All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Efavirenz / emtricitabine / tenofovir disoproxil (as fumarate) (Atripla®) for the treatment of HIV-1 infection in adults

Bristol-Myers Squibb and Gilead Sciences Ltd

Advice No: 0209 – February 2009

Recommendation of AWMSG

Efavirenz / emtricitabine / tenofovir disoproxil (as fumarate) (Atripla®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in adults with virological suppression to HIV-1 RNA levels of <50 copies/ml on their current combination antiviral therapy for more than three months and in accordance with current BHIVA guidance.

AWMSG is of the opinion that efavirenz / emtricitabine / tenofovir disoproxil (as fumarate) (Atripla®) 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: 25th February 2009

The recommendation of AWMSG is:

Efavirenz / emtricitabine / tenofovir disoproxil (as fumarate) (Atripla®) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in adults with virological suppression to HIV-1 RNA levels of <50 copies/ml on their current combination antiviral therapy for more than three months and in accordance with current BHIVA guidance.

AWMSG is of the opinion that efavirenz / emtricitabine / tenofovir disoproxil (as fumarate) (Atripla®) is not suitable for shared care within NHS Wales.

Additional note:

- AWMSG is of the view that Atripla® should be considered for use in circumstances where concordance may be a problem.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Atripla® is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with virologic suppression to HIV-1 ribonucleic acid (RNA) levels of <50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Atripla® prior to initiation of their first antiretroviral treatment regimen[1].

The demonstration of the benefit of Atripla® is primarily based on 24 week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to Atripla®. No data are currently available from clinical studies with Atripla® in treatment-naïve or in heavily pre-treated patients. No data are available to support the combination of Atripla® and other antiretroviral agents[1].

2.2 Dosing

The recommended dose of Atripla® is one tablet taken at bedtime on an empty stomach. Separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. Atripla® is not recommended for patients aged under 18 years and insufficient numbers of elderly patients have been evaluated in clinical studies of the components of Atripla® to determine whether they respond differently than younger patients. Caution should be exercised when prescribing Atripla® to the elderly. See the Summary of Product Characteristics (SPC) for further details[1].

2.3 Market authorisation date

EU marketing authorisation was granted 13th December 2007[2].

2.4 UK Launch date

Atripla® was launched in the UK on 19th December 2007.

3.0 DECISION CONTEXT

The 2008 British HIV-1 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[3]. A full baseline assessment, including HIV-1 resistance testing, screening for hepatitis B and C co-infection and a cardiovascular (CV) risk assessment, should be undertaken before initiating treatment. 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[3].

Co-formulated, fixed-dose antiretroviral products are a convenient option for patients and their availability has led to the majority of patients who are starting treatment being prescribed one of the three two-NRTI combinations as their backbone[3]. The BHIVA guidelines recommend that Truvada® (emtricitabine/tenofovir DF)[4] or Kivexa® (abacavir/lamivudine)[5] should be the first choice for the nucleoside backbone to be used with efavirenz[3]. Kivexa®, however, should be reserved for patients who are HLA-B*5701 negative and should be used with caution in those with viral loads over 100,000 copies/mL or where there is significant risk for CV disease[3]. Combivir® (zidovudine/lamivudine)[6] is the co-formulation of choice for the prevention of mother-to-child transmission.

Atripla® is a fixed-dose combination of emtricitabine, tenofovir disoporoxil (as fumarate) and efavirenz. These are preferred components of a complete HAART regimen in newly diagnosed HIV-1 patients in whom treatment is recommended[3], and their combination in a single tablet has the potential to reduce the pill burden for patients. Truvada® (fixed-dose combination of emtricitabine and tenofovir disoporoxil [as fumarate]) has previously been recommended by the All Wales Medicines Strategy Group (AWMSG) as an option for the treatment of HIV-1 infected adults who are treatment-naive and in line with the BHIVA guidelines[7]. Atripla®, however, is licensed only for use in patients with virologic suppression to HIV-1 RNA levels of <50 copies/ml on their current combination antiretroviral therapy for more than three months[1]. Therefore, Atripla® is not licensed for use as initial therapy in treatment-naive patients. The licensed indication is not limited to patients whose current combination antiretroviral therapy consists of the individual components of Atripla®[1].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Evidence of the efficacy of Atripla® is supported by the evidence that is available for its individual components. This includes study 934, an open-label, phase III study, which demonstrated that a regimen of emtricitabine, tenofovir DF and efavirenz was superior to Combivir® plus efavirenz in achieving HIV RNA levels less than 400 copies/mL through up to 144 weeks of follow-up. Direct evidence for Atripla® includes a single-arm extension study (study 934E) and a comparative study (study 073), which does not permit a comparison of Atripla® against its individual components. Twenty four week data demonstrate that Atripla® is efficacious in maintaining HIV RNA levels less than 400 copies/mL and 200 copies/mL, respectively. In study 934E there was a reduction in the CD4 cell count over the 24 weeks of Atripla® treatment, and 12 week data indicated a reduction in the proportion of patients maintaining a viral load less than 50 copies/mL, although it should be noted that these data relate to the last 12 or 24 weeks of up to a total of 168 weeks of treatment. Further data are required from these ongoing studies to confirm or refute these interim findings. When Atripla® is taken on an empty stomach, as recommended, the bioavailability of the tenofovir DF component is significantly reduced and it is unclear if this may result in a clinically meaningful reduction in effectiveness compared with when tenofovir DF is taken with food, as is recommended for Truvada® or when taken separately as Viread®. The SPC for Atripla® notes that limited data on adverse reactions are available for the fixed-dose combination product, but adverse reactions associated with the individual components may be expected to occur with the fixed-dose combination tablet.

4.2 Review of the evidence on cost-effectiveness

Cost utility analyses of Atripla® compared with efavirenz plus Truvada®, Combivir® or Kivexa® in treatment-naive patients have been conducted using a Markov model. For the Atripla® arm it is assumed that patients start treatment on Truvada® plus efavirenz before a proportion switch to Atripla® in the first year. The model does not consider a switch from any other regimen to Atripla®. It is assumed that treatment with a fixed-dose combination product leads to improved adherence compared with taking the individual components separately. It is further assumed that improved adherence to treatment leads to an improvement in virological suppression. As there are no direct data to support this assumption for Atripla®, retrospective analyses of prescription refill data related to other regimens have been used to adjust the efficacy data from study 934. The associated assumptions and extrapolations are subject to significant uncertainty and result in improved efficacy being modelled for Atripla® and Truvada® compared with the individual components taken separately. The extent to which all relevant adverse events (and associated costs) are captured in the model would also seem uncertain.

In the base case analyses, Atripla® is estimated to be less expensive and more effective than Truvada® plus efavirenz (by -£319, and +0.01 quality-adjusted life years [QALYs] over a lifetime) or Kivexa® plus efavirenz (by -£1,846 and +0.11 QALYs over a lifetime), i.e. Atripla® is dominant over these regimens. Compared with Combivir® plus efavirenz, Atripla® is estimated to have an incremental cost per QALY gained of £2,544. A range of sensitivity analyses have been conducted, but not specifically for the comparison of Atripla® against Truvada®. The model provided by the company indicates that removal of the assumption of improved adherence with Atripla® and Truvada® appears to have little impact on the model outputs.

5.0 LIMITATIONS OF DECISION CONTEXT

- There are no direct data to support the assertion that treatment with Atripla® leads to improved adherence and outcomes for patients compared with treatment using either its individual components or other antiviral regimens.
- Direct efficacy data for Atripla® are currently limited to 24-week interim analyses of studies that do not permit comparison of the triple combination product against either Truvada® plus efavirenz or the individual components. Further data are required from these ongoing studies to confirm or refute the interim findings.
- Insufficient numbers of elderly patients have been evaluated in clinical studies of the components of Atripla® to determine whether they respond differently than younger patients. Caution should be exercised when prescribing Atripla® to the elderly.
- When Atripla® is taken on an empty stomach, as recommended, the bioavailability of the tenofovir DF component is significantly reduced and it is unclear if this may result in a clinically meaningful reduction in effectiveness compared with when tenofovir DF is taken with food, as is recommended for Truvada® or when taken separately as Viread®.

6.0 CLINICAL EVIDENCE

Three of the five studies detailed in the company submission are summarised in Table 1A, Appendix 1 and are discussed below. These are: (i) an open-label phase III study (study 934)[8-10] in which treatment-naive patients were randomised to treatment with a combination of emtricitabine and tenofovir or zidovudine/lamivudine, each in addition to efavirenz, for up to 144 weeks; (ii) an single-arm extension to this study (study 934E)[10] in which patients completing 144 weeks of treatment were given the option to switch to the Atripla® product; and (iii) an open label, phase IV study (study 073), in which patients who were responsive to and stabilised on their current HAART regimen for at least three months were randomised to continue with their current regimen or were switched to Atripla®[11].

Briefly, the two studies presented in the company submission, but not discussed in detail here are: (i) a bioequivalence study of the individual components of Atripla® and the fixed-dose preparation, which was conducted in healthy volunteers who took the single doses[10]. This demonstrated that the combination product was bioequivalent to the individual components when administered on an empty stomach, however this is contrary to the recommendations for administration of tenofovir DF and limits interpretation of the results (see section 7.2); and (ii) a 96-week efficacy and safety study of efavirenz versus lopinavir, both administered in addition to a backbone consisting of two NRTIs[12]. This study supports the use of efavirenz as per the BHIVA guidelines[3], and included tenofovir but not emtricitabine as an NRTI[12].

6.1 Clinical efficacy

6.1.1 Emtricitabine plus tenofovir versus zidovudine/lamivudine, in addition to efavirenz (study 934)

In this phase III, non-inferiority study, antiretroviral-naïve adults with HIV-1 RNA levels >10,000 copies/ml, regardless of CD4 cell count, were randomised to receive a once daily regimen of efavirenz 600mg, emtricitabine 200mg and tenofovir DF 300mg (as separate tablets, without regard to meal times) or a regimen of efavirenz 600mg once daily plus a fixed-dose combination of zidovudine 300mg/lamivudine 150mg twice daily[8]. At 48 weeks, 84% of the group that received emtricitabine and tenofovir DF met the primary endpoint of achievement and maintenance of HIV RNA <400 copies/mL versus 73% of the zidovudine/lamivudine group. The 95% confidence interval (CI) for the difference between the groups was 4% to 19%; p=0.002, which met the pre-specified criterion for non-inferiority and indicated that the emtricitabine and tenofovir DF regimen was statistically superior to the zidovudine/lamivudine regimen. The secondary endpoints, which included the proportion achieving HIV RNA levels <50 copies/mL and changes in CD4 cell counts, also favoured the emtricitabine and tenofovir DF regimen[8] (see Table 1A, Appendix 1).

Follow-up data to 144 weeks are now available[9]. These indicate that a statistically significantly greater proportion of the emtricitabine and tenofovir DF recipients still had HIV RNA levels <400 copies/mL compared with the zidovudine/lamivudine recipients (71% versus 58%; p=0.004). There was no longer a statistically significant difference, however, in the proportion of patients with HIV RNA <50 copies/mL or in the mean change from baseline in CD4 cell counts[9].

Points to note:

- Baseline median CD4 cell counts for the two groups were within the range at which starting treatment would be considered (in accordance with BHIVA guidelines)[3].
- For the first 96 weeks of treatment, emtricitabine and tenofovir DF were provided as separate tablets, taken once daily without regard to the timing in relation to food. Between weeks 96 and 144 of treatment, patients taking these agents were switched to the fixed-dose combination product Truvada®[9].
- At week 48 there was no significant difference in rates of virological rebound (defined as confirmed HIV RNA level >400 copies/ml after achieving <400 copies/ml on one occasion) (1% in the emtricitabine and tenofovir DF group versus 3% in the zidovudine/lamivudine group; p=0.11)[8]. At 96 weeks, however, the rate of virological rebound was higher in the zidovudine/lamivudine group (<1% versus 5%; p=0.007)[13]. Rates for 144 weeks are not presented[9].
- Around 72% of the emtricitabine/tenofovir DF group and 56% of the zidovudine/lamivudine group completed a dosing questionnaire. Response rates (HIV RNA <400 or <50 copies/mL) were marginally greater in those patients who took their doses with/within an hour of food compared with those who took their doses without food[10]. These data should, however, be interpreted with caution as it appears the questionnaire was not pre-specified.
- Over the 144 weeks of follow-up, more patients in the zidovudine/lamivudine group discontinued their study regimen than in the entricitabine and tenofovir DF group (41% versus 29%; p=0.004). There were more discontinuations due to virological failure (6% versus 2%, respectively; p=0.038) and adverse events (11% versus 5%, respectively; p=0.01) in the zidovudine/lamivudine group. Most discontinuations occurred before 96 weeks, whereas there were only 4 discontinuations in the emtricitabine/tenofovir DF group and 10 in the zidovudine/lamivudine group between 96 and 144 weeks[9].

6.1.2 Extension to study 934 — Switch to Atripla® (study 934E)

All patients who achieved and maintained a HIV RNA level <400 copies/mL in study 934 were able to enter a single-arm 96 week extension study, in which they were switched from their current regimen to treatment with the fixed-dose combination product Atripla® taken on an empty stomach. Interim results are available from 160 patients who were receiving emtricitabine/tenofovir DF and 126 patients who were receiving zidovudine/lamivudine at week 144 in study 934[10]. At the start of treatment with Atripla®, 99% of these patients had HIV RNA levels <400 copies/mL, and 95% had levels <50 copies/mL. At 24 weeks, 97% of patients had maintained HIV RNA levels <400 copies/mL, which was not statistically significantly different from the start of Atripla® treatment. Twelve-week data, however, indicate that the proportion that had maintained HIV RNA levels <50 copies/mL had significantly reduced to 91% (p=0.02). The European Public Assessment Report (EPAR)[10], suggests that this finding may be due to the withdrawal of eight patients who all had HIV RNA levels <50 copies/mL at the start of the Atripla® treatment. The EPAR, also notes that there was a statistically significant reduction in CD4 cell counts at 24 weeks following the start of treatment with Atripla®[10]. It should be noted, however, that patients providing these 24 week data had been on treatment for up to a total of 168 weeks.

Points to note:

- The bioavailability of tenofovir DF is significantly reduced when administered on an empty stomach[4,10] (see section 7.2). The company submission states that Atripla® was administered on an empty stomach in study 943E[2]. The EPAR, however, states that this study was not considered appropriate for the demonstration that the reduced bioavailability of tenofovir DF when administered without food does not translate into a clinically relevant effect due to the lack of a control group, the highly pre-selected patient population, the lack of administration guidance before week 168, the short duration of therapy with Atripla®, as well as the lack of appropriate statistical analyses[10].

6.1.3 Switch to Atripla® versus continuing with current HAART (study 073)

This is an ongoing phase IV study in which patients with no history of virological failure, who were stabilised on a HAART regimen (two NRTIs plus either a PI or an NNRTI) for at least three months, and had achieved a HIV RNA level <200 copies/mL, were randomised to either switch to treatment with Atripla® once daily or continue with their current HAART regimen[10,11]. The primary endpoint is non-inferiority in relation to maintaining a viral load <200 copies/mL at 48 weeks. Interim data at 24 weeks are available which, when assessed on the basis that missing data is counted as treatment failure, indicate non-inferiority for treatment with Atripla® compared with continued HAART regimen for maintaining viral load <200 copies/mL (93.1% versus 93.8%) or <50 copies/mL (93.1% versus 90.7%). These finding were consistent when assessed using a variety of statistical approaches to the handling of missing data[10,11].

Points to note:

- Patients whose baseline HAART regimen consisted of emtricitabine plus tenofovir DF plus efavirenz (the individual components of Atripla®) were excluded from this study[10]. Therefore, this study does not clarify the issue of whether or not the reduced bioavailability of tenofovir DF when administered as Atripla® on an empty stomach, as recommended[1], translates into a clinically relevant reduced effect compared with administration of the separate components (emtricitabine and tenofovir DF) when taken with food as recommended[4].
- A range of exploratory sub-group analyses were conducted which, although should be interpreted with caution, indicate consistent results when comparing Atripla® against PI-based regimens, NNRTI-based regimens, tenofovir DF-containing regimens and non-tenofovir DF regimens[10].
- Around 8% of patients taking Atripla® had discontinued by week 24 compared with 6% of patients on their current regimen. The main reason in the Atripla® group was adverse events (4%), whereas the main reason in the continued HAART group was withdrawal of consent (4%)[11].
- The company submission states that 48 week results from this study are expected in the last quarter of 2008[2].

6.2 Safety

The SPC for Atripla® notes that limited data on adverse reactions are available for the fixed-dose combination product, but as it contains efavirenz, emtricitabine and tenofovir DF, adverse reactions associated with these individual agents may be expected to occur with the fixed-dose combination tablet[1]. Study 934 compared the individual agents and a dual fixed-dose combination of emtricitabine/tenofovir DF plus efavirenz against a fixed-dose combination of zidovudine/lamivudine plus efavirenz.

Data from 144 weeks of follow-up indicate that 69% of the emtricitabine/tenofovir DF group experienced a treatment-related adverse event compared with 76% in the zidovudine/lamivudine group. These included dizziness (25% versus 26%, respectively), nausea (18% versus 27%), abnormal dreams (17% versus 13%), rash (9% versus 7%), insomnia (8% versus 9%), fatigue (8% versus 10%), diarrhoea (7% versus 8%), headache (7% versus 7%) and somnolence (6% versus 6%)[10]. No patients in the emtricitabine/tenofovir DF group experienced anaemia compared with 7% in the zidovudine/lamivudine group. Treatment effects on body composition favoured the emtricitabine/tenofovir DF group, as evidenced by increases in mean body composition in limb fat (+1.13kg change from week 48 to week 144, $p<0.001$) compared with decreases in the lamivudine/zidovudine group (-1.09kg change from week 48 to week 96, $p=0.001$)[10]. Mean fasting total cholesterol increased significantly from baseline in both groups, but to a greater extent in the zidovudine/lamivudine group than in the emtriciabine/fenofovir DF group (36mg/dL [0.93mmol/L] versus 24mg/dL [0.62mmol/L], respectively; $p=0.005$)[9]. There was also a significant increase in mean fasting low density lipoprotein (LDL, 13mg/dL [0.34mmol/L] versus 16mg/dL [0.41 mmol/L]) and high density lipoprotein (HDL, 10mg/dL [0.26mmol/L] versus 12mg/dL [0.31mmol/L]) cholesterol from baseline in both groups, but which was not statistically significant between groups. Mean fasting triglycerides increased significantly from baseline in the zidovudine/lamivudine group (36mg/dL [0.41mmol/L]), but not the emtriciabine/fenofovir DF group (4mg/dL [0.05mmol/L][9].

Renal effects were similar across groups in this study, although there have been post-marketing reports of renal and urinary disorders associated with tenofovir DF treatment; frequent monitoring of renal function is required thoughout treatment with Atripla®[1]. Around 3% of patients experienced elevations in liver enzymes to more than five times the upper limit of normal in both groups[1]. Discontinuations due to adverse events in study 934 occurred in 5% of the emtricitabine/tenofovir DF group (mainly due to psychiatric disorders, drug eruption, nausea) versus 11% of the zidovudine/lamivudine group (mainly due to anaemia)[10]. Of the five deaths that occurred up to week 144, none were reported to be related to study drugs[10].

The extension study 934E provides limited safety data due to being an uncontrolled, single arm study. After 24 weeks of treatment with Atripla®, 61% of patients experienced a treatment-emergent adverse event, including gastrointestinal disorders (10%), infections (30%), psychiatric disorders (9%) and skin disorders (9%). Around 6% experienced grade 3 or 4 treatment-emergent adverse events overall[10]. Few safety data are currently available from study 073. Around 4% of patients who switched to Atripla® discontinued treatment due to adverse events (3% were central nervous system events), whilst there were no discontinuations due to adverse events in the group continuing with their HAART regime[11]. Full data are awaited from studies 934E and 073. The SPCs for Atripla®[1], Truvada®[4] and efavirenz (Sustiva®)[14] should be consulted for further details.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

HAART regimens should be individualised for patients[3], and there are potentially many different regimens. No data are currently available from clinical studies with Atripla® in treatment-naïve patients or in heavily pre-treated patients[1]. The licensed indication in the UK effectively excludes its first-line use in treatment-naive patients. The individual components of Atripla®, however, are recommended as an option for first-line use[3]. The company submission considers that the most likely patients to be considered for Atripla® are those who are taking their first antiretroviral regimen[2]. This could include

patients taking the individual components of Atripla®, or those taking other first-line regimens (e.g. Kivexa® plus efavirenz).

7.2 Comparative effectiveness

- The individual components of Atripla® (emtricitabine, tenofovir DF and efavirenz) are established antiretroviral agents. The BHIVA guidelines imply that these agents, when combined, make up a preferred first-line HAART regimen, and there is a wide body of evidence supporting their efficacy and safety when administered together in treatment-naive patients[3].
- Evidence of the efficacy of the once daily fixed-dose combination Atripla® is supported by the evidence that is available for the individual components (e.g. study 934, discussed in section 6.1.1), but at present direct evidence for Atripla® is limited to 24-week data from studies that have switched patients from an established, stable HAART regimen[10]. These include a single-arm extension study (934E) and a comparative study that excluded patients who were taking the individual components of Atripla® as their baseline regimen (study 073)[10]. Therefore, there are no direct comparative data of the efficacy of Atripla® versus a regimen made up of its individual components (or as Truvada® plus efavirenz) and taken as directed by the respective SPCs.
- Atripla® should be taken on an empty stomach, as food may increase efavirenz exposure and increase the frequency of adverse effects[1]. In contrast, the SPCs for tenofovir DF (Viread®)[15] and the fixed-dose combination of emtricitabine and tenofovir (Truvada®)[4] state that they should be taken with food, as there is a 35% reduction in the bioavailability of tenofovir when taken without food[10]. Although a bioequivalence study indicated that Atripla® and its individual components are bioequivalent, this only tested administration in healthy, fasting volunteers[10]. As there are no direct comparative data on the efficacy of Atripla® versus a regimen made up of its individual components, it is not clear if the reduced bioavailability of tenofovir, that occurs when Atripla® is taken on an empty stomach, translates into a clinically meaningful difference in efficacy compared with administration of the individual components.
- The limited data that are available from study 073 confirm that Atripla® is efficacious and is non-inferior to several comparator HAART regimens in maintaining a viral load less than 200 copies/mL over 24 weeks[10,11]. In study 934E, the proportion of patients with viral loads less than 400 copies/mL was maintained over 24 weeks when patients were switched to Atripla®. There was, however, a reduction in the CD4 cell count over the 24 weeks of Atripla® treatment, and 12 week data indicated a reduction in the proportion of patients maintaining a viral load less than 50 copies/mL[10]. Further data are required from these ongoing studies to confirm or refute these interim findings.
- Atripla® is licensed for use in adults with virologic suppression to HIV-1 RNA levels of less than 50 copies/mL on their current combination antiretroviral therapy for more than three months[1]. There are no direct data available to support its use in treatment-naive or heavily pre-treated patients[1].
- As a complete HAART regimen available in a once daily single tablet, Atripla® has the potential to reduce pill burden and increase convenience for patients. The company submission asserts that this can lead to increased adherence to treatment, which in turn produces greater viral suppression, and decreases the likelihood of regimen failure and the incidence of morbidity outcomes over time[2]. There are no direct data presented to support the assumption of improved adherence with Atripla® compared with other regimens. In addition, there are no direct data presented to support the assumption of improved outcomes with Atripla® compared with other regimens. This assumption is subject to further uncertainty due to the issues surrounding the bioavailability of tenofovir when

taken as Atripla® on an empty stomach and the lack of data to clarify whether or not this has a clinically meaningful impact on efficacy compared to when taken as a separate component to efavirenz. No data on the impact of Atripla® on health-related quality of life are presented.

- A switch to Atripla® may require patients to attend additional clinic visits compared with patients who remain on their stable HAART regimen. As a fixed-dose combination product, dose adjustment or substitution of individual components of Atripla® is not possible without a further switch in treatment.
- The safety profile of Atripla® is likely to reflect the safety profile of its individual component agents[1]. These are familiar, well established agents in practice. The extent to which a switch to Atripla® may or may not improve the adverse events being experienced by patients will depend on the individual HAART regimen being taken. Emtricitabine/tenofovir DF (Truvada®) is thought to have no significant impact on lipid profile and to be associated reduced lipodystrophy compared with zidovudine/lamivudine (Combivir®); however, there are reports of adverse renal effects with tenofovir compared with other NRTIs. Abacavir/lamivudine (Kivexa®) is associated with hypersensitivity reaction (HSR) and greater dyslipidaemia compared with zidovudine. Different HAART regimens are associated with different adverse events, as outlined in the BHIVA guidelines[3] and the respective SPCs. Individualisation of treatment will require consideration of this alongside many other factors.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by the fixed-dose combination product of emtricitabine, tenofovir DF and efavirenz over relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of emtricitabine, tenofovir DF and efavirenz is acceptable.

8.2. Description and critique of the company's submission

The company submission describes cost utility analyses of Atripla® compared with efavirenz plus Truvada®, Combivir® or Kivexa® in treatment-naive patients, conducted using a Markov model. For the Atripla® arm it is assumed that patients start treatment on Truvada® plus efavirenz before a proportion switch to Atripla® in the first year. Following first-line treatment, patients in the cohort may switch to second-line and subsequent-lines of therapy due to lack of initial efficacy or loss of efficacy over time (defined as viral load <400 copies/mL), or due to adverse events. Patients may also experience HIV-related or non-HIV-related death at any time[2].

Efficacy data for first-line treatment with Atripla® or Truvada® plus efavirenz, and for Combivir® plus efavirenz, are based on data from follow-up of study 934 up to 144 weeks. This study only used the individual components of Atripla® for the first 96 weeks, and then patients switched to Truvada® plus efavirenz; the Atripla® fixed-dose combination product was not used at all up to 144 weeks of follow-up[8-10]. It is assumed that treatment with a fixed-dose combination product leads to improved adherence compared with taking the individual components separately, and improved adherence to treatment is assumed to improve virological suppression. Importantly, there are no direct data to support this assumption for Atripla®. Therefore, virological suppression data from study 934 has been adjusted using data from a retrospective analysis of health insurance claims data for Combivir® versus its individual components in the USA. In addition, analysis of virological suppression by adherence rates was not conducted in study 934. Therefore, adherence rates from a study that used pharmacy

refill data to assess viral suppression to levels <500 copies/mL (rather than 400 copies/mL as implied in the current model) in treatment-naive patients taking a range of antiretroviral regimens have been adjusted and applied to the data from study 934 to estimate different levels of adherence given different degrees of viral suppression.

These assumptions and extrapolations are subject to significant uncertainty and result in improved efficacy being modelled for Atripla® and Truvada® compared with the individual components taken separately. A range of sensitivity analyses have been conducted but not for the comparison of Atripla® and Truvada®.

8.3 Population

The modelled population has the baseline characteristics of the modified intention to treat (mITT) population of study 934. This excluded patients with NNRTI resistance at baseline[8]. The company submission considers that these patients are similar to those included in study CNA30024[16], which is used to provide efficacy data for Kivexa®[2].

8.4 Perspective and time horizon

The analysis is conducted from the perspective of NHS Wales, and uses a life-time horizon[2]. The cycle length used in the model is one year[2].

8.5 Comparator

The company submission considers that the patients most likely to be considered for Atripla® are those who are taking their first antiretroviral regimen[2]. The model compares treatment with Truvada® plus efavirenz followed by a switch to Atripla® against: Truvada® plus efavirenz; Combivir® plus efavirenz; and Kivexa® plus efavirenz[2]. The model does not consider a switch from Combivir® or Kivexa® to Atripla®.

8.6 Clinical inputs

8.6.1 Efficacy data

Virological suppression with first-line therapy

Viral load determines when patients will switch from first-line to second-line treatment; those whose viral load is not maintained <400copies/mL are classed as failures and switch to second-line treatment. Virological suppression (to <400copies/mL) rates for first-line treatment with Atripla® or Truvada® plus efavirenz are reportedly based on data from follow-up of study 934 up to 144 weeks. This study only used the fixed-dose combination Truvada® after 96 weeks, and did not include the Atripla® fixed-dose combination product at all[8-10] (see section 6.1.1). Virological suppression rates with emtricitabine + tenofovir DF + efavirenz from this study have been adjusted on the assumption that adherence in patients taking the dual or triple fixed-dose combination products will be better than in those taking the individual components separately, and that this will lead to improved virological suppression[2]. These assumptions are not founded on direct evidence, as discussed below.

A retrospective analysis of health insurance claims data from the USA, which considered the percentage of patients who achieved 95% adherence with Combivir® and its individual components[18] based, essentially, on prescription refill data, has been used to model the assumed improvements in adherence with the fixed-dose combination products Atripla® and Truvada® over the individual components. This analysis compared prescription refill data for patients taking a regimen based Combivir® against those taking a regimen based on the separate tablets of zidovudine and lamivudine. Few details are provided of other antiretroviral agents being taken and the extent to which prescription refill data represent actual adherence to the regimen in terms of doses taken correctly is unclear. The improved adherence modelled for Atripla® and Truvada® compared with the other regimens is based around the reduction

in pill burden with Combivir® compared with its individual components, and the extent to which this shifted the proportion of patients achieving 95% adherence.

As the published data for study 934 only reports viral suppression at 48, 96 and 144 weeks[8-10], it appears that company data on file has been used to provide viral suppression rates at intervening time periods[2] (data not provided and so not verifiable). Analysis of viral suppression by adherence rates was not conducted in study 934. Therefore, data from a study that used pharmacy prescription refill data to represent adherence to treatment, and compared this against viral suppression to levels <500 copies/mL in treatment-naive patients taking a range of antiretroviral regimens[17], has been adjusted and applied to the data from study 934 to estimate different levels of adherence given different degrees of viral suppression[2]. In effect, this approach estimates adherence levels from virological suppression rates, rather than virological suppression rates from adherence rates.

Collectively, these assumptions and extrapolations are subject to significant uncertainty and result in improved efficacy being modelled for Atripla® compared with Truvada® and with each compared with the individual components when taken separately. These uncertainties have not been specifically explored in the sensitivity analyses reported in the company submission. However, the model does permit the removal of the assumption of improved adherence, which indicates that the model is not sensitive to these assumptions (see section 8.9.2).

As discussed in section 7.2, it is unclear if the reduced bioavailability of the tenofovir component of Atripla® results in a clinically significant reduction in efficacy compared with when taken as Truvada® or separately to efavirenz[10]. Any potential improvement in adherence rates that may lead to improved viral suppression with Atripla® could potentially be offset to some degree by the reduced bioavailability of tenofovir DF when taken as Atripla®. There is also the possibility that omissions of doses of once daily regimens, even if occurring at reduced probability, are more deleterious than missed doses from more frequent dosing regimens.

Virological suppression rates for Combivir® + efavirenz are based on the Combivir® + efavirenz arm of study 934[9]. Virological suppression data for Kivexa® + efavirenz are estimated based on the 48 week results of a head-to-head trial between abacavir + lamivudine + efavirenz and zidovudine + lamivudine + efavirenz, all given as separate tablets (study CNA30024)[16]. It is assumed that any difference in efficacy observed between the Combivir® + efavirenz arm of study 934 and the zidovudine + lamivudine + efavirenz arm of study CNA30024 can be attributed to differences in adherence due to differences in pill burden. Efficacy data for Kivexa® + efavirenz are estimated by multiplying the study 934 efficacy data for Combivir® + efavirenz by the relative difference between the abacavir + lamivudine + efavirenz and the zidovudine + lamivudine + efavirenz arms of study CNA30024[2].

Virological suppression with second- and subsequent-line treatments

After first-line treatment, the annual probabilities of switching therapy line are based on those observed in an analysis of time to treatment failure among over 3,600 patients attending HIV clinics in London, 1996-2002[19]. Therefore, drug-specific virological suppression is not considered following first-line treatment.

CD4 cell count changes with first- and subsequent lines of therapy

Six levels of CD4 cell counts are considered in the model, ranging from $\leq$50 to >500 cells/mm^3. The distribution of patients among these six categories at the start of the model is reportedly based on the baseline characteristics of patients in study 934[8]. It appears that company data on file has been used to provide these[2] (data not provided

and so not verifiable). Changes in CD4 cell counts with first-line treatment are based on results of study 934 up to week 144. It appears that increases in CD4 cell count are independent of the treatment received, as long as viral load remains suppressed below 400copies/mL. Beyond year 3, it is assumed that patients whose viral load remains suppressed below 400 copies/mL continue to gain half as many CD4 cells/mm^3 in each year as they did in year 3.

Annual CD4 cell count changes with second-line therapy are based on a study that analysed data from 984 patients enrolled in EuroSIDA starting their second PI-containing regimen[20] (rather than NNRTI-based regimens). The model uses data from the first six months on second-line therapy, then assumes an average increase of 10 cells/mm^3 from months 6 to 12 of second-line therapy, and finally assumes that the CD4 cell count will remain constant until second-line therapy begins to fail[2]. It is assumed that patients would remain on second-line therapy for a median of 4.3 years as observed in the analysis of time to treatment failure among over 3,600 patients attending HIV clinics in London, 1996-2002[19].

Annual change in CD4 cell count for individuals on third-line therapy is reportedly based on pooled data from two tipranavir clinical trials among highly treatment-experienced patients[21]. This study assessed the mean change in CD4 cell count from baseline to week 48 for individuals on boosted tipranavir and the model assumes individuals on third-line therapy would experience an increase in CD4 cell count similar to those individuals who received tipranavir in these clinical trials. It is assumed that the CD4 cell count remains constant after week 48 until third-line therapy begins to fail[2]. The average time on third-line therapy is assumed to be 4.2 years, as observed in the analysis of time to treatment failure among over 3,600 patients attending HIV clinics in London, 1996-2002[19].

Following failure of third-line therapy, patients are assumed to receive non-suppressive therapy until death[2]. Annual change in CD4 cell count for individuals on non-suppressive therapy is reportedly based on a study of almost 2,500 highly treatment-experienced HIV patients with virological failure to all three antiretroviral drug classes (i.e. NRTIs, NNRTIs, and PIs). This study assessed the association of CD4 cell count changes with various viral-load values using linear regression[22]. Patients starting non-suppressive therapy are assumed to have viral loads of ≥ 4.5 $\log_{10}$ copies/mL[2].

Mortality

HIV-related mortality is driven by CD4 cell counts in the model. Observational data from the late-HAART era of the EuroSIDA study[23] has been used to determine the annual probability of death for each of the six categories of CD4 cell count that have been modelled.

Non-HIV-related mortality is based on general population mortality rates, which have been adjusted to account for the elevated risk of death observed amongst patients with HIV and receiving HAART compared with the general population. This relative risk is based on a Danish observational study that found the risk of death amongst patients taking HAART and who achieved CD4 cell counts $\geq$200 cells/mm^3 was 3.6 times greater than that in the general population[24].

8.6.2 Adverse events

The only adverse events considered in the model are anaemia, HSR and lipodystrophy associated with first-line treatment. The company submission asserts that renal toxicity associated with the tenofovir component of Atripla® or Truvada® is considered within the need to switch treatment (which may be due to any reason, including renal toxicity). Any specific treatment required for the management of renal toxicity is assumed to be

incorporated in the costs involved in switching treatment. The model does not consider any treatment involved in the management of lipid changes associated with the different agents (see sections 6.2 and 7.2). The extent to which all relevant adverse events (and associated costs) are captured in the model would seem uncertain.

The incidence of anaemia and HSR for Atripla®, and Truvada® and Combivir® plus efavirenz, are based on those reported in study 934, but only up to week 96[8,13]. For Kivexa® plus efavirenz, anaemia incidence is based on study CNA30024[16], and the incidence of HSR is based on that reported in the Kivexa® SPC (5%)[5]. It should be noted that the risk of patients experiencing HSR with Kivexa® is reduced significantly if patients who screen positive for the HLA-B*5701 allele do not receive the drug[5]. The clinical trials from which the 5% rate for HSR is obtained did not involve screening patients for this allele; therefore, rates in practice will be lower than this if Kivexa® is used only in those who screen negative for the allele, as recommended in the SPC[5].

The key efficacy studies do not report incidences of lipodystrophy. Therefore, a range of other studies have been used to provide estimates. Some of these studies used regimens other than those modelled here[2], and so are subject to some uncertainty.

8.6.3 Utility weights

Utility values assumed in the model are associated with CD4 cell counts. The values that have been used are taken from a previous cost-effectiveness analysis of lopinavir compared with nelfinavir[25].

For adverse events, it is assumed that any decrement in quality of life associated with anaemia or HSR would be short-lived and so is not considered. For the adverse event of lipodystrophy, a decrement on 0.1 has been applied, based on results obtained from a published survey study of 75 HIV patients[26].

8.7 Healthcare resource utilisation and cost

It appears that all costs obtained from historical sources have been inflated to 2007 values.

8.7.1 Drug costs

For the first-line of therapy, antiretroviral drug costs of all first-line regimens are employed. Atripla® and Truvada® plus efavirenz have the same acquisition costs[27].

For each subsequent therapy line, the company submission states that the model considers a basket of regimens most commonly used in each line and the percentage of people using each regimen. Antiretroviral drug costs are calculated as the weighted average of the cost of each regimen and the percentage using it[2]. It is not stated, however, what proportion of patients are assumed to use each of the regimens that are considered, or what the source of such data is, and so the costs that have been assumed in the model for subsequent lines of therapy are not verifiable.

8.7.2 Adverse event costs

The annual costs of treating anaemia are reportedly based on the treatments received in study 934[9], with the application of published unit costs. These treatments are not verifiable from the data that has been provided. The costs for the treatment of HSR are based on those reported in a published cost-effectiveness analysis of HLA B*5701 screening[28], and inflated to 2007 prices. The costs of the management of lipodystrophy are assumed to persist until a switch in the line of therapy occurs and are reportedly based on a Spanish study of the costs of adverse events in HIV-1 treatment, with simple conversion from Euros to pounds sterling[2].

8.7.3 Other resource use and costs

Annual medical costs of management of HIV are based on those reported in a questionnaire study of resource use for patients with HIV in England and Wales, published in 1996[29]. Costs are correlated with CD4 cell count and by tracking the time spent in each CD4 category, the average life time costs are calculated following inflation to 2007 prices. This study considered patient resource use as far back as 1992[29] and it is unclear how representative these estimates of resource use and costs would be of those today. All arms of the model, however, use these estimates.

When patients switch treatment they are assumed to incur the costs for additional clinic visits plus additional lab tests, etc. Published unit costs have reportedly been used to cost these items of resource use. For patients who switch to Atripla® from Truvada®, it is assumed that fewer resources are required when compared with switching to a different regimen[2]. The actual basis of the reduced resource use, however, is not clear from the company submission.

8.8 Discounting

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

8.9 Results

8.9.1 Base case analysis

In the base case analyses, Atripla® is estimated to be less expensive and more effective than Truvada® plus efavirenz (by -£319, and +0.01 QALYs over a lifetime) or Kivexa® plus efavirenz (by -£1,846 and +0.11 QALYs), i.e. Atripla® is dominant over these regimens. Compared with Combivir® plus efavirenz, Atripla® is estimated to have an incremental cost per QALY gained of £2,544. This is based on additional costs of £684 and a gain of 0.27 QALYs.

Truvada® plus efavirenz is estimated to be dominant over Kivexa® plus efavirenz, and to be associated with an incremental cost per QALY of £3,823 compared with Combivir® plus efavirenz.

8.9.2 Sensitivity/Scenario analyses

The time horizon has a significant impact on the model outputs. When this is reduced from lifetime to 10 years, Atripla® still dominates Kivexa® but the incremental cost per QALY compared with Combivir® increases to around £18,000. Discount rates had little impact on the model outputs.

A range of other one way sensitivity analyses have been conducted for the comparisons of Atripla® or Truvada® plus efavirenz against Combivir® or Kivexa® (both plus efavirenz), but no other one way sensitivity analyses have been conducted for the comparisons of Atripla® against Truvada® plus efavirenz.

The one way sensitivity analyses indicate that the model is sensitive to the assumptions on antiretroviral costs in later lines of therapy; when the lowest cost of the regimens considered in the basket of subsequent line regimens is considered, the incremental cost per QALY generated in all cases exceeds £10,000. The model is also sensitive to the virological response assumed for the comparators; when explored at the upper end of the 95% CI, the incremental cost per QALY approaches or exceeds £20,000 in all cases[2]. The largest change from base case results occurred when exploring the 95% CI for the change from baseline in CD4 cell count with Atripla®; the company submission notes that this resulted in outputs that ranged from Atripla® being dominant to Atripla® being associated with a very small reduction in QALYs compared with the comparator, but cost savings.

No sensitivity analyses have been conducted specifically around the assumptions on the improved adherence to treatment with Atripla® (or Truvada®), or the assumed improvement in virological response with improved adherence. However, the model provided by the company does allow for the removal of the assumed improvement in adherence rates with the Atripla® and Truvada® fixed-dose combination products. When no improvement in adherence rates is assumed, the model outputs switch to Truvada® dominating Atripla®, due to the small additional clinic costs assumed with Atripla® when switching from Truvada®. The outputs for other comparisons remain much the same as in the base case analysis, indicating that the model is relatively insensitive to assumptions of improved adherence with fixed dose combination products.

8.9.3 Probabilistic sensitivity analyses (PSA)

PSA has been conducted for the comparison of Atripla® or Truvada® plus efavirenz against Combivir® or Kivexa® (both plus efavirenz), but not for the comparisons of Atripla® against Truvada® plus efavirenz.

At a willingness-to-pay threshold of £30,000 per QALY, the PSA predicts the following probabilities of Atripla® or Truvada® being cost effective:

Atripla® versus Combivir® plus efavirenz: 91.8%
Atripla® versus Kivexa® plus efavirenz: 89.1%
Truvada® versus Combivir® plus efavirenz: 92.2%
Truvada® versus Kivexa® plus efavirenz: 88.0%

Visually, the cost-effectiveness acceptability curves suggest similar probabilities at a willingness-to-pay threshold of £20,000 per QALY[2].

8.10 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP did not identify any published evidence on the cost effectiveness of Atripla® at the time of submission. A poster of a UK cost effectiveness model based on study 934 has been presented at conference[30] since the submission was made. This contains very few details and it is not possible to determine if this is model is intended to relate to the Atripla® fixed dose combination product, or to Truvada®, or simply to the individual components of these products.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

A simple costing exercise has been undertaken of the possible use of Atripla®. Welsh HIV incidence and prevalence data from 2006 has been used to estimate the number of patients with HIV in Wales over a five year period. It appears that this five year period commences in 2006, which would lead to underestimation of potentially eligible patients. There are a range of assumptions employed, but many are not supported by reference to data or sources. No attempt has been made to estimate the net budget impact of the use of Atripla® displacing other regimens and it appears that there are errors in the assumed costs of switching patients between regimens. Collectively, the uncertainties and approach taken in this analysis significantly limit its usefulness, and the cost estimates that have been provided should be interpreted with caution.

9.2 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].

9.3 Data sources

9.3.1 Incident and prevalent cases

Health Protection Agency (HPA) data indicate a prevalence of 30 per 100,000 population in Wales in 2006, equivalent to 884 patients, and an incidence of 154 cases per year[31].

On the assumption that the annual incidence is constant, and that the mortality of patients with HIV is 3.6 times greater than the general population[24] (see section 8.6.1), the company submission estimates that in year 1 there would be 1,012 HIV patients, rising to 1,604 in year 5[2]. Few details are provided, however, of the actual calculations and what year relates to year 1.

9.3.2 Projected rate of adoption and market share

The HPA data indicate that 67% of patients accessing care for HIV are receiving antiretroviral therapy[31]. Therefore, the company submission considers that 592 patients (67% of 884 patients in 2006) are on therapy[2]. It is assumed that one-third of patients are triple-class experienced and harbour resistant virus. Of the remaining 395 patients, approximately 8% (37 patients) are assumed to be ineligible due to having primary resistance. Therefore, it is estimated that 358 patients are eligible for treatment in Wales[2]. The basis of these assumptions in not stated or clear.

It is further assumed that 150 patients are currently taking the individual components of Atripla®, and are the patients that would be switched to the fixed-dose combination product initially. The other 208 patients are assumed to be taking other regimens and to be eligible to switch. The analysis, however, assumes that all of the first 150 patients would be switched, and that 84% of newly diagnosed patients would start treatment on Truvada® plus efavirenz and would switch to Atripla® once they were virologically suppressed to undetectable levels of HIV RNA.

9.3.3 Costs and resource use

The only costs considered in the analysis are the costs of the antiretrovirals and the costs associated with an extra clinic visit (claimed to be £370 in the budget impact analysis, and £350 in the economic model). It is assumed that all patients who start treatment on Atripla® in year 1 remain on the drug in year 5. There are assumed to be no deaths due to therapy failure.

9.4 Results

The analysis does not consider the net budget impact of the use of Atripla® instead of other regimens – it simply calculates the costs of Atripla® drug therapy and the cost of clinic visits based on the number of patients estimated to receive treatment in years 1 to 5. In addition to the uncertainties discussed above, the clinic costs in each year beyond year 1 appear to be incorrect. Therefore, the estimates presented in the company submission and below in Table 1 should be interpreted with caution.

Table 1. Company cost estimates for Atripla® therapy

	Year 1	Year 2	Year 3	Year 4	Year 5
No. patients	150	279	408	537	668
Drug cost	£94,035	£174,905	£255,775	£336,645	£417,515
Clinic cost	£55,500	£47,730	£47,730	£47,730	£47,730
Total	£149,535	£222,635	£303,505	£384,375	£465,265

9.5 Sensitivity analysis

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

9.6 Relevant comparator costs

There are many possible comparator first-line regimens for adult patients with HIV. Table 2 presents the 30-day cost for the main NNRTI-based regimens as discussed in the BHIVA guidelines[3].

Table 2. 30-day costs of example comparator regimens

NNRTI-based regimens	30-day costs[27]
Atripla®	£626.90
Truvada® + efevirenz (as Sustiva® 600mg tablet)	£626.90
Combivir® + efevirenz (as Sustiva® 600mg tablet)	£527.10
Kivexa® + efevirenz (as Sustiva® 600mg tablet)	£582.30
This table provides the costs of usual doses of drugs when taken as a NNRTI-based regimen. It does not imply therapeutic equivalence of the regimens	

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- BHIVA issued updated guidelines on antiretroviral treatment of HIV-1 in adults online in May 2008[3], as discussed in section 3.0 and throughout the ASAR.
- HPA, 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[32].
- Atripla® will be initiated by specialists and would not currently be deemed suitable for shared care.

10.2 Previous AWMSG advice

- Enfuvirtide (Fuzeon®) – recommended as an option for use for the treatment of patients with HIV-1, with restrictions; May 2004[33].
- Emtricitabine (Emtriva®) – recommended as an option for use within NHS Wales 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[34].
- Emtricitabine/tenofovir DF (Truvada®) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults who are treatment-naïve and in line with current BHIVA guidelines; June 2007[35].
- 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[36].
- 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[37].
- Raltegravir (Isentress®▼) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in treatment-experienced adults in accordance with British HIV Association (BHIVA) guidance; November 2008[38].
- Fixed dose abacavir and lamivudine (Kivexa®) – 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; November 2008[39].
- Atazanavir (Reyataz®▼) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-experienced patients, in accordance with BHIVA guidance; January 2009[40].

- Atazanavir (Reyataz®▼) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-naïve patients, in accordance with BHIVA guidance; January 2009[41].

10.3 Ongoing studies

- The 48 week data from study 073 are expected in the fourth quarter of 2008[2].
- A UK-based, phase IV, open-label study (ONCE) will evaluate virological response over 48 weeks in patients who are switched from a regimen of emtricitabine, tenofovir DF and efavirenz, all given individually, to once daily treatment with Atripla® given on an empty stomach. Results are expected in late 2009[2].
- A further phase IV study will assess the effect on lipid profile over 12 weeks of switching to Atripla® from a stable regimen of Kivexa® plus efavirenz in patients with raised cholesterol (Randomised Open label switch for Cholesterol elevation on Kivexa Evaluation Trial [ROCKET]). Results are expected sometime in 2009[2].

10.4 Patient organisation information

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

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[42].

Lipoatrophy:
A term referring specifically to the loss of the fat layer under the skin that makes the limbs, buttocks and face appear wasted. This may be a long term side effect of some antiretroviral agents[39].

Lipodystrophy:
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[43].

Prevalence:
The proportion of a population that are cases at a point in time[42].

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Appendix 1. Additional Clinical Information

Table 1A. Key studies of Atripla® or its components

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Treatment regimen	Outcome
8,10 **Study 934**	Phase III, randomised, open-label, non-inferiority trial Primary endpoint at 48 weeks (additional follow-up to 144 weeks – see below)	Randomised, n=517 exposed and analysed mITT population, n=487	ART-naive HIV-1 patients ≥18yrs old HIV-1 RNA >10,000 copies/mL No CD4 cell count stipulation	86-87% male 56-61% white Median age 36-37 yrs Median CD4 cell count: 233-241 copies/mm^3 (41-42% <200 copies/mm^3) Median HIV-1 RNA: 5 log_{10} copies/mL (50-52% ≥100,000 copies/mL) 40% had AIDS	Emtricitabine 200mg plus tenofovir DF 300mg, od (n=244) [No restriction on timing of doses in relation to food] versus Fixed-dose combined zidovudine 300mg/ lamivudine 150mg, bd (n=243) Both in addition to efavirenz 600mg od	Emtricitabine/tenofovir od versus zidovudine/lamivudine bd: **Primary endpoint (48 wks)†:** % HIV-1 RNA <400 copies/mL: 84% versus 73% (95% CI 4% to 19%; p=0.002) Non-inferiority criterion met and superiority claimed for emtricitabine/tenofovir plus efavirenz **Secondary endpoints:** %HIV-RNA <50 copies/mL: 80% versus 70% (95% CI 2% to 17%; p=0.02) Mean change from basline in CD4 (cells/mm^3): 190 versus 158; p=0.002 % change in CD4 cell count: 11% versus 10%; p=0.02
9,10 **Study 934 (follow up)**	As above Follow up to 144 weeks	Results based on 456 randomised patients (excludes 31 who achieved HIV-RNA <400 copies/mL at 48 weeks but did not consent to participate up to 144 weeks)	As above	Population as above	As above but at 96 weeks, those patients on emtricitabine plus tenofovir DF were switched to the fixed-dose preparation (Truvada®) od	Emtricitabine/tenofovir od versus zidovudine/lamivudine bd: **144 weeks results:** % HIV-1 RNA <400 copies/mL for emtricitabine/tenofovir od versus zidovudine/lamivudine bd 71% versus 58%; 95% CI for difference 4% to 22%; p=0.004 % HIV-1 RNA <50 copies/mL: 64% versus 56%; p=0.08 (NS) Mean change from baseline in CD4 (cells/mm^3) 312 versus 271; p=0.09 (NS)

Table 1A. Continued

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Treatment regimen	Outcome
10 **Study 934E**	Ongoing single arm extension of study 934 in patients who completed 144 weeks of treatment and follow up 96 weeks follow up planned	Results based on 286 patients (160 from the Truvada® group and 126 from zidovudine/ lamivudine group)	As above	Population as above % HIV-RNA <400 copies/mL at start of Atripla® (144 weeks): 99% % HIV-RNA <50 copies/mL at start of Atripla® (144 weeks): 95%	All patients switched to Atripla®, taken on an empty stomach preferably at bedtime	**Interim results** **24 weeks from start of Atripla®:** % HIV-1 RNA <400 copies/mL: 97% (NS from start of Atripla®) Change in CD4 cell counts: -14 copies/mm^3 (p=0.03 compared with at start of Atripla®) **12 weeks from start of Atripla®:** % HIV-1 RNA <50 copies/mL: 91% (p=0.02 compared with at start of Atripla®)
10,11 **Study 073**	Ongoing phase IV, randomised, open-label study 48 weeks follow up planned	Randomised, n=300	Patients on stable HAART regimen (2 NRTIs + either a PI or NNRTI) for at least 3 months HIV-RNA <200 copies/mL and no history fo virological failure	Mean age: 43 yrs Male: 88% Black: 29% HIV-RNA <50 copies/mL: 96% Mean CD4 cell count: 541 cells/mm^3 (≤200: 9%) PI at baseline: 53% NNRTI at baseline: 47% [NB: none taking emtricitabine plus tenofovir DF plus efavirenz at baseline]	Switch to Atripla® od (n=203) versus Continue on current HAART regimen (n=97)	**Interim results at 24 weeks*:** Atripla® versus Current HAART: HIV-RNA <200 copies/mL: 93.1% versus 93.8%, 95% CI for difference -6.4% to 6.4% HIV-RNA <50 copies/mL: 93.1% versus 90.7%, 95% CI for difference -4.0% to 10.3%

†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 <400 copies/mL) and remained suppressed (no confirmed viral rebound measurements) by week 48 of the trial. Missing data or early discontinuation = failure; * Analysis conducted on missing data = failure basis, results similar when conducted on pure virological failure basis; ART=antiretroviral therapy; bd = twice daily; CI = confidence interval; mITT= modified intention to treat population who received at least one dose of study drug and were not found to be resistant to NNRTI; NNRTI = non-nucleoside reverse transcriptase inhibitor; NS = not statistically significant; NRTI = nucleoside reverse transcriptase inhibitor; od = once daily; PI = protease inhinitor.