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THERAPEUTIC APPROACH TO HIV/ AIDS IN INTEGRATION WITH NANOTECHNOLOGY

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Abstract: HIV/AIDS is a deadly disease terrifying the entire world. If the record of death of HIV infected patients is worked out, it will be considered one of the top three infectious diseases behind the fatality of a huge number of patients. No proper preventive vaccine of HIV has been found till date. But works are going on in the hope of easing the treatment procedures of HIV. The concept of nanotechnology has been taken into account in the treatment of HIV/AIDS. Nanotechnology, combining with pharmacology, has been able to develop various innovative and interesting treatment procedures of HIV, be it diagnostic approach, identification, targeting, marking or even complete killing of HIV in the patient body. This review contains a list of nano based products, approaches, machineries and procedures to successfully treat HIV in the patients.

Keywords: Dendrimers, Polymeric Micelle, Drug-delivery, Niosomes, Gold nanoparticles, Melittin

1. INTRODUCTION

The Human Immunodeficiency Virus is a very dangerous disease. It leads to AIDS (Acquired Immunodeficiency Syndrome) which is fatal in nature. It is one of the most infectious and deadliest diseases of the world. HIV mainly spreads through unprotected sexual contact, transfusion of blood from receivers to donors, can spread through body fluids, can spread through exchange of infected needles or syringes, can transfuse from mother to child during pregnancy or through breast feeding.

This global pandemic has accounted for about 36.7 million people as of the record of the year 2016. In the worst affected countries, the life expectancy keeps falling due to this disease. An estimated death count of about 1.3 million people has been marked due to HIV and AIDs related disease. But there is still no proper preventive vaccine of HIV.

Research in nanotechnology in the fields of healthcare and medicine has been useful in dealing with the identification, diagnosis, fighting HIV [1-2]. Nanotechnology has been able to successfully integrate and combine the pharmacological profiles of different antiretroviral drugs with better competence of patients to HIV therapy and easier procedures of drug administration in the patient body.

Since date, scientists and researchers have been able to use some polymeric nano-particle (biodegradable in nature) in the development of a new cocktail type drug delivery system which can encapsulate non-nucleoside reverse transcriptase inhibitor, conjugated surface with HIV-1 fusion inhibitor. It aims to achieve developed and enhanced antiviral activities, improved and easier cellular uptake along with prolonged time for blood circulation.

The early treatment procedures revolve around the concept of the antiretroviral drugs which can be effective only up to a certain limit. Then there was the introduction of the protease inhibitor class of drugs; with that, there was the advent of the triple drug therapy system in the mid-1990s. It brought a remarkable change in the treatment idea of AIDS/HIV. This revolutionized the area of treatment of HIV and brought the concept of HAART (Highly Affective Anti Retroviral Therapy) into limelight.

2. ANTI-RETROVIRAL THERAPY

There are about more than 25 anti-retroviral drugs which have been recognised and approved for the use of patients infected with HIV/ AIDS. These have been marked from six particular mechanistic classes, these include the nucleoside / nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, protease inhibitors, integrase strand transfer inhibitors and the CCR5 antagonists.

Unfortunately, these drugs do not contain the potential to completely eradicate the viral reservoirs. Also, none of these drugs can be curative. The main goal or ides of therapy with these drugs revolve around the lifelong treatment procedure with durable viral suppression [3]. To long term suppression of the viral replication system may lead up to serious complications and severities like drug interactions, drug toxicity, non-adherence along with the inevitable and unstoppable sudden appearances of drug certain resistant mutations.

The integration and combination of nano-technology along with pharmacology seeks to point out some problems and complications by the creation and regulation of some of the following elements:

- Certain drug delivery systems that can optimize, regulate and maintain the distribution of tissues and bioavailability of some particular antiretroviral drugs. This helps in resisting and restricting the continuous fluctuation of certain drug toxicities and drug levels in the patients. Different patients have different body types, their molecular and genomic profiles too vary abruptly from one another. It can thus be well understood that different drugs will have different effects in different patients. This level of fluctuations and variations needs to be followed up in the patients; otherwise it might lead to negative side effects.
- Targeted drug delivery system with improved conditions of side effects that might happen in the patients post application of the drugs. Since the anti-retroviral drugs need to be consumed for a long duration of time, the drug delivery systems need to be updated to avoid any unnecessary consequences or side effects in the patient body.

- Drug delivery systems which can reduce the interaction of one drug with another so that any sudden or impulsive effects from the combination of two or more drugs, can be taken care of. Antiretroviral drugs are taken in a combination of two or more, which might lead to drug-drug competition or interaction between two different classes of drugs. So, the drug delivery systems are chosen and synthesised in such a manner that can reduce these interactions to avoid any dramatic or drastic changes in the patient body.
- Drugs with some novel mechanisms of action which should not show any resistance or cross resistance to known items. This is very important. There should not be any inhibition/ resistance or cross-inhibition or else it might lead to unwanted complications or severities.
- Drugs with much flexible and extended half-life are needed. This will be effective in reducing the dosage frequency of the drugs along with the reduction of intake of the capsules or tablets in the process.
- Easy delivery of some anti-HIV agents which are presently very difficult to deliver e.g., nucleic acids such as siRNA or DNA therapeutics, the delivery vehicle protects the nucleic acid against degradation and reduces immunogenicity.
- Certain new drugs and therapeutics in the effective treatment of HIV/AIDS disease is also important. Some newly identified and discovered antiretroviral drugs should be mentioned worthy in this point. This drug won't be of any other use in medical and clinical therapies because of certain issues marked in them (like that of their solubility property). By the application of certain nanotechnology procedures, these drugs can be rendered water soluble in nature.
- For the improvement of adherence property, co-delivery of antiretroviral agents can be done.
- Another important class of drugs are the ones which can effectively mark and eradicate the viral reservoirs.
- Different methods for the delivery of some particular antiviral drugs which can be successfully done with the help of certain alternative routes like that of the transdermal delivery process.

Following are some cases involving the use of Anti Retroviral therapies:

An Anti retroviral therapy (ART) programme (The Zithulele Anti retroviral therapy programme) was carried out in the deep rural communities of Africa. It included 5 innovative ideas like a) successful establish-ment of a district hospital that can work as the main centre for all patients requiring ART care in that rural community, b) for people suffering from HIV, necessary care was to be provided along with the clinical delivery of some prepacked ART medications along with therapies for other chronic diseases, c) central record keeping was to be established necessarily, d) Viral load monitoring incentivizing, and, e) For people suffering from complex cases, necessary hospital based cares were to be provided. It initially started with the enrollment of 882 HIV infected patients in the Zithulele ART programme. After 12 months of treatment, it was found that, 65.6% of the people remained in the

ART programme without facing any disturbance or interruption in the supplies of necessary medications or care taking; of the other remaining people who were suffering from HIV and had left the programme after some time, 4% were found dead, 12.6% were transferred from that area after a time period, 4.9% of them later returned again, 5.3% initially were lost to follow up but returned to care once again and 12.5% were lost to follow up and never returned back to the ART programme in Zithulele [4]. It was concluded that the Zithulele ART programme was challenged by the people living with HIV who were lost to follow up (defaulting treatment for about consecutive 3 months)

3. HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART)

HAART uses a combination of multiple classes of drugs which are simultaneously administered into the patient body. HAART (Figure 1) [5] has to be taken for a long duration of time along with the intake of multiple tablets/capsules per day, for which sometimes it starts showing drastic side effects and negative changes, which is not at all a matter of ease for the particular patients using it. Sometimes the treatment process can fail completely if the patient starts developing resistance to a particular class of drug or a combination of different classes of drugs. Thus, continuous efforts are being put forward in the hope of some innovative treatment processes or approaches when it comes to HIV disease.

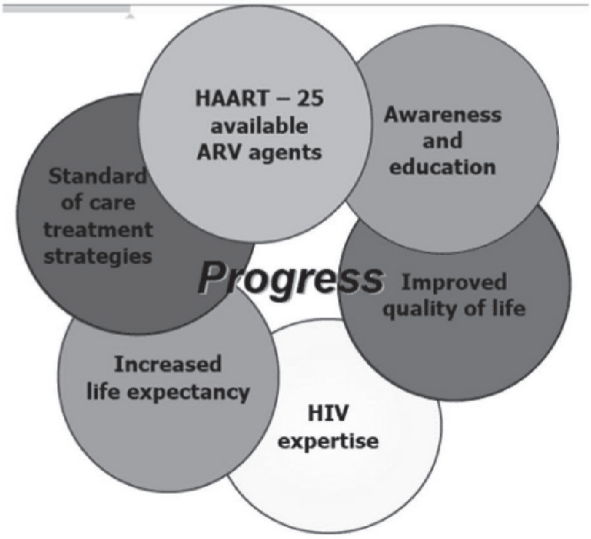

Fig 1: HAART (Highly Active Anti-Retroviral Therapy) [5]

Following are some cases involving the use of HAART :

- It has found that patients over the age of 50 can live and survive HIV, owing to the HAART [6]. It can help in prolonging the survival rates of these patients who are infected with HIV.
- Study of adherence to HAART medication concluded that it is the greatest and best patient enabled predictor of mortality and successful treatment to those people who have access to medications and drugs [7].
- In another report concerning HAART, researchers tried to study a population consisting of those individuals who initially started the HAART treatment and had one follow-up visit to the least. They tried to understand the reason behind discontinuing the HAART treatment so that they can identify the predictive factors required to reach the two end points [8]. It was concluded

that less than 10% of the patients had discontinued their HAART treatment because of failure after almost one year from the start of the initial therapy.

- In a research of neuropathology, it was found that there is a neuro inflammation that has a direct link with HIV related dementia. So after thoroughly analyzing it in the era of HAART, it was concluded that there is a surprisingly steep degree of ongoing inflammation in patients who are being treated with HAART, mainly in the hippocampus [9]. In future, this might lead to severe problems and complexities in those patients who have been and still continuing HAART therapy for a long course of time.

4. APPLICATION OF DIFFERENT NANO-PARTICLES IN HIV / AIDS TREATMENT

Nanotechnology can effectively put forward some treatment processes in the area. Some nanomaterials and nanoparticles themselves possess different therapeutic and medicinal properties.
The therapeutic approach for HIV/AIDS has been contained by different nanotech-based systems like polymeric micelles, liposomes, dendrimers, nanoparticles, niosomes, etc. (Figure 2) [10].

Nanoparticles and Nanomedicines have been found to have various remarkable effects in the treatment of HIV-

- It has been found that, in the near future, AIDs can be totally removed from the patient body through the successful application of nanoparticles and nano-polymers for delivering ARVs [11].

4.1 Polymeric Micelles

These are some extremely small nano sized structured molecules of about 100 nm diameter, which are formed due to the self-association of some amphiphilic block co-polymers when they are being mixed with an aqueous solvent. They are arranged in a core and shell appearance/ organization.

Polymeric micelles can effectively serve as a novel drug delivery system because of their superior stability of different physiological conditions, inherent property of target specificity, versatile and higher loading capacity, the property of functionalization of certain end groups for the conjugation of different targeting ligands, superior and higher accumulation of certain drugs at the site of their targets along with the controlled and sophisticated release of some hydrophobic anti-carcinogenic therapeutics and drugs.

Polymeric micelles are vividly used in drug delivery systems because of their different interesting properties like low level of toxicity, higher controlled release property, bio-compatible nature, the micellar association, potential of tissue penetration, core–shell arrangement, relatively high stability,nano sized structure and morphology.

A number of different medical and clinical applications are being offered by these polymeric micelles, like that of the solubilisation of some poorly soluble drugs, targeting of the disease site by different drug molecules, improvement of intestinal permeability, protection of some encapsulated drugs, etc. Not only HIV, polymeric micelles are vividly

used in the treatment of a number of other diseases too, like that of cancer, anti-influenza, antiviral, oestrogen therapy, etc.

- In several studies accounting the use of polymeric micelles, it has been found that the abilities of these particles as nanocarriers, are very much significant as per the commercial feasibility, availability and presence is taken into consideration. Not only for the treatment of HIV, polymeric micelles are being continuously studied and analysed for their development and improvement in acting as anticancer drugs and thus effectively used in drug delivery systems.
- Modification of polymeric micelle, given their automated advantage because of their size and structure, can produce better clinical success beit in the treatment of different cancer or AIDS [12]. On this aspect, the micelle forming materials needs to be taken into serious consideration.
- Studies have shown that multifunctional micelles have secured immense popularity because of their versatility in the incorporation of different varieties of payloads (imaging and therapeutic) simultaneously [12].

4.2 Liposomes

Liposomes are produced from one single (or uni-lamellar) or double (or bi-lamellar) or multiple lipid bilayers which consists of a single amphiphilic lipids or some more different lipids, which may be either charged or neutral in nature. Liposomes are extremely small in size and vary from 25 nm to several microns.

Liposomes can be used in the encapsulation of different therapeutic substances like different vaccines, drugs, proteins, enzymes, genetic materials, a number of biomolecules and oligonucleotides, etc.

Liposomes are also considered an effective, safe and important process for the introduction of different therapeutic agents, but may often suffer degradation or get removed from the blood streams if they start suffering opsonization.

When liposomes start entering inside the human body, they get recognized as foreign bodies and thus are easily taken away by the mononuclear phagocytic cells. Human immunodeficiency virus is present in these mononuclear phagocytic cells of the infected patients. Thus, the liposomes represent some suitable and useful carriers for the targeting of the anti human immunodeficiency virus drugs to the infected body cells of those patients. Thus, these liposomes can actually improve the efficacy of anti human immunodeficiency virus drugs and also reduce their side effects.

From studies conducted on liposomes for treating AIDS, following points can be noted-

- Liposomes are gaining popularity for being the successful carriers of HIV or AIDS treating drugs.
- Liposomes have been found to offer various advantages like protection of the drug from getting degraded in the patient body, successful loading of the

drug, successful drug targeting along with possessing bio-compatibility, low immunogenicity and cell specificity.

- Different categories of liposome based drug delivery systems (anionic, cataonic, sterically stabilised, immuno -liposomes) are being continuously studied for HIV/AIDS drug delivery.

4.3 Dendrimers

Dendrimers are nanosized compounds (less than 100 nm in size) that are extremely helpful in their applications in different fields of medicines, pharmaceuticals and therapeutics. These are man-made artificial compounds which are built around a core and possess different interesting and unique properties. They help in the enhancement, nurture and production of different medicinal stuffs, both pre-existing and newly made.

Dendrimers are formed by generations of layers of different branching groups, placed one upon another. This helps to define the morphology of the dendrimers, like their size, shape, and growth nature along with the micro-environment inside the dendrimer itself. The last generation, also called the final layer, helps in the incorporation of the surface molecules that leads to the formation and production of different materials and products for medicines, drug delivery, pharmaceuticals, etc.

Dendrimers are composed of a lot of tiny, smaller units called the 'dendrons'. These dendrites are formed after the complete removal of the core units and can be efficiently divided into the interior branching units, the empty core and the peripheral end groups.

The empty void space remaining inside the dendrons can be used in the purpose of entrapping of the drug molecules for controlled release, solubilisation, targeting, and protection from the surrounding environment if it starts to degrade.

Following are some cases involving the use of Dendrimers:

- It has been found that dendrimers possess an inherent antiviral activity along with their carrier roles in medicine. So for the work of delivering ARVs in medicines, they are considered very much useful [11-12].
- Another study has shown that Carbosilane dendrimers having amine or ammonium groups at their periphery are basically some nanocarriers that are the perfect vectors for successful gene therapy treatment against HIV/AIDS [13].
- In another review study conducted by P. Arshad [14], dendrimers have been considered a novel carrier in anti-HIV treatment

4.4 Nanoparticles

Nanoparticles are extremely small particles of size about 10-1000 nm. Nanoparticles can be found in different sizes, shapes and variable properties in the forms of nanorods, nanospheres, nano-chains, nano-fibres, nano-flowers, nano-stars, nano-boxes, nano-reefs, nano-whiskers, etc.

Nano particles are extensively used in drug delivery systems. Nanoparticles of gold,

silver, silicon dioxide, titanium dioxide, aluminium oxide, diamond, clay, carbon etc. are very much used in the field of medicines and therapeutics.

Three particular types of nanoparticles are generally used in the production and formation of different anti-HIV therapeutics. These are polymeric nanoparticles, inorganic nanoparticles and solid lipid nanoparticles along with nanostructured lipid carriers.

Different nanoparticles are also studied for the search of any improvement in the formulation and efficacy of different drugs containing some physiological limitations or drawbacks like that of solubility and poor stability. These nanoparticles are very carefully and thoroughly investigated for the targeted delivery of some specific anti-retroviral drugs to the HIV-infected cells. They can also control and maintain their drug release intensity and properties.

Encapsulation of drugs into such systems might lead to improved efficacy, decreased in the resistance to the drug; certain reduction in dosage also takes place along with some decrease in the systemic toxicity and the complex and negative side effects. This increases patient compliance and helps to improve and maintain their health.

These are some findings by various researchers regarding the use of nanoparticles in the treatment of HIV/AIDS

- Studies have shown that inorganic nanoparticles like gold and silver possess anti-HIV activity in vitro.
- Nanoparticles have shown significant potential as adjuvants and also as delivery systems for different vaccines.
- Nanoparticle antigen encapsulation can help in increasing the half life of an immunising agent.
- Another remarkable factor that has been noted in nanoparticle vaccines, is that these particles can be optimised for their administration through various routes.
- Nanoparticles based on the polymers of PLGA and PLA have been found to possess the ability of delivery of DNA-based and protein-based HIV vaccines.

4.5 Niosomes

Niosomes are non-ionic surfactant vessels. These are formed from the self-assembly of some synthetic and hydrated non-ionic surfactant monomers. Niosomes can be considered a novel drug delivery system in which the therapeutics or the medications can be well encapsulated inside the vesicles.

Thus because of their capability of entrapping a variety of drugs, these are useful in the same purpose, that is, drug delivery.

Niosomes are considered as an alternative to liposomes because they possess similar behaviours and characteristic features.

- In some studies conducted in 2018, niosomes have been considered a promising nano-carrier for natural delivery of drugs through blood-brain barriers [15].

- In another research conducted in 2016, niosomes haven been found to improve the stability of the entrapped drugs, along with helping in the reduction of the dose and enabling targeted delivery to a particular type of tissue [16].

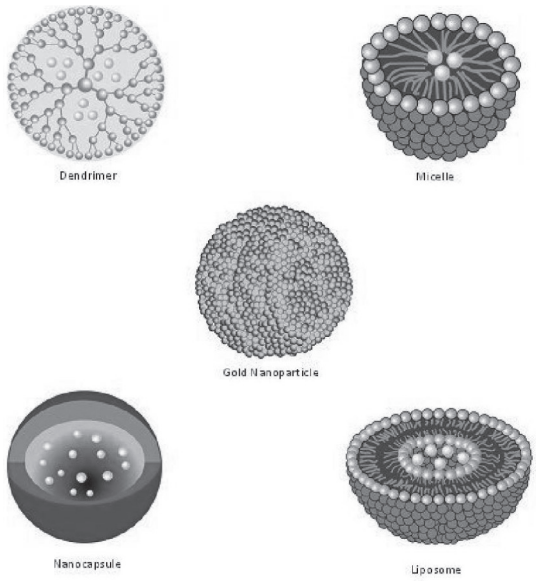

Fig 2: Different nanoparticles used in the treatment of HIV/AIDS [10]

5. DETECTION OF HIV WITH NANO-PARTICLE BIOSENSORS

Ultrasensitive identification or detection of the HIV-1 p24 antigen can be done with the help of a hybrid nanomechanical optoplasmonic platform along with the capacity of detection of HIV simply at the first week of infection. With the application and integration of gold nanoparticles along with some micro mechanical silicon structures (both being functionalized with the p-24 specific antibodies), this can be done.

With the help of immunoassay process, the p24 gets sandwiched between the micro mechanical silicon structures and the gold nanoparticles. The micro mechanical structures are outstanding mechanical sensors and the gold nanoparticles have got optical resonances called plasmons, which can efficiently scatter lights. Therefore, the combination of these two can help in the detection of the p24 by producing some optical and mechanical signals amplifying one another, which help in the process.

Not only HIV, this technology can also detect cancer at the earlier stages.

6. DETECTION OF HIV ANTIBODIES WITH DNA NANOMACHINES

A team of scientists have successfully designed and generated a DNA machine of nanometer scale which has got the efficiency to mark and recognise a particular antibody. As research is progressing in the present-day world, this invention has brought about a very important concept in the detection of the antibodies of various infectious, auto-immune and complicated diseases including HIV. It is at the same time, a low cost and versatile platform.

This DNA machine works with the principle of bonding or attaching of the antibodies to the DNA nanomachine, which in turn causes a structural change and switches on to generate a light signal. This sensor can act fast and rapid and doesn't show any requirement to get chemically activated. Thus, it helps in the easy detection of the targeted antibodies. This DNA nanomachine can be customised and regulated to identify a huge number of antibodies for various diseases, including HIV.

- A group of scientists in the University of Montreal have synthesized and successfully designed a DNA nanomachine of nanometer scale whose customised modification helps it to recognise a particular single or group of specific antibodies. It promises to support the innovation and development of a low-cost, rapid antibody detection system for the diagnosis and treatment of HIV/AIDS.
- In a case study conducted by Chava Angell et al. in 2018 [17], the uses of DNA nanomachines in biosensing, therapeutics, and diagnostics have been studied. They concluded that DNA based nanomachines will gradually become an integral point of care diagnostics and will be considered a site-specific, smart therapeutic delivery system in near future.

7. USE OF NANOTECHNOLOGY FOR THE DELIVERY OF DRUGS TO HIV PATIENTS

Nanotechnology is basically the manipulation of different matter on a nano scale. Nanomedicine is the general application of nanotechnology in the identification, prevention, treatment of a number of diseases in the human body. By producing smaller pills with the application of nanotechnology, that are both better equipped for patients and also requires lesser cost to manufacture, this evolving discipline has the capacity to drastically revolutionise the field of medical and clinical science. Studies are showing that it is already producing a huge impact in a number of clinically and medically used therapies, drugs, diagnostics and medications worldwide.

Presently, the treatment of HIV needs daily oral dosing of the HIV drugs along with chronic oral dosing. A number of complications can arise from this high burden of pills. With the help of nanotechnology, this huge pressure of high dosage of pill consumption can be lowered down. This will be advantageous to a number of aspects and applications.

- Recent study of a group of HIV infected patients has shown a desire to switch to nanomedicine alternatives than the normal therapeutic approaches. Common most medication and therapy procedures require the patients to continue medicine intake for a long duration of time, along with the high dosage of the medications. Needless to mention, over dosage of medications may arise as another complication in this area, which may eventually lead to the development of any other random disease or complications in the patient body. Nanotechnology based drugs or nanomedicines (Figure 3) [18] and medications have been very much useful in this area.

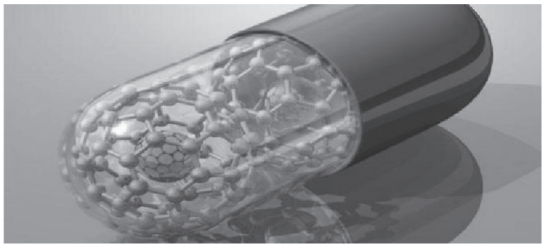

Fig 3: Structure of a Nanomedicine [18]

8. NANOTECHNOLOGY BASED VACCINE DESIGN APPROACHES TO TARGET HIV

For highly variable diseases such as HIV, the vaccine researchers desire to produce some antibodies that will protect against most or all of the viral strains possible- not just a few numbers of strains like that of the seasonal flu vaccines currently on the market, but almost all strains possible.

Vaccine researchers have been able to mark and identify most of these broadly neutralizing antibodies from long-term HIV-positive survivors by collecting and harvesting the antibody producing B-cells from their blood samples and then separate and retain their required coarse parts to identify the ones that can lead to the production of the antibodies which are capable of neutralizing a number of strains of HIV.

These broadly neutralizing antibodies generally work by blocking a number of critical functional sites of a virus which are conserved among different strains in spite of a number of high mutations elsewhere.

9. NANOPARTICLES INTEGRATED WITH BEE VENOM TO KILL HIV

Research and studies have found a specific toxin in bee venom, named 'melittin' that can kill HIV when combined and integrated with different nanoparticles. This melittin bee venom toxin has the capability of producing holes in the protective envelope of the human immunodeficiency virus.

These nanomaterials or nanoparticles can be loaded with this bee venom toxin which can destroy the human immunodeficiency virus from spreading in the patient body. It can efficiently kill HIV without even harming the surrounding normal cells of the patient body. This is because several protective bumpers are added to the nanoparticle surface. Thus, when the nanoparticles come in close contact with the normal cells (which are large in size), the particles get bounced off.

Avaginal gel [19] is developed with the combination of nanotechnology and the bee venom toxin, which helps in this purpose.

Melittin works by rupturing the viral protective covering of HIV. It is loaded with the nanoparticles which get fused with the viral protective envelope. Thus, by continuously attacking the physio-chemical properties of HIV, it can be ultimately killed. The only idea is to poke and rupture the double layered envelope of HIV, after which melittin loaded nanomaterials do their own work, ultimately killing off HIV in the patient's body.

Along with HIV, influenza, hepatitis B and C can also be treated in the same method mentioned. This vaginal gel can also target the sperms, if required.

10. CONCLUSION

It can thus be said that, with the integration of nanotechnology and pharmacology, HIV treatment can be progressed [20]. Nanotechnology has been successful in shedding some light in the therapeutics of HIV, be it identification, diagnosis or treatment of HIV [21]. As studies are progressing day by day, scientists are researching for further areas of improvement in the treatment of HIV with nano based products, medications and machineries. Nanotechnology is gradually emerging as a popular and potential branch of therapeutics and treatment. Nanomaterials and nanoparticles are used in drug deliveries, drug development, advanced and innovative medicinal applications and

approaches, etc [22-24]. Not only in HIV, nano based products are able to contribute to other complicated diseases like cancer, viral disease, hepatitis, influenza etc. Scientists are able to produce nanoproducts which might look extremely small in size, but are better equipped and much more efficient in providing patient treatment and care. It is just a matter of time before nanotechnology secures a permanent place in the areas of medicines and therapies. With further research and improvement, scientists have promised to develop better and more efficient applications, products and medications that will ease the treatment of the deadly HIV/AIDS disease [25-26].

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