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Ethical consideration of gene therapy in Indonesian HIV patients and its management: A narrative review

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ABSTRACT

Human Immunodeficiency Virus (HIV) infection remains a major global health issue, including in Indonesia. Gene therapy (GT) has emerged as a promising therapeutic approach for various diseases, including HIV. However, its application also raises significant ethical challenges, particularly within the Indonesian context. This article aims to explore the ethical considerations, potential, and challenges of implementing GT for patients with HIV in Indonesia. A comprehensive narrative review was conducted by examining current scientific literature and ethical frameworks related to GT and HIV management, with a focus on clinical feasibility, safety, and social implications within the Indonesian context. Gene therapy technologies such as zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) have shown promising potential in suppressing HIV infection. However, concerns remain regarding on- and off-target effects that may cause genomic instability and oncogenesis. Ethical challenges include the high cost of therapy, limited public understanding of GT, and the absence of specific regulations governing its application in HIV treatment. Indonesia's diverse sociocultural landscape further complicates equitable access and acceptance of this advanced technology. The implementation of GT for HIV in Indonesia requires careful ethical consideration, transparent communication, and robust policy development. Establishing national guidelines and conducting further research are essential to ensure that the adoption of GT is safe, equitable, and ethically responsible within the Indonesian healthcare system.

ABSTRAK

Infeksi *Human Immunodeficiency Virus* (HIV) masih menjadi masalah kesehatan utama di seluruh dunia, termasuk di Indonesia. Terapi gen (*gene therapy*, GT) telah muncul sebagai pendekatan terapeutik yang menjanjikan untuk berbagai jenis penyakit, termasuk HIV. Namun, penerapannya juga menimbulkan tantangan etis yang signifikan, khususnya dalam konteks Indonesia. Artikel ini bertujuan untuk mengeksplorasi pertimbangan etis, potensi, dan tantangan dalam penerapan terapi gen bagi pasien HIV di Indonesia. Kajian ini menggunakan pendekatan tinjauan naratif yang komprehensif dengan menelaah literatur ilmiah terkini serta kerangka etika yang berkaitan dengan terapi gen dan penatalaksanaan HIV, dengan fokus pada aspek kelayakan klinis, keamanan, serta implikasi sosial dalam konteks Indonesia. Teknologi terapi gen seperti *zinc-finger nucleases* (ZFNs), *transcription activator-like effector nucleases* (TALENs), dan *Clustered Regularly Interspaced Short Palindromic Repeats* (CRISPR) menunjukkan potensi yang menjanjikan dalam menekan infeksi HIV. Namun, masih terdapat kekhawatiran terhadap efek on-target dan off-target yang dapat menyebabkan ketidakstabilan genom dan risiko onkogenesis. Tantangan etis meliputi tingginya biaya terapi, keterbatasan pemahaman masyarakat tentang terapi gen, serta belum adanya regulasi khusus yang mengatur penerapannya dalam pengobatan HIV. Keberagaman sosial dan budaya di Indonesia juga memperumit akses yang adil dan penerimaan terhadap teknologi ini. Penerapan terapi gen untuk HIV di Indonesia memerlukan pertimbangan etis yang matang, komunikasi yang transparan, serta pengembangan kebijakan yang kuat. Penyusunan pedoman nasional dan penelitian lebih lanjut sangat diperlukan untuk memastikan bahwa penerapan terapi gen berlangsung secara aman, adil, dan bertanggung jawab secara etis dalam sistem kesehatan Indonesia.

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INTRODUCTION

Human Immunodeficiency Virus (HIV) infection remains a major global health challenge, including in Indonesia. Data from the World Health Organization's Global Health Observatory (2022), there were an estimated 39 million people living with HIV worldwide, and approximately 630,000 HIV-related deaths.[1] In Indonesia, data from the HIV Country Profile 2023 reports that there are approximately 540 thousand people living with HIV and 24 thousand people newly infected with HIV.[2] Antiretroviral therapy (ART) remains the main treatment for people living with HIV. The administration of antiretrovirals (ARVs) is expected to suppress the development of HIV in the body and can increase the patient's life expectancy. ARVs must be consumed by HIV patients every day for life and must be in accordance with doctor's instructions.[3] However, there are several problems related to treatment in HIV patients, one of which is the non-compliance of HIV patients in taking ARVs.[4] This can lead to therapeutic failure and ARV resistance, which can be fatal.[5]

Alongside these challenges, rapid progress in biomedical science has introduced gene therapy (GT) as a transformative innovation that directly targets the molecular basis of disease. The field has advanced through several technological milestones, beginning with Zinc Finger Nucleases (ZFNs) and Transcription Activator-Like Effector Nucleases (TALENs), which enabled targeted genome modifications but were limited by efficiency and specificity.[6] The advent of CRISPR-Cas systems has since revolutionized genome editing by providing a highly precise, cost-effective, and versatile platform, thereby accelerating the development of GT for both genetic and infectious diseases, including HIV.[7] These tools allow precise modification of host factors such as CCR5, a co-receptor essential for HIV entry, offering the possibility of long-term viral control and even a functional cure.[8] Despite these advances, profound ethical and societal concerns persist. The controversial case of CRISPR-edited embryos in China, aimed at conferring HIV resistance, exemplifies the global debate surrounding germline genome editing and its implications for future generations.[9]

Ethical considerations thus extend beyond somatic cell therapy to include questions of safety, justice, respect for autonomy, and intergenerational responsibility.[10] In the context of Indonesia, the discourse on GT must not only address scientific innovation but also broader social and economic realities. Critical issues include the realistic potential of GT to fulfill therapeutic expectations, its psychosocial impact on patients and families, and challenges of affordability and equitable access within the healthcare system.[11] The high costs of GT and its experimental nature raise concerns regarding feasibility in low- and middle-income countries.[12] Moreover, psychosocial dimensions, such as stigma, anxiety related to genetic manipulation, and unrealistic hopes of a "cure", must be carefully managed to prevent harm.[13] Equally important are Indonesia's contextual challenges: the absence of a comprehensive regulatory framework, limited institutional readiness, and the circulation of misinformation, which risk undermining public trust. Therefore, the application of normative ethical principles is essential to guide responsible, just, and sustainable development of GT. This narrative review aims to critically evaluate the opportunities and challenges of implementing for people with HIV in Indonesia, with particular emphasis on its ethical, social, and policy implications.

DISCUSSION

The potential of gene therapy

Since its introduction, gene therapy (GT) for HIV has undergone on a

journey marked by various advances and challenges. Early approaches encountered major obstacles, particularly regarding safety. However, advances in molecular techniques have since improved precision and expanded the potential impact of this strategy. Several previous studies have provided robust evidence supporting further GT development (TABLE 1). Overall, these developments confirm that GT represents a promising approach for managing HIV in the future.

TABLE 1. Previous research on the potentials of GT for HIV treatment

Authors	Year	Results	Potentials
Désaulniers, *et al.*[14]	2021	Knockdown of TRIM5α shows that HIV-1 can be inhibited by biallelic modification, i.e. both alleles contain R332G and R335G.	Biallelic modification of TRIM5α is essential to achieve significant levels of HIV-1 inhibition.
Vergara-Mendozaa, *et al.*[15]	2020	Cas9 expression is regulated by HIV-1 LTR, INS (Inhibitory sequences) and RRE (Rev Response Element) sequences, while gRNA is regulated to target Tat and RRE. As a result, HIV-1 replication was inactivated, the viral genome was partially excised by multiplex editing, and the viral capsid protein (CA-p24) was not detected.	The system can be used as a precise strategy to eliminate HIV-1 with minimal impact on infected cells.
Teque, *et al.*[16]	2020	PBMCs were made into iPSCs and edited (TALENs or CRISPR/Cas9 in combination with PiggyBac) to delete 32 bp naturally occurring in the CCR5 gene. The result was mutant iPSCs that were resistant to CCR5-tropic and HIV-1 CCR5/CXCR4 infection.	The system showed that iPSCs derived from PBMCs of HIV patients and subjected to gene editing can be resistant to different types of HIV-1. This is a therapeutic approach to cure HIV.
Gupta, *et al.*[17]	2019	An HIV-1-infected adult patient received allogeneic haematopoietic stem cell transplantation (HSCT) for Hodgkin's lymphoma using CCR5Δ32/Δ32 donor cells. HIV-1 remission was sustained for 18 months, HIV-1 RNA was undetectable at less than one copy per milliliter, HIV-1 DNA was undetectable in peripheral CD4 T lymphocytes.	A single allogeneic HSCT with homozygous CCR5Δ32 donor cells was sufficient to achieve HIV-1 remission with reduced intensity conditioning without radiation.
Tang, *et al.*[18]	2019	Binding of 2P23 to the cell membrane can prevent HIV-1, HIV-2 and SIV infection, effectively block HIV-1 Env-mediated cell fusion, make CD4+ T cells less permissive to infection and allow cells to survive longer.	It is a viable gene therapy strategy for HIV-1 and HIV-2 infection. It also plays a role in minimising the effects of antiretroviral therapy, such as cumulative toxicity and drug resistance.

Significant progress in gene therapy for HIV has been driven by advances in gene editing techniques (TABLE 2). Early strategies involved targeting viral genes to suppress replication, but this approach was limited by undesirable side effects and safety concerns. An important milestone was reached with the introduction of zinc finger nucleases (ZFNs), which enabled the targeted disruption of host cell receptors such as CCR5, a co-receptor essential for HIV entry. Subsequently, transcription activator-like effector nucleases (TALENs) were developed, offering improved specificity and efficiency in gene targeting. More recently, the CRISPR/Cas9 system has emerged as a powerful and versatile platform, capable of precisely cleaving integrated HIV proviral DNA and modifying host factors to confer resistance to infection. Collectively, these advances demonstrate the gradual refinement of gene editing technology and highlight its potential as an innovative therapeutic strategy for managing HIV.

TABLE 2. The development of gene editing techniques and their application as a therapy for HIV patients

Gene editing techniques	Mechanisms	Potentials
RNA *interference* (RNAi)	Long terminal repeat indexing mediated integration site sequencing (LTRi-Seq).[19] HEAL (HIV-1-enhanced lncRNA) silences or disrupts the HEAL-FUS ribonucleoprotein complex.[20] HIV-1 trans-activator of transcription (Tat) disrupts RNA silencing suppressor (RSS) activity and induces T-cell death.[21]	Became a new tool for studying HIV gene function in mammalian cells (especially humans) and applied to gene-specific therapy.
ZFN/TALEN	ZFN expression is activated by HIV-1 (Trans-Activator of Transcription) and successfully cleaves HIV-NL4-3-eGFP proviral DNA.[22] Insertion of a stop codon at the CCR5 locus. The results showed that approximately 0.5% of CD34+ cells successfully carried a stop codon at the CCR5 locus.[23]	Generated double-strand breaks (DSBs) are specifically targeted to genomic locations by nonhomologous end-joining (NHEJ) or homology-directed repair (HDR) mechanisms, facilitating genome editing.
B cell technique	Human B cells receive a synthetic antibody gene without an independent promoter capable of expressing neutralizing antibodies. The construct is inserted into the chromosomal heavy chain locus.[24]	Engineering B cells to produce neutralizing antibodies to overcome inadequate humoral immune responses to HIV.
CRISPR/Cas9	Lentiviral (vector) and SaCas9/gRNA-mediated HIV-1 genome editing successfully demonstrated the absence of off-target cleavage at predicted sites.[25] Addition of the KRAB (Kruppel-associated box) transcriptional repressor domain on dCas9 to dCas9-KRAB/gRNA suppresses HIV-1 transcription and reactivation of latent HIV-1 provirus.[26]	The use of CRISPR/Cas9 results in low toxicity, stable gene expression, efficient and precise targeting, and a broad serotype range.

The weaknesses of gene therapy

Currently, there is no successful vaccine or definitive cure for HIV infections. While available antiretroviral therapy can inhibit viral replication, its effectiveness relies on consistent intake of antiretroviral medications. HIV infiltrates the host immune system's cells and can create a persistent viral reservoir, which may be targeted and edited through GT. Gene editing methods have been widely utilized to target DNA within eukaryotic cells, demonstrating promise as an effective strategy for combating HIV infections and pursuing a potential cure.[27]

The outcomes of early-phase clinical trials have so far been promising. However, due to the limited number of patients involved in these trials, the safety of these therapies still requires comprehensive evaluation.[28] Gene editing therapies are designed to reduce off-target editing as much as possible. However, the potential for off-target activity, involving mutations occurring at sites different from the intended on-target site, continues to be a notable concern, especially within therapeutic and clinical applications.[29]

Such off-target activity has the potential to result in point mutations, deletions, insertions, or inversions. Although several GT methods have been successfully developed to diminish off-target effects, they still carry the risk of on-target damage following cleavage, which may lead to substantial chromosomal aberrations.[30-31] As genome editing advances towards *in vivo* therapeutic applications, making this link becomes even more vital as rare incidents could be harmful if they occur in an oncogenic setting.[32] The large chromosomal deletions may result in undesired gene silencing, the elimination of a tumor suppressor gene, or the activation of a proto-oncogene, potentially initiating uncontrolled cell proliferation and oncogenesis.[27] In addition, various algorithms, modified nucleases, and delivery vectors have been developed to address these issues. Therefore, developing on/off-target-specific biomarkers is urgently needed to monitor the efficacy and side-effects of GT.[33]

These scientific risks are not merely technical issues but also carry significant ethical implications, particularly concerning patient safety and researchers' moral responsibility to minimize harm. Inadequate management of genetic modification may undermine the core bioethical principles of beneficence and non-maleficence that guide biomedical research.[34] Beyond these scientific risks, the application of GT for HIV further raises broader ethical concerns. One major concern is equitable access, given that the high cost and complexity of GT technology could restrict its availability to patients in low- and middle-income countries, prompting questions about fairness and global justice.[35] Informed consent and patient autonomy must also be prioritized to ensure individuals are given sufficient information to understand the potential benefits and uncertainties of this new intervention.[36] Furthermore, the possibility of germline modification adds another dimension to the ethical debate, as genetic changes could be passed on to future generations with unpredictable consequences, prompting concerns about intergenerational responsibility.[37] Together, these ethical issues emphasize the importance of integrating scientific innovation with robust ethical frameworks and policies, ensuring that the development of GT for HIV is safe, socially responsible and accessible to those who need it most.

The challenges of gene therapy

Based on the description of some of the advantages and disadvantages of GT above, there are several challenges to the application of GT for HIV patients in Indonesia. The application of GT is still considered an expensive therapy.

The cost of GT based on the literature is $450,000 to $2 million per treatment.[38] Financial subsidies are therefore essential to help the underprivileged so that the entire community can obtain GT. The gap shown by research data in 2009 revealed that 96% of participants in genome association studies (GWAS) were of European descent and only 4% of participants in genome association studies were of African, Hispanic/ Latin, or Indigenous descent. This gap emphasizes the need for more inclusive research to ensure that the benefits of GT can be applied to all populations worldwide.[39] This is a global challenge that is also relevant for Indonesia, a country with enormous genetic diversity, requiring a representative approach to GT development.

In addition, there is a problem of lack of information and education about this GT among the public. So that there needs to be an introduction related to this GT in the medical community. Furthermore, medical staff can educate the public regarding GT, especially in HIV.[40] Then the next challenge is the regulations that regulate this GT in HIV treatment. The Regulation of the Minister of Health of the Republic of Indonesia No. 21 Year 2013 on HIV and AIDS Response has not mentioned this GT. This can be referred to article 33 related to the treatment of HIV and AIDS is carried out by means of treatment: therapeutic; prophylactic; and supporting. Therapeutic treatment includes ARV treatment, STI treatment, and treatment of opportunistic infection.[41]

Ethical regulations related to gene therapy in Indonesia

GT is currently a leading innovation in the development of therapy towards personalized medicine and targeted therapy. However, in Indonesia, GT has not yet become medical research.[42] Indonesia itself is a country with a very diverse level of societal heterogeneity, with a large cultural and religious population making the application of GT controversial regarding aspects of health an unavoidable challenge.[43] At present, there are no binding national regulations goverining the use of GT. However, the Indonesian Ministry of Health has created guidelines regarding aspects of genetic research starting from research design to special attention to the culture and religion adhered to by the community, which they hope will become the basis for developing GT in Indonesia.[44]

Indonesia, as a country with a Muslim majority, aspects of the medical sector are also a concern for religious values. A study by Izzah *et al*.,[45] shows that minority groups are more likely to approve of the use of GT for its use in matters other than therapeutic purposes such as enhancing human capabilities. This is in line with research on religious individuals who reject genome editing therapy because it conflicts with religious values.[46] There is a dilemma in the religious view that GT is an action that violates the destiny that has been determined by God and genetic manipulation is considered an action that exceeds moral boundaries which creates an imbalance in life.[47] On the other hand, there are religions which believe that GT is an effort to improve the quality of human life due to genetic defects and as a means of curing serious diseases.[48]

Saudi Arabia, as a comparable country with a large Muslim population, has approved the development of gene therapy. The Saudi Food and Drug Authority (SFDA) has announced the registration of Hemgenix (etranacogene dezaparvovec) for use in patients with moderate to severe hemophilia (B), a life-threatening genetic disorder. The SFDA confirmed that Hemgenix was approved after a rigorous evaluation of its efficacy, safety, quality, and compliance with required standards. The gene therapy utilizes an adeno-associated virus (AAV) vector to deliver a functional copy of the gene responsible for producing clotting factor IX. The registration of Hemgenix

reflects the SFDA's ongoing efforts to enhance the availability of advanced treatment options for patients in the Kingdom, particularly in the field of biotechnology.[49]

Ethical considerations in the application of GT in Indonesia are also inseparable from educational and socioeconomic factors. People with higher levels of education are more accepting of GT with genome editing in somatic cells as a treatment, but are against genome editing in embryonic cells.[50] Economic aspects also influence views on GT. People who live in developed environments tend to support the application of GT technology compared to people who live in underdeveloped areas. This may be related to the opinion that GT technology is still economically difficult to reach so that GT does not provide significant benefits.[51]

The regulatory and ethical framework for therapeutic applications varies by country. For example, in the United States, the Food and Drug Administration (FDA) enforces strict regulations for GT products. Oversight is conducted in collaboration with Institutional Review Boards (IRBs) and Institutional Biosafety Committees (IBCs) for safety and ethics within GT boards. Regulatory oversight of gene therapy is also carried out by Recombinant DNA Advisory Committees (RACs), which provide a public forum for reviewing human gene transfer protocols.[52] This system focuses on patient safety and efficacy, with clear boundaries between research ethics boards and regulatory bodies.

Meanwhile, Western European countries such as the United Kingdom, adopt a more centralized approach through the Human Fertilization and Embryology Authority (HFEA) which regulates not only GT, but also other reproductive technologies. The Gene Therapy Advisory Committee (GTAC) serves as a single ethics body overseeing these complex issues.[53] Although the US and the UK have comprehensive regulatory frameworks, their implementation and philosophical underpinnings differ. The US framework model is more focused on patient safety, such as long-term health impacts and equitable access. However, the UK framework model places more emphasis on patient safety considerations and prohibits genealogical modification, which is considered unethical due to the potential for heritable changes.

In Malaysia, a neighboring country to Indonesia, GT regulation has advanced further. A study by Mustapa *et al.*,[51] shows that respondents in the form of policy makers in Malaysia view GT positively. Stakeholders consider the benefits, religious acceptance, and strong desire to adopt GT in clinical applications. It is hoped that this study will be a useful basis for researchers, academics, policy makers and community leaders in formulating regulations regarding the use of GT in Malaysia.[51]

This international comparison highlights the need for Indonesia to develop an ethical and regulatory framework tailored to GT. While Indonesia can adopt the experiences of countries with more established systems, it also needs to consider its own varied cultural, religious, and socioeconomic conditions to ensure that regulations are effective and socially acceptable.

CONCLUSION

Gene therapy (GT) holds great potential as an innovative approach for improving treatment adherence and patient outcomes in HIV management. However, its clinical application still faces major scientific, economic, and ethical challenges. Both off-target and on-target genetic alterations remain critical safety concerns, while the high cost of therapy, limited public awareness, and the lack of specific regulations hinder its broader implementation. In Indonesia, ethical and cultural considerations further complicate adoption, emphasizing the need for collaboration

among researchers, policymakers, and community leaders to ensure that GT development aligns with societal values. Therefore, further studies are essential to explore stakeholders' perspectives and formulate a national framework that supports the responsible and equitable application of GT.

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