Application for Inclusion of Tenofovir Disoproxil Fumarate (TDF) On WHO Model List of Essential Medicines

Submitted By

Gilead Sciences, Inc.
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Application for Inclusion of TDF on WHO Model List of Essential Medicines

Drug is a member of the therapeutic class of HIV nucleoside analogue reverse transcriptase inhibitors (NRTIs)

1. Summary statement of the proposal for inclusion, change or deletion:

TDF is proposed for inclusion in the WHO Model List of Essential Medicines in combination with other antiretroviral agents for the treatment of HIV-1 infection. TDF was pre-qualified and listed in the 31st edition of the World Health Organization (WHO) List of Pre-qualified HIV/AIDS Drugs.

Limited resources in the developing world mandate a specific set of characteristics for antiretroviral (ARV) regimens. Oftentimes the isolated local clinics and hospitals require a regimen that is reliable, potent, and durable. The infrequent use of resistance testing and the potential for multi-drug resistant HIV infection necessitate a regimen that has a predictable and favourable resistance profile. Further, the shortage of medical staff and the need for HIV-infected individuals in the developing world to lead productive lives demand a regimen that is tolerable and safe.

TDF has demonstrated effectiveness in a wide variety of patients initiating their first ARV regimens. The co-administration of TDF with another nucleoside reverse transcriptase inhibitor (NRTI) and a non-NRTI (NNRTI) or protease inhibitor (PI) is associated with low rates of resistance, limited cross-resistance, and multiple successful second-line regimens. TDF may help improve adherence, as it is dosed as one tablet taken once-a-day in combination therapy. In addition, TDF has been shown to be well-tolerated and safe in long term studies.

The endorsement by the WHO of Triommune (stavudine [d4T] + lamivudine [3TC] + nevirapine [NVP]) as the most suitable regimen for initial therapy was made before the availability of TDF. A more recently revised guideline, the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents issued by the United States Department of Health and Human Services (DHHS) was updated in May 2006[1], and the International AIDS Society-USA (IAS) Treatment Recommendations for Adult HIV Infection was updated in July 2004.[2] Both of these guidelines recommend that TDF should be a component of first line ARV regimens containing efavirenz (EFV)[1] and/or a boosted PI.[2]

In resource-poor settings, the decision of which ARV therapy to utilize must be based on the expectation of a favourable outcome in addition to access price. The use of a TDF-containing regimen has demonstrated a more favourable safety and efficacy profile than regimens containing d4T.[1] Therefore, we propose that TDF tablet, approved by the US Food and Drug Administration (FDA) in 2001, be included on WHO Model List of Essential Medicines.

2. Name of the focal point in WHO submitting the application:

Charlie Gilks
HIV/AIDS Department
World Health Organisation

3. Name of the organization(s) consulted and/or supporting the application:

Not Applicable

4. International Nonproprietary Name:

tenofovir disoproxil fumarate

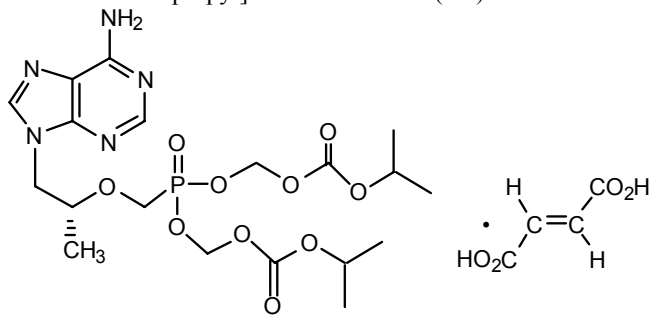
5. Formulation proposed for inclusion:

The formulation of tenofovir DF tablet is provided below.

Active Ingredient

Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. Please see Table 1 below for a listing of the active ingredients of the tenofovir DF tablet.

Table 1: Active Ingredients of the Tenofovir DF Tablet

Approved name	*Chemical name, structural and molecular formulae*	*Specification or Reference of such*	*Qty per tablet*	*Batch Qty**	*Purpose of Inclusion*
Tenofovir disoproxil fumarate	9-[(R)-2-[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy] propyl]adenine fumarate (1:1)  $C_{23}H_{34}N_5O_{14}P$	In-house	300 mg[a]	325 – 600 kg	Active

[a] Equivalent to 245 mg of tenofovir disoproxil.
The formula weight of tenofovir disoproxil fumarate ($C_{23}H_{34}N_5O_{14}P$) is 635.52, and the formula weight of tenofovir disoproxil ($C_{19}H_{30}N_5O_{10}P$) is 519.45.

$$300 \text{ mg tenofovir disoproxil fumarate} = 300 \text{ x } \frac{519.45}{635.52} \text{ tenofovi r disoproxil}$$

$$= 245 \text{ mg tenofovir disoproxil}$$

* Commercial batch size of the drug product varies depending on manufacturing site.
Altana: 325 kg
Patheon: 360 kg
Aspen: 600 kg

6. International availability:

TDF tablets will be manufactured, for Gilead Sciences, Inc., at any of the following facilities listed below (Table 2). A supplement to the US new drug application (NDA) to add Aspen Pharmacare as a manufacturing, packaging, and labelling site for TDF tablets submitted to the US FDA in April 2006, and approval is anticipated in the third quarter of 2006. In addition, a supplement providing for San Dimas to package TDF was submitted to the FDA on May 16, 2006, and approval is anticipated in the third quarter of 2006. All other sites listed are currently approved and listed in the US NDA.

The manufacturing steps conducted at all facilities are in compliance with European Union (EU) and US FDA Good Manufacturing Practices (GMP) guidelines.

Table 2: Manufacturing Facilities for Tenofovir DF Tablet

	Name	Manufacturing Plant Address*	Activity
1	Patheon, Inc.	2100 Syntex Court Mississauga, Ontario Canada L5N 7K9	Manufacturing, packaging, labelling and testing
		977 Century Drive Burlington, Ontario Canada L7L5J8	Testing
2	Altana Pharma Oranienburg GmbH	Lehnitzstrasse 70-98 16515 Oranienburg Germany	Manufacturing, packaging, labelling and testing
3	Cardinal Health Germany 405 GmbH	Steinbeisstrasse 2 D-73614 Schorndorf Germany	Packaging and labelling
4	Gilead Sciences, Limited	13 Stillorgan Industrial Park Blackrock Co. Dublin Ireland	Packaging, labelling, testing and release

7. Listing Type Requested:

Listing is requested on the Model List of Essential Medicines as an example of the therapeutic class of HIV NRTI. Other members of this class of drugs may serve as alternatives, depending on quality, price and local availability.

8. Information supporting the public health relevance of the submission:

8.1 Epidemiological information on disease burden

Since the first clinical evidence of acquired immune deficient syndrome (AIDS) was reported over 25 years ago, an estimated 25 million people have died as a result of HIV infection, making it one of the most destructive epidemics in recorded history.[2] In 2005, there were an estimated 3.1 million deaths due to AIDS. Current estimates suggest that some 40.3 million people worldwide are infected with HIV, up from an estimated 37.5 million in 2003, and twice as many as compared to 1995. In 2005, it is estimated that an additional 4.9 million individuals worldwide became infected with HIV, and 700,000 of these new infections were in children <15 years of age.

Of major concern is the prevalence of HIV/AIDS in developing countries. Approximately 95% of all HIV-infected people live in low- and middle-income countries.[3] Although there is new evidence that adult HIV infection rates have decreased in certain countries, the overall trends in HIV transmission are still increasing, and the overall number of people living with HIV has continued to increase in all regions of the world except the Caribbean.[4] The steepest increases in HIV infections have occurred in Eastern Europe and Central Asia, and in East Asia. In

Eastern Europe and Central Asia, there was a 25% increase in the number of people living with HIV (to 1.6 million) since 2003, and AIDS death rates almost doubled (to 62,000) during that time.[2] In East Asia, there was a 20% increase in the number of people living with HIV (to 870,000) since 2003. However, the worst affected area is Sub-Saharan Africa, with 64% of new infections (3.2 million) occurring here and with an estimated 2.4 million who died of HIV-related illnesses in 2005.[2,4]

The proportion of women who are affected by the epidemic continues to increase.[5] As of 2003, women accounted for nearly 50% of all people living with HIV worldwide.[5] In 2005, 17.5 million women were living with HIV, which is one million more than in 2003.[2] HIV infection levels among pregnant women vary widely in different countries, but levels often exceeding 30% have been recorded in some regions of Southern Africa.[2] Without HIV prevention measures, about 35% of children born to HIV-positive women will contract the virus.[2] In many countries, life expectancy and child survival rates have plummeted. For example, in seven African countries where HIV prevalence is >20%, the average life expectancy of a person born between 1995 and 2000 is now 49 years, which is 13 years lower than in the absence of AIDS.[5]

In countries already burdened by huge socio-economic challenges, HIV/AIDS threatens human social welfare, developmental progress and social stability on an unprecedented scale. HIV/AIDS continues to cripple the economic development of entire countries, because it often strikes people during their most productive period of life.[6] For example, of the 14,000 persons who became infected each day in 2005, about 12,000 (86%) were aged 15 to 49 years.[3] Overall, young people aged 15 to 24 years account for about half of all new HIV infections per day worldwide.[3] The introduction of potent ARV agents and the combined use of these drugs have markedly reduced the replication of HIV in many patients, and improved survival rates. Highly active antiretroviral therapy (HAART) is now the standard of care in the treatment of HIV infection. It is successful in reducing HIV RNA viral load, extending the asymptomatic phase of infection, and improving the quality of life for many infected individuals.[7]

8.2. Assessment of current use

The primary goals of ARV therapy are maximal and durable suppression of HIV RNA viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[8] Suppression of viral load as much as possible, for as long as possible, is an important and achievable goal of ARV therapy. However, this goal must be balanced against the need to preserve effective treatment options. The presence of breakthrough resistant (virus) mutations in treatment-experienced patients is a strong predictor of virologic failure and disease progression.

An emerging challenge in regard to the successful long-term management of HIV/AIDS is the increasing prevalence of drug resistance. The prevalence of HIV-1 drug resistance has been assessed in several studies. Early studies of US HIV-1 infected patients such as the HIV-1 Cost and Services Utilization study (1996-1999) indicated that resistance could be detected in 76% of viremic patients with >500 copies/ml of HIV-1 RNA with resistance to NRTIs, NNRTIs and PIs being detected in 71%, 25% and 41% of patients, respectively. [9] Surveys of large genotyping laboratory databases such as LabCorp and Monogram Biosciences have also evaluated the

prevalence of resistance in more recent years. In the LabCorp database of 37,924 US patient samples collected in 2002, the most frequent NRTI mutations detected included M184V/I (41% of patients), thymidine analogue mutations (TAMs) (11.3%) and a low but increasing frequency of K65R (1.7%). NNRTI mutations such as K103N and Y181C were found in 30% and 12% of patients respectively whereas PI mutations such as L90M, V82A and D30N were found in 15%, 8% and 6% of patients respectively.[10] This latter study included patients with repeat samples, however, in studies of the Monogram Biosciences database in which >16,000 individual US patient reverse transcriptase (RT) genotypes from 2003 were characterized, similar frequencies of NRTI mutations were observed.[11] Thus, there is now a significant proportion of HIV-1 infected patients carrying drug resistant viruses; development of resistance leads to decreased susceptibility to other NRTIs through cross-resistance, which limits viable treatment options.

As more HIV-1 patients are treated for longer periods of time, the transmission of drug resistant HIV-1 in newly diagnosed patients who are otherwise naïve to ARV treatment is also increasing. Current estimates are that approximately 10%-20% of treatment-naïve and recently infected patients in Western nations have been infected with drug-resistant virus as has been documented in several studies during the period 1996-2001.[12] A recent US study of 1,082 treatment-naïve HIV-1 patients found a prevalence of 8.3% of patients with any transmitted resistance, predominantly to NRTIs.[13] Two studies of recent European seroconverters have identified 9.6%[14] and 10.3%[15] of ARV therapy naïve patients as having transmitted primary resistance. Both studies showed that more recently infected patients were significantly more likely to have primary drug resistance than those who had been infected for more than one year, suggesting that the incidence of transmitted drug resistance is rising or it is underestimated in patients who have been chronically infected for longer periods of time, due to reversion.

The development and transmission of resistance-conferring mutations is also associated with a sub-optimal virologic response to initial ARV therapy.[16] Recent clinical trials such as study GS-01-934 have highlighted the importance of baseline resistance on response to ARV therapy. In this study of emtricitabine (FTC) + TDF + EFV versus 3TC/zidovudine(AZT) + EFV, NNRTI resistance was present at baseline in 4.3 % of ARV naïve patients enrolled in the study, and regardless of the treatment arm, was significantly associated with a poorer response to EFV-based therapy and was associated with development of additional resistance mutations to both NNRTIs and NRTIs.[17] Cross-resistance compromises the availability of future treatment options for subsequent courses of therapy in the aftermath of drug resistance. Furthermore, the extent of cross-resistance has also been shown to increase commensurate with the accumulation of additional drug resistance mutations.[18]

Taken together, these findings point to the urgent need for novel and improved ARV agents. These agents should have higher genetic barriers for the development of drug resistance and a broad spectrum of antiviral activity against HIV-1 strains harbouring resistance mutations in reverse transcriptase that confer diminished susceptibility to several of the currently licensed NRTIs. Current treatment strategies and guidelines recommend selecting potent regimens from all currently available classes of ARVs to maximise suppression of viral load and to minimise the replication and emergence of drug-resistant virus.

8.3.Target population

In contrast to earlier examples regarding developing countries, an estimated 1.6 million people are living with HIV in high income countries.[5] It is primarily in these high income countries where standards of treatment and care have evolved considerably.[19] For example, in the US, the age-adjusted HIV death rate declined by 70% between 1995 and 2002, largely due to the introduction of HAART therapy.[20]

Although the number of people in low- and middle-income countries receiving HIV ARV therapy has tripled since the end of 2001, overall access to ARV treatment and other HIV-related disease care remains low.[2,5] In order to improve access to treatment, several Latin American and Caribbean countries (including Argentina, Barbados, Chile, Costa Rica, Cuba, Mexico, and Uruguay) now offer universal coverage for ARV treatment.[5] In Brazil, the government estimates that the policy of universal access to ARV drugs has saved USD 2.2 billion in hospital care that would have otherwise been needed by people living with HIV.[5]

Other programs, such as the United Nation AIDS (UNAIDS) Drug Access Initiative Pilot Program and the WHO/UNAIDS "3 by 5 Initiative," are designed to increase ARV access to people in low- and middle-income countries.[19] Since its launch in 2003, ARV therapy coverage in these countries has more than doubled to about 1 million people in June 2005. Similarly, the UNAIDS Drug Access Initiative Pilot Program provided ARV therapy to the public sector in four low- and middle-income countries in the late 1990s.[19] The success of these, and other programs, has demonstrated that it is viable to treat people with HIV/AIDS in these environments.

9. Treatment details:

Recommended Dosage:
Adult: The dose of TDF in adults is 300 mg once daily (QD) taken orally in combination with other ARV agents, without regard to food.

Children: The safety and efficacy of TDF in patients under the age of 18 years have not been established.

Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal Insufficiency: Tenofovir is eliminated by renal excretion, and the exposure to tenofovir increases in patients with renal dysfunction. Dosing interval adjustment is required in all patients with creatinine clearance (CrCL) <50 ml/min, as detailed below. No safety and efficacy data are available in patients with renal dysfunction who received TDF using these guidelines in Table 3.

Table 3: Dosing Interval Adjustment in Patients with Renal Impairment

	Creatinine Clearance (ml/min)[a]			Haemodialysis Patients
	≥ 50	30-49	10-29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Twice a week	Every 7 days, or after a total of approximately 12 hours of dialysis[b]

[a]Calculated using ideal (lean) body weight.
[b]Generally once weekly assuming three haemodialysis sessions a week of approximately 4 hours duration. Tenofovir DF should be administered following completion of dialysis.

Hepatic impairment: Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Therefore, no dose adjustment is required in patients with hepatic impairment.

Concomitant ARV Therapy: TDF must be given in combination with other ARV medications.

Duration: ARV treatment is usually regarded as life-long, with the exceptions of post-exposure prophylaxis, and for the prophylaxis of infants of HIV-infected mothers.

Guidelines: TDF is an approved ARV agent included in the 2002 "WHO Antiretroviral Guidelines for Resource Limited Settings". In the "2006 U.S. DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents", TDF in combination with EFV and 3TC is recommended as a preferred first-line NNRTI-based regimen for treatment-naïve patients.[8] In addition, the International AIDS Society (IAS) recommends TDF as 1 of the preferred NRTIs in its 2004 guidelines.[21] The preferred regimens were selected by experts based on the totality of virologic, immunologic, and toxicity data of clinical trial results as well as pill size and burden, dosing frequency, food requirements, and potential for drug-drug interactions.

Special Requirements: Adequate resources for monitoring and specialist oversight are a pre-requisite for the introduction of this class of drugs.

10. Comparative effectiveness in clinical settings:

10.1. Identification of clinical evidence

In compiling the evidence for this drug, a search of several databases, including MEDLINE®, EMBASE®, BIOSIS Previews®, Current Contents/Clinical Medicine, and Current Contents/Life Sciences was conducted. We have also included data from trials that provided data and insights that may not normally be available from systematic reviews.

Details of literature searches conducted

The databases searched were:

- MEDLINE®
- EMBASE®
- Current Contents/Clinical Medicine
- Current Contents/Life Sciences
- BIOSIS Previews®

Search terms included:

- Tenofovir
- GS4331
- PMPA
- Viread

Study selection:

- Randomized, Phase 3 pivotal clinical trials that compared TDF to d4Tor TDF plus FTC to Combivir® in treatment-experienced patients, or clinical trails with TDF added on in treatment-experienced virologically failure patients.
- Other clinical studies that examined TDF-containing ARV regimens in HIV-infected patients

10.2. Summary of available data

TDF is indicated, in combination with other ARV agents, for the treatment of HIV-1 infected adults over 18 years of age. TDF is an oral prodrug of tenofovir, a novel acyclic nucleotide analogue with activity *in vitro* against HIV-1 and HIV-2.

ARV therapy requires combined potent and sustained efficacy with acceptable tolerability and practical dosing regimens. TDF exhibits distinct biological characteristics that help meet these requirements.

Potent antiviral activity *in vivo* results from efficient intracellular activation to the active metabolite, tenofovir diphosphate. Following absorption, TDF is rapidly converted to tenofovir which is metabolised intracellularly to tenofovir diphosphate by constitutively expressed cellular enzymes through only two phosphorylation reactions. The production of the active tenofovir diphosphate is catalysed by adenylate kinase and nucleotide diphosphate kinase which are highly active and ubiquitous, being present in activated cells as well as non proliferating lymphocytes and macrophages. This is in contrast to the main phosphorylator of d4T and AZT, thymidine kinase, which is present only in very low levels in non activated cells. Tenofovir diphosphate efficiently inhibits both RNA- and DNA-directed HIV-1 RT activity.[16] It competes with dATP for incorporation into DNA and, since it lacks a 3' hydroxyl group, causes premature termination of DNA synthesis upon its incorporation into the nascent DNA chain. Tenofovir diphosphate has a prolonged intracellular half-life ranging from 12 to 50 hours, which allows for once daily dosing. Simplifying HIV treatment regimens using once daily antiretroviral drugs may improve adherence and therapeutic outcomes.[17, 18]

A unique resistance profile has been established with activity against wild type and most nucleoside-resistant HIV. In pre-clinical studies, the K65R mutation in RT was selected by tenofovir *in vitro* resulting in a three- to four-fold decrease in susceptibility to tenofovir.[19] As observed in the clinical trials of TDF (see below), K65R emerges infrequently (< 3%) during long-term treatment with TDF.

The principal clinical studies that demonstrate the clinical efficacy of TDF 300 mg QD in treatment-naïve and treatment-experienced HIV-infected patients are described in the following sections. Additional details are provided in Attachment 1.

Efficacy in Treatment-Naïve HIV-1 Infected Patients

Clinical efficacy in ARV treatment-naïve HIV-infected patients has been demonstrated based on significant changes in established and validated surrogate markers for HIV-1 disease (plasma HIV-1 RNA levels) and immune competence (CD4 cell count), following up to 192 weeks of treatment with TDF in combination with 3TC and EFV.

Study 903

Study 903 was a Phase 3, randomized, double-blind, active-controlled, multicenter clinical trial designed to compare the efficacy and safety of TDF (300 mg QD) tod4T (40 mg for ≥60 kg or 30 mg for <60 kg twice daily [BID]) with a background regimen of 3TC (150 mg BID) and EFV (600 mg QD) in 600 treatment-naïve HIV-infected individuals.[1,22] At baseline, the median plasma HIV RNA level was 77,600 copies/mL (range: 417-5,130,000) and the mean CD4 cell count was 279 cells/mm^3 (range: 3-956). Patients had a mean age 36 years (range: 18-64), 26% were female, 36% were non-Caucasian, and 20% were black. Patients were stratified by baseline HIV RNA and CD4 count. Forty-three percent of patients had baseline HIV RNA >100,000 copies/mL and 39% had CD4 cell counts <200 cells/mm^3. While Gallant et al. (2004)[1] has presented results of this study based on intent-to-treat (ITT) analysis, 48- and 144-week treatment outcomes that are described in the TDF U.S. Prescribing Information are based on time to loss of virologic response (TLOVR) analysis (Table 4).

Table 4: Outcomes of Randomized Treatment in Study 903[1,22]

Outcomes	At Week 48		At Week 144	
	TDF (n = 299)	d4T (n = 301)	TDF (n = 299)	d4T (n = 301)
	%	%	%	%
TLOVR Analysis				
Responder*	79%	82%	68%	62%
Virologic failure†	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons‡	8%	7%	14%	15%
ITT Analyses				
M = F, antiretroviral Switch = F analysis§				
HIV RNA <400 copies/mL	79.9%	84.1%	70.6%	64.1%
HIV RNA <50 copies/mL	76.3%	79.7%	67.9%	62.5%
M = F analysis§				
HIV RNA <400 copies/mL	86.6%	87.0%	76.3%	72.1%
HIV RNA <50 copies/mL	81.6%	81.1%	73.2%	69.4%

Abbreviations: TDF, tenofovir disoproxil fumarate; d4T, stavudine; TLOVR, time to loss of virologic response; ITT, intent-to-treat; M = F, missing = failure

*Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48 and 144.

†Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.

‡Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.

§For Week 48, there were missing data for 27 patients in the TDF group and 28 patients in the d4T group. For Week 144, there were missing data for 57 patients in the TDF group and 64 in the d4T group

Achievement of plasma HIV RNA <400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV RNA concentration (> or ≤100,000 copies/mL) and CD4 cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of patients in the TDF and d4T arms, respectively, achieved and maintained confirmed HIV RNA <50 copies/mL. The mean increase from baseline in CD4 cell count was 263 cells/mm^3 for the TDF arm and 283 cells/mm^3 for the d4T arm.[22]

At the end of 96 weeks of treatment, the K65R mutation occurred in 2.7% (n = 8; 7 within 48 weeks) of the patients enrolled into the TDF arm compared to 0.7% (n = 2) of those enrolled into the d4T arm (*P* =.06). No additional cases of the K65R mutation were observed in either arm at Week 144. EFV- or both EFV- and 3TC-resistance mutations preceded or were coincident with the development of K65R in all cases; from both the genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir.[1,22-25] All patients began a new treatment regimen with a PI and other NRTIs. After a median follow up period of 155 weeks, 5 patients, including 2 who remained on TDF, achieved HIV RNA <50 copies/mL. Two patients were without follow up and 1 was non-adherent.[1,23,25] Based on an *in vitro* study, there appears to be a possible fitness barrier for the K65R mutant HIV *in vivo*.[26] This may help explain the low prevalence of K65R among antiretroviral-experienced patients (<2%),[27,28] as well as its low frequency of development in TDF-treated patients and lack of viral load rebound upon development.

Study 903 Extension Phase

After completing the Study 903 144-week phase, an additional 192-week, open-label, extension phase (903E) studying TDF+3TC+EFV QD regimen (3TC BID was switched to QD) has been occurring, in which 86 patients who were originally randomized into the TDF arm have continued on TDF, while 85 patients originally randomized into the d4T arm have switched to the TDF regimen. The 86 patients originally enrolled in the TDF arm have been on TDF-containing HAART for a median duration of 201 weeks (range: 156-213) with a mean±standard deviation (SD) HIV RNA level of 4.86±0.6 $\log_{10}$ copies/mL (range: 3.12-6.45) and CD4 cell count of 299±188 cells/mm^3 (range: 6-838) at baseline.[29]

Based on ITT (missing = failure) analysis, results at Week 192 revealed that 87% and 91% of the patients achieved HIV RNA <50 and <400 copies/mL, respectively. When using the ITT (missing = excluded) analysis, 92% and 95% of the patients achieved HIV RNA <50 and <400 copies/mL, respectively (Figures 1 and 2). In addition, based on the ITT (missing = excluded) analysis, CD4 cell count increased by a mean of 391 cells/mm^3 at Week 192.[29]

Figure 1: Percentages of Patients with HIV RNA <400 copies/mL Through Week 192[29]

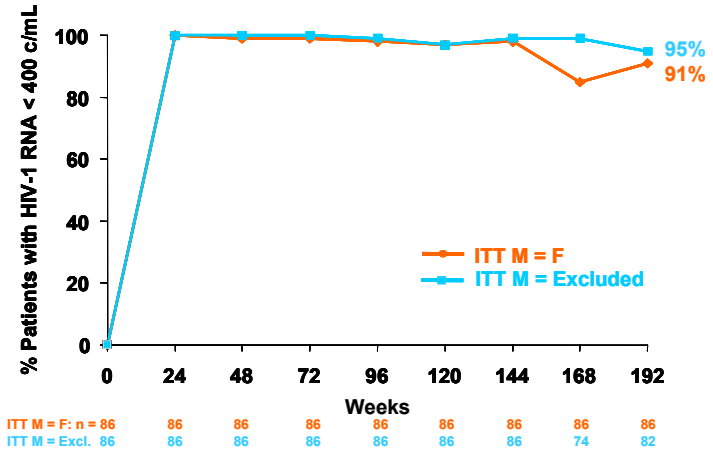
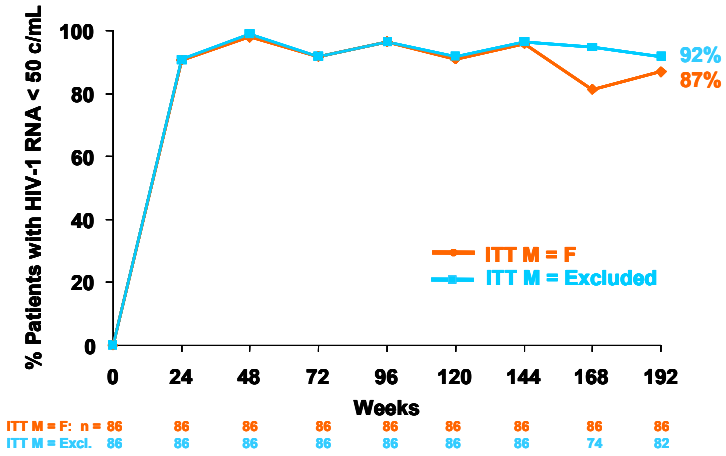


Figure 2: Percentages of Patients with HIV RNA <50 copies/mL Through Week 192[29]



Of the 85 patients who switched from d4T to TDF, they had been on d4T for a median duration of 152 weeks.[30] At the time of switch, 99% and 100% of the patients had HIV RNA <50 and <400 copies/mL, respectively, with a mean±SD CD4 cell count of 650±270 cells/mm^3 (range: 171-1,637). Two patients withdrew consent and discontinued from the study prior to Week 24.

Forty-eight weeks after switching to TDF, HIV RNA <400 and <50 copies/mL was maintained in 99% and 94% of the patients, respectively, based on the ITT (missing = failure) analysis. Based on the ITT (missing = excluded analysis), the corresponding rates were 97% and 92%.[30]

Study 934

This ongoing Phase 3, randomized, open-label, active-controlled, multicenter, 144 week non-inferiority study is designed to evaluate the safety and efficacy of a QD regimen containing FTC 200 mg + TDF 300 mg plus EFV 600 mg vs. 3TC 150mg/AZT 300 mg BID plus EFV 600 mg QD in treatment-naïve HIV-infected patients with HIV RNA >10,000 copies/mL.[22,31,32] A total of 511 patients were enrolled and randomized in a 1:1 ratio. Please see Table 5 below for baseline characteristics of the ITT population, excluding two treatment-experienced patients (n = 509).

Table 5: Baseline Characteristics (ITT)[32]

Parameter	FTC + TDF (n = 255)	AZT/3TC (n = 254)
Age (years)*	36	37
Female (%)	14	13
White (%)	56	61
Black (%)	25	20
Hispanic (%)	15	16
HIV RNA (log_{10} copies/mL)*	5.0	5.0
HIV RNA >100,000 copies/mL (%)	52	50
CD4 (cells/mm^3)*	233	241
CD4 <200 cells/mm^3 (%)	42	41
CD4 <50 cells/mm^3 (%)	15	11

Abbreviations: ITT, intent-to-treat; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine
*Median values.

The primary efficacy endpoint of the study was the percentage of patients with HIV RNA <400 copies/mL at Week 48 as defined by the FDA TLOVR algorithm using the mITT analysis set (excluding baseline NNRTI-R; n = 487). A total of 22 patients (11 from each group) had baseline NNRTI-R mutations and were excluded from the primary endpoint analysis at Week 48 according to the FDA's recommendation. The TLOVR algorithm is a multi-step algorithm that has been required by the FDA since 2002 to evaluate clinical trial treatment outcomes with all antiretroviral drugs for which plasma HIV RNA measurements are used to assess efficacy. TLOVR provides a more stringent definition for virologic success and failure than ITT, missing = failure and/or switch = failure analyses, by requiring that endpoint data be confirmed at more than 1 visit.[32] TLOVR is now included in the U.S. Prescribing Information of newly approved antiretroviral drugs.

Week 48 Results

Data analyses at Week 48 showed that significantly more patients in the FTC + TDF group vs. the AZT/3TC group achieved and maintained HIV RNA <400 and <50 copies/mL (TLOVR in ITT and mITT populations). In addition, increases in CD4 cell count at Week 48 were significantly higher in the FTC + TDF group (Table 6). These analyses demonstrated statistically superior virologic and immunologic outcomes in the FTC + TDF group as compared to the AZT/3TC group. Other treatment outcomes through week 48 for the mITT population are provided in Table 7.

Table 6: Clinical Efficacy Endpoints at Week 48[22,31,32]

Parameter	Population	FTC + TDF	AZT/3TC	*P*-Value (95% CI)
HIV RNA <400 copies/mL (%)	ITT n = 509	81	70	.005 (+3, +18)
HIV RNA <400 copies/mL (%)	mITT n = 487	84	73	.002 (+4, +19)
HIV RNA <50 copies/mL (%)	ITT n = 509	77	68	.03 (+1, +16)
HIV RNA <50 copies/mL (%)	mITT n = 487	80	70	.02 (+2, +17)
Mean Change in CD4 Cell Count (cells/mm^3)	As-treated n = 363	+190	+158	.002 (+9, +55)
Mean Change in CD4 Percentage (%)	As-treated n = 363	11	10	.02

Abbreviations: FTC, emtricitabine: TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine; NNRTI-R, non-nucleoside reverse transcriptase inhibitor resistance; CI, confidence interval; AAUCMB, average area under the curve minus baseline; ITT, intent-to-treat; mITT, modified intent-to-treat

Table 7: Other Treatment Outcomes at Week 48[22]

Outcome at Week 48	FTC + TDF (n = 244)	AZT/3TC (n = 243)
Virologic failure (%)	2	4
Rebound* (%)	1	3
Never Suppressed (%)	0	0
Change in ART (%)	1	1
CDC Class C Event (n)	7	5
Death (%)	<1	1
Discontinued due to AE (%)	4	9
Discontinued for Other Reasons† (%)	10	14

Abbreviations: FTC, emtricitabine: TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine; ART, antiretroviral therapy; AE, adverse event

*includes confirmed viral rebound and failure to achieve confirmed HIV RNA <400 copies/mL through Week 48

†includes lost to follow-up, patient withdrawal, non-compliance, protocol violation, and other reasons

Week 48 analysis demonstrated that 12 patients in the FTC + TDF group and 23 patients in the AZT/3TC group met the resistance analysis criteria (confirmed HIV RNA ≥400 copies/mL at Week 48 or at early discontinuation, or viral rebound). No patient in this study developed K65R by Week 48 and M184V/I developed less frequently in the FTC + TDF group than the AZT/3TC group, but this did not achieve statistical significance. Of the 2 patients in the FTC +TDF group who had virologic rebound, 1 had a wild-type virus and 1 had an EFV-resistance mutation. Of the 7 patients who had virologic rebound in the AZT/3TC group, all had EFV-resistance mutations, 5 had the M184V/I mutation, and 1 had a TAM. The differences in the frequency of viral rebound between the 2 groups were not statistically significant (*P* =.11).[32]

Week 96-Results

Ninety-six week efficacy data excludes patients with baseline NNRTI-R mutations and those who completed the Week 48 study with HIV-1 RNA levels below the limit of quantification but did not consent to participate in the study extension from Weeks 48-96.[33] Results showed that significantly more patients in the FTC + TDF arm than those in the AZT/3TC arm achieved and maintained HIV-1 RNA <400 copies/mL (75% vs. 62%, respectively; *P* = .004). Virologic rebound and discontinuation rate due to adverse events were observed in <1% and 5% of patients in the FTC + TDF arm as compared to 5% and 11% of those in the AZT/3TC arm, respectively (*P* = .007 and *P* = .023, respectively). In addition, the mean absolute increase in CD4+ cell count from baseline was higher in the FTC + TDF arm (270 versus 237 cells/mm^3; *P* = .036). The proportion of patients with HIV-1 RNA <50 copies/mL were 67% for the FTC + TDF arm and 61% for the AZT/3TC arm (*P* = .16).[33] Please see Table 8 below for more data on the treatment outcomes at Week 96.

Table 8: TLOVR Treatment Outcomes at Week 96 (96 Week Efficacy Patients)[33]

Parameter	**FTC + TDF (n = 232)**	**AZT/3TC (n = 231)**
Responder (%)*	75	62†
Non-Responder (%)	25	38
Lost to follow-up (%)	9	9
Adverse Event (%)	5	12‡
Withdrawal Consent/Non-compliance (%)	5	7
Virologic Rebound (%)	<1	5‡
Other (%)	2	2
Pregnancy (%)	2	1
Death (%)	<1	<1
Insufficient Virologic Response (%)	<1	<1

Abbreviations: TLOVR, time to loss of virologic response; FTC, emtricitabine: TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine

*Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 96.

†P = .004

‡P = .007

Through Week 96, 14 patients in the FTC + TDF + EFV arm and 29 patients in the AZT/3TC + EFV arm met the resistance analysis criteria (all virologic failure patients with confirmed HIV RNA ≥400 copies/mL at Week 48 or at early discontinuation). No patient in either arm developed the K65R mutation. However, development of the M184V/I mutation was significantly less in the FTC + TDF + EFV arm than the AZT/3TC + EFV arm (2 vs. 9; *P* = .036).[33]

ANRS 1207/IMEA 025 Study

This open-label, single-arm pilot study was designed to evaluate the antiviral activity and tolerance of a QD combination regimen of FTC+ TDF + EFV in 40 HIV-1 infected treatment-naïve patients with CD4 cell count <350 cells/mm^3 in West Africa.[34] The primary endpoint

was the percent of patients with plasma HIV RNA < 400 and < 50 copies/mL at week 48 based on ITT analysis. Tolerance assessment included all adverse events reported by the patient or observed by the investigator and the rate of adverse events ≥ Grade 3. At baseline, the median values for HIV RNA level and CD4 count were 5.3 $\log_{10}$ copies/mL (range: 2.6-5.9) and 122 cells/mm^3 (range: 3-310), respectively.

At week 48, 85% and 72.5% of patients had plasma HIV RNA < 400 and < 50 copies/mL, respectively (ITT analysis), and the mean CD4 count increase from baseline to week 48 was 185 ± 85 cells/mm^3.[34] Overall treatment adherence was assessed at six time points through week 48; 0%-8% of patients reported missing at least 1 drug over the last 3 days and 8%-12% of patients reported missing at least 1 drug over the last month. The main reasons reported for lack of adherence were forgetting (63%), travelling (16%), and other disease (8%).[34]

DART Study

Development of Anti-Retroviral Therapy in Africa (DART) is an ongoing, open-label, randomized trial evaluating different therapeutic approaches for resource poor settings: clinical monitoring only versus laboratory plus clinical monitoring, and structured treatment interruption versus continuous therapy.[35,36] A total of 3,315 treatment-naïve HIV-infected patients at WHO stages 2-4 with CD4 cell count <200 cells/mm^3 were enrolled; of those, 2,468 (74%) received the AZT/3TC + TDF regimen as first line antiretroviral therapy.

A retrospective sub-study (n = 300) of this trial was conducted by Mutuluuza et al.[35] to evaluate early virologic response to the AZT/3TC + TDF regimen.[35] At baseline, the median CD4 cell count was 100 cells/mm^3 (29% had CD4 <50 cells/mm^3) and the median HIV RNA level was 289,400 copies/mL (73% had HIV RNA >100,000 copies/mL). In addition, 23%, 48%, and 29% of the patients were at WHO stages 2, 3, and 4, respectively. Based on ITT analysis at Week 24 (n = 281), HIV RNA decreased by a mean of 3.7 $\log_{10}$ copies/mL and CD4 cell count increased by a mean of 106 cells/mm^3. In addition, 76% and 57% of the patients achieved HIV RNA <400 and <50 copies/mL, respectively. Of those that did not achieve HIV RNA <400 at 24 weeks, 47 (17%) and 18 (6%) of patients had HIV RNA >1000 or >10000 copies/mL.

Kaleebu et al.[37] presented 48-week efficacy data from the same sub-study population; of which 231 patients (77%) had been receiving this treatment regimen uninterrupted. At baseline, these patients had a median HIV RNA of 279,910 copies/mL and a median CD4 cell count of 100 cells/mm^3, with 30% of these patients had CD4 cell count <50 cells/mm^3. At Week 48, patients had a mean decrease in HIV RNA level of 4.10 copies/mL (ITT analysis; n = 272) and a mean increase in CD4 cell count of 126 cells/mm^3. HIV RNA <400 and <50 copies/mL was observed in 72% and 61% of the patients, respectively (ITT analysis). Although no patient reached clinical/immunological criteria for failure before Week 48, the proportion of patients with HIV RNA >1,000 and >10,000 copies/mL increased over time, but remained low, with 4%, 6%, 9%, and 16% of HIV RNA results >10,000 copies/mL at Weeks 12, 24, 36, and 48, respectively. Resistance mutations in those with HIV RNA >1000 copies/mL at 24 weeks (n = 20) showed that M184V with or without TAMs was the most common cause of resistance (n = 14), and K65R was identified infrequently (n = 3).

Munderi et al.[36] presented CD4 response in 1919 patients, enrolled into the DART trial through January 7, 2004, who received AZT/3TC + TDF as their first line regimen. At baseline, these patients had a median CD4 cell count of 82 cells/mm^3 (range: 0-199) with 35% of the patients had CD4 <50 cells/mm^3. By Weeks 12 and 24, these patients had their CD4 cell counts increased by a median of 70 cells/mm^3 and 84 cells/mm^3, respectively, with a significantly higher mean increase from Week 0-12 as compared to Week 12-24 (6.7 cells/mm^3 per week vs. 1.1 cells/mm^3 per week; P <.0001). A total of 35% and 41% of the patients had CD4 ≥200 cells/mm^3 at Weeks 12 and 24, respectively.

Efficacy in Treatment-Experienced Patients

The results of two intensification studies demonstrate the efficacy of TDF 300 mg QD, when used in combination with other ARV drugs for up to 48 weeks in HIV-1 infected patients who have failed or are intolerant to NRTI therapy, or are not controlled by their current ARV regimen.

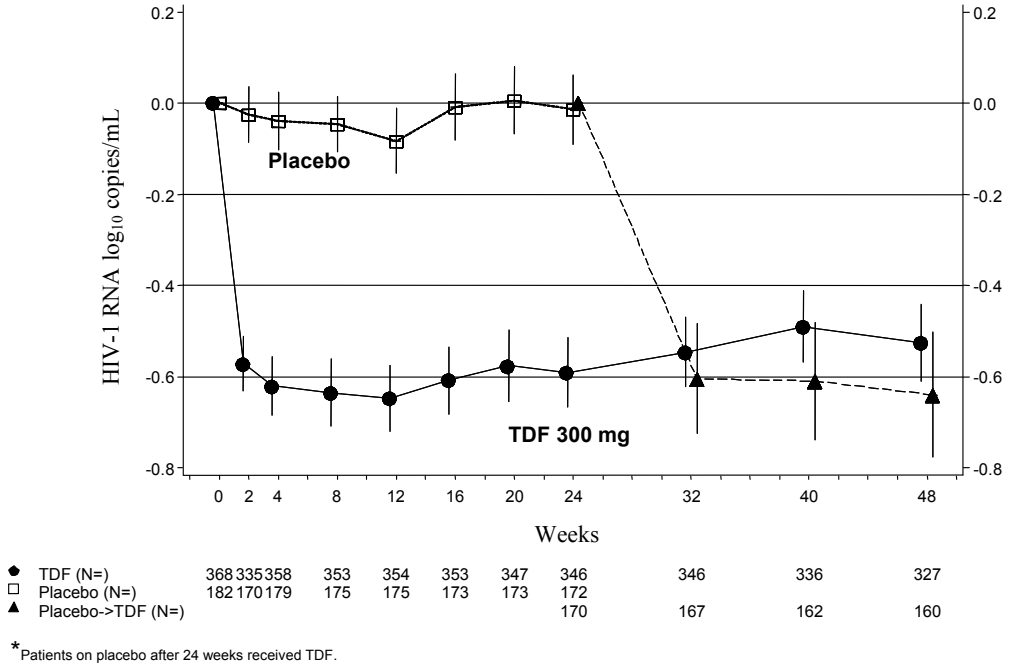
Study 907

Study 907 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study of the safety and efficacy of TDF, in combination with other ARV agents, administered to HIV-infected patients (n = 550) with plasma HIV RNA levels ≥400 copies/mL and ≤10,000 copies/mL.[22,38] These patients were on stable ARV therapy (≤4 active agents) for at least 8 weeks prior to study entry and were randomized 2:1 to add TDF 300 mg QD or placebo to their existing regimen. Patients were stratified according to HIV RNA level, CD4 cell count, and the number of ARV drugs prior to study entry. After 24-weeks of blinded, placebo-controlled dosing, all patients were allowed to receive open-label TDF 300 mg for a total 48-week study period. At baseline, patients had a median HIV RNA level of 2340 copies/mL (range: 50-75,000) and a mean CD4 cell count of 427 cells/mm^3 (range: 23-1,385). Prior to enrolment, patients had received ARV therapy for a mean duration of 5.4 years. The mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% were black and 12% were Hispanic.

Approximately half of all study participants (n = 253) were randomly assigned to a simultaneous virology sub-study of this clinical trial. Baseline genotypic analysis of HIV isolates from these patients revealed that 94% of patients had evidence of NRTI mutations, 58% had PI resistance mutations, and 48% had NNRTI resistance mutations.[39]

Changes from baseline in $\log_{10}$ copies/mL plasma HIV RNA levels over time up to week 48 are presented below in Figure 3.

Figure 3: Mean Change from Baseline in Plasma HIV RNA (log_{10} copies/mL) through Week 48: Study 907 (All Available Data)[22]



*Patients on placebo after 24 weeks received TDF.

The percent of patients with HIV RNA <400 copies/mL and outcomes of patients through 48 weeks are summarized in Table 9.

Table 9: Outcomes of Randomized Treatment through 48 Weeks in Study 907[22]

Outcomes	0-24 weeks		0-48 weeks	24-48 weeks
	TDF (n = 368) %	Placebo (n = 182) %	TDF (n = 368) %	Placebo crossover to TDF (n = 170) %
HIV RNA <400 copies/mL*	40%	11%	28%	30%
Virologic failure†	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons‡	3%	3%	5%	1%

Abbreviation: TDF, tenofovir disoproxil fumarate
*Patients with HIV-1 RNA <400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively.
†Patients with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV–1 RNA at Week 24 and 48 respectively.
‡Includes lost to follow up, patient withdrawal, noncompliance, protocol violation and other reasons.

At 24 weeks of therapy, there was a higher proportion of patients in the TDF arm compared to the placebo arm with HIV RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4 counts by week 24 was +11 cells/mm^3 for the TDF group and -5 cells/mm^3 for the placebo group. Mean change in absolute CD4 counts by week 48 was +4 cells/mm^3 for the TDF group.[22]

Study 902

In this Phase 2, multicenter, double-blind, randomized, placebo-controlled study, the safety and efficacy of TDF, in combination with other ARV agents, were evaluated in 189 HIV-infected treatment-experienced patients.[40,41] Patients enrolled were stable on ≤4 ARV agents for at least 8 weeks with baseline HIV RNA ≥400 and ≤100,000 copies/mL. The mean time on ARV therapy was 4.6 years. Mean baseline CD4 count and HIV RNA viral load were 374 cells/mm^3 and 3.7 $\log_{10}$ copies/mL, respectively. Baseline genotyping demonstrated that 94% of patients had NRTI mutations, 32% had NNRTI mutations, and 57% had PI resistance mutations. The frequency of mutations was similar across all groups. Patients with adequate renal function were randomized to receive one of three TDF doses at 75, 150, or 300 mg, or placebo (in a ratio of 2:2:2:1) in addition to their existing ARV regimen. Patients were stratified according to HIV RNA level (< or ≥20,000 copies/mL), CD4 cell count (< or ≥200 cells/mm^3), and number of ARV drugs prior to study entry (< or ≥4). Patients were encouraged to continue their baseline ARV therapies, in addition to the assigned study drug, for at least 4 weeks post-randomization.

Thereafter, changes in background ARV therapy were made as desired while continuing blinded study drug assignment. At 24-weeks post-randomization, patients initially assigned to placebo treatment were crossed over to TDF 300 mg QD, in a blinded fashion, for the remainder of the 48-week study. Following the completion of 48 weeks on study without treatment-limiting toxicity, patients (n = 135) were eligible to enter an extended dosing phase of the trial in which they received open-label TDF 300 mg QD. Ninety-six week efficacy data are summarized in the table below (Table 10).

Table 10: Mean Change in Plasma HIV RNA (log_{10} copies/mL) from Baseline[40,41]*

Double-Blinded Phase				
Week	**Placebo**	**TDF 75 mg**	**TDF 150 mg**	**TDF 300 mg**
24 (n)	- 0.12 (23)	- 0.43 (48)	- 0.38 (45)	- 0.68 (48)
48 (n)	-	- 0.40 (42)	- 0.58 (35)	- 0.62 (43)
Open-Label Phase				
		TDF 75/300 mg	**TDF 150/300 mg**	**TDF 300/300 mg**
72 (n)	-	-0.66 (35)	-0.64 (35)	-0.63 (37)
96 (n)	-	-0.86 (30)	-0.65 (31)	-0.87 (33)

Abbreviations: BL, baseline; TDF, tenofovir disoproxil fumarate
*Baseline HIV RNA (log_{10} copies/mL) for the 75/300 mg, 150/300 mg, and 300/300 mg groups is defined as the last pre-treatment assessment.

Mean change in absolute CD4 counts at Week 24 were -14 cells/mm^3 for the placebo group and +20 cells/mm^3 for the TDF 300 mg group. This result was not statistically significant. Mean change in CD4 count at Week 48 was +11 cells/mm^3 for the TDF 300 mg group.[41]

Studies 907 and 902 demonstrate statistically significant and sustained reductions in plasma HIV-1 RNA in treatment-experienced patients with high levels of nucleoside resistance at baseline treated with TDF. The viral load reductions seen in these studies are similar or greater than those seen with other licensed NRTI over similar periods of follow up. For example, in a similarly designed intensification study (CNA3002), abacavir (ABC) or placebo was added to stable background therapy in antiretroviral treatment-experienced individuals; baseline HIV-1 RNA and CD4 counts were similar to Studies 902 and 907, however, patients in the ABC study were less treatment-experienced than in the TDF studies with 94% having had <18 months prior NRTI treatment.[37] At Week 16, there was a viral load drop of approximately 0.44 log_{10} copies/mL in the group given ABC, and the proportion of patients with plasma HIV-1 RNA ≤ 400 copies/mL was 39%. By comparison, in Study 907 at Week 16, the median change in plasma HIV-1 RNA from baseline was -0.57 log_{10} copies/mL, and the proportion of patients with HIV-1 RNA ≤ 400 copies/mL was 43% in patients treated with TDF. The non-significant rise in CD4 count of 30 cells/mm^3 is consistent with the findings of the TDF studies.

Genotypic analyses performed in patients enrolled into the 902 and 907 studies showed that K65R developed in 14 (3.2%) patients between Weeks 12-96; most of the patients were taking ddI or ABC concomitantly, however, 7/14 patients were also taking either AZT or d4T. Patients

with this mutation showed a wide range of responses: 5 had <0.5-log decrease, 7 had >0.5-log decrease, and 2 were classified as rebounders due to the development of NNRTI resistance. Development of K65R in these studies was associated with the absence of baseline TAMs and the presence of baseline L74V.[42] Analyses with a more sensitive genotyping technique demonstrated that 2 patients with L74V at baseline also had low levels of K65R present at baseline due to their prior treatment regimens that included either ABC or ddI. Neither of these patients showed a virologic response upon adding TDF to their regimen.

11. Comparative Evidence on Safety:

Estimate of Patient Exposure to Date

Patient exposure to marketed TDF was estimated based on metrics from sales data; the number of bottles sold was multiplied by 30 to provide the number of tablets sold. As TDF is taken once daily, this figure was divided by 365 to provide patient-years of treatment.

The cumulative patient exposure to TDF since its first marketing approval in the US, 26 October, 2001, to 31 October, 2005 is estimated at 622,348 patient-years of treatment (see Table 11 below).

It should be noted that the use of sales data for patient exposure calculations generally overestimates patient exposure, due to distributor stocking and lag time between receiving orders and dispensing drug.

Table 11: Cumulative Estimated Patient Exposure to Marketed TDF through October 31st, 2005*

Geographic Area	Cumulative (Patient-Years)
Europe	
France	45,352
Germany	23,097
Italy	27,822
Portugal	6,975
Spain	43,663
United Kingdom & Ireland	23,618
Mid Mediterranean†	1,373
Distribution Region EU‡	3,957
USA	398,276
Canada	3,589
Latin America & Other	17,607
Australia	6,397
Asia (excluding Japan)	495
Japan	1,702
Africa	5,907
TOTAL	**622,348**

*Cut-off for sales data is at the end of each calendar month
†Greece, Turkey, Saudi Arabia, United Arab Emirates, Cyprus, Oman, Malta, Quatar, Indian, Egypt.
‡Austria, Belgium, Luxembourg Denmark, Finland, Iceland, Netherlands, Norway, Sweden, Switzerland.

Warnings and Precautions for Use

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other ARVs. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with TDF should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).[22]

Patients Co-infected with HIV and Hepatitis B Virus

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. TDF is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TDF have not been established in patients

co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued TDF. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TDF and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.[22]

Renal Impairment

Tenofovir is principally eliminated by the kidney. Dosing interval adjustment is recommended in all patients with creatinine clearance <50 mL/min. No safety data are available in patients with renal dysfunction who received TDF using these dosing guidelines.[22]

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of TDF. The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents; however, some cases occurred in patients without identified risk factors.[22]

TDF should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.[22]

Other

TDF should not be used in combination with the fixed-dose combination product Truvada since it is a component of that product.[22]

Drug Interactions

Precautions should be taken when TDF is co-administered with didanosine (ddI), atazanavir (ATV), lipinavir/ritonavir (LPV/r) and drugs that reduce renal function or compete for active tubular secretion. Didanosine should be discontinued in patients who developed ddI-associated adverse events and TDF should be discontinued in patients who developed TDF-associated adverse events.[22]

Bone Effects

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.[22]

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.[22]

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination ARV therapy, including TDF. During the initial phase of combination ARV treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.[22]

Animal Toxicology

Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 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.[22]

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, blood urea nitrogen (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 area under the curves [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.[22]

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.[22]

TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative when administered to male mice.[22]

There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.[22]

Pregnancy-Pregnancy Category B:

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, TDF should be used during pregnancy only if clearly needed.[22]

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TDF, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.[22]

Nursing Mothers: The US Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving TDF.[22]

Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.[22]

Geriatric Use

Clinical studies of TDF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.[22]

Undesirable Effects

Experience from Pivotal Clinical Studies

More than 12,000 patients have been treated with TDF alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase 1-3 clinical trials and expanded access studies. A total of 1,544 patients have received TDF 300 mg QD in Phase 1-3 clinical trials; over 11,000 patients have received TDF in expanded access studies.

Treatment-Naïve Patients

Study 903

Through Week 144, 8% of the patients in the TDF arm and 13% of patients in the d4T arm discontinued the study due to adverse events. The most common adverse reactions reported were mild to moderate gastrointestinal events and dizziness. Mild adverse events (Grade 1)

were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea.[22] Selected treatment-emergent moderate to severe adverse events are summarized in Table 12.

Table 12: Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 903 (0–144 weeks)[22]

Adverse Event	TDF (n = 299)	d4T (n = 301)
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal Pain	7%	12%
Back Pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic Disorders		
Lipodystrophy*	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy†	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash Event‡	18%	12%

Abbreviation: TDF, tenofovir disoproxil fumarate; d4T, satvudine

*Lipodystrophy represents a variety of investigator-described adverse events, not a protocol-defined syndrome.

†Peripheral neuropathy includes peripheral neuritis and neuropathy.

‡Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the d4T group (40% and 9%, respectively) compared to the TDF group (19% and 1%, respectively), laboratory abnormalities observed in this study occurred with similar frequency in the TDF and d4T treatment arms.[22] A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 13.

Table 13: Grade 3/4 Laboratory Abnormalities Reported in ≥1% of TDF-Treated Patients in Study 903 (0–144 weeks)[22]

Laboratory Abnormality	TDF (n = 299)	d4T (n = 301)
Any ≥Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L; F: >170 U/L)	5%	7%
ALT (M: >215 U/L; F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophil (<750/mm^3)	3%	1%
Fasting Triglyceride (>750 mg/dL)	1%	9%

Abbreviations: TDF, tenofovir disoproxil fumarate; M, male; F, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RBC/HPF, red blood cells per high power field; d4T, stavudine

Adverse events related to metabolic abnormalities were observed significantly higher in the d4T arm. At 144 weeks, the TDF-containing regimen was associated with significantly smaller increases in fasting triglycerides, total cholesterol (TC), direct low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) levels compared to the d4T-containing regimen. In addition, the percentage of patients with mitochondria-associated toxicities was also significantly lower in the TDF arm. Please see Tables 14 and 15 for more details.[1,43]

Table 14: Study 903 Metabolic Parameters through Week 144[1,43]

Parameter*	TDF (n = 299)	d4T (n = 301)	*P*-Value
Increase in Fasting Triglycerides (mg/dL)	1	134	<.001
Increase in Fasting Total Cholesterol (mg/dL)	30	58	<.001
Direct Low-Density Lipoprotein (mg/dL)	14	26	<.001
High-Density Lipoprotein (mg/dL)	9	6	=.003

Abbreviation: TDF, tenofovir disoproxil fumarate; d4T, stavudine
*Mean value; increases are from baseline.

Table 15: Study 903 Mitochondrial-Related Toxicity Reported at Week 144[1]

Parameter (All Grades)	TDF (n = 299)	d4T (n = 301)	*P*-Value
Patients with events (n [%])	17 (6%)	83 (28%)	<.001
Peripheral neuritis/neuropathy (n [%])	9 (3%)	31 (10%)	<.001
Lipodystrophy* (n [%])	9 (3%)	58 (19%)	<.001
Total Limb Fat (kg)	8.6	4.5	<.001
Lactic acidosis* (n [%])	0	3 (1%)	-
Pancreatitis (n [%])	0	0	-

Abbreviation: TDF, tenofovir disoproxil fumarate; d4T, stavudine
*Investigator defined.

Additionally, through Week 144, the renal safety profile was similar between the TDF and d4T-containing group. No patient in the TDF arm developed Fanconi syndrome or discontinued the study due to a renal abnormality and <1% of patients (n = 2) in both groups had serum creatinine >2.0 mg/dL. The incidence of proteinuria and/or glycosuria was also similar between the 2 groups.[44]

There was a significantly greater mean percentage decrease from baseline in bone mineral density (BMD) at the lumbar spine in the TDF arm (-2.2% ± 3.9) compared to d4T arm (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the TDF group vs. -2.4% ± 4.5 in the d4T group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated patients vs. 21% of the d4T-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the TDF group and 6 patients in the d4T group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide) in the TDF group relative to the d4T group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25-Vitamin D levels were also higher in the TDF group. Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.[22]

Study 903 Extension Phase

As observed in the total patient population treated with TDF from Study 903, in this subset of patients, decreases from baseline in spine and hip BMD occurred during the first 48 weeks and were non-progressive through Week 192. At Weeks 48, 144, and 192, the mean percentage decreases from baseline in spine BMD were 3.3%, 1.6%, and 1.0% and hip BMD were 3.3%, 2.9%, and 2.3%, respectively. Mean total limb fat remained stable from Week 96 (8.0 kg, n = 69) to 192 (8.1 kg, n = 65).[29]

Of the 85 patients who switched from d4T to TDF, they had been on d4T for a median duration of 152 weeks.[30] At the time of switch, 99% and 100% of the patients had HIV RNA <50 and <400 copies/mL, respectively, with a mean±SD CD4 cell count of 650±270 cells/mm^3 (range: 171-1,637). Two patients withdrew consent and discontinued from the study prior to Week 24.

Forty-eight weeks after switching to TDF, significant improvements in lipid parameters and limb fat were observed (Table 16). However, a small decrease in hip BMD (-0.8% at Week 24 and -1.5% at Week 48 [*P* <.001]) was seen after switching to TDF but there was no change in spine BMD (-0.2% at Week 24 and 0% at Week 48 [*P* =.700]).[30]

Table 16: Mean±SD (Range) Improvements in Lipid Parameters and Limb Fat at Week 48[30]

Fasting Parameter	Prior to Switch (n = 85)	Week 48 (n = 83)	*P*- Value
Triglycerides (mg/dL)	247±213 (47 to 1,559)	-72±182 (-1,165 to 331)	<.001
Total Cholesterol (mg/dL)	216±61 (109 to 522)	-38±46 (-312 to 53)	<.001
LDL-C (mg/dL)	128±49 (30 to 260)	-16±40 (-147 to 102)	<.001
HDL-C (mg/dL)	46±13 (24 to 80)	-1±10 (-40 to 33)	=.048
Total Cholesterol/HDL Ratio	5±2 (2 to 9)	-1±1 (-3 to 2)	<.001
Limb Fat (kg)	4.60*	5.02*	<.001

Abbreviations: SD, standard of deviation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol
*n = 74

Three patients discontinued from the study prior to Week 192, 1 due to Grade 3 amylase/Grade 4 lipase elevations, 1 due to pregnancy, and 1 withdrew consent. No patient discontinued from the study due to renal abnormalities and no Fanconi syndrome was reported.[29]

Study 934

Week 48 Results

Based on available 48-week safety data, the overall incidences of Grades 2-4 adverse events and laboratory abnormalities were similar between the 2 treatment groups and were generally consistent with those seen in previous studies (Tables 17 and 18). However, significantly fewer patients in the FTC + TDF group, 4% compared to 9% of those in the AZT/3TC group, discontinued from the study due to adverse events (Table 19). In addition, no cases of anemia were seen in the FTC + TDF arm as compared to 6% (n = 14) of patients in the AZT/3TC arm who discontinued the study drug due to anemia. Seven of these patients had received erythropoietin before discontinuation and 7 received blood transfusions.[22,32]

Table 17: Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in ≥3% in Any Treatment Group (0-48 weeks)[22]

Adverse Event	TDF + FTC (n = 257)	AZT/3TC (n = 254)
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper Respiratory Tract Infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal Dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine

Table 18: Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group (0–48 Weeks)[22]

Laboratory Abnormality	TDF + FTC (n = 257)	AZT/3TC (n = 254)
Any ≥Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L; F: >170 U/L)	3%	2%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%
Hyperglycemia (>250 mg/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophil (<750/mm^3)	3%	4%
Fasting Triglyceride (>750 mg/dL)	4%	2%

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; AZT/3TC, zidovudine/lamivudine; M, male; F, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RBC/HPF, red blood cells per high power field

Table 19: Adverse Events Leading to Study Drug Discontinuation through Week 48[32,45]

Parameter	FTC + TDF (n = 257)	AZT/3TC (n = 254)
Any Event*	10 (4%)	23 (9%)†
Anemia	0	14 (6%)‡
Nausea	1 (<1%)	4 (2%)
Fatigue	0	3 (1%)
Vomiting	0	2 (1%)
Rash (NNRTI-associated)	2 (1%)	0
Neutropenia	0	2 (1%)

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine; NNRTI, non-nucleoside reverse transcriptase inhibitor

*Occurring in ≥2 patient in either arm

†P =.02

‡P <.001; median (range) baseline hemoglobin and hematocrit levels were 13.8 g/dL (10.8−16) and 40% (31−47) respectively. Median (range) nadir hemoglobin and hematocrit levels were 6.9 g/dL (3.7−9.3) and 22% (11−33) respectively.

Hyperpigmentation was confirmed or could not be ruled out in 7 patients in the FTC + TDF group vs. 4 in the AZT/3TC group (P =.54). All cases were mild in severity except for 1 case in the AZT/3TC group. No patient discontinued from the study due to hyperpigmentation.[32]

There was no evidence of a TDF effect on renal function as measured by changes from baseline or maximum graded toxicity of serum creatinine or serum phosphorus concentrations. No confirmed graded abnormalities in serum creatinine or serum phosphorus were reported in the FTC + TDF group; however, 3 patients in the AZT/3TC group had graded abnormalities. No

cases of Fanconi's syndrome were reported in either group. Based on the Cockroft-Gault method, the median change from a baseline glomerular filtration rate (GFR) of 121 mL/min for both arms to Week 48 was −1 mL/min for the FTC + TDF group (*P* =.660 vs. baseline) and +6 mL/min for the AZT/3TC group (*P* <.001 vs. baseline). Based on the modification of diet in renal disease (MDRD) method, the change from baseline in both groups was <−1 mL/min/1.73 mm^3.[31,32]

Regarding to lipid parameters, at Week 48, the FTC + TDF group had smaller mean increases in fasting triglycerides, total cholesterol, LDL, and HDL levels compared to the AZT/3TC group (Table 20).[31]

Table 20: Increase in Fasting Lipid Parameters through Week 48[32]

Parameter	**FTC + TDF**	**AZT/3TC**	***P*-Value**
Triglycerides (mg/dL)	+3	+31	.38
Total Cholesterol (mg/dL)	+21	+35	<.001
LDL (mg/dL)	+13	+20	.01
HDL (mg/dL)	+6	+9	.004

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, lamivudine/zidovudine; LDL, low-density lipoprotein; HDL, high-density lipoprotein
*Mean change from baseline.

Week 96 Results

Through Week 96, adverse events leading to drug discontinuation were significantly higher in the AZT/3TC arm than the FTC + TDF arm (Table 21). Although the median GFR as estimated by the CG method was similar between the two groups, the median GFR as estimated by the MDRD method was significantly lower in the FTC + TDF arm than the AZT/3TC arm (100 versus 108 mL/min/1.73 m^2, respectively; *P* = .006). However, the GFR as estimated by both methods were stable through 96 weeks for both groups and there were no confirmed Grade 1-4 abnormalities in SCr reported in the FTC + TDF arm; two patients in the AZT/3TC arm had abnormalities (Grade 1 and Grade 2).[33]

Table 21: Adverse Events Leading to Study Drug Discontinuation through Week 96[33]

Parameter	FTC + TDF (n = 257)	AZT/3TC (n = 254)
Any Event*	12 (5%)	28 (11%)†
Anemia/↓Hgb	0	14 (6%)‡
Fatigue	0	5 (2%)
Nausea	1 (<1%)	4 (2%)
Rash (NNRTI-associated)	4 (2%)	1 (<1%)
Drug Eruption	2 (<1%)	0
Vomiting	0	2 (<1%)
Neutropenia	0	2 (<1%)

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine; NNRTI, non-nucleoside reverse transcriptase inhibitor
*Occurring in >1 patient in either arm, patients may have >1 event.
†P =.023
‡P <.001

Table 22: Serum Creatinine through Week 96[33]

Maximum Confirmed Toxicity Grade (mg/dL)*	FTC + TDF (n = 257)	AZT/3TC (n = 254)
1 (>1.5-2.0)	0	1 (<1%)
2 (2.1-3.0)	0	1 (<1%)
3 (3.1-6.0)	0	0
4 (>6.0)	0	0

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine
*Confirmed toxicity grade = two consecutive visits

Through Week 96, patients in the FTC + TDF group had a significantly greater median increase from baseline in weight gain compared to those in the AZT/3TC group (2.7 vs. 0.5 kg; P <.001).[33] There was no significant difference in mean weights between the two groups at baseline and both groups had comparable weight gain at Week 48 (2.1 kg with FTC + TDF versus 1.1 kg with AZT/3TC; P =.14).[32] Although baseline limb fat data by DEXA scan is not available, in a sub-study of patients in whom limb fat was measured via DEXA scans at Weeks 48 and 96, there was significantly more total limb fat in the FTC + TDF arm than the AZT/3TC arm (Table 23).[32,33]

Table 23: Study 934: Median Total Limb Fat (kg) at Weeks 48 and 96[33]

Week 48		Week 96	
FTC + TDF (n = 51)	**AZT/3TC (n = 49)**	**FTC + TDF (n = 144)**	**AZT/3TC (n = 136)**
7.4*	6.0*	7.7†	5.5†

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine
**P* =.034 for the difference between the FTC + TDF arm vs. the AZT/3TC arm at Week 48
†P <.001 for the difference between the FTC + TDF arm vs. the AZT/3TC arm at Week 96

In a subset of patients with 48-week total limb fat data, median total limb fat for those in the FTC + TDF arm increased significantly, from 7.4 kg at Week 48 to 8.1 kg at Week 96 ($P = .01$), as compared to a significant decrease for those in the AZT/3TC arm, from 6.0 kg at Week 48 to 5.5 kg at Week 96 ($P = .001$). The differences in total limb fat for these two groups at Week 96 were statistically significant ($P < .001$).[33]

ANRS 1207/IMEA 025 Study

In this study, tolerance assessment through 48 weeks included all adverse events reported by the patient or observed by the investigator as well as the rate of adverse events ≥ Grade 3.[34] Please see Table 24 below for a listing of Grade 2-3 treatment related adverse events; there was no Grade 4 treatment related adverse event. Reported Grade 3 or 4 laboratory abnormalities through week 48 included: haemoglobin < 7g/dL (n = 1), neutrophils < 700 /mm^3 (n = 3), and AST/SGOT > 5 x ULN (n = 1).[34] There was a significant decrease in mean CrCL, from 92 mL/min at baseline to 80 mL/min ($P = .03$) at week 48. Although mean triglyceride levels decreased significantly from 74 mg/dL at baseline to 57 mg/dL ($P = .04$) at week 48, a decrease in total cholesterol was not statistically significant (161 to 156mg/dL [$P = .14$]). Compared to baseline, an increase in body weight was observed in these patients at Week 48. Three patients died, one due to multifocal tuberculosis, one due to sepsis, and one of unknown cause.

Table 24: Treatment Related Adverse Events* through Week 48[34]

Adverse Event Grades 2-3†	n	% Patients
Dizziness	19	47.5
Nausea/vomiting	6	15
Diarrhea	5	12.5
Cutaneous eruption/pruritus	3	7.5
Headache	2	5
Fatigue	1	2.5
Total	36	

* Time of onset of treatment related adverse events before Week 4
†No reports of Grade 4 treatment related adverse events

Treatment-Experienced Patients

Studies 902 and 907

The adverse reactions seen in treatment-experienced patients were generally consistent with those seen in treatment-naïve patients including 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 (Study 907).[22] A summary of moderate to severe treatment-emergent adverse events that occurred during the first 48 weeks in Study 907 is provided in Table 25 below.

Table 25: Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0–48 weeks)[22]

Adverse Events	TDF (n = 368) (Week 0–24)	Placebo (n = 182) (Week 0–24)	TDF (n = 368) (Week 0–48)	Placebo Crossover to TDF (n = 170) (Week 24–48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal Pain	4%	3%	7%	6%
Back Pain	3%	3%	4%	2%
Chest Pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy*	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash Event†	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight Loss	2%	1%	4%	2%

Abbreviation: TDF, tenofovir disoproxil fumarate

*Peripheral neuropathy includes peripheral neuritis and neuropathy.

†Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory abnormalities observed in this study occurred with similar frequency in the TDF and placebo-treated groups.[22] A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 26 below.

Table 26: Grade 3/4 Laboratory Abnormalities Reported in ≥1% of TDF-Treated Patients in Study 907 (0–48 weeks)[22]

Laboratory Abnormality	TDF (n = 368) (Week 0–24)	Placebo (n = 182) (Week 0–24)	TDF (n = 368) (Week 0–48)	Placebo Crossover to TDF (n = 170) (Week 24–48)
Any ≥Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Urine Glucose (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L; F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750/dL)	1%	1%	2%	1%

Abbreviations: M, male; F, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TDF, tenofovir disoproxil fumarate

Pooled analysis from both of these studies showed that during the extended dosing period, the frequency of adverse events and laboratory abnormalities did not increase appreciably. Results are shown in Tables 27 and 28.

Table 27: Grade 3/4 Adverse Events and Laboratory Abnormalities Occurring in ≥2% of Patients in any Group from the Pooled 902 and 907 Studies[46]

Adverse Events or Laboratory Abnormalities	Placebo (0-24 weeks) (n = 210)	TDF (0-24 weeks) (n = 443)	All TDF* (Mean: 113 weeks; Maximum: 220 weeks) (n = 687)
Grade 3 or 4 Adverse Events			
Diarrhea	4 (2%)	4 (<1%)	21 (3%)
Depression	1 (<1%)	3 (<1%)	19 (3%)
Grade 3 or 4 Laboratory Abnormalities			
Creatine kinase (>782 U/L)	30 (14%)	36 (8%)	103 (15%)
Triglyceride (>750 mg/dL)	28 (13%)	37 (8%)	89 (13%)
Serum amylase (>175 U/L)	14 (7%)	21 (5%)	62 (9%)
AST (M: >180 U/L; F: >170 U/L)	6 (3%)	16 (4%)	59 (9%)
ALT (M: >215 U/L; F: >170 U/L)	4 (2%)	10 (2%)	42 (6%)
Urine glucose (3+ or 4+)	6 (3%)	12 (3%)	48 (7%)
Serum glucose (>250 mg/dL)	8 (4%)	8 (2%)	35 (5%)
Neutrophil (<650/mm^3)	3 (1%)	6 (1%)	19 (3%)*

Abbreviations: M, male; F, female; ALT, alanine aminotransferase; AST, aspartate aminotransferase
*Any patient who was taking TDF (75-300 mg).

Table 28: Frequency of Adverse Events Potentially Associated with Mitochondrial Dysfunction from the Pooled 902 and 907 Studies[47]

Adverse Events	Placebo (0-24 weeks) (n = 210)	TDF 300 mg (0-24 weeks) (n = 443)	All TDF* (Mean: 95 weeks; Maximum: 191 weeks) (n = 687)
Peripheral Neuritis	6 (3%)	9 (2%)	57 (8%)
Pancreatitis	2 (<1%)	2 (<1%)	15 (2%)
Lactic Acidosis[†]	0 (0%)	1 (<1%)	16 (2%)

Abbreviation: TDF, tenofovir disoproxil fumarate
*Any patient who was taking TDF (75-300 mg).
[†]All patients who developed lactic acidosis were also receiving stavudine or didanosine concomitantly.

Global Expanded Access Programs (EAPs)

The global TDF EAP was initiated in March 2001 and enrolled a total of 10,343 HIV-infected patients with advanced disease who had failed prior HAART and had limited treatment options.[48] Patients included were ≥18 years with no confirmed renal abnormality and were

given open-label TDF 300 mg QD in combination with other antiretroviral agents. Fifty-one percent of the patients were taking concomitant LPV/r and the median time of TDF exposure was 3,700 patient-years. Serious adverse events were monitored for all patients and SCr were collected in 1,699 patients. In addition, risk factors for development of graded creatinine abnormalities were determined using multivariate logistic regression models. A total of 631 patients (6%) reported a SAE, however, 211 patients (2%) had related SAEs. Please see Tables 29 and 30 below for the incidences of serious adverse events and serious renal adverse events reported during the EAP. In addition, specific adverse events of interest such as bone abnormalities, lactic acidosis, mitochondrial toxicity, neuropathy, and pancreatitis were reported in .1%, .1%, <.1%, <.1%, and .5%, respectively. Pancreatitis was reported significantly more in patients who were taking didanosine as compared to those who were not taking didanosine (.7% vs. .3%; *P* <.001).

Table 29: Serious Adverse Event from EAP Reported by ≥.1% of Patients[48]

Serious Adverse Events	EAP (N = 10,343) (3,700 person years)
	% of Patients Experiencing These Events
Anemia	.2
Diarrhea	.2
Fever	.4
Infection_Bacterial	.3
Lymphoma-like Reaction	.3
Nausea	.1
Vomiting	.2
Pneumonia	.6

Abbreviation: EAP, Expanded Access Program

Table 30: Serious Renal Adverse Event Categories*[48]

Serious Renal Adverse Events	EAP (N = 10,343) (3,700 person years)
	% of Patients Experiencing These Events
Any[†]	.5
Renal Failure	.3
Renal Other	.1
↑SrCr/BUN	<.1
Fanconi/Tubular Disorder/Hyposphatemia/Glycosuria	<.1
Nephrogenic Diabetes Insipidus	<.1
Nephritis	0
Proteinuria	0

Abbreviations: EAP, Expanded Access Program; SrCr, serum creatinine; BUN, blood urea nitrogen; ↑, increase
*Each category includes multiple related serious adverse event terms.
[†]Patients can have >1 event.

Of the 1,699 patients from the EAP with available SCr data, Grade 1, 2, 3, or 4 SCr elevations were reported in 32 (1.9%), 5 (0.3%), 3 (0.2%), and 2 (0.1%) patients, respectively. At baseline, SCr elevations were reported in 0, 2 (0.1%), 0, and 3 (0.1%) patients, respectively. Using data from 911 patients with a baseline and follow-up SCr, as well as relevant information on renal risk factors, multivariate analysis showed that risk factors significantly associated with unconfirmed ≥Grade 1 increase in SCr were: older age (*P* =.021), lower baseline CD4 (*P* <.001), lower baseline weight (*P* <.001), and concomitant use of nephrotoxic medications at baseline (*P* =.032). Similarly, risk factors significantly associated with unconfirmed ≥Grade 2 increase in SCr were elevated baseline SCr (*P* =.018) and lower weight at baseline (*P* =.001). Risk factors evaluated that did not reach statistical significance for either ≥ Grade 1 or 2 increase in SCr were concomitant use of ABC, ddI, LPV/r, 3TC, d4T, ACE inhibitors, or nephrotoxic antibiotics at baseline, baseline creatinine, HIV RNA, diabetes or hypertension and CDC classification, HBV co-infection, days since HIV diagnosis, and gender.[48]

RAVE Study

This is a randomized, open-label study (N = 105) designed to compare the effects of the substitution of TDF or ABC in patients with moderate to severe lipoatrophy with HIV RNA <50 copies/mL and no history of TDF or ABC use or resistance.[49] Baseline characteristics of patients in both arms were similar; however, 77% and 59% of the patients in the TDF and ABC arms were using d4T and 23% and 41% were using AZT, respectively. Results after 48 weeks of treatment showed that similar restorations of limb fat, trunk fat, abdominal fat, and total fat were observed in both groups; however, metabolic changes showed more improvement on the TDF arm (Table 31). In addition, only 1 patient in the TDF group needed a lipid lowering therapy (Day 273) compared to 8 patients in the ABC group (median: Day 91.5).

Table 31: Median Changes in Metabolic Parameters at Week 48[49]

Parameter	TDF	ABC	*P*-Value
Total Cholesterol (mmol/L)	-0.2	0	.016
HDL Cholesterol (mmol/L)	-0.01	0	.16
LDL Cholesterol (mmol/L)	-0.1	0	.043
Fasting Cholesterol (mmol/L)	-0.49	+0.22	.39
Triglyceride (mmol/L)	-0.17	0	.031
Lactate (mmol/L)	-0.3	-0.1	.27

Abbreviations: TDF, tenofovir disoproxil fumarate; ABC, abacavir; HDL, high density lipid; LDL, low density lipid

Virological suppression was maintained in both groups with no significant differences in the rates of HIV RNA <50 copies/mL or CD4 cell count increases. In addition, there were no significant differences between the two groups regarding changes in hemoglobin, SCr, BMD, or the proportions of patients with osteoporosis at Week 48. One patient in the TDF group discontinued the study due to diarrhea and 3 patients in the ABC group discontinued the study due to hypersensitivity reactions.[49]

From Post Marketing Surveillance

In addition to adverse reaction reports from clinical trials, the following possible adverse reactions have also been identified during post-approval use of tenofovir disoproxil 245 mg (as fumarate). Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting, or potential causal relationship with TDF.

IMMUNE SYSTEM DISORDERS
Allergic reaction

METABOLISM AND NUTRITION DISORDERS
Hypophosphatemia, lactic acidosis

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS
Dyspnea

GASTROINTESTINAL DISORDERS
Abdominal pain, increased amylase, pancreatitis

HEPATOBILIARY DISORDERS

Increased liver enzymes, hepatitis

RENAL AND URINARY DISORDERS
Renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, polyuria, nephritis

Overdose

Limited clinical experience at doses higher than the therapeutic dose of TDF 300 mg is available. In study 901, 600 mg TDF was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a four-hour hemodialysis session removed approximately 10% of the administered TDF dose.

Pharmacological Properties

Age and gender

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Tenofovir pharmacokinetics are similar in male and female patients.

Pharmacokinetic studies have not been performed in children (<18 years) or in the elderly (>65 years).

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

12.1 Range of costs of the proposed medicine

12.1.1 United States of America

TDF was approved by the US FDA on 26 October 2001, representing initial commercial availability of this one-tablet, once-daily antiretroviral. The monthly treatment cost of TDF varies among payers in the United States. The list price is USD 442.56; the following table indicates current pricing:

Table 32: Wholesale Acquisition Cost of Tenofovir DF Tablet in the United States[*50]

Country	Package	Average Package Price (USD)	Average Unit Price (USD)	Defined Daily Dose
United States	30 TAB	442.56	14.75	300 MG

[*]Ex-factory pricing, free on board (FOB) with no handling fees.

12.1.2 Developing Countries

Gilead Access Program

The Gilead Access Program is designed to expand access to the once-daily anti-HIV medications Truvada® (emtricitabine and tenofovir disoproxil fumarate) and Viread® (tenofovir disoproxil fumarate) in 97 developing countries. A 30-day supply of these medications can currently be obtained at the following prices: 26.25 USD for emtricitabine and tenofovir DF fixed dose combination tablet and 17.00 USD for tenofovir DF. Separate price structures are offered in middle income and developed world countries. This is based on ex-factory pricing, free on board from distribution facilities in either San Dimas, California, USA or Dublin, Ireland, not including shipping and handling fees. Gilead is seeking product registrations in all 97 countries to further improve access. Gilead has also established a partnership with Aspen Pharmacare in South Africa whereby tenofovir DF and tenofovir DF

fixed dose combination tablets are manufactured to GMP standards in South Africa for use throughout the Access Program countries. This partnership supplements three other manufacturing sites and further boosts the ability to meet the growing demand for Gilead drugs. Gilead has also offered voluntary licenses to other generic manufacturing companies in India for the manufacture and distribution of tenofovir DF in the developing countries. Both tenofovir DF, and emtricitabine and tenofovir DF fixed dose combination tablet are included in the WHO List of Pre-qualified Medicines.

Gilead Clinical Research Collaborations and Partnerships

To help determine more effective ways of treating HIV/AIDS in resource-poor settings, Gilead continues to collaborate with the US government and private research organizations, including the Bill and Melinda Gates Foundation, Family Health International, US National Institutes of Health (NIH), Medical Research Council of the UK (MRC), National Agency for AIDS Research (ANRS) and Rockefeller Foundation. Clinical trials conducted by these organizations are designed to evaluate the safety and efficacy of TDF-containing HAART, address scientific issues, and determine solutions for logistical obstacles to providing widespread ARV access in for patients developing countries. Gilead donates study drug and provides technical consultation for these investigative efforts, in which approximately 5,000 patients are receiving HAART and medical care.

12.2. Comparative cost-effectiveness presented as range of cost per routine outcome

12.2.1. Cost-Effectiveness of HAART

Traditional cost-effectiveness comparisons of ARVs for the treatment of HIV infection, including TDF, are not available. However, it is recognized that widespread use of highly active antiretroviral therapy has sharply reduced HIV/AIDS morbidity and mortality in regions of the industrialized world that have ample access to ARVs. Consequently, the HIV age-adjusted death rate AIDS deaths in the United States declined by 70 percent from 1995 to 2002, primarily as a result of the introduction of HAART.[20]

To attain these public health improvements, the primary goals of HAART are to achieve durable and maximal suppression of plasma viral load, restoration and/or preservation of immunologic function, improved quality of life and reduction of HIV-related morbidity and mortality. Treatment resulting in maximal suppression of viral load is a strong prognostic indicator in HIV infection, and can result in substantial clinical benefits. Chief among them, partial reconstitution of immune function induced by HAART has been shown to help delay the progression of HIV infection to AIDS-defining opportunistic infections (OIs). This might allow elimination of unnecessary therapies used for prevention and maintenance against OIs.[8] Likewise, successful HAART may reduce costs associated with use of healthcare provider and clinic resources, emergency care and hospital admissions.

Nonetheless, antiviral regimens are complex, have serious side effects, pose difficulty with adherence and carry serious potential consequences from the development of viral resistance because of non-adherence to the drug regimen or suboptimal levels of ARVs.[8] Therefore,

selection of ARVs that maximize viral suppression and immune response while providing acceptable tolerability and ease of use may positively influence cost-effectiveness of care.

Unique features of TDF make it well-suited for HAART administered in the developing world. Several clinical studies (up to 192 weeks) have demonstrated that TDF is effective, tolerable, and less prone to the development of resistance than other ARVs. In Study 934, significantly fewer patients in the emtricitabine + tenofovir DF group, 4% compared to 9% of those in the AZT/3TC group, discontinued from the study due to adverse events.[51] In addition, no cases of anemia were seen in the emtricitabine + tenofovir DF arm as compared to 6% (n = 14) of patients in the AZT/3TC arm who discontinued the study drug due to anemia. Seven of these patients had received erythropoietin before discontinuation and 7 received blood transfusions.[32] Although there have been no published studies on cost-effectiveness ratio of anemia treatment (erythropoietin, blood transfusion, etc.) in countries with low income, in a study of HIV-infected women in Tanzania, anemia was independently found to be associated with AIDS-related death and disease progression.[52] Compared to patients with normal haemoglobin, the risk of death was approximately 2-fold for those with moderate anemia and 3-fold for those with severe anemia. Another study in Mali found that severity of anemia was positively associated with HIV-2 infection and progression of HIV disease, and mortality was more frequently associated with anemia.[53] In HIV-infected women in Tanzania, anemia was one of the factors identified to be significantly contributed to mortality independent of HIV infection.[52]

Although it is well known that patients receiving a regimen containing AZT/3TC may experience anemia, there are currently no data regarding the extra costs that this may incur. Nevertheless, the potential extra cost is an important issue to consider when comparing HIV regimens. For example, although the daily cost of a regimen containing generic EFV 600 mg and 3TC 150 mg (Aurobindo pricing) + TDF at the no-profit cost is 0.10 USD more per day as compared to a generic regimen containing AZT/3TC + EFV (Aurobindo pricing; 1.95 USD/day versus 1.85 USD/day, respectively), therapy with TDF is less likely to cause anemia.[54]

13. Summary of regulatory status of the medicine (in country of origin and preferably in other countries as well):

Tenofovir DF received approval by US FDA on 26 October 2001, and currently has approval for marketing in a total of 55 countries.[50] Please see a listing of territories with marketing authorisation status in Table 33 below.

Table 33: Worldwide Marketing Authorisation Status – TDF Tablets[50]

Territory	Approval Date
United States (Commercial Product) United States (GAP Product)*	26 Oct 2001 23 Jan 2004
Japan	25 Mar 2004
Canada	18 Mar 2003
European Union	
Austria	05 Feb 2002

Territory	Approval Date
Belgium	05 Feb 2002
Cyprus	01 May 2004
Czech Republic	01 May 2004
Denmark	05 Feb 2002
Estonia	01 May 2004
Finland	05 Feb 2002
France	05 Feb 2002
Germany	05 Feb 2002
Greece	05 Feb 2002
Hungary	01 May 2004
Ireland	05 Feb 2002
Italy	05 Feb 2002
Latvia	01 May 2004
Lithuania	01 May 2004
Luxembourg	05 Feb 2002
Malta	01 May 2004
Netherlands	05 Feb 2002
Poland	01 May 2004
Portugal	05 Feb 2002
Slovak Republic	01 May 2004
Slovenia	01 May 2004
Spain	05 Feb 2002
Sweden	05 Feb 2002
United Kingdom	05 Feb 2002
Norway	20 Feb 2002
Iceland	28 Feb 2002
Switzerland	06 Dec 2002
Israel	25 Mar 2004
Australia	13 Aug 2002
New Zealand	13 Nov 2005
Argentina	01 Dec 2003
Brazil	27 June 2003
Mexico	31 Aug 2004
Guyana*	03 Apr 2006
Bahamas*	23 Sept 2004
Uruguay	Apr 2006
Dominica*	13 Jun 2006
Ghana*	18 July 2005
Uganda*	19 Nov 2004
Kenya*	19 Jan 2005
Zambia*	30 Nov 2004
Namibia*	19 July 2005
Botswana*	02 Jun 2005

Territory	Approval Date
Ethiopia*	23 Mar 2006
Rwanda*	11 Nov 2004
The Gambia*	13 Dec 2004
Democratic Republic of Congo (DRC) *	18 Aug 2005
Seychelles*	Product can be Marketed
Mauritius*	Product can be Marketed
Angola*	Product can be Marketed
Solomon Islands*	Product can be Imported

Abbreviations: GAP, Gilead Access Program;
*Marketing authorizations received for the TDF Tablets (For Export Only) available in countries that are listed on the Gilead Access Program and/or the United States President's Emergency Plan for AIDS Relief (PEPFAR) Initiative.

Gilead Sciences submitted TDF to be included in the Procurement, Quality and Sourcing Programme: Access to Antimalarial, Antituberculosis and HIV/AIDS Drugs and HIV/AIDS Diagnostics of Acceptable Quality. It was pre-qualified and listed in the 31st edition of the List of Pre-qualified HIV/AIDS Drugs with the pre-qualification number HA329.

14. Availability of pharmacopoeial standards:

British Pharmacopoeia: no
International Pharmacopoeia: no
United States Pharmacopoeia: no

15. Proposed (new/adapted) text for the WHO Model Formulary:

WHO Model Formulary 2007

Description:

In vivo, TDF is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. It belongs to a class of antiretroviral agents called Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) with activity against HIV-1 reverse transcriptase. It has efficacy against HIV-1 comparable to other NRTIs such as zidovudine, dideoxyinosine, didanlsine, dideoxycytidine, stavudine, lamivudine, and abacavir. It is effective in combination with other antiretroviral agents for the treatment of HIV infection.

How Supplied:

Tablets, TDF 300 mg, which is equivalent to 245 mg of tenofovir disoproxil.

Use:

For the treatment for HIV infection in adults in combination with other antiretroviral agents.

Contraindications:

Known hypersensitivity to tenofovir or to any of the components of the product.

Warnings:

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with TDF should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).[22]

Patients Co-infected with HIV and Hepatitis B Virus

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. TDF is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TDF have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued TDF. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TDF and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.[22]

Renal Impairment

Tenofovir is principally eliminated by the kidney. Dosing interval adjustment is recommended in all patients with creatinine clearance <50 mL/min. No safety data are available in patients with renal dysfunction who received TDF using these dosing guidelines.[22]

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of TDF. The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents; however, some cases occurred in patients without identified risk factors.[22]

TDF should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.[22]

Other

TDF should not be used in combination with the emtricitabine and tenofovir DF fixed dose combination tablet since it is a component of that product.[22]

Precautions:

Drug Interactions

Precautions should be taken when TDF is co-administered with didanosine (ddI), atazanavir (ATV), lipinavir/ritonavir, and drugs that reduce renal function or compete for active tubular secretion. Didanosine should be discontinued in patients who developed ddI-associated adverse events and TDF should be discontinued in patients who developed TDF-associated adverse events.[22]

When administered with TDF, the maximum concentration (C_{max}) and area under the curve (AUC) of ddI increased significantly. In adults weighing >60 kg, the ddI dose should be reduced to 250 mg when it is co-administered with TDF. Data are not available to recommend a dose adjustment of ddI for patients weighing <60 kg.[22]

TDF decreases the AUC and the minimum concentration (C_{min}) of ATV. When co-administered with TDF, it is recommended that ATV 300 mg is given with ritonavir 100 mg. ATV without ritonavir should not be co-administered with TDF.[22]

Bone Effects

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.[22]

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.[22]

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TDF. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, PCP, or tuberculosis), which may necessitate further evaluation and treatment.[22]

Animal Toxicology

Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 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.[22]

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.[22]

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.[22]

TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative when administered to male mice.[22]

There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.[22]

Pregnancy:

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-

controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, TDF should be used during pregnancy only if clearly needed.[22]

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TDF, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.[22]

Nursing Mothers: The U.S. Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving TDF.[22]

Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.[22]

Geriatric Use

Clinical studies of TDF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.[22]

Overdose:

Limited clinical experience at doses higher than the therapeutic dose of TDF 300 mg is available. In study 901, 600 mg TDF was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of TDF, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose. The elimination of tenofovir by peritoneal dialysis has not been studied

Dosage and Administration:
For adults 18 years of age and older, the dose of TDF is 300 mg once daily without regard to food.

Dose Adjustment in Patients with Renal Impairment
The dosing interval of TDF should be adjusted in patients with baseline creatinine clearance using the following guidelines:

	Creatinine Clearance (ml/min)[a]			Haemodialysis Patients
	≥ 50	30-49	10-29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Twice a week	Every 7 days, or after a total of approximately 12 hours of dialysis[b]

[a]Calculated using ideal (lean) body weight.
[b]Generally once weekly assuming three haemodialysis sessions a week of approximately 4 hours duration. TDF should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with CrCL <10 mL/min; therefore, no dosing recommendation is available for these patients.

Adverse effects:

The adverse reactions seen in treatment experienced patients were generally consistent with those seen in treatment naïve patients including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence. Less than 1% of TDF treated patients discontinued treatment due to the gastrointestinal events.

Laboratory abnormalities observed in patients in clinical trials occurred with similar frequency in the TDF arm compared to either the placebo or d4T group in all patients, with the exception of triglyceride elevations that were more common in the stavudine group (8%) vs. TDF (2%). Laboratory values that were evaluated included triglycerides, creatine kinase, serum amylase, urine glucose, AST, ASL, serum glucose, neutrophils, and hematuria.

Post-Marketing Experience
In addition to adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of TDF: allergic reaction, hypophosphatemia, lactic acidosis, dyspnea, abdominal pain, increased amylase, pancreatitis, increased liver enzyme, hepatitis, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, polyuria, and nephritis. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to TDF.

Patient advice:
Take TDF exactly as your healthcare provider prescribed it. May be taken with or without a meal. If you forget to take TDF, take it as soon as you remember that day. Do not take 2 doses at the same time. Tell your provider about all the medicines you take, including prescription and non-prescription medicines and dietary supplements. Contact your healthcare provider if you are not sure what to do.

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Attachment 1: Glossary of Abbreviations

3TC	Lamivudine
ABC	abacavir
ACE	Angiotensin converting enzyme
AZT	Zidovudine
AE	Adverse events
AIDS	Acquired immune deficient syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the curve
AZT/3TC	Zidovudine/lamivudine (Combivir®)
BID	Twice-daily
BL	Baseline
BMD	Bone mineral density
BUN	Blood urea nitrogen
CBV	Combivir®
CDC	Centers for disease control
CI	Confidence interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CrCL	Creatinine clearance
d4T	Stavudine
DART	Development of Anti-Retroviral Therapy in Africa

dATP	2'-deoxyadenosine 5'-triphosphate
ddI	didanosine
DF	disoproxil fumarate
DHHS	Department of Health and Human Services
dL	deciliter
DNA	Deoxyribonucleic acid
EAPs	Expanded Access programs
EFV	Efavirenz
EPO	erythropoietin
EU	European Union
F	Female
FDA	Food and Drug Administration
FTC	Emtricitabine
g	grams
GI	Gastrointestinal
GMP	Good Manufacturing Practices
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B Virus
HDL	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
IAS	International Aids Society
IQR	Interquartile Range
ITT	Intention-to-treat
kg	kilograms
KM	Kaplan Meyer
LDL	Low-density lipoprotein cholesterol
LFT	Liver function test

LPV/r	Lopinavir/ritonavir
M	Male
M = F	Missing = failure
MCV	Mean corpuscular volume
mg	milligrams
mITT	Modified intent-to-treat
n	Number of patients
NDA	New Drug Application
NF	National Formulary
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NNRTI-R	Non-nucleoside reverse transcriptase inhibitor-resistance
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OD	Observed data
OI	Opportunistic infection
PCP	*Pneumocystis jirovecii* pneumonia
PI	Protease Inhibitor
PSUR	Periodic safety update report
QD	Once-daily
RBC/HPF	Red blood cells per high power field
RNA	Ribonucleic acid
RT	Reverse Transcriptase
SAE	Serious adverse events
SATS	Symptoms, Adherence, and Treatment Satisfaction
SCr	Serum Creatinine
SD	Standard deviation

TAM	Thymidine analogue mutation
TC	Total cholesterol
TDF	Tenofovir disoproxil fumarate
TG	Triglycerides
TLOVR	Time to loss of virologic response
U/L	Unit/liter
ULN	Upper limit of normal
UNAIDS	United Nations Program on HIV/AIDS
US	United States
USD	United States Dollars
USP	United States Pharmacopoeia
VF	Virologic failure
WHO	World Health Organization

Attachment 2:

Summary of Principal Clinical Trials of Oral Tenofovir DF:

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
GS-98-903 (Gallant et al. JAMA 2004)	Randomised, double-blind, multicentre equivalence study of tenofovir DF versus stavudine (d4T) in a triple combination regimen with lamivudine (3TC) and efavirenz (EFV) in antiretroviral naïve patients.	144 weeks	Antiretroviral-naive, HIV-1-infected patients with plasma HIV-1 RNA levels > 5,000 copies/mL at screening. No restriction on CD4 count. Tenofovir DF 299: (220M, 79F, age 19-61) Active control 301: (225M, 76F, age 18-64)	The tenofovir DF regimen was equivalent to the stavudine control regimen in reducing plasma HIV-1 RNA levels. HIV RNA <400 copies/mL at Week 48, ITT (missing=failure)/TLOVR: TDF+3TC+EFV: 80% (79%) d4T+3TC+EFV: 84% (82%) HIV RNA <50 copies/mL at Week 48, ITT (missing=failure): TDF+3TC+EFV: 76% d4T+3TC+EFV: 80% HIV RNA <400 copies/mL at Week 144, ITT (missing=failure)/TLOVR: TDF+3TC+EFV: 76% (68%) d4T+3TC+EFV: 72% (62%) HIV RNA <50 copies/mL at Week 144, ITT (missing=failure): TDF+3TC+EFV: 73% d4T+3TC+EFV: 69% Tenofovir DF and stavudine were similarly effective in increasing mean CD4 cell counts with up to 144 weeks of treatment (263 vs. 283 cells/mm^3, respectively)	Tenofovir DF in combination with 3TC and EFV was well tolerated through 144 weeks of treatment. The assessment of clinical adverse events and laboratory abnormalities indicated that the safety profile of tenofovir DF 300 mg/day was similar to that of the stavudine active control. After 144 weeks of therapy, patients treated with a TDF-containing regimen showed significantly less mitochondria-associated toxicity, a better lipid profile, and similar renal profile compared to those treated with a stavudine-containing regimen. However, patients in the TDF arm had greater percentage decreases in bone mineral density (BMD) at the lumbar spine (but not the hip) and increases in biochemical markers of bone metabolism. In the tenofovir DF group 43 SAEs were reported in 34 patients (11%) compared with 39 SAEs in 31 patients (10%) in the control group. SAEs in 8 patients (4 patients in each group) were considered by the investigator to be possibly related to study drugs. Five patients (1 in the tenofovir DF group and 4 in the active control group) died during the first 48-week phase of the study. All five deaths were considered by the investigator as not related to study medications.

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
GS-934 (Gallant et al. 2006)	Phase 3, open-label, multicenter study to evaluate safety and efficacy of a FTC 200 mg + TDF 300 mg + EFV 600mg QD regimen vs. 3TC 150 mg/AZT 300 mg (CBV) BID + EFV 600 mg QD	96 weeks, open-label	Treatment-naïve HIV-infected patients with HIV RNA >10,000 copies/mL. Randomised 1:1 to: FTC 200 mg QD + TDF 300mg QD + EFV 600mg QD vs. 3TC 150mg/AZT 300mg BID + EFV 600mg QD Median HIV RNA: 5.0 log_{10} copies/mL for both groups Median CD4: 233 cells/mm^3 FTC + TDF arm vs. 241 cells/mm^3 3TC/AZT arm	**At Week 48:** HIV RNA <400 copies/mL: (TLOVR, ITT analysis): (p=0.005) o TDF+FTC+EFV: 81% o 3TC+AZT+EFV: 70% HIV RNA <400 copies/mL: (TLOVR, mITT analysis): (p=0.002) o TDF+FTC+EFV: 84% o 3TC+AZT+EFV: 73% HIV RNA <50 copies/mL: (TLOVR, ITT analysis): (p=0.03) o TDF+FTC+EFV: 77% o 3TC+AZT+EFV: 68% HIV RNA <50 copies/mL: (TLOVR, mITT analysis): (p=0.02) o TDF+FTC+EFV: 80% o 3TC+AZT+EFV: 70% Increase in CD4 cell count from baseline (as-treated analysis): (p=0.002) o TDF+FTC+EFV: 190 cells/mm^3 o 3TC+AZT+EFV: 158 cells/mm^3 Increase in CD4 cell count from baseline (as-treated analysis): (p=0.002) o TDF+FTC+EFV: 190 cells/mm^3 o 3TC+AZT+EFV: 158 cells/mm^3 **At Week 96**: HIV RNA <400 copies/mL (TLOVR analysis): (p=0.004) o TDF+FTC+EFV: 75% o 3TC+AZT+EFV: 62% HIV RNA <50 copies/mL (TLOVR analysis): (p=0.16) o TDF+FTC+EFV: 67% o 3TC+AZT+EFV: 61% Increase in CD4 cell count from baseline: (p=.036) o TDF+FTC+EFV: 270 cells/mm^3	At Week 48: Discontinued the study (TLOVR): (p=.02) o FTC+TDF+EFV: 4% o 3TC/AZT+EFV: 9% Discontinued due to anemia (TLOVR): (p=<.001) o FTC+TDF+EFV: 0% o 3TC/AZT+EFV: 6% At Week 96: Discontinued the study (p=0.023): o FTC+TDF+EFV: 5% o AZT/3TC+EFV: 11% Discontinued due to anemia (p<0.001) o FTC+TDF+EFV: 0% o AZT/3TC+EFV: 6% Median GFR (CG calculation) (p=0.51): o FTC+TDF+EFV: 119 mL/min o AZT/3TC+EFV: 118 mL/min Median GFR (MDRD calculation) (p=0.006): o FTC+TDF+EFV: 100 mL/min/1.73m^2 o AZT/3TC+EFV: 108 mL/min/1.73m^2 No patient in the FTC + TDF arm experienced confirmed Grade 1-4 renal abnormality as compared to two patients in the AZT/3TC arm. Median Total Limb Fat (p<0.001): o FTC+TDF+EFV: 7.7 kg o AZT/3TC+EFV: 5.5 kg

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
GS-99-907 (Squires et al. 2003)	Randomised, double-blind, placebo-controlled, multicentre intensification study to evaluate safety and efficacy of tenofovir DF 300 mg in treatment-experienced patients on stable antiretroviral therapy	48 weeks (double-blind phase 24 weeks, open label phase to 48 weeks)	HIV-1 infected patients on stable anti-retroviral regimen of not more than 4 antiretroviral agents with plasma HIV-1 RNA levels ≥400 copies/mL and ≤10 000 copies/mL. No restriction on CD4 count. Tenofovir DF 368: (309M, 59F, age 22-66) Placebo 182: (160M, 22F, age 27-70) 94% of patients had plasma HIV-1 expressing one or more primary nucleoside-associated resistance mutations in RT at baseline.	At Week 24, the DAVG log_{10} plasma HIV-1 RNA was significantly greater for the tenofovir DF group than for the placebo group (-0.61 vs. -0.03; p<0.0001). The proportion of patients with plasma HIV-1 RNA levels < 400 and < 50 copies/mL was greater in the tenofovir DF group compared to placebo from week 2 up to week 24. The antiviral effect of tenofovir DF was durable through 48weeks. HIV RNA < 400 copies/mL (< 50 copies/mL) at Week 24, ITT: Placebo: 13% (1%) TDF 300mg: 45% (22%) HIV RNA < 400 copies/mL (< 50 copies/mL) at Week 48, ITT: Placebo/TDF 300 mg: 44% (23%) TDF 300mg: 41% (18%) At week 24, the DAVG CD4 count was significantly greater for the tenofovir DF group than for the placebo group (p = 0.0008). Significant reductions in HIV-1 RNA levels with tenofovir DF were demonstrated in patients with HIV-1 expressing zidovudine/thymidine analogue resistance mutations, the M184V lamivudine/abacavir resistance mutation, NNRTI- and PI-associated resistance mutations, and combinations of these resistance mutations.	Overall the incidence of clinical adverse events was similar in the tenofovir DF and placebo groups. For 3 events (vomiting, flatulence and nausea), the incidence was ≥ 5% in the tenofovir DF group than in the placebo group. During 24 weeks, the incidence of ≥ Grade 3 clinical adverse events was 13% for the tenofovir DF group and 14% for the placebo group. Each individual event was reported in < 1% of tenofovir DF-treated patients. Grade 3 laboratory abnormalities reported in ≥ 1% of patients in either treatment group included elevated triglycerides, neutrophils, elevated AST and ALT, hyperglycaemia, elevated creatine kinase, elevated serum amylase, and urine glucose. Grade 4 toxicities reported in ≥ 1% of patients included elevated triglycerides and elevated creatine kinase. The pattern of adverse events and laboratory abnormalities was similar during the open-label phase. One patient died due to non-small cell lung cancer during the open-label phase. During the double-blind phase, 19 tenofovir DF patients (5%) and 13 placebo patients (8%) experienced an SAE. Individual events were reported in 1% or less of patients.

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
GS-98-902 (Schooley et al. 2002)	Randomised, double-blind, placebo-controlled, multicentre, intensification study to evaluate safety and efficacy of 3 tenofovir DF dose regimens (75 mg, 150 mg and 300 mg qd) in treatment-experienced patients on stable antiretroviral therapy	48 weeks double-blind period. Open-label extended dosing period.	HIV-1 infected patients on stable anti-retroviral regimen of not more than 4 antiretroviral agents with plasma HIV-1 RNA levels ≥400 copies/mL and ≤100 000 copies/mL No restriction on CD4 count. Tenofovir DF 158: (tenofovir DF 75 mg: 46M, 7 F; age 29-62 tenofovir DF 150 mg: 48M, 3 F; age 27-60; tenofovir DF 300 mg: 51M, 3 F ; age 27-60) Placebo 28: (26M, 2F, age 30-56) 94% of patients had plasma HIV-1 expressing one or more primary nucleoside-associated resistance mutations in RT at baseline.	There was a statistically significant difference in time weighted average change from baseline (DAVG) of log10 plasma HIV-1 RNA levels at weeks 4 and 24 for all three tenofovir DF doses compared to placebo. The antiviral effect was sustained through 48 week treatment with the 300 mg dose superior to the 75 mg and 150 mg doses. Mean DAVG4 / DAVG24 / DAVG48 HIV-1 RNA: Placebo: +0.02 / +0.02 TDF 75 mg : -0.22 / -0.26 / -0.33 (300 mg) TDF 150 mg: -0.44 / -0.34 / -0.34 (300 mg) TDF 300 mg: -0.62 / -0.68 / -0.62 HIV RNA < 400 copies/mL (< 50 copies/mL) at Week 24, As treated: Placebo: 4% (0%) TDF 75 mg : 9% (4%) TDF 150 mg: 12% (2%) TDF 300mg: 19% (11%) Changes in CD4 cell counts did not differ significantly between the tenofovir DF group and placebo groups. Open-Label Phase: Mean change in HIV-1 RNA (log_{10} copies/mL) levels at weeks 72 / 96: TDF 75/300 mg : -0.66 / -0.86 TDF 150/300 mg: -0.64 / -0.65 TDF 300/300 mg: -0.63 / -0.87	The incidence of most adverse events and laboratory abnormalities was similar amongst the tenofovir DF groups and the placebo group during the first 24 weeks of the study. Through 48 weeks, most adverse events and laboratory abnormalities did not show a dose response pattern among the tenofovir DF groups. During the first 24 weeks of the study, the most frequently reported adverse events were headache, asthenia, pain, diarrhoea, nausea, vomiting, rash and pharyngitis. Of these, only diarrhoea appeared slightly more common in the tenofovir DF groups. During this period, the most common grade 3 or 4 laboratory abnormalities were elevations of triglycerides and creatine kinase. Through 48 weeks, 35 SAEs were reported for 25 patients. One death (suicide) was reported during the double-blind phase. The long-term safety profile in the open-label extended dosing phase was similar to observed during the initial 48 weeks of the study.