All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Atazanavir (Reyataz®▼) for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-experienced patients

Bristol-Myers Squibb Pharmaceuticals Limited

Advice No: 2308 – December 2008

Recommendation of AWMSG

Atazanavir (Reyataz®▼) is 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 British HIV-1 Association (BHIVA) guidance.

Atazanavir (Reyataz®▼) is not suitable for shared care within NHS Wales.

Statement of use:
No part of this advice may be used without the whole of the advice being quoted in full.

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, 10th December 2008

The recommendation of AWMSG is:

Atazanavir (Reyataz®▼) is 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 British HIV-1 Association (BHIVA) guidance.

Atazanavir (Reyataz®▼) is not suitable for shared care within NHS Wales.

Additional notes:

- AWMSG advise that within the British HIV-1 Association (BHIVA) guidance, the choice of protease inhibitor (PI) should be influenced by the acquisition cost.
- AWMSG noted the potential for drug interactions which should be taken into consideration when prescribing.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Atazanavir (Reyataz®▼) is indicated for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products[1].

In antiretroviral treatment experienced patients, the demonstration of efficacy is based on a study comparing atazanavir 300mg once daily in combination with ritonavir 100mg once daily with lopinavir/ritonavir, each regimen in combination with tenofovir. Based on available virological and clinical data, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥4 PI mutations). The choice of atazanavir in treatment experienced patients should be based on individual viral resistance testing and the patient's treatment history[1].

2.2 Dosing

Atazanavir is available as oral capsules and as an oral powder. The recommended dose is 300mg once daily taken with ritonavir 100mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics. Therapy should be initiated by a physician experienced in the management of human immunodeficiency Virus (HIV) infection[1].

See the Summary of Product Characteristics (SPC) for full details[1].

2.3 Market authorisation date

Atazanavir was first licensed in March 2004[2].

2.4 UK Launch date

2004[2].

3.0 DECISION CONTEXT

The 2008 British HIV Association (BHIVA) guidelines[3] 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 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. In patients who experience first virological failure on this type of regimen, it is generally recommended that the regimen is switched to one including two different NRTIs plus a boosted protease inhibitor (PI); however, the choice of a new regimen should be guided by the results of current and previous resistance testing, treatment history and the ability of the patient to adhere to and tolerate individual drugs[3].

There are several PIs available. These include lopinavir (co-formulated with ritonavir, Kaletra®)[4], fosamprenavir (Telzir®▼)[5], saquinavir (Invirase®)[6], and atazanavir[1], which are licensed for use in treatment experienced and treatment naive patients. Darunavir (Prezista®▼)[7] and tipranavir (Aptivus®▼)[8] are licensed only for use in highly pre-treated patients who have failed on more than one PI-containing regimen. PIs differ in terms of their tolerability, convenience, drug interactions and lipid profiles[3]. The company submission reports that lopinavir and atazanavir are the most frequently prescribed PIs in Wales (referenced to data on file – not verified)[2].

Atazanavir was originally licensed only for treatment-experienced patients, but the license was extended in June 2008 to include treatment-naive patients[2]. Two separate submissions have been made by the company, and this report relates only to that covering the use of atazanavir in treatment-experienced patients.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main comparative efficacy data are derived from an open-label, randomised, phase III, non-inferiority trial (study AI424045) that compared atazanavir 300mg/ritonavir 100mg once daily against lopinavir 400mg/ritonavir 100mg twice daily. Patients were moderately pre-treated and had limited previous exposure to PIs. Over 48 weeks, atazanavir/ritonavir met the pre-defined criterion for non-inferiority in the primary endpoint of change from baseline in HIV ribonucleic acid (RNA) levels, and secondary endpoints of proportions of patients achieving HIV RNA <400 and <50 copies/mL, and changes CD4 count, were consistent, although numerically lopinavir/ritonavir was favoured. Results at 96 weeks were comparable. Exploratory *post hoc* analyses indicated that, in patients with viral strains harbouring more than four PI mutations, lopinavir/ritonavir was significantly superior to atazanavir/ritonavir. The European Public Assessment Report (EPAR) considers that, based on the virological and clinical data, no benefit is expected with atazanavir/ritonavir in patients with multi-PI resistant strains. Atazanavir/ritonavir had a more favourable lipid profile compared with lopinavir/ritonavir, which resulted in fewer patients requiring lipid-lowering therapy. It was also associated with less diarrhoea. Hyperbilirubinaemia was significantly more common with atazanavir/ritonavir, but was not considered to be associated with significant clinical consequences.

4.2 Review of the evidence on cost-effectiveness

A Markov-model based cost utility analysis is described, in which atazanavir/lopinavir is compared against lopinavir/ritonavir as per study AI424045. Progression through the health states of the model are based on differences in discontinuation-driven treatment switches, lipid profiles (and associated risks of cardiovascular disease [CVD]), and treatment compliance due to different dosing schedules (and associated risks of HIV-related mortality), rather than HIV RNA levels and CD4 counts. There are several uncertainties and limitations in the assumptions used in the model in relation to the risks of CVD, treatment compliance rates that are not informed by relevant trial data, and the probabilities of switching treatment. Collectively, these uncertainties in parameter inputs lead to significant uncertainty in the model outputs, as demonstrated by the confidence intervals (CIs) around the base case incremental cost and quality adjusted life year (QALY) point estimates.

In the base case analysis, the incremental cost per QALY gained for atazanavir/ritonavir compared with lopinavir/ritonavir is estimated to be £6,367. This is based on incremental costs of around £559 and a gain of 0.09 QALYs. Probabilistic sensitivity analysis estimates the 95% CI around the incremental costs to be -£23,900 to +£23,800, and for the incremental QALYs, the 95% CI was 0 to 0.15. On the basis of these data it is uncertain whether atazanavir/ritonavir may be associated with substantial extra costs, or substantial cost savings, and whether it may be associated with a gain in QALYs, or no gain, relative to lopinavir/ritonavir. This is reflected in the probabilistic sensitivity analysis which suggests that the probability of atazanavir being cost effective at a willingness to pay threshold of £20,000 is 56%, and at £30,000 is 58%.

5.0 LIMITATIONS OF DECISION CONTEXT

- There are no data presented on the clinical and cost effectiveness of atazanavir compared directly with PIs other than lopinavir/ritonavir.
- The approach taken to modelling in the company submission does not allow assessment of the cost effectiveness of atazanavir/ritonavir in important subgroups, such as patients with < or ≥ four PI mutations.

6.0 CLINICAL EVIDENCE

The main efficacy data in the company submission[2] is from an open-label, randomised, phase III, non-inferiority trial (study AI424045) of atazanavir 300mg/ritonavir 100mg once daily and atazanavir 300mg/saquinavir 1,200 mg once daily against lopinavir 400mg/ritonavir 100mg twice daily[9-12]. The atazanavir/saquinavir arm did not meet the criteria for non-inferiority for any endpoint at anytime point[10] and further details are not described here, as boosting of atazanavir with ritonavir is recommended[1]. The baseline characteristics and primary endpoint efficacy data are summarised in Table 1A in Appendix 1. Secondary endpoint data and results of exploratory analyses are presented in Table 2A in Appendix 1.

A further phase III trial in treatment-experienced patients (study AI424043) compared atazanavir 400mg once daily against ritonavir (100mg)-boosted lopinavir 400mg twice daily[10]. This study found lopinavir/ritonavir to be superior to atazanavir[10], but as atazanavir was unboosted, this study is not further discussed.

6.1 Clinical efficacy

Study AI424045 was an open-label, non-inferiority trial conducted in HIV-1 infected adults who were experiencing failure on their current HAART regimen and had experienced virological failure on two or more HAART regimens that cumulatively had included at least one drug from each of the classes NRTI, NNRTI and PI. All patients had baseline HIV RNA levels ≥1,000 copies/mL and CD4 cell counts ≥50 copies/mm^3. Patients with chronic hepatitis were eligible provided that their liver function enzymes (aspartate aminotransferase [AST] / alanine aminotransferase [ALT]) were less than three times the upper limit of normal.

Patients were randomised to atazanavir 300mg/ritonavir 100mg (n=120) once daily or lopinavir 400mg/ritonavir 100mg twice daily (n=123), all combined with tenofovir 300mg once daily plus a NRTI determined by baseline phenotypic testing. In the first two weeks following randomisation, only the PI or NNRTI component of the patient's current HAART regimen was replaced. After the two weeks, the baseline NRTI drugs were replaced with tenofovir and the additional NRTI determined by testing. The primary endpoint was the magnitude of the reduction in HIV RNA from baseline as assessed by time averaged difference (TAD) through 48 weeks. Non-inferiority was to be declared if the upper 97.5% CI limit for the TAD (atazanavir/ritonavir – lopinavir/ritonavir) was <0.5 $\log_{10}$ copies/mL[10]. Overall, the TAD was 0.13 (97.5% CI -0.12 to 0.39). The positive TAD favours lopinavir, but the CI indicated that atazanavir/ritonavor was non-inferior to lopinavir/ritonavir[10].

Secondary endpoints included the proportion of patients achieving HIV RNA viral load less than 400 and 50 copies/mL, and CD4 cell count changes. These were consistent with the primary endpoint finding, although several numerically favoured lopinavir (see Table 2A in Appendix 1). Exploratory *post hoc* analyses indicated that the number of baseline PI mutations was a predictor of response. In patients with fewer than four PI mutations, the TAD was 0.03 (95% CI -0.23 to 0.28), which suggests no significant difference between atazanavir and lopinavir. However, in those with four or more PI mutations at baseline, the TAD was 0.44 (95% CI 0.07 to 0.81) and the CI was wholly positive, favouring lopinavir[10].

Follow-up to 96 weeks indicated that the 48 week results were maintained[12] (see Table 2A in Appendix 1).

Points to note

- The median baseline HIV RNA of patients enrolled in study AI424045 was 4.45 $\log_{10}$ copies/mL, and the median CD4 cell count was 297cells/mm^3 (see Table 1A in Appendix 1). Only 25% had a viral load >5 $\log_{10}$ copies/mL and 30% had a CD4 count <200 copies/mm^3 [10]. 29% had experienced acquired immune deficiency syndrome (AIDS) defining events, but none had newly diagnosed HIV-related opportunistic infection. Around 17% of patients had evidence of chronic hepatitis B and/or C, but patients had good hepatic function.
- The EPAR considered that patients in study AI424045 were moderately pre-treated and had limited prior exposure to PIs (approximately 2.5 years)[9,10]. Only a limited number of patients had viruses with four or more PI mutations at baseline and approximately 40% of patients had viruses with <2 NRTI mutations[10].
- Some PI mutations are considered more critical than others for the emergence of resistance (protease gene mutations 10, 46, 54, 82, 84, and 90). There were too few patients with four or more of these more critical PI mutations to compare atazanavir and lopinavir, but the EPAR considers that reduced virological response may be anticipated among patients with four or more of these[10].
- Overall, 19% of patients discontinued treatment prior to 48 weeks. More discontinuations occurred in the atazanavir/ritonavir arm than the liponavir/ritonavir arm (22% versus 11%). This was mainly attributed to treatment failure or lack of efficacy (14% versus 5%)[2,10]. At week 96, 56% of patients randomised to atazanavir and 53% randomised to lopinavir remained on treatment[12].
- Study AI424045 randomised patients between November 2001 and August 2002[12]. New treatment options, including PIs and other classes of agent, have become available since that time.

6.2 Safety

The overall incidence of adverse events up to week 48 was comparable among treatment regimens, with over 80% of patients on each regimen reporting at least one adverse event[10]. Diarrhoea, infection, rash and peripheral neurological symptoms of any grade were more common in the lopinavir/ritonavir group, whereas jaundice, scleral icterus and headache were more common with atazanavir/ritonavir. Discontinuations due to adverse events occurred in 5% of patients on atazanavir/ritonavir and 4% on lopinavir/ritonavir[10].

Treatment-related grade 2 to 4 adverse events were experienced by 29% of patients treated with atazanavir/ritonavir and 25% of patients treated with lopinavir/ritonavir by week 48[11]. Jaundice occurred more frequently with atazanavir/ritonavir (6% versus 0%; p=0.01) and diarrhoea occurred more frequently with lopinavir/ritonavir (11% versus 3% with atazanavir/ritonavir; p=0.01)[11]. Forty-nine percent of patients in the atazanavir/ritonavir group experienced grade 3 or 4 elevations in bilirubin levels (9% grade 4) compared with <1% of patients in the lopinavir/ritonavir group. This led to dose reduction in 8% of patients receiving atazanavir/ritonavir at week 24 compared with none receiving lopinavir/ritonavir. However, there were no differences in the incidence of grade 3 or 4 elevations in hepatic enzymes (ALT/AST), and no discontinuations due to hepatic adverse events[10,11]. The EPAR states that chronic hyperbilirubinaemia does not appear to represent a safety concern for the use of atazanavir[10].

Lipid profiles were comparable at baseline for the atazanavir and lopinavir groups (mean total cholesterol 4.87 mmol/L and 4.69 mmol/L[2]), and the proportions of patients taking lipid-lowering agents at baseline were similar (5-6%). However, atazanavir/ritonavir was associated with a more favourable lipid profile over the course of the study than lopinavir/ritonavir. The reduction in low density lipoprotein (LDL)-cholesterol of 10% and reductions in high density lipoprotein (HDL)-cholesterol of 7% with atazanavir/ritonavir were numerically but not statistically significantly different to the gains of 1% and 2%, respectively, for lopinavir/ritonavir[11]. The changes from baseline to 48 weeks in total cholesterol (atazanaivir/ritonavir -8%; lopinavir/ritonavir +6%; $p \leq 0.005$) and fasting triglycerides (atazanaivir/ritonavir -4%; lopinavir/ritonavir +30%; $p \leq 0.005$) significantly favoured atazanaivir/ritonavir[11]. The proportion of patients with a total:HDL cholesterol ratio of <3 was reportedly the same (13%), but the proportion with a ratio >5 was reportedly lower with atazanavir/ritoavir (31% versus 45%)[2]. It should be noted that these figures include only observed data from subjects prior to any initiation of lipid-lowering agents; data from subjects initiating lipid-lowering therapy were censored upon initiation of such therapy. During the 48 weeks of the study, lipid-lowering therapy was used by more patients treated with lopinavir/ritonavir compared with atazanavir/ritonavir (19% versus 8%; $p<0.05$)[11]. Two percent of patients in the atazanavir group versus 14% of the lopinavir group initiated lipid-lowering therapy during the study[2]. Rates of lipodystrophy remained similar throughout[10,11].

Preclinical and clinical development studies have found atazanvir to have the potential to prolong the QT interval, although electrocardiogram (ECG) changes have been asymptomatic[10]. In study AI424045, minimal prolongations of QT and PR intervals were described and were comparable between treatment groups[10].

The 96 week follow up data are generally consistent with the 48 week data. No new adverse events emerged over the extended follow-up period[12].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

There are several licensed PIs available, as discussed in section 3.0. All are licensed for use in combination with low dose ritonavir as a pharmacokinetic booster, and all are licensed for use in treatment-experienced patients[1,4-8]. However, darunavir and tipranavir are only licensed for use in highly pre-treated patients[7,8]. The licensed indication for atazanavir states that no benefit is expected in patients with strains resistant to multiple PIs (≥4 PI mutations), and that the choice of atazanavir in treatment experienced patients should be based on individual viral resistance testing and the patient's treatment history[1]. The EPAR and SPC consider that patients in study AI424045, on which the licensed indication in treatment-experienced patients is based, were moderately pre-treated[1,10].

The company submission states that lopinavir and atazanavir are the most frequently prescribed PIs in Wales, based in market research[2]. Lopinavir/ritonavir would therefore be an appropriate comparator.

7.2 Comparative effectiveness

Table 1. Comparative table of ritonavir boosted PI profiles from 2008 BHIVA guidelines[3]

	Lopinavir	Saquinavir	Fosamprenavir	Atazanavir	Darunavir
Potency naives	++++	++++	++++	++++	++++
Durability data	++++	++	+++	++	++
Convenience	+++	++	+++	++++	+++
Tolerability	++	+++	++	+++	+++
Lipid profiles	+	++	+	+++	+++
Resistance barrier	++++	++++	++++	++++	++++
Interaction profile	+++	++	++	+	++
++++ Excellent; +++ very good; ++ moderately good; + not good; - poor					

- PIs differ in terms of their tolerability, convenience, drug interactions and lipid profiles. The 2008 BHIVA guidelines include a summary comparative table of ritonavir boosted PIs (excluding tipranavir) based mainly on data from treatment-naive patients (see Table 1)[3].
- In study AI424045, atazanavir/ritonavir was statistically non-inferior to lopinavir/ritonavir for the primary endpoint in the overall study population[11]. However, the EPAR notes that lopinavir/ritonavir was numerically superior for several secondary endpoints and considers that atazanavir/ritonavir is less potent than lopinavir/ritonavir[10].
- The results of the *post hoc* subgroup analysis in patients with viral strains harbouring more than four PI mutations were significantly in favour of lopinavir/ritonavir. Therefore, based on the virological and clinical data, no benefit is expected with atazanavir/ritonavir in patients with multi-PI resistant strains, and the EPAR states it is clear that atazanavir/ritonavir is not appropriate for salvage therapy[10].

- Following failure of an atazanavir-containing regimen in treatment-naive patients, a unique I50L mutation was seen. There was no evidence of cross-resistance between atazanavir and amprenavir, with the presence of the I50L and I50V substitutions yielding selective resistance to atazanavir and amprenavir, respectively[1].
- All PIs should be boosted with ritonavir[3]. Ritonavir capsules require storage at 2-8°C and must be taken alongside PIs except in the case of lopinavir/ritonavir (Kaletra®), which is the only co-formulated product available and does not require refridgeration[3,4]. The SPC-recommended dose of lopinavir/ritonavir is 400/100mg twice daily, which requires two Kaletra® 200/50mg tablets to be taken twice a day[4]. Of the available PIs, only atazanavir is specifically licensed for once daily administration[1]. Atazanavir may therefore be more convenient to patients in terms of their daily pill-taking burden.
- The lipid profile of atazanavir is more favourable than lopinavir and some other PIs[3]. In study AI424045, changes in total cholesterol and triglycerides significantly favoured atazanavir, although the proportion with a ratio of total:HDL cholesterol <3 at 48 weeks was reportedly the same[2]. The proportion of patients initiating lipid lowering therapy was higher in the lopinavir/ritonavir group than in the atazanavir/ritonavir group (14% versus 2% respectively), and any reduced need for lipid-lowering therapy may potentially impact on polypharmacy issues and CVD. However, hard outcomes data are lacking, and even treatment-naive patients with HIV appear to be at elevated risk of CVD[3].
- The main observed adverse event with atazanavir appears to be hyperbilirubinaemia, although the EPAR notes there are no specific safety concerns in this regard[10]. In study AI424045, lopinavir/ritonavir was associated with a greater incidence of diarrhoea. Overall discontinuations due to adverse events were similar (5% of patients on atazanavir/ritonavir and 4% on lopinavir/ritonavir)[10].
- Atazanavir and ritonavir are inhibitors of CYP3A4 and atazanavir is contraindicated with drugs that are substrates of this enzyme. The drug-interaction proflile of atazanavir is considered less favourable than that of other PIs[3] and the SPC should be consulted for full details of potential drug interactions.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by atazanavir (Reyataz®▼) over the relevant comparator(s) in treatment-experienced HIV-1 infected patients justify the additional costs and, if so, whether the total budgetary impact of supporting the use of atazanavir (Reyataz®▼) is acceptable.

8.2 Description and critique of the company's submission

A Markov model-based cost utility analysis of atazanavir/ritonavir compared against lopinavir/ritonavir in treatment-experienced patients, as per study AI424045, is described. It is assumed that patients failing on the atazanavir or lopinavir regimen are switched to a second regimen of darunavir 300mg/ritonavir 100mg twice daily plus tenofovir/emtricitabine once daily. Following failure of the second regimen, patients are assumed to be switched to a third regimen of darunavir 300mg/ritonavir 100mg plus raltegravir 400mg and enfuvirtide 90mg, all given twice daily, on which they remain until death due to HIV/AIDS, CVD or any other causes.

In the analysis it is assumed that the rates of virological suppression and immune reconstitution are the same with atazanavir and lopinavir, based on the results from the whole population of study AI424045. Therefore, contrary to several other economic models of HIV treatments, HIV RNA levels and CD4 counts are not specifically used to define progression through health states. The focus of the analysis is the differences in discontinuation-driven treatment switches (due to adverse events, poor compliance, lack of efficacy), lipid profiles (and associated risks of CVD), treatment compliance due to different dosing schedules (and associated risks of HIV-related mortality), and the incidence of diarrhoea as observed in study AI424045[2].

There are a number of assumptions employed in the model, which introduce a significant degree of uncertainty and may act to bias the model in favour of atazanavir. The probabilities of treatment switching are apparently based on a graph of treatment discontinuations in study AI424045; however, it is not clear what causes of treatment discontinuations are included in the data and the model is very sensitive to this parameter. CV risk and mortality are driven in large by observed differences in lipid profile. The lipid data from subjects initiating lipid-lowering therapy in study AI424045 were censored and it is not clear that the risk equations employed and the model account for the availability and use of lipid-lowering agents. Despite this, the costs of statin treatment are included.

Treatment compliance is modelled and is the driver of HIV-related mortality in the model. Importantly, compliance rates used in the model are not informed by the atazanavir/lopinavir trial data and it is implicitly assumed that the once daily dosing regimen for atazanavir will lead to a mortality benefit compared with twice daily dosing of lopinavir.

Other uncertainties include the application of utility values for a general state of HIV and the way in which utility values associated with CV events are applied over time. Collectively, these uncertainties in parameter inputs lead to significant uncertainty in the model outputs, as demonstrated by the CIs around the base case incremental cost and QALY point estimates. The model has been provided to the Welsh Medicines Partnership (WMP).

8.3 Population

The baseline characteristics of patients in the atazanavir/ritonavir and the lopinavir/ritonavir arms of study AI424045 (see Table 1 in Appendix 1A) are used to define the modelled population. These patients were moderately treatment-experienced and had a median of two PI and three NRTI mutations at baseline.

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. A lifetime horizon has been used in the base case analysis[2], which would appear appropriate. A one year cycle length is used, and a half cycle correction has been applied[2].

8.5 Comparator

Lopinavir/ritonavir would appear to be an appropriate comparator for the analysis, as discussed in section 7.1.

8.6 Clinical inputs

8.6.1 Efficacy data

It is assumed that atazanavir and lopinavir are equally effective in terms of virological and immunological response. The model focuses on differences in discontinuation-driven treatment switches (due to adverse events, poor compliance, lack of efficacy), lipid profiles (and associated risks of CVD), treatment compliance due to different dosing schedules (and associated risks of HIV-related mortality), and the incidence of diarrhoea[2]. The model therefore does not account for any differences in utility that might arise from changes in treatment response, CD4 count and HIV/AIDS status over time, and associated morbidity arising from opportunistic infections, etc.

8.6.1.1 Probability of treatment switching

The annual probability of switching from atazanavir or lopinavir in the first and subsequent years is calculated from patients in study AI424045 who discontinued treatment due to adverse events, poor compliance or lack of efficacy. The probability in the first year is reportedly based on 52 week data and is stated to be 27.8% for atazanavir, and 27.3% for lopinavir[2]. The company submission references this to a graph of time on initial therapy for treated patients. It is noteworthy that study AI424045 was originally designed as a 48 week study[9,11].

For subsequent years, the probabilities of switching from atazanivir or lopinavir treatment are assumed to be 26.87% and 29.02% respectively, reportedly based on 96 week data[2]. This is referenced to the same graph. The extent to which discontinuation in the second 48 week period of study AI424045 accurately reflects discontinuations in subsequent years is uncertain (the model predicts that patients remain on first-line atazanavir/ritonavir for 3.54 years versus 3.38 years for lopinavir/ritonavir). A one-way sensitivity analysis has been conducted in which the probabilities of switching treatment with lopinavir/ritonavir are set equal to those for atazanavir/ritonavir[2]. This analysis indicates that these probabilities are influential parameters in the model.

The annual probability of switching from the second line to third line regimen is reported to be based on 48 week data from the TITAN trial of darunavir[15]. Switching from the third-line regimen is not possible[2].

8.6.1.2 CVD risk and mortality

Framingham risk equations[16] have been used to estimate the age and gender-related annual probability of experiencing myocardial infarction (MI), stroke and angina, given the baseline and 96 week total and HDL-cholesterol levels observed in patients in study AI424045[12]. As a risk equation for angina is not available, the probability of angina was estimated by subtracting the probability of MI from the probability of all primary coronary heart disease (CHD)[2]. Due to a lack of data, it was assumed that second- and third-line regimens (based on darunavir/ritonavir) have the same lipid profile as lopinavir/ritonavir. The company submission considers this to be conservative on the basis that the TITAN study found that darunavir/ritonavir increased total cholesterol more than lopinavir/ritonavir[15]. It should be noted that the lipid data for atazanavir/ritonavir and lopinavir/ritonavir include only observed data from subjects prior to any initiation of lipid-lowering agents; data from subjects initiating lipid-lowering therapy were censored upon initiation of such therapy[12]. In using these lipid data, the model excludes any potential impact of statin therapy, and despite this, the costs of statin therapy are included in the model. Although the costs of statin therapy are small relative to the costs of antiviral agents, this approach would appear to bias the base case analysis in favour of atazanavir (see section 8.7.1). A supplementary sensitivity analysis provided by the company, in which the costs of statins were removed and the CV risk for atazanavir and lopinavir were set equal, suggests this has little impact on the model outputs.

It appears from the model that important CV risk factors such as smoking, diabetes, etc. have not been incorporated into the risk equations for patients from study AI424045. CV risk equations and charts rely on a range of risk factors to determine overall risk, and the initiation of lipid-lowering agents and other agents to manage that risk would depend on a range of factors. The baseline CV risk of patients in study AI424045 is not clear, although the company reports that there was no difference between groups. It should be considered that this was an open-label trial, and any preconceived idea that atazanavir may have a more favourable lipid profile may have contributed to the different rates of initiation of lipid-lowering therapy. However, one way sensitivity analysis indicates that, when lipid profiles are assumed to be the same, this is little impact on the model outputs. The model only permits one CV event during the patient's lifetime. Therefore, there would appear to be some uncertainty in the predicted probabilities of CVD events.

An analysis of the original Framingham Heart Study Cohort data that predicted subsequent life expectancy following CV events[17] has been used to estimate the relative reduction in life expectancy following the CV events MI, stroke and angina. In the absence of specific life expectancy estimate given a history of angina, life expectancy related to CHD has been used instead. Relative risks of death have been assumed to be half of those estimated in the cohort study to account for the different patient types, and these assumed relative risks have been applied to normal life expectancy estimates from Welsh life tables[2]. There would appear to some areas of uncertainty in the relative risks of death assumed in the base case model that are potentially compounded by the potential uncertainty in the CVD risk equations above. Supplementary sensitivity analyses provided by the company, in which the relative risks of death are half, or double, those assumed in the base case analysis, indicate that the model is relatively insensitive to the relative risk of death [Personal communication, BMS Pharmaceuticals Ltd, October 2008].

8.6.1.3 Treatment compliance and HIV-related mortality

The analysis assumes that compliance with treatment regimen has an impact on HIV-related mortality. A meta-analysis of studies across several therapeutic areas that used electronic monitoring devices to assess adherence found that mean compliance was 79% for patients taking once daily dosages versus 68% for patients taking twice daily dosages[18]. These rates are assumed to apply to patients taking atazanavir/ritonavir (administered once daily) and lopinavir/ritonvir (administered twice daily according to the SPC[4] and in study AI424045[11])[2]. However, it should be noted that the range of compliance rates on which the mean estimates were based was 35-97% across the 29 studies providing once daily administration compliance rates and was 38-90% across the 32 studies providing twice daily administration compliance rates. There was no statistically significant difference in compliance rates between once daily and twice daily dosing regimens, and across all studies that considered dose frequencies between once daily and four times daily, the mean treatment compliance was 71% (range 34-97%)[18]. The use of these data are therefore of questionable relevance.

Full compliance has been assumed to involve 95% or more of prescribed doses being taken as intended[2] on the basis of an observational study that found significantly better outcomes for patients taking 95% or more of their PI doses correctly, compared with those taking fewer[19]. It has then simply been assumed that half of non-fully adherent patients are partially adherent and take 75% of their doses correctly, and the remainder take 35% of their doses. These assumptions have been applied to the assumed atazanavir/ritonavir and lopinavir/ritonavir compliance rates above.

On the basis of a prospective observational study that examined the effect of medication adherence on survival over a median of 40.1 months in HIV patients, a mortality rate of 1.22% is assumed for patients who are fully (95%) compliant with their treatment regimen[20]. A 10% reduction in adherence is assumed to lead to a 16% increase in mortality on the basis of a prospective study that measured adherence to antiretroviral therapy issued in a population based programme between 1996-98[21]. This was calculated by dividing the number of months of documented prescriptions dispensed by the number of months of follow-up in the first year. Therefore, for full (95%), partial (75%) and non (35%) compliance, annual mortality rates of 1.22%, 1.61% and 2.49% have been assumed, respectively[2]. A weighted average of these has then been estimated based on the assumed compliance rates with atazanavir/ritonavir and lopinavir/ritonavir.

There are several uncertainties and limitations to this approach, which collectively may bias the model in favour of atazanavir. Compliance rates assumed in the model are not informed by the trial data for atazanavir and lopinavir. HIV-mortality has been tested in one-way sensitivity analysis and indicates that atazanavir dominates lopinavir when HIV-mortality is set equal (see section 8.10.1). Compliance and associated risks of mortality are included in the probabilistic sensitivity analysis.

8.6.2 Adverse events

The only adverse event (besides lipid effects) considered in the analysis is diarrhoea, which is considered in terms of patient quality of life. Incidence rates for grade 2 to 4 diarrhoea observed in study AI424045 through 96 weeks are used for atazanavir and lopinavir[12]. For the second and third line darunavir-based regimens, the rate of diarrhoea observed in the TITAN study[15], adjusted for the difference observed in the lopinavir arms of this and study AI424045, are used[2].

8.6.3 Utility weights

Utility values for states of HIV, diarrhoea, MI, angina, and stroke are reportedly derived from the literature. For a general state of having HIV infection, the baseline utility value (0.85) of patients in a 24 weeks study of atazanavir and lopinavir (study AI424043) has been used[22]. The extent to which this general HIV state utility value adequately reflects HIV status over the course of the patient's lifetime is uncertain. For diarrhoea, a utility value for "moderate" severity is assumed, which has been estimated as the mean average of utility values for patients with low or high impact diarrhoea in a cost effectiveness analysis of chemotherapy in patients with prostate cancer (0.82)[23]. For MI, a utility value of 0.91 is assumed, based on the mean average of four values reported in the literature (range 0.88 to 0.9329). The utility value for angina is assumed to be the same as for MI[2]. For stroke, a utility value of 0.66 is assumed, based on the mean average of values for major and minor stroke reported in the literature (range 0.35 to 0.91). Supplementary one way sensitivity analysis within these ranges of utility values for MI and stroke indicated the actual values had little impact on the model outputs.

The model employs a one cycle tunnel state for patients experiencing CV events to account for differences in costs over time. Disutilities associated with MI, angina and stroke, however, are assumed to apply for the remaining lifetime following a CV event. This would be associated with some uncertainty, which would act to favour the treatment that is modelled as having the lowest rate of CV events (i.e. atazanavir).

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

Drug costs in the model relate to antiviral costs (atazanavir/ritonavir and lopinavir/ritonavir for the first-line regimen, and darunavir and other antiviral costs for second- and third-line regimens), and lipid lowering agents, which are assumed to be statins. The antiviral drugs included in the second- and third-line treatment regimens are reported to have been informed by clinical experts[2]. The second-line regimen is assumed to consist of darunavir/ritonavir plus tenofovir/emtricitabine (Truvada®). The third-line regimen is assumed to consist of darunavir/ritonavir plus enfuvirtide plus raltegravir[2]. These are high cost drugs and their costs significantly impact on the model outputs (see sections 8.9.1 and 8.10.1).

Unit costs are based on British National Formulary (BNF) prices[26], with a weighted average cost of atorvastatin (74.5%), pravastatin (20.9%) and fluvastatin (4.6%) assumed for lipid lowering costs based on 2007 Prescription Cost Analysis (PCA) data. PCA data relate to all prescriptions dispensed in the community setting and it is unclear how the general prescribing pattern of these statins in the community setting relate to that in the management of patients with HIV, given that the SPC for atazanavir indicates that atorvastatin should be used with caution[1], and that the SPC for lopinavir/ritonavir states that if a statin is required, pravastatin or fluvastatin are recommended[4]. Lipid-lowering agents were used by 20% of patients taking lopinavir/ritonavir and 9% of patients taking atazanavir/ritonavir over the 96 weeks of study AI424045[12]. The cost of statins is small relative to the costs of antiviral therapy.

8.7.2 Adverse event costs

No adverse event costs for diarrhoea are included on the basis that they are negligible[2].

8.7.3 Other resource use and costs

The costs of CV events are considered in terms of shorter term event costs and longer term follow-up costs. The model employs a one-cycle tunnel state for patients experiencing CV events to account for these differences in costs over time. The event costs for MI and angina are based on 2005-6 NHS reference costs for NHS trusts in England[27], which are assumed to apply for one year in addition to the follow-up costs[2]. The follow-up costs are accrued thereafter, and are reportedly based on estimates used in previous studies of the costs of angina treatment[28] and MI[29], although it is not immediately clear which items of resource from these studies have been included. Stroke event and follow-up costs are based on a Health Technology Assessment of secondary prevention of occlusive vascular events with clopidogrel and dipyridamole[30], although it is not immediately clear which items of resource from this study have been included in the current model. All costs are inflated to 2008 values[2]. The costs of HIV death have been assumed to be £4,000[2].

8.8 Discounting

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

8.9 Results

8.9.1 Base-case analysis

In the mixed population that is modelled, the incremental cost per QALY gained for atazanavir/ritonavir compared with lopinavir/ritonavir is estimated to be £6,367. This is based on incremental costs of around £559 and a gain of 0.09 QALYs. Drug costs represent the majority of the total costs and CV events make up a small proportion. There is considerable uncertainty in the cost estimates, and hence the overall cost per QALY gained, as discussed in section 8.10.2.

8.10 Sensitivity analysis

8.10.1 One way sensitivity analyses

Several one-way sensitivity and scenario analyses have been conducted. However, these are rather selective.

The model appears very sensitive to the probabilities of treatment failure for atazanavir/ritonavir and lopinavir/ritonavir. When treatment failure of lopinavir/ritonavir is set equal to that for atazanavir/ritonavir, the incremental cost per QALY/gained increases to £26,880. This is an important finding as there appears to be some uncertainty in the probabilities assumed in the base case analysis around treatment switches, which incorporates treatment failure alongside discontinuations due to adverse events and poor compliance. The costs assumed for the second- and third-line treatment regimens are also significant drivers of the model outputs, with the incremental cost effectiveness ratio (ICER) increasing to £19,296 when the costs are assumed to be the same as for first-line lopinavir/ritonavir. This is an important consideration as treatment regimens need to be individually tailored to patients' treatment histories and resistance profiles[3].

When HIV mortality is set equal for atazanavir/ritonavir and lopinavir/ritonavir, the model predicts that atazanavir dominates (i.e. is less expensive and more effective than) lopinavir[2]. An analysis in which treatment failure that leads to treatment switching is based on virological failure defined as HIV RNA>50 copies/mL, atazanavir dominates lopinavir[2]. However, the 48 week and 96 week secondary endpoint data from study AI424045 indicate that there was no significant difference in the proportions of patients achieving HIV RNA levels <50 copies/mL and lopinavir/ritonavir was numerically superior (see Table 2A in Appendix 1)[11,12]. Also, the extent to which virological failure defined as a HIV RNA level of 50 copies/mL would result in treatment switches in practice would depend on several factors. The BHIVA guidelines indicate that, for practical reasons, many clinicians would accept a persistent (two values at least one month apart) viral load level of >400 copies/ml for consideration of a treatment switch, whilst others would consider a switch at sustained rebound between <50 and 400 copies/ml, if resistance is detected[3].

8.10.2 Probabilistic sensitivity analysis (PSA)

Distributions were fitted to key parameters within the model. Where distribution parameters were unavailable from the sources used to provide the base case analysis, these have been assumed. A sample of 1,000 patients has been simulated to generate a cost effectiveness acceptability curve. This indicates that the probability of atazanavir being cost effective at a willingness to pay threshold of £20,000 is 56%, and at £30,000 is 58%.

The 95% CI generated around the base case point estimate for incremental costs is -£23,900 to +£23,800, and for the incremental QALYs, the 95% CI was 0 to 0.15[2]. This indicates the significant uncertainty that exists in the point estimates in the base case analysis. On the basis of these data it is uncertain whether atazanavir/ritonavir may be associated with substantial extra costs, or substantial cost savings, and whether it may be associated with a gain in QALYs, or no gain, relative to lopinavir/ritonavir.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have identified two published papers on the cost effectiveness of lopinavir/ritonavir and atazanavir/ritonavir in treatment-experienced patients[31,32]. One was conducted in the USA[31] and one conducted using data from four European countries, including the UK[32]. Both were funded by Abbott, manufacturers of lopinavir/ritonavir, and used a Markov model that was developed using a combination of viral load and CD4 count as surrogate markers to define health states, in contrast to the model presented in the company submission. This leads to there being important differences in the approach to modeling survival and quality of life. Another important difference is that treatment switches in these studies were dependent only on virological failure, and did not include adverse events and compliance. There was no assumption of the treatment compliance on HIV mortality. Both studies concluded that lopinavir/ritonavir was associated with significant cost savings over 5-10 years and appears to be a highly cost-effective regimen relative to atazanavir/ritonavir over the lifetime horizon[31,32]. The UK analysis estimated a lifetime incremental cost per QALY gained of £3,034 for lopinavir/ritonavir compared with atazanavi/ritonavir, based on 2006 prices[32]. The long-term CHD risk associated with lopinavir/ritonavir was minimal compared with the increased risk of AIDS/death and costs projected for atazanavir.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The prevalence of HIV in Wales is taken from the Survey of Prevalent HIV Infections Diagnosed (SOPHID) and is combined with Welsh population statistic and Health Protection Agency (HPA) data to derive HIV patient numbers. Company market research data are used to estimate current prescribing patterns and are combined with the company's projections for atazanavir uptake, which is expected to increase by taking some of the market share of lipinavir/ritonavir. Based on study AI424045 data it is assumed that the use of atazanavir instead of lopinavir/ritonavir will result in cost savings in relation to antidiarrhoeal agents and the treatment of dyslipidaemia, which will offset some of the increase in costs due to greater uptake of atazanavir. However, the cost savings estimated by the company are uncertain.

The budget impact analysis assumes that there will be no increase in the prevalence or incidence of diagnosed HIV over the next five years, which would seem contrary to current trends that indicate an increase. Coupled with the assumptions around cost savings, the overall estimated budget impact would appear subject to some uncertainty.

9.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over a five year period[2].

9.3 Data sources

9.3.1 Incident and prevalent cases

SOPHID data for 2006 indicate a prevalence of HIV of 0.03% in Wales[33]. This prevalence has been applied to Welsh Government population estimates[34] to determine the number of patients with HIV in Wales in each year 2008-12. Incidence (5.1 per 100,000) and annual HIV mortality (0.95%) data are based on HPA data[35]. On the assumption that prevalence, incidence and mortality rates remain constant, the net number of patients with HIV in 2008 is estimated by the company to be 1,042 in 2008, rising to 1,062 in 2012 due to the projected increase in population size[2]. However, recent data indicate an increase in prevalence (between 2002 and 2006, the number of patients receiving treatment for HIV in Wales almost doubled[33]). The number of patients with HIV over the next five years may therefore have been underestimated by the company.

On the basis of market research, the company submission estimates that 77% of patients with HIV receive antiretrovirals in 2008 (not verifiable). The company submission assumes that this proportion will increase to 82% in 2012. Therefore, the number of patients receiving antiretrovirals has been estimated as 802 in 2008, rising to 871 in 2012[2].

9.3.2 Projected rate of adoption and market share

Based on market research, the company submission states that 14.7% of patients receiving antiretrovirals in 2007 received lopinavir/ritonavir, and 10% received atazanavir/ritonavir (not verifiable). It is assumed that atazanavir market share will increase by 2% each year by displacing lopinavir/ritonavir such that atazanavir will be received by 12% of patients in 2008, rising to 20% in 2012. This would amount to 96 patients receiving atazanavir in 2008, rising to 174 patients in 2012. The market share of all other agents are assumed to remain unchanged over time.

9.3.3 Costs and resource use

The PI costs are based on BNF listed prices[26] for the usual recommended doses. It is assumed that patients would receive the same backbone of Truvada® and so this cost is not included in the analysis[2].

It is assumed that the use of atazanavir/ritonavir instead of lopinavir/ritonavir would result in reduced costs associated with the treatment of diarrhoea and dyslipidaemia, as in the economic model. It is assumed that loperamide would be the antidiarrhoeal agent used, that 80% of these patients would receive it on NHS prescription and that it would be taken every day (at a dose of three capsules a day, based on the non-proprietary make). These costs are offset against the costs of atazanavir/ritonavir.

It is also assumed that the more favourable lipid profile observed for atazanavir/ritonavir in study AI424045 (see section 6.2) would result in lower costs associated with the management of dyslipidaemia. Based on the 48 week data from study AI424045, 8% of patients taking atazanavir/ritonavir used lipid-lowering agents compared with 19% of patients taking lopinavir/ritonavir[11]. These patients are assumed to receive statin therapy. As in the economic model, a weighted average cost of atorvastatin, pravastatin and fluvastatin is assumed, which may be subject to some uncertainty (see section 8.7.1). In addition, in the budget impact analysis, it is assumed that management of hyperlipidaemia would require three specialist visits per year at a total cost of £945[2]. No justification is provided for these specialist visit costs, and they appear not to have been included in the economic analysis. Their inclusion in the budget impact analysis would therefore introduce a degree of uncertainty and may bias the analysis against lopinavir/ritonavir.

The overall costs that are offset against atazanavir/ritonavir treatment amount to around £15,000 per year and would appear to be uncertain.

9.4 Results

Disregarding any cost offset due to reduced costs of the management of diarrhoea and dyslipidaemia, the company submission estimates the net budget impact of the increased use of atazanavir/ritonavir to be £8,198 in 2008, rising to £44,515 in 2012.

When the assumptions of offset costs are included, the net budget impact of the increased use of atazanavir/ritonavir is estimated as £6,121 in 2008, rising to £33,234 in 2012.

9.5 Sensitivity analysis

No sensitivity analysis was conducted for the budget impact analysis.

9.6 Comparator costs

Selected ritonavir-boosted PI costs are listed in Table 2, based on usual doses recommended in the BNF[26] over 28 days.

Table 2. 28-day costs of selected ritonavir-boosted PIs

PI	Example dose	28-day cost[26]
Atazanavir	Atazanavir 300mg / ritonavir 100mg od	£326
Lopinavir/ritonavir	Lopinavir 400mg / ritonavir 100mg (as Kaletra®) bd	£287
Fosamprenavir	Fosamprenavir 700mg ritonavir 100mg bd	£320
Saquinavir	Saquinavir 1000mg / ritonavir 100mg bd	£312
Darunavir	Darunavir 600mg / ritonavir 100mg bd	£480
Tipranavir	Tipranavir 500mg / ritonavir 100mg bd	£520
od= once daily, bd = twice daily		

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-related treatment or care[33].
- Atazanavir if endorsed for use within NHS Wales would need to be initiated by specialists and would not currently be deemed suitable for shared care.

10.2 Related advice

- Efavirenz / emtricitabine / tenofovir disoproxil (as fumarate) (Atripla®) for the treatment of HIV-1 infection in adults is scheduled for appraisal by AWMSG on 25th February 2009.

10.3 Previous AWMSG advice

- Enfuvirtide (Fuzeon®▼) – recommended for use within NHS Wales for the treatment of patients with HIV-1, with restrictions; May 2004[36].
- 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[37].
- 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[38].
- Darunavir (Prezista®▼) – recommended for use within NHS Wales 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[39].
- Tipranavir (Aptivus®▼) – recommended for use within NHS Wales 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[40].
- 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[41].
- 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[42].

10.4 Ongoing studies

- The results of a phase IIIB, open-label, randomised, multicentre study evaluating the effect on lipohypertrophy following a switch to atazanavir in treatment-experienced HIV patients (the REAL trial) may be reported in the next 12 months[2].

10.5 Patient organisation information

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

GLOSSARY

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

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. Prospective study of atazanavir in treatment-experienced patients with HIV-1 – Primary endpoint

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes
48 week study results						
9-11 Study AI424045	Randomised, open-label, phase III, multinational, non-inferiority trial South American: 46% North American: 35% European 19%	358 patients randomised	HIV-1 patients ≥16yrs Virological failure on ≥2 HAART regimens that included ≥ of each of a PI, NNRTI and NRTI; Currently failing HAART regimen with HIV RNA ≥1,000 copies/mL and CD4 cell count ≥50cells/mm^3; serum creatinine <1.5 x ULN; AST, ALT <3 x ULN; serum bilirubin <1.5 x ULN	Age†: 40 years Males: 78% White:Hispanic:Black= 60% : 22% : 15% HIV RNA†: 4.45 $\log_{10}$ copies/mL CD4†: 297 cells/mm^3 AIDS: 28% Hepatitis B/C: 17% Prior exposure: PI 2.5 years NNRTI 1.5 years NRTI 5.1 years Mutations†: PI 2, NRTI 3	**ATV/r od** (n=120) or ATV/SQV od (n=115) versus **LOP/r bd** (n=123) Each in combination with tenofovir 300mg od and one NRTI based on phenotypic testing	**Primary endpoint:** Overall TAD in reduction in HIV RNA from baseline at 48 weeks: Positive TAD favours LOP/r Non-inferiority declared if upper limit of CI <0.5 **ATV/r od – LOP/r bd** **0.13 (97.5% CI -0.12 to 0.39)*** **Non-inferiority criterion met** ATV/SQV od – LOP/r bd 0.33 (97.5% CI 0.07 to 0.60)* Non-inferiority criterion not met
96 week study results						
12	Extended follow-up to 96 weeks of study				**ATV/r od** Versus **LOP/r**	**Primary endpoint:** Overall TAD in reduction in HIV RNA from baseline at 96 weeks: **ATV/r od – LOP/r bd** **0.14 (97.5% CI -0.13to 0.42)** **Non-inferiority criterion met**

ATV/r od = Atazanavir 300mg/ritonavir 100mg once daily; ATV/SQV = Atazanavir 400mg/saquinavir 1200 once daily; CI = confidence interval; HAART = highly active antiretroviral treatment; LOP/r = Lopinavir 400mg/ritonavir 100mg twice daily; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; TAD = time averaged difference; ULN = upper limit of normal; * = Response based on minimum of two sequential HIV RNA measurements maintained through Week 48 without intervening replicated rebounds, newly diagnosed AIDS events, or treatment discontinuations, based on all randomised subjects; † = median

Table 2A. Secondary and exploratory endpoints for atazanavir/ritonavir versus lopinavir/ritonavir

Ref	Endpoint	Results (ATV/r versus LOP/r)	
Secondary endpoints:			
		48 weeks[10,11]	**96 weeks[12]**
10,11	Overall mean change in HIV RNA (log_{10} copies/mL)	-1.93 versus -1.87	-2.29 versus -2.08
	% with mean HIV RNA <400 copies/mL	53% versus 54%; HR 1.09 (95% CI 0.76 to 1.57)	43% versus 43% Difference 0.2 (95% CI -12.2 to 12.7)
	% with mean HIV RNA <50 copies/mL	36% versus 42%; HR 1.24 (95% CI 0.91 to 1.70)	32% versus 33% Difference -1.7 (-13.4 to 10.1)
	Change in CD4 cell count (cells/mm^3)	+110 versus +121 (means)	+160 versus +142 (medians)
	Overall TAD in CD4 cell count from baseline	-17.5 (95% CI -45.6 to 10.6) Negative TAD favours LPV/r; Non-inferiority criterion met	-
Post-hoc exploratory analyses:			
10-12	Mean change in HIV RNA (log_{10} copies/mL):		
	< 4 PI mutations at baseline:	-2.13 versus -2.10	
	≥ 4 PI mutations at baseline:	-1.38 versus -1.37	
	TAD in reduction in HIV RNA from baseline at 48 weeks (positive TAD favours LOP/r):		
	Sensitive to randomised PI at baseline:	0.03 (95% CI -0.21 to 0.26)	-
	Resistant to randomised PI at baseline:	0.45 (95% CI 0.03 to 0.86)	-
	< 4 PI mutations at baseline:	0.03 (95% CI -0.23 to 0.28)	0.04 (97.5% CI -0.23 to 0.31)
	≥ 4 PI mutations at baseline:	0.44 (95% CI 0.07 to 0.81)	0.44 (97.5% CI 0.06 to 0.83)

ATV/r od = Atazanavir 300mg/ritonavir 100mg once daily; CI = confidence interval; HR = hazard ratio; LOP/r = Lopinavir 400mg/ritonavir 100mg twice daily; PI = protease inhibitor; TAD = time averaged difference