ORIGINAL RESEARCH ARTICLE

Pharmacoeconomics 2000 Oct; 18 (4): 355-368
1170-7690/00/0010-0355/$20.00/0

Cost Effectiveness of Human Immunodeficiency Virus Postexposure Prophylaxis for Healthcare Workers

Dewey C. Scheid, Robert M. Hamm and *Kevin W. Stevens*

Clinical Decision Making Program, Department of Family and Preventive Medicine, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

Abstract

Objective: The United States Public Health Service (USPHS) published recommendations for human immunodeficiency virus (HIV) postexposure prophylaxis (PEP) of healthcare workers in May 1998. The aim of this study was to analyse the cost effectiveness of the USPHS PEP guidelines.

Design and setting: This was a modelling study in the setting of the US healthcare system in 1998. The analysis was performed from the societal perspective; however, only HIV healthcare costs were considered and health-related losses of productivity were not included.

Methods: A decision tree incorporating a Markov model was created for 4 PEP strategies: the current USPHS recommendations, triple drug therapy, zidovudine monotherapy or no prophylaxis. A probabilistic sensitivity analysis using a Monte Carlo simulation was performed. Confidence intervals (CIs) around cost-effectiveness estimates were estimated by a bootstrapping method.

Results: The costs (in 1997 US dollars) per quality-adjusted life-year (QALY) saved by each strategy were as follows: monotherapy $US688 (95% CI: $US624 to $US750); USPHS recommendations $US5211 (95% CI: $US5126 to $US5293); and triple drug therapy $US8827 (95% CI: $US8715 to $US8940). The marginal cost per year of life saved was: USPHS recommendations $US81 987 (95% CI: $US80 437 to $US83 689); triple drug therapy $US970 451 (95% CI: $US924 786 to $US1 014 429). Sensitivity testing showed that estimates of the probability of seroconversion for each category of exposure were most influential, but did not change the order of strategies in the baseline analysis. With the prolonged HIV stage durations and increased costs associated with recent innovations in HIV therapy, the marginal cost effectiveness of the USPHS PEP strategy was decreased to $US62 497/QALY saved. All 3 intervention strategies were cost effective compared with no postexposure prophylaxis.

Conclusions: Current USPHS PEP recommendations are marginally cost effective compared with monotherapy, but the additional efficacy of triple drug therapy for all risk categories is rewarded by only a small reduction in HIV infections at great expense. For the foreseeable future, assuming innovations in therapy that employ expensive drug combinations earlier in the HIV disease course to extend life expectancy and the increasing prevalence of HIV drug resistance, our model supports the use of the USPHS PEP guidelines.

It has been estimated that hospital-based healthcare workers experience at least 500 000 percutaneous blood exposures annually in the US alone.[1] Approximately 5000 of these exposures involve blood that is infected with human immunodeficiency virus (HIV). Although the average risk of transmission after percutaneous exposure has been estimated to be 0.3%, the risk is thought to be much higher with higher blood volume and viral load.

A United States Public Health Service (USPHS) interagency working group updated the previous USPHS statement on management of occupational exposure to HIV and recommendations for postexposure prophylaxis (PEP) in June 1996, prompted by the rapid accumulation of information suggesting the benefits of zidovudine prophylaxis, the potency of combinations of antiretroviral drugs, and the ability to stratify risk by type of exposure.[2] These provisional recommendations included a basic regimen of zidovudine prophylaxis and a double drug therapy for the highest risk group. All previous recommendations were again updated and consolidated in May 1998.[3] The latest USPHS PEP recommendations include a basic 4-week antiretroviral prophylaxis regimen using 2 drugs and an expanded regimen that includes the addition of a protease inhibitor, using an algorithm that varies the recommendations according to risk of transmission by type of exposure and the HIV status of the source.

Although PEP with zidovudine has been widely used after healthcare worker exposure to reduce the risk of transmission,[4-6] the only randomised controlled trial of postexposure zidovudine was terminated because an insufficient number of exposed workers were recruited.[7] The use of postexposure zidovudine is supported by an international case-control study of HIV seroconversion in healthcare workers after percutaneous exposure, in which use of zidovudine was associated with a 79% risk reduction.[8] Further evidence of benefit is based on a prospective trial of zidovudine administered to HIV-infected pregnant women that demonstrated a 67% reduction of perinatal HIV transmission.[9]

The cost effectiveness of the current USPHS guidelines for PEP has never been established. There have been 2 previous economic analyses of zidovudine chemoprophylaxis.[10,11] Assuming 75% efficacy of zidovudine and using both a societal and third-party payer perspective, Ramsey and Nettleman[10] reported a cost per life-year gained of $US3184 and $US15 788, respectively. The lower cost per year of life gained in the societal perspective was due to the conservation of healthcare worker productivity. Allen et al.,[11] in an analysis using a societal perspective and assuming 75% efficacy of zidovudine, determined that prophylaxis yielded a net saving of $US6 244 000 per case prevented. There has been 1 published cost-effectiveness analysis of triple drug PEP by Pinkerton et al.[12] This analysis found that triple drug therapy was favourable at $US37 148 per year of quality-adjusted life saved, assuming a 79% treatment efficacy and a seroconversion rate of 0.32%.

In the absence of a randomised controlled trial that compares different PEP regimens, we attempted to answer the question of what is the most cost-effective strategy for healthcare workers exposed to HIV with a cost-effectiveness analysis of USPHS PEP recommendations and 3 other PEP alternatives: no therapy, monotherapy with zidovudine and triple drug therapy.

Methods

Decision Analytic Model

A decision tree incorporating a Markov model was developed to compare 4 different PEP strategies for exposures in which the HIV status of the source was known:

- current USPHS recommendations
- triple therapy with zidovudine, lamivudine and indinavir for all exposures
- monotherapy with zidovudine for all exposures
- no PEP.

The model was adapted from a previous model of the 1996 provisional USPHS PEP guidelines.[13] The analysis was performed from the societal perspective, i.e. all costs and all health benefits were accounted for regardless of who incurred them.[14] However, only HIV healthcare costs were consid-

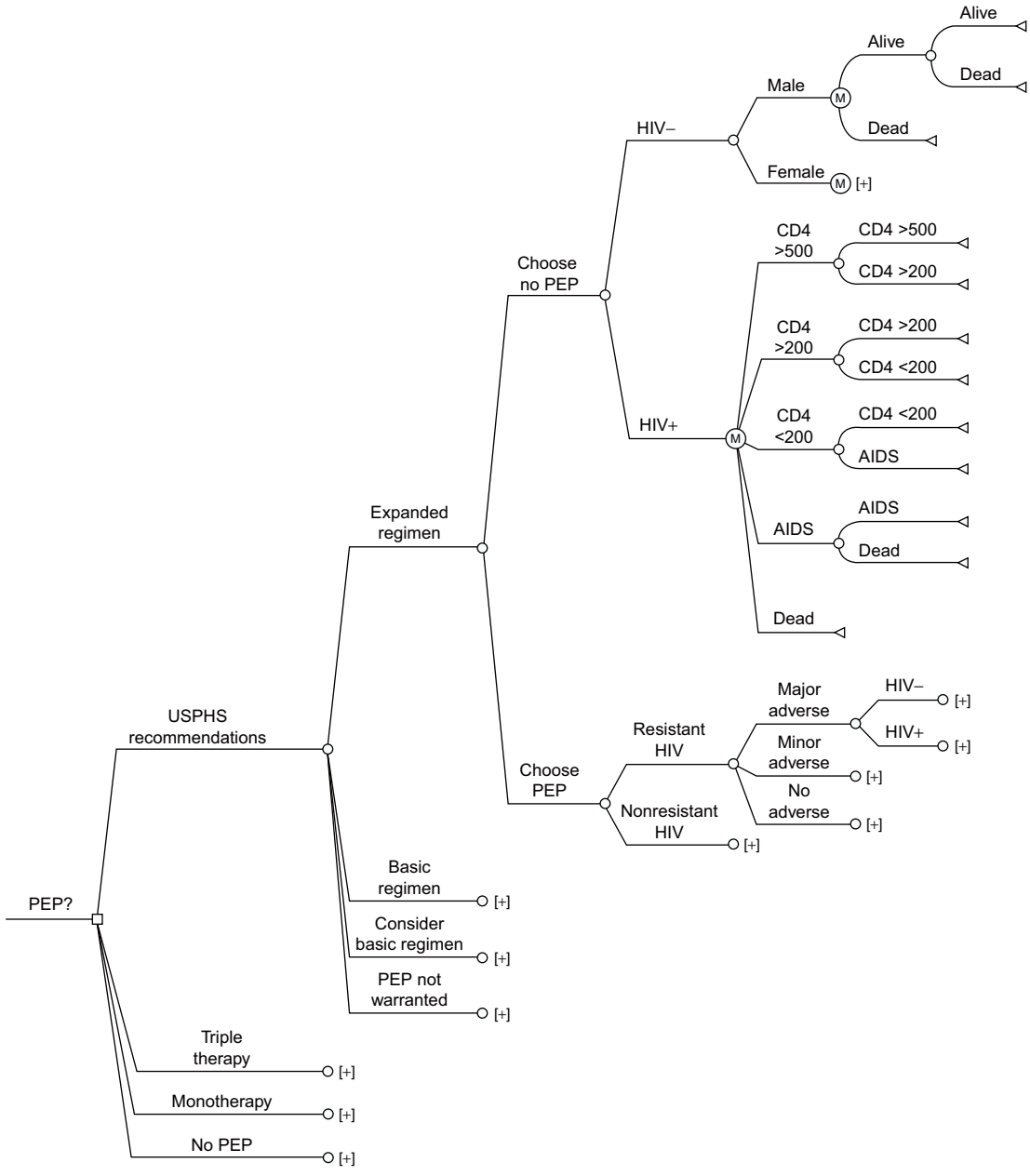

Fig. 1. Decision tree for HIV postexposure prophylaxis. [+] indicates truncated tree branches with identical subtrees, for example female [+] = male. Nodes labelled with M begin Markov subtrees. **CD4** = CD4+ count (cells/μl); **HIV–** HIV-negative; **HIV+** = HIV-positive; **PEP** = postexposure prophylaxis; **USPHS** = US Public Health Service.

ered and health-related losses of productivity were not included. The cost effectiveness with respect to 3 outcomes was evaluated: HIV infections, years of life saved and quality-adjusted life-years (QALYs). Monetary values are reported in 1997 US dollars. Years of life, QALYs and cost outcomes were discounted at 0, 3 and 5% for all strategies. Sensitivity analyses were performed to determine the robustness of the model.

A commercially available software product (DATA™ 3.0; TreeAge Software, Inc., Williamstown, MA, USA) was used to generate the model and analyse cost effectiveness. A partially expanded decision tree is presented in figure 1. Summaries of model input parameters, including baseline estimates, ranges and references, are included in tables I and II.

Exposure Categories

USPHS PEP guidelines were used to determine 4 categories of exposure and corresponding recommended PEP regimens:[3]

- expanded
- basic
- consider basic
- not warranted.

The USPHS PEP guidelines classify exposures according to the type of exposure (exposure code; EC) and HIV status of the exposure source (HIV status code; HIV SC). For instance, the most severe exposure code (EC3) includes exposures that are percutaneous and involve a hollow needle or visible blood on the device. We used a source with terminal AIDS as a surrogate for higher titre HIV status (HIV SC2). The expanded regimen is recommended for increased risk exposures, i.e. either the most severe exposure (EC3) regardless of HIV status code or less severe exposure combined with higher titre HIV status (EC2 and HIV SC2). The basic regimen is recommended for no increased risk exposures, i.e. less severe percutaneous exposure or large volume mucous membrane or skin exposure with lower titre HIV status (EC2 and HIV SC1). The basic regimen should be considered for negligible risk exposures, i.e. small volume mucous membrane or skin exposure with higher titre HIV status (EC1 and HIV SC2). PEP is not warranted with no known risk exposures, i.e. small volume mucous membrane or skin exposure with lower titre HIV status (EC1 and HIV SC1).

The probability of an exposure falling into one of these classification categories was estimated using data reported from large surveillance studies.[6,7,15,16] For example, we modelled the probability of EC3 by combining the independent probabilities of percutaneous exposure, penetrating exposure and visible blood on the device, such that:

$$EC3 = 0.661 \times 0.800 \times 0.309 = 0.164$$

(see table I for other probabilities and calculations). The exposure classification groups were then combined, as above, to determine the probability of an exposure for each of the USPHS PEP risk categories.

Transmission Probabilities

We could find no published data that reported the probability of transmission for groups similar to the USPHS exposure categories. Based on the calculated probability of falling into each of the exposure classification categories and the relative odds of seroconversion after exposures with specific risk factors reported in an international case control study, we estimated the probability of transmission for each of the classification categories.[17] Risks associated with exposure categories and the HIV status of the exposure source were combined to determine the risk of transmission for the 4 USPHS PEP risk categories. There is evidence to suggest that exposure risk and the risk associated with the HIV status of the source operate independently and hence the odds ratios are multiplicative.[1]

The reduction of HIV transmission following PEP with zidovudine was 79%.[8] Because there are no studies of the efficacy of multidrug PEP, the baseline efficacy of PEP therapy was assumed to be 90% for 3-drug therapy, i.e.:

$$\text{efficacy of triple therapy} = \text{efficacy of monotherapy} + dt \times (1 - \text{efficacy of monotherapy})$$

Table I. Summary of exposure, transmission and treatment parameters

Parameter	Baseline estimate	Range for sensitivity analysis	Reference or derivation
Demographic variables			
mean age of exposed healthcare workers (y)	33.5	18-65	5,6,15,16
female healthcare workers (%)	78.0	75.1-80.5	5,6,15,16
Exposure characteristics (%)			
percutaneous exposure (A)	66.1	63.7-68.4	5,6,15,16
penetrating exposure (B)	80.0	76.6-83.1	5,6,15,16
blood visible on device (C)	30.9	27.5-34.5	5,6,15,16
mucocutaneous, large volume (D)	11.7	7.2-17.8	5,6,15,16
source patient with terminal AIDS (E)	18.3	14.6-22.7	8
Exposure classification[a] (%)			
EC3 (more severe percutaneous)	16.4		Calculated as $A \times B \times C$
EC2P (less severe percutaneous)	49.7		Calculated as $A \times (1 - B \times C)$
EC2M (large volume mucocutaneous)	4.0		Calculated as $(1 - A) \times D$
EC1 (small volume mucocutaneous)	29.9		Calculated as $(1 - A) \times (1 - D)$
SC1 (lower titre exposure)	81.7		Calculated as 1 - E
SC2 (higher titre exposure)	18.3		Calculated as E
Relative odds of exposure classifications			
SC2 *vs* SC1	5.6	2.0-16	17
EC3 *vs* EC2P	6.2	2.2-21	17
EC2M *vs* EC1	6.2	2.2-21	Assumption
Transmission estimates (%)			
percutaneous exposure	0.32	0.12-0.47	18
mucocutaneous exposure	0.026	0.006-0.09	1,16
expanded regimen eligible[a]	0.72		Calculated[b]
basic regimen eligible[a]	0.08		Calculated[b]
consider basic regimen[a]	0.05		Calculated[b]
no regimen recommended[a]	0.009		Calculated[b]
Efficacy of therapy (% seroconversion)			
monotherapy	21	6-57	8
double therapy	15.5	3-57	Calculated[c]
triple therapy	10	1-57	Calculated[c]
Acceptance of therapy by regimen (%)			
expanded regimen[a]	76	58-86	6,7,19
basic regimen[a]	76	58-86	4,7,19
consider basic regimen[a]	21	14-31.1	4,7,19
Completion of therapy (%)	69	62.7-74.8	4,7,19,20
Partial completion (days)	8	3-28	4,7,19,20
Zidovudine resistance rate (%)	17.5		21-24
Major adverse effects (%)	0.001	0.0001-0.01	4,6,10,19,20

a From Public Health Service PEP guidelines.[3]

b Calculated using relative odds, exposure probability and transmission estimates for percutaneous or mucocutaneous exposure.

c Efficacy of triple therapy = efficacy of monotherapy + dt × (1 – efficacy of monotherapy), where dt = 0.5, range 0 to 1. Efficacy of double therapy = efficacy of monotherapy + dd × (efficacy of triple therapy – efficacy of monotherapy), where dd = 0.5, range 0 to 1.

dd = multiplier for improved double drug efficacy; **dt** = multiplier for improved triple drug efficacy; **EC** = exposure code; **PEP** = postexposure prophylaxis; **SC** = HIV status code.

where dt, the multiplier for improved triple drug efficacy, was set at 0.5, and 84% for 2-drug therapy, i.e.:

efficacy of double therapy = efficacy of monotherapy + dd × (efficacy of triple therapy – efficacy of monotherapy)

where dd, the multiplier for improved double drug efficacy, was set at 0.5.

Treatment Efficacy

Previous studies have shown a differential rate of acceptance and completion of PEP.[6,7,19] In our baseline analysis, 76% of healthcare workers with either an exposure classified as increased risk or no increased risk accepted PEP, whereas 21% of healthcare workers with a negligible risk exposure chose PEP. Although serious short term toxicity does not appear to be a major concern, up to 31% of healthcare workers do not complete PEP because of adverse effects.[6,7,19,20] For the healthcare workers who partially completed therapy, the efficacy of PEP was decreased as a function of the proportion of the therapeutic regimen they did not complete. This was modelled by multiplying the PEP efficacy by a logarithmic function, adjusted to vary from 0 to 1 as the days of therapy ranged from 0 to 28 using the formula log (10 × days/28), with zero effect if taken less than 3 days. For example, if a healthcare worker took the drugs for 8 days (the mean duration for those who did not complete the regimen[4,7,19,20]), the efficacy of PEP was 46% compared with 79% for monotherapy for those who completed the regimen.

The prevalence of zidovudine resistance is increasing.[21-23] Failures of zidovudine prophylaxis associated with zidovudine resistance have been reported.[24] The model accounted for encountering zidovudine resistance from the HIV exposure source: if the source had zidovudine resistance, the number of antiretroviral drugs would be increased by 1 (i.e. double therapy instead of monotherapy) without increasing the efficacy.

Costs

The cost of each PEP strategy was based on costs of postexposure counselling, costs of PEP, average healthcare costs of HIV-seropositive adults and the average healthcare costs of all adults. The cost of postexposure counselling included the cost of periodic office visits and HIV testing according to the recommended schedule. The cost of PEP included the average wholesale costs of antiviral drugs, periodic office visits, and toxicity monitoring as outlined in a current multicentre clinical trial of PEP.[18,25] Information regarding the toxicity of antiretroviral drugs for PEP is available only for zidovudine.[7,8,26] With the use of multidrug PEP, the potential for toxicity, subsequent need for monitoring and associated costs are substantially increased.[3] The probabilities and the costs of major adverse effects were included in the model. A summary of all PEP cost estimates is included in table II.

For healthcare workers who became HIV positive, we estimated direct HIV healthcare costs and life expectancy by using a staged Markov model[37,38] with 5 states:

- HIV stage with CD4+ cell count >500/μl
- HIV stage with CD4+ cell count >200/μl
- HIV stage with CD4+ cell count <200/μl
- AIDS
- death.

A summary of the cost of HIV healthcare by stage obtained from 3 previously published cost studies is included in table II.[29-31]

Life Expectancies

We obtained estimates of the durations of each HIV stage from the same cost studies.[29-31] The Markov model was simplified by allowing transition only through a progression of HIV stages to death. We used quality-of-life adjustments for HIV disease based on a survey of healthcare workers using a time trade-off method.[34] The median quality adjustments for the relevant states reported in this study were used. Quality-of-life adjustments for healthcare workers who did not seroconvert varied by age according to the community-based

Table II. Summary of cost and utility parameters. Costs are expressed in 1997 US dollars

Parameter	Baseline estimate	Range for sensitivity analysis	Reference or derivation
Cost of HIV PEP			
Cost of office visits (CPT 99212) [$US]	28.89	17.77-40	27
Number of office visits	3		18,25
Cost of toxicity monitoring laboratory tests ($US)			
complete blood count	15.97	7.93-24	27
blood chemistry	23.35	15.69-31	27
urinalysis (indinavir)	8.75	4.49-13	27
amylase (lamivudine)	14.60	9.20-20	27
number of times healthcare worker is tested	3		18,25
Cost of antiretroviral drugs ($US)			
zidovudine	257	221-284	28
lamivudine	206	178-223	28
indinavir	391	333-420	28
Cost of PEP strategy ($US)			
monotherapy	609		Calculated
double therapy	892		Calculated
triple therapy	1331		Calculated
Cost of major adverse effects	490		9
Healthcare costs for HIV disease by stage ($US)			
CD4+ >500 cells/μl	3384	1934-3528[a]	29-31
CD4+ >200 cells/μl	5160	5160-7584[a]	29-31
CD4+ <200 cells/μl	11 880	9031-15 720[a]	29-31
AIDS	33 168	25 239-67 713[a]	29-31
Duration of HIV stages (y)			
CD4+ >500 cells/μl	5.6	5.5-7	29,31-33
CD4+ >200 cells/μl	3.67	3.67-5.8	29,31-33
CD4+ <200 cells/μl	1.03	1.03-1.7	29,31-33
AIDS	2.08	1.3-6.2	29,31-33
Quality of life for HIV by stage (%)			
CD4+ >500 cells/μl	83	83-91	34,35
CD4+ >200 cells/μl	83	62-88	34,35
CD4+ <200 cells/μl	42	42-74	34,35
AIDS	17	17-80	34,35
Inflation factors (medical consumer price index)			
1995-1997	1.07		36
1992-1997	1.264		36

a Univariate and multiway sensitivity analyses were also performed using 95% confidence intervals, not shown.[29]

PEP = postexposure prophylaxis.

Beaver Dam Health Outcomes Study.[39] To assess the impact of new treatments on the cost of HIV healthcare, the model was adjusted by adding the costs obtained from Hellinger:[29] the net cost of triple drug therapy applied to all HIV stages where the CD4+ cell count was <500/μl and to the proportion (38%) of those with CD4+ cell counts >500/μl who would have HIV RNA viral copies >10 000/ml.

For healthcare workers who did not seroconvert following exposure, we estimated life expectancy

using a simple Markov model with 2 states: alive and dead. Healthcare workers entered the model with a mean age at time of exposure of 33.5 years. Transition probabilities were obtained from separate life tables for male and female healthcare workers at the start of each cycle year.[40]

Analysis

The cost effectiveness of each strategy with respect to 3 outcomes was evaluated: HIV infections prevented, years of life saved and QALYs saved. The marginal cost of an HIV infection prevented, the marginal cost per year of life saved, and the marginal cost per QALY saved were calculated for each strategy. This was repeated using each of the 3 cost models.

One-way sensitivity analysis was performed for transmission rates of each exposure category, efficacy of double and triple therapy, the probability of acceptance of PEP, the cost of antiviral drugs, quality of life and the cost of healthcare for HIV-seropositive healthcare workers. Sensitivity analysis bounds were the upper and lower 95% confidence intervals when known. The sensitivity analyses of calculated parameters varied the parameters over their entire range. For instance, the efficacy of triple drug therapy was calculated with the equation:

$$\text{efficacy of triple therapy} = \text{efficacy of monotherapy} + dt \times (1 - \text{efficacy of monotherapy})$$

For sensitivity analyses, the efficacy of monotherapy was varied according to published 95% confidence intervals. In addition, dt was varied from 0 to 1 so that the efficacy of triple drug therapy varied from the same as that of monotherapy up to 100%.

To further test model uncertainty, we performed a multiway probabilistic sensitivity analysis using a Monte Carlo simulation as described by Doubilet et al.[41] Normal distributions for healthcare workers' age at exposure and costs by HIV stage from the Hellinger[29] cost model were used. Costs for PEP were sampled from triangular distributions. Probabilities were sampled from a logistic normal distribution for exposure category, transmission, PEP efficacy, the probability of acceptance of PEP and completion of PEP. The Monte Carlo simulation used 10 000 trials to evaluate the model, producing a distribution of cost and QALY values. To model sample uncertainty, which may be of concern to

Table III. Cost effectiveness of HIV postexposure prophylaxis strategies based on the cost model of Hellinger.[29] Costs are expressed in 1997 US dollars

Strategy	Cost[a] ($US per 1000 healthcare workers)	Effectiveness[b] (per 1000 healthcare workers)	Cost effectiveness ($US per unit of effectiveness)	Marginal cost effectiveness[c] ($US per unit of effectiveness)
Infections prevented				
Monotherapy	22 000	2.08	10 577	
USPHS PEP	181 000	2.21	81 900	1 304 717
Triple therapy	307 000	2.22	138 288	12 273 996
Life-years saved				
Monotherapy	22 000	31.2	713	
USPHS PEP	181 000	33.0	5 485	87 139
Triple therapy	307 000	33.2	9 247	819 747
Quality-adjusted life-years saved				
Monotherapy	22 000	33.6	654	
USPHS PEP	181 000	35.6	5 087	80 865
Triple therapy	307 000	35.8	8 587	760 730

a Discounted 3% annually.

b Compared with no PEP, discounted 3% annually for life-years saved and quality-adjusted life-years saved.

c Compared with the previous strategy.

PEP = postexposure prophylaxis; **USPHS** = US Public Health Service.

Table IV. Cost effectiveness of HIV postexposure prophylaxis strategies by cost model; parentheses indicate cost saving. Costs are expressed in 1997 US dollars

Strategy	Cost[a] ($US per 1000 healthcare workers)	Effectiveness (QALYs saved per 1000 healthcare workers)[b]	Cost effectiveness ($US/QALY saved)	Marginal cost-effectiveness[c] ($US/QALY saved)
Hellinger cost model[29]				
Monotherapy	22 000	33.6	654	
USPHS PEP	181 000	35.6	5 087	80 865
Triple therapy	307 000	35.8	8 587	760 730
Gable et al. cost model[30]				
Monotherapy	98 000	33.6	2 915	
USPHS PEP	261 000	35.6	7 335	83 107
Triple therapy	388 000	35.8	10 853	762 972
Hurley et al. cost model[31]				
Monotherapy	(16 000)	32.0	(501)	
USPHS PEP	140 000	33.8	4 138	83 836
Triple therapy	267 000	34.0	7 855	798 880

a Discounted 3% annually.

b Compared with no PEP, discounted 3% annually.

c Compared with the previous strategy.

PEP = postexposure prophylaxis; **QALY** = quality-adjusted life-year; **USPHS** = US Public Health Service.

policy-makers, bootstrap samples of 5000 and 500 trials were chosen to represent 2 different healthcare worker population sizes for which PEP strategies could be implemented.[42] 1000 bootstrap samples were drawn by sampling with replacement from the distribution produced by the Monte Carlo simulation to determine the mean cost, QALYs saved, cost effectiveness and marginal cost effectiveness of each strategy.[42,43] Confidence intervals were determined by the 2.5th and 97.5th percentiles of the distribution of the bootstrapped replicants.[43]

Results

Baseline Analysis

The baseline cost, effectiveness, cost effectiveness and marginal cost effectiveness per infection prevented, per year of life saved and per QALY saved, based on the Hellinger[29] cost model and expressed in 1997 US dollars with an annual discount rate of 3%, are shown in table III. Monotherapy was the most cost-effective strategy: $US10 577 per infection prevented, $US713 per year of life saved and $US654 per QALY saved. The marginal cost effectiveness of USPHS PEP compared with monotherapy was $US1 304 717 per infection prevented, $US87 139 per year of life saved and $US80 865 per QALY saved. The marginal cost effectiveness of triple therapy compared with USPHS PEP was $US12 273 996 per infection prevented, $US819 747 per year of life saved and $US760 730 per QALY saved.

The baseline cost, effectiveness, cost effectiveness and marginal cost effectiveness for each strategy for all 3 cost models are shown in table IV. Effectiveness was the same for the Hellinger and Gable et al. cost models because they used the same source to estimate HIV stage durations.[29,30] The order of the estimates of cost effectiveness was stable across the 3 cost models. The most favourable estimates were obtained using costs and HIV stage durations from the Hurley et al. cost model, because baseline costs for no PEP were the highest of the 3 cost models. The costs of treating HIV infection were high enough that monotherapy saved $US501 per QALY saved and $US7692 per infection prevented. The marginal cost effectiveness of the USPHS PEP and triple therapy strategies for all 3 cost models were

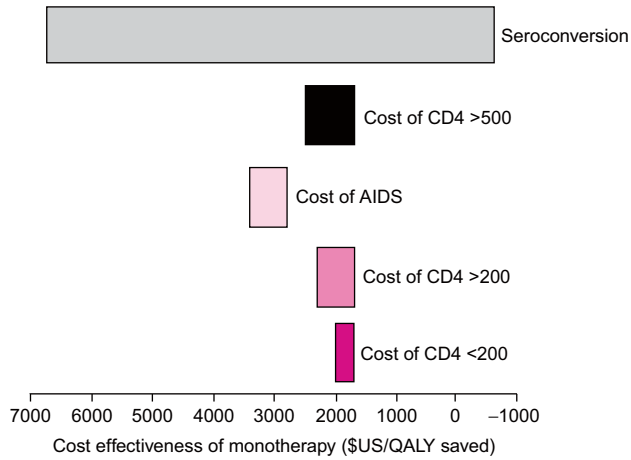

Fig. 2. Tornado diagram summarising 1-way sensitivity analyses of the cost effectiveness of postexposure prophylaxis of HIV with zidovudine monotherapy. Parameters were varied as follows: seroconversion after percutaneous exposure 0.18 to 0.46%; cost of CD4+ count >500 cells/μl stage $US214 to $US349; cost of AIDS stage $US2607 to $US2921; cost of CD4+ count >200 cells/μl stage $US351 to $US508; cost of CD4+ count <200 cells/μl stage $US839 to $US1141 (cost ranges are the 95% confidence intervals around the mean monthly costs[29]). Negative values for cost effectiveness indicate that monotherapy is cost saving. Costs are expressed in 1997 US dollars. **CD4** = CD4+ count (cells/μl); **QALY** = quality-adjusted life-year.

quite similar. The marginal cost effectiveness of the USPHS PEP guidelines was $US80 865 to $US83 836 per QALY saved across all 3 cost models.

Sensitivity Analysis

The parameters with the greatest impact on cost-effectiveness are shown in figure 2, a tornado diagram that displays a summary of 1-way sensitivity analyses using the Hellinger[29] cost model. Tornado diagrams allow comparison of a set of 1-way sensitivity analyses in a single graph. The horizontal bar for each variable represents the range of cost effectiveness generated by varying the variable. A wide bar indicates that the variable had a large potential influence on the uncertainty of cost-effectiveness estimates. The graph is called a tornado diagram because the horizontal bars are arranged in order with the widest bar at the top.

The probability of seroconversion after percutaneous exposure had the greatest effect on cost effectiveness. At a probability of seroconversion greater than 0.348%, monotherapy became cost-saving. Costs for HIV stages were also influential, but did not change the order of strategies from the baseline analysis. All other variables in the model had substantially less effect on model uncertainty. As the probability of zidovudine resistance increased, the cost effectiveness of USPHS PEP guidelines approached that of triple therapy. However, even when zidovudine resistance was 100%, the marginal cost effectiveness of triple therapy compared with USPHS PEP was still $US160 256 per QALY saved. The model was insensitive to differences in the efficacy of double or triple drug therapy. When the efficacies of double and triple therapies were equal to that of monotherapy, the cost effectivenesses of the 3 strategies were monotherapy $US654 per QALY saved, USPHS PEP $US5855 per QALY saved, and triple therapy $US8969 per QALY saved. When the efficacies of double and triple therapy were both 90%, the marginal cost effectiveness of the USPHS PEP and the triple therapy for all exposed healthcare worker strategies were $US72 525 per QALY saved and $US767 439 per

QALY saved, respectively. The model was also insensitive to varying the cost of major adverse effects from $US0 to $US980, varying the probability of major adverse effects from 0.0001 to 0.001%, or varying the quality-of-life adjustments for any of the HIV disease stages.

The results of the multiway probabilistic sensitivity analysis based on sample sizes of 5000 and 500 trials drawn from a Monte Carlo simulation of 10 000 trials are shown in table V. For both sample sizes, the 95% confidence intervals for cost of the 3 strategies did not overlap. However, for effectiveness, expressed in QALYs saved per 1000 healthcare workers, USPHS PEP and triple therapy had considerable overlap when using a sample size of 5000: 95% CIs for USPHS PEP were 34.1 to 34.8 and for triple therapy were 34.2 to 34.9. Using a sample size of 500, the effectiveness of all 3 strategies overlapped: 95% CIs for monotherapy were 31.4 to 33.5, for USPHS PEP were 33.4 to 35.5 and for triple therapy were 33.5 to 35.6.

We estimated the impact on cost effectiveness of improved survival[32,33] and increased costs associated with recent innovations in HIV chemotherapy. With prolonged HIV stage durations and increased costs associated with early HIV stage triple drug therapy when HIV RNA copies/ml were >10 000, the marginal cost effectivenesses of USPHS PEP and triple therapy were $US62 497 and $US564 475 per QALY saved, respectively.

Discussion

In our model, all 3 intervention strategies were cost effective compared with no intervention. Multiway probabilistic sensitivity analysis suggested that decision-makers could not expect to find any discernible differences in the effectiveness of triple therapy, USPHS PEP guidelines and monotherapy in a small population (500 exposures). In a larger population (5000 exposures), which would be similar to a nationwide implementation, monotherapy would be less effective than the other 2 alternatives, but USPHS PEP guidelines and triple drug therapy would be indistinguishable. A randomised controlled trial is under way to determine the efficacy of 2-drug and selective 3-drug PEP.[18,25] Given the low transmission rates following exposure of healthcare workers, demonstration of a clinically significant difference in the efficacy of monotherapy versus standard 2-drug with selective 3-drug PEP will require a large number of participants.

The marginal cost effectiveness of PEP USPHS guidelines compared with monotherapy falls within the range of many routinely provided healthcare interventions.[44] However, because of the low rates of transmission from patients to healthcare workers,

Table V. Multiway sensitivity analysis of cost effectiveness of HIV postexposure prophylaxis, based on a Monte Carlo simulation of 10 000 trials. Costs are expressed in 1997 US dollars

Strategy	Cost[a] ($US per 1000 healthcare workers)		Effectiveness[b] (QALYs saved per 1000 healthcare workers)		Cost effectiveness ($US/QALY saved)	
	mean	95% CI[c]	mean	95% CI[c]	mean	95% CI[c]
Sample size of 5000 trials						
Monotherapy	22 380	20 370-24 470	32.5	32.2-32.8	688	624-750
USPHS PEP	179 490	177 190-181 690	34.4	34.1-34.8	5211	5126-5293
Triple therapy	305 240	302 790-307 630	34.6	34.2-34.9	8827	8715-8940
Sample size of 500 trials						
Monotherapy	22 350	16 430-29 270	32.5	31.5-33.5	687	502-892
USPHS PEP	179 420	172 950-186 750	34.5	33.4-35.5	5209	4980-5490
Triple therapy	304 990	298 050-313 090	34.6	33.5-35.6	8827	9508-9185

a Discounted 3% annually.

b Compared with no PEP, discounted 3% annually.

c Based on 2.5th and 97.5th percentiles of a distribution of 1000 bootstrapped replicants.

CI = confidence interval; **PEP** = postexposure prophylaxis; **QALY** = quality-adjusted life-year; **USPHS** = US Public Health Service.

the additional efficacy of triple drug PEP would be rewarded by only a small reduction of HIV infections at great expense. The US healthcare system would have to spend on average an additional $US123 for each of 100 000 exposed healthcare workers to prevent 1 additional case of HIV. If about 10 000 healthcare workers were exposed to HIV each year, using triple drug therapy for all, instead of the USPHS recommendations, would cost an additional $US1 230 000 per year for 10 years to prevent 1 case of HIV.

The model has several limitations. Only exposure of a healthcare worker to a source for which the HIV status was known was considered. We did not have access to adequate information to model the clinical situation of exposure to a source in which the HIV status was not known. We would anticipate that application of the strategy of triple drug therapy for all exposures in which the HIV status was unknown would yield an extremely unfavourable marginal cost effectiveness. However, the safeguards of exposure classification and treatment according to risk in the USPHS PEP strategy would mitigate this problem. The model is stable despite considerable underlying parameter uncertainty. In fact, the parameter that has had the greatest scrutiny, the probability of seroconversion following percutaneous exposure, had the greatest impact on model uncertainty. Because the probability of seroconversion is so small, other parameters that modify this risk for which little information is available, such as efficacy of multidrug therapy or partial PEP, have minimal effect on model uncertainty.

Our measure of quality of life for HIV stages was estimated on the basis of a small survey of healthcare providers.[34] Holtgrave and Pinkerton[35] recently reviewed the literature regarding HIV and quality of life. The median estimate of the quality-of-life adjustment for the AIDS stage from 6 studies was 0.62, which contrasts with the 0.17 we used. Although our estimate may be more representative of the utilities of healthcare workers, the much lower quality-of-life adjustment values could potentially decrease the estimate of cost per QALY, particularly in the analysis of the impact of recently improved survival. Despite this concern, the model proved to be insensitive to varying quality-of-life adjustment values for any of the HIV stages.

Although our estimates of cost effectiveness differed by a factor of 4 from the results of previous researchers, this is due to different assumptions. The cost effectiveness of triple therapy in the analysis of Pinkerton et al.[12] was approximately $US37 000/QALY saved compared with $US8500/QALY saved in our analysis. Pinkerton et al.[12] estimated a lifetime cost of HIV medical care of $US98 000 and 7.83 QALYs saved per infection prevented. In our analysis, the lifetime cost of HIV medical care was estimated at $US138 288 and 16.1 QALYs saved per infection prevented. Pinkerton et al.[12] truncated the analysis at age 65 years and used a 5% annual discount rate for cost and effectiveness. We used a 3% annual discount rate and did not truncate the analysis at age 65 years. Adjusting our discount rate to 5% decreased the lifetime cost of HIV care to $US96 741 and the QALYs saved per infection prevented to 10.2. Additionally, Pinkerton et al.[12] assumed in the base case that triple drug therapy had an efficacy equivalent to that reported for zidovudine (79%) and that partial PEP was ineffective, whereas we assumed that partial PEP was partially effective. Using a 5% annual discount rate for cost and effectiveness, triple drug therapy efficacy of 79% and ineffective partial PEP in our model yielded a cost-effectiveness estimate for triple therapy of $US17 492/QALY saved compared with no PEP therapy.

Ramsey and Nettleman[10] reported the net cost of prophylactic zidovudine at $US3184 per life year gained compared with $US713 in our analysis. In their analysis, the cost of zidovudine prophylaxis was $US1108 compared with $US420 in our analysis because of reductions in the cost of zidovudine from 1992 to 1997. Using the same cost of zidovudine as Ramsey and Nettleman,[10] and not discounting life expectancy, yielded a cost-effectiveness estimate for monotherapy of $US2773 per life year gained in our model.

It is difficult to compare the results of Allen et al.,[11] in which zidovudine prophylaxis saved

$Can6 243 955 (1992 Canadian dollars) per infection prevented, because they incorporated indirect benefits and the cost of initially treating all exposures for 3 days pending results of HIV testing of the source. In addition, their estimation of the cost of medical care for HIV ($Can44 416 per infection) is much smaller than the estimates used in our analysis.

With allowances for minor differences in the models, our findings for the cost effectiveness of monotherapy and triple therapy are consistent with these previous HIV PEP cost-effectiveness analyses. Since the cost effectiveness of USPHS PEP recommendations falls between those of monotherapy and triple drug therapy, this increases our confidence in the accuracy of the estimate.

The treatment of HIV disease is undergoing rapid and exciting change. Triple drug therapy with zidovudine, lamivudine and a protease inhibitor has demonstrated a more sustained potent antiretroviral activity and reduced mortality.[45] Life expectancies for those infected with HIV are dramatically improving,[46] but so are costs associated with these improvements. When our decision model incorporated adjustments for extended life expectancy associated with aggressive multidrug therapy, the marginal cost effectiveness of USPHS PEP compared with zidovudine monotherapy was comparable to that of many medical interventions in common use.[44]

Conclusions

Current USPHS PEP recommendations are marginally cost effective compared with monotherapy, but the additional efficacy of triple drug therapy for all risk categories is rewarded by only a small reduction in HIV infections at great expense. Our analysis was sensitive to the probability of seroconversion and to the costs of treatment for HIV infections, but these did not affect the order of preferred strategies. For the foreseeable future, assuming innovations in therapy that employ expensive drug combinations earlier in the HIV disease course to extend life expectancy and the increasing prevalence of HIV drug resistance, our model supports the use of the USPHS PEP guidelines.

References

1. Bell DM. Occupational risk of human immunodeficiency virus infection in health care workers: an overview. Am J Med 1997; 102: 9-15
2. Centers for Disease Control and Prevention. Update: provisional public health service recommendations for chemoprophylaxis after occupational exposure to HIV. MMWR Morb Mortal Wkly Rep 1996; 45: 468-72
3. Centers for Disease Control and Prevention. Public health service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. MMWR Morb Mortal Wkly Rep 1998; 47: 1-33
4. Henderson DK, Gerberding JL. Prophylactic zidovudine after occupational exposure to the human immunodeficiency virus: an interim analysis. J Infect Dis 1989; 160: 321-7
5. Centers for Disease Control and Prevention. Public health service statement on the management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine postexposure use. MMWR Morb Mortal Wkly Rep 1990; 39: 1-14
6. Puro V, Ippolito G, Guzzanti E, et al. Zidovudine prophylaxis after accidental exposure to HIV. The Italian study group on occupational risk of HIV infection. AIDS 1992; 6: 963-9
7. Tokars JI, Marcus R, Culver DH, et al. Surveillance of HIV infection and zidovudine use among health care workers after occupational exposure to HIV-infected blood. Ann Intern Med 1993; 118: 913-9
8. Centers for Disease Control and Prevention. Case-control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV-infected blood – France, United Kingdom, and United States, January 1988 - August 1994. MMWR Morb Mortal Wkly Rep 1995; 44: 929-33
9. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994; 331: 1173-80
10. Ramsey SD, Nettleman MD. Cost-effectiveness of prophylactic AZT following needlestick injury in health care workers. Med Decis Making 1992; 12: 142-8
11. Allen UD, Read S, Gafni A. Zidovudine for chemoprophylaxis after occupational exposure to HIV-infected blood: an economic evaluation. Clin Infect Dis 1992; 14: 822-30
12. Pinkerton SD, Holtgrave DR, Pinkerton HJ. Cost-effectiveness of chemoprophylaxis after occupational exposure to HIV. Arch Intern Med 1997; 157: 1972-80
13. Scheid DC, Stevens K, Hamm RM. Cost-effectiveness of human immunodeficiency virus post-exposure prophylaxis. Med Decis Making 1997; 17: 525
14. Gold MR, Siegel JE, Russel LB, et al. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996
15. McCray E. Occupational risk of the acquired immunodeficiency syndrome among health care workers. N Engl J Med 1986; 314: 1127-32
16. Ippolito G, Puro V, De Carli G, et al. The risk of occupational human immunodeficiency virus infection in health care workers. Arch Intern Med 1993; 153: 1451-8
17. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. N Engl J Med 1997; 337: 1485-90
18. Gerberding JL. Prophylaxis for occupational exposure to HIV. Ann Intern Med 1996; 125: 497-501

19. Henderson DK. Postexposure chemoprophylaxis for occupational exposure to human immunodeficiency virus type 1: current status and prospects for the future. Am J Med 1991; 91: 312-9
20. Ippolito G, Puro V, Italian registry of antiviral prophylaxis. Zidovudine toxicity in uninfected healthcare workers. Am J Med 1997; 102: 58-62
21. Wainberg MA, Friedland G. Public health implications of antiretroviral therapy and HIV drug resistance. JAMA 1998; 279: 1977-83
22. Hirsch MS, Conway B, D'Aquilla RT, International AIDS Society – USA Panel, et al. Antiretroviral drug resistance testing in adults with HIV infection. JAMA 1988; 279: 1984-91
23. Mayers DL. Prevalence and incidence of resistance to zidovudine and other antiretroviral drugs. Am J Med 1997; 102: 70-5
24. Frankel LM, Wagner II LE, Demeter LM, et al. Effects of zidovudine use during pregnancy on resistance and vertical transmission of human immunodeficiency virus type I. Clin Infect Dis 1995; 20: 1321-6
25. Gerberding JL. Postexposure prophylaxis for human immunodeficiency virus at San Francisco General Hospital. Am J Med 1997; 102: 85-9
26. Fahrner R, Meekman SE, Koziol DE, et al. Safety of zidovudine (ZDV) administered as post-exposure prophylaxis to health care workers (HCW) sustaining HIV-related occupational exposures (OE). In: Program and abstracts – Interscience Conference on Antimicrobial Agents and Chemotherapy: 1994 Oct 4-7; Orlando (FL). Washington, DC: American Society for Microbiology, 1994: 133
27. Locality fee schedule report. Oklahoma City (OK): Health Care Financing Administration, 1997
28. Average wholesale price. Indianapolis (IN): Medispan Inc., 1997
29. Hellinger FJ. The lifetime cost of treating a person with HIV. JAMA 1993; 270: 474-8
30. Gable CB, Tierce JC, Simison D, et al. Cost of HIV+/AIDS at CD4+ counts disease stages based on treatment protocols. J Acquir Immune Defic Syndr Hum Retrovirol 1996; 12: 413-20
31. Hurley SF, Kaldor JM, Gardiner S, et al. Lifetime cost of human immunodeficiency virus-related health care. J Acquir Immune Defic Syndr Hum Retrovirol 1996; 12: 371-8
32. Longini IMJ, Clark WS, Karon JM. Effect of routine use of therapy in slowing the course of human immunodeficiency virus (HIV) infection in a population-based cohort. Am J Epidemiol 1993; 137: 1229-40
33. CAESAR Group. Randomized trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial. Lancet 1997; 349: 1413-4
34. Owens DK, Nease RFJ. Transmission of HIV infection between provider and patient: quantitative analysis of risk. In: Kaplan EH, Brandeau ML, editors. Modeling the AIDS epidemic: planning, policy, and prediction. New York (NY): Raven Press, 1994: 153-77
35. Holtgrave DR, Pinkerton SD. 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 1996; 12: 413-20
36. Consumer Price Index – all urban consumers, medical services. Series ID: CUUR0000SAM. Washington, DC: US Bureau of Labor Statistics [online]. Available from: URL: http://146.142.4.24/cgi-bin/surveymost?cu [Accessed 2000 Aug 14]
37. Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making 1983; 3: 419-58
38. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993; 13: 322-38
39. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993; 13: 89-102
40. National Center for Health Statistics. U.S. decennial life tables for 1989-1991. Hyattsville (MD): National Center for Health Statistics, 1997
41. Doubilet P, Begg CB, Weinstein MC, et al. Probabilistic sensitivity analysis using Monte Carlo simulation: a practical approach. Med Decis Making 1985; 5: 157-77
42. Hunink MGM, Bult JR, De Vries J, et al. Uncertainty in decision models analyzing cost-effectiveness: the joint distribution of incremental costs and effectiveness evaluated with a nonparametric bootstrap method. Med Decis Making 1998; 18: 337-48
43. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York (NY): Chapman and Hall, 1993
44. Laupacis A, Feeney D, Detsey AS, et al. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Can Med Assoc J 1992; 146: 473-80
45. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997; 337: 725-33
46. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998; 338: 853-60

Correspondence and offprints: Dr *Dewey Scheid*, Family Medicine Center, 900 Northeast 10th Street, Oklahoma City, OK 73104, USA.
E-mail: dewey-scheid@ouhsc.edu