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UMI
Cost-Effectiveness of Strategies for the Prophylaxis of *Mycobacterium avium* Complex Infection in Patients with Advanced Human Immunodeficiency Virus Disease

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Science Graduate Department of Community Health Subspecialization in Clinical Epidemiology University of Toronto

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ABSTRACT

Background: *Mycobacterium avium* complex (MAC) is the commonest bacterial opportunistic infection in patients with Human Immunodeficiency Virus (HIV) infection.

Objective: To determine the cost-effectiveness of strategies for MAC prophylaxis for patients with advanced HIV disease.

Design: Decision analysis model of advanced HIV, with direct estimates of utilities.

Measurements: Utilities were assessed with the standard gamble (SG) method and the time trade off (TTO) method, using standardized descriptors. Patients' own health was rated with the health utilities index (HUI).

Results: SG and TTO methods gave similar results for utility estimates. HUI scores were higher and did not differentiate between health states. Azithromycin was the most cost-effective regimen for MAC prophylaxis, and may be cost-saving. The optimal time to initiate azithromycin is between a CD4 count of 100 and 75 cells / µL.

Conclusions: Azithromycin, with sequential rifabutin, is the most cost-effective regimen for MAC prophylaxis in patients with advanced HIV disease.
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1. Outline

This study has several parts. First, it addresses a particular clinical question using a decision analysis approach, namely, the prophylaxis of *Mycobacterium avium* complex infection in patients with HIV. Second, it includes another study assessing the quality of life of various stages of HIV infection. Third, it examines how an alternative theory of decision making (cumulative prospect theory) could change the results of this decision analysis.

The structure of this thesis departs from the traditional structure of a scientific paper. The thesis starts with an introduction to the clinical topic, a statement of the research question and a review of previous HIV related decision analysis research. Next, two topics are reviewed in detail - methods of utility assessment, and theories of decision making under uncertainty. Next, the Markov model used for this decision analysis is presented. The three categories of input variables for the model are presented - transition probabilities, costs, and utilities. The statistical tests used for the analysis of the quality of life study are next reviewed.

The next section of the paper presents the results of the study. First, the utility analysis results are reviewed. Next, the results of the decision analysis model are presented. Finally, the model is used to answer several related aspects of the question. The next section reviews the sensitivity analysis, including the analysis using cumulative prospect theory. The paper finishes with a discussion and a conclusion.
2. Introduction

Human Immunodeficiency Virus (HIV) infection is a disease with substantial morbidity, nearly universal mortality, and high costs. These outcomes are increasingly common as the disease progresses and the risk of opportunistic infections increases. The most common bacterial opportunistic infection in HIV is disseminated *Mycobacterium avium* complex (MAC), with a cumulative lifetime incidence of 20 to 40% [1,2]. Disseminated MAC is associated with fevers, chills, night sweats, fatigue, weight loss, abdominal pain, nausea and vomiting, diarrhea, weight loss, and transfusion-dependent anemia [3]. MAC rarely causes death directly, but untreated MAC is strongly correlated with an increased mortality [4,5]. MAC is also linked with an increased risk of acquiring other opportunistic infections, suggesting that this infection may compromise an immune system already ravaged by HIV [6].

The strongest risk factor for the development of MAC is a declining CD4 count [7]. The median CD4 count at the development of MAC in one study was 25 cells / µL, and the median was 9 cells / µL [8]. MAC rarely occurs at a CD4 count of over 100 cells / µL and below this threshold, the risk rises dramatically. The presence of a prior AIDS defining illness (ADI), particularly CMV infection, may significantly increase the subsequent risk of developing MAC, independent of the CD4 count [6]. As well, MAC may be more common in some geographic areas than in others [2]. Gender, race, age, and method of HIV acquisition are not risk factors for the development of MAC [9].

Recent studies have shown that treatment can increase the survival of patients with MAC to approach that of matched controls [6,10]. Even with these regimens, only 31%
of blood cultures will be sterilized [10]. Furthermore, treating MAC may be only partially effective in decreasing symptoms, can have considerable toxicity, and can lead to significant costs [11-13].

The development of a safe, effective, and affordable regimen for preventing MAC would be a major advance in the treatment of late stage HIV patients. Three drugs, alone and in combination, are of proven efficacy for MAC prophylaxis - the rifamycin derivative rifabutin, and two macrolides, azithromycin and clarithromycin [14-17]. Azithromycin combined with rifabutin was the most effective regimen, with azithromycin monotherapy, clarithromycin monotherapy, and clarithromycin / rifabutin combination therapy all of approximately equal but lesser efficacy. Rifabutin monotherapy is the least efficacious regimen.

These agents may also have other positive effects, besides preventing MAC. Rifabutin may have activity in preventing bacterial infections (particularly pneumonia and sinusitis), PCP and toxoplasmosis, while the macrolides may prevent bacterial infections, cryptosporidiosis, and toxoplasmosis [16,18]. As well, rifabutin has been shown to decrease hospitalization and transfusion rates and increase quality of life scores [14]. Drugs used for MAC prophylaxis may increase survival, although this has been shown prospectively only for clarithromycin [15,18].

There are problems with prophylaxis, however. First, these drugs are expensive. In the province of Ontario, one month of prophylaxis costs $285 for rifabutin, $220 for clarithromycin, and $94 for azithromycin [19].
Second, prophylactic agents can be unpleasant [14-16]. A recent study showed that the median time of adherence to rifabutin (supplied without cost) was only nine months, possibly due to disease progression, side effects, or other inconvenience factors [20]. Prescribing these medications may contribute to polypharmacy - the prescribing of a large number and variety of medications, which is common in advanced HIV. Patients may therefore be averse to adding another expensive, unpleasant, and inconvenient medication to their regimen, which confers no immediate benefit.

Third, the widespread use of MAC prophylactic drugs can increase mycobacterial resistance. Up to 58% of breakthrough MAC isolates from patients taking clarithromycin are resistant to macrolides [15]. This can have important clinical ramifications - clarithromycin is the most effective drug for MAC treatment, but resistance is correlated with treatment failure [12,21]. Resistance has also been seen with azithromycin prophylaxis (and azithromycin resistance isolates are cross-resistant to clarithromycin), although not with rifabutin [16].

Fourth, other bacteria can also become resistant to these drugs. A particular concern is tuberculosis, as rifabutin use can lead to rifampin resistance [22]. The rise in multi-drug resistant tuberculosis can have serious consequences for both individual and public health [23]. Similarly, some bacteria which cause pneumonia, sinusitis or soft tissue infections may develop macrolide resistance and thereby be more difficult to treat.

Fifth, patients taking a large number of drugs have an increased risk of drug interactions. For example, fluconazole, a commonly used antifungal drug, increases the serum concentration of rifabutin, thereby increasing its toxicity and possibly, its
Another potentially important interaction exists between rifabutin and a new, potent class of antivirals called protease inhibitors [25]. Rifabutin may significantly decrease the serum levels of these drugs, which may lead to viral (HIV) resistance.

Two alternatives to medical prophylaxis may be considered. The first is a strategy of increased surveillance for MAC. Studies which have screened asymptomatic individuals who are at risk for developing MAC have found a point prevalence of approximately 3 % [14,17]. Patients who develop MAC initially have intermittently positive blood cultures, at a time when they are minimally symptomatic [26]. A strategy of regular surveillance and early treatment of patients with positive cultures may therefore be able to identify patients before they have a large mycobacterial load (when treatment may be more efficacious), while avoiding the problems of prophylaxis. Recent data comparing monthly surveillance and early treatment to combined surveillance and clarithromycin prophylaxis showed surveillance to be inferior [15]. The relative merits of surveillance compared to chemoprophylaxis without regular surveillance cultures and the cost-effectiveness of one strategy relative to the other remain to be determined.

Another alternative is to provide neither prophylaxis nor surveillance. Given the problems of the available strategies, some patients and physicians may reasonably choose this option [20,27]. Any decision about initiating MAC prophylaxis must therefore take into account several factors: the efficacy of the proposed strategy, its cost, its toxicity, patient preferences, the possibility of developing both antimicrobial
resistance, and the potential for adverse drug interactions [28]. The difficulty of this decision has led to considerable diversity in MAC prophylaxis practices [27].

Official practice recommendations have been inconstant and equivocal. After the initial reports of the efficacy of rifabutin in 1993, the United States Public Health Services Task Force released guidelines recommending rifabutin for all patients with a CD4 count of less than or equal to 100 cells / μL [29]. However, revised guidelines released in 1995 recommended rifabutin for patients with a CD4 count of 75 cells / μL or less, while stating that “some experts would wait until the count is < 50 / μL” [30]. No recommendations were made about initiating therapy according to disease stage; that is, no distinction was made between patients with a prior ADI at a given CD4 count and patients without a prior ADI. Guidelines have yet to be updated to include recent data about the efficacy of alternative regimens.

2.1 MAC prophylaxis: the evidence

Three published studies and one abstract have evaluated MAC prophylactic regimens [14-17]. Results are summarized in Table 1. Comparisons across studies are limited because some studies included only patients with a prior ADI, while others included all patients with HIV. Three of the four studies limited recruitment to subjects with CD4 counts less than 100 cells / μL. All studies used a similar endpoint for failure of prophylaxis, namely the occurrence of MAC bacteremia or a positive MAC culture from a sterile site. In general, all agents were more effective than placebo. Azithromycin and clarithromycin were more effective than rifabutin. No direct comparisons of azithromycin to clarithromycin have been conducted, but the effect size, when
compared to rifabutin is similar across studies. The combination of azithromycin and rifabutin is superior to either drug alone, but the combination of clarithromycin and rifabutin failed to demonstrate superiority over clarithromycin alone.

2.2 Other cost-effectiveness studies of MAC prophylaxis in AIDS

Three studies have examined the cost-effectiveness of MAC prophylaxis in patients with HIV. Simpson and colleagues estimated that the cost-utility of rifabutin prophylaxis was approximately $22,000 per quality adjusted life year [31]. Singh estimated that the cost-effectiveness of rifabutin prophylaxis was $18,468 per life year, but did not account for quality of life [32]. Neither of these studies used a Markov modeling approach, and may therefore not represent accurate models of the natural history of a disease with recurring, time-dependent events [33]. Freedberg and colleagues examined the cost-effectiveness of various prophylactic regimens in patients with advanced HIV infection, including rifabutin for MAC with a Markov model. Without adjusting for quality of life, they found that rifabutin had a minimal effect on prolongation of life and was associated with a cost-effectiveness ratio of $210,600 / life year, and azithromycin, initiated at a CD4 count of 50 cells / µL, to have a cost-effectiveness ratio of about $60,000 / life year [34]. None of these studies has yet been published, nor have they reported an incremental cost-effectiveness analysis of the available strategies.
3. The Research Question

The research question for this study was: "How cost-effective are available strategies for the prophylaxis of disseminated *Mycobacterium avium* complex infection in patients with HIV?"

This study compared the cost-effectiveness of individual agents, combination regimens, and sequential (crossover) strategies. To do so, the following issues were addressed. Is the decision regarding therapy different depending on the clinical stage of the patient? What is the optimum CD4 count at which to initiate therapy? Does the optimum time to initiate therapy depend on clinical disease stage? How important is resistance in determining cost-effectiveness? If these agents prevent other infections, how does this change their cost-effectiveness? Do drug interactions play a significant role in determining cost-effectiveness?

We performed our analysis accounting for both life expectancy and quality of life. To perform the latter, we focused particular attention on the measurement of utilities. Utilities are a summary measure of an individual's preference for a given state. One technique for measuring utilities, the standard gamble method, has strong conceptual advantages, but has limitations, both practical and theoretical. A major concern is that this method measures not only an individual's preference for a specific clinical state, but also their attitudes towards risk. Recently, a theory of decision making under uncertainty called cumulative prospect theory (CPT) has been advanced to "correct" for these errors in standard gamble utility assessments. We analyzed our results both with and without adjusted utilities, as determined by CPT.
4. Previous HIV Related Decision Analysis Research

Several published studies have used decision analysis to evaluate particular aspects of HIV infection. Decision analyses and cost-effectiveness analyses have been completed for antiretroviral therapies, *Pneumocystis carinii* prophylaxis and treatment, treatment of toxoplasmosis and screening policies [35-45]. Most of these studies were cost-effectiveness or cost-benefit analyses which did not adjust for quality of life factors, although some secondary analyses attempted to explicitly model a patient’s overall well-being [34,35,38,40].

Owens and colleagues have elicited utilities for health states associated with HIV infection from physicians, and estimated that asymptomatic HIV infection had a utility of 0.83, symptomatic HIV infection had a utility of 0.42, and AIDS had a utility of 0.17 [35]. Lamping estimated the utility of patients with HIV to be 0.69, although she did not differentiate between disease stages [46]. Revicki and colleagues estimated that asymptomatic HIV infection had a utility of 0.80 - 0.88, symptomatic HIV had a utility of 0.73 - 0.82, and AIDS had a utility of 0.74 - 0.80 [47]. Tsevat and colleagues estimated that asymptomatic HIV infection had a utility of 0.87, symptomatic HIV infection a utility of 0.77, and AIDS a utility of 0.79 [48].

5. Utility Assessment Methods

Utilities are summary measures of the valuation of defined outcome states under conditions of uncertainty [49]. They are intended to quantify quality of life information and reflect individual preferences towards both positive and negative issues. In a cost-
utility analysis, the outcomes are both costs incurred and benefits gained. Benefits are quantified as quality adjusted life years, or QALYs [50]. The amount of time in each health state is weighted by the utility of each health state to determine the expected overall quality adjusted survival. Thus, a QALY contains information about both the length of life and the quality of life. Marginal benefit is the difference in QALYs between two alternatives. Marginal cost is the difference in cost between the alternatives. Marginal cost-utility is calculated as the marginal cost divided by the marginal benefit. This value, measured in dollars/QALY, can be used to assess the cost-effectiveness of one treatment strategy relative to another [51].

The science of measuring utilities is relatively new and controversial [52-54]. Direct comparisons with other quality of life scales are important as checks of validity and for establishing a framework for interpreting results. Several methods have been developed to directly measure utilities, the most frequent being category rating scales, standard gamble, time-trade off and the use of a multi-attribute health utilities index [52]. No consensus has yet developed as to which is the best [55,56].

5.1 Category Rating Scale

Category rating scales (also called visual analog scales) ask participants to rate health states along a linear scale [52]. The end-points of the scale can be defined in various ways - for chronic health states, they are often “death” and “best possible health” (Figure 1). Participants are asked to rank health states in order of preference and then to rate these states along the scale according to their preferences. While this method is simple to complete and easy to interpret, there is no theoretical foundation for the use
of category rating scale assessments in decision analysis, and the value scores obtained do not represent true utilities.

5.2 Standard Gamble

The standard gamble (SG) method calculates utilities by asking participants to choose between two prospects (Figure 2) [52]. The first prospect is a gamble between achieving best possible health (with probability $p$) or immediate death (with probability $1-p$). The second prospect is a certainty of continuing in the current state of health. At a value of $p$, the "threshold probability," participants will be indifferent between the two prospects. This probability can then be used to calculate the utility of the current health state. The anchors of the risky prospect are chosen as is appropriate to the health state being assessed. Standard gamble techniques have the advantage that they are based directly on decision analysis theory. The major disadvantage of SG is that participants often have a difficult time with the cognitive effort required to complete the task and, even if successful, the utility values elicited may be distorted by the participants' attitude towards risk. For example, risk averse participants, relative to risk neutral participants, will overestimate the utility of some health states [57].

5.3 Time Trade Off

The time trade off (TTO) technique asks participants to imagine themselves in the current disease state for duration $t$ (Figure 3) [52]. Participants are then asked how much time in best possible health ($x$) they would consider to be equivalent to a defined duration in the disease state ($t$). Thus, the quality adjusted life years in best possible
health (utility of best possible health \( x \) duration in best possible health, \( x \)) are equal to the quality adjusted life years in the disease state (utility of disease state \( x \) duration in the disease state, \( t \)). By assigning a value score of 1 to the utility of best possible health, the value \( U_t \) can be measured by calculating \( x/t \) and is used to estimate the utility of the current disease state. The advantage of the TTO is that it is easy to understand and does not include attitudes toward risk. The disadvantages are that it does not have a theoretical basis in expected utility theory and the values may underestimate the utility of a health state if participants time discount the future relative to the present [58].

5.4 Multi-Attribute Utility Theory

Another approach is to assess utilities using Multi-Attribute Utility Theory [59]. In this method, health states are described in several different dimensions or “attributes” (such as sensation, cognition, pain, etc.). Each attribute has distinct levels, for example, the attribute “pain” may be scaled on a range varying from none to severe. Scores for each attribute are derived from a questionnaire and then translated into a utility with an empirically derived function. Thus, utilities can be easily calculated through the administration of a straightforward questionnaire. The major advantages of this technique are its feasibility and acceptability. The major disadvantage is the concern about validity; for example, multi-attribute values may overestimate the utility of a health state if two problems interact so that each worsens the other.
6. Decision Making Under Uncertainty

6.1 Expected Utility Theory and Its Limitations

The major theory of decision making under conditions of risk or uncertainty for the last four decades has been expected utility theory (EUT) [60]. The theory holds that for each set of prospects under conditions of uncertainty, participants should chose the prospect that produces the greatest net benefit after accounting for the probability of chance events. Expected utility is the sum of the utilities of all possible outcomes, with each outcome weighted by the probability of its occurrence. Thus, two variables are integral to EUT - the utility of a given state and the probability of its occurrence.

This theory is the basis for virtually all published decision analyses. It is a powerful theory that forces decision makers to explicitly evaluate the probabilities and values of all possible outcomes and should, its proponents claim, lead to more rational decision making. Even for skeptics, decisions based on EUT can be a useful tool to inform the health policy debate. Weaknesses in the theory may, however, limit its applicability [61]. For example, there is no theoretically sound method to aggregate utilities from individuals into summary values. Another problem is that EUT can assess the efficiency of an intervention, but does not address questions of equity in resource allocation decisions.

On an individual level, violations of EUT are common [62,63]. For example, descriptions of outcome states framed as gains rather than losses (a 90% chance of living instead of a 10% chance of dying) significantly influence the preference for that state [64,65]. Proponents of EUT hold that these violations are irrational and that EUT
is both a normative and a prescriptive theory of decision making under uncertainty, but
debate about the normative nature of EUT continues [66-70].

6.2 Probability Preference

One of the axioms of utility theory is the “independence principle” [66,57]. This principle
states that the utility of a possible outcome should be linear in its outcome probabilities.
Consider, for example a simple decision tree, such as that used to assess utilities with
the standard gamble (Figure 2). It can be seen that if best possible health is assigned
an outcome of 1, and death is assigned an outcome of 0, the expected utility of the
prospect is $p$. If $p$ is allowed to vary until the respondent is indifferent between the two
prospects, the expected utility of the outcome state is equal to $p$. If expected utility is
plotted against probability, the result is a linear relationship (Figure 4).

However, people often dislike gambling, and this attitude towards risk can have a
significant effect upon their valuation of outcomes. Consider, for example, the decision
trees depicted in Figure 5. In Decision I, the subject is offered the choice between
prospect A1, with a 40% chance of winning $4,000, or prospect B1, with a 50% chance
of winning $3,000. Most people will choose prospect A1 with its higher expected utility
($1,600 vs. $1,500), in accordance with EUT.

Now consider Decision II, in which the subject is offered a choice between prospect A2,
with an 80% chance of winning $4,000, or prospect B2, with a 100% chance of winning
$3,000. Note that the outcomes in Decision II are identical to Decision I, but the
probabilities have changed by the same relative degree, so that EUT states that the
same ordering of preferences should dominate (A2 preferred over B2). Empirical data has shown that individuals will consistently prefer prospect B2, a decision which is inconsistent with EUT [62,64]. This “certainty effect” was first described by Allais, and has come to be known as the Allais paradox [57]. It is one example in which an individual violates EUT by exhibiting “probability preference,” in which the preference for a given prospect is determined by not only the utility of the outcome, but also by the probability of its occurrence.

How can probability preference be explained? EUT explains this violation as an example of irrational reasoning. However, no clear definition of rationality exists [66]. To argue that this choice is irrational simply because it violates EUT is circular and unconvincing; rationality cannot be solely defined by EUT. An alternative approach is to try and explain this violation of EUT is to try and control for probability preference [71]. The basis for this approach can be found in prospect theory, as developed by Tversky and Kahneman [57,72]. According to this reasoning, this correction is necessary because the elicited utilities encompass not only preferences for (or attitudes towards) the outcome being assessed, but also distortions related to the subjective interpretation of probabilities.

6.3 Risk Attitude

How can we account for risk attitude? A risk averse individual, for example, will exhibit a dislike for the process of gambling, apart from their attitude towards the prospect. Consider again, the elicitation of standard gamble utilities as depicted by the decision tree in Figure 2. For a given outcome state, a risk averse individual will chose a higher
value of $p$ than a risk neutral individual when determining her indifference probability, and therefore a higher utility for that state will be estimated. If we consider utility to be the dependent variable and probability the independent variable, the relationship between probability and utility can be plotted. Figure 6 is one possible curve for such a risk averse individual. It is assumed that for a certain effect ($p = 0$ or $1$), no probability transformation is required. For any given intermittent probability, the risk averse individual will undervalue the associated utility (heavy line) compared to a risk neutral individual (dashed line). The concave shape is typical of a risk averse individual. A risk seeking individual will have a convex curve, indicating a greater utility for an outcome with a given probability compared to a risk neutral individual. To elicit utilities without assessing risk attitudes (i.e., to assess preference for outcomes independently of preference for probabilities), requires that a “correction” be applied to transform probabilities according to a respondent’s risk attitude. In Figure 6 this means transforming the heavy curved line into the diagonal dashed line.

6.4 Adjusting for Risk Aversion: An Example

What happens to our previous example of EUT violation if we transform probabilities, assuming the individual is risk averse? The probability for positive monetary outcomes have been transformed in Figure 7. In Decision II, prospect A2 now has a transformed probability of 0.64, and an expected value of $2,560. Prospect B2 with an expected value of $3,000, is preferred. After applying this transformation, the “certainty effect” no longer violates EUT.
The probabilities in Decision I should also be similarly transformed. Now, prospect A1 has an expected value of $640, while prospect B1 has an expected value of $750. Thus, EUT states that prospect B1 is preferred. Recall, however, that most subjects will choose prospect A1 in Decision I. The transformation which was applied above now leads to an apparent violation of EUT in Decision I, indicating that most individuals are not as risk averse for Decision I as this transformation would predict.

6.5 The Most Commonly Observed Probability Weighting Curve

Empirical data shows that risk attitude varies with probability. For probabilities in the range of 0.40 to 0.50 (as in Decision I), risk attitude may be less important than for probabilities in the range of 0.80 to 1 (as in Decision II). It is possible to derive empirically the shape of a probability weighting curve. The most common curve is depicted in Figure 8 [57]. The S-shaped curve suggests that individuals are risk seeking for low probabilities and risk averse for high probabilities. The curve is linear around 0.30 to 0.40, suggesting that probability preference is not a major concern (i.e., individuals are risk neutral) for probabilities in this range. The weighting function for this curve is derived from the formula:

\[
w(p) = \frac{p^\gamma}{(p^\gamma + (1-p)^\gamma)^\gamma} \quad [\text{Equation 1}].
\]

where \( p \) is the probability and \( \gamma \) is a weighting parameter, most commonly valued at 0.61 [57].

This weighting function is based on cumulative prospect theory (CPT), an advance on the initial description of prospect theory [57]. In brief, the major contribution of these
two theories is the derivation of the weighting function. In CPT, the weighted probability accounts for the situation of more than two possible outcomes, and weights the probability accordingly [57]. CPT can account for probability preferences, as well as for other limitations of EUT not discussed above, such as loss aversion (the consistent tendency to value losses greater than gains) and source dependence (the observed effect in which people are more willing to accept a gamble if they are aware of the source of uncertainty).

6.6 Adjusting for Risk Attitude with CPT: An Example

Let us again assess what happens to our previous example of EUT violation if we transform probabilities, this time according to CPT. The probability for positive monetary outcomes have been transformed according to Equation 1. In Decision I, prospect A1 has an expected value of $1,480, while prospect B1 has an expected value of $1,260; therefore, prospect A1 is preferred. In Decision II, prospect A2 has an expected utility of $2,440, while prospect B2 has an expected utility of $3,000; therefore, prospect B2 is preferred. This weighting of probabilities can maintain consistency, explain probability preference, and predict behaviour.

6.7 Risk Attitudes in Medical Situations

CPT will be important for situations where risk seeking or risk aversion may significantly effect decisions [73]. Risk aversion is frequent when choosing between a beneficial event with a high probability and a more advantageous event which carries a low probability of loss, such as a preventive health decision in which a patient in good
health refuses hepatitis B immunization [74]. Risk aversion is also common when choosing between undergoing or not undergoing an intervention with a relatively high probability of a potentially large associated loss, such as a treatment decision in which a patient with atrial fibrillation declines anticoagulation [75].

Risk seeking is frequent when choosing between an adverse event with is certain to happen and a worse choice with a lower, but substantial probability of happening, such as a patient with advanced AIDS receiving a baboon bone marrow transplantation [76]. Risk seeking is also common when choosing between undergoing or not undergoing an intervention with a low probability of a potentially large associated gain, for example, a patient who takes weight loss medication with a low risk of both success and of severe side-effects [77].

6.8 Alternative Theories of Decision Making

Other theories have attempted to formulate a normative framework for decision making under conditions of uncertainty. Examples include cumulative prospect theory, regret theory, disappointment-elation theory, and lottery-dependent expected utility theory [78]. A detailed review is beyond the scope of this thesis. Nevertheless, it will be appreciated that decision theory is evolving. A key point in the theoretical formulation is to have a theory which is both internally consistent and ensures that individuals have the greatest opportunity of obtaining their preferences. An ideal theory does not force individuals to fit a certain model but would be descriptive of a rational person’s actual decisions (and hence normative).
7. The Markov Model of Advanced HIV Disease

We used a Markov multi-state cycle to model the natural history of late stage HIV infection. Our primary outcomes were survival, quality of life, and incurred costs.

Our baseline case is an HIV positive patient with a CD4 count of 100 cells / µL and no prior AIDS defining illness (ADI), but with symptomatic HIV infection. The timeline for our analysis is the expected lifetime of the patient, defined in this model as a probability of dying of greater than 99%. The model has a cycle length of three months. Our analysis assumes the perspective of a third party payer. Indirect costs and costs incurred outside health care are not included in this model. Costs and utilities are discounted at a rate of 5% per year [58,79].

7.1 Strategies in the Model

We compared twelve strategies to prevent MAC (Figure 10). We modeled three strategies in which only a single drug was used - rifabutin, azithromycin, or clarithromycin. We modeled four strategies in which sequential therapy was used (rifabutin then azithromycin, rifabutin then clarithromycin, azithromycin then rifabutin, and clarithromycin then rifabutin). We modeled two other strategies by starting with combination therapy (rifabutin and azithromycin or rifabutin and clarithromycin) and then continuing sequential therapy with first rifabutin and then the macrolide (azithromycin or clarithromycin). We modeled two more strategies with the same initial combinations, but with the order of drugs for sequential therapy reversed (macrolide first, then rifabutin). Lastly, we modeled a strategy of no prophylaxis. In our baseline analysis, we did not include a strategy of surveillance, as this entails incorporating
many assumptions for which few data are available, but we include this model in a sensitivity analysis.

7.2 Disease States in the Markov Model

We characterized patients with advanced HIV disease as having one of seven states depending on their clinical history: HIV without an ADI, a minor ADI, one major ADI, multiple major ADIs, MAC without another ADI, MAC with another ADI, or death.

For each stage in which MAC was not present, the patient could be taking his initially assigned prophylactic regimen (monotherapy or combination therapy) or a sequential regimen. A patient who was intolerant of initial monotherapy prophylaxis either discontinued all prophylaxis or took sequential monotherapy. A patient who was intolerant of combination prophylaxis took sequential monotherapy. Patients change regimens due to the occurrence of a side effect severe enough to discontinue therapy. If such a side effect occurs, patients spend one cycle in the tree with an increased cost and an adjusted utility due to the side effect.

Therefore, each of the four states in which patients were alive and MAC was not present had two characteristics: first, the use of a prophylactic agent (initial prophylactic, first sequential, second sequential, or no prophylactic); and second, the existence of a side effect (present or absent, except for patient receiving no prophylactics, for whom it was always absent). This defines 28 states. States in which MAC was present had three characteristics: first, the existence of another ADI (present or absent); second, antibiotic resistant pattern (sensitive or resistant); and
third, occurring immediately after a side effect of prophylaxis (present or absent). This defines an additional 8 states. The final state is death, which is an absorbing state. Thus, this model has a total of 37 possible states for each decision strategy.

A simplified version of the model is shown in Figure 10 to Figure 12 as a decision tree and in Figure 13 as a Markov state cycle diagram. In Figure 13, each circle represents a state and each arrow represents a transition. Note that some transitions are not allowed. For example, HIV is modeled here as an irreversible disease; that is, once a given disease stage is reached, a patient cannot go back to a prior state of health. Also, a patient with HIV but no previous ADIs will not, in this model, develop multiple major ADIs in one cycle of the tree. Similarly, a patient with a minor ADI will develop only one major ADI in one cycle. A patient in the model progress to a subsequent stage of HIV infection at the first occurrence of an ADI.

In defining the states of HIV infection, we distinguished between minor and major ADIs because different AIDS related illnesses have different associated costs, quality of life and prognoses. We based these distinctions on published severity of illness scales and epidemiologic data [80-82]. Although early severity of illness scales classified PCP as an illness with intermediate severity, more recent literature characterizes it as a minor AIDS illness, in keeping with the recognition of improved outcomes following this infection [80,82-84]. We classified lymphoma as major ADI, although its prognosis may be much worse than other diseases [81]. The incidence of lymphoma is generally less than 5 % and is therefore unlikely to influence the strategies under study [1]. Recent evidence suggests that patients with multiple minor ADI have similar prognoses to
patients with only one minor ADI; therefore, we did not model multiple minor ADIs as a separate state [82].

Patients with multiple major ADIs have an increase in mortality compared to patients with only one major ADI [82]. We therefore included as a separate state the condition of having two or more major ADIs, not including MAC. We separated MAC from other major ADIs for this model to accurately model the effectiveness of prophylaxis. We modeled MAC in a similar way to our modeling of major ADIs, as either a single illness, or coexisting with another major ADI.

7.3 The Disutility of Prophylaxis

We have included the disutility of prophylactic medication in our analysis. We define the utility of prophylaxis as the inconvenience of taking medication and the minor associated side effects that do not warrant discontinuation; the disutility is defined as the complement of the utility. This disutility is not often included in cost-effectiveness models, although some previous analyses which have included it found that it may have an important impact on study results [40,85,86]. An argument against its inclusion is that the decision analysis model assumes that the patient has already consented to take the medication in question, indicating that the patient's preference towards taking medication may be low. We therefore performed the cost-utility analysis both with and without accounting for the disutility of prophylaxis.
7.4 Modeling the Effect of Disease Progression

In our baseline analysis, we examined the effect of initiating MAC prophylaxis when the CD4 was 100 cells / μL for a patient without any ADIs at baseline. We repeated our analysis to examine the decision for patients who already had clinical disease progression at baseline or had a lower CD4 count at initiation. Specifically, we examined whether cost-effectiveness changed if a patient had more advanced disease at baseline (a minor ADI, one major ADI, or multiple major ADIs) or if a patient had a lower CD4 cell count at baseline (75, 50, or 25 cells / μL).

We also examined the incremental cost-effectiveness of a strategy of waiting to initiate prophylaxis at a later stage of disease. First, we examined a strategy of waiting until the patient's CD4 count had dropped to 75, 50 or 25 cells / μL, and determined the incremental cost-effectiveness at each step. Second, we examined a strategy of waiting until the patient had clinical disease progression to a minor ADI, a major ADI, or multiple ADIs, and determined the incremental cost-effectiveness at each step. Lastly, we examined a strategy of waiting until the patient reached a combined laboratory and clinical outcome (for example, initiating therapy when a patient has the first of either a CD4 count of 50 cells / μL or a minor ADI).

7.5 Other Assumptions in the Model

We made several other assumptions in the model, as outlined below. We predict that the following assumptions result in a bias in our model against prophylaxis being cost-effective:
• we assumed that the sensitivity and specificity of MAC blood cultures were 100%, although we examined this assumption when we analyzed a strategy of surveillance.

• we assumed that all patients in the model also take antiretroviral and PCP prophylaxis medications. The rates for disease progression and rate of decline in CD4 are taken from natural history data, some of which comes from the era before combination antiretrovirals were common and when protease inhibitors were not yet available. We have chosen more recent data for our estimates, and included estimates from older data in our ranges for sensitivity analysis.

• we assumed that all patients with MAC are treated for their infections. We used a regimen of clarithromycin, ethambutol, and rifabutin. This regimen is proven to decrease both morbidity and mortality [10]. For organisms which are resistant to either a macrolide or to rifabutin, we modeled a regimen of the same three drugs with the addition of ciprofloxacin. We modeled only these two treatment regimens for simplicity, although patients with MAC may have difficulty tolerating medications, may not respond to their initial regimen, or may discontinue treatment for other reasons [12]. Thus in our model, patients with MAC may have organisms that are resistant to a certain antibiotic but still be taking that antibiotic.

We predict that the following assumptions result in a bias in our model in favour of prophylaxis being cost-effective:

• we assumed universal compliance with the prescribed medications.
we assumed that all patients who develop disseminated MAC are symptomatic. We examined this assumption in the surveillance model.

For the following assumption, we predict that the overall results will change minimally, but that the assumption biases the model in favour of starting prophylaxis at an earlier stage of HIV infection:

- we assumed that the effectiveness of prophylaxis is the same at different stages of disease. Therefore, the relative risk reduction of developing MAC while taking prophylactic medication was not dependent upon either the CD4 count or the clinical stage, although recent data suggest that such a trend may, in fact, exist [15,87].

7.6 Assumptions About Resistance

We made several important assumptions about the development of resistance to medications used for prophylaxis. First, we assumed universal cross-resistance to macrolides; that is, organisms resistant to azithromycin are resistant to clarithromycin, and vice-versa [88]. Second, we assumed that resistance only develops during the time that a patient takes a drug, so that a patient who discontinues a medication does not have an ensuing increased risk of harbouring a resistant organism. Third, we assumed that environmental isolates are fully sensitive to all antibiotics. Fourth, we assumed that the length of time on a prophylactic medication did not increase the rate at which MAC develops antibiotic resistance. Fifth, we assumed that microbiological resistance to a specific antibiotic translates into clinical failure of MAC treatment for that medication [21]. Fifth, we assumed that this treatment failure could be overcome by
increasing the number of medications in the regimen. In other words, we modeled the state of being infected with a resistant organism as having a higher cost, but not a lower utility or a worse prognosis. We tested some of these assumptions in a sensitivity analysis.

7.7 Other Consequences of Prophylaxis

Prophylaxis may have two other important consequences. First, these antibiotics may be useful in preventing other infections, such as sinusitis, pneumonia, or toxoplasmosis. This may significantly increase the benefits of prophylaxis and result in enhanced economic attractiveness. However, the antibiotics may also increase the likelihood of bacterial resistance, making infections more difficult to treat [8]. One important example of this is the potential development of Mycobacterium tuberculosis which is resistant to rifabutin and rifampin [23]. Second, these medications may have significant interactions with other drugs commonly used by patients with HIV. We modeled the following: a) fluconazole increasing the toxicity of rifabutin, b) the efficacy of rifabutin, or c) both, and d) rifabutin decreases the efficacy of protease inhibitors.

7.8 Modeling Surveillance

We included an analysis of a strategy of surveillance for MAC instead of prophylaxis. MAC is thought to start as a localized infection in most patients, before it spreads throughout the body [26]. Thus, there may be a time of persistent, low-level but detectable bacteremia prior to dissemination and the development of symptoms. If it
were possible to detect and treat MAC while patients were asymptomatic, morbidity, mortality and costs may be decreased. This is the goal of regular surveillance cultures.

To compare prophylaxis with surveillance, we modified our model of prophylaxis (Figure 14). In the prophylaxis strategy of the new model, a certain proportion of patients in each stage have symptoms compatible with MAC, although they may be due to other diseases. We modeled the frequency of these symptom as being proportional to the probability of having MAC at any given CD4 count. We assumed that all symptomatic patients are tested for MAC. Asymptomatic patients, including those with asymptomatic MAC, are not tested. We assumed that once a patient with MAC was symptomatic, he remained symptomatic (until diagnosed and treated), although patients with other reasons for MAC symptoms could have resolution of their symptoms. Patients with true positive and true negative results from MAC testing were either treated for MAC or received MAC prophylaxis, as appropriate.

Patients with false positive results were treated as if they had MAC infection. We assigned these states the cost of the underlying HIV state plus the cost of treating MAC, and the utility of the underlying state factored by the utility of MAC treatment. We assumed that their probability of future events was dependent upon their underlying state, but that the probability of MAC was modified by their medications.

Patients with false negative results have untreated MAC infection, but continue to receive prophylaxis. We assumed that they were not adequately treated, and that resistance could still develop. With time, they may be recognized as having MAC. We assigned these states the cost of having untreated MAC plus the cost of prophylaxis.
The utility is similarly the utility of having untreated MAC factored by the disutility of prophylaxis.

Each state in which a patient has false negative MAC result had three characteristics: first, the use of a prophylactic agent (initial prophylactic, first sequential, second sequential, or no prophylactic); second, the existence of a side effect (present or absent, except for patient receiving no prophylactics, for whom it was always absent); and third, the coexistence of another ADI (present or absent). This defines 14 states. Each state in which a patient has a false positive MAC result had three characteristics: first, the underlying HIV state (no ADIs, minor ADI, one major ADI, or multiple major ADIs); second, antibiotic resistant pattern (sensitive or resistant); and third, occurring immediately after a side effect of prophylaxis (present or absent). This defines an additional 16 states. With the 37 states in the initial model, there are a total of 67 states in the prophylaxis arm of the surveillance model. In the surveillance arm, a similar approach is used, although side effects do not occur because prophylaxis is not used, and asymptomatic MAC is modeled as a separate state (patients with asymptomatic MAC are modeled in the prophylaxis arm as being included in the "MAC-free" group). Each state in which a patient without symptoms receives surveillance cultures had two characteristics: first, the underlying HIV state (no ADI, minor ADI, one major ADI, or multiple major ADIs); and second, the coexistence of false-negative asymptomatic MAC infection (present or absent). This defines 8 states. Surveillance cultures were also performed for false-negative symptomatic MAC infection, which was characterized by the coexistence of another ADI (present or absent). This defines an additional 2 states.
Each state in which a patient has a false positive MAC result was characterized by the underlying HIV state (4 states). True positive asymptomatic MAC was also characterized by the underlying HIV state (4 states). True positive symptomatic MAC had two characteristics: first, antibiotic resistant pattern (sensitive or resistant); and second, the coexistence of another ADI. This defines an additional 4 states. The final state is death, for a total of 23 states in the surveillance arm of the surveillance model.

8. Probability Estimates

We estimated transition probabilities from the medical literature. Table 3 lists the probability variables, the estimate used in the baseline analysis, the range used in the sensitivity analyses and the sources for the estimates. Probabilities for the three month cycles of the model were calculated from annual probabilities with the formula

\[ p_{3\text{ months}} = 1 - e^{-\left(\frac{P_{\text{annual}}}{4}\right)} \]  

[Equation 2].

We estimated the annual probability of dying for a patient with a CD4 of 100 cells / μL and no prior ADI to be 6% [89-94]. Where the data was not directly available for this defined subgroup, we calculated this value using assumptions as in Table 3 for the relative risk of dying for patients with prior ADIs, assuming that from 9 to 33 % of patients with a CD4 count of 100 cells / μL had a prior ADI [95]. Estimates from studies conducted before the widespread use of antiretrovirals, estimated the risk of dying to be considerably higher than our baseline estimate, so we used a wide range for this variable in the sensitivity analysis.
We modeled an increase in the risk of death by both CD4 stratum and clinical stage. We also addressed whether the risk of death with MAC is higher than with other major ADIs. Although early studies suggested this possibility [9,96,97], more recent data suggest that with treatment, survival is not substantially different from patients with other major ADIs [6,98,99]. We therefore assumed no relative increase in mortality and used a wide range for our sensitivity analysis, including the possibility that treated MAC has lower mortality than other major ADIs. We assumed, in accordance with observational data, that MAC and another major ADI has a similar risk of dying as having any two other major ADIs [6].

We estimated the probability of developing an ADI other than MAC to be 25% per year [90,124]. We estimated that 55% of new ADIs would be minor, and 45% would be major [1,80]. We assumed that this proportion of minor to major ADIs was constant throughout the CD4 range in our study. We modeled an increasing risk of developing an ADI as the CD4 count fell [90]. MAC increases the risk of developing cytomegalovirus (CMV) disease by fourfold and so we modeled an increased risk of developing a major ADI if MAC was present, with a wide range in the sensitivity analysis [6].

CD4 cells decline at variable rates in patients with HIV and antiretrovirals may have a considerable effect on this rate. [92,100-102]. We therefore tested a broad range for this variable in the sensitivity analysis.

The annual probability of developing MAC without another ADI was estimated to be 6% [7-9,90,124]. We modeled a steep increase in the incidence of MAC as the CD4 count
fell, as suggested by several clinical studies [1,6,7, 9,124]. We assumed that minor ADIs does not change the risk of developing MAC at any CD4 count, but that the occurrence of a first major ADI increased this probability [6,9].

We estimated the efficacy of prophylaxis from three published randomized controlled trials and one abstract [14-17]. We also used these studies to estimate the probability of severe toxicity. We used a wide range for these estimates, recognizing that patients may stop medications more frequently in real life than in clinical trial settings. We also used these sources to estimate the frequency with which MAC resistant organisms develop while taking prophylaxis. In the sensitivity analysis, we tested a range from no resistance to full resistance.

We repeated our analysis with the variables for the probability of developing AIDS, MAC and dying modeled as a function of CD4 count according to published formulae in the literature [7,90].

8.1 Probability Variables Used in the Sensitivity Analyses

We defined several variables that were not relevant to the baseline analysis but are important for some of the sensitivity analyses. These are listed in Table 3. In general, the estimates for these variables are much less reliable than for those in our baseline analysis and so we tested a broad range of values in the sensitivity analysis.

Azithromycin has been shown to decrease the incidence of bacterial sinusitis and pneumonia, and PCP [37,35]. Clarithromycin may have similar antibacterial effects, although it is not reported to be effective against PCP [17]. Rifabutin may be active
against some bacteria, other mycobacteria, and toxoplasmosis [103]. We performed a sensitivity analysis to determine how these other effects of prophylaxis may influence cost-effectiveness.

To model surveillance adequately requires estimates of the sensitivity and specificity of MAC cultures. Reported sensitivities are from 73 to 97% [127]. Nightingale reported surveillance cultures were positive in approximately 1 in 100 patients per month when the CD4 count falls to 100 cells / µL, which would indicate a sensitivity well over 90% [7].

We used data from a clinical model to predict MAC infection to estimate what proportion of all patients have MAC symptoms [128]. In our model, we related this to the probability of developing MAC, according to clinical stage and CD4 count. The estimate reported here is for a patient with no prior ADIs. We used the same model to predict what proportion of all patients with MAC (symptomatic and asymptomatic) were asymptomatic. We assumed that the estimates of MAC prevalence used earlier estimated symptomatic disease only.

9. Cost Estimates

Reported costs of care for patients with HIV infection vary widely in the literature and are controversial [104-106,110]. Canadian costing studies are few, and even the most comprehensive has classified patients by CD4 count, but not by disease stage [107]. As well, patterns of resource use by patients with HIV may be changing rapidly, in Canada as well as in the United States [104,108,109]. We used charges as an
estimate of costs, as available in the literature. Costs are expressed in 1995 Canadian dollars assuming a 2% annual inflation rate and an exchange rate of $1 Can = $0.75 U.S. We used patterns of resource use reported in the literature and Canadian costing data where available to try and estimate the cost of each state in our model.

We also examined several different published estimates of cost of care. One of these studies used Australian data, one used costs from a U.S. public health care system, one from a mixture of U.S. sources, and one used projected costs based on practice guidelines and expert opinion, without examining actual resource use [104,105,110,111]. The estimates are summarized in Table 4. We assumed that patients with a minor ADI had treatment costs 33% greater than patients without an ADI, and that patients with multiple major ADIs had treatment costs similar to patients with only one major ADI [110]. We further assumed that patients with MAC had similar treatment costs to patients with one major ADI, and that patients with MAC and another ADI had treatment costs similar to patients with multiple major ADIs.

In accounting for costs from resource use, we estimated hospitalization costs, outpatient treatment costs, and medication costs. Data were derived from the literature and from charges at our institution (Table 5). We estimated that the treatment of MAC incurred the same inpatient and outpatient costs as a major ADI, but had different medication costs. Estimates for the variables were usually reported for patients with AIDS, without distinguishing between minor and major ADIs. We used these estimates for the cost of one major ADI and extrapolated from these values to estimate the costs of care for patients with minor ADIs and multiple major ADIs.
The cost of hospital care for AIDS patients rises significantly prior to death, but we assumed that this cost was incurred equally by patients in all treatment strategies and that the effect on marginal costs was negligible [112]. We similarly excluded palliative care, long term care, and home care costs [112].

We calculated total hospitalization costs by multiplying the per diem cost of hospitalization by the frequency and duration of hospitalization (Table 5). The cost per day of hospitalization was assumed to be equivalent at all stages of disease [105]. We calculated the per diem hospitalization cost by multiplying the cost per day of hospitalization in Canada, by the resource intensity weight assigned to patients with HIV and added an extra $60 per day for physician visits, including attending physicians and consultants [113-115]. The total estimated cost per day was $1,540 which agrees with published estimates [105,110,116].

We estimated outpatient treatment costs separately from medication costs, but including primary care physician visits, outpatient consultations, emergency department visits, and outpatient laboratory tests. We related these estimates to inpatient treatment costs. For example, we estimated that the outpatient treatment costs of a patient without an ADI were 55% of inpatient costs [104,105,110,130]. We used the same estimated for patients with a minor ADI. For patients with major ADIs (single or multiple), we estimated that outpatient treatment costs were 30% of inpatient treatment costs. As these estimates vary widely in the literature, we have set a broad range for the sensitivity analysis.
We calculated medication costs for drugs other than those used in the prophylaxis or treatment of MAC by multiplying the number of medications used in each state by the average cost per medication. We used costs to pharmacists in Canada to estimate the unit cost of MAC medications and excluded dispensing fees and mark-ups [19]. We estimated the cost of treating MAC as the combination of the cost of rifabutin, clarithromycin and ethambutol, and added the cost of ciprofloxacin for treating drug resistant MAC.

We estimated that the cost of a side effect was the cost of one additional outpatient visit, estimated to be $375 [105,110]. This includes physician and hospital visits, consultations, and incurred laboratory tests. In our baseline analysis, we did not assign a cost to testing for MAC cultures, but estimated this to be $60 in the surveillance model.

10. Utility Estimates

10.1 Methods

We directly assessed the utilities of six health states: living with symptomatic HIV infection, living with a minor AIDS defining illness, living with a major AIDS defining illness, living with MAC, inconvenience and mild side effects of prophylaxis, and experiencing severe side effects necessitating discontinuation of a medication. We assumed that the utilities assigned to the latter two stages were similar for all prophylactic agents analyzed. Multi-attribute utilities were assessed multiplicatively [59]. For example, the utility of a state in which a patient has both a minor ADI and a
side effect of medications was determined by multiplying the utilities of each of these states. For some sensitivity analysis, further utility estimates were required. We assigned utilities to the states of having untreated MAC (assigned a value of 85% of the utility of treated MAC) and to undergoing a MAC blood culture test (0.995). We tested a broad range for these assumptions in our sensitivity analysis.

We conducted semi-structured interviews lasting approximately 45 to 60 minutes at the Wellesley Hospital to directly assess the six health state utilities. All subjects provided informed consent. Subjects were recruited from a convenience sample of HIV positive inpatients and outpatients of the Wellesley Hospital. All HIV positive patients greater than 18 years old who were fluent in English and who provided informed consent were eligible. Patients were excluded if they were mentally or emotionally incapable of completing the interview. To calculate the sample size, we used a preliminary estimate of the utility of living with MAC of 0.65 (95% confidence interval 0.21 to 1.00), and calculated that approximately 50 patients would be required to decrease this uncertainty to an acceptable range (±0.10).

Subjects were asked to imagine that they were living in a defined health state. Each health state was described by a scenario presented to the subjects in both written and oral form (Appendix 3). Subjects were encouraged to discuss the scenarios and their own experiences. Utilities were assessed by the category rating scale, the standard gamble technique, the time trade-off technique and with the self-administered Health Utilities Index. The category rating scale was used as a test of validity to confirm that
the preference order is consistent across scales - values from this scale were therefore
not included in the utility analysis.

For the standard gamble (SG) method, subjects were asked to choose between living in
the described state or to try a hypothetical treatment which restores best possible
health (but does not extend life) but also carries a probability of immediate, painless
death. The probability was varied to determine the subject’s indifference probability
between the alternatives or, when subjects had difficulty expressing indifference, the
maximum acceptable probability of death was determined. This probability was used to
calculate the utility of the disease state. A probability wheel, a simple device consisting
of an adjustable disk with two sectors of adjustable size and different colours, was used
to help subjects to visualize the gamble [49]. The probability of each alternative is
represented by the relative amount of each colour displayed.

For the time trade off (TTO) method, subjects were asked to choose between living in
the described state of health for two years (followed by death) or living a shorter
amount of time in best possible health. The amount of time subjects were willing to give
up was varied until the subject was indifferent between the alternatives or, when
subjects had difficulty expressing indifference, the maximum acceptable time to trade
off was determined. This amount of time was used to calculate the utility of the disease
state. No visual aids were used for the TTO assessments.

To avoid anchoring effects, in both the SG and the TTO assessments the variable used
to assess preference (probability of dying or amount of time traded off) was varied in a
"ping-pong" fashion, in which initial values are presented at very high and low values,
and this range then narrowed to find the subject’s indifferent value [53]. To avoid framing effects, gambles and trade-offs were presented as both gains and losses [55]. For example, a probability of dying of 20% in the SG was presented as “a 20% chance of immediate, painless death or an 80% chance of best possible health.”

Quality of life was assessed by the Medical Outcomes Study - HIV (MOS-HIV) Quality of Life Scale. This self-administered questionnaire consists of ten subscales: pain, physical functioning, role functioning, social functioning, mental health, energy / fatigue, health distress, cognitive functioning, quality of life, and health transition. As well, this scale asks about how much patients were bothered by eight symptoms (bodily pain, fever or chills, night sweats, diarrhea, fatigue or malaise, nausea or appetite loss, skin complaints, and abdominal pain). For each patient, we recorded the number of symptoms which bothered him or her “quite a lot” or “a great deal”.

Subjects also self-administered the Multi-Attribute Health Utilities Index (HUI). This scale consists of seven subscales: sensation, mobility, emotion, cognition, self-care, pain and fertility. Scores from the questionnaire are weighted according to an empirically derived function to derive a single utility score [117].

Subjects who had difficulty reading were administered these questionnaires by the interviewer. Both of these questionnaires asked subjects to rank their own state of health in the past four weeks.
11. Analysis

All cost-effectiveness results are reported as incremental costs per life year gained or incremental costs per quality adjusted life years (QALYs) gained, where appropriate. Sensitivity analysis were performed for all variables included in the decision analysis model. A threshold of $50,000 per QALY was used to determine threshold values.

Differences between variables with continuous distributions were evaluated with a t-test, after first testing for significance of equality of variances. Tests of correlation were performed using analysis of variance for categorical variables and linear regression for continuous variables. We used linear regression techniques to model which variables predicted utility scores. Predictor variables found to be significant at an \( \alpha \) of 0.10 were entered into a multiple linear regression model, where the level of significance was set at \( \alpha = 0.05 \).

12. Results

A total of 50 patients were recruited for utility assessments. One patient was unable to complete the utility analysis due to incomprehension of the tasks and was excluded. Several patients exhibited extremes of risk seeking or risk aversion, or unwillingness to trade off life, as has been observed in other studies of quality of life assessment in patients with HIV.[118] These patients are nevertheless included in all analyses.
Our subjects were predominantly male (96%), white (94%), and had male-to-male sexual transmission as their risk factor for acquiring HIV (94%). The mean CD4 count of our subjects was 150 cells / μL, with a median of 70 cells / μL.

Subject were distributed across clinical stages, with 4% having asymptomatic HIV infection, 38% having symptomatic HIV infection but not having had an AIDS defining illness, 19% having had a minor AIDS defining illness, and 38% having had a major AIDS defining illness. Five patients (10%) were diagnosed as having MAC and were receiving treatment at the time of study. An additional patient had received empirical treatment for suspected MAC but had discontinued his medications pending blood culture results. Of the 5 patients receiving MAC treatment, 2 also had other major ADIs. In total, of the 18 patients with major ADIs (including MAC), 5 had experienced multiple major ADIs.

Table 6 lists characteristics of the population by clinical stage. As anticipated, subjects with clinical disease progression had lower CD4 counts. Most of our population had taken antiretrovirals, although 21% had discontinued them at the time of the interview. One patient eligible for PCP prophylaxis was not taking any. Most subjects, including those with low CD4 counts, were not using MAC prophylaxis. In general, subjects with more advanced disease were taking a larger number of medications.

12.1 Utility Analysis

Utility estimates as measured by standard gamble (SG), time trade off (TTO), and category rating scale (CRS) methods are listed in Table 7. In general, estimates were
similar between the SG and TTO methods, and lower with CRS. There was generally good agreement between SG and TTO scores (range of $r^2 = 0.24$ to 0.71 across disease states, $r^2 = 0.98$ for comparison of means), but lesser agreement between either SG and CRS scores or TTO and CRS scores, although mean values remained highly correlated (range of $r^2 = 0.02$ to 0.26 for individual scores, $r^2 = 0.99$ and 0.99 for comparisons of means for SG and TTO respectively). Estimates from the SG method were used in cost-utility assessments, except where indicated. The order of preference was similar for all three scales for mean utilities, although some participants gave inconsistent responses.

We assessed utilities with the health utilities index (HUI) for the respondent’s current state of health. Results are summarized in Table 8. HUI scores were similar across disease states. Specifically, patients without an ADI had a mean HUI of 0.81, patients with a minor ADI had an HUI of 0.77, and patients with a major ADI had an HUI of 0.75 ($p=0.35$ for comparisons of means). Also included in Table 8 are scores for disease states by the SG, TTO and CRS methods, as determined by subjects in those states. For all of these methods, the differences between states were statistically significant. It is important to note that the HUI scores asked subjects to rate their own health, while the SG and TTO methods asked subjects to rate hypothetical descriptors of “standardized” patients.

We further analyzed these results by HIV stage with respect to the Medical Outcomes Study Quality of Life scale. Compared to patients with an ADI (major or minor), patients without an ADI had higher mean scores on the following subscales: overall health (54
vs. 38, p=0.043), pain (74 vs. 59, p=0.049), role functioning (47 vs. 19, p=0.031) and physical functioning (58 vs. 30, p=0.001). When we compared patients with minor ADIs to patients with major ADIs, only the role functioning subscale was different (39 vs. 8, p=0.014).

We analyzed HUI scores to evaluate whether any demographic variables or MOS-HIV scores helped explain the observed variation better than clinical stage did. The following demographic variables were analyzed: sex, age, race, last recorded CD4 count, use of antiretrovirals (ever or never), use of PCP prophylaxis (ever or never), use of MAC prophylaxis (ever or never), and number of prescribed medications. None of the demographic variables were correlated at a level of p = 0.10 or less, but the following subscales of the MOS-HIV were: overall health, physical functioning, role functioning, pain, social functioning, mental health, energy/fatigue, cognitive functioning, quality of life, and number of severe symptoms. In the multivariate analysis, only pain was predictive of HUI score. Because pain is a feature of both questionnaires, we repeated the multivariate analysis examining all variables except pain and found that no variables reached standard levels of statistical significance.

12.2 Baseline Analysis

We assessed the total cost and benefit each of the twelve MAC prophylaxis strategies in the baseline analysis. Results are summarized in Table 9 and Figure 15. Without MAC prophylaxis, we estimated that a patient with a CD4 count of 100 cells / \( \mu L \) and no prior ADI would incur an average of $120,806 in direct medical costs before dying. MAC prophylaxis changed the cost of treating a patient with advanced HIV, but the
direction and amount of change depended upon the specific prophylactic strategy. At
one extreme, a strategy of using azithromycin for prophylaxis with no other medications
should intolerance develop, saved $2,270 compared to a strategy of no prophylaxis. At
the other extreme, a strategy of clarithromycin and rifabutin in combination, followed
sequentially by clarithromycin then rifabutin should intolerance develop, incurred
additional costs of $9,991.

Similar disparities are seen with changes in life expectancy. A strategy of azithromycin
and rifabutin in combination, followed sequentially by rifabutin then azithromycin for
intolerance, increased life expectancy by 2.7 months, from 35.5 months to 38.2 months.
A strategy of rifabutin with no sequential therapy increased life expectancy by 1.4
months. Not all of this time is spent in a high quality of life, however. The azithromycin
/ rifabutin combination strategy extended life by the equivalent of 1.7 months in best
possible health, while rifabutin without sequential therapy extended life by the
equivalent of 0.7 months in best possible health.

We calculated the incremental cost-effectiveness of each strategy relative to a strategy
of no prophylaxis. Results are summarized in Table 10. Azithromycin, either followed
or not followed by sequential rifabutin, was associated with a net gain in both life
expectancy and quality-adjusted life expectancy and a net savings in costs. Among the
other therapies, cost-effectiveness and cost-utility ratios ranged from a low of over
$24,000 / QALY for strategies starting with clarithromycin alone, to over $120,000 /
QALY for strategies using clarithromycin and rifabutin in combination.
We next performed an incremental cost-effectiveness analysis examining each strategy to the next less expensive and non-dominated strategy (Table 11). For example, we compared a strategy of azithromycin with rifabutin sequential therapy to one of azithromycin without sequential therapy. In a clinical situation, this is similar to asking, "Is it cost-effective for an average patient who is intolerant of azithromycin to change to rifabutin, or should they discontinue prophylaxis altogether?" The cost-effectiveness of this strategy was $52,552 / QALY. If no disutility was assigned to prophylaxis, the cost-utility of this strategy was $33,818 / QALY. Compared to this regimen, azithromycin and rifabutin in combination, followed by sequential therapy was associated with improved quality adjusted survival, but at an incremental cost-effectiveness of $781,302 / QALY. Assigning no disutility to prophylaxis decreased the cost-utility ratio slightly to $716,073 / QALY.

Using utilities derived from the time trade off model produced similar results. Including prophylaxis associated utilities, the cost-utility of azithromycin with rifabutin sequential therapy compared to azithromycin with no sequential therapy was $34,906 / QALY, while azithromycin and rifabutin combination compared to azithromycin with rifabutin sequential therapy had an incremental cost-utility of $472,045 / QALY.

12.3 Other Outcomes

We analyzed the decision model for outcomes other than survival. Results are summarized in Table 12 as an incremental benefit of each strategy compared to no prophylaxis. For example, a strategy of using rifabutin with no sequential therapy results in a net gain of 48 additional days without an ADI compared to no prophylaxis,
72 additional days without a major ADI, 109 additional days without MAC, and 1.4 fewer days in hospital. As with our previous analysis of survival, a strategy of azithromycin and rifabutin in combination has the greatest benefit in these health outcomes.

Cost-effectiveness can be evaluated for these phenomena as well. Azithromycin and rifabutin combination (with rifabutin and then azithromycin sequential therapy), compared to azithromycin with rifabutin sequential therapy, has a cost-effectiveness of $198,630 / life year gained. This is equivalent to $544 per day of life gained. Analyzing the model by other outcomes, this strategy has an incremental cost-effectiveness of $532 per life day free of any AIDS defining illness, $336 per life day free of any major ADI, $200 per life day free of MAC, and $19,469 per hospital day avoided.

12.4 Patients with More Advanced Disease

We next determined the cost-effectiveness of MAC prophylaxis in patients with more advanced disease. For example, what happens to cost-effectiveness ratios if a patient had a CD4 count of 50 cells / μL at baseline? We found that lowering the CD4 count for our baseline case had little effect on the results. Azithromycin remained cost-saving, and a strategy of azithromycin with rifabutin sequential therapy had an incremental cost-effectiveness ratio that was consistently between $40,000 and $50,000 / QALY.

We performed a similar analysis for patients with more advanced clinical disease at presentation. If our baseline case had a minor ADI at baseline, azithromycin was still cost-saving, but adding rifabutin as sequential therapy had an incremental cost-
effectiveness of $115,838/QALY. If the patient had a major ADI at baseline, azithromycin alone was no longer cost-saving, but instead had a cost-effectiveness ratio of $92,676/QALY. If a patient had multiple major ADIs at baseline, adding azithromycin resulted in both an increase in costs and a decrease in quality of life. Indeed, withholding prophylaxis dominated all medication strategies for this patient group.

12.5 Determining The Optimal Time to Initiate Therapy

An important question in deciding on MAC prophylaxis is the appropriate time to initiate therapy. Most recommendations have been made on the basis of CD4 counts, but the threshold for initiating treatment has been ill-defined [29,30]. We examined the incremental cost-effectiveness of initiating prophylaxis by CD4 count, by clinical disease stage, or by a combination of outcomes.

We first considered whether it is most cost effective to initiate prophylaxis at a given CD4 count or to wait until a lower threshold has been reached. Table 13 summarizes these results. We consider first a strategy of using rifabutin for prophylaxis, with azithromycin sequential therapy for intolerance. Compared to no prophylaxis, a strategy of waiting until the CD4 count reached 25 cells/μL to initiate prophylaxis had a cost-effectiveness of $25,882/QALY. A strategy of initiating prophylaxis when the CD4 count reached 50 cells/μL was next compared to the strategy of initiating prophylaxis when the CD4 count reached 25 cells/μL: the incremental cost-effectiveness of this strategy was $71,960/QALY. Similarly, the incremental cost-utility ratio of initiating prophylaxis when the CD4 count reached 75 cells/μL, compared to
initiating prophylaxis when the CD4 count reached 50 cells / µL was $517,936 / QALY. Initiating prophylaxis when the CD4 count is 100 was dominated by a strategy of waiting until the CD4 count had reached 75. Similar results were seen when the strategies considered were clarithromycin with rifabutin sequential therapy or azithromycin and rifabutin in combination. Similar effects, although with not as marked differences, were observed when survival not adjusted for quality of life was analyzed as the outcome.

The strategy of azithromycin with rifabutin sequential therapy was cost-saving at a CD4 count of 25 cells / µL. Further, at the next two CD4 strata (50 and 75 cells / µL), azithromycin both increased quality adjusted survival and decreased costs. However, initiating prophylaxis when the CD4 count was 100 cells / µL, compared to waiting until the CD4 count reached 75 cells / µL increased costs and decreased quality adjusted survival; therefore, the optimal time to initiate therapy with this strategy was when the CD4 count reached 75 cells / µL.

We performed a similar analysis for a strategy of azithromycin without rifabutin sequential therapy. Prophylaxis both decreased costs and improved quality adjusted survival at each of the lower three CD4 strata (25, 50 and 75 cells / µL). Comparing a strategy of initiating prophylaxis at a CD4 count of 100 cells / µL to one of waiting until the CD4 count reached 75 cells / µL, showed that this strategy was again associated with a savings in cost, but a further decrease in quality adjusted survival. The cost per quality adjusted life year foregone was $10,201 - in other words, this is the amount of money saved in return for giving up one quality adjusted life year. Note that when
money is saved at the expense of a decrease in quality adjusted survival, low cost-
effectiveness ratios are *undesirable*, in contrast to the more common situation, where
both cost and survival increase, and low cost-effectiveness ratios indicate increased
efficiency. However, the incremental costs and benefits are both very small and this
result is not robust.

We next examined whether a strategy of initiating prophylaxis (azithromycin with
sequential rifabutin) based on clinical stage was more cost effective than one based on
CD4 thresholds. For example, waiting until a patient had developed multiple major
ADIs, compared to no prophylaxis, decreased costs and decreased survival, for a cost-
effectiveness of $5,212 / QALY foregone. Waiting until a patient developed their first
major ADI increased both costs and quality adjusted survival, with a cost-effectiveness
ratio of $68,982, compared to no prophylaxis. The greatest savings in cost and
greatest increase in quality adjusted survival was seen when prophylaxis was initiated
before any ADIs had developed.

We next examined whether a strategy incorporating both CD4 counts and clinical stage
was more cost-effective for this same prophylaxis regimen (azithromycin with sequential
rifabutin) - that is, a strategy of initiating prophylaxis when either the CD4 count reached
a given threshold, or earlier if the patient developed an ADI. When only CD4 count was
considered, the optimum time to initiate prophylaxis was when the CD4 count reached
75 cells / μL, as discussed above. When clinical stage was considered, a strategy of
starting earlier in patients with multiple major ADI was associated with exceedingly
small savings in cost ($10) and gains in quality adjusted survival (0.0001 QALYs). In
other words, the most cost-effective regimen was to initiate prophylaxis when the CD4 count was 75 cells / μL, or earlier in patients who have a major ADI before this threshold, although the gains were small.

13. Sensitivity Analysis

We conducted a sensitivity analysis on our model to test the robustness of our results. All variables were analyzed with one-way sensitivity analysis. As well, we repeated the model using different sources for costing and probability data. Finally, we repeated the analysis making different assumptions about the effects of medication.

For the sensitivity analysis, we considered a strategy of azithromycin without sequential therapy, compared to no prophylaxis. In our baseline model, this strategy both decreased costs and increased quality adjusted survival. We report variables which increased the cost-utility of this strategy to more than $50,000 / QALY.

Sensitivity analysis revealed that our finding were robust. Variables to which the model were sensitive are listed in Table 14. The model was particularly sensitive to the relative risk of dying for patients with MAC, compared to other major AIDS defining illnesses. We assumed that this risk was not increased in our baseline analysis. If this relative risk is actually 70% or higher than for patients without MAC, the incremental cost-utility ratio of this strategy exceeds $50,000 / QALY.

Figure 16 represents the sensitivity of our model to the relative risk of dying with MAC, compared to other major AIDS defining illnesses. As the risk increases, the incremental cost-utility of the strategy increases. The rate of increase, however, is very dependent
upon the annual incidence of MAC. If MAC is relatively uncommon, even a small
increase in the relative risk of dying with MAC is associated with a steep increase in the
cost-effectiveness ratio. If the relative risk of dying with MAC is less than 1 (for
example, if very effective treatment were available), then prophylaxis is always cost-
effective and, except at very low incidences, cost-saving.

Another variable to which the model was sensitive is the disutility of prophylaxis - the
patient’s attitude towards taking the medication and the minor side effects associated
with it. We analyzed the effect of this variable on two treatment strategies - first,
azithromycin without sequential therapy compared to no prophylaxis, and second,
azithromycin with sequential rifabutin compared to azithromycin without sequential
therapy. Results are presented in Figure 17. At high values of this disutility, indicating
an aversion to prophylaxis, a strategy of no prophylaxis is preferred. At low levels of
this disutility (little detrimental effect from prophylaxis), the sequential addition of
rifabutin was preferred. Our model was particularly sensitive to this variable - with small
changes in the disutility of prophylaxis, significant effects on cost-effectiveness were
seen.

The availability of better treatments for HIV might alter the natural history. To
investigate this, we decreased the probability of developing MAC, AIDS, and dying by
25%, and decreased the rate of CD4 decline by 50%. Azithromycin was still cost-
savings, and a strategy incorporating rifabutin as sequential therapy was associated
with an incremental cost-utility of $63,183 /QALY.
13.1 Analysis Using Cumulative Prospect Theory Weighted Utilities

We examined the effect on cost-effectiveness of transforming utilities using cumulative prospect theory (CPT). Using mean values of transformed utilities resulted in a similar pattern of decreased costs and increased quality adjusted survival for azithromycin without sequential therapy, as seen in our baseline analysis. The incremental cost-effectiveness of adding rifabutin sequential therapy increased, however to $639,690 / QALY. If the disutility of prophylaxis was set at 0, the incremental cost-effectiveness of rifabutin sequential therapy was $37,923.

However, CPT seeks to account for individual risk preferences. We therefore analyzed the decision model for each individual comparing azithromycin without sequential rifabutin to a strategy of no prophylaxis. The strategy of no prophylaxis was dominated more frequently when utilities were based on EUT rather than CPT (88% vs. 69%, p=0.002). At a threshold of $50,000 / QALY, however, there was no significant difference between the two methods (EUT 92% of patients, CPT 89% of patients, p>0.2).

We defined the net gain in QALYs as the difference between the total QALYs gained by taking azithromycin compared to not taking prophylaxis. The average net gain in QALYs greater with EUT derived utilities than with CPT (0.133 vs. 0.045, p<.001), and was greater for more subjects with CPT than with EUT (80% vs. 20%, p<.001). Figure 18 depicts these net gains graphically.
13.2 Other Data Sources and Assumptions

We reanalyzed our model three additional ways, changing several variables simultaneously. First, we changed the way we modeled the probability of dying, developing MAC, and developing other ADIs using empirically derived formulae. Azithromycin was still cost saving, and using sequential rifabutin was associated with an incremental cost-utility of $56,872 compared to not using sequential rifabutin.

Second, we re-examined one of the underlying assumptions of our model, that when prophylaxis was effective, a patient who would have otherwise developed MAC has no increased risk of developing other AIDS defining illnesses. If biological or other factors exist, independent of CD4 count, which predispose a given patient to developing disease progression (such as viral load) these patients may be at higher than average risk of developing major ADIs. We examined the effect on our model if all patients who would otherwise have developed MAC instead develop a major AIDS defining illness. In this scenario, azithromycin still extends life, but now at a cost-effectiveness ratio of $58,255 / life year, and at a net decrease in quality of life. Similarly, adding rifabutin as sequential therapy, compared to no sequential therapy, is associated with an incremental cost-effectiveness of $664,419 / life year, but a further decrease in quality of life.

Third, we used costing data from different sources, as listed in Table 4. Varying the source of cost data had a significant influence on our results. For the comparison of azithromycin with no sequential therapy and no prophylaxis, cost-utility ratios varied
from cost-savings to $5,920 / QALY. The incremental cost-effectiveness of adding rifabutin sequential therapy was between $69,322 and $81,035 / QALY.

13.3 Surveillance

A strategy of surveillance was compared to one of no prophylaxis and to a strategy of azithromycin with sequential rifabutin for intolerance. Surveillance was associated with an increase in both costs and life expectancy, for a cost-effectiveness ratio of $68,906 / life year compared to no prophylaxis. When we accounted for quality of life, however, the cost-utility ratio was $2,204,978 / QALY, largely because of the adverse effects of having untreated MAC (false negative results). Furthermore, surveillance was dominated by a strategy of azithromycin prophylaxis.

We incorporated several additional variables in the surveillance strategy, including the cost of a MAC culture, the utility of untreated MAC infection (relative to treated MAC infection), the utility of having a test, the sensitivity and specificity of a MAC culture, and the frequency of MAC-like symptoms in patients with advanced HIV disease. In a sensitivity analysis, none of these variables decreased the cost or increased the effectiveness of surveillance sufficiently to make surveillance preferable to prophylaxis with azithromycin.

Several variables did have an effect on the cost-effectiveness of surveillance relative to no prophylaxis. For example, as the sensitivity of the test increased, the cost-utility ratio became more favourable, because the number of false negative results decreased. However, an opposite effect was seen when the specificity of the test was
varied. With a lower test specificity, greater health benefits were seen. The explanation for this effect is that the increasing number of false positive tests results in patients without MAC receiving prophylaxis, albeit intended as treatment of active disease.

13.4 Development of MAC Resistance

In the sensitivity analysis, the incidence of resistance was not an important determinant of cost-effectiveness. We examined the effect of changing several of these assumptions simultaneously. Specifically, we increased the costs associated with MAC resistance (assuming that these patients need more medications, which are also more expensive), the mortality relative to having MAC which is sensitive (assuming that effective treatment, which decreases mortality, is difficult to establish), and that the utility of MAC resistance was worse than that of sensitive MAC (due to incomplete treatment).

These assumptions had little effect on the cost, effectiveness, or quality adjusted life years of azithromycin. This was true even if the development of resistance to azithromycin was tested in a broad sensitivity analysis (but the effectiveness kept constant). These assumptions had a considerable effect, however, on the cost-effectiveness of clarithromycin, decreasing the life expectancy and quality of life in clarithromycin containing prophylactic regimens. With the decrease in life expectancy came a decrease in costs, but the net effect was to make clarithromycin regimens the least attractive.
13.5 Other Effects of Prophylactic Agents

We examined how other effects of prophylactic agents might change the cost-effectiveness estimates. We performed two analyses, first assuming that these drugs decreased minor ADIs but not major ADIs, and second, assuming that both major and minor ADIs were reduced.

If all prophylactic agents are preventative against minor ADIs, the strategy of using azithromycin without rifabutin sequential therapy is slightly more attractive. Compared to the baseline estimate, this strategy saved an additional $281 and increased quality adjusted life expectancy by an additional 0.0223 QALYs. If all prophylactic agents are preventative against both major and minor ADIs, the strategy of using azithromycin without rifabutin sequential therapy, compared to our baseline estimate, saved an additional $2,588 and increased quality adjusted life expectancy by an additional 0.1172 QALYs. Other strategies show similar improvements from baseline estimates, but in both scenarios, the improvements are small, the rank ordering of strategies does not change, and the incremental cost-effectiveness of adding rifabutin sequential therapy changed only slightly.

It is also possible that prophylactic agents may make bacterial infections more difficult to treat by inducing bacterial resistance. We modeled this by assuming that the use of a prophylactic agent was associated with a 10% increased risk of developing either a major or a minor ADI. Azithromycin without rifabutin sequential therapy was still associated with a savings in cost and an increase in quality adjusted life expectancy,
but the magnitude of these effects were smaller. The incremental cost-effectiveness of adding rifabutin sequential therapy increased to $110.583 / QALY.

13.6 Drug Interactions

Patients with HIV may experience drug interactions frequently, especially if they are taking a large number of medications. We specifically examined two interactions of rifabutin with other drugs that could be important in determining the cost-effectiveness of rifabutin containing regimens.

We assessed the interaction of fluconazole with rifabutin. Fluconazole increases serum rifabutin levels and has been associated with both increased efficacy and increased toxicity [24]. Modeling these effects - alone or in combination - had little effect on the incremental cost-effectiveness estimates.

Rifabutin may also interact with some protease inhibitors [25]. These are potent new agents which may slow or even reverse the rate of CD4 decline in patients with HIV disease, and may be effective in advanced disease [119]. We modeled this interaction by assuming that a patient taking protease inhibitors would have a rate of CD4 decline less than our baseline model, but that the administration of rifabutin negated this effect. Using azithromycin without sequential rifabutin was still cost saving and was associated with an increase in survival. If protease inhibitors decrease the rate of CD4 decline by 40 % or more, prophylaxis strategies which start with rifabutin decreased life expectancy. Similarly, adding sequential rifabutin to azithromycin therapy resulted in a
lower life-expectancy, albeit with lower costs, for a cost-effectiveness of $56,497 / QALY foregone.

14. Discussion

We evaluated several strategies for the prophylaxis of MAC in patients with advanced HIV disease. We found that all strategies improve health outcomes, whether measured as survival, quality adjusted survival, MAC free survival, AIDS free survival, major AD1 free survival or days spent in hospital. In other words, prophylaxis helps to keep people in an earlier, healthier stage of disease. What is the most cost-effective form of prophylaxis? In all of our analyses, a strategy using azithromycin was the most attractive in terms of cost expenditures and gains in quality of life. Using even unfavourable cost estimates, azithromycin had a maximum cost-utility ratio of less than $10,000 / QALY, which compares favorably with other medical interventions. Azithromycin in combination with rifabutin resulted in an additional gain in quality adjusted life expectancy, but at a prohibitive incremental cost-utility ratio of over $700,000 / QALY.

What is the most cost-effective strategy in patients who initiated therapy with azithromycin but discontinued it due to toxicity? A strategy of adding rifabutin was associated with a reasonable cost-utility ratio of just over $50,000 / QALY, except in two important situations. First, if protease inhibitors are used, the interaction may be significant enough that rifabutin use results in worse health outcomes. Second, if the
disutility of prophylaxis is high, the small gain in survival from adding another medication may be offset by its inconvenience and minor side effects.

Guidelines for MAC prophylaxis have been inconsistently translated into practice. In the United States, guidelines recommend rifabutin for prophylaxis, but do not give a firm recommendation about when to initiate prophylaxis. National guidelines in Canada do not exist. However, there is considerable variation between provincial drug formularies about which MAC prophylactic agent is included, and the appropriate time to initiate prophylaxis.

We evaluated the optimal time to initiate prophylactic therapy. In general, the most cost-effective time to initiate therapy for azithromycin was when the CD4 count was between 100 and 75 cells / μL. The most cost-effective time to initiate rifabutin or clarithromycin was at 50 cells / μL.

We used decision analysis methods to determine the cost-effectiveness of MAC prophylaxis. This method is powerful, but has certain inherent limitations. For example, most models are able to characterize the natural history of a given condition for a limited time period, making long-term conclusions difficult. Our model, of a terminal disease in its advanced stages, is able to avoid this limitation by using a time-frame which continues until death. Our model also incorporates several important features of the natural history of late stage HIV disease - it allows for an increasing risk of MAC, other ADIs and death as the CD4 count falls and it incorporates the observed interrelationship between MAC and some ADIs, specifically cytomegalovirus infections, where the occurrence of one event is a risk factor for the other.
Three previous models have examined the cost-effectiveness of MAC prophylaxis. Simpson reported a cost-utility analysis of rifabutin, suggesting a ratio of around $22,000 / QALY, which is lower than our estimate of $76,469 / QALY [31]. Singh reported a cost-effectiveness ratio for rifabutin prophylaxis of around $18,000 / life year, while Freedberg estimated this value to be $211,000 / life year; our estimate was $39,882 / life year [32,34]. Freedberg reported the cost-effectiveness ratio of azithromycin, initiated at a CD4 count of 50 cells / µL, was $63,000 / life year, while we estimated that such a strategy dominated a strategy of no prophylaxis. None of these studies has yet been published so a detailed analysis of differences in methods is not possible.

Three important modeling assumptions may explain some of the differences between our study and the previous results. The first assumption relates to what happens to patients who would have developed MAC if they had not taken prophylaxis. If these patients do not differ in any other way from patients with similar CD4 counts and disease stages, their risk of events other than MAC should not be increased. A more pessimistic model suggests that while prophylaxis may decrease MAC infection, these patients have other characteristics which predispose them to disease progression. The limited data available suggest that the first, more optimistic, scenario is more realistic, and we have built our model accordingly [18]. Under pessimistic assumptions, our estimate of the cost-effectiveness of rifabutin ($426,787 / life year, data not shown) and of azithromycin ($92,619 / life year) exceed those of Freedberg.
The second important modeling assumption relates to the frequency of MAC infection. Our baseline estimate of the probability of developing MAC results in a cumulative lifetime incidence of 42%, a value which is towards the high end of estimates in the literature [1,2,7]. The wide range of estimates may be due to differences between centres in surveillance, diagnostic suspicion, diagnostic accuracy, use of prophylaxis and true regional variation. Even at the lower end of these estimates, a strategy of azithromycin prophylaxis is cost-effective, although sequential rifabutin is associated with an incremental cost-effectiveness of over $100,000/QALY.

The third modeling assumption relates to the natural history of treated MAC infection. Our model is particularly sensitive to the relative risk of dying from MAC, compared to having other major AIDS defining illnesses. New treatments for both MAC and other ADIs means this risk is difficult to define. However, the most recent evidence, albeit with limited follow-up, suggests that treated patients with MAC have a survival similar to that of CD4 matched controls [5,9,10]. The ongoing characterization of the natural history of late stage HIV infection will help to clarify these issues and is an area for future research.

One counter-intuitive finding of our analysis is that if mortality from MAC is increased, the cost-utility of azithromycin prophylaxis is decreased. This may seem surprising because prophylaxis should be most attractive if it prevents a deadly illness. However, consider what happens to costs during azithromycin prophylaxis. There is an initial expenditure phase (relative to no prophylaxis) associated with taking the medication, followed by a phase of cost-savings as illness is prevented. With increased survival
there is again a time of net cost-expenditure from treating patients who would otherwise have died. The cumulative cost relative to no prophylaxis will depend on the amount of time and money spent in each of these phases. The cost-effectiveness will depend on both the cumulative cost and the increase in life expectancy. As the risk of death from MAC increases, there is less time spent in the cost-savings phase and cumulative costs become positive. The rise in costs occurs more rapidly than the rise in life expectancy, resulting in an increasing cost-effectiveness ratio as the risk of death with MAC increases.

Other estimates in our model must be considered carefully, including data about costs. First, we used charges instead of costs for many estimates. Second, we made assumptions about frequency of resource used to derive these costs. Third, the estimates in the literature varied widely. Our total costs for a given disease state may seem high in comparison with U.S. estimates of costs in the literature, but are on par with a recent Australian estimate [104]. Costs for HIV care per individual may be higher in Canada than in the U.S., given that the average resource use per individual in Canada is greater [120].

To account for some of the uncertainty of our cost estimates, we used a variety of different sources of costing data and conducted extensive sensitivity analysis. Strategies which initiated prophylaxis with azithromycin were still preferred, but their cost-effectiveness varied from cost-savings to under $10,000/QALY. This is still an attractive cost-utility ratio, but underscores the reliance of our findings on our assumptions of cost.
Two special features of MAC prophylaxis medications are: a) the potential for MAC to become antibiotic resistant and b) a high associated toxicity. We modeled MAC resistance in our baseline analysis as a relatively benign condition, and then re-examined it under a different, much less attractive, set of assumptions. The cost-effectiveness of azithromycin was largely unaffected, even at high rates of development of resistance. Clarithromycin, in contrast, became considerably less attractive and was, in some cases, dominated by a strategy of no prophylaxis. As patients may take long term clarithromycin for other reasons besides MAC prophylaxis (for example, chronic sinusitis), the characterization of the natural history of macrolide-resistant MAC is important for evaluating the clinical usefulness of these strategies. Similarly, bacterial resistance may have important effects for drugs such as rifabutin and bacteria such as *Mycobacterium tuberculosis*, but a detailed analysis exceeds the scope of our model.

The medications available for MAC prophylaxis generally have similar side effect profiles, although the combination regimes have a higher rate of intolerance. We found that the incidence of side effects severe enough to necessitate discontinuation to azithromycin would have to be greater than 50% per year before this medication stopped being cost effective, compared to a strategy of no prophylaxis. Although this is considerably higher than the rate seen in clinical trials, patients in real-life settings may have considerably lower adherence [20]. Observational data on the rates of discontinuation of MAC prophylactic medications will help to better define which is the most cost-effective regimen.
As with any representation of the natural history of disease, our model has several limitations. We defined states by clinical disease stage, and assigned a cost and a utility to each. However, the classification system used may not adequately differentiate between patients in a given disease state. We assumed that, on average, quality of life does decline as HIV disease progresses, and the MOS-HIV scale shows such a trend. To attempt to differentiate between states with greater precision, we subdivided clinical AIDS into mild and major severities, as established by clinical severity of illness scales [80,81]. Further, we examined our model without adjusting for quality of life and found that this did not change the direction of the results, although it did have an effect on the magnitude of cost-effectiveness.

Another assumption was that the probability of developing an ADI, developing MAC, and dying were related to two patient characteristics - clinical disease state and CD4 count. Our model assumes that each is independently predictive of future events [121]. This may be valid, but the estimates of the relative increase in magnitude of risk derived from the literature did not usually control for this interaction. The estimates of these probabilities and risks in our model may thus be overestimates. If the actual rates of developing MAC were lower than we predicted, the true cost-utility ratio would be higher than we reported. However, if the actual rates of developing AIDS or of dying were higher than we reported, the true cost-utility ratio would be lower than we reported.

We also assumed that once a patient enters a given disease state, their health does not improve substantially. This would be true for chronic complications such as MAC,
cytomegalovirus retinitis, or wasting syndrome, but may not be true of earlier states with minor ADIs. The insensitivity of our analysis to the utility of a minor ADI indicates that this did not effect the results substantially.

The probabilities in our model may reflect the natural history of a previous era of HIV. Antiretrovirals improve the average life expectancy of HIV patients, and with the advent of combination antiretrovirals and new classes of drugs, the natural history data available in the literature may already be out of date. If the rate of CD4 decline was lower than predicted, azithromycin was still preferred, as determined in the sensitivity analysis. Indeed, when we decreased the probability of all future adverse events by 25% and slowed the rate of CD4 decline by 50%, our findings were not substantially different.

Our model may also suffer from imprecision in utility assessments. We assessed utilities in a convenience sample of HIV patients. Although we made efforts to recruit patients from both the inpatient and outpatient units and across all disease stages, our sample may still reflect a group of patients who were not moribund and willing to participate in the survey. This might have the effect of biasing self-reported utilities upwards.

Utilities have not been evaluated as rigorously as have health related quality of life scores. Some insights about the validity of utility measurements may be obtained from comparisons with psychometric scales, as in our study which compared three different utility assessment instruments with the MOS-HIV quality of life scale. However, the intent of these two approaches is inherently different; utilities reflect patient preferences.
for a given disease state, while quality of life instruments reflect functional status. It may therefore be expected that utilities will have a wider variance. We found only weak correlations between some subscales of the MOS-HIV scale and patient derived utilities.

The reliability of utilities is also an important consideration. Preferences may be expected to change considerably as a given disease changes from a hypothetical, future state to a present reality. Indeed, we found that when we asked patients to rate their own health with the HUI, preferences were consistently higher than when patients were asked to rate hypothetical descriptors. However, patients who had advanced disease did not differ from patients with early disease in their ratings of the described states, suggesting that preferences may not change considerably in this population. This may be a particular feature of HIV disease and our population who were largely familiar with the natural history and expected outcomes of their disease.

We assessed utilities with SG and TTO by asking participants to rate descriptors of health states of hypothetical patients with HIV. We assessed utilities with the HUI by asking patients to rate their own health state. We found that SG scores and TTO scores were generally similar, and that they demonstrated a gradient across disease states. In contrast, HUI scores were similar across all disease states. Several previous studies have assessed utilities for states with HIV, but have found different results. Owens and colleagues found a gradient across scores when they asked physicians to rate HIV associated disease states, but their values were generally much lower than the current results, while both Revicki and Tsevat found that respondents gave similar
answers across disease states, similar to our findings with the HUI [35,47,48]. Several possible explanations for this finding exist. First, disease stage may not correlate well with quality of life as patients in the same disease stage may have significant differences in functional status. Utility measurements in subjects with coronary artery disease, for example, do not correlate with Canadian Cardiovascular Society Angina stage [122]. However, we were unable to show that any other demographic feature or any MOS subscale other than pain (which is also a subscale in the HUI) correlated with HUI scores. A second possible explanation is that the HUI is an insensitive measure of utility assessments in patients with HIV. Still, the HUI has been shown to correlate well with other disease states and it is unlikely that HIV is of a sufficiently different character to explain this discrepancy. A third explanation is that our descriptors of disease states were excessively gloomy, although many of our subjects commented that they had good face validity. A fourth explanation is that our subjects were healthier than average patients with advanced HIV. While we excluded subjects who were mentally unable to complete the interview, our subjects had a wide range of severity of illness, as measured by both laboratory and clinical parameters. A final possible explanation is that subjects with a given disease state express a higher than anticipated preference for the state, reflecting adaptation and accommodation to a severe illness. Indeed, Tsevat and colleagues, using the TTO method, found results which were strikingly similar to our results from the HUI [48].

In summary, utility scores varied considerably in our study depending on the method used to elicit the utilities. Similarly, utility scores in our study varied considerably from
utilities obtained by other investigators. If this wide observed variation is true, it likely reflects the true diversity in preferences between individuals for certain health states. This has significant implications for decision analysis studies. How, for example, should utilities be aggregated across individuals? We have followed the convention used in most decision analyses, which uses mean values, although there is no theoretical basis for this approach. If we examine the model for each patient individually, azithromycin is cost-effective for 92% of patients, indicating a high degree of concordance in this case with the findings from the “averaged” utility estimates. However, this approach is unconventional and subject to many other theoretical concerns. Another approach is to allow for a wide range in the sensitivity analysis. Our results were insensitive to the values included in the 95% confidence intervals for the utilities in the model. However, we included six different utilities in our model and a multi-way sensitivity analysis would not have been as robust. Finally, another approach which recognizes the limitations of utility assessments is to perform an analysis without adjusting for quality of life. In our model, azithromycin remained cost-saving, and the relative ranking of the available strategies for prophylaxis did not change significantly.

We included in our model the disutility associated with prophylaxis. Other investigators have found that the disutility of treatment may have a significant effect on quality adjusted survival [85,86]. In our model, a small change in disutility could have a significant effect on the cost-effectiveness of one strategy relative to another, although the range for this disutility was small in the utility assessments. This utility may, however, measure some aspects of quality of life that are measured by other variables.
in our model. For example, attitudes toward prophylaxis - in which present losses are incurred for the promise of future benefits - may be incorporated in the discount rate for utilities or in attitudes towards risk, which we attempted to control for by using CPT adjusted utilities. If we used only one of these adjustments rather than two or three, the cost-utility ratios obtained are very close to those obtained without adjusting for quality of life. Thus, this characteristic of prophylaxis may be important for adjusting for quality of life, but modeling it as a separate utility may result in overweighing its influence.

We examined the effect of using cumulative prospect theory decision weights to transform SG utility assessments from patients with HIV, although we used the most common observed weighting function instead of assessing each individual's risk attitude (and thereby, the parameters for their own weighting function). This weighting function has been derived from healthy volunteers and may differ for individuals with active disease. In our model, azithromycin prophylaxis was cost-saving for fewer patients when CPT-transformed utilities were used, compared to EUT-utilities, as assessed by the SG. The overall estimates of cost-effectiveness were, however, unchanged. These results suggest that the application of CPT to decision analysis models might have significant effects for individual patient recommendations, although perhaps not for policy analysis.

Cost-effectiveness research incorporates the limitations of decision analysis research discussed above, but has other problems of its own. For example, the cost-effectiveness of an intervention may change over time, either because the cost of the intervention changes or because more indications for its use are discovered. In our
model, we attempted to control for this limitation by examining how other actions of antibiotics affected cost-effectiveness. Our ability to model these activities is limited by the paucity of data on other prophylactic effects of these agents. As well, antibiotics may be used for other indications but nevertheless have significant effects on MAC prophylaxis.

A significant focus for future research will be the refinement of the natural history model of advanced HIV disease. Ongoing observational data is crucial because of the emergence of new treatments for both HIV and MAC. Similarly, data on other prophylactic effects, use, and abuse of antibiotics used for MAC prophylaxis can have significant impacts on cost-effectiveness. An important area of future modeling research will be the development of a model which will address the development of bacteria resistant to antibiotics for disease spread between humans.

We have found that cost assumptions can have a significant impact on our results. There is a need for high quality Canadian costing data with accurate assessment of charges. Similarly, we have found discrepancies between utilities assessed by asking subjects to rate their own health states and asking them to rate hypothetical scenarios. This is an important area for future research, and may have particularly important implications when utilities are assessed from individuals who are free of the disease in question.

The application of techniques of decision analysis and cost-effectiveness research to policy analysis and guideline formulation remains controversial. First, as discussed above, decision analysis models are built upon numerous assumptions. Second, even
cost-effective interventions requires an outlay of resources and, unless the intervention is cost-saving, this represents a net expenditure. In this respect, our finding that azithromycin may be cost-saving is particularly intriguing. Third, cost-effectiveness research is most convincing when comparing similar programs to each other - such as different methods of preventing MAC infection. Comparing different programs assumes similar methodologies in modeling, cost estimates, and utility estimates across studies. This is unlikely, and the degree of difference between studies may be sufficient to make meaningful comparisons impossible. Lastly, while cost-effectiveness may provide information about efficiency, it is neutral about equity. Factors beyond cost-effectiveness, including considerations of distributive justice and ethics, are necessary for policy makers to consider when making resource allocation decisions.

15. Conclusion

We found that the most cost-effective strategy for MAC prophylaxis is azithromycin, with crossover to sequential rifabutin if intolerance to azithromycin develops. For a patient with a CD4 count of 100 cells / µL and no previous AIDS defining illness, the most cost-effective strategy is to initiate prophylaxis when the CD4 count is between 100 and 75 cells / µL. Depending on the cost of treating patients with HIV, this strategy is consistently cost-effective and may even be cost-saving.

Using rifabutin as sequential therapy is not preferred in two situations. First, and most importantly, patients taking a protease inhibitor, may have a greater gain in quality of life from not using rifabutin. Second, if the inconvenience of taking prophylactic
medications is moderately high (but not so high as to not take any medication), there
may be no gain in quality of life from persisting with rifabutin after azithromycin
intolerance develops. All of these findings are dependent upon several assumptions,
one of which is particularly important: the mortality of treated MAC. Indeed, we found
that the better the available treatments for MAC, the more attractive azithromycin is for
prophylaxis.

We assessed an important new technique of "correcting" utilities derived by the
standard gamble method. This approach, based on cumulative prospect theory, may
have significant implications for applying the results of cost-utility analysis to individual
patients, but less of an effect on policy recommendations.
Appendix 1. Tables
<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Entry Criteria</th>
<th>Comparison</th>
<th>Relative Risk of MAC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nightingale [14]</td>
<td>AIDS, CD4 ≤ 200</td>
<td>Rifabutin vs. Placebo</td>
<td>0.45 (0.32 - 0.63)</td>
</tr>
<tr>
<td>Pierce [15]</td>
<td>AIDS, CD4 ≤ 100</td>
<td>Clarithromycin vs. Placebo</td>
<td>0.31 (0.18 - 0.53)</td>
</tr>
<tr>
<td>Havlir [16]</td>
<td>HIV+, CD4 ≤ 100</td>
<td>Azithromycin vs. Rifabutin</td>
<td>0.52 (0.34 - 0.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin and Rifabutin vs. Rifabutin</td>
<td>0.28 (0.16 - 0.49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin and Rifabutin vs. Azithromycin</td>
<td>0.53 (0.29 - 0.95)</td>
</tr>
<tr>
<td>Benson [17]</td>
<td>HIV+, CD4 ≤ 100</td>
<td>Clarithromycin vs. Rifabutin</td>
<td>0.56 (0.37 - 0.84)</td>
</tr>
<tr>
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<td></td>
<td>Clarithromycin and Rifabutin vs. Rifabutin</td>
<td>0.79 (0.48 - 1.31)</td>
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<td></td>
<td>Clarithromycin and Rifabutin vs. Clarithromycin</td>
<td>0.43 (0.27 - 0.69)</td>
</tr>
<tr>
<td>Variable</td>
<td>Baseline Value</td>
<td>Range</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Annual probability of dying (CD4 = 100 cells / µL, no prior ADI)</td>
<td>0.06</td>
<td>0.03 - 0.33</td>
<td>89,90,91,92,93,94</td>
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<tr>
<td>relative risk of dying</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CD4 76 - 100</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 51 - 75</td>
<td>1.8</td>
<td>1.0 - 2.1</td>
<td>89,91,92,93,94,</td>
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<tr>
<td>CD4 26 - 50</td>
<td>2.1</td>
<td>1.8 - 3.4</td>
<td>123</td>
</tr>
<tr>
<td>CD4 0 - 25</td>
<td>3.9</td>
<td>2.1 - 6.0</td>
<td></td>
</tr>
<tr>
<td>no prior ADI</td>
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<td></td>
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</tr>
<tr>
<td>minor ADI</td>
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<td>1.0 - 1.9</td>
<td>81,82,90,96,123</td>
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<td>1 major ADI</td>
<td>1.9</td>
<td>1.1 - 3.2</td>
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<tr>
<td>multiple major ADIs</td>
<td>2.8</td>
<td>1.9 - 5.1</td>
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<td>relative risk if MAC present (compared to one major ADI)</td>
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<td>0.4 - 4.4</td>
<td>6,98,99</td>
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<tr>
<td>Annual probability of developing an ADI other than MAC (CD4 = 100 cells / µL, no prior ADI)</td>
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<td>0.10 - 0.60</td>
<td>90,124</td>
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<td>proportion with a minor ADI</td>
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<td>0.10 - 0.90</td>
<td>1,80,90</td>
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<tr>
<td>proportion with a major ADI</td>
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<td>0.10 - 0.90</td>
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<tr>
<td>relative risk of developing an ADI</td>
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<td></td>
</tr>
<tr>
<td>CD4 76 - 100</td>
<td>1.0</td>
<td></td>
<td>6,90</td>
</tr>
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<td>CD4 51 - 75</td>
<td>1.1</td>
<td>1.0 - 1.3</td>
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<tr>
<td>CD4 26 - 50</td>
<td>1.2</td>
<td>1.0 - 1.3</td>
<td></td>
</tr>
<tr>
<td>CD4 0 - 25</td>
<td>1.4</td>
<td>1.0 - 2.0</td>
<td></td>
</tr>
<tr>
<td>relative risk if MAC present</td>
<td>2.8</td>
<td>1.0 - 4.0</td>
<td>6</td>
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<tr>
<td>Annual rate of CD4 cell decline (cells / µL / year)</td>
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<td>15 - 100</td>
<td>92,100,101,102</td>
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<td>Variable</td>
<td>Baseline Value</td>
<td>Range</td>
<td>References</td>
</tr>
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<td>-------------------------------------------------------------------------</td>
<td>----------------</td>
<td>------------------</td>
<td>-----------------------------</td>
</tr>
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<td>Annual probability of developing MAC (CD4 = 100 cells / μL, no prior ADI, no prophylaxis)</td>
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<td>0.03 - 0.11</td>
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<tr>
<td>relative risk of developing MAC</td>
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<td></td>
<td></td>
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<tr>
<td>CD4 76 - 100</td>
<td>1.0</td>
<td></td>
<td></td>
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<td>CD4 51 - 75</td>
<td>1.3</td>
<td>1.0 - 2.5</td>
<td>6, 7, 124, 125,</td>
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<td>CD4 26 - 50</td>
<td>2.7</td>
<td>2.5 - 3.8</td>
<td></td>
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<tr>
<td>CD4 0 - 25</td>
<td>4.2</td>
<td>2.8 - 8.0</td>
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</tr>
<tr>
<td>no prior ADIs</td>
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<tr>
<td>previous minor ADIs</td>
<td>1.0</td>
<td>1.0 - 2.6</td>
<td>6, 7, 9</td>
</tr>
<tr>
<td>one previous major ADI</td>
<td>1.5</td>
<td>1.0 - 2.6</td>
<td></td>
</tr>
<tr>
<td>multiple previous ADIs</td>
<td>1.5</td>
<td>1.0 - 2.6</td>
<td></td>
</tr>
<tr>
<td>Relative risk of MAC while taking:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>0.45</td>
<td>0.32 - 0.63</td>
<td>14, 15, 16, 17</td>
</tr>
<tr>
<td>CLA</td>
<td>0.31</td>
<td>0.37 - 0.84</td>
<td></td>
</tr>
<tr>
<td>AZI</td>
<td>0.24</td>
<td>0.24 - 0.85</td>
<td></td>
</tr>
<tr>
<td>CLA / RIF combination</td>
<td>0.25</td>
<td>0.27 - 0.69</td>
<td></td>
</tr>
<tr>
<td>AZI / RIF combination</td>
<td>0.13</td>
<td>0.16 - 0.49</td>
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<tr>
<td>Annual probability of a severe side effect:</td>
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<tr>
<td>RIF</td>
<td>0.08</td>
<td>0.02 - 0.50</td>
<td>14, 15, 16, 17</td>
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<tr>
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<td>0.02 - 0.50</td>
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<tr>
<td>CLA / RIF combination</td>
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<td>0.02 - 0.50</td>
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</tr>
<tr>
<td>AZI / RIF combination</td>
<td>0.12</td>
<td>0.02 - 0.50</td>
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<tr>
<td>Probability of MAC resistance</td>
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<tr>
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<td>0.00</td>
<td>0.00 - 1.00</td>
<td>14, 15, 16, 17</td>
</tr>
<tr>
<td>CLA</td>
<td>0.58</td>
<td>0.00 - 1.00</td>
<td></td>
</tr>
<tr>
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<td>0.11</td>
<td>0.00 - 1.00</td>
<td></td>
</tr>
<tr>
<td>CLA / RIF combination</td>
<td>0.25</td>
<td>0.00 - 1.00</td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>0.00</td>
<td>0.00 - 1.00</td>
<td></td>
</tr>
<tr>
<td>AZI / RIF combination</td>
<td>0.00</td>
<td>0.00 - 1.00</td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>0.00</td>
<td>0.00 - 1.00</td>
<td></td>
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</table>

RIF = rifabutin; CLA = clarithromycin; AZI = azithromycin
<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value</th>
<th>Multiway values</th>
<th>Range</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of dying from untreated MAC (relative to risk of dying with 1 major ADI)</td>
<td></td>
<td></td>
<td>1.1 - 4.4</td>
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<td>Risk of developing a minor ADI (relative to risk without prophylaxis):</td>
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</tr>
<tr>
<td>RIF</td>
<td>1.00</td>
<td>0.90</td>
<td>0.75 - 1.00</td>
<td>16,17,</td>
</tr>
<tr>
<td>CLA</td>
<td>1.00</td>
<td>0.90</td>
<td>0.75 - 1.00</td>
<td>18,126</td>
</tr>
<tr>
<td>AZI</td>
<td>1.00</td>
<td>0.85</td>
<td>0.75 - 1.00</td>
<td></td>
</tr>
<tr>
<td>CLA / RIF combination</td>
<td>1.00</td>
<td>0.90</td>
<td>0.75 - 1.00</td>
<td></td>
</tr>
<tr>
<td>AZI / RIF combination</td>
<td>1.00</td>
<td>0.85</td>
<td>0.75 - 1.00</td>
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<tr>
<td>Risk of developing a major ADI (relative to risk without prophylaxis):</td>
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<tr>
<td>RIF</td>
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<td>0.80</td>
<td>0.50 - 1.00</td>
<td>16,17,</td>
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<td>CLA</td>
<td>1.00</td>
<td>0.85</td>
<td>0.50 - 1.00</td>
<td>18,126</td>
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<tr>
<td>AZI</td>
<td>1.00</td>
<td>0.75</td>
<td>0.50 - 1.00</td>
<td></td>
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<tr>
<td>CLA / RIF combination</td>
<td>1.00</td>
<td>0.70</td>
<td>0.50 - 1.00</td>
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<td>AZI / RIF combination</td>
<td>1.00</td>
<td>0.65</td>
<td>0.50 - 1.00</td>
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<tr>
<td>MAC blood culture test</td>
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<td>sensitivity</td>
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<td>0.75</td>
<td>0.50 - 1.00</td>
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<tr>
<td>specificity</td>
<td>1.00</td>
<td>0.99</td>
<td>0.50 - 1.00</td>
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<tr>
<td>Annual probability of having symptoms compatible with MAC</td>
<td>0.06</td>
<td>0.17</td>
<td>0.07 - 0.23</td>
<td>128</td>
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<tr>
<td>(CD4 = 100 cells / μL, no prior ADI)</td>
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<td></td>
<td></td>
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<tr>
<td>Proportion of MAC patients who are asymptomatic</td>
<td>0.00</td>
<td>0.11</td>
<td>0.00 - 0.50</td>
<td>128</td>
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<tr>
<td>Proportion of MAC patients who are symptomatic</td>
<td>1.00</td>
<td>0.89</td>
<td>0.50 - 1.00</td>
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</tbody>
</table>

RIF = rifabutin; CLA = clarithromycin; AZI = azithromycin; Ref = references.

Multiway values are estimates used in various multiway sensitivity analyses as described in the text.
<table>
<thead>
<tr>
<th>Disease State</th>
<th>Baseline</th>
<th>Reference 104</th>
<th>Reference 105</th>
<th>Reference 110</th>
<th>Reference 111</th>
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</thead>
<tbody>
<tr>
<td>HIV, no ADI</td>
<td>$21,385</td>
<td>$20,960</td>
<td>$18,674</td>
<td>$16,806</td>
<td>$9,028</td>
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<td>minor ADI †</td>
<td>$28,259</td>
<td>$27,877</td>
<td>$24,836</td>
<td>$22,351</td>
<td>$12,041</td>
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<td>1 major ADI</td>
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<td>$73,840</td>
<td>$27,140</td>
<td>$46,921</td>
<td>$33,652</td>
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<tr>
<td>multiple major ADIs †</td>
<td>$78,960</td>
<td>$73,840</td>
<td>$27,140</td>
<td>$46,921</td>
<td>$33,652</td>
</tr>
</tbody>
</table>

ADI = AIDS defining illness

Costs are expressed in 1995 Canadian dollars

*calculated as 1.33 \times the cost of HIV without an ADI for references 104, 105, and 110.

† assumed equal to 1 major ADI except where indicated.

Baseline values are calculated as described in the text.
### Table 5  Variables used to Estimate Costs of Disease States

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value</th>
<th>Range</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per hospital day</td>
<td>$1,540</td>
<td>$1,000 - $1,600</td>
<td>105,110,113, 114,116</td>
</tr>
<tr>
<td>Hospital days per year</td>
<td></td>
<td></td>
<td>105,110,129,</td>
</tr>
<tr>
<td>HIV , no ADI</td>
<td>5</td>
<td>0 - 25</td>
<td>130</td>
</tr>
<tr>
<td>minor ADI</td>
<td>7</td>
<td>0 - 25</td>
<td></td>
</tr>
<tr>
<td>1 major ADI</td>
<td>25</td>
<td>0 - 90</td>
<td></td>
</tr>
<tr>
<td>multiple major ADIs</td>
<td>30</td>
<td>0 - 90</td>
<td></td>
</tr>
<tr>
<td>Ratio of outpatient to inpatient costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV only or minor ADI</td>
<td>0.55</td>
<td>0.30 - 1.00</td>
<td>104,105,110,</td>
</tr>
<tr>
<td>1 or more major ADIs</td>
<td>0.30</td>
<td>0.20 - 0.60</td>
<td>130</td>
</tr>
<tr>
<td>Annual cost per medication</td>
<td>$2,100</td>
<td>$600 - $2,500</td>
<td>19,110,131</td>
</tr>
<tr>
<td>Number of medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV , no ADI</td>
<td>4.5</td>
<td>1 - 5</td>
<td>112,131,132</td>
</tr>
<tr>
<td>minor ADI</td>
<td>5.5</td>
<td>2 - 9</td>
<td></td>
</tr>
<tr>
<td>1 major ADI</td>
<td>7</td>
<td>2 - 9</td>
<td></td>
</tr>
<tr>
<td>multiple major ADIs</td>
<td>9</td>
<td>2 - 11</td>
<td></td>
</tr>
<tr>
<td>Annual medication costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>$3,416</td>
<td>$1,000 - $5,000</td>
<td>19</td>
</tr>
<tr>
<td>CLA</td>
<td>$2,646</td>
<td>$1,000 - $5,000</td>
<td></td>
</tr>
<tr>
<td>AZI</td>
<td>$1,129</td>
<td>$500 - $4,000</td>
<td></td>
</tr>
<tr>
<td>ethambutol</td>
<td>$265</td>
<td>$50 - $1,000</td>
<td></td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>$3,403</td>
<td>$1,000 - $5,000</td>
<td></td>
</tr>
<tr>
<td>Cost of a side effect</td>
<td>$375</td>
<td>$50 - $750</td>
<td>105,115</td>
</tr>
<tr>
<td>Cost of a MAC blood culture test</td>
<td>$60</td>
<td>$25 - $250</td>
<td>111,115</td>
</tr>
</tbody>
</table>

ADI = AIDS defining illness; RIF = rifabutin; CLA = clarithromycin; AZI = azithromycin; Ref = reference
### Table 6  Demographic Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV, no symptoms (n=2)</th>
<th>symptomatic HIV, no ADI (n=18)</th>
<th>minor ADI (n=9)</th>
<th>major ADI (1 or more) (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>390</td>
<td>269</td>
<td>86</td>
<td>41</td>
</tr>
<tr>
<td>Median</td>
<td>390</td>
<td>300</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td><strong>Antiretroviral use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Current</td>
<td>2</td>
<td>15</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Past</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>PCP prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Current</td>
<td>1</td>
<td>12</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Past</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>MAC medication use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2</td>
<td>16</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Past</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Current prophylaxis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Current treatment</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td><strong>Number of medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.0</td>
<td>4.0</td>
<td>5.4</td>
<td>8.8</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 7  
Estimates of Utilities for Specific Health States

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Method</th>
<th>SG</th>
<th>TTO</th>
<th>CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV, no ADI</td>
<td></td>
<td>0.80 (0.03)</td>
<td>0.81 (0.04)</td>
<td>0.70 (0.02)</td>
</tr>
<tr>
<td>minor ADI</td>
<td></td>
<td>0.64 (0.04)</td>
<td>0.65 (0.05)</td>
<td>0.46 (0.02)</td>
</tr>
<tr>
<td>major ADI</td>
<td></td>
<td>0.42 (0.04)</td>
<td>0.42 (0.05)</td>
<td>0.24 (0.02)</td>
</tr>
<tr>
<td>MAC</td>
<td></td>
<td>0.48 (0.04)</td>
<td>0.45 (0.05)</td>
<td>0.28 (0.03)</td>
</tr>
<tr>
<td>prophylaxis</td>
<td></td>
<td>0.97 (0.01)</td>
<td>0.98 (0.01)</td>
<td>0.89 (0.02)</td>
</tr>
<tr>
<td>side effect</td>
<td></td>
<td>0.50 (0.05)</td>
<td>0.57 (0.05)</td>
<td>0.37 (0.04)</td>
</tr>
</tbody>
</table>

Values are expressed as mean utility (SE). HIV = symptomatic HIV without a prior AIDS defining illness; ADI = AIDS defining illness, prophylaxis = utility of minor side effects and inconvenience of taking medication; side effect = utility of side effect severe enough to necessitate discontinuing medication; SG = standard gamble; TTO = time trade-off; CRS = category rating scale.
<table>
<thead>
<tr>
<th>Disease State</th>
<th>Method</th>
<th>SG</th>
<th>TTO</th>
<th>CRS</th>
<th>HUI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV, no ADI</td>
<td></td>
<td>0.78 (0.06)</td>
<td>0.82 (0.05)</td>
<td>0.68 (0.04)</td>
<td>0.81 (0.04)</td>
</tr>
<tr>
<td>minor ADI</td>
<td></td>
<td>0.59 (0.06)</td>
<td>0.46 (0.10)</td>
<td>0.47 (0.05)</td>
<td>0.77 (0.06)</td>
</tr>
<tr>
<td>major ADI</td>
<td></td>
<td>0.47 (0.07)</td>
<td>0.52 (0.08)</td>
<td>0.24 (0.03)</td>
<td>0.75 (0.04)</td>
</tr>
</tbody>
</table>

Values are expressed as mean utility scores. HIV = symptomatic HIV without a prior AIDS defining illness; ADI = AIDS defining illness; SG = standard gamble; TTO = time trade-off; CRS = category rating scale; HUI = health utilities index.
<table>
<thead>
<tr>
<th>Initial</th>
<th>Medication Strategy</th>
<th>Cost</th>
<th>Years</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>$120,806</td>
<td>2.9569</td>
<td>1.8027</td>
</tr>
<tr>
<td>RIF</td>
<td>None</td>
<td>$125,340</td>
<td>3.0706</td>
<td>1.8620</td>
</tr>
<tr>
<td>RIF</td>
<td>AZI</td>
<td>$125,032</td>
<td>3.0993</td>
<td>1.8842</td>
</tr>
<tr>
<td>RIF</td>
<td>CLA</td>
<td>$125,729</td>
<td>3.0956</td>
<td>1.8800</td>
</tr>
<tr>
<td>AZI</td>
<td>None</td>
<td>$118,536</td>
<td>3.1292</td>
<td>1.9246</td>
</tr>
<tr>
<td>AZI</td>
<td>RIF</td>
<td>$119,133</td>
<td>3.1465</td>
<td>1.9360</td>
</tr>
<tr>
<td>CLA</td>
<td>None</td>
<td>$123,073</td>
<td>3.1031</td>
<td>1.8955</td>
</tr>
<tr>
<td>CLA</td>
<td>RIF</td>
<td>$123,885</td>
<td>3.1255</td>
<td>1.9098</td>
</tr>
<tr>
<td>AZI and RIF</td>
<td>AZI</td>
<td>$126,905</td>
<td>3.1736</td>
<td>1.9374</td>
</tr>
<tr>
<td>AZI and RIF</td>
<td>RIF</td>
<td>$126,005</td>
<td>3.1811</td>
<td>1.9448</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>CLA</td>
<td>$130,797</td>
<td>3.1349</td>
<td>1.8837</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>RIF</td>
<td>$130,454</td>
<td>3.1415</td>
<td>1.8914</td>
</tr>
</tbody>
</table>

RIF = rifabutin; CLA = clarithromycin; AZI = azithromycin; QALYs = quality adjusted life years.
### Table 10: Cost-effectiveness of MAC Prophylaxis Strategies

<table>
<thead>
<tr>
<th>Medication Strategy</th>
<th>Cost-effectiveness ($ / life year)</th>
<th>Cost-utility ($ / QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Sequential 1</td>
<td>Sequential 2</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>RIF</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>RIF</td>
<td>AZI</td>
<td>None</td>
</tr>
<tr>
<td>RIF</td>
<td>CLA</td>
<td>None</td>
</tr>
<tr>
<td>AZI</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>AZI</td>
<td>RIF</td>
<td>None</td>
</tr>
<tr>
<td>CLA</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CLA</td>
<td>RIF</td>
<td>None</td>
</tr>
<tr>
<td>AZI and RIF</td>
<td>AZI</td>
<td>RIF</td>
</tr>
<tr>
<td>AZI and RIF</td>
<td>RIF</td>
<td>AZI</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>CLA</td>
<td>RIF</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>RIF</td>
<td>CLA</td>
</tr>
</tbody>
</table>

RIF = rifabutin; CLA = clarithromycin; AZI = azithromycin; QALY = quality adjusted life year

*Strategies starting with azithromycin alone were preferred because they had lower costs and greater benefits.
### Table 11

**Incremental Cost-effectiveness of MAC Prophylaxis Strategies**

<table>
<thead>
<tr>
<th>Initial</th>
<th>Sequential 1</th>
<th>Sequential 2</th>
<th>Cost-effectiveness ($ / life year)</th>
<th>Cost-utility ($ / QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZI</td>
<td>None</td>
<td>None</td>
<td>$34,575</td>
<td>$52,552</td>
</tr>
<tr>
<td>AZI</td>
<td>RIF</td>
<td>None</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>CLA</td>
<td>None</td>
<td>None</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>CLA</td>
<td>RIF</td>
<td>None</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>RIF</td>
<td>AZI</td>
<td>None</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>RIF</td>
<td>None</td>
<td>None</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>RIF</td>
<td>CLA</td>
<td>None</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>AZI and RIF</td>
<td>RIF</td>
<td>AZI</td>
<td>$198,630</td>
<td>$781,302</td>
</tr>
<tr>
<td>AZI and RIF</td>
<td>AZI</td>
<td>RIF</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>RIF</td>
<td>CLA</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>CLA</td>
<td>RIF</td>
<td>dominated*</td>
<td>dominated*</td>
</tr>
</tbody>
</table>

*RIF = rifabutin; CLA = clarithromycin; AZI = azithromycin; QALY = quality adjusted life year

Strategies are ranked by cost in ascending order. Incremental cost-effectiveness is calculated for each strategy compared to the next, non-dominated strategy below it in rank.

*Dominated strategies have higher costs and lower benefits than the strategies to which they are compared.*
Table 12  Other Outcomes of Prophylaxis

<table>
<thead>
<tr>
<th>Initial</th>
<th>Medication Strategy</th>
<th>Sequential 1</th>
<th>Sequential 2</th>
<th>Additional days free of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>any ADI</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>RIF</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>48</td>
</tr>
<tr>
<td>RIF</td>
<td>AZI</td>
<td>None</td>
<td>None</td>
<td>57</td>
</tr>
<tr>
<td>RIF</td>
<td>CLA</td>
<td>None</td>
<td>None</td>
<td>56</td>
</tr>
<tr>
<td>AZI</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>70</td>
</tr>
<tr>
<td>AZI</td>
<td>RIF</td>
<td>None</td>
<td>None</td>
<td>76</td>
</tr>
<tr>
<td>CLA</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>61</td>
</tr>
<tr>
<td>CLA</td>
<td>RIF</td>
<td>None</td>
<td>None</td>
<td>68</td>
</tr>
<tr>
<td>AZI and RIF</td>
<td>AZI</td>
<td>RIF</td>
<td>None</td>
<td>87</td>
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<tr>
<td>AZI and RIF</td>
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<td>AZI</td>
<td>None</td>
<td>89</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>CLA</td>
<td>RIF</td>
<td>None</td>
<td>72</td>
</tr>
<tr>
<td>CLA and RIF</td>
<td>RIF</td>
<td>CLA</td>
<td>None</td>
<td>74</td>
</tr>
</tbody>
</table>

ADI = AIDS defining illness; hospital = days spent in hospital
Table 13  Incremental Cost effectiveness of Strategy by CD4 count

<table>
<thead>
<tr>
<th>Medication Strategy</th>
<th>CD4 count to initiate prophylaxis (cells / μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>RIF AZI None</td>
<td>$25,882</td>
</tr>
<tr>
<td>CLA RIF None</td>
<td>$15,944</td>
</tr>
<tr>
<td>AZI None None</td>
<td>preferred</td>
</tr>
<tr>
<td>AZI RIF None</td>
<td>preferred</td>
</tr>
<tr>
<td>AZI and RIF AZI</td>
<td>$19,034</td>
</tr>
</tbody>
</table>

RIF = rifabutin, CLA = clarithromycin, AZI = azithromycin

Strategies which are preferred have lower costs and greater benefits than strategies to which they are compared. Strategies which are dominated have greater costs and fewer benefits.

*Starting azithromycin without sequential therapy at a CD4 count of 100 cells / μL, compared to starting at 75 cells / μL, saves costs and decreases benefits, for a cost-effectiveness ratio of $10,201 per QALY foregone.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value</th>
<th>Range</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline annual probability of MAC</td>
<td>0.06</td>
<td>0.03 - 0.11</td>
<td>0.02</td>
</tr>
<tr>
<td>Relative risk of MAC with AZI</td>
<td>0.24</td>
<td>0.08 - 0.54</td>
<td>0.66</td>
</tr>
<tr>
<td>Baseline annual probability of an ADI other than MAC</td>
<td>0.25</td>
<td>0.10 - 0.60</td>
<td>0.66</td>
</tr>
<tr>
<td>Baseline annual probability of dying</td>
<td>0.06</td>
<td>0.03 - 0.33</td>
<td>0.27</td>
</tr>
<tr>
<td>Relative risk of dying with MAC</td>
<td>1.0</td>
<td>0.4 - 4.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Probability of a side effect with AZI</td>
<td>0.07</td>
<td>0.02 - 0.50</td>
<td>0.68*</td>
</tr>
<tr>
<td>Cost of AZI</td>
<td>$1,129</td>
<td>$500 - $4,000</td>
<td>$4,400</td>
</tr>
<tr>
<td>Utility of prophylaxis</td>
<td>0.966</td>
<td>0.95 - 1.0</td>
<td>0.87*</td>
</tr>
</tbody>
</table>

RIF = rifabutin, CLA = clarithromycin, AZI = azithromycin

Sensitivity analysis for azithromycin without sequential rifabutin compared to no prophylaxis. The threshold is set at $50,000 / QALY gained, except * for which the threshold is $50,000 / QALY foregone.
Appendix 2.
Figures
Figure 1  **Category Rating Scale.** Subjects rate the current health state on a scale with the anchors “Dead” and “Best possible health.”
Figure 2  **Standard Gamble.** Subjects chose between two prospects. The first prospect is a gamble between two possibilities - best possible health, with probability $p$, or immediate death. The second prospect is to continue in the current health state. At a given value for $p$, participants will be indifferent between the two prospects. The utility value of the current disease state is calculated from the threshold value of $p$. 
**Figure 3  Time Trade Off.** Subjects state how much time in the current disease state they would be willing to give up in return for best possible health. The time, $t$, is specified as the duration of the disease state until death. The duration $t-x$ is the time the participant would be willing to give up. The utility is measured by calculating $x/t$. 
Figure 4  The probability weighting curve for a risk neutral individual. Expected utility theory states that the expected value of an outcome should be independent of attitude towards risk, resulting in a linear probability weighting function. For example, the difference between a risk of 10% and 0% should be the same as the difference between a risk of 60% and 50%. Problems arise because individuals do not have the same attitude towards preferences throughout the possible values of $p$. 
In Decision I, the choice is between prospect A1, with a 40% chance of winning $4,000 and prospect B1, with a 50% chance of winning $3,000. Expected utility theory states that prospect A1, with an expected utility of $1,600 is preferred over prospect B1, with an expected utility of $1,500.

In Decision II, the same outcomes are possible, but the probability of winning has changed. Expected utility theory predicts that respondents choosing A1 in Decision I should chose A2 Decision II. However, empirical evidence confirms that most respondents will chose B2, with a certainty of winning $3,000 over prospect A2. This is one example of the certainty effect, a consistent violation of expected utility theory.
Figure 6  An example of a probability weighting curve for a risk averse individual. Risk averse individuals will tend not to gamble in risky situations, independent of the outcome. In a standard gamble utility assessment, this unwillingness to gamble leads to a consistently lower expected utility, (heavy line) than would have been expected if an individual was risk neutral (dashed line).
Figure 7  Transformed probabilities for a risk averse individual. The same decision trees as in Figure 5 is depicted, but the probabilities have been transformed according to the function depicted in Figure 6. Now, the expected utility of prospect A1 in Decision I is $0.16 \times \$4,000 = \$640$, while the expected utility of prospect B1 is $0.25 \times \$3,000 = \$750$, thus prospect B1 is preferred. In Decision II, the expected utility of prospect A2 is $0.64 \times \$4,000 = \$2,560$, while the expected utility of prospect B2 is $\$3,000$, thus prospect B2 is preferred. However, empirical findings suggest that most individuals prefer prospect A1 in Decision I (as would have been expected with non-transformed probabilities). An alternative weighting function is needed.
Figure 8  Empirically derived probability weighting function. Evidence from experiments has shown that individuals are risk averse at high probabilities, but are risk seeking at low probabilities. The curve shown here is the most common function.
Figure 9   Decision tree using transformed probabilities from cumulative prospect theory. The same decision trees as in Figure 5 is depicted, but the probabilities have been transformed using the method described in Figure 8. Now, the expected utility of prospect A1 in Decision I is $0.37 \times 4,000 = 1,480$, while the expected utility of prospect B1 is $0.42 \times 3,000 = 1,260$, thus prospect A1 is preferred. In Decision II, the expected utility of prospect A2 is $0.61 \times 4,000 = 2,440$, while the expected utility of prospect B2 is $3,000$, thus prospect B2 is preferred.
Figure 10  **The decision tree: Strategies.** Strategies for MAC prophylaxis include rifabutin, clarithromycin, azithromycin, combinations of rifabutin with one of the macrolides, and no prophylaxis. Not all strategies are shown for clarity.
Figure 11  The decision tree: Events. Possible events in one cycle include death, MAC (with or without another AIDS defining illness), multiple major AIDS defining illness, one major AIDS defining illness, minor AIDS defining illnesses and HIV without an AIDS defining illness. MAC which develops may be sensitive to antibiotics or resistant. Patients receiving prophylaxis may develop a dose-limiting side effect.
Figure 12  The decision tree: Outcomes. Outcome states include death, MAC with one or more other major AIDS defining illness, MAC with no other major AIDS defining illnesses, multiple major AIDS defining illness, 1 major AIDS defining illness, 1 or more minor AIDS defining illnesses, and symptomatic HIV infection without an AIDS defining illness. Not shown are other outcomes defined by the occurrence of side effects or MAC resistance. Each state is also characterized by the type of prophylactic agent used.
A Prophylaxis,
No surveillance

- Side effect
  - MAC symptoms
    - True Positive
      - MAC resistant
    - True Negative
      - No MAC
  - False Negative
    - No MAC symptoms
      - MAC
      - MAC sensitive
    - Minor ADI
      - HIV without an ADI
      - 1 major ADI
      - Multiple major ADIs
      - MAC resistant
      - MAC sensitive

see next page for legend
A Prophylaxis, No surveillance

- Side effect
  - True Positive
    - MAC resistant
    - MAC sensitive
  - False Positive
    - MAC resistant
    - MAC sensitive

- No side effect
  - MAC symptoms
    - False Negative
      - Multiple major ADIs
      - 1 major ADI
      - Minor ADI
      - HIV without an ADI
    - True Negative
      - No MAC
        - No MAC symptoms
          - MAC resistant
          - MAC sensitive

see next page for legend
Figure 14  The decision tree for MAC surveillance. Only events shown. Outcomes (not shown) include all outcomes in Figure 10, but also include several additional states: a) having MAC but being falsely diagnosed as having it, and thus receiving treatment (false positives); b) having MAC but not being diagnosed (false negatives); and c) having blood cultures positive for MAC but not being symptomatic. Panel A is the model for patients who receive prophylaxis, but no surveillance. They are tested for MAC only if they develop MAC symptoms, although not all patients with symptoms will have MAC. In panel B, all patients receive surveillance cultures once per cycle. Surveillance detects MAC early, both symptomatic cases and asymptomatic cases.
A = azithromycin, C = clarithromycin, R = rifabutin, AR = azithromycin and rifabutin in combination, CR = clarithromycin and rifabutin in combination. An arrow (→) indicates sequential therapy. For single and double sequence regimens, drugs are discontinued rather than substituted in subsequent regimens.
Figure 16 Sensitivity to the incidence and mortality of MAC. The cost-utility of azithromycin without sequential therapy is plotted as a function of the relative risk of dying with MAC, compared to the risk of dying with another major ADI. The heavy line represents an annual incidence of MAC of 6% (baseline assumption). If the relative risk of dying with MAC is less than 1.7, the strategy is cost-effective. The shape of the cost-effectiveness curve is dependent upon the annual incidence of MAC. At a low annual incidence, the cost-effectiveness of prophylaxis is very sensitive to the relative risk of dying.
Figure 17  Sensitivity to the disutility of prophylaxis. The solid line is a plot of dollars / QALY gained for a strategy of azithromycin with no sequential therapy compared to azithromycin with sequential therapy. At disutility values of 0.03 or less, sequential rifabutin is cost-effective. The dashed line is a plot of dollars / QALY foregone for a strategy of azithromycin without sequential therapy compared to no prophylaxis. At disutility values of 0.135 or more, prophylaxis is associated with a cost / QALY foregone of less than $50,000 / QALY and is therefore not cost-effective.
Figure 18  Net Utility Gains with prophylaxis as determined by EUT and CPT. For each subject, the net utility gained with azithromycin compared to no prophylaxis is plotted. Utilities for this analysis are as assessed by the standard gamble method under expected utility theory (EUT) assumptions and also by cumulative prospect theory (CPT) assumptions. For most subjects, there was a loss in net utility when moving from EUT assumptions to CPT assumptions, but 10 subjects had a gain in net utility. The heavy line represents mean net utility scores.
Appendix 3.
Scenarios for Outcome States
Living with symptomatic HIV infection

You have started to have symptoms from being HIV positive. You are able to do most of the activities that you have always done, but you get tired more easily than in the past. You are able to care for yourself and do not need any help with cooking, cleaning or household chores. You have lost ten pounds in the last year without dieting. You have night sweats once or twice a month that make you change the bed sheets. You remain mentally bright and in control of your personal affairs. Any pain you experience is mild and temporary. You can work at a job that is not too physically challenging or intellectually draining.

You have white plaques in your mouth called thrush. These are not painful and do not bleed, but you notice that you are unable to taste food as well as you did before. You can easily remove the plaques by brushing your teeth and tongue and by using mouthwashes. However, they come back quickly and you must perform mouth care twice each day to keep them away. Your doctor had given you a special mouthwash that cured this problem, but six weeks after you stopped using the mouthwash, the plaques came back. Your doctor then gave you pills to take which controls the problem. You find that this problem comes back about every two months, but clears after taking the pills for about five days.

In addition to the white plaques in your mouth, you have had herpes around your anus. These are small ulcers that are uncomfortable. This made it painful to have a bowel movement or even to sit down. Your doctor prescribed medication that cleared this up after about one week.

You now take four types of medications - one against HIV, one to prevent pneumonia, one for thrush and one for herpes.
Living with mild AIDS complications

You are less and less able to do many of the activities that you have always done. You are frequently tired and have had to decrease your work activities to a minimum. You have lost 20 pounds and are now taking medication to help stimulate your appetite. You have episodes of diarrhea three or four times a month. You also have fevers about once or twice a week with no apparent cause. Two or three times a month, you have severe night sweats which soak the bed sheets. You have an itchy rash on your arms, legs and body that is not getting better, even with several different creams and ointments.

Three months ago you had an episode of pneumonia caused by an organism called PCP. For two weeks, you had high fevers, a dry cough, and shortness of breath. You were treated for this infection for three weeks and developed a temporary rash from the treatment. After finishing the treatment, your breathing improved but you continued to feel very tired.

You are now taking medications against HIV, a medication to prevent pneumonia, medication to stimulate your appetite, a multivitamin, medication to decrease the diarrhea, medication to prevent thrush from coming back and another to prevent herpes from coming back.
Living with severe AIDS complications

You are tired for extended periods of time. You have lost about 35 pounds and find that you have no appetite. Sometimes you don't have any energy and spend the day in bed, but other days you are able to go shopping or out to see friends. You have stopped working because you are so tired. A home care worker comes to your house twice a week to help you with cleaning and laundry. You have been hospitalized once in the past for a serious complication.

You are becoming increasingly forgetful. You no longer trust yourself to run your own financial affairs and have asked friends to help you. You often don’t know where you are when you are not at home. You also find that your emotions are more unstable than before and you find yourself occasionally crying inappropriately. As time goes by, you are increasingly more confused and disoriented. You are unable to drive and must have somebody give you a ride or take a taxi. You have made plans for the day when your friends have to look after you totally.

You are now taking two medications against HIV, a medication to prevent pneumonia, medication to stimulate your appetite, a multivitamin, supplements, a monthly injection to help you gain weight, medication to decrease the diarrhea, medication to prevent thrush from coming back and another to prevent herpes from coming back. The medications make you somewhat nauseous and you vomit about once a week, but you persist in taking them.
Living with MAC

You are frequently very tired. You have now lost about 20 pounds. Sometimes you don't have any energy and spend the day in bed, but other days you are able to go shopping or out to see friends. You have stopped working. A home care worker comes to your house twice a week to help you with cleaning and laundry. You have been hospitalized once in the past for a serious complication.

You have high fevers and drenching sweats every night. As well, you have fevers and chills during the day. You have 6 diarrhea bowel movements every day. You have pain in your abdomen that feels like an ache all over your belly. It is moderately severe. You require a blood transfusion every 6 weeks because your hemoglobin keeps falling, making you feel even more tired. After receiving blood, you feel like your energy has improved, but it quickly drains away. You remain aware of everything that is happening. However, you are so tired that you worry that you are missing important things. You ask your family to double check everything you do.

Your doctor has prescribed three additional medications for you to take. You find that your fevers, chills and night sweats are decreased. You are able to regain about 5 pounds in weight. However, the pills make you nauseous and you vomit once a week. You visit your doctor about twice per month. As well as these 3 medications, you are taking two medications against HIV, a medication to prevent pneumonia, medication to decrease the diarrhea, medication to prevent thrush from coming back and another to prevent herpes from coming back.
Rifabutin on a regular basis

You have recently started taking a new medication called rifabutin. This medication does not treat any illnesses that you have; rather your doctor has recommended it to prevent you from becoming ill. You have to remember to take this medication once a day. The drug gives you a little nausea and an occasional headache, both of which are mild. Your urine has turned a bright shade of orange, which your doctor says is normal with this medication.
Severe side effects of rifabutin

You have recently started taking a new medication called rifabutin. This medication does not treat any illnesses that you have; rather your doctor has recommended it to prevent you from becoming ill. You develop severe nausea and vomit after every meal. You have six diarrhea bowel movements every day. You have abdominal pain associated with this. As well, you have a high fever throughout the day.
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