MEDICAL CARE
Volume 40, Number 5, pp 429–441
©2002 Lippincott Williams & Wilkins, Inc.

State AIDS Drug Assistance Programs

Equity and Efficiency in an Era of Rapidly Changing Treatment Standards

MIRA JOHRI, PHD, MPH,*† A. DAVID PALTIEL, PHD,‡ SUE J. GOLDIE, MD, MPH,§ AND KENNETH A. FREEDBERG, MD, MSC§¶

BACKGROUND. The 54 state AIDS Drug Assistance Programs (ADAP) provide medications to HIV-infected persons with limited resources. Eligibility and coverage vary, raising concerns about health inequities.

OBJECTIVE. To compare the relative clinical and economic performance of ADAP programs.

RESEARCH DESIGN. A state-transition simulation model of HIV disease was used to explore the clinical consequences and lifetime costs associated with selected state policies. Clinical data came from the Multicenter AIDS Cohort Study, AIDS Clinical Trials Group Protocol 320, and other published randomized trials. Cost data came from the national AIDS Cost and Services Utilization Survey, and the 1999 Red Book. ADAP data came from National Association of State and Territorial AIDS Directors reports and interviews.

MEASURES. Projected life expectancy, quality-adjusted life expectancy, total lifetime direct medical costs, cost-effectiveness in dollars per quality-adjusted life year (QALY) gained.

RESULTS. ADAPs vary considerably in terms of formulary policies, health outcomes, expected costs, and cost-efficiency. Conservative projections, based on a cohort with starting mean CD4 count of 250 cells/μL, yield life expectancies ranging from 5.36 to 6.81 life years (4.69–6.01 quality-adjusted life years [QALYs]). Total per person lifetime direct medical costs range from $81,200 to $112,700; higher costs reflect increased spending on medications. Expected costs per QALY gained range from $7000 to $28,000. Under pessimistic assumptions regarding initial CD4 counts, drug efficacy, and discounting, the most comprehensive policy remains below $33,000/QALY.

CONCLUSIONS. Even the most comprehensive ADAPs constitute a cost-effective use of HIV care resources. A uniform, national ADAP formulary warrants consideration.

Key words: Acquired immunodeficiency

*From the Department of Health Administration, Faculty of Medicine, University of Montreal, Montreal, Quebec.

†From the Centre for Clinical Epidemiology and Community Studies, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec.

‡From the Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, Connecticut.

§From the Center for Risk Analysis, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts.

¶From the Division of General Medicine and the Partners AIDS Research Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Supported by the Centers for Disease Control and Prevention (Cooperative Agreement U64/CCU 114927); by the National Institute of Allergy and Infectious Diseases via grant RO1-AI42006 to the Cost-effectiveness of Preventing AIDS Complications (CEPAC) project and CFAR grant 1P30AI4285101A2; the Adult AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases (Cooperative Agreement U01 AI38838); the Societal Institute for the Mathematical Sciences (SIMS) via Grant DA 09531 from the National Institute on Drug Abuse; and the National Institute on Mental Health via grant MH56826 to the Yale Center for Interdisciplinary Research on AIDS.

Address correspondence and reprint requests to: Mira Johri, Department of Health Administration, Faculty of Medicine, University of Montreal, C.P. 6128, succ. Centre-Ville, Montréal, QC Canada H3C 3J7. E-mail: mira.johri@umontreal.ca

Received April 5, 2001; initial review July 17, 2001; accepted December 20, 2001.

syndrome; economics; cost-benefit analysis; antiviral agents; health services accessibility; United States. (Med Care 2002;40:429–441)

AIDS Drug Assistance Programs (ADAPs) are federally funded, state-based programs providing medications to uninsured HIV-infected persons, or those with limited resources. Since 1996, ADAPs have struggled with explosive growth in budgets, expenditures and clients served.[1] This rapid expansion is caused by several factors, including the growth of the HIV epidemic in the United States,[2,3] its disproportionate impact on individuals less likely to have private insurance coverage[4,5] and, most importantly, the evolution of medical care for HIV/AIDS.

The development in the early to mid 1990s of new classes of antiretroviral drugs, including protease inhibitors and nonnucleoside reverse transcriptase inhibitors, precipitated a major change in the standard of care for HIV infection. From its initial use in late 1995, highly active antiretroviral therapy (HAART) based on aggressive combination drug treatment protocols has been found to suppress viral replication, increase CD4 cells, reduce morbidity, and prolong survival.[6–8] Although HAART is now the recommended standard of care in the United States for treating patients with HIV infection,[9,10] it is costly, ranging from $10,000–$12,000 per person annually.[11,12] Combination antiretroviral drug regimens now represent approximately 90% of total ADAP spending.[13]

Program expansions have led to renewed dilemmas concerning ADAP access. Although ADAPs receive the bulk of their funding from federal sources, each state and territory has considerable discretion in structuring its own policies.[1,13–15] This has led to widespread variations among programs. Although expenditures have more than tripled since 1996, budget limitations have persistently forced programs to limit formulary coverage, to use medical and financial criteria to manage demand and, not infrequently, to institute enrollment caps and waiting lists.[1,13–15] As of June 1999, financial eligibility criteria continued to range widely across ADAP programs, from 125% to 400% of the Federal Poverty Level, defined at $8240 for a single person in 1999.[13] Moreover, two states still provided no protease inhibitors on their formularies, six offered no drugs for opportunistic infections, 11 states had capped program enrollment, six had capped or restricted access to antiretroviral therapies, and more than 1130 qualified persons were reported to be waiting for entry to ADAP.[13]

Although the existence of substantial heterogeneity among ADAPs is now commonly acknowledged,[1,13–15] the impact of these policy choices on societal costs and health outcomes has not been previously studied. Public discussion surrounding ADAP has focused to date on issues of program affordability[11,16–18] and, more recently, public and patient attitudes toward drug rationing policies.[19] Given that access to therapies has a significant impact on health outcomes,[8,20] and that increased pharmaceutical costs under HAART may be partially offset by decreases in other costs of care,[21–26] a formal analysis of alternative ADAP spending decisions may serve to structure and inform public debate.

Our objective was to evaluate the relative clinical and economic performance of ADAP formulary policies. We used a mathematical model of HIV disease to assess the cost-effectiveness of selected ADAP policies from the perspective of the payer of direct medical costs.

Materials and Methods

Overview

We conducted this analysis using a computer-based simulation model of the natural history, treatment efficacy, and costs of HIV infection. The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model has been used previously to address a range of HIV clinical policy questions, including interventions against specific opportunistic infections,[27–30] the cost-effectiveness of highly active antiretroviral therapy,[31] and genotypic antiretroviral resistance testing.[32] In this analysis, we use the model to examine public policy toward the distribution of HIV/AIDS medications via ADAP. We select for analysis state ADAP programs encompassing a broad range of access policies, and utilize the model to consider the alternative treatment protocols, triggering mechanisms, and cost structures they represent.

Performance of alternative ADAP policies is measured by the incremental cost-effectiveness ratio, a measure of value for money, defined as the average additional cost required to yield one extra life-year or quality-adjusted life year (QALY) in the population under study. A higher cost-effectiveness ratio implies a lower degree of comparative value. Monetary values are reported in 1999 US dollars, adjusted where appropriate using the medical care component of the Consumer Price Index.[33] In accordance with the recommendations of the Panel on Cost-Effectiveness in Health and Medicine, future costs and quality-adjusted life-years (QALYs) were discounted at an annual rate of 3%.[34] Sensitivity analyses assessing the robustness of conclusions to reasonable uncertainty in several parameters are also presented.[34]

Model

Users may assign and alter input data on the monthly probabilities of clinical events including opportunistic infections, changes in CD4 lymphocyte count and HIV RNA, therapeutic efficacy and failure, toxic reactions to medication, development of drug resistance and death. Using Monte Carlo simulation, the clinical courses of a specified number of hypothetical patients can be followed from time of entry to the model until death. Specifying a cohort size of 1 million patients produced stable estimates of mean life expectancy, quality-adjusted life expectancy, and costs of care under a variety of scenarios representing different ADAP policies for administration of antiretroviral therapies and opportunistic infection prophylaxis.

Specifics of the model have been described elsewhere.[27–29,31,32,35] Briefly, the model defines health states that are predictive of patient health status, clinical prognosis, resource consumption, and quality of life. Health states fall into one of three general categories: chronic, acute, and death. Although patients usually reside in a chronic health state, the development of a clinical complication (eg, an opportunistic infection) triggers a temporary transition to one of the acute states, associated with lower quality of life and higher resource consumption levels and mortality rates. From these temporary health states patients can shift to a new chronic state, or die. Death can occur from either a chronic or acute state, and can also be attributed to non-AIDS related causes. Chronic and acute states are segmented along a number of dimensions, corresponding to features of clinical interest. These include CD4 cell count, HIV RNA, history of clinical complications, time (if any) since initiation of HAART, and prophylaxis (if any) against specific opportunistic infections.[29] Progression of HIV disease, risks of clinical events, treatment effects and resource consumption are linked to both CD4 cell count and HIV RNA.[29,31,32]

Analysis Plan

Eleven of the 54 ADAP programs, representing the spectrum of formulary and access policies, were selected for this analysis. We considered a number of state programs differing across dimensions potentially related to policy definition and program performance: ADAP formulary and access policies, geographic region, and state and HIV-infected population sizes. In addition, we considered all states reporting at least one of the following program attributes: medical access criteria contraindicated by current guidelines,[9,10,36] financial eligibility at or below the federal poverty level, failure to provide HAART or recommended drugs for opportunistic infections,[36] waiting lists, and enrollment caps. Because many ADAPs offered a similar standard of care, we narrowed the selection to 11 state ADAPs offering distinctive approaches. Formularies for each selected state were modeled at three points in time, representing fiscal years 1997, 1998, and 1999.

For purposes of our analysis, each ADAP formulary strategy is composed of two independent elements: the opportunistic infection (OI) prophylaxis strategy and the antiretroviral strategy. The OI prophylaxis strategy was defined on the basis of actual formulary offerings in each fiscal year (Table 1). Administration of prophylaxis drugs was modeled in accordance with medical best practice, as defined in ratings A and B of the United States Public Health Service/Infectious Diseases Society of America (USPHS/IDSA) guidelines on prevention of opportunistic infections.[36,37] We assumed that all individuals who developed an acute complication received appropriate treatment regardless of its availability via ADAP. The drug and medical costs of opportunistic infection treatment (as opposed to prophylaxis) were thus represented in total cost figures, but not in ADAP-associated costs.

Therapeutic options for antiretroviral drugs (Table 2), including drug combinations and their

TABLE 1. Formulary Strategies for Opportunistic Infection Prophylaxis

OI Strategy No.*	ADAP†	Prophylaxis Available PCP (3)‡	MAC (3)§	Toxoplasmosis (1)¶
0	GA97, GA98, GA99, NE98, NE99, OR97	0	0	0
1	AR97	2	0	0
2	AR98, AR99	2	2	1
3	NV97, NV98, NV99	2	1	0
4	OK97, OK98, OK99, FL97	2	3	0
5	FL99	2	3	1
6	MS97, MS98	3	1	0
7	TX99, MS99, NE97	3	2	0
8	SD97, SD98, SD99, TX97, TX98	3	3	0
9	OR98, OR99, MO97, MO98, MO99, FL98	3	3	1

*Number (arbitrarily assigned) denotes strategy for opportunistic infection prophylaxis.
†ADAP programs denoted by US Postal Service state abbreviations; year refers to fiscal year in which policy applies.
‡PCP: *Pneumocystis carinii* pneumonia. Number in parentheses denotes maximum number of prophylaxis drugs. These are trimethoprim-sulfamethoxazole (also effective against toxoplasmosis), dapsone and aerosolized pentamidine.
§MAC: *Mycobacterium avium* complex. Prophylaxis drugs: azithromycin, clarithromycin, rifabutin.
¶Prophylaxis drugs: pyrimethamine/leucovorin in combination.

sequence of administration within strategies, were specified on the basis of clinical plausibility, and drug administration was modeled in accordance with medical best practice as represented by the Panel on Clinical Practices for the Treatment of HIV Infection.[9,10,38] Transitions from initial to second-line to salvage drug regimens were triggered by therapeutic failure.[9,31] The effectiveness of each antiretroviral regimen was based on data extrapolated from randomized clinical trials.[6,39–43]

Significant uncertainty exists in estimates of antiretroviral drug efficacy and characteristics of the ADAP patient population. The performance of each ADAP program was assessed in scenarios defined along these two dimensions, so as to explore these factors and their interplay. We first distinguished scenarios via high and low estimates of antiretroviral therapy efficacy. The "high efficacy" scenario primarily uses data from the Dupont 006 trial, a randomized controlled trial of 450 patients not previously treated with any nonnucleoside reverse-transcriptase inhibitor or protease inhibitor. It showed 70% suppression (≤500 copies of HIV RNA per ml) at 48 weeks for the zidovudine/lamivudine/efavirenz arm.[39] The antiretroviral drug strategy represents each ADAP as following the most efficacious regimen permitted by its actual formulary holdings. In this scenario, in descending order of efficacy, these are Regimen 1, then Regimen 2, followed by Regimen 4 (Table 2). There are 19 distinct ADAP policies resulting from the combinations of distinct opportunistic infection prophylaxis and antiretroviral strategies.

The "low efficacy" scenario is based on data from the Johns Hopkins Clinical cohort, an observational study of HAART in 273 previously protease-inhibitor naive patients, which showed 44% suppression (≤500 copies of HIV RNA per ml) at 24 weeks.[41] These data may provide a more realistic estimate of effectiveness, as levels of adherence in actual practice are generally lower than those observed in randomized trials. Moreover, the demographic characteristics of the Hopkins cohort's patients more closely resemble ADAP clients. The antiretroviral drug strategy for this scenario, in descending order of efficacy, is Regimen 3 where available, otherwise Regimen 4 (Table 2). There are 15 distinct ADAP policies resulting from the combinations of distinct opportunistic infection prophylaxis and antiretroviral strategies.

We applied both scenarios to two distinct hypothetical target populations. The first consisted of individuals similar to those in the Multicenter AIDS Cohort Study, with a mean CD4 of 250 cells per μL.[44] The second consisted of individuals similar to those in the Dupont 006 trial, with a mean CD4 count of 350 cells per μL.[39] In both

TABLE 2. Antiretroviral Regimens Used in Analysis

	ART Drugs	Source	Reference No.
Regimen 1			
Initial	AZT/3TC/EFV	Dupont 006	39
2nd Line	AZT/3TC/IDV	Dupont 006	39
Salvage	2 generic NRTI + 1 generic PI + 1 generic NNRTI	GART	40
Regimen 2			
Initial	AZT/3TC/IDV	Dupont 006	39
2nd Line	2 generic NRTI + 1 generic PI + 1 generic NNRTI	GART	40
Salvage	2 generic NRTI + 1 generic NNRTI + 0.6 generic PI	GART	40
Regimen 3			
Initial	AZT/3TC/IDV	Johns Hopkins Clinical Cohort	41
2nd Line	2 generic NRTI + 1 generic PI + 1 generic NNRTI	GART	40
Salvage	2 generic NRTI + 1 generic NNRTI + 0.6 generic PI	GART	40
Regimen 4*			
Initial	AZT/DDI	INCAS	42
2nd Line	AZT/3TC	ACTG 320	43

*Although no longer recommended, 2-drug nucleoside analog therapy was the standard of care for a brief period prior to discovery of HAART (Hammer et al., 1996).

Abbreviations: AZT = zidovudine, a NRTI; 3TC = lamivudine, a NRTI; EFV = efavirenz, a NNRTI; IDV = indinavir, a PI; NRTI = Nucleoside reverse transcriptase inhibitor; PI = Protease inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; and DDI = didanosine, a NRTI.

cases the initial population was assumed to be 33 years of age and 80% male; these figures closely approximate national ADAP population statistics.[1,13–15]

Input Data

Clinical Data. The CEPAC model uses the Multicenter AIDS Cohort Study (MACS) dataset[44] to depict the natural history of HIV disease. Specifically, we used data from the MACS for the period from 1985 to 1994 to estimate the monthly decline in the CD4 cell count in the absence of antiretroviral therapy or OI prophylaxis and as a function of HIV RNA level, by means of a procedure previously described.[35] Efficacy data for antiretroviral therapies were derived from results of randomized trials and cohort studies undertaken in more representative patient populations,[6,39–43] and calibrated by a method described by Freedberg et al.[31]

Costs. We computed total lifetime direct medical costs, which include the costs of drugs, diagnosis and testing, and the costs of care across a variety of medical settings. Medication costs were based on wholesale prices from the 1999 Redbook,[12] and testing costs came from a hospital accounting system.[45] Other resource consumption data were derived from the AIDS Costs and Services Utilization Study, a national survey providing utilization and charge estimates for HIV-infected persons receiving health care services in 1991 to 1992.[46] A cost-to-charge ratio was derived from the AIDS Costs and Services Utilization Study to derive true economic costs.[35] Although data from the national HIV Costs and Services Utilization Study (HCSUS) would be more current, they are not yet publicly available. Moreover, recent studies by HCSUS investigators give us reason to believe that the cost estimates generated by the two datasets are similar. Specifically, a 1998 paper by Bozzette et al[47] used adjusted ACSUS costs to estimate prices of medical care services for patients in HCSUS with HIV/AIDS. The investigators assigned costs of $200 for outpatient visits, $338 for emergency department visits, and $1606 for hospital days. The same group published a paper in 2001, with cost information based exclusively on adjusted HCSUS data. The resulting

estimates were found by the authors to differ less than 6% from prior estimates: $178 for outpatient visits, $347 for emergency department visits, and $1657 for hospital days.[26] Although these findings are no guarantee of cost stability in opportunistic infections or other HIV-related events, they strongly suggest that cost differences of sufficient magnitude to change policy conclusions are unlikely. We have also considered a range of alternative cost structures in sensitivity analysis, and the policy conclusions do not change. Direct medical costs borne by ADAP were distinguished from total lifetime costs, by attributing medication costs for antiretroviral drugs and opportunistic infection prophylaxis to ADAP. Costs of care were derived by examining patients in the ACSUS dataset with or without OIs, as well as by CD4 stratum. Costs for CD4 strata without OIs were derived by summing total costs in each stratum using a random effects model, to calculate monthly costs. To capture the costs of diagnosis and treatment for OIs, we attributed charges to an infection if they occurred from 1 month before to 2 months after the diagnosis. Death costs were defined as all costs occurring in the month before death. Changes in medication costs were explored in sensitivity analyses. Productivity and patient time costs were not considered.

Heath Related Quality of Life Data. Data linking perceived health status to the model health states were obtained from the global health status question on the MOS-HIV questionnaire, a validated instrument presented to participants in AIDS Clinical Trials Group Protocols 019, 108, 154, and 204. Responses were transformed to approximate time-tradeoff utilities, using a method described elsewhere.[27,28,35,48] We also ran analyses unadjusted for health-related quality of life.

ADAP Formulary Data. ADAP formulary data were synthesized from annual reports of the National Association of State and Territorial AIDS Directors.[1,13,14] In addition, a semi-structured telephone interview was conducted at two points in time (June 1999 and April 2000) with officials from the 11 selected ADAPs (response rate 100%). The interview was designed to assess the impact of ADAP policies concerning waiting lists, gaps or restrictions in formulary coverage, financial and medical eligibility criteria, and spending caps on ADAP clients and the HIV-infected population in each state.

TABLE 3. Incremental Cost-Effectiveness Results for ADAP Formulary Strategies: "High Efficacy" Scenario*

ADAP Formulary Policy	Costs ($US)	Q-A Survival (y)	Incr. C/E ($/QALY)
AR97, OR97	77,800	5.30	—
NV97	80,100	5.61	dominated‡
SD97, SD98, SD99	80,100	5.61	dominated
MS97	80,200	5.61	7000§
AR98	80,200	5.61	dominated
GA97, NE98	119,400	7.08	dominated
FL97, OK97, OK98	122,100	7.38	dominated
MS98	122,100	7.38	dominated
OR98, MO97, MO98	122,100	7.38	dominated
TX97, TX98	122,100	7.37	dominated
NE97	122,800	7.38	dominated
GA98, GA99, NE99	145,500	9.23	dominated
OK99	148,800	9.55	17,000§
NV98, NV99	148,800	9.55	dominated
AR99	149,000	9.56	dominated
MS99, TX99	149,000	9.56	dominated
OR99, MO99, FL98, FL99	149,000	9.56	25,000§

*Incremental cost-effectiveness ratios (Incr. C/E) are in dollars per quality-adjusted (Q-A) life-year saved, or dollars per year of life saved ($/YLS), rounded to two significant digits. C/E ratios may not equal the ratio of costs to survival due to rounding.

‡Formulary policy eliminated due to dominance. A strategy is labelled "dominated" if it costs more and confers fewer benefits than some other strategy (or combination of strategies).

§Ratio is calculated relative to the next less costly alternative that has not already been eliminated by dominance. To calculate the CER, divide the difference in cost between the two policies by their difference in quality-adjusted survival.

Results

Reference Case Analyses

Different ADAP policies resulted in substantially different estimates of quality-adjusted survival, total lifetime direct medical costs, and overall cost-effectiveness. Results of the two extreme scenarios, "high efficacy" (based on the Dupont 006 initial cohort (CD4 350/μL), and Dupont 006 antiretroviral efficacy), and "low efficacy" (based

TABLE 4. Incremental Cost-Effectiveness Results for ADAP Formulary Strategies: "Low Efficacy" Scenario*

ADAP Formulary Policy	Costs ($US)	Q-A Survival (y)	Incr. C/E ($/QALY)
AR97, OR97	81,200	4.69	—
NV97	83,400	4.98	7000§
AR98	83,500	4.99	dominated‡
SD97, SD98, SD99	83,500	4.99	13,000§
MS97	83,600	4.99	dominated
GA97, GA98, GA99, NE98, NE99	109,700	5.70	dominated
NV98, NV99	112,500	6.00	dominated
MS99, NE97, TX99	112,500	6.00	dominated
AR99	112,500	6.01	dominated
MS98	112,600	6.01	dominated
FL97, OK97, OK98, OK99	112,600	6.02	28,000§
TX97, TX98	112,600	6.01	dominated
FL99	112,600	6.01	dominated
OR98, OR99, MO97, MO98, MO99, FL98	112,700	6.02	dominated

*Incremental cost-effectiveness ratios (Incr. C/E) are in dollars per quality-adjusted (Q-A) life-year saved, or dollars per year of life saved ($/YLS), rounded to two significant digits. C/E ratios may not equal the ratio of costs to survival due to rounding.

‡Formulary policy eliminated due to dominance. A strategy is labelled "dominated" if it costs more and confers fewer benefits than some other strategy (or combination of strategies).

§Ratio is calculated relative to the next less costly alternative that has not already been eliminated by dominance. To calculate the CER, divide the difference in cost between the two policies by their difference in quality-adjusted survival.

on the MACS initial cohort (CD4 250/μL), and Johns Hopkins antiretroviral efficacy) are presented.

Under the "high efficacy" scenario (Table 3), projected quality-adjusted life expectancy ranged from 5.30 to 9.56 years, total costs from $77,800 to $149,000, and cost-effectiveness from $7,000 to $25,000 per quality-adjusted life year (QALY) gained. Under the "low efficacy"scenario (Table 4), projected quality-adjusted life expectancy ranged from 4.69 to 6.02 years, total costs from $81,200 to $112,700, and cost-effectiveness from $7,000 to $28,000 per QALY gained.

Antiretroviral therapy constituted the most significant driver of costs and life-years gained (Table 5). We found that total lifetime costs increased with introduction of any HAART, reflecting both higher drug costs, and the increased time span during which therapy is administered. Because results were similar, only those for the high efficacy scenario are presented. Overall cost increases were reflected principally in higher medication costs, which ranged during a lifetime from $11,800 to $69,000. Projected inpatient care costs remained nearly constant, at $61,200 to $71,600. Consequently, for treatment strategies involving HAART and all appropriate OI prophylaxes, the share of total costs going to inpatient (48%) and outpatient (52%) components was similar. Annualized costs, however, showed an inverse relationship to expenditure on antiretroviral therapy.

Although access to HAART was the primary driver of increases in costs and survival, the opportunistic infection prophylaxis strategy played a key role in determining efficiency. In each scenario, three strategies were found to define the "efficient set." This is the set of strategies (or combination of strategies) that maximize the number of QALYs for any given cost (Tables 3 and 4). Moreover, no strategy without several agents for prophylaxis of *Pneumocystis carinii* pneumonia and some for prophylaxis of *Mycobacterium avium* complex was efficient. For example, Georgia ADAP, which offers HAART but as yet no OI coverage, was never part of the efficient set (Tables 3 and 4).

TABLE 5. Breakdown of Projected Costs Associated With Formulary Strategies: "High Efficacy" Scenario*′

ADAP Formulary Policy	Total Per Capita Costs ($US)	Total Per Capita ART‡ Costs	Total Per Capita OI§ Prophylaxis Costs	Total Per Capita Drug Costs¶	Total Per Capita Testing Costs	Total Per Capita Care Costs‖	% Drug and Testing Costs#	% Care Costs	Per Capita Annual ART Costs	Per Capita Annual Care Costs
AR97, OR97	77,850	11,830	0	11,830	4,790	61,230	21%	79%	1,970	10,220
NV97	80,100	12,000	1,450	13,450	5,070	61,580	23%	77%	1,890	9,690
SD97, SD98, SD99	80,140	12,000	1,490	13,490	5,080	61,580	23%	77%	1,890	9,680
MS97	80,150	12,000	1,480	13,490	5,080	61,580	23%	77%	1,890	9,680
AR98	80,220	12,000	1,530	13,530	5,080	61,620	23%	77%	1,890	9,680
GA97, NE98	119,350	46,960	0	46,960	6,300	66,090	45%	55%	5,950	8,380
FL97, OK97, OK98	122,070	47,740	1,290	49,020	6,580	66,470	46%	54%	5,800	8,070
MS98	122,110	47,680	1,310	48,990	6,580	66,540	46%	54%	5,790	8,080
OR98, MO97, MO98	122,120	47,710	1,380	49,090	6,580	66,450	46%	54%	5,790	8,070
TX97, TX98	122,130	47,700	1,320	49,020	6,570	66,540	46%	54%	5,800	8,090
NE97	122,750	47,700	1,960	49,660	6,580	66,500	46%	54%	5,790	8,070
GA98, GA99, NE99	145,520	66,400	0	66,400	8,040	71,080	51%	49%	6,520	6,980
OK99	148,780	67,870	1,060	68,930	8,330	71,520	52%	48%	6,440	6,780
NV98, NV99	148,810	67,890	1,060	68,940	8,330	71,540	52%	48%	6,440	6,780
AR99	148,960	67,900	1,120	69,020	8,330	71,620	52%	48%	6,430	6,780
MS99, TX99	149,010	67,920	1,090	69,010	8,330	71,670	52%	48%	6,430	6,790
OR99, MO99, FL98	149,040	67,920	1,150	69,070	8,340	71,640	52%	48%	6,430	6,780

*All costs are in US dollars.
‡ART = antiretroviral therapy.
§OI = opportunistic infection.
¶A proxy for ADAP expenditures.
‖Care costs (defined as total costs, minus the sum of drug and testing costs) are a proxy for inpatient costs.
#A proxy for outpatient costs.

Sensitivity Analyses

Cost-effectiveness results were most sensitive to changes in medication costs, somewhat sensitive to changes in the health of the starting cohort, and least sensitive to changes in quality-of life adjustment weights, discounting, and choice of comparator program.

Medication Costs

Pharmaceutical costs play a key role in shaping ADAP policy.[13,14] We assessed the likely impact of changes in the costs of antiretroviral and opportunistic infections medications, by halving and then doubling medication costs. When costs were halved, cost-effectiveness ratios decreased to $5,000/QALY to $18,000/QALY in the high efficacy scenario, and to $4,000/QALY to $18,000/QALY for the low efficacy scenario. When medication costs were doubled, the range was $13,000/QALY to $39,000/QALY in the high efficacy scenario to $13,000/QALY to $48,000/QALY for the low-efficacy scenario.

Health of the Starting Cohort

We explored the likely effect of a healthier ADAP clientele by examining the impact of a starting cohort with CD4 500 cells per μL. As compared with the original runs, the most comprehensive programs in the high efficacy scenario were more cost effective, at $18,000/QALY, whereas the most comprehensive programs in the low efficacy scenario were slightly less cost-effective, at $35,000/QALY.

Comparator Program

Reference case analyses compared programs incrementally to the most restrictive ADAP program, equivalent to availability of 2-drug nucleoside therapy. For purposes of comparison, we also ran the analyses compared with a no treatment strategy ("no drugs available"). Although this would not be the standard of care in the United States, it is in fact the standard in many parts of the world. Incremental results ranged from $10,000 to $27,000 per QALY in the high efficacy scenario, and from $12,000 to $28,000 per QALY in the low efficacy scenario. Implementation of only the most generous program as compared with the no treatment strategy yielded results of $15,000/QALY in the high efficacy scenario and $17,000/QALY in the low efficacy scenario.

Health-Related Quality of Life

To test the impact of the quality of life weights, we ran analyses unadjusted for health-related quality of life. Survival ranges widened slightly to 6.00 to 10.58 years in the high efficacy scenario, and 5.34 to 6.84 years in the low efficacy scenario. Unadjusted cost-effectiveness ratios decreased only slightly, with the most comprehensive programs estimated at $21,000/QALY and $27,000/QALY, for high and low efficacy scenarios respectively.

Discounting

As recommended by the Panel on Cost-effectiveness in Health and Medicine, we also ran undiscounted analyses.[34] Although the quantitative results changed slightly ($9000 to $25,000 per QALY in the high efficacy scenario and $9000 to $24,000 per QALY in the low efficacy scenario) the overall conclusions do not vary.

Discussion

We studied the economic and clinical impact of alternative ADAP policy choices concerning formulary coverage during fiscal years 1997 to 1999, as use of combination antiretroviral therapies became widespread. We found substantial variation among the 54 state and territorial AIDS Drug Assistance Programs in terms of projected life expectancy, quality-adjusted life expectancy, and costs. The most comprehensive ADAPs provided an estimated quality-adjusted life expectancy from 1.33 to 4.25 years longer than their most restrictive counterparts, depending on the modeling scenario. This gain in life expectancy was mainly a reflection of the survival benefit associated with highly active antiretroviral therapies. Along with improved survival, the most comprehensive programs incurred total costs from 39% to 91% higher, depending on the scenario chosen.

These cost findings are at variance with those of several observational studies, which report decreases in total HIV care costs, caused by reduced

inpatient hospital stays attributable to antiretroviral therapy.[21,23–25] This discrepancy is explained by the fact that all these observational studies used a short (less than 5-year) time horizon, whereas our analysis is based on estimation of direct medical costs during a lifetime. Our model concurs with the recent study by Bozzette et al[26] in projecting decreases in total annualized costs,[49] while suggesting that overall long-term costs will increase.

This analysis aims to lend a new perspective to the policy debate, by focusing not on costs, but on the ratio of the increase in lifetime costs to life expectancy. Cost-effectiveness ratios vary considerably across ADAP programs, with costs per quality-adjusted life year gained ranging from $7000 to $28,000. We found that most programs could improve the efficiency of current spending, principally by offering more prophylaxis drugs for opportunistic infections, especially agents for *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex. These results were consistent across analyses.

Our findings concerning cost-effectiveness are comparable to those of two recent studies of HAART in publicly funded health care systems. A UK study[50] comparing triple therapy to 2-drug nucleoside therapy found cost-effectiveness ratios in the range of £10,000–£14,400 per QALY ($14,600–$21,000, exchange rate 06/03/2001). Figures from our study comparing triple therapy to 2-drug nucleoside therapy range from $23,000/QALY to $28,000/QALY. A Swiss study estimated the value of HAART as compared with no drug therapy (considering only direct medical costs) at CHF 14,000 to 45,000 per QALY ($8,500–$27,000, exchange rate 06/03/2001).[51] Figures from our study comparing triple therapy to no drug therapy range from $16,000/QALY to $28,000/QALY. Thus, although we do not find either HAART[31] or ADAP programs to be cost-saving from a medical cost perspective, these studies jointly suggest that, at approximately $30,000 per QALY, even comprehensive ADAP programs offering the clinically recommended standard of care are cost-effective, by any reasonable comparison with other accepted medical interventions in high-income countries, such as the United States.[52]

This study has several limitations. First, although the model captures much of the complexity of HIV disease, it remains a simplification of a complicated disease process, and its results depend on the modeling assumptions and input data used. For example, the current clinical trial literature upon which our estimates of therapeutic efficacy are based does not fully capture the impact of important effects such as cross-resistance, long-term toxicities, or imperfect adherence to medication. Most published drug trials last for 1 or 2 years and are thus unable to assess how taking one drug may affect the outcome of other drugs several years in the future. We have attempted to capture these and other potential sources of bias in multiple sensitivity analyses on the efficacy of antiretroviral therapies, weights for quality-adjustment, the initial immune function of the cohort, discounting, the choice of appropriate comparator program, and medication costs. Although the quantitative estimates of costs, life expectancy, and quality-adjusted life expectancy were sensitive to assumptions concerning medication costs and cohort immune function, for the majority of parameters, relative program rankings and cost-effectiveness ratios remained robust. Second, our quality of life estimates were derived from patient responses to a question administered in four AIDS Clinical Trials Group Protocols, using a rating scale transformation to approximate a preference-based measure of health status.[31,35] It would be advantageous to incorporate newly available quality of life information for those with HIV/AIDS derived from general health status measures, such as the SF-36.[53] Members of our research group have done this using a recently developed technique to transform SF-36 data into approximations of utility measures, and found that inclusion of newer quality of life data results in virtually no change in the policy recommendations generated by our model.[54] Third, therapeutic nonadherence will reduce estimates of benefit, implying that estimates of HAART efficacy derived from randomized clinical trials may be unduly optimistic. However, our low efficacy scenario included an estimate of benefit from the Johns Hopkins clinical cohort, which includes the level of nonadherence seen in a population of relatively poor, urban clients closely resembling users of ADAP.[41] Fourth, in the past several years, newer therapeutic options and issues such as resistance, toxicity, and interruption of therapy have emerged. Although it was not possible to conduct this study on a dynamic basis, we modeled ADAPs at three junctures so as partially to capture these changes. Our results demonstrate that programs have evolved considerably over time, and indicate the importance of ongoing monitoring of these programs. Fifth, this analysis focuses on real world, actual ADAP pro-

grams rather than constructing hypothetical ADAP scenarios. Although this reflects our pragmatic approach to policy analysis, we recognize that future work could usefully tackle questions of program design and optimal resource allocation. Possible areas for future study include the cost-effectiveness of alternative formulary options and examination of different access criteria (eg, many drugs for fewer patients vs. fewer drugs for many patients).[49]

In interpreting the results, one limitation merits particular attention. We modeled only ADAP formularies, and abstracted from other potentially significant sources of program variation, such as financial access criteria[49] and waiting lists. For example, although Nebraska, Texas, and Georgia offer relatively comprehensive formularies, Nebraska and Texas have maintained waiting lists for protease inhibitors, and Georgia ADAP reported more than 800 persons waiting for entry at several junctures. Results for individual states should hence be viewed with caution. However, because restrictive access criteria and rationing measures generally accompany less comprehensive formularies, consideration of these factors would tend to exacerbate the likelihood of major differences between most and least comprehensive programs.

A motivation for this study was to inform public discussion of ADAP policies, by quantifying projected costs and disparities in health outcomes associated with unequal access. Our model suggests that restrictive ADAP programs incur lower medication costs and lower total costs for the system, but are associated with lower life expectancy. This is particularly worrisome, given that ADAP continues to serve a vulnerable population. At latest report, 80% of ADAP clients reported incomes below 200% of the Federal Poverty Level, and almost half had incomes below 100% of the Federal Poverty Level. More than 85% had no other public or private insurance, and many were members of traditionally underserved racial and ethnic populations.[13] Each of these characteristics has previously been linked to patterns of less adequate HIV/AIDS care.[20]

ADAP programs aim to reduce the multiple barriers facing this clientele concerning access to HIV/AIDS medications. The principal barrier is lack of (adequate) insurance, but access barriers caused by place of residence, or linguistic competence, are also addressed, albeit imperfectly. Although elimination of unequal access to medications for disadvantaged groups cannot be argued on exclusively economic grounds,[26,49] it is a matter of public concern. As recently shown, the rationing policies officially adopted by restrictive ADAPs do not reflect patient or public preferences.[19] In fact, interviews with ADAP officials suggest that programs themselves find informal ways around these difficult rationing choices. Although program officers from states with more generous ADAPs did not report use of external resources, those from ADAPs with formulary limitations, waiting lists and expenditure caps systematically aid clients to obtain necessary medications from other sources, particularly local charities and pharmaceutical company patient assistance programs. The latter have, in many places, replaced ADAP as the payer of last resort. Although this strategy moderates the extent of the health disparities produced by access limitations (and should attenuate the health disparities projected by our model), it is unlikely to eliminate them. Moreover, fragmentation of medication sources raises many informal barriers to access, and augments challenges for continuity of care, already problematic for these patients.[20]

ADAP programs offering the recommended standard of care are likely to increase life expectancy and constitute a cost-effective use of HIV care resources. Future work should consider these findings within a national policy context, taking into account other policy dimensions potentially affecting the quality of ADAP. These include financial eligibility requirements, level of state contribution to ADAP, and the impact of different state and federal financing mechanisms. We believe that such an informed policy discussion will support the view that a uniform national ADAP formulary, providing the recommended standard of care, is an appropriate and reasonable investment.

Acknowledgments

The authors thank Ariane Denis, Arnold Doyle, April Kimmel, and Mark Schlesinger, and the state ADAP directors and program officers who so generously provided information and assistance.

References

1. **Doyle A, Jefferys R, and Kelly J.** State AIDS Drug Assistance Programs: A National Status Report on Access. 1997. Henry J. Kaiser Family Foundation.

2. **Karon JM, Rosenberg PS, McQuillan G, et al.** Prevalence of HIV infection in the United States, 1984 to 1992. JAMA 1996;276:126–131.

3. **Holmberg SD.** The estimated prevalence and incidence of HIV in 96 large US metropolitan areas. Am J Public Health 1996;86:642–654.

4. **Centers for Disease Control and Prevention.** HIV/AIDS Surveillance Report. 8 (2), 1–39. Atlanta, GA: National Center for HIV, STD and TB Prevention; 1996.

5. **Centers for Disease Control and Prevention.** HIV/AIDS Surveillance Report. 11(2), 1–44. Atlanta, GA: National Center for HIV, STD and TB Prevention; 1999.

6. **Hammer SM, Katzenstein DA, Hughes MD, et al.** A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. N Engl J Med 1996;335:1081–1090.

7. **Detels R, Munoz A, McFarlane G, et al.** Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. JAMA 1998;280:1497–1503.

8. **Palella FJ, Jr., Delaney KM, Moorman AC, et al.** Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators N Engl J Med 1998;338:853–860.

9. **The Panel on Clinical Practices for Treatment of HIV.** Infection convened by the Department of Health and Human Services (DHHS) and the Henry J.Kaiser Family Foundation. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, The Living Document. Available at: http://hivinsite.ucsf.edu/medical/tx_guidelines/2098.3a62.html. Accessed 1/10/2001.

10. **Carpenter CC, Cooper DA, Fischl MA, et al.** Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel. JAMA 2000;283:381–390.

11. **Report to the Subcommittee on Labor, Health and Human Services and Education Committee on Appropriations US Senate.** HIV/AIDS Drugs: Funding Implications of New Combination Therapies for Federal and State Programs. GAO/HEHS-99–2, 1–36. 1998. Washington, DC, United States General Accounting Office.

12. **Drug Topics Red Book.** Medical economics data. Montvale, NJ: Medical Economics; 1999.

13. **Doyle A, Jefferys R.** National ADAP Monitoring Project: Annual Report, March 2000. Henry J. Kaiser Family Foundation.

14. **Doyle A, Jefferys R, Kelly J, et al.** National ADAP Monitoring Project: Annual Report, March 1999. Henry J. Kaiser Family Foundation.

15. **Doyle A, Jefferys R, Kelly J.** National ADAP Monitoring Project: Interim Technical Report, March 1998. Henry J. Kaiser Family Foundation.

16. **Pear, R.** Clinton to Seek More Money to Help Pay for AIDS Drugs. New York Times. December 30, 1997;A14.

17. **Pear R.** Expense means many can't get drugs for AIDS. New York Times. February 16, 1997;A1.

18. **McGinnis JM.** States move to ration promising AIDS drugs. The Wall Street Journal. August 22, 1996;B1.

19. **Green MJ, Fong S, Mauger DT, et al.** Rationing HIV medications: What do patients and the public think all allocation policies? J Acquir Immune Defic Syndr Hum Retrovirol 2001;26:56–62.

20. **Shapiro MF, Morton SC, McCaffrey DF, et al.** Variations in the care of HIV-infected adults in the United States: results from the HIV Cost and Services Utilization Study. JAMA 1999;281:2305–2315.

21. **Mole L, Ockrim K, Holodniy M.** Decreased medical expenditures for care of HIV-seropositive patients. The impact of highly active antiretroviral therapy at a US Veterans Affairs Medical Center. Pharmacoeconomics 1999;16:307–315.

22. **Moore RD.** Cost effectiveness of combination HIV therapy: 3 years later. Pharmacoeconomics 2000;17:325–330.

23. **Gebo KA, Chaisson RE, Folkemer JG, et al.** Costs of HIV medical care in the era of highly active antiretroviral therapy. AIDS 1999;13:963–969.

24. **Keiser P, Kvanli MB, Turner D, et al.** Protease inhibitor-based therapy is associated with decreased HIV-related health care costs in men treated at a Veterans Administration hospital. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:28–33.

25. **Floridia M, Massella M, Bucciardini R, et al.** Hospitalizations and costs of treatment for protease inhibitor-based regimens in patients with very advanced HIV-infection (CD4<50mm3). HIV Clinical Trials 2000;1:9–16.

26. **Bozzette SA, Joyce G, McCaffrey DF, et al.** Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy. N Engl J Med 2001;344:817–823.

27. **Scharfstein JA, Paltiel AD, Weinstein MC, et al.** The cost-effectiveness of prophylaxis for Mycobacterium avium complex in AIDS. Int J Technol Assess Health Care 1999;15:531–547.

28. **Paltiel AD, Scharfstein JA, Seage GR, III, et al.** A Monte Carlo simulation of advanced HIV disease: application to prevention of CMV infection. Med Dec Making 1998;18:S93–105.

29. **Paltiel AD, Goldie SJ, Losina E, et al.** A pre-evaluation of clinical trial data: The case of preemptive CMV Therapy in HIV. Clin Infect Dis 2001;32: 783-793

30. **Goldie SJ, Kaplan JE, Losina E.** Current Issues in Pneumocystis carinii pneumonia (PCP) prophylaxis in HIV: Using simulation modeling to inform clinical guidelines. Med Decis Making 1999.

31. **Freedberg KA, Losina E, Weinstein MC, et al.** The Cost Effectiveness of Combination Antiretroviral Therapy for HIV Disease. N Engl J Med 2001;344:824–831.

32. **Weinstein MC, Goldie SJ, Losina E, et al.** Use of Genotypic Resistance Testing To Guide HIV Therapy: Clinical Impact and Cost-Effectiveness. Ann Intern Med 2001;134:440–450.

33. **US Bureau of the Census.** Statistical Abstract of the United States: 1999. Washington, DC: US Bureau of the Census; 1999:119.

34. **Gold MR, Siegel JE, Russell LB, et al.** Cost-Effectiveness in Health and Medicine. 1st Ed. Oxford: Oxford University Press; 1996.

35. **Freedberg KA, Scharfstein JA, Seage GR, III, et al.** The cost-effectiveness of preventing AIDS-related opportunistic infections. JAMA 1998;279:130–136.

36. **USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with Human Immunodeficiency Virus.** USPHS/IDSA Prevention of Opportunistic Infections Working Group. Infectious Diseases Society of America Ann Intern Med 1999;131:873–908.

37. **USPHS/IDSA Prevention of Opportunistic Infections Working Group.** US Public Health Services/ Infectious Diseases Society of America. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. Clin Infect Dis 1997;25 Suppl 3:S313–1997;35:S313–S335.

38. **Gallant JE.** Strategies for long-term success in the treatment of HIV infection. JAMA 2000;283:1329–1334.

39. **Staszewski S, Morales-Ramirez J, Tashima KT, et al.** Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. N Engl J Med 1999;341:1865–1873.

40. **Baxter JD, Mayers DL, Wentworth DN, et al.** A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. AIDS 2000;14:F83–F93.

41. **Lucas GM, Chaisson RE, Moore RD.** Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann Intern Med 1999;131:81–87.

42. **Montaner JS, Reiss P, Cooper D, et al.** A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. JAMA 1998;279:930–937.

43. **Hammer SM, Squires KE, Hughes MD, et al.** A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med 1997;337:725–733.

44. **Multicenter AIDS Cohort Study (MACS) Public Data Set.** Release PO3. Springfield, VA, National Technical Information Survey, 1995.

45. **Boston Medical Center, Office of Payment.** Boston, MA. 2000.

46. **Berk ML, Maffeo C, and Schur CL.** Research design and analysis objectives. AIDS Costs and Services Utilization Survey (ACSUS) Report no.1. AHCPR Publication No. 93–0019. 1993. Rockville, MD, Agency for Health Care Policy and Research.

47. **Bozzette SA, Berry SH, Duan N, et al.** The care of HIV-infected adults in the United States. HIV Cost and Services Utilization Study Consortium. N Engl J Med 1998;339:1897–1904.

48. **Paltiel AD, Stinnett AA.** AIDS. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd Ed. New York, NY: Raven Press, 1996;1053–1062.

49. **Goldman DP, Bhattacharya J, Leibowitz AA, et al.** The impact of state policy on the costs of HIV infection. Med Care Res Rev 2001;58:31–53.

50. **Trueman P, Youle M, Sabin CA, et al.** The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom. HIV Clinical Trials 2000;1:27–35.

51. **Sendi PP, Bucher HC, Harr T, et al.** Cost effectiveness of highly active antiretroviral therapy in HIV-infected patients. Swiss HIV Cohort Study AIDS 1999;13:1115–1122.

52. **Tengs TO, Adams ME, Pliskin JS, et al.** Five-hundred life-saving interventions and their cost-effectiveness. Risk Anal 1995;15:369–390.

53. **Hays RD, Cunningham WE, Sherbourne CD, et al.** Health-related quality of life in patients with human immunodeficiency virus infection in the United States: results from the HIV Cost and Services Utilization Study. Am J Med 2000;108:714–722.

54. **Schackman BS, Goldie SJ, Freedberg KA, et al.** A comparison of health state utilities using community and patient preference weights derived from a survey of HIV/ AIDS patients. Med Decis Making 2001;In Press: