REVIEW　　　　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

Cost-effectiveness analysis of lopinavir, ritonavir, and nevirapine toward HIV AIDS patients as antiretroviral: a systematic review

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ABSTRACT

Background: The mobilization of resources to prevent and treat human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is unparalleled in the history of public health. Nevirapine resistance may decrease the effectiveness of viral suppression with nevirapine-based HIV in women infected with human immunodeficiency virus (HIV) with previous exposure to single-dose nevirapine. However, the alternative lopinavir/ritonavir–based antiretroviral therapy (ART) regimen is more expensive.

Objective: Our objectives were to project the tradeoffs regarding the cost-effectiveness of ART regimens for nevirapine-exposed and lopinavir/ritonavir.

Methods: A thorough literature search was conducted using PubMed and SAGE databases, employing search terms such as "cost-effectiveness analysis," AND "HIV AIDS," AND "lopinavir," OR "ritonavir," AND "nevirapine." Additionally, hand searches were carried out on Google Scholar with various combinations of these terms to ensure comprehensive coverage of relevant studies.

Results: Six studies met the our inclusion criteria and were reviewed. The analysis confirms that both nevirapine and lopinavir/ritonavir-based ART regimens are cost effective in a range of settings, despite differences in their relative efficacy and contexts in which they are used.

Conclusion: This systematic review collates recent studies on the cost-effectiveness of nevirapine and lopinavir/ritonavir in ART. It showed that in this finding, there are cost effective but this article had wide variation with comparison therapy. Cost-effectiveness results depended on the relative efficacy of lopinavir/ritonavir and nevirapine in both first-line and second-line ART.

Keywords: Human immunodeficiency virus, antiretroviral, cost-effectiveness analysis, lopinavir, ritonavir

Introduction

According to a report by World Health Organization, approximately 37.7 million people were living with human immunodeficiency virus (HIV) by the end of 2020, with 680,000 deaths attributed to HIV-related causes. In Italy, a study covering the years 1985-2008 reported that 42,747 patients had been diagnosed with HIV. Between 2007 and 2012, the incidence of new HIV diagnoses was 6.7 per 100,000 population [1]. Globally, approximately 3 million children live with HIV/AIDS, and nearly 260,000 infected annually. HIV-infected children below 3 years of age face high risks of AIDS and death without effective antiretroviral therapy (ART) [2].

Antiretroviral therapy has revolutionized the management of HIV, enabling patients' quality of life to mirror that of the general population. ART typically uses three-drug regimen to reduce the plasma viral load to undetectable levels, defined as fewer than 50 copies/mL, aiming to maintain this suppression. In

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most cases, current ART regimens often achieve partial immune system restoration, both quantitavely and qualitively, depending partly on the degree of baseline immunodeficiency levels. Overall, ART is considered one of the most significant medical interventions in terms of cost/efficacy ratios, including in developing countries [3].

Nevirapine and lopinavir/ritonavir are two frequently used as ART. In African programs, pediatric ART includes two sequential 'lines' of treatment: a 'first-line' regimen with nevirapine (a non-nucleoside reverse transcriptase inhibitor, or NNRTI)) and a 'second-line' regimen comprising lopinavir/ritonavir (a protease inhibitor, or PI)) [4]. Indonesia has implemented a national ART program since 2004, utilizing two NRTIs and one NNRTI, specifically zidovudine+lamivudine and nevirapine. The national guideline also suggests using lopinavir/ritonavir instead of NNRTIs when the first-line treatment fails to maintain clinical, immunological, and/or virologic parameters [5]. Similarly, Thailand initiated a national program for the preventing of mother-to-child transmission of HIV in 1997, adopting zidovudine/lamivudine with ritonavir-boosted lopinavir as the national regimen starting in 2010 [6].

Resistance to nevirapine can reduce the effectiveness of viral suppression in women with HIV previously exposed to the drug. Nevirapine is a low-cost, widely available drug that comes in fixed-dose combinations [3]. Conversely, the alternative lopinavir-ritonavir-based ART regimen is more expensive. A systematic review of the cost-effectiveness of lopinavir, ritonavir, and nevirapine in treating HIV/AIDS patients has not been previously conducted, underscoring the importance of this study to determine the more cost-effective ART regimen, focusing on the trade-offs between the nevirapine-exposed and lopinavir-ritonavir treatments.

Methods

We identified articles that directly compared antiretrovirals in HIV/AIDS patients to assess their economic worth and cost-effectiveness. This study was conducted through a search of online literature databases, identifying relevant articles, and examining cost-effectiveness findings related to the use antiretroviral in HIV/AIDS patients. The search and reporting of results were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [7].

Search strategy

We conducted a comprehensive search of the literature using two electronic databases: PubMed and SAGE. The search terms included "cost-effectiveness analysis" AND "HIV AIDS" AND "lopinavir" OR "ritonavir" AND "nevirapine." Additionally, we performed manual searches in Google Scholar using various keywords related to "cost-effectiveness analysis," "lopinavir," "ritonavir," and "nevirapine." We utilized matches across all keyword categories to search the databases and examined the reference lists of all included articles for additional citations.

Eligibility criteria and study selection

The criteria for inclusion in this systematic review were as follows: (i) original cost-effectiveness analysis, (ii) studies on antiretrovirals in HIV/AIDS patients (lopinavir or ritonavir and nevirapine), (iii) outcomes measured in terms of cost, efficacy, or quality-adjusted life years (QALYs) gained, and (iv) publication in English. We excluded review articles, commentary articles, and handbooks.

Study selection was independently conducted by four reviewers. After removing duplicates, we screened titles and abstracts for relevance based on inclusion criteria. Un the second stage, we reviewed the full text of potentially relevant publications for detailed evaluation.

Data abstraction and synthesis

Quality assessments were conducted using the Joanna Briggs Institute Critical Appraisal Checklists for Economic Evaluations. Reviewers independently evaluated a subset of articles, recording citations and their interpretations of the findings in a spreadsheet. Relevant data were extracted from the study. All included studies were summarized in a table (Table 1). Any discrepancies between reviewers were resolved through a discussion.

Results
Search outcome

Our search identified 342 articles. After eliminating duplicates from databases, we reviewed titles and abstracts for relevance to this systematic review. Through discussions focused on titles and abstracts meeting our inclusion criteria, we excluded 332 articles due to their failure to meet these criteria, such as being review articles, lacking available full texts, or
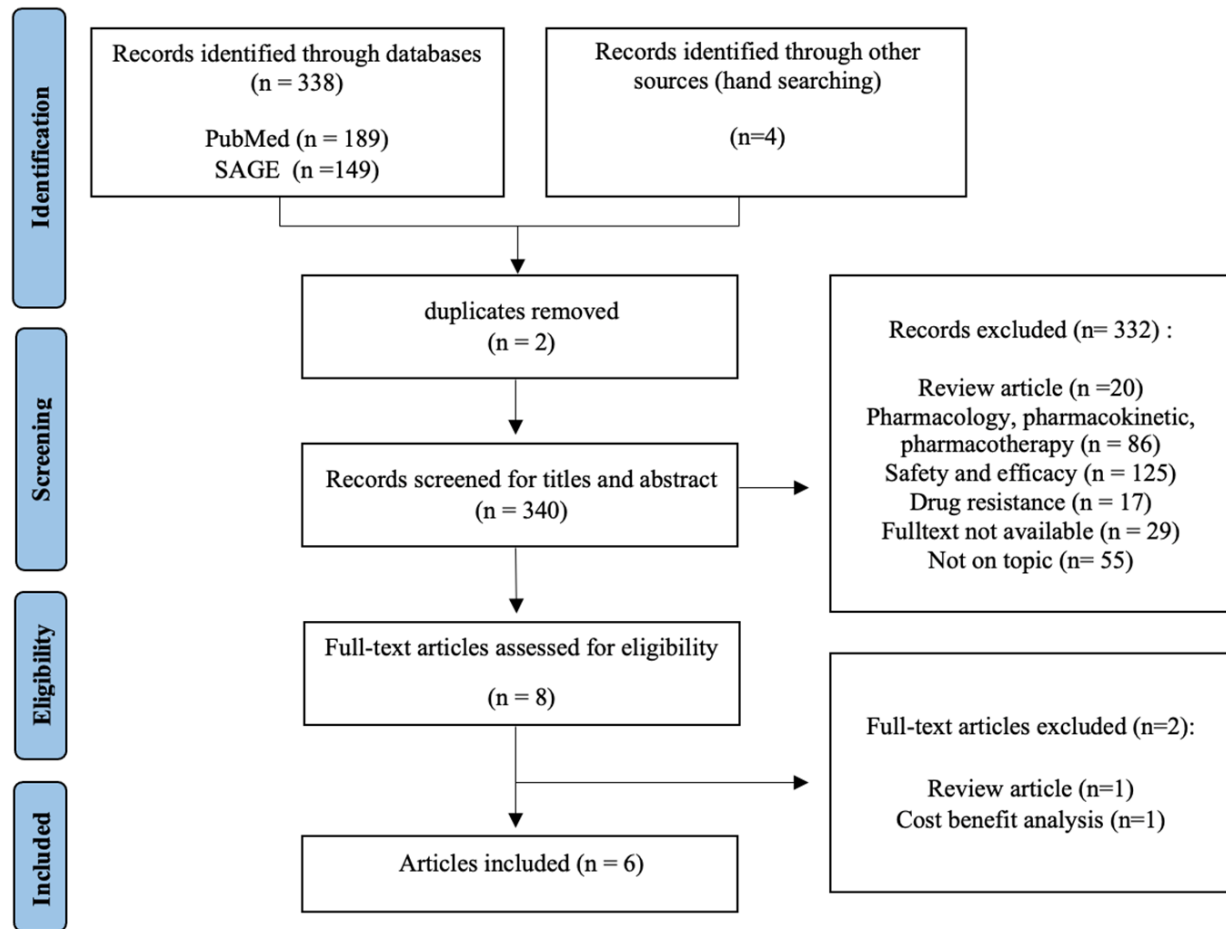
Figure 1. PRISMA Diagram

being irrelevant to our topic. Eight articles underwent thorough text analysis and eligibility assessment. The research team independently assessed the full texts of articles meeting the inclusion criteria and passing the title and abstract screenings, excluding two due to their nature as review articles and their focus on cost-benefit analysis. The discussion among the research team members resulted in data extraction and finalization, resulting in six articles included in our systematic review. Figure 1 illustrates the overall selection process.

Studies characteristic

The six included studies were conducted across various countries: Africa, Italy, South Africa, Thailand, Spain, and the USA, between 2006 and 2015. These studies examined the cost-effectiveness of HIV treatment, comparing the approaches used in different countries from both societal and payer perspective. Three studies analyzed the societal viewpoint [4,8,9], while three considered the payer's perspective [10–12]. The models' time horizons varied, ranging from 1 to 10 years, with one study considering lifetime [12]. Most studies applied a standard discount rate of 3% to 3.5% for base-case scenarios, except one that did not specify a discount rate [12]. Sensitivity analysis was crucial for most studies to account for potential changes in costs and benefits due to technological advancements; however, one study did not perform this analysis [12] (Table 1).

Outcome characteristics

The studies compared direct costs with various outcomes. Life expectancy was the outcome in two studies [8,9], CD4 cell count in two others [4,10], one study evaluated a combination of QALYs and CD4 cells [11], and another focused solely on QALYs [12]. Measurement cost-effectiveness analysis (CEA) was used to compare the studies of antiretroviral agents. CEA methodologies varied, with four studies utilizing ICER and Markov models [4,9,11,12], one employing ICER with Monte Carlo simulation [8,] and another using ICER with decision tree analysis [10] (Table 1).

Table 1. Characteristics cost-effectiveness analysis (CEA)

No	Author	Country	Cost perspective	Time horizon	Discount rate	Sensitivity analysis	Cost	Outcomes	Therapy	Measurement CEA
1	Holmes et al, 2006 (9)	Africa	Societal perspective	5-10 years	3%	Yes	Direct health cost: 1. Clinic visits 2. Treatment	Life expectancy	Five strategies: 1. Treatment of HIV without ART 2. Treatment with an nevirapine-based ART regimen 3. Treatment with a lopinavir-ritonavir–based ART regimen 4. Treatment with an nevirapine-based ART regimen followed by treatment with a lopinavir-ritonavir–based 5. Treatment with a lopinavir-ritonavir–based ART regimen followed by treatment with an nevirapine-based	ICER value and Marcov model
2	Colombo et al, 2011 (11)	Italy	Payer (Italian health care system (Servizio Sanitario Nazionale [SSN]))	10 years	3.5%	Yes	Direct health cost: 1. Hospitalizations 2. Laboratory test 3. Treatment	QALY, CD4 cell count	1. Tenofovir/emtricitabine + efavirenz (single tablet regimen) 2. Tenofovir/emtricitabine + efavirenz 3. Tenofovir/emtricitabine + ritonavir-boosted atazanavir 4. Tenofovir/emtricitabine + nevirapine 5. Tenofovir/emtricitabine + ritonavir-boosted darunavir 6. Tenofovir/emtricitabine + ritonavir-boosted lopinavir 7. Tenofovir/emtricitabine + raltegravir 8. Tenofovir/emtricitabine + efaviren 9. Abacavir/lamivudine + efavirenz 10. Abacavir/lamivudine + ritonavir-boosted atazanavir abacavir/lamivudine + ritonavir-boosted lopinavir	ICER and Marcov model
3	Ciaranello et al, 2011 (8)	South Africa	Societal perspective	8 years	3%	Yes	Direct non-medical cost 1. patients' costs for time 2. transportation	CD4 cell count	1. No ART 2. First-line nevirapine 3. Second-line lopinavir/ritonavir First-line lopinavir/ritonavir followed by second-line nevirapine	ICER, monte carlo simulation of HIV infection
4	Werayingyong et al, 2013 (12)	Thailand	Payer	Life time	3%	N/A	Total direrct cost	QALY	1. AZT and sd-nevirapine regimen 2. AZT + 3TC + EFV regimen 3. AZT + 3TC + LPV/r regimen NB: AZT (zidovudine); sd-nevirapine (single dose nevirapine); 3TC (lamivudine); EFV (efavirenz); LPV/r (lopinavir or ritonavir)	ICER value and Marcov model

No	Author	Country	Cost perspective	Time horizon	Discount rate	Sensitivity analysis	Cost	Outcomes	Therapy	Measurement CEA
5	Berenguer et al, 2015 (10)	Spain	Payer (the Spanish National Health System (NHS))	1 years	N/A	Yes	Direct costs	Effectiveness was defined as the probability of reporting a viral load <50 copies/mL at week 48, in an intention-to-treat analysis.	1. Abacavir/lamivudine + dolutegravir (preferred) 2. Tenofovir/emtricitabine + folutegravir (preferred) 3. Renofovir/emtricitabine + raltegravir (preferred) 4. Renofovir/emtricitabine / rilpivirine (alternative) 5. Tenofovir/emtricitabine / efavirenz (alternative) 6. Tenofovir/emtricitabine / elvitegravir/cobicistat (alternative) 7. Abacavir/lamivudine + raltegravir (alternative) 8. Tenofovir/emtricitabine + darunavir/ritonavir boosted (alternative) 9. Tenofovir/emtricitabine + atazanavir/ritonavir boosted (alternative) 10. Abacavir/lamivudine + atazanavir/ritonavir boosted (alternative) 11. Abacavir/lamivudine + efavirenz (other) 12. Tenofovir/emtricitabine + nevirapine (Other) 13. Abacavir/lamivudine + darunavir/ritonavir boosted (other) 14. Tenofovir/emtricitabine + lopinavir/ritonavir boosted (other) 15. Abacavir/lamivudine + lopinavir/ritonavir boosted (other) 16. Lamivudine + lopinavir/ritonavir boosted (other) 17. Raltegravir + darunavir/ritonavir boosted (other) 18. Raltegravir + lopinavir/ritonavir boosted (other)	ICER, decision treea nalyses.
6	Ciaranello et al 2015 (4)	USA	Societal perspective	5-10 years	3%	Yes	Direct health cost: 1. Clinic visits 2. Treatment	Life expectacy	1. Nevirapine with abacavir/lamivudine (first line) 2. Lopinavir/ritonavir/zidovudine/lamivudine (Second line)	ICER, Marcov model

Cost-effectiveness of therapy HIV

The cost-effectiveness of HIV therapy varied across studies. The results showed that nevirapine as the first line treatment, resulted in a higher life expectancy than single nevirapine treatment [9]. Additionally, nevirapine-based ART proved to be cost-saving in the short term and highly cost-effective in the long term compared to no ART [8]. Nevirapine was also evaluated as a second-line therapy for HIV. Studies found that a second-line combination of nevirapine yielded a higher Incremental Cost-Effectiveness Ratio (ICER) value, improved life expectancy, and increased total cost compared to using single nevirapine either as first-line treatment or in combination with other drugs as a first line treatment [9]. Moreover, nevirapine used as a second-line therapy was found to be more costly than other regimen combinations [12].

Lopinavir/ritonavir, another ART option, was assessed as a first-, second-, or third-line therapy. As a first-line therapy, the combination of lopinavir/ritonavir demonstrated a better impact on ICER value and life expectancy compared to lopinavir alone [9]. Other studies suggested that lopinavir/ritonavir-based ART substantially improves survival and is highly cost-effective in South Africa when compared to initiating therapy with nevirapine-based ART [8]. As a second-line therapy, the combination of lopinavir/ritonavir was shown to have a more favorable effect on ICER value, life expectancy, and total cost than using lopinavir/ritonavir alone as either a first-line or combined first-line therapy [9]. Finally, as a third-line therapy, lopinavir was found to be more cost-effective than nevirapine used as a second-line therapy [12] (Table 2).

Discussion

In this study, we aim to systematically review global studies on the cost-effectiveness analysis of ART. Our primary goal is to assess the cost-effectiveness of ART in various settings. This review is particularly valuable as a resource for advocacy in developing countries that have initiated free ART programs and are seeking to expand funding to enhance and maintain such initiatives. It also serves as a benchmark for other nations requiring evidence of ART program effectiveness, offering a basis for comparing methodologies and outcomes with the studies analyzed in this manuscript.

The impact of the two drugs examined in this review varies depending on their use as first, second, or third-line treatments in HIV therapy. Our findings highlight several key points. Firstly, combination therapy in HIV management presents significant clinical benefits, although it is associated with higher costs. Nonetheless, a pharmacoeconomic analysis reveals that ART combination therapy offers greater cost-effectiveness compared to monotherapy. Secondly, nevirapine, commonly used in first-line HIV therapy, demonstrates notable efficacy when used as a second-line treatment option [4,9,11]. Lastly, lopinavir is identified as cost-effective, with various studies indicating its lower cost relative to other combination therapies.

Nearly all examined articles applied a discount rate between 3% and 3.5%, with the exception of one study that did not specify a discount rate [10]. The practice of discounting health benefits is grounded in the concept of "positive time preference," which posits that society values immediate benefits more highly than future ones. Consequently, if future health outcomes are discounted, the perceived value of an intervention's future benefits might be undervalued. The likelihood of double discounting is reduced for disease-specific and surrogate outcomes, such as blood pressure reduction, where time is not a direct factor [13]. Economic evaluations, however, typically focus on generic outcomes such as life-years and quality-adjusted life-years (QALYs). Gravelle and Smith have suggested that applying a lower discount rate to health benefits than to costs accounts for any potential rise in the future value of health benefits [14]. These considerations include the pure rate of time preference, the elasticity of the marginal utility of consumption, the growth rate of income, and the degree to which health impacts income. Based on these factors, the authors propose that the discount rate for health effects should be 1% to 3.5% lower than that for costs [15].

Cost perspective used varied across studies. The analysis was carried out from the point of view of social society and payers. Three studies analyzed costs from a societal perspective [4,8,9], while another three focused on the perspective of payers [10–12]. Costs are categorized into several types, including direct, indirect, and intangible costs. Direct costs are further divided into medical and non-medical costs. Direct medical costs encompass expenses such as medications, hospital stays, diagnostic tests, procedures, and professional fees. Direct non-medical costs may include transportation to healthcare facilities, childcare during medical appointments, or domestic help during recovery. Indirect costs account for unpaid family assistance, work absenteeism, diminished productivity, and legal

Table 2. Cost effectiveness of therapy HIV

No	Author	Effectiveness therapy				
		Nevirapine as first-line	Lopinavir/ritonavir as first-line	Nevirapine as second-line	Lopinavir/ritonavir as second-line	Lopinavir/ritonavir as third-line
1	Holmes et al, 2006 (9)	The result show nevirapine as first line combination had higher life expectancy than single nevirapine.	The result show lopinavir/ritonavir as first line combination had better impact ICER value and life expectancy than single lopinavir	The result show nevirapine as second line combination had higher ICER value, life expectancy and total cost than single nevirapine as first line or combination nervirapine as first line	The result show lopiravir/ritonavir as second line combination had better impact ICER value, life expectancy and total cost than single lopiravir/ ritonavir as first line or combination lopiravir/ritonavir as first line	NA
2	Colombo et al, 2011 (11)	N/A	N/A	The TDF + 3TC + efavirenz (EFV) regimen (€8211) reveals a lower mean treatment cost, followed by TDF/FTC + nevirapine with €8231. tenofovir/emtricitabine + efavirenz (single tablet regimen) have appeared to be the most cost-effective therapeutic choice (€22,017), followed by TDF + 3TC + EFV (€24,526), TDF/FTC + nevirapine (€26,416)	Patient treated with abacavir/ lamivudine (ABC/3TC) + atazanavir/ritonavir has 0.731 QALY/year. Patient treated with tenofovir/emtricitabine + efavirenz (single tablet regimen) have a better quality of life, with a higher number of QALYs than with other therapeutic regimens (abacavir/ lamivudine (ABC/3TC) + atazanavir/ritonavir)	N/A
3	Ciaranello et al, 2011 (8)	Nevirapine-based ART is cost-saving in the short-term, and very cost-effective in the longterm, compared to no ART	Lopinavir/ritonavir-based ART improve survival further and very cost-effective in South Africa, compared to initiating nevirapine-based ART	N/A	N/A	N/A
4	Werayingyong et al, 2013 (12)	N/A	N/A	The result show nevirapine as a second line had more high cost than other regimen combination	N/A	Lopinavir as a third line was cost effective than nevirapine as second line
5	Berenguer et al, 2015 (10)	N/A	N/A	N/A	N/A	Considering all the regimens, 3TC + LPV/r, classified as "other" by the GESIDA/PNS consensus group, was the least expensive, one of the most efficacious (88% of response rate) and the most efficient (5280 Euros in the base case scenario)
6	Ciaranello et al 2015 (4)	The ICER of first-line lopinavir/ritonavir compared to no ART was $800/YLS	First-line nevirapine would be very cost-effective compared to no ART, with an ICER of $930/YLS.	N/A	N/A	N/A

expenses. Intangible costs, which cover pain and suffering, are notably difficult to quantify and identify.

Cost analysis commonly adopts four perspectives: provider, payer, patient, and societal. Providers, such as hospitals, focus on the expenses incurred to offer services, including personnel, medications, supplies, and equipment leasing. Indirect costs for providers may involve utilities, rent or mortgage expenses, and other overhead costs such as laundry, housekeeping, and office supplies. The societal perspective, the broadest of all, encompasses direct, indirect, and intangible costs, making it the most comprehensive and preferred viewpoint for cost-effectiveness analyses. This perspective, however, is also the most challenging to apply due to the need to capture a wide array of cost categories, assessing the full economic impact on society [16]. Our study should have extensively examined the implications of these various cost perspectives. Prior research has indicated the variability in reporting cost-effectiveness ratios: five cost-per-DALY (Disability-Adjusted Life Year) studies presented a total of 72 cost-per-DALY ratios (with an equal distribution of 36 ratios from each perspective), and 16 cost-per-QALY (Quality-Adjusted Life Year) studies reported 68 cost-per-QALY ratios, equally split between healthcare sector and societal perspectives [17].

Developing countries, particularly those with limited government health budgets, require similar cost estimates to secure additional funding for ART programs. Once initiated, ART programs need to be continuously expanded without cessation to ensure comprehensive coverage. Moreover, findings consistently demonstrate that strategies involving early detection of HIV and prompt initiation of treatment are cost-effective across different strategies and target groups. While the efficacy of ART is broadly recognized, concrete evidence significantly strengthens the advocacy for national AIDS control programs. It serves as a powerful negotiation tool for securing more resources for the health sector, thereby addressing other disease priorities and enhancing health systems in developing countries [18].

Our study has several limitations. First, our search was confined to only two databases, excluding potential sources such as reference lists of the articles, grey literature, and publications by international agencies, which may have led to the exclusion of pertinent studies. Second, the discussion on the use of nevirapine and lopinavir in combination therapies was not as comprehensive as it could have been. Given the variability in drug combinations across studies, drawing definitive conclusions about costs is challenging. Not all studies included sensitivity analyses, further limiting the robustness of our findings. For future reviews, a more extensive search across a broader range of databases is necessary to accurately compare the cost-effectiveness of different drug combinations.

Conclusion

This systematic review consolidates recent studies on the cost-effectiveness of nevirapine and lopinavir/ritonavir as components of ART. The findings indicate that both drugs are cost-effective options for ART; however, there is significant variation in their cost-effectiveness when compared with other therapeutic options. The determination of cost-effectiveness for both lopinavir/ritonavir and nevirapine, whether used as first-line or second-line treatments, is contingent upon their relative efficacy.

Acknowledgment

Conflict of Interest

The authors declare that we have no conflict of interests.

Author contributions

AMP, HRP, KIK, HP concept and designed this study; AMP, HRP analyzed and interpreted the data; KIK, HP drafted the article.

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