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INSTIs-centered antiviral regimens for first-line treatment of HIV/AIDS: a network meta-analysis and cost-effectiveness analysis

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Abstract

Objective This study evaluates the efficacy, safety, and cost-effectiveness of INSTI-based antiretroviral regimens compared to the national standard first-line treatment EFV/3TC/TDF for HIV/AIDS in China. The aim is to guide clinical decision-making and improve HIV/AIDS prevention and treatment.

Methods A network meta-analysis was conducted using ADDIS software on data from domestic and international randomized controlled trials comparing INSTI-based regimens with EFV/3 TC/TDF. Additionally, a Markov model assessed the cost-effectiveness of the representative INSTI regimen B/F/TAF (Bictegravir/Emtricitabine/Tenofovir Alafenamide) against EFV/3 TC/TDF. Costs and health outcomes were measured in US Dollars ($) and Quality-Adjusted Life Years (QALYs), respectively, evaluating incremental cost-utility ratios (ICERs) against a willingness-to-pay threshold of 1.5 times GDP per capita.

Results Seventeen trials involving 12,620 patients were analyzed. INSTI regimens showed no significant efficacy or safety advantages over EFV/3 TC/TDF but offered better drug resistance, adherence, and quality of life improvements. Economic analysis from the patient perspective showed that B/F/TAF had an ICER of $12,714.29/QALY, which is below the willingness-to-pay threshold, indicating cost-effectiveness. From the healthcare system perspective, B/F/TAF's ICER was $23,052.77/QALY, which is above the threshold, suggesting it is not cost-effective from this perspective. Sensitivity analyses confirmed these findings, with drug costs for B/F/TAF and the probability of CD4 count increase post-EFV/3TC/TDF treatment being the largest influencing factors. Additionally, probabilistic sensitivity analysis indicated that B/F/TAF has a varying probability of economic viability depending on the willingness-to-pay threshold, highlighting its potential value in specific economic contexts.

Conclusion INSTI-based regimens are as effective and safe as the national standard but offer additional benefits in drug resistance and patient compliance. B/F/TAF is economically viable from the patient perspective but does not present a cost-utility advantage from the healthcare system perspective. This study underscores the need for considering both clinical and economic factors in selecting first-line HIV/AIDS treatments in China.

Keywords INSTI-based regimens, Cost-effectiveness analysis, HIV/AIDS treatment, Network meta-analysis, Healthcare resource allocation

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Introduction

Acquired Immune Deficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus (HIV), is a condition that leads to severe immune deficiency, making individuals susceptible to opportunistic infections and malignancies, which can result in death. As of 2022, approximately 39 million people globally are living with HIV, with 1.3 million new infections and 630,000 AIDS-related deaths recorded annually [1]. In China, excluding Hong Kong, Macau, and Taiwan, there were 1.223 million reported cases of people living with HIV/AIDS by the end of 2022, including 689,000 HIV-positive individuals and 534,000 AIDS patients [2]. The same year saw 107,000 new HIV/AIDS cases reported in the country, posing a significant threat to public health and economic stability.

To mitigate the impact of HIV/AIDS, the Chinese government implemented the "Four Frees and One Care" policy in 2004, which was institutionalized by the "AIDS Prevention Regulation" in 2006 [3]. This policy provides free antiretroviral therapy (ART), outpatient examinations, mother-to-child transmission prevention, and education for orphans. Additionally, the "13 th Five-Year Action Plan for HIV/AIDS Prevention and Control" (2017) and the "2021–2031 Import Tax Policy on Anti-HIV Drugs" further strengthened these efforts [4]. These policies have substantially improved HIV/AIDS prevention and control in China, enhancing the availability of antiviral drugs, optimizing treatment regimens, and reducing patient costs [5]. Current strategies advocate for providing ART to all HIV-positive individuals regardless of $CD4^+$ T-cell counts, significantly reducing AIDS-related mortality and improving patient quality of life [6]. These comprehensive measures demonstrate the government's commitment to combating the HIV/AIDS epidemic and its determination to ensure that all citizens receive the necessary medical care and support.

HIV/AIDS is a lifelong condition requiring continuous ART regardless of $CD4^+$ T-cell levels, imposing a significant financial burden on individuals and the healthcare system. In 2022, the Chinese government allocated approximately $771.40 million for HIV/AIDS prevention, the highest among infectious disease programs. Despite the "Four Frees and One Care" policy, personalized treatment needs and ART-related side effects still pose economic challenges. Studies have shown that annual economic burdens for HIV/AIDS patients can range from $1,780.52 to $2,713.68, with some families experiencing up to $106,617.95 in economic losses due to AIDS-related deaths [7]. Moreover, the disease can lead to reduced employment and increased medical expenses, with the cost burden on families reaching 36.70% of their income. This highlights the urgent need for cost-effective treatment options that can alleviate the financial strain on patients and their families.

Six main classes of anti-HIV drugs exist: nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), and CCR5 inhibitors [8]. In China, free antiviral drugs primarily include NRTIs, NNRTIs, PIs, and INSTIs. Common free first-line regimens involve combinations such as efavirenz (EFV) + lamivudine (3TC) + tenofovir (TDF). Recently, single-tablet regimens (STRs) based on INSTIs, like B/F/TAF (Biktarvy), ABC/DTG/3 TC (Triumeq), and DTG/3TC (Dovato), have been approved, offering better patient adherence and fewer side effects. These drugs, although effective, are not covered by free treatment policies and require out-of-pocket payments. The development of these advanced treatment options underscores the progress in HIV/AIDS research and the potential for improved patient outcomes through better drug regimens.

Internationally, economic evaluations of HIV/AIDS interventions have focused on comparing different strategies and the cost-effectiveness of initiating ART at various stages of disease progression [9, 10]. For instance, the World Health Organization's model showed that early ART initiation in a South African community could significantly reduce HIV incidence and mortality over time. In China, research has predominantly assessed the cost-effectiveness of prevention services and intervention models, with limited studies evaluating self-funded antiviral drugs [11]. Comprehensive economic evaluations of first-line antiviral therapies, particularly INSTIs-based regimens, remain scarce [12]. This gap in research presents an opportunity to explore the economic and clinical impacts of these newer treatment options.

This study aims to bridge the existing knowledge gap by conducting a network meta-analysis and a cost-effectiveness analysis to evaluate the effectiveness, safety, and economic viability of INSTI-centered regimens compared to the standard national free first-line treatment, EFV/3TC/TDF, in China. By integrating both patient and healthcare system perspectives, the research seeks to provide insights that can guide clinical decision-making and enhance the level of AIDS prevention and treatment. Such findings are poised to potentially influence the future landscape of HIV treatment in China and similar regions where HIV remains a significant public health challenge. This research is not only pivotal for understanding the current state of HIV/AIDS treatment but also for shaping future policies and practices in the realm of infectious disease management.

Methods

This study adopts a dual approach involving a network meta-analysis and a cost-effectiveness analysis to assess the efficacy, safety, and economic viability of INSTI-based regimens compared to the standard treatment of EFV/3TC/TDF for HIV/AIDS in China.

Network meta-analysis

Literature search

To identify relevant studies for this network meta-analysis, systematic searches were performed in domestic databases (CNKI, VIP, WANGFANGDATA, CBM) and international databases (PubMed, Embase, Web of Science, Cochrane Library) up to December 15, 2023. The search strategy targeted randomized controlled trials (RCTs) comparing the efficacy and safety of antiretroviral regimens, including both INSTI-based and non-INSTI-based regimens. This comprehensive approach was essential to construct the evidence network required for the network meta-analysis. Further searches were conducted in the Chinese Clinical Trial Registry, Drug Clinical Trial Registration and Information Publicity Platform, and ClinicalTrials.gov to ensure complete coverage.

The search strategy incorporated specific keywords and combinations for different drug regimens and outcomes. These included INSTI-centered regimens such as Biktarvy (BIC/FTC/TAF), Genvoya (E/c/F/TAF), Triumeq (DTG/ABC/3TC), and others, alongside terms related to effectiveness, safety, and adverse events (Supplemental Table 1). To complement clinical trial searches, we also used detailed search strategies to identify relevant literature for economic models and economic evaluations (Supplemental Tables 2 and 3).

Supplemental Tables 1–3: Search Strategies.

This document summarizes the search strategies used to identify relevant literature for the meta-analysis and economic evaluations of antiretroviral therapy (ART) regimens.

- Supplemental Table 1: Lists the search terms and combinations for clinical trial literature focusing on INSTI-based regimens and their effectiveness and safety outcomes.
- Supplemental Table 2: Details the search strategy for economic models related to HIV/AIDS treatment, including terms for antiretroviral therapy and various economic modeling techniques.
- Supplemental Table 3: Provides search terms for economic evaluations, focusing on HIV/AIDS drug regimens, cost-effectiveness, and different evaluation methodologies.

These tables collectively ensure the inclusion of all relevant and high-quality studies necessary for the meta-analysis and economic evaluations.

Inclusion and exclusion criteria

The network meta-analysis focused on adult HIV-infected individuals who had not received any prior antiretroviral treatment. This population was chosen to ensure that the study results would be applicable to treatment-naïve patients, who represent a critical demographic for first-line therapy evaluations. The interventions involved comparing INSTI-based regimens (DTG, BIC, EVG, RAL) with non-INSTI-based regimens, including NNRTI-based (EFV/3TC/TDF, ANV/3TC/TDF) and PI-based regimens (LPV/r + 3TC). The comparison was based on randomized controlled trials assessing their efficacy and safety outcomes.

Exclusion criteria were meticulously applied to refine the study population. Studies involving patients with comorbid conditions such as malignancies, pregnant or lactating women, elderly individuals, and children were excluded to maintain a focus on the adult population typically considered for first-line antiretroviral therapy. Additionally, studies that included systematic reviews, literature reviews, reports, retrospective studies, observational studies, duplicated publications, and animal studies were excluded. This approach ensured that only high-quality randomized controlled trials (RCTs) were analyzed, providing robust and reliable results for the network meta-analysis.

Data extraction and management

Using Zotero software, duplicates were removed. Two researchers independently screened the literature, resolving discrepancies through discussion. The screening process involved title reading, abstract evaluation, and full-text review, excluding studies not officially registered on clinical trial platforms. Data collected included authors, publication year, clinical trial registration number, treatment and control schemes, participant numbers, age, baseline CD4, and viral load levels. Outcomes of interest were efficacy (proportion of patients with HIV-RNA < 50 copies/ml at 48 and 96 weeks, mean increase in CD4 from baseline) [13], and safety (rates of any adverse event, drug-related adverse events, serious adverse events) [14].

Quality assessment and PRISMA guidelines compliance

The quality of included studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs, evaluating random sequence generation, allocation concealment, blinding, baseline comparability,

and selective reporting. Discrepancies were resolved by consulting a third researcher.

This network meta-analysis was conducted following the PRISMA 2020 guidelines. A PRISMA checklist has been completed and is included as Supplemental Table 4, summarizing all key reporting items to ensure transparency and comprehensive reporting. Additionally, a PRISMA flowchart (Supplementary Fig. 1) illustrates the study selection process, detailing the steps taken to identify, screen, and select studies for inclusion. These steps include record identification, title screening, abstract screening, full-text review, and final inclusion.

Supplemental Table 4: PRISMA 2020 Item Checklist

This table provides the PRISMA 2020 checklist used in the manuscript, covering key sections such as title, abstract, introduction, methods (e.g., inclusion criteria, search strategy), results (e.g., study characteristics, bias assessment), and discussion. It ensures transparent and comprehensive reporting for systematic reviews and meta-analyses.

Statistical analysis

ADDIS software (version 1.16.6), based on a Bayesian framework using Markov chain Monte Carlo (MCMC) methods, was employed for data entry and network meta-analysis. The primary efficacy measure was the proportion of patients with HIV-RNA < 50 copies/ml at 48 weeks, and secondary efficacy was the mean increase in $CD4^+$ T lymphocytes at 48 weeks. Safety indicators included rates of any adverse events [15], drug-related adverse events, and serious adverse events. Effect sizes were expressed as odds ratios (OR) for dichotomous data and mean differences (MD) for continuous data, with their 95% credible intervals (95%CI). Comparisons were visualized using league tables, with probabilistic ranking presented in ranking plots. Consistency checks, potential scale reduction factors (PSRF), and inconsistency tests were conducted to ensure model reliability.

In accordance with clinical trial registration guidelines, we reviewed potential trial registration numbers. However, this study does not include a registered clinical trial. Therefore, the clinical trial number is not applicable to this analysis.

Cost-effectiveness analysis

Model structure and assumptions

A decision-tree Markov model was built using TreeAge Pro 2021 to simulate the disease progression of adult HIV/AIDS patients under different antiviral regimens (Fig. 1). The model assumed a cohort of 1000 patients per treatment group, simulating costs and utilities using cohort simulation methods. Health states were divided by $CD4^+$ T lymphocyte counts into five states: CD4 > 500, 350–500, 200–349, < 200, and death [16]. The cycle length was set at one year, with the model starting age at 33 years, based on clinical trial data. The distribution of patients entering the model was based on a survey of the Chinese population: 36.8% with CD4 < 200, 38.3% with CD4 200–349, 16.1% with CD4 350–500, and 8.8% with CD4 > 500 [17]. Half-cycle correction was applied, and the simulation horizon was 45 years.

Model input parameters

Efficacy and safety data for antiretroviral regimens were derived from clinical trials and published literature, with priority given to data relevant to the Chinese population. Input parameters, including utility values, are summarized in Table 1.

The annual transition probabilities between CD4 health states were derived from longitudinal studies and published literature that document HIV

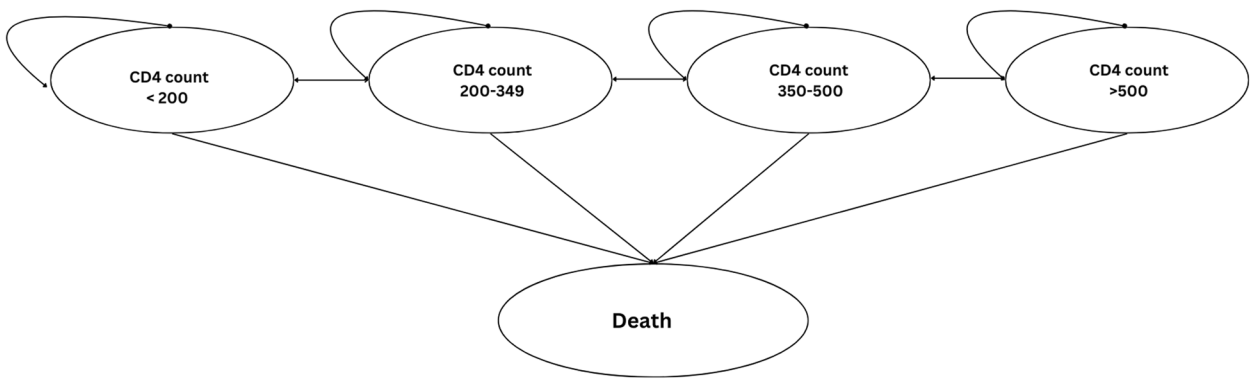

Fig. 1 HIV/AIDS Disease State Transition Model (This model visualizes the progression of HIV/AIDS in patients undergoing different antiviral treatment regimens. It shows transitions based on $CD4^+$ T lymphocyte counts with five health states: CD4 > 500, 350–500, 200–349, < 200, and death. Transitions are influenced by viral suppression success and treatment effectiveness over the model's 45-year simulation.)

Table 1 Model Input Parameters—Utility Values

Parameter	Utility	Distribution	Source
CD4 Count Range			
CD4 < 200	0.781 (0.603–0.863)	Beta	[18]
CD4 200–349	0.833 (0.719–0.933)	-	-
CD4 350–500	0.868 (0.784–0.970)	-	-
CD4 > 500	0.888 (0.798–0.970)	-	-
Opportunistic Infection	− 0.1956 (± 25%)	Beta	[19]
Adverse Events	− 0.012 (± 25%)	Beta	[18]

progression and the effects of antiretroviral therapy. These probabilities reflect the influence of HIV-RNA suppression (< 50 copies/mL) and CD4 count increases on immune recovery. Transition probabilities were adjusted to account for differences between CD4 states. For instance, patients transitioning from CD4 < 200 cells/μL to CD4 200–349 cells/μL were modeled with a higher probability of recovery than those transitioning from CD4 350–500 cells/μL to CD4 > 500 cells/μL. This ensures the model accurately reflects varying immune recovery potential. Viral suppression was shown to significantly improve the likelihood of CD4 recovery while reducing the risk of further declines. These probabilities were based on key studies, including Peng et al. (2015) [20] and Sax et al. (2023) [21].

CD4 count increase probabilities for B/F/TAF were derived from data used for EFV/3 TC/TDF and ABC/DTG/3TC [22], given its demonstrated non-inferiority in clinical trials. Adverse event (AE) incidence rates, including mild, moderate, and severe AEs, were sourced from clinical trial data and summarized in Table 2. For example, B/F/TAF demonstrated a drug-related AE rate of 21.9%, significantly lower than EFV/3TC/TDF's 89.2%. Mild AEs required minimal intervention, whereas severe AEs often necessitated hospital care. The lower AE rate for B/F/TAF highlights its better safety profile and suggests reduced costs associated with AE management compared to EFV/3TC/TDF.

The model assumes full treatment adherence due to the lack of specific adherence data for the target population. Preliminary interviews with physicians, nurses, and patients at a local infectious disease hospital revealed that most patients demonstrate high adherence levels, attributed to improved patient education, routine monitoring, and timely interventions. Quarterly health examinations consistently showed stable clinical parameters within normal ranges, supporting the assumption of 100% adherence, which aligns with the regional context and minimizes adherence-related variations in outcomes for the modeled population.

Table 2 Model Input Parameters—Probabilities

Parameter	Value	Distribution	Source
ART Start Age	33	-	-
Initial CD4 Distribution (%)			
CD4 < 200	36.8 (± 25%)	Beta	[22]
CD4 200–349	38.3 (± 25%)	-	-
CD4 350–500	16.1 (± 25%)	-	-
CD4 > 500	8.8 (± 25%)	-	-
HIV-RNA Suppression Rate (%)			
B/F/TAF	92 (± 25%)	Beta	[23–26]
EFV/3TC/TDF	86.8 (± 25%)	-	[27–29]
CD4 Count Increase Probability (%)			
B/F/TAF	66.00 (64.50–69.75)	Beta	[30]
EFV/3 TC/TDF	61.13 (44.25–63.00)	-	-
Opportunistic Infection Rate (%)			
CD4 < 200	28.6 (± 25%)	Beta	[31]
CD4 200–349	3.4 (± 25%)	-	-
CD4 350–500	2.5 (± 25%)	-	-
CD4 > 500	2 (± 25%)	-	-
Drug-Related Adverse Event Rate (%)			
B/F/TAF	21.9(± 25%)	Beta	[23, 24, 28, 32]
EFV/3TC/TDF	89.2 (± 25%)	-	-
HIV-Related Mortality Rate (%)			
CD4 < 200	16.9 (± 25%)	Beta	[33–35]
CD4 200–349	4.23 (± 25%)	-	-
CD4 350–500	1.52 (± 25%)	-	-
CD4 > 500	1.13 (± 25%)	-	-
Discount Rate (%)	5 (0–8)	Beta	[36]

Comprehensive cost analysis

Direct medical costs considered outpatient examination fees, hospitalization costs, and antiretroviral therapy (ART) drug costs. Outpatient examination fees and hospitalization costs were sourced from studies on the Chinese HIV patient population, while ART drug prices were obtained from literature and the Yaozhi Database (https://db.yaozh.com/) [20, 37]. From the patient perspective, the cost of EFV/3TC/TDF was considered zero as it is a nationally provided free drug. The annual cost of B/F/TAF was calculated by weighting the reimbursed price by medical insurance and the full out-of-pocket price according to the proportion of insured patients: Annual cost of B/F/TAF = (Reimbursed annual cost of B/F/TAF × 88.3%) + (Full out-of-pocket annual cost of B/F/TAF × 11.7%) (According to statistics, the insurance coverage rate in China was 88.3% in 2022).

From the health system perspective, the annual cost of EFV/3TC/TDF was derived from a Chinese study, while the annual cost of B/F/TAF was calculated from the single-box procurement price obtained through the Yaozhi

Database (https://db.yaozh.com/) (monthly dosage) multiplied by 12 months [37, 38].

Direct non-medical costs included transportation, caregiving, and nutrition expenses for patients and their families due to AIDS. Indirect costs referred to the loss of workdays for patients and their families caused by the disease, calculated using the human capital approach: Indirect cost = (Number of lost workdays due to AIDS × Daily wage loss).

The number of lost workdays was derived from literature, and the daily wage loss was calculated based on the 2022 per capita GDP: Daily wage loss = 2022 per capita GDP/365 [39].

Using the consumer price index (CPI) published by the National Bureau of Statistics from 2002–2022, all cost data from the literature were adjusted to 2023 currency values with an average inflation rate of 2.33%: 2023 currency value = X year's currency value/(1-0.0233)^(2023-X) [40].

Additionally, the costs related to drug-related adverse events, opportunistic infections, and HIV-related deaths were considered. The incidence rates of adverse events (AEs) for individuals receiving B/F/TAF were derived from clinical trials and observational studies [21, 41]. These rates included mild, moderate, and severe events. Mild AEs typically required over-the-counter medications, while severe AEs might necessitate hospitalization.

Discounting and willingness-to-pay threshold

The study adopted a 5% annual discount rate for costs and health outputs, as per the guidelines in the "Chinese Pharmacoeconomics Evaluation Guide" (2022). The base analysis used a 5% discount rate, with sensitivity analyses setting the range at 0–8%. The willingness-to-pay (WTP) threshold was set at 1.5 times the national per capita GDP, following suggestions to use 1–3 times the per capita GDP as the ICER threshold [42].

Statistical analysis

Using TreeAge Pro 2021, the cost-effectiveness of B/F/TAF was analyzed from both the patient perspective and the healthcare system perspective [43]. For the patient perspective, costs included direct medical expenses such as outpatient visits, hospitalizations, ART-related adverse event management, and end-of-life care. Additionally, direct non-medical costs, such as transportation and caregiving expenses, as well as indirect costs related to productivity losses from missed workdays, were included. From the healthcare system perspective, only direct medical costs were considered, encompassing outpatient visits, hospitalizations, ART-related adverse event management, and end-of-life care.

Health outcomes were measured in Quality-Adjusted Life Years (QALYs), with utility values sourced from published literature [18]. A 5% discount rate was applied to both costs and health outcomes, in accordance with international health economic evaluation standards. Sensitivity analyses were performed to assess parameter uncertainty and validate the robustness of the findings.

Sensitivity analysis

Both deterministic (DSA) and probabilistic sensitivity analyses (PSA) were conducted to test the robustness of the model results. One-way sensitivity analysis altered one key variable at a time to assess its impact on ICER, presented in tornado diagrams. Probabilistic sensitivity analysis used second-order Monte Carlo simulations (5000 iterations) to assess the impact of simultaneous changes in 38 parameters (including costs, utilities, probabilities, and discount rates) on ICER, comparing them with 0–3 times the per capita GDP to explore the economic probability of B/F/TAF vs EFV/3TC/TDF, presented in cost-effectiveness acceptability curves and incremental cost-utility scatter plots.

Validation

The model and its outcomes were validated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 guidelines [44]. The model structure, input parameters, and outcomes were assessed for face validity by the authors and external experts in clinical and health economic modeling. Cross-validation was conducted by comparing this model with other established models to ensure consistency. The model, built using TreeAge Pro 2021, underwent a quality-check process, including extreme-value and scenario testing, and validation of all equations, code, input data, and results. An independent review by an external expert further ensured the model's robustness. Sensitivity and scenario analyses evaluated the impact of parameter uncertainty and alternative assumptions. The CHEERS 2022 Checklist was completed to ensure comprehensive reporting. These validation steps confirmed the model's reliability and provided a solid foundation for the study's conclusions.

Results

Efficacy outcomes from network meta-analysis

This network meta-analysis included 17 randomized controlled trials (RCTs) evaluating 12 distinct antiretroviral therapy (ART) regimens, categorized into three major types: INSTI-based, NNRTI-based, and PI-based regimens. The INSTI-based regimens included dolutegravir (DTG), bictegravir (BIC), elvitegravir (EVG), and raltegravir (RAL). The NNRTI-based regimens included

EFV/3TC/TDF (efavirenz, lamivudine, tenofovir disoproxil fumarate), a commonly used first-line regimen for HIV/AIDS treatment. The PI-based regimen included LPV/r +3TC (lopinavir/ritonavir combined with lamivudine). The primary analysis compared INSTI-based regimens with non-INSTI-based regimens (NNRTI and PI-based regimens).

Of the 2682 records initially identified, 2575 remained after de-duplication, with 2025 excluded during title screening and 550 during abstract/full-text screening. Ultimately, 17 studies involving 12,620 patients were included. These studies evaluated 12 ART regimens, classified as INSTI-based (e.g., E/C/F/TAF, B/F/TAF), NNRTI-based (e.g., EFV/F/TDF, EFV/3TC/TDF), and PI-based (e.g., LPV/r +3TC), and demonstrated variability in design, sample sizes, and patient demographics, providing a diverse and comprehensive dataset.

Key characteristics of the included studies, such as sample size, baseline CD4 counts, and primary outcomes, are summarized in Supplemental Table 5. All studies were RCTs, with 15 registered internationally and 2 domestically. Among them, 13 were Phase 3 trials, 3 were Phase 2 trials, and one trial conducted in China (ChiCTR1900024611) did not specify its phase. This diverse collection strengthens the robustness of the analysis in evaluating ART regimens.

The Cochrane Collaboration's tool was used to assess study quality, focusing on the primary endpoint: achieving an HIV-RNA viral load of < 50 copies/mL at 48 weeks. All regimens demonstrated non-inferiority, with no statistically significant differences in viral suppression rates. Table 3 provides a summary of the odds ratios (ORs) for comparisons such as ABC/DTG/3 TC vs ANV/3TC/TDF, which had an OR of 1.1 (95% CI: 0.60, 2.16), and DTG/F/TAF vs EFV/3TC/TDF, with an OR of 0.8 (95% CI: 0.17, 3.68). Similarly, EFV/F/TDF vs LPV/r +3TC showed an OR of 0.8 (95% CI: 0.12, 6.15). These findings provide robust evidence supporting the clinical equivalence of the evaluated ART regimens in suppressing viral replication.

Table 3 Summary of Odds Ratios for Viral Suppression and Adverse Events

Category	Comparison	Odds Ratio (OR)	95% Confidence Interval (CI)
Viral Suppression (< 50 copies/mL at 48 weeks)	ABC/DTG/3TC vs ANV/3 TC/TDF	1.1	[0.60, 2.16]
	DTG/F/TAF vs EFV/3TC/TDF	0.8	[0.17, 3.68]
	EFV/F/TDF vs LPV/r + 3TC	0.8	[0.12, 6.15]
	DTG/F/TDF vs E/C/F/TAF	0.8	[0.30, 2.09]
Any Adverse Event Incidence	ABC/DTG/3TC vs B/F/TAF	2.53	[0.01, 463.54]
	DTG/F/TAF vs EFV/F/TDF	0.02	[0.00, 3.43]
	DTG/3TC vs DTG/F/TDF	0.91	[0.05, 16.61]
	B/F/TAF vs EFV/F/TDF	0.03	[0.00, 3.11]
	DTG/F/TDF vs EFV/F/TDF	0.01	[0.00, 4.66]
Severe Adverse Event Incidence	ABC/DTG/3TC vs B/F/TAF	2.14	[0.49, 13.27]
	DTG/F/TAF vs EFV/F/TDF	0.51	[0.06, 2.65]
	E/C/F/TDF vs EFV/3TC/TDF	1.75	[0.14, 27.64]
	DTG/F/TDF vs RAL/XTC/TDF	0.56	[0.07, 3.63]
	EFV/F/TDF vs RAL/XTC/TDF	0.82	[0.16, 4.00]
Drug-Related Adverse Event Incidence	ABC/DTG/3 TC vs ANV/3TC/TDF	1.30	[0.04, 48.00]
	DTG/F/TDF vs E/C/F/TDF	0.51	[0.01, 36.05]
	EFV/F/TDF vs RAL/XTC/TDF	1.87	[0.10, 34.46]
	ABC/DTG/3TC vs B/F/TAF	2.28	[0.06, 79.38]
	DTG/3TC vs DTG/F/TDF	0.50	[0.01, 18.83]

Description

Viral Suppression (< 50 copies/mL at 48 weeks): This compares the efficacy of ART regimens in achieving viral suppression at 48 weeks, supporting the conclusion of non-inferiority across regimens.

Any Adverse Event Incidence: This provides a comparison of the incidence of any adverse events across 12 ART regimens.

Severe Adverse Event Incidence: This compares the differences in the incidence of severe adverse events among ART regimens, showing no statistically significant differences between the regimens.

Supplemental Table 5: Characteristics of the 17 Studies Included in the Network Meta-Analysis

This table includes study names, sample sizes, baseline characteristics (e.g., age, CD4 count, viral load), interventions used (INSTI-based, NNRTI-based, PI-based), and the primary endpoints of interest (e.g., HIV RNA suppression rates at 48 weeks).

Safety outcomes from network meta-analysis

Table 3 summarizes the odds ratios (ORs) and 95% confidence intervals (CIs) for viral suppression rates and adverse event (AE) categories across 12 antiretroviral therapy (ART) regimens. The analysis highlights the consistent and comparable safety profiles of these regimens, with no statistically significant differences observed in any adverse event incidence, severe adverse event incidence, or drug-related adverse event incidence.

For overall adverse events, 10 ART regimens were analyzed, and no significant differences were found. For example, the OR for ABC/DTG/3TC vs B/F/TAF was 2.53 (95% CI: 0.01, 463.54), while DTG/F/TAF vs EFV/F/TDF had an OR of 0.02 (95% CI: 0.00, 3.43). Similarly, for severe adverse events, no significant differences were observed. For instance, ABC/DTG/3TC vs B/F/TAF had an OR of 2.14 (95% CI: 0.49, 13.27), while DTG/F/TAF vs EFV/F/TDF had an OR of 0.51 (95% CI: 0.06, 2.65). Drug-related AEs also showed no statistically significant differences, with ORs such as 1.30 (95% CI: 0.04, 48.00) for ABC/DTG/3TC vs ANV/3TC/TDF and 0.50 (95% CI: 0.01, 18.83) for DTG/3TC vs DTG/F/TDF.

Among the evaluated regimens, EFV/F/TDF showed the highest risk profile with an 88% probability of increased adverse events, requiring cautious use. In contrast, DTG/3TC demonstrated the best safety profile with a 39% probability of fewer adverse events, while EFV/3TC/TDF was less favorable. The uniformly low incidence of severe adverse events across all regimens reinforces their overall safety. These findings provide clinicians with valuable insights into regimen safety profiles, supporting personalized therapy and optimizing treatment outcomes.

Cost-effectiveness analysis

The cost parameters used in the model are detailed in Table 4. The base cost-utility analysis results for the representative integrase inhibitor B/F/TAF are shown in Table 5. From the patient's perspective, considering the direct medical costs, direct non-medical costs, and indirect costs of both regimens, the cohort analysis results indicate that B/F/TAF increases health benefits while also increasing costs. The treatment cost for B/F/TAF is \$29,598.36, with a health output of 7.23 QALYs. The national standard first-line antiretroviral therapy EFV/3TC/TDF has a cost of \$24,046.35 and a health output of 6.79 QALYs. The incremental cost of B/F/TAF is \$5,552.01, with an incremental effect of 0.44 QALYs. The incremental cost-effectiveness ratio (ICER) of B/F/TAF versus EFV/3TC/TDF is \$12,714.29/QALY. Using 1.5 times the per capita GDP of China in 2022 as the willingness-to-pay (WTP) threshold (\$17,790.0), the increased cost for health gains with B/F/TAF is considered worthwhile, indicating economic viability.

From the health system perspective, considering only the direct medical costs of both regimens, the cohort analysis results show that the treatment cost for B/F/TAF is \$31,987.18, with a health output of 7.23 QALYs. The cost of the national standard antiretroviral therapy EFV/3TC/TDF is \$21,920.62, with a health output of 6.79 QALYs. The incremental cost of B/F/TAF is \$10,066.56, with an incremental effect of 0.44 QALYs. The ICER of B/F/TAF versus EFV/3TC/TDF is \$23,052.77/QALY. Using 1.5 times the per capita GDP of China in 2022 as the WTP threshold (\$17,790.0), B/F/TAF does not demonstrate economic viability.

Uncertainty analysis

The one-way sensitivity analysis highlighted the significant influence of the probability of increased CD4 count following EFV/3 TC/TDF treatment on the incremental cost-effectiveness ratio (ICER) from the patient's perspective. Variations in this probability greatly impact cost-effectiveness, emphasizing its critical importance in guiding treatment decisions. Additionally, the cost of B/F/TAF and the utility values assigned to CD4 counts over 500 were identified as key determinants. As the cost of B/F/TAF rises, its economic attractiveness diminishes, underscoring the necessity for careful pricing strategies. From the healthcare system perspective, the drug cost of B/F/TAF was a critical factor affecting its ICER. Other influential factors include the probability of increased CD4 count after EFV/3TC/TDF treatment, the discount rate, and utility values for CD4 > 500 (refer to Fig. 2a and 2b).

The probabilistic sensitivity analysis, utilizing 5,000 Monte Carlo simulations, demonstrated that the probability of cost-effectiveness for B/F/TAF increases with the WTP threshold. From the patient's perspective, at 1.5 times the per capita GDP (\$17,790), B/F/TAF has a 55.0% likelihood of being cost-effective, compared to EFV/3TC/TDF's 45.0%. When the WTP threshold doubles to three times the per capita GDP (\$35,580), B/F/TAF's economic viability improves to 65.8% (see Fig. 3). From the healthcare system perspective, B/F/TAF shows a 38.0% probability of being cost-effective at 1.5

Table 4 Model Input Parameters – Costs (USD/person-year)

Item	Value	Distribution	Source
Direct Medical Costs			
Outpatient Fees			
- CD4 < 200	$142.94 (± 25%)	Gamma	[25]
- CD4 ≥ 200	$177.73 (± 25%)	Gamma	
Hospitalization Fees			
- CD4 < 200	$921.78 (± 25%)	Gamma	[45]
- CD4 200–349	$1403.13 (± 25%)	Gamma	
- CD4 350–500	$1117.11 (± 25%)	Gamma	
- CD4 > 500	$916.96 (± 25%)	Gamma	
Antiretroviral Drug Costs			
- Patient Perspective			
- B/F/TAF	$671.72 (± 25%)	Gamma	[46]
- EFV/3 TC/TDF	$0 (± 25%)	Gamma	
- Health System Perspective			
- B/F/TAF	$1514.45 (± 25%)	Gamma	[46]
- EFV/3 TC/TDF	$326.10 (± 25%)	Gamma	
Opportunistic Infection Prevention Costs	$45.21 (± 25%)	Gamma	[47]
Antiretroviral Treatment-related ADE	$94.78 (± 25%)	Gamma	
Costs Incurred by Death	$668.75 (± 25%)	Gamma	[48]
Direct Non-medical Costs			
Transportation Fees			
- CD4 < 200	$117.27 (± 25%)	Gamma	[45]
- CD4 200–349	$139.37 (± 25%)	Gamma	
- CD4 350–500	$164.22 (± 25%)	Gamma	
- CD4 > 500	$186.72 (± 25%)	Gamma	
Caregiving Fees			
- CD4 < 200	$272.10 (± 25%)	Gamma	[45]
- CD4 200–349	$246.38 (± 25%)	Gamma	
- CD4 350–500	$53.80 (± 25%)	Gamma	
- CD4 > 500	$73.60 (± 25%)	Gamma	
Nutrition Fees			
- CD4 < 200	$146.06 (± 25%)	Gamma	[45]
- CD4 200–349	$133.14 (± 25%)	Gamma	
- CD4 350–500	$97.32 (± 25%)	Gamma	
- CD4 > 500	$89.05 (± 25%)	Gamma	
Indirect Costs			
Loss of Work Costs			
- CD4 < 200	$157.14 (± 25%)	Gamma	[30]
- CD4 200–349	$131.01(± 25%)	Gamma	
- CD4 350–500	$104.86(± 25%)	Gamma	
- CD4 > 500	$91.64 (± 25%)	Gamma	

times the per capita GDP, but this increases to 55.6% at three times the per capita GDP (refer to Fig. 4). This analysis underscores the importance of balancing both individual and systemic perspectives in evaluating the economic impact of antiretroviral treatments.

Discussion

Implications for treatment guidelines and clinical practice

The findings of this study provide valuable insights into the use of INSTI-based antiretroviral regimens for first-line treatment of HIV/AIDS in China. The network meta-analysis revealed that while INSTI regimens do

Table 5 Economic Feasibility Analysis Results for Biktarvy Strategy

Item	Cost (USD)	Incremental Cost (USD)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER (IC/IE)
Patient Perspective					
EFV/3 TC/TDF	$24,046.35	-	6.79	-	-
B/F/TAF	$29,598.36	$5,552.01	7.23	0.44	$12,714.29
Health System Perspective					
EFV/3 TC/TDF	$21,920.62	-	6.79	-	-
B/F/TAF	$31,987.18	$10,066.56	7.23	0.44	$23,052.77

not significantly surpass the standard EFV/3TC/TDF in terms of efficacy and safety, they offer substantial benefits in drug resistance, adherence, and quality of life. The findings show that all evaluated ART regimens are effective in achieving viral suppression with comparable safety profiles, including severe and drug-related adverse events. The consistent odds ratios across regimens support clinical flexibility, allowing clinicians to tailor treatments to patient-specific needs, such as tolerability and comorbidities, without compromising efficacy or safety. This suggests that integrating INSTI-based regimens into clinical practice could enhance patient outcomes, particularly in terms of long-term treatment adherence and resistance management [49]. Given the increasing prevalence of HIV/AIDS and the financial burden it imposes, these findings highlight the potential for INSTI-based regimens to play a crucial role in optimizing HIV/AIDS management strategies in China [13]. Furthermore, the enhanced adherence associated with single-tablet regimens simplifies treatment protocols, which can lead to improved patient compliance and reduced risk of resistance development. Healthcare providers should consider these factors when designing treatment plans, ensuring that they are tailored to the needs of the patient population.

Economic viability and policy implications

From an economic standpoint, the cost-effectiveness analysis demonstrated that B/F/TAF is a viable option from the patient's perspective, with an ICER of $12,714.29 per QALY, which is below the willingness-to-pay threshold of 1.5 times the GDP per capita ($17,790). This indicates that B/F/TAF provides a cost-effective balance between health benefits and additional costs for individual patients. However, the analysis from the healthcare system perspective paints a different picture, with an ICER of $23,052.77 per QALY, exceeding the willingness-to-pay threshold. Since B/F/TAF was added to the national reimbursement drug list in December 2022, this discrepancy underscores the need for policy adjustments and ongoing price negotiations to make B/F/TAF economically viable from a broader healthcare perspective [50].

Policymakers should consider these findings when updating treatment guidelines and continuing to negotiate drug prices to ensure that the benefits of advanced treatment regimens are accessible to a larger patient population. Moreover, cost-effectiveness from the system's viewpoint could be improved through strategic interventions, such as further price reductions and continued inclusion of such regimens in national health insurance programs [51].

Clinical relevance of drug resistance and adherence

INSTI-based regimens exhibit a superior resistance barrier compared to EFV/3TC/TDF, as evidenced in this study. Safety analyses revealed EFV/F/TDF as the regimen with the highest adverse event risk, contrasting with DTG/3TC's optimal safety profile. Pretrial interviews with healthcare providers and patients highlighted strong ART adherence linked to comprehensive patient education, reinforced by quarterly health assessments confirming stable clinical parameters in most cases. These findings validate the real-world feasibility of INSTI-based regimens, where sustained adherence and routine monitoring are pivotal to mitigating lifelong resistance risks and preserving future treatment options [52]. INSTI-based single-tablet regimens further enhance adherence, a critical factor for sustained viral suppression and resistance prevention [53]. Emerging dual therapies, particularly DTG-based regimens, demonstrate potential in modulating inflammatory responses among PLWH. Viroimmunological data indicate reduced IL- 18 and IL- 36 levels in patients receiving DTG-based 2DR, suggesting long-term cardiovascular risk attenuation, though further validation is required [54]. INSTI-based therapies may improve long-term outcomes by minimizing pill burden and adverse effects, thereby enhancing quality of life and treatment durability [55]. Their integration into clinical practice could simplify management protocols and reduce resistance-driven regimen adjustments [56].

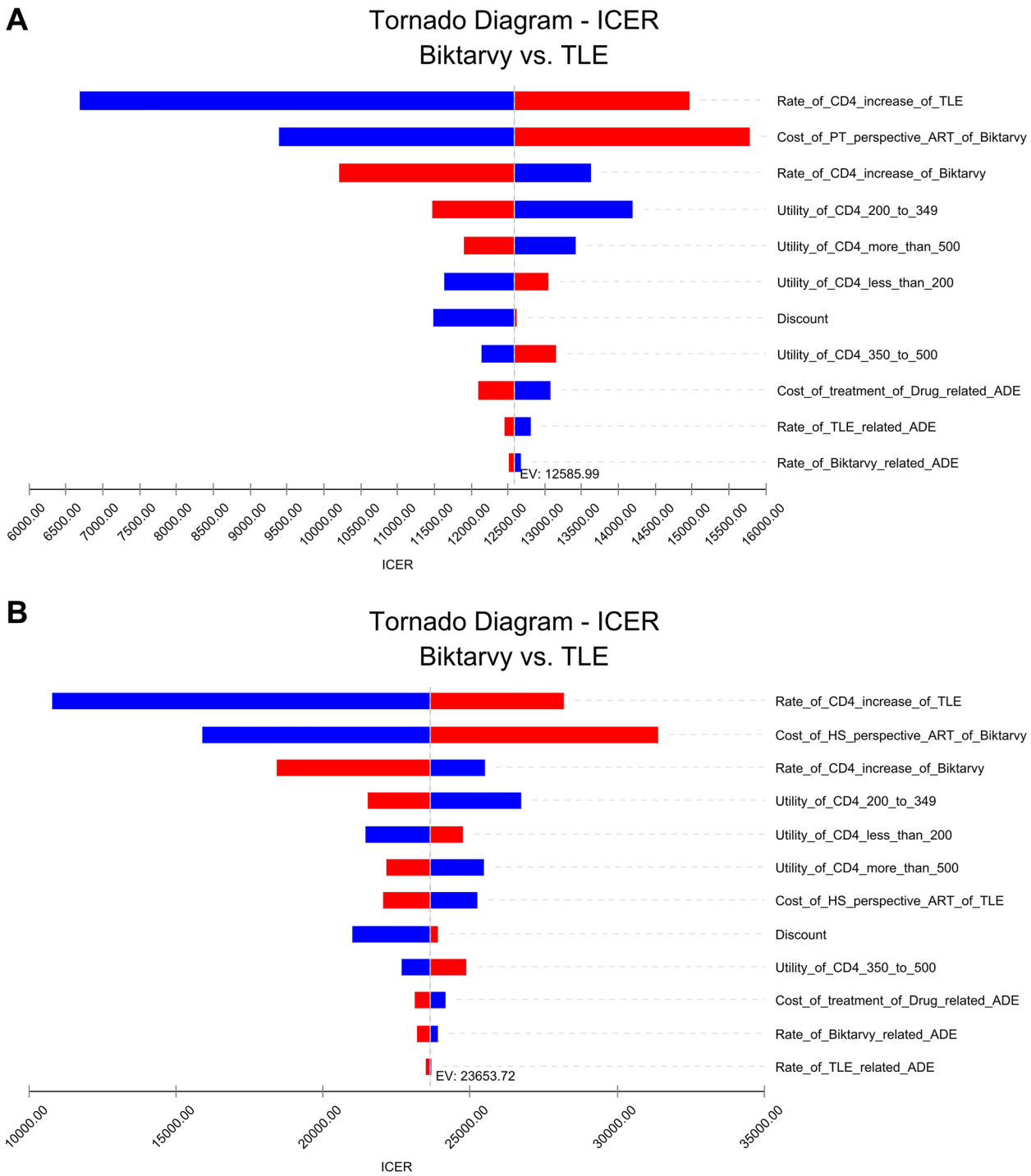

Fig. 2 Patient (A) and Healthcare System (B) Perspective B/F/TAF vs EFV/3TC/TDF Tornado Diagram—ICER

Integrating clinical and economic perspectives

The integration of clinical and economic perspectives is essential for the comprehensive evaluation of antiretroviral regimens. This study highlights the necessity of considering both efficacy and cost-effectiveness in treatment decision-making. From a clinical perspective, the added benefits of drug resistance and adherence offered by INSTI-based regimens make them attractive options [57]. However, the economic analysis indicates a need for strategic pricing and policy adjustments to ensure

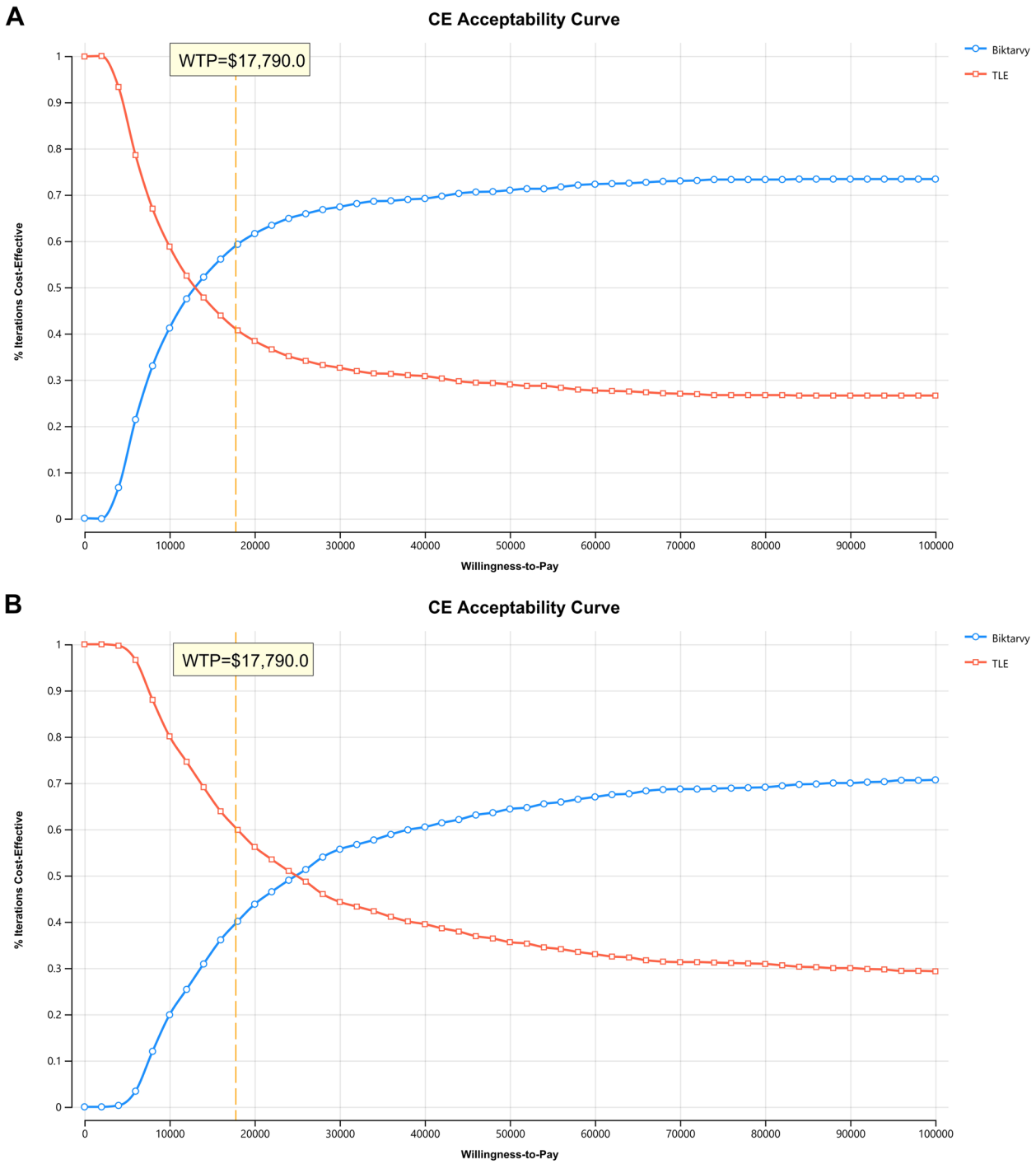

Fig. 3 Cost-Effectiveness Acceptability Curve from the Patient (A) and Healthcare System (B) Perspective

these treatments are accessible and sustainable within the healthcare system [58]. Balancing these factors is crucial for developing guidelines that optimize patient outcomes while maintaining economic viability. Such a holistic approach ensures that patients receive the most effective treatment without placing undue financial strain on the healthcare system. This balance is particularly pertinent in resource-limited settings where cost considerations are paramount. Future policy decisions should aim to harmonize these clinical and economic factors to create a sustainable and effective HIV/AIDS treatment framework.

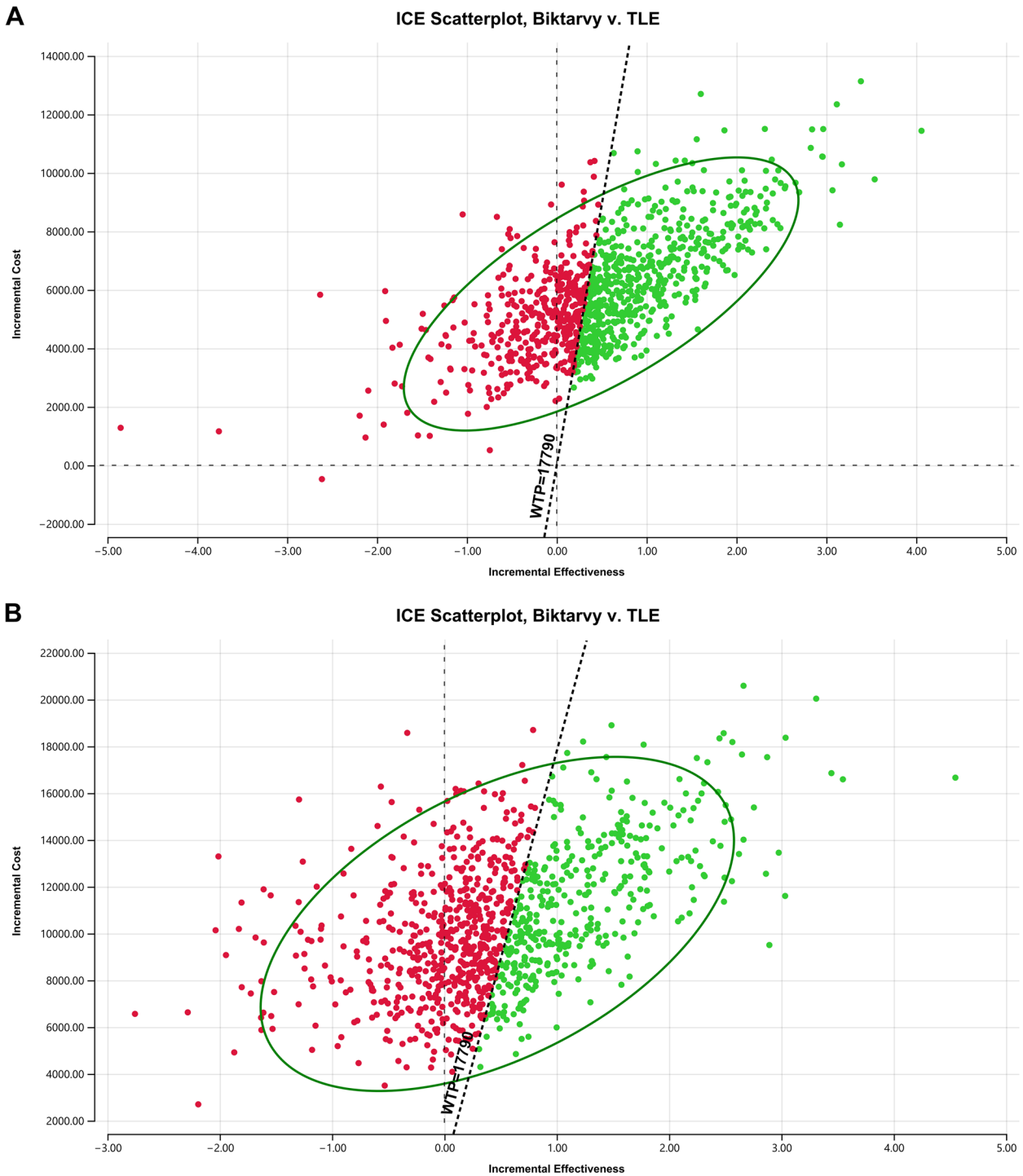

Fig. 4 Incremental Cost-Effectiveness Scatter Plot from the Patient (A) and Healthcare System (B) Perspective

Implications for global HIV/AIDS treatment strategies

While this study focuses on China, its implications extend to global HIV/AIDS treatment strategies. The benefits of INSTI-based regimens in terms of adherence and resistance are relevant in diverse healthcare settings, especially in regions with similar economic constraints [59]. The findings advocate for a tailored approach to HIV treatment, considering local economic conditions and healthcare infrastructures [60]. This global perspective is critical as countries strive

to meet international HIV/AIDS treatment goals and improve the quality of life for people living with HIV/AIDS worldwide [61]. Additionally, international collaborations and knowledge exchange can facilitate the adaptation of these findings to different contexts, promoting best practices and innovative solutions in HIV/AIDS treatment [62]. By considering both the clinical and economic aspects, healthcare providers and policymakers worldwide can better address the challenges of HIV/AIDS, ensuring that patients receive effective and sustainable care [63].

Study limitations and future research

This study has several limitations that should be considered when interpreting the findings. A key limitation is the assumption of 100% treatment adherence due to the lack of specific adherence data. In real-world settings, adherence rates vary due to factors such as socioeconomic status, healthcare access, and comorbidities, potentially resulting in virologic failure, slower CD4 recovery, increased healthcare utilization, and worse health outcomes. Excluding these variations may underestimate costs and overestimate effectiveness.

The network meta-analysis relied on data from randomized controlled trials (RCTs) with varying designs, patient populations, and protocols, potentially introducing biases and limiting generalizability. Additionally, variations in adverse event (AE) definitions and reporting across studies may affect the interpretation of safety profiles. The cost-effectiveness analysis was based on assumptions regarding drug prices and healthcare utilization that may not fully capture real-world complexities. Furthermore, the study's focus on the Chinese healthcare system limits the applicability of findings to other regions.

Future research should integrate real-world data on treatment adherence, drug resistance, and quality of life to enhance the accuracy and relevance of cost-effectiveness analyses. Consistent AE definitions and longitudinal studies involving diverse patient cohorts are essential for validating safety and efficacy trends. Investigations into advanced therapies and broader treatment strategies could further strengthen HIV/AIDS management and ensure the findings are widely applicable.

Conclusion

This study underscores the potential benefits of INSTI-based antiretroviral regimens for first-line HIV/AIDS treatment in China. While these regimens do not significantly outperform the standard EFV/3TC/TDF in terms of efficacy and safety, they offer important advantages in drug resistance, adherence, and patient quality of life—critical factors for long-term treatment success. Economically, B/F/TAF is viable from a patient perspective, with an ICER below the willingness-to-pay threshold, but it exceeds this threshold from the healthcare system perspective, highlighting the need for strategic pricing and policy adjustments. Integrating INSTI-based regimens into clinical practice could enhance patient outcomes and optimize HIV/AIDS management in China. Future research should validate these findings with larger, more diverse cohorts and explore additional treatment options to further refine HIV/AIDS management strategies, ensuring a balance between clinical benefits and economic feasibility.

Abbreviations

INSTIs	Integrase Strand Transfer Inhibitors
EFV	Efavirenz
3 TC	Lamivudine
TDF	Tenofovir Disoproxil Fumarate
B/F/TAF	Bictegravir/Emtricitabine/Tenofovir Alafenamide
QALYs	Quality-Adjusted Life Years
ICERs	Incremental Cost-Utility Ratios
GDP	Gross Domestic Product
ART	Antiretroviral Therapy
AIDS	Acquired Immune Deficiency Syndrome
HIV	Human Immunodeficiency Virus
RCTs	Randomized Controlled Trials
NRTIs	Nucleotide Reverse Transcriptase Inhibitors
NNRTIs	Non-Nucleotide Reverse Transcriptase Inhibitors
PIs	Protease Inhibitors
FIs	Fusion Inhibitors
STRs	Single-Tablet Regimens
PSA	Probabilistic Sensitivity Analysis
ICER	Incremental Cost-Effectiveness Ratio
ADE	Adverse Drug Event

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

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Clinical Trial Number

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Authors' contributions

Jian Yang (JY): Conceptualization, Writing-Original Draft Preparation, Project Administration; Xuejuan Zhao (XZ): Data Curation, Data Analysis; Fan Li (FL): Supervision, Funding Acquisition, Final Approval of the Version to Be Published. Jian Yang (JY) and Xuejuan Zhao (XZ) contributed equally to this work and are considered co-first authors. All authors have read and agreed to the published version of the manuscript.

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Data availability
Data used in this analysis were taken from published or publicly available sources. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study used previously published data and did not involve direct research with human participants or animals, thus ethical approval was not required according to institutional and national guidelines. All procedures followed the ethical standards of the responsible human experimentation committee and the Helsinki Declaration of 1975, revised in 2013. Any secondary data used was anonymized and accessed in compliance with data protection and privacy laws.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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