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, 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.

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

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 CXCR4. 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 CD4+ memory T cells rather than immature CD5RA+ naïve 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 naive 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 led 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 proinflammatory 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 phytotemagglutinin (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].
Immune responses to concurrent infections such as malaria or activation of the immune system generated by frequent infections has can be strongly affected by concurrent infections, and the persistent epidemiological evidence indicates that parasite transmission in general of the interaction between the immune system and HIV. Moreover, immune activations are likely to result in profound modifications cells that are able to support productive viral infection (Figure 2) [84].

Concurrent Infections and HIV Replication

As described above, concurrent infections in HIV-positive individuals may 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 Kisumu, 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 cytokine 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 *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 proinflammatory 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 *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, multication 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 microbiome 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.

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