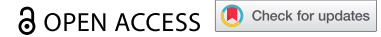


RESEARCH PAPER



HIV-1 genetic diversity a challenge for AIDS vaccine development: a retrospective bibliometric analysis

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ABSTRACT

Background: Despite recent advances in human immunodeficiency virus-1 (HIV-1) prevention, a fast, safe, and effective vaccine will probably be necessary to end the HIV/AIDS pandemic. This study was conducted to evaluate global research trends and map the key bibliometric indices in HIV-1 genetic diversity from 1998 to 2021.

Methods: A comprehensive online search was conducted in the Web of Science Core Collection database to retrieve published literature on HIV-1 genetic diversity. Key bibliometric indicators were calculated and evaluated using HistCiteTM, Bibliometrix: An R-tool, and VOSviewer software for windows.

Results: A total of 2,060 documents written by 9,201 authors and published in 250 journals were included in the final analysis. Year 2012 was the most productive year with 121 (5.87%) publications. The most prolific author was Shao Yiming (n = 74, 3.59%) from Chinese Center for Disease Control and Prevention. The United States of America was the highly contributing and influential country (n = 681, 33.05%). *AIDS Research and Human Retroviruses* was the most productive journal (n = 562, 27.2%). Network visualization shows that HIV-1 was the most widely used author keyword.

Conclusion: This study provides global research trends and detailed information on HIV-1 genetic diversity. The amount of scientific literature on HIV-1 genetic diversity research has rapidly increased in the last two decades. The maximum number of articles on HIV-1 genetic diversity was published in developed countries; therefore, a scientific research collaboration among researchers and institutes in low-income countries should be promoted and supported.

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Introduction

In the last few decades, human immunodeficiency virus-1 (HIV-1) seriously threatened global public health and disease surveillance systems, particularly in low-income countries. An estimated 37.6 million (30.2–45.0 million) people infected globally were living with HIV-1 in 2020, and 1.5 million (1.1–2.1 million) people were newly infected.¹ Despite the availability of HIV-1 antiretroviral drugs, approximately 690,000 (480,000–1 million) people died from acquired immunodeficiency syndrome (AIDS) related illnesses in 2020.¹ The currently available antiviral therapy is the only mean to prevent progression of HIV-1 infected patients to AIDS. The development of an effective vaccine is a necessity that may dwindle the need for antiviral therapy.²

HIV-1, like other human RNA viruses, has a high genetic variability that emanates from its high mutation rates,³ retroviral recombination, and high viral turnover.^{4,5} HIV-1 has been divided into four genetically distinct groups: M, O, N, and P. The vast majority of infections worldwide are caused by group M lineages, which have further diversified into 10 distinct subtypes A, B, C, D, F, G, H, J, K, and L.^{6–8} Genetic distance within a subtype can be 15 to 20%, whereas genetic distances between subtypes are normally

25 to 35%.³ Recombination between group M subtypes has led to the generation of circulating recombinant forms (CRFs) and unique recombinant forms (URFs).⁹ Till now, 118 distinct CRFs have been identified globally,¹⁰ and these CRFs responsible for 16.7% of all global HIV infections.⁶

The global HIV-1 genetic diversity is a major stumbling block to the successful design of an effective HIV/AIDS vaccine, as well as antiretroviral therapy, diagnostic and viral load assays.¹¹ Information about country-level HIV-1 diversity help in the successful design of subtype-specific vaccines that can benefit specific countries and regions.¹²

Bibliometric is the quantitative analysis of scholarly publications concerned about one special topic by statistical and mathematical methods.¹³ Bibliometric analysis is increasingly used when studying various aspects of science and how worldwide universities and institutions are ranked.^{14,15} In recent years, the quantity of bibliometric studies in various fields has significantly increased. Several bibliometric studies have been published on HIV/AIDS.^{16–18} However, to the best of our knowledge, no bibliometric analysis on HIV-1 genetic diversity research has been published to date. Bibliometric analysis of

the high number of research publications related to HIV-1 genetic diversity is not only useful providing crucial information for epidemiological assessments and public health interventions, but also to determine future research direction, and new research frontiers. Therefore, in this study we evaluated the global research output and mapped key bibliometric indices in HIV-1 genetic diversity research from 1998 to 2021.

Methods

Study design

The study used a retrospective bibliometric design.

Searching database

On May 15, 2021, the online search was conducted in the Web of Science Core Collection (WoSCC) database hosted by Clarivate Analytics to retrieve scientific publications on HIV-1 genetic diversity from 1998 to May 15, 2021. Web of Science is a comprehensive digital repository of published literature used globally.¹⁹

Search strategy and data collection

Two researchers (Abdur Rashid and Kang Li) independently conducted the online search, any disagreements related to inclusion and exclusion were resolved with the help of another researcher (Tauseef Ahmad). The search criteria for the included publications were the following: Topic: (HIV-1 genetic diversity), or Topic: (HIV-1 subtype), or Topic: (HIV-1 CRF), or Topic: (HIV-1 recombinant form), or Topic: (HIV-1 unique recombinant form), or Topic: (HIV-1 second-generation recombinant form), or Topic: (Novel HIV Type 1 recombinant form), or Topic: (HIV-1 genetic diversity and vaccine), or Topic: (HIV-1 genetic diversity impact on vaccine). The search was limited to English language and time span (from 1998 to May 15, 2021). To ensure data accuracy, the titles and abstracts of the published documents were screened carefully. The retrieved data were downloaded in plaintext and CSV format. The following data were extracted from the retrieved documents; title, author name, year of publication, journal, institution, country, and citations count. All the data were retrieved from WoSCC on May 15, 2021, to avoid bias in data collection because the WoSCC database is updated daily.

Data analysis

The obtained data were exported into Microsoft Excel 2019 and the values were presented in frequencies and percentages. The required graphs were generated using GraphPad Prism 8.0 software.

Bibliometric indicators analyses

Various bibliometric indicators, including the number of publications per year, most prolific authors, top journals, most active institutions, countries, frequently used author keywords, and highly cited articles were calculated and evaluated to assess the impact of the published articles using HistCiteTM([http://](http://www.histcite.com/)

www.histcite.com/).²⁰ Furthermore, Bibliometrix: An R-tool was used to construct corresponding authors' countries and wordcloud analysis, and calculate mean total citations per year.²¹ In addition, the obtained data were plotted for coauthorship countries, author keywords, and cited sources network visualization using VOSviewer software version 1.6.16 for windows (<http://www.vosviewer.com/>).²²

Ethical consideration

No ethical approval was required.

Results

The annual quantity of publications

In this study, a total of 2,060 documents published in English language on HIV-1 genetic diversity were analyzed. Majority of the documents were published in the form of original articles (n = 1831, 88.89%) and reviews (n = 98, 4.76%) as shown in Table 1. The changing trend of the annual quantity of publications between 1998 and 2021 is presented in Figure 1. After 1999, growing research productivity was observed, where the highest number of documents (n = 121, 5.87%) were published in 2012, followed by year 2019 (n = 120, 5.82%), while only (n = 22, 1.06%) documents were published in 1998. In the first few months of 2021, (n = 27, 1.31%) documents have been published, which are predicted to rise more in the coming months of the year 2021.

Most active authors

A total of 9,201 authors have been involved in HIV-1 genetic diversity publications. In total, only 184 authors had published at least 10 articles each. Based on number of publications, Shao YM was the most prolific author (n = 74, 3.59%), followed by

Table 1. Main information about the retrieved data on HIV-1 genetic diversity from WoSCC database.

Description	Results
Time span	1998–2021
Countries	125
Journals	263
Documents	2060
References	27556
Document type	
Articles	1831
Reviews	98
Proceedings paper	43
Meetings abstract	36
Letters	26
Editorial materials	11
Early access	10
Corrections	3
Data papers	1
Book chapters	1
Authors collaboration	
Single-authored documents	31
Documents per Author	0.224
Authors per Document	4.47
Coauthors per Documents	8.91
Collaboration Index	4.52

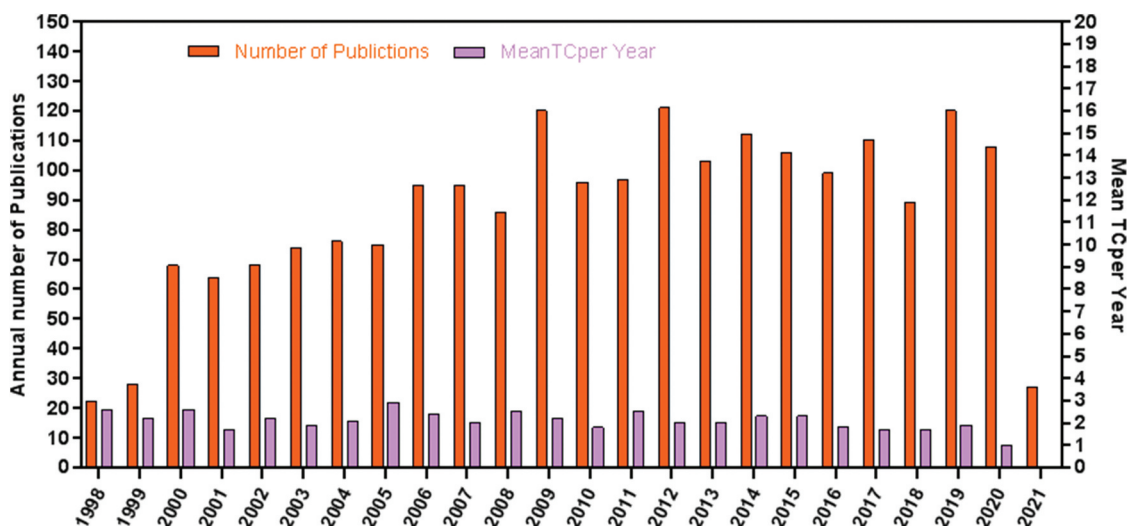


Figure 1. Annual distribution of publications on HIV-1 genetic diversity from 1998- May 15, 2021.

Table 2. Top 10 most prolific authors ranked by total number of publications.

Rank	Author	NP	Country	Affiliation	PY_start	h_index	TC	%
1	Shao YM	74	China	CDC, China	2000	19	1270	3.59
2	Peeters M	60	France	University of Montpellier	1998	30	3053	2.91
3	Feng Y	59	China	CDC, China	2004	13	570	2.86
4	McCutchan FE	52	USA	Henry M. Jackson Foundation	1998	31	3040	2.52
5	Xing H	49	China	CDC, China	2004	16	722	2.37
6	Carr JK	48	USA	School of Medicine University of Maryland	1998	26	2266	2.33
7	Li JY	47	China	Beijing Institute of Microbiology and Epidemiology	2008	13	473	2.28
8	Bello G	45	Brazil	Oswaldo Cruz Institute	2006	16	608	2.18
9	Morgado MG	45	Brazil	Oswaldo Cruz Institute	2000	18	962	2.18
10	Delaporte E	43	France	University of Montpellier	1998	24	1959	2.08

NP: Number of Publications, TC: Total Citations, PY: Publication Year.

Peeters M (n = 60, 2.91%), and Feng Y (n = 59, 2.86%) as presented in Table 2. Furthermore, the top 10 authors' productions over the time as shown in Figure 2.

Most productive journals

The retrieved documents (n = 2,060) were published in 250 journals. In total, only 30 journals published at least 10 articles on HIV-1 genetic diversity. Majority of documents were published in *AIDS Research and Human Retroviruses* (n = 562, 27.2%), followed by *PLoS ONE* (n = 156, 7.57%), and *AIDS* (n = 108, 5.2%). The top 10 journals published 61% of the analyzed documents as shown in Table 3. Among the top 10 most productive journals, the *Journal of Clinical Microbiology* holds the highest IF 5.345, a Q1 category journal published from the USA. An annual number of publications published by the top 10 listed journals as shown in Figure 3.

Most active institutions

A total of 2,821 institutions in 125 countries contributed to the articles, and amongst them, only 131 institutions published at least 10 articles on HIV-1 genetic diversity. Institutes that published 30 or more documents have been considered as the most active institutions. The top 10 active institutions, in terms of publishing original articles on HIV-1 genetic diversity, were the Chinese Center for Disease

Control and Prevention (n = 78, 3.78%), followed by the Center for Disease Control and Prevention, USA (n = 76, 3.68%), and Walter Reed Army Institute of Research, USA (n = 72, 3.5%) as shown in Table 4.

Most active corresponding authors' countries

A total of 125 countries were found to be involved in HIV-1 genetic diversity research; among them the most productive countries were USA (NP = 681, 33.0%), followed by China (NP = 329, 15.9%), Brazil (NP = 213, 10.3%), and UK (NP = 177, 8.5%). In addition, the USA was the most collaborative country with publications having authors from multiple countries publications (NP = 284), followed by China (NP = 65), and Brazil (NP = 44), as shown in Table 5. The annual distribution of HIV-1 genetic diversity research and the contributions of different countries are presented in Figure 4. The mutual collaboration between the most active corresponding authors' countries contributed to HIV-1 genetic diversity research is presented in Figure 4.

Top 20 highly cited publications

The top 20 highly cited publications on HIV-1 genetic diversity are presented in Table 6. Among the top 20 publications, 17 were research articles, and 3 were review

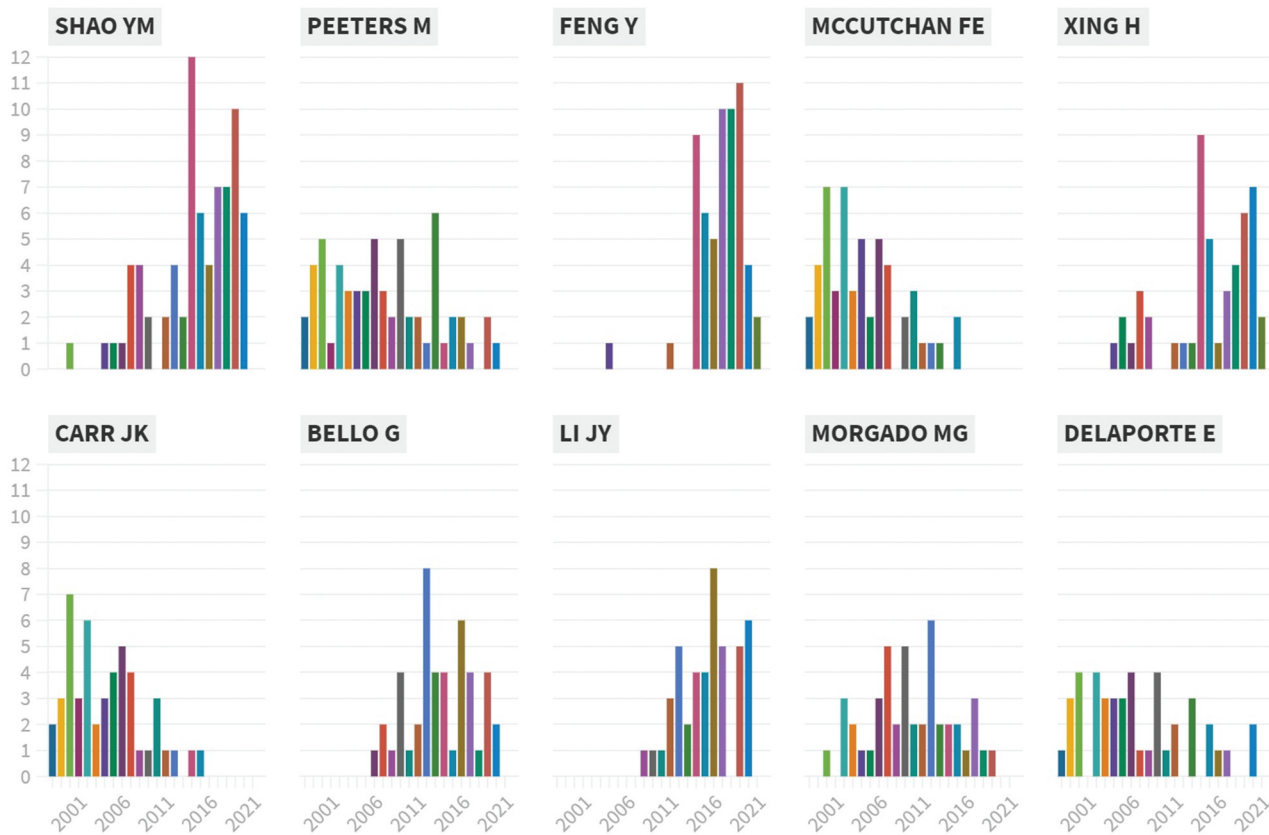


Figure 2. Top 10 most prolific authors' in HIV-1 genetic diversity.

Table 3. Top 10 journals in HIV-1 genetic diversity research.

Rank	Journal Name	NP	h_index	TC	%	2020 IF	5 Year IF	JQ	Publisher	PC
1	AIDS Research and Human Retroviruses	562	40	8477	27.28	2.205	2.096	Q4	Mary Ann Liebert	USA
2	PLoS ONE	156	23	2115	7.57	3.24	3.788	Q2	Open Access Scholarly Publisher	USA
3	AIDS	108	41	5352	5.24	4.177	4.759	Q3	Wolters Kluwer	USA
4	Journal of Virology	91	46	6946	4.41	5.103	5.078	Q1	American Society for Microbiology	USA
5	JAIDS-Journal of Acquired Immune Deficiency Syndromes	76	30	2160	3.68	3.731	4.064	Q3	Lippincott	USA
6	Journal of Medical Virology	69	19	1115	3.34	2.327	2.075	Q4	Wiley-Blackwell	USA
7	Infection Genetics and Evolution	60	15	932	2.91	3.342	3.188	Q3	Elsevier	Netherlands
8	Retrovirology	48	18	1080	2.33	4.602	4.199	Q2	BioMed Central	England
9	Journal of Clinical Microbiology	41	25	1654	1.99	5.948	5.345	Q1	American Society for Microbiology	USA
10	Virology	38	19	1170	1.84	3.616	3.967	Q3	Elsevier	USA

NP: Number of Publications. TC: Total Citations. IF: Impact Factor. JQ: Journal Quartile. PC: Publisher Country.

articles. The most highly cited document was a research article “Human immunodeficiency virus type 1 env clones from acute and early subtype B infections for standardized assessments of vaccine-elicited neutralizing antibodies” published in *Journal of Virology* by Li M *et al.*, 2005 cited 870 times, followed by “Timing the ancestor of the HIV-1 pandemic strains” published in *Science* by Korber B *et al.*, 2000 cited 622 times. The top 20 highly cited publications on HIV-1 genetic diversity had citations ranging from 195 to 870.

Coauthorship countries network visualization

Growing evidence shows that a scientific collaboration network between countries helps admire the countries with potential in the relevant research area.²³ The coauthorship countries analysis reflects the degree of collaboration among researchers from different countries based on total link strength. The minimum number of country publications was set at 10, and the number of coauthorship countries per/publication was set at 25. Among the analyzed countries, only 50 countries met the

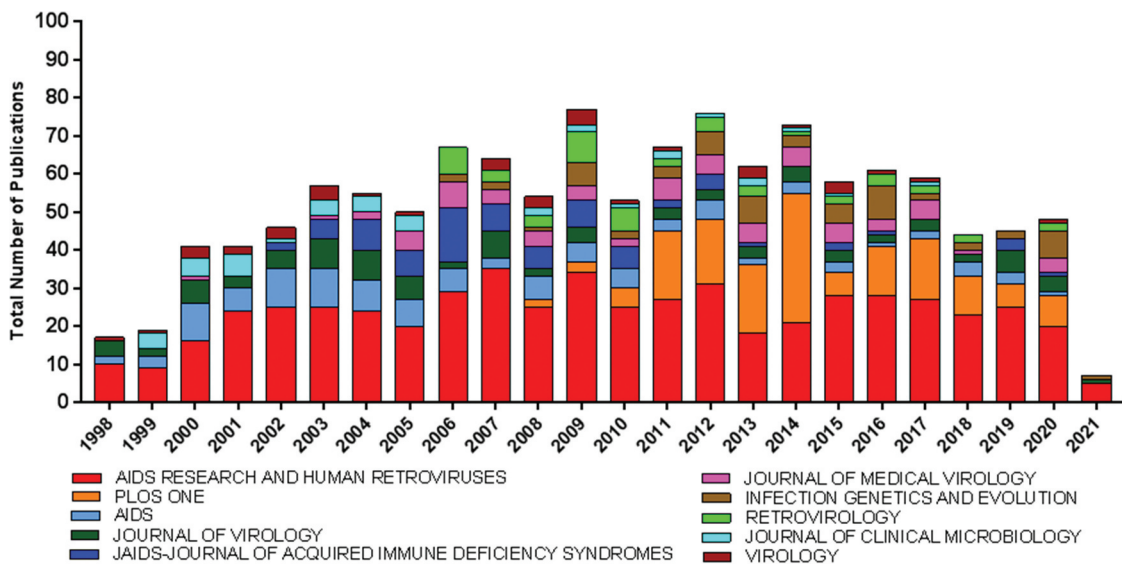


Figure 3. Top 10 journals annual distribution of publications on HIV-1 genetic diversity.

Table 4. Top 10 most productive institutions ranked by number of publications.

Rank	Institution	Country	NP	TC	%
1	CDC, China	China	78	988	3.78
2	CDC, USA	USA	76	2466	3.68
3	Walter Reed Army Institute of Research	USA	72	2799	3.49
4	University of Oxford	UK	68	3457	3.30
5	Instituto de Salud Carlos III	Spain	60	1724	2.91
6	Henry M. Jackson Foundation	USA	54	4073	2.61
7	National Institute of Infectious Diseases	USA	52	1299	2.52
8	Oswaldo Cruz Institute	Brazil	50	864	2.42
9	Harvard University	USA	50	1505	2.42
10	John Hopkins University	USA	49	1874	2.37

NP: Number of Publications, CDC: Center for Disease Control and Prevention, TC: Total Citations.

thresholds and formed 9 clusters. The size of each node represents the number of published documents by a country. The USA was the leading country with (TLS = 524), followed by China (TLS = 93), Brazil (TLS = 75), France (TLS = 119), and

England (TLS = 141). The USA and China are the most active countries, and both have a high frequency of international collaboration. The thickness of each link represents the strength of collaboration between two countries. The distance between two nodes represents the relatedness of the links they each have.²⁴ Network visualization map of coauthorship countries is shown in Figure 5.

Author keywords network visualization

Before submitting a manuscript to a journal, the author is required to write keywords that reflects the main ideas presented in the article. The keywords analysis provides a medium for discovering key research areas.²³ In this context, occurrence shows the number of articles where a keyword occurs, while co-occurrence means how often a keyword occurs with other

Table 5. Top 20 prolific corresponding authors countries and their collaborative publications.

Country	Total Articles	Total citations	Average Article Citations	Single Country Publications	Multiple Country Publications	Multiple Country Publications Ratio
USA	486	19,187	39.48	202	284	0.584
CHINA	323	3,161	9.79	258	65	0.201
BRAZIL	181	2,894	15.99	137	44	0.243
FRANCE	115	2,991	26.01	52	63	0.548
SPAIN	94	2,168	23.06	60	34	0.362
ITALY	66	964	14.61	47	19	0.288
JAPAN	62	1,332	21.48	18	44	0.71
UNITED KINGDOM	60	2,597	43.28	29	31	0.517
SOUTH AFRICA	54	892	16.52	18	36	0.667
CANADA	48	1,153	24.02	28	20	0.417
INDIA	43	529	12.3	35	8	0.186
BELGIUM	36	1,286	35.72	8	28	0.778
AUSTRALIA	28	465	16.61	17	11	0.393
GERMANY	26	454	17.46	4	22	0.846
THAILAND	26	707	27.19	10	16	0.615
ARGENTINA	25	325	13	11	14	0.56
SWEDEN	25	659	26.36	11	14	0.56
PORTUGAL	24	542	22.58	10	14	0.583
RUSSIA	23	296	12.87	16	7	0.304
NETHERLANDS	19	401	21.11	9	10	0.526

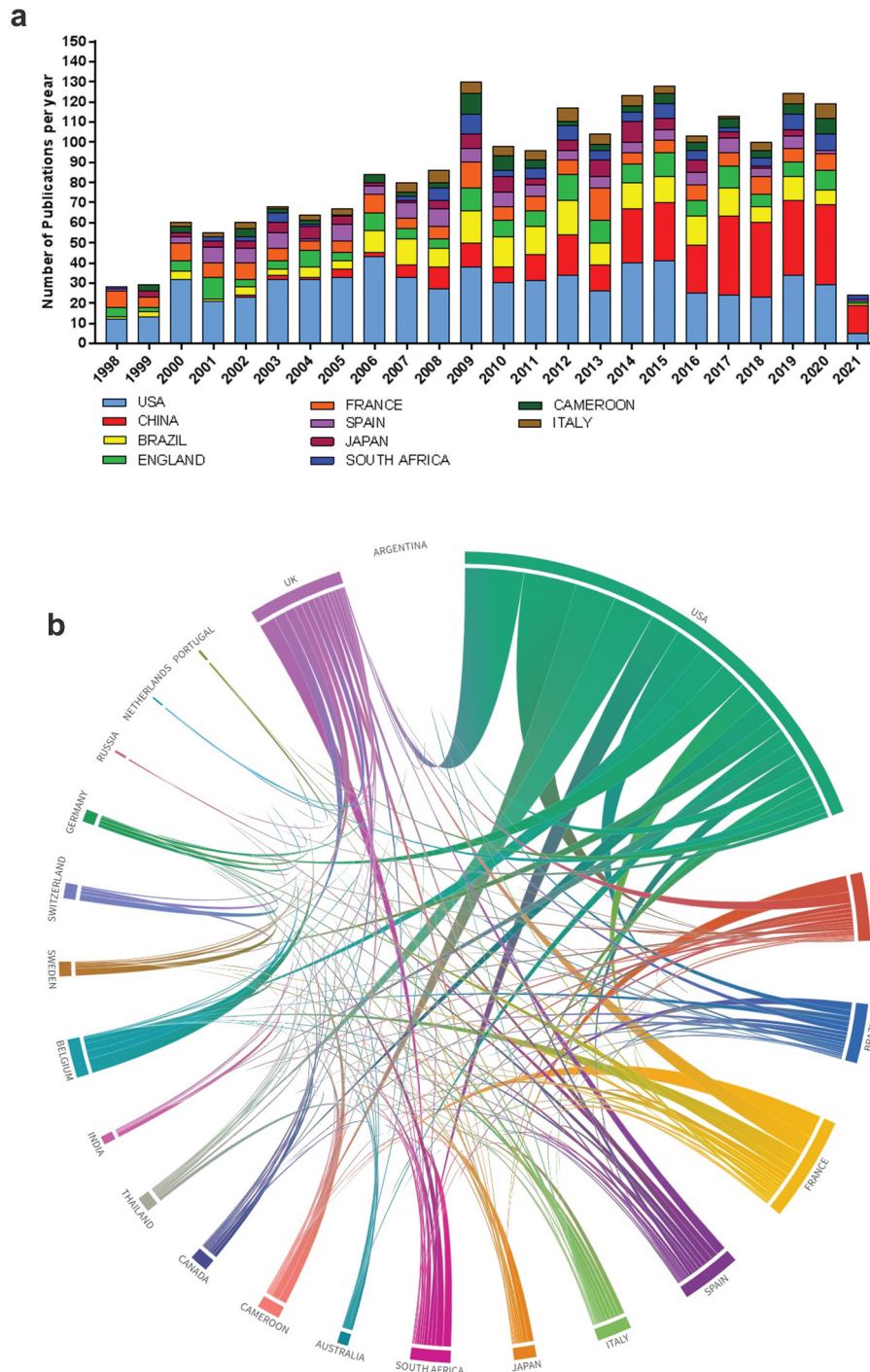


Figure 4. (a) Corresponding authors' countries annual distribution of publications. (b) Mutual collaboration between the corresponding authors' countries in HIV-1 genetic diversity research.

keywords. Keywords with a strong co-occurrence relationship can divulge research hotspots more accurately than a single keyword. A minimum occurrence of author keywords was set at 10. Among the analyzed keywords, only 62 met the threshold and formed 8 clusters. HIV-1 was the most frequently used author keyword (TLS = 362), followed by HIV (TLS = 160), molecular epidemiology (TLS = 97), subtypes (TLS = 80), and vaccine (TLS = 52). Keywords with the greatest total link strength as shown in Figure 6. The link strength between two keywords is premised on the number of documents both keywords mutually occur, exploring the specific research spot's relationship. The

link's thickness is proportional to the strength of the link in the network.²⁴ In our visualization analysis, closely connected keywords were colored the same, indicating that they might share something in common. The orange color keywords nodes are related to vaccine research (envelope, evolution, gp120, and diversity). The keywords in red and blue nodes are mainly related to epidemiology. The nodes in purple are related to virology (genotype, protease, mutation, drug resistance, antiretroviral therapy, reverse transcriptase, and AIDS). Wordcloud visualization of frequently used authors' keywords in the WoSCC database is presented in Figure 6.

Table 6. Top 20 highly cited publications on HIV-1 genetic diversity.

Title	Journal	Document type	Date of Publication	Corresponding author's Country	Total Citations (TC)	Average TC per Year	DOI
Human immunodeficiency virus type 1 env clones from acute and early subtype B infections for standardized assessments of vaccine-elicited neutralizing antibodies	<i>Journal of Virology</i>	Article	AUG 2005	USA	870	51.1765	10.1128/JVI.79.16.10108-10125.2005
Timing the ancestor of the HIV-1 pandemic strains	<i>Science</i>	Article	JUN 2000	USA	622	28.2727	10.1126/science.288.5472.1789
Global trends in molecular epidemiology of HIV-1 during 2000–2007	<i>AIDS</i>	Article	MAR 2011	England	520	47.2727	10.1097/QAD.0b013e328342ff93
Deciphering human immunodeficiency virus type 1 transmission and early envelope diversification by single-genome amplification and sequencing	<i>Journal of Virology</i>	Article	APR 2008	USA	448	32	10.1128/JVI.02660-07
Global and regional distribution of HIV-1 genetic subtypes and recombinants in 2004	<i>AIDS</i>	Article	OCT 2006	Switzerland	415	25.9375	10.1097/01aids.0000247564.73009.bc
Human Immunodeficiency Virus Type 1 Elite Neutralizers: Individuals with Broad and Potent Neutralizing Activity Identified by Using a High-Throughput Neutralization Assay together with an Analytical Selection Algorithm	<i>Journal of Virology</i>	Article	JUL 2009	USA	397	30.5385	10.1128/JVI.00110-09
Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960	<i>Nature</i>	Article	OCT 2008	USA	327	23.3571	10.1038/nature07390
The early spread and epidemic ignition of HIV-1 in human populations	<i>Science</i>	Article	OCT 2014	England	288	36	10.1126/science.1256739
Understanding the genetic diversity of HIV-1	<i>AIDS</i>	Review	2000	USA	285	12.9545	NA
An African HIV-1 sequence from 1959 and implications for the origin of the epidemic	<i>Nature</i>	Article	FEB 1998	USA	268	11.1667	10.1038/35400
Estimated global distribution and regional spread of HIV-1 genetic subtypes in the year 2000	<i>JAIDS</i>	Article	FEB 2002	Switzerland	259	12.95	NA
A recent outbreak of human immunodeficiency virus type 1 infection in southern China was initiated by two highly homogeneous, geographically separated strains, circulating recombinant form AE and a novel BC recombinant	<i>Journal of Virology</i>	Article	DEC 2000	USA	250	11.3636	10.1128/JVI.74.23.11286-11295.2000
Accurate sampling and deep sequencing of the HIV-1 protease gene using a Primer ID	<i>Proceedings of the national academy of sciences of the United States of America</i>	Article	DEC 2011	USA	246	22.3636	10.1073/pnas.1110064108
Antigenic conservation and immunogenicity	<i>Journal of Experimental medicine</i>	Article	May 2005	USA	241	14.1765	10.1084/jem.20042510
Inflammatory Genital Infections Mitigate a Severe Genetic Bottleneck in Heterosexual Transmission of Subtypes A and C HIV-1	<i>PLOS PATHOGENS</i>	Article	JAN 2009	USA	237	18.2308	10.1371/journal.ppat.1000274
A comprehensive panel of near-full-length clones and reference sequences for non-subtype B isolates of human immunodeficiency virus type 1	<i>Journal of Virology</i>	Article	JUL 1998	USA	237	9.875	10.1128/JVI.72.7.5680-5698.1998
Unprecedented degree of human immunodeficiency virus type 1 (HIV-1) group M genetic diversity in the Democratic Republic of Congo suggests that the HIV-1 pandemic originated in Central Africa	<i>Journal of Virology</i>	Article	NOV 2000	France	230	10.4545	10.1128/JVI.74.22.10498-10507.2000
Minireview- Human immunodeficiency virus type 1 subtype distribution in the worldwide epidemic: Pathogenic and therapeutic implications	<i>Journal of Virology</i>	Review	OCT 2007	Italy	217	14.4667	10.1128/JVI.00872-07
Selection for human immunodeficiency virus type 1 envelope glycosylation variants with shorter V1-V2 loop sequences occurs during transmission of certain genetic subtypes and impact viral RNA levels	<i>Journal of Virology</i>	Article	May 2005	USA	206	12.1176	10.1128/JVI.79.10.6528-6531.2005
Genetic diversity of HIV-1: the moving target	<i>AIDS</i>	Review	2000	France	195	8.8636	NA

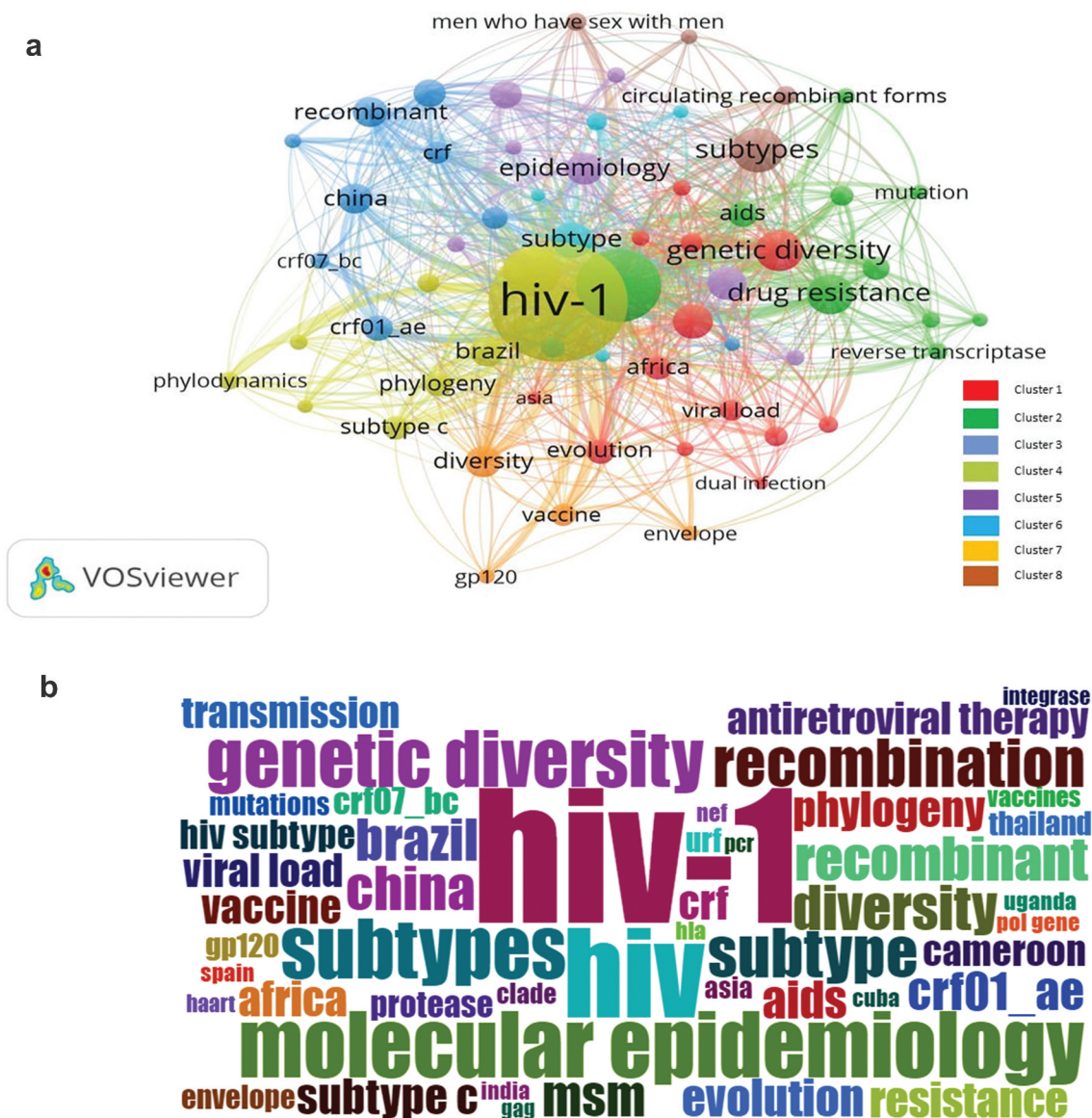


Figure 6. (a) Author keywords co-occurrence network visualization. Eight clusters were formed; Cluster 1: (13 keywords) Cluster 2: (10 keywords), Cluster 3: (9 keywords), Cluster 4: (9 keywords), Cluster 5: (7 keywords), Cluster 6: (6 keywords), Cluster 7: (4 keywords), cluster 8: (4 keywords). (b) Authors' keywords wordcloud visualization analysis.

adequate research funding and high international collaboration. *AIDS Research and Human Retroviruses* was the most prominent and productive journal contributing to HIV-1 genetic diversity research, followed by *the Journal of Virology* with total citations of 8,477 and 6,946. These top journals are very responsive to new emerging subtypes or recombinants of HIV-1 and with coverage ranging from the molecular basis of the virus to clinical trials on vaccines. All the top 10 journals' contributions to HIV-1 genetic diversity are stunning and promoted the effective dissemination of pedantic evidence to contend the variability of HIV-1 in developing an HIV-1 vaccine. Shao YM was the most active researcher in the field of HIV-1 genetic diversity research. His research laboratory identified different HIV-1 circulating recombinant forms CRFs among HIV-1 infected Chinese patients and submitted to Los Alamos National Laboratory CRF62_BC,³¹ CRF64_BC,³² CRF65_cpx,³³ CRF79_0107,³⁴ CRF106_cpx.³⁵

Among the most active authors who published more articles on HIV-1 genetic diversity came from the Chinese CDC, French National Research Institute for Sustainable Development (IRD),

or Henry M. Jackson Foundation. Most of these authors have collaborated in publishing articles on HIV-1 genetic diversity and belong to the same institutions. The above statement highlights that research collaboration among researchers from different countries needs to be promoted. It is interesting to note that 39.4% of the publications on HIV-1 genetic diversity were collaborative publications. Like other research areas,³⁶⁻⁴¹ the USA was the leading country in HIV-1 genetic research collaboration; the collaborative publications between the USA and China were 3.4%. Compared to developed countries, the collaboration between developing countries was negligible. Chinese institutions research is largely conducted in the area of HIV-1 epidemiology. The majority of highly cited articles research was about HIV-1 vaccine published by the institutions in USA. The country-wise publication pattern indicates that research on HIV-1 diversity in a developing country is very low highlights that research must be supported in developing countries to identify the most common HIV-1 strains circulating that can help in the development of a therapeutic vaccine against

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