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Global research landscape of two-drug regimens for HIV treatment: a visual bibliometric analysis

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Abstract

With the advancement of antiretroviral therapy, two-drug regimens have emerged as a viable and promising strategy for human immunodeficiency virus (HIV) care and management, offering potential advantages in safety, treatment adherence, and cost-effectiveness. Although scholarly interest in this field is growing, a comprehensive bibliometric analysis remains lacking; accordingly, this study aimed to map the research landscape, identify emerging trends, and explore collaborative networks in the field of two-drug HIV treatment regimens. To this end, studies on two-drug HIV treatment regimens were retrieved from the Web of Science Core Collection. After screening and deduplication, key bibliometric data were extracted. Subsequent analyses were performed using the Bibliometrix R-package and VOSviewer to visualize annual publication output, geographical distribution, institutional collaborations, journal influence, author networks, and keyword evolution trends. Ultimately, 3,262 publications were included, with an annual growth rate of 9.23%. The United States was the most productive country (974 publications, 29.9%), while Harvard University topped institutional rankings (430 publications). AIDS was the leading journal (199 publications), and core authors (e.g., Carr A) contributed substantially. Keyword analysis revealed that two-drug regimens are transitioning from "alternative options" to "mainstream choices" in HIV treatment, with their development reflecting a focus on balancing efficacy and safety, as well as aligning technological innovation with clinical demands. This bibliometric study delineates the evolving landscape of two-drug HIV treatment research, with North America and Europe making prominent contributions. It highlights key research foci and collaboration patterns, providing valuable insights for researchers, clinicians, and policymakers to prioritize future research and optimize HIV treatment strategies.

Keywords: *Bibliometric analysis. Two-drug regimens. Antiretroviral therapy. Research trends.*

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Introduction

The global management of HIV has evolved dramatically since the advent of antiretroviral therapy (ART), transforming HIV from a fatal illness to a manageable chronic condition[1,2]. Traditional three-drug ART regimens have been the cornerstone of treatment, achieving sustained viral suppression and reducing mortality[3]. However, concerns regarding long-term toxicity, pill burden, and drug resistance have spurred interest in simplified regimens, including two-drug combinations[4]. Two-drug regimens offer potential advantages such as reduced adverse effects, improved adherence, and lower costs, making them increasingly relevant in resource-limited settings and long-term maintenance therapy[5,6].

As research on two-drug regimens expands, a systematic understanding of publication patterns, collaborative networks, and emerging trends is critical to guide future research priorities. Bibliometric analysis provides a quantitative framework to map the intellectual structure of a field, identifying key contributors, influential works, and knowledge gaps[7,8]. While individual studies have explored specific two-drug regimens, no comprehensive bibliometric study has synthesized the global research landscape of this domain.

The objective of this research is to carry out a bibliometric mapping of publications focusing on two-drug HIV treatment regimens. By analyzing publication trends, geographic and institutional contributions, author collaborations, and keyword dynamics, we seek to characterize the evolution of this field and highlight emerging hotspots, ultimately informing researchers, clinicians, and policymakers in optimizing HIV treatment strategies.

Methods

Search strategy

In July 2025, an electronic literature search was performed via the Web of Science Core Collection (WoSCC) rature search was performed via the WoSCC ght emerging hotspots, ultimately informing[9,10]. WoSCC was chosen as the data source given its status as a high-quality academic literature repository, which researchers broadly recognize as the best option for bibliometric analyses. To guarantee comprehensive and precise search outcomes, the Science Citation Index Expanded was employed.

The retrieval approach integrated terms associated with HIV and those related to two-drug regimens, specifically using the following combination (topic terms including HIV, acquired immunodeficiency syndrome [AIDS], HIV) AND (topic terms including two-drug ART, two-drug regimens, two-drug antiretroviral regimens, dual ART, dual therapy).

Document types were confined to Articles and Reviews, with language restricted to English.

Data extraction

Full records and cited references of the included publications were exported in tab-delimited text format. Extracted bibliometric parameters encompassed titles, abstracts, keywords, authors, affiliations, countries/regions, publication year, journal names, and references. All data underwent double-verification to ensure accuracy; any inconsistencies were resolved by re-examining the original articles[11]. In addition, data generated through WoSCC's "analyze results" function were collected.

Keywords were consolidated using multiple criteria: semantic equivalence, morphological variations, abbreviations and their full forms, domain-specific terminological standards, and contextual links (where terms frequently co-occur and are closely related). These criteria were adopted to ensure that terms representing the same core concept were merged, thereby improving the replicability and clarity of the analysis.

Data analysis

For bibliometric assessments and the development of scientific knowledge maps, this study employed the Bibliometrix package within R software (version 4.4.3) and VOSviewer (version 1.6.20)[12,13]. The Bibliometrix R package focused on analyzing annual output, country-specific production, longitudinal author contributions, source-specific local impacts measured through the H index, and emerging research themes[14,15]. VOSviewer, a robust bibliometric tool, was utilized to generate knowledge maps from web-based data, as well as to visualize and explore such maps[16]. Owing to its user-friendly and precise performance in clustering analyses, VOSviewer was leveraged in this study to conduct cluster-based evaluations of countries, institutions, journals, authors, citations, and keywords[17].

Both tools examine co-occurrence patterns (e.g., concurrent keyword usage in publications) to map relational connections and identify inherent clusters of closely associated elements. While VOSviewer directly visualizes these networks and clusters from co-occurrence data – utilizing distance metrics and color coding – Bibliometrix computes the underlying matrices, provides statistical clustering techniques, and identifies trends through features such as temporal thematic evolution diagrams.

Results

Literature acquisition and time-related trends

Bibliometric landscape overview: a total of 3,262 documents (Fig. 1) were identified through searches on the Web of Science platform. Most of these retrieved publications were issued between 1992 and 2025, though a small number of earlier journal articles were also included. For subsequent analyses, a timeline-driven method was adopted, with the study period set as 1992 Science platform. Most of these retrieved publications were issued between 1992 and 2025, though a small number of earlier journal articles were also included. The retrieval outcomes encompassed 947 journals, with the annual growth rate of published articles reaching 9.23%. Each document was cited an average of 32.87 times, and the total number of contributing authors stood at 19,160 (Supplementary Table 1).

Publication dynamics: figure 2 illustrates the annual scientific output (measured by the number of articles) from 1992 to 2025. In the early phase (1992-1998), output remained low and grew slowly. From the late 1990s onward, it gradually showed an upward trend with minor fluctuations. Around 2010, growth began to accelerate sharply, leading to a series of peaks. A prominent peak emerged around 2018; thereafter, output has fluctuated at a relatively high level, with a trend of renewed growth in the past 2 years.

Geographical and institutional output

National productivity and collaboration: the national publication output analysis showed that 77 countries/regions contributed to the field. The country-wise distribution of publications is presented in table 1. The United States (n = 974) was the most prolific nation, accounting for 29.9% of all publications, followed by China (n = 280, 8.6%), Italy (n = 272, 8.3%), United Kingdom (n = 209, 6.4%), Spain (n = 205, 6.3%), and France (n = 153, 4.7%). To present the international collaborative network, we utilized the co-authorship-country module in VOSviewer. A total of 55 prolific countries/regions (with at least 10 publications) formed a cooperative network. Among these, the United States, the United Kingdom, France, Spain, and Italy emerged as large nodes with relatively thick links. The United States had the highest total link strength (TLS = 1,015) in cooperation and collaborated with 53 prolific countries. Among them, South Africa (TLS = 378) and the United Kingdom (TLS = 779) showed close academic cooperation with the United States (Supplementary Figs. 1 and 2).

Institutional leadership: among the top ten institutions with the highest number of publications (Table 2), Harvard University (USA) leads with 430 contributions, closely followed by Assistance Publique – Hôpitaux de Paris (France) with 426 publications and Université Paris Cité (France) with 305 publications.

Scholarly ecosystem: periodicals and researchers

Journal influence: a total of 3,262 articles from 947 journals were included in this study. The top 10 journals by publication volume, along with their 5-year impact factors (IF), are presented in table 3[18]. These journals comprise AIDS (n = 199, IF = 3.3), PLOS ONE (n = 121, IF = 3.2), *Journal of AIDS* (n = 110, IF = 2.8), *Journal of Antimicrobial Chemotherapy* (n = 97, IF = 4.1), and *Clinical Infectious Diseases* (n = 86, IF = 7.2). To assess the influence of these journals, the Bibliometrix R package was utilized, with measurements based on the H-index. *The Journal of AIDS* had the highest H-index[19]. For co-citation analysis, VOSviewer was used to analyze source titles, including journals with at least 200 citations. Ninety-seven journals were identified based on TLS. The top five journals with the highest TLS were *The Journal of AIDS* (251,977), *Journal of Virology* (135,916), *Clinical Infectious Diseases* (121,921), *Journal of Infectious Diseases* (118,795), and *The New England Journal of Medicine* (118,379) (Supplementary Fig. 3).

Key authors and collaborative networks: across the globe, 19,160 authors have contributed to publications in this field. In this analysis, the top 15 authors – ranked by their publication counts – were designated as key authors (Supplementary Table 2). While Di Giambenedetto S led in terms of publication quantity, Carr A achieved the highest total citations, h-index, and g-index. Authors with over 100 co-citations are highlighted, with

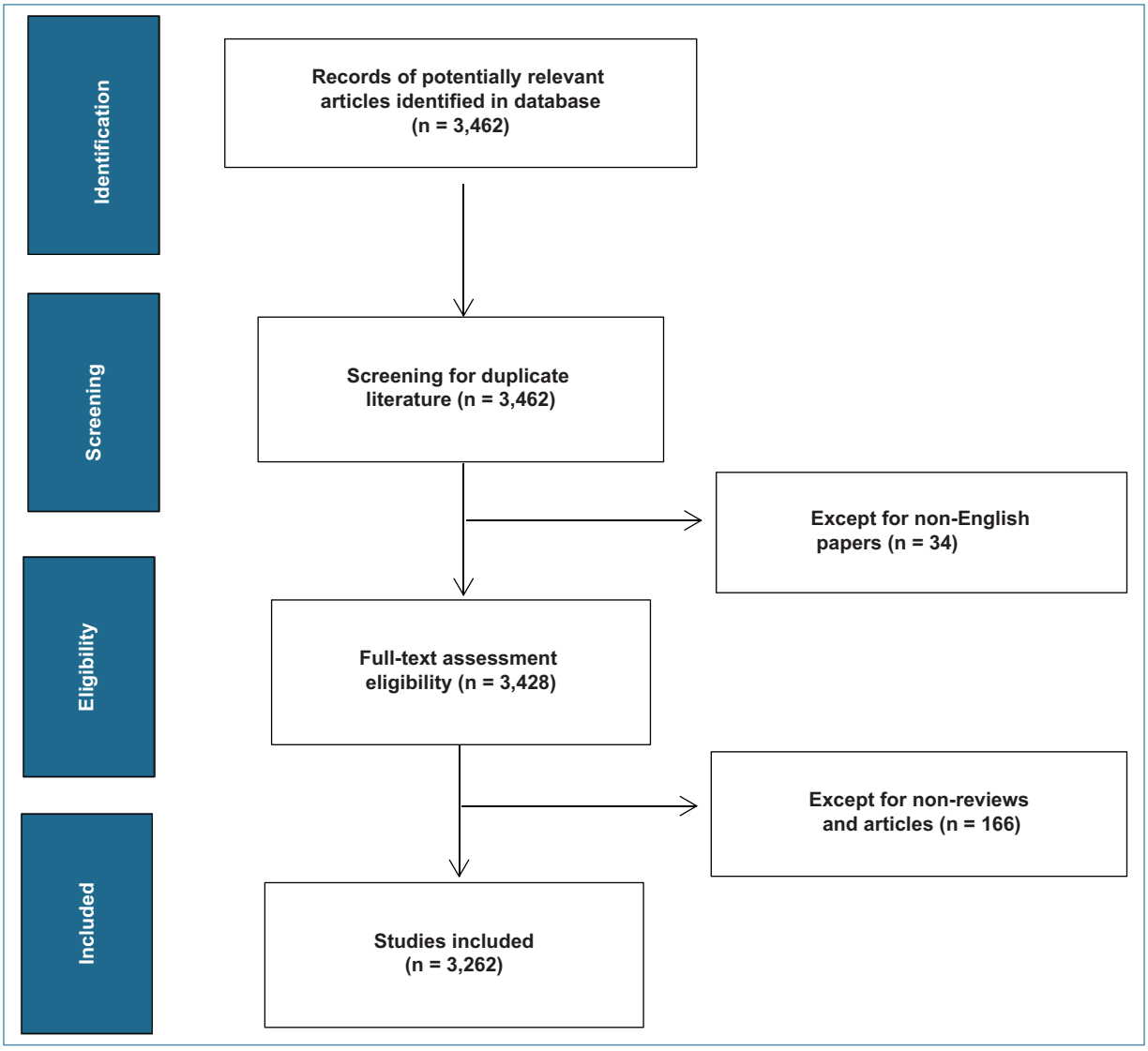

Figure 1. Flow diagram for the screening procedure.

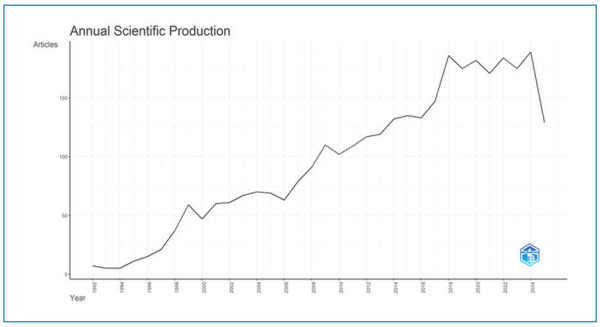

Figure 2. Distribution of yearly article outputs from 1992 to 2025.

the top three being Carr A (551 co-citations), Cahn P (371 co-citations), and Brown TT (367 co-citations) (Supplementary Fig. 4).

Keywords and research frontiers

Keyword standardization: a thesaurus was employed to enable more precise counting of keyword occurrence frequencies (Supplementary Table 3).

Clusters of keyword co-occurrence: A total of 6,990 author-assigned keywords were analyzed. The top 10 keywords were HIV (n = 1,735), active ART (n = 1,345), prevalence (n = 206), AIDS (n = 204), adults (n = 186), efficacy (n = 176), protease inhibitors (PIs) (n = 170), resistance (n = 170), open-label (n = 167), and risk (n = 163). Three colors represent distinct keyword clusters: the red cluster centers on HIV, including terms such as active ART, AIDS, and resistance; the green cluster centers on prevalence, including osteoporosis, lipodystrophy, and risk; and

Table 1. The 15 most productive nations in research on HIV two-drug regimens

Rank	Country	Articles	Articles (%)	SCP	MCP	MCP (%)
1	USA	974	29.9	740	234	24
2	China	280	8.6	237	43	15.4
3	Italy	272	8.3	208	64	23.5
4	United Kingdom	209	6.4	101	108	51.7
5	Spain	205	6.3	165	40	19.5
6	France	153	4.7	112	41	26.8
7	Australia	106	3.2	68	38	35.8
8	South Africa	95	2.9	47	48	50.5
9	Canada	90	2.8	58	32	35.6
10	The Netherlands	81	2.5	43	38	46.9
11	India	80	2.5	66	14	17.5
12	Brazil	71	2.2	55	16	22.5
13	Germany	65	2	35	30	46.2
14	Switzerland	58	1.8	26	32	55.2
15	Denmark	35	1.1	24	11	31.4

SCP: single country publications; MCP: multiple country publications.

Table 2. The top 10 institutions with the highest productivity

Rank	Title of the institution	Literature	Nation
1	Harvard University	430	USA
2	Assistance Publique – Hôpitaux de Paris	426	France
3	Université Paris Cité	305	France
4	University of London	294	UK
5	Institut National de la Santé et de la Recherche Médicale	291	France
6	University of California System	281	USA
7	Harvard University Medical Affiliates	221	USA
8	Sorbonne Université	212	France
9	Johns Hopkins University	168	USA
10	University College London	165	UK

the blue cluster centers on efficacy, including dual therapy, dolutegravir, and lamivudine (Supplementary Fig. 5).

Emerging research frontiers: in terms of research trends, key themes within this field that have emerged include quantum dots, growth factor beta, gene transfer, challenges, stress, regulatory T-cells, phase 3, photodynamic therapy, molecular mechanisms, nanoparticles, multicenter studies, rilpivirine (RPV), and drug delivery, among others.

Discussion

General information

This bibliometric analysis offers a thorough synthesis of research into HIV two-drug regimens, emphasizing the field's developmental path, primary contributors, and shifting areas of focus. The 9.23% annual growth rate reflects increasing recognition of two-drug regimens as a viable alternative to traditional ART, driven by their potential to address long-term treatment challenges[20,21]. The post-2010 acceleration aligns with clinical trials demonstrating the efficacy of dual therapy (e.g., dolutegravir [DTG]/lamivudine)[22], underscoring how clinical evidence fuels research momentum.

Geographically, the United States' dominance (29.9% of publications) is consistent with its historical

Table 3. The top 10 journals with the highest publication output

Ranking	Periodical	Publication counts	Proportion (%)	Impact Factor	Citation counts	Quartile ranking
1	*AIDS*	199	6.10	3.3	13,614	Q2
2	*PLos One*	121	3.71	3.2	2,816	Q2
3	*Journal of Acquired Immune Deficiency Syndromes*	110	3.37	2.8	3,015	Q3
4	*Journal of Antimicrobial Chemotherapy*	97	2.97	4.1	1,658	Q2
5	*Clinical Infectious Diseases*	86	2.64	7.2	5,097	Q1
6	*Aids Research and Human Retroviruses*	84	2.58	1.3	1,169	Q4
7	*HIV Medicine*	80	2.45	2.9	1,766	Q2
8	*Antiviral Therapy*	61	1.87	1.7	1,349	Q3
9	*Journal of Infectious Diseases*	47	1.44	4.5	2,520	Q1
10	*Antimicrobial Agents and Chemotherapy*	45	1.38	4.4	3,320	Q1

leadership in HIV research, supported by robust funding and established academic networks[23]. Strong international collaborations (30.47% of publications) highlight global efforts to address HIV, with notable ties between the United States and South Africa – a region heavily burdened by HIV – reflecting the importance of context-specific research[24]. China's emergence as the second-most prolific country (8.6%) may stem from its growing investment in global health and localized research on affordable regimens[25,26].

The institutional leadership of Harvard University and French research institutions highlights the pivotal role of academic medical centers in advancing clinical research. Coupled with Harvard's standing as a world-renowned academic medical center, the outstanding contributions of French institutions – most notably its extensive public hospital network – underscore how the synergy between academic excellence and integrated healthcare delivery systems shapes the global research agenda for two-drug HIV treatment regimens, thereby providing robust support for translating research findings into clinical practice[27].

Journals such as AIDS and PLOS ONE are pivotal in disseminating two-drug regimen research, though the presence of Q2/Q3 journals (Table 3) suggests opportunities to enhance the fieldst support for trans.

Core authors like Carr A, known for studies on ART efficacy[28], and Di Giambenedetto S, focused on treatment optimization[29], have shaped the field's direction through high-citation work.

Analysis of keywords and research frontiers

Research hotspots

Considering keyword co-occurrence clusters, keyword frequency, and keyword centrality, the research hotspots within this field can be summarized as follows.

Key two-drug combinations

Integrase strand transfer inhibitors (INSTI) + nucleoside reverse transcriptase inhibitors (NRTI) combinations represented by DTG + lamivudine (3TC), this is the most well-studied regimen to date[30-32]. International trials (GEMINI-1/2)[33] and real-world data[34] have confirmed that in treatment-naive patients (viral load < 500,000 copies/mL), its 48-week viral suppression rate reaches 91-96.4%, non-inferior to triple-drug regimens. It also has lower risks of adverse drug reactions and metabolic abnormalities and has been listed as a first-line recommendation in guidelines worldwide[35,36]. In addition, this regimen performs excellently in treatment-experienced patients with stable viral suppression undergoing switch therapy, with a 144-week maintenance rate of 96%[37]. Notably, the development of NRTI-sparing two-drug regimens, including DTG + 3TC, has addressed the long-standing concerns about NRTI-related toxicities, and recent studies have further confirmed their reliability in treatment-naive patients, even in some populations with moderate viral load, though caution is still needed in patients with high baseline viral load[38].

Long-acting injectable two-drug regimens: The long-acting injectable formulation of DTG + RPV has become an important option for treatment-experienced patients switching therapy. The SWORD trials showed that its 48-week viral suppression rate exceeds 95%, which is comparable to continued triple-drug therapy[39]. It also improves bone mineral density and renal function, addressing long-term bone and kidney toxicity associated with oral formulations, and significantly enhances patient treatment satisfaction[40]. However, this dual regimen has certain limitations that require attention: it is only suitable for treatment-experienced patients with stable viral suppression, and the virus must be fully susceptible to both DTG and RPV to avoid treatment failure. Moreover, while resistance is rare in patients failing on DTG-RPV, pre-existing resistance mutations to either component can reduce its efficacy. In addition, its application in special populations (e.g., patients with comorbidities or elderly individuals) still lacks sufficient long-term data[41,42].

PI + NRTI Combinations: darunavir/ritonavir (DRV/r) + 3TC and lopinavir/ritonavir (LPV/r) + 3TC have demonstrated non-inferiority in both treatment-naive and treatment-experienced patients[43,44]. These regimens, as part of NRTI-sparing strategies, have also shown potential in reducing drug exposure and long-term toxicities compared to traditional triple regimens, especially in patients intolerant to other drug classes. A meta-analysis of randomized controlled trials has further supported that PI-based dual regimens, similar to INSTI-based ones, have non-inferior efficacy and safety compared to triple regimens[45].

It is crucial to emphasize that simplification therapy, which includes the two-drug regimens discussed above, must prioritize agents with high barrier to resistance. Specifically, such regimens should include either second-generation INSTIs (e.g., DTG) or boosted PIs (e.g., DRV/r), as these agents can effectively reduce the risk of resistance development and treatment failure. This principle is supported by numerous clinical studies and reviews, which confirm that simplification therapy without high resistance barrier agents is associated with higher risks of subclinical failure and resistance mutations[42,45]. The non-inferiority of two-drug regimens to triple regimens in both efficacy and safety is largely dependent on the inclusion of these high resistance barrier components[41,45].

Target populations for two-drug regimens

Treatment-naive patients: focus on populations with viral load < 500,000 copies/mL, where DTG + 3TC is the preferred option[33]. Real-world studies in patients with high viral load (> 500,000 copies/mL) showed that DTG + 3TC still achieves a high suppression rate (95.5%), providing evidence for expanding its applicability[32,46].

Treatment-experienced patients with stable switch: A broader range of regimens is available. In addition to DTG + 3TC and long-acting injectables, combinations such as DRV/r + 3TC and DRV/r + DTG can maintain viral suppression while reducing toxicity from previous regimens[43,47].

Optimization for special populations: for patients with renal impairment, decreased bone mineral density, or cardiovascular risk, regimens without tenofovir (TDF) (e.g., DTG + 3TC, boosted PI (bPI) + DTG) are preferred to reduce risks of renal injury, bone loss, and dyslipidemia[48,49]. For NRTI-intolerant patients, "INSTI + NNRTI" combinations (e.g., DTG + efavirenz) have shown favorable efficacy[50].

Advantages of two-drug regimens

Enhanced safety: reduced drug exposure significantly lowers long-term toxicity. For example, TDF-free regimens avoid renal injury and bone loss, and the incidence of dyslipidemia in the DTG + 3TC regimen is lower than that in triple-drug regimens containing boosted PIs[51-53].

Improved adherence and cost-effectiveness: single-tablet formulations (e.g., DTG/3TC fixed-dose combination) and long-acting injectables reduce dosing frequency. The discontinuation rate of two-drug regimens (8%) is significantly lower than that of triple-drug regimens (15%)[54,55]. Costs are reduced by 10-20%, making them highly valuable for promotion in low- and middle-income countries[56,57].

Future trends

Bibliometric studies using keyword co-occurrence analysis and topic distribution diagrams indicate that research on two-drug regimens for HIV has focused on addressing key challenges in enhancing therapeutic efficacy, improving safety, and promoting global implementation. The future research trends in HIV two-drug regimens will include the following aspects.

New drug development

Doravirine/Islatravir (DOR/ISL) is an investigational, once-daily oral two-drug regimen[58]. DOR, a

non-nucleoside reverse transcriptase inhibitor, blocks the synthesis of the HIV-1 viral replication chain; ISL, a nucleoside reverse transcriptase translocation inhibitor, prevents viral DNA chain synthesis and induces chain termination. Their combination inhibits viral replication through complementary mechanisms, forming a synergistic therapeutic effect[59].

Expansion of applicability in special populations

Priority will be given to validating efficacy and safety in pediatric populations, pregnant women, and individuals coinfected with chronic hepatitis B (HBV), diabetes mellitus, or cardiovascular diseases. For example, long-term data on DTG + 3TC use in pregnant women will be explored, and strategies for "two-drug regimens + anti-HBV agents" in HBV-coinfected patients will be optimized[60].

Precision in drug resistance management

Regimens will be customized based on resistance gene testing[61]. For patients at high risk of resistance (e.g., those with a history of multiple drug resistance), combinations with high resistance barriers will be prioritized[62]. Long-term follow-up will be strengthened to monitor potential resistance mutations, reducing the risk of treatment failure[63]. Expanding on resistance risk management, the choice of two-drug regimens should be closely guided by resistance gene testing, especially in treatment-experienced patients with a history of drug resistance. For treatment-naive patients, while two-drug regimens such as DTG + 3TC have shown excellent resistance profiles, regular monitoring of viral load is still necessary to detect early virological failure and adjust regimens promptly. Studies have shown that two-drug regimens overall do not increase the risk of subclinical failure compared to triple regimens, but this advantage is only maintained when the regimen includes high resistance barrier agents[42]. In addition, for patients switching from triple to dual therapy, pre-switch resistance testing is essential to ensure susceptibility to the components of the dual regimen, which is a key measure to prevent resistance development[38,42]. A meta-analysis including 4852 patients found that DTG-based dual regimens had a low risk of resistance even in long-term use (up to 96 weeks), with no significant difference in resistance mutation rates compared to triple regimens[45]. However, for dual regimens with low resistance barriers, the risk of resistance is significantly higher, especially in patients with poor treatment adherence or high baseline viral load[41].

Exploring the potential for functional cure

Research on HIV cure is advancing step by step through technological innovations, mechanistic research, and clinical trials. Nanotechnology and gene editing have enabled more precise treatment; immunological and metabolic studies have identified the vulnerabilities of viral hiding spots; and multicenter trials have accelerated the translation of research findings into practical applications. However, challenges such as eliminating viral reservoirs and enhancing safety still require collaborative efforts from experts across different disciplines to address. With the wider availability of long-acting formulations and improved efficacy of gene editing, the cure for HIV may truly transform from a dream into reality.

Limitations

This analysis is subject to several limitations. First, exclusive reliance on the WoSCC could result in missed studies, thereby introducing bias. Second, the exclusion of non-English research overlooks valuable contributions from other regions. Third, despite careful review of keyword merging by two authors, certain errors or omissions may still persist.

Conclusions

Research on two-drug regimens for HIV is growing rapidly, driven by clinical demand for simplified, safe, and effective ART. Emerging trends suggest a shift toward personalized and innovative regimens. These results can guide researchers and policymakers in prioritizing high-impact domains, enhancing global collaborations, and converting research outcomes into accessible treatments – ultimately advancing HIV management on a global scale.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.25000029. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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