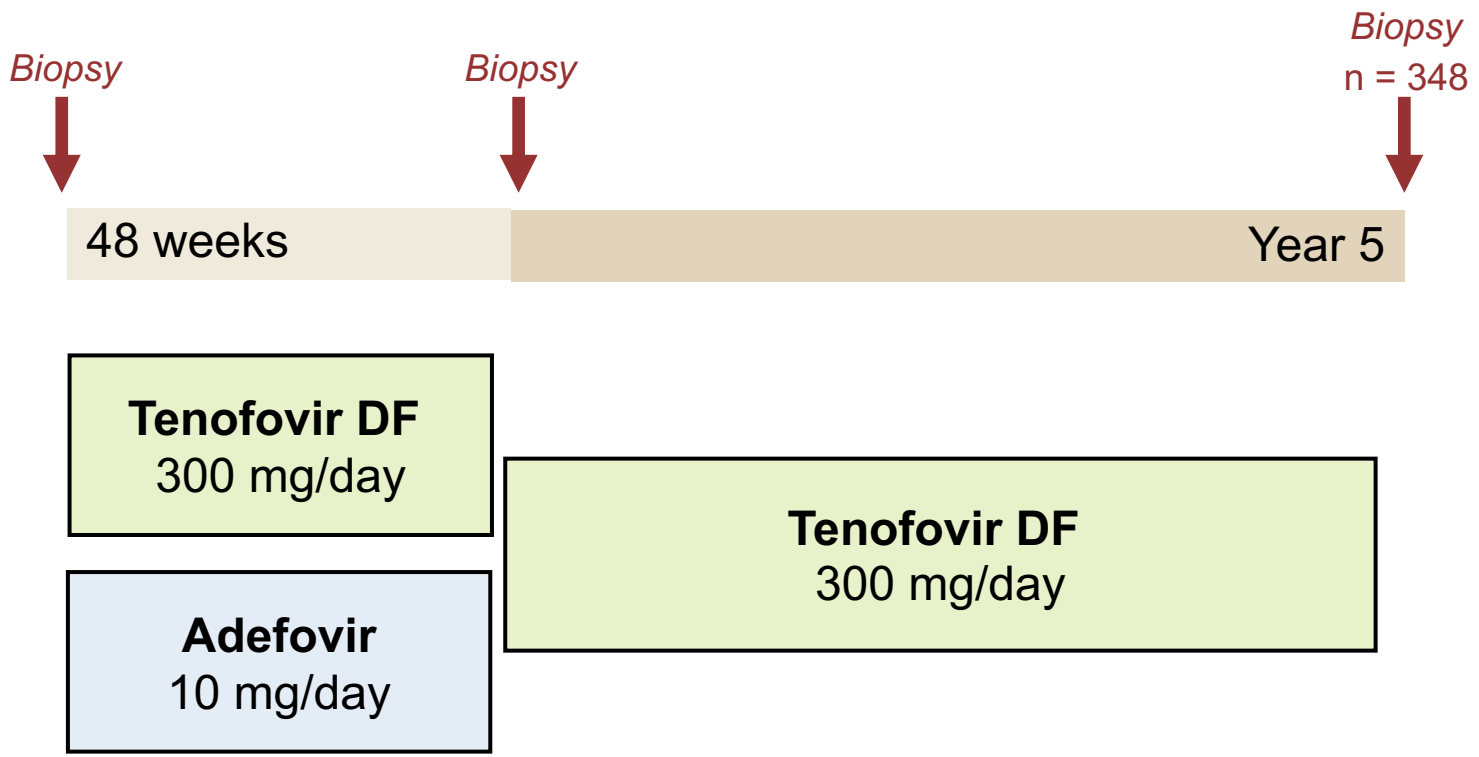
- **Background**
  - Open-label, single-arm continuation study of the 48-week phase 3 randomized controlled trials (Study 102, 103) of tenofovir DF vs adefovir
- **Subjects**
  - N = 348 with chronic HBeAg-negative or HBeAg-positive
  - All switched to open-label tenofovir DF after blinded phase complete
  - Had liver biopsies at baseline (year 1) and year 5 of follow-up.
- **Regimen**
  - Tenofovir DF 300 mg once daily
- **Study End-Points**
  - Histologic Response: ≥2-point decrease in the Knodell necroinflammatory score and no worsening in Knodell fibrosis score.
  - Fibrosis regression: ≥1-point decrease in Ishak fibrosis score

Source: Marcellin et. al. Lancet. 2013;381:468-75.

Impact of Tenofovir DF on Fibrosis and Cirrhosis

Study Design

Randomized Trial	Open-Label Phase	Completed Trial
n = 641	n = 585	n = 489



Source: Marcellin et. al. Lancet. 2013;381:468-75.

Impact of Tenofovir DF on Fibrosis and Cirrhosis

Characteristics of Participants with Baseline Cirrhosis

Baseline Characteristics of Participants with Cirrhosis at Baseline	No Cirrhosis at Year 5 n = 71	Cirrhosis at Year 5 n = 25	P-value
Age >40 years, n (%)	49 (69)	20 (80)	0.44
Male sex, n (%)	58 (92)	22 (88)	0.55
Asian origin, n (%)	19 (27)	3 (12)	0.17
BMI, mean kg/m^2 (SD)	25.7 (3.7)	29.0 (4.4)	0.007
Knodell necroinflammatory score, mean (SD)	8.8 (1.6)	9.0 (1.7)	0.69
HBV DNA level, mean $\log_{10}$ copies/ml (SD)	7.4 (1.5)	7.5 (1.2)	0.63
Ishak fibrosis stage, n (%) 5 6	 17 (24) 54 (76)	 2 (8) 23 (92)	0.14
Prior treatment, n (%) Interferon Lamivudine use >12 weeks	 16 (22) 16 (22)	 3 (12) 2 (8)	 0.38 0.14
Diabetes, n (%)	1 (1)	6 (24)	0.001

Source: Marcellin et. al. Lancet. 2013;381:468-75.

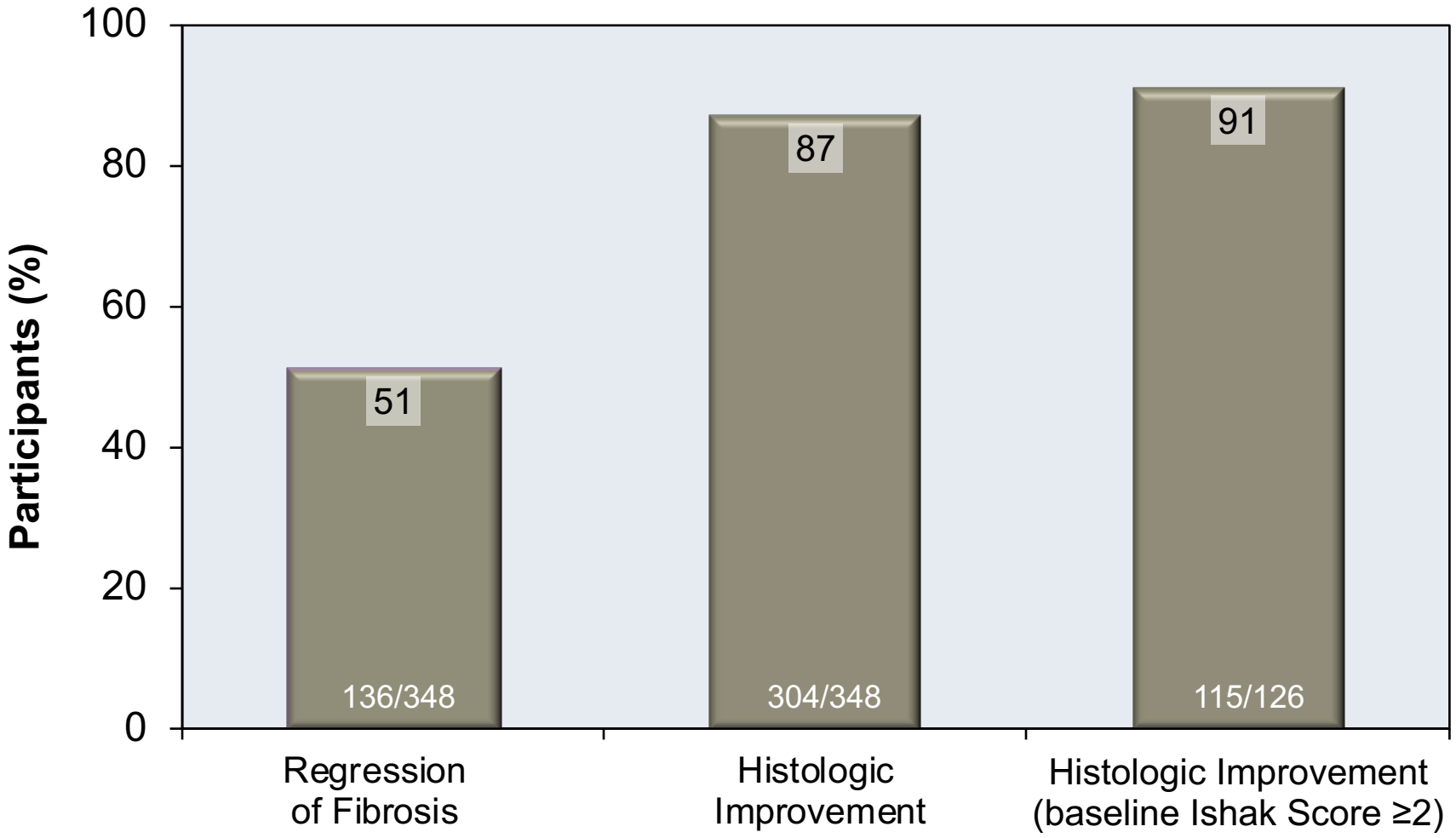
Impact of Tenofovir DF on Fibrosis and Cirrhosis
Characteristics of Participants with Baseline Cirrhosis

On-Treatment Characteristics of Participants with Baseline Cirrhosis	No Cirrhosis at Year 5 n = 71	Cirrhosis at Year 5 n = 25	P-value
HBV DNA <400 copies/mL, n/N (%)	69/69 (100)	24/24 (100)	
Normal ALT, n/N (%)	59/68 (87)	14/24 (58)	0.007
HBeAg loss, n/N (%)	12/23 (52)	6/7 (86)	0.193
Change from baseline to week 12 in HBsAg (10^6 IU/L), mean (SD)	-4.8 (19.7)	-0.22 (7.7)	0.804
Change from baseline Knodell score, mean (SD)	-5.6 (2.2)	-4.6 (2.4)	0.053
Knodell score at year 5, n (%) 0-3 4-6 7-9	 59 (83) 7 (10) 5 (7)	 13 (52) 7 (28) 5 (20)	0.007
HBsAg loss, n/N (%)	1/69 (1)	0/24 (0)	1.000

Source: Marcellin et. al. Lancet. 2013;381:468-75.

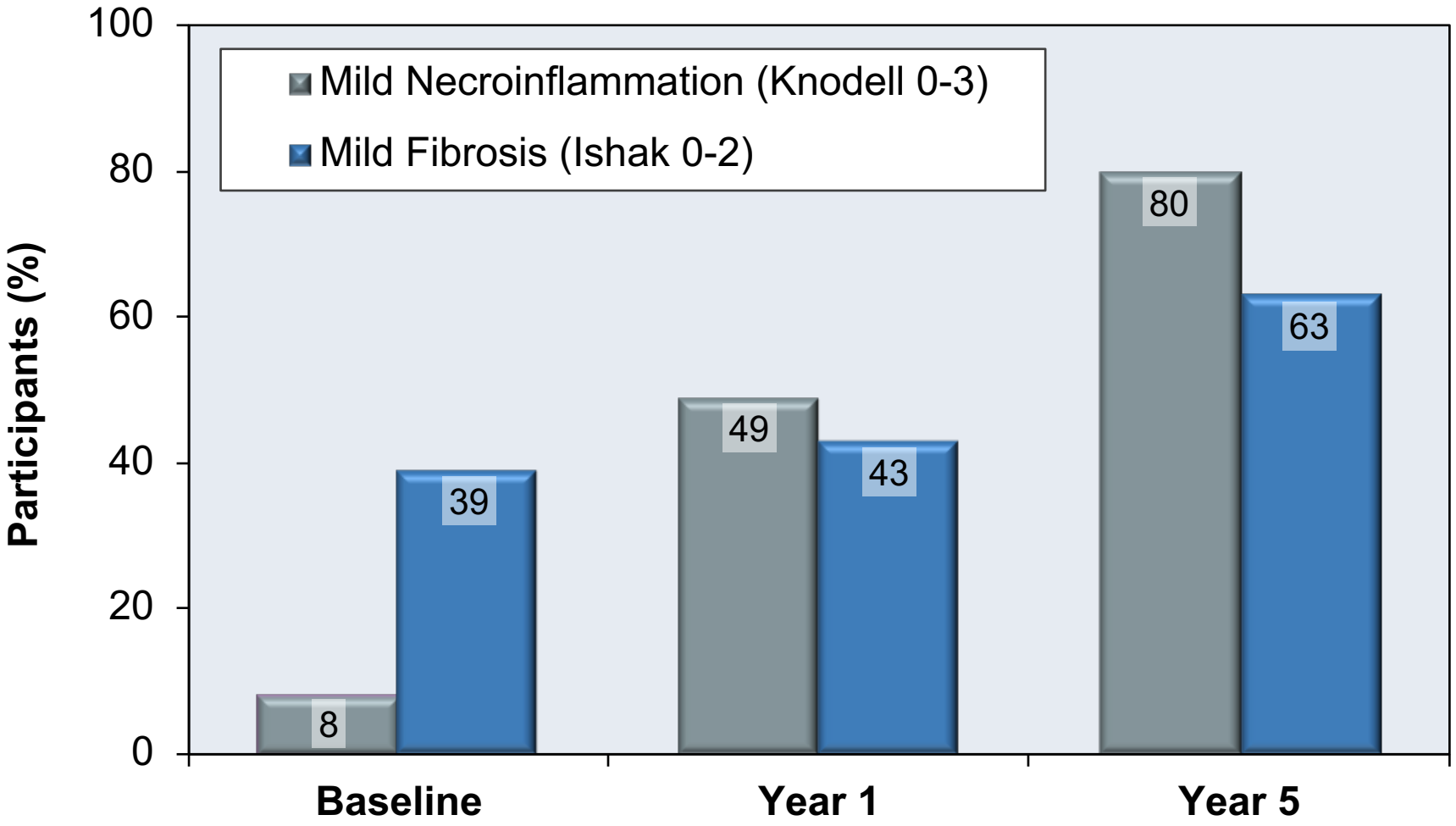
Impact of Tenofovir DF on Fibrosis and Cirrhosis

Histologic Improvement at Year 5 (All participants)



Source: Marcellin et. al. Lancet. 2013;381:468-75.

Impact of Tenofovir DF on Fibrosis and Cirrhosis
Changes in Knodell and Ishak Scores Among All Participants



Source: Marcellin et. al. Lancet. 2013;381:468-75.

Impact of Tenofovir DF on Fibrosis and Cirrhosis Conclusions

Conclusions: “In patients with chronic HBV infection, up to 5 years of treatment with tenofovir DF was safe and effective. Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis.”

Source: Marcellin et. al. Lancet. 2013;381:468-75.

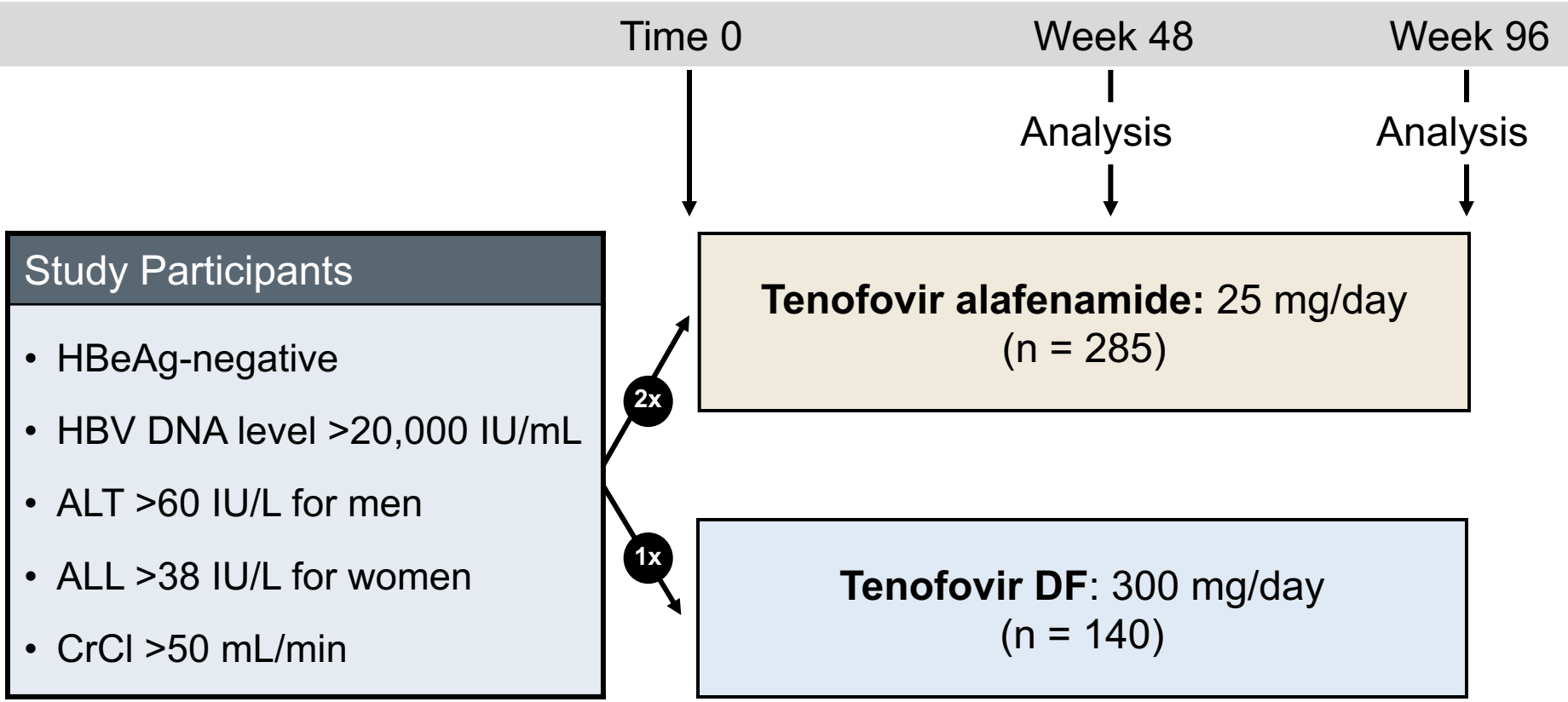
Tenofovir AF vs Tenofovir DF in HBeAg-Negative Study 108

Tenofovir AF vs Tenofovir DF for HBeAg-Negative Study 108: Design

- **Background**
  - Randomized double-blind placebo-controlled non-inferiority trial of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) in HBeAg-negative adults with chronic hepatitis B
- **Subjects (n = 426)**
  - Age ≥18 years
  - Chronic HBeAg-negative
  - HBV DNA level >20,000 IU/mL
  - ALT >60 IU/L in men, >38 IU/L in women; ALT <10 x ULN for both
- **Regimen**
  - Tenofovir AF: 25 mg once daily with matching placebo
  - Tenofovir DF: 300 mg once daily with matching placebo
- **Study End-Point**
  - HBV DNA level <29 IU/mL at week 48

Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.

Tenofovir AF vs Tenofovir DF for HBeAg-Negative Study 108: Design



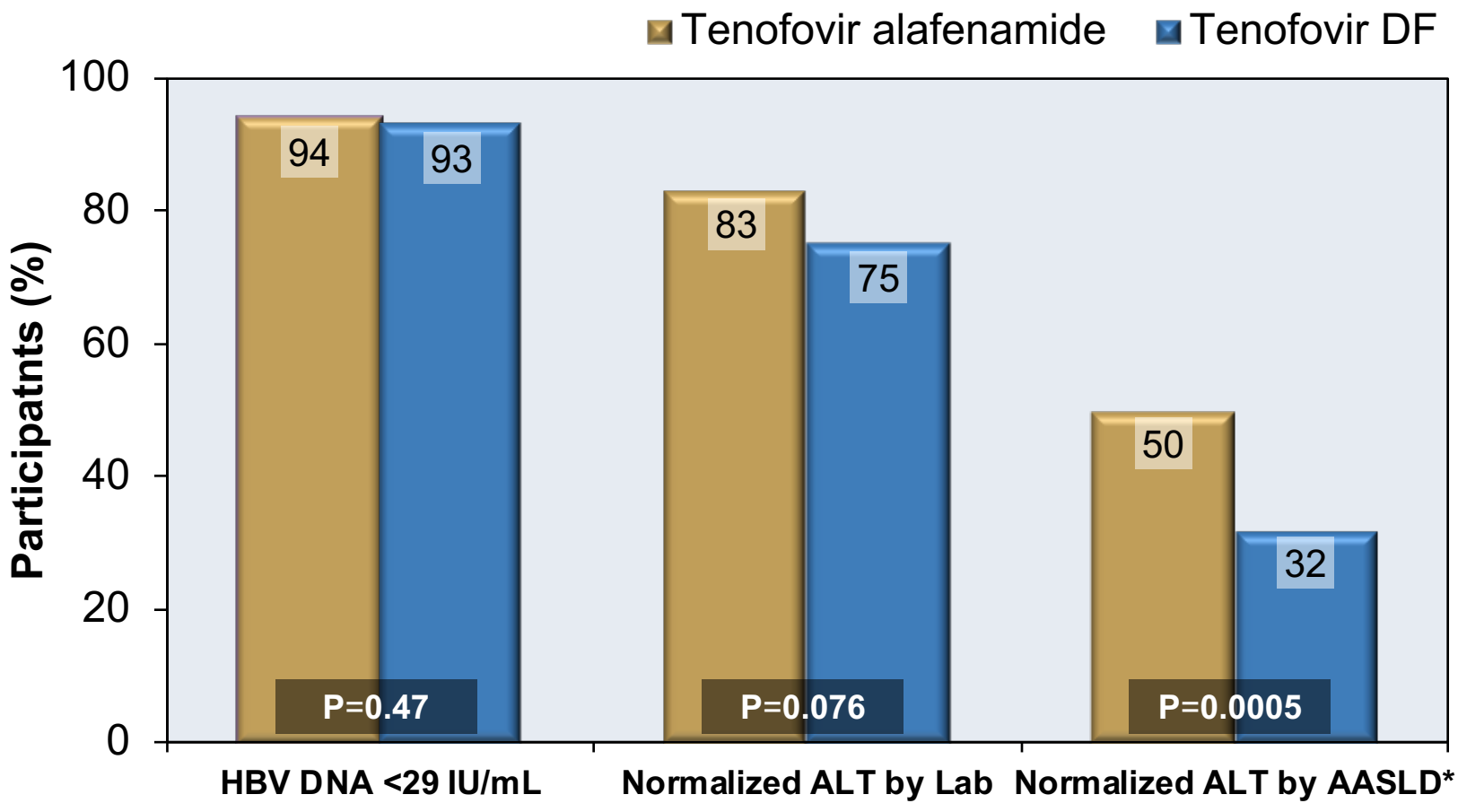
Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.

Tenofovir AF vs Tenofovir DF for HBeAg-Negative Study 108: Baseline Characteristics

Baseline Characteristic	Tenofovir AF (n = 285)	Tenofovir DF (n = 140)
Age, mean (±SD), years	45 (12)	48 (10)
Male, no. (%)	173 (61)	86 (61)
Race, no. (%)		
Asian	205 (72)	101 (72)
White	71 (25)	35 (25)
Black	5 (2)	3 (2)
Other	4 (2)	1 (1)
ALT > ULN by central lab, no. (%)	236 (83)	121 (86)
HBV DNA, $\log_{10}$ IU/mL (±SD)	5.7 (1.3)	5.8 (1.3)
FibroTest score ≥0.75, no. (%)	31/280 (11)	20/139 (14)
Previous nucleos(t)ide therapy, no. (%)	60 (21)	31 (22)
Previous interferon therapy, no. (%)	29 (10)	19 (14)

Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.

Tenofovir AF vs Tenofovir DF for HBeAg-Negative Study 108: Results at Week 48

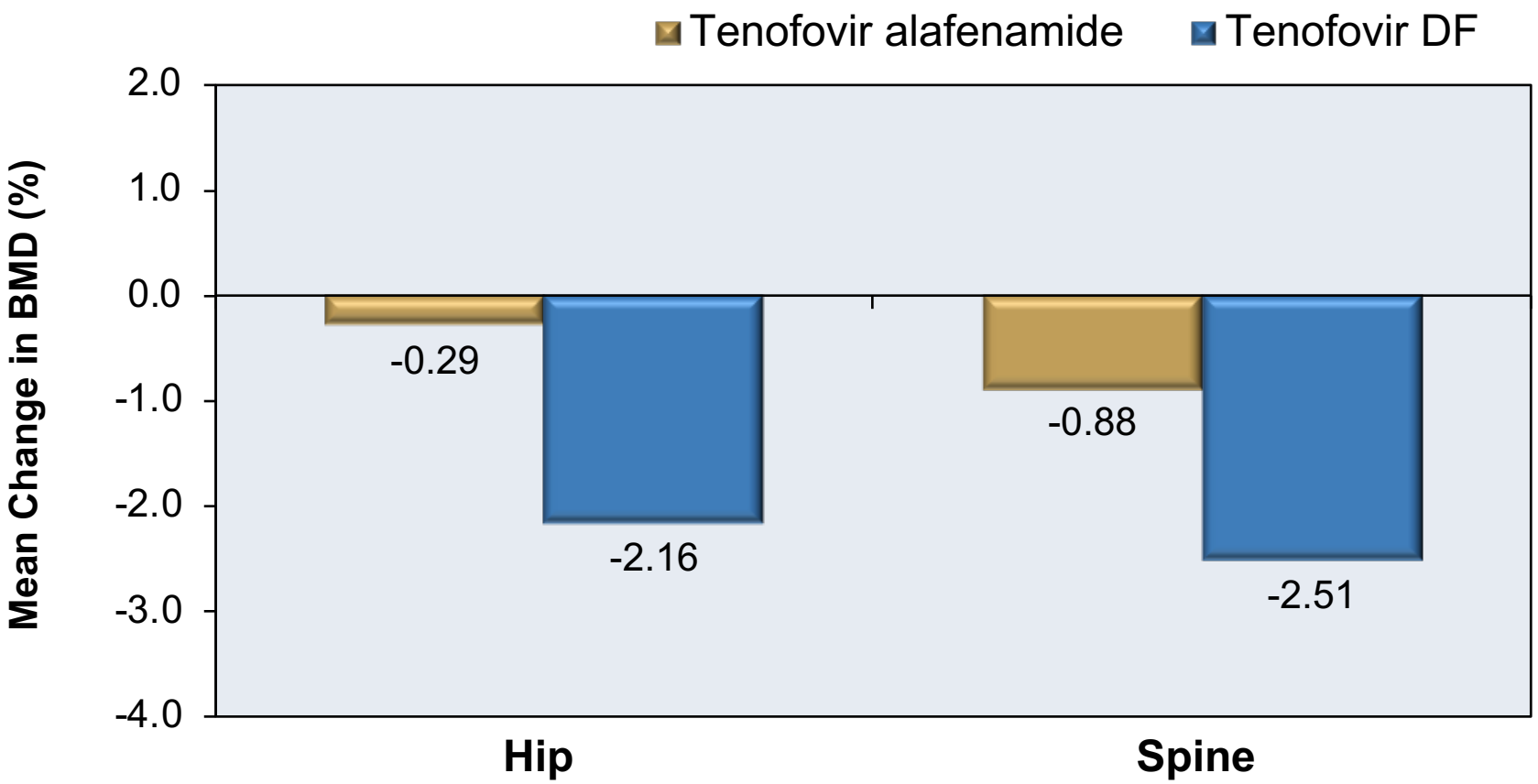


*Using normal ranges of ≤30 U/L for men and ≤19 U/L for women

Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.

Tenofovir AF vs Tenofovir DF for HBeAg-Negative Study 108: Adverse Effects

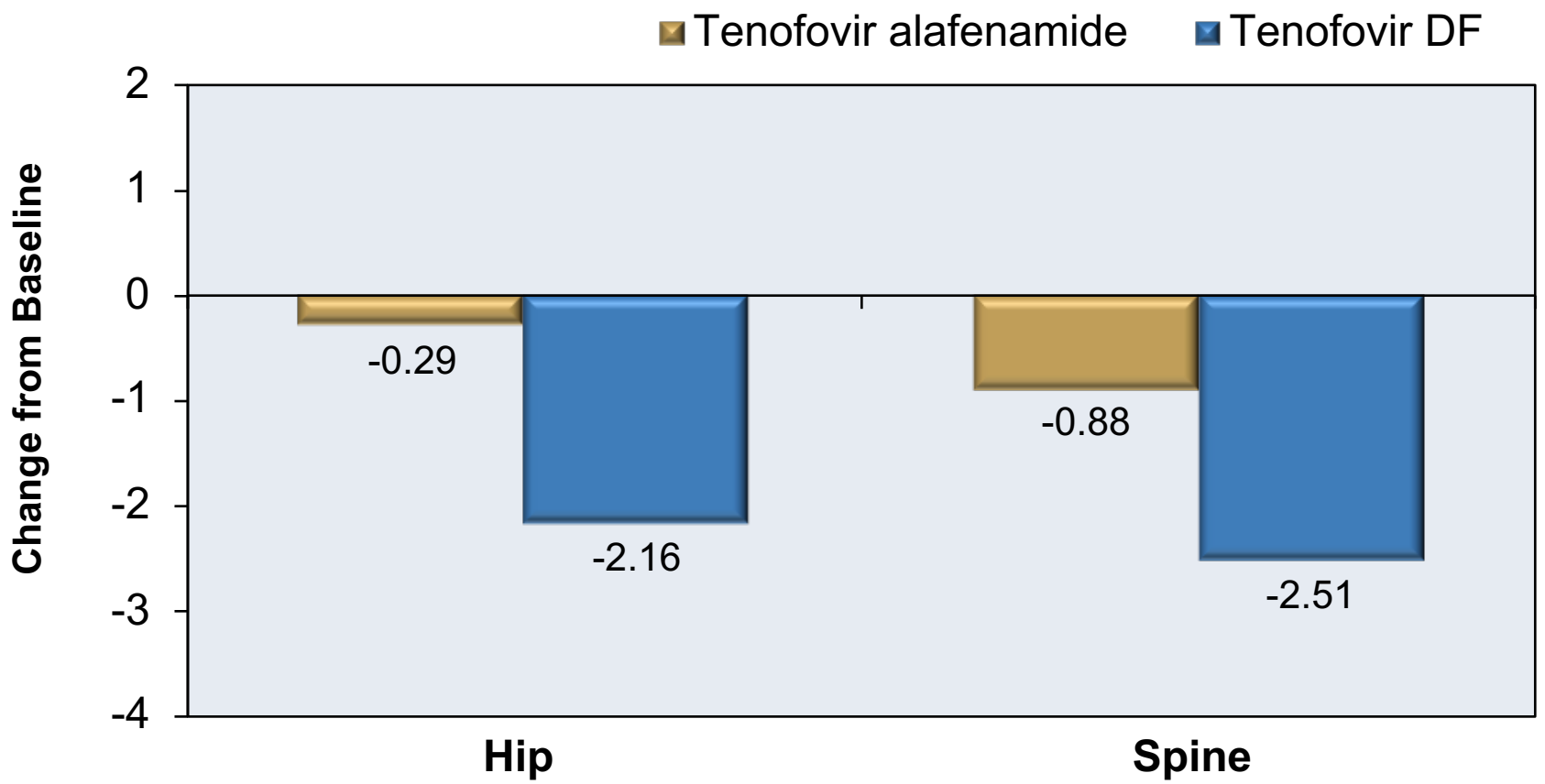
Week 48 Changes in Bone Mineral Density (BMD)



Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.

Tenofovir AF vs Tenofovir DF for HBeAg-Negative Study 108: Adverse Effects

Week 48 Changes in Bone Mineral Density (BMD)



Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.

Tenofovir AF vs Tenofovir DF for HBeAg-Negative Study 108: Results

Interpretation: “In patients with HBeAg-negative chronic HBV, the efficacy of tenofovir alafenamide was non-inferior to that of tenofovir disoproxil fumarate, and had improved bone and renal effects. Longer term follow-up is needed to better understand the clinical impact of these changes.”

Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.

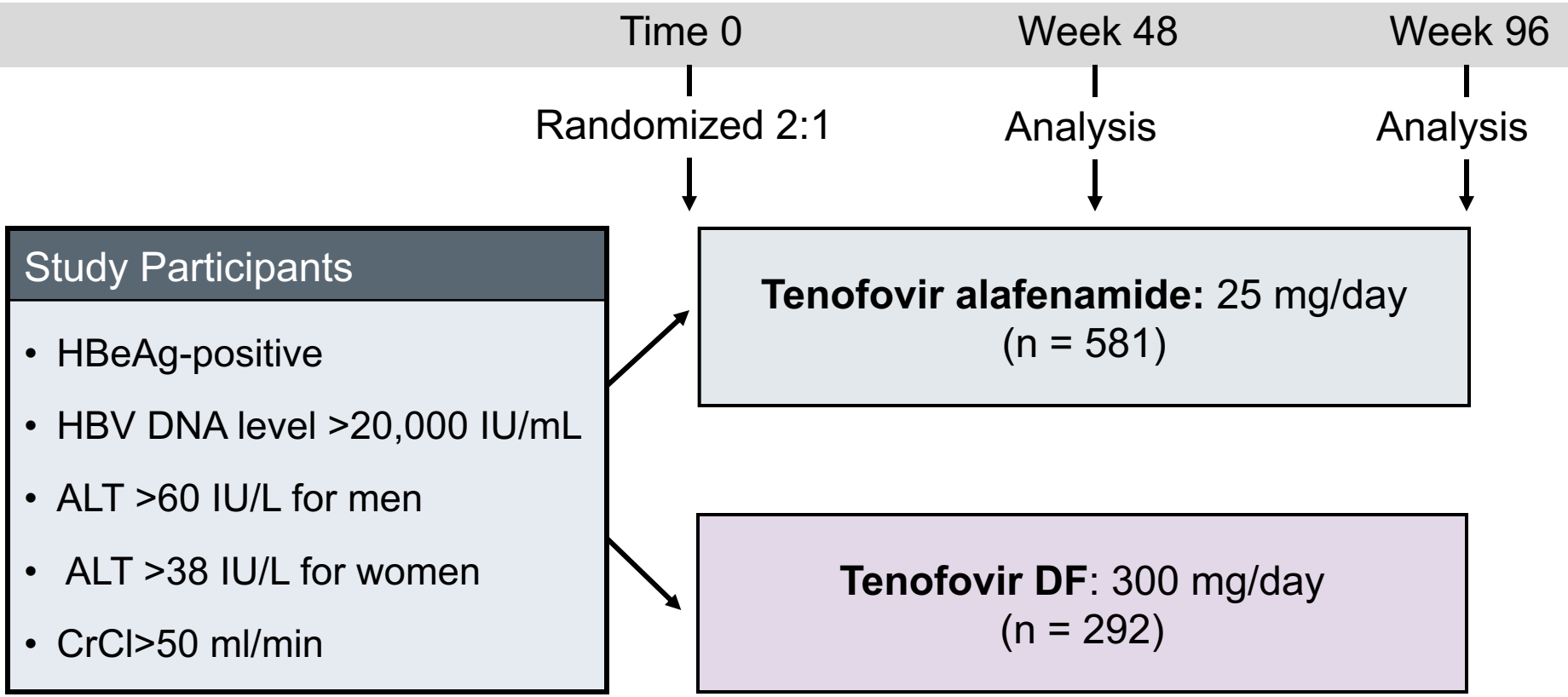
Tenofovir AF vs Tenofovir DF in HBeAg-Positive Study 110

Tenofovir AF vs Tenofovir DF for HBeAg-Positive Study 110: Design

- **Background**
  - Randomized double-blind placebo-controlled non-inferiority trial of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) in HBeAg-positive chronic hepatitis B patients
- **Subjects**
  - N = 1473 with chronic hepatitis B eAg-positive infection
  - HBV DNA level >20,000 IU/mL
  - ALT >60 IU/L in men, >38 IU/L in women; <10 x ULN for both
- **Regimens**
  - Tenofovir AF 25 mg once daily with matching placebo
  - Tenofovir DF 300 mg once daily with matching placebo
- **Study End-Point**
  - HBV DNA level <29 IU/mL at week 48

Source: Chan HL, et. al. Lancet Gastroenterol Hepatol. 2016;1:185-95.

Tenofovir AF vs Tenofovir DF for HBeAg-Positive Study 110: Design



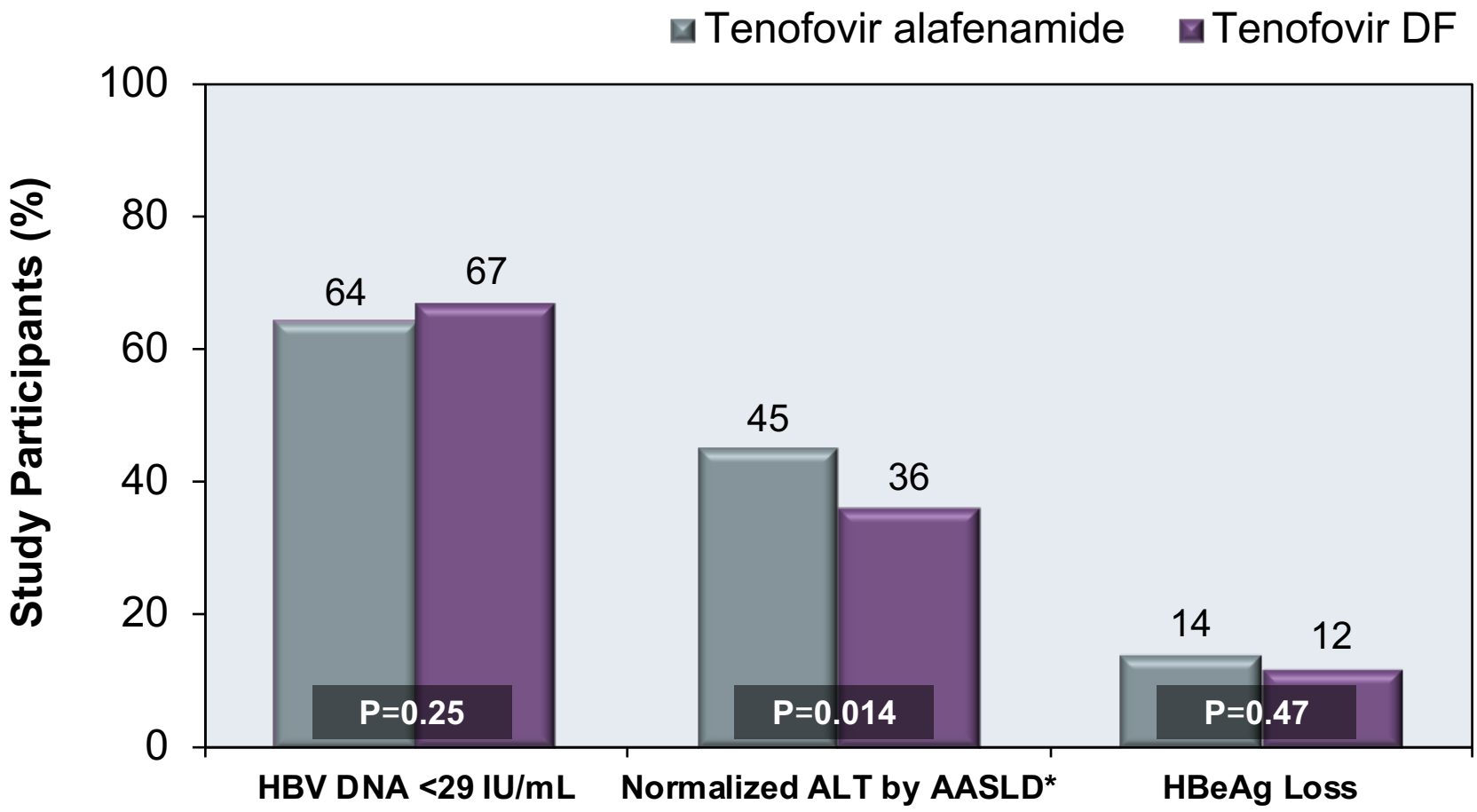
Source: Chan HL, et. al. Lancet Gastroenterol Hepatol. 2016;1:185-95.

Tenofovir AF vs Tenofovir DF for HBeAg-Positive Study 110: Baseline Characteristics

Baseline Characteristic	Tenofovir AF (n = 581)	Tenofovir DF (n = 292)
Age, mean (±SD), years	38 (11)	38 (12)
Male, no. (%)	371 (64)	189 (65)
Race, no. (%)		
Asian	482 (83)	232 (79)
White	96 (17)	53 (18)
Other	3 (1)	7 (2)
ALT > ULN by central lab, no. (%)	537 (98)	288 (99)
HBV DNA, $\log_{10}$ IU/mL (±SD)	7.6 (1.3)	7.6 (1.4)
FibroTest score, mean (±SD)	0.34 (0.23)	0.32 (0.22)
Cirrhosis, no. (%)	41 (7)	24 (8)
Serum creatinine, mean (±SD)	0.81 (0.17)	0.82 (0.16)

Source: Chan HL, et. al. Lancet Gastroenterol Hepatol. 2016;1:185-95.

Tenofovir AF vs Tenofovir DF for HBeAg-Positive Study 110: Results at Week 48

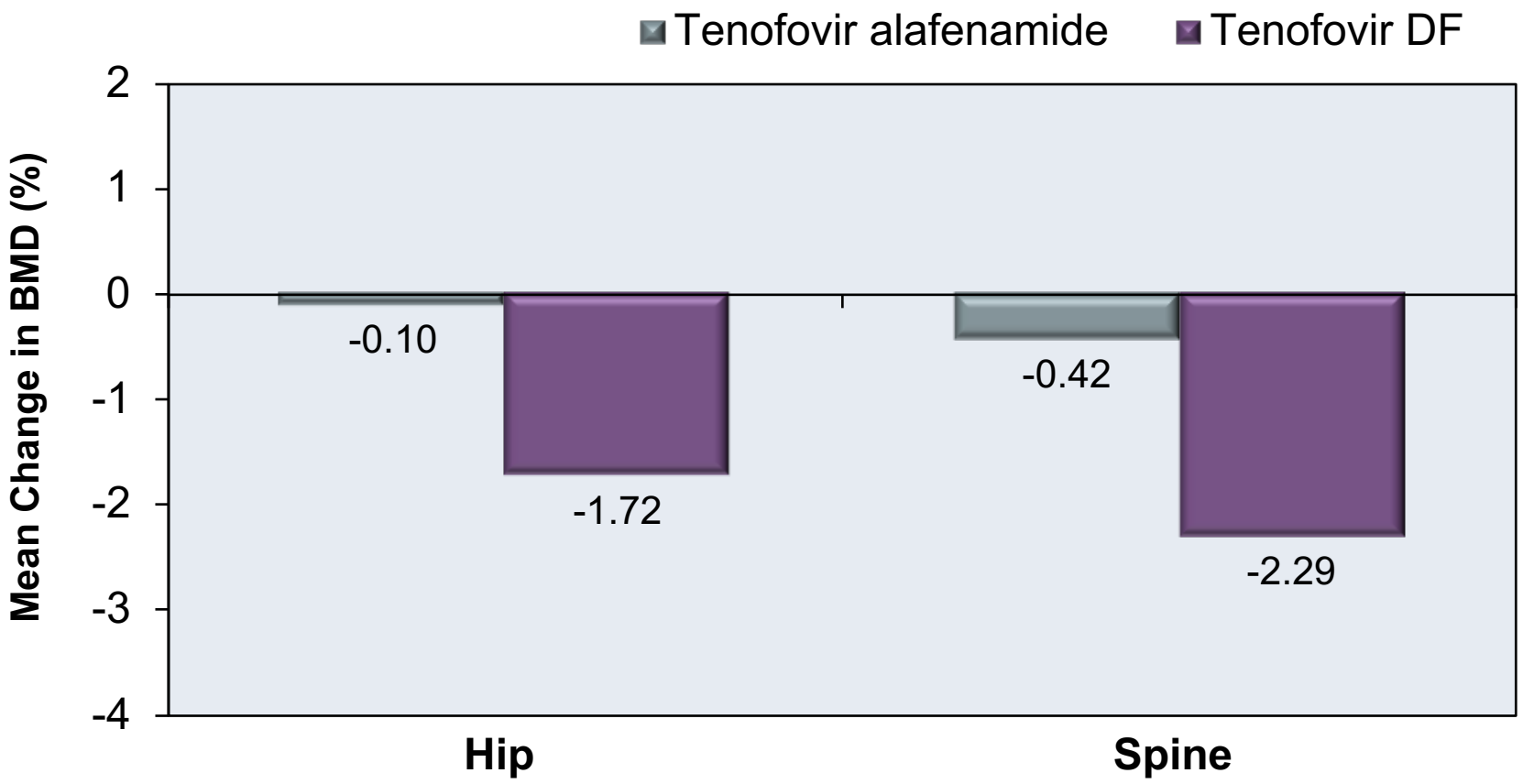


*Using normal ranges of ≤30 U/L for men and ≤19 U/L for women

Source: Chan HL, et. al. Lancet Gastroenterol Hepatol. 2016;1:185-95.

Tenofovir AF vs Tenofovir DF for HBeAg-Positive Study 110: Adverse Effects

Week 48 Changes in Bone Mineral Density (BMD)



Source: Chan HL, et. al. Lancet Gastroenterol Hepatol. 2016;1:185-95.

Tenofovir AF vs Tenofovir DF for HBeAg-Positive Study 110: Conclusion

Interpretation: “In patients with HBeAg-positive HBV infection, tenofovir alafenamide was non-inferior to tenofovir disoproxil fumarate, and had improved bone and renal effects. Longer term follow-up is needed to better understand the clinical impact of these changes.”

Source: Buti M, et. al. Lancet Gastroenterol Hepatol. 2016;1:196-206.