Pooja Jain
Lishomwa C. Ndhlovu *Editors*

Advanced Concepts in Human Immunology: Prospects for Disease Control

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The Chief Editor, Professor Pooja Jain, dedicates this book to her parents (Mr. Deshraj Jain and Mrs. Kiran Jain) from India as well as family/friends in the United States who have always supported and motivated her to work hard and maintain enthusiasm and balance toward her career and personal life!

The Coeditor, Professor Lishomwa C. Ndhlovu, dedicates this book to the family and circle of friends who impart indelible enlightening experiences to his life explorations and for whom he has indescribable gratitude and hopes they enjoy being a part of the readership!

Foreword

Immunological disorders afflict a considerable number of people across the world. A majority of immunological findings have been derived from the animal studies primarily rodents that comprise a majority of available textbooks on this topic. This book attempts to compile information derived primarily from human studies while keeping important research findings irrespective of the source. This text covers a wide range of topics from host-pathogen interactions to the evolution of the host immune response against cancer, allergic and autoimmune diseases, as well as neuroinflammatory disorders. The readers are provided with the latest information with clinical data related to these topics in addition to an in-depth discussion on the immune checkpoint inhibitors in the context of cancer, infection, and neuroinflammation. A detailed account on the immunoproteomics technology in cancer and infectious diseases represents a unique aspect of this book so as clinical perspectives on the polycystic ovarian syndrome (PCOS), which is rarely covered in the scientific literature.

Preface

This book covers a range of topics related to human immunology such as host-virus interactions, innate and adaptive immunity to allergens and self-antigens, current status of immune checkpoint inhibitors in cancer and infection as well as neuroinflammation, chimeric antigen receptor (CAR) T-cell therapy, and neuroprotective immunity against diseases of the central nervous system. In addition, the power of immunoproteomics technology has been highlighted for immunotherapy, and clinical perspectives on the polycystic ovarian syndrome (PCOS) have been provided as unique aspects of this book. The first chapter of the book covers health burden, viral pathogenesis, host immune response, current treatment, and status of future trends in research on antiviral immunoprophylaxis and pharmacotherapy. This chapter also provides a detailed account on coronaviruses with the last-minute addition on COVID-19 that has shaken global health causing worldwide mortality at an unprecedented rate. When the pandemic hit, this book was at the production state; thus, we felt obliged to include all plausible information pertaining to the intended audience.

The second chapter covers applications of immunoproteomic technology in peptide-based T-cell immunotherapy against cancer, infections, and autoimmune disease, while third and fourth chapters focus on the innate and adaptive immunity against allergic and autoimmune diseases. The cellular and molecular mechanisms underlying the immunopathogenesis of allergic eye disease are highlighted. The pharmacotherapy and immunotherapy of allergic eye disease have been discussed in detail along with the emerging role of microbiota in allergy. Autoimmune disease, in which adaptive immune system causes considerable disruption of normal cells and tissue due to loss of tolerance to self-antigens as depicted by type 1 diabetes, is discussed in detail in this textbook. Immune cells and molecules that play a role in the pathogenesis of type 1 diabetes with particular focus on loss of immune tolerance to beta cells of the pancreas and the subsequent destruction of these cells are also highlighted.

The fifth chapter highlights mechanisms of dendritic cell (DC)-regulated T-cell immunity and tolerance against acute myeloid leukemia (AML), a common hematologic malignancy in adult. Immunotherapies such as immune checkpoint inhibi-

tors and DC-based vaccination, which are potentially effective for treating and preventing AML, have been discussed in this chapter. Negative immune checkpoint receptors maintain homeostasis; however, an imbalance between activation and inhibition that biases toward overexpression of negative checkpoint regulators (NCR) results in impairment of T-cell-mediated immunity. Thus, sixth chapter discusses novel immunotherapies that inhibit NCR and reverse immune perturbation in these diseases. Along the same line, seventh chapter provides an up-to-date account on the power, limitations, and future of CAR T-cell therapy as personalized medicine and immunotherapy.

The eighth chapter on the neuroprotective immunity focuses on the role of innate and adaptive immune responses in the pathobiology of neurodegenerative and neuroinflammatory disorders. In addition, the role of nanomedicine in the diagnosis and treatment of cancer with emphasis on the use of nanoparticles to aid in the delivery of anticancer therapeutic agents to target cells in cancer and the use of nanotechnology to deliver diagnostic agents to enhance visibility of target cells in cancer during imaging studies are highlighted in this chapter. The last or ninth chapter focuses on PCOS, which is an endocrine abnormality and is the most common cause of anovulatory infertility in women of reproductive age. It has been suggested to be associated with autoimmune disease such as systemic lupus erythematosus. The chapter on PCOS covers the pathophysiology, comorbidities, diagnosis, and treatment of this condition.

In view of our theme, we have made considerable efforts to compile information derived primarily from human models with particular reference to humans. It is our hope that the readers of this textbook would have a broader and deeper understanding of the aspects of immunology relevant to humans that cover topics on viral pathogenesis and host immune response to viruses, interaction between cancer and host immune response, as well as overactive adaptive immune response to innocuous substances and self-antigens.

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Lishomwa C. Ndhlovu

Introduction

The human immune system is comprised of both immune surveillance and immune defense mechanisms. Both antiviral and antitumor immunities mediated mainly by natural killer (NK) cells and T cells constitute an important innate and adaptive interface in immune defense, whereas recognition of tumor and viral antigens serves as the principal drivers of immune surveillance. Current standard of care for cancers include chemotherapy, radiotherapy, and surgery whereas pharmacotherapy is the standard of care for viral infections. Immunotherapy involving modulating the immune system to induce immunity against tumor cells and viruses has recently emerged as effective therapeutic against resistant cancer to standard of care options. Immune checkpoint blockade and CAR T-cell therapy are the two current immunotherapeutic strategies that demonstrated significant clinical efficacy against a variety of cancers. Generally, immune checkpoint inhibitor is a passive immunotherapeutic strategy whereas CAR T-cell therapy is an active form of immunotherapy.

T-cell activation involves the action of cell surface co-signaling coinhibitory or costimulatory molecules. The balance between costimulatory and coinhibitory signals determines whether T cells would be activated or tolerated. Immune checkpoints are coinhibitory molecules expressed on immune cells at different stages of immune cell activation and play a role in maintaining immune homeostasis and peripheral immune tolerance. Chronic stimulation of the immune system by tumor antigens and viral antigens triggers overexpression of immune checkpoints on CD8 tumor-infiltrating lymphocytes (TIL) and virus-specific T cells, respectively. Tumor cells and viruses use immune checkpoints to enhance their progression and dissemination. Expression of immune checkpoint receptors on activated T cells in the setting of chronic viral infection and cancer correlates with T-cell exhaustion, a state of T-cell dysfunction, progression of infection, and tumor growth. However, blockade of immune checkpoint receptors with monoclonal antibodies targeting receptor-ligand interactions has been shown to restore immune function of exhausted T cells. Studies have demonstrated that blockade of CTLA-4 and PD-1 enhances antiviral immunity and antitumor immune response. It has been shown that brain metastases contain high levels of PD-1 due to high density of TIL in these tumors and this

makes them susceptible to immune checkpoint inhibitors. Unlike PD-1 inhibition, blockade of CTLA-4 is associated with depletion of regulatory T cells and loss of peripheral immune tolerance. Although both anti-PD-1- and anti-CTLA-4-based immunotherapies are FDA-approved as solid tumor cancer immunotherapies, not all forms of cancer respond to them. As such, there is heightened interest in biomedical research to develop immune checkpoint inhibitors against these other forms of cancer that are unresponsive to anti-PD-1 and anti-CTLA-4 due to factors such as varying expression of immune checkpoint levels as well as the safety and tolerability of these forms of therapy. The use of anti-CTLA-4, anti-TIM-3, and anti-PD-1 is associated with significant immune-related adverse effects, thus current research is focusing on discovering immune checkpoint inhibitors with a better side effect profile. It is of note that inhibiting TIGIT, B7-H3, and VISTA is associated with less systemic side effects. In addition, organ (GI, liver, thyroid, etc.) toxicity may also occur with use of immune checkpoint inhibitors but these side effects are generally not life-threatening.

CAR T cell, a genetically engineered method of immunotherapy, is a personalized therapeutic modality designed to target cells expressing specific antigens for elimination. In oncology, these modified T cells with laboratory-generated immune receptors have been shown to target transformed cells expressing surface-specific antigens. CAR T cell is a formidable therapeutic armament in the fight against cancer. Unlike T-cell receptor-mediated antigen identification involving major histocompatibility complex (MHC), CAR T cells recognize antigen in the absence of MHC. There are four generations of CAR T cells based on the presence of costimulatory domains. The genetically engineered receptors of CAR T cells consist of antigen identification domain that recognizes tumor antigen, hinge domain, T-cell receptor transmembrane domain, and intracellular signaling domain. Unlike the first-generation CAR T-cell therapy that had four domains, the second and third generation CAR T cells have co-stimulatory domains. The fourth generation CAR T cells have an additional element called TRUCK (T-cell redirected for universal cytokine-mediated killing) that enhances T-cell function and development of T-memory stem cells. These CAR T cells also overcome the tumor-induced immunosuppressive microenvironment, which is a major limitation associated with previous therapy. Chimeric autoantibody receptor CAAR T cell expresses autoantigens recognized by autoimmune B cells, and as such, this therapy could be beneficial for patients with autoimmune disease. The adverse effects of CAR T cells include cytokine releases syndrome, neurotoxicity, and anaphylaxis. These side effects are likely due to the release of pro-inflammatory cytokines by activated CAR T cells. High cost of treatment, resistance to CAR T-cell therapy due to antigen modulation, adverse effects of CAR T cell, type of tumor, and lymphodepletion pose a challenge to the use of CAR T cell in cancer immunotherapy. Cancer immunotherapy is undergoing rapid evolution with current and future basic and translational research being carried out to expand their clinical application in the field of oncology and beyond. In addition to the clinical use of CAR T cell in oncology medicine, it has clinical application in allergy, autoimmunity, and infection. Combination immunotherapies

are considered an attractive immunotherapy modality that allows for reduced dosing with increased efficacy, and it is hoped to have reduced adverse effect profile.

Loss of peripheral tolerance with associated immune-related adverse effects, therapeutic resistance, limited clinical therapeutic index, and cost of treatment are a few limitations to clinical application of immune checkpoint inhibitors as immunotherapies for cancer and chronic viral infection. Despite significant advance in immune checkpoint inhibitor immunotherapy, there is a need for ongoing research into ways of mitigating the above limitations. There are ongoing phase1/2 clinical trials focusing on safety, tolerability, and efficacy of immune checkpoint inhibitors and their clinical application as an immunotherapeutic strategy in cancer and chronic viral infection. Furthermore, discovery of new immune checkpoints could enhance immunotherapeutic strategies against cancer, chronic viral infection, and neurological disease.

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Contents

Human Acute and Chronic Viruses: Host-Pathogen Interactions and Therapeutics

Matilde Hoffman, DeGaulle I. Chigbu, Brenndan L. Crumley, Ravi Sharma, Sergey Pustylnikov, Thomas Crilley, Rashida Ginwala, Ronak Loonawat, Julie Joseph, Dominic Sales, Sydney Wilson, and Pooja Jain

Abstract Viruses are obligate intracellular pathogens that cause infection in susceptible host cells. Virus infections could be lytic, chronic, latent or immortalizing. Viruses causing latent infection are associated with high morbidity and mortality worldwide. The human body is protected from viral infection by physical and chemical barriers. However, when these barriers are breached, the body generates an antiviral immune response mediated by Natural killer (NK) cells, monocytes, Dendritic Cells (DCs), type I interferon (IFN), neutralizing antibodies, and T cells. DCs play an important role in generating a cell-mediated adaptive immune response to viruses, with conventional DCs playing a crucial role in the interactions between DCs and viruses. Crosstalk between NK cells and DCs facilitates DC maturation in antiviral innate immunity whereas crosstalk between DCs and T cells in antiviral adaptive immunity amplifies the function of mature DC. Viruses employ various strategies to evade the host immune system. They can block Pattern Recognition

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Receptors (PRRs) - mediated production of type I IFNs, inhibit maturation and functionality of DCs, and interfere with cell-mediated immunity. Here we will focus on important human disease-causing viruses including latest COVID19 that caused worldwide pandemic. Because of the high mortality rate associated with viral diseases, there is an urgent need to re-evaluate current antiviral agents with more research focusing on developing alternative anti-viral therapies with an enhanced therapeutic index and safety profiles. Future directions in approaching the development of vaccines should focus on specific vaccines that can induce $CD8^+$T cell responses and produce IFN-gamma to promote a Th1-biased $CD4^+$T-cell response.

Keywords Viruses · Dendritic cells · Viral infections · T cells · Treatment · Immunoprophylaxis

1 Introduction

Viruses are the smallest infectious agent that cause infectious disease with high morbidity and mortality on a global scale. Viruses are classified on the basis of the genomic type as either DNA or RNA viruses. There is further classification of the viral nucleic acid as either single-stranded or double-stranded. Viruses are able to cause infection in host cells with appropriate specific host cell receptors that facilitate viral attachment, entry, and invasion of the host cell. Viruses require host cells to replicate and survive. Destruction of the host cell by viral replication, along with immune response to the virus, results in clinical manifestations of viral infection. DNA viruses usually undergo replication in the nucleus of the host cell whereas majority of viruses with an RNA genome replicates in the cytoplasm of the host cell. Viral replication in the host cell results in disruption of normal cellular function, culminating in damage and death of the infected cell. When virus infection causes immediate cell death, this is termed lytic infection, wherein the infected cell is lysed as the virions emerge. However, many viruses are also known to cause persistent viral infection, which may take the form of a latent or persistent productive infection. In latent infection, viral nucleic acid persists inside the host cell without undergoing replication or killing the cell. Persistent productive infection, or immortalization, is associated with host cell senescence because of active viral replication. This occurs mostly with RNA viruses such as HTLV-1, during which the infected host cell becomes immortalized due to interference with normal cell cycle, this results in host cell transformation [1]. These forms of viral lifestyle are associated with the development of virus specific $CD8^+$T cells, which become stimulated during viral reactivation [2].

The human body is protected from viral infection by physical and chemical barriers. However, when these barriers are breached, different arms of the immune system come into action. The immune response involves the innate immune system mediated by Dendritic cells (DCs), Natural Killer (NK) cells, monocytes, and type I interferons (IFNs), and the adaptive immune response carried out by neutralizing antibodies and T cells. A complex interplay between different types of immune cellular and soluble factors of the innate and adaptive immune systems exists in

preventing and controlling chronic virus infections. NK cells, complement proteins and cytokines are specific components of the antiviral innate immune responses, with DCs operating as immunosurveillance and immunostimulatory cells that process and present viral antigen to T cells [3]. DCs are divided into plas-macytoid and conventional DCs. Plasmacytoid DCs respond to viral DNA and RNA to produce type I IFN that inhibit viral replication in both infected and noninfected cells [4, 5]. Conventional DCs are one of the first immune cells to encounter viruses at their port of entry into the host [6]. The three subsets of conventional dendritic cells, important in viral infection, include tissue-derived migratory DC, lymphoid-resident DC, and monocyte-derived DC [4, 7]. Tissue-derived migratory DCs include Langerhans' cells and dermal/interstitial DCs that reside and survey the skin and mucoepithelial tissue. Lymphoid-resident DCs exist as immature DCs in the lymph nodes, spleen, and thymus. Monocyte derived or inflammatory DCs are those that are generated from monocytes under inflammatory conditions [4, 7].

Dendritic cells are located in strategic parts of the body to ensure optimal performance of immunosurveillance and immunostimulatory functions with the intent of triggering both innate and adaptive immune response to the presence of viruses that breach the anatomical and chemical defense barrier of the host [7]. Siglec-1 (CD169), DC-SIGN, mannose receptor, Langerin, immune dendritic cell receptor (DCIR), heparan sulfate proteoglycan, FC gamma receptors, and syndecan-3 are surface attachment receptors on DCs that facilitate uptake of viruses by DCs [6]. Virus interaction with DCs can cause degradation of the virus within the cell to allow for antigen-MHC complex formation for presentation to T cells. This trigger the T cell mediated antiviral immune response [6, 7]. Viral antigens are either generated during intracellular replication in virus infected cells or generated from recognition of viral components from other infected cells [7]. Some viruses can bind to and replicate within DCs, with DCs acting as permissive cells that facilitate viral spread to other cells or tissues in the host, resulting in trans-infection of lymphocytes in regional lymph nodes. This type of infection is particularly seen when viral antigens are not complexed to MHC molecules [6] as another way to alert the immune system and activate T cells (Table 1).

Activation of PRRs on DCs by viral Pathogen Associated Molecular Patterns (PAMPs) is associated with maturation of DCs, processing and presenting of virus-derived peptide complexed to MHC class I molecules, upregulation of MHC molecules and costimulatory signals, production of antiviral pro-inflammatory cytokines, and induction of the adaptive immune response. Viral nucleic acid, capsomer, peplomer on viral capsid or envelope, and RNA replication intermediates are viral PAMPs that interact with PRRs [6]. The efficacy of PRR activation determines the level of viral titers and duration of infection [7–9]. PRRs have dual function of detecting viral PAMPs and alerting the immune system about the breach of the passive innate immune defense mechanism [7]. Toll-like receptors (TLR) on DCs are PRRs that undergo morphological and biochemical changes when they interact with cognate ligands [3]. TLR involved in viral recognition can induce the production of type I interferons. Intracellularly located nucleic acid sensing TLRs (TLR3, TLR7, TLR8, TLR9) within the endosome facilitate recognition of viral nucleic acid or viral genome. Activation of TLR3 results in the induction of phosphorylation of IRF3, whereas activation of TLR7 and TLR9 is associated with IRF7

Table 1 Epidemiology, virulence factors, clincal features, pathophysiology and management of chronic viruses

Virus	Epidemiology and disease burden	Characteristics and virulence factors	Clinical manifestations	Pathophysiology and immunology of disease	Treatment and prevention	Current clinical trials and research studies
Measles	Children, unvaccinated, malnourished, and immune compromised individuals are most at risk. Measles was declared eradicated in the US in 2000 but there are still spordic outbreaks. Still epidemics in Africa, parts of South East Asia, Eastern Europe and some parts of Western Pacific Area. Between 2000-2014, measles incidence decreased by 73% worldwide, and measles deaths fell by 79%, from 546,800 to 114,900.	It is a negative sense ssRNA virus that belongs to the Paramyxoviridae family. There is one serotype. H and F proteins are necessary for attachment and fusion with DCs and lymphoid cells. V and C proteins are indispensible for in-vivo infection. Measles virus induces cell-to-cell fusion, which results in multinucleated giant cells (syncytia) formation. It is highly infectious and transmitted thorugh aerosolized droplets and contact with respiratory secretions.	There is a 10–14 day incubation. Clinical manifestations include cough, fever, Koplik's spots, and maculopapular rash. Complications include pneumonia and bacterial superinfection. Patients with severe immunosuppression develop giant-cell pneumonia without a rash. Post-infectious encephalomyelitis (PIE) and subacute sclerosing panencephalitis (SSPE) are rare sequela of measles infection.	MV-H binds DC-SIGN on DCs resulting in upregulation of CD150 expression. Infected DC travels to lymph node and cause the infection of activated T and B cells via CD150. Infected T and B cells travel to other secondary sites such as the lungs where they enter epithelial cells at basolateral side binding PVLR4/Nectin4.	Live attenuated vaccine (Schwartz or Moraten variants of Edmonston B strain) administered as two doses after 1 year of age provides protective immunity. Immune serum globulin is used for post-exposure prophylaxis.	Studies have been conducted that compare the injected versus the aerosolized MV vaccine. Research that focuses on exploring other vaccine options of measles virus is required.

Dengue	Vectors include Aedes aegypti and Aedes albopictus mosquitoes. It is endemic in tropical and subtropical areas, e.g., Puerto Rico, Mexico, and Asia. It is especially endemic in areas with standing water and poor vector control. Transmission is highest between August & November. Vertical transmission from mother to newborn is possible. 2.5 billion people are currently at risk. WHO estimated an incidence of 50–100 infections/year and a death rate of 20,000 deaths/year.	Dengue virus is a spherical virus with positive sense ssRNA genome. It belongs to the Flaviviridae family & Flavivirus genus (related to Zika). It is transmitted by vectors through the blood (most active during the day). There are four serotypes, each a (+) sense RNA virus, with DENV2 considered the most virulent. The three structural proteins include Capsid, Envelope, and PrM/pre-membrane. Dengue virus encodes seven nonstructural (NS) proteins. E protein is critical for fusion of host and virus membranes.	Clinical course of DENV includes febrile, critical, and recovery phase. Febrile phase (~1 week) is characterized by hemorrhage/hemolysis, joint & muscle pain, and most cases resolve after this phase. Critical phase is characterized by systemic vascular hyperpermeability and subsequent vascular leakage (dengue shock syndrome). It lasts about 48-72 hours, after which vascular permeability normalizes (occasional fatigue follows).	DENV targets DC, macrophages, monocytes, and endothelial cells. It binds to a target cell via heparan sulfate, DC-SIGN, and mannose receptor. Virion binding is followed by clathrin-mediated endocytosis into the host cell with E protein inducing viral and host membrane fusion to host cell. New virions mature in the trans Golgi by furin protease and a re released by exocytosis. DCs exposed to the virus travel to lymph nodes, where they activate T cells. DENV blocks IFN I production. CTLs have low level of granulation but produce pro-inflammatory cytokines. Exposure to one serotype only provides immunity to that serotype. DENV infection is associated with increased severity of infection with another serotype via antibody-dependent enhancement (ADE). DENV-IgG complexes interact with FcγRIIA receptors on DCs, which leads to generation of pro-inflammatory cytokines.	No current prophylactic vaccines or DENV-specific treatment. Treatment is based on maintaining fluid balance in patients with DHF/DSS. Preventative methods are mainly centered around vector control e.g. limiting mosquito populations/infectious potential.	Sanofi Pasteur's CYD-TDV chimeric vaccine has been shown in trials to protect against all serotypes but DENV2 (currently in phase III). Papaya leaves have been reported to be a possible treatment/protective agent but active ingredient has yet to be identified. Most research is centered around adapting current therapies for other infections e.g. minocycline has been reportrd to have a dose-dependent activity in reducing DENV RNA.

(continued)

Table 1 (continued)

Virus	Epidemiology and disease burden	Characteristics and virulence factors	Clinical manifestations	Pathophysiology and immunology of disease	Treatment and prevention	Current clinical trials and research studies
Zika Virus	ZIKV acquired global health significance when it caused significant outbreaks in Yap Island, French Polynesia, and South America in 2007, 2014, and 2015 respectively. Aedes aegypti and Aedes albopictus are vectors of ZIKV with Aedes aegypti considered the primary vector responsible for the ZIKV outbreaks. Non-vector mode of transmission includes mother-to-fetus, sexual contact, blood transfusion and breastfeeding. WHO declared ZIKV a public health emergency of global concern due to the temporal and geographical association between ZIKV infection and microcephaly.	Zika virus is a enveloped virus with a nonsegmented positive sense, single stranded RNA genome and icosahedral capsid. It has three structural proteins (viral capsid, viral membrane protein, envelope glycoprotein) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). RNA replication is enzymatically mediated by NS3 and NS5 and processing of polyprotein is mediated by the interaction between NS3 and NS2B. Phylogenetic analysis of ZIKV strain identified the presence of African lineage and Asian lineage ZIKV strain.	The clinical manifestation of ZIKV infection include transient low-grade fever, pruritic maculopapular rash, arthralgia, nonpurulent conjunctivitis, retro-orbital pain, headache, myalgia, lymphadenopathy, fatigue, lower back pain, hematospermia, and subcutaneous bleeding. Guillain-Barre syndrome (GBS) and microcephaly are the major neurological complications associated with outbreaks of ZIKV infection. Current diagnostic test for ZIKV include IgM class capture enzyme-linked immunosorbent assay (MAC-ELISA) and Trioplex reverse transcriptase polymerase chain reaction.	Neurons, astrocytes, trophoblasts, microglia, macrophages, dendritic cells, endothelial cells, skin keratinocytes, and dermal fibroblasts are permissive cells that support ZIKV replication. Generating type I IFN is required for suppressing ZIKV replication in innate immunity. Neutralizing antibodies primarily directed at E protein play a major role in providing humoral protection against ZIKV infection. Cell-mediated immunity against ZIKV involves ZIKV-specific CD8 T cell and CD4 T cell.	There are currently no FDA approved therapeutic agent for treating ZIKV infection. The main goal of prevention is to avoid contact with Aedes mosquito as well as minimize risk of non-vector transmission. Pregnant women or women trying to conceive should avoid travel to Zika virus endemic areas and unprotected sexual contact with partners who are at risk for Zika virus infection.	Han and colleagues demonstrated that amodiaquine, an antimalarial drug could be therapeutically repurposed for ZIKV infection due to its antiviral capabilities against ZIKV. Mesci and colleagues demonstrated that Sofosbuvir (SOF), a FDA-approved RNA-dependent RNA polymerase (RdRp) inhibitor, had anti-ZIKV activity in both in vitro and in vivo models of ZIKV. Current ZIKV platform using prM/E as vaccine antigen are designed to provide correlates of immune protection based on generating neutralizing antibodies.

Adenovirus	Mode of transmission includes direct contact, aerosolized virus, fecal-oral route, and adenoviral contaminated swimming pool/water. Transmission rates are higher in day care centers and long term care facilities. Most prevalent adenovirus in civilian population is adenovirus type 3. Most prevalent adenovirus among military personnel is adenovirus type 4. In 1997, there was an outbreak of adenoviral-associated respiratory infection among military recruits in the USA. In 2011, there was an outbreak of adenovirus-related acute respiratory disease in Tayside, UK with a case mortality rate of 23%. Risk factors include recent solid-organ transplantation, hematopoietic stem cell transplantation, and immunocompromised state. Major disease burden include reactivation of a latent adenoviral infection and unavailability of suitable anti-adenoviral therapy for immunocompromised patients.	Adenovirus is a nonenveloped lytic viruses with a 36 kb linear double-stranded DNA genome that encodes more than 40 different proteins. it has an icosahedral capsid made up of 240 hexon proteins and 12 penton base proteins. Major structural proteins include hexon, penton base, and fiber protein whereas minor capsiid proteins include protein VI, protein III1, protein VIII, ad protein IX. Core proteins are terminal protein (Tp), protein MU, protein VII, protein Iva2, and protein V. Genus is Mastadenovirus and family is adenoviridae. There are seven groups (A through G) based on hemagglutination properties, serology, phylogenomics, host range, genomic composition, DNA homology, receptor usage, and tissue tropism.	Tissue and viral tropism are linked to affinity of host cellular receptor for fiber knob and penton base. Persistence of adenovirus in lymphoid tissue serves as a focal point of viral spread following viral reactivation. Pharyngoconjunctival fever is caused by HAdV type 1, 2, 3, 4, 5, and 7 and it is an ocular infection associated with swimming in insufficiently chlorinated swimming pool. Epidemic keratoconjunctivitis is caused by adenoviral types 8, 19, 37, 53 and 54. Respiratory tract disease is caused by HAdV type 1, 2, 3, 4, 5, 6, 7, 14, and 21. Gastrointestinal tract (GIT) disease is caused by adenovirus type 2, 3, 8, 31, 40 and 41. Adenoviral-induced genitourinary tract disease is caused by HAdV type 7, 11, and 21.	Viral entry is mediated by CAR/CD46-Fiber knob interaction. Viral internalization is via clathrin-mediated endocytosis via penton-integrin interaction, which is folowed by viral uncoating and release of vertex proteins as well as endosomalysis. This is followed by transportation of viral genome into the nucleus, where DNA replication and generation of progeny DNA. The last stage in replication is viral assembly and maturation. Innate immunity is mediated by NK cells, monocytes, and type 1 interferon. Adenoviral DNA interact with TLR9 on DC to signal through the MyD88 pathway to generate type I interferon. IgA-mediated mucosal immunity prevents productive adenoviral infection. Cell-mediated cytotoxicity by CTL and NK cells cause apoptosis of adenoviral-infected cells. Immune evasion strategies include inhibition of interferon response, TNF-alpha-mediated viral cytolysis, and MHC class I molecule expression on surface of virally infected cells.	No FDA-approved antiviral agents are available. Cidofovir, Ribavirin, and Brincidofovir have been shown to be beneficial for immunocompromised individuals. Maintenance of adequate or optimal levels of chlorinated swimming pools and improved personal hygiene can minimize transmission. Immunoprophylaxis via live oral vaccine are beneficial for preventing adenovirus types 4 and 7-induced respiratory infections in military recruits.	Current and future diresctions incluude the following: Ritonavir has been reported to be an inhibitor of adenoviral cysteine enzyme. RNAi-mediated viral gene silencing inhibits replication of adenovirus. RNAi-mediated suppression of CAR expression inhibits viral entry. Intravenous immunoglobulin (IVIG) against primary infection. Adoptive transfer of HAdV-specific immunity.

(continued)

Table 1 (continued)

Virus	Epidemiology and disease burden	Characteristics and virulence factors	Clinical manifestations	Pathophysiology and immunology of disease	Treatment and prevention	Current clinical trials and research studies
HBV	HBV has tropism for herpatocytes resulting in liver infection and subsequent liver failure. Transmitted via mother-to-infant and exposure to infected bodily fluids including genital fluids and blood. Acute HBV infection is usually cleared within 6 months of onset, whereas chronic HBV infection is associated with viral persistence due to failure of the immune system to clear the virus. According to WHO estimates, 257 million people have chronic HBV infection worldwide. In 2015, there were 887,000 recorded dates secondary to HBV-induced cirrhosis and/or hepatocellular carcinoma. The economic bursden associated with chronic HBV infection is in the neighborhood of $9 billion.	HBV is a non-cytolytic virus witth a dsDNA genome. The four major proteins include Polymerase, Core, Surface antigen, and HBx. HBV polymerase possess both DNA-dependent DNA polymerase and reverse transcriptase (RNA-dependent DNA ploymerase) acitvities. Surface protein (HBsAg) a biomarker of HBV infection in sera of HBV infected individuals. Core is a structural protein found in the capsid. HBx is a regulatory protein that plays a role in viral replication. HBeAg plays a role in promoting viral persistence.	In acute HBV infection, the immune system clears the infection. Chronic HBV infection is associated with viral persistence. Acute HBV infection is less damaging to the liver. Chronic HBV infection has four phases – immune tolerance phase, immune clearance phase, inactive HBsAg carrier state, and reactive phase (HBeAg-negative chronic hepatitis B phase). Intense liver inflammtion occurs in the reactivation phase.	HBsAg interacts with TLR4 to lead to production of proinflammatory cytokines tha recruit immune cells. HBV nucleocapsid interacts with TLR2 to generate type I IFN. Interaction between pgRNA and RIG-I generates type III IFN. HBsAg inhibits type I and III IFN production. HBx degrades MAVS, TRIF and IRF3. NK cells are effective via their cytolytic action on HBV infected hepatocytes. Antibody response is generated against HBsAg surface antigens. Cd4 and CD8 T cells provide adaptive cellular immune response.	Chronic HBV infection is resistant to therapy. Interferon-based therapy (e.g. conventional interferon therapy and PEGylated interferon-α therapy) boosts the immune system to clear HBeAg and HBsAg. Nuceoside analogs (e.g. lamivudine, adefovir, entecavir, tenofovir, and telbivudine) inhibits viral replication. HBV vaccine based on HBsAg provides protective immunity. Post-Exposure Prophylaxis uses HBV immunoglobulin and it is given to individuals exposed to HBV infected bodily fluids. Prevention strategies include safe sex practices, screening blood for HBV, and vaccination.	Increasing the efficacy of existing drugs such as PEG-interferon and nucelotide analogs. Generation of Tenofovir alafenamide that targets NTCP. Cyclosporin A inhibiting interaction between NTCP and HBV surface protein. Direct acting siRNA and HBsAg inhibitors are being developed.

HCV	HCV has tropism for the liver resulting in hepatitis and progression in a few HCV chronically infected individuals leads to the development of hepatocellular carcinoma. HCV is contracted via exposure to infected blood and sexual intercourse. HCV becomes chronic when the virus persists due to failure of clearance by the immune system. 71 milliomn of individuals on the earth have chronic HCV infection. Approximately 399,000 peolpe with chronic HCV die from liver failure and hepatocellular carcinoma. About $300 million is spent on liver transplant on patients with HCV-induced liver failure.	HCV belongs to the Flaviviridae family. It is an enveloped virus with a ssRNA genome. The large polyprotein is cleaved into structural (core, envelope E1, and envelope E2) and nostructural proteins (P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). Genetic makeup of the host has an impact on virulence of the virus.	Approximately 30% of patients with acute HCV have symptoms such as weakness, anorexia and jaundice. Persistence of HCV RNA in the blood for more than 6 months is characteristic of chronic HCV infection. Disease progression is slower with low ALT levels whereas very high ALT levels is associated with rapid disease progression. HCV coinfection with HBV or HIV is associated with increased risk of developing hepatocellular carcinoma.	Innate immunity is mediated by type I IFN. type III IFN and NK cells. CTL induce the apoptosis of HCV-infected hepatocytes through the action of perforin and granzyme. CTL and Th1 cells through the action of IFNγ inducing cytokine-mediated antiviral action, which inhibits viral replication. Neutralizing antibodies against E1 and E2 are formed but have a limited role in immunity to HCV.	Treatment directed at patients with chronic HCV infection. Direct acting antivirals (e.g., elbasvir/grazoprevir and sofosbuvir/velpatasir) target NS5B polymerase, NS3/4 protease, and NS5A protein; these proteins are essential for HCV replication cycle. No FDA-approved vaccines. Prevention strategies include needle awareness strategies, safe sex practices, and screening blood for HCV.	Bovine viral diarrhea virus is being investigated for its abilioty to HCV replication cycle. Polyphenols have been shown to inhibit HCV RNA replication. Caffeine has been reported to target HCV replication cycle without causing non-toxic adverse effects. Clinical trials are ongoing with focus on Samatasvir and Odulasavir, which have been reported to target polymerase and protease.

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Table 1 (continued)

Virus	Epidemiology and disease burden	Characteristics and virulence factors	Clinical manifestations	Pathophysiology and immunology of disease	Treatment and prevention	Current clinical trials and research studies
HPIV	HPIV is the second most common cause of acute respiratory infections in infants and children. HPIV is transmitted through contact or inhalation of respiratory droplets. It causes infections ranging from croup and bronchiolitis to pneumonia. Disease burden is most significant with HPIV3, as it causes severe respiratory tract infection in infants, elderly and immunocompromised individuals. Infants, the elderly and immunocompromised patients are at an increased risk due to immature or decreased function in the immune system.	It is an enveloped non-segmented negative sense ssRNA virus that replicates in the cytoplasm. Binding of HN with sialic acid on cellular membrane proteins of host cells initiates the infectious process of HPIV. F protein mediates fusion between the viral envelope and cell plasma membrane of the host cell. Release of the viral genome bound by nucleocapsid proteins (nucleoprotein, phosphoprotein and RNA-dependent RNA polymerase) allows RNA-dependent RNA polymerase to direct RNA genome replication. V and C proteins are important for survival of the virus through suppression of IFN induction and cell signaling in HPIV infected cells.	HPIV has an incubation period of 2–6 days and lasts 1–2 days after symptoms begin. HPIV Types 1-3 cause of severe lower respiratory tract infection in children and infants. HPIV Type 1 & 2 cause croup and HPIV Type 3 cause bronchiolitis or pneumonia in children. Laryngotracheobronchitis (croup) is the more severe manifestation of HPIV.	HPIV activates pattern recognition receptors leading to creation of an antiviral microenvironment. Mucosal IgA mediated protection is short lived but the longevity of the mucosal IgA response is enhanced with subsequent HPIV infections. Serum and mucosal neutralizing antibodies that target HN and F glycoprotein provide long-term protection against HPIV. CD8 and CD4 T cells provide cellular immunity that can clear the virus but T cell-mediated viral clearance following reinfection wanes over a few months.	There are no specific antiviral medications used. No live or attenuated vaccines have been effective HPIV can be inactivated by dryness and acid, and treatment is supportive.	National Institute of Allergy and Infectious Disease (NIAID) and MedImmune are working on a vaccine against HPIV infection. Majority of the HPIV3 vaccine variants have been shown to be safe and immunogenic. Phase I clinical trial of Bovine PIV3 (BPIV3) and HPIV3 vaccine revealed modest seroconversion rate for HPIV3. Recombinant Bovine/HPIV3 was well-tolerated in young children with a seroconversion of 100% in children under the age of 2 years.

Mumps	Mumps can cause infections ranging from mild parotitis to more severe systemic infections such as meningitis and encephalitis. MuV usually causes self-limited infection with fatalities only related to the 1% of infections that lead to encephalitis. It is of significant health burden particularly in regions with low MMR vaccination rates.	MuV are spherical, enveloped, negative sense, ss RNA viruses with only one serotype. They are human pathogens transmitted through aerosols or contact with infected respiratory secretions. MuV expresses the HN protein that allows it to interact with target host cells. MuV spreads through viremia and can affect multiple organ systems. MuV causes a lytic infection of epithelial cells of the URT. Cell-mediated immunity is necessary for controlling infection. Protein V is crucial in immune evasion.	MuV also causes systemic infection. It has an incubation period of 2–4 weeks, but one third of infections are usually asymptomatic. Mumps is associated with parotitis, orchitis, meningitis, encephalitis, encephalitis, transient sensorineural hearing loss, pancreatitis, pericarditis and myocarditis.	Dendritic cells, alveolar macrophages, T cells, and B cells are main players in the immune response to mumps virus infection. DC and alveolar macrophages initiate the immune response to measles and mumps. MuV has specific proteins that aid in establishing or spreading the infection. Small-hydrophobic (SH) proteins of MuV suppress TNF-α production. V protein blocks the production of type I IFN and IL-6.	Live MMR vaccine provides lifelong immunity.	Research in post-exposure prophylaxis of mumps. Innate immunity is mediated by type I interferon and NK cells while CTL provide cell-mediated immunity against the virus. NS1 and NS2 block generation of type I interferon. RSV impairs myeloid-derived DC presentation function. RSV blocks signaling via TLR and suppresses cell-mediated cytotoxicity. Ribavirin is beneficial for high risk patients.

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Table 1 (continued)

Virus	Epidemiology and disease burden	Characteristics and virulence factors	Clinical manifestations	Pathophysiology and immunology of disease	Treatment and prevention	Current clinical trials and research studies
RSV	RSV is the major cause of upper and lower respiratory tract infection in young children and elderly individuals. RSV is highly contagious and prevalent in the winter months. It is of significant public health concern because RSV causes fatal respiratory tract infections in infants and immunocompromised individuals. RSV poses a significant health burden due to inability of the infection to confer long-term protective immunity.	RSV is an enveloped negative sense ssRNA that contains 10 genes that encode 9 nonstructural proteins and 2 structural proteins. RSV invades the respiratory epithelium and forms syncytia in infected mucoepithelial tissue of the respiratory tract. RSV G proteins bind to a target cell. NS1 and NS2 interact with the immune system. Fusion (F) and matrix (M) proteins are highly conserves between RSV serotypes. Surface glycoprotein (G) protein is not fully conserved between RSV serotypes.	RSV is the most common cause of acute respiratory tract infections in infants and young children. Typical patient presents with a low-grade fever, tachypnea, tachycardia, and expiratory wheezes over the lungs. Bronchiolitis is usually self-limited, but it can be more dangerous in infants.	Innate immunity is mediated by type I interferon and NK cells while CTL provide cell-mediated immunity against the virus. Neutralizing antibodies against major surface glycoproteins restricts reinfection of RSV. RSV can inhibit Th1 polarization. RSV promotes creation of an immunosuppressive microenvironment that favors viral persistence. RSV G protein induces Th2 polarization and eosinophilia in infected lungs. NS1 and NS2 proteins decreases DC maturation. NS1 suppresses proliferation and activation of CD8+ T cells. RSV Fusion protein inhibits activation of T cells. NS1 and NS2 block generation of type I interferon.	Ribavirin for the treatment of high-risk patients such as pre-term infants, or those with poor respiratory tract development. Palivizumab and Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV) are FDA approved for treating RSV infection in infants and young children with chronic cardiopulmonary disease. There is no vaccine available for RSV.	There is ongoing research to develop vaccines for women in the third trimester of pregnancy. Subunit RSV-A vaccines containing purified Fusion, matrix, and G proteins have been demonstrated to be safe and immunogenic in the over 65-age group. Developing a RSV vaccine that minimizes Th2 mediated immunopathology is a challenge.

HTLV	HTLV-1 is the most clinically harmful subtype and it is endemic in Japan, Brazil, Iran, and parts of Sub-Saharan Africa. Probability of contracting HTLV-1 through blood transfusion and organ transplantation renders HTLV-1 a significant health burden. HTLV-1's main routes of transmission include unprotected sex, infected blood, and vertically between mother and baby.	HLTV is an enveloped positive sense ssRNA virus. HTLV-1 infects CD4 T cells. HTLV-1 genome carries several structural genes (gag, pol, & env). Genome contains genes such as Tax and HBZ (HTLV Zipper Factor). The trans-activating Tax protein initiates immune response against HTLV-1-infected cells. HBZ triggers is associated with chronic infection. Both Tax and HBZ have been a major focus of HTLV research. HTLV-1 is transmitted through an immunological synapse between DC and T cell.	ATL is a multi-organ system disease. It is characterized by atypically shaped lymphocytes. Patients present with erythema and plaques. Immunosuppression is common in the less aggressive subtypes. HLTV-1 infected patients are susceptible to opportunistic infections. HAM/TSP exerts a neurotoxic effect that leads to spinal cord inflammation. Patient's serum and CSF showing antibodies against HTLV-1 is diagnostic for HAM/TSP. GLUT-1 is utilized by HTLV virions to infect cells.	T cell is one of the key immune cells implicated in HTLV. Infected T cells express the Tax protein that suppresses their proliferation. HBZ protein enhances progression from HLTV-1 infection to ATL or HAM/TSP. DCs also play an important role in HLTV pathogenesis. DC-mediated transmission of HTLV-1 from infected DC to T cells. HTLV infected T cells and DCs are dysfunctional.	There is no FDA-approved therapy for HTLV-1 infection. Chemotherapy to counteract symptoms of leukemia and lymphoma. Combination therapy of AZT and interferon-alpha is effective in some patients with ATL. Education focused on safe sex practices and needle-sharing are preventative strategies.	Research is focused on what differentiates asymptomatic carriers from patients who progress to ATL and HAM/TSP. Further studies on the benefits of cyclosporine is required. Another area of research could focus on novel testing protocols for HTLV.

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Virus	Epidemiology and disease burden	Characteristics and virulence factors	Clinical manifestations	Pathophysiology and immunology of disease	Treatment and prevention	Current clinical trials and research studies
HSV	In 2012, the global burden of HSV-1 was 3.7 billion people with age less than 50 years. Maximum prevalence in Africa, South-East Asia and western pacific countries. Globally 417 million people in 15–49 year age group are infected HSV-2, with incidence rate of 19 million per year. An estimated 25–50% of HIV infections Are attributable to HSV-2 in high prevalence regions. Initially, HSV-1 was primary thought to be associated with oral infections, while HSV-2 with genital insult, but HSV-1 has now been shown to provoke first episode of genital herpes and neonatal herpes in developed world. HSV is acquired mainly through direct exposure of mucous membranes or abraded skin to the lesions or mucosal secretions of actively infected individuals.	HSV-1 and HSV-2 are members of the neurotrophic alpha-herpesviridae subfamily. HSV is an enveloped virus with a linear dsDNA genome. HSV gD mediate adhesion of the virus to the host cell surface. Fusion is facilitated by gD, gB, gH and gH glycoproteins. Following fusion, tegument proteins and nucleocapsid enter the host cell cytosol. HSV genes α, β and γ regulate viral genome translation and transcription of viral transcription factors. Vhs protein degrades host mRNA in infected cells.	Immunocompetent children and adolescents are susceptible to acquiring primary HSV infection. Primary HSV clinical features include painful and ulcerative vesicles in the skin and mucous membranes. HSV infects neurons and mucoepithelial cells. HSV is a neurotrophic virus that travels via retrograde transport to the trigeminal ganglia to establish latent infection. Immunocompromised individuals are prone to developing HSV associated complications because of HSV reactivation and recurrent HSV disease.	TLR2, TLR3, TLR7 and TLR9 recognize HSV PAMP to initiate the antiviral innate immune response. NK cells and type I IFNs mediate the antiviral innate immune response to HSV. CD8 T cells are the major players in cell-mediated immunity to HSV. VHS suppresses type I interferon and reduce production of pro-inflammatory cytokines. DC are prone to HSV infection because they express nectin-1, nectin-2 and HVEM. HSV downregulates costimulatory molecules and induce apoptosis of DC. HSV inhibits Th1 polarization.	FDA-approved nucleoside analogues for treating HSV infection include acyclovir, valacyclovir, penciclovir, and famciclovir. There is no viable therapeutic or preventive HSV vaccine. Development of resistance to nucleoside analogues in immunocompromised individuals is a health burden.	There is current research into developing an effective preventive and therapeutic HSV Vaccine. HSV vaccine success in animal models has not been translatable in human studies. GEN-003, a subunit vaccine of gD2 and ICP4, has been reported to decrease virus shedding by 55% in a phase IIb clinical trial.

HPV	HPV infection is of significant health burden because of the carcinogenic nature of HPV 16 and HPV 18. HPV is the most common sexually transmitted infection worldwide particularly in young individuals. HPV 16 and HPV 18 cause anal cancer, penile cancer, and cancers of the vagina, vulva, and cervix. Estimated financial burden of health in the U.S. is $8 billion.	HPV is a non-enveloped doubled-stranded DNA virus. The alpha subtype of HPV affects mucosal epithelium while the beta subtype of HPV infects skin. The dsDNA genome encodes 8 genes: E1, E2, E4, E5, E6, E7, and E8, L1, and L2. Viral proteins E6 and E7 proteins are necessary for cell immortalization via their interactions with p53 and pRB respectively. The icosahedral capsid of HPV consists of L1 major and L2 minor capsid proteins. Interaction between L1 and heparan sulfate proteoglycans (HSPGs) initiates the viral attachment. Internalization of HPV is followed by disassemble of viral capsid and L2 complexing with viral DNA to form L2-DNA complex. Viral DNA replication occurs in the nucleus.	The clinical presentation of HPV depends HPV subtype, the area of skin affected, and the immune status of the individual. The majority of HPV infections are asymptomatic. Persistent HPV infection manifests as warts. Anogenital warts are caused by HPV 6 and 11. Common warts are caused by HPV types 1, 4, and 7. Plantar warts are associated with HPV types 1 and 4. Condyloma acuminatum are caused by HPV 6 and 11. Giant condyloma acuminatum of buschke and löwenstein is caused by HPV 6, 11 and 16.	TLR-mediated interaction with HPV PAMP initiates innate immune responses to HPV. TLR3, TLR7 and TLR9 recognize HPV PAMP to initiate the antiviral innate immune response via production of type I interferon. NK cell-mediated immune response controls HPV infection in innate immunity. HPV downregulates antiviral innate immunity mediated by type I interferon. It decreases production of pro-inflammatory cytokine by keratinocytes. It downregulates MHC class I expression. HPV generates an IL-10 immunosuppressive environment.	There is no FDA-approved cure for HPV infection. Pharmacotherapy is focused on amelioration of symptoms Education on safe-sex practices are crucial in preventing HPV infection. L1 VLP vaccines include Cervarix that targets HPV16/18 and Gardasil that targets HPV6/11/16/18. A CDC study showed a 56% decrease in vaccine-related HPV strains for U.S. girls age 14-19. HPV vaccination is associated with a decrease in anogenital HPV-related disease.	Current vaccine research is looking at L2-based vaccines. Current research into therapeutic vaccines aim to generate cytotoxic T cell responses against the HPV early viral gene. Radio-immunotherapy targeted at E6 and E7 proteins is promising treatment.

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Virus	Epidemiology and disease burden	Characteristics and virulence factors	Clinical manifestations	Pathophysiology and immunology of disease	Treatment and prevention	Current clinical trials and research studies
HIV	Injecting drug users (IDUs), men who have sex with men (MSM), and people practicing high-risk sexual behavior are most at risk. HIV is a global epidemic: over 1 million people die annually and over 3 million people were infected in the last 5 years. Pandemic is stabilized in almost all regions of the world (number of newly infected people is not growing). Between 2010 and 2015 HIV treatment coverage increased from slightly over 20% to almost 50% and number of AIDS-related deaths decreased from about 1.5–1.1 million.	Retroviridae family, two positive sense single-stranded RNA, at least 7 serotypes. Env, trimer of heterodimers of gp120 and gp41 glycoproteins, is necessary for attachment and fusion with the target cells. Induce CD4 T cell death and severe immunodeficiency associated with opportunistic infections. Mode of transmission includes through infected blood, sexual contacts, and mother-to-fetus.	Four periods of disease: incubation (1-2 weeks), acute period (2-4 weeks), chronic infection (1-20 years), and HIV-induced AIDS (deadly if not treated). Complications: opportunistic infections (oral candidiasis, tuberculosis, herpes zoster, and bacterial pneumonia). Increased risk of disorders in cardiovascular, digestive, excretory, musculoskeletal and central nervous systems. HIV-related local and systemic inflammatory reactions. HIV-associated neurocognitive disorders.	HIV binds receptors, coreceptors and adhesive molecules on the target cells. In sexual transmission, mucosal DCs can transfer HIV to the lymph nodes, but mucosal T cells are also infected. In systemic infection, main places of HIV replication are the follicular T cells in the lymph nodes. In patients on ART the main viral reservoirs are the memory T cells.	HIV prevention tools include HIV counselling, testing and treatment in the high-risk groups, education in the general population. Number of vaccines have been tested, but only one has shown efficiency of about 30%; the protective effect was temporary.	The HIV vaccine RV144 has shown 31.2% efficacy and provided only temporary defense. Developing HIV vaccines that generate CD8 Treg cell response to prevent CD4 T cell activation and viral replication. There are therapeutic approaches on bNAbs being studied for passive immunotherapy and immunotherapy based on checkpoint blockers. Developing adoptive therapy with CAR T cells for development of antigen-specific cell-mediated response and use of single-chain CARs based on bNAbs.