Abacavir/lamivudine combination in the treatment of HIV: a review

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Abstract: Abacavir has been at the center of research and clinical interest in the last two years. The frequency of the associated abacavir hypersensitivity syndrome has decreased substantially since the introduction of routine testing for the HLA-B*5701 allele; the activity of the drug in HIV-infected persons with HIV RNA values more than 100,000 copies/mL has been questioned; the possible increased risk of myocardial infarction after recent exposure to abacavir has been debated; and the drug has been moved from the “recommended” category to the “alternative” category in several guidelines. Still, the drug remains a useful agent in combination with other drugs, including lamivudine, for the treatment of HIV infection. This review will focus on the pharmacokinetics, activity, side effects, and resistance profile of both abacavir and lamivudine, including a thorough review of all of the recent studies relevant to both drugs.

Keywords: HIV, abacavir, lamivudine

Introduction/background

It has been more than 20 years since the introduction of the first antiretroviral (ARV) drug, zidovudine (AZT, ZDV). Early ARV therapy regimens required patients to take many pills per dose multiple times per day, which often led to poor adherence and treatment failure. It is thus of no surprise that in later years, simplified regimens (fixed dose combinations, FDCs) have emerged. Current recommendations suggest starting treatment-naïve patients on 2 nucleoside reverse transcriptase inhibitors (NRTIs) with either a protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI).¹ One such NRTI combination is abacavir (ABC) and lamivudine (3TC) which is also available as a FDC. This article provides a comprehensive review of these two drugs.

Abacavir (ABC)

Abacavir is available as a single-agent, in dual combination with lamivudine (Epzicom®, ViiV Healthcare), and as a triple combination with zidovudine and lamivudine (Trizivir®, ViiV Healthcare). A generic form, abacavir sulfate is also available. The recommended adult dose of ABC is 300 mg twice daily or 600 mg once daily. No dose adjustment is required for renal dysfunction.¹

Chemistry and pharmacodynamics

Abacavir is a synthetic carbocyclic nucleoside analogue of the purine, guanine. It is converted to the active metabolite carbovir triphosphate (CBV-TP) through a three-step phosphorylation and deamination process by intracellular enzymes. The active metabolite...
CBV-TP is an analog of deoxyguanosine-5-triphosphate (dGTP), which competes with the endogenous dGTP and blocks its incorporation into the HIV viral DNA. This results in termination of chain elongation and inhibition of viral replication.

**Pharmacokinetics**

Abacavir is rapidly absorbed and is widely distributed. It has good bioavailability, (approximately 83%). Abacavir has significant penetration into cerebral spinal fluid (CSF)\(^1\) and has been recovered in the semen.\(^4\) Mean time to peak after single or multiple oral dosages is 0.7 to 1.7 hours. Approximately 50% of the drug binds to human plasma proteins. The primary route of elimination of ABC is metabolism by the two hepatic enzymes alcohol dehydrogenase (ADH) and glucuronyl transferase (GT). Alcohol dehydrogenase metabolizes approximately 36% of the dose to inactive carboxylate and GT metabolises approximately 30% of the dose to inactive glucuronide metabolite. Although ABC is metabolized by the liver, it does not inhibit or induce cytochrome P-450 (CYP-450) enzymes and therefore does not interact with medications metabolized by this system.\(^2\) Eighty-three percent of the dose of the drug is excreted primarily in the urine as metabolites, about 2% as unchanged drug; 66% of the dose is excreted as the two major metabolites, the 5'-carboxylate and the 5'-glucuronide.\(^2\)

The serum half-life of elimination (\(t_{1/2}\)) is about 1.5 hours but the drug has been shown in a number of pharmacokinetic and clinical studies to be efficacious when administered once daily.\(^3,9\) This is because the activity and efficacy of the drug is mainly determined by its intracellular concentration. When ABC is converted intracellularly to CBV-TP, the phosphorylation process essentially results in entrapment of the active metabolite in the cell leading to higher accumulation of the active agents than is achieved in the serum. Thus, the concentration of the active drug intracellularly is higher than that measured in the serum.\(^6\) As the frequency of drug administration is closely related to the pharmacokinetic properties of a drug, the key parameter is the half-life. However, the serum \(T_{1/2}\) of ABC, as is true of all NRTIs, is of little use in developing a dosing schedule. Rather, it is the intracellular half-life of the nucleoside triphosphate that is the relevant parameter.

Kewn et al showed in a pharmacokinetic study using the 300 mg dose once daily dose in six patients that CBV-TP levels remained above the inhibitory levels of the virus for 24 hours.\(^7\) Using the same method, Harris et al studied CBV-TP levels in peripheral mononuclear cells (PBMCs) of 5 HIV-positive adults taking ABC 600 mg once a daily for 5 to 17 months as a component of multiple drug rescue therapy. It was shown that the half life of CVB-TP was greater than 12 hours.\(^8\) A slightly larger study than that done by Harris et al was carried out by Piliero et al involving twenty patients given ABC 300 mg dose over a 24-hour period. Results showed a mean PBMC intracellular half-life of 20.64 and mean plasma half-life of 2.59 hours respectively.\(^6\)

Drusano et al\(^9\) using an *in vitro* pharmacodynamic model system, provided further support for once daily dosing. This group examined ABC dosing and ascertained the impact of the administration schedule on the activity of the drug. The antiviral effect and relationship to pharmacokinetics of a continuous infusion of ABC over 24 hours were compared with once-daily and twice-daily doses. A similar ABC exposure and antiviral effect was observed in all three regimens.

In an open-label, 2-period, crossover study, 34 HIV-infected male and female subjects stabilized on antiretroviral regimens containing either ABC 600 mg one daily or ABC 300 mg twice daily by Moyle et al\(^10\) the intracellular CBV-TP values were similar, providing further pharmacokinetic support for the interchangeability of these two regimens.

**Adverse events**

A significant number of patients have poor adherence to antiretroviral medications secondary to intolerance and adverse effects. The most important adverse event associated with ABC is the ABC hypersensitivity reaction (ABC HSR). The ABC HSR is an idiosyncratic multiorgan clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (i) fever; (ii) rash; (iii) gastrointestinal: nausea, vomiting, diarrhea or abdominal pain; (iv) constitutional: generalized malaise, fatigue or achiness; and (v) respiratory: dyspnea, cough, and/or pharyngitis. ABC HSR can be overlooked, as these symptoms may mimic various other disease conditions such as influenza, pneumonia, gastroenteritis. At one center, 15 HIV-positive patients who had symptoms of ABC HSR were compared with 30 HIV-positive patients who had symptoms of influenza.\(^11\) Gastrointestinal symptoms occurred in 60% of patients with ABC HSR versus 6% of patients with influenza. Although fever and myalgia were commonly observed in both groups, rash occurred in 47% of the patients with ABC HSR and in only 6% of patients with influenza. Although demographic characteristics, vital signs, and laboratory tests did not differ between the groups, respiratory symptoms that occurred without gastrointestinal symptoms were much more likely to be caused by influenza than by ABC HSR.
The overall incidence rate of ABC HSR is approximately 8% with some variability depending on genetic susceptibility of the population. More than 93% of ABC HSR reactions occur during the first 6 weeks of treatment. The median time to develop the reaction is 8 days. The reaction can develop on the first day of receipt of ABC therapy and has been reported to occur up to 160 days after initiation. Patients with a history of the ABC HSR who have been rechallenged with the drug have experienced unanticipated life-threatening consequences. Among 112 patients with ABC HSR who were rechallenged, an anaphylactic or immediate type of hypersensitivity reaction occurred in 20%. Therefore, patients with clinically suspected ABC HSR should not be rechallenged. There have been case reports of patients who developed the ABC HSR after re-initiation of ABC after a hiatus in taking the medication, but this occurrence is believed to be rare. Interestingly, these patients had no symptoms of HSR during the first period of ABC administration. A study of 145 patients who interrupted ABC treatment showed 1 case of hypersensitivity but no statistical difference in incidence between the study patients who did not interrupt ABC.

The ABC HSR is a clinical diagnosis. Physical findings associated with the ABC HSR in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually is maculopapular or urticarial, but may be variable in appearance. Abnormal laboratory findings may occur, but they are no means specific or diagnostic. Eosinophilia usually is not present. Leukopenia, lymphopenia and thrombocytopenia may all occur. Approximately 10%–15% of cases have elevated liver enzymes and a rise in creatinine phosphokinase levels also has been reported. Other abnormal laboratory values noted include elevations in alkaline phosphatase, blood urea nitrogen, serum creatinine, and lactate dehydrogenase levels. Disseminated intravascular coagulation has also been reported as a manifestation of ABC HSR.

A fever that develops within a few weeks after the initiation of therapy with abacavir may be due to causes other than hypersensitivity. Most common is the likelihood that simultaneous initiation of treatment with drugs, such as trimethoprim–sulfamethoxazole, efavirenz, or nevirapine, may be the cause. The incidence of adverse reactions, including hypersensitivity, to each of these drugs is greater than that of ABC. The presence of gastrointestinal or respiratory symptoms that accompany a rash or fever suggest ABC HSR as the likely cause. Opportunistic infections can manifest shortly after initiation of ARV as a result of immune reconstitution and should also be in the differential diagnosis.

Altered or unusual drug metabolism and a susceptible immune system are believed to be important cofactors for the development of drug-related hypersensitivity. HIV-infected persons are likely to be at special risk of developing hypersensitivity reactions because of the disease associated perturbations in the immune system. Two members of a family who were treated with ABC both developed the HSR suggesting a genetic component to ABC HSR. Multiple studies have shown an association of the ABC HSR with HLA-B*5701. The use of this screening test to identify high risk patients has been shown by Rauch et al to reduce the occurrence of the ABC HSR. In this cohort involving more than 260 patients, the authors observed that the use of HLA-B*5701 screening decreased ABC HSR from 7% to <1%. Similarly, the incidence of the ABC HSR decreased from 6.2% to 0.5% in a UK cohort of 185 patients treated with ABC using HLA screening.

The PREDICT-1 trial, a double-blind, prospective, randomized study involved 1956 patients from 19 countries, who were infected with human immunodeficiency virus type 1 and who had not previously received abacavir evaluated the effectiveness of prospective HLA-B*5701 screening to prevent the hypersensitivity reaction to abacavir. The study found a significantly lower incidence of ABC HSR in the prospective-screening group (3.4%) than in the control group (7.8%), (P < 0.001).

Similar results were obtained from the SHAPE study further strengthening the utility of prescreening with the HLA-B*5701 test prior to starting abacavir.

On the basis of these studies, the 2008 DHHS guidelines panel recommends screening for HLA-B*5701 before starting patients on an abacavir-containing regimen, to reduce the risk of hypersensitivity reaction (AI recommendation). In an analysis of 5,332 patients enrolled in ABC clinical trials, being ART-experienced at the start of ABC therapy and being of African descent were associated with a nearly 40% reduction in the risk of hypersensitivity. Patients of white race were found to be at significantly greater risk in another study of a population with a low percentage of ethnic minorities. Accumulated data suggest that factors that predict a lower likelihood to develop ABC HSR are: male sex, African racial origin, more advanced disease, and being an antiretroviral-experienced patient before initiation of ABC. There are no established interventions that will preempt the development of the ABC HSR. Patients randomized to receive prednisone 40 mg/day for the first 2 weeks when initiating ABC therapy in combination with nevirapine (NVP) and ZDV/3TC experienced a slightly higher incidence of hypersensitivity than those patients who did not receive prednisone (17% versus 10%, respectively).
The decision whether to stop ABC therapy or to cautiously continue it is an important one when ABC HSR cannot clinically be excluded. For instance, a rash may occur during ABC therapy without HSR. ABC may be an important component of an antiretroviral regimen that may be difficult to stop unless absolutely necessary because other alternatives may be lacking. However, the potential severity of ABC hypersensitivity calls for prudence. The overall case fatality rate is estimated to be 0.03%.\textsuperscript{19} ABC should be discontinued if the timing, severity, and combination of clinical symptoms are suggestive. When it is not clear if clinical symptoms are due to the ABC HSR, the drug may be continued under close clinical surveillance. For patients requiring hospitalization due to ABC HSR, treatment is supportive.

In a recent large, prospective observational cohort of HIV infected individuals by the Data Collection on Adverse Events of Anti-HIV Drugs (DAD), the risk of myocardial infarction in relation to exposure to NRTIs was studied.\textsuperscript{35} DAD is an international collaboration of 11 cohorts, following 33,347 HIV-1-infected individuals at 212 clinics in Europe, the US, and Australia.\textsuperscript{6,7,23} All participants were under active follow-up in their cohorts at the time of enrolment into DAD (December 1999 to January 2005). The study used Poisson regression models to quantify the relation between cumulative, recent (currently or within the preceding 6 months), and past use of zidovudine, didanosine, stavudine, lamivudine, and abacavir and development of myocardial infarction. The study found no associations between the rate of myocardial infarction and cumulative or recent use of zidovudine, stavudine, or lamivudine. However recent use of abacavir or didanosine was associated with an increased rate of myocardial infarction (compared with those with no recent use of the drugs, relative rate 1.90, 95% confidence interval [CI] 1.47 to 2.45 [\(P = 0.0001\)] with abacavir and 1.49, 1.14 to 1.95 [\(P = 0.003\)] with didanosine). After adjustment for predicted 10-year risk of coronary heart disease, recent use of both didanosine and abacavir remained associated with increased rates of myocardial infarction (1.49, 1.14 to 1.95 \(P = 0.004\) with didanosine; 1.89, 1.47 to 2.45 \(P = 0.0001\) with abacavir). It was concluded that an increased risk of myocardial infarction exists in patients exposed to abacavir and didanosine within the preceding 6 months. This excess risk was not explained by underlying established cardiovascular risk factors and was not present beyond 6 months after drug cessation.

The reproducibility of this finding in a different (but somewhat DAD-overlapping) dataset was explored and plausible biological mechanisms were sought by using the SMART study data. Biomarkers, ischemic changes on the electrocardiogram, and rates of various predefined types of cardiovascular disease (CVD) events according to NRTIs used were explored in the Strategies for Management of Anti-Retroviral Therapy (SMART) study.\textsuperscript{36} Patients receiving abacavir and not didanosine were compared with those receiving didanosine, and to those receiving NRTIs other than abacavir or didanosine (other NRTIs). Current use of abacavir was associated with an excess risk of CVD compared with other NRTIs. Adjusted hazard ratios for clinical myocardial infarction (\(n = 19\)), major CVD (myocardial infarction [MI], stroke, surgery for coronary artery disease, and CVD death \(n = 70\)); expanded CVD (major CVD plus congestive heart failure, peripheral vascular disease, coronary artery disease requiring drug treatment, and unwitnessed deaths \(n = 112\)) were 4.3 [95% CI 1.4 to 13.0], 1.8 (1.0 to 3.1), and 1.9 (1.3 to 2.9). At baseline in a subset of patients with biomarker data, high sensitivity-C-reactive protein and interleukin-6 were 27% \((P = 0.02)\) and 16% \((P = 0.02)\) higher for patients receiving abacavir \((n = 175)\) compared with those receiving other NRTIs \((n = 500)\). The analysis concluded that abacavir was associated with an increased risk of CVD and may cause vascular inflammation, which may precipitate a CVD event.

Analysis was performed by GlaxoSmithKline of GlaxoSmithKline-sponsored clinical trials with \(\geq 24\) weeks of combination antiretroviral therapy comprising 14,174 HIV-infected adults who received ABC \((n = 9502\); 7641 person-years) or not \((n = 4672\); 4267 person-years). The baseline demographics and HIV disease characteristics, including lipids and glucose values, were similar. MI rates were comparable among subjects exposed \([n = 16\) (0.168%; CI 0.096 to 0.273; 20.99 per 1000 person-years)] or not \([n = 11\) (0.235%; CI 0.118 to 0.421; 2.57 per 1000 person-years)] to ABC-containing therapy. In this analysis there were few MI events overall and no excess risk of MI with ABC therapy.\textsuperscript{37}

A study conducted by Veterans Affairs investigators, involving 19,424 people with an average 3.9 years of follow-up, showed a slight, statistically non-significant increase in MI with abacavir.\textsuperscript{38} The association of ABC use with AMI was much weaker after adjusting for traditional cardiovascular risk factors, including chronic kidney disease (CKD). Predictably, a significantly higher number of patients with estimated glomerular filtration rate below 60 received abacavir compared to tenofovir \((P < 0.0001)\), which has been associated with acute kidney injury and worsening renal function.

We have to keep the possibility of channeling bias in interpreting the DAD study results, since patients with CKD are more likely to be prescribed abacavir than tenofovir and...
drug reaches a maximum concentration of 0.5 to 1.5 hours. The absolute bioavailability is approximately 82% in adults. The pharmacokinetics of 3TC and ABC are different. Termination. It should be pointed out that the phosphorylation is inhibition of HIV reverse transcription via viral DNA chain termination. After 3TC is triphosphorylated, the principle mode of action is catalysis of the monophosphate. In the second step, the monophosphate is phosphorylated by cytidine monophosphate (deoxycytidine monophosphate kinase) to the diphosphate. Finally, the diphosphate is converted to the triphosphate by the enzyme nucleoside diphosphate kinase. After 3TC is triphosphorylated, the principle mode of action is inhibition of HIV reverse transcription via viral DNA chain termination. It should be pointed out that the phosphorylation pathways for 3TC and ABC are different.

Chemistry and pharmacodynamics
Lamivudine (3TC) is a cytosine analogue. It undergoes 3-step phosphorylation like ABC to form the active metabolite lamivudine triphosphate (3TC-TP) which competes with endogenous cytosine. In the first step, deoxycytidine kinase catalyzes the formation of the monophosphate. In the second step, the monophosphate is phosphorylated by cytidine monophosphate (deoxycytidine monophosphate kinase) to the diphosphate. Finally, the diphosphate is converted to the triphosphate by the enzyme nucleoside diphosphate kinase. After 3TC is triphosphorylated, the principle mode of action is inhibition of HIV reverse transcription via viral DNA chain termination. It should be pointed out that the phosphorylation pathways for 3TC and ABC are different.

Pharmacokinetics
3TC is rapidly absorbed after oral administration. The absolute bioavailability is approximately 82% in adults. The drug reaches a maximum concentration of 0.5 to 1.5 hours after oral administration. Less than 36% of the drug binds to plasma protein. The half life of elimination is 5 to 7 hours in adults but it is suitable to be administered as once daily dose as discussed in the next paragraph. Lamivudine is excreted primarily in the urine as unchanged drug.

In a study comparing the plasma pharmacokinetics of 3TC administered 150 mg twice daily and 300 mg once daily orally in 13 HIV-1 infected patients, Bruno et al were able to show that although there was statistically significant differences ($P < 0.05$) between the 2 schedules for $C_{\text{max}}$ and $C_{\text{min}}$ values, average concentration over the dosage interval and AUC over 2 dosage intervals (24 hours) were similar. The investigators concluded that their results provided the pharmacokinetic basis for using 3TC in a once daily regimen. Similar to ABC, with lamivudine, it is the intracellular concentration of the active metabolite that determines its activity, efficacy and suitability for once daily dosing.

Moore et al evaluated the pharmacokinetics of 3TC phosphorylation in peripheral blood mononuclear cells from 10 asymptomatic, antiretroviral-experienced HIV-1 infected patients who were receiving treatment with a regimen of 3TC and zidovudine (ZDV). The patients were randomly assigned to receive 3TC 150 mg twice a day or 300 mg twice a day for 14 days. The median half-life of intracellular 3TC-TP was 15.3 hours for the 150-mg dose and 16.1 hours for the 300-mg dose, a nonsignificant difference. Yuen et al compared the steady-state pharmacokinetics of 3TC in plasma and the active metabolite 3TC-TP in PBMCs. In this study, 60 healthy subjects received 3TC 300 mg once daily for 7 days and 150 mg twice daily for 7 days. Steady-state plasma 3TC pharmacokinetics following the once- and twice-daily regimens were bioequivalent with respect to both the AUC from 0 to 24 hours at steady state and average plasma 3TC concentration at steady state over the dosing interval. Steady-state intracellular 3TC-TP pharmacokinetics after the once- and twice-daily regimens were bioequivalent with respect to AUC and average plasma concentrations, as well as maximal 3TC concentrations. Overall, the results of this study suggest that for key pharmacokinetic parameters, 3TC 300 mg once daily is equivalent to 3TC 150 mg twice daily. A summary of the pharmacokinetic properties of ABC and 3TC is as shown in Table 1.

Drug interactions
The combination of 3TC and ABC as an NRTI backbone is ideal and effective because there is no intracellular competition for phosphorylation of these drugs. Furthermore, 3TC pharmacokinetics are not significantly affected by ABC.
Table 1 Pharmacokinetics of abacavir (ABC) and lamivudine (3TC) in adults

<table>
<thead>
<tr>
<th>Pharmacokinetic property</th>
<th>ABC</th>
<th>3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability (%)</td>
<td>83</td>
<td>82–86</td>
</tr>
<tr>
<td>C_{max} (µg/ml)</td>
<td>4.26</td>
<td>2.04</td>
</tr>
<tr>
<td>Mean time to C_{max} (hours)</td>
<td>0.7–1.7</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>AUC (µg *h/mL)</td>
<td>11.95</td>
<td>8.87</td>
</tr>
<tr>
<td>Plasma protein binding (1%)</td>
<td>50</td>
<td>&lt;36</td>
</tr>
<tr>
<td>Plasma T_{1/2} (hours)</td>
<td>1.5</td>
<td>5–7</td>
</tr>
<tr>
<td>Intracellular T_{1/2} (hours)</td>
<td>20.64</td>
<td>16–19</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Predominantly hepatic metabolism and then renal excretion (about 83%); 2% of the drug renally excreted as unchanged drug</td>
<td>5%–10% hepatic metabolism; predominantly renal excretion as unchanged drug via organic cationic transportation</td>
</tr>
</tbody>
</table>

Due to low protein binding, drug–drug interactions are infrequent. As a class, the NRTIs are predominantly excreted by the renal tubular system and interactions with drugs metabolized primarily by the cytochrome P-450 system are not encountered frequently. However, drugs influencing renal clearance or intracellular phosphorylation may cause interactions with all of the NRTIs.

The main interaction of 3TC and other drugs occurs with drugs that use renal tubular excretion for their elimination. In a randomized 2-way cross over study, 14 HIV-positive patients were given a 300 µg single dose 3TC and trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg for 5 days. It was noted that the area under the curve (AUC) of 3TC increased by 43%, and renal clearance of 3TC decreased by 30%. This increase was considered not significant, especially given the favorable safety profile of lamivudine. No significant change in any pharmacokinetic parameter occurred for TMP/SMX. Thus, no 3TC dosage adjustment is needed when used with TMP/SMX.

Lamivudine and zalcitabine (ddC) may inhibit the intracellular phosphorylation of one another and therefore such combination in any drug regimen should be avoided. In vitro data indicate that ribavirin reduces phosphorylation of 3TC, stavudine (d4T) and AZT. However, no pharmacokinetic or pharmacodynamic interaction was observed when ribavirin and 3TC (n = 18), d4T (n = 10), or AZT (n = 6) were co-administered as part of a multi-drug regimen to HIV/HCV co-infected patients.

There have been concerns about possible pharmacokinetic interaction between ABC and ethanol, as both are metabolized by alcohol dehydrogenase. However, in an open labeled randomized, 3-way crossover, phase 1 study, 24 HIV-positive males were given alcohol 0.7 g/kg and a single dose of 600 mg ABC. It was shown that ABC AUC increased by 41%, half-life of elimination increased by 26 %, and plasma maximum concentration increased by 15%. These changes were not considered statistically significant.

In a study of 11 HIV infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily) with 600 mg of ABC twice daily (twice the currently recommended dose), oral methadone clearance increased by 22% (90% CI = 6%–42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients. Lamivudine does not affect the clearance of methadone.

Both lamivudine and abacavir are listed as Pregnancy Category C drugs. No well-controlled trials of the FDC of abacavir + lamivudine (Kivexa®/Epzicom®) have been conducted in pregnant women. The drugs should be used in pregnancy only when the benefits outweigh the risks.

Clinical efficacy studies

ABC/3TC combination in comparison to other nucleotide combinations

CNA30024 study, a multicenter, randomized, double-blind trial compared the efficacy and safety of ABC/3TC versus AZT/3TC combined with efavirenz (EFV) in 649 antiretroviral-naive HIV-infected patients. Baseline median HIV-1 RNA level was 4.79 log_{10} copies/mL (39% of patients had HIV-1 RNA levels > 100,000 copies/mL). Baseline median CD4+ cell count was 264 cells/µL. Participants were randomized to receive either a 300-mg tablet of ABC and a placebo tablet, both administered twice daily, or a 300-mg tablet of AZT and a placebo tablet, both administered twice daily. All participants received a 150-mg tablet of 3TC twice daily plus 600 mg of EFV once daily. The primary objective was a comparison of the proportion of patients achieving plasma HIV-1 RNA levels (VL) ≤50 copies/mL through
week 48 of the study. At week 48, 70% of patients in the ABC group, compared with 69% in the AZT group, maintained a confirmed VL of ≤50 copies/mL (in the ITT exposed population). There was a significantly different CD4+ cell increase from baseline at 48 week: 209 cells/mm³ in the ABC group versus 155 cells/mm³ in the AZT group (P = 0.005). Although both groups had similar baseline CD4+ cell counts, the ABC group showed a better median absolute CD4+ cell response at all time points observed. The most common reported adverse effect in the AZT arm was nausea (37% versus 23% in the ABC arm). Reasons for discontinuation of drug in the ABC arm included nausea (2%), dizziness (1%), rash (3%) and suspected ABC HSR (8%); in the AZT arm, nausea, dizziness, rash (3% each) and anemia (4%) were the most common reasons for drug discontinuation.

The NRTI sub study of the FIRST study randomized 182 antiretroviral-naïve participants to receive abacavir + lamivudine versus didanosine + stavudine, each combined with a PI, an NNRTI, or both. Mean HIV RNA and CD4+ cell counts at baseline were 5.1 log₁₀ copies/mL and 212 cells/mm³. After a median follow-up of 28 months, there was no difference in rates of HIV RNA > 50 copies/mL between the two NRTI groups. However, there was a trend (0.05 = P < 0.10) for the abacavir + lamivudine group to be better than the didanosine + stavudine group for HIV RNA decreases, CD4+ cell count increases, and tolerability. The combination of didanosine + stavudine is no longer recommended, due to excessive toxicity observed in multiple clinical trials.

A5202 was a phase IIIB, randomized 4-arm study for treatment-naive subjects of double-blind ABC/3TC vs TDF/FTC with open-label efavirenz or atazanavir + ritonavir, stratified by screening HIV RNA (< vs > 100,000 copies/mL). The primary endpoints were time to virologic failure (VF) (confirmed HIV RNA > 1000 copies/mL at 16 to 24 weeks or 200 cells/mL at 24 weeks) and time to first Grade 3/4 adverse event (AE). A5202 enrolled 1858 eligible subjects; 797 had screening HIV RNA > 100,000 copies/mL. Median follow-up was 60 weeks. 85% were men, 26% Black, 25% Hispanic; mean baseline HIV RNA = 5.1 log₁₀ copies/mL, CD4 = 181/mm³. Among participants with entry HIV RNA ≥ 100,000 copies/mL, time to VF was significantly shorter in the ABC/3TC than TDF/FTC arm (HR = 2.33, 95% CI 1.46 to 3.72, P = 0.0003), occurring in 57 and 26 subjects respectively. In a secondary cross-sectional analysis (prior VF and regimen changes included), the proportion (95% CI) with HIV RNA <50 copies/mL at week 48 was 75% (69% to 80%) for ABC/3TC and 80% (74% to 85%) for TDF/FTC (P = 0.20). Subjects receiving ABC/3TC had a shorter time to grade 3/4 AEs (HR = 1.87, 95% CI 1.43 to 2.43, P < 0.0001), predominantly general body aches and lip increases. The comparisons of blinded NRTIs in the lower HIV RNA stratum and each regimen’s third drug in both strata are ongoing. Data safety monitoring board review prompted unblinding of NRTIs, additional analyses and recommendations to continue with NRTIs of choice due to the significant virologic efficacy differences by NRTIs for subjects with screening HIV RNA >100,000 copies/mL.

The HEAT study was the first completed, randomized clinical trial to directly compare the efficacy, safety, and tolerability of these agents, each in combination with lopinavir/ritonavir in antiretroviral-naïve patients. Six hundred and eighty-eight antiretroviral-naïve, HIV-1-infected patients were randomized in this double-blind, placebo-matched, multicenter, non-inferiority study to receive a once-daily regimen of either ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg, both with lopinavir/ritonavir 800 mg/200 mg. Primary endpoints were the proportion of patients with HIV-1 RNA below 50 copies/mL at week 48 (missing = failure, switch included analysis) and the proportion of patients experiencing adverse events over 96 weeks. At week 48, 68% in the ABC/3TC group vs. 67% in the TDF/FTC group achieved an HIV-1 RNA below 50 copies/mL (intent-to-treat exposed missing = failure, 95% confidence interval on the difference −6.63 to 7.40, P = 0.913), demonstrating the non-inferiority of ABC/3TC to TDF/FTC at week 48. Non-inferiority of the two regimens was sustained at week 96 (60% versus 58%, respectively, 95% confidence interval −5.41 to 9.32, P = 0.603). In addition, efficacy of both regimens was similar in patients with baseline HIV-1 RNA ≥ 100,000 copies/mL or CD4 cell counts below 50 cells/µL. In this analysis, both ABC/3TC and TDF/FTC provided comparable antiviral efficacy, safety, and tolerability when each was combined with lopinavir/ritonavir in treatment-naïve patients.

Only 2 studies are available comparing the ABC/3TC and TDF/FTC combinations head-on, with 1 (A5202) still not completed. Conflicting results were noted between both studies in terms of virologic failure and pending further studies, caution should be exercised in using abacavir/lamivudine in treatment naïve patients with baseline RNA > 100,000 cm³/mL.

**ABC/3TC as separate agents combined with a PI or NNRTI**

The NEAT trial was an international, multicenter, randomized, open-label study that compared the efficacy, durability, and tolerability of unboosted fos-amprnavir (f-AMV)
1400 mg twice daily, with nelfinavir (NFV) 1250 mg twice daily, in antiretroviral therapy (ART)-naive HIV-infected adults with plasma viral load at screening greater than or equal to 5000 copies/mL. Patients were randomly assigned to f-AMV or NFV (2:1) for a minimum of 48 weeks, with a background of ABC and 3TC. A total of 166 patients were on the f-AMV arm and 83 on the NFV arm. Most of the patients in the study had a previous CDC class C event. At the time of enrollment, the median HIV RNA level was 4.82 to 4.85 \( \log_{10} \) copies/mL and median CD4+ cell count was 212 to 214 cells/mm\(^3\). After 48 weeks of study, favorable virologic and immunologic responses were observed for both groups. The ABC/3TC backbone combined with either f-AMV or NFV was well-tolerated.

The SOLO study\(^{50}\) compared the magnitude and durability of the antiviral response to ritonavir-boosted fos-amprenavir (f-AMV/r) with NFV, each administered with ABC and 3TC. This was a randomized, open-label study in antiretroviral therapy-naive advanced HIV+ patients. Three hundred and twenty patients received f-AMV/r (1400/200 mg) once daily and 327 patients received NFV 1250 mg twice daily; both groups received the ABC/3TC backbone given twice daily. Median CD4+ cell count was 170 cells/mm\(^3\) and median HIV RNA level was 4.78 \( \log_{10} \) copies/mL. Diarrhea was the only adverse event to be statistically significantly different in incidence between treatment groups (16% for NFV versus 9% for f-AMV/r; \( P = 0.008 \)).

The ZODIAC study\(^{51}\) evaluated the efficacy and safety of once daily versus twice daily doses of ABC. This was a randomized double-blind study. Patients received 600 mg once daily (\( n = 384 \)) versus 300 mg administered twice daily (\( n = 386 \)) in combination with 300 mg 3TC and 600 mg of EFV each administered once daily in antiretroviral-naive patients over 48 weeks. The baseline median plasma HIV-1 RNA level was 4.89 \( \log_{10} \) copies/mL (44% of the patients had viral load > 100,000 copies/mL at baseline); median CD4+ cell count was 262 cells/mm\(^3\). ABC administered once daily was non-inferior to the twice-daily regimen, with 66% and 68% of patients in these respective treatment arms achieving a confirmed plasma HIV-1 RNA level < 50 copies/mL at 48 weeks. The ABC once-daily and twice-daily regimens were similar with respect to infrequency of virologic failure (10% vs 8%), emergence of resistance mutations, CD4+ cell count increases from baseline, safety profile, and incidence of ABC-related hypersensitivity reactions (9% versus 7%).

The CLASS study\(^{52}\) was an open-label, multicenter, randomized trial of up to 3 consecutive treatment regimens over 96 weeks. Two hundred ninety-one subjects received an ABC/3TC backbone with either efavirenz (NNRTI, \( n = 97 \)), ritonavir-boosted amprenavir (PI, \( n = 96 \)), or stavudine (NRTI, \( n = 98 \)). Participants receiving boosting amrenavir (APV/r) were later switched to boosted fos-amprenavir (f-AMV/r) to decrease pill burden. At week 96, there were no statistically significant differences between arms in the percentages of subjects with HIV RNA levels < 50 copies/mL by ITT analysis (missing data = failure): 68%, 58%, 61% on EFV, APV/r and d4T arms, respectively. The NNRTI arm had a statistically significantly greater percentages of participants with HIV RNA levels \( \leq 50 \) copies/mL at weeks 24 (\( P = 0.018 \)) and 48 (\( P = 0.047 \)). Twenty-one subjects had HSR attributed to ABC (7.3%). In conclusion, all treatment regimens demonstrated excellent 96-week results. Secondary analyses favored the NNRTI regimen over the PI and NRTI regimens.

**ABC/3TC fixed dose as backbone in studies comparing PI versus NNRTI**

The KLEAN (Kalera versus Lexiva with Epivir and Abacavir in ART-Naive patients) study\(^{53}\) compared ritonavir-boosted lopinavir (LPV/r) to ritonavir-boosted f-AMV/r combined with an ABC/3TC fixed-dose combination backbone. This was an open-label, non-inferiority study. Eight hundred seventy-eight antiretroviral-naive, HIV-1-infected persons were randomized to receive either f-AMV/r 700 mg/100 mg twice daily or LPV/r 400 mg/100 mg twice daily, each with ABC/3TC 600 mg/300 mg once daily. At week 48, noninferiority of f-AMV/r to LPV/r was shown, with 73% patients in the f-AMV/r group and 71% in the LPV/r group achieving HIV-1 RNA levels < 400 copies/mL. Treatment discontinuations due to an adverse event were few and occurred with similar frequency in the two treatment groups. The ABC HSR occurred in 6% of persons on the f-AMV/r arm versus 4% on the LPV/r arm.

In the ESS30008 study,\(^{54}\) ABC and 3TC administered twice daily were compared with fixed-dose combination (FDC) ABC/3TC administered once daily, both with either a PI or NNRTI in ARV-experienced persons. Two hundred sixty HIV-infected subjects with more than 6 months of ABC and 3TC administered twice daily plus a PI or NNRTI with an HIV RNA level < 400 copies/mL for > 3 months and a CD4+ cell count > 50 cells/mm\(^3\) were randomized 1:1 to continue...
ABC/3TC administered twice daily or switch to the FDC ABC/3TC administered once daily. At baseline, median time on ABC and 3TC administered twice daily was 22 months, and median CD4+ cell count and HIV RNA level were 554 cells/mm and <50 copies/mL, respectively. ABC/3TC FDC administered once daily was established as not inferior to ABC/3TC administered twice daily based on the proportion of nonvirologic failures. Proportions of persons in each group with an HIV-1 RNA level < 50 copies/mL were 81% (ABC/3TC FDC) and 82% (ABC + 3TC BID) at week 48 by ITT (missing data = failure). Virologic failure was rare (2 patients taking the once-daily regimen, 4 patients taking the twice-daily regimen). There was a low incidence of grade 2 through 4 adverse events and no drug-related serious adverse events or hypersensitivity reactions seen.

The CAL30001 study was a randomized, open-label study to compare the efficacy and safety of ABC/3TC FDC administered once daily to ABC (administered twice daily) and 3TC (administered once daily) given as separate entities, in combination with tenofovir (NRTI) and a new PI or NNRTI in antiretroviral-experienced adults experiencing VF defined as a VL > 1000 copies/mL at the time of enrollment with 3 or fewer NRTI-associated mutations. The primary efficacy endpoint was the time-averaged change from baseline (average area under the curve minus baseline) in plasma HIV RNA over 48 weeks. A total of 186 subjects were enrolled. No significant differences were seen in the primary efficacy endpoint or in the percentage of participants who achieved an HIV RNA level < 50 copies/mL. Tolerability was similar between the 2 groups.

Monotherapy with fixed dose combination of abacavir/lamivudine/zidovudine (trizivir) is not considered standard of care for initial therapy due to inferior virologic efficacy, compared to a regimen containing a drug from another class (efavirenz).

Safety, tolerability and adverse effects
As previously discussed, neither ABC nor 3TC is metabolized by the CYP-450 system. Consequently, drug–drug interactions are limited. Nucleoside analogs are associated, by varying degrees, with mitochondrial dysfunction. This toxicity can result in dyslipidemia, lipoatrophy and lactic acidosis. Lactic acidosis results from the inhibition of mitochondrial DNA synthesis by the nucleoside analogs, resulting in anaerobic glycolysis and intracellular accumulation of lactate. 3TC has greater affinity for mitochondrial DNA than does ABC. In vitro data have shown that neither 3TC nor ABC is associated with hepatic cytotoxicity or depletion of mitochondrial DNA. Furthermore, in a cohort study evaluating the risk factors for hyperlactatemia and lactic acidosis, ABC/3TC was associated with the lowest relative risk amongst NRTI pairs in the trial. The combination of ABC + 3TC also has been shown to have minimal or no effects on supplement terms of lipoatrophy as well as favorable lipid insulin and other metabolic effects. Replacing stavudine with abacavir or zidovudine has been shown to improve stavudine-induced lipoatrophy.

Resistance
ABC selects for mutations at positions 65 (K65R), 74 (L74V), 115 (Y115F), and 184 (M184V) in reverse transcriptase (RT). Lamivudine selects for mutations only at position 184 (M184V/I) in RT. The M184V/I mutations confers substantial resistance to both 3TC and emtricitabine, but only about a 2- to 3-fold increase in IC50 to abacavir. Thus, an isolated M184V/I mutation does not result in complete loss of activity to abacavir. In addition, the M184V/I mutations may enhance susceptibility to zidovudine, stavudine, and tenofovir. Furthermore, the presence of the M184V/I mutation typically results in impaired viral replication capacity, which has been shown to decrease HIV RNA levels by about 0.5 logs. When ABC + 3TC are used in combination with another class, the M184V mutation typically appears first and most frequently; the K65R mutation and L74V mutation are seen much less frequently. The abacavir-selected mutations K65R, L74V and Y115F each individually confer about three-to fourfold resistance to ABC, but in combinations of 2 or 3, they confer up to 8- to 10-fold resistance.

The thymidine analogue mutations (TAMs), which include M41L, D67N, L210W and T215Y/F, K219Q/E/N, are not selected by ABC but rather by the thymidine analogues ZDV and d4T. These mutations are associated with cross-resistance to all NRTIs, with increasing resistance as more of the TAMs accumulate. In isolation, they are associated with low-level resistance to 3TC and reduced virologic response to ABC. Patients with four TAMs in combination with M184V and L74V have minimal virologic responses to ABC-based regimens. Other mutations conferring high-level resistance to both ABC and 3TC in combination with TAMs are the T69 insertion mutation and the presence of E44D plus V118I. The Q151M complex also results in resistance to both drugs.

Conclusion and expert opinion
ABC/3TC is a well tolerated and effective NRTI backbone for both ARV-naive and ARV-experienced patients. The combination has been well studied and proven to
be efficacious in multiple studies. The flexibility of using this NRTI backbone with other classes is an additional advantage. Resistance mutations have not limited the clinical utility of this combination when used with other classes. The availability of the drugs in both FDC and individual formulations gives physicians the additional flexibility of dose adjustment when required. Other advantages of this combination are the relative paucity of significant drug-drug interactions and the option to take the medication with or without food. However, all patients should be screened for HLA-B5701, prior to initiating treatment with ABC to prevent the occurrence of abacavir-hypersensitivity syndrome. Recent studies, albeit with conflicting results, have suggested a possible increased risk of myoccardial infarction. One recent study showed a shortened duration to virologic failure in patients with pre-treatment HIV RNA > 100,000 cm⁻³/mL. Pending further studies, caution should be exercised in patients with underlying risk factors for CAD and baseline VL > 100,000 cm⁻³/mL. In patients without these risk factors and a negative HLA-B5701 screen, the abacavir/lamivudine combination is a suitable alternative especially in patients with renal disease and contraindications to tenofovir.

Disclosures

RDM is on the Speakers’ Bureau of ViiV Healthcare, and previously was a consultant to, and received grants from, GlaxoSmithKline.

References


