Human immunodeficiency virus (HIV) infection is the worst pandemic to ravage the world since the Black Death. The Second Bubonic Plague, caused by Yersinia pestis, emerged from Central Asia in the mid-fourteenth century. Within a few years, between 25% and 50% of the people of Europe, North Africa and parts of Asia perished in its wake, and populations continued to decline into the latter half of the fifteenth century. HIV infection was first described in 1981 in homosexual men. Since then it has spread rapidly to become the worst pandemic to ravage the world since the Black Death. The Second Bubonic Plague, caused by Yersinia pestis, emerged from Central Asia in the mid-fourteenth century. Within a few years, between 25% and 50% of the people of Europe, North Africa and parts of Asia perished in its wake, and populations continued to decline into the latter half of the fifteenth century. HIV infection was first described in 1981 in homosexual men. Since then it has spread rapidly to become the leading cause of death in many sub-Saharan African countries. More than 25 million adults and children have already died and more than 42 million people are currently living in the world with HIV/AIDS. Without effective prevention an additional 45 million people will become infected by 2010. South Africa is one of the worst affected countries. An estimated 4.74 million people or >11% of the population are currently infected.

In the early 1980s three research groups published reports describing the isolation of the virus that causes HIV infection. HIV belongs to a class of viruses known as retroviruses, whose distinguishing feature is the presence of a vireally encoded enzyme, reverse transcriptase. During the last two decades much has been learnt about how HIV subverts and ultimately destroys the immune system. A comprehensive description of the immunopathogenesis of HIV infection is beyond the scope of this article. This paper rather sets out to review key aspects of the immunopathogenesis of HIV infection, including the effect of highly active antiretroviral therapy (HAART) on immune function.

VIRAL ENTRY

The main targets of HIV are T cells, macrophages and probably dendritic cells. Infection occurs only after HIV attaches to and enters, the target cells by fusion and endocytosis. Efficient infection usually requires the interaction between HIV and two surface receptors on the target cell, namely CD4 and a chemokine co-receptor. The envelope glycoprotein prominences that are found on the surface of viral particles are trimeric structures, each comprising three gp120 and three gp41 molecules. CD4 binds to the variable loop of the gp120 molecule, exposing a binding site for the co-receptor (Fig. 1).

Chemokine co-receptors are G-protein-coupled signaling receptors that belong to the 7-transmembrane, chemokine-receptor family. At least 14 potential chemokine co-receptors have already been identified. However, CCR5 and CXCR4 are the dominant in vivo co-receptors utilised by HIV. A naturally occurring mutation, a 32-base pair deletion in the gene encoding CCR5 is present in up to 13% of Europeans. People who are homozygous for this mutation (1-2% of Caucasians) display almost complete resistance to HIV infection. Chemokine co-receptors are found in sphingolipid- and cholesterol-rich microdomains of the plasma membrane of target cells. These microdomains are referred to as lipid rafts. The lipid rafts serve to preserve the co-receptor’s conformation. Once a co-receptor is bound to the gp120 molecule, conformational changes occur predominantly in gp41 molecules. These changes facilitate the fusion of viral and cellular membranes, and hence viral entry. Natural ligands for co-receptors and peptide inhibitors of gp41 may prevent fusion occurring. Recently an HIV clone was isolated that infects CD8+ cells via the CD8 receptor. These CD8-trophic virions were also capable of infecting CD4+ cells using the CXCR4 co-receptor. CD8+ infection occurred independently of CXCR4 or CCR5 co-receptors. Significant alterations in the gene encoding gp120, especially in the important V3 loop may explain the altered tropism.

The mechanisms by which HIV gains entry to the body during mother-to-child transmission remain unclear. Evidence suggests that transmission may occur through CD4-CCR5 independent mechanisms. Recently, it was hypothesised that transmission results from contact between viral particles or infected cells and fetal or neonatal mucosal surfaces. The virus may employ alternative membrane receptors such as galactosyl ceramide and 3’ sulfogalactosyl ceramide (GalC/GalS) and the Fc receptor. GalC/GalS receptors are present on mucosal surfaces of enterocytes and M cells. According to the recent proposal, M cells play a central role in infection. Viral particles are rapidly transported across M cells by trans-
cytosis and may then infect CD4+ cells and macrophages in the mucosal-associated lymphoid tissue (MALT) found in the lamina propria of the mucosal surface.28,29 Submucosal dendritic cells may also facilitate the spread of infection from mucosal surfaces to lymphatic organs. Dendritic cells express a specialised attachment structure, DC-SIGN, a C-type lectin, which binds gp120 with high affinity. DC-SIGN enables dendritic cells to trap viral particles at mucosal surfaces or in the lamina propria. Dendritic cells then migrate to regional lymph nodes where they present the intact viral particles to CD4+ cells, hence initiating systemic infection.25

**CD4+ T-LYMPHOCYTE DYSFUNCTION**

The major immunological disturbances in HIV infection are progressive attrition and dysfunction of circulating CD4+ cells. Depletion of CD4+ cells happens throughout HIV infection. However, the rate at which attrition occurs is variable and probably increases towards the latter stages of the disease.26 A number of direct and indirect mechanisms have been proposed to explain the destruction of CD4+ cells (Table I).27 Cytopathic effects such as the accumulation of unintegrated DNA or inhibition of cellular protein synthesis may result in direct killing of HIV-infected CD4+ cells.28 Syncitial formation involving infected and uninfected CD4+ cells may also facilitate attrition.29 Specific antiviral immunity, including antibody-dependent, cell-mediated cytotoxicity and apoptosis induced by natural killer cells and cytotoxic T-lymphocyte (CTL)-mediated mechanisms by anti-HIV specific CD8+ cells, contribute to the destruction of virus-infected CD4+ cells.30

<table>
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<tr>
<th>Table I. Mechanisms of CD4+ cell depletion</th>
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<tr>
<td><strong>Direct</strong></td>
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<td>Single cell killing</td>
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<td>Syncitial formation</td>
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<td><strong>Indirect</strong></td>
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<td>Killing mediated by specific immunity</td>
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<td>Autoimmune mechanisms</td>
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<td>Superantigen-mediated destruction</td>
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A number of other indirect mechanisms have been identified including autoimmunity, superantigen-mediated destruction and apoptosis.31 Programmed cell death or apoptosis is the principal mechanism of T-cell depletion in HIV infection. Both infected and uninfected CD4+ cells as well as CD8+ cells show increased apoptotic rates. Apoptotic pathways particularly the Fas-Fas ligand pathway demonstrate increased activity, and anti-apoptotic regulatory molecules such as Bcl2 and BclXL are down-regulated during HIV infection. Binding and cross-linking of CD4+ cells by the viral envelope glycoprotein, gp120, results in Fas-mediated killing. Programmed cell death via this mechanism does not depend on the infection of all cells, merely viral-cell interaction, and therefore may explain increased apoptosis in both infected and uninfected CD4+ cells. Tat, nef and other viral proteins have also been implicated in HIV-mediated apoptosis.31 In HIV infection viable CD4+ cells show evidence of dysfunction. Deficiencies include depressed responses to soluble antigens such as tetanus toxoid, Candida albicans and Cryptococcus neoformans, defective interleukin (IL)-2 receptor expression and impaired lymphocyte activation.32 Functional deficiencies involve both naïve and memory CD4+ cells.33 HIV infection also compromises T-helper 1 (TH1) cytokine responses by decreasing IL-2, IL-12 and interferon (INF)-γ elaboration, and increasing the production of the TH2 cytokines IL-4 and IL-10.34 Suppression of TH1 responses allow the expansion of TH2 cells at the expense of naïve T cells and TH1 cells. Antibodies directed against IL-4 and IL-10 can restore the proliferative responses of T cells derived from HIV-infected individuals.35 Furthermore, recombinant human IL-2 has the ability to augment the action of HAART in restoring a range of cellular functions.36,37

**IMMUNE RESPONSES TO HIV**

Infected adults and children develop several immunological responses to HIV including neutralising antibodies, antibody-dependent cell-mediated cytotoxicity and HIV-specific cytotoxic T-lymphocytes (CTLs). Most infected individuals are able to generate high titres of antibodies to several HIV-1 gene products, particularly to epitopes on gp120 and gp41.38,39 Neutralising antibodies may play a role in clearing HIV from the blood after primary infection. However, during the advanced stages of infection, neutralising antibodies do not influence the vireaemia. This is probably because rapid evolution of gp120 genomic sequences occur during the course of HIV infection, rendering the antibody response ineffective.23 Antibody-dependent cell-mediated cytotoxicity is present throughout infection, and is primarily directed against gp120.32 Expression of several cytokines is altered during HIV infection. In in vitro experiments, cytokines such as IFN-α and IFN-β suppress HIV replication, whereas transforming growth factor (TGF)-β, IL-4, IL-10, IL-13 and INF-γ may either induce or suppress HIV expression. The altered cytokine network may therefore influence viral replication.40 In general, many viral infections are not cleared but rather controlled by an effective immune response. Both specific CD4+ cells and CD8+ CTLs are needed to limit replication during viral infection.41 In the early stages of HIV infection, specific CD8+ CTLs restrict viral replication and limit CD4+ cell attrition.41 Anti-HIV-specific CD8+ CTLs are typically activated via surface-expressed T-cell receptors after encountering HIV-specific antigen that is presented in association with major histocompatibility complex (MHC) class I molecules, on the surface of target cells. Consequently, CTLs lyse infected cells either by secreting proteases, granzyme A and B, and perforin or via Fas-mediated killing.42 CD8+ CTL further induces non-lytic inhibition of viral replication by MHC-restricted release of β-chemokines including MIP-1α, MIP-1β and RANTES.41,42,43 Despite early anti-HIV immunity, the majority of chronically infected children and adults progress to end-stage disease or AIDS. During chronic infection large numbers of functionally inert CTLs are present.44 CTL dysfunction is probably caused by weak or absent HIV-specific T-helper (TH) cell responses, observed throughout HIV infection.45 Many viral infections, including murine lymphocytic choriomeningitis virus infection and human cytomegalovirus (CMV) infection demonstrate the importance of TH cells in maintaining effective CTL immunity.46,47 An unusual group of HIV-infected adults have remained asymptomatic with normal CD4+ counts and low or undetectable viral loads for more than 20 years. These long-term non-progressors retain vigorous virus-specific CTLs and specific TH cell responses.48-50 Clonal deletion during the early stages of HIV infection may explain the HIV-specific TH cell deficiency in most infected individuals. Treatment of patients with HAART during the acute stages of infection appears to prevent the deletion of virus-specific TH cell
immune function. Improved proliferation responses and down-regulation of apoptosis and reduced T-cell activation are secondary to the expansion of existing memory T cells. Some responses are more easily regained than others, suggesting that they need verification and further exploration. Although there is a steady expansion of both CD4+ and CD8+ T cells from lymphoid tissue to the peripheral vascular compartment. During this phase naive CD4+ cells increase at a much slower rate. Increased CD4+ cell count is predominately due to rapid redistribution of central memory cells to lymphoid tissue to the peripheral vascular compartment. During this phase naive CD4+ cells increase at a much slower rate. After 8 - 12 weeks there is a steady expansion of both CD4+ and CD8+ naïve cells due to de novo production. Increased thymic activity is involved in reconstituting the naïve cell mass. After the initial phase, memory CD4+ cells increase although minimally, and memory CD8+ cells decrease, presumably as a result of reduced antigenic stimulation. Effective suppression of viral replication, down-regulation of apoptosis and reduced T-cell activation contribute to the observed improvements in immune function. Improved proliferation responses to a wide range of common recall antigens occur during immunological reconstitution. Some responses are more easily regained than others, suggesting that they are secondary to the expansion of existing memory cells. T-cell receptor VB diversity expands during reconstitution, and reflects the biphasic CD4+ cell repopulation kinetics observed during HAART. ELSpot assays have recently detected low levels of a wide repertoire of HIV-specific CD4+ cells after reconstitution with HAART. This interesting observation needs verification and further exploration. Although HAART has revolutionised management of HIV infection, in some patients reconstitution is incomplete. This may partly be due to damage to the lymphoid tissue architecture.

The kinetics of immune reconstitution in children differs from that of adults. In children a rapid increase in CD4+ cell count occurs throughout the first year of therapy. The typical biphasic pattern of adults is not observed. Approximately 75% of CD4+ cells that are gained during this period are naïve, and only a small rise in memory cells is observed. Recovery of the naïve CD4+ cell population during the initial phase of therapy is more rapid if HAART is commenced at a young age. After 1 year of therapy all children achieve the same level of immune restoration, irrespective of age at which HAART was commenced. Immune reconstitution occurs independent of the initial degree of immune suppression. Children with severe immune suppression have the best immunological response. Therefore, the introduction of antiretroviral therapy could be delayed during the initial stages of symptomatic HIV infection in children, without compromising their potential to respond. Thymic output is the major source of CD4+ repopulation in children. Long-term reconstitution is better in children with bigger thymuses.

Restoration of specific immunity against colonised microbes during the first few weeks of HAART increases the risk of paradoxical clinical deterioration or immune reconstitution disease (IRD). During this period immune responses are more likely to be dysregulated because only limited or partial reconstitution has occurred. These factors promote the development of IRD in a small proportion of HIV-infected individuals. The typical range of pathogens may induce IRD including Mycobacterium tuberculosis (MTB), M. avium complex, M. leprae, Cryptococcus neoformans, Aspergillus fumigatus, A. terreus, Candida albicans, Pneumocystis carinii, CMV, JC virus, human herpes viruses, human papillomavirus and hepatitis B and C viruses (HBV, HCV). IRD usually manifests during the first 6 weeks after starting HAART. One analysis showed that the median interval between the initiation of HAART and the onset of IRD was 11 days for mycobacteriosis and cryptococcosis. For viral infections including those caused by CMV, HBV and HCV the median interval was 42 days. Clinical presentations vary and depend on the causative organism and the organ system that is colonised. For example IRD caused by MTB may present with high fever, lymphadenopathy, worsening of the original tuberculous lesion, and/or deteriorating chest radiographic manifestations including the development of a military pattern or pleural effusion. Management of IRD has not been well studied. However, severe reactions may require glucocorticosteroids or temporary discontinuation of HAART.
CONCLUSION

In conclusion, research output over the last two decades has clarified many clinical and immunopathogenic aspects of HIV infection. Current insights will hopefully lead to new therapeutic approaches that combine antiretrovirals with immunotherapy, novel classes of antiretroviral agents, and ultimately effective therapeutic and preventative vaccination strategies.

REFERENCES

LOCAL PHYSICIAN ELECTED TO FELLOWSHIP IN LEADING SPECIALTY MEDICAL ASSOCIATION

Allan S. Puterman, MD FAAAAI, was recently elected as a Fellow of the American Academy of Allergy, Asthma and Immunology (AAAAI). The AAAAI is the largest professional medical specialty organisation in the USA representing allergist, asthma specialists, clinical immunologists, allied health professionals and others with a special interest in the research and treatment of allergic disease.

Fellows of the AAAAI have completed three years of membership within the AAAAI and have demonstrated proficiency in research or practice and continuing efforts to advance the field of allergy and immunology. Fellows are the only members with the right to formally vote, propose motions or serve on the Board of Directors.

Puterman received his undergraduate degree and earned his medical degree from the University of Cape Town. He completed his internship at Groote Schuur and Somerset Hospitals and his residency at Red Cross Children’s Hospital. Puterman performed his fellowship in paediatrics at Red Cross Children’s Hospital and in asthma and allergy at Red Cross Allergy and Asthma Clinic. He is certified by the College of Medicine of South Africa.

Currently, Puterman has a private practice, Cape Allergy & Asthma Clinics, in Claremont, Cape Town, South Africa. His research interests include paediatric allergy, asthma, eczema and allergy prevention. The AAAAI was established in 1943 and has nearly 6 000 members in the USA, Canada and 60 other countries. Allergy/Immunology specialists are paediatric or internal medicine physicians who have elected an additional two years of training to become specialised in the treatment of asthma, allergy and immunologic disorders.