

Review article

Underrepresentation of Africa in HIV cure research: A systematic review of the literature from 2010 to 2022

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ABSTRACT

Problem considered: Over the past decade, there has been a significant increase in research aimed at finding a cure or achieving long-term remission for HIV. However, the extent to which this research includes Africa—the continent with the highest HIV burden—remains unclear. To address this, we conducted a systematic review of the literature to assess Africa's contributions to HIV cure research.

Methods: We reviewed original HIV cure-related research published from January 1, 2010, to December 31, 2022, in Embase.com and Web of Science. Our search terms, 'HIV cure(s)' and 'research,' along with their synonyms like HIV latency, persistence, and reactivation, covered all languages and geographic locations. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: Of 1077 studies reviewed, 614 (57 %) were performed in North America, followed by Europe (24.3 %), Asia (17.2 %), and Australia 5.2 %. Africa contributed only 31 studies (2.9 %). Of the 31 African studies, Southern Africa accounted for 67.7 %, followed by Eastern Africa (19.4 %) and Western Africa (12.9 %). No cure-related studies were performed in Northern and Central African institutions. African contributions across the different types of studies were 18 (3.7 %) for ex vivo, 8 (10.7 %) for social science and epidemiological, 3 (3.3 %) for clinical trials, 4 (0.8 %) for basic science, and zero for animal studies. The NIH funded the majority of all cure-related studies.

Conclusions: This systematic review shows that African patients and scientists are contributing little to HIV cure research, and urgent measures are needed to remedy the disparity.

1. Introduction

HIV remains a significant public health problem, with over 1.2 million new cases annually and 38 million people living with the virus, out of which 70 % reside in Africa.^{1,2} HIV infection has no cure and requires a lifelong commitment to antiretroviral therapy (ART) to prevent the development of Acquired Immune Deficiency Syndrome (AIDS). However, ART may not be a viable strategy to end the HIV/AIDS pandemic due to non-adherence to medications, incomplete viral

suppression, drug resistance, unsustainable costs, and drug side effects.³ This is why institutions such as the International AIDS Society and the National Institutes of Health (NIH) have prioritized HIV cure in their activities and projections. The persistence of the HIV provirus in quiescent memory CD4⁺ T cells and other reservoirs is the main obstacle to an HIV cure.⁴ Based on the known characteristics of the HIV-1 provirus, scientists are working on several approaches for an HIV cure. First is the shock and kill approach (latency reactivation).^{5–9} In this method, small molecules are used to force proviral reactivation from latency

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under the cover of ART. Induction of de novo virion synthesis is expected to result in cell death from viral cytopathic effects or immune clearance, after which ART can be discontinued. Second, the block and lock approach, where patients on ART will be treated temporarily with drugs to modify the chromatin surrounding the provirus to make latency permanent, thus allowing patients to stop ART.^{10–16} Third, genetic methods like transcription activator-like effector nucleases (TALENs)^{17–21} and clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 that will either disable the virus, excise it from the genome or modify receptors used for viral entry.^{22–27} Fourth, immunotherapies such as the use of broadly neutralizing antibodies^{28–36} and therapeutic vaccines to suppress reactivation or CAR T cells (Chimeric Antigen Receptor T cells) to eliminate cells with reactivated virus.^{35,37–42} Finally, combination approaches involving one or more of the above methods are also being pursued.^{43,44} Through these methods, scientists envisage two main scenarios for an HIV cure. The first is a complete cure, where the virus is eliminated from the body, and the second is a functional cure, where the viral reservoir is reduced to a minimum such that ART can be stopped with periodic monitoring without the threat of immediate rebound.^{43,45}

The past decade has seen intensive research into the mechanisms of HIV latency, persistence, and cure, resulting in several early-phase clinical trials.^{46–55} However, though Africa bears the brunt of the HIV pandemic, a cursory look at the literature suggests that very little of the cure research is being done on the continent.⁵⁶ Cure research must be performed in Africa for several reasons. First, the continent has the most variety of HIV clades, subtypes, and recombinant forms, which may have differences in reservoir characteristics, immune response, clonality, and integration sites, among many parameters. Thus, the basic science of cure research must include subtypes A, C, and D, recombinant forms such as CRF02_AG, and even HIV-2.^{57,58} Second, most cure approaches will depend on some alteration of the immune system, such as latency reversal of CD4⁺ T cells, boosting CD8⁺ T cell responses, using broadly neutralizing antibodies, or therapeutic vaccinations.^{43,45} Since African people have different genetic make-up and are exposed to different pathogens, their immune responses may differ from those in Europe or the USA. These differences may also affect the reservoir's size and response to latency-reversing agents. Third, Africa has a high concentration of people living with HIV (PLWH) who started ART long after they knew their status because of previous CD4 count thresholds for starting ART. In addition, due to the WHO recommendation that a viral load of <1000 is acceptable in Africa,⁵⁹ many PLWH may have low-level viremia. These two factors may increase CD4⁺ T cell seeding and make it difficult to clear the reservoir. Finally, given the success of ART, it may take some convincing for African patients to participate in cure trials or accept cure interventions. For instance, while patients in Europe and America are generally amenable to participate in analytical treatment interruption (ATI) for cure research, a study from Ghana showed that 67 % of patients would not participate in ATI even if their physician monitored them closely.⁶⁰ It is possible that when patients see more African scientists involved in basic and clinical research, they are more likely to agree to clinical trials. In this study, we sought to determine how much of the literature on HIV cure research comes from Africa and involves African authors or patients. We considered cure research from basic, clinical, and epidemiological research.

2. Methods

This review protocol is published at PROSPERO with registration number CRD42023393383. We followed the relevant components of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.⁶¹ This review does not include a meta-analysis or analysis of the study effects; it concerns authorship, types of studies, and where the studies were performed. The study was performed between January 2023 to June 2024.

2.1. Types of studies

Studies involving HIV cure research, basic science, clinical trials, implementation science, social science, in vitro, and animal studies aimed at finding an HIV cure and published in peer-reviewed journals from January 2010 to December 2022 were included in this review. The search was conducted by a medical librarian using search terms of HIV AND cure, latency, reactivation, and persistence, with related synonyms covering all languages and geographic locations. The strategies were created using a combination of controlled vocabulary terms and keywords and were executed in [Embase.com](https://www.embase.com) and Web of Science. The full search strategy can be found in the appendix. Only original articles were included in our review. We excluded review articles, commentaries, editorials, abstracts without full text, case studies, vaccine studies, letters, editorials, notes, conference abstracts, conference papers, book chapters, or other studies unrelated to HIV cure. All database searches were completed on June 15, 2023. Results retrieved from the database literature search were imported to Endnote, where duplicate citations were identified and removed. The remaining citations were imported to Covidence software for screening. The screening was conducted independently by five reviewers, each of whom searched for articles published in a particular year (2010–2022). These were cataloged into the Research Electronic Data Capture (REDCap) for this purpose using a unique PubMed ID and DOI. Full-text papers were analyzed in REDCap for continent affiliation of authors, type of study, participants' origin, and funding sources.

2.2. Types of participants

Studies involving all categories of people were included. Our review was not limited to age, race, language, country, region, continent, or gender.

2.3. Settings

There were no restrictions on the study setting. Studies conducted in any setting were included.

2.4. Screening of articles

Article screening was accomplished in Covidence software. The flow chart in [Fig. 1](#) was followed to identify articles to be included in the review.

2.5. Extraction of data

The following study characteristics, PubMed ID, DOI, year of publication, open access, or not, were extracted from each journal article reviewed. The specific subject studied, HIV latency, HIV cure, or HIV persistence, was captured, as well as the author's details, including country and continent (Africa, North America, South America, Europe, Asia, Australia) of affiliation. For authors affiliated with African countries, their region and position on the author list (first, second, or corresponding author) were captured. The type of study was extracted as basic science (no cells from HIV patients), ex-vivo (cells from patients for laboratory studies), human clinical trials, animal studies (mice or monkeys), and social science/epidemiology. When a publication involved more than one study type (for example, a clinical trial that did ex vivo work), all that applied was captured. In addition, if the publication involved multiple continents, each continent was given credit for that study. We also extracted information on the country or continent where the study was conducted; for each study, all the continents involved were captured. Where the study was conducted in Africa, the region was captured as North, South, East, West, or Central. The REDCap software was used to capture and store all this information.

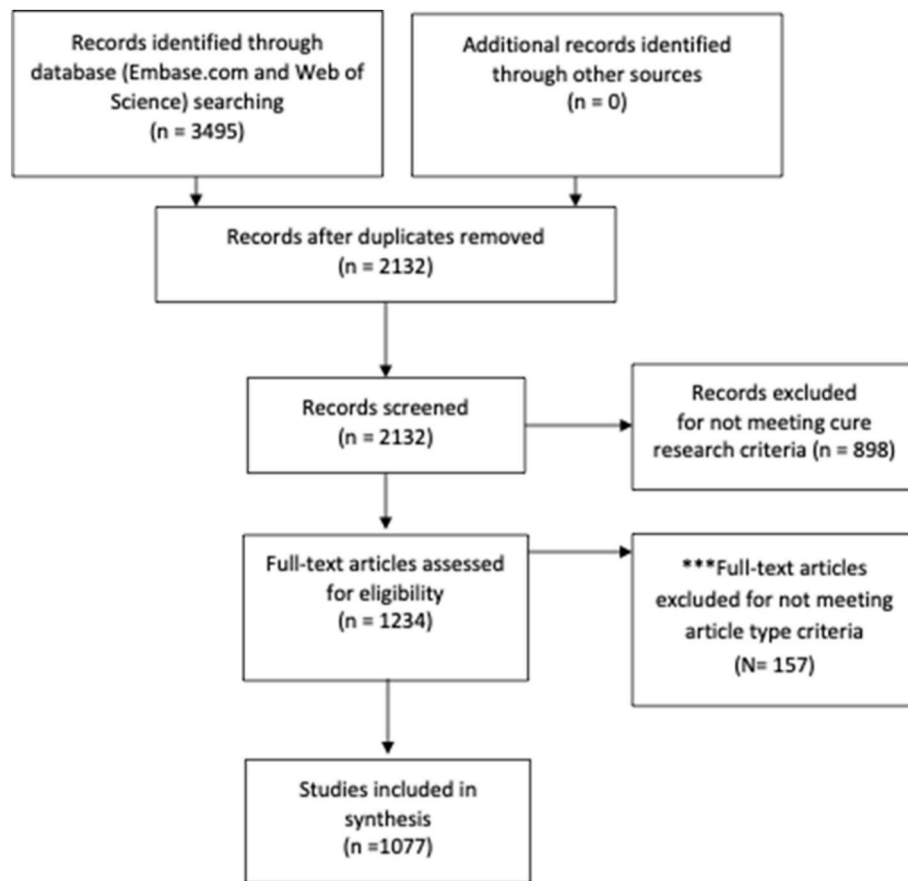


Fig. 1. Study Selection Flow Diagram

*** Full-text articles excluded at this stage were reviews, commentaries, and opinions.

2.6. Data analysis

We summarized data from each study included in the review and used descriptive statistics to present the proportions. We categorized studies based on the continent in which it was carried out, the continent of author affiliation, and funding sources. All analyses and reporting followed the updated PRISMA guidelines.⁶¹ Any amendments to the protocol were updated in PROSPERO.

3. Results

3.1. Inclusion of studies

The initial search resulted in 3495 studies, of which 1363 were excluded as duplicates. After reviewing the abstracts of the remaining 2132 studies, 898 studies were identified as not related to HIV cure and were excluded. A full-text review was conducted for the 1234 studies, but 157 did not meet the inclusion criteria and were excluded, leaving 1077 studies that met the inclusion criteria to be included in this review (Fig. 1).

3.2. Yearly publications of HIV cure studies

This review included 1077 studies published between 2010 and 2022. As shown in Fig. 2, there was a consistent rise in HIV cure-related studies during this period, with a notable tenfold increase in between 2010 and 2022.

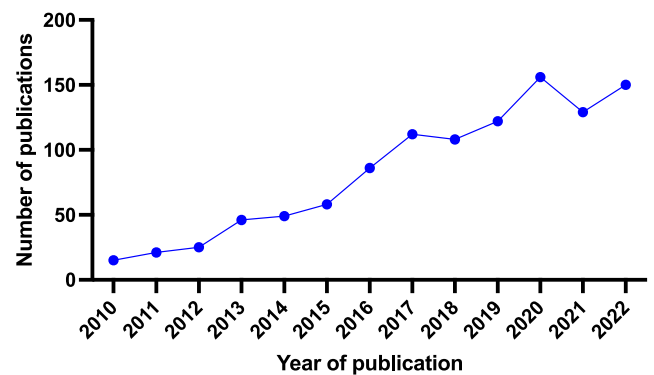


Fig. 2. Yearly distribution of HIV cure-related publications between 2010 and 2022.

3.3. Types of HIV cure studies

HIV cure studies were categorized into five groups: basic science (studies with cell lines or primary cells from non-HIV participants), ex-vivo (studies with primary cells or tissues obtained from PLWH), clinical trials, animal studies, and social science or epidemiological-related studies. Ex-vivo studies accounted for the largest portion of 45.3 %, followed by basic science at 44.5 %. Social science or epidemiological studies comprised the smallest number of studies at 7.0 % (Table 1).

Table 1
Types of HIV cure studies over the study period and the proportion from Africa.

Study Type	No. Studies (N = 1077) ^a	Study (%)	No. Studies in Africa (N = 31) [*]	Studies in Africa (%)
Basic science	479	44.5	4	0.8
Ex-vivo	488	45.3	18	3.7
Animal studies	113	12.3	0	0.0
Social science/epidemiology	75	7.0	8	10.7
Human clinical trials	91	8.4	3	3.3

^a Some studies fell into more than one study type and were counted for each category.

3.4. Participants involved in HIV cure studies

The studies reviewed included a total of 41,500 participants, categorized as follows: 25,883 ex-vivo participants, 10,277 from social sciences/epidemiological research, and 5390 from clinical trials. Europe contributed the highest number of participants at 15,246 (37.2 %), followed by North America with 13,883 (33.5 %), and Africa with 5859 (14.1 %). Of the participants from Africa, two studies accounted for 4332 (73.9 %) individuals, including one clinical trial involving 2019 participants and a social science study interviewing 2313 participants (Table 2). Only four basic science studies were performed in Africa, with zero cure-related animal studies.

3.5. Study performance sites and author affiliations

Out of the 1077 papers reviewed, the majority (614, or 57 %) originated from North America, mostly the USA, followed by Europe with 262 papers (24.3 %), Asia with 185 (17.2 %), Australia with 56 (5.2 %), and South America with 18 (1.7 %). Africa contributed 31 papers, making up only 2.9 % of the total. Additionally, 89 studies were collaborative efforts involving multiple continents; when this occurred, each continent was given credit for that study. The authors' affiliations followed a similar distribution (Fig. 3A): 694 publications (64.4 %) were linked to North American institutions, 333 (30.9 %) to Europe, 214 (19.9 %) to Asia, 82 (7.6 %) to Australia, 39 (3.6 %) to Africa, and 24 (2.2 %) to South America. Overall, 220 studies had authors' affiliations outside of where the studies were performed, accounting for the higher affiliation numbers compared to performance sites. Among the 39 publications from African-affiliated authors, Southern Africa was the most prominent contributor, accounting for two-thirds (67.7 %) of the output, while Eastern Africa contributed 19.4 %, and Western Africa made up 12.9 % (Fig. 3B). Of the 31 studies conducted in Africa, African-affiliated authors served as first authors in 16 (51.6 %) publications, second authors in 18 (58.1 %), and corresponding authors in 13 (41.9 %).

Table 2
Distribution of participants involved in HIV cure studies.

Continents	Ex-vivo (%)		Clinical Trial		Social Science		Total	
	N	%	N	%	N	%	N	%
Europe	11,364	43.9	1544	28.6	2338	22.9	15,246	37.2
North America	10,168	39.3	1446	26.8	2269	22.2	13,883	33.5
Asia	2831	10.9	50	0.9	1491	14.6	4372	10.5
Africa ^a	843	3.2	2118	39.3	2898	28.3	5859	14.1
Australia	469	1.8	109	2.0	1108	10.8	1686	4.1
South America	208	0.8	123	2.3	123	0.1	454	1.1
Total	25,883	62.4	5390	13	10,227	24.6	41,500	100.0

^a One study recruited 2019 participants, and another interviewed 2313 participants.

3.6. Sources of funding for HIV Cure Studies

The National Institutes of Health (NIH) was the primary supporter of HIV cure studies worldwide (Fig. 3C), funding 600 of the 1,077 studies (55.7 %). This was followed by European government agencies (22.6 %), Asian governments, mainly China (14.6 %), and Australian government agencies (5.2 %). African government agencies contributed to nine studies (0.8 %). Among non-governmental organizations, the American Foundation for AIDS Research (amfAR) supported 72 studies (6.6 %), while pharmaceutical and biotech companies contributed 5.2 %, the Bill and Melinda Gates Foundation 2.7 %, and the Wellcome Trust 1.4 % of the studies. The NIH was the main donor for African studies, supporting 25 of the 31 studies (80.6 %) (Fig. 3D).

4. Discussion

In this study, we examined the contributions of researchers and individuals living with HIV in Africa to the pursuit of a cure. Our key findings revealed that HIV cure research is limited on the African continent, with minimal involvement from African researchers and people living with HIV. We found that publications on HIV cure have increased 10-fold between 2010 and 2022, which is encouraging for the field and aligns with the priorities of organizations such as the NIH⁶² and the International AIDS Society.⁶³

Although we did not anticipate a large number of studies from the African continent, the finding that only 2.9 % of cure studies were conducted in Africa during the period was surprisingly lower than expected. Africa contributed 2.0 % to the preclinical studies (basic, ex vivo, animal studies), 3.3 % to clinical trials, and 10.7 % to the social/epidemiologic cure studies. This pattern shows that the lack of preclinical studies also translates to fewer clinical trials on the continent. Indeed, zero animal studies and four basic science studies were conducted in Africa over the 12 years. The lack of preclinical studies in Africa may stem from the high cost and specialized laboratory skills required, as well as the need for expensive reagents and instrumentation. However, over the past ten years, many African universities have significantly improved their basic science infrastructure, boosted by the COVID-19 pandemic.⁶⁴ These centers can perform most cure-related preclinical studies with the necessary focus and personnel training and should be incentivized and encouraged to do so. Increasing the number of African scientists in the basic science of HIV will accelerate the global cure research efforts. These scientists can then collaborate with their colleagues in the global north to expedite the cure research. In an era where 'parachute science' (where samples are just taken from Africa for research elsewhere) is frowned upon, there is a need to train basic scientists in Africa who can work with their northern colleagues on an equal footing to advance the cure research agenda. Indeed, the NIH has recognized this deficiency in HIV cure in Africa and recently issued a 5-year call for proposals addressing HIV basic research in diverse populations (NOT-AI-23-046). However, for such initiatives to be impactful in Africa, they should be linked with the training of African scientists in HIV basic science and cure research. In addition, such opportunities

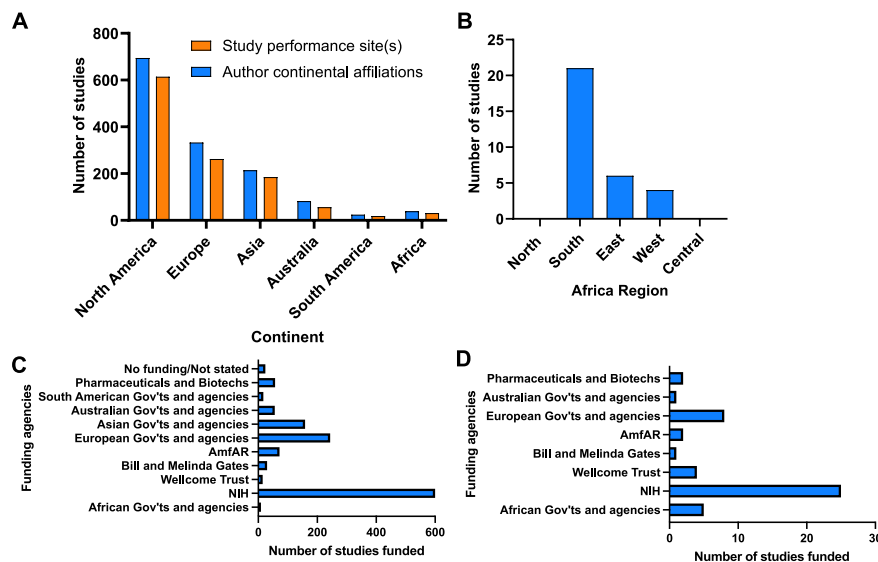


Fig. 3. HIV cure studies performance sites, author affiliations, and funding sources. (A) Overall study performance sites and author affiliations. The slight differences between performance sites and author affiliations are due to authors contributing to studies performed elsewhere. (B) Regional affiliations for studies performed in Africa. (C) Agencies that funded HIV cure research worldwide. (D) Agencies that funded HIV cure research in Africa.

should require that most of the laboratory work be done in African institutions, which will naturally translate to more cure clinical trials in Africa over time.

In line with where cure research occurs, the participants came mainly from the USA, Europe, and China. Participants from Africa constituted 14 % (5859), skewed by one clinical trial that recruited 2019 participants and a social science study that recruited 2313 participants. Aside from Africa, very little cure research occurred in South America and the Caribbean, although it is estimated that 2.5 million people live with HIV in this region.⁶⁵ Thus, efforts should be made to include African and South American participants in cure research. By far, the NIH was the main sponsor of cure research worldwide, supporting almost 60 % of the effort. This aligns with the organization's strategic plan for HIV, of which cure research is one of the priorities. One way to boost cure research in deficient areas like Africa and South America is to design specific funding opportunity announcements that build capacity in these regions. We noted that organizations like the Wellcome Trust and the EDCTP that fund translational research in Africa have yet to fund significant cure research on the continent. African governments should also be encouraged to devote more resources to HIV basic science training and cure research.

5. Conclusions

Involving African scientists and individuals living with HIV (PLWH) in cure research is both a scientific and ethical imperative. Their inclusion not only accelerates progress in finding a cure but also ensures that the methods developed are tailored to the needs of African populations. This approach enhances the relevance and acceptance of potential cures or long-term remission strategies when they reach clinical application. Our findings highlight a significant gap in the participation of African patients and researchers in cure studies and emphasize the urgent need for proactive measures to address this disparity.

List of abbreviations

None.

Authors' contributions

EYB designed the study, reviewed all titles, abstracts, and full-text papers, interpreted the results, wrote the initial draft manuscript, and reviewed the manuscript. JOA reviewed all titles, abstracts, and full-text papers, extracted data, interpreted the data, summarized the results, wrote the manuscript, and reviewed the manuscript. HL reviewed all titles and abstracts, interpreted the results, and reviewed the manuscript. ATB reviewed all titles, abstracts, and full texts, interpreted the results, and reviewed the manuscript. CZYA reviewed all titles and abstracts and reviewed the manuscript. BAL extracted data, summarized the results, and reviewed the manuscript, AH conducted the initial search, reviewed search results, removed duplicates, wrote the search method, reviewed the manuscript. GBK conceived and designed the study, reviewed all titles, abstracts, and full texts, assessed the study quality, interpreted the results, and edited the manuscript. All authors had full access to all the data in the study and agreed to submit it for publication.

Author information

None.

Ethics and consent statement

This is a systematic review and does not require ethical approval or consent.

Disclaimer

None.

Data availability statement

Raw data for this study is available upon written request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: George Kyei reports financial support was provided by European and Developing Countries Clinical Trials Partnership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix

Complete Search Strategies

Embase.com

= 1589 results on 6/14/2023; Results limited to 2010–2022; reviews, letters, editorials, notes, conference abstracts, and conference papers excluded from search results.

((HIV NEAR/2 cure*) OR (HIV NEAR/2 curative*) OR (HIV NEAR/2 latency) OR (HIV NEAR/2 reactivation) OR (HIV NEAR/2 reservoir*) OR (HIV NEAR/3 'shock and kill') OR (HIV NEAR/3 'block and lock') OR (HIV NEAR/2 remission*) OR (HIV NEAR/2 eradication)):ti,ab AND ('research'/exp OR 'clinical trial'/exp OR 'study'/exp OR 'clinical research'/exp OR 'drug research'/exp OR (research* OR trial* OR study OR studies):ti,ab) NOT (('review' OR 'letter' OR 'editorial' OR 'note' OR 'conference abstract' OR 'conference paper' OR 'case study'):it OR ('review'/exp OR 'letter'/exp OR 'editorial'/exp OR 'note'/exp OR 'conference paper'/exp OR 'conference abstract'/exp OR 'case study'/exp)) AND [2010–2022]/py.

Web of Science Core Collection

(Science Citation Index, Social Sciences Citation Index and the Arts & Humanities Citation Index).

= 1, 906 results on 6/24/2023; Results limited to 2010–2022; new items, book chapters, letters, proceeding papers, meeting abstracts, editorial material, and reviews excluded from search using database-supplied limits.

TS=((HIV NEAR/2 cure*) OR (HIV NEAR/2 curative*) OR (HIV NEAR/2 latency) OR (HIV NEAR/2 reactivation) OR (HIV NEAR/2 reservoir*) OR (HIV NEAR/3 'shock and kill') OR (HIV NEAR/3 'block and lock') OR (HIV NEAR/2 remission*) OR (HIV NEAR/2 eradication)) AND TS= (research* OR trial* OR study OR studies).

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