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Emtricitabine

An Antiretroviral Agent for HIV infection

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Contents

Abstract

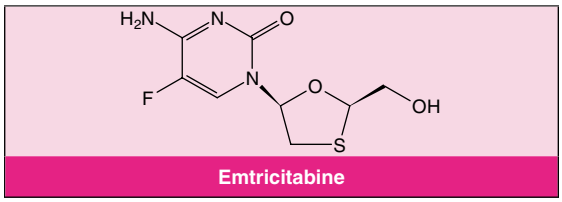
▲ Emtricitabine, a nucleoside reverse transcriptase inhibitor, is phosphorylated by cellular enzymes to emtricitabine 5′-triphosphate which, in turn, inhibits the activity of HIV-1 (HIV) reverse transcriptase by competing with the endogenous substrate. Incorporation of the triphosphate into the viral DNA causes chain termination, thereby inhibiting viral replication.

▲ In adult patients infected with HIV, combination therapy including emtricitabine 200mg once daily was as effective as triple therapy including lamivudine 150mg twice daily and significantly more effective than stavudine (at standard dosages) or protease inhibitor-based therapy at achieving and/or maintaining durable suppression of HIV levels after 24–48 weeks of therapy. In addition, 85% of emtricitabine recipients maintained virological success (<400 copies/mL) during 96 weeks of therapy.

▲ Triple therapy including emtricitabine 6 mg/kg once daily decreased (to <400 copies/mL) or maintained durable suppression of HIV RNA levels in ≈90% of children and adolescents (aged 13 months to 17 years) after 16–24 weeks of therapy.

▲ Emtricitabine-based therapy was generally well tolerated; most adverse events being mild to moderate in intensity. Emtricitabine-based regimens were as well tolerated as those with lamivudine, and better tolerated than those with stavudine.

Features and properties of emtricitabine (Emtriva™)	
Indications	
HIV infection	
Mechanism of action	
Antiviral	A nucleoside reverse transcriptase inhibitor
Dosage and administration	
Formulation	Capsules
Approved dosage	200mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (at steady state, 200mg once daily)	
Bioavailability	93%
Peak plasma concentration	1.7 μg/mL
Time to peak plasma concentration	2 hours
Area under the plasma concentration-time curve	10 μg • h/mL
Adverse events	
Most frequent treatment-emergent events in >5% of patients	Infection, nausea, headache, rash, flu-like syndrome and diarrhoea



Emtricitabine

Since the discovery of HIV in 1983,[1] more than 42 million people have been infected and suffer from either HIV or AIDS.[2] With no cure currently available, antiretroviral therapy (ART) focuses on being able to substantially suppress viral RNA levels, thereby preventing progression of the disease.[3] Highly active ART (HAART) using triple combination regimens are recommended for the treatment of patients with HIV infection in an attempt to overcome the drug resistance that can occur during monotherapy;[3] however, the unfavourable toxicity, drug interactions and tolerability of many HIV drugs have meant that there is still a need for new antiretroviral agents.

Emtricitabine (Emtriva™[1]) is a nucleoside reverse transcriptase inhibitor (NRTI) and, in combination with other antiviral agents, has shown efficacy against HIV after once-daily dosing.[4] The drug has recently been approved for use in combination therapy for the treatment of HIV infection.[5]

1. Pharmacodynamic Properties

The pharmacodynamic properties of emtricitabine have been examined in both cell culture and clinical studies. Most of these studies compared emtricitabine with the NRTI lamivudine.

Mechanism of Action

- Emtricitabine [(the (−)-enantiomer of 2′,3′-dideoxy-5-fluoro-3′-thiacytidine [FTC]) is phosphorylated by cellular enzymes to form a synthetic analogue of deoxycytidine (emtricitabine 5′-triphosphate).[4] In one study, emtricitabine was shown to be initially phosphorylated by 2′-deoxycytidine kinase.[6] Inhibition of HIV-1 (HIV) reverse transcriptase activity occurs as the triphosphate competes with the endogenous substrate 2′-deoxycitidine 5′-triphosphate; emtricitabine 5′-triphosphate is incorporated into the HIV DNA chain which causes chain termination.[4]

Anti-HIV Activity

- *In vitro*, emtricitabine demonstrated antiviral activity against clinical and laboratory strains of HIV in peripheral blood mononuclear cells (PBMC), monocytes and macrophages; mean 50% effective inhibitory concentration (IC_{50}) values were 0.0014–0.14 mmol/L for emtricitabine compared with 0.002–2.5 mmol/L for lamivudine.[7] On average, emtricitabine was 11-fold more active against HIV than lamivudine in these cells.[7] Similarly, emtricitabine demonstrated greater anti-HIV activity than lamivudine when tested against laboratory adapted strains of HIV in the human blastoid cell line MT4 (IC_{50} 530 vs 2030 nmol/L; $p < 0.001$).[8] In addition, the anti-HIV activity of emtricitabine (IC_{50} 0.002–0.0085 μmol/L) was up to 10-fold greater than that of lamivudine (IC_{50} 0.001–0.11 μmol/L), and similar to that of zidovudine (IC_{50} 0.003–0.0055 μmol/L) in human PBMCs infected with clinical or laboratory HIV isolates.[9]
- Cell culture studies demonstrate that both the (−)- and (+)-β-enantiomers of FTC exhibit antiviral activity, although the (−)-β-enantiomer appears to be approximately 20 times more potent against HIV.[9]
- Single nucleotide incorporation by HIV reverse transcriptase was similar for both (−)- and (+)-FTC in *in vitro* studies; however, the (−)-isomer (emtricitabine) was more efficiently taken into the cell and phosphorylated to the active triphosphate form.[10] Furthermore, relative to lamivudine triphosphate,

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

incorporation of emtricitabine triphosphate during HIV RNA-dependent DNA synthesis was 10-fold more efficient.[10]

- Similarly, in an animal study, emtricitabine 60 mg/kg administered for 1–6 days after infection prevented HIV development in mice reconstituted with human PBMCs but was only slightly more effective than the racemic (+/−)-FTC mixture (as measured by quantitative coculture) [quantitative data not available; abstract only].[11]
- These *in vitro* and animal studies are supported by clinical studies involving adults and children infected with HIV that showed that emtricitabine reduced HIV RNA levels and maintained viral suppression for up to 96 weeks (section 4) when used in combination therapy.[12-19]

Viral Resistance

- The potential for HIV resistance to emtricitabine was evaluated *in vitro* by serial passage of wild-type HIV in PBMC and MT-2 cells in the presence of increasing emtricitabine concentrations.[20] After two or more cycles of infection in MT-2 cells, the replicating viral population consisted mostly of highly drug-resistant HIV variants that were cross resistant to lamivudine.[20] In contrast, in PBMC, the emergence of highly drug-resistant HIV variants did not occur until 5 weeks of passage with emtricitabine compared with 2 weeks of passage with lamivudine.[20] Furthermore, reverse transcriptase derived from drug-resistant viral particles was >15-fold less susceptible to inhibition by the 5′-triphosphate of emtricitabine than the reverse transcriptase from the parent drug-susceptible virus.[20]
- As might be expected, passage of HIV in MT4 cells with a combination of emtricitabine and zidovudine delayed the emergence of emtricitabine-resistant virus.[21] *In vitro*, emtricitabine-resistant HIV variants showed no cross-resistance to didanosine, zidovudine or nevirapine.[21]
- Resistance to emtricitabine and lamivudine is associated with the development of the Met184→Val (M184V) point mutation in the HIV reverse transcriptase genome.[22] In patients receiving triple combination ART who experienced virological failure, the incidence of the M184V mutation was lower in emtricitabine-based regimens (17–32%,[22] 17%[23] and 30%[24]) than in those containing lamivudine (42–78%,[22] 59%[23] and 65%[24]) [$p \leq 0.01$ in two studies,[23,24] p-value not reported in the third[22]]. Furthermore, patients presenting with virological failure (i.e. >400 HIV RNA copies/mL) were more likely to have the wild-type virus at the time of failure when treated with emtricitabine (43–75%[22] and 43% of patients[23]) than those receiving lamivudine-based triple therapy (12–40% [p-values not reported][22] and 12% [$p < 0.026$][23]).

Other Effects

- No effects on fertility, sperm count or early embryonic development in mice were observed after treatment with emtricitabine 250–1000 mg/kg/day.[25] In addition, there was no change in the incidence of mouse or rabbit embryo-fetal malformations in toxicology studies after treatment with emtricitabine.[25]
- Mitochondrial DNA was not affected by either (–)-β-FTC, (+)-β-FTC or (+/−)-FTC after 14 days of incubation in HepG2 cells.[26]

2. Pharmacokinetic Properties

The pharmacokinetic properties of emtricitabine have been evaluated in animals[27-29] and in volunteer patients with HIV infection.[4,15,30-35] This section focuses on human pharmacokinetic studies.

Absorption and Distribution

- In a randomised, double-blind trial in 18 patients with HIV infection (primarily without AIDS), emtricitabine 100–1200mg displayed linear pharmaco-

kinetics following a single oral dose.[30] The mean area under the plasma concentration-time curve (AUC) values were 3.87–57.8 μg • h/mL, with mean peak plasma concentrations (C_{max}) of 1.01–11.5 μg/mL reached after 1.25–1.61 hours (t_{max}).[30] The consumption of a high-fat meal with a single dose of emtricitabine 400mg prolonged t_{max} (2.8 hours), and decreased C_{max} (by ≈23%) but had no effect on AUC values (specific values not reported).[30]

• Similarly, in a second study, emtricitabine 100–1200mg was rapidly absorbed in 12 HIV-infected patients who received single doses of the drug with a 6-day washout period between doses (t_{max} = 3 hours; C_{max} not reported).[30]

• Mean steady-state C_{max}, t_{max} and AUC values were 1.7 μg/mL, 2 hours and 10.0 μg • h/mL, respectively, in 6 patients with HIV after treatment with emtricitabine 200mg once daily for 10 days.[36] Twenty-four hours after the dose, the mean steady-state plasma trough concentration was 0.09 μg/mL.[36] The mean oral bioavailability of emtricitabine was 93%,[4] and was unaffected by food (specific values not reported).[31]

• In a dose-escalation study in which patients infected with HIV received emtricitabine 25mg twice daily, 100mg once or twice daily or 200mg once or twice daily (eight patients per dosage group) for 14 days, steady-state plasma emtricitabine concentrations were maintained above the mean *in vitro* IC_{90} (value not reported) for at least 24 hours with dosages of 100–400 mg/day.[32] In addition, mean steady-state trough concentrations with emtricitabine 100 or 200mg once daily were two to four times higher than the mean IC_{90} (no data reported in abstract).[32]

• At emtricitabine concentrations of 0.02–200 μg/mL, <4% of the drug is bound to human plasma protein in *in vitro* studies.[4] At C_{max}, the drug partitions approximately equally into the plasma and blood cells.[4]

Metabolism and Elimination

• The mean plasma elimination half-life ($t_{1/2}$) of emtricitabine was approximately 8–10 hours in adult patients with HIV.[4,32] An additional study reported that $t_{1/2}$ was approximately 2.7 hours after a single dose of emtricitabine 100–1200mg (this results in this study may be underestimated because of a short 24-hour sampling schedule).[30] In this same study, apparent total body clearance (CL/F) decreased over the range of emtricitabine 100–1200mg (from 6.33 to 4.99 mL/min/kg; significance not reported).[30]

• After multiple doses of emtricitabine 200 mg/day, an intracellular $t_{1/2}$ of ≈39 hours was observed.[36]

• Emtricitabine was completely recovered after ^{14}C-labelled oral administration (≈86% in the urine and ≈13% and faeces).[4] A small proportion of the dose (13%) was recovered in the urine as metabolites.[4] Of this, ≈9% resulted from oxidation of the thiol moiety to form the 3′-sulfoxide diastereomers and ≈4% was due to conjugation with glucuronic acid to form 2′-*O*-glucuronide. No other metabolites were identified.[4]

• Elimination of emtricitabine is thought to occur by both glomerular filtration and active tubular secretion, as the renal clearance of emtricitabine is greater than the estimated creatinine clearance (values not reported).[4]

Special Populations

• In an open-label, multicentre trial, 23 children and adolescents (aged 2–17 years) who were either exposed to or infected with HIV were given a single oral dose of emtricitabine 60 mg/m^2 followed by a 120 mg/m^2 dose 7 days later.[35] Plasma levels of emtricitabine increased in a near linear manner with these two doses (specific values not reported; abstract only).[35] No significant differences were observed for the mean rate or extent of absorption in

children and adolescents aged 2–5, 6–12 and 13–17 years, and absorption with the 120 mg/m^2 dose in children and adolescents was similar to that reported in adults receiving a 200mg dose.[35]

- These data were supported by another study in 28 children and adolescents (aged 3 months to 17 years) with HIV infection who received emtricitabine 6 mg/kg once daily.[15] Pharmacokinetic evaluation, conducted on week 2, showed that mean steady-state C_{max} values were 1.75–2.56 μg/mL (t_{max} not reported). As well, mean AUC_{24} values moderately increased with age (8.1, 9.2, 12.9 and 14.5 μg • h/mL in children and adolescents with a mean age of 1.2, 5.0, 9.8 and 14.8 years, respectively; significance not reported), although values for all age groups were similar to those reported in adults (≈10 μg • h/mL).[15]
- The $t_{1/2}$ of emtricitabine in children and adolescents was approximately 11 hours across all age groups after a single oral 60 or 120mg dose.[35] In the other study, $t_{1/2}$ was 7.9–9.5 hours in children and adolescents after 2 weeks of therapy (6 mg/kg/day).[15] In addition, one study reported that the CL/F was not significantly different in children and adolescents aged 2–17 years.[35]
- The C_{max} and AUC values of emtricitabine are increased in patients with creatinine clearance <50 mL/min or with end-stage renal disease requiring dialysis due to a reduction in renal clearance of the drug.[4] The dosing interval must be modified in such patients (section 6).

Drug Interactions

- Emtricitabine is not metabolised by cytochrome P450 (CYP) isoenzymes and thus has limited potential to interact with coadministered agents that are metabolised by these enzymes.[4] In *in vitro* studies, supratherapeutic doses of emtricitabine had no effect on the pharmacokinetics of drugs metabolised by CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.[4]
- The pharmacokinetic profile of emtricitabine 200mg once daily was not affected by the coadministration of didanosine (standard doses) or efavirenz (600mg once daily) in treatment-naive patients after 4 weeks of combination therapy.[33] Steady-state median AUC_{24}, C_{max} and t_{max} values of 7.3 μg • h/mL, 1.7 μg/mL and 1.5 hours, respectively, were reported for emtricitabine during the 36-hour dosing interval.[33]
- Similarly, the pharmacokinetics of a single dose of emtricitabine 200mg were not affected by coadministration with zidovudine 300mg, stavudine 40mg or famciclovir 500mg in 24 patients.[34] Furthermore, following coadministration for 7 days in 19[37] and 30[38] healthy volunteers, neither zidovudine 300mg twice daily[38] or tenofovir 300mg once daily[37] had any effect on the pharmacokinetic parameters of emtricitabine 200mg once daily, although the AUC and C_{max} values of zidovudine were increased by 13% and 17%.[38]

3. Therapeutic Efficacy

The efficacy of emtricitabine in combination with two or more antiretroviral drugs (including didanosine, efavirenz, stavudine, nevirapine and lopinavir/ritonavir) was investigated in patients with HIV in a number of studies, including two randomised comparisons,[14,16] one of which was double blind,[16] two nonrandomised, open-label comparisons[15,39] and two noncomparative trials.[12,13]

In most studies, trial duration ranged from 24 to 48 weeks. One study is ongoing and reported preliminary results at week 16.[13] In addition, results from an ongoing noncomparative 4-year triple-therapy trial have been presented from various timepoints during the course of the trial (24,[17] 64[40] and 96[41] weeks). As well, the results of two randomised, comparative triple-therapy trials (one double-blind, the other open-label) have been presented together in a single poster[18] with additional longer-

term results (mean duration 140 weeks) of one study reported separately.[19]

Data are also available from two small, randomised, dose-finding studies of 12–14 days' duration (n = 41[42] and 81[43]).

With the exception of two studies in children and adolescents,[13,15] all studies involved adults infected with HIV (mean age 32–43 years). Patients were either ART-naive (generally with plasma HIV RNA levels ≥5000 copies/mL)[12,13,16-18,42,43] or ART-experienced (with plasma HIV RNA levels ≤400 copies/mL).[14,18] In addition, one study included both ART-naive and ART-experienced patients.[15]

Where defined, clinical endpoints were the surrogate markers of suppression of HIV viral RNA to ≤400 copies/mL (virological success)[12-18,42,43] [primary endpoint in one study[17]], and the change in CD4+ cell counts.[12-15,17] Intention-to-treat analyses were reported for four studies,[13-15,17] with the nature of analyses not reported in remaining studies. With the exception of one fully published trial,[17] all studies are presented as abstracts and/or conference proceedings.

In Adults

- Two small, dose-finding trials established that the optimal dosage of emtricitabine in patients with HIV infection was 200mg once daily.[42,43] After 14 days of treatment, emtricitabine 50–400 mg/day produced significant reductions from baseline in median plasma HIV RNA levels (1.3–1.9 $\log_{10}$ copies/mL; p = 0.02 correlated with dose).[42] Maximal reductions in median HIV RNA levels from baseline occurred with emtricitabine dosages ≥200 mg/day, with reductions with emtricitabine 200mg once or twice daily of 1.92 and 1.87 $\log_{10}$ copies/mL (baseline RNA levels were 4.58 and 4.68 copies/mL).[42]

- In the larger (n = 571), double-blind trial, emtricitabine-based triple combination therapy provided better efficacy than stavudine-based therapy in terms of virological and immunological response rates.[16] The incidence of virological success (HIV RNA ≤400 copies/mL) after 24 weeks of triple combination therapy was significantly higher in patients receiving emtricitabine 200 mg/day than in those receiving stavudine at standard dosages with didanosine and efavirenz (dosages not reported) [87% vs 79%; p = 0.02], and more patients had HIV RNA levels of <50 copies/mL (81% vs 70%; p = 0.002).[16] Preliminary results also suggest that a greater number of patients maintained viral suppression at week 60 when given emtricitabine compared with stavudine (79.4% vs 62.8%; p < 0.0001).[44] In addition, the mean increase from baseline (median 288 cells/mm^3) in CD4+ cell count was significantly greater with emtricitabine than with stavudine at week 52 (440 vs 405 cells/mm^3; p = 0.004).[16]

- A triple combination-therapy regimen of emtricitabine, efavirenz and didanosine maintained the suppression of viral load in patients switched from protease inhibitor (PI)-based triple therapy.[14] In this open-label, multicentre trial (n = 355), the number of patients with HIV RNA <50 copies/mL after 48 weeks was significantly higher in patients who switched to emtricitabine 200mg once daily therapy (n = 178) than in those who continued to receive PI-based therapy (n = 177) [95% vs 87%; p = 0.01], although the difference in median increase in CD4+ cell count between treatment groups was not statistically significant (21 vs 13 cells/mm^3; baseline CD4+ cell count not reported).[14]

- Emtricitabine- and lamivudine-based combination therapy demonstrated similar efficacy in two trials involving ART-naive (study 302) and ART-experienced patients (study 303) [results of the two studies have been presented together in a poster].[18] At 48 weeks in study 303, 67% and 72% of patients receiving emtricitabine 200mg once daily (n = 294) and lamivudine 150mg twice daily (n = 146) had HIV RNA levels of <50 copies/mL.[4] In addition, the overall incidence of virological failure between

treatment groups was similar in both studies (10% in each arm of study 302 and 8.0% in each arm of study 303).[18] In study 302, ART-naive patients (n = 468) were randomised to receive emtricitabine or lamivudine in combination with stavudine and either nevirapine or efavirenz (dosages not reported).[18] In study 303, ART-experienced patients (n = 440) continued on lamivudine-based triple therapy while maintaining the background regimen or switched from lamivudine to emtricitabine in the treatment regimen.[18]

- In an extension of study 303 (study 350), 294 patients (77% with HIV RNA <400 copies/mL) continued to receive or switched to emtricitabine-based triple therapy for a mean duration of 140 weeks.[19] At week 72, 61% (179/294) maintained suppression of HIV RNA levels below 400 copies/mL.[19] Furthermore, the probability of virological failure at 72 weeks was 11%[19] and the Kaplan Meier probability of virological failure through 4 years was 11%.[45]

- Data from further studies support the efficacy of emtricitabine 200mg once daily as a component of triple therapy.[12,17] In one study (ANRS-091; n = 40), HIV RNA levels after 24 weeks of therapy were reduced from baseline (median 4.77 $\log_{10}$ copies/mL) to <400 copies/mL in 98% of ART-naive patients (median reduction 3.5 $\log_{10}$ copies/mL).[17] Furthermore, long-term treatment in the ARNS-091 trial indicated that the percentage of patients with HIV RNA <400 copies/mL decreased to 90% at week 64[40] and to 85% at week 96 (intention-to-treat analyses).[41] In addition, 80% of patients had HIV RNA levels of <50 copies/mL after 96 weeks of therapy[41] compared with 93% at week 24 (significance not reported).[17]

- In a small pilot study in which ART-naive patients received either emtricitabine 200mg once daily (n = 18) or abacavir 300mg twice daily (n = 19) in a background of stavudine and efavirenz (dosages not reported), more patients in the emtricitabine group decreased their viral HIV levels from baseline (4.6 $\log_{10}$ copies/mL) to <50 copies/mL after 24 weeks (83.3% vs 63.2%) although the difference was not significant due to the small sample size.[39]

- In a subset analysis of study 302, there appeared to be no statistical difference in the proportion of men or women receiving emtricitabine 200mg once daily who presented with virological failure (viral load >400 copies/mL) [14% vs 10%], nor were there differences in the CD4+ cell response (increased to 203 vs 182 cells/mm^3) [baseline CD4+ cell count and significance vs baseline not reported].[12] In the ANRS-091 trial the median CD4+ cell count increased from 373 cells/mm^3 at baseline to 532 (42%), 592 (59%) and 632 (69%) cells/mm^3 after 24,[17] 64[40] and 96[41] weeks of therapy, respectively.

- Furthermore, in subset analyses of studies 301 (230 of 571 patients) and 302 (74 of 468 patients), the Kaplan Meier probability of virological failure (viral load >400 copies/mL) in patients with a high pretreatment viral load (>100 000 copies/mL) was lower in patients receiving emtricitabine 200mg once daily than in those receiving stavudine at standard dosages (8.5% vs 23.6%; study 301) or lamivudine 150mg twice daily (6.5% vs 11.0%; study 302) [significance not reported].[46]

In Children and Adolescents

- The efficacy of emtricitabine in children and adolescents has only been evaluated in two small studies.[13,15] In the completed nonrandomised trial, 51 ART-naive and 31 ART-experienced children and adolescents with HIV infection (aged 3 months to 17 years) were given emtricitabine 6 mg/kg once daily (maximum 200 mg/day) as part of triple therapy (ART-naive patients also received stavudine and lopinavir/ritonavir [at standard dosages]; ART-experienced patients replaced lamivudine in their existing regimen with emtricitabine [other drugs

were not specified]).[15] After 24 weeks of therapy, 92% and 84% of ART-naive and ART-experienced patients achieved and/or maintained durable suppression of HIV RNA level <400 copies/mL (63% and 71% of patients achieved RNA <50 copies/mL). Furthermore, a similar number of patients in both treatment groups experienced virological failure (HIV RNA >400 copies/mL or >1 $\log_{10}$ increase within 1 month) [5.9% vs 6.5%].[15]

- In the second ongoing study,[13] 30 patients aged 3–21 years (median age 10.5 years) who were either ART-naive or minimally treated (<6 weeks) received emtricitabine 6 mg/kg once daily as part of triple therapy with didanosine (240 mg/m^2) and efavirenz (standard dosages). Preliminary findings at week 16 reported that 87% and 74% of patients had HIV RNA levels of <400 and <50 copies/mL.[13]
- CD4+ cell count increased by 9%[13] and 28%[15] after 16[13] and 24[15] weeks in these two studies.

4. Tolerability

- Emtricitabine was generally well tolerated in dose-finding monotherapy studies (12–14 days)[42,43] and during combination therapy in trials discussed in section 3.[12,13,15-18,47] The most frequent treatment-emergent adverse events (i.e. in >5% of patients) in trials of up to 48 weeks duration included infection, nausea, headache, rash, flu-like syndrome and diarrhoea.[12,16-18]
- Emtricitabine was well tolerated at dosages of 50–400 mg/day during 14 days of monotherapy in adult patients with HIV infection.[42] No serious or severe adverse events were reported and moderate adverse events occurred in only a small number of patients (nausea [4/41; 9.8%], headache [3/41; 7.3%], diarrhoea [2/41; 4.9%] and pharyngitis [2/41; 4.9%]).[42]
- During therapy with emtricitabine (in combination with didanosine and efavirenz[16,17] or stavudine and either efavirenz or nevirapine[12,18]) for 24–48 weeks, ART-naive patients experienced treatment-emergent adverse events that were generally mild to moderate in severity. Infection (26–42%), headache (20–34%), rash (10–33%) and diarrhoea (22–33%) were the most common events reported. In the smallest of these trials (n = 40),[17] 73% of patients experienced CNS complaints during the first few days of therapy (including sleep disturbances with insomnia, abnormal dreaming, mood changes and depression), although events appeared to be transitory.
- In another trial in patients (n = 234) with HIV infection, the incidence of adverse events was similar between men and women (12% vs 11%), although more women than men were lost to follow-up (6% vs 1%) or discontinued for other reasons (8% vs 3%).[12] Skin discolouration (including hyperpigmentation of the palms and/or soles) was also reported by patients receiving emtricitabine 200mg once daily (number not specified); however, it was generally mild and asymptomatic.[4]
- Emtricitabine-based triple therapy was as least as well tolerated as stavudine-based triple therapy in a double-blind, multicentre trial.[16] After a median follow-up of 42 weeks, the incidences of diarrhoea, nausea, paraesthesia and symptomatic hyperlactacidaemia/lactic acidosis were significantly lower in ART-naive patients treated with emtricitabine 200mg once daily than in those receiving stavudine at standard doses (both in combination with once-daily didanosine and once-daily efavirenz) [all $p \leq 0.05$; figure 1].[16] Furthermore, the number of patients discontinuing treatment because of adverse events was twice as high with stavudine as with emtricitabine (13.9% vs 6.7%; $p < 0.03$).[16]
- Overall, the incidence of treatment-emergent adverse events with emtricitabine 200 mg/day was similar to that with lamivudine 150mg twice daily as part of triple therapy in both ART-naive and ART-experienced patients after 48 weeks in studies 302 and 303.[18] In treatment-naive patients, the most common adverse events reported with emtricitabine

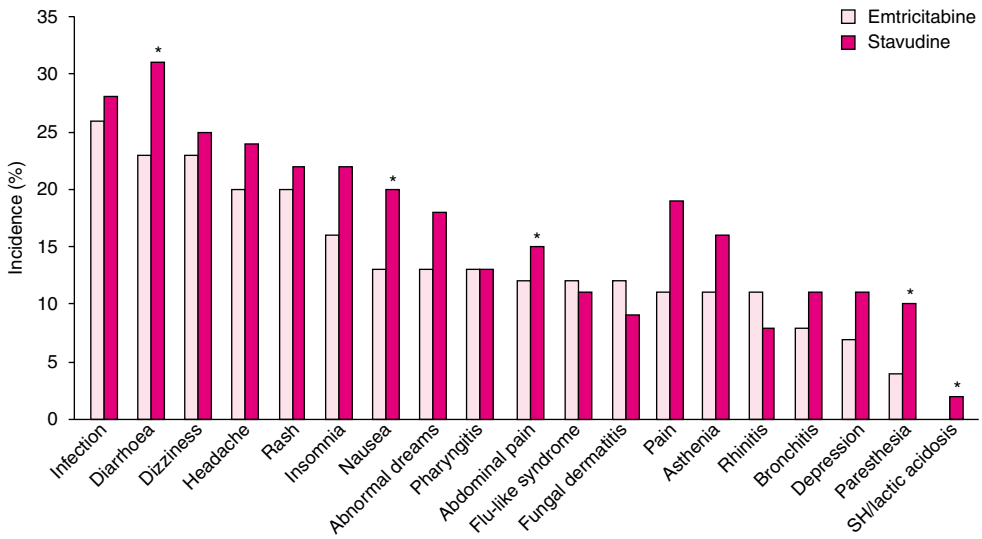


Fig. 1. Comparative tolerability profile of emtricitabine- and stavudine-based triple therapy. In a randomised, double-blind, mutlicentre trial, antiretroviral therapy-naive patients with HIV infection received emtricitabine 200 mg/day (n = 286) or stavudine at standard dosages (n = 285) in combination with once-daily didanosine and once-daily efavirenz (dosages not reported) during a median of 42 weeks of therapy. * $p \leq 0.05$ vs emtricitabine; **SH** = symptomatic hyperlactacidaemia.[16]

(n = 234) and lamivudine (n = 234) were infection (42% vs 50%), CNS events (35% vs 39%), headache (34% vs 38%) and rash (33% vs 29%), although flu-like syndrome, nausea and abdominal pain were also experienced by >20% of patients in both treatment groups.[18] In the second study (study 303), neither patients continuing on lamivudine-based therapy (n = 294) nor those switching to emtricitabine (n = 146) reported CNS events. Infection, diarrhoea, nausea and rhinitis were the most common events in this study, occurring in 18–30% of patients receiving emtricitabine and in 12–21% of patients receiving lamivudine.[18]

- Emtricitabine-based triple therapy was also generally well tolerated in children and adolescents.[13,15] During 24 weeks of therapy with emtricitabine 6 mg/kg/day only five adverse events were reported by a total of 82 children and adolescents aged 4 months to 16 years.[15] Pancreatitis, vomiting and pleural effusion were each reported by 1 of 51 ART-naive children and adolescents, with leucopenia and anaemia each reported by 1 of 31 ART-experienced children and adolescents.[15] In addition, 1 of 30 children and adolescents discontinued therapy with emtricitabine at or before week 16 in a second, ongoing study due to rash.[13]

Laboratory Values

- In several studies, abnormal laboratory values (including creatine kinase, alkaline phosphatase, total bilirubin, serum amylase, serum lipase and neutrophil levels) were observed in up to 16% of adults treated with emtricitabine 200 mg/day.[16-18,47]
- In general, there was no between-group difference in the incidence of treatment-emergent laboratory abnormalities in recipients of emtricitabine-based triple therapy versus those receiving stavudine-based triple therapy.[16] However, serum amylase levels were elevated in a significantly greater number of ART-naive patients receiving stavudine compared with those receiving emtricitabine (9% vs 3%; $p < 0.05$). Patients also received once-daily didanosine and once-daily efavirenz in this study.[16]

• The incidence of grade 3 and 4 laboratory abnormalities with emtricitabine-based triple therapy was also generally similar to that with lamivudine-based triple therapy in two 48-week trials;[24,47] data from the largest (open-label) trial is shown in figure 2.[24] In the second trial, which involved 468 patients, there was no between-group difference in the incidence of treatment-emergent grade 4 elevations in liver enzymes (aspartate transaminase [AST], alanine aminotransferase [ALT], alkaline phosphatase and bilirubin) during 48 weeks of triple therapy with stavudine and either nevirapine or efavirenz (9% vs 12%). However, the occurrence of elevated liver enzymes was twice as high in female patients than in male patients (12% vs 6%; $p < 0.05$) and two patients died of liver failure during therapy (treatment group not reported; available as an abstract).[47] Investigators attributed the incidence of elevated liver enzymes and liver toxicity to the use of nevirapine in combination with stavudine during triple drug therapy.[47]

• During longer-term therapy with emtricitabine 200 mg/day (72 weeks) in 294 patients with HIV infection, most laboratory abnormalities were mild to moderate in intensity, with an incidence of grades 3 and 4 laboratory abnormalities (including creatine kinase, triglycerides, AST, ALT and neutrophil levels) of 18% and 15%.[19]

• The incidence of grades 3 and 4 laboratory abnormalities was low in children and adolescents aged between 4 months and 16 years during 24 weeks of therapy; overall, only 6 of 82 children and adolescents (7.3%) experienced an abnormality (including ALT, haemoglobin, neutrophils, serum amylase or serum lipase levels).[15]

5. Dosage and Administration

Emtricitabine has recently been approved by the US FDA for use in combination with other antiretroviral agents for the treatment of HIV infection.[5] Emtricitabine is recommended for patients aged >18 years at a dosage of 200mg once daily, either with or without food.[4] The dosing interval should be adjusted to 48–96 hours in patients with renal impairment (creatinine clearance ≤50 mL/min).[4] In addition, caution should be used when administering the drug to patients aged >65 years.[4] Patients receiving emtricitabine should be monitored for lactic acidosis and hepatotoxicity, and treatment should be suspended if either condition occurs.[4]

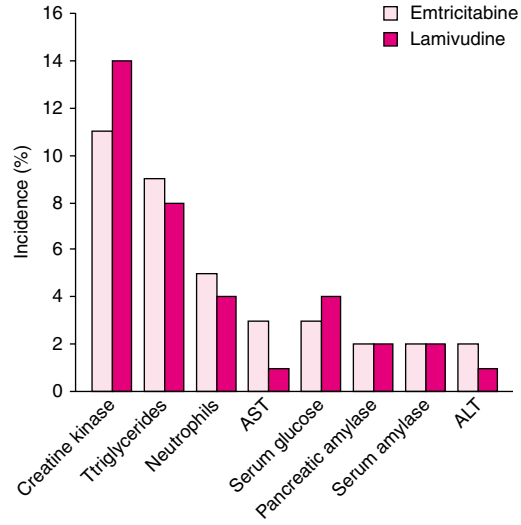


Fig. 2. Comparative incidence of grade 3 and 4 laboratory abnormalities. In a randomised, open-label 48-week trial antiretroviral therapy-experienced patients infected with HIV received emtricitabine 200mg once daily (n = 294) or lamivudine 150mg twice daily (n = 146) in combination with stavudine and zidovudine (dosages not reported). **ALT** = alanine aminotransferase; **AST** = aspartate transaminase; between-group significance not reported.[18]

6. Emtricitabine: Current Status

Emtricitabine is a once-daily NRTI which has recently been approved in the US for use in combination therapy for the treatment of HIV infection in adults. In combination therapy, emtricitabine significantly reduced or maintained suppression of HIV RNA levels in the majority of patients for up to 96 weeks. Emtricitabine-based therapy was generally well tolerated. Treatment-emergent adverse events were mild to moderate in intensity and included

infection, nausea, headache, rash, flu-like syndrome and diarrhoea.

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