The cost-effectiveness of highly active antiretroviral therapy, Canada 1991–2001

Eduard J. Beck[a,b], Sundhiya Mandalia[c], Maurice Gaudreault[a], Carl Brewer[b], Hanna Zowall[b], Norbert Gilmore[b,d], Marina B. Klein[b,d], Richard Lalonde[b,d], Alain Piché[e] and Catherine A. Hankins[a,b]

Aim: To estimate the cost-effectiveness ratio of highly-active antiretroviral therapy (HAART) in Canada.

Design: A before-and-after analysis to calculate incremental cost of life year gained (LYG) between 1991 and 1995 (pre-HAART period) and between 1997 and 2001 (HAART period) for non-AIDS and AIDS groups (CDC stage of HIV infection).

Methods: For two Quebec HIV hospital clinics, mean inpatient (IP) days, outpatient (OP) visits and direct health care costs per patient-year (PPY) were calculated. Cox's proportional hazards models calculated disease progression, stratified by study periods and adjusted for gender, age at cohort entry, sexual orientation, injecting drug use and baseline CD4 cell count.

Results: For non-AIDS patients, mean IP days was 1.6 (pre-HAART period) compared with 0.8 PPY (HAART period); mean OP visits increased from 2.8 to 5.5 PPY. Total cost was US$ 4265 (pre-HAART period) and US$ 9445 PPY (HAART period) of which 66 and 84%, respectively were spent on antiretroviral drugs. Median progression time was 6.3 years in the pre-HAART period compared with 12.5 years in HAART period (log rank $\chi^2 = 270$, $P < 0.0001$). Incremental cost per LYG between periods was US$ 14 587. For AIDS patients, mean IP days decreased from 13.3 to 4.4 PPY between periods; OP visits increased from 8.3 to 9.2 PPY. Total costs increased from US$ 9099 to US$ 11 754 PPY, while expenditure on antiretroviral drugs increased from 29 to 72% of total cost. Median progression time was 3.8 years in the pre-HAART period, which increased to 13.3 years in the HAART period (log rank $\chi^2 = 158$, $P < 0.0001$); incremental cost per LYG between periods was US$ 12 813.

Conclusion: HAART appeared a cost-effective intervention in Canada.

© 2004 Lippincott Williams & Wilkins

AIDS 2004, **18**:2411–2418

Keywords: use and costs services, cost-effectiveness, highly active antiretroviral therapy, life year gained, CDC stage of HIV infection

Introduction

The efficacy of triple combination antiretroviral therapy (ART) was first reported during the XI International Conference on AIDS in Vancouver in 1996 [1]. By 1997 highly active antiretroviral therapy (HAART) was the new standard of HIV treatment and care and introduced into routine clinical care in Canada. There

From the [a]Departement de sante publique de Montréal-centre, Quebec, the [b]Joint Departments of Epidemiology, Biostatistics and Occupational Health McGill University, Quebec, Canada, the [c]St. Stephen's Centre, Chelsea & Westminster Hospital, Imperial College, London, UK, the [d]Immunodeficiency Service, Institut thoracique de Montréal, McGill University Health Centre, Quebec, Canada and [e]Centre Universitaire de Santé de l'Estrie, Quebec, Canada.

Correspondence to Dr E. J. Beck, Strategic Information and Research (SIR) Unit, HIV Department, HIV-Tuberculosis - Malaria Cluster, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland.

E-mail: becke@who.int or eduard.beck@mcgill.ca

Received: 30 May 2004; revised: 24 August 2004; accepted: 14 September 2004.

have been no recent studies evaluating the cost-effectiveness of HAART in Canada, despite the increasing number of people being treated with these relatively expensive drugs [2]. A recent study estimated the cost of HIV service provision in Canada [3]. Although cost-of-illness studies provide useful information on the affordability of an intervention [4], such information does not give an indication of the trade-off between the costs of that intervention and its clinical benefits [4]. To assess the clinical outcomes and costs of HAART, data from two Quebec HIV hospital clinics were combined and analyzed to calculate the cost-effectiveness of HAART for 1997–2001 (HAART period) compared with 1991–1995 (pre-HAART period).

Methods

Data were obtained on HIV-infected patients seen between 1 January 1991 and 31 December 2001 at two university hospital HIV clinics in Quebec: one in Montreal and one in Sherbrooke. All data were collected prospectively and stored electronically.

Analysis

This study was a 'before-and-after' analysis of the introduction of HAART to observe the population effects both in terms of the clinical outcome – disease progression or life year gained (LYG) by Centers for Disease Control (CDC) stage of HIV infection – and the cost of HIV service provision. 1996 was the year in which triple HAART was demonstrated to be more efficacious compared with other antiretroviral regimens [1]. HAART was introduced into routine clinical management in late 1996 in Canada, and 1996 was therefore considered to be the 'watershed' year for this study; the HAART period was defined as beginning on the 1 January 1997.

Patients were classified by CDC classification of HIV infection as either being in stage A or B (non-AIDS) or CDC stage C (AIDS). Outcomes were compared for patients seen and managed during the pre-HAART period, 1 January 1991 to 31 December 1995, with those seen during the HAART period, 1 January 1997 to 31 December 2001. The number of LYG between the two periods were calculated by CDC stage of HIV infection and – combined with the annual costs of service provision – the incremental costs per LYG were estimated for the non-AIDS and AIDS populations.

Use and cost of services

Information on use of hospital inpatient and outpatient services was obtained from computerized information systems used in both hospitals. The mean numbers of inpatient days and outpatient visits per patient-year (PPY) were calculated for each study period and stratified by CDC stage of HIV infection, non-AIDS and AIDS. A patient-year was defined as 365.25 days of follow up. The methods used for calculating the mean use of services were similar to those used in previous studies [5–8]. The denominator consisted of the total duration of follow up for all patients in their respective CDC stage of HIV infection during each of the two study periods, from when they were first seen until the end of the respective study period if still alive and in the same CDC stage or when they progressed or died or when they were lost to follow up, which ever came first; numerators were calculated by summing the use of inpatient or outpatient services during the respective follow up period by CDC stage of HIV infection. Mean use of service PPY and 95% confidence intervals (CI) were compared between study periods. Mean use of service PPY were calculated using the Poisson regression test and 95% CI using the exact method.

The χ^2 statistic was used to test for associations between two categorical variables and comparisons for continuous variables that were normally distributed were made using the Student's *t*-test. Continuous variables that were right-skewed, such as CD4 cell counts, were first $\log_{10}$ transformed to stabilize the variance before using parametric statistics for analyses.

Direct medical costs, including hospital care, inpatient and outpatient physician services, outpatient management care costs, and costs of ART and 'other' drug costs were estimated. HIV-specific hospital costs were calculated using the standard cost methodology provided by the Canadian Institute for Health Information [9] where Canadian inpatient data are translated into case-mix groups (CMGs), similar to diagnostic-related groups. Inpatient and outpatient physician fees were calculated using reimbursement fee schedules from the provinces of Ontario and Quebec [10–13]. Costs of ART drugs were obtained from the Canadian IMS Health database [14]. Costs of other outpatient services, including diagnostic tests were estimated using the provincial databases from Ontario and Quebec [10–13,15,16].

The unit cost for an average inpatient day was estimated at US$ 414 per day; the average cost for an outpatient visit for the non-AIDS group was US$ 157 per visit compared with US$ 144 per visit for AIDS patients. The lower cost per visit for AIDS group relative to non-AIDS group was due to AIDS patients having fewer CD4 and viral load tests performed.

The cost for ART was calculated as the sum of the daily dose cost for each drug used during each calendar year. Since a number of different ART combinations

were used, a weighted average annual price of each of these drug combinations was calculated. These were in turn averaged over the year and the years were averaged over each of the 5-year periods. As precise local costs for non-ART drugs used were unavailable, cost estimates published by Krenz *et al.* were used [3]: US$ 459 per year before 1996 and US$ 362 after 1996.

The overall cost of hospital inpatient and outpatient care was obtained by adding inpatient and outpatient costs, to the costs of ART and 'other' drugs. Inpatient and outpatient costs were obtained by multiplying the mean number of inpatient days and outpatient visits by their respective unit costs. The study was performed from a public service perspective [17] and all costs were scaled up to Canadian 2002 dollars using the health care component of the consumer price index (CPI) as provided by Statistics Canada [18] and converted to US dollars (2002 average conversion rate US$ 1 = Can$ 1.57 [19]).

Life year gained by CDC stage of HIV infection

Progression times were calculated from date of entry into CDC stage A or B to date of progression to CDC stage C or death for non-AIDS patients and from entry into CDC stage C to death for AIDS patients. For those not known to have progressed, data were censored at either the time of loss to follow-up or last inpatient or outpatient visit during the study period. These analyses were conducted using Cox's proportional hazards models, stratified by the two study periods and adjusted for gender, age when diagnosed, baseline CD4 count when they first entered their respective cohort, sexual orientation and injecting drug use history. Based on differences in the estimated median progression times for each of the CDC HIV stages, the additional life years gained in each of these stages were calculated as were the incremental cost per LYG for the non-AIDS and AIDS groups. All analyses were performed using SAS version 8.0 statistical software (SAS Institute, Cary, North Carolina, USA).

Results

Between 1 January 1991 and 31 December 2001, 2004 HIV-infected individuals were seen in the two HIV clinics; 1533 patients were seen between 1 January 1991 and 31 December 1995 (pre-HAART period), of whom 33% had AIDS. Between the 1 January 1997 and 31 December 2001 (HAART period), 614 new patients were seen, of whom 27% had AIDS.

The non-AIDS population (CDC stages A or B)

Women comprised 15% of the 1026 non-AIDS patients during the pre-HAART period, compared with 27% of the 450 non-AIDS patients seen during HAART period ($\chi^2 = 28.1$, $P < 0.0001$). The mean age of patients when first seen in the pre-HAART period was significantly lower at 36.0 years (SD = 9.1) compared with 38.2 years in the HAART period ($t = -4.2$, $P < 0.0001$). In the pre-HAART period, mean baseline CD4 cell count was 156×10^6 cells/l compared with 211×10^6 cells/l for those first seen in the HAART period ($t = -3.5$, $P < 0.0005$).

Eighty-five percent of the men and 75% of the women were born in Canada or the Caribbean. Nine percent of women seen in the pre-HAART period were born in sub-Saharan Africa compared with 30% during the HAART period ($\chi^2 = 19.8$, $P < 0.001$; Table 1). Among men, men who had sex with men (MSM) comprised the largest exposure category for both

Table 1. Mode of HIV transmission and country of origin of men and women in the non-AIDS population between pre-HAART period (1991–1995) and HAART period (1997–2001).

	Pre-HAART period men	HAART period men	All men	Pre-HAART period, women	HAART period, women	All women
Country of origin						
Canada	717 (82)	263 (80)	980	81 (53)	48 (40)	129
Caribbean	44 (5)	22 (7)	66	45 (29)	32 (27)	77
Sub-Saharan Africa	12 (1)	14 (4)	26	14 (9)	36 (30)	50
Other	95 (11)	30 (9)	125	13 (8)	4 (3)	17
Missing	4 (1)	1 (0)	5	1 (1)	0 (0)	1
Total	872	330	1202	154	120	274
Transmission characteristics						
Men-sex-men	439 (50)	173 (52)	612	NA	NA	NA
Heterosexual	29 (3)	22 (7)	51	40 (26)	40 (33)	80
IDU heterosexual	80 (9)	63 (19)	143	29 (19)	13 (11)	42
Endemic country	23 (3)	33 (10)	56	40 (26)	53 (44)	93
Missing and other	301 (35)	39 (12)	340	45 (29)	14 (12)	59
Total	872	330	1202	154	120	274

Values are numbers (%). IDU, injecting drug users; NA, not applicable.

periods at 50 and 52%, respectively, whereas the proportion of heterosexual male IDUs increased from 9 to 19% between periods ($\chi^2 = 22.5$, $P < 0.001$; Table 1). For women, the proportion born in HIV endemic areas increased from 38 to 57% between study periods, and from 6 to 11% for men (Table 1).

Cost per life-year-gained for the non-AIDS Population (CDC stage A or B)

The mean number of inpatient days PPY was 1.6 for the pre-HAART period, compared with 0.8 in the HAART period, resulting in a reduction of average inpatient costs from US$571 PPY to US$285 PPY (Table 3). Mean number of outpatient visits doubled from 2.8 to 5.5 PPY, with costs increasing from US$ 441 to US$ 865 PPY. Expenditure on ART tripled from US$ 2796 to US$ 7931 PPY with the annual cost for overall inpatient and outpatient care increasing from US$ 4265 to US$ 9445 PPY. Comparing the two periods, median estimated progression time for people with non-AIDS doubled significantly from 6.3 to 12.5 years (Fig. 1), resulting in an incremental cost of US$ 14 587 per LYG for people with non-AIDS (CDC stage A or B).

The AIDS population (CDC stage C)

Women comprised 11% of the 507 patients who were diagnosed with AIDS (CDC stage C) during the pre-HAART period, which was not significantly different during the HAART period, when 15% of the 164 patients seen were women ($\chi^2 = 2.1$, $P = 0.14$). The mean age of the patients when first seen in the pre-HAART period was significantly lower at 37.7 years (SD = 8.8) compared with 40.2 years (SD = 8.8) in the HAART period ($t = -3.2$, $P = 0.0015$). For the pre-HAART period, the baseline mean CD4 cell count was 52×10^6 cells/l compared with 62×10^6 cells/l for those first diagnosed with AIDS in the HAART period ($t = -1.3$, $P = 0.21$).

Again, most men and women were born in Canada or the Caribbean (Table 2). Among men, MSM comprised the largest exposure category in each of the periods. However, the proportion of heterosexual male IDUs increased as did the proportion of HIV-infected heterosexual men coming from endemic areas. For women, the proportion born in endemic areas increased between the periods from 38 to 54% (Table 2).

Cost per life-year-gained for the AIDS population (CDC stage C).

There was a three-fold decrease in the mean number of inpatient days from 13.3 in the pre-HAART period to 4.4 PPY in the HAART period. Average inpatient costs decreased concurrently from US$ 4743 PPY to US$ 1569 PPY (Table 3). Mean number of outpatient visits increased from 8.3 to 9.2 PPY, with OP costs increasing from US$ 1195 to US$ 1324 PPY and expenditure on ART tripling from US$ 2703 to US$ 8499 PPY. The overall cost for inpatient and outpatient care increased only by 29% from US$ 9099 to US$ 11 754 PPY. Median estimated progression time increased from 3.8 to 13.3 years (Fig. 2), generating an incremental cost of US$ 12 813 per LYG between the HAART and the pre-HAART periods for people with AIDS.

Discussion

This study employed a 'before-and-after' scenario to estimate the population effect of the introduction of HAART both in terms of the outcome – disease

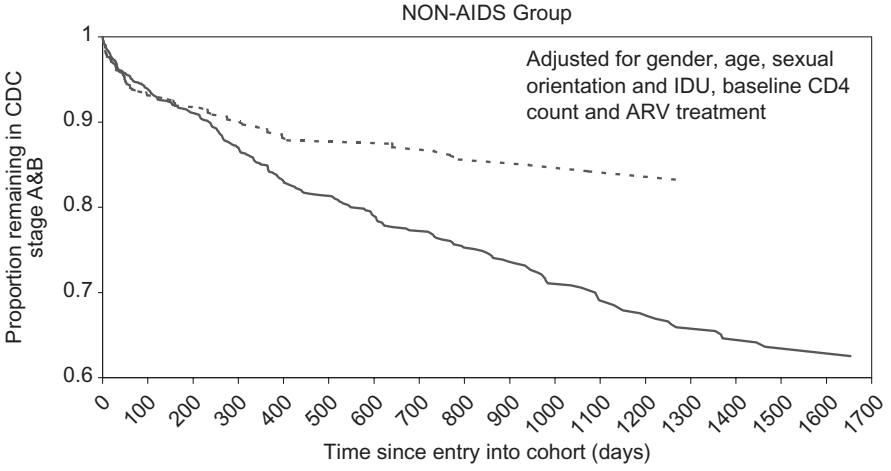

Fig. 1. Progression of HIV-infected people from CDC stage A or B. Solid lines, 1991–1995; broken line, 1997–2001; CDC, Centers for Disease Control; IDU intravenous drug use; ARV, antiretroviral.

Table 2. Mode of HIV transmission and country of origin of men and women in the AIDS population between HAART period (1991–1995) and HAART period (1997–2001).

	Pre-HAART period, men	HAART period, men	All men	Pre-HAART period, women	HAART period, women	All women
Country of origin						
Canada	367 (81)	97 (69)	464	29 (55)	11 (46)	40
Caribbean	24 (5)	17 (12)	41	15 (28)	9 (37)	24
Sub-Saharan Africa	3 (1)	7 (5)	10	5 (9)	4 (17)	9
Other	59 (13)	19 (14)	78	3 (6)	0	3
Missing	1 (0)	0 (0)	1	1 (2)	0	1
Total	454	140	594	53	24	77
Transmission characteristics						
Men-sex-men	214 (47)	86 (62)	300	NA	NA	NA
Heterosexual	11 (2)	16 (11)	27	17 (32)	7 (29)	24
IDU heterosexual	20 (5)	13 (9)	33	8 (15)	4 (17)	12
Endemic country	12 (3)	19 (14)	31	7 (13)	12 (50)	19
Missing & Other	197 (43)	6 (4)	203	21 (40)	1 (4)	22
Total	454	140	594	53	24	77

Values are numbers (%). IDU, injecting drug users; NA, not applicable.

Table 3. Mean number of inpatient days, outpatient visits, 95% confidence intervals (95%CI) and associated cost, median progression time and inter quartile ranges (IQR), differences in median progression times and additional cost per life-year-gained by Centers for Disease Control (CDC) group and period (costs are in 2002 prices and US$).

	Non-AIDS		AIDS	
	1991–1995	1997–2001	1991–1995	1997–2001
Mean number of inpatient days PPY (95% CI)	1.6 (1.5–1.7)	0.8 (0.7–0.9)	13.3 (13.1–13.6)	4.4 (4.3–4.5)
Average inpatient day costs PPY (95% CI) (US$)	571 (535–606)	285 (250–321)	4743 (4672–4850)	1569 (1533–1605)
Mean number of outpatient visits PPY	2.8 (2.7–2.9)	5.5 (5.4–5.6)	8.3 (8.1–8.5)	9.2 (9.1–9.4)
Average costs outpatient visits PPY (95% CI) (US$)	441 (425–456)	865 (850–881)	1195 (1166–1223)	1324 (1310–1353)
Average ART drug costs PPY (US$)	2796	7931	2703	8499
Average other drug costs PPY (US$)	459	362	459	362
Average total cost PPY (US$)	4265	9445	9099	11754
(95% CI) (US$)	(4214–4316)	(9393–9495)	(8999–9234)	(11705–11819)
Median years in stage of HIV infection before progression	6.3	12.5	3.8	13.3
IQR	(2.8–9.7)	(5.7–19.4)	(2.1–5.5)	(6.5–20.2)
Median differences in median progression times (IQR)	Log rank $\chi^2 = 270$, $P < 0.0001$ 6.3(2.9–9.7 years)		Log rank $\chi^2 = 158$, $P < 0.0001$ 9.53 (4.4–14.7 years)	
Incremental cost per life year gained by stage of HIV infection (US$)	14587		12813	

PPY, per patient-year; ART, antiretroviral.

progression or LYG in each stage – and the cost of service provision before and after 1996. A similar method was recently used on a study of Italian AIDS patients [20]. In comparison with the pre-HAART period, a greater proportion of women and patients born in HIV-endemic countries were seen during the HAART period. Although baseline mean CD4 counts increased between periods for people with non-AIDS, they remained the same for the AIDS population.

Most people were managed with HAART between 1997 and 2001, resulting in increased expenditure on ART compared with 1991 to 1996, when most people were managed with mono- or dual therapy. The cost of treating HIV-infected people increased by 121% for people with non-AIDS compared with 29% for people with AIDS. Similar estimates of the cost of care were recently been reported from Southern Alberta [3], at US$ 7122 for people with non-AIDS, compared with US$ 11 677 per annum for people with AIDS [21]. The smaller increases in costs over time among Quebec AIDS patients reflect the substitution of inpatient costs by HAART drug costs, a phenomenon which has been observed in other industrialized countries [8,22].

Costs, however, vary at different stages of HIV infection. Patients who present late, especially if more

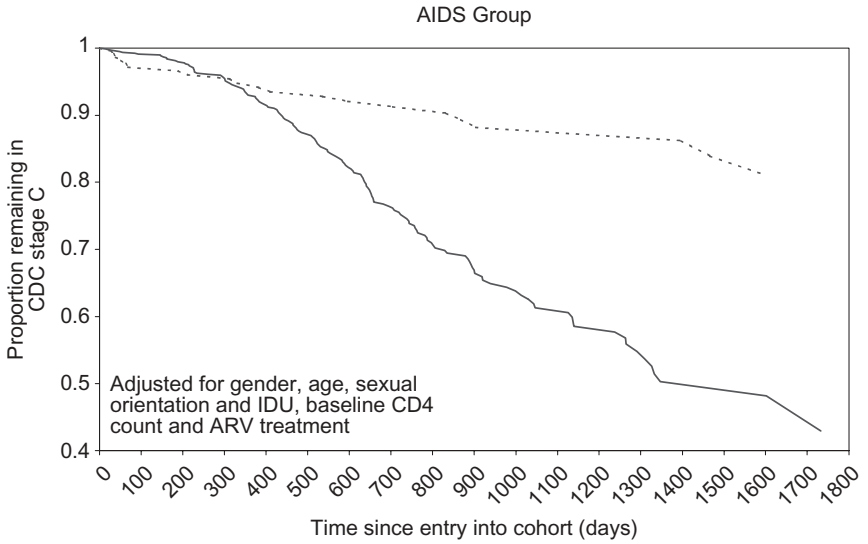

Fig. 2. Progression of HIV-infected people from CDC stage C. Solid lines, 1991–1995; broken line, 1997–2001; CDC, Centers for Disease Control; IDU intravenous drug use; ARV, antiretroviral.

immuno-suppressed, use more services at greater cost than those who are less immuno-suppressed [23,24].

Between 1996 and 1999, the Quebec healthcare system underwent profound changes, resulting in the closure of hospitals, increased pressure on beds and reduction in inpatient days for many conditions. Between April 1993 and March 1999, the mean annual number of bed-days per patient for a number of chronic conditions decreased by 24% (Table 4) [25], compared with the 66% drop for AIDS patients. Although the recent Quebec health care system changes may have had some effect, this is likely to be small compared with the introduction of HAART.

For both non-AIDS (CDC stages A or B) and AIDS populations (CDC stage C), the estimated LYG increased significantly, whereas the incremental costs per LYG in either stage was around US$ 12 736. Based on the 1992 suggested cut-off point of US$ 12 736 for an intervention to be considered cost-effective in Canada [26], the introduction of HAART can be considered to have been a cost-effective intervention, even by this outdated criterion.

An earlier cost-effectiveness modelling study from British Columbia [27], produced considerably higher estimates of the incremental cost-effectiveness of HAART, compared with the Quebec findings. HAART compared with monotherapy produced an incremental cost-effectiveness of US$ 37 448 per LYG, whereas HAART compared with dual therapy produced a cost-effectiveness of US$ 29 911 per LYG [27]. HAART has also been demonstrated to have been a cost-effective intervention in other industrialized countries [28–36]. Most of these studies, however, were modelling exercises, whereas the Quebec study is one of the first studies based on context-specific observational data [37]. Although modelling exercises provide useful information, their limitations have recently been described as they often have to rely on particular assumptions, which may or may not reflect the reality in a particular context [37].

The Quebec estimates did not include primary or community care costs nor indirect costs. If they had been included, this was likely to have demonstrated that HAART is even more cost-effective as studies from other industrialized countries have demonstrated that from a public sector perspective indirect costs can comprise between 58 and 124% of direct treatment costs for HAART or between 45 and 102% if considered from a societal perspective [38,39].

Table 4. Weighted mean inpatient days for patients hospitalized in Montreal for colorectal cancer, myocardial infarction and chronic obstructive pulmonary disease 1 April 1993–30 March 1999 [21]

Year	1993–1994	1994–1995	1995–1996	1996–1997	1997–1998	1998–1999
Mean inpatient days per year	16.7	15.9	14.4	14.3	13.1	12.3

It is important that more specific analyses be performed to directly compare triple, dual and monotherapy regimens, not only when used as first-line therapy but also as second-line therapy or later in the course of treatment with ART. Different drugs and combinations of drugs may behave differently when they are used as first-line therapy compared with the increasing proportion of people who are now on salvage therapy [40]. Furthermore, the nature and costs of adverse effects are also likely to differ between drugs, affecting their long-term effectiveness due to toxicity or intolerance to particular regimens. Furthermore the indirect costs and benefits of HAART should also be studied, as well as the cost implications of research.

The currently available treatment regimens have well-recognized limitations and, with an increasing number of new antiretroviral drugs coming on the market, many issues surrounding their most cost-effective and acceptable use remain unresolved, even in industrialized societies. In order to be able to perform the relevant analyses, basic and contemporary information on the use, cost and outcome of HIV service provision needs to be available. However, such information is often either unavailable or very difficult to obtain [41]. In a number of Canadian provinces [42,43], as well as some other industrialized countries [44–46], multi-center prospective monitoring systems are now being developed not only to improve patient management but also provide pertinent information to monitor and evaluate treatment and care services at both individual and population levels [39]. More importantly, as ART-related treatment and care is being scaled up in middle- and lower income countries, through programs such as WHO/UNAIDS '3 by 5' [47] or the US 'President's Emergency Plan for AIDS Relief', patient management and monitoring, and program monitoring and evaluation will be very important. However, despite the current prevailing rhetoric concerning the 'need for evidence-based medicine', the track record of funders of research or governments in many countries has to date, unfortunately, been suboptimal in terms of providing the required resources to set up and maintain those systems which could regularly provide such strategic information [48].

Acknowledgements

Support for earlier work concerning ethics, community consultations and logistics of data collection related to these analyses was provided through the Reseau sida-maladies infectieuses du Fonds de Recherches en santé du Québec, Montreal. Were are also grateful to the ongoing collaboration of the patients and staff in both clinics and members of the Department de la santé publique de montréal centre. We are particularly indebted to Tanya Murphy, Robert W. Platt, Jean Roy and Annie de la Sablonnière for their invaluable contributions to the success of the study.

Sponsorship: This study was funded by an unrestricted educational grant from GlaxoSmithKline, Canada.

References

1. NIAID *AIDS Agenda. New Findings bring Hope to Vancouver AIDS Conference*. September 1996. http://www.naid.nih.gov/publications/agenda/0996/page1.htm (accessed 10/3/2004).
2. Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B, *et al*. **Enfuvirtide, an HIV-1 fusion inhibitor, for drug resistant HIV infection in North and South America.** *N Engl J Med* 2003; **348**:2175–2185.
3. Krentz HB, Auld MC, Gill MJ for the HIV Economics Study Group. **The changing direct costs of medical care for patients with HIV/AIDS, 1995–2001**. *CMAJ*, 2003; **169**:106–110.
4. Beck EJ, Miner AH. **Effectiveness and efficiency in the delivery of HIV services: economic and related considerations**. In: Gazzard BG, Johnson M, Miles A (editors): *The Effective Management of HIV/AIDS*. UK Key Advances in Clinical Practice. London: Aesculapius Medical Press; 2001. pp. 113–138
5. Beck EJ, Whitaker L, Kennelly J, McKevitt L, Wadsworth J, Miller DL, *et al*. **Changing presentation and survival, service utilization and costs for AIDS patients: insights from a London referral centre.** *AIDS*, 1994; **8**:379–384.
6. Beck EJ, Kennelly J, McKevitt C, Whitaker L, wadsworth J, Miller DL, *et al*. **Changing use of hospital services and costs at a London AIDS referral center, 1983–1989.** *AIDS* 1994; **8**: 367–377.
7. Beck EJ, Tolley K, Power A, Madalia S, Rutter P, Izumi J, *et al* for the NPMS Steering Group. **Use and cost of HIV service provision in England**. *Pharmacoeconomics* 1998; **14**:639–652.
8. Beck EJ, Mandalia S, Williams I, Power A, Newson R, Molesworth A, *et al* for the NPMS Steering Group. **Decreased morbidity and use of hospital services in English HIV infected individuals with increased uptake of anti-retroviral therapy 1996–1997.** *AIDS* 1999; **13**:2157–2164.
9. Canadian Institute for Health Information. *DAD Resource Intensity Weights and Expected Length of Stay 2002*. Ottawa: Canadian Institute for Health Information; 2002.
10. Ontario Ministry of Health and Long-Term Care. *Schedule of Benefits for Physician Services under the Health Insurance Act. April 1, 2002*. Ottawa: Ontario Ministry of Health and Long-Term Care 2003.
11. Regie de l'assurance maladie du Quebec. *Manuel des Medecins Specialistes. RAMQ, Quebec*. Regie de l'assurance maladie du Quebec 2003.
12. Regie de l'assurance maladie du Quebec. *Manuel des Medecins Specialistes. Services de laboratoire en etablissement. RAMQ, Quebec*. Regie de l'assurance maladie du Quebec. Quebec: 2003.
13. Regie de l'assurance maladie du Quebec. *Manuel des Medecins Omipracticiens. RAMQ, Quebec*. Regie de l'assurance maladie du Quebec. Quebec: 2003.
14. IMS Health. *Canadian CompuScript October 2001*. Pointe Claire, Quebec: IMS Canada 2001.
15. Ontario Ministry of Health and Long-Term Care. *Ontario Health Insurance Schedule of Benefits and Fees: Schedule of Benefits for Laboratory Services. April 1, 2002*. Ottawa: Ontario Ministry of Health and Long-Term Care 2003.
16. Ministere de la sante et des services sociaux. *Laboratoires de biologie medicale: measure de la production 2003–2224*. Ministere de la sante et des services sociaux 2003.
17. Drummond, M.F., O'Brien, B., Stoddart, G.L., Torrance, G.W. *Methods for the economic evaluation of health care programmes - 2nd Edition*, Oxford: Oxford University Press, 1997:52–53.
18. Statistics Canada. *CANSIM Matrix P100200*. . Ottawa: Statistics Canada 2003.
19. Bank of Canada. *Average Canadian – US Dollar Exchange rate*

2002. http://www.bank-banque-canada.ca/cgi-bin/famecgi.fdps (accessed 31 July 2004).
20. Tramarin A, Campostrini S, Postma MJ, Calleri G, Tolley K, Parise N, *et al*. **A multicentre study of patient survival, disability, quality of life and cost of care: among patients with AIDS in northern Italy.** *Pharmacoeconomics*, 2004; **22**:43–53.
21. Krentz H, Gill MJ, De Forest J. **The impact of AIDS on the direct cost of medical care since the introduction of highly active antiretroviral therapy (HAART).** *Can J Infect Dis* 2004; **Suppl 15**:60A [abstract 337P].
22. Stoll M, Class C, Schutle E, Graf Von Der Sculenburg JM, Schmidt RE. **Direct costs for the treatment of HIV-infection in a German cohort after introduction of HAART.** *Eur J Med Res* 2002; **7**:463–471.
23. Mandalia S, Parmar D, Fisher M, Pozniak A, Tang A, Youle M, *et al*. on behalf of the NPMS-HHC Steering Group. **Correlation between CD4 response and cost of hospital treatment in antiretroviral naïve hiv infected patients started on triple HAART**. *XIV International AIDS Conference*, Barcelona, Spain, July 2002 [abstract ThPeA7023].
24. Krenz HB, Auld MC, Gill MJ. **The high cost of medical care for patients who present later (CD4 < 200 cells/μl) with HIV infection.** *HIV Med* 2004; **5**:93–98.
25. Tousignant P, Lavoie G, Poirier L-R, Lamontagne D, Dupont MA, Roy D. *Évaluation de l'impact de la reconfiguration du réseau sur la santé et le bien-être de la population de Montréal-Centre: Résultats du monitorage*. Montreal: Direction de la santé publique, RRSSS-Montréal-Centre, 2000.
26. Laupacis A, Feeny D, Detsky AS, Tugwell PX. **How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations.** *Can Med Assoc J* 1992; **146** :473–481.
27. Anis AH, Guh D, Hogg RS, Wang X, Yip B, Craib KJP, *et al*. **The cost effectiveness of antiretroviral regimes for the treatment of HIV/AIDS** *Pharmacoeconomics* 2000; **18**:393–404.
28. Freedberg KA, Losina E, Weinstein MC, Paltiel AD, Cohen CJ, Seager GR, *et al*. **The cost effectiveness of combination anti-retroviral therapy for HIV disease.** *N Engl J Med* 2001; **344**: 824–831.
29. Sendi PP, Bucher HC, Harr T, Craig BA, Schwietert M, Pfluger D, *et al*. on behalf of the Swiss HIV Cohort Study. **Cost effectiveness of highly active antiretroviral therapy in HIV-infected patients.** *AIDS* 1999; **13**:1115–1122.
30. Schackman BR, Goldie SJ, Weinstein MC, Losina E, Zhang H, Freedberg KA. **Cost-effectiveness of earlier initiation of antiretroviral therapy for uninsured HIV-infected adults.** *Am J Public Health* 2001; **91**:1456–1463.
31. Schackman BR, Freedberg KA, Weinstein MC, Sax PE, Losina E, Zhang H, *et al*. **Cost-effectiveness implications of the timing of antiretroviral therapy in HIV-infected adults.** *Arch Intern Med* 2002; **162**:2478–2486.
32. Schackman BR, Goldie SJ, Freedberg KA, Losina E, Brazier J, Weinstein MC. **Comparison of health state utilities using community and patient preference weights derived from a survey of patients with HIV/AIDS**. *Med Decis Making* 2002; **22**:27–38.
33. Moore RD, Bartlett JG. **Combination antiretroviral therapy in HIV infection. An economic perspective.** *PharmacoEconomics* 1996; **10**:109–113.
34. Cook J, Dasbach E, Coplan P, Monkson L, Yin D, Meibohm A *et al*. **Modeling the long-term outcomes and costs of HIV antiretroviral therapy using HIV RNA levels: application to a clinical trial.** *AIDS Res Hum Retroviruses* 1999; **15**:499–508.
35. Miners AH, Sabin CA, Trueman P, Youl M, Mocroft A, Johnson M. *et al*. **Assessing the cost-effectiveness of HAART for adults with HIV in England.** *HIV Med* 2001; **2**:52–58.
36. Trueman P, Youle M, Sabin CA, Miners AH, Beck EJ. **The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom**. *HIV Clin Trials* 2000; 1:27–35.
37. Harling G, Wood R, Beck EJ. The Efficiency of Interventions in HIV Infection: a review from institutional and community perspectives. Disease Management of Health Outcomes (Accepted for publication).
38. Mullins CD, Whitelaw G, Cooke JL, Beck EJ. **The indirect cost of HIV infection in England.** *ClinTherapeut* 2000; **22**:1333–1345.
39. Beck EJ, Mandalia S. **The cost of HIV treatment and care in England since HAART: Part 1**. *Br J Sexual Med* 2003; **27**:19–23.
40. Youle M. **Salvage treatment in HIV disease.** *Int J STD & AIDS* 2001; **12**:286–293.
41. Beck EJ, Miners AH, Tolley K. **The cost of HIV treatment and care: a global review**. *PharmacoEconomics* 2001; **19**:13–39.
42. Beck EJ, P Robillard P, Coté P, *et al*. *Réseau Informatique de Sida au Québec*. Montreal, Canada: Unité Maladies Infectieuses, Direction de la santé publique, Regie Regionale de la Sante et Des Services Sociaux De Montreal-Centre, 2001.
43. Ontario HIV Treatment Network. http://www.ohtn.on.ca/hiipfacts.html. (accessed 29 May 2004).
44. Direction des Hospitaux, Mission SIDA. *DMI2: an Information System Built Around the Patient*. INSERM - SC4. Paris, France: Ministere de la Sante et de l'action Humanitaire, 1993.
45. De Wolf F, Lange JMA, Bossuyt PMM, *et al* for the Athena Project. *Monitoring of Human Immunodeficiency Virus Type-1 (HIV-1) Infection in the Netherlands*. Amsterdam: Stichting HIV Monitoring, Natec, AMC; 2001.
46. Beck EJ, Mandalia S. **The cost of HIV treatment and care in England since HAART: Part 2**. *Br J Sexual Med* 2003; **27**:21–23.
47. WHO *Scaling up Antiretroviral Therapy in Resource-limited Settings: Treatment for a Public Health Approach*. 2003 revision. Geneva 2004 http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf (accessed 4 June 2004).
48. Beaglehole R, Bonita R. *Public Health at the Crossroads: Achievements and Prospects*. Cambridge, UK: Cambridge University Press; 1997, pp. 124–125.