

Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study

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Objective: To evaluate the safety and efficacy of once daily doses of tenofovir DF (TDF) administered in combination with other antiretroviral therapy (ART) in treatment-experienced HIV-1-infected patients with incomplete virological suppression.

Design: One-hundred and eighty-nine subjects with plasma HIV-1 RNA levels between 400 and 100 000 copies/ml and stable ART (≥ 8 weeks) were randomized (2 : 2 : 2 : 1 ratio) to add TDF 75 mg, 150 mg, or 300 mg or placebo to existing ART in a double-blinded manner. After 24 weeks, patients initially randomized to placebo received blinded TDF 300 mg.

Methods: Efficacy was analyzed by the mean changes HIV-1 RNA levels (\log_{10} copies/ml plasma; DAVG_{xx}) from week 0 to weeks 4, 24, and 48. Safety was analyzed by incidence of grade 3 or 4 clinical and laboratory adverse events.

Results: At baseline, patients had mean 4.6 years prior ART use with 94% having HIV-1 with nucleoside-associated resistance mutations. There were statistically significant decreases in DAVG₄ and DAVG₂₄ for all doses of TDF compared with placebo, with the greatest effect seen with TDF 300 mg (DAVG₄, -0.62 , $P < 0.001$; DAVG₂₄, -0.58 ; $P < 0.001$; DAVG₄₈, -0.62). The incidence of adverse events was similar among the TDF groups and placebo through week 24. Throughout the 48-week study, no significant changes in renal function were observed.

Conclusions: In treatment-experienced patients with baseline nucleoside resistance mutations, TDF provided dose-related, durable reductions in HIV-1 RNA. Through 24 weeks, the safety profile of TDF was similar to that of placebo.

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Introduction

The current approach to treating HIV-1 infection is a regimen of highly active antiretroviral therapy (HAART), with the goal of suppressing plasma viral replication for as long as possible. Unfortunately, many patients do not achieve or sustain long-term virological

suppression, which is a primary unmet need in the treatment of HIV-1 infection.

Tenofovir (PMPA) is an acyclic nucleotide reverse transcriptase inhibitor (NtRTI) with activity *in vitro* against HIV-1 and HIV-2 [1,2]. Further, tenofovir has a favorable resistance profile, as it is active against wild-

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type and most nucleoside-resistant HIV-1 strains [3,4]. In preclinical studies, the K65R mutation in reverse transcriptase was selected by tenofovir *in vitro*, resulting in a three- to fourfold decrease in susceptibility to tenofovir [3]. Although the K65R mutation can be selected by zalcitabine, abacavir and didanosine, *in vitro* or *in vivo*, its prevalence in treatment-experienced patients is rare (<2%) [5]. Because the presence of a phosphonate group limits the oral bioavailability of tenofovir, a prodrug, tenofovir disoproxil fumarate (tenofovir DF), was developed, which is orally bioavailable and is rapidly converted to tenofovir following absorption [6].

This phase II study (GS-98-902) investigated the use of multiple doses of tenofovir DF in a population of treatment-experienced HIV-1-infected patients with evidence of suboptimal virological suppression. Three doses of tenofovir DF were evaluated (75 mg, 150 mg, and 300 mg), administered once daily in addition to the patient's existing antiretroviral regimen. These doses were chosen based on the phase I/II study, GS-97-901, during which four doses of tenofovir DF were evaluated (75 mg, 150 mg, 300 mg, and 600 mg) as monotherapy for 28 days [7]. No safety issues were identified in this short-term study, while the greatest antiviral response was seen in the antiretroviral-naïve patients in the 300 mg arm: a median 1.6 log₁₀ copies/ml reduction from baseline in plasma HIV-1 RNA. In the present study, antiviral efficacy and the durability of initial antiviral responses were also compared among the various groups in the study. This study consisted of a 48-week, double-blinded phase and an ongoing open-label phase. The results from the double-blinded phase of the study are presented.

Methods

Study population and design

An Institutional Review Board reviewed the study protocol and consent form for each study center and all patients provided written informed consent. One-hundred and eighty-nine HIV-1 infected adults were enrolled into the study at 22 centers in the USA. Eligible patients had plasma HIV-1 RNA levels between 400 and 100 000 copies/ml and were on stable antiretroviral therapy (ART; no more than four agents) for at least 8 weeks prior to randomization. Patients were assigned randomly in a 2:2:2:1 ratio to add 75 mg, 150 mg, or 300 mg of tenofovir DF or identical appearing placebo once daily to their existing regimen in a double-blinded manner. Tenofovir DF was supplied by Gilead Sciences, Inc., as white to off-white, round, standard biconvex tablets containing 75 mg of the active ingredient. Placebo tablets matched the tenofovir DF tablets in physical appearance and con-

tained denatonium benzoate to match the bitterness of the active tablets. Patients were encouraged to maintain their background antiretroviral regimen for at least 4 weeks post-randomization. Patients were stratified by site according to HIV-1 RNA level (< 20 000 or ≥ 20 000 copies/ml), CD4 cell count (< 200 × 10⁶ or ≥ 200 × 10⁶ cells/l), and the total number of antiretroviral drugs (< 4 or ≥ 4) used in past and current regimens at study entry. At 24 weeks post-randomization, patients initially assigned to the placebo arm were crossed over to tenofovir DF 300 mg once daily, in a blinded fashion, for the remainder of the study. After completing 48 weeks of the study, patients were given the option to continue to receive open-label tenofovir DF 300 mg once daily.

Interactive Clinical Technologies, Inc. (ICTI) was selected to develop and maintain an interactive voice response system (IVRS), which centralized patient randomization and drug dispensing. Through the IVRS system, ICTI generated the random allocation sequence, and enrolled and assigned patients to their treatment groups. In order to conceal the allocation sequence for the duration of the 48-week study, ICTI assigned patients with blinded kit numbers.

The co-primary efficacy end points were the time-weighted mean change in plasma HIV-1 RNA (log₁₀ copies/ml) from baseline to weeks 4 (DAVG₄) and 24 (DAVG₂₄). In addition, the time-weighted mean change in HIV-1 RNA levels from baseline to week 48 (DAVG₄₈) was assessed for the three active treatment groups. This parameter was used in lieu of traditional analyses (measuring only HIV-1 RNA changes from baseline) as DAVG reflects treatment experience with all patients and all data contributing to the endpoint. DAVG₂₄ is defined as the subject's time-weighted mean marker value between baseline and week 24 minus the subject's baseline value. Specifically, if the AUC₂₄ is the area-under-the-curve of log₁₀ HIV-1 RNA copies/ml between baseline and week 24 (using the trapezoidal rule with available marker data between weeks 0 and 24 inclusive), then DAVG₂₄ is defined as: $[AUC_{24} - 24 \cdot Y_0]/24 = DAVG_{24}$ where time is measured in weeks and Y₀ denotes the value of log₁₀ RNA copies/ml at time 0, taken to be the average of the prebaseline and baseline values. For subjects with marker data only through week *w* (*w* < 24), DAVG₂₄ is taken to be $[AUC_w - w \cdot Y_0]/w$. Similar measures were calculated using values at week 48.

The primary safety end-point was the percentage of patients with grade 3 or 4 abnormalities (clinical adverse events and laboratory toxicities occurring after treatment initiation through 30 days following administration of the last dose of study drug). Additional safety assessments included the effects of tenofovir DF on renal and bone parameters, organs that preclinical (ani-

mal) studies indicated may be areas of potential concern.

Assessments

Unless otherwise specified, all referenced laboratory values were obtained from samples sent to a central laboratory. Plasma HIV-1 RNA level was assessed at the screening visit using the standard Amplicor HIV-1 Monitor Test [lower limit of quantitation (LLQ), 400 copies/ml] (Roche, Nutley, New Jersey, USA). Subsequently, plasma HIV-1 RNA levels were measured at prebaseline, baseline and at the end of weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 using the Ultrasensitive HIV-1 Monitor Test (LLQ, 50 copies/ml) (Roche). CD4 cell counts were performed at screening, baseline and at the end of weeks 4, 8, 12, 24, 36, and 48. Plasma for genotypic analyses of the HIV-1 reverse transcriptase and protease genes was stored at the prebaseline, baseline and at the end of weeks 2, 4, 12, 16, 20, 24, 32, 40 and 48. Genotypic analyses were performed with HIV-1 TruGene technology (Visible Genetics, Toronto, Canada). Safety and tolerance were evaluated by assessing adverse events and clinical laboratory values at weeks 2, 4, 8 and every 4 weeks thereafter until completion of the study. Bone mineral density was assessed with dual-energy X-ray absorptiometry (DXA) scanning of the L1–L4 vertebral column every 3 months at selected centers.

Any adverse event with an onset date after study drug administration or within 30 days following study completion was recorded as an adverse event, regardless of the severity or relationship to study medication.

Statistical analysis

A sample size of 50 patients per group for each of the tenofovir DF arms was calculated to provide at least 80% power to detect a 30% difference at the 5% significance level between the treatment groups using a two-sided test.

Data were analyzed for ‘intent-to-treat’ (ITT, missing = failure) populations. ITT was the primary population for all analyses of efficacy and baseline characteristics, which included data from all patients who were randomized into the study and received one dose of study medication with no data exclusions. The safety population included all patients who received at least one dose of the study medication.

Safety analyses included the percentage of patients who developed grade 3 or 4 toxicity (clinical and/or laboratory). Efficacy was analyzed as the time-weighted average change from baseline in \log_{10} HIV-1 RNA copies/ml up to week 4 (DAVG₄) and week 24 post-randomization (DAVG₂₄). Pair-wise comparisons of treatment groups were based on the Wilcoxon rank sum test. P values < 0.05 were considered statistically significant.

Results

Subject population

The study period lasted from 2 September 1998 (first patient randomized) to 16 March 2000 (final patient observation for 48-week blinded phase of study). One-hundred and eighty-nine adults were enrolled into the study: 54 subjects were assigned to the tenofovir DF 75 mg group, 51 to the tenofovir DF 150 mg group, 56 to the tenofovir DF 300 mg group, and 28 to the placebo group. The majority of patients in this study had symptomatic HIV-1 infection or AIDS. Baseline characteristics for the ITT population, which are summarized in Table 1, were similar in the four treatment arms. The overall mean plasma HIV-1 RNA level at entry was 3.7 \log_{10} copies/ml and the overall mean CD4 count was 374×10^6 cells/l. There were no statistically significant differences between the groups in CD4 cell counts or HIV-1 RNA levels at baseline.

Table 1. Baseline characteristics of subjects.

	Tenofovir DF				Overall
	Placebo (n = 28)	75 mg (n = 53)	150 mg (n = 51)	300 mg (n = 54)	
Number treated	28	53	51	54	186
Male (%)	93	87	94	94	92
Mean age (years)	41	43	42	41	42
Mean CD4 cell count ($\times 10^6$ cells/l)	298	374	410	381	374
Mean plasma HIV RNA (\log_{10} copies/ml)	3.8	3.6	3.6	3.7	3.7
Mean prior ART use (months)	54	58	54	54	55
NRTI resistance (%)	92	94	94	94	94
NNRTI resistance (%)	31	26	37	31	32
PI Resistance (%)	69	51	53	61	57

ART, Antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

Patients participating in this study had substantial prior exposure to ART, with an overall mean duration of 55 months. Almost all of the patients in this study had HIV-1 drug resistance mutations at baseline. The proportion harboring HIV with mutations was similar in all groups: 94% had resistance mutations associated with NRTI; 57% had primary resistance mutations (any amino acid change from wild-type for D30, G48, I50, V82 or L90) associated with protease inhibitors; and 32% had primary resistance mutations (K103N or Y181C) associated with non-nucleoside reverse transcriptase inhibitors (NNRTI). HIV-1 reverse transcriptase mutations associated with nucleoside resistance were defined according to the Resistance Collaborative Group definition as one or more of the following: M41L, A62V, K65R, D67N, T69D/N, K70R, L74V/I, V75T, F77L, Y115F, F116Y, Q151M, M184V, L210W, T215Y/F or K219Q [8].

Subject accountability

Three patients did not receive study drug. During the first 24 weeks of the study, more patients in the placebo group (25%) compared to those in the tenofovir DF groups (9–16%) discontinued study drug (Fig. 1). Through 48 weeks, 24–26% of patients in the three tenofovir DF-treated groups discontinued study drug.

Plasma HIV-1 RNA response

Patients adding tenofovir DF once daily to a stable background antiretroviral regimen resulted in statisti-

cally significant mean decreases in the co-primary efficacy endpoints, the average change in HIV-1 RNA from week 0 to week 4 (DAVG₄) and week 0 to week 24 (DAVG₂₄) (Table 2). The DAVG₄ was 0.02, -0.22 (P = 0.008), -0.44 (P < 0.001), and -0.62 (P < 0.001) for the placebo, tenofovir DF 75 mg, 150 mg, and 300 mg groups, respectively. These changes remained statistically significant with a DAVG₂₄ of 0.02, -0.26 (P = 0.013), -0.34 (P = 0.002), and -0.58 (P < 0.001) in log₁₀ copies/ml plasma HIV-1 RNA for the placebo, tenofovir DF 75 mg, 150 mg, and 300 mg groups, respectively. The antiviral response to tenofovir

Table 2. Average change from baseline DAVG_{xx} HIV-1 RNA in log₁₀ copies/ml for weeks 4, 24, and 48 (intention to treat population).

DAVG _{xx} /dose group	Mean	P ^a
DAVG ₄		
Placebo	+0.02	-
75 mg	-0.22	0.008
150 mg	-0.44	< 0.001
300 mg	-0.62	< 0.001
DAVG ₂₄		
Placebo	+0.02	-
75 mg	-0.26	0.013
150 mg	-0.34	0.002
300 mg	-0.58	< 0.001
DAVG ₄₈		
75 mg	-0.33	-
150 mg	-0.34	-
300 mg	-0.62	-

^aP versus placebo, Wilcoxon rank sum test.

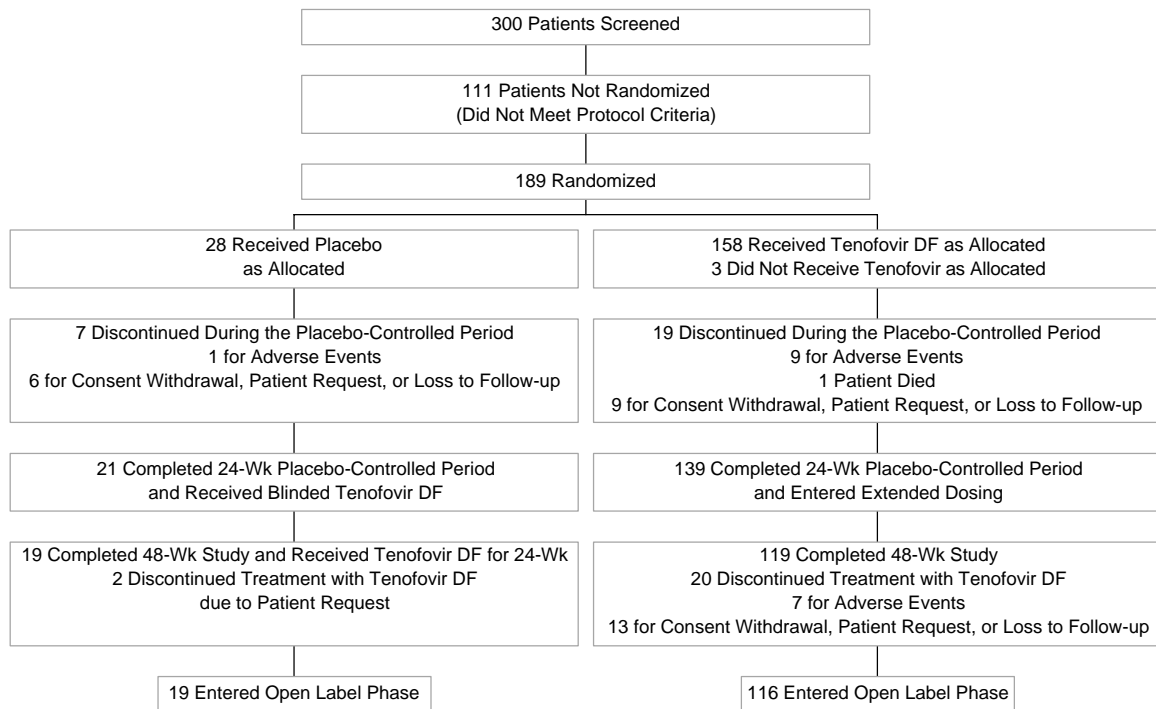


Fig. 1. Recruitment and disposition flowchart.

DF was durable and sustained with a DAVG₄₈ of -0.33 , -0.34 and -0.62 in \log_{10} copies/ml plasma HIV-1 RNA for the tenofovir DF 75 mg, 150 mg and 300 mg groups, respectively.

The incidence of modifications to background anti-retroviral treatment was balanced among all four groups during the first 24 weeks on study (placebo, 32%; 75 mg, 27%; 150 mg, 27%; 300 mg, 31%). As a consequence, the significant antiviral responses seen through week 24 were unlikely to be influenced by changes in background ART. Through 48 weeks, the incidence of modifications in background ART remained balanced among the groups (75 mg 44%, 150 mg 47%, 300 mg 47%).

HIV resistance data

Genotypic and phenotypic resistance testing was also performed, and is described fully in a separate paper [9].

CD4 cell count response

Pairwise comparisons revealed no statistically significant differences between treatment groups in mean change in CD4 cell count at any pretreatment or on-treatment time point. By 24 weeks of treatment, mean changes in CD4 cell counts were $+20 \times 10^6$ cells/l, $+18 \times 10^6$ cells/l, 0 cells/l, and -14×10^6 cells/l in the placebo, 75 mg, 150 mg, and 300 mg groups, respectively. After 48 weeks of treatment, mean changes in CD4 counts were $+10 \times 10^6$ cells/l, $+20 \times 10^6$ cells/l and $+11 \times 10^6$ cells/l in the tenofovir DF 75 mg, 150 mg, and 300 mg groups, respectively.

Adverse event profile

In the first 24 weeks, headache, asthenia, pain, diarrhea, nausea, vomiting, pharyngitis, and rash were the most common clinical adverse events seen in this study, each occurring in $> 20\%$ of study patients. Of these, only diarrhea appeared to be more common in the tenofovir DF groups (21–25%) than in the placebo group (14%).

Table 3. Grade 3 or 4 adverse events and laboratory abnormalities at weeks 24 and 48.

	Placebo (0-24 weeks) (n = 28)	Tenofovir DF		
		75 mg (n = 53)	150 mg (n = 51)	300 mg (n = 54)
Patients who experienced any grade 3 or 4 adverse event through 24 weeks [n (%)]	4 (14)	10 (19)	9 (18)	9 (17)
Type of abnormality occurring in two or more patient in any group				
Depression	0	2 (4)	0	3 (6)
Asthenia	1 (4)	0	2 (4)	0
Allergic reaction	0	0	0	2 (4)
Patients who experienced any grade 3 or 4 laboratory abnormality through 24 weeks [n (%)]	9 (32)	18 (34)	16 (31)	16 (30)
Type of abnormality occurring in three or more patients in any group				
Triglyceride elevation	4 (14)	9 (17)	4 (8)	5 (9)
Creatine kinase	4 (14)	5 (9)	4 (8)	6 (11)
Aspartate aminotransferase elevation	1 (4)	3 (6)	3 (6)	4 (7)
Neutropenia	1 (4)	3 (6)	1 (2)	3 (6)
Serum glucose elevation	0	3 (6)	2 (4)	0
Patients who experienced any grade 3 or 4 adverse event through 48 weeks [n (%)] ^a		15 (28)	15 (29)	14 (26)
Type of abnormality occurring in two or more patient in any group				
Depression		2 (4)	1 (2)	3 (6)
Allergic reaction		0	0	2 (4)
Anxiety		2 (4)	0	0
Asthenia		0	2 (4)	0
Drug dependence		2 (4)	0	0
Gastroenteritis		0	2 (4)	0
Headache		0	2 (4)	0
Patients who experienced any grade 3 or 4 laboratory abnormality through 48 weeks [n (%)]		20 (38)	22 (43)	21 (39)
Type of abnormality occurring in three or more patients in any group				
Triglyceride elevation		11 (21)	8 (16)	6 (11)
Creatine kinase		7 (13)	5 (10)	6 (11)
Aspartate aminotransferase elevation		4 (8)	3 (6)	5 (9)
Neutropenia		3 (6)	2 (4)	4 (7)
Amylase elevation		3 (6)	2 (4)	3 (6)
Serum lipase elevation		2 (4)	3 (6)	3 (6)
Serum glucose elevation		3 (6)	2 (4)	0
Total bilirubin elevation		3 (6)	1 (2)	1 (2)

^aThrough 30 days post discontinuation.

By 48 weeks, additional events occurring in > 20% of patients were viral infection, abdominal pain, flu-like symptoms, back pain, rhinitis, and cough. No dose-related increase in the incidence of any adverse events was observed.

The incidences of grade 3 or 4 clinical adverse events were similar in all four groups and none of the comparisons between these groups through weeks 24 or 48 were statistically significant (all P-values > 0.05), as shown by the Wilcoxon rank sum test (Table 3). Apart from depression (6% in the 300 mg group), no grade 3 or 4 event occurred in more than 5% of patients in any group throughout the 48-week study period.

Grade 3 or 4 laboratory abnormalities occurring in $\geq 10\%$ of the patients during the first 24 weeks included elevated levels of creatine kinase (10% overall) and triglycerides (12% overall), but for both parameters the incidence in the tenofovir DF 300 mg group was less than that in the placebo group (Table 3). No additional grade 3 or higher laboratory abnormalities were seen through 48 weeks and there was no evidence of a dose effect for any of these parameters.

No clinically significant renal abnormalities were observed and no patient was discontinued from study because of serum creatinine elevations. The median serum creatinine values for the four original dose groups remained constant from 0.8 to approximately 0.9 mg/dl through 48 weeks on treatment. Two patients (75 mg group and placebo crossover to 300 mg group) developed a confirmed grade 1 (two consecutive values 0.5 mg/dl greater than the baseline value) serum creatinine elevation, but both resumed dosing with tenofovir DF and completed the 48-week study. During the 48-week study, no patient developed a grade 2 (2.1–3.0 mg/dl) or higher serum creatinine elevation.

No marked changes from baseline in median phosphorus levels occurred in any treatment group through week 24 or in the three tenofovir DF groups through week 48. The incidence of treatment emergent grade 2 hypophosphatemia (1.5–1.9 mg/dl) at 24 weeks was similar between the placebo (4%) and tenofovir DF groups (2%–7%). Notably, none of the placebo patients developed grade 1–4 hypophosphatemia after crossing over to tenofovir DF 300 mg for 24 weeks. The incidence of grade 2 hypophosphatemia at week 48 was similar to that at week 24. Through 48 weeks, no patient developed treatment emergent grade 3 or 4 hypophosphatemia.

The incidence of grade 2 proteinuria at 24 weeks was similar between the placebo (14%) and tenofovir DF groups (6%–7%). Through 48 weeks, no patient in any

group experienced grade 3 or 4 proteinuria. Further, the incidence of graded urine protein abnormalities was similar across the active treatment groups, and there was no evidence of a dose effect.

Sixty-two patients at selected sites were monitored for bone mineral density using DXA. Baseline bone mineral density was similar among the four groups, with mean values ranging from 1.071 to 1.160 g/cm². The median percentage changes from baseline at week 24 were –2.00%, –0.16%, –0.15%, and –1.19% for the placebo, tenofovir DF 75 mg, 150 mg, and 300 mg dose groups, respectively, and were within the range of measurement error and not statistically significant. At week 48, the median changes from baseline were +0.68%, –1.64%, and –1.35% for the 75 mg, 150 mg, and 300 mg dose groups, respectively, suggesting no dose effect.

Discussion

In treatment-experienced patients with baseline nucleoside resistance mutations the addition of tenofovir DF to stable antiretroviral regimens resulted in significant reductions in the average change in plasma HIV-1 RNA from week 0 to weeks 4 and 24. Furthermore, these reductions were durable. Exhibiting a safety profile similar to placebo through 24 weeks, this study illustrates that tenofovir DF is both safe and well tolerated. No dose-related increase in the incidence of any adverse event was observed during this study. Furthermore, no significant changes in renal function were observed through 48 weeks.

There are few similar studies with patient populations as treatment-experienced as the GS-98-902 population. In the CNA3002 study, abacavir or placebo was added to background therapy in patients with HIV-1 RNA between 400 and 50 000 copies/ml [10]. Only 5% of patients had more than 18 months of prior ART while in GS-98-902 patients had a mean 55 months of prior ART. The addition of abacavir resulted in a median change from baseline in log₁₀ copies/ml plasma HIV-1 RNA of –0.44 at week 16. The addition of tenofovir DF 300 mg resulted in a statistically significant average change from baseline to week 24 in log₁₀ copies/ml HIV-1 RNA (DAVG₂₄) of –0.58. In CNA3002 and GS-98-902, the change in median CD4 cell count from baseline did not differ significantly between the active and placebo arms. These results suggest that in treatment-experienced patients, the addition of a single antiretroviral agent to stable background therapy may result in only small changes in CD4 cell counts.

The next generation of antiretroviral agents will include efficacious and durable regimens that offer con-

venience, ensure tolerability, and preserve future treatment options. Based on the results from this clinical trial a regimen containing tenofovir DF has the potential to address each of these needs by offering a safe and convenient single tablet, once daily NtRTI that can be effective in patients with pre-existing NRTI resistance. Further, tenofovir DF may represent a long-term component of any antiretroviral regimen, with only rare emergence of drug resistance mutations [9], leading to long-term viral suppression.

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References

1. Balzarini J, Holy A, Jindrich J, *et al.* Differential antiherspesvirus and antiretrovirus effects of the (S) and (R) enantiomers of acyclic nucleoside phosphonates: potent and selective in vitro and in vivo antiretrovirus activities of (R)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine. *Antimicrob Agents Chemother* 1993, **37**:332–338.
2. Robbins BL, Srinivas RV, Kim C, Bischofberger N, Fridland A. Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-R-(2-phosphonomethoxypropyl)adenine (PMPA), Bis(isopropylloxymethylcarbonyl) PMPA. *Antimicrob Agents Chemother* 1998, **42**:612–617.
3. Wainberg MA, Miller MD, Quan Y, *et al.* In vitro selection and

characterization of HIV-1 with reduced susceptibility to PMPA. *Antivir Ther* 1999, **4**:87–94.

4. Shirasaka T, Kavlick MF, Ueno T, *et al.* Emergence of human immunodeficiency virus type 1 variants with resistance to multiple dideoxynucleosides in patients receiving therapy with dideoxynucleosides. *Proc Natl Acad Sci USA* 1995, **92**:2398–2402.
5. Bloor S, Kemp SD, Hertogs K, *et al.* Patterns of HIV drug resistance in routine clinical practice: a survey of almost 12,000 samples from the USA in 1999. *Antivir Ther* 2000, **5**(Suppl 3):132.
6. Shaw J-P. In vitro stability of bis POC PMPA (GS 4331) in the biological fluids. Gilead Sciences Report. No. 97-Vit-1278-001. March 7, 1997.
7. Barditch-Crovo P, Deeks S, Collier A, *et al.* Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2001, **45**:2733–2739.
8. DeGruttola V, Dix L, D'Aquila R, *et al.* The relation between baseline HIV drug resistance and response to antiretroviral therapy: re-analysis of retrospective and prospective studies using a standardized data analysis plan. *Antivir Ther* 2000, **5**:41–48.
9. Margot NA, Isaacson E, McGowan I, *et al.* Genotypic and phenotypic analyses of HIV-1 in antiretroviral-experienced patients treated with tenofovir DF. *AIDS* 2002, **16**:1227–1235.
10. Katlama K, Bonaventura C, Plettenberg A, *et al.* The role of abacavir (ABC, 1592) in antiretroviral therapy-experienced patients: results from a randomized, double-blind trial, CNA3002 European Study Team. *AIDS* 2000, **14**:781–789.

Appendix

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