Application for Inclusion of Emtricitabine On WHO Model List of Essential Medicines

Submitted By

Gilead Sciences, Inc.
Foster City, California, USA

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Contact Person:
Daniel E. Kates, M.D.
Director
Medical Communications
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404 USA
Phone:650-522-5357
Fax: 650-522-5466
dkates@gilead.com

Application for Inclusion of Emtricitabine on World Health Organization (WHO) Model List of Essential Medicines

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

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

Emtricitabine is proposed for inclusion in the WHO Model list of essential medicines in combination with other antiretroviral agents for the treatment of HIV-1 infection. Although emtricitabine is not currently available as a single agent in many parts of the world, the importance of this application is related to the use of emtricitabine as part of fixed-dose combination regimens.

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

Charlie Gilks
HIV/AIDS Department
World Health Organisation

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

Not applicable.

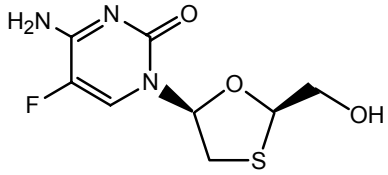
4. International Nonproprietary Name:

emtricitabine

5. Formulation Proposed for Inclusion

The formulation composition of the emtricitabine capsules and oral solution are provided below. The capsule and oral solution both contain emtricitabine as the active pharmaceutical ingredient. See Table 1 for information on the active ingredient of emtricitabine.

Table 1: Active Ingredient of Emtricitabine

Approved Name	Chemical Name, Structural and Molecular Formulae
Emtricitabine	5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine  $C_8H_{10}FN_3O_3S$

Emtricitabine Capsule
Each capsule contains 200 mg of emtricitabine and the inactive ingredients, crospovidone, magnesium stearate, microcrystalline cellulose, and povidone.

Emtricitabine Oral Solution
One millilitre (1 mL) of emtricitabine oral solution contains 10 mg of emtricitabine in an aqueous solution with the following inactive ingredients: cotton candy flavour, FD&C yellow No. 6, edetate disodium, methylparaben, and propylparaben (added as preservatives), sodium phosphate (monobasic), propylene glycol, water, and xylitol (added as a sweetener). Sodium hydroxide and hydrochloric acid may be used to adjust pH.

6. International Availability

Emtricitabine capsules and oral solution may be manufactured, tested, packaged and labelled, for Gilead Sciences, Inc., at the following facilities listed below (Table 2). All facilities are currently approved in the United States'(US) New Drug Application and the operations performed at all facilities are in compliance with European Union (EU) and US Food and Drug Administration (FDA) Good Manufacturing Practices (GMP) guidelines.

Table 2: Manufacturing, Testing, Packaging, and Labelling Facilities for Emtricitabine Capsules and Oral Solution

Name and Address of Facility	Function	Dosage Form
Abbott Laboratories 100 and 200 Abbott Park Road Abbot Park, IL 60064 USA	Manufacturing, packaging and testing	Capsules
Gilead Sciences, Inc. 542 Covina Boulevard San Dimas, CA 91773 USA	Packaging and labelling and testing	Capsules
Abbott Laboratories 1401 Sheridan Road North Chicago, IL 60064 USA	Manufacturing, packaging, labelling and testing	Oral solution
Gilead Sciences, Inc. 650 Covina Boulevard San Dimas, CA 91773 USA	Labelling and testing	Oral solution
Gilead Sciences Limited Unit 13, Stillorgan Industrial Park Blackrock, Co. Dublin Ireland	Packaging, labelling, and testing	Capsules and Oral solution

7. Listing Type Requested:

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

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

8.1 Epidemiological information on disease burden

Since the first clinical evidence of AIDS was reported over 25 years ago, an estimated 25 million people have died as a result of HIV infection, making it one of the most destructive epidemics in recorded history.[1] In 2005, there were an estimated 3.1 million deaths due to AIDS. Current estimates suggest that some 40.3 million people worldwide are infected with HIV, up from an estimated 37.5 million in 2003, and twice as many as compared to 1995. In 2005, it is estimated that an additional 4.9 million individuals worldwide became infected with HIV, and 700,000 of these new infections were in children <15 years of age.

Of major concern is the prevalence of HIV/AIDS in developing countries. Approximately 95% of all HIV-infected people live in low- and middle-income countries.[2] Although there is new evidence that adult HIV infection rates have decreased in certain countries, the overall trends in HIV transmission are still increasing, and the overall number of people living with HIV has continued to increase in all regions of the world except the Caribbean.[3] The steepest increases in HIV infections have occurred in Eastern Europe and Central Asia, and in East Asia. In Eastern Europe and Central Asia, there was a 25% increase in the number of people living with HIV (to 1.6 million) since 2003, and AIDS death rates almost doubled (to 62,000) during that time.[1] In East Asia, there was a 20% increase in the number of people living with HIV (to 870,000) since 2003. However, the worst affected area is Sub-Saharan Africa, with 64% of new infections (3.2 million) occurring here and with an estimated 2.4 million who died of HIV-related illnesses in 2005.[1,3]

The proportion of women who are affected by the epidemic continues to increase.[4] As of 2003, women accounted for nearly 50% of all people living with HIV worldwide.[4] In 2005, 17.5 million women were living with HIV, which is one million more than in 2003.[1] HIV infection levels among pregnant women vary widely in different countries, but levels often exceeding 30% have been recorded in some regions of Southern Africa.[1] Without HIV prevention measures, about 35% of children born to HIV-positive women will contract the virus.[1] In many countries, life expectancy and child survival rates have plummeted. For example, in seven African countries where HIV prevalence is >20%, the average life expectancy of a person born between 1995 and 2000 is now 49 years, which is 13 years lower than in the absence of AIDS.[4]

In countries already burdened by huge socio-economic challenges, HIV/AIDS threatens human social welfare, developmental progress and social stability on an unprecedented scale. HIV/AIDS continues to cripple the economic development of entire countries, because it often strikes people during their most productive period of life.[5] For example, of the 14,000 persons who became infected each day in 2005, about 12,000 (86%) were aged 15 to 49 years.[2] Overall, young people aged 15 to 24 years account for about half of all new HIV infections per day worldwide.[2] The introduction of potent antiretroviral agents and the combined use of these drugs have markedly reduced the replication of HIV in many patients, and improved survival rates. Highly active antiretroviral therapy (HAART) is now the standard of care in the treatment of HIV infection. It is successful in reducing viral load, extending the asymptomatic phase of infection, and improving the quality of life for many infected individuals.[6]

8.2 Assessment of current use

Emtricitabine is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in patients over three months of age. Emtricitabine is currently included as a preferred first-line regimen in international treatment guidelines, including the WHO Guidelines for the Use of Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resource-Limited Settings, the International AIDS Society-USA (IAS) Treatment Recommendations for Adult HIV Infection, and the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents issued by the United States Department of Health and Human Services (DHHS).[7-9] In addition, emtricitabine is also available as a component of fixed-dose

combination regimen with tenofovir DF, and more recently, as part of a triple combination fixed-dose regimen containing tenofovir DF and EFV.

The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[9] Suppression of viral load as much as possible, for as long as possible, is an important and achievable goal of antiretroviral therapy. However, this goal must be balanced against the need to preserve effective treatment options. The presence of breakthrough resistant (virus) mutations in treatment-experienced patients is a strong predictor of virologic failure and disease progression.

An emerging challenge in regard to the successful long-term management of HIV/AIDS is the increasing prevalence of drug resistance. The prevalence of HIV-1 drug resistance has been assessed in several studies. Early studies of US HIV-1 infected patients such as the HIV-1 Cost and Services Utilization study (1996-1999) indicated that resistance could be detected in 76% of viremic patients with HIV-1 RNA >500 copies/mL, with resistance to NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) being detected in 71%, 25%, and 41% of patients, respectively.[10] Surveys of large genotyping laboratory databases such as LabCorp and Monogram Biosciences have also evaluated the prevalence of resistance in more recent years. In the LabCorp database of 37,924 US patient samples collected in 2002, the most frequent NRTI mutations detected included M184V/I (41% of patients), thymidine analogue mutations (TAMs) (11.3%) and a low but increasing frequency of K65R (1.7%). NNRTI mutations such as K103N and Y181C were found in 30% and 12% of patients, respectively, whereas PI mutations such as L90M, V82A and D30N were found in 15%, 8% and 6% of patients, respectively.[11] This latter study included patients with repeat samples, however, in studies of the Monogram Biosciences database in which > 16,000 individual US patient reverse transcriptase (RT) genotypes from 2003 were characterized, similar frequencies of NRTI mutations were observed.[12] Thus, there is now a significant proportion of HIV-1 infected patients carrying drug resistant viruses; development of resistance leads to decreased susceptibility to other NRTIs through cross-resistance, which limits viable treatment options.

As more HIV-1 infected patients are treated for longer periods of time, the transmission of drug resistant HIV-1 in newly diagnosed patients who are otherwise naïve to antiretroviral treatment is also increasing. Current estimates are that approximately 10%-20% of treatment-naïve and recently infected patients in Western nations have been infected with drug-resistant virus as has been documented in several studies during the period 1996-2001.[13] A recent US study of 1,082 treatment-naïve HIV-1 patients found a prevalence of 8.3% of patients with any transmitted resistance, predominantly to NRTIs.[14] Two studies of recent European seroconverters have identified 9.6%[15] and 10.3%[16] of antiretroviral therapy naïve patients as having transmitted primary resistance. Both studies showed that more recently infected patients were significantly more likely to have primary drug resistance than those who had been infected for more than one year, suggesting that the incidence of transmitted drug resistance is rising or it is underestimated in patients who have been chronically infected for longer periods of time, due to reversion.

The development and transmission of resistance-conferring mutations is also associated with a sub-optimal virologic response to initial antiretroviral therapy.[17] Recent clinical trials such as

study GS-01-934 have highlighted the importance of baseline resistance on response to antiretroviral therapy. In this study of emtricitabine + tenofovir DF + efavirenz (EFV) versus zidovudine (AZT)/ lamivudine(3TC) + EFV, NNRTI resistance was present at baseline in 4.3% of antiretroviral naïve patients enrolled in the study and regardless of the treatment arm, was significantly associated with a poorer response to EFV-based therapy and was associated with development of additional resistance mutations to both NNRTIs and NRTIs.[18] Cross-resistance compromises the availability of future treatment options for subsequent courses of therapy in the aftermath of drug resistance. Furthermore, the extent of cross-resistance has also been shown to increase commensurate with the accumulation of additional drug resistance mutations.[19]

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

8.3 Target population

In contrast to earlier examples regarding developing countries, an estimated 1.6 million people are living with HIV in high income countries.[4] It is primarily in these high income countries where standards of treatment and care have evolved considerably.[20] For example, in the US, the age-adjusted HIV death rate declined by 70% between 1995 and 2002, largely due to the introduction of HAART therapy.[21]

Although the number of people in low- and middle-income countries receiving HIV antiretroviral therapy has tripled since the end of 2001, overall access to antiretroviral treatment and other HIV-related disease care remains low.[1,4] In order to improve access to treatment, several Latin American and Caribbean countries (including Argentina, Barbados, Chile, Costa Rica, Cuba, Mexico and Uruguay) now offer universal coverage for antiretroviral treatment.[4] In Brazil, the government estimates that the policy of universal access to antiretroviral drugs has saved 2.2 billion US dollars in hospital care that would have otherwise been needed by people living with HIV.[4]

Other programs, such as the United Nations AIDS (UNAIDS) Drug Access Initiative Pilot Program and the WHO/UNAIDS "3 by 5 Initiative," are designed to increase antiretroviral access to people in low- and middle-income countries.[20] Since its launch in 2003, antiretroviral therapy coverage in these countries has more than doubled to about 1 million people in June 2005. Similarly, the UNAIDS Drug Access Initiative Pilot Program provided antiretroviral therapy to the public sector in four low- and middle-income countries in the late 1990s.[20] The success of these, and other programs, has demonstrated that it is viable to treat people with HIV/AIDS in these environments.

9. Treatment details:

Emtricitabine is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in patients over three months of age.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 48 weeks duration in antiretroviral-naïve patients and antiretroviral-treatment-experienced patients who were virologically suppressed on an HIV treatment regimen.

In antiretroviral treatment-experienced patients, the use of emtricitabine may be considered for patients with HIV strains that are expected to be susceptible to emtricitabine as assessed by genotypic or phenotypic testing.

Formulations: Emtricitabine 200 mg capsules and 10 mg/mL oral solution.

9.1 Recommended Dosage

Due to a difference in the bioavailability of emtricitabine between the capsule and oral solution, 240 mg emtricitabine administered as the oral solution (24 mL) should provide similar plasma levels to those observed after administration of one 200 mg emtricitabine capsule.

Adults (18 years of age and older): The dose of emtricitabine in adults is one 200 mg capsule administered once daily, or 240 mg (24 mL) of 10 mg/mL oral solution administered once daily, taken orally in combination with other antiretroviral agents, without regard to food.

Paediatric Patients (3 months through 17 years): The safety and effectiveness in paediatric patients below the age of 3 months have not been established.

The recommended dose of emtricitabine 10 mg/mL oral solution is 6 mg/kg up to a maximum of 240 mg (24 mL) once daily taken orally in combination with other antiretroviral agents, without regard to food.

Children who weigh at least 33 kg may either take one emtricitabine 200 mg capsule daily or emtricitabine 10 mg/mL oral solution up to a maximum of 240 mg once daily in combination with other antiretroviral agents, without regard to food.

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

Renal Insufficiency: Significantly increased drug exposures were seen when emtricitabine was administered to patients with renal impairment. Therefore, the dosing interval of emtricitabine should be adjusted in patients with baseline creatinine clearance <50 mL/min using the following guidelines (see Table 3). The safety and effectiveness of these dose adjustment

guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 3: Dose Adjustment for Adult Patients with Renal Impairment

Formulation	Creatinine Clearance (ml/min)			
	≥ 50 mL/min	**30-49 mL/min**	**15-29 mL/min**	**< 15 mL/min or on haemodialysis***
Capsule (200 mg)	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours
Oral Solution (10 mg/mL)	240 mg every 24 hours (24 mL)	120 mg every 24 hours (12 mL)	80 mg every 24 hours (8 mL)	60 mg every 24 hours (6 mL)

*Haemodialysis patients: If dosing is on day of dialysis, give dose after dialysis.

Although there are insufficient data to recommend a specific dose adjustment of emtricitabine in paediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval similar to adjustments for adults should be considered.

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

Concomitant Antiretroviral Therapy: Emtricitabine must be given in combination with other antiretroviral medications.

Due to similarities between emtricitabine and 3TC, emtricitabine should not be coadministered with other drugs containing 3TC, including Combivir®, Epivir®, Epivir-HBV®, Epzicom™, Kivexa™, or Trizivir®. Emtricitabine should not be used with Truvada® or ATRIPLA® since it is a component of these products.

9.2 Drug Interactions

The potential for drug interactions with emtricitabine has been studied in combination with zidovudine (AZT), indinavir, stavudine (d4T), famciclovir, and tenofovir DF. There were no clinically significant drug interactions for any of these drugs.

9.3 Duration

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

9. 3 Guidelines

Guidelines for the treatment of HIV infection recommend that standard HAART treatment contain a combination of two NRTIs plus an NNRTI or PI.[7-9] In the August 2006 revision of the WHO Treatment Guidelines for Adults in Resource-Limited Settings, emtricitabine is recommended as a first-line preferred NRTI in combination with tenofovir DF and an NNRTI. [7]

Similarly, the IAS Treatment Recommendations for Adult HIV Infection (updated in May 2005) recommend emtricitabine as one of the components of initial antiretroviral therapy in combination with tenofovir DF and an NNRTI or boosted PI.[8] The Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents issued by the United States Department of Health and Human Services (DHHS) (updated in October 2006) also recommend that emtricitabine, as part of a fixed-dose combination regimen containing tenofovir DF, should be a component of first-line ARV regimens containing EFV and/or a boosted PI (DHHS Guidelines).[9] In addition, the IAS and DHHS guidelines also list emtricitabine (or lamivudine) as a recommended component of alternative second-line regimens in combination with an NNRTI or boosted PI.[8,9]

9.4 Special Requirements

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

10. Comparative effectiveness in clinical settings:

10.1 Identification of clinical evidence

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

Details of literature searches conducted

The databases searched were:

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

Search terms included:

- Emtricitabine
- FTC
- Coviracil
- Emtriva

- bw524
- bw524w91

Study selection:

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

10.2 Summary of Available Data

Emtricitabine is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infected patients over three months of age. Emtricitabine is a synthetic analogue of cytidine. As a nucleoside analogue, emtricitabine is efficiently and selectively incorporated into the growing chains of viral DNA with potent activity against HIV-1 and HIV-2 virus. Structurally, emtricitabine is most similar to 3TC, which is another analogue of cytosine. However, emtricitabine is ~5 fold more potent *in vitro* than 3TC against laboratory strains and primary clinical isolates of HIV.[22,23]

The US FDA has previously indicated that emtricitabine is comparable to 3TC, as described in the original treatment indication for emtricitabine and tenofovir DF fixed-dose combination tablets. An excerpt from this indication statement is provided below.

> *"Since emtricitabine and 3TC are comparable in their structure, resistance profiles, and efficacy and safety as part of multi-drug regimens, existing data from the use of 3TC and tenofovir DF in combination have been extrapolated to support use of emtricitabine and tenofovir DF fixed-dose combination tablets for the treatment of HIV-1 infection in adults. Therefore, in treatment naïve patients, emtricitabine and tenofovir DF fixed-dose combination tablets should be considered as an alternative to the combination of tenofovir DF + 3TC for those patients who might benefit from a once-daily regimen."*

Emtricitabine is also considered to be an equivalent alternative to 3TC in international treatment guidelines, including the August 2006 revision of the WHO Treatment Guidelines for Adults in Resource-Limited Settings, the May 2005 update to the IAS Treatment Recommendations for Adult HIV Infection, and the October 2006 update to the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents issued by the United States Department of Health and Human Services (DHHS).[7-9]

Once-daily dosing of emtricitabine is supported by the plasma and intracellular triphosphate half lives. Plasma emtricitabine concentrations decline in a multi-exponential manner, with a half-life of approximately 10 hours. At 24 hours post-dose, the plasma concentrations exceed the mean *in vitro* IC_{90} by about 4-fold and remain above *in vitro* IC_{90} for wild-type virus 84 hours after a 200 mg dose at steady state. Furthermore, the intracellular half-life of the active form of emtricitabine is approximately 39 hours. The extended half-life of emtricitabine in plasma, as well as the long intracellular half-life of emtricitabine triphosphate, allows for once daily dosing to provide continued viral suppression with a forgiving dosing regimen.[24] Simplifying HIV

treatment regimens using once daily antiretroviral drugs may improve adherence and therapeutic outcomes.

The only identified mutation that confers resistance to emtricitabine is M184V mutation. The M184V mutation also confers resistance to 3TC and zalcitabine, but retains sensitivity to tenofovir DF, AZT, d4T, abacavir (ABC), didanosine (ddI), and NNRTIs.[25] However, *in vitro*, the M184V mutation develops more slowly with emtricitabine than with 3TC.[22]

The principal clinical studies that demonstrate the clinical efficacy of emtricitabine 200 mg once daily in treatment-naïve and treatment-experienced HIV-infected patients are described in the following sections.

10.2.1 Summary of clinical data

- Results from pivotal clinical trials (FTC-301A and FTC-303) demonstrate that emtricitabine in combination with other antiretroviral agents, including NRTIs, NNRTIs and PIs, is effective in treatment of HIV infection in treatment-naïve and treatment-experienced patients. Assessment of adverse events from these studies showed that the most commonly reported adverse events are headache, diarrhoea, nausea, and rash. Overall, adverse events and laboratory abnormalities observed in clinical trials were similar between emtricitabine and control treatment groups.

Treatment-naïve patients

- Treatment-naïve patients treated with emtricitabine 200 mg once daily had superior efficacy responses after 48 weeks and after 60 weeks of treatment compared to patients treated with d4T. Both arms contained a background regimen of once-daily ddI and EFV. All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the emtricitabine treated group. (Study FTC-301A)

- Treatment-naïve patients treated with once daily emtricitabine versus twice-daily 3TC, each in combination with d4T and EFV or nevirapine (NVP), showed that similar proportions of patients achieved HIV RNA <50 copies/ml in the emtricitabine and 3TC-containing treatment arms. Emtricitabine was well tolerated with the majority of adverse events being mild to moderate in severity; the majority of treatment emergent adverse events occurred with equivalent incidence between treatment arms. (Study FTC-302)

- Significantly more patients treated with a once-daily regimen containing emtricitabine 200 mg and tenofovir DF 300 mg achieved and maintained HIV RNA <400 copies/mL at 48 and 96 weeks of treatment compared to patients who received treatment with AZT/3TC. Both arms contained a background regimen of EFV. Through Week 96, a total of 5% of patients in the emtricitabine + tenofovir DF group compared to 11% of those in the AZT/3TC group discontinued from the study due to an adverse event (P = .008). (Study GS-01-934)

- A once daily combination of emtricitabine 200 mg + tenofovir DF 300 mg with once or twice-daily lopinavir/ritonavir (LPV/r) demonstrated efficacy and safety in treatment naïve patients through 96 weeks of study. Through Week 96, 17% of patients in the once daily group and 9% of those in the twice daily group discontinued the study due to adverse events. Gastrointestinal adverse events were the most common cause for discontinuation and were the most common adverse events overall. (Study M02-418).

- A once-daily combination regimen of emtricitabine + tenofovir DF + EFV demonstrated efficacy and safety through 48 weeks in West African patients. Reported Grade 3 or 4 adverse events included dizziness, nausea/vomiting, diarrhoea, coetaneous eruption/pruritus, headache and fatigue; no Grade 4 treatment related adverse events occurred. (ANRS 1207/IMEA 025 Study)

Treatment-experienced patients

- In patients on a stable 3TC-containing HAART regimen, switching to emtricitabine 200 mg once daily demonstrated comparable efficacy compared to continuing 3TC 150 mg twice daily through 48 weeks of treatment. Both medications were given in combination with a NRTI and a PI or NNRTI. All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the emtricitabine treated group. All adverse events leading to discontinuation were of mild to moderate in severity. (Study FTC-303)

- Long-term data (4 years) have demonstrated that emtricitabine-treated patients have durable suppression of plasma HIV RNA levels with a Kaplan-Meier (KM) probability of virologic failure equal to 11% through the fourth year of follow-up. During the 4 years of treatment, with a median duration of follow-up of 140 weeks, the KM probability of treatment-limiting adverse events requiring discontinuation of emtricitabine was 13%.[26,27] Most adverse events observed were mild to moderate in severity. (Study FTC-350)

- Patients on a stable PI-based HAART regimen who simplified their treatment to an entirely once daily emtricitabine-based regimen had similar virologic outcomes for HIV-1 RNA < 400 copies/mL and significantly better outcomes for plasma HIV-1 RNA < 50 copies/mL after 48 weeks compared to those who remained on a PI-based regimen. At Week 48, the percentage of patients who had treatment discontinuation due to adverse events was similar between the two arms based on KM estimates (9% once daily arm vs. 10% PI arm, *P*=.8). (Study ANRS-099 [ALIZE])

- Patients switched from a stable HAART regimen containing AZT/3TC + EFV to a once-daily regimen containing emtricitabine, tenofovir DF + EFV had similar virologic outcomes for HIV-1 RNA < 400 copies/mL and significantly better outcomes for plasma HIV-1 RNA < 50 copies/mL at 24 weeks compared to baseline. Results through Week 24 demonstrate that there were statistically significant improvements from baseline at Week 24 in haemoglobin level (31% had >1 g/dL increase from baseline), absolute neutrophil count (ANC), mean corpuscular volume (MCV), and fasting lipid parameters. Overall, nausea,

diarrhoea, headache, and insomnia were the most commonly reported adverse events, occurring in 5%, 5%, 3%, and 3% of the patients, respectively. (COMET Study)

Paediatric Patients

- A regimen containing emtricitabine 6 mg/kg once daily + d4T and LPV/r demonstrated efficacy and safety in HIV-infected, treatment-naïve children aged 3 months to 17 years old. Similarly, treatment-experienced children switched from 3TC to emtricitabine with a stable background antiretroviral regimen also demonstrated efficacy at 48 and 96 weeks. Seven patients experienced an adverse event that was at least moderate in severity (Grade 2) and possibly or probably related to the study drug. All events were resolved except for one patient who experienced Grade 2 skin discoloration. (FTC-203)

- A regimen containing emtricitabine 6 mg/kg once daily + ddI and EFV demonstrated efficacy in treatment-naïve children ages 3-21 years. Two patients experienced Grade 3 symptoms (rash, dizziness) which were attributed to the treatment regimen. These symptoms occurred during Week 1 and resolved spontaneously. No deaths or new Category C diagnoses occurred during the study. (PACTG 1021 [FTC-202])

10.3 Summary of comparative effectiveness

A summary of clinical data from the emtricitabine pivotal clinical trials (FTC-301A and FTC-303) is included in the following sections. Additional data from other clinical studies that examined the use of emtricitabine in HIV-infected adults are also included for both treatment-naïve (Study FTC-302, Study GS-01-934, Study 418, ANRS/IMEA 025) and treatment-experienced patients (ANRS 099 [ALIZE], COMET). Available data from clinical studies that evaluated the use of emtricitabine in HIV-infected paediatric patients are also summarized below (FTC-105, PACTG 1021 [FTC-202], FTC-203).

10.3.1 Summary of Data in HIV-infected Adult Patients

Treatment-naïve patients

Clinical efficacy in antiretroviral treatment-naïve HIV-infected patients has been demonstrated in multiple clinical trials that have evaluated the use of emtricitabine in combination with other antiretrovirals including ddI, tenofovir DF, d4T, LPV/r, NVP and EFV.

Study FTC-301A (Pivotal Trial)

Study 301A was a Phase 3, 48-week, randomized, double-blind, multi-centre study comparing emtricitabine 200 mg once daily to d4T 40 mg twice daily (30 mg if <60 kg) with a background regimen of ddI (400 mg once daily if ≥60 kg, 250 mg once daily if <60 kg) and EFV (600 mg once daily).[25,28-30] At baseline, adult patients (N = 571) enrolled in this study had a median HIV RNA level of 4.9 $\log_{10}$ copies/mL (range 2.6–7.0) and a mean CD4 cell count of 318 cells/mm^3 (range 5-1317); 38% had HIV RNA levels >100,000 copies/mL and 31% had CD4 cell counts

<200 cells/mm^3. The primary endpoint of the study was persistent virologic response, defined as achieving and maintaining plasma HIV RNA levels at or below the limit of assay quantification calculated through weeks 24, 48, and 60. The end point followed the US FDA TLOVR algorithm. The TLOVR algorithm is a multi-step algorithm that has been required by the FDA since 2002 to evaluate clinical trial treatment outcomes with all antiretroviral drugs for which plasma HIV RNA measurements are used to assess efficacy. TLOVR provides a more stringent definition for virologic success and failure than ITT, missing = failure and/or switch = failure analyses, by also requiring confirmation of virologic success at two consecutive visits (Guidance for Industry, U.S. FDA 2002).[31] TLOVR is now included in the U.S. Prescribing Information of newly approved antiretroviral drugs.

Results at 48 weeks demonstrated that patients treated with emtricitabine had a superior response than those treated with d4T. Forty-eight week results are shown in Table 4.

Table 4: Results at Week 48 by TLOVR Analysis[25,29]

Key Parameters	**Emtricitabine + ddI + EFV (n = 286)**	**d4T + ddI + EFV (n = 285)**
Responder* <400 copies/mL[†] (<50 copies/mL)[†]	81% (78%)	68% (59%)
Virologic Failure[‡]	3%	11%
Study Discontinuation		
Due to Adverse Events	7%	13%
For Other Reasons[§]	9%	8%
Death	0%	<1%

Abbreviation: NS, not significant

*Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48.

[†]P<.001 for the difference between treatment arms

[‡]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/mm^3 for the emtricitabine arm and 134 cells/mm^3 for the d4T arm (P =.15; as-treated analysis). Through 48 weeks, 5 patients (1.7%) in the emtricitabine group experienced a new CDC Class C event, compared to 7 patients (2.5%) in the d4T group.[25,29]

Based on a protocol planned interim analysis when the last randomized patient completed Week 24, the Data and Safety Monitoring Board (DSMB) recommended termination of the double-blind comparative phase of the study and offering all patients open-label access to the emtricitabine treatment regimen.[29,32] After the last enrolled patient switched to open-label emtricitabine, the KM analysis of the entire double-blind follow-up phase (median duration: 60 weeks; range: 48-108 weeks) also demonstrated that the emtricitabine arm had a superior response compared to the d4T arm. Week 60 results are shown in Table 5.

Table 5: Efficacy Results at Week 60 by TLOVR Analysis[29,32]*

Parameter	Emtricitabine + ddI + EFV (n = 286)	d4T + ddI + EFV (n = 285)	*P*-Value
KM probability of response (≤400 copies/mL)	79%	63%	<.001
KM probability of response (≤50 copies/mL)	76%	54%	<.001
KM probability of Virologic Failure	4%	12%	<.001
Mean Change in CD4 Cell Count (cells/mm^3)†	+165	+137	=.06
Study Discontinuation Due to Adverse Event	7%	17%	=.0028

Abbreviation: KM, Kaplan-Meier
*Median duration: 60 weeks, range: 48-108 weeks.
†Last observation carried forward.

To evaluate the association between baseline genotypic mutations and the incidence of virologic failure (VF), genotypic analysis was performed retrospectively on baseline HIV RNA samples in 546/571 (95.6%) of patients, 276 in the d4T arm and 270 in the emtricitabine arm.[33] In this population, at Week 48, the incidence of VF was significantly greater in the d4T arm than the emtricitabine arms,13% d4T vs. 5% emtricitabine (*P* <.001), similar to what was observed in the intent-to-treat (ITT) analysis, 11% d4T vs. 3% emtricitabine (*P* =.001).[25,33] Overall, 18.5% of patients in the emtricitabine arm and 14.5% of patients in the d4T arm had baseline mutations, with no difference in the prevalence or mutation types between the groups (Table 6). NRTI associated mutations were found in 7.8% of patients in the emtricitabine arm and 4.7% of patients in the d4T arm. Additionally, NNRTI associated mutations were found in 9.3% of patients in the emtricitabine arm and 8.3% of patients in d4T arm. The incidence of VF at Week 60 was significantly higher in the d4T arm compared to the emtricitabine arm in patients with wild-type genotype at baseline (11% d4T vs. 4% emtricitabine; *P* =.006) and patients with baseline mutations (30% d4T vs. 10% emtricitabine, *P* =.028).[33]

Furthermore, the presence of NNRTI associated mutations at baseline was found to be predictive of VF in both the d4T and emtricitabine arms (*P* =.003 d4T and *P* =.026 emtricitabine). The K103N mutation, found in 2.5% of patients in emtricitabine and d4T arms, was the only NNRTI mutation found to be predictive of VF in both arms (*P* =.001). By contrast, the presence of NRTI associated mutations at baseline was only predictive of VF in the d4T arm.[33] Many HAART regimens contain thymidine analogues, such as d4T. Resistance to d4T develops when mutations occur in various sites in the gene encoding RT. Emtricitabine is not cross-resistant with d4T. Study FTC-301A showed that patients treated with emtricitabine develop fewer resistance mutations than patients treated with d4T.

.

Table 6: Baseline Genotypes[33]

Characteristics	Emtricitabine + ddI + EFV Arm (N = 270) n (%)	d4T + ddI + EFV Arm (N = 276) n (%)
WT	220 (81.5)	236 (85.5)
Mutant	50 (18.5)	40 (14.5)
NRTI only*	21 (7.8)	13 (4.7)
Single	17 (6.9)	8 (2.9)
Multiple	4 (1.5)	5 (1.8)
NNRTI only†	25 (9.3)	23 (8.3)
Single	22 (8.1)	21 (7.6)
Multiple	3 (1.1)	2 (0.7)
K103N‡	7 (2.5)	7 (2.5)
NRTI and NNRTI	4 (1.5)	4 (1.4)

Abbreviations: WT, wild type; NRTI, nucleotide/nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors

*NRTI mutations: M41, K65, D67, T69, K70, L74, V75, M184, L210, T215, K219.

†NNRTI mutations: A98, L100, K101, K103, V106, V108, Y181, Y188, G190, P225.

‡Alone or in combination with NRTI or NNRTI.

Overall, the incidence of new mutations at time of failure in patients experiencing VF was significantly lower in the emtricitabine arm than the d4T arm. In addition, for patients who entered the study with wild-type virus, the incidence of new mutations was significantly greater in the d4T arm than the emtricitabine arm (P =.012). The M184V/I mutations occurred significantly more frequently in the emtricitabine arm than the d4T arm (P <.001). Results are shown in Table 7.

Table 7: Incidence of New Mutations in Patients with Virologic Failure[34]*

Mutation	Emtricitabine + ddI + EFV Arm (n = 16)	d4T + ddI + EFV Arm (n = 41)
Any	11 (69%)	35 (85%)
NNRTI†	10 (63%)	35 (85%)
Any TAMs‡	0	6 (15%)
L74V, K65N	1 (6%)	3 (7%)
M184V/I	6 (37.5%)	0
No Change	5 (31%)	6 (15%)

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; TAM, thymidine analogue mutations; ddI: didanosine

*Defined as never achieving <400 copies/mL or rebound >400 copies/mL on 2 consecutive measurements.

†NNRTI mutations: K103N, L100I, G190A/E/S, Y188C/Y, K101E/N, V106I/M, A98G, V108I, P225H.

‡TAM mutations: T215F/I/S/Y, D67G, K219N; ddI mutations: L74V, K65N.

Study FTC-301A demonstrated that antiretroviral-naïve patients who begin therapy with an emtricitabine-based entirely once-a-day regimen achieved and maintained superior efficacy and safety responses compared to patients treated with d4T twice daily in combination with once daily ddI and EFV.

Supportive Studies

Study FTC-302

This randomised, double-blind, double-dummy, multi-centre study compared the safety and efficacy of emtricitabine 200 mg once daily versus 3TC 150 mg twice daily, each in combination with d4T and either EFV or NVP in treatment-naïve HIV infected patients in the Republic of South Africa.[35,36] Patients were stratified to receive either NVP or EFV based on baseline HIV RNA levels below or above 10^5 copies/mL (Table 8). Overall, 200 patients were enrolled in Stratum 1/2, and 50 patients were enrolled in Stratum 3. This differentiation of treatment by stratum was on FDA advice and was due to the absence of conclusive data to support the efficacy of NVP in patients with HIV-RNA >100,000 copies/ml.[36]

Table 8: Study 302 Treatment Stratification by Baseline HIV RNA Level[36]

Stratum	Baseline HIV RNA	Treatment Regimen
1	≥ 5,000 and ≤ 20,000 copies/ml	FTC or 3TC + d4T + NVP
2	> 20,000 and ≤100,000 copies/ml	FTC or 3TC + d4T + NVP
3	> 100,000 copies/ml	FTC or 3TC + d4T + EFV

Abbreviations: FTC, emtricitabine; 3TC, lamivudine; d4T, stavudine; NVP, nevirapine; EFV, efavirenz

The primary assessment of efficacy was the proportion of randomised and treated patients with durable suppression of plasma HIV RNA less than the limit of assay detection (LOD) through 48 weeks of study; HIV RNA levels ≤ 50 and ≤ 400 copies/ml were considered co-primary endpoints. Non-inferiority was considered to have been demonstrated if the lower 95% confidence interval around the difference between the two treatments in the proportion of patients whose plasma HIV RNA was ≤ 400 copies/ml at Week 48 was within –12.5%. Patients who discontinued the study or were lost to follow-up were considered failures (NC = F).[36]

Overall, 71% in the emtricitabine and 77% in the 3TC group completed treatment up to week 48. Twenty patients in each treatment group withdrew due to VF (defined as either loss of virologic response [plasma HIV RNA > 400 copies/ml on two consecutive measurements after achieving a plasma HIV RNA ≤400 copies/ml] or lack of virological response [failure to achieve plasma HIV RNA ≤ 400 copies/ml by Week 12]) with genotypic evidence of resistance, and 22 patients in each treatment group withdrew due to adverse events prior to completing week 48. Demographic characteristics were well balanced between treatment groups. Overall, 59% of patients were female, with 77 % of Black origin and a mean age of 33 years. The mean baseline HIV-RNA was 4.5 $\log_{10}$ copies/ml. Approximately 15% of patients had baseline HIV-RNA > 100,000 copies/ml and mean CD4 count of 389 cells/mm^3. Approximately 82% were stratified to NVP and about 78% did not have any history of HIV related events.[36]

In the ITT and as-treated populations, slightly lower proportions of patients in the emtricitabine treatment group achieved and maintained suppression of plasma HIV RNA < 400 copies/ml through Week 48. Also, the stratum-adjusted 95% CI showed that the lower limit was > 12.5% for the ITT population. However, proportions of patients that achieved HIV RNA <50 copies/ml were very similar between treatments and the lowest 95% CI was –12.6% (Table 9).[36]

Table 9: Primary Efficacy Endpoint at Week 48[36]

Endpoint	FTC + d4T + EFV or NVP (N=234)	3TC+ d4T + EFV or NVP (N=234)	Difference* (FTC – 3TC)	95% CI*
% ≤ 400 copies/ml (ITT; NC=F)	145/225 (64.4%)	164/230 (71.3%)	-6.9	-15.5, 1.6
% ≤ 400 copies/ml (AT)	145/168 (86.3%)	164/182 (90.1%)	-5.4	-11.8, 1.0
% ≤ 50 copies/ml (ITT; NC=F)	136/226 (60.2%)	148/232 (63.8%)	-3.8	-12.6, 5.1
% ≤ 50 copies/ml (AT)	136/168 (81.0%)	148/182 (81.3%)	-1.6	-9.6, 6.3

Abbreviations: FTC, emtricitabine; 3TC, lamivudine; CI, confidence interval; NC=F, non-completer = failure analysis; AT, as treated analysis

*All differences and CIs are stratum-adjusted.

Please refer to the Summary on the Comparative Evidence on Safety (Section 11.3.1.1) for a discussion of the safety results of this study.

Study GS-01-934

This ongoing Phase 3, randomized, open-label, active-controlled, multi-centre, 144 week non-inferiority study is designed to evaluate the safety and efficacy of a once daily regimen containing emtricitabine 200 mg + tenofovir DF 300 mg plus EFV 600 mg vs. AZT 300 mg/3TC 150 mg twice daily plus EFV 600 mg once daily in treatment-naïve HIV-infected patients with HIV RNA >10,000 copies/mL.[37-39] Patients were stratified on the basis of CD4 cell counts (< or ≥200 cells/mm^3). A total of 517 patients were enrolled and randomized in a 1:1 ratio; 511 patients were treated with study medication. Please see Table 10 below for baseline characteristics of the ITT population, excluding two treatment-experienced patients (n = 509), as presented in Gallant et al.

Table 10: Baseline Characteristics (ITT)[39]

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

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

The primary efficacy endpoint of the study was the percentage of patients with HIV RNA <400 copies/mL at Week 48 as defined by the FDA TLOVR algorithm using the modified ITT (mITT) analysis set (excluding baseline NNRTI-R; n = 487). A total of 22 patients (11 from each group) had baseline NNRTI-R mutations and were excluded from the primary endpoint analysis at Week 48 according to the FDA's recommendation.

Week 48 Results

Data analyses at Week 48 showed that significantly more patients in the emtricitabine + tenofovir DF group vs. the AZT/3TC group achieved and maintained HIV RNA <400 and <50 copies/mL (TLOVR in mITT population).[39] The difference in the proportion of patients who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the AZT/3TC group in this open-label study.[38] In addition, increases in CD4 cell count at Week 48 were significantly higher in the emtricitabine + tenofovir DF group (Table 11). Treatment outcomes through Week 48 for the mITT population are provided in Tables 11 and 12.

Table 11: Clinical Efficacy Endpoints at Week 48[37-39]

Parameter	Population	FTC + TDF + EFV (n = 244)	AZT/3TC + EFV (n = 243)	*P*-Value (95% CI)
HIV RNA <400 copies/mL (%)	mITT n = 487	84	73	.002 (+4, +19)
HIV RNA <50 copies/mL (%)	mITT n = 487	80	70	.02 (+2, +17)
Mean Change in CD4 Cell Count (cells/mm^3)	Available n = 363	+190	+158	.002 (+9, +55)
Mean Change in CD4 Percentage (%)	Available n = 363	11	10	.02

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

Table 12: TLOVR Treatment Outcomes at Week 48 (mITT)[38,40]

Outcome at Week 48	FTC + TDF + EFV (n = 244)	AZT/3TC + EFV (n = 243)
Responder* (%)	84	73
Virologic failure† (%)	2	4
Rebound (%)	1	3
Never Suppressed (%)	0	0
Change in ART (%)	1	1
Death (%)	<1	1
Discontinued due to AE (%)	4	9
Discontinued for Other Reasons‡ (%)	10	14

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

*Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48.

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

‡Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation, and other reasons.

Through 48 weeks, 7 patients in the emtricitabine +tenofovir DF group and 5 patients in the AZT/3TC group experienced a new CDC Class C event.[38]

Week 48 analysis demonstrated that 12 patients in the emtricitabine + tenofovir DF group and 23 patients in the AZT/3TC group met the resistance analysis criteria (confirmed HIV RNA ≥400 copies/mL at Week 48 or at early discontinuation, or viral rebound). No patient in this study developed K65R by Week 48 and M184V/I developed less frequently in the emtricitabine + tenofovir DF group than the AZT/3TC group, but this did not achieve statistical significance. Of the two patients in the emtricitabine + tenofovir DF group who had virologic rebound, one had a wild-type virus and one had an EFV-resistance mutation. Of the seven patients who had virologic rebound in the AZT/3TC group, all had EFV-resistance mutations, five had the

M184V/I mutation, and one had a TAM. The differences in the frequency of viral rebound between the two groups were not statistically significant (P =.11).[39] Please see Table 13 for more detailed information.

Table 13: Resistance Development at Week 48 in all Patients with ≥400 HIV RNA Copies/mL (mITT)[38,39,41]

Parameter	FTC + TDF + EFV (n = 244)	AZT/3TC + EFV (n = 243)
Genotyping Population	12	23*
Any Resistance Mutation	9	17
Any EFV-R[†]	9	16
Any M184V/I	2	7
EFV-R + M184V	2	6
Any TAMs	0	1
K65R[‡]	0	0
Wild-type	3	5

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine; EFV-R, efavirenz resistance; TAMs, thymidine analogue mutations; mITT, modified intent-to-treat (22 patients with baseline NNRTI resistance mutations were excluded from the analysis)

*Genotyping of one patient failed due to technical reasons.

[†]K103N developed in 21/25 patients. Other NNRTI-R mutations that developed included K101E, K103E, V108I/M, V179D, Y188H, G190A/S/E, P225H, M230L.

[‡]In addition, no K65R developed in the patients with baseline NNRTI-R.

Week 96 Results

Ninety-six week efficacy data excludes patients with baseline NNRTI-R mutations and those who completed the Week 48 study with HIV-1 RNA levels below the limit of quantification but did not consent to participate in the study extension from Weeks 48-96. Results showed that significantly more patients in the emtricitabine + tenofovir DF arm than those in the AZT/3TC arm achieved and maintained HIV-1 RNA <400 copies/mL (75% vs. 62%, respectively; P = .004). Virologic rebound and discontinuation rate due to adverse events were observed in <1% and 5% of patients in the emtricitabine + tenofovir DF arm as compared to 5% and 11% of those in the AZT/3TC arm, respectively (P = .007 and P = .023, respectively). In addition, the mean absolute increase in CD4 cell count from baseline was higher in the emtricitabine + tenofovir DF arm (270 versus 237 cells/mm^3; P = .036). The proportions of patients who achieved and maintained HIV RNA <50 copies/mL were 67% in the emtricitabine + tenofovir DF arm vs. 61% in the AZT/3TC arm (P = .16).[42] Please see Table 14 below for more data on the treatment outcomes at Week 96.

Table 14: TLOVR Treatment Outcomes at Week 96 (96 Week Efficacy Patients)[42]

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

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

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

†P = .004

‡P = .007

Through Week 96, 14 patients in the emtricitabine + tenofovir DF arm and 29 patients in the AZT/3TC arm met the resistance analysis criteria (all VF patients with confirmed HIV RNA ≥400 copies/mL at Week 48 or at early discontinuation). No patient in either arm developed the K65R mutation. However, development of the M184V/I mutation was significantly less in the emtricitabine + tenofovir DF arm than the AZT/3TC arm (P = .036).[42] Please see Table 15 for more detailed information.

Table 15: Resistance Development through Week 96[42]*

Parameter	FTC + TDF + EFV (n = 244)	AZT/3TC + EFV (n = 243)
Genotyping Population	14	29†
Wild Type	4	7
Any Resistance	10	20
EFV-R	10	18
M184V/I	2	9‡
TAMs	0	1
K65R	0	0

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; AZT/3TC, zidovudine/lamivudine; EFV-R, efavirenz resistance; TAMs, thymidine analogue mutations

*Excludes patients with baseline NNRTI-R mutations (n = 487)

†P = .017

‡P = .036

Study M02-418

This was a randomized, open-label, multi-centre study designed to compare LPV/r 800/200 mg once daily (n = 115) vs. LPV/r 400/100 mg twice daily (n = 75) with a background regimen of tenofovir DF 300 mg once daily and emtricitabine 200 mg once daily in HIV-infected antiretroviral-naïve patients with HIV RNA >1,000 copies/mL.[43-45] At baseline, patients had a mean age of 39 years (range: 19-75), 46% were non-Caucasian, and 22% were female. Mean baseline CD4 cell count was 260 cells/mm^3 (range: 3-1,006) and mean baseline HIV RNA level was 4.8 $\log_{10}$ copies/mL (range: 2.6-6.4 $\log_{10}$ copies/mL).[44]

Results at Weeks 48 and 96 revealed that similar proportions of patients in both groups achieved HIV RNA <50 copies/mL. In addition, increases in CD4 cell counts were similar between the two groups. Detailed data on ITT, TLOVR and observed analysis are presented in Table 16 below.

Table 16: Results at Week 48 and 96[43,45]

Parameter	Week 48			Week 96		
	Once daily (n = 115)	Twice daily (n = 75)	*P*-value	Once daily (n = 115)	Twice daily (n = 75)	*P*-value
% of subjects with HIV RNA <50 copies/mL						
ITT (NC = F) Analysis	70%	64%	.43	57%	53%	.58
TLOVR Analysis	71%	65%	.42	57%	55%	NA
Observed Data	NA	NA	NA	89% (n = 74)	91% (n = 44)	NA
Mean Change in CD4 Cell Count (cells/mm^3)	+185	+196	.67	+244 (n = 74)	+264 (n = 45)	NA

Abbreviations: ITT, Intent-to-treat; NC = F, non-completer = failure; TLOVR; time to loss of virologic response; NA, not available

Resistance testing results were available in 23 patients, 15 in the once daily group and eight in the twice daily group.[43] Genotypic analysis did not identify any LPV/r or tenofovir DF resistance mutations. Resistance to emtricitabine was identified in a total of four patients (three in the once daily group and one in the twice daily group) (Table 17).

Table 17: Genotypic Testing through Week 96[43]

Parameter	Once Daily (n = 115)	Twice Daily (n = 75)
Patients Qualifying for Resistance Testing	17	11
Available Genotypic Results (n)*	15	8
TDF-Resistance (K65R)	0/15 (0%)	0/8 (0%)
Emtricitabine-Resistance (M184V/I)	3/15 (20%)	1/8 (12%)
Lopinavir-Resistance	0/15 (0%)	0/8 (0%)

Abbreviation: TDF, tenofovir disoproxil fumarate

*Samples from patients with HIV RNA >500 copies/mL between Week 12-96 were submitted for genotypic testing.

ANRS 1207/IMEA 025 Study

This open-label, single-arm pilot study was designed to evaluate the antiviral activity and tolerance of a once daily combination regimen of emtricitabine + tenofovir DF + EFV in 40 HIV-1 infected treatment-naïve patients with CD4 cell count <350 cells/mm^3 in West Africa.[46] The primary endpoint was the percent of patients with plasma HIV RNA < 400 and < 50 copies/mL at week 48 based on ITT analysis. Tolerance assessment included all adverse events reported by the patient or observed by the investigator and the rate of adverse events ≥ Grade 3. At baseline, the median values for HIV RNA level and CD4 count were 5.3 $\log_{10}$ copies/mL (range: 2.6-5.9) and 122 cells/mm^3 (range: 3-310), respectively.

At week 48, 85% and 72.5% of patients had plasma HIV RNA < 400 and < 50 copies/mL, respectively (ITT analysis), and the mean CD4 count increase from baseline to week 48 was 185 ± 85 cells/mm^3.[46] Overall treatment adherence was assessed at six time points through week 48; 0%-8% of patients reported missing at least one drug over the last three days and 8%-12% of patients reported missing at least one drug over the last month. The main reasons reported for lack of adherence were forgetting (63%), travelling (16%), and other disease (8%).[46]

Pooled Virology Analysis for Emtricitabine in Clinical Trials FTC-301, 903 and GS-01-934

To characterize the frequency of the M184V/I mutation development in treatment-naïve patients experiencing virologic failure on regimens containing either emtricitabine or 3TC in combination with another NRTI and EFV, McColl et al.[47] analyzed data from three recent Phase 3 clinical trials: FTC-301 (emtricitabine + ddI + EFV vs. d4T + ddI + EFV), 903 (3TC + tenofovir DF + EFV vs. 3TC + d4T + EFV), and GS-01-934 (emtricitabine + tenofovir DF + EFV vs. 3TC + AZT + EFV). Analysis were done using the TLOVR algorithm, which included VF patients who were classified as rebound, never suppressed, or had another antiretroviral agent added, and clinical virology algorithm, which included all TLOVR VF patients and patients who failed the regimen due to adverse events, lost of follow-up, or for other reasons. These two pooled analyses showed that by Week 48, significantly lower rate of M184V/I mutation development was seen with patients treated with emtricitabine as compared to those treated with 3TC. Please see Table 18 below for more detailed information.

Table 18: Summary of M184V/I Development at Week 48 in Pooled Emtricitabine-Treated or Lamivudine-Treated Populations[47]

TLOVR Analysis	M184V/I Development by Week 48		*P*-Value
	Emtricitabine	Lamivudine	
In All Treated Patients	3/522 (0.6%)	20/841 (2.4%)	.015
In Virologic Failure Patients	3/14 (21.4%)	20/37 (54%)	.058
Clinical Virology Algorithm Analysis			
In All Treated Patients	5/522 (0.96%)	27/841 (3.2%)	.009
In Virologic Failure Patients	5/26 (19.2%)	27/76 (35.5%)	.147

Abbreviation: TLOVR, time to loss of virologic response

Treatment-experienced patients

Clinical efficacy in antiretroviral treatment-experienced HIV-infected patients has been demonstrated in multiple clinical trials that have evaluated the use of emtricitabine in combination with other antiretrovirals including d4T, AZT, ddI, tenofovir DF, and EFV.

Study FTC-303 (Pivotal Trial)

Study FTC-303 was a 48-week, randomised, open-label, multi-centre non-inferiority study comparing emtricitabine (200 mg once daily) to 3TC (150 mg twice daily), in combination with d4T (40 mg twice daily) or AZT (300 mg twice daily) and a PI or NNRTI in 440 patients who were on a 3TC-containing triple-antiretroviral regimen for at least 12 weeks prior to study entry and had HIV-1 RNA < 400 copies/mL.[25,26,48] Patients were randomised 1:2 to either continue therapy with 3TC or to switch to emtricitabine; the stable background regimen was maintained. The primary endpoint was the percentage of patients with plasma HIV-1 RNA levels ≤ 50 copies/mL and those with levels ≤ 400 copies/mL after 48 weeks using the Roche Amplicor® Ultrasensitive Test. The secondary endpoint was the percentage of patients experiencing confirmed VF due to loss of response, which was defined as a rebound of HIV RNA > 400 copies/mL from previously reduced levels on two consecutive visits during the study.

At study entry, the median duration of prior antiretroviral in the emtricitabine and 3TC arms was 37.3 and 31.3 months, respectively. The median plasma HIV RNA was 1.7 $\log_{10}$ copies/mL, and the mean CD4 cell count was 527 cells/mm^3. Results at Week 48 are shown in Table 19. An ITT analysis was used, with patients who did not complete the study counted as treatment failures. There were no statistically significant differences between emtricitabine and 3TC treatment arms.

Table 19: Results at Week 48[25]

Parameters	**Emtricitabine + AZT/d4T + NNRTI/PI (n = 294)**	**3TC + AZT/d4T + NNRTI/PI (n = 146)**
Responder*	77% (67%)	82% (72%)
Virologic Failure†	7%	8%
Death	0%	<1%
Study Discontinuation		
Due to Adverse Events	4%	0%
For Other Reasons‡	12%	10%

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

The mean change increase from baseline in CD4 cell count was 29 cells/mm^3 for the emtricitabine arm and 61 cells/mm^3 for the 3TC arm. Through Week 48, 2 patients (0.7%) in

the emtricitabine group experienced a new CDC Class C event, compared to 2 patients (1.4%) in the 3TC group.[25]

A total of 7% (n = 21) of patients in the emtricitabine arm and 8% (n = 11) of patients the 3TC arm had VF (defined as patients who failed to achieve virologic suppression or HIV RNA rebounded to >400 copies/mL after achieving virologic suppression).[26] Genotypic analysis was attempted retrospectively on these patients; however, due to the low plasma HIV RNA level at baseline, M184 sequence was only obtained for 18 emtricitabine and four 3TC patients. Of these patients, 16 and three, respectively, had the M184V mutation at baseline.

Patients with HIV RNA ≥50 copies/mL at baseline failed more frequently than those with HIV RNA <50 copies/mL at baseline (39% vs. 5%, *P* <.0001). Among patients with HIV RNA ≥50 copies/mL at baseline, those with the M184V mutation at baseline were significantly more likely to fail than those without the mutation (50% vs. 9%; *P* =.0277). These findings were similar between both treatment arms.[49]

This study demonstrated that simplifying a regimen from 3TC 150 mg twice daily to emtricitabine 200 mg once daily, while keeping all other medications the same, is equally safe and effective after 48 weeks of follow-up. Patients with HIV RNA < 400 copies/mL at Week 48 were invited to participate in Study 350, a long-term study of Study FTC-303.

Study 350 (Study 303 Extension)

This is an open-label extension of Study FTC-303. Patients participating in this study are those with plasma HIV RNA < 400 copies/mL at Week 48 who continued emtricitabine (n = 215) or switched from 3TC to emtricitabine (n = 74).[26,27]

Through 4 years of follow-up, with a median duration on emtricitabine of 140 weeks, the KM probability of VF was 11%.[26,27] There was no significant difference in the overall probability of VF between patients originally randomized to the emtricitabine or 3TC groups. Thus, after 4 years of therapy, the majority of patients continued to have HIV RNA <400 copies/mL without treatment-limiting adverse events.

Supportive Studies

Study ANRS-099 (ALIZE)

This was a randomized, open-label, multi-centre, 48-week study comparing the continued treatment of a stable PI-based regimen (2 NRTIs + 1 PI) versus switching to a once daily combination regimen containing emtricitabine (200 mg), ddI (250 mg if <60 kg , 400 mg if ≥60 kg), and EFV (600 mg).[50] Participants in this study were naïve to NNRTI, no previous use of ddI monotherapy, 3TC-based HAART if treated with NRTIs alone before PI-based regimen, plasma HIV RNA <400 copies/mL for at least 6 months, and have CD4 cell counts ≥100 cells/mm^3 at screening. Important baseline characteristics were similar among both groups as shown in Table 20.

Table 20: Baseline Characteristics[50]

Characteristic	Once Daily Arm (FTC + ddI + EFV) (N = 178)	PI Arm (2NRTI + PI) (N = 177)
Plasma HIV RNA <50 copies/mL (%)	92	89
Median CD4 cell count (cells/mm^3)	509	547
Median duration of HAART (months)	36	34

Abbreviations: FTC, emtricitabine; ddI, didanosine; EFV, efavirenz; PI, protease inhibitor; HAART, highly active antiretroviral therapy

At Week 48, 90.5% of patients in the once daily arm and 87.6% of patients in the continued PI arm maintained HIV RNA <400 copies/mL (ITT). Furthermore, the probability of the proportion of patients with HIV RNA <50 copies/mL was significantly higher in the once daily arm than the continued PI arm (87% vs. 79% respectively; P <.05) using KM estimates. VF, defined as HIV RNA ≥400 copies/mL from two consecutive measurements during baseline to Week 48, was observed in 17 patients (10%) enrolled in the once daily arm compared to 22 patients (12%) in the continued PI arm (P =.50). The median increase in CD4 cell count was 16 cells/mm^3 for the once daily arm and 15 cells/mm^3 for the continued PI arm (P = .68) .[50]

Long Term Safety and Efficacy Study (extension from the ALIZE)

Molina et al. conducted a separate open-label, cohort study to further assess the once daily (once daily arm) combination (emtricitabine + ddI + EFV) of the ALIZE study (48-week) to evaluate the long-term safety and efficacy of these patients.[51] Patients who completed the initial 48-week follow-up could continue on the once daily regimen for an additional 24 months (total of 36 months). Enrolled patients were followed for VF (first occurrence of HIV RNA ≥ 400 copies/mL), median change of CD4 cell count from baseline, Grade 4 adverse events, lipodystrophy, and metabolic disorders.

Of the patients (N = 178) who were initially randomized to the once daily arm from the 48-week ALIZE study, 152 (85%) patients participated in the extended evaluation, in which patients continued the once daily regimen and were followed for a total of 36 months. Eighty-three percent (147/178) of the patients reached the 36-month endpoint. At month 36, the probability of VF occurred in 23% of the patient and the median increase in CD4 cell count (from baseline) was 44 cells/mm^3 (P <0.05), which were derived from patients with a CD4 cell count of 535 cells/mm^3 measured at study entry.[51]

Switch Study (extension from the ALIZE)

Molina et al. conducted a switch study in which patients from the PI arm (N = 152) of the ALIZE trial could either continue the PI regimen of AZT+3TC+PI or switch to the once daily regimen of emtricitabine+ddI+EFV to evaluate the haematological benefit between the two regimen.[52] The subset of patients enrolled were on a stable PI-containing HAART regimen with HIV RNA < 400 copies/mL. At week 48, patients were evaluated for change from baseline in haemoglobin, neutrophils, CD4 cell count, and HIV RNA levels.

A total of 152 patients from the PI arm in the ALIZE study were followed for 48 weeks. Of these patients, 78 continued on the current PI regimen while 74 patients switch to the once daily regimen. Results at Week 48 showed that the change in CD4 cell count (+9 PI arm,+34 once daily arm) and HIV RNA levels < 400 copies/mL (90% PI arm, 95% once daily arm) were also greater in the once daily arm compared to the PI arm; however, these changes were not statistically significant.[52]

COMET Study

The COMET study was a 24-week, prospective, multi-centre, single-arm, phase 4 clinical trial designed to evaluate the impact of switching virologically suppressed (HIV RNA <400 copies/mL on AZT/3TC + EFV for ≥8 weeks), treatment-experienced, HIV-infected patients from a twice daily regimen containing AZT/3TC + EFV to a once daily regimen containing emtricitabine and tenofovir DF fixed dose combination tablet + EFV.[53] The objective of this study was to characterize the risks and potential benefits of switching from a AZT/3TC + EFV regimen to a emtricitabine and tenofovir DF fixed dose combination tablet + EFV regimen. Assessments included in this study were efficacy, safety, tolerability, adherence and quality of life (Symptoms, Adherence, and Treatment Satisfaction [SATS] questionnaire) at baseline and at Weeks 4, 12, and 24 post-switch. Quality of life was also assessed at baseline and Week 24 using the SF-36 survey instrument. The study protocol was also later amended to include fasting lipid profile, for which data through 24 weeks are available for 160 patients.

A total of 411 patients were enrolled into the study, however, 9 patients were not evaluable (8 patients enrolled at a single site which did not enter any data, one patient was not dosed). Thus, post-baseline results are currently available for 402 patients who received at least one dose of study drug, including 30 patients who discontinued early from the study.[53] At baseline, 83% of these patients were male and 67% were Caucasian. Their median age was 43 years (interquartile range [IQR]: 38 – 49 years). These patients had been taking AZT/3TC or AZT + 3TC for a median of 3.9 years (IQR: 1.9 - 5.5 years) with 90% having taken AZT/3TC for >1 year. Reasons for switching to the emtricitabine and tenofovir DF fixed-dose combination tablet regimen included regimen simplification (84.3%), AZT/3TC -related adverse events (3.2%), and both (12.4%).[53]

Week 24 efficacy data are available for 366 patients; please refer to Table 21 for detailed HIV RNA results, based on both ITT, missing = exclude (M = E) and ITT, missing = failure (M = F) analyses, as well as CD4 results.

Table 21: HIV RNA and CD4 Results at Week 24[53]

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

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

Results from a validated questionnaire of patient-reported (n = 352) SATS demonstrated that by Week 24, significantly fewer patients complained of bothersome adverse events, fatigue, and nausea/vomiting (all $P < .001$, McNemar test) as compared to baseline. In addition, compared to baseline, significantly more patients reported being "very satisfied" with the emtricitabine and tenofovir DF fixed-dose combination tablet regimen in regards to general satisfaction with the emtricitabine and tenofovir DF fixed-dose combination tablet regimen, convenience/simplicity, tolerability, and control of the their HIV (all $P < .001$, McNemar test). Furthermore, when treatment adherence was assessed by SATS questionnaire, the number of patients who reported full (100%) adherence on ≥ 95% of days was significantly higher at Week 24 versus baseline for both 1-week and 1-month recall periods (both $P = .002$). According to pill count analysis, 87% of patients achieved ≥ 95% adherence to the study regimen.[53]

10.3.2 Summary of Data in HIV-infected Paediatric Patients

Pharmacokinetic Data in Paediatric Patients

Study FTC-105

This was a Phase 1, multi-centre, open-label trial designed to evaluate the safety, tolerability, and pharmacokinetics of single doses of emtricitabine at two dose levels, 60 mg/m^2 and 120 mg/m^2, in an oral solution formulation (10 mg of emtricitabine/mL) in HIV-infected children <18 years of age.[54] All patients received the first dose of emtricitabine at the level of 60 mg/m^2. If this dose was tolerated, a second dose of emtricitabine at the level of 120 mg/m^2, up to a maximum of 200 mg, was administered following a washout period of ≥ 4 days. Children

≥6 years of age who tolerated the 120 mg/m^2 dose and could swallow solid dosage forms also received a second dose of 120 mg/m^2 (up to a maximum of 200 mg) emtricitabine to the nearest 25 mg in a capsule formulation after a second washout period of ≥ 4 days. Eligible patients could be antiretroviral naïve or experienced. With the exception of 3TC therapy, all children who were receiving concomitant antiretroviral medication at the time of study enrolment continued their usual regimen without interruption. Patients who were receiving 3TC at study enrolment were required to withhold 3TC dosing for 12 hours before and until 24 hours after each dose of emtricitabine, and were required to have a plasma HIV-1 RNA level of > 400 copies/mL at the screening evaluation. Almost all children were withheld food intake for one hour before and after the emtricitabine dose, and 80% of children were withheld food intake until two hours post dose.

Plasma pharmacokinetics were evaluated up to 48 hours after each emtricitabine dose using non-compartmental methods. A total of 25 patients with a median age of 7.6 years (range: 1.8-17.8 years) and a median weight of 24.5 kg (range: 10.2-76 kg) were enrolled in the study. All 25 patients completed the first two doses evaluating the emtricitabine oral solution (60 and 120 mg/ m^2) doses and 12 patients completed the third dose of 120 mg/m^2 emtricitabine in capsule form. Mean plasma concentration-versus-time profiles at each dose level were similar across age groups. In addition, the emtricitabine apparent total body clearance (CL/F) values normalized to body surface area (BSA) and the overall pharmacokinetic properties of emtricitabine were comparable among children of all age groups. Emtricitabine pharmacokinetics parameter estimates following each dose are summarized by age group in Table 22.

Table 22: Emtricitabine Pharmacokinetic Parameters by Age[54]*

Age Group	n	Dose and Formulation	C_{max} (μg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (h•μg/mL)	$T_{1/2}$ (hr)	CL/F (mL/min/ 1.73m^2)
22-23 months	2	60 mg/m^2, solution	1.02±0.78	1.54±0.65	4.81±2.19	6.43±0.21	401±184
		120 mg/m^2, solution	1.51±0.53	1.52±0.66	8.13±0.25	11.93±1.11	426±15
2-5 years	8	60mg/m^2, solution	1.13±0.36	1.17±0.60	4.32±1.14	9.51±2.53	434±158
		120 mg/m^2, solution	1.99±0.47	1.20±0.54	7.70±2.17	9.65±2.71	484±139
6-12 years	8	60 mg/m^2, solution	1.06±0.34	0.96±0.66	4.45±1.23	10.37±2.85	417±118
		120 mg/m^2, solution	1.91±0.83	1.54±1.13	8.02±2.51	11.7±2.3	465±126
		120mg/m^2, capsule†	2.49±0.87	1.85±0.42	10.93±3.49	10.17±3.5	338±84
13-17 years	7	60 mg/m^2, solution	0.89±0.26	1.61±0.49	4.15±0.75	9.29±3.53	427±69
		120 mg/m^2, solution	1.55±0.26	1.58±0.53	8.45±3.42	11.08±2.17	442±119
		120mg/m^2, capsule†	2.15±0.53	1.32±0.5	9.38±3.03	10.77±0.88	387±112

Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time at which maximum concentration occurred; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero with extrapolation to infinite time; $T_{1/2}$, plasma half-life; CL/F/1.73, apparent total body clearance normalized to body surface area

*Values are means ± standard deviations

†n = 6 for the capsule formulation.

Based on the area under the plasma concentration-time curve ($AUC_{0-\infty}$) data obtained following the 120 mg/m^2 dose, along with the body weight data, it was projected that a 6 mg/kg dose (up to a maximum of 200 mg) of emtricitabine would produce plasma AUCs of emtricitabine in children comparable to that of adults given a 200 mg dose. The 6 mg/kg dose was therefore selected as the paediatric dosage for evaluation in studies PACTG 1021 (FTC-202) and FTC-203.

The relative bioavailability for the capsule formulation (compared to an equal dose in solution) averaged ~120% over the age range of 6 to 17 years but was variable between subjects. The slightly higher bioavailability of the capsule formulation was not thought to be expected to result in clinically significant differences in plasma emtricitabine exposure when switching between formulations. In a bioequivalence study in adults, the relative bioavailability of emtricitabine oral solution was ~80% compared to emtricitabine capsules.[25]

Study FTC-116

This study was designed to evaluate the pharmacokinetics and safety of multiple dose administration of emtricitabine over the first three months of life in infants born to HIV-1 infected mothers, and to determine how the maturing kidney function in neonates under three months of age may affect emtricitabine pharmacokinetics.[55] The study enrolled 22 neonates born to women with confirmed HIV-1 infection who were thus exposed to HIV in utero. Testing for HIV-1 DNA and RNA was conducted at birth and at Weeks 6, 12, and 24; positive test results excluded the infant from the study. All study subjects were Black South Africans, 16 of 22 whom were male, with a mean birth weight of 2.9 kg (range 2.0-3.8 kg). Beginning within 24 hours of birth, each infant received six weeks of AZT therapy for HIV prophylaxis. The infants were enrolled into one of four groups in which they were to receive two 4-day courses of emtricitabine at a dose of 3 mg/kg daily. Each course was separated by a period of ≥ 2 weeks, and the start time for each course was staggered between the groups to ensure a continuum of assessment data over the first three months of life. Pharmacokinetic evaluations using standard non-compartmental methods were performed 48 hours following the last dose of emtricitabine for both courses.

Twenty infants completed the two courses of emtricitabine and both pharmacokinetic assessments. The exposure to emtricitabine as indicated by AUC in neonates receiving 3 mg/kg emtricitabine once daily was in the range of paediatric patients ≥ 3 months of age receiving the recommended dose of 6 mg/kg daily and adults receiving the recommended dose of 200 mg daily. The emtricitabine AUC decreased with increasing age over the first three months of life, correlating with an increase in CL/F. Pharmacokinetic parameters are summarized by age group in Table 23.

Table 23: Mean (%CV) Emtricitabine Pharmacokinetic Parameters on Day of Assessment by Age

Parameter	Age Group 0-21 Days (n = 18)	Age Group 22-42 Days (n = 10)	Age Group 43-90 Days (n = 12)
Mean Age (Range)	13 days (5-21)	33 days (23-42)	55 days (43-81)
C_{max} (µg/mL)	1.601 (28)	1.416 (23)	1.639 (52)
C_{min} (µg/mL)	0.126 (41)	0.065 (42)	0.091 (89)
AUC_{0-24} (hr•µg/mL)	13.44 (28)	8.55 (15)	9.27 (48)
$T_{1/2}$ (hr)	12.5 (23)	11.5 (36)	11.8 (21)
CL/F (mL/min)	13 (31)	22 (19)	29 (64)

Abbreviations: %CV, coefficient of variation; C_{max} = maximal plasma concentration; C_{min} = minimal plasma concentration; AUC_{0-24} = area under the plasma concentration time curve from time zero to 24; $T_{1/2}$ = plasma half-life; CL/F = total body clearance; hr = hours; n = number of pharmacokinetic assessments performed

Overall, this study found that the emtricitabine dose of 3 mg/kg daily in neonates < 3 months old produced similar emtricitabine AUC to those doses previously shown to be safe and efficacious in HIV-infected children ≥ 3 months old and in adults.

Clinical Trials in Paediatric Patients

Study FTC-203

FTC-203 was a Phase 2, open-label, multi-centre study conducted to assess the pharmacokinetic, antiviral activity, and safety profiles of emtricitabine in combination with other antiretroviral agents in treatment-naïve (HIV RNA ≥5,000 but ≤500,000 copies/mL) and experienced (on a stable 3TC-containing regimen for ≥3 months and HIV RNA ≤400 copies/mL) HIV-infected children aged 3 months to 17 years old.[56-60] Treatment-naïve patients were given emtricitabine (6 mg/kg once daily, up to a maximum of 200 mg once daily as capsules or 240 mg once daily as oral solution), d4T twice daily, and LPV/r twice daily. Treatment-experienced patients were switched from 3TC to emtricitabine and their background antiretroviral regimen could be changed at the investigator's discretion. Please refer to Table 24 for detailed characteristics at baseline and Table 25 for Week 48 and Week 96 efficacy results.

Table 24: Study FTC-203 - Baseline Characteristics[57,58]

Parameter	**Treatment-Naïve (n = 71)**	**Treatment-Experienced (n = 45)**	**Total (N = 116)**
Ethnic Origin, n (%) Black Caucasian Other	 63 (89%) 0 8 (11%)	 17 (38%) 4 (9%) 24 (53%)	 80 (69%) 4 (3%) 32 (28%)
Mean (range) Age (years)	5 (0.3-12)	7 (1-16)	6 (0.3-16)
Median (range) HIV RNA (log_{10} copies/mL)	5 (3.8-5.9)	1.7 (1.7-3.7)	4.5 (1.7-5.9)
Median (range) CD4 Cell Count (cells/mm^3)	714 (186-1,886)	1,045 (360-2,650)	817 (186-2,650)
Median (range) prior ART (years)	NA	4 (1-14)	NA
CDC Disease Category, n(%) B C	 35 (50%) 13 (19%)	 28 (62%) 9 (20%)	 63 (54%) 22 (19%)

Abbreviations: ART, antiretroviral therapy; NA, not applicable

Table 25: Study FTC-203 - Efficacy Results at 48 and 96 Weeks[57-60]

Parameter	Treatment-Naïve (n = 71)	Treatment-Experienced (n = 45)
Week 48 Results (ITT, NC = F)		
HIV RNA ≤400 copies/mL	93%	87%
HIV RNA ≤50 copies/mL	78%	78%
Week 48 Results (ITT, M = F)		
HIV RNA ≤400 copies/mL	90%	81%
HIV RNA ≤50 copies/mL	74%	68%
Week 96 Results (ITT, M = F)		
HIV RNA ≤ 400 copies/mL	76%	69%
HIV RNA ≤ 50 copies/mL	65%	55%

Abbreviations: ITT, NC = F, intent-to-treat, non-completer equals failure analysis; ITT, M = F, intent-to-treat, missing equals failure analysis

Eight patients (5 treatment-naïve and 3 treatment-experienced) had confirmed VF at Week 48.[58,60] Genotypic analysis of paired viral samples obtained at baseline and at the time of VF showed the M184V mutation developed in 4 out of 5 treatment-naïve patients. No treatment emergent mutations were observed in the treatment-experienced patients who had VF. The overall incidence of M184V mutation at Week 48 was 3.5% (4/116).

PACTG 1021 (FTC-202)

This is an ongoing, Phase 1/2 open-label study designed to evaluate the pharmacokinetics, safety, and efficacy of a once daily regimen of emtricitabine (6 mg/kg once daily, maximum of 200 mg once daily), ddI (240 mg/m^2, maximum of 400 mg once daily) and EFV (adjusted by body weight to a maximum of 600 mg once daily as capsules or 720 mg once daily as oral liquid) in treatment-naïve paediatric patients infected with HIV.[61,62] A total of 37 children and young adults between the ages of 3-21 years were enrolled (median 10.5 years); there were 21 subjects in the Age 3-12 year old subset and 16 subjects in the Age 13-21 year old subset. At baseline, the overall median HIV RNA level and CD4 cell count were 47,775 copies/mL and 310 cells/µL, respectively. The median baseline percentage of CD4 cells was 17%.[61,62] Results at 24 and 96 weeks are shown in Table 26.

Table 26: PACTG 1021 Study - Efficacy at Weeks 24 and 96[61,63]

Parameter	Week 24 n = 37	Week 96 n =37
HIV RNA <400 copies/mL (n)*	81%	(32/37) 86%
HIV RNA <50 copies/mL (n)*	78%	(26/37) 70%
Median Change in CD4 Cell Count (cells/µL)†	+254 (n = 33)	+329 (n = not specified)

*Intent-to-treat: discontinued = failure.

†Results are "as treated" because no measurements were made after the cessation of study drug.

11. Comparative evidence on safety:

11.1 Estimate of Patient Exposure To Date

Clinical Trials[25]

More than 2,000 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 1-3 clinical trials.

Post Marketing[64]

Cumulative patient exposure to emtricitabine as a single agent, and not a part of fixed-dose combinations, since first marketing approval in the US on 02 July 2003 to 30 June 2006 is estimated to be 52,039 patient-years of treatment (Table 27). For cumulative patient exposure to emtricitabine as part of the emtricitabine and tenofovir disoproxil fumarate fixed dose combination tablet, please refer to Table 11 (Section 11.1) of the application for inclusion of the emtricitabine and tenofovir disoproxil fumarate fixed dose combination tablet on the WHO Model List of Essential Medicines.

Patient exposure to marketed emtricitabine is estimated from sales data. For emtricitabine capsules, the number of bottles sold during the reporting period was multiplied by 30 to provide the number of tablets sold. As emtricitabine is taken as a once daily dose, the total numbers of tablets were divided by 365.25 to provide an estimate of patient-years of treatment. For emtricitabine oral solution, the number of bottles sold during the reporting period was multiplied by 170 (as each bottle contains 170 mL oral solution) and divided by 24 (as the recommended dose of emtricitabine 10 mg/mL oral solution is 240 mg [24 mL] once daily for adults), then divided by 365.25 to provide an estimate of patient-years of treatment. It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure, due to the accumulation of drug stocks at distributors.

Table 27: Cumulative Estimated Patient Exposure to Marketed Emtricitabine through 30 June 2006[64]

Geographic Area	Cumulative Patient-Years of Exposure*
USA	32,254
Europe	
France	8,047
Germany	2,449
United Kingdom and Ireland	2,088
Distributor Region EEA†	1,754
Portugal	786
Spain	1,475
Italy	1,691
Mid Mediterranean‡	352
Latin America§	712
Japan	131
Australia	300
TOTAL	**52,039**

*Cut-off for sales data is at the end of each calendar month
†Austria, Baltics, Belgium, Czech Republic, Hungary, Poland, Russia, Slovak Republic, Slovenia, Netherlands, Sweden and Switzerland
‡Greece, Cyprus, Malta, Turkey, Israel, Egypt, Lebanon, Oman, Saudi Arabia, United Arab Emirates, Kuwait and India
§Argentina and Mexico

11.2 Descriptions of adverse effects/reactions

11.2.1 Warnings and Precautions for Use[25]

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including emtricitabine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with emtricitabine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients Co-infected with HIV and Hepatitis B Virus (HBV)

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

Patients with Impaired Renal Function

Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of emtricitabine is recommended for patients with impaired renal function.

Drug Interactions

The potential for drug interactions with emtricitabine has been studied in combination with AZT, indinavir, d4T, famciclovir, and tenofovir DF. There were no clinically significant drug interactions for any of these drugs

Fat Redistribution

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

Immune Reconstitution Syndrome

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: 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 (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

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

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

<u>*Pregnancy*</u>

Pregnancy Category B

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at AUC approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, emtricitabine should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry
To monitor fetal outcomes of pregnant women exposed to emtricitabine, an antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1–800–258–4263.

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

<u>*Paediatric Use*</u>

Safety and effectiveness in paediatric patients below the age of 3 months have not been established.

The safety and efficacy of emtricitabine is supported by data from three open-label, non-randomized clinical studies in which emtricitabine was administered to 169 HIV-1 infected treatment naïve and experienced (defined as virologically suppressed on a 3TC containing regimen for which emtricitabine was substituted for 3TC) patients between 3 months and 21 years of age. Patients received once-daily emtricitabine oral solution (6 mg/kg to a maximum of 240 mg/day) or emtricitabine capsules (a single 200 mg capsule once daily) in combination with at least two other antiretroviral agents. Patients had a mean age of 7.9 years (range 0.3–21), 49% were male, 15% Caucasian, 61% Black, and 24% Hispanic. Patients had a median baseline HIV RNA of 4.6 $\log_{10}$ copies/mL (range 1.7-6.4) and a mean baseline CD4 cell count of 745

cells/mm^3 (range 2-2,650). Through 48 weeks of therapy, the overall proportion of patients who achieved and sustained an HIV RNA <400 copies/mL was 86%, and <50 copies/mL was 73%. The mean increase from baseline in CD4 cell count was 232 cells/mm^3 (-945, +1512). The adverse event profile observed during these clinical trials was similar to that of adult patients, with the exception of a higher frequency of hyperpigmentation

Geriatric Use

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

11.2.2 Effects on ability to drive and use machines

No studies of the effect of emtricitabine on the ability to drive or use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with emtricitabine.

11.2.3 Overdose

There is no known antidote for 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. If overdose occurs the patient should be monitored for signs of toxicity, and standard supportive treatment applied as necessary.

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

11.3 Undesirable effects:

11.3.1 Results from Controlled Clinical Studies

More than 2,000 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 1-3 clinical trials. Assessment of adverse events from two pivotal studies (FTC-301A and FTC-303) showed that the most commonly reported adverse events are headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity. Overall, adverse events and laboratory abnormalities observed in clinical trials were similar between emtricitabine and control treatment groups. All adverse events were reported with similar frequency in the emtricitabine

and control treatment groups, with the exception of skin discoloration, which was reported with higher frequency in the emtricitabine treated group.

Recently, pooled safety data from three emtricitabine controlled clinical trials (FTC-301A, FTC-302, and FTC-303) revealed that skin discoloration, manifested by hyperpigmentation mainly on the palms and/or soles, was generally mild, asymptomatic and of little significance. The mechanism is unknown. Additional data on the incidence of skin discoloration in emtricitabine clinical trials is included below.

Incidence of Skin Discoloration in Emtricitabine Clinical Trials

Mondou et al. analyzed the incidence of skin discoloration in adult patients infected with HIV or HBV who received emtricitabine 200mg once daily for 48-weeks from 4 randomized, controlled, multi-centre Phase 3 clinical trials.[65] In the emtricitabine HIV trials (Studies FTC-301A, FTC-303, and FTC-302), the control groups were d4T or 3TC with the background regimen of ddI + EFV in Study FTC-301A and d4T with nevirapine (NVP) or EFV in Study FTC-302 while the treatment-experienced patients continued their entry background regimen in Study FTC-303.[25,28,30,48] In Study FTCB-301, an emtricitabine HBV monotherapy trial, the control group was placebo.[66]

In these studies, skin discoloration was spontaneously reported as an adverse event by the investigators with no pre-specified definition and no uniform or special evaluation required by the protocols. A total of 33/981 cases (3%) and 7/746 cases (1%) of skin discoloration were reported by the investigators in the emtricitabine group and the control group, respectively. In all studies, skin discoloration, generally manifested by hyperpigmentation on the palms and/or soles, was observed in a higher percentage of patients enrolled into the emtricitabine arms (2-6%) as compared to the control arms (<1-1%). The overall incidence was low but more frequent in non-Caucasian patients (Tables 28 and 29).

Table 28: Incidence of Skin Discoloration in Adults[65]

Study	**FTC-301A***		**FTC-303**		**FTC-302***		**FTCB-301**	
Treatment	FTC	d4T	FTC	3TC	FTC	3TC	FTC	Placebo
N	286	285	294	146	234	234	167	81
Cases (%)	10 (3%)	1 (< 1%)	5 (2%)	2 (1%)	14 (6%)	3 (1%)	4 (2%)	1 (1%)

Abbreviations: FTC, emtricitabine; d4T, stavudine; 3TC, lamivudine

**P* <.02 Fisher's Exact Test for the difference in incidence between treatment arms.

Table 29: Incidence of Skin Discoloration in Emtricitabine-Treated Adults by Ethnic Group[65]

Ethnic Group n/N (%)	FTC-301A (N = 286)	FTC-303 (N = 294)	FTC-302 (N = 234)	FTCB-301 (N = 167)	Total (N = 981)
Black	7/52 (13%)	4/59 (7%)	14/208 (7%)	0/3 (0%)	25/322 (8%)
Asian	0/3 (0%)	0/3 (0%)	0/2 (0%)	4/97 (4%)	4/105 (4%)
Hispanic	2/77 (3%)	1/34 (3%)	0/0 (0%)	0/0 (0%)	3/111 (3%)
Caucasian	1/136 (1%)	0/193 (0%)	0/24 (0%)	0/65 (0%)	1/418 (<1%)

Skin discoloration was generally observed on palms and/or soles of feet. In a few cases, discoloration was observed on the tongue, nails, or other sites.[65] For some patients, discoloration was observed in more than one location. Please refer to Table 30 for the incidence of skin discoloration in emtricitabine-treated adults by locations. There was no association between skin discoloration and other dermatologic or systemic conditions.

Table 30: Incidence of Skin Discoloration in Emtricitabine-Treated Adults by Locations[65]

Location* n (%)	FTC-301A (N = 286)	FTC-303 (N = 294)	FTC-302 (N = 234)	FTCB-301 (N = 167)	Total (N = 981)
Hands and/or feet	8 (3%)	2 (1%)	11 (5%)	1 (1%)	22 (2%)
Nails	1 (<1%)	0 (0%)	0 (0%)	2 (1%)	3 (<1%)
Tongue	0 (0%)	0 (0%)	2 (1%)	1 (1%)	3 (<1%)
Other site	2 (1%)	3 (1%)	2 (1%)	1 (1%)	8 (1%)

*Discoloration could occur at more than one location.

Twenty-nine of the 33 reported cases (88%) of skin discoloration in emtricitabine-treated patients were mild in severity at diagnosis and 4 cases (12%) were of moderate severity. In all cases, the event did not progress beyond the grade observed at diagnosis. None of the cases were considered serious and no patient discontinued the HIV studies due to skin discoloration. The median time to the onset of skin discoloration in the emtricitabine-treated patients in the HIV and HBV trials was 88 days (range: 10 to 490 days) and 70 days (range: 12 to 131 days), respectively. Overall, discoloration resolved with continuation of emtricitabine treatment in 5 HIV-infected patients and with discontinuation of emtricitabine in 2 HBV-infected patients; the ongoing cases remained mild to moderate.[65] No association of skin discoloration with clinically important systemic reactions was found. Furthermore, there are no other associated risk factors that would aid in a hypothesis regarding its etiology.

11.3.1.1 Summary of Safety Data in HIV-infected Adult Patients

Pivotal studies (Studies FTC-301A and FTC-303)

48-Week results

Study FTC-301A was a 48-week, randomized, double-blind, multi-centre study comparing emtricitabine 200 mg once daily to d4T 40 mg twice daily with a back ground regimen of ddI

(400 mg once daily if ≥60 kg, 250 mg once daily if <60 kg) and EFV (600 mg once daily)[25,28-30] At baseline, the median HIV RNA level was 4.9 $\log_{10}$ copies/mL and the mean CD4 cell count was 318 cells/mm^3; 38% had HIV RNA level >100,000 copies/mL and 31% had CD4 cell counts <200 cells/mL.

Study FTC-303 was a 48-week, randomized, open-label, multi centre study comparing emtricitabine (200 mg once daily) to 3TC (150 mg twice daily), in combination with d4T (40 mg twice daily) or AZT (300 mg twice daily) and a PI or NNRTI in 440 adult patients who were on a 3TC-containing triple-antiretroviral regimen for at least 12 weeks prior to study entry and had HIV RNA <400 copies/mL.[25,26,48] Patients were randomized 1:2 to either continue therapy with 3TC or to switch to emtricitabine; the stable background regimen was maintained. At study entry, the median duration of prior antiretroviral therapy was 27.6 months, the median plasma HIV RNA was 1.7 $\log_{10}$ copies/mL, and the mean CD4 cell count was 527 cells/mm^3.

The most common adverse events that occurred in adult 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 due to these events. All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the emtricitabine treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.[25] A summary of emtricitabine treatment-related adverse events in studies 301A and 303 is provided below (Table 31).

Table 31: Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥ 3% of Emtricitabine-Treated Patients in Either Study FTC-301A or FTC-303 (0-48 Weeks)[25]

Adverse Event	Study FTC-303		Study FTC-301A	
	FTC + AZT/d4T + NNRTI/PI (n = 294)	3TC + AZT/d4T+ NNRTI/PI (n = 146)	FTC+ ddI + EFV (n = 286)	d4T + ddI + EFV (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%
Paresthesia	5%	7%	6%	12%
Respiratory				
Increased Cough	14%	11%	14%	8%
Rhinitis	18%	12%	12%	10%
Skin				
Rash Event*	17%	14%	30%	33%

Abbreviations: AZT, zidovudine; d4T, stavudine; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; 3TC, lamivudine; ddI, didanosine; EFV, efavirenz

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

In Study FTC-301A, the number of patients who experienced serious adverse event was not statistically different between the two groups, with an overall incidence of 8% (24/286) in the emtricitabine group and 14% (39/285) in the d4T group (P =0.13).[29] Additionally, at Week 24, the probability of developing a treatment-limiting adverse event through Week 60 was statistically greater in the d4T group (15%) versus the emtricitabine group (7%) (P =.005). With the exception of cough and skin discoloration, fewer adverse events were noted in the emtricitabine group versus the d4T group. Pancreatitis (n = 4) and symptomatic

hyperlactatemia/lactic acidosis (n = 7) were observed only in the d4T group. Skin discoloration was observed in 10 patients (3%) (n = 9 for grade 1, n = 1 for grade 2) in the emtricitabine group and one patient (grade 1) in the d4T group.

In Study FTC-303, the frequency of adverse events was comparable between the two treatment groups and the majority of adverse events were of mild or moderate severity (77% emtricitabine, 80% 3TC). The percentage of patients who experienced a serious adverse event was similar between the two treatment groups (10% emtricitabine, 9% 3TC), but all serious adverse events occurred with a frequency of 2% or less. Skin discoloration occurred in 1.7% of patients in the emtricitabine group, versus 1.4% in the 3TC group, and was generally mild and asymptomatic.

Laboratory abnormalities in these studies occurred with similar frequency in the emtricitabine and comparator groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 32 below.

Table 32: Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Emtricitabine-Treated Patients in Either Study FTC-301A or FTC-303 (0-48 Weeks)[25]

Laboratory Abnormalities	Study FTC-303		Study FTC-301A	
	FTC + AZT/d4T + NNRTI/PI (n = 294)	3TC + AZT/d4T + NNRTI/PI (n = 146)	FTC + ddI + EFV (n = 286)	d4T + ddI + EFV (n = 285)
Total	31%	28%	34%	38%
ALT (>5 x ULN)	2%	1%	5%	6%
AST (>5 x ULN)	3%	<1%	6%	9%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine Kinase (>4 x ULN)	11%	14%	12%	11%
Neutrophils (<750 mm^3)	5%	3%	5%	7%
Pancreatic Amylase (>2 x ULN)	2%	2%	<1%	1%
Serum Amylase (>2 x ULN)	2%	2%	5%	10%
Serum Glucose (<40 or >250 mg/dL)	3%	3%	2%	3%
Serum Lipase (>2 x ULN)	<1%	<1%	1%	2%
Triglycerides (>750 mg/dL)	10%	8%	9%	6%

Abbreviations: ULN, upper limit of normal; AST, alanine aminoaspartate; ALT, alanine aminotransferase; AZT, zidovudine; d4T, stavudine; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; 3TC, lamivudine; ddI, didanosine; EFV, efavirenz

Lipid Profile and Body Habitus Results in Study 301A

In order to evaluate changes in body habitus and lipid profiles in the emtricitabine and d4T treatment arms in study 301A, a fasting lipid profile and body measurements were obtained at baseline, every 12 weeks, and at each study visit until the last randomized patient completed the Week 48 evaluation. When the last randomized patient completed Week 48, a total of 260 patients (n = l27 for the emtricitabine arm and n = 133 for the d4T arm) had completed 72 weeks of the double-blind follow-up.

Lipid Profile

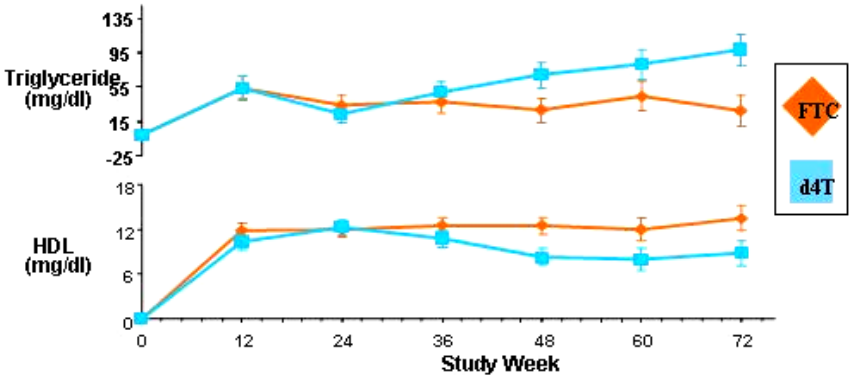
At Week 72, statistically significant differences between the two treatment arms were observed for changes from baseline in high density lipoprotein (HDL) cholesterol and fasting triglyceride levels. Compared to those in the d4T arm, patients in the emtricitabine arm had a significantly higher mean increase from baseline in HDL cholesterol level (+13.5 mg/dL for emtricitabine arm vs. +8.8 mg/dL for d4T arm, P =.001) and smaller mean increase from baseline in fasting triglycerides (+27.7 mg/dL for emtricitabine arm vs. +97.8 mg/dL for d4T arm, P <.001).[67] Mean changes from baseline in fasting serum lipid profile at Week 72 and in fasting serum HDL cholesterol and triglycerides by study week are shown in Table 33 and Figure 1, respectively.

Table 33: Study 301A Mean (95% CI) Changes from Baseline in Fasting Serum Lipids at Week 72[67]

Parameter	FTC + ddI + EFV (n = 127)	d4T + ddI + EFV (n = 133)	Δ FTC – d4T	*P*-Value
HDL Cholesterol (mg/dL)	+13.5	+8.8	+5.1	.001
LDL Cholesterol (mg/dL)	+17.4	+15.3	+1.6	.768
Total Cholesterol (mg/dL)	+37.2	+43.8	-7.3	.131
Triglycerides (mg/dL)	+27.7	+97.8	-60.6	<.001

Abbreviations: FTC, emtricitabine; d4T, stavudine; Δ FTC–d4T, difference between treatment arms; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Figure 1: Study 301A Mean (95% CI) Changes in Serum Lipids from Baseline by Study Week[67]



Body Habitus

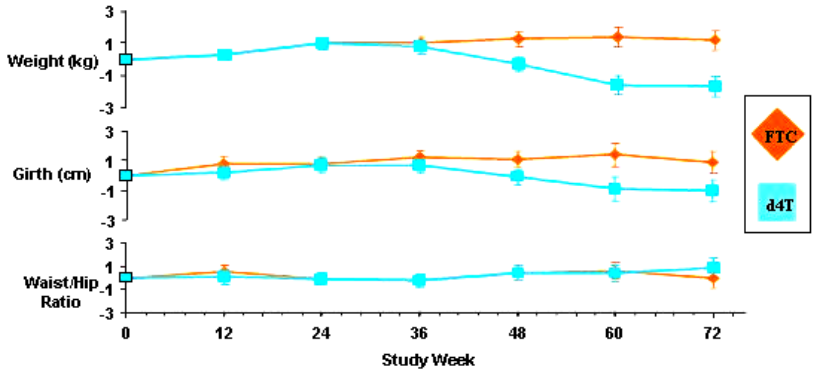
Patients in the d4T arm gained weight initially, but had significantly lower body weight (*P* <.001) and body mass index (BMI) (*P* <.001) compared to patients in the emtricitabine arm at Week 72.[67] Additionally, waist, hip and chest circumferences were significantly lower in patients in the d4T arm. Mean changes from baseline in body habitus at Week 72 and by study week are shown in Table 34 and Figure 2, respectively.

Table 34: Study 301A Mean (95% CI) Changes from Baseline in Body Habitus at Week 72[67]

Parameter	FTC + ddI + EFV (n = 127)	d4T + ddI + EFV (n = 133)	Δ FTC – d4T	*P*-Value
Body Weight (kg)	+1.2	-1.7	+3.0	<.001
Body Mass Index (kg/m^2)	+0.4	-0.6	+1.0	<.001
Abdominal Girth (cm)	+0.9	-0.8	+2.1	.002
Waist Circumference (cm)	+0.7	-1.0	+2.0	.015
Hip Circumference (cm)	+0.6	-1.7	+2.3	.003
Waist to Hip ratio (%)	0	+0.9	-1.3	.131
Chest Circumference (cm)	+0.8	-1.1	+1.7	.006

Abbreviations: FTC, emtricitabine; d4T, stavudine; Δ FTC–d4T, difference between treatment arms

Figure 2: Study 301A Mean (95% CI) Changes from Baseline in Body Habitus by Study Week[67]



Lipodystrophy

Lipodystrophy was reported by the investigators as an adverse event during the double-blind phase of the study. The incidence of lipodystrophy was reported in 6% of the patients in the d4T arm and in 0.4% of patients in the emtricitabine arm.[67]

Long-term Data (Study 350)

Study 350 is an open-label extension of Study 303. Patients participating in this study are those who had plasma HIV-1 RNA <400 copies/mL at Week 48 and who continued emtricitabine (n = 215) or switched from 3TC to emtricitabine (n = 74).[26,27]

During the 4 years of treatment, with a median duration of follow-up of 140 weeks, the KM probability of treatment-limiting adverse events requiring discontinuation of emtricitabine was 13%.[26,27] Most adverse events observed were mild to moderate in severity. The annualized incidences of Grade 3/4 laboratory abnormalities were: creatinine kinase (7%), hypertriglyceridemia (5%), aspartate aminotransferase (AST) (2%), neutropenia (2%), alanine aminotransferase (ALT) (2%), glucose (2%), and amylase (1%). A total of seven deaths occurred during the study, but none were considered related to the use of emtricitabine.

Supportive Studies

Study FTC-302

This randomised, double-blind, double-dummy, multi-centre study compared the safety and efficacy of emtricitabine 200 mg once daily versus 3TC 150 mg twice daily, each in combination with d4T and either EFV or NVP in treatment-naïve HIV infected patients in the Republic of South Africa.[35,36] The study enrolment was terminated by the Medicine Control Council of South Africa and the study was placed on clinical hold by the U.S. FDA. Subsequent analysis by the study investigators of the cause of the adverse events leading to termination of

enrolment revealed that the proportion of subjects with or without hepatotoxicity was similar between the emtricitabine and 3TC treatment groups (*P* =.3). The investigators concluded that the lack of hepatotoxicity in the EFV group and the balanced incidence between the emtricitabine and 3TC groups strongly suggests that the hepatotoxic agent was NVP.[35]

Through 48 weeks of double-blind follow-up, the overall incidence of adverse events was equivalent between the emtricitabine and 3TC treatment group, with the exception of accidental injury and gastroenteritis, which occurred more frequently in the 3TC group.[48] Most adverse events were mild to moderate in severity; the most frequently reported adverse events (>10% incidence in at least one treatment group) included infection, CNS event, headache, rash event, flu syndrome, diarrhoea, nausea, abdominal pain, vomiting, accidental injury, pain, pharyngitis, cough increased, fungal dermatitis, rhinitis, bronchitis, gastroenteritis, lymphadenopathy, back pain, and vaginal moniliasis. Grade 3 and 4 laboratory abnormalities that occurred with >1% incidence included elevations in ALT, AST, creatine kinase, alkaline phosphatise, total bilirubin, serum amylase, serum lipase, serum glucose, triglycerides, and neutrophils. All elevations of liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) occurred in subjects in the NVP stratum and none occurred in those subjects who received EFV.[48]

In an effort to identify risk factors and symptoms associated with the emergence of early hepatotoxicity in this study, Sanne et al. conducted an additional analysis of the safety data.[35] Overall, hepatotoxicity, occurred in 66/468 subjects (14% of subjects who received at least one dose of blinded study medication). All cases of hepatotoxicity occurred in the NVP group and none in the EFV group (*P* <.001), and the incidence of hepatotoxicity was comparable between the emtricitabine and 3TC treatment groups (15% and 19%, respectively; *P* =.28). The median onset of hepatotoxicity was on Day 29 (range: days 19-426).

Early hepatotoxicity, defined as treatment-emergent Grade 3 or 4 increases in ALT or AST within the first 12 weeks of therapy, occurred in 53/66 (80%) subjects (23/194 [11.9%] in the emtricitabine group and 30/191 [15.7%] in the 3TC group (*P* =.30). Of the 53 subjects who developed early hepatotoxicity, 15 (28%) permanently discontinued therapy within a median time of 3.5 days; hepatotoxicity resolved in 18 (34%) subjects while they were still receiving NVP. Multiple regression analysis also revealed that the proportion of subjects with or without hepatotoxicity was similar between the emtricitabine and 3TC treatment groups (*P* =.3).

Study GS-01-934

Week 48 Results

This ongoing Phase 3, randomized, open-label, active-controlled, multi-centre, 144 week non-inferiority study is designed to evaluate the safety and efficacy of a once daily regimen containing emtricitabine 200 mg + tenofovir DF 300 mg plus EFV 600 mg vs. AZT 300 mg/3TC 150 mg twice daily plus EFV 600 mg once daily in treatment-naïve HIV-infected patients with HIV RNA >10,000 copies/mL.[37-39] Patients were stratified on the basis of CD4+ cell counts (< or ≥200 cells/mm^3). A total of 517 patients were enrolled and randomized in a 1:1 ratio; 511 patients were treated with study medication.

The 48-week safety data are based on 511 patients who received at least one dose of study medication. The overall incidences of Grades 2-4 adverse events and laboratory abnormalities were similar between the two treatment groups and were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients receiving tenofovir DF or emtricitabine (Tables 35 and 36).[38] However, significantly fewer patients in the emtricitabine + tenofovir DF group, 4% compared to 9% of those in the AZT/3TC group, discontinued from the study due to adverse events (Table 37). In addition, no cases of anaemia were seen in the emtricitabine + tenofovir DF arm as compared to 6% (n = 14) of patients in the AZT/3TC arm who discontinued the study drug due to anaemia. Seven of these patients had received erythropoietin before discontinuation and seven received blood transfusions.[39]

Table 35: Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in ≥3% in Any Treatment Group (0-48 weeks)[38,40]

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

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

Table 36: Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group (0–48 Weeks)[38,40]

Laboratory Abnormality	TDF + FTC + EFV (n = 257)	AZT/3TC + EFV (n = 254)
Any ≥Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L; F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L; F: >170 U/L)	3%	2%
ALT (M: >215 U/L; F: >170 U/L)	2%	2%
Haemoglobin (<8 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophil (<750/mm^3)	3%	4%
Fasting Triglyceride (>750 mg/dL)	4%	2%

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

Table 37: Adverse Events Leading to Study Drug Discontinuation through Week 48[39,68]

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

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

*Occurring in ≥2 patient in either arm

†P =.02

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

Hyperpigmentation was confirmed or could not be ruled out in seven patients in the emtricitabine + tenofovir DF group vs. 4 in the AZT/3TC group (*P* =.54). All cases were mild in severity except for 1 case in the AZT/3TC group. No patient discontinued from the study due to hyperpigmentation.[39]

Renal safety profile was similar between the two groups, as measured by changes from baseline or maximum graded toxicity of serum creatinine or serum phosphorus concentrations. No confirmed graded abnormalities in serum creatinine or serum phosphorus were reported in the emtricitabine + tenofovir DF group; however, three patients in the AZT/3TC group had graded abnormalities. No cases of Fanconi's syndrome were reported in either group. Based on the Cockroft-Gault (CG) method, the median change from a baseline glomerular filtration rate (GFR) of 121 mL/min for both arms to Week 48 was −1 mL/min for the emtricitabine + tenofovir DF group (*P* =.660 vs. baseline) and +6 mL/min for the AZT/3TC group (*P* <.001 vs. baseline). Based on the modification of diet in renal disease (MDRD) method, the change from baseline in both groups was <−1 mL/min/1.73 mm^3.[37,39]

Regarding lipid parameters, at Week 48, the emtricitabine + tenofovir DF group had smaller mean increases in fasting triglycerides, total cholesterol, LDL, and HDL levels compared to the AZT/3TC group (Table 38).[37]

Table 38: Increase* in Fasting Lipid Parameters through Week 48[39]

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

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

Week 96 Results

Through Week 96, adverse events leading to drug discontinuation were significantly higher in the AZT/3TC arm than the emtricitabine + tenofovir DF arm (Table 39). Although the median GFR as estimated by the CG method was similar between the two arms (119 emtricitabine vs. 118 mL/min/1.73 m^2; *P* = .51), the median GFR as estimated by the MDRD method showed that the emtricitabine + tenofovir DF arm had a significantly lower rate than the AZT/3TC arm (100 vs. 108 mL/min/1.73 m^2; *P* = .006). However, no patient in the emtricitabine + tenofovir DF arm experienced confirmed Grade 1-4 renal abnormality as compared to two patients in the AZT/3TC arm (Table 40).

Table 39: Adverse Events Leading to Study Drug Discontinuation through Week 96[39]

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

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

Table 40: Serum Creatinine through Week 96[39]

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

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

Through Week 96, patients in the emtricitabine + tenofovir DF group had a significantly greater median increase from baseline in weight gain compared to those in the AZT/3TC group (2.7 vs. 0.5 kg; P <.001).[42] There was no significant difference in mean weights between the two groups at baseline and both groups had comparable weight gain at Week 48 (2.1 kg with emtricitabine + tenofovir DF versus 1.1 kg with AZT/3TC; P =.14).[39] Although baseline limb fat data by DEXA scan is not available, in a sub-study of patients in whom limb fat was measured via DEXA scans at Weeks 48 and 96, there was significantly more total limb fat in the emtricitabine + tenofovir DF arm than the AZT/3TC arm (Table 41).[39,42]

Table 41: Study GS-01-934: Median Total Limb Fat (kg) at Weeks 48 and 96[42]

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

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

†*P* <.001 for the difference between the emtricitabine + tenofovir DF arm vs. the AZT/3TC arm at Week 96

In a subset of patients with 48-week total limb fat data, median total limb fat for those in the emtricitabine + tenofovir DF arm increased significantly, from 7.4 kg at Week 48 to 8.1 kg at Week 96 (*P* = .01), as compared to a significant decrease for those in the AZT/3TC arm, from 6.0 kg at Week 48 to 5.5 kg at Week 96 (*P* = .001). The differences in total limb fat for these two groups at Week 96 were statistically significant (*P* < .001).[42]

Study M02-418

This was a randomized, open-label, multi-centre study designed to compare LPV/r 800/200 mg once daily (n = 115) vs. LPV/r 400/100 mg twice daily (n = 75) with a background regimen of tenofovir DF 300 mg once daily and emtricitabine 200 mg once daily in HIV-infected antiretroviral-naïve patients with HIV RNA >1,000 copies/mL.[43-45] At baseline, patients had a mean age of 39 years (range: 19-75), 46% were non-Caucasian, and 22% were female. Mean baseline CD4 cell count was 260 cells/mm^3 (range: 3-1,006) and mean baseline HIV RNA level was 4.8 $\log_{10}$ copies/mL (range: 2.6-6.4 $\log_{10}$ copies/mL).[44]

Available safety information has been gathered from the LPV/r 2005 Prescribing Information, and from study results presented by Molina et al in 2005.[43,44] Through Week 96, a total of 37% (42/115) of patients in the once daily group and 39% (29/75) of patients in the twice daily group discontinued the study, 17% and 9% due to adverse events, respectively. Gastrointestinal adverse events were the most common cause for discontinuation and were the most common adverse events overall (>3%). Diarrhoea was reported more frequently in the once daily vs. the twice daily group (17% vs. 5%; *P* =.014). The most common Grade 3/4 laboratory abnormalities (>3%) reported were increased ALT (>5 x upper limit of normal [ULN]), AST (>5 x ULN), triglyceride (>750 mg/dL), cholesterol (>300 mg/dL), and amylase (>2 x ULN) levels; no significant differences between the two groups were observed.

Acute renal failure (ARF) occurred in one patient in each group.[43] One patient was a 75-year-old male with a baseline creatinine clearance (CrCL) of 40 mL/min who was given full-dose tenofovir DF. Tenofovir DF dosing recommendations implemented after initiation of this study indicate that every other day dosing of tenofovir DF would have been most appropriate for this subject based on CrCL[40,43] He developed ARF at Week 34. Renal biopsy demonstrated non-specific changes with some renal tubules showing focal degenerative signs (cytoplasmic vacuolisation). The other patient was a 54-year-old male. ARF occurred at Week 38, requiring temporary haemodialysis. Renal biopsy demonstrated tubulo-interstitial nephritis. Both patients improved upon discontinuation of study drug; one discontinued all antiretrovirals and the other had tenofovir DF replaced with d4T 30 mg twice daily and the dose of emtricitabine was reduced to 200 mg every 72 hours as part of the HAART regimen.

At Week 96, significant increases from baseline in total cholesterol, HDL, LDL, and triglyceride levels were observed in both groups.[43] However, the mean 10-year coronary heart disease risk and analysis of risk rates by each category did not change significantly from baseline.[69]

Study ANRS-099 (ALIZE)

This was a randomized, open-label, multi-centre, 48-week study comparing the continued treatment of a stable PI-based regimen (2 NRTIs + 1 PI) versus switching to a once daily regimen containing emtricitabine (200 mg), ddI (250 mg if < 60 kg, 400 mg if ≥ 60 kg), and EFV (600 mg).[50] Patients enrolled in this study were naïve to NNRTI and ddI and had HIV RNA levels < 400 copies/mL for at least 6 months and CD4 cell counts ≥ 100 cells/mm^3 at screening. A total of 355 patients were assigned to either the once daily arm (N=178) or the PI arm (N=177).

At Week 48, the percentage of patients who had treatment discontinuation due to adverse events was similar between the two arms based on KM estimates (9% once daily arm vs. 10% PI arm, *P*=.8).[50] The incidence of grade 4 adverse reaction was also similar in both groups, 6% in the once daily arm vs. 5% in the PI arm (*P* =.64). However, more patients in the once daily arm experienced Grade 2-4 adverse events (48% vs. 38%; *P* = .06) and increases in liver aminotransferase levels (12 vs. 3) compared to the PI arm. There was a significant increase in the median HDL cholesterol level in the once daily arm compared to the PI arm (+7.8 mg/dL vs. +0.4 mg/dL; *P*<0.0001). In both groups, the proportion of patients with lipohypertrophy remained unchanged, yet lipoatrophy increased in the PI arm from 46% at baseline to 60% at 48 week while it remained steady in the once daily arm, 43% at baseline to 42% at 48 week.[50]

Long Term Safety and Efficacy Study (extension from the ALIZE)

Molina et al. conducted a separate open-label, cohort study to further assess the once- daily combination (emtricitabine + ddI + EFV) of the ALIZE study (48-week) to evaluate the long-term safety and efficacy of these patients.[51] Patients who completed the initial 48-week follow-up could continue on the once daily regimen for an additional 24 months (total of 36 months). Enrolled patients were followed for VF (first occurrence of HIV RNA ≥ 400 copies/mL), median change of CD4 cell count from baseline, grade 4 adverse events, lipodystrophy, and metabolic disorders.

Of the patients (N=178) who were initially randomized to the once daily arm from the initial 48-week ALIZE study, 152 (85%) patients decided to participate in the extended evaluation, in which patients continued the once daily regimen and were followed for a total of 36 months. Serious adverse events occurred in 29 (16%) patients before week 48 while 17 (10%) patients experienced a serious adverse event up to 36 months. Compared to baseline, the incidence of lipodystrophy (both lipoatrophy and lipohypertrophy) remained unchanged after 36 months and no patient discontinued study treatment because of worsening of lipoatrophy. There was a slightly statistically significant increase in plasma glucose level ($P<0.05$); however, only 2% to 5% had glucose levels > 126 mg/dL. There was no increase in total cholesterol or LDL levels, yet there was a 11.6 mg/dL increased in HDL levels from baseline up to month 36 ($P<.0001$). Furthermore, 42% of the patients had a HDL levels > 60 mg/dL at month 36, compared to 20% at baseline.[51]

Switch Study (extension from the ALIZE)

Molina et al. conducted a switch study in which patients from the PI arm (N=152) of the ALIZE trial could either continue the PI regimen of AZT+3TC+PI or switch to the once daily regimen of emtricitabine+ddI+EFV to evaluate the haematological benefit between the two regimen.[52] The subset of patients enrolled were on a stable PI-containing HAART regimen with HIV RNA < 400 copies/mL. At week 48, patients were evaluated for change from baseline in haemoglobin, neutrophils, CD4 cell count, and HIV RNA levels.

A total of 152 patients from the PI arm in the ALIZE study were followed for 48 weeks. Of these patients, 78 continued on the current PI regimen while 74 patients switch to the once daily regimen. Results at Week 48 showed that there was a significant improvement (from baseline to week 48) in haemoglobin and neutrophil count in the patients who switch to the once daily regimen while virological control was maintained. The change in haemoglobin was -0.4 vs. +0.7 ($P<.01$) and the change in neutrophil was +82 vs. +607 ($P<.03$) in the PI arm compared to the once daily arm, respectively.[52]

ANRS 1207/IMEA 025 Study

This open-label, single-arm pilot study was designed to evaluate the antiviral activity and tolerance of a once daily combination regimen of emtricitabine + tenofovir DF + EFV in 40 HIV-1 infected treatment-naïve patients with CD4 cell count <350 cells/mm^3 in West Africa.[46] The primary endpoint was the percent of patients with plasma HIV RNA < 400 and < 50 copies/mL at week 48 based on ITT analysis. Tolerance assessment included all adverse events reported by the patient or observed by the investigator and the rate of adverse events ≥ Grade 3. At baseline, the median values for HIV RNA level and CD4 count were 5.3 $\log_{10}$ copies/mL (range: 2.6-5.9) and 122 cells/mm^3 (range: 3-310), respectively.

In this study, tolerance assessment through 48 weeks included all adverse events reported by the patient or observed by the investigator as well as the rate of adverse events ≥ Grade 3.[46] Please see Table 42 below for a listing of Grade 2-3 treatment related adverse events; there was no Grade 4 treatment related adverse event. Reported Grade 3 or 4 laboratory abnormalities

through week 48 included: haemoglobin < 7g/dL (n = 1), neutrophils < 700 /mm^3 (n = 3), and AST/SGOT > 5 x ULN (n = 1).[46] There was a significant decrease in mean CrCL, from 92 mL/min at baseline to 80 mL/min (*P* = .03) at week 48. Although mean triglyceride levels decreased significantly from 74 mg/dL at baseline to 57 mg/dL (*P* = .04) at Week 48, a decrease in total cholesterol was not statistically significant (161 to 156mg/dL [*P* = .14]). Compared to baseline, an increase in body weight was observed in these patients at Week 48. Three patients died, one due to multifocal tuberculosis, one due to sepsis, and one of unknown cause.

Table 42: Treatment Related Adverse Events* through Week 48[46]

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

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

COMET

The COMET study was a 24-week, prospective, multi-centre, single-arm, phase 4 clinical trial designed to evaluate the impact of switching virologically suppressed (HIV RNA <400 copies/mL on AZT/3TC + EFV for ≥8 weeks), treatment-experienced, HIV-infected patients from a twice daily regimen containing AZT/3TC + EFV to a once daily regimen containing emtricitabine and tenofovir DF fixed dose combination tablet + EFV.[53] The objective of this study was to characterize the risks and potential benefits of switching from a AZT/3TC + EFV regimen to a emtricitabine and tenofovir DF fixed dose combination tablet + EFV regimen. Assessments included in this study were efficacy, safety, tolerability, adherence and quality of life (SATS questionnaire) at baseline and at Weeks 4, 12, and 24 post-switch. Quality of life was also assessed at baseline and Week 24 using the SF-36 survey instrument. The study protocol was also later amended to include fasting lipid profile, for which data through 24 weeks are available for 160 patients.

Results through Week 24 demonstrate that there were statistically significant improvements from baseline at Week 24 in haemoglobin level (31% had >1 g/dL increase from baseline), ANC, MCV, and fasting lipid parameters. Although a small but statistically significant decrease from baseline in HDL was observed, the total cholesterol/HDL ratio did not change.[53] Please refer to Table 43 and Figure 3 below for additional details on available safety results.

Table 43: Baseline and Change from Baseline in Selected Haematological Parameters at Week 24[53]

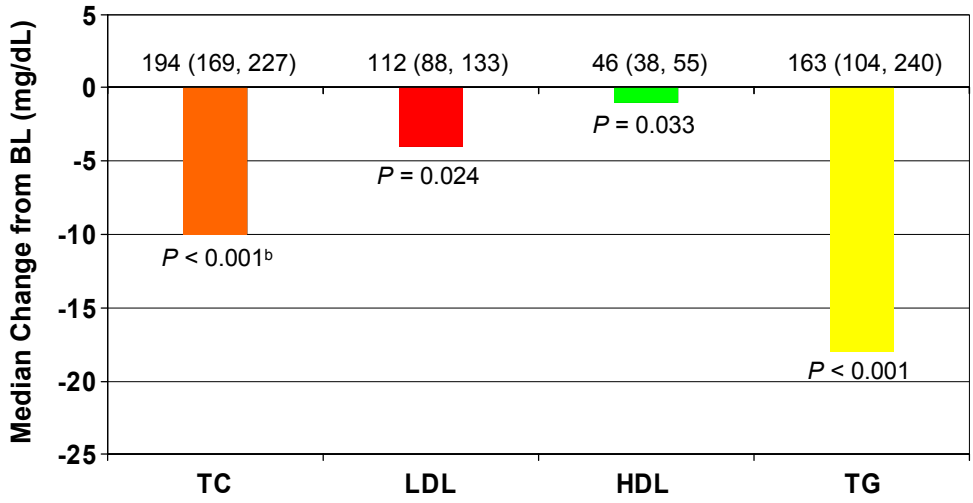
Parameter	Baseline Value	Change from Baseline at Week 24*	*P*-value†
Median (IQR) Haemoglobin (g/dL)	14.7 (13.6, 15.6)	0.6 (0.0, 1.2)	< .001
-↑ >1 g/dL from BL (% of patients) -↓ >1 g/dL from BL (% of patients)		31% 2%	
Median (IQR) ANC (cells/mm^3)	2789 (1991, 3784)	302 (-226, 1043)	< .001
Median (IQR)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

Abbreviations: IQR, interquartile range; BL, baseline; ANC, absolute neutrophil count; MCV, mean corpuscular volume

*Patients with both baseline and Week 24 data available.

†Wilcoxon Sign-Rank test

Figure 3: Fasting Lipids at Baseline (Median, IQR) and Change from Baseline at Week 24[53a]



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

b. Wilcoxon Sign-Rank test

Of the 30 patients who discontinued the study early, 2 (0.5%) were due to pregnancy, 4 (1%) for non-compliance/protocol violation, 9 (2%) due to loss to follow-up, 10 (2.5%) for adverse events (5 patients due to gastrointestinal effects [dry mouth, diarrhoea, nausea/vomiting, cramps, bloating], 3 due to central nervous system effects [EFV-related mental status change, headache, dizziness], and one each due to asthenia and abnormal liver function tests, 4 (1%) for others reasons (including withdrawal of consent), and 1 (< 0.5%) due to VF (HIV RNA ≥400 copies/mL on 2 occasions separated by ≥4 weeks).[53] Overall, nausea, diarrhoea, headache, and insomnia were the most commonly reported adverse events, occurring in 5%, 5%, 3%, and 3% of the patients, respectively.[53] Grade 3/4 laboratory abnormalities occurred in 1% of patients; 2 cases each of neutropenia and increase in triglycerides, and one case of thrombocytopenia. In

addition, Grade 2 confirmed increase in serum creatinine occurred in 1 patient, but returned to normal range while on treatment during the study. At baseline, the median (IQR) CrCL was 102 mL/min (87, 121); at Week 24, CrCL had a median change from baseline of -8 mL/min (IQR: -15, 0.0; $P < .001$).[53]

11.3.1.2 Summary of Safety Data in HIV-infected Paediatric Patients

<u>*Pharmacokinetic Data in Paediatric Patients*</u>

Study FTC-105

In Study FTC-105, emtricitabine doses were well tolerated by all subjects. Overall, 29 adverse events were reported in 15 of 25 (60%) patients. One serious adverse event occurred which was considered unrelated to the study drug by the investigator (moderate cellulitis following an insect bite that required hospitalization for parenteral antibiotics). Thirteen events occurring in seven patients (13/29, (45%) were considered to be drug-related.[54] Most of the adverse events (22/29, 76%) were reported during the first dosing period, when the lower dose of 60 mg/m^2 of emtricitabine was administered. Seven events were reported during the second dosing period, and no events were reported in the third dosing period.

The most frequently reported adverse events were vomiting (n = 5), diarrhoea (n = 4), abdominal pain (n= 3), and headache (n = 2). All drug-related adverse events were mild in intensity. Additionally, no subject experienced a treatment-emergent laboratory abnormality of ≥Grade 3 toxicity and none of the abnormal test results was considered to be clinically significant. The most frequently reported out of normal range parameters were haematologic, including low red blood cell count, low haemoglobin, increased MCV, low hematocrit, low ANC, and low white blood cell count. The most frequently reported out of normal range serum chemistries were increased cholesterol, increased lactate dehydrogenase, and increased total protein. The number of patients with laboratory values outside of the normal range was generally similar to the number observed at the screening evaluation.

Study FTC-116

This study was designed to evaluate the pharmacokinetics and safety of multiple dose administration of emtricitabine over the first three months of life in infants born to HIV-1 infected mothers, and to determine how the maturing kidney function in neonates under three months of age may affect emtricitabine pharmacokinetics.[55] The study enrolled 22 neonates born to women with confirmed HIV-1 infection who were thus exposed to HIV in utero. All study subjects were Black South Africans, 16 of 22 whom were male, with a mean birth weight of 2.9 kg (range 2.0-3.8 kg). Beginning within 24 hours of birth, each infant received six weeks of AZT therapy for HIV prophylaxis. The infants were enrolled into one of four groups in which they were to receive two 4-day courses of emtricitabine at a dose of 3 mg/kg daily. Safety evaluations including physical examination, vital signs, and laboratory blood testing were performed at birth, at Weeks 2, 6, 12, and 24, and before and after the last dose of each emtricitabine course.

Two of the 22 patients enrolled in this study did not complete the study; one patient was lost to follow-up following receipt of three doses of emtricitabine and one patient was discontinued from the study due to Grade 3 anaemia prior to beginning the first course of emtricitabine. [55] The only serious adverse events reported included bronchopneumonia and gastroenteritis in one patient, and bronchiolitis in one patient. All serious adverse events were assessed as unrelated to either emtricitabine or AZT. All 20 infants who completed the study were found to be HIV infection-free at 6 months postpartum. Overall, the study found that short (4-day) courses of emtricitabine dosed at 3 mg/kg daily were safe and well tolerated in neonates <3 months old.

Clinical Trials in Paediatric Patients

Assessment of adverse reactions is based on data from 169 HIV-infected paediatric patients who received emtricitabine through week 48. The adverse event profile in paediatric patients was generally comparable to that observed in clinical studies of emtricitabine in adult patients.[25]

Selected treatment-emergent adverse events, regardless of causality, reported in patients during 48 weeks of treatment were the following: infection (44%), hyperpigmentation (32%), increased cough (28%), vomiting (23%), otitis media (23%), rash (21%), rhinitis (20%), diarrhoea (20%), fever (18%), pneumonia (15%), gastroenteritis (11%), abdominal pain (10%), and anaemia (7%). Treatment emergent grade 3/4 laboratory abnormalities were experienced by 9% of paediatric
patients, including amylase >2.0 x ULN (n=4), neutrophils <750/mm^3 (n=3), ALT >5 x ULN (n=2), elevated creatinine phosphokinase (>4 x ULN) (n=2) and one patient each with elevated bilirubin (>3.0 x ULN), elevated gamma glutamyl transpeptidase (>10 x ULN), elevated lipase (>2.5 x ULN), decreased haemoglobin (<7 g/dL), and decreased glucose (<40 mg/dL).[25]

Study FTC-203

FTC-203 is an ongoing, Phase 2, open-label, multi-centre study conducted to assess the pharmacokinetic, antiviral activity, and safety profiles of emtricitabine in combination with other antiretroviral agents in treatment-naïve (HIV RNA ≥5,000 but ≤500,000 copies/mL) and experienced (on a stable 3TC-containing regimen for ≥3 months and HIV RNA ≤400 copies/mL) HIV-infected children aged 3 months to 17 years old.[56-59] Treatment-naïve patients were given emtricitabine (6 mg/kg once daily, up to a maximum of 200 mg once daily as capsules or 240 mg once daily as oral solution), d4T twice daily, and LPV/r twice daily. Treatment-experienced patients were switched from 3TC to emtricitabine and their background antiretroviral regimen could be changed at the investigator's discretion.

The median time on study was 96.1 weeks (range: 6-172 weeks).[58,60] Serious adverse events were reported in 19 (27%) treatment-naïve patients and in 5 (11%) treatment-experienced patients. Seven patients experienced an adverse event that was at least moderate in severity (Grade 2) and possibly or probably related to the study drug. These included two events of leucopoenia, one event of anaemia, one event of herpes zoster, one event of vomiting, one patient who experienced pancreatitis and pleural effusion, and one patient who experienced Grade 2 skin discoloration. All events were resolved except the skin discoloration event. The overall incidence of Grade 3/4 laboratory abnormalities was 9% (10/116); 7% (n = 5) in the

treatment-naïve and 11% (n = 5) in the treatment-experienced patients (Table 44). Two patients, one treatment-naïve and one treatment-experienced, discontinued the study before Week 48 due to adverse events (anaemia and pancreatitis). One study discontinuation occurred due to death (leukaemia).[57]

Table 44: Study FTC-203 - Incidence of Grade 3 or 4 Laboratory Abnormalities[58,60]

Laboratory Parameter	Treatment-Naïve (n = 71)	Treatment-Experienced (n = 45)
Overall Incidence*, n (%)	5 (7%)	5 (11%)
ALT	2 (2.8%)	1 (2.2%)
AST	1 (1.4%)	0
Haemoglobin	0	1 (2.2%)
Neutrophils	0	2 (4.4%)
Serum Amylase	1 (1.4%)	1 (2.2%)
Total Bilirubin	2 (2.8%)	0
Lipase	1 (1.4%)	0
Platelets	1 (1.4%)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase
*Each patient is counted no more than once at the maximum severity recorded for individual tests.

PACTG 1021 (FTC-202)

This is an ongoing, Phase 1/2 open-label study designed to evaluate the pharmacokinetics, safety, and efficacy of a once daily regimen of emtricitabine (6 mg/kg once daily, maximum of 200 mg once daily), ddI (240 mg/m^2, maximum of 400 mg once daily) and EFV (adjusted by body weight to a maximum of 600 mg once daily as capsules or 720 mg once daily as oral liquid) in treatment-naïve paediatric patients infected with HIV.[61,62] A total of 37 children and young adults between the ages of 3-21 years were enrolled (median 10.5 years); there were 21 subjects in the Age 3-12 year old subset and 16 subjects in the Age 13-21 year old subset. At baseline, the overall median HIV RNA level and CD4 cell count were 47,775 copies/mL and 310 cells/µL, respectively. The median baseline percentage of CD4 cells was 17%.[61,62]

Ten out of 37 patients discontinued study treatment, including 2 patients who discontinued due to Grade 2 or 3 rash and three study discontinuations that occurred due to virologic failure.[62] Two patients developed Grade 3 creatine phosphokinase elevation. One patient developed Grade 4 hypoglycaemia, which resolved after four days without a change in study treatment. These adverse events were judged to be possibly related to the study medications.[61] Two patients experienced Grade 3 symptoms (rash, dizziness) which were attributed to the regimen. These symptoms occurred during Week 1 and resolved spontaneously. No deaths or new Category C diagnoses occurred during the study.[62]

11.3.1.3 Summary of Safety Data in HIV-infected Pregnant Patients

There are no adequate and well-controlled studies on the use of emtricitabine in pregnant women. Available data on the use of emtricitabine in pregnant women is contained in the Antiretroviral Pregnancy Registry (APR).

Gilead is one of several pharmaceutical companies which sponsor the APR. The Registry provides an important source of pregnancy information on antiretroviral drugs, including emtricitabine. It is designed to provide an early signal of potential risks of birth defects associated with antiretroviral drugs. An independent advisory committee reviews the data periodically and establishes a consensus on the results at that time. Membership consists of specialists in maternal and fetal medicine, infectious disease, teratology, epidemiology and biostatistics. Gilead and the APR exchange information on reports of pregnancy in patients receiving emtricitabine. APR interim analysis reports are produced at 6-month intervals and the latest report was issued in June 2006 (data to 31 January 2006).[70] The APR report can be accessed at www.APRregistry.com. The data for emtricitabine is presented below.

A total of 38 first trimester exposure and 13 second/third trimester exposure prospective cases of live births involving exposure to emtricitabine were presented. There was one case of a birth defect following first trimester exposure and one case of a birth defect following second/third trimester exposure. No conclusions can be drawn for the emtricitabine prospective data as there are currently insufficient cases to compare the prevalence of birth defects to the general population.[70]

Retrospective cases of birth defects involving in utero exposure to emtricitabine were evaluated by the Registry experts, along with all other retrospective reports for other antiretroviral drugs. Retrospective birth defect cases involving emtricitabine are not distinguished from other retrospective cases in the APR report.[70]

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

12.1 Range of costs of the proposed medicine

12.1.1 United States of America

Emtricitabine was approved by the US FDA on 02 July 2003. The monthly treatment cost of emtricitabine varies among payers in the US. The following table indicates current pricing (Table 45).

Table 45: Wholesale Acquisition Cost of Emtricitabine in the US[*64]

Formulation	Package Size	Average Package Price (USD)	Average Unit Price (USD)	Defined Daily Dose
Capsules (200 mg)	30 capsules	$292.80	$9.76/cap	200 mg
Oral Solution (10 mg/mL)	170 mL	$69.14	$0.41/mL	240 mg

Abbreviation: USD, US dollar

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

12.1.2 Developing World

Although not available as a single-agent in the developing world, emtricitabine is available as part of the fixed-dose combination Truvada® (tenofovir DF + emtricitabine) through the Gilead Access Program. The Gilead Access Program is designed to expand access to the once-daily anti-HIV medications Truvada® (emtricitabine and tenofovir DF fixed dose combination tablet) and Viread® (tenofovir DF) in 97 developing countries. A 30-day supply of these medications can currently be obtained at the following prices: 26.25 USD for emtricitabine and tenofovir DF fixed dose combination tablet and 17.00 USD for tenofovir DF. Separate price structures are offered in middle income and developed world countries. This is based on ex-factory pricing, free on board from distribution facilities in either San Dimas, California, USA or Dublin, Ireland, not including shipping and handling fees. Gilead is seeking product registrations in all 97 countries to further improve access. Gilead has also established a partnership with Aspen Pharmacare in South Africa whereby tenofovir DF and tenofovir DF fixed dose combination tablets are manufactured to GMP standards in South Africa for use throughout the Access Program countries. This partnership supplements three other manufacturing sites and further boosts the ability to meet the growing demand for Gilead drugs. Gilead has also offered voluntary licenses to other generic manufacturing companies in India for the manufacture and distribution of tenofovir DF in the developing world countries. Both tenofovir DF and emtricitabine and tenofovir DF fixed dose combination tablet are included in the WHO List of Prequalified Medicines.

Gilead Clinical Research Collaborations and Partnerships

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

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

Table 46: Worldwide Marketing Authorization Status for Emtricitabine[64]

Territory	Approval Date	Launch Date
United States	02 July 2003 (28 September 2005*)	07 July 2003 (22 November 2005*)
European Union	24 October 2003	-
France	24 October 2003	08 January 2004 (21 February 2005*)
United Kingdom	24 October 2003	01 December 2003 (14 April 2005*)
Germany	24 October 2003	01 December 2003 (15 January 2005*)
Portugal	24 October 2003	24 January 2004 (21 January 2005*)
Ireland	24 October 2003	02 March 2004 (07 July 2005*)
Spain	24 October 2003	07 September 2004 (14 February 2005*)
Netherlands	24 October 2003	01 June 2004
Denmark	24 October 2003	05 March 2004
Sweden	24 October 2003	05 March 2004
Greece	24 October 2003	30 June 2004
Austria	24 October 2003	01 August 2004
Italy	24 October 2003	08 March 2005 (26 April 2005*)
Finland	24 October 2003	05 March 2004
Luxembourg	24 October 2003	30 September 2005
Belgium	24 October 2003	30 September 2005
Norway	24 October 2003	05 March 2004
Iceland	24 October 2003	05 March 2004
Czech Republic	01 May 2004	09 November 2005
Estonia	01 May 2004	Pending
Hungary	01 May 2004	Pending
Lithuania	01 May 2004	Pending
Latvia	01 May 2004	Pending
Malta	01 May 2004	Pending
Poland	01 May 2004	01 July 2005
Slovak Republic	01 May 2004	Pending
Slovenia	01 May 2004	Pending
Cyprus	01 May 2004	Pending
Israel	13 July 2004	Pending

Territory	Approval Date	Launch Date
Argentina	26 January 2004	31 August 2004
Switzerland	24 October 2004	02 February 2005
Mexico	06 September 2004	December 2004
Australia	21 December 2004	01 April 2005
Japan	23 March 2005	19 April 2005
New Zealand	27 October 2005	Pending
Canada	21 November 2005	15 March 2006

* Launch of Emtriva 10mg/ml oral solution.

14. Availability of pharmacopoieal standards:

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

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

WHO Model Formulary 2007

Description:

Emtricitabine is a synthetic nucleoside analogue of cytosine with activity against HIV-1 reverse transcriptase. It belongs to a class of antiretroviral agents called Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NRTIs).

How Supplied:

Emtricitabine is available as 200 mg capsule and 10 mg/mL oral solution.

Use:

Emtricitabine is indicated, in combination with other antiretroviral agents, for the treatment for HIV-1 infection in patients over three months of age.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 48 weeks duration in antiretroviral-naïve patients and antiretroviral-treatment-experienced patients who were virologically suppressed on an HIV treatment regimen.

In antiretroviral-treatment-experienced patients, the use of emtricitabine may be considered for patients with HIV strains that are expected to be susceptible to emtricitabine as assessed by genotypic or phenotypic testing.

Contraindications:

Emtricitabine is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

Warnings:

Lactic Acidosis/Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including emtricitabine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with emtricitabine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

Precautions:

Patients with Impaired Renal Function
Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of emtricitabine is recommended for patients with impaired renal function.

Drug Interactions
The potential for drug interactions with emtricitabine has been studied in combination with AZT, indinavir, d4T, famciclovir, and tenofovir DF. There were no clinically significant drug interactions for any of these drugs.

Fat Redistribution
Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy.

The mechanism and long-term consequences of these events are unknown. A causal relationship has not been established.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:
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 (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose)

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

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

Pregnancy and Lactation
Pregnancy Category B

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at AUC approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, emtricitabine should be used during pregnancy only if clearly needed.

The U.S. Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether emtricitabine is secreted into human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving emtricitabine.

To monitor fetal outcomes in pregnant women exposed to emtricitabine, an antiretroviral pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling the Antiretroviral Registry at 1-800-258-4263.

Paediatric Use
Safety and effectiveness in paediatric patients below the age of 3 months have not been established.

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

Dosage and Administration:
Due to a difference in the bioavailability of emtricitabine between the hard capsule and oral solution presentations, 240 mg emtricitabine administered as the oral solution should provide similar plasma levels to those observed after administration of one 200 mg emtricitabine hard capsule.

Adult Patients (≥ 18 years): one 200 mg capsule or 240 mg (24 mL) administered once daily orally.

Paediatric Patients (3 months through 17 years): 6 mg/kg up to a maximum of 240 mg (24 ml) once daily. For children weighing more than 33 kg who can swallow in intact capsule, one 200 mg capsule administered once daily orally.

Due to similarities between emtricitabine and 3TC, emtricitabine should not be coadministered with other drugs containing 3TC, including Combivir®, Epivir®, Epivir-HBV®, Epzicom™, Kivexa™, or Trizivir®. Emtricitabine should not be used with Truvada® or ATRIPLA® since it is a component of these products.

Dose Adjustment in Patients with Renal Impairment
Significant increased drug exposures were seen when emtricitabine was administered to patients with renal impairment. Therefore, the dosing interval of emtricitabine should be adjusted in patients with baseline CrCL < 50 ml/min. The safety and effectiveness of these dose adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients. Although there are insufficient data to recommend a specific dose adjustment of emtricitabine in paediatric patients with renal impairment, a dose reduction in the dose and/or an increase in the dosing interval similar to adjustment for adults should be considered.

Dose Adjustment in Adult Patients with Renal Impairment[25]

Formulation	**Creatinine Clearance (mL/min)**			
	≥ 50	**30-49**	**15-29**	**<15 or on HD***
Capsule (200 mg)	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours
Oral Solution (10 mg/mL)	240 mg every 24 hours (24 mL)	120 mg every 24 hours (12 mL)	80 mg every 24 hours (8 mL)	60 mg every 24 hours (6 mL)

*Haemodialysis patients: if dosing on day of dialysis, give dose after dialysis.

Overdose:

There is no known antidote for 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 effect of higher doses is not known. If overdose occurs, the patient should be monitored for signs of toxicity and standard supportive treatment applied as necessary.

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

Adverse effects:

More than 2,000 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 1-3 clinical trials. Assessment of adverse reactions is based on data from pivotal studies FTC-301A and FTC-303 in which 571 treatment-naïve (FTC-301A) and 440 treatment-experienced (FTC-303) patients received emtricitabine 200 mg (n = 580) or comparator drug (n = 431) for 48 weeks.[25]

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 due to these events.

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

Laboratory abnormalities in these studies occurred with similar frequency in the emtricitabine and comparator groups. Treatment-emergent Grade 3/4 laboratory abnormalities reported in ≥1% of emtricitabine-treated patients in either Study 301A or 303 were: elevations in ALT (>5.0 x ULN), AST (>5.0 x ULN), bilirubin (>2.5 x ULN), creatine kinase (>4.0 x ULN), pancreatic/amylase (>2.0 x ULN), serum lipase (<2.0 x ULN), triglyceride (>750 mg/dL) levels, decrease in neutrophils (<750 mm^3), and abnormal serum glucose level (<40 or >250 mg/dL).

Patient advice:

Take emtricitabine exactly as your healthcare provider prescribes it. May be taken with or without a meal. If you forget to take emtricitabine, take it as soon as you remember that day. Do not take more than one dose of emtricitabine in a day. Contact your healthcare provider if you are not sure what to do.

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Attachment 1: Glossary of Abbreviations

3TC	Lamivudine
AIDS	Acquired immune deficient syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APR	Antiretroviral Pregnancy Registry
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the curve
AZT	Zidovudine
AZT/3TC	Zidovudine/lamivudine (Combivir®)
BL	Baseline
BMD	Bone mineral density
BUN	Blood urea nitrogen
CDC	Centers for Disease Control
CI	Confidence interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central Nervous System
CrCL	Creatinine clearance
d4T	Stavudine
ddI	didanosine
DF	disoproxil fumarate
DHHS	Department of Health and Human Services
dL	decilitre
DNA	Deoxyribonucleic acid
EFV	Efavirenz
EPO	Erythropoietin
EU	European Union
F	Female

FDA	Food and Drug Administration
FTC	Emtricitabine
g	grams
GMP	Good Manufacturing Practices
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B Virus
HDL	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
IAS	International Aids Society
IDV	Indinavir
IQR	Interquartile Range
ITT	Intention-to-treat
kg	kilograms
KM	Kaplan Meier
LDL	Low-density lipoprotein cholesterol
LFT	Liver function test
LPV/r	Lopinavir/ritonavir
M	Male
M = F	Missing = failure
MCV	Mean corpuscular volume
mg	milligrams
mITT	Modified intent-to-treat
mL	Millilitre
mm^3	Cubic millimetre
n/N	Number of patients
NDA	New Drug Application
NF	National Formulary
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor

NNRTI-R	Non-nucleoside reverse transcriptase inhibitor-resistance
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PCP	*Pneumocystis jirovecii* pneumonia
PI	Protease Inhibitor
RBC/HPF	Red blood cells per high power field
RNA	Ribonucleic acid
RT	Reverse Transcriptase
SATS	Symptoms, Adherence, and Treatment Satisfaction
SCr	Serum Creatinine
SD	Standard deviation
TDF	Tenofovir disoproxil fumarate
TG	Triglycerides
TLOVR	Time to loss of virologic response
U/L	Units/litre
ULN	Upper limit of normal
UNAIDS	United Nations Program on HIV/AIDS
US	United States
USD	United States dollars
USP	United States Pharmacopoeia
VF	Virologic failure
WHO	World Health Organization

Attachment 1
Summary of Principal Clinical Trials of Emtricitabine (Emtriva®)

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
FTC-301A (Pivotal Trial) (Saag et al. 2004; Emtriva Prescribing Information)	Randomised, double-blind, double-dummy, multi-centre study of emtricitabine (FTC) vs. stavudine (d4T) in a triple antiretroviral regimen with didanosine (ddI) and efavirenz (EFV) in treatment-naïve patients.	48 weeks of treatment with a median follow-up duration of 60 weeks	HIV-infected treatment-naïve patients with HIV RNA >5,000 copies/mL randomised to: FTC once daily (QD) + ddI + EFV: (n=286) or d4T twice daily (BID) + ddI + EFV: (n=285)	FTC QD demonstrated greater virologic efficacy and durability of response compared with d4T BID when used with ddI and EFV at Weeks 24, 48, and 60. <u>Week 48:</u> HIV RNA ≤400: 81% FTC vs. 68% d4T ; *P*<.001 HIV RNA ≤50 : 78% FTC vs. 59% d4T; *P*<.001 CD4 (cells/µL) : +168 FTC vs. 134 d4T : *P*=.15 <u>KM probabilities through Week 60:</u> HIV RNA ≤400: 79% FTC vs. 63% d4T; *P*<.001 HIV RNA ≤50 : 76% FTC vs. 54% d4T ; *P*<.001 Virologic Failure (VF) = 4.0% FTC vs 12% d4T; *P*<.001 The M184V/I mutations occurred significantly more frequently in the FTC arm than the d4T arm (*P* <.001).	All adverse events (AEs) were mild to moderate. Serious AEs were similar between the 2 groups (8% FTC vs. 14% d4T; *P* =.13). Incidence of most AEs comparable between FTC and d4T arms. Diarrhoea, nausea, lipodystrophy, abnormal dreams, paresthesia, and neuropathy were significantly greater in the d4T arm. Pancreatitis and symptomatic hyperlactatemia/lactic acidosis were observed only in the d4T arm. Cough and skin discoloration were significantly greater in the FTC arm.
FTC-303 (Pivotal Trial) (Sanne et al. 2002; Emtriva Prescribing Information)	Randomised (2:1), open label, multi-centre, non-inferiority study of FTC vs. 3TC in treatment-experienced patients on a stable triple antiretroviral regimen containing lamivudine (3TC), d4T or zidovudine (AZT), and a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)	48 weeks	HIV-infected treatment-experienced patients with HIV RNA <400 copies/mL on a stable triple therapy regimen (≥ 12 weeks) containing 3TC 150mg BID: FTC QD + stable HAART background regimen excluding 3TC (n=294) or Maintained on the 3TC BID containing HAART (n=146)	Study results showed that simplifying a regimen from 3TC 150 mg BID to FTC 200 mg QD, while keeping all other medications the same, is equally effective and safe after 48 weeks of therapy. <u>Week 48:</u> HIV RNA ≤ 400 copies/mL (ITT): 77% FTC vs.82% 3TC HIV RNA ≤50 copies/mL, ITT: 67% FTC vs. 72% 3TC VF: 7% FTC vs. 8% 3TC CD4 cell count (cells/mm^3): +29 FTC vs. + 613TC	Results at 48 weeks showed that FTC and 3TC are comparable in their safety profiles as part of multidrug regimens. Majority of AEs were mild to moderate with incidence being equivalent in both FTC and 3TC arms. Most frequent reported AEs (≥ 15%) include infection, diarrhoea, nausea, rhinitis, asthenia, rash event and pain.

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
FTC-302 (Sanne et al. JID 2005; EMEA EPAR Report ; Sanne et al. 2002)	Randomised, double-blind, double-dummy, multi-centre study compared the safety and efficacy of FTC vs. 3TC, each in combination with d4T and either EFV or NVP in treatment-naïve HIV infected patients in the Republic of South Africa	48-weeks	HIV infected treatment-naïve patients in the Republic of South Africa with HIV RNA > 5,000 copies/mL randomised to: FTC QD + d4T and either EFV or NVP or 3TC BID + d4T and either EFV or NVP (Approximately 82% were stratified to NVP) <u>Baseline</u> Mean HIV-RNA: 4.5 $\log_{10}$ copies/ml Mean CD4 count: 389 cells/mm^3	The results of this study support the equivalent antiviral efficacy of FTC as compared to twice daily 3TC through 48 weeks of treatment in treatment-naïve patients. <u>Week 48:</u> HIV RNA ≤ 400 copies/mL (ITT; NC=F): 64.4% FTC vs. 71.3% 3TC HIV RNA ≤ 400 copies/mL (AT): 86.3% FTC vs. 90.1% 3TC HIV RNA ≤ 50 copies/mL (ITT; NC=F): 60.2% FTC vs. 63.8% 3TC HIV RNA ≤ 50 copies/mL (AT): 81.0% FTC vs. 81.3% 3TC 20 patients in each treatment group withdrew due to VF (defined as either loss of virologic response [plasma HIV RNA > 400 copies/ml on two consecutive measurements after achieving a plasma HIV RNA ≤400 copies/ml] or lack of virological response [failure to achieve plasma HIV RNA ≤ 400 copies/ml by Week 12]) with genotypic evidence of resistance.	22 patients in each treatment group withdrew due to adverse events prior to completing week 48 Through 48 weeks, the overall incidence of adverse events was equivalent between the emtricitabine and 3TC treatment group, with the exception of accidental injury and gastroenteritis, which occurred more frequently in the 3TC group. Most adverse events were mild to moderate in severity. All elevations of liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) occurred in subjects in the NVP stratum and none occurred in those subjects who received EFV. Overall, hepatotoxicity, occurred in 66/468 subjects (14% of subjects who received at least one dose of blinded study medication). All cases of hepatotoxicity occurred in the NVP group and none in the EFV group (P <.001), and the incidence of hepatotoxicity was comparable between the emtricitabine and 3TC treatment groups (15% and 19%, respectively; P =.28). Multiple regression analysis revealed that the proportion of subjects with or without hepatotoxicity was similar between the emtricitabine and 3TC treatment groups (P =.3).

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
GS-01-934 (Pozniak et al. 2005; Gallant et al. 2006)	Phase 3, open-label, multi-centre study to evaluate safety and efficacy of a FTC 200 mg + TDF 300 mg + EFV 600mg QD regimen vs. 3TC 150 mg/AZT 300 mg (AZT/3TC) BID + EFV 600 mg QD	96 weeks	Treatment-naïve HIV-infected patients with HIV RNA >10,000 copies/mL. Randomized 1:1 to: FTC 200 mg QD + TDF 300mg QD + EFV 600mg QD vs. 3TC 150mg/AZT 300mg BID + EFV 600mg QD <u>Baseline:</u> Median HIV RNA: 5.0 $\log_{10}$ copies/mL for both groups Median CD4: 233 cells/mm^3 FTC + TDF arm vs. 241 cells/mm^3 AZT/3TC arm	<u>At Week 48:</u> HIV RNA <400 copies/mL: (TLOVR, mITT analysis): (*P*=0.002) o TDF+FTC+EFV: 84% o AZT/3TC+EFV: 73% HIV RNA <50 copies/mL: (TLOVR, mITT analysis): (*P*=0.02) o TDF+FTC+EFV: 80% o AZT/3TC+EFV: 70% Increase in CD4 cell count from baseline (as-treated analysis): (*P*=0.002) o TDF+FTC+EFV: 190 cells/mm^3 o AZT/3TC+EFV: 158 cells/mm^3 VF: o TDF+FTC+EFV: 2% o 3TC+AZT+EFV: 3% <u>At Week 96:</u> HIV RNA <400 copies/mL (TLOVR analysis): (*P*=0.004) o TDF+FTC+EFV: 75% o AZT/3TC+EFV: 62% HIV RNA <50 copies/mL (TLOVR analysis): (*P* =0.16) o TDF+FTC+EFV: 67% o AZT/3TC+EFV: 61% Increase in CD4 cell count from baseline (*P* =.036): o TDF+FTC+EFV: 270 cells/mm^3 ° AZT/3TC+EFV: 237 cells/mm^3 K65R development: none in both groups M184V/I development (*P* = .036): o TDF+FTC+EFV: 2 o 3TC+AZT+EFV: 9	<u>At Week 48:</u> Discontinued the study (TLOVR): (*P* =.02) o FTC+TDF+EFV: 4% o AZT/3TC+EFV: 9% Discontinued due to anaemia (TLOVR): (*P* <.001) o FTC+TDF+EFV: 0% o AZT/3TC+EFV: 6% <u>At Week 96:</u> Discontinued the study (*P* =0.023): o FTC+TDF+EFV: 5% o AZT/3TC+EFV: 11% Discontinued due to anaemia (*P* <0.001) o FTC+TDF+EFV: 0% o AZT/3TC+EFV: 6% Median GFR (CG calculation) (*P* =0.51): o FTC+TDF+EFV: 119 mL/min o AZT/3TC+EFV: 118 mL/min Median GFR (MDRD calculation) (*P* =0.006): o FTC+TDF+EFV: 100 mL/min/1.73m^2 o AZT/3TC+EFV: 108 mL/min/1.73m^2 No patient in the FTC + TDF arm experienced confirmed Grade 1-4 renal abnormality as compared to two patients in the AZT/3TC arm. Median Total Limb Fat (*P* <0.001): o FTC+TDF+EFV: 7.7 kg o AZT/3TC+EFV: 5.5 kg

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
M02-418 (Molina et al. 2005; Johnson et al. 2006)	Randomized, open-label, multi-centre study to compare lopinavir/ritonavir (LPV/r) 800mg/200mg QD vs. LPV/r 400mg/100mg BID with TDF and FTC in treatment-naïve HIV-infected patients	96 weeks	Treatment-naïve HIV-infected patients with HIV RNA>1,000 copies/mL. 190 patients enrolled: n=115 for LPV/r QD+TDF+FTC n=75 for LPV/r BID+TDF+FTC <u>Mean Baseline:</u> CD4: 260 cells/mm^3 HIV RNA: 4.8 log_{10} copies/mL	Results at Weeks 48 and 96 revealed that similar proportions of patients in both groups achieved HIV RNA <50 copies/mL. <u>Week 48:</u> HIV RNA < 50 copies/mL ITT (NC=F analysis): o LPV/r QD + TDF + FTC: 70% o LPV/r BID + TDF + FTC: 64% TLOVR analysis: o LPV/r QD + TDF + FTC: 71% o LPV/r BID + TDF + FTC: 65% Change in CD4 cell count (cells/mm^3): o LPV/r QD + TDF + FTC: +185 o LPV/r BID + TDF + FTC: +196 <u>Week 96:</u> HIV RNA < 50 copies/mL ITT (NC=F analysis): o LPV/r QD + TDF + FTC: 57% o LPV/r BID + TDF + FTC: 53% TLOVR analysis: o LPV/r QD + TDF + FTC: 57% o LPV/r BID + TDF + FTC: 55% Change in CD4 cell count (cells/mm^3): o LPV/r QD + TDF + FTC: +244 o LPV/r BID + TDF + FTC: +264 Resistance testing results were available in 23 patients, 15 in the once-daily group and eight in the twice-daily group. Resistance to FTC was identified in a total of four patients (three in the once-daily group and one in the twice-daily group).	Through Week 96, a total of 37% (42/115) of patients in the once-daily group and 39% (29/75) of patients in the twice-daily group discontinued the study, 17% and 9% due to adverse events, respectively. Gastrointestinal adverse events were the most common cause for discontinuation and were the most common adverse events overall (>3%). Diarrhoea was reported more frequently in the once-daily vs. the twice-daily group (17% vs. 5%; *P* =.014). The most common grade 3/4 laboratory abnormalities (> 3%) reported were increased ALT (> 5 x upper limit of normal [ULN]), AST (> 5 x ULN), triglyceride (> 750 mg/dL), cholesterol (>300 mg/dL), and amylase (> 2 x ULN) levels; no significant differences between the 2 groups were observed. Acute renal failure (ARF) occurred in 1 patient in each group. One was a 75 year-old male with a creatinine clearance of 40 mL/min at baseline who was given full dose of TDF and developed ARF at Week 34. The other patient was a 54 year-old male. ARF occurred at Week 38, requiring temporary haemodialysis. Renal biopsy demonstrated tubulointerstitial nephritis. At Week 96, significant increases from baseline in total cholesterol, high density lipid (HDL), low density lipid (LDL), and triglyceride levels were observed in both groups.

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
ANRS-099 (ALIZE) (Molina et al. JID 2005)	Randomised, open-label study comparing the continuation of a PI-based regimen (2 NNRTIs+a PI) vs. switching to a QD combination of FTC+ddI+EFV regimen	48 weeks	HIV infected patients who were: naïve to NNRTI and ddI on a stable HIV therapy with HIV RNA< 400 copies/mL for 6 months and CD4 ≥ 100 cells/mm^3 at screening QD = 178 PI = 177	HIV RNA < 400 copies/mL at Week 48, ITT: 90.5% for the QD arm vs. 87.6% in the PI arm HIV RNA < 50 copies/mL at Week 48, ITT: 87% for the QD arm vs. 79% in the PI arm (P<.05) Median CD4 count cells/mm3 increase +16 for the QD arm vs. +15 for the PI arm (P = .68) Virologic failure, defined (HIV RNA ≥400 copies/mL from two consecutive measurements during baseline to Week 48): 10% for the QD arm vs. 12% in the PI arm (P=.50)	Rates of treatment discontinuation were similar between the QD and PI arms The incidence of grade 4 adverse reaction was also similar in both groups, 6% in the QD arm vs. 5% in the PI arm (p=.64) More patients in the QD arm experienced Grade 2-4 adverse events (48% vs. 38%; *P* = .06) and increases in liver aminotransferase levels (12 vs. 3) compared to the PI arm. Significant increase in the median HDL cholesterol level in the QD arm compared to the PI arm (+7.8 mg/dL vs. +0.4 mg/dL; p<0.0001) The portion of patients with lipohypertrophy remained unchanged in both groups, yet lipoatropy increased in the PI arm from 46% at baseline to 60% at 48 week while it remained steady in the QD arm, 43% at baseline to 42% at 48 week. Also, there was a significant increase in the median HDL cholesterol level in the QD arm compared to the PI arm (+7.8 mg/dL vs. +0.4 mg/dL; *P*<0.0001)
ANRS-099 (ALIZE Extension) (Molina et al. CROI 2005)	Randomised, open-label study to assess the QD arm combination (FTC + ddI + EFV) of the ALIZA study (48-week) to evaluate the long-term safety and efficacy of these patients	Up to 36 month	Patients whom completed the initial 48-week follow-up could continue on the QD regimen for an additional 24 months (total of 36 months) 152 (85%) patients decided to participate in the extended evaluation	Probability of virological failure occurred in 23% of the patients Median increase in CD4 cell count (from baseline) was +44 cells/mm3 (p<0.05)	Serious adverse events occurred in 29 (16%) patients before week 48 vs. 17 (10%) up to 36 months. Incidence of lipodystrophy (both lipoatrophy and lipohypertrophy) remained unchanged and no patient discontinued study treatment because of worsening of lipoatrophy. Slightly statistically significant increase in plasma glucose level (p<0.05) No increase in total cholesterol or LDL levels A +11.6 mg/dL increased in HDL levels from baseline up to month 36 (p<.0001). Furthermore, 42% of the patient had a HDL levels > 60 mg/dL at month 36 vs. 20% at baseline.

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
ANRS-099 (ALIZE Switch Study) (Molina et al. CROI 2005)	Switch study in which patients from the PI arm (N=152) of the ALIZA trial could either continue the PI regimen of AZT +3TC+PI or switch to the once-daily (QD) regimen of FTC+ddI+EFV to evaluate the haematological	48 weeks	Patients were stable PI-containing HAART regimen with HIV RNA levels < 400 copies/mL Evaluated the change from baseline in haemoglobin, neutrophils, CD4 cell count, and HIV RNA levels at week 48 152 patients from the PI arm in the ALIZA: continued on the current PI regimen (N= 78) vs. switching to the QD regimen (N=74)	Patients maintained virological control. Insignificant greater change in the QD arms: change in CD4 (+9 PI arm vs.+34 QD arm) and HIV RNA levels < 400 copies/mL (90% PI arm vs. 95% QD arm)	Significant improvement (from baseline to week 48) in haemoglobin and neutrophil count in the patients who switch to the QD regimen. The change in haemoglobin was -0.4 PI arm vs. +0.7 QD arm (p<.01) Change in neutrophil was +82 PI arm vs. +607 QD arm (p<.03)
COMET (DeJesus et al. 2006)	Prospective, multi-centre, single-arm, phase 4 clinical trial evaluating the impact of switching virologically suppressed patients from a BID regimen containing AZT/3TC + EFV to a QD regimen containing FTC + TDF + EFV	24-weeks	411 HIV-infected, treatment-experienced, virologically suppressed patients with HIV RNA <400 copies/mL on AZT/3TC + EFV for ≥8 weeks. (Post-baseline results available for 402 patients). Switched to a QD regimen containing FTC + TDF + EFV <u>Baseline:</u> 71.1% of patients had HIV RNA <50 copies/mL. Median CD4: 558 cells/mm^3	<u>RNA < 400 copies/mL at Week 24:</u> ITT (missing = excluded) analysis: 95% ITT (missing = failure) analysis: 87% HIV RNA < 50 copies/mL at Week 24: ITT (missing = excluded) analysis: 81%; *P* <.001 ITT (missing = failure) analysis: 74%; *P* =.38 Median (IQR) CD4 Cell Count increased from baseline by 12 cells/mm^3; *P* = .023 A Validated questionnaire of patient-reported showed that significantly fewer patients complained of bothersome adverse events, fatigue, and nausea/vomiting (all *P* < .001) as compared to baseline. In addition, significantly more patients reported being "very satisfied" with the FTC/TDF regimen. Furthermore, the number of patients who reported full (100%) adherence on ≥ 95% of days was significantly higher at Week 24 versus baseline (*P* = .002).	Thirty patients discontinued the study early. The most commonly reported adverse events were nausea, diarrhoea, headache, and insomnia. Grade 3/4 laboratory abnormalities occurred in 1% of patients; 2 cases each of neutropenia and increase in triglycerides, and one case of thrombocytopenia. Grade 2 confirmed increase in serum creatinine occurred in 1 patient, but returned to normal range while on treatment during the study. There were statistically significant improvements from baseline at Week 24 in haemoglobin level (31% had >1 g/dL increase from baseline), ANC, MCV, and fasting lipid parameters.

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
ANRS 1207/IMEA 025 Study (Landman et al. 2006)	Open-label, single-arm pilot study evaluating antiviral activity and tolerance of a QD combination FTC + TDF + EFV	48 weeks	40 HIV-1 infected treatment-naïve patients with CD4 cell count <350 cells/mm^3 in West Africa <u>Median Baseline:</u> HIV RNA: 5.3 log_{10} copies/mL CD4: 122 cells/mm^3	85% of patients had HIV RNA < 400 copies/mL at Week 48 (ITT analysis) 72.5% of patients had HIV RNA < 50 copies/mL at Week 48 (ITT analysis) The mean CD4 count increase from baseline to week 48 was 185 ± 85 cells/mm^3	Grade 2-3 treatment related adverse events included dizziness, nausea/vomiting, diarrhoea, cutaneous eruption/pruritus, headache, and fatigue. There were no Grade 4 treatment-related adverse events. Reported Grade 3 or 4 laboratory abnormalities included: haemoglobin < 7g/dL (n = 1), neutrophils < 700 /mm^3 (n = 3), and AST/SGOT > 5 x ULN (n = 1). There was a significant decrease in mean CrCL, from 92 mL/min at baseline to 80 mL/min (*P* = .03) at week 48. Mean triglyceride levels decreased significantly from 74 mg/dL at baseline to 57 mg/dL (*P* = .04) at week 48; decrease in total cholesterol was not statistically significant (161 to 156mg/dL [*P* = .14])

Study Number (Publication)	Design	Duration of Treatment	Population Number of Subjects by Treatment Arm	Clinical Efficacy	Safety and Tolerability
FTC-203 (Paediatric Trial) (Saez-Llorens et al. CROI 2003; Violari et al. IAS 2004; Ndiweni et al 2004; Harris et al. ICAAC 2004; Chittick et al. 2005)	Phase 2, open-label, multi-centre study conducted to assess the pharmacokinetic, antiviral activity, and safety profiles of FTC in combination with other antiretroviral agents in paediatric patients	96 weeks	HIV-infected children aged 3 months to 17 years old. 71 Treatment-naïve (HIV RNA ≥5,000 but ≤500,000 copies/mL) and 45 treatment-experienced (on a stable 3TC-containing regimen for ≥3 months and HIV RNA ≤400 copies/mL) Treatment: *Treatment-naïve patients*: FTC 6 mg/kg QD, up to a maximum of 200 mg QD as capsules or 240 mg QD as oral solution, d4T twice daily, and LPV/r BID *Treatment-experienced patients*: switched from 3TC to FTC and their background antiretroviral regimen could be changed at the investigator's discretion. Baseline: Average age: 6 years Median HIV RNA: 4.5 $\log_{10}$ copies/mL Median CD4 Cell Count: 817 cells/mm^3	HIV RNA < 400 copies/mL at Week 48: *ITT (NC = F) analysis:* Treatment naïve pts: 93% Treatment experienced: 87% *ITT (M = F) analysis:* Treatment naïve pt: 90% Treatment experienced: 81% HIV RNA < 50 copies/mL at Week 48: *ITT (NC = F) analysis:* Treatment naïve pts: 78% Treatment experienced: 78% *ITT (M = F) analysis:* Treatment naïve pt: 74% Treatment experienced: 68% HIV RNA < 400 copies/mL at Week 96: *ITT (M = F) analysis:* Treatment naïve pts: 76% Treatment experienced: 69% HIV RNA < 50 copies/mL at Week 96: *ITT (M = F) analysis:* Treatment naïve pts: 65% Treatment experienced: 55% Eight patients had confirmed virologic failure at Week 48. The overall incidence of M184V mutation at Week 48 was 3.5% (4/116).	Serious adverse events were reported in 19 (27%) treatment-naïve patients and in 5 (11%) treatment-experienced patients. Seven patients experienced an adverse event that was at least moderate in severity (Grade 2) and possibly or probably related to the study drug. The overall incidence of Grade 3/4 laboratory abnormalities was 9% (10/116); 7% (n = 5) in the treatment-naïve and 11% (n = 5) in the treatment-experienced patients. Two patients, one treatment-naïve and one treatment-experienced, discontinued the study before Week 48 due to adverse events (anaemia and pancreatitis). One study discontinuation occurred due to death (leukaemia)
PACTG 1021 (FTC-202) (Paediatric Trial) (McKinney et al. CROI 2004; McKinney et al CROI 2006)	Phase 1/2 open-label study designed to evaluate the pharmacokinetics, safety, and efficacy of a QD regimen of FTC 6 mg/kg QD (maximum of 200 mg QD), ddI, and EFV in treatment-naive paediatric patients infected with HIV.	96 weeks	HIV-infected paediatric patients: 37 children and young adults between the ages of 3-21 years Median Baseline: HIV RNA level: 47,775 copies/mL CD4 cell count: 310 cells/µL	HIV RNA < 400 copies/mL at Week 96 (ITT; discontinued = failure) analysis: 86% HIV RNA < 50 copies/mL at Week 96 (ITT; discontinued = failure) analysis: 70% Median change in CD4 count at 96 weeks: +329 cells/µL	Ten out of 37 patients discontinued study treatment, including 2 patients who discontinued due to Grade 2 or 3 rash. Three study discontinuations occurred due to virologic failure. Two patients experienced Grade 3 symptoms (rash, dizziness) which were attributed to the regimen. These symptoms occurred during Week 1 and resolved spontaneously. No deaths or new Category C diagnoses occurred during the study