

## Conventional Vaccine to Prevent AIDS – A Paradigm or A Paradox? A SWOT Analysis

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### Abstract

AIDS as a disease afflicts mankind for more than 3 decades. HIV, the causative is not yet checked with a prophylactic vaccine. The plausibility of the prevention by conventional prophylactic strategies based on Jenner's conventional method of inducing memory response is reviewed here. In order to find the right direction towards achieving this goal, a SWOT analysis is represented here with a Venn diagram. Our increasing awareness on the viral genome and the antiviral treatment with the sensitive diagnostic tools strengthen the efforts, while the viral nature privileges its replenishment by hampering the host immune memory. Though antiviral drugs promise a notable degree of control, they render selection pressure favoring viral escapism with perking quasispecies or circulating recombinant forms (CRF). Few historical clinical trials teach us to frame new opportunities for the conduct of such trials that assures safety. The knowledge has exponentially increased on the host immune response, human genetics, retrovirology, drug development, gene delivery system to understand that HIV is the only pathogen that had the greatest consumption of our time and resources. The technological advancements add to our strength. However, the virus with its biological features proves its intrinsic competency for survival. Though the antiviral therapy confers some hope, the resistant forms pose a threat to their continuation. It emphasizes the need for prevention and suggests novel, unconventional prophylaxis. Treatment as a means of prevention and the use of immunomodulators to decrease the disease progression can help us to win the belligerence against AIDS.

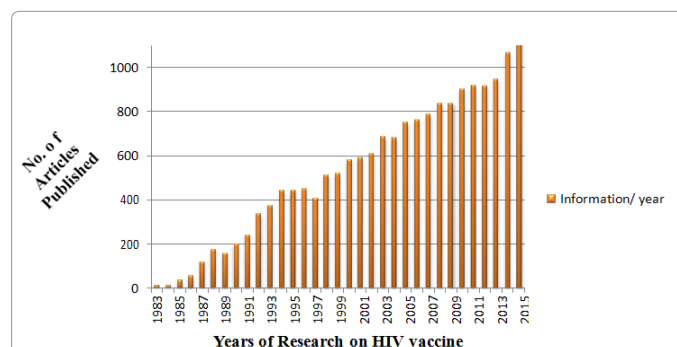
**Keywords:** AIDS; HIV; SWOT analysis; Prophylaxis

### Introduction

The field of medicine has victoriously won the battle against many dreaded infections that challenged the anthropogeny across the centuries. Vaccination and immunization strategies improvised across the decades in accordance with the advancing technology have always served as powerful tools in combating the infectious diseases like Small pox, Polio, Measles, Rubella, Rabies etc., [1]. The conventional vaccine strategies based on the *prima facie* of Jenner's contribution with primitive knowledge and crude techniques have given the substantial memory response against Small pox that protects for almost the complete human life span [2]. For most licensed vaccines their indisputable safety with indubitable efficacy to elicit neutralizing antibodies has been achieved for human use [3]. Also the proportionate improvisation of technology has given different generations of recombinant and edible vaccines with Hepatitis B Virus as an example [4]. This expansion of knowledge and technology facilitate to unravel different aspects of the biological systems at the molecular level. Despite, the attempts to design a prophylactic vaccine for AIDS has not seen the fruition for the three decades of discovery and research on the etiological agents [5]. The Human Immunodeficiency Virus with its unifying features [6] increases in prevalence across the globe with approximately 6500 new infections every day [7]. Here a SWOT analysis is presented to conflate the strenuous efforts and strategies and the factors influencing the achievability of the need of the time.

### Knowledge

Ever since the first report of the etiological agents that cause AIDS, there has been increasing reports on the routes of transmission, the epidemiology and the molecular mechanisms of the genome organization. The science community attempts for achieving the vaccine reports through the decades from every part of the world. Figure 1 represents the yearly rate of articles published on HIV and the vaccine strategies. The number of articles published every year has been increasing over the last three decades. In spite of this profuse expansion of knowledge, the HIV epidemiology increases over the years in contrast



**Figure 1:** Graphical representation of the number of articles published on HIV vaccine every year after the first report on the syndrome in 1983. to any disease that is contained with a licensed prophylactic vaccine.

### Networking

The invention of the computer aided tools and softwares has certainly meliorated the analysis and interpretation of the biological data. The computational biology has emerged parallelly with the timeline of HIV research from the early 1980s [8]. The networking of the research community across the globe is inevitable to avoid redundancy of the strategies and for sharing the knowledge. A network of tools developed for studying different aspect of the vaccine research on HIV is made available by the Los Alamos National laboratory <http://www.hiv.lanl.gov/content/sequence/HIV/mainpage.html> & [www.hiv.lanl.gov](http://www.hiv.lanl.gov)

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lanl.gov. This compendium helps the researchers from any part of the world to study HIV biology by providing updates on vaccine research, the emergence of strains and their sequences, immunology of the viral pathogenesis and every feature reported by the three decade efforts of vaccine research. Such networking and databases have voguishly privileged us for the analysis and presentation of data. Epitopes that can drive both the cellular and the humoral immune response can be selected using bioinformatic tools for evaluating candidate vaccines in a short span, which would otherwise consume decades [9]. The reactivity of the residues constituting the epitopes can be studied using computational methods [10]. Though the networking and the use of computers have tremendously contributed to the research on HIV, the vaccine is not yet realized. These programs have helped us in unraveling the wonders of the molecular operation of the biological systems. Yet, they may sometimes fail by reporting a problem as ‘Unsolvable’. These are referred to as “Intractable” problems. There are chances that the solvable problems can evolve as an intractable one when they grows in their magnitude [11]. The HIV antibody and the neutralization problem to design a conventional vaccine seem to an intractable problem in the current scenario.

## Technology

The discoveries and inventions spanning the decades reflect the magnitude of the technological advancement towards unraveling the mysterious wonders. The evolving technology has resolved the problems that once afflicted mankind. The field of vaccinology also has seen such breakthroughs. This growth of science and technology has helped to know more about the molecular mechanisms of HIV infection, pathogenesis and related complications [12] and favors the search for the neutralizing antibodies like the one found with most of the licensed vaccine [3]. The latest antiviral agents in combination with the bone marrow gene therapy are being formulated to cure HIV [13]. But newer and more breakthroughs are needed to design such a vaccine for HIV [14]. The phylogenetic evidence of HIV sequences in the archived samples from the African province had dated back to the beginning of the last century [15]. This implies that the technology fueled by our knowledge is lagging behind the unidentified but existing challenges. The successful, traditional and novel approaches applied in the formulation of vaccines for other viruses have been substantially limited in the designing of HIV vaccine [5]. The key advances in the immune-biology that has been made, in terms of knowledge and discovery to advance for achieving the vaccine are listed in Table 1.

## Diagnosis

Some observations strongly support the theory that the transmission of AHI had a disproportionate effect on its spreading and this explains the prevalence rate [16]. The detection during the acute infection stage, even with no seroconversion can greatly prevent the transmission of the infection [17]. The sensitive detection systems with effective treatment have grown simultaneously to impart a hope of reaching the destiny and there has been notable reductions in transmission with the encouraging antiviral therapy [18]. The acute HIV infection can now be diagnosed and staged with the fourth generation immuno- assay. The primary diagnosis of HIV infection is equally important for the prevention of spreading if it overcomes false negatives or undetected asymptomatic infections [19]. The protocols are revised and updated for better detection systems within and across borders for an expanded, widespread screening of the virus [20]. Such detection systems can help in the improving prevention of the transfusion associated HIV transmission if the donor is in the window period [21].

## Lack of animal model

The virus as a pathogen is restricted to only humans and not to any other animal including the other members of the Primate taxon.

Discovery	Year
Monoclonal Antibodies Discovery	1984
Genes & Antibody diversity	1987
Organ transplantation	1990
Phosphorylation Switches	1992
Introns in Eukaryotic DNA	1993
Gene Controlled Embryo Development	1995
T cell targeted MHC presentation	1996
Prions	1997
Proteins controlling cell division	2001
RNAi	2006
Knock Outs	2007
Activation of Innate Immunity	2011
Stem Cells from Mature Cells	2012
Vesicle Trafficking	2013

**Table 1:** Yearwise discovery of the facts that adds magnitude and knowledge for achieving the HIV prophylaxis.

This fact has consequentially impaired the research with no appropriate animal model. The lack of a perfect animal model that is indispensable for demonstrating the Koch's Postulates and for studying the vaccine efficacies has been an impediment in AIDS research [22]. Despite the productive infection in chimpanzees, the ethical concern in the use of the endangered species is constrained as they do not develop AIDS [23]. But the discovery of the Simian Immunodeficiency virus that causes AIDS like syndrome in the Asian macaques resembles HIV infection and pathology has helped in AIDS research [24]. However, the large genetic divergence of SIV has limited its use as a model of the non- human primate systems [22]. Also the species specificity of the retroviruses determined by the TRIM5α [25], a restriction factor that barricades the retroviral replication after the entry of the virion core into the cytoplasm [26]. It prevents the virus entry into the cells of the old world monkeys [27]. This TRIM5α has expanded in the independent evolutionary paths within species and it is divergent across humans, cows, rabbits and it is more distant in rodents [28]. It also modulates the innate immune response with its role in the cell signaling, proliferation and apoptosis [29]. Such divergence across species has increased the specificity of the retroviruses and thus hampers the appropriation of the animal model for AIDS research.

## The genome organization of HIV

The inherent hyper-mutability of HIV found in some DNA viruses also, is due to the genome architecture, replication speed [30]. This property of the viruses commingles with the RNA that is the genetic material and helps for swifter evolution. Its melds with the recombination and the reverse transcription which add exponentially to the viral evolutionary competence [31]. The template switching of the reverse transcriptase according to the copy choice model also supports for the evolution [32].

## Reverse transcription

Viruses with RNA genomes have shown that they are the nature's swiftest evolvers as they have added strength of the high mutation and their replication rate favors their evolutionary competency [33]. This unifying feature challenges not only the vaccine designing, but also the drug regimens that are resisted due to the mutations allowed by the erroneous reverse transcriptase. Though the therapeutic agents have

saved more than three million lives, the development of resistance is the misfortune to completely eradicate the HIV infection in patients [34]. *In vitro* studies to determine the fidelity of the DNA synthesis catalyzed by the viral reverse transcriptase has shown that the extensive diversity is due to the inability of the enzyme to proof read [35]. The mutations occurring in such ways offer resistance to the drug for which the virus would have been sensitive during the start of therapy [36]. The kinetics of the enzyme in the synthesis of DNA have been evaluated to understand the mechanics of reverse transcription and the occurrence of mutations that offer resistance to drugs [36]. The rates of errors occur at a frequency of 1/2000 to 1/4000 nucleotides and has been estimated to be the most effective way of hyper-mutability of the virus [37]. Nevertheless, in the mutational hotspots the frequency of erroneous substitution is 1/70 bases [35].

### Recombination

The genetic exchange across non-segmented RNA is not uncommon in viruses [38]. In an evolutionary perspective, the recombination phenomena has been efficiently exploited by the viruses with RNA genomes [31]. This ability enables the creation and spread of the advantageous traits and removal of deleterious genes to bestow a fitness for any population to survive [39]. The epidemiology of the HIV strains has once been the biological barriers for the recombination to occur across different strains of HIV [40]. But the recombinant forms are found to be circulating among populations and are termed as Circulating Recombinant Forms (CRF) which has been dated to have evolved in the early 1990s [41]. The possible recombination between the HIV and SIV bolt-on with the behavioral and socio-economic status of the past has led to the spread of new epidemic [42]. The cross species transmission of the retroviruses [43] poses a threat of recombination of HIV with other lentiviruses that infect the cattle and the felines [40]. The recombinant forms according to a decade old analysis contributed to 18% of the total infection across the globe [44]. Hence, recombination in an evolutionary perspective is exponentially advantageous to the virus for dampening the efforts and strategies of vaccine designing.

### Glycosylation

The glycosylation as a feature of the virus greatly impacts the vaccine strategies and challenges the virologists [45]. The glycans shields the envelope glycoproteins that can be studied better by deglycosylation [46]. The neutralizing ability of the antibodies targeted to specific epitopes is less efficient due to the carbohydrate shield without which the antibodies would neutralize better [47]. It has been predicted that the neutralizing antibodies (4E10, 10E8 and z13) are less efficient in the case of mutations that can be potentially glycosylated [48]. The removal of the glycosylation has increased the sensitivity of the virus to the neutralizing antibodies [49]. On the other hand, the presence of glycans on the envelope proteins affects the viral infectivity and the tropism and favors the viral progression [50].

### Immune response

Despite the advances in the understanding of the HIV pathogenesis, the obstacles to a successful vaccine remains elusive [5]. The antibody responses established in the lymphoid tissues are directed by the CD<sub>4</sub><sup>+</sup> T cells [51]. These germinal centers established during the primary immune response of an infection play a crucial role in affinity maturation [52]. The CD<sub>4</sub> cells are the members of the diverse immune cells that have memory and the effector functions [53]. But the pathogenesis of HIV results in a heavy depletion of the CD<sub>4</sub><sup>+</sup> T-cells, that is co-indicated by the viremia [54]. The CD<sub>4</sub><sup>+</sup> depletion hampers affinity maturation that is essential for a memory response. A profound decline in CD<sub>4</sub><sup>+</sup>

T- cell population results in the syndrome due to lack of memory that prevents the egression of the opportunistic pathogens [55]. Though HIV induces a vigorous immune response, its replication in the host remains completely uncontrolled [56]. In order to target the epitopes specifically, mechanisms for the generation of high affinity monoclonal antibodies to accomplish neutralization have been studied extensively [57]. When the elicited neutralizing antibodies are less in titer, they cannot neutralize efficiently. The immune pressure on the B or T cell epitope directs the rapid appearance of the escape mutations [56]. The rate of immune escape is determined by the pressure rendered by the Cytotoxic T-Lymphocytes which can render selection pressure and impact on vaccine designing [58]. The antibodies evolving in response to the infecting virus must attain affinity maturation to neutralize the whopping levels of the circulating virus [59].

### Viral tropism

The tropism or viral ability to replicate in a particular human cell varies based on the viral strain and it is determined by the preceding events of provirus formation [60]. HIV virus particles interact with specific receptors on the surface of the human cells. The CD<sub>4</sub> receptor and the CCR-5 coreceptor act serially to induce the fusion of the viral and the cell membranes and contributes for the virus entry into cells [61]. These receptors found on the human cells help to classify the viral strain and the coreceptor tropism serves as an important prerequisite indicator for therapy [62]. The tropism of the cytolytic virus serves for the survival advantage as its host is a key for the orchestration of the memory response. The virus also resides in the macrophages, which serves as a reservoir and the tropism may also be shifted to prefer macrophages in the later stage of infection [63]. The infection of a single host cell with more than one strain or variants can result in the enhanced evolutionary competency [64].

### Latent viral reservoir

The latency is a viral strategy adopted by many viruses and contributes to their pathogenesis [65,66]. HIV latency in the hematopoietic cells and the monocyte-macrophage lineage in the bone marrow privileges the virus for the percolation across the blood brain barrier. The cells of the myeloid lineages serving as latent reservoirs and their potential roles in the HIV latency has been critically investigated [67]. These latent reservoirs are the barriers for the complete eradication of HIV [68]. This quiescence of the virus in the CD<sub>4</sub><sup>+</sup> cells remains intensely debatable. The viral load turned undetectable on antiretroviral therapy, followed by a dramatic surge of viremia has been demonstrated in plasma of patients [69]. A better understanding of the viral tropism in relation to the quiescence is needed for the advancing of research on HIV relapse [70]. Though small in numbers, these latently infected T-cells that have to be eliminated for the complete eradication of the infection. NFκB and NF-AT (Nuclear Factor of Active T cells) play roles in the cellular signals and in the activation of latent HIV. The bystander proliferation of the quiescent T cells occurs in no relevance to the plasma viremia and the intervention of therapy enables the viral latency and replication [71]. Though the viral loads have been reduced by the HAART regimen, the complete eradication efforts are staggered due to the reactivation of these latent reservoirs [72]. However, the immune regulation of HIV in the reservoirs needs modulation of both HIV-1 latency and its replenishment opens up conceptual models that vouches for HIV cure strategies [73]. The unchecked integration of the viral genes into the germline of the host can cause a mayhem to the existing human race when it remains as a part of the human genome [6]. Hence the HIV latency, is of a greater magnitude. than any other challenge in the prevention strategies and the management of HIV infection.

### Host genetics and polymorphism



The viruses as metabolic parasites due to lack of machinery and depend on their host cells for their survival. In precision, the host cell environment decides the adaptability of the virus and drives it to retard viral adaptability [74]. The comprehensive sequencing nowadays gives knowledge on the complete genome of the host individuals and catalogues human variations and their significance [75]. The host diversity is accounted for the 25% of the differences that are found in the control of HIV with HLA-I polymorphism as a vital determinant [76]. The HLA allele B\*5701 has been reported as the host element in association with the endogenous retroviral element [77]. The impact of the ancestry of population with this allele has been investigated across populations from different parts of the world [78,79]. Systems biology in hands with a multidisciplinary approach has done a statistical estimation for understanding the host-virus interaction. This fact has been shifting the focus from the candidate gene studies towards an unbiased genome wide studies of genes and their functions [80]. The host genetic polymorphisms are not only the determining the susceptibility to HIV or AIDS, but are also with the development of HAND (HIV Associated Neurodegenerative Disorders), [81]. The CDC survey done in the past has reported on the age, gender, race or ethnicity and the routes of acquisition in categorizing the stages of infection [82]. So the host genetics and their polymorphism are to be essentially considered as it is so much influential on the achievement of a universal vaccine.

### Quasispecies

Over the last three decades the RNA viral evolution has been understood on the basis of the quasispecies theory. In the 1970s, a model was proposed to explain the molecular evolution, its adaptability, and the rapid evolution of simple replicons that were found during the origination of life on the planet. The quasispecies theory with Hepatitis B and Hepatitis C, the other two blood borne viruses are studied for designing vaccine and to understand the survival race [83]. The RNA viruses of the present day's world, particularly those are challenging the vaccine designing strategies resemble those replicons [84]. This term has given birth to a transdisciplinary research with both the experimental and theoretical biology with one complementing the other that favors to understand the viral quasispecies behavior. This has been reviewed on the other two blood borne viruses Hepatitis B and Hepatitis C viruses with clinical significance. This feature is considered as a misnomer by few virologists as the real viral quasispecies is always misinterpreted, while some consider this as an unnecessary phenomena to explain the RNA virus biology [85]. A quasispecies is a cloud of diverse variants that are genetically linked through mutations and interact with coherence, thus together contribute to the characteristics of a population [86]. It contributes to the rapid evolution of the RNA viruses that complicates the management or the prevention strategies for the viruses that exist as quasispecies that lack a defined RNA genome [87]. Though it is said to be an outcome of the error prone reverse transcription, it is not devoid of biological relevance. This is explained by the evolutionary competence that is reflected in the viral pathogenesis that also embeds the memory of the viral genome and its lineage [88]. The development of quasispecies *in vivo* has been demonstrated in patients who were followed up to be on treatment ever since they acquired the virus [89]. Understanding the viral quasispecies to a greater extent may help in pragmatic medical approaches to predict the future outcome of the current treatment strategies [87]. The increase in knowledge of the viral quasispecies is aimed at bringing down its fitness ability and challenging its replication competency. The relation of the viral evolution with the disease progression and the recombination as an influencing factor has been modeled and observed in the inpatient viral evolution that declines in its rate as the disease progresses [90]. The frequency of recombination gets increased with the multiple infection that favors

the quasispecies evolution or the viral progression [64]. Thus the viral quasispecies or diversity contribute for the viral evolution and thus challenge the strategies of therapy or prophylaxis.

### Clinical trials

The stringent but essential regulations are always there for every candidate drug. These regulations are for channelization of the ideas to adhere to the ethical codes that should never be compromised. Apart from the efficacy of the candidate drug under trial, the safety is an inevitable for the conduct of these trials. The HIV vaccine trials of the past have imparted few valuable lessons towards the goal with the directions for it [91]. The present state of the HIV-1 vaccine research outlines strategies that are being explored to overcome these roadblocks. The T cell based HIV-1 vaccines have failed to show the required efficacy [92]. With remarkable progress and the limitations the strategies are reviewed for a change in the face of HIV-1 vaccine research [93]. A retrospection of the vaccine trials shows us new arena for the biomedical intervention to prevent HIV [94]. Besides the scientific advancements, the realization of prophylactic vaccine has socio-personal barriers that constrains the participants. The measure of sexual behaviors that is in line with the culture is essential for understanding the transmission dynamics of the sexually transmitted diseases. This also includes the measurement of errors in survey research with a participation bias influenced by the ethnographic and cultural differences [95]. Few subjects of the RV144 clinical trial had HIV infections after being vaccinated for HIV [96]. Such previous reports of the vaccine efficacy trials did not affect the progression to AIDS [97]. The recombinant gp120 that was successfully evaluated for the efficacy has not prevented the infection or the disease progression [98]. Such risks and the costs are involved for the participant. Prejudiced by such misconceptions or threats, their participation can be disallowed for the trials of vaccine candidates even if they are conferring efficacy [99]. The intractability of the participants to comply with the regulations of the trial has been a barrier in interpreting the results of the vaccine efficacy trials.

### Antiretroviral therapy

The advancements in the antiretrovirals have turned the viral infection to a chronic, but manageable one to a certain extent [100]. The antiretroviral therapy has increased the longevity of the patients infected with HIV. ART regimen can prevent the HIV infection across serodiscordant couples when initiated earlier [101]. It has resulted in undetectable HIV viremia in the patients adhering to the antiviral treatment [102]. Approximately, 26 drugs have been approved by the FDA for the clinical use towards managing HIV till the last decade [103]. The access to the drugs and their affordability with the update on its usage terms differs with the economy and the availability of the sensitive diagnostic systems to study the performance of the drugs [104]. The evolution of the drug resistance is due to the selection pressure rendered by the drugs [105]. The recombination occurs in order to gain the survival advantage and the resistant strains recombine to form the Circulating Recombinant Forms that challenges the established regimens of antiretroviral therapy [106].

### Alternative methods of therapy

Besides the partially successful antiretroviral therapy, there are other suggested means of therapy [13]. The genetic means of treating this infection that gets integrated in the genome seems to confer a hope. The intracellular immunization mode of gene therapy promises to progress for the clinical trials. This genetic intervention refers to any form of gene delivery into cells to provide a cellular resistance to HIV infection [107]. The genes that are delivered into the cells remain

biologically active and suggests a conventional means of therapy and have reached the phase 2 trials [108]. The Vesicular stomatitis virus glycoprotein G being delivered to hematopoietic stem cells has shown a multifaceted clinical application [109]. Insertion of the CCR-5 along with Tat-Rev siRNA into the third generation of the lentiviral vectors has given out T cells that are resistant to HIV infection and it has been demonstrated in mouse models [110].

Method

SWOT analysis

The investigation on the factors critically influencing on our efforts towards any goal can take us forward to cross milestones. The SWOT analysis (Strengths, Weaknesses, Opportunities, Threats) helps to prioritize these factors in ascertaining the achievability [111] has been analyzed. The virology has been investigated and such analysis has been already presented on the viral biology [112]. The market implementation of the vaccine for the influenza pandemic to highlight the burden due to the influenza has also been analyzed in similar way [113]. The realization of the HIV vaccine, like anyone of those listed in the governmental schedules for vaccination is due for the last three decades of research. The technical advancements and the knowledge of the present era of science or medicine is exponentially greater than that of the first vaccination by E.Jenner, albeit meagerly explained [114]. Hence and still, the prophylaxis based on the conventional strategies for a vaccine is impeded. The elements that either individually or interdependently factoring for the vaccine or the measures towards it are presented here. A retrospection of the advancement in techniques that enhances the knowledge for the successful prevention or management of HIV are reviewed here. A Venn diagram is constructed to depict the influencing factors that add to the strengths, weaknesses, opportunities, and threats or to more than one of these using Venny 2.0 [115] (Table 2 and Figure 2).

Conclusion

On retrospection, the listed influential factors are interdependent and few of them have contributed in more than one and contrary ways. The blend of the skill and technology (Figure 1 and Table 1) has been adding tremendous strengths to our attempts the goal during the last three decades of research. The antiviral therapy strengthens the management strategy as it enables the reduction of the viral loads to undetectable levels [102]. On the contrary, the antiviralst have also derided the ultimate goal, by rendering selection pressure on the virus to gain resistance in treated patients or transmitted by them [116] to cause new infections as circulating recombinant forms (CRFs) [117]. Though it seemed to have strengthened our efforts, it also poses a threat by driving the viral drift and recombination. The increase in the sensitivity of the diagnostic systems have contributed to the reduction in the transmission rate [17] and the time of detection has critical impact on the mortality [118]. Yet the diagnostic systems has also been leaky in transmitting HIV infections [119]. Though the technical advancements have exponentially enhanced knowledge, the progress towards the goal remains speculative. Also the clinical trials have imparted few lessons to be always remembered in designing any vaccine strategy [91]. The unconventional viral genetic algorithm swindles the immune surveillance and attenuates the immune memory privileging the opportunistic infections. The cytolytic virus with its tropism and pathogenicity diminishes the memory by depleting the CD<sub>4</sub> [120]. Jenner's basis of immunization that imparts lifetime memory, conferred a hope to banish the small pox [121]. But in favor of the the virus, the viral quasispecies also has memory genomes to compete in their race with the host immune system [122,59]. Also the recombination of the

Strengths	Weaknesses
Knowledge/ Technology/ networking of resources/ antiretroviral therapy/ gene editing approaches diagnostics/ Increasing awareness	Time (30 years of research) & Investments/ Immune escape / viral tropism/ viral diversity/ antiretroviral therapy/ latent viral reservoirs/ reverse transcription/ recombination/ Integration into host genome/ glycosylation/ Hampered immune memory/ host genetic diversity/ lack of animal model & awareness quasispecies/ & its memory/
Opportunities	Threats
Gene therapy/ networking of resources/ clinical research/ ethical scrutiny/ Elite controllers	Social stigma/ Non-participation in trials/ safety issues/ Antiretroviral therapy/ diagnostics/ Transfusion associated transmission

Table 2: SWOT analysis – Factors influencing the achievability of the vaccine for HIV.

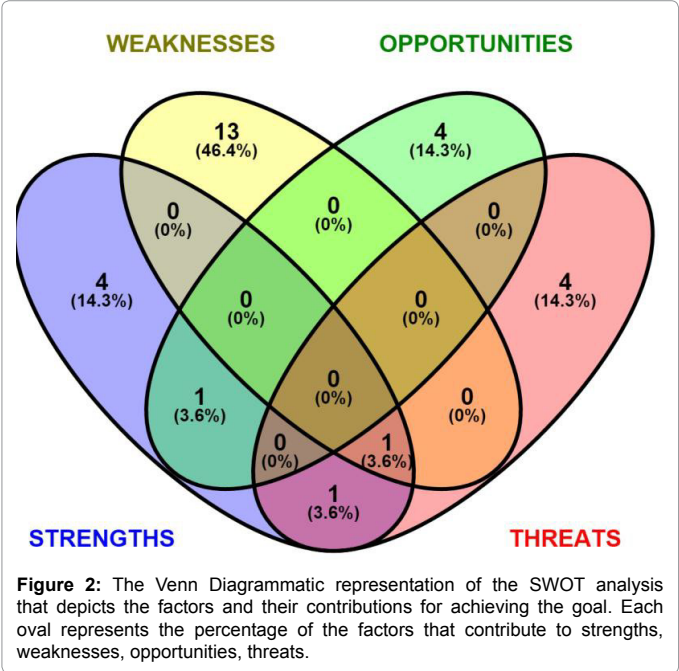


Figure 2: The Venn Diagrammatic representation of the SWOT analysis that depicts the factors and their contributions for achieving the goal. Each oval represents the percentage of the factors that contribute to strengths, weaknesses, opportunities, threats.

virus with CRFs and its ability for cross species transmission is a serious threat to be considered for gauging the future risk [15].

Hence, novel approaches that differ from reliance on the immune memory is needed for the prophylaxis, as the viral biology and tropism features the knocking off the immune memory. The conventional strategies of a vaccine are derided by the inherent genome organization that gives its evolutionary competency. In this scenario, treatment as a means of prevention seems better and appreciable than the 'yet unrealized' prophylaxis which is the most needed. The experience of three decades research has given us the directions by denoting the scientific challenges ahead, suggesting cure as a means of prevention [123]. Research on NHP models, human immunology with its genetics, retrovirology, drug development and gene delivery systems have been greatly understood with HIV and AIDS than with any other pathogen [124]. But the fruition of all these efforts is still awaited with the invested time and other resources. The increase in awareness has strengthened our attempts and it requires diligent continuity to prevent acquisition by uninfected individuals. Hence, the onus on the research community and its every member is emphasized to contemplate on the strengths, weaknesses, opportunities and threats to hit the Achilles heel

of HIV to win in the belligerence of AIDS against mankind.

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