COST EFFECTIVENESS OF USING LOPINAVIR/RITONAVIR VS. NELFINAVIR AS THE FIRST HIGHLY ACTIVE ANTIRETROVIRAL THERAPY REGIMEN FOR HIV INFECTION

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Running head: Lopinavir/r vs Nelfinavir Cost Effectiveness
ABSTRACT

Purpose: Selecting the optimal treatment regimen for antiviral naïve patients may be difficult, given the concern about the antiviral activity, the development of drug resistance and the increase in drug costs. This study evaluates the costs and effectiveness of using lopinavir/ritonavir (LPV/r) vs. nelfinavir (NFV), both coadministered with stavudine and lamivudine, as the first HAART regimen in treating HIV patients, based on the results from the published clinical trial M98-863. Method: A Markov model was developed using a combination of viral load (VL) and CD4 count as surrogate markers to define health states. VL and CD4 count data from the 48-week analysis of the clinical trial were used as measures of effect. The impact of resistance difference between NFV and LPV/r was also examined. Results: Over the first five years, the model estimated that LPV/r could save total HIV care cost at $3,461 per patient compared with NFV. If the resistance advantage of LPV/r was taken into account, the cost savings by LPV/r was increased to $5,546. For longer-term projection, without considering the resistance difference, the incremental cost effectiveness ratio (CER) for LPV/r vs. NFV was at $6,653 per quality-adjusted life-year (QALY). This CER compares favorably to therapies for HIV-disease and for common drug treatments for other conditions, and is well within accepted thresholds for health policy makers. Conclusion: When considering treatment options, this study suggests that use of LPV/r in the first ARV regimen, as compared to NFV, is cost effective based on improved efficacy and resistance. Key words: lopinavir, nelfinavir, cost-effectiveness, resistance
Lopinavir co-formulated with ritonavir (LPV/r, Kaletra®) was introduced in 2000 as an important option for antiretroviral therapy (ART) naïve patients who wish to start a highly active antiretroviral therapy (HAART) regimen containing a protease inhibitor (PI). Published studies of this PI have documented its high efficacy and safety profile, the sustainability of its effects, as well as important advantages related to viral resistance to subsequent HAART regimens [1-6]. Furthermore, the daily cost of this drug to most payers in the United States are similar to the cost of competing PIs on the market [7]. However, it is impossible to compare competing HAART regimens by looking at individual indicators of differences in effects and costs, because these factors often interact and are associated in a non-linear manner. Only a mathematical model can capture the joint effects of advantages in multi-factors, including surrogate marker values, sustainability of initial HAART regimen, differences in the resistance profile for subsequent regimens, and drug costs.

The objective of this paper is to estimate the joint effects of the advantages (and disadvantages) of a LPV/r-containing HAART regimen compared to a NFV-containing regimen for antiretroviral naïve patients, using a decision model that integrates data and information from many sources under a clearly specified set of assumptions. Such models are useful for informing discussions for and against specific policy choices regarding new therapies [8]. A number of such models have been published for HIV-disease [9-12]. However, none of these models is able to incorporate all of the key variables that must be considered in an era where persons with HIV/AIDS may expect treatment with sequential
HAART-regimens, multi-drug rescue therapy, regular viral load monitoring and switches informed by resistance tests. A Markov model was developed that incorporated information on all of these factors. It is structured as a set of three conditional Markov processes which capture treatment-modified disease progression through 12 mutually exclusive and jointly exhaustive health states. Risk in each health state is translated into estimates of number of opportunistic events, quality of life and costs, based on epidemiological data from large cohorts of people with HIV/AIDS [13, 14] and cost data from several sources [24]. The model was used in this study to evaluate the lifetime costs and effectiveness of using LPV/r versus nelfinavir (NFV) as a component of the first ARV regimen in treating HIV patients, incorporating results from the published clinical trial M98-863 [1].

**METHOD**

**Model Design**

The model used in this study was based on a three-compartment Markov model. This model was developed using a combination of viral load (VL) and CD4 count to define the model health states. Validation of this model was reported previously [24]. The cost-effectiveness analysis was completed from a health system perspective. The cost-effectiveness analysis was conducted from the time of beginning of a HAART regimen (either LPV/r + 2 NRTIs or NFV + 2NRTIs) until 50 percent of patients died. This approach allowed our estimates to avoid any bias that a “lifetime” modeling approach could introduce and reflect expected median population survival. Costs and outcomes
occurring beyond 1 year were discounted at 3%. Expected costs, life expectancy and quality-adjusted life years were calculated by the decision model implemented in Excel. The incremental cost-effectiveness ratio (CER) determined the additional lifetime cost of LPV/r+d4T+3TC (TxGroup) per additional life year gained or quality adjusted life year (QALY) gained, compared to NFV+d4T+3TC (Control Group). Incremental CER were calculated using the formula:

\[
\frac{(\text{Lifetime TxGroup Cost} - \text{Lifetime Control Group Cost})}{(\text{TxGroup Outcomes} - \text{Control Group Outcomes})}
\]

**Population**

The analysis was conducted on a theoretical cohort of persons with HIV representative of study subjects in the M98-863 clinical trial: average age 37, naïve to ART and ART initiated with CD4 cell count below 500 cells/µL and detectable viral load > 400 copies/mL (RNA copies/ mL, Roche Amplicor HIV-1 Monitor). Baseline patient demographics and 48 week results of the M98-863 study are summarized in Table 1.

**Disease States**

In the model, people with HIV are at risk for the 22 most common opportunistic infections (OI) and other HIV events. This risk varies by 12 health states defined by CD4 cell count and VL levels (see Table 2). The model assumes that only one type of OI event can occur to the same patient at any one time, thus it will tend to under estimate
interactive effects between OIs observed in real practice. However, this simplification was necessary to reflect the limitations associated with incidence density rates as a measure of risk of OIs. Chronic types of OI were counted only once for each patient, thus patients could not be assigned lifetime cost for a chronic condition more than once. The literature reports that certain types of OIs tend to happen more frequently at specific CD4 count levels. We examined our data for this effect, but did not find significant differences in the relative occurrence rates for specific OIs within our data. Thus we did not use differentially weighted OI rates for the model health states. The relative incidence density rates occurring in a 3-month cycle for each health state for the 22 HIV-related events were based on estimates for US and Dutch patients on HAART reported by Ghani and colleagues [13, 14]. These estimates were validated with data from a US cohort of 1456 patients in community practices (Simpson unpublished data), and were quite similar to OI risks recently reported Gebo and colleagues for the Johns Hopkins Moore Cohort [15]. The risk of OI events for each health state is summarized in Table 2. The distribution of types of OIs is provided in Table 3.

**Clinical Progression and Events**

The model is structured into three Markov stages (see Figure 1) that reflect treatment practices and progression.

**Stage 1**

All patients enter the model as ART naïve patients (Stage 1) and start one PI (LPV/r or NFV) plus two NRTIs (d4T and 3TC) therapy. Their distribution in the initial health states reflect the baseline CD4 cell and VL values observed in the clinical trial. Each
patient may progress into another (better or worse) health state at the end of every three-month period, or remain where he/she started. This movement is reflected in transition matrix (see details below in Transition Matrix).

Stage 2
Patients enter stage 2 when they are switched to a new PI regimen due to treatment failure defined as a health state with CD4 <500 cells/µL and detectable VL (≥400 copies /mL). Each time when patients move into a new stage of therapy, they were assumed to improve health for the first few months, which is reflected by having them stay in the intermediate period 1 for 3 months. They then progress through the 12 health states in Stage 2 until they reach a health state that represent failure of second-line therapy or death. The rate of progression in Stage 2 is specified by a progression matrix that reflects average progression rates for PI-experienced patients (see below).

Stage 3
Patients enter stage 3 when they are switched to a new regimen composed of two PIs plus two NRTIs due to treatment failure defined as a health state with CD4 <350 cells/µL and detectable VL (≥400 copies /mL). Similar to entering stage 2, patients start in a health state in Stage 3 that capture the improvements (through intermediate period 2) in CD4 cell and VL values expected with starting new therapy. Patients then progress through the health state in Stage 3 until they enter the Death health state. The progression in Stage 3 is regulated by a progression matrix that captures the average rate of progression for highly ARV-experience patients. The model runs until 50 percent of
patients have reached the death health state. The specific assumptions and the data used to derive the transition matrices are described in detail below.

**Transition Matrix**

In stage 1, movements from one health state to another in the initial four time periods is determined by classifying each patient in the M98-863 study into one health state for each 3-month period, based on their raw CD4 and VL data during that particular time in the trial. This classification is based on an intent-to-treat analysis (missing values equal failure) of the data from M98-863 performed by Simpson and Chumney. After exhausting the 48-week data from the clinical trial, a second transition matrix that is based on the analysis of long term LPV/r Phase II trial data M97-720 [2] provides the transitions for the remaining cycles in stage 1. This transition matrix is modified for the NFV arm of the model to produce a difference between the LPV/r arm and NFV arm in viral breakthrough rate at 72 weeks that is equivalent to the difference observed at the end of the 48 weeks of the M98-863 trial. This approach captures the assumption that there is no additional divergence in the survival curve of viral load breakthrough between the two study arms (the most conservative assumption). Since viral load and CD4 cell counts can vary greatly from visit to visit, and patients in the M98-863 trial have three visits during a three-month period, a decision had to be made regarding which of the three visit measures to use for each of the 3-month periods. For CD4 cell count, a geometric mean of the three available measures was used. For the VL values, the highest measured VL value in a quarter until the patient’s VL becomes undetectable was used, and once they are classified as having reached suppression, the
highest measured VL value was used to classify them after VL breakthrough. Thus, any patient who reaches undetectable status is assumed to spend at least 3 months in this condition (1 cycle). All data analyses were performed using SAS software version 8.

For Stage 2 and 3, the transition matrices for the model were based on transitions observed for patients on HAART from the third quarter of therapy and until the end of the observational period from two large databases analyzed by Ghani and colleagues and described elsewhere [13, 14]. (Detailed information on the transition matrices is available from the senior author.) This transition matrix was used together with a one-time health state-specific increase in the intermediate period in CD4 cell count and suppression in viral load to undetectable levels that are representative of average patient responses to a 2nd HAART and 3rd HAART regimen. The response rates to 2nd HAART used in the model assumes an average increase of 50 CD4 cells/μL and a suppression to VL below 400 copies/μL of 70%. This is estimated by a percentage shift to a health state with the next higher CD4 cell category. In the sensitivity analysis testing the effect of resistance, NFV patients with 30% PI resistance were assumed to reach a suppression rate of 64%. Response to 3rd HAART regimen assumes an increase of 30 CD4 cells/μL and an undetectable VL rate of 30% of patients. These are empirical estimates based on analysis from HIV/AIDS patients treated in the infectious disease clinics of the Medical University of South Carolina (MUSC) or in practices that are part of the MUSC Primary Care Research Network (unpublished data Simpson 2000). The impact of resistance difference between patients started with NFV and those started with LPV/r was captured by the PI resistance difference observed in the M98-863 study (33% for NFV vs. 0% for
LPV/r observed through 48 weeks). This assumption is likely to underestimate the true resistance effect since it does not capture the 44% higher rate of resistance to 3TC reported for NFV patients who had viral breakthrough during the M98-863 clinical trial (81% for NFV vs. 37% for LPV/r, p<0.001).

Costs

Relevant resource utilization for routine HIV care, switching ART regimens and treatment for opportunistic infections were determined from analysis of 1998 and 1999 Medicaid data from South Carolina. Charges for inpatient care reported on the UB92 standard reporting form for Medicare billing were adjusted to approximate opportunity costs by using the HIV-specific cost-to-charge ratio reported by Andrulis and colleagues [16]. Costs of care for chronic OI conditions were based on the average cost per year observed in the Medicaid cohort, multiplied by the average survival time for patients with the OI condition. The 1998 and 1999 average cost weights were inflated to represent US costs in 2002 using the medical care portion of the consumer price index [17]. The cost weights derived by the costing methods described above are listed in Table 3.

Routine costs were estimated at $293 based on a routine visit including lab tests at the HIV clinic once every 3 months. The additional 3-month switch costs were estimated at $293, including 1 extra HIV clinic visit, 2 extra lab visits and genotyping, which was assumed for 50% of patients. We did not include any costs of changes in a HAART regimen due to toxicities and the treatment of toxicities in the model.
Daily antiretroviral drug costs were $18.52 for LPV/r and $19.92 for NFV, $14.50 for the 3TC and d4T backbone based on wholesale acquisition cost for the drugs reported by PriceProbe for 2002 [7]. Antiretroviral drug costs for model stage 2 and 3 were $50.50 and $58.00, respectively.

**Quality of Life**

Health related quality of life (HRQoL) was estimated specifically for each health state based on analysis of data from about 21,000 clinical trial patients assessed by the EuroQol quality of life instrument (EQ-5D) [18]. The preference weight modeling transformation developed by Dolan (1997)[18] was used to transform the original questionnaire responses. The EQ-5D data used came from patients enrolled in clinical trials with a large proportion of patients receiving ritonavir, and therefore predominantly reflect the side effect profile common to ritonavir. To reduce the potential bias from quality of life measures reflecting ritonavir-specific side effects, we adjusted the QALY weights by regression analysis to reflect levels of side effects (such as asthenia, depression, abdominal pain, diarrhea and headache) that were reported as average for patients in the M98-863 clinical trial. The resulting set of QALY weights are provided in Table 2.

**Model Assumptions**

A model is a simplification of reality and it can never reflect the incredible complexity observed in real practice data. One of the study goals was for this model to capture best clinical practices in HIV-disease as per recent Department of Health and Human Services
(DHHS) guidelines [19]. The model tried to capture these practices through specific
design choices and through the use of practice-relevant parameters. The progression
through the three stages in the model assumes that the relevant pattern of ART includes
two HAART regimens plus “salvage” therapy. Further, the decision to switch to new
therapy depends on ART history. The first switch will occur when a detectable VL is
reached after the trial data are exhausted. This reflects the goal of maximal viral
suppression[19]. A second switch happens when VL is detectable again, and a CD4 count
below 200 cells/μL has been reached. The speed of progression through model stages
(after the initial clinical trial data are exhausted) are based on epidemiologic data from
our data sources which shows that the average time with undetectable VL decreases as
ART history increases. The model also captures the fact that an initial CD4 cell count
increase from switching therapies occurs, but that the magnitude of this increase
diminishes as ARV treatment history increases. It is assumed that the percent of patients
who achieve undetectable VL as a result of switching ARV regimen diminishes as ARV
treatment history increases. The actual magnitudes of these dynamics in the model are
based on epidemiologic data of patients on HAART.

Sensitivity Analysis
Starting from the base-case analysis, the values of key cost and probability parameters
were varied to test their impact on overall cost and event rates. In the series of sensitivity
analyses, the point value of cost or probability parameters where the relative incremental
CER or cost-utility ratio (CUR, i.e., cost per QALY) became more advantageous (lower)
than $50,000 was considered the threshold value. The cutoff of $50,000 was chosen
because all published CERs or CURs for new HIV interventions that have become part of practice guidelines fall below this amount [9-11]. A clinically relevant range over which to vary the values of parameters was derived from referenced sources. If a threshold value fell within the ranges, then the analysis was sensitive to these parameters and the overall base case results were not conclusively in favor of either drug combination. If the threshold value fell outside indicated ranges, then the base case analysis was robust and conclusive.

**RESULTS**

The time that patients remain on their initial HAART regimen with undetectable VL is considered by experts to be one of the most important indicators of a regimen’s effectiveness. In clinical trials, this characteristic of a regimen is reported as the percent of patients with undetectable VL at the end of the trial in an intent-to-treat analysis. The percent of patients with VL < 400 copies/mL at 48 weeks in the M98-863 study was 75% for the LPV/r arm and 63% for the nelfinavir arm (Table 1). The assumptions behind the modeled time to loss of virologic response do not allow differences between treatment groups to widen after Week 48. Available data from study 863 beyond Week 48 suggests the magnitude of difference between treatment groups grows through Week 96 [20].

Thus, the modeled differences in the time to loss of virologic response may be expected to underestimate the true disparity between the treatment groups. When the model was stopped at precisely 50% survival for each arm, the median estimated time on the initial regimen for the LPV/r regimen was 962 days, compared to 837 days for the nelfinavir regimen.
The economic implications of this difference in the timing of the change to second-line HAART may relate to substantial savings in laboratory costs related to changing HAART as well as in avoidance of cost for the more expensive second-line regimen. Over the first five years, the model estimated that LPV/r could save total HIV care cost at $3,461 per patient compared with NFV, when PI resistance for subsequent regimens was not considered (Table 4). If the resistance advantage of LPV/r was taken into account, the cost savings by LPV/r was increased to $5,546 per patient over the first 5 years (Table 4).

The short term cost saving expected from the LPV/r treatment compared to the NFV treatment will eventually disappear because patients starting HAART on LPV/r are expected to live longer than patients starting HAART on NFV. This fact constitute the “economic penalty for survival” that is usual for interventions for patients with complex chronic conditions. However, early savings are valued (rightly or wrongly) by payers, and may indeed have substantial impacts on the present ability of state public programs to continue to provide drug therapy to all eligible patients. If it is assumed that ART naïve patients covered by public funding mechanisms (ADAP or Medicaid) constituted 30% to 50% of CDC’s estimated HIV infected individuals (850,000- 950,000) in 2001, and that an additional 10% to 20% of patients with AIDS were ART naïve and initiated therapy in 2001, then between 67,000 and 119,000 ART naïve patients would have initiated HAART in 2001. If these 67,000 ART naïve patients are placed on a HAART regimen with early savings and clinical outcomes similar to those reported here, the model predicts cost savings of $232 million over 5 years, even without a resistance advantage. If
the resistance advantage were included, the predicted savings over 5 years would be $372 million. If the ART naïve population who initiate HAART annually is closer to the upper range expected (about 119,000), the expected 5-year savings would be estimated at $412 (without the resistance benefit) and $660 million (with the resistance benefit) for the U.S. This level of saving would enable the program to fund nearly 7,000 more ART naïve patients for 5 years given the same public budget allocation.

Thus, using a 5-year time horizon, from a public payer budgetary perspective, the benefits of using a HAART regimen with early cost savings and similar or better clinical outcomes appear obvious. However, only an examination of the predicted lifetime cost and benefit differences can determine if a HAART regimen provides good value for the money invested, given the existence of high end-of life costs. As shown in Table 4, over lifetime, the model predicted that LPV/r therapy added 25.4 years survival per 100 ARV-naïve HIV patients compared to NFV therapy, at an incremental cost of $288,828 (undiscounted). This (when discounted at 3 percent per annum) resulted in the cost-effectiveness ratio (CER) for LPV/r over NFV at $6,376 per life year gained without taking the PI resistance difference into account, or an incremental cost utility ratio (CUR) at $6,653 per quality adjusted life year (QALY) gained. The classical economic indicator of “good value” is the CER or the CUR. While no accepted standard ratio exists, many authors consider $50,000 per year of life gained to indicate “good value” for expenditures related to improvement in care in the U.S. medical care system, and a value below $100,000 per QALY gained (CUR) to be acceptable. Our model prediction thus suggests that LPV/r is cost effective over nelfinavir when used in first line HAART therapy.
When the benefit of the PI resistance profile to 2\textsuperscript{nd} line therapy observed with LPV/r is included, both cost savings and a survival benefit for LPV/r therapy is expected (Table 4). In such cases, the CER or CUR for LPV/r over NFV cannot be calculated; instead the convention in economics is to report a prediction of LPV/r therapy as a “dominant” therapy.

**Sensitivity Analysis**

All cost value, utility value and OI event parameters were tested in the sensitivity analysis over relevant ranges. Varying the utility values from 50\% to 100\% and varying the clinical event (opportunistic infection) rates per health state from 50\% to 200\% over the base-case value did not alter the base case analysis conclusions. When the cost for opportunistic infection events were varied from 50\% to 200\% of the baseline cost, a 20\% increase in cost was observed, resulting in a decrease of the cost utility ratio by about 5\% from $6,653/QALY to $6,019/QALY. This result did not change the conclusion of the analysis, instead, it moved to the direction more in favor of LPV/r over NFV. When varying the discount rate from a range of 0 to 5\%, switch costs 50\% to 200\%, or routine cost from 50\% to 200\%, the conclusion of the base case analysis was not changed.

The cost per daily dose of LPV/r was the only cost parameter that affected the conclusions of the analysis. If the cost per daily dose of LPV/r was less than $17.45, LPV/r was a dominant therapy, indicating both improved survival and lifetime cost savings compared to nelfinavir. If LPV/r cost per daily dose was equivalent to nelfinavir
($19.92) then the undiscounted incremental cost per life year gained of LPV/r over NFV was $11,389 and the corresponding cost per QALY was $12,058, which still indicated that LPV/r therapy was very cost-effective compared to NFV therapy.

**DISCUSSION**

Laupacis and colleagues recommended that new technologies with cost savings or an incremental CER < $50,000 per life year saved should be considered for adoption in practice and are considered moderately cost-effective [22]. According to this criterion, LPV/r (with 2 NRTIs) is cost effective over NFV and should therefore be included in physicians’ choice for treating patients with HIV-disease. In a head to head clinical trial of first-line therapy for treatment naïve HIV patients, LPV/r+ 2 NRTIs resulted in a significantly greater proportion of patients achieving undetectable viral load (< 400 and < 50 copies/mL) than NFV+ 2 NRTIs at 48 weeks. Our model applied the 48-week results to project the expected effects of the trial results on life expectancy. As a result, the increased clinical response of LPV/r was translated to an increase of at least three months gain in life expectancy compared to NFV+ 2 NRTIs, for additional cost at $2,888 per patient over a lifetime. Further, when we extrapolated the point where exactly 50% of the population in each arm were still in the initial stage of the model, the time on 1st line therapy showed an expected 837 days for NFV, to 962 days for the LPV/r cohort.

Prospective data over a lifetime of treatment is preferred for making decisions on the adoption of new therapies. However, when such data are unavailable, a modeling analysis based on clinical trials are necessary. Therapy compliance was assumed to be the same as in randomized controlled trials (approximately 90%). The model, by necessity, greatly
simplifies the sequence of treatment decisions for a person with HIV, especially after the diagnosis of AIDS. However, this model improves our previous Markov-type models [9-10] by incorporating VL into the health state definition as suggested by the simulation model by Freedberg and colleagues [19], and by capturing the effects of sequential ARV regimen as demonstrated in our previously published simulation model [21]. Thus, the current model uses a state-transition (or Markov-type) structure to estimate disease progression by the CD4 cell count and VL values actually exhibited by patients enrolled in the LPV/r vs. NFV clinical trial. In addition, the model’s uncertainties were tested in the extensive sensitivity analysis. Our results capture the outcomes expected for two therapies with a 12% difference in undetectable VL at 48 weeks as reported in the clinical trial, given the cost differential for the two PIs used in this trial. The reported economic results may be expected to be different for regimens with different clinical outcomes and different drug costs. While it is important to note the limitations of this analysis, generally, the findings from this modeling study are robust to variations in all key parameters except efficacy differences and drug costs.

Based on 48-week trial data, the model predicts improved survival and savings of $3,461 per patient for the first five years for LPV/r compared to NFV. The cost effectiveness ratio for the LPV/r arm compared to the NFV arm indicates excellent value at $6,653/QALY for US patients. Sensitivity analysis suggests that the superior results for LPV/r are robust over a large range of values and assumptions. The CER and CUR results found in this study compares favorably to that of other therapies used in HIV-disease. Freedberg and colleague reported that antiretroviral therapy with three drugs vs.
two drugs has a cost of $13,000/QALY gained if patients start therapy when their CD4 cell count is about 500 cells/μL. Their estimate was $18,600/QALY when patients wait to start this treatment until their CD4 cell count declines below 100 cells/μl [11]. Goldie and colleagues reported a CUR of $8,700/QALY for prophylaxis against PCP with trimethoprim sulfa, as compared to no PCP prophylaxis [12]. The CUR found for LPV/r vs. nelfinavir also compares well to the value reported for general improvement in access to HAART and other needed care for people with HIV/AIDS. The U.S. Institute of Medicine reports a cost of $42,975 per QALY gained from implementing a public financing program for HIV/AIDS patients [23]. Thus, our base estimate of CUR at $6,653/QALY gained for LPV/r vs. NFV is well within the commonly accepted range that indicates good to excellent value for the money invested in a new therapy for U.S. patients.

These analyses indicate that LPV/r with 2 NRTIs provides important clinical improvements at a reasonable cost and thus is more attractive than NFV both medically and economically. The model predicts short term cost savings, and long-term incremental cost-effectiveness and cost-utility ratios for LPV/r (with 2 NRTIs) versus NFV (with 2 NRTIs), which are clearly well below the threshold for cost effective innovations in developed countries.

ACKNOWLEDGEMENTS
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REFERENCES


7. Price Probe Data Base 2002


Figure 1

Diagram of the Markov Model Structure

EVENTS

DEATH
absorbing state

Model Stage 1
LPV/r or NFV + 2 NRTIs

Intermediate Period 1
(3 months)
Switch to new therapy
Health state improves

Model Stage 2
New PI
plus New NRTIs
or NNRTI

Intermediate Period 2
(3 months)
Switch to new therapy
Health state improves,
but not as much as in 1

Model Stage 3
2 New PI, new NRTIs
perhaps NNRTI
Table 1. Clinical Trial M98-863 patient demographics and 48-week results

<table>
<thead>
<tr>
<th></th>
<th>LPV/r</th>
<th>NFV</th>
<th>p Value</th>
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<tbody>
<tr>
<td>N</td>
<td>326</td>
<td>327</td>
<td></td>
</tr>
<tr>
<td>% Male</td>
<td>80%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Average Age in years (Range)</td>
<td>38.4 (19-84)</td>
<td>37.3 (20-68)</td>
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</tr>
<tr>
<td>% Caucasian</td>
<td>56%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Median Baseline VL (Range)</td>
<td>5.01log$_{10}$</td>
<td>4.98 log$_{10}$</td>
<td></td>
</tr>
<tr>
<td>(RNA copies/ mL, Roche)</td>
<td>(2.60-6.82)</td>
<td>(2.79-6.84)</td>
<td></td>
</tr>
<tr>
<td>Amplicor HIV-1 Monitor)</td>
<td>copies/mL</td>
<td>copies/mL</td>
<td></td>
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<tr>
<td>Median Baseline CD4</td>
<td>232 cells/μL</td>
<td>232 cells/μL</td>
<td>(2-944)</td>
</tr>
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</table>

48 week Results

- Dropouts any cause
  - 17% LPV/r, 24% NFV

- VL < 400 copies/mL (ITT M=F)
  - 75% LPV/r, 63% NFV, p < 0.001

- VL < 400 copies/mL (OT) 93% LPV/r, 82% NFV, p < 0.001

- VL < 50 copies/mL (ITT M=F)
  - 67% LPV/r, 52% NFV, p < 0.001

- VL < 50 copies/mL (OT) 83% LPV/r, 68% NFV, p < 0.001

- CD4 change from baseline
  - LPV/r + 207 cells/μL, NFV 195 cells/μL, not stated

Notes:

ITT M=F: Intent to Treat and Missing=Failure. The ITT analysis included all randomized subjects with at least one post-baseline measurement. Missing =Failure: A
missing HIV RNA value for any reason at a given visit was considered above the limit of quantitation (400 copies/mL or 50 copies/mL).

OT: On treatment. The analysis included all observed data while subjects were on the assigned regimen. Missing values were excluded from the analysis, as were values obtained while treatment had been interrupted for at least 3 days.
Table 2 Model Health State Definitions, Risk of HIV-related Events, and Preference Weights for QALY Estimation.

<table>
<thead>
<tr>
<th>Health State</th>
<th>CD4 Range</th>
<th>VL Range</th>
<th>AIDS Events*</th>
<th>QALY Weight</th>
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</thead>
<tbody>
<tr>
<td>HS 1</td>
<td>&gt; 500</td>
<td>&lt; 400</td>
<td>1.71</td>
<td>.954</td>
</tr>
<tr>
<td>HS 2</td>
<td>&gt;500</td>
<td>&gt;=400</td>
<td>2.18</td>
<td>.938</td>
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<tr>
<td>HS 3</td>
<td>351-500</td>
<td>&lt; 400</td>
<td>1.71</td>
<td>.934</td>
</tr>
<tr>
<td>HS 4</td>
<td>351-500</td>
<td>&gt;=400</td>
<td>2.18</td>
<td>.931</td>
</tr>
<tr>
<td>HS 5</td>
<td>201-350</td>
<td>&lt; 400</td>
<td>2.84</td>
<td>.929</td>
</tr>
<tr>
<td>HS 6</td>
<td>201-350</td>
<td>400-19,999</td>
<td>3.31</td>
<td>.931</td>
</tr>
<tr>
<td>HS 7</td>
<td>201-350</td>
<td>&gt;= 20,000</td>
<td>4.25</td>
<td>.933</td>
</tr>
<tr>
<td>HS 8</td>
<td>50-200</td>
<td>&lt; 400</td>
<td>5.11</td>
<td>.863</td>
</tr>
<tr>
<td>HS 9</td>
<td>50-200</td>
<td>400-19,999</td>
<td>5.58</td>
<td>.865</td>
</tr>
<tr>
<td>HS 10</td>
<td>50-200</td>
<td>20,000-100,000</td>
<td>9.79</td>
<td>.856</td>
</tr>
<tr>
<td>HS 11</td>
<td>50-200</td>
<td>&gt; 100,000</td>
<td>14.47</td>
<td>.826</td>
</tr>
<tr>
<td>HS 12</td>
<td>&lt; 50</td>
<td>Any level</td>
<td>17.87</td>
<td>.781</td>
</tr>
<tr>
<td>HS 13- Dead</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Number of events expected over 3-month period for 100 patients
Table 3  HIV-related AIDS Events and Cost per Event

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Percent of All AIDS Events*</th>
<th>Cost per Event 2002 US Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis, oral or systemic</td>
<td>9.0</td>
<td>2,342</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>0.3</td>
<td>1,052</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>1.2</td>
<td>35,834</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>2.3</td>
<td>2,136</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>4.5</td>
<td>192,311</td>
</tr>
<tr>
<td>retinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other CMV infection</td>
<td>0.9</td>
<td>8,072</td>
</tr>
<tr>
<td>Coccidiosis</td>
<td>0.2</td>
<td>2,136</td>
</tr>
<tr>
<td>HIV-dementia</td>
<td>3.2</td>
<td>18,197</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>0.3</td>
<td>9,406</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>0.3</td>
<td>16,246</td>
</tr>
<tr>
<td>Kaposi Sarcoma, cutaneous</td>
<td>3.8</td>
<td>5,407</td>
</tr>
<tr>
<td>Kaposi Sarcoma, visceral</td>
<td>0.9</td>
<td>38,633</td>
</tr>
<tr>
<td>Lymphoma, not of central nervous system</td>
<td>0.6</td>
<td>25,337</td>
</tr>
<tr>
<td>Lymphoma of central nervous system</td>
<td>2.4</td>
<td>86,798</td>
</tr>
<tr>
<td>Event</td>
<td>Proportion</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>5.8</td>
<td>65,953</td>
</tr>
<tr>
<td>Pneumocystic pneumonia</td>
<td>13.0</td>
<td>5,027</td>
</tr>
<tr>
<td>Progressive multifocal leucoencephalopathy</td>
<td>1.4</td>
<td>24,203</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20.1</td>
<td>2,258</td>
</tr>
<tr>
<td>Salmonella sepsis</td>
<td>0.2</td>
<td>3,240</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>4.9</td>
<td>20,302</td>
</tr>
<tr>
<td>Toxoplasmic encephalitis</td>
<td>1.0</td>
<td>30,550</td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>22.8</td>
<td>46,602</td>
</tr>
</tbody>
</table>

*Expected proportion of all AIDS events by event type*
**Table 4.** Model Cost and Event Estimates for 100 Patients: Initial Five Years and Lifetime Cost Effectiveness and Cost Utility Ratios.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Total Cost</th>
<th>Total Cost</th>
<th>Cost Difference</th>
<th>Added Years</th>
<th>Cost Effectiveness Ratio</th>
<th>Cost Utility Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r</td>
<td>1,862,400</td>
<td>1,918,300</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm=A</td>
<td>1,882,179</td>
<td>1,980,796</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US $</td>
<td>2,075,217</td>
<td>2,156,184</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>2,273,943</td>
<td>2,338,229</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>2,397,764</td>
<td>2,444,135</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years Total</td>
<td>10,491,502</td>
<td>10,837,643</td>
<td>(346,141)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Total</td>
<td>28,526,301</td>
<td>28,237,473</td>
<td>288,828</td>
<td>25.4</td>
<td>$6,376/LY</td>
<td>$6,653/QALY</td>
</tr>
</tbody>
</table>

If PI Resistance included:

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Total Cost</th>
<th>Cost Difference</th>
<th>Added Years</th>
<th>Cost Effectiveness Ratio</th>
<th>Cost Utility Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years Total</td>
<td>(554,600)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Total</td>
<td>(61,100)</td>
<td>27.4</td>
<td>Cost saving</td>
<td>Cost saving</td>
<td></td>
</tr>
</tbody>
</table>