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OPTIMIZING DRUG FORMULARY DECISIONS FOR THE ANTIRETROVIRAL TREATMENT OF HIV-1 INFECTION: A TREATMENT OUTCOMES MAXIMIZATION APPROACH BASED ON STAKEHOLDER OBJECTIVES AND PREFERENCES

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ABSTRACT

This study examined the optimization of formulary decisions concerning the selection of therapeutic options for reimbursement. It sought to identify an appropriate procedure to facilitate formulary decision making and guide healthcare policy in satisfying multiple therapeutic objectives representing an acceptable level of healthcare outcomes to be achieved with respect to the values and preferences of stakeholders.

Multiattribute decomposition measurement and goal-programming methods were combined to optimize the selection of antiretroviral agents used in the treatment of HIV-1 infection. The case study method employed focused specifically on the antiretroviral treatment of an asymptomatic, treatment-naive HIV infected population with regard to the achievement of defined therapeutic objectives, and subject to clinical management decision constraints.

The research questions were studied through the development and validation of a goal programming formulary decision model specific to the selection of evidence-based antiretroviral pharmacotherapy aimed at optimizing health outcomes through formulary reimbursement policies. The optimization of health outcomes was defined in terms of maximizing the achievement of therapeutic objectives.

This study identified an optimal formulary selection reimbursement policy, determined its corresponding funding requirements, and quantified the tradeoffs made in defining the patient-specific optimal therapeutic selection under conditions of unrestricted cost-based reimbursement.

The study also examined the potential impact of restricted drug formulary reimbursement policies on the maximal achievement of therapeutic objectives and related health outcomes by quantifying the magnitude and extent of tradeoffs required to compensate for shifting optimal solutions when progressively restricted cost-based constraints on reimbursement were introduced.

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CHAPTER 1

INTRODUCTION

Over the past 10 years, annual provincial drug benefit plan cost increases have averaged 18% per year while private sector drug plans have been reporting cost increases averaging 15% annually, far in excess of changes in the consumer price-index.[1,2] Johnson and Bootman (1994) suggest that the greatest challenge of the next decade will be making the best use of limited available resources to attain the highest quality healthcare for the lowest cost. In the struggle to control the rapidly escalating costs of drug benefit plans, drug plan sponsors have increasingly been forced to implement a variety of cost-control measures in administering and designing drug benefit plans. One principal method of controlling drug benefit plan costs has been the implementation of restricted formularies which are essentially lists of pharmaceutical products that a given health benefit plan will choose to reimburse plan enrollees for the treatment of specific conditions based on their therapeutic value and cost.[3,4]

According to McElwain (1993), the major points of contention concerning the implementation of formularies relate to their impact on the quality of patient care and total healthcare costs. Rucker and Schiff (1990) advocate that paramount of the organizing principles of a drug formulary is to "maximize cost-effectiveness and benefits by excluding more expensive agents when possible, without compromising patient care." However, an examination of the literature reveals that the implementation of these restrictive policies has often resulted in paradoxical consequences. While costs associated with the drug plan may in fact decline, unintended negative effects on the achievement of

optimal patient health outcomes, as well as increased total health care costs and increased stakeholder dissatisfaction often result.[5]

Skaar, Oki, and Elenbaas (1992) and Dunne and Soberman (1993) concur that such problems most often are the result of using inadequate decision criteria to support formulary decisions by largely ignoring the benefit profiles of competing drug therapies. Government and private sector third-party payers, and their benefit consultants focusing their formulary design efforts on minimizing drug benefit plan costs is a recurrent theme in the literature.[6] The focus on drug cost often causes formulary decision-makers to eliminate or not list costly, new drug therapies irrespective of the long-term benefits they provide. Brogan (1993) suggests that comparative evaluations of alternate drug therapies that consider drug benefits must be incorporated into formulary decisions to ensure wise spending of healthcare dollars.

In this context, formulary decisions are generally treated as a drug selection problem in which the decision makers essentially rank and select the drugs for formulary reimbursement based on the highest multiattribute ranking which will contribute the most to minimizing the cost of the drug plan. In this scenario, the principal objective consists of minimizing the drug plan costs, with the contributory variable of drug costs being so heavily weighted that the clinical benefit profiles that differentiate the alternative drugs are virtually ignored. However, in a comprehensive review of pharmacoeconomic assessment techniques, Bootman, Townsend and McGhan (1991), and Freund and Dittus (1992) clearly identify the principle limitation of cost-minimization analysis in its fundamental assumption that only alternative drug therapies of equal benefit can be properly evaluated using this technique. In reality, drugs in a given therapeutic class

being evaluated for inclusion in formularies are frequently not of equal benefit. Consequently, this fundamental assumption in cost-minimization analysis with respect to formulary design is almost always violated, rendering this type of analysis inadequate to support formulary design processes and drug selection decisions.

Rucker and Schiff (1990) assert that the application of a carefully designed formulary theoretically provides the foundation for guiding clinicians in choosing the safest, most-effective agents for treating particular medical problems. They suggest that the objective of drug formularies should be the promotion of rational drug therapy that minimizes social cost through the maximization of cost-effectiveness and health benefits without compromising patient care. While this notion is generally accepted in theory, its real world promise has yet to be realized.

If maximizing cost-effectiveness of a formulary relates to deriving the maximal health outcome benefits for a given level of resources, four observations can be made. The first relates to the notion that any given formulary should satisfy at least one therapeutic objective such that resulting health outcomes achieve an acceptable level of healthcare. The second relates to the reality that health care decisions are almost always characterized by multiple therapeutic objectives. The third observation relates to the fact that stakeholder preferences, whether patient, physician, or formulary decision maker, vary across each of these distinct attributes. The fourth and final observation highlights the linear relationship between health outcomes and health expenditures alluded to in Montague et al (1997), where health care expenditures are limited and act as a constraint rather than as sole measure of a formulary's effectiveness.

This study approaches the formulary drug selection problem as a multiple criteria decision making problem, where an appropriate and comprehensive decision analytic framework is developed to optimize the achievement of multiple therapeutic objectives subject to budgetary constraints. In setting objective levels of particular decision attributes such that they contribute to the realistic achievement of defined goals, the preferences of stakeholders in the formulary decision process must be taken into account.

This study necessitates that a decision framework be developed and tailored to the specific complexities inherent in a particular therapeutic/disease scenario. For the purposes of this study, the antiretroviral drug therapy class used in managing HIV infection has been selected. The HIV antiretroviral drug therapy class provides an interesting case study in which to study and evaluate the proposed formulary design framework that forms the basis of this research because of the recent convergence of drug-plan cost expansion and critical health-outcomes maximization issues. However, it is thought that the general approach in developing the formulary decision framework could be adapted and applied to other therapeutic areas.

Until recently there were very few therapeutic options available to people living with HIV/AIDS and the efficacy of the available agents as well as the knowledge to clinically manage this disease was extremely limited. However, since 1996 a number of new therapeutic agents, including protease inhibitors, have been made available in Canada and abroad to these individuals with generally very positive results leading to decreased morbidity and mortality, as well as hospitalizations.[7] Despite rising reports of HIV infection, disease progression to AIDS has leveled off in the period 1993-1995, and has shown a decline in 1996 for the first time in Canada. Additionally a 20-30% decline

in deaths attributable to AIDS has been reported. Health Canada attributes these dynamics to the effect of new therapeutic and prophylactic regimens, and improved overall management of persons living with HIV.[8]

However the provision of these agents and their appropriate management to achieve the desired health outcomes for a growing population is very costly. In fact Highleyman (1997) sites numerous U.S. studies which demonstrate a two to three fold increase in HIV antiretroviral drug plan costs as patients make more extensive use of new combination drug regimens. In Canada, given the catastrophic nature of HIV disease, antiretroviral therapy is largely subsidized or provided free to a rapidly growing afflicted patient base by provincial drug plans with little or no restriction.

However, a number of factors are diminishing the financial ability of drug benefit programs to sustain the current level of benefits and could cause the optimal allocation of limited health care resources in this area to become increasingly important in the very near future. These factors include an expanding treatment-seeking patient base, numerous new and expensive antiretroviral agents coming to market, and increasingly complex and costly drug regimens being advocated by treatment experts.

In seeking to support appropriate prescribing, the primary objective of this study was to identify the optimal formulary drug selection solution or policy to optimize therapeutic objectives and related health outcomes with respect to antiretroviral agents used in the initial treatment of asymptomatic, treatment naive persons infected with HIV. This objective was achieved through the formulation and solution of a weighted goal-

programming formulary design model specific to the selection of evidence-based antiretroviral pharmacotherapy combinations.

A secondary objective of this study was aimed at identifying and quantifying the impact of cost-based restricted reimbursement policies on the optimal selection of antiretroviral agents used in the treatment of HIV as well as the potential consequences of such policies with respect to the achievement of optimal health outcomes.

This study is organized as follows. The next two chapters review formulary decision making, and the use of HIV antiretroviral therapies. Chapter 4 presents the research questions, and the decision problem studied. Chapters 5 presents the experiment and methods supporting the formulation of the goal programming model utilized in structuring and solving the decision problem. Chapter 6 analyses and discusses the results of the experiment. The conclusion and suggestions for further research are presented in Chapter 7.

CHAPTER 2

FORMULARY DEVELOPMENT AND DECISION MAKING

Formulary development is the process by which a formulary, a preferred list of drug products reimbursed by a particular drug benefit plan, is constructed and continuously revised to reflect improvements in available marketed therapies based on clinical experience and scientific data.[9] The application of a carefully designed formulary theoretically provides the foundation for guiding clinicians in choosing the safest, most effective agents for treating particular medical problems.[10] The concept and use of drug formularies in fostering rational prescribing can be traced back several centuries.[11]

Historically, formularies have been used in a hospital setting to improve prescribing behavior by directing prescribing to the drugs selected by a pharmacy and therapeutics (P&T) committee or the medical staff.[12,13] However, the formulary concept has expanded beyond institutions to include managed healthcare groups and government sponsored drug programs such as Medicaid in the United States and the provincial drug plans in Canada as a principal method of cost-containment.[14,15,16,17,18]

In Canada, provincial governments, on behalf of their beneficiaries, represent the largest purchasers of drug products and nearly all employ formularies in identifying which drugs will be reimbursed for their respective eligible populations. As such, decisions regarding drug reimbursement through formulary drug selection are made at the provincial level by independent review committees that advise their respective Ministries of Health regarding the addition or deletion of formulary items.[19]

Whether in the government or private sector setting, drug selection in formulary development, like other healthcare resource allocation decisions, is complex because formulary decision makers must simultaneously achieve multiple quality and cost-containment objectives in an environment of competing interests with limited information, resources and ability to analyze the complex environment.[20,21] Further complications and controversy stem from the fact that associated costs and benefits are not generally expressed in terms of dollar figures or program budgets. Instead, the real costs of healthcare interventions are viewed as the opportunity costs in terms of the health outcomes achievable from other programs foregone by committing resources to the programs or interventions in question. In other words, the lives saved and diseases cured must be comparatively evaluated against the lives that could have been saved and the diseases that could have been cured had the resources been allocated differently.[22]

2.1 Drug Formulary Objectives and Restrictions

As an effective cost-control measure, the formulary's primary purpose is to direct prescribing behavior towards improving therapeutic outcomes, while controlling costs.[23] It is important, however, to distinguish between quality and cost objectives as the raison d'être of a formulary. In trying to respect fixed drug budgets, P&T committee members often focus on their cost-cutting objectives, resulting in confusion about the primary purpose of their formulary, and increased antagonism and resistance between those making formulary decisions and those clinicians and patients bound by them.[24]

Rucker and Schiff (1990) identify the basic objectives and operational requirements of an effective formulary (outlined in Table 1). Their basic objectives 3 and

4, as well as their operational requirements 2, 3, and 4 reflect some of the basic rationale and methods of restricting formularies.

Table 1: Characteristics of an Effective Formulary

Basic Objectives: 1. Specify drugs of choice as determined by relative safety and efficacy. 2. Include second-line alternatives in categories where needed 3. Minimize therapeutic redundancy by excluding superfluous/inferior preparations. 4. Maximize cost effectiveness and benefits by excluding more expensive agents when possible without compromising patient care
Operational Requirements: 1. Content and procedures determined by representative group of knowledgeable physicians and pharmacists 2. Deletion/addition decisions based on criteria consistent with scientific information that supports basic objectives 3. Newly marketed products added when evidence of unique therapeutic contribution is accumulated. 4. Non-formulary orders permitted only under well-controlled protocol. 5. Communication methods support user productivity and understanding. 6. Adequate administrative support.

Adapted from Rucker T.D., Schiff G. (1990). Drug Formularies: Myths-in-Formation. Medical Care, Vol.28, No.10, p.929.

The more drugs are excluded for reimbursement, the more 'restricted' the formulary. Whether aimed at cost containment or directing prescribing behavior, the resulting impacts of formulary restrictions and their associated methods of restriction have become the subject of increasing scrutiny and controversy. For a formulary restriction to be considered cost effective, the total healthcare costs of treating patients, including hospitalization and other medical services, after the exclusion should be less than the total cost of the patient treatment mix prior to the restriction. An extensive and growing international literature questions the effectiveness of restricted drug formularies both as a means of containing drug and/or overall healthcare costs and in promoting optimum patient care. [25]

Rucker and Schiff's fourth basic objective relates to maximizing cost-effectiveness, a frequently recurring theme in the formulary literature. Doubilet, Weinstein, and McNeil (1986), however question the precise definition of "cost effectiveness" as a description of a medical practice's associated costs and benefits. The generic term "cost effectiveness" can be misleading as it is frequently used to describe strategies that are "cost saving," "effective," "cost saving, with an equal or better health outcome," or "having an additional benefit worth the additional cost." The distinctions between these meanings are critical in defining the objectives and decision criteria used in designing a formulary. They assert that appropriate use of the term cost-effective must take into account both costs and effectiveness, as well as the critical inherent tradeoffs between costs and effectiveness. Consequently, they recommend that the term "cost-effective" be restricted to situations where a given medical practice offers additional benefit worth additional cost with respect to the available alternatives.

2.1.1 Restricted Formularies in Guiding Appropriate Prescribing

Nash, Catalano, and Wordell (1993) identify three basic types of formularies that vary in terms of their degree of restriction on prescribing. These include:

1. Open and unrestricted formularies which place no limits on which drugs can be prescribed;
2. Mixed formularies in which selection is unlimited but where generic substitution is permitted; and
3. Closed or restricted formularies that are strictly controlled in which only certain pharmaceuticals are reimbursed and therapeutic substitution with the most recognized agent within a pharmacological class is standard procedure.

The restricted formulary is an accepted method of achieving safe, effective, and cost-conscious use of medications for patients in the hospital setting as reflected by the considerable literature detailing the operation of formularies in the institutional setting[26]. While the hospital based formulary literature documents the high level of acceptance and many examples of formulary restrictions resulting in successful maintenance of patient care and achieving cost savings, literature concerning jurisdictional formularies in the outpatient setting is generally less positive.[27]

While the original intentions of the formulary system are to improve prescribing and minimize drug therapy costs, there is limited evidence to support the success of traditional formularies in achieving these goals in the outpatient setting.[28] Rucker and Schiff (1990) concur that the promise of rational prescribing of the drugs of choice has yet to be realized.

McElwain (1993) traces the major points of contention regarding restrictive formularies to the appropriateness of therapeutic substitution and the resulting effects of substitution on the costs and quality of patient care. He cites differences in the operational setting of a formulary, inpatient vs. outpatient, as well as failure to consider predictable inappropriate therapeutic-substitution behaviors as major weaknesses of restricted formulary programs. Kozma, Reeder and Lingle (1990) also site differences between relatively controlled hospital settings and outpatient settings in achieving the actual vs. intended objectives of a formulary.

In their comprehensive examination of the effects of formulary restrictions on patient care, Soumerai et al. (1990) list the following situational factors that cause

hospital formularies to be more accepted and potentially more successful than jurisdictional formularies.

1. Prescribing physicians in a hospital setting have shared goals/incentives and are more likely to sympathize and comply with, as well as reap the benefits of cost containment objectives of their local hospital, than of a government setting jurisdictional formulary policies.
2. Hospital formularies are more likely to be supported with in-service education and administrative control designed to minimize the problems of sub-optimal therapeutic substitution due to formulary restriction.
3. Patients in a hospital setting generally face acute conditions and require a more restricted set of medications than the more heterogeneous outpatient population using jurisdictional-wide formularies, where the chronic use of drugs highlights the importance of patient tolerance of and compliance with certain medications.

In healthcare research, efficacy is defined as proof of an intervention's therapeutic value supported by well defined clinical trials for a restricted patient population in a highly controlled setting; whereas effectiveness relates to the degree of efficacy of a therapeutic intervention in the whole population at risk in an uncontrolled real-world setting.[29]

These distinctions and factors highlight that in order to be effective in directing prescribing behavior to "effective" rather than simply "efficacious" products, formularies need to be tailored for a specific institution, organization, or population, and should be supported by appropriate education and communication strategies.[30,31]

2.1.2 Restricted Formularies in Cost Containment

McElwain (1993), Nash, Catalano, and Wordell (1993), and Kozma et al. (1993) identify the most prevalent restrictive formulary based cost-containment strategies. These include:

1. Delisting non-essential drugs from the formulary;
2. Rejecting newly marketed products for formulary addition until evidence is presented documenting "unique" therapeutic contributions;
3. Developing and implementing restrictive and monitored drug policies or treatment protocols for expensive and high-risk drugs;
4. Curtailing the use of non-formulary drugs;
5. Generic and/or therapeutic substitution.
6. Delaying the addition of new drugs, despite evidence of clinical benefit, to defer costs of new medications.

Formulary advocates defend rejection and delisting decisions to exclude superfluous or inferior medications, and restricted policies guiding the use of expensive and high-risk drugs as legitimate parts of a process to encourage evidence supported rational prescribing.[32] Conversely, formulary opponents question the long-term impact of such restrictive policies citing evidence that patient health status levels often fall while the total costs to the health care system and taxpayers, overall private sector sponsored health benefit costs, and costs shouldered by employers with respect to increased absenteeism and decreased productivity all increase thereby offsetting the reduced cost of the drug plan. [33,34, 35, 36,37]

Soumerai et al. (1990) comprehensively examine the impact of eliminating a large number of prescription drugs that were judged to be ineffective or marginally effective from the formularies of Medicaid and other public programs in the United States. Their findings indicate that while both desirable and unimproved therapeutic substitutions resulted, curtailment of reimbursement for those agents did not necessarily reduce either drug costs or total healthcare costs. They further suggest that supplementing restrictions

with education is necessary to promote practices that are more therapeutically and economically more appropriate.

Delays in formulary listing, usually caused by unreasonable lengthy approval process requirements and/or by conscious decisions to defer the cost of new medications, are equally criticized by pharmaceutical industry representatives and formulary advocates in the medical community alike, for both harming the quality of patient care, and for denying the cash flow rewards to firms that have invested in these medical advances. In spite of this, such intentional delays appear to be increasing in frequency in Canada, as drug plan managers are increasingly finding that the deferral of new listings is one of the only expenditure management options open to them. [38]

In their 1994 study of issues influencing new drug submission listings on the Ontario Drug Benefit formulary, Benjamin and Katsanis examine the interrelated issues of ambiguity in drug listing decision criteria, envelope or "silo" budgeting, cost-containment, fears of market expansion, with respect to formulary listing delay tactics. Their study reveals that:

1. Both price and overall cost to the drug budget were identified by both government and industry representatives as the main formulary decision making criteria;
2. A general perception exists among pharmaceutical industry representatives that contrived provincial government concerns regarding safety and efficacy are used to reject or delay listings due to cost concern issues and fears of market expansion;
3. While government representatives assert that economic information must be reviewed in order to protect consumers/tax payers' interests, they are ambiguous in identifying which specific criterion are critical in decisions, giving credence to industry claim that the demand for economic analysis is being used to create additional delays in listing drugs;

4. Due to envelop budget cutting, government objectives have shifted from maximizing cost effectiveness to maximizing cost-savings or cost-minimization, a condition viewed as unfavorable to listing new more effective, though more expensive therapeutic agents;

5. Where governments' publicly stated objectives are to maximize cost-effectiveness or value for the money,[39]" of their formulary, their actual formulary decision criteria is aimed at minimizing cost. This is indicative of a lack of transparency in the decision making process, as well as inconsistencies between the types of information that government requests from the pharmaceutical industry in terms of demonstrating cost-effectiveness and the types of evidence that will result in achieving listing;

6. The Ministry of Health allocates separate (silo) budgets to each department administering a particular aspect of the healthcare system. While each department is fighting for a bigger piece of the pie, there is no incentive or mechanism either to track or transfer funds or costs savings between departments.

This raises an important issue: is drug market expansion a negative consequence to be avoided? The cost-containment focused government position advocates that market shifts and market expansion is often not attributable to increased beneficial effects, but are rather the outgrowth of the pharmaceutical industry's marketing and publicity campaigns to expand overall use of drugs and to switch utilization from older, low-cost, generic drugs to newer and more expensive brandname drugs. Conversely, the industry position counters that pharmaceuticals remain the most cost-effective therapeutic modality known to modern medical science[40] and that market expansion translates into more people being treated, saving money in the long-run through preventive medicine.[41] The answer lies somewhere between the two diametrically opposed positions, and is the subject of world-wide debate and research.[42]

2.2 Impact of Formularies on Drug Plan and Total Health Care Costs

In theory, perfectly operating restricted formularies eliminate only those redundant drugs for which lower cost substitutes are available, forcing physicians to

prescribe more "efficient" drugs in order to save money. When formularies fail to operate perfectly, they do more than simply exclude patients from receiving high priced duplicate goods. They set off a chain reaction of unintended effects, that potentially compromise the quality of patient healthcare and often cause total health care costs to rise rather than fall in a phenomena that Moore and Newman (1992) refer to as the 'service substitution effect.' This effect causes the actual outcome of a restricted formulary to differ from the intended outcome and is the direct or indirect consequence of two factors. 1) As a method to correct what is viewed as a market failure or deviation from ideal medical practice, formulary restrictions often function worse than the supposed defect of the market failure or treatment deviation that they are supplanting. 2) The degree of "drug efficiency" that formulary restrictions seek to increase is difficult and costly to predict as patients vary and frequently respond differently to drugs.

While there are numerous studies evaluating the effectiveness of formularies in cost-containment in the United States, there is no published literature in Canada replicating those U.S. Medicaid studies. However, the theoretical issues faced by Canada's pharmacare programs are similar to those in the United States.[43]

Jang (1988) comprehensively reviews a number of state-specific studies conducted in the United States, evaluating the short term effects of state Medicaid programs moving from open to more restricted formularies. Studies that focused solely on the effects of restricted formularies on prescription expenditures reported mixed results. While he criticizes some of the earlier studies in terms of weaknesses in their methodologies, most, but not all, of the studies concluded that restricted formularies did reduce Medicaid expenditures on pharmaceutical services. However, many of these

studies also noted that the change in degree of formulary restriction had significant increases on other parts of the total Medicaid budget. Jang concludes his review by stating that formulary restrictions often cause dynamic changes in the total Medicaid program of a complex and costly nature and require considerable careful thought and analysis prior to implementing such restrictions.

Glennie et al. (1993) corroborate Jang's findings citing evidence that lower drug expenditures accrue in hospitals that utilize restrictive drug formularies. However, they highlight that the impact of such restrictions on the quality of pharmacotherapy is less clear and still debated. In their 1990 analysis of US Medicaid drug formularies, Kozma, Reeder and Lingle concluded that the various aspects of healthcare are interdependent; therefore policy makers' tendency to minimize expenditures in each program area contributes to overall suboptimal allocation of resources.

In attempting to refine and analyze the interrelationship of prescription drug availability and the use and cost of other services, Moore and Newman (1992) studied the long-term effects of restricted formularies on the total Medicaid healthcare expenditures as well as on prescription drug expenditures. After accounting for differences with regard to recipient population, economic conditions, and other cost-containment environment characteristics, they found that restrictive formularies did lower prescription drug expenditures per capita by 13.4%. However, they found no significant impact on total Medicaid expenditures, as the savings in drug expenditures were completely offset by service substitution elsewhere in the system. They conclude that the implementation of formulary restrictions does not save money when the impact of a restricted formulary on total healthcare costs is considered, and to the extent that formulary restrictions entail

administrative costs, the adoption of such a policy might actually increase overall Medicaid expenditures.[44]

2.3 Formulary Decision Making

The contradictions in the literature regarding the ability of formularies in either managing healthcare costs or optimizing patient outcomes reflect limitations in the processes and analytical frameworks that currently support formulary decisions.[45] Faced with inadequate formulary design and decision support methods, payers struggle to manage drug budgets through short-sighted restrictive measures that deny patients and clinicians access to proven therapies, often compromising the delivery of optimal health outcomes, and increasing total healthcare costs.[46,47]

Cano and Fujita (1988) characterize the process of formulary decision making as being "very subjective" and prone to resulting in hasty, emotional, and ill-advised decisions in the absence of comprehensive and well documented drug evaluation. They further promote the belief that an objective and comprehensive means of evaluating drugs for formulary purposes is required.

Drummond, Stoddart, Labelle, and Cushman (1987), also acknowledge the subjectiveness of the formulary evaluation process. They relate that choices in health care, whether in health policy planning or treatment mode, inevitably involve value judgements and indicate the importance of acknowledging this reality and explicitly identifying these values when possible.

Eddy (1990) reports that the quality of medical care is determined by two main factors: the quality of the decisions that determine what actions are to be taken, and the quality with which those actions are implemented. If the wrong actions are taken, the quality of care will suffer. Similarly, if the correct actions are chosen but the execution is flawed, the quality of care will suffer.

He further states that the goal of health practice decisions should be to select the action that would most likely deliver the outcomes that patients find desirable, whereas the decision process consists of first, estimating the outcomes of the alternative practices; then comparing the desirability of each outcome. The comparisons involved in the second step consist of:

1. Comparing the benefits of a practice with respect to the harms;
2. Comparing the health outcomes with respect to the costs that have to be paid;
3. If resources are limited and it is not possible to do everything, the amount of benefit gained and the resources consumed by a practice must be compared with respect to other practices so as to give priority to those practices that have the highest yield.

2.3.1 Formulary Drug Selection Decision Methodologies

In theory, formulary decisions based on cost minimization analysis (CMA) are relatively simple: the least expensive but equally effective agent is chosen for approval.[48] Whether, selected agents are truly equally effective in actual decision making is debatable, given the magnitude of service substitution effects and the formulary/expenditure paradoxes explained by Moore and Newman (1992) and reviewed by Jang (1988). The appropriate selection of "effective" agents often depends on subjective judgements concerning the actual treatment objectives, acceptable standards of

medical practice, the ability to achieve various health outcomes in an uncontrolled real-world setting, as well as value placed on the various health outcomes as viewed by patients, healthcare providers, and policy makers.

Drummond, Stoddart, Labelle, and Cushman (1987), advocate an alternate view of the formulary evaluation process where the primary focus should fall on an examination of the marginal costs and benefits, rather than those of the whole healthcare activity. They believe that in the health care field there is a mistaken tendency to present choices on an absolute all or nothing basis, whereas the real relative decisions must determine how much of a given intervention ought to be delivered to a particular individual patient or population. However, they fail to present any decision analytic model or method that can be used to facilitate such an examination of the marginal costs and benefits.

In their 1988-formulary analysis of third-generation cephalosporins, Cano and Fujita advocate the use of using decision analysis as a method of supporting objective formulary review to promote rational drug prescribing and achieve cost savings. Decision Analysis has been defined as "a systematic approach to decision making under conditions of uncertainty" where decision-makers must select from numerous alternatives in achieving multiple objectives.[49] The selection should be based on the probability of the possible consequences of each alternative and the decision-makers' preferences for those consequences.[50] Glennie et al. (1993) also note that the use of clinical decision analysis is worth consideration in the formulary development process. Kresel et al. (1987) demonstrate the use of decision analysis in supporting drug selection decisions for formulary addition applied to primary antimicrobial therapeutic regimens. Freund and

Dittus (1992) advocate the use of decision trees, influence diagrams, Markov processes, and logical networks in developing comprehensive modeling frameworks to support economic analyses of drug therapy to examine the benefits and costs of alternative possible decisions.

Multiattribute utility theory (MAUT) provides a procedure for identifying, characterizing, and comparing many variables that may influence a decision. Nash, Catalano and Wordell (1993) as well as Bootman, Townsend and McGhan (1991) suggest the use of MAUT as a systematic approach that provides a common basis for measuring and comparing dissimilar variables involved in the formulary decision making process. Schumacher (1991) demonstrates the use of MAUT evaluation in formulary decision making as applied to calcium-channel blockers in the single agent treatment of chronic stable angina in ambulatory patients for one year based on effectiveness, safety, patient acceptance and cost decision attributes. The steps used by Schumacher in his application of MAUT to formulary decisions are listed in Table 2 on page 22.

Table 2.

Steps of the Multiattribute Utility Theory Decomposition Method	
1.	**Determine the viewpoint of the decision-makers.** Who are the decision-makers?
2.	**Identify the decision alternatives.** What alternatives (e.g. drug products) are to be compared?
3.	**Identify what attributes are to be evaluated.** What variables (e.g. safety, effectiveness, and cost) are to be considered in evaluating decision alternatives?
4.	**Identify what factors are to used in evaluating the attributes.** What factors (e.g. frequency of adverse reactions as a measure of the safety attribute)?
5.	**Establish a Utility Scale of 0-100 for scoring each factor.** What range of values for each factors represents the worst (0) to best (100) plausible scores?
6.	**Transform the values for each factor to scores on its utility scale.** Where does the value for a factor (e.g. drug cost per month) fit on the 0-100 scale.
7.	**Determine the relative weight for each attribute and factor.** What is the relative importance of each attribute and factor in the decision process?
8.	**Calculate the total utility score for each decision alternative.** For each alternative, sum the utility scores or each attribute multiplied by its weight.
9.	**Determine which decision alternative has the greatest total utility score.** The alternative with the greatest total utility score is the best choice, given the attributes, factors, and weights selected for the evaluation.
10.	**Perform a sensitivity analysis.** Vary the weights of the attributes, and perhaps the scales for the some of the factors, to see if the decision changes.

Adapted from Schumcher 1991.

2.3.2 Traditional Decision Criteria: Safety, Efficacy, and Cost

On the basis of three primary parameters, safety, efficacy, and cost, Hanson, Shepherd and Pleil (1992), and Shepherd and Salzman (1994) cite evidence that efficacy is considered the most important of the three parameters among P&T committee members in the United States. Cost and adverse effects, although important, appear to carry less weight in the decision making process.

However, their findings are countered by empirical evidence cited by Sclar (1993), in his testimony delivered to United States Congress Human Resources & Intergovernmental Relations Subcommittee Hearings, relating that the operational objective of government administered health programs and health maintenance organizations (HMOs) is to "minimize pharmaceutical expenditures, and to view pharmaceuticals as an independent line item in a profit and loss statement, rather than as an essential and interactive component in a global health budget," reflecting a primary focus on cost.

In Canada, there appear to be variations in the perception of most important criteria for government formulary listing. Where pharmaceutical industry representatives cite cost, as well as its impact on the drug budget, as government's deciding factor, government respondents are more inclined to identify both effectiveness and cost as equally important criteria.[51]

In can be argued that safety and efficacy for any particular drug have been already been established by the time it is approved for sale by the Food and Drug Administration (FDA) in the United States, or by the Health Protection Branch (HPB) in Canada.

However, in designing formularies, P & T committees comparatively evaluate safety and efficacy, as well as cost, between agents in a particular class with respect to the treatment indication that the manufacturer is submitting for formulary acceptance. This differs from FDA and HPB approval that is concerned with the safety and efficacy of individual pharmaceuticals with respect to the manufacturer's labeled use or indication.

Pharmaceutical drug prices are also monitored and regulated in Canada by the Patented Medicine Prices Review Board (PMPRB) to ensure that prices of patented medicines charged by the patentees are not excessive with respect to the established guidelines. The PMPRB guidelines evaluate the price of the medications with regard differences in efficacy, safety, time required to achieve optimal effect, length of treatment, percentage of the population treated effectively, success rate, and degree of technological innovation.

Because cost-containment is a major reason for maintaining a restricted formulary, a pharmaceutical's cost relative to other comparable agents within a therapeutic class is a very important consideration taken into account in deciding whether or not to list a particular product. Formularies generally reduce drug expenditures by selecting less costly medications, theoretically, without compromising patient care.[52]

However, market prices generally reflect an amalgam of the valuations consumers place on goods and services and their alternative uses.[53] So by eliminating more expensive drugs, it can also be argued that decision-makers are often trading-off therapeutic benefits valued by patients to reap cost savings and should ensure that they

are not sacrificing quality below accepted standards of medical treatment solely for the purpose of minimizing costs.

2.3.3 Effectiveness and Other Important Drug Selection Criteria

The importance of appreciating the difference between drug efficacy (how the drug performs under carefully controlled conditions) and drug effectiveness (actual performance in clinical practice) cannot be overstated.[54]

The nature of systemic inefficiencies must be considered in formulary decision making process for two reasons. 1) The efficacy demonstrated in clinical trials may not be achieved in actual clinical practice due to those systemic inefficiencies. 2) A critical assumption is that resources saved by selecting efficient healthcare interventions will be appropriately used in other efficient healthcare programs. "However if these resources are instead wasted, society may realize an increase in cost without a corresponding improvement in healthcare."[55]

Shepherd and Salzman (1994) pay particular attention to the ease of product use by both the patient and health care provider and demographic characteristics of a particular patient base as important determining factors of patient compliance and effectiveness that should be taken into account in making formulary decisions.

2.3.4 Use of Pharmacoeconomic Data in Drug Selection Decisions

As pressure to control the costs of drug benefit plans continues to grow in Canada, pharmacoeconomic analyses, which include cost-benefit, cost minimization,

cost-effectiveness, and cost-utility analyses, are increasingly stressed in the selection of pharmaceutical products for listing on formularies. Pharmacoeconomic analyses are aimed at evaluating the costs and consequences of drug therapy to healthcare systems and society. These types of analysis are appropriate and useful only after having established the safety, efficacy, and availability of the intervention in question.[56]

In the larger context of formulary design, pharmacoeconomic analyses are of limited use to the decision maker because, even in the context of the most comprehensive cost-effectiveness and cost-utility analyses, individual drugs are evaluated against a single comparator rather than being studied in the context of all relevant therapeutic options available within a given system. Furthermore, the data utilized is most often based on that of randomized controlled clinical trials over a limited set of homogeneous patients rather than targeted to the population characteristics for which the formulary is designed. The net result is that the "average" formulary is designed for the "average" patient, while the actual needs of individual patients who deviate from average are not fulfilled leading to suboptimal outcomes and increased total healthcare costs for the population as a whole.

Healthcare resource allocation decisions must be made on the basis of limited resources, imperfect information, and difficult tradeoffs, supported by less than perfect analytical methods and models. Weinstein and Stason (1977) assert that imperfect analyses are preferred to no analyses at all in supporting complex resource allocation decisions. However, they do concede and caution that because the conclusions of the most comprehensive analyses rest on uncertain data and subjective values, even with all

possible sensitivity analyses, flexibility should be maintained in making and interpreting resulting policies.

2.3.5 Use of Sensitivity Analysis in Drug Selection Decisions

In the context of any modeling framework, the issue of uncertainty in the data, or its interpretation, must be addressed. The standard method of evaluating the impact of uncertainty regarding any particular parameter or combination of parameters on the conclusions derived from a given modeling exercise is to conduct sensitivity analyses.[57] Detsky (1993), and Briggs, Sculpher and Buxton (1994) emphasize the importance of sensitivity analysis in "assessing the robustness of the qualitative conclusions while identifying areas where more research is needed to precisely estimate the values of 'sensitive' variables." While Briggs et al. suggest numerous types of sensitivity analysis that can be conducted to evaluate various sources of uncertainty, they do not present a comprehensive decision framework within which these types of analysis can be applied to specifically support the formulary decision process and carried out practically.

Another area of particular concern with regard to the use of pharmacoeconomic methods in making formulary decisions relates to the limitations of methods in systematically handling uncertainty with respect to achieving desired therapeutic outcomes and incorporating the conflicting objectives of the various stakeholders in the formulary drug selection process. [58,59] Critics of cost-effectiveness analysis in medical or healthcare decision-making argue that conditions of uncertainty render useless all attempts to quantify the health-related benefits of a given intervention. Its supporters counter that resource allocation decisions must be supported by a coherent analytical

decision making framework incorporating the best available information in conjunction with sensitivity analyses on a range of subjective estimates to account the effects of uncertainty.[60]

This ongoing debate is indicative of a need to develop an integrated formulary decision-making framework so as to improve the processes by which drugs formularies are designed. Such a framework would facilitate the drug selection processes, as well as the evaluation of formulary decisions in achieving explicitly stated therapeutic objectives, the determination of the impact of resource constraints and potential variation of sensitive parameters, as well as the identification and assessment of the resulting trade-off impacts.

2.4 STAKEHOLDERS IN FORMULARY DECISIONS

Given the subjective nature of formulary decision making, Drummond et al. (1987) raise two complex questions:

1. Who should set health service planning priorities? and
2. Whose values should be used in evaluating benefits and making choices?

2.4.1 Formulary Decision Makers: The Role of Policy Makers

In socialized or subsidized medical systems, policy makers and payers are charged with ensuring an equitable allocation of finite healthcare resources among their covered population in an era of continuous healthcare improvement. Continuous healthcare improvement raises the minimal accepted standards of medical practice but comes at a cost that policy makers and payers are not necessarily willing to pay due to budget constraints. Efforts to be equitable to the population as a whole and accountable to taxpayers often results in restrictive policy decisions which sacrifice the healthcare

quality and achievement of optimal healthcare outcomes of individuals. This also highlights the need to ensure that policy decisions are making efficient use of the public purse to maximize whatever health outcomes can be achieved given their constrained nature.

If patients were treated in a world without resource considerations, it would be considered wrong to withhold treatment on the basis of cost. However, as Drummond, Stoddart, Labelle, Cushman (1987) point out a problem arises once resources considerations enter the picture in that if a disproportionately high level of resources is allocated to one patient, someone else will lose out according to both opportunity cost and zero-sum game principles.

Formulary decision-makers are charged with the task of selecting drugs for inclusion in a formulary that will essentially define a practice policy. The process of defining a formulary and therapeutic guidelines requires that time, resources, and analytical skills be applied in order to facilitate the task of the prescribing physician in improving actual patient outcomes.[61]

In the context of the "benevolent dictator" as explained by Keeney and Kirkwoods (1975), and considering the "quality" concept in clinical decision making outlined by Eddy (1990), the formulary decision maker should not only incorporate scientific facts and clinical evidence, but more importantly the personal values and preferences of clinicians and patients.[62]

2.4.2 Healthcare Providers: Physicians and Pharmacists

Attempting to base medical decisions on both health and monetary considerations is a difficult task that raises serious ethical issues. On a basic level, some argue that it is inappropriate for physicians to consider costs and that the ethics of their profession demand that they should do everything that they believe may benefit each patient.[63]

However, Drummond, Stoddart, Labelle, Cushman (1987) point out the distinction between medical decisions made on behalf of an individual patient and those made on behalf of a group of patients or population. In their view, it is entirely consistent for clinicians to give each individual patient as much care as their condition requires, while participating in a decision making process that evaluates competing claims for the allocation of resources or the development of services in consideration of the wider social perspective.

Physicians often view formulary restrictions, mandated generic substitutions and therapeutic interchange as encroaching upon their independent decision-making (Nash, Catalano, and Wordell, (1993)). Some healthcare providers believe that only the clinician caring for the patient can appreciate a patient's unique individual characteristics and thus select the appropriate drug. Any attempt to narrow therapeutic options fails to confront the real world of disease and patient heterogeneity and may ultimately result in causing patients harm.[64,65] However, Rucker and Schiff 1990 counter by asserting that an effective formulary does not constitute a restriction on clinical freedom, but rather acknowledges the reality that each clinician prescribes from a limited subset of 25 to 400 preparations out of the entire universe of available agents numbering in the thousands.

2.4.3 Patients

Cost containment measures that restrict patient access and choice, and control physicians' practices cause the quality of healthcare to stagnate and lead to public dissatisfaction.[66] In a 1996 US national survey of 12 industries, health insurers and managed care organizations ranked third from last in terms of effectively meeting the needs of their customers; with the tobacco industry ranked last.[67]

In order to achieve improved health outcomes and increase patient satisfaction, treatment decisions should be based on outcomes that are important to patients. The logic for this principle stems from the ultimate purpose of all medical practice: to improve and maintain the health of patients. The only way to achieve this is to focus on the health outcomes that patients experience and care about.[68] However, patients, as the ultimate healthcare consumer, frequently do not have the knowledge to make informed decisions. This means that their clinicians become key players as the patients' advocates in determining the demand for care on behalf of their patients in what economists refer to as an agency relationship.[69] While it is possible to find many examples in the literature where the health care provider's values have been assessed and have been proven to vary from the values of the patients, their actions and demands for particular services are a general reflection of patients' demands.[70]

Traditionally, patients have been viewed as a "passive vehicle, whose role is to carry out a specified treatment regimen."[71] However, as health care research expands to examine the patients' contemporary roles in treatment, patients are increasingly being described as health care consumers to be satisfied. Holmes-Rovner, Kroll and Schmitt

(1996) relate the middle ground view that envisions patients and healthcare providers working collaboratively in complex decision environments in selecting appropriately from among treatment alternatives, of which none is perfect in the eyes of patient, provider, or payer.

CHAPTER 3

HIV ANTIRETROVIRAL THERAPIES

3.1 Human Immunodeficiency Virus (HIV) Infection, Acquired Immune Deficiency Syndrome (AIDS), and Disease Progression.

Human immunodeficiency virus (HIV) infection is an infection caused by the HIV-1 retrovirus that progressively destroys white blood cells called $CD4^+$ T lymphocytes, causing acquired immune deficiency syndrome (AIDS) and other related diseases that result from the impaired immunity and increased vulnerability to infection. HIV-1 infection is most common in the Western Hemisphere, Europe, Asia, and in Central, South, and East Africa.[72] However, in certain parts of the world, primarily West Africa, AIDS is most often caused by HIV-2, a related retrovirus that differs from HIV-1 in terms of its genetic makeup as well as its lower pathogenicity.[73] While HIV-2 also represents a significant health problem, this study focuses exclusively on HIV-1 infection.

Bartlett 1997 divides the natural progression of HIV infection into seven distinct stages: 1) viral transmission, 2) primary HIV infection, 3) seroconversion, 4) clinical latency period, 5) early symptomatic HIV infection, 6) AIDS and 7) advanced HIV infection. Please refer to appendix 1A for a description of the characteristics of each disease stage. In the absence of treatment directed at HIV, the entire process of disease progression for an average patient is approximately ten years in duration from seroconversion to death. The average annual rate of decline of $CD4^+$ cells is about $50/mm^3$ and the average viral burden without therapy is 30,000-50,000 copies/ml. The

prognosis in terms of time to AIDS and death increases with a steeper $CD4^+$ decline and a higher viral burden.[74] However, as a consequence of recent changes in the management and treatment of HIV infection, the life expectancy of a patient newly diagnosed with HIV infection may be as high as 15-20 years.[75]

Two important variables that have been found to predict the rate of HIV related disease progression are the viral load and the $CD4^+$ count.[76,77] HIV viral load measures the number of copies of HIV viral RNA/mL and accurately assesses the level of viral replication, as well as its associated rate of $CD4^+$ T cell destruction, as an indicator of HIV disease progression and to facilitate clinical assessment of when to initiate and change a therapeutic regimen.[78,79] Mellors et al (1995) and Mellors et al (1997) research findings continue to support that the key element in HIV pathogenesis is the high level of productive HIV-1 viral infection, measured by viral load testing, and characterized by an intense rate of HIV virion turnover. Minimal estimates derived from kinetic data suggest that at least 10 billion HIV virion particles are produced and destroyed each day by the immune system of an infected person.[80,81] In parallel, $CD4^+$ cell counts reflect the level of immune system damage caused by HIV infection and the level of disease progression characterized by the downward spiral of wasting and the development of opportunistic infections and rare cancers. Because HIV disease is a state of chronic immune activation aimed at fighting HIV infection, productively infected $CD4^+$ cells also experience similarly high turnover rates estimated between 1.8 and 2.6×10^9 $CD4^+$ cells being produced, infected and destroyed each day.[82,83]

3.2 Epidemiology of HIV and AIDS

In December 1997, a United Nations epidemiological study reported that an estimated 30.6 million people, 29.5 million adults and 1.1 million children, worldwide were living with HIV/AIDS. This indicates that approximately one in every 100 adults aged 15 to 49 is infected with HIV, the etiologic agent of acquired immunodeficiency syndrome (AIDS)[84,85,86]. The same report estimates that 5.8 million new HIV infections occurred during 1997; representing a daily transmission rate of 16,000 new infections each day, with more than 90% of these new infections occurring in developing countries.

In Canada alone, the Bureau of HIV/AIDS and STD estimates that as of the end of 1996, a cumulative total of 50,000-54,000 Canadians had been infected with HIV and that 32,000-36,000 are estimated to currently be living with HIV. [87] While the reported numbers of HIV infection continue to rise, the disease progression to AIDS leveled off in the period 1993-1995, has shown a decline in 1996 for the first time. Additionally a 20-30% decline in deaths attributable to AIDS has been reported. Health Canada attributes these findings to the effect of new therapeutic and prophylactic regimens, and improved overall management of persons living with HIV. [88]

3.3 HIV Infection Treatment Objectives and Outcomes

Since 1995, startling advances in understanding the pathogenesis of HIV, the development of new treatment agents, and the development and validation of new-monitoring techniques have made a major impact on the clinical management of HIV infection. Bartlett (1997) identifies the four treatment strategies proven to prolong survival: 1) Antiretroviral therapy, 2) Pneumocystis carinii prophylaxis, 3)

Mycobacterium avium prophylaxis, and 4) care by a physician experienced in treating HIV and AIDS. This research study is concerned strictly with antiretroviral treatment.

In the literature, the primary therapeutic objective relates to durably suppressing HIV viral replication to undetectable levels as long as possible. This ultimately leads to preventing further disease progression, improving the quality of life, and prolonging the survival of afflicted patients.[89,90] An undetectable viral load after 12 weeks of therapy predicts a durable response to that regimen at 24 weeks. This is significant in that an undetectable viral load after 24 weeks of therapy is associated with a decreased relative risk of developing opportunistic infections, improved quality of life, and prolonged survival of afflicted patients.[91,92] Emerging evidence also suggests that complete suppression of HIV viral replication is the mechanism by which the emergence of drug-resistant variants can be prevented thereby allowing the long-term maintenance of these potent antiretroviral regimens and their associated benefits.[93]

3.4 HIV Infection Antiretroviral Treatment Strategies

Markowitz 1996 emphasizes that effective antiretroviral therapy should be introduced early in the disease process. This rationale is based on the premise that treatment is more likely to succeed, with the patient less likely to develop drug-resistance, if treatment is initiated while the viral population is still relatively homogeneous and the treatment consists of multiple, non-cross resistant agents with no overlapping toxicity. Additionally, Ho (1996) emphasizes that the enormous turnover of HIV and the resulting extensive immunological damage being sustained by the patient as massive numbers of CD4+ cells are infected and destroyed each day also supports the rationale of early and aggressive therapeutic intervention in HIV infection. Given the

widespread support of an early intervention HIV treatment strategy, the formulary design exercise to be evaluated in this study will be aimed at supporting this treatment strategy.

3.4.1 Clinical Considerations for Initiating Treatment

Numerous sets of therapeutic guidelines have been developed and published consisting of expert panel based recommendations on the use of antiretroviral agents in treating HIV-1 infection. Most notable of these guidelines are those recently published by the U.S. Department of Health and Human Services (DHHS) which serves as a companion document to the report formulated by the National Institutes of Health (NIH) panel to define principles of therapy of HIV infection summarized in Appendix 2. The purpose of both documents is to translate the dramatic scientific advances in understanding and treating HIV infection into information that health practitioners and their patients can utilize in making informed decisions regarding the use of the new therapies and monitoring tools to achieve the greatest and most durable clinical benefits. As rates of HIV related disease progression vary among individuals, there is consensus in the literature among various sets of antiretroviral therapeutic guidelines that treatment decisions should be individualized by the level of risk indicated by plasma HIV RNA levels and $CD4^+$ T cell counts as listed in Appendix 3.[94,95,96,97]

However, there are other considerations that need to be taken into account in deciding whether or not to begin early intervention therapy in asymptomatic patients. The factors that should be considered are: 1) the willingness of the patient to begin therapy; 2) the risk of disease progression as determined by plasma HIV RNA; 3) the degree of existing immunodeficiency as determined by $CD4^+$ T cell count; 4) the potential risks and benefits of initiating therapy in asymptomatic individuals (listed in Appendix 4); 5) and

the likelihood of adherence to the prescribed treatment regimen.[98] These factors are critical in making appropriate treatment decision as to whether or not to initiate therapy for a given patient. However, this study is focused on the selection and provision of optimal antiretroviral therapy through a formulary based system once the decision has been made to initiate therapy in treatment-naïve patients with asymptomatic HIV infection.

3.4.2 Combination Therapy

Monotherapy with even the most potent antiretroviral agents has been found insufficient to achieve long-term suppression of HIV replication. This is based on inter-related effects of the massive rate at which HIV virions are produced in conjunction with the rapid rate at which HIV-1 viral enzymes generate mutations that cause drug resistance. In other words, the more HIV virions that are produced, the more likely the virus is to mutate and become resistant to drug therapy.

This becomes very important as Abdullah (1997) explains that monotherapy generally requires the virus to make only 1-3 mutations to resist a single drug, whereas three or four drug combinations that attack two or more viral enzyme systems simultaneously require the virus to mutate simultaneously at many more codons to evade drug therapy. As a result, the maximal chance of viral suppression occurs when several potent agents are used simultaneously and the virus remains relatively homogeneous.[99] Incomplete viral suppression of HIV replication in the presence of treatment offers the opportunity for the accumulation mutations that will result in high-level drug resistance to even the most potent drugs available. [100]

In addition, it has been shown repeatedly in clinical trials that treatment with combinations of antiretroviral agents vs. monotherapy leads to more potent and durable HIV suppression as well as improved clinical benefits, decreased morbidity and mortality.[101] Monotherapy antiretroviral treatment is not recommended because it leads to the rapid development of resistance,[102] and thus has been excluded from consideration in this study.

The preferred initial antiretroviral treatment regimen is one that is most likely achieve viral suppression reflected by the reduction and maintenance of plasma RNA levels below the level of detection using the most sensitive viral load tests available. Currently, such a regimen would include 2 nucleoside reverse transcriptase inhibitors (NRTI) and a protease inhibitor (PI) with high in vivo potency.[103] Other important desirable characteristics of drugs that are used in combination antiretroviral therapy include:

- Synergistic or additive anti-HIV activity,
- No cross resistance or overlapping toxicities, antiviral activity in all cellular and tissue reservoirs of HIV,
- The lack of antagonistic and harmful pharmacodynamic interactions between drugs of the antiretroviral regimen and between other important or commonly used drugs.
- Easy to take in terms of tolerability and ease of dose administration and frequency
- (Relatively) low cost[104]

3.4.3 HIV Infection Treatment Options

When initiating therapy in antiretroviral naïve patients, the U.S. guidelines emphasize that one should begin with a regimen that is expected to reduce virus replication to undetectable levels. Based on the scientific evidence presented to date, the preferred treatment strategy to achieve this consists of 2 NRTI's and 1 PI. Alternative

regimens, some consisting of 2 PI's, have also been employed. However, the safety of such regimens has not been demonstrated according to FDA guidelines. For the list of antiretroviral agents for the treatment of HIV infection and the treatment strategies recommended by the US. Department of Health and Human Services treatment guidelines please consult Appendix 5a. The rating scheme for clinical practice recommendations as determined by the panel on clinical practices for the treatment guidelines of HIV Infection, convened by the US Department of Health and Human Services can be found in Appendix 5b.

3.5 Formulary Issues in Antiretroviral Therapy for HIV Infection

3.5.1 Cost Impacts of Advances in HIVAntiretroviral Treatment

The economic burden of HIV/AIDS to Canadian society is massive and continues to grow. If the HIV epidemic remains uncontrolled in Canada, Health Canada forecasts that HIV will cost the Canadian economy as much as $22.2 billion over the next five years. As the epidemic spreads, more cases are being diagnosed, and more people are embarking on more effective, expensive antiretroviral therapeutic regimens and thus living longer. It is estimated that each individual with HIV costs the economy $153,000 in direct healthcare costs such as drugs, hospitalization, ambulatory treatment, diagnostic and laboratory costs, chronic and long-term hospice care; as well as $600,000 in indirect costs associated with the loss of productive members of society.[105]

Traditionally, the overwhelming costs of acute hospitalization and treatment of opportunistic infections, particularly in late-stage disease, have been reported as the major cost drivers in HIV disease.[106] However, with the development and more

widespread use of therapeutic regimens effective in achieving durable suppression of HIV viral replication, and improving measures of immune system function and predictors of clinical disease progression, increasing numbers of patients are being diagnosed and are seeking treatment. In addition, the expansion of HIV treatment guidelines has dramatically increased the intensity and costs of outpatient HIV management. While emerging data reflects a significant shifting of costs from acute hospitalization to drug, outpatient and home care resulting in a net annual savings of 20-30%, concerns about the durability of these treatment effects has in-turn raised concerns that this may be a short-term cost-deferment rather than a life-time cost avoidance.[107]

Combination therapeutic regimens, while more effective, are more expensive than monotherapy regimens. However, Moore and Bartlett (1996) suggested that these costs are likely to be offset by decreases in other healthcare costs associated with a reduced burden of illness if disease progressions can be slowed and survival improved. In their study, Moore and Bartlett projected the costs of antiretroviral therapy in a model to assess the incremental cost-effectiveness of triple combination regimens over monotherapy regimens. Based on a three year increase in the average life-span and only $30,000US of additional healthcare costs, given assumed healthcare offsets, over six years of survival, HIV combination therapy would yield a cost-effectiveness ratio of $10,000 per life-year gained. In the unlikely scenario that there were no other healthcare cost offsets, the incremental cost of combination regimens would yield cost-effectiveness ratio of $18,000 per life-year gained. They conclude that incremental cost-effectiveness compares favorably with respect to other therapeutic regimens used in the treatment of cardiovascular disease, renal failure or cancer prevention.

However, more recently increasing evidence is emerging that supports the notion that more effective therapy will generate cost saving offsets in more expensive health services and lower total healthcare costs. In a study of the John Hopkins AIDS treatment program, acute hospitalizations were reduced by 40-50%. Given that the average hospitalization cost is approximately $10,309US, the offset savings are substantial. At present, hospitalization accounts for 52% of the program's costs and continues to drop due to combination antiretroviral therapy, whereas pharmacy costs account for 19% of costs. Ambulatory clinic care, home care, and chronic care respectively represent 16%, 6%, and 7% of the total program costs.[108] Therefore, they conclude that limiting access to combination retroviral therapy, solely on the basis of drug costs would be short sighted, leading to both greater subsequent costs of care and an increased clinical burden of illness and early mortality that is now avoidable in patients with HIV Infection.[109]

Given the strength of emerging clinical evidence, and revised international, U.S., and the soon to be released Canadian HIV antiretroviral therapeutic guidelines, clinicians are being encouraged to achieve optimal health outcomes by treating infected individuals early and aggressively to suppress HIV viral replication in the hope of preserving cellular immunity, delaying disease progression and death, while hopefully enhancing quality of life. Concurrently, health care payers and providers are being advised to maintain access to effective antiretroviral therapeutic combinations in the hopes of reducing the need for very expensive acute hospitalization, and providing more cost-effective healthcare to their patient populations.[110]

3.5.2 HIV Antiretroviral Treatment Formulary Design Issues

The system cost of any healthcare intervention depends on the product of the intervention cost and the number of people to which it is applied. However, the value or cost-effectiveness of the incremental costs needs to be determined with regard to the benefits derived from the intervention. In addition, the benefits need to be evaluated and adjusted with regard to improvements in survival, quality of life, and patient preferences. In the case of antiretroviral treatment, prolongation of life may be valued differently depending at which point in the disease stage process that it occurs. If the resulting longevity only prolongs suffering, it can be argued that the intervention will be less desirable to patients. Conversely, it is assumed that those patients prefer that life be prolonged at the asymptomatic stages earlier in the disease process.[111]

In designing an effective formulary, it is important to explicitly define the relevant patient population, their and other stakeholder needs, as well as preferences and values in determining the criteria for drug selection decisions with regard to achieving specific therapeutic objectives. This particular study in formulary design is concerned with optimal antiretroviral combination treatment of the asymptomatic, treatment naïve population for whom early therapeutic intervention is advised in an environment of constrained financial resources.

The adoption of arbitrary formulary restrictions based solely on drug acquisition costs in the area of HIV could have potentially devastating consequences because of inter-patient variability in therapeutic response to treatment, ability to tolerate and self-administer complex regimens that vary in terms of adverse drug reactions frequency and severity, and often the prevalence of drug resistant strains of the virus passed on from a

pretreated infection source to a treatment naïve host. The ability of physicians and patients to establish a mutually acceptable treatment plan should not be hampered by the selection of an arbitrary one, two, or three therapeutic combinations to be included in a formulary. The combinations that should be selected for formulary listing should be those that optimally satisfy treatment objectives as valued by a given patient population, in conjunction with their healthcare providers, given resource constraints.

To date, no clinical studies have demonstrated the long-term clinical benefits of combination antiretroviral treatment for patients with $CD4^-$ T Cell counts greater than 500cells/mm^3. However, the scientific research findings of Ho, Mellors. Markowitz and their colleagues, discussed in section 3.4, as well as the 1997 International Aids Society Antiretroviral Treatment guidelines, the NIH Principles of Antiretroviral Therapy, and the most recent treatment guidelines published by the British Columbia Centre of Excellence in AIDS, support early intervention treatment strategies in patients with viral load levels greater than 5000 copies /mL regardless of CD4+ levels based on the rationale that theoretical clinical benefit is likely to be realized. Factors supporting this strategy relate to the presence of a more homogeneous viral population, a more complete lymphocyte repertoire that is more capable of reconstituting the immune system, and an improved ability of asymptomatic patients who are otherwise in good health to tolerate and comply with antiretroviral regimens. In addition, it is hypothesized that early initiation of antiretroviral treatment will render such treatment more cost-effective by prolonging life in the asymptomatic disease stage when it is most valuable and productive to patients.[112]

3.5.3 HIV Antiretroviral Therapeutic Objectives and Constraints

While recognizing the constrained nature of real-world health-care resources, this study aims to identify the optimal selection of antiretroviral therapeutic regimens aimed at maximizing the best available care that can be provided to patients for a given resource level. Consequently, it is important to explore the therapeutic decision objectives that figure prominently in the clinical setting. Therapeutic objectives should be reflected by the formulary decision objectives although they may not correspond exactly due to differences in the purpose, focus and setting of the decision making activity. Based on the therapeutic objectives identified in this section, formulary decision objectives for antiretroviral therapy are defined in Chapter 4 with respect to the decision problem being studied.

In the context antiretroviral treatment for HIV infection, objectives can be defined in terms of efficacy, safety/ tolerability, ease of use, and potential to develop resistance as listed in Table 3. The role of cost also figures prominently among antiretroviral therapeutic issues. However, cost issues are generally treated as constraints rather than objectives. This is based on Drummond et al. (1987) view that in a world without resource constraints it would be unethical to deny patients access to the best available care.

The recent guidelines on the appropriate treatment of HIV infection and AIDS released by the Panel on Clinical Practices for the Treatment of HIV infection appear to concur as they suggest that aggressive anti-HIV therapy should be offered to all

Table 3:

HIV Antiretroviral Therapeutic Objectives	**Sources**
Efficacy:	
1. Achieve maximum durable suppression of HIV replication	1,2,3,4,5,6,7,8
2. Minimize immune system destruction/Maximize immunological benefit	1,4,5,6,7,8
3. Maximize clinical benefit in terms of disease progression and survival.	1,4,5,6,8
Safety/Tolerability:	
1. Minimize the potential of patients developing drug related adverse effects	1,4,5,6,8
2. Minimize the potential of patients experiencing antagonistic or toxic drug interactions	1,4,5,6,8
Ease of Use: Minimize the complexity of the regimen	1,3,5,6,8,10
1. Dosing Frequency	
2. Total number of pills/day	
3. Diet Constraints	
4. Recommendations to minimize adverse effects	
5. Storage Recommendations	
Resistance: Minimize the potential development of viral mutations that result in the decreased susceptibility of the virus to antiretroviral therapy and limit future therapeutic options.	1,3,4,5,6,9
1. Potential for developing resistance	
2. Potential for developing cross-resistance	
3. Downstream therapeutic options in case of treatment failure or intolerance	

***Sources**: 1.) Carpenter et al. (1997), 2.) National Institute of Health (1997), 3.) US Department of Health and Human Services (1997), 4.) British Columbia Center for Excellence in AIDS (1997), 5.) Abdullah (1997), 6.) Bartlett JG. (1997). 7.) Saag (1996), 8.). Grubb and McClure (1997). 9.) Condra and Emini (1997).10.) Williams (1997)*

asymptomatic patients with CD4+ cell counts of $< 500/mm^3$ or with viral load of $>$ 10,000 copies/mL measured by the bDNA test or $>$ 20,000 copies/mL measured by the RT-PCR test. In Canada the most recent antiretroviral therapeutic guidelines published by

the British Columbia Centre for Excellence for the treatment of HIV/AIDS are even more aggressive as their eligibility criteria includes HIV+ patients with CD4+ cell counts of < 500/mm^3 or with viral load of > 5,000 copies/mL. However neither set of guidelines addresses the high cost of treatment.

Cost constraint issues have raised concern among AIDS activist movement that the costs of treatment would render it inaccessible for the majority of afflicted patients. The position of the National Association of People with AIDS on the guidelines states that 'for these guidelines to truly make a difference there must be commitment from both the public and private sector to find the resources to allow all people the ability to access the best treatment available.'[113] This view raises three practical questions that are central to this study:

1. What constitutes "best treatment available?"
2. What is the resource level required to make it available?
3. Does "best treatment" constitute an effective deployment of available resources?

In trying to define "best" or "optimal" antiretroviral treatment for an individual or a population with regard to the efficacy of antiretroviral treatment, there is great consensus in the literature supporting the achievement of maximum durable suppression of HIV replication preferably to undetectable levels as the primary objective of therapy; and hence a key determinant of optimal treatment. The suppression of HIV replication is associated with other treatment goals relating to the prevention of further disease progression, improvements in the quality of life, and prolonging the survival of afflicted patients. However, recognizing the significant limitations of currently available

antiretroviral therapy as well as the difference between efficacy and effectiveness, other factors must be taken into account in decisions pertaining to the selection of "optimal" therapeutic regimens in the context of patient needs and preferences.

These factors include the demands of therapeutic regimens in terms of safety and tolerability, and ease of use, as well as the impact of such regimens on future therapeutic decisions with regard to the development of resistance and cross-resistance between antiretroviral agents.

Patient adherence to a prescribed antiretroviral regimen is critical to achieving success with such therapy. Patient adherence can be enhanced by maximizing the ease of use of the selection of therapeutic combinations so as to enhance patient compliance and decrease the potential of developing resistance by minimizing the complexity of the dosing regimen.[114]

It is also critically important to recognize the tradeoffs between such factors that need to be made in defining "optimal" therapy. For example: a given therapeutic combination may be the most efficacious in suppressing viral replication. However, if a patient cannot tolerate the regimen due to adverse effects, a less toxic regimen carrying less than maximal potency may be more effective in the long term and thus more appropriate. Conversely, if a patient is willing to put up with the side effects and rigors of a complex dosing schedule to obtain maximum suppression of viral replication for a very efficacious therapeutic regimen, this may be the appropriate decision and the most effective treatment option for this particular patient. This highlights Eddy's (1990) view that the objective of health practice decisions should be aimed at selecting the course of

action that is most likely to deliver the outcomes that patients find desirable and value most highly.

3.5.4 HIV Antiretroviral Therapeutic Decision Attributes and Factors

Structuring drug formulary decisions so that critical therapeutic goals are optimized requires the systematic identification, measurement, comparison and analysis of the numerous variables involved in the decision making process. In order to facilitate this process, objectives, decision alternatives and constraints can be represented in the form of decision attributes and factors in accordance with the Multi-Attribute Utility Theory (MAUT) procedure proposed by Schumacher (1991).

Table 4: HIV Antiretroviral Therapy Formulary Decision Attributes and Factors

Attribute	Factor	Sources
Efficacy	1. Viral load suppression 2. Immunological benefit 3. Clinical Benefit Impact (reduced morbidity/mortality) 4. Treatment Guideline Recommendations 5. Strength of Scientific Evidence	1,2,3,4,5,6, 7,8
Safety / Tolerability	1. Potential for Adverse Effects 2. Potential for Drug Interactions	1,4,5,6,8
Ease of Use	1. Dosing frequency 2. Total number of pills per day 3. Diet Constraints 4. Storage Recommendations 5. Recommendations to minimize adverse effects	1,3,5,6,8
Resistance	1. Potential for drug resistance 2. Potential for protease inhibitor cross-resistance 3. Downstream therapeutic options	1,3,4,5,6
Cost	1. Drug Acquisition Costs 2. Drug Monitoring Costs 3. Direct Health Care Costs 4. Indirect Health Care Costs	6,8,9

Sources: *1.) Carpenter et al. (1997), 2.) National Institute of Health (1997), 3.) US Department of Health and Human Services (1997), 4.) British Columbia Center for Excellence in AIDS (1997), 5.) Abdullah 1997), 6.) Bartlett JG. (1997). 7.) Saag (1996), 8.) Grubb and McClure (1997), 9.) Tseng and Fletcher (1997)*

For the purposes of this study, the decision attributes have been defined as a series of therapeutic objectives or goals that can be used to differentiate various decision options under consideration. Each attribute consists of one or more components or factors that can be used to quantify and evaluate the relative contribution of a given attribute in achieving a specified objective within the decision process. The decision attributes and factors used to represent these objectives, decision alternatives and constraints are listed in Table 4 on the previous page. It is from among this list that the relevant decision attributes and factors in formulary decision making were selected for inclusion in the formulation of the decision problem presented in Chapter 4.

Treatment guideline recommendations for various treatment strategies as well as particular treatments can also serve as decision attributes that favor the selection of alternatives supported by appropriate scientific evidence and bear the strongest recommendations of the most recent treatment guidelines.

3.5.5 HIV Antiretroviral Stakeholder Preferences in Therapeutic Decision Making:

As previously stated it is important to incorporate the viewpoints of the multiple stakeholders as they relate to the decision process in question to ensure that all relevant attributes, which vary across perspectives, can be appropriately integrated into the evaluation of alternatives and the decision making process. It is also important to valuate the therapeutic objectives, attributes, factors, and constraints with regard to the preferences of patient and clinician stakeholders as they relate to the decision process in question. This helps to ensure that the values of relevant attributes, which vary across

perspectives, can be appropriately captured and integrated into the evaluation of alternatives in the decision making process.

This is especially important given the limitations of current antiretroviral treatment options in terms of side effects, complex dosing regimens, storage difficulties and cost. While many people have seen the benefits of advances in antiretroviral treatment, not all people living with HIV have benefited to the same degree, whereas some have not been able to tolerate or adhere to these therapeutic regimens and thus have not benefited from the new treatments at all.[115]

In seeking to maximize the effectiveness of these regimens and achieve optimal outcomes for patients, tradeoffs between efficacy for the sake of perceived effectiveness often need to be made. However, because of the complexity of the decision problem, and the ambiguity surrounding the relationship between efficacy and other treatment objectives, such tradeoffs may well compromise the patient's long-term well being if not evaluated carefully. Given the need for such tradeoffs it also is important to weight these preferences with respect to the valuation of health outcomes and treatment characteristics.[116] Patients should be encouraged to take an active role in the treatment decision making process, and necessary tradeoffs in terms of long-term suppression of viral replication must be acceptable to patients in view of the constraints on future therapeutic options.[117]

CHAPTER 4

THE RESEARCH QUESTIONS & THE DECISION PROBLEM

The aim of this study is to investigate the optimization of formulary decisions concerning the selection of therapeutic options for reimbursement. This study attempts to identify an appropriate procedure that can facilitate formulary decision making and guide healthcare policy to maximally achieve therapeutic objectives which contribute to achievement of optimal health outcomes, while incorporating the needs and preferences of stakeholders with regard to therapy. As a result of this procedure, reimbursement decisions in this study are directed towards the maximization of treatment objectives and related health outcomes of a specific patient population, at a given resource level, subject to clinical management or therapeutic objectives, while incorporating the needs and preferences of patients and their healthcare providers. This chapter presents the research questions and the decision problem central to this study.

4.1 RESEARCH QUESTIONS

As previously discussed, one of the primary goals of a formulary is to promote rational prescribing by directing prescribing behavior to the most cost-effective medications without compromising patient care.[118] If this goal is to be achieved and patient care is not to be compromised, prescribing behavior must be supported by a policy that directs such behavior to optimal therapy.

This study approaches the identification of cost-effective medications in two steps. First the relative effectiveness of various therapies under consideration is assessed

and the optimal selections are identified. The second step evaluates the cost levels required to deliver optimal selections for a given population. If various optimal solutions all yield the same level of effectiveness without compromising the level of patient care, the least expensive may then be selected.

This approach is consistent with the goal of patient advocacy and healthcare professionals in providing best care to patients. While recognizing the fact that best care is subjective and must be defined according to stakeholder objectives and preferences, this study attempts to identify the resource levels required to make best care accessible and clarify the tradeoffs that result when resource constraints are introduced.

This study first seeks to identify an optimal reimbursement policy and the corresponding level of financial resources required to direct efforts at maximizing healthcare outcomes as valued by patients their healthcare providers under conditions of no budgetary constraints. The study then investigates the potential impact of cost-based restricted drug formulary reimbursement policies on the achievement of optimal healthcare outcomes.

4.1.1 Identifying the optimal formulary reimbursement policy to maximize health-outcomes

Formulary reimbursement policy decisions vary from treatment decisions in that the decision-maker must take into account the heterogeneous needs and preferences of many patients, opposed to the homogeneous needs of an individual patient.

Identifying the optimal formulary reimbursement policy to maximize health-outcomes essentially consists of identifying a treatment selection solution that best serves

patients by contributing most to satisfying specific treatment objectives across a defined patient population. If a formulary reimbursement policy is selected and implemented to support the optimal satisfaction of patients needs, it can be argued that the service substitution effects that result from arbitrary cost-based formulary restrictions discussed by Moore and Newman (1992) can be avoided. Given this scenario, budget constraints and cost are not considered in defining best care.

Best healthcare is relative. Choices in health care, whether in health policy planning or treatment mode, inevitably involve value judgements. While Eddy advocates the position that healthcare choices must be determined in the context of patient objectives, needs and preferences, patients frequently do not have the knowledge to make informed decisions. This means that healthcare providers determine care on behalf of their patients in what economists refer to as an agency relationship. However, because health care provider's values have often varied from the values of the patients this study seeks to capture, compare, and incorporate patient and healthcare provider values concerning objectives and preferences for treatment.

4.1.2 Assessing the potential impact of restricted reimbursement on the achievement of optimal health outcomes.

The primary research question was concerned with identifying the formulary decision policy that would yield best care for a given population under conditions with no budgetary constraints. The secondary research question is concerned with defining best "available" care under conditions of budgetary constraints.

While it is understood that best care is always the most desirable care, tradeoffs in the level of care provided must often be made due to the reality that healthcare resources

are not unlimited. However, when decisions are made in determining cost-based formulary restrictions and the level of funding to commit to any given therapeutic area, the consequences of those decisions need to be carefully evaluated. When those decisions result in the provision of a sub-optimal level of healthcare, it should always be remembered that patients, and potentially the health care system as a whole, will pay a price in terms health outcome opportunity costs.

This second research question is aimed at identifying the nature and implications of those costs so that they can be more fully appreciated prior to implementing arbitrary cost-based restrictions that can have unnecessary and potentially damaging consequences to patients, the healthcare system, and society as a whole. This research question is studied through the introduction of a cost-based reimbursement constraint into the validated goal-programming formulary decision model previously used to identify the optimal selection of therapeutic regimens in a formulary reimbursement policy, and the execution of sensitivity analyses on the cost parameter at various levels restriction.

4.2 THE DECISION PROBLEM

The problem to be considered in this study relates to identification of an optimal formulary reimbursement policy to maximize health-outcomes with respect to the treatment of HIV infection with antiretroviral agents in a population of asymptomatic, treatment naive patients whose viral loads are in excess of 10,000 copies per mL and whose CD4+ counts range between 200-500 cells per mm^3. The optimal policy being sought is one that will best satisfy the concurrent achievement of multiple therapeutic goals which serve as decision attributes in this problem and are listed in Table 5.

These objectives have been repeatedly cited in the peer review literature (i.e. Carpenter et al. (1997), Abdullah (1997), Condra and Emini (1997)), and at numerous recent scientific meetings by experts such as Dr. D. Ho and Dr. J Mellors. These objectives are now widely recognized as critical determinants of long-term success in treating people infected with HIV. These goals are more fully discussed in Chapter 3.

Table 5:
Antiretroviral Treatment Formulary Goals / Decision Attributes

1	Achieve durable suppression of HIV replication
2	Prevent or delay disease progression
3	Minimize antiretroviral drug related adverse effects
4	Maximize ease of use of an antiretroviral regimen
5	Minimize the potential of developing resistance to antiretroviral therapy
6	Treat HIV infection according to most recent evidence-based peer-review antiretroviral treatment guidelines
7	Maximize the number of therapeutic options available in case of therapeutic failure

In seeking to satisfy these goals, ten therapeutic decision options are being considered. In this particular therapeutic area, the antiretroviral therapeutic decision option or entity is defined as a combination of multiple antiretroviral agents. This is due to relatively recent research, which has found that mono-antiretroviral therapy is inadequate to achieve therapeutic goals and any clinical benefit derived is transient and not generally sustained, as previously discussed in section 3.4.2.

The antiretroviral therapeutic combinations being evaluated for inclusion in a hypothetical formulary have been identified through a recent market research study conducted by ISIS Research in August 1997 and are listed in Table 6. In their study of

more than 674 patients and 34 physicians, of which 14 were HIV specialists, the most frequently used combinations were identified by their current overall antiretroviral market share. Treatment combinations most commonly used as first-line antiretroviral therapy, and to initiate treatment for a therapy naïve patient were also identified. All specified combinations displayed in table 6 (shaded in gray) that have not since been categorically rejected by current treatment guidelines have been included for evaluation in this decision problem.

Table 6: Most Commonly Used Antiretroviral Drug Combination by Market Share

Total Antiretroviral Drug Combination Market Shares			**First line antiretroviral therapy market shares by date initiated – 1997**			**Antiretroviral therapy used to initiate treatment for a therapy naïve patient.**		
1	d4T+3TC+Ind	14%	1	AZT+3TC+Ind	25%	1	AZT+3TC+Ind	33%
2	AZT+3TC+Ind	12%	2	AZT+3TC	20%	2	Triple combination with a PI (unspecified)	17%
3	AZT+3TC	10%	3	d4T+3TC+Ind	25%	3	AZT+3TC	14%
4	AZT+3TC+Saq	8%	4	AZT+3TC+Saq	10%	4	d4T+3TC+Ind	14%
5	d4T+3TC+Rit	6%	5	3TC+d4T	5%			
6	3TC+d4T	4%	6	AZT + ddC	n/s*			
7	d4T+3TC+Saq	3%	7	AZT + ddI	n/s*			
8	d4T+3TC+Rit+Saq	2%	8	AZT	n/s*			
9	AZT+3TC+Rit	2%						
10	d4T + ddI + Ind	2%						

Source: ISIS Research. (1997). Treatment of HIV Disease in Canada: Phase IX. August, pp.9,13.
**n/s = not specified, very low usage. Unexplained market share % are patients either on infrequently used marketed therapy, experimental therapy, or not on any therapy.*

While there are numerous other agents currently being studied in asymptomatic HIV infected patients, these agents have not been approved for sale in Canada at present and therefore would not be eligible for formulary acceptance at present. The agents

excluded from consideration include the protease inhibitor, nelfinavir, as well as an entire new class of medications called non-nucleoside-reverse-transcriptase inhibitors including neverapine, delavirdine, and DMP-266.

All therapeutic decision options under consideration for inclusion in the hypothetical formulary can be evaluated in accordance with the goals listed in Table 5 and with regard to the following decision attributes:

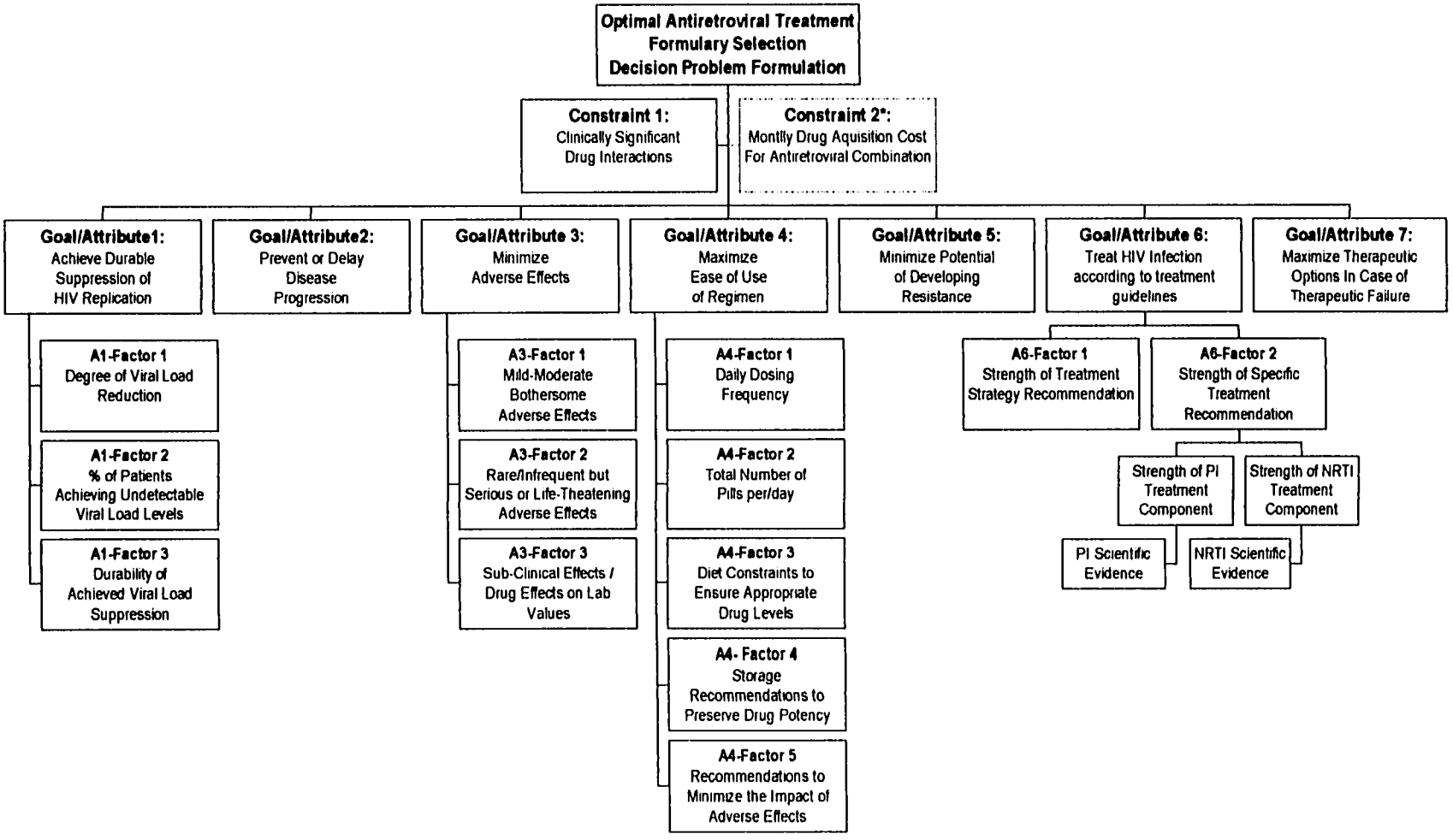
1. HIV viral load suppression,
2. Prevention or delay of disease progression,
3. Drug-related adverse effects,
4. Ease of use,
5. Resistance,
6. Level of support of recent treatment guidelines,
7. Downstream therapeutic options in case treatment failure.

These decision attributes or goals have been broken down into their respective components or factors to impose structure on the decision problem have been organized in the form of a decision value tree displayed in Table 7 on page 59.

While antiretroviral therapy can undoubtedly be characterized by numerous other attributes, they are not relevant to the formulary decision problem under study and have been excluded from the decision problem to produce a parsimonious, focused formulary decision model.

A number of potentially relevant attributes were also excluded from consideration in the decision problem due to the fact that there is not enough clear scientific evidence to adequately support their inclusion at this time. Prime among these is the cross-resistance between protease inhibitors within a combination. This was eliminated as a distinct

Table 7: HIV Antiretroviral Therapy Formulary Decision Value Tree



**Monthly Drug Acquisition Cost Constraints are only incorporated in the second part of the analysis once optimal therapy has been identified.*

attribute due to the fact that the relationship between genotypic resistance, in-vitro phenotypic resistance findings, and clinical significance regarding the sequencing of protease inhibitors is still unclear and much debated.[119,120]

Based on consultation with experts in the field of antiretroviral therapy, drug interactions have been included in the decision problem as clinical constraints for a sub-population rather than objectives, due to the fact that they are not necessarily relevant to most patients within this population. Given that most asymptomatic patients are usually early in the disease process, they may not require the great majority of the medications subject to drug-interactions with antiretroviral agents. If the analysis was considering the selection of treatment for a patient group more advanced in the disease process, the minimization of drug interactions would likely need to be incorporated as an objective.

In addition to therapeutic objectives, therapeutic constraints have also been included in the decision problem. This reflects reality in that while not all therapeutic objectives can be met, due to tradeoffs required in satisfying prioritized objectives, certain objectives should achieve at least a minimum level of care to be considered acceptable to patients and/or healthcare professionals.

Costs and budget limitations are only included as constraints in the second part of the analysis of the decision problem aimed at assessing the potential impact of restricted reimbursement on the achievement of optimal health outcomes. The costs included are strictly limited to monthly drug acquisition costs. Costs beyond the scope of this analysis relate to other drug related costs such as pharmacy dispensing fees and monitoring costs, total direct healthcare costs, and indirect costs in terms of costs to society due to lost productivity, morbidity and mortality attributable to the burden of HIV infection and its

progressive debilitating disease process. Drug related pharmacies dispensing fees and monitoring costs are relatively common across combination therapy and do not serve as principal differentiating factors between antiretroviral combinations. However, total direct healthcare costs and indirect costs are more significant but could not be adequately captured given the scope of this study and have been excluded from the current analysis. This decision was based on the assumption that the impact of effective antiretroviral drug therapy has prevented disease progression and reduced the need for more costly inpatient services which is supported by increasing evidence from the leaders in HIV disease management such as the John Hopkins and San Francisco General Hospital's HIV treatment programs in the United States which have demonstrated overall cost savings attributable to antiretroviral therapy.

CHAPTER 5

THE EXPERIMENT

5.1 SUBJECTS

This study is concerned with adequately capturing and incorporating the objectives and preferences of patients and healthcare professionals into a highly specific formulary drug selection decision model. Therefore, a case study approach focusing on the objectives and preferences of patients and healthcare professionals with regard to antiretroviral drug therapy was utilized in executing the experiment. A total of eleven individuals were recruited to participate in the study. The respondents representing healthcare professionals consisted of two leading infectious disease specialists who are experts in the treatment of HIV infected patients, and two highly regarded clinical pharmacists specialized in the field of HIV treatment.

Seven patients were recruited to participate in the study through an AIDS advocacy organization in Toronto. Each patient was pre-screened by this organization to ensure that they were representative of asymptomatic patients who are initiating antiretroviral treatment and that their awareness of issues surrounding HIV treatment was adequate to properly understand and answer the questions related to the assessment of their objectives and preferences. Only six of the seven patients, completed the interview. The seventh patient failed to present himself for the interview.

5.2 Study Design and Methodology

The initial problem of antiretroviral formulary reimbursement was first identified following the approval of numerous new and costly agents in 1996. Following an extensive review of the peer-reviewed literature; the abstracts of numerous scientific conferences; and discussions with patient advocacy organizations, pharmaceutical industry representatives, and healthcare professionals, several major issues relating to the selection and reimbursement of antiretroviral therapy were identified. These issues include:

1. Determining the optimal treatments that will maximally and durably suppress viral replication in an HIV infected patient to prevent disease progression, and the development of resistance to therapy.
2. Optimizing the selection of effective antiretroviral treatment by tailoring it to satisfy specific patient needs in terms of tolerability, and ease of use.
3. Considering downstream therapeutic options from the currently selected regimen in case of failure.
4. Making this optimal treatment accessible to patients by ensuring that reimbursement policy supports and is consistent with optimal treatment recommendations.

These issues made it necessary to focus on a particular aspect of the HIV infected population that could serve as a feasible case study, rather than the population as a whole who are at varying stages of the disease process and have different needs that would define optimal treatment. The patient population selected consisted of asymptomatic, treatment naive patients whose baseline viral load was in excess of 10,000 copies/mL and CD4+ cell counts were between 200-500 per mm^3 who had made the decision to initiate therapy and were either in the process of selecting therapy or who had already selected

therapy within the previous six months. This particular population was selected for several reasons:

1. Early intervention strategies (i.e. hit hard/hit early) are gaining increasingly widespread support in attempts to eradicate the virus.
2. The first therapeutic regimen should be selected to achieve maximal, durable suppression of HIV replication because in all likelihood subsequent regimens post-failure of the initial regimen are less likely to be effective
3. Formulary decision-makers are most likely to restrict therapeutic intervention on the basis of cost in this growing early-stage, asymptomatic treatment seeking population.

Once the patient population and major treatment issues had been defined, the next step in determining the appropriate formulary reimbursement policy was the identification of the relevant decision options, therapeutic objectives, decision attributes and factors.

Based on extensive review, data extraction, and synthesis of the peer review literature, the major issues previously identified were broken down into seven distinct therapeutic objectives or decision attributes which were assumed to be independent (non-interactive) for the purposes of this study. These decision attributes composed of one or more component factors are organized in a decision value tree which is displayed in Table 7 on page 59. The benefits and harms of the ten alternative treatments (decision options) under consideration were then identified from the literature and assessed in terms of distinctness, quantitative or qualitative characteristics.

Once it became apparent that the formulary drug selection problem was in fact a multi-objective problem whose distinct decision attributes consisted of both quantitative and qualitative characteristics which were measurable in dissimilar units, two

requirements were identified in terms of the methods used to address this decision problem. These requirements included:

1. An overall decision framework that could appropriately structure the decision problem by modeling the decision attributes as therapeutic objectives in need of satisfaction in a quantitative manner that could be employed to systematically identify one or more optimal solutions in selecting from various decision alternatives. Further the overall decision framework would need to be capable of facilitating the systematic handling of sensitivity analysis to assess tradeoffs necessary to achieve optimal care through the optimal reimbursement policy.
2. A measurement strategy capable of measuring the various dissimilar variables that could be employed to convert qualitative measures into a linear value function in order to be appropriately incorporated into the quantitative analysis.

Both MAUT decision analysis and goal programming methods were evaluated to determine which would be best suited to structure and analyze the decision problem in addition to identifying an optimal solution. As an overall decision framework MAUT was limited due to its inability to set target levels for specific goals. In addition, its need to aggregate utilities in making a decision makes it difficult and cumbersome to systematically assess the tradeoffs made between decision attributes or objectives in designing a formulary reimbursement policy.

A weighted goal-programming model was selected as an overall decision framework due to its ability to set specific targets for the defined goals. This target setting defined the minimal or maximal standard or level of a given objective that must be achieved to best satisfy a therapeutic objective that contributes to the maximization of health outcomes.

Because of the multiple and sometimes conflicting objectives, weighted-goal programming facilitated the identification and assessment of tradeoffs required to

minimize deviation from the series of defined goals which were prioritized through the incorporation of penalties and deviation variables in the objective function. Non-preemptive weighted goal programming was more suited to this particular decision problem than lexicographic goal programming given the nature of the objectives and preferences of patients and their healthcare professionals. For example: It is very important to achieve the maximal durable suppression of HIV viral replication. However, to achieve and/or maintain this degree of HIV suppression it is necessary for patients to be able to adhere to and tolerate these medications. Therefore, lexicographic goal-programming was generally expected to be incompatible with the utility functions of the decision makers in this case resulting in an inadequate, unacceptable solution with potentially harmful consequences.

In the case of the formulary decision problem under study, the decision attributes and factors were measured using the multiattribute decomposition method demonstrated by Schumacher (1991), and Clemen (1996). Each of the ten decision options under consideration were subsequently reviewed and assessed with respect to the defined therapeutic objectives (decision attributes) and factors which were discussed in Chapter 4. The resulting data synthesis displayed in Appendix 8, provided a basis on which to construct a formulation of decision problem.

Cross sectional data from the synthesis was utilized to develop measurement scales for each of decision attributes and its respective factors. Each measurement scale was then applied to consistently evaluate the ten decision options. These measurement scales for each decision attribute and its contributing factors are displayed in Tables 8a-k at the end of this chapter.

This process allowed a preliminary formulation of the weighted-goal-programming model that was used in studying the research questions. This preliminary formulation is displayed in Table 10 at the end of this chapter. However, significant information was required but lacking to appropriately complete the formulation. This information related to:

1. The conversion of various qualitative factors into linear value functions so they could be adequately measured and incorporated into the model;
2. The assessment of patient and healthcare professional preferences with regard to the relative importance of various treatment objectives; and
3. The assessment of patient and healthcare professional preferences with regard to the relative importance and value of various antiretroviral attributes and factors involved in the selection decision.

This lacking information was captured through the development and administration of healthcare professional and patient questionnaires tailored for the aforementioned purposes and attached in Appendices 9 and 10 respectively. Upon examination of the comprehensive questionnaires, it was decided that to feasibly derive the required information, only a limited number of participants representing patients and healthcare professionals could be interviewed to the extent necessary to complete those lengthy questionnaires.

Participating healthcare professionals were contacted and recruited directly by telephone in order to administer interviews based on the questionnaire. Asymptomatic, HIV infected patients over the age of 18 years were recruited from AIDS advocacy organizations. In order to protect the confidentiality of these patients given the stigmatized nature of HIV and AIDS, the interviews were conducted through a third party. This interviewer is highly experienced in interviewing HIV patients and is also

very aware of antiretroviral therapy, as well as important issues concerning political-correctness, and appropriate protocol when dealing with members of the HIV infected community.

Once the interviews had been administered and data was collected and compiled, an observational assessment of the data suggested a high degree of consistency between healthcare professional respondents, and the presence of significant variation between patient respondents with respect to:

1.) The relative importance and desirability of achieving various treatment objectives.

2.) The valuation of each attribute and/or factor levels.

3.) The minimum acceptable levels of each relevant attribute and/or factor.

Given the apparent variations between respondents and the need to accurately represent the preferences of the respondents in selecting optimal therapy, four goal-programming models were constructed. Each model incorporated the relevant decision attributes in addition to important constraints on the minimal acceptable level of each attribute as a quality control level that could not be waived in making tradeoffs to achieve competing goals. Each model was subsequently validated against a corresponding MAUT decomposition decision model used as a comparative benchmark, to:

1.) Identify inter-patient variability with regard to therapeutic objectives and strength of preferences and its impact on the selection of optimal treatment.

2.) Determine the appropriate level of preference aggregation for patients (i.e. by individual patient, patient type, or aggregated population)

3.) Identify differences with regard to therapeutic objectives and strength of preferences between patients and healthcare professionals

4.) Determine the appropriate level of preference aggregation weighting between patients and healthcare professionals (i.e. 70/30%, 50/50%, 30/70%)

The four goal-programming models and respective MAUT benchmark decision models were formulated based on the following:

1.) Individual patient level preferences and linear value functions

2.) Weighted-averaged patient population preferences and linear value functions

3.) Weighted-averaged healthcare professional population preferences and linear value functions

4.) Combined weighted-averaged (50/50%) patient and healthcare professional preferences and linear value functions

In structuring this decision problem model to derive meaningful and valid solutions, weighted-goal programming required that a scaling and normalizing procedure be applied to the goals prior to solving any of the aforementioned formulations. If left unadjusted, the incommensurable nature of the goals in this problem would result in the introduction of an artificial bias that was not reflective of the actual decision maker preferences.

In this case, utilizing the scaling method demonstrated by Romero (1991), each goal incorporated in the proposed goal programming decision problem was normalized to a maximum optimal level set at 100 with the coefficients of the integer decision variables adjusted accordingly. Since each goal was set to the maximum level and it is not possible to surpass this level, only negative or underachievement deviational variables were incorporated in each goal programming model. The goal programming formulations for each of the four models are displayed in Tables 11-14 at the end of this chapter.

Each goal-programming model was subsequently solved as an integer goal-programming problem using LINDO to identify the optimal selection of antiretroviral combinations without cost constraints. The goal programming solutions for each of the four models are displayed in Tables 15-18 at the end of this chapter. Corresponding MAUT analyses were also carried out models. Because MAUT does not handle decision constraints, the analysis first consisted of ranking the decision alternatives based on the relevant decision-maker preferences. Once the rank ordering was complete, the ability of each regimen to satisfy the minimal acceptable level of care constraints was determined manually. The analyses are displayed for each of the models in Tables 19-22 at the end of this chapter.

Inconsistent selections between 3 of the 4 formulations were identified on comparing the goal programming solutions vs. the MAUT solutions. Those comparisons and their implications are presented in Table 25 in Chapter 6. The first model based on individual preferences and linear value functions proved to be the only valid model based on its accuracy in selecting optimal therapy which addressed inter-patient variation when compared against the six individual patient MAUT analyses in determining the optimal treatment selection for the population displayed in Table 15.

The findings of this analysis and validation procedure permitted the selection of an appropriate weighted goal programming formulary decision model that yielded a unique optimal, and thus Pareto-efficient solution. The level of resources required to achieve the optimal solution was then calculated using monthly drug acquisition costs for each of the therapeutic combinations under consideration. Those cost values can be found

in Table 9. The calculated resource levels for each of the four models is presented in Table 26 in Chapter 6.

At this point, cost-based reimbursement constraints were introduced into the model to represent the monthly level of formulary reimbursement. The revised formulation and solution based on the unrestricted optimal solution are displayed respectively in Tables 23 and 24 at the end of this chapter. The impact of cost-based reimbursement policies was assessed through sensitivity analysis on the level of restriction of the right-hand side value of monthly drug acquisition costs for the entire population at three sub-optimal levels. These levels were identified by calculating the three drug acquisition costs for each of the therapeutic combinations under consideration using the solutions from the three other models found to be inferior to the one previously selected as most appropriate and valid. The calculations for this sensitivity analysis were executed by rerunning the model in LINDO due to inability to interpret shadow prices and reduced costs in the LINDO output which refer to sub-problems generated during the branch and bound solution rather than the proper integer-programming solution.

Through this sensitivity analysis procedure, the impact of those cost-based formulary restrictions on the achievement of therapeutic objectives was identified, and implications on the achievement of optimal health outcomes were evaluated.

The results of all of the aforementioned analyses are presented and discussed in Chapter 6.

Tables 8a-k: HIV Antiretroviral Formulary Decision Attribute / Factor Measurement Scales:

Table 8a: Formulary Decision Attribute 1 **The Ability of Antiretroviral Therapy to Durably Suppress HIV Replication**		
Relative Weight:	**FACTOR:**	**Measurement:**
	Degree of viral load suppression (log10 reduction in viral load, assay limit of detection 500 copies/mL)	Actual log reduction converted into a linear value function
	% of patients achieving undetectable levels at 500 copies/mL at six months/24 weeks (proportion of patients deriving durable benefit from treatment)	Actual % converted into a linear value function
	Durability of Effect	The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:
		Sustained suppression of plasma viral load in most patients.
		Less likely to provide sustained suppression of plasma viral load in most patients.
		Suppression of plasma viral load is not sustained in most patients
		Suppression of plasma viral load is not achieved in most patients.

Table 8b: Formulary Decision Attribute 2 **Clinical Benefit of Antiretroviral Treatment:** **The ability of antiretroviral therapy to prevent or delay disease progression**	
FACTOR:	**Measurement:** The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:
Demonstrated clinical benefit in terms of reduced morbidity and mortality:	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit.
	Some evidence of clinical benefit reduction in disease progression or AIDS related mortality)
	Transient clinical benefit, does not alter long-term natural history of the disease
	No demonstrated clinical benefit

Table 8c: Formulary Decision Attribute 3: **Antiretroviral Drug Related Adverse Effects**	
Relative Weight:	Mild to moderate bothersome adverse effects
	Serious or Potentially Life Threatening Adverse Effects
	Sub-clinical effects / Drug effects on Lab Values

Table 8d: Mild to Moderate Bothersome Adverse Effects	
Measurement: The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:	
Baseline adverse effects occurring with similar frequency on average across most antiretroviral combinations: Abdominal pain, anorexia (reduced appetite), arthralagia (joint pain), chills, constipation, depression, diarrhea, dizziness, fatigue, fevers, headache, insomnia, malaise, myalgia (muscle pain), nausea, neurological symptoms, neuropathy, pancreatitis, paresthesia (numbness, prickling, tingling), rash, vomiting	
Baseline + each of the following side effects which occur with increased frequency and/or severity for specific antiretroviral combinations	
	Rash
	Nephrolithiasis (kidney stones); Benign Hyperbilirubinemia sometimes associated with Jaundice
	Altered taste; Numbness, prickling, tingling sensation; Rash
	Altered taste; Reduced appetite; Numbness, prickling, tingling sensation; Rash; Frequent and often severe Diarrhea, Nausea, and Vomiting
	Altered taste; Dizziness; Numbness; Rash; Reduced appetite; prickling, tingling sensation; Frequent and often severe Diarrhea, Nausea, and Vomiting
	Nephrolithiasis (kidney stones); Benign Hyperbilirubinemia sometimes associated with Jaundice; Altered taste; Reduced appetite; Numbness, prickling, tingling sensation
	Altered taste; Constipation; Nausea; Nephrolithiasis (kidney stones); Benign Hyperbilirubinemia sometimes associated with Jaundice; Rash; Diarrhea
	Dizziness; Numbness, prickling, tingling sensation; Rash; Frequent and often severe Diarrhea, Nausea, and Vomiting.

Table 8e: Serious or Potentially Life Threatening Adverse Effects	
	Measurement: The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:
	Bone marrow suppression (anemia or neutropenia)
	Neuropathy (15-21%); Pancreatitis (1%)
	Seizures<1%; Neuropathy (34%); Pancreatitis (10%)

Table 8f: Sub-clinical effects / Drug effects on Lab Values	
	Measurement: The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:
	No significant sub-clinical effects / Drug effects on Lab Values
	Elevated Creatinine
	Elevated Bilirubin; Elevated Triglycerides
	Anemia; Elevated Bilirubin; Elevated Triglycerides; Neutropenia
	Anemia; Elevated Bilirubin; Elevated Creatinine; Neutropenia
	Elevated Alkaline Phosphatase; Elevated Creatinine; Elevated Liver Functions; Elevated Triglycerides
	Elevated Alkaline Phosphatase; Elevated Amylase; Elevated Creatinine; Elevated Liver Functions; Elevated Triglycerides
	Anemia; Elevated Alkaline Phosphatase; Elevated Creatinine; Elevated Liver Functions; Elevated Triglycerides; Neutropenia

Table 8g: Formulary Decision Attribute 4 **Ease of Use of Antiretroviral Regimens**	
Relative Weight :	Dosing Frequency
	Total number of pills per day
	Diet Constraints
	Storage Recommendations
	Recommendations to minimize the impact of adverse effects.

Table 8h: Ease of Use Factors

Factor:	Measurement:
Dosing Frequency	Total number of times drug combination taken per day converted into a linear value function.
Total number of pills per day	Total number of pills, tablets, capsules per day converted into a linear value function.
Diet Constraints	**Measurement:** The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:
	No food restrictions.
	Take 2 of 2 doses with food.
	Take 2 of 2 doses with large, preferably high-fat meal.
	Take 3 of 4 doses on an empty stomach or with a light meal or fat free snack.
	Take 3 of 3 doses with a large, preferably high-fat meal.
	Take 3 of 4 doses with a large, preferably high-fat meal
	Take 3 of 4 doses on an empty stomach or with a light meal or fat free snack. 4th dose must be taken on an empty stomach.
Storage Recommendations	**Measurement:** The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:
	Store at room temperature, protect from light and moisture.
	Store at room temperature, protect from light and moisture. Protease Inhibitor capsules must be kept refrigerated
Recommendations to minimize the impact of adverse effects.	**Measurement:** The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:
	Minimize alcohol intake.
	Take in an upright position with a full glass of water. To minimize nausea take with food.
	Minimize alcohol intake. Drink at least 1.5 liters of water/liquids during each day to decrease the chance of developing kidney stones
	Take in an upright position with a full glass of water. To minimize nausea take with food. Drink at least 1.5 liters of water/liquids during each day to decrease the chance of developing kidney stones

Table 8i: Formulary Decision Attribute 5 **Probability of developing resistance on a given antiretroviral treatment regimen**	
Measurement: The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:	
	Low probability of developing resistance: < 20% of adherent patients resistant at 1 year on treatment
	Moderate probability of developing resistance: between 21-79% of adherent patients resistant at 1 year on treatment
	High probability of developing resistance: > 80% of adherent patients resistant at 1 year on treatment

Table 8j: Formulary Decision Attribute 6

Strength of Treatment Guideline Recommendations

Relative Weight:	Factor:	Measurement:
	Strength of recommendation regarding treatment strategy	Preferred Alternative Not Generally Recommended Not Recommended
	Strength of recommendation regarding specific treatment.	
	NRTI component strength of recommendation	Strong - should always be offered Moderate - can usually be offered Optional - can sometimes be offered Should generally not be offered Should never be offered
	NRTI quality of scientific evidence	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints Clinical trials with laboratory endpoints Expert Opinion
	PI component strength of recommendation	Strong - should always be offered Moderate - can usually be offered Optional - can sometimes be offered Should generally not be offered Should never be offered
	PI quality of scientific evidence	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints Clinical trials with laboratory endpoints Expert Opinion Not applicable - No PI

Table 8k: Formulary Decision Attribute 7 **Future Options for change in therapy in case of treatment failure**	
Measurement: The following qualitative measures were ranked and weighted by stakeholders and converted into a linear value function:	
	From Dual NRTI therapy: • 2 new NRTI's/PI • 2 new NRTI's/NNTRI • new NRTI/PI/NNRTI* • 2 PI'S/NRTI* • *2 PI'S/NNRTI**
	From Triple Therapy (2 NRTI's +1 PI): • 2 new NRTI's/NNTRI • new NRTI/PI/NNRTI* • 2 PI'S/NRTI* • *2 PI'S/NNRTI**
	From Quadruple Therapy (2 NRTI's + 2 PI's): • 2 new NRTI's / NNRTI

*Only limited data supporting the use of these treatments is available

Table 9: Cost of Antiretroviral Treatment Combinations

	Drug Combination	Total cost/month of drugs in combination
1	d4T (40mg/BID)+3TC (150mg/BID)+Ind (800mg/q8h)	$1,004.19
2	AZT (200mg/TID)+3TC (150mg/BID)+Ind (800mg/q8h)	$1,158.09
3	AZT (200mg/TID)+3TC (150mg/BID)	$673.30
4	AZT (200mg/TID)+3TC (150mg/BID)+Saq (600mg/TID)	$1,164.70
5	d4T (40mg/BID)+3TC (150mg/BID)+Rit (600mg/BID)	$1,000.14
6	d4T (40mg/BID)+3TC (150mg/BID)	$519.40
7	d4T (40mg/BID)+3TC (150mg/BID)+Saq (600mg/TID)	$1,010.80
8	d4T (40mg/BID)+3TC (150mg/BID)+Rit (400mg/BID) + Saq (400mg/BID)	$1,058.29
9	AZT (300mg/BID)+3TC (150mg/BID)+Rit (600mg/BID)	$1,154.04
10	ddI (400mg /QD) +d4T (40mg/BID) +Ind (800mg/q8h)	$924.59

10 most frequently prescribed antiretroviral combinations, with indicated dosing, or with recommended dosing adjustments due to synergistic effects (Table 5) x cost of antiretroviral agents (Appendix 6).

Table 10:

Definition of Decision Variables:

Let X_{jk} = the patient j, put on therapeutic combination k.

Where patient j = 1 to 6, where j = the patient number identifier
Where therapeutic combination k = 1 to 10

Let g_{ij} = the goal i, for patient j.

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Let n_{ij} = the underachievement deviational variable related to goal i, for patient j.

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Let α_{ij} = the penalty coefficient related to the underachievement deviational variable n, for goal i, and patient j.

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Let c_{ij} = the therapeutic constraint representing a minimal acceptable level of care to be satisfied by goal i, for patient j

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Let t_{ij} = the Target for goal i, for patient j

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Table 10 cont: **Goal Programming Formulation of Antiretroviral Treatment Formulary Decision Problem**

k =	***Antiretroviral Therapeutic Combination***
1	d4T (40mg/BID) + 3TC (150mg/BID) + Ind (800mg/q8h)
2	AZT (200mg/TID) + 3TC (150mg/BID) + Ind (800mg/q8h)
3	AZT (200mg/TID) + 3TC (150mg/BID)
4	AZT (200mg/TID) + 3TC (150mg/BID) + Saq (600mg/TID)
5	d4T (40mg/BID) + 3TC (150mg/BID) + Rit (600mg/BID)
6	d4T (40mg/BID) + 3TC (150mg/BID)
7	d4T (40mg/BID) + 3TC (150mg/BID) + Saq (600mg/TID)
8	d4T (40mg/BID) + 3TC (150mg/BID) + Rit (400mg/BID) + Saq (400mg/BID)
9	AZT (300mg/BID) + 3TC (150mg/BID) + Rit (600mg/BID)
10	ddI (400mg /QD) + d4T (40mg/BID) + Ind (800mg/q8h)

g =	***Antiretroviral Treatment Formulary Decision Objectives***
g1j	Maximize durable suppression of HIV replication
g2j	Maximize clinical benefit - prevent or delay disease progression
g3j	Minimize antiretroviral drug related adverse effects
g4j	Maximize ease of use of an antiretroviral regimen
g5j	Minimize the potential of developing resistance to antiretroviral therapy
g6j	Treat HIV infection according to most recent evidence-based peer-review antiretroviral treatment guidelines
g7j	Maximize the number of therapeutic options available in case of therapeutic failure

Table 10 cont: Goal Programming Formulation of Antiretroviral Treatment Formulary Decision Problem

Objective Function:

$$\text{MIN} \quad \sum_{j=1}^{6} (\alpha_{1j}n_{1j} + \alpha_{2j}n_{2j} + \alpha_{3j}n_{3j} + \alpha_{4j}n_{4j} + \alpha_{5j}n_{5j} + \alpha_{6j}n_{6j} + \alpha_{7j}n_{7j})$$

SUBJECT TO:

	Antiretroviral Combination Contribution to Goal Achievement										negative variable n_g	$Goal_g$ (Target Level)	Penalty Weights
Treatment Combination $_k$	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			
Goal g / Constraint c	X_{j1}	Xj_2	Xj_3	Xj_4	X_{j5}	X_{j6}	X_{j7}	Xj_8	Xj_9	Xj_{10}			α_{ij}
g_{1j}											$+ n_{1j}$	$= t1_j$	
g_{2j}											$+ n_{2j}$	$= t2_j$	
g_{3j}											$+ n_{3j}$	$= t3_j$	
g_{4j}											$+ n_{4j}$	$= t4_j$	
g_{5j}											$+ n_{5j}$	$= t5_j$	
g_{6j}											$+ n_{6j}$	$= t6_j$	
g_{7j}											$+ n_{7j}$	$= t7_j$	
c_{1j}												≥ min. acceptable level	
c_{2j}												≥ min. acceptable level	
c_{3j}												≥ min. acceptable level	
c_{4j}												≥ min. acceptable level	
c_{5j}												≥ min. acceptable level	
c_{6j}												≥ min. acceptable level	
c_{7j}												≥ min. acceptable level	

Table 11: Goal Programming Formulation Based on Individual Patient Level Preferences and Linear Value Functions

Variable Definition:

Let X_{jk} = the patient j, put on therapeutic combination k.

Where patient j = 1 to 6, where j = the patient number identifier
Where therapeutic combination k = 1 to 10

Let g_{ij} = the goal i, for patient j.

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Let n_{ij} = the % underachievement of goal i, for patient j.

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Let α_{ij} = the penalty coefficient related to the underachievement deviational variable n, for goal i, and patient j.

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

Let c_{ij} = the therapeutic constraint representing a minimal acceptable level of care to be satisfied by goal i, for patient j

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where i = the goal number identifier

```
MIN     10 N11 + 100 N12 +     N13 +  10 N14 +  99 N15 +  90 N16 +
        10 N21 + 100 N22 + 100 N23 + 100 N24 + 100 N25 + 100 N26 +
                 75 N32 +     N33 +     N34 + 100 N35 +  90 N36 +
           N41 +  20 N42 +     N43 +           98 N45 +     N46 +
        10 N51 +     N52 + 100 N53 +  10 N54 +  90 N55 +  10 N56 +
         5 N61 +  40 N62 +              N64 + 100 N65 +  50 N66 +
         3 N71 +  40 N72 +   3 N73 +     N74 +     N75 +   80 N76
```

SUBJECT TO

G11) 76 X11 + 76.2 X12 + 1.2 X13 + 7 X14 + 76 X15 + 4.6 X16
+ 7.8 X17 + 100 X18 + 75.4 X19 + 76 X110 + N11 = 100

G12) 77.55 X21 + 77.88 X22 + 1.32 X23 + 11.55 X24 + 77.55 X25
+ 7.59 X26 + 12.21 X27 + 99 X28 + 76.56 X29 + 77.55 X210 + N12
= 100

G13) 72.5 X31 + 72.5 X32 + 2 X33 + X34 + 72.5 X35 + X36 + 2 X37
+ 100 X38 + 72.5 X39 + 72.5 X310 + N13 = 100

G14) 49.69 X41 + 49.69 X42 + 2.7 X43 + 3.87 X44 + 49.6 X45
+ 2.79 X46 + 5.67 X47 + 100 X48 + 49.33 X49 + 49.6 X410 + N14
= 100

G15) 74.05 X51 + 74.06 X52 + 1.93 X53 + 1.32 X54 + 74.05 X55
+ 1.2 X56 + 2.26 X57 + 100 X58 + 74.02 X59 + 74.05 X510 + N15
= 100

G16) 60.4 X61 + 60.73 X62 + 1.99 X63 + 11.56 X64 + 60.4 X65
+ 70.6 X66 + 12.88 X67 + 100 X68 + 59.41 X69 + 60.4 X610 + N16
= 100

G21) 100 X11 + 100 X12 + 50 X13 + 100 X14 + 100 X15 + 50 X16
+ 100 X17 + 100 X18 + 100 X19 + 100 X110 + N21 = 100

G22) 100 X21 + 100 X22 + 2 X23 + 100 X24 + 100 X25 + 2 X26 + 100 X27
+ 100 X28 + 100 X29 + 100 X210 + N22 = 100

G23) 100 X31 + 100 X32 + 20 X33 + 100 X34 + 100 X35 + 20 X36
+ 100 X37 + 100 X38 + 100 X39 + 100 X310 + N23 = 100

G24) 100 X41 + 100 X42 + 50 X43 + 100 X44 + 100 X45 + 50 X46
+ 100 X47 + 100 X48 + 100 X49 + 100 X410 + N24 = 100

G25) 100 X51 + 100 X52 + 90 X53 + 100 X54 + 100 X55 + 90 X56
+ 100 X57 + 100 X58 + 100 X59 + 100 X510 + N25 = 100

G26) 100 X61 + 100 X62 + 50 X63 + 100 X64 + 100 X65 + 50 X66
+ 100 X67 + 100 X68 + 100 X69 + 100 X610 + N26 = 100

G31) 87.17 X11 + 57.42 X12 + 77.39 X13 + 92.32 X14 + 1.32 X15
+ 70.25 X16 + 100 X17 + 23.05 X18 + 12.07 X19 + 19.76 X110 + N31
= 100

G32) 77.74 X21 + 50.81 X22 + 90.55 X23 + 74.59 X24 + 34.96 X25
+ 100 X26 + 78.07 X27 + 12.05 X28 + 14.65 X29 + 1.95 X210
+ N32 = 100

G33) 94.8 X31 + 49.27 X32 + 100 X33 + 68.47 X34 + 0.68 X35
+ 93.22 X36 + 76.95 X37 + 23.73 X38 + 11.86 X39 + 20.11 X310
+ N33 = 100

G34) 56.43 X41 + 60.48 X42 + 100 X43 + 69.98 X44 + 0.2 X45
+ 90.26 X46 + 78.01 X47 + 40.16 X48 + 11.04 X49 + 21.18 X410
+ N34 = 100

G35) 90.09 X51 + 68.97 X52 + 100 X53 + 70.26 X54 + 38.15 X55 + 55.71 X56 + 79.31 X57 + 13.79 X59 + 16.81 X510 + N35 = 100

G36) 66.06 X61 + 22.76 X62 + 100 X63 + 70.73 X64 + 0.2 X65 + 94 X66 + 79 X67 + 29.78 X68 + 10.87 X69 + 26.42 X610 + N36 = 100

G41) 72.78 X11 + 43.55 X12 + 81.67 X13 + 24.65 X14 + 75.62 X15 + 100 X16 + 60.65 X17 + 66.63 X18 + 39.64 X19 + 53.02 X110 + N41 = 100

G42) 21.1 X21 + 9.9 X22 + 100 X23 + 55.24 X24 + 37.23 X25 + 55.76 X26 + 26.23 X27 + 37.05 X28 + 51.44 X29 + 17.38 X210 + N42 = 100

G43) 46.03 X31 + 41.78 X32 + 94.75 X33 + 37.19 X34 + 38.53 X35 + 99 X36 + 59.56 X37 + 38.95 X38 + 0.28 X39 + 43.9 X310 + N43 = 100

G44) 60.14 X41 + 49.52 X42 + 92.47 X43 + 28.04 X44 + 54.7 X45 + 100 X46 + 51.19 X47 + 54.7 X48 + 15.93 X49 + 26.55 X410 + N44 = 100

G45) 50.82 X51 + 51.86 X52 + 100 X53 + 49.03 X54 + 79.59 X55 + 82.68 X56 + 23 X57 + 75.88 X58 + 55.67 X59 + 20.99 X510 + N45 = 100

G46) 38.27 X61 + 34.01 X62 + 100 X63 + 31.94 X64 + 70.67 X65 + 93.33 X66 + 38.87 X67 + 47.47 X68 + 50.67 X69 + 34.93 X610 + N46 = 100

G51) 100 X11 + 100 X12 + 100 X15 + 100 X18 + 100 X19 + 100 X110 + N51 = 100

G52) 100 X21 + 100 X22 + 100 X25 + 100 X28 + 100 X29 + 100 X210 + N52 = 100

G53) 100 X31 + 100 X32 + 100 X35 + 100 X38 + 100 X39 + 100 X310 + N53 = 100

G54) 100 X41 + 100 X42 + 100 X45 + 100 X48 + 100 X49 + 100 X410 + N54 = 100

G55) 100 X51 + 100 X52 + 100 X55 + 100 X58 + 100 X59 + 100 X510 + 100 N55 = 100

G56) 100 X61 + 100 X62 + 100 X65 + 100 X68 + 100 X69 + 100 X610 + N56 = 100

G61) 77 X11 + 100 X12 + 11 X13 + 9 X14 + 77 X15 + 7 X16 + 50 X17 + 66 X18 + 100 X19 + 100 X110 + N61 = 100

G62) 75 X21 + 100 X22 + 38 X23 + X24 + 75 X25 + 13 X26 + 25 X27 + 75 X28 + 100 X29 + 100 X210 + N62 = 100

```
G64)   55 X41 + 100 X42 + 6 X43 + X44 + 55 X45 + 5 X46 + 50 X47
       + 52 X48 + 100 X49 + 100 X410 + N64 =    100

G65)   97 X51 + 100 X52 + 50 X53 + X54 + 97 X55 + 25 X56 + 26 X57
       + 95 X58 + 100 X59 + 100 X510 + N65 =    100

G66)   75 X61 + 100 X62 + 13 X63 + X64 + 75 X65 + 13 X66 + 50 X67
       + 63 X68 + 100 X69 + 100 X610 + N66 =    100

G71)   50 X11 + 50 X12 + 100 X13 + 50 X14 + 50 X15 + 100 X16 + 50 X17
       + 10 X18 + 50 X19 + 50 X110 + N71 =    100

G72)   98 X21 + 98 X22 + 100 X23 + 98 X24 + 98 X25 + 100 X26 + 98 X27
       + X28 + 98 X29 + 98 X210 + N72 =    100

G73)   100 X31 + 100 X32 + 100 X33 + 100 X34 + 100 X35 + 100 X36
       + 100 X37 + 100 X39 + X310 + N73 =    100

G74)   10 X41 + 10 X42 + 100 X43 + 10 X44 + 10 X45 + 100 X46 + 10 X47
       + 10 X49 + 10 X410 + N74 =    100

G75)   67 X51 + 67 X52 + 100 X53 + 67 X54 + 67 X55 + 100 X56 + 67 X57
       + 33 X58 + 67 X59 + 67 X510 + N75 =    100

G76)   10 X61 + 10 X62 + 100 X63 + 10 X64 + 10 X65 + 100 X66 + 10 X67
       + X68 + 10 X69 + 10 X610 + N76 =    100

C11)   76 X11 + 76.2 X12 + 1.2 X13 + 7 X14 + 76 X15 + 4.6 X16
       + 7.8 X17 + 100 X18 + 75.4 X19 + 76 X110 >=   38

C12)   77.55 X21 + 77.88 X22 + 1.32 X23 + 11.55 X24 + 77.55 X25
       + 7.59 X26 + 12.21 X27 + 99 X28 + 76.56 X29 + 77.55 X210
       >=   61.71

C13)   72.5 X31 + 72.5 X32 + 2 X33 + X34 + 72.5 X35 + X36 + 2 X37
       + 100 X38 + 72.5 X39 + 72.5 X310 >=   0.51

C14)   49.69 X41 + 49.69 X42 + 2.7 X43 + 3.87 X44 + 49.6 X45
       + 2.79 X46 + 5.67 X47 + 100 X48 + 49.33 X49 + 49.6 X410
       >=   48.6

C15)   74.05 X51 + 74.06 X52 + 1.93 X53 + 1.32 X54 + 74.05 X55
       + 1.2 X56 + 2.26 X57 + 100 X58 + 74.02 X59 + 74.05 X510 >=   0.8

C16)   60.4 X61 + 60.73 X62 + 1.99 X63 + 11.56 X64 + 60.4 X65
       + 7.6 X66 + 12.88 X67 + 100 X68 + 59.41 X69 + 60.4 X610
       >=   36.234

C21)   100 X11 + 100 X12 + 50 X13 + 100 X14 + 100 X15 + 50 X16
       + 100 X17 + 100 X18 + 100 X19 + 100 X110 >=   50

C24)   100 X41 + 100 X42 + 50 X43 + 100 X44 + 100 X45 + 50 X46
       + 100 X47 + 100 X48 + 100 X49 + 100 X410 >=   50

C25)   100 X51 + 100 X52 + 90 X53 + 100 X54 + 100 X55 + 90 X56
       + 100 X57 + 100 X58 + 100 X59 + 100 X510 >=   90
```

```
C26)   100 X61 + 100 X62 + 50 X63 + 100 X64 + 100 X65 + 100 X66
       + 50 X67 + 100 X68 + 100 X69 + 100 X610 >=   50

C31)   86.17 X11 + 57.52 X12 + 77.39 X13 + 92.32 X14 + 1.32 X15
       + 70.25 X16 + 100 X17 + 23.05 X18 + 12.07 X19 + 19.76 X110 >=  0

C32)   77.74 X21 + 50.81 X22 + 90.55 X23 + 74.59 X24 + 34.96 X25
       + 100 X26 + 78.07 X27 + 12.05 X28 + 14.66 X29 + 1.95 X210
       >=   27.8

C33)   94.8 X31 + 49.27 X32 + 100 X33 + 68.47 X34 + 0.68 X35
       + 93.22 X36 + 76.95 X37 + 23.73 X38 + 11.68 X39 + 20.11 X310
       >=   6.99

C34)   56.43 X41 + 60.24 X42 + 100 X43 + 69.98 X44 + 0.2 X45
       + 90.26 X46 + 78.01 X47 + 40.16 X48 + 11.04 X49 + 21.18 X410
       >=   60

C35)   90.09 X51 + 68.97 X52 + 100 X53 + 70.26 X54 + 38.15 X55
       + 55.71 X56 + 79.31 X57 + 13.79 X59 + 16.81 X510 >=   64

C36)   60.06 X61 + 22.76 X62 + 100 X63 + 70.73 X64 + 0.2 X65 + 94 X66
       + 79 X67 + 29.78 X68 + 10.87 X69 + 24.62 X610 >=   14.65

C41)   72.78 X11 + 43.55 X12 + 81.87 X13 + 24.56 X14 + 75.62 X15
       + 100 X16 + 60.65 X17 + 66.63 X18 + 39.64 X19 + 53.02 X110
       >=   3.8

C42)   21.1 X21 + 9.9 X22 + 100 X23 + 55.24 X24 + 37.23 X25
       + 55.76 X26 + 26.23 X27 + 37.05 X28 + 51.44 X29 + 17.38 X210
       >=   0

C43)   46.03 X31 + 41.78 X32 + 94.75 X33 + 37.19 X34 + 38.53 X35
       + 99 X36 + 59.56 X37 + 38.95 X38 + 0.28 X39 + 43.9 X310 >=   0

C44)   60.14 X41 + 49.52 X42 + 92.47 X43 + 28.04 X44 + 54.7 X45
       + 100 X46 + 51.19 X47 + 54.7 X48 + 15.93 X49 + 26.55 X410
       >=   37.5

C45)   50.82 X51 + 51.86 X52 + 100 X53 + 49.03 X54 + 79.59 X55
       + 82.68 X56 + 23 X57 + 75.88 X58 + 55.67 X59 + 20.99 X510
       >=   2.36

C46)   38.27 X61 + 34.01 X62 + 100 X63 + 31.94 X64 + 70.67 X65
       + 93.33 X66 + 38.87 X67 + 47.47 X68 + 50.67 X69 + 34.93 X610
       >=   26.25

C51)   100 X11 + 100 X12 + 100 X15 + 100 X18 + 100 X19 + 100 X110
       >=   50

C53)   100 X31 + 100 X32 + 100 X35 + 100 X38 + 100 X39 + 100 X310
       >=   0

C54)   100 X41 + 100 X42 + 100 X45 + 100 X48 + 100 X49 + 100 X410
       >=   50
```

```
C55)   100 X51 + 100 X52 + 100 X55 + 100 X58 + 100 X59 + 100 X510
       >=   50

C56)   100 X61 + 100 X62 + 100 X65 + 100 X68 + 100 X69 + 100 X610
       >=   0

C61)   77 X11 + 100 X12 + 11 X13 + 9 X14 + 77 X15 + 7 X16 + 50 X17
       + 66 X18 + 100 X19 + 100 X110 >=   76

C62)   75 X21 + 100 X22 + 38 X23 + X24 + 75 X25 + 13 X26 + 25 X27
       + 75 X28 + 100 X29 + 100 X210 >=   91

C64)   55 X41 + 100 X42 + 6 X43 + X44 + 55 X45 + 5 X46 + 50 X47
       + 52 X48 + 100 X49 + 100 X410 >=   50

C66)   75 X61 + 100 X62 + 13 X63 + X64 + 75 X65 + 13 X66 + 50 X67
       + 63 X68 + 100 X69 + 100 X610 >=   75

C71)   50 X11 + 50 X12 + 100 X13 + 50 X14 + 50 X15 + 100 X16 + 50 X17
       + 10 X18 + 50 X19 + 50 X110 >=   50

C72)   98 X21 + 98 X22 + 100 X23 + 98 X24 + 98 X25 + 100 X26 + 98 X27
       + X28 + 98 X29 + 98 X210 >=   98

C74)   10 X41 + 10 X42 + 100 X43 + 10 X44 + 10 X45 + 100 X46 + 10 X47
       + 10 X49 + 10 X410 >=   10

C75)   67 X51 + 67 X52 + 100 X53 + 67 X54 + 67 X55 + 100 X56 + 67 X57
       + 33 X58 + 67 X59 + 67 X510 >=   67

C76)   10 X61 + 10 X62 + 100 X63 + 10 X64 + 10 X65 + 100 X66 + 10 X67
       + X68 + 10 X69 + 10 X610 >=   10

C81)   47.56 X11 + 44.6 X12 + 92.13 X13 + 67.52 X14 + 96.16 X16
       + 60.74 X17 + 1.74 X18 + 4.71 X19 + 12.36 X110 >=   42.75

C82)   48.11 X21 + 48.07 X22 + 99.98 X23 + 79.65 X24 + 94.51 X26
       + 74.06 X27 + 2.57 X29 + 14.43 X210 + 2 53X28 >=   46.39

C83)   52.13 X31 + 51.7 X32 + 98.88 X33 + 79.97 X34 + 88.72 X36
       + 68.35 X37 + 5.1 X38 + 5.52 X39 + 21.18 X310 >=   47.15

C84)   52.13 X41 + 51.7 X42 + 98.88 X43 + 79.97 X44 + 88.72 X46
       + 68.35 X47 + 5.1 X48 + 5.52 X49 + 21.18 X410 >=   47.15

C85)   44.73 X51 + 42 X52 + 93.75 X53 + 68.66 X54 + 100 X57
       + 66.31 X58 + 2.35 X59 + 7.8 X510 >=   42

C86)   48.48 X61 + 48.48 X62 + 100 X63 + 79.96 X64 + 93.8 X66
       + 73.81 X67 + 2.8 X68 + 2.8 X69 + 15.15 X610 >=   46.53

N1)   X11 + X12 + X13 + X14 + X15 + X16 + X17 + X18 + X19 + X110 =    1

N2)   X21 + X22 + X23 + X24 + X25 + X26 + X27 + X28 + X29 + X210 =    1

N3)   X31 + X32 + X33 + X34 + X35 + X36 + X37 + X38 + X39 + X310 =    1
```

```
N4)   X41 + X42 + X43 + X44 + X45 + X46 + X47 + X48 + X49 + X410 =    1

N5)   X51 + X52 + X53 + X54 + X55 + X56 + X57 + X58 + X59 + X510 =    1

N6)   X61 + X62 + X63 + X64 + X65 + X66 + X67 + X68 + X69 + X610 =    1

  END

  SUB       X11         1.00000
  INTE       X11
  SUB       X12         1.00000
  INTE       X12
  SUB       X13         1.00000
  INTE       X13
  SUB       X14         1.00000
  INTE       X14
  SUB       X15         1.00000
  INTE       X15
  SUB       X16         1.00000
  INTE       X16
  SUB       X17         1.00000
  INTE       X17
  SUB       X18         1.00000
  INTE       X18
  SUB       X19         1.00000
  INTE       X19
  SUB      X110         1.00000
  INTE      X110
  SUB       X21         1.00000
  INTE       X21
  SUB       X22         1.00000
  INTE       X22
  SUB       X23         1.00000
  INTE       X23
  SUB       X24         1.00000
  INTE       X24
  SUB       X25         1.00000
  INTE       X25
  SUB       X26         1.00000
  INTE       X26
  SUB       X27         1.00000
  INTE       X27
  SUB       X28         1.00000
  INTE       X28
  SUB       X29         1.00000
  INTE       X29
  SUB      X210         1.00000
  INTE      X210
  SUB       X31         1.00000
  INTE       X31
  SUB       X32         1.00000
  INTE       X32
  SUB       X33         1.00000
  INTE       X33
  SUB       X34         1.00000
  INTE       X34
  SUB       X35         1.00000
```

```
INTE      X35
SUB      X36         1.00000
INTE      X36
SUB      X37         1.00000
INTE      X37
SUB      X38         1.00000
INTE      X38
SUB      X39         1.00000
INTE      X39
SUB     X310         1.00000
INTE     X310
SUB      X41         1.00000
INTE      X41
SUB      X42         1.00000
INTE      X42
SUB      X43         1.00000
INTE      X43
SUB      X44         1.00000
INTE      X44
SUB      X45         1.00000
INTE      X45
SUB      X46         1.00000
INTE      X46
SUB      X47         1.00000
INTE      X47
SUB      X48         1.00000
INTE      X48
SUB      X49         1.00000
INTE      X49
SUB     X410         1.00000
INTE     X410
SUB      X61         1.00000
INTE      X61
SUB      X62         1.00000
INTE      X62
SUB      X63         1.00000
INTE      X63
SUB      X64         1.00000
INTE      X64
SUB      X65         1.00000
INTE      X65
SUB      X66         1.00000
INTE      X66
SUB      X67         1.00000
INTE      X67
SUB      X68         1.00000
INTE      X68
SUB      X69         1.00000
INTE      X69
SUB     X610         1.00000
INTE     X610
SUB      X51         1.00000
INTE      X51
SUB      X52         1.00000
INTE      X52
SUB      X53         1.00000
INTE      X53
```

```
SUB       X54         1.00000
INTE       X54
SUB       X55         1.00000
INTE       X55
SUB       X56         1.00000
INTE       X56
SUB       X57         1.00000
INTE       X57
SUB       X58         1.00000
INTE       X58
SUB       X59         1.00000
INTE       X59
SUB      X510         1.00000
INTE      X510
```

Table 12: Goal Programming Formulation Based on Weighted-averaged patient population Preferences and Linear Value Functions

Variable Definition:

Let X_k = the number of patients put on therapeutic combination k

Where therapeutic combination k = 1 to 10

Let g_i = the goal i, (for all patients).

Where the goal i = 1 to 7

Let n_i = the % underachievement of goal i, (for all patients).

Where the goal i = 1 to 7

Let α_i = the penalty coefficient related to the underachievement deviational variable n, for goal i, (for all patients).

Where the goal i = 1 to 7

Let c_{ij} = the therapeutic constraint representing a minimal acceptable level of care to be satisfied by goal i (for all patients).

Where the goal i = 1 to 7

```
MIN      6.8 N1 + 12.9 N2 + 2.5 N3 + N4 + 6.8 N5 + 3.3 N6 + 2.4 N7

SUBJECT TO

G1)   11.88 X1 + 11.91 X2 + 0.28 X3 + 1.11 X4 + 11.88 X5 + 0.75 X6
       + 1.27 X7 + 16.67 X8 + 11.79 X9 + 11.88 X10 + N1 =    100

G2)   16.67 X1 + 16.67 X2 + 7.28 X3 + 16.67 X4 + 16.67 X5 + 7.28 X6
       + 16.67 X7 + 16.67 X8 + 16.67 X9 + 16.67 X10 + N2 =    100

G3)   14.24 X1 + 7.78 X2 + 16.67 X3 + 12.58 X4 + 1.19 X5 + 14.65 X6
       + 14.52 X7 + 2.74 X8 + 0.79 X9 + 1.84 X10 + N3 =    100

G4)   8.83 X1 + 5.56 X2 + 16.67 X3 + 6.63 X4 + 8.46 X5 + 15.18 X6
       + 7.94 X7 + 8.1 X8 + 5.14 X9 + 6.34 X10 + N4 =    100
```

```
G5)   16.67 X1 + 16.67 X2 + 16.67 X5 + 16.67 X8 + 16.67 X9
       + 16.67 X10 + N5 =    100

G6)   13.33 X1 + 16.67 X2 + 3.67 X3 + 5.67 X4 + 13.33 X5 + 1.83 X6
       + 5.67 X7 + 10 X8 + 16.67 X9 + 16.67 X10 + N6 =    100

G7)   8.68 X1 + 8.68 X2 + 16.67 X3 + 8.68 X4 + 8.68 X5
       + 16.67 X6 + 8.68 X7 + 8.68 X9 + 8.68 X10 + N7 =    100

C1)   71.3 X1 + 71.4 X2 + 1.7 X3 + 6.7 X4 + 71.3 X5 + 4.5 X6 + 7.6 X7
       + 100 X8 + 70.7 X9 + 71.3 X10 >=   316.2

C2)   100 X1 + 100 X2 + 43.7 X3 + 100 X4 + 100 X5 + 43.7 X6 + 100 X7
       + 100 X8 + 100 X9 + 100 X10 >=   374.6

C3)   83.9 X1 + 45.8 X2 + 98.2 X3 + 74.1 X4 + 7 X5 + 86.3 X6
       + 85.5 X7 + 16.1 X8 + 4.7 X9 + 10.8 X10 >=   140.7

C4)   49.7 X1 + 31.3 X2 + 93.8 X3 + 37.3 X4 + 47.6 X5 + 85.4 X6
       + 44.7 X7 + 45.6 X8 + 28.9 X9 + 35.6 X10 >=   74.4

C5)   100 X1 + 100 X2 + 100 X5 + 100 X8 + 100 X9 + 100 X10 >=   300

C6)   80 X1 + 100 X2 + 22 X3 + 34 X4 + 80 X5 + 11 X6 + 34 X7 + 60 X8
       + 100 X9 + 100 X10 >=   318

C7)   52.2 X1 + 52.2 X2 + 100 X3 + 52.2 X4 + 52.2 X5 + 100 X6
       + 52.2 X7 + 52.2 X9 >=   313.2

C8)   47.68 X1 + 45.28 X2 + 93.63 X3 + 69.86 X4 + 95.78 X6 + 63.28 X7
       + 1.9 X8 + 4.3 X9 + 12.8 X10 >=   54.88

C9)   X1 + X2 + X3 + X4 + X5 + X6 + X7 + X8 + X9 + X10 =    6

END
  GIN        X1
  GIN        X2
  GIN        X3
  GIN        X4
  GIN        X5
  GIN        X6
  GIN        X7
  GIN        X8
  GIN        X9
  GIN       X10
```

Table 13: Goal Programming Formulation Based on Weighted-averaged Healthcare Professional Population Preferences and Linear Value Functions

Variable Definition:

Let X_k = the number of patients put on therapeutic combination k

Where therapeutic combination k = 1 to 10

Let g_i = the goal i, (for all patients).

Where the goal i = 1 to 7

Let n_i = the % underachievement of goal i, (for all patients).

Where the goal i = 1 to 7

Let α_i = the penalty coefficient related to the underachievement deviational variable n, for goal i, (for all patients).

Where the goal i = 1 to 7

Let c_{ij} = the therapeutic constraint representing a minimal acceptable level of care to be satisfied by goal i (for all patients).

Where the goal i = 1 to 7

```
MIN     3.5 N1 + 3.92 N2 + 2.8 N3 + 2.6 N4 + 2.75 N5 + 1.6 N6 + N7

SUBJECT TO

G1)   13.18 X1 + 13.24 X2 + 1.11 X3 + 2.82 X4 + 13.18 X5 + 2.16 X6
       + 2.92 X7 + 16.67 X8 + 13.02 X9 + 13.18 X10 + N1 =    100

G2)   16.67 X1 + 16.67 X2 + 6.46 X3 + 16.67 X4 + 16.67 X5 + 6.46 X6
       + 16.67 X7 + 16.67 X8 + 16.67 X9 + 16.67 X10 + N2 =    100

G3)   9.77 X1 + 7.92 X2 + 16.67 X3 + 12.46 X4 + 1.38 X5 + 15.77 X6
       + 12.25 X7 + 0.49 X8 + 1.14 X9 + 2.44 X10 + N3 =    100

G4)   4.01 X1 + 4.16 X2 + 16.67 X3 + 4.83 X4 + 9.979998 X5 + 16.09 X6
       + 7.35 X7 + 9.28 X8 + 4.38 X9 + 3.17 X10 + N4 =    100

G5)   16.7 X1 + 16.7 X2 + 16.7 X5 + 16.7 X8 + 16.7 X9 + 16.7 X10 + N5
       =    100
```

```
G6)    13 X1 + 16.67 X2 + 1.83 X3 + 8.33 X4 + 13 X5 + 1.83 X6
        + 8.33 X7 + 10.5 X8 + 16.67 X9 + 16.67 X10 + N6 =    100

G7)    7.96 X1 + 7.96 X2 + 16.67 X3 + 7.96 X4 + 7.96 X5 + 16.67 X6
        + 7.96 X7 + 7.96 X9 + 7.96 X10 + N7 =    100

C1)    79.1 X1 + 79.43 X2 + 6.65 X3 + 16.9 X4 + 79.1 X5 + 12.94 X6
        + 17.54 X7 + 100 X8 + 78.11 X9 + 79.1 X10 >=    406

C3)    30.86 X1 + 47.49 X2 + 100 X3 + 74.73 X4 + 8.25 X5 + 94.59 X6
        + 73.5 X7 + 2.96 X8 + 6.86 X9 + 14.62 X10 >=    0

C4)    47.68 X1 + 23.6 X2 + 94.5 X3 + 27.41 X4 + 56.58 X5 + 91.25 X6
        + 41.67 X7 + 52.64 X8 + 24.83 X9 + 18 X10 >=    103.1

C6)    78 X1 + 100 X2 + 11 X3 + 50 X4 + 78 X5 + 11 X6 + 50 X7 + 63 X8
        + 100 X9 + 100 X10 >=    210

C7)    47.76 X1 + 47.76 X2 + 100 X3 + 47.76 X4 + 47.76 X5 + 100 X6
        + 47.76 X7 + 47.76 X9 + 47.76 X10 >=    286.6

C8)    23.1 X1 + 45.28 X2 + 93.63 X3 + 69.86 X4 + 95.78 X6 + 63.28 X7
        + 1.9 X8 + 4.3 X9 + 12.8 X10 >=    38.7

C9)    X1 + X2 + X3 + X4 + X5 + X6 + X7 + X8 + X9 + X10 =    6
 END
  GIN         X1
  GIN         X2
  GIN         X3
  GIN         X4
  GIN         X5
  GIN         X6
  GIN         X7
  GIN         X8
  GIN         X9
  GIN        X10
```

Table 14: Goal Programming Formulation Based on Combined Weighted-averaged (50/50%) Patient and Healthcare Professional Preferences and Linear Value Functions

Let X_k = the number of patients put on therapeutic combination k

Where therapeutic combination k = 1 to 10

Let g_i = the goal i, (for all patients).

Where the goal i = 1 to 7

Let n_i = the % underachievement of goal i, (for all patients).

Where the goal i = 1 to 7

Let α_i = the penalty coefficient related to the underachievement deviational variable n, for goal i, (for all patients).

Where the goal i = 1 to 7

Let c_{ij} = the therapeutic constraint representing a minimal acceptable level of care to be satisfied by goal i (for all patients).

Where the goal i = 1 to 7

```
MIN     3.04 N1 + 4.96 N2 + 1.56 N3 + 1.07 N4 + 2.8 N5 + 1.43 N6 + N7

SUBJECT TO

G1)   12.53 X1 + 12.57 X2 + 0.69 X3 + 1.96 X4 + 12.53 X5 + 1.45 X6
       + 2.1 X7 + 16.67 X8 + 12.4 X9 + 12.53 X10 + N1 =    100

G2)   16.67 X1 + 16.67 X2 + 6.87 X3 + 16.67 X4 + 16.67 X5 + 6.87 X6
       + 16.67 X7 + 16.67 X8 + 16.67 X9 + 16.67 X10 + N2 =    100

G3)   12.11 X1 + 8.189999 X2 + 16.67 X3 + 12.5 X4 + 1.24 X5
       + 15.22 X6 + 13.46 X7 + 1.67 X8 + 0.94 X9 + 92.16 X10 + N3
       =    100

G4)   6.42 X1 + 4.86 X2 + 16.67 X3 + 5.73 X4 + 9.22 X5 + 15.64 X6
       + 7.65 X7 + 8.689999 X8 + 4.76 X9 + 4.76 X10 + N4 =    100

G5)   16.67 X1 + 16.67 X2 + 16.67 X5 + 16.67 X8 + 16.67 X9
       + 16.67 X10 + N5 =    100
```

```
G6)    13.17 X1 + 16.67 X2 + 2.75 X3 + 7 X4 + 13.17 X5 + 1.83 X6
        + 7 X7 + 10.25 X8 + 16.67 X9 + 16.67 X10 + N6 =     100

G7)    8.33 X1 + 8.33 X2 + 16.67 X3 + 8.33 X4 + 8.33 X5 + 16.67 X6
        + 8.33 X7 + 8.33 X9 + 8.33 X10 + N7 =     100

C1)    75.18 X1 + 75.43 X2 + 4.17 X3 + 11.78 X4 + 75.18 X5 + 8.72 X6
        + 12.59 X7 + 100 X8 + 74.41 X9 + 75.18 X10 >=    361.35

C2)    100 X1 + 100 X2 + 41.21 X3 + 100 X4 + 100 X5 + 41.21 X6
        + 100 X7 + 100 X8 + 100 X9 + 100 X10 >=    487.32

C3)    72.64 X1 + 49.13 X2 + 100 X3 + 74.99 X4 + 7.43 X5 + 91.35 X6
        + 80.75 X7 + 10.03 X8 + 5.62 X9 + 12.95 X10 >=    94.77

C4)    38.52 X1 + 29.17 X2 + 100 X3 + 34.4 X4 + 55.32 X5 + 93.82 X6
        + 45.87 X7 + 52.17 X8 + 28.57 X9 + 28.53 X10 >=    88.77

C5)    100 X1 + 100 X2 + 100 X5 + 100 X8 + 100 X9 + 100 X10 >=    450

C6)    79 X1 + 100 X2 + 16.5 X3 + 42 X4 + 79 X5 + 11 X6 + 42 X7
        + 61.5 X8 + 100 X9 + 100 X10 >=    264

C7)    49.98 X1 + 49.98 X2 + 100 X3 + 49.98 X4 + 49.98 X5 + 100 X6
        + 49.98 X7 + 49.98 X9 + 49.98 X10 >=    299.88

C8)    47.68 X1 + 45.28 X2 + 93.63 X3 + 69.86 X4 + 95.78 X6 + 63.28 X7
        + 1.9 X8 + 4.3 X9 + 12.8 X10 >=    42.87

C2)    X1 + X2 + X3 + X4 + X5 + X6 + X7 + X8 + X9 + X10 =     6

END
  GIN         X1
  GIN         X2
  GIN         X3
  GIN         X4
  GIN         X5
  GIN         X6
  GIN         X7
  GIN         X8
  GIN         X9
  GIN         X10
```

Table 15: MAUT Decision Analysis Based on Individual Patient Level Preferences and Linear Value Functions

Scaled Individual Patient MAUT Model											
Patient 1		**Relative Importance of Decision Attributes**	X1	X3	X4	X5	X6	X7	X8	X9	X10
g11	Durable Viral Load Suppression	**26%**	19.49	0.31	1.79	19.49	1.18	2.00	25.64	19.33	19.49
g21	Clinical Benefit	**26%**	25.64	12.82	25.64	25.64	12.82	25.64	25.64	25.64	25.64
g31	Adverse Effects	**0%**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
g41	Ease of Use	**3%**	1.87	2.09	0.63	1.94	2.56	1.56	1.71	1.02	1.36
g51	Resistance	**26%**	25.64	0.00	0.00	25.64	0.00	0.00	25.64	25.64	25.64
g61	Treatment guidelines	**13%**	9.87	1.41	1.15	9.87	0.90	6.41	8.46	12.82	12.82
g71	Future options	**8%**	3.85	7.69	3.85	3.85	7.69	3.85	0.77	3.85	3.85
		Total	86.35	24.32	33.07	86.43	25.15	39.45	87.86	88.30	88.80
		Rank	6	10	8	5	9	7	4	3	1
		Satisfies All Constraints	yes	no	no	no	no	no	no	no	no

Patient 1	**Selection**									
Total # of Violated Constraints		0.00	4.00	3.00	1.00	4.00	3.00	3.00	1.00	1.00
c11	Durable Viral Load Suppression	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c21	Clinical Benefit	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c31	Adverse Effects	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c41	Ease of Use	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c51	Resistance	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c61	Treatment guidelines	0.00	1.00	1.00	0.00	1.00	1.00	1.00	0.00	0.00
c71	Future options	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c81	Drug Interactions	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00

Scaled Individual Patient MAUT Model											
Patient 2		**Relative Importance of Decision Attributes**	X1	X3	X4	X5	X6	X7	X8	X9	X10
g12	Durable Viral Load Suppression	**27%**	20.63	0.35	3.07	20.63	2.02	3.25	26.60	20.36	20.63
g22	Clinical Benefit	**27%**	26.60	0.53	26.60	26.60	0.53	26.60	26.60	26.60	26.60
g32	Adverse Effects	**20%**	15.51	18.06	14.88	6.97	19.95	15.57	2.40	2.92	0.39
g42	Ease of Use	**5%**	1.12	5.32	2.94	1.98	2.97	1.40	1.97	2.74	0.92
g52	Resistance	**0%**	0.27	0.00	0.00	0.27	0.00	0.00	0.27	0.27	0.27
g62	Treatment guidelines	**11%**	7.98	4.04	0.11	7.98	1.38	2.66	7.98	10.64	10.64
g72	Future options	**11%**	10.43	10.64	10.43	10.43	10.64	10.43	0.11	10.43	10.43
		Total	82.52	38.95	58.02	74.85	37.48	59.90	65.92	73.95	69.87
		Rank	1	9	8	3	10	7	6	4	5
		Satisfies All Constraints	no	no	no	no	no	no	no	no	no

Patient 2		**Selection**									
Total # of Violated Constraints			1.00	4.00	3.00	2.00	4.00	3.00	4.00	2.00	2.00
c12	Durable Viral Load Suppression		0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c22	Clinical Benefit		0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c32	Adverse Effects		0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00
c42	Ease of Use		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c52	Resistance		0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c62	Treatment guidelines		1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00
c72	Future options		0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c82	Drug Interactions		0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00

Scaled Individual Patient MAUT Model											
Patient 3		**Relative Importance of Decision Attributes**	X2	X3	X4	X5	X6	X7	X8	X9	X10
g13	Durable Viral Load Suppression	**0%**	0.35	0.01	0.00	0.35	0.00	0.01	0.49	0.35	0.35
g23	Clinical Benefit	**49%**	48.54	9.71	48.54	48.54	9.71	48.54	48.54	48.54	48.54
g33	Adverse Effects	**0%**	0.24	0.49	0.33	0.00	0.45	0.37	0.12	0.06	0.10
g43	Ease of Use	**0%**	0.20	0.46	0.18	0.19	0.49	0.29	0.19	0.00	0.21
g53	Resistance	**49%**	48.54	0.00	0.00	48.54	0.00	0.00	48.54	48.54	48.54
g63	Treatment guidelines	**0%**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
g73	Future options	**1%**	1.46	1.46	1.46	1.46	1.46	1.46	0.00	1.46	1.46
		Total	99.34	12.12	50.52	99.09	12.11	50.67	97.88	98.95	99.21
		Rank	2	9	8	4	10	7	6	5	3
		Satisfies All Constraints	yes	no	no	no	no	no	no	no	no
Patient 3		**Selection**									
Total # of Violated Constraints			0.00	2.00	1.00	2.00	2.00	1.00	2.00	1.00	1.00
c13	Durable Viral Load Suppression		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c23	Clinical Benefit		0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c33	Adverse Effects		0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00
c43	Ease of Use		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c53	Resistance		0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c63	Treatment guidelines										
c73	Future options		0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c83	Drug Interactions		0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00

Scaled Individual Patient MAUT Model												
Patient 4		**Relative Importance of Decision Attributes**	X1		X3	X4	X5	X6	X7	X8	X9	X10
g14	Durable Viral Load Suppression	**8%**	4.03		0.22	0.31	4.03	0.23	0.46	8.13	4.01	4.03
g24	Clinical Benefit	**81%**	81.30		40.65	81.30	81.30	40.65	81.30	81.30	81.30	81.30
g34	Adverse Effects	**1%**	0.46		0.81	0.57	0.00	0.73	0.63	0.33	0.09	0.17
g44	Ease of Use	**0%**	0.00		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
g54	Resistance	**8%**	8.13		0.00	0.00	8.13	0.00	0.00	8.13	8.13	8.13
g64	Treatment guidelines	**1%**	0.45		0.05	0.01	0.45	0.04	0.41	0.42	0.81	0.81
g74	Future options	**1%**	0.08		0.81	0.08	0.08	0.81	0.08	0.00	0.08	0.08
		Total	94.45		42.54	82.27	93.99	42.46	82.88	98.31	94.43	94.53
		Rank	4		9	8	6	10	7	1	5	3
		Satisfies All Constraints	no		no	no	no	no	no	no	no	no
Patient 4		**Selection**										
Total # of Violated Constraints			1.00		3.00	4.00	2.00	3.00	2.00	3.00	3.00	3.00
c14	Durable Viral Load Suppression		0.00		1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c24	Clinical Benefit		0.00		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c34	Adverse Effects		1.00		0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00
c44	Ease of Use		0.00		0.00	1.00	0.00	0.00	0.00	0.00	1.00	1.00
c54	Resistance		0.00		1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c64	Treatment guidelines		0.00		1.00	1.00	0.00	1.00	0.00	0.00	0.00	0.00
c74	Future options		0.00		0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c84	Drug Interactions		0.00		0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00

Scaled Individual Patient MAUT Model											
Patient 5		**Relative Importance of Decision Attributes**	X2	X3	X4	X5	X6	X7	X8	X9	X10
g15	Durable Viral Load Suppression	**17%**	12.47	0.32	0.22	12.47	0.20	0.38	16.84	12.46	12.47
g25	Clinical Benefit	**17%**	17.01	15.31	17.01	17.01	15.31	17.01	17.01	17.01	17.01
g35	Adverse Effects	**17%**	11.73	17.01	11.95	6.49	9.47	13.49	0.00	2.35	2.86
g45	Ease of Use	**17%**	8.64	16.67	8.17	13.26	13.78	3.83	12.65	9.28	3.50
g55	Resistance	**15%**	15.31	0.00	0.00	15.31	0.00	0.00	15.31	15.31	15.31
g65	Treatment guidelines	**17%**	17.01	8.50	0.17	16.50	4.25	4.42	16.16	17.01	17.01
g75	Future options	**0%**	0.11	0.17	0.11	0.11	0.17	0.11	0.06	0.11	0.11
		Total	82.27	57.98	37.63	81.14	43.18	39.24	78.01	73.52	68.26
		Rank	2	7	10	3	8	9	4	5	6
		Satisfies All Constraints	yes	no	no	no	no	no	no	no	no

Patient 5	**Selection**								
Total # of Violated Constraints		0.00	3.00	2.00	2.00	4.00	2.00	3.00	2.00	2.00
c15	Durable Viral Load Suppression	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c25	Clinical Benefit	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c35	Adverse Effects	0.00	0.00	0.00	1.00	1.00	0.00	1.00	1.00	1.00
c45	Ease of Use	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c55	Resistance	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c65	Treatment guidelines	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c75	Future options	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c85	Drug Interactions	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00

Scaled Individual Patient MAUT Model											
Patient 6		**Relative Importance of Decision Attributes**	X2	X3	X4	X5	X6	X7	X8	X9	X10
g16	Durable Viral Load Suppression	**21%**	12.98	0.43	2.47	12.91	1.62	2.75	21.38	12.70	12.91
g26	Clinical Benefit	**24%**	23.75	11.88	23.75	23.75	11.88	23.75	23.75	23.75	23.75
g36	Adverse Effects	**21%**	4.87	21.38	15.12	0.04	20.10	16.89	6.37	2.32	5.65
g46	Ease of Use	**0%**	0.08	0.24	0.08	0.17	0.22	0.09	0.11	0.12	0.08
g56	Resistance	**2%**	2.38	0.00	0.00	2.38	0.00	0.00	2.38	2.38	2.38
g66	Treatment guidelines	**12%**	11.88	1.54	0.12	8.91	1.54	5.94	7.48	11.88	11.88
g76	Future options	**19%**	1.90	19.00	1.90	1.90	19.00	1.90	0.19	1.90	1.90
		Total	57.83	54.46	43.44	50.06	54.37	51.33	61.66	55.05	58.55
		Rank	4	6	10	9	7	8	2	5	3
		Satisfies All Constraints	yes	no	no	no	no	no	no	no	no
Patient 6		**Selection**									
Total # of Violated Constraints			0.00	4.00	3.00	2.00	4.00	3.00	3.00	2.00	1.00
c16	Durable Viral Load Suppression		0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c26	Clinical Benefit		0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c36	Adverse Effects		0.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00	0.00
c46	Ease of Use		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c56	Resistance		0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c66	Treatment guidelines		0.00	1.00	1.00	0.00	1.00	1.00	1.00	0.00	0.00
c76	Future options		0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c86	Drug Interactions		0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00

Table 16: MAUT Decision Analysis Based on Weighted-averaged patient population Preferences and Linear Value Functions

Scaled AGG. Patient MAUT Model		Relative Importance of Decision Attributes	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10
g1	Durable Viral Load Suppression	**19%**	13.60	13.63	0.32	1.27	13.60	0.86	1.46	19.08	13.49	13.60
g2	Clinical Benefit	**36%**	36.19	36.19	15.81	36.19	36.19	15.81	36.19	36.19	36.19	36.19
g3	Adverse Effects	**7%**	6.05	3.54	6.98	5.25	0.46	6.15	6.14	1.19	0.30	0.79
g4	Ease of Use	**3%**	1.49	0.94	2.81	1.12	1.43	2.56	1.34	1.37	0.87	1.07
g5	Resistance	**19%**	19.08	19.08	0.00	0.00	19.08	0.00	0.00	19.08	19.08	19.08
g6	Treatment guidelines	**9%**	7.32	9.15	2.01	3.11	7.32	1.01	3.11	5.49	9.15	9.15
g7	Future options	**7%**	3.50	3.50	6.70	3.50	3.50	6.70	3.50	0.00	3.50	3.50
		Total	87.23	86.03	34.63	50.45	81.58	33.08	51.74	82.41	82.59	83.38
		Rank	1	2	9	8	6	10	7	5	4	3
		Satisfies All Constraints	yes	yes	no	no	no	no	no	no	no	no
		Selection	**X**									

Total # of Violated Constraints		0.00	0.00	4.00	3.00	2.00	4.00	3.00	3.00	2.00	1.00
c1	Durable Viral Load Suppression	0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c2	Clinical Benefit	0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c3	Adverse Effects	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00
c4	Ease of Use	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c5	Resistance	0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c6	Treatment guidelines	0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c7	Future options	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c8	Drug Interactions	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	0.00

Table 17: MAUT Decision Analysis Based on Weighted-averaged Healthcare Professional Population Preferences and Linear Value Functions

Scaled AGG. HCP MAUT Model		Relative Importance of Decision Attributes	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10
g1	Durable Viral Load Suppression	**19%**	15.30	15.36	1.29	3.27	15.30	2.50	3.39	19.34	15.10	15.30
g2	Clinical Benefit	**22%**	21.55	21.55	8.35	21.55	21.55	8.35	21.55	21.55	21.55	21.55
g3	Adverse Effects	**16%**	9.07	7.35	15.47	11.56	1.27	14.63	11.37	0.46	1.07	2.26
g4	Ease of Use	**14%**	3.45	3.59	14.36	4.17	8.60	13.87	6.33	8.00	3.77	2.74
g5	Resistance	**15%**	14.92	14.92	0.00	0.00	14.92	0.00	0.00	14.92	14.92	14.92
g6	Treatment guidelines	**9%**	6.90	8.84	0.97	4.42	6.90	0.97	4.42	5.57	8.84	8.84
g7	Future options	**6%**	2.64	2.64	5.52	2.64	2.64	5.52	2.64	0.00	2.64	2.64
		Total	73.81	74.24	45.97	47.60	71.16	45.85	49.70	69.84	67.89	68.23
		Rank	2	1	9	8	3	10	7	4	6	5
		Satisfies All Constraints	yes	yes	no	no	no	no	no	no	no	yes
		Selection		X								
Total # of Violated Constraints			0.00	0.00	4.00	2.00	1.00	4.00	2.00	2.00	1.00	0.00
c1	Durable Viral Load Suppression		0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c2	Clinical Benefit		0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c3	Adverse Effects		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c4	Ease of Use		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c5	Resistance		0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c6	Treatment guidelines		0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c7	Future options		0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c8	Drug Interactions		0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	0.00

Table 18: MAUT Decision Analysis Based on Combined Weighted-averaged (50/50%) Patient and Healthcare Professional Preferences and Linear Value Functions

Scaled Combined (50/50) MAUT Model		Relative Importance of Decision Attributes	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10
g1	Durable Viral Load Suppression	19%	14.41	14.46	0.80	2.26	14.41	1.67	2.41	19.17	14.26	14.41
g2	Clinical Benefit	31%	31.25	31.25	12.88	31.25	31.25	12.88	31.25	31.25	31.25	31.25
g3	Adverse Effects	10%	7.15	4.84	9.85	7.38	0.73	8.99	7.95	0.99	0.55	1.28
g4	Ease of Use	7%	2.59	1.96	6.71	2.31	3.71	6.30	3.08	3.50	1.92	1.92
g5	Resistance	18%	17.68	17.68	0.00	0.00	17.68	0.00	0.00	17.68	17.68	17.68
g6	Treatment guidelines	9%	7.14	9.04	1.49	3.80	7.14	0.99	3.80	5.56	9.04	9.04
g7	Future options	6%	3.15	3.15	6.30	3.15	3.15	6.30	3.15	0.00	3.15	3.15
		Total	83.37	82.38	38.03	50.15	78.08	37.14	51.64	78.15	77.86	78.72
		Rank	1	2	9	8	5	10	7	4	6	3
		Satisfies All Constraints	yes	yes	no	no	no	no	no	no	no	no
		Selection	X									

Total # of Violated Constraints		0.00	0.00	4.00	3.00	2.00	4.00	3.00	3.00	2.00	1.00
c1	Durable Viral Load Suppression	0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c2	Clinical Benefit	0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
c3	Adverse Effects	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00
c4	Ease of Use	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
c5	Resistance	0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c6	Treatment guidelines	0.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.00	0.00
c7	Future options	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00
c8	Drug Interactions	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	1.00	0.00

Table 19: Goal Programming Solution Based on Individual Patient Level Preferences and Linear Value Functions

OBJECTIVE FUNCTION VALUE

1) 32790.01

VARIABLE	VALUE	REDUCED COST
X11	.000000	-1972.780000
X12	1.000000	-1945.550000
X13	.000000	-383.670000
X14	.000000	-234.650000
X15	.000000	-1975.620000
X16	.000000	-436.000000
X17	.000000	-278.650000
X18	.000000	-2086.630000
X19	.000000	-1933.640000
X110	.000000	-1953.020000
X21	.000000	-27927.500000
X22	1.000000	-25716.750000
X23	.000000	-13123.250000
X24	.000000	-21774.050000
X25	.000000	-25041.600000
X26	.000000	-13574.200000
X27	.000000	-21520.850000
X28	.000000	-21584.750000
X29	.000000	-23703.550000
X210	.000000	-22168.850000
X31	1.000000	-512.430000
X32	.000000	-462.650000
X33	.000000	-495.850000
X34	.000000	-405.760000
X35	.000000	-410.810000
X36	.000000	-492.320000
X37	.000000	-437.610000
X38	.000000	-161.780000
X39	.000000	-383.740000
X310	.000000	-138.610000
X41	.000000	-1568.330000
X42	1.000000	-1617.380000
X43	.000000	-183.000000
X44	.000000	-69.680000
X45	.000000	-1511.200000
X46	.000000	-173.160000
X47	.000000	-144.710000
X48	.000000	-2042.160000
X49	.000000	-1564.340000
X410	.000000	-1577.180000
X61	1.000000	-25969.670000
X62	.000000	-23348.110000
X63	.000000	-22929.100000
X64	.000000	-18288.040000
X65	.000000	-20074.670000

X66	.000000	-28557.330000
X67	.000000	-21608.070000
X68	.000000	-24957.670000
X69	.000000	-22175.870000
X610	.000000	-23648.730000
X51	1.000000	-31176.310000
X52	.000000	-29467.220000
X53	.000000	-25090.070000
X54	.000000	-12127.620000
X55	.000000	-28801.770000
X56	.000000	-16391.440000
X57	.000000	-13074.740000
X58	.000000	-26958.240000
X59	.000000	-24318.640000
X510	.000000	-21224.970000
N11	23.800000	.000000
N12	22.120000	.000000
N13	27.500000	.000000
N14	50.310000	.000000
N15	25.950000	.000000
N16	39.600000	.000000
N21	.000000	10.000000
N22	.000000	.000000
N23	.000000	100.000000
N24	.000000	100.000000
N25	.000000	100.000000
N26	.000000	.000000
N32	49.190000	.000000
N33	5.199997	.000000
N34	39.520000	.000000
N35	9.910004	.000000
N36	33.940000	.000000
N41	56.450000	.000000
N42	90.100000	.000000
N43	53.970000	.000000
N45	49.180000	.000000
N46	61.730000	.000000
N51	.000000	.000000
N52	.000000	1.000000
N53	.000000	100.000000
N54	.000000	.000000
N55	.000000	.000000
N56	.000000	10.000000
N61	.000000	5.000000
N62	.000000	40.000000
N64	.000000	.000000
N65	3.000000	.000000
N66	25.000000	.000000
N71	50.000000	.000000
N72	2.000000	.000000
N73	.000000	.000000
N74	90.000000	.000000
N75	33.000000	.000000
N76	90.000000	.000000
N31	42.580000	.000000
N44	50.480000	.000000

ROW	SLACK OR SURPLUS	DUAL PRICES
G11)	.000000	-10.000000
G12)	.000000	-100.000000
G13)	.000000	-1.000000
G14)	.000000	-10.000000
G15)	.000000	-99.000000
G16)	.000000	-90.000000
G21)	.000000	.000000
G22)	.000000	-100.000000
G23)	.000000	.000000
G24)	.000000	.000000
G25)	.000000	.000000
G26)	.000000	-100.000000
G31)	.000000	.000000
G32)	.000000	-75.000000
G33)	.000000	-1.000000
G34)	.000000	-1.000000
G35)	.000000	-100.000000
G36)	.000000	-90.000000
G41)	.000000	-1.000000
G42)	.000000	-20.000000
G43)	.000000	-1.000000
G44)	.000000	.000000
G45)	.000000	-98.000000
G46)	.000000	-1.000000
G51)	.000000	-10.000000
G52)	.000000	.000000
G53)	.000000	.000000
G54)	.000000	-10.000000
G55)	.000000	-.900000
G56)	.000000	.000000
G61)	.000000	.000000
G62)	.000000	.000000
G64)	.000000	-1.000000
G65)	.000000	-100.000000
G66)	.000000	-50.000000
G71)	.000000	-3.000000
G72)	.000000	-40.000000
G73)	.000000	-3.000000
G74)	.000000	-1.000000
G75)	.000000	-1.000000
G76)	.000000	-80.000000
C11)	38.200000	.000000
C12)	16.170000	.000000
C13)	71.990000	.000000
C14)	1.090000	.000000
C15)	73.250000	.000000
C16)	24.166000	.000000
C21)	50.000000	.000000
C24)	50.000000	.000000
C25)	10.000000	.000000
C26)	50.000000	.000000
C31)	57.520000	.000000

C32)	23.010000	.000000
C33)	87.810010	.000000
C34)	.240002	.000000
C35)	26.090000	.000000
C36)	45.410000	.000000
C41)	39.750000	.000000
C42)	9.900000	.000000
C43)	46.030000	.000000
C44)	12.020000	.000000
C45)	48.460000	.000000
C46)	12.020000	.000000
C51)	50.000000	.000000
C53)	100.000000	.000000
C54)	50.000000	.000000
C55)	50.000000	.000000
C56)	100.000000	.000000
C61)	24.000000	.000000
C62)	9.000000	.000000
C64)	50.000000	.000000
C66)	.000000	.000000
C71)	.000000	.000000
C72)	.000000	.000000
C74)	.000000	.000000
C75)	.000000	.000000
C76)	.000000	.000000
C81)	1.849998	.000000
C82)	1.680000	.000000
C83)	4.980000	.000000
C84)	4.549999	.000000
C85)	2.730000	.000000
C86)	1.950001	.000000
N1)	.000000	10.000000
N2)	.000000	.000000
N3)	.000000	.900000
N4)	.000000	50.000000
N5)	.000000	1.000000
N6)	.000000	.000000

NO. ITERATIONS= 351
BRANCHES= 6 DETERM.= 1.000E 0

Table 20: Goal Programming Solution Based on Weighted-averaged patient population Preferences and Linear Value Functions

OBJECTIVE FUNCTION VALUE

1) 771.4300

VARIABLE	VALUE	REDUCED COST
X1	5.000000	-518.458000
X2	.000000	-510.264000
X3	1.000000	-206.280000
X4	.000000	-300.238000
X5	.000000	-485.463000
X6	.000000	-196.864000
X7	.000000	-307.486000
X8	.000000	-489.705000
X9	.000000	-491.553000
X10	.000000	-495.990000
N1	40.320000	.000000
N2	9.369999	.000000
N3	12.130000	.000000
N4	39.180000	.000000
N5	16.650000	.000000
N6	29.680000	.000000
N7	39.880000	.000000

ROW	SLACK OR SURPLUS	DUAL PRICES
G1)	.000000	-6.800000
G2)	.000000	-12.900000
G3)	.000000	-2.500000
G4)	.000000	-1.000000
G5)	.000000	-6.800000
G6)	.000000	-3.300000
G7)	.000000	-2.400000
C1)	42.000000	.000000
C2)	169.100000	.000000
C3)	377.000000	.000000
C4)	267.900000	.000000
C5)	200.000000	.000000
C6)	104.000000	.000000
C7)	47.799990	.000000
C8)	277.150000	.000000
C2)	.000000	.000000

NO. ITERATIONS= 291

BRANCHES= 33 DETERM.= 1.000E 0

Table 21: Goal Programming Solution Based on Weighted-averaged Healthcare Professional Population Preferences and Linear Value Functions

OBJECTIVE FUNCTION VALUE

1) 552.3518

VARIABLE	VALUE	REDUCED COST
X1	.000000	-223.943400
X2	5.000000	-225.235400
X3	.000000	-138.824200
X4	.000000	-143.950400
X5	.000000	-215.973400
X6	1.000000	-138.471200
X7	.000000	-150.264400
X8	.000000	-211.916400
X9	.000000	-206.053400
X10	.000000	-207.107400
N1	31.640000	.000000
N2	10.190000	.000000
N3	44.630000	.000000
N4	63.110000	.000000
N5	16.500000	.000000
N6	14.820000	.000000
N7	43.530000	.000000

ROW	SLACK OR SURPLUS	DUAL PRICES
G1)	.000000	-3.500000
G2)	.000000	-3.920000
G3)	.000000	-2.800000
G4)	.000000	-2.600000
G5)	.000000	-2.750000
G6)	.000000	-1.600000
G7)	.000000	-1.000000
C1)	4.090001	.000000
C3)	332.040000	.000000
C4)	106.150000	.000000
C6)	301.000000	.000000
C7)	52.199990	.000000
C8)	283.480000	.000000
C9)	.000000	.000000

NO. ITERATIONS= 687

BRANCHES= 156 DETERM.= 1.000E 0

Table 22: Goal Programming Solution Based on Combined Weighted-averaged (50/50%) Patient and Healthcare Professional Preferences and Linear Value Functions

OBJECTIVE FUNCTION VALUE

1) 383.5101

VARIABLE	VALUE	REDUCED COST
X1	5.000000	-220.374500
X2	.000000	-217.716700
X3	1.000000	-100.617400
X4	.000000	-132.612700
X5	.000000	-206.413300
X6	.000000	-98.248100
X7	.000000	-136.590300
X8	.000000	-206.597000
X9	.000000	-205.782900
X10	.000000	-348.481300
N1	36.660000	.000000
N2	9.780000	.000000
N3	22.780000	.000000
N4	51.230000	.000000
N5	16.650000	.000000
N6	31.400000	.000000
N7	41.680000	.000000

ROW	SLACK OR SURPLUS	DUAL PRICES
G1)	.000000	-3.040000
G2)	.000000	-4.960000
G3)	.000000	-1.560000
G4)	.000000	-1.070000
G5)	.000000	-2.800000
G6)	.000000	-1.430000
G7)	.000000	-1.000000
C1)	18.720000	.000000
C2)	53.889990	.000000
C3)	368.430000	.000000
C4)	203.830000	.000000
C5)	50.000000	.000000
C6)	147.500000	.000000
C7)	50.019990	.000000
C8)	289.160000	.000000
C2)	.000000	.000000

NO. ITERATIONS= 527

BRANCHES= 88 DETERM.= 1.000E 0

Table 23: Goal Programming Formulation Based on Individual Patient Level Preferences and Linear Value Functions with Unrestricted Cost-Based-Constraints

Definition of Decision Variables:

Let X_{jk} = the patient j, put on therapeutic combination k

Where patient j = 1 to 6, where j = the patient number identifier
Where therapeutic combination k = 1 to 10

Let g_{ij} = the goal i, for patient j

Where patient j = 1 to 6, where j = the patient number identifier
Where the goal i = 1 to 7, where g = the goal number identifier

```
MIN      10 N11 + 100 N12 +     N13 +  10 N14 +  99 N15 +  90 N16 +
         10 N21 + 100 N22 + 100 N23 + 100 N24 + 100 N25 + 100 N26 +
                  75 N32 +     N33 +     N34 + 100 N35 +  90 N36 +
            N41 +  20 N42 +     N43 +           98 N45 +     N46 +
         10 N51 +     N52 + 100 N53 +  10 N54 +  90 N55 +  10 N56 +
          5 N61 +  40 N62 +              N64 + 100 N65 +  50 N66 +
          3 N71 +  40 N72 +   3 N73 +     N74 +     N75 +  80 N76

  SUBJECT TO

G11)    76 X11 + 76.2 X12 + 1.2 X13 + 7 X14 + 76 X15 + 4.6 X16
        + 7.8 X17 + 100 X18 + 75.4 X19 + 76 X110 + N11 =    100

G12)    77.55 X21 + 77.88 X22 + 1.32 X23 + 11.55 X24 + 77.55 X25
        + 7.59 X26 + 12.21 X27 + 99 X28 + 76.56 X29 + 77.55 X210 + N12
        =    100

G13)    72.5 X31 + 72.5 X32 + 2 X33 + X34 + 72.5 X35 + X36 + 2 X37
        + 100 X38 + 72.5 X39 + 72.5 X310 + N13 =    100

G14)    49.69 X41 + 49.69 X42 + 2.7 X43 + 3.87 X44 + 49.6 X45
        + 2.79 X46 + 5.67 X47 + 100 X48 + 49.33 X49 + 49.6 X410 + N14
        =    100

G15)    74.05 X51 + 74.06 X52 + 1.93 X53 + 1.32 X54 + 74.05 X55
        + 1.2 X56 + 2.26 X57 + 100 X58 + 74.02 X59 + 74.05 X510 + N15
        =    100

G16)    60.4 X61 + 60.73 X62 + 1.99 X63 + 11.56 X64 + 60.4 X65
        + 70.6 X66 + 12.88 X67 + 100 X68 + 59.41 X69 + 60.4 X610 + N16
        =    100
```

```
G21)   100 X11 + 100 X12 + 50 X13 + 100 X14 + 100 X15 + 50 X16
       + 100 X17 + 100 X18 + 100 X19 + 100 X110 + N21 =    100

G22)   100 X21 + 100 X22 + 2 X23 + 100 X24 + 100 X25 + 2 X26 + 100 X27
       + 100 X28 + 100 X29 + 100 X210 + N22 =    100

G23)   100 X31 + 100 X32 + 20 X33 + 100 X34 + 100 X35 + 20 X36
       + 100 X37 + 100 X38 + 100 X39 + 100 X310 + N23 =    100

G24)   100 X41 + 100 X42 + 50 X43 + 100 X44 + 100 X45 + 50 X46
       + 100 X47 + 100 X48 + 100 X49 + 100 X410 + N24 =    100

G25)   100 X51 + 100 X52 + 90 X53 + 100 X54 + 100 X55 + 90 X56
       + 100 X57 + 100 X58 + 100 X59 + 100 X510 + N25 =    100

G26)   100 X61 + 100 X62 + 50 X63 + 100 X64 + 100 X65 + 50 X66
       + 100 X67 + 100 X68 + 100 X69 + 100 X610 + N26 =    100

G31)   87.17 X11 + 57.42 X12 + 77.39 X13 + 92.32 X14 + 1.32 X15
       + 70.25 X16 + 100 X17 + 23.05 X18 + 12.07 X19 + 19.76 X110 + N31
       =    100

G32)   77.74 X21 + 50.81 X22 + 90.55 X23 + 74.59 X24 + 34.96 X25
       + 100 X26 + 78.07 X27 + 12.05 X28 + 14.65 X29 + 1.95 X210 + N32
       =    100

G33)   94.8 X31 + 49.27 X32 + 100 X33 + 68.47 X34 + 0.68 X35
       + 93.22 X36 + 76.95 X37 + 23.73 X38 + 11.86 X39 + 20.11 X310
       + N33  =    100

G34)   56.43 X41 + 60.48 X42 + 100 X43 + 69.98 X44 + 0.2 X45
       + 90.26 X46 + 78.01 X47 + 40.16 X48 + 11.04 X49 + 21.18 X410
       + N34  =    100

G35)   90.09 X51 + 68.97 X52 + 100 X53 + 70.26 X54 + 38.15 X55
       + 55.71 X56 + 79.31 X57 + 13.79 X59 + 16.81 X510 + N35 =    100

G36)   66.06 X61 + 22.76 X62 + 100 X63 + 70.73 X64 + 0.2 X65 + 94 X66
       + 79 X67 + 29.78 X68 + 10.87 X69 + 26.42 X610 + N36 =    100

G41)   72.78 X11 + 43.55 X12 + 81.67 X13 + 24.65 X14 + 75.62 X15
       + 100 X16 + 60.65 X17 + 66.63 X18 + 39.64 X19 + 53.02 X110 + N41
       =    100

G42)   21.1 X21 + 9.9 X22 + 100 X23 + 55.24 X24 + 37.23 X25
       + 55.76 X26 + 26.23 X27 + 37.05 X28 + 51.44 X29 + 17.38 X210
       + N42 =    100

G43)   46.03 X31 + 41.78 X32 + 94.75 X33 + 37.19 X34 + 38.53 X35
       + 99 X36 + 59.56 X37 + 38.95 X38 + 0.28 X39 + 43.9 X310 + N43
       =    100

G44)   60.14 X41 + 49.52 X42 + 92.47 X43 + 28.04 X44 + 54.7 X45
       + 100 X46 + 51.19 X47 + 54.7 X48 + 15.93 X49 + 26.55 X410 + N44
       =    100
```

```
G45)   50.82 X51 + 51.86 X52 + 100 X53 + 49.03 X54 + 79.59 X55
       + 82.68 X56 + 23 X57 + 75.88 X58 + 55.67 X59 + 20.99 X510 + N45
       =    100

G46)   38.27 X61 + 34.01 X62 + 100 X63 + 31.94 X64 + 70.67 X65
       + 93.33 X66 + 38.87 X67 + 47.47 X68 + 50.67 X69 + 34.93 X610
       + N46 =    100

G51)   100 X11 + 100 X12 + 100 X15 + 100 X18 + 100 X19 + 100 X110
       + N51 =    100

G52)   100 X21 + 100 X22 + 100 X25 + 100 X28 + 100 X29 + 100 X210
       + N52 =    100

G53)   100 X31 + 100 X32 + 100 X35 + 100 X38 + 100 X39 + 100 X310
       + N53 =    100

G54)   100 X41 + 100 X42 + 100 X45 + 100 X48 + 100 X49 + 100 X410
       + N54 =    100

G55)   100 X51 + 100 X52 + 100 X55 + 100 X58 + 100 X59 + 100 X510
       + 100 N55 =    100

G56)   100 X61 + 100 X62 + 100 X65 + 100 X68 + 100 X69 + 100 X610
       + N56 =    100

G61)   77 X11 + 100 X12 + 11 X13 + 9 X14 + 77 X15 + 7 X16 + 50 X17
       + 66 X18 + 100 X19 + 100 X110 + N61 =    100

G62)   75 X21 + 100 X22 + 38 X23 + X24 + 75 X25 + 13 X26 + 25 X27
       + 75 X28 + 100 X29 + 100 X210 + N62 =    100

G64)   55 X41 + 100 X42 + 6 X43 + X44 + 55 X45 + 5 X46 + 50 X47
       + 52 X48 + 100 X49 + 100 X410 + N64 =    100

G65)   97 X51 + 100 X52 + 50 X53 + X54 + 97 X55 + 25 X56 + 26 X57
       + 95 X58 + 100 X59 + 100 X510 + N65 =    100

G66)   75 X61 + 100 X62 + 13 X63 + X64 + 75 X65 + 13 X66 + 50 X67
       + 63 X68 + 100 X69 + 100 X610 + N66 =    100

G71)   50 X11 + 50 X12 + 100 X13 + 50 X14 + 50 X15 + 100 X16 + 50 X17
       + 10 X18 + 50 X19 + 50 X110 + N71 =    100

G72)   98 X21 + 98 X22 + 100 X23 + 98 X24 + 98 X25 + 100 X26 + 98 X27
       + X28 + 98 X29 + 98 X210 + N72 =    100

G73)   100 X31 + 100 X32 + 100 X33 + 100 X34 + 100 X35 + 100 X36
       + 100 X37 + 100 X39 + X310 + N73 =    100

G74)   10 X41 + 10 X42 + 100 X43 + 10 X44 + 10 X45 + 100 X46 + 10 X47
       + 10 X49 + 10 X410 + N74 =    100

G75)   67 X51 + 67 X52 + 100 X53 + 67 X54 + 67 X55 + 100 X56 + 67 X57
       + 33 X58 + 67 X59 + 67 X510 + N75 =    100
```

```
G76)   10 X61 + 10 X62 + 100 X63 + 10 X64 + 10 X65 + 100 X66 + 10 X67
       + X68 + 10 X69 + 10 X610 + N76 =     100

C11)   76 X11 + 76.2 X12 + 1.2 X13 + 7 X14 + 76 X15 + 4.6 X16
       + 7.8 X17 + 100 X18 + 75.4 X19 + 76 X110 >=    38

C12)   77.55 X21 + 77.88 X22 + 1.32 X23 + 11.55 X24 + 77.55 X25
       + 7.59 X26 + 12.21 X27 + 99 X28 + 76.56 X29 + 77.55 X210
       >=    61.71

C13)   72.5 X31 + 72.5 X32 + 2 X33 + X34 + 72.5 X35 + X36 + 2 X37
       + 100 X38 + 72.5 X39 + 72.5 X310 >=    0.51

C14)   49.69 X41 + 49.69 X42 + 2.7 X43 + 3.87 X44 + 49.6 X45
       + 2.79 X46 + 5.67 X47 + 100 X48 + 49.33 X49 + 49.6 X410 >=   48.6

C15)   74.05 X51 + 74.06 X52 + 1.93 X53 + 1.32 X54 + 74.05 X55
       + 1.2 X56 + 2.26 X57 + 100 X58 + 74.02 X59 + 74.05 X510 >=    0.8

C16)   60.4 X61 + 60.73 X62 + 1.99 X63 + 11.56 X64 + 60.4 X65
       + 7.6 X66 + 12.88 X67 + 100 X68 + 59.41 X69 + 60.4 X610
       >=    36.234

C21)   100 X11 + 100 X12 + 50 X13 + 100 X14 + 100 X15 + 50 X16
       + 100 X17 + 100 X18 + 100 X19 + 100 X110 >=    50

C24)   100 X41 + 100 X42 + 50 X43 + 100 X44 + 100 X45 + 50 X46
       + 100 X47 + 100 X48 + 100 X49 + 100 X410 >=    50

C25)   100 X51 + 100 X52 + 90 X53 + 100 X54 + 100 X55 + 90 X56
       + 100 X57 + 100 X58 + 100 X59 + 100 X510 >=    90

C26)   100 X61 + 100 X62 + 50 X63 + 100 X64 + 100 X65 + 100 X66
       + 50 X67 + 100 X68 + 100 X69 + 100 X610 >=    50

C31)   86.17 X11 + 57.52 X12 + 77.39 X13 + 92.32 X14 + 1.32 X15
       + 70.25 X16 + 100 X17 + 23.05 X18 + 12.07 X19 + 19.76 X110 >=   0

C32)   77.74 X21 + 50.81 X22 + 90.55 X23 + 74.59 X24 + 34.96 X25
       + 100 X26 + 78.07 X27 + 12.05 X28 + 14.66 X29 + 1.95 X210
       >=    27.8

C33)   94.8 X31 + 49.27 X32 + 100 X33 + 68.47 X34 + 0.68 X35
       + 93.22 X36 + 76.95 X37 + 23.73 X38 + 11.68 X39 + 20.11 X310
       >=    6.99

C34)   56.43 X41 + 60.24 X42 + 100 X43 + 69.98 X44 + 0.2 X45
       + 90.26 X46 + 78.01 X47 + 40.16 X48 + 11.04 X49 + 21.18 X410
       >=    60

C35)   90.09 X51 + 68.97 X52 + 100 X53 + 70.26 X54 + 38.15 X55
       + 55.71 X56 + 79.31 X57 + 13.79 X59 + 16.81 X510 >=    64

C36)   60.06 X61 + 22.76 X62 + 100 X63 + 70.73 X64 + 0.2 X65 + 94 X66
       + 79 X67 + 29.78 X68 + 10.87 X69 + 24.62 X610 >=    14.65
```

```
C41)   72.78 X11 + 43.55 X12 + 81.87 X13 + 24.56 X14 + 75.62 X15
       + 100 X16 + 60.65 X17 + 66.63 X18 + 39.64 X19 + 53.02 X110
       >=   3.8

C42)   21.1 X21 + 9.9 X22 + 100 X23 + 55.24 X24 + 37.23 X25
       + 55.76 X26 + 26.23 X27 + 37.05 X28 + 51.44 X29 + 17.38 X210
       >=   0

C43)   46.03 X31 + 41.78 X32 + 94.75 X33 + 37.19 X34 + 38.53 X35
       + 99 X36 + 59.56 X37 + 38.95 X38 + 0.28 X39 + 43.9 X310 >=   0

C44)   60.14 X41 + 49.52 X42 + 92.47 X43 + 28.04 X44 + 54.7 X45
       + 100 X46 + 51.19 X47 + 54.7 X48 + 15.93 X49 + 26.55 X410
       >=   37.5

C45)   50.82 X51 + 51.86 X52 + 100 X53 + 49.03 X54 + 79.59 X55
       + 82.68 X56 + 23 X57 + 75.88 X58 + 55.67 X59 + 20.99 X510
       >=   2.36

C46)   38.27 X61 + 34.01 X62 + 100 X63 + 31.94 X64 + 70.67 X65
       + 93.33 X66 + 38.87 X67 + 47.47 X68 + 50.67 X69 + 34.93 X610
       >=   26.25

C51)   100 X11 + 100 X12 + 100 X15 + 100 X18 + 100 X19 + 100 X110
       >=   50

C53)   100 X31 + 100 X32 + 100 X35 + 100 X38 + 100 X39 + 100 X310
       >=   0

C54)   100 X41 + 100 X42 + 100 X45 + 100 X48 + 100 X49 + 100 X410
       >=   50

C55)   100 X51 + 100 X52 + 100 X55 + 100 X58 + 100 X59 + 100 X510
       >=   50

C56)   100 X61 + 100 X62 + 100 X65 + 100 X68 + 100 X69 + 100 X610
       >=   0

C61)   77 X11 + 100 X12 + 11 X13 + 9 X14 + 77 X15 + 7 X16 + 50 X17
       + 66 X18 + 100 X19 + 100 X110 >=   76

C62)   75 X21 + 100 X22 + 38 X23 + X24 + 75 X25 + 13 X26 + 25 X27
       + 75 X28 + 100 X29 + 100 X210 >=   91

C64)   55 X41 + 100 X42 + 6 X43 + X44 + 55 X45 + 5 X46 + 50 X47
       + 52 X48 + 100 X49 + 100 X410 >=   50

C66)   75 X61 + 100 X62 + 13 X63 + X64 + 75 X65 + 13 X66 + 50 X67
       + 63 X68 + 100 X69 + 100 X610 >=   75

C71)   50 X11 + 50 X12 + 100 X13 + 50 X14 + 50 X15 + 100 X16 + 50 X17
       + 10 X18 + 50 X19 + 50 X110 >=   50

C72)   98 X21 + 98 X22 + 100 X23 + 98 X24 + 98 X25 + 100 X26 + 98 X27
       + X28 + 98 X29 + 98 X210 >=   98
```

```
C74)   10 X41 + 10 X42 + 100 X43 + 10 X44 + 10 X45 + 100 X46 + 10 X47
       + 10 X49 + 10 X410 >=   10

C75)   67 X51 + 67 X52 + 100 X53 + 67 X54 + 67 X55 + 100 X56 + 67 X57
       + 33 X58 + 67 X59 + 67 X510 >=   67

C76)   10 X61 + 10 X62 + 100 X63 + 10 X64 + 10 X65 + 100 X66 + 10 X67
       + X68 + 10 X69 + 10 X610 >=   10

C81)   47.56 X11 + 44.6 X12 + 92.13 X13 + 67.52 X14 + 96.16 X16
       + 60.74 X17 + 1.74 X18 + 4.71 X19 + 12.36 X110 >=   42.75

C82)   48.11 X21 + 48.07 X22 + 99.98 X23 + 79.65 X24 + 94.51 X26
       + 74.06 X27 + 2.57 X29 + 14.43 X210 + 2 53X28 >=   46.39

C83)   52.13 X31 + 51.7 X32 + 98.88 X33 + 79.97 X34 + 88.72 X36
       + 68.35 X37 + 5.1 X38 + 5.52 X39 + 21.18 X310 >=   47.15

C84)   52.13 X41 + 51.7 X42 + 98.88 X43 + 79.97 X44 + 88.72 X46
       + 68.35 X47 + 5.1 X48 + 5.52 X49 + 21.18 X410 >=   47.15

C85)   44.73 X51 + 42 X52 + 93.75 X53 + 68.66 X54 + 100 X57
       + 66.31 X58 + 2.35 X59 + 7.8 X510 >=   42

C86)   48.48 X61 + 48.48 X62 + 100 X63 + 79.96 X64 + 93.8 X66
       + 73.81 X67 + 2.8 X68 + 2.8 X69 + 15.15 X610 >=   46.53

N1)   X11 + X12 + X13 + X14 + X15 + X16 + X17 + X18 + X19 + X110 =    1

N2)   X21 + X22 + X23 + X24 + X25 + X26 + X27 + X28 + X29 + X210 =    1

N3)   X31 + X32 + X33 + X34 + X35 + X36 + X37 + X38 + X39 + X310 =    1

N4)   X41 + X42 + X43 + X44 + X45 + X46 + X47 + X48 + X49 + X410 =    1

N5)   X51 + X52 + X53 + X54 + X55 + X56 + X57 + X58 + X59 + X510 =    1

N6)   X61 + X62 + X63 + X64 + X65 + X66 + X67 + X68 + X69 + X610 =    1

COST)    1004.19 X11 + 1158.09 X12  +   673.3 X13 + 1164.7 X14
       + 1000.14 X15 +  519.4 X16   +  1010.8 X17 + 1058.29 X18
       + 1154.04 X19 +  924.59 X110 + 1004.19 X21 + 1158.09 X22
       +  673.3 X23  + 1164.7 X24   + 1000.14 X25 +  519.4 X26
       + 1010.8 X27  + 1058.29 X28  + 1154.04 X29 + 924.59 X210
       + 1004.19 X31 + 1158.09 X32  +  673.3  X33 + 1164.7 X34
       + 1000.14 X35 +  519.4 X36   + 1010.8  X37 + 1058.29 X38
       + 1154.04 X39 +  924.59 X310 + 1004.19 X41 + 1158.09 X42
       +  673.3  X43 + 1164.7 X44   + 1000.14 X45 + 519.4 X46
       + 1010.8 X47  + 1058.29 X48  + 1154.04 X49 + 924.59 X410
       + 1004.1 X61  + 1158.09 X62  +  673.3  X63 + 1164.7 X64
       + 1000.14 X65 + 519.4 X66    + 1010.8  X67 + 1058.29 X68
       + 1154.04 X69 + 924.59 X610  + 1004.19 X51 + 1158.09 X52
       + 673.3 X53   + 1164.7 X54   + 1000.14 X55 + 519.4 X56
       + 1010.8 X57  + 1058.09 X58  + 1154.04 X59 + 924.59 X510
       <=   6486.84
  END
```

```
SUB      X11        1.00000
INTE      X11
SUB      X12        1.00000
INTE      X12
SUB      X13        1.00000
INTE      X13
SUB      X14        1.00000
INTE      X14
SUB      X15        1.00000
INTE      X15
SUB      X16        1.00000
INTE      X16
SUB      X17        1.00000
INTE      X17
SUB      X18        1.00000
INTE      X18
SUB      X19        1.00000
INTE      X19
SUB     X110        1.00000
INTE     X110
SUB      X21        1.00000
INTE      X21
SUB      X22        1.00000
INTE      X22
SUB      X23        1.00000
INTE      X23
SUB      X24        1.00000
INTE      X24
SUB      X25        1.00000
INTE      X25
SUB      X26        1.00000
INTE      X26
SUB      X27        1.00000
INTE      X27
SUB      X28        1.00000
INTE      X28
SUB      X29        1.00000
INTE      X29
SUB     X210        1.00000
INTE     X210
SUB      X31        1.00000
INTE      X31
SUB      X32        1.00000
INTE      X32
SUB      X33        1.00000
INTE      X33
SUB      X34        1.00000
INTE      X34
SUB      X35        1.00000
INTE      X35
SUB      X36        1.00000
INTE      X36
SUB      X37        1.00000
INTE      X37
SUB      X38        1.00000
INTE      X38
SUB      X39        1.00000
INTE      X39
SUB     X310        1.00000
INTE     X310
SUB      X41        1.00000
INTE      X41
SUB      X42        1.00000
INTE      X42
SUB      X43        1.00000
INTE      X43
SUB      X44        1.00000
INTE      X44
SUB      X45        1.00000
INTE      X45
SUB      X46        1.00000
INTE      X46
SUB      X47        1.00000
INTE      X47
SUB      X48        1.00000
INTE      X48
SUB      X49        1.00000
INTE      X49
SUB     X410        1.00000
INTE     X410
SUB      X61        1.00000
INTE      X61
SUB      X62        1.00000
INTE      X62
SUB      X63        1.00000
INTE      X63
SUB      X64        1.00000
INTE      X64
SUB      X65        1.00000
INTE      X65
SUB      X66        1.00000
INTE      X66
SUB      X67        1.00000
INTE      X67
SUB      X68        1.00000
INTE      X68
SUB      X69        1.00000
INTE      X69
SUB     X610        1.00000
INTE     X610
SUB      X51        1.00000
INTE      X51
SUB      X52        1.00000
INTE      X52
SUB      X53        1.00000
INTE      X53
SUB      X54        1.00000
INTE      X54
SUB      X55        1.00000
INTE      X55
SUB      X56        1.00000
INTE      X56
```

```
SUB       X57         1.00000
INTE       X57
SUB       X58         1.00000
INTE       X58
SUB       X59         1.00000
INTE       X59
SUB      X510         1.00000
INTE       X510
```

Table 24: Goal Programming Solution Based on Individual Patient Level Preferences and Linear Value Functions with Unrestricted Cost-Based-Constraints

OBJECTIVE FUNCTION VALUE

1) 32790.01

VARIABLE	VALUE	REDUCED COST
X11	.000000	-913.480000
X12	1.000000	-865.550000
X13	.000000	-383.770000
X14	.000000	-236.550000
X15	.000000	-916.320000
X16	.000000	-439.700000
X17	.000000	-243.650000
X18	.000000	-1037.230000
X19	.000000	-853.640000
X110	.000000	-873.020000
X21	.000000	-7887.500000
X22	1.000000	-5676.750000
X23	.000000	-12683.250000
X24	.000000	-1734.050000
X25	.000000	-5001.600000
X26	.000000	-13134.200000
X27	.000000	-1480.850000
X28	.000000	-1544.750000
X29	.000000	-3663.550000
X210	.000000	-2128.850000
X31	1.000000	-113.330000
X32	.000000	-63.550000
X33	.000000	-176.750000
X34	.000000	-6.660000
X35	.000000	-11.710000
X36	.000000	-173.220000
X37	.000000	-38.510000
X38	.000000	-62.680000
X39	.000000	15.360000
X310	.000000	-36.510000
X41	.000000	-463.330000
X42	1.000000	-467.380000
X43	.000000	-177.000000
X44	.000000	-18.680000
X45	.000000	-406.200000
X46	.000000	-168.160000
X47	.000000	-44.710000
X48	.000000	-940.160000
X49	.000000	-414.340000
X410	.000000	-427.180000
X61	1.000000	-16969.670000
X62	.000000	-14348.110000
X63	.000000	-17929.100000
X64	.000000	-8288.040000
X65	.000000	-11074.670000
X66	.000000	-23557.330000

X67	.000000	-11608.070000
X68	.000000	-15957.670000
X69	.000000	-13175.870000
X610	.000000	-14648.730000
X51	1.000000	-31177.310000
X52	.000000	-29468.220000
X53	.000000	-25091.070000
X54	.000000	-12128.620000
X55	.000000	-28802.770000
X56	.000000	-16392.440000
X57	.000000	-13075.740000
X58	.000000	-26959.240000
X59	.000000	-24319.640000
X510	.000000	-21225.970000
N11	23.800000	.000000
N12	22.120000	.000000
N13	27.500000	.000000
N14	50.310000	.000000
N15	25.950000	.000000
N16	39.600000	.000000
N21	.000000	10.000000
N22	.000000	200.000000
N23	.000000	101.000000
N24	.000000	101.000000
N25	.000000	100.000000
N26	.000000	100.000000
N32	49.190000	.000000
N33	5.199997	.000000
N34	39.520000	.000000
N35	9.910004	.000000
N36	33.940000	.000000
N41	56.450000	.000000
N42	90.100000	.000000
N43	53.970000	.000000
N45	49.180000	.000000
N46	61.730000	.000000
N51	.000000	10.000000
N52	.000000	1.000000
N53	.000000	100.000000
N54	.000000	10.000000
N55	.000000	.000000
N56	.000000	.000000
N61	.000000	5.900000
N62	.000000	40.000000
N64	.000000	1.000000
N65	3.000000	.000000
N66	25.000000	.000000
N71	50.000000	.000000
N72	2.000000	.000000
N73	.000000	3.000000
N74	90.000000	.000000
N75	33.000000	.000000
N76	90.000000	.000000
N31	42.580000	.000000
N44	50.480000	.000000

ROW	SLACK OR SURPLUS	DUAL PRICES
G11)	.000000	-10.000000
G12)	.000000	-100.000000
G13)	.000000	-1.000000
G14)	.000000	-10.000000
G15)	.000000	-99.000000
G16)	.000000	-90.000000
G21)	.000000	.000000
G22)	.000000	100.000000
G23)	.000000	1.000000
G24)	.000000	1.000000
G25)	.000000	.000000
G26)	.000000	.000000
G31)	.000000	.000000
G32)	.000000	-75.000000
G33)	.000000	-1.000000
G34)	.000000	-1.000000
G35)	.000000	-100.000000
G36)	.000000	-90.000000
G41)	.000000	-1.000000
G42)	.000000	-20.000000
G43)	.000000	-1.000000
G44)	.000000	.000000
G45)	.000000	-98.000000
G46)	.000000	-1.000000
G51)	.000000	.000000
G52)	.000000	.000000
G53)	.000000	.000000
G54)	.000000	.000000
G55)	.000000	-.900000
G56)	.000000	-10.000000
G61)	.000000	.900000
G62)	.000000	.000000
G64)	.000000	.000000
G65)	.000000	-100.000000
G66)	.000000	-50.000000
G71)	.000000	-3.000000
G72)	.000000	-40.000000
G73)	.000000	.000000
G74)	.000000	-1.000000
G75)	.000000	-1.000000
G76)	.000000	-80.000000
C11)	38.200000	.000000
C12)	16.170000	.000000
C13)	71.990000	.000000
C14)	1.090000	.000000
C15)	73.250000	.000000
C16)	24.166000	.000000
C21)	50.000000	.000000
C24)	50.000000	.000000
C25)	10.000000	.000000
C26)	50.000000	.000000
C31)	57.520000	.000000
C32)	23.010000	.000000
C33)	87.810010	.000000
C34)	.240002	.000000

C35)	26.090000	.000000
C36)	45.410000	.000000
C41)	39.750000	.000000
C42)	9.900000	.000000
C43)	46.030000	.000000
C44)	12.020000	.000000
C45)	48.460000	.000000
C46)	12.020000	.000000
C51)	50.000000	.000000
C53)	100.000000	.000000
C54)	50.000000	.000000
C55)	50.000000	.000000
C56)	100.000000	.000000
C61)	24.000000	.000000
C62)	9.000000	.000000
C64)	50.000000	.000000
C66)	.000000	.000000
C71)	.000000	.000000
C72)	.000000	.000000
C74)	.000000	.000000
C75)	.000000	.000000
C76)	.000000	.000000
C81)	1.849998	.000000
C82)	1.680000	.000000
C83)	4.980000	.000000
C84)	4.549999	.000000
C85)	2.730000	.000000
C86)	1.950001	.000000
N1)	.000000	.000000
N2)	.000000	40.000000
N3)	.000000	.000000
N4)	.000000	.000000
N5)	.000000	.000000
N6)	.000000	.000000
COST)	.089966	.000000

NO. ITERATIONS= 155
BRANCHES= 2 DETERM.= 1.000E 0

CHAPTER 6

RESEARCH FINDINGS & DISCUSSION OF RESULTS

This study was concerned with two principal research questions:

1. Identifying an optimal reimbursement policy and the corresponding level of financial resources required to direct efforts at maximizing healthcare outcomes as valued by patients and their healthcare providers under conditions of no cost-based restrictions.
2. Quantifying the potential impact of cost-based restricted drug formulary reimbursement policies on the achievement of therapeutic objectives and related optimal health outcomes.

These research questions were studied through the formulation and solution of a weighted integer goal-programming formulary design model applied to the selection of evidence-based antiretroviral pharmacotherapy combinations used in the initial treatment of asymptomatic, treatment naive persons infected with HIV. This chapter will present the results of this research experiment in answer to the aforementioned questions.

6.1 FINDINGS ON THE IDENTIFICATION OF THE OPTIMAL FORMULARY REIMBURSEMENT POLICY TO MAXIMIZE HEALTH OUTCOMES

The identification of an optimal reimbursement policy or selection of therapies was the culmination of a generally straightforward linear goal-programming formulation process. This process essentially consisted of defining specific therapeutic objectives or decision attributes and evaluating the ability of alternative therapies or decision options in satisfying these objectives.

One of the major obstacles in identifying an optimal reimbursement policy, was to assess and address the significance of the level of variation observed between individual patients, as well as between healthcare professionals and patients as a group. In order to determine whether or not the differences were significant three integer goal-programming

models were formulated and solved. Each yielded a unique optimal solution. In each case this solution represented the optimal assignment of patients to antiretroviral therapeutic combinations under consideration as determined by the model. The results are summarized below in Table 25.

Table 25: Four Model Comparison of Goal Programming vs. MAUT as an Overall Formulary Drug Selection Decision Framework.

	Individual Patients	**Aggregated Patients**	**Aggregated Healthcare Professionals**	**Combined Healthcare Professionals and Patients (50%/50%)**
Goal Programming Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: 5 patients Combo 3: 1 patient	Combo 2: 5 patients Combo 6: 1 patients	Combo1: 5 patients Combo 3: 1 patient
MAUT Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: all patients	Combo 2: all patients	Combo1: all patients
GP Solution Evaluation	Optimal Selection	3 patients receive suboptimal care, 2 patients placed on therapy not best satisfying needs, and 1 patient placed on inadequate therapy	3 patients receive suboptimal care, 2 patients placed on therapy not best satisfying needs, and 1 patient placed on inadequate therapy	3 patients receive suboptimal care, 2 patients placed on therapy not best satisfying needs, and 1 patient placed on inadequate therapy
MAUT Solution Evaluation	Optimal Selection	3 patients receive suboptimal care. 3 patients placed on therapy not best satisfying needs.	3 patients receive suboptimal care. 3 patients placed on therapy not best satisfying needs.	3 patients receive suboptimal care. 3 patients placed on therapy not best satisfying needs.
Validity	**Valid**	**Not Valid**	**Not Valid**	**Not Valid**

Based on the fact that each of the first three goal-programming models (individual patient, aggregated patient, and aggregated healthcare professional) yielded a different optimal solution, one can conclude that the observed variations are indeed significantly different. This conclusion, while not surprising, raised three important questions:

1. Do the objectives and preferences of healthcare professionals or patients carry more weight?
2. Are each of the identified optimal solutions and corresponding decision models valid?
3. If more than one of the models and solutions are valid, which should be used in supporting a decision?

To answer to the first question a fourth model was formulated and solved where the objectives and preferences of aggregated healthcare professionals and aggregated patients were combined in varying ratios to determine which had the stronger preferences and should carry more weight in making a decision. The three relative weightings between healthcare professionals and patients evaluated were respectively 50%:50%, 70%:30%, and 30%,70%. In each of the three cases the optimal solution remained the same. The results from the model generated from the 50%:50% relative weighting between healthcare professionals and patients are shown in Table 25. Those results support the conclusion that patients had significantly stronger preferences than did healthcare professionals with regard to the selection of treatment. This is based on the fact that the optimal solution from the combined model is equal to the solution generated from the aggregated patient model.

In order to determine which, if any, of the decision models were valid a two step evaluation process was conducted with respect to each of the four models. First each of

the four formulations were adapted, modeled and solved as a MAUT decomposition method decision-analysis problem. Each MAUT decision analysis yielded a rank order for the ten alternative therapeutic decision options being evaluated. The constraints were applied manually in rank order to each of the solutions generated by the four models. The optimal MAUT solution selection which satisfies all decision constraints is displayed in Table 25 and served as a bench mark against which to evaluate the optimal solution generated the corresponding goal programming model.

The second step of the evaluation process consisted of evaluating each of the optimal solutions derived through either MAUT or goal-programming to determine whether they best satisfied therapeutic objectives at the group level and at the individual level. While each of the goal programming models did in fact minimize the deviations from the therapeutic objectives at the group level, it appears that maximization of the objectives for the majority of patients came at the expense of 1 patient who had indicated a greater willingness to trade-off maximum durable viral load suppression for increased tolerability and ease of use and was consequently assigned by all but the individual patient model to inadequate therapy. This is also problematic for patients assigned to the more potent agents who would desire increased tolerability and ease of use but not necessarily at the expense of a trade-off in viral load suppression. The net result is that the aggregated patient model, the aggregated healthcare professional model, and the combined model traded off individual benefit to achieve greater group benefit. This in essence replicates a frequent complaint of policies aimed at "average" patients rather than addressing the need of real patients who deviate from average and end up deprived of optimal care.

Similarly the MAUT decision analysis models corresponding to the aggregated patient, the aggregated healthcare professional, and the combined goal-programming model traded off individual benefit to achieve greater group benefit. However, the results were generally more positive with the MAUT models. While all patients were assigned the same therapeutic combinations yielding an adequate level of care within a given model, 3 patients received optimal treatment while three others were assigned to adequate treatment that however did not best satisfy their defined objectives and preferences.

The individual patient goal-programming model yielded the best optimal solution in that all patients were assigned to therapeutic combinations that best satisfied their individual defined therapeutic objectives and preferences. In order to validate the individual patient goal-programming model and its corresponding optimal solution, MAUT decision analyses were conducted for each of the six patients. The six MAUT decision analyses yielded the same solution as the individual patient goal-programming model. Based on these and the previous findings, one can conclude that of the four goal-programming models evaluated, the individual patient goal-programming model yielded the only truly valid and optimal solution based on the individual objectives and preferences of the interviewed patients, and thus can be used in supporting a decision for this particular population.

However, given that this analysis is based on individual preferences of a very small selection of patients, these results cannot be generalized and assumed to be reflective of the objectives and preferences of other patients. This poses a problem in terms of feasibly applying such a methodology and model to a substantially larger population numbering in the hundreds or thousands. Obviously not all patients can be

interviewed to capture individual objectives and preferences. Nonetheless, if a sampling method could be applied to identify statistically significant homogeneous population subgroups which share enough similarities to be optimally assigned the same treatment, the objectives and preferences of patient subgroups could be modeled as were the patients in this example. While this is an interesting area to explore further, it is beyond the scope of this study and is suggested as an area for future research.

6.2 Financial Resources Required For Optimal Formulary Reimbursement Policies

Table 26: Four Model Comparison of Monthly Drug Acquisition Costs Required for a Six Patient Formulary.

	Individual Patients	**Aggregated Patients**	**Aggregated Healthcare Professionals**	**Combined Healthcare Professionals and Patients (50%/50%)**
Goal Programming Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: 5 patients Combo 3: 1 patient	Combo 2: 5 patients Combo 6: 1 patients	Combo1: 5 patients Combo 3: 1 patient
MAUT Optimal Therapeutic Selection	Combo1: patients 3,5,6 Combo 2: patients 1,2,4	Combo1: all patients	Combo 2: all patients	Combo1: all patients
Monthly Drug Acquisition Financial Resources Required for six patients - GP	$6,486.84	$5,694.25	$6,309.85	$5,694.25
Monthly Drug Acquisition Financial Resources Required for six patients - MAUT	$6,486.84	$6,025.14	$6,948.54	$6,025.14

The previous section was concerned with identifying the most appropriate formulary reimbursement model and its corresponding optimal solution. The solution identified assigned three patients to the therapeutic combination d4T + 3TC + Indinavir, whereas the other three patients were assigned to AZT + 3TC + Indinavir. Given that each combination has a per/patient monthly drug acquisition cost of respectively $1004.19 and $1158.09, the total calculated financial resources required to provide this optimal formulary therapeutic selection for those six patients is $6486.84 per month. The level of financial resources required by the optimal solutions derived through the other models are displayed on the previous page in Table 26.

However the level of financial resources does little to explain the level of therapeutic objectives satisfied by this optimal solution for each of the six patients. Table 27 displayed below summarized the level of each therapeutic objective satisfied and conversely the level of tradeoffs made for each patient by the identified optimal solution. However, these values reflect the values of individual patients and cannot be compared directly between patients. The interpretable levels of therapeutic attributes achieved by the optimal solution for assigned patients are related in Table 28 on the following page.

Table 27: Level of Therapeutic Objectives Satisfied Each of Six Patients

100%-Nij	Patient 1 Combo 2	Patient 2 Combo 2	Patient 3 Combo 1	Patient 4 Combo 2	Patient 5 Combo 1	Patient 6 Combo 1
Goal 1	76.2%	77.88%	72.5%	49.69%	74.05%	60.04%
Goal 2	100%	100%	100%	100%	100%	100%
Goal 3	57.42%	50.81%	94.81%	60.48%	90.09%	66.06%
Goal 4	43.55%	9.9%	46.03%	49.52%	50.82%	38.27%
Goal 5	100%	100%	100%	100%	100%	100%
Goal 6	100%	100%	n/a	100%	97%	75%
Goal 7	50%	98%	100%	10%	67%	10%

Table 28:
Level of Therapeutic Objectives Satisfied by the Optimal Solution

	Combo 1: **Patients 3,5,6**	**Combo 2:** **Patients 1,2,4**
Degree of Durable Viral Load Suppression Achievable	100-1000 fold reduction in viral load achieved in 90% of patients and sustained for at least one year in most patients	100-1000 fold reduction in viral load achieved in 91% of patients and sustained for at least one year in most patients
Degree of Prevention or Delay of Disease Progression	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality.	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality.
Adverse Effect Profile	Nephrolithiasis (kidney stones) Benign Hyperbilirubinemia	Nephrolithiasis (kidney stones) Benign Hyperbilirubinemia Altered taste Reduced appetite Numbness, prickling, tingling sensation
Ease of Use of Regimen		
Daily Dosing Frequency:	4 times per day	4 times per day
Total Number of Pills/day:	10	14
Diet Constraints:	Taking Indinavir on an empty stomach or with a light, low-fat meal.	Taking Indinavir on an empty stomach or with a light, low-fat meal.
Storage Recommendations:	No Refrigeration Required	No Refrigeration Required
Recommendations to minimize side effects:	Indinavir: Drinking at least 1.5 litres of water per day to minimize chance of developing kidney stones. d4T Minimizing alcohol intake.	Indinavir: Drinking at least 1.5 litres of water per day to minimize chance of developing kidney stones. AZT: Take in an upright position with a full glass of water. To minimize nausea take with food.
Potential of developing Resistance at 1 year	< 20% of compliant patients developing drug resistance at one year.	< 20% of compliant patients developing drug resistance at one year.

Table 28 continued:
Level of Therapeutic Objectives Satisfied by the Optimal Solution

	Combo 1: **Patients 3,5,6**	**Combo 2:** **Patients 1,2,4**
Degree of Support of Treatment Guidelines for:		
Treatment Strategy:	Preferred Strategy	Preferred Strategy
Particular Treatment:	Strong Support for both PI and NRTI Components. However d4T + 3TC scientific evidence does not have clinical endpoint data.	Strong Support for both PI and NRTI Components. However AZT + 3TC scientific evidence has clinical endpoint data.
Therapeutic Options Available in Case of Failure from Selected Regimen	2 new NRTI's/NNTRI new NRTI/PI/NNRTI* 2 PI'S/NRTI* 2 PI'S/NNRTI*	2 new NRTI's/NNTRI new NRTI/PI/NNRTI* 2 PI'S/NRTI* 2 PI'S/NNRTI*
Monthly Drug Acquisition costs per patient	$1004.19	$1158.09

*only limited data available

6.3 Findings on the Impact of Cost Based Restricted Reimbursement of Antiretroviral Treatment on the Achievement of Therapeutic Objectives and Related Health Outcomes

In the previous section, the level of resources was identified that supports the optimal formulary reimbursement policy in achieving the maximum level of defined therapeutic objectives in relation to individual patient preferences. However, two observations should be noted. The first recognizes that the optimal solution was not able to fully satisfy all objectives for any of the patients and that tradeoffs were required as no therapy was without imperfections in the eyes of patients. The objective of the previous exercise was simply to minimize the tradeoffs required to best satisfy those competing objectives. The second observation is that the optimal solution obtained was independent of cost in that

even if more money were applied to the decision problem, the optimal solution would not change because it is restricted by the limitations of currently available therapy. However, if the level of funding would fall below the level required to fund the optimal solution, the optimal solution would be forced to shift, causing patients to make further tradeoffs in trying to satisfy all of the competing therapeutic objectives.

In order to assess the impact of cost-based restricted reimbursement of antiretroviral treatment on the achievement of therapeutic objectives and resulting shifts in the optimal solution, the individual patient goal-programming was run at three progressive levels of cost-based restriction. The three levels of cost-based restriction evaluated for six patients were respectively: $6309.85, $6025.14, and $5694.25. These levels of restricted monthly drug acquisition costs were derived from the inferior "optimal" solutions generated by the three goal-programming models previously rejected as invalid. While, other values based on other rationales could have also have been incorporated, these were selected because they also represent three distinct coping strategies that policy-makers could potentially adopt in trying to maximize the overall achievement of therapeutic objectives of a given patient population at expense of individual patients. These strategies include:

1. **Prioritizing the allocation of optimal therapy to patients until the money runs out:**

   Give optimal therapy until the money runs out, then give inadequate therapy to whoever is left that will accept less than optimal therapy.

2. **Treating patients equally (within the population evaluated):**

   Give affordable adequate therapy, but not necessarily optimal therapy, to everybody.

3. **Rationing the allocation of optimal therapy to patients based on their strength of preferences:**

Give optimal therapy to only patients who will not accept anything less. Give cheap but adequate therapy to everybody else who will accept it until the money runs out. Then give inadequate therapy to who ever is left that will accept it.

Table 29: Therapeutic Objective Achievement Tradeoffs at Three Levels of Cost-based Restriction

Strategy 1: Net Level of Therapeutic Tradeoffs Under Cost-based Restrictions @$6309.85 Compared to No Cost Restriction Scenarios

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
100%-Nij	Combo 2	Combo 2	Combo 3	Combo 2	Combo 1	Combo 1
Goal 1	0%	0%	-71%	0%	0%	0%
Goal 2	0%	0%	-80%	0%	0%	0%
Goal 3	0%	0%	5%	0%	0%	0%
Goal 4	0%	0%	49%	0%	0%	0%
Goal 5	0%	0%	-100%	0%	0%	0%
Goal 6	0%	0%	n/a	0%	0%	0%
Goal 7	0%	0%	100%	0%	0%	0%

Strategy 2: Net Level of Therapeutic Tradeoffs Under Cost-based Restrictions @$6025.14 Compared to No Cost Restriction Scenarios

	Patient 1	Patient 2*	Patient 3	Patient 4*	Patient 5	Patient 6
100%-Nij	Combo 1	Combo 1	Combo 1	Combo 1	Combo 1	Combo 1
Goal 1	0%	0%	0%	0%	0%	0%
Goal 2	0%	0%	0%	0%	0%	0%
Goal 3	30%	27%	0%	-4%	0%	0%
Goal 4	29%	11%	0%	11%	0%	0%
Goal 5	0%	0%	0%	0%	0%	0%
Goal 6	-23%	-25%	n/a	-45%	-3%	-25%
Goal 7	0%	0%	100%	0%	0%	0%

** Decision problem infeasible unless minimal acceptable level of Constraint 6 (Therapeutic Guideline Recommendations) for patient 2, and Constraint 3 (adverse effects) for patient 4 are relaxed.*

Strategy 3: Net Level of Therapeutic Tradeoffs Under Cost-based Restrictions @$5694.25 Compared to No Cost Restriction Scenarios

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
100%-Nij	Combo 10	Combo 2	Combo 6	Combo 2	Combo 1	Combo 10
Goal 1	0%	0%	-72%	0%	0%	0%
Goal 2	0%	0%	-80%	0%	0%	0%
Goal 3	-38%	0%	-2%	1%	0%	-40%
Goal 4	9%	0%	53%	0%	0%	-3%
Goal 5	0%	0%	-100%	0%	0%	0%
Goal 6	0%	0%	n/a	0%	-3%	0%
Goal 7	0%	0%	100%	0%	0%	0%

When compared to the optimal solution, where each patient receives the best therapy, each progressive cost-based constraint and resulting coping therapeutic selection and allocation strategy leaves something to be desired. The comparison of shifting optimal solutions given progressive cost-based restrictions is displayed in Table 29 and highlights the incremental tradeoffs compared against the unrestricted optimal solution, required from each patient (indicated by negative numbers) for the overall benefit of the population.

The first strategy resulting from the least progressive level of restriction tries to maintain optimal therapy for patients until the financial resources are consumed. The inadequacy of this solution stems from the observation that patient three received an inadequate level of care simply because the resources are not available. Given that one patient (patient 3) is forced to tradeoff adequate viral load suppression and clinical benefit strictly on the basis of cost restriction, this strategy would violate the mandate that charges policy makers in ensuring an equitable allocation of finite healthcare resources among patients.

The second strategy assigns all six patients to the first therapeutic combination. When compared against the other selection in the unrestricted optimal solution, the therapies are similar in that the both offer an adequate level of durable viral load suppression and clinical benefit. However, this solution violates the minimal acceptable level of Constraint 6 (Therapeutic Guideline Recommendations) for patient 2, and Constraint 3 (adverse effects) for patient 4. To make this a feasible solution those patient level constraints had to be relaxed.

The third and final strategy attempts to ration optimal therapy on the basis of strengths of preferences. This strategy being the most restrictive is also the most ethically problematic in that it consistently discriminates against patients who are more willing to make concessions. Those patients who express strong preferences are less likely to be shifted from therapies previously assigned as optimal. Patients who indicated a willingness to tolerate higher levels of adverse effects were shifted off of optimal therapy to adequate, less expensive therapy that had a worse side effect profile. Patient 3, consistently the most willing patient to make concessions on all attributes, was shifted to the least expensive therapy that offered an inadequate level of viral load suppression and clinical benefit.

CHAPTER 7

CONCLUSION

7.1 Concluding Remarks

This study examined the optimization of formulary decisions concerning the selection of therapeutic options for reimbursement through the development of a goal programming formulary design model. This decision model was specifically tailored to address the selection of evidence-based antiretroviral pharmacotherapy combinations, based on the maximization of therapeutic objectives and their related health outcomes, as valued by stakeholders.

The goal programming method facilitated the appropriate structuring of the decision problem by modeling the decision attributes as therapeutic objectives in need of satisfaction in a quantitative manner. This method had the added advantage that it could be employed to systematically identify one or more optimal solutions in selecting from a multitude of decision alternatives. This method also facilitated the identification of tradeoffs necessary to achieve optimal care by maximizing the satisfaction of prioritized therapeutic objectives. The study found that goal programming was more appropriate than a MAUT decision analysis model in that it allowed more flexibility in modeling the complexities inherent in formulary drug selection, especially with regard to incorporating decision constraints and ensuring that minimal acceptable levels of particular therapeutic objectives were achieved and not compromised through tradeoffs.

The study also found that the MAUT decomposition method provided a suitable assessment method capable of measuring the various dissimilar variables. MAUT was

also useful in facilitating the conversion of qualitative measures into linear value functions. This conversion process permitted the incorporation of important qualitative factors into the goal-programming quantitative analysis. The 0-100 linear scaling of the MAUT derived linear value functions simplified the task of scaling or normalizing the goal-programming objectives by setting the targeted maximal level of all goals to 100.

While the MAUT decomposition measurement method was valuable in measuring stakeholder objectives, preferences, and tradeoffs, it was limited as an overall decision framework for the purposes of this decision problem due to the fact that it did not tailor therapy for varying patient needs. Rather, MAUT applied the weighted averaged preferences of the decision-maker consistently to the entire population. This sacrificed individual patient requirements for a conceptual group benefit in favor of the majority.

The major difficulty encountered in the application of the goal-programming methodology to determine the optimal formulary drug selection solution or reimbursement policy was related to the significant level of variation observed within the small case study sample of respondents. While the preference structure of healthcare professionals exhibited a high degree of consistency with regard to their valuation of therapeutic objectives, decision attribute component factors, and tradeoffs, patients exhibited a much greater degree of heterogeneity. Given the small sample, it is impossible to generalize whether the high level of variation observed in the therapeutic objectives, decision attributes, and tradeoffs is reflective of the asymptomatic, treatment naive HIV infected population as a whole or just this limited sample.

Another unexpected observation was the variation between healthcare professionals and patients. Given that healthcare professionals are frequently called upon to determine the best treatment for their patient in the agency relationship discussed by Drummond, Stoddart, Labelle, and Cushman (1987) it is disturbing that the values and preferences of healthcare professionals differ significantly from those of patients. However, this finding supports Eddy's (1990) contention that if optimal health outcomes are to be achieved they must be defined in terms of the health outcomes that patients experience and care about.

Four goal programming models were developed to study the decision problem. These four models were based on individual patient preferences, aggregated patient preferences, aggregated healthcare professional preferences, and combined patient and healthcare preferences. Given the differences identified in the various optimal solutions generated, this study found that variations observed between healthcare professionals and patients were significant enough to shift the optimal solution.

The optimal solution generated using the goal programming model based on the preferences at the individual level was found to be most reflective of the actual decision-makers values and preferences. This solution was equivalent to the selections generated by conducting an individualized MAUT decision analysis for each of the patients using manually applied decision constraints in a rather long and tedious process

This optimal solution or identified reimbursement policy specifically assigned 3 patients to the therapeutic combination d4T + 3TC + Indinavir, and 3 patients to the combination AZT + 3TC + Indinavir. This selection is consistent with the market

research study results conducted by ISIS Canada that identified these selections as the two therapeutic combinations with the largest shares of the antiretroviral therapy market. In addition, four of the six participants had actually been initiated on either of these two therapeutic combinations. The same therapies were selected for three of these four patients indicating the methods used to capture and determine the values and preferences of individual patients were fairly consistent with their actual treatment decisions.

The optimal solution generated by the individual patient model required $6486.84 per month in financial resources to pay for the monthly drug acquisition costs for the collective six patients. When sensitivity analysis was applied to model using three progressively restrictive levels of cost-based reimbursement constraints, the strengths of the values and preferences expressed by patients dictated the nature of the "coping strategies" identified by shift in optimal solution to maximize the achievement of the defined therapeutic objectives and minimize the level of tradeoffs made. Patients indicating a willingness to make tradeoffs and accept a lower minimal acceptable level of therapy were most often disadvantaged. The sensitivity analysis found that the assignment of optimal therapy given increasingly restricted resources was skewed in favor of patients who indicated an inflexible attitude towards the minimal acceptable level of treatment that they would accept. These patients' values and preference were so strong that several decision constraints had to be artificially relaxed in order to derive and identify a feasible solution that would guarantee an equitable distribution of adequate therapy to all six patients under restricted resource constraints.

7.2 SUGGESTIONS FOR FUTURE RESEARCH

The principal limitation identified in utilizing multiatribute utility measurement in combination with goal-programming stems from the significant level of heterogeneity in respondent preferences regarding the various treatment attributes observed in the small study sample and suspected in the asymptomatic, treatment naive HIV infected population. Given the limited scope of the small sample evaluated it is impossible to reliably comment on the population characteristics. However, if the significant level of variation exhibited in this case study reflects the nature of a population to which this type of analysis may be applied in the future, it is suggested that efforts be directed at modeling the population as a series of subgroups, within which individuals share similar attitudes and preferences in regard to distinct therapeutic objectives and decision attributes. While it unrealistic to suggest that each and every patient within a population should be interviewed and the magnitude of their objectives and preferences identified, sampling techniques can be applied to identify these distinct patient subgroups who share preferences and would select the same therapies on the basis of those preferences.

ENDNOTES

[1] Lakshman C. The Managed Care Syndrome. Benefits Canada, 18(6):45-47, June 1994.

[2] Moclair P. Fighting an uphill battle. Benefits Canada, 17(5):31-33, May 1993.

[3] Shachner M. Employers prescribe cure for rising drug costs. Business Insurance. 28(12):11-12, March 21,1994.

[4] Mandelker J. Controlling the cost of branded drugs. Business & Health. 11(13):44-48, November 1993.

[5] Montague T, Sidel J, Erhardt B, Nakhle G, Caron L, Croteau D, Kader M, Haket J, Skilton K, and McLeod B. Patient Health Management: A Promising Paradigm in Canadian Healthcare. The American Journal of Managed Care vol.3, NO.8; 1175-1182.

[6] Sachs G. The Importance of New Middlemen in the US Market. Scrip Magazine. 24, February 4, 1994.

[7] Highleyman L. Declines in AIDS-Related Deaths and Hospitalizations. Beta, March 1997, 7-11.

[8] Health Canada. (1997a) AIDS in Canada: Quarterly Surveillance Update. Division of HIV/AIDS Surveillance, Bureau of HIV/AIDS and STD. LCDC, HPB, Health Canada, May 1997, p.6.

[9] Rucker T.D., Schiff G. (1990). Drug Formularies: Myths-in-Formation. Medical Care. Vol. 28, No.10, p.928.

[10] Rucker and Schiff, p.928.

[11] Glennie J.L., Woloschuk D.M.M., Hall K.W. (1993) High Technology Drugs for Cancer: The Decision Process for Adding to a Formulary. *PhamacoEconomics,* Vol. 4, No. 6, p.405.

[12] Glennie, Woloschuk, and Hall, p.405.

[13] Nash D.B., Catalano M.L., Wordel C.J. (1993). The formulary decision-making process in a US academic medical centre. *PharmacoEconomics*, Vol. 3, No.1. p.23.

[14] Johnson J.A., Bootman J.L. (1994). Pharmacoeconomic analysis in formulary decisions: an international perspective. American Journal of Hospital Pharmacy. Vol.51, No.20, p.2594.

[15] Jang R. (1988). Medicaid Formularies: A Critical review of the literature. J Pharmaceutical Marketing and Management. Vol. 2, No.3, p.41.

[16] Kozma C.M., Schultz R.M., Dickson W.M., Dye J.T., Cox E.R., Holdford D.A., Michael L., Yates W.N., Young T.L. (1993). Economic Impact of Cost Containment Strategies in Third Party Programmes in the US, Part II. *PharmacoEconomics,* Vol. 4, No.3, p.188.

[17] Moore W.J., Newman R.J. (1992). US Medicaid Drug Formularies: Do they work? *PharmacoEconomics* Vol. 1, Suppl.1, p.28.

[18] Benjamin R, Katsanis LP. (1994) Issues Influencing New Drug Submission Listings on the Ontario Formulary. *Concordia University Pharmaceutical Management Centre Research Paper Series*, p.1.

[19] Johnson and Bootman, p.2594.

[20] Kresel J.J., Hutchings H.C., MacKay D.N., Weinstein M.C., Read J.L., Taylor-Halvorsen K., Ashley H. (1987). Application of decision analysis to drug selection for formulary addition. *Hospital Formulary,* Vol. 22, pp.661.

[21] Rucker and Schiff, p.928.

[22] Drummond MF, Stoddart GL, & Torrance GW. (1987). *Methods for the Economic Evaluation of Health Care Programs*. Oxford: Oxford Medical Publications, p.7.

[23] Nash, Catalano and Wordel, p.27.

[24] Rucker and Schiff, p.933.

[25] McElwain M.W. (1993). *Lessons from literature on the effectiveness of restricted formularies: Two approaches for regulatory reform to encourage pharmaceutical Investment and development in Ontario.* Ottawa: PMAC, May 26, p.1.

[26] Nash, Catalano, and Wordell, p. 27.

[27] McElwain, p.7.

[28] Glennie et al., p.406.

[29] Montague et al., p.1177.

[30] Shepherd M.D., Salzman R.D. (1994) The Formulary Decision-Making Process in a Health Maintenance Organization Setting. *PharmacoEconomics.* Vol.5, No.1, p.30.

[31] Kozma C.M., Reeder C.E., Lingle E.W. (1990) Expanding Medicaid Drug Formulary Coverage: Effects on Utilization of Related Services. *Medical Care, Vol.* 28, p. 964.

[32] Rucker and Schiff, p.929.

[33] Jang, p.39.

[34] Soumerai S.B., Ross-Degnan D., Gortmaker S., Avorn J. (1990). Withdrawing payment for nonscientific drug therapy: Intended and unexpected effects of a large scale natural experiment. *JAMA.* Vol. 263, p.831.

[35] Pharmaceutical Manufacturers Association of Canada. (PMAC) (1993). *A Five-Year Report on the Canadian Brand-Name Pharmaceutical Industry: 1988-1993*, Ottawa: PMAC Public Affairs Department, p.50.

[36] Fazio L. (1994) Giving Drug Plans Their Due. *Group Healthcare Management*, May; p.26.

[37] Giguere M. (1994). Time to Abandon Tradition and 'Get Smart.' *Canadian Healthcare Manager*, Spring, p.25.

[38] McElwain, p.6.

[39] Ontario Ministry of Health. (1994). *Ontario Guidelines for Economic Analysis of Pharmaceutical Products.* Toronto: Queen's Printer for Ontario, p.11.

[40] Sclar D.A. (1993) State Medicaid Formularies: Is there restricted access to needed medications. *Testimony delivered to United States Congress Human Resources & Intergovernmental Relations Subcommittee Hearings, June 9,1993*, p. 3.

[41] Benjamin and Katsanis, p.17.

[42] Montague et al., p.1177.

[43] McElwain, p.5.

[44] Moore and Newman, pp.30-31.

[45] Kozma et al. (1993), pp.189-191.

[46] Rucker and Schiff, p.932.

[47] Montague et al., p.1175.

[48] Glennie et al., p.406.

[49] Cano SB, Fujita N.(1988). Formulary evaluation of third-generation cephalosporins using decision analysis. *American Journal of Hospital Pharmacy* Vol.45, p.566.

[50] Keeney R.L. (1982). Decision Analysis: An Overview. *Operations Research,* Vol.30, No.5, p.806.

[51] Benjamin and Katsanis, p.14.

[52] Shepherd and Salzman, p.33.

[53] Drummond M., Stoddart G., Labelle R., Cushman R. (1987). Health Economics: An Introduction for Clinicians. *Annals of Internal Medicine,* Vol.107, p.90.

[54] Rucker and Schiff, p.932.

[55] Freund D.A., Dittus R.S. (1992) Principles of Pharmacoeconomic Analysis of Drug Therapy. *PharmacoEconomics, Vol.*1, No.1,p. 31.

[56] Bootman JL, Townsend RJ, McGhan WF. (1991). *Principles of Pharmacoeconomics.* Cincinnati: Harvey Whitney Books Company, pp.8-9.

[57] Freund and Dittus, p. 31.

[58] Briggs A, Sculpher M, & Buxton M. (1994) Uncertainty in the Economic Evaluation of Health Care Technologies: The Role of Sensitivity Analysis. *Health Economics, Vol.*3, p.101.

[59] Canadian Public Health Association (CPHA). (1993). *Benefit, Risk and Cost Management of Drugs. Report of the Canadian Public Health Association National Advisory Panel on the Risk/Benefit Management of Drugs.* Toronto, p.25.

[60] Weinstein M.C., Stason W.B. (1977). Foundations of Cost-Effectiveness Analysis for Health and Medical Practices. *New England Journal of Medicine,* Vol.296, No. 13, p.720.

[61] Eddy D.M. (1990). Anatomy of a Decision. *JAMA,* January 19; Vol.263, No.3, 442.

[62] Eddy, p.442.

[63] Doubilet, Weinstein, and McNeil, p.255.

[64] Rucker and Schiff. p. 931

[65] Soumerai et al., p.831.

[66] Montague et al., p.1175.

[67] Kassirer J.P.(1997). Managing managed care's tarnished image. *New England Journal of Medicine,* Vol. 337, p.338.

[68] Eddy D.M. (1990). Anatomy of a Decision. *JAMA*, Vol.263, No.3 p.442.

[69] Drummond, Stoddart, Labelle, and Cushman, p.90.

[70] Drummond, Stoddart, Labelle, and Cushman, p.90.

[71] Holmes-Rovner M., Kroll J., and Schmitt N. (1996). Patient Satisfaction with Health Care Decisions: The Satisfaction with Decision Scale. *Medical Decision Making,* Vol. 16, No.1, p.58.

[72] Merck & Co. The Merck Manual of Medical Information: Home Edition. 1997, p.926.

[73] Mildvan D. (Editor) Atlas of Infectious Diseases, Volume I: AIDS. 1995, p.2.2.

[74] Bartlett JG. (1997). *Medical Management of HIV Infection.* Baltimore: Port City Press. p.1.

[75] Abdullah G. (1997). AIDS Therapy: Hitting a moving target. *Patient Care,* July 15, p.43.

[76] Bartlett, p.1.

[77] Mellors J.W., Rinaldo C.R., Gupta P., White R.M., Todd J.A., Kingsley L.A. (1996). Prognosis in HIV-1 Infection Predicted by the Quantity of Virus in Plasma. *Science,* Vol.272, p. 1167.

[78] Abdullah, p.45.

[79] National Institute of Health (NIH.) (1997). *Report of the NIH Panel to Define Principles of Therapy of HIV Infection.* Bethesda. pp.2-3.

[80] Carpenter CCJ, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JSG, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni G., and Volberding PA. (1997). Antiretroviral Therapy for HIV Infection in 1997: Updated Recommendations of the International AIDS Society – USA Panel. *JAMA.* Vol. 277, No24, p.1962.

[81] Ho D. (1996). Pathogenesis of HIV Infection. *XI International Conference on AIDS, Satellite Symposium Highlights*: July 11, p.3.

[82] Carpenter et al., p.1962.

[83] Ho (1996), p.3.

[84] Sclar D.A., Robison L.M., Skaer T.L., Terriff C.M., Garrision M.W. (1997). International Expenditure Projections for Pharmacotherapeutic Advances in the Treatment of HIV/AIDS. *Clinical Therapeutics.* Vol.19, No.1, pp. 86-94.

[85] Global AIDS Policy Coalition. (1996). Status and Trends of the HIV/AIDS Pandemic as of January 1996. Harvard University Press, p.1.

[86] UNAIDS. (1997) Report on the Global HIV/AIDS Epidemic.

[87] Health Canada. (1997b) HIV/AIDS EPI Update. Division of HIV/AID Surveillance, Bureau of HIV/AIDS and STD. LCDC, HPB, Health Canada, May 1997,p.1.

[88] Health Canada. (1997a), p.6.

[89] Abdullah, p.52.

[90] US Department of Health and Human Services. (1997) Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. p.2.

[91] Abdullah, p.52.

[92] US Department of Health and Human Services, p. 6.

[93] Markowitz M. (1996). Treatment intervention in newly infected patients. XI International Conference on AIDS, Satellite Symposium Highlights: July 11, p.7.

[94] British Columbia Center for Excellence in AIDS. (1997). Therapeutic Guidelines for the treatment of HIV/AIDS and Related Conditions, p.2.

[95] Carpenter et al., p.1964,

[96] NIH, p.7.

[97] US Department of Health and Human Services, p.2.

[98] US Department of Health and Human Services, p.5.

[99] Ho D. (1995). Time to Hit HIV, Early and Hard- editorial. The New England Journal of Medicine. Vol. 333 No.7, pp.450-451.

[100] Feinberg M. (1997). Hidden dangers of incompletely suppressive antiretroviral therapy. The Lancet. Vol. 349, pp.1408-1409.

[101] Lange JMA. (1996). Combination Antiretroviral Therapy. Changing the Paradigm: Emerging Strategies in the Treatment of HIV Disease. July 7, p.8.

[102] Abdullah, p.45.

[103] Carpenter et al., p.1964.

[104] Lange, p.8.

[105] Campbell M. AIDS' economic impact massive, study shows. (1997) *Globe and Mail, eastern edition November 19, 1997, p.A1.*

[106] Becker S.(1997). The Economics of AIDS and Cost Effective Antiretroviral Therapy. *Healthcare Communications Group.* Vol.3, No.3, p.1.

[107] Haburchak D.R. (1997). The Economics of AIDS in America. *The AIDS Reader.*, Vol. 7., No.5, p.156.

[108] Hopkins' Moore Option AIDS Program Increases Patient Survival, Saves Money. (1997) *Disease Management News, Vol.3, No.5, p.6.*

[109] Moore R.D., Bartlett J.G. (1996) Combination Antiretroviral Therapy in HIV Infection: An Economic Perspective. *PharmacoEconomics* Vol.10, No.2, p.112.

[110] Haburchak, p.156.

[111] Haburchak, p.157.

[112] Haburchak, p.157.

[113] Reuters Health (online): (1997). Guidelines call for three-drug HIV therapy. June 20, 1997. Available from:URL:http://www.reutershealth.com, p.1.

[114] Williams A. (1997). Adherence, Compliance, and HAART. AIDS Clinical Care, Vol.9, No.7, p.54.

[115] Grubb I., McClure C. (1997). *How are we doing on protease inhibitors? An electronic town hall forum for people living with HIV/AIDS on Combination Therapy. p.1.*

[116] Schumacher GE. (1991) Multiattribute evaluation in formulary decision making as applied to calcium-channel blockers. American Journal of Hospital Pharmacists, Vol.48, February, p.301.

[117] US Department of Health and Human Services, p.5.

[118] Rucker and Schiff, p.932.

[119] Tsoukas CM. (1996) HIV Infection: Update on Indinavir and Resistance Issues. Physician perspective, Nov3-7, Birminham, U.K. p.3

[120] Hertogs K, et al. (1998) Patterns of Cross-Resistance Among Protease Inhibitors in 483 Clinical Isolated. *Fifth Conference on Retrovirus and Opportunistic Infections*, February 1-5, abstract 395.

REFERENCES

Abdullah G. (1997). AIDS Therapy: Hitting a moving target. *Patient Care*, July 15, pp.43-70.

Bartlett JG. (1997). *Medical Management of HIV Infection*. Baltimore: Port City Press.

Becker S.(1997). The Economics of AIDS and Cost Effective Antiretroviral Therapy. *Healthcare Communications Group*. Vol.3, No.3, pp.1-5.

Benjamin R, Katsanis LP. (1994) Issues Influencing New Drug Submission Listings on the Ontario Formulary. *Concordia University Pharmaceutical Management Centre Research Paper Series*.

Bootman JL, Townsend RJ, McGhan WF. (1991). *Principles of Pharmacoeconomics*. Cincinnati: Harvey Whitney Books Company

Briggs A, Sculpher M, & Buxton M. (1994) Uncertainty in the Economic Evaluation of Health Care Technologies: The Role of Sensitivity Analysis. *Health Economics, Vol.*3, pp. 95-104.

British Columbia Center for Excellence in AIDS. (1997). *Therapeutic Guidelines for the treatment of HIV/AIDS and Related Conditions, Vancouver*. November 4, 1997.

Brogan T. (1993) *Health Economics: Issues and Implications*. Toronto: IMS International Strategic Information Services.

Campbell M. AIDS' economic impact massive, study shows. (1997) *Globe and Mail, eastern edition November 19, 1997. pp A1-A4.*

Canadian Pharmaceutical Association. (1997) Compendium of Pharmaceuticals and Specialties. Thirty-second Edition.

Canadian Public Health Association (CPHA). (1993). *Benefit, Risk and Cost Management of Drugs. Report of the Canadian Public Health Association National Advisory Panel on the Risk/Benefit Management of Drugs*. Toronto.

Cano SB, Fujita N.(1988). Formulary evaluation of third-generation cephalosporins using decision analysis. *American Journal of Hospital Pharmacy* Vol.45, pp.566-569.

Carpenter CCJ, Fischl MA, Hammer SM, et al, for the International AIDS Society- USA. Antiretroviral therapy for HIV infection in 1996: recommendations of an international panel. JAMA, Vol.276, No.2, pp.146-154.

Carpenter CCJ, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JSG, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S,

Yeni G., and Volberding PA. (1997). Antiretroviral Therapy for HIV Infection in 1997: Updated Recommendations of the International AIDS Society – USA Panel. *JAMA.* Vol. 277, No24, pp.146-154.

Clemen RT. (1996). Making Hard Decisions: An Introduction to Decision Analysis. Scarborough: Duxbury Press, pp.530-573.

Condra JH, and Emini EA. (1997). Preventing HIV-1 Drug Resistance. *Science & Medicine.* Vol.4, No.1.p.2-11.

Detsky A.S. (1993). Guidelines for economic analysis of pharmaceutical products: a draft document for Ontario and Canada. *Pharmacoeconomics,* Vol.3, No.5, pp. 354-361.

Doubilet P., Weinstein M.C., McNeil B.J. (1986) Use and misuse of the term "cost-effective" in medicine. *New England Journal of Medicine,* Vol. 314, No.4, pp.253-256.

Drummond M., Stoddart G., Labelle R., Cushman R. (1987). Health Economics: An Introduction for Clinicians. *Annals of Internal Medicine,* Vol.107, pp.88-92.

Drummond MF, Stoddart GL, & Torrance GW. (1987). *Methods for the Economic Evaluation of Health Care Programs.* Oxford: Oxford Medical Publications.

Dunne D, Soberman D. (1993*) Thirty Party Payers in Canada: A Strategic Analysis.* Toronto*:* IMS Canada Strategic Information Services.

Eddy D.M. (1990). Anatomy of a Decision. *JAMA,* January 19; Vol.263, No.3, pp.441-443.

Fazio L. (1994) Giving Drug Plans Their Due. *Group Healthcare Management,* May; pp.24-26.

Feinberg M. Hidden. (1997) Dangers of incompletely suppressive antiretroviral therapy. *Lancet.* Vol. 349, pp.1408-1409.

Fischer G.W. (1979). Utility Models for multiple objective decisions: Do they Accurately Represent Human Preferences? *Decision Sciences,* Vol.10,pp. 451-479.

Freund D.A., Dittus R.S. (1992) Principles of Pharmacoeconomic Analysis of Drug Therapy. *PharmacoEconomics, Vol.*1, No.1,pp.20-32.

Giguere M. (1994). Time to Abandon Tradition and 'Get Smart.' *Canadian Healthcare Manager,* Spring, pp.25-26.

Glennie J.L, Woloschuk D.M.M., Hall K.W. (1993). High Technology Drugs for Cancer: The Decision Process for Adding to a Formulary. *PhamacoEconomics, Vol.*4,

No.6, pp.405-413.

Global AIDS Policy Coalition. *(1996). Status and Trends of the HIV/AIDS Pandemic as of January 1996.* Boston: Harvard University Press.

Grubb I., McClure C. (1997). *How are we doing on protease inhibitors? An electronic town hall forum for people living with HIV/AIDS on Combination Therapy. pp. 1-33.*

Haburchak D.R. (1997). The Economics of AIDS in America. *The AIDS Reader.*, Vol. 7., No.5,pp.155-160.

Hanson C, Shepherd M, Pleil A. (1992) How P&T Committee Members in HMO's Make Formulary Decisions. *Pharmacy and Therapeutics.* February, pp.247-254.

Health Canada. (1997a). *AIDS in Canada: Quarterly Surveillance Update.* Division of HIV/AIDS Surveillance, Bureau of HIV/AIDS and STD. LCDC, HPB, Health Canada, May.

Health Canada. (1997b). *HIV/AIDS EPI Update.* Division of HIV/AID Surveillance, Bureau of HIV/AIDS and STD. LCDC, HPB, Health Canada, May 1997.

Hertogs K, et al. (1998) Patterns of Cross-Resistance Among Protease Inhibitors in 483 Clinical Isolated. *Fifth Conference on Retrovirus and Opportunistic Infections*, February 1-5, abstract 395.

Highleyman L. (1997). Declines in AIDS-Related Deaths and Hospitalizations. *Beta*, March , pp. 7-11.

Ho D. (1995). Time to Hit HIV, Early and Hard- editorial. *New England Journal of Medicine*, Vol. 333, No7, pp.450-451.

Ho D. (1996). Pathogenesis of HIV Infection. *XI International Conference on AIDS, Satellite Symposium Highlights*: July 11, p.3.

Hogg RS, et al. (1998) Decreased Morbidity and Mortality among HIV+ individuals following initiation of antiretroviral therapy. *Fifth Conference on Retrovirus and Opportunistic Infections*, February 1-5, abstract 197.

Holmes-Rovner M., Kroll J., and Schmitt N. (1996). Patient Satisfaction with Health Care Decisions: The Satisfaction with Decision Scale. *Medical Decision Making*, Vol. 16, No.1, pp.58-64.

Hopkins' Moore Option AIDS Program Increases Patient Survival, Saves Money. (1997) *Disease Management News, Vol.3, No.5, pp1-6.*

ISIS Research..(1997). *Treatment of HIV Disease in Canada: Phase IX.* August.

Jang R. (1988). Medicaid Formularies: A Critical review of the literature. *Journal Pharmaceutical Marketing and Management*, Vol.2, No. 3. pp.39-61.

Johnson J.A., Bootman J.L.(1994). Pharmacoeconomic analysis in formulary decisions: an international perspective. *American Journal of Hospital Pharmacy, Vol.* 51,No.20, pp.2593-2598.

Kassirer J.P. (1997). Managing managed care's tarnished image. *New England Journal of Medicine,* Vol.337, pp.338-339.

Katlama C, et al. (1997). ALTIS: A pilot open study of d4T/3TC in antiretroviral naïve and experienced patients. 4th Conference on Retroviruses and Opportunistic Infections; late-breaker abstract.

Keeney R.L. (1982). Decision Analysis: An Overview. *Operations Research,* Vol.30, No.5, pp.803-838.

Keeney R.L., Kirkwood C.W. (1975). Group Decision Making using Cardinal Social Welfare Functions. *Managment Science,* Vol.22, No.4), pp.430-437.

Kozma C.M., Reeder C.E., Lingle E.W. (1990). Expanding Medicaid Drug Formulary Coverage: Effects on Utilization of Related Services. *Medical Care, Vol.* 28, pp. 963-977.

Kozma C.M., Schultz R.M., Dickson W.M., Dye J.T., Cox E.R., Holdford D.A., Michael L., Yates W.N., Young T.L. (1993). Economic Impact of Cost Containment Strategies in Third Party Programmes in the US, Part II. *PharmacoEconomics,* Vol. 4, No.3, pp.187-202.

Kresel J.J., Hutchings H.C., MacKay D.N., Weinstein M.C., Read J.L., Taylor-Halvorsen K., Ashley H. (1987). Application of decision analysis to drug selection for formulary addition. *Hospital Formulary,* Vol. 22, pp.658-676.

Lakshman C. (1994). The Managed Care Syndrome. *Benefits Canada,* Vol.18, No.6, pp.45-47.

Lange J.M.A. (1996) Combination Antiretroviral Therapy. *Changing the Paradigm: Emerging Strategies in the Treatment of HIV Disease*, July 7, p.8.

Long JW, and Rybacki JJ. (1995). The Essential Guide to Prescription Drugs. New York: HarperPerennial.

Mandelker J. (1993). Controlling the cost of branded drugs. *Business & Health.* Vol.11, No.13, pp.44-48.

Markowitz M. (1996). Treatment intervention in newly infected patients. *XI International Conference on AIDS, Satellite Symposium Highlights*: July 11, p.7.

McElwain M.W. (1993). *Lessons from literature on the effectiveness of restricted formularies: Two approaches for regulatory reform to encourage pharmaceutical Investment and development in Ontario.* Ottawa: PMAC, May 26.

Mellors J.W., Kinsley L.A., Rinaldo C.R., et al. (1995).Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Annals of Internal Medicine*, Vol. 122, pp.573-579.

Mellors J.W., Munoz A.M., Giorgi V.J., et al. (1997). Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Annals of Internal Medicine.* UPDATE

Mellors J.W., Rinaldo C.R., Gupta P., White R.M., Todd J.A., Kingsley L.A. (1996). Prognosis in HIV-1 Infection Predicted by the Quantity of Virus in Plasma. *Science*, Vol.272.,pp.1167-1170.

Merck & Co. (1997). *Merck Manual of Medical Information: Home Edition.* West Point: Merck Research Laboratories.

Merck Frosst Canada Inc. (1998). Drug Fact Sheets. *HIV Therapy Scheduler v.2.0.*

Merck Frosst Canada Inc. (1998). Drug Interactions Reference. *HIV Therapy Scheduler v.2.0.*

Mildvan D. (Editor) (1995). *Atlas of Infectious Diseases, Volume I: AIDS.* Philadelphia: Current Medicine Inc.

Moclair P. (1993). Fighting an uphill battle. *Benefits Canada*, Vol.17, No.5, pp.31-33.

Montague T., Sidel J., Erhardt B., Nakhle G., Caron L., Croteau D., Kader M., Haket J., Skilton K., and McLeod B. Patient Health Management: A Promising Paradigm in Canadian Healthcare.(1997). *American Journal of Managed Care, V*ol.3, No.8, pp.175-1182.

Moore R.D., Bartlett J.G. (1996) Combination Antiretroviral Therapy in HIV Infection: An Economic Perspective. *PharmacoEconomics* Vol.10, No.2, pp.109-113.

Moore W.J., Newman R.J. (1992). US Medicaid Drug Formularies: Do they work? *PharmacoEconomics*, Vol.1,Suppl. I, pp.28-31.

Nash D.B., Catalano M.L., Wordel C.J. (1993). The formulary decision-making process in a US academic medical centre. *PharmacoEconomics*, Vol.3, No.1, pp. 22-35.

National Institute of Health (NIH.) (1997). *Report of the NIH Panel to Define Principles of Therapy of HIV Infection.* Bethesda.

Ontario Ministry of Health. (1994). *Ontario Guidelines for Economic Analysis of*

Pharmaceutical Products. Toronto: Queen's Printer for Ontario.

Opravil M, et al. (1997). EARTH Study: AZT + 3TC vs. AZT+3TC+Ritonavir in asymptomatic patients with early HIV Infection. *37th ICAAC Conference September 28- October 1, 1997;* abstract I-94.

Patented Medicine Prices Review Board. (1994) *Compendium of Guidelines, Policies, and Procedures.* Ottawa: PMPRB..

Pharmaceutical Manufacturers Association of Canada. (PMAC) (1993). *A Five-Year Report on the Canadian Brand-Name Pharmaceutical Industry: 1988-1993,* Ottawa: PMAC Public Affairs Department.

Project Inform. (1995) PI Perspective No.17 What's all this stuff about 'logs?': The low down on reading the PCR test.p.2

Project Inform. (1996). Project Inform Protease Inhibitors Fact Sheet: Update on Protease Inhibitors. May 28, p1-7.

Project Inform. (1997) Project Inform's Drug Side Effects Fact Sheet Protease Inhibitors Fact Sheet: Update on Protease Inhibitors. August, p1-4.

Reuters Health (online): (1997). Guidelines call for three-drug HIV therapy. June 20, 1997. Available from:URL:http://www.reutershealth.com

Romero C. (1991). *Handbook of Critical Issues in Goal Programming.* Toronto: Pergamon Press.

Rucker T.D., Schiff G. (1990). Drug Formularies: Myths-in-Formation. *Medical Care,* Vol.28, No.10, pp.928-942.

Saag MS. (1996). How Long Should Treatment for Primary Infection Continue. *Improving the Management of HIV Disease, Vol. 4, suppl.1, p.4.*

Sachs G. (1992). The Importance of New Middlemen in the US Market. *Scrip Magazine,* Vol. 1894, p.24.

San Francisco AIDS Foundation. (1997). 3-Drug Therapy Reduces Deaths and New AIDS-Related Ilnesses by 50%. *Beta,* March 1997, p.3.

San Francisco AIDS Foundation. (1998). 4 Drug Combination Twice Daily Leads to 100% Undetectable Viral Load, *Beta,* January 1998, p.49.

San Francisco AIDS Foundation. (1998). Indinavir/d4T plus 3TC or ddI as Effective as Indinavir/AZT/3TC. *Beta,* January 1998, pp.53-54

San Francisco AIDS Foundation. (1998). Saquinavir Combination Decreases AIDS and Death by 50%. Beta – January, p.54.

Schumacher GE. (1991). Multiattribute evaluation in formulary decision making as applied to calcium-channel blockers. American Journal of Hospital Pharmacists, Vol. 48, February, pp. 301-308

Sclar D.A. (1993) State Medicaid Formularies: Is there restricted access to needed medications. *Testimony delivered to United States Congress Human Resources & Intergovernmental Relations Subcommittee Hearings, June 9,1993*, pp.1-6.

Sclar D.A., Robison L.M., Skaer T.L., Terriff C.M., Garrision M.W. (1997). International Expenditure Projections for Pharmacotherapeutic Advances in the Treatment of HIV/AIDS. *Clinical Therapeutics.* Vol.19, No.1, pp. 86-94.

Shachner M. (1994). Employers prescribe cure for rising drug costs. *Business Insurance.* Vol. 28, No.12, pp.11-12.

Shepherd M.D., Salzman R.D. (1994) The Formulary Decision-Making Process in a Health Maintenance Organization Setting. *PharmacoEconomics.* Vol.5, No.1, pp.29-38.

Skaar D.J., Oki J.C., Elenbaas R.M. (1992). Clinical Pharmacists Can Ensure Quality at Acceptable Costs. *Healthcare Financial Management*, pp. 90-92.

Soumerai S.B., Ross-Degnan D., Gortmaker S., Avorn J. (1990). Withdrawing payment for nonscientific drug therapy: Intended and unexpected effects of a large scale natural experiment. *JAMA.* Vol. 263, pp. 831-839.

Tseng A., Fletcher D.(1997*). HIV Drug Therapy: Recommendations and Associated Costs.* Toronto: Toronto Hospital Immunodeficiency Clinic:

Tseng AL,and Foisy MM. (1997). Management of Drug Interactions in Patients with HIV. *The Annals of Pharmacotherapy.* Vol. 31, pp.1040-1058.

Tsoukas CM. (1996) HIV Infection: Update on Indinavir and Resistance Issues. Physician perspective, Nov3-7, Birminham, U.K.

UNAIDS. (1997) *Report on the Global HIV/AIDS Epidemic.*

US Department of Health and Human Services.(1997*). Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents.*

Use of protease inhibitors in AIDS makes economic sense. (1997). *PharmacoEconomics & Outcomes News*, No.137, p.3.

Weinstein M.C., Stason W.B. (1977). Foundations of Cost-Effectiveness Analysis for Health and Medical Practices. *New England Journal of Medicine,* Vol.296, No. 13, pp.716-721.

Williams A. (1997). Adherence, Compliance, and HAART. AIDS Clinical Care, Vol.9,

No.7, pp.51-58.

APPENDIX 1A: HIV INFECTION PROGRESSIVE DISEASE STAGES

	Disease Stage	Characteristics
1	Viral transmission	HIV infection is usually acquired through sexual intercourse with an infected person, exposure to contaminated blood, or perinatal transmission.
2	Primary HIV infection,	Characterized by an acute retroviral syndrome that may either be symptomatic or asymptomatic. This acute phase is normally accompanied by tremendous and escalating viral production, even in the absence of symptoms with a corresponding drop in CD4 cells. While the CD4 cell drop is transient, they generally never return to baseline pre-infection levels. Symptomatic primary infection has been reported in all risk categories with a frequency ranging from 50-90%. There are many typical symptoms. However the five most common symptoms observed are fever, sore throat, fatigue, myalgia and weight loss. Complete clinical recovery (remission of symptoms) and reduced viremia follows, presumably due to a cellular immune response (CTL) which preceeds detectable humoral response.
3	Seroconversion	Seroconversion, where an infected individual develops a positive HIV serology (becomes HIV+), generally takes place with >95% seroconverting within 5.8 months following a viral transmission event. The CTL response is associated with a sharp reduction of viral load in the blood and clinical recovery from the acute retroviral syndrome.
4	Asymptomatic Infection:	A clinical latent asymptomatic, period with or without persistent generalized lymphadenopathy, no longer associated with viral latency.[1] This period represents a steady state period in which massive immune system mediated killing and replacement of CD4 cells, in response to the high level of HIV replication and infection, is in near balance.
5	Early symptomatic HIV infection	Early symptomatic HIV infection is characterized by the development of common complications (Class B

[1] Abdullah G. AIDS Therapy: Hitting a moving target. Patient Care. July 15, 1997

		conditions listed in Appendix 1b) that are more serious and/or more difficult to treat in the presence of HIV infection, but are not AIDS indicator conditions. In parallel, the CD4 cell count gradually declines over several years with a more accelerated decline usually observed 1.5-2 years prior to developing an AIDS defining illness.
6	Acquired Immune Deficiency Syndrome (AIDS)	The clinical definition of AIDS is based on the CDC disease classification as first defined in 1987 and later revised in 1993. This classification system utilizes a matrix form of nine mutully exclusive categories representing a combination of 3 CD4 levels and the varying presence of symptoms or AIDS defining conditions. The diagnosis of AIDS is now indicative of a CD4 count below 200/mm^3 and/or the presence of an AIDS defining condition as listed in Appendix 1c.
7	Advanced HIV infection	Characterized by a CD4 cell count <50/mm^3. Patients in this category generally have a limited life expectancy with a median survival of 12-18 months. Virtually all patients who die of HIV/AIDS related complications are in this CD4 range.

Adapted from Bartlett JG. Medical Management of HIV Infection. 1997 Edition, pp2-7.

APPENDIX 1B: AIDS SURVEILLANCE CASE DEFINITION FOR ADOLESCENTS AND ADULTS: 1993

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, PGL or acute HIV Infection	B Symptomatic with class B symptoms*	C AIDS indicator condition (1987 revised 1995) See Appendix 1c
1) >500 CD4/mm^3	A1	B1	C1
2) 200-499 CD4/mm^3	A2	B2	C2
3) <200 CD4/mm^3	A3	B3	C3

*Class B symptoms include but are not limited to bacillary angiomatosis, thrush, vulvovaginal candidiasis, moderate or sever cervical dysplasia, cervical carcinoma, constitutional symptoms such as fever (38.5°C) of diarrhea >1 month, oral hairy leukoplakia, Herpes zoster involving two episodes, listeriosis, pelvic inflammatory disease, and peripheral neuropathy.

All patients in categories A3,B3,C1,C2,and C3 are reported as AIDS with conditions indicative of severe immunosuppression.

Adapted from Bartlett JG. Medical Management of HIV Infection. 1997 Edition, table 1-3a.

APPENDIX 1C: INDICATOR CONDITIONS IN AIDS CASE DEFINITION FOR ADULTS: 1995

Candidiasis, of esophagus, trachea, bronchi or lungs
Cervical cancer, invasive
Coccidioidomycosis, extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis with diarrhea >1month
Cytomegalovirus or any organ other than liver, spleen, or lymphnodes; eye
Herpes simplex with mucocutaneous ulcer >1 month or bronchitis, pneumoitis, esophagitis
Histoplasmosis, extrapulmonary
HIV-associated dementia: Disabling cognitive and/or other dysfunction interfering with occupation or activities of daily living.
HIV-associated wasting (Wasting Syndrome): Involuntary weight loss > 10% of baseline plus chronic diarrhea > 30 days or chronic weakness and documented enigmatic fever > 30 days.
Isoporosis with diarrhea >1month
Kaposi's sarcoma in patients under 60 years
Lymphoma,
Mycobacterium avium, disseminated
Mycobacterium tuberculosis, disseminated or pulmonary
Nocardiosis
Pneumocystis carinii pneumonia
Pneumonia, recurrent bacterial
Progressive multifocal leukoencephalopathy
Salmonella septicemia (non-typhoid), recurrent
Strongyloidosis, extraintestinal
Toxoplasmosis of internal organs

Adapted from Bartlett JG. Medical Management of HIV Infection. 1997 Edition, table 1-3b

APPENDIX 2: SUMMARY OF PRINCIPLES OF THERAPY OF HIV INFECTION

	Principles of Therapy of HIV Infection
1	Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful, and true long-term survival free of clinically significant immune dysfunction is unusual.
2	Plasma HIV RNA levels indicate the magnitude of HIV replication and it associated rate of CD4+ T cell destruction, while CD4+ T cell counts indicate the extent of HIV induced immune damage already suffered. Regular, periodic measurement of plasma HIV RNA levels and CD4+ T cell counts is necessary to determine risk of disease progression in an HIV infected individual and to determine when to initiate or modify antiretroviral treatment regimens.
3	As rates of disease progression differ among individuals, treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4+ T cell counts.
4	The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive HIV RNA assay limits the potential for selection of antiretroviral resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.
5	The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
6	Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.
7	The available effective antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in antiretroviral therapy increases future therapeutic constraints.
8	Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9	The same principles of antiretroviral therapy apply to both HIV infected children and adults, although treatment of HIV infected children involved unique pharmacologic, virologic, and immunologic considerations.
10	Persons with acute primary HIV infections should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.
11	HIV infected persons, even those with viral loads below detectable limits, should be considered infectious and should be counseled to avoid sexual and drug-use behaviors that are associated with transmission or acquisition of HIV and other infections.

Adapted from the 1997 final Report of the NIH Panel to Define Principles of Therapy of HIV Infection.

APPENDIX 3: RECOMMENDATIONS FOR THE INITIATION OF ANTIRETROVIRAL THERAPY IN THE CHRONICALLY HIV-INFECTED PATIENT.

Clinical Category	$CD4^+$ T Cell Count & HIV RNA	Recommendation
Symptomatic (AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	$CD4^+$ T Cells <500/mm^3 **Or** HIV RNA >10,000 (bDNA) Or > 20,000 (RT-PCR)	Treatment should be offered. Strength of recommendation is based on prognosis for disease-free survival and willingness of the patient to accept therapy.*
Asymptomatic	$CD4^+$ T Cells >500/mm^3 **Or** HIV RNA <10,000 (bDNA) Or < 20,000 (RT-PCR)	Many experts would delay therapy and observe; however, some experts would treat.

* Some experts would observe patients with $CD4^+$ T cell counts between 350-500/mm^3 and HIV RNA levels <10,000 (bDNA) or < 20,000 (RT-PCR). Adapted from *Table V. Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV Infected Patient. US Dept. of Health and Human Services.*

APPENDIX 4: RISKS AND BENEFITS OF EARLY INTERVENTION OF ANTIRETROVIRAL THERAPY IN THE ASYMPTOMATIC HIV-INFECTED PATIENT

Potential Benefits	• Control of viral replication and mutation, reduction of viral burden • Prevention of progressive immunodeficiency; potential maintenance or reconstitution of a normal immune system • Delayed progression to AIDS and prolongation of life • Decreased risk of selection of resistant virus • Decreased risk of drug toxicity
Potential Risks	• Reduction in quality of life from adverse drug effects and inconvenience of current maximally suppressive regimens • Earlier development of resistance • Limitation in future choices of antiretroviral agents due to the development of resistance • Unknown long-term toxicity of antiretroviral drugs • Unknown duration of effectiveness or current antiretroviral therapies

- Adapted from Table III: Risks and Benefits of Early Intervention of |Antiretroviral Therapy in the Asymptomatic HIV-Infected Patient- US Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. November 5, 1997

APPENDIX 5A: RECOMMENDED ANTIRETROVIRAL AGENTS FOR TREATMENT OF ESTABLISHED HIV INFECTION

1. Preferred strategy: based on strong evidence of clinical benefit and/or sustained suppression of plasma viral load. One choice each from column A and column B.

Column A: **Protease Inhibitors**	Strength of Recommendation / Quality of scientific evidence supporting recommendation	Column B: **Nucleoside Reverse Transcriptase Inhibitors**	Strength of Recommendation / Quality of scientific evidence supporting recommendation
Indinavir +	A/I	**Zidovudine (AZT) + Didanosine (ddI)**	A/I
Ritonavir +	A/I	**Zidovudine (AZT) + Lamivudine(3TC)**	A/I
Nelfinavir* +	A/II	**Zidovudine (AZT) + Zalcitabine (ddC)**	A/I
Ritonavir + Saquinavir	B/II	**Stavudine(d4T) + Didanosine (ddI)**	A/II
		Stavudine (d4T) + Lamivudine (3TC)	A/II

** not currently approved for use in Canada*

2. Alternate strategies: less likely to provide sustained suppression of plasma viral load

Nevirapine NNRTI +	2 NRTI's (Column B above)	B/II
Saquinavir PI +	2 NRTI's (Column B above)	B/I

3. Not generally recommended strategies: Strong evidence of clinical benefit but initial viral suppression is not sustained in most patients.

2 NRTI's (Column B above)	B/I

4. Not recommended strategies: Evidence against use, virologically undesirable, or overlapping toxicities.

All monotherapies	D/I
Stavudine (D4T)+ Zidovudine (AZT)	D/I
Zalcitabine (ddC) + Didanosine (ddI)	D/I
Zalcitabine (ddC) + Stavudine (D4T)	D/I
Zalcitabine (ddC) + Lamivudine (3TC)	D/I

Adapted from

APPENDIX 5B: RATING SCHEME FOR CLINICAL PRACTICE RECOMMENDATIONS AS DETERMINED BY THE PANEL ON CLINICAL PRACTICES FOR THE TREATMENT GUIDELINES OF HIV INFECTION, CONVENED BY THE US DEPARTMENT OF HEALTH AND HUMAN SERVICES.

Strength of recommendation	**Quality of scientific evidence supporting recommendation**
A: Strong, should always be offered B: Moderate, should always be offered C: Optional D: Should generally not be offered E: Should never be offered	I: At least one randomized clinical trial with clinical endpoints II: Clinical trials with laboratory endpoints (surrogate markers) III: Expert opinion

APPENDIX 6: COST OF ANTIRETROVIRAL TREATMENT AGENTS

Cost of individual medications for human immunodeficiency virus infection.

Medication	Usual Dosage	1 Month Expense (CAD$)
Nucleoside analogues:		
Zidovudine (AZT)	200 mg TID	408.90
Zidovudine (AZT)	500 mg po daily	340.70
Didanosine (ddI)	200 mg po BID	184.80
Didanosine (ddI)	125 mg po BID	115.50
Zalcitabine (ddC)	0.375 mg po TID	154.80
Zalcitabine (ddC)	0.75 mg TID	193.50
Stavudine (D4T)	20-40 mg BID	255.00*
Stavudine (D4T)	15-30 mg po BID	226.80*
Lamivudine (3TC)	150 mg BID	264.40
Protease Inhibitors:		
Indinavir	800 mg q8h	484.79
Ritonavir	600 mg BID	480.74
Saquinavir	600 mg TID	491.40
Non-nucleoside reverse transcriptase inhibitors:		
Nevirapine	200 mg BID	Investigational not available for sale in Canada

All costs sourced from: A. Tseng and D. Fletcher: HIV Drug Therapy: Recommendations and Associated Costs; January 1997

* Reported costs have been corrected from source and confirmed with author.

APPENDIX 7: COST CALCULATIONS OF ANTIRETROVIRAL TREATMENT COMBINATIONS

		Total number of drugs in combination	AZT (200mg/TID) $408.90	ddI (200mg po/BID) $184.80	d4T (40mg/BID) $255.00	3TC (150mg/BID) $264.40	Ind (800mg/q8h) $484.79	Rit (600mg/BID) $480.74	Saq (600mg/TID) $491.40
1	d4T (40mg/BID)+3TC (150mg/BID)+Ind (800mg/q8h)	3.0	0	0	1	1	1	0	0
2	AZT (200mg/TID)+3TC (150mg/BID)+Ind (800mg/q8h)	3.0	1	0	0	1	1	0	0
3	AZT (200mg/TID)+3TC (150mg/BID)	2.0	1	0	0	1	0	0	0
4	AZT (200mg/TID)+3TC (150mg/BID)+Saq (600mg/TID)	3.0	1	0	0	1	0	0	1
5	d4T (40mg/BID)+3TC (150mg/BID)+Rit (600mg/BID)	3.0	0	0	1	1	0	1	0
6	d4T (40mg/BID)+3TC (150mg/BID)	2.0	0	0	1	1	0	0	0
7	d4T (40mg/BID)+3TC (150mg/BID)+Saq (600mg/TID)	3.0	0	0	1	1	0	0	1
8	d4T (40mg/BID)+3TC (150mg/BID)+Rit (400mg/BID))+Saq (400mg/BID)	3.1	0	0	1	1	0	0.67	0.44
9	AZT (300mg/BID)+3TC (150mg/BID)+Rit (600mg/BID)	3.0	1	0	0	1	0	1	0
10	ddI (400mg QD) +d4T (40mg/BID) +Ind (800mg/q8h)	3.0	0	1	1	0	1	0	0

		Total cost of drugs in combination							
1	d4T (40mg/BID)+3TC (150mg/BID)+Ind (800mg/q8h)	$1,004.19	$0.00	$0.00	$255.00	$264.40	$484.79	$0.00	$0.00
2	AZT (200mg/TID)+3TC (150mg/BID)+Ind (800mg/q8h)	$1,158.09	$408.90	$0.00	$0.00	$264.40	$484.79	$0.00	$0.00
3	AZT (200mg/TID)+3TC (150mg/BID)	$673.30	$408.90	$0.00	$0.00	$264.40	$0.00	$0.00	$0.00
4	AZT (200mg/TID)+3TC (150mg/BID)+Saq (600mg/TID)	$1,164.70	$408.90	$0.00	$0.00	$264.40	$0.00	$0.00	$491.40
5	d4T (40mg/BID)+3TC (150mg/BID)+Rit (600mg/BID)	$1,000.14	$0.00	$0.00	$255.00	$264.40	$0.00	$480.74	$0.00
6	d4T (40mg/BID)+3TC (150mg/BID)	$519.40	$0.00	$0.00	$255.00	$264.40	$0.00	$0.00	$0.00
7	d4T (40mg/BID)+3TC (150mg/BID)+Saq (600mg/TID)	$1,010.80	$0.00	$0.00	$255.00	$264.40	$0.00	$0.00	$491.40
8	d4T (40mg/BID)+3TC (150mg/BID)+Rit (400mg/BID))+Saq (400mg/BID)	$1,058.29	$0.00	$0.00	$255.00	$264.40	$0.00	$320.49	$218.40
9	AZT (300mg/BID)+3TC (150mg/BID)+Rit (600mg/BID)	$1,154.04	$408.90	$0.00	$0.00	$264.40	$0.00	$480.74	$0.00
10	ddI (400mg QD) +d4T (40mg/BID) +Ind (800mg/q8h)	$924.59	$0.00	$184.80	$255.00	$0.00	$484.79	$0.00	$0.00

APPENDIX 8A
EFFICACY DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 1	COMBO 2	COMBO 3
	d4T(40mg/BID) + 3TC(150mg/BID) + Ind(800mg/q8h)	AZT (200mg/TID) + 3TC (150mg/BID) + Ind (800mg/q8h)	AZT (200mg/TID) + 3TC (150mg/BID)
EFFICACY			
Degree of viral load suppression (log10 reduction)	2 to 3 log reduction (s.3)	2 to 3 log reduction (s.3)	1 to 1.5 log reduction (s.3)
% of patients achieving undetectable levels(nadir) at 500 copies/mL	90% (s.7)	91% (s.6)	0% (s.6)
Durability of viral load suppression	Sustained suppression of plasma viral load in most patients. (s.1)	Sustained suppression of plasma viral load in most patients. (s.1)	Suppression of plasma viral load is not achieved in most patients. (s.1)
Clinical Benefit (linear value function)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit. (s.1)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit. (s.1 & s.11)	Some evidence of clinical benefit: reduction in disease progression or AIDS related mortality over monotherapy. (s.1 & s.9)
Strength of DHHS Treatment Guideline Recommendations re:treatment strategy	Preferred (s.1)	Preferred (s.1)	Not Generally Recommended. (s.1)
NRTI Component Strength of recommendation	Strong - should always be offered (s.1)	Strong - should always be offered (s.1)	Optional - may be offered. (s.1)
PI Component Strength of recommendation	Strong - should always be offered (s.1)	Strong - should always be offered (s.1)	No PI - Should generally not be offered. (s.1)
NRTI Component Quality of Scientific evidence for recommendation	Clinical trials with laboratory endpoints. (s.1)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)
PI Component Quality of Scientific evidence for recommendation	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	Not applicable - No PI (s.1)

APPENDIX 8A
EFFICACY DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 4	COMBO 5	COMBO 6
	AZT (200mg/TID) + 3TC (150mg/BID) + Saq (600mg/TID)	d4T (40mg/BID) + 3TC (150mg/BID) + Rit (600mg/BID)	d4T (40mg/BID) + 3TC (150mg/BID)
EFFICACY			
Degree of viral load suppression (log10 reduction)	0.5 - 1 log reduction (s.3)	2 to 3 log reduction (s.3)	0.5 - 1 log reduction (s.3 & s.4)
% of patients achieving undetectable levels(nadir) at 500 copies/mL	33% (s.10)	90% (s.1,a.3)	21% (s.12,a.1)
Durability of viral load suppression	Suppression of plasma viral load is not achieved in most patients. (s.1)	Sustained suppression of plasma viral load in most patients.(s.1)	Suppression of plasma viral load is not achieved in most patients.(s.1)
Clinical Benefit (linear value function)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit. (s.5)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit.(s.1)	Some evidence of clinical benefit: reduction in disease progression or AIDS related mortality over monotherapy. (s.1 & s.9)
Strength of DHHS Treatment Guideline Recommendations re:treatment strategy	Not Recommended. (s.1)	Preferred. (s.1)	Not Generally Recommended. (s.1 & s.9)
NRTI Component Strength of recommendation	Strong - should always be offered. (s.1)	Strong - should always be offered. (s.1)	Optional - may be offered. (s.1)
PI Component Strength of recommendation	Should generally not be offered. (s.1)	Strong - should always be offered (s.1)	No PI - Should generally not be offered. (s.1)
NRTI Component Quality of Scientific evidence for recommendation	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	Clinical trials with laboratory endpoints. (s.1)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)
PI Component Quality of Scientific evidence for recommendation	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints (s.5 & s.6)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	Not applicable - No PI (s.1)

APPENDIX 8A
EFFICACY DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 7	COMBO 8
	d4T (40mg/BID) + 3TC (150mg/BID) + Saq (600mg/TID)	d4T (40mg/BID) + 3TC (150mg/BID) + Rit (400mg/BID) +Saq (400mg/BID)
EFFICACY		
Degree of viral load suppression (log10 reduction)	0.5 - 1 log reduction (s.3)	> 3 log reduction (s.4)
% of patients achieving undetectable levels(nadir) at 500 copies/mL	33% (s.10 a.4)	100% (s.8)
Durability of viral load suppression	Suppression of plasma viral load is not achieved in most patients.(s.1)	Sustained suppression of plasma viral load in most patients.(s.1)
Clinical Benefit (linear value function)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit. (s.5)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit.(s.1)
Strength of DHHS Treatment Guideline Recommendations re:treatment strategy	Not Recommended. (s.1)	Preferred. (s.1)
NRTI Component Strength of recommendation	Strong - should always be offered. (s.1)	Strong - should always be offered. (s.1)
PI Component Strength of recommendation	Should generally not be offered. (s.1)	Moderate - can usually be offered. (s.1)
NRTI Component Quality of Scientific evidence for recommendation	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)
PI Component Quality of Scientific evidence for recommendation	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints (s.5 & s.6)	Clinical trials with laboratory endpoints. (s.1)

APPENDIX 8A
EFFICACY DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 9	COMBO 10
	AZT (300mg/BID) + 3TC (150mg/BID) + Rit (600mg/BID)	ddI (400mg QD) + d4T (40mg/BID) + Ind (800mg/q8h)
EFFICACY		
Degree of viral load suppression (log10 reduction)	2 to 3 log reduction (s.3)	2 to 3 log reduction (s.3)
% of patients achieving undetectable levels(nadir) at 500 copies/mL	87% (s.13,a.2)	90% (s.7)
Durability of viral load suppression	Sustained suppression of plasma viral load in most patients.(s.1)	Sustained suppression of plasma viral load in most patients.(s.1)
Clinical Benefit (linear value function)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit. (s.1)	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality over dual-therapy benefit.(s.1)
Strength of DHHS Treatment Guideline Recommendations re:treatment strategy	Preferred. (s.1)	Preferred. (s.1)
NRTI Component Strength of recommendation	Strong - should always be offered. (s.1)	Strong - should always be offered. (s.1)
PI Component Strength of recommendation	Strong - should always be offered. (s.1)	Strong - should always be offered. (s.1)
NRTI Component Quality of Scientific evidence for recommendation	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)
PI Component Quality of Scientific evidence for recommendation	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)	At least one clinical trial with clinical endpoints + clinical trials with laboratory endpoints. (s.1)

APPENDIX 8B
EASE OF USE, RESISTANCE, AND COST DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 1	COMBO 2	COMBO 3
	d4T(40mg/BID) + 3TC(150mg/BID) + Ind(800mg/q8h)	AZT (200mg/TID) + 3TC (150mg/BID) + Ind (800mg/q8h)	AZT (200mg/TID) + 3TC (150mg/BID)
EASE OF USE			
Dosing Frequency	4x per day	4x per day	2x per day
Total number of pills, tablets, capsules per day	10	14	8
Diet Constraints	Indinavir: Take on an empty stomach or with a light meal or fat free snack.	Indinavir: Take on an empty stomach or with a light meal or fat free snack.	No food restrictions.
Storage Recommendations	Store at room temperature, protect from light and moisture.	Store at room temperature, protect from light and moisture.	Store at room temperature, protect from light and moisture.
Recommendations to minimize the impact of adverse effects.	D4T:Minimize alchohol intake. Indinavir: Drink at least 1.5 litres of water/liquids during each day to decrease the chance of developing kidney stones	AZT:Take in an upright position with a full glass of water. To minimize nausea take with food. Indinavir: Drink at least 1.5 litres of water/liquids during each day to decrease the chance of developing kidney stones	AZT:Take in an upright position with a full glass of water. To minimize nausea take with food.
RESISTANCE			
p(Developing Resistance) (s.14,a.5)	L	L	H
Protease Inhibitor Cross Resistance	76% CR to SAQ; 91% CR to RIT; 60% CR to NFV	76% CR to SAQ; 91% CR to RIT; 60% CR to NFV	n/a
Future Therapeutic Options Available	AZT/ddI/2nd PI AZT/ddI/NNRTI RIT/SAQ/NRTI	d4T/ddI/2nd PI d4T/ddI/NNRTI RIT/SAQ/NRTI	d4T/ddI/2nd PI d4T/ddI/NNRTI* RIT/SAQ/NRTI
COST			
Drug Acquisition Costs/month	$1,004.19	$1,158.09	$673.30

APPENDIX 8B
EASE OF USE, RESISTANCE, AND COST DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 4	COMBO 5	COMBO 6
	AZT (200mg/TID) + 3TC (150mg/BID) + Saq (600mg/TID)	d4T (40mg/BID) + 3TC (150mg/BID) + Rit (600mg/BID)	d4T (40mg/BID) + 3TC (150mg/BID)
EASE OF USE			
Dosing Frequency	4x per day	2x per day	2x per day
Total number of pills, tablets, capsules per day	17	16	4
Diet Constraints	Take Saquinavir with a large, preferably high-fat meal	Ritonavir: Take with food if possible.	No food restrictions.
Storage Recommendations	Store at room temperature, protect from light and moisture.	d4T + 3TC: Store at room temperature, protect from light and moisture. Ritonavir capsules must be kept refrigerated	Store at room temperature, protect from light and moisture.
Recommendations to minimize the impact of adverse effects.	AZT:Take in an upright position with a full glass of water. To minimize nausea take with food.	d4T: Minimize alchohol intake.	d4T: Minimize alchohol intake.
RESISTANCE			
p(Developing Resistance) (s.14,a.5)	H	L	H
Protease Inhibitor Cross Resistance	74% CR to IND; 91% to RIT; 58% c.r. to NFV	80% c.r. to IND; 62% c.r. to SAQ; 59% c.r. NFV	n/a
Future Therapeutic Options Available	d4T/ddI/2nd PI d4T/ddI/NNRTI RIT/SAQ/NRTI	AZT/ddI/2nd PI AZT/ddI/NNRTI RIT/SAQ/NRTI	AZT/ddI/1st PI AZT/ddI/NNRTI RIT/SAQ/NRTI
COST			
Drug Acquisition Costs/month	$1,164.70	$1,000.14	$519.40

APPENDIX 8B
EASE OF USE, RESISTANCE, AND COST DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 7	COMBO 8
	d4T (40mg/BID) + 3TC (150mg/BID) + Saq (600mg/TID)	d4T (40mg/BID) + 3TC (150mg/BID) + Rit (400mg/BID) +Saq (400mg/BID)
EASE OF USE		
Dosing Frequency	3x per day	2x per day
Total number of pills, tablets, capsules per day	13	16
Diet Constraints	Take Saquinavir with a large, preferably high-fat meal.	Ritonavir: Take with food if possible. Saquinavir: Take with a large, preferably high-fat meal.
Storage Recommendations	Store at room temperature, protect from light and moisture.	d4T + 3TC+Saq: Store at room temperature, protect from light and moisture. Ritonavir must be kept refrigerated
Recommendations to minimize the impact of adverse effects.	d4T: Minimize alchohol intake.	d4T: Minimize alchohol intake.
RESISTANCE		
p(Developing Resistance) (s.14,a.5)	H	L
Protease Inhibitor Cross Resistance	74% CR to IND; 91% to RIT; 58% c.r. to NFV	
Future Therapeutic Options Available	AZT/ddI/2nd PI AZT/ddI/NNRTI RIT/SAQ/NRTI	2 new NRTI's/NNRTI
COST		
Drug Acquisition Costs/month	$1,010.80	$1,058.29

APPENDIX 8B
EASE OF USE, RESISTANCE, AND COST DECISION ATTRIBUTES AND COMPONENT FACTORS

	COMBO 9	COMBO 10
	AZT (300mg/BID) + 3TC (150mg/BID) + Rit (600mg/BID)	ddI (400mg QD) + d4T (40mg/BID) + Ind (800mg/q8h)
EASE OF USE		
Dosing Frequency	2x per day	4x per day
Total number of pills, tablets, capsules per day	20	12
Diet Constraints	Ritonavir: Take with food if possible.	DDI: must be taken on an empty stomach. Indinavir: Take on an empty stomach or with a light meal or fat free snack.
Storage Recommendations	AZT + 3TC: Store at room temperature, protect from light and moisture. Ritonavir must be kept refrigerated	Store at room temperature, protect from moisture.
Recommendations to minimize the impact of adverse effects.	AZT:Take in an upright position with a full glass of water. To minimize nausea take with food.	d4T: Minimize alchohol intake.Indinavir:Drink at least 1.5 litres of water/liquids during each day to decrease the chance of developing kidney stones
RESISTANCE		
p(Developing Resistance) (s.14,a.5)	L	L
Protease Inhibitor Cross Resistance	80% c.r. to IND; 62% c.r. to SAQ; 59% c.r. NFV	76% CR to SAQ; 91% CR to RIT; 60% CR to NFV
Future Therapeutic Options Available	d4T/ddI/2nd PI d4T/ddI/NNRTI RIT/SAQ/NRTI	AZT/3TC/2nd PI AZT/3TC/NNRTI RIT/SAQ/NRTI
COST		
Drug Acquisition Costs/month	$1,154.04	$924.59

Appendix 8C – 1: Mild-Moderate Bothersome Adverse Effects (occuring more often than average)

COMBO 1	COMBO 2	COMBO 3	COMBO 4	COMBO 5	COMBO 6	COMBO 7	COMBO 8	COMBO 9	COMBO1 0
d4T/3TC + Indinavir	AZT/3TC + Indinavir	AZT/3TC	AZT/3TC + Saquinavir (Invirase)®	d4T/3TC + Ritonavir	d4T/3TC	d4T/3TC + Saquinavir (Invirase)®	d4T/3TC + Ritonavir + Saquinavir (Invirase)®	AZT/3TC + Ritonavir	.ddI/d4T + Indinavir
Nephrolithiasis (kidney stones) Benign Hyperbilirubinemia	Nephrolithiasis (kidney stones) Benign Hyperbilirubinemia Altered taste Reduced appetite Numbness, prickling, tingling sensation	average	Altered taste Numbness, prickling, tingling sensation; Rash	Altered taste Dizziness Numbness Reduced appetite; prickling, tingling sensation; Frequent and often severe Diarrhea, Nausea, and Vomiting Rash	average	Rash	Dizziness; Numbness, prickling, tingling sensation Frequent and often severe diarrhea, nausea, and vomiting Rash	Altered taste; Reduced appetite Numbness, prickling, tingling sensation Frequent and often severe diarrhea, nausea, and vomiting Rash	Altered taste Constipation Diarrhea Nausea Nephrolithiasis (kidney stones); Benign Hyperbilirubinemia Rash

Appendix 8C – 2: Infrequent or Rare Adverse Effects

COMBO 1	COMBO 2	COMBO 3	COMBO 4	COMBO 5	COMBO 6	COMBO 7	COMBO 8	COMBO 9	COMBO1 0
d4T/3TC + Indinavir	AZT/3TC + Indinavir	AZT/3TC	AZT/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir	d4T/3TC	d4T/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir + Saquinavir (Invirase)	AZT/3TC + Ritonavir	.ddI/d4T + Indinavir
Neuropathy (15-21%); Pancreatitis (1%)	Bone marrow suppression (anemia or neutropenia)	Bone marrow suppression (anemia or neutropenia)	Bone marrow suppression (anemia or neutropenia)	Neuropathy (15-21%); Pancreatitis (1%)	Neuropathy (15-21%); Pancreatitis (1%)	Neuropathy (15-21%); Pancreatitis (1%)	Neuropathy (15-21%); Pancreatitis (1%)	Bone marrow suppression (anemia or neutropenia)	Seizures (1%); Neuropathy (34%); Pancreatitis (10%)

Appendix 8C – 3: Subclinical Effects / Drug Effects on Lab Values

COMBO 1	COMBO 2	COMBO 3	COMBO 4	COMBO 5	COMBO 6	COMBO 7	COMBO 8	COMBO 9	COMBO1 0
d4T/3TC + Indinavir	AZT/3TC + Indinavir	AZT/3TC	AZT/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir	d4T/3TC	d4T/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir + Saquinavir (Invirase)	AZT/3TC + Ritonavir	.ddI/d4T + Indinavir
Elevated Bilirubin; Elevated Triglycerides	Anemia; Elevated Bilirubin; Elevated Triglycerides; Neutropenia		Anemia; Elevated bilirubin; Elevated Creatinine; Neutropenia	Elevated Alkaline Phosphatase; Elevated Creatinine; Elevated Liver Functions; Elevated Triglycerides		Elevated Creatinine	Elevated Alkaline Phosphatase; Elevated Creatinine; Elevated Liver Functions; Elevated Triglycerides	Anemia; Elevated Alkaline Phosphatase; Elevated Creatinine; Elevated Liver Functions; Elevated Triglycerides; Neutropenia	Elevated Alkaline Phosphatase; Elevated Amylase; Elevated Creatinine; Elevated Liver Functions; Elevated Triglycerides

Appendix 8C – 4: Drug Interactions Requiring Dose Adjustment

COMBO 1	COMBO 2	COMBO 3	COMBO 4	COMBO 5	COMBO 6	COMBO 7	COMBO 8	COMBO 9	COMBO1 0
d4T/3TC + Indinavir	AZT/3TC + Indinavir	AZT/3TC	AZT/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir	d4T/3TC	d4T/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir + Saquinavir (Invirase)	AZT/3TC + Ritonavir	.ddI/d4T + Indinavir
INDINAVIR: ketoconazole, rifabutin, phenytoin, phenobarbital, antacids reduce indinavir levels unless taken > 1 hour apart. 3TC: Dose adjustments for renal impairment: TMP	INDINAVIR: ketoconazole, rifabutin, phenytoin, phenobarbital. antacids reduce indinavir levels unless taken > 1 hour apart. AZT: gancyclovir, probenecid, rifampin, high dose TMP-SMX, sulfadiazine/ pyrimethamine; 3TC: Dose adjustments for renal impairment: TMP	AZT: gancyclovir, probenecid, rifampin, high dose TMP-SMX, sulfadiazine/ pyrimethamine; 3TC: Dose adjustments for renal impairment: TMP	SAQUINAVIR: Levels ↑ by ketoconazole, and grapefruit juice. Saquinavir levels reduced by rifampin, rifabutin, and possibly phenobarbital, phenytoin, dexamethasone, carbamazepine. AZT: gancyclovir, probenecid, rifampin, high dose TMP-SMX, sulfadiazine/ pyrimethamine; 3TC: Dose adjustments for renal impairment: TMP	RITONAVIR: Potent inhibitor of cytochrome p450. Ritonavir increases levels of clarithromycin and desipramine. Ritonavir decreases levels, theophylline, sulfamethoxazol e and zidovudine. Rifampin decreased ritonavir AUC by 35%, ritonavir dose may need to be ↑. *Interaction with ethinyl estradiol in oral contraceptives requires dosage modification or use of alternative contraceptive 3TC: Dose adjustments for renal impairment: TMP	3TC: Dose adjustments for renal impairment: TMP	SAQUINAVIR: Saquinavir levels ↑ by ketoconazole, and grapefruit juice. Saquinavir levels reduced by rifampin, rifabutin, and possibly phenobarbital, phenytoin, dexamethasone, and carbamazepine. 3TC: Dose adjustments for renal impairment: TMP	RITONAVIR: Potent inhibitor of cytochrome p450. Ritonavir increases levels of clarithromycin and desipramine. Ritonavir decreases levels, theophylline, sulfamethoxazol e and zidovudine. Rifampin decreased ritonavir AUC by 35%, ritonavir dose may need to be ↑. SAQUINAVIR: levels ↑ by ritonavir, ketoconazole, and grapefruit juice. Saquinavir levels reduced by rifampin, rifabutin, phenytoin, phenobarbital, dexamethasone, and carbamazepine.	RITONAVIR: Potent inhibitor of cytochrome p450. Ritonavir increases levels of clarithromycin and desipramine. Ritonavir decreases levels, theophylline, sulfamethoxazol e and zidovudine. Rifampin decreased ritonavir AUC by 35%, ritonavir dose may need to be ↑. AZT: gancyclovir, probenecid, rifampin, high dose TMP-SMX, sulfadiazine/ pyrimethamine; 3TC: Dose adjustments for renal impairment: TMP	INDINAVIR: ketoconazole, rifabutin, phenytoin, phenobarbital .Didanosine and antacids reduce indinavir levels unless taken > 1 hour apart. DDI: Interference with absorption of either drugs: ciprofloxacin, dapsone, demeclocycline, doxycycline, indinavir, itraconazole, ketoconazole, minocycline, norofloxacin, ofloxacin, tetracycline, antacids, oral gancyclovir.

Appendix 8C – 5: Drug Interactions potentially exacerbating risk of adverse effects

d4T/3TC + Indinavir	AZT/3TC + Indinavir	AZT/3TC	AZT/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir	d4T/3TC	d4T/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir + Saquinavir (Invirase)	AZT/3TC + Ritonavir	.ddI/d4T + Indinavir
D4T: ↑ risk of neuropathy: metronidazole, chloramphenicol, cisplatin, isoniazide, dapsone, lithium, ethambutol, ethionamide, nitrofurantoin, phenytoin, vincristine 3TC: ↑ risk of headache, myalgia, nausea, neutropenia, diarrhea: TMP/SMX: ↑ risk of Pancreatitis ethanol, pentamidine, valproic acid	AZT: ↑ risk of bone marrow toxicity: amphotericin B, cisplatin, clozapine, cyclophosphamide, dactinomycin, daunorubicin, doxorubicin, dapsone, etoposide, fluorouracil, fluconazole, flucytosine, hydroxyurea, indomethacin, methotrexate, paclitaxel, pentamidine, primaquine, sulfadiazine/pyrimethamine, sulfasalasine, trimetrexate, gancyclovir, TMP-SMX, vinblastine. 3TC: ↑ risk of headache, myalgia, nausea, neutropenia, diarrhea: TMP/SMX: ↑ risk of Pancreatitis: ethanol, pentamidine, valproic acid	AZT: ↑ risk of bone marrow toxicity: amphotericin B, cisplatin, clozapine, cyclophosphamide, dactinomycin, daunorubicin, doxorubicin, dapsone, etoposide, fluorouracil, fluconazole, flucytosine, hydroxyurea, indomethacin, methotrexate, paclitaxel, pentamidine, primaquine, sulfadiazine/pyrimethamine, sulfasalasine, trimetrexate, gancyclovir, TMP-SMX, vinblastine. 3TC: ↑ risk of headache, myalgia, nausea, neutropenia, diarrhea: TMP/SMX ↑ risk of Pancreatitis: ethanol, pentamidine, valproic acid	AZT: ↑ risk of bone marrow toxicity: amphotericin B, cisplatin, clozapine, cyclophosphamide, dactinomycin, daunorubicin, doxorubicin, dapsone, etoposide, fluorouracil, fluconazole, flucytosine, hydroxyurea, indomethacin, methotrexate, paclitaxel, pentamidine, primaquine, sulfadiazine/pyrimethamine, sulfasalasine, trimetrexate, gancyclovir, TMP-SMX, vinblastine 3TC: ↑ risk of headache, myalgia, nausea, neutropenia, diarrhea: TMP/SMX ↑ risk of Pancreatitis: ethanol, pentamidine, valproic acid SAQUINAVIR ↑ risk of saquinavir toxicities: enzyme inducers (I.e. azoles, clarithromycin, erythromycin) ↑ risk of cardiotoxicity, GI upset, excessive sedation. calcium-channel blockers, clindamycin, dapsone, quinidine, terfenadine, triazolam	D4T: ↑ risk of neuropathy: metronidazole, chloramphenicol, cisplatin, isoniazide, dapsone, lithium, ethambutol, ethionamide, nitrofurantoin, phenytoin, vincristine. 3TC: ↑ risk of headache, neutropenia, myalgia, nausea, diarrhea: TMP/SMX: ↑ risk of Pancreatitis: ethanol, pentamidine, valproic acid	D4T: ↑ risk of neuropathy: metronidazole, chloramphenicol, cisplatin, isoniazide, dapsone, lithium, ethambutol, ethionamide, nitrofurantoin, phenytoin, vincristine. 3TC: ↑ risk of headache, neutropenia, myalgia, nausea, diarrhea: TMP/SMX: ↑ risk of Pancreatitis: ethanol, pentamidine, valproic acid. SAQUINAVIR ↑ risk of saquinavir toxicities: enzyme inducers (I.e. azoles, clarithromycin, erythromycin). ↑ risk of cardiotoxicity, GI upset, excessive sedation. calcium-channel blockers, clindamycin, dapsone, quinidine, terfenadine, triazolam	D4T: ↑ risk of neuropathy: metronidazole, chloramphenicol, cisplatin, isoniazide, dapsone, lithium, ethambutol, ethionamide, nitrofurantoin, phenytoin, vincristine 3TC ↑ risk of headache, neutropenia, myalgia, nausea, diarrhea: TMP/SMX: ↑ risk of Pancreatitis: ethanol, pentamidine, valproic acid. SAQUINAVIR: ↑ risk of saquinavir toxicities: enzyme inducers (I.e. azoles, clarithromycin, erythromycin) ↑ risk of cardiotoxicity, GI upset, excessive sedation. calcium-channel blockers, clindamycin, dapsone, quinidine, terfenadine, triazolam	AZT: ↑ risk of bone marrow toxicity amphotericin B, cisplatin, clozapine, cyclophosphamide, dactinomycin, daunorubicin, doxorubicin, dapsone, etoposide, fluorouracil, fluconazole, flucytosine, hydroxyurea, indomethacin, methotrexate, paclitaxel, pentamidine, primaquine, sulfadiazine/pyrimethamine, sulfasalasine, trimetrexate, gancyclovir, TMP-SMX, vinblastine 3TC: ↑ risk of headache, neutropenia, myalgia, nausea, diarrhea: TMP/SMX ↑ risk of Pancreatitis: ddI, ethanol, pentamidine, valproic acid	D4T: ↑ risk of neuropathy: ddI, metronidazole, chloramphenicol, cisplatin, isoniazide, dapsone, lithium, ethambutol, ethionamide, nitrofurantoin, phenytoin, vincristine DDI: ↑ risk of didanosine toxicity (diarrhea, pancreatitis, peripheral neuropathy): gancyclovir, d4T, chloramphenicol cisplatin, divalproex Na, ethambutol, ethionamide, isoniazid, lithium, metronidazole, nitrofurantoin, pentamidine, primaquine, valproic acid, vincristine.

Appendix 8C – 6: Contraindicated drugs due to toxicity of drug interactions

COMBO 1	COMBO 2	COMBO 3	COMBO 4	COMBO 5	COMBO 6	COMBO 7	COMBO 8	COMBO 9	COMBO1 0
d4T/3TC + Indinavir	AZT/3TC + Indinavir	AZT/3TC	AZT/3TC + Saquinavir (Invirase)	d4T/3TC + Ritonavir	d4T/3TC	d4T/3TC + saquinavir (Invirase)	d4T/3TC + Ritonavir + Saquinavir (Invirase)	AZT/3TC + Ritonavir	ddI/d4T + Indinavir
amiodarone, astemizole, cisapride, diazepam, midazolam, rifampin, ritonavir, saquinavir, terfenadine, triazolam, ergot alkaloids, zalcitabine, zidovudine	amiodarone, astemizole, cisapride, diazepam, midazolam, rifampin, ritonavir, saquinavir, stavudine, terfenadine, triazolam, ergot alkaloids, zalcitabine,	stavudine, zalcitabine	astemizole, carbamazepine, cisapride, dexamethasone, ergot alkaloids, phenytoin, phenobarbital, rifampin, rifabutin, stavudine, terfenadine, zalcitabine,	alprazolam, amioderone, amlodipine, astemizole, bepridil, bupropion, cisapride, clozapine, clorazepate, cyclosporine, diazepam, diltiazem,disopyramide, disulfiram, encainide, ergot alkaloids, estrazolam, etoposide, felodipine, fentanyl, flecainide, flurazepam, indinavir, lidociane, meperidine, metronidazole, mexiletine, midazolam, nefazodone, nicardipine, nifedipine, nimodipine, pacliaxel, pimozide, piroxicam, propoxyphene, propafenone, quinidine, rifabutin, tamoxifen, terfenadine, triazolam, verapamil, vinblastine, vincristine, warfarin, zalcitabine, zidovudine, zopidem,	zalcitabine, zidovudine	astemizole, carbamazepine, cisapride, dexamethasone, ergot alkaloids, phenytoin, phenobarbital, rifampin, rifabutin, terfenadine, zalcitabine, zidovudine	alprazolam, amioderone, amlodipine, astemizole, bepridil, bupropion, carbamazepine, cisapride, clozapine, clorazepate, cyclosporine, dexamethasone, diazepam, diltiazem,disopyramide, disulfiram, encainide, ergot alkaloids, estrazolam, etoposide, felodipine, fentanyl, flecainide, flurazepam, indinavir, lidociane, meperidine, metronidazole, mexiletine, midazolam, nefazodone, nicardipine, nifedipine, nimodipine, pacliaxel, phenytoin, phenobarbital, pimozide, piroxicam, propoxyphene, propafenone, quinidine, rifampin, rifabutin, tamoxifen, terfenadine, triazolam, verapamil, vinblastine, vincristine, warfarin, zalcitabine, zidovudine, zopidem,	alprazolam, amioderone, amlodipine, astemizole, bepridil, bupropion, cisapride, clozapine, clorazepate, cyclosporine, diazepam, diltiazem,disopyramide, disulfiram, encainide, ergot alkaloids, estrazolam, etoposide, felodipine, fentanyl, flecainide, flurazepam, indinavir, lidociane, meperidine, metronidazole, mexiletine, midazolam, nefazodone, nicardipine, nifedipine, nimodipine, pacliaxel, pimozide, piroxicam, propoxyphene, propafenone, quinidine, rifabutin, stavudine, tamoxifen, terfenadine, triazolam, verapamil, vinblastine, vincristine, warfarin, zalcitabine, zopidem,	amiodarone, astemizole, cisapride, diazepam, midazolam, rifampin, ritonavir, saquinavir, terfenadine, triazolam, ergot alkaloids, zalcitabine, zidovudine

APPENDIX 9:
SAMPLE HEALTHCARE PROFESSIONAL QUESTIONNAIRE

Optimizing Drug Formulary Decisions for the Antiretroviral Treatment of HIV-1 Infection: A Health Outcomes Maximization Approach Adjusted for Multiple Stakeholder Preferences

Research Study Participant Briefing:

In this research study, we are attempting to develop methods to improve formulary decision making by better addressing the needs of people living with HIV and their healthcare providers. This is important because continued formulary reimbursement (government payment) of HIV drugs is critical in making and/or keeping these drugs accessible to the people who need them. In making decisions of what drugs to pay for, formulary decision-makers should take into account the treatment objectives and preferences of the people going on therapy. You have been asked to participate in this study in order to help us gain a better understanding of these objectives and preferences.

There are many factors involved in selecting antiretroviral drug therapy for your patients. We are trying to identify these factors and their relative importance to you in making treatment decisions for a population of asymptomatic, treatment naive patients whose viral loads are in excess of 10,000 copies per mL and whose CD4+ counts range between 200-500 cells per mm^3.

In this interview you are requested to assume the role of the healthcare professional who is guiding a formulary drug and therapeutics committee in selecting the most appropriate therapy for asymptomatic patients meeting the above criteria who have already decided to go on anti-retroviral therapy. The purpose of this exercise is to help the formulary drug and therapeutics committee to select any or all of the 10 most frequently used therapeutic combinations that will best satisfy you and your patients' therapeutic goals and preferences. For the purpose of the exercise, the objective of the formulary being designed is aimed at directing prescribing behavior to the therapies that are most likely to maximize the long-term health outcomes of patients.

Based on your responses we will assess your preference and tradeoffs among the various factors. Your preferences will then be used to evaluate the most frequently used antiretroviral combinations that are eligible for reimbursement at this time (i.e. have received approval for sale in Canada). Your preferences and treatment objectives will also be incorporated, along with those of other healthcare providers, and people living with HIV, into a decision model to help determine the best hypothetical selection of drugs for formulary reimbursement.

If you have any questions, please feel free ask me at anytime during the interview.

If you would like a summary of the final study results, please let me know and I will forward you a copy after April 15th, 1998 at which time they will be available.

Thank you for participating and making this study possible.

Monica Kader

CONSENT FORM TO PARTICIPATE IN STUDY

This is to state that I agree to participate in the research study being conducted by Monica Kader as part of her Master of Science in Administration Thesis research under the supervision of Dr. J. Etezadi Amoli of the Department of Decision Sciences at Concordia University. This research is being funded by a grant from Merck Frosst Canada Inc.

A. PURPOSE

I have been informed that the purpose of this research is to help develop improved formulary drug selection processes that aim to optimize the health outcomes of people living with HIV subject to their needs and preferences and those of their healthcare providers.

B. PROCEDURES

- The research questionnaire will be administered in an interview format lasting approximately 1 hour.

C. CONDITIONS OF PARTICIPATION

- I understand that I am free to withdraw my consent and discontinue my participation at anytime.
- I understand that my participation in this study is strictly CONFIDENTIAL and that under no circumstances will my identity be disclosed.
- I understand that the data from this study may be published.
- I understand the purpose of this study and know that there is no hidden motive of which I have not been informed.

I HAVE CAREFULLY STUDIED THE ABOVE AND UNDERSTAND THIS AGREEMENT. I FREELY CONSENT AND AGREE TO PARTICIPATE IN THIS STUDY.

NAME _____ DATE _____

SIGNATURE_____ WITNESS _____

1. ART Selection Goals

In deciding to go on HIV antiretroviral therapy there are many factors involved. Rank the treatment goals listed below according to their importance to you in selecting a drug regimen for your patients.

Rank	ART Treatment Goals:	Ratio weight
	Achieve durable suppression of HIV replication	
	Prevent or delay disease progression	
	Minimize bothersome antiretroviral drug related adverse effects	
	Maximize ease of use of an antiretroviral regimen	
	Minimize the potential of developing resistance to antiretroviral therapy	
	Treat HIV infection according to most recent evidence-based peer-review antiretroviral treatment guidelines	
	Maximize the number of therapeutic options available in case of therapeutic failure	

Rank goals from 1 – 7 (1 = most important, 7 = least important)

Determine ratio weights by :

1. *Setting least important goal ratio weight to 1.*
2. *Determining the ratio weight of next least important goal with respect to ratio weight of least important goal. (i.e. if goal ranked 6 is twice as important as goal ranked 7 (least important), the ratio weight of goal 6 is = 2)*
3. *Determine the ratio weights for the remaining goals by order of increasing importance ending with the most important goal in the same manner as step 2. Remember to always compare the goal currently being evaluated against the least important goal in setting ratio weights.*

2. Viral Load Suppression Factors:

The ability of a particular regimen to suppress HIV viral replication is characterized by the factors below. Please indicate their relative importance to you in selecting a drug regimen for your patients.

Rank	Viral Load Suppression Factors:	Ratio weight
	Degree of viral load suppression *(reduction in viral load, assay limit of detection 500 copies/mL)*	
	% of patients achieving undetectable levels at 500 copies/mL at six months/24 weeks *(proportion of patients deriving durable benefit from treatment)*	
	Durability of Effect	

Rank viral load suppression factors from 1 – 3 (1 = most important, 3 = least important)

Determine ratio weights by :

1. *Setting least important factor ratio weight to 1.*
2. *Determining the ratio weight of next least important factor with respect to ratio weight of least important factor.*
3. *Determine the ratio weights for the remaining factor in the same manner as step 2. Remember to always compare the factor currently being evaluated against the least important factor in setting ratio weights.*

3. Degree of viral load suppression in plasma

Rank	**Degree of viral load suppression** *(assay limit of detection 500 copies/mL)*	
	log_{10} reduction	**X fold reduction**
1	> 3 log reduction	> 1000 fold reduction
2	2 to 3 log reduction	100-1000 fold reduction
3	1 to 1.5 log reduction	10-31 fold reduction
4	0.5 - 1 log reduction	3-10 fold reduction

Under the most challenging of circumstances, if you have to trade off some degree of viral load suppression for your patients to tolerate the drug regimen, what is the minimal acceptable degree of viral load suppression you would find acceptable in selecting a drug regimen for your patients? Please specify, Rank _____.

4. % of patients achieving undetectable levels

The % of patients achieving undetectable levels at 500 copies/mL at six months/24 weeks characterizes the proportion of patients deriving durable benefit from a given treatment.

Rank	% of patients achieving undetectable levels (at 500 copies/mL at six months/24 weeks)
1	**100%** (associated with therapy combination A)
2	**90%** (associated with therapy combination B)
3	**87%** (associated with therapy combination C)
4	**33%** (associated with therapy combination D)
5	**21%** (associated with therapy combination E)
6	**0%** (associated with therapy combination F)

If tolerability and future therapeutic options in the case of long-term treatment failure are a concern, what is the lowest % of patients achieving undetectable levels you would find acceptable in selecting a drug regimen for your patients?
Please specify, Rank _____.

5. Durability of Effect:

Rank	Durability of Effect:	Ratio Weight
1	**Sustained suppression of plasma viral load in most patients.**	
2	**Less likely to provide sustained suppression of plasma viral load in most patients.**	
3	**Suppression of plasma viral load is not sustained in most patients**	
4	**Suppression of plasma viral load is not achieved in most patients.**	
5	**Suppression of plasma viral load is not achieved in any patients.**	**1**

If tolerability and future therapeutic options in the case of long-term treatment failure are a concern, what is the lowest durability of effect you would find acceptable in selecting a drug regimen for your patients? Please specify, Rank _____.

Durability of Effect measures have been ranked from 1 – 5 (1 = most valuable, 5 = least valuable).

Least valuable measure ratio weight has been set to 1.

1. *Determining the ratio weight of next least valuable measure with respect to ratio weight of least valuable measure.*
2. *Determine the ratio weights for the remaining measures in the same manner as step 1. Remember to always compare the measure currently being evaluated against the least valuable measure in setting ratio weights.*

6. Demonstrated Clinical Benefit:

Demonstrated clinical benefit characterizes the proven ability of a treatment to reduce disease progression (i.e. opportunistic infections) and mortality.

Rank	Demonstrated clinical benefit (reduced morbidity and mortality)	Ratio weight
1	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality.	
2	Some evidence of clinical benefit reduction in disease progression or AIDS related mortality	
3	Transient clinical benefit, does not alter long-term natural history of HIV disease	1
4	No demonstrated clinical benefit	0

Under any circumstances, what is the lowest level of Demonstrated clinical benefit you would find acceptable in selecting a drug regimen for your patients?
Please specify, Rank _____.

*Demonstrated clinical benefit measures have been ranked from 1 – 4 (1 = most valuable, 4 = **not** valuable).*

The ratio weight for the measure having the lowest level of value (not no value), has been set to 1.

1. *Determining the ratio weight of next least valuable measure with respect to ratio weight of least valuable measure.*
2. *Determine the ratio weights for the remaining measures in the same manner as step 1. Remember to always compare the measure currently being evaluated against the least valuable measure in setting ratio weights.*

7. Treatment Guideline Recommendations:

The 'Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents' make recommendations with regard to treatment strategies and also particular treatments.

Please rank the importance of those recommendations for treatment strategies and particular treatments according to their importance in helping you select treatment for your patients.

Rank	Weight of Treatment Guideline Recommendations:	Ratio weight
	Treatment strategy (i.e. double therapy, triple therapy...)	
	Particular treatment (i.e. d4T/ddI, AZT/3TC/Indinavir, ...)	

_____ ***Both factors are equally important***

_____ ***One factor is more important than the other.***

Please rank both factors and specify how much more important it is when the less important factor is set to a ratio weight of 1.

_____ **I do not *consider the treatment guideline recommendations in selecting therapy.***

Do you believe other health care providers should follow these treatment guideline recommendations in selecting treatment for their patients?

Yes _____ ***No*** _____

8. Strength of Treatment Strategy Recommendations:

The Strength of treatment strategy expresses the preferences of HIV experts in selecting or recommending various treatment approaches (mono therapy, double therapy, triple therapy etc...) for their patients.

Assign ratio weights below to indicate how you would weight their recommendation in selecting your treatment.

Rank	Strength of Treatment Strategy	Ratio Weight
1	Preferred	
2	Alternative	
3	Not Generally Recommended	1
4	Not Recommended	0

What is lowest level of HIV expert recommendations with regard to treatment strategies that you would find acceptable in the selection treatment for your patients?

Please specify, Rank _____.

9. Relative Importance of Components of a Particular Treatment

Recommended treatment regimens are made up of 2 components: Nucleoside Reverse Transcriptase Inhibitors (NRTI's) and Protease Inhibitors (PI's).

Are both components equally important to you in selecting therapy for your patients? Yes _____ No _____

Rank	9. Relative importance of components of a particular treatment	Ratio weight
	Nucleoside Reverse transcriptase Inhibitor (NRTI) (i.e. AZT, d4T, 3TC, ddI, ddC)	
	Protease Inhibitor (PI) (i.e. indinavir, saquinavir, ritonavir)	

If one component is more important than the other, please rank the two components below according to their relative importance to you in selecting treatment. (1= more important, 2 = less important).

Specify how much more important this component is, if the less important component is set to a ratio weight of 1.

10. Strength of Recommendation for NRTI Component

Please set ratio weights below to indicate the relative value of treatment guideline recommendations for the NRTI component in selecting therapy for your patients.

Rank	Strength of recommendation for NRTI Component	Ratio Weight
1	Strong – should always be offered	
2	Moderate – can usually be offered	
3	Optional – can sometimes be offered	
4	Should generally not be offered	1
5	Should never be offered	0

What is the minimum level of treatment guideline recommendations for the NRTI component of treatment you would find acceptable in selecting therapy for your patients?
Please specify, Rank _____.

11. Strength of recommendation for PI Component

Please set ratio weights below to indicate the relative value of treatment guideline recommendations for the PI in selecting therapy for your patients?

Rank	11. Strength of recommendation for PI Component	Ratio Weight
1	Strong - should always be offered	
2	Moderate - can usually be offered	
3	Optional - can sometimes be offered	
4	Should generally not be offered	1
5	Should never be offered	0

What is the minimum level of treatment guideline recommendations for the PI component of treatment you would find acceptable in selecting therapy for your patients?

Please specify, Rank _____.

12. Quality of Scientific evidence for NRTI Component

Please set ratio weights below to indicate the relative importance you would place on the quality of scientific evidence supporting treatment guideline recommendations for the NRTI component of treatment.

Rank	Quality of Scientific evidence for NRTI Component	Ratio Weight
1	**At least one clinical trial with clinical endpoints** *(improvements in disease progression and mortality captured)* **+** **Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
2	**Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
3	**Expert Opinion** *(educated hypothesis, experts clinical experience, not scientifically proven)*	1

What is lowest quality of scientific evidence you would find acceptable in selecting a nucleoside reverse transcriptase inhibitors? Please specify, Rank _____.

13. Quality of Scientific Evidence for PI Component

Please set ratio weights below to indicate the relative importance you would place on the quality of scientific evidence supporting treatment guideline recommendations for the PI component of treatment.

Rank	Quality of Scientific evidence for PI Component	Ratio Weight
1	**At least one clinical trial with clinical endpoints** *(improvements in disease progression and mortality captured)* **+** **Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
2	**Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
3	**Expert Opinion** *(educated hypothesis, experts clinical experience, not scientifically proven)*	1
4	**Not applicable - No PI**	0

What is lowest quality of scientific evidence you would find acceptable in selecting a protease inhibitor?
Please specify, Rank _____.

14. Relative Importance of Adverse Effects:

- Antiretroviral treatment has been known to result in numerous adverse effects. Some of these effects are bothersome and occur relatively frequently and while not usually life threatening these effects can make you feel tired or ill and generally make staying on long-term therapy more difficult.
- Other adverse effects can be serious and potentially life threatening and could make it necessary to alter your therapy. However, these effects only occur in a small percentage of the population.
- Subclinical effects are usually without symptoms or discomfort. They generally represent the effects of drug therapy on lab values. However, they can indicate elevated risks of developing other common conditions if therapy is continued over the long-term.

Please indicate relative importance of the various types drug related adverse effects in selecting therapy for your patients.

Rank	Relative Importance of Adverse Effects:	Ratio weight
	Common Mild-Moderate Bothersome Adverse Effects	
	Infrequent or rare Serious or Potentially Life Threatening Adverse Effects	
	Sub-clinical effects (Drug effects on Lab Values)	

Rank each type of adverse effect. (1= more important, 3 = less important) and specify how much more important it is by assigning ratio weights, when the least important type is set to a ratio weight of 1

15. Relative Importance of Drug Interactions:

Antiretroviral treatment has been known to result in numerous drug interactions. However, drug interactions generally become more problematic in the later stages of HIV infection.

- Some of these drug interactions require dosing adjustments to ensure appropriate drug levels (not too high, not too low) and can complicate the administration of these drugs. Doses may need to be increased or decreased and in some cases these adjustments may require the active involvement of the patient in spacing drugs taking apart.
- Other drug interactions with prescription or over the counter drugs can worsen the incidence and severity of drug interactions. These interactions can usually be managed if the benefit outweighs the risks.
- A number of drug interactions occur with other prescription or over the counter drugs resulting in serious toxicities. While other drug interactions and their effects can be managed, the seriousness of these types of drug interactions prevents the use of these drugs together. This can complicate the treatment of a number of conditions, and opportunistic infections generally occurring in the later stages of HIV infection.

Please indicate relative importance of the various types drug interactions in selecting therapy for your patients.

Rank	Relative Importance of Drug Interactions	Ratio weight
	Drug Interactions requiring dose adjustment	
	Drug Interactions potentially exacerbating risk of adverse effects	
	Contraindicated drugs due to toxicity of drug interactions	

Rank each type (1= more important, 3 = less important) and specify how much more important it is by assigning ratio weights, when the less important type is set to a ratio weight of 1

16. Mild-Moderate Bothersome Adverse Effects:

Rank	Antiretroviral Combination	Ratio Weight
	Combo 1: d4T/3TC/Indinavir	
	Combo 2: AZT/3TC/Indinavir	
	Combo 3: AZT/3TC	
	Combo 4: AZT/3TC/Saquinavir (Invirase)	
	Combo 5: d4T/3TC/Ritonavir	
	Combo 6: d4T/3TC	
	Combo 7: d4T/3TC/Saquinavir (Invirase)	
	Combo 8: d4T/3TC/Ritonavir + Saquinavir (Invirase)	
	Combo 9: AZT/3TC/Ritonavir	
	Combo 10: ddI/d4T/Indinavir	

Rank 1-10 (1=best, 10 = worst).
Set Ratio Weights

Knowing that drug potency is important but sometimes related to increased levels of adverse effects, What is the maximum (worst) level of adverse effects that your patients should be able and willing to tolerate in order to achieve therapeutic goals?

Please specify, Rank _____.

17. Infrequent or Rare Adverse Effects

Rank	Antiretroviral Combination	Ratio Weight
	Combo 1: d4T/3TC/Indinavir	
	Combo 2: AZT/3TC/Indinavir	
	Combo 3: AZT/3TC	
	Combo 4: AZT/3TC/Saquinavir (Invirase)	
	Combo 5: d4T/3TC/Ritonavir	
	Combo 6: d4T/3TC	
	Combo 7: d4T/3TC/Saquinavir (Invirase)	
	Combo 8: d4T/3TC/Ritonavir + Saquinavir (Invirase)	
	Combo 9: AZT/3TC/Ritonavir	
	Combo 10: ddI/d4T/Indinavir	

Rank 1-10 (1=best, 10 = worst).
Set Ratio Weights

Knowing that drug potency is important but sometimes related to increased levels of adverse effects, What is the maximum (worst) level of adverse that your patients should be able and willing tolerate in order to achieve therapeutic goals?

Please specify, Rank _____.

18. Subclinical effects / Drug effects on Lab Values

Rank	Antiretroviral Combination	Ratio Weight
	Combo 1: d4T/3TC/Indinavir	
	Combo 2: AZT/3TC/Indinavir	
	Combo 3: AZT/3TC	
	Combo 4: AZT/3TC/Saquinavir (Invirase)	
	Combo 5: d4T/3TC/Ritonavir	
	Combo 6: d4T/3TC	
	Combo 7: d4T/3TC/Saquinavir (Invirase)	
	Combo 8: d4T/3TC/Ritonavir + Saquinavir (Invirase)	
	Combo 9: AZT/3TC/Ritonavir	
	Combo 10: ddI/d4T/Indinavir	

Rank 1-10 (1=best, 10 = worst).
Set Ratio Weights

Knowing that drug potency is important but sometimes related to increased levels of adverse effects, What is the maximum (worst) level of adverse effects that your patients should be able and willing tolerate in order to achieve therapeutic goals? Please specify, Rank _____.

19. Drug Interactions requiring dose adjustment

Rank	Antiretroviral Combination	Ratio Weight
	Combo 1: d4T/3TC/Indinavir	
	Combo 2: AZT/3TC/Indinavir	
	Combo 3: AZT/3TC	
	Combo 4: AZT/3TC/Saquinavir (Invirase)	
	Combo 5: d4T/3TC/Ritonavir	
	Combo 6: d4T/3TC	
	Combo 7: d4T/3TC/Saquinavir (Invirase)	
	Combo 8: d4T/3TC/Ritonavir + Saquinavir (Invirase)	
	Combo 9: AZT/3TC/Ritonavir	
	Combo 10: ddI/d4T/Indinavir	

Rank 1-10 (1=best, 10 = worst).
Set Ratio Weights

Knowing that drug potency is important but sometimes related to increased levels of adverse effects, Is there a maximum (worst) level of drug interactions requiring dosing adjustments that your patients should be able and willing tolerate in order to achieve therapeutic goals?

No_____. Yes._____ If Yes, please specify, Rank _____.

20. Drug Interactions potentially exacerbating risk of adverse effects

Rank	Antiretroviral Combination	Ratio Weight
	Combo 1: d4T/3TC/Indinavir	
	Combo 2: AZT/3TC/Indinavir	
	Combo 3: AZT/3TC	
	Combo 4: AZT/3TC/Saquinavir (Invirase)	
	Combo 5: d4T/3TC/Ritonavir	
	Combo 6: d4T/3TC	
	Combo 7: d4T/3TC/Saquinavir (Invirase)	
	Combo 8: d4T/3TC/Ritonavir + Saquinavir (Invirase)	
	Combo 9: AZT/3TC/Ritonavir	
	Combo 10: ddI/d4T/Indinavir	

Rank 1-10 (1=best, 10 = worst).
Set Ratio Weights

Knowing that drug potency is important but sometimes related to increased levels of adverse effects, Is there a maximum (worst) level of drug interactions that potentially worsen the risk of adverse effects that your patients should be able and willing tolerate in order to achieve therapeutic goals?

No_____ Yes_____ If Yes, please specify, Rank _____.

21. Contraindicated drugs due to toxicity of drug interactions

Rank	Antiretroviral Combination	Ratio Weight
	Combo 1: d4T/3TC/Indinavir	
	Combo 2: AZT/3TC/Indinavir	
	Combo 3: AZT/3TC	
	Combo 4: AZT/3TC/Saquinavir (Invirase)	
	Combo 5: d4T/3TC/Ritonavir	
	Combo 6: d4T/3TC	
	Combo 7: d4T/3TC/Saquinavir (Invirase)	
	Combo 8: d4T/3TC/Ritonavir + Saquinavir (Invirase)	
	Combo 9: AZT/3TC/Ritonavir	
	Combo 10: ddI/d4T/Indinavir	

Rank 1-10 (1=best, 10 = worst).

Set Ratio Weights

Knowing that drug potency is important but sometimes related to increased levels of drug interactions, Is there a maximum (worst) level of contraindications that your patients should be able and willing tolerate in order to achieve therapeutic goals?

No_____ Yes_____ If Yes, please specify, Rank _____.

22. Relative importance of Ease of Use factors

Antiretroviral therapy involves numerous medication requirements that can at times be inconvenient. Of the ease of use factors below please rank these factors according to their relative importance to you in selecting a drug regimen for your patients.

Rank factors below from 1 – 5 (1 = most important, 5 = least important)

Rank	Relative importance of Ease of Use factors:	Ratio weight
	Dosing Frequency (# of times drug combination is taken per day)	
	Total number of pills *# tablets, capsules, etc ... taken per day)	
	Diet Constraints. (i.e. special attention needed in taking medication with/without food or with certain kinds of food)	
	Storage Recommendations (i.e. need for refrigeration of medications)	
	Recommendations to minimize the impact of adverse effects. (i.e. having to do special things like drink water, take over the counter medications, sit up while medications to minimize the impact or likelihood of getting side effects)	

Determine ratio weights by :

1. *Setting least important factor ratio weight to 1.*
2. *Determining the ratio weight of next least important factor with respect to ratio weight of least important factor. (i.e. if factor ranked 4 is twice as important as factor ranked 5 (least important), the ratio weight of factor 4 is = 2)*
3. Determine the ratio weights for the remaining factors by order of increasing importance ending with the most important factor in the same manner as step 2. Remember to always compare the factor currently being evaluated against the least important factor in setting ratio weights.

Antiretroviral treatment regimens differ in the required number of pills to be taken per day and the times a day medication needs to be taken. While no therapeutic combination is perfect, some treatments have been found to be significantly more effective than others.

23. Total number of pills:

In achieving therapeutic goals, what would be the absolute maximum number of pills a day a patient can be expected to take to get the maximum benefit from therapy?

Please select from the options below _____.

Total number of pills, tablets, capsules etc... (Antiretrovirals / HIV Medications only)
4
8
10
12
13
14
16
17
20

24. Dosing Frequency:

What is the maximum number of times a day your patients can be expected to reliably take HIV drugs?
Please select from the options below___

How many times a day you have to take drugs.
2
3
4

25. Diet Constraints:

Please rank the diet constraints above from best to worst (2-7).

The 'no food restrictions' option has already been ranked best (#1).

Rank	25. Diet Constraints	Ratio weight
1	No food restrictions.	
	2 of 2 daily drug taking intervals with food.	
	2 of 2 daily drug taking intervals with large, preferably high-fat meal.	
	3 of 4 daily drug taking intervals on an empty stomach or with a light meal or fat free snack.	
	3 of 3 daily drug taking intervals with a large, preferably high-fat meal.	
	3 of 4 daily drug taking intervals with a large, preferably high-fat meal	
	3 of 4 daily drug taking intervals on an empty stomach or with a light meal or fat free snack. 4th dose must be taken on an empty stomach.	

**Daily drug taking intervals where any or all antiretrovirals can be taken according to an optimized drug schedule.*

Determine ratio weights by:

1. *Setting worst diet constraints measure ratio weight to 1.*
2. *Determining the ratio weight of next worst diet constraint with respect to ratio weight of worst diet constraint. (i.e. if diet constraint ranked 6 is twice as good as factor ranked 7 (worst), the ratio weight of factor 7 is = 2)*
3. *Determine the ratio weights for the remaining diet constraints by order of increasing value ending with the best diet constraint in the same manner as step 2.*

In order to achieve treatment goals, what is the maximum (worst) level of diet constraints you can realistically expect your patients to comply with?

Please specify, Rank _____.

26. Storage Recommendations
Store at room temperature, protect from light and moisture.
Store at room temperature, protect from light and moisture. Protease Inhibitor capsules must be kept refrigerated

In achieving your treatment goals are your patients generally able and willing to put up with having to refrigerate medications?

Yes _____ No_____.

27. Recommendations to minimize the impact of adverse effects.

HIV treatments are known to cause common and sometimes bothersome adverse effects. However, there are things your patients can do to help minimize these effects. The recommendations to minimize these effects for some common drug combinations are shown below.

Please rank them in order of your preference from 1-4 (1=best, 4=worst).

Rank	Recommendations to minimize the impact of adverse effects.	Ratio weight
	Minimize alcohol intake.	
	Take in an upright position with a full glass of water. To minimize nausea, take with food.	
	Minimize alcohol intake. & Drink at least 1.5 liters of water/liquids during each day to decrease the chance of developing kidney stones	
	Take in an upright position with a full glass of water. & To minimize nausea, take with food. & Drink at least 1.5 liters of water/liquids during each day to decrease the chance of developing kidney stones	

Determine ratio weights by:

1. *Setting worst recommendation ratio weight to 1.*
2. *Determining the ratio weight of next worst recommendation with respect to ratio weight of worst recommendation. (i.e. if recommendation ranked 3 is twice as good as factor ranked 4 (worst), the ratio weight of factor 3 is = 2)*
3. *Determine the ratio weights for the remaining recommendations by order of increasing value ending with the best recommendation in the same manner as step 2.*

28. Probability of developing resistance

An antiretroviral treatment's likelihood of allowing the development of viral resistance has a strong potential to limit future therapy. Antiretroviral treatment regimens differ with regard to their likelihood of developing resistance. While no therapeutic combination is perfect, some treatments have been found to be significantly better than others in this respect.

Knowing the implications on future treatment, what would be the maximum probability of developing resistance that you would accept in selecting an initial antiretroviral drug regimen for your patients?

Please select from options below and specify, Rank _____.

Rank	Probability of developing resistance
1	Low probability of developing resistance: < 20% of adherent patients resistant at 1 year on treatment
2	Moderate probability of developing resistance: between 21-79% of adherent patients resistant at 1 year on treatment
3	High probability of developing resistance: > 80% of adherent patients resistant at 1 year on treatment

29. Future Therapeutic Options

In planning long-term HIV drug treatment for your patients, indicate the relative value (ratio weight) of future potential therapeutic regimens 1 and 2, above and beyond regimen 3 (worst scenario).

Future Options for change in therapy in case of treatment failure			
Treatment Options from:	**Regimen 1**	**Regimen 2**	**Regimen 3**
Future Options	**2 new NRTI's/PI** **2 new NRTI's/NNTRI** **new NRTI/PI/NNRTI*** **2 PI'S/NRTI*** **2 PI'S/NNRTI***	**2 new NRTI's/NNTRI** **new NRTI/PI/NNRTI*** **2 PI'S/NRTI*** **2 PI'S/NNRTI***	**2 new NRTI's / NNRTI**
Rank	**1**	**2**	**3**
Ratio weight			**1**

- *only limited data available*

30. Costs of Antiretroviral Therapy

Cost is increasingly becoming an important factor in making antiretroviral therapy accessible to the people who need it. Below are the monthly drug acquisition costs for 10 of the most frequently prescribed antiretroviral combinations.

In your opinion and given constrained financial resources, is there a maximum level that should be reimbursed for asymptomatic patients? Yes _____ No _____

If Yes, please specify from the options below. #_____

#	Drug Combination	Monthly cost of antiretroviral combination
1	d4T / 3TC	$519.40
2	AZT / 3TC	$673.30
3	ddI / d4T / Indinavir	$924.59
4	d4T / 3TC / Ritonavir	$1,000.14
5	d4T / 3TC / Indinavir	$1,004.19
6	d4T / 3TC / Saquinavir*	$1,010.80
7	d4T / 3TC / Ritonavir / Saquinavir*	$1,058.29
8	AZT / 3TC / Ritonavir	$1,154.04
9	AZT / 3TC / Indinavir	$1,158.09
10	AZT / 3TC / Saquinavir*	$1,164.70

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APPENDIX 10: SAMPLE PATIENT QUESTIONNAIRE

Optimizing Drug Formulary Decisions for the Antiretroviral Treatment of HIV-1 Infection: A Health Outcomes Maximization Approach Adjusted for Multiple Stakeholder Preferences

Research Study Participant Briefing:

In this research study, we are attempting to develop methods to improve formulary decision making by better addressing the needs of people living with HIV and their healthcare providers. This is important because continued formulary reimbursement (government payment) of HIV drugs is critical in making these drugs accessible to the people who need them. In making decisions of what drugs to pay for, formulary decision-makers should take into account the treatment objectives and preferences of the people going on therapy. You have been asked to participate in this study in order to help us gain a better understanding of these objectives and preferences.

Having gone on antiretroviral therapy (HIV Drugs) fairly recently, there were probably many factors involved in making your decision regarding which drug regimen to go on. We are trying to identify the factors and their relative importance to you in making this decision.

In this interview you are requested to assume role of an asymptomatic patient who has already decided to go on anti-retroviral therapy and now has to select a drug regimen that will best satisfy his or her treatment goals and life style.

Based on your responses we will assess your preference and tradeoffs among the various factors. Your preferences will then be used to evaluate the most frequently used antiretroviral combinations that are eligible for reimbursement at this time (i.e. have received approval for sale in Canada). Your preferences and treatment objectives will also be incorporated, along with those of other people living with HIV and healthcare providers, into a decision model to help determine the best hypothetical selection of drugs for formulary reimbursement.

If you have any questions, please feel free ask your interviewer.

If you would like a summary of the final study results, please contact Monica Kader at (514) 428-8567 after April 15th, 1998 at which time they will be available.

Thank you for participating and making this study possible.

Monica Kader

CONSENT FORM TO PARTICIPATE IN STUDY

This is to state that I agree to participate in the research study being conducted by Monica Kader as part of her Master of Science in Administration Thesis research under the supervision of Dr. J. Etezadi Amoli of the Department of Decision Sciences at Concordia University.

A. PURPOSE

I have been informed that the purpose of this research is to help develop improved formulary drug selection processes that aim to optimize the health outcomes of people living with HIV subject to their needs and preferences and those of their healthcare providers.

B. PROCEDURES

- The research questionnaire will be administered in an interview format lasting approximately 1 hour.
- In the case of people living with HIV, the interview will be administered by Stephanie Burnett, a third party, who is bound under a professional code of ethics regarding confidentiality and undertakes to keep the identity of the participant anonymous.
- This consent form will be retained by the third party. Only the anonymous completed questionnaire will be forwarded to the researcher.

C. CONDITIONS OF PARTICIPATION

- I understand that I am free to withdraw my consent and discontinue my participation at anytime.
- I understand that payment of the honorarium of $50.00 will be made by the third party only on completion of the interview questionnaire.
- I understand that my participation in this study is strictly CONFIDENTIAL and that under no circumstances will my identity be disclosed.
- I understand that the data from this study may be published.
- I understand the purpose of this study and know that there is no hidden motive of which I have not been informed.

I HAVE CAREFULLY STUDIED THE ABOVE AND UNDERSTAND THIS AGREEMENT. I FREELY CONSENT AND AGREE TO PARTICIPATE IN THIS STUDY.

NAME _____ DATE _____

SIGNATURE_____ WITNESS _____

1. ART Selection Goals

In deciding to go on HIV antiretroviral therapy there are many factors involved. Rank the treatment goals listed below according to their importance to you in selecting a drug regimen.

Rank	ART Treatment Goals:	Ratio weight
	Achieve durable suppression of HIV replication	
	Prevent or delay disease progression	
	Minimize bothersome antiretroviral drug related side effects	
	Maximize ease of use of an antiretroviral regimen	
	Minimize the potential of developing resistance to antiretroviral therapy	
	Treat HIV infection according to most recent evidence-based peer-review antiretroviral treatment guidelines	
	Maximize the number of therapeutic options available in case of therapeutic failure	

2. Viral Load Suppression Factors:

The ability of a particular regimen to suppress HIV viral replication is characterized by the factors below. Please indicate their relative importance to you in selecting a drug regimen.

Rank	Viral Load Suppression Factors:	Ratio weight
	Degree of viral load suppression *(reduction in viral load, assay limit of detection 500 copies/mL)*	
	% of patients achieving undetectable levels at 500 copies/mL at six months/24 weeks *(proportion of patients deriving durable benefit from treatment)*	
	Durability of Effect	

3. Degree of viral load suppression in plasma

Rank	**Degree of viral load suppression** *(assay limit of detection 500 copies/mL)*	
	X fold reduction	**Example of viral load reductions from baseline of 50,000 copies/mL**
1	> 1000 fold reduction	From 50,000 to 50 copies/mL
2	100-1000 fold reduction	From 50,000 to 500 copies/mL
3	30 fold reduction	From 50,000 to 1500 copies/mL
4	10 fold reduction	From 50,000 to 5000 copies/mL

If you have to trade off some degree of viral load suppression to tolerate the drug regimen, what is the minimal acceptable degree of viral load suppression you would find acceptable?
Please specify, Rank _____.

4. % of patients achieving undetectable levels

The % of patients achieving undetectable levels at 500 copies/mL at six months/24 weeks characterizes the proportion of patients deriving durable benefit from a given treatment.

Rank	**% of patients achieving undetectable levels** (at 500 copies/mL at six months/24 weeks)
1	**100%** (associated with therapy combination A)
2	**90%** (associated with therapy combination B)
3	**87%** (associated with therapy combination C)
4	**33%** (associated with therapy combination D)
5	**21%** (associated with therapy combination E)
6	**0%** (associated with therapy combination F)

If tolerability and future therapeutic options in the case of long-term treatment failure are a concern, what is the lowest % of patients achieving undetectable levels you would find acceptable? Please specify, Rank _____.

5. Durability of Effect:

Rank	Durability of Effect:	Ratio Weight
1	Sustained suppression of plasma viral load in most patients.	
2	Less likely to provide sustained suppression of plasma viral load in most patients.	
3	Suppression of plasma viral load is not sustained in most patients	
4	Suppression of plasma viral load is not achieved in most patients.	
5	Suppression of plasma viral load is not achieved in any patients.	0

If tolerability and future therapeutic options in the case of long-term treatment failure are a concern, what is the lowest durability of effect you would find acceptable? Please specify, Rank _____.

6. Demonstrated Clinical Benefit:

Demonstrated clinical benefit characterizes the proven ability of a treatment to reduce disease progression (i.e. opportunistic infections) and mortality.

Rank	Demonstrated clinical benefit (reduced morbidity and mortality)	Ratio weight
1	Strong evidence of clinical benefit > = 50% reduction in disease progression and/or AIDS related mortality.	
2	Some evidence of clinical benefit reduction in disease progression or AIDS related mortality	
3	Transient clinical benefit, does not alter long-term natural history of HIV disease	1
4	No demonstrated clinical benefit	0

Under any circumstances, what is the lowest level of Demonstrated clinical benefit you would find acceptable? Please specify, Rank _____.

7. Treatment Guideline Recommendations:

Treatment guidelines written by experts make recommendations with regard to treatment strategies and also particular treatments.

Please rank the guideline recommendations for treatment strategies and particular treatments according to their importance in helping you select treatment.

Rank	Weight of Treatment Guideline Recommendations:	Ratio weight
	Treatment strategy (i.e. double therapy, triple therapy...)	
	Particular treatment (i.e. d4T/ddI, AZT/3TC/Indinavir, ...)	

_____ ***Both factors are equally important***

_____ ***One factor is more important than the other.***

Please rank both factors and specify how much more important it is when the less important factor is set to a ratio weight of 1.

_____ **I would not *consider the treatment guideline recommendations in selecting therapy.***

Do you believe your health care provider should follow these treatment guideline recommendations in helping you to select treatment?

Yes _____ ***No*** _____

8. Relative Importance of Components of a Particular Treatment

Recommended treatment regimens are made up of 2 components: Reverse Transcriptase Inhibitors (NRTI's) and Protease Inhibitors (PI's).

Are both components equally important to you in selecting your therapy? Yes _____ No _____

Rank	8. Relative importance of components of a particular treatment	Ratio weight
	Reverse transcriptase Inhibitor (NRTI) (i.e. AZT, d4T, 3TC, ddI, ddC)	
	Protease Inhibitor (PI) (i.e. indinavir, saquinavir, ritonavir)	

If one component is more important than the other, please rank the two components below according to their relative importance to you in selecting your treatment. (1= more important, 2 = less important).

Specify how much more important this component is, if the less important component is set to a ratio weight of 1.

9. Strength of Recommendation for NRTI Component

Please set ratio weights below to indicate the relative value of treatment guideline recommendations for the NRTI component in selecting your treatment.

Rank	Strength of recommendation for NRTI Component	Ratio Weight
1	Strong – should always be offered	
2	Moderate – can usually be offered	
3	Optional – can sometimes be offered	
4	Should generally not be offered	1
5	Should never be offered	0

What is the minimum level of treatment guideline recommendations for the NRTI component of treatment you would find acceptable in making a decision about treatment?

Please specify, Rank _____.

10. Strength of recommendation for PI Component

Please set ratio weights below to indicate the relative value of treatment guideline recommendations for the PI component in selecting your treatment?

Rank	11. Strength of recommendation for PI Component	Ratio Weight
1	Strong - should always be offered	
2	Moderate - can usually be offered	
3	Optional - can sometimes be offered	
4	Should generally not be offered	1
5	Should never be offered	0

What is the minimum level of treatment guideline recommendations for the PI component of treatment you would find acceptable in making a decision about treatment?

Please specify, Rank _____.

11. Quality of Scientific evidence for NRTI Component

Please set ratio weights below to indicate the relative importance you would place on the quality of scientific evidence supporting treatment guideline recommendations for the NRTI component of treatment.

Rank	Quality of Scientific evidence for NRTI Component	Ratio Weight
1	**At least one clinical trial with clinical endpoints** *(improvements in disease progression and mortality captured)* **+** **Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
2	**Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
3	**Expert Opinion** *(educated hypothesis, experts clinical experience, not scientifically proven)*	1

What is lowest quality of scientific evidence you would find acceptable in selecting a nucleoside reverse transcriptase inhibitor? Please specify, Rank _____.

12. Quality of Scientific Evidence for PI Component

Please set ratio weights below to indicate the relative importance you would place on the quality of scientific evidence supporting treatment guideline recommendations for the PI component of treatment.

Rank	Quality of Scientific evidence for PI Component	Ratio Weight
1	**At least one clinical trial with clinical endpoints** *(improvements in disease progression and mortality captured)* **+** **Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
2	**Clinical trials with laboratory endpoints** *(viral load and CD4 numbers)*	
3	**Expert Opinion** *(educated hypothesis, experts clinical experience, not scientifically proven)*	1
4	**Not applicable - No PI**	0

What is lowest quality of scientific evidence you would find acceptable in selecting a protease inhibitor?
Please specify, Rank _____.

13. Relative Importance of Side Effects:

- Antiretroviral treatment has been known to result in numerous side effects. Some of these effects are bothersome and occur relatively frequently and while not usually life threatening these effects can make you feel tired or ill and generally make staying on long-term therapy more difficult.
- Other side effects can be serious and potentially life threatening and could make it necessary to alter your therapy. However, these effects only occur in a very small percentage of the population.
- Subclinical effects are usually without symptoms or discomfort. They generally represent the effects of drug therapy on lab values. However, they can indicate elevated risks of developing other common conditions if therapy is continued over the long-term.

Please indicate relative importance of the various types drug related side effects in selecting your treatment.

Rank	Relative Importance of Side effects:	Ratio weight
	Common Mild-Moderate Bothersome Side effects	
	Infrequent or rare Serious or Potentially Life Threatening Side effects	
	Sub-clinical effects (Drug effects on Lab Values)	

Rank each type of adverse effect. (1= more important, 3 = less important) and specify how much more important it is by assigning ratio weights, when the least important type is set to a ratio weight of 1

14. Relative Importance of Drug Interactions:

Antiretroviral treatment has been known to result in numerous drug interactions. However, drug interactions generally become more problematic in the later stages of HIV infection.

- Some of these drug interactions require dosing adjustments to ensure appropriate drug levels (not too high, not too low) and can complicate the administration of these drugs. Doses may need to be increased or decreased and in some cases these adjustments may require the active involvement of the patient in spacing drugs taking apart.
- Other drug interactions with prescription or over the counter drugs can worsen the incidence and severity of drug interactions. These interactions can usually be managed if the benefit outweighs the risks.
- A number of drug interactions occur with other prescription or over the counter drugs resulting in serious toxicities. While other drug interactions and their effects can be managed, the seriousness of these types of drug interactions prevents the use of these drugs together. This can complicate the treatment of a number of conditions, and opportunistic infections generally occurring in the later stages of HIV infection.

Please indicate relative importance of the various types drug interactions in selecting your treatment.

Rank	Relative Importance of Drug Interactions	Ratio weight
	Drug Interactions requiring dose adjustment	
	Drug Interactions potentially exacerbating risk of side effects	
	Contraindicated drugs due to toxicity of drug interactions	

Rank each type (1= more important, 3 = less important) and specify how much more important it is by assigning ratio weights, when the less important type is set to a ratio weight of 1

Mild-Moderate Bothersome Side Effects occurring consistently with average frequency across all antiretroviral combinations:

Abdominal Pain
Anorexia (reduced appetite)
Arthralagia (joint pain)
Chills
Constipation
Depression
Diarrhea
Dizziness
Fatigue
Fevers
Headache
Insomnia
Malaise
Mylagia (muscle pain)
Nausea
Neurological Symptoms
Neuropathy
Pancreatitis
Rash
Vomiting

15. Mild-Moderate Bothersome Side Effects (occuring more often than average)

COMBO 1	COMBO 2	COMBO 3	COMBO 4	COMBO 5	COMBO 6	COMBO 7	COMBO 8	COMBO 9	COMBO1 0
d4T/3TC + Indinavir	AZT/3TC + Indinavir	AZT/3TC	AZT/3TC + Saquinavir (Invirase)®	d4T/3TC + Ritonavir	d4T/3TC	d4T/3TC + Saquinavir (Invirase)®	d4T/3TC + Ritonavir + Saquinavir (Invirase)®	AZT/3TC + Ritonavir	.ddI/d4T + Indinavir
Nephrolithiasis (kidney stones) Benign Hyperbilirubinemia	Nephrolithiasis (kidney stones) Benign Hyperbilirubinemia Altered taste Reduced appetite Numbness, prickling, tingling sensation	average	Altered taste Numbness, prickling, tingling sensation; Rash	Altered taste Dizziness Numbness Reduced appetite; prickling, tingling sensation; Frequent and often severe Diarrhea, Nausea, and Vomiting Rash	average	Rash	Dizziness; Numbness, prickling, tingling sensation Frequent and often severe diarrhea, nausea, and vomiting Rash	Altered taste; Reduced appetite Numbness, prickling, tingling sensation Frequent and often severe diarrhea, nausea, and vomiting Rash	Altered taste Constipation Diarrhea Nausea Nephrolithiasis (kidney stones); Benign Hyperbilirubinemia Rash

Rank 1-10 (1=best, 10 = worst).

Knowing that drug potency is important but sometimes related to increased levels of side effects, What is the maximum (worst) level of side effects that you are willing to put up with to achieve therapeutic goals? Please specify, Rank _____.

16. Recommendations to minimize the impact of side effects.

HIV treatments are known to cause common and sometimes bothersome side effects. However, there are things you can do to help minimize these effects. The recommendations to minimize these effects for some common drug combinations are shown below.

Rank	Recommendations to minimize the impact of side-effects.	Ratio weight
	Minimize alcohol intake.	
	Take in an upright position with a full glass of water. To minimize nausea, take with food.	
	Minimize alcohol intake. & Drink at least 1.5 liters of water/liquids during each day to decrease the chance of developing kidney stones	
	Take in an upright position with a full glass of water. & To minimize nausea, take with food. & Drink at least 1.5 liters of water/liquids during each day to decrease the chance of developing kidney stones	

- Rank from 1-4 (1=best, 4=worst).
- Set Ratio Weights.

17. Relative importance of Ease of Use factors

Antiretroviral therapy involves numerous medication requirements that can at times be inconvenient. Of the ease of use factors below please rank these factors according to their relative importance to you in selecting a drug regimen.

Rank factors below from 1 – 5 (1 = most important, 5 = least important)

Rank	Relative importance of Ease of Use factors:	Ratio weight
	Dosing Frequency (# of times drug combination is taken per day)	
	Total number of pills *# tablets, capsules, etc ... taken per day)	
	Diet Constraints. (i.e. special attention needed in taking medication with/without food or with certain kinds of food)	
	Storage Recommendations (i.e. need for refrigeration of medications)	
	Recommendations to minimize the impact of side effects. (i.e. having to do special things like drink water, take over the counter medications, sit up while medications to minimize the impact or likelihood of getting side effects)	

Antiretroviral treatment regimens differ in the required number of pills to be taken per day and the times a day medication needs to be taken. While no therapeutic combination is perfect, some treatments have been found to be significantly more effective than others.

18. Total number of pills:

Total number of pills, tablets, capsules etc... (Antiretrovirals / HIV Medications only)
4
8
10
12
13
14
16
17
20

In achieving your therapeutic goals, what would be the absolute maximum number of pills a day you are willing to take to get the maximum benefit from therapy?

Please select from the options ABOVE _____.

19. Dosing Frequency:

If you had to take HIV drugs four times a day to achieve your goals of therapy, could you? Yes _____ No _____.

If not, what is the maximum number of times a day you are willing to take HIV drugs? Please select from the options below___

How many times a day you have to take drugs.
2
3
4

20. Diet Constraints:

Please rank the diet constraints above from best to worst (2-7).

The 'no food restrictions' option has already been ranked best (#1).

Rank	20. Diet Constraints	Ratio weight
1	No food restrictions.	
	2 of 2 daily drug taking intervals with food.	
	2 of 2 daily drug taking intervals with large, preferably high-fat meal.	
	3 of 4 daily drug taking intervals on an empty stomach or with a light meal or fat free snack.	
	3 of 3 daily drug taking intervals with a large, preferably high-fat meal.	
	3 of 4 daily drug taking intervals with a large, preferably high-fat meal	
	3 of 4 daily drug taking intervals on an empty stomach or with a light meal or fat free snack. 4th dose must be taken on an empty stomach.	

**Daily drug taking intervals where any or all antiretrovirals can be taken according to an optimized drug schedule.*

In order to achieve your other treatment goals, what is the maximum (worst) level of diet constraints you are willing to put up with when selecting treatment?

Please specify by rank _____.

21. Storage Recommendations
Store at room temperature, protect from light and moisture.
Store at room temperature, protect from light and moisture. Protease Inhibitor capsules must be kept refrigerated

*** Having to refrigerate medications is _____ times more inconvenient that not having to refrigerate medications.**

In achieving your treatment goals are you willing to put up with having to refrigerate medications? Yes _____ No_____.

22. Probability of developing resistance

An antiretroviral treatment's likelihood of allowing the development of viral resistance has a strong potential to limit future therapy. Antiretroviral treatment regimens differ with regard to their likelihood of developing resistance. While no therapeutic combination is perfect, some treatments have been found to be significantly better than others in this respect.

Knowing the implications on future treatment, what would be the maximum probability of developing resistance that you would accept in order to be able to tolerate and adhere to your treatment in selecting your *1st* antiretroviral drug regimen?
Please select from options below and specify, Rank _____.

Rank	Probability of developing resistance
1	Low probability of developing resistance: < 20% of adherent patients resistant at 1 year on treatment
2	Moderate probability of developing resistance: between 21-79% of adherent patients resistant at 1 year on treatment
3	High probability of developing resistance: > 80% of adherent patients resistant at 1 year on treatment

23. Future Therapeutic Options

In the event that the HIV drug treatment that you are considering for selection fails at some undetermined time in the future, indicate the relative value (ratio weight) of future potential therapeutic regimens 1 and 2, above and beyond regimen 3 (worst scenario).

Future Options for change in therapy in case of treatment failure			
Treatment Options from:	**Regimen 1**	**Regimen 2**	**Regimen 3**
Future Options	**2 new NRTI's/PI** **2 new NRTI's/NNTRI** **new NRTI/PI/NNRTI*** **2 PI'S/NRTI*** **2 PI'S/NNRTI***	**2 new NRTI's/NNTRI** **new NRTI/PI/NNRTI*** **2 PI'S/NRTI*** **2 PI'S/NNRTI***	**2 new NRTI's / NNRTI**
Rank	**1**	**2**	**3**
Ratio weight			**1**

- *only limited data available*

24. Costs of Antiretroviral Therapy

Cost is increasingly becoming an important factor in making antiretroviral therapy accessible to the people who need it. Below are the monthly drug acquisition costs for 10 of the most frequently prescribed antiretroviral combinations.

In your opinion, is there a maximum level that should be reimbursed for asymptomatic patients? Yes _____ No _____

If Yes, please specify from the options below. #_____

#	Drug Combination	Monthly cost of antiretroviral combination
1	d4T / 3TC	$519.40
2	AZT / 3TC	$673.30
3	ddI / d4T / Indinavir	$924.59
4	d4T / 3TC / Ritonavir	$1,000.14
5	d4T / 3TC / Indinavir	$1,004.19
6	d4T / 3TC / Saquinavir*	$1,010.80
7	d4T / 3TC / Ritonavir / Saquinavir*	$1,058.29
8	AZT / 3TC / Ritonavir	$1,154.04
9	AZT / 3TC / Indinavir	$1,158.09
10	AZT / 3TC / Saquinavir*	$1,164.70

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Please indicate the following

Sex: Male _____ Female_____

Age: _____

What antiretroviral treatment (HIV drugs) are you currently on?

For how long?

Pre-treatment baseline viral load: _____

Pre-treatment CD4+ count: _____

Latest viral load: _____

Latest CD4+ count: _____