Cost Effectiveness of Lopinavir/Ritonavir Compared to Atazanavir + Ritonavir Tablets in Antiretroviral (ARV) Experienced Patients in the UK, Spain, Italy and France Based on Efficacy Results from BMS AI424-045

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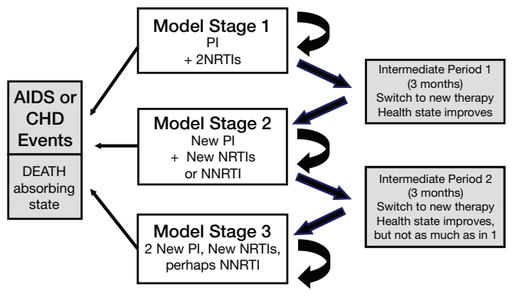
Objective

To estimate the long-term combined effects of HIV disease and ARV-related risk for coronary heart disease (CHD) on quality-adjusted survival and health care costs for ARV-experienced patients in the UK, Spain, Italy and France.

Methods

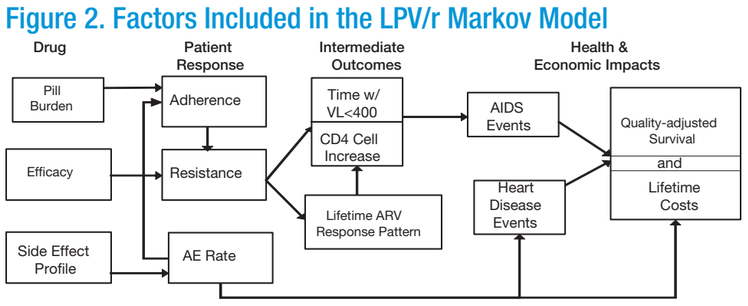
- A cost-effectiveness Markov model, which uses the Framingham equation to predict risk of a myocardial event based on total cholesterol data from BMS study AI424-045, was created. This model was populated with predicted proportions of patients with plasma HIV-1 RNA viral load (VL) below 400 and below 50 copies/mL, reflecting the results from the same study, overall health care, lower pill-burden with lopinavir/ritonavir (LPV/r) tablets, and costs of drugs.

Figure 1. Schematic Overview of the Model



- The model simulates outcomes in terms of Quality-Adjusted Life Years (QALY) and costs for a cohort of patients starting on LPV/r and compares them with those for a cohort of patients starting on ritonavir boosted Atazanavir (ATV + RTV).
- The structure used is a Markov model, which allows for transitions between 12 health states defined by CD4+ T-cell count and VL levels every 3 months. These health states capture the differential effects of VL suppression and CD4 cell increases reported in the clinical trial for each regimen. Once the time period for the clinical trial results is exhausted, health state progression is based on data from large clinical cohorts of patients on ART. The relationships captured in the model are shown in **Figure 2**.

Figure 2. Factors Included in the LPV/r Markov Model



- Patients can pass through up to three successive treatment regimens or can pass from any treatment stage to death. The CD4+ T-cell count and VL values that specify the 12 live health states are provided in **Table 1**.
- There are two further health states associated with death: Death due to HIV and death due to cardiovascular disease.
- Transitions between health states can occur every three months. Transition between treatment stages occur when a patient fails treatment. This is accompanied by a switch to a new therapy and temporary improvement in health state.

Table 1. CD4 T-Cell Count and Plasma HIV-1 RNA Level of the 12 Health States in Each Stage of the Model

Health State	CD4+ T-Cell Count (cells/mm^3)	HIV-1 RNA (copies/mL)
HS1	>500	<400
HS2	>500	≥400
HS3	351 – 500	<400
HS4	351 – 500	≤400
HS5	201 – 350	<400
HS6	201 – 350	≥400
HS7	201 – 350	400 – 19,999
HS8	50 – 200	≥20,000
HS9	50 – 200	<400
HS10	50 – 200	400 – 19,999
HS11	50 – 200	20,000 – 100,000
HS12	<50	Any level

Methods (cont.)

- The risk of an AIDS event depends on the health state (CD4 count and VL), and the risk of a cardiovascular event depends on the cholesterol level associated with the ART regimen. These cardiovascular disease risks are derived from the Framingham study equation.
- Each health state is associated with a utility (which can be considered as a "quality of life" weighting between 0 for death and 1 for perfect health) and a cost.
- The model is run until 80% of patients have died.
- The outcome is calculated by multiplying the utility of health state by total time spent in that health state and summing that across all patients for the time the model is run.
- Costs take into account the drug costs associated with the treatment stage (increase in cost with later stage treatments), the costs of HIV and CHD events, and the other costs associated with the health state (CD4 count and HIV-RNA level).

Table 2. Data Sources for the Model

Type of Data	Source
Efficacy Data	Clinical trial VL suppression data from BMS-045
Cardiovascular Risk	Study 418 (Gathe, et al., 2004)[1], and total cholesterol levels from BMS-045 are used to calculate the risk of myocardial infarction for ATV+RTV relative to LPV/r
Mortality Rate per Cardiovascular Event	Framingham Study (Wong, et al., 2001)[2]
Transition Probabilities	Study M98-863 and from two large databases (Ghani, et al., 2001)[3,4] and hazard of viral breakthrough in year two as reported by Mocroft, et al.[5]
AIDS Event Data	(Ghani, et al., 2001)[3,4]
Utilities	Archival data from 21,000 EuroQoL responses for patients on HAART transformed by the utility weights reported for EuroQoL health states in the study by Dolan (1998)[6], and the impact of cardiovascular disease on utilities from Castiel, et al. (1992)[7]

- Cost data are country-specific.
- The cost of an AIDS event for each country were developed originally in 2000 by the country affiliates using local expert panels or data sources. They have been adjusted to reflect 2006 costs of care.
- Drug costs are 2006 current drug prices in respective countries.
- The costs accounted for include ARV treatment, HIV events, cardiovascular events and lipid-lowering drug (pravastatin). Unit costs can be found in **Table 3**.

Table 3. 2006 Local Currency Costs for Economic Model of LPV/r Tablets Compared to ATV+RTV

Type of Cost	UK (£)	Spain (€)	Italy (€)	France (€)
LPV/r per day	10.25	12.12	11.41	15.01
Atazanavir per day	10.52	14.55	10.65	14.32
Ritonavir/day	1.01	1.50	0.76	0.91
2nd HAART regimen/day*	44.80	54.09	56.44	53.51
3rd HAART regimen/day*	54.20	66.96	63.43	63.77
Statins/day	0.16	1.08	1.48	1.35
CHD event per episode**	3,182	3,780	10,887	4,619
HIV event per episode	5,431	7,163	10,543	11,878
Discount rate	3.5%***	3.0%	3.0%	3.0%

* Weighted costs of all available drugs are based on published data on best current regimen.

** Costs are estimated from Gandjour, et al. (2002)[8]

*** 3.5% accounts for the official NICE required discount rate.

Results for the EU Models

- In the countries examined, an ARV-experienced patient would be expected to have a net gain of 5.6 quality-adjusted life months of survival over the first 5 – 10 years if treated with lopinavir/ritonavir tablets (LPV/r) rather than atazanavir + ritonavir (ATV+ RTV), after the death and morbidity effects from heart disease due to differences in total cholesterol have been subtracted. The model predicted that the regimen containing LPV/r tablets is clinically and economically superior over the first 5 – 10 years vs. the regimen using ATV+ RTV with cost savings per patient for all countries as shown in **Table 4**.

Table 4. Net Gain in QALMs and Overall Cost Savings

Outcome	UK	Spain	Italy	France
Benefit in quality-adjusted life months	5.6	5.6	5.6	4.6
5-year overall savings or per person	£3,416	€7,769	€2,584	€1,233
10-year overall savings or (increase) per person	£3,175	€7,903	€2,222	(€461)
Lifetime cost per QALY	£3,502	Dominant*	€10,297	€10,250

LPV/r is clearly cost-effective as dominant (i.e., both cost-saving and improving QALYs), so ICER is not calculated.

Sensitivity Analysis

- Data from many sources are integrated in the base model.
- One model parameter with the greatest amount of uncertainty is the long-term effect of VL suppression below 50 copies/mL. This model makes the conservative assumption that the hazard of viral breakthrough in year two is valid for the subsequent years that patients remain on a regimen.
- The base model assumes a 7% decreased risk of viral breakthrough after 48 weeks for LPV/r based on the reported differences in suppression below 50 copies/mL. However, the marginal contribution of even a 2 percent decrease in breakthrough risk was examined in the sensitivity analysis and a gain of 1.9 QALMs and lifetime cost savings for LPV/r were estimated for Spain.
- Sensitivity analysis performed on data from Italy is illustrated in **Table 5**.

Table 5. Sensitivity Analysis for Italy of LPV/r Tablet Compared to ATV+RTV

Condition Varied	LPV/r 5-Year Saving (Increase)	LPV/r 10-Year Saving (Increase)	QALY Months Gained	Cost Per QALY
Baseline values: 93% RR of viral breakthrough (BT) for VL <50 copies/mL	€2,584	€2,222	5.6 mos	€10,297
AIDS event cost 150%	€3,011	€3,044	5.6 mos	€9.700
AIDS event cost 50%	€2,157	€1,401	5.6 mos	€10,894
$1,000 switch cost	€2,654	€2,207	5.6 mos	€10,304
$200/day salvage ARV	€8,407	€12,087	5.6 mos	€12,963
LPV/r price = 140% to €15,97/day	(€3,181)	(€5,194)	5.6 mos	€29,934/ QALY
ICER Threshold = €50,000 98% RR of BT and no improvement for tablet formulation LPV/r price = 141% AIDS event = 50% Statin cost = 200% CHD cost = 200%	(€539)	(€785)	2.3 mos	€49,992/ QALY

Conclusions

- The survival benefit of using LPV/r for ARV-experienced patients is mostly due to the differences in the proportion of patients with VL suppressed to 50 copies/mL or below, while the economic benefit is due to the complex interactions of both the lower cost of LPV/r and the savings incurred by slower rates of disease progression.
- These estimates are robust to large variations in costs, but quite sensitive to assumptions related to the viral rebound for patients with suppression to VL below 400 and below 50 copies/mL.

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