Drugs 2003; 63 (11): 1089-1098
0012-6667/03/0011-1089/$33.00/0

Lamivudine/Zidovudine/Abacavir

Triple Combination Tablet

Tim Ibbotson and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ The triple combination tablet containing lamivudine (150mg), zidovudine (300mg) and abacavir (300mg, as abacavir sulfate) is a new formulation of three nucleoside analogue reverse transcriptase inhibitors.

▲ Two studies in treatment-naive patients (one double-blind, one nonblind) have reported that lamivudine/zidovudine (dual combination tablet) plus abacavir showed efficacy similar to that of lamivudine/zidovudine plus indinavir. In both studies, similar numbers of patients in each treatment group had plasma HIV RNA levels ≤400 copies/mL at week 48 (51% vs 51% and 64% vs 50%).

▲ In treatment-experienced patients with baseline plasma HIV RNA levels <50 copies/mL, switching to lamivudine/zidovudine/abacavir (triple combination tablet) was as effective as remaining on highly active antiretroviral treatment (mainly protease inhibitor [PI]-based). Virological failure, the primary endpoint, defined as two consecutive plasma HIV RNA values >400 copies/mL, was reported in 22% of patients in both treatment groups at week 48.

▲ Treatment-naive patients receiving lamivudine/zidovudine/abacavir combination therapy experienced several adverse events, including nausea, malaise/fatigue and vomiting.

Features and properties of the lamivudine (LAM)/zidovudine (ZDV)/abacavir (ABA) triple combination tablet (Trizivir®)	
Indication	
HIV infection	
Mechanism of action	
Antiviral	Nucleoside analogue reverse transcriptase inhibitors (NRTIs)
Dosage and administration	
Usual doses in clinical trials	LAM 150mg/ZDV 300mg/ABA 300mg
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile of oral LAM 150mg/ZDV 300mg/ABA 300mg after single administration as a single combination tablet to fasted healthy volunteers	
Area under the plasma concentration-time curve (mg • h/L)	LAM 6.06, ZDV 2.07, ABA 7.31
Peak plasma concentration (mg/L)	LAM 1.57, ZDV 1.36, ABA 3.29
Time to peak plasma concentration (h)	LAM 1.35, ZDV 0.84, ABA 0.96
Adverse events	
Serious events (monotherapy or combination therapy)	Hypersensitivity reaction (ABA); lactic acidosis, hepatomegaly with steatosis (NRTIs and other antiretroviral agents); bone marrow suppression, neutropenia, anaemia, myopathy (ZDV)
Most common (triple combination therapy)	Nausea, malaise/fatigue, vomiting, headache, diarrhoea, loss of appetite/anorexia, fever.

The estimated number of individuals with HIV infection or AIDS throughout the world was 36 million at the end of 2000.[1] In the US alone, up to 900 000 people are infected with HIV and at least 200 000 of them are not aware of their infection.[2] Worldwide, among infectious diseases, HIV/AIDS is the second leading cause of death (2 673 000 in 1999).[1]

US and British guidelines[3-5] endorse the use of highly active antiretroviral therapy (HAART) as initial therapy for patients with HIV infection. Such regimens include the combination of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or two PIs with or without NRTIs.[3-5] In particular, PI-containing HAART is recommended because these regimens have been associated with significant reductions in morbidity and mortality (reviewed by Plosker and Noble[6]). Moreover, three- or four-drug maintenance regimens are associated with significantly lower rates of virological failure compared with two-drug regimens.[7] Triple NRTI therapy has been recommended as an alternative treatment based on data from clinical trials evaluating surrogate endpoints.[3] Nevertheless, as for two NRTIs plus an NNRTI, data are not yet available on clinical outcome in patients receiving triple NRTI therapy. Moreover, these regimens may show suboptimal virological efficacy in patients with high baseline HIV RNA levels.

Most antiretroviral regimens are complex. They produce major adverse events, pose adherence and compliance difficulties, and may induce viral resistance because of nonadherence to the drug regimen and/or suboptimal levels of antiretroviral agents. Current guidelines recommend that antiretroviral therapy should be individualised based on the quality of supporting data, regimen potency, tolerability, adverse event profile, potential for drug interactions, convenience of treatment and potential adherence to therapy.[3,4] Adherence to treatment is a key determinant of both the extent and duration of virological response and several clinical trials have shown that 90–95% of doses must be taken in order to achieve maximum viral suppression.[3] Potential advantages of triple NRTIs regimens include ease of use and adherence (compared with PIs), sparing of PIs and NNRTIs for later use, and limited cross-resistance within the NRTI class.[3]

This profile focuses on the recently developed triple combination tablet (Trizivir®[1]) containing three NRTIs: lamivudine 150mg, zidovudine 300mg and abacavir 300mg. In addition, for completeness, information on this combination of drugs administered as a lamivudine/zidovudine double combination tablet plus abacavir or as individual drugs are also discussed.

Guidelines for the use of antiretroviral agents suggest several strategies to improve patients' adherence to treatment.[3] These include, among others, reduction of dose frequency and number of pills, simplifying food requirements and avoiding drug interactions. The lamivudine/zidovudine/abacavir triple combination tablet was designed with the intention of reducing these complicating factors and thus improving adherence.

1. Pharmacodynamic Profile

- The mechanism of action of NRTIs involves the intracellular conversion of the drugs to their active 5′-triphosphate metabolites. Lamivudine, zidovudine and abacavir are synthetic nucleoside analogues that are converted to lamivudine triphosphate (L-TP), zidovudine triphosphate (ZDV-TP) and carbovir triphosphate, respectively. L-TP, ZDV-TP and carbovir triphosphate inhibit HIV-1 reverse transcriptase activity mainly via DNA chain termination after incorporation of the nucleoside analogue. Moreover, carbovir triphosphate competes with deoxyguanosine triphosphate (dGTP), the natural substrate of HIV-1 reverse transcriptase.[8]
- The pharmacodynamic properties of lamivudine, zidovudine and abacavir, as single agents or in combination, have been studied extensively and are reviewed in detail elsewhere.[9-13]

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

Antiviral Activity

● The *in vitro* antiviral activity of lamivudine, zidovudine and abacavir against HIV has been assessed in a number of cell lines and each of these agents have been shown to have good activity against HIV.[9,10,12] Lamivudine, zidovudine and abacavir show synergistic and/or additive activity against HIV *in vitro* when administered with each other or in combination with several other antiretroviral drugs.[8-10,12,13] However, the relationship between the *in vitro* activity of these agents against HIV and the *in vivo* inhibition of HIV replication has not been established.

Resistance

● HIV isolates with reduced sensitivity to lamivudine, zidovudine or abacavir have been detected *in vitro* and in HIV-infected patients receiving lamivudine, zidovudine, abacavir or lamivudine plus zidovudine.[8-10,12]

● In lamivudine-treated patients, viral resistance was caused by mutations in the HIV reverse transcriptase gene at codon 184 from methionine to isoleucine or valine. Patients treated with zidovudine showed HIV isolates with amino acid substitutions in the HIV reverse transcriptase gene (M41L, D67N, K70R, K219Q, L210W and T215Y/F).[8,13,14] HIV isolates from patients treated with abacavir showed mutations that resulted in amino acid substitutions in the HIV reverse transcriptase gene at positions K65R, L74V, Y115F and M184V.[8,15,16] In patients receiving abacavir monotherapy for 24 weeks followed by the addition of lamivudine and zidovudine for 24 weeks, high level resistance to abacavir was induced by the combination of M184V and zidovudine- or abacavir-related mutations.[15,16] Walter et al. reported that the presence of any three of M184V, M41L, L210W, T215Q/F/C mutations conveyed high-level resistance (>5.5-fold reduced susceptibility measured by phenotyping) to abacavir.[15]

● In a meta-analysis of four trials in NRTI-experienced patients (n = 120; baseline plasma HIV RNA levels >400 copies/mL) who received abacavir in addition to stable background therapy,[17] a decrease in viral load of >0.5 $\log_{10}$ copies/mL occurred in 50% of patients after a median of 24 weeks' follow-up, despite a reduction in phenotypic susceptibility of between 4.5- and 6.5-fold. Only a phenotypic resistance of >6.5-fold conveyed a significant reduction in the viral load response to abacavir, with only 14% of affected patients having a >0.5 $\log_{10}$ decrease in HIV RNA levels.

● Data presented in a poster[18] showed that after at least 16 weeks' treatment with lamivudine/zidovudine plus abacavir, 90% (35 of 39) of patients showing virologic failure harboured wild type or M184V genotype HIV-1 (approximately 12% of total study population). Only 10% of patients exhibited isolates containing M184V plus other mutations. By week 48, the proportions were 44 and 56%, respectively.[18] This study only included patients (n = 43) who showed virological failure after 48 weeks of double combination tablet (lamivudine and zidovudine) plus abacavir treatment[19] (study CNA 3005) and were followed for an additional 48 weeks.[18] During this time patients were allowed to remain on their initial regimen.

● Lamivudine/zidovudine/abacavir triple combination therapy suppressed the emergence of resistance-conferring mutations to a greater extent than lamivudine/zidovudine treatment.[20] In antiretroviral treatment-naive HIV-infected patients (phase III study CNA 3003 published as an abstract), treatment with lamivudine/zidovudine/abacavir (administered as a dual combination tablet plus abacavir; n = 72) induced the appearance of viral isolates containing resistance-associated mutations in only 17% (12 of 72) of patients after 48 weeks.[20] Among these resistant viral isolates, 75% (9 of 12) contained only the M184V mutation, 16% (2) double abacavir-resistant mutations (M184V/L74V and M184V/Y115F) and 8% (1) contained a triple mutation (M184V/M41L/T215Y).[20]

Cross-Resistance

● Cross-resistance among NRTIs has been previously reported. In general, it appears that multiple mutations need to be present in the HIV isolates to induce multiple drug resistance.[8,15]

• Isolates containing mutations that conferred abacavir resistance were also resistant to lamivudine, didanosine and zalcitabine *in vitro*. Isolates that show cross-resistance between lamivudine and zidovudine have not been reported. In patients receiving zidovudine plus didanosine or zidovudine plus zalcitabine for ≥1 year, isolates resistant to lamivudine, zidovudine, didanosine, zalcitabine and stavudine have been recovered.[8]

Metabolic Effects

• Patients switched from treatment with NRTIs plus a PI to lamivudine/zidovudine/abacavir combination therapy (see section 3) had significant decreases from baseline in nonfasting cholesterol (by a median of 35 mg/dL [0.91 mmol/L] at week 4, remaining less than baseline thereafter) and triglyceride levels (reduction of 43 mg/dL [1.11 mmol/L] at week 48) in a randomised comparative trial.[21] In contrast, cholesterol and triglyceride levels did not change markedly from baseline in the patients who continued to receive NRTI plus PI therapy. The between-group differences in changes from baseline in cholesterol and triglyceride levels were significant ($p < 0.05$) at all evaluation timepoints. Similarly in the TRIZAL-AZL30002 study significantly higher reductions in fasting total cholesterol and triglycerides occurred in patients receiving the lamivudine/zidovudine/abacavir triple combination tablet than in those continuing with HAART (both $p < 0.001$).[22]

• Data from a nonblind, randomised study, published in an abstract,[23] indicated that patients receiving the lamivudine/zidovudine/abacavir triple combination tablet showed a reduced incidence of lipodystrophy abnormalities and significant reductions in cholesterol and triglycerides compared with those continuing on HAART which was mainly PI-based. At endpoint (week 48), 28 and 42% of patients receiving the triple combination tablet or HAART, respectively, showed ≥ one lipodystrophy symptom ($p < 0.05$). Changes from baseline of cholesterol (−0.80 vs −0.44 mmol/L, $p < 0.001$) and triglycerides (−0.17 vs +0.01 mmol/L, $p < 0.01$) were also reported in both treatment groups.[23]

• Similar results in patients' fasting lipid concentrations were reported in an abstract that evaluated the effect of switching from PIs to abacavir treatment for 12 months (study design was not specified).[24] This study included patients (n = 31) with PI-related metabolic abnormalities. After 12 months of treatment, abacavir monotherapy was associated with an improvement of insulin sensitivity compared with PI treatment (+58 vs −6 μmol/L/min, respectively).

• In patients receiving quadruple HIV therapy with lamivudine/zidovudine plus abacavir each twice daily in combination with efavirenz (600mg) once daily, median cholesterol levels and fasted glucose levels were increased significantly at week 48 relative to week 2 (cholesterol, 5.3 vs 4.6 mmol/L; fasted glucose 5.05 vs 4.55 mmol/L: both $p < 0.001$).[25]

2. Pharmacokinetic Properties

• The pharmacokinetic profiles of lamivudine, zidovudine and abacavir have been reviewed in detail previously.[9,10,12] Oral bioavailability values for lamivudine, zidovudine and abacavir are 86%, 64% and 86%, respectively.[8]

• Data from a nonblind, crossover study[26] (n = 12) showed that the lamivudine/zidovudine/abacavir triple combination tablet and a double combination tablet (lamivudine/zidovudine) plus abacavir were bioequivalent in patients infected with HIV. In patients receiving the triple combination tablet or the double combination tablet plus abacavir, respectively, area under the plasma concentration-time curve (AUC) values were 5.51 versus 5.53 mg • h/L (lamivudine), 1.38 versus 1.46 mg • h/L (zidovudine) and 6.08 versus 5.87 mg • h/L (abacavir). Maximum plasma concentration (C_{max}) values were 1.26 versus 1.40 mg/L (lamivudine), 1.19 versus 1.15 mg/L (zidovudine) and 3.09 versus 3.19 mg/L (abacavir). Median time to C_{max} (t_{max}) was 1.5 versus 1.24 hours (lamivudine), 0.75 versus 0.75 hours (zidovudine) and 0.75 versus 0.75 hours (abacavir). Apparent clearance values were 27 versus 27 L/h (lamivudine), 217 versus 206 L/h (zidovudine) and 51 versus 49 L/h (abacavir).[26]

• The triple combination tablet containing lamivudine 150mg, zidovudine 300mg and abacavir 300mg was bioequivalent to the individual drugs given separately when administered under fasting conditions to healthy volunteers (n = 24).[27] AUC, C_{max} and t_{max} values were similar after administration of the triple combination tablet or the individual drugs sequentially. AUC values for lamivudine, zidovudine and abacavir (administered under fasting conditions) were 6.06, 2.07 and 7.31 mg • h/L, respectively, corresponding C_{max} values were 1.57, 1.36 and 3.29 mg/L, and t_{max} values were 1.35, 0.84 and 0.96 hours.[27] When the triple combination tablet was administered with food, the rate of absorption was slowed, t_{max} was delayed and C_{max} of all three components was reduced.[27] Mean elimination half-life ($t_{1/2}$) values among patients receiving the triple combination tablet without or with food, respectively, were 6.47 versus 5.69 hours (lamivudine), 2.50 versus 2.63 hours (zidovudine) and 1.69 versus 1.96 hours (abacavir).[27] According to the manufacturer's prescribing information,[8] lamivudine, zidovudine and abacavir have plasma elimination $t_{1/2}$ values of 5–7, 0.5–3 and 1.45 hours, respectively, when administered to fasting patients.

Drug Interactions

• In general, no clinically significant pharmacokinetic interactions occur between lamivudine, zidovudine and abacavir in HIV-infected adults. Lamivudine, zidovudine and abacavir are not significantly metabolised by cytochrome P450 enzymes; therefore, occurrence of clinically significant drug interactions with drugs metabolised through these pathways is unlikely.[8] No clinically significant interactions were observed when different combinations of lamivudine, zidovudine and abacavir were administered to HIV-infected patients.[8]

• Data from studies with the individual drugs, presented in the triple combination tablet prescribing information,[8] show that AUC values of lamivudine, zidovudine or abacavir may be altered by co-administration with: nelfinavir or cotrimoxazole (trimethoprim/sulfamethoxazole) [lamivudine AUC ↑10 or 43%, respectively]; atovaquone, fluconazole, methadone, nelfinavir, probenecid, ritonavir, valproic acid (zidovudine AUC ↑31, ↑74, ↑43, ↓35, ↑106, ↓25 and ↑80%, respectively) and ethanol (alcohol) [abacavir AUC ↑41%]. In these studies, the dosages of lamivudine, zidovudine and abacavir were often different from the triple combination tablet dosage.

3. Therapeutic Trials

The efficacy of the triple combination of lamivudine 150mg, zidovudine 300mg and abacavir 300mg, administered twice daily, has been evaluated in several clinical trials in antiretroviral therapy-naive or -experienced patients with HIV infection. One randomised, nonblind, comparative, replacement trial published as an abstract[22] (TRIZAL-AZL30002) evaluated the efficacy of the triple combination tablet. However, this combination was generally administered twice a day as a fixed-dose double combination tablet (Combivir®) containing lamivudine 150mg and zidovudine 300mg, plus one abacavir 300mg tablet.[19,21,28-33] The efficacy of lamivudine, zidovudine and abacavir in quadruple therapy regimens with efavirenz and amprenavir has also been investigated.[25,34]

In all studies, surrogate endpoints (usually plasma HIV RNA levels and CD4+ cell counts) were used to assess drug efficacy. The primary endpoint in several trials reviewed in this section was virological failure, defined as two consecutive plasma HIV RNA values of >400 copies/mL.

• Compared with patients receiving conventional antiretroviral treatment (two NRTIs plus a PI), patients treated with lamivudine/zidovudine plus abacavir showed similar suppression of HIV RNA levels in several trials.[19,28,31,32] Two 48 week, randomised studies (one double-blind [CNA3005], n = 562[19]; one nonblind [CNA3014] published as an abstract, n = 342[28]) have compared abacavir- (300mg twice daily) with indinavir- (800mg three times daily) containing regimens in antiretroviral-naive, HIV-infected adults receiving lamivudine/zidovudine (150mg/300mg) twice daily.[19,28,35]

• At baseline, patients in both studies had CD4+ counts of 299–360 cells/μL and 4.78–4.88 $\log_{10}$

copies/mL of HIV RNA. At week 48 in CNA3005, similar proportions of patients receiving abacavir and indinavir regimens had plasma HIV RNA levels <400 copies/mL (51% vs 51%, figure 1); however, in CNA3014 significantly more patients receiving the abacavir regimen had plasma HIV RNA levels <400 copies/mL than those receiving the indinavir regimen (66% vs 50%; p = 0.002).[35] The number of patients with plasma HIV RNA levels <50 copies/mL was similar in both studies (60% vs 50% and 40% vs 46%, respectively). In each study, patients in both treatment groups showed comparable increases in CD4+ cell count at week 48 relative to baseline (CNA3005, +149 and +142 cells/μL; CNA3014, +148 and +153 cells/μL).[35]

- In CNA3005,[19] indinavir appeared more effective than abacavir in patients with baseline plasma HIV RNA levels >100 000 copies/mL (45% vs 31% of patients with <50 copies/mL at 48 weeks; figure 1). However, in CNA3014, similar proportions of patients from each treatment group with equally high baseline plasma HIV RNA achieved <400 copies/mL by week 48 (abacavir 60% vs indinavir 51%).[35] Significantly more patients receiving the abacavir regimen missed ≤1 dose/week during the final 4 weeks of CNA3014 compared with those receiving the indinavir regimen (72% vs 45%, p < 0.001).[35]

- Data from the TRIZAL-AZL30002 study[22] indicated that switching to treatment with the triple combination tablet containing lamivudine 150mg, zidovudine 300mg and abacavir 300mg (n = 106) twice daily, was as efficacious as remaining on a triple HAART (n = 103) regimen. Treatment-experienced patients (of whom 63% had previously received two NRTIs plus a PI) included in this study had baseline plasma HIV RNA levels of <50 copies/mL.[22] At endpoint (week 48), 22% of patients in both treatment groups showed evidence of virological failure (figure 2). Also, 18 and 22 patients receiving the triple combination tablet or HAART, respectively, discontinued treatment.

- In the TRIZAL-AZL30002 study, patients receiving the lamivudine 150mg/zidovudine 300mg/abacavir 300mg triple combination tablet (twice daily) found their treatment easier to take than those patients continuing triple HAART (p < 0.001).[22] No specific details about this finding were provided.

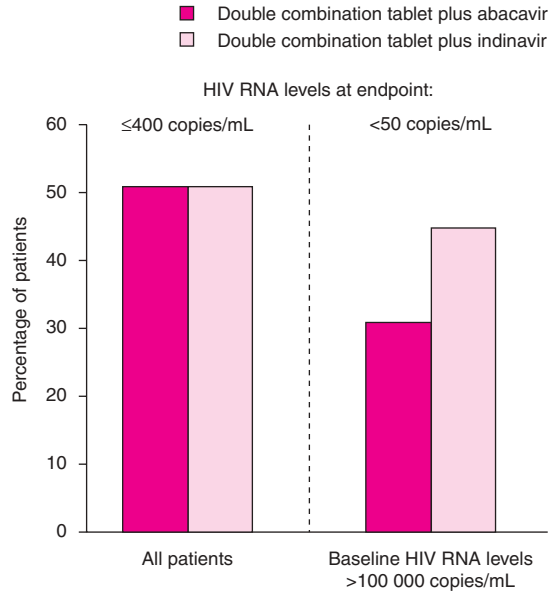

Fig. 1. Effects of triple therapy with lamivudine/zidovudine plus abacavir or indinavir in antiretroviral therapy-naive patients with HIV infection. Data from a 48-week, phase III, randomised, double-blind, multicentre study (CNA3005; n = 562, baseline HIV plasma level ≥10 000 copies/mL).[19] Patients received treatment with lamivudine (LAM) 150mg/zidovudine (ZDV) 300mg double combination tablet plus abacavir 300mg (twice daily) or LAM 150mg/ZDV 300mg plus indinavir 800mg (administered every 8 hours).[19] At treatment endpoint (week 48) the proportion of patients with plasma HIV RNA levels ≤400 copies/mL (primary endpoint) was determined. The figure also shows the proportion of patients showing HIV plasma levels <50 copies/mL in the subgroup of patients with baseline plasma HIV RNA levels >100 000 copies/mL.

- Switching to treatment with the lamivudine/zidovudine double combination tablet plus abacavir, twice a day for 48 weeks, was at least as efficacious as continued treatment with a triple HAART (PI-based) regimen in another trial.[32] Before enrolment, 94% and 86% of patients had received PI-containing combination therapy in the abacavir and PI treatment groups, respectively; 69% and 52% had received indinavir, and 65% and 68% had received lamivudine plus zidovudine. In this nonblind, randomised, multicentre, 48-week comparative trial[32] (n = 211; baseline plasma HIV RNA level <50 copies/mL), treatment failure (plasma HIV RNA

level >400 copies/mL, primary endpoint) was reported in 12% and 23% of patients receiving lamivudine/zidovudine plus abacavir or lamivudine/zidovudine plus a PI, respectively ($p < 0.05$). A significantly longer time to treatment failure was shown by patients receiving the triple NRTI regimen at 48 weeks ($p < 0.05$).[32]

- In a randomised comparative trial that enrolled patients previously treated with NRTIs plus a PI, virological failure (plasma HIV RNA levels >400 copies/mL in two consecutive samples) was reported in 6% of 79 patients continuing with the previous treatment regimen and in 15% of 84 patients (intention-to-treat data) who switched to a simpler treatment regimen of lamivudine/zidovudine plus abacavir ($p = 0.08$).[21] All of the study participants had experienced suppressed HIV RNA levels for at least 6 months prior to enrolment; patients with an archived reverse transcriptase mutation at codon 215 at baseline were excluded from the trial.

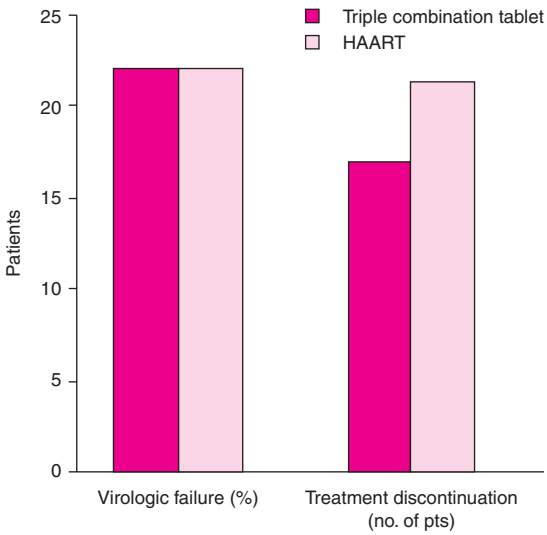

Fig. 2. Efficacy of switching to a triple combination tablet containing lamivudine 150mg, zidovudine 300mg and abacavir 300mg or remaining in triple highly active antiretroviral therapy (HAART) in a randomised, nonblind, comparative trial (the TRIZAL study).[22] Treatment-experienced patients with baseline plasma HIV RNA levels <50 copies/mL were randomised to switch to treatment with the triple combination tablet (n = 106) or remain on HAART (n = 103). The figure shows the percentage of patients with virological failure (defined as 2 consecutive plasma HIV RNA values of >400 copies/mL, primary endpoint) and the number of patients who had discontinued treatment at 48 weeks.

- Data from a nonblind, single arm study (n = 87) showed significant reductions from baseline in plasma HIV RNA levels in antiretroviral-experienced patients (some patients were PI-naive) receiving the lamivudine/zidovudine dual combination tablet plus abacavir.[33] After 48 weeks of treatment, 82% and 56% of patients had plasma HIV RNA levels of <400 copies/mL and <50 copies/mL, respectively.[33]
- Treatment of patients infected with HIV with the triple combination of lamivudine, zidovudine and abacavir was associated with increases from baseline in the CD4+ cell count, although statistical significance was not usually provided.[19,21,29,30,32,33]
- Two small, noncomparative studies have also examined the use of lamivudine, zidovudine and abacavir in quadruple therapy regimens, with efavirenz[25] or amprenavir.[34] Antiretroviral-naive HIV-1 infected adults (n = 31) received lamivudine/zidovudine (150mg/300mg), plus abacavir (300mg) both twice daily and efavirenz (600mg) once daily for 48 weeks.[25] At week 48, median CD4+ cell counts had increased relative to baseline (322 cells/μL vs 404 cells/μL) and 77% of patients had plasma HIV RNA levels <50 copies/mL (patients who switched medications were considered treatment failures under this analysis).[25]
- In lamivudine- and PI-naive patients (intent to treat population n = 41) who received lamivudine/zidovudine, (150mg/300mg) abacavir (300mg) and amprenavir (1200mg) each twice daily, all patients had plasma HIV RNA levels <500 copies/mL after 48 weeks treatment.[34] Within this study, 27 patients were newly infected with HIV, and 14 patients had chronic infections. At week 48, 65% and 57% of these patients has plasma HIV RNA levels <50 copies/mL, and mean increases in CD4+ cell counts were 150 cells/μl and 155 cells/μl, respectively.[34]

4. Tolerability

- Treatment-naive patients receiving the combination tablet (lamivudine 150mg/zidovudine 300mg) plus abacavir 300mg (twice daily) or indinavir 800mg (every 8 hours) for 48 weeks showed similar adverse events profiles (figure 3).[19] In CNA3014,

9% of patients receiving lamivudine/zidovudine plus abacavir and 37% of patients receiving lamivudine/zidovudine plus indinavir reported difficulty taking the regimen.[28] Addition of abacavir for 16 weeks to lamivudine 150mg and zidovudine 300mg treatment did not induce substantial changes in the incidence of adverse events. The most commonly reported adverse events among treatment-naive patients (n = 262) receiving lamivudine/zidovudine/abacavir for 48 weeks included nausea (60% of patients), malaise/fatigue (44%), nausea and vomiting (30%), headache (28%), diarrhoea (26%), loss of appetite/anorexia (15%), and fever and/or chills (20%).[8] Combined data from four clinical trials of lamivudine 300 mg/day plus zidovudine 600 mg/day indicated that 7.2% (n = 237) and 2.9% (n = 241) of patients had neutropenia and anaemia, respectively.[8]

- Approximately 5% of patients receiving abacavir develop a hypersensitivity reaction which usually occurs within 6 weeks of initiating treatment although rare cases have been reported after 6 months. Although the syndrome may be mild initially, death may occur if abacavir treatment is not discontinued.[8,9] Symptoms of hypersensitivity are well documented and include skin rash, fever, fatigue, nausea, vomiting, diarrhoea, abdominal pain, lethargy, myalgia, myolysis, arthralgia, oedema, cough, dyspnoea, headache and paraesthesia. The hypersensitivity reaction usually resolves within 24 hours of discontinuing abacavir. However, fatal or severe hypersensitivity reactions can occur upon re-introduction of abacavir to patients with an unidentified history or symptoms of hypersensitivity. Abacavir should therefore not be restarted following a hypersensitivity reaction.[8]

- Patients in two noncomparative studies examining the use of lamivudine/zidovudine plus abacavir in combination with efavirenz[25] or amprenavir,[34] reported nausea and/or vomiting (42% and 93%), malaise/fatigue (26% and 44%) and skin rash (23% and 37%). Headache (61%) and loose stools (46%)[34] and dizziness/vertigo (39%) and sleep disorders (19%)[25] were also reported.

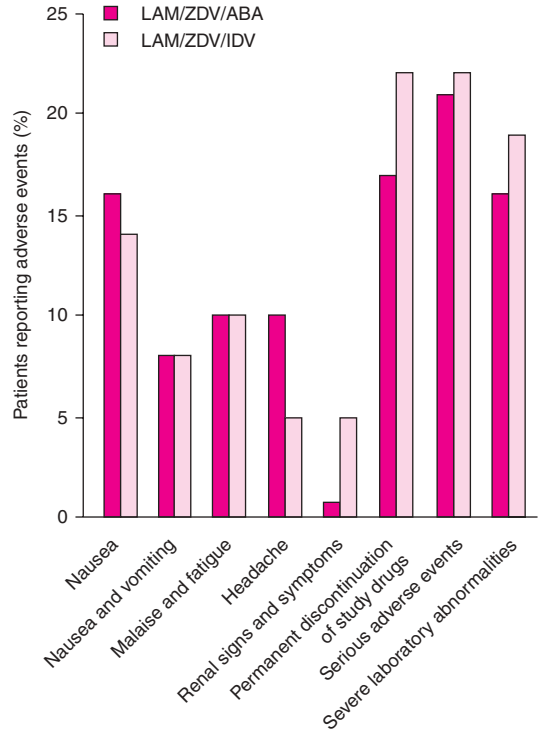

Fig. 3. Adverse event profile of lamivudine (LAM)/zidovudine (ZDV) plus abacavir (ABA) combination therapy in antiretroviral treatment-naive patients with HIV infection in a phase III, randomised, double-blind, multicentre study (CNA3005; n = 562, baseline plasma HIV RNA level ≥10 000 copies/mL).[19] Patients received LAM 150mg and ZDV 300mg (double combination tablet) plus ABA 300mg (twice daily) or LAM, ZDV plus indinavir (IDV; 800mg administered every 8 hours) for 48 weeks. Patients were counted only once even if they had two or more episodes of the same adverse event.

5. Dosage and Administration

- The triple combination tablet contains fixed doses of lamivudine 150mg, zidovudine 300mg and abacavir 300mg. The recommended oral dosage for adults is one tablet twice daily; the tablet can be administered with or without food.[8] Adults or adolescents who weigh less than 40kg, patients with creatinine clearance values ≤3 L/h (50 mL/min) or patients experiencing dose-limiting adverse events should not be given the triple combination tablet. The triple combination tablet is not recommended for the treatment of patients with hepatic impairment.[8]

6. Current Status

• The triple combination tablet containing lamivudine 150mg, zidovudine 300mg and abacavir 300mg is a new formulation of three NRTIs. In the only available comparative trial, the efficacy of this triple combination tablet was assessed measuring surrogate endpoints. In this study, switching to this new formulation appeared as effective as continuing HAART (mainly PI-based) in HIV-infected patients with baseline plasma HIV RNA levels <50 copies/mL. The incidence of adverse events was similar among patients receiving lamivudine/zidovudine/abacavir, lamivudine/zidovudine/indinavir or lamivudine/zidovudine. Clinical outcome data in HIV-infected patients receiving this triple combination tablet are not as yet available.

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Correspondence: *Caroline M. Perry*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz