The Cost-effectiveness of Preventing AIDS-Related Opportunistic Infections

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**Context.**—Multiple options are now available for prophylaxis of opportunistic infections related to the acquired immunodeficiency syndrome (AIDS). However, because of differences in incidence rates as well as drug efficacy, toxicity, and costs, the role of different types of prophylaxis remains uncertain.

**Objective.**—To determine the clinical impact, cost, and cost-effectiveness of strategies for preventing opportunistic infections in patients with advanced human immunodeficiency virus (HIV) disease.

**Design.**—We developed a Markov simulation model to compare different strategies for prophylaxis of *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, *Mycobacterium avium* complex (MAC) infection, fungal infections, and cytomegalovirus (CMV) disease in HIV-infected patients. Data for the model were derived from the Multicenter AIDS Cohort Study, randomized controlled trials, and the national AIDS Cost and Services Utilization Survey.

**Main Outcome Measures.**—Projected life expectancy, quality-adjusted life expectancy, total lifetime direct medical costs, and cost-effectiveness in dollars per quality-adjusted life-year (QALY) saved.

**Results.**—For patients with CD4 cell counts of 0.200 to 0.300 × 10⁹/L (200-300/μL) who receive no prophylaxis, we projected a quality-adjusted life expectancy of 39.08 months and average total lifetime costs of $40 288. Prophylaxis for PCP and toxoplasmosis with trimethoprim-sulfamethoxazole for patients with CD4 cell counts of 0.200 × 10⁹/L (200/μL) or less increased quality-adjusted life expectancy to 42.56 months, implying an incremental cost of $16 000 per QALY saved. Prophylaxis for MAC for patients with CD4 cell counts of 0.050 × 10⁹/L (50/μL) or less produced smaller gains in quality-adjusted life expectancy; incremental cost-effectiveness ratios were $35 000 per QALY saved for azithromycin and $74 000 per QALY saved for rifabutin. Oral ganciclovir for the prevention of CMV infection was the least cost-effective prophylaxis ($314 000 per QALY saved). Results were most sensitive to the risk of developing an opportunistic infection, the impact of opportunistic infection history on long-term survival, and the cost of prophylaxis.

**Conclusions.**—The cost-effectiveness of prophylaxis against HIV-related opportunistic infections varies widely, but prophylaxis against PCP or toxoplasmosis and against MAC delivers the greatest comparative value. In an era of limited resources, these results can be used to set priorities and explore new alternatives for improving HIV patient care.

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**For editorial comment see p 160.**

The issues posed by these effective but expensive medications are clearly illustrated by the problems encountered by the AIDS Drug Assistance Programs. These are state-based programs in the United States, created to provide medications to HIV-infected patients with limited resources. They range widely in their coverage of medications, budgets, and patient eligibility. In early 1997, for example, New York State covered 182 medications while Georgia covered only 3. Sixteen states had waiting lists for eligible patients, and 11 states had cut back coverage because of budget constraints caused by the availability and cost of new medications. This variation in coverage suggests that the clinical and economic consequences of decisions regarding HIV medications are neither well understood nor agreed on.

To promote better clinical and policy decisions, we combined data on the natu-
METHODS
Model Overview

We developed a computer-based, probabilistic simulation model of the natural history of HIV infection and AIDS in patients whose CD4 lymphocyte counts decline to less than 0.3 \times 10^9/L (300/µL). Monthly probabilities of clinical events, including opportunistic infections, changes in CD4 lymphocyte count, toxic reactions to medications, and death, were used to simulate the course of disease in a hypothetical cohort of 1 million individuals. Monthly costs and health-related quality-of-life weights were assigned. Rates of opportunistic infection development, survival time, quality-adjusted survival time, and costs of care were assessed under a variety of scenarios for prophylaxis intervention, including the timing of prophylaxis. The model was developed using the C/C++ programming language (Microsoft, Seattle, Wash).

The analysis was performed from the societal perspective, following as closely as possible the reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine. Effectiveness data were derived from randomized controlled trials either published or presented at scientific meetings or, in 1 case, a meta-analysis of those trials. Economic costs of patient care and treatment were derived from a national AIDS data set (ACUSUS). Time preference was included by discounting future costs and quality-adjusted life-years (QALYs) saved at an annual rate of 3%. Sensitivity analysis was performed to determine the robustness of the cost-effectiveness results in the face of reasonable variation in the underlying data assumptions. Performance of alternative prophylactic strategies was measured by the incremental cost-effectiveness ratio, defined as the extra cost of a specific strategy divided by its extra effectiveness in years of life saved or QALYs saved. This is a measure of value for money, denoting the average, additional resource consumption required to extend life expectancy in the population by 1 year. A higher cost-effectiveness ratio implies a lower degree of comparative value.

Figure 1.—The Markov model has 3 broad categories of states: chronic, acute, and death. Each is further stratified by CD4 cell count and history of opportunistic infection (OI). Death may be caused by an acute OI, a chronic acquired immunodeficiency syndrome (AIDS) condition, or non-AIDS causes. See the “Methods” section for details of transitions between states.

Model Structure

Progression of disease, risks of clinical events, and resource consumption were all linked to CD4 lymphocyte count. Because data on CD4 cell counts suggest that onset of the most common opportunistic infections can be grouped on the basis of particular CD4 cell count thresholds, the model defines 4 CD4 lymphocyte count strata: 0.201 to 0.3 \times 10^9/L (201-300/µL), 0.101 to 0.200 \times 10^9/L (101-200/µL), 0.051 to 0.100 \times 10^9/L (51-100/µL), and 0.000 to 0.050 \times 10^9/L (0-50/µL). For each 1-month time cycle, the stratum-specific probabilities and costs associated with CD4 cell count changes and other clinical events were identified. A single hypothetical patient was followed in the model until death. The model specified PCP, toxoplasmosis, MAC infection, fungal infections, and CMV infection as distinct opportunistic infections, all of which are observed to occur in AIDS patients with CD4 cell counts less than 0.3 \times 10^9/L (300/µL). Other complications of AIDS, such as wasting syndrome, lymphoma, Kaposi sarcoma, tuberculosis, and bacterial infections, were grouped together as “other AIDS,” since they were not the specific targets of prophylactic strategies in the model.

For the analysis we used a Markov (state-transition) model, a mathematical representation of HIV illness and AIDS. Markov models depict the natural history of disease as an evolving sequence of mutually exclusive “health states,” defined to capture important clinical traits, such as CD4 level and acute event history. They also make the assumption that patients assigned to a given health state incur similar economic costs and enjoy comparable quality of life. Markov models use what is known about the population, the disease, and the effect of interventions to govern the transitions into and out of the various states. Figure 1 provides a simplified illustration of our Markov modeling framework. We classified the natural history of HIV illness into 3 broad categories of states: chronic, acute, and death. Each live state was further stratified on the basis of CD4 cell count level and opportunistic infection history. Patients entered the system via the chronic state. The development of an acute opportunistic infection triggered a transition from the chronic state to an acute state. Survivors returned to a chronic state that captured their opportunistic infection history; all others proceeded to the death state. Deaths from either chronic AIDS (eg, wasting) and non–AIDS-related causes (eg, motor vehicle crashes) also occurred directly from the chronic state.

The model depicted drug efficacy as a percent reduction in the incidence of opportunistic infections. For each type of acute opportunistic infection, prophylaxis could be started in any of the 4 CD4 strata. The model incorporated combinations of prophylaxis against different opportunistic infections and included crossover to second- and third-line agents as a result of toxic effects. Adherence in the main analysis was assumed to be comparable with the level of adherence in the clinical trials, so the efficacy estimates found in the trials reflect some degree of underlying nonadherence. Adherence could be decreased further by assuming that some percentage of patients took less than the prescribed dosage of medication and had a decrease in prophylaxis efficacy. Drug resistance was modeled by assuming that a fixed percentage of patients with breakthrough opportunistic infections while receiving prophylaxis had resistant organisms.
The model distinguished between 2 types of CD4 lymphocyte counts. An individual’s “true” underlying CD4 lymphocyte count determined the risk of opportunistic infections and had a probability of declining each month regardless of whether a CD4 test was done. An individual’s “observed” CD4 cell count, reflecting results of the most recent CD4 tests, was the information available to individuals and clinicians for decisions regarding prophylaxis. The model allowed for CD4 lymphocyte testing to be done monthly or at less frequent intervals. In the main analysis, we assumed that CD4 testing was done every 3 months.

Clinical Data

CD4 Cell Count Decline and Risk of Opportunistic Infections.—Data on the monthly risk of CD4 cell count decline and of developing opportunistic infections were derived from the MACS. This is an ongoing, prospective study of 2076 HIV-infected men followed up since 1984 in 4 cities in the United States.21 Details of the cohort have been described elsewhere.16,19,20 Estimates of CD4 cell count declines and incidence of opportunistic infections were developed using an incidence density analysis.21 We assumed that the decline was constant between each 2 consecutive CD4 cell count assessments. Using MACS data, the event of interest was defined as change from 1 CD4 stratum to the next lower stratum, and follow-up time (month-months) a participant spent in each CD4 stratum was summed. This analysis also allowed individuals to move into the next higher CD4 stratum. The analysis was repeated, using opportunistic infections and death as events. Because CD4 cell counts tended to be missing at the time of the occurrence of opportunistic infections and death, a random-effects model was used to impute the missing data.22,23 Based on CD4 cell count data from MACS, individuals were stratified by their last CD4 cell count into the 4 groups corresponding to the CD4 strata described above. For each group, a separate model with random intercept and fixed slope (CD4 cell count decline per 6 months) was fitted. The fixed slope was applied to the last available CD4 cell count to obtain the CD4 level at occurrence of opportunistic infection or death (Table 1).

Our choice of a 1-month cycle length reflects the realities of HIV clinical care. However, CD4 transition rates obtained from the MACS data set are reported on a 6-month basis. The translation of semiannual data into monthly transition probabilities was accomplished via a process described by Beck and Pauker.24

Because members of the MACS cohort were receiving either no antiretroviral drugs (before 1989) or zidovudine monotherapy in the data available for this analysis, estimates of CD4 cell count decline and risk of opportunistic infections reflect less intensive use of antiretroviral therapy than is now standard. The impact of current combination antiretroviral use on the analysis is considered in the sensitivity analysis below.

Efficacy and Toxicity Data.—For each prophylactic regimen, the efficacy in preventing the opportunistic infection, as well as rates of minor and major toxic effects, was derived from published literature. All efficacy data were from randomized controlled trials.21,25 In the case of CMV prophylaxis, we chose to use the study by Spector et al as our source for the baseline ganciclovir efficacy estimate (49%). However, because this estimate differs so greatly from the 0% efficacy reported by Brosgart et al,26 we explored values ranging from 0% to 100% in sensitivity analysis. Rates of toxicity in the model were defined according to the criteria of the AIDS Clinical Trials Group.26 Minor toxic effects (grades 1 and 2) did not require discontinuation of therapy; major toxic effects (grades 3 and 4) required discontinuation of therapy and crossover to a second- or third-line agent for prophylaxis.

Cost Data

Cost data were estimated from the 1995 Red Book and the ACSUS data set.12,13,27 This data set was a national survey of nearly 2000 HIV-infected persons designed to provide utilization and charge estimates for health care services for March 1991 through August 1992. The survey sampled AIDS patients in 10 cities in the United States.

For our analysis, medical chart abstracts and hospital billing data from ACSUS were used to assign charges and person-months of follow-up, stratified according to history of opportunistic infection, current opportunistic infection, prophylaxis use, and months in which death from AIDS or other causes occurred. For each hospitalized person, the cost of care was calculated as total charges accumulated in the given state, divided by the corresponding months of follow-up. To derive true economic costs from charges,21 we calculated a single cost-to-charge ratio for the ACSUS data set. We developed a city-specific cost-to-charge ratio for each of the 10 cities included in ACSUS. The 1991 cost-to-charge ratio for each hospital that admitted AIDS patients in a city (obtained from Medicare) was weighted by that hospital’s percent contribution to total 1991 inpatient AIDS admissions for the city.27 Each city-specific ratio was then weighted by that city’s percent contribution to total 1991 inpatient AIDS admissions for the 10 cities.27 The resulting weighted average ratio of 0.5995 was applied to the charges derived from ACSUS to estimate costs (Table 1). The cost of a CD4 test was derived from the Boston Medical Center cost accounting system. All costs were converted to 1995 dollars using the medical care component of the consumer price index.20 Costs for diseases other than AIDS were excluded because they are small compared with AIDS-related costs for this target population.

Health-Related Quality-of-Life Data

Data linking perceived health status to the states defined by our model were obtained from AIDS Clinical Trials Group protocols 019, 108, 157, and 204. No preference-weighted health status

<table>
<thead>
<tr>
<th>CD4 Stratum, No. of Cells x 10^9/L</th>
<th>Monthly Risk, %*</th>
<th>Cost, $†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.201-0.300 (201-300)</td>
<td>0.0476</td>
<td>480</td>
</tr>
<tr>
<td>0.101-0.200 (101-200)</td>
<td>0.0462</td>
<td>453</td>
</tr>
<tr>
<td>0.051-0.100 (51-100)</td>
<td>0.0725</td>
<td>192</td>
</tr>
<tr>
<td>0.0-0.050 (0-50)</td>
<td>...</td>
<td>629</td>
</tr>
</tbody>
</table>

*Probability of moving from current CD4 stratum to adjacent CD4 stratum below.
†Costs are derived from the AIDS Cost and Services Utilization Survey.15 For opportunistic infections, costs include toxic effects, was derived from published literature.
instruments were used in these trials. The closest proxy was a global health status question, “How would you rate your current state of health?” Possible responses of excellent, very good, good, fair, and poor were assigned point values of 100, 80, 60, 40, and 20, respectively. These were then converted to quality weights using the power transformation method of Torrance. This method shows that rating scale (RS) scores are related to time trade-off (TTO) scores by the following function:

\[ \text{TTO} = 1 - (1 - \text{RS})^{1.25} \]

By using clinical trial–based responses for patients without opportunistic infections, with acute opportunistic infections, and with a history of opportunistic infections, we derived utility weights for each state in the model (Table 2).

**RESULTS**

Reference Case Analysis

Different strategies for prophylaxis produced differences in quality-adjusted survival, total lifetime costs of care, and cost-effectiveness. Quality-adjusted life expectancy ranged from 39.08 months with no prophylaxis to 42.56 months with the use of trimethoprim-sulfamethoxazole prophylaxis for PCP and toxoplasmosis for patients with CD4 cell counts of 0.200×10^9/L (200/µL) or less (Table 3). Prophylaxis for MAC with azithromycin, clarithromycin, or rifabutin, for fungal infections with fluconazole, and for CMV infections with oral ganciclovir, all began when CD4 cell counts were 0.050×10^9/L (50/µL) or less, had smaller impacts on quality-adjusted life expectancy.

In the absence of prophylaxis, projected total lifetime costs were $40,288 (Table 3). Prophylaxis for PCP and toxoplasmosis with trimethoprim-sulfamethoxazole increased costs to $44,786, primarily because of the longer life expectancy associated with PCP prophylaxis. The incremental cost-effectiveness ratio for PCP prophylaxis was $16,000 per QALY saved, compared with no prophylaxis. For MAC, fungal, or CMV prophylaxis, total lifetime costs ranged from $40,749 to $46,009. In terms of cost-effectiveness, the MAC prophylaxis strategies ranged from $35,000 per QALY saved for azithromycin, through $8,000 per QALY saved for clarithromycin, to $74,000 per QALY saved for rifabutin; fluconazole was $100,000 per QALY saved, and oral ganciclovir was $314,000 per QALY saved, each compared with no prophylaxis.

**Mortality With a History of Opportunistic Infection**

Analysis of the MACS cohort suggests that patients with a history of an opportunistic infection have significantly higher monthly mortality, controlling for CD4 cell count, than those without a history of an opportunistic infection (unpublished data; see also Moore and Chaisson and Finkelstein et al). Accounting for these differential mortality estimates produces the most optimistic cost-effectiveness ratios for prophylaxis, because the greater the degree to which mortality is attributed to an opportunistic infection, the more attractive prevention will be. We also ran the model limiting the “attributable” mortality from an opportunistic infection to that which occurred within 30 days of diagnosis (Table 3). In this case, all prophylactic interventions had a smaller impact on life expectancy, and prophylaxis was generally less cost-effective. Nevertheless, there was no change in the relative ranking of strategies for prophylaxis.

**Health-Related Quality of Life**

To test the impact of the quality weights in the model, we also ran the analysis unadjusted for health-related quality of life. Table 4 demonstrates that there were only small differences in the unadjusted cost-effectiveness ratios. Prophylaxis for PCP and MAC remained most cost-effective; fungal and CMV prophylaxis was least cost-effective.

**Drug Timing and Incidence of Opportunistic Infections**

The cost-effectiveness of prophylaxis was highly dependent on the incidence

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**Table 2.—Health-Related Quality-of-Life Adjustments for Patients With Acute Opportunistic Infections or CD4 States Without Opportunistic Infections**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RS Score</th>
<th>QALY Adjusted Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>2.2</td>
<td>0.61</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>2.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>2.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>2.4</td>
<td>0.65</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>2.4</td>
<td>0.65</td>
</tr>
<tr>
<td>Other AIDS diagnoses</td>
<td>2.0</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**Table 3.—Costs, Life Expectancy, and Cost-effectiveness of Different Strategies for Preventing Opportunistic Infections, Adjusted for Health-Related Quality of Life**

<table>
<thead>
<tr>
<th>Prophylaxis Strategy</th>
<th>Agent*</th>
<th>CD4 Stratum, No. of Cells ×10^9/L (No. of Cells/µL)</th>
<th>Quality-Adjusted Life Expectancy, mo</th>
<th>Cost-effectiveness, $/QALY†</th>
<th>30-d Attributable Risk Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis</td>
<td></td>
<td>0.200 (±0.200)</td>
<td>40 288</td>
<td>39.08</td>
<td>43 880</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>Trимethoprim-sulfamethoxazole</td>
<td>0.050 (±0.050)</td>
<td>40 749</td>
<td>39.24</td>
<td>35 000</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td></td>
<td>0.050 (±0.050)</td>
<td>41 164</td>
<td>39.26</td>
<td>50 000</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Fluconazole</td>
<td>0.050 (±0.050)</td>
<td>41 426</td>
<td>39.22</td>
<td>100 000</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Ganciclovir</td>
<td>0.050 (±0.050)</td>
<td>46 009</td>
<td>39.30</td>
<td>314 000</td>
</tr>
</tbody>
</table>

*Dosages for prophylaxis were as follows: trimethoprim-sulfamethoxazole, 160/800 mg/d; azithromycin, 1200 mg/week; clarithromycin, 500 mg twice a day; rifabutin, 300 mg/d; fluconazole, 100 mg/d; and ganciclovir, 1000 mg 3 times a day.
†The difference in cost divided by the difference in quality-adjusted life expectancy for each strategy compared with no prophylaxis. $/QALY indicates dollars per quality-adjusted life-year saved, rounded to nearest $1000.
‡Fungal infections include esophageal and systemic candidiasis, cryptococcus, histoplasmosis, and coccidioidomycosis.
Table 4.—Costs, Life Expectancy, and Cost-effectiveness of Different Strategies for Preventing Opportunistic Infections, Unadjusted for Health-Related Quality of Life and Assuming Combination Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Prophylaxis Strategy</th>
<th>Agent†</th>
<th>CD4 Stratum, No. of Cells ×10^6/L (No. of Cells/µL)</th>
<th>Unadjusted for Quality of Life</th>
<th>Assuming Combination Antiretroviral Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Costs, $</td>
<td>Life Expectancy, mo</td>
<td>Cost-effectiveness, $/QALY†</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td></td>
<td>40 288</td>
<td>45.07</td>
<td>. . .</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia/ toxoplasmosis</td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>≤0.200 (≥200)</td>
<td>44 786</td>
<td>49.80</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>Azithromycin</td>
<td>≤0.050 (≥50)</td>
<td>40 749</td>
<td>45.85</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>≤0.050 (≥50)</td>
<td>41 164</td>
<td>45.87</td>
</tr>
<tr>
<td></td>
<td>Rifabutin</td>
<td>≤0.050 (≥50)</td>
<td>41 486</td>
<td>45.81</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Fluconazole</td>
<td>≤0.050 (≥50)</td>
<td>41 426</td>
<td>45.81</td>
</tr>
<tr>
<td>Cytomegaloovirus</td>
<td>Ganciclovir</td>
<td>≤0.050 (≥50)</td>
<td>46 009</td>
<td>45.93</td>
</tr>
</tbody>
</table>

*Incorporates monthly costs of lamivudine (150 mg twice a day) and indinavir (800 mg 3 times a day) and assumes a 20% decrease in the risk of CD4 cell count decline compared with zidovudine monotherapy.

†See first footnote to Table 3 for doses.

‡Each strategy compared with no prophylaxis. $/QALY indicates dollars per quality-adjusted life-year saved; $QALY, dollars per quality-adjusted life-year saved.

Table 5.—Impact of Medication Cost on Cost-effectiveness of Prophylaxis in Human Immunodeficiency Virus–Infected Patients

<table>
<thead>
<tr>
<th>Agent†</th>
<th>Current Annual Cost, $</th>
<th>Cost-effectiveness, $/QALY‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>1450</td>
<td>12 000</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2455</td>
<td>23 000</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>2140</td>
<td>32 000</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2472</td>
<td>55 000</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>15 600</td>
<td>134 000</td>
</tr>
</tbody>
</table>

*All prophylaxis begun with CD4 cell count of 0.050×10^6/L (50/µL) or less. Doses appear in the first footnote to Table 3. $/QALY indicates dollars per quality-adjusted life-year saved compared with no prophylaxis, based on a 50% reduction in current cost for each medication.12

Table 6.—Cost-effectiveness of Combinations of Prophylaxis

<table>
<thead>
<tr>
<th>Prophylaxis Strategy*</th>
<th>Lifetime Costs, $</th>
<th>Quality-Adjusted Life Expectancy, mo</th>
<th>Cost-effectiveness, $/QALY†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No prophylaxis</td>
<td>40 288</td>
<td>39.08</td>
<td>. . .</td>
</tr>
<tr>
<td>2. Trimethoprim-sulfamethoxazole</td>
<td>44 786</td>
<td>42.56</td>
<td>16 000</td>
</tr>
<tr>
<td>3. Trimethoprim-sulfamethoxazole, azithromycin</td>
<td>45 944</td>
<td>43.04</td>
<td>29 000</td>
</tr>
<tr>
<td>4. Trimethoprim-sulfamethoxazole, fluconazole</td>
<td>47 046</td>
<td>43.01</td>
<td>Dominated</td>
</tr>
<tr>
<td>5. Trimethoprim-sulfamethoxazole, azithromycin, fluconazole</td>
<td>48 596</td>
<td>43.60</td>
<td>59 000</td>
</tr>
<tr>
<td>6. Trimethoprim-sulfamethoxazole, ganciclovir</td>
<td>54 628</td>
<td>43.20</td>
<td>Dominated</td>
</tr>
<tr>
<td>7. Trimethoprim-sulfamethoxazole, azithromycin, ganciclovir</td>
<td>56 812</td>
<td>43.83</td>
<td>Dominated</td>
</tr>
<tr>
<td>8. Trimethoprim-sulfamethoxazole, fluconazole, ganciclovir</td>
<td>58 082</td>
<td>43.80</td>
<td>Dominated</td>
</tr>
<tr>
<td>9. Trimethoprim-sulfamethoxazole, azithromycin, fluconazole, ganciclovir</td>
<td>61 119</td>
<td>44.62</td>
<td>147 000</td>
</tr>
</tbody>
</table>

*Strategy numbers correspond to those in Figure 2. Doses are detailed in the first footnote to Table 3. All strategies were initiated with CD4 cell count of 0.050×10^6/L (50/µL) or less, except for trimethoprim-sulfamethoxazole, which was started at CD4 cell count of 0.200×10^6/L (200/µL) or less.

†All cost-effectiveness ratios are incremental compared with next less costly, nondominated strategy. For example, strategy 5 is compared with strategy 3. $/QALY indicates dollars per quality-adjusted life-year saved. Dominated was defined as alternative allocations producing higher life-expectancy at lower cost.24

Medication Cost

The cost of each prophylactic agent also had an impact on the cost-effectiveness of prophylaxis. If the cost of MAC prophylaxis medications was reduced by 50%, then the cost-effectiveness ratios for azithromycin, clarithromycin, and rifabutin decreased by about 23%, 12%, and 25%, respectively (Table 5). To achieve a cost-effectiveness threshold of $50 000 per QALY saved, however, the cost of fluconazole would have to be reduced to approximately $100 per month (>50% reduction) and oral ganciclovir to about $350 per month (a 73% reduction).

Antiretroviral Medications and CD4 Cell Count Decline

The base-case analysis used data from MACS patients who were receiving either no antiretrovirals or zidovudine monotherapy, the standard of care from 1987 to 1991.24 To understand the cost-effectiveness of prophylaxis for opportunistic infections in the current setting, we used time-varying hazards for the risk of MAC infection, fungal infections, Mycobacterium avium complex, and toxoplasmosis defined as alternative allocations producing higher life-expectancy at lower cost.36

The cost-effectiveness of prophylaxis for opportunistic infections did not change substantially, and CMV prophylaxis remained the least cost-effective, with a ratio of $342 000 per QALY saved.

Combinations of Prophylaxis

We found that using multiple preventive agents simultaneously was generally more cost-effective than using them individually (Table 6). This is because preventing one opportunistic infection makes others relatively more common. In the case of CMV prophylaxis, however, the incremental cost-effectiveness ratio of oral ganciclovir remained higher than $140 000 per QALY saved, regardless of what other types of prophylaxis the patient was already receiving. Figure 2 presents the available strategy alternatives in terms of total lifetime costs and quality-adjusted life expectancy. The most attractive programs are in the upper left corner of the figure (greater health benefits at lower cost). Some strategies are clearly more attractive than others; for example, strategy 3 (trimethoprim-sulfamethoxa-
zole and azithromycin) costs less and delivers greater health benefits than strategy 4 (trimethoprim-sulfamethoxazole and fluconazole). In this sense, strategy 4 may be said to be “dominated.” Strategy 3, however, does not dominate strategy 5 (trimethoprim-sulfamethoxazole, azithromycin, and fluconazole); while strategy 5 costs more, it delivers greater health benefits. Because strategies 1, 2, 3, 5, and 9 deliver increasing benefits for additional expenditures, they belong to what economists refer to as the “efficient set” of strategies. Allocation of resources within this set yields the greatest possible health benefit.

COMMENT

Opportunistic infections remain a common cause of morbidity, mortality, and cost for patients with advanced HIV disease. Previous cost-effectiveness analyses in this area have focused on individual opportunistic infections and have generally found both primary and secondary PCP prophylaxis to be reasonably cost-effective, while MAC, fungal, and CMV prophylaxis are less cost-effective. To understand the relative cost-effectiveness of different strategies for prophylaxis, both individually and in combination, we developed a comprehensive simulation model of advanced HIV disease.

We found little variation in life expectancy, consistent with clinical trials of prophylaxis, but total costs and cost-effectiveness varied widely. Prophylaxis for PCP begun with CD4 cell counts of 0.200 × 10^9/L (200/µL) or less increased quality-adjusted life expectancy by 3.48 months compared with no prophylaxis and had a cost-effectiveness ratio of $16,000 per QALY saved. For MAC prophylaxis, the choice of initial agent had an important effect on the results. Beginning with CD4 cell counts of 0.050 × 10^9/L (50/µL) or less, azithromycin was the most cost-effective ($35,000 per QALY saved), followed by clarithromycin ($38,000 per QALY saved), while rifabutin was the least cost-effective ($74,000 per QALY saved). Reducing the cost of any of these agents by 50% improved the cost-effectiveness ratios; starting prophylaxis with CD4 cell counts of 0.100 × 10^9/L (100/µL) or less, rather than 0.050 × 10^9/L (50/µL) or less, made prophylaxis less cost-effective.

The sensitivity analysis also delineated areas in which more research may be helpful. One such area is so-called chronic mortality (i.e., AIDS-related deaths not associated with an acute infection). Our analysis showed that the degree to which chronic deaths were attributable to a patient’s history of a given opportunistic infection had an important impact on the cost-effectiveness of preventing that infection. There are also no good quality-of-life data available for specific opportunistic infections that could be used to track people through the course of HIV disease. The quantitative cost-effectiveness ratios changed when adjusted and unadjusted for quality of life, but the relative rankings and policy implications did not.

The analysis also showed that cost-effectiveness was highly dependent on both the incidence of opportunistic infections and the assumed level of patient adherence. This suggests that MAC prophylaxis was much more cost-effective when initiated at patient CD4 cell counts of 0.050 × 10^9/L (50/µL) rather than at 0.100 × 10^9/L (100/µL). If patients at increased risk of CMV disease could be identified (for example, with the use of CMV polymerase chain reaction), then CMV prophylaxis might become substantially more cost-effective. If adherence in actual practice were lower than we have modeled, resulting in lower efficacy, then prophylaxis would be less cost-effective.

There are several important limitations to this analysis. Although the model captures much of the complexity of HIV disease, it is still a simplification of a complicated disease process. Ideally, we would explicitly model other important complications of HIV, including, for example, bacterial infections and tuberculosis. In addition, efficacy and toxicity data from randomized trials may not be representative of clinical practice. If efficacy in practice were actually lower, each strategy would be less cost-effective than we have shown.

The clinical risks incorporated into the model were also based on patients generally receiving zidovudine monotherapy, which is no longer the standard of care. Because no good natural history data are yet available regarding the risk of each opportunistic infection in patients receiving combination antiretroviral drugs, we examined the impact of these newer medications in sensitivity analysis. When we modeled the impact of combination antiretroviral drugs as a reduction in the probability of CD4 cell count decline, then overall life expectancy increased. This also has the effect of making prophylaxis for individual opportunistic infections less cost-effective, assuming that the higher CD4 cell counts attributable to combination antiretroviral drugs are associated with fewer opportunistic infections. However, regardless of assumptions about CD4 cell count decline, the relative ranking and qualitative cost-effectiveness results did not change for different prophylaxis strategies. Three levels of HIV viral RNA have also recently become standard practice, particularly for defining prognosis and monitoring the effect of antiretroviral medications. As data become available on the risk of opportunistic infections stratified on both CD4 cell count and HIV viral RNA level, these can be incorporated into the model.

The model was structured to parallel important HIV clinical policy questions, and the results support the 1997 US Public Health Service–Infectious Diseases Society of America Guidelines for the Prevention of Opportunistic Infections. These guidelines suggest that trimethoprim-sulfamethoxazole (in patients with a CD4 cell count of <0.200 × 10^9/L [200/µL]) and either azithromycin or clarithromycin (in patients with a CD4 cell count of <0.050 × 10^9/L [50/µL]) be strongly recommended as standard of care, while fluconazole (in patients with a CD4 cell count of <0.050 × 10^9/L [50/µL]) and oral ganciclovir (in patients with a CD4 cell count of <0.050 × 10^9/L [50/µL]) are generally not recommended.

These results are also directly applicable to current decisions being made with regard to state-based AIDS Drug Assistance Programs. From a policy perspective, if the goal is to make the most effective use possible of available funds, then PCP prophylaxis should be made available to all patients. The next priority should be MAC prophylaxis, where azithromycin is most cost-effective as first-line therapy. Only when patients have access to those medications is it reasonable, from a cost-effectiveness perspective, to consider fluconazole and
then perhaps oral ganciclovir. This con-
trasts with the current policies in some states
where all medications are available
to those enrolled in programs, but
waiting lists exist for others who are eli-
gible. Those types of policies should be re-
considered.

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To the Editor: The article by Drs Lederle and Simel1 brings to the clinician’s attention the serious nature of abdominal aortic aneurysms (AAAs). While the article will serve as a valuable reference for clinicians, their last sentence must be disputed. When a ruptured AAA is suspected, imaging studies such as ultrasonography or computed tomography should not be performed. When a patient presents to the emergency department or a physician’s office with hypotension, a pulsatile abdominal mass, and associated flank or abdominal pain, the patient should be taken directly to the operating room for exploration and repair of a ruptured AAA. Delaying operation with imaging studies only allows the patient’s condition to become more unstable. Patients may die as a result of delay while awaiting preoperative studies. It has always been my contention that more patients will die of an AAA on the table of a computed tomography scanner than will die on the operating table. It is better to treat a nonruptured aneurysm as an emergency than to treat a ruptured aneurysm electively.

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1. Lederle FA, Simel DL. Does this patient have abdominal aortic aneurysm? JAMA. 1999;281:77-82.

To the Editor: Drs Lederle and Simel1 state “the only physical examination maneuver of demonstrated value for the diagnosis of an AAA is abdominal palpation.” This is not quite accurate. I have found that visual observation of the relaxed abdominal wall in medium and large AAAs often gives the examiner a sense of a pulsatile mass in the mid abdomen, especially if the clinician observes the abdominal wall somewhat tangentially from the patient’s side, rather than from directly over the patient’s abdomen. When this finding is demonstrated to medical students and residents, it is quite instructive for them to actually visualize the location of the pulsatile mass in the central abdomen.

Second, it may be too basic to mention, but it is common to witness students, residents, and practicing physicians palpating for a pulsatile mass without holding their hands still. The pulsatile nature of an intra-abdominal structure cannot be appreciated when the examiner’s hands are in motion.

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South Bend, Ind

1. Lederle FA, Simel DL. Does this patient have abdominal aortic aneurysm? JAMA. 1999;281:77-82.

In Reply: We agree with Dr Callis that patients with abdominal pain and shock should be taken directly to the operating room. However, many patients with ruptured AAAs have a more subtle presentation, and, in these cases, diagnostic confirmation is often necessary.1 Our intention was to emphasize that once a ruptured AAA is suspected, physical examination alone should not be relied on to exclude the diagnosis.

Dr Friend has proposed a physical finding that, to our knowledge, has not been previously reported in the literature. Until data are presented demonstrating its value, we stand by our statement. We have recently evaluated a similar finding, the transmitted epigastric pulse, and found it to be without value (unpublished data, 1999). We agree that the examiner’s hands should not be moving as the aorta is assessed between the 2 index fingers and hope that this was implied in our description, but we thank Friend for emphasizing this point.

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CORRECTIONS

Incorrect Data: In the Original Contribution entitled “The Cost-effectiveness of Preventing AIDS-Related Opportunistic Infections” published in the January 14, 1998, issue of THE JOURNAL (1998;279:130-136), the cost-effectiveness ratios in dollars for Pneumocystis carinii pneumonia and toxoplasmosis prophylaxis were incorrect. In Table 3 on page 133, the ratio should be 2300 (not 16 000) per quality-adjusted life-year saved. In Table 4 on page 134, in the analyses unadjusted for mortality, the ratios should be 1900 (not 13 000) per year of life saved; and 10 200 (not 22 000) per quality-adjusted life-year saved, respectively. In Table 6 on page 134, the ratio for strategy 2 should be 2300 (not 16 000) per quality-adjusted life-year saved. The revised data do not affect the article’s policy conclusions.

Incorrect Number: In the Original Contribution entitled “Starting Insulin Therapy in Patients With Type 2 Diabetes: Effectiveness, Complications, and Resource Utilization” published in the November 26, 1997, issue of THE JOURNAL (1997;278:1663-1669), there was an incorrect number in the “Results” section. On page 1666, in line 20 of the first full paragraph, the percentage should be 15%.