Polymeric Nanoformulation In the Management Of HIV Associative neurocognitive Disorder.

1.Pooja Gadekar 2.Vaishali Gaikwad 3 . Komal Gadekar 4.Snehal Daud.

5.Dr .D.K .Vir Sir

Objective

1. Discuss the pathophysiology of HAND and the limitations of conventional antiretroviral therapy in achieving effective central nervous system (CNS) drug delivery.
2. Examine various polymeric nanoparticles—such as PLGA, PEG, and chitosan-based systems—used to enhance the bioavailability and brain-targeted delivery of antiretroviral drugs.
3. Analyze recent preclinical and clinical findings on the efficacy, safety, and pharmacokinetic profiles of polymeric Nanoformulation.
4. Identify key challenges, safety concerns, and future perspectives for translating these nanotechnologies into clinical use for HAND management.

Abstract:

HIV-associated neurocognitive disorder (HAND) continues to be a significant complication among individuals receiving antiretroviral therapy. The persistence of viral reservoirs within the central nervous system (CNS) and the poor ability of many antiretroviral drugs to cross the blood–brain barrier (BBB) limit effective viral suppression in neural tissues. Polymeric Nanoformulation provide a novel strategy to overcome these challenges by improving drug stability, bioavailability, and targeted delivery to the brain. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan have been widely explored for encapsulating antiretroviral agents and enabling controlled or prolonged drug release. Functionalization of nanoparticles with surface ligands or employing intranasal delivery routes enhances their brain uptake and therapeutic potential. Experimental studies have demonstrated improved drug accumulation in microglia and macrophages, leading to reduced neuroinflammation and viral replication. Despite promising preclinical results, further work is needed to address toxicity, large-scale production, and regulatory challenges before clinical translation. Polymeric Nanoformulation thus represent a powerful and evolving platform for the effective management of HAND.

Keywords: Polymeric nanoparticles; HIV-associated neurocognitive disorder; Antiretroviral therapy; Blood–brain barrier; Central nervous system targeting; PLGA;

Introduction:

Human Immunodeficiency Virus (HIV) infection continues to be a major global health concern despite major progress in treatment and prevention. The introduction of combination antiretroviral therapy (cART) has greatly reduced mortality and improved the quality of life for patients. However, the virus can still enter and persist within the central nervous system (CNS), where it contributes to a group of neurological problems collectively known as HIV-associated neurocognitive disorders (HAND). These disorders range from mild cognitive issues to severe forms of dementia and are reported in a significant proportion of individuals living with HIV, even when viral levels in the blood are well controlled.

One of the main reasons for the continued occurrence of HAND is the limited ability of many antiretroviral drugs to cross the blood–brain barrier (BBB). The BBB restricts the entry of most therapeutic molecules into the brain, leading to poor drug concentrations in neural tissues. As a result, viral reservoirs and chronic inflammation persist within the CNS, causing neuronal injury and progressive cognitive decline. Therefore,

developing a safe and efficient method to deliver antiretroviral agents into the brain has become a critical research focus.
Polymeric Nano formulations offer a promising approach to overcome these limitations. These nan carriers are made from biodegradable and biocompatible materials such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan. They can protect drugs from degradation, allow controlled or sustained release, and enhance their penetration across the BBB. In addition, surface modification with specific targeting ligands like transferrin or lactoferrin can improve drug transport into the CNS through receptor-mediated mechanisms. Intranasal delivery of polymeric nanoparticles is also being studied as a non-invasive route to directly target the brain.
This review focuses on recent developments in polymeric Nanoformulation for the management of HAND. It explores the mechanisms of neurocognitive impairment in HIV infection, limitations of conventional therapy, and the design principles behind polymeric nanoparticles. Furthermore, it summarizes current experimental findings, safety aspects, and the future scope of nanotechnology in improving brain-targeted antiretroviral therapy.

Literature Survey:
C Lomas, RC Dubey, G Perez-Alvarez… - …, 2025 - Taylor & Francis :- Substance use disorders (SUD) and HIV-associated neurocognitive disorders (HAND) work synergistically as a significant cause of cognitive decline in adults and adolescents globally .
Directing the antiretroviral drugs to the brain reservoir: A nanoformulation approach for NeuroAIDS

B Nabi, S Rehman, FH Pottoo… - Current Drug …, 2021 - ingentaconnect.com
Background: Human immunodeficiency virus (HIV)/AIDS is one of the principal concerns contributing to the global burden and the accompanying deleterious outcomes could not be …
N Aggarwal, Sachin, B Nabi, S Aggarwal… - Drug delivery and …, 2022 - Springer
Even though the dawn of highly active antiretroviral therapy (HAART) proved out to be a boon for acquired immunodeficiency syndrome (AIDS) patients, management of HIV
Nanotechnology applications for improved delivery of antiretroviral drugs to the brain
HL Wong, N Chattopadhyay, XY Wu… - Advanced drug delivery …, 2010 - Elsevier
Human immunodeficiency virus (HIV) can gain access to the central nervous system during the early course of primary infection. Once in the brain compartment the virus actively …
Getting into the brain: Potential of nanotechnology in the management of NeuroAIDS
M Nair, RD Jayant, A Kaushik, V Sagar - Advanced drug delivery reviews, 2016 - Elsevier
In spite of significant advances in antiretroviral (ARV) therapy, the elimination of human immunodeficiency virus (HIV) reservoirs from the periphery and the central nervous system …
Modern approaches in nanomedicine for NeuroAIDS and CNS drug delivery
A Belgamwar, S Khan, P Yeole - … in Neurodegenerative Diseases, 2019 - Springer
Human immunodeficiency virus is neurotropic which invades the central nervous system (CNS) in early course of systemic infection and makes the CNS an important dominant
NanoART, neuroAIDS and CNS drug delivery
A Nowacek, HE Gendelman - Nanomedicine, 2009 - Taylor & Francis
A broad range of nanomedicines is being developed to improve drug delivery for CNS disorders. The structure of the blood–brain barrier (BBB), the presence of efflux pumps
Nanoformulated antiretrovirals for penetration of the central nervous system: state of the art
L Fiandra, A Capetti, L Sorrentino, F Corsi - Journal of Neuroimmune …, 2017 - Springer
The central nervous system is a very challenging HIV-1 sanctuary. But, despite complete suppression of plasmatic viral replication with current antiretroviral therapy.

Polymeric Nanoformulation
Polymeric nanoformulations are nanoscale colloidal carriers composed of a polymeric matrix capable of encapsulating or adsorbing therapeutic molecules. These systems typically range between 1–1000 nm in size and are designed to transport a variety of agents, including hydrophilic and hydrophobic drugs, vaccines,

peptides, and large biomolecules. Their structure protects sensitive drug molecules from environmental degradation, thereby improving bioavailability, stability, and therapeutic efficiency.

Polymeric nanoformulations are mainly categorized into nanocapsules and nanospheres.

Nanocapsules contain an oily core in which the drug is dissolved, surrounded by a polymeric shell that regulates the drug's release.

Nanospheres consist of a solid polymeric matrix in which the drug is either dispersed throughout or adsorbed onto the surface.

These systems allow controlled and targeted drug release through various administration routes, making them valuable in chronic and complex conditions such as neurological disorders, cancer, and infectious diseases.

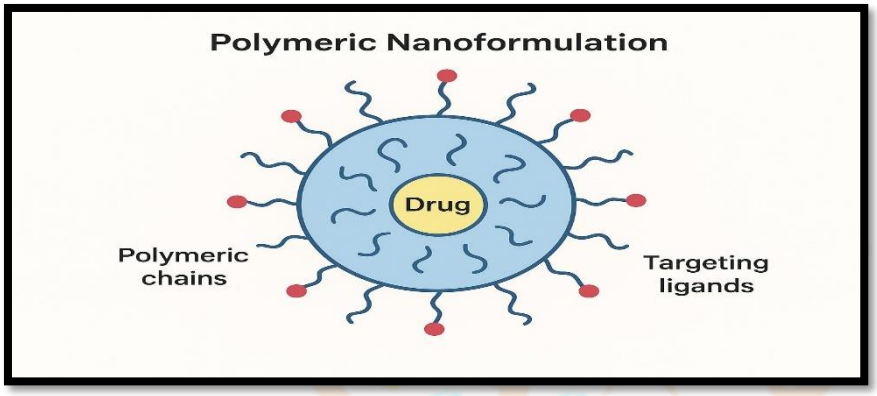

Fig-1.1 Polymeric Nanoformulation

Mechanism of action polymeric Nanoparticles HIV associated neurocognitive Disorder,

HIV-Associated Neurocognitive Disorder develops when the virus enters the brain and disrupts normal neural functioning. HIV crosses the blood–brain barrier mainly through infected monocytes, which later transform into macrophages and microglial cells inside the CNS. Although neurons are not directly infected, HIV targets supportive cells such as microglia, macrophages, and astrocytes. These infected cells release harmful viral proteins like gp120, Tat, and Vpr, which trigger inflammation, oxidative stress, and synaptic damage. Continuous release of inflammatory cytokines and toxic molecules such as TNF-α, IL-1β, nitric oxide, and reactive oxygen species further worsens neural injury. Astrocyte dysfunction also causes excessive glutamate accumulation, which overstimulates NMDA receptors and leads to calcium imbalance and excitotoxic death of neurons. Mitochondrial damage caused by viral proteins reduces energy production and promotes neuronal apoptosis. In addition, chronic inflammation damages the blood–brain barrier, allowing more infected immune cells to enter the brain. These combined processes result in progressive synaptic loss, impaired neurotransmission, and ultimately cognitive, motor, and behavioral deficits characteristic of HIV-Associated Neurocognitive Disorder.

Classification of Polymeric Nanoformulation in the management of HIV associated neurocognitive Disorder

Polymeric nanoformulations used for managing HIV-Associated Neurocognitive Disorder can be classified according to the type of polymer, the structural design of the nano-system, and the therapeutic function they perform within the central nervous system. Based on the polymer source, these systems are divided into natural polymer carriers such as chitosan, alginate, gelatin, dextran, and albumin, which are appreciated for their biocompatibility and low toxicity, and synthetic polymer carriers like PLGA, PLA, PEG-modified polymers, polycaprolactone, and polyethyleneimine, which offer greater control over drug release and stability. Structurally, polymeric nanoformulations include polymeric nanoparticles, micelles, dendrimers, nanogels, and polymer-coated liposomes, each providing unique advantages for transporting antiretroviral drugs into the brain. Polymeric nanoparticles and micelles help improve solubility and sustain the drug levels, while dendrimers and nanogels enable targeted and stimuli-responsive release inside infected microglia or macrophages. Another important category involves targeting strategies, where nanoparticles are functionalized with ligands such as transferrin, lactoferrin, mannose, or antibodies to enhance selective delivery to brain endothelial cells and HIV-infected immune cells. Finally, these nanoformulations can also

be grouped based on their therapeutic purpose: systems designed mainly for antiretroviral drug delivery, nanoformulations carrying neuroprotective agents to reduce inflammation and oxidative stress, and hybrid formulations that combine both antiviral and neuroprotective effects. Together, these classifications highlight the versatility of polymeric nano-drug delivery systems in improving treatment outcomes for HAND.

Antiretroviral therapy for HIV Disorder: Antiretroviral therapy (ART) is the primary treatment approach for controlling HIV infection and preventing its progression to AIDS. It works by using a combination of medications that suppress the ability of the virus to multiply, allowing the immune system to recover and function more effectively. ART regimens typically include drugs from different classes—such as reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitors—so that the virus is blocked at multiple steps of its life cycle. The most widely recommended first-line therapy includes a combination of dolutegravir, tenofovir, and lamivudine due to its strong viral suppression and low side-effect profile. By consistently reducing the viral load to undetectable levels, ART not only improves patients' health and longevity but also prevents transmission of the virus to others. Long-term adherence to ART significantly reduces the risk of opportunistic infections, enhances quality of life, and lower likelihood of developing HIV-associated neurocognitive disorders.

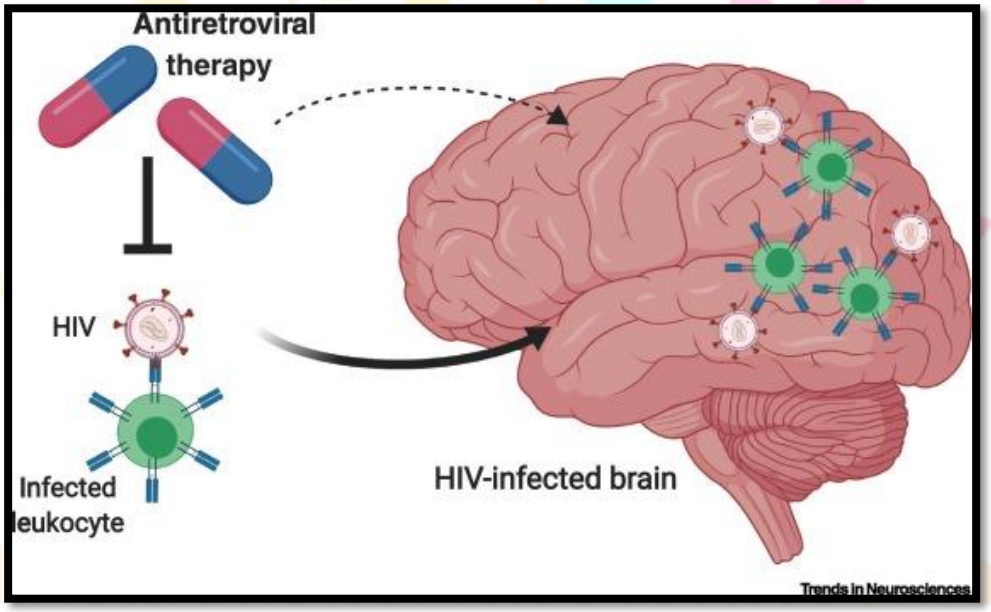

Fig-1.2 Antiretroviral therapy

Blood Brain Barrier for HIV

The blood–brain barrier (BBB) is a highly selective protective interface that normally shields the brain from harmful substances, but in HIV infection this barrier becomes compromised and plays a major role in the development of HIV-Associated Neurocognitive Disorder. HIV typically enters the brain when infected monocytes cross the BBB through the "Trojan horse" pathway and transform into macrophages and microglial cells within the central nervous system. Once inside, these infected cells release viral proteins such as gp120, Tat, and Vpr, which damage endothelial cells and disrupt tight junctions that maintain BBB integrity. Chronic inflammation further contributes to BBB breakdown, as cytokines like TNF-α, IL-1β, and IL-6 increase permeability and oxidative stress, weakening the barrier's protective function. Activated microglia and astrocytes also release neurotoxic molecules that impair nutrient transport and structural support to the BBB. As the barrier becomes more permeable, more HIV-infected cells and inflammatory mediators enter the brain, creating a cycle of inflammation, neuronal injury, and cognitive dysfunction. This progressive weakening of the BBB is therefore a central factor in the brain damage seen in HIV-Associated Neurocognitive Disorder.

Central Nervous S ystem Targeting: Targeting the central nervous system (CNS) in HIV-associated neurocognitive disorder is essential because HIV can cross the blood–brain barrier early after infection and establish a long-lasting viral reservoir in the brain. Once inside the CNS, the virus infects microglia and macrophages, causing chronic inflammation, oxidative stress, and neuronal damage. However, treating HIV within the brain is challenging because many antiretroviral drugs have poor penetration into the CNS due to the protective nature of the blood–brain barrier.

To improve CNS targeting, newer therapeutic approaches focus on using drugs with high CNS penetration effectiveness (CPE) scores, allowing better drug delivery to brain tissues. Nanotechnology-based systems such as polymeric nanoparticles, liposomes, and solid lipid nanoparticles further enhance the transport of antiretroviral agents into the brain by improving drug stability, prolonging circulation time, and facilitating crossing of the blood–brain barrier. These targeted delivery strategies help reduce viral replication within the CNS, decrease neuroinflammation, and lower the risk of cognitive impairment associated with HIV. Effective CNS targeting therefore plays a crucial role in managing HAND and improving neurological outcomes in affected individuals.

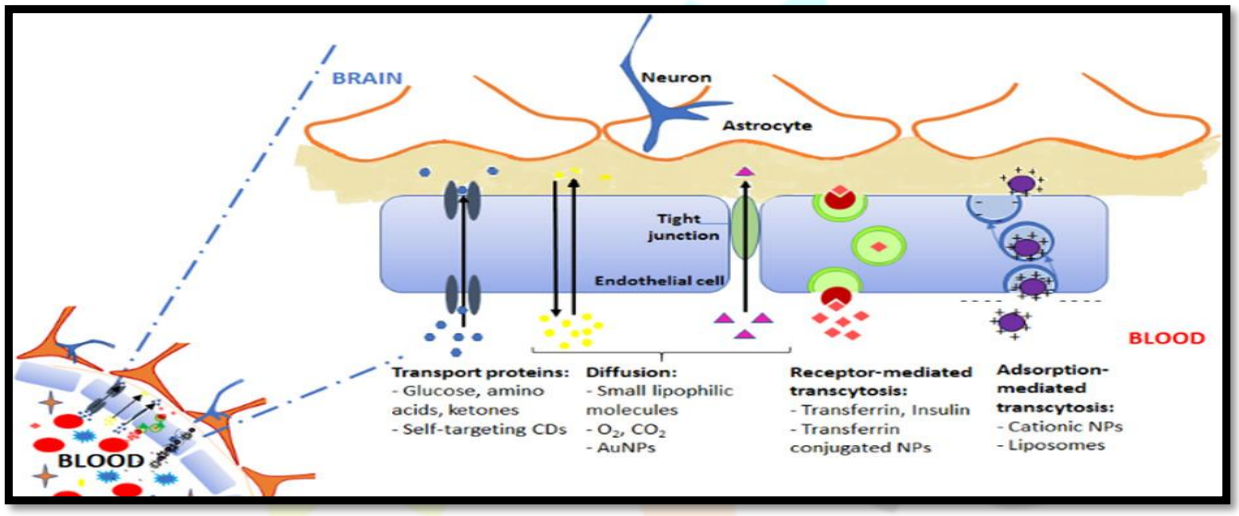

fig-1.3 CNS Targeting

Nanomedicine

Nanomedicine helps improve the treatment of HIV-associated neurocognitive disorder (HAND) by enabling better delivery of antiretroviral drugs to the brain. Polymeric nanoformulations, such as PLGA or PEG-based nanoparticles, are small enough to cross the blood–brain barrier and can be designed to target infected brain cells like microglia and macrophages. These nanoparticles protect the drug, release it slowly, and maintain higher drug levels in the central nervous system. As a result, they enhance viral suppression in the brain, reduce neuroinflammation, and minimize systemic side effects. Overall, polymeric nanocarriers offer a promising strategy to manage HAND more effectively than conventional ART.

PLGA:

PLGA (poly-lactic-co-glycolic acid) is one of the most widely used polymers for developing nanoparticles aimed at treating HIV-associated neurocognitive disorder. Its biodegradable and biocompatible nature makes it suitable for safely delivering antiretroviral drugs to the brain.

PLGA Helps in HAND Management:

1. Improves Brain Delivery of ARVs

PLGA nanoparticles can be engineered to cross the blood–brain barrier (BBB), allowing higher levels of antiretroviral drugs to reach the central nervous system—where HIV persists in microglia and macrophages.

2. Sustained and Controlled Drug Release
PLGA slowly degrades in the body, releasing the drug over an extended period. This helps maintain stable therapeutic concentrations of ARVs in the brain, which is necessary for controlling HIV replication in CNS reservoirs.

3. Targets HIV-infected Brain Cells
PLGA nanoparticles are easily taken up by macrophages and microglia. This is beneficial because these cells are major HIV reservoirs in the brain, contributing to HAND.

4. Reduces Systemic Toxicity
Encapsulating ARVs inside PLGA reduces exposure to other organs, lowering side effects associated with long-term antiretroviral therapy.

5. Protects Drug Stability
Many ARVs degrade quickly in the bloodstream. PLGA nanoparticles protect the drug until it reaches the brain, increasing its effectiveness

Pharmacokinetic Profile Of Polymeric Nanoformulation:

Polymeric nanoformulations significantly modify the pharmacokinetics of therapeutic agents by altering their absorption, distribution, metabolism, and excretion. Because these nanoparticles are engineered at the nanoscale, they can protect drugs from degradation, improve tissue targeting, and prolong systemic circulation.

1. Absorption

Polymeric nanoparticles enhance drug absorption by improving solubility and stability of poorly soluble drugs.

Their small size enables transport across biological membranes through endocytosis, transcytosis, or paracellular pathways.

Surface modifications (e.g., PEGylation, ligand attachment) further increase uptake by specific tissues or receptors.

2. Distribution

Once in systemic circulation, polymeric nanoformulations show controlled and prolonged distribution.

They can evade rapid clearance by the mononuclear phagocyte system (MPS), especially when stabilized with hydrophilic coatings.

Their biodistribution can be tailored to accumulate in target organs such as the brain, liver, lymph nodes, or tumor tissues using passive or active targeting mechanisms.

3.Metabolism
Encapsulation protects drugs from enzymatic degradation and first-pass metabolism.

Biodegradable polymers such as PLGA, PLA, PCL, and chitosan undergo gradual hydrolysis into non-toxic metabolites.

Controlled polymer degradation allows sustained and predictable release of the active compound.

4. Excretion

Polymer degradation products are eliminated through renal or hepatic pathways.

Nanoparticles below 10 nm may be filtered by the kidneys, while larger particles are cleared more slowly through the reticuloendothelial system.

Long-circulating nanoparticles show slower elimination, improving therapeutic efficiency.

.Management of HIV associated neurocognitive Disorder

There is no specific cure for HAND, but antiretroviral therapy (ART) helps reduce viral load, increase CD4 levels, and improve cognitive function. Drugs that enter the CNS more effectively show better control of HIV in the brain, and ART agents are given CNS penetration scores based on their CSF levels and clinical performance. Medicines like efavirenz, lamivudine, and zidovudine have high penetration scores, while abacavir has low penetration. Although high CNS penetration may improve cognition, some drugs can also cause neurotoxicity.

Treatment of HAND requires a multidisciplinary approach involving neurologists, psychiatrists, psychologists, nurses, and social workers. Other medical issues such as psychiatric disorders, hormonal problems, drug side effects, and substance abuse must be managed first. Antidepressants (SSRIs, TCAs) and drugs like selegiline may provide symptom relief. New therapies such as intranasal insulin are also being studied as potential treatments.

Future Perspective of Polymeric Nanoformulation in the management of HIV associated neurocognitive Disorder

Polymeric nanoformulations are expected to greatly improve the treatment of HIV-associated neurocognitive disorder. Future research will focus on designing nanoparticles that cross the blood–brain barrier more effectively and deliver antiretroviral drugs directly to the brain. Long-acting polymeric systems may provide sustained drug release and help patients maintain stable therapy with fewer doses.

Another important direction is the development of multifunctional nanoparticles that carry both antiviral and neuroprotective agents to reduce inflammation and protect neurons. Although safety testing and large-scale production remain challenges, polymeric nanoformulations have strong potential to offer more targeted, long-lasting, and effective treatment options for HAND.

Summary:

Polymeric nanoformulations offer a promising approach for treating HIV-associated neurocognitive disorder by improving drug delivery across the blood–brain barrier and increasing drug concentration in the brain. These nanoparticles can provide targeted, long-acting, and more effective antiretroviral delivery. Future research aims to develop safer, multifunctional, and clinically applicable nano-drug systems to better control HAND and protect brain function.

Conclusion :

Polymeric nanoformulations represent a promising advancement in the management of HIV-associated neurocognitive disorder by enhancing antiretroviral delivery to the brain and overcoming the limitations of conventional therapy. Their ability to improve drug penetration, sustain release, and target viral reservoirs offers a strong foundation for future therapeutic strategies. Continued research on safety, scalability, and clinical translation is essential to fully realize their potential in improving neurological outcomes for individuals living with HIV.

Reference:

1] A Review on the Anti-Inflammatory properties of Bael (Aegle marmelKaramoat O Oyeliran, Department of Pharmaceutics & Pharmaceutical Technology, University of Lagos, Lagos, Nigeria. WJPPS Volume 11, Issue 3, March 2022.

2] Antinori, A., et al. (2007). "Updated research NOSOLOGY for HIV-associated neurocognitive disorders." Neurology, 69 (18), 1789-1799.

3] Heaton, R.K., et al. (2010). "HIV-associated neurocognitive disorders persist: In the era of potent antiretroviral therapy." Neurology, 75 (23), 2087-2096.

4] Dou, H., et al. (2009). "Pathways for neuroprotective polymeric nanoparticles to cross the blood-brain barrier." Biomaterials, 30 (23), 4053-4062.

5] Nair, M., et al. (2010). "Nanotechnology based approaches to enhancing HIV treatment." Drug Discovery Today, 15 (19-20), 842-850.

6] World Health Organization (WHO). (2021). Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery & Target Monitoring. Geneva: WHO Press.

7] Panel on Antiretroviral Guidelines for Adults and Adolescents. (2024). Guidelines for the Use of Antiretroviral Agents in Adults and Adolescent with HIV. U.S. Department of Health and Human Service.

8] Cohen, M.S., et al. (2011). "Prevention of HIV-1 infection with early antiretroviral therapy." New England Journal of Medicine, 365 (6), 493-505.

9] Persidsky, Y., et al. (2006). "Blood-brain barrier: structural components and function under physiologic and pathologic condition." Journal of Neuroimmune Pharmacology, 1 (3), 223-236.

10] Bertrand, L., et al. (2015). "HIV-1 and CNS dysfunction."

11] Bertrand, L., et al. (2019). "HIV infection and the blood-brain barrier: Overviews of mechanisms." Journal of Neurobiology and Neurovirology, 25 (1), 1-16.

12] Kumar, P., & Kumar, A. (2019). "Nanocarrier-based drug delivery systems for CNS targeting in HIV-associated neurocognitive disorders." Journal of Controlled Release, 301, 55-70.

13] Zhong, Y., & Bellamkonda, R.V. (2008). "Dysfunction of the blood-brain barrier in neuroAIDS." Progress in Neurobiology, 84 (3), 228-248.

14] Letendre, S. (2011). "Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder." Topics in Antiviral Medicine, 19 (4), 137-142.

15] Eggert, D., Dash, P.K., Gorantha, S., et al. (2015). "HIV infection of the central nervous system and neuroAIDS: Current prespectives." Journal of Neurovirology, 21 (2), 126-136.

16] Gerson, T., & Mankowski, neurocognitive disorders: strategies. *Nature Reviews*

17] Puligujja, P., et al. (2015). Antiretroviral drug delivery) of HIV-1 infection. AAPS

18] Dou, H., et al. (2021). Nan Advanced drug delivery ap outcomes. *Advanced Drug*

19] Nance, E., et al. (2022). N to improve CNS drug deliv neurocognitive disorder. J 646–659.

20] Kumar, P., et al. (2019). P brain-targeted antiretrovir future prospects. *Internat* 565, 441–457.

21]Dash, P. K., et al. (2018). I nanoformulations for impl viral reservoirs. *Journal of NeuroVirology, 24*(6), 678–690.

22] Kaushik, A., et al. (2020). Nose-to-brain delivery of antiretroviral drugs using polymeric nanocarriers. *Drug Delivery and Translational Research, 10,* 826–840

23] Gang, Y., Zhi, K., Nagesh, P. K. B., et al. (2020). An elvitegravir nanoformulation crosses the blood-brain barrier and suppresses HIV-1 replication in microglia. *Viruses*, *12*(5), 564.

24] Destache, B., *et al*. (2014). New hope for eradication of HIV from the body: The role of polymeric nanomedicine in HIV/AIDS pharmacotherapy. *Journal of Nanobiotechnology*, *12*(9).

25] Nance, E., Zhang, C., & Kannan, R. M. (2014). Drug delivery to the central nervous system using polymeric nanoparticles. *Advanced Drug Delivery Reviews*, *71*, 22–35. (Includes PLGA based strategies for improving BBB penetration.)

26] Gerson, T., & Makarov, E. (2021). Polymeric nanoparticles for enhanced CNS delivery of antiretroviral drugs. *Journal of NeuroVirology*, *27*(3), 410–425. (Discuss PLGA nanoparticles for brain targeting in HIV infection.)

27**] Torchilin, V. P. (2014).** Passive and active drug targeting: Drug delivery systems. *Journal of Controlled Release, 190,* 9–12. (Discusses distribution, targeting, circulation time)

28] Jain**, K. K. (2012).** Nanomedicine: Application of nanobiotechnology in medical practice. *Clinical Pharmacology & Therapeutics, 91*(1), 7–11. (Explains nanoformulation impact on ADME profile)

29] **Panyam, J., & Labhasetwar, V. (2003).** Biodegradable nanoparticles for drug and gene delivery. *Advanced Drug Delivery Reviews, 55*(3), 329–347. (Details absorption, metabolism, polymer degradation)

30] Mohanraj**, V. J., & Chen, Y. (2006).** Nanoparticles—a review. *Tropical Journal of Pharmaceutical Research, 5*(1), 561–573. (General PK behavior, tissue distribution, MPS clearance)

31] Desai**, M. P., Labhasetwar, V., Amidon, G. L., & Levy, R. J. (1996).** Gastrointestinal uptake of biodegradable microparticles. *Pharmaceutical Research, 13*(12), 1838–1845. (Mechanisms of polymeric nanoparticles)