OPEN ACCESS JOURNAL

BIOINTERFACE RESEARCH IN APPLIED CHEMISTRY

PhD Review | www.BiointerfaceResearch.com | ISSN 2069-5837

Volume I, Issue 5, 2011, 166-183

Received: 1.09.2011 / Accepted: 25.09.2011 / Published on-line: 15.10.2011

HIV pathogenesis and cytokine secretion patterns in AIDS-related opportunistic infections and HIV-1/HBV co-infections

Chukwunomso Ekene Osakwe [1]*, Carmen Chifiriuc[1], Veronica Lazar[1]

ABSTRACT

HIV infection, a disease caused by the human immunodeficiency virus (HIV), is rapidly becoming one of the greatest public health challenges faced by medical doctors, public health experts, implementers, biomedical scientists, governments, medical institutions, non-governmental organisations, as well as communities and the vulnerable population in any one society, such as, the women and children. HIV-1 infection is characterised by chronic immune activation which often results in impaired effector functions, such as alterations in cytokine production, which may contribute to the development of opportunistic infections especially during the late stage of the disease. Co-infection with hepatitis b virus (HBV) is very common among hiv-1 infected patients due to their common routes of transmission. However, studies elucidating the interactions between HBV, HIV-1 and the immune system are not very common and as such a lot remains undiscovered. a host of cytokines both pro- and anti-inflammatory cytokines; have been implicated in the pathogenesis of HIV disease and in HBV/HIV-1 co-infections. However, in most cases it has been quite difficult to allocate distinct roles to specific cytokines, due to the fact that cytokines are pleiotropic in nature and have a huge tendency to interchange roles. Therefore, further studies will be required in order to correlate specific cytokine secretion patterns with specific opportunistic infections, and HIV-1/HBV co-infections. These will in-turn enable scientists to further understand the existing relationships between HIV-1 and the immune system as well as interactions between HIV-1 and HBV.

Keywords: *HIV-1, HBV, Mucosal Immunity, Cytokines*

1. Introduction

HIV infection, a disease caused by the Human Immunodeficiency Virus (HIV), is rapidly becoming one of the greatest public health challenges faced by medical doctors, public health experts, implementers, biomedical scientists, governments, medical institutions, non-governmental organisations, as well as communities and the vulnerable population in any one society, such as, the women and children. Since the discovery of HIV-1 in 1983 [1, 2], HIV research has witnessed a tremendous upsurge in information, leading to additional discoveries on the pathogenesis and molecular characteristic of the virus, as well as the human immunologic response to the virus. These discoveries have further resulted in the development of highly effective preventive and treatment methods which has lead to a general improvement in the standard of living of HIV infected individuals, giving them a chance to lead 'normal lives'. Today most HIV researchers agree that the

[1] Faculty of Biology, University of Bucharest, Bucharest, Romania
*Corresponding author e-mail address: ***ekeneosakwe@yahoo.com***

challenges posed by the Acquired Immune Deficiency Syndrome (AIDS) pandemic, can better be handled by the development of an effective AIDS vaccine. However, despite technology advancements in the study and management of the virus, creating this vaccine has proved to be a long and arduous task. This apparent difficulty has largely been blamed on the genetic variability of the virus due to its high mutability rate, leading to the general conclusion that a better understanding of the human immune responses to the virus, especially at the earliest stage of infection, is vital to the development of an effective HIV vaccine.

2. HIV epidemiology

The HIV-1 pandemic is a complex mix of diverse epidemics within and between countries and regions of the world, and is undoubtedly the defining public-health crises of our time [3]. Recently, the global prevalence of HIV-1 infection has stabilised at 0.8% [4], with an estimated 33 million people living with the disease, 2.7 million new infections, and 2 million AIDS-related deaths in 2007 [5]. The most affected region is sub-Saharan Africa, bearing about 67% of the global burden, and heterosexual transmission is the major means of disease spread in this region [6]. Whilst other factors such as male-male sex and injection drug use have been identified as the main causes of disease spread in other regions [5]. HIV infection rates are declining in some regions of the world but climbing in other regions such as eastern Europe and central and southeast Asia [7], due to the rapid spread of HIV-1 through injecting drug use [3]. Another major concern is the impact of this pandemic on women, which have been shown to make up about 42% of infected people worldwide, 70% of whom reside in sub-Saharan Africa [8]. Also, HIV-1 infection rates have been found to be three to six times higher in female adolescents than in male adolescents [7, 9-11], which is also a major source of concern. Other factors which contribute substantially to the transmission of the virus include, HIV prevalence rates in a population, sexual practices, prevalence rates of other sexually transmitted diseases, and mobility for economic or disaster purposes [12-15]. There is evidence that shows that HIV transmission is directly linked to viral load [16], therefore, the higher the viral load levels in a patient, the higher the propensity for transmission. Higher load levels are generally observed at the acute infection stage, which is the earliest stage of infection and at the very late stage of infection [17]. It is therefore of great importance to quickly identify and treat those recently infected with the virus. However, since most people who are infected with HIV are unaware of their status at the early stage of infection, they remain potential transmitters of the virus. Co-infections with sexually transmitted diseases can also enhance HIV transmission at rates similar to the acute infection stage [18].

3. The pathogenesis of HIV infection

The importance of acquiring a proper understanding of the immunopathogenesis of HIV-1 infection cannot be over-emphasized as it is bound to help in the development of improved therapeutic strategies, immunotherapeutics and prophylactic vaccines [19]. There is always the tendency for the course of HIV-1 infection to vary between individuals, even among those with a common source of primary infection [20]. A defective virion has been identified and shown to be responsible for the extremely slow progression to AIDS observed in long-term non-progressors [21]. Therefore, it can be concluded that a defective virus, incapable of replicating like a competent virus, can result in a delay in the clinical course of HIV-1 infection [19]. Other factors which can also influence clinical

progression to AIDS include host factors, such as immunological defense mechanisms and genetic factors [19]. However, a lot remains to be discovered in the identification and characterisation of the specific host factors that influence HIV-1 disease progression. HIV-1 belongs to the genus *Lentivirus* in the *Retroviridae* family [22]. Infections caused by lentiviruses are typically slow with persistent viral replication [19] hence; Lentiviruses are sometimes called slow viruses. During viral replication, HIV-1 transcribes its RNA into DNA using the viral reverse transcriptase, which migrates into the host cell nucleus and integrates with the host's DNA [22]. The replication process of the virus is extremely prone to error due to its extensive viral replication rates and high spontaneous mutation rates. Mutations occur because the virus lacks a proof reading mechanism for the reverse transcription process. Hence, each replication cycle usually results in an average number of 1 – 10 errors per genome, per cycle [19]. Therefore, each infected individual is a carrier of many genetic variants of the virus which could pose as a major challenge to the current HIV treatment and prevention strategies being developed. In addition, it is necessary to ask why HIV causes disease, due to observations in the Simian Immunodeficiency Virus (SIV), a Lentivirus which does not cause disease in monkeys, its natural hosts. For example, SIVsmm and SIVagm have their natural hosts as sooty mangabeys and African green monkeys respectively, but they do not cause disease in their natural hosts despite extremely high levels of viral replication which usually exceed viral levels in the human host [23].

4. The underlying cause of disease in HIV infection

HIV-1 infection is characterised by chronic immune activation and a rapid deterioration of the cellular immune system [24]. There is a steady decline in the number of $CD4^+$ T-cells, which eventually results in AIDS, defined by the manifestation of opportunistic infections. The rate at which immunodeficiency occurs correlates with the plasma levels of HIV-1 RNA [23]. Therefore, the higher the viral load levels, the greater the loss of plasma $CD4^+$ T-cells, and the greater the host's susceptibility to disease. This seemingly simple and straightforward relationship led scientists to conclude that the HIV-1 virus itself is responsible for the loss of plasma $CD4^+$ T-cells by directly infecting and killing the cells [24]. However, recent observations of SIV which does not cause disease in natural hosts despite high viral load levels have raised questions on the plausibility of this simple hypothesis. As a result a lot of studies have been done to determine the actual factors that result in $CD4^+$ T-cells depletion. One of such studies reported that nef, a small protein present in all primate lentiviruses, which down-regulates CD4, CD28 and MHC-I, may be responsible for the protection bequeathed on most monkeys by modulating the expression of the T-cell receptor-CD3 complex (TCR-CD3) [25]. 30 nef alleles from 30 different primates were analyzed and it was observed that they all down-regulated CD4 and MHC-1 molecules, as well as TCR-CD3, except the nef alleles of HIV-1 and SIVcpz, which did not seem to have any effect on the TCR-CD3 cell surface expression [19]. In this study, nef alleles which down-regulated TCR-CD3 belonged to viruses such as SIVsmm which do not cause disease in its natural host as a result of reduced T-cell activation and reduced cell apoptosis. In contrast, nef alleles which could not reduce TCR-CD3 cell surface expression belonged to viruses such as HIV-1 and resulted in disease due to increased immune activation and cell death. Other studies on pro- and anti-inflammatory cytokines in pathogenic SIVmac infection of rhesus macaques and non-pathogenic SIVagm infection of African green monkeys showed that a pathogenic SIV elicits a pro-inflammatory response while a non-pathogenic SIV elicits an anti-inflammatory response [26]. These studies, as well as the observation

that suppression of HIV using antiretroviral therapy does not immediately change the high death rates of CD4+ T-cells [30], support the evidence that viremia alone is not responsible for the depletion of CD4+ T-cells but virus-induced immune activation, coupled with other host factors are more likely to be responsible for disease progression in HIV-1 patients. HIV-1 disease progression can be classified into two major stages: - Acute Infection Stage; Chronic Infection Stage, which eventually leads to AIDS.

4.1. The Acute Infection Stage. Studies have shown that in macaque SIV model, the first targets of infection are the mucosal $CCR5^+$ memory $CD4^+$ T-cells, regardless of the route of infection [32, 33]. Further studies which involved analysing the gut of HIV-infected and HIV-uninfected individuals, showed that there was a preferential and substantial depletion of gut-derived $CCR5^+$ $CD4^+$ T-cells in HIV-infected patients as compared to lymph node-derived $CD4^+$ T-cells and peripheral blood-derived $CD4^+$ T-cells [31]. Therefore, during acute infection, the first target of the virus is the entire compartment of memory $CD4^+$ T-cells, which eventually leads to their disappearance [30]. It is therefore safe to say that majority of memory $CD4^+$ T-cells are lost during the acute infection stage. This has serious implications for immune recovery considering that the memory $CD4^+$ T-cells rarely return to normal levels even after commencement of antiretroviral therapy. This is due to the reason that CD4+ T-cell reconstitution is limited and age dependent [30].

4.2. The Chronic Infection Stage. This stage is characterised by a continuous stream of immune activation which attempts to restore the memory $CD4^+$ T-cells but only results in a further depletion of the memory cells, because when they become activated, they eventually die [30]. A constant cycle of immune activation and cell death will result in a slow but definite reduction of the memory compartment. Also, immune activation usually results in viral proliferation, leading to the production of more HIV-1. This chronic stage is slow but eventually results in a depletion of the memory $CD4^+$ T-cells, which will consequently result in the manifestation of AIDS.

The depletion of the memory cells at the acute stage is consequential in determining when to commence treatment in HIV-infected individuals; as earlier treatment might prevent this depletion from occurring in the first place, giving the human host a better chance for survival. Immunologists are beginning to support the concept that $CD4^+$ T-cell depletion is not caused by viremia alone, but by immune activation as well. Immune activation levels usually decrease with effective HIV therapy [27-29] and in most HIV-1 infected patients, suppression of viral levels results into an increase in $CD4^+$ T-cell counts. However, much remains to be discovered about HIV-induced immune activation pathways and how such knowledge can be utilised for the development of novel therapeutic and preventive strategies.

5. HIV prevention and treatment

Despite the increase in global commitment to control HIV/AIDS pandemic and the development of novel treatment regimens, the world has witnessed a rapid spread of the virus to its various parts. Today, HIV can be isolated from populations in every continent and in every country. However, the prevalence rates of the virus in the various parts of the world differ by region. HIV infection rates have been linked to socio-economic and political factors. Therefore, in the developed world where there is a significant amount of economic and political stability, the prevalence rate is quite minimal, in contrast to the developing world with its socio-economic and political challenges where the prevalence rate quite high. Sub-Saharan Africa remains the most widely affected region, although the pandemic is also now being rapidly spread in parts of Asia and parts of Eastern Europe [34].

Heterosexual transmission is the major means of transmission in sub-Saharan Africa, while most infections in parts of Asia and Eastern Europe can be attributed to injecting drug use. Sexual intercourse is the major mode of transmission of the virus in the world, accounting for about 80% of all HIV infections [35]. In sub-Saharan Africa, sexual intercourse accounts for more than 90% of all HIV infections in the region. Therefore, a reduction of sexual transmissions, especially heterosexual transmissions, is crucial to the control of the epidemic in many part of the world, especially in sub-Saharan Africa [7]. The risk of sexual transmission of HIV is determined by risky behaviours that influence the propensity of exposure to an infected individual and by infectivity in the event of exposure [34]. The per contact infectivity of HIV from sexual transmission is a variable and is dependent on the kind of sexual activity [36]. Transmission of HIV is more likely to occur during anal intercourse than during penile-vaginal intercourse, and male-female transmission occurs more frequently than female-male transmission [34]. A number of biological factors which influence infectivity are untreated sexually transmitted diseases, vaginal infections, circumcision and viral load levels [34]. Sexually transmitted infections (STIs) increase the risk of HIV transmission by several-fold [37]. STIs such as genital herpes simplex virus 2 (HSV-2) in particular, enhances the transmission and acquisition of HIV by providing entry points in form of lesions or ulcers in the HIV uninfected individual. Also, HIV infection results in a more frequent reactivation of HSV-2 [34]. Therefore, the importance of controlling HSV-2 infection for HIV prevention cannot be over-emphasized. A vaccine is currently being developed for the prevention of HSV-2 infections [38] However, antivirals such as aciclovir and valaciclovir are currently being used as controls to reduce viral shedding and HSV-2 transmission in discordant heterosexual couples [39, 40]. Vaginal infections such as trichomonas has been proven to increase the risk for HIV seroconversion [41], and higher trichomonas rates have been reported in regions with higher HIV rates [42]. Other vaginal infections which include bacterial vaginosis, and vulvovaginal candiosis have also been shown to increase the risk for HIV acquisition in African women [43, 44]. These findings are crucial to the development of HIV prevention methods for women, who are more vulnerable to the disease. Therefore, prevention options which will give women sole rights to protect themselves are currently being developed and they include cervical caps, invisible condoms, diaphragms and microbicides [45]. Studies carried out on the influence of circumcision on HIV transmission, have shown that uncircumcised men are almost twice as likely to be infected with HIV more than circumcised men [46]. Other studies which have taken into consideration high-risk populations and populations with controlled risk, high-prevalence areas and low-prevalence areas, have also confirmed the protective effect of circumcision [34, 47, 48]. Also results from a randomized controlled trial in South Africa showed that the risk of HIV acquisition is reduced by more than 60% in circumcised men [49]. However, crucial studies on social acceptability of procedure, behaviour change due to circumcision, surgical complication rates and logistics of undertaking the procedure have to be conducted before policies regarding circumcision as a means of preventing HIV infection will be formulated and adopted [50, 51]. Evidence exists which shows that the probability of an uninfected individual being infected sexually is strongly correlated to plasma viral load levels of the infected individual [52]. HIV-infected individuals are mostly infectious at the acute infection stage and the very late stage of the disease, when viral load levels are high. However, antiretroviral therapy has been demonstrated to drastically reduce viral load to undetectable levels [53] and during this period, infectiousness is reduced. A study in Africa also showed that the risk of sexual transmission in discordant couples was strongly related to the viral load levels of the infected partner [34]. Therefore researchers have begun to consider the possibility of reducing viral load levels in an infected partner using antiretroviral drugs, as a means of bestowing some degree of protection on the uninfected partner.

6. Treatment as prevention

A recent study led by Myron Cohen which was presented at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, held in Rome, showed the prevention benefits of early HIV treatment [54]. The phase 3 clinical trial HPTN 052, conducted by the HIV Prevention Trials Network and funded by the US National Institutes of Health showed a 96% reduction in risk of HIV transmission between discordant couples. 1763 HIV discordant couples from different parts of Asia, Africa and the USA were recruited for this trial and the HIV-infected couples with CD4 count levels between 350 – 550 cells per μL commenced HIV treatment. Finally, it was discovered that of the 877 HIV-infected partners who did not receive HIV treatment immediately, 27 transmitted HIV to their uninfected partners; while only one HIV-infected partner in the group that commenced treatment immediately, transmitted the virus. These results are likely to make a huge impact on current policies in HIV treatment, most probably encouraging earlier treatment for HIV-infected partners among discordant couples. However, caution must still be taken in the formulation of new policies, taking into consideration the cost implications of providing antiretroviral drugs in resource-limited regions, as well as the possibility of drug resistance. Developing a safe, effective and cheap vaccine is the only most effective way of effectively controlling the HIV pandemic [55]. However, despite all the efforts put into this notable task and all the advancements made in understanding the pathogenesis of the virus and the immune response, the realisation of a suitable vaccine for HIV remains elusive. The use of live-attenuated virus as immunogen as obtained in other vaccines, has been prohibited due to safety concerns [56]. Therefore, scientists have developed many recombinant technologies an attempt to create immunogens that can elicit a strong enough immune response that can offer adequate protection against HIV [3]. Initial attempts focusing on inducing HIV-1 neutralising antibodies using recombinant monomeric envelope gp120 (AIDSVAX) as immunogen, failed [57 – 59]. Therefore, since CD8 T-cell responses to some extent control viral replication, recent vaccine studies have focused on eliciting cellular immune responses [3]. However, understanding the true correlates of protection has remained a great challenge [60] and it is generally accepted that both humoral and cell mediated immunity must be considered in the development of HIV vaccines [55]. Pending the arrival of a suitable vaccine foe HIV, the only effective options available to aid in at least slowing down the AIDS pandemic are prevention and access to antiretroviral treatments. However, implementing these policies especially in resource-limited regions will require the development of improved infrastructures and the partnership of civil societies with the public sector [3].

7. Mucosal Immunity to HIV: An immune response controls but does not eliminate HIV

Since the discovery of HIV in 1983, research on the AIDS virus has come a long way leading to a better understanding of the virus and how it is transmitted, as well as its interaction with the human immune system. These discoveries have resulted in the development of highly active antiretroviral drugs which have drastically reduced HIV-related morbidity and mortality rates. However, a lot remains undiscovered in many vital areas of the disease such as, understanding the exact correlates of immunity, determinants of disease progression, and ways of eradicating the viral reservoirs in the body. These limitations have resulted in futile attempts in the development of a cure for the disease

as well as an effective vaccine to prevent infection. Mucosal surfaces are constantly exposed to foreign antigens and the ability to protect the host from disease arises from 'immune surveillance' carried out by several mechanisms at the host-environment interface [61]. They also serve as the major portal of entry for HIV and accommodate majority of the lymphocytes, including $CD4^+$ T-cells which are the major targets of infection. HIV is a mucosal pathogen as proven by a number of studies which identified AIDS-related diarrhoea and wasting syndrome [62, 63], as well as a preferential depletion of the $CD4^+$ T-cells in the gastrointestinal lamina propria at the early stage of infection [64, 65]. Similar results have been observed in SIV-infected macaques which also showed a preferential depletion of mucosal $CD4^+$ T-cells at the acute infection stage [66, 67]. Therefore, a significant number of recent studies have been dedicated understanding host-pathogen interactions in the gastrointestinal and genitourinary tracts, in order to clarify the role of mucosal immunity in controlling HIV infection. Infection with HIV generates a strong immune response that only contains the virus without completely eliminating it. Therefore, in most cases of HIV infection, the virus is only contained by the immune system for a while, after which there is a gradual but definite decline in the number of $CD4^+$ T-cells which eventually results in disease. The major antigen-presenting cells of the immune system are dendritic cells, macrophages and B cells [19]. Dendritic cells are considered to be essential for the initiation of primary antigen-specific immune reactions and are therefore regarded as the most potent inducers of specific immune responses [19]. Their mechanism of action involves migrating from the bone marrow towards the primary lymphatic organs, into the submucosal tissue of the gut, the genitourinary system and the respiratory tract. Along the way, they usually pick up and process soluble antigens before migrating into the secondary lymphatic organs where they are bound to activate antigen-specific T cells [19]. Due to their vital role in adaptive immune response, dendritic cells are being considered as possible tools to be used in inducing or expanding HIV-specific T cells. Consequently, studies have been carried out which have attempted the use of dendritic cells in vaccination [68]. Various studies which tried to show what happens during the first few days of HIV infection, have shown that there is extensive viral replication in the lymphatic tissue [69, 70] and a preferential depletion of $CD4^+$ T-cells in the intestinal lamina propria [71]. A special study on macaques that were intravaginally inoculated with SIV was carried out by Li and his colleagues to show the extent of viral replication at the mucosal regions during the early stage of infection [72]. In this study, in-situ hybridisation and immunohistochemistry was used to generate a digital map which showed the locations of SIV RNA^+ cells in the cervix and vagina, after the first 10 days of infection. There was an early increase in the expression of MIP-3α, which was associated with an infux of $CD123^+$ plasmacytoid dendritic cells (pDC). The pDC cells secreted chemokines that attracted $CCR5^+CD4^+$ T-cells to the endocervix, leading to further spread of the infection [19]. In addition, the early infection stage of HIV is also characterised by an abundant production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, which further promotes viral replication [19]. However, this study also showed the possibility of interrupting infection and keeping it from spreading beyond the transmission site by the addition of an anti-inflammatory compound such as glycerol monolaurate (GML) to the cervicovaginal mucosa [72]. Therefore, GML-treated macaques were observed to be completely protected from high-dose mucosal challenge with SIVmac, leading to the conclusion that a naturally occurring compound can provide protection from mucosal exposure by simply inhibiting immune activation and the production of pro-inflammatory cytokines [72]. Cytotoxic T cells (CTL) have the ability of recognising and eliminating virus-infected cells and they are also known to invade sites of HIV replication, where they kill infected cells before the infected virus is released [73], thereby containing the viral load levels. Studies which identified the clinical importance of viral load control by cytotoxic T cells, showed an inverse correlation between CD8 cytotoxic T cells level and viral RNA levels [73]. Therefore, patients with higher CD8 T cells levels, showed slower progression to disease than those with lower levels of CD8 T cells. Other experiments conducted on macaques also showed similar relationship between viral levels and cytotoxic T cells levels. It was further shown that treatment of these infected animals with monoclonal antibodies that remove CD8 T cells was followed by a significant increase in viral load levels [73]. Evidence exists which shows that the in-vivo ratio

between CD8+ effector cells and infected CD4+ T-cells (E : T) at the acute stage of HIV infection, may be critical for controlling viral dissemination and HIV disease progression [71]. Earlier studies have suggested that the immune system eventually fails in its fight against the virus because the mucosal HIV/SIV specific cytotoxic T-cells are elicited in small quantities and not early enough during infection [74]. Further studies by a team of scientists which used a combination of in-situ hybridisation and MHC class I tetramer staining to quantify infected cells and SIV-specific CTL in mucosal tissues, found significant reductions in viral load during early infection was associated with E:T ratios of at least 100:1 in the female reproductive tract [75]. Therefore, eliciting a cell-mediated immune response near the portal of entry soon enough and in the right quantities, could help to prevent viral dissemination [75]. CTL responses have also been studied in chronic HIV infection to determine its relevance and two studies showed that Gag-specific rectal CD8+ T-cell responses in chronically infected patients were positively associated with CD4 cell count and inversely related to plasma viral load [76, 77]. However, the protective role for these CTL responses during the chronic stage remains inconclusive as there is the possibility that the robust CTL responses are as a result of the CD4+ T-cell preservation and relatively low viral load levels [71]. Nonetheless another study which measured rectal CTL responses in 28 patients who control HIV without therapy, showed that polyfunctional Gag-specific CD8+ T-cells were significantly more abundant their rectal mucosa than in non-controllers and patients on antiretroviral therapy [78]. Therefore strong CTL responses during the chronic HIV infection stage can be associated with a significant delay in disease progression. Unlike CTL responses, HIV-1 specific humoral immune response and the course of disease is less understood. During HIV infection antibodies against gp120 and gp41 envelope viral proteins are usually produced in response to the infection, but do not succeed in clearing the infection [73]. There is strong evidence which suggests that antibodies cannot significantly control already established disease [79]. However, an antibody cocktail of various neutralising antibodies was able to prevent mucosal SIV infection in an SIV model [80], suggesting that antibodies are extremely important in the development of a preventive vaccine. Other studies have shown high titres of anti-p24 antibodies [81], persistence of neutralising antibodies against primary and autologous viruses [82] and lack of antibodies against certain gp120 epitopes [83], in patients with slow progression to disease. While in highly exposed persistently seronegative (HEPS) individuals, the specific mucosal antibodies which confer this protection have remained controversial [84]. Several studies have reported HIV-specific IgA which have been shown to neutralise HIV infectivity in vitro, in the plasma or mucosal secretions of HEPS individuals [85 – 87], while other studies have failed to identify such antibodies [88 – 90].

8. Mucosal immune reconstitution after ART

Previous studies have shown that immune activation in HIV/SIV infection is associated with a disruption of lymphoid tissue architecture and deposition of collagen in lymph nodes, thereby limiting CD4+ T-cell repopulation after the commencement of ART [91]. Recent studies have further reported more extensive collagen deposition in ileal Peyer's patches than in lymph nodes during CD4+ T-cell depletion [92]. Therefore, the commencement of ART during early infection resulted in an increase in CD4+ central memory cells in Peyer's patches but there was no such increase in effector memory cells in the ileal lamina propria [73]. In addition to the inability of the CD4+ T-cells to repopulate the gastrointestinal tract after ART, studies have also shown a persistence of HIV proviral DNA in CD4+ T-cells from terminal ileum even after 9.9 years of effective therapy [93]. However, a study on 23 HIV-infected patients on long-term ART with durable suppressed viral load levels, showed CD4+ T-cell reconstitution in their sigmoid colon to levels statistically equivalent to uninfected individuals [94]. The extent of repopulation in the

terminal ileum of these patients remains unknown [73]. An analysis of jejunal biopsies of 14 patients on long-term ART showed that most of the patients had detectable mucosal proviral DNA despite undetectable plasma viremia and CD4+ T-cell percentages comparable to uninfected controls [95]. This shows a partial immune reconstitution in the jejunal mucosa following ART. Therefore, it can be said that there is a partial restoration of gastrointestinal CD4+ T-cells in patients on long-term ART [73]. However, this restoration might be hindered by factors such as immune activation or collagen deposition, and enhanced by a durable control of viral replication [73].

9. The role of cytokines in HIV-1 infection

Cytokines are cellular proteins which regulate immune function and mediate interaction between various immune cells. They are pleiotropic and redundant in nature, contributing to chemical signalling pathways that regulate development, tissue repair, haematopoiesis, inflammation and immune responses [96]. HIV-1 infection stimulates the production of a variety of cytokines which play a key role in HIV-1 pathogenesis and disease progression. The role of cytokines in HIV-1 infection, although now better understood still remains to be completely elucidated. While some cytokines have been found to enhance viral replication, others inhibit viral replication; and there are cytokines which enhance viral replication under certain conditions but inhibit HIV-1 replication under different conditions. During HIV-1 infection, early pro-inflammatory responses are very important for the development of innate and adaptive immunity [96]. The acute infection stage is characterised by pro-inflammatory cytokines that includes IL-1, IL-6, TNF-α and IFN-α/β/γ; and anti-inflammatory cytokines which includes IL-4, IL-10 and IL-13 [96]. However, as the disease progresses, there is a peak in TNF-α, IL-10 and IL-6 cytokines at the later stages of infection [97-99]. In addition to chronic immune activation, cytokine production may be directly induced by viral proteins. For instance, gp120 has been shown to induce the secretion of IL-1, IL-6, IL-8, TNF-α, IL-4, IL-10 and IL-13 [100, 101]; Tat, a regulatory protein induces IL-2, IL-6, IL-8, TGF-β1, TNF-α and MCP-1 [102, 103]; and Nef induces IL-1β, IL-6, IL-10, IL-15, TNF-β and IFN-γ [104, 105]. Cytokines are mainly produced by T cells namely, Th1 cells which secrete IL-2 and IFN-γ and are mainly involved in cellular immune responses, such as cytotoxic T cells proliferation; and Th2 cells which produce IL-4, IL-5, IL-6, IL-10 and IL-13 and are characterised by an increase in humoral responses [106]. Also recently discovered are the Th17 cells which produce the cytokines IL-17A [107] and IL-17F [108]; and have been shown to act on antigen-presenting cells such as the macrophages, and induce cytokine and chemokine production [109]. Th17 cytokines are also known to act as a bridge between innate and adaptive immune responses in host defense against pathogens at the mucosal region [61]. A Th1 – Th2 hypothesis of HIV-1 infection was postulated by Clerici and Shearer, which suggested that there is a reduction in Th1 cell activity and an increase in Th2 cell activity, as the disease progresses to AIDS [110]. However, whether this cytokine shift from Th1 to Th2 is really associated with HIV-1 disease progression remains to be confirmed. Various studies have revealed specific roles played by various cytokines in HIV-1 infection. They are mainly known to induce inflammatory responses, especially at the early stage of infection which is characterised by chronic immune activation, partly driven by an increased expression of pro-inflammatory cytokines [111]. As a result, the host attempts to counterbalance this immune activation by inducing the production of anti-inflammatory cytokines and other mediators of immune suppression. Consequently, recent studies have shown an increased expression of IL-32 in both the gut and lymphatic tissue of HIV-1 infected individuals, which may play a role as a mediator of immune

expression [112]. Although IL-32 moderates chronic immune activation to prevent immune associated disease, it also dampens antiviral immune response, thereby supporting HIV-1 replication [112]. Apart from inflammatory functions during HIV-1 infection, cytokines are also known to be involved in other important functions such as homeostatic functions. IL-7 for instance, is responsible for the maintenance of CD4 T-cell homeostasis in HIV-1 infected individuals [96]. Resting T cells which are normally resistant to HIV-1 infection can become susceptible to HIV-1 infection when stimulated with IL-2, IL-4, IL-7 or IL-15 or at a lower level, with IL-6, in the absence of any other stimuli [113]. IL-2, IL-7 and especially IL-15 have the potentials of reversing HIV-1 specific T cell anergy and can be further investigated for inducing non-specific T cell responses [114].

10. Cytokine secretions and AIDS-associated opportunistic infections

HIV-1 infection is characterised by chronic immune activation which often results in impaired effector functions, such as alterations in cytokine production [115], which may contribute to the development of opportunistic infections especially during the late stage of the disease. Although antiretroviral therapy has contributed immensely to the reduction of the incidence of opportunistic infections, many HIV-infected individuals remain susceptible to disease due to the persistence of viral reservoirs, as well as treatment failure or drug resistance due to non-adherence to treatment [116]. Pulmonary infections are the major contributors of morbidity and mortality rates in HIV-1 infection [117] and patients infected with HIV-1 remain susceptible to pulmonary infections, even with the application of antiretroviral therapy. Recent studies suggest that this predisposition to pulmonary infections might be attributed to changes in the innate immune function [116]. In the lung, alveolar macrophages are the first line of defence against pathogens through protective innate immune effector functions such as the induction of the pro-inflammatory cytokine TNF-α [116]. However, in patients infected with HIV-1, decreased concentrations of TNF-α was observed in their bronchoalveolar lavage fluid samples [116]. It was therefore concluded that HIV infection alters the expression of Toll-like receptors with subsequent changes in mitogen-activated protein kinase signalling and cytokine production, ultimately leading to deficiencies in innate immune responses that predisposes HIV-positive patients to pulmonary infections [116]. Earlier studies on HIV-1 infected patients with *Mycobacterium avium* infections showed that these patients had higher secretion levels of IL-1, IL-6 and TNF-α, as compared to HIV-1 infected patients with other opportunistic infections [118]. *Mycobacterium avium* was also associated with increased viral load levels and diminished immune response to viral antigens as compared to AIDS patients with other opportunistic infections [118]. This therefore means that *Mycobacterium avium* contributes negatively to disease progression in HIV-1 infected patients. *Mycobacterium tuberculosis* is one of the commonest opportunistic infections observed in HIV-1 infected patients, with mortality rates as high as 20% in some parts of the world [119]. Unlike other opportunistic infections *Mycobacterium tuberculosis* occurs quite early in HIV-1 infection in a significant number of HIV infected patients with relatively high CD4+ T-cell counts [120]. However, the reason for this high rate of infection in HIV-infected patients is not well understood. In a recent study, it was found that in vitro HIV infection of alveolar macrophages from healthy persons reduced both TNF-α release and alveolar macrophage apoptosis in response to virulent or irradiated *Mycobacterium tuberculosis* [121]. TNF-α depended apoptosis of human macrophages is a critical innate immune response in the control of *M. tuberculosis* infection [121]. Therefore, since HIV seems to impair this innate host cell response to *M. tuberculosis*, HIV-1 infected patients lack the ability to effectively control this infection which

may also contribute to disease progression. Immune dysfunction which is central in AIDS also results in increased susceptibility to another very common opportunistic infection known as *Pneumocystis carinii*. Cell-mediated immunity which includes the production of cytokines and different T cell subsets is believed to be the major mechanism by which the host controls *P. carinii* infection [122]. A study which examined the proliferative capacity and cytokine secretion pattern of peripheral blood mononuclear cells (PBMC) from HIV-1 infected patients in response to the major surface glycoprotein (MSG) of *P. carinii* showed significantly less proliferative responses to MSG and less secretion of IFN-γ than in healthy controls [123]. This immune dysfunction in HIV-1 infected individuals may be responsible for the high prevalence of the disease among HIV-infected patients and also for the high potentials of disease recurrence in treated patients.

11. The pattern of cytokine secretion in HIV/HBV co-infected patients

Co-infection with Hepatitis B virus (HBV) is very common among HIV-1 infected patients due to their common routes of transmission [124]. However, studies elucidating the interactions between HBV, HIV-1 and the immune system are not very common and as such a lot remains undiscovered. Chronic immune activation is one of the major features of HBV replication [125] and it has been stipulated that this could result in faster CD4 T-cell declines in HIV/HBV co-infected individuals [126]. However, the influence of HBV on HIV disease progression is not clearly understood and studies aimed at elucidating this have produced conflicting results. It is known that HIV infection impacts negatively on all the phases of HBV, resulting in increased rates of persistent infection, higher HBV DNA levels, lower rates of hepatitis B e antigen loss, increased risk for cirrhosis and increased rates of liver-related mortality [124]. Therefore, understanding the mechanisms behind this event is a key factor in the management of hepatitis B in HIV infection. HBV specific T cells play a key role in the control of HBV replication and in the pathogenesis of liver disease [127]. However, various studies have shown an impairment in T-cell mediated immunity in HIV/HBV co-infected individuals. A study by Chang and colleagues which examined HBV specific T-cell responses in HIV-1/HBV co-infected patients and in HBV monoinfected patients, showed that there was no significant difference in the overall magnitude of HBV-specific T-cell responses between both groups of patients; however, the quality of response was significantly impaired in the co-infected individuals compared with the HBV monoinfected individuals [127]. The co-infected patients rarely produced more than one cytokine and responded to fewer HBV proteins than the monoinfected patients [127]. Also, quality of HBV-specific T-cell responses was found to increase with an overall increase in $CD4^+$ T-cell levels [127]. Another study which measured Th1 and Th2 cytokine levels in HIV-1/HBV co-infected patients and HBV monoinfected patients showed that HIV-1/HBV co-infections had lower expression of Th1 cytokines with an enhancement of Th2 cytokine expression [128]. Therefore, it is stipulated that HIV may induce an increase in HBV replication by decreasing Th1 responses [128]. The study of immune responses to HIV/HBV co-infection by measuring cytokine levels is crucial to understanding the pathogenesis of both diseases. Both viral infections are characterised by immune activation which results in increased viral replication. Liver disease caused by chronic HBV infection is currently an important cause of morbidity and mortality among HIV-infected patients in the western world, where most AIDS-related opportunistic infections have declined dramatically due to the widespread use of potent antiretroviral therapies [129, 130]. Over the past few years several reports have addressed the issue of viral hepatitis and HIV infection. However, as a result of the larger impact of hepatitis C virus (HCV), many studies have focused

mainly on HIV and HCV co-infection [131], with only a few studies dedicated to HIV/hepatitis B virus co-infections [132]. HBV pathogenesis is largely immune mediated and an intrahepatic inflammatory leukocyte infiltrate is the histological marker of disease severity [133]. Consequently HBV infected individuals with impaired immune responses such as HIV-positive individuals suffer less overt disease in the acute phase [134]. Experimental evidence suggests that immune response factors, especially pro-inflammatory cytokines, play an important role in liver injury induced by HBV [135– 137]. Recent studies also suggest that treatment outcomes may depend on the development of type Th1 and Th2 cell responses [138]. Specifically, activation of Th1 immunity may contribute to successful treatment of hepatitis B [139]. It has been shown that patients who clear HBeAg have higher IL-2 cytokine levels, which promote differentiation of CD8+ T cells [140]. Therefore, pro-inflammatory cytokines which play an important role in liver injury are also involved in the regeneration of liver tissue after injury [137]. A host of other cytokines both pro- and anti-inflammatory cytokines, have also been implicated in the pathogenesis of HIV disease and in certain cases it has been quite difficult to allocate distinct roles to specific cytokines, due to the fact that cytokines are pleiotropic in nature and have a huge tendency to interchange roles. However, further studies will be required in order to correlate specific cytokine secretion patterns with specific opportunistic infections, and HIV-1/HBV co-infections. These will in-turn enable scientists to further understand the existing relationships between HIV-1 and the immune system as well as interactions between HIV-1 and HBV.

12. References

[1] Barre-Sinoussi F, Chermann JC, Rey F, et al, Isolation of a T-lymphotropic retrovirus from a patient at risk for AIDS, *Science*, 220, 868-71, **1983**

[2] Gallo RC, Sarin PS, Gelmann EP, et al, Isolation of human T cell leukemia virus in acquired immune deficiency syndrome (AIDS), *Science*, 220, 865-7, **1983**

[3] Viviana Simon, David D Ho, Quarraisha Abdool Karim, HIV/AIDS epidemiology, pathogenesis, prevention, and treatment, *The Lancet*, 368 (9534), 489 – 504, **2006**

[4] Kilmarx PH, Global epidemiology of HIV, *Curr Opin HIV AIDS,* 4, 4, 240-6, **2009**

[5] UNAIDS, Report on the global AIDS epidemic, Geneva, 2**008**

[6] UNAIDS, Report on the global AIDS epidemic, a UNAIDS 10th anniversary special edition, **2006**

[7] Quinn C, Overbaugh J, HIV/AIDS in women, an expanding epidemic, *Science*, 308, 1582-1583, **2005**

[8] Abdool-Karim Q, Abdool-Karim SS, The evolving HIV epidemic in South Africa, *Int J Epidemiol*, 31, 37-40, **2002**

[9] Pettifor AE, Rees HV, Kleinschmidt I, et al, Young people's sexual health in South Africa, HIV prevalence and sexual behaviors from a nationally representative household survey, *AIDS*, 19, 1525-1534, **2005**

[10] Shisana O, Davids A, Correcting gender inequalities is central to controlling HIV/AIDS, *Bull World Health Organ*, 82, 812, **2004**

[11] Siegfried N, Muller M, Volmink J, et al, Male circumcision for prevention of heterosexual acquisition of HIV in men, *Cochrane Database Syst Rev*, 3, CD003362, **2003**

[12] Aral SO, Padian NS, Holmes KK, Advances in multilevel approaches to understanding the epidemiology and prevention of sexually transmitted infections and HIV, an overview, *J Infect Dis*, 191, suppl 1, S1-S6, **2005**

[13] Bloom SS, Urassa M, Isingo R, *et al*, Community effects on the risk of HIV infection in rural Tanzania, *Sex Transm Infect*, 78, 261-266, **2002**

[14] Nunn AJ, Wagner HU, Kamali A, *et al*, Migration and HIV-1 seroprevalence in a rural Ugandan population, *AIDS*, 9, 503-506, **1995**
[15] Quinn TC, Wawer MJ, Sewankambo N, *et al,* Viral load and heterosexual transmission of human immunodeficiency virus type 1, Rakai Project Study Group, *N Engl J Med*, 342, 921-929, **2000**
[16] Wawer MJ, Gray RH, Sewankambo NK, *et al*, Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda, *J Infect Dis*, 191, 1403-1409, **2005**
[17] Galvin SR, Cohen MS, The role of sexually transmitted diseases in HIV transmission, *Nat Rev Microbiol*, 2, 33-42, **2004**
[18] Andrea Rubbert-Roth, Georg Behrens and Mario Ostrowski HIV, **2009***
[19] Liu SL, Schacker T, Musey L, *et al,* Divergent patterns of progression to AIDS after infection from the same source, HIV type 1 evolution and antiviral responses, J Virol, 71, 4284-95, **1997**
[20] Kirchhoff F, Greenough TC, Brettler DB, Sullivan JL, Desrosiers RC, Brief report, Absence of intact nef sequences in a long-term survivor with nonprogressive HIV-1 infection, *N Engl J Med*, 332, 228-32, **1995**
[21] Levy J.A., Pathogenesis of HIV infection, *Microbiol Rev*, 57, 183-289, **1993**
[22] Stephen M Smith, The pathogenesis of HIV infection, stupid may not be so dumb after all, *Retrovirology*, 3, 60, **2006**
[23] Vergis EN, Mellors JW, Natural history of HIV-1 infection, *Infect Dis Clin North Am*, 14, 809-825, **2000**
[24] Schindler M, Munch J, Kutsch O, Li H, *et al,* Nef-mediated suppression of T cell activation was lost in a lentiviral lineage that gave rise to HIV-1, *Cell*, 125,1055-1067, **2006**
[25] Ploquin MJ, Desoutter JF, Santos PR, Pandrea I, *et al*, Distinct Expression Profiles of TGF-beta1 Signaling Mediators in pathogenic SIVmac and non-pathogenic SIVagm Infections, *Retrovirology*, 3, 37, **2006**
[26] Giorgi JV, Lyles RH, Matud JL, Yamashita TE, *et al,* Predictive value of immunologic and virologic markers after long or short duration of HIV-1 infection, *J Acquir Immune Defic Syndr*, 29, 346-355, **2002**
[27] Giorgi JV, Majchrowicz MA, Johnson TD, Hultin P, *et al,* Immunologic effects of combined protease inhibitor and reverse transcriptase inhibitor therapy in previously treated chronic HIV-1 infection, *AIDS*, 12,1833-1844, **1998**
[28] Hazenberg MD, Otto SA, van Benthem BH, Roos MT, *et al,* Persistent immune activation in HIV-1 infection is associated with progression to AIDS, *AIDS*, 17,1881-1888, **2003**
[29] Daniel Douek, Making Sense of HIV Pathogenesis, *The PRN Notebook*, 10(3), 9-12, **2005**
[30] Mattapallil JJ, Douek DC, Hill B, et al, Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection, *Nature*, 434, 7037, 1093-7, **2005**
[31] Veazey RS, DeMaria M, Chalifoux LV, et al, Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection, *Science*, 280, 5362, 427-3, **1998**
[32] Louis J Picker and David I Watkins, HIV pathogenesis, the first cut is the deepest, *Nature Immunology*, 6, 430 – 432, **2005**
[33] Stefano Bertozzi, Nancy S, Padian, Jeny Wegbreit, *et al*, HIV/AIDS Prevention and Treatment, Disease Control Priorities in Developing Countries, 331-369,*
[34] Askew, I,, and M, Berer, The Contribution of Sexual and Reproductive Health Services to the Fight against HIV/AIDS, A Review, *Reproductive Health Matters* , 11, 22, 51–73, **2003**
[35] Royce,R,A,,A,Sena,W,Cates,M,S,Cohen, ,SexualTransmission of HIV, *New England Journal of Medicine* , 336 15, 1072–78, **1993**
[36] Institute of Medicine, *The Hidden Epidemic, Confronting Sexually Transmitted Diseases*, Washington, DC, National Academy Press, **1997**
[37] Hosken NA, Development of a therapeutic vaccine for HSV-2, *Vaccine*, 23, 2395-2398, **2005**
[38] Corey L, Wald A, Celum CL, Quinn TC, The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission, a review of two overlapping epidemics, *J Acquir Immune Defic Syndr*, 35, 435-445, **2004**
[39] Nagot N, Foulongne V, Becquart P, et al, Longitudinal assessment of HIV-1 and HSV-2 shedding in the genital tract of West African women, *J Acquir Immune Defic Syndr*, 39, 632-634, **2005**

[40] Buve, A, "HIV Epidemics in Africa, What Explains the Variations in HIV Prevalence?" *International Union of Biochemistry and Molecular Biology Life*, 53, 4–5, 193–95, **2002**

[41] Gregson, S,, P, R, Mason, G, P, Garnett, et al, A Rural HIV Epidemic in Zimbabwe? Findings from a Population-Based Survey, **2005**

[42] Mbopi Keou, F, X,, G, Gresenguet, P, Mayaud, *et al,* Genital Herpes Simplex Virus Type 2 Shedding Is Increased in HIV-Infected Women in Africa, *AIDS* 13, 536–37, **1999**

[43] Schwebke JR, Abnormal vaginal flora as a biological risk factor for acquisition of HIV infection and sexually transmitted diseases, *J Infect Dis*, 192, 1315-1317, **2005**

[44] van der Straten A, Kang MS, Posner SF, et al, Predictors of diaphragm use as a potential sexually transmitted disease/HIV prevention method in Zimbabwe, *Sex Transm Dis*, 32, 64-71, **2005**

[45] Weiss, H, A,, M, A, Quigley, and R, J, Hayes, Male Circumcision and Risk of HIV Infection in Sub-Saharan Africa, A Systematic Review and Meta-Analysis, *AIDS* , 14, 15, 2361–70, **2000**

[46] Auvert, B,, A, Buve, E, Lagarde, *et al,* Male Circumcision and HIV Infection in Four Cities in Sub-Saharan Africa, *AIDS* , 15 Suppl, 4, S31–40, **2001**

[47] Donnelly, J, Circumcised Men Less Likely to Get AIDS, *Boston Globe* **2004**

[48] Auvert, B,, A, Puren, D, Taljaard, et al, Impact of Male Circumcision on the Female-to-Male Transmission of HIV, Paper presented at the 3rd IAS Conference on HIV Pathegenosis and Treatment, Rio de Janeiro, July 24–27, **2005**

[49] Halperin DT, Fritz K, McFarland W, Woelk G, Acceptability of adult male circumcision for sexually transmitted disease and HIV prevention in Zimbabwe, *Sex Transm Dis*, 32, 238-239, **2005**

[50] Garenne M, Male, Circumcision and HIV control in Africa, *PLoS Med*, 3, e78, **2006**

[51] Quinn, T, C,, M, J, Wawer, N, Sewankambo, *et al,* Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1, Rakai Project Study Group, *New England Journal of Medicine* 342, 13, 921–29, **2000**

[52] Palella, F, J,, K, M, Delaney, A, C, Moorman, *et al,* Declining Morbidity and Mortality among Patients with Advanced Human Immunodeficiency Virus Infection,"HIV Outpatient Study Investigators, *New England Journal of Medicine*, 338, 13, 853–60, **1998**

[53] Smith K, Powers KA, Cohen MS *et al,* HIV-1 treatment as prevention, the good, the bad, and the challenges *Current Opinion in HIV & AIDS*, 6, 4, 315–325, **2011**

[54] Ho DD, Huang Y, The HIV-1 vaccine race, *Cell*, 110, 135–38, **2002**

[55] Sheppard HW, Inactivated- or killed-virus HIV/AIDS vaccines, *Curr Drug Targets Infect Disord*, 5, 131–41, **2005**

[56] Wyatt R, Sodroski J, The HIV-1 envelope glycoproteins, fusogens,antigens, and immunogens, *Science*, 280, 1884–88, **1998**

[57] Pantophlet R, Burton DR, GP120, target for neutralizing HIV-1 antibodies, *Annu Rev Immunol*, 24, 739–69, **2006**

[58] Cohen J, Public health, AIDS vaccine trial produces disappointment and confusion, *Science*, 299, 1290–91, **2003**

[59] Jamieson BD, Ibarrondo FJ, Wong JT, et al, Transience of vaccine-induced HIV-1-specifi c CTL and defi nition of vaccine"response", *Vaccine*, 24, 3426–31, **2006**

[60] Lokesh Guglani, Shabaana A,Khader, Th17 cytokines in mucosal immunity and inflammation, *Current Opinion in HIV and AIDS*, 5, 120-127, **2010**

[61] Kotler DP, HIV infection and the gastrointestinal tract, *AIDS*, 19,107–117, **2005**

[62] Kotler DP, Gaetz HP, Lange M, et al, Enteropathy associated with the acquired immunodeficiency syndrome, *Ann Intern Med*, 101, 421–428, **1984**

[63] Schneider T, Jahn HU, Schmidt W, et al, Loss of CD4 T lymphocytes in patients infected with human immunodeficiency virus type 1 is more pronounced in the duodenal mucosa than in the peripheral blood, Berlin Diarrhea/Wasting Syndrome Study Group, *Gut*, 37, 524–529, **1995**

[64] Schneider T, Ullrich R, Bergs C, et al, Abnormalities in subset distribution, activation, and differentiation of T cells isolated from large intestine biopsies in HIV infection, The Berlin Diarrhoea/Wasting Syndrome Study Group, *Clin Exp Immunol*, 95, 430–435, **1994**

[65] Heise C, Miller CJ, Lackner A, et al, Primary acute simian immunodeficiency virus infection of intestinal lymphoid tissue is associated with gastrointestinal dysfunction, *J Infect Dis*, 169,1116–1120, **1994**

[66] Heise C, Vogel P, Miller CJ, et al, Simian immunodeficiency virus infection of the gastrointestinal tract of rhesus macaques, Functional, pathological, and morphological changes, *Am J Pathol*, 142,1759–1771, **1993**

[67] Lu W, Arraes LC, Ferreira WT, Andrieu JM, Therapeutic dendritic-cell vaccine for chronic HIV-1 infection, *Nat Med*, 10, 1359-1365, **2004**

[68] Embretson J, Zupancic M, Ribas JL, et al, Massive covert infection of helper T lymphocytes and macrophages by HIV during the incubation period of AIDS, *Nature*, 362, 359-62, **1993**

[69] Pantaleo G, Graziosi C, Demarest JF, et al, HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease, *Nature*, 362, 355-8, **1993**

[70] Barbara L, Shacklett, Immune Responses to HIV and SIV in Mucosal Tissues, "Location, Location, Location, *Curr Opin HIV AIDS*, 5, 2, 128–134, **2010**

[71] Li Q, Estes JD, Schlievert PM, et al, Glycerol monolaurate prevents mucosal SIV transmission, *Nature*, 458, 1034–1038, **2009**

[72] Kenneth Murphy, Paul Travers, Mark Walport, Janeway's Immunobiology, seventh edition, Garland Science, Taylor & Francis Group, LLC, ISBN 0815341237 (9780815341239), **2008**

[73] Reynolds MR, Rakasz E, Skinner PJ, et al, CD8+ T-lymphocyte response to major immunodominant epitopes after vaginal exposure to simian immunodeficiency virus, too late and too little, *J Virol*, 79, 9228–9235, **2005**

[74] Li Q, Skinner PJ, Ha SJ, et al, Visualizing antigen-specific and infected cells in situ predicts outcomes in early viral infection, *Science*, 323,1726–1729, **2009**

[75] Critchfield JW, Lemongello D, Walker DH, et al, Multifunctional human immunodeficiency virus (HIV) gag-specific CD8+ T-cell responses in rectal mucosa and peripheral blood mononuclear cells during chronic HIV type 1 infection, *J Virol*, 81,5460–5471, **2007**

[76] Critchfield JW, Young DH, Hayes TL, et al, Magnitude and complexity of rectal mucosa HIV-1-specific CD8+ T-cell responses during chronic infection reflect clinical status, *PLoS One*, 3, e3577, **2008**

[77] Ferre AL, Hunt PW, Critchfield JW, et al, Mucosal immune responses to HIV-1 in elite controllers, a potential correlate of immune control, *Blood*, 113, 3978–3989, **2009**

[78] Schmitz JE, Kuroda MJ, Santra S et al, Effect of humoral immune responses on controlling viremia during primary infection of rhesus monkeys with simian immunodeficiency virus, *J Virol*, 77, 2165-2173, **2003**

[79] Ferrantelli F, Rasmussen RA, Buckley KA et al, Complete protection of neonatal rhesus macaques against oral exposure to pathogenic simian-human immunodeficiency virus by human anti-HIV monoclonal antibodies, *J Infect Dis*, 189, 2167-2173, **2004**

[80] Hogervorst E, Jurriaans S, de Wolf F, et al, Predictors for non-and slow progression in HIV type 1 infection, low viral RNA copy numbers in serum and maintenance of high HIV-1 p24-specific but not V3-specific antibody levels, *J Infect Dis*, 171, 811-21, **1995**

[81] Montefiori DC, Pantaleo G, Fink LM, et al, Neutralizing and infection-enhancing antibody responses to HIV type 1 in long-term nonprogressors, *J Infect Dis*, 173, 60-7, **1996**

[82] Wong MT, Warren RQ, Anderson SA, et al, Longitudinal analysis of the humoral immune response to HIV type 1 gp160 epitopes in rapidly progressing and nonprogressing HIV-1 infected subjects, *J Infect Dis*, 168, 1523-7, **1993**

[83] Shacklett BL, Understanding the "lucky few", the conundrum of HIV-exposed, seronegative individuals, *Curr HIV/AIDS Rep*, 3, 26–31, **2006**

[84] Beyrer C, Artenstein AW, Rugpao S, et al, Epidemiologic and biologic characterization of a cohort of human immunodeficiency virus type 1 highly exposed, persistently seronegative female sex workers in northern Thailand, Chiang Mai HEPS Working Group, *J Infect Dis*, 179,59–67, **1999**

[85] Hirbod T, Kaul R, Reichard C, et al, HIV-neutralizing immunoglobulin A and HIV-specific proliferation are independently associated with reduced HIV acquisition in Kenyan sex workers,*AIDS*, 22,727–735, **2008**

[86] Hirbod T, Reichard C, Hasselrot K, et al, HIV-1 neutralizing activity is correlated with increased levels of chemokines in saliva of HIV-1-exposed uninfected individuals, *Curr HIV Res*, 6, 28–33, **2008**

[87] Skurnick JH, Palumbo P, De Vico A, et al, Correlates of non-transmission in United States women at high risk of HIV-1 transmission through sexual exposure, *Journal of Infectious Diseases*, 185, 428–438, **2002**

[88] Dorrell L, Hessell AJ, Wang M, et al, Absence of specific mucosal antibody responses in HIV-exposed uninfected sex workers from the Gambia, *AIDS*, 14,1117–1122, **2000**

[89] Mestecky J, Humoral immune responses to the human immunodeficiency virus type-1 (HIV-1) in the genital tract compared to other mucosal sites, *J Reprod Immunol*, 72, 1–17, **2006**

[90] Estes JD, Haase AT, Schacker TW, The role of collagen deposition in depleting CD4+ T cells and limiting reconstitution in HIV-1 and SIV infections through damage to the secondary lymphoid organ niche, *Semin Immunol*, 20,181–186, **2008**

[91] Estes J, Baker JV, Brenchley JM, et al, Collagen deposition limits immune reconstitution in the gut, *J Infect Dis*, 198, 456–464, **2008**

[92] Chun TW, Nickle DC, Justement JS, et al, Persistence of HIV in Gut-Associated Lymphoid Tissue despite Long-Term Antiretroviral Therapy, *J Infect Dis,* **2008**

[93] Sheth PM, Chege D, Shin LY, et al, Immune reconstitution in the sigmoid colon after long-term HIV therapy, *Mucosal Immunol*, 1, 382–388, **2008**

[94] Macal M, Sankaran S, Chun TW, et al, Effective CD4+ T-cell restoration in gut-associated lymphoid tissue of HIV-infected patients is associated with enhanced Th17 cells and polyfunctional HIV-specific T-cell responses, *Mucosal Immunol*, 1,475–488, **2008**

[95] A, Llano, J,A, Esté, Chemokines and other cytokines in human immunodeficiency virus type 1 (HIV-1) infection, *Inmunología*, 24, 2, 246-260, **2005**

[96] Graziosi C, Gantt KR, Vaccarezza M, Demarest JF, Daucher M, Saag MS et al, Kinetics of cytokine expression during primary human immunodeficiency virus type 1 infection, *Proc Natl Acad Sci*, *USA*, , 93, 4386-4391, **1996**

[97] Rinaldo CR, Jr,, Armstrong JA, Kingsley LA, Zhou S, Ho M, Relation of alpha and gamma interferon levels to development of AIDS in homosexual men, *J Exp Pathol*, 5(3), 127-32, **1990**

[98] Clerici M, Hakim FT, Venzon DJ, et al, Changes in interleukin-2 and interleukin-4 production in asymptomatic, human immunodeficiency virus-seropositive individuals, *J Clin Invest*, 91,759-765, **1993**

[99] Patella V, Florio G, Petraroli A, Marone G, HIV-1 gp120 induces IL-4 and IL-13 release from human Fc epsilon RI+ cells through interaction with the VH3 region of IgE, *J Immunol*, 164, 589-595, **2000**

[100] Ameglio F, Capobianchi MR, Castilletti C, et al, Recombinant gp120 induces IL-10 in resting peripheral blood mononuclear cells, correlation with the induction of other cytokines, *Clin Exp Immunol*, 95, 455-458, **1994**

[101] Chen P, Mayne M, Power C, Nath A, The Tat protein of HIV-1 induces tumor necrosis factor-alpha production, Implications for HIV-1-associated neurological diseases, *J Biol Chem*, 272, 22385-22388, **1997**

[102] Lim SP, Garzino-Demo A, The human immunodeficiency virus type 1 Tat protein up-regulates the promoter activity of the beta-chemokine monocyte chemoattractant protein 1 in the human astrocytoma cell line U-87 MG, role of SP-1, AP-1, and NF-kappaB onsensus sites, *J Virol,* 74, 1632-1640, **2000**

[103] Quaranta MG, Camponeschi B, Straface E, Malorni W, Viora M, Induction of interleukin-15 production by HIV-1 nef protein, a role in the proliferation of uninfected cells, *Exp Cell Res*, 250, 112-121, **1999**

[104] Brigino E, Haraguchi S, Koutsonikolis A, Cianciolo GJ, Owens U, Good RA et al, Interleukin 10 is induced by recombinant HIV-1 Ne f prot e in involving the cal c ium/calmodul in-dependent phosphodiesterase signal transduction pathway, Proc Natl *Acad Sci USA*, 94, 3178-3182, **1997**

[105] Mosmann TR, Coffman RL, TH1 and TH2 cells, different patterns of lymphokine secretion lead to different functional properties, *Annu Rev Immunol*, 7, 145-73, **1989**

[106] Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al, A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17, *Nat Immunol*, 6, 11, 1133–41, **2005**

[107] Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al, IL-23 drives a pathogenic T cell population that induces autoimmune inflammation, *J Exp Med*, 201, 2, 233–40, **2005**

[108] Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, et al, Differential roles of interleukin-17A and -17F in host defense against mucoepithelial bacterial infection and allergic responses, *Immunity*, 30, 1,108–19, **2009**

[109] Clerici M, Shearer GM, A TH1-->TH2 switch is a critical step in the etiology of HIV infection, *Immunol Today*, 14,107-111, **1993**

[110] Appay, V,, and D, Sauce, Immune activation and inflammation in HIV -1 infection, causes and consequences, *J, Pathol*, 214, 231–241, **2008**

[111] Smith AJ, Toledo CM, Wietgrefe SW, et al, The Immunosuppressive Role of IL-32 in Lymphatic Tissue during HIV-1 Infection, *J Immunol*, 186, 11, 6576-84, **2011**

[112] Derya Unutmaz, Vineet N, KewalRamani, Shana Marmon, Dan R, Littman, Cytokine Signals Are Sufficient for HIV-1 Infection of Resting Human T Lymphocytes, *J, Exp, Med*, 189, 11, 1735–1746, **1999**

[113] Gu XXJ, Yue FY, Kovacs CM, Ostrowski MA, The Role of Cytokines which Signal through the Common γ Chain Cytokine Receptor in the Reversal of HIV Specific CD4+ and CD8+ T Cell Anergy, *PLoS ONE*, 2, 3, e300, **2007**

[114] Georges Herbein, Audrey Varin The macrophage in HIV-1 infection, From activation to deactivation? *Retrovirology*, 7, 33, **2010**

[115] Marlynne Q,N, Jean-Marie M, Albertina P, *et al*, Immunodeficiency Virus Infection Alters Tumor Necrosis Factor Alpha Production via Toll-Like Receptor-Dependent Pathways in Alveolar Macrophages and U1 Cells, *J Virol*, 82, 16, 7790–7798, **2008**

[116] Corbett, E, L,, C, J, Watt, N, Walker, *et al*, The growing burden of tuberculosis, global trends and interactions with the HIV epidemic, *Arch, Intern, Med*, 163, 1009-1021, **2003**

[117] M Denis, E Ghadirian, Mycobacterium avium infection in HIV-1-infected subjects increases monokine secretion and is associated with enhanced viral load and diminished immune response to viral antigens, *Clin Exp Immunol*, 97, 1, 76–82, **1994**

[118] Liza King, and Shama Ahuja, TB and HIV Coinfection, Current Trends, Diagnosis and Treatment Update Published in New York City by the Physicians' Research Network, Inc, **2006**

[119] Sonnenberg P, Glynn JR, Fielding K,, *et al*, How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners, *J, Infect, Dis*, 191, 150-158, **2005**

[120] Naimish R, Patel, Katharine Swan, Xin Li, Impaired *M, tuberculosis*-mediated apoptosis in alveolar macrophages from HIV+ persons, potential role of IL-10 and BCL-3, *Journal of Leukocyte Biology,* 86, 1, 53-60, **2009**

[121] Eric Y, Denker, Ricardo T, Gazzinelli, Regulation and Function of T-Cell-Mediated Immunity during*Toxoplasma gondii* Infection, *Clinical Microbiology Reviews*, 11, 569-588, **1998**

[122] Sue AT, Niraj SA, George S, Peter DW, Proliferative and cytokine responses of human T lymphocytes isolated from Human Immunodeficiency Virus-infected patients to the major surface glycoprotein of *pneumocystis carinii, The Journal of Infectious Diseases,* 177, 1, 238-241, **1998**

[123] Konopnicki D, A, Mocroft, S, de Wit, F, Antunes, *et al,* Hepatitis B and HIV, prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort, *AIDS*, 19, 593–601, **2005**

[124] George JM Webster, Antonio Bertoletti, Control or persistence of hepatitis B virus, The critical role of initial host–virus interactions, *Immunology and Cell Biology*, 80, 101–105, 1440-1711, **2002**

[125] Massimo Puotia, Carlo Tortia, Raffaele Brunob, *et al,* Natural history of chronic hepatitis B in co-infected patients *Journal of Hepatology*, 44, Supplement 1, S65-S70, **2006**

[126] J, Judy Chang, Sunee Sirivichayakul, Anchalee Avihingsanon, et al, Impaired quality of the Hepatitis B Virus (HBV)-specific T-Cell response in Human Immunodeficiency Virus Type 1 -HBV coinfection, *Journal of Virology*, 83, 7649–7658, **2009**

[127] Jian-Rong Li, Rui-Yu Gong, Kun-Lun Tian, *et al,* Study on the blood-borne virus co-infection and T lymphocyte subset among intravenous drug users, *J Gastroenterol* , 13, 16,, 2357-2362 ISSN 1007-9327, **2007**

[128] Abbott RealTime HIV-1 PMA BP060002 Amendment 19, Summary of safety and effectiveness, **2007**

[129] Thio C, Hepatitis B in the HIV-infected patient, epidemiology, natural history and treatment, *Semin Liver Dis*, 23, 125-136, **2003**

[130] Brook MG, Gilson R, Wilkins E, on behalf of the British HIV Association, BHIVA guidelines , coinfection with HIV and chronic hepatitis B, *HIV Med*, 4, 42-51, **2003**

[131] Nunez M, Puoti M, Camino N, Soriano V, Treatment of chronic hepatitis B in the HIV-infected patients, present and future, *Clin Infect Dis*, 37, 1678-1685, **2003**

[132] Rehermann B, Intrahepatic T cells in hepatitis B, viral control versus liver cell injury, J Exp Med, 191, 1263-1268, **2000**

[133] Lau JY, Wright TL, Molecular virology and pathogenesis of hepatitis B, *Lancet*, 342, 1335-1340, **1993**

[134] Schvoerer E, Navas MC, Thumann C, et al, Production of interleukin -18 and interleukin-12 in patients suffering from chronic hepatitis C virus infection before antiviral therapy, J *Med Viol*, 70, 588-593, **2003**

[135] Petruzzi M, De Benedittis M, Loria MP, et al, Immune response in patients with oral lichen planus and HCV infection, Int J Immunopathol Pharmacol, 17, 93-98, **2004**

[136] Musso T, Cappello P, Stornello S, et al, IL-10 enhances CCL2 release ad chemotaxis induced by CCL16 in human monocytes, *Int J Immunopathol Pharmacol*, 18, 339-349, **2005**

[137] Bertoletti A, D'Elios MM, Boni C, et al, Different cytokine profile of intrahepatic T cells in chronic hepatitis B and hepatitis C virus infection, *Gastroenterology*, 112, 193-199, **1997**

[138] Tsai SL, Sheen IS, Chien RN, et al, Activation of Th1 immunity is a common mechanism for the successful treatment B and C, tetramer assay and therapeutic implications, *J Biomed Sci*, 10, 120-135, **2003**

[139] Hsu HY, Chang MH, Hsieh RP, et al, Humoral and cellular immune responses to hepatitis B vaccination in hepatitis B surface antigen-carrier children who cleared serum-hepatitis B surface antigen, *Hepatology*, 24, 1355-1360, **1996**

[140] Jiang R, Feng X, Guo Y, et al, T helper cells in patients with chronic hepatitis B virus infection, *Chin Med J*, 115, 422-424, **2002**