Title

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Authors

Samimi, Yusef
Schultz, Eva
Vance, Jessica
et al.

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Daniel Gonzalez

Yusef Samimi

Eva Schultz

Jessica Vance

Gloria Zhang

Undergraduate Student Mentor: Daniel Gonzalez

ULAB Public Health & Health Science Division

University of California, Berkeley

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Abstract

Although the development of antiretroviral treatment has been successful in mitigating and suppressing HIV/AIDS infections globally, it has not changed the fact that 1.7 million new infections have occurred in 2019.[1]The objective of the literature review is to determine the current treatments for HIV and their shortcomings, future approaches using nanotechnology, and the current related health disparities which may be mitigated by advances in this field. Both globally and in the United States, the main demographic of HIV/AIDs victims are from disadvantaged communities that lack access to treatment and prevention education. Despite the use of antiretroviral treatment reaching global access and its successful efforts, there are still many challenges with the containment of the virus since the treatment does not effectively suppress the virus. Future approaches using nanotechnology are quite varied in the types of particles used but are mainly used to increase delivery efficiency and show promising results in the pre-clinical and clinical stage. There is significant evidence that nanotechnology can increase the efficacy of drugs targeting HIV and several implications that these improved drugs can help mitigate some health disparities on the national and global level.

Introduction

HIV/AIDS (Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome) is an epidemic that has devastated many communities, with approximately 38 million people worldwide having the disease in 2019.[1] The first case of AIDS officially reported was in 1981 and two years later, HIV was identified as the cause of the autoimmune deficiency disease. HIV is a retrovirus that, through attacking immune system cells, increases a person's susceptibility to

[1] From "The Global HIV/AIDS Epidemic," HIV.gov, November 25, 2020.

other dangerous diseases/infections. HIV, without treatment, leads to AIDS. AIDS is the last stage of HIV and signifies that the body's immune system is highly damaged. Individuals with HIV cannot be cured, but with treatment, their life may be prolonged considerably. According to a Kaiser Permanente study, the estimated number of remaining years at age 20 for HIV positive subjects increased from 19 to 53 years from 1996 to 2011 while HIV- subjects saw a smaller increase from 63 to 65 years.[2] AIDS however allows individuals to only live about 3 years.[3]

The HIV/AIDS epidemic has exposed that this crisis is not only an issue of infectious disease and finding treatment, but it is also about ensuring those treatments reach communities who need it most. According to Pellowski et al., the HIV/AIDS epidemic has been allowed to grow through its relationships with biological, social and behavioral factors, and its transmission is highly dependent on "social context and behavioral practices."[4] The epidemic affects low-income marginalized communities more than any other group. It has been shown that those most at risk for contracting HIV are men who have sex with men (MSM) and ethnic and racial minorities. As is stated by the aforementioned study, "AIDS is the 3rd leading cause of death among Black men and women between ages 35 and 44, and the fourth leading cause of death among Latinos of the same group." Based on existing literature listed under references, many scientists agree that these realities are the symptoms of disparities within health care access. Although prevention, testing, and treatment for HIV/AIDS exists, these resources are not often made available to those of lower socioeconomic status. These health disparities are sorely under researched despite their importance in diagnosing and treating HIV/AIDS.

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[2] From the "Conference on Retroviruses", Macolini, 2016,Narrowing the gap in life expectancy for HIV+ compared with HIV- individuals...Life Expectancy Gap Between HIV+ and HIV- Narrows But Persists.
[3] From "What are HIV and AIDS?," HIV.gov, June 5, 2020.
[4] From "A pandemic of the poor: social disadvantage and the U.S. HIV epidemic," by J. Pellowski, et al., 2014, American Psychological Association, p. 197-209

On March 19, 1987, the United States' Food and Drug Administration approved zidovudine as the first drug to treat HIV, and since then 57 total drugs have been approved.[5] Zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI) and works by blocking the virus' reverse transcriptase. Besides this category of drugs, other classifications include non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors (FI), CCR5 antagonists, integrase strand transfer inhibitors (ISTI), attachment inhibitors, post-attachment inhibitors, and pharmacokinetic enhancers, as well as combination HIV medicines. On the other hand, current preventative measures, such as the use of condoms, have not been proven to be entirely effective. There are promising clinical trials, however no vaccines have been approved, primarily because of a lack of efficient delivery systems.

The general trend has been a shift from NRTIs in the 1990s to Fixed-Dose Combination medicines, especially in the 2010s. The first revolution in the HIV treatment space were protease inhibitors, which block protease, an HIV enzyme necessary in the replication of the virus. This was followed by triple-drug therapy in 1995-1996, also known as Highly Active Antiretroviral therapy (HAART). This combines three or more different classes of drugs to be administered simultaneously and has greatly increased efficacy.[6]

As HIV/AIDs medications have reached astonishing efficacy since its peak in the 1990's, current approaches still have obstacles to overcome. These obstacles exist primarily in solubility and dosing. Current approaches have limited solubility which leads to lower bioavailability of the drug. HIV resides in "latent reservoirs" within macrophage, monocyte, and memory CD4+ T cells, as well as specific sites like the central nervous system, gut, lungs, liver, testes, secondary

[5] From FDA Approval of HIV Medicines, 2021, NIH
[6] From "Emerging nanotechnology approaches for HIV/AIDS treatment and prevention," by T. Mamo, et al., 2010, Nanomedicine (London, England), p. 269-285

lymphoid tissue, and kidney.[5] Current medications often fail to arrive in these desired locations due to poor solubility, which leads to an untouched virus and poor uptake of the drug in the body. Due to the fact that so little of the drugs are typically used up by the body, larger quantities and dosages are required. This leads to the next issue of inadequate dosing. The most important part of HIV/AIDs treatment is consistency in order to minimize the viral load, since eradication is as of now impossible. Current approaches require daily dosing for the entire lifetime of a patient, resulting in high treatment failure due to poor patient compliance. Furthermore, the virus in some patients develop resistance to certain drug combinations mainly because of the virus's constant mutation and the diversity of HIV. Higher doses can solve resistance, however poorly soluble drugs can lead to biotoxicity and associated side effects, such as liver damage, cancer, and heart disease. Dosing for pediatric and geriatric communities also creates an issue as liquid oral forms are favored over the more popular oral medication.

Nanotechnology, or nanotech for short, is technology on the molecular or atomic level which provides an alternative with increased strength, lighter weight, and greater chemical reactivity. Nanoparticles typically range from one to 100 nanometers where one nanometer is a billionth of a meter or 10-9 of a meter, approximately one hundred thousand times smaller than the width of human hair. This length is necessary because it allows nanotech to pass through barriers that would otherwise be impossible to permeate because of size. Scientists are developing the ability to create nanostructures where atoms of an object have been rearranged, changing their properties. In the field of HIV/AIDs medicine specifically, nanomedicine serves to come up with new methods for treating areas that lack effectiveness in terms of medicine and patient adherence to treatment. The small size and chemical alteration of nanomedicine works to:

have more specific drug targeting and delivery while reducing the toxicity of the drugs to maintain the therapeutic effects.

Methodology

For this literature review, experiments were recorded from research papers, and statistics and data analysis were collected from government websites and international organizations' databases. These were all accumulated to develop an overview of the goals of this paper.

To find such papers, search criteria were identified based on their relevance to the following questions that this paper attempted to address: What are the shortcomings of current implementations? What is the future outlook of innovation for nanotechnology treatment? What are the current related health disparities that can be mitigated through these advances in the field? Accordingly, search terms such as "nanomedicine HIV/Aids treatment", "ethical limitations of nanomedicine treatment", "HIV/aids disparities", among other terms were utilized to find appropriate current publications. We conducted these searches using one or more of these keywords on multiple different data search engines, such as PubMED, Google Scholars, SciFinder, Nature, and more existing publishers. From the resulting papers, the criteria for reducing and selecting the most beneficial papers for our study included the following thought process: the study must have been in the recent few years between 2010 to present in order to ensure we were looking at the most relevant advances and current implementations in nanomedicine treatment. Moreover, to ensure a new outlook on current research, papers that discussed only secondary information ranging from literature reviews, meta-analyses, or systematic reviews were excluded. Analogous literature reviews were only used to discover the original publications that the review itself was mentioning which would then be analyzed to see

if it could be beneficial for the analysis at hand. Studies that met the inclusion criteria were chosen if they were recent publications, demonstrated the future potential and outlook of nanomedicine treatment, and if they had sufficient information in the methodology so as to be reproducible with similar success. In total, 25 papers were selected by the described methodology and procedure.

Discussion

Global and national health disparities in HIV:

Studies from recent years show that the number of people globally who live with HIV has been increasing, with 30.7 million in 2010, and now 38 million in 2019.[1] These results reveal that there are constant infections and people are living longer with HIV. Of those who are currently affected, 36.2 million are adults, and 1.8 million are children under 15 years old.[7] Global prevalence among adults (people between ages 15-49) has leveled since 2001 and was 0.7% in 2019. Younger people account for approximately a third of new HIV infections. In fact, people residing in Eastern and Southern Africa make up the majority of AIDs cases and deaths.[7] More detailed information about the prevalence and mortality of HIV/AIDS in different regions around the world can be found in Table 1 below. The data in the table serves as evidence that despite global progress in reducing HIV/AIDS infection, this progress is unequal throughout the world. These statistics act as a call to action to emphasize the need for more advancements in the field of medicine. Despite methods of treatment improving, this evidence has shown that the numbers aren't changing.

[7] From "The Global HIV/AIDS Epidemic," by the Kaiser Family Foundation, 2021, *Global Health Policy.*

Figure 1: Global Distribution of HIV/AIDS prevalence and new cases

Table 1: Snapshot of Global Epidemic Today, by Region

Region	% of Adults Living with HIV (Adult Prevalence)	# of People Living with HIV (% of Global Total)	# of People Newly Infected with HIV	# of AIDS-Related Deaths
Global, Total	**0.7%**	**38.0 million (100%)**	**1.7 million**	**690,000**
Eastern and Southern Africa	6.7%	20.7 million (54%)	730,000	300,000
Western and Central Africa	1.4%	4.9 million (13%)	240,000	140,000
Asia and the Pacific	0.2%	5.8 million (15%)	300,000	160,000
Western and Central Europe and North America	0.2%	2.2 million (6%)	65,000	12,000
Latin America	0.4%	2.1 million (6%)	120,000	37,000
Eastern Europe and Central Asia	0.9%	1.7 million (4%)	170,000	35,000
The Caribbean	1.1%	330,000 (<1%)	13,000	6,900
Middle East and North Africa	<0.1%	240,000 (<1%)	20,000	8,000

NOTES: Reflects 2019 data.
SOURCES: UNAIDS. *AIDSinfo* website; accessed July 2020. UNAIDS. *Core Epidemiology Slides*; July 2020.

[8]

Considering that there are no current prevention techniques or cures for HIV/AIDs the rapid spread of the virus has become a serious issue, especially among disadvantaged demographics and communities. As of right now, the risk of acquiring HIV for some demographics is as follows: 26 times higher for men who have intercourse with men, 29 times higher for those who inject drugs, 30 times higher for sex workers, and 13 times higher for transgender people.[9]

With women at greater risk of contracting HIV/AIDS due to their anatomy and societal expectations, young women are disproportionately impacted. In sub-Saharan Africa for example, young women ages 15-24 account for 19% of new HIV infections in the region in 2019.[10] Especially among pregnant women, HIV can cause difficulties that may result in death. Gender

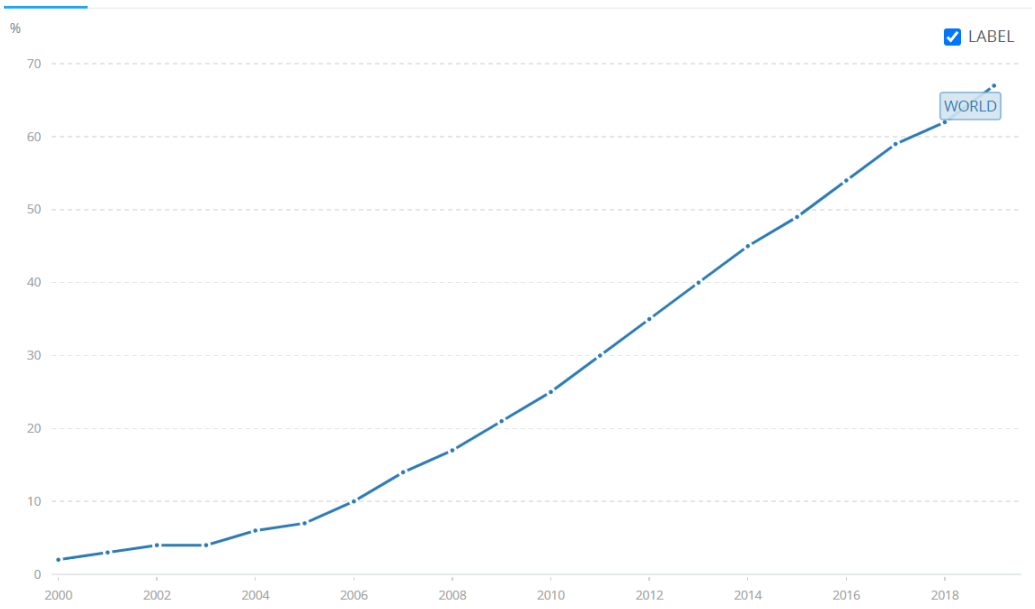
[8] From "The Global HIV/AIDS Epidemic," by the Kaiser Family Foundation, 2021, *Global Health Policy.*
[9] From "Global HIV & AIDS statistics -- 2020 fact sheet," by UNAIDS, 2020, *Joint United Nations Programme on HIV/AIDS.*
[10] From "The Global HIV/AIDS Epidemic," by the Kaiser Family Foundation, 2021, *Global Health Policy.*

inequalities, access to service, and sexual violence are all factors that increase women's vulnerability to HIV.

With the absence of a cure and difficulty spreading education about prevention, antiretroviral treatment (ART) has become more important than ever. Although there have been significant declines in new infections since the mid-1990s, there were still about 1.7 million new infections in 2019 or about 5,000 new infections per day.[11] However, the rate of this decline varies by age group, sex, and region. Combination ART, which was first introduced in 1996, has produced dramatic reductions in morbidity and mortality, and access has increased in recent years. The percentage of pregnant women receiving ART for the prevention of mother-to-child transmission of HIV increased to 85% in 2019 compared to 45% in 2010. Access to ART among children has more than doubled since 2010, with treatment coverage rising from 18% in 2010 to 53% in 2019. As of the end of June 2020, 26.0 million people were accessing antiretroviral therapy which is a 7.6 million increase from 2009.[12] For a better visualization, the graph below shows the worldwide percentage of antiretroviral treatment coverage between the years 2000-2018.

[11] From "The Global HIV/AIDS Epidemic," by the Kaiser Family Foundation, 2021, *Global Health Policy.*
[12] From "Global HIV & AIDS statistics -- 2020 fact sheet," by UNAIDS, 2020, *Joint United Nations Programme on HIV/AIDS.*

Figure 2: Worldwide antiretroviral coverage therapy (% of people living with HIV)[13]



In 2018, as HIV infections surged to 37,968 positive cases (CDC:HIV in the United States and Dependent Areas), clear demographic distributions of the virus can clearly be seen with 69% of new diagnoses being gay and bisexual men (men who tend to have sexual relations with other men) and racial and ethnic minorities. Even across groups of different sexual orientations, people of color (especially Black/African American and Hispanic/Latine communities) are disproportionately affected by the HIV epidemic. This is evident by the fact that the Black/African American community accounts for 42% of new diagnoses despite the fact they only make up 13% of the US population. The Hispanic/Latino community accounts for 27% of new diagnoses while only making up 18% of the US population.[14] Additionally, of age groups

[13] From "Antiretroviral therapy coverage (% of people living with HIV)," by The World Bank, 2019, *UNAIDS estimates.*
[14] From "HIV in the United States and Dependent Areas," by Centers for Disease Control and Prevention, 2018, *HIV Statistics Center.*

affected by HIV, those aged 25-34 had the highest infection rates, most likely due to increased sexual activity.

Though treatment is a scientific issue, the containment and spread of HIV expands throughout all of the public health field is a greater public health issue. Demographics most affected within the US are related to those globally in that it is generally disadvantaged, impoverished communities most at risk of contracting HIV. These communities most likely experience redlining, which can be defined as the "discriminatory and unethical practice of systematic denial of providing services", including those of healthcare[15]. Access to healthcare does not only include physical proximity of clinics, but also the level of trust patients have in the healthcare system. Historically, many marginalized communities have been left behind by the healthcare system due to a variety of factors including but not limited to: racism, poverty, homophobia, heteronormative care. In a study conducted by Dr. Donald Musa et al. titled "Trust in the Health Care System and the Use of Preventive Health Services by Older Black and White Adults," it is found that not only "Blacks were less likely to have a regular health care provider and to have supplemental health insurance" but were also "less likely to have trust in their own doctor."[16] Although the study focuses strictly on those differences between the relationships of white and black individuals with healthcare, this is a model example of how because of historic inaccessibility of healthcare, marginalized communities are less inclined to trust that the healthcare system is there to work for them. This healthcare disparity directly influences who is most at risk for HIV/AIDS as those who are unable or refuse to go to the doctor will have less

[15] From "What is Redlining?", by Corporate Finance Institute, 2021.
[16] From "Trust in the Healthcare System and the Use of Preventative Health Services by Older Black and White Adults", by Donald Musa, et al., 2009, Results.

access to preventative measures (such as Pre-exposure Prophylaxis and Post-exposure Prophylaxis) in addition to reduced accessibility to treatment after diagnosis.

As shown by Center for Disease Control (CDC) statistics, rates of new HIV diagnoses are highest among gay and bisexual men. Medicalization is the "process by which organisms, tangible objects, or social constructions are rendered into biomedical terms" of queer bodies. As discussed in the research study "A case for the Demedicalization of Queer Bodies," it is illustrated how queerness has always been seen through a scrutinous medical eye and Dr. Eckhert goes so far to state that "all queer bodies were shaped by medicalization."[17] This medicalization has only gone to further heteronormativity in educational aspects, most importantly within sexual education. The absence of proper sexual education for queer individuals has substantially impacted how queer people view sex and how they practice safely (or not). To illustrate, according to the Guttmacher Institute, only "11 states and DC require inclusive content with regard to sexual orientation" while another 6 states mandate "only negative information [...] on homosexuality and/or positive emphasis on heterosexuality."[18] This lack of appropriate sexual education for LGBTQ+ youth has long term consequences and will, in turn, increase the risk of HIV contraction and infection among queer individuals.

The HIV/AIDS epidemic exposes the issue of healthcare access in not only the United States but also globally. For this reason it is imperative treatments be found that enhance the efficiency and efficacy of current HIV drug systems which we believe could be supported by the growing interest in nanomedicine techniques.

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[17] From "A Case for the Demedicalization of Queer Bodies," by E. Eckhert, 2016, *The Yale journal of biology and medicine*, 89, p. 239-246
[18] From "Sex and HIV Education" by the Guttmacher Institute, May 1, 2021, *State Laws and Policies.*

Current and Future Approaches:

Since March 19, 1987 when the United States' Food and Drug Administration approved Zidovudine as the first drug to treat HIV, 56 more treatments have been developed and approved as a result of advancing technology and better understanding of HIV in the body. This area of research is vital to improving public health because there are 38 million people estimated to have the virus worldwide who, in the absence of treatment, will die within five to ten years.[19] As of April 2020, there have only been two cases recorded where total HIV-viral clearance has been observed. Because of the severity of HIV/AIDs in both population and mortality, new advances in the form of nanomedicine are being discovered and implemented.

Current Approaches:

Shortcomings in current treatments are a result of several issues, including poor delivery, existence of reservoirs with latent HIV virus, poor solubility, and short half-lives of drugs. For example, an inherent issue to HIV treatment is the absence of unique surface markers on latently infected cells, which impedes scientists' attempts to completely eradicate the virus from those cells.

Bioavailability, protein binding, solubility, and half lives all play a major role in the efficacy of a drug, but trying to find the perfect combination of all these factors is challenging, especially given their wide variability. According to data presented by Kumar et al., current drugs approved by the FDA have a half-life ranging from 0.5 to 55 hours, with the majority falling below ten hours. In terms of protein binding, some drugs are highly efficient at 99 percent while others are negligible or below five percent. The drugs that have low protein binding

[19] From "Nanotechnology: A magic bullet for HIV AIDS treatment," by L. Kumar, et al., 2015, *Artificial Cells, Nanomedicine, and Biotechnology*, 43, p. 71-86

however, generally have greater solubility, still ranging from 27.3 mg/ml to 83 mg/ml. The drugs with high protein binding have solubility that ranges from <0.001 mg/ml to 1.98 mg/ml. One example is Zidovudine, which has a half-life of three to five hours, protein binding percentage of 30 to 38 percent, solubility of 20.1 mg/ml, and needs to be taken twice a day. The bioavailability of current drugs range from 23 percent to 100 percent.[18]

In terms of dosage form, there are multiple types, such as capsules, tablets, powders, liquids, syrups, and solutions. Each of these approaches have their benefits and drawbacks. Pills for instance are much easier to prescribe and access compared to an injectable, however their efficacy could be less effective. One current treatment, Lopinavir, is undesirable in certain populations because of its hydrophobic qualities. Due to its poor water solubility, Lopinavir is often combined with Ritonavir and alcohol. This combination creates an unideal and inaccessible dosing for pediatric and neonatal populations due to the alcohol intake and pill form. Understanding the unique needs of particular demographics, such as pediatric and geriatric communities, makes dosing much more difficult as standardized oral pills are less effective.[20]

HAART is the most popular current treatment and has shown great success in developed countries; however the commitment of daily dosing for a lifetime is one of its biggest drawbacks. Due to the short half-life times of the ARV drugs used in HAART, there is a decrease in their presence at reservoir sites. Over time, higher and higher doses are required to fight the resistance, often instead resulting in toxicity.[21]

Future Approaches:

[20] From "The potential value of nanomedicine and novel oral dosage forms in the treatment of HIV," by J. Hobston, et al., 2018, *Nanomedicine (Lond.)*, 13, p. 1964
[21] From "Nanosystems Applied to HIV Infection: Prevention and Treatments," by M. Macchione, et al., 2020, *International journal of molecular sciences*, 21, p. 8647

These current drugs, while promising, have difficulty optimizing effectiveness due to challenging delivery. This is where nanomedicine steps in. The types of nanoparticles considered for treating HIV infections include organic, polymeric, nanocapsules, nanospheres, liposomes, micelles, dendrimers, solid lipid nanoparticles (SLNs), inorganic, gold nanoparticles (GNPs), and Silver Nanoparticles (SNPs), each with its own advantages. For example, metal nanoparticles (GNPs and SNPs) are relatively stable, have a large surface area to volume ratio, and can be functionalized with multiple groups. On the other hand, liposomes, micelles, and dendrimers mimic bodily behavior and encapsulate the drugs inside for greater efficiency in delivering the drugs to the target sites. Nanotechnology offers a wide range of advancements by modifying the way in which current treatments interact with other cells -- this means new drugs do not have to be developed but rather modified in the way that they are delivered. Furthermore, nanoparticles protect antigens from certain enzymes, increase antigen uptake, and are biodegradable and biocompatible.

Several researchers have developed a long-acting slow-effective release of HAART agents (“LASER ART”), which as its name implies, uses nanoparticles to control the release of HAART agents. This is important as it encourages better patient adherence with less of a commitment to their treatment regimen, and encourages lower dosing as lower concentrations of the drugs are needed. In an experiment, Dr. Gnanadhas DP, Dash PK, Sillman B, Bade AN, Lin Z, Palandri DL, et al. showed that a nucleoside reverse transcriptase inhibitor created as a nanocrystallized product of lamivudine (coined NM23TC) maintained antiretroviral activity for 30 days in HIV-1-infected macrophages. After a single dose, NM23TC remained in high concentration in whole blood, and at day 23, a metabolized derivative of lamivudine was found

in high concentrations in the liver, spleen, and lymph nodes, indicating that the nanoparticle may potentially help drugs reach these specific areas where HIV remains latent.[22] In a study done by Dash et al., two of seven infected mice that received the treatments of LASER ART and AAV9-CRISPR-Cas9 recovered from a viral rebound and restored all of the CD4+ T cells. HIV-1 RNA was undetectable in the brain, plasma, spleen, liver, and gut.[21]

Christopher J. Destache, et al. used Poly Lactic-co-glycolic acid (PLGA) to create nanoparticles enclosed by efavirenz, ritonavir, and lopinavir (ART drugs). The nanoparticle remained in the system for beyond 4 weeks while free drugs disappeared after 48 hours. A single dose of a drug that has a stand-alone life of 38 hours in nanosuspensions resulted in a release for 3 weeks in mice and over 12 weeks in dogs.[23]

Scientists are also currently studying silver and gold nanoparticles to increase uptake and reduce toxicity. In an experiment, Jose Luis Elechiguerra, et al. showed that most likely due to silver nanoparticles' unhindered surfaces, they interacted better with host cells infected by HIV reduced to the point where it was not detected by syncytium formation when dosed with silver concentrations above 25 μg/mL. With each silver nanoparticle preparation characterized by a different surface chemistry, researchers found only moderate cell toxicity for in vitro cells.[24] A separate experiment revealed that silver nanoparticles hinder HIV viruses in its life cycle after its entry by binding to gp120 in such a way that the virus cannot bind to CD4, a necessary step in HIV infection. Additionally, silver particles were found to be effective against transmission from

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[22] From "Nanoparticle-Based Immunoengineered Approaches for Combating HIV," by A. Bowen et al., 2020, *Frontiers in Immunology*, 11, p. 789
[23] From "Antiretroviral release from poly(DL-lactide-co-glycolide) nanoparticles in mice," by C. Destache et al., 2010, *The Journal of antimicrobial chemotherapy*, 65, p. 2183-2187
[24] From "Interaction of silver nanoparticles with HIV-1," by J. Elechiguerra et al., 2005, *Journal of nanobiotechnology*, 3, p. 6

chronically infected PBMC and H9 (members of the human lymphoid cell line), with transmission reduced by 50 percent.[25]

In an experiment conducted with gold nanoparticles by Garrido, et al., three mice were injected in the tail with diluted particles in PBS solution. After 24 hours they were euthanized, and the resulting analysis from examining the organs showed that cells gradually increased their uptake of the nanoparticles, with Cy5 (ligand) reaching 54% of the targeted cells after 24 hours. Furthermore, after incubating peripheral blood mononuclear cells with gold nanoparticles, at 24, 38, and 72 hours, no toxicity was observed in the cells.[26]

Other classes of nanoparticles have also been researched and the findings are listed below. Lipid nanoparticles have shown a five-fold increase in bioavailability of existing HAART drugs in lymph nodes as well as sustained release over a week. LRA and protease inhibitors enclosed in them also have prevented HIV-1 viral spread and reversed latency. Lactoferrin nanoparticles have shown four-fold increased bioavailability and increased anti-HIV activity. PLGA nanoparticles enclosing TLR-agonists have improved vaccine immunogenicity as well as reduced the dosage requirements. They also can be coated to act as a "decoy" and limit viral binding.[21]

Different approaches taken to increase bioavailability can be seen in the work of Belgamwar et al. which developed intranasal cyclodextrin-grafted chitosan with loaded efavirenz for better delivery to the blood-brain barrier. An IN approach led to better bioavailability, as the drug had a shorter journey and therefore faced less biological and chemical degradation. The

[25] From "Mode of antiviral action of silver nanoparticles against HIV-1," by H. Lara et al., 2010, *Journal of nanobiotechnology*, 8, p. 1
[26] From "Gold nanoparticles to improve HIV drug delivery," by C. Garrido et al., 2015, *Future Medicinal Chemistry*, 7

CD-g-chitosan increased efavirenz's solubility which led to better acceptance into the CNS. These nanomedicines were approximately 200nm and had five times higher permeability and twelve times greater bioavailability than free drug efavirenz.[20] Solubility is greatly important in order for greater bioavailability of the drug. In terms of HIV-1 protease inhibitor Saquinavir, researchers found that creating a PEG conjugate and an ester connection to cysteine, the drug became more water soluble resulting in greater plasma half life and bioavailability.[20]

Research conducted by Sun and Soh has developed a 3D modeling technique that produces orally dosed tablets surrounded in a biodegradable polymer that affects the release of dyes in current research, and ARVs offer a promising translation. By changing the surface of the polymer shell, they were able to alter how the dyes were released in both quantity and over time. Their research even showed the possibility of releasing different substances in different ways, which is ideal for current HAART therapy. Other research ascertaining drug delivery methods is done by Desimone et al. who created the Particle Replication in Non-wetting Templates or PRINT technique. This approach molds nanoparticles in a fluorinated perfluoropolyether (PFPE) which is able to control both the shapes and size of the particles aiding with their delivery.[27] By expanding research past the medicine itself and into delivery methods that affect the drug's shape and availability represent a new path to follow.

Baert L, et al. studied how a stabilized nanosuspension of rilpivirine in dogs and mice sustained over time. The study found that a dose of the drug was released over three months in dogs and three weeks in mice. This suspension compared to the free drug half-life of 38 hours shows how nanotechnology drug application results in the need for lower dosages and improved

[27] From "Nanomedicine for Global Health," by N. Tsai et al., 2014, *Journal of Laboratory Automation*, 19, p. 511-516

adherence.[5] Strengthening the idea of the efficacy of long-acting approaches, Dou et al. showed how Indinavir suspended in a surface of Lipoid E80 in macrophages in mice showed antiviral activity in the brain and quantities of drug for up to 14 days, where the current Indinavir dose half life is just two hours.[5] Nanosuspension of drugs in liposomes is a promising approach as macrophages the main reservoir cite for HIV has a plethora of receptors; through nanosuspensions, drugs are able to be directly absorbs into cites where they are needed the most and last longer due to their availability as opposed to a free floating form of the drug.

There are several vaccines and treatments currently in the pipeline from the preclinical phase to Phase III clinical trials, and use a mix of PLGA nanoparticles, nanoemulsion, and dendrimers. The DermaVir patch is one of the first nanotech treatments to reach Phase II clinical trials. Using polyethylenimine mannose, glucose and HIV antigen coding DNA plasmid to create a targeted nanoparticle system of approximately 100nm, Dermavir is administered under a skin patch and effect epidermal Langerhans cells which mature on their way to the lymph nodes.[5]

While this paper does not focus on advancements in diagnostic testing and prevention, there are experiments to develop methods that use nanotechnology to improve these two areas. Currently, standard testing for HIV-1 involves nucleic acid amplification by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), which involves extensive monetary and time investment in laboratory equipment, training laboratory technicians, and developing high-quality infrastructures. As a result, less than ten percent of people worldwide have access to this type of testing.[28] Another method uses polyethyl glycol (PEG) precipitation and ultracentrifugation, requiring more time and increasing the percentage of false-positive rates due to interference with

[28] From "Dendronized magnetic nanoparticles for HIV-1 capture and rapid diagnostic," by A. Barrios-Gumiel et al., 2019, *Colloids and Surfaces B: Biointerfaces*, 181, p. 360-368

the PCR performed afterwards. To reduce late diagnosis of HIV, magnetic nanoparticles (MNPs) can be functionalized with carbosilane dendrons, which can capture multiple kinds of HIV-1 isolates.

Kirtane et al. created a combination tablet of dolutegravir, cabotegravir and rilpivirine (approved drugs on the market) that achieved therapeutic dosing in blood plasma in just one weekly dosing. Their tablet was a drug-polymer matrix with six drug-loaded flexible arms centered around a core of elastomer. Using population-based modelling, they predicted a once weekly oral pre-exposure prophylactic format providing up to 20% increased efficacy when compared with a daily oral format.[29] The application of HAART multidrug techniques in a nanotech shell allows the drug to be more effective and help with prevention.

Implications and Additional Considerations:

While nanotechnology offers a great range of development for antiretroviral therapy, there are still some obstacles in the way. The most obvious is the need for more research and clinical trials. Many of the experiments mentioned in this review are still *in vitro* giving little to know realistic data on how the research translates to real patients. Furthermore, unfortunately an estimated five to 78 percent of people infected with HIV-1 are resistant to antiretroviral therapy, so in addition to improving antiretroviral therapy with nanotechnology, more treatments should be developed to address this shortcoming.[30]

Conclusion

Nanotechnology in AIDS/HIV treatment represents a new path for bettering the shortcomings of most current treatments focusing on drug delivery and enhancing bioavailability.

[29] From "The potential value of nanomedicine and novel oral dosage forms in the treatment of HIV," by James Hobson et al., 2018, futuremedicine.com, p. 1964
[30] From "Silver Nanoparticles and HIV," by C. Shaffer, 2019, News-Medical.Net

The different approaches ranging from long acting injectables to metallic additions offer promising results, but are unfortunately still in the works with very few nanomedicines on the market. The growing world of nanotechnology can hopefully address the unequal distribution between systematically oppressed minority groups affected by HIV/AIDs both globally and in the US. The correlations between communities most affected globally and those in the US expose the even greater disparities within healthcare including but most definitely not limited to access to inclusive sexual education, preventative care, and appropriate treatment. The ability for the nanomedicine techniques discussed in the previous section to remain in the body longer, access typically hard to reach reservoir sites and be more effective when combating the disease mean a less strict regimen, resulting in less doctor visits and prescription costs -- problems at the heart of the systemic issues of healthcare in the United States. Nanotechnology offers a wide range of advancements both in terms of scientific expansion and in changing the current distribution patterns of demographics most affected. While nanotechnology offers promise for more accessibility to treatment, it is important to understand the demographic disparities are more systematic than medical advances, and a deeper holistic approach is necessary to create healthcare equity for everyone. It is necessary to keep these aspects in mind while advancing care involving nanotechnology as the two will work conjointly towards bringing an end to the HIV/AIDS epidemic.

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