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A bibliometric analysis of HIV-1 drug-resistant minority variants from 1999 to 2024

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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 drug-resistant minority variants have garnered increasing attention. Few studies have analyzed the hotspots and trends in this field, which bibliometrics can effectively address.

Methods Publications related to HIV-1 DRMinVs from 1999 to 2024 were searched on the Web of Science Core Collection database. Visual knowledge maps and bibliometric analyses were generated using VOSviewer and Bibliometrix.

Results In total, 289 publications concerning HIV-1 drug-resistant minority variants were identified from 1999 to 2024, demonstrating a steady increase in publication output over the years. Although developed countries, led by the United States, are the main contributors, 9.57% and 2.48% of the research from the top five publishing countries focus on populations in Africa and other developing countries, respectively. Most contributing institutions are universities and public health organizations, with the University of Washington having the highest publication output. The Journal of Antimicrobial Chemotherapy holds the highest prominence among journals in this domain. The main hotspots include "drug classes," "drug resistance surveillance," "mother-to-child transmission," "treatment outcomes," and "targets of HIV-1 drug resistance testing," And we found several noteworthy shifts in research trends in HIV-1 drug-resistant minority variants studies, including changes in drug resistance testing technologies, the primary study population, and drug classes.

Conclusions This is the first bibliometric analysis of publications related to HIV-1 DRMinVs from 1999 to 2024. We analyzed the key research contributions across countries, institutions and journals. Based on keyword co-occurrence and cluster analysis, we identified several noteworthy shifts in research trends in HIV-1 DRMinVs studies, including changes in drug resistance testing technologies, the primary study population, and drug classes.

Keywords HIV-1, Drug-resistant minority variants, Bibliometrics, Hotspots

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Introduction

The rapid initiation of antiretroviral therapy (ART) has become an international trend. By the end of 2022, 29.8 million individuals with human immunodeficiency virus (HIV) were receiving lifelong ART [1], which has substantially decreased global morbidity and mortality among individuals living with HIV [2]. HIV is an RNA virus with a high mutation rate due to the low fidelity of its reverse transcriptase and rapid replication [3, 4]. Additionally, the accumulation of proviral variants and genetic recombination from co-infection increases its genetic diversity [5]. If mutations occur at specific sites leading to drug resistance, the efficacy of ART may be compromised [6]. The large effective population size [7], high replication rate, high mutation rate, and high recombination rate, combined with host immune selection pressure [8], not only drive the genetic diversity of HIV but also lead to the emergence of various mutations within each untreated individual on a daily basis. This means that drug-resistant mutations (DRMs) already exist in all patients before the initiation of treatment [9]. Even in treatment-naïve patients initially infected with wild-type viruses, some low-frequency mutations may still be present, which can also confer drug resistance to the virus [10, 11].

The gold standard for drug resistance detection is often based on sanger sequencing (SS) which detects DRMs present in ≥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 [12]. Fortunately, advancements in drug resistance detection technologies and the advancement of next-generation sequencing (NGS) have revolutionized HIV-1 sequencing and the investigation of DRMinVs. Numerous studies have demonstrated that DRMinVs have the potential to rapidly proliferate under selective drug pressure, leading to treatment failure [13, 14]. Although the World Health Organization (WHO) recommends a regimen primarily based on dolutegravir (DTG) as the preferred first-line therapy [15], the majority of regions still utilize non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. In treatment-naive individuals, DRMinVs may result from viral diversity or transmission, while in treatment-experienced patients, they often emerge from drug-resistant strains with reduced fitness after therapy cessation [16]. Existing research indicates that both acquired and transmitted NNRTI-related DRMinVs can result in virological failure (VF) [17, 18]. A systematic review showed that, among treatment-naive HIV individuals, 11 out of 25 studies (44.0%) reported a significant association between HIV-1 DRMinVs and the risk of VF [19]. Despite ongoing clinical controversies surrounding their relevance, it is undeniable that these mutations have impacted treatment efficacy in certain patients.

Bibliometric methods have been extensively used in fields like cancer [20], diabetes [21] and artificial intelligence [22] to analyze research hotspots and trends. In the field of HIV-1 DRMinVs, which countries and institutions have made the most significant contributions? Which journals publish the most literature in this domain? What are the the current state of research and hotspot topics in this area? Therefore, the aim of this study was to employ bibliometric methods to analyze institutions, countries, journals, and keywords in the DRMinVs field. This approach reveals the evolution of research trends in HIV-1 DRMinVs and identifies current research hotspots.

Methodology

Database source

Web of Science is a widely used academic database that includes over 12,000 high-impact journals. It is considered more comprehensive and reliable for bibliometric analysis compared to other databases like Scopus and PubMed [23, 24]. We used the Web of Science Core Collection (WOSCC), a comprehensive and independent global citation database covering diverse research fields, and it is widely utilized by VOSviewer for bibliometric analysis. Using advanced search, we retrieved literature published from the database's inception until December 31, 2024. All eligible records were exported in plain text format, including "full record and cited references" information.

Search strategy

This study utilized Medical Subject Headings (MeSH) terms from the PubMed database to enhance the comprehensiveness of article retrieval. We conducted a search in the WoSCC using the following search formula: (((TS=(HIV OR HIV infections OR Acquired Immune Deficiency Syndrome OR Human Immunodeficiency Virus* OR AIDS)) AND TS=(minority OR low abundance OR low frequency)) AND TS=(variant* OR mutation* OR quasispecies)) AND TS=("drug resistance").

Screening protocol and criteria

A total of 665 records were retrieved based on the search strategy. Since this study only included research papers and was limited to English publications, two researchers independently conducted the screening process, ultimately selecting 601 records. These records were manually screened based on their title, abstract, and keywords for relevance to "HIV-1 drug-resistant minority variants." When there was insufficient information to make a judgment, full-text evaluation was performed. The two researchers independently identified 273 and 304 articles, respectively. Discrepancies were resolved

through arbitration, resulting in the inclusion of 289 articles. The screening process is illustrated in Fig. 1.

Data analysis

This study included a total of 289 articles that met the inclusion criteria, which were exported and downloaded in plain text format. Vosviewer is capable of displaying the broad external characteristics of subject areas and offers distinct advantages, particularly in clustering analysis [25]. Bibliometrix package, as an open-source R tool, allows data analysis without the need for coding, greatly reducing the barrier to entry and enabling researchers from diverse backgrounds to easily get started [26]. We used VOSviewer version 1.6.19 (https://www.vosviewer.com/) to identify countries, institutions, and keywords related to the articles and to create co-occurrence maps. The bibliometrix package in R Studio version 4.2.3 (https://www.bibliometrix.org) was used

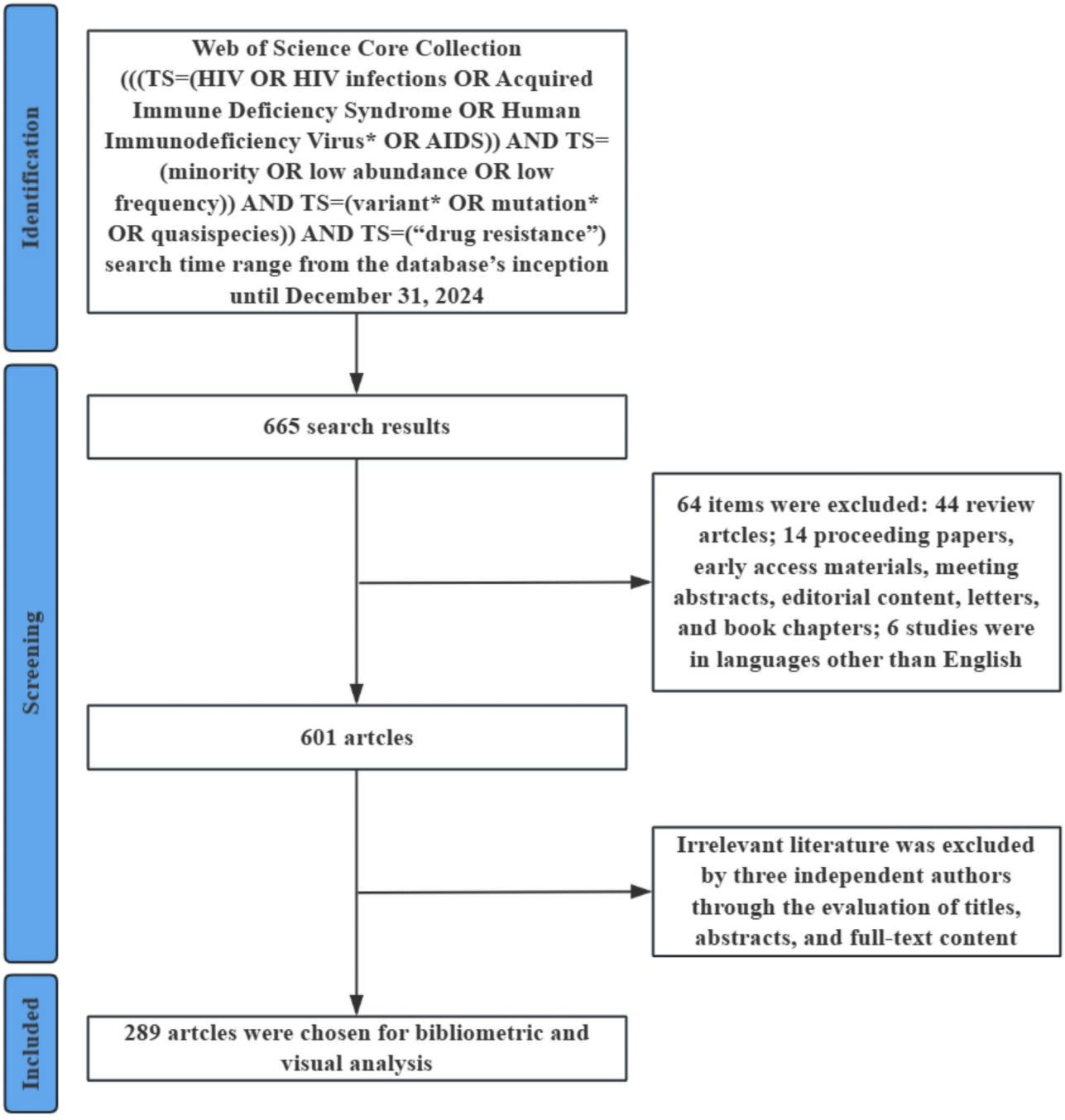

Fig. 1 The process of literature retrieval and selection

for visualizing three-field plots for authors, keywords, and institutions, as well as for journal analysis and the study of highly cited articles. Microsoft Office Excel 2021 was used for data management and publication trend analysis.

Analysis results and visualization

Analysis of publication output

According to the search strategy and selection criteria, a total of 289 articles were included, covering the period from January 1, 1999, to April 30, 2024. Global research on HIV-1 DRMinVs steadily increased, peaking in 2020 with 24 publications. The lowest output occurred in 1999 and 2003, with only one article each. The average annual output remained around 2 publications until 2005, after which it increased sevenfold, marking 2005 as a key year in the field's growth (Fig. 2).

Analysis of countries and institutions

A total of 56 countries and 668 institutions were involved in HIV-1 DRMinVs research. Developed countries, especially the United States ($n = 147$), were the main contributors. It was noteworthy that South Africa had frequent collaborations with the United States. Most of the contributing institutions were universities and public health organizations. Among them, the University of Washington had the highest output, with 15 publications; however, its collaborative model remained relatively independent, whereas other institutions had formed more closely integrated research networks (Fig. 3).

Subsequently, we quantified the research populations in the top five developed countries (which totaled 282 publications). We found that 27 studies (9.57%) focused on HIV-1 infected individuals in Africa, and 7 studies (2.48%) focused on HIV-1 infected individuals in other developing countries, including Mexico, Argentina, Turkey, the Philippines, Brazil and Ghana. Additionally, using Bibliometrix, we generated a three-fields plot for the top 10 contributing institutions and the top 15 authors and keywords. The plot reveals a focus on topics such as "failure," "risk," "virological failure," "reverse-transcriptase," "transmission," and "treatment-naive" (Fig. 4).

Analysis of journals

These 289 papers were published in 67 different journals, reflecting a diverse range of sources for research on HIV-1 DRMinVs. The Journal of Antimicrobial Chemotherapy and Plos One had the highest number of publications, with the former demonstrating strong academic influence in the field of HIV-1 DRMinVs, as indicated by its H-index, G-index, and M-index.

Table 1 presents the top ten most influential journals in HIV-1 DRMinVs research, ranked based on various bibliometric indicators. H-index reflects both the productivity and citation impact of a journal. G-index gives more weight to highly cited articles. M-index measures the maturation rate of a journal's impact. TC (Total Citations) represents the total number of citations received, while NP (Number of Publications) indicates the total number of published articles related to HIV-1 DRMinVs.

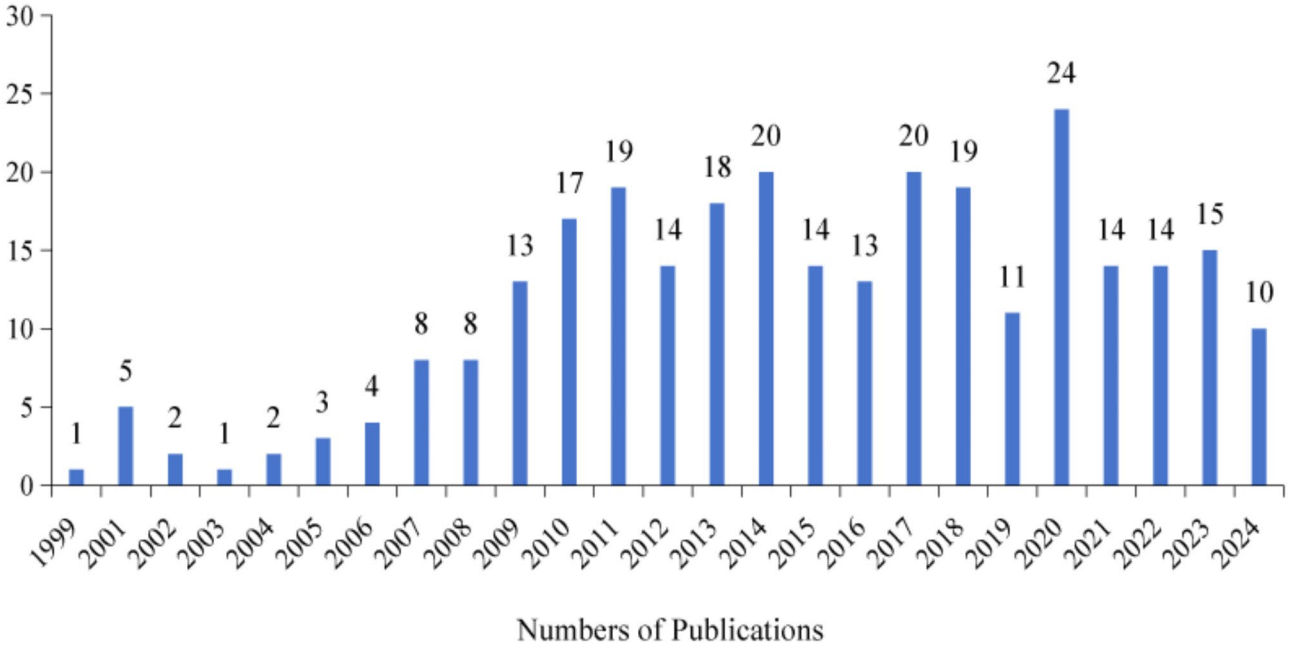

Fig. 2 Annual output of research of HIV-1 DRMinVs

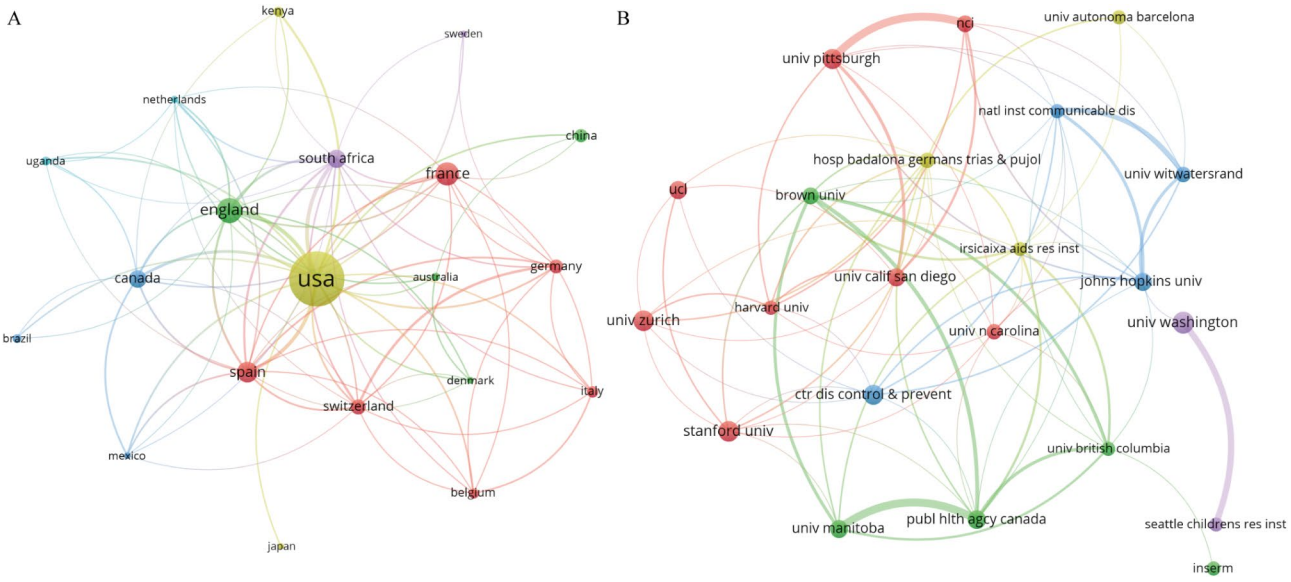

Fig. 3 **(A)** The visualization of countries with at least 5 papers. **(B)** The visualization of institutions with at least 8 papers. Larger nodes represent a higher number of published papers, while thicker lines indicate a higher frequency of collaboration. Nodes of the same color indicating a closely related collaboration network

Analysis of most global cited documents

Table 2 lists the top ten most cited papers. The most frequently cited article was "Multiple, linked human immunodeficiency virus type 1 drug resistance mutations in treatment-experienced patients are missed by standard genotype analysis" by Palmer S et al., published in Journal of Clinical Microbiology in 2005. This paper has been cited 411 times since publication, with an average of 19.57 citations per year. However, in terms of annual impact, the paper by Günthard HF et al. had the highest citation rate (19.86 citations/year).

Table 2 presents the ten most globally cited publications in HIV-1 DRMinVs research, ranked based on total citations. "Total Citations" (TC) represents the overall number of citations each paper has received. "TC per Year" reflects the average number of citations per year since publication. "Normalized TC" adjusts the citation count relative to the publication year to account for differences in citation windows.

Current state of research and hotspot topics

Furthermore, we utilized VOSviewer to perform cluster analysis on keywords with at least three occurrences. The keywords within each cluster were synthesized to identify commonalities in the research. Figure 5 illustrates five themes represented by different colors, with each color corresponding to a specific research focus within HIV-1 DRMinVs.

The red cluster focuses on "drug classes," including antiretroviral agents, integrase inhibitor, protease inhibitor, nucleoside reverse transcriptase inhibitor, high-throughput sequencing, allele-specific real-time PCR, ultra-deep pyrosequencing, and transmission. The blue cluster pertains to "drug resistance surveillance," comprising surveillance drug resistance mutations, transmitted drug resistance, genotypic resistance testing, sanger sequencing, deep sequencing, next-generation sequencing, single-genome sequencing, raltegravir, and bioinformatics. The yellow cluster is linked to "mother-to-child transmission," featuring mother-to-child HIV transmission, prevention of mother-to-child transmission, antiretroviral therapy, nevirapine, quasispecies, and drug resistance. The green cluster relates to "treatment outcomes," encompassing non-nucleoside reverse transcriptase inhibitor, efavirenz, rilpivirine, treatment failure, allele-specific PCR, real-time PCR, ultra-deep sequencing, and pyrosequencing. The purple cluster is associated with "targets of HIV-1 drug resistance testing," including drug resistance mutations, reverse transcriptase, protease, integrase, subtype, Illumina MiSeq.

We also constructed a keyword co-occurrence map over the past decade based on temporal evolution (Fig. 6), providing a visual representation of the dynamic changes in research hotspots on HIV-1 DRMinVs over time. The transition from green to red rectangles highlights that the research focus in the past five years has been on topics such as "antiretroviral agents," "next-generation sequencing," "integrase inhibitor," and "protease inhibitor."

Discussion

Bibliometric analysis can identify trends within a specific academic field by offering a comprehensive overview of the current research landscape [27]. Since 1999, the number of publications has steadily increased, while the rapid

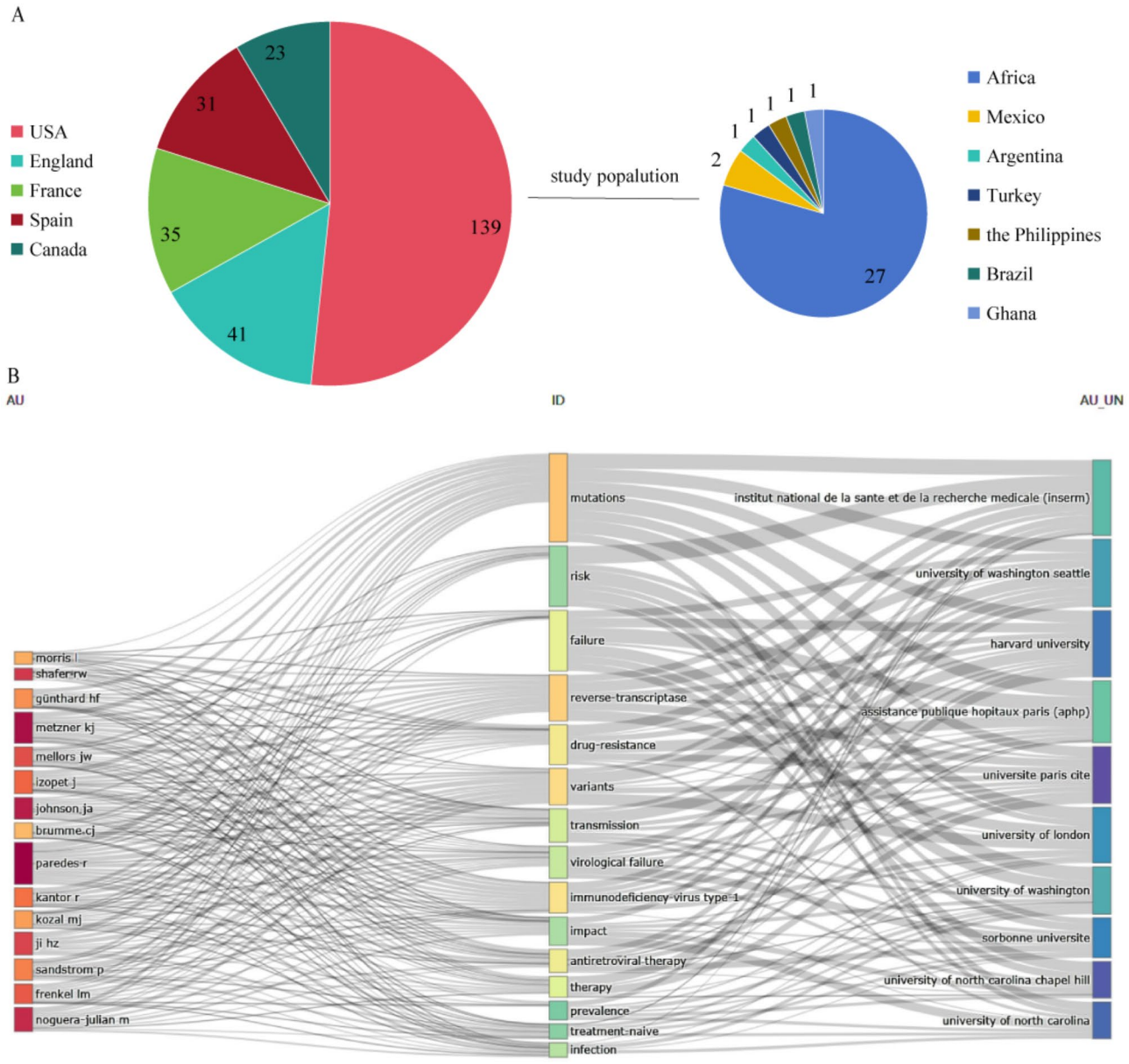

Fig. 4 **(A)** The main contributors are developed countries in terms of publication output and research populations. **(B)** The three-field plot of authors, keywords, and institutions. Darker colors indicate a greater contribution to the field, while larger rectangles suggest a broader range of research involvement in the field

increase in publication output in 2005 can be attributed to revolutionary advancements in the study of HIV-1 DRMinVs, facilitated by the emergence of NGS [28].

Developed countries have shown significant attention to Africa, one of the regions most severely affected by the epidemic. One of the research focuses is on women and infant populations [29], particularly regarding drug resistance and treatment outcomes after the use of antiretroviral drugs for preventing mother-to-child transmission, as well as studies on adolescents [30], a vulnerable group. The Journal of Antimicrobial Chemotherapy is the most prominent journal contributing to HIV-1 DRMinVs research, covering a wide range of topics, including the pathogenesis, epidemiology, and therapeutic outcomes of HIV-1 DRMinVs.

Based on the retrieved data, the most cited paper was authored by Sarah Palmer and colleagues from the National Cancer Institute in the United States. They developed a single-genome sequencing technology with greater sensitivity than SS, capable of detecting mutations below 20% and linked drug resistance mutations, enhancing our understanding of viral evolution and ART responses [16]. The second most cited publication comes from Chunlin Wang and colleagues at Stanford

Table 1 Top ten most influential journals for research on HIV-1 DRMinVs

Journal	H_index	G_index	M_index	TC	NP
Journal of Antimicrobial Chemotherapy	14	20	0.737	487	31
Plos One	13	24	0.684	623	27
Journal of Infectious Diseases	12	15	0.500	819	15
AIDS	11	17	0.550	691	17
Journal of Clinical Microbiology	11	13	0.407	702	13
Journal of Virology	11	12	0.440	595	12
Journal of Virological methods	10	13	0.588	207	13
Journal of Clinical Virology	8	13	0.381	203	13
Aids Research and Human Retroviruses	7	11	0.412	128	12
Antimicrobial Agents and Chemotherapy	7	7	0.412	239	7

Table 2 Top ten most globally cited documents on HIV-1 DRMinVs

Paper	DOI	Total Citations	TC per Year	Normalized TC
PALMER S, 2005, J CLIN MICROBIOL	https://doi.org/10.1128/JCM.43.1.406-413.2005	411	19.57	2.46
WANG CL, 2007, GENOME RES	https://doi.org/10.1101/gr.6468307	338	17.79	3.81
SIMEN BB, 2009, J INFECT DIS	https://doi.org/10.1086/596736	332	19.53	5.46
JOHNSON JA, 2008, PLOS MED	https://doi.org/10.1371/journal.pmed.0050158	307	17.06	3.86
JABARA CB, 2011, P NATL ACAD SCI USA	https://doi.org/10.1073/pnas.1110064108	287	19.13	6.45
HENN MR, 2012, PLOS PATHOG	https://doi.org/10.1371/journal.ppat.1002529	255	18.21	5.01
HOFFMANN C, 2007, NUCLEIC ACIDS RES	https://doi.org/10.1093/nar/gkm435	184	9.68	2.07
METZNER KJ, 2009, CLIN INFECT DIS	https://doi.org/10.1086/595703	169	9.94	2.78
ZAGORDI O, 2010, NUCLEIC ACIDS RES	https://doi.org/10.1093/nar/gkq655	153	9.56	3.69
GÜNTHARD HF, 2019, CLIN INFECT DIS	https://doi.org/10.1093/cid/ciy463	139	19.86	5.38

University, who also investigated the detection of DRMinVs using ultra-deep pyrosequencing in clinical samples. They developed a statistical method to differentiate between true minority variants in clinical samples and sequencing errors [31].

Our bibliometric analysis reveals several noteworthy shifts in research trends in HIV-1 DRMinVs studies.

The shift of drug resistance testing technologies

Common methods for detecting DRMinVs include Allele-Specific PCR (AS-PCR), 454 pyrosequencing, and the Illumina NGS platform. AS-PCR is more sensitive than traditional sequencing, with a detection limit ranging from 0.01 to 2%, and is commonly used in treatment-naive patients [32, 33]. But it can only detect one mutation at a time and cannot analyze linked mutations [34]. Pyrosequencing provides a more comprehensive picture of drug resistance, with a detection threshold ranging from 0.1–2% [35, 36]. and researchers commonly use a 1% threshold to exclude novel sequence variations and sequencing artifacts [37]. However, due to its higher error rate and cost, along with the emergence of NGS platforms like Illumina, pyrosequencing is gradually being phased out.

NGS has shown high concordance with Sanger sequencing at a 20% detection threshold in several studies [38, 39]. However, NGS is particularly prone to artifacts, such as PCR errors and APOBEC-mediated hypermutation, which are less common in SS [40]. The Primer-ID approach effectively addresses these issues [41]. Nonetheless, the optimal detection threshold for NGS in clinical applications remains unclear. Earlier studies recommended a 5% threshold [42, 43], while recent analysis by Emma R. Lee and colleagues suggested that a 2% threshold may be more reliable for detecting and reporting DRMs using NGS technologies [44]. Furthermore, caution is advised when using thresholds that significantly reduce sequencing accuracy, especially in relation to sensitivity for minority variants below 1% [45]. Therefore, the question of when NGS should complement sanger sequencing requires further investigation, and future research should focus on developing more cost-effective and technologically simpler methods for detecting DRMinVs.

The shift in the primary study population

In resource-limited settings, single-dose nevirapine (NVP) was widely utilized as a preventive measure for HIV-1 mother-to-child transmission [46]. Researchers at the time focused on the presence of DRMinVs in mothers and infants exposed to NVP and their impact on virological outcomes. NVP-resistant viruses can persist as low-frequency variants for several years post-exposure, potentially influencing virological outcomes when mothers and infants continue using regimens containing NVP [47–49]. In 2017, the WHO included dolutegravir DTG-ART in its first-line treatment recommendations [50]. However, the impact of DTG on virological outcomes in this population remains an area requiring further

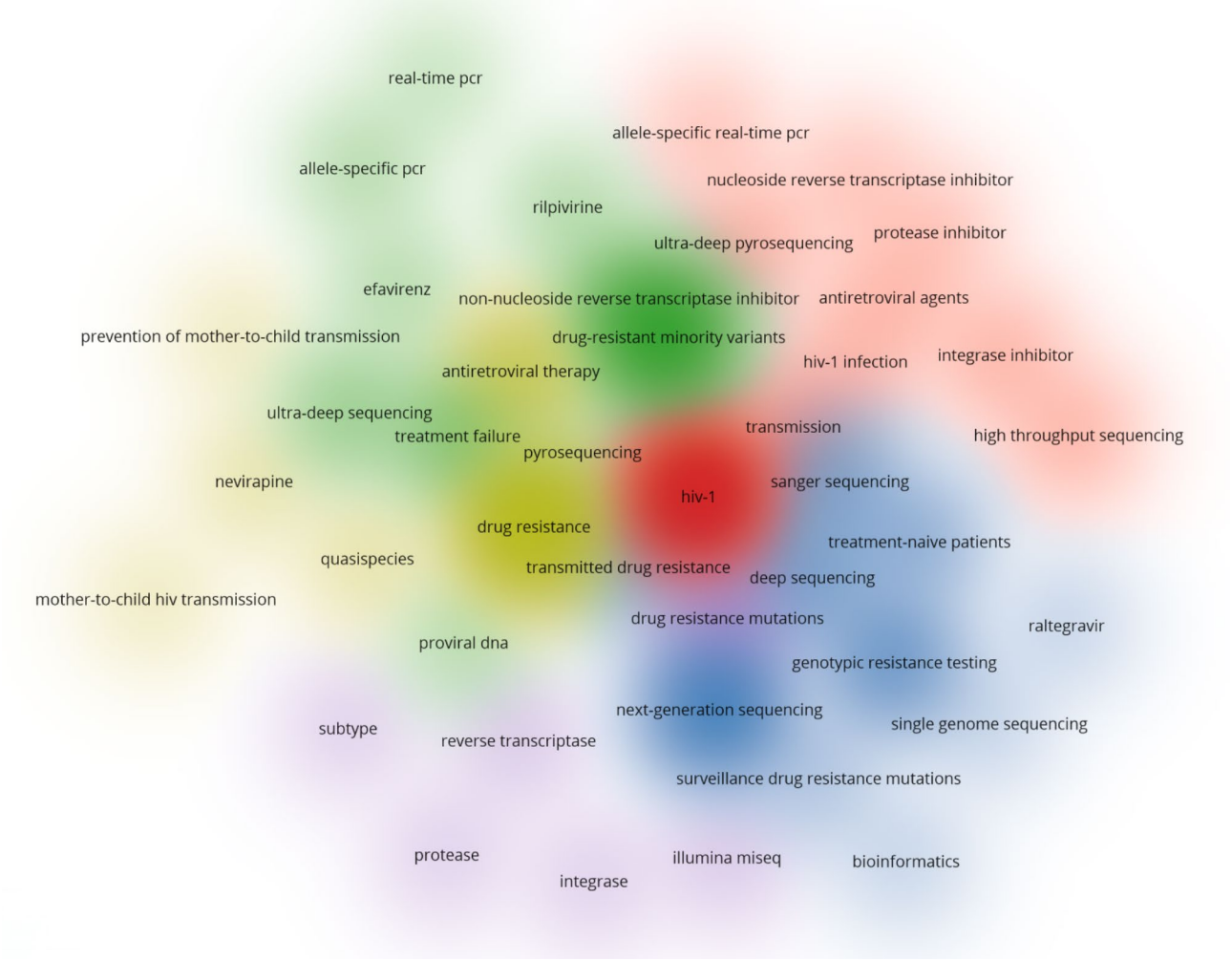

Fig. 5 Keywords cluster analysis of HIV-1 DRMinVs (occurrence ≥ 3 times). The darker the color, the higher the frequency of keyword occurrence, with the same color indicating similar research directions

investigation. Subsequent studies have shifted their focus to treatment failure and ART-naive individuals. In AIDS Clinical Trials Group study 398, Elias K. Halvas et al. demonstrated that NNRTI DRMinVs were more frequently detected in treatment-experienced individuals and were associated with an increased risk of VF [51]. However, the impact of baseline DRMinVs on virological outcomes in ART-naive patients remains contentious [52, 53], underscoring the need for extensive clinical studies to clarify these findings. HIV-1 genetic diversity and deep sequencing errors can contribute to DRMinVs in ART-naive patients. These mutations may also be transmitted during acute or recent seroconversion, but there is no strong evidence for transmission among men who have sex with men [54, 55], making it a controversial area for future research.

The shift in drug classes

Common DRMs associated with reverse transcriptase inhibitors, such as K103N and Y181C, have been shown to adversely affect treatment outcomes [13, 56]. It is noteworthy that DRMinVs have a broad range of mutation loads, suggesting that future research should not focus solely on the impact of mutation frequency on treatment outcomes [57]. The genetic barrier is high for PIs, necessitating the presence of multiple mutations to impart substantial resistance [58]. In treatment-naive patients initiating a first-line regimen with a protease inhibitor (PI) like atazanavir or lopinavir, those achieving virological success showed a higher baseline prevalence of PI minority resistant variants compared to patients with VF [59]. This suggests indirectly that these mutations have a limited impact on the virological response to an initial PI-based treatment regimen, consistent with the findings of Marine Perrier et al.'s study [60]. However, Ross LL et al.'s study have demonstrated the detection of DRMinVs

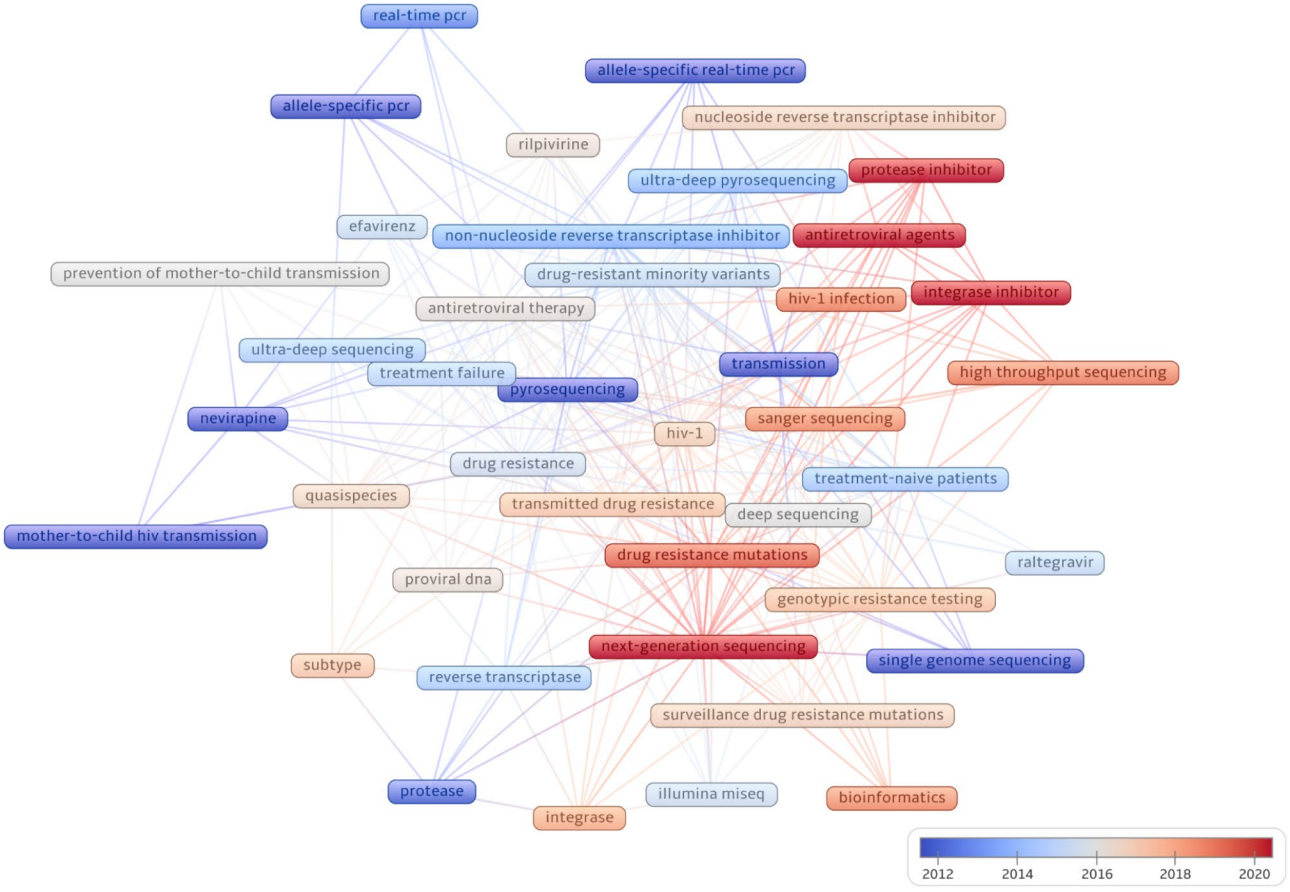

Fig. 6 Temporal keywords co-occurrence analysis in HIV-1 DRMinVs (occurrence ≥ 3 times). The color transition from purple to red represents the progression of time

related to protease inhibitors (PIs) in patients on PI-based regimens upon treatment failure [61]. Currently, resistance to integrase strand transfer inhibitors (INSTI) is rarely observed in antiretroviral-naïve patients, with major DRMs primarily presenting as DRMinVs [62–65]. 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 [66–68]. 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 [62, 69].

However, our study still has limitations. 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.

Conclusion

In conclusion, HIV-1 DRMinVs have become a globally important topic of interest. This study utilizes literature from the WoSCC to identify the key contributors and their scientific collaborations in the field of HIV-1 DRMinVs research from 1999 to 2024. Based on keyword co-occurrence and cluster analysis, we identified several noteworthy shifts in research trends in HIV-1 DRMinVs studies, including changes in drug resistance testing technologies, the primary study population, and drug classes. It is noteworthy that the high frequency of the keyword "NGS" in recent years reflects the close attention of researchers to this area.

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
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PIs	Protease inhibitors
INSTIs	Integrase strand transfer inhibitors

VF	Virologic failure
AS-PCR	Allele-specific PCR
SS	Sanger sequencing

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12981-025-00739-3.

Supplementary Material 1

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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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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Transparency declarations

None to declare.

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References

1. UNAIDS [Internet]. [cited 2023 Sep 16]. Available from: https://www.unaids.org/en
2. Egger M, Hirschel B, Francioli P, Sudre P, Wirz M, Flepp M, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. BMJ. 1997;315:1194–9.
3. Mansky LM. Retrovirus mutation rates and their role in genetic variation. J Gen Virol. 1998;79:1337–45.
4. Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. Science. 1995;267:483–9.
5. Ghimire D, Rai M, Gaur R. Novel host restriction factors implicated in HIV-1 replication. J Gen Virol. 2018;99:435–46.
6. Clavel F. HIV Drug Resistance. The New England Journal of Medicine. 2004.
7. Kemp SA, Charles OJ, Derache A, Smidt W, Martin DP, Iwuji C, et al. HIV-1 evolutionary dynamics under nonsuppressive antiretroviral therapy. Mbio. 2022;13:e0026922.
8. Pandit A, de Boer RJ. Reliable reconstruction of HIV-1 whole genome haplotypes reveals clonal interference and genetic hitchhiking among immune escape variants. Retrovirology. 2014;11:56.
9. Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. Sci (n Y NY). 1995;267:483–9.
10. Kearney M, Palmer S, Maldarelli F, Shao W, Polis MA, Mican J, et al. Frequent polymorphism at drug resistance sites in HIV-1 protease and reverse transcriptase. Aids. 2008;22:497–501.
11. Palmer S, Boltz V, Maldarelli F, Kearney M, Halvas EK, Rock D, et al. Selection and persistence of non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 in patients starting and stopping non-nucleoside therapy. AIDS (lond Engl). 2006;20:701–10.
12. Paredes R, Marconi VC, Campbell TB, Kuritzkes DR. Systematic evaluation of allele-specific real-time PCR for the detection of minor HIV-1 variants with pol and Env resistance mutations. J Virol Methods. 2007;146:136–46.
13. Simen BB, Simons JF, Hullsiek KH, Novak RM, MacArthur RD, Baxter JD, et al. Low-Abundance Drug-Resistant viral variants in chronically HIV-Infected, antiretroviral treatment–Naive patients significantly impact treatment outcomes. J Infect Dis. 2009;199:693–701.
14. Li JZ, Low-Frequency. HIV-1 drug resistance mutations and risk of NNRTI-Based antiretroviral treatment failure: A systematic review and pooled analysis. JAMA. 2011;305:1327.
15. Consolidated. guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a public health approach [Internet]. [cited 2024 May 7]. Available from: https://www.who.int/publications-detail-redirect/9789240031593
16. Palmer S, Kearney M, Maldarelli F, Halvas EK, Bixby CJ, Bazmi H, et al. Multiple, linked human immunodeficiency virus type 1 drug resistance mutations in Treatment-Experienced patients are missed by standard genotype analysis. J Clin Microbiol. 2005;43:406–13.
17. Casadellà M, Manzardo C, Noguera-Julian M, Ferrer E, Domingo P, Pérez-Álvarez S, et al. Clinical value of ultradeep HIV-1 genotyping and tropism testing in late presenters with advanced disease. AIDS (Lond Engl). 2015;29:1493–504.
18. Metzner KJ, Giulieri SG, Knoepfel SA, Rauch P, Burgisser P, Yerly S, et al. Minority quasispecies of Drug-Resistant HIV-1 that lead to early therapy failure in Treatment-Naive and -Adherent patients. Clin Infect Dis. 2009;48:239–47.
19. Li JZ, Paredes R, Ribaudo HJ, Svarovskaia ES, Metzner KJ, Kozal MJ, et al. Low-frequency HIV-1 drug resistance mutations and risk of NNRTI-based antiretroviral treatment failure: A systematic review and pooled analysis. JAMA. 2011;305:1327–35.
20. Zhang R, Jiang Q, Zhuang Z, Zeng H, Li Y. A bibliometric analysis of drug resistance in immunotherapy for breast cancer: trends, themes, and research focus. Front Immunol. 2024;15:1452303.
21. Tang F, Zhao F, Jiang Y, Zhang T, Wang B. Global hotspots and trends in diabetic peripheral neuropathy research from 2011 to 2023. Med (Baltim). 2024;103:e39295.
22. Deng J, Qin Y. Current status, hotspots, and prospects of artificial intelligence in ophthalmology: A bibliometric analysis (2003–2023). Ophthalmic Epidemiol. 2024;1–14.
23. Marzi G, Caputo A, Garces E, Dabić M. A three decade mixed-method bibliometric investigation of the IEEE transactions on engineering management. IEEE Trans Eng Manage. 2020;67:4–17.
24. Wu H, Li Y, Tong L, Wang Y, Sun Z. Worldwide research tendency and hotspots on hip fracture: A 20-year bibliometric analysis. Arch Osteoporos. 2021;16:73.
25. Yang Y, Reniers G, Chen G, Goerlandt F. A bibliometric review of laboratory safety in universities. Saf Sci. 2019;120:14–24.
26. Aria M, Cuccurullo C. *bibliometrix*: an R-tool for comprehensive science mapping analysis. J Informetr. 2017;11:959–75.
27. Chiari W, Damayanti R, Harapan H, Puspita K, Saiful S, Rahmi R, et al. Trend of polymer research related to COVID-19 pandemic: bibliometric analysis. Polymers. 2022;14:3297.
28. Casadellà M, Paredes R. Deep sequencing for HIV-1 clinical management. Virus Res. 2017;239:69–81.
29. Milne RS, Silverman RA, Beck IA, Mckernan-Mullin J, Deng W, Sibley TR, et al. Minority and majority pretreatment HIV-1 drug resistance associated with failure of first-line nonnucleoside reverse-transcriptase inhibitor antiretroviral therapy in Kenyan women. AIDS. 2019;33:941–51.

30. Novitsky V, Nyandiko W, Vreeman R, DeLong AK, Manne A, Scanlon M, et al. Added value of next generation over Sanger sequencing in Kenyan youth with extensive HIV-1 drug resistance. Microbiol Spectr. 2022;10:e0345422.
31. Wang C, Mitsuya Y, Gharizadeh B, Ronaghi M, Shafer RW. Characterization of mutation spectra with ultra-deep pyrosequencing: application to HIV-1 drug resistance. Genome Res. 2007;17:1195–201.
32. Nishizawa M, Hattori J, Shiino T, Matano T, Heneine W, Johnson JA, et al. Highly-sensitive allele-specific PCR testing identifies a greater prevalence of transmitted HIV drug resistance in Japan. PLoS ONE. 2013;8:e83150.
33. Delobel P, Saliou A, Nicot F, Dubois M, Trancart S, Tangre P, et al. Minor HIV-1 variants with the K103N resistance mutation during intermittent efavirenz-containing antiretroviral therapy and virological failure. PLoS ONE. 2011;6:e21655.
34. Gianella S, Richman DD. Minority variants of drug-resistant HIV. J Infect Dis. 2010;202:657.
35. Sili U, Aksu B, Tekin A, Hasdemir U, Soyletir G, Korten V. Assessment of transmitted HIV-1 drug resistance mutations using ultra- deep pyrosequencing in a Turkish cohort. Curr HIV Res. 16:216–21.
36. Alteri C, Santoro MM, Abbate I, Rozera G, Bruselles A, Bartolini B, et al. Sentinel mutations in standard population sequencing can predict the presence of HIV-1 reverse transcriptase major mutations detectable only by ultra-deep pyrosequencing. J Antimicrob Chemother. 2011;66:2615–23.
37. Pingen M, van der Ende M, Wensing A, el Barzouhi A, Simen B, Schutten M, et al. Deep sequencing does not reveal additional transmitted mutations in patients diagnosed with HIV-1 variants with single nucleoside reverse transcriptase inhibitor resistance mutations. HIV Med. 2013;14:176–81.
38. Alidjinou EK, Deldalle J, Hallaert C, Robineau O, Ajana F, Choisy P, et al. RNA and DNA Sanger sequencing versus next-generation sequencing for HIV-1 drug resistance testing in treatment-naive patients. J Antimicrob Chemother. 2017;72:2823–30.
39. Nicot F, Jeanne N, Raymond S, Delfour O, Carcenac R, Lefebvre C, et al. Performance comparison of deep sequencing platforms for detecting HIV-1 variants in the pol gene. J Med Virol. 2018;90:1486–92.
40. Tzou PL, Ariyaratne P, Varghese V, Lee C, Rakhmanaliev E, Villy C, et al. Comparison of an in vitro diagnostic Next-Generation sequencing assay with Sanger sequencing for HIV-1 genotypic resistance testing. J Clin Microbiol. 2018;56:e00105–18.
41. Jabara CB, Jones CD, Roach J, Anderson JA, Swanstrom R. Accurate sampling and deep sequencing of the HIV-1 protease gene using a primer ID. Proc Natl Acad Sci USA. 2011;108:20166–71.
42. Ávila-Ríos S, García-Morales C, Matías-Florentino M, Romero-Mora KA, Tapia-Trejo D, Quiroz-Morales VS, et al. Pretreatment HIV-drug resistance in Mexico and its impact on the effectiveness of first-line antiretroviral therapy: A nationally representative 2015 WHO survey. Lancet HIV. 2016;3:e579–91.
43. Huber M, Metzner KJ, Geissberger FD, Shah C, Leemann C, Klimkait T, et al. MinVar: A rapid and versatile tool for HIV-1 drug resistance genotyping by deep sequencing. J Virol Methods. 2017;240:7–13.
44. Lee ER, Parkin N, Jennings C, Brumme CJ, Enns E, Casadella M, et al. Performance comparison of next generation sequencing analysis pipelines for HIV-1 drug resistance testing. Sci Rep. 2020;10:1634.
45. Kireev DE, Lopatukhin AE, Murzakova A, Pimkina E, Speranskaya AS, Neverov AD, et al. Evaluating the accuracy and sensitivity of detecting minority HIV-1 populations by illumina next-generation sequencing. J Virol Methods. 2018;261:40–5.
46. Lehman DA, Wanalwa DC, McCoy CO, Matsen FA, Langat A, Chohan BH, et al. Low-frequency nevirapine resistance at multiple sites May predict treatment failure in infants on nevirapine-based treatment. J Acquir Immune Defic Syndr. 2012;60:225.
47. Loubser S, Balfe P, Sherman G, Hammer S, Kuhn L, Morris L. Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother-to-child HIV transmission. AIDS. 2006;20:995–1002.
48. Coovadia A, Hunt G, Abrams EJ, Sherman G, Meyers T, Barry G, et al. Persistent minority K103N mutations among women exposed to single-dose nevirapine and virologic response to nonnucleoside reverse-transcriptase inhibitor-based therapy. Clin Infect Dis. 2009;48:462–72.
49. Rowley CF, Boutwell CL, Lee EJ, MacLeod IJ, Ribaudo HJ, Essex M, et al. Ultrasensitive detection of minor drug-resistant variants for HIV after nevirapine exposure using allele-specific PCR: clinical significance. AIDS Res Hum Retroviruses. 2010;26:293–300.
50. Milne RS, Silverman RA, Beck IA, Mckernan-Mullin J, Deng W, Sibley TR et al. Minority and majority pre-treatment HIV-1 drug resistance associated with failure of 1st-line NNRTI ART in kenyan women. AIDS (London, England). 2019;10.1097/QAD.0000000000002134.
51. Halvas EK, Wiegand A, Boltz VF, Kearney M, Nissley D, Wantman M, et al. Low frequency nonnucleoside reverse-transcriptase inhibitor-resistant variants contribute to failure of efavirenz-containing regimens in treatment- experienced patients. J Infect Dis. 2010;201:672–80.
52. Su B, Zheng X, Liu Y, Liu L, Xin R, Lu H, et al. Detection of pretreatment minority HIV-1 reverse transcriptase inhibitor-resistant variants by ultra-deep sequencing has a limited impact on virological outcomes. J Antimicrob Chemother. 2019;74:1408–16.
53. Nicot F, Sauné K, Raymond S, Jeanne N, Carcenac R, Lefebvre C, et al. Minority resistant HIV-1 variants and the response to first-line NNRTI therapy. J Clin Virol. 2015;62:20–4.
54. Chaillon A, Nakazawa M, Wertheim JO, Little SJ, Smith DM, Mehta SR, et al. No substantial evidence for sexual transmission of minority HIV drug resistance mutations in men who have sex with men. J Virol. 2017;91:e00769–17.
55. Metzner KJ, Scherrer AU, Preiswerk B, Joos B, von Wyl V, Leemann C, et al. Origin of minority drug-resistant HIV-1 variants in primary HIV-1 infection. J Infect Dis. 2013;208:1102–12.
56. Johnson JA, Li J-F, Wei X, Lipscomb J, Irlbeck D, Craig C, et al. Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naive populations and associate with reduced treatment efficacy. PLos Med. 2008;5:1112–22.
57. Gupta S, Lataillade M, Kyriakides TC, Chiarella J, John EPS, Webb S, et al. Low-frequency NNRTI-resistant HIV-1 variants and relationship to mutational load in antiretroviral-naïve subjects. Viruses. 2014;6:3428.
58. Tang MW, Shafer RW. HIV-1 antiretroviral resistance: scientific principles and clinical applications. Drugs. 2012;72:e1–25.
59. Lataillade M, Chiarella J, Yang R, Schnittman S, Wirtz V, Uy J, et al. Prevalence and clinical significance of HIV drug resistance mutations by ultra-deep sequencing in antiretroviral-naïve subjects in the CASTLE study. PLoS ONE. 2010;5:e10952.
60. Perrier M, Visseaux B, Landman R, Joly V, Todesco E, Yazdanpanah Y, et al. No impact of HIV-1 protease minority resistant variants on the virological response to a first-line PI-based regimen containing Darunavir or Atazanavir. J Antimicrob Chemother. 2018;73:173–6.
61. Ross LL, Weinberg WG, DeJesus E, Fischl MA, Horton JH, Pappa KA, et al. Impact of low abundance HIV variants on response to Ritonavir-Boosted Atazanavir or Fosamprenavir given once daily with Tenofovir/Emtricitabine in Antiretroviral-Naive HIV-Infected patients. AIDS Res Hum Retroviruses. 2010;26:407–17.
62. Gibson RM, Weber J, Winner D, Miller MD, Quiñones-Mateu ME. Contribution of Human Immunodeficiency Virus Type 1 Minority Variants to Reduced Drug Susceptibility in Patients on an Integrase Strand Transfer Inhibitor-Based Therapy. Sluis-Cremer N, editor. PLoS ONE. 2014;9:e104512.
63. Inzaule SC, Hamers RL, Noguera-Julian M, Casadellà M, Parera M, De Rinke TF, et al. Primary resistance to integrase strand transfer inhibitors in patients infected with diverse HIV-1 subtypes in sub-Saharan Africa. J Antimicrob Chemother. 2018;73:1167–72.
64. Mbisa JL, Ledesma J, Kirwan P, Bibby DF, Manso C, Skingsley A, et al. Surveillance of HIV-1 transmitted integrase strand transfer inhibitor resistance in the UK. J Antimicrob Chemother. 2020;75:3311–8.
65. Baxter J, Dunn D, Tostevin A, Marvig R, Bennedbæk M, Cozzi-Lepri A, et al. Transmitted HIV-1 drug resistance in a large international cohort using next-generation sequencing: results from the strategic timing of antiretroviral treatment (START) study. HIV Med. 2021;22:360–71.
66. Armenia D, Vandenbroucke I, Fabeni L, Van Marck H, Cento V, D'Arrigo R, et al. Study of genotypic and phenotypic HIV-1 dynamics of integrase mutations during raltegravir treatment: A refined analysis by ultra-deep 454 pyrosequencing. J Infect Dis. 2012;205:557–67.
67. Abram ME, Ram RR, Margot NA, Barnes TL, White KL, Callebaut C, et al. Lack of impact of pre-existing T97A HIV-1 integrase mutation on integrase strand transfer inhibitor resistance and treatment outcome. PLoS ONE. 2017;12:e0172206.
68. Nguyen T, Fofana DB, Lê MP, Charpentier C, Peytavin G, Wirden M, et al. Prevalence and clinical impact of minority resistant variants in patients failing an integrase inhibitor-based regimen by ultra-deep sequencing. J Antimicrob Chemother. 2018;73:2485–92.

69. Fonager J, Larsson JT, Hussing C, Neess Engsig F, Nielsen C, Fischer TK. Identification of minority resistance mutations in the HIV-1 integrase coding region using next generation sequencing. J Clin Virology: Official Publication Pan Am Soc Clin Virol. 2015;73:95–100.

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