

TENOFOVIR DISOPROXIL EMTRICITABINE VIATRIS

1. Product Name

Tenofovir Disoproxil Emtricitabine Viatris 300 mg / 200 mg film coated tablets

2. Qualitative and Quantitative Composition

Tenofovir Disoproxil Emtricitabine Viatris immediate release film-coated tablets, each contains 300 mg tenofovir disoproxil maleate (equivalent to 245 mg tenofovir disoproxil) and 200 mg emtricitabine.

Tenofovir disoproxil maleate 300mg is equivalent to tenofovir disoproxil fumarate 300 mg. Maleate and fumarate are isomers of each other. This data sheet makes reference to both the fumarate and maleate salt form.

Excipient(s) with known effect

Tenofovir Disoproxil Emtricitabine Viatris tablets contain lactose. For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

A light green, film-coated, capsule shaped, biconvex tablet debossed with 'M' on one side of the tablet and 'ETM' on the other side.

Dimensions: 19.80 mm x 9.00 mm (Length x Width).

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of HIV-1 infection

Tenofovir Disoproxil Emtricitabine Viatris is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.

Pre-exposure Prophylaxis

Tenofovir Disoproxil Emtricitabine Viatris is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples (see section 5.1).

4.2 Dose and method of administration

Tenofovir Disoproxil Emtricitabine Viatris tablets cannot be halved.

Recommended Dose for Treatment of HIV-1 Infection

Adults

The recommended dose of Tenofovir Disoproxil Emtricitabine Viatriis is one tablet (containing 300 mg tenofovir disoproxil maleate and 200 mg emtricitabine), taken orally, once daily with or without food.

Recommended Dose for Pre-exposure Prophylaxis

Adults

The dose of tenofovir disoproxil/emtricitabine in HIV-1 uninfected adults is one tablet (containing 300 mg tenofovir disoproxil maleate and 200 mg of emtricitabine), taken orally, once daily. In order to optimise the absorption of tenofovir, it is recommended that Tenofovir Disoproxil Emtricitabine Viatriis should be taken with food.

Special populations

Paediatric

The safety and efficacy of tenofovir and emtricitabine in combination have not been established in patients under the age of 18 years. Consequently, Tenofovir Disoproxil Emtricitabine Viatriis should not be administered to children or adolescents.

Elderly

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

Renal impairment

Treatment of HIV-1 Infection

Significantly increased drug exposures occurred when tenofovir or emtricitabine were administered to patients with moderate to severe renal impairment (see individual data sheets for tenofovir and emtricitabine). Therefore, the dosing interval of Tenofovir Disoproxil Emtricitabine Viatriis should be adjusted in patients with baseline creatinine clearance <60 mL/min using the recommendations in Table 1. 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 1. Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) ^a		
	≥ 60	30-59	<30 (Including Patients Requiring Haemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	Tenofovir Disoproxil Emtricitabine Viatriis should not be administered.

^a Calculated with Cockcroft Gault equation using ideal (lean) body weight.

Pre-exposure Prophylaxis

Do not use tenofovir disoproxil/emtricitabine for a PrEP indication in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min (see section 4.4).

Routine monitoring of estimated creatinine clearance should be performed in all individuals with mild renal impairment. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using tenofovir disoproxil/emtricitabine for PrEP, evaluate potential causes and reassess potential risks and benefits of continued use (see section 4.4).

Hepatic impairment

The pharmacokinetics of tenofovir disoproxil/emtricitabine, or emtricitabine have not been studied in subjects with hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in tenofovir dosing is required in patients with hepatic impairment. Emtricitabine is not significantly metabolised by liver enzymes, so the impact of hepatic impairment should be limited.

4.3 Contraindications

Tenofovir Disoproxil Emtricitabine Viatris is contraindicated in patients with known hypersensitivity to tenofovir, tenofovir disoproxil fumarate, tenofovir disoproxil maleate, emtricitabine or any other components of the tablet (see section 6.1).

Tenofovir Disoproxil Emtricitabine Viatris must not be administered to children or adolescents under the age of 18 years.

Tenofovir Disoproxil Emtricitabine Viatris is a fixed-dose combination of tenofovir disoproxil maleate and emtricitabine. Tenofovir Disoproxil Emtricitabine Viatris should not be administered concomitantly with: medicines containing tenofovir disoproxil maleate or tenofovir disoproxil fumarate; medicines containing emtricitabine; medicines containing tenofovir alafenamide, lamivudine; or with adefovir dipivoxil.

Do not use Tenofovir Disoproxil Emtricitabine Viatris for PrEP in individuals with unknown or positive HIV-1 status.

Tenofovir Disoproxil Emtricitabine Viatris should be used in HIV-infected patients only in combination with other antiretroviral agents.

4.4 Special warnings and precautions for use

General

Patients receiving tenofovir disoproxil/emtricitabine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should also be informed that tenofovir disoproxil/emtricitabine therapy is not a cure for HIV infection.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues alone or in combination, in the treatment of HIV infection. 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 analogues to any patient or uninfected individual with known risk factors for liver disease, however, cases have also been reported in HIV-1 patients with no known risk factors.

Treatment with tenofovir disoproxil/emtricitabine should be suspended in any patient or uninfected individual 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).

Renal Impairment

Tenofovir and emtricitabine are principally eliminated by the kidney.

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 (see section 4.8).

Tenofovir disoproxil/emtricitabine should be avoided with concurrent or recent use of a nephrotoxic agent.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during tenofovir disoproxil/emtricitabine therapy. Patients at risk for, or with a history of, renal dysfunction including patients who have previously experienced renal events while receiving adefovir dipivoxil should be routinely monitored for changes in serum creatinine and phosphorus.

Treatment of HIV-1 infection

Dosing interval adjustment of tenofovir disoproxil/emtricitabine is required in all patients with creatinine clearance <60 mL/min (calculated using the Cockcroft Gault equation), (see section 4.2). Renal function should be closely monitored in these patients. The safety and efficacy of tenofovir and emtricitabine therapy have not been established in patients with creatinine clearance between 30 and 59 mL/min, and so the potential benefit of tenofovir disoproxil/emtricitabine therapy should be assessed against the potential risk of renal toxicity. Tenofovir disoproxil/emtricitabine should not be administered to patients with creatinine clearance <30 mL/min or patients requiring haemodialysis.

Pre-exposure Prophylaxis

Tenofovir disoproxil/emtricitabine for a PrEP indication should not be used if estimated creatinine clearance is less than 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using tenofovir disoproxil/emtricitabine for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see section 4.2).

Bone Effects

Bone toxicities including a reduction in bone mineral density have been observed in tenofovir disoproxil fumarate studies in three animal species. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) of tenofovir in HIV-1 infected adults and were also not seen in studies in HIV-1 uninfected individuals but long term data are lacking in this population. However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8).

If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

Hepatitis B Virus (HBV) Co-infection

Individuals should be tested for the presence of chronic hepatitis B virus (HBV) before initiating tenofovir disoproxil/emtricitabine. Discontinuation of tenofovir disoproxil/emtricitabine therapy in patients co-infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients with HIV infection co-infected with HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping tenofovir disoproxil/emtricitabine treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Early Virologic Failure

Clinical studies in HIV-infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance mutations have been reported in clinical studies of combinations of tenofovir, lamivudine

and abacavir or tenofovir, lamivudine and didanosine. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiviral therapy, including emtricitabine and tenofovir disoproxil fumarate.

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment.

Comprehensive Management for use in Pre-exposure Prophylaxis (PrEP)

Tenofovir disoproxil/emtricitabine should only be used for PrEP as part of a comprehensive prevention strategy including other HIV-1 prevention measures, because tenofovir disoproxil/emtricitabine is not always effective in preventing the acquisition of HIV-1.

Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhoea). Counsel uninfected individuals prior to initiation of PrEP about risk and benefits, precautions and limitation of pre-exposure prophylaxis using tenofovir disoproxil/emtricitabine.

Tenofovir disoproxil/emtricitabine should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV-negative immediately prior to initiating and routinely reconfirmed while taking tenofovir disoproxil/emtricitabine for PrEP. Drug resistant HIV-1 variants have been identified in individuals with undetected HIV-1 infection who are taking tenofovir disoproxil/emtricitabine for a PrEP indication, because, tenofovir disoproxil/emtricitabine alone does not constitute a complete treatment regimen for HIV-1 infection.

When considering tenofovir disoproxil/emtricitabine for pre-exposure prophylaxis, the uninfected individuals should be counselled about the importance of strict adherence to the recommended tenofovir disoproxil/emtricitabine dosing schedule. The effectiveness of tenofovir disoproxil/emtricitabine in reducing the risk of acquiring HIV-1 is strongly correlated with patient adherence and detectable drug blood levels.

- Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating tenofovir disoproxil/emtricitabine for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g. fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g. unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.
 - If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm negative HIV-1 status.
- While using tenofovir disoproxil/emtricitabine for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative HIV-1 infection status is confirmed.

Tenofovir disoproxil/emtricitabine does not reduce the risk of other sexually transmitted infections and regular monitoring is recommended. Monitoring of renal function, such as with urine dipstick testing, should be considered for patients at risk for renal disease (see section 4.4).

When considering tenofovir disoproxil/emtricitabine for pre-exposure prophylaxis the following factors may help to identify individuals at high risk of acquiring HIV-1 infection:

- Has partner(s) known to be HIV-1 infected, or
- Engages in high risk sexual behavior (see section 5.1) or sexual activity within a high prevalence area or social network or has partners from high prevalence areas.

When tenofovir disoproxil/emtricitabine is used to reduce the risk of acquiring HIV-1, advise uninfected individuals about the importance of the following:

- Confirming that they are HIV-negative before starting to take tenofovir disoproxil/emtricitabine to reduce the risk of acquiring HIV-1.
- Hepatitis B vaccination should be offered as appropriate.
- Tenofovir disoproxil/emtricitabine should only be used as part of a complete prevention strategy including other prevention measures. In clinical trials, tenofovir disoproxil/emtricitabine only protected some subjects from acquiring HIV-1.
- Using condoms consistently and correctly to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- Knowing their HIV status and the status of their partner(s).
- In the case of use of tenofovir disoproxil/emtricitabine for PrEP in an uninfected partner in a serodiscordant relationship, the importance of effective antiretroviral treatment of the HIV-1 infected partner in accordance with the current treatment guidelines should be fully explained.
- Getting tested regularly (at least every 3 months) for HIV-1 and ask their partner(s) to get tested as well.
- Counselling about the importance of safety risks including monitoring of kidney function.
- HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking tenofovir disoproxil/emtricitabine, because tenofovir disoproxil/emtricitabine alone does not constitute a complete regimen for HIV-1 treatment (see section 4.3, 4.4).
- Reporting any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- Signs and symptoms of acute infection include: fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- Getting tested for other sexually transmitted infections such as syphilis and gonorrhoea that may facilitate HIV-1 transmission.
- Learning about sexual risk behavior and getting support to help reduce sexual risk behaviour.
- Taking tenofovir disoproxil/emtricitabine on a regular dosing schedule and strictly adhere to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses (see section 4.4).
- Risks and benefits of tenofovir disoproxil/emtricitabine in women who may be pregnant or intending to become pregnant.

Paediatric

Safety and effectiveness in paediatric patients have not been established.

Elderly

Clinical studies of tenofovir and emtricitabine did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Tenofovir disoproxil fumarate and emtricitabine

The steady state pharmacokinetics of tenofovir and emtricitabine were unaffected when tenofovir disoproxil fumarate and emtricitabine were administered together versus each agent dosed alone.

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown the potential for CYP450 mediated interactions involving tenofovir disoproxil fumarate and emtricitabine with other medicinal products is low.

Tenofovir and emtricitabine are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of tenofovir disoproxil/emtricitabine with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or the co-administered drug. Drugs that decrease renal function may increase serum concentrations of tenofovir and/or emtricitabine.

No clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and abacavir, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, sofosbuvir and tacrolimus. In a study conducted in healthy volunteers dosed with a single 600 mg dose of ribavirin, no clinically significant drug interactions were observed between tenofovir disoproxil fumarate and ribavirin. Similarly, no clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, d4T, AZT and tenofovir disoproxil fumarate.

In drug interaction studies between regimens containing tenofovir disoproxil fumarate and ledipasvir/sofosbuvir, sofosbuvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, increases in tenofovir exposure were observed. Patients receiving a regimen containing tenofovir disoproxil fumarate concomitantly with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir should be monitored for adverse reactions associated with tenofovir disoproxil fumarate. Table 2 summarises the changes in pharmacokinetic parameters for tenofovir DF in the presence of ledipasvir/sofosbuvir, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

Table 2: Drug interactions: Changes in pharmacokinetic parameters for Tenofovir^a in the presence of the co-administered drug

Co-administered Drug	Dose of Co-administered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters ^b (90% CI)		
			C _{max}	AUC	C _{min}
Ledipasvir/ Sofosbuvir ^{c,d}	90/400 oncedaily x 10 days	24	↑47 (↑37 to ↑58)	↑35 (↑29 to ↑42)	↑47 (↑38 to ↑57)
Ledipasvir/ Sofosbuvir ^{c,e}		23	↑64 (↑54 to ↑74)	↑50 (↑42 to ↑59)	↑59 (↑49 to ↑70)
Co-administered Drug	Dose of Co-administered	N	% Change of Tenofovir Pharmacokinetic Parameters ^b (90% CI)		
Ledipasvir/ Sofosbuvir ^f	90/400 once daily x 14 days	15	↑79 (↑56 to ↑104)	↑98 (↑77 to 123)	↑163 (↑132 to ↑197)
Ledipasvir/ Sofosbuvir ^g	90/400 oncedaily x 10 days	14	↑32 (↑25 to ↑39)	↑40 (↑31 to ↑50)	↑91 (↑74 to ↑110)
Ledipasvir/ Sofosbuvir ^h		29	↑61 (↑51 to ↑72)	↑65 (↑59 to ↑71)	↑115 (↑105 to ↑126)

Sofosbuvir ⁱ	400 once daily	16	↑25 (↑8 to ↑45)	↔	↔
Sofosbuvir/ Velpatasvir ^j	400/100 once daily	24	↑55 (↑43 to ↑68)	↑30 (↑24 to ↑36)	↑39 (↑31 to ↑48)
Sofosbuvir/ Velpatasvir ^k		29	↑55 (↑45 to ↑66)	↑39 (↑33 to ↑44)	↑52 (↑45 to ↑59)
Sofosbuvir/ Velpatasvir ^l		15	↑77 (↑53 to ↑104)	↑81 (↑68 to ↑94)	↑121 (↑100 to ↑143)
Sofosbuvir/ Velpatasvir ^m		24	↑36 (↑25 to ↑47)	↑35 (↑29 to ↑42)	↑45 (↑39 to ↑51)
Sofosbuvir/ Velpatasvir ⁿ		24	↑44 (↑33 to ↑55)	↑40 (↑34 to ↑46)	↑84 (↑76 to ↑92)
Sofosbuvir/ Velpatasvir ^o		30	↑46 (↑39 to ↑54)	↑40 (↑34 to ↑45)	↑70 (↑61 to ↑79)
Sofosbuvir/Velpatasvir/ Voxilaprevir ^p		400 /100 /100 + Voxilaprevir ^q 100 once daily	29	↑48 (↑36 to ↑61)	↑39 (↑32 to ↑46)

- a. Subjects received tenofovir DF 300 mg once daily.
- b. Increase = ↑; Decrease = ↓; No Effect = ↔
- c. Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.
- d. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/ tenofovir DF.
- e. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/ tenofovir DF.
- f. Study conducted with efavirenz / tenofovir disoproxil/emtricitabine coadministered with ledipasvir/sofosbuvir.
- g. Study conducted with emtricitabine/rilpivirine/tenofovir DF coadministered with ledipasvir/sofosbuvir.
- h. Study conducted with tenofovir disoproxil/emtricitabine + dolutegravir coadministered with ledipasvir/sofosbuvir.
- i. Study conducted with tenofovir disoproxil/emtricitabine coadministered with sofosbuvir.
- j. Comparison based on exposures when administered as atazanavir/ritonavir + tenofovir disoproxil/emtricitabine.
- k. Comparison based on exposures when administered as darunavir/ritonavir + tenofovir disoproxil/emtricitabine.
- l. Study conducted with efavirenz/ tenofovir disoproxil/emtricitabine coadministered with sofosbuvir/velpatasvir.
- m. Study conducted with elvitegravir/cobicistat/ tenofovir disoproxil/emtricitabine coadministered with sofosbuvir/velpatasvir.
- n. Study conducted with efavirenz/ tenofovir disoproxil/emtricitabine coadministered with sofosbuvir/velpatasvir.
- o. Administered as raltegravir + tenofovir disoproxil/emtricitabine.
- p. Comparison based on exposures when administered as darunavir/ritonavir + tenofovir disoproxil/emtricitabine.
- q. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Sofosbuvir

In a drug interaction study of a regimen containing tenofovir disoproxil fumarate given concomitantly with sofosbuvir, tenofovir C_{max} increased by 25%. Tenofovir AUC and C_{min} were unaltered by sofosbuvir coadministration. No dose adjustment of efavirenz/ tenofovir disoproxil/emtricitabine or tenofovir disoproxil/emtricitabine is required (see Table 2).

When unboosted atazanavir (400 mg) was co-administered with tenofovir disoproxil fumarate, atazanavir increased tenofovir C_{max} by 14% and AUC by 24%. Similarly, lopinavir (400 mg)/ritonavir (100 mg) increased tenofovir AUC by 32%.

Co-administration of tenofovir disoproxil fumarate with didanosine and atazanavir results in changes in the pharmacokinetics of didanosine and atazanavir that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. Higher didanosine concentrations could

potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily. In adults weighing ≥ 60 kg, the didanosine dose should be reduced to 250 mg daily when it is co-administered with tenofovir disoproxil/emtricitabine. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg.

When co-administered, tenofovir disoproxil/emtricitabine and didanosine EC may be taken under fasted conditions or with a light meal (< 400 kcal, 20% fat). Co-administration of didanosine buffered tablet formulation with tenofovir disoproxil/emtricitabine should be under fasted conditions. **Co-administration of tenofovir disoproxil/emtricitabine 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.**

Tenofovir disoproxil fumarate affects the pharmacokinetics of atazanavir (see Table 3). Tenofovir decreases atazanavir concentration. Tenofovir disoproxil/emtricitabine should only be administered with boosted atazanavir (ATZ 300 mg/RTV 100 mg). The safety and efficacy of this regimen has been substantiated over 48 weeks in a clinical study.

Table 3 summarises the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine and atazanavir.

Table 3: Drug interactions Change in pharmacokinetic parameters for didanosine and atazanavir in the presence of tenofovir DF

Co-administered Drug	Dose of Co-administered Drug (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters ¹ (90% CI)		
			C _{max}	AUC	C _{min}
Didanosine ³ enteric-coated capsules	400 once / with or without food ²	26	↑ 48–64% (↑ 25–↑ 89)	↑ 48–60% (↑ 31–↑ 79)	NC
	250 once / Simultaneously with tenofovir DF, fasted ⁴	28	↔	↑ 14 (0–↑ 31)	NC
	250 once / Simultaneously with tenofovir DF, fed ^{2, 4}	28	↓ 29 (↓ 39–↓ 18)	↓ 11 (↓ 23–↑ 2)	NC
Atazanavir ⁵	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/Ritonavir ⁶ 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5) ⁶	↓ 25 (↓ 42 to ↓ 3) ⁶	↓ 23 (↓ 46 to ↑ 10) ⁶

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. See PRECAUTIONS regarding use of didanosine with tenofovir disoproxil fumarate.
4. Relative to 400 mg alone, fasted.
5. REYATAZ™ Prescribing Information (Bristol-Myers Squibb).
6. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone (REYATAZ™ March 2004 United States Package Insert).

Since tenofovir and emtricitabine are primarily eliminated by the kidneys, co-administration of tenofovir disoproxil/emtricitabine with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or other renally eliminated drugs.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B3

No clinical data are available for pregnant women being treated with tenofovir disoproxil fumarate or emtricitabine. No embryofoetal development studies have been conducted with tenofovir disoproxil fumarate and emtricitabine in combination.

Reproductive toxicity studies performed in rats and rabbits did not reveal any evidence of harm to the foetus due to tenofovir at respective exposures (AUC) of 4-13 and 66-fold the human exposure. Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced foetal serum phosphorus concentrations. No evidence of embryofoetal toxicity or teratogenicity was observed in mice or rabbits at respective emtricitabine exposures (AUC) of 50 and 130 fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse foetal effects. Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil/emtricitabine should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking tenofovir disoproxil/emtricitabine for a PrEP indication, careful consideration should be given to whether use of tenofovir disoproxil/emtricitabine should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

Breast-feeding

Because of the potential for HIV transmission and for serious adverse reactions in nursing infants, mothers should be instructed not to breast feed if they are receiving tenofovir disoproxil/emtricitabine for treatment or to reduce the risk of acquiring HIV-1.

Tenofovir disoproxil fumarate: In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low concentrations (estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC_{50}) (50% maximal inhibitory concentration). Tenofovir associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

Emtricitabine: Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} (minimal expected trough concentration in adults) achieved from oral administration of emtricitabine. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Fertility

No reproductive toxicity studies have been conducted with tenofovir disoproxil fumarate and emtricitabine in combination. Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir disoproxil fumarate dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the expected value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50-80 times the exposure in humans. The fertility of offspring was

unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

4.7 Effects on ability to drive and use machines

No studies on the effects of tenofovir disoproxil/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 disoproxil fumarate and emtricitabine.

4.8 Undesirable effects

Adverse Effects for Clinical Trials Experience in HIV-1 Infected Patients

Four hundred and forty seven HIV-1 infected patients have received combination therapy with emtricitabine and tenofovir disoproxil fumarate 300 mg tablet with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 48 weeks in ongoing clinical studies.

Study 934 – Treatment Emergent Adverse Events

Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either emtricitabine + tenofovir disoproxil fumarate administered in combination with efavirenz (n=257) or lamivudine/zidovudine administered in combination with efavirenz (n=254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table 4). Adverse events leading to study drug discontinuation occurred in significantly smaller number of patients in the tenofovir disoproxil/emtricitabine group compared to the lamivudine/zidovudine group (5% vs 11%, p=0.010). The most frequently occurring adverse event leading to study drug discontinuation was anaemia (including decreased haemoglobin), no patient in the tenofovir disoproxil/emtricitabine group and 6% of patients in the lamivudine/zidovudine group.

Table 4. Frequency of Adverse Reactions to Emtricitabine and/or Tenofovir Disoproxil Fumarate (Grade 2-4) Occurring in ≥ 3% of Patients Receiving Emtricitabine and Tenofovir Disoproxil Fumarate (or Tenofovir disoproxil/emtricitabine) in Study 394 (0-144 weeks)¹

Adverse Reaction	Tenofovir and Emtricitabine ² + Efavirenz N=257	Lamivudine/ Zidovudine + Efavirenz N=254
Gastrointestinal Disorders		
Diarrhoea	9%	5%
Nausea	9%	7%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Insomnia	5%	7%
Abnormal Dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

1. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
2. Patients received emtricitabine and tenofovir disoproxil fumarate up to week 96 and switched to tenofovir disoproxil/emtricitabine from week 96 to 144.

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 5).

Table 5. Grade 3/4 Laboratory Abnormalities Reported in >1% of Patients of Either Treatment Group, Study 934 (0-144 weeks)

	Tenofovir and Emtricitabine¹ + Efavirenz N=254	Lamivudine/ Zidovudine + Efavirenz N=251
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%
Hyperglycaemia (>250 mg/dL)	2%	1%
Haematuria (>75 RBC/HPF)	3%	2%
Neutrophil (<750/mm ³)	3%	5%
Triglyceride (>750 mg/dL)	5%	3%
Haemoglobin (<7.0 g/dL)	0%	2%

1. Patients received emtricitabine and tenofovir disoproxil fumarate up to week 96 and switched to tenofovir disoproxil/emtricitabine from week 96 to 144.

Tenofovir Disoproxil Fumarate

From Clinical Studies

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

Treatment-Experienced Patients

Treatment-Emergent Adverse Events

The most common adverse events that occurred in patients receiving tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in Table 6 (below).

Table 6. Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in ≥ 3% in Any Treatment Group in Study 907 (0-4 weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0–24)	Placebo (N=182) (Week 0-24)	Tenofovir disoproxil fumarate (N=368) (Week 0–48)	Placebo Crossover to Tenofovir disoproxil fumarate (N=170) (Week 24–48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal Pain	4%	3%	7%	6%

Back Pain	3%	3%	4%	2%
Chest Pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhoea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral Neuropathy ¹	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash Event ²	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight Loss	2%	1%	4%	2%

1. Peripheral neuropathy includes peripheral neuritis and neuropathy.

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

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 7 (below).

Table 7. Grade 3/4 Laboratory Abnormalities Reported in \geq 1% of Tenofovir Disoproxil Fumarate-Treated Patients in Study 907 (0-48 weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	Tenofovir disoproxil fumarate (N=368) (Week 0–48)	Placebo Crossover to Tenofovir disoproxil fumarate (N=170) (Week 24–48)
	(%)	(%)	(%)	(%)
Any \geq Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Urine Glucose (\geq 3+)	3%	3%	3%	2%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%	4%	5%

ALT (M: >215 U/L) (F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750 mg/dL)	1%	1%	2%	1%

Treatment-Naïve Patients

Treatment-Emergent Adverse Effects

The adverse reactions seen in a double-blind active controlled study in which 600 treatment-naïve patients received tenofovir disoproxil fumarate (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were generally consistent, with the addition of dizziness, with those seen in treatment- experienced patients (Table 8).

Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhoea and nausea.

Table 8. Selected Treatment-Emergent Adverse Events (Grade 2-4) Reported in ≥ 5% in Any Treatment Group in Study 903 (0-144 weeks)

	Tenofovir disoproxil fumarate + lamivudine + efavirenz	Stavudine + lamivudine + efavirenz
	N=299	N=301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Back Pain	9%	8%
Fever	8%	7%
Abdominal Pain	7%	12%
Asthenia	6%	7%
Digestive System		
Diarrhoea	11%	13%
Nausea	8%	9%
Vomiting	5%	9%
Dyspepsia	4%	5%
Metabolic Disorders		
Lipodystrophy	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Anxiety	6%	6%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral Neuropathy ¹	1%	5%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash Event ²	18%	12%

1. Peripheral neuropathy includes peripheral neuritis and neuropathy

2. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesicubullous rash, and pustular rash

Laboratory Abnormalities: With the exception of triglyceride elevations that were more common in the stavudine group (14%) compared with tenofovir disoproxil fumarate (3%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 9.

Table 9. Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Patients in Study 903 (0-144 weeks)

	Tenofovir disoproxil fumarate + lamivudine + efavirenz	Stavudine + lamivudine + efavirenz
	N=299	N=301
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
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%
Haematuria (>100 RBC/HPF)	7%	7%
Neutrophil (<750/mm ³)	3%	1%
Triglyceride (>750 mg/dL)	3%	13%

Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Adult Subjects

No new adverse reactions to tenofovir disoproxil/emtricitabine were identified from two randomised placebo-controlled clinical trials (iPrEx, Partners PrEP) in which 2830 HIV-1 uninfected adults received tenofovir disoproxil/emtricitabine once daily for pre-exposure prophylaxis. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. These trials enrolled HIV-negative individuals ranging in age from 18 to 67 years. The iPrEx trial enrolled only males or transgender females of Hispanic/Latino (72%), White (18%), Black (9%) and Asian (5%) race. The Partners PrEP trial enrolled both males (61-64% across treatment groups) and females in Kenya and Uganda. Table 10 provides a list of all adverse events that occurred in ≥2% of patients in any treatment group in the iPrEx and Partners PrEP trials.

Laboratory Abnormalities: Table 11 provides a list of laboratory abnormalities observed in both trials. Six subjects in the Tenofovir Disoproxil Fumarate-containing arms of the Partners PrEP trial discontinued participation in the study due to an increase in blood creatinine compared with no discontinuations in the placebo group. One patient in the tenofovir disoproxil/emtricitabine arm of the iPrEx trial discontinued from the study due to an increase in blood creatinine and another due to low phosphorous.

In addition to the laboratory abnormalities described above, Grade 1 proteinuria (1+) occurred in 6% of subjects receiving tenofovir disoproxil/emtricitabine in the iPrEx trial. Grades 2-3 proteinuria (2-4+) and glycosuria (3+) occurred in less than 1% of subjects treated with tenofovir disoproxil/emtricitabine in the iPrEx trial and Partners PrEP trial.

Table 10. Selected Adverse-Events (All Grades) Reported in ≥ 2% in Any Treatment Group in the iPrEx Trial and Partners PrEP Trial

	iPrEx Trial		Partners PrEP Trial	
	Emtricitabine/Tenofovir Disoproxil Fumarate (N=1251)	Placebo (N=1248)	Emtricitabine/Tenofovir Disoproxil Fumarate (N=1579)	Placebo (N=1584)
Gastrointestinal Disorders				
Diarrhoea	7%	8%	2%	3%
Abdominal pain	4%	2%	- ^a	-
Infections and Infestations				
Pharyngitis	13%	16%	-	-
Urethritis	5%	7%	-	-
Urinary tract infection	2%	2%	5%	7%
Syphilis	6%	5%	-	-
Secondary syphilis	6%	4%	-	-
Anogenital warts	2%	3%	-	-
Musculoskeletal and Connective Tissue Disorders				
Back pain	5%	5%	-	-
Nervous System Disorders				
Headache	7%	6%	-	-
Psychiatric Disorders				
Depression	6%	7%	-	-
Anxiety	3%	3%	-	-
Reproductive System and Breast Disorders				
Genital ulceration	2%	2%	2%	2%
Investigations				
Weight decreased	3%	2%	-	-

a. Not reported or reported below 2%.

Table 11. Laboratory Abnormalities (Highest Toxicity Grade) Reported for Each Subject in the iPrEx Trial and Partners PrEP Trial

	Grade ^b	iPrEx Trial		Partners PrEP Trial	
		Emtricitabine/Tenofovir Disoproxil Fumarate N= 1251	Placebo N=1248	Emtricitabine/Tenofovir Disoproxil Fumarate N=1579	Placebo N=1584
Creatinine	1 (1.1 - 1.3 x ULN)	27 (2%)	21 (2%)	18 (1%)	12 (<1%)
	2-4 (>1.4 x ULN)	5 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
Phosphorus	1 (2.5 - <LLN mg/dL)	81 (7%)	110 (9%)	NR ^a	NR ^a
	2-4 (<2.0 mg/dL)	123 (10%)	101 (8%)	140 (9%)	136 (9%)
AST	1 (1.25 - <2.5 x ULN)	175 (14%)	175 (14%)	20 (1%)	25 (2%)
	2-4 (> 2.6 x ULN)	57 (5%)	61 (5%)	10 (<1%)	4 (<1%)
ALT	1 (1.25 - <2.5 x ULN)	178 (14%)	194 (16%)	21 (1%)	13 (<1%)
	2-4 (> 2.6 x ULN)	84 (7%)	82 (7%)	4 (<1%)	6 (<1%)
Hemoglobin	1 (8.5 - 10 mg/dL)	49 (4%)	62 (5%)	56 (4%)	39 (2%)
	2-4 (< 9.4 mg/dL)	13 (1%)	19 (2%)	28 (2%)	39 (2%)

Neutrophils	1 (1000 - 1300/mm ³)	23 (2%)	25 (2%)	208 (13%)	163 (10%)
	2-4 (<750/mm ³)	7 (<1%)	7 (<1%)	73 (5%)	56 (3%)

a. Grade 1 phosphorus was not reported for the Partners PrEP trial.

b. Grading is per DAIDS criteria.

Changes in Bone Mineral Density:

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from -0.4% to -1.0% across total hip, spine, femoral neck, and trochanter in the tenofovir disoproxil/emtricitabine group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving tenofovir disoproxil/emtricitabine vs. 6% of subjects receiving placebo lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the tenofovir disoproxil/emtricitabine group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted (see section 5.1). The Partners PrEP trial found similar fracture rates between treatment and placebo groups (0.8% and 0.6%, respectively). No BMD evaluations were conducted during this trial (see section 5.1).

From Post Marketing Surveillance

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of tenofovir disoproxil fumarate.

Immune System Disorders

Allergic reaction (including angioedema).

Metabolism and Nutrition Disorders

Hypokalaemia, hypophosphataemia, lactic acidosis.

Respiratory, Thoracic and Mediastinal Disorders

Dyspnoea.

Gastrointestinal Disorders

Increased amylase, abdominal pain, pancreatitis.

Hepatobiliary Disorders

Hepatic steatosis, increased liver enzymes (most commonly AST, ALT, gamma GT), hepatitis.

Skin and Subcutaneous Tissue Disorders

Rash.

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures).

Renal and Urinary Disorders

Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

General Disorders and Administration Site Conditions

Asthaenia.

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.

Adverse reactions attendant to class: Nephrotoxicity (elevation in serum creatinine and urine protein, and decrease in serum phosphorus) is the dose-limiting toxicity associated with other nucleotide analogues (cidofovir and high doses of adefovir dipivoxil evaluated for HIV disease (60 mg and 120 mg)).

Emtricitabine

More than 2000 adult patients with HIV infection have been treated with emtricitabine alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 303 and 301A in which 440 treatment experienced (303) and 571 treatment naïve (301A) patients received emtricitabine 200 mg (N=580) or comparator drug (N=431) for 48 weeks.

The most common adverse events 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 these events. All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discolouration which was reported with higher frequency in the emtricitabine treated group.

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

In addition to the adverse reactions reported in adults, anaemia has been reported commonly and hyperpigmentation very commonly, in paediatric patients.

A summary of emtricitabine treatment emergent clinical adverse events in studies 303 and 301A is provided in Table 12.

Table 12. Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥ 3% of Emtricitabine-Treated Patients in Either Study 303 or 301A (0-48 Weeks)

	303		301A	
	Emtricitabine + Zidovudine/ Stavudine + NNRTI/PI (N=294)	Lamivudine + Zidovudine/ Stavudine + NNRTI/PI (N=146)	Emtricitabine + Didanosine + Efavirenz (N=286)	Stavudine + Didanosine + Efavirenz (N=285)
Body as a Whole				
Abdominal Pain	8%	11%	14%	17%
Asthenia	16%	10%	12%	17%
Headache	13%	6%	22%	25%
Digestive System				
Diarrhoea	23%	18%	23%	32%
Dyspepsia	4%	5%	8%	12%
Nausea	18%	12%	13%	23%
Vomiting	9%	7%	9%	12%

Musculoskeletal				
Arthralgia	3%	4%	5%	6%
Myalgia	4%	4%	6%	3%
Nervous System				
Abnormal Dreams	2%	<1%	11%	19%
Depressive Disorders	6%	10%	9%	13%
Dizziness	4%	5%	25%	26%
Insomnia	7%	3%	16%	21%
Neuropathy/Peripheral Neuritis	4%	3%	4%	13%
Paresthaesia	5%	7%	6%	12%
Respiratory				
Increased Cough	14%	11%	14%	8%
Rhinitis	18%	12%	12%	10%
Skin				
Rash Event ¹	17%	14%	30%	33%

1. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

Laboratory Abnormalities: Laboratory abnormalities observed in the emtricitabine studies occurred with similar frequency in the treatment and placebo-treated/comparator groups.

A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 13.

Table 13. Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in > 1% of Emtricitabine-Treated Patients in Either Study 303 or 301A

	303		301A	
	Emtricitabine + Zidovudine/ Stavudine + NNRTI/PI (N=294)	Lamivudine + Zidovudine/ Stavudine + NNRTI/PI (N=146)	Emtricitabine + Didanosine + Efavirenz (N=286)	Stavudine + Didanosine + Efavirenz (N=285)
Percentage with Grade 3 or Grade 4 laboratory	31%	28%	34%	38%
ALT (>5.0 x ULN ¹)	2%	1%	5%	6%
AST (>5.0 x ULN)	3%	<1%	6%	9%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine Kinase (>4.0 x ULN)	11%	14%	12%	11%
Neutrophils (<750 mm ³)	5%	3%	5%	7%
Pancreatic Amylase (>2.0 x ULN)	2%	2%	<1%	1%
Serum Amylase (>2.0 x ULN)	2%	2%	5%	10%
Serum Glucose (<40 or >250 mg/dL)	3%	3%	2%	3%
Serum Lipase (>2.0 x ULN)	<1%	<1%	1%	2%
Triglycerides (>750 mg/dL)	10%	8%	9%	6%

1. ULN=Upper limit of normal.

From Post Marketing Surveillance

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

Tenofovir disoproxil/emtricitabine

From Post Marketing Surveillance

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to infectious pathogens (active or inactive) may arise (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

There is no known antidote for Tenofovir Disoproxil Emtricitabine Viatrix. If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir disoproxil fumarate

Clinical experience of doses higher than the therapeutic dose of tenofovir disoproxil fumarate is available from two studies. In one study, intravenous tenofovir, equivalent to 16.7 mg/kg/day of tenofovir disoproxil fumarate, was administered daily for 7 days. In the second study, 600 mg of tenofovir disoproxil fumarate was administered to patients orally for 28 days. No unexpected or severe adverse reactions were reported in either study. The effects of higher doses are not known.

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

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. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30% of the emtricitabine dose over a three-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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations; nucleoside and nucleotide reverse transcriptase inhibitors. ATC code: J05AR03.

Mechanism of action

Tenofovir disoproxil maleate: Tenofovir disoproxil maleate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into

DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α , β , ϵ and mitochondrial DNA polymerase γ .

Antiviral activity *in vitro*

Tenofovir plus Emtricitabine: In combination studies evaluating the *in vitro* antiviral activity of tenofovir and emtricitabine together, synergistic antiviral effects were observed. Additive to synergistic effects were observed in combination studies with protease inhibitors, integrase strand transfer inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV-1 reverse transcriptase.

Tenofovir disoproxil fumarate: The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04-8.5 μM . In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine (3TC), stavudine (d4T), zalcitabine, zidovudine (AZT)), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5-2.2 μM). In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Emtricitabine: The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} value for emtricitabine was in the range of 0.0013-0.64 μM (0.0003-0.158 $\mu\text{g/mL}$). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, 3TC, d4T, zalcitabine, AZT), nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007-0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007-1.5 μM).

Prophylactic Activity in a Nonhuman Primate Model of HIV Transmission

Emtricitabine and Tenofovir Disoproxil Fumarate: The prophylactic activity of the combination of daily oral emtricitabine and tenofovir disoproxil fumarate was evaluated in a controlled study of macaques inoculated once weekly for 14 weeks with SIV/HIV-1 chimeric virus (SHIV) applied to the rectal surface. Of the 18 control animals, 17 became infected after a median of 2 weeks. In contrast, 4 of the 6 animals treated daily with oral emtricitabine and tenofovir disoproxil fumarate remained uninfected and the two infections that did occur were significantly delayed until 9 and 12 weeks and exhibited reduced viremia. An M184I-expressing FTC-resistant variant emerged in 1 of the 2 macaques after 3 weeks of continued drug exposure.

Anti-Hepatitis B Virus Activity *in vitro*

Tenofovir disoproxil fumarate: Tenofovir inhibits HBV production in HepG2 2.2.15 cells with an IC_{50} value of 1.1 μM .

Emtricitabine: Emtricitabine inhibits HBV production against laboratory strains of HBV with IC_{50} values in the range of 0.01 to 0.04 μM .

Drug Resistance

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2-4 fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, tenofovir and lamivudine.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir disoproxil fumarate in combination with other antiretroviral agents. In treatment-naïve patients treated with tenofovir disoproxil fumarate + lamivudine + efavirenz through 144 weeks, viral isolates from 8/47 (17%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-naïve patients treated with emtricitabine + tenofovir disoproxil fumarate + efavirenz through 144 weeks, none of the HIV isolates from 19 patients analyzed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R mutation. In treatment-experienced patients, 14/304 (4.6%) of the tenofovir disoproxil fumarate-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed the K65R mutation in the HIV-1 reverse transcriptase gene.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected *in vitro*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naïve patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene. In a second study in treatment-naïve patients, genotyping of viral isolates from 2/12 (17%) patients showed development of the M184V/I mutation.

iPrEx Trial: In a clinical study of HIV-1 seronegative subjects (see section 5.1), no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the tenofovir disoproxil/emtricitabine group and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrollment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the tenofovir disoproxil/emtricitabine group and 1 of 8 in the placebo group). One of the two subjects in the tenofovir disoproxil/emtricitabine group harbored wild type virus at enrollment and developed the M184V substitution 4 weeks after enrollment. The other subject had indeterminate resistance at enrollment but was found to have the M184I substitution 4 weeks after enrollment.

Partners PrEP Trial: In a clinical study of HIV-1 seronegative subjects (see section 5.1), no variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the tenofovir disoproxil/emtricitabine group, 15 subjects in the tenofovir disoproxil fumarate group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrollment (3 in the tenofovir disoproxil/emtricitabine group, 5 in the tenofovir disoproxil fumarate group, and 6 in the placebo group). One of the three subjects in the tenofovir disoproxil/emtricitabine group who was infected with wild type virus at enrollment selected an M184V expressing virus by week 12. Two of the five subjects in the tenofovir disoproxil fumarate group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrollment developed a K65R substitution by week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at week 60, although baseline virus was not genotyped and it is unclear if the resistance emerged or was transmitted. Following enrollment, 4 subjects (2 in the tenofovir disoproxil fumarate group, 1 in the tenofovir disoproxil/emtricitabine group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to NNRTIs but have not been associated with tenofovir or emtricitabine and may have been present in the infecting virus.

Cross-resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognized.

Tenofovir disoproxil fumarate: The K65R and K70E substitutions can also be selected by abacavir or didanosine and result in reduced susceptibility to these agents plus abacavir, didanosine, emtricitabine, tenofovir and lamivudine. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, d4T, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to d4T and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

Clinical efficacy and safety

Clinical study 934, which demonstrated the safety and efficacy of emtricitabine tablet and tenofovir disoproxil fumarate 300 mg tablet in combination with efavirenz in treatment-naïve adults, supports the use of tenofovir disoproxil/emtricitabine tablets for the treatment of HIV-1 infection. Additional supportive data are derived from study 903, in which lamivudine and tenofovir were used in combination in treatment-naïve adults. In clinical study 303 emtricitabine and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens. For additional information about these trials, please refer to the individual Data Sheet for tenofovir disoproxil fumarate and Data sheet for emtricitabine. The iPrEx study and Partners PrEP study support the use of tenofovir disoproxil/emtricitabine tablets to help reduce the risk of acquiring HIV-1.

Tenofovir disoproxil/emtricitabine

Study 934: Emtricitabine + tenofovir disoproxil fumarate + efavirenz compared with lamivudine/zidovudine + efavirenz

Study 934 is a randomized, open-label, active controlled multicentre study comparing two different dosing regimens in 511 antiretroviral-naïve HIV-1 infected patients. Patients were randomised to receive either emtricitabine + tenofovir disoproxil fumarate administered in combination with efavirenz or lamivudine/zidovudine administered in combination with efavirenz. For patients randomised to receive emtricitabine + tenofovir disoproxil fumarate the two drugs were administered individually for the first 96 weeks and then switched to tenofovir disoproxil/emtricitabine (fixed dose combination) during weeks 96 to 144, without regard to food.

For inclusion in the study, antiretroviral treatment naïve adult patients (≥ 18 years) with plasma HIV RNA greater than 10,000 copies/mL, must have an estimated glomerular filtration rate as measured by Cockcroft-Gault method of ≥ 50 mL/min, adequate haematologic function, hepatic transaminases and alanine aminotransferases ≤ 3 ULN, total bilirubin ≤ 1.5 mg/dL, serum amylase ≤ 1.5 ULN and serum phosphorus ≥ 2.2 mg/dL. Exclusion criteria included: a new AIDS defining condition diagnosed within 30 days (except on the basis of CD4 criteria), ongoing therapy with nephrotoxic drugs or agents that interacted with efavirenz, pregnancy/lactation, a history of clinically significant renal / bone disease or malignant disease other than Kaposi's sarcoma or basal-cell carcinoma, or a life expectancy of less than one year. If efavirenz-associated central nervous system toxicities occurred, nevirapine could be substituted for efavirenz. Patients who were not receiving their originally assigned treatment regimen after week 48 or 96 and during the 30-day extension study window were not eligible to continue to weeks 96 or 144 respectively.

Patients had a mean age of 38 years (range 18 to 80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm³ (range 2 to 1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56 to 6.54). Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm³); 41% had CD4 cell counts <200 cells/mm³ and 51% of patients had baseline viral loads > 100,000 copies/mL. Treatment outcomes at 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 14.

Table 14. Outcomes of Randomised Treatment at Weeks 48 and 144 (Study 934) in Treatment Naïve Patients

Outcome at Weeks 48 and 144	WEEK 48		WEEK 144	
	Emtricitabine + tenofovir disoproxil fumarate + efavirenz (N=244)	Lamivudine/ zidovudine + efavirenz (N=243)	Tenofovir disoproxil/ emtricitabine ⁴ + efavirenz (N=227)	Lamivudine/ Zidovudine + efavirenz (N=229)
Responder ¹	84%	73%	71%	58%
Virologic failure ²	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death ³	<1%	1%	1%	1%

1. Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL.

2. Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL.

3. All deaths were unrelated to study drugs.

4. Patients received emtricitabine and tenofovir disoproxil fumarate up to week 96 and switched to tenofovir disoproxil/emtricitabine from week 96 to 144.

In this study, emtricitabine + tenofovir disoproxil fumarate in combination with efavirenz was statistically significantly superior to lamivudine/zidovudine in combination with efavirenz with regards to the primary and secondary endpoints: achieving and maintaining HIV-1 RNA < 400 copies/mL through 48 and 144 weeks (Table 14). The difference in the proportions of responders between the emtricitabine + tenofovir disoproxil fumarate group and the lamivudine/zidovudine group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at week 48 and a difference of 12.9% (95% CI was 4.2% to 21.6%, p=0.004) at week 144.

Through 48 weeks of therapy, 80% and 70% of patients in the emtricitabine + tenofovir disoproxil fumarate and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA < 50 copies/mL. The difference in the proportions of responders between the emtricitabine + tenofovir disoproxil fumarate group and the lamivudine/zidovudine group was 9.1%, and the 95% CI was 1.6% to 16.6% (p=0.021) at week 48. The proportion of patients responding at 144 weeks of therapy was higher in the tenofovir disoproxil/emtricitabine group (64%) compared with the lamivudine/zidovudine group (56%); p=0.082, a difference of 8.1% and the 95% CI was -0.8% to 17.0%.

The mean increase from baseline in CD4 cell count was 190 cells/mm³ and 312 cells/mm³ for the emtricitabine + tenofovir disoproxil fumarate + efavirenz arm, and 158 cells/mm³ and 271 cells/mm³ for the lamivudine/zidovudine + efavirenz arm (p=0.002 and p=0.088) at weeks 48 and 144 respectively.

Resistance analysis was performed on HIV isolates from all patients with > 400 copies/mL of HIV-1 RNA at week 144 while on study drug or after treatment switch. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed in both treatment groups. Resistance to efavirenz occurred in 68% (13/19) analysed patients in the tenofovir disoproxil/emtricitabine group and in 72% (21/29) analysed patients in the lamivudine/zidovudine group. The M184V mutation, associated with resistance to emtricitabine and lamivudine developed significantly less in the analysed patients in the tenofovir disoproxil/emtricitabine group 11% (2/19) compared with the analysed patients in the lamivudine/zidovudine group, 34% (10/29). Two patients in the lamivudine/zidovudine group developed thymidine analog mutations, specifically D67N or K70R mutations in the reverse transcriptase gene. No patient in either treatment group developed the K65R mutation, which is associated with reduced susceptibility to tenofovir disoproxil fumarate.

iPrEx Trial

The iPrEx trial was a randomised double-blind placebo-controlled multinational study evaluating tenofovir disoproxil/emtricitabine in 2499 HIV-seronegative men or transgender women who have sex with men and with evidence of high risk behaviour for HIV-1 infection. Evidence of high risk behaviour included any one of the following reported to have occurred up to six months prior to study screening: no condom use during anal intercourse with an HIV-1 positive partner or a partner of unknown HIV status; anal intercourse with more than 3 sex partners; exchange of money, gifts, shelter or drugs for anal sex; sex with male partner and diagnosis of sexually transmitted infection; no consistent use of condoms with sex partner known to be HIV-1 positive.

All subjects received monthly HIV-1 testing, risk-reduction counselling, condoms and management of sexually transmitted infections. Of the 2499 enrolled, 1251 received tenofovir disoproxil/emtricitabine, and 1248 received placebo. The mean age of subjects was 27 years, 5% were Asian, 9% Black, 18% White, and 72% Hispanic/Latino.

Subjects were followed for 4237 person-years. The primary outcome measure for the study was the incidence of documented HIV seroconversion. At the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the tenofovir disoproxil/emtricitabine group and 83 occurred in the placebo group, indicating a 42% (95% CI: 18% to 60%) reduction in risk.

In a post-hoc case control study of plasma and intracellular drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable intracellular tenofovir. Efficacy was therefore strongly correlated with adherence.

Partners PrEP Trial

The Partners PrEP trial was a randomised, double-blind, placebo-controlled 3 arm trial conducted in 4758 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1589) and FTC/TDF (N=1583) versus (parallel comparison) placebo (N=1586), in preventing HIV-1 acquisition by the uninfected partner.

All subjects received monthly HIV-1 testing, evaluation of adherence, assessment of sexual behaviour, and safety evaluations. Women were also tested monthly for pregnancy. Women who became pregnant during the trial had study drug interrupted for the duration of the pregnancy and while breastfeeding. The uninfected partner subjects were predominantly male (61-64% across study drug groups), and had a mean age of 33-34 years.

Following 7827 person-years of follow up, 82 emergent HIV-1 seroconversions were reported, with an overall observed seroincidence rate of 1.05 per 100 person-years. Of the 82 seroconversions, 13 and 52 occurred in partner subjects randomised to tenofovir disoproxil/emtricitabine and placebo, respectively. Two of the 13 seroconversions in the tenofovir disoproxil/emtricitabine arm and 3 of the 52 seroconversions in the placebo arm occurred in women during treatment interruptions for pregnancy. The risk reduction for tenofovir disoproxil/emtricitabine relative to placebo was 75% (95% CI: 55% to 87%). In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence.

Tenofovir disoproxil fumarate

The demonstration of benefit of tenofovir disoproxil fumarate is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of tenofovir disoproxil fumarate 300 mg tablet in treatment-naïve adults and in treatment-experienced adults.

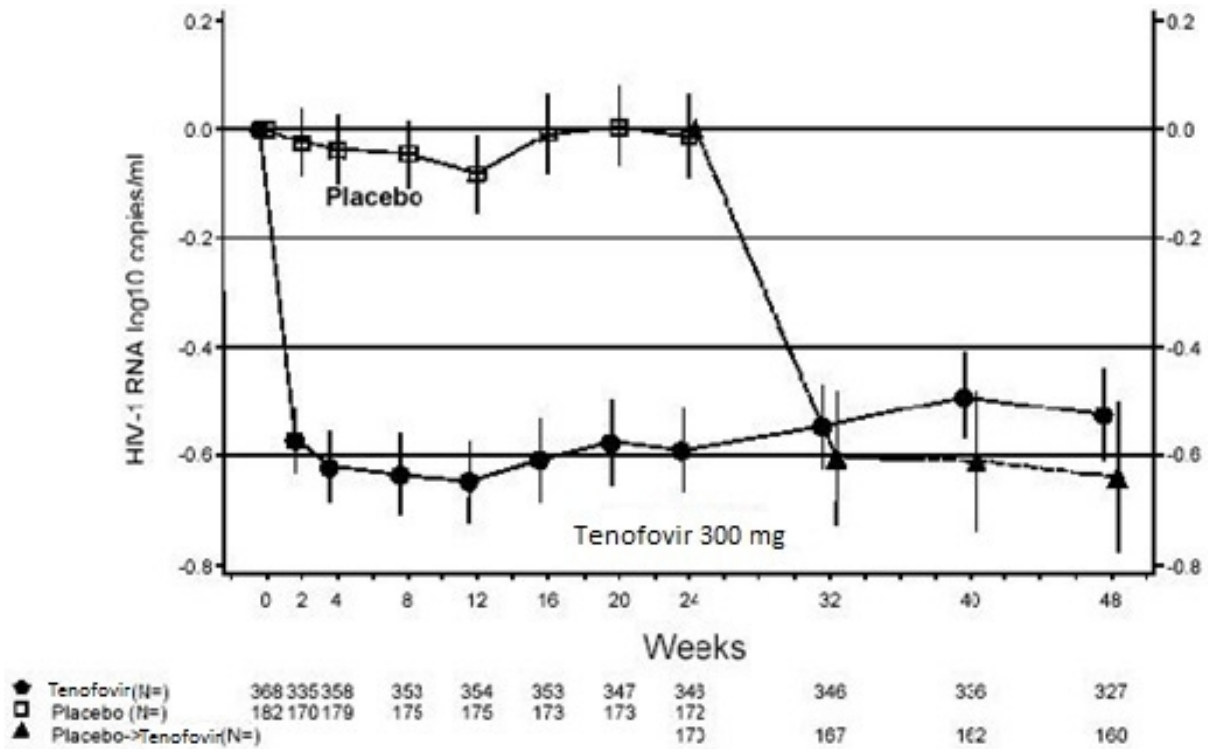
Treatment-Experienced Patients

Study 907: Tenofovir + Standard Background Therapy (SBT) Compared With Placebo + SBT

Study 907 was a 24 week, double-blind placebo-controlled multicentre study of tenofovir disoproxil fumarate added to a stable background regimen of antiretroviral agents in 550 treatment-experienced patients. After 24 weeks of blinded study treatment, all patients continuing on study were offered open-label tenofovir disoproxil fumarate for an additional 24 weeks. Patients had a mean baseline CD4 cell count of 427 cells/mm³ (range 23-1385), median baseline plasma HIV RNA of 2340 (range 50–75,000) copies/mL, and mean duration of prior HIV treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% Black and 12% Hispanic.

Changes from baseline in log₁₀ copies/mL plasma HIV-1 RNA levels over time up to week 48 are presented in Figure 1.

Figure 1. Mean Change from Baseline in Plasma HIV-1 RNA (Log₁₀ Copies/mL) Through Week 48: Study 907 (All Available Data)



†Patients on placebo after 24 weeks received Tenofovir.

The percent of patients with HIV RNA < 400 copies/mL and outcomes of patients through 48 weeks are summarised in Table 15.

Table 15. Outcomes of randomised treatment (Study 907)

Outcomes	0-24 weeks		0-48 weeks	24-48 weeks
	Tenofovir disoproxil fumarate (N=368) % (95% CI)	Placebo (N=182) % (95% CI)	Tenofovir disoproxil fumarate (N=368) %	Placebo Crossover to tenofovir disoproxil fumarate (N=170) %

HIV RNA < 400 copies/mL ¹	40% ⁴ (35% to 45%)	11% ⁴ (6% to 16%)	28%	30%
Virologic Failure ²	53%	84%	61%	64%
Discontinued Due to Adverse Event	3%	3%	5%	5%
Discontinued for Other Reasons ³	3%	3%	5%	1%

1. Patients with HIV RNA < 400 copies/mL and no prior study drug discontinuation at weeks 24 and 48 respectively.
2. Patients with HIV RNA ≥ 400 copies/mL efficacy failure or missing HIV RNA at weeks 24 and 48 respectively.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.
4. Difference 29%, p < 0.001.

At 24 weeks of therapy, there was a higher proportion of patients in the tenofovir disoproxil fumarate arm compared to the placebo arm with HIV RNA < 50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4 counts by week 24 was +12 cells/mm³ for the tenofovir group and -5 cells/mm³ for the placebo group. Mean change in absolute CD4 counts by week 48 was +4 cells/mm³ for the tenofovir disoproxil fumarate group.

Treatment-Naïve Patients

Study 903: Tenofovir disoproxil fumarate + Lamivudine + Efavirenz Compared to Stavudine + Lamivudine + Efavirenz

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicentre study comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine, lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4 cell count was 279 cells/mm³ (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Patients were stratified by baseline HIV-1 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/mL. Treatment outcomes through 144 weeks are presented in Table 16 below.

Table 16. Outcomes of Randomized Treatment (Study 903)

Outcomes	At Week 48		At Week 144	
	Tenofovir + lamivudine + efavirenz (N=299)	Stavudine + lamivudine + efavirenz (N=301)	Tenofovir disoproxil fumarate + lamivudine + efavirenz (N=299)	Stavudine + lamivudine + efavirenz (N=301)
	%	%	%	%
Responder ¹	79% ⁴	82% ⁴	68% ⁵	62% ⁵
Virologic failure ²	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 ³	8%	7%	14%	15%

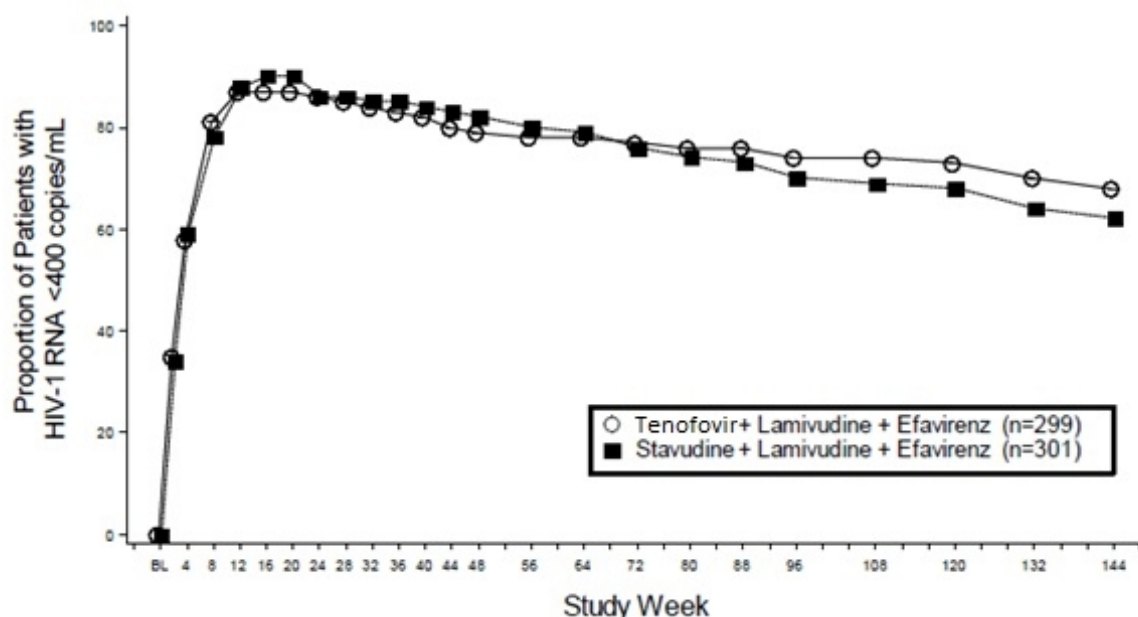
1. Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Weeks 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Weeks 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.
4. Difference -3.0% (-9.2% to 3.1%) p=0.48. The difference and confidence interval are stratum weighted on baseline HIV-1 RNA and CD4.
5. Difference 6.1% (-1.4% to 13.7%) p=0.11. The difference and confidence interval are stratum weighted on baseline HIV-1 RNA and CD4.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (\leq or $>$ 100,000 copies/mL) and CD4 cell count ($<$ or \geq 200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of patients in the tenofovir disoproxil fumarate 300 mg tablet and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA < 50 copies/mL. The mean increase from baseline in CD4 cell count was 263 cells/mm³ for the tenofovir disoproxil fumarate arm and 283 cells/mm³ for the stavudine arm.

The proportion of patients who achieved and maintained confirmed HIV RNA < 400 using intent-to-treat analysis through 144 weeks of treatment in study 903 is presented in Figure 2 below.

Genotypic analyses of patients with virologic failure showed development of efavirenz-associated and lamivudine-associated mutations to occur most frequently and with no difference between the treatment arms. The K65R mutation occurred in 8 patients on the tenofovir disoproxil fumarate arm and in 2 patients on the stavudine arm. Of the 8 patients who developed K65R in the tenofovir disoproxil fumarate 300 mg tablet arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and the last one at week 96. Among these patients, 5/8 patients subsequently gained full virologic control (< 50 copies/mL) upon switching to new regimens that included a protease inhibitor in combination with nucleoside reverse transcriptase inhibitors through a median of 155 weeks of follow-up. From both genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir disoproxil fumarate.

Figure 2. Virologic Response Through Week 144, Study 903**



* Roche Amplicor HIV-1 Monitor Test.

** Responders at each visit are patients who had achieved and maintained HIV-1 RNA < 400 copies/mL without discontinuation by that visit.

Genotypic Analyses of Tenofovir Disoproxil Fumarate in Patients with Previous Antiretroviral Therapy (Study 902 and 907)

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment experienced patients participating in trials 902 and 907. In both of these studies, 94% of the participants evaluated had baseline HIV isolates expressing at least one NRTI mutation. These included resistance mutations associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), the lamivudine/abacavir-associated mutation (M184V), and others. In addition the majority of participants evaluated had mutations associated with either PI or NNRTI use. Virologic responses for patients in the genotype substudy were similar to the overall results in studies 902 and 907.

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Descriptions of numerical differences in HIV RNA response are displayed in Table 17. Because of the large number of potential comparisons, statistical testing was not conducted.

Varying degrees of cross-resistance to tenofovir disoproxil fumarate from pre-existing zidovudine-associated mutations were observed and appeared to depend on the number and type of mutations. Tenofovir disoproxil fumarate 300 mg tablet-treated patients whose HIV expressed 3 or more zidovudine-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo. The presence of the D67N, K70R, T215Y/F or K219Q/E/N mutation did not appear to affect responses to tenofovir disoproxil fumarate therapy. The HIV RNA responses by number and type of baseline zidovudine-associated mutations are shown in Table 17.

Table 17. HIV RNA Response at Week 24 by Number of Baseline AZT-Associated Mutations in Studies 902 and 907 (Intent-To-Treat)¹

Number of baseline AZT-associated mutations ²	Change in HIV RNA ³ (N)	
	Tenofovir disoproxil fumarate	Placebo
None	-0.80 (68)	-0.11 (29)
Any	-0.50 (154)	0 (81)
1 – 2	-0.66 (55)	-0.04 (33)
≥ 3 including M41L or L210W	-0.21 (57)	+0.01 (29)
≥ 3 without M41L or L210W	-0.67 (42)	+0.07 (19)

1. Genotypic testing performed by Virco Laboratories and Visibly Genetics TruGene™ technology

2. M41L, D67N, K70R, L210W, T2/15Y/F or K219Q/E/N in RT

3. Average HIV RNA change from baseline through week 24 (DAVG₂₄) in log₁₀ copies/mL

In the protocol defined analyses, virologic response to tenofovir disoproxil fumarate was not reduced in patients with HIV that expressed the lamivudine/abacavir-associated M184V mutation. In the absence of zidovudine-associated mutations, patients with the M184V mutation receiving tenofovir disoproxil fumarate showed a -0.84 log₁₀ copies/mL decrease in their HIV RNA relative to placebo. In the presence of zidovudine-associated mutations, the M184V mutation did not affect the mean HIV RNA responses to tenofovir disoproxil fumarate treatment. HIV-1 RNA responses among these patients were durable through week 48.

There were limited data on patients expressing some primary nucleoside reverse transcriptase inhibitor mutations and multi-drug resistant mutations at baseline. However, patients expressing mutations at K65R (N=6), or L74V without zidovudine-associated mutations (N=6) appeared to have reduced virologic responses to tenofovir disoproxil fumarate.

The presence of at least one HIV protease inhibitor or non-nucleoside reverse transcriptase inhibitor mutation at baseline did not appear to affect the virologic response to tenofovir disoproxil fumarate.

Cross-resistance between tenofovir disoproxil fumarate and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Phenotypic Analyses of Tenofovir Disoproxil Fumarate in Patients with Previous Antiretroviral Therapy (Study 902 and 907)

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline phenotype (N=100) in treatment experienced patients participating in trials 902 and 907. Phenotypic analysis of baseline HIV from patients in Studies 902 and 907 demonstrated a correlation between baseline susceptibility to tenofovir disoproxil fumarate and response to tenofovir disoproxil fumarate therapy. Table 18 summarises the HIV RNA response by baseline tenofovir disoproxil fumarate susceptibility.

Table 18. HIV RNA Response at Week 24 by Baseline Tenofovir Disoproxil Fumarate Susceptibility in Studies 902 and 907 (Intent-to-treat)¹

Baseline tenofovir disoproxil fumarate Susceptibility ²	Change in HIV RNA ³ (N)
≤ 1	-0.74 (35)
> 1 and ≤ 3	-0.56 (49)
> 3 and < 4	-0.3 (7)
≤ 4	-0.61 (91)
> 4	-0.12 (9)

1. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram™ assay (Virco)
2. Fold change in susceptibility from wild-type
3. Average HIV RNA change from baseline through week 24 (DAVG₂₄) in log₁₀ copies/mL

Emtricitabine

Treatment-Experienced Patients

Study 303: Emtricitabine once daily + Stable Background Therapy (SBT) Compared to Lamivudine twice daily + SBT

Study 303 was a 48 week, open-label, active-controlled multicentre study comparing emtricitabine (200 mg once daily) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV RNA ≤ 400 copies/mL.

Patients were randomised 1:2 to continue therapy with lamivudine (150 mg twice daily) or to switch to emtricitabine (200 mg once daily). All patients were maintained on their stable background regimen. Patients had a mean age of 42 years (range 22–80), 86% were male, 64% Caucasian, 21% African-American and 13% Hispanic. Patients had a mean baseline CD4 cell count of 527 cells/mm³ (range 37–1909), and a median baseline plasma HIV RNA of 1.7 log₁₀ copies/mL (range 1.7–4.0). The median duration of prior antiretroviral therapy was 27.6 months. Treatment outcomes through 48 weeks are presented in Table 19.

Table 19. Outcomes of randomised treatment at week 48 (Study 303)

Outcome at Week 48	Emtricitabine + zidovudine/ stavudine + NNRTI/PI (N=294)	Lamivudine + zidovudine/ stavudine + NNRTI/PI (N=146)
Responder ¹	77% (67%)	82% (72%)
Virologic Failure ²	7%	8%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	4%	0%
Study Discontinuation For Other Reasons ³	12%	10%

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 mL) through week 48.
2. 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/mm² for the emtricitabine arm and 61 cells/mm³ for the lamivudine arm.

Treatment-Naïve Patients

Study 301A: Emtricitabine once daily + Didanosine once daily + Efavirenz once daily Compared to Stavudine twice daily + Didanosine once daily + Efavirenz once daily

Study 301A was a 48 week double-blind, active-controlled multicentre study comparing emtricitabine (200 mg once daily) administered in combination with didanosine and efavirenz versus stavudine, didanosine and efavirenz in 571 antiretroviral naïve patients. Patients had a mean age of 36 years (range 18-69), 85% were male, 52% Caucasian, 16% African-American and 26% Hispanic. Patients had a mean baseline CD4 cell count of 318 cells/mm³ (range 5-1317) and a median baseline plasma HIV RNA of 4.9 log₁₀ copies/mL (range 2.6-7.0). Thirty-eight percent of patients had baseline viral loads > 100,000 copies/mL and 31% had CD4 cell counts < 200 cells/mL. Treatment outcomes through 48 weeks are presented in Table 20.

Table 20. Outcomes of randomised treatment at week 48 (Study 301A)

Outcome at Week 48	Emtricitabine + Didanosine + Efavirenz (N=286)	Stavudine + Didanosine + Efavirenz (N=285)
Responder ¹	81% (78%)	68% (59%)
Virologic Failure ²	3%	11%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	7%	13%
Study Discontinuation For Other Reasons ³	9%	8%

- 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 168 cells/mm³ for the emtricitabine arm and 134 cells/mm³ for the stavudine arm.

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults: One tenofovir disoproxil fumarate/emtricitabine tablet was bioequivalent to one tenofovir disoproxil fumarate tablet (300 mg) plus one emtricitabine capsule (200 mg) following single-dose administration to fasting healthy subjects (N=39).

Tenofovir disoproxil fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarised in Table 21. Following oral administration of a tenofovir disoproxil fumarate 300 mg tablet, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01-25 µg/mL. Approximately 70-80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir disoproxil fumarate 300 mg, the terminal elimination half-life of tenofovir is approximately 17 hours.

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 21. Following oral administration of emtricitabine 200 mg, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1-2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02-200 µg/mL. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of

glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine 200 mg, the plasma emtricitabine half-life is approximately 10 hours.

Table 21. Single Dose Pharmacokinetic Parameters for Tenofovir and Emtricitabine in Adults¹

	<u>Tenofovir</u>	<u>Emtricitabine</u>
Fasted Oral Bioavailability (%)	25	93
Plasma Terminal Elimination Half-Life (hr)	17	10
C _{max} (µg/mL)	0.30 ± 0.09	1.8 ± 0.7 ²
AUC (µg*hr/mL)	2.29 ± 0.69	10.0 ± 3.1 ²
CL/F (mL/min)	1043 ± 115	302 ± 94
CL _{renal} (mL/min)	243 ± 33	213 ± 89

1. Data presented as mean values.

2. Data presented as steady state values.

Effects of Food

Tenofovir Disoproxil Emtricitabine Viartis may be administered with or without food. Administration of tenofovir disoproxil/emtricitabine following a high fat meal (~700-1000 kcal containing 40-60% fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. An increase in tenofovir AUC of approximately 40% and an increase in C_{max} of approximately 14% were observed. Similar findings were observed when tenofovir disoproxil/emtricitabine were administered with a light meal. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when tenofovir disoproxil/emtricitabine was administered with either a high fat or a light meal. See section 4.2.

Special Populations

Age, gender and ethnicity

Children and Elderly Patients: Pharmacokinetics of tenofovir and emtricitabine have not been fully evaluated in children (<18 years) or in the elderly (>65 years) (see section 4.4).

Gender: Tenofovir and emtricitabine pharmacokinetics are similar in male and female patients.

Patients with Impaired Renal Function

The pharmacokinetics of tenofovir and emtricitabine are altered in subjects with renal impairment (see section 4.4). In subjects with creatinine clearance <50 mL/min, or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and AUC_{0-∞} of tenofovir and emtricitabine were increased. It is required that the dosing interval for tenofovir disoproxil/emtricitabine be modified in HIV-infected patients with creatinine clearance <60 mL/min (see section 4.2).

Tenofovir disoproxil/emtricitabine should not be used in patients with creatinine clearance <30 mL/min and in patients with ESRD requiring dialysis (see section 4.4).

Tenofovir disoproxil/emtricitabine for a PrEP indication should not be used in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using tenofovir disoproxil/emtricitabine for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see section 4.2).

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate 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 tenofovir disoproxil/emtricitabine, or emtricitabine alone, 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.

5.3 Preclinical safety data

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.

Carcinogenicity and Mutagenicity

No carcinogenicity studies have been conducted with tenofovir disoproxil fumarate and emtricitabine in combination. In a long-term carcinogenicity study conducted in mice with tenofovir disoproxil fumarate there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15 times the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5 times the human systemic exposure at the therapeutic dose based on AUC).

In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 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).

Tenofovir disoproxil fumarate was mutagenic in an *in vitro* mouse L5178Y lymphoma cell assay (*tk* locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage. Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro*, nor clastogenic in mouse micronucleus test *in vivo*.

6. Pharmaceutical Particulars

6.1 List of excipients

Tenofovir Disoproxil Emtricitabine Viatris tablets also contain:

- microcrystalline cellulose

- ferric oxide red
- lactose monohydrate,
- hydroxypropyl cellulose
- silica colloidal anhydrous
- magnesium stearate
- hypromellose
- titanium dioxide
- triacetin,
- FD & C Blue No.1
- iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle or Aluminium blister packs containing 30, 60 or 90 film-coated tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

16 February 2017

10. Date of Revision of the Text

9 June 2022

Summary table of changes

Section	Summary of new information
All	Product name change to Tenofovir Disoproxil Emtricitabine Viatrix.