Mayo Clinic HIV eCurriculum Series
Essentials of HIV Medicine
Module 3
The Immunology of HIV Infection
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LEARNING OBJECTIVES

Upon conclusion of this module, participants should be able to understand:

1. How HIV impacts the innate immune response.
2. How HIV impacts the adaptive immune response.
3. Prospects for immune based therapies and vaccines for HIV.

INTRODUCTION

HIV infection causes profound effects on virtually all arms of the immune system. The purpose of this review is to provide an overview of the immune dysregulation that occurs during HIV infection. It is anticipated that the reader has some basic knowledge of HIV virology and replication. This overview is not meant to be an exhaustive discussion of all mechanisms, and the reader is referred to many excellent topic-specific reviews for further details.

OVERVIEW OF THE IMMUNE SYSTEM AND HIV-INDUCED ABNORMALITIES

The immune system is generally classified into innate and adaptive arms. All of the cellular elements of the immune system derive from a common pluripotent hematopoietic stem cell residing in the bone marrow.

Innate Immunity

The innate immune system comprises dendritic cells, natural killer (NK) cells, monocytes/macrophages, and granulocytes which together represent the first line of defense against invading pathogens. These immune cells exert their efforts through the use of preformed nonspecific and broadly specific effector mechanisms designed to counteract invading pathogens. HIV-induced alterations in the innate immune system are depicted in Figure 1.

1. **Monocytes and Macrophages.** Monocytes and macrophages derive from a common myeloid progenitor cell. Monocytes reside in the peripheral blood, and following activation these monocytes migrate to tissues where they differentiate into macrophages. Following the invasion of a microorganism across an epithelial barrier, such organisms are recognized, in most cases, by tissue macrophages and engulfed through phagocytosis resulting in the invading pathogen
residing in a phagosome. Phagosomes merge with lysosomes contained within the macrophage, and the fusion of the phagosome with the lysosome creates a phagolysosome within which antimicrobial enzymes, peptides, and nitric oxide destroy the invading pathogen. The process of phagocytosis activates macrophages to undergo a respiratory burst that produces hydrogen peroxide and hydroxyl radicals, and also stimulates macrophages to secrete chemokines and cytokines which result in chemotaxis of other cellular immune elements to the site of infection. Finally, after the invading pathogen has been digested by the macrophage, microbial peptides are
processed and presented on the surface of the macrophage for recognition by elements of the adaptive immune system. Following HIV infection, a variety of functions of macrophages are altered as follows:

- Altered expression of cell surface molecules associated with antigen-presenting function (such as HLA Class II expression)
- Altered gene transcriptional profiling, upregulation of genes associated with transcription, upregulation of chemokine genes, and upregulation of genes promoting cell cycle arrest
- Increased production of cytotoxic ligands, including Fas ligand and tumor-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), which have been implicated as a potential mechanism by which CD4 T-cells are depleted
- Increased production of proteins which confer unresponsiveness to type I interferon signaling
- Altered production of cytokines, such as decreased production of interleukin (IL)-12 (which is required to obtain maximal cytotoxic activity of NK cells and CD8 T-cells)

2. **Granulocytes.** Granulocytes derive from a common granulocyte/macrophage progenitor cell and can differentiate into neutrophils, eosinophils, or basophils. Neutrophils are the second major family of phagocytes, aside from monocytes and macrophages, and are short-lived cells that are abundant in blood but not present in normal tissues. They can be recruited to sites of tissue inflammation by the effects of chemokines. Unlike monocytes and macrophages, neutrophils are not directly infected by HIV; however, neutrophil function is altered in HIV-infected patients as follows:

- Increased neutrophil cell number
- Enhanced rates of spontaneous apoptosis of neutrophils in the peripheral blood of HIV-infected patients
- Reduced phagocytic function of neutrophils from HIV-infected patients
- Reduced optimization of bacteria in neutrophils from HIV-infected patients

3. **Natural Killer Cells.** NK cells are bone marrow-derived granular leukocytes which have been implicated in the control and clearance of virally infected cells and malignanT-cells as well as in generation of autoimmunity. They kill target T-cells by producing high levels of interferon (IFN)-
γ, as well as surface expression of cytotoxic ligands including Fas ligand and TRAIL. In addition, they can kill target T-cells through perforin and granzyme expression. NK cells also produce high levels of other proinflammatory cytokines such as macrophage inflammatory protein (MIP)-1β and granulocyte macrophage colony-stimulating factor (GM-CSF). Additional effects of NK cells include enhancing cytotoxicity by virtue of antibody-dependent cellular cytotoxicity (ADCC) and expression of killer immunoglobulin receptors (KIR) which bind to MHC Class I molecules, thus aiding in the differentiation of self from nonself. During HIV infection, the phenotype of NK cells is altered. In HIV-infected patients, a novel subset of NK cells are present who are CD3 negative, CD56 negative, and CD16 positive, and these cells have impaired effector functions including impaired killing, ADCC, and cytokine secretion. The importance of NK cell-mediated function in control of HIV disease is supported by novel observations that patients who co-express the killer cell immunoglobulin-like receptor (KIR) receptor, KIR3DL1, in conjunction with the HLA allele BW4801 are protected from the development of HIV disease. Alterations that are seen in NK cells in HIV-infected patients are as follows:

- Decreased expression of activating natural cytotoxicity receptors such as NKGDG2D
- Altered immunophenotype compared to uninfected controls
- Reduced NK cell-mediated cytotoxicity against cancer cell lines
- Enhanced NK cell-mediated lysis of autologous CD4 T-cells from HIV-infected patients which have downregulation of MHC Class I expression

4. **Dendritic Cells.** Dendritic cells arise from myeloid or lymphoid progenitors and exist in 2 different functional classifications. The first is conventional (myeloid) dendritic cells that function primarily in antigen presentation and activation of naïve T-cells. The second is plasmacytoid dendritic cells, whose principal function is to produce large amounts of type I interferons. Dendritic cells are present in most solid organs primarily as immature dendritic cells, which become activated and mature upon recognizing and ingesting foreign pathogens. Uptake of pathogens by dendritic cells can result in antigen presentation through Class I molecules, which activate CD8 T-cells. Alternatively, peptides can be presented on MHC Class II molecules to activate naïve CD4 T-cells. Plasmacytoid dendritic cells express chemokine receptors, which enable them to migrate into lymph nodes following viral infection. These
plasmacytoid dendritic cells produce high levels of proinflammatory cytokine IL-12, as well as high levels of type I interferons. Of particular relevance to HIV infection, dendritic cells also express dendritic Cell-specific intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) which allows dendritic cells to capture HIV on their surface. A normal function of dendritic cells is to interact with CD4 T-cells through an interaction between lymphocyte function-associated antigen (LFA)-1 expressed on the T-cell and intercellular adhesion molecule (ICAM)-1 expressed on the dendritic cell. Therefore, virus which is captured on the surface of dendritic cells is able to be passed to the recruited T-cell. Altered functions of dendritic cells in HIV-infected patients include the following:

- Phenotype, cytokine secretion, and beta chemokine production by DC from HIV-infected patients are unchanged from uninfected patients
- Dendritic cells may become physically infected by HIV, although the frequency is likely low
- HIV may block the maturation of dendritic cells
- Co-cultures of HIV-infected DCs and T-cells results in enhanced production of IL-10 leading to enhanced immunodeficiency

### Adaptive Immunity

The adaptive immune system is the arm of the immune system that is antigen-specific, exhibits immunological memory and reacts primarily with the antigen that induced the response. Figure 2 illustrates HIV-induced alterations of the adaptive immune system.

- **CD4 T-cells.** Following activation by antigen-presenting cells, CD4 T-cells differentiate into a number of different effector CD4 T-cells that differ based upon their cytokine production profiles and immune regulatory functions. The four CD4 T-cells subsets now recognized are TH1, TH2, TH17 and regulatory T-cells.
  - TH1 cells participate in cell mediated immunity and are important for control of intracellular pathogens. They are produced following interaction with a dendritic cell and secrete IL-12, IL-18, and IFN-γ. In addition, TH1 cells secrete high levels of tumor necrosis factor (TNF) -β and IFN-γ, which stimulate macrophages to kill organisms that have been phagocytosed. Macrophages then recruit other lymphocytes to sites of inflammation.
TH2 cells provide help for B cells and are therefore essential for antibody-mediated immunity, which is important for control of extracellular pathogens. TH2 cells secrete IL-4, which has 2 effects; first, it promotes class switching in B cells, leading to synthesis of immunoglobulin (Ig)E antibodies; and second, it prevents cells from entering the TH1 pathway. In addition, TH2 cells secrete IL-13 and IL-5.

TH17 cells are a recently identified subset of CD4 T-cells that are formed in response to transforming growth factor (TGF) -β and IL-6 as well as IL-21. They are defined by their ability to secrete IL-17 and the expression of a receptor for IL-23. TH17 cells are located primarily in epithelial surfaces and protect against bacterial infection by secreting defensins and recruiting neutrophils to the site. TH17 cells have also been implicated as effector mechanisms of autoimmune disorders.

Regulation T-cells (T-regs) are stimulated in response to IL-2 as well as TGF-β in the absence of IL-6. They are characterized by production of IL-10 and therefore are intrinsically immunosuppressive and anti-inflammatory.

- Abnormalities that occur in CD4 T-cells during HIV infection include the following:
  - There is a shift away from TH1 profile CD4 T-cells towards TH2 profile CD4 T-cells.
  - CD4 T-cell numbers are reduced by a variety of mechanisms (see below).
  - There is inappropriate immune activation of CD4 T-cells.
  - CD4 T-cell help towards the generation of CD8 T-cells is impaired, potentially by upregulation of molecules including PD-1 and CTLA-4.
  - There is an increased number of regulatory CD4 T-cells in patients infected with HIV that correlates with HIV viral load. It is controversial whether T-regs are detrimental by impairing HIV-specific immunity or beneficial by reducing immune activation.
  - CD4 T-cells from HIV-infected patients have impaired formation of the immunologic synapse due to inefficient targeting of T-cell receptors and leukocyte-specific protein tyrosine kinase (Lck) to the cell surface. CD4 T-cells have impaired cytokine production and enhanced IL-2 secretion in HIV-infected patients.
There is preferential loss of TH17 cells in the gut of HIV-infected patients. This renders HIV-infected patients more susceptible to infection with intestinal pathogens, such as salmonella.

- **CD8 T-cells.** CD8 T-cells differentiate into cytotoxic cells following contact with costimulatory signals presented on the surface of antigen-presenting cells. CD4 help is provided in the form of CD4 T-cell recognizing related antigens presented on the surface of the same antigen-presenting cell, and then providing signals which increase the costimulatory signals for activation of the CD8 T-cells. In HIV infection, CD8 T-cell function remains intact until very late in the disease; however, CD4 T-cell help...
for HIV-specific responses is impaired, resulting in attenuated CD8 T-cell responses to HIV-specific antigens compared to non-HIV antigens. Specific abnormalities in CD8 T-cells seen in HIV-infected patients include:

- Inappropriate immune activation
- Reduced expression of selected cytotoxic molecules, including granzyme B and perforin
- Enhanced expression of cytotoxic ligands, including Fas ligand.
- Skewed maturation of CD8 T-cells
- Increased programmed death (PD1) expression on HIV-specific CD8 T-cells
- Decreased antigen and mitogen induced secretion of IL-2

B-Cells. A common lymphoid progenitor cell gives rise to pro B-cells in which immunoglobulin gene rearrangement occurs. As B-cells mature they migrate to the bone marrow where the diversity of B-cell antigen receptor repertoire is enhanced. Ultimately, there are 3 gene rearrangement events that give rise to a diverse number of possible antigen specificities. Once the immunoglobulin is fully rearranged, IgM is expressed on the cell surface and the cell becomes an immature B-cell. At this point, cells are tested for auto-reactivity, and auto-reactive B-cells are depleted. The surviving cells then migrate to peripheral lymphoid organs where they proliferate and give rise to plasma cells and memory B-cells if they encounter cognate antigen. Specific abnormalities seen in B-cells from HIV-infected patients include:

- Increased proportion of activated B-cells
- Polyclonal hypergammaglobulinemia
- Increased B-cell apoptosis
- Increased proportion of immature B-cells
- Decreased number of memory B-cells
- Enhanced rates of autoimmunity
- Increased number of B-cell malignancies

Virus-Specific Host Immune Responses

Although HIV is an immunodeficiency disease, there is a wide range of host immune responses that are directed against HIV. Critical to understanding the pathogenesis of HIV is the central premise that not
all immune responses are beneficial or protective against an underlying infection. Indeed, a variety of immune responses may be harmful and may actually exacerbate infection, and as is the case in HIV, many immune responses are misdirected towards non-neutralizing epitopes. Finally, it is essential to understand that individuals of different host genetic backgrounds will have different host immune responses to the invading pathogen. In the case of HIV, this is of critical importance and may explain the variable penetrance of HIV disease phenotype.

1. **CD4 T-cells.**
   - There is a quantitative and qualitative reduction in CD4 T-cell number and function during HIV disease.
   - There is a global decrease in CD4 T-cell proliferative responses in HIV infection.
   - CD4 T-cells that are HIV-specific are functionally impaired more than CD4 T-cells that are specific to other pathogens.
   - Functional exhaustion in CD4 T-cells is associated with enhanced expression of PD-1 and enhanced expression of cytotoxic T-lymphocyte antigen (CTLA)-4.
   - HIV preferentially infects HIV-specific CD4 T-cells. Consequently, there is increased destruction of HIV-specific CD4 T-cells.

2. **B Cells.**
   - The antibody response that occurs early in HIV infection is directed against the non-neutralizing epitopes of the HIV envelope.
   - The B-cell responses that occur later during HIV infection are directed against other potentially neutralizing epitopes, but these are ineffective due to lagging behind a rapidly diversifying virus.
   - There is reduced immunoglobulin class switching, such that HIV-specific IgA responses at mucosal sites is low compared to other classes of immunoglobulin.
   - There is a polyclonal proliferation of B-cells resulting in hypergammaglobulinemia.

3. **CD8 T-cells**
   - The reduction in viremia that is seen following acute infection is temporally associated with the development of HIV-specific CD8 T-cell responses.
   - CD8 T-cells are in some circumstances associated with control of HIV.
• In most cases, lack of HIV-specific CD4 help results in low-level and ineffective HIV-specific CD8 responses.
• Immunodepletion of CD8 T-cells from simian immunodeficiency virus (SIV)-infected macaques results in enhanced viral replication and disease progression.
• Certain human leukocyte antigen (HLA) Class I molecules are consistently associated with slower HIV disease progression and lower viral set points (HLA-B27, HLA-B57).
• HIV-infected subjects with high viral loads have impaired effector functions of CD8 T-cells, including reduced production of IFN-γ, IL-2, chemokine ligand (CCL-5), and granzyme or perforin.

4. **HIV-induced CD4 T Cell Depletion.** A central underlying problem in HIV immune responses is the profound depletion of CD4 T-cells. Much work has been devoted to understanding mechanisms by which CD4 T-cells are killed during HIV infection, and a variety of mechanisms have been proposed. It is important to recognize that, with few exceptions, it remains unclear whether or not these processes occur in vivo, and if so, whether they contribute to the CD4 T-cell loss. Furthermore, it is important to understand that both infected and uninfected CD4 T-cells are lost during HIV disease. It is unknown whether the majority of lost CD4 T-cells are infected or uninfected; however, early reports suggest that the majority of CD4 T-cells dying during HIV infection are uninfected. These reports have not been re-examined since the availability of newer, more sensitive assays to discriminate infected from uninfected cells. Mechanisms to potentially explain CD4 T-cell loss during HIV infection are as follows:

• Inappropriate immune activation. Following a primary adaptive immune response, CD4 T-cells are activated. This activation causes a proliferation and in the absence of encounter with cognate antigen, these CD4 T-cells die through a process of negative selection. HIV infection is associated with a cytokine milieu which promotes activation (high levels of TNF, IL-6, etc.). In addition, a variety of HIV-specific proteins including Tat, Nef, and Env promote immune activation. This inappropriate immune activation contributes to enhanced CD4 T-cell death.
• Infected cell death. It is clear that following HIV infection of an individual CD4 T-cell, in most cases the CD4 T-cell dies. The morphologic features of death share some features of apoptosis and some features of necrosis. The underlying signals which
contribute to infected cell death are thought to be mediated by HIV protease cleaving of a variety of host structural and regulatory proteins.

- Autologous cell-mediated killing. A variety of accessory cell types, notably monocytes and macrophages, can be productively infected by HIV. This infection results in enhanced production of cytotoxic ligands on accessory cells, notably Fas ligand. Consequently, when monocytes and macrophages interact with activated CD4 T-cells, for example in the context of antigen presentation, a Fas-mediated CD4 T cell death occurs.

- Toxic effects of HIV proteins. Most HIV proteins, depending on context, are capable of killing cells. For example, treatment of CD4 T-cells from uninfected donors with HIV Env causes death in a variety of pathways through binding to either the CD4 receptor, the CXC chemokine receptor CXCR 4, or the chemokine receptor CCR5. Other mechanisms of cell death have been described following treatment of cells with Tat, Nef, Vpr, or expression of protease.

- The principal function of CD8 T-cells is to kill virally-infected cells. It is therefore of no surprise that CD8 T-cells are capable of killing HIV-infected CD4 T-cells or CD4 T-cells which express viral proteins on their surface.

- Antibody-dependent cell mediated cytotoxicity (ADCC). As described above, there are a large number of antibodies directed against HIV during the various phases of disease. These antibodies will predictably bind to infected cells promoting death by favoring NK cell-mediated ADCC of infected cells.

- Syncitia formation. HIV-infected CD4 T-cells which contain viral protein such as gp120 on their surface have the ability to bind to and fuse with uninfected cells by virtue of the CD4 receptor. This fusion event causes a formation of a giant cell termed syncitium, which dies through the process of apoptosis. Although it is clear this can occur in vitro, it remains debatable whether syncitia formation occurs in vivo.

Host Genetic Factors That Impact HIV Disease Progression

Data over the recent years have provided increasing evidence that some HIV-infected patients are capable of controlling HIV disease progression. This is most poignantly demonstrated in a recent whole-genome association study of major determinants for host control of HIV. That study identified a
significant number of host genes which are statistically associated with control of HIV replication. Most notable among these were the associations with HLA Class A, B, and C molecules. In addition, a variety of other host factors have been implicated in control of HIV disease progression as follows:

1. HIV entry requires a chemokine coreceptor, either CCR5 or CXCR4. Δ32 mutations within CCR5 are associated with a delayed disease progression from HIV.
2. Certain CCR2 alleles are associated with delayed HIV disease progression, since this CCR2 allele interacts with and reduces expression of CCR5.
3. CCL3 is a gene which encodes macrophage inflammatory protein (MIP)-1β, a natural ligand for CCR5. Certain CCR5 alleles decrease MIP-1β expression and consequently accelerate AIDS progression.
4. Certain IL-10 alleles decrease IL-10 expression and accelerate AIDS progression.
5. HLA-B27 and HLA-B57 are associated with enhanced CD8 T cell responses to HIV, reduced HIV viral replication, and delayed disease progression.
6. Other HLA A, B, and C alleles have been associated with altered rates of HIV disease progression.
7. The natural killer of cell receptor KIR3DS1, which interacts with the HLA-Bw4 molecule is associated with improved control of HIV disease and delayed HIV disease progression.

IMMUNOTHERAPEUTIC APPROACHES

Given the diverse abnormalities within immunoregulation that occur during HIV disease, it is not surprising that a large number of approaches have been proposed and studied to modify inappropriate immune responses associated with HIV. Some such approaches have progressed to the point of being licensed; others have been fully evaluated and found to be ineffective; while still others are in the early phase of evaluation. Examples of immunotherapeutic approaches include the following:

1. Enfuvirtide is a peptide antagonist that binds to the first heptad repeat in the gp41 subunit of the viral envelope which prevents conformational changes required for viral entry. It has received Food and Drug Administration (FDA) approval.
2. Maraviroc is an antagonist of the CCR5 coreceptor which prevents viral entry by CCR5 tropic HIV strains. It has been FDA approved.
3. IL-2 has been extensively evaluated in a variety of studies and shown to cause proliferation of CD4 T-cells with a consequent effect on increased CD4 T-cell number. However, these increases
in CD4 T-cell number are not accompanied by improvements in CD4 T-cell function, and the
effects are transient. Two landmark trials evaluating the utility of IL-2 in improving clinical
outcomes in patients receiving combination antiretroviral therapy have been completed. These
studies conclusively show that the increases in CD4+ T cell counts that were observed due to IL-
2 therapy did not translate into demonstrable clinical benefits.

4. IL-7 shares a common alpha chain with IL-2, and has recently been tested in an Open Phase
IA/IIA trial, where administration of IL-7 was associated with increased CD4 T cell number, and
that the expanded T-cells responded to HIV antigen with production of IFN-γ and IL-2. Further
studies are proposed with IL-7 therapy.

5. Since early in the HIV epidemic, IFN has been proposed as a novel immunotherapy for HIV.
While IFN has some intrinsic antiviral activity, it has a negative effect on CD4 T cell counts and
therefore is not being pursued.

6. Since HIV is associated with inappropriate immune activation, a variety of agents have been
tested for their ability to block immune activation. Most such trials have involved cyclosporin
and have found minimal effects on T cell activation, with negative effects on viral replication,
and no change in immune function.

7. A number of case reports have reported “eradication” of HIV following bone marrow transplant.
In the most recent report, donor cells from a CCR5Δ32 homozygous individual were used and
HIV remained undetectable several months following the transplant. It is unclear whether or not
this will achieve eradication, more likely the conditioning regimen for bone marrow transplant
killed the majority of HIV reservoirs, and donor cells have yet to become infected. It will be of
great interest to determine whether HIV will remain undetectable in this individual. In any case,
such an approach to therapy is untenable for widespread use.

8. A variety of other immunotherapeutic approaches have been proposed based on in vitro
observations, but have yet to be evaluated in patients. Examples of such approaches include
treatment with recombinant TRAIL, which has been shown to selectively kill HIV-infected cells,
or treatment with a CD4 immunotoxin which is designed to bind to cells expressing gp120.

The Prospects for Developing an HIV Vaccine
When discussing the concept of an HIV vaccine, it is important to distinguish the two categories of HIV
vaccination. The first is a therapeutic HIV vaccine wherein vaccination of HIV-infected individuals is
intended to exert some degree of antiviral control. The second is a prophylactic HIV vaccination is intended to prevent HIV-seronegative individuals from acquiring HIV infection.

These two different contexts for vaccination have different requirements. From a logistics standpoint, determining when the goal has been achieved and how much efficacy is adequate has been problematic. In the case of a therapeutic vaccination, comparing the pre-and post-vaccination viral load setpoint can be used to determine efficacy. However, the magnitude of an adequate vaccine effect has not yet been determined. From the preventative vaccine standpoint, the logistics and ethics of comparing a vaccine approach to placebo in a high-risk population has been hotly debated.

Further confounding issues surrounding the development of an HIV vaccine is the central concept that immunogenicity (i.e., the availability of a vaccine to illicit an immune response) does not translate to effectiveness either in the therapeutic or preventative context. Most early trials of vaccines are capable of showing immunogenicity with both T cell and humeral responses being detected. However, determining whether these immune responses will have any meaningful impact on either HIV replication or protection from HIV acquisition is problematic.

A third confounder is also emerging. As described above, it is apparent that different immune responses to the same antigen are present in individuals of different genetic backgrounds. In the case of individuals with HLAB27 or HLAB57, immune responses to certain epitopes within the gag peptide appear to correlate with controlled viral replication. Immune responses against the same peptide in patients with different HLAB alleles is not associated with immune control. Therefore, it has been proposed that different vaccines may be required for individuals with different genetic backgrounds.

Finally, it remains uncertain as to what elements of an immune response are protective in a given individual versus which elements of immune response are not helpful. As alluded to above, some elements of immune response can actually favor HIV infection through ADCC, enhancing phagocytosis, etc. The problems of developing an HIV vaccine are exemplified in the following:

- In the recent STEP trial, HIV-uninfected patients at risk for acquiring HIV disease were immunized with an adenovirus vector encoding gag, pol, and nef epitopes. All vaccine recipients developed a robust T cell response and antibody response. However, recipients
who had prior existing immunity to the adenovirus backbone developed an increased risk of contracting HIV. The trial was stopped for ethical reasons.

- Numerous other approaches of delivering HIV antigens have been tested and proven to be highly immunogenetic. It remains untested whether or not they confer protection against HIV acquisition. Such approaches have included DNA vaccination, recombinant peptide approaches, and peptides encoded by polio virus, vaccinia virus, and canary pox virus vectors.
Immunology of HIV

Post-Test

1. Which statement is INCORRECT concerning macrophages infected with HIV?
   a. Macrophages infected with HIV die by apoptosis.
   b. Macrophages infected with HIV have altered HLA Class II expression.
   c. Macrophages infected with HIV have increased FasL expression.
   d. Macrophages infected with HIV are a source of HIV.
   e. Macrophages infected with HIV have increased transcription of chemokine genes.

2. Which statement is INCORRECT concerning the antibody response to HIV?
   a. Within weeks of infection, a diverse group of HIV specific antibodies are produced.
   b. There is an increase in the amount of HIV specific and HIV non-specific antibodies in the serum of an infected patient.
   c. HIV specific antibodies can effectively control HIV replication \textit{in vivo}.
   d. There is an increased proportion of immature B cells in HIV-infected patients compared to uninfected patients.
   e. HIV-infected patients have an increased rate of B cell malignancies.

3. Concerning NK cells in patients infected with HIV, which of the following is INCORRECT?
   a. NK cells from HIV-infected patients have reduced expression of activating receptors.
   b. NK cells from HIV-infected patients have impaired cytotoxicity against tumor cells.
   c. NK cells from HIV-infected patients can kill autologous CD4 T cells.
   d. NK cells from HIV-infected patients kill cells expressing low levels of MHC Class I.
   e. NK cells from HIV-infected patients are phenotypically similar to NK cells from HIV negative patients.

4. Proposed mechanisms of CD4 T cell depletion include the following EXCEPT:
   a. Thymic involution
   b. CD4 T cell apoptosis
   c. Inappropriate immune activation
d. Loss of CD4 T cells through the gut
e. Toxic effects of HIV proteins

5. Host genetic factors known to influence HIV disease progression include the following EXCEPT:
   a. Δ32 mutations in CCR5
   b. HLA B27 / HLA B57
   c. Certain IL-10 alleles which decrease IL-10 production
   d. Polymorphisms in FasL, which produce nonfunction FasL
   e. CCR2 alleles which decrease CCR5 expression

6. Concerning vaccine approaches to HIV, which of the following is INCORRECT?
   a. Therapeutic vaccines are designed to control HIV disease progression.
   b. Prophylactic vaccines are designed to prevent HIV infection.
   c. Most therapeutic vaccines fail because they fail to elicit robust immune responses.
   d. Most prophylactic vaccine trials have failed to prevent infection.
   e. Many therapeutic vaccine trials have reduced HIV viral load to a limited degree.

7. Concerning immune based therapies for HIV, which of the following is INCORRECT?
   a. A peptide that binds the first heptad repeat in gp41 effectively reduces HIV replication.
   b. Co-receptor antagonists can block HIV replication.
   c. IL-2 therapy increases CD4 T cell number.
   d. IL-2 therapy increases CD4 T cell function and improves clinical outcome.
   e. IL-7 therapy increases CD4 T cell number and function.

8. Increased apoptosis is seen in all of the following cell types in HIV-infected patients EXCEPT:
   a. CD4 T-cells
   b. CD8 T-cells
   c. B cells
   d. Dendritic cells
9. Concerning CD4 T-cells subsets in HIV-negative patients, which of the following is INCORRECT?
   a. There is a decrease in TH17 cells.
   b. There is an increase in T reg cells.
   c. There is a decrease in TH1 cells.
   d. There is an increase in TH2 cells.
   e. There is an increase in naïve CD4 T-cells.

10. Concerning dendritic cells (DC) and HIV infection, the following are true EXCEPT:
    a. DC can capture HIV via DC-SIGN.
    b. DC can be infected by HIV.
    c. DC cells infected with HIV have increased IL-10 production.
    d. HIV accelerates the maturation of DC.
    e. DC from HIV-infected patients are phenotypically normal.