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Meeting the NICE Requirements: A Markov Model Approach

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ABSTRACT

The National Institute of Clinical Excellence (NICE) was established in the United Kingdom in April 1999 to issue guidance for the National Health Service (NHS) on the use of selective new health care interventions. This article describes the NICE requirements for both incidence-based cost-effectiveness analyses and prevalence-based estimates of the aggregate NHS impact of the new drug. The article demonstrates how both of these requirements can be met using Markov modeling techniques. A Markov model for a hypothetical new treatment for HIV infection is used as an illustration of how to generate the estimates that are required by NICE. The article concludes with a discussion of the difficulties of obtaining data of sufficient quality to include in the Markov model to ensure that the submission meets all the NICE requirements and is credible to the NICE advisory board.

Keywords: aggregate benefits, aggregate costs, cost utility analysis, Markov model, National Health Service, National Institute of Clinical Excellence (NICE).

Introduction

The National Institute of Clinical Excellence (NICE) was established in the United Kingdom in April 1999. NICE plans to issue guidance for selective new treatments and products as to whether or not they can be recommended for routine use in the National Health Service (NHS) [1, p13]. The guidance may also specify for which indications use is recommended as well as for which patient subgroups. New treatments and products will be identified that are likely to have a major impact on NHS costs or patient health. Evidence on the clinical outcomes and the cost-effectiveness of these innovations will be collected and used to determine the NICE guidance [1, pp7–8]. The first guidance, "Not recommended for routine use by the NHS," was issued in October 1999 for zanamivir, a new treatment for influenza. A number of other guidance documents have been issued including guidance for taxanes for breast cancer and for proton pump inhibitors for dyspepsia (http://www.nice.org.uk).

The evaluation of the costs and benefits of the chosen treatments will be completed jointly by the sponsor of the treatment (if there is one), patient groups, and the NICE appraisal staff or organizations commissioned by them [1, pp3,4]. The NICE requirements for the evaluation are set out in their discussion document (1, AnnexC, pp29–32, http://www.doh.gov.uk). These requirements include estimates of the incremental costs and utility (quality-adjusted life-years) gains attributable to the treatment compared to an appropriate comparator therapy, taking a lifetime perspective and using these estimates to compute an incremental cost-utility ratio. NICE also requires estimates of the impact of the treatment on the NHS as a whole, which includes estimates of the impact of the new treatment on total NHS budgets and NHS resources such as manpower.

The NICE discussion paper gives some guidelines as to how the cost utility estimates should be developed and presented [1, Annex C, pp30–32]. These guidelines stress that estimates of the impact of the treatment on different patient subgroups should be presented, as well as the impact on the total population with the condition of interest. The guidelines also request that estimates of the timing of the costs and benefits be presented. The impact of the treatment on drug costs, other health care costs, and social service costs should be presented separately as well as in total. The methods used to derive the costs and benefits should be transparent and adhere to current standards for these analyses.

The guidelines for the aggregate cost impact analysis [1, Annex C, p32] require that an estimate be made of the size of the population eligible for the new treatment. Estimates should be made of the total increase or decrease in costs to the

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NHS if the whole eligible population were to adopt the new treatment (assuming a 100% market penetration). A time profile of these costs and a sensitivity analysis based on the proportion of eligible population receiving the treatments should also be presented.

These guidelines raise questions about whether current methods that have been used for cost-effectiveness analyses can provide the information that NICE requires for making its decisions. There are two issues here: first, whether the methods used provide the estimates in the format required, and second, whether the data available are sufficient to produce such estimates.

Currently, cost-effectiveness analyses are produced using an incidence-based approach [2,3] where the incremental costs and effectiveness for a new treatment are estimated for a single cohort of individuals with the condition of interest. For a chronic illness, these estimates need to span the person's remaining lifetime and take into account lifetime treatment patterns. Less often, estimates are obtained for the costs and effectiveness of a new treatment that take a prevalence-based perspective [3–5]. In this perspective, outcomes of the disease with current treatments are estimated for a representative prevalence population and the impacts of the new treatment are estimated as the impact on annual population (e.g., NHS) costs and health outcomes in Year 1, Year 2, and so on after introduction of the new treatment. The prevalence population is dynamic over time, with new patients acquiring the disease and others either being cured or dying from the disease or from other causes. To provide NICE with the full economic evaluation that it requires, both incidence-based and prevalence-based economic evaluations should be completed.

In this article, I demonstrate how to use a Markov modeling approach to generate both incidence-based and prevalence-based estimates of the costs and effectiveness of a hypothetical new treatment for human immunodeficiency virus (HIV). These estimates, derived using a Markov model, would fulfill the information needs for NICE. In the discussion, the feasibility of the data requirements for the comprehensive estimates required by NICE is reviewed.

Methods

Overview

A set of hypothetical treatment and cost assumptions for HIV infection is made to illustrate the use of a Markov model to estimate outcomes that fulfill the NICE requirements. Markov modeling is commonly used in economic evaluation of new therapies for chronic illness where discrete disease stages can be identified and estimates of the rate of progression between these stages can be estimated from the epidemiology and clinical trial literature. This type of modeling has frequently been used in cost-effectiveness studies for new HIV treatments [6–8].

The hypothetical model used in this article is similar to that used in Mauskopf et al. [7] and defines disease states in HIV infection as ranges in the number of CD4 cells in the circulating blood. There are five ranges of CD4 cells used in the analysis, $<100/mm^3$, $100–200/mm^3$, $200–350/mm^3$, $350–500/mm^3$, and $>500/mm^3$. Utility weights for each disease state were taken from Holtgrave and Pinkerton [9] based on their review of empirical studies. The cycle period for the model is 1 year and transitions are assumed to occur only between adjacent states (see Fig. 1). Utility weights, annual treatment costs for the United Kingdom (only those likely to change with the new treatment need be included), incidence rates of opportunistic diseases, and hospital days for each CD4 cell count range are taken from published estimates (see Table 1), which are described below. A discount rate of 3% is used.

Transition Probabilities

Transition probabilities between adjacent states (probability of moving to the next most severe disease state) for patients receiving no antiretroviral therapy (ART) were estimated using data from Hellinger [10] who presented estimates of the average time spent in each CD4 cell range. The transition probability was computed as the reciprocal of these times.

Annual Treatment Costs

Annual treatment costs and community costs in each disease state for the United Kingdom (UK) were estimated using data from the Chancellor et al. [6] study and inflated to 1999 GBP (Great Britain pounds) using the UK Hospital and Community Health Service price index. The treatment costs include the hospital inpatient and outpatient costs for treating a patient exclusive of the costs of ART. These include the costs of treating the opportunistic diseases (ODs) that occur at each CD4 cell range as well as for general disease monitoring. The costs of treating ODs change over time and so these costs are illustrative only. The impact of combination therapy on the incidence of ODs is captured in the shift to higher CD4 cell count ranges. The community costs include the costs of social services as well as general practitioner services.

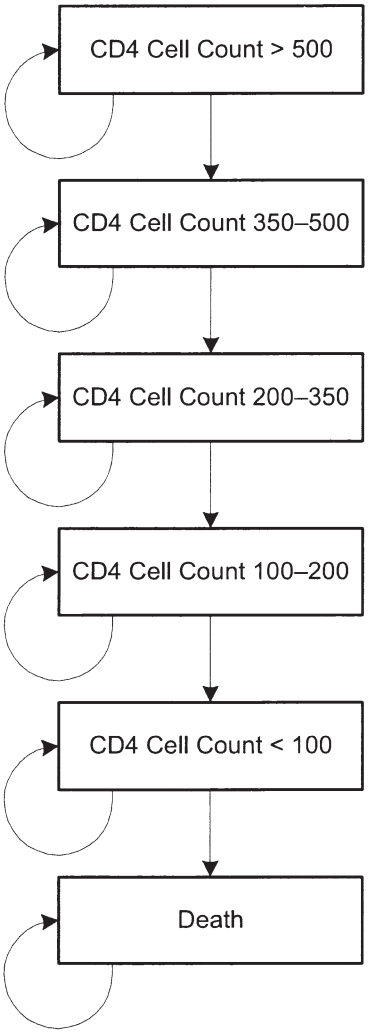

Figure 1 State transition diagram for Markov model (HIV infection).

Annual Incidence of Opportunistic Infections

Estimates of the annual incidence of cytomegalovirus (CMV) disease at each CD4 cell level were included in the Markov model. These estimates were based on the incidence rates for those with CD4 cell counts of <100 from Bacellar et al. [11] and modified to span all CD4 cell count ranges using data from Simpson et al. [12]. CMV incidence was used in the model to illustrate how the model can be used to estimate the annual number of cases of the opportunistic diseases.

Annual Number of Hospital Days

The annual number of days in the hospital was estimated for each CD4 cell range using 1993 data from Beck et al. [13] and adjusting it to match the disease states defined in Chancellor et al. [6] using the method shown in Table 3 in the Chancellor article. The impact of the new drug on hospital days was estimated to illustrate how the Markov model estimates the impact of the new drug on NHS resources. Use of hospital inpatient care rather than hospital outpatient care may change over time and so these estimates are illustrative only.

Assumptions about Lifetime Treatment Patterns

NICE requires cost-effectiveness analyses for chronic diseases to be performed for the person's remaining lifetime. They also require estimates of the budget impact of the new therapy to be made for different time periods after the introduction of the new drug. To produce such estimates using a Markov model, information is required about the current lifetime treatment patterns and health outcomes for the chronic disease as well as how the treatment patterns and outcomes will be impacted by a new drug. In the case of the hypothetical new HIV drug, the analysis assumes that it will be used in combination with existing therapies and will result in an increased life expectancy. The assumptions are discussed in more detail below.

In the base case, lifetime treatment for HIV infection is assumed to consist of sequential treatments with different double or triple combination therapies. Specifically, the patient starts with treatment with a double combination therapy at 11.50 GBP per day (daily prices for zidovudine and lamivudine from Duncan [14]) for 1 year, and then continues with several different regimens of triple combination therapy for 4 years. The triple combination therapies are each assumed to cost 18.75 GBP per day (daily prices for zidovudine, lamivudine, and indinavir from Duncan [14]). Several different combinations are necessary because not all patients respond to any given combination and, over time, each combination loses its effectiveness in those who initially responded. Effective treatment is assumed to result in an initial increase in CD4 cell count, moving the patient into the next higher CD4 cell count range and followed by no decline in CD4 cell count for the effective time period. The total time period with effective treatment is assumed to be 3 years in the hypothetical base case, after which transitions to the lower CD4 cell count ranges occur at the no-ART transition rates despite a further 2 years of combination therapy.

With the introduction of the new drug, the total time period on combination therapy is assumed to increase from 5 to 6 years. The cost per day is assumed to be 11.50 GBP per day with double combination therapy for 1 year, 21.00 GBP per day

Table 1 Input assumptions for the HIV Markov model

	CD4 cell count range				
Input data	>500	350–500	200–349	100–199	<100
Average time in disease state (no ART) (years)*	2 (after diagnosis)	1.8	1.8	1.5	1.3
Transition probability to next worse disease state (no ART)†	0.5	0.5556	0.5556	0.6667	0.7692
Annual hospital inpatient and outpatient costs (no ART)‡ (GBP)	1,834	1,834	1,834	1,912	7,490
Annual community services costs (no ART)‡ (GBP)	1,137	1,137	1,137	1,378	2,230
Utility weight§					
No ART	0.91	0.76	0.76	0.65	0.62
Combination therapy	0.82	0.76	0.76	0.65	0.62
Annual CMV incidence‖	0.0024	0.0024	0.0024	0.0750	0.2550
Annual hospital days¶	1.13	1.13	1.13	2.87	29.9

*Reference [10]. †Transition probability is equal to (1/time in state). ‡Reference [6] (1995 GBP inflated to 1999 GBP using the hospital and community health services price index). §Reference [9]. ‖References [11,12]. ¶References [6,13].
ART, antiretroviral therapy; CMV, cytomegalovirus; GBP, Great Britain pounds.

for triple combination therapy with the new drug for 2 years, and 18.75 GBP per day with current triple combination therapies for 3 years. The total time period with effective treatment with the addition of the new drug is assumed to be 4 years, after which transitions to the lower CD4 cell count ranges occur at the no-ART rate.

Use of the Markov Model to Generate NICE Estimates

The incidence-based economic evaluation starts the Markov model with two cohorts of 1000 patients who either start therapy in a mix of different CD4 cell count ranges or who all start therapy in a single CD4 cell count range. The cohort with the new drug is started on a double combination, followed by a triple combination therapy including the new drug, followed by further triple combinations as described above. The base case cohort is started on double combination, followed by currently available triple combinations. The patients are followed for their remaining lifetime and incremental lifetime costs, quality-adjusted life-years gained, and incremental costs per quality-adjusted life-year gained are computed attributable to the new drug. Both costs and life-years are discounted at 3%.

The prevalence-based economic evaluation starts the Markov model with a cohort of 10,680 patients, the estimated number of patients alive with diagnosed HIV infection in the United Kingdom in 1994 [15], before the use of combination therapy. These patients are distributed across the different CD4 cell count ranges in the proportion that would be expected in the prevalent population based on disease natural history [16]. Each year a cohort of newly diagnosed patients is added to the existing patients. The size of the newly diagnosed cohort is assumed to be equal to 1,258, the estimated annual number of people newly diagnosed with HIV infection in the United Kingdom [15]. Patients only leave the diagnosed population when they die. The Markov model is used to track the HIV population over the next 20 years with or without the new drug. For each year after the introduction of the new drug, the model computes annual NHS costs, number of persons alive with HIV infection in the population, quality-adjusted life-years experienced by the diagnosed population, annual cases of CMV (as one example of an opportunistic infection), and annual number of hospital days for the diagnosed population. The outcomes estimates presented in this article for Years 1, 3, and 6, are not discounted to Year 0, but discounted estimates could easily be computed using the Markov model.

Results

The results of the incidence-based analysis are shown in Table 2. The lifetime costs, quality-adjusted life-years, and the incremental cost per quality-adjusted life-year gained are estimated for the prevalent population (an initial cohort distributed across all "CD4 ranges") assuming that the new drug is started in the first year for all patients no matter what their current CD4 cell count. The same estimates are also presented for different population subgroups, assuming that ART is started at different CD4 cell ranges. In addition, the lifetime antiretroviral drug costs, hospital inpatient and outpatient care costs, and community services costs are shown for the initial cohort. The incremental cost per quality-adjusted life-year gained is 17,541 GBP for the hypothetical new drug for the initial cohort. In a footnote to Table 2, the lifetime costs and quality-adjusted life-years for the initial cohort without ART are shown for reference.

Table 2 Cost utility estimates

Patient population (CD4 cell count range)	Lifetime costs (GBP)	Quality-adjusted life-years remaining	Incremental cost/QALY (GBP)
Initial cohort*			17,541
Combination, current		5.26	
Total	58,476		
ART	28,539		
Hospital	19,787		
Community	10,150		
Combination, new		5.79	
Total	67,801		
ART	35,803		
Hospital	21,003		
Community	10,995		
CD4 < 100			17,892
Combination, current	50,257	3.15	
Combination, new	60,083	3.69	
CD4 200–349			17,030
Combination, current	58,681	5.31	
Combination, new	67,952	5.85	
CD4 350–500			17,830
Combination, current	62,594	6.37	
Combination, new	71,751	6.88	

*Assumed initial cohort distribution with current combination therapy is 45.2% CD4 > 500; 21.4% CD4 350–500; 17.9% CD4 200–349; 15.5% CD4 100–199; and 0% CD4 < 100. Lifetime costs for initial cohort with no ART is 23,378 GBP and quality-adjusted life-years remaining is 3.57.
ART, antiretroviral therapy; GBP, Great Britain pounds; QALY, quality-adjusted life-years.

Table 3 Aggregate impact of hypothetical new drug on UK population diagnosed as HIV positive*

Annual outcomes	Year 1	Year 3	Year 6
Cost (GBP)			
Combination, current ($\times 10^6$)	66.9	113.6	78.7
Combination, new ($\times 10^6$)	66.9	123.4	151.6
Persons			
Combination, current	11,938	14,454	16,868
Combination, new	11,938	14,454	17,804
Cost/person (GBP)			
Combination, current	6,260	8,610	4,845
Combination, new	6,260	9,353	8,829
QALYs			
Combination, current	8,439	10,250	11,814
Combination, new	8,439	10,250	12,535
CMV cases			
Combination, current	149	155	562
Combination, new	149	155	502
Hospital days			
Combination, current	16,200	19,000	63,759
Combination, new	16,200	19,000	60,665

*Assumed initial population distribution with current combination therapy is 45.2% CD4 > 500; 21.4% CD4 350–500; 17.9% CD4 200–349; 15.5% CD4 100–199; and 0% CD4 < 100. Annual outcomes for prevalent population with no ART are total cost 29.1 million GBP, 10,680 persons, 2,725 GBP/person, 7,357 QALYs, 581 CMV cases, and 62,775 hospital days.
ART, antiretroviral therapy; CMV, cytomegalovirus; GBP, Great Britain pounds; QALYs, quality-adjusted life-years.

The results of the prevalence-based analysis are shown in Table 3 for Years 1, 3, and 6 after the introduction of the new drug. The annual hospital (inpatient and outpatient) costs for the population with diagnosed HIV infection are shown with and without the new drug. The difference is small until Year 6, when the effect of the prolonged life expectancy with the new drug impacts the costs. In addition, estimates are shown, for each year, of the number of people with diagnosed HIV infection, the quality-adjusted life-years experienced in the year by those with diagnosed HIV infection, the number of CMV cases, and the number of hospital days with and without the new drug. With the additional treatment regimen, the total number of people alive in any year increases over time after Year 5. CMV cases and hospital days are also lower in Year 6 with the new treatment compared to the current treatment. In a footnote to Table 3, the annual costs and other outcomes for the prevalent population without ART are shown for reference.

Discussion

The Markov model estimates for a hypothetical new drug for HIV infection show that a new drug that increases time on combination therapy and life expectancy has an incremental cost-effectiveness ratio of less than 20,000 GBP. However, the results of the cost-effectiveness analysis are sensitive to the assumptions made about how long the person continues to take ART after it is no longer effective. The additional NHS costs with the new therapy will be quite small in the first 5 years after its introduction. In the sixth year the incremental costs will be large because of the assumed extra year on combination therapy with the new drug. After that there will be a continuing but smaller impact on NHS budgets because of the increased size of the prevalent population.

The results of the analysis show that a Markov model can easily be adjusted to compute both incidence-based and prevalence-based economic evaluations. These two types of evaluations are necessary if the NICE requirements for both cost-utility analyses and aggregate estimates of the impact on the NHS costs and resources are to be met. The Markov model allows for dynamic estimates that show how the aggregate impacts are likely to vary over time for the first few years after the introduction of new treatments for chronic diseases.

The model assumed 100% market penetration for the new drug in the first year for all eligible patients as required by NICE. However, not all eligible patients might be treated the first year or even in any subsequent year. A sensitivity analysis in which the size of the treated population is varied

is requested by NICE. In the HIV model, to do such a sensitivity analysis, the proportion of the population treated could be assumed to be equal across all CD4 cell ranges in our example, or treatment could be targeted to different CD4 cell ranges in the early years of availability. Thus, the prevalence-based Markov model can readily be adjusted to allow for staged uptake of the new drug and would demonstrate the timing of the associated outcomes at the population level.

Data requirements are a possible problem in several areas when performing an economic evaluation using a Markov model for a chronic illness at the time that the NICE appraisal takes place. First, to compute cost-effectiveness ratios across the remaining lifetime of the patient may be difficult with the available data. Information from clinical trials is generally only available for a 6-month to 1-year follow-up period at the time a new treatment is approved for a chronic illness. Thus, there is no clinical trial and frequently no observational data about the duration of treatment or long-term effectiveness of the new treatment. Extrapolations must be made and the results of the analysis can be very sensitive to these extrapolations. In addition, how a new drug will impact lifetime treatment patterns with existing drugs for a patient with a chronic disease is not known at the time that a new drug is approved. This certainly is true for HIV infection as well as for Parkinson's disease where newer drugs can be used in different sequences and combinations with current drugs [17].

Second, the clinical trial data may not include sufficient information to compute cost-effectiveness ratios for different population subgroups as required by NICE. For example, in the zanamivir submission, NICE stated that there were not sufficient clinical trial data on the high-risk group (those with chronic conditions or those over 65 years of age) to estimate the cost effectiveness of zanamivir in that subpopulation (http://www.nice.org.uk).

Third, cost impacts of the new drug that are estimated using protocol-driven resource use data from clinical trials might not reflect the resource use and costs experienced in natural practice. In addition, costs while first using the new treatment might be higher than those experienced once physicians become more familiar with its attributes.

Fourth, in order to compute the aggregate impacts of a new treatment, the number of patients in the population at different levels of disease severity must be known, as well as the rate at which patients enter and leave the prevalent population for each treatment used in the analysis. Assumptions must also be made about the effectiveness of the new drug in the natural population as compared to its efficacy in the clinical trial population. Finally, data must be collected on the impact of the new treatment on treatment patterns for the diseased population—for example, additional physician visits for influenza.

Although this article has focused on the use of a Markov modeling approach for generating economic estimates that fulfill the NICE requirements, the data issues raised apply to any other type of modeling technique used to generate the estimates. Markov models are quite restrictive for modeling complex diseases with complex treatment patterns and health outcomes. For example, for HIV infection, if viral load as well as CD4 cell count are included as markers of disease severity, then the required number of states and estimates of transition probabilities become quite large. Also, the requirement that transitions be independent of history is also a problem for modeling chronic diseases. Monte Carlo simulation is a good substitute modeling technique in these cases and can be used to generate both incidence-based and prevalence-based estimates.

This article has shown that NICE submissions can be prepared using standard economic evaluation techniques such as Markov models, if they are used to produce both incidence-based and prevalence-based estimates. Such analyses can compute cost-effectiveness and aggregate impacts by population subgroups and can estimate the timing of the aggregate impacts. The main problem likely to be experienced in satisfying the NICE requirements is a lack of experimental data to give the level of detail that is desired. Extrapolation from the trial data is likely to be needed as well as estimates from other data sources. Inevitably, some of the estimates will have a stronger data foundation than others.

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References

1 National Health Service Executive. Faster access to modern treatment: how NICE appraisal will work: a discussion paper. Leeds, UK: National Health Service Executive, 1999.
2 Gold M, Siegel J, Russell L, Weinstein M, eds.

Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.
3 Mauskopf J. Prevalence based economic evaluation. Value Health 1998;1:251–9.
4 Weinstein M, Coxson P, Williams L, et al. Forecasting coronary heart disease incidence, mortality, and cost: the coronary heart disease policy model. Am J Public Health 1987;77:1417–26.
5 Caro JJ, Huybrechts KF. Stroke treatment economic model (STEM): predicting long-term costs from functional status. Stroke 1999;30:2574–9.
6 Chancellor J, Hill A, Sabin C, et al. Modeling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. Pharmacoeconomics 1997;12:54–66.
7 Mauskopf J, Lacey L, Kempel A, et al. The cost-effectiveness of treatment with lamivudine and zidovudine compared to zidovudine alone: a comparison of Markov model and trial data estimates. Am J Manag Care 1998;4:1004–12.
8 Moore R, Bartlett J. Combination antiretroviral therapy in HIV infection: an economic perspective. Pharmacoeconomics 1996;10:109–13.
9 Holtgrave D, Pinkerton S. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. J Acquir Immune Defic Syndr Hum Retrovirol 1997;16:54–62.
10 Hellinger F. The lifetime cost of treating a person with HIV. JAMA 1993;270:474–8.
11 Bacellar H, Munoz A, Hoover D, et al. Incidence of clinical AIDS conditions in a cohort of homosexual men with CD4+ cell counts, 100/mm^3. J Infect Dis 1994;170:1284–7.
12 Simpson K, Hatziandreu E, Andersson F, et al. Cost-effectiveness of antiviral treatment with zalcitabine plus zidovudine for AIDS patients with CD4+ cell counts less than 300/ul in 5 European countries. Pharmacoeconomics 1994;6:553–62.
13 Beck EJ, Kennelly J, McKevitt C, et al. Changing use of hospital services and costs at a London AIDS referral centre, 1983–1989. AIDS 1994;8:367–77.
14 Duncan C, ed. Monthly Index of Medical Specialties. London: Haymarket Publishing Services Ltd., 2000.
15 CDR Review. The incidence and prevalence of AIDS and prevalence of other severe HIV disease in England and Wales for 1995 to 1999: projections using data to the end of 1994. Communicable Disease Report 1996;6(Review 1):R1–21.
16 Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997;126:946–54.
17 Philips P. Several classes of new drugs emerging for Parkinson's disease. JAMA 1999;282:929–31.