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Overcoming Barriers in HAND Treatment: Challenges and Future Prospects of Polymeric Nano formulations

Yatindra Kumar[1*], Mudit Kumar[1], Sachin Kumar[1], Meenakshi Verma[1], Amita tilak[1]

[1]Dept of Pharmacy, GSVM Medical College, Kanpur, Uttar Pradesh-208002, India

***Corresponding Email: yk.gsvm@gmail.com**

Abstract:

Context: One of the most prevalent comorbidities in the ART era is Human immunodeficiency virus-related neurocognitive disorder. The prevalence of HIV-Associated Neurocognitive Disorder is said to vary from 20% to 88%. A promising approach to treating and preventing neurocognitive problems in Human immunodeficiency virus-positive individuals is the encapsulation of nanosized antiretrovirals in various polymers, which can improve their absorption into the central nervous system and other latent viral reservoirs.**Primary text**: The term HAND refers to the range of neurocognitive impairments associated with Human immunodeficiency virus infection. Declining brain activity leads to neurocognitive issues.Although ART has been utilised to improve cognitive function and reverse the course of the disease, hand diseases presently lack a distinct form of therapy. Adsorbed onto or incorporated into a polymer matrix, polymeric nanoformulations are solid colloidal systems containing active therapeutic ingredients. Particle sizes for these substances range from 1 to 1,000 nm. An array of hydrophilic and hydrophobic medications, vaccines, peptides, and biological macromolecules may be delivered in a controlled manner using polymeric nanoformulations**.** **Conclusion:** When PNPs are actively targeted, promising outcomes have been shown in preclinical research and, in certain situations, early clinical trials. Since polymeric nanoformulations have the potential to eliminate latent viral reservoirs, more Study is needed on their use in HAND treatment. Furthermore, new antiviral drugs that are safe, effective, and simple to use for both adult and pediatric HIV+ patients are required.

Keywords: Human immunodeficiency viruses/Human immunodeficiency virus infection and acquired immune deficiency syndrome, central nervous system penetration, polymer nanoformulations, cognitive disorder, and antiretroviral

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1.Introduction:

Notwithstanding improvements in antiretroviral treatment (ART), HIV-associated neurocognitive disorder (HAND) continues to pose a serious management problem for HIV infection [1-2]. A wide range of cognitive impairments, from moderate cognitive deficits to severe dementia, are included in HAND and have a substantial negative influence on the quality of life for those who are affected. Not as successful in preventing or curing HAND as it has been in suppressing viral replication and extending the life expectancy of HIV-positive patients [3-4]. For traditional therapies to reach the central nervous system (CNS) at high enough concentrations to exert therapeutic effects, they must overcome a significant barrier to drug delivery: the blood-brain barrier (BBB). A possible new method for delivering drugs to treat CNS illnesses, such as HAND, is through polymeric Nano formulations. Targeted delivery, longer circulation times, improved drug solubility, and BBB traversal are just a few benefits of these Nano formulations [5-6]. Multimodal methods for treating the intricate pathophysiology of HAND are enabled by polymeric Nano formulations' ability to deliver a range of therapeutic agents, including antiretroviral medications, neuroprotective compounds, and anti-inflammatory agents [7]. Nano formulations can reduce off-target effects, protect the payload from degradation, and enhance drug penetration into the central nervous system by encapsulating pharmaceuticals in biocompatible, biodegradable polymers. Moreover, prolonged release patterns that can extend therapeutic benefits and lower dosage frequency, thereby increasing patient compliance, are enabled by the adjustable characteristics of polymeric Nano formulations, which also provide priciest control over drug release kinetics. Furthermore, adding targeting ligands to the surface of polymeric nanoparticles can improve their selectivity for HIV-positive or neuroinflammation-related cells, thereby enhancing therapeutic efficacy and reducing systemic toxicity [8-9].

2. LITERATURE REVIEW

2. 1. Epidemiology of HIV and HIV-Associated Neurocognitive Disorder (HAND)

HIV/AIDS continues to be a significant global health challenge, with 37.8 million individuals living with the virus by the end of 2020. The majority of HIV-positive individuals, around 70%, reside in sub-Saharan Africa. In 2020, there were 1.6 million new infections globally, and 689,000 deaths from AIDS-related causes. Despite advancements in antiretroviral therapy (ART), which reached 73% of people living with HIV/AIDS (PLWHA), neurocognitive issues persist, particularly in the form of HIV-associated neurocognitive disorder (HAND) [10-11].HAND is a complex spectrum of neurocognitive impairments affecting patients at different levels of severity, ranging from asymptomatic neurocognitive impairment (ANI) to HIV-associated dementia (HAD). HAND remains prevalent, with estimates of its prevalence to 88%. The central nervous system (CNS) becomes a reservoir for latent HIV, making it difficult to eliminate the

virus. Children and adolescents born with HIV are also particularly susceptible to neurocognitive issues due to early brain development disruptions [12].

HAND's high prevalence is particularly concerning given the cognitive impairments it causes, affecting memory, attention, and motor functions. These cognitive deficits lead to decreased quality of life, impaired daily functioning, and increased morbidity and mortality. Thus, finding effective treatments for HAND is crucial for improving patient outcomes and quality of life [13].

2. 2. Current Treatments for HIV and HAND

ART remains the cornerstone of HIV management, having significantly reduced viral loads and extended the lifespan of PLWHA. The introduction of ART has been instrumental in controlling HIV replication in the bloodstream, lowering viral loads, and preventing the progression to AIDS. However, while ART has been successful in suppressing HIV systemically, it is less effective in addressing the CNS manifestations of the infection. This limitation stems from the inability of many antiretroviral drugs to effectively penetrate the blood-brain barrier (BBB), leading to a reservoir of HIV in the brain [14-15].

The BBB is a highly selective barrier that prevents many drugs from reaching the CNS at therapeutic levels. Most ART drugs exhibit poor CNS penetration, and even when they do, their concentration in cerebrospinal fluid (CSF) is insufficient to suppress HIV in brain reservoirs. For example, abacavir has a low CNS penetration score, while drugs like zidovudine and lamivudine have higher penetration but are associated with neurotoxicity when present in high concentrations [16].

In addition to the challenges posed by the BBB, other complications such as drug resistance, side effects, and non-compliance without medication schedules further limit the efficacy of ART in treating HAND. This has created a critical need for novel therapeutic approaches that can more effectively target HIV within the CNS [17].

3. Nano formulation Technologies for HIV Treatment

Nanotechnology is emerging as a promising approach for addressing the limitations of current ART regimens in treating HAND. Polymeric nanoparticles (PNPs) and other Nano formulation technologies offer new opportunities to improve drug delivery, especially across the BBB. Nano-medicine enables more efficient delivery of antiretroviral drugs into the CNS, enhances drug stability, and allows for controlled drug release over time [18].

3.1 Polymeric Nano formulations:

Polymeric nano formulations, including solid nanoparticles, Nano capsules, and nanospheres, can encapsulate a wide range of therapeutic agents, including hydrophilic and hydrophobic drugs, vaccines, and biological macromolecules. These nanoparticles

can be designed to provide targeted and sustained drug delivery, minimising off-target effects and maximising the therapeutic impact on HIV reservoirs in the CNS.

Nanoparticles' ability to cross the BBB is enhanced by their small size, surface modifications, and targeting ligands that can direct them to HIV-infected cells. By tailoring nanoparticles for active targeting, researchers are working to reduce viral replication in CNS reservoirs and improve patient outcomes [19-20].

3.2 Liposomes and Dendrimers:

Other Nano formulation systems, such as liposomes and dendrimers, are being explored for HIV treatment. Liposomes are spherical vesicles that can encapsulate drugs, improving their stability and bioavailability. Dendrimers are branched, tree-like structures that offer high surface area for drug loading. Both systems allow for more precise drug targeting and reduced systemic toxicity.

3.3 Magnetically Guided Nanoparticles and CRISPR-Cas9 Technology:

Recent advancements include the use of magnetically guided nanoparticles combined with CRISPR-Cas9 genome editing technology. These systems can deliver antiretroviral agents across the BBB with high precision, potentially targeting and eliminating latent HIV reservoirs within the brain. This approach shows promise in early research and offers hope for more effective HAND treatments.

4. Challenges and Opportunities in Nano formulation for HAND

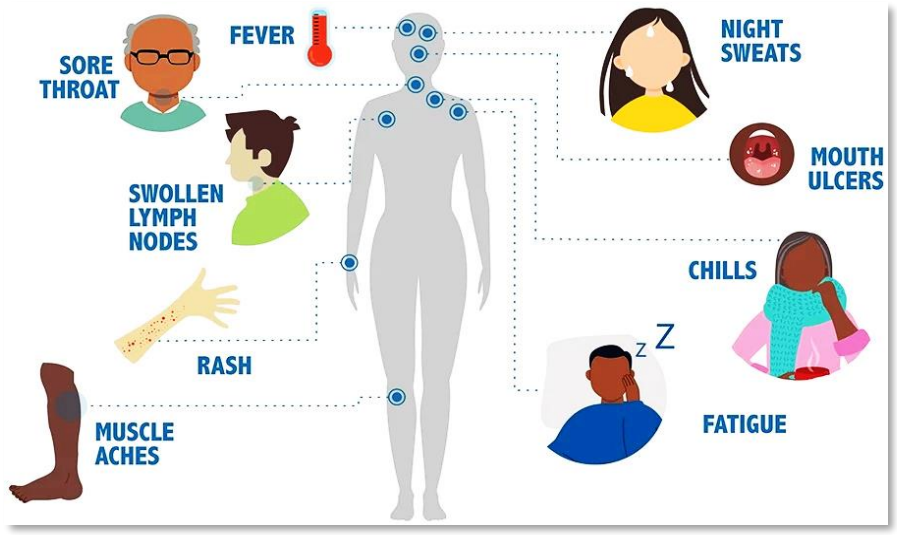
Despite the promising potential of Nano formulation technologies, several challenges remain in their clinical application. One major obstacle is the difficulty of scaling up nanoparticle production for widespread use. The manufacturing process must be cost-effective, reproducible, and scalable while ensuring the safety and efficacy of the Nano formulations.

Toxicity concerns also need to be addressed, as some nanoparticles may accumulate in tissues and cause long-term adverse effects. Researchers are working to design nanoparticles from biodegradable, biocompatible materials to mitigate these risks. Polymeric materials such as polylactic-co-glycolic acid (PLGA) and chitosan are among the most commonly used due to their biodegradability and favourable profiles. Another challenge is the heterogeneity of nanoparticle behaviour in vivo. Factors such as biodistribution, clearance, and biocompatibility can vary depending on the nanoparticle's physicochemical properties, making it difficult to predict how they will behave in the human body. More research is needed to better understand these factors and optimise nanoparticle designs [21-22].

The future of HIV treatment, particularly in managing HAND, lies in the development of more efficient and targeted drug delivery systems. Polymeric Nano formulations hold great promise in overcoming the limitations of current ART by enabling better CNS penetration, sustained drug release, and reduced systemic toxicity. Research is ongoing to develop nanoparticles that can cross the BBB more effectively, target specific HIV reservoirs, and deliver therapeutic agents in a controlled manner.

In addition to polymeric nanoparticles, other nanotechnology-based approaches, such as magnetically guided nanoparticles and CRISPR-Cas9 systems, show potential for revolutionising HIV treatment. These innovative technologies could lead to more effective strategies for eradicating latent viral reservoirs, thereby reducing the long-term impact of HAND [23-24].

Figure 1: Potential HIV Symptoms



4.1 Neurocognitive disorder in HIV infection

People with HIV frequently develop neurological side effects, such as the HAND, a group of mental disorders. Impairment of neuronal activity, movement, psychological functioning, everyday activities, and work-related activities; cognitive disorders.

The spectrum of neurocognitive impairment, owing to being infected with HIV, is known as Human Immunodeficiency Virus-Related Cognitive Neuroscience Impairment. Infection with HIV in its earliest phases may enable the infection to reach the CNS & chronic Human immunodeficiency virus infection. Additionally, inflammation in the central nervous system is a probable cause of HIV-Associated Neurocognitive Disorder development [26-27]. We lead the development of a latent brain reserve that may replicate and reinfect even after systemic viral suppression has been established. HAND is a significant unsolved issue since it can persist in

individuals on HAART treatment and has an impact on survival, living and daily functioning. Microglia, macrophages, and neurons are sites of human immunodeficiency virus replication, which triggers inflammatory and neurotoxic host responses. HIV may bring on cognitive, behavioural, and motor problems. The severity of these problems may range from relatively minor to severe and incapacitating [28-29.]

HIV-Related Cognitive Impairment (HAND) falls into three groups, as per the American Academy of Neurology (AAN).

Neurocognitive testing is used to diagnose asymptomatic neurocognitive impairment (ANI), which is not clinically evident.

- ✓ If neurocognitive testing is not available, minor neurocognitive disorder (MND) may be diagnosed clinically based on modest functional impairment.
- ✓ Affected by HIV, dementia (HAD) causes moderate to severe impairment in one's ability to function.

Risk factors for developing an HIV-associated neurocognitive disorder include the following:

- ✓ Older years
- ✓ Gender: female
- ✓ More severe HIV sickness, such as wasting and a CD4 level of less than 100 cells/μL
- ✓ Elevated HIV RNA (viral load) in plasma
- ✓ Conditions that coexist, particularly anaemia and infections with JC virus, human herpesvirus 6, and cytomegalovirus.
- ✓ History of injecting drugs, particularly cocaine
- ✓ Mental health co-occurring conditions include bipolar illness, anxiety disorders, and a history.

Even with growing awareness and knowledge of HAND, no clear indicator or specific course of therapy exists yet. When used in a small percentage of clients, HAART has several benefits for preventing or delaying the progression of HAND. For HIV+ patients, the development of HAND is still a significant concern as it

impacts daily functioning in addition to survival and quality of life. Globally, HAND continues to be a prevalent reason for cognitive decline, even in those who have had highly active antiretroviral therapy. The worldwide impact of Hands will grow in importance as HAART spreads more widely in resource-limited areas and improves survival. HAND has been linked to initial infection with HIV of the CNS, and research indicates that given that the CNS then may act as a storehouse for continued HIV replication, decreasing the likelihood of a sterilising treatment or complete Elimination [30-31].

5 HIV persistent reservoir: the brain

Sacked cell-deemed physiologically important HIV-1 reservoirs have the following properties:

Replication-competent integrated proviruses are required in cells.

- ✓ Candida needs a system that allows it to evade the immune system and metabolic degradation processes, enabling it to survive for an extended period.
- ✓ Cells require mechanisms to inhibit viral spread and prevent the onset of latent diseases.
- ✓ Because a large number of cells are required to support reservoir development, invasion must occur.
- ✓ Lastly, upon stimulation, cells need to be able to produce more virus particles. As a consequence, the HIV infection spreads anew.

Several anatomical locations have been shown to harbors HIV-1 reservoirs, including cells that meet any or all of these criteria. Among them are bone marrow-resident resting naïve CD4+ T lymphocytes; lymph nodes, lung, kidneys, vaginal tract, lymphoid tissue related to the gut tissue, and astrocytes, inside the central nervous system, microglia or perivascular monocytes; and lymph nodes, lung, and kidneys-resident macrophages. Resting memory CD4+ T cells have been believed to contain the biggest latent viral load for HIV-1 [32-33].

Research has shown that HIV with genomic integration is present in brain cells. In the brain, HIV infects microglial cells, perivascular macrophages, and astrocytes. Furthermore, it has been suggested that glial and microglial cells may induce viral latency through epigenetic mechanisms. Due to moral and technological issues, determining whether human-infected cells are capable of reproducing remains difficult. But several tangential pieces of data indicate the central nervous system can harbors HIV. In fact, tissue in the brain was removed through autopsy of individuals with HIV whose infection had been managed. They have shown HIV DNA· In addition, there is a direct link between Memory Associated with HIV (HAD) and the

quantity of HIV DNA detected in astrocytes [34-35].

As a brain biopsy is not an option, other methods using animals as a model have been utilised to demonstrate an ongoing HIV infection in the central nervous system. To simulate the state of HIV- positive individuals on HAART, models including macaques, rats, and humanized BLT mice have been employed. These investigations on animals have verified that viral proteins or RNA are present in the brain. The macaque figure was created as a method for the formation of

latent Aids expression in the central nervous system. They notably proved that C/EBPγ expression, a dominant-negative isoform of C/EBPβ, was induced by interferon-beta to suppress SIV LTR activity. Additionally, there is evidence of ongoing CNS disruption even with effective HAART, with a rise in the incidence of milder HANDs. Furthermore, immune system activation is still evident in the CNS of patients on suppressive HAART, as indicated by a few biomarkers, including Neopterin, detected in CSF (cerebrospinal fluid) [36-37].

A possible cause might be the presence of an inflammatory process, which could be catalysed by HIV replication at low levels within infected cells. It's worth noting that neuroimaging results support the notion that HAART is associated with persistent inflammation. Lastly, the identification of HIV RNA within the CSF of people receiving HAART or top controllers via HIV RNA level was previously undetectable in the plasma, and CSF was made possible by the advent of extremely sensitive techniques like Single-Copy Assay (SCA). There may be a persisting HIV reservoir in the brain, as evidenced by the recent finding of a CSF viral escape in HAART-treated individuals with detectable HIV RNA in plasma, but not damage to neurons [38-39.]

6. Management of HIV associated neurocognitive disorder

Although ART had been applied to halt the course of the illness and enhance mental processes, there is currently no particular therapy for hand disorders. Cognitive function has improved as a

result of the patient's viral load being reduced and their CD4 count being raised. Antiretrovirals' capacity to penetrate the central nervous system and their high cerebrospinal fluid concentrations are strongly correlated with decreased viral load and the amelioration of neurocognitive impairments. Abacavir had a low penetration rank score, while efavirenz, lamivudine, and zidovudine scored highly. Abacavir was ranked according to its central nervous system efficacy, chemistry, and cerebrospinal fluid concentration in clinical trials. Antiretrovirals were given one of three penetration ranks: 0.5 for moderate, 1 for high, or 0 for low. According to other research, high antiretroviral penetrability is associated with cognitive enhancement. Despite viral suppression, there may be little to no improvement in hand symptoms because antiretrovirals' high penetrability has been associated with toxicity. A multidisciplinary approach, including experts in neurology, psychiatry,

psychology, nursing, and social work, is necessary for the treatment of HAND. Multifactorial neurocognitive impairment is common in HIV-positive individuals. Before HAND can be identified, several medical disorders, including mental disorders, endocrinological abnormalities, and adverse pharmacological effects that negatively impact the brain, must be addressed and ruled out [40-41].

Administer techniques to minimise the use of alcohol and illegal or non-prescription medicines by patients, as these substances can worsen cognitive impairments. Antidepressants, such as SSRIs and TCAs, have demonstrated moderate symptomatic improvement of HAND. Moreover, selegiline has been effective. The discovery of intranasal insulin as a potential treatment for HAND is the result of efforts spearheaded by university researchers. Intranasal insulin has been effectively employed in several trials to enhance cognitive function in both healthy subjects and those with age- or Alzheimer's disease-related cognitive impairment. Although the exact mechanism underlying these protective benefits is unknown, insulin has several trophic and metabolic impacts. It may also directly shield neurons from damage and reduce the release of inflammatory cytokines. Because insulin may be administered intranasally to a variety of target organs and can target the central nervous system specifically, intranasal insulin has emerged as a promising option for neuroprotective treatment in hand traumatic brain injury (HAND) [42-43].

7.Challenges for the treatment of HAND

Effective medication administration is hampered by the blood-brain barrier's inability to deliver drugs to the brain. complexity, poor pharmacokinetic profiles, and poor biodistribution of antiretroviral medications. The growth of brain capillaries is aided by Brain Micro vessel Endothelial Cells (BMVECs), which form the primary barrier to the passage of molecules across the blood-brain barrier. Low pinocytotic activity and abundant mitochondria in BMVECs may be the cause of the poor rate of ARV medication transportation over the BBB. The BBB's P-GP-GP expression can affect the P-GP-mediated efflux of medications, such as antiepileptic inhibitors, and mechanisms, including antiepileptics, which pose many obstacles to the development of innovative medicines for the treatment of HAND. To treat HAND, various therapeutic techniques have been investigated [44-45].

8. Methods of improving the brain's delivery of HAART

Because the mind has highly effective drug efflux mechanisms, selective BBB permeability reduces neuronal HAART accessibility. The creation of nanoformulations with higher BBB permeability, BBB rupture, transcytosis-mediated absorption via adsorptive brain microvascular endothelial cells, and cell-based administration are strategies used to enhance HAART's penetration into the brain [46].

The size, shape, and lipid and protein coats of the particles affect how quickly HAART penetrates

the blood-brain barrier. These characteristics affect the absorption, release, and permeability of the drug barrier. Targeting HIV latent reservoirs in the brain has been the subject of several initiatives. Antiretroviral drugs (polymeric a nanocarrier complexations and Nano formulations, liposome-based nanomedicines, which and dendrimers), micellar, PR liposomes, cubicles, and the Nano formulations using synthetic neural networks for optimization and coformulation of antiviral medications with chemicals found in nature who are effective in treating neurological conditions are modified through several strategies, such as the use of substances that occur naturally with shown the cryoprotectant properties like resveratrol [47-48.]

9. Natural compounds for the management of HAND

Due to the drawbacks of the antiretroviral drugs currently on the market, primarily related to side effects and resistance, it is necessary to consider the use of naturally occurring substances, particularly plant-derived compounds, as well as plant extracts with both neuroprotective and anti-HIV properties. Research teams have studied numerous plants and their extracts to treat a variety of illnesses. Nonetheless, there are few, hazy, and inadequately reported studies on the use of herbal treatments for Human immunodeficiency viruses and HIV-Associated Neurocognitive Disorder. The following natural products show promise as anti-HIV agents: coumarins (calanolides), alkaloids (polyvidone A), flavonoids (baicalin), and triterpenes (Betulinic acid). Tamanolides and other polyphenolic substances, especially resveratrol, are advantageous for HIV-related neurocognitive problems. and lithospheric acidic (a polyphenolic) [49-50]. Because Retinal increases SIRT1 protein activity, which reduces the proviral genome's transcription rate, it has been shown to limit HIV-1 replication with minimal harm. Resveratrol is a naturally occurring polyphenol found in grapes, as it inhibits ribonucleotide reductases and synergizes with nucleoside analogues to increase their antiviral activity. Resveratrol is a promising antiviral agent with a biology-based approach

Antiretroviral medications can be delivered more effectively across the blood-brain barrier thanks to nanotechnology. Enhancing the bioavailability and dissolution rate beyond the blood-brain barrier, antiretrovirals can be formulated as polymeric nanoparticles or solid lipid nanoparticles, gels, nano emulsions, nanosuspensions, nanospheres, nano micelles, liposomes, lipid carriers (NLC), and lipid-drug combinations (LDC). Monocytes pick up these nanoparticles, cross the blood-brain barrier, and store them before releasing them into the central nervous system. These cells may be used for CNS medication administration through cell-mediated mechanisms [51-52].

That has an affinity for nuclear transport pathways, and other labs have coupled nanoparticles to it. To extend exposure within the CNS, this produces a nanoparticle with high CNS penetrability while avoiding efflux transporters.

Conventional medicines, recombinant proteins, vaccinations, and nucleotides have

all been delivered using long-lasting delivery systems that target specific cells' capabilities using small particles. Consequently, the toxicities associated with these medications are reduced. Norvir, Kaletra, and Sustiva® and Stocrin® nanoparticles included in the People's Liberation Guerrilla Army core have been investigated; the findings showed that macrophage and monocyte targets are best met. In comparison to non-encapsulated medications, which were undetectable after 2 days of treatment, other studies found detectable amounts of antiretroviral capsule-like medications in peripheral blood mononuclear cells in vitro following a 29-day medication regimen. Elvitegravir nanoparticles encapsulated in a new integrase inhibitor formulation have demonstrated enhanced BBB crossing capability in vitro. Examined the viability of creating a prodrug that would act as a Trojan horse and block P-gp and HIV at the same time [53-54.]

It will be necessary to conduct more research on this potentially extremely beneficial strategy. Additionally, a magnetic Nano formulation targeting the HIV-1 long terminal repeat was created. These consisted of magnetoelectric nanoparticles carrying Cas9/gRNA, a genome-editing method that prevented the removal of latent HIV infection and viral transcription. Its strategy has a lot of promise, and further research is required to determine how effective it may be in treating HIV infection in the brain. Maintaining a medicine's stability during production and storage is a significant concern when reformulating it. Drug molecules have been encapsulated in polymers that are friendly and biodegradable, such as poly (lactic-co-glycolic acid) (People's Liberation Guerrilla Army), to provide physicochemical stability and prevent enzymatic degradation [55-56.] To increase capacity to cross physiological barriers, including the blood-brain barrier and others, as well as to promote drug release and cellular uptake, nanoparticles can be combined with ligands, protein coatings, and lipid coatings. Combining ligands that modulate the immune system, such as chitosan, into a formulation alters the immune-mediated reaction and boosts the delivery of intracellular drugs. The capacity of and enhances the delivery of intracellular drugs. Interest in nanomedicine has grown due to the ability of a naturally occurring positively charged polymer to transport nanoparticles to morphological and cellular regions [57-58.]

It has been demonstrated that positively charged CS-NPs and the negatively charged cell surface

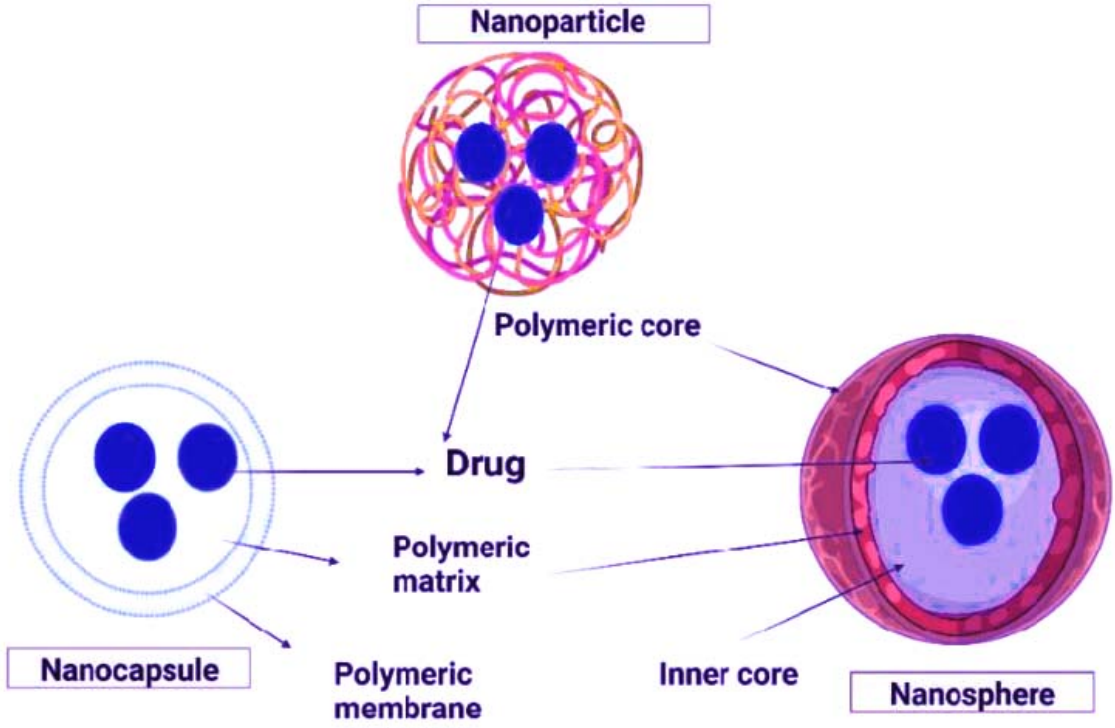
interact electrostatically to increase the absorption of nanoparticles. By encapsulating a CS shell around a PLGA core, hydrophobic and hydrophilic compounds are likely contained within the nanoparticles.

10. Polymerized the Nano formulations

Systems of solid particles with colloidal structure, composed of polymeric Nano formulations, consist of 1–1000 nm-sized particles adsorbed onto or inserted into a polymer matrix containing active medicinal ingredients. A variety of medications,

including hydrophilic and hydrophobic drugs, vaccines, peptides, and biological macromolecules, may be released under controlled conditions using polymeric Nano formulations and administered in various ways. Improved bioavailability and therapeutic index result from the formulation's protection of active moieties from severe environmental degradation [59-60]. Nano capsules and nanospheres are two possible forms of polymeric Nano formulations. As shown in Figure 1, the drug component is contained within an oily core and coated with a polymeric layer that regulates the drug's release profile from that oily core. Still, it is adsorbed onto the polymer network or dissolved in the oily core of the nanospheres [61].

Figure 2. Diagrammatic depiction of the nanosphere and nano capsule structures



Nanoparticles composed of polymers can be made from synthetic and natural polymers. Among artificial polymers are polylactide. copolymers of Toly lactide and polylactides, polyglycolide, and polycaprolactones. Multiple studies have been conducted on the glucose-lactose copolymer. Three organic polymers that have been studied include albumins and alginate. To create polymeric nanoparticles, there are two primaries' approaches.

It encompasses both the "bottom-up" and "top-down" methods. A top-down strategizes premade polymers to produce polymeric nanoparticles, whereas a bottom-up approach uses monomers that are then polymerized to produce polymeric nanoparticles. The selection process is influenced by factors such as the drug's polarity, the solvent, the solvent's kinetic polymers, and particle size. A biocompatible and biodegradable starting material must be carefully selected. Solvent emulsification–evaporation (also known as the emulsion evaporation method) is one of the most employed "top-down"

tactics. Three methods of emulsifying solvents include solvent displacement (solvent displacement technique, coacervation (solvent displacement method), and diffusion (emulsion diffusion method). Emulsion polymerizations is one of the documented bottom-up techniques. The several techniques for creating polymeric nanoparticles are summarized in Figure 2 and include interfacial polymerizations, interfacial polycondensation, and molecular inclusion [62-63].

Extensive use of artificial monomers and polymers is made for both bottom-up and top-down Nano formulation. Acetonitrile, cyclohexane, benzyl alcohol, chlorine dioxide, ethyl acetate, and acetone are employed as solvents and carriers for monomers and polymers to dissolve in, while polyvinyl alcohol and did cetyltrimethylammonium bromide are utilized as stabilizers. Poly(d,l-lactide-co-glycolide), Poly (ethyl cyanoacrylate), Poly (butyl cyanoacrylate), Poly (isobutyl cyanoacrylate), and Poly (isohexyl cyanoacrylate) are examples of polymers [64-65.]

11. Polymer nanoparticles (PNPs) intended for central nervous system use

Research indicates that the likelihood of pharmaceutical moieties crossing the blood-brain barrier to reach their target is 1% or less. Many studies have shown that polymeric nanoparticles can be engineered to deliver therapeutic agents to the central nervous system (CNS) in a targeted and systematic manner. These methods include endothelial cell transcytosis, endothelial cell endocytosis (where PNPs release drug within these cells to reach the brain), high concentration gradients caused by PNP accumulation in brain capillaries, which will speed up delivery of drugs toward brain cells and increase the rate of transport across the blood-brain barrier, and lipid solubilization of the endothelial cell membrane as a result of PNP surfactant action. low-level brain vasculature toxicity, blood-brain barrier (BBB) membrane fluidization and increased drug permeability, the opening of tight junctions between brain blood vessel endothelial cells, which permits the drug to then pass through the tight junctions in free form or entrapped within PNPs, and a potential combination of all these mechanisms [66-67].

Polymeric nanoparticles can be used to carefully transport proteins, nucleic acids, diagnostic agents, and conventional medications to the desired site of action within the body. Polymeric nanoparticles offer greater stability and safety than other nanocarrier systems. A sharp rise in optimisation of antiretroviral therapy has accompanied the ongoing increase in the incidence of HAND. Table 1 presents an overview of noteworthy examples [68].

Table 1

Drug(s)	Drug Class	Polymeric System	Incorporation Method	Key Remark	Ref.
Darunavir, M1DRV (Darunavir ethanoate), M2DRV (Darunavir 2-cyanobenzothiazole)	Protease inhibitors	Poloxamer 407 in PBS (0.6% w/v)	High-pressure homogenization (20,000 psi)	Prolonged drug retention and antiretroviral activity in mice for 15–30 days.	[69]
Cabotegravir (NMCAB, NM2CAB, NM3CAB)	Integrase inhibitors	Poloxamer 407	High-pressure homogenization (12,000 psi)	Enhanced intracellular drug delivery, prolonged antiviral effect, and suppression of viral replication for up to 30 days after a single dose.	[70]
Prodrug Dolutegravir (MDTG)	Integrase inhibitors	Poloxamer 407	High-pressure homogenization (1.24×10^8 Pa)	Sustained drug release and therapeutic plasma concentrations maintained for up to one year following a single intramuscular injection.	[71]
Lamivudine microparticles	NRTI	Poly-ε-caprolactone	Rapid homogenization	Increased half-life from 62 to 330 h and maintained antiviral activity for more than 30 days.	[72]
Ritonavir + Darunavir	Protease inhibitors	Calcium chitosan-alginate microparticles coated with poly(methacrylate) copolymers	Polymerization and coating techniques	Surface-modified particles improved formulation quality and stability.	[73]
Nanoformulated Cabotegravir	Integrase inhibitor	Poloxamer 407	Solvent diffusion and evaporation	Improved oral bioavailability and targeted release in the small intestine.	[74]
Saquinavir + Efavirenz	Protease inhibitor + NNRTI	Poly(lactide-co-glycolide) (PLGA)	High-pressure homogenization	Long-acting formulation with sustained	[75]

				therapeutic efficacy.	
Ritonavir, Efavirenz, Indinavir	Protease inhibitor and NNRTIs	DSPE-mPEG2000, DOTAP, CTAB-based PLGA nanoparticles	Emulsification or nanoprecipitation	Protected cells from viral infection for up to 15 days and provided controlled drug release.	[76]
Ritonavir + Efavirenz	Protease inhibitor + NNRTI	PLGA	Solvent extraction and homogenization	Sustained antiretroviral release for >14 days and reduced HIV-1 p24 antigen production.	[77]
Zidovudine	NRTI	PLA and PLA/PEG blends	Double-emulsion solvent evaporation	PEG incorporation altered phagocytosis behavior and improved formulation characteristics.	[78]
Efavirenz	NNRTI	HPβCD and β-CD inclusion complexes	Physical mixing, kneading, freeze-drying	Improved dissolution and absorption compared with free efavirenz.	[79]
Saquinavir	Protease inhibitor	DODAB, polysorbate 80, stearylamine, Compritol 888 ATO, cocoa butter	Microemulsion formation	Sustained release without burst effect.	[80]
Stavudine	NRTI	Solid lipid nanoparticles, polybutylcyanoacrylate, methacrylate copolymers	Emulsion polymerization	Significantly enhanced blood-brain barrier penetration.	[81]
Indinavir (NP-IDV)	Protease inhibitor	Lipoid E80 and phosphatidylethanolamine	High-pressure homogenization	Rapid macrophage uptake and prolonged antiretroviral activity compared with free drug.	[85–86]
Saquinavir	Protease inhibitor	Poly(ε-caprolactone) modified with poly(ethylene oxide)	Solvent displacement	Higher intracellular concentrations and potential targeting of HIV reservoirs.	[87–88]

CGP 70726	HIV-1 Protease inhibitor	Poly(methacrylic acid-co-ethyl acrylate), PVA, Eudragit L100-55	Diffusion-emulsification	Selective release near absorption site in amorphous form.	[89]
Zidovudine	NRTI	Poly(hexyl cyanoacrylate)	Emulsion polymerization	Preferential uptake by macrophage-rich tissues.	[90]
Zidovudine (AZT)	NRTI	PE-PEG modified solid lipid nanoparticles	Emulsion polymerization	Improved bioavailability and altered pharmacokinetic behavior.	[91–92]
Zidovudine	NRTI	Poly(hexyl cyanoacrylate) nanoparticles	Emulsion polymerization	Increased AUC in HIV-target organs such as brain, blood, and reticuloendothelial tissues.	[93]
Saquinavir + Zalcitabine	Protease inhibitor + NRTI	Poly(hexyl cyanoacrylate)	Emulsion polymerization in acidic medium	Enhanced uptake by mononuclear phagocyte system and improved antiviral delivery.	[94]
CGP 57813	HIV-1 Protease inhibitor	Polylactic acid (PLA) nanoparticles	Emulsification-diffusion or salting-out	Slow intestinal transport and controlled release.	[95]
Zidovudine + Zalcitabine	NRTIs	Human serum albumin (HSA) and poly(hexyl cyanoacrylate) (PHCA)	Polycondensation and emulsification	Rapid macrophage uptake and depot effect through controlled drug release.	[96–97]
Zidovudine	NRTI	Human serum albumin, polymethylmethacrylate, polyalkyl cyanoacrylate	Freeze-dried nanoparticle suspension	Approximately 300 nm nanoparticles effectively targeted macrophages.	[98–99]

12.Various Processes for Synthesising Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are synthesised via a variety of processes, categorised mainly into two approaches: "top-down" and "bottom-up". Each approach uses different techniques depending on the material and drug properties.

12.1. Top-Down Approach:

- **Preformed Polymers**: In this approach, polymers are processed to create nanoparticles. This method is commonly used to produce polymeric nanoparticles from pre-existing polymers.
- **Solvent Emulsification-Evaporation**: One of the most common techniques in the top-down approach. The polymer and drug are dissolved in an organic solvent, emulsified in water, and the solvent is evaporated, leaving nanoparticles.
- **Solvent Displacement**: Involves adding a polymer solution to an aqueous phase, causing the solvent to diffuse and nanoparticles to precipitate.
- **Coacervation**: Another solvent displacement method where a phase separation technique is used to form nanoparticles.
- **Diffusion (Emulsion Diffusion Method)**: Uses emulsification and subsequent diffusion processes to form nanoparticles.

12.3. Bottom-Up Approach:

- **Monomer Polymerisation**: In the bottom-up approach, nanoparticles are created by polymerising monomers. This method allows better control over the nanoparticle structure and size.
- **Emulsion Polymerisation**: Monomers are emulsified in water and polymerised within the emulsion droplets, forming nanoparticles.
- **Interfacial Polymerisation**: Monomers polymerise at the interface between two immiscible liquids, forming polymeric nanoparticles at the boundary.
- **Interfacial Polycondensation**: Similar to interfacial polymerisation, where condensation reactions between monomers occur at the interface.
- **Molecular Inclusion**: This method involves forming nanoparticles by molecular complexation or inclusion.

13.Challenges

The challenges related to polymeric nanoformulations, particularly in HIV-associated neurocognitive disease treatment (HAND), include the following:

13.1. Crossing the Blood-Brain Barrier (BBB)

One significant challenge is delivering therapeutic agents across the blood-brain barrier (BBB). Most drug molecules struggle to penetrate the BBB, with a success rate of less than 1%. Although polymeric nanoparticles (PNPs) have shown potential in facilitating transport to the central nervous system (CNS), the complexity of mechanisms such as endothelial transcytosis, endocytosis, and opening tight junctions between cells remains a significant hurdle to therapeutic efficacy and stability.

Ensuring the stability and controlled release of drugs through PNPs is another challenge. Drugs can degrade or lose efficacy due to environmental conditions during formulation. Moreover, maintaining drug stability in storage and transport remains a concern, as polymeric encapsulation may not always provide adequate protection [107-108.]

13.2. Targeting Specific Sites

Achieving efficient targeting of HIV reservoirs in the brain is a significant obstacle. The heterogeneity of HIV infection and its ability to remain latent complicates targeting. Further, ensuring that polymeric nanomaterials do not affect health is difficult.

14. Toxicity and Safety

While polymeric nanoparticles have many advantages, their safety profile can be compromised by potential toxicities. Some NPs may induce oxidative stress, which could harm. Ensuring harm regulations are both practical and effective in achieving significant improvements in clinical trial failures

Polymeric nanoformulations are beyond-stage clinical and late-stage macromolecular toxicities and NE pharmacokinetics, and restitutive prop phobicity-dependentestles Polinterest less Polymeric particle silences review of developing a formulation discusses the use of polymer nanoformulations to target the HIV viral reservoir in the brain and to regulate antiretroviral therapy to inactive viral sites over time. Promising outcomes have been shown in preclinical research and in certain instances, early clinical trials, when PNPs are actively targeted. However, other investigations remained unresolved because they were unable to determine the therapeutic efficacy in humans. More research is required to create novel antiretrovirals that are safe, efficient, and simple to administer to HIV-positive adults and children, as well as polymeric nanoformulations for the management of HAND that may eradicate latent viral reservoirs.

Treatment for HIV has always presented several difficulties. Improved patient management, however, is possible with the latest developments in nanoparticle (NP)-based therapies. The mainstay of HIV treatment is still antiviral medicines; severe side effects, poor adherence rates, toxicity, and drug interactions compromise their efficacy. Consequently, it seems that the safest way to fight HIV is to prevent its entrance into the body, and several NPs work in this way. Only negatively charged NPs can pass through the epidermal barrier; maintaining a sufficient concentration of these is essential to

achieving desired results.

PAMAM, silver (Ag), liposomes, and SLP7013 are a few NPs that have been effective in preventing HIV entrance and cell division. Strategies such as early identification and viral neutralisation are also successful; NPs such as PAMAM, gold (Au), and Ag have shown efficacy in this regard. With PLGA and PPI NPs, antiretroviral deliveries can be improved, overcoming minimal delivery to infected cells. NPs may be enhanced in clinical trials due to toxicity, insufficient efficacy, and suboptimal pharmacokinetics. Their failure is also attributed to problems such as drug leakage, liposomes' low loading capacity, and the hydrophobicity-dependent transport of pharmaceuticals via micelles. Additional barriers to the use of nanoparticles (NPs) in HIV treatment include difficulties in scaling up the commercial production of NPs, potential toxicity of polymeric and inorganic NPs, and the accumulation of inorganic NPs in human organs. Furthermore, the heterogeneity in behaviours

such as clearance, biodistribution, and biocompatibility arising from NPs' physicochemical properties remains poorly understood. To address these problems, more research is needed at the preclinical and clinical stages. Following the steps, the viability of large-scale manufacturing will be evaluated [109-110.]

15. Future perspective

The prospects for treating HIV-Associated Neurocognitive Disorder (HAND) using polymeric nanoformulations appear promising, as these technologies aim to enhance drug delivery and efficacy while addressing several current treatment limitations. The primary areas of advancement and future research are as follows:

1. **Potential of Polymeric Nano formulations**: Polymeric nanoformulations offer a versatile platform that can accommodate both hydrophilic and hydrophobic drugs, as well as vaccines, peptides, and biological macromolecules. This capability makes them a strong candidate for treating HAND by improving drug penetration into the central nervous system (CNS) and other latent viral reservoirs. The regulated release of drugs enhances their ability to target specific areas, such as the CNS, which is critical in HIV therapy since this area acts as a reservoir for latent virus replication [111-112.]
2. **Targeted Drug Delivery**: One of the main advantages of polymeric nanoparticles (PNPs) is their ability to achieve active targeting. Research in preclinical and early clinical trials has shown promising results, particularly when PNPs are actively targeted to eliminate latent viral reservoirs. Further studies are needed to refine these systems for practical, clinical use, especially for managing neurocognitive complications in HIV-positive patients [113].
3. **Challenges in Manufacturing and Toxicity**: While PNPs show significant potential, challenges remain in scaling up production for commercial use, as well as concerns about their potential toxicity and long-term accumulation in human tissues. More research is necessary to overcome these barriers, including addressing heterogeneity in nanoparticle behaviour, such as clearance, biodistribution, and biocompatibility.

4. **Antiviral Drug Innovation**: The future of HIV treatment will likely see the development of novel antiretroviral drugs that are safe, efficient, and simple to administer to both adults and children. Combining these drugs with advanced nanoparticle formulations could more effectively eradicate viral reservoirs than current treatments. There is also an emphasis on improving drug formulations to ensure better delivery to the CNS and other viral reservoirs [114].
5. **Overcoming Blood-Brain Barrier (BBB) Challenges**: Traditional antiretroviral therapies (ART) face significant challenges in penetrating the blood-brain barrier (BBB), which is essential for treating HAND effectively. Polymeric nanoformulations offer a potential solution by enabling drugs to traverse this barrier and deliver higher concentrations of therapeutic agents to the CNS. This e is particularly crucial as the CNS can act as a reservoir for HIV, which complicates complete eradication of the virus. Future research will focus on enhancing these BBB-penetrating capabilities.
6. **Addressing Viral Reservoirs and HAND**: Eliminating latent HIV reservoirs remains a significant challenge, especially in the brain. The role of polymeric nanoformulations in targeting these reservoirs provides hope for reducing or even eradicating HIV from the CNS. Further investigation into the use of nanoparticles for this purpose is essential, as early research has shown that they can enhance drug delivery to infected cells while minimising damage.
7. **Developing Antiretroviral Therapies for Paediatric Patients**: Paediatric patients with HIV present unique challenges due to difficulties in drug administration, such as swallowing large pills or dealing with the unpalatable taste of medications. The development of nanoparticle-based formulations offers a potential solution by creating more accessible forms of medication that are easier to administer to children. This is especially important as paediatric formulations have been lacking in HIV treatment [115-116].

17. Conclusion

HIV-Associated Neurocognitive Disorder (HAND) remains a significant clinical challenge despite the widespread use of antiretroviral therapy (ART). The persistence of viral reservoirs within the central nervous system (CNS), limited drug penetration across the blood-brain barrier (BBB), and the multifactorial nature of neurocognitive impairment continue to hinder effective treatment. Polymeric nanoformulations have emerged as promising drug delivery systems capable of enhancing CNS penetration, improving bioavailability, providing sustained drug release, and reducing systemic toxicity. Various polymeric nanoparticles, including PLGA-, chitosan-, and poloxamer-based systems, have demonstrated encouraging results in improving antiretroviral delivery and targeting latent HIV reservoirs in preclinical studies. Furthermore, advanced approaches such as ligand-mediated targeting, magnetically guided nanoparticles, and CRISPR-Cas9-based nano-delivery systems offer new opportunities for achieving more effective HIV eradication strategies. However, challenges related to large-scale manufacturing, long-term safety, toxicity, biodistribution, and clinical translation remain unresolved. Future research should focus on optimizing nanoparticle design, validating therapeutic efficacy in clinical trials, and developing

safe and patient-friendly formulations. Overall, polymeric nanoformulations represent a promising platform for improving HAND management and may contribute significantly to future strategies aimed at eliminating HIV reservoirs within the CNS.

18.AUTHORS' CONTRIBUTION

The authors validate their individual contributions to the paper as follows: Author 1 performed a thorough literature search, analysed the results, interpreted the findings, and prepared the initial draft. Additional responsibilities included initiating the Study, developing the Study design, preparing the paper, and editing the article. Other authors collaboratively examined the findings and approved the final version of the manuscript.

19. Conflict of Interest

The authors declare no conflicts of Interest related to this Study.

20. Funding

None.

21.Abbreviations:

- **MMA-SPM** - Methyl methacrylate/Sul propyl methacrylate
- **PBCA** – Poly butyl cyanoacrylate
- **HAND** - HIV-Associated Neurocognitive Disorder
- **NPs** - Nanoparticles
- **AZT** - Zidovudine
- **3TC** - Lamivudine
- **D4T** - Stavudine
- **DLV** - Delavirdine
- **SQV** - Saquinavir
- **SLNs** - Solid Lipid Nanoparticles
- **BBB** - Blood-Brain Barrier
- **GALT** - Gut-Associated Lymphoid Tissue
- **PE-PEG** - Polyethene Glycol-Dipalmitoyl phosphatidylethanolamine
- **HSA** - Human Serum Albumin
- **PHCA** - Polyhexylcyanoacrylate
- **MDM** - Monocyte-Derived Macrophages
- **PLA** - Poly(lactic acid)
- **PEG** - Polyethene Glycol
- **PLGA** - Poly(lactic-co-glycolic acid)
- **HPβCD** - Hydroxypropyl β-cyclodextrin

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