Journal of
Clinical & Cellular Immunology

Cuadros and Abu-Raddad, J Clin Cell Immunol 2012, S7
DOI: 10.4172/2155-9899.S7-003

Review Article Open Access

From Individuals to Populations: Immunological and Epidemiological Significance of Co-infection in the Dynamics of HIV

Diego F. Cuadros[1,2]* and Laith J. Abu-Raddad[1,2,3]

[1]*Infectious Disease Epidemiology Group, Weill Cornell Medical College - Qatar, Cornell University, Qatar Foundation - Education City, Doha, Qatar*
[2]*Department of Public Health, Weill Cornell Medical College, Cornell University, New York, USA*
[3]*Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA*

Abstract

Immunological activation in response to an invading organism is essential in order to support an effective host response to an invading pathogen. Paradoxically, it also provides an optimal immunological environment for the viral replication in HIV-positive individuals. Indeed, the life cycle of HIV is closely related to the activation state of its host cells since it depends on host cell surface receptor expression for entry, and also on many cellular pathways and transcription machinery for viral gene expression. In this review, we focused on the overall impact of immune activations generated by co-infection in the viral life cycle at host level leading to increases in HIV replication. Moreover, we discussed the epidemiological implications of this increment on the HIV viral load generated by co-infection. Here, we described how the intimate relationship between HIV and the activation state of the host immune system supporting viral replication results in a synergistic interaction between HIV and concurrent infections such as herpes simplex virus type 2 and malaria. A common denominator of these co-infections is the systemic immune activation resulting in an enhancement of the HIV viral load that ultimately might facilitate the transmission of the virus. There is a need, however, for more population-based studies of concurrent infections, and microbe-microbe interaction at the host level to better understand the impact of co-infections on the natural history of HIV.

Keywords: HIV; Co-infection; Immune system; Herpesvirus 2; Malaria

Introduction

Acquired immunodeficiency syndrome (AIDS) was first described in 1981 in homosexual men in North America [1] followed by the first report in patients from Central Africa in 1983 [2]. Three years later it was evident that HIV had spread into populations around the globe and had become an enormous public health problem, particularly in sub-Saharan Africa [3]. Of the estimated 40 million HIV-seropositive patients in 2001, 70% were from sub-Saharan Africa, residence of less than 10% of the human population [4,5].

Notable progress towards understanding the pathogenesis and control of HIV infection has been made since the first case was reported. Epidemiological and statistical models have been developed to estimate the probability of HIV transmission from an infected person to an HIV-negative sex partner during a single episode of sexual intercourse [6-10]. This event is ultimately a biological episode, which depends on the infectiousness of the HIV-infected person and the susceptibility of the uninfected partner [11].

During the first years of the epidemic, most of the studies focused on estimating the risk of HIV transmission assuming a constant per contact probability of transmission and ignoring possible temporal and individual variations. In the past years, however, increased attention has focused on subjects with early (acute) HIV infections, which has allowed a better understanding of the transmission [7,9,12-14]. The most relevant finding from these studies is that infectiousness can be directly correlated with the concentration of HIV-RNA in blood, which indicates shedding of the virus into genital track secretions.

In a pioneer study attempting to correlate the viral load and the transmission of the virus, Quinn and coworkers [15] measured the HIV-RNA load in the blood of more than 15,000 subjects. They found that the virus was rarely transmitted by infected subjects with less than 1500 copies of HIV-RNA/mL, whereas individuals with more than 50,000 copies infected their sexual partners at a rate of 23 per 100 person-years over 30 months. A similar study conducted with discordant couples for HIV status in Uganda also showed the existence of a strong correlation between HIV plasma viral load and HIV transmission rates [16]. The Uganda study indicated that a ten-fold increment in viral load could increase the risk of HIV transmission per sexual contact in 2.45-fold (95% confidence interval (CI) 1.85-3.26).

The acute stage of the infection, lasting only about 2-3 months [17], is followed by a significant decline in the number of viruses to a low level called the set point, which is presumed to be maintained during the chronic stage of the infection [12]. Accordingly, it is believed that infected persons in the chronic stage may be less likely to transmit the virus to their sex partners than persons in the acute stage of the infection [7]. Despite the possible primary role played by the early stage of the HIV infection in the viral load, and therefore in the risk of transmission, growing evidence has suggested the existence of additional biological factors, such as those arising from immune activations, that cause variations in the viral load during the chronic stage of the infection.

The relationship between immune activations generated by concurrent infections and viral load was first documented in the nineties

***Corresponding author:** Diego F. Cuadros, Ph.D, Infectious Disease Epidemiology Group, Weill Cornell Medical College – Qatar, Qatar Foundation - Education City, P.O. Box 24144, Doha, Qatar, Tel: +(974) 4492-8489; Fax: +(974) 4492-8333; E-mail: dfc2002@qatar-med.cornell.edu

Received September 02, 2012; **Accepted** September 06, 2012; **Published** September 13, 2012

Citation: Cuadros DF, Abu-Raddad LJ (2012) From Individuals to Populations: Immunological and Epidemiological Significance of Co-infection in the Dynamics of HIV. J Clin Cell Immunol S7:003. doi:10.4172/2155-9899.S7-003

[18-20]. Many prospective and cross-sectional studies conducted to elucidate the biological and behavioral factors influencing the transmission of HIV in sub-Saharan Africa have consistently found that the presence of other infections such as sexually transmitted infections (STIs) increase the risk of HIV transmission during the chronic stage of the infection [21-25]. These studies evidenced that the viral set point is actually not constant and may be disturbed by reactivations of the immune system such as those resulting from the invasion of other pathogens [26]. Changes in the host immune response may account for variations in the viral load that could make the host more infectious and increase the risk of HIV transmission during the chronic stage of the infection (Figure 1).

To explore the effect of co-infection on the replication of the virus in more detail, and the consequently increment in transmission risk, it becomes essential to study this potentially synergistic relationship at host level. Individual and temporal variations in HIV transmission generated by biological factors such as concurrent infections might explain the heterogeneity and severity of the HIV epidemic, especially in sub-Saharan Africa. This review summarizes current concepts and knowledge about the epidemiological and immunological interrelationship between HIV and concurrent infections that are useful to achieve an understanding of its natural history and pathogenesis. We primarily focus on two infectious diseases, herpes simplex virus type 2 (HSV-2) and malaria, infections that have been proposed as key drivers of the HIV epidemic, particularly in sub-Saharan Africa [27-30].

The Immunology of HIV Infection

Virus biology

HIV is a member of the lentivirus subfamily of retroviruses that produces chronic infections in the host and gradually degenerates the host's immune system [31,32]. The virus structure is composed of a double layer of lipids derived from the host cell that contains two key viral glycoproteins, gp120 and gp41 [33]. These proteins mediate viral entry by the recognition of the cell surface CD4 molecule and a chemokine receptor (either CXCR4 or CCR5) [34,35]. CXCR4 and CCR5 chemokine receptors characterized the tropism of the HIV strains divided into two categories: macrophage tropic (M-tropic) strains and T-cell tropic (T-tropic) strains. M-tropic strains (also referred as R5 viruses), use the CCR5 β-chemokine as a coreceptor [36], which is critical in the initial establishment of the infection. Conversely, disease progression is usually associated with the emergence of T-tropic strains (also referred to as X4 viruses), which use the CXCR4 α-chemokine coreceptor mostly expressed in $CD4^+$ T cells [37,38].

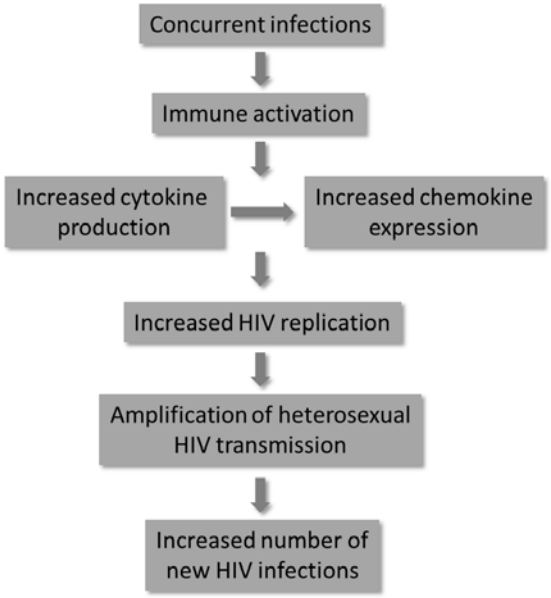

Figure 1: Schematic representation of the impact of concurrent infections on the natural history of HIV.

Two strands of RNA consisting of about 92,000 nucleotide bases, an integrase, a protease, a reverse transcriptase, and two other proteins, p6 and p7, fit inside the viral core [39]. The core of the virus is also composed by three structural proteins: p24, which forms the capsid that encloses two genomic RNA strands and the viral enzymes; p16, anchored to the internal face of the envelope; and p9, a nucleocapsid protein not covalently attached to the viral RNA [40].

Retroviruses such as HIV use a reverse transcriptase enzyme to produce DNA from the virus's RNA template [31]. The cycle begins with the binding of the viral surface glycoprotein gp120 to the cellular CD4 receptor, which triggers a conformational change in gp120. This conformational change allows the interaction between gp120 and the chemokine receptors CCR5 or CXR4. Later, a subsequent formation of a six-helix bundle between the two helical regions of the trimeric gp41 complex mediates the fusion of the virus followed by the release of the viral RNA genome and proteins into the cytoplasm. Subsequently, the viral enzyme reverse transcriptase reverse-transcribes the viral RNA into complementary DNA (cDNA) [41], which is later transported to the nucleus with the activity of the HIV proteins Vpr and Vif.

The virus replicates preferentially in $CD4RO^+$ memory T cells rather than immature $CD5RA^+$ naive lymphocytes [42]. The viral cDNA integrates randomly into the host cell genome by the viral enzyme integrase. After the integration, spliced mRNA transcripts are produced to encode the regulatory proteins Tat, Rev, and Nef. Tat plays an important role on transcription by binding the 5' end of the viral DNA sequence to increase the viral transcription up to 1000-fold [43]. Rev mediates the nuclear export of incompletely spliced transcripts encoding structural proteins, and full-length mRNA virus genome [44]. Nef has multiple functions such as enhancement of virion infectivity, modulation of signal transduction, and facilitating HIV entry into target cells [45]. This proviral transcription is strongly influenced by the state of host cell activation, and is also regulated by sequences in the 5' long terminal repeat (LTR) of the viral genome. LTR is composed by three functional regions: the transactivation response, the core promoter, and the modulatory enhanced region [46].

After the proviral HIV makes complementary copies of RNA strands, some of these strands are cut into segments suitable for protein synthesis required for the production of more viruses. In the second phase, unspliced RNA segments become new viral strands and migrate into the cytoplasm. Two size classes of RNA are produced in this phase: a long unspliced strand that comprises the RNA genome, and a medium length transcript that encodes the coat and the enzymatic proteins. This material is enclosed within the viral core protein to become new viruses and then migrate out of the cell [39].

The host immune system

There are three major types of T cells present in the human immune system: cytotoxic T cells, suppressor T cells and helper T cells (Th).

The presence of specialized receptors on the surface of T cells allows the identification of one of many millions of possible antigens that may invade the body [47]. Each T cell expresses a receptor that binds with the complementary antigen on the foreign particle to neutralize or destroy it. Cytotoxic and suppressor T cells carry the CD8 receptor and are also referred to as cytotoxic cell lymphocytes (CTL), whereas the helper T cells carry the CD4 receptor. HIV mainly targets $CD4^+$ T lymphocytes and cells of monocyte lineage that express the $CD4^+$ receptor [48]. A healthy human adult has about 1000 $CD4^+$ T cells per μL of blood, but in an HIV infected patient the abundance of $CD4^+$ T cells declines to a very low number. A sustained count of $CD4^+$ T cells less than 200/mL in HIV-infected individuals is used as the clinical definition of AIDS [49].

Most activities of Th cells are mediated by the production of proteins called cytokines. The type of Th they become (Th0, Th1, Th2 or Th3) will depend on the type of cytokines these cells will produce [50,51] and will be largely dependent on the nature of the infectious agent. Differentiation of Th1 cells from naïve Th cells is promoted by gamma interferon (IFN-γ). These cells are able to produce interleukin-2 (IL-2), IFN-γ, and tumor necrosis factor alpha and beta (TNF-α and -β) which are not produced by Th2 cells. Conversely, Th2 cells are able to synthesize IL-4, IL-5, IL-6 and IL-10 [50,51].

Intracellular organisms such as virus, bacteria and protozoa typically induce a dominant Th1 immune response that reflects their ability to stimulate IFN-α/β and IL-12 production by macrophages [51], and the induction of IFN-γ production by natural killer (NK) cells and T cells. In contrast, Th2 lymphocyte immune response is triggered by extracellular organisms including helminthic infections, and is characterized by absence of IFN-γ and production of IL-4 [52]. It has been hypothesized that this qualitative Th-type response may also impact AIDS pathogenesis. A switch in the response from Th1 to Th2 and the production of associated cytokines may be related to, and facilitate, disease progression [53].

As described above, HIV infection is characterized by a progressive loss of the $CD4^+$ helper subset of lymphocytes. The loss of Th cells leads to severe damage to the immune function and consequently permits opportunistic infections that would not occur in persons with a healthy immune system [54]. In general, the pattern of HIV infection progression can be subdivided into three phases. The primary or acute phase, which comprises the first weeks after infection, the infected individual usually develops a high virus load and $CD4^+$ T cell concentration transiently falls followed by a recovery to almost normal levels. At the end of this phase there is a decrease of viral load followed by the second (chronic) phase of HIV infection characterized by the lack of any symptomatic signs, which can last 5-11 years [49]. Although during the chronic phase the infection is largely asymptomatic, the virus continues its replication and $CD4^+$ T cell concentration falls gradually, leading to the late phase of the infection and the progression to AIDS [55]. During the course of infection, there is also heightened state of systemic immune activation in both macrophages and lymphocytes leaded by the gp120 glycoprotein [56] and proinflammatory cytokines [57,58].

Immune Activation

Although immune activation in response to an invading organism is essential in order to support an effective host response to an invading pathogen, it may also provide an optimal immunological environment for the viral replication in HIV-positive persons. Immune activations in response to the presence of exogenous pathogens could have a substantial impact in the viral life cycle at host level leading to increases in HIV replication systematically or localized anatomical sites. The common denominator of external viral induction of HIV expression is the ability of these concurrent infections to induce an immune response along with the expression of proteins that are used by HIV to regulate virus production. Furthermore, the life cycle of HIV is closely related to the activation state of its host cells since it depends on host cell surface receptor expression for entry, and also on many cellular pathways and transcription machinery for viral gene expression.

A variety of concurrent infections may facilitate the cellular entry of HIV and virus transmission and propagation between the host's immune cell pool. Immune activation consequence of the presence of other infections, or the antigenic stimulus generated by HIV infection itself, may affect the surface expression of these coreceptors in mononuclear cells, thus modulating their susceptibility to the virus [59]. For instance, immune activations associated with the high prevalence of co-infections among HIV-positive individuals in settings such as Africa may be responsible for the increased CCR5 expression in mononuclear cells in persons living in this region [60]. High local concentrations of proinflammatory cytokines and HIV along with heightened immune activation provide a suitable environment for intercellular spread and propagation of the virus [61,62]. Furthermore, antigen presentation results in the activation and clonal expansion of the pool of susceptible HIV target cells such as $CD45RO^+$ memory $CD4^+$ T lymphocytes [62].

Inflammatory immune response to concurrent infections also provides a suitable environment for cell to cell HIV transmission during the process of antigen presentation conducted by antigen-presenting cells (APCs), which are important reservoirs of the virus [61]. During this process, intercellular signaling augments the induction of cellular activation and proinflamatory cytokine secretion leading to up-regulation of viral transcription in infected cells [63,64]. Since viral replication is closely regulated by the host cell transcriptional machinery, the state of host cell activation is a key element for the enhancement of HIV proviral transcription regulated by sequences in the LTR (Figure 2).

The key mechanism by which immune activation enhances virus transcription is the recognition of several inducible host transcription factors by the modulatory enhanced region located upstream of the core promoter region within the LTR [46]. This region contains several defined elements that bind cellular transcription factors such as the nuclear-factor-κB (NF-κB) [65]. The LTR also contains transcriptional regulatory sequences including TATA box, three SP1 binding sites [66], a core enhancer region, and a negative regulatory region [67,68]. HIV also encodes Tat whose target is located in the TAR area of the LTR [69]. Tat, as described before, is involved in several activities including transcriptional activation and post-transcriptional enhancement of HIV mRNA [69-71].

Previous studies found that HIV replicates poorly in T cells in the absence of activation signals such as phytohemagglutinin (PHA) and IL-2 [72,73]. In uninfected cells, exposure to PHA induces the production of NF-κB that binds to specific segments of the host cell DNA that encode for IL-2 and IL-2 receptors [74]. In the case of HIV infected cells, NF-κB molecules interact with the NF-κB binding sites located in the LTR region resulting in the stimulation of HIV RNA transcription, and ultimately, virus expression [75].

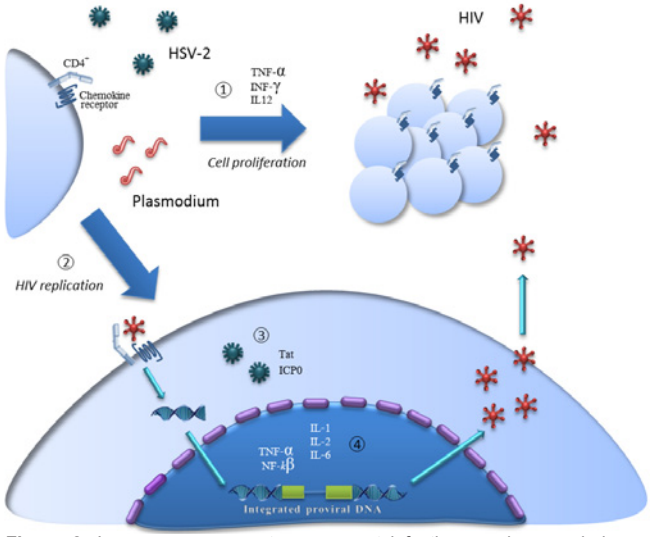

Figure 2: Immune responses to concurrent infections such as malaria or HSV-2 provide a suitable environment for HIV infection and replication by the rise of certain modulators that promote cellular activation and the consequent increment in the pool of HIV target cells (1), and up-regulation of viral replication (2). Cellular activation also increases the concentration of modulators in the host cell that facilitate virus expression (3), and viruses such as HSV-2 have regulatory proteins that interact with the HIV LTR up-regulating HIV replication (4).

Moreover, cytokine biology might provide a suitable framework to understand the effect of co-infection in the transmission of HIV. Cytokines are signaling molecules that enable communication among cells of the immune system in response to infection, such as polarization [76,77] and amplification of immune responses [78]. They are key elements of immune cell activation that act as physiological inductive signals in the regulation of immune responses. As mentioned previously, one of such cytokines is the TNF-α, which has been shown to stimulate virus expression in chronically infected Th cell and monocytes. TNF-α induces HIV transcription in both macrophages and Th lymphocytes by mediating the activation of NF-κB, and represents an important mechanism by which concurrent infections with bacteria, viruses and other immunological stimuli may enhance HIV replication. Other cytokines such as IL-6 and IL-1 enhance viral replication by synergize with TNF-α [79].

Furthermore, cytokines can also suppress viral expression. For instance, IFN-α is able to decrease HIV expression by inhibiting the budding of virions [80]. On the other hand, cytokines such as transforming growth factor-β (TGFβ) down-regulates virus expression by blocking both transcriptional and post-transcriptional mechanisms depending on the inductive signaling [81-83].

Concurrent Infections and HIV Replication

As described above, concurrent infections in HIV-positive individuals might exacerbate the cellular activation raising the cytoplasmic concentration of certain modulators that facilitate virus expression. Furthermore, co-infection might increase the pool of target cells that are able to support productive viral infection (Figure 2) [84]. Immune activations are likely to result in profound modifications of the interaction between the immune system and HIV. Moreover, epidemiological evidence indicates that parasite transmission in general can be strongly affected by concurrent infections, and the persistent activation of the immune system generated by frequent infections has been hypothesized to be involved in the spread and pathogenesis of HIV, particularly in sub-Saharan Africa [26,79,85].

Viral infections (HSV-2)

The existence of a synergistic relationship between HIV and HSV-2 has been evidenced by many observational and biological studies in which HSV-2 has been implicated as a biological cofactor for the transmission and acquisition of HIV [86,87]. The rapid spread of HIV as a sexually transmitted disease is exceeded by that of HSV-2 [88]. The prevalence of HSV-2, which may be as high as 75% among women in parts of sub-Saharan Africa [89], has reached a prevalence of up to 90% in HIV-positive persons [87]. HSV-2 infection has a complex dynamic, characterized as chronic, with frequent and typically unrecognized reactivations [90], and by its relatively high probability of transmission per sexual act.

An important characteristic of HSV-2 is that infected individuals do not recover from the infection; but after the 10-year chronic stage, individuals stop transmitting the HSV-2 infection [91]. While bacterial STIs such as gonorrhea and syphilis tend to be concentrated in high risk groups [92], the biological characteristics of HSV-2 previously described allow this virus to be sustainable in the general population; thus its prevalence can reach very high levels such as those observed in sub-Saharan Africa [93]. Consequently, as the HIV epidemic reaches the general population, the epidemiological overlap between HSV-2 and HIV is significantly larger than any other STI [30].

The enhanced HIV infectivity caused by HSV-2 co-infection has also been corroborated by population-based studies suggesting a relative risk of two to five fold of HIV transmission from co-infected individuals compared to HSV-2 seronegative individuals infected with HIV [7,93,94], and suppression of HSV-2 with acyclovir was associated with a measurable decrease on the HIV-RNA levels [95]. These data indicate epidemiologic synergy between the two infectious diseases at the population level, and suggest that HSV-2 may be playing a key role fueling the HIV epidemic in sub-Saharan Africa [27]. Furthermore, mathematical and simulation models have also demonstrated the essential role played by co-infections with other STIs, particularly HSV-2, in understanding the geographical differences in HIV prevalence [96].

HSV-2 might facilitate the expression of HIV RNA by two main mechanisms: the local influx of activated $CD4^+$ T lymphocytes in HSV-infected lesions, and by the transactivation of the HIV Tat protein and LTR by HSV-2 proteins (Figure 2). Replication of HSV is mostly limited to the epidermis or mucosal squamous keratinocytes [97]. During symptomatic infection, antigen specific $CD4^+$ T cells and NK cells infiltrate the subjacent dermis after two days of the lesion formation. This influx of HSV-2 specific $CD4^+$ cells might raise the number of HIV target cells into recurrent HSV-2 lesions [98].

Furthermore, several HSV regulatory proteins enhance HIV replication through interactions with the HIV LTR [99]. HSV replication is regulated by three classes of genes expressed at different stages [100]. The intermediate-early (alpha) genes (ICP0, ICP4, ICP22, ICP27, and ICP47) appear to be regulatory in nature. Some of these proteins might be implicated in the enhancement of the HIV replication. Since transcription of all HIV mRNA originates in the LTR, agents that are able to bind the NF-κB and Sp1 sites might activate HIV LTR transcription [101-103]. Some studies have suggested that HSV immediate-early genes ICP4 and ICP0 could transactivate the LTR region of the virus genome [104-106], probably by the induction and

binding of NF-κB and Sp1 to their respective sites on the LTR [104]. More recent studies, however, have indicated that ICP0, but not ICP4, was essential for up-regulation of HIV replication [99,107].

Parasitic infections (Malaria)

The activation of the immune system, however, is not only produced by STIs such as HSV-2. Parasitic infections such as malaria, helminthic infections, and leishmaniasis might produce a strong response from the immune system and consequently generate similar effects on the replication of the virus in HIV co-infected individuals [108-112]. On special interest, and due to the geographical overlap observed between infections, malaria in particular has generated a major attention regarding its possible interaction with HIV in sub-Saharan Africa [113].

Malaria occurs throughout the tropical world, where it remains one of the most prevalent infectious diseases, with an estimated 300 million cases per year [114]. Malaria is a disease caused by protozoa of the genus *Plasmodium*, which are transmitted as sporozoites through bites of infected female *Anopheles* mosquitoes. During this life cycle stage, the sporozoites invade hepatocytes and replicate asexually, followed by the invasion of mature red blood cells (erythrocytes) by merozoites. The rupture of an infected erythrocyte releases a few dozens of merozoite progeny that are competent to infect new erythrocytes and thus begin a new cycle [115,116].

The evidence of the interaction between malaria and HIV comes from various sources. Several *in vitro* studies have found that malaria antigens significantly enhanced HIV replication [110,111,117,118]. Furthermore, population-based studies conducted with HIV infected adults have indicated that the HIV-RNA concentration almost doubled between baseline and those co-infected with malaria. Authors concluded that HIV-positive individuals co-infected with malaria had a significantly increased viral load, and possibly increased infection transmission and accelerated disease progression [110].

Researchers estimated that, on average, malaria generates a 0.25 (95% CI 0.11-0.39) log10 increment on the mean HIV-RNA concentration [110]. We generated a mathematical model to examine the impact of this increment on the HIV epidemic in Kisimu, Kenya [28]. Using the functional relationship between HIV plasma viral load and transmission probability per coital act, in which a logarithmic increase in viral load is associated with a 2.45-fold increase in transmission probability [15], we demonstrated that the enhancement on the HIV infectivity of co-infected individuals may account for a cumulative 8500 excess HIV infections in Kisumu district. Supporting this mathematical model, we examined the geographical overlap between malaria and HIV [29]. We found that those who live in areas with high *Plasmodium falciparum* parasite rate have about twice the risk of being HIV-positive compared to individuals who live in areas with low parasite rate in East sub-Saharan Africa.

Immunity to malaria is complex and still not well understood. The activation of the immune system is considered more important in controlling liver-stage infections, where the sporozoite (liver stage) represents the first encounter of the immune host with the parasite, although humoral immune mechanisms could be more important in controlling the blood stages. Several genes are involved in these immune responses including class I and class II major histocompatibility complex (MHC) molecules, inducible nitric oxide synthase (iNOS), mannose-binding protein (MBP), cytokines and cytokines receptors. The parasite induces a specific immune response by stimulating the release of cytokines from peripheral blood mononuclear cells (PBMC) [119,120], which is a key step for the activation of monocytes, neutrophils, Th cells and NK cells [120-123].

Initial antigen presentation leads to recognition by CTLs and posterior killing of the infected cell or stimulation of NK and $CD4^+$ T cells to produce IFN-γ, which triggers a cascade of immunological reactions that ultimately lead the elimination of the intracellular parasite [124]. In the blood stage, at the time of erythrocyte rupture, parasite antigens are released into the bloodstream stimulating the release of TNF-α among others [125]. The release of TNF-α has a role in the regulation of macrophage IL-12 production, and it is also an important co-factor for IL-12-induced production of IFN-γ by KN cells [126]. The immunodulatory cytokine IL-12 appears to stimulate antibody production in B cells and promote the differentiation of T cells belonging to the Th1 subset [127]. The Th1 effectors generate the production of IFN-γ which is a direct consequence of $CD4^+$ and $CD8^+$ T cell activation [127].

Anti-inflammatory responses also play an important role in the immune response to malaria. During mild malaria, inflammatory responses might be down-regulated by anti-inflammatory cytokines such as IL-4, IL-10, and TGFβ. The cytokine TGFβ, which is produced by macrophages, NK, T, and B cells among others, has a pivotal role in the control of the transition between proinflammatory (Th1) and anti-inflammatory (Th2) response during acute and recovery phases of malaria infection [128]. *In vitro*, the TGFβ concentration is a key element for macrophage activation [128]. Immature monocytes or macrophages have high concentration of TGFβ receptors and are highly sensitive to low concentrations of TGFβ, which promote macrophage maturation. When the concentration of TGFβ rises, the production of TGFβ is down-regulated stopping the activation process [128]. Furthermore, TGFβ inhibits IFN-γ and TNF-α production, and up-regulates IL-10 [129], a cytokine produced by monocytes, Th2 cells and B cells, that inhibits cytokine production in Th1 and $CD8^+$ T cells [130].

Several proinflamatory cytokines induced by malaria previously described (e.g TNF-α and IL-6) could play a role in the enhancement of HIV expression. Indeed, the greater viral load observed in patients co-infected with malaria correlated with a marked increase in the pro-inflammatory cytokine response to the parasite, and generated systemic immune response originated from macrophages [118]. *In vitro* studies, however, have shown conflicting results. First, exposure of PBMCs to soluble pigments from *P. falciparum* enhanced HIV replication associated with the induction of TNF-α and subsequent activation of the LTR viral transcription [117]. Later, it was reported that short stimulation with *P. falciparum* antigens down-regulated CCR5 but not CXCR4. Long stimulations, however, up-regulated CCR5 through the induction of IFN-γ with the subsequent blocking of HIV replication [131]. In a following work, it was shown that mononuclear cell activation by malaria antigens increases the susceptibility of these cells to HIV infection and reactivates replication of endogenous HIV in cells from HIV-positive individuals [132]. A recent challenge system study confirmed the enhanced replication of HIV in PBMCs co-cultured with malaria pigments [133]. They also found that HIV replication was accompanied with an enhancement in the secretion of proinflammatory cytokines TNF-α, IFN-γ, and macrophage inflammatory protein-1α (MIP-1α), and the accompanied increment of activated $CD4^+$ T cells [133].

Other parasitic infections such as helminthic infections and

leishmaniasis generate immune responses that are able to enhance virus replication [26,134]. Helminthic infections are one of the most common in several developing countries. All helminthic infections are associated with a strong immune response dominated by Th2 response with increased IL-4, IL-5 and IL-10 secretion along with an enhancement on cell activation and apoptosis [135-138]. Moreover, chronic immune activation due to helminthic infections is associated with increment in the expression of CCR5 and CXCR4 co-receptors along with increased susceptibility for HIV infection *in vitro* [60].

Besides, low $CD4^+$ T cell count and high viral load are characteristics of the HIV-leishmaniasis co-infection. *Leishmania* antigens are capable to up-regulate HIV replication in PBMC, and in mononuclear cells *in vivo* [139], and might be associated with three main mechanisms: 1) cellular activation and increased expression of cellular immune activation markers (CD25, HLA-DR) in the CD4 cell pool; 2) increased secretion of TNF-α, IL-2, and IL-6 [140,141]; and 3) by altering the Th1-Th2 balance. *Leishmania* tends to depress the activity of Th1 and induce the activity of Th2, and whose switch of cytokine profile is associated with the enhancement of HIV replication [142].

Conclusion

The intimate relationship between HIV and the activation state of the host immune system supporting viral replication results in a synergistic interaction between HIV and concurrent infections. A common denominator of co-infection is the systemic immune activation resulting in an enhancement of the HIV viral load that ultimately facilitates the transmission of the virus (Figure 1). Despite the evidence for this interaction, the quantitative effect of these co-infections on HIV transmission or acquisition remains to be determined. Cofactor values are commonly estimated from population-based observations that monitored HIV transmission and co-infection status in individuals or couples [143]. For instance, the association between the transmission of HIV and concurrent infections is expressed in terms of odd ratios, hazard ratios or relative risk per sexual contact [144]. These estimates, however, can be particularly difficult to interpret as a consequence of multiple potential biases that may inflate or deflate these values.

To reduce confounding effects resulting from other behavioral and biological risk factors, estimates of cofactor effects are statistically adjusted for the influence of these risk factors. These analyses may not completely control for the confounding effects because infections such as STIs, HIV and other behavioral and biological risk factors may cluster not only in study subjects but also in the unknown partners of the individuals included in the study [143]. Furthermore, the confounding generated by the characteristics of the sexual network such as concurrency, mixing patterns and numbers of sexual partners is virtually impossible to completely control for the confounding effects [143].

Moreover, the lack of knowledge regarding possible interactions between cofactors due to concurrent STIs or parasitic infections obscures cofactor estimation when there is more than one concurrent infection present [145]. The effect generated by multiple concurrent infections in the transmission of HIV may be additive, multiplicative or more complex functions of cofactor values. If the cofactor effects result from different biological mechanisms, multiplication of their values seems to be biologically plausible. On the other hand, in cases where cofactor effects result from the same mechanism, as for example, the enhancement of the viral load, a saturation function might describe the cofactor effect more accurately. This uncertainty emphasizes the need for more field studies on the interaction among concurrent infections and the risk of HIV transmission, and on the impact of control interventions, especially in sub-Saharan Africa.

The remarkably high HIV prevalence observed in sub-Saharan Africa may reflect the particular environment that is unique to this setting, and highlight the role of co-infection as a contributing factor in the successful spread and survival of HIV in this part of the world. This in turn suggests that an HIV epidemic may be mitigated or halted through measures that decrease viral infectivity. The control and treatment of several common infectious diseases could decrease the incidence of HIV over the long-term [145]. The epidemiological perspectives of these interactions, however, are still not entirely clear. Some studies [146,147] highlight the role of biological and epidemiological differences that could alter the effect of co-infection and underscore the importance of identifying these factors for the implementation of effective control interventions focused on co-infection. Therefore, there is a need for more population-based studies of concurrent infections, and microbe-microbe interaction at the host level to better understand the impact of co-infections on the natural history of HIV, and the potential impact of co-infection on interventions aimed to reduce the incidence of HIV. This conclusion is particularly important in developing settings, where concurrent infections are very common and the access to antiretroviral therapy is still scarce.

Acknowledgement

We thank M. Torres and S. Riome for a critical reading of the paper. This work was supported by the Qatar National Research Fund (QNRF), a Qatar Foundation funded program (NPRP 08-068-3-024).

References

1. Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, et al. (1981) Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 305: 1425-1431.
2. Clumeck N, Mascart-Lemone F, de Maubeuge J, Brenez D, Marcelis L (1983) Acquired immune deficiency syndrome in Black Africans. Lancet 1: 642.
3. Quinn T, Mann J, Curran J, Piot P (1986) AIDS in Africa an epidemiologic paradigm. Science 234: 955-963.
4. UNAIDS/WHO (2001) AIDS epidemic update 2001. World Health Organization.
5. UNAIDS Joint United Nations Programme on HIV/AIDS (2000) Report on the global HIV/AIDS epidemic 2000. UNAIDS.
6. Gisselquist D, Potterat JJ (2003) Heterosexual transmission of HIV in Africa: an empiric estimate. Int J STD AIDS 14: 162-173.
7. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, et al. (2001) Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet 357: 1149-1153.
8. Padian NS, Shiboski SC, Jewell NP (1990) The effect of number of exposures on the risk of heterosexual HIV transmission. J Infect Dis 161: 883-887.
9. Pinkerton SD, Abramson PR (1996) Implications of increased infectivity in early-stage HIV infection. Application of a Bernoulli-process model of HIV transmission. Eval Rev 20: 516-540.
10. Boily MC, Baggaley RF, Wang L, Masse B, White RG, et al. (2009) Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis 9: 118-129.
11. Chakraborty H, Sen PK, Helms RW, Vernazza PL, Fiscus SA, et al. (2001) Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. AIDS 15: 621-627.
12. Pilcher CD, Joaki G, Hoffman IF, Martinson FE, Mapanje C, et al. (2007) Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. AIDS 21: 1723-1730.

13. Pao D, Fisher M, Hué S, Dean G, Murphy G, et al. (2005) Transmission of HIV-1 during primary infection: relationship to sexual risk and sexually transmitted infections. AIDS 19: 85-90.

14. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, et al. (2005) Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 191: 1403-1409.

15. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, et al. (2000) Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med 342: 921-929.

16. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM (2008) Relation between HIV viral load and infectiousness: a model-based analysis. Lancet 372: 314-320.

17. Cohen MS, Pilcher CD (2005) Amplified HIV transmission and new approaches to HIV prevention. J Infect Dis 191: 1391-1393.

18. McLean AR, Nowak MA (1992) Models of interactions between HIV and other pathogens. J Theor Biol 155: 69-86.

19. Modjarrad K, Chamot E, Vermund SH (2008) Impact of small reductions in plasma HIV RNA levels on the risk of heterosexual transmission and disease progression. AIDS 22: 2179-2185.

20. Modjarrad K, Vermund S (2010) Effect of treating co-infections on HIV-1 viral load: a systematic review. Lancet Infect Dis 10: 455-463.

21. Rakwar J, Lavreys L, Thompson ML, Jackson D, Bwayo J, et al. (1999) Cofactors for the acquisition of HIV-1 among heterosexual men: prospective cohort study of trucking company workers in Kenya. AIDS 13: 607-614.

22. Auvert B, Buvé A, Ferry B, Caraël M, Morison L, et al. (2001) Ecological and individual level analysis of risk factors for HIV infection in four urban populations in sub-Saharan Africa with different levels of HIV infection. AIDS 15 Suppl 4: S15-30.

23. Nzila N, Laga M, Thiam MA, Mayimona K, Edidi B, et al. (1991) HIV and other sexually transmitted diseases among female prostitutes in Kinshasa. AIDS 5: 715-721.

24. Nunn AJ, Kengeya-Kayondo JF, Malamba SS, Seeley JA, Mulder DW (1994) Risk factors for HIV-1 infection in adults in a rural Ugandan community: a population study. AIDS 8: 81-86.

25. Vernazza PL, Eron JJ, Fiscus SA, Cohen MS (1999) Sexual transmission of HIV: infectiousness and prevention. AIDS 13: 155-166.

26. Bentwich Z, Maartens G, Torten D, Lal AA, Lal RB (2000) Concurrent infections and HIV pathogenesis. AIDS 14: 2071-2081.

27. Abu-Raddad LJ, Magaret AS, Celum C, Wald A, Longini IM Jr, et al. (2008) Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. PLoS One 3: e2230.

28. Abu-Raddad LJ, Patnaik P, Kublin JG (2006) Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 314: 1603-1606.

29. Cuadros DF, Branscum AJ, Crowley PH (2011) HIV–malaria co-infection: effects of malaria on the prevalence of HIV in East sub-Saharan Africa. Int J Epidemiol 40: 931-939.

30. Cuadros DF, Crowley PH, Augustine B, Stewart SL, García-Ramos G (2011) Effect of variable transmission rate on the dynamics of HIV in sub-Saharan Africa. BMC Infect Dis 11: 216.

31. Fauci AS (1988) The human immunodeficiency virus: infectivity and mechanisms of pathogenesis. Science 239: 617-622.

32. Hu WS, Temin HM (1990) Retroviral recombination and reverse transcription. Science 250: 1227-1233.

33. Freed EO, Martin MA (1995) The role of human immunodeficiency virus type 1 envelope glycoproteins in virus infection. J Biol Chem 270: 23883-23886.

34. Dalgleish AG, Beverley PC, Clapham PR, Crawford DH, Greaves MF, et al. (1984) The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 312: 763-767.

35. Klatzmann D, Champagne E, Chamaret S, Gruest J, Guetard D, et al. (1984) T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. Nature 312: 767-768.

36. Zhu T, Mo H, Wang N, Nam DS, Cao Y, et al. (1993) Genotypic and phenotypic characterization of HIV-1 patients with primary infection. Science 261: 1179-1181.

37. Moore JP, Trkola A, Dragic T (1997) Co-receptors for HIV-1 entry. Curr Opin Immunol 9: 551-562.

38. Tokunaga K, Greenberg ML, Morse MA, Cumming RI, Lyerly HK, et al. (2001) Molecular basis for cell tropism of CXCR4-dependent human immunodeficiency virus type 1 isolates. J Virol 75: 6776-6785.

39. Greene WC (1993) AIDS and the immune system. Sci Am 269: 98-105.

40. Chinen J, Shearer WT (2002) Molecular virology and immunology of HIV infection. J Allergy Clin Immunol 110: 189-198.

41. Cen S, Khorchid A, Javanbakht H, Gabor J, Stello T, et al. (2001) Incorporation of lysyl-tRNA synthetase into human immunodeficiency virus type 1. J Virol 75: 5043-5048.

42. Woods TC, Roberts BD, Butera ST, Folks TM (1997) Loss of inducible virus in CD45RA naive cells after human immunodeficiency virus-1 entry accounts for preferential viral replication in CD45RO memory cells. Blood 89: 1635-1641.

43. Parada CA, Roeder RG (1996) Enhanced processivity of RNA polymerase II triggered by Tat-induced phosphorylation of its carboxy-terminal domain. Nature 384: 375-378.

44. Emerman M, Malim MH (1998) HIV-1 regulatory/accessory genes: keys to unraveling viral and host cell biology. Science 280: 1880-1884.

45. Schaeffer E, Geleziunas R, Greene WC (2001) Human immunodeficiency virus type 1 Nef functions at the level of virus entry by enhancing cytoplasmic delivery of virions. J Virol 75: 2993-3000.

46. Gaynor R (1992) Cellular transcription factors involved in the regulation of HIV-1 gene expression. AIDS 6: 347-363.

47. Nathanson N, Ahmed R, Biron CA, Brinton MA, Chow L, et al. (2002) Viral Pathogenesis and Immunity. (1stedn) Lippincott Williams & Wilkins, Philadelphia.

48. Pope M, Haase AT (2003) Transmission, acute HIV-1 infection and the quest for strategies to prevent infection. Nat Med 9: 847-852.

49. Hutchinson JF (2001) The biology and evolution of HIV. Annu Rev Anthropol 30: 85-108.

50. Powrie F, Coffman RL (1993) Cytokine regulation of T-cell function: potential for therapeutic intervention. Immunol Today 14: 270-274.

51. Romagnani S (1994) Lymphokine production by human T cells in disease states. Annu Rev Immunol 12: 227-257.

52. D'Andrea A, Rengaraju M, Valiante NM, Chehimi J, Kubin M, et al. (1992) Production of natural killer cell stimulatory factor (interleukin 12) by peripheral blood mononuclear cells. J Exp Med 176: 1387-1398.

53. Maggi E, Mazzetti M, Ravina A, Annunziato F, de Carli M, et al. (1994) Ability of HIV to promote a TH1 to TH0 shift and to replicate preferentially in TH2 and TH0 cells. Science 265: 244-248.

54. Ho DD, Pomerantz RJ, Kaplan JC (1987) Pathogenesis of infection with human immunodeficiency virus. N Engl J Med 317: 278-286.

55. McMichael AJ, Rowland-Jones SL (2001) Cellular immune responses to HIV. Nature 410: 980-987.

56. Capobianchi MR (1996) Induction of lymphomonocyte activation by HIV-1 glycoprotein gp120. Possible role in AIDS pathogenesis. J Biol Regul Homeost Agents 10: 83-91.

57. Khanna KV, Yu XF, Ford DH, Ratner L, Hildreth JK, et al. (2000) Differences among HIV-1 variants in their ability to elicit secretion of TNF-alpha. J Immunol 164: 1408-1415.

58. Merrill JE, Koyanagi Y, Chen IS (1989) Interleukin-1 and tumor necrosis factor alpha can be induced from mononuclear phagocytes by human

immunodeficiency virus type 1 binding to the CD4 receptor. J Virol 63: 4404-4408.

59. Wahl SM, Greenwell-Wild T, Peng G, Hale-Donze H, Orenstein JM (1999) Co-infection with opportunistic pathogens promotes human immunodeficiency virus type 1 infection in macrophages. J Infect Dis 179 Suppl 3: S457-460.

60. Kalinkovich A, Weisman Z, Leng Q, Borkow G, Stein M, et al. (1999) Increased CCR5 expression with decreased beta chemokine secretion in Ethiopians: relevance to AIDS in Africa. J Hum Virol 2: 283-289.

61. Mancino G, Placido R, Bach S, Mariani F, Montesano C, et al. (1997) Infection of human monocytes with Mycobacterium tuberculosis enhances human immunodeficiency virus type 1 replication and transmission to T cells. J Infect Dis 175: 1531-1535.

62. Shattock RJ, Burger D, Dayer JM, Griffin GE (1996) Enhanced HIV replication in monocytic cells following engagement of adhesion molecules and contact with stimulated T cells. Res Virol 147: 171-179.

63. Mikovits JA, Lohrey NC, Schulof R, Courtless J, Ruscetti FW (1992) Activation of infectious virus from latent human immunodeficiency virus infection of monocytes in vivo. J Clin Invest 90: 1486-1491.

64. Ott M, Emiliani S, Van Lint C, Herbein G, Lovett J, et al. (1997) Immune hyperactivation of HIV-1-infected T cells mediated by Tat and the CD28 pathway. Science 275: 1481-1485.

65. Baeuerle PA (1991) The inducible transcription activator NF-kappa B: regulation by distinct protein subunits. Biochim Biophys Acta 1072: 63-80.

66. Dynan WS, Tjian R (1985) Control of eukaryotic messenger RNA synthesis by sequence-specific DNA-binding proteins. Nature 316: 774-778.

67. Johnson PA, Everett RD (1986) The control of herpes simplex virus type-1 late gene transcription: a 'TATA-box'/cap site region is sufficient for fully efficient regulated activity. Nucleic Acids Res 14: 8247-8264.

68. Jones KA, Tjian R (1985) Sp1 binds to promoter sequences and activates herpes simplex virus 'immediate-early' gene transcription in vitro. Nature 317: 179-182.

69. Rosen CA, Sodroski JG, Goh WC, Dayton AI, Lippke J, et al. (1986) Post-transcriptional regulation accounts for the trans-activation of the human T-lymphotropic virus type III. Nature 319: 555-559.

70. Cullen BR (1986) Trans-activation of human immunodeficiency virus occurs via a bimodal mechanism. Cell 46: 973-982.

71. Wright CM, Felber BK, Paskalis H, Pavlakis GN (1986) Expression and characterization of the trans-activator of HTLV-III/LAV virus. Science 234: 988-992.

72. Popovic M, Sarngadharan M, Read E, Gallo R (1984) Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 224: 497-500.

73. Levy JA, Hoffman AD, Kramer SM, Landis JA, Shimabukuro JM, et al. (1984) Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. Science 225: 840-842.

74. Greene WC, Böhnlein E, Ballard DW (1989) HIV-1, HTLV-1 and normal T-cell growth: transcriptional strategies and surprises. Immunol Today 10: 272-278.

75. Nabel G, Baltimore D (1987) An inducible transcription factor activates expression of human immunodeficiency virus in T cells. Nature 326: 711-713.

76. Kourilsky P, Truffa-Bachi P (2001) Cytokine fields and the polarization of the immune response. Trends Immunol 22: 502-509.

77. Abbas AK, Murphy KM, Sher A (1996) Functional diversity of helper T lymphocytes. Nature 383: 787-793.

78. Germain RN (2001) The art of the probable: system control in the adaptive immune system. Science 293: 240-245.

79. Lawn SD, Butera ST, Folks TM (2001) Contribution of immune activation to the pathogenesis and transmission of human immunodeficiency virus type 1 infection. Clin Microbiol Rev 14: 753-777.

80. Poli G, Orenstein JM, Kinter A, Folks TM, Fauci AS (1989) Interferon-alpha but not AZT suppresses HIV expression in chronically infected cell lines. Science 244: 575-577.

81. Poli G, Kinter AL, Justement JS, Bressler P, Kehrl JH, et al. (1991) Transforming growth factor beta suppresses human immunodeficiency virus expression and replication in infected cells of the monocyte/macrophage lineage. J Exp Med 173: 589-597.

82. Butera ST, Roberts BD, Folks TM (1993) Regulation of HIV-1 expression by cytokine networks in a CD4+ model of chronic infection. J Immunol 150: 625-634.

83. Folks TM, Justement J, Kinter A, Dinarello CA, Fauci AS (1987) Cytokine-induced expression of HIV-1 in a chronically infected promonocyte cell line. Science 238: 800-802.

84. Kinoshita S, Chen BK, Kaneshima H, Nolan GP (1998) Host control of HIV-1 parasitism in T cells by the nuclear factor of activated T cells. Cell 95: 595-604.

85. Hazenberg MD, Otto SA, van Benthem BH, Roos MT, Coutinho RA, et al. (2003) Persistent immune activation in HIV-1 infection is associated with progression to AIDS. AIDS 17: 1881-1888.

86. Glynn JR, Crampin AC, Ngwira BM, Ndhlovu R, Mwanyongo O, et al. (2008) Herpes simplex virus type 2 trends in relation to the HIV epidemic in northern Malawi. Sex Transm Infect 84: 356-360.

87. Weiss HA, Buvé A, Robinson NJ, Van Dyck E, Kahindo M, et al. (2001) The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations. AIDS 15 Suppl 4: S97-108.

88. O'Farrell N (1999) Increasing prevalence of genital herpes in developing countries: implications for heterosexual HIV transmission and STI control programmes. Sex Transm Infect 75: 377-384.

89. WHO/UNAIDS/LSHTM (2001) Herpes simplex virus type 2 programmatic and research priorities in developing countries. World Health Organization.

90. Wald A, Zeh J, Selke S, Warren T, Ryncarz AJ, et al. (2000) Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. N Engl J Med 342: 844-850.

91. Freeman EE, Orroth KK, White RG, Glynn JR, Bakker R, et al. (2007) Proportion of new HIV infections attributable to herpes simplex 2 increases over time: simulations of the changing role of sexually transmitted infections in sub-Saharan African HIV epidemics. Sex Transm Infect 83: i17-i24.

92. Brunham RC, Plummer FA (1990) A general model of sexually transmitted disease epidemiology and its implications for control. Med Clin North Am 74: 1339-1352.

93. Corey L, Wald A, Celum CL, Quinn TC (2004) 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.

94. Buvé A, Caraël M, Hayes RJ, Auvert B, Ferry B, et al. (2001) The multicentre study on factors determining the differential spread of HIV in four African cities: summary and conclusions. AIDS 15 Suppl 4: S127-131.

95. Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L (2002) Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. J Infect Dis 186: 1718-1725.

96. Orroth KK, Freeman EE, Bakker R, Buvé A, Glynn JR, et al. (2007) Understanding the differences between contrasting HIV epidemics in east and west Africa: results from a simulation model of the Four Cities Study. Sex Transm Infect 83 Suppl 1: i5-16.

97. Kiviat NB, Paavonen JA, Wølner-Hanssen P, Critchlow CW, Stamm WE, et al. (1990) Histopathology of endocervical infection caused by Chlamydia trachomatis, herpes simplex virus, Trichomonas vaginalis, and Neisseria gonorrhoeae. Hum Pathol 21: 831-837.

98. Koelle DM, Posavad CM, Barnum GR, Johnson ML, Frank JM, et al. (1998) Clearance of HSV-2 from recurrent genital lesions correlates with infiltration of HSV-specific cytotoxic T lymphocytes. J Clin Invest 101: 1500-1508.

99. Golden MP, Kim S, Hammer SM, Ladd EA, Schaffer PA, et al. (1992) Activation of human immunodeficiency virus by herpes simplex virus. J Infect Dis 166: 494-499.

100. Honess RW, Roizman B (1974) Regulation of herpesvirus macromolecular synthesis. I. Cascade regulation of the synthesis of three groups of viral proteins. J Virol 14: 8-19.

101. Duh EJ, Maury WJ, Folks TM, Fauci AS, Rabson AB (1989) Tumor necrosis factor alpha activates human immunodeficiency virus type 1 through induction of nuclear factor binding to the NF-kappa B sites in the long terminal repeat. Proc Natl Acad Sci U S A 86: 5974-5978.

102. Ensoli B, Lusso P, Schachter F, Josephs SF, Rappaport J, et al. (1989) Human herpes virus-6 increases HIV-1 expression in co-infected T cells via nuclear factors binding to the HIV-1 enhancer. EMBO J 8: 3019-3027.

103. Harrich D, Garcia J, Wu F, Mitsuyasu R, Gonazalez J, et al. (1989) Role of SP1-binding domains in in vivo transcriptional regulation of the human immunodeficiency virus type 1 long terminal repeat. J Virol 63: 2585-2591.

104. Margolis DM, Rabson AB, Straus SE, Ostrove JM (1992) Transactivation of the HIV-1 LTR by HSV-1 immediate-early genes. Virology 186: 788-791.

105. Mosca JD, Bednarik DP, Raj NB, Rosen CA, Sodroski JG, et al. (1987) Activation of human immunodeficiency virus by herpesvirus infection: identification of a region within the long terminal repeat that responds to a trans-acting factor encoded by herpes simplex virus 1. Proc Natl Acad Sci U S A 84: 7408-7412.

106. Mosca JD, Bednarik DP, Raj NB, Rosen CA, Sodroski JG, et al. (1987) Herpes simplex virus type-1 can reactivate transcription of latent human immunodeficiency virus. Nature 325: 67-70.

107. Albrecht MA, DeLuca NA, Byrn RA, Schaffer PA, Hammer SM (1989) The herpes simplex virus immediate-early protein, ICP4, is required to potentiate replication of human immunodeficiency virus in CD4+ lymphocytes. J Virol 63: 1861-1868.

108. Pisell TL, Hoffman IF, Jere CS, Ballard SB, Molyneux ME, et al. (2002) Immune activation and induction of HIV-1 replication within CD14 macrophages during acute Plasmodium falciparum malaria coinfection. AIDS 16: 1503-1509.

109. Bentwich Z, Kalinkovich A, Weisman Z (1995) Immune activation is a dominant factor in the pathogenesis of African AIDS. Immunol Today 16: 187-191.

110. Kublin JG, Patnaik P, Jere CS, Miller WC, Hoffman IF, et al. (2005) Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet 365: 233-240.

111. Rénia L, Potter SM (2006) Co-infection of malaria with HIV: an immunological perspective. Parasite Immunol 28: 589-595.

112. Korenromp EL, Williams BG, de Vlas SJ, Gouws E, Gilks CF, et al. (2005) Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. Emerg Infect Dis 11: 1410-1419.

113. Idemyor V (2007) Human immunodeficiency virus (HIV) and malaria interaction in sub-Saharan Africa: the collision of two Titans. HIV Clin Trials 8: 246-253.

114. Mali S, Steele S, Slutsker L, Arguin PM; Centers for Disease Control and Prevention (CDC) (2010) Malaria surveillance - United States, 2008. MMWR Surveill Summ 59: 1-15.

115. Hellriegel B (1992) Modelling the immune response to malaria with ecological concepts: short-term behaviour against long-term equilibrium. Proc Biol Sci 250: 249-256.

116. Malaguarnera L, Musumeci S (2002) The immune response to Plasmodium falciparum malaria. Lancet Infect Dis 2: 472-478.

117. Xiao L, Owen SM, Rudolph DL, Lal RB, Lal AA (1998) Plasmodium falciparum antigen-induced human immunodeficiency virus type 1 replication is mediated through induction of tumor necrosis factor-alpha. J Infect Dis 177: 437-445.

118. Pisell TL, Hoffman IF, Jere CS, Ballard SB, Molyneux ME, et al. (2002) Immune activation and induction of HIV-1 replication within CD14 macrophages during acute Plasmodium falciparum malaria coinfection. AIDS 16: 1503-1509.

119. Doolan DL, Beck HP, Good MF (1994) Evidence for limited activation of distinct CD4+ T cell subsets in response to the Plasmodium falciparum circumsporozoite protein in Papua New Guinea. Parasite Immunol 16: 129-136.

120. Esparza I, Männel D, Ruppel A, Falk W, Krammer PH (1987) Interferon gamma and lymphotoxin or tumor necrosis factor act synergistically to induce macrophage killing of tumor cells and schistosomula of Schistosoma mansoni. J Exp Med 166: 589-594.

121. Djeu JY, Serbousek D, Blanchard DK (1990) Release of tumor necrosis factor by human polymorphonuclear leukocytes. Blood 76: 1405-1409.

122. Yokota S, Shirasaka T, Nishikawa H, Hosoe S, Ikeda T, et al. (1988) Augmentative effect of Nocardia rubra cell-wall skeleton (N-CWS) on lymphokine-activated killer (LAK) cell induction. Cancer Immunol Immunother 26: 11-17.

123. Ostensen ME, Thiele DL, Lipsky PE (1987) Tumor necrosis factor-alpha enhances cytolytic activity of human natural killer cells. J Immunol 138: 4185-4191.

124. Wang R, Charoenvit Y, Corradin G, De La Vega P, Franke ED, et al. (1996) Protection against malaria by Plasmodium yoelii sporozoite surface protein 2 linear peptide induction of CD4+ T cell- and IFN-gamma-dependent elimination of infected hepatocytes. J Immunol 157: 4061-4067.

125. Snounou G, Jarra W, Preiser PR (2000) Malaria multigene families: the price of chronicity. Parasitol Today 16: 28-30.

126. Tripp CS, Wolf SF, Unanue ER (1993) Interleukin 12 and tumor necrosis factor a are costimulators of interferon gamma production by natural killer cells in severe combined immunodeficiency mice with listeriosis, and interleukin 10 is a physiologic antagonist. Proc Natl Acad Sci U S A 90: 3725-3729.

127. O'Garra A, Arai N (2000) The molecular basis of T helper 1 and T helper 2 cell differentiation. Trends Cell Biol 10: 542-550.

128. Tsunawaki S, Sporn M, Ding A, Nathan C (1988) Deactivation of macrophages by transforming growth factor-beta. Nature 334: 260-262.

129. Maeda H, Shiraishi A (1996) TGF-beta contributes to the shift toward Th2-type responses through direct and IL-10-mediated pathways in tumor-bearing mice. J Immunol 156: 73-78.

130. Nakabayashi T, Letterio JJ, Geiser AG, Kong L, Ogawa N, et al. (1997) Up-regulation of cytokine mRNA, adhesion molecule proteins, and MHC class II proteins in salivary glands of TGF-beta1 knockout mice: MHC class II is a factor in the pathogenesis of TGF-beta1 knockout mice. J Immunol 158: 5527-5535.

131. Moriuchi M, Moriuchi H, Mon HM, Kanbara H (2002) Dichotomous effects of Plasmodium falciparum antigens on expression of human immunodeficiency virus (HIV) coreceptors and on infectability of CD4 cells by HIV. J Infect Dis 186: 1194-1197.

132. Froebel K, Howard W, Schafer JR, Howie F, Whitworth J, et al. (2004) Activation by malaria antigens renders mononuclear cells susceptible to HIV infection and re-activates replication of endogenous HIV in cells from HIV-infected adults. Parasite Immunol 26: 213-217.

133. Orlov M, Vaida F, Finney OC, Smith DM, Talley AK, et al. (2012) P. falciparum Enhances HIV Replication in an Experimental Malaria Challenge System. PLoS One 7: e39000.

134. Cacopardo B, Nigro L, Preiser W, Famá A, Satariano MI, et al. (1996) Prolonged Th2 cell activation and increased viral replication in HIV-Leishmania co-infected patients despite treatment. Trans R Soc Trop Med Hyg 90: 434-435.

135. Bentwich Z, Weisman Z, Moroz C, Bar-Yehuda S, Kalinkovich A (1996) Immune dysregulation in Ethiopian immigrants in Israel: relevance to helminth infections? Clin Exp Immunol 103: 239-243.

136. Yazdanbakhsh M (1999) Common features of T cell reactivity in persistent helminth infections: lymphatic filariasis and schistosomiasis. Immunol Lett 65: 109-115.

137. Maizels RM, Bundy DA, Selkirk ME, Smith DF, Anderson RM (1993) Immunological modulation and evasion by helminth parasites in human populations. Nature 365: 797-805.

138. Messele T, Abdulkadir M, Fontanet AL, Petros B, Hamann D, et al. (1999) Reduced naive and increased activated CD4 and CD8 cells in healthy adult Ethiopians compared with their Dutch counterparts. Clin Exp Immunol 115: 443-450.

139. Nigro L, Cacopardo B, Preiser W, Braner J, Cinatl J, et al. (1999) In vitro production of type 1 and type 2 cytokines by peripheral blood mononuclear cells from subjects coinfected with human immunodeficiency virus and Leishmania infantum. Am J Trop Med Hyg 60: 142-145.

140. Bernier R, Barbeau B, Tremblay MJ, Olivier M (1998) The lipophosphoglycan of Leishmania donovani up-regulates HIV-1 transcription in T cells through the nuclear factor-kappaB elements. J Immunol 160: 2881-2888.

141. Wolday D, Akuffo H, Demissie A, Britton S (1999) Role of Leishmania donovani and its lipophosphoglycan in CD4+ T-cell activation-induced human immunodeficiency virus replication. Infect Immun 67: 5258-5264.

142. Clerici M, Shearer GM (1994) The Th1-Th2 hypothesis of HIV infection: new insights. Immunol Today 15: 575-581.

143. Korenromp EL, de Vlas SJ, Nagelkerke NJ, Habbema JD (2001) Estimating the magnitude of STD cofactor effects on HIV transmission: how well can it be done? Sex Transm Dis 28: 613-621.

144. Boily MC, Anderson RM (1996) Human immunodeficiency virus transmission and the role of other sexually transmitted diseases. Measures of association and study design. Sex Transm Dis 23: 312-332.

145. Stillwaggon E (2012) Living with uncertainty. Trends Parasitol 28: 261-266.

146. Cuadros DF, Branscum AJ, García-Ramos G (2011) No evidence of association between HIV-1 and malaria in populations with low HIV-1 prevalence. PLoS One 6: e23458.

147. Cuadros DF, García-Ramos G (2012) Variable effect of co-infection on the HIV infectivity: within-host dynamics and epidemiological significance. Theor Biol Med Model 9: 9.

This article was originally published in a special issue, **Immune regulation and HIV** handled by Editor(s). Dr. Haishan Li, University of Maryland School of Medicine, USA