

Perspective

Cost-Effectiveness of HIV Interventions: From Cohort Studies and Clinical Trials to Policy

Incremental cost-effectiveness ratios quantify the additional cost of an intervention relative to the additional benefit associated with its use. Whether an intervention is considered cost-effective depends largely on policy decisions regarding whether the additional benefit is worth the additional cost in the context of competing needs for resources. In the United States, cost-effectiveness analyses have been instrumental in guiding changes in HIV policy supporting antiretroviral therapy, genotypic resistance testing, and expanded programs for HIV screening. The cost-effectiveness of HIV screening compares favorably with that of accepted screening practices for other chronic diseases. This article is a summary of a presentation made by Rochelle P. Walensky, MD, MPH, at the International AIDS Society-USA Chicago program held in May 2009. The original presentation is available as a Webcast at www.iasusa.org.

Mathematical simulation models for quantifying benefits and costs of interventions in HIV disease are important tools for assessing the impact of care from a public health perspective and for informing policy on expenditure of health care resources. Because the models project both efficacy and costs, these tools allow assessment of cost-effectiveness of a variety of interventions, from opportunistic infection prophylaxis and antiretroviral treatment to use of genotypic assays and screening for HIV infection.

Survival Benefit and Cost of HIV Care

A computer simulation model of HIV disease and treatment, the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, has been used to estimate survival benefits of HIV interventions, the costs of the interventions, and their incremental cost-effectiveness ratios. To assess benefits associated with different treatment interventions for patients with AIDS, survival was examined according to treatment “eras.” Each era was defined as a period during which an interven-

tion was considered standard of care. To characterize improvements in antiretroviral treatment efficacy over time, antiretroviral therapy was subdivided into 4 separate eras. Table 1 shows the per-person and total survival benefits

for treated patients with AIDS compared with untreated disease during these eras. The study projects that patients diagnosed with AIDS in antiretroviral therapy era 4 (2003) have a survival benefit of 160 months compared with patients with untreated disease (Walensky et al, *J Infect Dis*, 2006). Overall, the study estimated that by 2005, almost 3 million life-years had been saved due to AIDS therapy alone. Such per-person survival benefits associated with AIDS treatment exceed reported gains associated with treatment interventions for many other chronic diseases in the United States (Figure 1).

The CEPAC model has also been used to estimate costs of HIV care (Schackman et al, *Med Care*, 2006). Using data from a cohort of people with

Table 1. Per-Person Survival Benefit in AIDS Patients by Treatment Era

Years	Intervention	Per-Person Survival Benefit (months)	No. of Patients Diagnosed and Entering Care	Total Survival Benefit (years)
1989-1992	PCP prophylaxis	3.1	158,370	40,912
1993-1995	PCP prophylaxis + MAC prophylaxis	24.4	226,458	460,465
1996-1997	PCP prophylaxis + MAC prophylaxis + ART Era 1	93.7	72,716	567,788
1998-1999	PCP prophylaxis + MAC prophylaxis + ART Era 2	132.6	52,702	582,359
2000-2002	PCP prophylaxis + MAC prophylaxis + ART Era 3	138.8	71,946	832,179
2003	PCP prophylaxis + MAC prophylaxis + ART Era 4	159.9	24,780	330,189
Total				2,813,892

ART indicates antiretroviral therapy; Eras 1-4, periods characterized by improvements in antiretroviral therapy over time; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis jirovecii* pneumonia. Adapted from Walensky et al, *J Infect Dis*, 2006.

Dr Walensky is associate professor of medicine at Harvard Medical School.

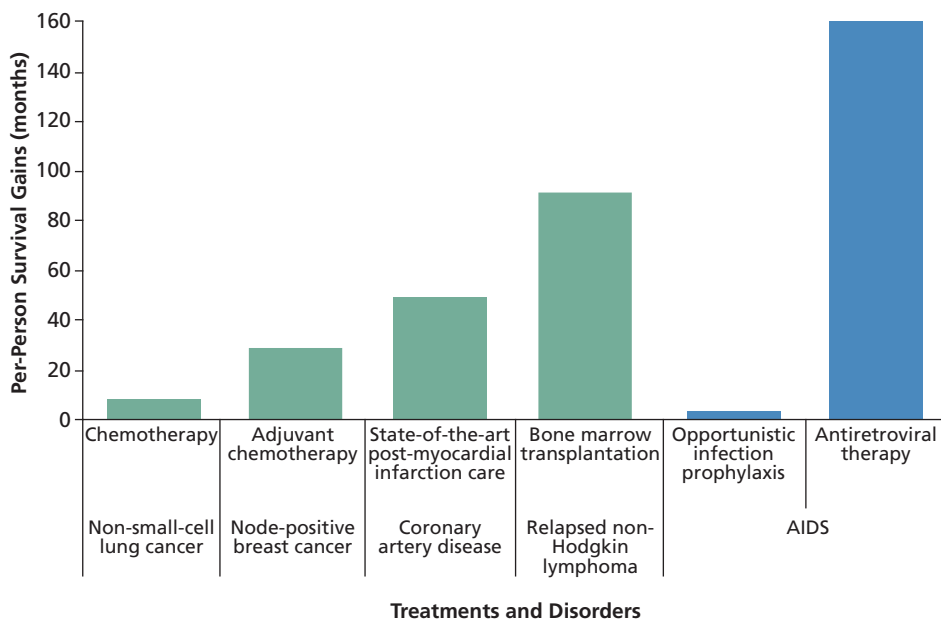


Figure 1. Per-person survival gains with treatment in patients with AIDS compared with gains associated with interventions for other common diseases in the United States. Adapted from Walensky et al, *J Infect Dis*, 2006.

HIV infection with a mean CD4+ count of 310 cells/ μ L and an average projected life expectancy of 24.2 years, the undiscounted lifetime cost of care was estimated to be \$618,900 (discounted cost \$385,200), with antiretroviral therapy accounting for 77% of the cost and inpatient costs for 10%.

Cost-Effectiveness of HIV Care

To calculate the incremental cost-effectiveness of an intervention, analyses must consider the added efficacy (generally measured in years of life saved [YLS] or quality-adjusted life-months or -years [QALM or QALY]) and the additional costs of the intervention. The cost-effectiveness ratio is then calculated with incremental costs in the numerator and incremental benefits in the denominator (\$/QALY). An intervention may be considered cost-effective if the additional benefit provided by the treatment is considered “worth” the additional cost. The World Health Organization (WHO) Commission on Macroeconomics and Health (WHO, 2009) suggested that interventions may be considered very cost-effective when the cost-effectiveness ratio (\$/QALY) is less than 1 times the

per-capita gross domestic product (GDP) for an individual country and cost-effective when the ratio is less than 3 times the per-capita GDP. As a point of reference, the estimated GDP per capita in the United States in 2008 US dollars (USD) is \$46,500 (International Monetary Fund, 2008).

Is antiretroviral therapy cost-effective in the United States? In 2001, Freedberg (principal investigator of the CEPAC group) and colleagues analyzed the cost-effectiveness of antiretroviral therapy. This analysis simulated patients in a clinical trial setting (Dupont 006) and patients in a published clinical cohort from the Johns Hopkins Moore (HIV) Clinic (Freedberg et al, *N Engl J Med*, 2001). The clinical trial population had a mean CD4+ count of 350 cells/ μ L and was intended to examine the antiretroviral therapy impact in a highly motivated, healthier patient population characteristic of clinical trial enrollees. In contrast, the published cohort had a mean CD4+ count of 217 cells/ μ L and simulated patients from the setting of a “real world” inner-city clinic. In the clinical trial population, projected annual costs were \$59,790 (in 1998 USD) for patients not receiving antiretroviral therapy versus \$94,290

for those receiving treatment with efavirenz/zidovudine/lamivudine, and projected QALM values were 47.52 versus 79.56, respectively, yielding a cost-effectiveness ratio (\$/QALY) of approximately \$13,000. In the simulation of the clinical cohort, per-person costs were projected to be \$54,150 for patients not receiving therapy versus \$80,460 for those receiving treatment with indinavir/zidovudine/lamivudine, and projected QALM values were 35.04 versus 53.16, respectively, yielding a cost-effectiveness ratio of approximately \$17,000 per QALY. In both of these settings, antiretroviral therapy may be considered very cost-effective.

Cost-effectiveness analysis of genotypic resistance testing helped motivate guideline development regarding the use of this test in clinical practice (Weinstein et al, *Ann Intern Med*, 2001). Analysis of use of genotypic resistance testing at the time of HIV treatment failure showed costs of \$90,360 with no testing versus \$93,650 with testing (in 1998 USD) and QALM values of 60.9 versus 63.1, respectively. These values yielded a cost-effectiveness ratio of \$17,900 per QALY. The cost increase associated with testing reflects more than the then approximately \$400 cost of the test; most of the increase comes from the cost of additional antiretroviral treatment during the duration of life added by use of the intervention.

Subsequently, genotypic resistance testing was also shown to be cost-effective in antiretroviral therapy-naïve patients (Sax et al, *Clin Infect Dis*, 2005). An analysis was performed over a range of assumptions of prevalence of major HIV drug resistance mutations of 0.25% to 10.0% and for the possible genotypic test costs of \$200, \$400, and \$800. Cost-effectiveness ratios were within the range likely to be considered cost-effective except at combinations of the highest test costs and the lowest prevalences of major resistance mutations. At the actual estimated prevalence of major mutations of 8.3%, the incremental cost associated with testing was \$2000 and the incremental increase in life expectancy was 1.0 QALM, yielding

a cost-effectiveness ratio of \$23,900 per QALY at a test cost of \$400 (\$21,600/QALY at test cost of \$200; \$28,600/QALY at test cost of \$800).

Cost-Effectiveness of HIV Screening

Table 2 shows cost-effectiveness ratios for several HIV-related interventions and for screening programs for other chronic diseases including breast cancer, colon cancer, and diabetes that are currently considered standard of care in the United States. The ratios for HIV screening in inpatients and in high-risk outpatient populations compare favorably with ratios for other accepted

screening programs. Although cost-effectiveness ratios differ according to the models and assumptions employed, several studies of HIV screening in the outpatient setting have generally yielded consistent results at the policy level. Paltiel and colleagues from the CEPAC group (*N Engl J Med*, 2005) found that at a 1% prevalence of undiagnosed HIV infection in the outpatient setting, routine testing every 5 years had a ratio of \$71,000 per QALY, whereas Sanders and colleagues (*N Engl J Med*, 2005) found at the same prevalence a ratio of \$41,700 per QALY for routine screening. In an updated analysis, Paltiel and colleagues (*Ann Intern Med*, 2006) reported that with inclusion of trans-

mission effects (fewer transmissions associated with increased case detection), routine screening in a population with a prevalence of undiagnosed HIV infection of 0.2% had a cost-effectiveness ratio of \$50,000 per QALY. These findings contributed to the rationale for recommendations for routine HIV screening in the United States (Branson et al, *MMWR Recomm Rep*, 2006).

Figure 2 shows cost-effectiveness ratios of HIV screening at different levels of the prevalence of undiagnosed HIV infection in the population and at different test costs. At a baseline test cost of \$26 (indicated by squares), the cost-effectiveness ratio remains below \$50,000 per QALY for all prevalences of undiagnosed HIV infection ranging from 0.1% to 100%. Even at test costs as high as \$104 (eg, for testing plasma HIV RNA level), cost-effectiveness ratios are below \$100,000 per QALY in the prevalence range examined. The data also show that once a 1% prevalence of undiagnosed HIV infection is exceeded, the cost-effectiveness ratio plateaus at about \$36,000 per QALY.

These findings reflect both that the cost-effectiveness ratio for state-of-the-art HIV care (primarily reflecting the cost of antiretroviral therapy) is approximately \$36,000 per QALY and that care of identified HIV-infected patients drives both cost and benefits. Compared with the costs of care, testing costs are much less important. It is often overlooked by those objecting to the cost of routine HIV testing that the real costs and the real benefits to screening accrue over time in the course of successful treatment.

Recent analysis has examined the cost-effectiveness of the entire screening process itself: offering the test, accepting the test, returning for test results, and linking to appropriate care. Walensky and colleagues defined the “index of participation” as the product of the probability of test offer and acceptance and the probability of returning for results and linkage to care (*Med Decis Making*, 2005). For example, the index of participation for a screening program with a test offer-and-accept rate of 37% and a return-and-link rate of 88% would be 33% ($0.37 \times 0.88 =$

Table 2. Cost-Effectiveness Ratios for Select HIV-Related Interventions and for HIV and Non-HIV-Related Screening Interventions

Intervention	Drug	Cost-Effectiveness Ratio (\$/QALY) ^a	Reference
HIV Interventions			
PCP/toxoplasmosis prophylaxis	TMP-SMX	\$2600	Freedberg et al, <i>JAMA</i> , 1998
Antiretroviral therapy	Zidovudine/lamivudine/efavirenz	\$13,000	Freedberg et al, <i>N Engl J Med</i> , 2001
Genotypic resistance test, at treatment failure	NA	\$17,900	Weinstein et al, <i>Ann Intern Med</i> , 2001
Genotypic resistance test, treatment-naive	NA	\$20,200	Sax et al, <i>Clin Infect Dis</i> , 2005
Inpatient HIV screening	NA	\$15,100	Walensky et al, <i>Am J Med</i> , 2005
MAC prophylaxis	Azithromycin	\$44,500	Freedberg et al, <i>JAMA</i> , 1998
HIV and Other Screening Interventions			
HIV screening every 5 years in patients at high risk	NA	\$42,200	Paltiel et al, <i>N Engl J Med</i> , 2005
Breast cancer screening: annual mammogram, 50-69 years old	NA	\$57,500	Salzmann et al, <i>Ann Intern Med</i> , 1997
Colon cancer screening: FOBT + sigmoidoscopy every 5 years, 50-85 years old	NA	\$53,600	Frazier et al, <i>JAMA</i> , 2000
Type 2 diabetes: one-time FPG, > 25 years old	NA	\$63,000	CDC, <i>JAMA</i> , 1998

CDC indicates Centers for Disease Control and Prevention; FOBT, fecal occult blood test; FPG, fasting plasma glucose; MAC, *Mycobacterium avium* complex; NA, not applicable; PCP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

^aAll costs adjusted to 2001 US dollars. Ratios from Walensky et al, *Am J Med*, 2005.

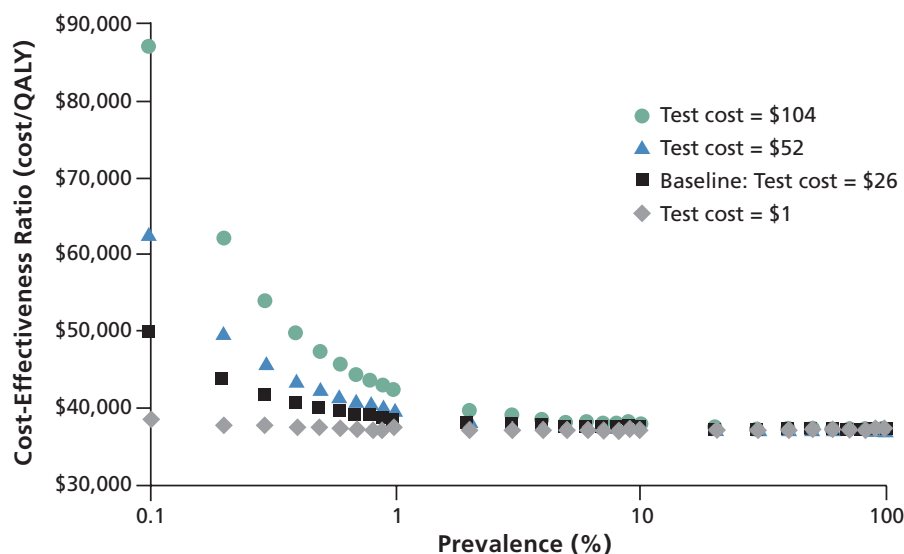


Figure 2. Cost-effectiveness ratios of HIV screening according to prevalence of undiagnosed HIV infection in the testing population and different hypothetical test costs. QALY indicates quality-adjusted life-years. Adapted from Walensky et al, *Am J Med*, 2005.

0.33); a program with an offer-and-accept rate of 88% and a return-and-link rate of 37% would have the same 33% index of participation. The authors examined the cost-effectiveness of HIV screening associated with a wide range of values for the index of participation by varying offer-and-accept and return-and-link rates from 0% to

100% in 10% intervals (undiagnosed HIV prevalence of 1%; Figure 3). The ratio for the hypothetical case of a 33% index of participation (37% offer-and-accept rate and 88% return-and-link rate) is \$38,600 per QALY; a program with only a 20% offer-and-accept rate and 20% return-and-link rate (0.04, or 4% index of participation) still has a

cost-effectiveness ratio of \$43,400 per QALY. Indeed, cost-effectiveness ratios were lower than \$50,000 per QALY for any index of participation greater than 1% (0.01).

Further investigation examined whether it is more important from a cost-effectiveness viewpoint to have higher offer-and-accept rates or higher return-and-link rates (Figure 3). Cost-effectiveness ratios were lower for index of participation values reflecting higher return-and-link rates, compared with identical indices of participation with higher offer-and-accept rates. Thus, if a choice has to be made regarding resource expenditure for a screening program, it is more cost-effective to ensure that the patient identified with a positive test result begins HIV care than to offer testing to another patient.

Conclusion

HIV simulation models are powerful tools for informing public health policy and for understanding survival, costs, and cost-effectiveness of clinical interventions. Cost-effectiveness analyses have motivated changes in policy supporting antiretroviral therapy, geno-

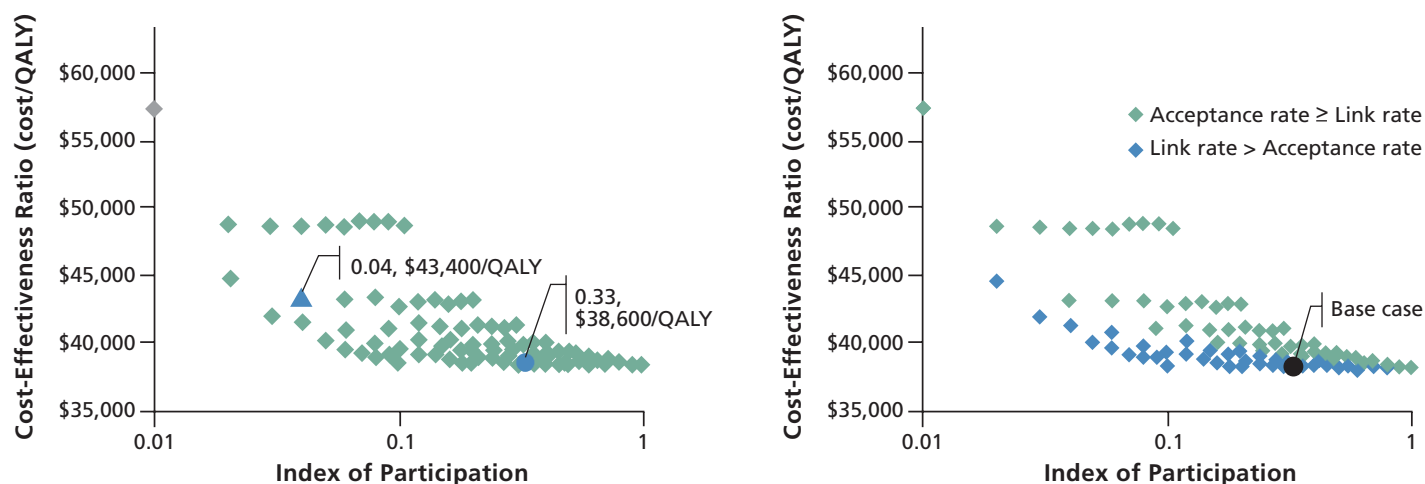


Figure 3. Left, cost-effectiveness ratios for index of participation values obtained by varying offer-and-accept rates and return-and-link rates from 0% to 100% in 10% intervals. Results assume a prevalence of undiagnosed HIV infection of 1.0%. Triangle indicates cost-effectiveness ratio associated with a 0.04 index (20% offer-and-accept rate × 20% return-and-link rate); circle, ratio for the hypothetical case of a screening program with an index of 0.33; QALY, quality-adjusted life-years. Right, same analysis with results distinguished according to whether the offer-and-accept (acceptance) rate was greater than or equal to the return-and-link (link) rate or the return-and-link rate was greater than the offer-and-accept rate. Base case indicates a hypothetical case of 0.33 index. Adapted from Walensky et al, *Med Decis Making*, 2005.

typic testing in treatment-experienced and treatment-naive patients, and expanded programs for HIV screening and linkage to care.

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Suggested Reading

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Correction

There was an error in a figure in the article "Occupational and Nonoccupational Postexposure Prophylaxis for HIV in 2009" (*Topics in HIV Medicine* 2009;17[3]:104-108). On page 106, the colors for the labels for the 2 drug regimens in the bottom graph of Figure 1 were inadvertently switched from the original. The figure posted on our Web site (www.iasusa.org) is correct.

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