ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2006; 45 (11): 1115-1124
0312-5963/06/0011-1115/$39.95/0

Pharmacokinetics and Dosing Recommendations of Tenofovir Disoproxil Fumarate in Hepatic or Renal Impairment

Brian P. Kearney, Kitty Yale, Jaymin Shah, Lijie Zhong and *John F. Flaherty*

Gilead Sciences Inc., Foster City, California, USA

Abstract

Background: Tenofovir disoproxil fumarate is the prodrug of the acyclic nucleotide reverse transcriptase inhibitor tenofovir that is indicated for use in the treatment of HIV. Tenofovir is eliminated as unchanged drug in the urine, with a significant component of active tubular secretion. The aim of this study was to evaluate the pharmacokinetics of tenofovir in subjects with renal or hepatic impairment, both of which are common in HIV-infected individuals.

Patients and methods: HIV seronegative and otherwise healthy subjects with varying degrees of renal or hepatic function were recruited, and tenofovir pharmacokinetics were evaluated over 48 hours (hepatic impairment study) and 96 hours (renal impairment study) following a single tenofovir disoproxil fumarate 300mg dose. Subjects with hepatic dysfunction were categorised based upon Child-Pugh-Turcotte score, and subjects with renal impairment were categorised based upon their calculated creatinine clearance (CL_{CR}) using the Cockcroft-Gault method.

Results: As expected for a renally eliminated drug, subjects with and without hepatic impairment displayed similar tenofovir systemic exposures without evidence of substantial alterations in drug disposition, and therefore no dosage adjustments were warranted in these patients. In contrast, in subjects with renal impairment, two distinct groups were observed: (i) subjects with CL_{CR} ≥50 mL/min in whom tenofovir pharmacokinetics were similar to subjects with normal renal function; and (ii) subjects with CL_{CR} <50 mL/min (moderate or severe impairment) in which tenofovir renal clearance was substantially reduced and thus drug exposures increased. Subjects with end-stage renal disease (ESRD) demonstrated no extrarenal route of tenofovir elimination. Simulations of once-daily or modified dosing regimens demonstrated the need for tenofovir disoproxil fumarate dose-interval adjustment to prevent unnecessary drug accumulation. In patients with ESRD, high-flux haemodialysis efficiently removed tenofovir, with an elimination rate of 134 mL/min and an extraction coefficient of 54%.

Conclusion: No tenofovir disoproxil fumarate dose adjustment is warranted in the setting of hepatic impairment. Tenofovir disoproxil fumarate 300mg every 48 hours in individuals with moderate renal impairment and twice weekly corresponding to every 72–96 hours in those with severe renal impairment is recommended in order to target steady-state tenofovir exposures consistent with those observed in subjects with normal renal function receiving tenofovir disoproxil

fumarate 300mg once daily. For subjects receiving thrice-weekly 4-hour maintenance haemodialysis sessions, tenofovir disoproxil fumarate 300mg administered every 7 days after a haemodialysis session is recommended. HIV-infected patients with significant end-organ dysfunction should be monitored in accordance with clinical practice, including close management of their viral suppression and clinical chemistries.

Background

The development and widespread use of highly active antiretroviral therapies (HAART) has dramatically changed the management of HIV infection and significantly decreased the incidence of opportunistic infections, progression to AIDS and death.[1] The selection of antiretroviral agents to be included in patient-specific HAART regimens is dependent upon a number of factors. Those include past drug intolerabilities, the potential for drug-drug interactions, resistance patterns (including current and archived mutations) and pre-existing co-morbid medical conditions that could significantly alter the pharmacokinetics of these agents, thus increasing the potential for adverse drug events.[2]

Tenofovir disoproxil fumarate, the prodrug of the acyclic nucleotide reverse transcriptase inhibitor tenofovir, is indicated for use in combination antiretroviral regimens for treatment of HIV. Clinical trials in both treatment-naive and -experienced subjects have shown this agent to be well tolerated and highly efficacious when utilised as a component of HAART regimens.[3-5] Tenofovir is eliminated by the kidneys via a combination of glomerular filtration and active tubular secretion.[6,7] Therefore, alterations in renal clearance (CL_R) would be expected to result in alterations in tenofovir clearance and systemic exposures. Given that tenofovir disoproxil fumarate is not metabolised, significant alterations in drug exposures would not be expected in patients with liver dysfunction.

Diseases or adverse events that affect the kidney or liver can significantly affect the pharmacokinetics of drugs. Hepatic impairment may occur in subjects that are co-infected with either hepatitis B virus (HBV) or hepatitis C virus (HCV), those with prior or current alcohol (ethanol) abuse or by way of drug-induced hepatitis from medications commonly used to treat HIV.[2,8,9] In addition, HIV-associated nephropathy has been commonly reported and can manifest as either chronic renal disease or more acutely upon renal insult from nephrotoxic agents, dehydration or systemic infections.[10,11] This article presents the findings from two studies in which the pharmacokinetics of tenofovir were characterised in subjects with varying degrees of renal insufficiency (including subjects with end-stage renal disease [ESRD] receiving haemodialysis) or in subjects with impaired hepatic function.[12,13] Results from these studies serve as the basis for tenofovir disoproxil fumarate dosing recommendations in patients with renal or hepatic impairment.

Materials and Methods

Study Population and Design

Two separate phase I, open-label, single-dose pharmacokinetic studies were conducted in non-HIV-infected subjects. The protocol, subject's informed consent and investigator's brochure were reviewed and approved by each study site's institutional review boards (renal impairment study: DaVita Clinical Research, Minneapolis, MN, USA; Orlando Clinical Research Center, Orlando, FL, USA; New Orleans Center for Clinical Research, New Orleans, LA, USA; hepatic impairment study: Groupe Hospitalier Pitie-Salpétrière; Paris, France; Aster-Cephac; Paris, France; Orlando Clinical Research Center; Orlando, FL, USA) prior to study initiation. Subjects underwent screening assessments within 28 days of dosing to determine their eligibility. Male and female subjects who met the following key criteria were eligible for enrolment: no serological evidence of HBV/HCV infection, aged 18–75 years (18–70 years for hepatic study); in good health based on medical history, physical examination findings and laboratory testing; ability to understand and sign the consent form; no active

alcohol or chemical dependency; and, for females of childbearing potential, a negative serum pregnancy test at screening and continuing use of a suitable method of contraception. In addition, all subjects could not be receiving treatment with agents known to affect renal excretion, known hepatotoxic or nephrotoxic agents or drugs known to alter tenofovir pharmacokinetics.

Subjects in the renal study were classified into five different groups based upon their renal function as assessed by calculated creatinine clearance (CL_{CR}) using the Cockcroft-Gault equation:[14] (i) CL_{CR} >80 mL/min (normal renal function); (ii) CL_{CR} 50–79 mL/min (mild impairment); (iii) CL_{CR} 30–49 mL/min (moderate impairment); (iv) CL_{CR} 10–29 mL/min (severe impairment); and (v) requiring haemodialysis (ESRD). Stable renal function, defined as two CL_{CR} determinations with the second measurement found to be within 25% of the first when performed ≥72 hours of each other, was required for inclusion into the study. Subjects undergoing haemodialysis were required to have a post-haemodialysis bodyweight within 35% of that specified by the 1999 Metropolitan Height and Weight table for men and women. Clinical laboratory results at screening were required to be within the normal ranges of the institution's reference ranges for subjects with normal renal function and within expected ranges, depending upon the degree of renal insufficiency for subject in the other treatment groups. Subjects could not be receiving treatment with nephrotoxic agents within 3 months of study entry.

In the hepatic study, subjects were differentiated into three functional groups based on clinical signs and laboratory values as defined by the Child-Pugh-Turcotte (CPT) scoring system: subjects with no evidence or history of liver disease (normal hepatic function); those with a CPT score between 7 and 9 (moderate hepatic impairment); or those with a CPT score >9 (severe hepatic impairment). All subjects had a life expectancy >3 months and stable liver disease within 4 weeks of study entry. Laboratory screening values varied depending upon treatment group. Normal hepatic function subjects had haematology, chemistries and urinalysis laboratory values within the normal range of the study site with a platelet count ≥100 000/mm^3. Hepatically impaired subjects had ALT values ≤20 times the upper limit of normal on two occasions 1 month apart (with last ALT value within 4 weeks prior to study entry) and platelet values ≥90 000/mm^3 and ≥60 000/mm^3 for moderately and severely impaired hepatic function, respectively. Subjects could not be receiving treatment with hepatotoxic agents within 2 months of study entry, or agents known or suspected of being hepatic enzyme inducers or inhibitors within 1 month of study entry.

All eligible subjects reported to the respective clinic sites the evening prior to dosing and fasted from midnight until 4 hours following study drug administration. A single dose of tenofovir disoproxil fumarate 300mg was administered by study site personnel to each subject with 240mL of water. Subjects who participated in the renal study had tenofovir disoproxil fumarate serum pharmacokinetic sampling performed for 96 hours following study drug administration. Subjects with ESRD were administered dose following haemodialysis and then had two consecutive 48-hour sampling periods: the first 48 hours to establish tenofovir pharmacokinetics in the absence of renal function (referred to as the interdialysis period), and the second 48 hours, which included a 4-hour period of haemodialysis to establish parameters of drug clearance (the intradialysis period). Subjects that participated in the hepatic study had tenofovir serum pharmacokinetic sampling performed for 48 hours following study drug administration.

Pharmacokinetic Assessments and Methods

Subjects were confined at the study centres throughout the entire blood collection periods for both studies. Blood samples were obtained pre-dose and following study drug administration at frequent timepoints over 48 (both renal and hepatic studies), 72 and 96 hours (renal study only). Blood sampling for the renal study: 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hours post-dose. No samples collected in the hepatic study at hours 2.5, 72 or 96. Urine was collected throughout the study at regular intervals, volume measured and aliquots taken for tenofovir pharmacokinetic analysis. In subjects with ESRD, blood samples were obtained pre-dose, and following study drug administration at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours during the interdialysis period. The second

48-hour period occurred with the onset of a 4-hour haemodialysis session (intradialysis period) using a Fresenius E Machine and a Fresenius Hemoflow F70NR dialysis cartridge, with blood being obtained at similar timepoints from a venous access catheter in the arm contralateral to the arteriovenous access for haemodialysis. In addition, blood samples were collected from both the influx (arterial) and efflux (venous) lines of the dialysing unit at 30-minute intervals to calculate drug clearance by haemodialysis.

Analysis of tenofovir concentrations in serum was performed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay by MDS Pharma Services, Inc. (Montreal, QC, Canada) as described previously.[15] The standard curve spanned a concentration range of 3.00–600 ng/mL with between-batch precision (coefficient of variance [CV]) and accuracy (% nominal) metrics for the lower limit of quantification (LLQ) [3.01 ng/mL] of 9.2% and 98.0%, respectively.

Pharmacokinetic parameters of tenofovir were assessed by application of a nonlinear curve-fitting software (WinNonlin, Pharsight Corporation, Mountain View, CA, USA) using non compartmental methods. The area under the serum concentration versus time curve over the dosing interval from zero to the last detectable timepoint (t_{last}) in hours (AUC_{last}) was extrapolated to infinity (AUC_{∞}) using the linear/log trapezoidal method. The time to maximum observed drug concentration (t_{max}) was the actual observed value. The terminal elimination half-life ($t_{1/2}$) was calculated by dividing the natural log of two by the terminal elimination rate constant ($0.693/\lambda_z$). Tenofovir CL_R was calculated using the absolute amount of drug excreted in the urine divided by the time-matched AUC. Among patients receiving haemodialysis, the haemodialysis clearance was calculated as $E_{dial} \bullet Q_b$ where E_{dial} is the extraction ratio equal to $(C_{in} - C_{out})/C_{in}$ (where C_{in} and C_{out} are the tenofovir concentrations entering and exiting the dialyser) and Q_b is the blood flow rate (mL/min) through the dialyser. The amount of drug removed by haemodialysis was also directly measured through collection and measurement of tenofovir in dialysate. Tenofovir pharmacokinetics were also modelled using a two-compartment model in WinNonlin to assess the impact of renal impairment on steady-state drug exposures and explore alternative dosing regimens.

Safety Assessments

Adverse events, including date and time of onset, severity and potential relationship to study drug, were assessed starting from the time of tenofovir disoproxil fumarate dosing. Haematology and serum chemistries were performed on all subjects at screening, pre-dose on day 0 and upon study completion (subjects receiving haemodialysis had an additional set of haematology and serum chemistries performed on day 3 prior to onset of haemodialysis). A complete physical examination, including vital signs, was performed at screening, and symptom-directed physical examinations occurred at pre-dose on day 0 and upon study completion.

Statistical Analyses

Demographic and pharmacokinetic data were summarised using descriptive statistics by study group. In both studies the relationship between tenofovir pharmacokinetics and clinical measures of end-organ dysfunction were explored using linear regression and/or correlation analyses.

The sample sizes used in these studies were in accordance with current scientific practice and regulatory guidance for the evaluation of drug disposition in special populations. Specifically, eight patients per group were studied to identify the potential for substantial alterations in tenofovir pharmacokinetics in the setting of hepatic or renal dysfunction. Based on the known pharmacokinetic profile of tenofovir disoproxil fumarate, these sample sizes were expected to provide >75% power to discriminate 20% differences in tenofovir exposures.

Results

Subject Enrolment

In the renal study, 41 subjects were enrolled (28 men and 13 women) and included in the safety population. Forty subjects completed the study and were included in the pharmacokinetic summary (one subject experienced a significant adverse event that was not related to study medication [arterial abnor-

mality]). Serum concentration data from this subject were excluded from the tenofovir disoproxil fumarate pharmacokinetic analysis during the intradialysis period. Based upon CL_{CR} calculations on the day of pharmacokinetic assessment, three subjects had normal renal function, ten subjects had mild renal impairment, eight subjects had moderate renal impairment, 11 subjects had severe renal impairment, and nine subjects had ESRD. Of the 41 study subjects, 22 were Caucasian (54%) and 18 were African American (44%). The mean (range) age and bodyweight were 56 years (27–76 years) and 80kg (53–117kg), respectively.

In the hepatic study, 24 subjects were enrolled (14 men and 10 women) and included in the safety population. All 24 subjects completed the study, with 23 subjects having their data included in the pharmacokinetic analysis (one subject participated in the study despite a protocol violation of impaired renal function; therefore, this subject's data were excluded from pharmacokinetic analysis). Of the 24 study subjects, 17 were Caucasian (71%) and four were Black (17%). Seventy-one percent had a history of alcohol consumption. The mean (range) age and bodyweight were 51 years (33–70 years) and 71kg (48–98kg), respectively.

Pharmacokinetics

Renal Impairment Study

Following oral administration of tenofovir disoproxil fumarate 300mg, maximum drug concentrations (C_{max}) were observed between 0.5 and 4.0 hours following dosing in subjects with normal renal function or mild or moderate renal impairment. Subjects with severe renal impairment experienced C_{max} values over a wider range of time from 0.75 to 6.0 hours after dosing (figure 1a, table I). Tenofovir exposures (AUC_{∞}, C_{max}, and concentration at t_{last} [C_{last}]) were roughly similar between subjects with normal renal function and mild renal impairment. However, subjects with moderate and especially severe renal insufficiency had substantially (>3-fold) higher systemic drug exposures (figure 1a, table I). Figure 2a demonstrates the relationship between tenofovir AUC and calculated CL_{CR}. As overall renal function decreased, tenofovir CL_R decreased and $t_{1/2}$ increased (table I).

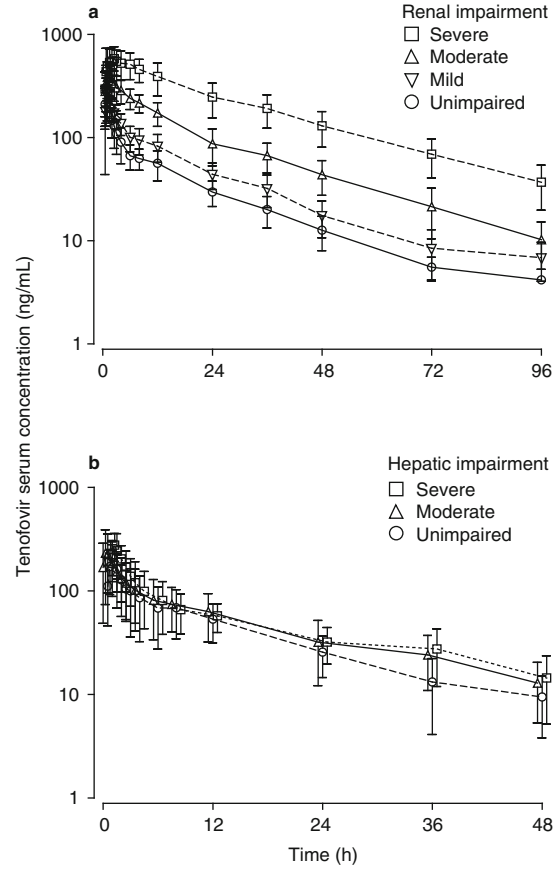

Fig. 1. Tenofovir serum concentration-time profile following a single dose of tenofovir disoproxil fumarate 300mg in (**a**) subjects with normal (unimpaired) renal function (creatinine clearance [CL_{CR}] >80 mL/min), mild renal impairment (CL_{CR} 50–79 mL/min), moderate renal impairment (CL_{CR} 30–49 mL/min) or severe renal impairment (CL_{CR} 10–29 mL/min); and (**b**) subjects with normal (unimpaired) hepatic function, moderate hepatic impairment or severe hepatic impairment.

Using derived elimination rate and volume of distribution constants from compartmental modelling, subjects with moderate or severe renal impairment, respectively, were predicted to exhibit excess accumulation of tenofovir and elevations in steady-state tenofovir C_{max} of 1.6- and 3.2-fold and AUC of 2.0- and 6.5-fold. Simulations of dosing every two (48h), three (72h), four (96h), and seven (168h) days were also performed. For patients with moderate renal impairment, pharmacokinetic modelling indicates that a 48-hour dosing interval will achieve tenofovir C_{max}, AUC_{last} and trough concentration

Table I. Single-dose tenofovir disoproxil fumarate pharmacokinetic parameters in subjects with varying degrees of renal and hepatic function[a,b]

Parameter	Renal study				Hepatic study		
	normal function (n = 3)	mild impairment (n = 10)	moderate impairment (n = 8)	severe impairment (n = 11)	normal function (n = 8)	moderate impairment (n = 7)	severe impairment (n = 8)
C_{max} (ng/mL)	346	325	403	528	224	256	298
	(300–360)	(261–426)	(153–566)	(381–1030)	(120–353)	(163–552)	(210–440)
AUC_{∞} (ng • h/mL)	2060	2910	5400	17 500	1830	2190	2470
	(2020–2480)	(1530–4580)	(2530–10 300)	(5820–30 200)	(1090–4060)	(1220–4340)	(1460–5230)
$t_{1/2}$ (h)	18.3	18.2	21.1	25.2	12.7	17.0	18.0
	(16.9–18.4)	(15.4–32.6)	(17.8–28.3)	(19.5–40.0)	(10.1–23.2)	(13.1–19.3)	(9.74–26.5)
CL_R (mL/min)	246	167	92.3	32.0			
	(209–275)	(128–214)	(67.2–153)	(10.6–109)			
CL_{CR} (mL/min)[c]	86.5	64.2	33.8	18.6			
	(82.5–101)	(51.7–79.8)	(31.9–42.7)	(12.3–27.8)			
Ae_{∞} (%)[d]	22.0	20.2	20.4	22.5			
	(21.9–24.0)	(13.1–26.9)	(16.0–33.6)	(12.5–32.6)			

a Results expressed as median values (range).

b See text for definition of study groups.

c Calculated using Cockcroft-Gault method.

d Data from two, nine, seven and ten patients in normal, mild, moderate and severe groups, respectively.

Ae_{∞} = cumulative amount of drug excreted in urine from time zero to infinity; **AUC_{∞}** = area under the serum concentration-time curve from time zero to infinity; **CL_{CR}** = creatinine clearance; **CL_R** = renal clearance; **C_{max}** = maximum serum concentration; **$t_{1/2}$** = elimination half-life.

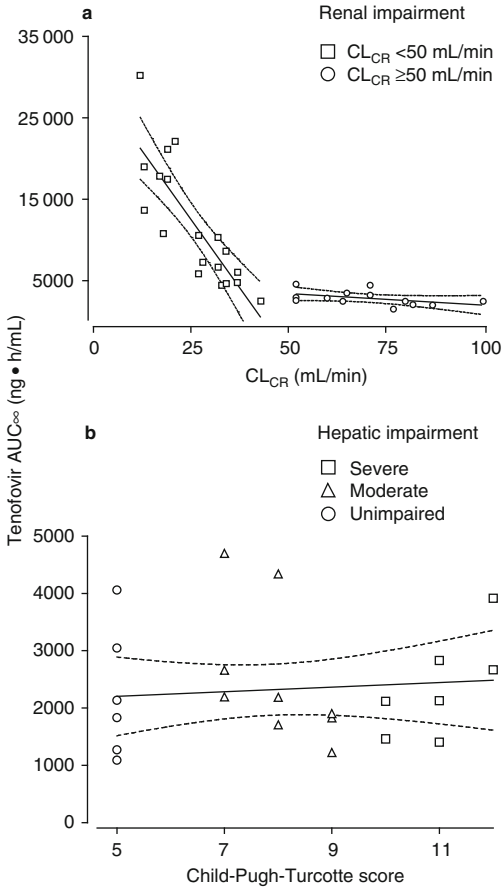

Fig. 2. Relationship (linear regression with 95% confidence intervals) between tenofovir area under the serum concentration-time curve from time zero to infinity (AUC_∞) and (**a**) calculated creatinine clearance (CL_{CR}) and (**b**) Child-Pugh-Turcotte Score.

(C_{trough}) ratios of 126%, 98.5% and 65.4%, respectively, relative to those observed in subjects with CL_{CR} ≥50 mL/min receiving tenofovir disoproxil fumarate 300mg once daily (figure 3). Subjects with severe renal impairment have substantial reductions in tenofovir renal elimination and therefore require a more prolonged dosing interval, with modelling data suggesting a tenofovir disoproxil fumarate 300mg dose every 72–96 hours to achieve C_{max}, AUC_{last} and C_{trough} ratios of 162–216%, 174–183% and 63.6–121%, respectively (figure 3).

In subjects receiving haemodialysis, a single tenofovir disoproxil fumarate 300mg dose displayed considerable interpatient variability in tenofovir exposures, with a median C_{max} of 1050 ng/mL (range 607–1420 ng/mL) occurring over a range of 0.5–48 hours after study drug administration. Immediately prior to haemodialysis (48 hours after dose), tenofovir concentrations were only slightly less than C_{max}, demonstrating lack of metabolism or extrarenal elimination of drug. Over 4 hours of haemodialysis, tenofovir concentrations decreased to a median of 192 ng/mL (range 89.7–375 ng/mL) and subsequently rebounded over the next 8 hours to a median of 303 ng/mL (range 139–454 ng/mL). This rebound to concentrations similar to C_{max} for a tenofovir disoproxil fumarate dose in adults with normal renal function is likely the result of redistribution of drug from the tissues. The median amount of tenofovir recovered in the dialysate during haemodialysis was 10% of the administered dose (136mg) and ≈50% of the estimated orally bioavailable tenofovir dose in tenofovir disoproxil fumarate 300mg. This degree of recovery was also consistent with the measured extraction coefficient of the dialyser (54%). The median haemodialysis clearance of tenofovir during high-flux haemodialysis was calculated to be 134 mL/min.

Hepatic Impairment Study

Tenofovir pharmacokinetics did not exhibit substantial differences in patients with moderate and severe hepatic impairment relative to unimpaired controls (table I, figure 1b). Following a single tenofovir disoproxil fumarate 300mg dose, the tenofovir C_{max} occurred within 2 hours of dosing and was slightly higher in subjects with moderate or severe hepatic impairment compared with normal controls. Overall tenofovir exposures (AUC_{last} and AUC_∞) were not substantially altered in subjects with hepatic impairment. No relationship was observed between CPT score and tenofovir AUC_∞, AUC_{last} and C_{max} values (figure 2b).

Safety and Tolerability

Thirteen of the 41 subjects in the renal study (32%) and 8 of the 24 subjects in the hepatic study (33%) reported at least one adverse event. In the renal study, headache, nasal congestion and hypokalaemia (haemodialysis subjects) were experienced by more than one study subject. The frequency of adverse events was similar, with no obvious

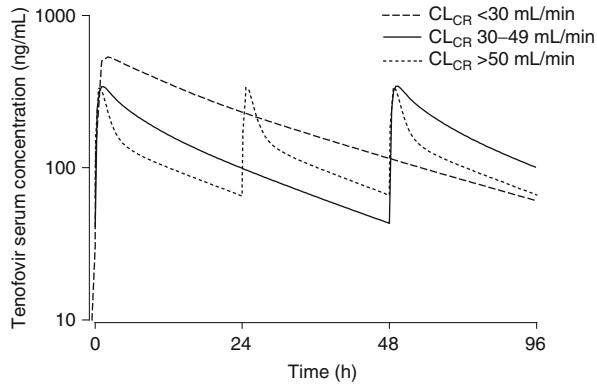

Fig. 3. Simulated tenofovir steady-state concentrations following tenofovir disoproxil fumarate 300mg dose every 24 hours for subjects with creatinine clearance (CL_{CR}) ≥50 mL/min, every 48 hours in subjects with CL_{CR} 30–49 mL/min, or every 96 hours for subjects with CL_{CR} 10–29 mL/min.

trends in occurrence of adverse events observed based on renal function grouping. Only two adverse events were investigator-assessed as possibly being related to study drug: diarrhoea in a subject in the mild renal impairment group and headache in a subject in the severe renal impairment group. One serious adverse event was reported (arterial abnormality [infection] in a patient with a haemodialysis access graft), which required hospitalisation and was assessed by the investigator as being unrelated to the study drug. No grade 3 or 4 laboratory abnormalities were reported in the normal, mild and moderate renal function groups. During the study, 8 of the 11 subjects in the severe impairment group had grade 3 serum creatinine values, and one subject had serum creatinine values that were categorised as grade 2. None of these 11 subjects experienced a worsening in grade for serum creatinine during the study period. Similarly, all nine subjects in the ESRD group had either grade 3 or grade 4 serum creatinine values, which were consistent with the nature of their underlying renal disease. Grade 3 in serum amylase values were reported in two subjects with severe impairment and in three ESRD subjects. Each of these subjects had abnormal serum amylase values of the same grade at screening and/or baseline. Two subjects, both with a history of diabetes mellitus, experienced grade 3 hyperglycaemia during the study, including the baseline visit.

In the hepatic study, the only adverse events experienced by more than one subject were headache (two subjects in the normal hepatic function group) and decreased urine volume (two subjects in the severe hepatic impairment group). The reported decrease in urine volume was not associated with any clinical or laboratory evidence of renal dysfunction. Five adverse events were assessed as being possibly related to the study drug. Two subjects in the normal hepatic function group reported headache. One of those subjects also reported nausea and vomiting (10 hours post-dosing). Decreased urine volume was reported by one subject in the moderate hepatic impairment group and two subjects in the severe impairment group. One subject with severe hepatic impairment and decompensated cirrhosis, ascites, jaundice and recent hospitalisations for alcoholic cirrhosis and septic shock was hospitalised for treatment of a bacterial infection and subsequently developed sepsis and died 24 days after study drug administration. This death was not considered by the investigator to be study drug related. No subjects with normal hepatic function experienced a grade 3 or 4 laboratory abnormality post-dosing, whereas four subjects in the moderate hepatic impairment group and five subjects in the severe hepatic impairment group reported post-dosing grade 3 laboratory abnormalities. With the exception of one subject in the severe hepatic impairment group with a grade 3 serum amylase on day 3, all abnormalities were reported at baseline or at screening.

Discussion

The pharmacokinetics of tenofovir following a single 300mg dose were evaluated in non-HIV-infected subjects with either normal renal or hepatic function or with varying degrees of renal or hepatic insufficiency. As predicted, no significant alterations in tenofovir pharmacokinetics were observed among subjects with moderate or significant hepatic disease given that tenofovir is eliminated by the renal pathway. Although slight increases in C_{max} and AUC values were observed, these small alterations are not likely to be of clinical relevance, and therefore a tenofovir disoproxil fumarate dosage adjustment in these patients is not recommended.[7,16]

Among subjects with varying degrees of renal impairment, as renal function declined, tenofovir clearance declined and $t_{1/2}$ increased. This is not surprising given that a linear relationship between tenofovir CL_R and calculated CL_{CR} was observed. Of interest, tenofovir CL_R was roughly 2- to 3-fold higher than the calculated CL_{CR}, indicating preservation of tenofovir tubular secretion in the presence of impaired renal function.

Systemic exposures to tenofovir in subjects with renal impairment was found to be best described by two distinct groups: (i) subjects with CL_{CR} ≥50 mL/min (normal renal function or mild impairment) without significant pharmacokinetic alterations; and (ii) subjects with CL_{CR} <50 mL/min (moderate or severe renal impairment) that experienced substantially reduced tenofovir CL_R and hence increased drug exposures (figure 2a and 2b). These levels of renal impairment would be expected to result in excessive accumulation of drug. Thus, patients should have renal function carefully assessed throughout tenofovir disoproxil fumarate therapy, and the dosage should be adjusted to reduce the potential for adverse events. The recommended dosage adjustments based upon pharmacokinetic modelling is tenofovir disoproxil fumarate 300mg given every 48 hours in subjects with moderate renal impairment (CL_{CR} 30–50 mL/min), and twice weekly or every 72–96 hours in subjects with severe renal impairment (CL_{CR} 10–29 mL/min) [table II].[16]

Subjects with ESRD who received a single dose of tenofovir disoproxil fumarate 300mg displayed little, if any, extrarenal elimination as evidenced by a plateau in the tenofovir concentration-time profile until high-flux haemodialysis was introduced 48 hours after dosing. Haemodialysis efficiently removed tenofovir with an extraction coefficient of 54% and an elimination rate of 134 mL/min. Given tenofovir's low molecular weight (<300Da) and minimal protein binding (<10%), this finding is not unexpected. Ten percent, representing ≈50% of the orally bioavailable tenofovir disproxil fumarate dose, was eliminated in the dialysate and is concordant with the observed extraction coefficient of the dialyser. These data indicate that each cumulative 12 hours of haemodialysis should provide for removal of the majority of a tenofovir disoproxil fumarate dose, preventing undue accumulation of drug. In patients receiving long-term maintenance haemodialysis on a thrice-weekly schedule of approximately 4 hours per dialysis session, a once-weekly dosing interval with drug administration following completion of dialysis is recommended.[16] The safety, efficacy and pharmacokinetics of tenofovir disoproxil fumarate using the dosing nomogram derived from this renal impairment study in HIV-infected patients with underlying renal dysfunction is currently ongoing.

Conclusion

Tenofovir disoproxil fumarate was well tolerated in subjects with both renal and hepatic impairment, with no obvious trends in adverse drug events being observed among one particular group. Tenofovir

Table II. Dosing interval recommendations for tenofovir disoproxil fumarate 300mg

Creatinine clearance (mL/min)[a]			Haemodialysis patients
≥50	30–49	10–29	
Every 24 hours	Every 48 hours	Once weekly (every 72–96 hours)	Every 7 days or after approximately 12 hours of haemodialysis[b]

a Calculated using ideal (lean) bodyweight.

b Normally, once-weekly dosing, assuming three haemodialysis sessions per week of approximately 4 hours of duration.

disoproxil fumarate can be administered without dosage adjustment at the full 300mg dose once daily in patients with hepatic dysfunction and/or with a calculated CL_{CR} ≥50 mL/min. In patients with moderate or severe renal impairment, tenofovir disoproxil fumarate 300mg should be administered at extended dosing intervals to prevent unnecessary drug accumulation and should be monitored in accordance with clinical practice, including close management of their viral suppression and clinical chemistries.

Acknowledgements

These data were presented in part at the Sixth International Congress on Drug Therapy in HIV Infection, Glasgow UK, November 2002 and the 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, USA, February 2004.

These studies were conducted by Gilead Sciences, Inc. The authors are employees of Gilead Sciences, Inc. The authors would like to thank the subjects who participated, the investigators, Sandra Hayashi, Dion Coakley, Li Hsu, Marianne Poblenz and Blake Doherty for their valuable contributions to this work.

References

1. Palella Jr FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998; 338 (13): 853-60
2. Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [online]. Available from URL: http://AIDSinfo.nih.gov [Accessed 2005 Oct 6]
3. Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. J Infect Dis 2004 Mar 1; 189 (5): 837-46
4. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA 2004 Jul 14; 292 (2): 191-201
5. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med 2006; 354 (3): 251-60
6. Barditch-Crovo P, Deeks SG, Collier A, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in HIV-1 infected adults. Antimicrob Agents Chemother 2001; 45 (10): 2733-9
7. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. Clin Pharmacokinet 2004; 43 (9): 595-612
8. Rodriguez-Rosado R, Garcia-Samaniego J, Soriano V. Hepatotoxicity after introduction of highly active antiretroviral therapy [letter]. AIDS 1998 Jul 9; 12 (10): 1256
9. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000 Jan 5; 283 (1): 74-80
10. D'Agati V, Appel GB. Renal pathology of human immunodeficiency virus infection. Semin Nephrol 1998 Jul; 18 (4): 406-21
11. Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med 2001 Jun 28; 344 (26): 1979-84
12. Kearney BP, Liaw S, Yale K, et al. Pharmacokinetics following single dose administration of tenofovir DF in subjects with renal impairment [poster]. Sixth International Congress on Drug Therapy in HIV Infection; 2002 Nov 17-21; Glasgow
13. Kearney BP, Benhamou Y, Flaherty J, et al. Tenofovir pharmacokinetics in hepatic impairment and drug interaction potential with agents used to treat viral hepatitis [poster no. 600]. 11th Conference on Retroviruses and Opportunistic Infections; 2004 Feb 8-11; San Francisco (CA)
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16 (1): 31-41
15. Kearney BP, Ramanathan S, Cheng AK, et al. Systemic and renal pharmacokinetics of adefovir and tenofovir upon coadministration. J Clin Pharmacol 2005 Aug; 45 (8): 935-40
16. Viread. VIREAD® (US Prescribing Information). Foster City (CA): Gilead Sciences Inc, 2005

Correspondence and offprints: Dr *Brian P. Kearney*, Gilead Sciences Inc., 333 Lakeside Drive, Foster City, 94404 CA, USA.
E-mail: bkearney@gilead.com