Systematic Review Article

The use of Microneedles as an Alternative to Injections and Oral Medications for HIV Patients

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ABSTRACT

HIV/AIDS is a chronic disease that requires lifelong antiretroviral (ARV) therapy. However, conventional delivery methods such as oral and injectable medications, often present challenges including pain, poor adherence, and limited access to healthcare services, particularly in remote areas. This study aimed to systematically review the effectiveness of microneedle technology as an alternative ARV drug delivery method. A comprehensive literature search was conducted using PubMed, Scopus, ScienceDirect, SpringerLink, and Google Scholar databases. Studies were selected based on inclusion criteria following the PICOS framework, and data synthesis was performed in accordance with the PRISMA guidelines. The study demonstrated that microneedles (particularly the soluble and hydrogel varieties) are capable of effectively delivering ARVs through the skin, with promising pharmacokinetic responses. This technology is minimally invasive, painless, and easier to self-administer, potentially improving adherence in HIV patients. Microneedle-based drug delivery technology is promising as an alternative to ARV therapy. Further research is needed to test long-term effectiveness and patient acceptability on a broader clinical scale.

Keywords: HIV, antiretroviral, microneedle, drug delivery, systematic review

INTRODUCTION

HIV/AIDS remains one of the most serious global public health challenges. According to the UNAIDS Global Update 2023 report, approximately 39 million people worldwide are living with HIV, and approximately 1.3 million people are infected annually.[1] In Indonesia, more than 543.100 people were reported to be living with HIV in 2023, with over 30.000 new cases recorded each year. These figures indicate that HIV not only affects individuals but also places a substansial burden on healthcare systems and national economies.[2]

One of the main keys to controlling HIV is antiretroviral therapy (ARV), a treatment that can suppress viral replication and maintain the patient's quality of life. However, this therapy is long-term and must be carried out consistently every day for life.[3] This consistency is very important to prevent drug resistance, suppress viral load, and reduce the risk of transmission. Although effective, conventional ARV therapy, whether through daily oral consumption or periodic injections, still faces many challenges, such as low patient compliance, side effects, psychological burden, and accessibility of health services.[4] WHO data shows that less than 75% of patients in developing countries show optimal adherence to ARV therapy.[5] This indicates that efforts to maintain the effectiveness of HIV treatment require innovation in therapy strategies, including the development of more convenient, safe, and painless drug delivery systems.

Although antiretroviral (ARV) therapy has been proven effective in suppressing HIV replication and improving patients' quality of life, current drug delivery methods, both oral (by mouth) and injectable (by injection), still face significant challenges.[6] Oral ARV drugs are generally taken daily, and this demands high compliance from patients. However, in practice, adherence rates often decline due to various factors, such as forgetting to take medication, fatigue with therapy (treatment fatigue), or discomfort from having to take medication for a long time.[7] In addition, oral drug consumption can also cause gastrointestinal side effects, such as nausea, vomiting, and diarrhea, which also reduce patient motivation to continue therapy. On the other hand, injection therapy is also not without its obstacles.[8] Although some long-acting ARV drugs are already available as monthly or bimonthly injections, this method can cause pain

at the injection site, psychological trauma due to fear of needles, and in some cases, local inflammation.[9]

Injection therapy also requires medical personnel to screen and access health facilities, which may not always be available in areas with limited infrastructure, such as remote areas or developing countries.[10] This therapy method ultimately poses challenges in terms of availability, convenience, and patient acceptance. Many HIV patients feel burdened by the therapy routine, both for physical and emotional reasons, thereby reducing the effectiveness of long-term treatment programs.[11] Therefore, alternative approaches are needed that are more innovative, minimally invasive, and support increased patient adherence to ARV therapy. As medical science and health technology develop, various innovations in drug delivery systems have emerged that aim to overcome the challenges of conventional therapy. One breakthrough that is currently gaining widespread attention is the use of microneedles .

Microneedles are a system of very small microneedles that penetrate only the outer layer of the skin without touching nerve endings, so they are painless.[12] These microneedles can dissolve or gradually release drugs into the subcutaneous tissue. Both technologies have several advantages, including enabling controlled and sustained drug release, increasing drug bioavailability, and allowing patients to use them independently at home without the assistance of medical personnel.[5, 8, 12] Thus, the use of patches and microneedles not only has the potential to improve patient compliance, but also provides a more practical, efficient, and user-friendly solution, especially for HIV patients undergoing long-term therapy.

In line with the increasing need for easier, safer, and more practical HIV therapy, several scientific studies have highlighted the potential of microneedles and transdermal patches as alternative delivery media for antiretroviral (ARV) drugs.[7,8,13] This technology is considered very relevant for HIV patients who must undergo long-term and routine therapy, but often face obstacles in terms of adherence, comfort, and access to medical services. Research by Peng et al., in 2021 showed that microneedles are able to deliver efavirenz effectively through the skin with a sufficient level of penetration to achieve therapeutic levels in the blood.[13] The study used a dissolvable microneedle system and successfully demonstrated the potential of this technology to replace oral methods, especially for patients who experience digestive disorders or have difficulty accessing health facilities.

Meanwhile, research by Bui et al., in 2022 developed a microneedle system for the delivery of cabotegravir, a long-acting ARV drug usually administered as an injection. The results showed that the microneedle was able to provide a controlled and stable drug release, and reduced the need for repeated medical interventions, making it suitable for use in communities with limited resources.[14] In addition to pharmacological effectiveness, patch and microneedle technology are also considered capable of increasing patient satisfaction, reducing the stigma often attached to open use of HIV drugs, and facilitating drug distribution in remote areas without the need for complex storage or logistics.[11,12,13,14,15,16] This innovation has the potential to be a game changer in HIV control, especially in areas with limited access to and infrastructure for health services. The use of microneedles as a drug delivery medium offers an innovative, more patient-friendly alternative compared to conventional methods such as oral drugs and injections.[3] Although the potential of this technology is quite promising in the context of HIV therapy, especially because of its ability to reduce pain, increase comfort, and allow independent use by patients, to date there has not been much systematic research that thoroughly provides effectiveness, safety, and the level of acceptability of its use specifically in HIV patients.

Most existing research remains fragmented, limited to preclinical trials or small-scale studies, and does not provide a complete picture of the technology's feasibility as a long-term alternative solution for HIV therapy. Yet, HIV patients generally require lifelong, routine treatment that is not only clinically effective but also accessible, convenient, and supports high adherence. Therefore, there is a significant knowledge gap regarding how microneedles can be integrated into HIV treatment protocols in a practical and sustainable manner. In this context, a systematic literature review is crucial and urgent. Such a review is needed to synthesize the diverse research findings, provide an overview of the available scientific evidence, and highlight critical, under-explored aspects, including pharmacokinetics, clinical effectiveness, patient response, and potential application across geographic and socioeconomic settings.

This study is expected to provide a strong scientific foundation (evidence base) for the development of more humane and innovative HIV therapy technologies. Through this systematic synthesis, researchers, medical practitioners, and policymakers will have a clearer reference point in encouraging the implementation of minimally invasive, painless, and more practical therapy methods for everyday use, particularly in areas with limited access to healthcare. Therefore, this research also makes a significant contribution to

DOI: 10.20527/jbk.v11i2.23577 2025; 11(2): 108-117

encouraging the transition from invasive therapies to more adaptive and patient-friendly technology-based treatments.

METHOD

This study uses a qualitative approach with a Systematic Literature Review (SLR) design following the PRISMA guidelines. The aim is to collect and synthesize studies on the use of transdermal patches and microneedle technology as alternative delivery systems for antiretroviral (ARV) drugs in HIV/AIDS patients. Literature searches were conducted from January to June 2025 through PubMed, ScienceDirect, Scopus, SpringerLink, and Google Scholar, using keywords such as “HIV”, “antiretroviral therapy”, “transdermal patch”, “microneedle”, and “drug delivery system”. Publications from 2019–2025 in English or Indonesian were included, limited to peer-reviewed articles. The study was carried out in Indonesia during the 2025 research period. The literature search flow in this study can be seen in Figure 1 below:

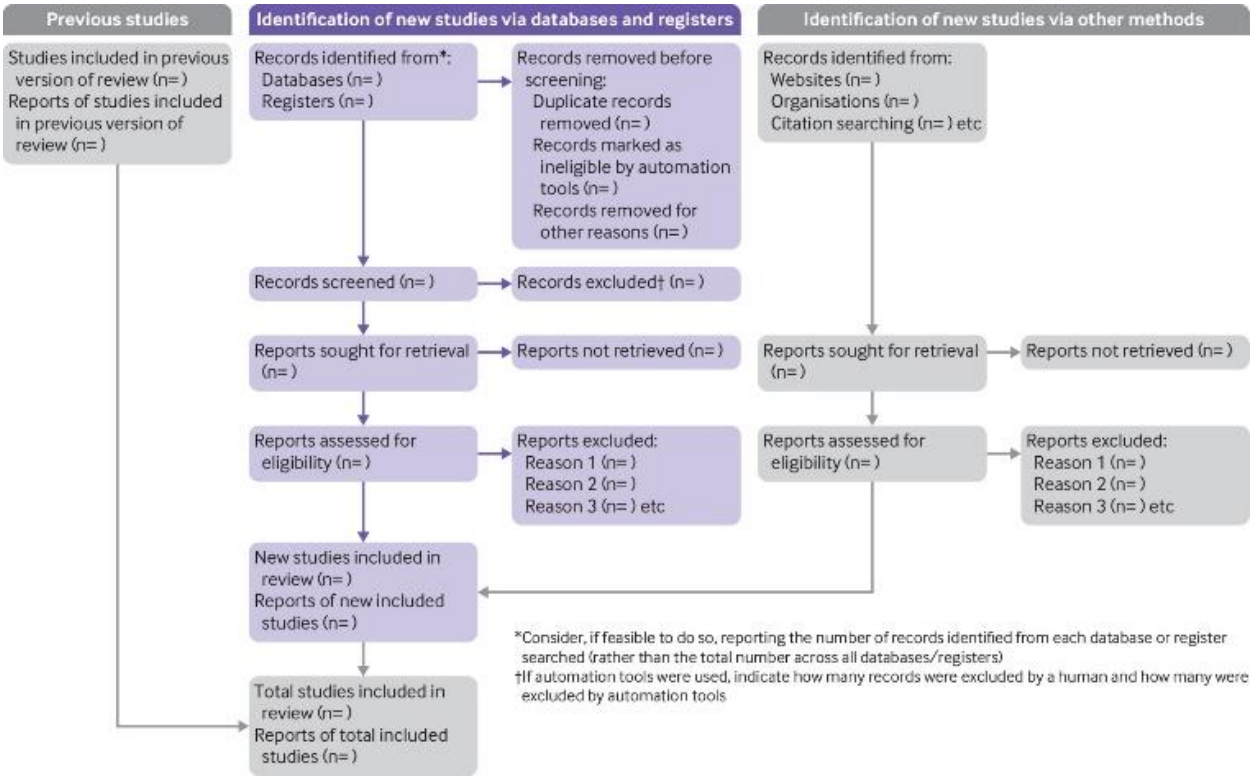

Figure 1. Article Search Flowchart

The preparation of the literature review begins with determining PICOS (Population, Intervention, Comparison, Outcome, Study Design) which is summarized in Table 1.

Table 1. Literature review inclusion criteria based on the PICOS framework

Criteria	Description
Population	HIV patients, both adults and children, without geographical limitations.
Intervention	Use of transdermal patches and microneedles for drug administration.
Comparison	Comparison with conventional methods, namely injections and oral medication.
Outcome	Treatment effectiveness, patient compliance, comfort, and side effects.
Study Design	Relevant clinical studies, observational studies, and meta-analyses.

Articles were screened through titles and abstracts to ensure relevance, followed by full-text reviews assessing content, methodology, and scientific contribution. Studies unrelated to

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HIV, unavailable in full text, or non-empirical were excluded. Methodological quality was evaluated using the Critical Appraisal Skills Program (CASP). Selected studies were then analyzed qualitatively using thematic analysis to identify recurring themes such as transdermal system types, drug delivery mechanisms, pharmacokinetic responses, comparative effectiveness, and patient perceptions. The analysis also explored the technology's potential to improve adherence, reduce stigma, and enhance therapy access in limited-resource settings.

RESULT AND DISCUSSION

Transdermal route as an option for biomacromolecular delivery

Human skin is divided into three main layers, namely the epidermis, dermis, and subcutaneous tissue. The epidermis and dermis are separated by a basement membrane, while there is no separating membrane between the dermis and subcutaneous tissue. The epidermis, as the outermost layer, is composed of four tiered sublayers: the stratum corneum (outermost), the stratum granulosum, the stratum spinosum, and the stratum basale (innermost). The dermis contains additional skin structures, such as hair follicles, sebaceous glands, and eccrine and apocrine sweat glands. In addition, the dermis is also home to sensory nerve endings, lymphatic vessels, and blood vessels that play a role in systemic circulation. Meanwhile, the deepest layer of skin is the subcutaneous tissue or hypodermis, which consists of fatty tissue (adipose).[16]

Transdermal drug delivery can occur through two main routes: first, through the epidermis layer either between cells (intercellular) or directly through cells (transcellular); second, through accessory structures of the skin such as hair follicles and sweat glands, as shown in Figure 1.[9] In the intercellular route, drug molecules move between the intercellular spaces of corneocytes, while in the transcellular route, molecules penetrate directly into the keratin-rich corneocyte cells. Another alternative is the trans-appendageal route, which bypasses hair follicles and sweat glands as a shortcut. The choice of route depends on the individual's skin condition and the physicochemical properties of the drug. Drugs with lipophilic properties tend to be more effective via the transcellular route due to the lipid structure of the stratum corneum, while hydrophilic drugs are more suitable via the intercellular route. Although the trans-appendageal route does not have a stratum corneum layer, this route is not the main route because the accessory skin only covers about 0.1% of the total skin surface area.[11]

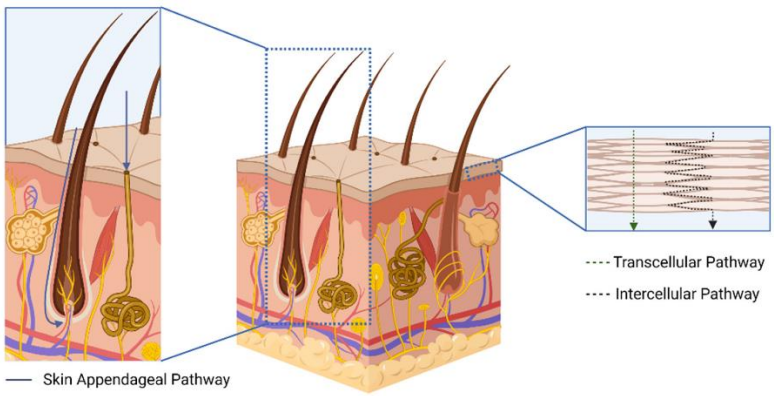

Figure 2. Schematic Illustration of Drug Penetration into Human Skin

The stratum corneum, as the outermost layer of the skin, serves as the primary barrier preventing drug entry into the body. Therefore, only molecules with specific physicochemical properties are able to effectively penetrate this layer. Drugs suitable for transdermal delivery generally have a molecular weight below 600 Daltons, balanced solubility in water and oil with a logP value between 1 and 3, and are in a non-ionic form at physiological pH.[5] Currently, researchers are developing advanced technologies to support the delivery of macromolecules, such as genetic material, stem cells, and their secretory compounds. To improve the penetration ability of less suitable drug molecules, a number of approaches have been developed, both passive and active methods. Passive strategies include the use of chemical penetration enhancers that can interact with certain components of the skin, especially the intercellular lipid layer in the stratum corneum. However, it should be noted that long-term use of chemical enhancers can damage the skin's natural barrier function and cause side effects such as irritation or toxicity.[4]

Meanwhile, physical strategies involve the use of external energy such as electricity, ultrasonic waves, or mechanical pressure to

temporarily open the skin barrier and facilitate drug entry. Electrical-based methods such as electroporation and iontophoresis have been shown to be effective in enhancing penetration for both lipophilic and hydrophilic drugs with larger molecular sizes.[11] Sonophoresis, which utilizes ultrasonic energy, works by increasing the local temperature of the skin, thereby increasing its permeability to drug molecules. One innovative approach currently gaining attention is microneedle technology , a small plate-based device equipped with micron-sized needles, generally ranging from 100 to 1000 micrometers. These microneedles are able to penetrate the outermost protective layer of the skin (stratum corneum) and specifically reach the epidermis without touching pain nerve endings or blood vessels, making their use painless. This technology allows the formation of microcanals in the skin that serve as new pathways for the delivery of hydrophilic drugs and large biopharmaceutical molecules.[8]

Microneedles are considered a practical and effective method for delivering various types of therapeutic compounds, including proteins, vaccines, and antiviral drugs. Another advantage of this technology is its ability to be used independently by patients, without the assistance of medical personnel, thus improving adherence to treatment. The success of skin penetration with microneedles depends heavily on various design aspects, such as the height and diameter of the needle tip, geometric shape, distance between needles, and the density of needles in a single plate. For example, the higher and larger the needle size, the less skin resistance to penetration, resulting in more efficient drug diffusion. However, this design requires attention to the depth of the puncture to prevent damage to nerve tissue or blood vessels. Needles with a tip diameter of less than 15 micrometers and a sufficiently wide distance between needles tend to penetrate the skin more easily.[19]

Microneedles can be designed in various shapes such as cones, pyramids, beveled, or arrowheads. Among these shapes, pyramid designs provide better structural strength than cones due to their more favorable cross-sectional area and length-to-base ratio. In addition, increasing the number of needles can improve penetration efficiency, but too many needles can actually cause puncture resistance and uncomfortable effects such as pressure on the skin (the “spike bed” effect). Overall, the design and application of microneedle technology are relatively simple compared to other transdermal delivery techniques such as electroporation, iontophoresis, or the use of ultrasound, which require specialized equipment.[20] Based on their great potential in delivering macromolecular drugs efficiently and painlessly, microneedles are seen as one of the promising future transdermal therapy solutions.

Microneedle types and utilization of microneedle platforms for delivering genetic material, stem cells, and secretome.

There are five main types of microneedles based on their delivery mechanism: solid, coated, hollow, dissolvable, and hydrogel microneedles, as shown in Table 1 and Figure 2.[3,21,22] The simplest type is the solid microneedle, usually made of materials such as metal or silicone. These needles are used to create microchannels in the skin, which are then coated or covered with a patch or topical preparation containing the drug. The drug is then absorbed into the skin through these channels. However, this approach requires two stages of application. To overcome this limitation, coated microneedles were developed, where the drug is directly coated on the surface of the needle. When inserted into the skin needle, the drug layer dissolves and is absorbed into the skin tissue.[8] This type is more practical because it only requires one application stage. However, the success of this type of formulation is highly dependent on the viscosity of the drug preparation, so that the drug remains attached to the needle during storage and use. The main limitation of this method is that the volume of drug that can be delivered is very limited due to the small surface area of the needle, making it not ideal for high-dose drug delivery. Another type is the hollow microneedle, which has an internal cavity like a miniature syringe. This structure allows the delivery of liquid drugs directly into the skin layer through a hole in the center of the needle when the device is applied.[23]

Hollow microneedles have an internal chamber that allows for a larger drug capacity than previous types, thus overcoming the limitations of drug volume. Meanwhile, soluble microneedles consist of a combination of drug and polymer materials in a single structure, which, although practical, has the disadvantage of a relatively low drug loading capacity. When applied, these needles are dissolved by the interstitial fluid in the skin, thus releasing the drug directly into the skin tissue.[14] On the other hand, hydrogel-based microneedles are designed to increase drug capacity through the presence of a separate reservoir, while the needle portion is made of a hydrogel polymer material. When applied to the skin, these needles absorb interstitial fluid and swell, creating a diffusion pathway that allows the drug from the reservoir to flow into the skin through the expanded hydrogel network. In addition to the type of material and delivery system, needle geometry also plays an

DOI: 10.20527/jbk.v11i2.23577 2025; 11(2): 108-117

important role in drug loading ability. Parameters such as base width, height, and physical shape of the needle can be optimized to increase the volume of drug that can be carried by each needle, regardless of its type.[20]

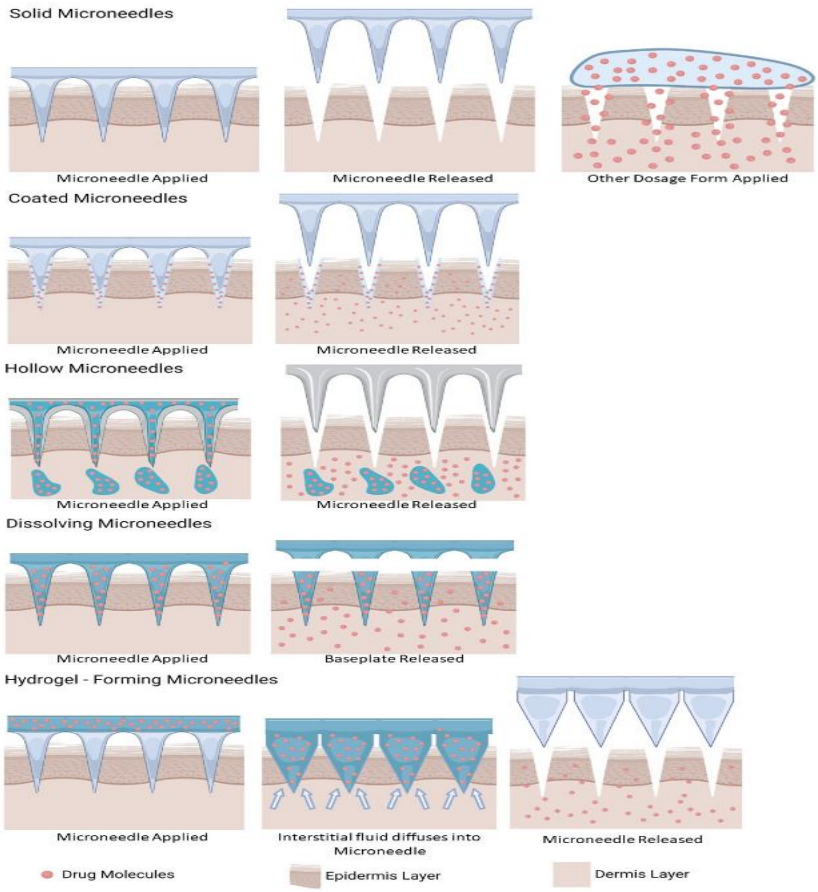

Figure 3. Schematic Illustration of The Types of Microneedles

Various microneedle manufacturing techniques can be selected according to the type of material used. For solid, coated, and hollow microneedles, which are generally made of metal or silicone, techniques such as laser cutting and dry and wet etching can be applied. Specifically for coated microneedles, additional steps are required to coat the drug on the needle surface, for example through repeated spraying or dipping techniques. Meanwhile, hollow microneedles can also be made from glass by utilizing dry/wet etching technology and micropipette pulling techniques. Meanwhile, polymer-based microneedles such as coated, soluble, and hydrogel-forming types are usually produced using methods such as solvent casting or lithography, which can be adjusted depending on the properties and characteristics of the polymer.[21]

Table 2. Summary of materials, applications, advantages, and disadvantages of microneedle types

Types of Micro Needles	Material	Application	Profit	Lack
Solid Microneedle	Silicon, silica glass, metal (stainless steel, titanium)	Two steps	▪ High mechanical strength for effective penetration ▪ Can be combined with other dosage forms (gel, cream, patch)	▪ Not biodegradable → produces sharp waste ▪ Prone to cracking and leaving residue on the skin ▪ Requires two stages of application (“poke with

Types of Micro Needles	Material	Application	Profit	Lack
			▪ Can be formed into various sizes/shapes	patch")
Coated Microneedle	Ceramic, silicone, silica glass, metal (stainless steel, titanium)	One step	▪ Requires only one application step ("coat and prick")	▪ Does not have a drug reservoir ▪ Not biodegradable ▪ Limited drug capacity ▪ A complex coating process to ensure the drug adheres perfectly
Hollow Micro Needles	Ceramic, glass, metal (stainless steel, titanium)	One step	▪ Fast and simple application ▪ Can provide high dose liquid formulations ▪ Design resembles a conventional syringe	▪ Not biodegradable ▪ Expensive and complex fabrication methods ▪ Risk of blockage during installation
Dissolving Microneedles	Biodegradable and biocompatible polymers	One step	▪ Biodegradable → does not produce sharp waste ▪ Simple and inexpensive manufacturing process ▪ Suitable for controlled drug release ▪ Fast application	▪ Limited drug capacity ▪ Requires proper material selection to ensure appropriate strength and dissolution rate
Hydrogel-Forming Microneedle	Cross-linked biocompatible polymer	One step	▪ High drug capacity ▪ Can be combined with hydrogel patches ▪ Drug release kinetics can be controlled ▪ Cannot be reinstalled → risk of infection decreases	▪ Longer application time ▪ Some polymers are not biodegradable → produce sharp waste

Genetic material-based therapy for HIV treatment

Gene therapy is an approach that aims to modify the genetic material in cells to produce therapeutic proteins, prevent disease, or correct abnormal genes. This approach focuses on repairing the genes being treated in human somatic cells, either by stopping the transcription and translation of damaged genes, replacing them with healthy genes, or adding new genes for therapeutic purposes. Once the gene is transferred into the target cell nucleus, the cell begins to produce specific proteins that play a crucial role in disease control.[5] However, the delivery of nucleic acids such as DNA and RNA, the main components of gene therapy, faces significant challenges due to their instability and difficulty in effectively reaching target cells. The complexity of the environment inside and outside the cell also poses additional obstacles in this process. In addition, the negatively charged and hydrophilic nature of nucleic acids makes it

difficult for them to penetrate the cell nucleus efficiently. Therefore, a structured strategy is needed to ensure that gene therapy can achieve optimal effects with minimal risk of side effects. In this regard, vectors, specifically designed carriers to protect and present genetic material, play a key role in increasing effectiveness and directing delivery to target cells. In the context of gene therapy for HIV, there are two main approaches to gene delivery: ex vivo and in vivo. In the ex vivo approach, genetic material packaged in a vector is first introduced into target cells outside the body (under laboratory conditions), such as T cells or hematopoietic cells. After being genetically modified, the cells are then returned to the patient (see Figure 3). In contrast, the in vivo method involves directly administering the gene-carrying vector into the patient, allowing the vector to directly target host cells.[19]

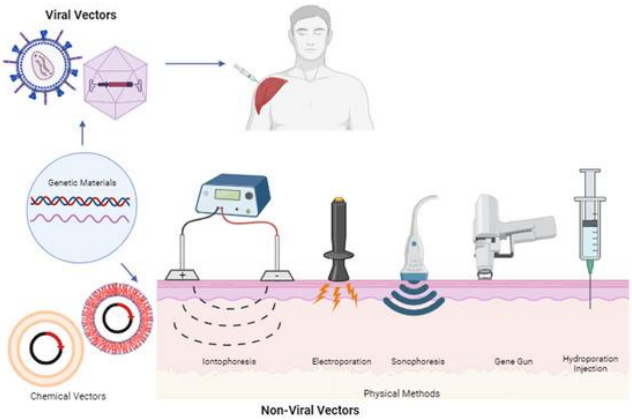

Figure 4. Illustration of Genetic Material Delivery Method

Selecting a suitable vector is a crucial step in gene therapy design, as it determines the efficiency and specificity of genetic material delivery. Vectors are generally classified into two main types: viral and non-viral vectors. Viral vectors exploit the natural ability of viruses to infect and insert genetic material into cells, making them widely used in gene therapy strategies. Some viruses frequently used as vectors include adenoviruses, adeno-associated viruses (AAVs), and retroviruses. Retrovirus-based gene therapy is particularly relevant in the treatment of HIV due to its ability to permanently insert genetic material into the genome of target cells. This allows for long-term gene editing, such as in gene knockout strategies for the CCR5 receptor, a key receptor used by HIV to enter T cells. For example, Strimvelis® therapy utilizes retroviruses to insert the genetic sequence encoding the enzyme adenosine deaminase in the treatment of acquired immunodeficiency disease (ADA-SCID), and this principle is also used in experimental gene therapy approaches for HIV. Some gene therapies are also exploring the use of AAV as a vector for the delivery of genes inhibiting HIV replication or producing targeted neutralizing antibodies, while non-viral vector systems such as lipid nanoparticles are also being investigated to improve safety and reduce the risk of immune responses. [2,5,19]

In contrast to viral-based vectors, non-viral vectors offer alternative genetic delivery systems without the use of viral components. These vectors fall into two main categories: physical approaches and chemical approaches. Physical approaches include techniques such as direct injection, ballistic DNA, electroporation, sonoporation, photoporation, magnetofection, and hydroporation. Meanwhile, chemical approaches involve the use of synthetic carriers, such as lipids (e.g., lipoplexes, liposomes, and solid lipid nanoparticles) and synthetic polymers such as polyethyleneimine (PEI), chitosan, and poly(lactic-co-glycolic acid) (PLGA). In the context of gene therapy for HIV, non-viral methods, particularly physical approaches such as electroporation, have shown significant potential in improving the efficiency of plasmid DNA delivery. For example, the TriGrid® electroporation device (Ichor Medical Systems, Inc., San Diego, USA) has been shown to increase HIV-1-specific antigen expression after intramuscular injection of HIV-1 plasmid DNA in healthy human volunteers. This technique allows plasmids to enter cells more efficiently by increasing the permeability of the cell membrane, which supports the immune system against viruses.[23]

In addition, chemical approaches using lipid or polymer nanoparticles are also being developed to support gene delivery in HIV therapy. Nanoparticle systems, for example, can be used to transport genes or small RNAs (such as siRNA or miRNA) designed to inhibit HIV replication or target receptors the virus uses to enter cells, such as CCR5. This method not only

reduces the risk of immune reactions as can occur with viral vectors, but also provides greater flexibility in design and production. The use of non-viral vectors is increasingly attractive for long-term HIV therapy strategies due to their higher safety, potential for repeated use, and ability to be combined with target-directed systems. However, major challenges remain regarding delivery efficiency and genetic stability in the complex host environment, which are under study for further refinement.[19]

CONCLUSION

Based on this systematic literature review, microneedle technology shows strong potential as an alternative delivery system for antiretroviral (ARV) drugs in HIV patients. Compared with conventional oral and injectable methods, microneedles offer several advantages, including minimal invasiveness, reduced pain, ease of self-administration, and the potential to improve long-term treatment adherence. In particular, soluble and hydrogel-forming microneedles demonstrate effective drug delivery to targeted skin layers and pharmacokinetic profiles comparable to injection-based therapies.

In addition, this technology may help reduce social stigma related to HIV treatment and improve access to therapy in areas with limited healthcare facilities. However, most available evidence is derived from preclinical studies or early-phase trials. Therefore, further large-scale clinical studies are required to evaluate long-term safety, effectiveness, and patient acceptability. Continued development of microneedle-based ARV delivery systems is essential to support more patient-centered, efficient, and sustainable HIV treatment strategies.

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