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REVIEW

A narrative review of cost-effectiveness analysis of people living with HIV treated with HAART: from interventions to outcomes

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Background: Since its introduction in 1996, highly active antiretroviral therapy (HAART), which involves the combination of antiretroviral drugs, has resulted in significant improvements in the morbidity, mortality, and life expectancy of HIV-infected patients. Numerous studies of the cost-effectiveness of HAART from different perspectives in HIV have been reported.

Aim: To investigate the economic outcomes and relevance of HAART for people living with HIV.

Materials and methods: A narrative literature review was conducted on 22 peer-reviewed full economic evaluations of people living with HIV treated with different HAART regimens and published in English between January 2005 and December 2014. Information regarding study details, such as interventions, outcomes, and modeling methods, was extracted. The high heterogeneity of the included studies rendered a meta-analysis inappropriate; therefore, we conducted a comparative analysis of studies grouped according to the similarity of the different intervention types and outcomes.

Results: Most of the economic evaluations of HAART focused on comparisons between the specific HAART regimens and others from the following perspectives: injecting drug users versus noninjecting drug users, HIV-infected adults without AIDS versus those with AIDS, regimens based on developed world guidelines versus those based on developing world guidelines, self-administered HAART versus directly observed HAART, and "ideal" versus "typical" regimens.

Conclusion: In general, HAART is more cost-effective than other therapeutic regimens adopted so far. Further investigations, especially head-to-head comparisons of "ideal" and "typical" trials of different regimen combinations, are required to identify the optimal HAART regimens.

Keywords: narrative review, cost-effectiveness, HAART

Introduction

AIDS, which is caused by HIV, is recognized as one of the world's greatest health problems. HIV is transmitted in human body fluids by three major routes: 1) sexual intercourse; 2) direct injection with HIV-contaminated drugs, needles, syringes, blood, or blood products; and 3) from HIV-infected mother to fetus in utero, through intrapartum inoculation from mother to infant or during breastfeeding. $CD4^+$ T-cell count ranges are a major indicator of the disease stage. In the peripheral blood of a normal healthy individual, the level of $CD4^+$ T-cells is between 800 and 1,200/mm^3, and once this number reaches 200 or below in an HIV-infected patient, the person is classified

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as having AIDS. The data for the prevalence and incidence of HIV presented by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) showed that 33.3 million people around the world were HIV-infected in 2009, while in 2013 the number had reached 35 million.[1]

Since highly active antiretroviral therapy (HAART) became available in the mid-1990s, clinical trial results have demonstrated its effectiveness and the life expectancy of patients has increased significantly.[2,3] At the same time, the introduction of antiretroviral therapy has dramatically reduced mortality for people with HIV infection. HAART usually comprises a cocktail of multiple anti-HIV drugs, including reverse-transcriptase inhibitors, protease inhibitors (PIs), fusion inhibitors, coreceptor antagonists, and integrase inhibitors. It has been suggested that increasing coverage with HAART among people infected with HIV with medical indication for HAART may help to prevent new infections.[4] In the published literature, most studies have focused on specific comparisons of HAART from different perspectives. In this review, we focus on the effects of HAART to identify the optimal regimen to obtain more economically viable outcomes.

Materials and methods

Study design

We searched major databases (Embase, Medline, and Web of Science) for reports published between 2005 and 2014. We constructed two search strings to identify as many relevant studies as possible: ((HAART[Title Abstract]) AND HIV[Title Abstract]) AND cost[Title Abstract], or ((HAART[Title Abstract]) AND HIV[Title Abstract]) AND economic[Title Abstract]. References of retrieved publications and relevant overview publications were checked to identify additional studies. The review considered both random and nonrandom controlled studies. The literature-search and selection process is presented in Figure 1.

Data extraction

Two authors carried out the data extraction independently using a set format. Information from the 22 selected publications are provided in Tables 1 and 2, including author, region, perspective, study population, modeling, timescale, discount, interventions, and outcome and sensitivity analyses. Outcome measures were divided into several categories: quality-adjusted life-years (QALYs)/disability-adjusted life-years (DALYs), life-years gained, net benefit, and incremental cost-effectiveness ratio (ICER).

Results

The database search yielded 371 possible studies for the review. The number was reduced to 83 articles after removal of duplicates and an initial selection on the basis of titles. After screening of the titles, abstracts, and full text, 22 studies were included in this review.

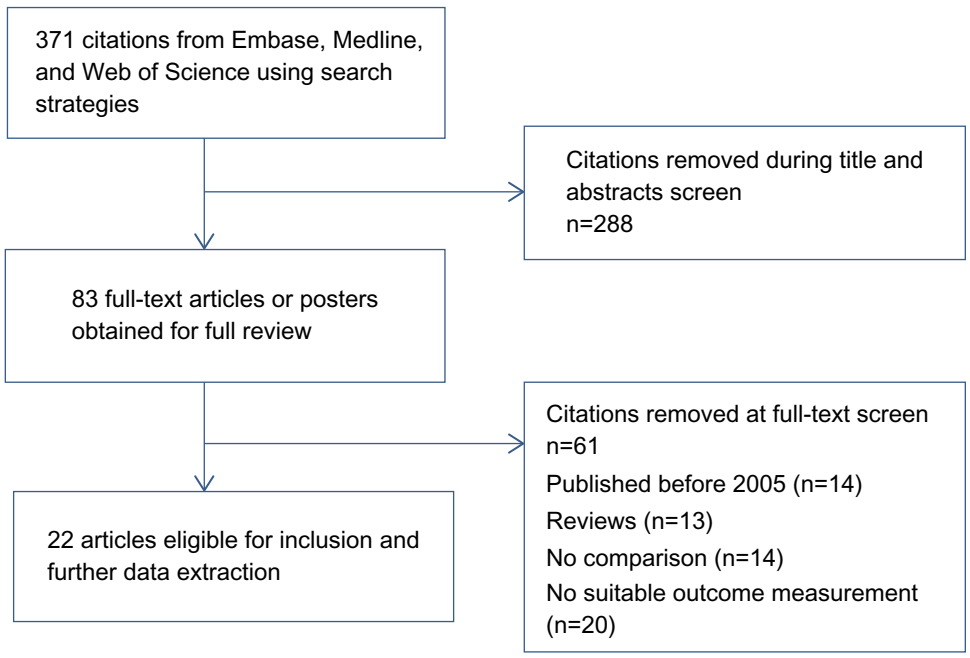

Figure 1 Summary of study-search and selection process.

Table 1 Study characteristics

Reference	Region	Perspective	Population	Modeling	Timescale	Discount
Moeremans et al[5]	Belgium, Italy, Sweden, UK	Reimbursement authorities	HIV-infected adults	Markov model	Lifetime	Based on local guidelines
Long et al[6]	St Petersburg, Russia	NA	IDUs and non-IDUs	Dynamic HIV-epidemic model	20 years	3%
Vijayaraghavan et al[7]	South Africa	NA	HIV-positive adults	Markov model	Lifetime	NA
Hubben et al[8]	The Netherlands	Dutch health care	HIV-infected patients	Markov model	Lifetime	4%, 1.5%
Johnston et al[9]	British Columbia, Canada	Payers	Asymptomatic HIV patients	Mathematical model	30 years	NA
Binagwaho et al[10]	Rwanda	Health care payers	Pregnant women	NA	Lifetime	3%
Orlando et al[11]	Malawi	Private, public	Pregnant women	NA	NA	15%
Brogan et al[12]	USA	Societal	HIV-infected adults	Markov model	Lifetime	3%
Simpson et al[13]	USA	Payers	Treatment-experienced HIV Patients	Markov model	Lifetime	3%
Badri et al[14]	South Africa	Public healthcare system	HIV-infected adults without AIDS and with AIDS	NA	NA	NA
Marseille et al[15]	Rural Uganda	Societal	HIV-infected patients	NA	15 years	3%
Rizzardini et al[16]	Italy	Lombardy Regional Health Service	Adult HIV subjects who received HAART therapy for the first time	Markov model	2 years	None
Colombo et al[17]	Italy	Italian National Health Service	HIV-infected patients	Markov model	10 years	3.50%
McCabe et al[18]	NA	Societal	HIV-infected pregnant women	Mathematical model	Lifetime	3%
Munakata et al[19]	NA	Societal	HIV patients on an initial regimen of HAART	Markov model	Lifetime	3%
Colombo et al[20]	Italy	Italian health care system	HIV-infected patients	Markov model	10 years	3.50%
Granich et al[21]	South Africa	NA	HIV-infected patients	Epidemic model	40 years	3%
Fang et al[22]	Taiwan	National health insurance	HIV-positive patients and AIDS	NA	NA	NA
Ono et al[23]	Thailand	NA	HIV-infected patients	Markov model	NA	3%
Badri et al[24]	Sub-Saharan Africa	Public health	HIV-infected patients	Markov model	Lifetime	8%
Mauskopf et al[25]	NA	NA	HIV-infected patients	Markov model	25 years	3%
Mauskopf et al[26]	USA	NA	Treatment-experienced patients	Markov model	5 years, lifetime	3%

Abbreviations: NA, not applicable; IDUs, injecting drug users; HAART, highly active antiretroviral therapy.

Study characteristics

The 22 studies included different regions (Table 1); most focused on the West, where HAART is widely used, and African countries, where HIV is a more severe problem. Most of the studies were conducted from societal[12,15,18,19] and payer[8–11,13,14,16,17,20,24] perspectives (Table 1), while some of them did not mention these aspects (Table 1).[6,7,21,23,25,26] The majority of studies (18 of 22) focused on HIV-infected patients, while three focused on pregnant women and one on infected drug users.

Timescale and discount

For cost-effectiveness analyses of HAART, these studies were generally based on a lifetime perspective (ten of 22), while other studies considered timescales ranging from 2 to 40 years. What is apparent from all the analyses of specific HAART regimens presented in this review paper was that although the results were consistent with each other, they varied depending on the timescale under consideration. Most of the individual studies applied a discount of 3%,[6,10,12,13,15,18,19,21,23,25,26] while discounts of 1.5%,[8] 3.5%,[17,20] 4%,[8] 8%,[24] and 15%[11] were also applied in some studies.

Interventions

Because of the diversity of the interventions (Table 2), the high heterogeneity of the data rendered a meta-analysis inappropriate; therefore, we conducted a comparative analysis of studies grouped according to the similarity of the different intervention types and outcomes.

One group comprised all the studies that contained the specific regimen of HAART (eight).[5,8,12,13,16,17,20,26] The variety of combination-treatment regimens represented in this group

Table 2 Study characteristics of outcomes

Reference	Interventions	QALYs/DALYs	LYG	NB	ICER	Sensitivity analyses
Moeremans et al[5]	DRV/r versus LPV/r	QALYs 0.785 in Belgium, 0.608 in Italy, 0.584 in Sweden, 0.550 in the UK	NA	NA	€6,964/QALY gained in Belgium, €9,277/QALY gained in Italy, €6,868/QALY gained in Sweden, €14,778/QALY gained in the UK	PSA
Long et al[6]	HAART treating HIV-infected IDUs versus non-IDUs	NA	NA	NA	$1,501/QALY gained if treat IDUs, $2,572/QALY gained if treat non-IDUs, $1,827/QALY gained if treat untargeted	One-way, two-way
Vijayaraghavan et al[7]	HAART (developed-world guidelines versus developing-world guidelines)	3.00 QALYs	NA	$39.4 billion	$3,956 per QALY gained	One-way, multiway
Hubben et al[8]	TPV/r versus CPI/r	0.51 QALYs gained	0.52	NA	€42,500 per QALY gained	One-way
Johnston et al[9]	HAART expansion versus no HAART	NA	NA	$900 million	NA	PSA
Binagwaho et al[10]	Dual ARV prophylaxis with either 12 months breastfeeding or replacement feeding; short-course (Sc)-HAART prophylaxis with either 6 months' breastfeeding, 12 months' breastfeeding, or 18 months' breastfeeding; Sc-HAART prophylaxis with replacement feeding	NA	NA	Highest net costs with Sc-HAART with 6 months' breastfeeding ($213,912,837); lowest net costs with Sc-HAART and 18 months' breastfeeding ($210,410,727)	Sc-HAART with 12 months' breastfeeding allowing for more children to be alive and HIV-uninfected by 18 months than Sc-HAART with 6 months' breastfeeding, for an incremental cost per child alive and uninfected of $11,882	One-way
Orlando et al[11]	HAART versus no intervention	DALYs: 10,449 saved	NA	$998 per person, $–261 by public	NA	One-way
Brogan et al[12]	DRV/r versus LPV/r	QALYs: 0.493	NA	NA	$23,057 per QALY gained	PSA
Simpson et al[13]	TPV/r versus CPI/r	QALYs: 0.64	NA	NA	$56,517 per QALY gained	PSA
Badri et al[14]	HIV-infected adults without AIDS versus with AIDS	NA	NA	NA	$1,622 per LYG without AIDS, $675 per LYG with AIDS	One-way
Marseille et al[15]	HAART and cotrimoxazole prophylaxis versus cotrimoxazole	DALYs: 6,861 saved	NA	$4.09 million	NA	One-way, multiway
Rizzardini et al[16]	TDF FTC: EFV versus TDF FTC, ATZ RTV versus TDF FTC, LPV/r RTV versus AZT 3TC LPV/r RTV	NA	NA	NA	TDF + FTC + EFV €34,965, remaining strategies ranged from €53,000 to €62,000 per QALY (compared with untreated)	One-way
Colombo et al[17]	TDF/FTC + RPV (STR), TDF/FTC + RPV, TDF/FTC + EFV, TDF/FTC + ATV/r, TDF/FTC + DRV/r, TDF/FTC + RAL, ABC/3TC + EFV, ABC/3TC + ATV/r	NA	NA	NA	STR the most cost-effective choice (€13,655.00), followed by TDF/FTC + RPV (€15,803.00) and TDF/FTC + EFV (€16,181.00) (compared with untreated)	One-way
McCabe et al[18]	Self-administered HAART versus directly observed HAART versus No HAART	NA	NA	$14,233	NA	Univariate, bivariate
Munakata et al[19]	"Ideal" (based on clinical trials) and "typical" (based on observational studies in actual practice)	QALYs: 1.2	NA	NA	$29,400/QALY gained	One-way, two-way

Colombo et al[20]	TDF/FTC + EFV; (STR) TDF/FTC + EFV; TDF/FTC + ATV/r; TDF/FTC + NVP; TDF/FTC + DRV/r; TDF/FTC + LPV/r; TDF/FTC + RAL; TDF + 3TC + EFV; ABC/3TC + EFV; ABC/3TC + ATV/r; ABC/3TC + LPV/r	NA	NA	NA	TDF/FTC + EFV (STR) €22,017, TDF/FTC + EFV €24,526, TDF/FTC + NVP €26,416, TDF/FTC + EFV €26,558 (compared with untreated)	One-way
Granich et al[21]	HAART to CD4 <200, CD4 <350, CD4 <500, all CD4	Expanding ART to CD4 count <350 cells/mm^3 reduced DALYs by 14% from 109 to 93 million over 40 years	NA	Costs drop $504 million over 5 years and $3.9 billion over 40 years	NA	Univariate, bivariate
Fang et al[22]	Pre-HAART era versus HAART era	NA	AIDS group $5,189, non-AIDS group $6,652	NA	AIDS group $7,109/QALY gained, non-AIDS group, $9,782/QALY gained	One-way
Ono et al[23]	HAART versus vaccine versus combined	NA	NA	NA	HAART versus vaccine versus combined $75, $610, $267 per DALY compared with no treatment	One-way
Badri et al[24]	HAART to CD4 <200, CD4 <350, CD4 >350, no HAART	NA	NA	NA	Therapy at <200 $54 per QALY versus no ART; at 200–350 had an ICER of $616 versus therapy initiation at <200; therapy initiation >350 had an ICER of $1,137 versus therapy initiation at 200–350	One-way
Mauskopf et al[25]	HAART to CD4 >350, 200< CD4 <350	QALYs 0.61	1.21	NA	$31,266 per QALY gained	One-way
Mauskopf et al[26]	DRV/r versus control PIs	5 years: 0.2 QALYs; lifetime: 1.27 QALYs	NA	NA	$30,046 per QALY gained	One-way and PSA

Abbreviations: QALYs, quality-adjusted life-years; DALYs, disability-adjusted life-years; LYG, life-years gained; NB, net benefit; ICER, incremental cost-effectiveness ratio; NA, not applicable; DRV/r, darunavir boosted with low-dose ritonavir; LPV/r, lopinavir + ritonavir; PSA, probabilistic sensitivity analysis; HAART, highly active antiretroviral therapy; IDUs, injecting drug users; TPV/r, ritonavir-boosted tipranavir; CPI/r, ritonavir-boosted comparator protease inhibitor; ARV, antiretroviral; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; ATZ, atazanavir; RTV, ritonavir; AZT, zidovudine; 3TC, lamivudine; STR, single tablet regimen; RAL, raltegravir.

demonstrate the importance of identifying and standardizing the optimal regimen in further pharmacoeconomic evaluations.

The second group comprised studies that compared HAART with no intervention (three)[9,11,22] with the aim of performing an economic evaluation of these approaches. Outcomes estimated were cost for DALYs saved and incremental net benefit. The results supported the cost-effectiveness of HAART.

The third group comprised the studies that aimed to determine the optimal initiation time for HAART from the perspective of $CD4^+$ T-cell count ranges (three).[21,24,25] This population is an essential component of the immune system, and the numbers of these cells are important in confirming the effect of AIDS treatment. Furthermore, identifying the optimal time to treat with HAART could reduce the cost of therapy and reduce the DALYs.

The fourth group comprised studies that compared HAART applied among different groups of people (three),[6,10,14] such as injecting drug users (IDUs) versus non-IDUs, HIV-infected adults without AIDS versus those with AIDS, and different alternatives of breastfeeding duration for HIV-positive pregnant women.

The fifth group comprised studies that compared the effects of different types of HAART (three),[7,18,19] administered on the basis of developed-world guidelines versus developing-world guidelines, self-administered HAART versus directly observed HAART versus no HAART, and "ideal" treatment (based on clinical trials) versus "typical" treatment (based on observational studies in actual practice).

The last group comprised studies that compared HAART with other types of treatment (two),[15,23] such as HAART + cotrimoxazole prophylaxis versus cotrimoxazole, and HAART versus vaccine versus HAART + vaccine.

Study outcomes

Outcomes of the 22 selected publications are provided in Table 2. The effectiveness of therapeutic regimens for treating HIV infection was evaluated using several outcome measures. Most of the studies took life-years gained (LYG),[8,22,25] QALYs,[5,7,8,12,13,19,25,26] and ICER[5–8,10,12–14,16,17,19,20,22–26] as the main outcomes, which are the most important measurement indicators in an economic evaluation, especially ICER. Some other studies used DALYs[11,15,21] and net benefit[7,9,10,11,15,18,21] as the primary indicators to measure the averted loss of life-years and cost by HAART.

Studies were categorized into the following types based on the outcomes: 1) cost-effectiveness/cost-utility analyses, 2) cost–benefit analyses, and 3) studies focusing on life-year loss averted due to HAART. We identified eight studies comparing the cost-effectiveness analyses of the specific HAART regimens; two compared darunavir + low-dose ritonavir (DRV/r) with lopinavir + ritonavir.[5,12] Comparable studies were performed in five different countries, with incremental QALYs gained of 0.785 in Belgium, 0.608 in Italy, 0.584 in Sweden, 0.550 in the UK, and 0.493 in the US, as well as ICERs of €6,964/QALY gained in Belgium, €9,277/QALY gained in Italy, €6,868/QALY gained in Sweden, €14,778/QALY gained in the UK, and $23,057/QALY gained in the US. Two of them compared ritonavir-boosted tipranavir to an investigator-selected ritonavir-boosted comparator PI,[8,13] with incremental QALYs gained ranging from 0.51 to 0.64 and ICERs ranging from €42,500 to $56,517. One of the reported life year gained was 0.52.

Three studies compared four to seven types of therapeutic combinations. Rizzardini et al[16] indicated that compared with untreated controls, the ICER of tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) + efavirenz (EFV) was €34,965, and remaining strategies ranged from €53,000 to €62,000 per QALY. Colombo et al[20] showed that compared with untreated controls, the ICER of TDF/FTC + EFV (single-tablet regimen) was €22,017, while that of TDF/FTC + EFV was €24,526, TDF/FTC + NVP was €26,416, and TDF/FTC + EFV was €26,558. Colombo et al[17] also reported similar research demonstrating that compared with untreated controls, the ICER of the single-tablet regimen was €13,655, followed by TDF/FTC + RPV and TDF/FTC + EFV with ICERs of €15,803.00 and €16,181.00, respectively. Another study compared DRV/r to other control PIs.[26] The incremental QALYs gained were 0.2 in a 5-year scenario and 1.27 in a lifetime scenario. The ICER was $30,046 per QALY gained.

We also identified three cost-effectiveness analyses of comparisons between HAART and no interventions. Johnston et al[9] showed that the HAART-expansion scenario was associated with a net benefit of $900 million over 30 years. They also reported a significant gap wherein from a private perspective, the cost for HIV infection averted was $998 per person and cost per DALY saved was $35.36; from a public perspective, the results were $–261 and $–16.55 (lower cost than that of therapy for an HIV^+ child), respectively, for pregnant women. They divided the population into two groups. In the AIDS group, the cost was $5,189 per LYG and $7,109 per QALY gained, while in the non-AIDS group, it was $6,652 per LYG and $9,782 per QALY gained.

Three of the studies compared the different scenarios in terms of $CD4^+$ T-cell count ranges. Granich et al[21] indicated

that compared to CD4 counts <200 cells/mm^3, expanding ART to CD4 counts <350 cells/mm^3 reduced DALYs by 14%, from 109 to 93 million over 40 years. Costs dropped by $504 million over 5 years and by $3.9 billion over 40 years, with breakeven by 2013. Expanding ART to all CD4 levels reduced HIV infections by 3.3 million (45%) and treatment costs by $10 billion over 40 years. Badri et al[14] showed that therapy started at CD4 <200 cells/mm^3 displayed an ICER of $54 per QALY versus no ART. Treatment initiated at CD4 of 200–350 cells/mm^3 exhibited an ICER of $616, while therapy started at CD4 counts <200 cells/mm^3 and CD4 >350 cells/mm^3 showed an ICER of $1,137. Mauskopf et al[25] conducted a comprehensive study showing that compared to the treatment group initiated at CD4 counts of 200–350 cells/mm^3, starting HAART at CD4 counts >350 cells/mm^3 increased years of life by 1.21, discounted QALYs by 0.61, and showed an ICER of $31,266 per QALY. It was determined that economic implications were associated with the clinical efficacy of alternative treatments, because treatment of HIV-infected individuals in the later stages is the most costly. Early therapy was more cost-effective when the impact of HAART on well-being was smaller.

Three analyses focused on the application of HAART among different populations. Long et al[6] compared the cost-effectiveness of HAART between IDUs and non-IDUs. Compared with no intervention, $1,501 per QALY gained was required to treat an IDU, while $2,572 per QALY gained was necessary to treat a non-IDU and $1,827 per QALY gained if treatment-eligible IDUs and non-IDUs received HAART. Binagwaho et al[10] modeled the cost-effectiveness of six HAART regimens classified by breastfeeding duration for HIV-positive pregnant women, and found that short course HAART was optimal for 6 or 12 months' breastfeeding. Badri et al[14] demonstrated that HIV-infected adults cost $1,622 per LYG, whereas AIDS patients cost $675 per LYG.

Another three studies compared the roles of different types of HAART. Vijayaraghavan et al[7] concluded that compared to the HAART based on developing-world guidelines, the ICER of HAART based on developed-world guidelines was $3,956 per QALY and the net benefit was $39.4 billion. McCabe et al[18] demonstrated that both self-administered HAART and directly observed ART were associated with decreased costs and increased life expectancy compared to no HAART. Munakata et al[19] built a model to compare two adherence scenarios: HAART in "ideal" (based on clinical trials) and in "typical" (based on observational studies in actual practice). With typical adherence, patients lost 1.2 QALYs that could be gained with ideal adherence. The improvement of adherence to "ideal" levels exhibited cost-effectiveness at $29,400 per QALY gained.

The last two studies compared HAART with other types of treatment. Marseille et al[15] indicated that compared with cotrimoxazole + prophylaxis treatment, the HAART program averted 6,861 incremental DALYs. The net program cost was $4.09 million. Ono et al[23] demonstrated that HAART, vaccine treatment, and combined therapy averted $75, $610, and $267 per DALY, respectively, compared to no intervention.

For the sensitivity analysis, most of the studies conducted an extensive one-way sensitivity analysis (Table 2), performed to illustrate the impact of individual parameter values on the results, as well as a two-way and probabilistic sensitivity analysis (Table 2), which demonstrated the impact of the results of all the combined uncertainty for all the parameter values.

Discussion

To our knowledge, this is the first review that summarizes economic evaluations related to HAART published over the course of the last 10 years. We identified 22 reports describing cost-effectiveness analyses of people living with HIV treated with HAART. The studies were grouped according to the similarity of the different intervention types and outcomes.

Cost-effectiveness analyses of comparisons between the specific HAART regimens adhered to the general guidelines of pharmacoeconomic evaluations. We did not undertake quality assessment of the reports, due to the limitation of length of article. In terms of results, an intervention may be considered cost-effective if the additional benefit provided by the treatment is considered "worth" the additional cost. ICERs per QALY tend to be the gold standard for economic evaluation. The advantage of using this parameter is the capacity to improve the comparability of studies and provide information that can therefore be used to aid policy makers regarding resource-allocation decisions. The WHO Commission on Macroeconomics and Health suggests that interventions may be considered quite cost-effective when the ICER is less than the per-capita gross domestic product, and can be accepted when the ICER is less than three times the per-capita gross domestic product.[27] For example, some studies in this review indicated that DRV/r-based HAART was more cost-effective than other standard-of-care PI-based regimens among people living with HIV. The ICER was well below typical benchmark values and the ratios were robust, as demonstrated by one-way sensitivity and variability analyses or probabilistic sensitivity analyses. However, most of

the studies that focused on specific HAART regimens only performed one-way or two-way sensitivity analysis, but not probability sensitivity analysis, which is the most effective method to check the stability of the model. Further studies are required to clarify this point.

In addition, it is difficult to compare the results of studies that analyze different kinds of HAART separately, since these are based on studies and trials that use different methodologies, including different study perspectives: payer, health system, or societal. The societal perspective is wider, since it considers the benefits and cost as a whole, especially cost. In theory, all costs, both direct and indirect, should be included in an economic evaluation from a social perspective. Moreover, in general, many analyses were actually based on comparisons with no intervention. The lack of head-to-head comparisons may reduce the value and reliability of results. Therefore, as this review demonstrates, more clinical trials or "typical" research based on different HAART regimens are required to provide more valuable results for health care decision making.

There are a number of limitations to this review. First, we included only studies published in the English language between January 2005 and December 2014, and earlier cost-effectiveness analyses, especially in the HAART era from 1996 to 2004, were omitted. Second, we did not evaluate the quality of these studies, because of the limitation of length of article. The effectiveness of HAART regimens is also influenced by patient adherence. Patient adherence may be reduced by the complexity of HAART or the onset of adverse events. Among the studies included in this review, only one study[19] considered patient adherence in comparison between HAART regimens; therefore, further studies should be conducted to determine how patient adherence affects the cost-effectiveness of HAART. Finally, the review included a heterogeneous set of studies, such that it was not possible to consider pooling data for a meta-analysis. Therefore, this review is a comparative analysis, but not a quantitative analysis. Further studies should be conducted to determine the cost-effectiveness of HAART.

Conclusion

Our literature search revealed that many studies have been conducted to evaluate HAART from different perspectives. Most focused on comparisons between the specific HAART regimens, while others conducted analyses from the perspective of different people, such as IDUs versus non-IDUs and HIV-infected adults without AIDS versus those with AIDS, different types of regimens based on developed-world guidelines versus those based on developing-world guidelines, self-administered HAART versus directly observed HAART, and "ideal" versus "typical" studies. In terms of economic outcomes, we conclude that HAART is a better choice to deal with AIDS than other regimens or no intervention.[9,11,15–18,20,22,23] Compared with HAART, tipranavir boosted with ritonavir[5,12,26] seems to be a more cost-effective choice when compared with other specific regimens. No consistent conclusions were drawn from other comparisons.[8,13] From the perspective of clinical biomarkers,[21,24,25] treatment is more cost-effective if initiated early when CD4 counts >350 cells/mm^3.

In general, HAART is more cost-effective than other therapeutic regimens available to date. As combination antiretroviral regimens have become more potent and popular in both developed countries and developing countries, it is important to administer HAART at the appropriate time and among appropriate people. To identify the most suitable combination of HAART, further investigations are needed, especially analysis of head-to-head analyses based on "ideal" and "typical" trials of different combination of regimens.

Author contributions

All authors read and approved the final manuscript. WFT, WY, and WH contributions include selecting studies, collecting data, analyzing and presenting results, and writing and revising the manuscript. WH is responsible for the final content of the paper.

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Disclosure

The authors report no conflicts of interest in this work.

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