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Abacavir plus Lamivudine

A Review of their Combined Use in the Management of HIV Infection

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Data Selection

Sources: Medical literature published in any language since 1980 on lamivudine/abacavir, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'lamivudine' and 'abacavir'. EMBASE search terms were 'lamivudine' and 'abacavir'. AdisBase search terms were 'lamivudine' and 'abacavir'. Searches were last updated 12 November 2004.

Selection: Studies in patients with HIV infection who received lamivudine and abacavir. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: HIV, lamivudine, abacavir, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Abacavir and lamivudine (two nucleoside analogue reverse transcriptase inhibitors [NRTIs]), as separate formulations in combination with other antiretroviral agents, are effective in the reduction of HIV RNA levels in antiretroviral-naive patients with HIV infection, and are generally well tolerated. A fixed-dose combination tablet of abacavir/lamivudine (Epzicom™, Kivexa™) has been developed for once-daily use and preliminary efficacy data are promising. Although further experience with this formulation is needed to fully determine its position in the management of HIV infection, a single, once-daily tablet that may be taken irrespective of food intake should aid adherence to treatment, a key factor in determining the success of an antiretroviral regimen. Thus, abacavir and lamivudine are two established components of first-line antiretroviral regimens for the management of HIV infection and the fixed-dose abacavir/lamivudine tablet has the potential to be an effective, easily adhered to and generally well tolerated component of first-line therapy.

Pharmacological Properties

The active metabolites of abacavir and lamivudine inhibit the HIV reverse transcriptase enzyme. The two drugs show additive or synergistic *in vitro* activity against HIV isolates.

HIV variants with reduced susceptibility to abacavir or lamivudine have been selected for *in vitro* and have also been isolated from patients receiving abacavir and/or lamivudine. Both drugs select for a methionine to valine substitution at position 184 (M184V) of the HIV reverse transcriptase enzyme. Other substitutions associated with abacavir monotherapy are leucine to valine at position 74 (L74V), lysine to arginine at position 65 (K65R) and tyrosine to phenylalanine at position 115 (Y115F).

A single dose of fixed-dose abacavir/lamivudine 600mg/300mg was bioequivalent to single doses of abacavir 600mg plus lamivudine 300mg, based on the values for systemic absorption and peak plasma concentration in healthy volunteers. Systemic exposure to the drugs following administration of the fixed-dose tablet is not altered by food.

Abacavir and lamivudine are both rapidly absorbed after oral administration. Both drugs are eliminated predominantly in the urine: abacavir primarily as metabolites and lamivudine mainly unchanged.

The pharmacokinetic properties of abacavir and lamivudine, including the intracellular pharmacokinetics of their active metabolites, support their use as once-daily therapy.

Therapeutic Efficacy

Abacavir plus lamivudine (administered as separate formulations) have shown efficacy as the backbone of triple or quadruple antiretroviral therapy for antiretroviral-naive adult patients with HIV infection. When concomitant abacavir and lamivudine were used in combination with another NRTI, a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor for 48 weeks, up to 76.3% of recipients achieved plasma HIV RNA levels of <50 copies/mL and up to 82.5% achieved levels <400 copies/mL in intent-to-treat analyses.

The efficacy of abacavir plus lamivudine in combination with efavirenz was non-inferior to that of zidovudine plus lamivudine in combination with efavirenz.

Once-daily abacavir was non-inferior to twice-daily abacavir, both administered in combination with lamivudine and efavirenz, in adult patients with HIV infection.

Abacavir plus lamivudine was significantly more effective than zidovudine plus lamivudine in the reduction of viral load from baseline in children and adolescents with HIV infection, after results were corrected for concomitant nelfinavir or placebo.

At 24 weeks, 69% and 77% of antiretroviral treatment-naive patients receiving a fixed-dose abacavir/lamivudine 600mg/300mg tablet once daily plus efavirenz 600mg once daily achieved plasma HIV RNA levels of <50 and <400 copies/mL (intention-to-treat analysis). The other arm of this ongoing 48-week trial (fixed-dose abacavir/lamivudine plus tenofovir disoproxil fumarate) was discontinued after early virological nonresponse was observed in 49% of patients. The efficacy of the fixed-dose abacavir/lamivudine tablet was non-inferior to that of abacavir plus lamivudine as separate formulations (both arms as part of triple or quadruple antiretroviral therapy regimens) after 24 weeks in two trials in antiretroviral treatment-experienced patients.

Tolerability

As individual agents, abacavir and lamivudine are generally well tolerated; as yet, tolerability data for the fixed-dose combination tablet are limited. The most common (≥15%) treatment-emergent adverse events reported in early monotherapy trials in lamivudine recipients included diarrhoea, malaise and fatigue, headache, coughing, sleep disorders, muscle pain, abdominal pain or discomfort, temperature regulation disturbance, nausea and vomiting, and anxiety. Those reported in recipients of concomitant abacavir, lamivudine and zidovudine in several other trials were nausea and vomiting, diarrhoea, fever and headache. Approximately 5% of abacavir recipients developed a hypersensitivity reaction.

The incidence of drug-related adverse events was similar between the two treatment groups when once-daily abacavir was compared with twice-daily abacavir, both administered in combination with lamivudine and efavirenz in patients with HIV infection. A regimen of concomitant abacavir, lamivudine plus efavirenz was generally at least as well tolerated as that of zidovudine, lamivudine plus efavirenz.

Antiretroviral-naive patients with HIV infection receiving concomitant abacavir, lamivudine and efavirenz had a significantly lower rate of lipoatrophy compared with those receiving lamivudine, stavudine and efavirenz.

1. Introduction

At the end of 2003, the estimated number of people with HIV infection or AIDS throughout the world was 40 million, with an estimated 5 million people newly infected in 2003.[1] Eradication of HIV infection is not possible with currently available antiretroviral agents.[2] Consequently, one of the main goals of HIV treatment is optimal and prolonged suppression of viral load.

Recent US guidelines recommend that antiretroviral-naive patients with HIV infection be treated initially with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), two NRTIs plus one or two protease inhibitors (PIs), or three NRTIs.[2] However, the latter is recommended only if one of the first two regimens cannot, or should not, be used as first-line therapy.

Although recent advances in antiretroviral therapy have markedly improved clinical outcomes for patients with HIV infection, many patients still experience persistent HIV replication. Adherence to treatment, which is a key factor in determining the

effectiveness of long-term antiretroviral therapy, is likely to be improved by formulations that reduce the pill burden and the frequency of administration, and can be administered without regard to food intake.[2,3]

A fixed-dose combination tablet (Epzicom™, Kivexa™)[1] containing the two NRTIs abacavir 600mg and lamivudine 300mg is available in the US for once-daily use. This review focuses on the use of oral regimens containing abacavir plus lamivudine for the management of HIV infection, and outlines preliminary efficacy data for the once-daily, fixed-dose abacavir/lamivudine tablet. The pharmacological properties of abacavir[4,5] and lamivudine[6] have been extensively reviewed previously and are only very briefly overviewed here.

2. Pharmacodynamic Properties

Abacavir and lamivudine are members of the NRTI class of antiretroviral drugs. Each drug is converted intracellularly to its active 5′-triphosphate metabolite, carbovir triphosphate or lamivudine triphosphate (section 3).[7] Carbovir triphosphate competes with deoxyguanosine triphosphate and lamivudine triphosphate competes with deoxycytidine triphosphate for incorporation into HIV DNA, thereby terminating the viral DNA chain growth and inhibiting the activity of the viral reverse transcriptase.

Individually, abacavir and lamivudine showed good *in vitro* activity against HIV-1 and -2 in various cell lines and clinical isolates.[8,9] When combined, the two drugs showed additive or synergistic *in vitro* activity against HIV isolates.[4] This combination also showed additive to synergistic *in vitro* antiviral activity in combination with NRTIs (emtricitabine, stavudine, tenofovir, zalcitabine and zidovudine), NNRTIs (delavirdine, efavirenz and nevirapine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir) and a fusion inhibitor (enfuvirtide).[7]

2.1 Resistance

HIV variants with reduced susceptibility to abacavir or lamivudine have been selected for *in vitro* and have also been isolated from patients receiving abacavir and/or lamivudine.[6,7,10-16]

Both *in vitro* and in lamivudine-treated patients, lamivudine resistance is caused by a single amino acid substitution from methionine to either isoleucine or valine at position 184 of the HIV reverse transcriptase enzyme.[6] Although this substitution emerges rapidly and confers high-level phenotypic resistance, only partial loss of virological response occurs; it has been suggested that the substitution places a functional compromise on the HIV reverse transcriptase enzyme.[6]

In vitro passaging of HIV-1 isolates in the presence of increasing concentrations of abacavir resulted in amino acid substitutions at positions 184 (methionine to valine [M184V]), 74 (leucine to valine [L74V]), 65 (lysine to arginine [K65R]) and 115 (tyrosine to phenylalanine [Y115F]) of the HIV reverse transcriptase enzyme.[10] The same four amino acid substitutions were observed in HIV isolates from patients receiving abacavir monotherapy.[11] Both *in vitro* and in HIV isolates from patients, a single substitution conferred only a marginal reduction in susceptibility to abacavir (<4-fold); variants containing two or three substitutions displayed a 4- to 8-fold reduction in susceptibility to abacavir, while some with three substitutions, including M184V, were >8-fold less susceptible to abacavir.[10,11]

When abacavir and lamivudine were given concomitantly for 48 weeks with efavirenz, virological failure occurred in 20 of 324 (6%)[14] and 70 of 770 (9%)[12] antiretroviral-naive patients with HIV infection (trials CNA30024[14] and CNA30021: ZODIAC [Ziagen Once Daily In Antiretroviral Combination therapy];[12] see section 4.1.1 for design details). The M184V substitution was observed in isolates from 31%[14] and 48%[12] of patients with available post-failure genotypes. Other NRTI-associated substitutions observed were L74V (26%[12] and 8%[14]), K65R (3%[12]) and Y115F (6%[12]). Notably, in the ZODIAC trial, the selection of substitutions was influenced by the presence of baseline resistance.[17] When only samples from patients infected with wild-type virus at baseline were analysed, the M184V and L74V substitutions were

1 The use of trade names is for product identification purposes only and does not imply endorsement.

observed in 42% and 12% of samples, and the K65R and Y115F substitutions were not observed.[17] The resistant HIV isolates in one trial were considered likely to be still susceptible to other NRTIs.[12] However, there appeared to be a numerically higher incidence of K65R substitutions (24% of patients who experienced virological failure) in a trial in which patients received lamivudine, tenofovir disoproxil fumarate (tenofovir DF) and efavirenz.[18] The K65R substitution confers resistance to multiple NRTIs, leaving only zidovudine as a fully active option within this class, and thus may compromise the long-term efficacy of combination antiretroviral therapy (see section 2.1.1).[19,20]

Virological failure was observed in 12 of 36 antiretroviral-naive patients with HIV infection after treatment with concomitant abacavir, lamivudine and tenofovir DF for 3–6 months in a 12-month pilot study (the TONUS study).[16] Both K65R and M184V mutations were observed in 11 of these patients and, in one patient, only the M184V mutation was observed. High rates of virological failure were also seen with co-formulated abacavir/lamivudine plus tenofovir DF in a large clinical trial[21] (section 4.2). The authors of the TONUS study concluded that these results, together with data showing no pharmacokinetic interactions between abacavir and tenofovir DF (section 3.3), support the hypothesis that virological failure results from a low genetic barrier to resistance.[16]

In a retrospective chart search of the genotypes of 900 HIV isolates from patients receiving antiretroviral treatment, the K65R substitution was observed infrequently in isolates from patients receiving abacavir plus lamivudine and not at all in those from patients receiving abacavir, lamivudine and zidovudine.[15]

In children and adolescents with HIV infection, it took significantly ($p = 0.03$) longer for the M184V substitution to appear in isolates from those receiving abacavir plus lamivudine than from those receiving lamivudine plus zidovudine (the M184V substitution was estimated to be present in 14% and 41% of patients after treatment for 48 weeks; see section 4.1.2 for trial design).[13]

2.1.1 Cross-Resistance

Cross-resistance among NRTIs has been reported.[22] HIV isolates resistant to multiple NRTIs have been isolated from patients receiving zidovudine plus didanosine or zalcitabine.[8]

In vitro, abacavir-resistant recombinant laboratory strains of HIV which contained multiple mutations were cross-resistant to lamivudine, didanosine and zalcitabine.[9] In addition to abacavir, the K65R substitution confers resistance *in vivo* to didanosine, lamivudine and tenofovir.[20]

Lamivudine is a common choice for a component of first-line therapy because lamivudine-resistant mutants carrying the M184V substitution remain susceptible to thymidine analogues; however, its use with emtricitabine is not recommended as the two NRTIs have similar resistance profiles.[2]

In vitro, the M184V substitution reduces the susceptibility of HIV to didanosine and zalcitabine, but increases the susceptibility of HIV to zidovudine, stavudine and tenofovir.[22] However, in one trial in patients with HIV with the M184V substitution, significantly fewer patients who switched from lamivudine- to didanosine-containing therapy experienced virological failure, compared with those who continued to receive lamivudine.[23] Additionally, of those didanosine recipients who experienced virological failure, the majority had lost the M184V substitution.

2.2 Effects on Lipid Levels

Didanosine plus stavudine reduced high- and low-density lipoprotein cholesterol levels from baseline by significantly more than abacavir plus lamivudine in a substudy ($n = 96$) of the randomised, open-label CPCRA 058 (FIRST [Flexible Initial Retrovirus Suppressive Therapies]) trial in treatment-naive patients with HIV infection (in both arms, patients also received a PI, an NNRTI or both).[24,25] Respective changes in lipoprotein levels were −0.08 versus +0.12 mg/dL/month ($p < 0.01$) [high density] and −0.60 versus −0.21 mg/dL/month ($p = 0.02$) [low density] after a median follow-up of 33 months. There were no significant between-group differences in the changes from baseline in total cholesterol or triglyceride levels.

Several randomised, open-label, multicentre studies in patients with HIV infection have assessed

the effects on lipid levels of switching one drug in an antiretroviral regimen to abacavir 300mg twice daily.[26,27] In a 28-[28] (n = 104) and a 48-[26] (n = 207) week trial, switching from two NRTIs plus a PI to two NRTIs plus abacavir in patients with HIV infection resulted in improvements in total cholesterol,[26,28] low-density lipoprotein[28] and triglyceride[26,28] levels. In the 48-week trial,[26] the median change from baseline for the abacavir and PI regimens was −0.14 versus +0.04 mmol/L (p = 0.035) for plasma triglyceride levels (baseline 1.76 and 1.64 mmol/L) and −0.51 versus −0.11 mmol/L (p < 0.001) for total cholesterol levels (baseline 5.2 and 5.3 mmol/L). However, in a third study,[27] there were no significant between-group differences in total cholesterol or triglyceride levels at 24 weeks in patients with HIV infection (n = 111) who switched from zidovudine or stavudine to abacavir, compared with those remaining on their existing antiretroviral treatment. In another 48-week trial in patients with HIV infection (n = 237),[29] fasting total cholesterol and triglyceride levels increased (p < 0.001) from baseline in both the abacavir, lamivudine plus efavirenz group and the lamivudine, stavudine plus efavirenz group (no further data reported).

3. Pharmacokinetic Properties

3.1 General

3.1.1 Abacavir/Lamivudine (Fixed-Dose Combination)

A single dose of fixed-dose abacavir/lamivudine 600mg/300mg was bioequivalent to single doses of abacavir 600mg plus lamivudine 300mg, based on the 90% confidence intervals for the geometric least squares mean ratios for the area under the plasma concentration-time curve from zero to infinity (AUC_∞) and peak plasma concentration (C_{max}) values in 25 fasting, healthy volunteers (see table I).[30] In the same trial, administration of the fixed-dose tablet with a high-fat meal reduced the mean C_{max} values (to ≈80% of that in fasting volunteers) and increased the mean time to C_{max}, but did not significantly alter the AUC_∞ values; these effects are consistent with those observed with the individual abacavir and lamivudine tablets and no food restrictions are necessary.[30]

Table I. Bioequivalence of abacavir/lamivudine (fixed-dose combination) to abacavir plus lamivudine (individual formulations). Healthy, fasting volunteers (n = 25) received, in a crossover manner, single doses of fixed-dose abacavir/lamivudine 600mg/300mg or abacavir 600mg plus lamivudine 300mg. Values are expressed as geometric least squares (GLS) means

Parameter	Fixed-dose combination	Individual formulations	GLS mean ratio[a] [90% CI[b]]
Abacavir			
C_{max} (μg/mL)	4.68	4.94	0.946 [0.855, 1.048]
AUC_∞ (μg • h/mL)	14.15	14.15	1.000 [0.954, 1.048]
Lamivudine			
C_{max} (μg/mL)	2.64	2.84	0.930 [0.865, 0.999]
AUC_∞ (μg • h/mL)	12.60	13.23	0.952 [0.912, 0.994]

a Fixed dose : individual formulations.

b A 90% CI within 0.80, 1.25 meets bioequivalence criteria.

AUC_∞ = area under the concentration-time curve from zero to infinity; **C_{max}** = maximum plasma drug concentration.

3.1.2 Abacavir and Lamivudine (Separate Formulations)

The pharmacokinetic properties of oral abacavir (after a single dose of 600mg or at steady-state after administration of twice-daily 300mg) and oral lamivudine (at steady state after administration of twice-daily 150mg or once-daily 300mg) are presented in table II.[31-33] Some data in this section were obtained from the manufacturer's prescribing information for the individual drugs[8,9] or the co-formulated tablet;[7] whether the values were means or medians was not always indicated.

When the pharmacokinetics at steady state of once-daily lamivudine 300mg were compared with those of twice-daily lamivudine 150mg in patients with HIV infection, there was no significant between-group difference in plasma exposure (table II); however, the mean C_{max} was significantly higher (table II) and the mean minimum plasma concentration (C_{min}) was significantly lower (0.15 vs 0.33 μg/mL; p = 0.03) for patients receiving the once-daily dosage.[33] The authors noted that these differences did not necessarily reflect changes in intracellular lamivudine triphosphate levels. Indeed, the steady-state area under the concentration-time curve from zero to 24 hours and maximum concentration values for intracellular lamivudine triphos-

phate in the peripheral blood mononuclear cells (PBMCs) of healthy volunteers who received once-daily lamivudine 300mg were equivalent to those in the PBMCs of patients who received twice-daily lamivudine 150mg.[34] The mean minimum intracellular concentration was lower (18–24%) for once-daily recipients than twice-daily recipients.[34]

Both drugs were rapidly absorbed after oral administration.[7] The mean absolute bioavailability of abacavir from a 300mg tablet was 83%[9] and that of lamivudine from a 150mg tablet was 86%.[8] After intravenous administration, the apparent volume of distribution values were 0.86 L/kg for abacavir[9] and 1.3 L/kg for lamivudine;[8] these values suggest that the drugs are distributed into extravascular spaces.

Abacavir is primarily metabolised by alcohol dehydrogenase and glucuronyl transferase, and undergoes very little metabolism by cytochrome P450 (CYP) enzymes.[9] The drug is mainly excreted in the urine as metabolites. Lamivudine undergoes limited metabolism, and is mainly excreted unchanged in the urine.[8] Both abacavir and lamivudine have relatively short elimination half-lives ($t_{1/2}\beta$) [table II];[8,9] however, these values do not necessarily reflect the intracellular levels of the active metabolites of the drugs.

Table II. Pharmacokinetics of oral abacavir (ABC) and lamivudine (LAM). Reported values (means[31,33] or geometric means[32]) relate to a single dose (sd)[31] or steady-state[32,33] administration in patients with HIV infection

Parameter	LAM[33]a		ABC	
	300mg od (n = 12)	150mg bid (n = 12)	600mg sd (n = 13)[31]	300mg bid[b] (n = 20)[32]
AUC (μg • h/mL)	16.6[c]	17.1[d]	11.3[e]	2.56[c]
C_{max} (μg/mL)	3.5*	2.1	4.24	0.88
t_{max} (h)	2.2	1.6	1.29	2.00
$t_{1/2}\beta$ (h)	7.9	6.1	1.5	2.59

a Crossover study.[33]

b Patients had one afternoon dose withheld; pharmacokinetic samples were obtained for up to 24 hours after that morning dose.

c AUC_{24}.

d $AUC_{12} \times 2$.

e AUC_{∞}.

AUC_x = area under the plasma concentration-time curve from zero to *x*; **bid** = twice daily; **C_{max}** = maximum plasma drug concentration; **od** = once daily; **t_{max}** = time to C_{max}; **$t_{1/2}\beta$** = elimination half-life; * p = 0.0045 vs twice-daily LAM.

The terminal half-life ($t_{1/2}\gamma$) of intracellular carbovir triphosphate (the active moiety of abacavir) in PBMCs was estimated to be 12–19 hours in seven patients with HIV infection who received abacavir (600mg once daily or 300mg twice daily [T. Hawkins, personal communication]) as part of triple-NRTI therapy ($t_{1/2}\gamma$ values were calculated using estimates of intracellular decay rates after patients discontinued abacavir treatment).[35] In another study,[32] based on a mean $t_{1/2}\gamma$ of ≈20 hours for intracellular carbovir triphosphate in the PBMCs of 20 patients with HIV infection treated with twice-daily abacavir 300mg (steady state [see table II for study design details]), the authors concluded that abacavir may be suitable for once-daily administration (see also section 4.1.1).

3.2 Special Populations

The pharmacokinetics of lamivudine are not significantly altered by sex, race or diminished hepatic function.[8] In patients with HIV infection and impaired renal function, the mean AUC_{∞}, C_{max} and half-life ($t_{1/2}$) of lamivudine increased and the apparent total oral clearance decreased (see section 6).[8]

The effects of sex, race, advanced age (>65 years) and impaired renal function on the pharmacokinetic properties of abacavir have not been determined.[9] While the effects of moderate-to-severe hepatic impairment are also not yet known,[9] the AUC and $t_{1/2}$ values of abacavir increased by 89% and 58% in patients with HIV infection and mild hepatic impairment (Child-Pugh score 5–6) who received a single oral dose of abacavir 600mg (see section 6).[36]

At steady state, the pharmacokinetics of both once-daily abacavir (16 mg/kg) and lamivudine (8 mg/kg) were not inferior to those of twice-daily abacavir (8 mg/kg) and lamivudine (4 mg/kg), respectively, in 20 children with HIV infection, as determined by geometric mean ratios for once-daily versus twice-daily dosages of >1 for AUC and C_{max} values.[37] The mean C_{max} value for once-daily lamivudine was approximately double that for twice-daily lamivudine (2.09 vs 1.11 mg/L), suggesting dose-proportional pharmacokinetics. For abacavir,

the mean once-daily C_{max} value was more than double the twice-daily value (4.80 vs 2.14 mg/mL), suggesting more than dose-proportional pharmacokinetics.[37]

3.3 Drug Interactions

Abacavir is unlikely to interact with drugs metabolised by CYP2C9, CYP2D6 or CYP3A4, as the drug did not inhibit these CYP isoforms in human liver microsomes.[9] When abacavir was coadministered with lamivudine or zidovudine, there were no clinically relevant changes in the pharmacokinetics of any of these drugs.[9] When 24 male patients with HIV infection received a single dose of abacavir 600mg plus ethanol 0.7 g/kg (equivalent to five alcoholic drinks), the abacavir AUC_∞ and $t_{1/2}\beta$ increased by 41% and 26%.[9] No dosage recommendations have been made for abacavir recipients who consume a large amount of alcohol. Oral methadone clearance increased by 22% when 11 patients with HIV infection received methadone maintenance therapy (40 or 90mg daily) with twice-daily abacavir 600mg (twice the recommended dosage); however, the majority of patients do not need to alter their methadone dosage when receiving abacavir.[9]

Because lamivudine is mainly eliminated in the urine by active cationic secretion, it is possible that the drug may interact with other drugs eliminated in the same way.[8] Although once-daily cotrimoxazole (trimethoprim/sulfamethoxazole) 160mg/800mg increased the mean AUC of lamivudine by 44%, no dosage adjustment of either drug is required.[8] No other data are available concerning drug interactions between lamivudine and drugs with similar renal clearance mechanisms. As lamivudine and zalcitabine may inhibit the intracellular phosphorylation of each other, their combined use is not recommended.[8]

After a high rate of early virological nonresponse in patients treated once-daily with the fixed combination of abacavir/lamivudine plus tenofovir DF in a randomised trial (see section 4.2),[21] several studies have investigated the possibility of a pharmacokinetic interaction between these drugs.[16,35,38,39] The plasma pharmacokinetics of abacavir and tenofovir DF were not affected to a clinically relevant degree when the two drugs were coadministered in eight healthy volunteers.[38] After patients with HIV infection had received concomitant abacavir, lamivudine and tenofovir DF for 1 month in a 12-month pilot study, 32 of 37 patients had adequate C_{min} values for all three drugs.[16] Additionally, when abacavir and tenofovir DF were administered in combination, the intracellular concentrations of the active metabolites of either drug were not altered when assessed *in vitro* in human lymphoid cells[39] or in the PBMCs of patients with HIV infection.[35]

4. Therapeutic Efficacy

4.1 Abacavir and Lamivudine (Separate Formulations)

4.1.1 In Adults

The efficacy of oral abacavir plus lamivudine as separate formulations in combination with other oral antiretroviral agents has been assessed in several large (n > 100), 48-week, randomised, multicentre trials in antiretroviral-naive adult patients with HIV infection;[40-44] this section focuses on these trials. The triple-nucleotide combination of abacavir, lamivudine and zidovudine has been extensively studied and recently reviewed;[45] these data are not covered in this article because triple NRTI therapy is no longer a preferred first-line treatment option in most antiretroviral-naive patients (see section 1).[2] Two of the trials covered in this section are fully published,[41,43] and the others are available as abstracts[40,42,44] and conference posters.[40,42] Where stated, patients were required to have HIV RNA levels >400,[41] >1000[44] or ≥5000[40,43] copies/mL.

Abacavir and lamivudine were given as part of triple or quadruple therapy. The agents used in combination with abacavir plus lamivudine were the NRTI stavudine,[40] the NNRTI efavirenz[40-42] and the PIs amprenavir,[40] fosamprenavir,[43,44] nelfinavir[43,44] and ritonavir[40,44] (see table III for trial designs and dosages). In one trial,[42] the lamivudine dosage was 300mg once daily in both arms and the abacavir dosage was 600mg once daily in one arm and 300mg twice daily in the other arm. In the other trials,[40,41,43,44] the abacavir dosage was 300mg twice daily and the lamivudine dosage was 150mg twice daily.

Where stated, the primary endpoint in the trials was the number of patients with plasma viral RNA

Table III. Efficacy of regimens containing oral abacavir (ABC) plus lamivudine (LAM) in patients (pts) with HIV infection. The drugs were administered separately or as a fixed-dose combination tablet, in combination with other antiretroviral agents in randomised, double-blind[41,42] or open-label,[21,40,43,44] multicentre trials in antiretroviral-naive adult pts. All data are from the intention-to-treat (ITT) population (defined in variable ways[a]) with the exception of the ≥8 week data from the trial by Gallant et al.[21] The endpoint of all trials was 48 weeks; only data from interim analyses are available for one trial[21]

Study	Treatment (mg)	Plasma HIV RNA levels			CD4+ cell count (cells/mL)	
[trial name]	[no. of pts]	baseline (median log_{10} copies/mL)	<50 copies/ mL (% pts)	<400 copies/ mL (% pts)	baseline (median)	increase from baseline (mean)
Separate formulations						
Bartlett et al.[40] [ESS40001:	ABC 300 bid, LAM 150 bid, EFV 600 od [97]	4.90 (mean)	76.3*	82.5	307 (mean)	195[b]
CLASS][c]	ABC 300 bid, LAM 150 bid, APV 1200 od, RTV 200 od[d] [96]	4.85 (mean)	62.2	75	306 (mean)	170[b]
	ABC 300 bid, LAM 150 bid, STV 30 or 40 bid [98]	4.81 (mean)	59.4	79.6	296 (mean)	190[b]
DeJesus et al.[41] [CNA30024]	ABC 300 bid, LAM 150 bid, EFV 600 od [324]	4.81	70	74	267	209**
	ZDV 300 bid, LAM 150 bid, EFV 600 od [325]	4.76	69	71	258	155
Gazzard et al.[42] [CNA30021:	ABC 600 od, LAM 300 od, EFV 600 od [386]	4.9	66		264	188
ZODIAC][c]	ABC 300 bid, LAM 300 od, EFV 600 od [384]	4.9	68		259	200
Rodriguez-French et al.[43] [NEAT]	ABC 300 bid, LAM 150 bid, FPV 1400 bid [166]	4.82	55	66	214	201 (median)
	ABC 300 bid, LAM 150 bid, NFV 1250 bid [83]	4.85	41	51	212	216 (median)
Schurmann et al.[44] [SOLO][c]	ABC 300 bid, LAM 150 bid, FPV 1400 od, RTV 200 od [322]	4.8[e]	56	68	170[e]	
	ABC 300 bid, LAM 150 bid, NFV 1250 bid [327]	4.8[e]	52	65	170[e]	
Fixed-dose combination tablet						
Gallant et al.[21,47] [ESS30009][cf]	ABC/LAM 600/300 od, EFV 600 od [92] (≥8 weeks)	4.71		90	280.5	117
	[169] (24 weeks)	4.8	69	77	263	
	ABC/LAM 600/300 od, TDF 300 od [102] (≥8 weeks)	4.53		49	252.5	61

a Definitions for the ITT populations were as follows: missing = failure;[40,44] exposed (using time to loss of virological response algorithm);[41,42] rebound or discontinuation = failure,[43] exposed, missing = failure.[47] An observed-case analysis was used for the ≥8 week data in the trial by Gallant et al.[21]

b Values estimated from a graph.

c Studies available as abstract,[21,40,42,44,47] poster[40,42,47] or oral presentation.[21]

d Pts in this arm were switched to FPV and RTV od at varying times throughout the study.

e Baseline values given for all pts, not separate treatment groups.

f An unplanned interim analysis for patients with ≥8 weeks' data was performed after several cases of early virological failure in the ABC/LAM plus TDF arm were reported. This arm of the trial was discontinued. Therefore, 24-week data from a planned interim analysis are available only for the other arm of the trial.

APV = amprenavir; **bid** = twice daily; **CLASS** = Clinically significant Long-term Antiretroviral Sequential Sequencing study; **EFV** = efavirenz; **FPV** = fosamprenavir; **NFV** = nelfinavir; **od** = once daily; **RTV** = ritonavir; **STV** = stavudine; **TDF** = tenofovir disoproxil fumarate; **ZDV** = zidovudine; **ZODIAC** = Ziagen Once Daily In Antiretroviral Combination therapy; * $p < 0.05$, ** $p \leq 0.005$ vs comparator arm(s).

levels reduced to <50 copies/mL[41,42] or <400 copies/mL[43] after 48 weeks (see table III for baseline viral RNA levels). Analyses were based on the intention-to-treat populations (ITT) [see table III for definitions].[40-44]

In addition, a substudy of the randomised, open-label FIRST trial compared abacavir plus lamivudine (n = 93) with didanosine plus stavudine (n = 89) in treatment-naive patients with HIV infection; in both arms, patients also received a PI, an NNRTI or both.[46] In this trial, the primary endpoint was the time to an HIV RNA level >50 copies/mL or death after at least 8 months of treatment.

Generally, after 48 weeks of treatment with antiretroviral regimens containing both abacavir and lamivudine, there were no significant differences between treatment groups in the proportion of patients with plasma HIV RNA levels reduced to <50 copies/mL (table III).[40-44] However, in one open-label trial,[40] significantly more patients receiving abacavir, lamivudine and efavirenz had viral RNA levels reduced to <50 copies/mL compared with those receiving abacavir, lamivudine, amprenavir and ritonavir, or abacavir, lamivudine and stavudine (both $p < 0.05$; table III).

There were no statistical differences between groups in the proportion of patients with HIV RNA levels <400 copies/mL after 48 weeks of treatment with regimens containing abacavir plus lamivudine (table III).[40,41,43,44]

In terms of the proportion of patients with HIV RNA levels <50 copies/mL at 48 weeks, the combination of abacavir, lamivudine and efavirenz was non-inferior to the combination of zidovudine, lamivudine and efavirenz (95% CI for between-group difference −6.3%, 7.9%; table III).[41] For this endpoint, once-daily abacavir 600mg was non-inferior to twice-daily abacavir 300mg, both administered in combination with once-daily lamivudine and efavirenz (95% CI −8%, 5%; table III).[42] Both studies used the intention-to-treat exposed population based on a time to loss of virological response algorithm, and non-inferiority was defined as a two-sided 95% CI excluding a difference as large as 12%.[41,42]

As with other antiretroviral regimens, recipients of regimens containing abacavir plus lamivudine experienced an improvement in mean[40-42] or median[43] CD4+ cell counts from baseline (statistical analyses not reported) [table III]. In one trial,[41] the mean increase in CD4+ cell counts from baseline was significantly greater in the abacavir, lamivudine and efavirenz group than in the zidovudine, lamivudine and efavirenz group (table III).

After at least 8 months of treatment, the number of patients (per 100 patient-years) who had HIV RNA levels >50 copies/mL or who had died did not differ significantly between the abacavir plus lamivudine-regimen group and the didanosine plus stavudine-regimen group in the substudy of the FIRST trial (65.8 vs 81.8 per 100 patient-years).[46]

4.1.2 In Children and Adolescents

In a multicentre trial,[48] 127 children and adolescents with HIV infection (aged 0.3–16.7 years; median 5.3 years) [intention-to-treat population] were randomised to receive one of three NRTI regimens: (i) abacavir (16 mg/kg/day administered as two daily doses) plus lamivudine (8 mg/kg/day administered as two daily doses); (ii) lamivudine at the same dosage as in (i) plus zidovudine (360 mg/m^2/day administered as two or three daily doses); or (iii) abacavir plus zidovudine at the same dosages as in (i) and (ii) [figure 1]. Symptom-free children (n = 55) were also randomised to receive nelfinavir (75–90 mg/kg/day administered as three daily dosages) or placebo in a blinded manner, while children with advanced disease (n = 72) all received open-label nelfinavir. The mothers of nine patients had received zidovudine during pregnancy, and seven of these children also received zidovudine for up to 13 weeks after birth. All other children were antiretroviral treatment-naive.

The primary endpoint for the comparison between the three NRTI regimens was the change from baseline in plasma HIV RNA levels at weeks 24 and 48.[48] At baseline, the mean plasma HIV RNA levels and median CD4+ cell counts were 5.13 $\log_{10}$ copies/mL and 602 cells/mL for abacavir plus lamivudine recipients, 4.89 $\log_{10}$ copies/mL and 530 cells/mL for abacavir plus zidovudine recipients and 5.03 $\log_{10}$ copies/mL and 496 cells/mL for lamivudine plus zidovudine recipients.

After 24 and 48 weeks of treatment, abacavir plus lamivudine was significantly more effective at reducing viral load than lamivudine plus zidovudine, after correction for receipt of nelfinavir and minor

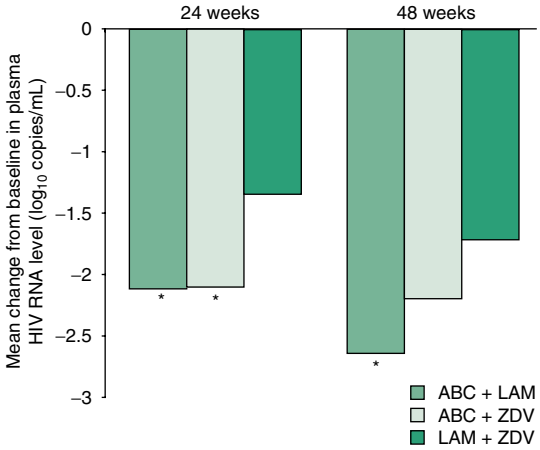

Fig. 1. Reduction in viral load (primary endpoint) with abacavir (ABC) plus lamivudine (LAM) as separate formulations in children and adolescents with HIV infection.[48] In a multicentre trial, 127 children and adolescents (intention-to-treat population) aged 0.3–16.7 years were randomised to receive ABC 8 mg/kg twice daily (bid) plus LAM 4 mg/kg bid (n = 47), LAM 4 mg/kg bid plus zidovudine (ZDV) 120 mg/m^2 three times daily (tid) or 180 mg/m^2 bid [n = 36] or ABC 8 mg/kg bid plus ZDV 120 mg/m^2 tid or 180 mg/m^2 bid (n = 44). Data shown are 24- and 48-week results corrected for receipt of nelfinavir or placebo and minor differences in baseline characteristics. Baseline mean plasma HIV RNA levels were 4.89–5.13 log_{10} copies/mL. * $p < 0.005$ vs LAM + ZDV.

baseline differences ($p < 0.005$; figure 1).[48] Abacavir plus zidovudine was also significantly more effective than lamivudine plus zidovudine at week 24, but not at week 48 ($p < 0.005$; figure 1).

The abacavir plus lamivudine combination was also at least as effective as the other regimens based on other endpoints.[48] Although at 24 weeks there were no intergroup differences in the proportion of patients with plasma viral RNA levels reduced to <50 copies/mL (range 39–49% of patients), at 48 weeks, significantly more abacavir plus lamivudine recipients than lamivudine plus zidovudine recipients had plasma HIV RNA levels reduced to <50 copies/mL (56% vs 31%; $p = 0.03$). In addition, a greater proportion of abacavir plus lamivudine recipients than lamivudine plus zidovudine recipients had plasma RNA levels <400 copies/mL at weeks 24 (76% vs 44%; $p = 0.006$) and 48 (71% vs 44%; $p = 0.02$). Improvements in immunological profiles were not significantly different between treatment groups; the increases from baseline in median CD4+ cell counts ranged from 162 to 223 cells/mL for the three treatment groups at 24 weeks and 182 to 272 cells/mL at 48 weeks.[48]

4.2 Abacavir/Lamivudine (Fixed-Dose Combination)

The efficacy of the fixed-dose combination tablet containing abacavir (600mg) and lamivudine (300mg) as part of triple or quadruple therapy is being assessed in three 48-week, randomised, open-label, multicentre trials for which interim results are available.[21,47,49,50] One trial is in antiretroviral treatment-naive patients (section 4.2.1)[21,47] and the other two are in antiretroviral treatment-experienced patients (section 4.2.2).[49,50]

4.2.1 Antiretroviral Treatment-Naive Patients

Antiretroviral treatment-naive adults (n = 340 randomised) with plasma HIV RNA levels of ≥5000 copies/mL received the fixed-dose combination tablet once daily plus either once-daily efavirenz 600mg or once-daily tenofovir DF 300mg.[21,47] The primary endpoint in this ongoing trial is the proportion of patients with plasma HIV RNA levels <50 copies/mL at week 48.[21] Baseline HIV RNA levels and CD4+ cell counts are presented in table III. An unplanned interim analysis for patients with ≥8 weeks' data was performed after several cases of early virological nonresponse for patients in the abacavir/lamivudine plus tenofovir DF arm were reported.[21] In addition, 24-week results for the abacavir/lamivudine plus efavirenz arm were presented at a recent conference.[47]

After at least 8 weeks, 90% of evaluable recipients in the abacavir/lamivudine plus efavirenz group experienced a reduction in viral load to <400 copies/mL and the mean CD4+ cell count had increased by 117 cells/mL (observed-case analysis, table III).[21] At 24 weeks, 69% and 77% of patients in the abacavir/lamivudine plus efavirenz arm had a reduction in HIV RNA levels to <50 and <400 copies/mL.[47] Respective reductions using an as-treated analysis were 86% and 97% (n = 126).

Notably, after treatment for at least 8 weeks, significantly more patients in the abacavir/lamivudine plus tenofovir DF arm than the abacavir/lamivudine plus efavirenz arm experienced virological nonresponse, defined as either a <2.0 log_{10} copies/mL decline in HIV RNA by week 8 or a ≥1 log_{10}

rebound from nadir at any subsequent visit (49% vs 5.4%; $p < 0.001$). Consequently, the abacavir/lamivudine plus tenofovir DF arm of the trial was discontinued. Proposed reasons for this nonresponse include an intracellular pharmacological interaction and/or a low genetic resistance barrier to abacavir/lamivudine plus tenofovir DF. Results of investigations thus far support the latter hypothesis (sections 2.1 and 3.2).

4.2.2 Antiretroviral Treatment-Experienced Patients

Twenty-four-week interim results are available for two trials comparing fixed-dose abacavir/lamivudine with abacavir plus lamivudine as separate formulations in antiretroviral treatment-experienced patients with HIV infection.[49,50]

In one trial,[49] patients with virological failure (HIV RNA level >1000 copies/mL and ≤3 NRTI-associated mutations) were randomised to receive either once-daily fixed-dose abacavir/lamivudine (n = 94; intention-to-treat, observed analysis) or twice-daily abacavir 300mg plus once-daily lamivudine 300mg (n = 87), both in combination with tenofovir DF and a new PI or NNRTI. Patients were tenofovir DF-naive at baseline. The median HIV RNA level and CD4+ cell count were 3.92 $\log_{10}$ copies/mL and 309 cells/mL at baseline in the fixed-dose abacavir/lamivudine arm; respective values in the other treatment arm were 4.22 $\log_{10}$ copies/mL and 304 cells/mL. Patients were stratified based on HIV RNA levels and the presence of the M184V/I mutation.

In the other trial,[50] patients (n = 260) had had HIV RNA levels <400 copies/mL for >3 months and had received twice-daily abacavir plus lamivudine (as separate formulations, dosage not stated) and a PI or NNRTI for more than 6 months. Patients were randomised to continue receiving twice-daily abacavir plus lamivudine or to switch to fixed-dose abacavir/lamivudine. At baseline, patients had received abacavir plus lamivudine for a median of 22 months; the median HIV RNA level and CD4+ cell count were <50 copies/mL and 554 cells/mL. Analyses were based on the intention-to-treat, missing = failure population.

In both trials,[49,50] the fixed-dose abacavir/lamivudine-containing regimen was non-inferior to the abacavir plus lamivudine-containing regimen. In the trial in which patients had virological failure at baseline,[49] non-inferiority was established using a time-averaged viral load measurement; the median average area under the curve minus baseline values were −1.60 and −1.87 $\log_{10}$ copies/mL in the fixed-dose abacavir/lamivudine and abacavir plus lamivudine groups (values adjusted for stratification groups). Respective proportions of patients with HIV RNA levels <50 copies/mL were 57% and 48%. In the other trial,[50] non-inferiority was established based on the proportion of patients who did not experience virological failure (90% CI −8, 1.8; complete data not stated). The proportion of patients with HIV RNA levels <50 copies/mL was 89% for recipients of the fixed-dose abacavir/lamivudine regimen and 86% for recipients of the abacavir plus lamivudine regimen.[50] Additionally, patients' satisfaction with treatment convenience was significantly ($p = 0.004$) greater for recipients of fixed-dose abacavir/lamivudine-containing regimens than for recipients of abacavir plus lamivudine-containing regimens.[51]

5. Tolerability

The tolerability profiles of abacavir[4,5] and lamivudine[6] have been reviewed separately in *Drugs*. In early monotherapy trials, the most common (≥15%) treatment-emergent adverse events in lamivudine recipients included diarrhoea, malaise and fatigue, headache, coughing, sleep disorders, muscle pain, abdominal pain or discomfort, temperature regulation disturbance, nausea and vomiting, and anxiety.[6] In several trials, the most common (≥ 15%) treatment-emergent adverse events in patients receiving abacavir, lamivudine and zidovudine included nausea and vomiting, diarrhoea, fever and headache.[9] Approximately 5% of abacavir recipients in clinical trials developed a hypersensitivity reaction, symptoms of which included fever, skin rash, fatigue, gastrointestinal symptoms and respiratory symptoms.[9] These reactions were sometimes fatal (incidence not reported).[9]

Limited tolerability data are available from three trials of the fixed-dose abacavir/lamivudine tablet, one in antiretroviral-treatment naive patients with HIV infection[47] and two in antiretroviral-treatment experienced patients with HIV infection[49,50] (see section 4.2 for trial details). Common adverse events

included hypersensitivity reactions (7% of patients), rash (5%) and insomnia (4%) when 169 treatment-naive patients received abacavir/lamivudine plus efavirenz for 24 weeks.[47] In 93 treatment experienced patients who received fixed-dose abacavir/lamivudine in combination with tenofovir DF and a PI or an NNRTI for 24 weeks,[49] the most common (≥5% of patients) drug-related adverse events were nausea (12%), diarrhoea (11%), drug hypersensitivity (possibly due to abacavir) [9%], fatigue (6%) and vomiting (5%). In the other trial, the most common grade 2–4 adverse events were upper respiratory infection, nasopharyngitis, nausea and headache (incidence not stated) in 260 treatment-experienced patients who received either fixed-dose abacavir/lamivudine or twice-daily abacavir plus lamivudine (as separate formulations), both in combination with a PI or an NNRTI.[50]

Abacavir hypersensitivity or possible hypersensitivity reactions were reported 4–10% of patients (who were abacavir-naive at baseline) from trials discussed in this review.[40-43,47-49,52-54] One death in these studies was attributed to abacavir hypersensitivity, but this occurred after rechallenge with abacavir following resolution of an initial hypersensitivity reaction; the rechallenge was in breach of the study protocol (see also section 6).[53]

Where reported,[40-43,52-54] adverse events experienced by antiretroviral-naive recipients of regimens containing abacavir plus lamivudine (as separate formulations) in the trials discussed in section 4 appeared to be similar to those reviewed previously.[4-6] In a double-blind trial comparing once-daily abacavir with twice-daily abacavir, both in combination with once-daily lamivudine plus once-daily efavirenz, the most common drug-related adverse event (incidence >1%) in both arms was abacavir hypersensitivity (figure 2).[42] The incidence of all other drug-related grade 2-4 adverse events was similar between the two groups (statistical analysis not reported) [figure 2].

A regimen of concomitant abacavir, lamivudine and efavirenz was generally at least as well tolerated as that of zidovudine, lamivudine and efavirenz.[41] Significantly fewer abacavir-regimen recipients experienced nausea (23% vs 37%), fatigue (16% vs 26%) and/or vomiting (12% vs 21%) [all $p \leq 0.004$], whereas the incidence of cough was higher in this group than in the zidovudine-regimen group (13% vs 8%; $p = 0.04$).

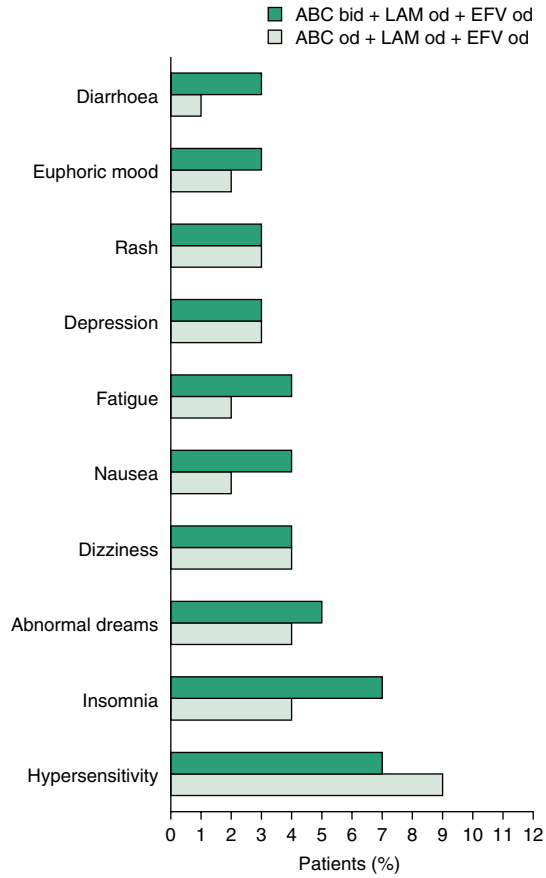

Fig. 2. Tolerability of concomitant oral abacavir (ABC), lamivudine (LAM), and efavirenz (EFV) in antiretroviral-naive patients with HIV infection. Drug-related grade 2–4 adverse events occurring in >1% of patients are shown.[42] In a 48-week, multicentre, randomised, double-blind study, ABC 600mg once daily (od) [n = 384] was compared with ABC 300mg twice daily (bid) [n = 386], both in combination with LAM 300mg od and EFV 600mg od. Statistical analysis was not reported.

Recipients of abacavir plus lamivudine had significantly less fat loss than recipients of didanosine plus stavudine in a substudy (n = 96) of the randomised, open-label FIRST trial in treatment-naive patients with HIV infection (in both arms, patients also received a PI, an NNRTI or both).[24,25] After a median follow-up of 33 months, the mean changes from baseline (per month) were +0.10 versus −0.09kg for total body fat and +0.03 versus −0.22, −0.02 versus −0.35 and +0.58 versus −0.70 cm^2 for

fat area in the mid-arm, mid-thigh and waist, respectively (all $p < 0.01$).

At 48 weeks, the incidence of subjectively-assessed, moderate-to-severe lipoatrophy was significantly lower in antiretroviral-naive patients (n = 237) receiving concomitant abacavir, lamivudine and efavirenz than in those receiving stavudine, lamivudine and efavirenz in an open-label, multicentre trial (3% vs 20%; $p = 0.001$).[29] Significantly more stavudine-regimen than abacavir-regimen recipients were perceived to have fat loss from the buttocks (11% vs 1%; $p = 0.02$), arms (12% vs 1%; $p = 0.011$) and face (15% vs 1%; $p = 0.002$). These subjective assessments correlated with changes in dual x-ray absorptiometry measures; for patients who were still receiving initial therapy at 48 weeks, fat loss was greater in the lamivudine, stavudine and efavirenz group than the abacavir, lamivudine and efavirenz group (overall −1152 vs +1749g; $p = 0.015$; arms −177 vs +136g; $p = 0.013$; legs −1234 vs +519g; $p < 0.001$).

In an open-label, multicentre trial in patients with HIV infection and moderate or severe lipoatrophy in at least one region (n = 111), replacing stavudine or zidovudine with abacavir for 24 weeks resulted in significantly greater increases in regional fat mass or area, compared with continuing existing therapy: limb fat mass (+0.39 vs +0.08kg; $p = 0.02$), subcutaneous right mid thigh fat area (+3.3 vs −1.2cm^2; $p = 0.01$), subcutaneous right mid-humeral fat area (+3.5 vs 0.0cm^2; $p < 0.001$) and abdominal fat area at the 4th lumbar vertebra (+13.9 vs −1.2cm^2; $p = 0.001$).[27] However, overall lipoatrophy severity, as assessed by physicians, did not improve significantly in the abacavir group compared with the stavudine or zidovudine groups. Approximately 80% of these patients were receiving lamivudine as part of their antiretroviral therapy.[27]

6. Dosage and Administration

In the US and the EU, the oral, fixed-dose abacavir/lamivudine 600mg/300mg tablet is approved for once-daily use, in combination with other antiretroviral agents, in adult patients with HIV infection. It is not recommended for use with other NRTIs.[7] The tablet may be administered without regard to food.

As individual agents, (in combination with other antiretroviral agents) the approved dosages for abacavir[9] and lamivudine[8] are 600mg/day[9] and 300 mg/day[8] (administered as one or two daily doses) in adult patients with HIV infection. The dosages of both agents can be adjusted for use in paediatric patients.

Abacavir has been associated with hypersensitivity reactions which were sometimes fatal (see section 5). Development of symptoms of hypersensitivity requires permanent discontinuation of the drug.[7,9]

Because the dosage of abacavir in the fixed-dose abacavir/lamivudine tablet cannot be adjusted, the fixed-dose tablet is contraindicated for patients with hepatic impairment or those with creatinine clearance <3L/h (50 mL/min).

Further information on warnings, precautions and drug interactions are contained in the manufacturer's prescribing information.[7]

7. Place of the Combined Use of Abacavir plus Lamivudine in the Management of HIV Infection

Since their discovery in the late 1980s, NRTIs have been the cornerstone of antiretroviral therapy.[55] With the availability of new classes of drugs and increasing knowledge of HIV, treatment regimens have become more complex. In recent US and British treatment guidelines, dual NRTI therapy forms the backbone of all suggested first-line treatment options for patients with HIV infection.[2,3] These guidelines recommend initiating treatment with two NRTIs plus either an NNRTI, a PI or a third NRTI. However, some clinical trials have shown triple NRTI regimens to be less effective than PI- or NNRTI-containing regimens.[2] Thus, US guidelines recommend that this type of regimen is prescribed as initial therapy only when a PI- or NNRTI-containing regimen cannot, or should not, be used. British treatment guidelines state that the choice of which NRTI backbone to use is governed by adherence and toxicity issues.[3]

Several double NRTI combinations are not recommended for use in patients with HIV infection.[2] The combination of stavudine plus didanosine should not be used because of a high incidence

of toxicities; additive peripheral neuropathy may be observed with stavudine plus zalcitabine and didanosine plus zalcitabine. Stavudine and zidovudine are antagonistic, while emtricitabine and lamivudine have similar resistance profiles and therefore combination therapy offers no additional treatment benefit.[2]

The two NRTIs abacavir (300mg twice daily or 600mg once daily) plus lamivudine (150mg twice daily or 300mg once daily) as separate formulations have shown efficacy as the backbone of antiretroviral regimens in numerous trials in antiretroviral-naive adults with HIV infection, in terms of improvements in virological and immunological markers (see section 4.1.1). Coadministered agents were another NRTI (stavudine), an NNRTI (efavirenz) or PIs (amprenavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir and nelfinavir). Antiretroviral regimens that contained abacavir and/or lamivudine also showed efficacy in a 48-week trial in children and adolescents (section 4.1.2).

The once-daily, fixed-dose combination tablet of abacavir 600mg and lamivudine 300mg, in combination with efavirenz, reduced HIV RNA levels to <50 copies/mL in 69% of antiretroviral-naive patients at 24 weeks in an interim analysis of an ongoing, 48-week trial (section 4.2.1). By contrast, nearly half of the patients receiving the fixed-dose tablet in combination with tenofovir DF experienced early virological nonresponse. Initial investigations support the hypothesis that this early nonresponse was because of a low genetic barrier to resistance (section 2.1). Because of this finding, combining lamivudine plus abacavir with tenofovir DF is contraindicated in US guidelines.[2] Similarly, the triple-NRTI combination of lamivudine, tenofovir DF and didanosine is also contraindicated because of the high rate of early virological nonresponse with this combination.[2] Additionally, the efficacy of fixed-dose abacavir/lamivudine tablet was non-inferior to that of abacavir plus lamivudine as separate formulations, both as part of triple or quadruple antiretroviral therapy, after 24 weeks in two ongoing trials in antiretroviral treatment-experienced patients with HIV infection (section 4.2.2).

One of the key determinants of the long-term success of antiretroviral therapy is adherence to treatment.[2] Suboptimal adherence is associated with virological failure and the development of treatment-resistant variants of HIV. Patients must take 90–95% of doses in order to achieve optimal virological control. Numerous strategies for achieving good treatment adherence have been proposed, including patient-, clinician- and regimen-related strategies. Suggestions in the latter category include reducing the pill burden and complexity of regimens and using agents that may be taken without regard to food.

Co-formulating two or more antiretroviral agents is one strategy for reducing the daily pill burden for patients with HIV infection. Currently, three dual NRTI fixed-dose combination tablets are available in the US: abacavir/lamivudine, emtricitabine/tenofovir DF and lamivudine/zidovudine. As yet, there are no published data comparing the efficacy of fixed-dose abacavir/lamivudine with the other two dual NRTI co-formulations. However, as individual formulations, twice-daily abacavir plus lamivudine was non-inferior to twice-daily lamivudine plus zidovudine, both in combination with once-daily efavirenz, in a 48-week trial in antiretroviral-naive patients (section 4.1.1).

Given that once-daily therapy is desirable in terms of treatment adherence and convenience for patients,[2] the once-daily, fixed-dose formulations of abacavir/lamivudine and emtricitabine/tenofovir DF offer an advantage over the fixed dose lamivudine/zidovudine formulation which is administered twice daily. Moreover, the co-formulated abacavir/lamivudine tablet, unlike didanosine, can be taken without regard to meals. Notably, the individual formulations of lamivudine, abacavir and three other NRTIs (didanosine, tenofovir DF and stavudine) are also approved for once-daily administration in the US.

As with all currently available antiretroviral agents, HIV variants with reduced susceptibility to abacavir or lamivudine have been selected for *in vitro* and have also been isolated from patients receiving abacavir and/or lamivudine (section 2.1). Although both drugs select for the M184V mutant, this substitution alone is not enough to confer resistance to abacavir. When abacavir and lamivudine are administered with efavirenz, the patterns of resistance observed indicate that the drug-resistant HIV variant is likely to still be susceptible to some

other NRTIs, as well as other classes of antiretroviral drugs (based on two 48-week trials). Thus, if a patient experiences virological failure while receiving abacavir and lamivudine, other NRTIs may still be efficacious. Lamivudine is a common choice for a component of first-line therapy because lamivudine-resistant mutants carrying the M184V substitution remain susceptible to thymidine analogues.[2]

Abacavir and lamivudine are both generally well tolerated (section 5). Lamivudine is commonly used as one of the two backbone NRTIs in antiretroviral treatment because it has almost no toxicity.[2] Hypersensitivity reactions (incidence ≈5%) associated with abacavir are treatment limiting and have proved fatal in some patients who continued to receive abacavir or were rechallenged with the drug after a reaction (section 5).

Lipoatrophy, which most commonly affects the face and extremities, can decrease a patient's willingness to continue with therapy.[2,56] Stavudine appears to be associated with a higher incidence of lipoatrophy than other NRTIs.[3] Recipients of abacavir, lamivudine and efavirenz had a significantly lower rate of lipoatrophy than those receiving lamivudine, stavudine and efavirenz in antiretroviral-naive patients with HIV infection (section 5).

Forty-eight-week results of the trial of the fixed-dose abacavir/lamivudine tablet in combination with efavirenz are awaited with interest.[47] In addition, trials comparing co-formulated abacavir/lamivudine with the other co-formulated dual NRTIs (in particular, emtricitabine/tenofovir DF) would be useful. The abacavir/lamivudine and emtricitabine/tenofovir DF combination tablets are not included in published treatment guidelines[2,3] as they have only recently been approved for use.

In conclusion, abacavir plus lamivudine, in combination with other antiretroviral agents, are effective in reducing HIV RNA levels in antiretroviral-naive patients, and are generally well tolerated. Further experience with the fixed-dose abacavir/lamivudine tablet is needed to determine its position in the management of HIV infection. However, preliminary efficacy data are promising and adherence to treatment, which is a key factor in determining the success of an antiretroviral therapy regimen, should be improved by a single, once-daily tablet that may be taken irrespective of food intake. Thus, abacavir and lamivudine are two established components of first-line antiretroviral regimens for the management of HIV infection and the fixed-dose abacavir/lamivudine tablet has the potential to be an effective, easily adhered to and generally well tolerated component of first-line therapy.

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