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-naive patients

Bristol-Myers Squibb Pharmaceuticals Limited

Advice No: 2408 – 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-naive patients, in accordance with British HIV 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-naive 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 for treatment-experienced patients. A license extension for use in treatment-naive patients was granted in June 2008[2].

2.4 UK Launch date

Atazanavir was first launched in 2004.

3.0 DECISION CONTEXT

The 2008 British HIV Association (BHIVA) guidelines emphasise that highly active antiretroviral treatment (HAART) regimens must be individualised for patients with HIV-1 in order to achieve the maximum potency, durability, adherence and tolerability, and to avoid long term toxicities and any likely drug interactions[3]. 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 generally 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). First-line use of boosted PIs should usually be reserved for specific groups of patients, such as those with primary NRTI and/or NNRTI resistance, women who wish to become pregnant, and in some patients with psychiatric problems[3]. However, the choice of any regimen should be guided by the results of resistance testing, and other factors such as the ability of the patient to adhere to and tolerate individual drugs[3].

There are several PIs available and they differ in terms of their tolerability, convenience, drug interactions and lipid profiles[3]. Those that are licensed for use in both treatment-experienced and treatment-naive patients include lopinavir (co-formulated with ritonavir, Kaletra®)[4], fosamprenavir (Telzir®▼)[5], saquinavir (Invirase®)[6], and atazanavir[1]. 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. 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-naive patients.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main comparative efficacy data in treatment-naive patients are derived from an open-label, randomised, phase IIIb, non-inferiority trial (CASTLE) that compared atazanavir 300mg/ritonavir 100mg once daily against lopinavir 400mg/ritonavir 100mg twice daily. Over 48 weeks, atazanavir/ritonavir met the pre-defined criterion for non-inferiority in the primary endpoint of proportion of patients with HIV ribonucleic acid (RNA) of less than 50 copies/mL. Secondary endpoints of proportions of patients achieving HIV RNA less than 400 copies/mL, and changes in CD4 count, were consistent with this finding although increases in CD4 cell counts were numerically greater with lopinavir/ritonavir. Atazanavir/ritonavir had a less negative lipid profile compared with lopinavir/ritonavir, which resulted in fewer patients requiring initiation of lipid-lowering therapy. Atazanavir/ritonavir was also associated with less diarrhoea. Hyperbilirubinaemia was significantly more common with atazanavir/ritonavir, but appears not 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 the CASTLE study. 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.

In the base case analysis, atazanavir/ritonavir is estimated to be less expensive and more effective than lopinavir/ritonavir. Sensitivity analyses indicate that the model is sensitive to the assumptions around treatment failure; when treatment failure with lopinavir/ritonavir is plausibly assumed to be the same as with atazanavir/ritonavir the model output switches from atazanvir/ritonavir being dominant to having an incremental cost per quality adjusted life year (QALY) gained of £27,015 compared with lopinavir/ritonavir.

5.0 LIMITATIONS OF DECISION CONTEXT

- There are no data presented of the clinical and cost effectiveness of atazanavir compared directly with PIs other than lopinavir/ritonavir.

6.0 CLINICAL EVIDENCE

The main efficacy data in the company submission[2] is from an open-label, randomised, phase IIIb, non-inferiority trial (CASTLE) of atazanavir 300mg/ritonavir 100mg once daily against lopinavir 400mg/ritonavir 100mg twice daily[9,10,11]. The baseline characteristics, and primary and secondary endpoint efficacy data, are summarised in Table 1A in Appendix 1. Sub-group data are presented in Table 2A in Appendix 1.

A phase IV non-inferiority trial in treatment-naive patients (study AI424089) compared atazanavir 300mg/ritonavir 100mg against unboosted atazanavir 400mg once daily[12]. As unboosted atazanavir 400mg is not a recommended dose[1], this study is considered only in the safety section (see section 6.2).

6.1 Clinical efficacy

CASTLE was an open-label, non-inferiority trial conducted in HIV-1 infected adults who were essentially treatment-naive. All patients had baseline HIV RNA levels $\geq$5,000 copies/mL and around 88% had CD4 cell counts $\geq$50 copies/mm^3. Patients with chronic, but not acute, hepatitis B or C were eligible[9].

Patients were randomised to atazanavir 300mg/ritonavir 100mg (n=440) once daily or lopinavir 400mg/ritonavir 100mg twice daily (n=443), all combined with once daily fixed dose combination of tenofovir 300mg/emtricitabine 200mg. The primary endpoint was the proportion of patients with HIV RNA of less than 50 copies/mL at week 48 in the intention-to-treat population (where non-completers were classed as failures), and non-inferiority was to be declared if the lower limit of the 95% confidence interval (CI) for the difference in proportions was greater than -10%. At 48 weeks, 78% of the atazanavir/ritonavir group achieved HIV RNA of less than 50 copies/mL, versus 76% of the lopinavir/ritonavir group (figures have been rounded). The difference of 1.7% (95% CI -3.8 to 7.1) met the criterion for non-inferiority of atazanavir/ritonavir[2,9].

Secondary endpoints included the proportion of patients achieving HIV RNA viral load less than 400 copies/mL, and mean changes from baseline in HIV RNA levels and CD4 cell count. These were consistent with the primary endpoint finding of no statistically significant difference between atazanavir and lopinavir (see Table 1A in Appendix 1). Sub-group analyses by baseline stratification factors (HIV RNA < or $\geq$100,000 copies/mL; CD4 cell count <50, 50 to <100, 100 to <200, $\geq$200 cells/mm^3) also indicated no statistically significant difference between atazanavir/ritonavir and lopinavir/ritonavir (see Table 2A in Appendix 1). The proportion of patients achieving HIV RNA less than 50 copies/mL was numerically greater in those with a lower HIV RNA at baseline in both treatment groups. *Post hoc* analyses by baseline CD4 cell counts indicated that lower baseline CD4 counts were associated with lower response rates for lopinavir/ritonavir (p=0.0085) but not for atazanavir/ritonavir (p=0.51)[9]. However, increases in CD4 cell counts were numerically greater with lopinavir/ritonavir than with atazanavir/ritonavir[10]. The European Public Assessment Report (EPAR) considered that the magnitude of the differences in CD4 cell counts was not important[11].

Virological failure (defined as rebound after achieving a confirmed viral load of less than 400 copies/mL without resuppression, discontinuation due to insufficient viral load response before week 48, or failure to achieve a confirmed viral load of less than 400 copies per mL on study and at week 48) occurred in 6% of patients in each treatment group[9]. Among patients with virological failure on atazanavir/ritonavir, emerging PI substitutions were observed only in those who entered the study with pre-existing PI substitutions. No patient with virologic failure in either group who had a wild-type isolate at baseline developed resistance[11].

Points to note

- Two-thirds of patients had HIV subtype B. The median baseline HIV RNA of patients enrolled in the CASTLE study was 4.98 $\log_{10}$ copies/mL, and the median CD4 cell count was 205 cells/mm^3 (see Table 1A in Appendix 1). Almost half had a viral load >5 $\log_{10}$ copies/mL. Around 5% had experienced acquired immune deficiency syndrome (AIDS)-defining events, and 5% and 8% had chronic hepatitis B and C, respectively[9].
- At baseline, nine (2%) patients in the atazanavir/ritonavir group and 11 (3%) of those in the lopinavir/ritonavir group had major PI-resistance substitutions; 136 (31%) and 168 (39%) had minor PI-resistance substitutions, respectively[9].
- Patients randomised to lopinavir/ritonavir were required to take the soft capsule formulation (three capsules twice daily), which has now been discontinued, rather than the film-coated tablets that are now available (two tablets twice daily)[4]. Adherence to the two treatments was similar at 48 weeks (82% for atazanavir versus 84% for lopinavir)[9].
- Overall, 9% of those receiving atazanavir/ritonavir group and 13% of those receiving lopinavir/ritonavir discontinued the study before 48 weeks. The most common reason in both groups was adverse effects[9].
- Response rates for HIV RNA less than 50 copies/mL were higher in both treatment groups for baseline hepatitis B/C negative versus positive. Response rates varied across regions and were consistently lowest in patients from North America and highest in those from Asia. The distribution of response rates across regions and treatment groups was confounded with HIV subtype. Rates on lopinavir/ritonavir were slightly higher than atazanavir/ritonavir in Asia and Africa, where HIV subtypes AE and C were predominant, respectively (see Table 2A in Appendix 1).

6.2 Safety

Atazanavir has been available for treatment-experienced patients since 2004. There were no new safety concerns with its use in treatment-naive patients[10]. The overall incidence of adverse events up to week 48 in the CASTLE study was comparable among treatment regimens, with 91% of patients reporting at least one adverse event[11]. Treatment-related adverse events of any grade that were reported with at least 5% greater frequency with atazanavir/ritonavir than with lopinavir/ritonavir were jaundice (15% versus < 1%), hyperbilirubinemia (10% versus 0), and ocular icterus (8% versus 0). Those that occurred with a lower frequency with atazanair/ritonavir than with lopinavir/ritonavir included diarrhoea (11% versus 46%), nausea (15% versus 22%), and hypertriglyceridaemia (2% versus 8%). Discontinuations due to adverse events occurred in 2% of patients on atazanavir/ritonavir and 3% on lopinavir/ritonavir[11].

Treatment-related grade 2 to 4 adverse events were experienced by 26% of patients treated with atazanavir/ritonavir and 30% of patients treated with lopinavir/ritonavir. Hepatobiliary disorders occurred more frequently with atazanavir/ritonavir than with

lopinavir/ritonavir (9% versus <1%), including jaundice (4% versus 0) and hyperbilirubinaemia (6% versus 0). Gastrointestinal disorders occurred more frequently with lopinavir/ritonavir than with atazanavir/ritonavir (19% versus 9%), including diarrhoea (11% versus 2%) and nausea (8% versus 4%)[11].

Thirty-four percent of patients in the atazanavir/ritonavir group experienced grade 3 or 4 elevations in bilirubin levels compared with <1% of patients in the lopinavir/ritonavir group. However, the incidence of grade 3 or 4 elevations in hepatic enzymes (aspartate aminotransferase [AST] / alanine aminotransferase [ALT]) was similar (2% versus ≤1%), and there were no discontinuations stated to be due to hepatic adverse events[9-11]. The EPAR for atazanavir in relation to its use in treatment-experienced patients states that chronic hyperbilirubinaemia does not appear to represent a safety concern for the use of atazanavir[13].

Lipid profiles were comparable and within the preferred range at baseline for the atazanavir/ritonavir and lopinavir/ritonavir groups (e.g. mean total cholesterol approximately 3.87mmol/L and mean low density lipoprotein (LDL)-cholesterol approximately 2.39mmol/L[11]). Both treatment regimens resulted in increased lipid parameter values, although atazanavir/ritonavir was associated with a less negative lipid profile over the course of the study than lopinavir/ritonavir. The respective mean percentage increases from baseline in total cholesterol (13% versus 25%) and triglycerides (15% versus 52%) were statistically significantly lower with atazanavir/ritonavir than with lopinavir/ritonavir ($p<0.0001$), and were numerically but not statistically lower for high density lipoprotein (HDL)-cholesterol (29% versus 37%) and LDL-cholesterol (14% versus 19%)[11]. 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. Two percent of patients in the atazanavir/ritonavir group versus 8% of the lopinavir/ritonavir group initiated lipid-lowering therapy during the study[9]. Rates of lipodystrophy remained similar and low (<1%) throughout the 48 weeks[11].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

There are several licensed PIs available, as discussed in section 3.0. Those that are licensed for use in treatment-naive patients include lopinavir (co-formulated with ritonavir, Kaletra®)[4], fosamprenavir (Telzir®)[5], saquinavir (Invirase®)[6], and atazanavir[1].

The company submission states that lopinavir and atazanavir are the most frequently prescribed PIs in Wales, based in market research[2].

7.2 Comparative effectiveness

- 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].
- 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[1].

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					

- All PIs should be boosted with ritonavir. 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]. The 2008 BHIVA guidelines note that evidence supports its once daily administration in treatment-naive patients[3], although the Welsh Medicines Partnership (WMP)-sought expert opinion suggests this occurs rarely in practice. 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 less negative than lopinavir and some other PIs[3]. In the CASTLE study, increases in total cholesterol and triglycerides were significantly lower, and increases in HDL-cholesterol and LDL-cholesterol were numerically lower, with atazanavir/ritonavir as compared to lopinavir/ritonavir. The proportion of patients initiating lipid lowering therapy was higher in the lopinavir/ritonavir group than in the atazanavir/ritonavir group (8% versus 2%), and any reduced need for lipid-lowering therapy may potentially impact on polypharmacy issues and CVD. However, hard CV 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 hyperbiliruninaemia, although the EPAR for atazanavir in treatment-experienced patients notes there are no specific safety concerns in this regard[13]. In the CASTLE study, lopinavir/ritonavir was associated with a greater incidence of diarrhoea. Overall discontinuations due to adverse events were similarly low (2% of patients on atazanavir/ritonavir and 3% on lopinavir/ritonavir)[10].
- Atazanavir and ritonavir are inhibitors of CYP3A4 and atazanavir is contraindicated with drugs that are substrates of this enzyme and have a narrow therapeutic index. The drug-interaction proflile of atazanavir is considered less favourable than that of other PIs[3] and the SPC[1] should be consulted for full details of potential drug interactions.

  The CASTLE study is planned to follow patients up to 96 weeks.

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-naive HIV-1 infected patients justify any 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-naive patients, as per the CASTLE study, 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 CASTLE study. 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 the CASTLE study[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 for atazanavir/ritonavir and lopinavir/ritonvir in the first and subsequent years are based on the 48 week data from the CASTLE study. Treatment switching is related to the incidence of treatment failure, poor compliance and adverse events, and appears subject to some uncertainty. CV risk and mortality are driven in large part by observed differences in lipid profile. The lipid data from subjects initiating lipid-lowering therapy in the CASTLE study 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. The model has been provided to WMP.

8.3 Population

The baseline characteristics of patients in the atazanavir/ritonavir and the lopinavir/ritonavir arms are based on the CASTLE study (see Table 1 in Appendix 1A) are used to define the modelled population[2].

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 consider 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/ritonavir or lopinavir/ritonavir in the first and subsequent years is calculated from patients in the CASTLE study who discontinued treatment due to adverse events, poor compliance or lack of efficacy. The probability of discontinuation in the first year is reportedly based on 48 week data that has been transformed to 52 weeks by assuming constant rates of discontinuation (5.16% for atazanavir/ritonavir, and 7.56% for lopinavir/ritonavir)[2]. These annual probabilities of discontinuations are assumed for subsequent years as well, which may be a source of uncertainty, as the largest contributor of discontinuations considered here was adverse events[2]. Sensitivity analysis indicates that the model is sensitive to the rates of treatment failure (see section 8.10.1)[2].

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[14]. Switching from the third-line regimen is not possible[2].

8.6.1.2 CVD risk and mortality
Framingham risk equations[15] 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[2]. 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[14]. 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. In using these lipid data, the model appears to exclude 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 lipid profile 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 the CASTLE study. 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 the CASTLE study is not clear, but the company reports that there were no differences between groups in the baseline CV risk. It should also 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[16] 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 analysis that are potentially compounded by the 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.

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[17]. These rates are assumed to apply to patients taking atazanavir/ritonavir (administered once daily) and lopinavir/ritonvir (administered twice daily)[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%)[17]. 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[18]. 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[19]. 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[20]. 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/ritonavir and lopinavir/ritonavir. It is noteworthy that in the CASTLE study the number of discontinuations due to poor or non-compliance was similar between the two treatment arms[9]. The number of patients who remained adherent to treatment at 48 weeks was also similar (82% on atazanavir/ritonavir and 84% on lopinavir/ritonavir)[9]. HIV-mortality has been tested in one-way sensitivity analysis and indicates that atazanavir still 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 the CASTLE study are used for atazanavir and lopinavir[9]. For the second- and third-line darunavir-based regimens, the rate of diarrhoea observed in the TITAN study[14], adjusted for the difference observed in the lopinavir/ritonavir arms of this and the CASTLE study, is assumed[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 treatment-experienced patients in a 24 week study of atazanavir and lopinavir (study AI424043) has been used[21]. The extent to which this general HIV state utility value adequately reflects HIV status in patients who are initially treatment-naive over the course of their lifetime is uncertain, but a supplementary sensitivity analysis, in which the utility of treatment-naive patients is assumed to 1.0 and reduces to 0.85 when treatment-experienced, indicates that the model output is relatively insensitive to this assumption. 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 impact or high impact diarrhoea in a cost effectiveness analysis of chemotherapy in patients with prostate cancer (0.82)[22]. 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], 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[2]. 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[25], 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 initiated by 8% of patients taking lopinavir/ritonavir and 2% of patients taking atazanavir/ritonavir over the 48 weeks of the CASTLE study[9]. 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[26], 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[27] and MI[28], 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[29], 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 base-case analysis, atazanavir/ritonavir is estimated to be more effective (associated with a gain of 0.24 QALYs) and less expensive (associated with a cost saving of £17,600) compared with lopinavir/ritonavir in treatment-naive patients (i.e. atazanavir/ritonavir dominates lopinavir/ritonavir). 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, 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 model outputs switch from atazanavir/ritonavir being dominant over lopinavir/ritonavir, to having an incremental cost per QALY gained of £27,015. A supplementary analysis provided by the company, in which treatment failure in year 1 is as per the base case analysis but in year 2 and beyond is assumed to be the same for atazanavir/ritonavir and lopinavir/ritonavir, produces an incremental cost per QALY gained of £14,293. These are important findings, as the numbers of patients providing data on treatment failures due to each of adverse events, poor/non-compliance and lack of efficacy are low, and may be subject to the play of chance. 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 £24,667 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/ritonavir still dominates (i.e. is less expensive and more effective than) lopinavir/ritonavir[2]. When treatment failure that leads to treatment switching based on virological failure is defined as HIV RNA >50 copies/mL, atazanavir/ritonavir still dominates lopinavir/ritonavir[2]. However, 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]. When lipid profiles were set equal, atazanavir/ritonavir still dominated lopinavir/ritonavir.

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 90%, and at £30,000 is 92%.

The model provided by the company indicates that the 95% CI generated around the base case point estimate for incremental costs is -£54,978 to +£15,999, and for the incremental QALYs, the 95% CI was 0.11 to 0.41. This indicates the uncertainty that exists in the point estimates in the base case analysis.

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have identified a published Abbott-funded (manufacturers of lopinavir/ritonavir) cost effectiveness analysis of lopinavir/ritonavir and unboosted atazanavir in treatment-naive patients conducted in a USA health setting[30]. A Markov model was developed, which employed 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. The incremental cost per QALY gained for lopinavir/ritonavir compared to atazanavir was $6,797 based on year 2004 prices. The long-term CHD risk associated with lopinavir/ritonavir was minimal compared with the increased risk of AIDS/death and costs projected for a less efficacious PI-based regimen[30]. The results of this analysis are of limited value to the current decision problem due to the comparison of lopinavir/ritonavir against unboosted atazanavir, and the differences between healthcare settings.

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 in the base case analysis is expected to increase by taking some of the market share of lipinavir/ritonavir. Based on the CASTLE study data it is assumed that the use of atazanavir/ritonavir instead of lopinavir/ritonavir will result in cost savings in relation to antidiarrhoeal agents and the treatment of dyslipdaemia, which will offset some of the increase in costs due to greater uptake of atazanavir.

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 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[31]. This prevalence has been applied to Welsh Government population estimates[32] 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[33]. 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[31]). These estimates of

the number of patients with HIV over the next five years may therefore have been underestimated.

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 by 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 2007 market research data, the company submission states that lopinavir/ritonavir makes up 50% of the PI market share and that atazanavir/ritonavir makes up 32%, saquinavir/ritonavir makes up 9% and fosamprenavir/ritonavir makes up 5% (not verifiable). A simplifying assumption is made that these four PIs make up the entire PI market, and so the company submission assumes that, by scaling to 100%, the approximate market shares are: lopinavir/ritonavir 51%, atazanavir/lopinavir 34%, saquinavir/ritonavir 10%, fosamprenavir/ritonavir 5%[2]. Further, the company submission assumes that the proportion of use of NNRTIs to PIs is 70:30. Therefore, the estimated overall market share of the NNRTIs and PIs considered here are: lopinavir/ritonavir 15.2%, atazanavir/ritonavir 10.3%, saquinavir/ritonavir 2.9%, fosamprenavir/ritonavir 1.6%, efavirenz 44.1%, and nevirapine 25.9%[2].

It is assumed that the market share of atazanavir/ritonavir estimated here applies equally to the treatment-experienced and treatment-naive patient population. Company market share projections are that atazanavir/ritonavir use will increase by an absolute 2% each year so that in 2008 it will account for 12.3% of the market share, rising to 20.3% in 2012[2]. This is assumed to be taken from the lopinavir/ritonavir market share, which drops by 2% each year, with all other agents maintaining a constant market share[2]. Application of these estimates to the treated HIV population estimated in section 9.3.1 produces an estimated number of patients expected to be treated with atazanavir in 2008 of 99 patients, rising to 177 in 2012.

9.3.3 Costs and resource use

The PI costs are based on BNF listed prices[25] 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 (although the small costs of diarrhoea are not included in the economic model). Reportedly based on the 48 week data from the CASTLE study, 6% of patients taking atazanavir/ritonavir used antidiarrhoeal agents compared with 13% of patients taking lopinavir/ritonavir[2]. 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).

It is also assumed that the more favourable lipid profile observed for atazanavir/ritonavir in the CASTLE study (see section 6.2) would result in lower costs associated with the management of dyslipidaemia. Based on these data, 2% of patients taking atazanavir/ritonavir initiated lipid-lowering agents compared with 8% of patients taking lopinavir/ritonavir[9]. 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.

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 (due to the estimated lower costs of diarrhoea and CVD) are included, the net budget impact of the increased use of atazanavir/ritonavir is estimated as £7,006 in 2008, rising to £38,040 in 2012[2].

9.5 Sensitivity / scenario analysis

No specific sensitivity analysis has been performed, but a scenario analysis is included. This considers the 2% increase in market share for atazanavir/ritonavir gained from efavirenz and nevirapine (drop of 1% each) instead of from lopinavir/ritonavir. The budget impact excluding any offset costs due to diarrhoea and lipids is estimated to be £40,056 in 2008, rising to £217,491 in 2012. However, there appears to be an error in the assumed cost of nevirapine. This agent should be taken as 200mg twice daily[25] but the costs in the budget impact analysis appear to relate to 200mg once daily administration, which would actually bias the analysis against atazanavir/ritonavir. A further analysis considers the costs of lipids and diarrhoea, but the assumed rates of these for efavirenz and nevirapine are not stated[2].

9.6 Comparator costs

Selected ritonavir-boosted PI costs and NNRTI costs are listed in Table 2, based on usual doses recommended in the BNF[25] over 28 days.

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

	Example dose	Approximate 28-day cost[26]
PIs		
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
NNRTIs		
Efavirenz	600mg od	£195
Nevirapine	200mg bd	£149
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[31].
- Atazanavir will 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[34].
- 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-naive patients in line with current BHIVA guidelines; June 2007[35].
- 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[36].
- 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[37].
- 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[38].
- 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[39].
- 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[40].

10.4 Ongoing studies

- The results of a phase IV, open-label, randomised, multi-centre study assessing the efficacy of a treatment maintenance phase with unboosted atazanavir 400mg versus atazanavir 300mg/ritonavir 100mg after an induction phase with atazanavir 300mg/ritonavir 100mg in treatment-naive HIV patients may report results in the next 12 months[2]. Additional metabolic and body composition data from ongoing studies may also report 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. Pivotal study of atazanavir/ritonavir versus lopinavir/ritonavir in treatment-naive patients with HIV-1

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (ATV/r versus LOP/r)
48 week study results						
9,10, 11 CASTLE study	Randomised, open-label, phase IIIb, multinational, non-inferiority trial	883 patients randomised African: 15% Asian: 9% European: 15% North American: 15% South American: 46%	HIV-1 patients aged ≥18 years; Antiretroviral-naive*; HIV RNA ≥5000 copies/mL; Creatinine clearance ≥60 mL/min No acute hepatitis B/C (chronic hepatitis B/C allowed)	Median age: 35 years Males: 69% White: 48% Black: 18% Other:33% HIV subtype B: 66% Median HIV RNA: 4.98 log_{10} copies/mL (49% ≥ 100,000 copies/mL) Median CD4: 205 cells/mm^3 (12% <50 cells/mm^3) AIDS: 5% Chronic hepatitis B/C: 5%/8%	ATV/r od (n=440) versus LOP/r bd (n=443) Each in combination with fixed dose combination tenofovir 300mg/ emtricitabine 200mg od	**Primary endpoint (ITT analysis):** Proportion with HIV RNA < 50 copies/mL at week 48: 78% versus 76% - figures rounded (difference 1.7%, 95% CI -3.8 to 7.1) Non-inferiority criterion met **Secondary endpoints:** Proportion with HIV RNA < 400 copies/mL at week 48: 86% versus 82% - figures rounded (difference 3.3%, 95% CI -1.5 to 8.1) Mean change from baseline HIV RNA†: -3.09 versus -3.13 log_{10} copies/mL (difference 0.05, 95% CI -0.05 to 0.15) § Mean change from baseline CD4 count†: 203 versus 219 cells/mm^3 (difference -16.4, 95% CI -35.9 to 3.1)
ATV/r od = Atazanavir 300mg/ritonavir 100mg once daily; LOP/r = Lopinavir 400mg/ritonavir 100mg twice daily; * = (<1 week previous antiretroviral exposure, except in setting of post-exposure prophylaxis or prevention of mother-to-child transmission, in which case <6 weeks of previous antiretroviral exposure was allowed); † = observed values; § = statistical comparisons of HIV RNA changes from baseline were not pre-planned.						

Table 2A. Sub-group analyses from the pivotal study of atazanavir/ritonavir versus lopinavir/ritonavir

Ref	Baseline stratification factor	Proportion achieving HIV RNA <50 copies/mL (ATV/r versus LOP/r)
9,10 CASTLE study	HIV RNA (copies/mL): <100,000 ≥100,000	 82% versus 81% 74% versus 72%
	CD4 cell count (cells/mm^3): <50 50 to <100 100 to <200 ≥200	 78% versus 63% 76% versus 69% 75% versus 78% 80% versus 80%
ATV/r od = Atazanavir 300mg/ritonavir 100mg once daily; LOP/r = Lopinavir 400mg/ritonavir 100mg twice daily. Note: additional data were provided to WMP, but these remain commercial/academic in confidence.		