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Cost-effectiveness of azithromycin for preventing *Mycobacterium avium* complex infection in HIV-positive patients in the era of highly active antiretroviral therapy

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We conducted a cost-effectiveness analysis to determine the clinical and economic consequences of *Mycobacterium avium* complex (MAC) prophylaxis in HIV-infected patients in the era of highly active antiretroviral therapy (HAART) in a health care system with access unrestricted by financial barriers. The analysis was performed from a health care perspective and compared azithromycin (1200 mg/week) with no prophylaxis over a period of 10 years based on data from the Swiss HIV Cohort Study (SHCS) and randomized controlled trials. The main outcome measures were: expected survival; average health care costs; and cost-effectiveness in 1997 Swiss francs (£1 corresponds to about 2.3 CHF) per life-year saved. In patients with an initial CD4 count <50 cells/mm^3 and no AIDS, azithromycin increased expected survival by 4 months. In patients with AIDS, HAART durability had a major impact on expected survival and costs. Incremental survival increased from 2 to 4 months if we assumed a 10 year, instead of a 3 year, HAART effect. The cost-effectiveness of azithromycin relative to no prophylaxis in patients without AIDS was between 47,000 CHF (3-year HAART effect) and 60,000 CHF (10-year HAART effect) per life-year saved. The cost-effectiveness ratio increased to 118,000 CHF per life-year saved in patients with symptomatic AIDS. In conclusion, in the era of HAART, MAC prophylaxis with azithromycin increases expected survival and reduces health care costs substantially. Starting MAC prophylaxis in patients without AIDS is more effective and cost-effective than in patients with AIDS.

Introduction

Disseminated *Mycobacterium avium* complex (MAC) infection in severely immunosuppressed HIV-infected patients is associated with increased morbidity and mortality.[1] Randomized controlled trials have documented the benefit of MAC prophylaxis with macrolides in HIV-infected patients with advanced immunosuppression.[2–4] Economic studies, based on models with clinical data gathered before[5,6] and after[7] highly active antiretroviral therapy (HAART) became widely available, have investigated the policy implications of MAC prophylaxis in the USA. However, the cost-effectiveness of MAC prophylaxis within a European setting has not yet been evaluated. The Swiss health care system, as an example of a Western European-type health care system, provides unrestricted access to all approved therapies for patients with HIV infection. The majority (66.2%) of the Swiss health care resources are funded by consumers either directly (out-of-pocket payment) or indirectly (insurance companies).[8] Official federal organizations fund most of the remainder.[8]

We conducted a cost-effectiveness analysis from the health care perspective to address the clinical and economic implications of MAC prophylaxis with azithromycin in the era of HAART. Our analysis is based on the Swiss HIV Cohort Study (SHCS).[9] This study offers additional

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insights about the consequences of MAC prophylaxis in HIV-infected individuals receiving care in a system with access unrestricted by financial barriers. In addition, we applied Bayesian analytical techniques to reflect *overall* parameter uncertainty.[10]

Methods

The model

We developed a Markov (or state-transition) model[11] that describes the disease history of HIV-infected subjects as a sequence of monthly health states. We defined four broad categories of health: No AIDS (asymptomatic HIV-positive), AIDS (non-MAC), MAC and death. We used the European classification for AIDS.[12] The No AIDS and AIDS states were further stratified into three CD4-cell count categories: 0–49 cells/mm^3, 50–74 cells/mm^3 and $\geqslant$75 cells/mm^3. A patient currently in a No AIDS state is at risk of dying from non-AIDS-related causes, developing MAC or developing an AIDS-defining disease other than MAC. A patient with AIDS is at risk of dying from AIDS or developing MAC. A patient with MAC is at risk of dying from MAC. Prophylactic drug efficacy is expressed as a reduction in MAC incidence. A low adherence in turn is modelled as a low drug efficacy. Severe drug toxicity results in discontinuation of MAC prophylaxis. The model was implemented in DATA 3.0 (TreeAge Software, Williamstown, MA, USA) and self-written FORTRAN 90 code. The validation procedures applied to our model are described in detail elsewhere.[13] Expected survival and average costs were computed over a 10-year period using matrix multiplication. We felt that 10 years would be the maximum realistic time-horizon for extrapolation in this highly dynamic and changing field where far-reaching predictions are rarely possible.

In Switzerland, HAART was introduced in 1996.[14] There is a paucity of data on the long-term efficacy of HAART. Therefore, we analysed this model under three scenarios assuming different levels of HAART durability: a continuous time effect scenario (CTES), a 5 year effect scenario (5-YES) and a 3 year effect scenario (3-YES). We used Swiss HIV Cohort Study (SHCS) data from 1996–1997 to estimate the transition probabilities in the era of HAART. We used probability estimates derived from the SHCS 1993–1995 data set, before those therapies became widely available, to reflect the loss of HAART effect.

Costs in Swiss francs (£1 corresponds to about 2.3 CHF) and survival were discounted at an annual rate of 4% to correspond with the discounting practice of major Swiss insurance companies (Schweizerische Unfallversicherung sanstalt, personal communication, 1998).[15]

Clinical data

The SHCS,[9] a multi-centre, prospective study, started in 1988, has enrolled more than 9000 patients over a period of 10 years. We used the SHCS data set to obtain maximum likelihood estimates of transition probabilities describing the natural history of HIV disease. Formation of posterior distributions for the Bayesian analysis is available on request from the authors.

For estimating transition probabilities among CD4 count strata, we included only patients with a CD4 count $<$75 cells/mm^3 after 1 January 1993 and at least one follow-up. Individuals contributed to the model from the first data characterized by a CD4-cell count $<$75/mm^3. A rise in CD4-cell count above 75/mm^3 after that date was accepted. We pooled follow-up data recorded before and after 31 December 1995 separately, to estimate the probabilities for the two periods. We converted these 6 month transition matrices into 1 month transition matrices applying matrix decomposition (Table I).[16]

Probability estimates for developing an AIDS-defining disease (MAC/non-MAC) and dying from AIDS given a specified CD4-cell stratum were also extracted from the SHCS (Table II). The monthly risk of dying from MAC was derived from an analysis by Low and colleagues.[17] Pre-AIDS mortality may vary among different populations.[18,19] We integrated this assumption into our model using SHCS data and Swiss life-table estimates. The base case was a

Table I. Monthly probabilities of transitions among CD4-cell count strata in two time periods in the SHCS

SHCS period	Initial CD4-cell stratum (cells/mm^3)	Final CD4-cell stratum		
		0–49	50–74	$\geqslant$75
1993–1995	0–49	0.9819	0.0122	0.0059
	50–74	0.1766	0.7517	0.0717
	$\geqslant$75	0.0177	0.0933	0.8830
1996–1997	0–49	0.8785	0.0735	0.0480
	50–74	0.1226	0.6607	0.2167
	$\geqslant$75	0.0096	0.0249	0.9655

33-year-old HIV-infected individual to coincide with the mean age of SHCS participants.

Efficacy and toxicity estimates for azithromycin were extracted from a randomized controlled trial.[4] We computed for azithromycin (1200 mg once weekly) an efficacy of 0.6561 and a monthly risk of severe toxicity of 0.006. We did not include clarithromycin in our analysis. Its efficacy and toxicity are comparable to azithromycin but it is much more expensive in Switzerland.[2,4,20] Furthermore, the dosing schedule with azithromycin (once weekly) is favourable since it reduces the pill burden of patients. Rifabutin was excluded from our analysis because it is less effective, more toxic and more expensive than azithromycin.[3,20]

Cost data

Since we chose the viewpoint of the health care system, only treatment costs are considered. We reviewed a random sample of charts of HIV-infected patients enrolled in the SHCS to estimate use of health care resources. These patients receive their main ambulatory care at the internal medicine outpatient services in four university hospitals (Basel, Bern, Geneva and Zurich). We included 46 patients with MAC infection and 62 patients with an AIDS-defining disease other than MAC.

Quantities of resource use were abstracted on a per patient basis. We estimated each component of resource use (micro-costing).[21] As protease inhibitors were not available at the time of cost data collection (1993–1995), the central cost for protease inhibitors was derived from an estimated 70% of patients taking protease inhibitors[22] at a daily cost of 21 CHF.[23] The 'hotel component' of hospital expenditure in case of stationary health care was estimated on the basis of patient-days (assuming average daily hotel costs). We assumed that patients who were asymptomatic had regular check-up visits, routine laboratory examinations, *Pneumocystis carinii* prophylaxis and antiretroviral drugs. Costing details are described elsewhere.[24]

Table II. Monthly probabilities of *Mycobacterium avium* complex infection and other opportunistic diseases stratified by CD4-cell count in two time periods in the SHCS

Opportunistic infection	CD4-cell stratum (cells/mm^3)	Monthly risk	Reference SHCS period
M. avium complex	0–49	0.0204	93–95
		0.0076	96–97
	50–74	0.0099	93–95
		0.0016	96–97
	⩾75	0.0052	93–95
		0.0003	96–97
Other AIDS-defining diseases	0–49	0.0393	93–95
		0.0212	96–97
	50–74	0.0305	93–95
		0.0103	96–97
	⩾75	0.0167	93–95
		0.0013	96–97

Table III. Monthly costs (CHF)[a] of care for AIDS-free patients, patients with MAC and patients with other AIDS-defining diseases in the SHCS

Location	No AIDS[b]	AIDS without MAC[c]	AIDS with MAC[c]
Basel	–	8244	11191
Bern	–	5675	7353
Geneva	–	7272	9841
Zurich	–	7751	8937
Mean	1017	7235	9330

[a] Inflated to 1997 Swiss francs (CHF) using the Swiss CPI for health care. £1 corresponds to about 2.3 CHF.
[b] Includes regular check-up visits, laboratory examinations, *Pneumocystis carinii* prophylaxis, antiretroviral drugs.
[c] Costs were extracted from a random sample of patient charts from four Swiss university hospitals. Costs for protease inhibitors were added.

Monthly cost estimates were averaged for each institution. We then linked these average resource use estimates to the three states: No AIDS (pre-AIDS), AIDS with MAC and AIDS without MAC (Table III). For patients receiving MAC prophylaxis we added the wholesale price of azithromycin (200 CHF per month).[20] Azithromycin toxicity was assumed not to lead to additional costs, since these are captured by the regular physician visits and laboratory tests for check-up examinations. All costs were inflated to 1997 CHF using the Swiss consumer price index for health care (Swiss Federal Statistics Office, Bern Switzerland).

Bayesian analysis

The expected survival and average costs are both functions of the model parameters. Therefore, it is important to account for the joint uncertainty in the parameters when comparing prophylactic strategies.[25] Bayesian analysis relies on the idea that uncertainty can be described by a distribution. We took a Bayesian approach thereby creating a joint distribution of model parameters (posterior) which is conditional on the model, prior opinion and the data. In turn, 5000 samples from this joint distribution were used to approximate distributions of expected survival and average costs. For each set of sampled model parameters, we computed the expected survival and average costs of the two strategies using matrix multiplication. These results were then combined to form the approximate distributions of each summary. The resulting distributions reflect our joint uncertainty of the model parameters. A detailed description of the Bayesian methodology is available on request from the authors.

Results

Baseline analysis

The survival curves in patients with a CD4 count <50 cells/mm^3 and without MAC prophylaxis are shown in Figure 1. In all scenarios with the exception of the CTES the survival probability was about 10% or below at year 10. Expected survival and costs are shown in Table IV. Starting

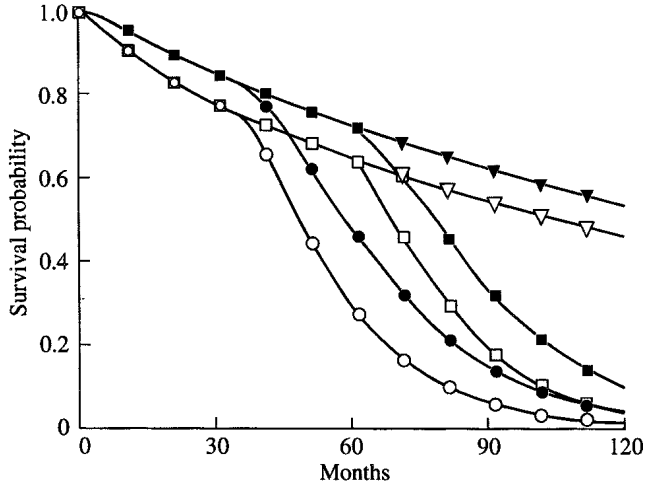

Figure 1. Survival probability in patients with an initial CD4 count <50 cells/mm^3. We used different scenarios concerning highly active antiretroval therapy durability. CTES denotes continuous-time effect scenario, 5-YES denotes 5 year effect scenario, 3 YES denotes 3-year effect scenario, A denotes AIDS (patients with AIDS initially), NA denotes No AIDS (patients without AIDS initially). ▼, NA, CTES; ■, NA, 5-YES; ●, NA, 3-YES; ▽, A, CTES; □, A, 5-YES; ○, A, 3-YES.

Table IV. Costs, life-expectancy and cost-effectiveness of preventing *M. avium* complex infection with azithromycin in patients with an initial CD4 count <50 cells/mm^3

		No AIDS			AIDS		
Scenario[a]	Strategy[b]	Costs (CHF)[c]	LE[d] (months)	ICER[e] (CHF/YLS)	Costs (CHF)[c]	LE[d] (months)	ICER[e] (CHF/YLS)
CTES	no prophylaxis	210,155	73.77		487,554	66.95	
	azithromycin	230,885	77.94	60,000	522,319	70.50	118,000
5-YES	no prophylaxis	189,064	62.66		395,756	53.98	
	azithromycin	205,629	66.47	52,000	421,149	56.56	118,000
3-YES	no prophylaxis	165,242	52.27		316,766	43.01	
	azithromycin	179,589	55.95	47,000	335,490	44.92	118,000

[a] Scenario relates to HAART durability assumptions. CTES denotes continuous-time effect scenario, 5-YES denotes 5 year effect scenario, 3-YES denotes 3 year effect scenario.
[b] Doses for prophylaxis were 1200 mg once weekly for azithromycin.
[c] All costs are in 1997 CHF (Swiss francs).
[d] Life expectancy over a 10 year period.
[e] ICER denotes incremental cost-effectiveness ratio (rounded up to nearest 1000 CHF), which is the difference in cost divided by the difference in life-expectancy in terms of years of life saved (YLS) for azithromycin compared with no prophylaxis.

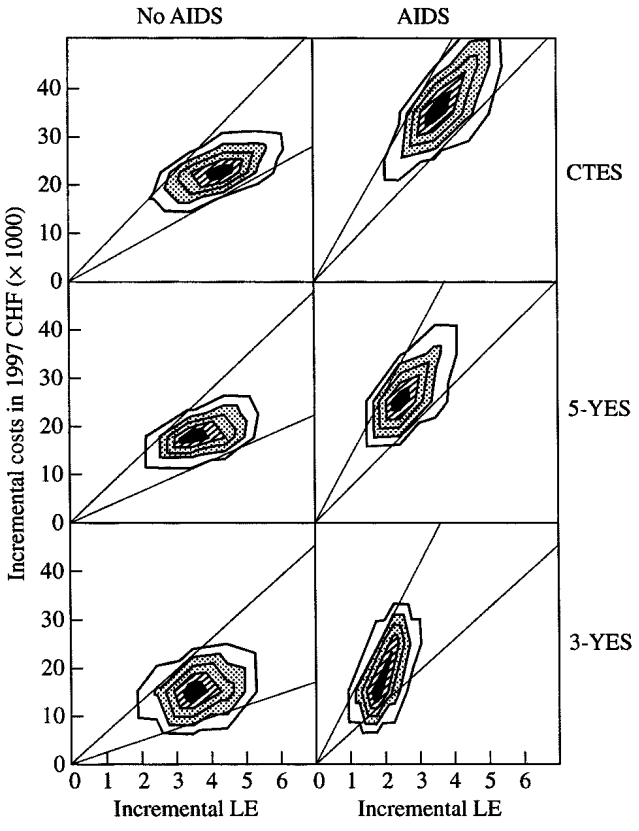

Figure 2. Iso-probability contour plots of the joint distribution of the mean incremental costs and effectiveness for starting azithromycin prophylaxis in patients with and without AIDS. CHF, Swiss Francs, rounded to nearest 1000. LE, Life-expectancy (months). We used different scenarios concerning highly active antiretroval therapy durability. CTES denotes continuous-time effect scenario, 5-YES denotes 5 year effect scenario, 3-YES denotes 3 year effect scenario.

prophylaxis at a CD4 cell level of 50–74 cells/mm^3 instead of 0–49 cells/mm^3 was always less cost effective. All calculations were also done undiscounted and at an annual discount rate of 8% but no major effect on the incremental cost-effectiveness ratios was observed.

Bayesian analysis

The 95% confidence intervals for incremental costs, life-expectancy and cost-effectiveness ratios are shown in Table V. We present for azithromycin (Figure 2) the joint posterior distribution of incremental costs and incremental effectiveness as iso-probability contour plots.[26] The size of the contour plot reflects the level of uncertainty in the estimates. The central contour circumscribes the area where the joint posterior for incremental costs and effectiveness will lie with highest probability. Average costs and life-expectancy are positively correlated leading to the depicted characteristic shape of the contour plots. This correlation is positive because only treatment costs were included. The higher the expected survival, the more resources are needed to treat a chronic disease condition. This is shown by the contour plots shifting upward and to the right when we move from the 3-YES to the CTES. When MAC prophylaxis is started in asymptomatic HIV-infected patients, this shift is less pronounced. The slopes of the two lines in each cell reflect the upper and lower limits of the 95% confidence interval of the incremental cost-effectiveness ratio. These slopes suggest that starting antibiotic prophylaxis in patients with AIDS is less cost effective than in patients without AIDS.

Discussion

In the era of HAART, MAC infection is still one of the most frequent opportunistic infections among HIV-

Table V. 95% credible intervals for incremental costs, life-expectancy and cost-effectiveness ratios of preventing *M. avium* complex infection with azithromycin in patients with an initial CD4 count <50 cells/mm^3

Initial status	Outcome[a]	CTES	5-YES	3-YES
No AIDS	incremental costs (CHF)[b]	17,000–31,000	12,000–26,000	9000–24,000
	incremental LE (months)	2.63–6.13	2.35–5.48	2.25–5.36
	ICER (CHF/YLS)[b]	48,000–88,000	37,000–81,000	29,000–76,000
AIDS	incremental costs (CHF)[b]	25,000–54,000	17,000–49,000	12,000–29,000
	incremental LE (months)	2.31–5.58	1.64–3.90	1.17–2.92
	ICER (CHF/YLS)[b]	91,000–151,000	86,000–157,000	79,000–165,000

[a] Incremental costs is the difference in costs for azithromycin compared with no prophylaxis. Incremental life-expectancy (LE) is the difference in life-expectancy for azithromycin compared with no prophylaxis. ICER denotes incremental cost-effectiveness ratio, which is the difference in costs divided by the difference in life-expectancy for azithromycin compared with no prophylaxis.
[b] Rounded to nearest 1000 CHF.
Abbreviations as in Table IV.

positive individuals in Switzerland and parts of Europe.[27] None the less, the incidence of AIDS-defining diseases, including MAC, has declined since the introduction of HAART,[14,28] which disfavours antibiotic prophylaxis.[29] However, the expected survival of patients with advanced CD4 cell depletion has increased remarkably. This, in contrast, makes MAC prophylaxis more beneficial.[29] Although HAART lowers the monthly risk of acquiring MAC at a given CD4 cell level and may also partially restore immune function, our model shows that these effects are by far outweighed by a higher cumulative risk of MAC infection associated with a higher life-expectancy. This is documented by an increasing gain in survival with azithromycin in the more optimistic scenarios of HAART durability. Azithromycin was only discontinued when severe toxic reactions were experienced, but not when HAART increased the CD4 cell count above the cut-off point ($\leqslant$50 CD4 cells/mm^3) for MAC prophylaxis.[30] We found an average gain in survival comparable to the estimates reported by Bayoumi and Redelmeier[7] for a North American setting.

MAC prophylaxis leads to a substantial amount of resource consumption within the Swiss health care sector. Antibiotic prophylaxis in patients with AIDS increases direct medical costs more than in AIDS-free patients and results in a lower gain in survival. This translates into a cost-effectiveness ratio that is higher. It would not be uncommon for the cost-effectiveness ratio for azithromycin in patients with AIDS to exceed 150,000 CHF per life-year saved. If MAC prophylaxis is started in AIDS-free patients, there is a negligible chance that this would cost 100,000 CHF per life-year saved. If the health care system wants to contain costs, it needs to cancel programmes where the loss in health terms is lower than the health gains from the azithromycin programme.[31] Alternatively, policy decision-makers should find ways to increase the health care budget.

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References

1. Horsburgh, C. R. (1991). *Mycobacterium avium* complex infection in the acquired immunodeficiency syndrome. *New England Journal of Medicine* **324**, 1332–8.

2. Pierce, M., Crampton, S., Henry, D., Heifets, L., LaMarca, A., Montecalvo, M. *et al.* (1996). A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. *New England Journal of Medicine* **335**, 384–91.

3. Havlir, D. V., Dube, M. P., Sattler, F. R., Forthal, D. N., Kemper, C. A., Dunne, M. W. *et al*. (1996). Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *New England Journal of Medicine* **335**, 392–8.

4. Oldfield, E. C., Fessel, W. J., Dunne, M. W., Dickinson, G., Wallace, M. R., Byrne, W. *et al*. (1998). Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind placebo-controlled multicenter trial. *Clinical Infectious Diseases* **26**, 611–9.

5. Freedberg, K. A., Cohen, C. J. & Barber, T. W. (1997). Prophylaxis for disseminated *Mycobacterium avium* complex (MAC) infection in patients with AIDS: a cost-effectiveness analysis. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* **15**, 275–82.

6. Freedberg, K. A., Scharfstein, J. A., Seage, G. R., Losina, E., Weinstein, M. C., Craven, D. E. *et al.* (1998). The cost-effectiveness of preventing AIDS-related opportunistic infections. *Journal of the American Medical Association* **279**, 130–6.

7. Bayoumi, M. B. & Redelmeier, D. A. (1998). Preventing *Mycobacterium avium* complex in patients who are using protease inhibitors: a cost-effectiveness analysis. *AIDS* **12**, 1503–12.

8. Bundesamt für Statistik (1998). *Anstieg der Gesundheitskosten*. Pressemitteilung Nr. 32/98, Bern, Switzerland.

9. Ledergerber, B., von Overbeck, J., Egger, M. & Lüthy, R. (1994). The Swiss HIV Cohort Study: rationale, organization and selected baseline characteristics. *Sozial- und Präventivmedizin* **39**, 387–94.

10. Craig, B. A., Fryback, D. G., Klein, R. & Klein, B. E. K. (1999). A Bayesian approach to modelling the natural history of a chronic condition from observations with intervention. *Statistics in Medicine* **18**, 1355–71.

11. Sonnenberg, F. A. & Beck, J. R. (1993). Markov models in medical decision making: a practical guide. *Medical Decision Making* **13**, 322–38.

12. Ancelle-Park, R. A., Alix, J., Downs, A. M. & Brunet, J. B. (1995). Impact of 1993 revision of adult/adolescent AIDS surveillance case-definition for Europe. National Coordinators for AIDS Surveillance in 38 European countries. *Lancet* **345**, 789–90.

13. Sendi, P. P., Craig, B. A., Pfluger, D., Gafni, A. & Bucher, H. C. (1999). Systematic validation of disease models for pharmacoeconomic evaluations. *Journal of Evaluation in Clinical Practice* **5**, 283–95.

14. Egger, M., Hirschel, B., Francioli, P., Sudre, Ph., Wirz, M., Flepp, M. *et al.* (1997). Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. *British Medical Journal* **315**, 1194–9.

15. Krahn, M. & Gafni, A. (1993). Discounting in the economic evaluation of health care interventions. *Medical Care* **31**, 403–18.

16. Craig, B. A. & Sendi, P. P. (1998). *Estimating the Transition Matrix of a Homogeneous Markov Chain*. Technical Report #98–12, Department of Statistics, Purdue University, West Lafayette, IN, USA.

17. Low, N., Pfluger, D. & Egger, M. (1997). Disseminated *Mycobacterium avium* complex disease in the Swiss HIV Cohort Study: increasing incidence, unchanged prognosis. *AIDS* **11**, 1165–71.

18. Laurichesse, H. A., Mortimer, J., Evans, B. G. & Farrington, C. P. (1998). Pre-AIDS mortality in HIV-infected individuals in England, Wales and Northern Ireland, 1982–1996. *AIDS* **12**, 651–8.

19. Prins, M., Hernandez Aguado, I. H., Brettle, R. P., Robertson, J. R., Broers, B., Carre, N. *et al*. (1997). Pre-AIDS mortality from natural causes associated with HIV disease progression: evidence from the European Seroconverter Study among injecting drug users. *AIDS* **11**, 1747–56.

20. Documed AG (1997). *Arzneimittelkompendium der Schweiz*. Website: http://www.kompendium. ch/app/search_d.cfm.

21. Drummond, M. F., O'Brien, B., Stoddart, G. L. & Torrance, G. W. (1997). *Methods for the Economic Evaluation of Health Care Programmes*, 2nd edn. Oxford University Press, Oxford.

22. Sendi, P. P., Bucher, H. C., Craig, B. A., Pfluger, D. & Battegay, M. (1999). Estimating AIDS-free survival in a severely immunosuppressed asymptomatic HIV-infected population in the era of antiretroviral triple combination therapy. Swiss HIV Cohort Study. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* **20**, 376–81.

23. Flepp, M., Jost, J., Malinverni, R., Vernazza, P., Battegay, M., Bernasconi, E. *et al*. (1997). *Neue Empfehlungen zur Behandlung der HIV-Infektion bei Erwachsenen. Bundesamt für Gesundheit (BAG). Bulletin 20.*

24. Meier, G. (1992). *Kosteneffektivität der Mycobakterium avium Komplex Prophylaxe bei HIV Infektion in der Schweiz*. Thesis, University of Basel, Switzerland.

25. O'Brien, B. J., Drummond, M. F., Labelle, R. J. & Willan, A. (1994). In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. *Medical Care* **32**, 150–63.

26. Hunink, M. G., Bult, J. R., de Vries, J. & Weinstein, M. C. (1998). Uncertainty in decision models analyzing cost-effectiveness: the joint distribution of incremental costs and effectiveness evaluated with a nonparametric bootstrap method. *Medical Decision Making* **18**, 337–46.

27. Egger, M. *Opportunistic infections in the era of HAART*. (1998). Twelfth World AIDS Conference, Geneva, Switzerland, 1998. Available from: URL: http://www.webcast.aids98.org.

28. Gebhardt, M., Rickenbach, M. & Egger, M. (1998). Impact of antiretroviral combination therapies on AIDS surveillance reports in Switzerland. Swiss HIV Cohort Study. *AIDS* **12**, 1195–201.

29. Wright, J. C. & Weinstein, M. C. (1998). Gains in life expectancy from medical interventions—standardizing data on outcomes. *New England Journal of Medicine* **339**, 380–6.

30. USPHS/IDSA Prevention of Opportunistic Infections Working Group (1997). 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Morbidity and Mortality Weekly Report* **46**, (RR-12), 1–46.

31. Birch, S. & Gafni, A. (1992). Cost effectiveness/utility analyses. Do current decision rules lead us where we want to be? *Journal of Health Economics* **11**, 279–96.

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