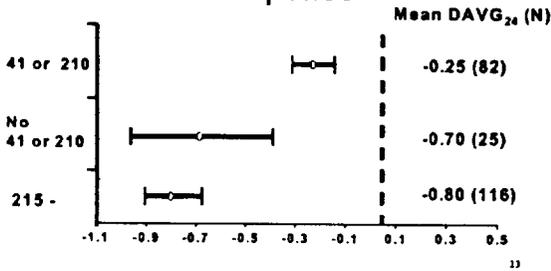


Table 9.4.1.D: Impact of T215Y/F Mutation on Virologic Response

Baseline Mutations ¹	Mean DAVG ₂₄ (N)		Net Treatment Effect
	Placebo	Tenofovir	
T215Y/F	+0.03 (53)	-0.35 (106)	-0.38
No T215Y/F	-0.07 (57)	-0.80 (116)	-0.73
T215Y/F / No 41 or 210	-0.01 (13)	-0.70 (25)	-0.69
T215Y/F + 41 or 210	+0.04 (40)	-0.25 (82)	-0.29
D67N+K70R+T215Y/F +K219Q/E/N	+0.37 (3)	-0.60 (12)	-0.97
T215Y/F alone	+0.18 (2)	-1.02 (8)	-1.20

¹Patients included in these subgroups may have other zidovudine-associated mutations or mutations in addition to the baseline zidovudine-associated mutations listed

Figure 5: Impact of 215 Mutation on HIV RNA Response



This finding was also observed in another FDA analysis of HIV RNA response by common baseline ZDV-associated mutation patterns. Diminished responses were again seen in patients expressing the M41L, L210W at baseline. The presence of the 215 mutation without the 41 or 210 did not appear to affect response to tenofovir.

Common ZDV-associated Mutations	Mean DAVG ₂₄ (N)	
	Tenofovir	Placebo
67+70+219	-0.71 (28)	-0.04 (12)
41+215	-0.36 (24)	+0.15 (10)
41+210+215	-0.15 (24)	+0.12 (9)
67+70+215+219	-0.60 (12)	+0.37 (3)
41+67+210+215	-0.13 (13)	-0.24 (5)

It also appears that the number and type of zidovudine-associated mutations present at baseline also affected tenofovir efficacy. Tenofovir efficacy was diminished in patients with >3 zidovudine-associated mutations in the presence of the M41L or L210W mutation compared to patients with ≥ 3 zidovudine-associated mutations in the absence of the M41L or L210W mutation. HIV RNA responses by number and type of baseline zidovudine-associated mutations are summarized in Table 9.4.1.E.

Table 9.4.1.E: HIV RNA Response by Number of Baseline zidovudine-associated mutations

# baseline zidovudine-associated mutations	Mean DAVG ₂₄ (N)	
	Tenofovir	Placebo
None	-0.80 (68)	-0.11 (29)
Any	-0.50 (154)	0 (81)
1-2	-0.66 (55)	-0.04 (33)
3	-0.44 (59)	+0.04 (29)
> 4	-0.35 (40)	+0.03 (19)
≥ 3 including the M41L or L210W	-0.21 (57)	+0.01 (29)
≥ 3 without the M41L or L210W	-0.67 (42)	+0.07 (19)

The affect of other primary NRTI mutations on tenofovir efficacy was also assessed. However for some primary NRTI mutations or multi-drug resistance NRTI mutations, there were too few patients expressing these mutations at baseline to determine the clinical significance. The L74V/I mutation, a primary mutation conferring resistance to abacavir, didanosine and zalcitabine, also affected tenofovir efficacy. Patients with the L74V/I mutation did not appear to respond to tenofovir treatment. The mean DAVG₂₄ for this group was $-0.17 \log_{10}$. Patients expressing the L74V/I mutation at baseline were further evaluated to determine if the diminished response was attributed to the presence of other NRTI mutations, specifically zidovudine-associated mutations. Response rates were similar (-0.12 to $-0.19 \log_{10}$) regardless if the M41L or L210W mutation was present or absent. This finding suggests the potential for cross resistance between tenofovir and didanosine; however, more data from patients with this mutation are needed to make any definitive conclusions.

Viruses expressing the K65R mutation have been shown to reduce susceptibility to tenofovir in vitro. Other NRTIs can also select for this mutation; therefore an analysis was conducted to determine if K65R mutation at baseline affected tenofovir activity. Six patients in the tenofovir group had the K65R mutation present at baseline. No placebo patients expressed this mutation at baseline. Patients with the K65R mutation did not appear to respond to tenofovir treatment (mean DAVG₂₄ = 0). However, there are too few patients to make any definitive conclusions regarding the clinical significance of this mutation at this time.

9.4.2 Development of HIV mutations by Week 24:

Study 907:

In study 907, the proportions of patients who developed NRTI, primary NNRTI or PI associated mutations by week 24 were less in the tenofovir group compared to placebo. The development of ZDV associated mutation by week 24 did not appear to adversely affect response. The mean DAVG₂₄ was -0.64 [redacted] for the 18 tenofovir treated patients who developed any ZDV mutation by week 24. The majority of tenofovir treated patients developed the M41L, D67N or K70R mutation by week 24. Development of L210W, T215Y/F and K219E/Q/R was infrequent.

Five patients in study 907 developed the K65R mutation by week 24. The mean DAVG₂₄ for these patients was -0.29 [redacted]. It is unclear if the development of this mutation was due to tenofovir or other NRTIs such as abacavir, or didanosine. More patients are needed in order to assess the clinical relevance of the development of this mutation.

Study 902:

For study 902, the development of NNRTI or PI associated mutations was infrequent (8-9%). Twenty-two percent and 39% of patients in the 300 mg group developed a RT mutation by week 24 and 48, respectively. The development of these mutations did not appear to affect response.

Patients who developed a RT mutation had a mean DAVG₂₄ and DAVG₄₈ of $-0.59 \log_{10}$. This response was similar to the all treated group, which had a mean DAVG₄₈ of $-0.62 \log_{10}$. Again it is difficult to evaluate the development of RT mutations because treatment switches were permitted throughout the study. Two patients developed the K65R mutation; however both patients received either didanosine or abacavir. These patients did not appear to respond to tenofovir at weeks 24 or 48. Overall in both studies 902 and 907, 7 patients developed the K65R mutation and all patients did not appear to respond to tenofovir. More patients are needed in order to assess the clinical relevance of the development of this mutation.

9.5 Phenotypic Analyses:

The mean baseline susceptibility is displayed in Table 9.5.A

Table 9.5.A Mean Baseline Susceptibility:

NRTI	Mean Fold Change in Susceptibility (compared to wild-type control IC ₅₀ values)	
	Placebo (n=29)	Tenofovir (n=100)
Tenofovir	1.9 (0.2 – 8.1)	1.6 (0.1 – 6.1)
Zidovudine	8 (0.4 – 58.3)	7.4 (0.3 – 49.7)
Lamivudine	> 33.7 (0.4 – 130)	> 30.8 (0.3 – 134)
Abacavir	3.3 (0.5 – 22.8)	4 (0.2 – 19.4)
Stavudine	1.2 (0.2 – 5)	1.3 (0.3 – 5)
Didanosine	2.4 (0.7 – 19)	2.1 (0.4 – 30.4)

Vol 3.66 table 11

Responses to tenofovir treatment by baseline susceptibility are summarized in Table 9.5.B. Since there is no agreement on susceptibility breakpoints for most antiretroviral agents, the following FDA analyses used the median fold change in susceptibility as a cut off and determined response rates accordingly. With the exception of lamivudine, responses to those with tenofovir were less in patients with baseline NRTI susceptibility was greater than or equal to the median compared to susceptibility less than the median. This data also suggests some degree of phenotypic cross resistance between tenofovir and zidovudine, stavudine and abacavir. Phenotypic cross resistance between didanosine and tenofovir is difficult to assess because 41% of patients in the virology substudy never received prior didanosine treatment. However some degree of genotypic cross resistance between didanosine and tenofovir is apparent in patients with baseline M74V/I or K65R mutation.

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Table 9.5.B FDA Analysis Response to Tenofovir by Median baseline NRTI Susceptibility

Baseline NRTI Susceptibility	Tenofovir (n=100) Mean DAVG ₂₄ (n)
Tenofovir (median 1.4) < 1.4 ≥ 1.4	-0.72 (48) -0.42 (52)
Zidovudine (median 3) < 3 ≥ 3	-0.81 (48) -0.33 (51)
Lamivudine (median 31.2) < 31.2 ≥ 31.2	-0.49 (47) -0.63 (52)
Didanosine (median 1.2) < 1.2 ≥ 1.2	-0.58 (47) -0.55 (53)
Stavudine (median 1.1) < 1.1 ≥ 1.1	-0.66 (49) -0.47 (51)
Abacavir (median 2.4) < 2.4 ≥ 2.4	-0.67 (50) -0.46 (50)

Genotypic analyses of baseline zidovudine-associated mutations demonstrated the potential for cross resistance between tenofovir and zidovudine. Given these results, responses to tenofovir treatment by baseline ZDV and tenofovir susceptibility were evaluated. These results are summarized in Table 9.5.C below. Patients with baseline tenofovir susceptibility within 3 fold of wild type virus experienced a -0.55 to -0.74 log₁₀ decrease in HIV RNA through week 24. Nine patients had a greater than 4 fold reduced susceptibility to tenofovir at baseline. These patients did not respond to tenofovir therapy, (mean DAVG₂₄ -0.12 log₁₀). Although there are too few patients to determine a susceptibility breakpoint for tenofovir at this time, this dataset shows that tenofovir efficacy is diminished in patients with reduced susceptibility to tenofovir and zidovudine at baseline. This finding is compatible with the genotypic analyses, in that tenofovir efficacy is reduced in the presence of ≥3 zidovudine-associated mutations that include the M41L or L210W or the K65R mutation.

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Table 9.5.C HIV RNA Response by Baseline Tenofovir and ZDV Susceptibility

	Tenofovir Mean DAVG ₂₄ (n)
Baseline Tenofovir Susceptibility	
≤ 1	-0.74 (35)
> 1 and ≤ 2	-0.57 (36)
> 2 and ≤ 3	-0.55 (13)
> 3 and ≤ 4	-0.3 (7)
≤ 4	-0.61 (91)
> 4	-0.12 (9)
Baseline ZDV Susceptibility	
≤ 1	-0.84 (18)
> 1 and ≤ 4	-0.73 (39)
> 4 and ≤ 10	-0.37 (21)
> 10	-0.23 (21)

The applicant also determined the effect of the M184V mutation on tenofovir susceptibility. Their analysis showed an approximate 2 fold increase in tenofovir susceptibility associated with the M184V mutation among all analyzed patients and patients with any baseline ZDV associated mutation. However this increase in tenofovir susceptibility was not correlated with better virologic response rates. In both the genotype and phenotype substudy, response rates were similar regardless if the M184V mutation was present with ZDV-associated mutations at baseline.

In study 907, changes in tenofovir and other NRTI susceptibility during treatment were also assessed. A total of 35 and 24 patients had baseline and post baseline phenotype in the tenofovir and placebo groups, respectively. The mean post baseline fold change in tenofovir susceptibility increased from 1.6 fold at baseline to 2.2 at week 24. The mean DAVG₂₄ for the tenofovir treated patients (n=35) was -0.36 log₁₀. The applicant cites that the inter-assay variation is 2.5 fold. Twelve patients had greater than 2.5 fold change in susceptibility. According to the applicant, 5 of these patients were still within the 2.5 fold of wild-type since hypersusceptibility was noted at baseline. For the remaining seven patients no clear genotypic changes were observed, in fact 6 of the 7 patients did not develop any new NRTI associated mutations. The applicant's assessment appears accurate in that few patients developed a change in tenofovir susceptibility beyond assay variation of 2.5 fold through week 24. Two patients in the phenotype substudy developed the K65R mutation. These patients had a mean 3 fold change in tenofovir susceptibility from baseline. More patients in this subgroup are needed to make definitive conclusions.

Changes in susceptibility to other NRTIs were also assessed. It does not appear that treatment with tenofovir is altering the susceptibility of other NRTIs over 24 weeks compared to placebo. The largest change in susceptibility was for ZDV and was most prominent in patients who developed a ZDV mutation during the study.

Pts Developing New NRTI Mutations	N	Mean fold change in Susceptibility from Baseline					
		Tenofovir	ZDV	D4T	DDI	3TC	ABC
Tenofovir Group:	35	2.2	3.6	2.2	1.7	1.4	1.7
None by week 24	27	2.1	3.2	2.2	1.6	1.3	1.7
Yes by week 24	6	2.5	5.5	2.4	2.2	1.6	2
K65R	2	3	2.5	2.2	1.2	2.2	0.5
Placebo Group	24	1.5	2.6	2.5	1.3	1.8	1.5
None by week 24	19	1.6	2.4	2.3	1.1	1.3	1.4
Yes by week 24	5	1.2	3.3	3.2	2.1	3.7	2.2
All Patients Analyzed	59	1.9	3.2	2.3	1.5	1.6	1.6

Source vol 3-66 table 18

Summary of Results:

Although this NDA included more clinical resistance data than any previous NDA for an antiretroviral drug, the large amount of potential comparisons in evaluating the impact of resistance limits the ability to conduct tests for statistical significance. Many of the analyses presented above were exploratory and described numerical differences. Given these caveats, the genotypic data suggest potential for some cross resistance between tenofovir and specific NRTI mutations or patterns of mutations. However for some primary NRTI mutations or multi-drug resistance NRTI mutations, there were too few patients expressing these mutations at baseline to determine the clinical significance. Cross resistance was not observed between lamivudine and tenofovir. The M41L or L210W mutation diminished tenofovir efficacy whereas, the D67N, K70R, T215Y/F or K219Q/E/N mutations did not appear to affect tenofovir efficacy. It appears that the number and type of Zidovudine-associated mutations present at baseline affect tenofovir efficacy. Tenofovir efficacy is reduced in patients with ≥ 3 zidovudine-associated mutations which include the M41L or L210W mutation compared to patients with ≥ 3 zidovudine-associated mutations without the M41L or L210W mutation.

Viruses expressing the K65R mutation show reduced susceptibility to tenofovir in vitro. Overall 6 patients expressed this mutation at baseline; all 6 patients were in the tenofovir group. These patients did not respond to tenofovir treatment. It appears that the K65R mutation affects tenofovir activity, however, more data on patients expressing this mutation at baseline are needed in order to make any definitive conclusions regarding the clinical significance of this mutation at this time.

Phenotypic analyses showed lower response rates when tenofovir susceptibility was reduced 3 to 4 fold. Also decreased susceptibility to zidovudine at baseline affected response. It does not appear that treatment with tenofovir altered the susceptibility of other NRTIs over 24 weeks compared to placebo.

10. Integrated Summary of Safety (ISS)

The FDA's ISS focuses on pooled data from studies 902 and 907. Data from these studies were pooled because both studies had similar designs and enrolled treatment-experienced patients. In addition, baseline demographics were comparable for the two studies. Patients had on average 4-5 years prior antiretroviral treatment experience. Adverse events and laboratory abnormalities for the placebo and 300 mg tenofovir groups are summarized through week 24. Adverse events and laboratory abnormalities noted in 908 are presented separately unless otherwise noted. Detailed analyses of the adverse events and laboratory abnormalities in studies 701 and 901 are not included in this review. The types of adverse events and laboratory abnormalities observed in these studies were similar to those in studies 902, 907 and 908. No new events or abnormalities were observed. Also safety results from studies 909 and 914 are not included in this section. These were clinical pharmacology studies conducted in healthy volunteers. In general, the FDA analysis of the safety data confirmed the applicant's findings. There were only minor differences between the two analyses, which did not affect the overall results and conclusions.

10.1 Overview of Adverse Events

Data for 1057 HIV + patients who received at least one dose of IV or oral tenofovir are included in the applicants ISS. Table 10.1.A. summarizes the studies and patients who are included in the ISS.

Table 10.1.A. Safety Population

Study	Number Evaluable for Safety	Mean duration	Number Discontinued
701	20 4 placebo 16 tenofovir	7 days	
901	59	Cohorts 3 and 6 = 10.5 months (range 2.1 to 15.2 months)	
902	Total 186 28 placebo 179 tenofovir (includes placebo crossover)	42 weeks for tenofovir arms; 22 weeks for placebo followed by 22 weeks on tenofovir	Total = 48 39 patients in tenofovir arms 7 patients in placebo 2 patients placebo- tenofovir
907	Total 552 184 placebo 368 tenofovir	23 weeks for both groups	Total = 34 11 placebo 23 tenofovir
908	291	24.6 (+/- 9.5) weeks	63

As noted above the ISS focuses on the combined safety data from the 2 pivotal trials, 902 and 907 unless otherwise noted. In these studies, 653 patients were evaluable for safety; 443 receiving tenofovir 300 mg and 210 receiving placebo for 24 weeks. The number of patients experiencing at least one adverse event was similar between the group; 90% and 89% in the 300 mg group and placebo group, respectively.

Without regard to causality, the most common events reported were asthenia (19%), headache (14%), diarrhea (22%), nausea (20%) and pharyngitis (18%). More patients randomized to tenofovir 300 mg compared to placebo experienced GI events, including diarrhea (22% vs 17%), flatulence (6% vs 2%), nausea (20% vs 15%) and vomiting (12% vs 6% p=0.0225).

Table 10.1.B. lists the treatment emergent adverse events that are possibly, probably or of unknown relationship to study drug and of mild, moderate, severe or life threatening intensity. The analysis the adverse event profile appears similar for both treatment groups. The most common adverse events that occurred in patients receiving VIREAD with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events.

Table 10.1.B. Treatment-Emergent Events Occurring in >3 percent of Patients That Are Possibly or Probably Related to Tenofovir/Placebo and Mild, Moderate, Severe or Life-threatening Intensity Through Week 24: Studies 902 and 907

	TNF 300 mg (N=443)	Placebo (N=210)
Nausea	11%	10%
Diarrhea	9%	8%
Asthenia	8%	8%
Headache	6%	7%
Vomiting	5%	2%
Flatulence	4%	0%
Abdominal Pain	3%	3%
Anorexia	3%	1%

Study 902 provided information to determine if there was a dose relationship with respect to adverse events and to determine if the incidence of adverse events increased with long term tenofovir exposure. FDA analyses concluded that there was not a dose relationship for adverse events. In addition, there did not appear to be an increase in adverse events from week 24 to 48. In the open label phase there did not appear to be significant changes in the types of events noted when compared to the 48 week blinded phase results. However this is based on a small dataset and after week 24 there was no placebo comparison. It will be important to assess the long-term effects of tenofovir. This information will largely come from study 903, the applicant's confirmatory trial which is currently ongoing and not included in this submission. Table 10.1.C. summarizes the adverse events that are possibly or probably related to study drug and of moderate, severe or life-threatening intensity.

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In study 908 the types of adverse events reported were similar to that described above. No new events were noted. The most common individual grade 3 or 4 events were pneumonia (4%) and diarrhea (4%). The most common related adverse events were nausea, vomiting and diarrhea.

10.2 Other Events of Interest:

Results from drug interaction studies, preclinical studies and events associated with the class of nucleoside analogues guided a more detailed analyses of the specific events described below.

Drug Interactions: Didanosine-Associated Adverse Events

Results from a drug interaction study with tenofovir and didanosine showed a 28% increase in the C_{max} and a 44% increase in the AUC of didanosine. Tenofovir pharmacokinetics were unchanged. It is possible that increased concentrations of didanosine could lead to an increased incidence of didanosine associated adverse events or laboratory abnormalities. FDA conducted several analyses to evaluate the adverse event profile through week 24 for patients who received didanosine and tenofovir versus those who received tenofovir without didanosine. Commonly reported didanosine related events such as diarrhea, vomiting, nausea, neuropathy and pancreatitis (see pancreatitis section below) were evaluated. All available data through 24 weeks and without regard to causality was used for the analyses summarized in Table 10.2.A. The incidence of these GI events and peripheral neuropathy was numerically higher in patients receiving tenofovir and didanosine compared to those who received tenofovir without didanosine and the overall tenofovir group. It is unclear if these differences are clinically significant. In any event, clinicians should be aware of this interaction and the possibility of increased didanosine associated adverse events.

Table 10.2.A. FDA analyses of Didanosine Associated Adverse Events Through Week 24

	Placebo		Tenofovir		Placebo (n=210)	Tenofovir (N=443)
	With DDI (n=60)	Without DDI (n=150)	With DDI (N=130)	Without DDI (N=312)		
Diarrhea	5 (8%)	31 (21%)	33 (25%)	64 (21%)	36 (17%)	97 (22%)
Nausea	6 (10%)	26 (17%)	37 (28%)	51 (18%)	32 (15%)	88 (20%)
Vomiting	3 (5%)	9 (6%)	20 (15%)	31 (10%)	12 (6%)	51 (12%)
Peripheral Neuropathy	2 (3%)	4 (3%)	10 (8%)	5 (2%)	6 (3%)	15 (3%)

Pancreatitis:

For studies 902, 907 and 908, the incidence of pancreatitis in patients receiving tenofovir 300 mg is 0.7%. In comparison the incidence of pancreatitis in patients receiving placebo was approximately 1%. Four cases of pancreatitis were reported in the tenofovir 300 mg treatment groups compared to two cases in placebo groups. Of note one case was reported in a patient receiving tenofovir 75 mg. All patients were receiving other agents known to cause pancreatitis, such as didanosine, stavudine, lamivudine, ritonavir and indinavir. It appears that these cases are most likely related to other agents in the regimen and not to tenofovir. However there is a concern that the pharmacokinetic interaction between tenofovir and didanosine could lead to an increased risk of pancreatitis. FDA conducted an analysis to determine the incidence of pancreatitis in patients who received both tenofovir and didanosine. In studies 902, 907 and 908, a total of 212 patients in the tenofovir 300 mg group included didanosine as part of their background regimen at baseline. The incidence of pancreatitis in these patients was 1.4% (3/212). Of note the frequency of didanosine associated pancreatitis is dose related. In phase 3 studies with buffered formulations of didanosine, incidence ranged from 1% to 10% with doses higher than are currently recommended and 1% to 7% with the currently recommended dose. FDA analyses showed that the interaction between didanosine and tenofovir did not result in a

higher incidence of didanosine associated pancreatitis than what has been previously observed in other trials.

The applicant also conducted analyses to evaluate the incidence of pancreatitis or associated laboratory abnormalities when didanosine was concomitantly administered with tenofovir. The applicant reported similar rates of serum amylase elevations in placebo and tenofovir treated patients who received didanosine. Increased serum amylase, or serum lipase was higher in placebo patients who received didanosine (46%) compared to tenofovir treated patients who received didanosine (39%). The applicant also determined that the available data did not reveal any evidence of an increased frequency of pancreatitis or associated laboratory abnormalities therefore suggesting that the observed drug interaction with didanosine and tenofovir may not be clinically significant. Pancreatitis will be monitored in future clinical trials and during postmarketing.

Renal Events:

Preclinical studies showed renal tubular epithelial karyomegaly, individual cell necrosis, tubular dilatation, degeneration/regeneration and pigment accumulation and interstitial nephritis. In addition increases in serum creatinine, glycosuria, proteinuria, phosphaturia and/or calciuria and increased urinary output were observed. Given the preclinical evidence for renal toxicity, renal events were monitored closely during the trials. Several renal events were noted in patients receiving tenofovir that included kidney calculus/stones, kidney tubular necrosis, renal insufficiency and renal failure. Details on these events are summarized below. Events that occurred in the studies submitted with the NDA (902, 907 and 908) and events noted in the expanded access program and study 903 are summarized. At present, it is unclear whether tenofovir was causally related to any of these events. The majority of the renal events were attributed to other agents in the regimen or underlying infection or disease state.

Kidney calculus/stones:

A total of thirteen (1.3%) patients receiving tenofovir developed a kidney stone in studies 902, 907 and 908. No cases occurred in the placebo groups. Table 10.2.B summarizes these events. Three of the patients were also receiving indinavir, which is known to cause nephrolithiasis in up to 9.3% of patients. All five patients in study 908 who developed a kidney stone were receiving lopinavir/ritonavir based regimens. These events occurred over a range of 10 days – 2 years on study. Renal parameters, including serum creatinine, phosphate, bicarbonate, and serum calcium were within normal limits with the exception of a few patients. Two patients developed subsequent renal stones 1-3 months after the initial event. The majority of patients continued tenofovir treatment without interruption.

This reviewer had access to the safety data from Abbott's study # 863, lopinavir/ritonavir vs nelfinavir study and the adefovir study 408. The incidence of renal stones in these studies was also approximately 1%. In sum, the overall incidence of kidney stones in the safety database for tenofovir does not appear different than what has been reported in two other trials. However it is interesting to note that all the events occurred in patients receiving tenofovir and no events occurred on the placebo arm. It is important to note that there were much fewer patients receiving placebo as a result of the randomization scheme. It is difficult to determine if these events were related to tenofovir. It is also difficult to determine a potential mechanism for this toxicity. This event will be monitored in other clinical trials and during the postmarketing period.

Table 10.2.B. Summary of Kidney calculus/stone Events

Study/PT #	Baseline Regimen	Time to Event	Relevant Labs Prior to or at the time of event	Study Drug Disposition/Comments
902-0110-1282	TNF 150 mg + ZDV+3TC+DLV	@ 4 months	Urine and blood cultures negative	Continued without interruption
902-0354-1726	TNF 300 mg +ZDV+d4T+NLV+SQV	@ 15 months	UA: 35 RBC/hpf 3+ blood	Continued without interruption

902-0362-1527 (2 events)	TNF 300 mg + ddl+ d4T+RTV (IDV was taken at some point during the study)	@ 21 months @ 2 years (off TNF for 2 months when event occurred)	Grade 1 serum creatinine at 11 month visit (1.7 mg/dL) and upon retest (1.9 mg/dL)	Permanently discontinued due to persistent grade 1 elevation of serum creatinine
907-0074-3000	TNF 300 mg + ZDV +3TC+RTV+ IDV	10 days	UA within normal limits	Continued without interruption
907-0302-2085	TNF 300 mg + ZDV+3TC	@ 2 months	History intermittent renal calculi since 1979 CA oxalate crystals (1+) noted in several US prior to diagnosis	Interrupted for 6 days – pt underwent lithotripsy
907-0390-2261	TNF 300 mg + d4T+3TC+NVP+ABC	@ 6 months	CA oxalate crystals (4+)	Continued without interruption Pt underwent cystoscopy, bilateral retrograde pyelography followed by left ureteroscopy with Holmium laser and lithotripsy and ureteral stent
907-0464-5414	TNF 300 mg +ABC+IDV+3TC+d4T (IDV use in past)	@ 4 months	UA: 6 RBC/hpf	Continued without interruption
907-0672-2747	TNF 300 mg+ABC+d4T+ EFV (IDV use in past)	@ 4 months	Lab tests within normal limits	Continued without interruption
908-0386-4134	TNF 300 mg + APV + ABC + 3TC + LPV/RTV	@ 4 months	UA: 2 weeks prior to diagnosis RBC TNTC and 3+ blood (baseline 1+ blood) Serum creatinine increased 0.3 mg/dL Phosphate decreased to 1.8 mg/dL (2.6 mg/dL at baseline)	Continued without interruption
908-0597-4047	TNF 300 mg +LPV/RTV	@ 4 months	UA: RBC TNTC and 3+ blood 2 months prior to event (baseline 9-14 RBC and 3+ blood)	Continued without interruption
908-0748-4165	TNF 300 mg + LPV/RTV + ABC + 3TC +d4T	@ 1 month	UA: 5 RBC/hpf and 1+ blood Grade 2 hypophosphatemia (1.8 mg/dL (base: 2.7 mg/dL)	Continued without interruption
908-996-4146 (2 events)	TNF 300 mg + LPV/RTV+AMP+ddl	@ 2 months @ 3 months	UA: 30 RBC/hpf	Continued without interruption
908-0730-4029	TNF 300 mg + LPV/RTV+3TC+ABC+ EFV	@ 9 months	4 months prior to event UA: 3+ blood and 2+ proteinuria Hematuria resolved but proteinuria persisted. Hematuria worsened again and then improved despite reinitiation of therapy	Permanent Discontinuation @ 1 month after event

Kidney tubular necrosis

One case of kidney tubular necrosis was reported in the NDA application. This event was thought to be related to indinavir and not related to tenofovir use. Details of the case are presented below.

In study 902, patient 0356-1432 received tenofovir 150 mg in combination with zidovudine, lamivudine and indinavir. After approximately 3 months on study urinalysis revealed 45 RBC/hpf and 3+ blood. Serum creatinine was 1.5 mg/dL (baseline 1.4 mg/dL). Three months later, urinalysis revealed only 3 RBC/hpf, but serum creatinine rose to 1.7 mg/dL. On this visit an adverse event of "poor renal flow – indinavir toxicity (grade 2) was reported. Indinavir and zidovudine were discontinued and replaced with stavudine and nevirapine. Tenofovir was continued without interruption. Serum creatinine and urinalysis returned to normal at the next visit (creatinine 1.2 mg/dL and negative urinalysis). The investigators assessment that this event was not related to tenofovir appears reasonable.

Abnormal Kidney Function:

One patient in study 902 permanently discontinued tenofovir treatment due to persistent grade 1 elevation of serum creatinine. The patient received tenofovir for approximately 21 months. In addition the patient also received indinavir. It is unclear if the creatinine elevation was due to tenofovir or indinavir use.

A second case of abnormal kidney function was noted in study 908. This event appears to be related to underlying dehydration and UTI and not related to tenofovir use. Details of the case are presented below.

In study 908 a case of abnormal kidney function was reported in a 51 year old male with dehydration and urinary tract infection. After 6 months on study and following the addition of ritonavir and nevirapine to his regimen, the patient developed lower extremity swelling, coagulopathy with bleeding, elevated PTT and serum creatinine (2 mg/dL). The investigator attributes this event to an interaction between ritonavir/nevirapine and warfarin (patient was taking for prior DVT and pulmonary embolus), dehydration and UTI. The patient recovered with rehydration and treatment for UTI. It appears that this event was not related to tenofovir.

Renal Insufficiency

One event of renal insufficiency was reported in study 902. This case was related to underlying infection, pyelonephritis, and not related to tenofovir. Details of the case are presented below.

This patient received tenofovir 300 mg for approximately 1 month when she was hospitalized for suspected pyelonephritis and renal insufficiency. Serum creatinine was 2.8 on admission and IV ceftriaxone was started. Urinalysis revealed > 100 RBCs, 50-100 WBCs and E coli. WBC was 15,200 cells/uL. Renal insufficiency was corrected with hydration and creatinine decreased to 1.4 mg/dL 3 days later. Study medications were restarted 9 days later when the renal insufficiency resolved. This event did not appear to be related to tenofovir use.

Kidney Failure

As of September 2001, a total of 13 cases of acute kidney or renal failure were reported as serious adverse events in patients receiving tenofovir. Five cases have been attributed to tenofovir use. Details of these events are provided below. The remaining events were not considered related to tenofovir use. These events occurred in patients with various confounding conditions including advanced HIV infection. History of renal insufficiency and development of severe infections such as pseudomonas pneumonia, and CMV were noted in several cases. Other cases involved patients receiving known nephrotoxic agents such as cidofovir and ganciclovir.

The first case involved a 37 year old male who was enrolled in the expanded access program. He received tenofovir for 6 weeks before being hospitalized for fever and diarrhea. Upon admission he had an elevated creatine (4.7 mg/dL) and BUN (62 mg/dL), decreased hematocrit

(25.8%) and hemoglobin (8.8 mg/dL) and left lower lobe pneumonia. At the last follow-up the hematocrit and hemoglobin were still dropping and the creatinine was 3.2 mg/L. Additional information is pending. The investigator attributed the renal event to tenofovir use.

A second case was seen in a 49 year old male who also was enrolled in the expanded access program. He was hospitalized after 5 weeks of tenofovir for fever and hypotension. He was found to be in renal failure with metabolic acidosis. He also had positive blood cultures for staphylococcus. The patient improved with intravenous hydration and bicarbonate. The investigator attributed this event to tenofovir use. Additional details of this case were not provided, therefore it is difficult to assess if this case was attributed to tenofovir use or underlying advanced HIV infection and staph infection.

A third case involved a 36 year old male in study 903. This patient had a history of MAC, CMV, toxoplasmosis and herpes. After four months of blinded treatment (tenofovir or stavudine) the patient developed abdominal pain, bloating and nausea and was hospitalized. Upon admission he had a serum creatinine of 6 and a BUN of 42 mg/dL. A kidney biopsy was done and showed diffuse acute tubular necrosis. The patient underwent hemodialysis for 3 months. The creatinine returned to 1.1 mg/dL at the time dialysis was stopped.

A fourth case was seen in a 49 year old male in study 908. This patient received tenofovir for approximately ten months. Then all medications were stopped for anemia and pancytopenia. After a 3 month cessation of all medications the patient began tenofovir treatment again. After 12 weeks he developed nausea and vomiting and was found to have a creatinine of 2.2 mg/dL. He was diagnosed with acute renal failure and pancreatitis. Although it is possible that tenofovir contributed to this event, the patient was also receiving medications noted to cause renal failure, ritonavir and saquinavir.

The fifth case involved a 42 year old male who developed lactic acidosis and renal failure. See Lactic acidosis section for further details.

Liver events:

Eight cases of liver events, including cirrhosis, hepatic failure, enlarged liver and hepatitis were reported in studies 902, 907 and 908. The cases of cirrhosis, enlarged liver and hepatitis were not related to tenofovir use. These events were attributed to prolonged antiretroviral treatment and hepatitis A infection..

Hepatic failure was reported in 3 patients. See section 10.6 for details on patient 902-1085. The remaining two events were not related to tenofovir use and were thought to be due to substance abuse and advanced HIV infection. The investigator's assessment of these cases appear reasonable.

Lactic acidosis

Four cases of lactic acidosis have been reported in patients receiving tenofovir. It is difficult to assess if these events were related to tenofovir use or other concomitant NRTIs. Details of the four cases are provided below.

In study 902 a 36 year old male received tenofovir 75 mg for approximately 38 weeks. Concomitant medications included stavudine, didanosine, efavirenz and nelfinavir. At week 38 lactic acidosis was diagnosed. The patient experienced symptoms of fatigue and shortness of breath two weeks prior to the diagnosis. Serum lactate was 22 mg/L. Upon retest the lactate levels were 8 mg/dl. Tenofovir, efavirenz and indinavir were restarted 2 months later. The patient continues on this regimen without a recurrence of lactic acidosis. It is difficult to determine if this event is related to tenofovir use. The patient was receiving concomitant medications known

to cause lactic acidosis, stavudine and didanosine. Additionally, the event did not recur after rechallenge with tenofovir.

In study 903, a 58 year old female patient with baseline CD4 of 29 cells and HIV RNA of 437,288 copies/mL was randomized to receive blinded tenofovir or stavudine. Her medical history is significant for diastolic dysfunction secondary to hypertension. At week 36 of study, the patient complained of tachycardia, shortness of breath, and nausea. The following day all medications were stopped. The patient was admitted to the hospital for elevated lactic acidosis and decreased bicarbonate. The event resolved off study drugs. The event is still blinded therefore causality can not be determined.

In study 907 a 50 year old male developed lactic acidosis and low bicarbonate accompanied by grade 2 ALT and AST elevation. The investigator attributed the event to stavudine but could not rule out causality with tenofovir or didanosine.

In the expanded access program, lactic acidosis resulting in death was reported in a 42 year old male with a CD4 cell count > 1000 cells and HIV RNA < 50 copies/mL. This patient was concurrently enrolled in both the ESPRIT study (study to evaluate IL-2) and the expanded access program at the time of the event. The patient's medical history is significant for severe lactic acidosis and pancreatitis which were attributed to stavudine, didanosine and saquinavir. The patient began treatment with tenofovir, lopinavir/ritonavir and indinavir. On the last day of IL-2 treatment the patient was evaluated for sore throat. At this time the patient had a low bicarbonate level of 13 mEq/L, a lactate level of 6.4, anion gap of 21.8, and elevated serum creatinine. All medications were stopped and he was admitted to the hospital for IV fluids and bicarbonate. During the hospitalization, serum creatinine continued to rise and sputum culture was positive for staphylococcus aureus. Chest X-ray showed a mass suggestive of lymphoma. Later the patient became jaundiced. Treatment with ciprofloxacin and fluconazole was initiated. Lactate level returned to within normal limits. The patient expired on day 8 of hospitalization due to a sudden asystolic cardiac arrest. The investigator cited tenofovir, IL-2 and indinavir to be possibly related to the events of lactic acidosis and renal failure. Additional information is pending.

Bone abnormalities

Reductions in bone mineral density occurred in three animal species following tenofovir administration. Bone mineral loss was noted in juvenile rhesus monkeys following ten months of subcutaneous administration of tenofovir 30 mg/kg/day. Decreased bone mineral content and density was observed in rats at oral doses of 300 and 1000 mg/kg and in dogs at doses of 30 mg/kg given for 13 or 42 weeks. The applicant has suggested two possible mechanisms for bone abnormalities. First, changes in bone mineral density are thought to be secondary to renal tubular reabsorption defects. This is supported by hypophosphatemia in monkeys and hypercalciuria seen in rats and dogs. The second mechanism is via a direct drug-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density as seen in rat and monkey studies.

Preclinical studies show that renal tubular dysfunction and bone mineral losses are dose-related and generally reversible. Long term administration (up to 10 months) of low dose tenofovir or short term administration with high doses of tenofovir was not associated with bone abnormalities. Bone abnormalities were observed following chronic administration of intermediate and high doses of tenofovir. It is not known if chronic administration (> 42 weeks) of low dose tenofovir will cause bone abnormalities. Observations for each animal species are summarized below.

Bone Abnormalities: Monkeys

Bone lesions were observed in monkeys after 10 months of daily subcutaneous administration of tenofovir 30 mg/kg/day. Bone toxicities were also noted at 2 and 7.5 months of age in neonates

following tenofovir exposure in utero during the second trimester. These animals received both pre and postnatal chronic tenofovir treatment.

Bone toxicity characterized by abnormal growth plates and trabeculae, bone deformities and displacements, bone fractures, joint swelling and decreased bone density in the spine or pelvis were noted following tenofovir 30 mg/kg/day SQ. Also moderate to marked decreases in serum phosphorus, increases in alkaline phosphatase, non-hyperglycemic glycosuria and proteinuria were seen in conjunction with the bone changes. A tenofovir dose of 10 mg/kg SQ administered to newborn monkeys daily for 2 years was not associated with skeletal changes or changes in alkaline phosphatase, phosphorus, non-hyperglycemic glucosuria or proteinuria.

A separate study was conducted as part of a master's thesis to evaluate the effects of tenofovir on bone metabolism and cortical bone strength in fetal and juvenile monkeys. Microradiographs showed completely unmineralized secondary osteons consistent with osteomalacia. As a result of these findings, assessment of osteoid accumulation, bone porosity, determination of mineral content, and evaluation of bone fragility were conducted on all bone specimens. Wide osteoid seams were noted in 50% of the tenofovir treated juvenile monkeys. Normal bone remodeling was noted in all untreated juvenile specimens. The applicant concluded that tenofovir 30 mg/kg/day SQ was associated with defective mineralization of osteoids. When the dose was reduced to 10 mg/kg/day or when tenofovir dosing was discontinued osteoid width normalized or showed improvement. It is important to note that the most severely affected monkeys received tenofovir for four months or longer. The author of the master's thesis also concluded, "Although these data clearly show a significant effect of high dose tenofovir administration on bone remodeling, the data presented are largely inconclusive with regard to the relationship between osteoid seam width, microdamage accumulation and bone strength."

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Bone Abnormalities: Rats and Dogs

Renal toxicity, including increases in creatinine and marked hypercalciuria, was observed in rats following 42 weeks with tenofovir. No evidence of renal phosphate wasting was observed. There was evidence for increased bone turnover, with loss of mineral from both cortical and trabecular bone. In dogs, hypercalciuria, glycosuria, and proteinuria associated with increased bone turnover (bone markers) and loss of bone mineral were observed. In addition to loss of bone mineral and changes in bone turnover markers in rats and dogs, there were increases in PTH levels and decreases in levels of 1,25-dihydroxyvitamin D₃.

Bone Abnormalities: Reproductive-Toxicology Data

No bone abnormalities were observed in monkey fetuses exposed to tenofovir, at AUCs ten times greater than the human exposure, in utero for final two-thirds of gestation. In addition no abnormal bone development in newborn rats or rabbits exposed in utero in reproductive toxicology studies were noted.

The Division is currently reviewing data to assess if tenofovir has direct toxicity to bone. At this time a definitive conclusion cannot be made until additional data has been submitted and reviewed. Further nonclinical studies may be necessary to determine if tenofovir treatment has any direct effects on bone metabolism. However, there is supportive evidence that tenofovir may not be directly toxic to bone.

Bone Abnormalities: Relationship of Animal Exposure to Human Dose

Review of exposure data and bone abnormalities noted in animal studies gives some reassurance that there is a margin of safety for the 300 mg daily dose to be used in humans. AUCs of 18 µg*hr/ml, 30 µg*hr/ml and 97.9 to 240 µg*hr/ml in rats, dogs, and monkeys, respectively were noted in conjunction with bone abnormalities. The average AUC in humans receiving tenofovir 300 mg is 3.34 µg*hr/ml. Reductions in bone mineral density in rats and dogs occurred at exposure levels 6-10 times higher than the human clinical exposures following administration of tenofovir at 300 mg/day. Bone abnormalities in monkeys were noted at exposure levels 29-80 times higher than the human clinical exposures with tenofovir 300 mg. However, safety margins were lower at doses of tenofovir that elicited no effects in animal toxicology studies.

The variability of drug concentrations in humans were minimal over time, thus providing assurances that individual patient exposures were not approaching those associated with bone abnormalities in the animal studies.

Bone Abnormalities: Clinical Data from Studies 902 and 907

Because of the findings of bone toxicity in three animal species, the Division asked the sponsor to monitor markers of bone metabolism using measurements such as bone mineral density (BMD), serum calcium and phosphate, alkaline phosphatase, vitamin D and PTH. However for some measurements, data were only collected for a subset of patients. Vitamin D data was not interpretable because baseline and post baseline data was not available for a given patient. In addition, the sponsor calculated fractional urinary excretion of calcium and phosphate. These data are discussed below.

Clinical Assessment of Bone Abnormalities: BMD

BMD changes of the spine, as measured by DEXA, were evaluated in studies 902 and 907 and were available for 21 patients receiving placebo and 40 patients receiving tenofovir 300 mg. The "All Tenofovir" group includes patients randomized to 75 and 150 mg and patients who were

initially randomized to placebo but later crossed over to tenofovir 300 mg. Table 10.2.C summarizes mean percent changes from baseline for BMD of the spine. Overall small changes were observed. These changes were not thought to be clinically significant. For study 902 there did not appear to be any dose effect.

Table 10.2.C: BMD Results: Percent Change From Baseline* – Studies 902 and 907

Time Point	Placebo (0-24 weeks)	Tenofovir 300 mg (0-24 weeks)	All Tenofovir
Week 24			
Mean	N=18 0.6 +/- 3.46	N=33 -1.3 +/- 2.41	N=58 -0.8 +/- 2.42
Median	0.9	-0.7	-0.7
Range			
Week 48			
Mean	--	--	N=46 -0.8 +/- 3.44
Median			-0.7
Range			
Week 72			
Mean	--	--	N=35 -1.4 +/- 3.87
Median			-1.3
Range			
Week 96			
Mean	--	--	N=17 -0.1 +/- 4.48
Median			-1.7
Range			

*BMD was measured as g/cm²

The applicant assessed "marked changes" in BMD (marked defined as >5% decrease from baseline at the lumbar spine) during the 24 week placebo controlled period. The incidence of marked changes was 6% for placebo vs. 9% tenofovir.

BMD changes of the hip were evaluated in study 907. No differences were noted between groups. Mean loss of BMD at week 24 was 0.1% and 0.8% in the tenofovir and placebo groups, respectively. No spontaneous fractures of the hip or other weight-bearing bones were reported.

Clinical Assessment of Bone Abnormalities: PTH (Study #902)

PTH was evaluated for those patients participating in the BMD substudy of study 902. Samples were collected at baseline, weeks 24, 48, 72 and 96. The applicant reported no marked changes from baseline in median or mean PTH levels in any treatment group through week 24 or in the three tenofovir dose groups through week 96. There did not appear to be a dose relationship for PTH changes. Mean changes in PTH levels from baseline are summarized in Table 10.2.D.

Table 10.2.D: PTH Results – Substudy 902

Time Point	Placebo (0-24 weeks)	75 mg / 300 mg	150 mg / 300 mg	300 mg / 300 mg
Baseline	21.9 (+/- 9.2) N=8	28.1 (+/- 10.8) N=18	21.6 (+/-7) N=11	24.6 (+/- 12) N=16
Mean change at Week 24	-4.8 (+/- 4.5) N=6	1.2 (+/-10.5) N=17	2.3 (+/-8.8) N=11	-0.9 (+/-11.7) 13
Mean change at Week 48	NA	3.4 (+/-20.3) N=14	10.1 (+/-16.7) N=7	3.4 (+/-11.2) N=10
Mean change at Week 72	NA	10.4 (+/-15.5) N=14	4.3 (+/-11.2) N=8	-0.1 (+/-11.3) N=10

Source: serial 034 dated July 5, 2001

Clinical Assessment of Bone Abnormalities: Serum Phosphate and Fractional Excretion of Phosphorus

Serum phosphate changes were assessed over 24 weeks for the 300 mg and placebo groups in studies 902 and 907. Additionally, phosphate abnormalities are summarized below for these groups and the "All Tenofovir" group. The "All Tenofovir" group includes patients randomized to 75 and 150 mg and patients who were initially randomized to placebo but later crossed over to tenofovir 300 mg. Results of these analyses are presented in Table 10.2.E below. Through week 24, there was a slightly higher incidence of grade 2 hypophosphatemia in the tenofovir group compared to placebo. Phosphorus abnormalities occurred sporadically throughout the course of treatment in studies 902 and 907, and generally resolved without treatment interruption. Of the 62 patients with a grade 2+ phosphate abnormality, 51 (82%) patients had an abnormal value at only one visit. The abnormality resolved by the subsequent visit. Ten patients had a sustained (≥ 2 consecutive values) grade 2 abnormality. Additionally FDA pooled all available phosphorus data in studies 902 and 907. Based on this analysis, the incidence and severity of phosphate abnormalities did not worsen with increasing duration of tenofovir treatment. This finding is important because the applicant contends that the mechanism for bone abnormalities observed in animals may be mediated via renal phosphate wasting or decreases in intestinal absorption of phosphate.

Table 10.2.E: Serum Phosphate Changes: Studies 902 and 907

	Placebo (N=210) (weeks 0-24)	Tenofovir 300 mg (N=443) (weeks 0-24)	All Tenofovir (N=687)
Mean change from baseline	0.66 mg/dL	0.04 mg/dL	ND
Grade 1 (2-2.2 mg/dL)	10 (5%)	27 (6%)	51 (7%)
Grade 2 (1.5-1.9 mg/dL)	5 (2%)	28 (6%)	58 (8%)
Grade 3 (1-1.4 mg/dL)	1 (<1%)	0	3 (<1%)
Grade 4 (< 1 mg/dL)	0	1 (<1%)	1 (<1%)

Fractional excretion of phosphorus was also calculated for studies 902 and 907 using spot urine samples. In study 902, patients originally randomized to receive tenofovir had an increase in excretion of urinary phosphorus at each study visit through week 48. The mean change from baseline ranged from 0.2% to 2.3%. At week 24 there was a statistically significant difference between placebo and the tenofovir 300 mg group; -2.3% placebo vs 2.3% tenofovir.

In study 907, no significant differences were noted between groups. Mean change from baseline in fractional excretion of phosphorus at week 24 was 0.4% and -0.9% for the tenofovir and placebo groups, respectively.

Clinical Assessment of Bone Abnormalities: Calcium and Fractional Excretion of Calcium

In study 902, the mean change in calcium from baseline through week 96 ranged from -0.2 mg/dL to +0.4 mg/dL. There did not appear to be a dose effect for reductions in serum calcium. Changes from baseline in fractional excretion of calcium were small and were similar for all dose groups and placebo. At week 96, the mean change ranged from -0.4% to +0.2%.

In study 907, mean change from baseline in calcium was similar at every time point through week 24 for both treatment groups. The mean change from baseline was +0.19 mg/dL and 0.17 mg/dL for the tenofovir and placebo groups, respectively.

Overall the incidence of hypocalcemia was similar between both groups. Calcium abnormalities were not clinically significant. These results are summarized in Table 10.2.F.

Table 10.2.F: Calcium Abnormalities (weeks 0-24): Studies 902 and 907

Toxicity Grade	Placebo	Tenofovir
Grade 1 (3-2.4 mg/dL)	10%	8%
Grade 2 (2.5-2.9 mg/dL)	<1%	1%
Grade 3 (2-2.4 mg/dL)	0	<1%
Grade 4 (< 2 mg/dL)	0	0

Clinical Assessment of Bone Abnormalities: Alkaline Phosphatase

The incidence of elevations in alkaline phosphatase was similar between groups and not thought to be clinically significant. No patients developed grade 3+ elevations in alkaline phosphatase.

Clinical Assessment of Bone Abnormalities: Incidence of Clinical Fractures:

The incidence of fractures was evaluated in all studies. A total of ten patients (5.5%) developed a fracture in study 902. All fractures occurred in patients receiving tenofovir and were observed with all three tenofovir doses (75, 150 and 300 mg). All fractures occurred as a result of trauma/accidental injury and no spontaneous fractures or vertebral compression fractures were documented in study 902. Time to fracture ranged from 8 to 135 weeks. Five patients developed a fracture during the first 48 weeks of study and five patients developed a fracture after 48 weeks of tenofovir treatment. In study 907 the percentage of patients who sustained a fracture was lower, 1% (5/488), but duration of treatment was shorter in 907 compared to study 902.

The applicant cited prolonged protease inhibitor (PI) use as a possible risk factor for fractures; however, to date it is not known if PI use is related to an increased risk for fractures. Reports in the literature have suggested that HIV + patients receiving PI regimens may develop osteopenia and osteoporosis at higher rates than HIV – controls or HIV + patients receiving no treatment or non- PI regimens. However, the clinical significance of the reported loss of bone mineral in HIV + patients is unknown. To better understand these issues and to explore the frequency of fractures in other studies of antiretrovirals, FDA conducted a retrospective analysis of 13 trials to evaluate fracture rates in patients receiving PI vs Non PI containing regimens. Commercial phase 3 studies submitted to the Division between 1999 and 2001 were chosen for the analyses. Trials included principal studies that were used to support accelerated and traditional approval or a dosing change. All 13 trials in this analysis enrolled antiretroviral naïve patients or patients with limited nRTI experience. All studies were designed to have a minimum of 48 weeks of follow up in at least 1 treatment arm. All of the approved antiretroviral agents were represented in this sample. Data collected included: number of patients with clinical fractures in each treatment group; time to fracture; CD4, HIV RNA level and weight at baseline and at time of fracture; steroid use; and other risk factors. Overall in this meta-analysis of 13 studies, 2% of patients (202/10166) developed a clinical fracture. The proportion of patients who developed a fracture in the PI and Non PI group was 1.7% (97/5565) and 2.3% (105/4601), respectively. The mean time to fracture event was 296 days. The majority of fractures were a result of trauma/accidental injury.

The proportion of patients who experienced a fracture in study 902 was higher than that in seen in the meta-analysis. Due to the small sample size of study 902, this observation may in fact be an anomaly. However, further investigation of this potential safety signal is warranted.

To evaluate the potential for fractures following tenofovir treatment, overall fracture rates were calculated for study 902, study 907 and studies 902 and 907 combined. No reports of vertebral compression fractures were noted in studies 902 and 907 through 116 weeks. Results for overall rates are summarized below in Table 10.2.G.

Table 10.2.G Overall Fracture Rate in Studies 902, 907 and Both Studies Combined

	Study 902		Study 907		Pooled	
	TNF n=179	Placebo n=28	TNF n=538	Placebo n=182	TNF n=717	Placebo n=210
Fractures (#)	10	0	5	3	14	3
Exposure (person-years)	311	13	488	86	800	99
Fracture Rate (95% C.I.)	3.2 (1.5 – 5.9)	0 (0 – 28.4)	1 (0.3 – 2.4)	3.5 (0.7 – 10.2)	1.8 (1.0 – 2.9)	3.0 (0.6 – 8.9)

After reviewing the entire animal toxicity and pharmacokinetic data, along with human pharmacokinetics and fracture data, it is unlikely that tenofovir-related clinical fractures will occur over 48 weeks assuming the mechanism for bone abnormalities is mediated by renal phosphate wasting or decreases in intestinal absorption of phosphate. As discussed above no significant changes in renal parameters, in particular phosphate, were observed. However, to evaluate whether risk of fractures were increasing with longer term treatment, fracture rates were calculated according to 6 month time intervals as shown in Table 10.2.H below. The data did not indicate an increase in the fracture rate over successive 6 month intervals.

Table 10.2.H Number of Fractures and Fracture Rates in 6 month Intervals

Study Treatment	Study 902		Study 907		Pooled	
	TNF	Placebo	TNF	Placebo	TNF	Placebo
0-6 Months						
Fractures/patients(#)	3/179	0/28	3/538	3/182	5/349	3/210
Rate (person yr.) (95% C.I.)	3.5 (0.7 – 10.2)	0 (0 – 30.7)	1.1 (0.2 – 3.3)	3.6 (0.7 – 10.6)	1.4 (0.5 – 3.3)	3.2 (0.7 – 9.2)
6-12 Months						
Fractures/patients(#)	2/161	0/2	0/474	0/9	2/635	0/11
Rate (person yr.) (95% C.I.)	2.6 (0.3 – 9.5)	0 nd	0 (0 – 2)	0 (0 – 92.2)	0.8 (0.1 – 2.7)	0 (0 – 92.2)
12-18 Months						
Fractures/patients(#)	3/136	0/2	2/216	0/3	5/352	0/4
Rate (person yr.) (95% C.I.)	4.8 (1.0 – 14.1)	0 (0 – na)	5.3 (0.6 – 19)	0 (0 – na)	5 (1.6 – 11.7)	0 (0 – na)
18-24 Months						
Fractures/patients(#)	1/115	--	0/4	--	1/119	--
Rate (person yr.) (95% C.I.)	1.9 (0.1 – 10.7)	--	0 (0 – na)	--	1.9 (0.1 – 10.7)	--
>24 Months						
Fractures/patients(#)	1/92	--	--	--	1/92	--
Rate (person yr.) (95% C.I.)	2.9 (0.1 – 15.9)	--	--	--	2.9 (0.1 – 15.9)	--

However, insufficient numbers of patients receiving prolonged tenofovir treatment and lack of a control group past 24 weeks make it difficult to conclude whether or not tenofovir use will cause clinical fractures. More patients are needed to determine if the risk of fracture increases over time. However, with the available data, no obvious increases in fracture rates were observed over time.

A summary of all fractures from studies 901, 902, 903, 907, 908 and 910 is presented in Appendix A. To date, a total of 30 bone fractures have been reported. The majority of fractures were related to trauma/accidental injury. Fractures occurred over a range of 7-135 weeks. Calcium and renal laboratory parameters were within normal limits unless otherwise stated. The majority of patients did not have any known history of hypogonadism, hyperparathyroidism, thyroid disease, corticosteroid use, malnutrition, recent immobilization or other osteoporosis risk

factors. Bone mineral densities are noted for those patients participating in the 902 or 907 BMD substudies in whom a fracture developed. All fractures were confirmed by radiograph unless otherwise noted. Several patients had follow up X-rays that demonstrated healing. No patient developed a subsequent fracture while continuing on tenofovir treatment.

Summary of Bone Fractures

Study/Pt#	Sex Age Race	Fracture Site/History	Tenofovir Dose	Weeks on Tenofovir	Relevant Labs or Medical history/Comments
902-427-1568	39 Female Black	Right distal radius Fall on outstretched hand while rollerblading	150 mg	8	PI use 2+ years Hydrocortisone use 1 month Discontinued at week 28 for noncompliance
902-110-1283	37 Male White	Right clavicle, right and left tibias Motorcycle accident	150 mg	24	Episodic alcohol abuse Continue in study through 136 weeks with no additional bone fractures
902-362-1533	38 Female White	Right distal radius Fall while attempting to disembark from a moving boat	300 mg	16	PI use 2.5+ years Continued on study through 116 weeks with no additional bone fractures
902-255-1004	41 Male White	Right index finger Work related traumatic injury Fracture was not confirmed by radiograph	75 mg	39	Tobacco use (duration and amount unknown) Methylprednisolone X 5 days PI use 3 years Discontinued from study after 92 weeks due to lack of virologic response
902-427-1569	35 Male White	Left Thumb Bicycle Accident	150 mg	37	BMD: not performed Continued on tenofovir through 100 weeks with no additional bone fractures Discontinued 5/2001 due to structured treatment interruption
902-354-1723	44 Male Black	Right Femur Fall down stairs post hip replacement for avascular necrosis	300 mg	64	HIV related AVN (1998) PI use 4+ years BMD + 3.5% from baseline (spine) 2+ year use androstanolone Decreased mobility post operatively but no other risk factors* Continued on tenofovir through 127 weeks with no additional bone fractures
902-441-1485	54 Male White	Left Femur Loss of balance with fall in hospital bathroom	300 mg	56 weeks (20 weeks QOD)	Tobacco use (duration and amount unknown) Bedridden x 18 days prior to event for pneumonia and CMV encephalitis PI use 4+ years Hypogonadism BMD Jan 2000: -11.9% spine and -3.9% hip BMD April 2, 2000: -13.5% spine Discontinued when moved

					out of state in June 2000
902-427-1562	46 Male White	Left Lateral malleolus Jumped 4 ft from delivery truck onto uneven pavement	300 mg	60	Tobacco use (duration and amount unknown) Hypogonadism but no other risk factors* Continued on tenofovir through 92 weeks with no additional fractures Discontinued 8/31/00: investigators choice
902-362-1526	56 Male White	Left 10 th rib Fall in bathtub	300 mg	87	Crohn's disease (1992) Chronic diarrhea (1992) PI use 4+ years Continued on tenofovir through 132 weeks with no additional fractures
902-407-1761 (rolled over into study 910)	41 Male White	Tibia, fibula, right hip, pelvis and ribs Hit by a car on the freeway while riding a motorcycle	300 mg	87 (plus an additional 48 weeks on 150 mg)	Wasting syndrome Hypogonadism PI use 3+ years
907-407-3081	66 Male White	Right toe, fifth digit Toe crushed under chair leg while sitting in chair	300 mg	24	Prior traumatic fractures to same toe C4 and C5 disc herniation Hypogonadism but no other risk factors* Testosterone use 2+ years Clinically demonstrated interval healing with no follow up X-ray taken, but reinjured same toe six weeks later
907-546-3772	38 Male White	Right tibia 8 foot fall from ladder	300 mg	19	Tobacco use (1 pack/day for > 30 years) PI use 4+ years Decreased mobility due to case BMD: week 24 +2.9% change from baseline (spine) and +2.1% (hip) Week 48: -7.2% change from week 24 (spine) and -5.2% (hip) Continued on tenofovir through 30 weeks
907-692-5128	49 Male White	Left arm Fall from ladder	300 mg	10	Ex-smoker Continued on tenofovir through 64 weeks
907-645-2410 (rolled over into study 910)	30 Male White	C1 and C2 vertebrae Flipped over handlebars while mountain biking	300 mg	68	PI use Fluticasone inhaler 2 + years
907-302-2108 (rolled over into study 910)	32 Male Black	Hairline fracture of right distal tibia Fell and twisted ankle during contact sport activity	300 mg	53	PI use 3+ years Continued on tenofovir through 65 weeks
907-654-2823 (rolled over into study 910)	36 Male White	Multiple left-sided rib fractures Coughing	300 mg	68	PI use 4+ years History of multiple rib fractures due to coughing Previous use of high dose IV and PO corticosteroids and

					continued use of inhaled corticosteroids
907-685-5335	51 Male White	Left calcaneus Fell down a flight of stairs	Placebo	NA	PI Use: 7 months
907-599-2176	48 Female Black	Left small toe Accidental injury Not confirmed radiographically	Placebo	NA	PI use 3+ years
907-881-5699	70 Male White	Right femur Fall Not confirmed radiographically	Placebo	NA	PI use 3+ years
908-774-4236	38 Male White	Left Lateral Maleolus Slipped off Curb	300 mg	30	Wasting syndrome Chronic diarrhea Malnutrition (TPN use) Hypogonadism PI use (unknown duration) Nandrolone use 1+ years Discontinued after 32 weeks of study due to progression of HIV
908-835-4350	48 Male White	Left 5 th finger Injury during basketball game	300 mg	18	Hypogonadism (5+ years) Wasting syndrome Prior broken wrist from basketball game (1981) History PI use (5+ years) History testosterone use (5+ years) Continued on tenofovir through 64 weeks
908-730-4025	66 Male White	Left femur Slipped and fell in driveway	300 mg	58	Osteonecrosis of left hip and recently underwent core hip decompression procedure to promote blood flow to left hip Hypogonadism (5+ years) PI use (5+ years) Continued on tenofovir through week 70
908-356-4240	46 Male White	Right Wrist Fall from a motorcycle accident	300 mg	54	Hypogonadism Wasting syndrome PI use 1+ year Inhaled steroids 2+ years
908-1031-4340	49 Male White	Compression Fracture L3 Fell at home secondary to orthostatic hypotension	300 mg	60	PI use 5+ years Tobacco use 20+ years Hypogonadism Wasting syndrome Malnutrition Chronic oral and inhaled corticosteroid use for adrenal insufficiency
908-730-4389	48 Female Hispanic	Compression fracture (T6, T8 & T10) Patient complained of scapula pain during hospitalization for pancreatitis Discharge summary notes compression fractures – MRI revealed compression fractures, which were secondary to	300 mg	19	Long standing osteoporosis. At screening pt was wheelchair dependent due to right ankle fracture and severe debilitation Hypogonadism Wasting Syndrome Chronic Diarrhea Discontinued from study after 32 weeks due to a change in antiretroviral regimen

		old, not acute, trauma			
908-121-4409	46 Male White	Right radius Loss of balance and fell while riding moped Not confirmed radiographically	300 mg	25	Hypogonadism Wasting syndrome Hypotestosteronemia
903-731-8776	37 Male White	Right femur Fell 3-6 feet from the sidewalk while under the influence of alcohol	300 mg or d4T	24	ETOH abuse Malnutrition Tobacco use (20 cigarettes/day) Patient remains on study
903-987-8129	35 Male White	Right great toe Fell down a flight of stairs	300 mg or d4T	7	Tobacco use (1/2 pack/day for 14 years) Continues on study through 36 weeks
903-1021- 8428	41 Male White	Right clavicle Hit by automobile while riding bike	300 mg or d4T	20	None Continues on tenofovir through 48 weeks
901-117-0126 (rolled over into study 910)	50 Male White	Right distal fibula Twisted right foot in a pavement hole while crossing street	300 mg	133 (includes 13 months in cohort 6 75 mg + HU)	PI use (4+ years) BMD: z scores of -1 (spine); - 1.2 (hip) Continues on study through 145 weeks

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10.3 Drug Discontinuations Due to Adverse Events:

Discontinuations due to adverse events were assessed for patients who received placebo or tenofovir 300 mg in studies 902 and 907. Through week 24, 2% of patients in both the placebo and tenofovir groups prematurely discontinued study due to adverse events. More patients in the tenofovir group discontinued for a GI related event compared to placebo. Nausea was the most common adverse event leading to discontinuation during tenofovir treatment. It is difficult to determine if the discontinuations are directly related to tenofovir or to concomitant antiretroviral therapy. The reasons for discontinuations due to adverse events through week 24 are listed in Table 10.3.A. Of note, patients may have experienced more than one adverse event at the time of discontinuation.

Table 10.3.A. Discontinuations Due to Adverse Events Through Week 24 (Studies 902 and 907)

Dose Group	Number of Patients Who Discontinued	Event
Placebo (N=210)	5 (2%)	Asthenia Abdominal Pain (2) Dehydration Diarrhea (2) Headache Hyperlipemia Impotence Nausea (2) Pancreatitis Pregnancy* Rash
Tenofovir 300 mg (N=443)	11 (2%)	Abdominal pain Asthenia (3) Carcinoma (2) Diarrhea (2) Eructation Headache Malaise Nausea (5) Pain Pancreatitis Pregnancy* Somnolence (2) Urinary frequency Vomiting

*Outcomes of the pregnancies are not known at this time

In study 902 similar proportions of patients randomized to the 3 tenofovir dose groups discontinued due to adverse events through week 48 (9-11%). With the exception of the 150 mg dose group, the proportion of premature discontinuations increased 6-7 % from week 24 through 48. An additional 10 patients discontinued during the open label phase. No new events or new types of adverse events were noted in the open label phase.

In the safety update, the mean duration of follow up for patients receiving tenofovir 300 mg was 58 weeks. A total of 35 patients (5%) discontinued due to an adverse event. No event occurred in more than 1% of patients. The most common reasons for discontinuation were asthenia, nausea, abdominal pain, weight loss and peripheral neuritis.

In study 908, 42 patients (14%) prematurely discontinued study drug due to an adverse event through the safety update cut off. The most common events occurring in $\geq 1\%$ of patients and

leading to discontinuation were infection, nausea, vomiting, encephalopathy, and pneumonia. The types of events that led to discontinuation were similar to those observed in studies 902 and 907 and with those expected in this advanced study population.

10.4 Serious Adverse Events:

Serious adverse events were defined as an adverse event (clinical or laboratory abnormality) that resulted in any of the following outcomes: death, life-threatening situation (patient is at immediate risk of death), inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity; or congenital anomaly/birth defect.

Table 10.4.A. summarizes the serious adverse events reported in two or more tenofovir treated patients. The types and frequency of serious adverse events were similar for the placebo and tenofovir groups. The majority of events were considered not related to study drug. Five events were considered related, hepatic failure, lactic acidosis, nausea, osteopenia and pancreatitis. These events and fractures are discussed in the events of interest section.

Table 10.4.A. Serious Adverse Events Reported in ≥ 2 Tenofovir Treated Patients in Studies 902 and 907

Event	Placebo N = 210 (weeks 0-24)	Tenofovir 300 mg N=443 (weeks 0-24)	All Tenofovir N=687	Safety Update All Tenofovir N=687
# Patients Experiencing SAE	15 (7%)	18 (4%)	44 (6%)	89 (13%)
Body as A Whole				
Bacterial Infection	1 (<1%)	1 (<1%)	3 (<1%)	6 (<1%)
Cellulitis	1 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)
Allergic Reaction	0	1 (<1%)	2 (<1%)	2 (<1%)
Abscess	1 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)
Accidental Injury	0	0	3 (<1%)	3 (<1%)
Fever	1 (<1%)	0	2 (<1%)	2 (<1%)
Abdominal Pain	0	0	2 (<1%)	2 (<1%)
Nervous System				
Depression	1 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)
Digestive				
Colitis	1 (<1%)	0	1 (<1%)	2 (<1%)
Nausea	0	1 (<1%)	1 (<1%)	2 (<1%)
Diarrhea	0	0	0	2 (<1%)
Pancreatitis	0	2 (<1%)	3 (<1%)	7 (1%)
Musculoskeletal				
Joint disorder	2 (<1%)	0	1 (<1%)	4 (<1%)
Fracture	1 (<1%)	0	3 (<1%)	6 (<1%)
Respiratory				
Lung Disorder	0	1 (<1%)	1 (<1%)	3 (<1%)
Asthma	0	1 (<1%)	0	2 (<1%)
Pneumonia	0	2 (<1%)	6 (<1%)	12 (2%)
Pneumothorax	0	1 (<1%)	2 (<1%)	2 (<1%)
Urogenital				
Kidney Calculus	0	0	3 (<1%)	3 (<1%)
Pyelonephritis	0	1 (<1%)	2 (<1%)	3 (<1%)
UTI	0	0	1 (<1%)	2 (<1%)

Source: Appendix D, Table 15, Table 5-5 ISS and Table 6-1 safety update

In study 908, the incidence of serious adverse events is higher than that seen in studies 902 and 907. Overall 75 patients (26%) experienced a serious adverse event through the safety update cut off date. The most common SAE was pneumonia (5%), pancreatitis (2%), abdominal pain (2%) and fever (2%). SAEs related to tenofovir were reported in 11 patients (4%). Of the related

cases, only pancreatitis (3 cases) was reported in more than one patient. The other related events were encephalopathy, abdominal pain/diarrhea/nausea/vomiting, fever, AVN (avascular necrosis), thrombocytopenia, elevated creatinine, renal insufficiency and elevated transaminases. These events occurred in one patient each. The type of SAEs were similar to those observed in studies 902 and 907.

10.5 Deaths:

A total of 19 deaths were reported in all the tenofovir trials submitted in the NDA. Sixteen deaths occurred in study 908. These deaths were consistent with those seen in other compassionate use trials in patients with advanced AIDS. One death occurred in study 901. A patient with a history of depression died of an overdose 30 days after treatment discontinuation. Two patients died in study 902. These cases are described in detail below.

Patient 442-1608 committed suicide after approximately 6 months on study drug. A suicide note was found at the scene. The patient had a history of depression, chronic alcoholism and one prior suicide attempt. The coroner cited cause of death as acute intoxication by combined effects of amitriptyline, doxepin, fluoxetine, chlorpheniramine and ethanol. The investigators assessment appears accurate in that the patient's death was not related to study drug.

Patient 052-1085 had chronic HCV and HIV (baseline CD4= 229 and RNA = 18,021) and received tenofovir 300 mg for approximately 1 ½ years when antiretroviral therapy was discontinued due to grade 4 bilirubin (6.1 mg/dL). Concomitant medications included ritonavir, indinavir, delavirdine, stavudine and lamivudine. According to the applicant, the patient was admitted to the hospital approximately 2 months after all medications were discontinued for either pancreatitis or spontaneous bacterial peritonitis. He was treated with antibiotics for bacterial peritonitis due to his pre existing liver disease and ascites. The patient started to improve then worsened and became increasingly encephalopathic with decreased urine output and hyperkalemia. He developed acute renal failure and anuria probably related to a combination of hepatorenal syndrome and contrast nephropathy, not a prerenal etiology. The patient declined with worsening coagulopathy, encephalopathy, hyperbilirubinemia and hypoglycemia and died 8 days after hospitalization. The investigators assessment that the death was not related to tenofovir appears reasonable. The death occurred approximately 2 months after all medications were discontinued. The patient also had a history of elevated transaminases and chronic HCV. The liver failure was most likely related to HCV, although long term antiretroviral therapy may have contributed to the increases in bilirubin and transaminases.

10.6 Age/Gender/Race Analyses:

The applicant conducted the following analyses on the pooled safety data from studies 902 and 907; adverse events by age, gender and race. These results were confirmed in the FDA analyses of these groups. The applicant reports no notable differences in the frequencies of adverse events between patients 40 years of age or younger and patients over 40 years old. Similar frequencies of adverse events were noted in males and females, with the exception of diarrhea. Diarrhea was 2 fold higher in males (23%) compared to females (11%). No notable differences were noted in the frequencies of individual adverse events by race. The incidence of adverse events was somewhat lower in non-white patients when compared to white patients. This finding does not appear to be clinically significant.

10.7 Laboratory Abnormalities:

The FDA analysis primarily focused on the incidence of grade 3+ laboratory abnormalities and the mean change from baseline for selected laboratory tests. Results from preclinical data guided the more detailed analyses of specific laboratory tests.

Generally grade 3+ laboratory abnormalities were similar between placebo and tenofovir with few exceptions. Triglyceride, creatinine kinase, amylase and serum glucose elevations occurred more frequently in the placebo group compared to tenofovir. Also the frequency of these laboratory abnormalities were higher in the placebo group compared to the "All Tenofovir" group in which patients received longer duration of tenofovir treatment. The types of laboratory abnormalities noted during the trial are consistent with what is expected in patients receiving multiple antiretroviral agents. Overall it was difficult to determine if the changes were due to tenofovir, concomitant antiretrovirals or underlying disease. For example, the majority of patients with grade 3+ elevations in triglycerides were also receiving protease inhibitors, agents known to cause these changes. Table 10.7.A. summarizes the grade 3+ laboratory abnormalities through week 24.

Table 10.7.A. Grade 3+ laboratory Abnormalities

Grade 3+ Laboratory Abnormality	Placebo (n=210) (weeks 0-24)	Tenofovir (N=443) (weeks 0-24)	All Tenofovir (687)
Triglyceride (> 750 mg/dL)	28 (13%)	37 (8%)	57 (8%)
Creatine kinase (> 792 U/L)	39 (19%)	47 (11%)	78 (11%)
Serum amylase (> 175 U/L)	14 (7%)	21 (5%)	32 (5%)
AST (> 180 U/L)	6 (3%)	16 (4%)	31 (5%)
Urine glucose (3+ or 4+)	6 (3%)	12 (3%)	16 (2%)
ALT (> 215 U/L)	4 (2%)	10 (2%)	19 (3%)
Serum glucose (> 250 mg/dL)	8 (4%)	8 (2%)	13 (2%)
Neutrophil (< 750/mm ³)	3 (1%)	6 (1%)	11 (2%)

Discontinuations due to laboratory abnormalities were infrequent. During the first 24 weeks, four patients (2%) and 2 patients (<1%) discontinued from the placebo and tenofovir groups, respectively due to laboratory abnormalities. In the safety update a total of 12 patients who received tenofovir 300 mg discontinued due to a laboratory abnormality. No abnormalities occurred in more than 1% of patients. The most common laboratory events leading to discontinuation were transaminase and CK elevations.

Table 10.7.B. summarizes the grade 3+ laboratory abnormalities for study 908. Generally the incidence of grade 3+ laboratory abnormalities are higher than that observed in studies 902 and 907. However these changes are consistent with advanced AIDS and with extensive prior antiretroviral therapy. No new abnormalities were noted. Again, it is difficult to assess if these abnormalities are related to tenofovir use. For example, seventy-nine patients developed triglycerides > 750 mg/dL. Overall 93% of patients were receiving lopinavir/ritonavir with or without another protease inhibitor. Hypertriglyceridemia has been documented in patients receiving protease inhibitors, particularly ritonavir based regimens. Therefore it is likely that the triglyceride changes observed in this study were related to lopinavir/ritonavir use and not related to tenofovir. Also, 16 of the 25 patients that developed a grade 3+ amylase elevation received didanosine concomitantly.

Twelve patients (4%) discontinued from study due to laboratory abnormalities. The most common reasons for discontinuation were proteinuria (2%) and increases in CK, triglyceride, glucose and ALT (1% each).

Overall, in studies 902, 907 and 908, tenofovir treatment did not appear to cause significant laboratory abnormalities.

Table 10.7.B. Study 908: Grade 3+ Laboratory Abnormalities

Grade 3+ Laboratory Abnormality	Tenofovir 300 mg (study 908) (N=291)	All Tenofovir Group (studies 902 and 907) N=687
Triglyceride (> 750 mg/dL)	79 (27%)	57 (8%)
Serum amylase (> 175 U/L)	25 (9%)	32 (5%)
Lipase (> 125 U/L)	25 (9%)	NA
Creatine kinase (> 792 U/L)	23 (8%)	78 (11%)
Neutrophil (< 750/mm ³)	18 (6%)	11 (2%)
AST (> 180 U/L)	15 (5%)	31 (5%)
ALT (> 215 U/L)	11 (4%)	19 (3%)
Alkaline Phosphatase	11 (4%)	0%
Serum glucose (> 250 mg/dL)	11 (4%)	13 (2%)
Urine glucose (3+ or 4+)	11 (4%)	16 (2%)

10.8 Review of Selected Abnormalities:

10.8.1 Hematologic Parameters:

The applicant did not conduct assessing changes from baseline for hematologic parameters in study 902. These analyses were conducted for study 907 and for the ISS. Changes from baseline was summarized by treatment group for RBC, WBC, hemoglobin, hematocrit and platelet count in the respective study reports. No statistical testing was performed on change from baseline values. The applicant notes that changes from baseline (increases or decreases) were minor and not considered to be clinically significant. Differences between treatment groups were not apparent.

Of note 4 patients discontinued study in part due to thrombocytopenia. Three cases in studies 902 and 907 and 1 case in study 908. In two cases it appears that thrombocytopenia was related to tenofovir use. Summaries of the cases are described below. Thrombocytopenia will be monitored in other clinical trials and post-marketing.

Patient 110-1286 discontinued tenofovir in the open label phase due to thrombocytopenia. This patient was randomized to 75 mg. His medical history is significant for HIV-associated thrombocytopenia. After 14 months of treatment tenofovir and d4t were interrupted due to decreased platelets, bleeding gums and small submucosal hemorrhages in mouth and abdomen. The hemorrhages were considered stable, despite the platelet count declining to 5,000. The patient refused hospitalization for treatment. The patient was subsequently discontinued due to missed scheduled visits. The investigator's assessment seems reasonable that this event was not related to study drug, given the past history of HIV-associated thrombocytopenia and stability with no improvement off study drug for 2 months.

Patient 052-1085 discontinued tenofovir treatment at study week 84 due to grade 4 thrombocytopenia, grade 3 AST, grade 2 CK and grade 4 bilirubin. At baseline medications

included nevirapine, saquinavir, ritonavir and stavudine. The patient's medications were later changed to stavudine, lamivudine, delavirdine, indinavir and ritonavir. His medical history is significant for thrombocytopenia since March 1997. Platelet count at baseline was 117×10^3 /uL. At week 12 the platelet count fell to $73-97 \times 10^3$ /uL (grade 1/2) and was stable in this range through week 40. At week 44 platelets decreased to 20×10^3 /uL (grade 4) and tenofovir dosing was interrupted for approximately 3 months. Platelets increased to 31×10^3 /uL at week 48 and 46×10^3 /uL at week 56. Tenofovir was restarted on approximately week 60 and platelets declined to 22×10^3 /uL at week 80. The investigator felt that these subsequent decreases in platelets were related to tenofovir use. However, it is important to note that this patient had a history of thrombocytopenia since March 1997. It is unknown if tenofovir contributed to this recent episode of decreased platelets.

Patient 362-1535 discontinued tenofovir treatment after approximately 1 month on study due to thrombocytopenia. Baseline and week 2 platelets were 107×10^3 /uL and 108×10^3 /uL, respectively. Platelets declined to 44×10^3 /uL at week 4 and on a repeat test of platelets were 31×10^3 /uL. The only medication taken prior to the initial decline in platelet count was loperamide. It is possible that these decreases are related to tenofovir use.

Patient 324-4101 discontinued tenofovir treatment after approximately 10 months on study due to thrombocytopenia. Baseline platelet count was 148,000. At month 2, platelet counts decreased to 88,000 and tenofovir treatment was interrupted for 2 weeks. Platelet counts increased and tenofovir was restarted. Platelet counts progressively declined. A hematology consult concluded that the patient had idiopathic thrombocytopenia purpura. It appears that this event was possibly related to tenofovir. Platelet counts improved after interruption of tenofovir and progressively declined following rechallenge.

10.8.2 Transaminases:

The incidence of all grades of transaminase elevations was similar between placebo and tenofovir with the exception of grade 1 ALT. Thirty-three percent of patients in the tenofovir group developed grade 1 ALT changes compared to 26% of patients in the placebo group. Overall, less than 1% of patients discontinued tenofovir due to ALT elevations. There does not appear to be an increase in transaminase elevations over time. Through the safety update cut off, 3 additional patients discontinued for ALT elevations; however the overall incidence is still < 1%.

FDA conducted several analyses regarding transaminase elevations and baseline hepatitis B or C. Fifty-one (12%) and 18 (9%) patients had baseline hepatitis B or C in the tenofovir 300 mg and placebo groups respectively. The incidence of grade 3+ abnormalities in these patients was similar between groups. The majority of these patients had elevated transaminases at baseline. The applicant stated that the presence of hepatitis B or C was significantly associated with increased ALT elevations. Patients with underlying hepatitis had a 2.7 fold greater risk of ALT elevations ($p < 0.0001$). Clinicians should be aware of the increased risk of transaminase elevations in patients with underlying hepatitis.

10.8.3 ALT/Bilirubin

No cases of concomitant grade 3+ elevations in ALT and bilirubin were attributed to tenofovir use. One patient in study 902 developed concomitant grade 3+ ALT and bilirubin, however this patient was diagnosed with acute hepatitis A and thus his liver abnormalities were considered unrelated to tenofovir use.

In study 908, one patient developed concomitant grade 3+ bilirubin and ALT. These events occurred within the first month of study. The patient had grade 2 bilirubin and ALT at baseline. The events resolved without treatment interruption.

10.8.4 Renal Parameters:

Preclinical studies showed evidence of renal toxicity in 4 animal species, mouse, rat, dog and monkey. Kidney changes were directly associated with exposure to tenofovir. Renal tubular toxicity occurred after 56 days to 42 weeks of tenofovir treatment in the mouse, rat, dog and monkey. Interstitial nephritis was noted after chronic dosing in dogs. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed in varying degrees in these animals. These toxicities were noted at exposure levels 2-20 times higher than the human clinical exposures following administration of tenofovir at 300 mg/day. In addition, decreased renal clearance of tenofovir and a Fanconi-like syndrome with glucosuria and hypophosphatemia occurred in monkeys following a dose of 30 mg/kg (subcutaneously) for 11-24 months.

Given the preclinical evidence for renal toxicity, renal parameters were monitored closely during the trials. FDA analyses of renal parameters focused on changes in creatinine, phosphate, bicarbonate, proteinuria and glycosuria. The FDA analysis of mean change from baseline for selected laboratory parameters utilized the data provided in the SAS transport files. With the available data there does not appear to be any significant renal toxicity associated with tenofovir use. It is important to note that another antiretroviral from the class of nucleotide analogues, adefovir, was associated with delayed nephrotoxicity. It will be important to assess long term changes with tenofovir use over time.

10.8.4.1 Serum Creatinine

FDA analysis of mean change from baseline utilized the data provided in the SAS transport files. Mean and median change from baseline through week 24 were consistent for both groups; -0.02 mg/dL for placebo and 0.007 mg/dL for tenofovir 300 mg group (see Table 10.8.4.1.A-B). Overall changes noted were minimal and not thought to be clinically significant. Study 902 provided some long term data to assess changes over time. Mean changes from baseline through week 24 and 48 were consistent for all dose groups. There was not a dose response relationship for changes in creatinine.

Table 10.8.4.A. Serum Creatinine Data through week 24: Studies 902 and 907

	Placebo (n=210)	Tenofovir (n=443)
Mean/Median change from baseline (range)	-0.02 mg/dL 0	0.01 mg/dL 0 mg/dL

Table 10.8.4.B. Serum Creatinine Data through weeks 24 and 48: Study 902

	Placebo	Tenofovir					
		75 mg (n=53)		150 mg (n=51)		300 mg (n=54)	
	Wk 24	Wk 24	Wk 48	Wk 24	Wk 48	Wk 24	Wk 48
Mean/Median change from baseline (range)	-0.03	0	+0.01	+0.01	-0.01	+0.01	+0.03

Table 10.8.4.C summarizes grade 1-4 serum creatinine abnormalities. FDA analysis of serum creatinine differs from that of the applicant. The data provided in SAS transport format showed that no patients developed a grade 2 or higher increase in serum creatinine. However after reviewing selected summary narratives and case report forms, cases of grade 2 serum creatinine were uncovered. This information was not captured in the datasets provided to the Division. The

applicant stated that the data provided to the Division included those laboratory parameters collected and analyzed by the protocol specified central laboratory occurring within 30 days of treatment discontinuation. Data collected and analyzed by [redacted] was not integrated with the central laboratory data and therefore not provided in the datasets. FDA then requested the applicant to review all renal parameters from both the central laboratory, [redacted] and data from local (as opposed to central) laboratories and provide all renal related abnormalities.

Five events of grade 2 or greater serum creatinine elevations were noted in patients in studies 902, 907 and 908. One event in study 907 was a transcription error; the actual creatinine value was 1.4 mg/dL. Another event occurred approximately 80 days following permanent study drug discontinuation and thus was outside the window for inclusion in the NDA database (30 days). Overall 3 cases of grade 2 serum creatinine abnormalities (<1%) were noted in studies 902 and 907. The FDA table differs from that of the applicant in that the cases of grade 2 serum creatinine abnormalities from study 902 are included in Table 10.8.4.C below. A summary of these cases can be found below.

Table 10.8.4.C. Serum Creatinine Abnormalities: Studies 902 and 907

	ISS			Safety Update
	Placebo (n=210) (weeks 0-24)	Tenofovir (n=443) (weeks 0-24)	All Tenofovir (N=687)	All Tenofovir (N=687)
Grade 1 (≥ 0.5 mg/dL increase from baseline)	3 (1%)	6 (1%)	25 (4%)	35 (5%)
Grade 2 (2.1-3 mg/dL)	0	1 (<1%)	2 (<1%)	3 (<1%)
Grade 3 (3.1-6.0 mg/dL)	0	0	0	0
Grade 4 (> 6 mg/dL)	0	0	0	0

Patient 443-1884 began treatment with tenofovir 75 mg in February 1999. Study medication was interrupted, November 1999, due to elevated serum creatinine (1.6 mg/dL; 0.6 mg/dL increase from baseline), hypophosphatemia (1.8 mg/dL), decreased serum potassium and bicarbonate and 2+ proteinuria). At this time the patient also had a MRI with gadolinium contrast for back pain. The patient was diagnosed with L4/L5 discitis with associated epidural abscess and started treatment with vancomycin, levofloxacin and ceftriaxone. The patients serum creatinine increased to 2.2 mg/dL. This could have been caused by vancomycin, however the contribution of tenofovir to the rise in creatinine is unknown. Serum creatinine decreased to 1.4 mg/dL about 10 days later and remained within normal limits. The patient restarted tenofovir 75 mg at every other day dosing 2 months later.

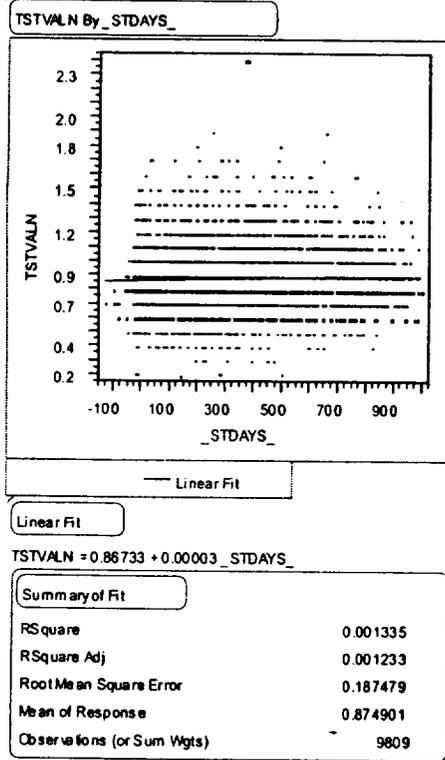
Patient 362-1533 received tenofovir 300 mg for approximately 1 month when she was hospitalized for suspected pyelonephritis and renal insufficiency. Serum creatinine was 2.8 on admission and IV ceftriaxone was started. Urinalysis revealed > 100 RBCs, 50-100 WBCs/culture grew out E coli. WBC was 15,200 cells/uL. Renal insufficiency was corrected with hydration and creatinine decreased to 1.4 mg/dL 3 days later. Study medications were restarted 9 days later when the renal insufficiency resolved. Serum creatinine remained within normal limits throughout the study. It appears that this event was not related to tenofovir use.

Overall changes in serum creatinine from baseline were minimal and not clinically significant. One percent of patients in each group developed a grade 1 abnormality (> 0.5 mg/dL increase from baseline) through week 24. The majority of the grade 1 abnormalities observed through the safety cut off date were isolated. Only one patient discontinued for persistent grade 1 creatinine elevations. Less than one percent of patients in the tenofovir group developed a grade 2 abnormality. No patients developed a grade 3 or 4 serum creatinine abnormality.

At the time of the safety update cut off, a total of 32 patients (5%) had a grade 1 creatinine abnormality. Of the 32 patients with a grade 1 abnormality, 18 (3%) had serum creatinines >1.5 mg/dL, with a maximum of 1.9 mg/dL. The majority of patients had an isolated grade 1 creatinine abnormality. Eight patients had a grade 1 abnormality on ≥ 2 study visits. No grade 3 or 4 abnormalities were reported.

Figure 6 is a scatterplot displaying creatinine data on the y-axis (TSTVALN) and study duration on the x-axis (_STDDAYS_). Based on this analysis, the incidence and severity of creatinine abnormalities did not appear to worsen with increasing duration of tenofovir treatment.

Figure 6:



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Study 908:

Changes from baseline through week 48 for serum creatinine were minimal. The median change from baseline through week 48 ranged from -0.3 mg/dL to 0.10 mg/dL. Thirty-three (11%) patients developed a grade 1 abnormality. Fourteen (42%) were isolated events. Approximately half of the grade 1 abnormalities remained in the normal range (< 1.5 mg/dL). Two patients discontinued tenofovir due to a grade 1 serum creatinine increase. Both of these events resolved. Three patients (<1%) developed a grade 2 abnormality. One patient developed an isolated grade 2 event. The second patient developed a grade 2 event at week 28, no follow up data was available. Follow up data was available for the third case and this event was most likely due to amphotericin B treatment and not tenofovir. Similarly, two patients (<1%) developed a grade 3 abnormality. One case was an isolated event and the other occurred at week 8, but no follow up data was available.

In the safety update the incidence of grade 1 creatinine abnormalities increased from 11% to 16%. A comparison of the creatinine abnormalities from the original NDA and the safety update are summarized in Table 10.8.4.D. Overall two patients discontinued for a grade 2 and 3 creatinine abnormality. The remaining grade 2 and 3 creatinine abnormalities were considered isolated events.

Table 10.8.4.D. Creatinine Abnormalities: Study 908

	Original NDA Submission Tenofovir 300 mg (N=291)	Safety Update Tenofovir 300 mg (N=291)
Grade 1 (≥ 0.5 mg/dL increase from baseline)	33 (11%)	49 (16%)
Grade 2 (2.1-3 mg/dL)	2 (<1%)	6 (2%)
Grade 3 (3.1-6.0 mg/dL)	2 (<1%)	4 (1%)
Grade 4 (> 6 mg/dL)	0	0

10.8.4.2 Phosphate:

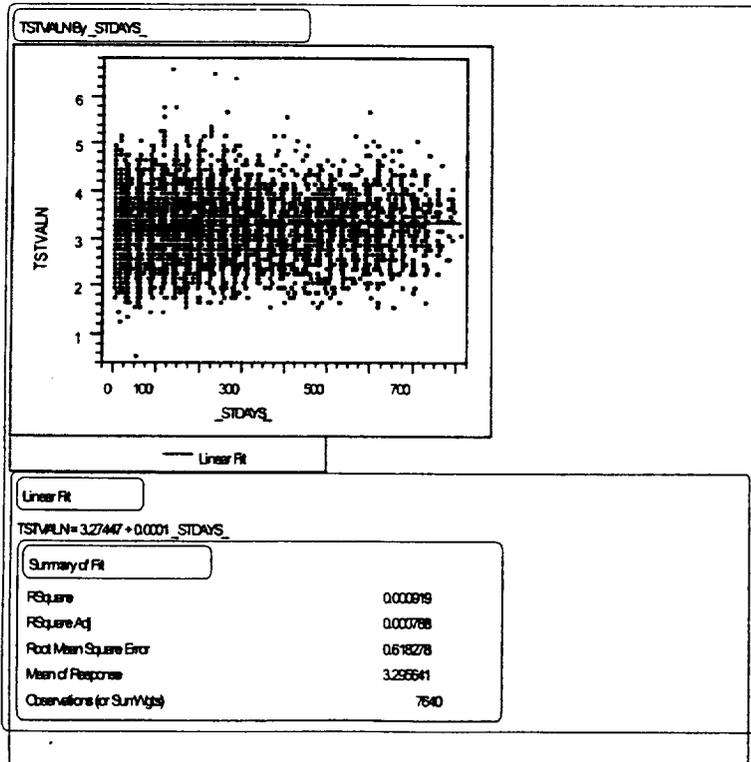
Through week 24, there was a slightly higher incidence of grade 2 hypophosphatemia in the tenofovir group compared to placebo. Phosphorus abnormalities occurred sporadically throughout the course of treatment in studies 902 and 907, and generally resolved without treatment interruption. Of the 62 patients with a grade 2+ phosphate abnormality, 51 (82%) patients had an abnormal value at only one visit. The abnormality was resolved by the subsequent visit. Ten patients had a sustained (2 consecutive values) grade 2 abnormality. One patient had 3 consecutive grade 2 values. Four patients developed a grade 3+ phosphate abnormality. One of these patients had a grade 3 abnormality at baseline. For the other patients with a grade 3+ abnormality, the abnormality resolved within 10 days without treatment interruption. The grade 4 event was an isolated event, the repeat test failed to confirm the grade 4 abnormality. Table 10.8.4.2.A summarizes the phosphorus data in studies 902 and 907.

Table 10.8.4.2.A: Phosphate Abnormalities: Studies 902 and 907

	Original NDA Submission			Safety Update
	Placebo (N=210) (weeks 0-24)	Tenofovir (N=443) (weeks 0-24)	All Tenofovir (N=687)	All Tenofovir (N=687)
Mean change from baseline (range)	0.07 mg/dL	0.04 mg/dL	0.07 mg/dL	ND
Grade 1 (2-2.2 mg/dL)	10 (5%)	27 (6%)	43 (7%)	51 (7%)
Grade 2 (1.5-1.9 mg/dL)	5 (2%)	28 (6%)	48 (7%)	58 (8%)
Grade 3 (1-1.4 mg/dL)	1 (<1%)	0	2 (<1%)	3 (<1%)
Grade 4 (< 1 mg/dL)	0	1 (<1%)	1 (<1%)	1 (<1%)

There is concern that hypophosphatemia may develop with prolonged tenofovir use. In study 902, the incidence of grade 2 hypophosphemia increased from 9% in the blinded phase to 19% in the open-label phase. This finding may be due to chance and not to tenofovir treatment, in that the probability of finding an isolated abnormality increases with increasing numbers of data points. To further investigate this issue, FDA pooled all available phosphorus data in studies 902 and 907. Figure 7, is a scatterplot displaying phosphate data on the y-axis and study duration on the x-axis. Based on this analysis, the incidence and severity of phosphate abnormalities did not worsen with increasing duration of tenofovir treatment. This finding is important because it is thought that the mechanism for bone abnormalities may be mediated via renal phosphate wasting or decreases in intestinal absorption of phosphate.

Figure 7:



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Study 908:

The incidence of phosphate abnormalities in study 908 was similar to that observed in studies 902 and 907 (see Table 10.8.4.2.B). The majority of the grade 1 and 2 abnormalities resolved while the patient remained on study drug. Six patients developed a grade 3 abnormality. One of these patients had a grade 2 abnormality at baseline. All six patients had a phosphate value that was normal or a decreased grade (grade 2) at the last available assessment prior to data cut off. Two events resolved while on study, and two events resolved during study drug interruption. One patient developed a grade 4 abnormality. Phosphate was within normal limits until week 32 when the phosphate level decreased to 0.7 mg/dL. The patient discontinued study and no follow up data were available.

Table 10.8.4.2.B: Phosphate Abnormalities: Study 908

	Tenofovir (N=291)
Grade 1 (2-2.2 mg/dL)	23 (8%)
Grade 2 (1.5-1.9 mg/dL)	30 (10%)
Grade 3 (1-1.4 mg/dL)	6 (2%)
Grade 4 (< 1 mg/dL)	1 (<1%)

10.8.4.3 Bicarbonate:

No significant changes in bicarbonate levels associated with tenofovir use was observed in studies 902 and 907. No grade 3 or 4 decreases in bicarbonate were reported through 24 weeks. The incidence of grade 1 or 2 decreases in bicarbonate was similar for both groups and ranged from approximately 1-2%.

In study 908, no grade 3 or 4 decreases in bicarbonate were observed. The incidence of grade 1 or 2 decreases was slightly higher (4%) than in studies 902 and 907 (1-2%).

10.8.4.4 Proteinuria:

No grade 3 or 4 cases of proteinuria were observed in studies 902 and 907 through week 24. The incidence of grade 1 or proteinuria was similar for placebo and tenofovir groups. Low grade proteinuria is difficult to assess in that small fluctuations are common in HIV + individuals. Overall no significant changes in urine protein was noted.

Of note, one patient (902) prematurely discontinued study drug secondary to proteinuria. Renal function tests and electrolytes (serum creatinine, BUN, phosphorus and bicarbonate) remained within normal limits throughout the study. It is unclear if tenofovir use contributed to proteinuria.

In study 908, no patients developed grade 3+ proteinuria. Grade 1 and 2 urine protein values were common, 24% and 29%, respectively.

Safety Summary:

Treatment with tenofovir appears to be well tolerated. The safety profile of tenofovir 300 mg did not change significantly with extended dosing. The most common events reported were asthenia (19%), headache (14%), diarrhea (22%), nausea (20%) and pharyngitis (18%). More patients randomized to tenofovir compared to placebo experienced GI events; including diarrhea (22% vs 17%), flatulence (6% vs 2%), nausea (20% vs 15%) and vomiting (12% vs 6%). Overall, 2% of patients in the placebo and tenofovir groups prematurely discontinued study due to adverse events through week 24.

Grade 3 or 4 laboratory abnormalities were similar between placebo and tenofovir groups. Discontinuations due to laboratory abnormalities were infrequent. During the first 24 weeks, four patients (2%) and 2 patients (<1%) discontinued from the placebo and tenofovir groups, respectively due to a laboratory abnormality.

Overall there did not appear to be any significant renal events that could be clearly attributed to tenofovir use. The incidence and severity of creatinine and phosphate abnormalities did not worsen with increasing duration of tenofovir treatment. With respect to phosphate abnormalities, this finding is important because it is thought that the mechanism for bone abnormalities may be mediated via renal phosphate wasting or decreases in intestinal absorption of phosphate.

Regarding bone abnormalities, no clinically significant changes in phosphate, calcium, PTH or BMD were observed over time; however PTH and BMD data were only available for a limited number of patients. No obvious increases in fractures were seen over time. However insufficient number of patients receiving tenofovir for prolonged duration and lack of a control arm past week 24 make it difficult to conclude whether or not treatment with tenofovir will cause clinical fractures over time or if the risk will increase over time. This safety concern will be further characterized in the applicant's two year blinded confirmatory trial.

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11 Review of Package Insert

The package insert and patient package insert underwent several revisions from the initial proposed inserts included in the May 1, 2001 submission. Selected pertinent revisions are highlighted below.

BOX WARNING:

The following BOX WARNING was included in the label. This warning is consistent with nucleoside reverse transcriptase inhibitor package inserts. The rationale for inclusion of the Box Warning is as follows:

- Although *in vitro* studies may suggest a lack of mitochondrial toxicity, it is unclear if these results are predictive *in vivo*
- Case reports of lactic acidosis in clinical trials and expanded access program
- Tenofovir is considered to function as a nucleoside analogue and therefore should carry the same class warnings as other NRTIs

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

INDICATIONS AND USAGE:

Based on the discussion at the advisory committee meeting, specifically the limited efficacy data in antiretroviral naïve patients and potential for long term bone effects, the following indication was included.

VIREAD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in a controlled study of VIREAD of 24 weeks duration and in a controlled, dose ranging study of VIREAD of 48 weeks duration. Both studies were conducted in treatment experienced adults with evidence of HIV-1 viral replication despite ongoing antiretroviral therapy. Studies in antiretroviral naïve patients are ongoing; consequently, the risk-benefit ratio for this population has yet to be determined.

Additional important information regarding the use of VIREAD for the treatment of HIV infection:

- There are no study results demonstrating the effect of tenofovir on clinical progression of HIV.
- The use of VIREAD should be considered for treating adult patients with HIV strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history. (See Description of Clinical Studies)

Description of Clinical Studies

Based on recommendations from the advisory committee, results from studies 902 and 907 with regard to baseline genotype and phenotype were included in tabular format. Specifically, HIV RNA responses by zidovudine associated mutations and by baseline VIREAD susceptibility were included in this section.

WARNINGS:

Please refer to the BOX WARNING section for rationale for inclusion of the lactic acidosis/severe hepatomegaly with steatosis warning.

Therefore, the Division of Antiviral Drug Products feels that all approved antiretrovirals should include information on fat redistribution in the package insert

- In studies 902 and 907, 2.7% of patients receiving tenofovir 300 mg developed fat redistribution, in varying degrees. Nine cases (2%) were considered to be possibly or probably related to tenofovir use.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Bone and Renal Toxicity:

The following sections regarding results from animal studies with respect to bone effects and renal toxicity and clinical monitoring for these effects were also included in the PRECAUTION section.

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) between 6 and 12 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. 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(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2-20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Clinical Monitoring For Bone and Renal toxicity

It is not known if long term administration of VIREAD (> 1 year) will cause bone abnormalities. Therefore if bone abnormalities are suspected then appropriate consultation should be obtained.

Although tenofovir-associated renal toxicity has not been observed in pooled clinical studies for up to one year, long term renal effects are unknown. Consideration should be given to monitoring for changes in serum creatinine and serum phosphorus in patients at risk or with a history of renal dysfunction.

12 REGULATORY RECOMMENDATION

Based on the data submitted by Gilead Sciences, it is recommended that this application receive an approval action. The information contained in this application fulfills the intent of the accelerated approval regulations. The results from 4 clinical trials in adults receiving tenofovir DF tablets clearly demonstrate a favorable safety and efficacy profile for patients with HIV-1 infection.

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Division of Antiviral Drug Products