Background: The appropriate time to initiate antiretroviral therapy is controversial for human immunodeficiency virus (HIV)–infected patients with CD4 cell counts between 200/µL and 350/µL and low levels of HIV RNA, potentially leading to barriers to treatment access.

Objective: To examine the effect of cholesterol changes and fat redistribution symptoms on the clinical benefits and cost-effectiveness of early antiretroviral therapy in these patients.

Methods: We used a state-transition model to compare initiating antiretroviral therapy at CD4 cell counts of 350/µL (early therapy) with initiating therapy at CD4 cell counts of 200/µL (deferred therapy) in patients with HIV RNA levels of 10,000 to 30,000 copies/mL. Data were from randomized clinical trials, cohort studies, and other published literature.

Results: If cholesterol changes associated with antiretroviral therapy resulted in a permanent increase in coronary heart disease risk, life expectancy with early therapy was 16.54 years (vs 16.66 years without this risk) and with deferred therapy was 13.73 years (vs 13.80 years without this risk). Early therapy was a more efficient use of resources (ie, dominated) compared with deferred therapy. Early therapy cost $13,000 per quality-adjusted life-year compared with no therapy with or without increased coronary heart disease risk, and $17,000 to $24,000 per quality-adjusted life-year taking into account the quality-of-life reduction in patients with fat redistribution symptoms. Early therapy had a higher quality-adjusted life expectancy than deferred therapy as long as this quality-of-life reduction was 70% or less.

Conclusions: Changes in cholesterol or quality of life associated with antiretroviral therapy do not justify limiting access to early HIV treatment. The effect of fat redistribution symptoms on quality of life will determine the optimal choice of early vs deferred therapy for an individual patient.
consequences of antiretroviral therapy, including cholesterol changes and fat redistribution symptoms, could affect decisions about the timing of treatment initiation for asymptomatic patients with low levels of HIV RNA (10,000-30,000 copies/mL). We analyzed how the adverse effects could affect life expectancy, quality of life, and cost-effectiveness outcomes of alternative treatment initiation strategies for HIV-infected patients.

### METHODS

#### OVERVIEW

The target population was patients with starting CD4 cell counts of 350/µL and HIV RNA levels of 10,000 to 30,000 copies/mL. Cost-effectiveness analyses were conducted using the Cost-effectiveness of Preventing AIDS Complications model, a computer-based state-transition simulation model of the progression of HIV disease.2-4 The model was programmed in C and compiled in VC++ 6.0 (Microsoft Corp, Redmond, Wash). A hypothetical cohort of 1 million asymptomatic HIV-infected adults presenting for medical care with HIV RNA levels of 10,000 to 30,000 copies/mL and CD4 cell counts of 350/µL entered the model 1 person at a time, and each person was observed in the model until death. Health states were categorized as chronic or acute and were stratified by CD4 cell count and HIV RNA levels.

### CLINICAL DATA

The model requires input variables that reflect the natural history of HIV disease in the absence of antiretroviral therapy, including the monthly rate of CD4 cell count decline and the monthly risks of the development of opportunistic infections, acute mortality, and chronic AIDS mortality. These variables were derived from the Multicenter AIDS Cohort Study (Table 1).1,10 Although participants in this study were mainly white homosexual men, the natural history of HIV infection predicted by the model was consistent with observations among women, nonwhites, and injection drug users.10

In the model, patients received standard opportunistic infection prophylaxis and had HIV RNA and CD4 cell count levels measured every 3 months, as well as a lipid profile test at initiation of therapy and every 6 months thereafter while receiving therapy.13,21-22 Patients in the model received a maximum of 4 antiretroviral regimens. The efficacy of each antiretroviral regimen was defined by an HIV RNA reduction leading to an increase in CD4 cell count. The efficacy of first-line antiretroviral therapy was based on the results of 3-drug therapy with zidovudine, lamivudine, and efavirenz in the Dupont 006 trial (70% of patients with no detectable HIV RNA level <500 copies/mL and a mean increase of 201 CD4 cells/µL at 48 weeks).23 The efficacy of second-line antiretroviral therapy was based on the results of 3-drug therapy with zidovudine, lamivudine, and abacavir in the Diabalo06 trial (70% of patients with no detectable HIV RNA level <500 copies/mL and a mean increase of 91 CD4 cells/µL at 24 weeks).23 The efficacies of third- and fourth-line antiretroviral therapy were based on the results with and without genotypic testing in the 2 treatment arms of the Community Programs for Clinical Research on AIDS 046 trial (34% and 22% of patients with no detectable HIV RNA level <500 copies/mL and mean increases of 25 and 18 CD4 cells/µL at 12 weeks, respectively).24

We evaluated a hypothetical cohort of 37-year-old patients that was 88% male, based on the age and sex distribution of patients in the Dupont 006 trial.21 We compared a strategy of initiating antiretroviral therapy immediately at a CD4 cell count of 350/µL (early therapy) with a strategy of initiating therapy after 6 months (delayed therapy). Outcomes included years of life gained, quality-adjusted life years (QALYs) gained, and lifetime costs. Cost-effectiveness ratios were calculated as incremental cost per QALY gained compared with the next best strategy after eliminating dominated strategies.

### ACUTE TOXICITIES FROM ANTIRETROVIRAL THERAPY

Acute drug toxicities reported in the clinical trials were incorporated into the model. In clinical trials of protease inhibitors, these toxicities included diarrhea, nausea, abdominal pain, and (for indinavir) nephrolithiasis.28 In the Dupont 006 trial, acute

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**Table 1. Monthly Probability of Opportunistic Infections and of Chronic AIDS Death**

<table>
<thead>
<tr>
<th>Event</th>
<th>0-50</th>
<th>51-100</th>
<th>101-200</th>
<th>201-300</th>
<th>301-500</th>
<th>&gt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>3.700</td>
<td>3.100</td>
<td>0.960</td>
<td>0.373</td>
<td>0.085</td>
<td>0.041</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>0.270</td>
<td>0.140</td>
<td>0.067</td>
<td>0.042</td>
<td>0.009</td>
<td>0.003</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>1.220</td>
<td>0.375</td>
<td>0.101</td>
<td>0.022</td>
<td>0.006</td>
<td>0.006</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>1.857</td>
<td>0.523</td>
<td>0.214</td>
<td>0.058</td>
<td>0.013</td>
<td>0.006</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>1.123</td>
<td>0.591</td>
<td>0.135</td>
<td>0.029</td>
<td>0.028</td>
<td>0.009</td>
</tr>
<tr>
<td>Other infections†</td>
<td>3.940</td>
<td>2.460</td>
<td>0.716</td>
<td>0.224</td>
<td>0.087</td>
<td>0.047</td>
</tr>
<tr>
<td>Chronic AIDS death</td>
<td>1.853</td>
<td>0.861</td>
<td>0.149</td>
<td>0.106</td>
<td>0.009</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Data are given as percentages and are taken from Freedberg et al.19,20 AIDS indicates acquired immunodeficiency syndrome.
†Other infections include bacterial infections, tuberculosis, and Kaposi sarcoma.
drug toxicities associated with efavirenz included rash and central nervous system symptoms (dizziness, impaired concentration, insomnia, and abnormal dreaming). Severe lactic acidosis and hepatic steatosis associated with antiretroviral therapy were also incorporated as acute toxicity, based on reports in the literature. In the model, an acute drug toxicity resulted in a temporary decrease in quality of life and in additional patient care costs in the month in which the toxicity occurred. For example, based on results from the clinical trials, we assumed a 21% probability of a minor acute toxicity occurring in the third month after treatment initiation. Patients in the model who experienced this toxicity incurred a reduction of 0.10 QALY and an incremental cost of approximately $1,400 in that month.

CHOLESTEROL EFFECTS OF ANTIRETROVIRAL THERAPY

For patients receiving protease inhibitors, we assumed a 26% increase in low-density lipoprotein (LDL) cholesterol and a 15% decrease in high-density lipoprotein (HDL) cholesterol, while for patients not receiving protease inhibitors, we assumed a 13% decrease in HDL cholesterol. The LDL cholesterol effect of protease inhibitors was based on the effect observed for indinavir in the Swiss HIV Cohort (mean LDL cholesterol, 151 mg/dL [3.91 mmol/L] after treatment vs 120 mg/dL [3.11 mmol/L] at baseline; P = .06). The HDL cholesterol effects were based on observations of significant effects in Australian and French cohorts of patients with fat redistribution symptoms and do not take into account improvements in HDL cholesterol that have been observed in patients receiving nonnucleoside reverse transcriptase inhibitors.

The effect of these cholesterol changes on the results was assessed with and without lipido-lowering drug therapy. Without lipid-lowering treatment, the effect of changes in HDL and LDL cholesterol levels on coronary heart disease–specific mortality was estimated using risk ratio formulas derived by Schulman et al from data in men with elevated cholesterol levels. Table 2 gives the resulting increase in the probability of non-AIDS death by age and sex. These increases were assumed to begin 2 years after the mean time of initiation of treatment, and we conservatively assumed that they continued until death, although there is some evidence that lipid levels may improve after a change in antiretroviral regimen.

Table 2. Increase in Monthly Probability of Non-AIDS Death Because of Cholesterol Increases

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-40</td>
<td>0.904</td>
<td>0.567</td>
<td>5.089</td>
<td>3.196</td>
</tr>
<tr>
<td>&gt;40-45</td>
<td>1.865</td>
<td>0.920</td>
<td>10.502</td>
<td>5.181</td>
</tr>
<tr>
<td>&gt;45-50</td>
<td>2.810</td>
<td>1.366</td>
<td>15.826</td>
<td>7.693</td>
</tr>
<tr>
<td>&gt;50-55</td>
<td>3.222</td>
<td>1.720</td>
<td>18.707</td>
<td>9.684</td>
</tr>
<tr>
<td>&gt;55-60</td>
<td>3.574</td>
<td>2.110</td>
<td>20.127</td>
<td>11.885</td>
</tr>
<tr>
<td>&gt;60-65</td>
<td>3.654</td>
<td>2.496</td>
<td>20.574</td>
<td>14.058</td>
</tr>
<tr>
<td>&gt;65-70</td>
<td>3.722</td>
<td>2.849</td>
<td>20.960</td>
<td>16.046</td>
</tr>
<tr>
<td>&gt;70-75</td>
<td>3.771</td>
<td>3.258</td>
<td>21.229</td>
<td>18.345</td>
</tr>
<tr>
<td>&gt;75-80</td>
<td>3.830</td>
<td>3.701</td>
<td>21.561</td>
<td>20.839</td>
</tr>
<tr>
<td>&gt;80-85</td>
<td>3.938</td>
<td>4.098</td>
<td>22.162</td>
<td>23.067</td>
</tr>
<tr>
<td>&gt;85-90</td>
<td>4.069</td>
<td>4.369</td>
<td>22.886</td>
<td>24.581</td>
</tr>
</tbody>
</table>

*Data are given as percentages and are taken from Periard, Carter, Saint-Marc, and Schulman and their colleagues. AIDS indicates acquired immunodeficiency syndrome.

As an alternative strategy, we assumed that patients with LDL cholesterol of 160 mg/dL (4.14 mmol/L) or higher (21% of patients treated with indinavir) also had 2 or more cardiovascular risk factors. In accord with recommendations of the Adult AIDS Clinical Trials Group to treat cholesterol increases associated with antiretroviral therapy using National Cholesterol Education Program guidelines, we assumed that these patients would be treated with a lipid-lowering drug and that patients with LDL cholesterol less than 160 mg/dL would not be treated with a lipid-lowering drug. We chose pravastatin sodium as the lipid-lowering agent, because it is recommended for patients being treated with antiretroviral therapy and has been successfully tested in a small clinical trial in this patient population. The percentage changes in HDL and LDL cholesterol levels for patients treated with pravastatin (40 mg/d) were from pooled estimates of the results of long-term studies of pravastatin treatment for primary coronary heart disease prevention. These changes were used to revise the previously estimated increases in coronary heart disease–specific mortality.

FAT REDISTRIBUTION SYMPTOMS

The main clinical features of fat redistribution associated with antiretroviral therapy are peripheral fat loss in the face, limbs, and buttocks and central body fat accumulation. We estimated the effect of fat redistribution symptoms on the cost-effectiveness of early antiretroviral therapy, assuming an 80% prevalence of any symptoms that adversely affected quality of life, which is similar to the highest prevalence reported in the literature, and conducted sensitivity analyses on lower prevalence rates. A recent review estimated that the prevalence of fat redistribution ranges from 1% to 84% in patients receiving protease inhibitors and from 0% to 41% in patients not receiving protease inhibitors. We varied the quality-of-life effect of the symptoms to consider the mean effect of different levels of symptom severity. In an Australian cohort of 111 men and 2 women receiving protease inhibitors who were followed up for a mean of 21 months, 11% of patients reported severe symptoms, 30% reported moderate symptoms, 42% reported mild symptoms, and 17% reported no symptoms.

QUALITY OF LIFE

Quality-of-life weights ranging between 0 (death) and 1 (perfect health) were assigned to each health state in the model (Table 3). Quality-of-life weights assigned to chronic health states were derived from data collected in the HIV Cost and Services Utilization Study, using methods described elsewhere. Briefly, the HIV Cost and Services Utilization Study survey included several items from the Medical Outcomes Study.
36-Item Short-Form Health Survey (SF-36), enabling us to reconcile the responses to these items to construct the SF-6D, a simplified health state classification based on selected items from the SF-36. The SF-6D results were then converted to quality-of-life weights using an algorithm derived by Brazier et al. This algorithm was obtained from a fixed effects regression model that predicted quality-of-life weights for a subset of SF-6D health states that had been valued by a convenience sample of health professionals, managers, and patients in the United Kingdom.

Quality-of-life weights were also specified for acute opportunistic infection health states, as well as in the month before death from any cause. For these temporary health states, data were not available to derive weights from the perspective of a community member. Instead, rating scale values were derived from responses about overall health status by patients enrolled in AIDS Clinical Trials Group protocols 019, 108, 157, and 204 and were converted to quality-of-life weights that represented the patients' own values, using a transformation function from Torrance et al. Several types of quality-of-life impairments associated with fat redistribution symptoms have been noted, including impairments in self-esteem and social relations, anxiety related to forced HIV identification, and depression. To estimate the quantitative effect of these symptoms, the quality-of-life weight of each health state that a patient experienced after the onset of fat redistribution symptoms was reduced by a percentage that was varied between 0% and 100%. We assumed that fat redistribution symptoms would occur 10 months after the median time to onset of these symptoms reported in AIDS Clinical Trials Group protocols 019, 108, 157, and 204. We conservatively assumed the percentage reduction in quality-of-life weight did not diminish over time, because no effective treatments for fat redistribution symptoms have been reported and because the symptoms appear to persist after patients switch antiretroviral regimens.

### COSTS

Table 4 gives the base case values for drug and test costs. Drug costs were average wholesale prices (AWP) published in the 1999 Red Book. Patient care costs were derived from charges reported in the AIDS Cost and Service Utilization Survey, which were converted to estimates of costs using a national cost-to-charge ratio as previously described. Using other reported data on patient care costs does not have a large effect on cost-effectiveness ratios for 3-drug antiretroviral therapy.

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine, lamivudine, and efavirenz</td>
<td>11,490</td>
</tr>
<tr>
<td>Zidovudine, lamivudine, and indinavir</td>
<td>12,320</td>
</tr>
<tr>
<td>Third-line regimen†</td>
<td>16,930</td>
</tr>
<tr>
<td>Fourth-line regimen†</td>
<td>15,590</td>
</tr>
<tr>
<td>Pravastatin sodium</td>
<td>127.8</td>
</tr>
<tr>
<td>CD4 cell count cost (per test)</td>
<td>83.0</td>
</tr>
<tr>
<td>Human immunodeficiency virus RNA cost (per test)</td>
<td>110.0</td>
</tr>
<tr>
<td>Lipid profile cost (per test)</td>
<td>19.0</td>
</tr>
</tbody>
</table>

*Data are expressed in 1999 US dollars and are taken from Freedberg et al.‡, 1999 Red Book, and the Health Care Financing Administration Web site.† Third- and fourth-line regimens are 2 nucleoside reverse transcriptase inhibitors, 1 protease inhibitor, and up to 1 nonnucleoside reverse transcriptase inhibitor.

Costs of CD4 cell counts and HIV RNA tests were obtained from the Boston Medical Center, Boston, Mass, cost accounting system, and the cost of lipid profile tests was obtained from a Medicare reimbursement schedule. All cost-effectiveness results were expressed in 1999 US dollars, with future costs and benefits discounted at an annual rate of 3%.

### RESULTS

#### LIFE EXPECTANCY BENEFIT OF EARLY THERAPY

We compared a strategy of initiating antiretroviral therapy immediately at a CD4 cell count of 350/µL (early therapy) with a strategy of initiating therapy at a CD4 cell count of 200/µL (deferred therapy) for patients with HIV RNA levels of 10000 to 30000 copies/mL. The mean duration of early antiretroviral therapy resulting from the model simulation was 7.92 years, the mean duration of deferred antiretroviral therapy was 7.30 years, and the mean delay between early and deferred therapy was 2.50 years.

The mean life expectancy for a 37-year-old patient receiving early therapy was 16.54 years vs 16.66 years without increased coronary heart disease mortality. The mean life expectancy for the same patient receiving deferred therapy was 13.73 years vs 13.80 years without increased coronary heart disease mortality.

**Figure 1** shows the undiscounted life expectancy effect of early vs deferred therapy taking into account the increased risk of coronary heart disease mortality. The life expectancy benefit of 2.81 years for early vs deferred therapy was derived from lower HIV-related morbidity and mortality during the period in which therapy was not delayed and from a reduction in attributable mortality because of averted early opportunistic infections. Patients receiving early therapy also benefited from spending more time on average in health states with lower mortality and morbidity risks (ie, health states defined by a CD4 cell count >200/µL) than patients receiving deferred therapy, taking into account their CD4 cell count trajectory before and after treatment failure. Even if we assumed that for

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Figure 1. Survival analysis for a hypothetical cohort of human immunodeficiency virus (HIV)-infected adults with HIV RNA levels of 10000 to 30000 copies/mL.
Table 5. Cost-effectiveness of Early (350 CD4 Cells/µL) vs Deferred (200 CD4 Cells/µL) Antiretroviral Therapy (ART) for Human Immunodeficiency Virus (HIV)–Infected Adults With HIV RNA Levels of 10 000 to 30 000 Copies/mL

| Strategy of ART | Base Case | | | Continued ART Cost Case | | |
|---|---|---|---|---|---|
| | Quality-Adjusted | Lifetime Cost | Cost-effectiveness Ratio | Lifetime Cost | Cost-effectiveness Ratio |
| With increased coronary heart disease (CHD) mortality risk | Life Expectancy, y | | | | |
| None | 4.30 | 61 600 | NA | 61 600 | NA |
| Deferred | 9.31 | 139 700 | Dominated† | 189 800 | 26 000 |
| Early | 11.19 | 152 900 | 13 000 | 239 400 | 26 000 |
| Without increased CHD mortality risk | | | | | |
| None | 4.30 | 61 600 | NA | 61 600 | NA |
| Deferred | 9.34 | 140 200 | Dominated | 196 700 | 26 000 |
| Early | 11.25 | 153 500 | 13 000 | 240 700 | 26 000 |
| With lipid-lowering agent (pravastatin sodium) for patients with low-density lipoprotein cholesterol ≥160 mg/dL | | | | | |
| None | 4.30 | 61 600 | NA | 61 600 | NA |
| Deferred | 9.31 | 141 100 | Dominated | 192 200 | 26 000 |
| Early | 11.21 | 154 600 | 13 000 | 243 100 | 27 000 |

*Data are expressed in 1999 US dollars unless otherwise indicated. Cost-effectiveness ratios are given as cost per quality-adjusted life-year (QALY). The no ART strategy is derived from the Multicenter AIDS Cohort Study data set. Because in the base case deferred antiretroviral therapy had a higher (ie, less attractive) cost-effectiveness ratio than early antiretroviral therapy, it was weakly dominated by early therapy and represented an inefficient use of resources. NA indicates not applicable.

†In the base case, the incremental cost-effectiveness ratio for deferred therapy vs no therapy was $16 000 per QALY and the incremental cost-effectiveness ratio for early therapy vs deferred therapy was $7000 per QALY.

all patients with a CD4 cell count greater than 200/µL, there was no risk of opportunistic infection or of death from other HIV-related causes, the life expectancy benefit from initiating therapy at a CD4 cell count of 350/µL was 1.15 years. If we assumed no maximum duration of efficacy for antiretroviral regimens, the life expectancy benefit was 3.00 years, and if we extended the delay of CD4 cell count decline after virologic failure from 12 months to 24 months, the life expectancy benefit was 3.37 years.

**COST-EFFECTIVENESS OF EARLY THERAPY**

Taking into account the increased risk of coronary heart disease mortality, the incremental cost-effectiveness ratio for deferred therapy vs no therapy was $16 000 per QALY gained, and the incremental cost-effectiveness ratio for early therapy vs deferred therapy was $7000 per QALY gained. Because early therapy was more effective than deferred therapy and had a more attractive (i.e., lower) cost-effectiveness ratio, it weakly dominated deferred therapy. A strategy that is dominated represents an inefficient use of resources. Therefore, we report the incremental cost-effectiveness ratio for early therapy vs no therapy, which was $13 000 per QALY gained (Table 5). When the analysis was conducted without considering the increased risk of coronary heart disease mortality, results were similar.

We considered an alternative scenario that continued antiretroviral therapy for patients with detectable HIV RNA after all 4 lines of antiretroviral therapy had failed, assumed no additional benefit of partial suppression of HIV RNA in these patients, and continued to assign the monthly cost of antiretroviral therapy until each patient's death. In this scenario, deferred therapy was no longer dominated by early therapy, and the incremental cost-effectiveness ratio of early therapy vs deferred therapy was $26 000 per QALY (Table 5).

We also conducted sensitivity analyses that tested the effect of antiretroviral drug choice, age, and sex on our results. In a scenario with higher coronary heart disease risk, the LDL cholesterol effect observed in the Swiss HIV Cohort for ritonavir (mean LDL cholesterol, 162 mg/dL [4.20 mmol/L] after therapy vs 108 mg/dL [2.80 mmol/L] at baseline; \(P = .001\)) was assumed for all regimens containing protease inhibitors, and we considered an all-male cohort with an age at cohort entry of 55 years. In this scenario, deferred therapy remained an inefficient use of resources, and the incremental cost-effectiveness ratio for early therapy vs no therapy was relatively unchanged ($14 000 per QALY). When there was no risk of opportunistic infection or of death from other HIV-related causes for all patients with a CD4 cell count greater than 200/µL, discounted quality-adjusted life expectancies increased as much as 39%, but cost-effectiveness ratios were relatively unchanged.

**TREATMENT WITH A LIPID-LOWERING AGENT**

When patients with LDL cholesterol 160 mg/dL or higher were assumed to have 2 or more coronary heart disease risk factors and were treated with pravastatin, discounted lifetime costs increased by less than 2%. This was because pravastatin costs were low compared with the lifetime costs of treating HIV infection, and because only 21% of patients were treated with pravastatin. Because there were also small gains in quality-adjusted life expectancy, the incremental cost-effectiveness ratios for early therapy vs deferred therapy were similar (Table 5). Based on these results, a treatment strategy of early antiretroviral therapy for all patients and pravastatin therapy for patients with LDL cholesterol 160 mg/dL or higher...
had an incremental cost-effectiveness ratio of $132,000 per QALY compared with a treatment strategy of early antiretroviral therapy alone. In the scenario in which antiretroviral therapy was continued for patients with detectable HIV RNA after all 4 lines of therapy had failed, the corresponding incremental cost-effectiveness ratio was $280,000 per QALY. For the all-male cohort with age at entry of 55 years and the more severe LDL cholesterol effect, the incremental cost-effectiveness ratio of the early treatment strategy that included pravastatin therapy for patients with LDL cholesterol 160 mg/dL or higher (62% of patients receiving antiretroviral therapy) was $37,000 per QALY compared with early antiretroviral therapy alone. If antiretroviral therapy was continued after all 4 lines of therapy had failed, the corresponding incremental cost-effectiveness ratio for this cohort was $76,000 per QALY. The improvements in the cost-effectiveness ratios that occurred in the older cohort reflect the greater life expectancy benefit of successfully treating older, high-risk patients with pravastatin.

**EFFECT OF FAT REDISTRIBUTION ON QUALITY-ADJUSTED LIFE EXPECTANCY**

*Figure 2* shows the undiscounted quality-adjusted life expectancy of early vs deferred therapy for patients with HIV RNA levels of 10,000 to 30,000 copies/mL under alternative assumptions regarding the quality-of-life effect of fat redistribution symptoms. Assuming an 80% probability of symptoms for each treatment regimen, the quality-adjusted life expectancy benefit of early therapy was 2.84 years with no reduction in health state quality-of-life weights, 2.05 years with a 20% permanent reduction, and 1.26 years with a 40% permanent reduction. The quality-adjusted life expectancy remained greater for early therapy compared with deferred therapy, unless there was a 70% permanent reduction in health state quality-of-life weights associated with fat redistribution symptoms. *Table 6* gives cost-effectiveness results assuming an 80% probability of symptoms for each treatment regimen and a 20% or 40% permanent reduction in health state quality-of-life weights associated with these symptoms. In the base case, deferred therapy remained an inefficient use of resources, and with a 20% permanent reduction in health state quality-of-life weights, the incremental cost-effectiveness ratio of early therapy compared with no therapy was $17,000 per QALY. With a 40% permanent reduction, the incremental cost-effectiveness ratio of early therapy compared with no therapy was $24,000 per QALY. In the scenario in which antiretroviral costs were continued until death, early therapy did not have a lower cost-effectiveness ratio than deferred therapy. The incremental cost-effectiveness ratio for early therapy compared with deferred therapy was $38,000 per QALY with a 20% permanent reduction in health state quality-of-life weights and $71,000 per QALY with a 40% permanent reduction. These results were not sensitive to the time of onset of symptoms, and they did not vary substantially when baseline quality-of-life weights from the patient’s perspective were used for all HIV health states. When it was assumed that only half of the symptomatic cases were severe enough to result in any permanent reduction in quality of life, the incremental cost-effectiveness ratios were more favorable to early therapy. For instance, in the scenario in which antiretroviral therapy was continued until death, the incremental cost-effectiveness ratio for early therapy compared with deferred therapy was $32,000 per QALY with a 20% permanent reduction in health state quality-of-life weights and $41,000 per QALY with a 40% reduction.

**Figure 2.** Undiscounted quality-adjusted life expectancy with an 80% probability of fat redistribution. Effect of hypothetical permanent quality-of-life reductions associated with fat redistribution symptoms for human immunodeficiency virus (HIV)-infected adults with HIV RNA levels of 10,000 to 30,000 copies/mL.

Current recommendations regarding when to initiate antiretroviral therapy in asymptomatic HIV-infected adults reflect the uncertainty about the long-term adverse effects of therapy, including the potential risk of premature cardiovascular disease and the quality-of-life effect of fat redistribution symptoms. We used a simulation model of HIV disease to compare a strategy of initiating antiretroviral therapy immediately at a CD4 cell count of 350/µL (early therapy) with a strategy of initiating therapy at a CD4 cell count of 200/µL (deferred therapy) for patients with HIV RNA levels of 10,000 to 30,000 copies/mL, because the timing of treatment initiation in these patients is controversial. The life expectancy effect of an increased risk of coronary heart disease mortality resulting from cholesterol changes associated with antiretroviral therapy was small. Early antiretroviral therapy remained cost-effective compared with deferred therapy under a range of assumptions regarding this increased risk. The cost-effectiveness ratio for early vs deferred therapy was below the median cost-effectiveness ratio for all medical interventions reported in the United States ($23,600 per life-year saved in 1999 US dollars) and below the cost-effectiveness ratio for the use of statins for primary prevention of coronary heart disease in men ($58,000-$450,000 per QALY in 1999 US dollars). We assumed that 80% of patients developed fat redistribution symptoms on each treatment regimen. When we also assumed that all patients with fat redistribution symptoms experienced a permanent 20% reduction in qual-
Continued ART Cost Case

In this analysis, early antiretroviral therapy is compared to deferred therapy. The incremental cost-effectiveness ratio for early vs deferred therapy was $19,000 per QALY. The incremental cost-effectiveness ratio for early vs deferred therapy was $10,000 per QALY.

Table 6. Effect of Quality-of-Life Impairment Associated With Fat Redistribution Symptoms on the Cost-effectiveness of Early (350 CD4 Cells/µL) vs Deferred (200 CD4 Cells/µL) Antiretroviral Therapy (ART)*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4.30</td>
<td>61 600</td>
<td>NA</td>
<td>61 600</td>
</tr>
<tr>
<td>Deferred</td>
<td>8.34</td>
<td>140 200</td>
<td>Dominated†</td>
<td>190 700</td>
</tr>
<tr>
<td>Early</td>
<td>9.65</td>
<td>153 500</td>
<td>17 000</td>
<td>240 700</td>
</tr>
<tr>
<td>None</td>
<td>4.30</td>
<td>61 600</td>
<td>NA</td>
<td>61 600</td>
</tr>
<tr>
<td>Deferred</td>
<td>7.34</td>
<td>140 200</td>
<td>Dominated</td>
<td>190 700</td>
</tr>
<tr>
<td>Early</td>
<td>8.05</td>
<td>153 500</td>
<td>24 000</td>
<td>240 700</td>
</tr>
</tbody>
</table>

*Data are expressed in 1999 US dollars unless otherwise indicated. Cost-effectiveness ratios are given as cost per quality-adjusted life-year (QALY). The no ART strategy is derived from the Multicenter AIDS Cohort Study data set. Because in the base case deferred antiretroviral therapy had a higher (ie, less attractive) cost-effectiveness ratio than early antiretroviral therapy, it was weakly dominated by early therapy and represented an inefficient use of resources. NA indicates not applicable. In the base case, the incremental cost-effectiveness ratio for deferred therapy vs no therapy was $19,000 per QALY and the incremental cost-effectiveness ratio for early therapy vs deferred therapy was $10,000 per QALY.

consistent with ratios derived from clinical trial results, even though projected life expectancies are shorter. We did not examine possible differences in the effect of adverse effects on adherence and decisions to interrupt early vs deferred therapy. If adverse effects have a greater negative effect on adherence to early therapy than on adherence to deferred therapy, then the projected life expectancy benefit of early therapy could be reduced. The magnitude of the effect would depend on the likelihood of developing resistant mutations as a result of poor adherence. We did not examine differences between early and deferred therapy in the likelihood of transmission of HIV to uninfected individuals. We also did not model a treatment benefit from partial suppression of HIV RNA or alternative treatment strategies for patients with discordant HIV RNA and CD4 cell count responses. We assumed the benefit of early antiretroviral therapy in this analysis was the avoidance of HIV-related morbidity and mortality risks. The probabilities of these clinical events were derived from the Multicenter AIDS Cohort Study, and there were limited data in this cohort for patients at higher CD4 cell counts. However, our results were consistent even when we assumed that there was no risk of HIV-related morbidity and mortality above a CD4 cell count of 200/µL.

Our estimates of the effect of cholesterol levels on coronary heart disease mortality were derived from results in men with elevated cholesterol levels who were not HIV-infected, and we used published nonfasting lipid levels on the effect of antiretroviral therapy on cholesterol levels. However, these assumptions bias our analysis against early antiretroviral therapy, because they may overestimate the severity of the increase in coronary heart disease risk associated with therapy. We did not compare treatment with a lipid-lowering agent with alternative treatment modalities, such as dietary intervention, because we assumed that most patients with elevated LDL cholesterol levels had additional coronary heart disease risk factors. In addition, we did not consider potential interactions between HIV disease or antiretroviral therapy and these other risk factors. Because the baseline quality-of-life weights we used were derived from patients in...
the HIV Cost and Services Utilization Study survey, most of whom were not receiving highly active antiretroviral therapy, we may have underestimated offsetting quality-of-life benefits of antiretroviral therapy. The percentage reductions in quality-of-life associated with fat redistribution symptoms were assumed to permanently affect all subsequent health states and to be independent of the decision when to initiate therapy.

Although treatment guidelines suggest flexibility about when to start antiretroviral therapy, early initiation of antiretroviral therapy in accord with these guidelines remains cost-effective even when chronic drug toxicities are considered. Changes in cholesterol levels or quality of life associated with antiretroviral therapy should not be used by government or private payers to justify placing limitations on access to early HIV treatment. The results also support the current recommendation to treat patients with elevated cholesterol levels associated with antiretroviral therapy in accord with National Cholesterol Education Program guidelines, including appropriate use of lipid-lowering agents. This analysis is not intended to substitute for decisions by individual patients and clinicians about when it is best to initiate antiretroviral therapy. Decisions about initiating antiretroviral therapy must take into account factors such as an individual patient’s readiness to adhere to potentially complex treatment regimens, cardiovascular disease history and risk factors, and potential psychological vulnerability to symptoms such as fat redistribution. For individual patient decisions, the most important factor to consider is the magnitude of the treatment adverse effects, particularly fat redistribution symptoms, on quality of life.

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