Research Review
PRODUCT REVIEW

Abacavir/lamivudine (Kivexa®)

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ABBREVIATIONS USED IN THIS REVIEW

ART	=	antiretroviral therapy
BMD	=	bone mineral density
CKD	=	chronic kidney disease
CRP	=	C-reactive protein
CV	=	cardiovascular
IL	=	interleukin
MI	=	myocardial infarction
MSM	=	men who have sex with men
NRTI	=	nucleoside analogue reverse-transcriptase inhibitor
PI	=	protease inhibitor
RCT	=	randomised controlled trial

This review discusses the evidence in support of the coformulation of abacavir/lamivudine (Kivexa®) for the treatment of HIV infection. Following an overview on HIV infection in NZ and general information about Kivexa®, including pharmacokinetics and dosing, the review summarises key trials that have examined the evidence for the efficacy of Kivexa® (and its components), which has been shown to be comparable with other agents/ART regimens, and the latest data on its safety, including its effects on lipid and bone metabolism, and CV and renal effects. Previous concerns regarding hypersensitivity reactions with abacavir can now be largely mitigated with *HLA-B*5701* testing. In essence, the Kivexa® combination product has an important place in the management of HIV infection, particularly for certain patient populations.

Kivexa® is an orally administered film-coated tablet NRTI coformulation of abacavir sulfate 600mg and lamivudine 300mg for once daily use in the treatment of HIV infection in patients aged >12 years.[Medsafe] The two component agents have an additive effect and the efficacy of the combination has been well established. It is often used as backbone therapy with other antiretrovirals, with synergy reported *in vitro* between abacavir and amprenavir, nevirapine and zidovudine, and high synergy between lamivudine and zidovudine. Abacavir also has additive effects with didanosine and zalcitabine. While there is potential for resistance to develop to either of the component agents of Kivexa®, cross-resistance between them and antiretrovirals from other classes is considered unlikely.

Previously, abacavir-associated hypersensitivity was a major obstacle for the use of the agent, but the advent of *HLA-B*5701* testing has allowed for the identification of patients who are likely to experience this, so can be deselected for treatment with Kivexa®. Data regarding CV safety of Kivexa®, particularly the abacavir component, are conflicting, and until resolved, patients with CV risk factors should avoid this coformulation. However, current Kivexa® data on bone metabolism and renal effects suggest that Kivexa® may be one of the options for patients for whom these factors are likely to be an issue.

Incidence, prevalence and diagnosis of HIV in NZ

The NZ Ministry of Health has reported that 150–180 new diagnoses of HIV infection were typically made each year during 2003–2010, with the annual diagnosis rate since 2005 being greater than that seen prior to 2000, with the exception of a decline in 2011.[MOH] There were 537 diagnoses of HIV infection made in MSM during 2002–2011. Most transmission among MSM occurred in NZ, and their ethnicities closely matched the ethnicity distribution of the NZ male population. While heterosexual transmission still predominates globally,[de Cock] such transmission was reported in 59 women and 44 men during the same time period in NZ. While these individuals were mainly European, the highest relative risk was seen in those of 'other' ethnicity (mainly African), and women of Māori, Pacific or Asian descent had a higher relative risk than European women. In contrast to MSM, most heterosexual transmission among New Zealanders occurred overseas.

MSM have been largely refractory to preventative interventions to limit HIV transmission at a global level,[de Cock] and high-risk sexual behaviour continues in NZ and other high-income settings. Less concern due to awareness of improved disease management is a possible explanation for such behaviour. In addition, an Auckland study suggests that around one in five men with HIV infection may not be aware of their status.[Saxton] NZ's ongoing *'Get it On!'* social marketing programme to increase condom use in MSM during anal sex is targeted mainly at highly sexualised (at-risk) and young MSM, the latter being a group in which declining condom use has been documented.[MOH] Among diagnoses of HIV made in NZ (1985–2011), 2.1% were in individuals aged <15 years and 10.1% were in those aged 15–24 years.

Most individuals being diagnosed with AIDS at present have not previously been aware of their positive HIV status, and are therefore not receiving ART. Furthermore, around half of individuals diagnosed with HIV during 2005–2010 presented with CD4-cell counts below the recommended treatment threshold.[MOH] These data demonstrate that many HIV-positive individuals are not aware of their status, and as such do not receive effective therapy at an early stage to prevent complications.

Disease burden

The burden of HIV/AIDS continues to rise due to stable incidence rates and effective treatment regimens leading to more prolonged survival.[de Cock] Biomedical prevention strategies hold promise for the future, with pre-exposure prophylaxis and early ART becoming increasingly important for preventing HIV spread. However, despite the relatively stable incidence of new HIV infection in NZ, PHARMAC data show a steady increase in the number of patients receiving funded ART over the last 7 years, with corresponding expenditure increases (from $8.9 million in the 2004–5 financial year to $16.8 million in 2010–11); PHARMAC currently funds 19 different antiretroviral therapies for HIV infection.[MOH, PHARMAC] Extensive resources are applied to HIV infection prevention, testing, counselling, support and research programmes and initiatives by both the NZ Ministry of Health and the NZ AIDS Foundation, including the *'Get it On!'* programme and community-based rapid testing. However, despite these interventions, there has been little change in the incidence of HIV infection and the prevalence is rising.

Pharmacokinetics of Kivexa®

Both abacavir and lamivudine are rapidly absorbed following oral administration, with respective absolute bioavailabilities in adults of 83% and 80–85% and respective mean T_{max} values of 1.5 and 1.0 hours.[Medsafe] A single oral dose of abacavir 600mg results in a mean C_{max} of 4.26 mg/mL and a mean $AUC_{0-\infty}$ of 11.95 mg·h/mL, and oral lamivudine 300mg once daily for 7 days results in a mean steady-state C_{max} of 2.04 mg/mL and a mean AUC_{0-24} of 8.87 mg·h/mL. The pharmacokinetics of Kivexa® are bioequivalent to the two components administered separately. When abacavir 600mg and lamivudine 150mg were coadministered, lamivudine's mean $AUC_{0-\infty}$ was decreased by ~15%, its mean C_{max} was decreased by ~35%, and its median T_{max} was delayed by ~1 hour, but these effects were not considered to be clinically significant.[Wang 1999]

Abacavir and lamivudine exhibit low-to-moderate and low plasma protein binding, respectively, and both can penetrate the blood-brain barrier.[Medsafe] Most abacavir undergoes hepatic metabolism, with <2% excreted unchanged by the kidneys, while lamivudine is mostly cleared unchanged by renal excretion – hepatic metabolism is <10%. Abacavir has a mean $T_{½}$ of ~1.5 hours, while the observed $T_{½}$ of lamivudine is 5–7 hours.

Registered uses, availability and profile

Efficacy

Kivexa® (abacavir 600mg/lamivudine 300mg) is indicated for ART combination therapy for the treatment of HIV infection in patients aged ≥12 years with bodyweight >40kg. The efficacy of abacavir/lamivudine in HIV-1 infections has been well established, with trends for better efficacy over other combinations such as didanosine/stavudine.[MacArthur 2004] A number of studies have also shown Kivexa® to be effective as an NRTI backbone for a variety of other antiretrovirals.[Echeverría 2010, Young 2010, Elion 2008, Squires 2010, Bartlett 2006]

Kivexa® versus tenofovir/emtricitabine

The fixed-dose combination of tenofovir/emtricitabine became available around the same time as Kivexa®. The tenofovir/emtricitabine combination has been shown to be associated with longer times to virological failure and first adverse event than abacavir/lamivudine, but no difference in changes in baseline CD4 cell count at week 48 in the scheduled interim analysis of the A5202 study.[Sax 2009] The BICOMBO study reported that abacavir/lamivudine did not meet noninferiority criteria for treatment failure when compared with the tenofovir/emtricitabine combination but the BICOMBO study did not undertake HLA-B*5701 screening.[Martinez 2009] However, the STEAL study reported no differences in virological efficacy parameters at 96 weeks.[Martin 2009] In addition, the HEAT Study (featured in the review) reported noninferiority between the two combination products in terms of virological efficacy.[Smith 2009] These conflicting findings were addressed by a meta-analysis of 12 clinical trials (n=5168) covering 21 treatment arms of these two combinations and ritonavir-boosted regimens.[Hill 2009] The authors concluded that the effects on HIV-RNA suppression for both regimens were higher for participants with baseline viral loads <100,000 copies/mL, and that although abacavir/lamivudine was typically associated with lower responses, confounding due to baseline characteristics, patient management or adherence may have contributed. Similar efficacy between the two combinations in patients with low HIV-RNA levels was highlighted in the final results of the A5202 study, although efficacy in patients with high HIV-RNA levels was found to be inferior for abacavir/lamivudine.[Sax 2011]

Formulations/dosing

Studies have also shown that administration of the combination Kivexa® product rather than individual agents improves both compliance and patient satisfaction with treatment,[Maitland 2008] and is similarly tolerated and noninferior in terms of reductions in plasma HIV-RNA levels.[LaMarca 2006, Sosa 2005] Thus, the Kivexa® represents a convenient and effective fixed-dose combination treatment for HIV infection. The recommended dose is one tablet each day. Kivexa® tablets must be taken whole, and can be taken with or without food.[Medsafe] Kivexa® is not suitable for children aged <12 years, and factors such as hepatic, renal and cardiac dysfunction, and concomitant medicines or diseases need to be considered before its use in patients aged >65 years. Kivexa® is not suitable for patients with mild hepatic impairment or renal impairment, due to the separate requirements for dose adjustments for abacavir in hepatic impairment and for lamivudine in renal impairment. Abacavir pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment, and Kivexa® is therefore contraindicated in such patients. Kivexa® is also contraindicated in patients with known sensitivity to abacavir, lamivudine or any of the product's excipients. Drug-drug interactions are consistent with those for the individual components of Kivexa®.

Safety

Bone effects

Abacavir/lamivudine has been shown to be associated with smaller decreases in spine and hip BMD and fewer bone events than tenofovir/emtricitabine.[McComsey 2011, Martin 2009, Stellbrink 2010] Furthermore, a substudy of BICOMBO showed improvements in BMD at 96 weeks when participants were switched from NRTI to fixed-dose combination therapy with either Kivexa® or fixed-dose tenofovir/emtricitabine;[Curran 2012] however, when these two were compared after switching from zidovudine/lamivudine, Kivexa® was associated with increased BMD and decreased bone turnover markers compared with tenofovir/emtricitabine.[Rasmussen 2012]

Renal effects

Trials have demonstrated no significant differences between abacavir/lamivudine and tenofovir/emtricitabine for glomerular filtration rate, and one trial has reported increased markers of tubular dysfunction with the tenofovir/emtricitabine, although the authors noted that the implications of this are not clear.[Martinez 2009, Post 2010]

Lipid/CV effects

The recently published A5202 substudy (A5224s) reported that Kivexa® and tenofovir/emtricitabine have similar effects on fat mitochondrial DNA, but the effect on complex I/IV activity levels has been reported to be lower with Kivexa®.[McComsey 2013] Furthermore, fixed-dose combination therapy with either Kivexa® or tenofovir/emtricitabine has been shown to increase limb fat in lipoatrophic patients after 96 weeks, with baseline factors associated with severe lipoatrophy factor predictive of such recovery.[Curran 2012, Martin 2011] Long-term abacavir/lamivudine has also been shown to increase subcutaneous tissue, compared with losses seen with stavudine or zidovudine combined with lamivudine.[Schlay 2008] Despite these findings, a more atherogenic profile (including a smaller low-density lipoprotein size) is often seen with abacavir/lamivudine.[Martinez 2010, Saumoy 2011, Schlay 2005]

There have been concerns over CV safety with the abacavir/lamivudine combination in some studies.[Martin 2009] A recent retrospective case-control study reported that HIV patients exposed to abacavir had a significantly increased risk of coronary heart disease (adjusted odds ratio 2.10; p=0.03).[Trevillyan 2013] Furthermore, another case-control study proposed a possible increase in ischaemic CV events with abacavir via *in vivo* platelet activation and induction of platelet hyper-reactivity by blunting the inhibitory effects of nitric oxide on platelets.[Falcinelli 2013] However, in contrast to a number of observational studies, meta-analyses from secondary analyses of RCTs, included in the featured papers, found no association between abacavir and increased risk of CV disease,[Bavinger 2013] and analyses of ACTG A5001/ALLRT study data and those pooled from 52 GSK-sponsored studies showed no association between abacavir-containing ART and MI.[Ribaudo 2011, Brothers 2009]

While increased lipid and cholesterol levels have been seen with abacavir/lamivudine versus tenofovir/emtricitabine, the abacavir/lamivudine combination has not been associated with increased inflammation, endothelial dysfunction, insulin resistance or hypercoagulability in virologically suppressed patients with HIV infection.[Martinez 2010] In terms of inflammatory markers, Kivexa® has been associated with greater high-sensitivity CRP changes than tenofovir/emtricitabine, but no reduction in IL-6 levels, which has been seen with tenofovir/emtricitabine.[McComsey 2012] However, a recent analysis of ARIES study data showed stable inflammatory markers during 144 weeks of treatment with abacavir/lamivudine in patients with Framingham Risk Score <6% or ≥6% (see featured paper).[Young 2013]

MAJOR CLINICAL TRIAL DATA FOR ABACAVIR/LAMIVUDINE IN THE MANAGEMENT OF HIV-1 INFECTION

Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/ emtricitabine with lopinavir/ritonavir for initial HIV treatment[Smith 2009]

Authors: Smith KY et al., for the HEAT study team

Summary: ART-naïve patients with HIV-1 infection (n=688) were randomly assigned to receive once-daily abacavir/lamivudine 600mg/300mg or tenofovir/emtricitabine 300mg/200mg, both with lopinavir/ritonavir 800mg/200mg and matching placebos to achieve blinding, in this noninferiority study. The difference in the proportion of participants with HIV-RNA level <50 copies/mL at week 48 (primary endpoint) was not significant between the abacavir/lamivudine and tenofovir/emtricitabine arms (68% vs. 67%, respectively; p=0.913), with noninferiority persisting out to week 96 (60% vs. 58%; p=0.603). There was also no between-group difference for median CD4+ cell recovery at 96 weeks (250 and 247 cells/mL), or in the subgroups of participants with baseline HIV-1 RNA ≥100,000 copies/mL and CD4+ cell counts <50 cells/mL. The discontinuation rate due to adverse events was 6% in both arms, and the protocol-defined virological failure rate was 14% in both arms.

Comment: This large RCT directly compared abacavir/lamivudine versus tenofovir/emtricitabine, both in combination with lopinavir/ritonavir, in treatment-naive patients. Prescreening for the *HLA-B*5701* allele was not undertaken. By all efficacy endpoints, including high baseline viral load, there was no significant difference in outcomes between the two groups. This finding was at odds with the ACTG A5202 study, which demonstrated a shorter time to virological failure in patients taking abacavir/emtricitabine as compared with tenofovir/emtricitabine, but was in keeping with the ARIES study and other smaller RCTs. In addition, there was no significant difference in protocol-defined virological failures. With regards to safety, there was also no overall difference between the two treatment limbs. As there was no *HLA-B*5701* screening, it was not surprising to find that suspected abacavir hypersensitivity reaction was more frequent in the abacavir/lamivudine group. Similarly, progression to more advanced CKD was more common in the tenofovir/emtricitabine group, although the numbers in each limb were low, and no patients progressed to stage 4 CKD. In regard to CV events, these were infrequent with four in the tenofovir and two in the abacavir limb, and none considered related to the study drugs. A *post hoc* analysis of inflammatory markers demonstrated declines in both treatment limbs of high-sensitivity CRP, IL-6 and soluble vascular adhesion molecule-1 levels.

Abacavir/lamivudine fixed-dose combination with ritonavir-boosted darunavir: a safe and efficacious regimen for HIV therapy[Trottier 2012]

Authors: Trottier B et al.

Summary: These researchers investigated abacavir/lamivudine 600mg/300mg once daily (Kivexa® or Epzicom®) administered with darunavir 400mg boosted with ritonavir 100mg once daily in 42 treatment-naïve and 35 treatment-experienced patients with HIV infection. None of the 56 participants with available results were *HLA-B*5701* positive, and the mean viral loads for treatment-naïve and -experienced participants were 4.8 and 2.3 log copies/mL, respectively. Twelve patients discontinued the study treatment before the endpoint was reached. A viral load of <50 copies/mL at week 48 was seen in 79% of participants. Treatment-naïve participants had a significantly greater increase in median CD4 cells than treatment-naïve participants (273 vs. 102 cells; p=0.002). No participants experienced grade ≥2 liver enzyme elevation.

Comment: This small open-label observational study explored the efficacy of abacavir/lamivudine plus darunavir/ritonavir in both treatment-naive and treatment-experienced patients. In none of the treatment experienced patients was there evidence of resistance to any of the study drugs. At the time the study was initiated, DHHS (Department of Health and Human Services) guidelines gave this combination a low ranking because of a lack of safety and efficacy data. After 48 weeks, 79% of individuals in an intent-to-treat analysis had an undetectable viral load and 98% in an on-treatment analysis. These results are comparable with results obtained in studied of tenofovir/emtricitabine plus darunavir/ritonavir. The study is clearly limited by its observational design and small size. Nevertheless, it gives support to the use of abacavir/lamivudine as an alternative to tenofovir/emtricitabine in treatment-naive and some treatment-experienced patients. On the basis of this study, the DHHS has upgraded their recommendation of this treatment combination to 'alternative regimen'.

ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine[Squires 2012]

Authors: Squires KE et al., for the ARIES Study Team

Summary: This paper reported on an open extension phase of a trial in which ART-naïve patients with HIV infection initially received abacavir/lamivudine and atazanavir/ritonavir, and were then randomised at 36 weeks to maintain or discontinue ritonavir for an additional 108 weeks. Noninferiority was shown at week 84, and 369 participants entered the extension phase of their randomised regimen for a further 60 weeks. Compared with the ritonavir-nonboosted regimen, the boosted regimen was associated with similar proportions of participants who maintained an HIV RNA level of <50 copies/mL at week 144 (77% vs. 73%), but a higher rate of postrandomisation grade 2–4 treatment-related adverse events (23% vs. 13%), particularly elevated serum bilirubin level (14% vs. 6%), and a significantly greater increase in median fasting triglyceride level (28.5 vs. –8.5 mg/dL; p=0.001).

Comment: This study confirms that abacavir/lamivudine plus unboosted atazanavir remains effective long term and has a favourable side effect profile and effects on blood lipids. After achieving virological control with boosted atazanavir/abacavir/lamivudine, the majority of patients on this regimen continued to have undetectable virus. In the few patients with virological failure, either noncompliance or treatment interruption could be identified as a cause. Compared with the ritonavir-boosted atazanavir regimen, the unboosted atazanavir regimen showed a more favourable side effect profile and greater declines in total and low-density lipoprotein cholesterol levels. Abacavir/lamivudine plus unboosted atazanavir is an effective and well-tolerated treatment option, and may be suitable for patients unable or unwilling to take ritonavir.

No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis[Ding 2012]

Authors: Ding X et al.

Summary: This trial-level meta-analysis conducted by the US FDA included 26 controlled trials (n=9868) in which participants were randomised to combined ART with (n=5028) or without (n=4840) abacavir. It found similar MI event rates for regimens that included abacavir versus those that did not (0.48% vs. 0.46%; risk difference 0.008% [95% CI 20.26, 0.27]).

Comment: This is the largest meta-analysis of RCTs to date assessing the risk of MI with abacavir. The authors set out to perform a subject-level meta-analysis that used a consistent definition of MI, but unfortunately were unable to obtain full datasets from several trials. The analysis was therefore limited to a trial-level meta-analysis. Overall, there were 24 events in 5028 subjects receiving abacavir, and 22 events in 4840 subjects not receiving the agent. The average duration of follow-up across the trials was relatively short, and overall was 1.43 years for the abacavir group and 1.49 years for the group that did not receive abacavir. Only two trials had an average follow-up of >2 years. The overall meta-analysis found no statistically significant association between abacavir and MI. Additionally, there was no difference between trials of different durations of follow-up. The authors concluded that this and other negative studies raised doubt over a relationship between abacavir use and MI, and suggested that only an adequately powered RCT could give a clearer understanding.

Risk of cardiovascular disease from antiretroviral therapy for HIV[Bavinger 2013]

Authors: Bavinger C et al

Summary: This systematic review and meta-analysis of studies reporting CV events with ART found a significantly increased risk of MI with recent (typically within 6 months) exposure to abacavir (relative risk 1.92 [95% CI 1.51, 2.42]) based on data from two observational studies. However, the increased CV risk with abacavir contrasted to no such increased CV risk reported by published meta-analyses based on secondary analyses of RCTs.

Comment: Bavinger and colleagues have performed a comprehensive and rigorous review of English language comparative studies describing the association between antiretroviral agents and CV events. They screened over 1450 unique citations and performed a full text review of 247 articles. Twenty-seven met their strict inclusion criteria and were included in the analysis. These 27 articles included observational studies, RCTs and three prior meta-analyses (including the previous study undertaken by Ding et al.). Each study was rated good, fair and poor by accepted criteria. With regard to abacavir use and CV risk, there was considerable inconsistency across the studies. The pooled analysis of two observational studies demonstrated an association between recent (<6 months) abacavir exposure and risk of MI. In addition, a combined analysis of the p values from all six studies that evaluated comparable definitions of recent exposure to abacavir also suggested adverse CV outcomes with its early use. However, there were significant inconsistencies across the studies in quality and findings, with three of the six studies showing no increased CV risk, and only one study graded high quality. In regard to cumulative exposure to abacavir, only one of three fair-quality observational studies found an association with CV risk. The three meta-analyses of RCTs were consistent in showing no association between abacavir and MI. However, the RCTs included in these meta-analyses were not primarily designed to study this relationship, tended to be of short duration and generally underpowered to detect a differential MI risk. The authors concluded that, based on the overall evidence, there remained uncertainty whether the use of abacavir increased CV risk, and recommended further prospectively designed studies to clarify these issues.

Inflammatory biomarker changes and their correlation with Framingham cardiovascular risk and lipid changes in antiretroviral-naive HIV-infected patients treated for 144 weeks with abacavir/lamivudine/atazanavir with or without ritonavir in ARIES[Young 2013]

Authors: Young BG et al., for the ARIES (EPZ108859) Study Team

Summary: These researchers analysed data from the phase IIIb/IV ARIES study, in which patients with ART-naïve HIV infection were initially treated with abacavir/lamivudine plus atazanavir/ritonavir for 36 weeks, with those who exhibited virological suppression by week 30 then randomised to continue or stop ritonavir for a further 108 weeks. For ritonavir-boosted and -nonboosted groups combined, high-sensitivity CRP and IL-6 levels did not change significantly between baseline and week 144 in participants with Framingham Risk Scores <6% (1.6 to 1.4 mg/L and 1.6 to 1.4 pg/mL, respectively) and ≥6% (1.9 to 2.0 mg/L and 2.0 to 2.2 pg/mL, respectively). Significant reductions were seen at between baseline and week 144 for median lipoprotein-associated phospholipase-A2 (Lp-PLA2) levels in participants with Framingham Risk Scores <6% (197 to 168 nmol/min/mL [p<0.001]) and ≥6 (238 to 175 nmol/min/mL [p<0.001]).

Comment: The findings from observational cohorts of a possible association between exposure to abacavir as well as some PIs and CV events have prompted studies to better understand the potential mechanisms of such a link. Changes in several biomarkers, including Lp-PLA2, high-sensitivity CRP, and IL-6, have been independently associated with CV risk. Hence the authors of this study set out to measure the serum levels of these biomarkers over time in patients taking abacavir with either atazanavir or atazanavir with ritonavir boosting. The participants in the study had relatively low prestudy Framingham CV risk scores, and over the 144 weeks of the study these did not change significantly. Correspondingly, there was no change in levels of high-sensitivity CRP and IL-6, and there was a modest but significant drop in Lp-PLA2 levels. Therefore, any increase risk of CV disease with abacavir cannot be easily explained by changes in these biomarkers.

Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202[McComsey 2011]

Authors: McComsey GA et al.

Summary: Treatment-naive patients with HIV infection (n=269) were randomised to receive abacavir/lamivudine or tenofovir/emtricitabine along with open-label efavirenz or atazanavir/ritonavir in the four-arm A5202 study; the A5224s substudy investigated BMD outcomes. Compared with tenofovir/emtricitabine, abacavir/lamivudine was associated with significantly smaller reductions in baseline spine and hip BMD measures at week 96 (primary endpoints; –1.3% vs. –3.3% [p=0.004] and –2.6% vs. –4.0% [p=0.024], respectively); reductions in spine BMD measures were significantly smaller with efavirenz versus atazanavir/ritonavir, but reductions in hip BMD measures were not.

Comment: Loss of BMD is associated with HIV infection, and is related to CD4 count, HIV viral load and duration of infection. In addition, there is a 2–6% loss in BMD in the first 24 months of ART. This study confirms earlier research showing a greater loss of spine and hip BMD in patients receiving tenofovir than those receiving abacavir. The bone loss in both groups of patients occurred in the first 48 weeks of therapy, and then BMD remained static or improved modestly over the next 168 weeks of the study. The magnitude of tenofovir-associated bone loss was equivalent to that seen in the first 2 years after menopause. Although there was no demonstrable increased risk of fractures in the tenofovir group, the study participants were largely younger men, who have a low rate of fracture. Longer term studies will be needed to address what happens to BMD over time and whether there is an increased fracture rate with tenofovir therapy. The mechanism of tenofovir-associated bone loss is not clear, but may be related to proximal tubular toxicity.

Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients[Mocroft 2010]

Authors: Mocroft A et al., EuroSIDA Study Group

Summary: These researchers investigated the long-term effects of exposure to antiretroviral agents on CKD in a cohort of 6843 patients with HIV infection, 225 (3%) of whom developed CKD during 482 person-years of follow-up. After adjustments, a significant association was seen between CKD and cumulative exposure to tenofovir, indinavir, atazanavir and ritonavir-boosted lopinavir, while there was no association with exposure to abacavir, efavirenz, zidovudine and stavudine.

Comment: Renal disease occurs with HIV infection through HIV-associated nephropathy, immune complex disease and acute renal failure. Since the introduction of antiretroviral drugs, there has been a decline in renal disease in HIV-infected individuals. However, a number of antiretroviral drugs have been specifically associated with impaired renal function. This large study was undertaken within the EuroSIDA cohort. Relatively few patients developed CKD, and in those who did, there was a strong association of renal dysfunction with the traditional risk factors such as diabetes, hypertension and aging. In addition, increasing exposure to tenofovir and the PIs indinavir, atazanavir and, to a lesser extent, lopinavir were independently linked to CKD. Tenofovir-associated CKD was most commonly seen in individuals with other pre-existing risk factors for renal disease. The link between CKD and tenofovir has not been shown in earlier clinical trials, but in general these have been of shorter duration and included fewer individuals with CKD risk factors than in the current study. The link between tenofovir and CKD could not be explained by the coadministration of boosted PIs. Withdrawal of tenofovir was associated with a gradual return of renal function over 12 months, indicating that the renal toxicity is at least partially reversible.

Concluding remarks

Kivexa® is a convenient, well tolerated and effective antiretroviral coformulation of abacavir and lamivudine. Hypersensitivity reactions, which may occur in around 4% of individuals exposed to abacavir, are now rare since the introduction of *HLA-B*5701* testing, which identifies those likely to experience a reaction.

There has been considerable debate over the relative efficacy of Kivexa® in comparison with tenofovir/emtricitabine. The ACTG 5202 trial concluded that participants with viral loads >100,000 copies/mL were more likely to experience virological failure when given Kivexa® compared with tenofovir/emtricitabine. In response to this finding, the DHHS guidelines downgraded Kivexa® to 'alternative' status. However, more recent studies, including the HEAT study included in this review, have found no difference in antiviral activity between different regimens containing either Kivexa® or tenofovir/emtricitabine. One potential contributing factor for the discrepancies is that the earlier studies did not have access to *HLA-B*5701* testing, and as a consequence there was a relatively higher dropout rate in participants receiving Kivexa® due to hypersensitivity reactions.

Various studies have shown that Kivexa® with efavirenz, ritonavir-boosted PIs, including darunavir, atazanavir and lopinavir, and the integrase inhibitor raltegravir, are all effective regimens. Kivexa® is also effective with unboosted atazanavir; however, tenofovir co-administration with atazanavir results in lower atazanavir serum concentrations and the combination is not recommended.

Kivexa® has a good safety profile. Compared with tenofovir/emtricitabine, it appears to cause less bone thinning, and in one large study was associated with fewer instances of renal toxicity. There remains some uncertainty over the relative risk of CV disease with Kivexa® due to considerable diversity of the results from different studies. Whilst some cohort studies, including the large D.A.D study of >33,000 patients, have suggested a link with MI, other studies, including several meta-analyses of RCTs, have found no such association. Overall, there remains some concern that in comparison with other ARTs, abacavir may be linked to increased CV events, and until this issue is clarified, it is reasonable to use other options in patients with significant CV risk.

Overall, Kivexa® has similar efficacy and safety to tenofovir/emtricitabine for the treatment of HIV infection. These recent efficacy and safety data have resulted in Kivexa® being given 'recommended' status along with tenofovir/emtricitabine in the European EACS guidelines and the IAS-USA Panel guidelines. Kivexa® remains an alternative regimen in the BHIVA and DHHS guidelines. Tenofovir/emtricitabine has the advantage of coformulation with efavirenz making it possible to treat HIV infection effectively with one tablet per day. The combination of tenofovir/emtricitabine is definitely preferred in patients who are co-infected with hepatitis B virus, and is probably preferred in those with high CV risk. However, on the basis of current understanding, Kivexa® is probably preferred in those with, or at increased risk of, renal disease or osteoporosis.

References

1. NZ Ministry of Health. Country progress report New Zealand. Reporting period: January 2010 – December 2011. Available from http://www.health.govt.nz/system/files/documents/publications/hiv-aids-country-progress-2012-report.pdf
2. de Cock KM et al. The evolving epidemiology of HIV/AIDS. AIDS 2012;26(10):1205–13
3. Saxton PJW et al. Actual and undiagnosed HIV prevalence in a community sample of men who have sex with men in Auckland, New Zealand. BMC Public Health 2012;12:92
4. Pharmac. Online Pharmaceutical Schedule; Oct 14, 2013. Available from http://pharmac.govt.nz/healthpros/PharmaceuticalSchedule/Schedule?code=A16
5. Mesdafe – New Zealand Medicines and Medical Devices Safety Authority. New Zealand data sheet. Kivexa® film coated tablet: abacavir + lamivudine fixed dose combination. Available from http://www.medsafe.govt.nz/profs/Datasheet/k/Kivexatab.pdf
6. Wang LH et al. Single-dose pharmacokinetics and safety of abacavir (1592U89), zidovudine, and lamivudine administered alone and in combination in adults with human immunodeficiency virus infection. Antimicrob Agents Chemother 1999;43(7):1708–15
7. MacArthur RD et al., 058 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. Efficacy and safety of abacavir plus lamivudine versus didanosine plus stavudine when combined with a protease inhibitor, a nonnucleoside reverse transcriptase inhibitor, or both in HIV-1 positive antiretroviral-naive persons. HIV Clin Trials 2004;5(6):361–70
8. Echeverría P et al. Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ritonavir, administered with abacavir/lamivudine (Kivexa), in antiretroviral-naive patients: a 48-week, multicentre, randomized study (Lake Study). Antiviral Res 2010;85(2):403–8
9. Young B et al., Shield Study Team. A pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naive HIV-1-infected patients: 48-week results of the SHIELD trial. HIV Clin Trials 2010;11(5):260–9
10. Elion R et al., COL102060 Study Team. Once-daily abacavir/lamivudine and ritonavir-boosted atazanavir for the treatment of HIV-1 infection in antiretroviral-naive patients: a 48-week pilot study. HIV Clin Trials 2008;9(3):152–63
11. Squires KE et al., ARIES Study Team. Safety and efficacy of a 36-week induction regimen of abacavir/lamivudine and ritonavir-boosted atazanavir in HIV-infected patients. HIV Clin Trials 2010;11(2):69–72
12. Bartlett JA et al., Clinically Significant Long-Term Antiretroviral Sequential Sequencing Study (CLASS) Team. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. J Acquir Immune Defic Syndr 2006;43(3):284–92
13. Sax PE et al., AIDS Clinical Trials Group Study A5202 Team. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med 2009;361(23):2230–40
14. Martinez E et al., BICOMBO Study Team. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. J Acquir Immune Defic Syndr 2009;51(3):290–7
15. Martin A et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. Clin Infect Dis 2009;49(10):1591–601
16. Smith KY et al., for the HEAT study team. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/ emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 2009;23(12):1547–56
17. Hill A & Sawyer W. Effects of nucleoside reverse transcriptase inhibitor backbone on the efficacy of first-line boosted highly active antiretroviral therapy based on protease inhibitors: meta-regression analysis of 12 clinical trials in 5168 patients. HIV Med 2009;10(9):527–35
18. Sax PE et al., AIDS Clinical Trials Group Study A5202 Team. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. J Infect Dis 2011;204(8):1191–201
19. Maitland D et al. Switching from twice-daily abacavir and lamivudine to the once-daily fixed-dose combination tablet of abacavir and lamivudine improves patient adherence and satisfaction with therapy. HIV Med 2008;9(8):667–72
20. LaMarca A et al, on behalf of the CAL30001 Study Team. Efficacy and safety of a once-daily fixed-dose combination of abacavir/lamivudine compared with abacavir twice daily and lamivudine once daily as separate entities in antiretroviral-experienced HIV-1-infected patients (CAL30001 Study). J Acquir Immune Defic Syndr 2006;41(5):598–606
21. Sosa N et al. Abacavir and lamivudine fixed-dose combination tablet once daily compared with abacavir and lamivudine twice daily in HIV-infected patients over 48 weeks (ESS30008, SEAL). J Acquir Immune Defic Syndr 2006;40(4):422–7
22. McComsey GA et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis 2011;203(12):1791–801
23. Stellbrink HA et al., ASSERT Study Group. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis 2010;51(8):963–72
24. Curran A et al. Changes in body composition and mitochondrial DNA in HIV-1-infected patients switching to fixed-dose abacavir/lamivudine or tenofovir/emtricitabine: a substudy of the BICOMBO trial. Antivir Ther 2012;17(4):711–8
25. Rasmussen TA et al. Comparison of bone and renal effects in HIV-infected adults switching to abacavir or tenofovir based therapy in a randomized trial. PLoS ONE 2012;7(3):e32445
26. Post FA et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J Acquir Immune Defic Syndr 2010;55(1):49–57
27. McComsey GA et al. Changes in fat mitochondrial DNA and function in subjects randomized to abacavir-lamivudine or tenofovir DF-emtricitabine with atazanavir-ritonavir or efavirenz: AIDS Clinical Trials Group study A5224s, substudy of A5202. J Infect Dis 2013;207(4):604–11
28. Martin A et al., STEAL Study Group. Predictors of limb fat gain in HIV positive patients following a change to tenofovir-emtricitabine or abacavir-lamivudine. PLoS ONE 2011;6(10):e26885
29. Schlay JC et al. Long-term subcutaneous tissue changes among antiretroviral-naive persons initiating stavudine, zidovudine, or abacavir with lamivudine. J Acquir Immune Defic Syndr 2008;48(1):53–62
30. Saumoy M et al., Bicombo-met Substudy Team. Low-density lipoprotein size and lipoprotein-associated phospholipase A2 in HIV-infected patients switching to abacavir or tenofovir. Antivir Ther 2011;16(4):459–68
31. Martinez E et al., BICOMBO Study Team. Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction. AIDS 2010;24(3):F1–9
32. Schlay JC et al., Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Body composition and metabolic changes in antiretroviral-naive patients randomized to didanosine and stavudine vs. abacavir and lamivudine. J Acquir Immune Defic Syndr 2005;38(2):147–55
33. McComsey GA et al. Inflammation markers after randomization to abacavir/lamivudine or tenofovir/emtricitabine with efavirenz or atazanavir/ritonavir. 2012;26(11):1371–85
34. Trevillyan JM et al. Abacavir exposure and cardiovascular risk factors in HIV-positive patients with coronary heart disease: a retrospective case-control study. Sex Health 2013;10(2):97–101
35. Falcinelli E et al. In vivo platelet activation and platelet hyperreactivity in abacavir-treated HIV-infected patients. Thromb Haemost 2013;110(2):349–57
36. Bavinger C et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS ONE 8(3):e5955
37. Ribaudo HJ et al., for the ACTG A5001/ALLRT Protocol Team. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. Clin Infect Dis 2011;52(7):929–40
38. Brothers CH et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. J Acquir Immune Defic Syndr 2009;51(1):20–8
39. Young B et al. Inflammatory biomarker changes and their correlation with Framingham cardiovascular risk and lipid changes in antiretroviral-naive HIV-infected patients treated for 144 weeks with abacavir/lamivudine/atazanavir with or without ritonavir in ARIES. AIDS Res Hum Retroviruses 2013;29(2):350–8
40. Trottier B et al., for the ARIES (EPZ108859) Study Team. Abacavir/lamivudine fixed-dose combination with ritonavir-boosted darunavir: a safe and efficacious regimen for HIV therapy. HIV Clin Trials 2012;13(6):335–42
41. Squires KE et al., for the ARIES Study Team. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. HIV Clin Trials 2012;13(5):233–44
42. Ding X et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. J Acquir Immune Defic Syndr 2012;61(4):441–7
43. Mocroft A et al., EuroSIDA Study Group. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010;24(11):1667–8