Nanomedicine to Counter Syndemic Tuberculosis and HIV Infection: Current Knowledge and State of Art

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Abstract This review examines, current knowledge, of the impact of the HIV-TB disease syndemic with an eye on its zoonotic impact and discusses the current knowledge and the potential of nanomedicine to improve intracellular disease therapy by offering properties such as targeting, sustained drug release, and drug delivery to the pathogen's intracellular location. Besides the aim of this review is also to identify the gap between available medications and the need of the hour, drugs, to counter multi-drug resistance (mdr) and extensively drug-resistant (XDR) tuberculosis. This review is the first of its kind to take into consideration the multifaceted angles ranging from recent drugs to novel nano molecules, from human to avian tuberculosis and from ideal characteristics of TB drug to where we stand now. Vaccine against tuberculosis is beyond the scope of this review. Key messages: There exists a major gap between the present state of art of drugs available to combat tuberculosis and the present multifaceted complications of the disease like Drug resistance, adverse drug reactions, etc. Drugs for tuberculosis failed to address the basic inherent problems like intracellular drug delivery etc. Thus requires new technology intervention. Transmissions from non human sources have been often overlooked. Complete eradication of TB is not possible in a piecemeal approach. Nanoparticles find various applications in biomedical and material science research due to the tuning-ability of their physicochemical properties such as shape, size, charge, surface group, etc. Nanoparticles might provide a cutting edge to counter MDR/XDR TB and its co infection with HIV by novel mechanism of action.

Keywords Tuberculosis, HIV, Nanomedicine, Nanosilver

space it's multi-factorial complexities and potency as an opportunistic pathogen the burden of tuberculosis toll is still heavy on the globe even after 100 years of its discovery. Besides with the advent of HIV, tuberculosis establishes a symbiotic relationship to evolve as a deadliest burden to the human world. Syndemic relation of tuberculosis with other diseases like diabetes, chronic lung diseases also added to the problem but its concurrent relationship with HIV made the problem even worse. A syndemic is defined as the convergence of two or more diseases that act synergistically to magnify the burden of disease. The syndemic interaction between the human immunodeficiency virus (HIV) and tuberculosis (TB) epidemics has had deadly consequences around the world. HIV-associated TB contributes substantially to the burden of TB-associated morbidity and mortality. Diseases such as tuberculosis, hepatitis, and HIV/AIDS are caused by intracellular pathogens and are a major burden to the global medical community. The pathogens reside within intracellular compartments of the cell, which provide additional barriers to effective treatment. Further, Transmissions from non human sources have been often overlooked. Many domestic animals (Cow, Buffalo, and Pig etc), Wild animals (cat family, Deer etc) and birds are affected from tuberculosis and their role as a reservoir and potent source of transmission to human is often underestimated. In birds intestinal from of tuberculosis is common then the lung from where cheesy exudates are found in the intestine of the birds. To sum up tuberculosis is a dynamic multifaceted problem which is becoming complex with time due to its syndemic relation with other diseases like HIV. This left us with no other choice but to search for newer technologies among which Nanotechnology is the most promising. Herein we try to discuss these multifaceted angles of this age old disease, its drugs, ideal tuberculosis drug and how far are we from having a ideal tuberculosis drug in near future.

1. Introduction

Tuberculosis is an age old disease. Many diseases have been eradicated since the discovery of tuberculosis but its potency as a major killer disease still continues. TB registers maximum mortality by a single pathogen. With time and

1.1. Tuberculosis

Tuberculosis is a disease caused by *Mycobacterium tuberculosis*. *M. tuberculosis* is an acid fast bacterium with a very thick cell wall, which is characteristic of the

Mycobacterium species. The thick cell wall provides an excellent permeability barrier, making mycobacteria resistant to a wide variety of antimicrobial agents. [1] *M. tuberculosis* may reside and duplicate within macrophages of the lungs. An important factor is the bacteria's ability to avoid the cell-mediated immune response through granuloma formation, [2] such that treatment of TB remains a challenge. Individuals with poor immune response or complicating factors such as HIV infection may develop an active TB infection.[3] People with active infections typically experience pain in the chest and a cough with blood or sputum (phlegm) lasting more than 3 weeks. [4] These symptoms could also be accompanied by fatigue, weight loss, fever, chills, or night sweats. [5]

Some antibiotic drugs like aminoglycosides and β -lactams have limited cellular penetration, whereas others such as fluoroquinolones or macrolides have the ability to penetrate host cells but are poorly retained and therefore inefficient.[6] Therapeutic drugs targeting the intracellular pathogens should overcome the cell membrane barriers and release and retain the drug intracellularly at the therapeutic level for a desired time period. Moreover, multidrug resistance is increasing [7-13] and is making intracellular disease treatment more challenging. Therefore, there is a need for the development of advanced treatment methods to better control intracellular infections. Conventional treatments for these diseases typically consist of long-term therapy with a combination of drugs, which may lead to side effects and contribute to low patient compliance.

At present, the treatment of choice for an active TB infection is long-term antibiotic therapy, with an initial “intensive phase” consisting of the four first-line anti-TB drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) followed by a typical 4 month course of rifampicin and isoniazid alone. [14] This has been the most effective treatment to date, although, due to the length of antibiotic therapy, side effects frequently develop [15] and the cost is high. These factors may lead to low patient compliance and contribute to the development of drug-resistant bacteria. [16]

Present State of art of drugs against tuberculosis [17] is listed below in Table 1.

2. TB in Animals and Birds: Zoonoses

2.1. Animals

Historically the link between animal and human tuberculosis (TB) has always been strong. From the early 1800s TB has been described in cattle in slaughterhouses. In 1865 Villemin showed that infected tuberculous material could be injected from one species to another to cause disease and, in 1882, Koch pointed out that there was a danger that TB could be transmitted from animals to humans. In 1902 Ravenel demonstrated *Mycobacterium bovis* in a child with tuberculous meningitis.[18]

Table 1. Present State of art of drugs against tuberculosis

Fluoroquinolones	Fluoroquinolones are broad-spectrum antimicrobial drugs that target DNA gyrase. Several members of this class have been used as second-line drugs for the treatment of MDR tuberculosis. Gatifloxacin and moxifloxacin, the most recently developed fluoroquinolones, have shown better in-vitro activity against <i>M. tuberculosis</i> than ofloxacin and ciprofloxacin, the older fluoroquinolones.
Nitroimidazoles	Nitroimidazoles are antimycobacterial compounds that are equally active against drug-susceptible and drug-resistant tuberculosis. These compounds exert their antimycobacterial activity through bioreduction of the nitroimidazole pharmacophore that is mediated by two deazaflavin-dependent enzymes. Reactive chemical species generated through the bioreduction are presumed to be responsible for the bactericidal activity.
Diarylquinoline	TMC-207, an ATP synthase inhibitor, was discovered from high-throughput screening against <i>Mycobacterium smegmatis</i> . It is highly potent against drug-susceptible and drug-resistant strains of <i>M. tuberculosis</i> . Compared with isoniazid or rifampicin, TMC-207 showed no early bactericidal activity for at least the first 4 days, but showed similar activity to rifampicin or isoniazid from 5–7 days when administered at 400 mg per day. This delayed onset of activity could be explained by the time requirement for depleting ATP stocks, and drug accumulation because of the long terminal half-life of TMC-207.
Rifamycins	Rifamycins are potent inhibitors of bacterial RNA polymerase. Three semisynthetic rifamycins—rifampicin, rifapentine, and rifabutin—have been introduced for the treatment of various microbial infections. Rifampicin is the key component of the first-line treatment for tuberculosis.
Oxazolidinones	Oxazolidinones exert their antimicrobial activity by inhibiting protein synthesis by binding to the 70S ribosomal initiation complex. These compounds have a broad spectrum of activity against anaerobic and gram-positive aerobic bacteria, and mycobacteria. Linezolid, the only approved drug in the class, has low in-vitro activity against <i>M. tuberculosis</i> . Although linezolid has been used off-label in combination regimens for the treatment of MDR tuberculosis, its contribution to such combinations is unclear.
Ethylenediamines	SQ-109 is a derivative of ethambutol, but seems to differ in its mode of action. It interacts synergistically with isoniazid and rifampicin.

During the 1930s tuberculin testing was introduced in cattle in the UK; 40% were found to be reactors. With introduction of pasteurization the control of TB had been possible. Till date diagnosis of TB in cattle is done by the old fashioned tuberculin skin test. The new gamma-interferon blood tests which had been pioneered in cattle can detect infection earlier than the skin test. Used together they could form a more sensitive test for infection than either alone. Developed countries had been by far able to control TB transmission to human by better screening and stamping out the affected animal but the same had not been the case with developing countries. Species identification in order to ascertain Zoonotic transmission in developing and underdeveloped countries is a distant reality.

The role of wild life which in many cases act as an reservoir of wild life diseases has often been overlooked by researchers, policy makers, Government and others related to tuberculosis. Very little data is available for transmission of tuberculosis from animal to human. Data on bovine tuberculosis for many countries of the world are unavailable which does not mean that bovine tuberculosis is absent in that country. No assessment of the global impact of zoonotic tuberculosis and its co-occurrence with HIV is done.

2.2. Birds

All avian species are susceptible to infection by *M. avium*. Humans, most livestock species, and other mammals can also become infected.

There are many authenticated cases of *M. avium* infection in people, although humans are considered highly resistant to this organism. Avian tuberculosis is generally considered not contagious from an infected person to an uninfected person. Infection is more likely to occur in persons with preexistent diseases, especially those involving the lungs, and in persons whose immune systems are impaired by an illness, such as AIDS or steroid therapy.

The above facts re-assure that only piecemeal approach for human TB eradication is not a viable idea, even with ideal novel TB drug. Rather, a holistic approach combating TB in both human and animal kingdom with an ideal novel drug in near future is a possibility.

3. Syndemic Tuberculosis and HIV Infection

Infection with HIV is a significant ongoing problem worldwide. As HIV infection progresses, infected individuals develop AIDS. According to the latest statistics from the World Health Organization, there are 33.3 million people living with HIV/AIDS.[19] Many of those infected live in sub-Saharan Africa, where access to treatment is extremely costly or unavailable. There have been major developments in the treatment of HIV/AIDS since the approval of zidovudine (Retrovir®; GlaxoSmithKline,

Durham, NC) in 1987. [20] Current therapeutic efforts consist of a combination of several drugs,[21] typically from different classes of antiviral drugs.[22,23] This regimen is referred to as highly active antiretroviral therapy (HAART) and has become the standard of care for those infected with HIV. There are five classes of drugs available for HIV/AIDS treatment, including nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and viral fusion and integrase inhibitors. Typical regimens are combinations of three or four drugs, with subsequent modifications made based on the patient's response to therapy.[24] Changes made to a patient's regimen are often based on drug resistance testing, and take into consideration toxicity and tolerability of the new treatment strategy.[24] Although HAART has increased the median survival time of HIV/AIDS patients from less than a year to about 10 years, patients often develop multidrug-resistant strains of the virus over the course of therapy, leading to poor treatment outcomes.[24] Worldwide, TB is the most common opportunistic infection affecting HIV-seropositive individuals, and it remains the most common cause of death in patients with AIDS. HIV infection has contributed to a significant increase in the worldwide incidence of TB. By producing a progressive decline in cell-mediated immunity, HIV alters the pathogenesis of TB, greatly increasing the risk of disease from TB in HIV-co infection.

Similarly due to chronic disease like diabetes which affects the immune system the chance of being concurrently infected with tuberculosis is also very high. People with diabetes have 2-3 times higher risk of TB compared to people without diabetes. About 10% of the global TB cases can be linked with tuberculosis. Likely other chronic diseases and malnutrition which alters immune system has a syndemic relationship in flaring up the incidence of tuberculosis. Relationship of TB with different diseases is diagrammatically represented in figure 1.

Figure 1. Syndemic relationship of TB with other diseases

4. Nanomedicine and Multi Drug Resistance Tuberculosis

4.1. Background

Despite discovery of the pathogen more than 100 years ago, tuberculosis (TB) continues to be a major killer disease worldwide. Currently a third of world population is suffering from one or other infectious disease and multiple-drug-resistant (mdr) TB registers maximum mortality by a single pathogen [25] accounting for about 3 million deaths and about 10 million new cases each year.. This corresponds to more than 7000 deaths per day and 1000 new cases per hour each day [26]. In India each year, about 2 million patients develop active disease and up to half a million death [27]. Moreover, emergence of multi-drug-resistant (mdr) strains and their sinister association with HIV/AIDS has posed a serious threat to the TB control program worldwide [28]. Mdr is associated with high mortality rate of 50–80% and spans a relatively short time (4–16 weeks) from diagnosis to death [29]. Chemotherapy for TB was possible with the discovery of streptomycin in mid-1940s. The introduction of Rifampicin in the early 1970s heralded the era of effective short course treatment. Pyrazinamide and INH also contributed much to it. But, even today effective chemotherapy requires 6 to 18 months of treatment depending on the nature and site of the disease. Failure of remission by first line of drugs in 3–4 months requires introduction of a second line of drugs. Nanomedicine provides enormous opportunity for developing novel drugs. Adverse drug reactions (ADR) of commonly used anti- TB drugs, worldwide like Streptomycin, Rifampicin, Pyrazinamide, and INH ranges from intolerance to hepatitis, neuropathy, optic nerve atrophy, etc. They should be used with extreme caution in pregnancy and lactation due to narrow margin of safety. Moreover, continuous monitoring of liver function test, neurological deficiencies, etc. is required. The total cost of the treatment is also high considering the relatively long span of treatment [30].

Multidrug-resistant tuberculosis (MDR-TB) caused by *Mycobacterium tuberculosis* that is resistant to both isoniazid and rifampicin with or without resistance to other drugs, is a phenomenon that is threatening to destabilize global tuberculosis (TB) control. MDR-TB is a worldwide problem, being present virtually in all countries that were surveyed. While host genetic factors may contribute to the development of MDR-TB, incomplete and inadequate treatment is the most important factor leading to its development, suggesting that it is often a man made tragedy. Efficiently run TB control programs based on a policy of directly observed treatment, short course (DOTS), are essential for preventing the emergence of MDR-TB. In particular, the increasing prevalence of multidrug-resistant (MDR)-TB has greatly contributed to the increased difficulties in the control of TB. Because of the global health

problems of TB, the increasing rate of MDR-TB and the high rate of a co-infection with HIV, the development of potent new anti-TB drugs without cross-resistance with known antimycobacterial agents are urgently needed.

The modern, standard short-course therapy for TB recommended by the World Health Organization is based on a four-drug regimen that must be strictly followed to prevent drug resistance acquisition, and relies on direct observation of patient compliance to ensure effective treatment. Mycobacteria show a high degree of intrinsic resistance to most antibiotics and chemotherapeutic agents due to the low permeability of its cell wall. Nevertheless, the cell wall barrier alone cannot produce significant levels of drug resistance. *M. tuberculosis* mutants are resistant to any single drug are naturally present in any large bacterial population, irrespective of exposure to drugs. The frequency of mutants resistant to rifampicin and isoniazid, the two principal antimycobacterial drugs currently in use, is relatively high and, therefore, the large extra-cellular population of actively metabolizing and rapidly growing tubercle bacilli in cavitary lesions will contain organisms which are resistant to a single drug. Consequently, monotherapy or improperly administered two-drug therapies will select for drug-resistant mutants that may lead to drug resistance in the entire bacterial population. Thereby, despite the availability of effective chemotherapy and the moderately protective vaccine, new anti-TB agents are the need of the hour, to decrease the global incidence of TB. The resumption of TB, mainly caused by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains and HIV epidemics, led to an increased need to understand the molecular mechanisms of drug action and drug resistance, which should provide significant insight into the development of newer compounds. The latter should be effective to combat both drug-susceptible and MDR/XDR-TB. [31]

4.2. Nanomedicines as an Emerging Therapeutic Approach

Nanoparticles find various applications in biomedical and material science research due to the tuning-ability of their physicochemical properties such as shape, size, charge, surface group, etc.

Moreover, the physicochemical properties of nanoparticles are strongly dependent on their interactions with capping agent molecules. Indeed, the surface chemistry of nanoparticles can modify their interactions with external systems. Nanotechnology provides the cutting edge to engineer these properties of nanomaterials for need-based application in bioscience such as biomedicine, biosensor, etc. Due to increase in surface to volume ratio and high mobility across physiological barriers nanoparticles can be used as a therapeutic drug in biomedicine.

Nanoscience has provided mankind with several unique and comparatively more effective drug delivery carriers, encompassing liposomal-mediated drug delivery, solid lipid nanoparticles, polymeric nanoparticles, dendrimers,

nanoemulsions, nanosuspensions and other nanosystems exploiting the extraordinary properties of matter at the nanoscale. Nanoparticle-based assays have shown significant improvements in diagnosis, treatment and prevention of TB. Nanoparticles as drug carriers enable higher stability and carrier capacity along with immense improvement of drug bioavailability which further leads to reduction in dosage frequency.

The various advantages of nanoparticles as drug carriers include high stability (i.e., long shelf life); high carrier capacity (i.e., many drug molecules can be incorporated in the particle matrix); feasibility of incorporation of both hydrophilic and hydrophobic substances; and feasibility of variable routes of administration, including oral administration and inhalation. These carriers can also be tailor made to enable controlled (sustained) drug release from the matrix.

4.3. Drug Delivery and Chemotherapy Explored in TB

4.3.1. Liposomes

Lipid-based micelles (encapsulating vesicles formed by a single phospholipid layer, ranging from ~5 to 100 nm in diameter) and mostly liposomes (vesicles delimited by a phospholipid bilayer, with sizes from 50 nm to several micrometers) Liposomes are small spherical vesicles formed of amphiphilic lipids enclosing an aqueous core. They are widely studied as carrier systems for hydrophilic drugs [32]. Gentamicin incorporated liposomes were evaluated for antibacterial activity in *M. avium* infected mouse model. The drug encapsulated liposomes significantly reduced the bacterial count in spleen and liver as compared to free drug.

4.3.2. Polymeric Nanoparticles

Polymers are macromolecules that result from covalent linkage of smaller structural units or repeats referred to as monomers, and can be designed from fully synthetic to biological blocks. In Polymeric nanoparticles, the drug is attached, entrapped or encapsulated in polymeric core and depending upon the method of preparation, they are called as nanoparticles, nanospheres or nanocapsules [33]. Polymeric nanoparticles represent an attractive alternative to liposomes [34]. Pandey et al., [35] developed sustained release RIF, INH and PYZ loaded poly(lactide-co-glycolide) (PLG) nanoparticles for oral delivery.

4.3.3. Nanoemulsions

Nanoemulsion, many times referred as miniemulsions or sub-micronemulsions by dispersing mainly oil in water. Thermodynamically stable nanoemulsion (mean particle size of 80.9 nm and polydispersity index of 0.271) of ramipril, were developed for oral administration.

4.3.4. Nanosuspensions

Nanosuspensions, poor water soluble drugs are dispersed in aqueous phase containing stabilizing agent. Presently more than 8 candidates are in clinical trials [36]. Another

drawback to the low aqueous solubility is the inability to conduct preliminary biological and clinical evaluations of new drug candidates [37]. Clofazimine, a riminophenazine compound, is an agent considered for treating patients with *M. avium* infection. However, use of this drug was restricted because of its poor solubility. Clofazimine was formulated as a nanosuspension (385 nm) and administered to mice intravenously. It resulted in a considerable reduction of bacterial loads in the liver (72.5 mg/kg tissue), spleen (81.4 mg/kg tissue), and lungs (35.0 mg/kg tissue) of mice infected with *M. avium* [38], when compared with pharmacokinetic data, drug concentrations in these organs reached high concentrations, well in excess of the minimal inhibitory concentration for most *M. avium* strains. The effects of clofazimine nanocrystals were comparable to those of the liposomal formulation used as a control in this study. This study was specially planned to overcome the poor solubility and toxicity.

4.3.5. Solid Lipid Nanoparticles (SLN)

In SLN, the drug is mainly entrapped in solid lipid matrix to produce lipid nanoparticles of size range 50-1000 nm and they produced using hot or cold high pressure homogenization technique. It is noteworthy that the solid lipid nanoparticles display important advantages, such as the composition (physiologic compounds) and the possibility of large-scale production favoured by the feasibility to avoid organic solvents in the manufacturing process [39]. A sterilizing effect was achieved after administration of solid lipid nanoparticles [40]. No tubercle bacilli could be detected in the lungs/spleen after seven doses of treatment of infected guinea pigs.

4.3.6. Micelles

Micelles are submicroscopic aggregates (20-80 nm) of surfactant molecules resulting in liquid colloid. Jiang et al., synthesized thermoresponsive poly(ϵ -caprolactone-co-glycolide)-poly(ethylene glycol)-poly(ϵ -caprolactone-co-glycolide) (P(CL-GA)-PEG-P(CL-GA)) block copolymers having micelle-forming and gelation properties. They can be used for development of drug depot system. INH-poly(ethyleneglycol)-poly(aspartic acid) conjugates were studied for sustained release of the drug. A 5.6-fold increase in anti-tuberculosis activity against *M. tuberculosis* was found for micelle-forming prodrug as compared to the free drug [41].

4.3.7. Dendrimers

Dendrimers represent a novel class of structurally controlled three dimensional macromolecules that radiate from a central core and are mainly derived from a branches-upon-branches structural design. Dendrimers are well defined, highly branched macromolecules. Kumar et al. developed mannosylated fifth generation (5G) PPI dendrimeric nanoparticles for delivery of RIF to macrophages. Drug encapsulation mainly depends on hydrophobic interactions and hydrogen bonding contributing

to the physical binding of the drug to the core.

4.3.8. Silver Nano Particles as a Novel Putative Drug

It was previously demonstrated that surface-modified-lipophilic-nanosilica could be effectively used to combat malaria and 100% lethal virus, BmNPV [42, 43]. We have reported the clinical demonstration of fighting *M. tuberculosis* including *mdr* strains with the help of surface-modified nanosilver. High resolution (HR) SEM studies revealed that BSA-capped nano-Ag wrinkles the cell surface and affects the integrity of the surface of the bacterial cell wall. Eventually, the cytoplasmic material is extruded from the cell leading to the collapse of the cell. Therefore, BSA-capped nano-Ag kills Mycobacterium in a completely different fashion from that of antibiotics commonly used for treating TB. We may conclude that these nanoparticles damage the cell wall and also on gaining entry into the cell tend to disrupt physiological processes via pathways ill understood at present. The combination of both these effects might be the reason for the startling observation that *mdr* strains fail to survive at higher dose of nanosilver [44].

4.4. Limitations of Nanomedicine in TB disease therapy:

The main concern with nanoparticles as a putative drug for TB therapy is its toxicity. The detail knowledge about nano toxicity is the key issues which should be addressed for implementation of nanoscience for health application. The physiochemical properties of nanoparticles like aggregations, etc change with PH. While considering nanoparticles as an oral drug it is therefore important to address its stability in different PH ranging from PH 2-7. It is also important to addresses issues related to toxicity of nanoparticles at cellular level like alteration of redox potential of mitochondria, size dependent permeability of nuclear membrane, etc. The Toxicity of carrier molecules also should be treated with utmost importance. Since the size of the nanoparticles are extremely small rendering it the ability to cross different biological barriers like blood- brain barrier and blood -testis barrier, its application in health system should be applied with extreme caution only under the guidance of proper regulatory agencies.

5. Perspectives for the Future

An ideal drug combination should consist of at least three drugs that are active against MDR and XDR tuberculosis, and have potent, synergistic, and complementary activities against various subpopulations of *M. tuberculosis*. Such a combination should be equally effective against drug-susceptible and drug-resistant tuberculosis, and produce a stable cure in a much shorter period than does the standard treatment. Additionally, such novel combinations should be useful for the treatment of patients with *M. tuberculosis* and HIV co-infection because the drug interactions with antiretroviral drugs could be avoided by removal of rifampicin from the regimen. The characteristic of an ideal TB therapeutic drug is represented in nut shell in Figure 2.

BSA-capped nano-Ag kills Mycobacterium in a completely different fashion from that of antibiotics commonly used for treating TB. As the mechanism of action is physical, by disrupting the cell wall of the bacteria, it is very unlikely to develop resistance against such a mechanism as human beings will hardly ever develop immunity against bullets. This will be effective against almost all strains of mycobacterium as already demonstrated. The toxicity concern related issues are wisely resolved by capping these particles by bovine serum albumin and as documented in micro-array experiments.[44] Thus, satisfying the first criteria of an ideal TB drug. Nanoparticles as drug carriers enable higher stability and carrier capacity along with immense improvement of drug bioavailability which further leads to reduction in dosage frequency, satisfying the second criteria. Nano particles are also found to be effective against different viruses and as demonstrated that silver nanoparticles undergo a size dependent interaction with HIV-1, with nanoparticles exclusively in the range of 1–10 nm attached to the virus. The regular spatial arrangement of the attached nanoparticles, the center-to-center distance between nanoparticles, and the fact that the exposed sulfur-bearing residues of the glycoprotein knobs would be attractive sites for nanoparticle interaction suggest that silver nanoparticles interact with the HIV-1 virus via preferential binding to the gp120 glycoprotein knobs. Due to this interaction, silver nanoparticles inhibit the virus from binding to host cells, as demonstrated in vitro. [45] Thus, where we stand now in compassion to an ideal TB therapeutic drug is represented in Figure 3.

Figure 2. Characteristics of ideal TB drug

Figure 3. Nanotechnology: Where we stand now

<p><u>STRENGTH</u></p> <ul style="list-style-type: none"> ✓ Genome Project Completed ✓ Vaccine Development ✓ Easy Screening test (Tuberculin test) 	<p><u>WEAKNESS</u></p> <ul style="list-style-type: none"> ✓ Syndemic relation with HIV ✓ Flare Up in other immunosuppressive conditions ✓ Zoonotic aspect is overlooked ✓ Ability to proliferate and survive within macrophage is challenge to immune system and drug delivery ✓ Long term Treatment and Adverse drug reaction
<p><u>OPPORTUNITY</u></p> <ul style="list-style-type: none"> ✓ New Novel Drugs in Pipeline ✓ Novel Nano Medicines 	<p><u>THREAT</u></p> <ul style="list-style-type: none"> ✓ multidrug-resistant (MDR) strains ✓ extensively drug-resistant (XDR) strains

Figure 4. SWOT analysis for Tuberculosis disease

But the same nano drug effective against both TB and HIV is not yet demonstrated but is quite possible in nanobiotechnology. It has not escaped the vicinity of the authors the constraints of the TB drug clinical trials and regulatory constraints but the emergence of nanotechnology as a novel cutting edge tool might solve the age old riddle of TB soon in near future.

6. Conclusion

To conclude the authors tried to provide a SWOT (Strength, Weakness, Opportunity, and Threat) analysis to solve the critical issues related to TB eradication by 2050. The SWOT analysis is provided in figure 4.

From the analysis it is clear that the weaknesses of eradication are much stronger than the strengths. Further, the

condition is even more worsening by presence of deadly threats like emergence of MDR and XDR strains. To counter the same the opportunities should be explored extensively followed by effective and efficient materialization. To achieve the goal of elimination of tuberculosis by 2050, all responsible parties need to work together to support the discovery of new drugs and the development of novel regimens for tuberculosis. Regulatory agencies worldwide could help by developing, streamlining, and harmonising regulatory guidelines to allow for testing of several new drugs in combination, and by addressing other clinical development issues. With a joint effort, we have reasons to be optimistic that the challenges of tuberculosis drug research and development are surmountable, and a new revolutionary treatment for tuberculosis in the form of nanobiotechnology will soon become reality.

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