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

Submitted By

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

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

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

Truvada™ (TVD), 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.

Expanding but still relatively 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 resistance HIV infection necessitate a regimen that has a predictable and favourable resistance profile. The growing but still limited availability of widespread adherence support requires a regimen that is convenient. Finally, 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.

The components of Truvada, emtricitabine and tenofovir DF, have demonstrated effectiveness in a wide variety of patients initiating their first ARV regimens. The co-administration of TDF and FTC (or structurally-similar lamivudine) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) is associated with low rates of resistance, minimal cross-resistance, and multiple successful second-line regimens. Truvada, emtricitabine and tenofovir DF fixed dose combination tablet, may improve adherence, as it is dosed as one tablet taken once-a-day. 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 Triommmune (d4T+3TC+NVP) as the most suitable regimen for initial therapy was made before the availability of TDF, FTC and most recently the fixed dose combination of Truvada. In contrast, 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) were updated in March 2004,¹ and the International AIDS Society-USA (IAS) Treatment Recommendations for Adult HIV Infection were updated in July 2004.² Both of these updated guidelines recommend that TDF+FTC should be a component of first line ARV regimens containing efavirenz (DHHS Guidelines) and/or a boosted PI (IAS Guidelines).
In resource-poor settings, the decision to which ARV therapy to utilize must be based on the expectation of a favourable outcome in addition to access price. The use of FTC and TDF, the components of the fixed dose combination of Truvada, has demonstrated a more favourable safety and efficacy profile than regimens containing d4T+3TC. Therefore, we propose that Truvada, recently approved by the US Food and Drug Administration (FDA), be included on WHO Model List of Essential Medicines.

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

Jos Perriëns MD
Director Care
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

5. 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.

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

6.1 Epidemiological information on disease burden

The impact of HIV continues to erode economies, devastate communities, and exhaust already fragile healthcare systems in the developing world. In developing countries, about one third of the population - 1.3 billion people - live on incomes of less than USD 1.00 a day. Almost one in three children is malnourished, and one in five is not fully immunized by their first birthday. In addition, over one third of the world's population lacks access to essential drugs. As a result, most deaths from infectious diseases occur in developing countries - countries with the least money to spend on health care.

Since the first clinical evidence of AIDS was reported over 20 years ago, an estimated 25 million people have died as a result of HIV infection. Current estimates suggest that approximately 40 million people worldwide are infected with HIV and more than 90% of all HIV-infected people live in the developing world. In 2001, 5 million individuals worldwide became infected with HIV, and 3 million others died from HIV/AIDS-related causes. The worst affected area is Sub-Saharan Africa. In some countries, up to one in four of the adult population is now living with
HIV/AIDS. In some areas of Zimbabwe, 20%-50% of pregnant women are infected with HIV and risk infecting their newborns. In addition, an increasing number of maternal deaths are now due to infections contracted by HIV-positive women during delivery. In many countries, life expectancy and child survival rates have plummeted. For example, in Botswana life expectancy at birth has fallen from 70 to around 50 years.5

Eastern Europe — particularly the Russian Federation — continues to experience the fastest-growing epidemic in the world. In 2001, there were an estimated 250,000 new infections in this region, bringing the total number of people living with HIV to 1 million. In Asia and the Pacific, approximately 1 million people became infected in 2001; about 7.1 million individuals in this region are now living with HIV/AIDS.6 Even more staggering, is the fact that 1.8 million people in Latin America and the Caribbean are living with HIV/AIDS. This number includes 190,000 adults and children who were diagnosed in 2001.

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.5 For example, of the 14,000 persons who became infected each day in 2001, about 12,000 (86%) were aged 15 to 49 years.7 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 and extending the asymptomatic phase of infection and improving the quality of life for many infected individuals.8

6.2 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. Recently, it has been reported that the development of drug resistance to any class of antiretroviral drug may be as high as 50% in certain cohorts. Moreover, it has also been shown that in the presence of detectable viremia, resistance to the nucleoside analog reverse transcriptase inhibitors (NRTIs) could be detected in up to 70% of patients.9 The development of resistance leads to decreased susceptibility to other NRTIs through cross-resistance, which limits viable treatment options. This is an increasing problem as patients stay on therapy longer. This problem is further complicated by the fact that resistant virus can be transmitted to others.10
The development and transmission of resistance-conferring mutations is also associated with a sub-optimal virologic response to initial antiretroviral therapy.\textsuperscript{11} This may contribute to increased levels of cross-resistance within NRTIs, which are the backbone of HIV therapy. Cross-resistance also 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.\textsuperscript{12}

Taken together, these findings point to the urgent need for novel and improved antiretroviral agents. These agents should have a more robust genetic barriers for the development of drug resistance and a broader spectrum of antiviral activity against HIV-1 strains, harboring resistance mutations in reverse transcriptase that confer diminished susceptibility to several of the currently licensed NRTIs.

Current treatment strategies and guidelines recommend selecting potent regimens from all currently available classes of ARVs to maximize suppression of viral load and to minimize the replication and emergence of drug-resistant virus. Despite the improvements in morbidity and mortality, a substantial number of patients do not achieve adequate suppression of HIV-1 viral load.\textsuperscript{13}

\subsection{6.3 Target population}

In contrast to earlier examples regarding developing countries, an estimated 1.5 million people are living with HIV in high income countries. In the US, the introduction of triple drug therapy in 1996 led to a decline of 42\% in deaths attributable to HIV/AIDS in 1996-97. Therefore, new ARVs are needed in order to individualize therapy for patients who cannot tolerate, adhere to, or who are currently failing, antiretroviral therapy. As patients remain on effective therapies for longer periods of time, there is an urgent need for drugs with simpler dosing regimens, improved adverse event profiles, and potent and durable antiviral effects with a decreased propensity for the development of drug resistance

The viability, efficacy and tolerability associated with antiretroviral therapy have been adequately demonstrated in a number of clinical programs worldwide. For example, in Brazil, the policy of universal access to antiretroviral drugs has reduced the number of AIDS-related deaths by nearly 50\% and cut the incidence of opportunistic infections by 60\% to 80\%.\textsuperscript{14} Between 1997 and 2000, Brazil saved approximately USD 677 million in averted hospitalizations and treatment of HIV-related infections.

In Argentina a program similar to that of Brazil provides even greater access to ARVs. A special fund has been established to pay for antiretroviral drugs for those not covered by social security (such as street vendors, small business people, the unemployed and low-income pregnant women).\textsuperscript{15}

Through the UNAIDS Drug Access Initiative Pilot Program, 6 treatment centres in Abidjan, Côte d’Ivoire, offer antiretroviral therapy. Of the patients who received therapy, 72\% were heavily symptomatic upon initiation. Nonetheless, the overall survival rate was 93\% at 6 months, 90\% at 12 months, and 86\% at 18 months. When survival rates are re-calculated using a worst-case
scenario in which patients lost to follow-up are assumed to have died immediately after their last clinic visit, 75% survived at 6 months, 64% at 12 months, and 55% at 18 months.\textsuperscript{16}

With constantly emerging data from high and mid-income countries supporting the use of ARVs in developing countries, along with the continued evolution of improved funding and delivery mechanism to resource-limited countries, the above factors clearly support the addition of Truvada, emtricitabine and tenofovir DF fixed dose combination tablet, to the WHO Model List of Essential Medicines.

7. 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. Safety and efficacy studies using emtricitabine and tenofovir DF in combination are ongoing.\textsuperscript{17}

Both components of emtricitabine and tenofovir DF fixed dose combination tablets have been studied individually, as part of multidrug regimens, and have been found to be safe and effective. Since emtricitabine and lamivudine (3TC) are comparable in their structure, resistance profiles, and efficacy and safety as part of multidrug regimens, existing data from the use of lamivudine and tenofovir DF in combination have been extrapolated to support use of emtricitabine and tenofovir DF fixed dose combination tablets for the treatment of HIV-1 infection in adults. Therefore, in treatment-naïve patients, emtricitabine and tenofovir DF fixed dose combination tablets should be considered as an alternative to the combination of tenofovir DF + 3TC for those patients who might benefit from a once-daily regimen. In treatment-experienced patients, the use of emtricitabine and tenofovir DF fixed dose combination tablets should be guided by laboratory testing and treatment history.

Additional important information regarding the use of Truvada for the treatment of HIV-1 infection:

- There are no study results demonstrating the effect of Truvada on clinical progression of HIV-1
- It is not recommended that Truvada be used as a component of a triple nucleoside regimen

**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.

*Children:* The safety and effectiveness of emtricitabine and tenofovir DF fixed dose combination tablet in patients under the age of 18 years have not been established.

*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.

**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 data are available in patients with renal dysfunction who received emtricitabine and tenofovir DF fixed dose combination using these guidelines in Table 1.

**Table 1. Dosage Adjustment for Patients with Altered Creatinine Clearance**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)¹</th>
<th>≥50</th>
<th>30–49</th>
<th>&lt;30 (Including Patients Requiring Hemodialysis)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Dosing Interval</td>
<td>Every 24 hours</td>
<td>Every 48 hours</td>
<td>Should not be administered.</td>
</tr>
</tbody>
</table>

¹ Calculated using ideal (lean) body weight.

**Hepatic impairment:** The pharmacokinetics of tenofovir following a 300 mg dose 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 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.

**Formulations:** 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil).

**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).

**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.

**Guidelines:** Truvada, emtricitabine and tenofovir DF fixed dose combination tablet, was recently approved by the US Food and Drug Administration on 02 August, 2004. Hence, it has not been included in any guidelines. The endorsement by the World Health Organization (WHO) of Triommmune (d4T+3TC+NVP) as the most suitable regimen for initial therapy was made before the availability of tenofovir DF, FTC and most recently Truvada, the fixed dose combination of FTC and TDF. In contrast, both 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) DHHS guidelines (updated in March 2004) and the International AIDS Society-USA (IAS) Treatment Recommendations for Adult HIV Infection (updated in July 2004) 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 efavirenz (DHHS Guidelines) and/or a boosted protease inhibitor (IAS Guidelines).1,2

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

Monitoring Parameters: Regular monitoring of virologic and immunologic status is rare in the developing world.

Therapeutic: Periodic determinations of plasma HIV RNA (viral load) and CD4 cell count, hepatitis B prior to initiation of therapy, and periodic determinations of HBV DNA

Toxic: Complete blood counts and routine serum chemistry periodically during therapy, signs and symptoms of toxicity (eg, skin rash, gastrointestinal symptoms)

8. Comparative effectiveness in clinical settings:

8.1 Identification of clinical evidence

In compiling the evidence for this and related submissions for anti-retroviral drugs, a search of several databases, including MEDLINE®, EMBASE®, BIOSIS Previews®, and SciSearch®, was conducted. Because Truvada, emtricitabine and tenofovir DF fixed dose combination tablet, was recently approved on 02 August 2004, 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:
  o MEDLINE®
  o EMBASE®
  o SciSearch®
  o BIOSIS Previews®

Search terms included:
  o Emtricitabine
  o FTC
  o BW524
  o BW524W91
  o 524W91
  o Coviracil
  o Emtriva
Study selection:
- Randomized, Phase 3 pivotal clinical trials that compared emtricitabine to lamivudine or examined the combination of tenofovir DF and lamivudine in HIV-infected adults
- Other clinical studies that examined the combination of emtricitabine and tenofovir DF in HIV-infected patients

8.2 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 lamivudine (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 TDF and FTC (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 also improve adherence, as it is dosed as one tablet taken once-a-day.

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 lamivudine 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 Truvada, emtricitabine and tenofovir DF fixed dose combination tablet, is included below. Additional information from clinical trials (Studies GS-934 and M02-418) that examined the combined use of emtricitabine and tenofovir DF are also included. For detailed information regarding the safety and effectiveness of tenofovir DF or emtricitabine in the treatment of HIV-1 infection, please refer to the applications for the inclusion of both components of Truvada, emtricitabine and tenofovir DF, on the WHO Model List of Essential Medicines.

8.2.1 Summary of clinical data
• In a Phase 3 study (Study GS-903), similar proportions of treatment-naïve patients in the TDF-containing regimen and the stavudine-containing regimen achieved HIV RNA <50 copies/mL (81.6% vs. 81.1%, respectively) and <400 copies/mL (86.6% vs. 87%, respectively) at Week 48. Comparable increases in CD4 cell counts were also observed for patients in both groups (169 vs. 167 cells/mm³ for TDF and d4T, respectively). These results are durable through 144 weeks.

• Results from a Phase 3 study (Study FTC-303) showed that, in treatment-experienced patients who were on a stable lamivudine-containing HAART regimen, switching to emtricitabine 200 mg QD demonstrated comparable efficacy compared to continuing lamivudine 150 mg BID through 48 weeks of treatment. Both medications were given in combination with a NRTI and a PI or NNRTI.

• Preliminary 24-week data from an ongoing Phase 3, open-label study (Study GS-934) comparing the safety and efficacy of a QD regimen containing FTC 200 mg and TDF 300 mg plus EFV 600 mg vs. 3TC 150 mg/AZT 300 mg (Combivir®) BID plus EFV 600 mg QD showed that significantly more patients in the FTC/TDF group achieved and maintained HIV RNA < 400 copies/mL using the Time to Loss of Virologic Response (TLOVR) algorithm (p=0.019).

• In Study M02-418, FTC 200 mg and TDF 300 mg QD were used in regimens containing lopinavir/ritonavir designed to compare the safety and efficacy of lopinavir/ritonavir QD vs. BID. At Week 48, an intent-to-treat (ITT) analysis showed that 70% of patients in the QD group and 64% of patients in the BID group had HIV RNA < 50 copies/mL. In addition, mean CD4 cell counts increased by 185 and 188 cells/mm³ in the QD and BID groups, respectively.

8.2.2 Summary of comparative effectiveness in HIV-infected adults

Treatment-naïve HIV-infected patients

Study GS-934

This ongoing Phase 3, open-label, multicenter, 96-week study is designed to evaluate the safety and efficacy of a QD regimen containing FTC 200 mg and TDF 300 mg (FTC/TDF) plus EFV 600 mg vs. 3TC 150 mg/AZT 300 mg (Combivir®) BID plus EFV 600 mg QD in treatment-naïve HIV-infected patients with HIV RNA levels > 10,000 copies/mL. The primary endpoint of the study is the percentage of patients with HIV RNA < 400 copies/mL (TLOVR analysis) at Week 48. Patients (n=517) were randomized in a 1:1 ratio. Excluded were 30 patients who were either never dosed, major protocol violators, or had baseline NNRTI resistance. Thus, the preliminary 24-week pre-specified ITT analysis included 487 patients, 244 patients in the FTC/TDF group and 243 patients in the 3TC/AZT group. Eighty-eight percent of patients in the FTC/TDF group compared to 80% of patients in the 3TC/AZT group achieved and maintained HIV RNA < 400 copies/mL at Week 24 using the TLOVR algorithm (p=0.019; 95% CI, +0.8% to +13.3%). The increase in CD4 cell count from baseline was 129 cells/mm³ for the FTC/TDF group and 111 cells/mm³ for the 3TC/AZT group. In the TLOVR algorithm, 3% of patients in the FTC/TDF group compared to 9% of patients in the 3TC/AZT group discontinued from the study due to adverse events (p=0.013). The
incidence of grade 3 or 4 clinical adverse events was 9% for the FTC/TDF group vs. 15% for the 3TC/AZT group.

Study M02-418

This was a randomized, open-label, multicenter study designed to compare lopinavir 800 mg/ritonavir 200 mg QD vs. lopinavir 400 mg/ritonavir 100 mg BID with the background regimen of FTC 200 mg and TDF 300 mg QD in antiretroviral-naïve patients with HIV RNA >1,000 copies/mL. A total of 190 patients between the ages of 19-75 years were enrolled; 115 to the QD arm and 75 to the BID arm. At baseline, the median HIV RNA levels for patients in the QD and BID arms were 4.8 and 4.6 log_{10} copies/mL and the median CD4 cell counts were 214 and 232 cells/mm^3, respectively. Overall, approximately 45% of patients had CD4 cell count < 200 cells/mm^3 and 38% had HIV RNA > 100,000 copies/mL. Results at Weeks 24 and 48 revealed that a similar proportion of patients achieved HIV RNA < 50 copies/mL (95% confidence interval at Week 48 [ITT missing = failure analysis: −7%; 20%]). In addition, increase in CD4 cell counts was similar between the 2 groups. Detailed data are presented in Table 2 below.

### Table 2. Results at Week 24 and 48 – Intent-to-Treat Analysis (Observed Analysis)^20-22†

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QD</td>
<td>BID</td>
</tr>
<tr>
<td>% with HIV RNA &lt; 50 copies/mL</td>
<td>57% (68%)</td>
<td>57% (78%)</td>
</tr>
<tr>
<td></td>
<td>(n=97)</td>
<td>(n=61)</td>
</tr>
<tr>
<td>Mean Change in CD4 Cell Count</td>
<td>+128</td>
<td>+103</td>
</tr>
<tr>
<td>(cells/mm^3)</td>
<td>(n=99)</td>
<td>(n=62)</td>
</tr>
<tr>
<td></td>
<td>+185</td>
<td>+188</td>
</tr>
<tr>
<td></td>
<td>(n=88)</td>
<td>(n=55)</td>
</tr>
</tbody>
</table>

*Intent-to-treat analysis: missing=failure; observed analysis: missing=exclusion
†QD: once daily; BID: twice daily; n: number of patients

Study GS-903 (TDF+3TC+EFV compared with d4T+3TC+EFV)

This is an on-going, Phase 3, 3-year, randomized, double-blind, active-controlled, multicenter clinical trial designed to compare the efficacy and safety of TDF (300 mg QD) to d4T (40 mg BID) with a background regimen of 3TC (150 mg BID) and EFV (600 mg QD) in 600 treatment-naïve HIV-infected individuals. At baseline, the mean HIV RNA levels for the ITT population was 4.9 log_{10} copies/mL and the mean CD4 cell count was 279 cells/mm^3. The mean age of the patients was 36 years and 64% of patients were Caucasian. Results at 48 weeks showed that similar numbers of patients in both regimens experienced reduction in HIV RNA levels to <50 copies/mL and <400 copies/mL. The mean increases in CD4 cell counts were also comparable in both groups. These values were durable through Week 144 (Figures 1 and 2). Additionally, when results were stratified by baseline HIV RNA levels (≤ or >100,000 copies/mL) and CD4 cell counts (< or ≥200 cells/mm^3), similar percentages of patients were found to have HIV RNA <50 copies/mL and <400 copies/mL at Week 144 in both the TDF and d4T arms.
Figure 1. Percentage of Patients with HIV RNA < 50 copies/mL Through Week 144\textsuperscript{23}

Intent to Treat (Missing=Failure)

![Graph showing percentage of patients with HIV RNA < 50 copies/mL through Week 144 for (TDF+3TC+EFV) and (d4T+3TC+EFV).]

Figure 2. Mean Increase from Baseline in CD4 Cell Count Through Week 144\textsuperscript{23}*

![Graph showing mean increase from baseline in CD4 cell count through Week 144 for (TDF+3TC+EFV) and (d4T+3TC+EFV).]

* 95% Confidence Interval for the difference, -54 to 11

_Treatment-experienced HIV-infected patients_

_Study FTC-303 (FTC QD vs. 3TC BID with stable background therapy)_

Study FTC-303 was a Phase 3, 48-week, randomized, open-label, multicenter study comparing FTC (200 mg QD) to 3TC (150 mg BID), in combination with stavudine (d4T) (40 mg BID) or zidovudine (AZT) (300 mg BID) and a PI or NNRTI in 440 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.\textsuperscript{17,25,26} Patients were randomized 1:2 to either continue therapy with 3TC or to switch to FTC; the stable background regimen was maintained. Patients had a mean age of 42 years (range 22-80), 86% were male, 64% Caucasian, 21% African-American, and 13% Hispanic. 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\textsubscript{10} copies/mL (range 1.7-4.0), and the mean CD4 cell count was
527 cells/mm$^3$ (range 37-1,090). Results at Week 48 are shown in Table 3. There were no statistically significant differences between treatment arms.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Emtricitabine (n=294)</th>
<th>Lamivudine (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders†</td>
<td>77% (67%)</td>
<td>82% (72%)</td>
</tr>
<tr>
<td>Virologic Failure (&gt;400 copies/mL)‡</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Rebound</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Never Suppressed through Week 48</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Study Discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to Adverse Events</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>For Other Reasons§</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

*n: number of patients  
†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 reason

The mean increase from baseline in CD4 cell count was 29 cells/mm$^3$ for the FTC arm and 61 cells/mm$^3$ for the 3TC arm. 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.

9. Comparative evidence on safety:

9.1 Estimate of total patient exposure to date

Truvada, emtricitabine and tenofovir DF fixed dose combination tablet, was first approved in the United States on 02 August 2004. It is estimated that 283 HIV-1 infected patients have received combination therapy with tenofovir DF and emtricitabine with either a NNRTI or PI for 24 to 48 weeks in ongoing clinical studies. However, there is very limited post-marketing exposure to emtricitabine and tenofovir DF fixed dose combination tablets, with no estimate of patient exposure currently available. Safety and efficacy studies using emtricitabine and tenofovir DF fixed dose combination tablets or using emtricitabine and tenofovir DF in combination are ongoing.

9.2 Descriptions of adverse effects/reactions

9.2.1 Warning and precautions for use

9.2.1.1 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. 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).
9.2.1.2 HIV and HIV 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.

9.2.1.3 Renal Impairment

Tenofovir DF: Tenofovir DF is primarily excreted by the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphatemia and Fanconi syndrome have been reported with the use of tenofovir DF in clinical practice. The majority of these cases occurred in patients with underlying renal disease or in combination with nephrotoxic agents.

Dosing interval adjustment is required in all patients with creatinine clearance <50 mL/min.

No safety data are available in patients with renal dysfunction who received tenofovir DF using these guidelines. Tenofovir DF should be avoided with concurrent or recent use of a nephrotoxic agent. Routine monitoring should be performed for changes in serum creatinine and serum phosphorus in patients with a history of, or at risk for, renal dysfunction.

Emtricitabine: Emtricitabine is principally eliminated by the kidney by both glomerular filtration and active tubular secretion. It is recommended that the dosing interval for emtricitabine be modified in patients with impaired renal function. There may be competition for other compounds that are also renally eliminated.

9.2.1.4 Lipodystrophy

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.

9.2.1.5 Hepatic Impairment

Tenofovir DF: Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed therefore no dose adjustment is required in patients with hepatic impairment.

Emtricitabine: Emtricitabine has not been evaluated in patients with hepatic impairment; however, emtricitabine is not metabolized by liver enzymes, so the impact of liver impairment should be limited.
9.2.1.6 Bone Effects

_Tenofovir DF_: Bone toxicity, including a reduction in bone mineral density, was seen in animals following treatment with tenofovir or tenofovir disoproxil. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years). If bone abnormalities are suspected then appropriate consultation should be obtained.

9.2.1.7 Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

9.2.1.8 Geriatric Use

Clinical studies of Emtriva or Viread 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.

9.2.1.9 Drug Interactions

_Tenofovir DF_: Co-administration of tenofovir DF and the buffered tablet or enteric-coated formulation of didanosine at a dose of 400 mg daily resulted in increased systemic exposure to didanosine. As a result of this increased exposure, patients receiving tenofovir DF and didanosine concomitantly should be carefully monitored for didanosine-related adverse events e.g. pancreatitis, lactic acidosis. The dose of didanosine should be reduced to 250 mg daily in patients weighing in excess of 60 kg. Data are not adequate to support a specific recommendation for dosing in subjects weighing less than 60 kg.

Tenofovir DF affects the pharmacokinetics of atazanavir. Tenofovir DF should only be administered with boosted atazanavir (ATZ 300mg/RTV 100mg). The safety and efficacy of this regimen has been substantiated over 48 weeks in a clinical study.

_Emtricitabine_: At concentrations up to 14 fold higher than those observed in vivo, emtricitabine did not inhibit _in vivo_ drug metabolism mediated by any of the following human CYP450 isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation. Based on the results of these in vitro experiences and the known elimination pathways of emtricitabine, the potential for CYP450 mediated interactions involving emtricitabine with other medicinal products is low.

There are no clinically significant drug interactions when emtricitabine is co-administered with either indinavir, zidovudine, stavudine, famciclovir, or tenofovir disoproxil fumarate.

9.2.3 Pregnancy and lactation

_Tenofovir DF_: Animal studies do not indicate direct or indirect harmful effects of tenofovir DF with respect to pregnancy, fetal development, parturition or postnatal development.

Tenofovir DF should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or fetal parameter.

In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Therefore, it is recommended that mothers being treated with tenofovir DF do not breast-feed their infants.

**Emtricitabine**: Reproductive studies were conducted in rats, mice, and rabbits. Animal studies (performed at 60-120 fold human exposure) did not indicate harmful effects of emtricitabine with respect to fertility, pregnancy, fetal parameters, parturition or postnatal development.

Emtricitabine should be used during pregnancy only if clearly needed.

It is not known whether emtricitabine is secreted into human milk. Therefore, it is recommended that mothers being treated with emtricitabine do not breast-feed their infants.

To monitor congenital birth defects in pregnant women exposed to emtricitabine and tenofovir DF, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling the Antiretroviral Registry.

### 9.2.4 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.

### 9.3 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 Emtriva. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported.

### 9.4 Undesirable effects

#### 9.4.1 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. Two hundred eighty three HIV-1 infected patients have received combination therapy with tenofovir DF and emtricitabine with either
a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 24 to 48 weeks in ongoing clinical studies. Based on these limited data, no new patterns of adverse events were identified and there was no increased frequency of established toxicities.

9.4.1.1 Tenofovir DF

The most common adverse events that occurred in patients receiving tenofovir DF with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting, flatulence and dizziness. Less than 1% of patients discontinued participation in the clinical studies because of gastrointestinal adverse events.

Other adverse events have been reported in 1-15% of patients receiving tenofovir DF. They include asthenia, pain, headache, abdominal pain, back pain, chest pain, fever, dyspepsia, anorexia, arthralgia, depression, insomnia, abnormal dreams, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash), sweating, myalgia and weight loss.

Grade 3 / 4 elevations of ALT and AST (≥ 5 x ULN), creatine kinase (> 4 x ULN), serum amylase (>5 x ULN), urine glucose (≥ 3+), serum glucose (> 250 ULN) and serum triglycerides (> 750 mg/dL), hematuria (>100 RBC/HPF) and decreased neutrophils (<750 mm3) have been reported to occur in 2-12% of patients receiving Viread.

9.4.1.2 Emtricitabine

The most common adverse reactions that occurred in patients receiving emtricitabine with other antiretroviral agents in clinical trials were headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies because of to these events.

Other adverse events have been reported in 2-25% of patients receiving emtricitabine. They include abdominal pain, asthenia, dyspepsia, vomiting, arthralgia, myalgia, abnormal dreams, depressive disorder, dizziness, insomnia, neuropathy, peripheral neuritis, paresthesia, increased cough, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).

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 Emtriva treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Grade 3 / 4 elevations of ALT and AST (≥ 5 x ULN), bilirubin (> 2.5 x ULN), creatine kinase (> 4 x ULN), decreased neutrophils (<750 mm3), pancreatic amylase (>2.0 x ULN), serum amylase (>5 x ULN), serum glucose (<40 or >250 mg/dL), serum lipase (>2.0 x ULN) and triglycerides (> 750 mg/dL) have been reported to occur in 1-12% of patients receiving emtricitabine.

9.4.2 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, Pancreatitis

**RENAL AND URINARY DISORDERS**
Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis

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

### 9.4.3 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 283 HIV-1 infected patients who have received emtricitabine and tenofovir DF together with either a NNRTI or PI for 24 to 48 weeks in the ongoing clinical studies. Safety results from selected clinical trials are included below. For additional detailed safety information regarding emtricitabine or tenofovir DF, the components of Truvada (emtricitabine and tenofovir DF fixed dose combination tablets), in combination with other antiretroviral agents, please consult the individual applications for their inclusion on the WHO Model List of Essential Medicines.

**Study GS-934 (Ongoing Phase 3 Clinical Trial)**

This ongoing Phase 3, open-label, multicenter, 96-week study is designed to evaluate the safety and efficacy of a QD regimen containing FTC 200 mg and TDF 300 mg (FTC/TDF) plus EFV 600 mg vs. 3TC 150 mg/AZT 300 mg (Combivir) BID plus EFV 600 mg QD in treatment-naïve HIV-infected patients with HIV RNA levels > 10,000 copies/mL. The primary endpoint of the study is the percentage of patients with HIV RNA < 400 copies/mL (TLOVR analysis) at Week 48. Patients (n=517) were randomized in a 1:1 ratio. Excluded were 30 patients who were either never dosed, major protocol violators, or had baseline NNRTI resistance. Thus, the preliminary 24-week pre-specified ITT analysis included 487 patients, 244 patients in the FTC/TDF group and 243 patients in the 3TC/AZT group. In the TLOVR algorithm, 3% of patients in the FTC/TDF group...
compared to 9% of patients in the 3TC/AZT group discontinued from the study due to adverse events (p=0.013). The incidence of grade 3 or 4 clinical adverse events was 9% for the FTC/TDF group vs. 15% for the 3TC/AZT group.

Study M02-418

This randomized, open-label, multicenter study was designed to compare lopinavir 800 mg/ritonavir 200 mg QD vs. lopinavir 400 mg/ritonavir 100 mg BID with the background regimen of FTC 200 mg and TDF 300 mg QD in antiretroviral-naïve patients with HIV RNA >1,000 copies/mL.20-22 A total of 190 patients between the ages of 19-75 years were enrolled; 115 to the QD arm and 75 to the BID arm.

At Week 48, a total of 19% of patients in the QD group and 25% of patients in the BID group discontinued the study; 12% and 5% due to adverse events, respectively. Gastrointestinal adverse events were the most common cause for discontinuation. Overall, the most common adverse events (> 3%) reported were diarrhoea, nausea, and vomiting, with diarrhoea being reported significantly higher in the QD group (16% vs. 5%; p=0.04). The most common grade 3/4 laboratory abnormalities (> 3%) reported were increased ALT (> 5 x upper limit of normal [ULN]), AST (> 5 x ULN), triglyceride (> 750 mg/dL), and amylase (> 2 x ULN) levels; no significant differences between the 2 groups were observed.21

Acute renal failure (ARF) occurred in 1 patient in each group. One was a 75 year-old male with a creatinine clearance of 40 mL/min at baseline who was given full dose of TDF and 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 haemodialysis. Renal biopsy demonstrated tubulointerstitial nephritis. Both patients improved upon discontinuation of study drug, 1 discontinued all ARVs and the other substituted TDF with d4T as part of the HAART regimen, with serum creatinine returning to ≤ 1.7 mg/dL.21

At Week 48, significant increases from baseline in total cholesterol, HDL, LDL, and triglyceride levels were observed in both groups. However, the mean 10-year coronary heart disease risk and analysis of risk rates by each category did not change significantly from baseline.21

Study GS-903

Through Week 48, grades 2-4 adverse events and grades 3/4 laboratory abnormalities were similar between the 2 groups in this Phase 3, 3-year, randomized, double-blind, active-controlled, multicenter clinical trial. Adverse events that occurred in > 5% of patients receiving TDF in combination with other antiretrovirals in clinical trials included: headache, nausea, diarrhoea, vomiting, rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash), depression and dizziness. Less than 1% of patients discontinued the studies because of gastrointestinal adverse events.17

Through Week 144, 18% of the patients in the TDF arm and 21% of patients in the d4T arm discontinued the study; 1% and 2% due to adverse events, respectively.23 Grades 3/4 adverse events
and laboratory abnormalities were similar between the 2 arms. However, metabolic abnormalities were observed significantly more common in the d4T arm. Please see Tables 4-6 below for more detailed information.

**Table 4. Grade 3/4 Adverse Events Reported ≥ 2% in any Treatment Group through Week 144**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TDF+3TC+EFV (n=299)</th>
<th>d4T+3TC+EFV (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage with Events</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Bacterial Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Depression</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Fever</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Fracture</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*TDF: tenofovir DF; 3TC: lamivudine; EFV: efavirenz; d4T: stavudine; n: number of patient

**Table 5. Grade 3/4 Laboratory Abnormalities Reported ≥ 3% in any Treatment Group through Week 144**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TDF+3TC+EFV (n=295)</th>
<th>d4T+3TC+EFV (n=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage with Abnormalities</td>
<td>36%</td>
<td>42%</td>
</tr>
<tr>
<td>Creatine Kinase</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Amylase</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>AST</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>ALT</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Triglycerides†</td>
<td>3%</td>
<td>14%</td>
</tr>
</tbody>
</table>

*TDF: tenofovir DF; 3TC: lamivudine; EFV: efavirenz; d4T: stavudine; n: number of patients; AST: aspartate aminotransferase; ALT: alanine aminotransferase

†p<0.001

**Table 6. Metabolic Parameters through Week 144**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TDF+3TC+EFV</th>
<th>d4T+3TC+EFV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in Fasting Triglycerides (mg/dL)</td>
<td>1</td>
<td>134</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increase in Fasting Total Cholesterol (mg/dL)</td>
<td>30</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Limb Fat (kg)</td>
<td>8.6</td>
<td>4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% with Lipodystrophy (Investigator Defined)</td>
<td>3%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†mean values

*P value indicates the statistical significance of the difference between the two treatment groups.

A Kaplan-Meier analysis of time to use of first lipid-lowering agents excluding patients receiving lipid-lowering agents at baseline showed that a significantly larger percentage of patients in the d4T arm initiated a lipid-lowering agent compared to those in the TDF arm, 16% vs. 5%, respectively (p<0.001). Additionally, through Week 144, no patient in the TDF arm discontinued the study due to renal-related abnormality or developed Fanconi syndrome. Two patients (<1%) in each group
developed a serum creatinine >2.0 mg/dL, while hypophosphatemia (<2.0 mg/dL [<176.8 µmol/L]) was observed in 10 patients receiving TDF and 8 patients receiving d4T. The incidence of proteinuria and/or glycosuria was similar between the 2 groups. Mean decreases in lumbar spine and hip bone mineral density from baseline to Week 144 were 2.8% and 2.2% for the TDF arm and 2.4% and 1% for the d4T arm, respectively. Bone mineral density reduction observed in this study was non-progressive with no substantial changes from the 24-48 week interval to Week 144. There were 5 fractures in the TDF arm compared to 11 in the d4T arm; all were associated with trauma except for a vertebral compression fracture in a patient in the d4T arm. No fractures were reported in women, who comprised 26% of the study population. The percentage of patients with mitochondrial-associated toxicities (peripheral neuritis/neuropathy, lipodystrophy, and lactic acidosis) was also significantly lower in the TDF arm, 6% compared to 28% in the d4T arm.

**Study FTC-303**

The most common adverse events that occurred in >5% of patients receiving FTC with other antiretroviral agents in clinical trials including Study FTC-303 were abdominal pain, asthenia, headache, diarrhoea, nausea, vomiting, dizziness, 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 FTC and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the FTC 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.

In Study FTC-303, 13 patients discontinued from the FTC group due to adverse events, including 7 patients whose adverse events were considered unrelated to the drug. The other 6 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.

Grade 3/4 laboratory abnormalities occurred with similar frequency in the FTC and 3TC groups. A summary of grade 3 and 4 laboratory abnormalities is provided in Table 7 below.
Table 7. Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥1% of FTC-Treated Patients in Study FTC-303 (0-48 Weeks)²⁶*  

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>FTC+ZDV/d4T+NNRTI/PI (n=294)</th>
<th>3TC+ZDV/d4T+NNRTI/PI (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>ALT (&gt;5 x ULN)</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>AST (&gt;5 x ULN)</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Bilirubin (&gt;2.5 x ULN)</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Creatine Kinase (&gt;4 x ULN)</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>Neutrophils (&lt;750 mm³)</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreatic Amylase (&gt;2 x ULN)</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Serum Amylase (&gt;2 x ULN)</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Serum Glucose (&lt;40 or &gt;250 mg/dL)</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Serum Lipase (&gt;2 x ULN)</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Triglycerides (&gt;750 mg/dL)</td>
<td>10%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*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

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

10.1. Range of costs of the proposed medicine

10.1.1 Western Hemisphere

The Gilead fixed dose combination tablet of the two antiretrovirals, emtricitabine 200mg and tenofovir disoproxil fumarate 300mg (Truvada™), 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 Truvada varies among payers in the United States. The list price is USD 650.83 as detailed following table indicates current pricing:

<table>
<thead>
<tr>
<th>Country</th>
<th>Package</th>
<th>Average Package Price (USD)</th>
<th>Average Unit Price (USD)</th>
<th>Defined Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>30 TAB</td>
<td>650.83</td>
<td>21.69</td>
<td>500 MG</td>
</tr>
</tbody>
</table>

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

On 15 March 2004, Gilead submitted the Marketing Authorisation Application (MAA) for the fixed dose co-formulation to the European Agency for the Evaluation of Medicinal Products (EMEA). Gilead will continue to manufacture the components of Truvada as individual
antiretrovirals in the United States and other territories in which it may receive marketing approval.

10.1.2 Least Developed Countries

Gilead No-Profit Access Program

Recognizing the urgent need for ARV treatment in developing countries, Gilead established its Global Access Program in 2002 to ensure that as many people who need Truvada and Viread® (tenofovir disoproxil fumarate 300mg) are able to access them. The program makes both ARVs available in 69 countries, including all 53 nations in Africa and 16 additional countries (included are Afghanistan, Bangladesh, Bhutan, Cambodia, Haiti, Kiribati, Laos, Maldives, Myanmar, Nepal, Samoa, Solomon Islands, E Timor, Tuvalu, Vanuatu, and Yemen), designated as “least developed” by the United Nations. Collectively, these 69 nations account for 70 percent of the global population afflicted with HIV/AIDS. In these regions, the Gilead non-profit price of Truvada is USD 0.99 per day. This is based on ex-factory pricing, free on board from California, US without handling fees. Additionally, in order to maintain the lowest possible drug cost, Gilead only contracts with organizations that agree to conduct business on a non-profit basis.

Gilead Clinical Research Collaborations and Partnerships

To help determine more effective ways of treating HIV/AIDS in resource poor settings, Gilead continues to collaborate with the US government and private research organizations, including the Bill and Melinda Gates Foundation, Family Health International, National Institutes of Health (NIH), Medical Research Council of the UK (MRC) and Rockefeller Foundation. Clinical trials conducted by these organizations are designed to evaluate the safety and efficacy of tenofovir DF- and Truvada-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 more than 3,000 patients are receiving HAART and medical care.

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

10.2.1 Cost-Effectiveness of HAART

Traditional cost-effectiveness comparisons of antiretrovirals for the treatment of HIV infection, including tenofovir DF, 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, AIDS deaths in the United States declined by 70 percent from 1995 to 2000, primarily as a result of HAART.29

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. 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. 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 Truvada make it well-suited for HAART administered in the developing world. Several clinical studies (up to 144 weeks) have demonstrated that tenofovir DF is optimally effective, long-lasting, highly 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.

Clinical trials as well as worldwide clinical experience in more than 168,000 patients demonstrate that tenofovir DF taken once daily as part of combination therapy consistently achieves the stated goals of HAART, and may provide a more cost-efficient option to older, more complex ARVs. Table 8 summarizes developing world costs as published in the 2003 International Drug Price Indicator Guide. Note that new no-profit pricing for tenofovir DF is favourable in respect to comparators in its pharmacologic (AZT, ABC) and therapeutic class (EFV).

**Table 8. ARV – Supplier Pricing: Mission for Essential Drugs and Supplies**

<table>
<thead>
<tr>
<th>Treatment – Supplier Pricing</th>
<th>Package</th>
<th>Daily Dose</th>
<th>Package Price (USD)</th>
<th>Supplier Unit Price (USD)</th>
<th>Daily Price (USD)</th>
<th>Monthly Price (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF 300mg (Viread®)</td>
<td>30 TAB</td>
<td>300 MG</td>
<td>24.71</td>
<td>0.82366</td>
<td>0.82</td>
<td>24.71</td>
</tr>
<tr>
<td>Emtricitabine+tenofovir DF (Truvada)</td>
<td>30 TAB</td>
<td>500 MG</td>
<td>29.75</td>
<td>0.99166</td>
<td>0.99</td>
<td>29.75</td>
</tr>
<tr>
<td>Lamivudine 150mg+zidovudine 300mg</td>
<td>60 TAB</td>
<td>900 MG</td>
<td>22.94</td>
<td>0.3824</td>
<td>0.76</td>
<td>22.94</td>
</tr>
<tr>
<td>Abacavir 300 mg</td>
<td>60 TAB</td>
<td>600 MG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lamivudine 150mg</td>
<td>60 TAB</td>
<td>300 MG</td>
<td>6.37</td>
<td>0.1063</td>
<td>0.21</td>
<td>6.37</td>
</tr>
<tr>
<td>Stavudine 40mg</td>
<td>56 TAB</td>
<td>80 MG</td>
<td>4.77</td>
<td>0.0852</td>
<td>0.17</td>
<td>9.54</td>
</tr>
<tr>
<td>Zidovudine 100mg</td>
<td>100 TAB</td>
<td>600 MG</td>
<td>18.55</td>
<td>0.1855</td>
<td>1.11</td>
<td>37.10</td>
</tr>
<tr>
<td>Efavirenz 200mg</td>
<td>90 TAB</td>
<td>600 MG</td>
<td>52.15</td>
<td>0.5798</td>
<td>1.73</td>
<td>52.15</td>
</tr>
</tbody>
</table>

*No handling fees charged; shipping cost to destination not included

†Two bottles month/patient required at recommended dosages: zidovudine-600mg/day; stavudine-80mg/day
11. Summary of regulatory status of the medicine (in country of origin and preferably in other countries as well):

Truvada, emtricitabine and tenofovir DF fixed dose combination tablet, received the approval by US FDA on 02 August 2004. On 15 March 2004, Gilead submitted the Marketing Authorisation Application (MAA) for the fixed dose co-formulation to the European Agency for the Evaluation of Medicinal Products (EMEA).

<table>
<thead>
<tr>
<th>Territory</th>
<th>Approval Date</th>
<th>Tradename</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>02 August 2004</td>
<td>Truvada™</td>
</tr>
</tbody>
</table>

12. Availability of pharmacopeial standards:

British Pharmacopoeia: no
International Pharmacopoeia: no
United States Pharmacopoeia: Will be included in 2005 Edition

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

**WHO Model Formulary 2004**

**Description:**

Emtricitabine and tenofovir DF fixed dose combination (Truvada™) tablets contain emtricitabine and tenofovir disoproxil fumarate. Emtriva is the brand name for emtricitabine, a synthetic nucleoside analog of cytidine. Tenofovir disoproxil fumarate (Viread, 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:**

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 Viread + Epivir for those patients who might benefit from a once-daily regimen. 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 Truvada 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 creatine 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 disoproxil fumarate:_ When tenofovir disoproxil fumarate was administered with didanosine the C<sub>max</sub> 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 Truvada. 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<sub>min</sub> 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 disoproxil fumarate:_ 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.

Truvada 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™, or Trizivir®.

Bone Effects
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. Bone toxicity, including a reduction in bone mineral density, was seen in animals following treatment with tenofovir or tenofovir disoproxil. Clinically relevant bone abnormalities have not been seen in long-term clinical studies (> 3 years). 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.

Paediatric Use
Safety and effectiveness in paediatric patients have not been established.

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.

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.

Pregnancy and Lactation

Pregnancy Category B:

*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.
**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 Truvada 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.

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)(a)</th>
<th>≥50</th>
<th>30–49</th>
<th>&lt;30 (Including Patients Requiring Hemodialysis)(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Dosing Interval</td>
<td>Every 24 hours</td>
<td>Every 48 hours</td>
<td>Should not be administered.</td>
</tr>
</tbody>
</table>

\(a\) Calculated using ideal (lean) body weight.

**Adverse effects:**

**Clinical Trials**
Safety and efficacy studies using emtricitabine and tenofovir DF fixed dose combination (Truvada) tablets or using emtricitabine and tenofovir DF in combination are ongoing. Two hundred eighty three HIV-1 infected patients have received combination therapy with emtricitabine or tenofovir DF with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 24 to 48 weeks in ongoing clinical studies. Based on these limited data, no new patterns of adverse events were identified and there was no increased frequency of established toxicities.
For additional safety information about emtricitabine or tenofovir disoproxil fumarate in combination with other antiretroviral agents, also consult the WHO Model Formulary 2004 for these products.

**Emtricitabine:**
Adverse events that occurred in >5% of patients receiving emtricitabine with other antiretroviral agents in clinical trials include abdominal pain, asthenia, headache, diarrhoea, nausea, vomiting, dizziness, and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).

Approximately 1% of patients discontinued participation in the clinical studies because of these adverse events. Other adverse events reported include dyspepsia, arthralgia, myalgia, abnormal dreams, depressive disorder, insomnia, neuropathy, peripheral neuritis, paresthesia, increased cough, and rhinitis.

All adverse events were reported with similar frequency in Emtriva and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the Emtriva treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Grade 3/4 elevations of ALT and AST (>5 x ULN), bilirubin (>2.5 x ULN), creatine kinase (>4 x ULN), decreased neutrophils (<750/mm³), pancreatic amylase (>2.0 x ULN), serum amylase (>2 x ULN), serum glucose (<40 or >250 mg/dL), serum lipase (>2.0 x ULN) and triglycerides (>750 mg/dL) have been reported to occur in 1–12% of patients receiving emtricitabine.

**Tenofovir Disoproxil Fumarate:**
Adverse events that occurred in >5% of patients receiving tenofovir DF with other antiretroviral agents in clinical trials included: headache, nausea, diarrhoea, vomiting, rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash), and depression. Less than 1% of patients discontinued participation in the clinical studies because of gastrointestinal adverse events.

Other adverse events include asthenia, pain, abdominal pain, back pain, chest pain, fever, flatulence, dizziness, dyspepsia, anorexia, arthralgia, insomnia, abnormal dreams, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, sweating, myalgia and weight loss.

Grade 3/4 elevations of ALT and AST (>5 x ULN), creatine kinase (>4 x ULN), serum amylase (>5 x ULN), urine glucose (≥3+), serum glucose (>250 mg/dL) and serum triglycerides (>750 mg/dL), hematuria (>100 RBC/HPF) and decreased neutrophils (<750/mm³) have been reported to occur in 2–12% of patients receiving Tenofovir DF.
Post Marketing Experience

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

Tenofovir Disoproxil Fumarate:
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 to tenofovir DF.

IMMUNE SYSTEM DISORDERS
Allergic reaction

METABOLISM AND NUTRITION DISORDERS
Hypophosphatemia, Lactic acidosis

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS
Dyspnea

GASTROINTESTINAL DISORDERS
Abdominal pain, Pancreatitis

RENAL AND URINARY DISORDERS
Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis

Patient advice:
Take emtricitabine and tenofovir DF fixed dose combination tablets exactly as your healthcare provider prescribed 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.
References:


5. ibid

6. ibid

7. ibid


### Attachment 1:
**Summary of Key Clinical Trials of Oral Emtricitabine and Tenofovir DF Fixed Dose Combination Tablets:**

<table>
<thead>
<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>
</thead>
<tbody>
<tr>
<td>GS-903 (Gallant et al. 2004.)</td>
<td>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.</td>
<td>144 weeks</td>
<td>Antiretroviral-naive, HIV-1-infected patients with plasma HIV-1 RNA levels &gt;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)</td>
<td>The tenofovir DF regimen was equivalent to the stavudine control regimen in reducing plasma HIV-1 RNA levels, both overall and in all subgroups of the ITT population based on stratification factors at randomisation. HIV RNA &lt; 400 copies/mL at Week 48, ITT missing=failure (as treated): o TDF+3TC+EFV: 80% (98%) o d4T+3TC+EFV: 84% (98%) HIV RNA &lt; 50 copies/mL at Week 48, ITT missing=failure (as treated): o TDF+3TC+EFV: 76% (93%) o d4T+3TC+EFV: 80% (94%) HIV RNA &lt; 400 copies/mL / &lt; 50 copies/mL at Week 96, ITT missing=failure: o TDF+3TC+EFV: 82% / 78% o d4T+3TC+EFV: 78% / 74% HIV RNA &lt; 400 copies/mL / &lt; 50 copies/mL at Week 144, ITT missing=failure: o TDF+3TC+EFV: 76% / 73% o d4T+3TC+EFV: 72% / 69%</td>
<td>Tenofovir DF in combination with 3TC and EFV was well tolerated through 96 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. Compared with the stavudine control group, the tenofovir DF group showed significantly (p &lt;0.0001) smaller increases in serum cholesterol concentrations and no change in serum triglyceride concentrations. 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.</td>
</tr>
<tr>
<td>Study Number (Publication)</td>
<td>Design</td>
<td>Duration of Treatment</td>
<td>Population Number of Subjects by Treatment Arm</td>
<td>Clinical Efficacy</td>
<td>Safety and Tolerability</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------</td>
<td>----------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------</td>
<td>------------------------</td>
</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 &lt; 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.</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FTC (n=294)</th>
<th>3TC (n=146)</th>
</tr>
</thead>
<tbody>
<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</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Never Suppressed</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Study Discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to Adverse Events</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>For Other Reasons‡</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</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 (3TC).
<table>
<thead>
<tr>
<th>Study Number (Publication)</th>
<th>Design</th>
<th>Duration of Treatment</th>
<th>Population</th>
<th>Clinical Efficacy</th>
<th>Safety and Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-934 (Gilead Press Release 2004)</td>
<td>Phase 3, open-label, multicenter study to evaluate safety and efficacy of a FTC and TDF QD regimen vs. 3TC and AZT BID regimen + EFV 600 mg QD</td>
<td>96 weeks, open-label</td>
<td>Treatment-naive HIV-infected patients with HIV RNA &gt;10,000 copies/mL. Randomised 1:1 to: FTC 200 mg QD + TDF 300 mg QD + EFV 600 mg QD vs. 3TC 150 mg/AZT 300 mg BID + EFV 600 mg QD</td>
<td>Preliminary 24-week pre-specified ITT (244 patients in FTC/TDF group and 243 in 3TC/AZT group) HIV RNA &lt; 400 copies/mL: (TLOVR analysis): (p=0.019) o TDF+FTC+EFV: 88% o 3TC+AZT+EFV: 80% Increase in CD4 cell count from baseline: (p=0.02 AAUCMB; p=0.07 for point estimate analysis) o TDF+FTC+EFV: 88% o 3TC+AZT+EFV: 80%</td>
<td>Preliminary 24-week results Discontinued the study (TLOVR): o FTC+TDF+EFV: 3% o 3TC/AZT+EFV: 9% Grade 3/4 adverse events: o FTC+TDF+EFV: 9% o 3TC/AZT+EFV: 15%</td>
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<td>At Week 48, a total of 19% of patients in the QD group and 25% of patients in the BID group discontinued the study; 12% and 5% due to adverse events, respectively. Gastrointestinal adverse events were the most common cause for discontinuation. Overall, the most common adverse events (&gt;3%) reported were diarrhea, nausea, and vomiting, with diarrhea being reported significantly higher in the QD group (16% vs. 5%; p=0.04). The most common grade 3/4 laboratory abnormalities (&gt;3%) reported were increased ALT (&gt;5 x upper limit of normal [ULN]), AST (&gt;5 x ULN), triglyceride (&gt;750 mg/dL), and amylase (&gt;2 x ULN) levels; no significant differences between the 2 groups were observed. Acute renal failure (ARF) occurred in 1 patient in each group. One was a 75 year-old male with a creatinine clearance of 40 mL/min at baseline who was given full dose of TDF and developed ARF at Week 34. Renal biopsy demonstrated non-specific changes with some renal tubules showing focal degenerative signs (cytoplasmic vacuolization). The other patient was a 54 year-old male. ARF occurred at Week 38, requiring temporary haemodialysis. Renal biopsy demonstrated tubulointerstitial nephritis. Both patients improved upon discontinuation of study drug, 1 discontinued all ARVs and the other substituted TDF with d4T as part of the HAART regimen, with serum creatinine returning to ≤1.7 mg/dL.</td>
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