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THE COST-EFFECTIVENESS OF PROPHYLAXIS FOR *MYCOBACTERIUM AVIUM* COMPLEX IN AIDS

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Abstract

Objective: To develop a simulation model to project costs, life expectancy, and cost-effectiveness in discounted dollars per quality-adjusted life-year (QALY) saved for clinical strategies to prevent *Mycobacterium avium* complex (MAC) in patients with AIDS.
Methods: We used natural history data from the Multicenter AIDS Cohort Study, efficacy and toxicity data from randomized clinical trials, and cost data from the AIDS Cost and Services Utilization Survey. The model permits timing of prophylaxis to be stratified by CD4 count (201–300, 101–200, 51–100,

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and ≤ 50/mm^3), and allows combinations of prophylaxis, crossover to second- and third-line agents for toxicity, and consideration of adherence, resistance, and quality of life.
Results: The model projects that the average HIV-infected patient with a beginning CD4 count between 201 and 300/mm^3 has total lifetime costs of approximately $43,150 and a quality-adjusted life expectancy of 42.35 months. If azithromycin prophylaxis for *M. avium* complex is begun after the CD4 declines to 50/mm^3, costs and quality-adjusted survival increase to approximately $44,040 and 42.78 months, respectively, for an incremental cost-effectiveness ratio of $25,000/QALY compared with no *M. avium* complex prophylaxis. Other prophylaxis options (i.e., rifabutin, clarithromycin, and combination therapies) either cost more but offer shorter survival, or have cost-effectiveness ratios above $260,000/QALY. Sensitivity analysis reveals that, for reasonable assumptions about quality of life, risk of infection, prophylaxis cost, adherence, and resistance, azithromycin remains the most cost-effective prophylaxis option.
Conclusions: Azithromycin prophylaxis, begun after the CD4 count has declined to 50/mm^3, is the most cost-effective *M. avium* complex prophylaxis strategy. Consistent with new United States Public Health Service guidelines, it should be the first-line prophylaxis option.

Keywords: AIDS, Incremental cost-effectiveness ratio, *Mycobacterium avium* complex, Azithromycin, Clarithromycin, Rifabutin, Prophylaxis

With the development of modern combination antiretroviral therapy, which can prevent progression of AIDS and reduce the incidence of opportunistic infections, HIV is increasingly being seen and treated as a long-term, chronic condition (8;40). As part of this transition, clinicians and patients have a growing set of treatment and prophylaxis options at their disposal. At the same time, however, clinicians and policy makers are confronted with the dilemma of how scarce AIDS care resources should be allocated across the range of alternatives.

Mycobacterium avium complex infection is one of the most common opportunistic infections affecting patients with AIDS. Two randomized controlled trials by Nightingale et al. (32) in 1993 showed that the incidence of *M. avium* complex, at approximately 17.6% over a mean of 202 days of follow-up in patients receiving a placebo with a median CD4 lymphocyte count at baseline of 25/mm^3, could be decreased by about 50% using rifabutin.

More recently, AIDS Clinical Trials Group Protocol 196 (ACTG 196) found that daily clarithromycin, either alone or in combination with daily rifabutin, was more effective than rifabutin alone for the prevention of *M. avium* complex (3). A second trial by Pierce et al. (36) found that clarithromycin reduced the incidence of *M. avium* complex by 64% compared with placebo and was associated with improved survival. Combination therapy appears to reduce the risk of resistance from clarithromycin alone, but results in more toxicity (3).

Other recent studies suggest that azithromycin (once weekly) and the combination of azithromycin and rifabutin are both more effective than rifabutin alone (19;33). However, as in ACTG 196, azithromycin was associated with the selection of resistant organisms in 11% of breakthrough cases.

Although not considered explicitly in these clinical trials, costs are also important to consider in policy decisions. At currently recommended doses, the annual wholesale per-person cost for prophylaxis ranges from $1,452 for azithromycin alone to $4,595 for clarithromycin/rifabutin combination therapy (48).

Based on these new data, the U.S. Public Health Service recently recommended either azithromycin or clarithromycin as initial *M. avium* complex prophylaxis for CD4 counts below 50/mm^3 (9). As part of a comprehensive HIV simulation model incorporating data on multiple opportunistic infections as well as resistance, toxicity,

and adherence (17), we examine different strategies for *M. avium* complex prophylaxis to determine the costs and cost-effectiveness of alternative policy options.

METHODS

Structure of the Model

We have modeled the natural history of HIV disease and AIDS using a Monte Carlo simulation (20), in which one hypothetical patient at a time is followed from a CD4 (helper) lymphocyte count between 201 and 300/mm^3 to death. The model, written in the C programming language, is run for a hypothetical cohort of 1 million individuals, assessing the development of opportunistic infections, survival time, quality-adjusted survival time, and costs of care under a variety of scenarios for the timing and type of prophylaxis.

Risks and costs are based on four CD4 lymphocyte strata in order of increasing risk of opportunistic infection incidence: 201–300/mm^3, 101–200/mm^3, 51–100/mm^3, and 50/mm^3 or less. The state space is further divided to consider five major opportunistic infections individually: *Pneumocystis carinii* pneumonia (PCP), *M. avium* complex, toxoplasmosis, fungal infections, and cytomegalovirus, as well as an acute "other" opportunistic infection state (e.g., bacterial infections, tuberculosis) (23;35). Details of the model and analyses involving the four other major opportunistic infections have been described elsewhere (17).

Figure 1 outlines the natural history of HIV disease as simulated for a single patient. In general, the chronic state captures patients receiving routine medical care either before or after recovery from (i.e., post-acute care) one or more opportunistic infections. The acute state includes patients who are currently suffering from an opportunistic infection.

Analysis

Five different *M. avium* complex drug regimens, all in the setting of zidovudine monotherapy and prophylaxis for *P. carinii* pneumonia (beginning with trimethoprim-sulfamethoxazole at recommended doses [5]), are considered in this analysis. Each regimen outlines a prophylaxis choice for first-line therapy and up to two additional options (i.e., second- and third-line agents) for use in the case of drug discontinuation due to major toxicity. The five regimens are (arrows indicate a change in therapy due to major toxicity):

1. rifabutin→azithromycin→clarithromycin;
2. azithromycin→clarithromycin→rifabutin;
3. clarithromycin→azithromycin→rifabutin;
4. azithromycin/rifabutin combination therapy→clarithromycin; and
5. clarithromycin/rifabutin combination therapy→azithromycin.

Doses used in the model are 300 mg daily for rifabutin, 1,200 mg per week for azithromycin, and 500 mg twice daily for clarithromycin (3;19;32;36).

For each *M. avium* complex drug regimen, there is an option to begin prophylaxis after the CD4 has declined to 200/mm^3 ($\leq$ 200), to 100/mm^3 ($\leq$ 100), or to 50/mm^3 ($\leq$ 50). This yields a total of 15 *M. avium* complex policies for consideration; a sixteenth strategy assumes that patients receive zidovudine monotherapy and *P. carinii* pneumonia prophylaxis only.

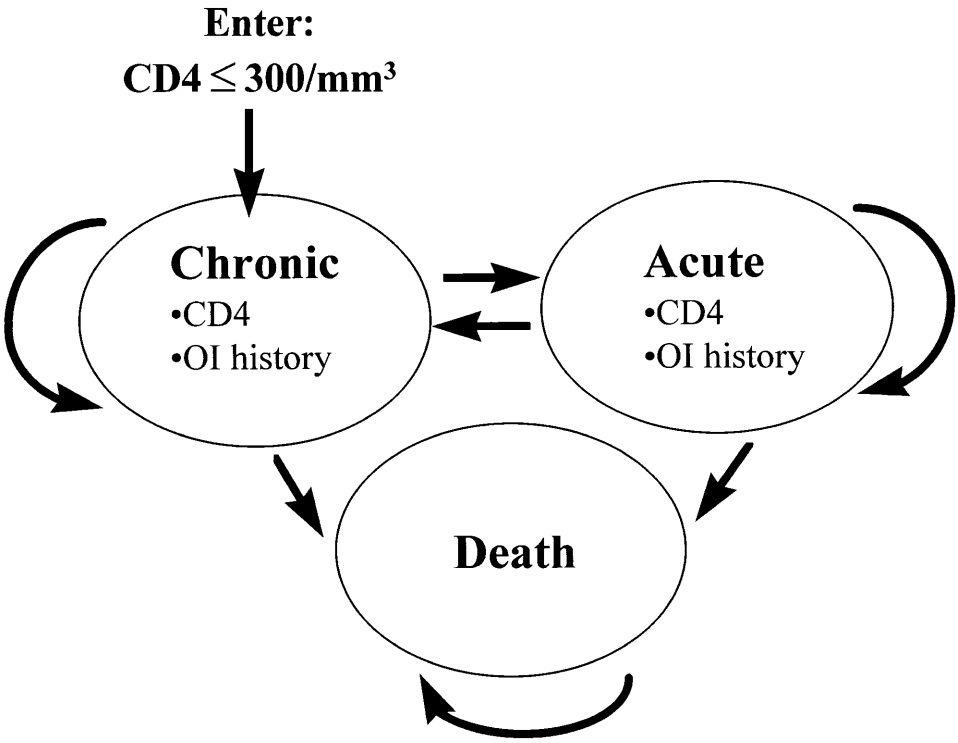

Figure 1. General model overview with three broad categories of states: chronic, acute, and death. Each is further stratified by CD4 count and history of opportunistic infection (OI). Death may be caused by an acute OI, a chronic AIDS condition (e.g., wasting), or non-AIDS causes.

The life expectancies and costs produced under the different policy alternatives, all discounted at an annual rate of 3% (26), serve as inputs to an incremental cost-effectiveness analysis. After eliminating strategies that are strongly dominated (i.e., cost more but produce less benefit), these ratios are ordered by increasing cost to calculate incremental cost-effectiveness ratios (45). This ratio is defined as the additional cost required to produce one extra life-year or quality-adjusted life-year (QALY). When a policy has a higher incremental cost-effectiveness ratio than its next most costly alternative, it is considered an inefficient use of resources (i.e., is weakly dominated) and is eliminated from consideration before ratios are recalculated (7;44;45).

Data

The model requires data relating to a variety of parameters, all based on a monthly time increment. Data for the model are described in detail in Tables 1–3.

Incidence Data. Estimates in Tables 1 and 2 are from the medical literature or from data on the prospective surveillance (1984–91) of approximately 2,000 homosexual and bisexual men in the Multicenter AIDS Cohort Study (MACS) (22).

Applying the incidence density approach (28) to patients receiving zidovudine monotherapy, we estimated the monthly rate of developing a primary opportunistic infection by CD4 level in the absence of prophylaxis. The CD4 count at the time of a diagnosis was estimated using a random effects model (17;24). Rates were

Table 1. Baseline Incidence Data for HIV-infected Patients, Stratified by CD4 Count below 300/mm^3

Parameter	Reference no.	CD4 level[a,b]			
		201–300	101–200	51–100	0–50
Primary acute infection					
Systemic fungal	31	0.0290	0.1350	0.5910	1.1230
PCP	31	0.3730	0.9600	3.1000	3.7000
TOXO	31	0.0420	0.0670	0.1400	0.2700
MAC	31	0.0220	0.1010	0.3750	1.2200
CMV	31	0.0580	0.2140	0.5230	1.8570
Other OI	31	0.2240	0.7160	2.4600	3.9400
Death					
Chronic AIDS (no OI history)	31	0.1060	0.1490	0.8610	1.8530
Chronic AIDS (OI history)	31	2.7490	2.1450	2.3320	9.6820
Non-AIDS	27	0.0710	0.0710	0.0710	0.0710
CD4 Decline[c]	31	4.7593	4.6163	7.2480	N/A

Abbreviations: PCP = *Pneumocystis carinii* pneumonia; TOXO = toxoplasmosis; MAC = *Mycobacterium avium* complex; CMV = cytomegalovirus; OI = opportunistic infection; N/A = not applicable.
[a] Expressed in CD4 cells/mm^3.
[b] Monthly probability (%) of the defined event.
[c] Indicates risk (%) of moving from the given CD4 level to the adjacent level below.

converted into monthly probabilities (Table 1) using the method outlined by Miller and Homan (28). Incidence estimates for patients receiving combination antiretroviral therapy are considered in sensitivity analysis.

Chronic AIDS mortality is defined as death from a nonacute, AIDS-related cause. The analysis of chronic AIDS mortality assumes that there is additional chronic mortality risk for any patient with a history of one or more opportunistic infections. Chronic mortality risks were calculated using the incidence density method (Table 1). An age-, sex- and race-adjusted risk of death (27) was subtracted from these estimated rates to account for deaths from non-AIDS causes. The incidence density approach (28) was also applied to the MACS data set to estimate the monthly probability of decline from a given CD4 count level to the adjacent CD4 range below (Table 1).

Estimates of the risk of surviving an acute infection (Table 2) are based on 30-day mortality in the MACS data set. Prophylaxis efficacy and the risks of acute relapse infection and toxicity are from the medical literature (Table 2).

Cost Data. The model accounts for the following categories of direct medical cost: routine medical care, acute infection care, death, prophylaxis medication, and care after recovery from an opportunistic infection (i.e., post-acute care). Productivity and patient time costs were not considered.

Direct medical costs were calculated as the sum of relevant component costs, such as hospital care, outpatient care, home health and long-term care, laboratory, and pharmacy. To account for inflation, all costs were converted into 1995 dollars by means of the Medical Care Component of the Consumer Price Index (42).

In Table 3, baseline charge data are summarized. All data were estimated from a combination of the 1995 Red Book (48) and the AIDS Cost and Services Utilization Survey (ACSUS) (4). This was a national survey of HIV-infected persons designed to provide utilization and charge estimates for health care services. The survey sampled HIV-infected persons in 10 cities in the United States during 1991–92.

Table 2. Baseline Incidence Data for HIV-infected Patients with CD4 Counts below 300/mm^3

Parameter	Reference no.	Baseline value[a,b]	Parameter	Reference no.	Baseline value[a,b]
Acute relapse infection			*Survive acute infection*		
Systemic fungal	6;37;46	0.4265	Systemic fungal	31	94.34
PCP	21	0.4600	PCP	31	93.68
TOXO	34	1.8982	TOXO	31	82.14
MAC	13	0.5540	MAC	31	84.15
CMV	12	5.0000	CMV	31	89.47
Minor (major) toxicity			Other OI	31	92.51
TMP-SMX (DS qd)	21	40.00 (23.20)	*Prophylaxis efficacy*		
AP (300 mg q month)	21	20.00 (0.21)	TMP-SMX (PCP-DS qd)	21	95.96
Dapsone (50 mg bid)	21	37.00 (21.00)	TMP-SMX (TOXO-DS qd)	21	65.00
Rifabutin (300 mg qd)	3;32	0.00 (0.91)	AP (300 mg q month)	21	63.00
Azithromycin (1,200 mg qw)	19;33	0.00 (0.42)	Dapsone (50 mg bid)	21	76.77
Clarithromycin (500 mg bid)	3;32;36	0.00 (0.69)	Rifabutin (300 mg qd)	3;32	51.46
Azithromycin/rifabutin	19;33	0.00 (0.91)	Azithromycin (1200 mg qw)	19;33	63.35 (79.37[c])
Clarithromycin/rifabutin	3;32	0.00 (1.67)	Clarithromycin (500 mg bid)	3;32;36	71.99 (76.52[c])

Abbreviations: PCP = *Pneumocystis carinii* pneumonia; TOXO = toxoplasmosis; MAC = *Mycobacterium avium* complex; CMV = cytomegalovirus; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; AP = aerosolized pentamidine; DS = double strength; qd = per day; q = per; bid = twice daily; qw = per week.

[a] Monthly probability (%) of the defined event or, in the case of prophylaxis efficacy, a percent reduction in the monthly probability of primary infection.

[b] Risks allowed to vary by CD4 count level in sensitivity analysis.

[c] In combination with rifabutin, 300 mg qd.

Table 3. Baseline Charge Data for HIV-infected Patients with CD4 Counts below 300/mm^3

Parameter	Reference no.	Baseline charge[a,b]	Parameter	Reference no.	Baseline charge[a,b]
Miscellaneous			*Acute infection care*[c]		
routine care[d]	2	801[e]	Systemic fungal	2	5,256 (1,024)
CD4 test[f]		139	PCP	2	14,673 (1,041)
Minor toxicity	2	586	TOXO	2	9,375 (771)
Major toxicity (death)	2	1,000 (10,000)	MAC	2	8,854 (3,309)
			CMV	2	16,281 (2,373)
Death			Other OI	2	6,111
Non/chronic AIDS	2	15,000/10,317	*Prophylaxis*		
Fungal	2	24,433	TMP-SMX (DS qd)	48	9
PCP	2	15,572	AP (300 mg q month)	48	144
TOXO	2	18,613	Dapsone (50 mg bid)	48	5
MAC	2	17,575	Rifabutin (300 mg qd)	48	178
CMV	2	17,055	Azithromycin (1,200 mg qw)	48	121
Other OI	2	20,390	Clarithromycin (500 mg bid)	48	204

Abbreviations: PCP = *Pneumocystis carinii* pneumonia; TOXO = toxoplasmosis; MAC = *Mycobacterium avium* complex; CMV = cytomegalovirus; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; AP = aerosolized pentamidine; DS = double strength; qd = per day; q = per; bid = twice daily; qw = per week.

[a] Monthly direct medical charges in 1995 dollars; prophylaxis is average wholesale cost.

[b] Dollar amounts are assumed constant CD4 levels.

[c] Post-acute care charges shown in parentheses.

[d] Not incurred during a month in which post-acute care is given.

[e] Charges are \$801, \$756, \$320, and \$1,049 for the 201–300, 101–200, 51–100 and ≤ 50/mm^3 CD4 count levels, respectively.

[f] Derived from the Boston Medical Center Cost Accounting System.

Medical abstracts and provider billing data from ACSUS were used to assign charges and person-months of follow-up to chronic, acute, and death states as patients' CD4 count level, prophylaxis use, opportunistic infection history, and survival status changed.

In order to derive costs from charges, we calculated a single cost-to-charge ratio for ACSUS (43). Details of the method have been described elsewhere (17). The cost of a CD4 test was derived from the Boston Medical Center Cost Accounting System. Medication costs were based on average wholesale prices (48).

Quality-of-Life Data. To estimate the quality-of-life weights for different states, data from the MOS-HIV questionnaire, a validated 30-item instrument presented to patients enrolled in AIDS Clinical Trial Group Protocol 204 (ACTG 204), ACTG 019, ACTG 108, and ACTG 157 (10;14;25;38;47) were used.

A perceived health status question on the MOS-HIV asks patients to rate their current state of health (excellent, very good, good, fair, or poor). We mapped responses to this question onto a numerical scale ranging in value between zero and one, such that "excellent" was equivalent to 1.0, "poor" was 0.2, and "dead" equaled 0.0.

By making the assumption that this transformation approximates the results that would have been observed if the patients' values had been assessed using a rating scale, one can use the Torrance Power Transformation (41) to convert patient responses to time trade-off utilities. The quality-of-life data inputs and details of the method are described elsewhere (17).

Toxicity Data. Toxicity was defined according to the criteria of the AIDS Clinical Trials Group (ACTG) (18). In the model, the patient was assessed for risks of minor and major toxicity whenever a prophylaxis was initiated. Both minor and major toxic events produced a one-time cost increase and quality-of-life reduction. If, based on the prophylaxis regimen chosen during population initialization, a second- or third-line prophylaxis was available, the patient crossed over to it after a major toxic event. Toxicity-related risk, cost, and quality-of-life estimates (shown in Tables 2 and 3) were based primarily on either published literature or presented abstracts.

Drug Adherence and Resistance. Two additional features of the model are drug adherence and resistance. Because of a lack of data on adherence and resistance, these issues are considered in sensitivity analysis.

In the model, each hypothetical patient was labeled as either an adherer or nonadherer by comparing an independently generated random number between zero and one to the risk of being nonadherent. Prophylaxis efficacy was reduced by a fixed factor for nonadherers. Medication costs were left unchanged.

Resistance was modeled in a manner similar to that of toxicity. If resistance developed, the efficacy of the relevant prophylaxis could be reduced, and both the cost of treating and the mortality from a breakthrough infection rose.

RESULTS

Baseline Analysis

Results of the baseline analysis reflect adjustments for quality of life and are shown in Table 4. Also in Table 4 are results unadjusted for quality of life, discussed in the section on sensitivity analysis. The 16 different prophylaxis regimens are ranked by increasing cost.

Table 4. Incremental Cost-effectiveness Results for the Average HIV-infected Patient with a CD4 Count below 300/mm^3 [a]

		Adjusted for quality		Unadjusted for quality	
Policy[b]	Costs (*$*)	Q-A survival (*months*)	Incr. C/E (*$/QALY*)	Survival (*months*)	Incr. C/E (*$/YLS*)
PCP prophylaxis only	43,150	42.35	—	49.60	—
Azithromycin ≤ 50	44,040	42.78	25,000	50.12	21,000
Rifabutin ≤ 50	44,480	42.69	Dominated[c]	50.01	Dominated[c]
Clarithromycin ≤ 50	44,740	42.85	[d]	50.21	[d]
Azithromycin ≤ 100	44,750	42.97	47,000[e]	50.34	40,000[e]
Azithro/Rif ≤ 50	45,550	42.91	Dominated[c]	50.28	Dominated[c]
Rifabutin ≤ 100	45,650	42.84	Dominated[c]	50.18	Dominated[c]
Clarithromycin ≤ 100	46,070	43.06	[d]	50.45	[d]
Clarithro/Rif ≤ 50	46,210	42.88	Dominated[c]	50.25	Dominated[c]
Azithromycin ≤ 200	46,420	43.12	130,000[e]	50.51	110,000[e]
Azithro/Rif ≤ 100	47,590	43.14	[d]	50.55	[d]
Rifabutin ≤ 200	48,200	42.96	Dominated[c]	50.32	Dominated[c]
Clarithro/Rif ≤ 100	48,880	43.10	Dominated[c]	50.50	Dominated[c]
Clarithromycin ≤ 200	48,970	43.24	260,000[e]	50.65	220,000[e]
Azithro/Rif ≤ 200	51,930	43.34	360,000	50.77	300,000
Clarithro/Rif ≤ 200	54,450	43.30	Dominated[c]	50.72	Dominated[c]

[a] For ease of presentation, discounted costs and survival are shown rounded to four significant digits. Incremental cost-effectiveness ratios (Incr. C/E) are in dollars per quality-adjusted (Q-A) life-year saved ($/QALY) or dollars per year of life saved ($/YLS), rounded to two significant digits. C/E ratios may not equal the ratio of costs to survival due to rounding. Assumes prophylaxis (≤ 200) for *Pneumocystis carinii* pneumonia (PCP) with trimethoprim-sulfamethoxazole.

[b] Identifies first-line therapy in the prophylaxis regimen as rifabutin, azithromycin, clarithromycin, azithromycin/rifabutin (azithro/rif) or clarithromycin/rifabutin (clarithro/rif), and the threshold for beginning prophylaxis expressed in CD4 cells/mm^3.

[c] Regimen is eliminated by strong dominance. To calculate the CER relative to PCP prophylaxis only, divide the difference in cost between the two policies by their difference in quality-adjusted survival, and multiply by 12.

[d] Regimen is eliminated by weak dominance. To calculate the CER relative to PCP prophylaxis only, divide the difference in cost between the two policies by their difference in quality-adjusted survival, and multiply by 12.

[e] Ratio is calculated relative to the next less costly alternative that has not already been eliminated by dominance.

Quality-adjusted Survival. Quality-adjusted life expectancy for the "PCP prophylaxis only" strategy is 42.35 months. All *M. avium* complex prophylaxis regimens increase projected life expectancy beyond that of PCP prophylaxis only. When comparing regimens that begin at the same CD4 level (e.g., rifabutin ≤ 50 versus azithromycin ≤ 50), rifabutin produces the smallest quality-adjusted survival gains. The azithromycin/rifabutin combinations offers the greatest gains in quality-adjusted survival.

Costs and Cost-effectiveness. Projected total lifetime direct medical costs for the average HIV-infected patient with a beginning CD4 count between 201 and 300/mm^3 on PCP prophylaxis only are $43,150. All *M. avium* complex prophylaxis regimens increase costs beyond that of *P. carinii* pneumonia prophylaxis alone. Comparing regimens that begin at the same CD4 level, azithromycin costs the least, ranging from $44,040 to $46,420 per person for the ≤ 50 and ≤ 200 options, respectively. The clarithromycin/rifabutin combination is the most expensive alternative.

These results translate into a variety of implications for cost-effectiveness. From Table 4, all rifabutin alone and clarithromycin/rifabutin policies, as well as azithromycin/rifabutin ≤ 50, are dominated, meaning that there are other strategies that cost less and are associated with longer projected, quality-adjusted survival. After eliminating these eight options, an incremental cost-effectiveness analysis reveals that only azithromycin strategies produce ratios below $260,000 per QALY. Initiating azithromycin prophylaxis after the CD4 count has fallen to 50/mm^3 has an incremental cost-effectiveness ratio of $25,000/QALY, relative to PCP prophylaxis only. Starting azithromycin prophylaxis earlier in the course of HIV disease, such as the ≤ 100 and ≤ 200 policies, increases both costs and survival, resulting in incremental cost-effectiveness ratios of $47,000/QALY and $130,000/QALY, relative to ≤ 50 and ≤ 100, respectively.

Sensitivity Analysis

To account for uncertainty in the baseline input data, we performed sensitivity analyses on the parameters described earlier. This form of analysis is meant to reveal how sensitive the conclusions of the model are to reasonable changes in the data.

Natural History and Incidence of M. avium Complex. The MACS data utilized in this analysis reflect zidovudine monotherapy, a therapeutic approach that is no longer standard (8). In order to understand the implication of combination antiretroviral therapy, we did a sensitivity analysis that considered triple drug therapy (zidovudine/lamivudine/indinavir) by stopping the monthly probability of CD4 decline for 12 months and adding the costs of lamivudine and indinavir ($543 per month [49]) to the baseline cost of zidovudine. Viral load testing, at a cost of $110 every 3 months (derived from the Boston Medical Center Cost Accounting System), was also assumed. From Table 5, total quality-adjusted survival for PCP prophylaxis only increases to 48.56 months and total costs to $54,520. Azithromycin ≤ 50 increases quality-adjusted life expectancy to 48.94 months, costs to $55,320, for an incremental cost-effectiveness ratio of $26,000/QALY. Thus, although both incremental costs and incremental quality-adjusted life expectancy are greater in the presence of triple therapy, their ratio remains nearly unchanged. Strongly dominated policies are not shown in Table 5.

Table 5 also illustrates the impact of doubling the risk of primary *M. avium* complex infection, by CD4 count level, as might be the case if one could identify a high-risk group of patients. All rifabutin and clarithromycin/rifabutin strategies, as well as azithromycin/rifabutin ≤ 50, are strongly dominated.

Beginning a regimen of azithromycin prophylaxis after the CD4 count has fallen to 50/mm^3 has a cost-effectiveness ratio of $13,000/QALY relative to PCP prophylaxis only if risks are doubled. Starting azithromycin prophylaxis even earlier in the course of HIV increases both costs and survival, resulting in incremental cost-effectiveness ratios of $21,000/QALY (≤ 100) and $59,000/QALY (≤ 200).

Quality of Life. Table 4 also displays the results of an analysis in which quality-adjusted survival is replaced with unadjusted survival. All life expectancies increase, reflecting the disutility associated with chronic HIV, toxicity, acute opportunistic infections, and care after recovery from an opportunistic infection. However, cost-effectiveness results are similar to those of the baseline analysis. The azithromycin ≤ 50 policy has a cost-effectiveness ratio of $21,000 per year of life saved relative to PCP prophylaxis only, compared with $25,000/QALY in the baseline analysis.

Table 5. Impact of Changes in Natural History and the Risk of Primary *Mycobacterium avium* Complex Infection on Incremental Cost-effectiveness[a]

	Triple drug therapy[b]			Risk of infection doubled[c]		
Policy[d]	Cost ($)	Q-A survival (*months*)	Incr. C/E ($/QALY)	Cost ($)	Q-A survival (*months*)	Incr. C/E ($/QALY)
PCP prophylaxis only	54,520	48.56	—	43,870	41.29	—
Azithromycin ≤ 50	55,320	48.94	26,000	44,560	41.92	13,000
Clarithromycin ≤ 50	55,940	49.00	[e]	45,170	42.04	[f]
Azithromycin ≤ 100	55,970	49.08	54,000[g]	45,120	42.24	21,000[g]
Clarithromycin ≤ 100	57,130	49.16	[e]	46,320	42.41	[e]
Azithromycin ≤ 200	57,460	49.23	130,000[g]	46,610	42.54	59,000[g]
Azithro/Rif ≤ 100	58,480	49.23	[e]	47,760	42.56	[e]
Clarithromycin ≤ 200	59,750	49.33	270,000[g]	49,060	42.76	140,000[g]
Azithro/Rif ≤ 200	62,380	49.42	340,000	51,930	42.94	180,000

[a] For ease of presentation, discounted costs and quality-adjusted (Q-A) survival are shown rounded to four significant digits. Incremental cost-effectiveness ratios (Incr. C/E) are in dollars per quality-adjusted life-year saved ($/QALY), rounded to two significant digits. C/E ratios may not equal the ratio of costs to survival due to rounding. Assumes prophylaxis (≤ 200) for *Pneumocystis carinii* pneumonia (PCP) with trimethoprim-sulfamethoxazole.
[b] Triple drug therapy with zidovudine, lamivudine, and indinavir assumed by stopping CD4 decline for 12 months, adding the cost of antiretroviral therapy, and allowing for viral load testing every 3 months.
[c] Risks doubled from baseline values of 0.000014, 0.00101, 0.00375, and 0.01220 for the 201–300, 101–200, 51–100 and ≤ 50/mm^3 CD4 levels, respectively.
[d] Identifies first-line therapy in the prophylaxis regimen as rifabutin, azithromycin, clarithromycin, azithromycin/rifabutin (azithro/rif), or clarithromycin/rifabutin (clarithro/rif), and the threshold for beginning prophylaxis, expressed in CD4 cells/mm^3.
[e] Regimen is eliminated by weak dominance.
[f] Regimen is eliminated by strong dominance.
[g] Ratio is calculated relative to the next less costly alternative that has not already been eliminated by dominance.

Table 6. Impact of Different Quality-of-life Weights for Post-acute *Mycobacterium avium* Complex Care on Incremental Cost-effectiveness[a]

		Post-acute weight = 0.40[b]		Post-acute weight = 0.00[b]	
Policy[c]	Cost ($)	Q-A survival (*months*)	Incr. C/E (*$/QALY*)	Q-A survival (*months*)	Incr. C/E (*$/QALY*)
PCP prophylaxis only	43,150	41.91	—	41.42	—
Azithromycin ≤ 50	44,040	42.46	20,000	42.09	16,000
Clarithromycin ≤ 50	44,740	42.54	[d]	42.20	[d]
Azithromycin ≤ 100	44,750	42.71	34,000[e]	42.42	26,000[e]
Clarithromycin ≤ 100	46,070	42.83	[d]	42.57	[d]
Azithromycin ≤ 200	46,420	42.93	91,000[e]	42.71	70,000[e]
Clarithromycin ≤ 200	48,970	43.08	200,000	42.90	160,000
Azithro/Rif ≤ 200	51,930	43.21	270,000	43.07	210,000

[a] For ease of presentation, discounted costs and quality-adjusted (Q-A) survival are shown rounded to four significant digits. Incremental cost-effectiveness ratios (Incr. C/E) are in dollars per quality-adjusted life-year saved ($/QALY), rounded to two significant digits. C/E ratios may not equal the ratio of costs to survival due to rounding. Assumes prophylaxis (≤ 200) for *Pneumocystis carinii* pneumonia (PCP) with trimethoprim-sulfamethoxazole.
[b] The assumed quality-of-life weight for individuals with a history of *Mycobacterium avium* complex.
[c] Identifies first-line therapy in the prophylaxis regimen as rifabutin, azithromycin, clarithromycin, azithromycin/rifabutin (azithro/rif), or clarithromycin/rifabutin (clarithro/rif), and the threshold for beginning prophylaxis, expressed in CD4 cells/mm^3.
[d] Regimen is eliminated by weak dominance.
[e] Ratio is calculated relative to the next less costly alternative that has not already been eliminated by dominance.

In an effort to improve quality-adjusted cost-effectiveness ratios, scenarios were run in which the quality-of-life weight for those with a history of *M. avium* complex (i.e., the post-acute care state), was assumed to be below its baseline value of 0.772. In general, the lower the quality weight after surviving an infection, the worse it is to live month after month with a history of that infection, and the more important it is to initially prevent the primary infection.

Results for postacute care quality weights of 0.40 and 0.00 are shown in Table 6, where a quality weight of 0.00 represents a best-case scenario for the cost-effectiveness of *M. avium* complex prophylaxis. All rifabutin and clarithromycin/rifabutin regimens, as well as azithromycin/rifabutin ≤ 50 and ≤ 100, are strongly dominated; these programs are not listed in Table 6. Among the available strategies, only azithromycin produces ratios below $160,000/QALY saved.

Prophylaxis Cost. We also identified the prophylaxis cost required for the cost-effectiveness ratios of ≤ 50 regimens to fall below a $100,000/QALY threshold. Rifabutin ≤ 50 meets this criterion after lowering its monthly cost from $178 to $95, a 47% reduction. Similar analyses indicate that if the monthly cost of: a) clarithromycin is reduced 27%, from $206 to $150; b) azithromycin/rifabutin combination therapy is reduced 40%, from $299 to $180; or c) clarithromycin/rifabutin combination therapy is reduced 57%, from $383 to $165, the corresponding ≤ 50 regimens achieve incremental cost-effectiveness ratios below $100,000/QALY.

Resistance and Adherence. In another scenario, we assumed that resistant organisms developed in 11% and 29% of patients who developed *M. avium* complex while on azithromycin or clarithromycin, respectively, for 6 months or more (19;36), and that among such patients, the mortality and cost associated with a breakthrough *M. avium* complex infection doubled. In this situation, rifabutin and clarithromycin/

rifabutin programs continue to be strongly dominated, as are all of the clarithromycin regimens. Only when azithromycin is begun late in the course of HIV is prophylaxis an efficient option, with cost-effectiveness ratios of $25,000/QALY and $47,000/QALY for the < 50 and < 100 regimens.

Because of the intention-to-treat design of clinical trials, the efficacy data in this analysis incorporate a level of adherence equal to that seen in the trials. Results of an analysis in which a further 20% of the simulated population is assumed to be nonadherent, where nonadherence reduces the efficacy of all prophylaxis by 20% (39), suggest that the relative ranking of prophylaxis regimens for *M. avium* complex prophylaxis is unchanged, with a cost-effectiveness ratio of $34,000/QALY for the azithromycin < 50 alternative, relative to PCP prophylaxis only.

Scenario Analysis for Medication Toxicity. Patients may have known sensitivities, in the form of prior toxicity, to one or more types of prophylaxis. In contrast to the prior analyses, in this situation specific drugs are excluded from consideration at the outset. When azithromycin is excluded from the analysis, the lowest ratio of $38,000/QALY corresponds to clarithromycin < 50 (with rifabutin as second-line prophylaxis) relative to PCP prophylaxis only. All rifabutin regimens, as well as clarithromycin/rifabutin < 50 and < 100, continue to be dominated, while other (nondominated) regimens produce cost-effectiveness ratios above $77,000/QALY.

DISCUSSION

We developed a model to evaluate the cost-effectiveness of different regimens of prophylaxis against the major opportunistic infections associated with advanced HIV disease, and we used the model to project costs, life expectancy, and cost-effectiveness of different prophylaxis strategies against disseminated *M. avium* complex. Results suggest that the strategy beginning with azithromycin and changing to clarithromycin, and then rifabutin if needed after major toxicity, is the most cost-effective of the five options. In the baseline analysis, for HIV-infected patients who receive *P. carinii* pneumonia prophylaxis after the CD4 count has declined to 200/mm^3, initiating a regimen of azithromycin prophylaxis after the CD4 count has declined to 50/mm^3 has a cost-effectiveness ratio of $25,000/QALY relative to prophylaxis for *P. carinii* pneumonia only. If the model were to include the beneficial effects of azithromycin on the incidence of sinusitis and pneumonia, azithromycin prophylaxis would appear even more cost-effective.

Other cost-effectiveness analyses of *M. avium* complex prophylaxis have similarly concluded that azithromycin is the most cost-effective option (16;29). However, both analyses by Freedberg et al. (16) and Moore et al. (29) use a decision-tree structure. As a result, they are unable to capture the risk and value of *M. avium* complex prophylaxis over time. By incorporating more of the relevant complexity of AIDS, this model captures more meaningful cost, incidence, and quality-of-life data than do either of the others, and reflects the impact of competing risks (i.e., other important opportunistic infections).

Sensitivity analysis revealed that, even in a setting where the quality of life after surviving *M. avium* complex is made equivalent to the state of death, preventing the infection using a prophylaxis other than azithromycin is expensive. If the risk of *M. avium* complex is lower, as appears to be the case with combination antiretroviral therapy (30), azithromycin remains the best option. Among patients at higher risk for *M. avium* complex, it may not make sense to incur added costs and switch to a prophylaxis (e.g., clarithromycin) with efficacy greater than that of azithromycin.

Prophylaxis costs must be reduced by a minimum of 27% for clarithromycin prophylaxis, and a maximum of 57% for clarithromycin/rifabutin combination prophylaxis, in order to achieve cost-effectiveness ratios below $100,000/QALY for each of the rifabutin, clarithromycin, azithromycin/rifabutin, and clarithromycin/rifabutin ≤ 50 regimens. The impact of resistance on the cost-effectiveness of azithromycin ≤ 50 appears to be relatively minor, but azithromycin prophylaxis early in the course of HIV (i.e., ≤ 200) is no longer an efficient option. Only in a setting where azithromycin is not a viable option because of known sensitivities to the prophylaxis is it appropriate to consider other prophylaxis regimens, particularly clarithromycin < 50, as first-line therapy.

Any clinical policy model is limited by the quality of the input data. We used natural history data based on a prospective cohort study of HIV-positive patients (MACS) from 1984 to 1991 (22). These risks reflect CD4 decline for patients receiving zidovudine or didanosine monotherapy. Current combination antiretroviral therapy is associated with a lower risk of CD4 decline, and in fact CD4 count increases (8). Natural history data on the risk of *M. avium* complex in patients receiving combination antiretroviral therapy can be incorporated as they become available (1). Two specific points about rifabutin are worth mentioning. First, it has some potential benefit over azithromycin and clarithromycin because it may prevent tuberculosis (9). Second, this is likely more than offset by its pharmacokinetic interactions with protease inhibitors, thus limiting its use in patients on combination antiretroviral therapy (15). Cost data are from a national survey (ACSUS) of HIV-positive patients in 1991 and 1992 (4), and a variety of assumptions were employed in order to derive cost estimates for the model.

ECONOMIC IMPLICATIONS

For policy makers, conclusions based on the model's results may provide guidance as to the clinical and cost impact of practice guidelines and financial coverage for medications. For example, baseline results suggest that it would cost $4.3 billion to care for 100,000 patients with AIDS from a CD4 count of 300/mm^3 to death if *P. carinii* pneumonia prophylaxis were begun at a CD4 count of 200/mm^3. An additional $89 million buys azithromycin prophylaxis begun at a CD4 count of 50/mm^3 and increases quality-adjusted survival by approximately 3,583 years of the entire cohort.

This information can be used by policy makers to allocate limited resources in a more efficient manner. In particular, the state-based AIDS Drug Assistance Programs (ADAPs) provide medications to patients with HIV who do not qualify for Medicaid but cannot otherwise afford necessary drugs. Because each state develops its list of qualifying medications independently, there have been wide variations in available drugs across states. For example, the state of New York offered 212 drugs in early 1998, while Louisiana approved only four (11). Cost-effectiveness analysis based on the output of this model could be used to resolve the discrepancies among states. The result would be a list of medications that is prioritized to offer the greatest impact on quality-adjusted survival for a given budget.

The application of this model to prophylaxis for *M. avium* complex is a first step toward developing such a list. As more data on the impact of combination antiretroviral medications become available (8), it will be important to reconsider the costs and clinical value of strategies to prevent individual opportunistic infections

via drug prophylaxis. Clinical trials are currently under way to examine the role of *M. avium* complex prophylaxis in the setting of improved immune function (1).

Whether enough data and experience with current regimens exist to understand the value of prophylaxis, clinical and resource allocation decisions are already being made (as illustrated by the example of the ADAPs). We conclude that recent U.S. Public Health Service recommendations to begin *M. avium* complex prophylaxis after the CD4 count is below 50/mm^3 (9) are reasonable. Specifically, azithromycin prophylaxis after the CD4 has declined to 50/mm^3 is the most cost-effective option. To achieve more benefit for a given budget, prophylaxis targeted at populations facing a higher risk of *M. avium* complex could be considered.

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