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Trends and perspectives in the HIV vaccine research over the past thirty-five years: a scientometrics analysis through CiteSpace

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Abstract

Despite advances in antiretroviral therapy, developing an effective human immunodeficiency virus (HIV) vaccine remains pivotal for epidemic control. Through a scientometric analysis of 19,863 publications from the Web of Science Core Collection (1989-2023) using CiteSpace, this study delineates evolving trends and emerging frontiers in HIV vaccine research. The United States dominated contributions, with institutions like the National Institutes of Health and Harvard leading productivity. Clustering revealed two interconnected research trajectories, which are broad neutralizing antibody development, broad neutralizing antibody precursors, and immune mechanism exploration. Despite efficacy trials not resulting in licensed HIV vaccine advancements in antigen design and adjuvant strategies, they show promise. Key findings indicated structural biology, germinal center (GC) dynamics, antibody-dependent cellular cytotoxicity, and glycosylation shielding as pivotal research domains. Critical barriers include generating a specific immune response to new epitopes and glycosylation-mediated immune evasion. Future efforts should prioritize GC optimization to enhance B-cell affinity maturation, structure-guided epitope targeting through cryo-electron microscopy, and advances in antigen delivery. In addition, engineering vaccines to expand CXCR5+ T follicular helper cell populations may improve durable humoral immunity. This analysis underscores the necessity of multidisciplinary approaches to overcome HIV vaccine hurdles.

Keywords: *Vaccine. CiteSpace. Visualization analysis. Emerging trends.*

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Introduction

Due to the global prevalence of HIV, 40.4 million people have died, with an estimated 39.0 million individuals currently living with HIV worldwide[1]. This number remains high, indicating that HIV is still a serious global public health concern. HIV targets CD4+ lymphocytes, leading to progressive depletion of these immune cells and subsequent immunodeficiency, predisposing patients to opportunistic infections and malignancies. While combination antiretroviral therapy and pre-exposure prophylaxis have significantly reduced HIV transmission and improved the life expectancy of patients[2,3], implementation barriers persist, particularly in resource-limited settings. Consequently, developing a safe, effective, and scalable prophylactic vaccine remains essential for epidemic control.

The design of an effective HIV vaccine faces challenges due to the virus's unique replication mechanisms, rapid envelope (Env) protein mutation, and a dense glycan shield obscuring critical epitopes[4,5]. In 2009, RV144 demonstrated that vaccines might be feasible, which used the viral vector prime and a boost with glycoprotein gp120 of HIV to produce 31.2% vaccine effectiveness[6]. While the efficacy of the RV144 ALVAC HIV vaccine was confirmed through independent, alternative statistical methods, the results indicated that the immune responses boosted by additional vaccinations were short-lived[7]. Subsequently, a regimen based upon the RV144 regimen announced the failure of the recombinant canarypox vector vaccine (ALVAC-HIV) due to the incidence of HIV-1 infection being similar between the vaccinated group and the placebo group, with a hazard ratio of 1.02 ($p = 0.84$), indicating no significant protective effect[8]. The RV144 trial suggested that non-neutralizing antibodies, through Fc receptor-mediated effector functions like antibody-dependent cellular cytotoxicity (ADCC), may contribute to protection against HIV transmission, prompting further vaccine designs to enhance such responses. Emerging strategies show promise, including a novel mRNA-LNP vaccine platform in stimulating robust immune responses, containing high levels of T follicular helper (Tfh) cells and germinal center (GC) B cells, which were linked to long-lasting protection and high-affinity neutralizing antibodies[9], novel Env trimers that induce broadly neutralizing antibodies (bnAbs)[10], potential novel viral vectors, such as the rhesus cytomegalovirus[11], and other discoveries. Reflecting on past research and summarizing and analyzing the current situation can provide valuable insights for developing future HIV vaccines.

Bibliometric analysis has become an indispensable tool across biological sciences for monitoring scientific progress and evaluating disciplinary development. Moreover, objective bibliometric methods can also obtain more comprehensive results. Knowledge domain visualization employs bibliometrics to identify significant changes in the knowledge domain more readily and to detect and track the evolution of the domain. For example, CiteSpace employs visualization processing technology based on a Java application developed by Professor Chaomei Chen in 2004[12]. No study has yet applied temporal network analysis to map the evolving HIV vaccine research domain. Therefore, it is critical to provide an overview of the current status of HIV vaccine research, make recommendations for future paths for the field, and get insights into the development and trending topics of this area.

Methods

Data collection

Since the Web of Science Core Collection (WoSCC) is the only database that fully uses the features of CiteSpace, we collected data on HIV vaccines from it[13]. A broad search formula was adopted in this study to reduce the effects of biased and subjective information filtering. The retrieved formula was (TS = HIV OR TS = "Human Immunodeficiency Virus" OR TS = "Human T Cell Lymphotropic Virus Type III" OR TS = LAV-HTLV-III OR TS = "Lymphadenopathy Associated Virus" OR TS = "Human T Lymphotropic Virus Type III" OR TS = "AIDS Virus" OR TS = "Acquired Immune Deficiency Syndrome Virus") AND (TS = "vaccine" OR TS = "vaccines"). Our study focuses on both since we did not distinguish between HIV-1 and HIV-2 in the search formula. In addition, only articles and reviews written in English can be included. The CiteSpace version employed is 6.2.R7 Advance.

Figure 1 displays the diagram of the retrieval procedure. The period covered was from January 1, 1989, to December 31, 2023. With the "remove duplicates" tool of CiteSpace, both researchers evaluated the retrieval formula and inclusion and exclusion criteria, respectively. These data were gathered on January 28, 2024, to counteract the impact of the search library improvement on this project. The data export was limited to

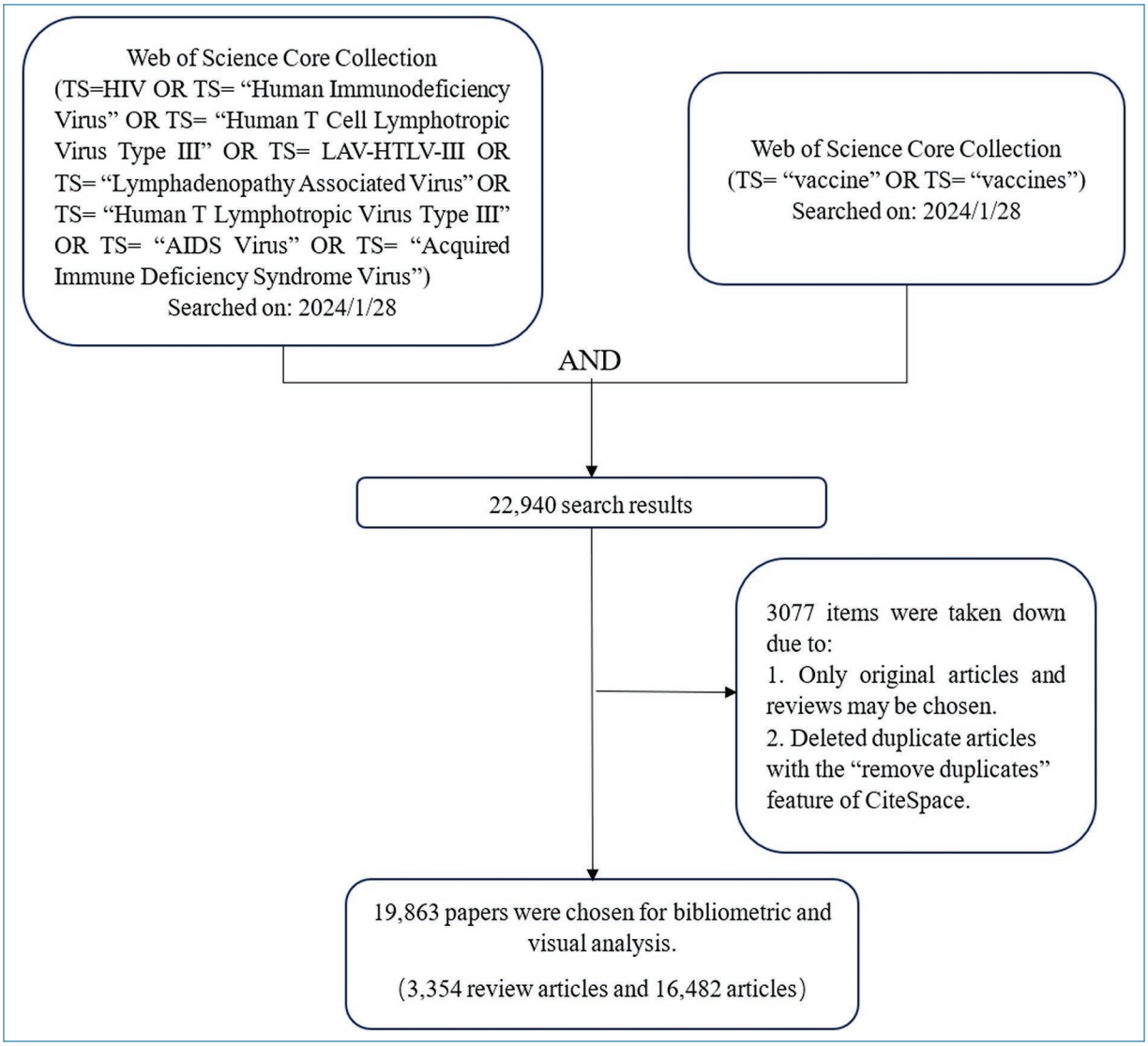


Figure 1. Flowchart depicting the article selection process. The initial search used specific phrases combined with the logical operator "AND," identifying 22,940 articles for initial consideration. Following this, we applied basic exclusion criteria to filter out 3,077 articles. In total, 19,863 publications were included, consisting of 3,354 reviews and 16,482 experimental research.

1989-2023, potentially excluding earlier relevant publications due to database indexing limitations.

Data export

19,863 documents were exported through WoSCC as "full record and cited references" after being screened. First-place to 500th-place data were imported into a file called "download_1-500.txt," data from the 501st to the 1,000th place were imported into a folder called "download_501-1000." Data exports followed this pattern until all 19,863 publications were processed.

Bibliometrics and visualization analysis

Before network construction, the WoSCC dataset was preprocessed in CiteSpace (v6.2.R7) through deduplication and standard format conversion. The option "term source" selection criteria were k = 25. For institutional collaboration and keyword timeline analyses, k = 15 was selected to highlight key points given the scale of the dataset. Pruning mode to "Minimum Spanning Tree" and "Pruning Sliced Networks." This feature enhances the output efficiency by filtering and prioritizing critical results. Thus, the total output results are less than the

actual data volume (data volume = 19,836). "Years Per Slice" was set to 1 year in the graph for visual analysis from January 1, 1989, to December 31, 2023. The g-index serves as a measure to regulate the density of network nodes and filter out key literature. For each time interval, the criterion for selecting nodes is defined by the following formula:

$$g^2 \le k\sum_{i\le g} c_i, k \in Z^+$$

Σc_i denotes the total citation count of publications, indicating their overall scholarly influence. The parameter k acts as a scaling factor, balancing the breadth and focus of the analysis. A higher k-value broadens the network by lowering citation thresholds, whereas a lower k-value emphasizes nodes with greater impact. Modularity (Q) is used as an indicator to assess the quality of clusters, and is computed according to the equation below:

$$Q = \frac{1}{2m}\sum_{ij}\left(a_{ij} - p_{ij}\right)\sigma\left(C_i, C_j\right)$$

Network visualization encodes node size as frequency weight, color gradient as temporal distribution (warmer hues indicating recency), and link thickness as co-occurrence strength. Nodes with a purple border have a high betweenness centrality (centrality ≥ 0.1). A graph-theoretic attribute called "centrality" measures how significant a node's position is within a network[13], whose formula is:

$$g(v) = \sum_{s\neq v\neq t}\frac{\sigma_{st}(v)}{\sigma_{st}}$$

Vertex v's centrality value is indicated by $g(v)$, the number of shortest paths between s and t that pass through v is shown by $\sigma_{st}(v)$, and the overall number of shortest paths between s and t is indicated by σ_{st}[14]. The burst-detection method can identify sudden increases in devotion to a field[13]. In the final figures generated by CiteSpace, several key parameters are utilized to shape the network topology. The Link Retention Factor (LRF) determines the probability of retaining connections within the network. Higher values result in a denser network with more connections retained. The Lines per Node (L/N) parameter specifies the maximum number of connections each node can possess, thereby controlling the overall complexity of the network. A higher L/N value leads to a more intricate network structure. The look-back years parameter sets the maximum backtracking period, ensuring that only past N-year references are included. In addition, the Edge Count (E) reflects the total number of connections in the network, with larger E values indicating a higher density of connections between nodes. These parameters were configured using the software default settings. Density reflects the compactness of connections among nodes in a network, where higher values suggest a more tightly interconnected structure. A highly modular network is characterized by loosely connected sub-networks, approaching the upper limit of modularity (Modularity Q = 1). In contrast, a tightly integrated network with closely connected components approaches the lower limit of modularity (Modularity Q = 0). Meanwhile, the silhouette score of a cluster assesses the homogeneity within the cluster, indicating how well cluster members are grouped based on shared characteristics. Essentially, a higher silhouette score signifies a more meaningful and cohesive cluster than a lower score[15,16]. The elevated value of the Harmonic Mean (Q/S) serves as a robust indicator of clustering reliability, signifying that the clustering outcomes exhibit both a pronounced modularity structure (characterized by a high Q value) and substantial internal homogeneity (evidenced by a high S value). This dual characteristic enhances the credibility of the clustering attributes of the network.

Results

Analysis of annual outputs of publications

Fig. 2 illustrates the longitudinal publication trend. The vertical axis presents papers published annually, while the horizontal axis shows the published years. The number of academic papers published each year reflects field changes over time. There are a total of 19,836 documents about the HIV vaccine in the WOSCC until 2023, which include 16,482 articles and 3,354 reviews. In 1987, the WoSCC collected the first study about the HIV vaccine, which Robson conducted[17]. It described a computer method for analyzing protein sequences to predict potential artificial vaccines. Subsequent decades witnessed sustained growth, peaking at 1,243 publications in 2021.

Distribution of countries and institutions

The country and institutions of software output are derived from the author's information in the source article. The output results include the country and

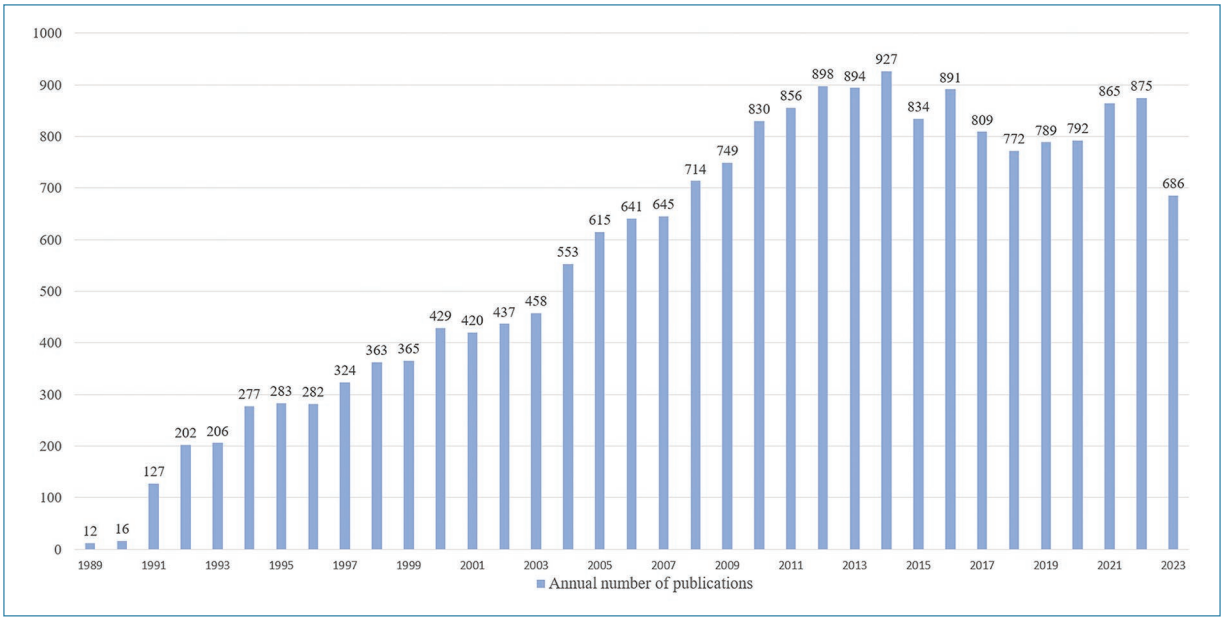


Figure 2. Annual chart of publications. This bar chart presents the yearly count of publications in the field from 1989 to 2023, showing an overall increasing trend with some fluctuations.

institution information of all authors for 19,836 articles. Figure 3A has 168 (countries) nodes and 1086 lines, which depict the close cooperation represented by the USA and England. The USA published many more papers than any other country. The contribution of global institutions to the HIV vaccine is shown in Figure 3B, which contains 2847 lines and 687 (institutions) nodes. In the national output results, the initial sample size is 30,955, whereas for institutions, it is 58,026. The discrepancy between this number and the total count of 19,836 is due to including all authors associated with each article in the calculation. Table 1 presents the rankings of the top 10 countries and institutions based on publication counts, respectively. The top 5 countries in terms of publication volume were the USA (11308, 57.01% in total), England (2206, 11.12% in total), South Africa (1272, 6.41% in total), France (1263, 6.37% in total), and China (1150, 5.80% in total). The top 5 institutions were the National Institutes of Health (NIH) (4070, 20.52% in total), Harvard University (2698, 13.60% in total), the University of Washington (1754, 8.84% in total), the University of California (1372, 6.92% in total), and Duke University (1087, 5.48% in total).

Distribution of authors

Figures 3C and D depict high-yield and high-impact authors encompassing all co-authors. The co-cited author is defined as an individual whose work has been cited together with other authors' work in a third-party publication. This co-occurrence reveals shared research focus areas. Figure 3C illustrates the number of publications over time, with 1793 nodes (authors) and 2738 lines, showing the strong collaboration among researchers studying the HIV vaccine. Figure 3D visualizes co-citation networks (2,780 author nodes, 8,073 citation links). Tables 2 and 3 rank the top 10 authors by publication volume and co-citation frequency. Higher citation counts indicate a more significant academic impact. Regarding the number of published authors and co-cited authors, the initial sample sizes are 19,341 and 218,340, respectively. The top three authors with the most publications were David C. Montefiori (355 publications), Barton F. Haynes (273 publications), and Georgia D. Tomaras (223 publications). The top three co-cited authors were Burton DR (1921 citations), Haynes BF (2080 citations), and Burton DH (2275 citations). Figure 3C is divided at 2009, with the left segment depicting pre-2009 data and the right segment representing post-2009 findings. It may be ascribed to the significant achievements of RV144. Besides, no nodes achieved betweenness centrality ≥ 0.1 in this network configuration. The emergence of nodes with purple borders is influenced by the ratio of N to E. Specifically, a smaller value of N or a larger E tends to reduce betweenness centrality, thereby diminishing the

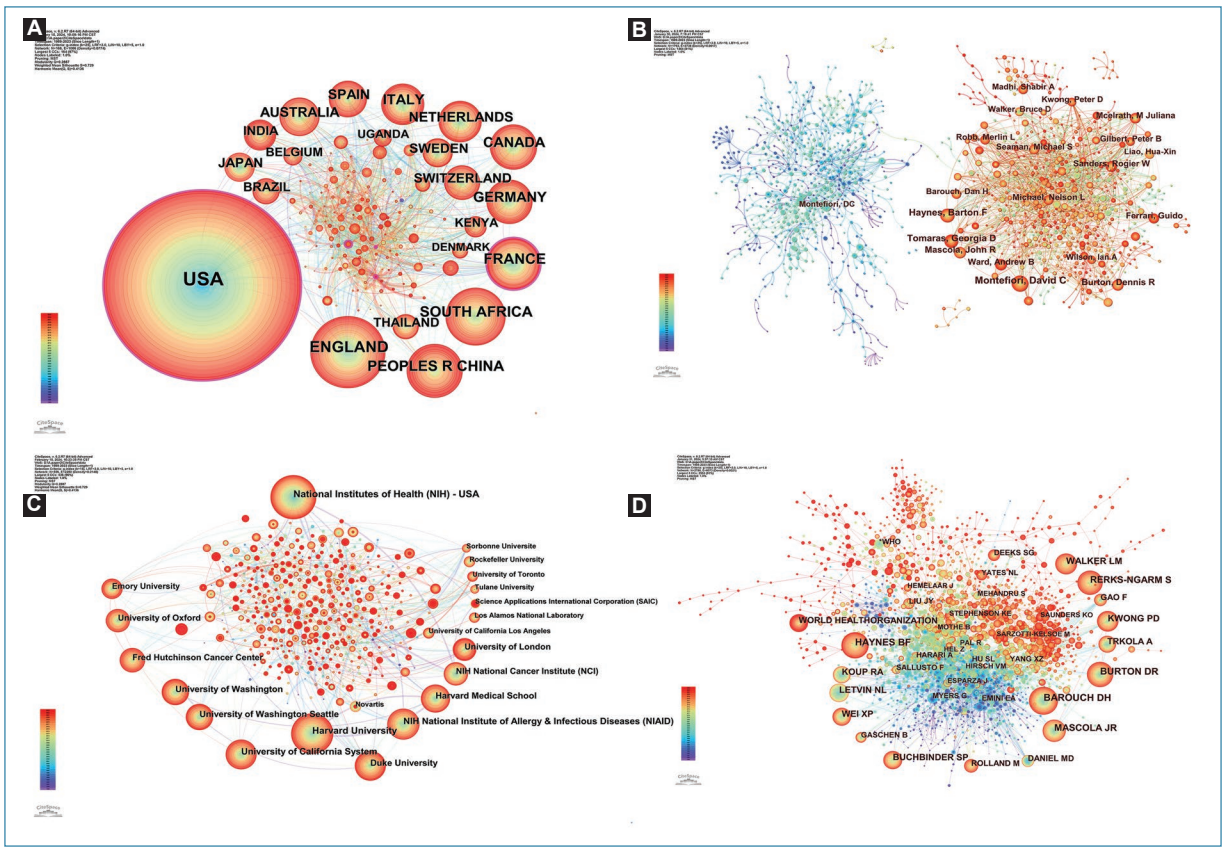


Figure 3. Co-occurrence network diagram. This diagram consists of four parts. Each node represents a country, institution, or author. The color changed from purple to red between 1979 and 2023. The strength of the cooperation is reflected by the thickness of these lines, where a thicker link signifies closer collaboration. The nodes with purple edges show high centrality. **A:** network map of countries. **B:** network map of institutions. **C:** network visualization of a co-author regarding the HIV vaccine. **D:** the network visualization illustrates the co-cited authors within the publications.

Table 1. Top 10 countries and institutions with published articles related to the HIV vaccine from 1989 to 2023

Rank	Countries	Count	Institution	Count
1	USA	11308	National Institutes of Health (NIH) - USA	2086
2	England	2206	Harvard University	1760
3	South Africa	1272	NIH National Institute of Allergy and Infectious Diseases (NIAID)	1169
4	France	1263	University of California System	1142
5	People's R China	1150	Duke University	1087
6	Canada	998	Harvard Medical School	937
7	Germany	958	University of Washington	881
8	Italy	901	University of Washington Seattle	873
9	Netherlands	814	NIH National Cancer Institute (NCI)	815
10	Australia	813	Fred Hutchinson Cancer Center	766

Table 2. Top 10 authors with published articles related to HIV vaccine from 1989 to 2023

Rank	Author	Count
1	Montefiori, David C	355
2	Haynes, Barton F	273
3	Tomaras, Georgia D	223
4	Mascola, John R	192
5	Burton, Dennis R	179
6	Ward, Andrew B	153
7	Ferrari, Guido	152
8	Michael, Nelson L	147
9	Mcelrath, M Juliana	141
10	Sanders, Rogier W	141

Table 3. Top 10 co-cited authors related to HIV vaccine from 1989 to 2023

Rank	Co-cited author	Count
1	Barouch, Dan H	2275
2	Haynes, Barton F	2080
3	Burton, Dennis R	1921
4	Mascola, John R	1728
5	Rerks-Ngarm, Supachai	1627
6	Kwong, Peter D	1341
7	Walker, Laura M	1200
8	Letvin, Norman L	1178
9	Wei Xi P	1131
10	Koup, Richard A	1078

likelihood of such nodes appearing. This phenomenon is common in CiteSpace analyses, particularly when dealing with highly interconnected datasets. Stratified analysis separated research articles from reviews to control for publication type bias. We then conducted separate analyses to identify high-yield authors within each category. The results are presented in Supplementary Figures 1A and B. In addition, Supplementary Tables 1 and 2 provide detailed counts of contributions and betweenness centrality for authors in both categories. Haynes, BF, and Mascola, JR were simultaneously the top 10 co-cited and top 10 high-yield authors.

Analysis of journal: overlay map

Figure 4A was generated with the overlay mapping function of CiteSpace to analyze the journal distribution of HIV vaccine-related publications. The elliptic curve displays the proportion between authors and publications. The longer the horizontal axis of the ellipse, the more authors there were. The journal published more papers on the vertical axis lengthening of the ellipse. Colored lines denote citation relationships between journals. Cited articles are the cornerstone of the domain from a domain development standpoint. Major pathways connected research domains, including molecular biology, genetics, healthcare sciences, and clinical medicine, with key citations originating from molecular biology, immunology, and clinical medicine journals.

Analysis of reference

Analysis of highly co-cited reference

The top ten co-cited references are listed in table 4. Co-citation is the simultaneous citation of two or more references within third-party publications. The most referenced research was published by Rerks-Ngarm et al.,[6]. This study, generally called RV144, validated the viability of the ALVAC-HIV. The second most cited reference found that the vaccine that induces a higher level of V1V2 antibodies and a lower level of Env-specific IgA antibodies can be more effective against HIV-1 infection than the RV144 vaccine[18]. The study by Buchbinder, S. P. et al.[19], a double-blind, phase 2 trial that demonstrated the ineffectiveness of the MRKAd5 HIV-1 gag/pol/nef vaccine, was the third most cited reference in our data. Furthermore, two additional broadly effective antibodies were discovered in the fourth highly co-cited reference, which had 0.11 betweenness centrality[20]. According to our statistics, this reference has the highest betweenness centrality, meaning this study connects documents from different subdomains.

Visual analysis of the development of HIV vaccine: reference clustering and landscape

Figures 4B was constructed to examine the evolution of the HIV vaccine through co-cited references. This section illustrates clusters and their dependency

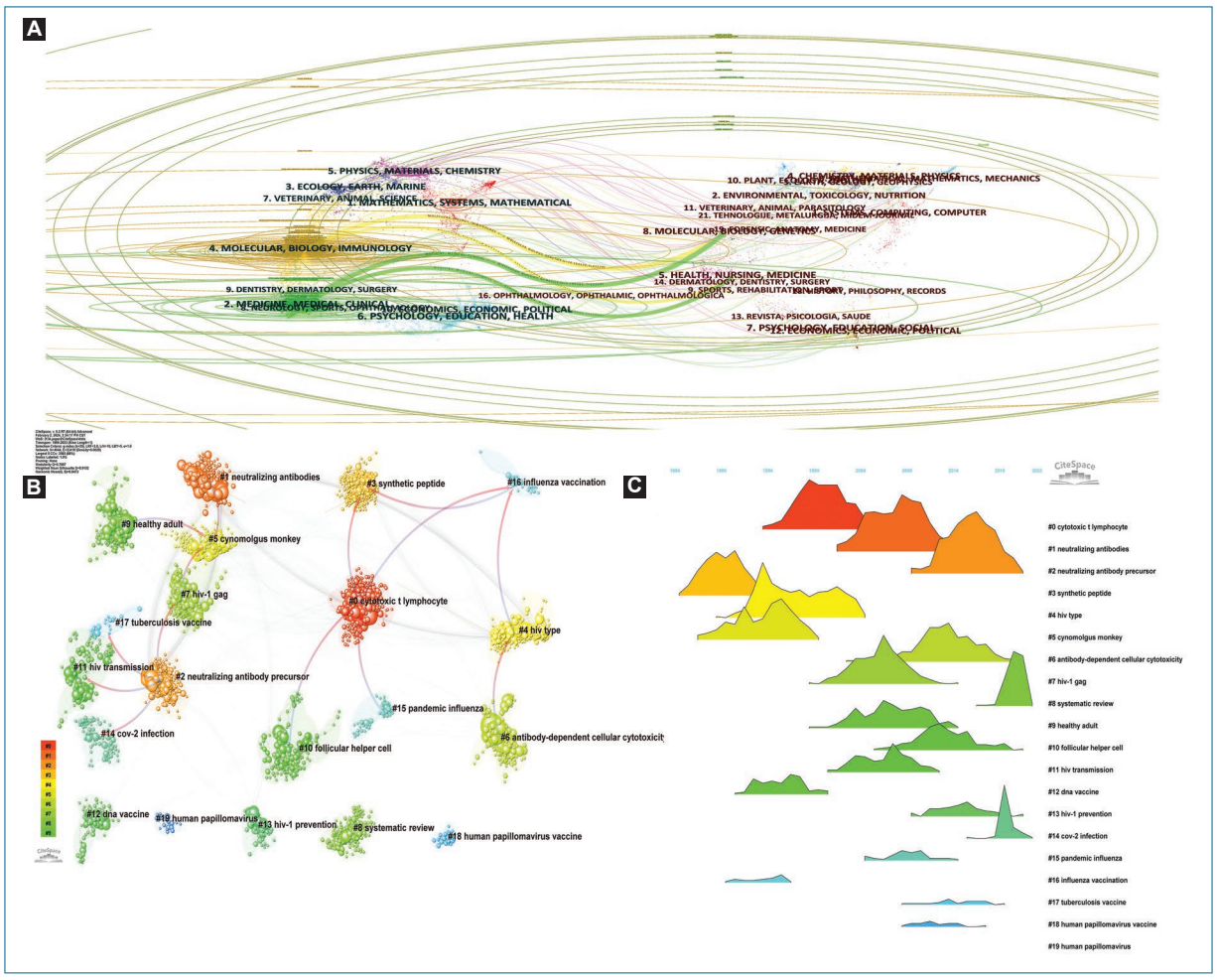


Figure 4. **A:** the overlay map of journals related to the HIV vaccine. The relationship between citing and cited journals is shown on the left and right. The citation link can be seen in the yellow and green curves. **B:** the cluster's dependencies map of reference related to the HIV vaccine. Different colors are used to depict the various clusters. The arrow between clusters represents the citation relationship between clusters. **C:** the landscape of reference clusters related to the HIV vaccine. The height of the peaks over time shows a change in clustering. The peak represents the year with the highest number of articles in the cluster.

relationships. Generating cluster names relies on the log-likelihood ratio algorithm. This algorithm ultimately captures representative words as the cluster name by evaluating the co-occurrence of co-cited references. Clusters may vary due to subtle differences in research focus, reflecting even minor keyword variations in the literature. The clustering result is considered reasonable if the average contour value (S) exceeds 0.5 and remarkable if it surpasses 0.7. The clustering module value Q is a critical indicator for assessing the rationality of cluster results. The cluster community structure is well-defined when Q exceeds 0.3[13]. Our clustering result is efficient and highly reliable, as demonstrated by the Q (0.7887) and S (0.9152) values. Colored lines show cluster dependency relationships. For example, the arrow pointing from #9 (healthy adult) to #5 (cynomolgus monkey) represents those papers in cluster #9 citing those in cluster #5. This relationship reflects the development of the field of HIV vaccines. The analysis comprises 20 clusters. Clusters with weak interconnections located at the bottom of the network due to dataset complexity were excluded from further analysis to prioritize core dependency relationships. There are two core structures in this image, which include 15 clusters. One core structure contains #1 neutralizing antibodies, #2 neutralizing antibody precursor, #5 cynomolgus monkey, #7 HIV-1 Gag, #9 healthy adult, #11 HIV transmission, #14 cov-2 infection, and #17 tuberculosis vaccine. The other core structure consists of #0 cytotoxic T lymphocyte, #3 synthetic peptide, #4 HIV type, #6

Table 4. The top 10 co-cited references related to the HIV vaccine

Rank	Title	Count	Publication time	Centrality
1	Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand	754	DEC 3 2009	0.01
2	Immune-correlates analysis of an HIV-1 vaccine efficacy trial	641	APR 5 2012	0.01
3	Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomized, placebo-controlled, test-of-concept trial	450	NOV-DEC 2008	0.01
4	Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target	411	OCT 9 2009	0.11
5	Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine	386	APR 6 2001	0.01
6	Broad neutralization coverage of HIV by multiple highly potent antibodies	379	SEP 22 2011	0.02
7	Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1	368	AUG 13 2010	0.01
8	Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity	345	JAN 17 2002	0.04
9	Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus	333	APR 25 2013	0.03
10	Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination	320	OCT 20 2000	0.01

ADCC, #10 follicular helper cell, #15 pandemic influenza, and #16 influenza vaccination. Figure 4C depicts the temporal evolution of research clusters through a landscape map. From the perspective of clustering evolution, this result is consistent with the result of the dependency of clusters in terms of time.

Analysis of keyword

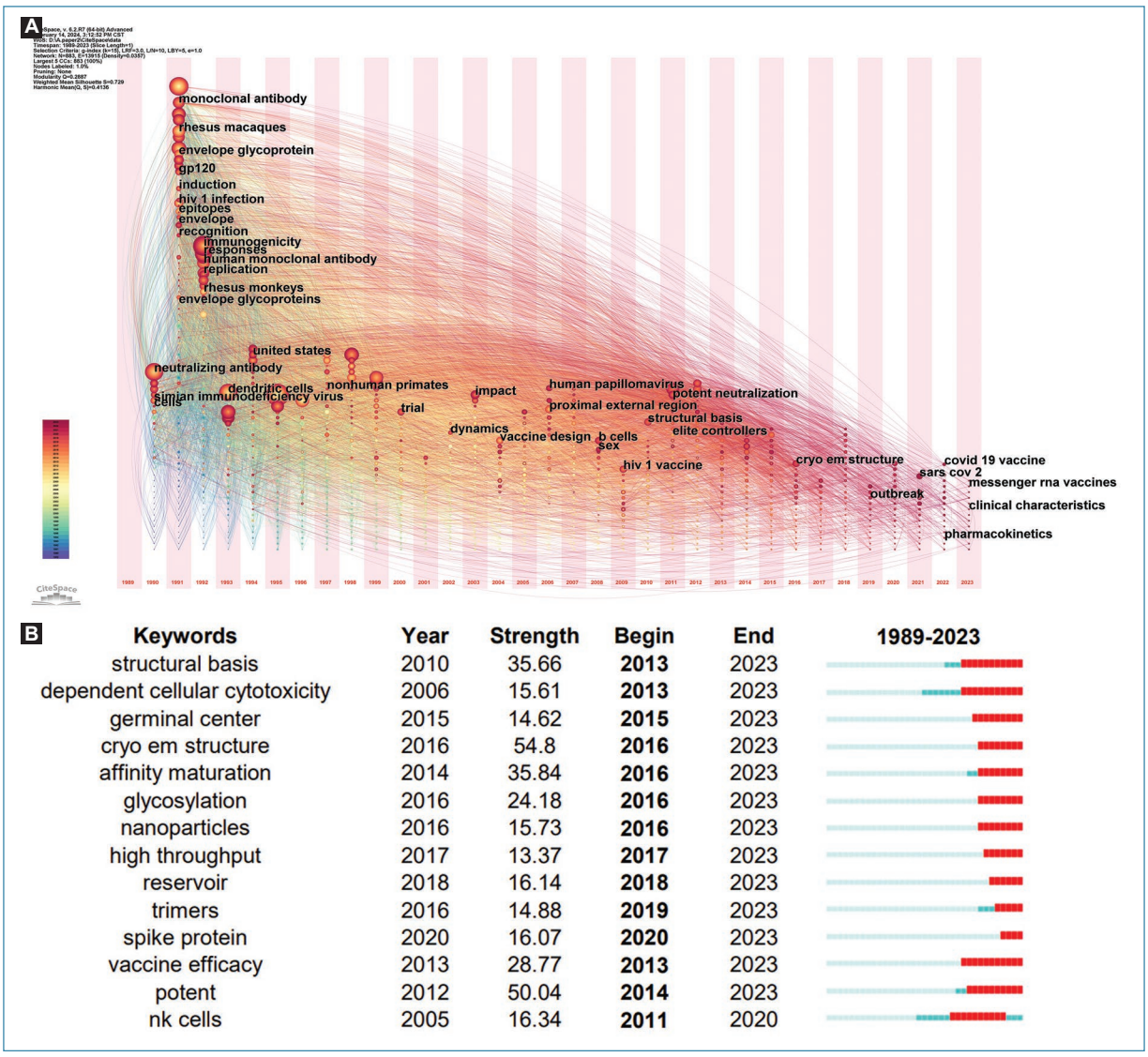
Figure 5A illustrates the temporal trends of HIV vaccine keywords. Following a sharp increase in 1991, keyword activity declined gradually until 2010, when a second surge occurred. Subsequent growth remained limited, indicating a stabilization of research activity in this field. Keyword counts increased in multiple citations, reflecting a significant emphasis during the academic cycle. Keyword burst analysis, which identifies hotspots and potential research directions, provides valuable insights into focal points and emerging trends in HIV vaccine research. Figure 5B reveals the top 14 keywords with the highest citation bursts related to HIV vaccines based on burst detection methodologies. These 14 keyword bursts persist until 2020, 2021, or 2023, which can be divided into four parts, including hotspots in HIV vaccine research methods, experiments on the HIV vaccine, obstacles to vaccine studies, and research directions worth noting.

Discussion

Early HIV vaccine research focused on candidate immunogen selection, preclinical assessment in animal models, and rigorous clinical trial monitoring to ensure vaccine safety and efficacy[21]. From 1989 to 2014, the number of publications increased steadily and peaked in 2014. Fluctuations in the annual publication count continued until 2023, with 686 publications (3.46%), marking the lowest output in the past decade. The deceleration in publication growth since 2015 suggests a field maturation, accompanied by a shift toward highly specialized and mechanistic investigations.

Countries, institutions, and journals

Among all countries, the USA was the leading contributor to HIV vaccine research, and its node betweenness centrality exceeded 0.1, indicating a high level of international cooperation. The purple-bordered nodes represent close collaboration in HIV vaccine development among different nations. The filtered data encompasses 168 countries, underscoring the profound significance and widespread engagement in HIV vaccine research across the globe. This extensive international collaborative effort is pivotal for expediting vaccine development and attaining global health objectives. The top ten institutions with papers published



B

Keywords	Year	Strength	Begin	End	1989-2023
structural basis	2010	35.66	**2013**	2023	
dependent cellular cytotoxicity	2006	15.61	**2013**	2023	
germinal center	2015	14.62	**2015**	2023	
cryo em structure	2016	54.8	**2016**	2023	
affinity maturation	2014	35.84	**2016**	2023	
glycosylation	2016	24.18	**2016**	2023	
nanoparticles	2016	15.73	**2016**	2023	
high throughput	2017	13.37	**2017**	2023	
reservoir	2018	16.14	**2018**	2023	
trimers	2016	14.88	**2019**	2023	
spike protein	2020	16.07	**2020**	2023	
vaccine efficacy	2013	28.77	**2013**	2023	
potent	2012	50.04	**2014**	2023	
nk cells	2005	16.34	**2011**	2020	

Figure 5. **A:** time zone view of keywords for the HIV vaccine. The location of the node on the horizontal axis indicates the year of the initial appearance of keywords. The larger the node, the more often co-occurrences occur. The size of the node indicates the frequency of co-occurrence. When two keywords appear together, it is shown by lines connecting the nodes. **B:** keywords with burst periods lasting from 2021 to 2023 related to the HIV vaccine. The blue line in the figure signifies the general period. The red line highlights explicitly periods during which there was a significant surge in the keyword.

were all in the USA. Given the vast number of institutions and numerous connections between nodes in our results, close collaboration among different institutions is evident, even without purple nodes. The overlay map analysis shows the citation relationships between different disciplinary fields and reveals how academic research is conducted across disciplines. Our research indicates that two main citation paths reflect fundamental vaccination research and basic clinical vaccine testing. In addition, citation relationships mainly occur between molecular biology, immunology, genetics, medicine, and clinical type journals. The inter-journal citation patterns suggest that interdisciplinary research in the HIV vaccine field may not be as prominent as previously anticipated.

Authors and co-cited authors

Our analysis reveals that, despite the absence of purple-border nodes among authors of research

articles, the lines between these nodes highlight substantial collaboration among researchers in the relevant experimental fields. This observation may result from the low connectivity of significant nodes within the context of large-scale data. In contrast, the betweenness centrality of authors of review articles has been determined as zero, likely due to the nature of review articles. The relative underrepresentation of high-yield authors in the co-citation network may reflect the broad interdisciplinary scope of their contributions. Their work spans diverse subfields, leading to distributed citations across distinct research trajectories rather than concentrated co-citation clusters. This phenomenon underscores the multifaceted nature of scholarly impact, where foundational contributions may be embedded in broader research narratives rather than isolated co-citation nodes. Barouch, Dan H., was the most prominent co-cited writer among all of them. Two of his highly cited papers, published in *SCIENCE* and *NATURE*, respectively, are titled "Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination" and "Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys." The former study demonstrates the potential of interleukin-2 as an adjuvant for HIV vaccines[22]. The latter highly cited article proved that in rhesus monkeys challenged with highly pathogenic, heterologous, and neutralizing-resistant SIVMAC251, the improved vector vaccine significantly protected against infection[23]. These studies serve as a valuable reference for further investigation into the adjuvants, precursors, and vaccine modes of action for the HIV vaccine.

Highly cited references and their clustering

Highly cited reference

This analysis highlights the top four highly cited references, with the fourth publication having the highest betweenness centrality. The RV144 trial and subsequent analysis are the subjects of the first two highly cited articles[6,18]. Even though the ALVAC-HIV trial was deemed unsuccessful in later studies, RV144 provided researchers with significant encouragement and paved the way for further investigation. The third most frequently cited reference demonstrated that the recombinant adenovirus type 5 HIV-1 vaccine was ineffective[19]. The fourth reference can act as a bridge linking the other articles because it has the highest betweenness centrality among the top 10 highly cited references. This study identified two novel bnAbs from an HIV-positive African donor. In addition to the HIV vaccine, this study holds significance in other fields, such as immunotherapeutic approaches[24].

Reference clustering dependencies

Our results show that #5 cynomolgus monkey influences #1 neutralizing antibodies and #7 HIV-1 Gag, and #7 HIV-1 Gag affects #2 neutralizing antibody precursor. Consequently, #5 cynomolgus monkey bridges the two major clusters, #0 cytotoxic T lymphocyte and #1 neutralizing antibodies. The development of #7 HIV-1 Gag, #11 HIV transmission, #14 cov-2 infection, and #17 tuberculosis vaccine influenced #0 cytotoxic T lymphocyte. In the context of HIV vaccines, #14 HIV type and #17 tuberculosis vaccine exhibit weak direct correlations with neutralizing antibodies. This may be attributed to some research on neutralizing antibodies, which depends on the success of SARS-CoV-2 and the tuberculosis vaccine.

The clinical and experimental study of the HIV-1 vaccine is responsible for the creation of #1 neutralizing antibodies and #2 neutralizing antibody precursor, #5 cynomolgus monkey, and #7 HIV-1 Gag. Macaques are often used to study infection-induced antibody responses and evaluate vaccine candidates[25]. Simian immunodeficiency virus (SIV)-infected cynomolgus exhibits a disease pathogenesis pattern more similar to human HIV-1 infection than rhesus macaques[26]. Since bnAbs can target multiple conserved regions of HIV-1, one of the primary goals of vaccination is to induce bnAbs against the HIV-1 Env[27]. The immunogenicity and protective effectiveness of cynomolgus macaques were tested using HIV native Tat and V2 loop-deleted Env proteins. The HIV-1 Gag encodes the structural proteins of the matrix (p17) and core (p24, p7, p6)[28]. The relationship between Gag and cynomolgus is mainly reflected in the development of vaccines[29,30]. These vaccines were developed using the cynomolgus SIV model, which includes vaccines targeting the entire Gag and Env genes and vaccines based on the HIV clade-C Gag gene. In rhesus macaques, Virnik et al. employed vaccines delivered by rubella vectors, which elicited a strong and long-lasting immune response to the Gag and may stimulate the generation of bnAbs[31]. The #2 neutralizing antibody precursor is the third-largest cluster in this study. Prioritizing the activation of the bnAb precursor initiates specific germline-precursor B cell affinity maturation, which can produce bnAbs with greater affinity for the Env of HIV isolates[32]. In addition,

because Env glycoprotein is the primary target for vaccine design[33], another crucial aspect of HIV vaccines is the stimulation of precursor B cells for bnAbs.

The right side of figure 4B represents exploring the HIV vaccine mechanism. The core structure of this part contains #0 cytotoxic T lymphocyte, #3 synthetic peptide, and #10 follicular helper cell. A significant component of several early HIV vaccine investigations was synthetic peptide-based vaccines[34-36]. Synthetic peptides can minimize vaccine side effects while directing immune responses to precisely defined epitopes[37]. De Lucca et al. employed a cytotoxic T lymphoid (CTL) epitope synthetic peptide to activate CTLs successfully[38]. It proved the potential of synthetic peptides as an HIV vaccine.

During phase I clinical trials, synthetic peptide vaccines containing the immunogens PCLUS 6.1-18MN and PCLUS 3-18MN envelope peptides elicited strong CTL responses[39]. This study demonstrated that a vaccine can be designed to trigger HIV-specific cellular adaptive immune responses. In the GC, Tfh is a specific type of CD4+ T cell that supports B cells in producing durable, high-affinity humoral responses. The generation of bNAbs is likely influenced by the type and number of Tfh responses post-vaccination[40]. Consequently, the long-term bnAbs impact that Tfh induces continues to be essential for creating vaccines that have long-lasting effects.

The Landscape map shows how the clusters evolved. Among the early clusters, #3 synthetic peptide, #4 HIV type, #5 cynomolgus monkey, and #16 influenza vaccination can be considered in the foundation-laying phase. #2 neutralizing antibody precursor and #10 follicular helper cells have persisted until recent years and can be regarded as the vanguard of the HIV vaccine.

Keywords with time zone

Our study suggested that researchers demonstrated significant enthusiasm for developing an HIV vaccine in the early years. This growth peaked in 1991 as numerous keywords emerged. This era is a crucial phase, as investigators undertook numerous groundbreaking efforts, including exploring viral epitopes and antigens[41,42]. Many novel mechanisms were discovered and incorporated into vaccine design throughout the 2010s, for example, the "elite controllers" defined in 2005[43]. Despite not receiving antiretroviral medication, this group can sustain a steady viral load for an extended period. Given their unique capacity to regulate the viral load, this population has emerged as a critical resource for detecting HIV-neutralizing antibodies[44]. Compared to the 2010s, few new keywords have emerged, indicating no noteworthy advancement has occurred in the last few years.

Keywords with citation bursts

The keywords "cryo-EM structure," "nanoparticles," and "high throughput" can be considered key research frontiers and emerging methodologies in HIV vaccine design. Cryo-electron microscopy (cryo-EM) techniques have revolutionized infectious disease research by enabling multiscale visualization of biological structures in their near-native state[45]. This technology has facilitated the identification of potential specific epitope structures in recent years[46,47]. Nanotechnology has significantly advanced HIV vaccine development through multiple mechanisms, including nanoparticles that enhance immunogenicity, nanovaccines that can specifically target dendritic cells, and nanoparticles that facilitate the co-delivery of antigens while reducing adjuvant toxicity[48]. Meanwhile, high-throughput screening technology has proven highly effective in isolating antibodies from HIV-positive patients[49], making it a standard tool for identifying suitable antigens in antibody screening. Owing to the extensive use of these technologies, numerous novel antigenic epitopes and promising targets have emerged in recent years.

The effectiveness of vaccines has long been a subject of interest. From 2013 to 2023, "vaccine efficacy" emerged as a prominent keyword. Three exemplary studies were selected to illustrate the evolution and advancements in vaccine efficacy research from 2013 to 2023. A study led by Hammer et al. (2013) evaluated the efficacy of the DNA prime-recombinant adenovirus type 5 boost vaccine in 2,504 subjects[50]. The trial was eventually discontinued as it did not demonstrate sufficient efficacy. In 2017, Bradley et al. developed an ALVAC-based pentavalent B/E/E/E/E vaccine and tested it on rhesus monkeys. Ultimately, the study indicated that the vaccine reduced the risk of rhesus monkeys contracting neutralization-resistant viruses[51]. Recent research has highlighted the potential of priming using a mosaic antigen[52]. Although early vaccine efficacy was suboptimal, ongoing research advancements and the emergence of new technologies continue to yield promising findings and outcomes.

We extracted two significant obstacles to HIV vaccine design from the burst keywords: "reservoir" and "glycosylation." When ART is discontinued, HIV reservoir cells may reactivate and repopulate the virus[53]. This poses

a significant challenge to vaccine efficacy. A prolonged HIV latency period may contribute to vaccine failure. Fortunately, Zhao et al. found evidence that follicular regulatory T could assist in eradicating HIV reservoirs[54]. Pathogens frequently employ glycosylation to evade the immune system, as viruses can shield immunogenic epitopes using their polysaccharides[55]. Therefore, glycosylation presents opportunities and challenges in vaccine development that must be fully appreciated.

Eight keywords were extracted to guide subsequent vaccine research, including "structural basis," "antibody-dependent cellular cytotoxicity," "germinal center," "trimers," "spike protein," "affinity maturation," and "NK cell." Antibodies target specific structures on the surface of the virus to mediate immune responses. Most antibodies target the Env protein within the gp120 cluster A region[56]. On the Env gp41 subunit, the membrane-proximal external region is highly conserved[57]. After manual management, the keyword "dependent cellular cytotoxicity" outputted by the software should be "antibody-dependent cellular cytotoxicity." Recently, numerous researchers have extensively studied the potential of ADCC to elicit an immunological response. Most antibodies bind to Env on the surface of virus-infected cells, facilitating ADCC-mediated clearance of infected cells[58]. Relevant data indicated that the risk of infection in the vaccine trial was inversely correlated with ADCC[59]. Therefore, controlling the ADCC at a high level is crucial to vaccine security and effectiveness. GC in secondary lymphoid organs generates plasma cells and memory B lymphocytes, which mediate humoral immune memory[60]. Evidence is growing that the duration of the GC reaction is a key determinant of antibody response strength[61,62]. It means that the creation of vaccines is related to understanding the factors that improve GC duration. Antibody affinity maturation protects the immune system against various diseases[63]. Mature antibody affinity is crucial for an effective vaccine. Nevertheless, multiple factors constrain the process, including the mutability of immunoglobulin genes, the development of activation-induced cytidine deaminase targeting mechanisms within them, and biases in targeting specific epitope B cells[64]. The protective immunity against HIV infection conferred by the vaccine has been associated with indirect NK cell-mediated ADCC[65]. Increasing NK cell activity can help prevent disease or eradicate viral reservoirs before or during infection[66]. Thereby, additional research on NK cells may play a role in advancing the development of HIV vaccines.

Obstructions and prospects

This study focused on the history and frontiers of the HIV vaccine, providing insights into advancements and challenges in this field. Even though numerous trials have been conducted, most human trials have demonstrated suboptimal efficacy. Based on the keyword burst analysis results, viral reservoirs and the difficulty in generating potent bnAbs are the main challenges of concern to researchers. Preliminary findings suggest that these issues may be resolved. Research into glycosylation, a viral mechanism that aids immune evasion, may facilitate adjuvant development and enhance vaccine efficacy. Pathogen epitopes have been extensively explored as antigenic targets to induce long-term, effective neutralizing antibodies. In recent years, new technologies, including cryo-EM, nanotechnology, and high-throughput screening, have improved the ability to investigate these epitopes. These technological advancements, combined with in-depth research into physiological processes such as affinity maturation, function of GC, and ADCC, promise to enhance HIV vaccine efficacy. Future studies should separately target Tfh/GC B cell-driven antibody maturation and NK cell-mediated Fc-dependent effector functions to enhance vaccine durability comprehensively. Overall, integrating these research directions and technologies could be instrumental in addressing current challenges and developing a successful HIV vaccine.

Limitation

Because of CiteSpace's limit, our data can only be downloaded from WOSCC, which leads to insufficient data collection. It is necessary to conduct more in-depth analysis on paper using more databases. It is inevitable that during the retrieval process, papers unrelated to the topic will surface to guarantee that as many relevant topic papers as possible are included in the experiment, which may cause a few minuscule variations in the structure. More articles will be released in the future. Therefore, this analysis may not adequately capture the exact nature of ongoing HIV research. In addition, the study design and the software tools used limit our ability to fully explore statistical interactions, confounding factors, or hierarchical associations between or across the variables. While we have attempted to mitigate this limitation through manual verification, the potential for misinterpretation analysis remains. This limitation may influence the interpretation of some visual findings.

Conclusion

This study provides a comprehensive scientometric analysis of HIV vaccine research over the past 35 years, highlighting key trends, emerging technologies, and persistent challenges. The US has been the dominant contributor, with institutions such as the NIH and Harvard University at the forefront of research output. Transformative technologies such as cryo-EM and nanoparticle delivery systems have emerged as critical tools. Structural biology, GC dynamics, ADCC, and glycosylation shielding are central to advancing HIV vaccine development. Despite the lack of a licensed HIV vaccine, progress in antigen design, adjuvant strategies, and advanced technologies offers hope for future breakthroughs. However, significant challenges persist, including eliciting targeted immune responses to novel epitopes and overcoming glycosylation-mediated immune evasion. Future research should optimize GC reactions to enhance B-cell affinity maturation, leverage cryo-EM for structure-guided epitope targeting, and advance antigen delivery. In addition, integrating studies on Tfh cell dynamics could address challenges related to the durability of immune responses. This analysis underscores the importance of multidisciplinary approaches, combining mechanistic insights with innovative technologies, to overcome the hurdles in HIV vaccine development and ultimately achieve success.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.25000018. 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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Author contributions

X. Chen: Methodology, Data Curation, Visualization, Writing – Original draft preparation. Y. Zhuo: Data curation, Investigation, Validation, Writing – Review & Editing. Y. Lai: Validation, Project administration, Funding acquisition, Writing — Reviewing, and Editing.

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Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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