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Economic evaluation of ARTs in resource-limited countries

S Loubiere[1], **C Meiners**[1,2], **C Sloan**[3], **KA Freedberg**[3], and **Y Yazdanpanah**[4,5]

[1] INSERM/ IRD/ University of the Mediterranean - UMR 912 “Economics & Social Sciences, Health Systems & Societies” and Southeastern Health Regional Observatory (ORSPACA), Marseille, France

[2] Institute of Economics, Federal University of Rio de Janeiro (IE/UFRJ), Brazil

[3] Divisions of General Medicine and Infectious Diseases and the Partners AIDS Research Center, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[4] Service Universitaire des Maladies Infectieuses et du Voyageur, Centre Hospitalier de Tourcoing, Faculté de Médecine de Lille, France

[5] EA2694, Faculté de Médecine, Lille, France

Abstract

Purpose of review—In the face of increasing economic constraints, it is critically important to evaluate how best to utilize available resources. In this article, we review the growing number of cost-effectiveness analyses of HIV treatment with antiretroviral therapy (ART) in resource-limited settings. We focus on studies that evaluate *when to start therapy*, *what therapy to start with* and *what to switch to based on what criteria*.

Recent findings: Recent findings show that earlier ART initiation based on CD4 count criteria (CD4 counts <350/mm^3) can be cost-effective in most resource-limited settings. They also suggest that initiating ART with tenofovir as a component of the first-line regimen is an efficient use of resources compared with initiating ART with stavudine. Finally, they show that HIV RNA monitoring combined with CD4 monitoring is more effective than CD4 count monitoring alone, although this strategy was not found to be cost-effective in all studies. Nearly all studies show, however, that the cost-effectiveness of HIV RNA monitoring will become more attractive as the cost of HIV RNA tests and second-line ART regimens decrease.

Summary—Substantial research shows that antiretroviral therapy for HIV disease in resource-limited settings is cost-effective. Improved initial regimens and increased laboratory monitoring both provide clinical benefit and good value for money.

Keywords

HIV/AIDS; cost; cost-effectiveness; antiretroviral therapy; resource-limited countries

INTRODUCTION

The present decade has witnessed an unprecedented mobilization of resources and engagement of governments and international and non-governmental organizations for the expansion of access to antiretroviral therapy (ART) for HIV-infected people in low- and middle-income settings (1). Combination ART has become the standard of HIV care around the world and produces comparable clinical results in both developed and developing

countries (2-5). Despite the dramatic rise in global funding for HIV/AIDS and reductions in drug prices (6), many resource-limited countries will have difficulty sustaining long-term therapy due to logistical and political barriers and, more importantly, substantial resource constraints.

Among patients who are able to initiate ART and reach treatment goals, one main concern is the frequency with which costly laboratory tests should be administered to monitor treatment efficacy and toxicity, as well as the choice of subsequent therapeutic regimens, in which most drugs are still patented and thus very costly compared to first-line regimens (7). This situation suggests a growing trade-off between program coverage and treatment quality objectives in many resource-limited settings.

In the face of economic constraints, it is critically important to evaluate how best to utilize available resources (Gold*, Drummond*....). Cost-effectiveness analysis (CEA) is a well-established methodology for understanding, prioritizing and optimizing health care services. By comparing treatment alternatives in light of their relative advantages and costs, cost-effectiveness analysis can serve as one element to inform HIV/AIDS treatment guidelines (Goldie NEJM 2006).

In this article, we review the growing number of cost-effectiveness analyses of HIV treatment in resource-limited settings that use either cohort studies or mathematical models. Several studies conducted in resource-limited settings have already shown that a single line of ART is cost-effective and very cost-effective in certain settings compared to no ART (17-22). We focus on studies that evaluate *when to start ART*, *what therapy to start with* and *what to switch to based on what criteria*, topics that are central to the recently revised World Health Organization (WHO) treatment guidelines for developing countries (REF WHO 2009*). First, we describe studies that assess the impact of earlier compared to deferred ART initiation in resource-limited settings, since recent trials have shown that starting ART earlier is associated with longer survival (8-10). Second, we review studies that evaluate strategies that reduce severe ART-related toxicities (11, 12). Finally, we discuss studies that compare different strategies for monitoring ART efficacy and we examine several criteria for switching to second-line regimens when they are available.

REVIEW OF RECENT STUDIES ON THE COST-EFFECTIVENESS OF ART

We used the Medline and AIDSLINE online databases to conduct a literature search of articles published between January 2006 and October 2009. We then reviewed citation and reference lists to identify additional studies. Table 1 provides a summary of the results and describes the methodological features of each analysis that evaluates the cost-effectiveness of ART in resource-limited settings.

Although there is no clearly defined threshold at which any health intervention can be considered “cost-effective”, the guidelines of the WHO Commission on Macroeconomics and Health can be used to establish the comparative value of alternative interventions in a given country, taking into account its ability to pay for goods and services (REF). According to these guidelines, a strategy is considered cost-effective if the incremental cost-

*Gold MR, Siegel JE, Russell LB, Weinstein MC (1996). Cost-effectiveness in health and medicine. Oxford: Oxford University Press.
This is a key reference work on the economic evaluation of health technologies.
*Drummond M F, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL (2005). Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press.
This is a key reference work on the economic evaluation of health technologies.
*WHO. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. Geneva: Available at http://www.who.int/; November 2009 [electronic version].
This publication informs on the latest discussion on HIV/AIDS guidelines revision for developing countries.

effectiveness ratio (ICER) is below 3 times the annual *per capita* Gross Domestic Product (GDP) of the country and very cost-effective if the ICER is below one times the annual *per capita* GDP (16).

Cost-effectiveness of antiretroviral therapy: *When to start ART*

The WHO recently updated its 2006 guidelines, entitled "Antiretroviral therapy for HIV infection in adults and adolescents," using emerging evidence on the optimal timing of ART initiation and new drug regimens (REF WHO 2009*). The guidelines outline the standard of care for HIV-infected people, while taking into account the risks and benefits, acceptability, feasibility, cost and financial implications of various treatment strategies (13). The guidelines strongly recommend starting ART at WHO clinical stage 3 or 4 irrespective of CD4 count, or at CD4 counts <350/mm^3 irrespective of clinical symptoms (14). These recommendations are based on recent clinical data from cohort studies suggesting that early initiation reduces morbidity and mortality (8-10, 15). These higher thresholds will increase the number of eligible patients as well as affect overall costs. The value for the additional money spent, or cost-effectiveness, of earlier initiation must be assessed in order to determine its economic consequences.

Treatment tends to become less cost-effective (ICERs increase) as CD4 counts at ART initiation increase. Using retrospective observational data from a Moroccan hospital, Loubière *et al*. showed that treatment was very cost-effective when patients initiated ART at CD4 counts <200/mm^3 (Morocco 2008 per capita GDP: $2,570; (ref)). Additional analysis was carried to check cost-effectiveness beyond the CD4 count threshold of 200/mm^3. The ICER increased to nearly three times GDP per capita when threshold for treatment initiation was increased to 350/mm^3, whereas above this threshold the ICER was no longer cost-effective (22**). Badri *et al*. used data from the Cape Town AIDS Cohort study and found that initiating ART at CD4 counts >350/mm^3 produced an ICER of $1,310 per quality-adjusted life year (QALY) gained compared to initiating ART at CD4 counts 200-350/mm^3, while the latter strategy was associated with an ICER of $710/QALY compared to initiating ART at CD4 counts <200/mm^3 (South Africa 2008 per capita GDP, $6,190) (ref) (17**).

Most studies conducted in resource-limited settings suggest that ART initiation at CD4 counts <350/mm^3 is cost-effective (17, 19-21). In these studies, ICERs were most sensitive to the cost of ART. In Morocco, treatment was very cost-effective at CD4 counts 200-350/mm^3 when public sector ART costs were halved. In South Africa, Badri *et al*. found that if ART costs were reduced by 40%, treatment was cost-saving compared to no ART, regardless of CD4 count at initiation. Given these findings, mechanisms should be developed to assure long-term supplies of antiretroviral drugs at affordable costs, especially if HIV diagnoses occur increasingly early in the course of disease, as a result of the successful expansion of HIV testing, and a growing number of patients begin switching to costlier second-line regimens.

Although earlier ART initiation is cost-effective in many resource-limited settings, the benefits of treatment will only provide good value if rates of adherence and retention in care are high (see Ken's comments?). In a recent study, Anglaret *et al*. used a simulation model of HIV to demonstrate that early ART improves survival, except when adherence and retention are lower among patients starting ART earlier (23). Although this study did not consider costs, it is likely that rates of adherence, adverse events, and loss to follow-up will affect the cost-effectiveness of ART.

Cost-effectiveness of antiretroviral therapy: *What to start with*

Even when patients are virologically suppressed on ART, they are susceptible to both drug resistance and toxicity (24). Management of resistance and toxicity over time will emerge as a significant challenge in the fight against disease progression in both low- and high-income countries (25-27).

Serious toxicities not only incur considerable quality of life loss and additional costs (28), but also increase the risk of loss to follow-up which can lead to drug resistance. Guidelines should be revised regularly to incorporate new data on ART-related adverse events and recommend drugs with lower toxicity profiles. In Africa, guidelines are frequently not followed due to financial reasons. For example, most first-line ART regimens continue to include stavudine, even though the WHO recommends regimens containing rather tenofovir or zidovudine, and despite the well-known association of stavudine with long-term side-effects such as mitochondrial toxicity and dyslipidaemia (29-32).

Several studies have evaluated the cost-effectiveness of first-line regimens containing alternative drugs in low- and middle-income countries. Rosen *et al*. recently showed that adding tenofovir to an initial regimen containing lamivudine or emtricitabine is cost-effective over a two-year period at the current cost of tenofovir in South Africa (33**). The increased cost of tenofovir was offset by the cost of managing stavudine-related toxicities. The tenofovir strategy was then found very cost-effective with modest reductions in cost (from $17/month to $12/month).

In India, Bender *et al*. evaluated the clinical outcomes, cost, and cost-effectiveness of four first-line ART regimens in India: 1) stavudine-containing ART; 2) stavudine-containing ART, followed by substitution of stavudine with zidovudine after six months to reduce the risk of lipodystrophy and lactic acidosis; 3) zidovudine-containing ART; and 4) tenofovir-containing ART(Bender et al[**]). When the current cost of tenofovir-containing ART ($14/month) was used, initiating ART with tenofovir, lamivudine and nevirapine was associated with an ICER of $760/YLS compared to no ART (India 2008 per capita GDP, $1,090). Alternative strategies were less cost effective. Both stavudine and zidovudine resulted in lower life expectancies than tenofovir, likely because the higher rates of virologic suppression and lower rates of toxicity associated with tenofovir reduced the likelihood of switching to a second-line regimens, thus making the tenofovir regimen more durable.

These studies, as well as evidence that drug toxicities reduce treatment efficacy, strongly support WHO guidelines revision to phase out stavudine in favor of initial regimens containing tenofovir or zidovudine.

Cost-effectiveness of antiretroviral therapy: *What to switch to based on what criteria*

As an increasing number of HIV-infected patients initiate ART in low- and middle-income settings and reports of drug resistance and interruptions in ART roll-out grow, decision makers and national HIV/AIDS programs need robust information on the cost and clinical outcomes associated with long-term HIV care. Particularly in the context of resource constraints, evaluations of the cost-effectiveness of first-, second- and then third-line ART regimens are critical. Furthermore, different strategies for monitoring ART efficacy must be assessed.

[**]Bender MA, Kumarasamy A, Mayer KH, Wang B, Walensky RP, Flanigan T, Schackman BR, Scott CA, Lu Z, and Freedberg KA, for the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)–International Investigators. Cost-Effectiveness of Tenofovir as First-Line Antiretroviral Therapy in India. CID 2010 (1 February);50 (in press).

Most cost-effectiveness analyses in resource-limited settings have compared single lines of ART, although second-line regimens have been considered in sensitivity analysis (20, 21, 35, 36). Most studies found that adding a second-line regimen after failure of the first-line regimen increases both life expectancy and costs, but is not cost-effective given the high costs of second-line therapy. If the cost of second-line ART decreases, however, this strategy would become of good value.

Some authors have assessed the cost-effectiveness of various sequences of ART regimens. Using a simulation model of HIV, Walensky *et al*. (2007) evaluated the outcomes associated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and a boosted protease inhibitor (PI)-based regimen administered in alternative orders (37**). The study consistently favoured initiation with an NNRTI-based regimen, regardless of the population prevalence of NNRTI resistance (up to 79 percent) and the efficacy of NNRTI-based ART. The most influential parameters were the cost and efficacy of the boosted PI-based regimen.

Bendavid *et al*. recently compared two three-regimen strategies using cost and effectiveness data from South Africa: 1) three nucleoside reverse transcriptase inhibitors (NRTI), two NRTIs plus one NNRTI, and two NRTIs plus one boosted PI; and 2) two NRTIs plus one NNRTI, two NRTIs plus one boosted PI, and a regimen containing a second-generation boosted PI, such as ritonavir-boosted darunavir (38**). The authors concluded that initiating ART with three NRTIs is not cost-effective. The second strategy was cost-effective when CD4 count monitoring was available. HIV RNA monitoring was cost-effective in countries with annual per capita GDPs >$2,000. The 2009 WHO guidelines recommend that national programs establish standard third-line ART regimens containing new drugs such as integrase inhibitors and second generation NNRTIs and PIs that have proven effective in treatment-experienced patients (REF WHO 2009[*]).

In many resource-limited countries, CD4 count and HIV RNA tests are not routinely available, and their use has been the subject of considerable international debate (39-41). Several studies have examined whether investments in CD4 count and HIV RNA tests are economically justifiable. These studies demonstrated that CD4 count monitoring was cost-effective when compared to a symptom-based approach for determining the timing of treatment initiation. Furthermore, CD4 count tests benefitted a substantial proportion of individuals for whom treatment would otherwise have been delayed until the appearance of life-threatening symptoms (21, 42).

Studies on the use of laboratory monitoring to determine when to switch regimens, particularly virologic monitoring, have been less consistent. Phillips *et al*. stated that the benefits of HIV RNA and/or CD4 count tests over clinical monitoring alone for switching therapy were modest (40**). Others found that HIV RNA monitoring led to considerable benefits in low-income countries, but that this strategy was associated with high ICERs ($16,520/QALY in Bishai *et al*. and $6,760/QALY in Bendavid *et al*.) (42**, 43**). Kimmel *et al*., in a study using data from Côte d'Ivoire, recently found that HIV RNA tests were associated with favorable ICERs when used to guide the timing of ART switches (REF 44 in press at JAIDS**). They estimated that at an HIV RNA test cost of $87, $50, and $25, the ICERs of biannual HIV RNA tests were $4,240, $3,260, and $2,580/YLS, respectively (Côte d'Ivoire 2008 per capita GDP: $1,120) (REF). The results of these studies are not always consistent with each other, due to differences in model structure and input variables. The cost of the test, first-line ART efficacy, and the impact of resistance on the efficacy of second-line ART had an impact on cost-effectiveness, but nearly all studies showed that the cost-effectiveness of HIV RNA monitoring was more attractive when the cost of second-line treatment decreases. The new WHO guidelines recommend the use of HIV RNA tests, where available, to confirm treatment failure. When HIV RNA tests are routinely available,

they should be used to detect viral replication every six months. When they are not available, immunological criteria should be used to confirm clinical failure.

CONCLUSIONS

Many studies have now assessed the cost-effectiveness of HIV treatment in resource-limited settings. It is difficult to compare the results directly, because choice of time horizon, design, incorporation of the public health effects of ART in decreasing transmission, and costs differ among these studies. In order to provide information that is both clinically useful and policy-relevant, cost-effectiveness analyses must be up-to-date, relevant to local settings, and available and understandable to decision-makers. Studies that reflect the most current understanding of HIV epidemiology and treatment should be continually refined and updated.

The studies described in this article report several important results. First, earlier ART initiation, based on CD4 criteria, is cost-effective in most countries. Second, the high cost of first-line tenofovir-based ART may be offset by lower rates of long-term toxicity compared to first-line stavudine-based ART as well as by its decreasing cost over time. Third, HIV RNA monitoring combined with CD4 count monitoring is more clinically effective than CD4 count monitoring alone, but this strategy is not cost-effective in all studies because HIV RNA tests and second-line regimens are often costly. Finally, third-line ART containing a second-generation boosted PI may be cost-effective. Further work is needed to determine the optimal sequence of ART regimens in terms of both survival and cost, the long-term consequences of alternative laboratory monitoring strategies, and the feasibility of incorporating these strategies into HIV/AIDS programs in low- and middle-income settings.

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** for outstanding interest (it refers to papers on cost-effectiveness analyses that have been specially described in the text as well as in the table)

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Table 1

Cost-effectiveness of HIV ART in resource-limited settings

Reference	Setting	Compared Interventions	Methods	Cost Measure	Effectiveness Measure
Goldie *et al.* 2006	Côte d'Ivoire	No treatment ART and Bactrim Start ART at CD4 threshold	State-transition Monte Carlo simulation model	Medical care costs	Life-years saved
Freedberg *et al.* 2007	India	No ART Start ART at CD4 <200/μl Start ART at CD4 <250/μl Start ART at CD4 <350/μl	State-transition Monte Carlo simulation model	Direct medical care costs	Life-years saved
Badri *et al.* 2006	South Africa	No ART Start ART at CD4 <200/μl Start ART at CD4 200-350/μl Start ART at CD4 >350/μl	Monte Carlo simulation Markov state-transition model; data from Cape Town AIDS cohort study	Medical care costs	Quality-adjusted life-years
Cleary *et al.* 2006	South Africa	No ART Start 2 lines of ART at CD4 <200/μl + any WHO stage OR WHO stage IV + any CD4	Observational cohort; Markov state-transition model	Medical care costs	Life-years saved; quality-adjusted life-years
Loubiere *et al.* 2008	Morocco	No ART Start ART at CD4 <100/μl Start ART at CD4 100-200/μl Start ART at CD4 >200/μl	Observational cohort	Direct medical care costs	Life-years saved
Bender *et al.* 2010	India	No ART Start ART with d4T+3TC + NVP Start ART with TDF +3TC+ NVP Switch d4T to AZT at 6 months Start ART with AZT +3TC+ NVP	State-transition Monte Carlo simulation model	Medical care costs	Life-years saved
Bishai *et al.* 2007	Resource-limited setting	ART; no laboratory monitoring ART + total lymphocyte count ART + CD4 count ART + CD4 count + HIV RNA	Computer-based discrete event simulation model of HIV	Medical care costs	Quality-adjusted life-years
Rosen *et al.* 2008	South Africa	1 line of ART: d4T-based 2 lines of ART: substitute d4T with TDF	Observational cohort; state-transition model	Medical care costs	Quality-adjusted life-years
Walensky *et al.* 2007	Cote d'Ivoire	No ART 1st-line: NNRTI-based; 2nd-line: PI-based 1st-line: PI-based; 2nd-line: NNRTI-based	State-transition Monte Carlo simulation model	Medical care costs	Life-years saved

Reference	Time Horizon	Discount Rate	Perspective	Results	Sensitivity Analysis
Goldie *et al.* 2006	Lifetime	3%	Societal	Reference group Consistently cost-effective $1,430/YLS vs. starting ART at severe OI	Costs of routine care, ART, and CD4 test

Reference	Time Horizon	Discount Rate	Perspective	Results	Sensitivity Analysis
Freedberg *et al.* 2007	Lifetime	3%	Societal	Reference group Dominated $480/YLS $620/YLS	Cost of 2nd-line ART; stop ART at immunologic failure
Badri *et al.* 2006	Lifetime	3%	Public-sector health care payer	Reference group $60/QALY $710/QALY $1,310/QALY	ART cost reduced 40% (consistently cost-saving)
Cleary *et al.* 2006	Lifetime	3%	Provider	Reference group $1,170/LY; $1,310/QALY	ART efficacy; health-related quality of life; mortality
Loubiere *et al.* 2008	5 years	3%	Hospital	Reference group €612 €962 €9,881	ART costs; total costs; ART efficacy
Bender *et al.* 2010	Lifetime	3%	Societal	Reference group Dominated $760/YLS Dominated Dominated	Access to and cost of additional lines of ART; TDF efficacy and cost; nephrotoxicity rate
Bishai *et al.* 2007	10 years	3%	Societal	Reference group 1 line: dominated by CD4 strategy; 2 lines: $1,260/QALY 1 line: $270/QALY; 2 lines: $9,730/QALY 1 line: $18,180/QALY; 2 lines: $16,520/QALY	Efficacy of 1st- and 2nd-line ART
Rosen *et al.* 2008	2 years	None	Government	Reference group $9,340/QALY	d4T-related LTFU; TDF cost
Walensky *et al.* 2007	Lifetime	3%	Societal	Reference group $939/YLS Dominated	Changes in CD4 count decline rates; drug costs; 2nd-line efficacy
Walensky *et al.* 2009	South Africa	No ART Start ART at CD4 <250/μl Start ART at CD4 <350/μl	State-transition Monte Carlo simulation model	Medical care costs	Life-years saved
Bendavid *et al.* 2009	South Africa	1st-line: NNRTI-based; 2nd-line: Pi-based 1st-line: 3 NRTI; 2nd-line: NNRTI-based; 3rd-line: Pi-based 1st-line: NNRTI-based; 2nd-line: Pi-based; 3rd-line: second generation PI-based	State-transition Monte Carlo simulation model	Medical care costs	Life-years saved
Phillips *et al.* 2008	Resource-limited settings	Switch at HIV RNA >500 copies/ml Switch at HIV RNA >10,000 copies/ml Switch at WHO stage 3/4 event Switch at CD4 decline from peak	Stochastic computer simulation model	Medical care costs	Life-years saved
Kimmel *et al.* 2008	Côte d'Ivoire	Switch at 50% CD4 decline from peak	State-transition Monte Carlo	Medical care costs	Life-years saved

Reference	Time Horizon	Discount Rate	Perspective	Results	Sensitivity Analysis
		Switch at 90% CD4 decline from peak Switch at 1 severe OI Switch at 0.5 log_{10}copies/ml increase or return to pre-ART HIV RNA	simulation model		
Walensky *et al.* 2009	Lifetime	None	Societal	Reference group $1,190/YLS $1,300/YLS	ART efficacy; mortality; ART lines and cost; switching and stopping criteria
Bendavid *et al.* 2009	Lifetime	3%	Societal	Reference group Dominated $2,680/YLS ($6,760/YLS when HIV RNA tests are available)	ART efficacy; drug and HIV RNA test costs
Phillips *et al.* 2008	20 years	3%	Societal	$1,500/YLS $4,010/YLS $470/YLS $9,680/YLS	ART initiation criteria
Kimmel *et al.* 2008	Lifetime	3%	Societal	Reference group $14,080/YLS Dominated $18,920/YLS	Delay to ART switch; drug resistance; ART cost