Cost-effectiveness of managing HIV infection

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The worldwide spread of HIV infection continues, particularly in economically vulnerable, developing and emerging countries. There is a lack of resources to supply effective prevention measures and apply highly active antiretroviral therapies. In the regions concerned, economical effects of morbidity- and mortality-associated productivity losses in those of a working age remain serious. Thus, the United Nations Program on HIV/AIDS and the World Health Organization have predicted a dramatic decrease of South Africa's and other African states' domestic product in the coming years. Therefore, with the world economical consequences from the HIV pandemic, a large political challenge in the next 10 years will arise.

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Infection with the HIV retrovirus leads to AIDS by impairment of certain parts of the immune system, predominantly the cellular division. During the asymptomatic incubation period, usually a short time (up to a few weeks) after transmission of HIV, the number of viruses increases without clinical symptoms. At the onset of specific immune responses against HIV, a prolonged 'flu-like' acute retroviral syndrome develops, which usually lasts up to a few weeks.

After this acute symptomatic phase, clinical symptoms disappear and the clinically latent chronic phase of HIV infection begins. HIV destroys the body's immune system predominantly by striking the immune system's helper T-cells ($CD4^+$ T-cells). These cells are the targets for HIV, and the virus replicates inside them. The degree of viral replication, which can be measured by viral load quantification (the number of viruses per ml blood) indicates the damage to the immune system and correlates with the velocity of progress to immune deficiency. The absolute number of $CD4^+$ helper T-cells, measured per µl blood (CD4 value), predicts the immune system's strength. The smaller the number of $CD4^+$ helper T-cells, the worse the functioning of the patient's immune system.

At the end of the chronic phase, usually after several years with asymptomatic progress of immune deficiency, unspecific symptoms or diseases arise, indicating a disturbance of the cellular immune defence. These are referred to as clinical category B patients within the Center for Disease Control classification of HIV disease. AIDS defining diseases (clinical category C) emerge as a final stage of HIV disease. After 14 years, approximately 70% of the HIV infected fall ill with AIDS [102]. In this immune deficiency state – without antiretroviral treatment – death usually follows the first complication of AIDS within months or a few years.

Epidemiology

In 2003, approximately 5 million new HIV infections occurred, creating a total of 40 million people living with the HIV infection and AIDS (PLWHA) worldwide. In the same year, more than 3 million PLWHA died [101].

Transmission occurs predominantly by mucosal or parenteral exposition to the virus. Therefore, during the first decade of the HIV pandemic, transmission was more common in individuals with particular risk behavior. However, in the last few years, heterosexual contacts became the predominant

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transmittion route for new HIV infections. HIV is primarily transmitted by unprotected sex with an HIV infected person, drug users sharing injection equipment and mother-to-child transmission. In 2003, nearly 25.5–28.9 million people in Africa lived with HIV or AIDS, with the figure at 4.6–8.2 million in South and South-East Asia. In contrast to the increasing spread of HIV in most developing countries, in North America, Western Europe, Australia and New Zealand, the incidence (new infections per year) has stabilized to a low level. However, overall, the pandemic of HIV proceeds. In spite of all prevention efforts, a duplication of infected persons is expected until 2010 [2].

The whole dramatic dimension of the HIV pandemic shows itself not only in epidemiological data but also with the health-care situation of HIV infected people. In high income countries, approximately one-third, and in Latin America/the Caribbean, 8.9% of HIV patients were treated with antiretroviral active substances in 2001. Worldwide, less than 5% of HIV patients have access to appropriate antiretroviral therapy [4–8]. Due to the lack of treatment options, especially in rural areas of developing countries, the prognosis of the advanced stages of the HIV infection is poor. Therefore, in developing countries, the natural course of the disease in its early stages resembles the natural history of HIV in industrialized countries in the past when highly active antiretroviral therapy (HAART) was still not available [9]. Recently, some countries such as Brazil, India and South Africa have made attempts to enhance HAART access by a national production program of certain antiretrovirals.

Healthcare costs

Health economic evaluation studies can be differentiated into cost-of-illness studies and comparative cost-effectiveness analysis. Descriptive cost-of-illness studies aim to quantify the budget-impact of costs of each case of the disease as a whole. Whereas cost-effectiveness analysis evaluate different courses of action regarding their relationship between inputs and outcome, the later sophisticated approach aims to improve case and/or disease management. Depending upon the study perspective, different input and outcome components are included in the analysis. The direct costs of HIV/AIDS include all prevention measures and utilization of healthcare and long-term care resources.

Table 1. Minimum monitoring program of HIV patients [11].

	Under ART (annual)	Untreated (annual)
Hemogram, glucose, lipid panel, liver panel, creatinine, lipase, uric acid	4–6 x	2–4 x
Viral load	4 x	2–4 x
$CD4^+$ T-cell count	2–4 x	2–4 x
Physical examination	2-4 x	1–2 x
Gynecological examination	1 x	1 x
Funduscopy if $CD4^+$ T-cells <100 µl	2–4 x	4 x (and under HAART)

ART: Antiretroviral therapy; HAART: Highly active antiretroviral therapy.

Prevention

Prevention measures are an important course of action in the case of transferable diseases and patient treatment. HIV/AIDS prevention includes different interventions, such as safer-sex campaigns, educational advertising, health education, screening and consulting programs of vulnerable groups, prevention of mother-to-child transmission, syringe exchange and condom disposal programs, postexposition prophylaxis and selective blood safety measures.

In industrialized countries, the cost-effectiveness ranges from US$406 to 1.2 million for a prevented HIV infection and strongly depends on its prevalence in the region [10]. Therefore, prevention measures have higher cost-effectiveness in developing countries, which are more affected by the HIV pandemic [1]. The range is between US$1 per disability-adjusted life year (DALY) gained for selective blood safety measures and by targeted condom distribution and up to US$75 for single-dose nevirapine (Viramune®, Boehringer Ingelheim, Germany) and short-course zidovudine (AZT; Retrovir®, GlaxoSmithKline plc., London, UK) for prevention of mother-to-child transmission, voluntary counselling and testing and tuberculosis treatment [2].

Treatment of the infection

Medical care

The first utilization of medical services due to HIV is in the form of an HIV test. They often take place in the case of a suspected infection, for example, if certain symptoms appear or on special occasions such as a new partnership, after risky sexual contact or pregnancy. The price of search tests ranges between €20 and 30, and the price of confirmation tests ranges between €150 and 300.

For the surveillance of disease progression and due to the complexity and toxicity of antiretroviral treatment, patient monitoring is indicated [11]. The viral load (number of copies/ml) should be determined two- to four-times annually at the beginning of the antiretroviral therapy and in the case of a treatment change, every 4 weeks. If the viral load is under the detection limit, one measurement every 3 months is considered to be sufficient.

Apart from immunological values, a routine laboratory test is recommended (TABLE 1) [11,102,103]. The program refers to asymptomatic patients. If antiretroviral therapy starts and/or changes or complaints emerge more frequently, depending upon the problem, extended investigations may be necessary. Routine tests include electrocardiograms, x-ray examinations, ultrasound sonography, serology and lipid and lactate profiles. Durability of virology suppression and long-term success of HAART depends upon its ability to reach sufficient drug levels

in all compartments of the body. Therefore, pharmacokinetics and therapeutic drug monitoring recently became an important tool for individualized therapy monitoring. It will presumably be increasingly used in the future.

Opportunistic infections (OI) caused by certain virus, fungus, parasite or bacterial agents are defined as diseases which an intact immune system can fend off or keep in check. As a consequence of HIV-associated immune deficiency, such infections may be severe or life threatening. AIDS-defining OI usually arises at $CD4^+$ T-cell counts below 200 per µl (TABLE 2). Some imminent infections may require pre-emptive chemotherapy or primary prophylaxis, if the $CD4^+$ T-cell count falls below a certain value. A suppression or maintenance therapy (secondary prophylaxis) usually follows after the specific treatment of intercurrent overt opportunistic disease. Certain malignancies, such as cancer or malignant lymphoma, arise more frequently in HIV infection and AIDS. They may require irradiation, chemotherapy and surgical treatment.

Incidence of most opportunistic diseases has decreased since HAART became available because immunological reconstitution occurs under HAART [12,13]. Nevertheless, the number of the cancer cases may rise again in the future, since life expectancy under HAART increases. Currently, OIs occur in patients with an unknown HIV infection who apply to a physician for the first time. For example, in Germany, four out of five patients did not know they had contracted an existing HIV infection or were antiretroviral-naive in 2000. Detailed North-American OI-prophylaxis recommendations exist, but to transfer these to other countries is difficult due to the different risk and distribution of HIV prevalence [14].

Certain opportunistic diseases are usually life-threatening, therefore inpatient care is necessary. Despite all medical evolution some problems remain unsolved. Progressive multifocal leukoencephalopathy and cryptosporidiosis are still without proven treatment options. Resistance against antimicrobial chemotherapeutics and antiretroviral drugs still arise worldwide.

During the first years of the HIV pandemic, before the introduction of antiretroviral therapy, health economics focused mainly on the prognosis of future development of AIDS-related inpatient care. Since HAART became available, the economic impact on hospitalization clearly decreased [15,16]. A reason for this decrease may still be an introduction effect of HAART, which will swing to a higher level over time. Similar statements apply to long-term care and hospice services.

Table 2. Overview of opportunistic events.

Threshold level CD4 cells/ml	Opportunistic event
No bounds	Kaposi's sarcoma Tuberculosis Varicella zoster virus disease Bacterial pneumonia Lymphoma
<250	*Pneumocystis carinii* pneumonia Candida esophagitis Progressive multifocal leukoencephalopathy Herpes-simplex virus disease
<100	Toxoplasmosis HIV encephalopathy Cryptococcosis Miliar tuberculosis
<50	Cytomegalovirus disease Cryptosporidiosis Disseminated infection with *Mycobacterium avium* complex

Antiretroviral therapy

The primary goal of HIV treatment is a continuous and complete suppression of HIV replication. Correspondingly, researchers search for specific anti-HIV substances. Currently, there is a set of drugs available against HIV, however, eradication of HIV in the sense of a cure is unrealistic [17].

Three classes of antiretroviral agents are currently available for the treatment of HIV infection including nucleoside and nucleotide analogs (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Approximately 20 drug products have been licensed, including formulations of both individual and combined antiretroviral agents. The fusion inhibitor T-20 (enfuvirtide, Fuzeon®, Hoffmann-La Roche Inc., Switzerland) was launched in 2003 as the prototype of a fourth drug class. A number of additional drugs and new classes of drugs are in the pipelines of clinical research and some are expected to be licensed within the next few years.

Nucleoside analogs (nukes) target HIV enzyme reverse transcriptase. Acting as alternative substrates or false building blocks, they compete with physiological nucleosides but differ by small modifications. The incorporation of nucleoside analogs aborts viral DNA synthesis.

As with the nucleoside analogs, the target enzyme of NNRTIs is reverse transcriptase. They do not inhibit competitively as false building blocks for DNA synthesis but polymerization is significantly slowed down by noncompetitive blocking. The three currently available NNRTIs: nevirapine, delavirdine (Rescriptor®, Pharmacia, NJ, USA) and efavirenz (Sustiva®, Bristol-Myers Squibb, NY, USA; Stocrin®, Hoffmann-La Roche Inc.), were introduced between 1996 and 1998. Their convenient, simple dosage and advantageous tolerability have led nevirapine and efavirenz to become increasingly important components of the HAART regimens. However, no study provides clear evidence that one of these NNRTI is superior to the other.

Inhibition of HIV protease leads to the prevention of viral maturation by the release of virus particles which are unable to infect new cells. In the early 1990s, the first PIs were designed to fit exactly into the enzyme active site of the HIV protease. Since 1995, PIs have revolutionized the treatment of HIV infections when HAART became available by

allowing the possibility to combine three or more antiretroviral drugs. Toxicity profiles of available PIs differ, but differences in the effectiveness did not demonstrate clear superiority of one protease inhibitor over any other. However, there are two exceptions – the (unboosted) hard gel capsule saquinavir-HGC (Invirase®, Hoffmann-La Roche Inc.) and ritonavir (Norvir®, Abbott laboratories, IL, USA). Saquinavir survived by the development of soft gel capsules with improved bioavailability but also by boosting with ritonavir, a potent inhibitor of cytochrome P450. Small doses of ritonavir lead to increased plasma levels (boosting) of almost all PIs. A further booster combination consists of saquinavir (Fortovase®, Hoffmann-La Roche Inc.) and nelfinavir (Viracept®, Hoffmann-La Roche Inc.).

Due to country-specific price discrepancies, the annual costs of antiretroviral therapy in country comparison vary. In TABLE 3, the annual costs in Euros are given in accordance with the German pharmaceutical retail prices.

Until the mid-1990s, antiretroviral monotherapies were commonly used and were the only available treatment. Monotherapy led rapidly to viral resistance against the antiretroviral drug. The combinations of AZT and didanosine (DDI; Videx®, Bristol-Myers Squibb) or AZT and zalcitabine (DDC; HIVID®, Hoffmann-La Roche Inc.) improved success. Finally, the introduction of PIs and NNRTIs brought further progress in reduction of HIV replication and long-term control of viral replication. These combination treatments involved common PIs and NNRTIs. They were summarized under HAART.

Not all conceivable combinations are therapeutically meaningful. This generally applies for all kinds of monotherapies and most twofold combinations. A combination of AZT plus stavudine (D4T; Zerit®, Bristol-Myers Squibb) and lamivudine (3TC; Epivir®, GlaxoSmithKline plc.) plus DDC should be avoided, since the drugs work antagonistically. DDI plus DDC, as well as D4T plus DDC, should not be combined due to the increased risks of side effects. Also, combinations of abacavir (Ziagen®, GlaxoSmithKline plc.) and NNRTIs should not be combined in one step at the same time, since the similar side effects can hardly be differentiated and require different management. The suitability of the combination D4T plus DDI has been reconsidered recently, since additive mitochondrial toxicity of this certain combination has been discussed. Unsuitable single agents are ritonavir (pronounced side effects), amprenavir (Agenerase®, GlaxoSmithKline plc.) and saquinavir (daily high pill number), delavirdin (missing proof for primary therapy).

Table 3. Antiretroviral drugs[§].

Drug class	Brand name	Abbreviation	Active agent	German annual costs (€) 2003 [104]
Nucleoside reverse transcriptase inhibitors	Epivir®	3TC	Lamivudine	3872
	HIVID®	DDC	Zalcitabine	3078
	Retrovir®	AZT	Zidovudine	5137
	Videx®	DDI	Didanosine	4861
	Viread®	TDF	Tenovofir	7021
	Zerit®	D4T	Stavudine	4609
	Ziagen®	ABC	Abacavir	5792
Non-nucleoside reverse transcriptase inhibitors	Rescriptor®	DLV	Delavirdine	[§§]~2700
	Sustiva®	EFV	Efavirenz	6495
	Viramune®	NVP	Nevirapine	5678
Protease inhibitors	Agenerase®	APV	Amprenavir	9708
	Crixivan®	IDV	Indinavir	5740
	Fortovase®	SQV-FTV	Saquinavir	8020
	Kaletra®	LPV	Lopinavir/ritonavir	9761
	Viracept®	NFV	Nelfinavir	8055
Fusion inhibitors	Fuzeon®[§§§]	T-20	Enfuvirtide	~26,500

[§]Incomplete and without combinations.
[§§]Not licensed in the EU.
[§§§]Approved in the USA and the EC (June 2003).

Despite increasing frequencies of transmissions of resistant HIV genotypic resistance, tests in antiretroviral-naive individuals are not recommended in order to choose an individualized optimal initial therapy. However, under these circumstances, it is more efficient in a setting with virology failing antiretroviral treatment to identify acquired resistance under HAART genotypically [18].

Most classical HAART regimens include two nucleoside analogs as a backbone (nukes backbone). Many studies have been engaged regarding the best combination of two nucleoside analogs, however, a superior combination is still not apparent. The HAART combination is complete either with a PI, NNRTI or third nucleoside analog. Alternative HAART regimens may be available in the future by the introduction of boosted double PIs or nuke-sparing combinations of PI and NNRTI. In addition, the introduction of fusion inhibitors may further increase the spectrum of HAART combinations. TABLE 4 gives an overview of combinations for initial therapy that have been recently recommended.

Table 4. Recommended initial therapy [105].

Preferred:	Lamivudine + zidovudine or	+	Efavirenz	or
	Lamivudine + stavudine		Lopinavir/ritonavir	
	Lamivudine + tenofovir	+	Efavirenz	
Alternative	Lamivudine + didanosine	+	Efavirenz	or
			Nevirapine	
	Lamivudine + zidovudine or	+	Efavirenz	or
	Lamivudine + stavudine		Nevirapine	or
			Amprenavir/saquinavir	or
			Indinavir	or
			Indinavir/saquinavir	or
			Nelfinavir	or
			Saquinavir	or
			Abacavir	

Starting the initial therapy

The optimal time to initiate antiretroviral therapy is controversialy. However, most physicians increasingly refrain from the 'hit hard and early' hypothesis as being the most appropriate approach [19]. The indication for antiretroviral therapy is based on clinical assessment, $CD4^+$ cell count and viral load, and also taking into account comorbidity, adherence, comedications, intake modalities, drug interaction, side effects and the individual patient's situation. A clear recommendation to start the therapy is given on the basis of randomized studies with clinical end points, if:

- Patient symptoms are of classification B or C
- CD4 cell decline is under 200 per µl.

On the basis of studies with surrogat markers, an initiation therapy start can be recommended if $CD4^+$ T-cell count is between 200 and 350 per µl or between 350 and 500 per µl and the viral load is above 50,000. In comparison with the early days of HIV, most physicians delay initiation of HAART until the $CD4^+$ T-cell count drops to between 200 and 350 per µl [20–22,106].

Adverse effects under antiretroviral therapy

Under HAART, adverse side effects are a frequent problem and up to 70% of HIV patients change therapies within the first 9 months of treatment [23]. Approximately 20% of all patients refuse to begin HAART due to concerns regarding the side effects. As a coping strategy, either additional medicines must be taken to treat the side effects or suspected substances must be changed with another. However, both alternatives are associated with additional costs.

Gastrointestinal side effects are the most common adverse events of most antiretroviral drugs. They commonly occur during the early stages of therapy. Typical symptoms include abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting. Antiemetics may relieve symptoms if simple modifications do not alleviate nausea and vomiting. Loperamid (Imodium®, Janssen-Cilag Ltd, NJ, USA) or fibers are frequently administered if diarrhea does not improve.

In up to 40% of patients treated with efavirenz, CNS side effects such as dizziness, mood swings, depression and depersonalizations have been described. Discontinuation of therapy becomes necessary in only 3% of patients. Most peripheral polyneuropathy is caused by the nucleoside analogs DDC, DDI and D4T. HIV infection can lead to peripheral polyneuropathy but drug-induced forms may become apparent much earlier.

Renal toxicity occurs particularly in patients treated with the PI indinavir (Crixivan®, Merck & Co., NY, USA) or the recently licensed nucleotide analog tenofovir (Viread®, Gilead Sciences Inc., CA, USA). Tenofovir is associated with tubulopathies. Indinavir is able to induce cristalluria and approximately 10% of patients suffer from renal colic. Elevated liver functions occur in 2–18% of patients under HAART independent of the drug classes used. Severe hepatic damages have been observed during treatment with nevirapine, indinavir and ritonavir. Of patients taking zidovudine, 5–10% develop anemia or other hematotoxicity. In cases of severe anemia, zidovudine should be given in reduced doses or must be discontinued.

More than 50% of hyperallergic skin reactions (NNRTI allergies) resolve despite continuation of therapy. Antihistamines are helpful. In total, 7% of patients discontinued treatment with nevirapine and delavirdine, and 2% with efavirenz. Abacavir causes a hypersensitivity reaction in approximately 2–8% of patients, which may be life-threatening. In patients without pre-existing resistant virus, the options for a change

of therapy due to side effects under otherwise sufficient therapy is of low risk if the suspicious active agent is replaced by another. In this case, the switch occurs predominantly to a drug from the same class.

Metabolic complications are common under HAART. Although their physiologic background path is not yet fully understood, they are believed to be long-term side effects of HAART. Hyperglycaemia occurs predominantly under treatment with PI containing HAART. Hyperlipidemia is presumed to be associated with nucleoside analogs. Impacts of metabolic abnormalities on cardiovascular risks have been discussed. However, treatment options of HAART-associated metabolic disorders are limited and not yet generally recommended [24].

In addition, therapeutic approaches for the lipodystrophy-syndrome (abnormal body fat distribution) are still under debate. Proposed interventions cover general recommendations (e.g., diet and sport), a change of therapy such as NNRTIs in exchange for PI or switch from d-substances (i.e., D4T, DDI and DDC) to another NRTI, is also an attempt to treat with metabolic effective agents.

Clinical surveillance under antiretroviral therapy

Success of treatment can be evaluated by using virological (decrease in viral load), immunological (rise of $CD4^+$ T-cells) and clinical (constitutional improvement and prevention of AIDS) criteria. The long-term success is disappointing. In a meta-analysis of HAART studies to first-line treatment, virologic success could be maintained in only 25–75% of patients after 48 weeks of treatment [25]. PI-based HAART failed in up to 94% of patients after a median follow-up of only half a year, when their adherence was less than 70% [26]. However, it also appears promising that in another study, well-adjusted patients with good compliance showed therapy failure in only 5.2% after 3.3 years [27].

If the viral load cannot be lowered to below the detection limit of 50 copies/ml within a period of 3–4 months, treatment failure has to be assumed. If the missing success of HAART is due to virology failure of HAART rather than to insufficient adherence to the treatment, as many drug components as possible must be exchanged. The most important risk factors for long-term virology failure are intensive pretherapy with antiretroviral agents and a poor compliance.

Effective medications can be identified by the use of resistance tests. Depending upon selected procedures and laboratory total costs add up to €350–500 in the case of genotype resistance testing, twice as much in phenotype resistance testing. A problem of both methods is their requirement of a minimum quantity of 500–5000 copies/ml. Without resistance testing, patients with exclusive nukes pretherapy should change empirically to new nukes plus NNRTI plus PI. For patients failing under nukes and NNRTI therapy, the use of a PI is recommended.

If the PI regimen fails, the salvage area with 3 or more new antiretroviral agents takes off, although the term 'salvage' is used differently. Only a minority of the patients have long-term benefits from the salvage therapy but the introduction of new drugs such as the PI tipranavir or the FI enfuvirtide may in future improve these results.

Cost-effectiveness

Under HAART the treatment of HIV has led to a decline of morbidity and mortality. The direct healthcare costs are effectively refinanced by reduced treatment for opportunistic diseases and hospitalization. In addition, a study at a German hospital outpatient unit demonstrated, that the average annual healthcare costs decreased from €35,865 per patient in 1997 to €24,482 per patient in 2001 [15]. The corresponding average drug expenses declined from €17,746 to 16,007 but their relative impact within total direct costs increased from 49 to 64%. Although the acquisition costs of HAART are substantial, they ensure sustained success of healthcare in treatment of HIV-infection.

Until recently, there have been few scientific publications of economic evaluations of HAART. TABLE 5 provides an overview of studies in different national healthcare settings cited by Moore and colleagues [28]. As shown, they are the latest estimation from the US health service perspective and vary from US$13,000 23,000 per quality-adjusted year of life. Although comprehensive and long-term modelling over a broad range of HAART regimens are missing, the benefits of HAART can still be seen. Cost-intensive treatments of opportunistic diseases and hospital care could be increasingly avoided by use of HAART. Due to the therapy's complexity and the limited experience horizon, future treatment guidelines may be changed in order to manage HAART regimens efficiently in the long run.

In contrast to industrialized nations, the situation presents itself differently for developing countries. From their perspective, the prohibitive high drug prices are rationing the access to HAART [9]. Even with substantial price reductions, the cost-effectiveness of HAART lags behind the cost-effectiveness of prevention measures.

Not only should pure drug costs be taken into account by the evaluation, an imperative precondition is a working healthcare system with an integrated supply, logistics and availability [35,36]. Nevertheless, healthcare for PLWHA in threshold countries with a high prevalence of HIV, such as Brazil, may benefit from drug price reductions and generic drugs.

Indirect cost

In addition to the visible direct costs of HIV, there are also the indirect costs, which should be considered. Many diseases, in particular HIV, are characterized by a huge loss of human capital. From a healthcare perspective, indirect costs are irrelevant and therefore production loss, which results from morbidity (decreased manpower, absence from work, increased unemployment and occupational disability), is often ignored in economic evaluation (TABLE 5), although most of these studies refer to symptomatic diseases and AIDS rather than to the early disease stages. By taking a societal perspective, indirect costs should always be taken into consideration in health economic evaluations.

Table 5. Published economic evaluations of HAART.

Cost values	HAART	Comparator	Horizon	Perspective	Cost–effectiveness ratio	Ref.
1996	2 backbones + indinavir	Two drug combination and monotherapy	6 years	Direct cost	US$10,000 per life year gained	[29]
1997	1 protease inhibitor + 2 non-nucleoside reverse transcriptase inhibitors	Nonantiretroviral therapy		Direct cost Indirect cost	CHF14,000–45,000 per life year gained. The optimistic scenario is cost saving	[30]
1996	Zidovudine + lamivudine + indinavir	Zidovudine + lamivudine	5 years	Direct cost	US$13,299 per life year gained (incremental)	[31]
1997	2 nucleoside reverse transcriptase inhibitors + 1 protease inhibitor or + 1 non-nucleoside reverse transcriptase inhibitors	Different non-HAART combinations		Direct cost	CDN$47,000–59,000 per life year gained	[32]
1998	Zidovudine + lamivudine + efavirenz	Zidovudine + lamivudine + indinavir	15 years	Direct cost	Not stated precisely, dominance of EFV	[33]
1998	Zidovudine + lamivudine + indinavir	Two drug combination	Maximum 3.51 years	Direct cost	US$13,000–23,000 per QALY	[34]

CDN: Canadian dollars; CHF: Swiss franc; EFV: Efavirenz; HAART: Highly active antiretroviral therapy; QALY: Quality-adjusted life year.

In general, the human capital approach is used to estimate the indirect costs in which the inherent possible added-value-potential of a person is assessed in this approach [37]. The present value in future expected income of a person is determined as the measure for the added value. From the economic point of view, the human capital approach is often criticized due to the underlying assumption of full employment and production at marginal costs. More recent approaches, such as the friction cost approach, avoid this over-estimation and assume that if a person is absent from work they will be replaced by competing employees within a short period. In these models, production losses per case and period persist maximally for the duration of an average vacancy. In a German sample of the friction approach, costs add up to only one-tenth of the amount derived from the human capital approach [38]. In a competitive job market situation with high unemployment, indirect costs may be less important as a result of early disability retirement.

Effective HAART allows an increasing portion of HIV infected persons to remain in their job and therefore, indirect costs can be reduced [30]. In countries with high employment rates, there is clear evidence that consideration of indirect costs may create additional cost savings [30].

Summary & conclusion

The worldwide spread of HIV continues, especially in the economically vulnerable, developing and emerging countries. Prevention measures have a higher cost–effectiveness ratio in developing countries. From a developing country perspective, prohibitive high drug prices ration the access to HAART. However, despite substantial price reductions, the cost-effectiveness of HAART lags behind prevention measures and working healthcare systems are regularly missing. Industrial nations with a strong economic power are unimpressed by HIV-associated costs. Under the assumption that in the future it will be possible to stabilize HIV prevalence on a low level, national healthcare expenditures for HIV will not trouble the future economic development of these countries. Many developing countries suffer from HIV [3]. Although healthcare expenditures on HIV are still low in these countries, premature deaths cause high indirect costs which threaten national economies and economic growth. Within the global economic network this will also affect the economies of industrial nations. Therefore, bridging the gap between industrial and developing nations may be rational – even from an economic point of view.

Expert opinion

Despite initial optimism in the early phase after the introduction of HAART, the use of recently approved therapeutics will not lead to a cure for the HIV-infection, either in the early phase of infection ('acute retroviral syndrome') or in the chronic or advanced stages of the disease. As a consequence, success of recently available treatment options is dependent upon its durable potency and tolerability during long-term administration. Currently, 17 substances from four different classes of antiretrovirals are available. Regularly updated treatment guidelines summarize the growing evidence from clinical studies. They emphasize to offer treatment to all patients with the HIV infection when cellular immunity is impaired but before opportunistic diseases become apparent. Different options are available to tailor an individualized antiretroviral combination with respect to toxicity, comorbidity, convenience and lifestyle.

Concerns over the uncertainty of long-term toxicity, such as a potentially elevated risk for coronary heart disease due to HAART-associated dyslipoproteinaemia, do not overweight the proven benefit of HAART in reducing morbidity and mortality when appropriate treatment is chosen.

Although virologic treatment failure occurs increasingly during the long-term administration of HAART, immunologic and clinical success may be preserved for a longer time period. In the future, new drugs from recent clinical trials with low toxicity and sustained antiretroviral potency may preserve the clinical sucess of HAART in most patients. This is also the case in heavily-treated patients.

Five-year view

The pipelines of pharmaceutical developments contain many new and promising drugs for antiretroviral therapy. They include new members of the classic antiretroviral substance classes, such as NRTIs, NNRTIs and PIs. Their potential advantages are reduced toxicity and drug–drug interactions, more convenient administration and superior antiretroviral potency, especially against resistant HIV isolates. In addition, new classes of drugs such as fusion inhibitors, entry inhibitors, chemokine receptor inhibitors and integrase inhibitors now are directly *ante portas*. They will increase the existing repertoire of options to control retroviral replication and therefore, will maintain the long-term success of HAART.

Developing diagnostic procedures, such as pharmacokinetics, pharmacogenetics and advances in susceptibility tests of antiretrovirals against individual HIV isolates may allow individually choosing a more rational therapy and therefore, more effective and less toxic HAART regimens.

International attempts to develop vaccines against HIV have been initiated. Some trials with certain vaccine constructs have reached clinical studies of Phase III. Therefore, it may be that one or more of them will influence the last period of the five-year view. Different approaches with some candidate vaccines may result in thier sucessful use. A preventive vaccine will reduce the risk of infection and increasing spread of the HIV pandemic. An immunotherapeutic vaccine will boost the immune response to HIV in a person already infected with the virus. The combination of both vaccination approaches would bring success even low efficacy of the vaccine candidate. The spread of HIV would decrease and the natural course of HIV infection in the vaccinated individual would change to a long-term nonprogressing chronic infection. In that way the HIV retrovirus may become 'friendly' without causing disease in (vaccinated) humans, as is the case for the genetically-related virus in certain primates and SIV.

Information resources

Recent developments in HIV vaccine:

- www.hvtn.org
  (Accessed January 2004)
- www.who.int/vaccine_research/diseases/hiv/en/
  (Accessed January 2004)

Treatment guidelines:

- www.aidsinfo.nih.gov
  (Accessed January 2004)

HIV-related topics and discussion platforms:

- www.hiv.net
  (Accessed January 2004)
- www.amedeo.com
  (Accessed January 2004)
- www.aegis.com
  (Accessed January 2004)

Key issues

- In 2003, there were estimated to be 5 million new HIV infections, more than 3 million deaths and approximately 40 million people living with HIV or AIDS worldwide. Most of which occured in developing countries.
- The cost-effectiveness of prevention measures depends strongly on prevalence and ranges. In industrialized countries, the cost is from US$406 to 1.2 million for a prevented HIV infection, and in developing countries the range is between US$1 and 75 per disability-adjusted life year gained.
- HIV drug expenses dominate the direct costs. Highly active antiretroviral drug regimens emanate from US$13,000 to 23,000 per quality-adjusted life year.
- Industrial nations are currently unimpressed by the HIV-associated costs but developing countries are threatened in an already weak economic situation.
- Recently, some countries are offering generic antiretroviral combinations. Certain three drug combinations are produced in Brazil (stavudine + lamivudine + nevirapin or stavudine + didanosine + lamivudine) and in India (triomune: stavudine + lamivudine + nevirapin), which reduces the daily drug costs per case by more than tenfold to less than €1.

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