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HIV, FOR AN ETHICS OF CURE: AN ANALYSIS OF THE BIOETHICAL ASPECTS OF CURRENT RESEARCH WITH HIV AND CRISPR-CAS9

HIV, POR UMA ÉTICA DA CURA: UMA ANÁLISE SOBRE OS ASPECTOS BIOÉTICOS DAS ATUAIS PESQUISAS COM HIV E CRISPR-CAS9

VIH, POR UNA ÉTICA DE LA CURACIÓN: UN ANÁLISIS DE LOS ASPECTOS BIÓTICOS DE LA INVESTIGACIÓN ACTUAL CON VIH Y CRISPR-CAS9

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ABSTRACT

The search for a cure for HIV infection remains ongoing. Although conventional methods do not eradicate the virus, they allow people living with HIV to have a better quality of life, provided they correctly follow their medication treatment. With the advancement of biotechnology and genetic engineering, especially through the CRISPR-Cas9 technique, new therapeutic possibilities have been explored. This study conducted an integrative review and bioethical analysis of current research aimed at a functional cure for HIV through genetic manipulation of the human genome. Using the PubMed database, 115,538 articles with the descriptor "HIV" were identified; including "CRISPR" yielded 444 results, and adding "cure" yielded 83, of which 80 were analyzed after exclusions due to thematic irrelevance. The research highlighted the development of HIV control methods and associated bioethical violations, such as lack of representation, failures in informed consent, and unequal access to treatments. The conclusion is that, despite the potential of CRISPR-Cas9 technology, significant ethical concerns persist. Interventional bioethics, based on the principles of prudence, protection, precaution, and prevention, should guide this research. Equitable access and the involvement of the pharmaceutical industry are essential to ensuring ethical and inclusive advances, fostering an ongoing dialogue between science and bioethics.

Keywords: Bioethics. Integrative Review. Access to Health. CRISPR-Cas9.

RESUMO

A busca pela cura da infecção pelo HIV permanece contínua. Embora os métodos convencionais não alcancem a erradicação do vírus, permitem que pessoas vivendo com HIV tenham qualidade de vida, desde que sigam corretamente o tratamento medicamentoso. Com o avanço da biotecnologia e da engenharia genética, especialmente por meio da técnica CRISPR-Cas9, novas possibilidades terapêuticas têm sido exploradas. Este estudo realizou uma revisão integrativa e análise bioética das pesquisas atuais que visam uma cura funcional do HIV por meio da manipulação genética do genoma humano. Utilizando a base de dados PubMed, foram identificados 115.538 artigos com o descritor HIV; ao incluir

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CRISPR, obtiveram-se 444 resultados, e com o acréscimo de cure, restaram 83, dos quais 80 foram analisados após exclusões por irrelevância temática. A pesquisa destacou o desenvolvimento de métodos de controle do HIV e as violações bioéticas associadas, como ausência de representatividade, falhas no consentimento informado, e desigualdade no acesso aos tratamentos. Conclui-se que, apesar do potencial da tecnologia CRISPR-Cas9, persistem preocupações éticas relevantes. A bioética de intervenção, fundamentada nos princípios da prudência, proteção, precaução e prevenção, deve orientar essas pesquisas. A equidade no acesso e o envolvimento da indústria farmacêutica são essenciais para garantir avanços éticos e inclusivos, promovendo um diálogo contínuo entre ciência e bioética.

Palavras-chave: Bioética. Revisão Integrativa. Acesso à Saúde. CRISPR-Cas9.

RESUMEN

La búsqueda de una cura para la infección por VIH continúa. Si bien los métodos convencionales no erradican el virus, permiten a las personas con VIH tener una mejor calidad de vida, siempre que sigan correctamente su tratamiento farmacológico. Con el avance de la biotecnología y la ingeniería genética, especialmente mediante la técnica CRISPR-Cas9, se han explorado nuevas posibilidades terapéuticas. Este estudio realizó una revisión integrativa y un análisis bioético de la investigación actual dirigida a una cura funcional del VIH mediante la manipulación genética del genoma humano. Utilizando la base de datos PubMed, se identificaron 115.538 artículos con el descriptor "VIH"; al incluir "CRISPR" se obtuvieron 444 resultados, y al añadir "cura", 83, de los cuales 80 se analizaron tras exclusiones por irrelevancia temática. La investigación destacó el desarrollo de métodos de control del VIH y las violaciones bioéticas asociadas, como la falta de representación, las fallas en el consentimiento informado y el acceso desigual a los tratamientos. La conclusión es que, a pesar del potencial de la tecnología CRISPR-Cas9, persisten importantes preocupaciones éticas. La bioética intervencionista, basada en los principios de prudencia, protección, precaución y prevención, debe guiar esta investigación. El acceso equitativo y la participación de la industria farmacéutica son esenciales para garantizar avances éticos e inclusivos, fomentando un diálogo continuo entre la ciencia y la bioética.

Palabras clave: Bioética. Revisión Integrativa. Acceso a la Salud. CRISPR-Cas9.

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1 INTRODUCTION

Technological development and improvement have enabled humanity to modify and interfere more and more in the different aspects of its life, in a constant search for the improvement of its physical and mental capacities. This scenario raises an ethical debate about the limits and the need to modify oneself and one's genetic code. With the advent of CRISPR-Cas9 technology for genetic manipulation (DOUDNA *et al.*, 2014), new therapeutic approaches for diseases that are now considered incurable have been suggested. Among these is HIV infection, which was once challenging and commonly evolving into AIDS, which, although still without a cure, is currently controllable with the use of Antiretroviral Therapy (ART).

In the past, several ethical infractions were observed during research seeking treatment for AIDS. These infractions included issues related to inequity in the studies (EPSTEIN *et al.*, 1996), problems with informed consent (RACITI *et al.*, 2021), the use of placebos in control groups (PETER; WOLFE, 1997) and the use of animals infected with SIV (BAROUCH *et al.*, 2012). More recently, a researcher committed ethical violations by using CRISPR-Cas9 technology to make individuals resistant to HIV infection through eugenics (RYDER *et al.*, 2018). There is the possibility that practices such as these, or worse, will continue or return to happen for financial gain or professional recognition, which may bring unknown risks to the patient's health. It is assumed that the development of a technique such as this is necessary only if the benefits outweigh the risks, since the use of ART allows people living with HIV (PLWHA) to have longer survival and good quality of life, reducing complications related to retroviral infection (CARVALHO *et al.*, 2019).

In view of this, it is necessary to understand how ethical elements are being considered in research for the development of a cure for HIV infection using the CRISPR-Cas9 method. Possible interventions and recommendations necessary for studies should be evaluated in order to prevent an increase in the incidence of vulnerabilities in PLWHA. The present study

sought to examine, from the perspective of bioethics, the conduct of current research aimed at establishing a functional or sterilizing cure for HIV through the CRISPR-Cas9 genetic manipulation methodology. To better outline this objective, the study presents the evolution of research and methods of HIV control already known and established. In doing so, the research highlights how bioethical assumptions have been violated in this process, and then compares how studies using the CRISPR-Cas9 technique have been conducted and evaluates their ability to produce vulnerabilities in their participants.

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2 METHODOLOGY

The present research is an integrative review of scientific literature, aiming to map the ethical issues related to current research that uses genetic techniques in search of a cure for HIV infection. Considered the broadest approach among the reviews, the integrative review allows the inclusion of experimental and non-experimental studies, enabling a complete understanding of the object or phenomenon studied, as well as a joint analysis of the theoretical and practical literature. It also allows for the structuring and development of theoretical knowledge, with possible practical applicability (ROSANELI; FISCHER, 2024)

The objective of this research was to characterize how ethical elements are being considered in research for the development of a cure for HIV infection, which uses the CRISPR/Cas9 method of genetic engineering. The question was based on the conclusion of studies aimed at the control or cure of retroviral infection, but questioned about the appropriation of bioethical assumptions in the planning, execution and dissemination of data with the potential to inflict harm on individuals and even societies. In the literature, there are several examples of research that has been discredited as to its ethical potential (PETER; WOLFE, 1997; RYDER *et al.,* 2018), so it is hoped that new research will not make the same mistakes as in the past in favor of curing a disease for which it is already possible to control well, seeking to respect the principles of principlistic Bioethics: justice, autonomy, beneficence and non-maleficence (BEAUCHAMP; CHILDRESS, 2002).

Due to the large volume of information currently available, common databases for systematic reviews in health and other areas were used, as well as specific databases for the subject of HIV/AIDS. The present review used the following databases and electronic journals: PubMed, LILACS and SciELO. The research considered evaluating publications generated up to 10 years after the development of the CRISPR-Cas9 method (JINEK *et al.*, 2013)

The inclusion criteria adopted to guide the search and selection of articles were: studies that addressed the HIV/AIDS theme, that involved or cited the CRISPR/Cas9 genetic engineering technique, seeking a cure; Studies in English, published in international and national journals, in the period from 2014 to 2023, since it is a technique with recent discovery, not having many previous articles that relate HIV to CRISPR/Cas9. Only free, full, and peer-reviewed texts were included.

The selected articles were analyzed and categorized into general and specific variables, qualitatively and quantitatively evaluating the citations of the terms of interest, with

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subcategories determined a posteriori. Descriptive statistics and semantic content analysis were used, according to Bardin (1977). The pre-defined categories and subcategories were divided into: a) General variables: Local (Continents); Area of Expertise (Genetics, Immunology, etc.); Type of Research (Experimental/Theoretical); Year (2014-2023); Objective (Technical/Ethical); Objects/Individuals (In-vitro, Animals, People); Animal Research (Absent, Mice, Monkeys); Bioethical Terms (Justice, Beneficence, etc.); Research with Children (Absent/Present); Submission to the Ethics Committee. b) Specific variables: b1) Conservative Techniques (ART, Vaccine, CRISPR, etc.), subcategorized into Limitations (Economic, Social, Technical) and Prospects for Cure (Social, Technical); b2) Genetic Techniques (CRISPR, ZFNs, TALENs), evaluated in Limitations (Technical, Social, Ethical, Economic) and Benefits (Technological). Each aspect was analyzed qualitatively and quantitatively, considering presence/absence in the texts.

3 RESULTS AND DISCUSSION

The search suggestions after submitting the criteria and exclusion resulted in the inclusion of 81 articles in the analysis. Among the articles analyzed, there was a predominance (54.7%) of research being carried out in the United States of America, followed by China (10.5%) and the Netherlands (8.1%), and some of these were still carried out in partnership with American universities (Figure 1). The prominence of the USA can be explained by the amount of funding for research in the health area, both primary (of government origin) and secondary (of private origin, promoted by large companies, such as multinationals) (CHNEEGANS *et al.*, 2021). In the USA, an intersectoral relationship between colleges, research institutions and the financial market is equally common, in addition to high government investments in the basic research sector, there is a high investment by the private sector in the area of biotechnology, in which genetic engineering is included, with potential for use in agriculture and medical sciences. When it comes to the number of biotech companies, the 6,213 registered companies place the U.S. in the lead, followed by Spain (1,715), France (1,481) and South Korea (885). In 2011, Brazil had 237 biotectology companies and ranked 13th (OECD, 2012).

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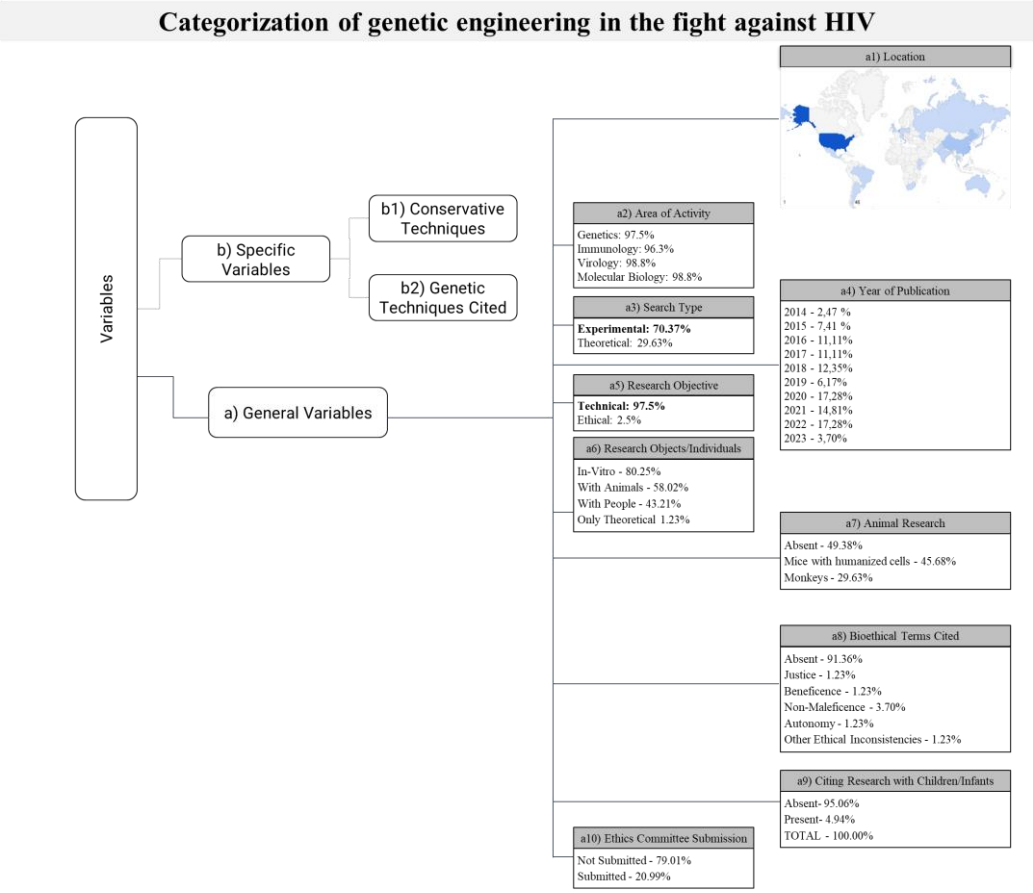
Figure 1

Flowchart of the categorization of the integrative review



Source: the authors from the integrative review.

When considering the high interference of the private sector in genetic engineering research, positive and negative considerations arise. Among the positive ones, the accelerated development stands out, due to the significant resources allocated to the area, resulting in direct benefits for society (SILVA; ROCHA, 2023), and the increase in the specialization and efficiency of methods, made possible by the companies' infrastructure to test, develop and commercialize products, generating discoveries that would hardly occur in other ways (MARTINS; FERREIRA, 2022). Among the negative aspects, conflicts of interest stand out, since companies prioritize profit, being able to direct research to more profitable treatments than necessary (SANTOS; ALMEIDA, 2023). This creates problems of access and equity, especially in low- and middle-income countries, as well as a lack of transparency when the results do not favor commercial interests. Patents limit the circulation of knowledge, delaying scientific progress. The search for financial return can also divert public funds from priority areas (LIMA; MORAES, 2023).

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The integrative review showed a predominance of technical objectives (97.5%) over ethical ones (2.5%) (HENDRIKS *et al.*, 2018; KALIDASSAN; TEVA, 2020). This absence of an ethical focus may be linked to the attraction for the recognition of technical applicability and financial potential, since much research was funded by private industry (SANTOS; ALMEIDA, 2023).

The CRISPR-Cas9 technique is recent: started in the late 1980s, it gained momentum in 2010, when Sylvain Moineau demonstrated the possibility of DNA breaks in predictable locations (METZL, 2020). In 2012, Charpentier and Doudna reprogrammed the system for intentional cuts, and in 2020 they were awarded the Nobel Prize in Chemistry. The method has become simpler and cheaper than ZFN and TALENs (GUPTA; MUSUNURU, 2014). This advance explains the predominance of the technical focus and the beginning of HIV research from 2014 onwards, with growth until 2019. However, the controversial case of Chinese researcher He Jiankui, who in 2018 genetically manipulated embryos, leading to the birth of twin girls supposedly immune to HIV, generated condemnation in 2019 (BBC NEWS, 2019) and may have delayed publications. With the Covid-19 pandemic, the scenario changed, favoring advances in biotechnology and expanding publications after 2020.

Most of the studies analyzed were experimental (70.37%), in the pre-clinical phase, reflecting the need to assess risks before clinical trials in humans (MUSUNURU, 2019). Rigorous trials are essential for the approval of therapies by regulatory agencies such as the FDA and EMA (COSTA, 2024). The most frequent areas were genetics (97.5%), immunology (96.3%), virology (98.8%), and molecular biology (98.8%), which are fundamental for understanding the HIV cycle and developing strategies with CRISPR-Cas9 (DOUDNA; CHARPENTIER, 2014; FLEXNER *et al.*, 2018).

As for the research objects, *in vitro use predominated* (80.2%), followed by animals (58%) and humans (43.2%). In vitro is preferred for safety, experimental control and lower cost, in addition to allowing tests before in vivo applications (KHALILI *et al.*, 2015). This pattern reflects preclinical phases, but there is already an increase in in vivo studies. References to research with people, such as the case of He Jiankui, rekindle ethical concerns already experienced in studies with women in Africa and Asia in the 1990s, when placebo was used instead of standard treatment (RACITI *et al.*, 2021; PETER; WOLFE, 1997). Some articles (4.9%) mention babies (KALIDASAN; THEVA, 2020; HENDRIKS *et al.*, 2018; XIAO *et al.*, 2019; PHAM; MESPLÈDE, 2018), but the majority (95%) did not even mention children.

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To prevent violations, the Research Ethics Committees (REC) evaluate scientific validity, consent, and risks, ensuring international standards (MS, 2012). However, only 29.82% of the studies that could be submitted to the REC were actually submitted to the CEP. Even *in vitro research* with human biological material requires submission, which indicates potential ethical complications (FLEXNER *et al.*, 2018). CRISPR-Cas9 offers unprecedented opportunities, but raises ethical dilemmas such as unforeseen effects, transmissibility to future generations, and equity in access (POTTER, 1971). The ideal would be to submit all works to the CEP, even without legal requirement. Regarding the use of animals, mice (45.7%) and monkeys (29.6%) stand out. Doubts persist about risks, benefits and respect for the principles of the 3Rs (CONCEA, 2016).

3.1 CONSERVATIVE TECHNIQUES

Among the conservative techniques presented in the scientific literature that are part of this review, there was a prevalence of ART (61.5%) (Figure 2). Currently, ART is the only treatment of choice for controlling HIV infection. The treatment consists of the combined use of antiretroviral drugs, which is extremely effective and aims to reduce the HIV viral load in the patient to an undetectable level, inhibiting the progression of the disease, as well as the transmission of the virus to third parties, (LUNDGREN *et al.*, 2015). ARV treatment allows PLWHA to have a longer life expectancy, with quality, reducing the occurrence of opportunistic infections and other complications, substantially reducing the risks of transmission to uninfected sexual partners, allowing discordant serum couples to have children (CARVALHO et al, 2019). However, even with these benefits, the use of ART can still have some side effects, such as kidney failure, hepatitis, anemia, pancreatitis, and lipodystrophies, among others (REUST, 2011). Another situation that is difficult to manage would be correct adherence to treatment. Non-adherence or poor adherence to ART, in addition to being able to generate the common complications of HIV for the patient, due to the recurrence of the virus in the circulation, can increase the resistance of the virus to ARVs, which may make it necessary to increase the amount of drugs to control the disease. As well as an increased chance of transmission, and the emergence of new treatment-resistant strains (DRACHLER *et al.*, 2016). Several drugs are proscribed or should be used with caution in PLWHA, as they can reduce the effectiveness and reach of ART (REUST, 2011).

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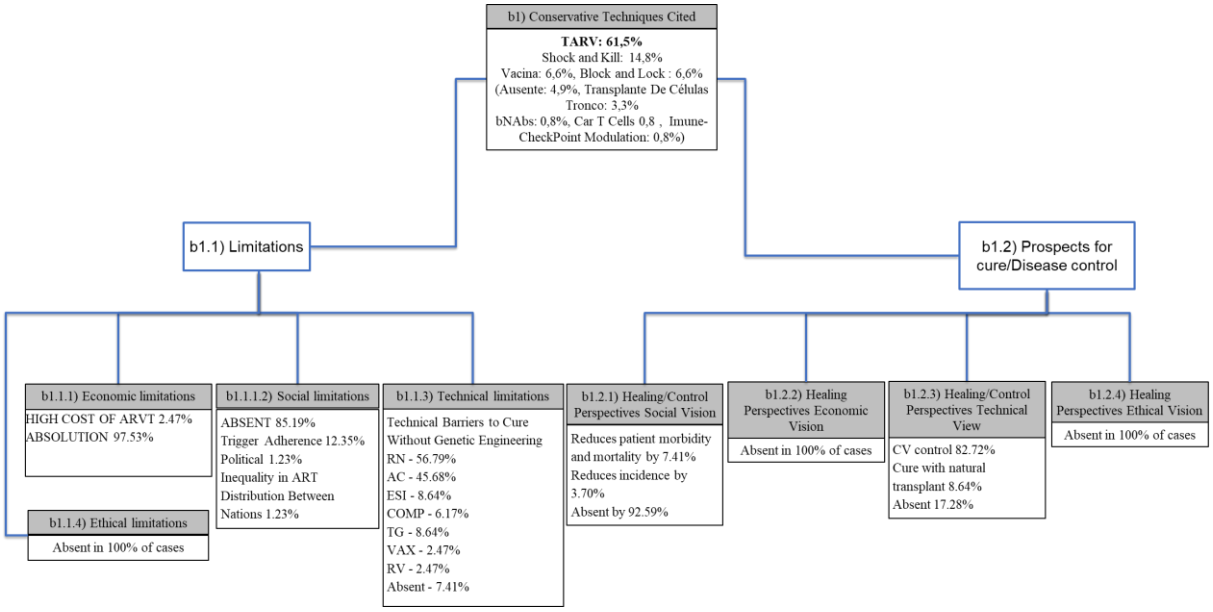
Figure 2

Summary of the categorization of conservative techniques used in HIV and CRISPR-Cas9 studies



Source: The authors.

The high number of articles that mention the use of ART is justified since it is the standard treatment in the fight against HIV. However, it is still unable to eliminate the natural reservoirs of the virus and the discontinuation of treatment brings a recurrence of AIDS, causing the patient to need to take the drugs continuously throughout life (LUNDGREN *et al.*, 2015). In order to antagonize this and ensure a functional cure without the complications inherent in the use of ART, several researchers have tried to discover another treatment, using the CRISPR-Cas9 technique (HERRERA-CARRILLO *et al.*, 2020), so it is natural for articles to cite, relate and compare the current treatment with CRISPR-Cas9 research.

In addition to ART and genetic techniques, there are other researches that try to control/cure HIV in another way. These are techniques that have not yet been successful, or present some adversity for their application in such a way that it becomes unfeasible or less effective than ART (ATKINS *et al.*, 2021). In the articles analyzed, there were mentions about the Shock and Kill technique (14.8%), a technique that stimulates the host's immune system, with the use of medications, to recognize and eliminate the natural reservoirs of the virus (ATKINS *et al.*, 2021). In 6.6% of the articles, there were citations about the development or production of an HIV vaccine, which was often flawed (KALIDASAN; THEVA, 2020). Also 6.6% of the articles cited the '*Block and Lock*', a technique that aims to block viral

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transcription, and keep the virus in its latent state, however, this approach has been flawed because it is only transitory, which causes recurrence in the circulation of the virus after some time (ATKINS *et al.*, 2021).

Another approach that was discussed for treatment was the transplantation of stem cells from donors, whose cells are naturally resistant to viral infection, aiming to replicate situations in which patients presented functional cure, such as the "Berlin patient" (HUTTER *et al.*, 2009) and the Essen patient (KORDELAS *et al.*, 2014). This approach, presented in 8.6% of the articles, is unfeasible in practice, since it is necessary to find a donor compatible with the patient and who has a specific mutation (ΔCCR5 mutation), a very rare situation, and difficult to apply in practice, except in cases in which there was a recurrence of the viral load after some time after the transplant (ANANWORANICH; ROOB, 2014; HENRICH *et al.,* 2014).

Finally, three techniques had a low prevalence (0.8%) but were equivalent (Figure 2): Broadly Neutralizing Antibodies (bNAbs), use of HIV neutralizing antibodies; Chimeric Antigen Receptor (CAR) T-Cell Therapy, in which we have a modification of CD8+ T cells off with an antigen receptor, and after reintroducing these cells into the host, these aim to destroy HIV-1 infected cells; and Immune Check-Point Modulation, would be a technique that aims to improve the immune response of the CD4+ T lymphocyte in order to help control the virus and the disease does not evolve with immunosuppression, a technique that has already been successfully used in the treatment of cancer (ATKINS *et al.,* 2021). With the exception of ART, none of the other techniques has been as successful in eliminating the virus and controlling the disease, or even as effective, and none of them is successful in eliminating the natural reservoirs of the virus, which makes the disease still incurable (ATKINS *et al.*, 2021).

Even with the benefits of these techniques, after analyzing the articles, several limitations are evident, especially the economic ones, with 2.47% of the articles reporting the high cost of developing, producing and selling ART. ARV manufacturing requires a lot of time and investment to conduct extensive research and development. Identification of viral targets, manufacturing of compounds, preclinical testing, and various phases of clinical trials are all part of the process. The mutability of HIV makes the situation more complicated, and the continuous development of new drugs is necessary to combat resistant strains (MEYER-RATH; OVER, 2012). In addition, strict safety and efficacy standards are imposed by regulatory agencies, such as the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in Europe. These agencies are responsible for approving

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new drugs. Large-scale, high-quality clinical studies are necessary to meet these standards, which significantly increases development costs (MEYER-RATH; OVER, 2012).

ARV production involves complex manufacturing processes and, in some cases, the need for specialized production facilities. Additionally, quality assurance and compliance with Good Manufacturing Practices (GMP) are essential, which adds further operating costs. There is also the patent system that gives developers market exclusivity for a limited period of time, in order to protect R&D investments, and to compensate for development costs with a temporary monopoly, but drugs cost more while the patent lasts (MEYER-RATH; OVER, 2012). Funders and health systems face further obstacles due to the need to make ART accessible around the world, especially in low- and middle-income countries. While price reductions and global access programs are essential to improving ART supply, they require negotiations and agreements with various stakeholders, including governments, non-governmental organizations, and the pharmaceutical sector (UNITED STATES, 2019).

Even with several factors involved in the development, production and sale of drugs, this is a topic that is very little addressed in the analyzed studies, when taken into account, it comes to justify the production of a genetic method, which establishes a functional cure in such a way that it is no longer necessary to use these drugs for life, in theory reducing the costs of production and development of these drugs, but do not compare the production costs of ART with the probable cost of production of the new gene therapy, which apparently also has high levels of production, if not higher than those of ART, since it is beyond needing to go through all the stages that ART has already gone through mentioned above, it may still have problems with scale production, in addition to high complexity in therapeutic procedures (IGI, 2022), further increasing the cost compared to ART. This would explain an alleged attempt by the authors to omit certain information regarding the costs of a gene therapy.

Among the social limitations, about 12.35% of the articles indicated poor adherence to conventional treatment. Among the main causes of poor adherence, the following stand out: the presence of adverse side effects of ART, which can range from mild to severe, discouraging the continuous use of medications; therapeutic regimens with multiple doses, in addition to dietary restrictions due to medication; HIV/AIDS stigma can lead people to avoid taking medications regularly, especially in public, for fear of being identified as PLWHA. Some socioeconomic factors such as financial difficulties, lack of access to high-quality health services, and housing insecurity can have an impact on medication adherence, as well as

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other emotional and psychological factors such as depression, anxiety, and other mental health problems (CARVALHO et.al, 2019).

Low adherence to treatment has a certain prevalence mainly in theoretical articles, which try to justify the need to achieve a functional cure for HIV, and this becomes a crucial point as one of the justifications of studies, which in short tried to abolish ART with genetic techniques, in order to avoid these problems. Other social issues that are less addressed would be political interest since HIV infection affects more than 35 million people around the world, becoming a public health problem (ZHANG *et al.,* 2015), addressed by 1.23% of the articles, as well as an inequality in the distribution of ART. Such an approach can be justified by the focus of the research and the descriptors.

An interesting point is that none of the articles presented a specific approach, referring to the ethical limitations of conservative techniques, although it lacked an in-depth ethical discussion about what was previously done in the development of these techniques. Only the results obtained, mostly failures, when we do not refer to ART. This result should be taken as a warning, as there were several ethical dilemmas involved in the discovery of HIV and the development of ART, which may resurface with the use of this new genetic technique, which were completely disregarded by the authors. This situation makes it possible for ethical crimes to occur again, such as problems with the use of animals in research, use of placebo in research, problems with informed consent, lack of equity in research, confidentiality, approach to vulnerabilities (EPSTEIN, 1996, PETER; WOLF, 1997). Thus, evidencing the lack of interest and lack of concern of researchers in not repeating the mistakes already made previously.

Finally, technical limitations were identified, directly related to intrinsic factors of the virus, as well as the inefficiency of cure and control of the disease, among them: RN (does not eliminate Natural Reservoirs) in 56.79% of cases, which is directly related to CA (Absence of Cure) in 45.68% of cases and ESI (Evasion of the Immune System) in 8.64%. These three aspects are directly related, as the cause of the fact that a functional or sterilizing cure for HIV infection has not yet been found lies in the fact that it maintains several natural reservoirs. This fact would be one of the mechanisms of evasion of the immune system, which are nothing more than the insertions of viral DNA into the host's DNA, and which can be located in various tissues of the body (CHOMONT *et al.*, 2023). As well as several other mechanisms of evasion of the immune system such as expression of viral proteins, which the immune system has difficulty recognizing, and others that decrease the activity of the immune system.

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It is expected that the prevalence of these limitations will be higher in the selected articles, since it is these characteristics of the disease that have not yet allowed a cure to be achieved, so new genetic methods seek to remedy this deficiency, making this the focus of research with CRISPR-Cas9. Therefore, it is necessary to address this theme as one of the main justifications of the studies carried out.

Another problem evidenced was COMP (health complications with the use of antiretrovirals) present in 6.17% of the articles. Adverse effects of ART include an increased risk of metabolic complications, cardiovascular disease, kidney dysfunction, bone loss, and weight gain. This can worsen in the long term (UNITED STATES, 2019). Articles tend to use these data in order to justify clinical trials and the need to obtain a new treatment methodology. The use of ART with TG (Associated Gene Therapy) was pointed out in 3.7% of the texts analyzed, and the use of ART associated with CRISPR-cas9 has achieved greater prominence, especially after the efficacy demonstrated in some studies (DASH, 2020). However, it is expected that its associated use will be reduced in research initially, since the concomitant use of ART can be considered a confounding bias during research and even the development of a safe method that involves only genetics tends to be avoided.

The VAX (Inefficient vaccine) cited by 2.47% of the texts, indicate failure in the development of vaccines to combat HIV, especially with regard to viral mutation, even with several studies trying to produce an effective vaccine, the high and accelerated viral mutagenicity is a challenge, as it causes several different strains to exist in the environment, as well as leaves vaccines with an inherent validity to the time of mutation of the virus, making its cost-benefit unfeasible in practice (GAO, 2018). Finally, it is worth mentioning that VR (Viral Drug Resistance), cited in 2.47% of the selected articles, basically consists of a mutation in the viral genome, which allows the virus to survive even with the use of ART. Articles tend to use the limitations of conservative techniques to justify the introduction of a new therapeutic approach, but if one can only base oneself on the limitations of these techniques to justify a new approach, there is a need to also evaluate the benefits brought by it today in order to compare the two.

When analyzing the benefits of conservative therapy, as much as there are many, as previously mentioned, the selected articles when addressing the subject, it is briefly, emphasizing again the focus of the research, which would be the development of a new genetic technique. It tends to appear more to justify the need to establish a new technique, which can maintain the achievements achieved or the search for justifications that antagonize

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conservative treatment. In the technical view, most of the articles (82.7%) focus on viral load control, which is done through the use of ART, a basic objective to be achieved by the new therapeutic methodology (PETERSON; MACLEAN, 2019), since it is what guarantees the control of the disease and consequently improving the quality of life of PLWHA (CARVALHO *et al.*, 2019), even allowing them to have a life expectancy similar to that of an individual in the general population (SAMJI *et al*, 2013), such arguments are used by the authors as research objectives, but through the use of CRISPR-Cas9, instead of ART and that is why they tend to appear in such an expressive way.

Another method cited (8.6%) was the cure performed through bone marrow transplantation, for now the only current method that has achieved functional cures (HUTTER *et al,* 2009). This alternative emerged after cases of cure had been reported, after a bone marrow transplant in PLWHA with the marrow of donors who have a mutation in a specific gene (CCR5 gene), which hinders the infection of the CD4 T lymphocyte by HIV, and associated with this the donors must have a marrow compatible with the recipients, due to this series of associated factors and the rarity of finding bone marrow compatible with each other with a rare mutation, in addition to the risks involving bone marrow transplants when compared to the use of ART, it becomes an unfeasible method in clinical practice (HUTTER *et al,* 2009). However, studies seek to mimic this propaedeutic using CRISPR-Cas9 technology, making this a starting point for research.

From a social perspective, the studies address a reduction in the morbidity and mortality of patients (7.4%). In individuals with HIV, ART effectively lowers viral load to undetectable levels in the blood. It also allows a restoration and/or preservation of immune function, restoring and maintaining the number of CD4 + T lymphocytes, reducing the risk of opportunistic infections, as well as other comorbidities related or not to HIV (LUNDGREN *et al,* 2015), thus ensuring a significant improvement in the quality of life of carriers of the virus. About 3.70% of the articles discuss the reduction of the incidence of the disease, whose cause is directly associated with the transmissibility of HIV. Currently, ART also acts to prevent the spread of the virus and the development of AIDS, reducing the probability of viral transmission by up to 96% (COHEN *et al.,* 2011). The terms increased quality of life, decreased morbidity and mortality, and decreased infectivity, appear in the articles only as one of the objectives of CRISPR research, they do not present a great focus since this is already achieved with the use of ART and may raise an ethical conflict, since we would be replacing a therapy, which, although it does not cure, has its adverse effects well known and

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effectively controls viral replication, by a therapy with unknown and possibly permanent side effects on the patient's genome (DUBÉ *et al.,* 2022).

The economic perspective of traditional therapies was not found in pertinent citations in the articles, it is worth mentioning that the implementation of ART initially had a high cost due to the complexity of its development and the need to recover investments in research and development. The first antiretroviral drugs were introduced in the late 1990s, were often patented, limiting competition and keeping prices high. In addition, early HIV treatments involved complicated regimens that required several expensive drugs. For many patients, especially in low- and middle-income countries, prices were unaffordable due to the scarcity of generics and the relatively small market, concentrated mainly in high-income countries (HOEN *et al.,* 2011).

Health activists and international organizations drove the push to make HIV drugs more affordable in the late 1990s and early 2000s. In 2001, the Doha Declaration, a milestone in the history of the WTO, was concluded due to a series of disputes and public pressure. The Declaration reaffirmed the ability of WTO member countries to circumvent drug patents in public health emergencies. Developing nations were able to manufacture or import generic antiretroviral drugs at significantly lower prices, allowing millions of people to obtain life-saving treatment (WTO, 2001). International funding programs have been essential to make HIV drugs more affordable, in addition to efforts to produce generics. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR), launched in 2003, along with the Global Fund to Fight AIDS, Tuberculosis and Malaria, have provided significant resources for the purchase and distribution of antiretrovirals in developing countries. These programs not only provided money to purchase medicines, but also helped build the health infrastructure needed to administer treatments efficiently. Governments, local communities, and international organizations have been working together to increase access to treatment, improving survival rates and quality of life for PLWHA (UNITED STATES, 2024). It is understood that when comparing the long road already trodden, and the global struggle to reduce costs to develop, produce and distribute ARVs, with the costs that this new gene therapy can bring; The authors' lack of interest in expressing the economic costs of conventional therapy is understandable, since it would be a counter-argument of strong intensity in the justification of carrying out these studies.

The ethical perspectives offered by the authors regarding conventional treatment are not cited, as well as the ethical limitations of conservative techniques, corroborating an

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understanding that there is a lack of interest on the part of researchers in considering these ethical aspects. Perhaps, when pondering on some aspects of the genetic technique, it makes one think about the real need to carry out these researches, as well as to establish a cure, making the information counterproductive for research. One of the issues that can be raised would be equitable access to treatment. Currently, the distribution of conventional treatment has faced several challenges, but the breaking of patents and promoting programs to combat HIV (UNITED STATES, 2024), has allowed costs to decrease in addition to increasing accessibility. The costs of developing and maintaining a gene therapy would increase dramatically, so comparatively not everyone would have access to the new treatment. It should be considered that the risks of establishing a new gene therapy could not outweigh the benefits to be achieved by it, generating potentially irreversible and harmful DNA alterations (exacerbated immune response, oncogenic) (DUBÉ *et al.,* 2022), which does not happen in conventional therapy.

3.2 GENETIC TECHNIQUES

The revolutionary gene-editing technique called CRISPR-Cas9 has been changing molecular biology since its discovery. The development of CRISPR-Cas9 began in the 1980s, when scientists discovered repeated sequences in the DNA of bacteria. These sequences were later called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). It is a bacterial immune system that uses these RNA and Cas9 protein sequences to identify and cut the DNA of invading viruses (HORVATH; BARRANGOU, 2010). Researchers such as Philippe Horvath and Rodolphe Barrangou demonstrated in 2007 how CRISPR can be used to give industrial bacteria resistance against viruses (HORVATH; BARRANGOU, 2010). In 2012, Jennifer Doudna and Emmanuelle Charpentier elucidated in detail the specific function of the Cas9 protein, which is necessary for the DNA cutting process, a milestone in biotechnology (JINEK *et al.*, 2013).

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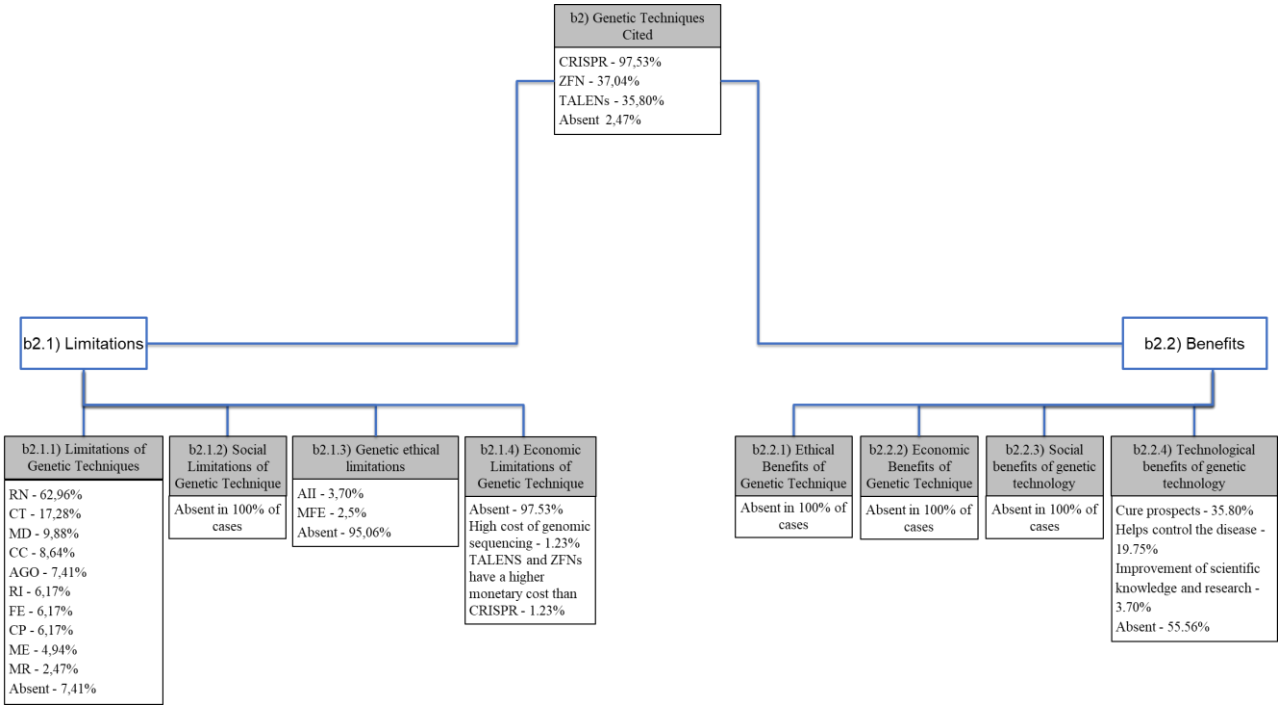
Figure 3

Summary of the categorization of genetic techniques used in HIV and CRISPR-Cas9 studies



Source: The authors.

With the publication of Doudna and Charpentier in 2012, CRISPR-Cas9 became a popular tool for gene editing. By using this technique, researchers can add, remove, or change specific parts of the genome, making precise cuts in the DNA (CONG, 2013).

CRISPR-Cas9 is being used to treat several genetic diseases, such as muscular dystrophy and cystic fibrosis. Its use in medical research has rapidly increased to treat more complex diseases such as cancer and HIV (CONG, 2013). Because of its ability to integrate into the host genome and remain latent, HIV is a difficult target for CRISPR. But researchers are using CRISPR-Cas9 to extract viral DNA from infected cells. The research has been successful in cells and animal models, but the implementation in humans still faces important problems, such as providing editing technology safely and effectively and ensuring that the virus does not develop resistance (XIAO *et al.*, 2019). So far, several clinical studies are being developed or are in their early stages to verify whether CRISPR-Cas9 is safe and effective in the treatment of HIV in humans. These studies are essential to determine whether the method can become a safe and practical therapy for HIV (XIAO *et al*, 2019).

In addition to CRISPR-Cas9, other genetic manipulation techniques have been used previously, such as ZFN, which consist of specific enzymes with the ability to recognize and

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cut specific DNA sequences that can be programmed (URNOV *et al.,* 2010). There are also TALENs, which function similarly to ZFNs, but use a different DNA-binding domain that comes from effector proteins of pathogenic plant bacteria. Due to the modularity and specificity of the DNA sequences that TALENs can recognize, TALENs tend to be considered more accurate than ZFNs (JOUNG et al, 2013).

Among the methods analyzed, citations about CRISPR-Cas9 were found in 97.53% of the cases, on the other hand, ZFNs in 37.64% and 35.80% of citations with TALENs, this low incidence of the articles can be justified because the descriptors selected directed to CRISPR-Cas9, and not to the other techniques. It is important to consider the fact that the CRISPR-Cas9 method has revolutionized biotechnology and genetic engineering, as it has been considered much more effective and of better applicability than the other methods (DOUDNA *et al.*, 2014), increasing its relevance when it comes to new genetic treatments, further justifying its prevalence as a method of choice. Among its advantages, we can highlight (GUPTA; MUSURUNU, 2014): 1) Ease of use: The gRNA, or RNA guide, used by CRISPR-Cas9, can be easily adapted to almost any desired genomic sequence. On the other hand, ZFNs and TALENs need to design and build specific proteins for each new DNA target, a process that can be very technical; 2) Cost and Time: The implementation of CRISPR-Cas9 is less costly and faster than the protein engineering required for ZFNs and TALENs. This is due to the fact that gRNA synthesis or assembly is usually lower cost and less complicated; 3) Versatility and Multiplexing: Adding multiple gRNAs to the system can easily change the target of CRISPR-Cas9, for multiple genes at the same time. ZFN and TALEN require the creation of a new set of binding proteins for each target, making this multiplexing process more difficult and ineffective. 4) Efficiency in editing: While TALENs and ZFNs are extremely accurate, the CRISPR-Cas9 process generally works best in terms of editing rates. As a result, there is a higher probability that a CRISPR-Cas9 edit will be successful in the target DNA; 5) Versatility for advanced modifications: In addition to causing DNA breaks, CRISPR-Cas9 can be modified to perform a number of different functions, such as activating or repressing genes without altering the DNA sequence, or even creating precise base edits using systems such as CRISPR-base editors. All these topics justify the greater relevance of research using CRISPR-Cas9, when compared to TALENs and ZFNs. However, it is necessary to understand the limitations of these studies, and their benefits, in order to confront traditional methods to evaluate the cost and benefit of the technique and prevent ethical transgressions from occurring. Among the limitations found are:

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Of the articles analyzed, 62.96% reported concerns or failure in the complete elimination of the natural reservoirs of the virus (RN). While CRISPR-Cas9 can be programmed to alter and target the integrated viral DNA, it is extremely difficult to identify all cells containing the latent viral genome. In addition, due to the high mutation rate of HIV, genetic variation may decrease the effectiveness of an RNA guide sequence (WANG *et al.,* 2016). Viral reactivation by viruses from unidentified or unedited reservoirs can reactivate, even after successful editing of viral DNA, resulting in new viral replication and spread of infection. Considering that this technique aims precisely to accomplish what ART has not yet been able to achieve, which is the destruction of the natural reservoirs of the virus, if it were to present the same limitation, it would not justify its use to the detriment of conservative ones, since the possible deleterious effects are not yet known.

Lack of technical knowledge (TC) was reported by 17.28% of the articles needed to achieve the goal of cure. One of the greatest difficulties is the complete identification and characterization of the latent sources of HIV. These HIV-infected cells, which do not actively produce the virus, can remain hidden in the immune system and other tissues. For a cure to be effective, CRISPR-Cas9 needs to be applied to each of these cells. However, our abilities to identify and access each of these cells are still limited (CHUN *et al.*, 1997). Another issue of high importance would be the development of realistic models and tests, the ability to test new therapies is limited by the lack of animal or laboratory models that faithfully reproduce the complexity of HIV infection in humans. Current models cannot take into account the full genetic diversity of HIV or the complexity of viral reservoirs in various tissues of the human body (AKKINA, 2016).

This opens the discussion to the difficulty of genetic manipulation in cells that are outside the bone marrow (MD), reported by 9.88% of the articles, due to the difficulty in ensuring the efficacy and safety of the application of the CRISPR-Cas9 system in all infected cells. Currently, viral vectors are the most capable of transmitting CRISPR-Cas9. However, they also come with risks, such as an immune response or unwanted genomic insertion. The development of delivery methods that are reliable and effective on a large scale is still the subject of much study (YIN *et al.,* 2017).

Early research on CRISPR-Cas9, and HIV, primarily targeted gene editing of CCR5. The objectives of these studies were to replicate the cases of HIV cure achieved after transplantation of cells that contained a mutation in this gene, generating the mutant gene ΔCCR5, making it impossible for the virus to adhere to the cell (HENRICH, *et al.,* 2014).

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However, about 8.6% of the studies found that even so this did not prevent cell-cell infection (CC), in some cases an increase in the expression of viral strains that used another co-receptor (CP), CXCR4, to infect the TCD4+ lymphocyte, was observed, after decreasing the expression of CCR5, causing a natural selection of other more resistant viral strains.

Another concern of the researchers, evidenced in 7.4% of the articles, would be the uncertain genetic and oncogenic alterations (AGO). To prevent unwanted mutations such as the development of cancer, the extreme accuracy of CRISPR-Cas9 must be ensured. While advances in CRISPR continue to increase its accuracy, ensuring that only HIV DNA is altered without affecting other vital genes is still a major technical challenge (SLAYMAKER *et al.*, 2016). In addition to the genetic response, the possibility of an immune or cytotoxic (IR) response against genetically altered cells is suggested, cited by 6.17% of the total articles.

The CRISPR-Cas9 gene-editing technique can cause unexpected changes in cellular antigens or protein expression, which can trigger an autoimmune response. The altered cells can be recognized by the immune system as foreign or altered. This is particularly concerning in HIV treatment in situations where the immune system is already compromised or overactive as a result of the viral infection. The CRISPR-Cas9 technique breaks DNA to introduce genetic changes. If not controlled correctly, this can cause stress and cell death. In addition, the introduction of the CRISPR-Cas9 complex can be thought of as a viral or bacterial invasion of cells, which can cause apoptosis or inflammation (IHRY *et al.*, 2018). Due to the bacterial origin of Cas9, it can be identified as a pathogen by the immune system and trigger an immune response against it, triggering inflammation and other harmful immune reactions, as well as decreasing the effectiveness of gene editing (CHARLESWORTH *et al.*, 2019). The effective and safe delivery of the CRISPR-Cas9 system remains a challenge, as viral vectors used to introduce CRISPR-Cas9 can cause changes in the immune system to combat this vector, thus decreasing the effectiveness of the treatment (WANG et al, 2017).

The most recent research has raised the possibility of associating ART with gene therapy, aiming to achieve more effective results (Dash et al, 2023), increasing the dependence on factors external to gene therapy (EF), cited by 6.17% of the articles. ART reduces viral load to undetectable levels in the bloodstream, decreasing the likelihood of new cell-to-cell infections (Deeks et al, 2013), during CRISPR-Cas9 treatment by suppressing viral replication, which can increase the effectiveness of gene editing, and decrease the chance of the emergence of a new mutant strain, which would lead to viral escape, becoming resistant to CRISPR-Cas9 and ART. Other findings were the lower effectiveness of the

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precursor methods of CRISPR-Cas9, TALENs and ZFNs, (ME), when comparing the effectiveness of CRISPR-Cas9, found in 4.9% of the articles (GUPTA; MUSUNURU, 2014). Justifying the lesser mention of these techniques as well as their limitations that were overcome by CRISPR-Cas9, already evidenced in the topics above. Another condition also explained is the existence of multiple HIV co-receptors (RM), CCR5 and CXCR4, mentioned in 2.47% of the articles.

The limitations were not addressed in 7.4% of the total articles, such a low percentage is explained by the fact that the goal of completely eliminating all latent natural reservoirs of the virus has not yet been achieved even with the use of CRISPR-Cas9 (WANG *et al.,* 2016). And this is precisely what CRISPR-Cas9 seeks, to differentiate itself from conservative ones, so this argument is preponderant and used as the main justification in the development of the articles and its absence of other limitations already mentioned, would trigger a situation in which these researches would not be justified to be carried out. And this absence of limitations is present in theoretical articles, which seek alternatives to the traditional method, or have other scopes of research.

No articles were found that cited social limitations of the application of CRISPR-Cas9, evidencing a lack of concern among researchers with the vulnerabilities of research individuals, as well as the applicability of the technique to society. This absence of citations related to social limitations draws attention when we think about problems previously faced in the 1990s. Problems such as the use of placebos or a control group that does not have access to any therapy (PETER; WOLF, 1997), absence or partiality in informed consent (RACITI et al, 2021), problems involving secrecy or confidentiality of the research subjects, in addition to lack of equity in research (BENATAR, 2003).

Among the ethical limitations, there are citations about uncertain alterations in individuals (AII), in 3.7% of the studies, described by the authors as potentially more harmful than beneficial to the individual, citations such as probable carcinogenic alterations, potential for cytotoxicity and activation of autoimmunity, already seen in the technical limitations, but were analyzed separately from the technical limitations because the authors have ethical concerns and as an analysis of the individual and not about the technique itself, seeking to establish a balance between beneficence, with the least possible maleficence for the use of the technique. They are presented in small numbers precisely because the type of research is more experimental (70.4%) than theoretical (29.6%), corroborated by the little focus on the ethical objective (2.5%), with more technical objectives (97.5%).

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Only two articles (2.5%) presented a focus on multiple ethical themes (MFE) (HENDRIKS *et al.,* 2018; KALIDASAN; THEVA *et al.*, 2020), covering topics already mentioned such as: Eugenics (JIANKUI *et al.,* 2018; RYDER *et al.*, 2018), risk and benefit assessment, from the perspective of principlistic bioethics, even if they do not mention it directly, such as non-maleficence and beneficence, always addressing in full the possible harm to those involved in the research such as the safety of the individuals involved; effectiveness; quality of life of the individuals involved; existence of clinical or alternative need; biodiversity and ecosystems; animal homo sapiens (i.e., related to effects on humans as a species); life and human dignity; trust in regulation; justice; costs; argument from nature; rights and duties of parents; and autonomy (HENDRIKS *et al.,* 2018). The other articles did not report ethical interests in their studies.

As previously evidenced, the TALEN and ZFN methods are more complex, less effective, and more expensive techniques when compared to CRISPR-Cas9 (GUPTA; MUSUNURU, 2014), this detail was addressed by only 1 article (1.23%) (XIAO *et al.*, 2019), given that in general it does not contribute to a limitation of the CRISPR-Cas9 technique, but to the other techniques previously used, thus justifying the use of CRISPR-Cas9 to the detriment of the others, as previously explained. However, an important detail mentioned by one of the articles (1.2%) would be the high cost of genomic sequencing. The use of CRISPR-Cas9 requires precise genomic sequencing to determine which DNA sites need to be altered. Considering that high-depth sequencing is necessary to ensure accuracy in edits, this tends to increase the cost of procedures since it is an expensive technique. It can make it financially unfeasible for large-scale treatments or in places with few resources (CHRISTENSEN *et al.*, 2015). However, even so, several economic limitations were omitted, either due to lack of interest from researchers, or to avoid contraindications for conducting research, so other considerations must be taken into account. Depending on the genetic variations of HIV, CRISPR-Cas9 therapy may need to be customized for each patient. Creating personalized treatments involves developing RNA guides for CRISPR and repeated sequencing cycles, which increases research and development costs. Performing sequencing and gene editing requires sophisticated laboratory infrastructure and state-of-the-art technology, in addition to the direct costs associated with sequencing. The costs associated with installing and maintaining this infrastructure are significant. To ensure the safety and efficacy of new gene therapies, such as those based on CRISPR-Cas9, extensive clinical trials are needed. Notoriously, clinical trials are expensive, and the need for detailed genomic sequencing to

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track results increases costs (ANLIKER *et al.*, 2022). The complexity of genomic sequencing and implementation costs may limit the adoption of genomic sequencing in low- and middle-income countries, even after the development and approval of CRISPR-Cas9 therapy.

Among the studies analyzed, there is a perspective of cure/control of the disease through the control of viral load (82.7%). This cure can be achieved in two different ways: a functional cure, which would not completely eliminate the virus, leaving only a residual but controlled natural reservoir, not allowing the progression of the disease (KALIDASSAN; TEVA, 2020), similar to what already occurs with the use of ART, but there would be no need to use the drug continuously to control the disease (LUNDGREN *et al.,* 2015); and a sterilizing cure which would eliminate all viral residues from infected cells so that the viral RNA found is equal to or less than 1 copy/ml (KALIDASSAN; TEVA, 2020). We found a high prevalence in this method, since this would be the main objective of these studies as well as one of the justifications for not using ART if this objective is achieved. Some articles also mention the performance of allogeneic or heterogeneous transplants, after bone marrow cells are treated with CRISPR-Cas9, in vitro and then reintroduced into the individual 8.64% , but as previously discussed this would imply a highly invasive technique for the individual, not without risks, when compared to conventional treatment, difficult to apply if we consider heterogeneous transplantation (HENRICH *et al.*, 2014).

From a social perspective, the articles address a reduction in patient morbidity and mortality (7.4%) with the use of the method, however this reduction in morbidity and mortality is something that is already achieved with the use of ART (LUNDGREN *et al.,* 2015; SAMJI *et al.*, 2013; CARVALHO *et al.*, 2019). Another issue addressed would be the probable decrease in viral incidence and infectivity of 3.7%, but again this is already achieved with the use of drugs through ARVs (LUNDGREN *et al.*, 2015) in a safe manner with already known side effects and adverse effects, compared to those of the CRISPR-Cas9 technique, which are still unknown (NOHAMA *et al.*, 2023). No approaches referring to economic benefits or any ethical benefit were obtained in the citations, reinforcing the idea of the researchers' lack of concern with some areas, prioritizing technique and results more, as previously mentioned.

3.3 BIOETHICAL PERSPECTIVE

The bioethical analysis of the perspective of a cure for AIDS is based on three theoretical lines: the Bioethics of Protection, the Ethics of Responsibility and the Bioethics of Intervention. Principialist bioethics, based on the principles of autonomy, beneficence, non-

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maleficence and justice (BEAUCHAMP; CHILDRESS, 2002), guides the evaluation of new research. Currently, AIDS is a manageable disease, and individuals on conservative antiretroviral (ARV) treatment tend to have a life similar to that of uninfected people (SAMJI *et al.*, 2013), with reduced risks compared to the past (CARVALHO *et al.*, 2019). Although some authors consider the side effects of ART, such as nausea and toxicities (United States, 2019), which can lead to low adherence (12.3%) and viral resistance (2.47%) (CARVALHO *et al.*, 2019), the new technique, which seeks to eliminate viral reservoirs (56.6%) or control the disease without ART (45.7%), needs to demonstrate that its benefits outweigh the harms, protecting human dignity (SCHRAMM, 2021). The replacement of conventional therapy, whose risks are known and controllable (UNITED STATES, 2019), with an innovative technique with unknown risks and complications, such as potential carcinogenesis (7.4%), immune responses (6.2%), and failure to eliminate the virus (63%), would be contraindicated from the perspective of protection bioethics, as it could increase the vulnerabilities of the sick.

The Ethics of Responsibility, proposed by Hans Jonas (JONAS, 2006), is crucial, as techniques such as CRISPR can have an intergenerational reach (NOHAMA et.al, 2023), requiring full informed consent on all risks, contrary to what has been observed in previous studies for the development of ART (ACTG, 1994; RACITI et al, 2021). Justice and equity are also a central point, as the high cost of the new therapy, which is higher than that of known drugs (CHRISTENSEN *et al.*, 2015), could restrict access and deepen the inequalities already seen at the beginning of the epidemic, when research was concentrated in developed countries and treatments were inaccessible to the majority (EPSTEIN *et al.,* 1996).

Finally, the Bioethics of Bottle Intervention (2005), with its principles of prudence, protection, precaution and prevention, applicable to several areas (FISCHER *et al.* 2022), guides action. It is necessary to avoid the repetition of past ethical violations, such as compromising confidentiality (KLITZMAN; BYER, 2003), high costs ('t HOEN *et al.*, 2009), conflicts of interest (BAKER, 2008) and the use of animals in research (BAROUCH *et al.*, 2012), ensuring supervision by ethics committees. Precaution is vital in the face of uncertainties about the effects of CRISPR-Cas9 (HENDRIKS *et al.,* 2018), and prevention seeks to mitigate risks such as the emergence of resistant strains (DARCIS *et al.*, 2019), possibly associating the new technique with ART (DASH, 2020). In addition, the principle of Perseverance, proposed by Rosaneli et.al (2021), drives the continuous search for an effective and inclusive cure, in a responsible and dedicated way to global health.

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4 CONCLUSION

The contemporary era, marked by technological advances, has driven the development of new treatments in the health area, but has also inaugurated complex bioethical dilemmas. Technologies such as CRISPR-Cas9, which allow the editing of the human genome in a simpler and more accessible way, are an example of this. Currently, the focus of many researchers is on the application of this method in the search for a cure for HIV infection, a condition that has been historically stigmatized and still without a definitive solution. Historical analysis of the development of Antiretroviral Therapy (ART) reveals several ethical violations, such as the lack of equity in the representation of minority groups, problems with informed consent, conflicts of interest of the pharmaceutical industry and the questionable use of placebos. Understanding these precedents is essential to guide research into new therapies, avoiding the repetition of unethical practices. However, concern about ethical conduct in current research remains. A notorious example was the experiment conducted by Chinese scientist He Jiankui, who used CRISPR-Cas9 to edit the CCR5 gene in human embryos, under the pretext of making them immune to HIV. This attitude replaced safe and effective prevention therapy with a method of unknown risks, exposing children and their families to unnecessary dangers. In addition, science has already indicated that the alteration of the CCR5 gene does not guarantee immunity, but maximum resistance, and can even select more aggressive viral strains. The researcher's motivation seems to have been professional recognition, and not the protection of individuals, which demonstrates a disrespect for human dignity and the ethical principles of research.

The analysis of recent studies on the subject shows that many researchers ignore crucial ethical issues, such as equity in access to future treatment. A cure for HIV, based on high-cost technologies and personalized medicine, could be restricted to a small portion of the population with high purchasing power, deepening social inequalities. If, on the one hand, the discovery of a cure would bring hope and improve the quality of life of people living with HIV (PLWHA), on the other hand, it could generate exorbitant profits for the industry and perpetuate the marginalization of those who cannot afford treatment. Despite the challenges, conducting research based on bioethical values and principles makes it possible to achieve a future in which healing is accessible to all. To this end, a continuous dialogue between the scientific community and bioethics is essential, aiming at the establishment of new ethical and normative standards that respect human dignity and the value of scientific research.

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