space for poster number

Economic and Clinical Impact of Using a Protease Inhibitor Regimen Containing ATV + RTV vs. Lopinavir/Ritonavir in Antiretroviral (ARV) Experienced Patients: Modeling the Lifetime Impacts of the 48-Week Results from BMS AI424-045

Kit N. Simpson, DrPH, Medical University of South Carolina, Charleston, SC, U.S.A.
and George MacKinnon, PhD, Abbott, Abbott Park, IL, U.S.A.

Objective

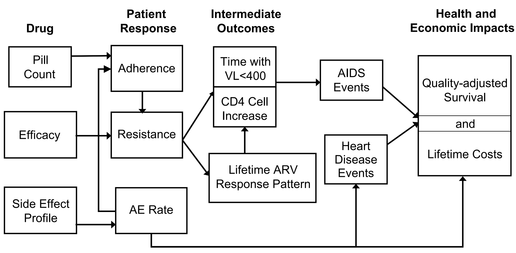
To compare the long-term combined effects of HIV disease and antiretroviral (ARV)-related risk for coronary heart disease (CHD) on quality-adjusted survival and health care costs for:

- ARV-experienced patients treated with LPV/r capsule vs. those treated with ATV + RTV.
- ARV-experienced patients treated with LPV/r tablet vs. those treated with ATV + RTV.

Methods

- A previously validated Markov model was updated and supplemented with the Framingham CHD risk equation.[1]
- This model was populated by data and assumptions reflecting the antiretroviral-experienced study population enrolled in BMS study 045, and the study results reported for the comparison of ATV + RTV and LPV/r.[2]
- The proportion of patients who were undetectable at Week 48 was increased by 2.2% for the LPV/r arm to reflect the 2 pills per day decrease with LPV/r tablets as reported by Bartlett.[3]
- The hazard of breakthrough in the model transition matrix used after Week 48 was modified to reflect a RR of .93 for LPV/r. This reflects the difference in the relative risk of viral rebound in the 2nd year reported by Mocroft[4] for patients with plasma HIV-I RNA (VL) suppression below 50 copies/mL vs. VL suppression between 50 and 400 copies/mL. The adjustment was based on the relative proportions of patients in each VL grouping in study BMS-045 at Week 48.

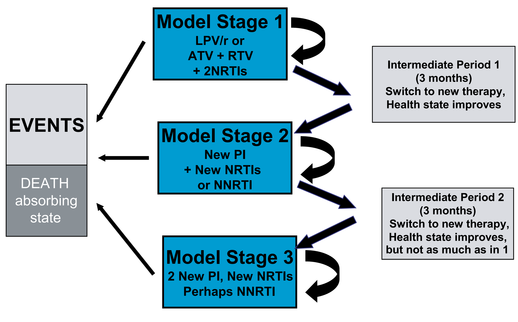
Figure 1. HIV-Disease Conceptual Model



Data Description

- The average patient was male, age 37, with baseline 10-year CHD risk at 4.6% and had failed at least one previous highly active antiretroviral treatment (HAART) regimen.
- Patients started with either LPV/r or ATV + RTV as protease inhibitor (PI) in a regimen.
- Clinical trial results were used to estimate the differences between these two therapies.
- The daily PI costs were $18.52 for LPV/r and $22.08 for ATV + RTV. Other costs were estimated from databases.
- All model costs are reported as the 2005 present value in U.S. currency. The perspective of the analysis is that of the health care system and does not include indirect costs in the model cost estimates.
- Various CHD risk levels were tested in the sensitivity analysis.

Figure 2. Diagram of the Markov Model Structure



- Each stage has 12 health states.

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

Health State	CD4 Cell Count	HIV-1 RNA Level	Percent Patients With AIDS Event/Cycle	QALY Weight Applied to Health State Without CHD	QALY Weight Applied to Health State With CHD
HS1	>500	<400	1.71	.954	.574
HS2	>500	≥400	2.18	.938	.563
HS3	351 – 500	<400	1.71	.934	.560
HS4	351 – 500	≥400	2.18	.931	.559
HS5	201 – 350	<400	2.84	.929	.557
HS6	201 – 350	≥400	3.31	.931	.559
HS7	201 – 350	400 – 19,999	4.25	.933	.560
HS8	50 – 200	≥20,000	5.11	.863	.518
HS9	50 – 200	<400	5.58	.865	.519
HS10	50 – 200	400 – 19,999	9.79	.856	.514
HS11	50 – 200	20,000 – 100,000	14.47	.826	.496
HS12	<50	Any Level	17.87	.781	.469

- Each health state has a specific event risk in a 3-month period. Types of events include:
  - Cervical cancer
  - CMV retinitis
  - CMV other site
  - Cocidiosis/Isosporiasis
  - Crypto. meningitis
  - Cryptosporidium
  - Dementia
  - Herpes simplex
  - Histoplasmosis
  - KS cutaneous
  - KS visceral
  - CNS lymphoma
  - Other lymphoma
  - Esophageal Candida
  - MAC
  - PCP
  - PML
  - Pneumonia recurrent
  - Salmonella sepsis
  - Tuberculosis
  - Toxoplasmosis Encephalitis
  - Wasting syndrome

Data Description (cont.)

Table 2. Data Sources

Type of Data	Source
Efficacy data	Clinical trial VL suppression data from BMS-045 for model vs. ATV + RTV
Cardiovascular risk	Study 418 (Gathe, et al. 2004)[a] 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)[b]
Transition probabilities	Study M98-863 and from two large databases (Ghani, et al. 2001a&b)[c,d] and hazard of viral breakthrough in year two as reported by Mocroft and colleagues
AIDS event data	(Ghani, et al. 2001a&b)[c,d]
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,[e] and the impact of cardiovascular disease on utilities from Castiel, et al. 1992[f]

[a] Gathe JD, Podzamezr D, Johnson M, et al. Once-daily vs. twice-daily lopinavir in antiretroviral-naïve patients: 48-week results. 11th Conference on Retroviruses and Opportunistic Infections, February 2004, Poster 570.

[b] Wong ND, Wilson PW, Kannel WB, et al. Serum cholesterol as a prognostic factor after myocardial infarction: the Framingham Study. *Ann Intern Med* 1991;11:687-93.

[c] Ghani AC, de Wolf F, Ferguson NM et al. Surrogate markers for disease progression in treated HIV infection. *JAIDS* 2001a;28:226-31.

[d] Ghani AC, Henley WE, Donnelly CA, et al. Comparison of the effectiveness of non-nucleoside reverse transcriptase inhibitor-containing and protease inhibitor-containing regimens using observational databases. *AIDS* 2001b: 15:1133-42.

[e] Dolan P. Modeling valuations for EuroQoL health states. *Medical Care* 1998;35:1095-1108.

[f] Castiel D, Herve C, Gaillard M, et al. Cost-utility analysis of early thrombolytic therapy. *Pharmacoeconomics* 1:438-42.

Results

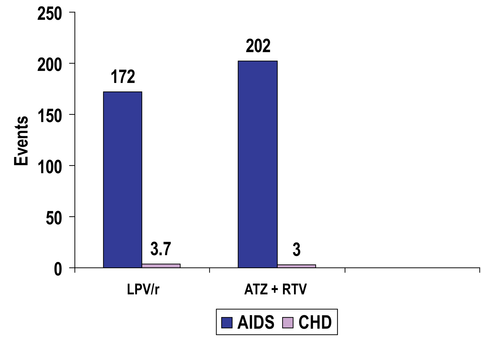
Table 3. Comparisons of LPV/r Capsule vs. ATV + RTV and LPV/r Tablet vs. ATV + RTV, Using 2005 Prices

Country – LPV/r Formulation – Price Per Day	Lifetime Benefits in Quality-Adjusted Life Months	5-Year Cost Savings	10-Year Cost Savings	Lifetime Cost per QALY
U.S. capsules – $24.60	4.6	$12,284	$14,117	Dominant*
U.S. tablets – $26.54	5.6	$10,411	$11,427	Dominant*

* LPV/r is clearly cost-effective as it is "dominant" (i.e., both increased health benefits and lifetime cost savings were predicted). Therefore incremental cost-effectiveness ratio (ICER) cannot be calculated.

- An ARV experienced patient, similar to patients included in the BMS-045 study, would be expected to gain a net benefit of 4.6 quality-adjusted months of survival if treated with LPV/r instead of ATV + RTV after the death and morbidity effects from heart disease due to differences in total cholesterol levels have been subtracted. Based on the improvement expected from the decrease in pill count, this benefit may be expected to increase to 5.6 quality-adjusted life months with the new LPV/r tablet formulation.
- Patients on the LPV/r regimen would be expected to incur $12,283 less in total costs during the first five years of therapy. Cost savings would be $14,117 over the initial 10 years of treatment and a lifetime savings of $3,600 may be expected, despite the "penalty" for longer survival incurred by patients on the LPV/r regimen.

Figure 3. Difference in Estimated AIDS and MI Events



Sensitivity Analysis

- When the model's structural assumption – that the marginal CHD risk for the two regimens was constant over time – was relaxed, LPV/r still appeared to be highly cost-effective.
- If an annual increase of 26% in the CHD risk is assumed in both arms of the model, as reported by the D:A:D study investigators,[5] then the lifetime cost savings disappear, but the cost/QALY remain below $5,000.
- The model was not very sensitive to changes in the cost of AIDS or CHD events, cost of switching regimens or relative prices of ARV or lipid-lowering drugs. When the cost parameters were varied by 20% increases or decreases for any of these parameters, cost saving for LPV/r was retained.

Conclusions

- Based on the objective assumptions of the model, it appears that the cost of lipid-lowering drug therapy and medical care for CHD is insignificant compared to the economic effects of the more rapid progression to AIDS that the model displayed in patients treated with a less effective antiretroviral regimen.
- Thus, the choice of a new HAART regimen for ARV-experienced patients with average CHD risk should be based on an ARV-regimen's expected effects on viral suppression, CD4 increase, and resistance to subsequent regimens.
- Differences between ARV-regimens in the proportion of patients with VL <50 copies/mL as compared to a 50 ≥VL <400 copies/mL at 48 weeks may translate into a relatively large difference in the time that the average patient's VL remain suppressed.
- As illustrated by this modeling example using LPV/r and ATV + RTV, the CHD health benefit conferred on the average patient by ATV is minimal compared to the increased risk of AIDS and/or death to be expected for patients treated with a less efficacious HAART regimen.

References

1. Simpson KN, Luo MP, Chumney E, et al. Cost-Effectiveness of Lopinavir/r versus ATV in treating antiretroviral-naïve patients: modeling the combined effect of HIV and heart disease. Submitted to *Pharmacoeconomics*.
2. E DeJesus, B Grinsztejn, C Rodriguez, L Nieto-Cisneros, J Coco, A Lazzarin, K Lichtenstein, M Johnson, A Rightmire, S Sankoh and R Wilber. Efficacy and Safety of Atazanavir (ATV) With Ritonavir (RTV) or Saquinavir (SQV) vs. Lopinavir/Ritonavir (LPV/RTV) in Patients Who Have Experienced Virologic Failure on Multiple HAART Regimens: 48-Week Results from BMS AI424-045. Poster #J33 547, 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004; San Francisco, CA.
3. Bartlett JA, DeMasi R, Quinn J, et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naïve HIV-1 infected adults. *AIDS* 2001;15:1369-1377.
4. Mocroft A, Ruiz L, Reiss P, et al. Virological rebound after suppression on highly active antiretroviral therapy. *AIDS* 2003;17(12) 1741-51.
5. D:A:D: Cardio- and cerebrovascular events in HIV-infected persons. *AIDS* 2004;18:13:1811-17.