OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	21-356 SE2 033
Submission Date	September 25, 2009
Brand Name	Viread
Generic Name	Tenofovir disoproxil fumarate
Reviewer	Shirley K. Lu, Ph.D.
Team Leader	Sarah M. Robertson, Pharm.D.
OCP Division	DCP IV
OND Division	DAVP
Sponsor	Gilead
Relevant IND(s)	52,849
Submission Type; Code	Efficacy supplement (pediatric)
Formulation; Strength(s)	300 mg tablet
Dosing regimen (Approved in Adults)	300 mg once daily
Proposed dosing regimen	Adolescents ages 12 to <18 years old: 300 mg once daily
Indication	Treatment of HIV-1

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1. Executive Summary

Tenofovir disoproxil fumarate (TDF, Viread®) is the prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor indicated for the treatment of HIV-1 as well as hepatitis B (HBV). The current recommended dosing for Viread in the treatment of HIV-1 in adults is 300 mg once daily. The sponsor is seeking to extend the adult dosing regimen to adolescents ≥12 to <18 years of age based on one safety and efficacy study (GS-US-104-0321).

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the information submitted in this efficacy supplement and agrees that it supports the proposal to extend the adult dosing regimen (300 mg once daily) to adolescents 12 to <18 years of age and weighing at least 35 kg for the treatment of HIV.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

TDF is approved in adults for the treatment of both HIV-1 and HBV. The sponsor is proposing to extend the same adult dosing regimen in HIV-1 to adolescents between 12 and 18 years of age and weighing at least 35 kg.

In a previous adult study, the 300 mg/day dose demonstrated better efficacy than the 75-mg and 150-mg doses with acceptable safety margins (study 902). No further benefit was derived from a higher dose (600 mg). Although 300 mg is safe and effective in adults, the sponsor did not perform formal PK/PD analyses and thus the exposure-response relationship in adults has not been clearly defined.

One safety and efficacy study with a PK substudy in adolescents was completed in support of this efficacy supplement (study 321). In study 321, either 300 mg/day TDF or placebo (1:1 ratio) was added to a newly created optimized and genotype-guided antiretroviral regimen in treatment-experienced adolescents (n=87). The primary efficacy endpoint was time-weighted average change from baseline through week 24 ($DAVG_{24}$) in plasma HIV-1 RNA (log_{10} copies/mL). At the start of treatment, all subjects had an HIV-1 RNA count of ≥1,000 copies/mL. In the overall study population, subjects in the tenofovir arm did not demonstrate superior efficacy over the placebo arm. Upon further analysis, it was discovered that there was a disproportionately higher number of subjects in the placebo arm who had a genotypic sensitivity score (GSS) of greater than 1, indicating that the placebo arm had a more highly active optimized background regimen (OBR) than the tenofovir arm. Thus, any advantage in viral load reduction by adding tenofovir to a subject's regimen was masked by the highly active OBR in the placebo group. When a subgroup analysis was performed for subjects with GSS scores ≤1, the TDF arm was superior to the placebo arm in terms of average change in baseline viral load at week 24 (primary efficacy endpoint) and week 48 (secondary efficacy endpoint).

Tenofovir exposure was similar in a subset of adolescents in this study (N=8) as compared with exposure in adults in historical studies (GS-97-901 and GS-99-907). Thus, the pharmacokinetic data supports adolescent dosing at the adult dose.

2 Question Based Review (QBR)

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of a bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo,* tenofovir disoproxil fumarate (TDF) is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir then undergoes intracellular phosphorylation to become the active moiety. TDF is commercially available as a 300-mg tablet with the following formulation:

Ingredient	%w/w	Mg/Tablet
Tablet core		
Tenofovir DF	(b) (4)	300.00
Pregelatinized starch, NF		(b) (4)
Croscarmellose sodium, NF		
Lactose monohydrate, NF		
Microcrystalline cellulose, NF		
Magnesium stearate, NF		
(b) (4)		
Film coating		
Opadry II Y-30-10671-A		
(b) (4)		

(b) (4)

Adolescents received the commercially available 300 mg tenofovir tablet in study 321.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

TDF is an oral prodrug of tenofovir, a nucleotide analogue. It requires initial diester hydrolysis (by esterases) for conversion to tenofovir and subsequent phosphorylation by cellular enzymes to form tenofovir diphosphate and intracellularly inhibit HIV reverse transcriptase. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate

deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

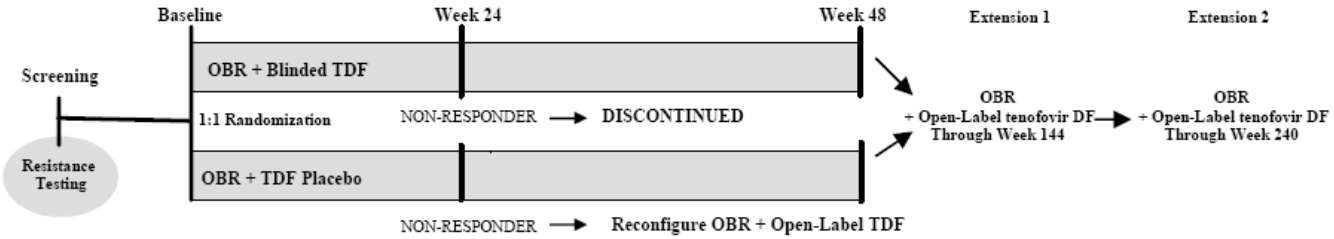
The proposed oral dose of TDF for adolescents 12 years of age and older and weighing ≥35 kg is 300 mg once daily without regard to food.

2.2 General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The study used to support dosing in adolescents (GS-US-104-0321) consisted of a 48-week randomized, double-blind, placebo-controlled study evaluating the safety, efficacy, and tolerability of TDF in adolescents ages 12 to <18 years. The primary objective was to assess the efficacy of TDF plus a genotype-guided OBR compared to placebo + OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥1000 copies/mL at baseline, following 24 weeks of drug exposure. Two 96-week extension periods are currently ongoing to evaluate the long-term safety, efficacy, and tolerability of TDF. A total of 100 evaluable subjects were planned for this study. The design scheme is shown in the figure below.

Study Schema



The primary efficacy endpoint was time-weighted average change from baseline through week 24 ($DAVG_{24}$) in plasma HIV-1 RNA (log_{10} copies/mL). Efficacy was assessed via plasma HIV-1 RNA levels and CD4 cell count (and percentage) at every visit. In addition, an intensive PK substudy was performed on a subset of subjects (n=8) who were switched to open-label TDF at week 24, and had been taking open-label TDF for at least 4 weeks. Subjects in the open-label extension may also have been eligible for the PK substudy.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoints for TDF used for the basis of the original NDA approval are reduction in viral load (measured as copies/mL of HIV RNA) and

increase in CD4 cell counts. High viral load correlates with mortality and morbidity and CD4 cell counts are an indication of the status of the immune system. The number of copies of HIV RNA is a validated surrogate endpoint for viral load and thus, efficacy.

In study 0321 in adolescents, the clinical endpoint was time-weighted average change in baseline through week 24 ($DAVG_{24}$) in plasma HIV RNA.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the sponsor measured the amount of tenofovir in plasma. Once TDF is converted to become tenofovir *in vivo*, tenofovir is phosphorylated intracellularly to its active moiety, tenofovir diphosphate. Thus, the measurement of tenofovir in plasma is an appropriate surrogate for its intracellular active form.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The sponsor did not conduct formal PK/PD studies to evaluate exposure-response relationships in the original NDA submission. However, there appears to be a dose-response relationship favoring the 300 mg once daily dosing regimen based on decreases in HIV RNA observed in studies GS-97-901 and GS-97-902 in adults.

In the short-term dose ranging study (study 901), initial decreases in HIV RNA were greater in the 300-mg dose group as compared to the 75-mg and 150-mg groups over 21 days. The 600-mg group did not exhibit further reductions in viral load. In study 902, reductions in HIV RNA were also greater in the 300-mg dose group as compared to the 75-mg and 150-mg groups over 48 weeks. (The 600-mg dosing regimen was not evaluated and PK samples were not collected in study 902.)

2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No clear exposure-response relationship with respect to safety has been identified. However, the two main safety concerns that arose out of preclinical studies for tenofovir were renal toxicity and reductions in bone mineral density. Preclinical studies showed evidence of renal toxicity in 4 animal species: mouse, rat, dog, and

monkey. Kidney changes were associated directly with exposure to tenofovir. However, the toxicity was noted at plasma exposure levels 2-20 times higher than the human clinical exposures following administration of TDF at 300 mg/day. In humans, renal disorders have been reported as part of post-marketing experience (as indicated in the label). However, an association with drug exposure has not been evaluated. Since tenofovir is primarily renally eliminated, dosage adjustments are indicated for patients with renal impairment (see section 2.3.1).

Reductions in bone mineral density were noted in three animal species following tenofovir administration: rats, dogs, and monkeys. Tenofovir and TDF administered to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism behind the bone toxicity is unknown. Decreases in bone mineral density (BMD) have been observed in HIV-infected adults treated with tenofovir. In study 321, bone effects in adolescents were similar to that of adult patients. While lumbar spine BMD increased as expected in this population, the overall rate of bone gain was less in the tenofovir-treated group compared to the placebo group. However, an exposure-response relationship for bone toxicity could not be assessed, as PK data were only collected from a small subset of patients.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the proposed dosing regimen is supported by well-established PK and efficacy data in adults (see 2.2.4.1 above). In addition, a previous single-dose pediatric study (study 983) demonstrated that a dose of 8 mg/kg would likely match the exposures resulting from a 300-mg dose in adults. In the current study, enrollment was limited to adolescents who weighed at least 35 kg in order to approximate 8 mg/kg and to ensure that no subject would significantly exceed this dose. There are no unresolved dosing or administration issues for adolescent dosing.

2.2.5. What are the PK characteristics of tenofovir?

The systemic exposures of tenofovir (C_{max} and AUC) in HIV-infected adults are dose proportional following single and multiple administrations of TDF at doses ranging from 75 to 600 mg. The PK of TDF is similar between healthy and HIV-infected subjects as well as between single and multiple doses. As shown in Table 1, AUC_{tau} and Cmax in adolescents following 4 weeks of dosing with 300 mg/day are similar to adult values. The average age of subjects selected for the PK substudy was 15 years with a range of 13 to 17 years. The overall mean of all subjects' ages in the main study was also 15 years, with a range of 12 to 17 years. Mean weight for

subjects in the substudy was 46.7 kg while in the overall study it was 48.4 kg. Thus, the PK substudy subjects are a fair demographic representative of the population in the overall study.

Table 1 Mean Steady-State PK Parameters for Tenofovir in Adolescents (GS-US-104-0321) and Adults from Historical Studies (GS-97-901 and GS-99-907)

TFV Plasma PK Parameter (Units)	GS-US-104-0321[a] 300 mg/day (N = 8)	GS-97-901[b] 300 mg/day		GS-99-907[b] 300 mg/day			
		8th Dose (N = 8)	28th Dose (N = 8)	12 Weeks (N = 12)	24 Weeks (N = 12)	36 Weeks (N = 7)	48 Weeks (N = 7)
AUC_{tau} (ng•h/mL)[c] Mean (% CV)	3390.6 (36.0)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
$AUC_{0\text{-last}}$ (ng•h/mL) Mean (%CV)	2256.4 (32.7)	—	—	—	—	—	—
C_{max} (ng/mL) Mean (%CV)	377.5 (35.6)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{last} (ng/mL) Mean (%CV)	133.4 (42.6)	—	—	—	—	—	—
C_{tau} (ng/mL)[c] Mean (%CV)	64.4 (52.6)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.98 (1.46, 2.99)	3.0	2.3	2.3	2.3	1.5	2.5
T_{last} (h) Median (Q1, Q3)	12.00 (11.96, 12.00)	—	—	—	—	—	—
$T_{½}$ (h)[c] Median (Q1, Q3)	10.54 (9.02, 15.30)	13.7	14.4	14.0	14.9	12.4	14.5

a Measured after a minimum of 4 weeks of treatment with tenofovir DF.
b Historical data in HIV-1 infected adults.
c Parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour time point.

2.3 Analytical Section

2.3.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Tenofovir and the internal standard (adefovir) were resolved on a reverse phase HPLC and detected by a mass spec system (MS/MS). Quantitation of tenofovir is based on peak area ratio (tenofovir to adefovir) using a linear least squares regression with 1/concentration^2 weighting. The calibration curve ranges from 10 to 1000 ng/mL and the limit of quantitation is 10 ng/mL tenofovir based on a 100 µL plasma sample.

2.3.2. Which metabolites have been selected for analysis and why?

Tenofovir was selected for quantitation for this study. TDF is converted to become tenofovir *in vivo*. Tenofovir is then phosphorylated intracellularly to its active moiety, tenofovir diphosphate. Thus, the measurement of tenofovir in plasma is an appropriate surrogate for its intracellular active form. No metabolites of tenofovir were selected for measurement.

2.3.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Although it is unspecified, tenofovir was most likely measured in its total form. Tenofovir exists as approximately 93% unbound in plasma. Thus in this case, the distinction between the measurement of free or total drug is virtually inconsequential since a large majority of the drug is unbound in plasma.

2.3.4 What bioanalytical methods are used to assess concentrations?

Tenofovir and the internal standard (b) (4) were resolved on a reverse phase HPLC and detected by a mass spec system (MS/MS). The quantitation of tenofovir was based on the ratio of the peak areas of tenofovir to adefovir within each run.

The quantification of tenofovir has been validated in the range of 10 to 1000 ng/mL using a sample volume of 0.10 mL. The following table shows key pre-study method validation data.

Analyte	Precision*		Accuracy**	
	Intra-assay	Inter-assay	Intra-assay	Inter-assay
Emtricitabine	2.44% to 7.44%	3.98% to 9.47%	-2.0% to 1.5%	-1.7% to 8.0%
Tenofovir	2.24% to 8.33%	4.37% to 7.85%	-2.0% to 8.1%	-5.2% to 4.0%

* Precision is expressed as % relative standard deviation (% RSD)
** Accuracy is expressed as % bias (mean percent difference from nominal concentration)

The percent accuracy for the calibration standards (concentration range: 10-1000 ng/mL) ranged from 95.6% to 103.6%. The precision range was 103.42% to 112.27%. These values are within an acceptable range. The within-assay precision and accuracy data for the quality control samples are detailed in the table below:

Nominal conc. of QCs (ng/mL)	Measured Concentration of QCs (ng/mL)								
	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	n	Mean[a] (ng/mL)	Precision (%RSD)	Accuracy (%bias)
9.9	10.8	10.6	11.5	9.4	11.1	5	10.7	7.40	8.1
24.7	22.1	26.9	24.3	*36.0	23.5	4	24.2	8.33	-2.0
494.5	483.2	488.0	500.8	483.6	470.5	5	485.2	2.24	-1.9
741.8	735.3	775.4	734.1	750.5	787.5	5	756.6	3.17	2.0

[a] The calculated mean was rounded to the nearest tenth of a unit.
Precision and accuracy were calculated using the rounded values for mean.
* Value excluded because it did not meet the acceptance criteria. It is not used in the statistical calculations.

The long term stability of tenofovir in human plasma stored at -80°C for 460 days was evaluated using quality control samples. The study samples were received by the analytical laboratory between June 12, 2008 and July 16, 2008 and were analyzed between September 3, 2008 and October 8, 2008. Thus, the samples were stored for a maximum of 119 days. The long-term storage stability data is acceptable. The quality controls were analyzed in replicates of six at three different concentrations. Accuracy ranged from 93.6% to 101.7%. The bioanalytical validation is acceptable.

3. Labeling Recommendations

The following label includes the division's revisions. There are no major clinical pharmacology-related changes to the sponsor's proposed labeling.

38 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

4. Appendix

4.1 Individual Study Review

Title (Study GS-US-104-0321)

"A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1-Infected Adolescents"

Objectives

The primary objective of this study (Weeks 0–24) was as follows:

- To assess the efficacy of TDF plus a genotype-guided OBR compared to placebo+ OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥1000 copies/mL, through 24 weeks of drug exposure.

The secondary objectives of this study were as follows:

- To assess the efficacy of TDF plus a genotype-guided OBR compared to placebo+OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥1000 copies/mL, through 48 weeks of drug exposure.
- To evaluate the safety and tolerability of TDF plus OBR compared to placebo+OBR.
- To measure changes in BMD in the two treatment groups.
- To evaluate the long-term efficacy, safety, and tolerability of treatment with TDF through up to 240 weeks of drug exposure.

Study Design

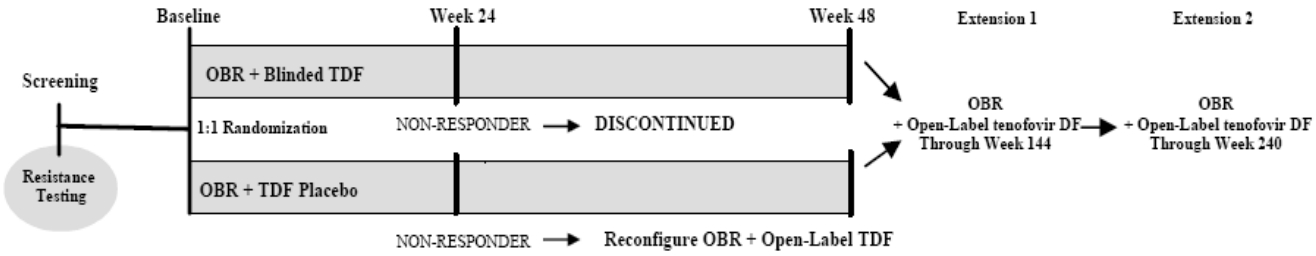
The first 48 weeks of this study was a randomized, double-blind, placebo-controlled, treatment period evaluating the safety, efficacy, and tolerability of TDF in adolescents ages 12 to <18 years. Two 96-week extension periods are currently ongoing to evaluate the long-term safety, efficacy, and tolerability of TDF. A total of 100 evaluable subjects were planned for this study.

Subjects were randomized 1:1 to receive either 300 mg TDF or placebo once daily. The OBR was designed based on ARV history and genotyping results at screening. HIV-1 genotyping was performed at screening to assist in the construction of each subject's OBR (defined as at least 3, but no more than 5 antiretroviral agents, not including TDF, placebo, or PK boosters such as low-dose ritonavir). Subjects were instructed to take their TDF daily dose without regard to meals.

PK samples were taken from a subset of 8 subjects who received at least 4 weeks of open-label TDF following the Week 24 Visit. Blood samples were drawn at the following timepoints: 0, 1, 2, 4, 8, and 12 hours post-dose. Subjects in the open-label extension may also have been eligible for the pharmacokinetic substudy.

At week 24 if a subject was adherent to drug treatment but did not experience ≥0.5 $\log_{10}$ copies/mL decrease in baseline HIV RNA, then they were considered non-responders and were unblinded. Non-responders who were randomized to the placebo group were given the option to continue on-treatment and receive TDF open label with an appropriate OBR as determined by the investigator. Non-responders who were randomized to the TDF group were discontinued.

Figure 1 Study Schema



Key Inclusion Criteria:

- 12 to <18 years of age
- Weight ≥35 kg
- HIV-1 RNA ≥1,000 copies/mL
- Treatment-experienced with at least two antiretroviral drug classes (treatment is defined as >8 weeks)
- Absence of the K65R mutation
- Ability to construct an OBR that does not contain didanosine
- ALT/AST values ≤3 X ULN
- Estimated CrCl ≥80 mL/min/1.73 m^2 (using Schwartz Formula)
- Adequate renal function with serum creatinine below the following parameters:

Age (Years)	Maximum Serum Creatinine (mg/dL)
> 10 to 15	1.2
> 15	1.5

Key Exclusion Criteria:

- Any medication contraindicated with any antiretroviral within an OBR
- Pregnant or lactating subjects
- Required didanosine in background regimen
- Needed ongoing therapy with any of the following:
    - nephrotoxic agents
    - systemic chemotherapeutic agents
    - systemic corticosteroids (short courses <2 weeks were allowable)
    - interleukin-2 (IL-2) and other immunomodulating agents
    - investigational agents (except with the approval from Gilead)
- History of significant renal disease (i.e., nephrotic syndrome, renal dysgenesis, polycystic kidney disease, congenital nephrosis)

<u>Formulation(s) Used</u>

Commercially available 300-mg Viread tablets were used in this study. Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, croscarmellose sodium, and magnesium stearate. The tenofovir DF tablets were film-coated to mask taste. The film coating consisted of lactose monohydrate, hypromellose, titanium dioxide, triacetin, and FD&C Blue No. 2 aluminum lake.

Results

A total of 90 subjects in sites from Brazil and Panama were randomized in the study (46 in the TDF treatment arm, 44 in the placebo arm). However, due to 3 subjects never receiving treatment and 2 subjects who had baseline HIV RNA <1,000 copies/mL, only 85 subjects were included in the ITT analysis.

Figure 2 represents the mean concentration vs. time profile for subjects in the PK subset. As shown in Table 2, AUC_{tau} and Cmax in adolescents following 4 weeks of dosing are similar to adult values at all time periods (8th dose, 28^{h} dose, 12 weeks, 24 weeks, 36 weeks, and 48 weeks). Variability, expressed as % coefficient of variation, is also not significantly different between the two populations. In addition, the average age of subjects selected for the PK substudy was 15 years with a range of 13 to 17 years. The overall mean of all subjects' ages in the main study was also 15 years, with a range of 12 to 17 years. Mean weight for subjects in the substudy was 46.7 kg while in the overall study it was 48.4 kg. Thus, the PK substudy subjects are a fair demographic representative of the population in the overall study.

Figure 2 Mean Steady-State Plasma Concentrations of Tenofovir (log-linear)

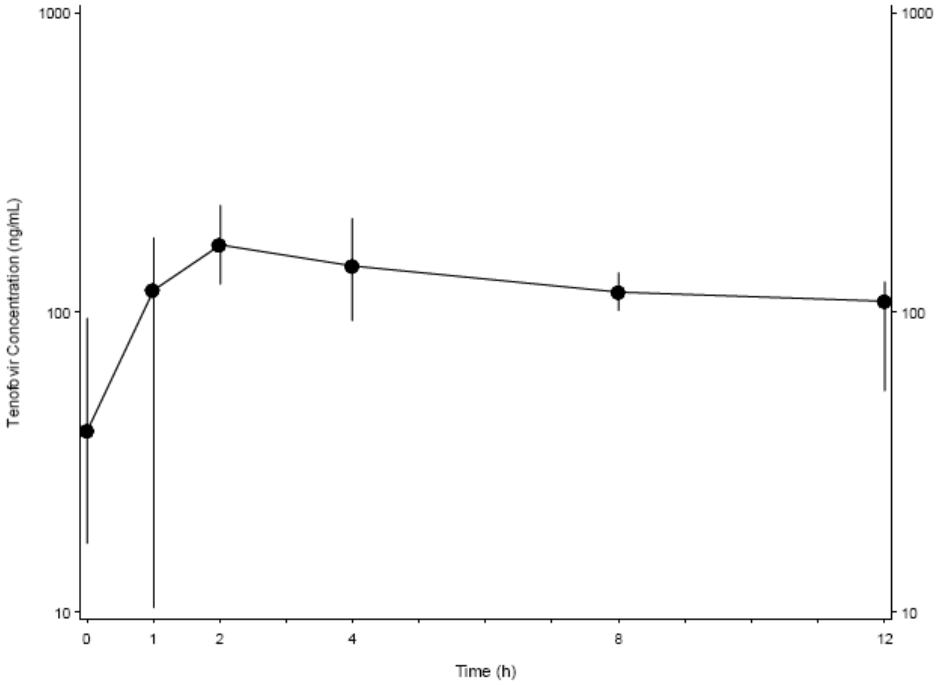


Table 2 Mean Steady-State PK Parameters for Tenofovir in Adolescents (GS-US-104-0321) and Adults from Historical Studies (GS-97-901 and GS-99-907)

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		8th Dose (N = 8)	28th Dose (N = 8)	12 Weeks (N = 12)	24 Weeks (N = 12)	36 Weeks (N = 7)	48 Weeks (N = 7)
AUC_{tau} (ng•h/mL)[c] Mean (% CV)	3390.6 (36.0)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
$AUC_{0\text{-last}}$ (ng•h/mL) Mean (%CV)	2256.4 (32.7)	—	—	—	—	—	—
C_{max} (ng/mL) Mean (%CV)	377.5 (35.6)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{last} (ng/mL) Mean (%CV)	133.4 (42.6)	—	—	—	—	—	—
C_{tau} (ng/mL)[c] Mean (%CV)	64.4 (52.6)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.98 (1.46, 2.99)	3.0	2.3	2.3	2.3	1.5	2.5
T_{last} (h) Median (Q1, Q3)	12.00 (11.96, 12.00)	—	—	—	—	—	—
$T_{½}$ (h)[c] Median (Q1, Q3)	10.54 (9.02, 15.30)	13.7	14.4	14.0	14.9	12.4	14.5

a Measured after a minimum of 4 weeks of treatment with tenofovir DF.

b Historical data in HIV-1 infected adults.

c Parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour time point.

The primary efficacy endpoint was time-weighted average change from baseline through week 24 ($DAVG_{24}$) in plasma HIV-1 RNA (log_{10} copies/mL). In the analysis of the total intent-to-treat population, there was no significant difference in $DAVG_{24}$ between the TDF arm and placebo arm (Table 3). However, subgroup analysis of $DAVG_{24}$ and $DAVG_{48}$ was performed for subjects with baseline GSS ≤1.0 and baseline GSS >1.0 to investigate whether differences exist between these two sets of subjects. Subjects with a GSS score of ≤1.0 (using either the Stanford 3-point or 5-point scales) benefitted the most from TDF treatment as compared with placebo. The mean difference in change in viral load ranged from -1.17 to -1.318 log_{10} copies/mL at week 24 depending on whether the 3-point or the 5-point GSS scale was used (Table 4). Subjects with a GSS score of ≤1.0 using the ANRS 3-point GSS scale (determined for use *a priori*) also benefitted from TDF treatment, but to a lesser extent. The difference in change in viral load was -0.518 log_{10} copies/mL (Table 5). In subjects with GSS scores >1, there was a slightly higher change in baseline viral load in the placebo group, but the difference is not likely to be clinically significant (*please refer to the medical officer's review for further details on efficacy*).

Table 3 Time-weighted Average Change from Baseline Through Week 24

Time-Weighted Average Change in HIV-1 RNA (log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)[a, b, c]	Tenofovir DF (N = 44)	Placebo (N = 41)	p-value[d]
DAVG Through Week 24			
N	44	41	0.55
Mean (SD)	–1.246 (1.1160)	–1.346 (1.2449)	
Median	–1.580	–1.549	
Q1, Q3	–2.15, –0.27	–2.36, –0.34	
Min, Max	–2.81, 0.89	–3.09, 0.88	

a DAVG through time X is the time weighted average between the first postbaseline value through the last value up to week X minus the baseline value.

b HIV-1 RNA analyzed using (b) (4) PCR Ultrasensitive assay (range 50 to 100,000 copies/mL); or PCR (b) (4) as a reflex test.

c HIV-1 RNA collected after first dose of open-label tenofovir DF or after last randomized dose date + 2 days (if terminated) for double-blind groups was excluded.

d p-value is from a Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or > median [median GSS is 2].

Table 4 Time-weighted Average Change from Baseline Through Week 24 (Subgroup Analysis Using Stanford GSS Scales)

Time-Weighted Average Change in HIV-1 RNA (Log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)[a, b, c]	OBR GSS <= 1		OBR GSS > 1	
	Tenofovir DF	Placebo	Tenofovir DF	Placebo
5-point GSS OBR				
DAVG Through Week 24				
N	15	7	29	34
Mean (SD)	–1.116 (1.1806)	–0.393 (1.1682)	–1.313 (1.0964)	–1.542 (1.1824)
Median	–1.206	0.036	–1.639	–1.723
Q1, Q3	–2.00, 0.07	–1.22, 0.81	–2.19, –0.60	–2.43, –0.72
Min, Max	–2.75, 0.89	–2.29, 0.88	–2.81, 0.71	–3.09, 0.77
p-value[d]: Tenofovir DF vs. Placebo	0.26		0.40	
3-point GSS OBR				
DAVG Through Week 24				
N	14	6	30	35
Mean (SD)	–1.170 (1.2059)	–0.281 (1.2383)	–1.281 (1.0913)	–1.529 (1.1677)
Median	–1.381	0.063	–1.622	–1.682
Q1, Q3	–2.00, 0.07	–1.22, 0.81	–2.19, –0.36	–2.43, –0.72
Min, Max	–2.75, 0.89	–2.29, 0.88	–2.81, 0.71	–3.09, 0.77
p-value[d]: Tenofovir DF vs. Placebo	0.23		0.37	

a DAVG through time X is the time weighted average between the first postbaseline value through the last value up to week X minus the baseline value.

b HIV-1 RNA analyzed using (b) (4) PCR Ultrasensitive assay (range 50 to 100,000 copies/mL); or PCR (b) (4) as a reflex test.

c HIV-1 RNA collected after first dose of open-label tenofovir DF or after last randomized dose date + 2 days (if terminated) for double-blind groups was excluded.

d p-value (comparing randomized treatment groups) is from a Wilcoxon rank sum test.

Table 5 Time-weighted Average Change from Baseline Through Week 24 (Subgroup Analysis Using ANRS GSS Scale)

Time-Weighted Average Change in HIV-1 RNA (Log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)[a, b, c]	OBR GSS <= 1		OBR GSS > 1	
	Tenofovir DF (N = 18)	Placebo (N = 10)	Tenofovir DF (N = 26)	Placebo (N = 31)
DAVG Through Week 24				
N	18	10	26	31
Mean (SD)	–1.308 (1.0912)	–0.888 (1.2649)	–1.203 (1.1523)	–1.494 (1.2223)
Median	–1.658	–1.140	-1.471	–1.682
Q1, Q3	–2.00, –0.76	–2.23, 0.09	–2.19, –0.18	–2.48, –0.49
Min, Max	–2.75, 0.61	–2.41, 0.88	–2.81, 0.89	–3.09, 0.77
p-value[d]: Tenofovir DF vs. Placebo	0.40		0.33	

a DAVG through time X is the time weighted average between the first postbaseline value through the last value up to week X minus the baseline value.

b HIV-1 RNA analyzed using (b) (4) PCR Ultrasensitive assay (range 50 to 100,000 copies/mL); or PCR (b) (4) as a reflex test.

c HIV-1 RNA collected after first dose of open-label tenofovir DF or after last randomized dose date + 2 days (if terminated) for double-blind groups was excluded.

d p-value (comparing randomized treatment groups) is from a Wilcoxon rank sum test.

TDF treatment was well-tolerated in this study (*please refer to the medical officer's review for further details on safety*). Briefly, no serious adverse events considered related to study drug were reported, and only 1 subject discontinued study drug due to an adverse event (vomiting). Adverse events (AE's) considered related to study drug were reported for 12 subjects in the TDF group and for 6 subjects in the placebo group in the double-blind treatment period. AE's considered related to study drug and reported for more than 1 subject were as follows: vomiting (4 subjects in the tenofovir DF group); osteopenia (5 subjects receiving TDF and 1 subject in the placebo group); and gastritis and dizziness (each reported for 1 subject in each treatment group).

Changes in bone mineral density are a concern for subjects taking TDF. Ostepenia was reported for a total of 5 subjects who received TDF either in the randomized period or the open-label period. All cases reported were classified as non-serious; however, all events were considered related to study drug. *(Please refer to the medical officer's review for a detailed review of changes in bone mineral density.*) Overall, the safety profile in adolescent subjects was consistent with the known safety profile in adults. The biggest differences between TDF and placebo groups in reported AE's were for mild to moderate gastrointestinal disorders (vomiting, nausea, and diarrhea).

<u>Conclusion</u>

Study 321 was the first randomized, controlled study to investigate the long-term safety, efficacy, and pharmacokinetics of TDF in adolescent patients. Upon first inspection, the primary efficacy endpoint was not met for this study in the overall intent-to-treat population (n=85). There was no significant difference in mean change in viral load from baseline between the TDF group and placebo group (-1.246 vs, -1.346 log_{10} copies/mL, respectively). However, upon further analysis, a higher proportion of subjects in the placebo group had an active OBR than the TDF group. Thus, when these groups were analyzed separately, the results showed that at week 24, subjects in the TDF group with a

Stanford GSS score of ≤1 had a mean change of -1.116 log_{10} copies/mL in viral load compared to -0.393 log_{10} copies/mL in the placebo group (difference = -0.723). Using the ANRS GSS scale, subjects with a GSS score of ≤1 had a mean change of -1.658 log_{10} copies/mL in viral load compared to -1.14 log_{10} copies/mL in the placebo group (difference = -0.518). This is considered a significant difference in efficacy when taking into account the adult efficacy data. In the original phase 3 studies in treatment-experienced adults (GS-98-902 and GS-99-907), TDF was added to each subject's existing antiretroviral regimen. These additions did not include a change in the regimen as was performed in the present study. The change in $DAVG_{24}$ in HIV-1 RNA was approximately −0.5 log_{10} copies/mL in the TDF group compared to no change in the placebo group. Thus, the present study demonstrated comparable efficacy to historical adult data.

Overall, the safety data collected in this study is consistent with previous safety results in adults. TDF was generally safe and well-tolerated when given in combination with an OBR in this study. Thus, the present study demonstrated comparable safety to historical adult data.

A previous single-dose pediatric study (study 983) demonstrated that a dose of 8 mg/kg would likely match the exposures resulting from a 300-mg dose in adults. In the current study, enrollment was limited to adolescents who weighed at least 35 kg in order to approximate 8 mg/kg and to ensure that no subject would significantly exceed this dose. Comparison of the PK data from the current study to historical adult data following long-term TDF administration (studies GS-97-901 and GS-99-907) shows that tenofovir PK in adolescents and adults are similar. These data confirm the appropriateness of the 300 mg once daily dose of TDF for adolescents.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21356	SUPPL-33	GILEAD SCIENCES INC	VIREAD(TENOFOVIR DISOPROXIL FUMARATE)300

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/s/

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