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Review

Corresponding author
Michael Ochieng Otieno
Department of Biochemistry and Molecular Biology
Georgetown University
Washington DC, USA
E-mail: mikeotson@yahoo.com

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Why Novel Nanoparticle-based Delivery Platforms Hold Key for HIV/AIDS Treatment and Prevention?

Michael Ochieng Otieno*

Department of Biochemistry and Molecular Biology, Georgetown University, Washington DC, USA

KEYWORDS: Nanoparticle; Regimens; Nanotechnology; nanoART.

ABBREVIATIONS: HAART: Highly active antiretroviral therapy; nanoART: nanoformulated ART; ATV: Atazanavir; FA: Folic Acid; RTV: Ritonavir; MDM: Monocyte-derived macrophage; P407: Poloxamer 407; RNAi: RNA interference; RISC: RNA Induced Silencing Complex; CNTs: Carbon nanotubes; SWNTs: Single-walled nanotubes; SPIONS: Super paramagnetic iron oxide nanoparticles; DCs: Dendritic Cells; APCs: Antigen-Presenting Cells; MHCs: Major Histocompatibity Complex; LC: Langerhans Cells; CTL: Cytotoxic T-lymphocyte.

INTRODUCTION

The administration of highly active antiretroviral therapy (HAART) to HIV/AIDS patients has greatly reduced their morbidity and mortality. However, HAART regimens have myriad of limitations, which make it difficult to completely eradicate HIV/AIDS from the body. Cells harboring latent HIV reside in restricted areas in the body: cellular and anatomical reservoirs. The residing of HIV in these restricted sanctuaries makes HAART regimens incapable of completely eliminating HIV from the body. In addition, HAART regimens have to be taken for a lifetime making AIDS patients develop resistance to the drugs. When HIV/AIDS patients take HAART regimens overtime, the drugs result in side effects, such as drug toxicities and treatment fatigue. The development of nanotechnology has revolutionized medicine today. Nanotechnology have the potential to mitigate the challenges that doctors and scientists are facing with the current treatment and prevention of HIV/AIDS. In this review, I discuss the challenges of HAART regimens and how the novel nanoparticle-based delivery platforms can be advanced for HIV/AIDS treatment and prevention.

NANOTECHNOLOGY-BASED PLATFORMS FOR SYSTEMIC DELIVERY OF ANTIRETROVIRAL DRUGS

Complete eradication of HIV from the body with current HIV regimens is becoming a nightmare to scientists. Memory CD4+ T cells and macrophages act as latent reservoirs for HIV with the later serving as a host for viral genetic recombination producing an elusive mutant viral genotypes.[1-4] In addition, cells harboring latent HIV reside in restricted parts of the body. These cells are highly concentrated in specific anatomical sites: secondary lymphoid tissues, testes, liver, kidney, lungs, gut and CNS.[3-5] Taking the current HIV regimens overtime result in side effects that are detrimental to HIV/AIDS patients: drug toxicity, treatment fatigue, drug-drug interaction.[6]

Novel nanoparticle-based delivery systems are key in eradicating the virus from reservoirs. They are, therefore, effective in HIV prevention and treatment. Nanotechnology is a scientific discipline that involves fabricating materials at molecular level. Nanotechnology is the study of structures with approximately 1-100 nm in size in at least one dimension. However,

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the applications of nanotechnology also consider structures up to several hundreds of nanometers.[4,7]

Nanotechnology-based platforms have revolutionized medicine regarding treatment of various diseases. In the recent past, the application of nanomedicine for treatment and prevention of HIV and AIDS has gained much attention. The current novel nanoparticle-based delivery systems have been used not only to boost conventional treatments of HIV/AIDS; they have also been use to advance therapeutic strategies: gene therapy, immunotherapy and vaccine developments.[4]

There are several advantages of nanotechnology-based platforms for systemic delivery of ART as compared to conventional methods. Nanotechnology-based platforms improve adherence to the drugs by keeping the circulation of drugs at therapeutic concentrations for longer durations. Their small size enhances and modulates the distribution of hydrophobic and hydrophilic drugs in tissues because of their large surface to volume ratio.[4] Targeted delivery of nanocarriers to CD4 cells and macrophages and to other organs ensures that the ART reach latent reservoirs.[4] The nanocarriers have properties that improve drug delivery: increased drug stability, enhance intestinal absorption and bioavailability, prolonged pharmacokinetics, optimized drug bio-distribution, improved toxicity profiles, and selective drug delivery.[5,8-10]

In what follows, I describe the recent nanotechnology-based novel platforms for systemic delivery of antiretroviral drugs. Drug polymer conjugates have been used to deliver ART because: they increase stability, reduce toxicity and enhance long circulation duration and can permeate across physiological barriers due to their small size.[8] Drug polymer conjugates are used to deliver nucleoside reverse transcriptase inhibitor. Nano-sized monophosphate-polymer conjugate delivery system investigated by Yang, et al. was made using stavudine (d4T). In this nanoparticle, Phosphoramide linkage was used to conjugate d4T to chitosan to yield chitosan-*O*-isopropyl-5′-O-d4T monophosphate conjugate. This conjugate was found to enhance the activity of ART and had low toxicity compared to native nucleoside d4T.[8]

Another nanocarrier used to deliver ART is Poloxamer 407-coated nanocrystals, a nanoformulated ART (nanoART). A nanoART facilitates drug delivery within intracellular compartments and within the sites of viral replication cycle as investigated by Dongwei Guo, et al. Poloxamer 407-coated nanocrystals containing a protease inhibitor Atazanavir (ATV) easily accumulated in macrophages. The concentrations of nanoATV were found to be approximately higher in cells compared to those that could be achieved by the native drug.[11] From this experiment, it can be deduced that the nanocarrier enhances the retention of drugs in subcellular compartments as compared to the native drug.

Biocompatible polymers such as NanoART used as nanocarrier in nanomedicine to deliver ART can be improved by coating it with Folic Acid (FA) to increase drug targeting and retention of drug in the cell. It has been reported that biocompatible polymers, such as Poloxamer 407 (P407) and poloxamer 188 (P188) covalently linked to FA to encapsulate known hydrophobic ART – atazanavir (ATV) and Ritonavir (RTV) increases the retention capacity of the drug and slow the dissociation of drug inside human Monocyte-derived macrophage (MDM) carrier.[12] Coating nanoART with FA particle not only improves intracellular drug targeting; it also improves pharmacokinetics and pharmacodynamics of the drug. Pharmacodynamics of long-acting folic acid-receptor targeted ritonavir-boosted atazanavir nanoformulations.[12-14]

ALTERNATIVE APPROACHES FOR HIV/AIDS TREATMENT

Due to elusive nature of HIV, its eradication from the human body is becoming a herculean task to scientists. However, there are alternative approaches that have been developed in the recent past to eradicate HIV, such as gene therapy, nano-immunotherapy and vaccinology.

NEW NANOTECHNOLOGY PLATFORMS USED IN GENE THERAPY FOR HIV/AIDS

Gene therapy is the direct transfer of genetic material to cells or tissues to treat acquired diseases, such as AIDS and inherited disorders. Once a gene is inserted into a cell infected by HIV-1, it interferes with the viral infection and replication. Viral vectors are being used for delivering agents and various clinical trials are in progress.[15,16] However, it has been found that using viral vectors for gene delivery have a lot of limitations: toxicity, immunogenicity, insertion mutagenesis and scale-up procedures.[4,17,18]

RNA interference (RNAi) holds some promise for therapeutic potential for HIV/AIDS[15,19] RNAi contributes to gene silencing. When a double stranded RNA is introduced into an appropriate cell, it is cleaved by an enzyme called Dicer into 21 base pair nucleotides to produce double stranded siRNA.[6] These siRNAs are incorporated into RNA Induced Silencing Complex (RISC). The single-stranded RNAs in the RISC guide the cleavage of mRNAs that contains sequences complimentary to the single-stranded RNAs in the RISC leading to gene silencing.[6]

The siRNA has been implicated in interfering with HIV-1 by degrading mRNA.[6] The siRNA interferes with viral replication cycle by blocking the translation and transcription of viral genes and by doing so prevents the production of proteins and genomic RNA. The siRNA can also inhibits the entry and fusion of the virus by interfering with production of cell receptors or co-receptors such as CD4, CCR5, and/or CXCR4, which are responsible for viral entry.

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To realize the potential of RNAi, there has to be sufficient technique to deliver it to targeted tissues. The emergence of new nanoparticle-based delivery systems has contributed immensely to efficient and safe delivery of RNAi. The use of inorganic nanoparticles, such as Carbon nanotubes (CNTs) is preferable in gene delivery because: they have good storage ability and are not susceptible to microbial attack. Also, they can easily cross the plasma membrane using endocytosis without causing cell death due to their nanometer needle structure.[16,20-22]

One such nanoparticle-based delivery system to deliver RNAi is Single-walled nanotubes (SWNTs). SWNTs have been used to deliver C×CR$_4$ and CD$_4$-specific siRNA to human T cells in HIV infections.[23] Low biocompatibility and solubility in aqueous solution of SWNTs can be improved by surface modifications or functionalization.[24] Aside from SWNTs, Super paramagnetic iron oxide nanoparticles (SPIONS) have been shown to be excellent carrier for delivering siRNA to cells because of their biocompatibility and target functionalized.[23]

NANOIMMUNOTHERAPY FOR HIV/AIDS TREATMENT

Unlike gene therapy and ART that target HIV, immunotherapy modulates the immune response against HIV.[4] Hence, immunotherapy is aimed at restoring the regular function of the immune system as a therapeutic approach against HIV/AIDS.[25] In this regard, strategies to reconstitute the immune function seem to be a promising approach to eradicate HIV/AIDS. Immunotherapy involves the use of immunomodulatory agents such as cytokines or antigens to modulate the immune response to restore cellular and humoral immunity in HIV-infected patients.[4] The development of cellular and humoral immunity requires the presence of Antigen-Presenting Cells (APCs), such as Dendritic Cells (DCs). The DCs are very instrumental in activating and functioning of both innate and adaptive immunity.[26]

The DCs initiates cellular and humoral immunity by processing and presenting the antigens on their surface through Major Histocompatibity Complex (MHCs) to CD4$^+$ and CD8$^+$ T cells. Since the delivery of immunogenic factors through viral vectors targeting DCs have various risks, the development of polymeric systems to deliver immunogenic factors targeting DCs is showing potential for immunotherapy.[4]

A new developed platform for nanomedicine for immunotherapy is DermaVir patch, which is on its phase II clinical trials.[27] DermaVir consists of an HIV-1 antigen-encoding plasmid DNA that is chemically formulated in a nanoparticle. DermaVir patch got its name from where it is administered. It is administered under a patch after a skin preparation that aids the nanoparticle delivery to Langerhans Cells (LC). The LC mature into dendritic cells when transiting and transporting the nanomedicine to draining lymph nodes. The dendritic cells eventually process and present the DNA-encoded antigens to naïve T-cells that induce the cellular immunity.

NANOPARTICLE-BASED DELIVERY SYSTEMS FOR HIV/AIDS VACCINES

The development of HIV/AIDS vaccine has been confronted with a plethora of challenges: diversity of viral strain and sequence, the evasion of cellular and humoral immunity responses by the virus and lack of methods to elicit neutralizing antibodies and cytotoxic T cells that are broadly reactive.[28]

To generate effective immunity, both humoral and cellular immunity have to be elicited. For cellular immunity, the antigens have to be processed and presented in form of peptides by the APCs, such as DCs to T cells. The MHC class I present intracellular antigens to CD8$^+$ cells and MHC class II presents extracellular antigens to CD4$^+$ cells.[29]

Nanoparticle-based delivery platforms for vaccines have several advantages over conventional vaccines. There is controlled release of antigens that could lead to the prolonged and stronger initiation of the immune response. The encapsulation of the antigen by the nanoparticle protects the antigen from the body fluid thereby increasing the half-life of the immunizing antigen.[4] The surface of the nanoparticle can be functionalized to target antigen delivery to DCs to effectively deliver antigens and initiate an immune response.[4] Nanoparticle can be designed to elicit both cellular and humoral immunity. For instance, nanoparticle can be designed to present the antigen to DCs by encapsulating antigens eliciting cellular immunity or directly present the antigen directly to B cells to elicit humoral immunity by functionalizing the surface of the nanoparticle to absorb the antigen.[35] Unlike conventional vaccines that are limited to one route of administration, that is, intramuscularly, nanoparticles can be administered through oral, dermal, vaginal and nasal routes where mucosal immunity could be induced.[30]

The p24-PLA nanoparticles has been successfully used to elicit both humoral and cellular immunity. HIV antigen p24 was loaded into surfactant-free anionic poly (dl-lactic acid) (PLA) and subsequently injected into the rabbits, mice and macaques. The p24-PLA nanoparticles elicited very high antibody titers and strong Cytotoxic T-lymphocyte (CTL) responses in mice, rabbits and macaques as compared to soluble antigen.[31] The p24-PLA nanoparticles can be used to induce maturation of DCs to enhance cellular immunity. For instance, incubating DCs and p24 antigen adsorbed in PLA nanoparticles was capable of inducing the maturation of dendritic cells. This enhanced the maturation of cell surface markers, such as MHC classes I and II, CD40, CD80 and CD86 as well as the production of cytokines, such as IL-4 and IL-7.[32]

CONCLUSION AND FUTURE PERSPECTIVES

While the nanoparticle-based delivery platforms have been advanced for HIV/AIDS treatment and prevention, there are certain limitations that need to be addressed to realize the po-

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tential of nanomedicine. Some of the nanoparticles administered may not reach their targeted tissues because of their premature degradation. For instance, some of the nanoparticles administered orally are degraded in the gut or are unable to penetrate the gut compromising their absorption.[22] In some cases, the body may respond by getting rid of some of the nanoparticles administered through phagocytosis and other mechanisms[33] compromising their targeted functions. Nanoparticles may not only generate adverse immunological responses, they may also accumulate in the body leading to toxicity.[34] The immunological responses and toxicity may have adverse effects to the HIV/AIDS patients. There is no data on metabolic processing of nanoparticles. Therefore, there is dire need of much research in nanotoxicology.[23] Scaling up in nanotechnology is much expensive. Optimization is much simpler at a laboratory scale as compared to industrial level.[35]

Therefore, more work needs to be done in the field of nanotechnology to make nanocarrier therapeutic approach feasible and to translate nanotechnology from lab to clinical settings. Nanotechnology should offer significant cost to benefit ratio to gain wide acceptability.[4] There is a need to use better surface modifiers for nanocarriers for improved targeting and longer duration and action of drug. Since use of combination of drugs have been found to be more effective in eradicating HIV, studies should be conducted in nanocarriers for combined delivery strategies. In addition, much research should be done on toxicity of nanocarriers.[36] Generally, nanoparticle based delivery platforms have contributed a great deal in advancing HIV/AIDS treatment and prevention. They have improved drug delivery in many ways: they have improved adherence to the drugs increasing their stability, their targeted delivery achieve more efficient distribution, they have reduced drug toxicity levels significantly and they provide a means of permeating blood brain barrier.

REFERENCES

1. Lamers SL, Salemi M, Galligan DC, et al. Extensive HIV-1 intra-host recombination is common in tissues with abnormal histopathology. *PLoS One.* 2009; 4(3): E5065. doi: 10.1371/journal.pone.0005065

2. Marsden MD, Zack JA. Eradication of HIV: Current challenges and new directions. *J Antimicrob Chemother.* 2009; 63(1): 7-10. doi: 10.1093/jac/dkn455

3. Richman DD, Margolis DM, Delaney M, Greene WC, Hazuda D, Pomerantz RJ. The challenge of finding a cure for HIV infection. *Science.* 2009; 323(5919): 1304-1307. doi: 10.1126/science.1165706

4. Mamo T, Moseman EA, N Kolishetti N, et al. Emerging nanotechnology approaches for HIV/AIDS treatment and prevention. *Nanomedicine (Lond)*. 2010; 5(2): 269-285. doi: 10.2217/nnm.10.1

5. Nowacek A, Gendelman HE. Nanoart, neuroAIDS and CNS drug delivery. *Nanomed.* 2009; 4(5): 557-574. doi: 10.2217/nnm.09.38

6. Leonard B. Class presentation on Core methods of Biotechnology. 21.

7. Farokhzad OC. Nanotechnology for drug delivery: The perfect partnership. *Expert Opin Drug Deliv.* 2008; 5(9): 927-929. doi: 10.1517/17425247.5.9.927

8. Edagwa BJ, Zhou T, McMillan JM, Liu XM, Gendelman HE. Development of HIV Reservoir Targeted Long Acting Nanoformulated Antiretroviral Therapies. *Curr Med Chem*. 2014; 21(36): 4186-4198.

9. Destache CJ. Chapter 12-Brain as an HIV sequestered site: Use of nanoparticles as a therapeutic option. *Progress in brain research*. 2009; 180: 225-233. doi: 10.1016/S0079-6123(08)80012-X

10. Wong HL, Chattopadhyay N, Wu XY, Bendayan R. Nanotechnology applications for improved delivery of antiretroviral drugs to the brain. *Advanced Drug Delivery* Reviews. 2010; 62(4-5): 503-517. doi: 10.1016/j.addr.2009.11.020

11. Guo D. Endosomal Trafficking of Nanoformulated Antiretroviral Therapy Facilitates Drug Particle Carriage and HIV Clearance. *Journal of Virology*. 2014; 88: 9504-9513. doi: 10.1128/JVI.01557-14

12. Puligujja P, Balkundi SS, Kendrick LM, et al. Pharmacodynamics of long-acting folic acid-receptor targeted ritonavir-boosted atazanavir nanoformulations, *Biomaterials.* 2015; 41: 141-150. doi: 10.1016/j.biomaterials.2014.11.012

13. Guo D, Zhang G, Wysocki TA, et al. Endo-somal trafficking of nanoformulated antiretroviral therapy facilitates drug particle carriage and HIV clearance. *J Virol.* 2014; 88: 9504-9513. doi: 10.1128/JVI.01557-14

14. Puligujja P, McMillan J, Kendrick L, et al. Macrophage folate receptor-targeted antiretroviral therapy facilitates drug entry, retention, antiretroviral activities and biodistribution for reduction of human im- munodeficiency virus infections. *Nanomed Nanotechnol Biol Med.* 2013; 9: 1263-1273. doi: 10.1016/j.nano.2013.05.003

15. Rossi JJ, June CH, Kohn DB. Genetic therapies against HIV. *Nat Biotechnol.* 2007; 25(12): 1444-1454. doi: 10.1038/nbt1367

16. Dizaj SM, Jafari S, Khosroushahi AY. A sight on the current nanoparticle-based gene delivery vectors. *Nanoscale Research Letters.* 2014; 9: 252. doi: 10.1186/1556-276X-9-252

ISSN 2377-8377 Open Journal http://dx.doi.org/10.17140/HARTOJ-2-113

17. Lundin KE, Simonson OE, Moreno PM, *et al*. Nanotechnology approaches for gene transfer. *Genetica.* 2009; 137(1): 47-56. doi: 10.1007/s10709-009-9372-0

18. Mintzer MA, Simanek EE. Nonviral vectors for gene delivery. *Chem Rev.* 2009; 109(2): 259-302. doi: 10.1021/cr800409e

19. Haasnoot J, Westerhout EM, Berkhout B. Rna interference against viruses: strike and counterstrike. *Nat Biotechnol.* 2007; 25(12): 1435-1443. doi: 10.1038/nbt1369

20. Lee JM, Yoon TJ, Cho YS. Recent developments in nanoparticle-based siRNA delivery for cancer therapy. *Biomed Res Int.* 2013; 782041(10): 17. doi: 10.1155/2013/782041

21. Lian J, Xin Z, Ming L, Yan D, Nongyue H. Current progress in gene delivery technology based on chemical methods and nano-carriers. *Theranostics.* 2014; 4(3): 240-255. doi: 10.7150/thno.6914

22. Li M, Al-Jamal KT, Kostarelos K, Reineke J. Physiologically based pharmacokinetic modeling of nanoparticles. *ACS Nano.* 2010; 4: 6303-6317. doi: 10.1021/nn1018818

23. Solmaz Mamo T, Moseman EA, Kolishetti N, et al. Emerging nanotechnology approaches for HIV/AIDS treatment and prevention. *Nanomedicine.* 2010; 5(2): 269-285. doi: 10.2217/nnm.10.1

24. Ramos-Perez V, Cifuentes A, Coronas N, Pablo A, Borrós S. Modification of carbon nanotubes for gene delivery vectors: nanomaterial interfaces in biology. *Methods Mol Biol.* 2013; 1025: 261-268. doi: 10.1007/978-1-62703-462-3_20

25. Rinaldo CR. Dendritic cell-based human immunodeficiency virus vaccine. *J Intern Med.* 2009; 265(1): 138-158. doi: 10.1111/j.1365-2796.2008.02047.x

26. Jihed C, Campbell Donald E, Livio A, et al. Persistent decreases in blood plasmacytoid dendritic cell number and function despite effective highly active antiretroviral therapy and increased blood myeloid dendritic cells in hiv-infected individuals. *J Immunol.* 2002; 168: 4796-4801. doi: 10.4049/jimmunol.168.9.4796

27. Lori F, Calarota SA, Lisziewicz J. Nanochemistry-based immunotherapy for HIV-1. *Curr Med Chem.* 2007; 14(18): 1911-1919.

28. Barouch DH. Challenges in the development of an HIV-1 vaccine. *Nature* 2008; 455(7213): 613-619. doi: 10.1038/nature07352

29. Guermonprez P, Valladeau J, Zitvogel L, Thery C, Amigorena S. Antigen presentation and t cell stimulation by dendritic cells. *Ann Rev Immunol.* 2002; 20: 621-667. doi: 10.1146/annurev.immunol.20.100301.064828

30. Csaba N, Garcia-Fuentes M, Alonso MJ. Nanoparticles for nasal vaccination. *Adv Drug Deliv Rev.* 2009; 61(2): 140-157. doi: 10.1016/j.addr.2008.09.005

31. Date AA, Destache CJ. A review of nanotechnological approaches for the prophylaxis of HIV/AIDS. *Biomaterials*. 2013; 34(26): 6202-6228. doi: 10.1016/j.biomaterials.2013.05.012

32. Aline F, Brand D, Pierre J, et al. Dendritic cells loaded with HIV-1 p24 proteins adsorbed on surfactant-free anionic PLA nanoparticles induce enhanced cellular immune responses against HIV-1 after vaccination. *Vaccine.* 2009; 27: 5284-5289. doi: 10.1016/j.vaccine.2009.05.028

33. Raveen P, Maguire GEM, Govender P, Kruger HG. Nanotechnology and the Treatment of HIV Infection. *Viruses.* 2012; 4: 488-520. doi: 10.3390/v4040488

34. Müller RH, Gohla S, Keck CM. State of the art of nanocrystals-Special features, production, nanotoxicology aspects and intracellular delivery. *Eur. J. Pharm. Biopharm.* 2011, 78: 1-9. doi: 10.1016/j.ejpb.2011.01.007

35. Ochekpe NA, Olorunfemi PO, Ngwuluka NC. Nanotechnology and drug delivery part 2: Nanostructures for drug delivery. *Trop. J. Pharm. Res.* 2009; 8: 275-287.

36. Rama M, Lisa RC. Progress in antiretroviral drug delivery using nanotechnology. *International Journal of Nanomedicine.* 2010; 5: 533-547.