All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Abacavir 600mg/lamivudine 300mg (Kivexa®) in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus infection in adults and adolescents from 12 years of age

GlaxoSmithKline

Advice No: 2008 – October 2008

Recommendation of AWMSG

Fixed dose abacavir and lamivudine (Kivexa®) is recommended as an option for use within NHS Wales in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents from 12 years of age.

Use should be in accordance with the British HIV Association (BHIVA) guidance.

Fixed dose abacavir and lamivudine (Kivexa®) is not suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 15th October 2008

The recommendation of AWMSG is:

Fixed dose abacavir and lamivudine (Kivexa®) is recommended as an option for use within NHS Wales in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents from 12 years of age.

Use should be in accordance with the British HIV Association (BHIVA) guidance.

Fixed dose abacavir and lamivudine (Kivexa®) is not suitable for shared care within NHS Wales.

Additional note:

- Kivexa® should only be used in patients who, upon screening for the HLA-B*5701 allele, are found not to be carriers. As a negative test does not rule out the possibility of a hypersensitivity reaction (HSR), the need for careful counselling and monitoring for abacavir HSR remains.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Kivexa® is a fixed-dose combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents from 12 years of age[1].

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-1-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing[1]. Further details are provided in the Summary of Product Characteristics (SPC)[1].

2.2 Dosing

The recommended dose of Kivexa® in adults and adolescents is one tablet once daily. Kivexa® is a fixed-dose tablet and should not be prescribed for patients weighing less than 40kg or those requiring dosage adjustments. Separate preparations of abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated[1].

2.3 Market authorisation date

EU marketing authorisation was granted 17 December 2004[2,3].

2.4 UK Launch date

Kivexa® is already launched in the UK.

3.0 DECISION CONTEXT

The 2008 British HIV Association (BHIVA) guidelines emphasise that highly active antiretroviral treatment (HAART) regimens must be individualised for patients with HIV-1 in order to achieve the maximum potency, durability, adherence and tolerability and, to avoid long-term toxicities and any likely drug interactions. A full baseline assessment, including HIV-1 resistance testing, screening for hepatitis B and C co-infection and a cardiovascular risk assessment, should be undertaken before initiating treatment[4]. A HAART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs), in addition to a non-nucleoside reverse transcriptase inhibitor (NNRTI) (preferably efavirenz), is the preferred first line regimen in newly diagnosed HIV-1 patients in whom treatment is recommended. Where treatment with an NNRTI is not appropriate, for example where there is primary resistance, then a boosted protease inhibitor (PI) should be considered[4].

Co-formulated antiretroviral products may be a convenient option for patients. There are four NRTI co-formulations launched in the UK: Combivir® (zidovudine/lamivudine)[5], Truvada® (emtricitabine/tenofovir DF)[6], Kivexa® (abacavir/lamivudine)[1], and Trizivir® (zidovudine/lamivudine/abacavir)[7]. In addition, a fixed-dose combination of tenofovir, emtricitabine and efavirenz (Atripla®)[8] is launched in the UK. Truvada® has been appraised by AWMSG (refer to section 9.2). The BHIVA guidelines recommend against using triple NRTI therapy as it is less potent than a regimen containing two NRTIs plus a NNRTI. Of the two-NRTI combinations, it is recommended that Combivir® is reserved for patients with contraindications to the other products, or where antiretroviral therapy is used to prevent mother-to-child transmission[4].

In clinical studies, approximately 5% of subjects receiving abacavir (a component of Kivexa®) have developed a hypersensitivity reaction (HSR), some of these cases were life-threatening and resulted in a fatal outcome despite taking precautions[1]. Carriage of the HLA-B*5701 allele is associated with a significantly increased risk of developing a HSR[1]. Avoidance of Kivexa® in those who screen positive for this allele significantly reduces this risk[1]. Therefore, Kivexa® should only be used in patients who, upon screening for this allele, are found not to be carriers. However, a negative test does not rule out the possibility of HSR and the need for careful counselling and monitoring for abacavir HSR remains[1,4]. The BHIVA guidelines also recommend that, based on recent trial data, Kivexa® should be used with caution in patients with a baseline viral load of >100,000 copies/mL or where there is significant risk of cardiovascular disease[4]. Therefore, the BHIVA guidelines recommend that both Truvada® and Kivexa® are appropriate first-choice nucleoside backbones to be used with efavirenz, but that Kivexa® should be reserved for patients in whom Truvada® is contraindicated. This advice may change when more detailed study data become available[4].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Several company-sponsored studies have demonstrated the non-inferiority of the Kivexa® fixed dose combination product or its component NRTIs against Truvada® and the components of Combivir® in terms of virological failure over 48 weeks. These were mainly conducted in treatment-naive patients or those who were well controlled on current treatment. Interim data analyses from a recent non-company sponsored trial suggested an excess risk of virological failure with Kivexa® treatment in patients who had high baseline viral loads (>100,000 copies/mL). Reasons for this inconsistent finding are unclear.

Abacavir-containing regimens have been in use for several years. They are known to be associated with a risk of severe hypersensitivity reaction and screening of patients for the HLA-B*5701 allele associated with this reaction is now recommended before initiating abacavir treatment. A large, prospective, observational study has recently found that current or recent use of abacavir is associated with an increased risk of myocardial infarction. This is a new finding and, although subject to further analysis, the BHIVA guidelines suggest caution in the use of Kivexa® in patients with a high risk of cardiovascular disease.

4.2 Review of the evidence on cost-effectiveness

A primary cost utility analysis is presented that compares a strategy of screening for the HLA-B*5701 allele followed by initial conditional treatment with Kivexa® against a strategy of initial unconditional treatment with Truvada®. A secondary analysis against unconditional treatment with Combivir® is also presented. A two-phase model that simulates a cohort of patients is described. There are some uncertainties in the model inputs, including the efficacy inputs, utility weights and the assumptions around the key parameter of negative predictive value of the screening test.

In the primary base case analysis, the strategy of screening and conditional Kivexa® treatment is estimated to be cost saving (by £3,366) and marginally more effective (by 0.00185 QALYs) than Truvada®. However, the result is highly sensitive to small changes in key inputs. When the lifetime QALYs associated with the three main regimen pathways was explored within small plausible ranges in one-way sensitivity analyses, the strategy of screening followed by conditional Kivexa® treatment switched from being dominant over Truvada® to having an incremental cost per QALY gained

that was well in excess of £30,000. In the secondary analysis, the incremental cost per QALY gained over unconditional Combivir® was £39,355, and no sensitivity analyses have been conducted around that comparison.

5.0 LIMITATIONS OF DECISION CONTEXT

- Most evidence for Kivexa® is from trials involving treatment-naive patients. Although trials have been conducted in treatment-experienced patients, these patients were generally well controlled and not failing on their current treatment before switching to Kivexa®. There appear to be little robust data on the use of Kivexa® in patients who are failing on their current regimens.
- Inconsistencies in the company-sponsored trial data and the recent non-company sponsored data, in terms of the virological efficacy of Kivexa in patients with high baseline viral loads and the risk of myocardial infarction with recent use of abacavir, have not yet been resolved.

6.0 CLINICAL EVIDENCE

The company submission provides details of all known studies involving abacavir and lamivudine, either as separate entities or as the fixed dose combination Kivexa®[2]. The ASAR aims to provide a brief discussion of the key studies that are best able to address the current decision problem regarding Kivexa®. Only those studies that randomised patients to treatment with Kivexa® or abacavir plus lamivudine, and assessed outcomes of HIV-1 RNA levels and/or CD4 cell counts, are considered here.

Kivexa® was granted a marketing authorisation primarily on the basis of studies that demonstrated the non-inferiority of once daily compared with twice daily administration of the individual component NRTIs[3]. Details of the main studies[9,10] are included in Table 1A of Appendix 1 and briefly discussed below. Key studies that compared Kivexa® or abacavir plus lamuvidine against relevant comparators of Truvada® or Combivir® (or their co-administered separate entities)[11-13] are included in Table 1B of Appendix 1 and are briefly discussed below. A brief discussion of important interim results of an ongoing head-to-head study of Kivexa® and Truvada® (ACTG 5202)[14] is also included.

6.1 Clinical efficacy

6.1.1 Kivexa® or once daily administration of abacavir plus lamivudine compared with twice daily administration of abacavir plus lamivudine

The main efficacy study supporting the marketing authorisation of Kivexa® (CNA30021) was a phase III, double-blind, randomised trial that was designed to demonstrate the non-inferiority of the separate components of Kivexa® (abacavir 600mg once daily plus lamivudine 300mg once daily) against abacavir 300mg twice daily plus lamivudine 300mg once daily[3,9]. All patients also received the NNRTI efavirenz 600mg once daily. The trial was conducted in antiretroviral-naive adults, 76% of who were asymptomatic[9].

The proportion of patients with plasma HIV-1 RNA <50 copies/mL at week 48 (primary endpoint) met the pre-specified criterion for non-inferiority of the once daily versus the twice daily abacavir regimen. There was no significant difference between groups in the median increase from baseline in CD4 cell counts (188 versus 200 copies/mm^3 for abacavir once daily versus twice daily, respectively)[3,9]. In the 31 patients with sufficient genotypic data, there were numerically more with treatment-emergent resistance mutations in the abacavir once daily group (13/16) compared with the twice daily group (10/15), but the small sample size warrants caution in the interpretation of this finding.

An open-label, randomised, phase III study (ESS30008, SEAL) assessed the ability of the fixed dose combination product Kivexa® to maintain virological response in patients who were previously stabilised on twice daily abacavir 300mg and lamivudine 150mg[10]. Patients who had been taking twice daily abacavir 300mg and lamivudine 150mg, in addition to a NNRTI (approximately 66%) or a PI (34%), for at least 24 weeks and who had HIV-1 RNA level < 400 copies/mL for more than three months and a CD4 count > 50 cells/mm^3, were randomised to stay on their twice daily abacavir and lamivudine regimen or to switch to once daily Kivexa®. The primary efficacy end point was the proportion of responders (defined as subjects who did not meet the protocol definition of virologic failure of HIV-1 RNA ≥1265 copies/mL on two consecutive occasions) at week 48, assessed in the ITT population.

At week 48, the difference estimate of 1.5% (90% CI -3.4 to 6.4) met the pre-specified criterion for non-inferiority (although the definition of non-inferiority based on a 90% CI is less strict than one based on a 95% CI as used in study CNA30021). Refer to Appendix 1, Table 1A for secondary endpoints. The company submission reports that patient satisfaction was improved with Kivexa® relative to the separate components in terms of treatment convenience and flexibility[2]. However, there was no statistically significant difference in these aspects between Kivexa® and the separate components after adjustment for multiple testing[10a]. Patients whose antiretroviral drugs were given once daily had greater improvements in overall satisfaction and treatment convenience when compared to those on multiple daily dose regimens[10a].

6.1.2 Kivexa® or abacavir plus lamivudine versus Combivir® or Truvada® (or their component NRTIs)

6.1.2.1 Abacavir plus lamivudine versus zidovudine plus lamivudine

A phase III, randomised, double-blind, non-inferiority trial, conducted in treatment-naive patients, compared abacavir 300mg against zidovudine 300mg, both given twice daily, in addition to lamivudine 150mg twice daily plus efavirenz 600mg once daily (CNA30024)[11]. Patients had HIV-1 RNA >400 copies/mL (median 4.79 $\log_{10}$ copies/mL) and CD4 count >50 cells/mm^3 (median 264 cells/mm^3) at baseline. The primary endpoint, assessed in the exposed ITT population (those who had received at least one dose of study drug), was the proportion of patients with HIV-1 RNA ≤50 copies/mL, stratified by baseline HIV-1 RNA (≤100,000 or >100,000 copies/mL), at 48 weeks[11].

The difference of 0.8% (95% CI -6.3 to 7.9) met the pre-specified criterion for non-inferiority of abacavir versus zidovudine. Refer to Appendix 1, Table 1B for primary and secondary endpoints. The company submission also reports an analysis of the as-treated population, the results of which were 88% for the abacavir group and 95% for the zidovudine group (95% CI for the difference -11.4 to -1.6), which also met the non-inferiority criterion (2-sided 95% CI needed to lie entirely to the right of the value of -12%)[2]. However, these results are not presented in the cited reference.

6.1.2.2 Kivexa® versus Truvada®

The HEAT study is an ongoing 96-week phase IV, randomised, double-blind, multicentre, non-inferiority trial of Kivexa® versus Truvada®, both given in addition to ritonavir-boosted lopinavir, in treatment-naive patients[12]. The primary efficacy outcome, was the proportion of patients with HIV-1 RNA <50 copies/mL at 48 weeks, assessed in the exposed ITT population in which regimen switches for any reason were not considered treatment failures. These data are currently only available as a poster presentation[12].

An open-label, randomised study (BICOMBO)[13] compared the efficacy of switching patients who were stabilised on a lamivudine-based HAART regimen for at least six months, with HIV-1 RNA <200 copies/mL, to a regimen containing Kivexa® or Truvada®. Median antiretroviral treatment exposure at baseline was around four years. The most commonly previously used NRTIs in addition to lamivudine were zidovudine (32%) and tenofovir (30%); around 9% had received abacavir[2]. The primary endpoint was the proportion of patients experiencing treatment failure for any reason at 48 weeks. Results are available only in a conference abstract and presentation[13].
Refer to Appendix 1, Table 1B for further information.

6.1.3 Interim data from study ACTG 5202: Kivexa® versus Truvada®

Study ACTG 5202[14] is an ongoing 96-week, phase IIIb, randomised trial to compare double-blind Kivexa® and Truvada® in combination with open-label atazanivir plus ritonavir or efavirenz, in 1,858 treatment-naive patients[2,14]. Randomisation for the study was stratified by screening plasma HIV-1 RNA levels ≥100,000 or <100,000 copies/mL and the primary endpoint is time to virologic failure. A routine interim review of efficacy and safety data found that virologic failure rates were significantly higher amongst those randomised to Kivexa® than to Truvada®. The excess virologic failures occurred within the high viral load stratum with an estimated hazard ratio of 2.33 (95% CI 1.46 to 3.72; p=0.0003). As a result of these findings, blinded follow-up of Kivexa® in the subjects within the high viral load stratum has been stopped[14]. The company submission states that six clinical trials in which Kivexa® or its components were used have been analysed and have found no substantial difference in efficacy between patients with baseline viral loads above or below 100,000 copies/mL, and that the findings of the interim ACTG analysis are inconsistent with previous clinical trial experience with Kivexa®[2]. No further data from the company-analyses are provided.

6.1.4 Points to note from all studies:

- The trials of abacavir discussed above have not involved screening of patients for HLA-B*5701 allele before patients commenced treatment. In most cases, the small proportion of patients who experienced a suspected or confirmed hypersensitivity reaction would be classed as treatment failures in the ITT analyses. In clinical practice, patients should be screened for this allele and those who test positive would not receive abacavir[1].
- Two key trials (CNA30021 and CNA30024) have assessed the separate NRTI components of Kivexa®, rather than the fixed dose combined product[9,11]. Once daily administration of the separate NRTIs abacavir 600mg and lamivudine 300mg is considered bioequivalent to the once daily administration of the fixed dose combination product[3].
- The threshold for the definition of virological failure in the primary efficacy analyses varies in the above trials between HIV-1 RNA levels of 50 and 1265 copies/mL.
- Most of the available trial data are from antiretroviral treatment-naive patients who are generally asymptomatic with low levels of hepatitis B and/or C virus co-

infection or other comorbidities. In the trials that were conducted in treatment-experienced patients, the patients were virologically and immunologically well controlled at baseline on their current antiretroviral regimens.

- There appear to be little data on the use of Kivexa® in patients who are failing on their current regimens. In study CAL30001, 182 treatment-experienced patients with virologic failure (HIV-1 RNA >1000 copies/mL) were randomised and received treatment with either Kivexa® once daily or abacavir 300mg twice daily plus lamivudine 300 mg once daily, both in combination with tenofovir and a PI or an NNRTI for 48 weeks[1,3]. The results indicate that the Kivexa® group was non-inferior to the abacavir twice daily group. The proportions with HIV-1 RNA <50 copies/mL (50% versus 47%) and <400 copies/mL (54% versus 57%) were similar in each group (ITT population). However, only moderately experienced patients were included in this study and there was an imbalance in baseline viral load between the arms, which warrants caution in the interpretation of the results[1,3]. Furthermore, this study assessed triple NRTI therapy, which according to the BHIVA guidelines is not generally recommended in the management of treatment-naive or treatment-experienced patients[3,4].

6.2 Safety

The adverse reactions reported for Kivexa® are generally consistent with the known safety profiles of abacavir and lamivudine when given as separate medicinal products[1]. In clinical studies, approximately 5% of subjects receiving abacavir developed a HSR, usually within six weeks (median 11 days) of starting treatment. Some cases of these were life-threatening and resulted in a fatal outcome despite taking precautions[1]. A large trial (PREDICT-1)[15], in which 1,956 abacavir-naive patients were randomised in a double-blind fashion to receive an abacavir regimen with or without pre-screening for the HLA-B*5701 allele, found that screening significantly reduced the rate of clinically suspected HSR (3.4% versus 7.8% in the screened and non-screened groups, respective, p<0.001). Immunologically confirmed HSR were eliminated with screening for the allele and occurred in 2.7% of the non-screened group[15]. The Kivexa® SPC recommends that HLA-B*5701 screening should be carried out in all patients before initiating abacavir-containing therapy[1]. However, a negative test does not rule out the possibility of HSR and the need for careful monitoring for abacavir HSR remains[4].

The BHIVA guidelines state that dyslipidaemia with Kivexa® is greater than that seen with zidovudine, and that Truvada® has no significant effect on lipid profile[4]. Several studies of Kivexa® against Truvada® (or their separate components) have found changes in total cholesterol and low-density lipoprotein cholesterol that have favoured tenofovir over abacavir, although effects on other lipid parameters have been mixed[12,13,16,17]. The 48-week data from the HEAT study numerically favoured tenofovir in terms of total cholesterol and low-density lipoprotein cholesterol concentrations, but the ratio of total:high-density lipoprotein cholesterol remained below 5 in each arm[12]. Interpretation of the lipid data can for example be limited by baseline use of lipid modifying agents and the other antiretroviral agents in the regimen [12,13,16,17].

An ongoing prospective observational study of the risk of myocardial infarction (MI) with the use of NRTIs in over 33,000 patients (the D:A:D study)[18] has recently reported an increased risk with current or recent use (within the preceding six months) of abacavir, and didanosine. Compared with those patients with no recent use of abacavir, the relative risk (RR) of MI in patients with recent use of abacavir was 1.90 (95% CI 1.47 to 2.45; p=0.0001), and remained elevated after adjustment for predicted 10 year risk of coronary heart disease (RR 1.89; 95% CI 1.47 to 2.45; p=0.0001). However, the absolute increase in risk was greatest in those at higher risk of coronary heart disease. Risk was not significantly increased in those who stopped using abacavir more than six

months previously[18]. Importantly, tenofovir was not considered in the study. In response to these findings, the company have conducted an analysis of 54 company-sponsored studies, which is reported to show no significant difference in the relative risk of MI for abacavir and non-abacavir-treated patients[19]. However, concern has been expressed that the company analysis is not sufficiently powered to detect a meaningful difference in MI rates, as the number of events are too small[20] (16 in the abacavir recipients and 11 in the non-abacavir recipients)[19]. The 2008 BHIVA guidelines caution against the use of Kivexa® in patients with significant risk for cardiovascular disease[4].

The HEAT and ACTG 5202 studies[12,14] are ongoing and will provide longer term efficacy and safety data[2].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications

The main competitors to Kivexa® are the two combination NRTIs lamivudine/zidovudine (Combivir®)[5] and tenofovir/emtricitabine (Truvada®)[6]. A fixed-dose combination of tenofovir/emtricitabine/efavirenz (Atripla®)[8] has also recently been launched in the UK, but has yet to be considered by AWMSG.

7.2 Comparative effectiveness

- Company-sponsored trials and studies of Kivexa®, or once daily co-administered abacavir/lamivudine, have consistently shown its non-inferiority to tenofoivir/emtricitabine and zidovudine/lamivudine in terms of virological response. The interim data from study ACTG 5202[14], which indicate excess virologic failures with Kivexa® in patients with baseline HIV-1 RNA >100,000 copies/mL appear inconsistent with that reported in company-sponsored trials. The regulatory authorities have not required any change in the wording of the license for Kivexa® as a result of these data. However, the 2008 BHIVA guidelines recommend caution in the use of Kivexa® in patients with baseline viral loads above 100,000 copies/mL. They state that its guidance will be informed by further data, analysis of ACTG 5202, and additional studies comparing Kivexa® and Truvada®[4].
- Kivexa®, Truvada® and Combivir® have some important differences in their adverse event profiles. Due to the association of abacavir with HSR, screening for the HLA-B*5701 allele is required before initiating treatment with Kivexa®[1]. A recent audit of screening methods and costs in the UK found that routine turnaround time was five to 14 days at a cost of £35-£90[21].
- Recent interim data from a large observational study have suggested an increased risk of MI in patients with current or recent use of abacavir in the preceding six months[18], and dyslipidaemia is considered greater than with zidovudine treatment[4].
- Tenofovir is considered to have a no significant effect on lipid parameters but is potentially associated with adverse renal effects. Baseline testing and routine monitoring of urea, electrolytes and urinalysis are required for patients receiving tenofovir[6], and Truvada® should not be given to patients who have severe renal impairment[6]. A phase IV, randomised, open-label trial (ASSERT) is ongoing to specifically compare the change from baseline in estimated glomerular filtration rate at 48 weeks in patients receiving Kivexa® and Truvada®. Results are expected in 2009[2].

- Zidovudine treatment is associated with haematological adverse effects, including anaemia, neutropenia and leucopenia[5]. Haematological parameters should therefore be carefully monitored in patients receiving Combivir®. These haematological effects are not usually observed before four to six weeks of therapy. For patients with advanced symptomatic HIV-1 disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter. In patients with early HIV-1 disease haematological adverse reactions are infrequent and, depending on the overall condition of the patient, blood tests may be performed less often[5]. Zidovudine treatment is also associated with development of lipodystrophy[4,5].
- The available trial data for Truvada® and Kivexa® are mainly from treatment-naive or moderately treatment experienced patients. The BHIVA guidelines position these products as options for first-line treatment, in addition to an NNRTI or PI, with Truvada® being the preferred product[4]. Combivir® is recommended to be reserved for those with contraindications to Truvada® and Kivexa® [4].
- The BHIVA guidelines recommend resistance testing in all newly diagnosed patients who are eligible for treatment, and in those who are failing on treatment[4]. Rates of virological failure have been low in the Kivexa® studies and, combined with assay limitations, the number of patients providing paired baseline and post-failure genotypic data is low. This warrants caution in the interpretation of available genotypic data. In study CNA30021 (abacavir 600mg once daily versus abacavir 300mg twice daily) there were numerically more patients with treatment-emergent resistance mutations in the abacavir once daily group (13/16) compared with the twice daily group (10/15)[3,9]. In the HEAT study (Kivexa® versus Truvada®), the 48-week overall incidence of treatment-emergent mutations associated with resistance was higher in the Truvada® group than in the Kivexa® group (53% versus 34%) but these results are based on data from only around 10% of the total HEAT study population[12].
- Kivexa® and Truvada® are both once-daily preparations[1,6], and Combivir® is a twice-daily preparation[5]. All are given in addition to an NNRTI (e.g. efavirenz) or PI. A simplified treatment regimen may be expected to be preferred by patients, but specific comparisons are lacking. The triple combination product tenofovir/emtricitabine/efavirenz (Atripla®), combines the 2008 BHIVA guideline-preferred fixed dose combination NRTI product with the preferred NNRTI[4]. A therapeutic drug assessment (TDA) submission by the market authorisation holders of Atripla® is pending.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues AWMSG to consider

The key economic issues for AWMSG to consider is whether any additional benefits offered by the fixed combination product of abacavir 600mg/lamivudine 300mg (Kivexa®) over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of abacavir is acceptable.

8.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of Kivexa®.

8.3 Review of company submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

In the primary cost utility analysis, a strategy of initial screening for HLA-B*5701 allele followed by conditional treatment with Kivexa® (in those who screen negative) plus efavirenz is compared with a treatment strategy of Truvada® plus efavirenz. In a secondary analysis, a strategy of initial screening for HLA-B*5701 allele followed by conditional treatment with Kivexa® is compared with treatment with Combivir®.

A two-phase model based on a decision tree structure is described. In the short-term phase (first 60 days), a patient is either genetically screened for the HLA-B*5701 allele and conditionally prescribed Kivexa® based on the results of the screen, or prescribed a comparator dual-NRTI backbone. It is assumed that the HAART regimens in the short-term phase are all equally effective. Patients who screened negative for the HLA-B*5701 allele but who subsequently experience HSR are switched immediately to an alternative NRTI backbone. Following the initial 60 day treatment period, patients enter a discrete event simulation model (ADVANCE model) in which Monte Carlo simulation is used to model their remaining lifetime.

The treatment strategies modelled for the primary analysis appear compatible with current BHIVA guidelines. However, there are a number of limitations to the model and analyses. Efficacy data for the first-line treatment strategies with Kivexa® and Truvada® are derived from patients with different baseline characteristics, which may favour Kivexa®. Efficacy data for second-line strategies are derived from trials conducted in treatment-naive patients. There appears to be considerable uncertainty in the disutility assumed for lipoatrophy in patients taking Combivir®.

The model is very sensitive to small changes in the negative predictive value of the HLA-B*5701 allele screening test. The model is also very sensitive to small, plausible changes in the lifetime QALYs gained for the three regimen pathways considered in the base case analysis. Copies of the model and its outputs have been provided to WMP.

8.3.2 Population

Only HAART-naive patients are considered in the model[2]. It would appear that 10,000 patients have been simulated, with an age at diagnosis of 40 years, a baseline HIV-1 RNA level of 4.7 $\log_{10}$ copies/mL and a baseline CD4 cell count of 275 cells/mm^3. Around 30% are assumed to be female and that none are injecting drug users.

8.3.3 Perspective and time horizon

The model considers only direct costs from the perspective of the NHS Wales[2]. No consideration is given to any personal and social service costs/resources, which is a limitation of the model as these could feasibly be substantial for this patient group. A lifetime time horizon is stated to have been used[2], which appears from the model to be assumed as 40 years.

The model consists of two phases: a short term phase of 60 days to simulate HLA-B*5701 screening, and a long-term phase representing the remaining lifetime, based on a discrete event simulation model with a cycle length of three months[2].

8.3.4 Comparator

In the primary cost utility analysis, a strategy of initial screening for HLA-B*5701 allele followed by conditional treatment with Kivexa® (in those who screen negative) plus efavirenz is compared with a treatment strategy of Truvada® plus efavirenz. In patients who screen positive for the HLA-B*5701 allele or who screen negative but then experience HSR, Kivexa® is replaced with Truvada®. Upon virological failure, Kivexa®

is switched to Truvada® and vice versa, unless the patient has screened positive for HLA-B*5701 allele or has experienced HSR, in which case Truvada® is switched to Combivir®. Efavirenz is replaced with ritonavir-boosted lopinavir (Kaletra®) in all cases of virological failure on first line treatment[2]. The 2008 BHIVA guidelines recommend that all drugs should be changed following first virological failure, guided by resistance testing. The strategies compared in this analysis seem consistent with the BHIVA guidelines in terms of initial and subsequent treatment regimens[4].

In the secondary analysis, a strategy of initial screening for HLA-B*5701 allele followed by conditional treatment with Kivexa® (in those who screen negative) plus efavirenz is compared with a strategy of initial treatment with Combivir® plus efavirenz. In patients who screen positive for the HLA-B*5701 allele or who screen negative but then experience HSR, Kivexa® is replaced with Combivir®. Upon virological failure, both Kivexa® and Combivir® are switched to Truvada®, and efavirenz is replaced with ritonavir-boosted lopinavir (Kaletra®)[2]. The 2008 BHIVA guidelines recommend that Combivir® is reserved for use in patients with contraindications to Truvada® or Kivexa® (unless the aim of treatment is to prevent mother-to-child transmission, in which case Combivir® is the co-formulation of choice)[4]. The strategies compared in this alternative analysis are therefore not consistent with the current recommendations.

In each analysis, patients failing second line treatment are all assumed to receive the same third-line treatment as a proxy for a defined regimen, with efficacy based on a study of ritonavir-boosted PIs conducted in patients with multiple treatment failures[23].

8.3.5 Clinical inputs

The clinical inputs to the short-term and long-term phases of the model are not all well described in the company submission. References for the long-term phase of the model have not been provided by the company, and the information below is based on that observed in the model.

8.3.5.1 Drug treatment efficacy data

The company submission states that in the short-term phase of the model, which applies to the first 60 days that are assumed to cover the time between screening for HLA-B*5701, initiation of HAART and resolution of any HSR symptoms caused by Kivexa®, all HAART regimens are assumed to have similar clinical efficacy[2]. This efficacy does not feed into the long-term phase of the model.

For the long-term phase of the model, various clinical trials have been used to provide the proportion of patients achieving HIV-1 RNA levels <50 copies/mL and the increases in CD4 cell counts observed through 48 weeks.

For first-line Kivexa® (plus efavirenz), data has reportedly been taken from study CNA30024, which was a phase III trial, conducted in treatment-naive patients, that compared abacavir 300mg against zidovudine 300mg, both given twice daily, in addition to lamivudine 150mg twice daily plus efavirenz 600mg once daily (i.e. the separate NRTI components rather than the fixed dose products)[11]. Patients had baseline HIV-1 RNA levels and CD4 cell counts similar to those modelled here. Pre-screening for the HLA-B*5701 allele was not conducted in this trial. Therefore, data reported to be derived from the as-treated population, rather than the exposed ITT population, has been used in the model as the company submission claims that the data from the exposed ITT analysis would include the effect of early drop outs due to the occurrence of HSR. The company submission reports the proportion of patients achieving a HIV-1 RNA <50 copies/mL in the as-treated population to be 88% and the increase in CD4 cell counts to be 211 cells/mm^3 at 48 weeks[2]. These results are reported to be taken from the clinical study report (not verifiable). It is unclear whether

the difference in the reported proportion of patients achieving a HIV-1 RNA <50 copies/mL between the as-treated (88%[2]) and the exposed ITT populations (70%[11]) would be wholly attributable to drop outs due to HSR.

For first line Truvada® (plus efavirenz), data has been taken from an open-label trial of tenofovir, emtricitabine and efavirenz versus zidovudine, lamivudine and efavirenz[24]. This was conducted in treatment-naive patients whose median baseline HIV-1 RNA level was 5 $\log_{10}$ copies/mL, which is almost twice that of the patients modelled here (and that of patients in the CNA30024 study). The proportion of patients achieving a HIV-1 RNA <50 copies/mL was 79.5% in the exposed ITT population[23]. The imbalance in the baseline HIV-1 RNA levels may act to bias the model in favour of Kivexa®.

For second-line Kivexa®, Truvada® and Combivir® (all plus Kaletra®), data has been taken from studies that were conducted in treatment-naive patients[25-27]. The extent to which these would adequately represent treatment efficacy in treatment-experienced patients who have failed on first-line treatment is uncertain.

For patients who initially achieve HIV-1 RNA levels <50 copies/mL, a blanket assumption is made that the annual probability of virological failure will be 5%, which appears to have been applied after six months of treatment[2]. The 5% probability of virological failure is reported to be based on a data from EuroSIDA, which is a large observational study that prospectively collects data on HIV-1 patients attending outpatient clinics across Europe[28]. These data indicate that in patients who were treatment-naive prior to the start of their HAART, the rate of viral rebound (two consecutive values >400 copies/mL in patients who had achieved <50 copies/mL) across all drug regimens was 4.9/100 person-years[28]. However, the data also indicated that the rate of viral rebound varied depending on the drug regimen being used and, further, it was higher (8.0/100 person-years) in those who were NRTI-experienced prior to the start of their HAART[28].

Therefore, there are several sources of uncertainty in the model with respect to the assumed treatment efficacy. The extent to which these may bias the model is unclear.

CD4 cell counts at 48 weeks have also been extracted from the above trials. Based on the model provided, it appears that the ADVANCE part of the model considers increases in CD4 cell counts over two to four years based on baseline CD4 cell counts in those who remain virologically suppressed for more than one year. The model assumes that the increase in CD4 cell count in the first year is equally distributed over the third and fourth quarters in the first year if the patient achieved viral load < 50 copies/mL at 6 months. Patients then have an assumed increase in CD4 cell count in years 2, 3, and 4 of 67, 55, and 95 cells/mm^3, respectively, as long as the patient remains on therapy for those years, based on observations from a cohort study that followed patients over a four years[28a]. The CD4 cell count remains at this level until virological failure. The CD4 cell count increases are therefore assumed to be independent of the treatment regimen. The relative risk of HIV-related mortality is linked with CD4 cell counts, as is the monthly probability of experiencing opportunistic infections based on a published model of the cost effectiveness of ART[29].

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The ADVANCE model also considers adherence to treatment, which is considered to impact on treatment efficacy. The probabilities of achieving undetectable viral loads and of virological failure based on different levels of treatment adherence have been calculated from a number of different sources. As data from the as-treated population from study CNA30024 have been used for Kivexa®, adherence is assumed to be 100%. However, it is not clear how adherence to the other treatment strategies considered here is incorporated.

8.3.5.2 Screening efficacy

The effectiveness of screening for the HLA-B*5701 allele is a key aspect of the model. The negative predictive value, HLA-B*5701 allele carriage rate and proportion of patients who screen negative but subsequently develop symptoms of HSR are reported to be derived from the PREDICT-1 trial[15] (discussed in section 6.2) and two UK-based observational studies[29a, 29b]. In the base case analysis, a negative predicted value of 98.92% is assumed, based on the simple combination of patients from the two observational studies. This approach would seem subject to some uncertainty, as it is unclear whether or not any other studies that could have contributed to these results have been identified – the selective combining of two studies could potentially lead to inaccurate estimation of the negative predictive value. Sensitivity analyses indicate that the model is very sensitive to the negative predictive value of the screening test within the range 92% to 99.99% (see section 8.3.9). The negative predictive value observed in patients diagnosed clinically with HSR in the double-blind PREDICT-1 study was 95.5%[15]. The company asserts that the double-blind design would be expected to result in patient-suspected HSRs which may lead to unnecessary discontinuation of Kivexa. However, it should be noted that the SPC for Kivexa® considers that the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making[1].

8.3.5.3 Adverse events

The adverse events considered in the model are abacavir-associated HSR, tenofovir-associated acute renal failure, and zidovudine-associated lipoatrophy. All other adverse events are assumed to be similar among the NRTIs and so are not considered in the model[2]. This may be a source of bias in the model, for example dyslipidaemia with Kivexa® is considered to be greater than that seen with zidovudine[4], and may require greater intervention with lipid lowering agents. Concerns have also been raised about a possible increased risk of MI with current or recent abacavir treatment, especially in those at high risk for coronary heart disease (see section 6.2). If true, this would potentially be associated with significant additional resource use and costs.

8.3.5.4 Utility weights

A baseline utility weight associated with being HIV-1 positive (0.829) was assumed for all patients in the model[2]. This was reported to be based on an analysis of clinical trial data (five company-sponsored trials in which quality of life was assessed using the SF-36 instrument)[29c]. Utility decrement associated with experiencing HSR to abacavir is based on the same analysis, and is assumed to persist for nine days. Utility decrement associated with experiencing acute renal failure with tenofovir is reportedly based on a published estimate, and is assumed to persist for one cycle (three months). No published utility decrement for patients experiencing lipoatrophy were found and so five HIV UK clinicians were asked to complete the EQ-5D instrument for two hypothetical scenarios: (i) as a HIV-positive patient taking Combivir® without experiencing lipoatrophy, and (ii) as the same patient but diagnosed with lipoatrophy. There was great variability in the utility valuations estimated for patients with lipoatrophy (0.255 to 0.725). The mean of the estimated values (0.394) has been used to estimate the decrement from the baseline utility of 0.829 for patients with Combivir®-associated lipoatrophy (0.435). This decrement would appear to be subject to considerable uncertainty and has been assumed to apply for 10 years[2]. This may be a source of bias in the model.

8.3.6 Healthcare resource utilisation and cost

8.3.6.1 HAART drug costs

HAART drug costs are based on doses stated in the respective SPCs and prices listed in the British National Formulary (BNF)[30]. It is assumed that in the first 60 days (short-term phase) patients who experience HSR to abacavir do so at day 9 (on the basis of the median time to development of suspected HSR observed in the PREDICT-1 study[15]). Patients experiencing HSR with Kivexa® are assumed to switch immediately to an alternative NRTI backbone (but maintain the third drug in the regimen). Therefore, patients experiencing HSR are assumed to accrue the costs of 30 days of Kivexa and 51 days of the alternate NRTI treatment[2].

8.3.6.2 Screening, monitoring and adverse event costs

The cost of screening is based on an audit of screening methods and costs in the UK, which found cost to range from £35 to £90[21]. A value of £50 has been assumed in the base case analysis. This audit also found that routine turnaround time for the results of screening tests was five to 14 days[21]. The model does not consider a turnaround time for screening results, instead assuming that patients are screened as part of their baseline assessment.

The costs of managing suspected and diagnosed abacavir-related HSR are reportedly based on the application of published unit costs to resource use observed in patients with suspected and diagnosed HSR in the PREDICT-1 study[2]. The actual resource use assumed in the model appears to be based on data on file, so is not verifiable. No use of available UK data has been made[31].

For Truvada®, the SPC states that renal function needs to be monitored monthly in the first year and every three months thereafter[6]. As other NRTIs involve routine monitoring every three months, the costs of the eight additional outpatient clinic appointment in the first year of Truvada® treatment are included in the model. The incidence of adverse renal events with Truvada® are based on published data from an extended access programme[31a] and the costs of acute renal failure are based on published unit cost data[2].

For Combivir®, the incidence of lipoatrophy is reported to be based on published data[31b] and treatment is assumed to be composed of one outpatient dietitian visit and one clinical psychologist visit every three months for one year only[2]. Unit costs have been applied.

8.3.6.3 Other HIV treatment costs

The costs of routine disease monitoring, treatment of opportunistic infections and other disease-related costs (excluding HAART drug costs) are assumed from a published study from 1998[31c] that is reported to have used national and individual HIV treatment centre-level data in England, to provide population-based estimates of the costs of HIV service provision[2]. The costs are reported to be based on 1996 prices, so the extent to which these data adequately represent resource use and costs today is unclear. The costs have been inflated to 2008 prices and the average costs per patient per year for asymptomatic, symptomatic non-AIDS and AIDS patients are applied in the model to patients with CD4 counts of >200, 50-199, and <50 copies/mm^3, respectively[2].

8.3.7 Discounting

Costs and outcomes have been discounted at 3.5% per annum[2], which is the preferred discount rate.

8.3.8 Results

8.3.8.1 Primary analysis – Screening for the HLA-B*5701 allele followed by conditional treatment with Kivexa® compared with unconditional treatment with Truvada®

In the base-case analysis, screening followed by conditional treatment with Kivexa® is estimated to be cost saving (by £3,366) and associated with a gain of 0.00185 QALYs compared with unconditional treatment with Truvada® (i.e. screening followed by conditional treatment with Kivexa® is the dominant strategy)[2].

8.3.8.2 Secondary analysis - Screening for the HLA-B*5701 allele followed by conditional treatment with Kivexa® compared with unconditional treatment with Combivir®

The incremental cost per QALY gained for a strategy of screening followed by conditional treatment with Kivexa® compared with a strategy of unconditional treatment with Combivir® was £39,355 on the basis of incremental costs of £18,412 and a gain of 0.468 QALYs[2].

8.3.9 Sensitivity/Scanario analyses around the primary analysis

In a scenario analysis in which the second line agent of the primary analysis was Combivir®, a strategy of screening followed by conditional initial treatment with Kivexa® still dominated unconditional initial treatment with Truvada® [2].

A range of one way sensitivity analyses were conducted around several of the input parameters of the primary analysis. The results presented in the company submission indicate that the model is very sensitive to the negative predictive value of the HLA-B*5701 screening test. In the base case analysis, a negative predictive value of 98.92% is assumed based on two observational studies (see section 8.3.5.2). When the negative predictive value reduces to 96.66%, the model outputs switch from screening being dominant over unconditional treatment with Truvada® to having an incremental cost per QALY gained of £30,000[2]. When the negative predictive value is reduced to 92%, the incremental cost per QALY gained increases significantly to almost £970,000[2]. In the PREDICT-1 study, in patients diagnosed clinically with HSR, the negative predictive value was observed to be 95.5%[15], which would be associated with an incremental cost per QALY gained in excess of £30,000. The PREDICT-1 was a double-blind study, which may have led to an excess of patients being labelled as experiencing HSR on a clinical basis because their screening result was unknown. The company therefore asserts that the results of the unblinded observational studies would be more appropriate to use. It should be noted that the SPC for Kivexa® states that in any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making and that even in the absence of HLA-B*5701 allele, it is important to permanently discontinue abacavir and not re-challenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction[1].

The model is also very sensitive to the lifetime QALYs associated with the three different regimen pathways included in the base case analysis. The lifetime QALYs for each pathway were varied between the limits of the (relatively narrow) 95% CIs obtained for each from the ADVANCE phase of the model (see Table1).

Table 1. Sensitivity analyses around the lifetime QALYs associated with the three different regimen pathways included in the base case analysis[2]

Regimen pathway	95% CI around lifetime QALYs	Kivexa® ICER range (£ per QALY)
Truvada® (plus efavirenz) followed by Combivir® (plus Kaletra®)	11.940 to 11.780	Dominant to £625,574
Kivexa® (plus efavirenz) followed by Truvada® (plus Kaletra®)	12.04 to 11.87	Dominant to £47,473
Truvada® (plus efavirenz) followed by Kivexa® (plus Kaletra®)	12.03 to 11.86	Dominant to £38,191

8.3.9.2 Probabilistic sensitivity analysis (PSA)

The long-term phase of the model is itself probabilistic. However, cost effectiveness acceptability curves have not been presented in the company submission.

8.4 Review of evidence on budget impact

8.4.1 Description and critique of the company's submission

A simplistic budget impact analysis is presented. The original analysis used prevalence and incidence data derived from sources that were outdated and would have resulted in an underestimate of the treated HIV population in Wales. However, revised estimates have been provided based on data from the National Public Health Service for Wales[32]. Market research data is used to derive an estimate of the number of patients currently treated with Kivexa®, and uptake is based on a company assumption. The analysis compares the net costs of Kivexa® separately against Truvada® and Combivir®. The costs of genetic screening prior to initiation of Kivexa® are incorporated but these fail to take account of the costs of screening in patients who test positive and do not receive treatment with Kivexa®. The company estimated budget impact of Kivexa® is therefore likely to be an underestimate and should be viewed with caution.

8.4.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[2].

8.4.3 Data sources

8.4.3.1 Incident and prevalent cases

Recent surveillance data from the National Public Health Service for Wales indicates that there were 884 patients accessing HIV-related care in Wales in 2006[32]. Based on a study of the incidence of HIV in homosexual/bisexual men attending genitourinary medicine clinics across England, Wales and Northern Ireland in 2002, the annual incidence of HIV has been assumed in the company sumission to be 2.5%[33], and is further assumed to be constant. These data have been used to estimate that, in 2008, 929 patients would receive treatment for HIV in Wales[2], rising to around 1025 in 2012 (assuming no deaths).

Based on the incidence rate of 2.5% and an assumed 799 patients in 2007, the net number of patients with HIV estimated in the company submission in 2008 is 819, rising to around 900 in 2012 (assuming no deaths).

8.4.3.2 Rates of adoption

The company submission assumes that Kivexa® market share of NRTIs will be around 7% in 2008, rising to 30% in 2012. These rates of adoption are assumed to apply to the incident cases over this five year period, such that 14 patients will be treated with Kivexa® in 2008, rising to 34 in 2012[2] (these are cumulative figures, which implicitly assumes no discontinuations).

8.4.3.3 Costs

The 30-day costs of Kivexa® and relevant comparators are presented in Table 2.

Table 2. 30-day costs of selected NRTI products[30]

NRTI product	30-day costs
Kivexa®	£373.94
Individual components of Kivexa® (Ziagen® 300mg x2 plus Epivir® 300mg)	£221.81+£167.21=£389.02
Truvada®	£418.50
Combivir®	£318.60

The cost of screening for the HLA-B*5701 allele prior to initiating Kivexa® is assumed to be £50, as in the economic model (see section 8.3.6.2), and all patients initiating Kivexa® are assumed to undergo screening. The revised estimates have also included the cost of screening those patients who test positive for the HLA-B*5701 allele and do not receive Kivexa®.

8.4.4 Results

The revised budget impact analysis considers the net cost of the use of Kivexa® instead of Truvada® or Combivir® in those patients already estimated to be taking Kivexa® in 2008 plus subsequent incident HIV patients. Compared with Truvada®, the company submission estimates a net annual saving of around 9 to10%.

Table 3. Estimated net costs of Kivexa® versus Truvada® or versus Combivir®

	2008	2009	2010	2011	2012
Kivexa® costs	£62,136	£75,480	£95,330	£122,003	£155,694
Net cost of Kivexa® vs. Truvada®	-£6,137	-£7,695	-£10,028	-£13,173	-£17,154

8.4.5 Sensitivity analysis

No sensitivity analyses have been conducted in the budget impact analysis.

9.0 ADDITIONAL INFORMATION

9.1 Guidance and audit requirements

- The British HIV Association (BHIVA) issued updated guidelines on antiretroviral treatment of HIV-1 in adults online in May 2008[4], as discussed in section 3.0 and throughout the ASAR.
- The Health Protection Agency, in collaboration with National Public Health Survey for Wales, conduct an annual survey (SOPHID) of all patients seen for HIV-1-related treatment or care[34].

- Kivexa® will be initiated by specialists and would not currently be deemed suitable for shared care.

9.2 Previous AWMSG advice

- Enfuvirtide (Fuzeon®) – accepted for use for the treatment of patients with HIV-1, with restrictions; May 2004[35].
- Emtricitabine (Emtriva®) – recommended for use within NHS Wales as an option for the treatment of HIV-1 infected adults in combination with other antiretroviral agents for use in treatment-naïve patients in line with current BHIVA guidelines; June 2007[36].
- Emtricitabine/tenofovir DF (Truvada®) – recommended for use within NHS Wales as an option for the treatment of HIV-1 infected adults who are treatment-naïve and in line with current BHIVA guidelines; June 2007[37].
- Darunavir (Prezista®) – recommended for the treatment of HIV-1 infection in highly pre-treated adults who have failed more than one regimen containing a PI, and where resistance profiling suggests it is appropriate; August 2007[38].
- Tipranavir (Aptivus®) – recommended for the treatment of HIV-1 infection, only for the treatment of highly pre-treated adult patients who have failed multiple PIs, and where resistance profiling suggests it is appropriate; August 2007[39].

9.3 Ongoing studies

- The 96-week results of the HEAT study were presented at conference in August 2008[2]. Further analyses of these data are expected over the coming months.
- Results of the ACTG 5202 study are anticipated some time in 2009.
- A further ongoing study is assessing virological failure in patients on stable NRTIs who are switched to Truvada® or Kivexa® (STEAL study). This will complete in July 2008 and publication of the results is yet to be confirmed[2].
- The 48-week data from the ASSERT study, which is assessing renal function in patients randomised to Kivexa® or Truvada® (plus efavirenz for all patients) are anticipated mid 2009, and 96-week data are expected mid 2010[2].

9.4 Patient Organisation Information

A submission by the Terrence Higgins Trust was provided to AWMSG members.

GLOSSARY

Incidence:
The number of people falling ill with a specified disease during one year, in a specified population.

Lipoatrophy/lipodystrophy
Lipodystrophy is a general term for the disturbance of fat metabolism that involves the absence of fat and/or the abnormal distribution of fat in the body. Lipoatrophy refers specifically to the loss of the fat layer under the skin that makes the limbs, buttocks and face appear wasted. May be a long term side effect of some antiretroviral agents[40].

Negative predictive value
Negative predictive value is a measure of the performance of a test. It reflects the probability that a person is actually free of a disease or particular state, given that their test result is negative[41].

Prevalence:
The number of cases of a disease existing in a given population at a specified period of time or at a particular moment in time (point prevalence).

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Appendix 1. Additional Clinical Information

Table 1A. Randomised studies of once daily versus twice daily abacavir plus lamivudine

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Treatment regimen	Outcome
9 CNA30021	Phase III, randomised, double-blind, multicentre, non-inferiority trial 48 wks	Randomised, n=784 exposed ITT population: Abacavir 600mg od, n=384 Abacavir 300mg bd, n=386	ART-naive HIV-1 patients ≥18yrs old HIV-1 RNA >400 copies/mL, CD4 count >50 cells/mm^3	81% male 54% white Age 36 yrs* CD4 cell count: 262 copies/mm^3* (31% <200 copies/mm^3) HIV-1 RNA: 4.89 log_{10} copies/mL* (56% ≤100,000 copies/mL)	Abacavir 600mg od versus Abacavir 300mg bd Added to lamivudine 300mg od plus efavirenz 600mg od	**Primary endpoint (48 wks)†:** % HIV-1 RNA <50 copies/mL for abacavir 600mg od versus abacavir 300mg bd Stratified by baseline HIV-1 RNA copies/mL: ≤100,000: 65% versus 67% >100,000: 67% versus 69% difference -1.7% (95% CI -8.4 to 4.9) Unstratified: 66% versus 68%, difference -1.7% (95% CI -8.4 to 4.9) Non-inferiority established (2-sided 95% CI needed to lie entirely to the right of the value of -12%)

Table 1A. Continued

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Treatment regimen	Outcome
10 SEAL, ESS30008	Phase III, randomised, open-label, multicentre, non-inferiority trial 48 wks	Randomised, n=260 ITT population: Kivexa® od, n=130 Abacavir/ lamivudine bd, n=130	ART-experienced HIV-1 patients ≥18yrs old treated with abacavir 300mg bd and lamivudine 150mg bd plus a PI or NNRTI for ≥24 wks, HIV-1 RNA <400 copies/mL, CD4 count ≥50 cells/mm^3	82% male Age 38 yrs* CD4 cell count: 554 copies/mm^3*, HIV-1 RNA: 92% <50 copies/mL Prior abacavir and lamivudine exposure 22 months* (range 3 to 48)	Patients were switched to Kivexa® od or remained on abacavir 300mg bd and lamivudine 150mg bd Background treatment (approximate): PI 34% NNRTI 66%	**Primary endpoint (48 wks):** Virological failure defined as HIV-1 RNA ≥1,265 copies/mL (0.5 $\log_{10}$ copies/mL increase over 400 copies/mL) Non-virological failures for Kivexa® versus abacavir plus lamivudine: 95% versus 93%, difference 1.5% (90% CI -3.4 to 6.4) Non-inferiority established (2-sided 90% CI needed to lie entirely to the right of the value of -12%) **Secondary endpoints (48 wks) included:** HIV-1 RNA level <50 copies/mL in the Kivexa® versus the twice daily abacavir and lamivudine group: 81% and 82%. Median changes in CD4 counts from baseline (Kivexa®: 565 cells/mm^3 and twice daily: 549 cells/mm^3) were 28 and 24 copies/mm^3. Median adherence with treatment was 93% in both treatment groups, irrespective of background treatment.

†Primary endpoints defined by Time to Loss of Virological Response algorithm: a study responder was defined as a patient who had confirmed viral suppression (2 consecutive plasma HIV-1 RNA measurements <50 copies/mL) and remained suppressed (no confirmed viral rebound measurements) by week 48 of the trial
*Median values
od=once daily, bd=twice daily, ART=antiretroviral therapy, exposed ITT= intention to treat population who received at least one dose of study drug

Table 1B. Randomised studies of Kivexa® or abacavir plus lamivudine versus Combivir® or Truvada® (or their component NRTIs)

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimen	Outcome
11 CNA30024	Phase III, randomised, double-blind, multicentre, non-inferiority trial 48 wks	Randomised, n=654 exposed ITT population: abacavir 300mg bd, n=324 zidovudine 300mg bd, n=325	ART-naive HIV-1 patients ≥18yrs old HIV-1 RNA >400 copies/mL, CD4 count >50 cells/mm^3	81% male 51% white Age 35 yrs* CD4 cell count: 264 copies/mm^3* HIV-1 RNA: 4.79 log_{10} copies/mL* (61% ≤100,000 copies/mL)	Abacavir 300mg bd versus zidovudine 300mg bd Added to lamivudine 150mg bd plus efavirenz 600mg od	**Primary endpoint (48 wks):** % HIV-1 RNA ≤50 copies/mL for abacavir bd versus zidovudine bd Stratified by baseline HIV-1 RNA copies/mL: ≤100,000: 72% versus 70% >100,000: 67% versus 67% difference 0.8% (95% CI -6.3 to 7.9) Unstratified: 70% versus 69%, difference 0.8% (95% CI -6.3 to 7.9) Non-inferiority established (2-sided 95% CI needed to lie entirely to the right of the value of -12%) **Secondary outcomes (48 wks):** Virologic failure, defined as HIV-1 RNA >50 copies/mL, was infrequent in both groups (6% in the abacavir group and 4% in the zidovudine group). Median increase from baseline in CD4 cell counts at week 48 was 209 cells/mm^3 in the abacavir group and 155 cells/mm^3 in the zidovudine group (p=0.005).

Table 1B. Continued

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimen	Outcome
2,12 HEAT, EPZ104057 (Poster)	Phase IV, randomised, double-blind, multicentre, non-inferiority trial 96 wks safety; 48 wks efficacy	Randomised, n=688 exposed ITT population: Kivexa®, n=343 Truvada®, n=345	ART-naive HIV-1 patients ≥18yrs old, HIV-1 RNA ≥1000 copies/mL, Any CD4 count	82% male 50% white 36% black Age 35 yrs† CD4 cell count: 204 copies/mm^3* HIV-1 RNA: 4.87 $\log_{10}$ copies/mL* (57% <100,000 copies/mL)	Kivexa® od versus Truvada® od Added to lopinavir/ritonavir od	**Primary endpoint (48 wks):** % HIV RNA <50 copies/mL for Kivexa® od versus Truvada® od Stratified by baseline HIV-1 RNA copies/mL: <100,000: 71% versus 69% ≥100,000: 63% versus 65% Unstratified: 68% versus 67%, difference 0.39% (95% CI -6.63 to 7.40) Non-inferiority established (2-sided 95% CI needed to lie entirely to the right of the value of -12%) **Secondary endpoints:** Virological failures (defined as failure to achieve by week 24 and/or maintain after week 24 a HIV-1 RNA <200 copies/mL) were high in both the Kivexa® and the Truvada® groups (12% versus 13%, respectively)[2]. Median change from baseline in HIV-1 RNA: 3.142 versus 3.131 $\log_{10}$ copies/mL Increase in CD4 cell counts from baseline: +201 versus +173 cells/mm^3 (p=0.077)[2,12].

Table 1B. Continued

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimen	Outcome
13 BICOMBO (abstract and presentation)	Open-label, randomised non-inferiority study 48 wks	Enrolled, n=335 ITT population: Kivexa®, n=167 Truvada®, n=166	ART-experienced HIV-1 patients ≥18yrs old treated with lamivudine-containing regimen for ≥6 months with HIV-1 RNA <200 copies/mL	77% male Age 43 yrs* ART-exposure: 4 years CD4 cell count: 514 copies/mm^3* AIDS: 39% Previous NRTI lamivudine plus: Zidovudine 32% Stavudine 15% Didanosine 17% Tenofovir 30% Abacavir 9%	Patients were switched to Kivexa® od or Truvada® od Added to background NNRTI or PI	**Primary endpoint (48 wks):** % treatment failure for any reason‡ for Kivexa® od versus Truvada® od 19.2% versus 13.3% difference 5.9% (95% CI –2.1 to 14) Non-inferiority NOT established for treatment failure as upper limit of 95% CI exceeded pre-specified 12.5% **Secondary endpoints** Virological failure (HIV-1 RNA>200 copies/mL) met non-inferiority criterion 2.4% versus 0% difference 2.4% (95% CI 0.05 to 6.0) CD4 cell counts were statistically significantly increased in the Kivexa® group compared with the Truvada® group (+44 versus -3 cells/mm^3; p=0.03)[13]

*Median values
†Mean values
‡Treatment failure for any reason including HIV-1 RNA >200copies/mL, discontinuation, loss to follow up, development of AIDS defining event, death
od=once daily, bd=twice daily, ART=antiretroviral therapy, exposed ITT= intention to treat population who received at least one dose of study drug