Application for Inclusion of Emtricitabine and Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablet On the WHO Model List of Essential Medicines

Submitted By

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Application for Inclusion of Emtricitabine and Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablet (Truvada™) on WHO Model List of Essential Medicines

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

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

Emtricitabine (FTC) and tenofovir disoproxil fumarate (tenofovir DF, TDF) fixed dose combination tablet 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.

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.

Emtricitabine and tenofovir DF have demonstrated effectiveness in a wide variety of patients initiating their first ARV regimens. The co-administration of tenofovir DF and emtricitabine (or structurally-similar lamivudine) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) is associated with low rates of resistance, limited cross-resistance, and multiple successful second-line regimens. Emtricitabine and tenofovir DF fixed dose combination tablet may help improve adherence, as it is dosed as one tablet taken once-a-day in combination therapy. Both tenofovir DF and emtricitabine have been shown to be well tolerated and safe in long term studies.

The endorsement by the World Health Organization (WHO) of Triommune (stavudine [d4T] + lamivudine [3TC] + nevirapine [NVP]) as the most suitable regimen for initial therapy was made before the availability of tenofovir DF, emtricitabine and most recently the fixed dose combination of emtricitabine and tenofovir DF. 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 tenofovir DF + emtricitabine should be a component of first line ARV regimens containing efavirenz (EFV) (DHHS Guidelines) and/or a boosted PI (IAS Guidelines).

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 emtricitabine and tenofovir DF, the components of the fixed dose combination, has demonstrated a more favourable safety and efficacy profile than regimens containing d4T+3TC.[3] Therefore, we propose that emtricitabine and tenofovir DF fixed dose combination tablet 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 organisation(s) consulted and/or supporting the application:**

Not Applicable

4. **International Nonproprietary Name:**

emtricitabine and tenofovir disoproxil fumarate tablet

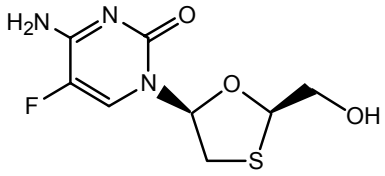
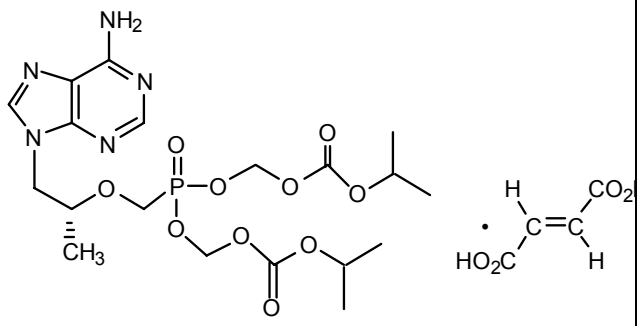
5. Formulation Proposed for Inclusion

The formulation composition of emtricitabine/tenofovir DF tablets is provided below:

Active Ingredients

Each tablet contains 200 mg emtricitabine and 300 mg of tenofovir DF, which is equivalent to 245 mg of tenofovir disoproxil. See Table 1 below for a listing of the active ingredients of the emtricitabine and tenofovir DF fixed dose combination tablet.

Table 1: Active Ingredients of Emtricitabine and Tenofovir DF Fixed Dose Combination Tablet

Approved Name	*Chemical Name, Structural and Molecular Formulae*	*Specification or Reference of such*	*Qty per Tablet*	*Qty per Batch*
Emtricitabine	5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine  $C_8H_{10}FN_3O_3S$	In-house	200 mg	80 kg*
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†	120 kg*

* Commercial batch size of the drug product varies depending on manufacturing site.
Altana: 325 kg
Patheon: 400 kg
Aspen: 600 kg

† Equivalent to 245 mg of tenofovir disoproxil.
The formula weight of tenofovir disoproxil fumarate (C23H34N5O14P) is 635.52, and the formula weight of tenofovir disoproxil (C19H30N5O10P) is 519.45.

$$300 \text{ mg tenofovir disoproxil fumarate} = 300 \text{ x } \frac{519.45}{635.52} = 245 \text{ mg tenofovir disoproxil}$$

6. International Availability

Emtricitabine and tenofovir DF fixed dose combination tablets will be manufactured, for Gilead Sciences, Inc., at any of the following facilities listed below (Table 2). A supplement to the US NDA will be submitted to add Aspen Pharmacare as a manufacturing, packaging, and labeling site. All other sites are currently approved in the 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 Emtricitabine and Tenofovir DF Fixed Dose Combination 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, Inc.	650 Cliffside Drive San Dimas, California 91773 USA	Packaging, labelling, testing and release
5	Gilead Sciences, Limited	13 Stillorgan Industrial Park Blackrock Co. Dublin Ireland	Packaging, labelling, testing and release
6	Aspen Phamracare	7 Fairclough Road Korsten, 6014 Port Elizabeth South Africa	Manufacturing, 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 nucleoside/nucleotide analogue reverse transcriptase inhibitors. 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 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.[4] 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.[5] 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.[6] 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.[4] 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.[4,6]

The proportion of women who are affected by the epidemic continues to increase.[7] As of 2003, women accounted for nearly 50% of all people living with HIV worldwide.[7] In 2005, 17.5 million women were living with HIV, which is one million more than in 2003.[4] 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.[4] Without HIV prevention measures, about 35% of children born to HIV-positive women will contract the virus.[4] 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.[7]

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.[8] For example, of the 14,000 persons who became infected each day in 2005, about 12,000 (86%) were aged 15 to 49 years.[5] Overall, young people aged 15 to 24 years account for about half of all new HIV infections per day worldwide.[5] The introduction of potent antiretroviral 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 viral load, extending the asymptomatic phase of infection, and improving the quality of life for many infected individuals.[9]

8.2. Assessment of current use

The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[1] Suppression of viral load as much as possible, for as long as possible, is an important and achievable goal of antiretroviral 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 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.[10] 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 (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.[11] This latter study included patients with repeat samples, however in studies of the Monogram Biosciences database in which > 16,000 individual US patient RT genotypes from 2003 were characterized, similar frequencies of NRTI mutations were observed.[12] 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 antiretroviral 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.[13] A recent US study of 1082 treatment-naïve HIV-1 patients found a prevalence of 8.3% of patients with any transmitted resistance, predominantly to NRTIs.[14] Two studies of recent European seroconverters have identified 9.6%[15] and 10.3%[16] of antiretroviral 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 antiretroviral therapy.[17] Recent clinical trials such as study GS-01-934 have highlighted the importance of baseline resistance on response to antiretroviral therapy. In this study of emtricitabine + tenofovir DF + EFV versus lamivudine(3TC)/zidovudine(AZT) + EFV, NNRTI resistance was present at baseline in 4.3 % of antiretroviral 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.[18] 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.[19]

Taken together, these findings point to the urgent need for novel and improved antiretroviral 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 antiretrovirals (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.[7] It is primarily in these high income countries where standards of treatment and care have evolved considerably.[20] 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.[21]

Although the number of people in low- and middle-income countries receiving HIV antiretroviral therapy has tripled since the end of 2001, overall access to antiretroviral treatment and other HIV-related disease care remains low.[4,7] 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 antiretroviral treatment.[7] In Brazil, the government estimates that the policy of universal access to antiretroviral drugs has saved USD 2.2 billion in hospital care that would have otherwise been needed by people living with HIV.[7]

Other programs, such as the UNAIDS Drug Access Initiative Pilot Program and the WHO/UNAIDS "3 by 5 Initiative," are designed to increase antiretroviral access to people in low- and middle-income countries.[20] Since its launch in 2003, antiretroviral 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 antiretroviral therapy to the public sector in four low- and middle-income countries in the late 1990s.[20] 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

Emtricitabine and tenofovir DF fixed dose combination tablet is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.[22]

Additional important information regarding the use of emtricitabine and tenofovir DF fixed dose combination tablet for the treatment of HIV-1 infection:

- It is not recommended that emtricitabine and tenofovir DF fixed dose combination tablet be used as a component of a triple nucleoside regimen.

- Emtricitabine and tenofovir DF fixed dose combination tablet should not be coadministered with emtricitabine, tenofovir DF or 3TC containing products.
- In treatment experienced patients, the use of emtricitabine and tenofovir DF fixed dose combination tablet should be guided by laboratory testing and treatment history.[22]

9.1. Recommended Dosage

Adult: The dose of emtricitabine and tenofovir DF fixed dose combination tablet in adults is one tablet (200 mg of emtricitabine and 300 mg tenofovir DF) once-daily taken orally in combination with other antiretroviral agents, with or without food.[22]

Children: Emtricitabine and tenofovir DF fixed dose combination tablet is not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, tenofovir DF, for which safety and efficacy have not been established in this age group.[22]

Elderly: Clinical studies of emtricitabine or tenofovir DF 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 patients 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]

Renal insufficiency: Emtricitabine and tenofovir are eliminated by renal excretion, and the exposure to emtricitabine and tenofovir increases in patients with renal dysfunction. Dosing interval adjustment is required in all patients with baseline creatinine clearance 30-49 ml/min, as detailed below. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients. No safety and efficacy data are available in patients with renal dysfunction who received emtricitabine and tenofovir DF fixed dose combination using these guidelines in Table 3.[22]

Table 3. Dosage Adjustment for Patients with Altered Creatinine Clearance[22]

	Creatinine Clearance (mL/min)*		
	≥50	**30–49**	**<30 (Including Patients Requiring Hemodialysis)***
Recommended Dosing Interval	Every 24 hours	Every 48 hours	Should not be administered.

* Calculated using ideal (lean) body weight.

Hepatic impairment: The pharmacokinetics of tenofovir following a 300 mg dose has been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared

with unimpaired patients. The pharmacokinetics of emtricitabine and tenofovir DF fixed dose combination tablet or emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.[22]

Concomitant Antiretroviral Therapy: emtricitabine and tenofovir DF fixed dose combination tablet must be given in combination with other antiretroviral medications (such as NNRTIs or PIs).[22]

Emtricitabine and tenofovir DF fixed dose combination tablet should not be coadministered with emtricitabine or tenofovir DF. Due to similarities between emtricitabine and 3TC, emtricitabine and tenofovir DF fixed dose combination tablet should not be coadministered with other drugs containing 3TC, including Combivir®, Epivir®, Epivir-HBV®, Epzicom™, Kivexa™, or Trizivir®.[22]

Drug Interactions: When tenofovir DF was administered with didanosine (ddI) the Cmax and AUC of ddI administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher ddI concentrations could potentiate ddI associated adverse events, including pancreatitis, and neuropathy. In adults weighing >60 kg, the ddI dose should be reduced to 250 mg when it is coadministered with emtricitabine and tenofovir DF fixed dose combination tablets. Data are not available to recommend a dose adjustment of ddI for patients weighing <60 kg. When coadministered, emtricitabine and tenofovir DF fixed dose combination tablets and Videx EC® may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of ddI buffered tablet formulation with emtricitabine and tenofovir DF fixed dose combination tablets should be under fasted conditions. Coadministration of emtricitabine and tenofovir DF fixed dose combination tablets and ddI should be undertaken with caution and patients receiving this combination should be monitored closely for ddI-associated adverse events. ddI should be discontinued in patients who develop ddI-associated adverse events.

Atazanavir (ATV) and lopinavir/ritonavir (LPV/r) have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving ATV and LPV/r and emtricitabine and tenofovir DF fixed dose combination tablet should be monitored for emtricitabine and tenofovir DF fixed dose combination tablet associated adverse events. Emtricitabine and tenofovir DF fixed dose combination tablet should be discontinued in patients who develop emtricitabine and tenofovir DF fixed dose combination tablet associated adverse events.

Tenofovir decreases the AUC and Cmin of ATV. When coadministered with emtricitabine and tenofovir DF fixed dose combination tablet, it is recommended that ATV 300 mg is given with ritonavir 100 mg. ATV without ritonavir should not be coadministered with emtricitabine and tenofovir DF fixed dose combination tablet.

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of emtricitabine and tenofovir DF fixed dose combination tablets with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of

emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir.

9.2. Duration

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

9.3. Guidelines

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) guidelines (updated in May 2006) recommend that emtricitabine and tenofovir DF, the individual components of the fixed dose combination tablet, should be a component of first line ARV regimens containing EFV (DHHS Guidelines).[1] Similarly, the International AIDS Society-USA (IAS) Treatment Recommendations for Adult HIV Infection (updated in July 2004) recommend that emtricitabine and tenofovir DF should be a component of first line ARV regimens containing EFV and/or a boosted protease inhibitor.[2]

9.4. 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 submission, 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:

- Emtricitabine
- FTC
- Coviracil

- Emtriva
- Tenofovir
- GS4331
- PMPA
- Viread
- Truvada

Study selection:

- Randomized, Phase 3 pivotal clinical trials that compared emtricitabine to 3TC or examined the combination of tenofovir DF and 3TC in HIV-infected adults
- Other clinical studies that examined the combination of emtricitabine and tenofovir DF in HIV-infected patients

10.2. Summary of available data

Safety and efficacy studies using emtricitabine and tenofovir DF fixed dose combination tablets or using emtricitabine and tenofovir DF in combination are ongoing. However, both components of emtricitabine and tenofovir DF fixed dose combination tablet have been studied individually, as part of multidrug regimens and have been found to be safe and effective. Since emtricitabine and 3TC are comparable in their structure, resistance profiles, and efficacy and safety as part of multidrug regimens, existing data from the use of 3TC and tenofovir in combination have been extrapolated to support the use of emtricitabine and tenofovir DF fixed dose combination tablets for the treatment of HIV-1 infection in adults.

Studies have also shown that the co-administration of tenofovir DF and emtricitabine (or structurally-similar 3TC) with a NNRTI or PI is associated with low rates of resistance, minimal cross-resistance, and multiple successful second-line regimens. Because of the long half-life of emtricitabine and tenofovir DF, the emtricitabine and tenofovir DF fixed dose combination tablets may help improve adherence, as it is dosed as one tablet taken once-a-day in combination therapy.

Therefore, in treatment naïve HIV-infected patients, emtricitabine and tenofovir DF fixed dose combination tablets should be considered as an alternative to the combination of tenofovir DF and 3TC for those patients who might benefit from a once-daily regimen. In treatment-experienced HIV-infected patients, the use of emtricitabine and tenofovir DF fixed dose combination tablets should be guided by laboratory testing and treatment history.

A summary of clinical data from the pivotal trials (Studies GS-903 and FTC-303) submitted to the US FDA for the approval of emtricitabine and tenofovir DF fixed dose combination tablet is included below. Additional data from pharmacokinetic and bioequivalence studies (Studies FTC-114 and GS-0172), as well as information from clinical trials and other studies (Studies GS-934, M02-418, ANRS 1207/IMEA 025, and COMET) that examined the combined use of emtricitabine and tenofovir DF are also included. For detailed information regarding the safety and effectiveness of tenofovir DF in the treatment of HIV-1 infection, please refer to the application for the inclusion of tenofovir DF on the WHO Model List of Essential Medicines.

10.3 Pharmacokinetic and Bioequivalence Data

One emtricitabine and tenofovir DF fixed dose combination tablet was bioequivalent to one emtricitabine capsule (200mg) plus one tenofovir DF tablet (300 mg) following single-dose administration to fasting healthy subjects (N = 39).[22] The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir DF were administered together versus each agent dosed alone.[22,24]

Study FTC-114

The potential for a significant pharmacokinetic drug-drug interaction between emtricitabine and tenofovir DF and the safety and tolerability when these 2 products are co-administered were evaluated in an open-label, randomized, 3-way crossover study.[24] A total of 19 healthy volunteers received each of the following three 7-day treatments over a 21-day treatment period; drugs were administered 30 minutes after a standardized breakfast on Days 1, 5, 6, and 7 of each treatment period:

-Treatment A: Emtricitabine 200 mg once-daily x 7 days
-Treatment B: Tenofovir DF 300 mg once-daily x 7 days
-Treatment C: Emtricitabine 200 mg + Tenofovir DF 300 mg once-daily x 7 days

Plasma pharmacokinetic parameters at steady-state were assessed over a 24-hour dosing interval following the last dose of each treatment using a non-compartmental analysis. Results showed that no clinically significant drug-drug interaction was observed.

Study GS-0172

A randomized, open-label, cross-over study was conducted to evaluate the pharmacokinetics, bioequivalence, and safety of the investigational fixed-dose combination of emtricitabine 200 mg/tenofovir DF 300 mg to the co-administration of the individual emtricitabine 200 mg capsule and tenofovir DF 300 mg tablet in healthy subjects.[25] Results showed that the emtricitabine and tenofovir DF fixed dose combination tablet was bioequivalent to co-administration of the individual emtricitabine capsule and tenofovir DF tablet, as the 90% confidence interval (CI) about the ratio of geometric means for maximum concentration (C_{max}) and area under the curve (AUC) fell within the range of 80%-125%. Pharmacokinetic parameters of emtricitabine and tenofovir were also shown to be similar when administered as the emtricitabine and tenofovir DF fixed dose combination tablet compared to the emtricitabine capsule plus the tenofovir DF tablet.

A total of 44 healthy volunteers were enrolled and 39 completed the study. Blood samples were obtained over 48 hours after each subject received a dose of the study drug following an overnight fast on 2 occasions, separated by a 1-week washout period.

Plasma pharmacokinetic parameters were calculated using non-compartmental methods, assessed through comparison of systemic exposures (C_{max} and AUC) of emtricitabine and tenofovir for the emtricitabine and tenofovir DF fixed dose combination tablet vs. the emtricitabine capsule plus the tenofovir DF tablet. Formulation bioequivalence was assessed by generation of geometric mean

ratios (90% CI) for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for the emtricitabine and tenofovir DF fixed dose combination tablet vs. co-administration of the emtricitabine 200 mg capsule and the tenofovir DF 300 mg tablet.

10.4 Summary of comparative effectiveness in HIV-infected adults

Treatment-naïve HIV-infected patients

Study 903

Study 903 is a Phase 3, randomized, double-blind, active-controlled, multicenter clinical trial designed to compare the efficacy and safety of tenofovir DF (300 mg once-daily) to d4T (40 mg for ≥60 kg or 30 mg for <60 kg twice-daily) with a background regimen of 3TC (150 mg twice-daily) and EFV (600 mg once-daily) in 600 treatment-naïve HIV-infected individuals.[3,26] 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 viral loads >100,000 copies/mL and 39% had CD4 cell counts <200 cells/mm^3. While Gallant et al. (2004)[3] has presented results of this study based on ITT analysis, 48- and 144-week treatment outcomes that are described in the tenofovir DF U.S. Prescribing Information are based on TLOVR analysis (Table 4).

Table 4: Outcomes of Randomized Treatment in Study 903[3,26]

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%

Outcomes	At Week 48		At Week 144	
	TDF (n = 299)	d4T (n = 301)	TDF (n = 299)	d4T (n = 301)
	%	%	%	%
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 tenofovir DF 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 tenofovir DF arm and 283 cells/mm^3 for the d4T arm.[26]

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 tenofovir DF 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.[3,26-29] All patients began a new treatment regimen with a PI and other NRTIs. After a median follow up period of 155 weeks, five patients, including two who remained on tenofovir DF, achieved HIV RNA <50 copies/mL. Two patients were without follow up and one was non-adherent.[3,27,29] Based on an *in vitro* study, there appears to be a possible fitness barrier for the K65R mutant HIV *in vivo*.[30] This may help explain the low prevalence of K65R among antiretroviral-experienced patients (<2%),[31,32] as well as its low frequency of development in tenofovir DF-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 tenofovir DF+3TC+EFV once-daily regimen (3TC twice-daily was switched to once-daily) has been occurring, in which 86 patients who were originally randomized into the tenofovir DF arm have continued on tenofovir DF, while 85 patients originally randomized into the d4T arm have switched to the tenofovir DF regimen. The 86 patients originally enrolled in the tenofovir DF arm have been on tenofovir DF-containing HAART for a median duration of 201 weeks (range: 156-213) with a mean±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.[33]

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.[33]

Figure 1: Percentages of Patients with HIV RNA <400 copies/mL Through Week 192[33]

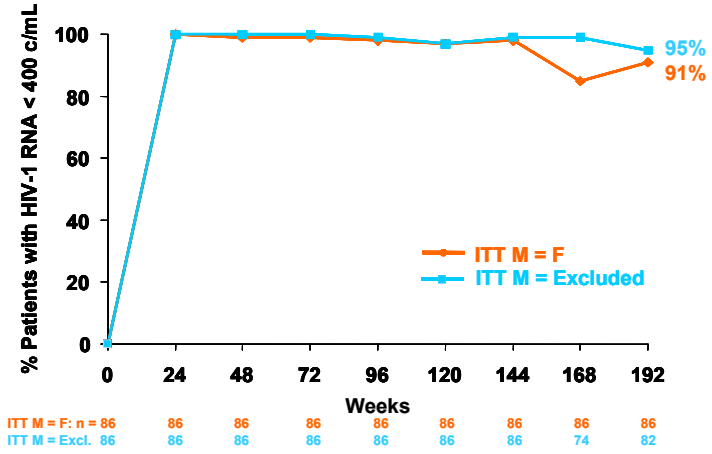
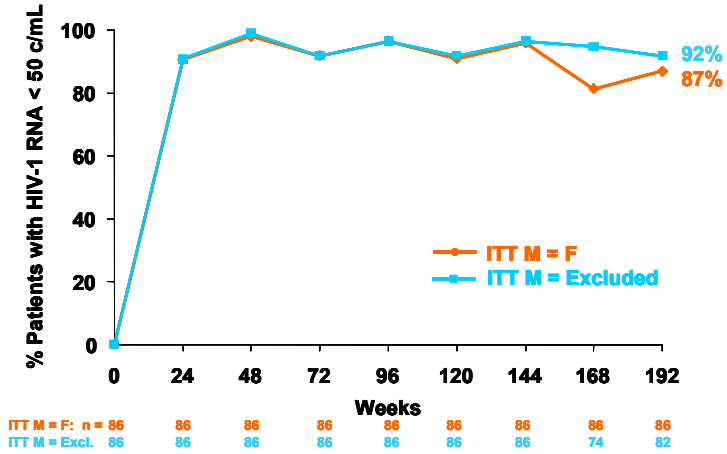


Figure 2: Percentages of Patients with HIV RNA <50 copies/mL Through Week 192[33]



Of the 85 patients who switched from d4T to tenofovir DF, they had been on d4T for a median duration of 152 weeks.[34] 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 tenofovir DF, 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%.[34]

Study GS-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 once-daily regimen containing emtricitabine 200 mg + tenofovir DF 300 mg plus EFV 600 mg vs. AZT 300 mg/3TC 150 mg (AZT/3TC) twice-daily plus EFV 600 mg once-daily in treatment-naïve HIV-infected patients with HIV RNA >10,000 copies/mL.[22,35,36] Patients were stratified on the basis of CD4+ cell counts (< or ≥200 cells/mm^3). A total of 517 patients were enrolled and randomized in a 1:1 ratio; 511 patients were treated with study medication. Please see Table 5 below for baseline characteristics of the ITT population, excluding two treatment-experienced patients (n = 509), as presented in Gallant et al.

Table 5: Baseline Characteristics (ITT)[36]

Parameter	FTC + TDF + EFV (n = 255)	AZT/3TC + EFV (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 also requiring confirmation of virologic success at two consecutive visits (Guidance for Industry, U.S. FDA 2002).[37] 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 emtricitabine + tenofovir DF group vs. the AZT/3TC group achieved and maintained HIV RNA <400 and <50 copies/mL (TLOVR in mITT population).[36] The difference in the proportion of patients who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the AZT/3TC group in this open-label study.[22] In addition, increases in CD4 cell count at Week 48 were significantly higher in the emtricitabine + tenofovir DF group (Table 6). Treatment outcomes through Week 48 for the mITT population are provided in Tables 6 and 7.

Table 6: Clinical Efficacy Endpoints at Week 48[22,35,36]

Parameter	Population	FTC + TDF (n = 244)	AZT/3TC (n = 243)	*P*-Value (95% CI)
HIV RNA <400 copies/mL (%)	mITT n = 487	84	73	.002 (+4, +19)
HIV RNA <50 copies/mL (%)	mITT n = 487	80	70	.02 (+2, +17)
Mean Change in CD4 Cell Count (cells/mm^3)	Available n = 363	+190	+158	.002 (+9, +55)
Mean Change in CD4 Percentage (%)	Available 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; mITT, modified intent-to-treat

Table 7: TLOVR Treatment Outcomes at Week 48 (mITT)[22,26]

Outcome at Week 48	FTC + TDF (n = 244)	AZT/3TC (n = 243)
Responder* (%)	84	73
Virologic failure† (%)	2	4
Rebound (%)	1	3
Never Suppressed (%)	0	0
Change in ART (%)	1	1
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
*Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48
†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

Through 48 weeks, 7 patients in the emtricitabine +tenofovir DF group and 5 patients in the AZT/3TC group experienced a new CDC Class C event.[22]

Week 48 analysis demonstrated that 12 patients in the emtricitabine + tenofovir DF 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 emtricitabine + tenofovir DF group than the AZT/3TC group, but this did not achieve statistical significance. Of the two patients in the emtricitabine + tenofovir DF group who had virologic rebound, one had a wild-type virus and one had an EFV-resistance mutation. Of the seven patients who had virologic rebound in the AZT/3TC group, all had EFV-resistance mutations, five had the M184V/I

mutation, and one had a TAM. The differences in the frequency of viral rebound between the two groups were not statistically significant (P =.11).[36]

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. Results showed that significantly more patients in the emtricitabine + tenofovir DF 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 emtricitabine + tenofovir DF 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 emtricitabine + tenofovir DF arm (270 versus 237 cells/mm^3; P = .036). The proportions of patients who achieved and maintained HIV RNA <50 copies/mL were 67% in the emtricitabine + tenofovir DF arm vs. 61% in the AZT/3TC arm (P = .16).[38] 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)[38]

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 emtricitabine + tenofovir DF arm and 29 patients in the AZT/3TC 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 emtricitabine + tenofovir DF arm than the AZT/3TC arm (P = .036).[38]

Study M02-418

This was an on-going, randomized , open-label, multicenter study designed to compare LPV/r 800/200 mg once-daily (n = 115) vs. LPV/r 400/100 mg twice-daily with a background regimen of tenofovir DF 300 mg once-daily and emtricitabine 200 mg once-daily (n = 75) in HIV-infected antiretroviral-naïve patients with HIV RNA >1,000 copies/mL.[39,40] At baseline, patients had a mean age of 39 years (range: 19-75), 46% were non-Caucasian, and 22% were female. Mean baseline CD4 cell count was 260 cells/mm^3 (range: 3-1006) and mean baseline HIV-1 RNA of 4.8 $\log_{10}$ copies/mL (range: 2.6-6.4 $\log_{10}$ copies/mL).

At Week 96, an ITT (non-completer = failure) analysis showed that 57% of patients in the once-daily group (n = 115) and 53% of patients in the twice-daily group (n = 75) had HIV RNA <50 copies/mL (95% CI: -10%, +19%, *P* =.58). The observed data (OD) method showed that through 96 weeks of therapy, 89% of patients in the LPV/r once-daily group (n = 74) and 89% of those in the LPV/r twice-daily arm (n = 44) achieved and maintained HIV RNA <50 copies/mL. Mean CD4 cell count increases, based on the OD method, at Week 96 were 244 cells/mm^3 for the LPV/r once-daily group and 264 cells/mm^3 for the LPV/r twice-daily group.[39]

Resistance testing results were available in 23 patients, 15 in the once-daily group and eight in the twice-daily group.[39] Genotypic analysis in those patients who qualified for resistance testing (HIV RNA >500 copies/mL between Weeks 12-96) did not identify any LPV/r or tenofovir DF resistance mutations. Resistance to emtricitabine was identified in a total of four patients (three in the once-daily group and one in the twice-daily group).

ANRS 1207/IMEA 025 Study

This open-label, single-arm pilot study was designed to evaluate the antiviral activity and tolerance of a once-daily combination regimen of emtricitabine + tenofovir DF + EFV in 40 HIV-1 infected treatment-naïve patients with CD4 cell count <350 cells/mm^3 in West Africa.[41] 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.[41] Overall treatment adherence was assessed at six time points through week 48; 0%-8% of patients reported missing at least one drug over the last three days and 8%-12% of patients reported missing at least one drug over the last month. The main reasons reported for lack of adherence were forgetting (63%), travelling (16%), and other disease (8%).[41]

Treatment-experienced HIV-infected patients

Study FTC-303

Study 303 was a Phase 3, 48-week, randomized, open-label, multicenter study comparing emtricitabine (200 mg once-daily) to 3TC (150 mg twice-daily), in combination with d4T (40 mg twice-daily) or AZT (300 mg twice-daily) and a PI or NNRTI in 440 adult patients who were on a 3TC-containing triple-antiretroviral regimen for at least 12 weeks prior to study entry and had HIV RNA ≤ 400 copies/mL.[42-44] Patients were randomized 1:2 to either continue therapy with 3TC or to switch to emtricitabine; the stable background regimen was maintained. At study entry, the median duration of prior antiretroviral and 3TC therapies were 27.6 and 18 months, respectively, the median HIV RNA was 1.7 $\log_{10}$ copies/mL, and the mean CD4 cell count was 527 cells/mm^3. Results at Week 48 are shown in Table 9. There were no statistically significant differences between treatment arms.

Table 9: Results at Week 48[42]

Parameters	**Emtricitabine (n = 294)**	**3TC (n = 146)**
Responder*	77% (67%)	82% (72%)
Virologic Failure†	7%	8%
Death	0%	<1%
Study Discontinuation Due to Adverse Events For Other Reasons‡	4% 12%	0% 10%

*Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48.
†Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
‡Includes lost to follow up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 29 cells/mm^3 for the emtricitabine arm and 61cells/mm^3 for the 3TC arm. Through Week 48, 2 patients (0.7%) in the emtricitabine group experienced a new CDC Class C event, compared to 2 patients (1.4%) in the 3TC group.[42]

A total of 7% (n = 21) of patients in the emtricitabine arm and 8% (n = 11) of patients the lamivudine arm had virologic failure (defined as patients who failed to achieve virologic suppression or rebounded to >400 HIV RNA copies/mL after achieving virologic suppression).[44] Genotypic analysis was attempted retrospectively on these patients; however, due to the low plasma HIV RNA level at baseline, M184 sequence was only obtained for 23 patients. Of these patients, 20 (87%) had the M184V mutation at baseline.

Patients with HIV RNA ≥50 copies/mL at baseline failed more frequently than those with HIV RNA <50 copies/mL at baseline (39% vs. 5%, P <.0001). Among patients with HIV RNA ≥50 copies/mL at baseline, those with the M184V mutation at baseline were significantly more likely to fail than those without the mutation (50% vs. 9%; P =.0277). These findings were similar between both treatment arms.[45]

COMET Study

The COMET study was a 24-week, prospective, multi-center, single-arm, phase 4 clinical trial designed to evaluate the impact of switching virologically suppressed (HIV RNA <400 copies/mL on AZT/3TC + EFV for ≥8 weeks), treatment-experienced, HIV-infected patients from a twice-daily regimen containing AZT/3TC + EFV to a once-daily regimen containing emtricitabine and tenofovir DF fixed dose combination tablet + EFV.[23] The objective of this study was to characterize the risks and potential benefits of switching from a AZT/3TC + EFV regimen to a emtricitabine and tenofovir DF fixed dose combination tablet + EFV regimen. Assessments included in this study were efficacy, safety, tolerability, adherence and quality of life (SATS questionnaire) at baseline and at Weeks 4, 12, and 24 post-switch. Quality of life was also assessed at baseline and Week 24 using the SF-36 survey instrument. The study protocol was also later amended to include fasting lipid profile, for which data through 24 weeks are available for 160 patients.

A total of 411 patients were enrolled into the study, however 9 patients were not evaluable (8 patients enrolled at a single site which did not enter any data, one patient was not dosed). Thus, post-baseline results are currently available for 402 patients who received at least one dose of study drug, including 30 patients who discontinued early from the study.[23] At baseline, 83% of these patients were male and 67% were Caucasian. Their median age was 43 years (IQR: 38 - 49). These patients had been taking AZT/3TC or AZT + 3TC for a median of 3.9 years (IQR: 1.9 - 5.5) with 90% having taken AZT/3TC for >1 year. Reasons for switching to the emtricitabine and tenofovir DF fixed dose combination tablet regimen included regimen simplification (84.3%), AZT/3TC -related adverse events (3.2%), and both (12.4%).[23]

Week 24 efficacy data are available for 366 patients; please refer to Table 10 for detailed HIV RNA results, based on both ITT, M = E and ITT, M = F analyses, as well as CD4 results.

Table 10: HIV RNA and CD4 Results at Week 24[23]

Parameter	**Baseline (n = 402)**	**Week 24 (n = 366)***	***P*-value**
HIV RNA <400 (copies/mL) (% of patients) -(ITT, M = E) -(ITT, M = F)	99.5%†	 95% 87%	 NA
HIV RNA <50 (copies/mL)‡ (% of patients) -(ITT, M = E) -(ITT, M = F)	71.1%	 81% 74%	 < .001§ .38
Parameter	**Baseline**	**Change from Baseline at Week 24***	***P*-value**
Median (IQR) CD4 Cell Count (cells/mm^3)	558 (381,784)	12 (-55, 88)	.023‖

Abbreviations: ITT, intention to treat; M = E, missing = excluded; M = F, missing = failure; NA, not applicable
*Patients with both baseline and Week 24 data available.
†Two patients had baseline HIV RNA ≥400 copies/mL. One patient with VL >1000 copies/mL (major protocol violation) was included in safety, but not efficacy analysis.
‡Or <75 copies/mL by bDNA (n = 28)
§McNemar test
‖Wilcoxon Sign-Rank test

Results from a validated questionnaire of patient-reported (n = 352) SATS demonstrated that by Week 24, significantly fewer patients complained of bothersome adverse events, fatigue, and nausea/vomiting (all $P < .001$, McNemar test) as compared to baseline. In addition, compared to baseline, significantly more patients reported being "very satisfied" with the emtricitabine and tenofovir DF fixed dose combination tablet regimen in regards to general satisfaction with the emtricitabine and tenofovir DF fixed dose combination tablet regimen, convenience/simplicity, tolerability, and control of the their HIV (all $P < .001$, McNemar test). Furthermore, when treatment adherence was assessed by SATS questionnaire, the number of patients who reported full (100%) adherence on ≥ 95% of days was significantly higher at Week 24 versus baseline for both 1-week and 1-month recall periods (both $P = .002$). According to pill count analysis, 87% of patients achieved ≥ 95% adherence to the study regimen.[23]

11. Comparative evidence on safety

11.1 Estimate of total patient exposure to date

Clinical Trials

Four hundred and forty-seven HIV-1 infected patients have received combination therapy with emtricitabine and tenofovir DF with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 48 weeks in clinical studies.[22]

Post-Marketing

Cumulative patient exposure to emtricitabine and tenofovir DF fixed dose combination tablets since first marketing approval in the US on 02 August 2004 to 31 January 06 is estimated to be 119,645 patient-years of treatment (Table 11).[46] Patient exposure to emtricitabine and tenofovir DF fixed dose combination tablet is estimated from sales data; the number of bottles sold during the reporting period was multiplied by 30 to provide the number of tablets sold. As emtricitabine and tenofovir DF fixed dose combination tablets are taken as a once-daily dose, the total number of tablets were divided by 365.25 to provide patient-years of treatment. It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure, due to the accumulation of drug stocks at pharmacies/distributors.[46]

Table 11: Cumulative Estimated Patient Exposure to Marketed Emtricitabine and Tenofovir DF Fixed Dose Combination Tablet through 31 January 2006[*46]

Geographic Area	Cumulative Patient-Years
USA	92,492
Europe	
Germany	4,757
United Kingdom & Ireland	3,413
Spain	1,864
Italy	705
France	601
Portugal	657
Distribution Region Europe[†]	214
Mid-Mediterranean[‡]	11
Asia (excluding Japan)	5
Japan	490
Australia	23
Latin America	7
Africa (non profit sales)	14,406
TOTAL	119,645

[*]Cutoff for sales data is at the end of each calendar month
[†]Austria, Baltics, Belgium, Czeck Republic, Hungary, Poland, Slovak Republic, Slovenia, Netherlands, Sweden (emtricitabine and tenofovir DF fixed dose combination tablet may not be actively marketed in all countries with marketing authorizations)
[‡]Greece, Cyprus, Malta

11.2 Descriptions of adverse effects/reactions

11.2.1 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 emtricitabine and tenofovir DF fixed dose combination tablets 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]

HIV and HBV co-infection

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

Renal Impairment

Emtricitabine and tenofovir DF are principally eliminated by the kidney. Dosing interval adjustment of emtricitabine and tenofovir DF fixed dose combination tablet is recommended in all patients with creatinine clearance 30–49 mL/min. Emtricitabine and tenofovir DF fixed dose combination tablet should not be administered to patients with creatinine clearance <30 mL/min or patients requiring hemodialysis.

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 tenofovir DF. 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.

Emtricitabine and tenofovir DF fixed dose combination tablet 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]

Hepatic Impairment

Tenofovir DF: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients.

Emtricitabine: The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Other

Emtricitabine and tenofovir DF fixed dose combination tablet is a fixed-dose combination of emtricitabine and tenofovir DF. Emtricitabine and tenofovir DF fixed dose combination tablet should not be coadministered with emtricitabine or tenofovir DF. Due to similarities between emtrictabine and 3TC, emtricitabine and tenofovir DF fixed dose combination tablet should not be coadministered with other drugs containing 3TC, including Combivir®, Epivir®, Epivir-HBV®, Epzicom™, Kivexa™, or Trizivir®.[22]

Drug Interactions

Tenofovir DF: When tenofovir DF was administered with ddI the Cmax and AUC of ddI administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher ddI concentrations could potentiate ddI associated adverse events, including pancreatitis, and neuropathy. In adults weighing >60 kg, the ddI dose should be reduced to 250 mg when it is coadministered with emtricitabine and tenofovir DF fixed dose combination tablets. Data are not available to recommend a dose adjustment of ddI for patients weighing <60 kg. When coadministered, emtricitabine and tenofovir DF fixed dose combination tablets and Videx EC® may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of ddI buffered tablet formulation with emtricitabine and tenofovir DF fixed dose combination tablets should be under fasted conditions. Coadministration of emtricitabine and tenofovir DF fixed dose combination tablets and ddI should be undertaken with caution and patients receiving this combination should be monitored closely for ddI-associated adverse events. ddI should be discontinued in patients who develop ddI-associated adverse events.

ATV and LPV/r have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving ATV and LPV/r and emtricitabine and tenofovir DF fixed dose combination tablets should be monitored for emtricitabine and tenofovir DF fixed dose combination tablet-associated adverse events. Emtricitabine and tenofovir DF fixed dose combination tablets should be discontinued in patients who develop emtricitabine and tenofovir DF fixed dose combination tablet-associated adverse events.[22]

Tenofovir decreases the AUC and Cmin of ATV. When coadministered with emtricitabine and tenofovir DF fixed dose combination tablets, it is recommended that ATV 300 mg is given with ritonavir 100 mg. ATV without ritonavir should not be coadministered with emtricitabine and tenofovir DF fixed dose combination tablets.[22]

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of emtricitabine and tenofovir DF fixed dose combination tablets with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are

not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir.[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 emtricitabine and tenofovir DF. 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, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.[22]

Animal Toxicology

Tenofovir and tenofovir DF 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. 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

In long-term oral carcinogenicity studies of emtricitabine, no drug related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose). Emtricitabine was not genotoxic in the

reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays. Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.[22]

Long-term oral carcinogenicity studies of tenofovir DF 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. Tenofovir DF 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, tenofovir DF was negative when administered to male mice.[22]

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF 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 and lactation

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

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, emtricitabine and tenofovir DF fixed dose combination tablets should be used during pregnancy only if clearly needed.[22]

To monitor fetal outcomes in pregnant women exposed to emtricitabine and tenofovir DF fixed dose combination tablets, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling the Antiretroviral Registry at 1-800-258-4263.

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. It is not known whether emtricitabine 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 emtricitabine and tenofovir DF fixed dose combination tablets.[22]

Pediatric Use

Emtricitabine and tenofovir DF fixed dose combination tablet is not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, tenofovir DF, for which safety and efficacy have not been established in this age group.[22]

Geriatric Use

Clinical studies of emtricitabine or tenofovir DF 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 patients 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]

11.2.2 Effects on ability to drive and use machines

Emtricitabine/tenofovir DF: No studies on the effects of either tenofovir DF or emtricitabine on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with both tenofovir DF and emtricitabine.

11.2.3 Overdosage

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

Tenofovir DF: Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In one study, 600 mg tenofovir DF was administered to 8 patients orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of Emtricitabine . In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported.

11.3 Undesirable effects

11.3.1 Experience from controlled clinical trials

Safety and efficacy studies using emtricitabine and tenofovir DF fixed dose combination tablets or using tenofovir DF and emtricitabine in combination are ongoing. Four hundred and forty-seven HIV-1 infected patients have received combination therapy with tenofovir DF and emtricitabine with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor 48 weeks in clinical studies.[22] Based on these limited data, no new patterns of adverse events were identified and there was no increased frequency of established toxicities.

Emtricitabine and tenofovir DF fixed dose combination tablet

Adverse events for emtricitabine and tenofovir DF fixed dose combination tablet are represented by those adverse events observed in Study 934, a randomized, open-label, active-controlled, multicenter study which used the individual components, emtricitabine and tenofovir DF, in combination with EFV. Adverse events observed in Study 934 were generally consistent with those seen in other studies in treatment-experienced or treatment-naïve patients receiving tenofovir DF or emtricitabine.[22] Grade 2-4 adverse events reported to occur in ≥3% of patients in this study included: diarrhea, nausea, vomiting, fatigue, sinusitis, upper respiratory tract infections, nasopharyngitis, somnolence, headache, dizziness, depression, insomnia, abnormal dreams and rash.

Laboratory abnormalities observed in Study 934 were generally consistent with those seen in other studies of tenofovir DF or emtricitabine. Significant laboratory abnormalities reported in ≥1% of patients included: Grade 3 / 4 elevations in fasting cholesterol (>240 mg/mL), creatine kinase (M: >990 U/L, F: >845 U/L), serum amylase (>175 U/L), alkaline phosphatase (>550 U/L), AST (M: >180 U/L, F: >170 U/L), ALT (M: >215 U/L, F: >170 U/L), hyperglycemia (>250 mg/dL), hematuria (>75 RBC/HPF), fasting triglyceride (>750 mg/dL), and decreases in hemoglobin (<8 mg/dL), and neutrophil (<750/mm^3).

Tenofovir DF

In addition to the events described above for Study 934, other adverse events that occurred in ≥5% of patients receiving tenofovir DF with other antiretroviral agents in clinical trials include arthralgia, anxiety, fever, pain, abdominal pain, back pain, peripheral neuritis, peripheral neuropathy, and pneumonia.[22]

In addition to the laboratory abnormalities for Study 934, Grade 3 / 4 elevations of urine glucose (≥3+) occurred in 3% of patients receiving tenofovir DF with other antiretroviral agents in clinical trials.

Emtricitabine

In addition to the events described above for Study 934, other adverse events that occurred in >5% of patients receiving emtricitabine with other antiretroviral agents in clinical trials include abdominal pain, asthenia, arthralgia, increase cough, depressive disorder, dyspepsia, myalgia, paresthesia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).[22]

Skin discoloration has been reported with higher frequency among emtricitabine treated patients. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance is unknown.

In addition to the laboratory abnormalities described above for study 934, grade 3 / 4 elevations of bilirubin (>2.5 x ULN), pancreatic amylase (>2.0 x ULN), serum glucose (<40 or >250 mg/dL) and serum lipase (>2.0 x ULN) occurred in <1–3% of patients treated with emtricitabine.

11.3.2 Post-marketing experience

Tenofovir DF: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of tenofovir DF. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting or potential causal connection tenofovir DF.

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

Emtricitabine: No additional events have been identified for inclusion in this section.

11.3.3 Comparative safety data from selected clinical trials

As stated above, no new patterns of adverse events or increased frequency of established toxicities were identified in 447 HIV-1 infected patients who have received emtricitabine and tenofovir DF together with either a NNRTI or PI for 48 weeks in the ongoing clinical studies. Safety results from selected clinical trials are included below. For additional detailed safety information regarding tenofovir DF in combination with other antiretroviral agents, please consult the individual application for inclusion on the WHO Model List of Essential Medicines.

Treatment-naïve HIV-infected patients

Study GS-903

Through Week 144, 8% of the patients in the tenofovir DF 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.[26] 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)[26]

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, stavudine
*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 tenofovir DF group (19% and 1%, respectively), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir DF and d4T treatment arms.[26] 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 Tenofovir DF-Treated Patients in Study 903 (0–144 weeks)[26]

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; d4T, stavudine; M, male; F, female; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RBC/HPF, red blood cells per high power field

Adverse events related to metabolic abnormalities were observed significantly higher in the d4T arm. At 144 weeks, the tenofovir DF-containing regimen was associated with significantly smaller increases in fasting triglycerides, total cholesterol, direct low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels compared to the d4T-containing regimen. In addition, the percentage of patients with mitochondria-associated toxicities was also significantly lower in the tenofovir DF arm. Please see Tables 14 and 15 for more details.[3,47]

Table 14: Study 903 Metabolic Parameters through Week 144[3,47]

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[3]

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 tenofovir DF and d4T-containing group. No patient in the tenofovir DF 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.[48]

There was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in the tenofovir DF 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 tenofovir DF 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 tenofovir DF-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 tenofovir DF 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 tenofovir DF 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 tenofovir DF group. Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.[26]

Study 903 Extension Phase

As observed in the total patient population treated with tenofovir DF 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).[33]

Of the 85 patients who switched from d4T to tenofovir DF, they had been on d4T for a median duration of 152 weeks.[34] 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 tenofovir DF, 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 tenofovir DF but there was no change in spine BMD (-0.2% at Week 24 and 0% at Week 48 [*P* =.700]).[34]

Table 16: Mean±SD (Range) Improvements in Lipid Parameters and Limb Fat at Week 48[34]

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.[33]

Study GS-934

Week 48 Results

The 48-week safety data are based on 511 patients who received at least one dose of study medication. 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 in treatment-experienced or treatment-naïve patients receiving tenofovir DF or emtricitabine (Tables 17 and 18).[22] However, 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 (Table 19). 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.[36]

Table 17: Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in ≥3% in Any Treatment Group (0-48 weeks)[22,26]

Adverse Event	TDF + FTC + EFV (n = 257)	AZT/3TC + EFV (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; EFV, efavirenz

Table 18: Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group (0–48 Weeks)[22,26]

Laboratory Abnormality	TDF + FTC + EFV (n = 257)	AZT/3TC + EFV (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%
Hemoglobin (<8 mg/dL)	0%	3%
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; EFV, efavirenz; 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[36,49]

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 emtricitabine + tenofovir DF 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.[36]

Renal safety profile was similar between the two groups, 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 emtricitabine + tenofovir DF group; however, three 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 emtricitabine + tenofovir DF 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.[35,36]

Regarding lipid parameters, at Week 48, the emtricitabine + tenofovir DF group had smaller mean increases in fasting triglycerides, total cholesterol, LDL, and HDL levels compared to the AZT/3TC group (Table 20).[35]

Table 20: Increase* in Fasting Lipid Parameters through Week 48[36]

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 emtricitabine + tenofovir DF arm (Table 21). Although the median GFR as estimated by the CG method was similar between the two arms, the median GFR as estimated by the MDRD method showed that the emtricitabine + tenofovir DF arm had a significantly lower rate than the AZT/3TC arm (100 vs. 108 mL/min/1.73 m^2; *P* = .006). However, no patient in the emtricitabine + tenofovir DF arm experienced confirmed Grade 1-4 renal abnormality as compared to two patients in the AZT/3TC arm (Table 22).

Table 21: Adverse Events Leading to Study Drug Discontinuation through Week 96[36]

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[36]

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 emtricitabine + tenofovir DF 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).[38] 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 emtricitabine + tenofovir DF versus 1.1 kg with AZT/3TC; *P* =.14).[36] 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 emtricitabine + tenofovir DF arm than the AZT/3TC arm (Table 23).[36,38]

Table 23: Study 934: Median Total Limb Fat (kg) at Weeks 48 and 96[38]

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 emtricitabine + tenofovir DF arm vs. the AZT/3TC arm at Week 48
†P <.001 for the difference between the emtricitabine + tenofovir DF 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 emtricitabine + tenofovir DF 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).[38]

Study M02-418

Available safety information has been gathered from the LPV/r 2005 Prescribing Information, and from study results presented by Molina et al. in 2005.[39,40] Through Week 96, a total of 37% (42/115) of patients in the once-daily group and 39% (29/75) of patients in the twice-daily group discontinued the study; 17% and 9% due to adverse events, respectively. Gastrointestinal adverse events were the most common cause for discontinuation and were the most common adverse events (>3%). Diarrhea was reported more frequently in the once-daily vs. twice-daily group (17% vs. 5%; P =.014). The most common Grade 3/4 laboratory abnormalities (>3%) reported were increased ALT (>5 x ULN), AST (>5 x ULN), triglyceride (>750 mg/dL), cholesterol (>300 mg/dL), and amylase (>2 x ULN) levels; no significant differences between the 2 groups were observed.[39,40]

Acute renal failure (ARF) occurred in one patient in each group.[39] One patient was a 75-year-old male with a baseline creatinine clearance of 40 mL/min who was given a full dose of tenofovir DF. Tenofovir DF dosing recommendations implemented after initiation of this study indicate that every other day dosing of tenofovir DF would have been most appropriate for this subject based on creatinine clearance[26,39] He developed ARF at Week 34. Renal biopsy demonstrated non-specific changes with some renal tubules showing focal degenerative signs (cytoplasmic vascuolization). The other patient was a 54-year-old male. ARF occurred at Week 38, requiring temporary hemodialysis. Renal biopsy demonstrated tubulointerstitial nephritis. Both patients improved upon discontinuation of study drug; one discontinued all ARVs and the other replaced tenofovir DF with d4T 30 mg twice-daily and the dose of emtricitabine was reduced to 200 mg every 72 hours as part of the HAART regimen.

At Week 96, significant increases from baseline in total cholesterol, HDL, LDL, and triglyceride levels were observed in both groups.[39] However, the mean 10-year coronary heart disease risk and analysis of risk rates by each category did not change significantly from baseline.[50]

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.[41] 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).[41] 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, 1 due to multifocal tuberculosis, 1 due to sepsis, and 1 of unknown cause.

Table 24: Treatment Related Adverse Events* through Week 48[41]

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 HIV-infected patients

Study FTC-303

The most common adverse events that occurred in adult patients receiving emtricitabine with other antiretroviral agents in clinical trials, including Study FTC-303, were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the emtricitabine treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic and did not lead to any discontinuations from the study. The mechanism and clinical significance are unknown.[17,26] A summary of emtricitabine treatment-related adverse events in study 303 is provided below (Table 25).

Table 25: Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥ 3% of Emtricitabine-Treated Patients in Study FTC-303 (0-48 Weeks)[42]

Adverse Event	Emtricitabine + ZDV/d4T + NNRTI/PI (n = 294)	3TC + ZDV/d4T+ NNRTI/PI (n = 146)
Body as a Whole		
Abdominal Pain	8%	11%
Asthenia	16%	10%
Headache	13%	6%
Digestive System		
Diarrhea	23%	18%
Dyspepsia	4%	5%

Adverse Event	Emtricitabine + ZDV/d4T + NNRTI/PI (n = 294)	3TC + ZDV/d4T+ NNRTI/PI (n = 146)
Nausea	18%	12%
Vomiting	9%	7%
Musculoskeletal		
Arthralgia	3%	4%
Myalgia	4%	4%
Nervous System		
Abnormal Dreams	2%	<1%
Depressive Disorders	6%	10%
Dizziness	4%	5%
Insomnia	7%	3%
Neuropathy/Peripheral Neuritis	4%	3%
Paresthesia	5%	7%
Respiratory		
Increased Cough	14%	11%
Rhinitis	18%	12%
Skin		
Rash Event*	17%	14%

Abbreviations: ZDV, zidovudine; d4T, stavudine; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; 3TC, lamivudine; ddI, didanosine; EFV, efavirenz
*Rash event includes rash, pruritis, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

In Study FTC-303, 13 patients discontinued from the emtricitabine group due to adverse events, including seven patients whose adverse events were considered unrelated to the drug. The other six patients discontinued the study due to anemia, diarrhoea/stomachache, peripheral neuropathy (present at baseline), stomachache, nausea/vomiting, and insomnia/anger. All adverse events leading to discontinuation were of mild to moderate in severity.[25]

Grade 3/4 laboratory abnormalities occurred with similar frequency in the emtricitabine and 3TC groups. A summary of grade 3 and 4 laboratory abnormalities is provided in Table 26 below.

Table 26. Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥ 1% of Emtricitabine-Treated Patients in Study FTC-303 (0-48 Weeks)[26*]

Laboratory Abnormality	FTC+ZDV/d4T +NNRTI/PI (n=294)	3TC+ZDV/d4T +NNRTI/PI (n=146)
Total	31%	28%
ALT (>5 x ULN)	2%	1%
AST (>5 x ULN)	3%	<1%
Bilirubin (>2.5 x ULN)	1%	2%
Creatine Kinase (>4 x ULN)	11%	14%
Neutrophils (<750 mm^3)	5%	3%
Pancreatic Amylase	2%	2%

Laboratory Abnormality	FTC+ZDV/d4T +NNRTI/PI (n=294)	3TC+ZDV/d4T +NNRTI/PI (n=146)
(>2 x ULN)		
Serum Amylase (>2 x ULN)	2%	2%
Serum Glucose (<40 or >250 mg/dL)	3%	3%
Serum Lipase (>2 x ULN)	<1%	<1%
Triglycerides (>750 mg/dL)	10%	8%

*ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ZDV: zidovudine; d4T: stavudine; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; 3TC: lamivudine; ddI: didanosine; EFV: efavirenz; FTC: emtricitabine; n: number of patients

COMET

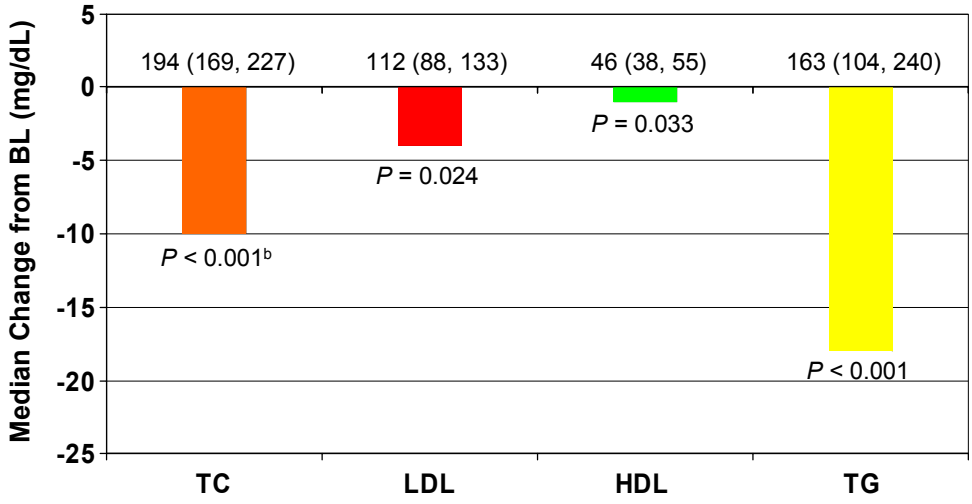
Results through Week 24 demonstrate that there were statistically significant improvements from baseline at Week 24 in hemoglobin level (31% had >1 g/dL increase from baseline), ANC, MCV, and fasting lipid parameters. Although a small but statistically significant decrease from baseline in HDL was observed, the TC/HDL ratio did not change.[23] Please refer to Table 27 and Figure 3 below for additional details on available safety results.

Table 27: Baseline and Change from Baseline in Selected Hematological Parameters at Week 24[23]

Parameter	Baseline Value	Change from Baseline at Week 24*	*P*-value†
Median (IQR) Hemoglobin (g/dL)	14.7 (13.6, 15.6)	0.6 (0.0, 1.2)	< .001
-↑ >1 g/dL from BL (% of patients) -↓ >1 g/dL from BL (% of patients)		31% 2%	
Median (IQR) ANC (cells/mm^3)	2789 (1991, 3784)	302 (-226, 1043)	< .001
Median (IQR) MCV (fL)	113 (108, 118)	-18 (-21, -14)	< .001

Abbreviations: IQR, interquartile range; BL, baseline; ANC, absolute neutrophil count; MCV, mean corpuscular volume
*Patients with both baseline and Week 24 data available.
†Wilcoxon Sign-Rank test

Figure 3: Fasting Lipids at Baseline (Median, IQR) and Change from Baseline at Week 24[23a]



a. The protocol was amended to collect fasting lipid data. N = 160 pts were enrolled post-amendment.
b. Wilcoxon Sign-Rank test

Of the 30 patients who discontinued the study early, 2 (0.5%) were due to pregnancy, 4 (1%) for noncompliance/protocol violation, 9 (2%) due to loss to follow-up, 10 (2.5%) for adverse events (5 patients due to GI effects [dry mouth, diarrhea, nausea/vomiting, cramps, bloating], 3 due to central nervous system effects [EFV-related mental status change, headache, dizziness], and one each due to asthenia and abnormal liver function tests [LFTs]), 4 (1%) for others reasons (including withdrawal of consent), and 1 (< 0.5%) due to virologic failure (HIV RNA ≥400 copies/mL on 2 occasions separated by ≥4 weeks).[23] Overall, nausea, diarrhea, headache, and insomnia were the most commonly reported adverse events, occurring in 5%, 5%, 3%, and 3% of the patients, respectively.[23] Grade 3/4 laboratory abnormalities occurred in 1% of patients; 2 cases each of neutropenia and increase in triglycerides, and one case of thrombocytopenia. In addition, Grade 2 confirmed increase in serum creatinine occurred in 1 patient, but returned to normal range while on treatment during the study. At baseline, the median (IQR) creatinine clearance was 102 mL/min (87, 121); at Week 24, creatinine clearance had a median change from baseline of -8 mL/min (IQR: -15, 0.0; *P* <.001).[23]

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

The Gilead fixed dose combination tablet of the two antiretrovirals, emtricitabine 200mg and tenofovir disoproxil fumarate 300mg, was approved by the US FDA on 02 August 2004,

representing initial commercial availability of this one-tablet, once-daily antiretroviral. The monthly treatment cost of emtricitabine and tenofovir DF fixed dose combination tablets varies among payers in the United States. The list price is USD 735.36; the following table indicates current pricing (Table 28):[46]

Table 28: Wholesale Acquisition Cost of Emtricitabine and Tenofovir DF Fixed Dose Combination Tablet in the United States*[46]

Country	Package Size	Average Package Price (USD)	Average Unit Price (USD)	Defined Daily Dose
United States	30 TAB	735.36	24.51	500 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 fixed dose combination tablet) 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 disoproxil fumarate 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 world countries. Both tenofovir DF and emtricitabine and tenofovir DF fixed dose combination tablet are included in the WHO List of Prequalified 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 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 tenofovir DF- and emtricitabine and tenofovir DF fixed dose combination tablet-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 antiretrovirals for the treatment of HIV infection, including emtricitabine and tenofovir DF fixed dose combination tablets, 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 for AIDS deaths in the United States declined by 70 percent from 1995 to 2002, primarily as a result of the introduction of HAART.[21]

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.[1] 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.[1] 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 emtricitabine and tenofovir DF fixed dose combination tablet make it well-suited for HAART administered in the developing world. Several clinical studies (up to 192 weeks) have demonstrated that tenofovir DF is effective, tolerable and less prone to the development of resistance than other ARVs. Characteristics such as its one pill, once-daily dosing, and lack of food restrictions may minimize the complexity of combination therapy for patients as well as healthcare staff in resource poor settings. Additionally, reduced ARV-related toxicity associated with tenofovir DF may minimize the expense of palliative therapy and clinical care often needed with older, more toxic 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.[22] 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.[36] Although there have been no published studies on cost-effectiveness ratio of anemia treatment (Erythropoietin [EPO],

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.[51] Compared to patients with normal hemoglobin, 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.[52] In HIV-infected children in Tanzania, anemia was one of the factors identified to be significantly contributed to mortality independent of HIV infection.[51]

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 (Aurobindo pricing) plus the emtricitabine and tenofovir DF fixed dose combination tablet at the no-profit cost is 0.32 USD more per day as compared to a generic regimen containing AZT/3TC + EFV (Aurobindo pricing; 2.17 USD/day versus 1.85 USD/day, respectively), therapy with emtricitabine and tenofovir DF fixed dose combination is less likely to cause anemia.[22,53]

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

Emtricitabine and tenofovir DF fixed dose combination tablet, received the approval by US FDA on 02 August 2004, and currently has approval for marketing in a total of 49 countries.[46] Please see a listing of territories with marketing authorisation status in Table 29 below.

In addition, Gilead Sciences submitted the emtricitabine and tenofovir DF fixed dose combination tablet 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 approved with the pre-qualification number HA343.

Table 29: Worldwide Marketing Authorisation Status
Emtricitabine and Tenofovir DF Fixed Dose Combination Tablets[46]

Territory	Approval Date
United States	02 Aug 2004
Japan	23 Mar 2005
Canada	6 Jan 2006
European Union	
Austria	23 Feb 2005
Belgium	23 Feb 2005
Cyprus	23 Feb 2005
Czech Republic	23 Feb 2005
Denmark	23 Feb 2005
Estonia	23 Feb 2005
Finland	23 Feb 2005

Territory	Approval Date
France	23 Feb 2005
Germany	23 Feb 2005
Greece	23 Feb 2005
Hungary	23 Feb 2005
Ireland	23 Feb 2005
Italy	23 Feb 2005
Latvia	23 Feb 2005
Lithuania	23 Feb 2005
Luxembourg	23 Feb 2005
Malta	23 Feb 2005
Netherlands	23 Feb 2005
Poland	23 Feb 2005
Portugal	23 Feb 2005
Slovak Republic	23 Feb 2005
Slovenia	23 Feb 2005
Spain	23 Feb 2005
Sweden	23 Feb 2005
United Kingdom	23 Feb 2005
Norway	23 Feb 2005
Iceland	23 Feb 2005
Switzerland	21 Mar 2006
Israel	31 May 2006
Australia	20 Sept 2005
New Zealand	17 May 2006
Argentina	04 Apr 2006
Mexico	15 Jun 2005
Guyana*	03 Apr 2006
Dominica*	14 Jun 2006
Nigeria*	26 Jun 2006
Ghana*	18 Apr 2005
Uganda*	10 Jan 2005
Kenya*	15 Jul 2005
Zambia*	3 May 2005
Botswana*	8 March 2006
Democratic Republic of the Congo (DRC)*‡	01 July 2006
Mauritius*	Product can be Marketed
Solomon Islands*	Product can be Imported
Seychelles*	Product can be Marketed
Angola*	Product can be Marketed

*Marketing authorizations received for the emtricitabine and tenofovir DF fixed dose combination tablet (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.
‡Provisional approval.

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:

Emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) fixed dose combination tablets contain emtricitabine and tenofovir disoproxil fumarate. Emtricitabine is a synthetic nucleoside analog of cytidine. Tenofovir disoproxil fumarate, also known as tenofovir DF, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Both emtricitabine and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

How Supplied:

Tablets, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate, (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients

Use:
Emtricitabine and tenofovir DF fixed dose combination tablets are indicated for the treatment for HIV infection in adults in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors). Emtricitabine and tenofovir DF fixed dose combination tablets should be considered as an alternative to the combination of tenofovir DF + lamivudine for those patients who might benefit from a once-daily regimen. It is not recommended that emtricitabine and tenofovir DF fixed dose combination tablet be used as a component of a triple nucleoside regimen. Emtricitabine and tenofovir DF fixed dose combination tablets should not be coadministered with emtricitabine, tenofovir DF or lamivudine containing products. In treatment experienced patients, the use of emtricitabine and tenofovir DF fixed dose combination tablets should be guided by laboratory testing and treatment history.

Contraindications:

Known hypersensitivity 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 emtricitabine and tenofovir DF fixed dose combination tablets 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).

Patients with HIV and Hepatitis B Virus Coinfection

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

Patients with Impaired Renal Function

Emtricitabine and tenofovir are principally eliminated by the kidney. Dosing interval adjustment of emtricitabine and tenofovir DF fixed dose combination tablets is recommended in all patients with creatinine clearance 30–49 mL/min, (see Dosage and Administration). Emtricitabine and tenofovir DF fixed dose combination tablets should not be administered to patients with creatinine clearance <30 mL/min or patients requiring haemodialysis.

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 tenofovir DF (see Adverse Effects). 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.

Emtricitabine and tenofovir DF fixed dose combination tablets 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.

Precautions:

Drug Interactions

Tenofovir DF: When tenofovir disoproxil fumarate was administered with didanosine the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations

could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with emtricitabine and tenofovir DF fixed dose combination tablets. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When co-administered, emtricitabine and tenofovir DF fixed dose combination tablet and Videx EC® may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Co-administration of didanosine buffered tablet formulation with emtricitabine and tenofovir DF fixed dose combination tablet should be under fasted conditions. Co-administration of emtricitabine and tenofovir DF fixed dose combination tablet and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and lopinavir/ritonavir and emtricitabine and tenofovir DF fixed dose combination tablet should be monitored for emtricitabine and tenofovir DF fixed dose combination tablets-associated adverse events. Emtricitabine and tenofovir DF fixed dose combination tablet should be discontinued in patients who develop emtricitabine and tenofovir DF fixed dose combination tablet-associated adverse events.

Tenofovir decreases the AUC and C_{min} of atazanavir. When coadministered with emtricitabine and tenofovir DF fixed dose combination tablet, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with emtricitabine and tenofovir DF fixed dose combination tablet.

Emtricitabine and tenofovir DF: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of emtricitabine and tenofovir DF fixed dose combination tablet with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

Emtricitabine and tenofovir DF fixed dose combination tablets should not be co-administered with emtricitabine or tenofovir DF. Due to similarities between emtricitabine and lamivudine, emtricitabine and tenofovir DF fixed dose combination tablet should not be co-administered with other drugs containing lamivudine, including Combivir®, Epivir®, Epivir-HBV®, Epzicom™, Kivexa™, or Trizivir®.

Bone Effects

In a 144-week study of treatment naïve patients, decreases in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir DF + lamivudine + efavirenz compared with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. 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 144 weeks. Twenty-eight percent of tenofovir DF-treated

patients vs. 21% of the comparator 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 tenofovir DF group and 6 patients in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in patients receiving tenofovir DF. The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the tenofovir DF prescribing information.

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

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.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine and tenofovir DF. 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, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine and tenofovir DF fixed dose combination tablets or emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir disoproxil fumarate: Long-term oral carcinogenicity studies of tenofovir DF 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.

Tenofovir disoproxil fumarate 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, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate 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.

Pregnancy and Lactation

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir disoproxil fumarate: 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, emtricitabine and tenofovir DF fixed dose combination tablets should be used during pregnancy only if clearly needed.

To monitor fetal outcomes in pregnant women exposed to emtricitabine and tenofovir DF fixed dose combination tablets, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling the Antiretroviral Registry at 1-800-258-4263.

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. It is not known whether emtricitabine 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 emtricitabine and tenofovir DF fixed dose combination tablet.[22]

Paediatric Use

Emtricitabine and tenofovir DF fixed dose combination tablets are not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, tenofovir DF, for which safety and efficacy have not been established in this age group.[22]

Geriatric Use

Clinical studies of emtricitabine or tenofovir DF 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 patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Adverse Effects:

Clinical Trials

Safety and efficacy studies using emtricitabine and tenofovir DF fixed dose combination tablets or using emtricitabine and tenofovir DF in combination are ongoing. Four hundred forty seven HIV-1 infected patients have received combination therapy with emtricitabine or tenofovir DF with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor 48 weeks in clinical studies. Based on these limited data, no new patterns of adverse events were identified and there was no increased frequency of established toxicities.

Emtricitabine and tenofovir DF fixed dose combination tablet:
Adverse events for emtricitabine and tenofovir DF fixed dose combination tablet are represented by those adverse events observed in Study 934, a randomized, open-label, active-controlled, multicenter study which used the individual components, emtricitabine and tenofovir DF, in combination with EFV. Adverse events observed in Study 934 were generally consistent with those seen in other studies in treatment-experienced or treatment-naïve patients receiving tenofovir DF or emtricitabine.[22] Grade 2-4 adverse events reported to occur in ≥3% of patients in this study included: diarrhea, nausea, vomiting, fatigue, sinusitis, upper respiratory tract infections, nasopharyngitis, somnolence, headache, dizziness, depression, insomnia, abnormal dreams and rash.

Laboratory abnormalities observed in Study 934 were generally consistent with those seen in other studies of tenofovir DF or emtricitabine. Significant laboratory abnormalities reported in ≥1% of patients included: Grade 3 / 4 elevations in fasting cholesterol (>240 mg/mL), creatine kinase (M: >990 U/L, F: >845 U/L), serum amylase (>175 U/L), alkaline phosphatase (>550 U/L), AST (M: >180 U/L, F: >170 U/L), ALT (M: >215 U/L, F: >170 U/L), hyperglycemia (>250 mg/dL), hematuria (>75 RBC/HPF), fasting triglyceride (>750 mg/dL), and decreases in hemoglobin (<8 mg/dL), and neutrophil (<750/mm^3).

Tenofovir DF:

In addition to the events described above for Study 934, other adverse events that occurred in ≥5% of patients receiving tenofovir DF with other antiretroviral agents in clinical trials include arthralgia, anxiety, fever, pain, abdominal pain, back pain, peripheral neuritis, peripheral neuropathy, and pneumonia.

In addition to the laboratory abnormalities for Study 934, Grade 3 / 4 elevations of urine glucose (≥3+) occurred in 3% of patients receiving tenofovir DF with other antiretroviral agents in clinical trials.[22]

Emtricitabine:

In addition to the events described above for Study 934, other adverse events that occurred in >5% of patients receiving emtricitabine with other antiretroviral agents in clinical trials include abdominal pain, asthenia, arthralgia, increase cough, depressive disorder, dyspepsia, myalgia, paresthesia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).

Skin discoloration has been reported with higher frequency among emtricitabine treated patients. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance is unknown.

In addition to the laboratory abnormalities described above for study 934, grade 3 / 4 elevations of bilirubin (>2.5 x ULN), pancreatic amylase (>2.0 x ULN), serum glucose (<40 or >250 mg/dL) and serum lipase (>2.0 x ULN) occurred in <1–3% of patients treated with emtricitabine.

Post Marketing Experience

Emtricitabine:
No additional events have been identified for inclusion in this section.

Tenofovir DF:
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of tenofovir DF. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting or potential causal connection tenofovir DF.

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

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

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

Dosage and Administration:

For adults 18 years of age and older, the dose of emtricitabine and tenofovir DF fixed dose combination tablets is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once-daily taken orally with or without food.

Dose Adjustment in Patients with Renal Impairment

Significantly increased drug exposures occurred when emtricitabine or tenofovir DF were administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of emtricitabine and tenofovir DF fixed dose combination tablets should be adjusted in patients with baseline creatinine clearance 30–49 mL/min using the recommendations in table below. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated, therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Recommended Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)*		
	≥50	**30–49**	**<30 (Including Patients Requiring Hemodialysis)***
Recommended Dosing Interval	Every 24 hours	Every 48 hours	Should not be administered.

*Calculated using ideal (lean) body weight.

Patient advice:

Take emtricitabine and tenofovir DF fixed dose combination tablets exactly as your healthcare provider prescribed it. It may be taken with or without a meal. If you forget to take emtricitabine and tenofovir DF fixed dose combination tablets, take it as soon as you remember that day. Do not take 2 doses at the same time. Do not breast-feed. Contact your healthcare provider if you are not sure what to do.

Information for Patients

Emtricitabine and tenofovir DF fixed dose combination tablets are not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using emtricitabine and tenofovir DF fixed dose combination tablets.

Patients should be advised that:

- the use of emtricitabine and tenofovir DF fixed dose combination tablets has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination,
- the long term effects of emtricitabine and tenofovir DF fixed dose combination tablets are unknown,
- emtricitabine and tenofovir DF fixed dose combination tablets are for oral ingestion only,
- it is important to take emtricitabine and tenofovir DF fixed dose combination tablet with combination therapy on a regular dosing schedule to avoid missing doses,
- redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.
- emtricitabine and tenofovir DF fixed dose combination tablet should not be coadministered with emtricitabine or tenofovir DF, or drugs containing lamivudine, including Combivir, Epivir, Epivir-HBV, Epzicom, Kivexa, or Trizivir.

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Attachment 1: Glossary of Abbreviations

3TC	Lamivudine
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	Zidovudine
AZT/3TC	Zidovudine/lamivudine (Combivir®)
BID	Twice-daily
BL	Baseline
BMD	Bone mineral density
BUN	Blood urea nitrogen
CDC	Centers for Disease Control
CI	Confidence interval
Cmax	Maximum concentration
Cmin	Minimum concentration
CrCL	Creatinine clearance
d4T	Stavudine
ddI	didanosine
DF	disoproxil fumarate
DHHS	Department of Health and Human Services
dL	deciliter
DNA	Deoxyribonucleic acid
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
mL	Millilitre
mm3	Cubic millimeter
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
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
TC	Total cholesterol
TDF	Tenofovir disoproxil fumarate
TG	Triglycerides
TLOVR	Time to loss of virologic response
U/L	Units/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 Key Clinical Trials of Oral Emtricitabine and Tenofovir DF Fixed Dose Combination Tablets:

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.

<table>
<tr><th>Study Number (Publication)</th><th>Design</th><th>Duration of Treatment</th><th>Population Number of Subjects by Treatment Arm</th><th>Clinical Efficacy</th><th>Safety and Tolerability</th></tr>
<tr>
<td>FTC-303

(Sanne et al. 2002)</td>
<td>Randomised, Phase 3, Open-Label Equivalence Study to evaluate efficacy and safety of FTC vs. Lamivudine in patients on a Stable Triple Antiretroviral Therapy Regimen Containing a Protease Inhibitor or a Non-Nucleoside Reverse Transcriptase Inhibitor</td>
<td>48 weeks, open-label, randomised</td>
<td>HIV-infected patients on 3TC containing triple-antiretroviral regimen for at least 12 weeks and had HIV RNA < 400 copies/mL.

Randomised 1:2 to either continue therapy with 3TC (n=146) or switch to FTC (n=294) while maintaining the background regimen.

Median duration of prior antiretroviral and 3TC therapies were: 27.6 and 18 months, respectively.

Median plasma HIV RNA: 1.7 $\log_{10}$copies/mL

Median CD4 cell count: 527 cells/mm^3</td>
<td>Results at Week 48 are shown in table below. An Intent-To-Treat (ITT) analysis was used, with patients who did not complete the study counted as treatment failures. No statistically significant differences found between FTC and 3TC treatment arms.

Results at Week 48
<table>
<tr><th>Parameters</th><th>FTC (n=294)</th><th>3TC (n=146)</th></tr>
<tr><td>Responder*</td><td>77% (67%)</td><td>82% (72%)</td></tr>
<tr><td>Virologic Failure†</td><td>7%</td><td>8%</td></tr>
<tr><td>Rebound
Never Suppressed</td><td>5%
2%</td><td>5%
3%</td></tr>
<tr><td>Study Discontinuation</td><td></td><td></td></tr>
<tr><td>Due to Adverse Events
For Other Reasons‡
Death</td><td>4%
12%
0%</td><td>0%
10%
<1%</td></tr>
</table>
*patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48
†includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression
‡includes lost to follow up, patient's withdrawal, non-compliance, protocol violation and other reasons

Mean increase from baseline in CD4 cell count was 29 cells/mm^3 (FTC) and 61 cells/mm^3 (FTC).</td>
<td>Majority of adverse events were mild to moderate, incidence was equivalent in both FTC and 3TC groups.

Most frequent reported AEs (≥15%) included infection, diarrhoea, nausea, rhinitis, asthenia, rash event and pain.

Thirteen patients discontinued from the FTC group due to adverse events:
o patients whose AE were considered unrelated to the drugs
o 6 patients due to anemia, diarrhoea/stomachache, peripheral neuropathy (present at baseline), stomachache, nausea/vomiting, and insomnia/anger.

Through Week 48, 2 patients (0.7%) in the FTC group experienced a new CDC Class C event, compared to 2 patients (1.4%) in the 3TC group.</td>
</tr>
</table>

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 (AZT/3TC) 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 AZT/3TC arm	<u>At Week 48:</u> 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 <u>At Week 96:</u> 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 o 3TC+AZT+EFV: 237 cells/mm^3	<u>At Week 48:</u> Discontinued the study (TLOVR): (p=.02) o FTC+TDF+EFV: 4% o AZT/3TC+EFV: 9% Discontinued due to anemia (TLOVR): (p=<.001) o FTC+TDF+EFV: 0% o AZT/3TC+EFV: 6% <u>At Week 96:</u> 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