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REVIEW

The Cost-Effectiveness of Dolutegravir in Combination with Tenofovir and Lamivudine for HIV Therapy: A Systematic Review

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Abstract: The World Health Organization (WHO) recommends dolutegravir (DTG), a human immunodeficiency virus (HIV) medicine, as the first- and second-line treatment for all populations because, when compared to an efavirenz (EFV) regimen, plus two nucleoside reverse transcriptase inhibitors (NRTIs) has demonstrated significant effectiveness in HIV suppression in persons. This study aims to review evidence of the cost-effectiveness of DTG in combination with tenofovir and lamivudine compared with the standard of care for HIV therapy. The systematic review involved searching electronic databases for articles published between January 2018 and May 2022. Electronic database sources include PubMed, ScienceDirect, and EBSCO for articles on DTG in combination with tenofovir and lamivudine as subjects with cost-effectiveness outcomes. The inclusion criteria in this systematic review were studies about the cost-effectiveness analysis (CEA) of DTG in combination with tenofovir and lamivudine, written in English. A total of 145 articles were identified from three databases. After removing nine duplicates, 142 articles were screened by title and abstract, excluding 123 articles. After a full-text screening of 19 articles, five articles were selected for further analysis. Five articles reviewed in sub-Saharan Africa, India, and China implemented different modelling methods for CEA but produced similar results. The results of these studies demonstrate that it is more cost-effective than standard care for HIV treatment. The study conducted in sub-Saharan Africa from 2018 to 2020 showed a cost-effective result with disability-adjusted life years averted (DALY averted) by 83%; in India, it resulted in incremental cost-effectiveness ratio (ICER) $130 per year of live-saved (YLS); and a study in China found that dolutegravir plus tenofovir and lamivudine led to 0.006 incremental quality-adjusted life years (QALYs) with cost savings of $64. The DTG regimen is cost-effective and recommended for HIV therapy in all studies that provide results.

Keywords: cost-effectiveness, antiretroviral therapy, human immunodeficiency virus, dolutegravir, efavirenz

Introduction

Antiretroviral therapy (ART) has played a significant role in HIV control, and integrase strand transfer inhibitors (INSTIs), such as dolutegravir (DTG), are becoming more widely used.[1] In 2016, the World Health Organization issued guidelines for the use of antiretroviral drugs for the treatment and prevention of HIV infection. Since 2018, WHO has recommended a combination of tenofovir disoproxil fumarate and lamivudine or emtricitabine plus DTG as the preferred first-line regimen for HIV therapy and updated this guidance in 2021.[2,3] This guideline provides a more comprehensive view of DTG as an ARV in the first-line due to the significant risk of neural tube defects risk and observed efficacy.[4]

DTG shows excellent efficacy and tolerability with a low risk of toxicities.[5,6] DTG with two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) has shown significant efficacy in HIV suppression in individuals.[7,8] DTG-based regimens may be more effective for CD4 recovery and virologic suppression than EFV-based regimens, making them a preferred treatment option for

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initial HIV treatment.[9] DTG also has fewer drug interactions than EFV, a better genetic barrier to developing drug resistance, and is particularly effective against HIV-2 infection, which is inherently resistant to EFV. The efficacy or effectiveness of health-care interventions has been assessed in clinical trials by measuring outcomes.

The availability of DTG as a once-daily generic fixed-dose formulation at lower prices in most low- and middle-income countries (LMICs) further supports the recommended use of DTG.[4] However, it must be determined whether the intervention is cost-effective and feasible to implement.[10] Cost-effectiveness analysis (CEA) is used to improve resource allocation efficiency and assess the relative costs and health benefits of various competing health therapies.[11] Comparing studies and interventions using cost-effectiveness analyses can assist stakeholders in making evidence-based health policies.[12]

Furthermore, initial regimens recommended for most people living with HIV are expenses over $36,000 per patient per year, with an average 6% increase since 2012, ART costs outpaced overall inflation rates.[13] The cost of antiretroviral therapy should be one of many factors considered in regimen selection because it can affect adherence and overall costs to the healthcare system, insurers, and society.[7] According to previous studies, DTG may result in lower costs for HIV treatment and be the most efficacious core agents belonging to integrase strand transfer inhibitors (INSTIs).[14,15] This study aims to review evidence of the cost-effectiveness of DTG in combination with tenofovir and lamivudine compared with the standard of care for HIV therapy.

Methods

Study Design and Search Strategies

This study was focused on a systematic review of CEA assessing DTG in combination with tenofovir and lamivudine for HIV treatment. A literature search was conducted in several electronic databases, such as PubMed, ScienceDirect, and EBSCO, by two principal investigators (SA and AMU). The time frame for the research database was set to run from January 2018 to May 2023. The research question was developed using the population, intervention, comparator, and outcome (PICO) format to conduct a systematic review most suitable to answer the research question (see Table 1). The search term strategies were used in combination with the problem or disease keyword "HIV" or "human immunodeficiency virus" the keyword intervention was "dolutegravir" or "combination of dolutegravir" the keyword comparison was "efavirenz regimen" and the keyword outcome was "cost-effectiveness." The authors used Mendeley Reference Manager version 1.19.8 to extract articles and check for duplicates, and the related articles were manually screened by two researchers based on the title and abstract. In particular, full-text screening was used to determine the studies potentially eligible according to the established inclusion criteria. As a result, the final articles collected were referred to the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist.[16] The quality rating of eligible studies was scored as excellent (100%), good (76–99%), moderate (51–75%) or low (<50%).[17,18]

Inclusion and Exclusion Criteria

The inclusion criteria were articles that studied cost-effectiveness of combination of tenofovir-lamivudine-DTG compared to tenofovir-lamivudine-efavirenz (TLE). The articles were published from January 2018 to May 2023, and the full-text articles are available in English. Articles that only examined clinical efficacy and cost-effectiveness studies were not compared with the EFV regimen; design studies were undertaken as review articles or systematic reviews; and not full-text articles were excluded.

Table 1 PICO for Search Term of Systematic Review

PICO Criteria	Main Concept	Synonyms/Abbreviations/More Specific Concepts
P – Problem	HIV	Human Immunodeficiency Virus; AIDS; Acquired Immune Deficiency Syndrome
I/E– Intervention/ Exposure	Dolutegravir (DTG)	Combination of tenofovir- lamivudine-DTG
C – Comparison	Efavirenz (EFV)	Combination of tenofovir-lamivudine-EFV
O – Outcome	Cost-effectiveness	Cost effectiveness; cost; cost saving; cost-effective

Results

Selected Studies

The search strategy identified 145 potential publications in PubMed, ScienceDirect, and EBSCO databases. After removing duplicates, 142 articles were manually screened for inclusion in the review based on title and abstract by two reviewers. A total of 123 articles were excluded after pre-assessing the title and abstract. From 19 articles included in the full-text assessment, 14 articles were excluded because the studies only discussed clinical efficacy, not compared with efavirenz regimen, not full-text articles, and one article was published before 2018. Only five articles met the inclusion criteria following the evaluation of full-text articles (see Table 2). The article selection process is presented in Figure 1.

Modelling Design

Table 2 provides a description of the study's characteristics. The selected studies were conducted in sub-Saharan Africa, India, and China. Cost-effectiveness analyses of tenofovir-lamivudine-DTG combinations conducted between 2018 and 2020 were also discussed. Three of the five studies used an individual-based simulation model of sexual HIV transmission, progression, and ART's effect on adults.[20,21,23] The cost-effectiveness of preventing AIDS complications international model[19] and the dynamic Markov model[22] have been implemented in other studies (see Table 3).

The studies discussed the following outcomes: disability-adjusted life-years (DALYs), quality-adjustable life-years (QALYs), and incremental cost-effectiveness ratio (ICER). Most studies have compared the cost-effectiveness of DTG in combination with tenofovir and lamivudine to that of existing standard treatments, such as tenofovir, lamivudine, and EFV.[19–23] Punekar et al used EFV and ritonavir-boosted lopinavir, both of which combined with two of the NRTI classes of ART in China.

A CEA should use time horizons extending beyond the present time to accurately assess the value of medical interventions.[24] The model's time horizon should be long enough to capture relevant differences in outcomes across strategies.[25] McCreesh investigated the effect of different time horizons on the cost-effectiveness of the model and concluded that cost-efficiency would increase over time. In the first year, implementation of the intervention was highly unlikely, but it was cost-effective for more than 10 years.[26] Philips et al applied a 20-year time horizon in all studies to

Table 2 Study Characteristics

Author	Year	Country	Title	Objective	Conclusion
Zheng et al[19]	2018	India	The cost-effectiveness and budgetary impact of a DTG-based regimen as first-line treatment of HIV infection in India.	This study used to examine the potential cost-effectiveness and budgetary impact of a DTG-based first line ART. strategy in India	A generic DTG-based regimen is likely to be cost-effective and should be recommended for the first-line treatment of HIV infection in India.
Phillips et al[20]	2018	Sub-Saharan Africa	Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study.	The objective of this research was to assess the efficacy and cost-effectiveness of alternative public health responses in sub-Saharan African countries with a high prevalence of pretreatment drug resistance to NNRTIs.	The transition from efavirenz to dolutegravir formulations in adult ART initiators is expected to be effective and cost-effective in low-income settings, depending on NNRTI resistance.
Phillips et al[21]	2019	Sub-Saharan Africa	Risks and benefit of DTG-based antiretroviral drug regimen in sub-Saharan Africa: a modelling study.	The objective is to provide policymakers a quantitative assessment of the risks and benefits of alternative policies for DTG.	The benefits of transitioning to tenofovir, lamivudine and DTG outweighed the risks in a DALY framework.
Punekar et al[22]	2019	China	Improving access to antiretrovirals in China: Economic analyses of DTG in HIV-1 patients.	The purpose of this study was to compare the cost-effectiveness of DTG (DTG + TDF/3TC) to efavirenz (EFV +TDF/3TC) in treatment-naive and ritonavir – boosted lopinavir (LPV/r + TDF/3TC) in HIV-1-infected patients on first-line ART in China.	DTG + TDF/3TC provides higher response rates and QALYs at lower costs than currently available ARV regimens, and inclusion of dolutegravir in the National Free AIDS Antiretroviral Drug List may offer an additional option in tackling HIV in China.
Phillips et al[23]	2020	Sub-Saharan Africa	Updated assessment of risk and benefits of DTG versus EFV in new antiretroviral treatment initiators in sub-Saharan Africa: modelling to inform treatment guidelines.	This study provides updated modelling results in response to WHO's request for the 2019 antiretroviral guidelines revision.	DTG-based ART is predicted to bring population health benefits and be cost-effective, supporting WHO's recommendation as a preferred drug in ART initiators.

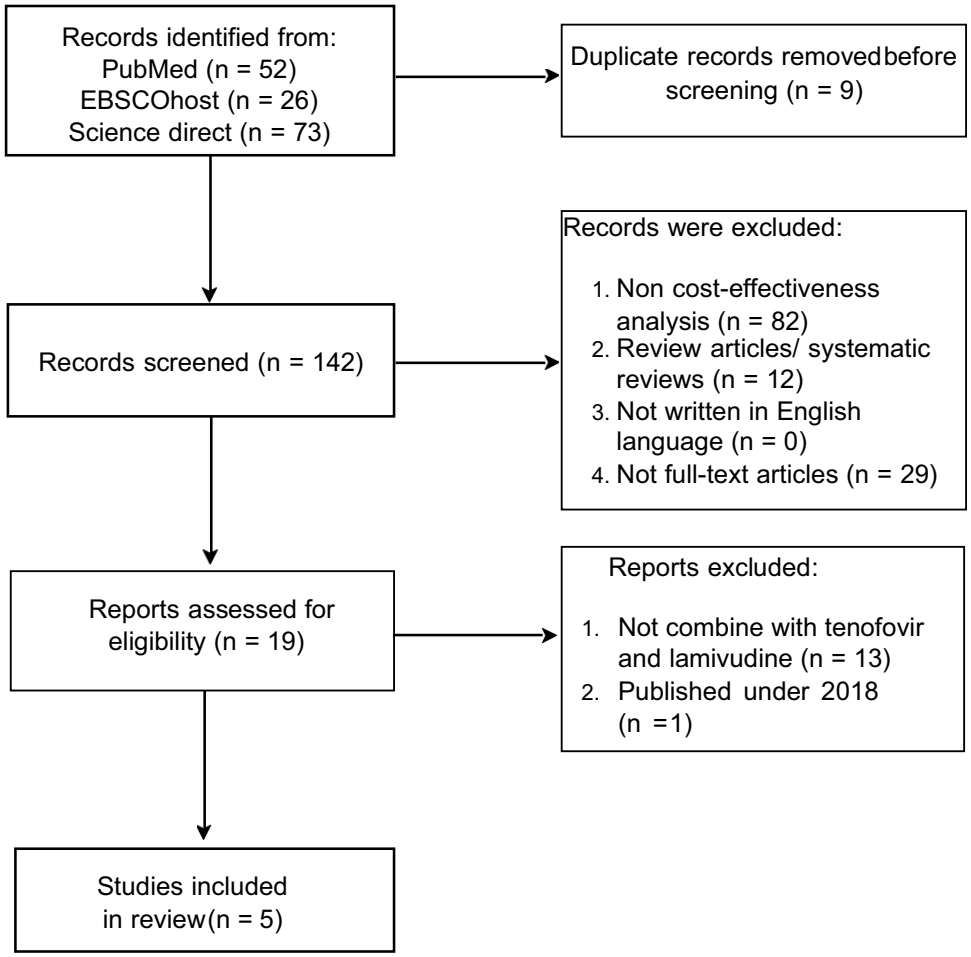

Figure 1 Article selection flow process.
Abbreviations: HIV, human immunodeficiency virus; WHO, World Health Organization; DTG, dolutegravir; ART, antiretroviral; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

consider the future implications of current decisions. Punekar et al employed a short-term horizon at 5-year intervals according to the mean period of first-line ART in China, and Zheng et al employed multiple time horizons.

Discount rate selection significantly impacts the outcomes of economic evaluations of health interventions and policies.[27] Almost all studies applied the same discount rate for costs and health outcomes, which was 3%, following the general discount rate in global health.[27] There is a distinction in the discount Punekar et al use to comply with China's inflation index, which was 2.3%.

Table 3 Modelling Method

Author	Year	Perspective	Time Horizon	Discounting Rate	Model	Sensitivity Analyses
Zheng et al[19]	2018	Public health	2 years, 5 years and lifetime	3%	The Cost-Effectiveness of Preventing AIDS Complications (CEPAC)- International model	One-way and multiway sensitivity analysis
Phillips et al[20]	2018	Public health	20 years	3%	Individual-based simulation model	Multiway sensitivity analysis
Phillips et al[21]	2019	Public health	20 years	3%	Individual-based simulation model	Multiway sensitivity analysis
Punekar et al[22]	2019	Public health	5 years	2.3%	Dynamic Markov model	Deterministic and probabilistic sensitivity analysis
Phillips et al[23]	2020	Public health	20 years	3%	Individual-based simulation model	Multiway sensitivity analysis

Outcome Summary

Implementing DTG, tenofovir, and lamivudine was cost-effective and cost-saving (see Table 4). The substitution of DTG with EFV in sub-Saharan Africa would likely impact public health owing to its efficacy, lower risk of side effects, and cost-effectiveness.[20,21,23] Phillips et al conducted a study in 2018 to describe the pretreatment HIV drug resistance of NNRTIs and provided a treatment option.

Over the 20 years, the results showed that 50,669 net DALYs were averaged for first-line DTG for all ART initiators, which was higher than that of the comparator.[20] Phillips et al continued those studies in 2019. They found that DTG-based regimens were the most cost-effective in 83% of setting scenarios, with net DALYs averted per year ranging from 30,000 to 85,000 compared with tenofovir, lamivudine, and EFV from a healthcare perspective. The last study was conducted by Phillips et al in 2020 to update the assessment of the risks and benefits of DTG-based regimens. In women planning pregnancy, initiation of tenofovir, lamivudine, and DTG averted more DALYs (83%), was cost-effective (87%), and showed net DALYs averted per year of 16,735.

According to Zheng et al DTG in combination with tenofovir and lamivudine is more cost-effective than the standard of care for HIV in India, with an ICER of $130/year of life-saved (YLS), which is less than 50% of India's annual Gross Domestic Product (GDP). A study in China by Punekar et al showed that incremental cost-effectiveness analyses of DTG plus tenofovir and lamivudine resulted in 0.006 incremental QALYs with cost savings of RMB 467 compared with EFV plus tenofovir and lamivudine. The report provided ART costs in Renminbi (RMB), the People's Republic of China's official currency.[22] Another result of the study was that compared to ritonavir-boosted lopinavir (LPV/r) in first-line failure, LPV/r had higher QALYs (4.224 vs 4.221) and a lower cost (RMB 238,746 vs RMB 244,364); thus, DTG in combination with tenofovir plus lamivudine dominated in both settings.

Sensitivity Analyses

Each study conducted a sensitivity analysis, and the types of sensitivity analyses applied were one-way, multiway, and probabilistic sensitivity analyses. Sensitivity analysis helps measure and evaluates the uncertainty of economic evaluation outcomes.[28,29] All models considered several critical parameters, such as clinical efficacy, prevalence of adverse events, cost, and utility varying within plausible ranges in the sensitivity analysis.[19–23] Zheng et al found two most essential parameters in one-way sensitivity analysis: the annual cost of the DTG regimen and the monthly probability of late virologic failure. Afterward, they conducted a multiway sensitivity analysis, simultaneously varying the annual cost of DTG and the monthly probability of virologic failure after 48 weeks on DTG, which remained cost-effective compared to standard of care (SoC). Regimen costing less than $102 per person per year was cost-effective, with an ICER less than

Table 4 Research Outcome

Author	Outcome
Zheng et al[19]	• Dolutegravir+Efavirenz/Lamivudine increased life expectancy from 22.0 to 24.8 years increased 5 years survival from 76.7% to 83.0% compared to standard of care in India. • A lifetime ICER of $130/YLS, which is less than 10% of GDP per capita.
Phillips et al[20]	First line dolutegravir for all ART initiator is the most cost effective with net DALY averted per year.
Phillips et al[21]	• The value of net DALYs averted per year ranges from 30,000 to 85,000 for treatment with tenofovir, lamivudine, and DTG in all scenarios. • Over 1–5 years, viral suppression decreased, but not significantly over 20 years.
Punekar et al[22]	• DTG+TDF/3TC resulted the viral suppression rates 75.3% that was higher than comparator. • In comparison to EFV +TDF/3TC, DTG +TDF/3TC resulted in 0.006 additional QALYs at a cost saving of RMB 467.
Phillips et al[23]	• In women planning pregnancy, initiation with tenofovir, lamivudine, and dolutegravir averted more DALYs 83%, was cost-effective 87%, and showed net DALYs averted per year of 16,735. • Pregnancy in women is predicted to benefit population health (10,990 DALYs averted per year) and be cost-effective ($2.9 million per year), resulting in a decrease in the overall population burden of disease of 16,735 net DALYs per year for a nation with a population size of 10 million adults. • ART initiation with a DTG-based regimen was cost-effective in 87% of setting scenarios and robust in sensitivity analyses.

50% of per capita GDP. Despite costing more than twice that of SoC ($200), DTG is cost-effective with an ICER of less than 50% of GDP, as long as the late virologic failure probability is less than 0.21% per month. Punekar et al assessed the model's robustness with multiple one-way deterministic sensitivity analyses by varying CD4+, adverse event prevalence, cost, and utilities combined with probabilistic sensitivity analyses to estimate the impact of these parameters. A one-way sensitivity analysis showed that improving CD4 and cost are critical drivers for cost-effectiveness and indicated that the cost-effectiveness of the DTG regimen was 98.2% in treatment-naive HIV.

Table 5 presents the quality evaluation results of the included CEAs using the CHEERS checklist. According to quality appraisal, the reporting quality varied from 84.6% to 94.2%. About 17 of 28 items were the most compliant with

Table 5 Quality Appraisal of Included Studies

	Item	Guidance for Reporting	Zheng et al	Phillips et al (2017)	Phillips et al (2018)	Punekar et al	Phillips et al (2020)	Total
Title								
Title	1	Identify the study as an economic evaluation and specify the interventions being compared	1	1	1	1	1	100%
ABSTRACT								
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses	1	1	1	1	1	100%
INTRODUCTION								
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice	1	1	1	1	1	100%
METHODS								
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available	1	1	1	1	1	100%
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics)	1	0.5	0.5	0.5	0.5	60%
Setting and location	6	Provide relevant contextual information that may influence findings	1	1	1	1	1	100%
Comparators	7	Describe the interventions or strategies being compared and why chosen	1	1	1	1	1	100%
Perspective	8	State the perspective(s) adopted by the study and why chosen	0.5	1	1	1	1	90%
Time horizon	9	State the time horizon for the study and why appropriate	1	1	1	1	1	100%
Discount rate	10	Report the discount rate(s) and reason chosen	1	1	1	1	1	100%
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s)	1	1	1	1	1	100%
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured	1	1	1	1	1	100%
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes	0.5	0.5	0.5	0.5	0.5	50%
Measurement and valuation of resources and costs	14	Describe how costs were valued	1	1	1	1	1	100%
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion	1	1	0.5	1	0.5	80%

(*Continued*)

Table 5 (Continued).

	Item	Guidance for Reporting	Zheng et al	Phillips et al (2017)	Phillips et al (2018)	Punekar et al	Phillips et al (2020)	Total
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed	1	1	1	1	1	100%
Analytics and assumptions	17	Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used	0.5	1	1	0.5	1	80%
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups	0	1	1	0	1	60%
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations	0	1	1	0	1	60%
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis	1	0.5	0.5	1	0.5	70%
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (eg, clinicians or payers) in the design of the study	n/a	n/a	n/a	n/a	n/a	n/a
RESULTS								
Study parameters	22	Report all analytic inputs (eg, values, ranges, references) including uncertainty or distributional assumptions	1	1	1	1	1	100%
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure	1	1	1	1	0.5	90%
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable	1	1	1	1	1	100%
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	n/a	n/a	n/a	n/a	n/a	n/a
DISCUSSION								
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice	1	1	1	1	1	100%
OTHER RELEVANT INFORMATION								
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	1	1	1	1	1	100%
Conflict of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements	1	1	1	1	1	100%
Overall quality			86.5%	94.2%	92.3%	88.5%	84.6%	

the CHEERS checklist (100%). Some studies needed to meet a few items in the CHEERS checklist, such as the characterizing heterogeneity and distributional effects as an approach to engage with patients and others affected by the study. Details on the CHEERS checklist criteria are provided in Supplementary Table S1.

Discussion

In 2021, the global HIV program was making decisions regarding new antiretroviral therapy (ART) regimens with fewer side effects and higher resistance barriers, which may improve adherence and viral suppression.[14] A fixed-dose combination of DTG, lamivudine, and tenofovir was available for over 18 million adults and 100,000 children in 60 countries, as reported in 2022.[30] Affordable antiretrovirals have played a significant role in increasing global antiretroviral therapy coverage.[31]

Research articles have been conducted in several countries to compare people living with HIV using a DTG-based regimen to a tenofovir-based regimen as therapy to assess its cost-effectiveness from a public health perspective. Based on the results of this review, the use of DTG in combination with tenofovir and lamivudine may be more effective for viral suppression in the treatment of HIV, and the transition to the DTG regimen was more cost-effective than first-line HIV therapy with tenofovir. Three studies were performed in sub-Saharan Africa, one of which was in India and China, where HIV prevalence was the highest in sub-Saharan Africa and India.[32] The WHO reported the situation and trends in 2022: the global number of people living with HIV was 39.0 million; the number of people living with HIV in the African Region and India was 25.6 and 2.5 million, respectively.[33]

The modelling method was used to assess the cost-effectiveness of the antiretroviral HIV policy. The outcomes of each study were distinct, but they all point to the same conclusion. Net costs, health benefits expressed as life-years or QALYs gained, and ICERS are the most common outcomes.[34] The CEA method used ICER/YLS, which defines the net cost per unit of benefit gained from intervention per year saved by using the DTG regimen.[19] DALY is a measure of the overall disease burden, expressed as the number of healthy years of life lost due to illness, disability, or early death. The net DALY is calculated as the sum of DALYs plus the ratio of costs to the cost-effectiveness threshold.[20] The viral suppression rate is higher than the EFV-based regimen (>75%).[19–23]

Even though this study is the first systematic review on the cost-effectiveness of DTG in combination with tenofovir and lamivudine for HIV therapy, it has several limitations. This study focused on specific interventions within specific patient characteristics that might lead to clinical variation in heterogeneity. Although an exhaustive search was performed, not all relevant studies were included. A search strategy that uses these terms results in irrelevant references. No additional relevant data in the search results discussed the cost-effectiveness of fixed-dose DTG with tenofovir and lamivudine in other countries. Nonetheless, policymakers in LMICs and high-income countries should consider using alternative therapies because of their cost-effectiveness. A DTG-based regimen is recommended as the preferred drug in antiretroviral initiators because of its population health benefits and cost-effectiveness, which aligns with the WHO recommendation. Overall, the reporting quality of the included studies varied from 84.6% to 94.2%, showing all the excellent quality.

Conclusion

This systematic review showed that the transition to HIV treatment using a combination of DTG, tenofovir, and lamivudine in several countries was potentially cost-effective or cost-saving because it can reduce the population burden of diseases. Since the HIV therapy guideline is a living document, further study is required when the guideline has been updated.

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Disclosure

The authors report no conflicts of interest in this work.

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