A bibliometric analysis of HIV-1 drug-resistant minority variants from 1994 to 2022

Chang Yan  
Beijing Ditan Hospital, Capital Medical University, Beijing

Fengting Yu  
Beijing Ditan Hospital, Capital Medical University, Beijing

Mengying Li  
Medical School, University of Chinese Academy of Sciences, Beijing

Xiaojie Yang  
Beijing Ditan Hospital, Capital Medical University, Beijing

Rui Sun  
Beijing Ditan Hospital, Capital Medical University, Beijing

Xuelei Liang  
Beijing Ditan Hospital, Capital Medical University, Beijing

Xiaojie Lao  
Beijing Ditan Hospital, Capital Medical University, Beijing

Hanxi Zhang  
Beijing Ditan Hospital, Capital Medical University, Beijing

Wenhao Lv  
Beijing Ditan Hospital, Capital Medical University, Beijing

Ying Hu  
Beijing Ditan Hospital, Capital Medical University, Beijing

Yuan Lai  
Beijing Ditan Hospital, Capital Medical University, Beijing

Yi Ding  
Beijing Ditan Hospital, Capital Medical University, Beijing

Fujie Zhang  

treatment@chinaaids.cn

Beijing Ditan Hospital, Capital Medical University, Beijing

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Abstract

Background

The rapid initiation of antiretroviral therapy has become an international trend, necessitating lifelong medication for all HIV patients. Sanger sequencing, as the gold standard for clinically detecting HIV drug resistance, often fails to detect mutations comprising less than 20% of the total viral population. With the advancement of detection technologies, HIV-1 DRMinVs have garnered increasing attention. However, there are few studies exploring the hotspots and trends in this field. Fortunately, bibliometrics, a novel approach to literature analysis, can fill this gap effectively.

Methods

Publications related to HIV-1 DRMinVs from 1994 to 2022 were searched on the WoSCC database. Visual knowledge maps and bibliometric analyses were generated using VOSviewers, CiteSpace, and the R package "bibliometrix."

Results

In total, 853 publications concerning HIV-1 DRMinVs were identified from 1994 to 2022, demonstrating a steady increase in publication output over the years. The United States, France, and the United Kingdom significantly lead in publication output. The main research institutions are Harvard University, University of Pittsburgh, Stanford University and National Cancer Institute. The Journal of Antimicrobial Chemotherapy holds the highest prominence among journals in this domain, while the Journal of Virology emerges as the most frequently co-cited journal. A total of 5687 authors have contributed to these publications. Among them, Vincent Calvez, Francesca Ceccherini-Silberstein, and John M. Coffin emerge as the most prolific authors, having published the highest number of articles. Additionally, Metzner, KJ emerges as the most frequently co-cited author. The main trends include the origins, molecular epidemiology, detection methods of DRMinVs, their impact on virological outcomes in drug-naïve patients, and novel research focuses primarily revolve around keywords such as "NGS," "ART," "VF," and "GRT."

Conclusions

The use of medication inevitably leads to drug resistance. For HIV-1 DRMinVs, the emergence of NGS has addressed the issue of missed detections by Sanger sequencing. However, its high cost and stringent laboratory requirements have limited its widespread application. Therefore, future research should focus on improving and refining NGS to make it simpler and more affordable, and explore when it can serve as a supplement to Sanger sequencing.

Introduction
The rapid initiation of antiretroviral therapy has become an international trend. By the end of 2022, 29.8 million individuals with human immunodeficiency virus (HIV) were receiving lifelong antiretroviral therapy (ART)[1], which has substantially decreased global morbidity and mortality among individuals living with HIV[2]. HIV is an RNA virus characterized by poor fidelity and lack of proofreading ability in its reverse transcriptase enzyme, coupled with a high replication rate, resulting in a propensity for mutation[3, 4]. Furthermore, the accumulation of archived pre-viral variants during HIV infection, along with genetic recombination occurring when different viral sequences infect the same cell, enhances the genetic variability of the virus[5]. The benefits of ART can be compromised if mutations arise at specific sites, leading to drug resistance[6].

The gold standard for drug resistance detection is often based on Sanger sequencing which detects drug-resistance mutations (DRMs) present at ≥ 20% of the viral population; however, it lacks reliability in detecting the presence of drug-resistant minority variants (DRMinVs) within the population of HIV-1 infected patients[7]. Fortunately, the progress of drug resistance detection technologies and the evolution of next-generation sequencing (NGS) have brought about revolutionary changes in HIV-1 sequencing and the study of DRMinVs. Numerous studies have demonstrated that DRMinVs have the potential to rapidly proliferate under selective drug pressure, leading to treatment failure[8, 9]. Although the World Health Organization (WHO) recommends a regimen primarily based on dolutegravir (DTG) as the preferred first-line therapy[10], the majority of regions still utilize non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. Existing research indicates that both acquired and transmitted NNRTI-related DRMinVs can result in virological failure (VF)[11, 12]. Additionally, studies have demonstrated the detection of DRMinVs related to protease inhibitors (PIs) in patients on PI-based regimens upon treatment failure[13]. Despite ongoing clinical controversies surrounding their relevance, it is undeniable that these mutations have impacted treatment efficacy in certain patients.

Moreover, there is a scarcity of reports on the long-term analysis of the characteristics and developmental trends of HIV-1 DRMinVs, hindering researchers from accurately comprehending the occurrence, developmental patterns, and attributes of this field. Therefore, the objective of this study was to employ bibliometrics to scrutinize the authors, institutions, countries, journals, keywords and other detailed information of HIV-1 DRMinVs publications over the preceding three decades from a qualitative and quantitative perspective. The objective is to confirm the primary contributors and the present status of research, while also forecasting the research trends in this field.

**Search Strategy**

We conducted a search in the Web of Science Core Collection (WoSCC) using the following search formula: (((TS=(HIV OR HIV Infections OR Acquired Immune Deficiency Syndrome Virus OR Human Immunodeficiency Virus* OR AIDS virus)) AND TS=(minority* OR low abundance OR low frequency)) AND TS=(variant* OR mutation* OR mutant* OR quasispecies)) AND TS=("drug resistance" OR resistance OR resistant). The search time range was from 1994 to 2022.

**Data analysis**
VOSviewer, available in version 1.6.19 (https://www.vosviewer.com/), is a software application designed for constructing and visualizing bibliometric networks. In our research, the software predominantly conducted analyses on nationalities, institutions, authors, journals, and the co-occurrence of keywords. These terms are visually represented as nodes within the maps constructed by VOSviewer. The color and size of each node respectively signify the categorization and volume of each project, while the thickness of the connecting lines reflects the degree of collaboration or mutual citation between terms.

Citespace, available in version 6.2.R6 (http://cluster.cis.drexel.edu/~cchen/citespace/), is a software designed by Dr. Chaomei Chen from Drexel University in the United States for visualizing patterns and trends in scientific literature. In our research, the software was primarily employed for the analysis of keyword bursts and dual-map overlay of journals.

The R package “bibliometrix”, available in version 4.2.3 (https://www.bibliometrix.org), was employed to construct a global distribution network of publications of HIV-1 DRMinVs. In addition, we used Microsoft Excel 2021 for quantitative analysis of publications.

**Inclusion and exclusion criteria**

The search results were screened and included in the papers and review papers related to “HIV-1 drug-resistant minority variants” in English were included. Articles such as proceeding papers, early access materials, meeting abstracts, editorial content, letters, and book chapters were excluded.

**Analysis Results and visualization**

**Publication Output Analysis**

Over the years, the publication output has reflected the theoretical level and development speed of the HIV-1 DRMinVs research field. This study incorporates a total of 853 documents, and the annual publication output is illustrated in Fig. 1. Global research on HIV-1 DRMinVs steadily increasing until reaching its peak in 2013 with 74 publications. To conduct a more detailed analysis of the growth trends and patterns in this literature, this study categorizes it into the following three stages: Initiation stage (1994–2004): During this period, there were relatively few papers related to HIV-1 DRMinVs, marking the initial exploration of this field. Stable growth stage (2005 to 2013), the publication output remained consistent and even showed growth throughout this period, which could be attributed to the revolutionary changes in studying HIV-1 DRMinVs, facilitated by the emergence of next-generation sequencing (NGS). Immature stage (2014–2022): the number of publications declined. Firstly, it could be attributed to the shortcomings of existing drug resistance detection technologies and the absence of new technological advancements. Secondly, the outbreak of the COVID-19 pandemic has likely led to the redirection of research resources and hindered scientific collaboration. However, it is undeniable that there is still significant development potential in this research field.

**Analysis of countries and institutions**
A total of 371 countries and 3622 institutions globally are focused on the research of HIV-1 DRMinVs. The top 10 countries are mainly distributed in Europe (n = 6) and North America (n = 2) (Table 1, Fig. 2A), while the remaining countries are distributed across South America, Africa, and Asia, among others. Among them, the United States (n = 352, 41.3%) has the highest number of publications, followed by France (n = 107, 12.5%) and the United Kingdom (n = 100, 11.7%), possibly due to their strong expertise and technical platforms in the research of HIV-1 DRMinVs. Subsequently, we created a collaborative network comprising 70 countries with a minimum of 2 publications each, visualizing their interactions and connections (Fig. 2B). It is noteworthy that collaborations between developed countries and developing countries are also extensive, indicating that HIV-1 DRMinVs have become a global focal point.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Counts</th>
<th>Citations</th>
<th>Institution</th>
<th>Publications</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA (North America)</td>
<td>352(41.3%)</td>
<td>3320</td>
<td>Harvard University (United States)</td>
<td>32(3.7%)</td>
<td>130</td>
</tr>
<tr>
<td>2</td>
<td>France (Europe)</td>
<td>107(12.5%)</td>
<td>116</td>
<td>National Cancer Institute (United States)</td>
<td>32(3.7%)</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>England (Europe)</td>
<td>100(11.7%)</td>
<td>874</td>
<td>University of Pittsburgh (United States)</td>
<td>30(3.5%)</td>
<td>129</td>
</tr>
<tr>
<td>4</td>
<td>Spain (Europe)</td>
<td>87(10.2%)</td>
<td>62</td>
<td>Stanford University (United States)</td>
<td>29(3.4%)</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>South Africa (Africa)</td>
<td>64(7.5%)</td>
<td>156</td>
<td>University of Washington (United States)</td>
<td>29(3.4%)</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>Germany (Europe)</td>
<td>60(7.0%)</td>
<td>385</td>
<td>University College London (United Kingdom)</td>
<td>28(3.3%)</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>China (Asia)</td>
<td>56(6.6%)</td>
<td>24</td>
<td>Johns Hopkins University (United States)</td>
<td>27(3.2%)</td>
<td>352</td>
</tr>
<tr>
<td>8</td>
<td>Italy (Europe)</td>
<td>56(6.6%)</td>
<td>1454</td>
<td>University of Zurich (Switzerland)</td>
<td>25(2.9%)</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>Canada (North America)</td>
<td>51(6.0%)</td>
<td>3697</td>
<td>Center for Disease Control and Prevention (United States)</td>
<td>24(2.8%)</td>
<td>190</td>
</tr>
<tr>
<td>10</td>
<td>Belgium (Europe)</td>
<td>48(5.6%)</td>
<td>437</td>
<td>French National Institute of Health and Medical Research (France)</td>
<td>23(2.7%)</td>
<td>211</td>
</tr>
</tbody>
</table>
As for the top ten institutions, most of them are located in United States (n = 7). In Table 1, the top contributors to publication output are mainly universities and research institutions. The top three institutions with the highest publication output are Harvard University (n = 32, 3.7%), the National Cancer Institute (n = 32, 3.7%), and the University of Pittsburgh (n = 30, 3.5%). In general, there is not a significant difference in the publication output among the top ten institutions. Following this, we screened 49 institutions with a minimum of 10 relevant publications and charted the journal network. (Fig. 3). As indicated in Fig. 3, the institutions collaborate closely, forming five distinct collaborative groups. We have found that universities and research institutions in developed countries pay more attention to the occurrence of DRMinVs, which is closely related to their treatment of patients. This may be because developed countries are able to treat HIV more promptly, which also leads to the earlier emergence of drug resistance.

Analysis of Journals

Publications connected to DRMinVs were published in 193 journals. Among them, the Journal of Antimicrobial Chemotherapy published the highest number of papers (n = 67, 34.7%), followed by Plos One (n = 63, 32.6%), and AIDS (n = 54, 28.0%). (Table 2). Within the top 15 journals, the Journal of Medical Virology boasts the highest impact factor (IF = 12.7), with Clinical Infectious Diseases close behind (IF = 11.8). In addition, we created a collaborative network involving 31 journals, each with at least 5 publications, and visualized it (Fig. 4A). Figure 4a shows that Plos One maintains frequent citation relationships with Journal of Antimicrobial Chemotherapy, Journal of Virology and AIDS.

Within the top 15 co-cited journals listed in Table 2, 5 journals received citations exceeding 1000 times. The most cited journal was the Journal of Virology (Co-citation = 2524), followed by AIDS (Co-citation = 2370), Journal of Infectious Diseases (Co-citation = 1855), Plos One (Co-citation = 1274) and AIDS Research and Human Retroviruses (Co-citation = 1034). In addition, the New England Journal of Medicine has the highest impact factor (IF = 158.5), followed by Nature (IF = 64.8) and Science (IF = 56.9). Journals with a minimum co-citation count of 100 were selected to construct the co-citation network (Fig. 4B). As shown in Fig. 4B, Journal of Virology maintains frequent co-citation relationships with Journal of Infectious Diseases, AIDS and AIDS Research and Human Retroviruses. Journal citations and co-citations reflect influential and core journals in the field of HIV-1 DRMinVs. Paying attention to these journals can provide insights into the current hotspots in research. Most research findings on HIV-1 DRMinVs are typically published in journals related to infectious diseases and immunology, indicating that breakthrough research outcomes have yet to be achieved in this field. In the future, more interdisciplinary collaboration and in-depth research will be necessary to deepen our understanding of HIV-1 DRMinVs and to explore new therapeutic strategies.
Table 2
Top 15 journals and co-cited journals for research of HIV-1 DRMinVs.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Journal</th>
<th>Count</th>
<th>IF</th>
<th>Q</th>
<th>Co-cited Journal</th>
<th>Co-citation</th>
<th>IF</th>
<th>Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Journal of Antimicrobial Chemotherapy</td>
<td>67(34.7%)</td>
<td>5.2</td>
<td>Q2</td>
<td>Journal of Virology</td>
<td>2524</td>
<td>5.4</td>
<td>Q2</td>
</tr>
<tr>
<td>2</td>
<td>Plos One</td>
<td>63(32.6%)</td>
<td>3.7</td>
<td>Q2</td>
<td>AIDS</td>
<td>2370</td>
<td>3.8</td>
<td>Q3</td>
</tr>
<tr>
<td>3</td>
<td>AIDS</td>
<td>54(28.0%)</td>
<td>3.8</td>
<td>Q3</td>
<td>Journal of Infectious Diseases</td>
<td>1855</td>
<td>6.4</td>
<td>Q1</td>
</tr>
<tr>
<td>4</td>
<td>AIDS Research and Human Retroviruses</td>
<td>51(26.4%)</td>
<td>1.5</td>
<td>Q4</td>
<td>Plos One</td>
<td>1274</td>
<td>3.7</td>
<td>Q2</td>
</tr>
<tr>
<td>5</td>
<td>Journal of virology</td>
<td>47(24.3%)</td>
<td>5.4</td>
<td>Q2</td>
<td>AIDS Research and Human Retroviruses</td>
<td>1034</td>
<td>1.5</td>
<td>Q4</td>
</tr>
<tr>
<td>6</td>
<td>Journal of Infectious Diseases</td>
<td>29(15.0%)</td>
<td>6.4</td>
<td>Q1</td>
<td>Clinical Infectious Disease</td>
<td>988</td>
<td>11.8</td>
<td>Q1</td>
</tr>
<tr>
<td>7</td>
<td>JAIDS-Journal of Acquired Immune Deficiency Syndromes</td>
<td>24(12.4%)</td>
<td>3.6</td>
<td>Q3</td>
<td>Antimicrobial Agents and Chemotherapy</td>
<td>946</td>
<td>4.9</td>
<td>Q1</td>
</tr>
<tr>
<td>8</td>
<td>Journal of Clinical Virology</td>
<td>23(11.9%)</td>
<td>8.8</td>
<td>Q2</td>
<td>Proceedings of the National Academy of Sciences of the United States of America</td>
<td>937</td>
<td>11.1</td>
<td>Q1</td>
</tr>
<tr>
<td>9</td>
<td>Antiviral Therapy</td>
<td>22(11.4%)</td>
<td>1.2</td>
<td>Q4</td>
<td>Antiviral Therapy</td>
<td>852</td>
<td>1.2</td>
<td>Q4</td>
</tr>
<tr>
<td>10</td>
<td>Journal of Clinical Microbiology</td>
<td>21(10.9%)</td>
<td>9.4</td>
<td>Q1</td>
<td>JAIDS-Journal of Acquired Immune Deficiency Syndromes</td>
<td>846</td>
<td>3.6</td>
<td>Q3</td>
</tr>
<tr>
<td>11</td>
<td>Journal of Virological methods</td>
<td>20(10.4%)</td>
<td>3.1</td>
<td>Q2</td>
<td>Science</td>
<td>790</td>
<td>56.9</td>
<td>Q1</td>
</tr>
<tr>
<td>12</td>
<td>Viruses-Basel</td>
<td>19(9.8%)</td>
<td>4.7</td>
<td>Q3</td>
<td>New England Journal of Medicine</td>
<td>764</td>
<td>158.5</td>
<td>Q1</td>
</tr>
<tr>
<td>13</td>
<td>Clinical Infectious Diseases</td>
<td>18(9.3%)</td>
<td>11.8</td>
<td>Q1</td>
<td>Journal of Clinical Microbiology</td>
<td>752</td>
<td>9.4</td>
<td>Q1</td>
</tr>
<tr>
<td>14</td>
<td>Antimicrobial Agents and Chemotherapy</td>
<td>17(8.8%)</td>
<td>4.9</td>
<td>Q1</td>
<td>Journal of Antimicrobial Chemotherapy</td>
<td>739</td>
<td>5.2</td>
<td>Q1</td>
</tr>
</tbody>
</table>
The dual-map overlay of journals can display the distribution of papers across different disciplinary domains and their citation trajectories[14]. As depicted in Fig. 5, papers published in the Molecular/Biology/Genetic journal on the right are primarily cited by papers published in the Molecular/Biology/Immunology journal and the Medicine/Medical/Clinical journal on the left. This indicates a shift in research focus regarding HIV-1 DRMinVs from mechanisms of mutation generation to their impacts on immune responses and clinical ART effectiveness.

**Analysis of Authors**

5687 authors worldwide are focusing on research related to HIV-1 DRMinVs. Roger Paredes (n = 31) leads the top 10 authors in terms of publication output, followed by Karin J. Metzner (n = 23) and John W. Mellors (n = 22) (Table 3). Subsequently, we created a collaborative network comprising 120 authors, each with five or more publications, and visualized it (Fig. 6A). As shown in Fig. 6A, these authors are structured into distinct core groups, distinguished by tight collaboration within each cluster and relatively sparse connections among different groups. Therefore, paying attention to their research content and direction can provide better insight into the developmental trends of HIV-1 DRMinVs.

All of the top 10 co-cited authors listed in Table 3 have received citations exceeding 100 times. The author with the highest number of co-citations was KJ Metzner (Co-citation = 294), followed by JZ Li (Co-citation = 247) and JA Johnson (Co-citation = 242) (Table 3). In addition, we selected 60 authors based on a minimum co-citation count of 37 and constructed the co-citation network (Fig. 6B). As indicated in Fig. 6B, there is close collaboration among the cited authors, such as KJ Metzner, BB Simen, JZ Li and S Palmer.
### Table 3
Top 10 authors and co-cited authors on research of HIV-1 DRMinVs.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Authors</th>
<th>Count</th>
<th>Co-cited Authors</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Roger Paredes</td>
<td>31</td>
<td>KJ Metzner</td>
<td>294</td>
</tr>
<tr>
<td>2</td>
<td>Karin J. Metzner</td>
<td>23</td>
<td>JZ Li</td>
<td>247</td>
</tr>
<tr>
<td>3</td>
<td>John W. Mellors</td>
<td>22</td>
<td>JA Johnson</td>
<td>242</td>
</tr>
<tr>
<td>4</td>
<td>Vincent Calvez</td>
<td>17</td>
<td>R Paredes</td>
<td>166</td>
</tr>
<tr>
<td>5</td>
<td>Hezhao Ji</td>
<td>17</td>
<td>S Palmer</td>
<td>165</td>
</tr>
<tr>
<td>6</td>
<td>Anne-Geneviève Marcelin</td>
<td>17</td>
<td>BB Simen</td>
<td>159</td>
</tr>
<tr>
<td>7</td>
<td>Robert W. Shafer</td>
<td>16</td>
<td>SY Rhee</td>
<td>146</td>
</tr>
<tr>
<td>8</td>
<td>Lisa M. Frenkel</td>
<td>15</td>
<td>RW Shafer</td>
<td>124</td>
</tr>
<tr>
<td>9</td>
<td>Charlotte Charpentier</td>
<td>14</td>
<td>DE Bennett</td>
<td>121</td>
</tr>
<tr>
<td>10</td>
<td>Diane Descamps</td>
<td>14</td>
<td>BA Larder</td>
<td>121</td>
</tr>
</tbody>
</table>

### Keywords with Burst Detection

The burstiness of keywords refers to a rapid increase in frequency occurring within a short period\[15\]. In our study, Citespace identified the top 25 keywords with the highest burst strength (Fig. 7). A higher burst intensity indicates more active research in the field of HIV-1 DRMinVs, enabling researchers to monitor its development trends. As time progresses, Fig. 7 illustrates the evolving dynamics of hotspots in HIV-1 DRMinVs research. We can observe transitions in these hotspots: initially, there is a focus on highly resistant strains post-Zidovudine use, followed by prevention of mother-to-child transmission. More recently, the hotspots have shifted towards the development of NGS for HIV-1 DRMinVs detection methods and the VF resulting from HIV-1 DRMinVs. The keywords corresponding to each stage are outlined in Table 4.

### Table 4
Keywords during different periods

<table>
<thead>
<tr>
<th>Time Span</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994–2008</td>
<td>zidovudine, high level resistance, disease progression, viral load, replication, HIV-1 infected patients, treatment interruption</td>
</tr>
<tr>
<td>2009–2014</td>
<td>in vivo, populations, lamivudine, single dose nevirapine, to child transmission, persistence, experienced patients, efficacy</td>
</tr>
<tr>
<td>2015–2022</td>
<td>genetic diversity, minority variants, naive patients, prevalence, next-generation sequencing, risk, virological failure</td>
</tr>
</tbody>
</table>

### Hotspots and Frontiers
Keywords co-occurrence analysis provides valuable insights into rapidly identifying research hotspots within a specific field. Table 5 shows the top 20 high-frequency keywords related to HIV-1 DRMinVs. Among them, NGS and VF each mentioned exceeding 20 times, representing the primary research directions in the field of HIV-1 DRMinVs, focusing on their association with VF and the exploration and improvement of detection methods.

Table 5
Top 20 keywords on research of HIV-1 DRMinVs

<table>
<thead>
<tr>
<th>Rank</th>
<th>keyword</th>
<th>Count</th>
<th>Rank</th>
<th>keyword</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>HIV-1</td>
<td>266</td>
<td>11</td>
<td>NNRTI</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>HIV-1 drug resistance</td>
<td>219</td>
<td>12</td>
<td>sanger sequencing</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>NGS</td>
<td>109</td>
<td>13</td>
<td>HIV-1 transmission</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>minority drug-resistant HIV-1 variants</td>
<td>70</td>
<td>14</td>
<td>HIV-1 quasispecies</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>antiretroviral therapy</td>
<td>67</td>
<td>15</td>
<td>molecular epidemiology</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>HIV-1 mutations</td>
<td>30</td>
<td>16</td>
<td>RT</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>virological failure</td>
<td>29</td>
<td>17</td>
<td>AIDS</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>drug resistance mutations</td>
<td>28</td>
<td>18</td>
<td>genetic polymorphism</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>genotypic resistance testing</td>
<td>27</td>
<td>19</td>
<td>integrase inhibitors</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>protease inhibitors</td>
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Furthermore, we conducted cluster analysis on keywords with occurrences six times or more. Figure 8 illustrates the formation of four clusters comprising keywords related to DRMinVs, each signifying a unique research direction, which include the origins, molecular epidemiology, detection methods of DRMinVs, their impact on virological outcomes in drug-naïve patients.

Figure 8 Keywords co-occurrence and cluster analysis.

**Discussion**

This study analyzed 853 articles related to HIV-1 DRMinVs in the WoSCC database using bibliometric methods. From 1994 to 2022, the publication volume showed an overall upward trend. It can be observed that technological advancements, researchers’ attention, collaboration in clinical and research settings have significantly promoted the development of this research field. The main countries engaged in research on HIV-1 DRMinVs are the United States, France, and the United Kingdom, with comparatively higher levels of international collaboration among them. This is likely due to the improvement in gross domestic product (GDP) and rapid economic expansion, leading to increased research funding and enhanced scientific productivity[16]. Additionally, collaboration with developed countries possessing advanced medical capabilities and research resources enhances efficiency. Therefore, strengthening collaboration with
developed countries is essential to boost scientific productivity. Among the top ten institutions, 70% belong to the United States. Although Johns Hopkins University does not have the highest publication count, it has the highest citation count for the articles it publishes. This suggests the institution's high-quality research on HIV-1 DRMinVs has significant impact.

The Journal of Antimicrobial Chemotherapy is evidently a popular journal in the field of HIV-1 DRMinVs, hosting the majority of research in this field (IF = 5.2, Q2). The top 15 journals, ranked by publication volume, are led by the Journal of Medical Virology, boasting the highest impact factor (IF = 12.7, Q1), followed closely by Clinical Infectious Diseases (IF = 11.8, Q1). The majority of co-cited journals, classified as Q1, indicate high impact factors, suggesting high-quality articles with substantial academic value. The articles published in these journals have laid the foundation for the research on HIV-1 DRMinVs. More importantly, research on HIV-1 DRMinVs has transitioned from mechanistic studies to investigations on immune responses and therapeutic efficacy, ultimately converging towards addressing practical clinical issues such as effective vaccines, sensitive detection methods, and improved treatment regimens.

From the authors' perspective, articles published by Roger Paredes, Karin J. Metzner, and John W. Mellors are the most prolific, with each of them having no fewer than 20 publications. The latest study, led by Roger Paredes and others, found that the prevalence of INSTI resistance mutations among treatment-naive individuals remains remarkably low in Spain. However, in 9.6% of the subjects, minority variants carrying integrase transmitted drug resistance (TDR) were detected, which have not yet been linked with virologic failure (VF)[17]. And their research findings suggested that setting a very low threshold (< 1%) when using NGS may affect the specificity of the test and lead to a high misjudgment rate, incorrectly categorizing patients with viral control as being at risk of VF[18]. Consistent with their research findings, the study conducted by Karin J. Metzner and colleagues also reported a higher prevalence of low-abundance pretreatment INSTI DRMs(4.7%)[19]. In addition, they reviewed the current application of NGS technology in HIV-1 drug resistance testing and discussed the challenges[20]. John W. Mellors and his team introduced a method called ultrasensitive Single-Genome Sequencing (uSGS) to construct and analyze NGS libraries, eliminating PCR errors and recombinants[21]. It is worth noting that a systematic review co-authored by Roger Paredes and Karin J. Metzner, indicates a significant dose-dependent correlation between NNRTI-resistant mutations and the risk of VF in first-line ART[9]. In summary, the studies mentioned above primarily focus on the detection of HIV-1 DRMinVs and their prevalence in integrase inhibitor-related DRMinVs, as well as their impact on treatment outcomes.

Regarding co-cited authors, KJ Metzner leads with 294 citations, trailed by JZ Li (citation = 247) and JA Johnson (citation = 242). In 2003, KJ Metzner demonstrated that DRMinVs frequently emerge and persist in individuals experiencing structured treatment interruptions (STI) following their initial successful ART regimen[22]. Subsequently, he found that traditional sequencing methods underestimated the transmission of DRMinVs. Among ten individuals with detectable drug-resistant viruses at the initiation of treatment, 50% of them showed the detection of minor viral quasispecies. Upon reintroduction of drug pressure, previously detected drug-resistant viruses quickly reappeared, impacting the effectiveness of ART[23]. In the same year, KJ Metzner and his research team compared ten methods for detecting DRMinVs and found that AS-PCR and a Ty1HRT yeast system were two techniques should help to determine the impact of DRMinVs on
the response to ART[24]. More importantly, an article published by KJ Metzner in Clinical Infectious Diseases in 2009 demonstrated that the detection of DRMinVs at baseline can quickly escalate, emerging as the predominant viral population, consequently resulting in premature therapy failure among treatment-naive patients undergoing ART with a low genetic resistance barrier[12]. Apparently, KJ Metzner’s achievements have evidently provided theoretical guidance for the research of HIV-1 DRMinVs.

The investigation into HIV-1 DRMinVs can be chronologically categorized into three phases. (Fig. 7 and Table 4). In the early stages of the study (1994–2008), in the context of the emergence of zidovudine resistance and early research on drug resistance mechanisms, researchers began to focus on the role of DRMinVs in resistance evolution and detection methods of them. The research conducted by Charlotte Charpentier and colleagues demonstrates that under the selection pressure of drugs, minority populations have the potential to evolve into dominant populations, thereby expediting the progression of drug resistance[25]. In addition, Sarah Palmer et al. have devised a single-genome sequencing (SGS) technique that exhibits higher sensitivity compared to standard genotyping methods for HIV-1 DRMinVs and permits detection of linked mutations that confer high-level drug resistance[26]. Interestingly, the presence of DRMinVs in both treatment-naive individuals and treated patients who re-initiate treatment after a period of discontinuation[27, 28]. This may have implications for subsequent treatments. In the middle of the research (2009–2014), studies began to explore the clinical significance of DRMinVs during the process of single-dose nevirapine treatment for preventing mother-to-child transmission. Christopher F. Rowley et al. found that pre-ART NVP-associated DRMinVs predicted later clinical failure under NVP treatment[29]. Shayne Loubser et al. studied the dynamic changes and persistence of DRMinVs in pregnant women infected with HIV who received nevirapine during childbirth. They found that the K103N drug-resistant mutation would decline over time, but persisted in cells when undetectable in plasma[30]. The research findings of Ashraf Coovadia et al. suggest that women harboring minority K103N mutations prior to treatment experienced decreased durability in virologic suppression[31]. Similar results were also found in other HIV-positive populations, so clinicians should pay attention to the detection of NNRTI DRMinVs in patients before initiating ART[32]. In the recent stage (2015–2022), with the increasing application of NGS, finding appropriate detection thresholds and more accurately detecting DRMs has become a direction of concern for researchers[33, 34]. More importantly, whether the low-frequency drug-resistant mutation sites detected by NGS have an impact on the treatment outcomes of HIV-1-infected individuals, especially in treatment-naive patients, is a key consideration.

Based on the analysis of keyword clustering (Fig. 8), our conclusion is that the research on HIV-1 DRMinVs predominantly centers on the following aspects:

1. Primary drug resistance, HIV-1 evolution, molecular epidemiology

Primary drug resistance, Molecular epidemiology: Drug resistance developed by HIV in the absence of ART is termed primary drug resistance. Bulk sequencing significantly underestimates the prevalence of drug-resistant mutations in individuals with primary HIV-1 infection[35, 36], likely due to the potential presence of drug-naive individuals harboring DRMinVs in this population[23, 35]. Furthermore, upon testing for NNRTI DRMinVs, their prevalence varied widely, ranging from 0.34–18.26%[37]. This could be attributed to
variations in the tested populations and detection methods. Indirect evidence supporting the transmission of DRMinVs in primary HIV-1 infection is provided by AS-PCR results in one study[38]. Therefore, the calculation of primary drug resistance prevalence should include those DRMinVs that are clinically relevant.

HIV-1 evolution: Patients diagnosed with HIV-1 during the acute phase, who received early and continuous suppressive ART for at least 5 years, did not show clear evidence of viral evolution. However, a slight variation in DRMinVs was observed[39]. Gantner et al. used UDS to study the long-term dynamics of viral resistant quasispecies in blood, which continued to evolve despite achieving virological supression[40]. Upon discontinuation of ART, drug-resistant viruses underwent a triphasic evolution. Initially, multiple-drug-resistant (MDR) mutations prevailed, but declined rapidly in the subsequent phase. Subsequently, minority populations of single-drug-resistant (SDR) viruses emerged, as wild-type viruses assumed dominance. Ultimately, minority SDR viruses remained detectable for up to 59 weeks post-treatment interruption[41]. The evolution of transmitted drug resistance in new hosts involves three pathways. Initially, there are rapid occurrences of DRMs that subsequently revert to the wild type. The second pathway involves the spread of DRMs facilitated by atypical amino acids. The third pathway is characterized by a sustained presence of DRMs[42]. This indicates that regular resistance testing and adjusting treatment plans based on the results are necessary to ensure effective ART and reduce the risk of VF.

1. Drug naïve patients, NNRTI, nucleoside reverse transcriptase inhibitor (NRTI), PIs, INSTIs

NNRTI, NRTI: Although pre-therapeutic DRMinVs are rare in naive patients[43, 44], Nicot et al.’s findings suggest a prevalence of DRMinVs in drug-naive patients chronically infected with HIV-1[45]. A review identified K103N, Y181C, and M184V as the most commonly observed mutations linked to drug resistance across different detection thresholds. In treatment-naive individuals, these mutations were prevalent as DRMinVs at rates of 33.0%, 10.0%, and 41.9%, respectively[46]. Furthermore, at baseline, minority variants carrying resistance-associated mutations (RAMs) in NNRTI were observed at exceedingly low frequencies[47].

PIs: The genetic barrier to resistance is high for PIs, necessitating the presence of multiple mutations to impart substantial resistance[48]. In treatment-naive patients initiating a first-line regimen with a protease inhibitor like atazanavir or lopinavir, those achieving virological success showed a higher baseline prevalence of protease inhibitor minority resistant variants compared to patients with VF[49]. This suggests indirectly that these mutations have a limited impact on the virological response to an initial protease inhibitor-based treatment regimen, consistent with the findings of Marine Perrier et al.’s and Max Lataillade et al.’s studies[49, 50]. However, another study revealed that in two patients undergoing virologic failure on PI-based regimens, pre-existing PI DRMinVs were selected[13]. Additionally, ART with ritonavir-boosted PIs can effectively suppress DRMinVs present at the time of primary HIV-1 infection, particularly those carrying the M184V mutation[51].

INSTIs: Resistance to INSTIs is rarely observed in antiretroviral-naïve patients, with major RAMs primarily presenting as DRMinVs[52–55]. Despite this, several studies have consistently shown that the presence of DRMinVs at baseline has a limited impact on the virological response to INSTI-based regimens[56–58]. However, compelling evidence suggests that ultrasensitive assays can detect DRMinVs of EVG and DTG,
potentially influencing the predicted susceptibility profiles of these drugs, especially in individuals with prior experience with INSTIs[55, 59].

The above studies suggest that among ART-naïve patients, DRMinVs related to NNRTIs are most common, followed by PIs and INSTIs. This may be attributed to the genetic barrier to resistance and efficacy of these drug classes. In recent years, with the emergence of new antiviral drugs, research on DRMinVs associated with these new drugs has also begun.

1. NGS, AS-PCR, transmitted drug resistance, genetic diversity

NGS, AS-PCR: Herbert A. Mbunkah and colleagues' summary of 103 studies indicates that the commonly used detection methods for DRMinVs primarily include the following three: AS-PCR and 454 pyrosequencing or Illumina NGS platforms.[46] NGS is emerging as a new standard for genotypic HIV-1 drug resistance testing, also known as 'second-generation,' 'massive parallel,' or 'deep' sequencing[60]. NGS-based HIV-1 drug resistance testing has demonstrated high concordance with Sanger sequencing, particularly at a 20% detection threshold, as indicated by several studies[61–63]. However, NGS exhibits exceptional sensitivity, making it susceptible to infrequently observed artifacts like PCR errors and APOBEC-mediated G-to-A hypermutation, which are less common in Sanger sequencing[62]. Fortunately, in recent years, Jabara et al. introduced a Primer-ID approach, effectively addressing numerous technical artifacts and biases[64]. However, an optimal NGS threshold is needed for accurate detection of DRMs in clinical applications. Previous studies have proposed a 5% threshold, indicating a reproducible and clinically relevant correlation with treatment outcomes[62, 65–67]. Nevertheless, a recent analysis by Emma R. Lee and colleagues, examining raw NGS data from six international laboratories using five distinct pipelines for NGS HIV-1 drug resistance data analysis, suggests that a 2% threshold may provide a more reliable cutoff for calling and reporting DRMs when utilizing NGS technologies[68]. The recent "Winnipeg Consensus" highlighted these inconsistencies as a major impediment to the extensive implementation of drug resistance genotyping based on NGS. This emphasizes the necessity for additional scrutiny and examination[69]. In addition, it is crucial to exercise caution when applying a threshold leading to a notable reduction in sequencing accuracy, particularly concerning sensitivity to minority variants below 1%[70]. Therefore, the question of when NGS serves as a complementary tool to Sanger sequencing still requires further investigation.

Transmitted drug resistance, genetic diversity: HIV reverse transcriptase, characterized by poor fidelity and lacking proofreading capabilities, contributes to genetic diversity during its highly replicative process[27, 71]. This diversity serves as a precursor to the emergence of DRMs, ultimately leading to the failure of ART. The variations in codon sequences at positions associated with DRMs can result in different amino acid substitutions encoded by various subtypes of the virus. As a consequence, the genetic diversity of HIV-1 may influence the types and rates of resistance mutations that may arise after exposure to drugs[72], constituting one of the sources of DRMinVs[73]. Controversy exists regarding the transmission of these mutations. Elizabeth S. Machado and colleagues initially observed the potential transmission of HIV-1 DRMinVs from mother to child[74]. Subsequently, Karin J. Metzner and colleagues confirmed the transmission of DRMinVs in acute or recent seroconverters[75]. However, research by Antoine Chaillon
found no substantive evidence supporting the transmission of DRMinVs among men who have sex with men (MSM)\[73\]. This perspective is consistent with studies by Jean L. Mbisa and Sara Gianella, which also indicated that DRMinVs were not transmitted\[76, 77\]. Finally, the presence of technical errors and limitations in deep sequencing methods contributes to the sources of variability\[75\]. As a result, the transmission of DRMinVs remains contentious and necessitates further investigation.

4. ART, VF, GRT

ART, GRT, VF: Durant and colleagues were among the pioneering teams to illustrate the utility of identifying DRMs in the selection of appropriate therapy\[78\]. GRT in HIV-1 utilize PCR amplification and population sequencing techniques. These methods identify mutations associated with resistance when they are present in the viral population at levels of 20% or higher. However, these DRMinVs may have clinical significance for the virological outcomes of HIV-1 patients undergoing ART. In patients who have experienced VF, the detection of DRMinVs can intensify the overall resistance burden, impacting not only INSTI but also PI, NRTI, and NNRTI\[79, 80\]. In the AIDS Clinical Trials Group (ACTG) study 398, Elias K. Halvas et al. found that the detection of NNRTI DRMinVs was more prevalent among individuals with treatment experience, correlating with an elevated risk of experiencing VF\[81\]. Other multiple studies have also shown similar results\[11, 82–87\]. For women with a history of sdNVP exposure, NVP DRMinVs are linked to an increased risk of ART failure with NVP\[88, 89\]. Additionally, DRMinVs multiple NVP resistance mutations in infants before NVP-based treatment may predict treatment failure\[90\]. Therefore, it is necessary to conduct DRMinVs testing when restarting treatment for individuals with previous NNRTI treatment experience. In recent years, there has been a growing body of research concentrating on the impact of DRMinVs on virological outcomes in treatment-naive patients. Numerous studies have been conducted to evaluate the effects of DRMinVs baseline on the rates of treatment failure associated with the initial ART regimen. A systematic review and pooled analysis of ten studies revealed that even with patient adherence exceeding 95%, HIV-1 DRMinVs, particularly involving NNRTI resistance, were significantly associated with a 2.5 to 3-fold increased risk of VF. Furthermore, a direct dose-effect relationship exists between the mutational load of NNRTI DRMinVs and the risk of VF\[91\]. The outcomes obtained in the majority of currently published articles align with the findings of this study\[32, 92–101\]. On the contrary, some studies demonstrated that the detection of DRMinVs at baseline were not significantly associated with virological outcome\[102–106\]. Observably, there is controversy regarding the influence of baseline DRMinVs on virological outcomes, necessitating extensive clinical studies for further validation.

Advantages and Disadvantages

This study presents several noteworthy advantages. Firstly, we conducted a comprehensive analysis of the research progress and trends in HIV-1 DRMinVs using three bibliometric tools. This contribution enhances scholars’ understanding of the developmental trajectory of HIV-1 DRMinVs, keeping them informed about cutting-edge topics. Additionally, compared to traditional reviews, our bibliometric analysis provides a novel perspective on the development direction of HIV-1 DRMinVs by examining authors, countries, institutions, and keywords.
However, our study still has limitations. Firstly, due to continuous database updates and the limited annual span analyzed by Citespace software, we focused on articles published from 1994 to 2022, excluding those published thereafter. Secondly, constrained by the functionality of the analysis software, our data is solely derived from the WoSCC database, potentially overlooking some relevant research. Moreover, the exclusion of non-English studies may lead to an underestimation of the contribution of these papers.

Conclusions

From the perspective of collaboration among countries, institutions, and authors, HIV-1 DRMinVs have attracted global attention. The overlay of dual graphs in journals indicates that some studies have transitioned from basic research to clinical applications, specifically focusing on the transition from understanding the mechanisms of drug resistance to assessing its impact on treatment outcomes. The yearly bursts of keywords also signify the transformation of hotspots in this field, with particular emphasis on the treatment failure caused by HIV-1 DRMinVs and the appropriate utilization of NGS methods. Despite the affordability and relative simplicity of Sanger sequencing, it remains the mainstream method for drug resistance detection. However, its challenge lies in the detection of HIV-1 DRMinVs with mutation frequencies below 20%. Although NGS addresses this issue, its high cost and stringent laboratory requirements limit its widespread application. Therefore, future research should concentrate on refining and improving NGS to make it simpler, more cost-effective, and determining when NGS can serve as a supplement to Sanger sequencing, thus reducing the spread of drug resistance and the occurrence of VF.

Abbreviations

HIV, human immunodeficiency virus; DRMinVs, drug-resistant minority variants; WoSCC, web of science core collection; ART, antiretroviral therapy; DRMs, drug-resistance mutations; DTG, dolutegravir; WHO, World Health Organization; NGS, next-generation sequencing; GDP, gross domestic product; SGS, single-genome sequencing; uSGS, ultrasensitive Single-Genome Sequencing; TDR, transmitted drug resistance; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PIs, protease inhibitors; InSTIs, integrase inhibitors; STI, structured treatment interruptions; VF, virologic failure; ACTG, AIDS Clinical Trials Group; MSM, men who have sex with men; sdNVP, single-dose nevirapine; RAMs, resistance-associated mutations; AS-PCR, allele-specific PCR; GRT, Genotypic resistance testing; SDR, single-drug-resistant; MDR, multiple-drug-resistant.

Declarations

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Author contributions

Conceived and designed the study: CY, FY, FZ; data collection: CY, ML, XY; data analysis and visualization: CY, ML, XY, RS, XL, XL, HZ; writing and revising the manuscript: CY, FZ, FY, ML; documents query and results sorting: CY, WL, YH, YL and YD.

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Availability of data and materials

The data are obtained through the public database. If a reasonable request is made, the corresponding author will provide the techniques used in this research.

Ethics approval and consent to participate

Not applicable.

Transparency declarations

None to declare.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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**Figures**

**FIGURE 1**

*Figure 1*

Annual output of research of HIV-1 DRMinVs.
Figure 2

The geographical distribution and visualization of countries on research of HIV-1 DRMinVs. (A) Geographical distribution of countries, with lines indicating collaboration between countries. Thicker lines represent more frequent collaboration. (B) Countries with at least two papers. Nodes represent countries, with larger nodes indicating a higher number of published papers. The lines between nodes represent collaboration between countries, with thicker lines indicating higher collaboration frequency. Colors denote clusters, with nodes of the same color belonging to the same cluster.
The visualization of institutions on research of HIV-1 DRMinVs. Institutions with at least ten papers. Nodes represent institutions, with larger nodes indicating a higher number of published papers. The lines between nodes represent collaboration between institutions, with thicker lines indicating higher collaboration frequency. Colors denote clusters, with nodes of the same color belonging to the same cluster.
Figure 4

The visualization of journals and co-cited journals on research of HIV-1 DRMinVs. (A) Journals with at least five papers. Journals with at least five papers. Nodes represent journals, with larger nodes indicating a higher number of published papers in that journal. The lines between nodes represent citation relationships between papers published in these journals, with thicker lines indicating higher citation frequency. Colors denote clusters, with nodes of the same color belonging to the same cluster. (B) Journals cited at least 100 times. Nodes represent journals, with larger nodes indicating a higher citation count. The lines between nodes represent papers published in these journals being co-cited by other journals, with thicker lines indicating higher co-citation frequency. Colors denote clusters, with nodes of the same color belonging to the same cluster.
Figure 5

The dual-map overlay of journals on research of HIV-1 DRMinVs.

Dual-map overlay of journals involved in HIV-1 DRMinVs research. The dual-map overlay displays the distribution of papers across different disciplines and their citation trajectories. Different colors represent clusters of journals in different disciplines. The left side represents citing journals, while the right side represents cited journals. Orange and green lines indicate papers published in molecular/biological/genetic journals being cited by papers in molecular/biological/immunological journals and medical/medical/clinical journals, respectively.

Figure 6

(A) and (B)
The visualization of authors and co-cited Authors on research of HIV-1 DRMinVs. (A) Authors with at least five papers. Nodes represent authors, with larger nodes indicating a higher number of papers published by that author. The lines between nodes represent citation relationships between papers authored by these authors, with thicker lines indicating higher citation frequency. Colors denote clusters, with nodes of the same color belonging to the same cluster. (B) Authors cited at least 100 times. Nodes represent authors, with larger nodes indicating a higher citation count. The lines between nodes represent papers authored by these authors being co-cited by another author, with thicker lines indicating higher co-citation frequency. Colors denote clusters, with nodes of the same color belonging to the same cluster.
Top 25 Keywords with the Strongest Citation Bursts

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**FIGURE 7**

**Figure 7**

Top 25 keywords with strong citation bursts. A red bar indicates a sudden or significant increase in frequency for that year.
Figure 8

Keywords co-currence and cluster analysis. Keywords occurring at least three times. Nodes represent keywords, with larger nodes indicating a higher frequency of occurrence. Lines between nodes represent the co-occurrence of two keywords in the same paper, with thicker lines indicating a higher co-occurrence frequency. Colors denote clusters, with nodes of the same color belonging to the same cluster.