

Preevaluation of Clinical Trial Data: The Case of Preemptive Cytomegalovirus Therapy in Patients with Human Immunodeficiency Virus

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We developed a mathematical simulation model to anticipate outcomes from an upcoming trial of targeted, preemptive cytomegalovirus (CMV) therapy in high-risk, human immunodeficiency virus (HIV)-infected patients identified by means of CMV polymerase chain reaction screening. We estimated the costs and consequences of CMV prophylaxis in patients with CD4⁺ counts ≤ 100 cells/ μ L under various assumptions regarding disease progression, complication rates, drug effects, and costs. Without CMV preemptive therapy, lifetime costs average \$44,600 with expected duration of survival of 19.16 quality-adjusted life-months and 213 CMV cases per 1000 patients. Targeted preemptive therapy with orally administered valganciclovir increases costs and duration of survival to \$46,900 and 19.63 quality-adjusted life-months, respectively. CMV cases decrease to 174 per 1000 patients. The cost per quality-adjusted life-year gained is \$59,000. This result compares favorably with other strategies in end-stage HIV disease but hinges on valganciclovir cost and efficacy assumptions and the absence of minimally effective salvage antiretroviral therapy for HIV. The upcoming trial should resolve the clinical uncertainty surrounding some of these assumptions.

In the early years of the AIDS epidemic, infection with cytomegalovirus (CMV) was an important cause of morbidity and mortality in HIV infection. CMV affected >50% of patients in the latter stages of HIV illness and was detectable in as many as 90% of AIDS patients at autopsy [1–4]. Effective therapies were de-

veloped, including iv and orally administered ganciclovir, foscarnet, and more recently cidofovir [5]. Even among patients who received treatment, however, the disease often resulted in serious morbidity and reduced duration of survival [5, 6].

Despite the importance of CMV disease, primary prophylaxis has not generally been recommended as standard care. For example, the US Public Health Service and Infectious Diseases Society of America guidelines for prevention of opportunistic infections in HIV describe CMV prophylaxis as “optional, not generally recommended” [7]. This is largely because of mixed evidence regarding the efficacy of orally administered ganciclovir and valganciclovir in preventing the development of CMV disease [8–10]. Moreover, CMV prophylaxis is costly (the current wholesale price of ganciclovir is \$15,600 per patient per year) and is associated

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with serious side effects, including both neutropenia and anemia. Several independent cost-effectiveness analyses have shown that routine CMV prevention compares unfavorably with alternative HIV-related therapies and preventive measures [11–15].

With the advent of highly active antiretroviral therapy (HAART), the incidence of all opportunistic infections has declined markedly, and thus the clinical benefits of prophylaxis against CMV have been reduced even further. In some settings, effective immune reconstitution appears to have so diminished the risk of CMV that the disease has been virtually unseen in the past several years among HIV-infected patients [16–18]. The issue of CMV prophylaxis now focuses primarily on patients who have either tried and failed to respond to antiretroviral therapies (due to some combination of difficulties with adherence, development of drug resistance, and the lack of effective salvage regimens) or who are otherwise unwilling or unable to receive HAART [19].

Recent technologic advances have reopened the question of the appropriateness of CMV prevention in these patients. First, clinicians now have more potent drugs at their disposal. Notable among these is valganciclovir, an agent that offers markedly increased bioavailability compared with orally administered ganciclovir [20]. Ongoing clinical trials are exploring the efficacy and safety of valganciclovir, both as treatment for newly diagnosed CMV retinitis and as induction and maintenance therapy in previously treated CMV retinitis. Second, several studies have demonstrated a relationship between quantitative CMV DNA and patient predisposition to developing CMV disease [21–23]. Because PCR techniques can be employed to measure CMV virus load, it has been suggested that an effective prevention strategy might be to identify patients at elevated risk and to target preemptive therapy to this smaller, more appropriate population of recipients [13, 24–26]. These developments have prompted the national AIDS Clinical Trials Group (ACTG) to design a new trial, ACTG A5030, entitled “Valganciclovir preemptive therapy for cytomegalovirus viremia as detected by plasma CMV DNA PCR assay.” The goals of this 2.5-year, prospective, randomized, double-blind trial are to evaluate the safety and effectiveness of preemptive therapy in preventing CMV end-organ disease and to compare the course of CMV disease in high-risk patients with and without prophylaxis [27].

This article aims to inform the priority-setting process in HIV clinical trials. It is motivated by questions about how the information that results from the proposed CMV preemptive therapy trial might be used. The goal is to address the following questions: Given what is currently known about the diagnostic accuracy of the PCR technology and the likely prophylactic efficacy of valganciclovir, what are the plausible clinical and health economic outcomes of the trial? What magnitude of clinical benefit might warrant a change in current practice

guidelines? What incremental costs must planners anticipate if a decision is made to provide targeted CMV preemptive therapy to patients who have failed to respond to HAART? In short, can we establish—before the trial is completed—standards of evidence that might guide later patient-care decisions?

METHODS

Analytic overview. We have developed a mathematical simulation model of HIV disease [15]. We have used previous versions of the model to evaluate the prevention of opportunistic infections in HIV [15], to assess the cost-effectiveness of antiretroviral therapy [28], and to consider specific interventions against *Mycobacterium avium* complex (MAC) [29], CMV [11], disseminated fungal infections [30], and *Pneumocystis carinii* pneumonia (PCP) [31]. Using data from clinical trials, observational cohort studies, and national cost data sets, we estimate changes in HIV-infected patient survival, quality-of-life, and cost under a range of different assumptions.

We use this model in this analysis to emulate the patient population of the proposed ACTG A5030 valganciclovir study [27]. Specifically, we consider a hypothetical cohort of HIV-infected individuals with CD4⁺ counts ≤ 100 cells/ μ L. In keeping with the ACTG A5030 protocol, the baseline analysis assumes that patients are either receiving stable HAART but have a detectable HIV RNA measurement or are not likely to receive any antiretroviral therapies. All patients are assumed to receive prophylaxis for both PCP (trimethoprim-sulfamethoxazole, 80–400 mg once daily) and disseminated MAC (azithromycin, 1200 mg weekly) [7].

We estimate the cost-effectiveness of 3 different clinical strategies: (1) standard clinical care with no CMV prophylaxis or preemptive therapy; (2) CMV PCR to identify candidates for targeted preemptive therapy with valganciclovir; and (3) CMV prophylaxis for all patients. For the second strategy, we assume that a single CMV DNA PCR test is performed at entry to the study (i.e., when the patient's CD4⁺ count first drops to ≤ 100 cells/ μ L) and that patients with qualitatively positive results receive preemptive therapy. (This represents a small departure from the ACTG A5030 protocol, which proposes to measure subjects' CMV DNA every 8 weeks. The impact of this modeling simplification is examined in the Discussion section, below.) For both prophylaxis interventions (strategies 2 and 3), we assume 900 mg of valganciclovir to be administered orally twice daily for 3 weeks, then 900 mg once daily for 9 weeks, and 450 mg daily thereafter [27]. Finally, it is assumed that any study patients who develop clinically evident CMV will receive standard treatment, regardless of the prophylaxis strategy used.

In keeping with the recommendations of the United States Panel on Cost-Effectiveness in Health and Medicine, all clinical and economic outcomes are assessed from the societal per-

spective and discounted at an annual rate of 3% [32]. Monetary values are reported in 1998 US dollars, adjusted when necessary by the medical care component of the Consumer Price Index [33]. The comparative value of alternative strategies is measured in dollars per quality-adjusted life-year gained (QALY). Sensitivity analyses are performed to assess the following: the robustness of conclusions to uncertainty in the epidemiology of CMV virus load and infection; the efficacy, toxicity, and costs of CMV preemptive therapy quality of life; and elements of the natural history of HIV disease [32].

Simulation model. Specific details on the mechanics of the simulation model have been published elsewhere [11, 15, 28]. In brief, we employ a state-transition framework wherein the progress of disease in an individual hypothetical patient is characterized as a sequence of monthly transitions from one “health state” to another. The analysis is implemented as a Monte Carlo simulation, meaning that a random number generator and a set of estimated probabilities are used to determine the sequence of state-to-state clinical pathways a given patient will follow. Each patient’s clinical course is tracked individually from the time of entry into the model until death. A running tally is maintained of all acute clinical events, the length of time spent in each health state, and the cost and quality-of-life effects associated with a given health state. On the patient’s death, summary statistics (such as overall survival, quality-adjusted survival, total direct medical costs, and cause of death) are recorded, and a new patient enters the model. The process is then repeated until a total of 1 million patients in the hypothetical cohort has passed through the model, at which point overall performance measures such as average life expectancy, quality-adjusted life expectancy, and cost are computed. The model is programmed in C and is compiled in the Visual C++ programming environment (Microsoft). With a 733-MHz Intel Pentium III processor, simulations with cohort sizes of 1 million patients are completed in ~8 min.

The health states are chosen to be descriptive of the patient’s current health, relevant history, quality of life, and resource utilization patterns. They are also assumed to be predictive of clinical prognosis, including disease progression, immune system deterioration, development and relapse of different opportunistic infections, toxic reactions to medications, and mortality. The model defines 3 general categories of health state: chronic, acute, and death. Most of the time, patients reside in one of the chronic states, where progression of disease and immune system deterioration take place. The development of an acute complication triggers a temporary transition to one of the acute states, in which quality of life is typically lower and both resource consumption levels and mortality rates are higher. Deaths can occur from either a chronic or an acute state and can be attributed to a particular opportunistic infec-

tion, chronic AIDS (wasting, for example), or non-AIDS-related causes.

The chronic and acute health states are segmented along a number of dimensions, including the following: current and lowest CD4⁺ lymphocyte count (>500 cells/ μ L; 301–500 cells/ μ L; 201–300 cells/ μ L; 101–200 cells/ μ L; 51–100 cells/ μ L; and \leq 50 cells/ μ L); current and set-point HIV RNA level (>100,000 copies/mL; 30,001–100,000 copies/mL; 10,001–30,000 copies/mL; 3,001–10,000 copies/mL; 501–3,000 copies/mL; and \leq 500 copies/mL); acute episodes and history of acute complications (yes/no for each of CMV, PCP, MAC, toxoplasmosis, invasive fungal infections, and “other,” which includes lymphoma, tuberculosis, and Kaposi’s sarcoma, among others); and time (if any) since the initiation of HAART and any prophylaxis against opportunistic infections.

The progression of underlying HIV disease is characterized in this model by the interplay between HIV RNA and CD4⁺ lymphocyte counts. The model treats HIV RNA as the primary driver of immune system decline; moreover, it treats the degree of immune dysfunction (as measured by CD4⁺ count) as the primary driver of morbidity and mortality. On entry to the model, a patient is randomly assigned to one of several HIV RNA strata by use of the distribution specified by Mellors et al. [34]. This assigned HIV RNA level then determines the rate at which the patient’s CD4⁺ cell count will decline. At any time, however, it is the patient’s CD4⁺ count that is the primary determinant of predisposition to opportunistic infections and HIV-related death.

CMV virus load and PCR technology. The model distinguishes between CMV infection and CMV disease. Although most HIV-infected patients are infected with CMV, the risk of developing clinical CMV disease increases with rising levels of CMV DNA. Three recent studies provide data on the quantitative relationship between CMV virus load (as measured by CMV PCR analysis) and the corresponding risk of CMV disease [21–23] (table 1). Aggregating the results from these 3 studies, we estimate that ~33% of the patient population will receive a positive CMV PCR analysis result at the time of entry into the model. Using the cumulative 12-month incidence of CMV disease as the “gold standard,” we compute the increased annual risk faced by CMV PCR-positive individuals as the ratio of the predictive value positive (58%) to the cumulative incidence in the general HIV-infected population (21%). Therefore, we estimate that the 33% of patients who have a positive result of CMV-PCR analysis are roughly 2.8 times (58%/21%) more likely to develop CMV disease over the course of a year than would be suggested by the published annual baseline risk. The remaining 67% of the population have negative PCR results and face an annual risk that is only 0.14 times (3%/21%) the baseline risk.

The cumulative annual CMV incidence estimate obtained

Table 1. Source data and calculation of the characteristics of cytomegalovirus (CMV) PCR analysis.

Variable	Formula used	Study 1 [21]	Study 2 [22]	Study 3 [23]	Aggregate	ACTG [27]
Raw data, no. of patients						
Sample size	<i>a</i>	97	200	94	391	
Cumulative incidence of CMV infection	<i>b</i>	19	38	26	83	
PCR positive	<i>c</i>	27	63	40	130	
“True” PCR positives ¹	<i>d</i>	16	36	23	75	
“True” PCR negatives ²	<i>e</i>	67	135	51	253	
Computed values, %						
Cumulative incidence of CMV infection	<i>b/a</i>	20	19	28	21	
Sensitivity	<i>d/b</i>	84	95	88	90	63
Specificity	<i>e/(a - b)</i>	86	83	75	82	97
PCR positive rate	<i>c/a</i>	28	32	43	33	
PCR negative rate	<i>(a - c)/a</i>	72	69	57	67	
Predictive value	<i>d/c</i>	59	57	58	58	60
Predictive value	<i>e/(a - c)</i>	96	99	94	97	94

NOTE. ACTG, AIDS Clinical Trials Group.

¹ Patients who received a positive CMV-PCR result and who also developed CMV disease.

² Patients who received a negative CMV-PCR result and who did not develop CMV disease.

from the literature and used above is significantly higher than the incidence figure assumed in the ACTG A5030 protocol [27]. The ACTG A5030 values (table 1) imply a population-wide, cumulative incidence of CMV in the range 11%–14%. Although our baseline estimate will tend to portray CMV preemptive therapy in a more favorable light, we explore the effects of the use of the less optimistic ACTG figures in the sensitivity analysis on monthly acute CMV incidence, described in the Results section, below.

Initialization. The simulation model is used to construct an incoming patient population that fits the inclusion criteria of the ACTG A5030 protocol. To accomplish this, an initialization phase is performed for patients whose basic characteristics are drawn from the published ACTG Protocol 320 [35]. Eighty-three percent of the patients who enter the initialization phase are assumed to be men, with an average age of 39 years (SD, 9 years). The incoming HIV RNA distribution, which is based on a mean log HIV RNA of 5.0 (SD, 0.6), is as follows: 47.1% >100,000 copies/mL; 31.0% 30,001–100,000 copies/mL; 17.2% 10,001–30,000 copies/mL; 4.1% 3001–10,000 copies/mL; 0.5% 501–3000 copies/mL; and 0.1% ≤500 copies/mL. All patients included in the initialization phase are assumed to receive 3-drug HAART, consisting of zidovudine, lamivudine, and indinavir, commencing when their CD4⁺ count first falls below 87 cells/μL. Patients who fail to respond to this regimen receive a subsequent regimen as well. Only those patients who fail to respond to HAART (both initial and subsequent regimens) and survive to CD4⁺ ≤100 cells/μL without a primary diagnosis of

CMV infection are retained for inclusion in the main analysis. By use of this approach, we estimate that patients who enter the main analysis have the following opportunistic infection histories: 6.6% PCP; 3.3% MAC; 1.0% toxoplasmosis; and 5.6% disseminated fungal infection.

Input data. Parameter estimates for the analysis were obtained from a variety of cohort studies, randomized clinical trials, and national resource utilization surveys. Baseline values, sources, and the methods used to produce input data in a format that could be used by the model have been presented and described elsewhere [11, 15, 28]. A summary of key data elements, ranges for sensitivity analysis, and sources is shown in table 2.

Data on the natural history of HIV infection without HAART are derived from the Multicenter AIDS Cohort Study, a prospective surveillance study of 2076 HIV-infected men followed from 1984 to 1990 in 4 cities in the United States [36, 39, 40]. Monthly probabilities of a decline in the CD4⁺ cell count, the incidence of primary acute opportunistic infection, secondary relapse, acute infection survival, and chronic mortality rate are computed from the Multicenter AIDS Cohort Study data set using an incidence density analysis [41]. Missing CD4⁺ counts at the time of death or infection are imputed using a random effects model [42].

The efficacy of preemptive therapy is modeled as a percentage reduction in the monthly rate of acute CMV disease episodes. We assume that the percentage reduction applies across all patients, regardless of their assigned risk categories. We use 49%

Table 2. Selected model variables: base case values, ranges for sensitivity analysis, and data sources.

Variable	Base case (range)	Source(s)
Acute CMV disease		
Monthly incidence, CD4 ⁺ 51–100 cells/ μ L, % of patients	0.52	[36]
Monthly incidence, CD4 ⁺ \leq 50 cells/ μ L, % of patients	1.86	[36]
Annual multiplier for PCR-positive patients	2.8 (2.0–4.3)	[21–23]
Annual multiplier for PCR-negative patients	0.14 (0–0.5)	[21–23]
CMV prophylaxis		
Monthly cost, US\$	720 (360–1440)	[37]
Efficacy, %	49 (0–100)	[8, 10]
Minor toxicity, %	0.89 (0–3.56)	[10]
Mean cost (range), US\$		
CMV infection (initial diagnosis)	16,280 (8000–32,000)	[38]
CMV infection (ongoing) ^a	2370 (1690–2870)	[38]
Prophylaxis minor toxicity	14,600	[10, 37]
PCR test	200 (50–200)	[13]

NOTE. CMV, cytomegalovirus.

^a Monthly costs incurred during the first 3 months following a diagnosis of CMV infection.

as the baseline efficacy estimate, reflecting the impact of orally administered ganciclovir as observed in the first published prophylaxis trial conducted by Spector and colleagues in the Roche Cooperative Oral Ganciclovir Study Group [10]. Because this figure is so different from the 0% efficacy result obtained in another widely reported trial of orally administered ganciclovir by Brosgart et al. [8], we explore values ranging from 0% to 100% in sensitivity analysis.

The criteria of the AIDS Clinical Trials Group are used to define rates of drug toxicity [43]. Analysis of data from the Roche Cooperative trial suggests that 2% of patients experience toxic reactions (mostly minor) to orally administered ganciclovir in any given month. Because dosages in the proposed ACTG A5030 are roughly half of those in the Roche trial, we assume a baseline minor toxicity rate of just under 1%. This may be an overly favorable assumption, however, because it is also true that the predicted plasma levels are much higher in patients receiving valganciclovir therapy. In the sensitivity analysis described in the Results section, below, we consider the possibility that there is no toxicity difference between valganciclovir and ganciclovir administered orally.

The average additional charge for a minor reaction is estimated to be \$14,600, a figure that includes 47 days of treatment with granulocyte colony-stimulating factor (G-CSF), 26 days of erythropoietin therapy, and the cost of related clinical and laboratory evaluations [10, 37]. In addition, we assume a 20% temporary decline in quality of life during the month in which a minor toxic reaction occurs, but we explore the impact of greater decrements in sensitivity analysis. Although any major hematological side effects in the Roche cooperative ganciclovir trial were dealt with by adding G-CSF and erythropoietin [10],

the model is capable of reflecting toxic reactions that result in the discontinuation of prophylaxis. For purposes of sensitivity analysis, therefore, we also consider the case where toxicity is dealt with by discontinuing valganciclovir and accepting the increased risk of CMV disease.

Adherence to prophylaxis and development of CMV resistance are both assumed to be comparable to that which might be observed in the clinical trial setting. Thus, the impacts of both imperfect patient adherence and increasing CMV viral resistance are implicit in the efficacy estimates used in this analysis. To examine the impact of increasing CMV viral resistance, we perform sensitivity analyses on the costs of acute CMV infection and the costs of CMV care after the acute phase.

Resource consumption data are drawn primarily from the AIDS Cost and Services Utilization Survey (ACSUS) [38, 44, 45]. This was a national survey of charges, derived from provider billing data and medical chart abstracts, for 1949 HIV-infected people in 10 US cities during the period 1991–1992. Because ACSUS does not provide any hospital-specific or geographic information on which to base a conversion to economic opportunity costs [46], we have estimated a cost-to-charge ratio of 0.6 that can be applied to all charges in the ACSUS data set. The derivation of this value is described elsewhere [15]. CD4⁺ lymphocyte and HIV RNA testing costs are obtained from the Boston University Medical Center cost accounting system. Costs for orally administered ganciclovir, antiretroviral therapy, PCP and MAC prophylaxis, and drugs intended to treat toxic reactions are based on published average wholesale prices [37]. The cost of the PCR test is assumed to be \$200 on the basis of data from Rose and Sacks [13]. PCR screening costs as low as \$50 per test are examined in the sensitivity analysis.

Table 3. Baseline results for clinical effectiveness and cost-effectiveness of preemptive cytomegalovirus (CMV) therapy.

Strategy	Quality-adjusted survival, mo	Cost, US\$		Cumulative incidence of primary CMV infection, %
		Total, average	Per QALY ^a	
No CMV prophylaxis	19.16	44,600	—	21.3
Targeted preemptive therapy	19.63	46,900	59,000	17.4
General CMV prophylaxis	19.77	55,600	793,000	16.2

NOTE. QALY, quality-adjusted life-year.

^a The difference in cost divided by the difference in quality-adjusted life expectancy for each strategy compared with the next most expensive strategy. This figure is expressed in dollars per QALY gained, rounded to the nearest \$100.

To date, published studies of patient quality of life in HIV clinical trials have not considered a sufficiently rich set of symptomatic health states to be suitable for use in this model [47, 48]. We explore the possible effects of quality-of-life considerations with an approximation to a preference-based measure of health status using data from the first question of the Medical Outcomes Study HIV Health Survey (MOS-HIV), a 30-item instrument that was administered to patients enrolled in AIDS Clinical Trials Group protocols 019, 108, 154, and 204 [49]. Although this utility estimation procedure has been described in several previous studies [11, 15, 29], we have subjected the quality-of-life assumptions to sensitivity analysis, as described in the Results section, below.

RESULTS

For patients who enter the model with CD4⁺ counts ≤ 100 cells/ μ L, receiving stable HAART with detectable HIV RNA (or no HAART), and receiving no CMV prophylaxis, discounted quality-adjusted life expectancy is 19.16 months, with total lifetime costs of \$44,600 per person (table 3). The model predicts that 21.3% of all patients will experience a primary symptomatic episode of CMV disease during their lifetime. A strategy of targeted CMV preemptive therapy to patients with positive CMV PCR results increases per-person costs to \$46,900 and confers a total of 19.63 quality-adjusted life-months, suggesting an incremental cost per QALY gained of \$59,000 compared with standard care. A strategy of universal prophylaxis for all patients further increases both quality-adjusted survival (to 19.77 quality-adjusted life-months) and costs (to \$55,600) at an incremental cost per QALY gained of \$793,000 compared with targeted preemptive therapy. Increasingly aggressive strategies are associated with reduced rates of primary CMV infection.

Sensitivity analysis. The results presented above represent best estimates of the clinical impact, cost, and cost-effectiveness of CMV preemptive therapy, largely on the basis of clinical data taken from the Roche Cooperative trial [10]. To explore the uncertainty in these estimates, we have conducted univariate sensitivity analysis (wherein a single parameter is varied over the range of plausible values that it might assume) on each of

the variables and data ranges listed in table 2. Figure 1 reveals that the cost-effectiveness result is robust in the face of changes in most of the uncertain variables, including rates of valganciclovir toxicity, the monthly risk of CMV, the cost of the CMV PCR test, and the cost of chronic care after an acute episode of CMV disease. The cost-effectiveness result is most sensitive to 2 critical parameters: the efficacy and the cost of valganciclovir.

We further examined the interaction of these 2 variables by performing a 2-way sensitivity analysis in which both parameters were simultaneously varied over their plausible ranges. Drug efficacy was varied from 0% (i.e., a drug that prevents no CMV disease) to 100% (i.e., a drug that prevents all CMV disease); the monthly cost of prophylaxis ranged from \$360 (half the baseline value of \$720) to \$1440. The results are depicted in figure 2. Higher monthly drug costs and lower drug efficacy were both associated with less favorable (i.e., higher) cost-effectiveness ratios. For example, at the baseline assumption of 49% efficacy, drug prices exceeding roughly \$1000 were associated with an incremental cost per QALY gained in excess of \$100,000. Similarly, at the baseline monthly price assumption of \$720, any drug efficacy $< 30\%$ exceeded \$100,000 per QALY gained.

The cost-effectiveness curves in figure 2 indicate that improvements in drug efficacy are associated with rapidly diminishing marginal returns. This means that incremental improvements in drug efficacy confer smaller and smaller benefits. The diminishing importance of efficacy can be explained by the substantial competing risks faced by patients with late-stage HIV infection [17]. Even complete prevention of CMV disease with a hypothetical, perfect drug only produces a 1.5-month improvement in overall quality-adjusted life expectancy in patients for whom effective HAART is not an option. In contrast, there is a near-linear relationship between drug costs and overall cost-effectiveness, as evidenced by the roughly constant distance between the 3 lines. Drug prices move in lockstep with cost-effectiveness because the drug itself is the primary source of cost for CMV preemptive therapy.

Scenarios. To explore further the range of likely outcomes for this analysis, we constructed plausible best- and worst-case

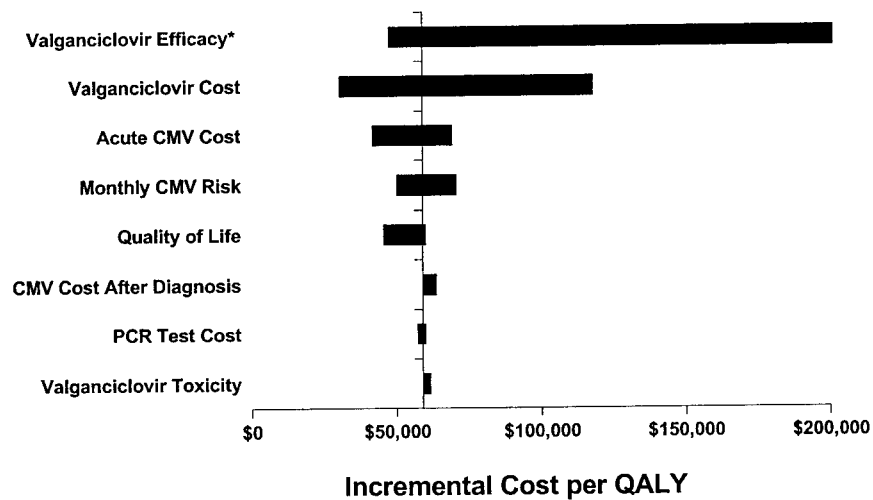


Figure 1. Incremental cost-effectiveness and summary of univariate sensitivity analyses for preemptive cytomegalovirus (CMV) therapy. Each horizontal bar represents a given model parameter. The vertical axis denotes the base case incremental cost-effectiveness estimate. Therefore, the length and position of a given bar denote the range of plausible cost-effectiveness outcomes produced by varying that specific parameter. *The bar denoting valganciclovir efficacy extends to infinity but has been truncated at \$200,000. QALY, quality-adjusted life-year.

scenarios. In the best-case scenario, we improved the drug efficacy assumption from the base case level of 49% to 80%. We further supposed that all other parameters listed in table 2 would assume values that biased the results in favor of targeted preemptive therapy. Under these conditions, targeted preemptive therapy increases quality-adjusted life expectancy from 19.16 to 20.16 months and confers a small (\$400) cost saving. To define a worst-case scenario, we assigned 0% efficacy to valganciclovir prophylaxis on the basis of data from Brosgart et al. [8] on the efficacy of ganciclovir prophylaxis. Increasing total costs and drug-related toxicities without conferring any clinical benefit led to an infinite cost-effectiveness ratio. A somewhat less pessimistic worst-case scenario was constructed with a baseline drug efficacy of 49% and setting all other model parameters in table 1 to their least favorable values. Under these assumptions, an incremental cost per QALY gained of roughly \$131,000 was obtained.

We performed one final scenario analysis to assess the impact of the quality-of-life assumptions. Once again, our aim was to portray preemptive CMV therapy in the most favorable light possible, from a quality-of-life point of view. To that end, we considered the hypothetical case where all patients who have not had clinical CMV disease are assigned a quality of life equivalent to perfect health (i.e., the quality adjustment value assigned to all states prior to the onset of CMV disease is 1.0), and all patients who have a history of CMV disease are assigned a quality of life value 0.0 (i.e., the development of CMV disease is considered equivalent to death). We further assumed that there would be no temporary loss of quality of life as a result of valganciclovir toxicity. Under this extreme scenario, the incremental cost-effectiveness ratio for preemptive CMV therapy improved, but only

to \$38,000. This result is also depicted in figure 1. From the point of view of cost-effectiveness, this suggests that the baseline quality of life assumptions are not introducing serious bias into the results.

A “what-if” comparison of CMV preemptive therapy to salvage antiretroviral therapy. Entry criteria of the ACTG A5030 study require that patients be receiving stable HAART and have detectable HIV RNA, or that patients be unlikely to receive HAART during the course of the study. With the expansion of the number of effective antiretroviral therapies, such patients may in the future have options for salvage antiretroviral therapy [50]. To place our results in perspective, therefore, we performed an analysis to compare preemptive CMV therapy with antiretroviral therapy. Specifically, we considered 3 hypothetical programs of late salvage antiretroviral therapy. The first, most optimistic intervention was intended to emulate the overall efficacy level reported in the 3-drug arm of the ACTG protocol 320 trial [35]. Therefore, we assumed that 60% of patients would achieve virological suppression (≤ 500 copies/mL) at 24 weeks, producing a CD4⁺ count increase of 120 cells/ μ L in the next 10 months. Under this scenario, we assumed a monthly per-patient drug cost of \$1080, representing the average wholesale costs of 2 nucleoside analogues and 1 protease inhibitor [37]. We found that salvage therapy produces a gain of roughly 16.4 quality-adjusted life-months and costs an additional \$23,500 compared with standard clinical care and no CMV prophylaxis. This implies an incremental cost-effectiveness ratio of \$17,200 per QALY gained, suggesting that salvage antiretroviral therapy would “dominate” (i.e., it would cost less and confer greater benefit than) CMV preemptive therapy.

A second, much less optimistic scenario assumed that salvage

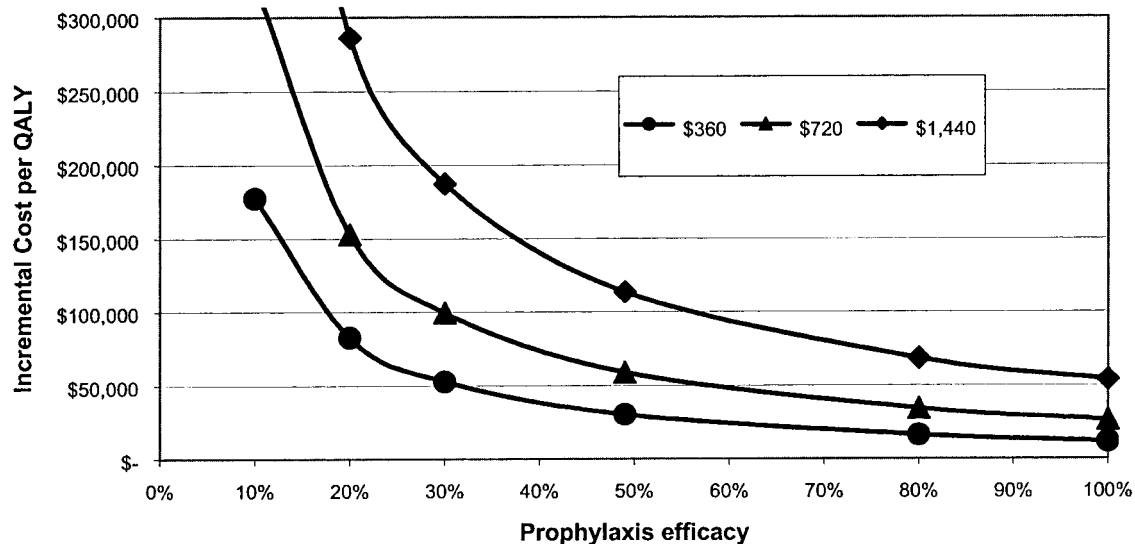


Figure 2. Incremental cost-effectiveness and sensitivity to drug cost and efficacy for preemptive cytomegalovirus therapy. Each line in the figure represents the sensitivity of the incremental cost-effectiveness result to changes in the assumed efficacy of valganciclovir. The lowest line represents a drug price of \$360. The middle and upper lines in the figure denote drug prices of \$720 (the baseline assumption) and \$1440, respectively. QALY, quality-adjusted life-year.

therapy achieves virological suppression (≤ 500 copies/mL at 24 weeks) in as few as 5% of patients and produces a $CD4^+$ count increase of as little as 30 cells/ μL in 10 months. Again assuming a monthly per-patient drug cost of \$1080, we found that salvage therapy confers 1.59 additional quality-adjusted life-months at an additional cost of \$5000. This implies an incremental cost-effectiveness ratio of \$37,500 per QALY gained, again suggesting that even a marginally effective salvage antiretroviral therapy would dominate CMV preemptive therapy.

To make the salvage intervention even less attractive, we increased its cost to \$2420 per patient per month (reflecting the average wholesale costs of a 7-drug regimen that includes 3 nucleoside analogues, 2 protease inhibitors, and 2 nonnucleosides [37]). This changed the magnitude of the effect but not the basic insight: the late salvage therapy strategy no longer achieves both a cost savings and a positive health benefit, but it remains a competitive alternative, delivering additional QALYs at an incremental cost of \$90,700 per QALY gained, relative to targeted preemptive therapy.

DISCUSSION

With the widespread availability of effective HAART and the decreased incidence of opportunistic infections, the issue of prophylaxis for CMV infection focuses primarily on patients who have either tried and failed to respond to antiretroviral therapies or who are either unable or unwilling to receive HAART. Yet despite the availability of new technologies to iden-

tify patients at greatest risk for overt CMV disease, the clinical benefits, costs, and cost-effectiveness of CMV prophylaxis remain uncertain. Our objective was to explore the range of plausible outcomes from an upcoming trial of targeted CMV preemptive therapy and to present decision makers, before the results of the trial are even known, with the question of what they would do with the data if they had it and what outcomes from the trial might lead to changes in existing practice guidelines [7].

To capture the essential features of the CMV preemptive therapy decision, we have introduced many simplifying assumptions and limitations to this analysis. We have assumed, for example, that a state-transition framework adequately captures the complex dynamics of HIV natural history. Although the model incorporates PCP, toxoplasmosis, MAC, CMV, and fungal infections as distinct opportunistic infections, other important AIDS-related complications (such as bacterial infections and tuberculosis) are not explicitly considered. We have assumed that a single parameter captures the full impact and efficacy of CMV prophylaxis with valganciclovir. Finally, we have assembled input data from a variety of clinical trials, observational cohorts, and other sources, each of which was developed subject to its own size, quality, and design limitations.

Despite these shortcomings, our findings are consistent with observed life expectancies in patients with $CD4^+$ counts ≤ 100 cells/ μL who do not receive effective antiretroviral therapy [51]. Moreover, they agree in most qualitative respects with results obtained by a previous economic assessment of targeted CMV preemptive therapy by Rose and Sacks [13]. The previous anal-

ysis produced less favorable results that we believe are attributable to modeling assumptions that greatly reduced baseline life expectancies. Specifically, Rose and Sacks assumed that all untreated PCR-positive patients would certainly develop CMV disease, an assumption that may have somewhat overstated baseline mortality rates, both with or without prophylaxis.

Our analysis departs from the proposed ACTG A5030 protocol with respect to the frequency of PCR testing for CMV. Where the ACTG study proposes to measure subjects' CMV DNA using PCR testing every 8 weeks, our analysis assumes that a single PCR test for CMV is performed at the moment of entry into the model and that this single test provides all the diagnostic benefit that repeat testing would typically confer. This assumption portrays the preemptive therapy strategy in a favorable light. First, it front-loads all the benefit of PCR screening for CMV, thus wiping out any of the rapidly diminishing marginal returns that are commonly observed in situations of repeat testing [52]. Second, it understates the costs of the CMV PCR testing program, though the magnitude of any bias here in favor of the preemptive CMV therapy intervention is small; even a 300% rise in the assumed price of the CMV PCR test has little impact on the cost-effectiveness result (figure 1). Our analysis also differs from the ACTG A5030 protocol by assuming a higher incidence of CMV disease in the patient population. However, as the sensitivity analysis in figure 1 demonstrates, this does not have a material impact on the policy conclusions we have drawn. Indeed, use of the lower estimate of the incidence of CMV infection provided in the ACTG A5030 protocol produces a less favorable cost-effectiveness result.

We find that in patients with CD4⁺ counts ≤ 100 cells/ μ L who have either tried and failed to respond to antiretroviral therapies or who are unable to receive HAART, preemptive CMV therapy costs \$59,000 per QALY gained, compared with a strategy that does not include any CMV prophylaxis. To put this result in some perspective, cost-per-QALY threshold levels in the range of \$20,000–\$100,000 are commonly reported for clinical interventions in HIV [15, 28, 29, 52–54]. Thus targeted CMV preemptive therapy may prove a reasonable use of scarce HIV clinical care resources in this patient population. However, this conclusion hinges critically on 3 important unknowns: the efficacy of valganciclovir prophylaxis; the market price of valganciclovir; and the absence of minimally effective salvage antiretroviral therapy. With regard to product pricing, it is not known what the manufacturer will charge for the drug, and this question will not be resolved by ACTG A5030. The same may be said about the question of salvage antiretroviral therapy. The future availability of effective, late-stage antiretroviral regimens remains uncertain [50]. The first source of major uncertainty—the efficacy of prophylaxis—will be addressed by ACTG A5030. If, however, the trial concludes that efficacy is in the range observed in previous CMV prophylaxis trials

(0%–49%), then the cost-effectiveness of preemptive CMV therapy is unlikely to compare favorably with that of other widely used and available HIV patient-care interventions [15, 28]. Only a combination of both favorable efficacy results and price reductions, as outlined in figure 2, will make this intervention attractive from the perspective of cost-effectiveness.

There are many points of view from which to consider the question of preemptive CMV therapy. This analysis suggests that for clinical decision makers who must prioritize among HIV patient-care alternatives [7], some of the major uncertainties that surround the use of CMV prophylaxis will not be resolved by the upcoming ACTG A5030 trial. However, for patients with advanced HIV disease and their providers, a trial to examine the efficacy of a program of targeted preemptive CMV therapy may provide important clinical and therapeutic information.

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