Costs associated with combination antiretroviral therapy in HIV-infected patients

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As more effective HIV therapies have become available, resource constraints and cost-effectiveness have increasingly been at the centre of the debate on HIV care. Economic analysis is an important methodological approach to the understanding and establishment of priorities for health interventions designed to combat HIV in both high-income and low-income countries. In this paper, I briefly discuss different types of clinical economic analysis, and then consider the cost, affordability and cost-effectiveness of combination antiretroviral therapy in HIV patients in high-income and low-income countries. In high-income countries, HIV disease has become an expensive treatable chronic disease, with annual expenditures per patient of about US$ 20 000. Cost-effectiveness analyses show that antiretroviral therapeutic regimens offer good value for the resources spent compared to many other accepted health care interventions. In low-income countries, major programmes of combination antiretroviral therapy distribution are being planned and becoming operational as drug prices plummet and resources increase. More refined cost-effectiveness analyses are needed to evaluate available HIV/AIDS prevention, treatment, and care, and to identify the interventions that provide the best value for money.

Keywords: pharmacoeconomics, low-income countries, high-income countries, antiretroviral therapeutic regimens

Introduction

By the end of 2003, 34–46 million people were infected with human immunodeficiency virus (HIV), according to the estimate of the joint United Nations programme on HIV/acquired immunodeficiency syndrome (AIDS).1 In high-income countries, where the number of people with HIV/AIDS is estimated at 1.6 million,1 HIV infection has become a treatable chronic illness, thanks to the advent of combination antiretroviral therapies in 1995.2 It is currently recommended that HIV-infected individuals should be treated with at least three medications.3 In low-income countries, where the great majority of HIV-infected people now live, antiretroviral treatment coverage is still hopelessly inadequate, largely because of the cost of antiretroviral regimens.1 Consequently, HIV/AIDS is a uniformly fatal illness. In sub-Saharan Africa, by far the region worst affected by the epidemic, AIDS killed about 2.3 million in 2003.1

In high-income countries, the cost of combination antiretroviral therapy ranges from US$ 10 000 to US$ 15 000 per patient per year. Compared to many drugs on the market, those used for this therapy are perceived as expensive. In low-income countries, the cost of antiretroviral therapy has dramatically decreased over the past few years, to about US$ 350 per patient-year. However, this therapy remains expensive compared to the per capita national health expenditures of those countries.4 Given demands for care and constrained resources, economic analysis is an important methodological approach for understanding and prioritizing health interventions in both high-income and low-income countries.5,6

Principles of clinical economics

To understand the role of economic analysis, it is critical to distinguish between the different types of such analyses, which include cost analysis (or cost-minimization analysis), cost-benefit analysis, and cost-effectiveness analysis. Cost analysis is a methodology which estimates the resources used for, or costs of, a particular type of care or a specific illness.7 The outcome of interest is cost, and these studies are used primarily for budgeting and planning purposes. Cost-benefit analysis attempts to incorporate both resources used for clinical interventions, as well as a measure of the value of those resources in terms of clinical benefits.7 As, the outcome measure is currency, this methodology requires valuing clinical benefits, such as years of life saved (YLS) or disability-adjusted life years (DALYs) saved, in monetary terms. Because estimating the value of a life in economic terms is challenging for both ethical and methodological reasons, formal cost-benefit analysis is rarely done for medical interventions. Unlike cost analysis and cost-benefit analysis, cost-effectiveness analysis explicitly examines two outcome measures: cost in monetary terms,
and effectiveness in YLS, DALYs, or quality-adjusted life years [QALYs].\textsuperscript{3} By convention, different clinical interventions and strategies are compared in terms of their cost-effectiveness ratio, defined as $(C_A-C_B)/(E_A-E_B)$, where $C_A-C_B$ is the difference between the cost of interventions A and B, and $E_A-E_B$ is the difference between the effectiveness of these interventions. These ratios are a measure of value for money; the higher the ratio, the less cost-effective the intervention. By using established conventions for cost-effectiveness analysis,\textsuperscript{5} one can compare the cost-effectiveness of different health interventions within a given clinical setting or country.

**High-income countries**

*Cost of combination antiretroviral therapy*

Although, as stated above, antiretroviral drugs are perceived as expensive compared to many drugs on the market, early reports from the United States, Canada and Europe on the cost of HIV disease, stated, shortly after their introduction in 1996, that combination antiretroviral therapy had reduced the cost of medical care for HIV disease.\textsuperscript{8,9} This was the result of a decrease in the incidence of opportunistic infections and a corresponding reduction in inpatient healthcare use after the initiation of this therapy.

However, the above reports, which were based on historical comparisons, were drafted shortly after the introduction of combination antiretroviral therapy. Over time, the standard of care moved toward treating patients earlier in the course of their disease. Costly laboratory techniques such as HIV RNA tests, drug resistance testing, and drug level monitoring were carried out to optimize treatment by antiretroviral therapy. In addition, the use of this therapy led to adverse effects including lipodystrophy, lactic acidosis, osteoporosis, an increased risk of coronary heart disease, and to costly treatments for these conditions.\textsuperscript{10-12} Improved survival increased the incidence of complications from co-morbidities such as hepatitis C, frequently associated with HIV disease,\textsuperscript{13} involving, again, costly treatment of these illnesses.

Consequently, although the costs associated with hospitalization decreased markedly after the introduction of antiretroviral combination therapies, the proportion of patients receiving these therapies, the pharmacy costs, and the costs of associated illnesses, increased dramatically with time.\textsuperscript{14} There was a large shift in the cost of caring for HIV-infected patients, from the inpatient area to the outpatient area and pharmacy. Recent studies therefore show that for HIV disease, the cost of care per person per year has increased over time, especially for patients in the early stages of the disease.\textsuperscript{14,15} Because of this increased cost in the early stages, and longer patient survival, the total lifetime costs of HIV disease are increasing. In the era of combination antiretroviral therapy, HIV disease has become a treatable but expensive chronic disease, with annual expenditures per patient of US$ 19 400 in the United States and US$ 23 100 in France (cost inflation-adjusted to 2001 US$).\textsuperscript{14,16}

*Will HIV-related health care costs continue to increase? Clinical trials and observational studies have demonstrated that in about 50% of patients on combination antiretroviral therapy, viral suppression is incomplete, and that patients do not achieve long-term viral load suppression, for reasons that include difficulty with drug adherence, the development of drug resistance, and adverse effects of drugs.\textsuperscript{17} These patients are obliged to switch from one combination of antiretroviral drugs to another. Over time, they are treated with more intensive salvage regimens, often including an increasing number of antiretroviral agents, thus incurring not only higher drug prices, but also higher associated costs such as those of toxicity. In addition, they are treated with new classes of drugs which are usually more expensive than the ‘older’ drugs. For example, the initial cost of the new fusion inhibitor enfuvirtide,\textsuperscript{18} the first of a new class of drugs approved by the US FDA in March 2003 for use in patients with limited therapeutic options, is roughly US$ 20 000 per person per year. This is more than twice the price of the next-most-expensive antiretroviral agent. Pharmacy costs, and consequently overall HIV-related costs, will therefore certainly increase in the future. Mechanisms such as structured treatment interruptions are thought to be ways of decreasing the total cost of care. However, they have not proved to be effective in patients with advanced disease and treatment failure because of multidrug-resistant HIV.\textsuperscript{19} They have also been studied in patients who have persistent suppression of plasma viremia below the limit of detection for long periods.\textsuperscript{20} However, because the present data are insufficient, they cannot be recommended for use in general practice and future research is necessary in this area.*

*Cost-effectiveness of combination antiretroviral therapy*

Does combination antiretroviral therapy offer good value for the resources spent? The cost-effectiveness of combination antiretroviral therapy has been assessed in several studies in the USA and Europe. In 1999, Sendi et al. estimated a cost-effectiveness ratio for combination antiretroviral therapy of US$ 25 900/YLS (cost inflation-adjusted to 2001 US$).\textsuperscript{21} This was followed by estimates from the UK of US$ 30 500/QALY, and from the USA, of US$ 13 600 to US$ 24 000/QALY gained.\textsuperscript{22,23} In a recent study that took into account the adverse events related to antiretroviral therapy, namely, the increased risks of coronary heart disease, and of abnormal fat distribution symptoms, as well as the impact of these events on the quality of life, the cost-effectiveness ratio of combination antiretroviral therapy was estimated at US$ 17 800 to US$ 25 000/QALY gained.\textsuperscript{24} Although the authors of these studies used different methods and different country-specific input data, their results are remarkably consistent, with an estimated cost-effectiveness ratio of about US$ 20 000/QALY for combination antiretroviral therapy compared with no therapy, based on drug costs and treatment patterns in both the United States and Europe. The cost-effectiveness of combination antiretroviral therapy thus compares favourably with that of other medical interventions such as the treatment of breast cancer (US$ 33 200/QALY gained), hypercholesterolaemia (US$ 52 000/QALY gained), and dialysis of patients expected to live for less than 6 months (US$ 166 100/QALY gained).\textsuperscript{25-27} These analyses suggest that in high-income countries, combination antiretroviral therapy for the treatment of HIV disease offers good value for the resources spent, compared to other available and accepted interventions.

Favourable incremental cost-effectiveness ratios for available therapeutic regimens do not necessarily mean that new therapeutic options will also be cost-effective. For example, the cost-effectiveness of the fusion inhibitor enfuvirtide was recently evaluated for use in patients with limited therapeutic options.\textsuperscript{28} At an annual cost for enfuvirtide of about US$ 20 000 per person, the incremental cost-effectiveness of adding it to an optimized background regimen for patients with multidrug-resistant HIV was estimated at US$ 74 400/QALY gained. For this indication, enfuvirtide is therefore less cost-effective than other commonly used combination antiretroviral strategies. Its cost-effectiveness ratio is higher than the ratio of US$ 50 000 per QALY for dialysis for end-stage renal disease, which is often considered as a benchmark for cost-effectiveness in developed countries, although some authors recently stated that this
threshold is too low, at least in the USA. To support this point, they mention that the US$ 50 000 per QALY threshold goes back to at least 1982, has persisted for two decades without adjustment, and that now society should probably be willing to spend more money for one QALY. In addition, they note several commonly used clinical examples, such as the common practice of carrying out annual Pap smear screening for women at low risk of cervical cancer, with cost-effectiveness ratios that exceed conventional thresholds. These authors therefore think that it is more appropriate to raise cost-effectiveness thresholds significantly, approaching US$ 200 000 per QALY. Nevertheless, HIV infection and its therapy change rapidly over time. Although available therapeutic regimens offer good value for the resources spent, further cost-effectiveness studies are needed to assess new therapeutic options.

Low-income countries

Cost and affordability of combination antiretroviral therapy

It is important to remember that the great majority of HIV-infected people live in low-income countries. At present, treatment for HIV infection is not widely accessible in these countries, although there is increasing evidence of its feasibility and efficacy. The barriers are partly social and logistic, but the overwhelming barrier is cost.

At more than US$ 10 000 per patient-year, treatment was clearly unaffordable in low-income countries. However, the efforts of treatment activists, combined with the increased availability of generic combination antiretroviral therapy formulations costing about US$ 350 per person per year, have led multinational pharmaceutical manufacturers to lower the prices of their medications in these countries. Yet the cost of making combination antiretroviral therapy available remains extremely high, and exceeds the per capita national health expenditures in many countries. Recent data from 44 sub-Saharan African countries illustrate that per capita government expenditures on health exceed US$ 40 in only four countries. In addition to the cost of making antiretroviral drugs available, the provision of treatment to patients living with HIV in these countries involves other major expenses, such as those of developing and sustaining health care structures, laboratory facilities, health care technologies, and distribution channels. These countries with limited financial resources cannot afford these costs, which must therefore be met, at least in part, by high-income countries. As a result, substantial new resources have become available for HIV/AIDS prevention, treatment and care. A Global Fund to fight AIDS, Tuberculosis, and Malaria became operational in January 2002, and the European Commission is committed to a major increase in spending on HIV/AIDS. The United States has announced a 5 year, US$ 15 billion emergency plan for AIDS relief, to provide antiretroviral therapy and prevention activities to patients with HIV/AIDS. Consequently, major programmes of treatment distribution in low-income countries are being planned and becoming operational.

Cost-effectiveness of combination antiretroviral therapy

In low-income countries, where resources remain scarce and needs are overwhelming, the way money is spent is even more important than in developed countries. Consequently, the interventions that are the most cost-effective and provide the best value for money should be identified. On the basis of the limited data available, some authors argue that HIV prevention activities in sub-Saharan Africa are likely to be substantially more cost-effective than the provision of antiretroviral therapy. Accordingly, they maintain that in this region, the prevention of HIV/AIDS should have priority over treatment. However, more refined cost-effectiveness analyses on combination antiretroviral therapy are needed. When considering the cost-effectiveness of combination antiretroviral therapy, productivity costs should be included in the analysis. One should remember that by reducing morbidity and prolonging the survival of young people, those chiefly affected by HIV disease, combination antiretroviral therapy results in years of productivity. In a private enterprise in Abidjan, Côte d’Ivoire, comparison of the 12 month period before and the 24 month period after the introduction of comprehensive HIV care with antiretroviral therapy, showed that there was a 78% decrease in new AIDS cases, and a 58% decrease in HIV-related mortality. This resulted in a 94% decrease in HIV-related absenteeism, and a saving of US$ 287 000 over the 24-month period as a result of reduced absenteeism. The inclusion of productivity costs in cost-effectiveness analysis would therefore make combination antiretroviral therapy more cost-effective in these settings. In addition, when evaluating the cost-effectiveness of interventions, one should discount costs or life years. Since the benefits of combination antiretroviral therapy are immediate, but those of prevention occur years later, such discounting would make antiretroviral therapy more cost-effective than prevention. The possibility that combination antiretroviral therapy may lower the risk of HIV transmission should also be considered. The risk of transmission from HIV-infected individuals with viral loads suppressed by antiretroviral treatment may be lower than the risk of transmission from those not receiving this therapy. Lastly, the availability of effective treatment may motivate people to come forward for voluntary HIV counselling and testing, because they know that a positive result is the beginning of effective care.

Conclusion

In high-income countries, antiretroviral drugs are expensive compared to many other drugs on the market. In low-income countries, these drugs remain expensive compared to other interventions such as those targeting the prevention of HIV/AIDS, even though prices have decreased enormously. However, when assessing the cost of health care interventions, one should not only include drug expenses, but all the costs associated with the current use and future consequences of these interventions. In addition, it is important to evaluate the health outcomes achieved with an intervention, and to compare the benefits and costs of the different interventions; cost-effectiveness analysis is the best way to do this. In high-income countries, cost-effectiveness analyses show that antiretroviral therapeutic regimens offer good value for the resources spent compared to many other accepted health care interventions. In low-income countries, better analyses are needed to evaluate the impact and cost-effectiveness of available HIV/AIDS prevention, treatment and care. By ensuring that such clinical economic evaluations are available, health planners and policy makers will be in a position to allocate resources better. However, these evaluations do not reflect everything of importance to decision makers. Factors such as concepts of fairness and justice, benefits and costs outside the health sector, and practical questions of affordability, feasibility and acceptability also need to be considered. Consequently, economic evaluations in general, and cost-effectiveness analysis in particular, should not be considered the endpoints of a decision-making process, but can constitute a crucially important aid in that process.
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References


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