ORIGINAL INVESTIGATION

Prophylaxis for Human Immunodeficiency Virus–Related *Pneumocystis carinii* Pneumonia

Using Simulation Modeling to Inform Clinical Guidelines

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Background: Human immunodeficiency virus (HIV)-infected patients receiving highly active antiretroviral therapy (HAART) have experienced a dramatic decrease in *Pneumocystis carinii* pneumonia (PCP), necessitating reassessment of clinical guidelines for prophylaxis.

Methods: A simulation model of HIV infection was used to estimate the lifetime costs and quality-adjusted life expectancy (QALE) for alternative CD4 cell count criteria for stopping primary PCP prophylaxis in patients with CD4 cell count increases receiving HAART and alternative agents for second-line PCP prophylaxis in those intolerant of trimethoprim-sulfamethoxazole (TMP/SMX). The target population was a cohort of HIV-infected patients in the United States with initial CD4 cell counts of 350/µL who began PCP prophylaxis after their first measured CD4 lymphocyte count less than 200/µL. Data were from randomized controlled trials and other published literature.

Results: For patients with CD4 cell count increases during HAART, waiting to stop prophylaxis until the first observed CD4 cell count was greater than 300/µL prevented 9 additional cases per 1000 patients and cost $9400 per quality-adjusted life year (QALY) gained compared with stopping prophylaxis at 200/µL. For patients intolerant of TMP/SMX, using dapsone increased QALE by 2.7 months and cost $4500 per QALY compared with no prophylaxis. Using atovaquone rather than dapsone provided only 3 days of additional QALE and cost more than $1.5 million per QALY.

Conclusions: Delaying discontinuation of PCP prophylaxis until the first observed CD4 cell count greater than 300/µL is cost-effective and provides an explicit "PCP prophylaxis stopping criterion." In TMP/SMX-intolerant patients, dapsone is more cost-effective than atovaquone.

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PNEUMOCYSTIS CARINII pneumonia (PCP) is the most common serious opportunistic infection among patients infected with human immunodeficiency virus (HIV) in the United States.[1-3] Initiating PCP prophylaxis at a CD4 cell count less than 200/µL has been the standard of care for the past decade.[4,5] In the past few years, however, there has been a dramatic reduction in the rates of opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy (HAART), prompting reassessment of the role of prophylaxis.[6-24] Several recent publications[25-28] suggest a convergence of opinion in favor of discontinuing PCP prophylaxis in patients whose CD4 cell counts have increased to greater than 200/µL with HAART.

In conjunction with cost-effectiveness analysis, simulation modeling has become an increasingly important tool for assisting in developing health policy.[29,30] Complementing the information from clinical trials with such modeling is particularly useful for HIV because clinical trials rely on intermediate surrogate markers of outcome (eg, CD4 cell counts and HIV RNA levels), cannot evaluate all the possible alternatives that should be considered, and cannot address all key policy questions before decision making. With respect to primary PCP prophylaxis, the following were among the important questions facing the 1999 US Public Health Service–Infectious Disease Society of America Prevention of Opportunistic Infections Working Group[5]: Is it appropriate to discontinue prophylaxis in patients with CD4 increases while receiving HAART, and, if so, at what CD4 cell count? Should the recommended agents for second-line PCP prophylaxis be changed given new data on the efficacy of those agents? Since publication of these guidelines,[5] new data have become available. We used a comprehensive mathematical model of HIV to inform the development of future editions of the US Public Health Service–Infectious Disease Society of America clinical guidelines. We assessed the cost-

MATERIALS AND METHODS

ANALYTIC OVERVIEW

A computer-based simulation model of HIV infection was used to incorporate changes in HIV RNA levels and CD4 cell counts with disease progression, risk of opportunistic infections, and the effectiveness of opportunistic infection prophylaxis and HAART.[29,31] A Monte Carlo simulation was conducted to compare alternative CD4 cell count criteria for stopping primary PCP prophylaxis with CD4 cell count increases to greater than 200/μL with HAART and alternative agents (eg, dapsone, atovaquone, and aerosolized pentamidine) for second-line prophylaxis in TMP/SMX-intolerant patients. The target population in both analyses was a cohort of HIV-infected patients in the United States with initial CD4 cell counts of 350/μL who were given PCP prophylaxis after their first measured CD4 lymphocyte count less than 200/μL. Model outcomes included total cases of PCP, lifetime costs, life expectancy, and quality-adjusted life expectancy. Comparative performance of alternative strategies was measured by using the incremental cost-effectiveness ratio, defined as the additional cost of a specific strategy divided by its additional clinical benefit compared with the next less expensive strategy. A societal perspective was adopted, although time costs were not included. Future costs and quality-adjusted life years (QALYs) were discounted at an annual rate of 3%.[29]

SIMULATION MODEL

Progression of HIV disease was modeled as a sequence of monthly transitions between health states, defined by a patient's current and maximum HIV RNA levels, CD4 cell counts, time receiving HAART, and history of previous effective and ineffective antiretroviral treatment and previous opportunistic infections. Health states were divided into 6 CD4 strata (>500/μL, 301-500/μL, 201-300/μL, 101-200/μL, 51-100/μL, and 0-50/μL) and 6 HIV RNA strata (>100 000, 30 001-100 000, 10 001-30 000, 3001-10 000, 501-3000, and ≤500 copies/mL). *Pneumocystis carinii* pneumonia was specified as one of several possible opportunistic infections, which also included toxoplasmosis, cytomegalovirus, *Mycobacterium avium* complex, fungal infections, and other complications of acquired immunodeficiency syndrome (AIDS). The prognosis for an individual patient depended on previous opportunistic infections, HIV RNA levels, and CD4 cell counts. Patients could die of an acute clinical event, chronic AIDS (eg, wasting), or non–HIV-related causes. Further description of the model is given in recent publications.[32-34]

A hypothetical cohort of 1 million individuals entered the model, 1 person at a time, in a Monte Carlo simulation, and each was followed until death.[31] Characteristics (age, sex, CD4 cell count, and HIV RNA level) of each person were randomly drawn from distributions derived from the Dupont 006 trial (mean CD4 cell count, 350/μL; median log HIV RNA level, 4.8 copies/mL) for the main analysis, although secondary analyses were conducted using data from other clinical trials.[35-37] On entry into the model, patients were given zidovudine, lamivudine, and efavirenz and were eligible for up to 4 sequential 3-drug antiretroviral regimens.[35-38] The efficacy of a regimen determined the success of HIV RNA suppression, which in turn resulted in a CD4 cell count rise.[35-38] The increased CD4 cell count corresponded to a reduction in the risk of acute opportunistic infections and AIDS-related deaths. CD4 and HIV RNA testing were performed every 3 months in stable patients, and decisions about prophylaxis for opportunistic infections and further changes in antiretroviral therapy were made based on results observed for CD4 cell counts and HIV RNA levels, respectively. In accordance with national guidelines, we assumed that all patients received PCP prophylaxis beginning with TMP/SMX (400 mg/80 mg daily) after their first measured CD4 lymphocyte count less than 200/μL, and for *Mycobacterium avium* complex disease with weekly azithromycin (1200 mg) after the first measured CD4 lymphocyte count less than 50/μL.[5]

We made the following assumptions: (1) immune function with CD4 cells regenerated via effective antiretroviral therapy was similar to that predating the CD4 cell count decline; (2) virologic failure was defined as a 0.5-log increase in HIV RNA levels in each of 2 consecutive months during HAART; (3) among patients with virologic failure, CD4 cell counts would not start to decline for at least 6 months[39]; (4) among patients who were still responding to therapy, a specific HAART regimen ceased to confer benefit after 5 years[40]; (5) the efficacy of subsequent antiretroviral regimens among patients who did not respond to

effectiveness of alternative CD4 cell count criteria for stopping PCP prophylaxis in patients receiving HAART and alternative drugs for prophylaxis in those intolerant of trimethoprim-sulfamethoxazole (TMP/SMX).

RESULTS

CRITERIA FOR STOPPING PCP PROPHYLAXIS WITH CD4 CELL COUNT INCREASES DURING HAART

In HIV-infected patients with initial CD4 cell counts of 350/μL (who were given PCP prophylaxis after their first measured CD4 lymphocyte count <200/μL), we considered different strategies to guide the decision to stop or continue PCP prophylaxis once CD4 cell counts increased to greater than 200/μL during HAART. In the base case analysis, we assumed that the risk of PCP was based on the actual new CD4 cell count (ie, fraction of benefit of 1.0). A CD4 cell count stopping criterion greater than 200/μL provided 3.6 months of quality-adjusted life expectancy and cost $5100 per QALY compared with no prophylaxis (**Table 2**). Discontinuing prophylaxis with a CD4 cell count greater than 300/μL prevented an additional 9 cases of primary PCP per 1000 patients at a cost of $9400 per QALY.

The clinical benefits of a CD4 cell count cutoff value greater than 300/μL compared with greater than 200/mL were sensitive to assumptions about the immune function that accompanied CD4 cell count increases higher

an initial regimen was represented as a reduction in the efficacy of the first-line regimen; (6) antiretroviral toxic effects were modeled as drug specific and triggered a switch to an alternative agent within the same class; and (7) the duration of viral suppression depended on adherence and the development of resistance, both of which were assumed to be included in the efficacy estimates derived from the intention-to-treat analyses of data from clinical trials. These assumptions were tested in sensitivity analysis.

CLINICAL DATA

Selected values and plausible ranges for the analysis are given in **Table 1**.[33,35,41-58] The monthly decline in the CD4 cell count, primary opportunistic infection incidence, acute mortality associated with an opportunistic infection, and chronic mortality in the absence of HAART were based on data from the Multicenter AIDS Cohort Study using methods described previously.[33,42,43,59-61] The efficacy of prophylaxis was modeled as a percentage reduction in the monthly incidence of an opportunistic infection.[44-46,50,57,58] Rates of toxic effects in the model were defined according to the AIDS Clinical Trial Group criteria[62]: minor toxic effects included grades 1 and 2 toxic effects that did not require discontinuation of therapy; major toxic effects included any grade 1 to 4 toxic effects that required discontinuation of therapy and crossover to a second- or third-line agent for prophylaxis. *Pneumocystis carinii* pneumonia prophylaxis could be initiated or discontinued at any CD4 cell count.

We used a weight to determine the risk of PCP and other clinical events in patients receiving HAART and referred to it as "fraction of benefit."[63,64] A fraction of benefit of 1.0 means that the risk of opportunistic infections was based on the actual new CD4 cell count (ie, the risk of PCP was similar to that in HAART-naive patients with the same CD4 cell count); a fraction of benefit of 0.0 means that these risks were based on the lowest-ever CD4 cell count; and a fraction of benefit of 0.5 means that these risks were based on the mean of the lowest-ever and current CD4 cell count. Recent data suggest that CD4 cell function with successful virologic suppression is associated with protection against PCP.[11-24] However, lower CD4 cell count nadirs may be associated with a greater risk of opportunistic infections, and we explored the implications of a lower fraction of benefit in patients with a CD4 cell count nadir less than 50/μL.[27,65] We also explored the effects of a fraction of benefit greater than 1.0 (implying a risk of PCP with CD4 cell count increases during HAART that was lower than the risk of PCP in the average untreated patient with that same CD4 cell count).

Trimethoprim-sulfamethoxazole is the preferred choice for PCP prophylaxis,[44,45,47,62,66-70] but intolerance often limits its use.[44,70,71] Alternative prophylactic agents include dapsone, aerosolized pentamidine, and, most recently, atovaquone.[50,68,72] Based on data from a randomized trial comparing atovaquone (1500-mg suspension daily) and dapsone (100-mg tablet daily) for PCP prophylaxis in TMP/SMX-intolerant patients, El-Sadr et al[50] reported similar rates of efficacy, tolerance, and survival in both groups. Because results for drug tolerance when stratified by dapsone use at baseline differed significantly, we explored these data in a sensitivity analysis (Table 1).

The efficacy of first-line antiretroviral therapy was based on the best 3-drug arm (zidovudine, lamivudine, and efavirenz) of the Dupont 006 trial (70% suppression at 48 weeks)[35]; second-line efficacy was based on the 3-drug arm (zidovudine, lamivudine, and indinavir) of the AIDS Clinical Trial Group 320 (60% suppression at 24 weeks)[36]; third-line efficacy was based on the intervention arm of the Community Program for AIDS Research Clinical Trial 046 (34% suppression at 12 weeks); and fourth-line efficacy was based on the control arm of the previously mentioned study (22% suppression at 12 weeks).[37] The methods used to derive transition probabilities using these clinical trial data are described elsewhere.[33]

Costs of prophylaxis and antiretroviral agents were obtained from the 1999 Red Book.[47] Other medical costs were derived from the AIDS Cost and Services Utilization Survey dataset using methods described previously,[33,48,49] although upper and lower bounds for sensitivity analyses were chosen to include other published estimates for the cost of HIV care.[56,73] All costs were converted to 1999 dollars using the Medical Care component of the Consumer Price Index.[51]

Data linking perceived health status to the states defined in the model were obtained from AIDS Clinical Trial Group protocols 019, 108, 154, and 204 by approximating a preference-based measure of health status, as described previously.[33,53] Although these weights were not derived using the preferred techniques of the standard gamble or time tradeoff, they were similar to utilities reported by others using these methods.[54-56]

than 200/μL in patients receiving HAART. When the true underlying risk of PCP was reflected by an individual's historical CD4 cell count nadir (fraction of benefit of 0.0), continuing prophylaxis once the CD4 cell count increased to greater than 200/μL became increasingly cost-effective, reflecting the longer duration of substantial risk of PCP with more years of life to be saved. When we assumed a fraction of benefit of 0.0 only in patients who had a CD4 cell count nadir less than 50/μL, or only in those with HIV RNA levels greater than 30 000 copies/mL, the results were unchanged. When we assumed that the fraction of benefit was greater than 1.0 (ie, the risk of PCP was even lower than the risk in an average untreated patient with the same CD4 cell count), a lower CD4 cell count stopping criterion became more efficient. For example, with a fraction of benefit of 1.5, stopping prophylaxis when the CD4 cell count was greater than 200/μL vs greater than 300/μL was more effective and less costly, dominating the latter strategy and costing only $2300 per QALY.

For patients starting with lower CD4 cell counts and in the later stages of HIV disease, the clinical benefits of waiting until the CD4 cell count was greater than 300/μL vs greater than 200/μL were much greater. For example, in patients similar to those in the AIDS Clinical Trial Group Protocol 320 (initial mean CD4 cell count, 87/μL), delaying discontinuation of prophylaxis until the CD4 cell count was greater than 300/μL prevented an additional 34 cases of primary PCP per 1000 patients compared with stopping at a CD4 cell count greater than 200/μL. The cost-

Table 1. Model Variables[a]

Variable	Base Case (Range[b])	Study
Distribution of initial HIV RNA level, %		
>100 000 copies/mL	36.2	Mellors et al,[41] 1997
30 001-100 000 copies/mL	31.3	
10 001-30 000 copies/mL	20.7	
3001-10 000 copies/mL	9.5	
501-3000 copies/mL	2.2	
0-500 copies/mL	0.1	
Monthly CD4 cell count decline by HIV RNA stratum, mean, cells/µL		
>30 000 copies/µL	6.375	Mellors et al,[41] 1997
10 001-30 000 copies/µL	5.400	
3001-10 000 copies/µL	4.600	
501-3000 copies/µL	3.733	
0-500 copies/µL	3.025	
Monthly probability of PCP by CD4 cell stratum[c]		
>500/µL	0.000410 (0.000-0.00041)	Multicenter AIDS Cohort Study,[42] 1995 Kaslow et al,[43] 1987
301-500/µL	0.000850 (0.000-0.0009)	
201-300/µL	0.003730 (0.000-0.0056)	
101-200/µL	0.009600 (0.0048-0.0144)	
51-100/µL	0.031000 (0.0155-0.0465)	
0-50/µL	0.037000 (0.0185-0.056)	
PCP prophylaxis efficacy, % decrease[d]		
TMP/SMX[e]	0.973 (0.940-0.980)	Ioannidis et al,[44] 1996 Bucher et al,[45] 1997 El-Sadr et al,[46] 1999 El-Sadr et al,[50] 1998
Atovaquone, 1500-mg suspension daily	0.896 (0.840-0.930)	
Dapsone, 100 mg/d	0.872 (0.810-0.910)	
Aerosolized pentamidine, 300 mg/mo	0.650 (0.600-0.800)	
Relative risk PCP, atovaquone vs dapsone[f]	0.850 (0.670-1.090)	
Drug-limiting toxic effects of PCP prophylaxis, %[g]		
High-dose TMP/SMX	23.2	Ioannidis et al,[44] 1996 Bucher et al,[45] 1997 El-Sadr et al,[46] 1999 El-Sadr et al,[50] 1998
Low-dose TMP/SMX	10.9 (8.6-13.5)	
Dapsone	20.28	
Aerosolized pentamidine	2.5	
Atovaquone[h]	20.25	
Annual cost of PCP prophylaxis, $		
High-dose TMP/SMX	65	Red Book,[47] 1999
Low-dose TMP/SMX	28	
Dapsone[i]	841	
Aerosolized pentamidine	1186	
Atovaquone	9617	
Cost of drug-related toxic effects, $		
Major episode[j]	1172	Hospital AIDS Cost and Services Utilization Survey,[48] 1991 AIDS Cost and Services Utilization Survey,[49] 1994
Minor episode[j]	586	
Cost of PCP treatment, $[k]		
Acute care PCP	14 673	Hospital AIDS Cost and Services Utilization Survey,[48] 1991 AIDS Cost and Services Utilization Survey,[49] 1994
PCP-related death	15 572	
Annual cost of antiretroviral regimens, $		
AZT, 3TC, efavirenz (DuPont 006)	10 400	Red Book,[47] 1999
AZT, 3TC, indinavir (ACTG 320)	11 610	
2 NRTIs, 1 PI, 1 NNRTI (CPCRA 046)	15 500	
2 NRTIs, 1 PI, 0.6 NNRTI (CPCRA 046)	14 180	
Cost of tests (per test), $		
Genotypic antiretroviral resistance	400	2000 Clinical Diagnostic Laboratory Fee Schedule,[52] 2000
CD4 cell count	83	
HIV-1 RNA	110	

(continued)

effectiveness ratio of this strategy, at $8200 per QALY, was more attractive than the cost-effectiveness ratio of stopping at a CD4 cell count greater than 200/µL, thereby dominating the latter strategy.[74] In contrast, in a cohort of patients starting with earlier HIV disease (mean CD4 cell count of 500/µL), delaying discontinuation of prophylaxis until the CD4 cell count was greater than 300/µL prevented only 5 additional cases of primary PCP per 1000 patients.

SECOND-LINE AGENTS IN TMP/SMX-INTOLERANT PATIENTS

We evaluated 7 possible strategies for PCP prophylaxis in patients intolerant of TMP/SMX and found that dapsone followed by aerosolized pentamidine and then atovaquone if toxic effects developed (dapsone→aerosolized pentamidine→atovaquone) increased

Table 1. Model Variables[a] (cont)

Variable	Base Case (Range[b])	Study
Health-related quality of life by CD4 cell stratum[l]		
>500/μL	4.1 (0.94 [0.76-1.0])	Torrance,[53] 1976 Tsevat et al,[54] 1996 Revicki et al,[55] 1995 Holtgrave and Pinkerton,[56] 1997
301-500/μL	4.1 (0.94 [0.60-1.0])	
201-300/μL	4.1 (0.94 [0.60-1.0])	
101-200/μL	3.6 (0.87 [0.59-1.0])	
51-100/μL	3.2 (0.81 [0.59-1.0])	
0-50/μL	3.1 (0.79 [0.59-1.0])	
PCP	2.2 (0.61 [0.17-1.0])	

[a]HIV indicates human immunodeficiency virus; PCP, *Pneumocystis carinii* pneumonia; TMP/SMX, trimethoprim-sulfamethoxazole; AZT, zidovudine; 3TC, lamivudine; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; ACTG 320, AIDS Clinical Trials Group Protocol 320; and CPCRA 046, Community Program for Clinical AIDS Research study 046.

[b]The indicated range for each variable reflects the confidence intervals reported in a clinical trial or the lowest and highest values reported in the literature. If no plausible range was specified, the value was varied ±50% in sensitivity analysis.

[c]Monthly probabilities for all other opportunistic infections are provided in a previously published analysis by Freedberg et al.[32,33]

[d]Efficacy of prophylaxis using azithromycin for *Mycobacterium avium* complex is 0.6335.[57,58]

[e]Low-dose TMP/SMX refers to 3 double-strength (DS) tablets weekly or 7 single-strength (SS) tablets weekly; high-dose TMP/SMX, 7 DS tablets weekly. A TMP/SMX DS tablet has 160 mg of trimethoprim and 800 mg of sulfamethoxasole; TMP/SMX SS tablet, 80 mg of trimethoprim and 400 mg of sulfamethoxasole.

[f]These data reported by El-Sadr et al[50] from the intention-to-treat analysis: relative risk of PCP, atovaquone vs dapsone, 0.85; 95% confidence interval, 0.67-1.09; $P = .20$. Results from the on-treatment analysis, relative risk of PCP, atovaquone vs dapsone, 0.80; 95% confidence interval, 0.59-1.07; $P = .13$, were used in sensitivity analyses.

[g]See the "Materials and Methods" section for details.

[h]These data reported by El-Sadr et al[50]: relative risk of discontinuation, atovaquone vs dapsone, 0.94; 95% confidence interval, 0.74-1.19; $P = .59$. Results from the subgroup analysis in patients on dapsone at baseline, relative risk of discontinuation, atovaquone vs dapsone, 3.78; 95% confidence interval, 2.37-6.01; $P < .001$, were used in sensitivity analyses. Results from the subgroup analysis in patients not taking dapsone at baseline, relative risk of discontinuation atovaquone vs dapsone, 0.42; 95% confidence interval, 0.30-0.58; $P < .001$, were used in sensitivity analysis.

[i]Monthly cost of pyrimethamine and leucovorin was added to strategies using dapsone.[47]

[j]Costs of grades 1 and 2 toxic effects were assigned to minor toxicity and costs of grades 3 and 4 toxic effects were assigned to major toxicity.

[k]Costs were assumed to be attributable to an acute episode of PCP if they occurred either as early as 1 month before or as late as 2 months after the diagnosis of PCP.

[l]Data are given as score on a rating scale from 1 to 5 (quality adjustment [0.0-1.0]).

Table 2. Costs, Clinical Impact, and Cost-effectiveness of Using Difference CD4 Cell Count Criteria for Stopping PCP Prophylaxis in Patients Receiving HAART*

Prophylaxis Strategy	Cost, $	Cases of Primary PCP per 1000 Patients, No.	Life Expectancy, mo	C/E Ratio,† $/YLS	QALE, mo	C/E Ratio,† $/QALY‡
Criteria Similar to Those in Dupont 006 (Mean CD4 Cell Count of 350/μL)§						
No prophylaxis	144 260	525	130.80		118.00	
Stop >200/μL	145 770	182	134.98	4300	121.60	5100
Stop >300/μL	146 310	173	135.71	8900	122.29	9400
Criteria Similar to Those in AIDS Clinical Trial Group Protocol 320 (Mean CD4 Cell Count of 87/μL)‖						
No prophylaxis	127 190	558	88.39		76.94	
Stop >200/μL	133 680	155	99.21	Dominated¶	86.70	Dominated¶
Stop >300/μL	135 320	121	101.44	7500	88.80	8200

**Pneumocystis carinii* pneumonia (PCP) prophylaxis is trimethoprim-sulfamethoxazole followed by dapsone and then aerosolized pentamidine in the event of toxic effects. Patients may receive up to 4 regimens of antiretroviral therapy. See the "Materials and Methods" section for details. HAART indicates highly active antiretroviral activity; C/E ratio, incremental cost-effectiveness ratio; YLS, year of life saved; QALE, quality-adjusted life expectancy; and QALY, quality-adjusted life year.

†The difference in cost divided by the difference in life expectancy or QALE for each strategy compared with the next least costly strategy.

‡The reference case reports the incremental cost-effectiveness ratio in dollars per QALY gained.

§Patients similar to those in DuPont 006 enter the model with a mean (SD) CD4 cell count of 350 (157)/μL; have an initial human immunodeficiency virus (HIV) RNA median log of 4.8; and are immediately given zidovudine, lamivudine, and efavirenz.[35]

‖Patients similar to those in the cohort in AIDS Clinical Trials Group Protocol 320 enter the model with a mean (SD) CD4 cell count of 87 (70)/μL; have an initial HIV RNA median log of 5.0; and are immediately given zidovudine, lamivudine, and indinavir.[36]

¶A CD4 cell count stopping criterion of 200/μL is weakly dominated by a stopping criterion of 300/μL because it has a higher (ie, less attractive) incremental cost-effectiveness ratio than this more effective alternative strategy.[74]

quality-adjusted life expectancy by 2.7 months and total lifetime costs by $1000, for an incremental cost-effectiveness ratio of $4500 per QALY compared with no prophylaxis (**Table 3**). All strategies that began with aerosolized pentamidine were less effective and more costly than dapsone→aerosolized pentamidine→ atovaquone. Compared with dapsone→aerosolized pentamidine→ atovaquone, the strategy of starting with atovaquone followed by dapsone and then aerosolized pentamidine provided only 2.7 extra days of life expectancy and cost $1.8 million per year of life gained. Unless the monthly cost of atovaquone was decreased by approximately 90% (equivalent to an annual cost of $962), the cost-effectiveness ratio for any strategy beginning with atovaquone remained greater than $100 000 per QALY.

Table 3. Cost-effectiveness of Second-Line Prophylaxis for Patients Intolerant of TMP/SMX*

Prophylaxis Strategy†	Cost, $	Primary PCP Cases per 1000 Patients, No.	Life Expectancy, mo	C/E Ratio,‡ $/YLS	QALE, mo	C/E Ratio,‡ $/QALY§
No prophylaxis	150 270	525	136.77		123.86	
Dapsone→AP→atovaquone	151 270	247	139.84	3900	126.52	4500
AP→dapsone→atovaquone	152 030	335	138.66	Dominated‖	125.49	Dominated‖
AP→atovaquone→dapsone	152 270	331	138.77	Dominated‖	125.58	Dominated‖
Dapsone→atovaquone→AP	153 200	230	139.67	Dominated‖	126.31	Dominated‖
Atovaquone→AP→dapsone	164 070	238	139.49	Dominated‖	126.15	Dominated‖
Atovaquone→dapsone→AP	164 330	221	139.98	1 151 200	126.61	1 793 000

*Patients enter the model with a mean (SD) CD4 cell count of 350 (157)/μL; have an initial human immunodeficiency virus RNA median log of 4.8; and receive up to 4 regimens of antiretroviral therapy. See the "Materials and Methods" section for details. TMP/SMX indicates trimethoprim-sulfamethoxazole; PCP, *Pneumocystis carinii* pneumonia; C/E ratio, incremental cost-effectiveness ratio; YLS, year of life saved; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year; and AP, aerosolized pentamidine.

†Doses: dapsone, 100 mg daily; AP, 300 mg monthly; and atovaquone, 1500-mg suspension daily.

‡The difference in cost divided by the difference in life expectancy or QALE for each strategy compared with the next best strategy.

§The reference case reports the C/E ratio as dollars per QALY gained.

‖Strategies that begin with AP are strongly dominated by dapsone→AP→atovaquone because they cost more but are less effective; atovaquone→AP→dapsone in analysis on highly active antiretroviral therapy is weakly dominated by atovaquone→dapsone→AP because it has a higher incremental C/E ratio than this more effective alternative strategy.[74] Atovaquone→AP→dapsone in analysis is strongly dominated by atovaquone→dapsone→AP because it costs more but is less effective.

We determined the plausible bounds for the efficacy and toxicity of dapsone and atovaquone based on data from the randomized trial of dapsone vs atovaquone using the confidence intervals from the intention-to-treat analysis, the subgroup analysis of the dapsone-naive patients, and the on-treatment analysis.[50] Despite the intentional bias against dapsone resulting from the latter 2 approaches, the cost-effectiveness ratio for a strategy that started with atovaquone was never less than $300 000 per QALY.

COMMENT

Pneumocystis carinii pneumonia prophylaxis was the most important improvement in the standard of HIV care during the first decade of the HIV epidemic, and it played a major role in reducing the rate of progression to AIDS before the availability of other opportunistic infection prophylaxis and HAART.[1-3] Its low cost makes it the least expensive HIV medication, and its cost-effectiveness suggests that it offers substantial clinical value for the resources spent.[32] There is a convergence of opinion in favor of discontinuing PCP prophylaxis in patients whose CD4 cell counts have increased to greater than 200/μL with HAART.[11-28] In HIV-infected patients with initial CD4 cell counts of 350/μL who started PCP prophylaxis after their first measured CD4 lymphocyte count less than 200/μL, stopping prophylaxis when the CD4 cell count increased to greater than 300/μL with HAART provided a small additional clinical benefit (eg, 9 cases of primary PCP averted per 1000 patients) compared with stopping at 200/μL. However, the additional costs are so low that continued prophylaxis has an attractive cost-effectiveness ratio nonetheless. For patients with more advanced disease, such as those in AIDS Clinical Trial 320 (CD4 cell counts of 87/μL), the incremental benefits of stopping prophylaxis at a CD4 cell count greater than 300/μL rather than greater than 200/μL are much greater (eg, 34 cases of primary PCP averted per 1000 patients). Lower CD4 cell count nadirs may be associated with a greater risk of opportunistic infections in patients with CD4 cell count increases during HAART.[65] However, even when we assumed a fraction of benefit of 0.0 in those with CD4 cell count nadirs of less then 50/μL, the overall cost-effectiveness results were unchanged.

For patients intolerant of TMP/SMX, we found that the most cost-effective strategy for PCP prophylaxis was to use dapsone followed by aerosolized pentamidine and then atovaquone in the event of toxic effects. This was the case even when the relative risks of failure and toxic effects with atovaquone use were assumed to be 50% of the base case. In fact, when the relative risk of stopping atovaquone therapy because of toxic effects was 0.42 compared with dapsone (recently reported in the subgroup analysis of dapsone-naive patients),[50] starting with atovaquone in TMP/SMX-intolerant patients still had a cost-effectiveness ratio exceeding $500 000 per QALY. Given the current annual wholesale cost of atovaquone of $9600, this would pay for not only dapsone for PCP prophylaxis but also for 10 months of zidovudine, lamivudine, and efavirenz for an individual patient. With limited available resources for costly HIV therapy,[75] using atovaquone before a trial of dapsone does not make policy sense.[76]

There are several limitations to this analysis. First, we did not incorporate the additional benefit of TMP/SMX in preventing bacterial infections, and we did not consider the possible impact of the development of TMP/SMX resistance with lifelong use. Second, the input data for efficacy and toxicity were based on multiple studies of varying size, design, and quality, although, when possible, we used data from randomized controlled trials. We did not include secondary PCP prophylaxis because there are fewer data, although thus far discontinuation with CD4 cell count increases seems safe.[13,77,78] Estimates of costs reflect practice before HAART; however, we modified these costs to reflect newer drug costs and HIV RNA

testing, and we conducted extensive sensitivity analyses on costs with little impact on the results. Finally, although cost-effectiveness analysis can help illustrate the tradeoffs with different policy alternatives, it serves as only one input to decision making.[29] There may be important qualitative considerations when developing guidelines, such as the potential psychological benefit of discontinuing treatment.[26]

Our results, in large part, support recent clinical guidelines.[5] The 1999 US Public Health Service–Infectious Disease Society of America Working Group suggested that stopping prophylaxis when the CD4 cell count has been greater than 200/mL for at least 3 to 6 months may be reasonable based on early data showing an extremely low risk of PCP in patients treated successfully with HAART. The analysis we conducted to address this issue involved the critical review of all published studies supporting safe discontinuation in patients with CD4 cell count increases with HAART; in most of these studies, the mean CD4 cell count at the time of discontinuation was greater than 300/μL.[11-24] Because these clinical studies described the immune status of their study populations using the mean CD4 cell count, we elected to use an absolute CD4 cell count rather than duration of time at a particular CD4 cell count for our primary prophylaxis discontinuation criterion. In fact, the clinical guidelines and our results are quite similar—whether there will be a clinically meaningful difference between "a CD4 cell count greater than 200/μL for at least 6 months" and "a measured CD4 cell count of at least 300/μL" is a question for future research.

The results of this analysis support the following conclusions: (1) Despite the relatively low risk of PCP in patients successfully treated with HAART, waiting to stop primary PCP prophylaxis until an observed CD4 cell count is greater than 300/μL will prevent PCP cases, is cost-effective, and provides an explicit and easily understandable PCP prophylaxis stopping criterion for patients and providers. (2) Regimens using atovaquone in TMP/SMX-intolerant patients have cost-effectiveness ratios that are much higher than those of well-accepted clinical interventions, and dapsone should be the initial choice for prophylaxis in these patients. These conclusions can be used to refine the optimal approach to PCP prophylaxis as treatment for HIV disease continues to evolve in this era of effective antiretroviral therapy.

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