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Review article

Immunotherapeutic strategies for sexually transmitted viral infections: HIV, HSV and HPV

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ABSTRACT

More than 1 million sexually transmitted infections (STIs) are acquired each day globally. Etiotropic drugs cannot effectively control infectious diseases therefore, there is a dire need to explore alternative strategies especially those based on the regulation of immune system. The review discusses all rational approaches to develop better understanding towards immunotherapeutic strategies based on modulation of immune system in an attempt to curb the elevating risk of infectious diseases such as HIV, HPV and HSV because of their high prevalence. Development of monoclonal antibodies, vaccines and several other immune based treatments are promising alternative strategies that are offering new opportunities to eradicate pathogens.

Contents

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1. Introduction

Practice to prevent and treat diseases by boosting, suppressing or stimulating immunity is known as immunotherapy. Though, antimicrobial drugs have developed rapidly in recent past but these drugs are of narrow spectrum and target certain groups of microbes leading to an increased resistance. Such hindrances in treatment compel scientists to investigate new ways of developing effective and cost-effective treatments especially immuno-therapies [1]. The alarming increase in prevalence of immunocom-promised people besides booming antimicrobial resistance and lack of novel antimicrobial agents form the basis of development of immunotherapeutic strategies. Frequently used immune-based therapies against infectious diseases span the use of cytokines and growth factors to boost natural immunity, increase effector cell response to restrain infectious diseases, introduction of anti-bodies against different organisms, use of monoclonal antibodies, hyperimmuneglobulins, cytokines, different interleukins and inter-feron [2,3].

The 20th century witnessed remarkable discoveries, including antimicrobial agents that changed the face of medical practice [4]. The use of antibiotics and preventive vaccines led to a decline in major endemics in industrialized countries and, to a lesser extent, in developing countries. However, pathogens developed resistance to antimicrobial agents in both developing and developed countries (Fig. 1) [5,6].

During the last century, infectious diseases have been the leading reason of morbidity and mortality in developing world. Likewise, millions people have lost their lives in different cities of Europe due to bacterial and viral infections [7]. In 1800, Edward
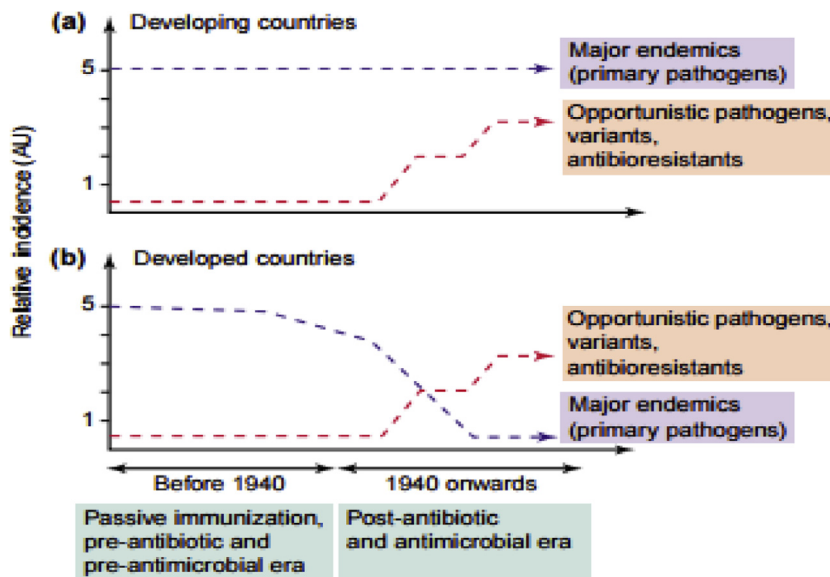

Fig. 1. Evolution of infectious diseases and microbial resistance [7].

Jenner reached to the first milestone in controlling infections when he demonstrated immunization by inoculating humans with material extracted from cowpox lesions [8]. The basis of immune-based therapy dates back to 1890, during which Emil von Behring and Shibasabura Kitasato introduced serum therapy and successfully cured children infected with diphtheria using horse anti-sera [9].

Whenever pathogen gains entry into the host, immune mediators are released to activate the immune system. This initial response controls the infection by stimulating phagocytic effector cells such as macrophages and neutrophils to eliminate infectious agents. Modulation of immune response is more reasonable approach to control infections as compared to antimicrobial chemotherapy [10].

Immunotherapy against infectious diseases includes modification of antigen-specific response (e.g., by using interferons), mobilization of immune response against pathogens (e.g., by using cytokine inhibitors and cytokines) and minimization of end-organ damage based on use of nonspecific anti-inflammatory agents (e.g., use of steroids) (Table 1) [2].

1.1. Active immunotherapy: vaccination and its immunological mechanism

Active immunotherapy has been proved effective against acute infectious diseases and the efficacy depend upon the use of suitable target antigens, optimization of antigenic peptide interaction with antigen presenting cells and T-cells, and concurrent blockage of negative regulatory mechanisms which inhibit immunotherapeutic impacts [11]. There are several different types of immune responses evolved qualitatively to avoid infections e.g., different subsets of T helper cells (e.g., TH1, TH2 and TH17), TFH (follicular helper T cells) [12] that secrete IL-21 (interleukin-21) and differentiates B cells to generate memory B cells [13]. In addition, memory T cells consist of distinct populations of effector memory cells and central memory cells both having distinct effector function along with homing capacity [14].

The mammalian immune system includes innate and adaptive components, which cooperate to protect the host against microbial infections. Innate immunity sense microbes using pattern-recognition receptors [15], like C-type lectin-like receptors [16], toll-like receptors [15], cytosolic nod-like receptors [17], and RIG-I-like receptors [18], which trigger the activation of adaptive immune response and antimicrobial responses. The adaptive immune system, in turn, activates innate effector mechanisms in an antigen-specific manner. Several different subsets of functionally distinct dendritic cells are also present and it has now been proved that pattern-recognition receptors and dendritic cells determine the quality and magnitude of acquired immunity [19,20]. Foreign agent or microbe is integrated by dendritic cells and translated to antigen specific B and T cells to boost the strength, persistence, and quality of the adaptive immune response [19].

2. Passive immunotherapy

Passive immunization was introduced in 1891, when a boy with diphtheria was injected with diphtheria antitoxin that cured him. anti-diphtheria serum because of its favourable results got public acceptance in all parts of Europe during 1894 [21]. Serum therapy had been used to control bacterial infections such as *Neisseria meningitidis* and *Streptococcus pneumoniae* since 20th century [22] but this practice was dumped in 1940s due to toxicity associated heterologous sera whereas the recent advancements such as development of monoclonal antibodies provide new insights for elimination of infectious organisms [23].

Passive immunotherapy is based on administration of immunoglobulins which is either combined with a toxic counterpart molecule or involve adoptive migration of an activated immune cell effector component to act against host's neoplasm. Cellular therapy includes adoptive transfer of specifically sensitized cytotoxic T lymphocytes and nonspecifically activated LAK (lymphocyte-activated killer) cells [24]. Passive immuno-therapies include use of

Table 1
Immunotherapeutic strategies against infections.

Immunotherapy	Function
Mobilization of immunity using vaccines	Inactivated vaccines contain killed microbes that stimulate body's immunity
	Live attenuated vaccines contain live pathogens with reduced virulence
	Toxoid vaccines consists of pathogen's toxin (poison) that has been made harmless but elicits immune response in host
	Subunit vaccines contain only antigenic part instead of entire microbe
	Conjugate vaccine is a combination of poor (polysaccharides) antigen and carrier protein belonging to same pathogen
	In DNA vaccination, genetic material is directly injected into living host that efficiently elicits humoral and cellular immunity to protein antigens
	Recombinant vector vaccines are produced by recombinant DNA technology and involve the use of attenuated virus or bacterium as vaccines which introduce pathogen DNA into body cells
Modification of specific antigen-based response	Use of antigen delivery to induce regulatory cell response
	Instigation of B cell tolerance
	Shifting of immune response from type 1 helper T cell to type 2 helper T cell
Cytokine immunomodulation	G-CSF and GM-CSF decrease the frequency and severity of infections
	IL-2 increases proliferative response of lymphocytes, enhance capacity for antibody responses, improve NK-cell mediated cytotoxic function
	IFN-a improve NK-cell mediated cytotoxic function and help in expansion of CD56dim NK cells
	IFN-ϒ diminishes the severity and frequency of infections
T cell based approaches	Engineered T cells with novel T cell receptors are infused into patients that attack and kill viral infected cells
	T cells are engineered to produce material such as an antiviral RNA that control viral replication
	T cells are engineered to produce an enzyme (zinc finger nuclease) that blocks viral infection
	Chimeric T cell receptor therapy (CAR-T) uses engineered receptors, which graft an arbitrary specificity onto an immune effector cell
Antibody based therapy	Monoclonal antibodies enhance immune function of host and cause minimal toxicity to host or targeted tissue
	Polyclonal antibodies recognize multiple epitopes on any one antigen
	Intravenous IgG type immunoglobulins stimulate humoral immunity in host
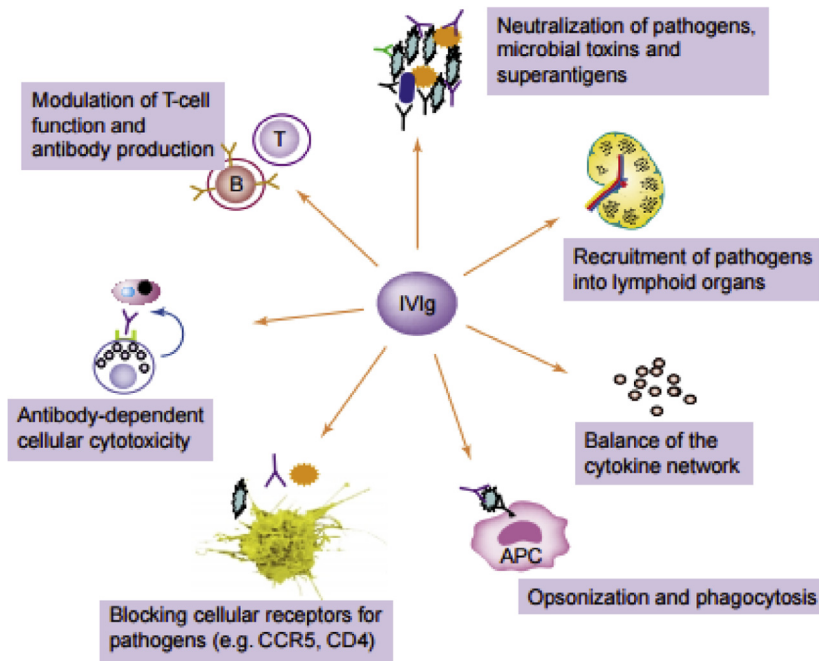
Fig. 2. Proposed mechanisms of action of intravenous immunoglobulin (IVIg) in infectious diseases. The mode of action of IVIg in infectious diseases involves its direct interaction with pathogens and various cellular and soluble components of the immune system [5].

polyclonal and monoclonal antibodies and other components of immune system such as interleukins, cytokines and interferons.

3. Intravenous immunoglobulins

Intravenous immunoglobulin therapy is being used in different clinical trials as therapeutic or prophylactic agent for infectious diseases and various studies have proved it a promising alternative strategy to control infections. Intravenous immunoglobulin preparations are made up of IgG type antibodies which recruit viruses into lymphoid organs where they are presented to B and T cells leading to an activation of immune response [5,25] (Fig. 2).

Immunocompromised patients are more susceptible to chronic infections and a study demonstrated that when patients with primary immunodeficiencies were treated with double amount of immunoglobulin (two times of standard dose), a significant decrease in severity and frequency of infection was observed [26]. Treatment of patients of West Nile virus encephalitis with intravenous immunoglobulins containing high titres of antibody has been found to be effective [27]. Intravenous immunoglobulin therapy can also clear viremia and re-establish cytokine balance in patients suffering from acute PV-B19 infection such as chronic fatigue syndrome. Cytomegalovirus and parvovirus B19 virus are the cause of glomerulopathy in transplanted kidneys but introduction of intravenous immunoglobulin preparation before transplantation eliminates the risk of viruses [28,29]. Intravenous immunoglobulin prepared from individuals exposed to HPV, HIV and HSV or any other outbreak may emerge as beneficial adjunct therapy.

4. Monoclonal antibodies

Injection of monoclonal antibodies is another attractive technique of passive immunotherapy that triggers recruitment of lymphocytes and activation of complement system. Most monoclonal antibodies that have been developed so far are for immunological disorders and cancer treatment whereas, monoclonal

antibodies against infectious diseases are still in progress [30]. The recently developed monoclonal antibodies against different strains of influenza virus have been raised the possibility of mitigating infectious epidemics [31]. The only approved monoclonal antibody palivizumab (Synagis) is leading to development of 2nd and 3rd generation monoclonal antibodies AstraZeneca/MedImmune against respiratory syncytial virus infection in infants [32]. Another study has suggested that clinical trial of monoclonal antibodies against Hendra and Nipah viruses in animals exhibited convincing results [33,34]. Likewise, antibody based treatment of Ebola, HIV, and HPV virus is under clinical trials [35].

5. Polyclonal antibodies

Polyclonal antibodies are more efficient and provide better protection against infections because of their ability to target different antigenic polymorphisms and serotypes. It provides an excellent opportunity to ameliorate the prognosis of emerging infectious diseases and neglected tropical diseases as well. Additionally, polyclonal antibodies can simultaneously target variety of epitopes and kill pathogens. Symphogen introduced effective methods to develop antigen-specific recombinant human polyclonal antibodies i.e., Symplex™ and Sympress™ techniques against infectious diseases and cancers. Sympress platform uses mammalian cell lines that express high level of single antibody molecule to develop reproducible and robust polyclonal antibodies.

Polyclonal antibodies have been efficaciously applied to intoxication, envenomation and rabies. Rabbit anti-Rabies virus Glycoprotein G polyclonal antibody (Catalog Number: CSB-PA14899A0Rb) induces the endocytosis of virion because this polyclonal antibody cause attachment of the virus to host cellular receptors. This fusion triggered by acidic pH of endosome leads to conformational changes in the glycoprotein trimer. This transmembrane glycoprotein is the viral attachment protein that promotes uptake of virus by infected cells, and acts as target of the host humoral immune response to infection [36,37]. Only two individuals developed rabies out of total 7660 Filipino

recipients of F (ab′)2 equine rabies immunoglobulin (ERIG), (Favirab, Sanofi Pasteur, Lyon, France). As per WHO guidelines none of them had given post-exposure prophylaxis (PEP) strictly [38,39]. There are limited therapeutic options available against viruses therefore polyclonal serum therapy will very soon be emerged as potent and effective technique against viral infections based on several researches and clinical studies that have demonstrated the effectiveness of animal-derived polyclonal antibody based treatments targeting different venoms, toxins and infections [40]. Currently, immunoglobulin therapy is targeting HPA1 (highly pathogenic avian influenza) viruses e.g., H7N9 and H5N1 are new targets for polyclonal F(ab′)2 immunoglobulin therapy. In mice, *in vivo* proof-of-concept studies of equine polyclonal F(ab′)2 to HPAI H5N1 (Highly pathogenic avian influenze-H5N1) have been found to prevent infection after an intranasal HPAI H5N1 attack [41]. According to another study, both prior (prophylaxis) or post (therapeutic) administration of four pepsin digested immunoglobulin H5N1 avian influenza equine F(ab′)2 preparations exhibited cytopathic effect against H5N1 infected cultured MDCK (Madin–Darby canine kidney) cells and provided protection to mice [42]. In another study, 100% survival rate was observed in influenza-infected-mice that was intravenously infused with high dose 320 μg) of anti-influenza IgG [43]. No serious adverse events were observed in phase 1 clinical trial carried out in 21–40 years old, 16 healthy human males who were injected with polyclonal F(ab′)2 to HPAI H5N1 [44]. Likewise, many animal based studies have demonstrated the clinical efficacy of polyclonal antibody therapy against various neglected tropical viral diseases. Unimmunized hamsters injected with West Nile Virus-immune hamster antisera (1 h before and 24 h after a West Nile Virus challenge) were protected from life-threatening West Nile Virus infection [45]. Decrease in disease and deaths were noticed when Marburg and Ebola filoviruses challenged non-human primates were injected with Marburg and Ebola filoviruses specific polyclonal antibodies obtained from non-human primates who had survived flavoviruses exposure [46]. Likewise, similar results were obtained when Ebola infected mice, guinea pigs, and monkeys were injected with polyclonal sera acquired from Ebola immunized mice [47,48]. Equine F (ab′)2 have been found effective in both hamsters and mice infected with SARS-CoV infection because a significant reduction in lung viral titres was observed compared to controls [49].

6. Advantages of immunoglobulin therapy

i) Immunoglobulin therapy acts as broad spectrum antimicrobial therapy active against all classes of infectious organisms and can be developed against any kind of pathogen. Human body is able to generate antibodies against all existing pathogens. Antibodies encoded by variable gene elements are assembled because combination of diverse gene elements in the germline increases the possibility of antibody production against large number of antigens. Induction of somatic mutations antibody genes leads to production of more diverse, more specific and high affinity antibodies [50].

ii) Therapeutic antibody development does not only target extracellular pathogens it has been reported that monoclonal antibodies are also effective against intracellular pathogens e.g., there are some intracellular viruses which can be neutralized by IgA monoclonal antibodies [51].

iii) Introduction of antibodies bring about antimicrobial action using different mechanisms such as antibody directed cellular toxicity, toxin and viral neutralization, opsonization, obstruction of microbial attachment and complement activation [52].

iv) Pharmacokinetics of immunoglobulin isotype IgG demonstrated it as an effective antimicrobial agent because of half life of 20 days [53] and good tissue penetration power [54]. The half life of murine monoclonal antibodies is shorter in humans and this usually triggers human antibody response. Humanized monoclonal antibodies and human-mouse chimeric antibodies are synthetic antibody preparations made up of human antibody protein sequences that maintain antigen binding region present on heterologous antibody and have longer half-lives [55].

7. Adoptive immunotherapy

Adoptive immunotherapy is the extraction and ex-vivo activation of native immune cells of patients followed by intravenous injection into human body to target infections [56]. It is an effective and efficient technique to build up immunity against viruses. T cells are depleted and progressively lose their function during cancer and chronic infections therefore, effective T cell responses can curb tumors and viral infections hence, techniques that either provide functional T cells based on adoptive immunotherapy or restore endogenous immune responses are being explored. CD8+T cells play key role in cancer and viral infections whereas but their function is supported by CD4+ T cells in addition to this, CD4+ T cells trigger optimal B-cell responses and boost up innate immunity. Therefore, adoptive immunoglobulin strategies based on exploitation of CD4+ T cells alone or in association with CD8+T cells, are effective against cancer and chronic infections [57,58]. T-cell immunotherapy can be ameliorated by following strategies:

Culture conditions for *ex vivo* T-cell expansion to produce T cells with desirable phenotype. Novel types of antigen presenting cells and cytokine combinations are able enough to produce functional T cells of peculiar phenotypes.

i) T cells are genetically modified for generation of T cells with high affinity towards desired antigen (by introducing chimeric antigen receptor along with specific T-cell receptor) or with specific characters (for example, T cells deficient in HIV co-receptors can be produced in HIV-infected patients).

ii) Adoptive immunotherapy can be combined with other immunotherapies to reconstitute *in vivo* function as well as expansion of the transferred T cells, to control inhibitory signals and to prevent exhaustion of the transferred T cells [57].

A study demonstrated that virus specific T cells produced in response to antigen presenting cells along with unmanipulated T cells are helpful in treatment of viral infections such as cytomegalovirus, HIV, Ebola virus and adenoviruses [59,60]. It is anticipated that adoptive immunotherapies that impede inhibitory pathways (such as PD-1 pathway) in association with adoptive T-cell therapy will lead to the long-term maintenance of effective immune responses to eliminate cancer and chronic infections [57].

8. Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV-1) is lentiretrovirus that causes acquired immuno deficiency syndrome (AIDS) and destroys immune system by interacting with variety of different body cells. This virus is transmitted vertically, sexually and through blood. HIV infection is associated with progressive exhaustion of CD4+ T cells due to their enhanced destruction and diminished production [61]. With CD4+ T cells, HIV replication leads to cell death, syncytium formation and persistent infection thus creating reservoirs for the virus in many cells and tissues [58]. About 78 million people

have suffered from HIV virus and 39 million have died since the beginning of this epidemic [62]. It is a major cause of morbidity and mortality in developing world. In 2002, the global prevalence of HIV was 31 million which was increased to 35·3 million in 2012. About 1.5 million deaths were reported in 2013 but the incidence is now decreasing due to expanded access to antiretroviral therapy [61]. Since last many years patients of HIV have been treated with cART (combined antiretroviral therapy) i.e., use of several antiretroviral drugs which suppress the replication of virus but virus is not completely eradicated therefore, trends are now shifting towards practice of immune based treatments. Other limitations associated with combined antiretroviral therapy are transmission of drug resistant HIV strains, emergence of multidrug resistance and cART does not always restore normal CD4+ T cell counts [63].

9. Immuno-based treatment of HIV

More than 30 million people are suffering from HIV type-1, initially this condition was considered lethal whereas, the combination of immune-based therapeutics results in longer life span in infected persons, decline viremia, limit HIV replication, inhibit disease progression, and trigger cytotoxic T lymphocyte mediated clearance of infected cells. Human immunodeficiency virus-1 impedes activity of CD4+ T lymphocytes leading to exhaustion of these cells and progressive immunodeficiency. Within initial three months of infection, high concentration of antibodies is developed against different viral proteins in HIV-1 infected patients and recent studies unfolded that antibodies, CD8+ T cell activity, and CD4+ helper responses lead to control of HIV virus. There are several different immunotherapeutic approaches against HIV infection that are currently being studied [64,65].

10. Vaccine development

There are several novel strategies that are being explored to discover preventive and therapeutic vaccines for prevention of HIV-1 infection. Current therapeutic vaccine approaches include administration of single or multiple antigens of HIV as DNA, autologous dendritic cells, inactivated whole HIV particle depleted of gp120 and viral vectors like poxviruses (ALVAC-HIV, vCP1433, vCP1452, fowlpox, MVA) and adenovirus (Ad5) [66]. To date, RV144 is the only vaccine that has shown some degree of efficacy [67]. Modest efficacy against HIV acquisition was observed in Thai Phase III clinical trial of RV144. Antibody responses against HIV-1 gp120 envelope (Env) were observed in plasma obtained from HIV-1-uninfected individuals administered with ALVAC-HIV (vCP1521) prime and AIDSVAX B/E boost. Peptide microarray analysis from six HIV-1 subtypes and group M consensus exhibited that vaccination triggered antibody responses to the V2 loop or second variable of gp120 of multiple subtypes. V2 responses were further evaluated by ELISA and surface plasmon resonance using linear and cyclic V2 loop peptides. Antibody responses against cyclic V2 at 2 weeks postimmunization were noticed in about 97% of vaccinated individuals. RV144 vaccination triggered antibodies that targeted a region of the second loop consisting of conserved epitopes. Early transmission events of HIV-1 involve second loop interactions and supports the evidence that in RV144 anti-V2 antibodies may contribute to viral inhibition [68].

11. Preventive Vaccines

11.1. Initial HIV vaccines using recombinant envelope proteins

During 1980s and 1990s preventative vaccine directed against HIV-1 infection was developed using 20 different recombinant envelope proteins belonging to different strains, anticipating the production of neutralizing antibodies for HIV. Two recombinant gp120 vaccines bivalent subtype B/E and bivalent subtype B/B were tested in phase 3 but none of these two vaccines proved efficacious [69]. Both vaccines triggered production of neutralizing and binding antibodies, but neutralizing antibodies were restricted to the strain used in the vaccine [70], the narrow neutralizing response is due to deletion and auto-reactivity of precursor B cells which induce the development of broadly reactive neutralizing antibodies [71]. Post hoc examination exhibited that individuals carrying high concentration of binding and blocking antibodies may develop considerable level of protection from acquisition [72].

11.2. Ad5 vector HIV vaccine

Non-efficacy of recombinant envelope vaccines shifted the focus towards development of immune response having cross-strain breadth. Early viral control is markedly influenced by breadth and magnitude of early CD8+ T-cells therefore, CTL-based vaccines or cytotoxic T lymphocyte vaccines were developed primarily to target post-infection viremia, and prevention of HIV acquisition was anticipated. Cytotoxic T lymphocyte responses against HIV proteins are induced by inserting HIV genes into recombinant viral vectors and shuttling these genes into Class I antigen-presenting pathway [73].

Replication defective recombinant adenovirus 5 vector with HIV-1 clade B nef/gag/pol inserts was the first T-cell vaccine that underwent clinical efficacy trials and exhibited significant increase in CD8+ T cell but these CD8+ immune responses targeted the variable but not the conserved regions of virus. Therefore, an issue of immune T cell breadth same as neutralizing antibody breadth was still there [74]. However, the tolerability, safety, and efficacy of conserved region Ad5 based vaccine has been registered under ClinicalTrials.gov NCT01151319. Researchers designed distinctive T-cell immunogen HIVconsv different from functionally conserved regions of the HIV-1 proteome that encountered body's immunity using heterologous prime-boost combination of non-replicating poxvirus and non-replicating simian (chimpanzee) adenovirus ChAdV-63, modified vaccinia virus Ankara, and plasmid DNA (ChAd63 vaccine). Administration of ChAdV63.HIVconsv combined with other vaccines elicited high frequencies of HIV-1-specific T cells capable of inhibiting HIV-1 replication and exhibited good tolerability and safety together with high immunogenicity [75].

11.3. Adenovirus 5 vector with DNA

This is another T-cell based approach in which adenovirus vector 5 is primed with DNA. To overcome T-cell and antibody breadth problem, different strains belonging to all major HIV-1 clade were used. The DNA vaccine (0, 1, 2 months) was a blend of six plasmids expressing env proteins from clades A, B, and C whereas, gag, pol, and nef from clade B followed by an adenovirus 5 vector boost during (6th month) leading to expression of env glycoproteins from clades A, B, and C along with gag-pol fusion protein from clade B [76]. Clinical study demonstrated CD4+ T cells response towards HIV-1 envelope, neutralizing antibodies and triggered antibodies towards gp41 and HIV gp120 [77].

11.4. Pox-vector and protein vaccine combination

RV144 (2004–2009) provided sound proof of vaccine reducing HIV acquisition exhibiting 60.5% efficacy at 1 year followed by 31.2% after 3.5 years with ALVAC-HIV (vCP1521) that is canarypox vector prime which expresses clade E env along with clade B gag and pro (0, 1, 3, 6 months) and protein boosts in association of alum adjuvant, AIDS-VAX1 clades B/E gp120 (3, 6 months). V2

region of HIV-1 is susceptible to be targeted by protective antibodies associated with vaccine efficacy of the RV144 regimen [78].

11.5. Building on RV144

Immediately after demonstration of RV144 results, pox protein public-private partnership (P5) collaborated to discover pox-protein regimen for sub-Saharan Africa. The immunologic response observed in people of South Africa was similar to responses observed in Thailand.

ALVAC vector with clade C env insert was designed by P5 to construct a bivalent clade C recombinant gp120. Currently, these vaccines with two adjuvants ASO1B and MF591 are under clinical trials in South African region to boost immunity. The results of HVTN 100, phase 1/2 study, ALVAC/gp120/ are pending and scheduled for efficacy evaluation trial in late 2016 [79].

Efficacy trials of six candidate vaccines VAX004, VAX003, Step, Phambili, RV144, and HVTN505 proved RV144 as the only HIV-1 vaccine trial that is effective against HIV acquisition. The antibodies are produced in response to V1V2 region of gp120 specifically. IgG1 and IgG3 subclass mediates ADCC (antibody-dependent cell-mediated cytotoxicity) and accord protection against HIV-1 acquisition [80–82].

11.6. Therapeutic vaccines

Therapeutic vaccines are developed to ameliorate immune response in order to ameliorate HIV infection. To date, there is not even single therapeutic HIV vaccine that has been approved by FDA. Instead, therapeutic vaccines directed against HIV infections are under clinical trials to evaluate the efficacy.

11.7. Tat therapeutic HIV vaccine

The Italian National AIDS Center is developing a vaccine directed against HIV-1 Tat (transactivator of transcription) protein that is a virulence factor and plays a significant role in HIV gene expression, progression and transmission of disease. Tat-specific antibodies may prevent HIV acquisition and transmission. Phase 1 study has proved Tat vaccination as immunogenic and safe. Phase II trial proposed that Tat had induced restoration of CD4+ and CD8+ T cell numbers, and memory cells. Considerable reduction in HIV-1 load in blood was observed in response to Tat vaccine. Phase 3 trials are being studied currently. Forty-eight long-term HIV-1 infected people with suppressed viral loads because of antiretroviral therapy (cART) were injected with Tat Oyi vaccine preparation. The clinical outcome of this phase I/IIa trial showed decrease in the extent of HIV RNA rebound after cART interruption. This study shows that Tat vaccine protects and activates HIV-infected cell in vitro [83]. Combined treatment of Tat Oyi vaccine and cART has found to increase CD4+ T-cell numbers. Phase III studies that has been conducted in South Africa (Trial registration ClinicalTrials.gov NCT01513135) unfolded that Tat vaccination induces cross-clade neutralizing anti-Tat antibodies in patients with different infecting viruses and belonging to different genetic backgrounds [84].

11.8. Adoptive T cell therapy

Adoptive T cell therapy is transfer of CD4+, CD8+ or autologous antigen specific T lymphocyte cells to HIV infected patients [85]. HIV specific CTL (cytotoxic T lymphocyte) response plays an important role in control of HIV infection. Researchers are finding novel approaches to ameliorate HIV-specific cytotoxic T lymphocyte response in an attempt to achieve long-term viral clearance. A research study based on hematopoietic stem progenitor cell (HSPC) approach reported the use of protective CAR (chimeric antigen receptor) to engineer immunity in HIV infected patients. CAR-modified HSPCs cells (Chimeric antigen receptor modified hematopoietic stem progenitor cell) differentiate into functional T cells along with natural killer cells which were resistant to HIV infection leading to cessation of HIV replication. Therefore, it has been proved that stem cell-based gene therapy with chimeric antigen receptor (CAR) is an effective and feasible strategy to treat chronic HIV infection [86].

Modification of human HSPCs (hematopoietic stem progenitor cells) with an HIV-specific CD4ζ CAR can differentiate HIV specific T cells and cells of other lineages that are able to decrease viral loads in vivo. This HSPC-based approach that use CAR has been demonstrated safe and feasible in mice whereas, human based multiple HSPC-based gene therapy that aims at protecting cells from HIV infection are currently under trials [ClinicalTrials.gov Identifiers: NCT01177059, NCT00569985, NCT01961063, NCT01734850]. The potential toxicities and adverse events related to the use of the CD4ζ CAR have not been studied yet therefore, future research must address this subject [86]. The special features present in CD4-10-17b CAR have made it a suitable candidate for genetic modification of T cells from HIV-1-infected individuals. The broad reactivity to genetically diverse HIV-1 isolates, minimal immunogenic potential, freedom from HIV entry receptor activity, and high potency of virus suppression all speak to the value of this CAR design [87].

11.9. Cytokine therapy

HIV infection is associated with cytokine production. Such cytokines influence viral replication and regulate immune system thus, contribute towards the progression of acquired immunodeficiency syndrome. Several cytokines involved in immune regulation exert opposite effects, like some stimulate cellular immune function and others induce production of antibodies. AIDS is characterized by diverse disturbances and imbalances in the regulation of cytokine expression. Different cytokines affect expression and replication of HIV differently [88]. Production of T-helper type 1 (Th1) cytokines e.g., antiviral interferon- γ, interleukin-2 (IL-2) are decreased whereas T-helper type 2 (Th2) cytokines e.g., interleukin-1, IL4, IL6, IL8, IL10, tumor necrosis factor are increased. IFN-α, IFN-β and IL-16, which inhibit HIV-1 replication in T cells and MDM (monocyte derived macrophages), and IL-10 and IL-13, which inhibit HIV-1 in monocyte derived macrophage act as HIV-suppressor cytokines. TNF-α, TNF-p, IL-1 and IL-6, which trigger HIV-1 replication in MDM and T cells, macrophage-colony stimulating factor, which stimulates HIV-1 in MDM and IL2, IL-7 and IL-15 which provoke HIV-1 in T cells act as HIV-inductive cytokines. IFN-γ, IL-4 and granulocyte-macrophage colony-stimulating factor act as bifunctional cytokines because of both inhibitory and stimulatory impacts on HIV-1 infection [89–91]. Therefore, cytokine therapy may suggest new ways to prevent progression to AIDS. HIV-1 patients experience significant decline in CD4$^+$ T cells but IL-2 therapy has been shown to improve CD4$^+$ counts [92] the findings of this study were in contrast to previous studies which suggested that IL-2 had no supplementary benefits in HIV-1 patients [93]. Levy et al. have also demonstrated considerable rise in CD4 cells in HIV-1 infected individuals administered with IL-2 in combination with highly active antiretroviral therapy. Naïve and memory CD4 cells count, natural killer cells, lymphocyte expression of CD25 and CD28 was higher in IL-2 group compared to controls [94]. Administration of IL-7 in HIV-1 infected individuals led to expansion of CD4$^+$, CD8$^+$ T cells, and IL-7 receptor alpha chain CD127$^+$. rhIL-7 amplify the numbers of naïve and central memory T cells [95]. Marked decrease in the production of virus-induced interferon (IFN)-α [96] and interferon-α producing cells (IPCs) has been observed in HIV patients. This study suggested

a direct link of interferon-α producing cells (IPCs) with control of HIV replication [97]. Phase II/III study showed lower rate of HIV progression in 40 of 122 IFN-α vaccine recipients [98]. Another study involving 34 patients of asymptomatic HIV infection administered with IFN-α showed decrease in HIV load. Of the 32 study patients followed after study (range, 5–33 months), no patients in the IFN-α group developed an AIDS compared with 5 patients in the placebo group [99].

11.10. Monoclonal antibodies

Several researchers have characterized and isolated neutralizing antibodies to target HIV-1 thus, introducing new ways in passive immunization. Vaccine trials in animal models has demonstrated that HIV-1 neutralizing antibodies are potent enough to suppress HIV infection [100]. VRC01 is human monoclonal antibody which targets CD4 binding site of human immunodeficiency virus gp120 [101]. Likewise, other monoclonal antibodies such as PGT121 [102], 3BNC117 [103], R1C7, A4F6, R5C4, R5F6 [104] CCR5 [103] and 10-1074 [105] have been proved effective in suppression of HIV infection in animal models. Monoclonal antibody A32 acts as a potent mediator of ADCC (antibody dependent cellular toxicity) activity and plays an important role in preventing HIV acquisition [106]. Accumulating evidences suggest that administration of monoclonal antibodies to humanized mice resulted in suppression of viral load. Likewise, injection of cocktail of HIV-1-specific monoclonal antibodies, as well as the single glycan-dependent monoclonal antibody PGT121 caused dramatic decline of plasma viraemia in rhesus monkey chronically infected with simian-human-immuno-deficiency virus [107]. Human monoclonal antibody F105 has successfully passed through phase I clinical trials (ClinicalTrials.gov Identifier: NCT00001105). F105 binds with CD4 binding site of HIV-1 gp120 and neutralizes laboratory and clinical HIV isolates [108]. Recently another antibody 3BNC117 has been reported to boost up humoral immunity against HIV-1 in animals and humans [109]. Human based follow up clinical studies and the complete evaluation of therapeutic potential of these monoclonal antibodies is currently under way.

11.11. Dendritic cell immunotherapy

Number of dendritic cells in blood reduces in case of HIV-1 infection and this can be reversed by dendritic cell therapy [110]. Several evidences suggest that development of dendritic cell based vaccines is a promising approach against HIV-1 infection. A significant decrease in viral load had been observed when HIV-1 infected individuals were treated with dendritic cell based vaccination [111]. Dendritic cell based therapy controls HIV replication by eliciting T-cell response [112]. Therefore, therapeutic vaccination based on monocyte-derived dendritic cells is feasible, safe and effective to control HIV infection [113].

11.12. Gc protein derived macrophage activating factor

Vitamin D3 binding protein or serum Gc protein acts as precursor of principal macrophage activating factor (MAF). MAF precursor activity or serum Gc protein is either lost or diminished in HIV infected individuals because of deglycosylation of Gc protein by alpha-N-acetylgalactosaminidase produced by HIV-infected cells. Thus, in HIV infected patients macrophages with deglycosylated Gc protein are inactivated and cause immunsuppression. Infusion of GcMAF into HIV infected individuals is an effective immunization strategy because it leads to complete elimination of virus [114].

11.13. Human papillomaviruses (HPVs)

Human papillomaviruses (HPVs) are DNA viruses which cause human neoplasias like warts and cancers. About 40 out of more than 100 human papillomavirus types infect anogenital region HPV infection is most prevalent sexually transmitted infection [115]. The most common types worldwide are HPV-16, HPV-18, HPV-52, HPV-31, HPV-45 and HPV-58 [116,117]. HPV can cause number of cancers such as cervical cancer [118], oropharyngeal cancer, anal cancer, vulval, vaginal and penile cancer [119]. There is no drug available that directly eliminates HPV but treatments are available for HPV associated health problems like gential warts, cervical change, cervical cancer etc. Scientists are looking for new opportunities to develop immune-based treatments to reduce the HPV associated cancer upsurge.

11.14. Immuno-based treatment of HPV

Besides chemotherapy, surgery or radiation, immunotherapeutic approaches and vaccines are an exciting addition to control precancerous diseases and cancer. Clinical and epidemiological data reveal that induction of T-cell responses correlates with clearance of HPV-associated lesions, induction of Th1- biased immune responses are known to be crucial for immunotherapy, HPV regulatory proteins E6 and E7 that are targeted as viral antigens and development of more potent Th-1 directed vaccine platform form the basis of HPV immune-based treatment especially efficacious vaccine development.

11.15. Vaccination

Viruses like particles (VLP) of HPV are used as vaccine directed against HPV associated cancer by activating natural killer cells which in association with dendritic cells induce immune response against viral infections and tumors. In the presence of HPV-VLP, natural killer cells increase maturation of dendritic cells by upregulating CD86, HLA-DR and IL-12p70. An increase in secretion of IFN- γ and cytotoxic activity against HPV ameliorates function of natural killer cell. Therefore, virus-like particle vaccine has been proved as best candidate to control HPV-associated malignancies [120]. Food and drug administration has approved three prophylactic vaccines Gardasil (quadrivalent HPV), Gardasil-9, and Cervarix, which are highly immunogenic and reduce the risk of HPV infections [121]. Vaccines formulation is based on use of virus-like particles originated from L1 proteins that resemble HPV but cannot multiply due to absence of genetic material [122]. HPV vaccines are potent enough to eradicate malignant tumors and pre-existing lesions by inducing cellular immunity directed against HPV-infected cells which express early viral proteins like E6 and E7 [123]. The vaccines raise the titer of serum immunoglobulin G antibody directed against different HPV types, secreted in cervico-vaginal region or discharged from micro-abrasions in epithelium directed against different HPV types [124].

11.16. Gardasil

Gardasil® is human papillomavirus quadrivalent recombinant vaccine composed of virus-like particles obtained from L1 capsid proteins belonging to HPV type 6, 11, 16 and 18. The vaccine was manufactured by Merck & Co and approved in 2006. This vaccine is effective against genital warts and precancerous lesions, vaginal pre-cancer and cancer, vulvar and cervical cancer in young women and adolescents. Individuals are treated with intramascular injection of three dose regimen. This vaccine proved highly immunogenic instigating persistent and high-HPV antibody titer. Phase III

trials has proved the efficacy of Gardasil in young women and male and female adolescents.

11.17. Gardasil 9

Gardasil 9 is a second generation of Merck's cervical cancer vaccine that has been approved by food and drug administration that will protect against anal, vaginal, and cervical cancers. The vaccine is effective against cancers associated with HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts associated with HPV types 6 and 11 [125]. A 3rd generation vaccine is still needed to achieve complete protection against all HPV types which cause cervical cancers [126,127].

11.18. Cervarix

Cervarix™ manufactured by GlaxoSmithKline is bivalent L1 virus-like particle vaccine effective against HPV types 16 and 18 both responsible for 70% of all cervical cancers [128]. This vaccine was developed by using insect cells infected with recombinant baculovirus and an adjuvant ASO4 consisting of alum combined with a TLR4 ligand, MPL (3-Odesacyl-4′-monophosphoryl lipid A). The efficacy trials have demonstrated that vaccines are immunogenic, 90.4% efficacious and increase the neutralizing antibody titer thus providing protection against CIN2 (cervical intraepithelial neoplasia) lesions and cancers caused by HPV16 and HPV18 [129].

11.19. Dendritic cell based vaccine

Dendritic cell based vaccination is another novel therapeutic paradigm to cure HPV- associated cancers. Dendritic cells are recognized as potent antigen presenting cells and lead to induction of T cell responses in vitro and in vivo providing new ways to treat several human malignancies. Autologous dendritic cell loaded with HPV16/18 E7 proteins may stimulate T and B cell responses in patients unresponsive to standard treatments. DC based vaccine is efficacious in only those cancer patients who are immunocompetent or at early stages of disease and have low tumor burden [130,131].

11.20. Other therapeutic vaccines

Several other therapeutic cancer vaccines mainly targeting HPV oncoproteins E6 and E7 are under clinical trials that stimulate T cell immune response against tumor specific antigen, thereby triggering the immunity to target cancer cells such as ADXS11-001 vaccine directed against HPV E7 protein to cure anal and cervical cancer [132], DNA construct INO-9012 that triggers production of interleukins to treat cervical cancer [133], VGX-3100 against HPV type 16 and 18 [134], TVGV-1 vaccine against HPV associated cervical pre-cancer, pNGVL4a/E7 (Detox)/HSP70 DNA vaccine provide protection against HPV-16 cervical intraepithelial neoplasia (Table 2) [135].

11.21. Immune modulators

Immunomodulators include both immunosuppressive and immunostimulatory agents that trigger secretion of cytokines from macrophages (IL-12, IFN-12, TNF- α) leading to increased Th1 response, antibody production in response to improved antigen presentation by dendritic cells, and cell-mediated immunity which is being used clinically to cure viral infections like herpes simplex virus, human papillomavirus and cancerous lesions in immunocompromised individuals [136]. PD-1 antibodies nivolumab (Opdivo®) and pembrolizumab (Keytruda®) against vaginal, vulvar and cervical cancer [137,138], anti-PD-L1 antibody durvalumab (MEDI4736) [139] in combination with tremelimumab against six cancer including cervical cancer and anti-CTLA-4 antibody ipilimumab (Yervoy®) [140] against cervical cancer are under clinical trials.

11.22. Monoclonal antibodies development against HPV associated cancer

The development of monoclonal antibodies is an emerging therapeutic strategy to cure cancer and viral infections because of low toxicity, high specificity and activation of immune system. A study elucidated that monoclonal antibodies 1G10.1C and 2C5.1C, AE3 and AG7 may form the basis of effective development of immunotherapy against HPV infections [141,142]. Several other monoclonal antibodies are under clinical trials such as bevacizumab (Avastin®) which is humanized anti–vascular endothelial growth factor monoclonal antibody against cervical and ovarian cancer [143,144], HuMax®-TF-ADC [145] and IMMU-132 are antibody drug conjugates which are being studied in phase I/II trial in an attempt to cure advanced cancers including cervical cancers [146].

11.23. Cytokines and adoptive T-cell therapy

Immunotherapeutic treatment based on infusion of cytokines and insertion of immunostimulatory genes in the tumor cell

Table 2
Different forms of HPV therapeutic vaccines that are under clinical trials.

Recent Therapeutic HPV Vaccine Clinical Trials Using Different Forms of Vaccines	
Bacterial vector based	Lm-LLoE7 (ADXS1 1–001; ADXSHPV)
Viral vector based	TG4001, MVA E2
Protein/peptide based	HPV16- SLP, GL- 0810, TA-CIN, TA-CIN + TAHPV
Nucleotide based	pNGVL 4asig/E7(d etox)/HSP70 + TA-HPV, GX- 188E, VGX- 3100,
Whole cell based	DC + KLH, DC
Currently Ongoing Therapeutic HPV Vaccine Clinical Trials for Different HPV associated Diseases	
Persistent HPV Infection and Low-Grade Squamous Intraepithelial Lesion	PDS0101, ProCervix,
Cervical Intraepithelial Neoplasia (CIN)/High-Grade Squamous Intraepithelial Lesion	GX-188E, pNGVL4asig/E7(detox)/ HSP70 + TA-HPV, pNGVL4aCRT/E7(detox), Pepcan + Candin, TVGV-1 + GPI-0100
Anal Intraepithelial Neoplasia (AIN)	ISA101 (SLP-HPV-01; HPV16-SLP)
HPV-Associated Incurable Solid Tumors	ISA101 (SLP-HPV-01; HPV16-SLP)
Head and Neck Cancer	ADXS11-001 (Lm-LLo-E7), INO-3112 (VGX-3100 + INO-9012)
Cervical Cancer	INO-3112 (VGX-3100 + INO-9012), ADXS11-001 (Lm-LLo-E7), TA-CIN + GPI-0100, ISA101 (SLP-HPV-01; HPV16-SLP)

LL-LLOE7 (*Listeria monocytogenes* – listeriolysin O envelope 7); TG (transgene); MVA (*Modified Vaccinia Ankara*); **SLP** (synthetic long peptide); GL (glycoprotein); TA-CIN (*Tissue Antigen – Cervical Intraepithelial Neoplasia*); TAHPV (Tissue antigen Human Papilloma virus); NGVL (National Gene Vector Laboratory); KLH (*Keyhole limpet hemocyanin*); **GPI** (Glycosylphosphatidylinositols); INO (inovio); AGX (Agenix); HSP (heat shock protein; ADXS (advaxis); DC (dendritic cells).

genome followed by cytokine based vaccination represents novel approach for therapy of HPV associated cancers. Researchers have recently proposed that tumor cells caused by HPV-16 can be genetically modified with DNA encoding immunostimulatory molecules specifically cytokines (IL-2, IL-12, GM-CSF) used for vaccination, and impede tumor growth. In order to ameliorate the antigen presentation in tumor bearing patients, dendritic cell-based vaccines loaded with hybrids of the dendritic and tumor cells or HPV 16 E6/E7 DNA have also been successfully employed. These encouraging approaches are still being studied [147]. Another study suggested that targeting HPV E6 and E7 oncoprotein with adoptive T-cell therapy could be an efficacious strategy against HPV-related cancers such as vagina, penis, vulva, cervical, anal, and oropharynx [148].

11.24. Herpes simplex viruses (HSV)

Herpes simplex viruses are enveloped, double stranded DNA viruses having two serotypes: HSV-1 infecting orofacial region and HSV-2 in the genital region [149]. Infections caused by herpes simplex virus are prevalent worldwide. Significant rate of neonatal morbidity and mortality is attributed to herpes labialis caused by HSV-1 [150] and herpes vulvovaginitis caused by HSV-2 [151]. Incidence rate of HSV infections in neonates is 1 per 3000–20,000 live births [152]. HSV cause number of infections such as labialis, conjunctivitis/keratitis, gingivostomatitis, herpetic whitlow, eczema herpeticum, herpes gladiatorum, encephalitis, balanitis, urethritis, vulvovaginitis, and external dysuria [153]. HSV infections can be treated with antiviral agents like acyclovir [154] but drug therapy is associated with toxic side effects, emergence of drug resistance strains, narrow spectrum, and drug treatment is effective only during initial stages of infection [155]. People infected with HSV-1 infection are at lesser risk of acquiring it again but they can still be infected with HSV-2 genital infection. HSV-2 also increases the risk of HIV infection [156].

11.25. Immuno-based treatment of HSV

The immunobiology of herpes simplex virus associated infections is complicated. Both humoral and cell mediated immunity are of paramount importance in immunologic responses against HSV infections, due to plethora of evolutionary changes virus evades the immune system, maintains the latency and cause intermittent reactivation of disease. These facts limit the utility of passive immunization to control HSV infections. Therefore, the subject of development of immunotherapeutic strategies against HSV infections is still being studied and need more research in the coming episodes.

11.26. Vaccination

The development of efficacious therapeutic and prophylactic vaccine against herpes virus infections has proven complicated due to complex life cycle (latency) of herpes simplex and poorly understood mechanism of immune control at primary and recurrent stage of disease. Previous studies have described that activated innate immunity and virus-specific T helper 1 (Th1) cytokines (like gamma interferon) prevent recurrent disease. Whereas, regulatory (suppressor) T cells and Th2 cytokines (e.g., interleukin-10 [IL-10]) down regulate this immune profile thereby, allowing the establishment of recurrent disease and replication of reactivated virus. Therefore, an efficacious vaccine must stimulate Th1 immunity and be defective in Th2 cytokine production especially IL-10 [157]. Gylcoprotiens gD and gB activate CD4+ T cells and ICP27 activate CD8+ T cells [158]. These facts form the basis of development of herpes simplex virus type 2 (HSV-2) glycoprotein-D-subunit vaccine with adjuvant alum and 3-O-deacylated-monophosphoryl lipid A which induce helper T cells Th1. The results of clinical trials phase I/II exhibited that glycoprotein D vaccine was efficacious against genital herpes in HSV-1 and HSV-2 sero-negative females whereas, not effective in men and those women who were HSV-1 sero-positive and HSV-2 sero-neagtive [159]. Another study suggested secreted glycoprotein G of HSV-2 as highly efficacious novel agent for development of prophylactic vaccine to control HSV-2 associated infections [160]. In an experiment carried out in guinea pigs, recombinant HSV-1 glycoproteins gB and gD formulated with an adjuvant were used as immunotherapeutic agents in order to control recurrent genital herpes and resulting increase in antibody titer supported the fact that gBgD immunotherapy could be effective against HSV associated genital infections [161].

An attenuated virus R7020 has been designed and provided immunogenicity against infections caused by HSV-1 and HSV-2 in mice and guinea pigs [162]. However, the area of HSV vaccine development needs further research.

11.27. Monoclonal antibodies

Though the mechanism of antibody treatment in HSV-1 or HSV-2 infections has not completely elucidated but passive immunization via antibodies is emerging as promising technology for controlling HSV infections however, experimental study in humans have yet to be performed [152]. Several evidences have suggested that passively transferred serum hyperimmune may effectively inhibit HSV-1 and HSV-2 spread and significantly reduce the severity of infection caused by these viruses [163]. In vitro studies have defined several mechanisms, including antibody-dependent cell-mediated cytotoxicity whereby antibody may participate in the destruction of virus infected cells [164].

Monoclonal antibodies HC1 and HD1 directed against HSV-1 glycoproteins gC and gD had been tested because of their ability to passively immunize mice in order to target acute virus-induced neurological disease and the study later on revealed that passive immunization of monoclonal antibody in mouse decreased the severity of disease and pathogen spread [165]. Likewise, nine other monoclonal antibodies aiming against HPS glycoproteins gB, gC, gD, gE had also been evaluated in mice and lead to blockage of HSV virus dissemination [166].

Monoclonal antibody hu2c holds promise for future development as a novel approach for the treatment of HSV infections. Humanized monoclonal antibody mAb hu2c were administered in mice and resulted in inhibition of cell-to-cell viral transmission a key mechanism by which HSV-1/2 escapes humoral immune surveillance. mAb hu2c was found to neutralize HSV fully independent of complement or/and recruit immune effector cell in a highly efficient manner [167,168]. These features guarantee the clinical development of mAb hu2c for treatment of HSV infections in drug-resistant and immunocompromised patients.

11.28. Adoptive immunotherapy

Components of innate immunity such as interferon, natural killer cells, and macrophages provide protection against HSV infections [169] but, T cells specifically CTLs (CD8+ cytotoxic T cells) are dominant determinants of protective immunity [170].

Fusion protein tgD-IL-2 consisting of human interleukin-2 and truncated HSV-1 glycoprotein D has been proved as efficacious immunotherapeutic agent that can elicit immune system against HSV associated genital infection [171]. Another experimental protocol demonstrated the role of dendritic cells in generation of protective immunity [172,173].

Adoptive transfer of virus-specific cytotoxic T lymphocytes has proven efficacious and safe at preventing and controlling viral infections, but there is room to explore expansion and activation protocols utilized to generate virus-specific CTL (cytotoxic T lymphocyte) lines in minimum possible time [174].

11.29. Future perspectives

Successful outcomes of CAR- T cells provide strong hope for control of infectious diseases. It is anticipated that immunizations with promising clinical outcomes will be available for myriad of infectious diseases and cancers. Development of polyclonal and monoclonal antibody therapies for severe neglected tropical widespread diseases is currently under investigation. Clinical data and pre-clinical studies highlight the potential of immunotherapies against HPV, HSV, and HIV thus, providing baseline data for future research.

12. Conclusion

Infectious diseases are major cause of morbidity and mortality thus, posing serious threats to lives. Drug therapy is associated with serious consequences such as emergence of drug-resistant strains and toxic side-effects. Therefore, trends are now shifting towards immune-based therapies that reawaken and harness the power of immune system to provide long-lasting protection. Therapeutic vaccines, adoptive T cell therapy, gm-csf therapy, cytokine therapy and monoclonal antibodies are being explored and getting popular for treatment of HIV and HPV associated infections in immunocompromised hosts. Although, the specific immunization strategy for HSV has not yet been developed but the overall progress made by researchers has increased understanding towards complexity of infections caused by HSV-1 and HSV-2 and described lot of issues that can now be explored and addressed.

Conflict of interest

The authors declared that they have no conflict of interest.

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