

Tenofovir Disoproxil Fumarate (TDF) Versus Emtricitabine Plus TDF (FTC/TDF) for Treatment of Chronic Hepatitis B (CHB) in Patients with Persistent Viral Replication Receiving Adefovir Dipivoxil



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44th Annual Meeting of the
European Association for the Study of the Liver
April 22 - 26, 2009
Copenhagen, Denmark

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Introduction

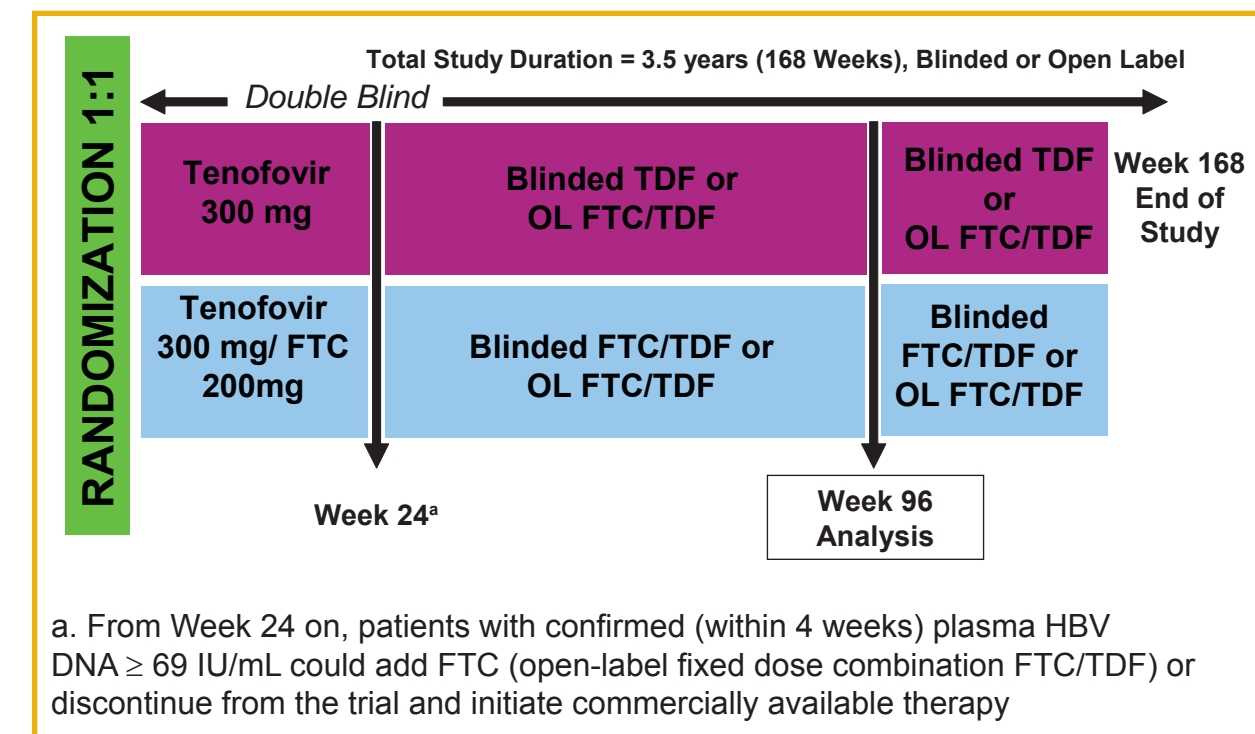
- Virologic suppression by adefovir dipivoxil (ADV) is incomplete in some cases, resulting in persistent viremia on treatment
- Options include switching to a single more potent drug or to two drugs with different resistance pathways
- TDF and FTC/TDF were well tolerated and achieved complete viral suppression in 81% of patients at week 48 in this population¹
- The preferred treatment strategy in this heavily pretreated population remains to be defined and requires continued evaluation beyond 1 year¹

Methods

Study Objectives

Compare the efficacy and safety/tolerability of TDF monotherapy versus the fixed dose combination of emtricitabine-tenofovir (FTC/TDF) for the treatment of chronic hepatitis B infection in patients with suboptimal antiviral efficacy on ADV (most with prior/current lamivudine [LAM] use) 96 Week Data

Figure 1. Study 106 Design



Primary Efficacy Analysis

- A comparison of two treatment strategies for ADV suboptimal responders, most with prior/current lamivudine (LAM) use
 - Compare the antiviral efficacy of
 - Monotherapy with TDF 300 mg QD (with option to add FTC 200 mg versus
 - Fixed-dose combination of FTC 200 mg + TDF 300 mg QD
- This analysis will consider patients as virologic failure if they have persistent HBV DNA \geq 400 copies/mL (69 IU/mL), or a confirmed loss of response or discontinuation prior to Week 96. The addition of FTC to TDF (FTC/TDF fixed dose combination) will be analyzed by pure Intent to Treat (ITT) non-completer=failure (NC=F), i.e., subjects on open-label FTC/TDF will not be considered failures unless they meet the criteria described above.

Methods (cont'd)

Secondary Efficacy Analysis

This analysis will consider patients as virologic failure if they have persistent HBV DNA \geq 400 copies/mL (69 IU/mL), or a confirmed loss of response, premature discontinuation from study prior to Week 96 or if they begin open-label FTC/TDF (fixed-dose combination) regardless of their original treatment assignment (i.e., subjects randomized to FTC/TDF who begin open-label FTC/TDF are counted as virologic failures, as are those who add FTC to TDF monotherapy)

Patient Population

- Key eligibility criteria
 - 18–69 years of age
 - HBeAg positive or negative
 - Currently treated with ADV 10 mg QD (for \geq 24 weeks but \leq 96 weeks)
 - Concomitant and past treatment with lamivudine permitted
 - HBV DNA \geq 172 IU/mL (1000 copies/mL) (Roche Cobas TaqMan Assay, lower limit of quantification 29 IU/mL [169 copies/mL])
 - ALT levels $<$ 10 x the upper limit of normal (ULN)
 - Compensated liver disease; no evidence of HCC
 - No co-infection with HCV, HIV, or HDV

Results

Table 1. Baseline Disease and Demographic Characteristics

	TDF (N=53)	FTC/TDF (N=52)
Mean Age	40	39
Race		
White	23 (44%)	21 (40%)
Asian	26 (49%)	18 (35%)
Male	38 (72%)	42 (81%)
HBeAg Positive	38 (72%)	39 (75%)
Mean HBV (log ₁₀ copies/mL)	6.06	5.87
ALT > ULN	27 (51%)	26 (50%)
Prior LAM exposure (\geq 12 weeks)	30 (57%)	31 (60%)
Mean prior ADV exposure (weeks; range)	62 (20-131)	59 (29-128)
HBV Viral Genotype (n)		
A	11	9
B	6	4
C	15	11
D	18	21
E	2	6

Figure 2. Patient Disposition at 2 years

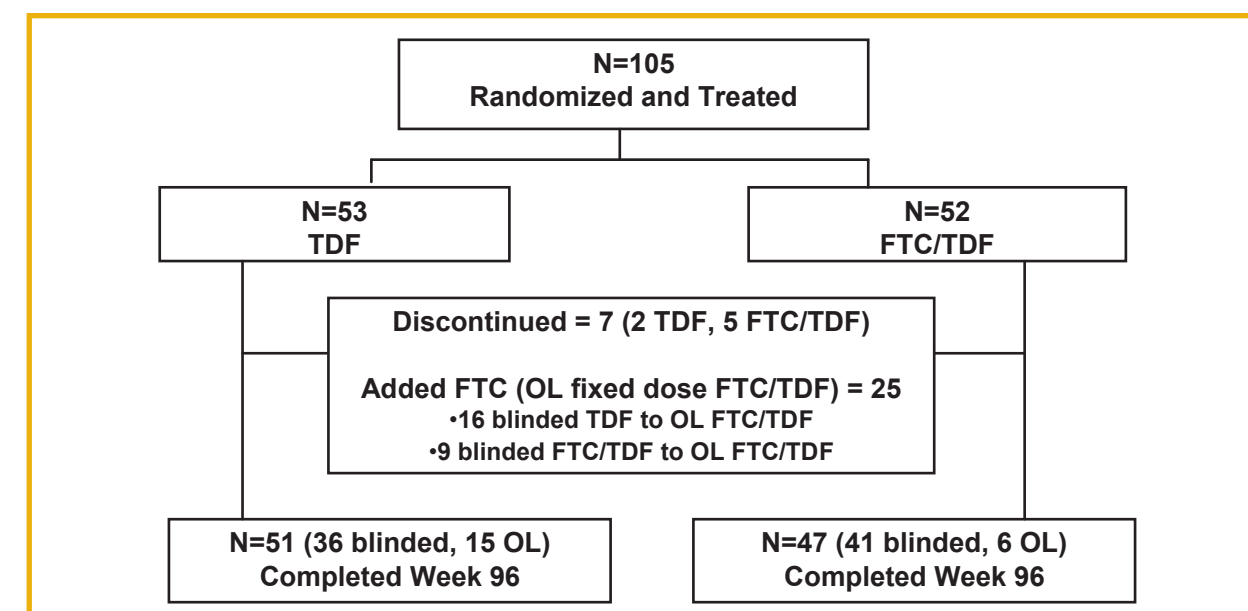


Figure 3. Primary Efficacy Analysis: Comparison of the Two Treatment Strategies % of Patients with HBV DNA < 400 copies/mL (69 IU/mL)

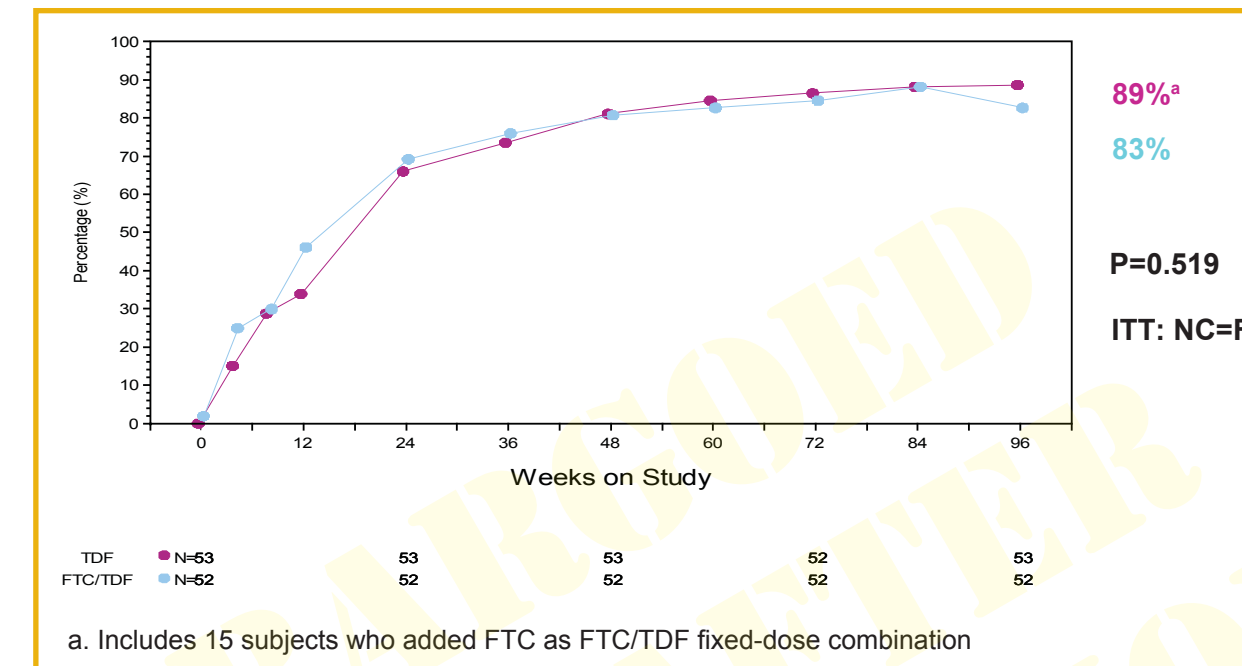


Figure 4. Secondary Efficacy Analysis: Comparison of Antiviral Efficacy of Monotherapy versus Combination Therapy % patients with HBV DNA < 400 copies/mL (69 IU/mL)

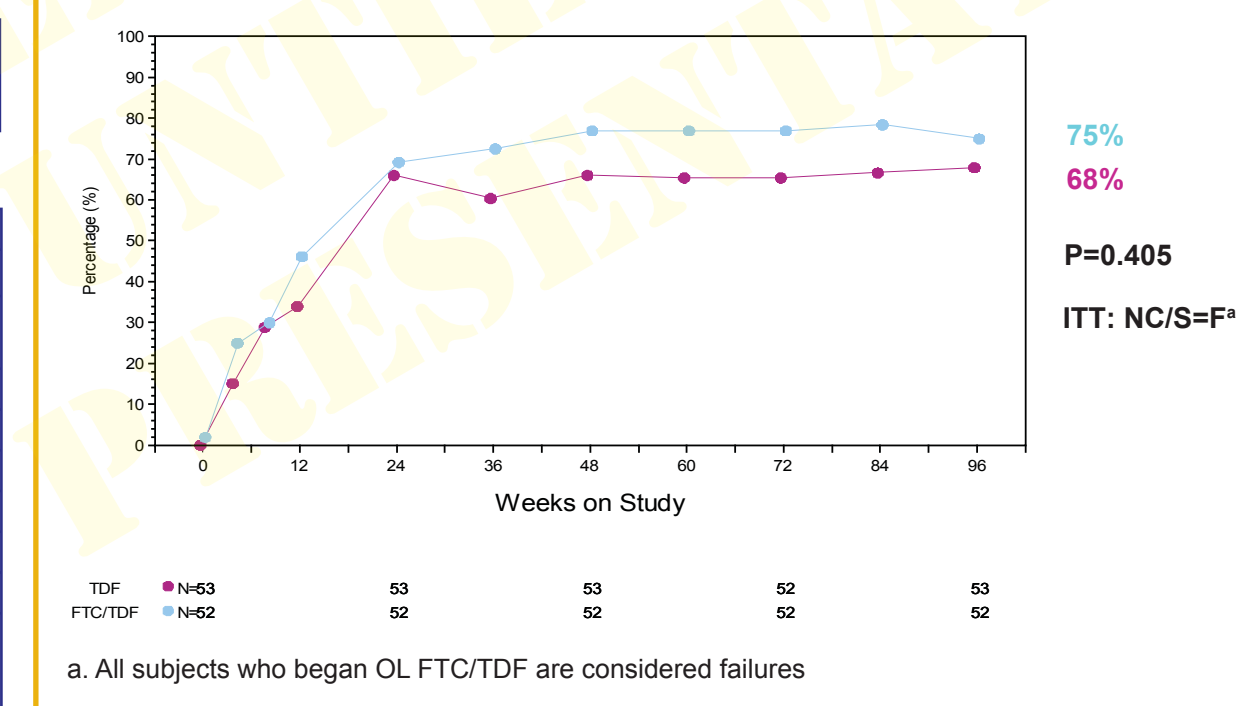
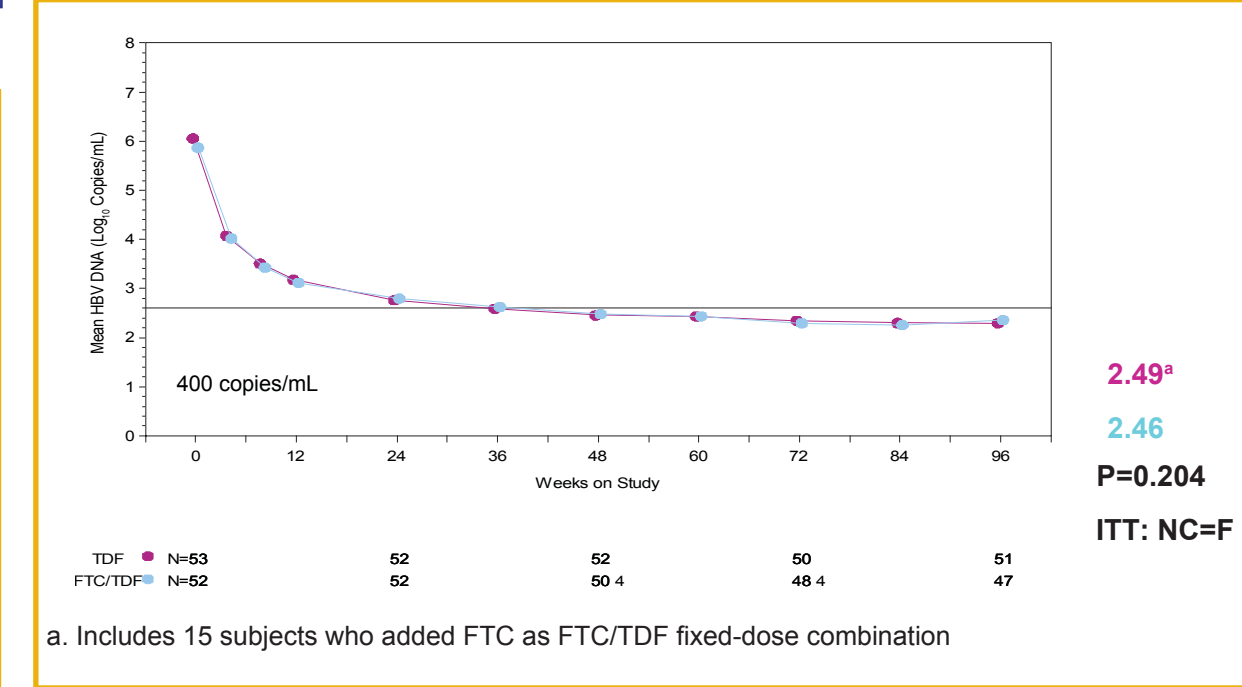


Figure 5. Mean HBV DNA (log₁₀) by Study Visit



Results (cont'd)

Figure 6. Proportion of Patients with ALT Normalized^a by Study Visit

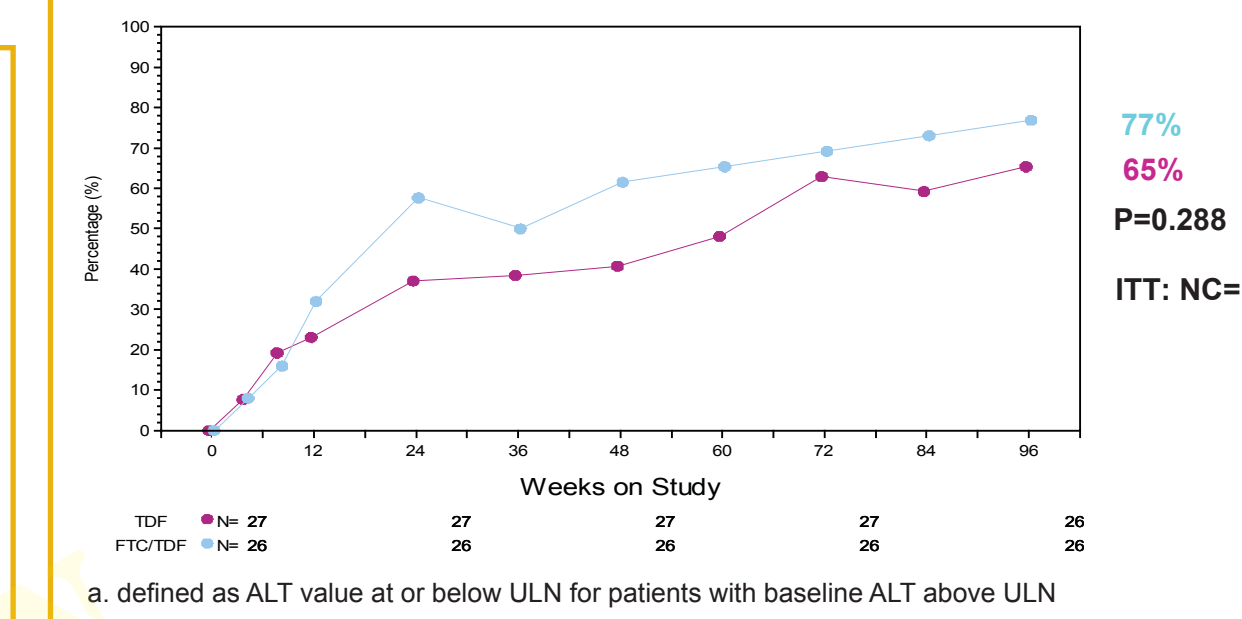


Table 2. Week 96 Results (cont'd)

	TDF (N=53)	FTC/TDF (N=52)
Proportion with HBeAg loss	5/38 (13%)	6/39 (15%)
Proportion with HBeAg seroconversion	3/38 (8%)	5/39 (13%)
Proportion with HBsAg loss	2/53 (4%)	0
Proportion with HBsAg seroconversion	1/53 (2%)	0

ITT non-completer = failure analysis

Table 3. Baseline Genotypic Analysis^a

Patient Population	N
All Enrolled	105
Patients with ADV-Resistance Mutations at Baseline	8 (7.6%)
rtA181V	2
rtN236T	2
rtA181T/V + rtN236T	4
Patients with LAM-Resistance Mutations at Baseline	13 (12.4%)
rtM204V/I	1
rtL180M+rtM204V/I	12
Patients with rtA181T at Baseline	2 (1.9%)
All patients with Mutations at Baseline	23 (22%)

a. population sequencing

Figure 7. Response (HBV DNA <400 copies/mL [69 IU/mL] at Week 96) by Resistance Mutations at Baseline

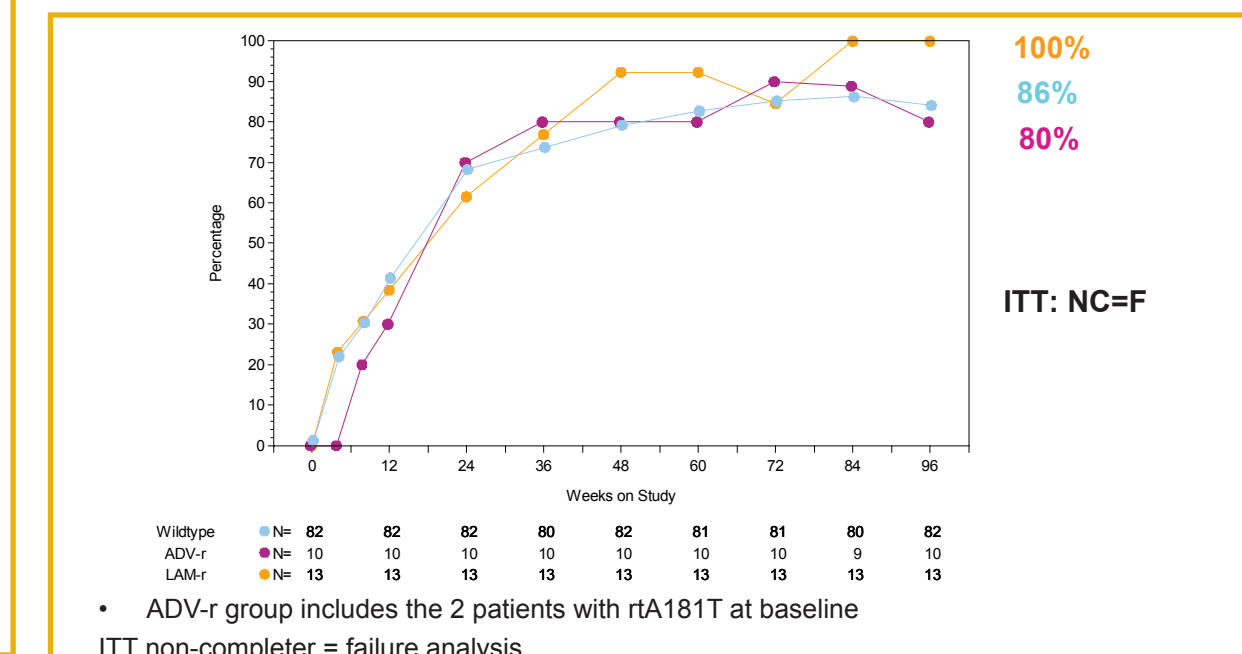


Table 4. Response by Treatment Strategy (HBV DNA <400 copies/mL [69 IU/mL]) at Week 96 by Resistance Mutations at Baseline

HBV DNA < 400 copies/mL	ADV-r		LAM-r	
	TDF	FTC/TDF	TDF	FTC/TDF
Week 48 (NC=F)	7/8 (88%)	1/2 (50%)	6/7 (86%)	6/6 (100%)
Week 96 (NC=F)	7/8 (88%)	2/2 (100%)	7/7 (100%)	6/6 (100%)

Table 4. Summary of Safety Data

Adverse Event, % patients with	TDF (N=53)	FTC/TDF (N=52)
Grade 3 or 4 AE	1 (2%)	5 (9%)
SAE (none reported as related to study drug)	4 (8%)	8 (15%)
AE that resulted in DC	0	0
Laboratory Abnormalities, Subject with		
Any G3/4 abnormality (total events)	7 (13%)	9 (17%)
G4 (ALT >10 x ULN) and > 2 x Baseline	0	2 (4%)
Confirmed 0.5 mg/dL increase in creatinine	0	0
Confirmed CLcr decline to <50mL/min	0	0
Confirmed serum phosphorus < 2mg/dL	0	0

Conclusions

- Both treatment strategies (TDF monotherapy with option to add FTC as combination FTC/TDF, or initial combination of FTC/TDF) were equivalent through 96 weeks of follow-up in this heavily pretreated, highly viremic population
- There is a non significant trend favoring combination for antiviral efficacy when considering subjects who added FTC or switched from blinded FTC/TDF to open-label as failures
- In patients with incomplete viral suppression on ADV majority with prior/current LAM use, the complete viral suppression noted in most patients at Week 48 on TDF or FTC/TDF (81% in both arms) was maintained at Week 96 (89% TDF; 85% FTC/TDF)
- Virologic response was independent of pre-existing ADV- or LAM-associated mutations

Acknowledgements

Germany G Gerken H Hartmann C Herold M-C Jung M Maara J Petersen U Spengler	France M Bourliere F Habersetzer P Mathurin P Cales G Riachi C Trepo	United States R Gish H-W Han J Jacobson H Pollack V Rustgi M Ryan M Shiffman T Tsang J Weising	Gilead Sciences Jill Fidgeon Todd Thompson Ellen Montgomery Susan Nonaka-Wong Sarah Charles James Somerville Angela Rose Megan Lyles Jennifer Girrell Atwell
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References

1. Berg et al, EASL 2008;