Published in final edited form as:
Curr HIV/AIDS Rep. 2009 February ; 6(1): 5–12.

Coinfecting Viruses as Determinants of HIV Disease

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Abstract

The human body constitutes a balanced ecosystem of its own cells together with various microbes ("host–microbe ecosystem"). The transmission of HIV-1 and the progression of HIV disease in such an ecosystem are accompanied by de novo infection by other microbes or by activation of microbes that were present in the host in homeostatic equilibrium before HIV-1 infection. In recent years, data have accumulated on the interactions of these coinfecting microbes—viruses in particular—with HIV. Coinfecting viruses generate negative and positive signals that suppress or upregulate HIV-1. We suggest that the signals generated by these viruses may largely affect HIV transmission, pathogenesis, and evolution. The study of the mechanisms of HIV interaction with coinfecting viruses may indicate strategies to suppress positive signals, enhance negative signals, and lead to the development of new and original anti-HIV therapies.

Introduction

HIV is the etiologic agent of AIDS. However, HIV transmission and disease progression are accompanied by de novo infection by other microbes or by activation of microbes that were present in the organism before HIV infection either in a latent state or under the control of the immune system. Herein, we present the data accumulated over recent years on the mechanisms of the interaction between coinfecting microbes—viruses in particular—with HIV. We suggest that non-HIV viruses may determine HIV transmission, pathogenesis, and evolution [1].

Our thinking about the interactions between the host and microbes has significantly changed throughout the last century. Microbe invasion in the host was previously thought to always result in disease. Now we know that even a healthy host is populated by an ample variety of microbes, and the notions of commensalism, colonization, persistence, and opportunism are widely recognized. These coinfecting microbes exist in a dynamic homeostatic equilibrium with the host; therefore, microbial pathogenesis is attributable neither to host response nor to the microbe alone but to the microbe-triggered perturbation of this equilibrium and to the host's consequential response.

HIV-1 infection affects and is affected by the balance between the host and other microbes. Human tissue that is critical for HIV-1 transmission and pathogenesis is populated by a variety of microbes. These microbes, plus new ones that breach host defenses once the efficiency of the immune system is impaired, are called *copathogens* and play an important role in HIV disease. Their role is emphasized by the Centers for Disease Control and Prevention's definition of AIDS: HIV-1 infection and a CD4 T-cell count below 200 cells/

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Disclosures
No potential conflicts of interest relevant to this article were reported.

μL or, alternatively, the presence of at least one of 25 AIDS-defining conditions, the great majority of which are sustained by other microbes [2].

The role of copathogens in the progression toward AIDS has also been emphasized by recent findings that in patients with HIV-1 infection, the damage of gut mucosa is associated with microbial translocation. Such a systemic invasion of microbes, mainly bacteria, that are normally confined to the surface of the gut fuels systemic immune activation and progression of HIV-1 disease [3••].

In most cases, invasion of a pathogen against HIV infection worsens the clinical course of the disease, as infection with two diseases is worse than infection with one disease. However, it is becoming clearer that the situation is not exhausted by this simple arithmetic. In particular, epidemiologic, clinical, and experimental observations indicate that coinfection by some microbes and HIV-1 may be detrimental to the latter. However, in the course of their evolution, microbes have "learned" how to exploit immune responses to their benefit and to create conditions favorable for their own maintenance. Various microbes have different requirements for their survival and spreading, and what is optimal for one microbe may be detrimental for another. Knowledge of this intricate network of signals that mediate viral interactions would possibly permit containment of HIV-1 infection and the control of HIV-1 disease progression.

In this article, we review published data on the mechanisms of these interactions. Because of the breadth of the topic, we limit this review to the interactions between HIV-1 and other viruses, although similar data are available on bacteria, fungi, and protozoa.

Hepatitis B Virus

Hepatitis B virus (HBV) belongs to the *Hepadnaviridae* family. It is a common HIV copathogen that shares risk factors and routes of transmission with HIV. In the United States and Europe, more than 50% of HIV-infected men who have sex with men have evidence of past HBV infection, and 7% to 10% have chronic HBV infection [4].

It has been demonstrated that HIV-1 infection greatly affects HBV. Patients with HIV-1 infection have higher levels of HBV DNA and a decreased likelihood of HBV clearance [4]. Thus, there are more chronic HBV infections among HIV-1–positive individuals than in HIV-1–negative patients [4]. Although HBV is a DNA virus, its replication occurs through an RNA intermediate that requires a reverse transcriptase activity by the HBV polymerase. Interestingly, the latter and HIV-1 reverse transcriptase share sensitivities to several inhibitors (eg, lamivudine, entecavir, tenofovir, and emcitrabine), thus complicating therapeutic decisions, as treating HBV infection in coinfected patients leads to selection of HIV-resistant mutants and vice versa [5].

Hepatitis C Virus

Hepatitis C virus (HCV) is a *Flavivirus*; its rate of coinfection is approximately 25% among individuals with HIV infection, and it reaches 50% to 95% in specific risk groups (eg, intravenous drug users) [6]. HIV-1 infection adversely affects the natural history of HCV infection, favoring high viral load, high viral persistence, and faster progression of liver disease [6]. The negative impact of HIV coinfection on HCV disease progression, together with the extended survival of HIV-infected individuals on highly active antiretroviral therapy, explains why HCV-related liver disease is a leading cause of death in this population, even among those with access to antiretroviral drugs [7].

HCV was originally considered to be a strictly hepatotropic virus, but several clinical and experimental studies have demonstrated that HCV also replicates in extrahepatic sites, including peripheral blood mononuclear cells [8]. The HCV-RNA negative strand, which is a viral replicative intermediate, is often found in circulating B cells, T cells, monocytes/macrophages, and lymph nodes, especially from patients with HIV-1 infection [9].

As with HIV, persistent HCV infection due to ineffective immune control results in a continuous immune activation. In particular, HCV activates CD4 and CD8 T cells and alters the maturation of CD8 T cells, affecting the expression and function of CD28 costimulatory molecules on their surfaces [10,11•,12•]. In patients with HIV-1 infection, enrichment in mature $CD28^-$ T cells that express an intermediate memory phenotype ($CD28^-CD27^+$) has been reported [13]. It seems that HIV and HCV skew CD8 T-cell maturation in opposite directions: HCV toward an early-differentiated phenotype and HIV toward a more mature one. A recent study found that an early memory CD8 phenotype, $CD28^+$, prevails in individuals with HIV-1/HCV coinfection, suggesting that HCV overcomes HIV in its effect on the maturation of CD8 T cells [12•]. Because HIV immune activation is recognized as a major driving force of CD4 T-cell depletion and immunodeficiency [14••], it is conceivable that the combination of HIV and HCV infection may accelerate progression to AIDS. To test this hypothesis, ex vivo models that can study coinfection under strict laboratory conditions are needed. Although such a system exists for HIV-1 and several other copathogens, an adequate ex vivo system to study HCV infection has not yet been developed.

GB Virus C

GB virus C (GBV-C) is a lymphotropic *Flavivirus*, but unlike HCV, it is not associated with any human disease. Transmitted predominantly parenterally, it is present in 20% to 40% of individuals with HIV infection [15]. Several epidemiologic studies have reported that GBV-C coinfection negatively correlates with HIV-1 disease progression. A meta-analysis of several clinical studies confirmed the protective effect of GBV-C on the survival of individuals with HIV infection [16•].

Several mechanisms for the GBV-C–mediated protective effect on HIV-1 disease progression have been identified [17–19]. Coinfected patients have lower HIV-1 RNA levels, higher CD4 T-cell counts, and unaltered T-helper type 1 and 2 cytokine profiles that are associated with a slower progression to AIDS [17]. The GBV-C suppression of HIV replication in vitro is mediated by downregulation of CCR5 and CXCR4 and by induction of their ligands [18]. The envelope protein E2 downregulates CCR5 after engagement of CD81 and upregulates regulated upon activation, normal T-cell expressed and secreted (RANTES) protein, whereas the nonstructural protein NS5A is efficient in downregulating CXCR4 and inducing stromal cell-derived factor-1 [18]. Recently, it was reported that the NS5A-mediated inhibitory activity against HIV-1 is also retained by the homologous gene of other flaviviruses, including yellow fever virus, HCV, and dengue virus [19]. Therefore, these viruses' effects on HIV replication should be now investigated.

Human T-Cell Leukemia Viruses 1 and 2

Human T-cell leukemia virus (HTLV)-1 and HTLV-2 belong to the *Retroviridae* family and both are HIV-1 copathogens. HTLV-1 and HTLV-2 cause different clinical diseases, have different cellular tropisms, and have diverse impacts on HIV-1 disease. HIV-1/HTLV-1 coinfection is more common in South America, Africa, the Caribbean, and Japan, whereas HTLV-2 coinfection is higher in the United States and Europe, where it exceeds 10% [20].

HTLV-1, like HIV-1, preferentially infects CD4 T cells and is the etiologic agent of adult T-cell leukemia and of chronic neurologic disorders. Results of clinical studies of the effect of

HTLV-1 coinfection on the course of HIV-1 disease are controversial; both acceleration and delay of HIV-1 disease progression have been reported [21].

The molecular bases for HIV-1/HTLV-1 interactions include increased production of interleukin (IL)-2 and CC chemokines and the transactivation of HIV-1 long terminal repeat (LTR) by HTLV-1 Tax, which is homologous to HIV-1 Tat [22]. Likewise, HTLV-1 Rex can replace the HIV-1 homologues Rev in mediating the nuclear export of partially spliced and unspliced viral transcripts of HIV-1 [23]. Because both HTLV-1 and HIV-1 infect CD4 T cells, it is plausible that these mechanisms play a role in vivo.

Interestingly, HIV-1/HTLV-1 coinfection differentially affects R5 and X4 HIV-1 variants. Whereas replication of HIV-1 R5 is inhibited, the growth of HIV-1 X4 is enhanced, which can explain conflicting results of the clinical studies. These opposite effects on different HIV-1 variants can be a result of the combination of Tax/Rex-mediated effects on HIV-1 transcription and the induction of CC chemokines.

In contrast to HTLV-1 and HIV-1, HTLV-2 preferentially infects CD8 T cells and does not seem to be associated with any human disease [20]. Clinical studies show that in patients with HTLV-2/HIV-1 coinfection, CD4 T-cell depletion is slower, HIV-1 RNA level is reduced, and HIV-1 disease progression is delayed compared with controls [24].

In coinfected individuals, increased production of CC chemokines and increased production of interferon-γ mediated by HTLV-2 Tax protein have been reported [25•]. Moreover, in a recent study, these patients had lower expression of CD38 in CD8 T cells and an altered profile of chemokine production in HIV-1-Gag–specific CD8 T cells compared with HIV^{+}/$HTLV\text{-}2^{-}$ individuals [24]. This may cause lower HIV-1 load in these patients, a reduced level of immune activation, or both of these factors.

HIV-2

HIV-2, like HIV-1, belongs to the *Lentivirus* genus in the *Retroviridae* family. HIV-2 infections represent a minority of all HIV infections and are predominantly found in West Africa, where HIV-2 prevalence is approximately 20% in the high-risk groups. HIV-2 produces an attenuated form of the HIV disease. Despite genetic and structural similarities, HIV-2 exhibits CD4 independence, is more efficiently controlled by the host immune system, and has a slower progression to AIDS than HIV-1. Nevertheless, HIV-2 epidemics are slowly but continuously spreading worldwide [26].

Epidemiologic data regarding the effect of HIV-2 on HIV-1 acquisition are controversial; some authors report that HIV-2 infection lowers the probability of HIV-1 acquisition, but other studies do not confirm those findings [26]. However, HIV-2 infection may influence HIV-1 disease progression, as HIV-1 RNA load is reduced in patients with HIV-2 coinfection. This reduction may be due to the vigorous production of CC chemokines and to the cross-reactivity with HIV-1 of the robust humoral and cellular immune response against HIV-2 [27,28].

Human Polyomavirus JC

JC virus (JCV) belongs to the *Polyomaviridae* family; it causes progressive multifocal leukoencephalopathy, an AIDS-defining illness. In AIDS patients, there is a significantly higher incidence of this disease than in other immunosuppressed individuals [29]. This may be related to the HIV-1 Tat–mediated upregulation of JCV transcription in coinfected astrocytes [29]. However, upregulation of JCV is accompanied by a reduction of HIV-1 production. Recently, the JCV-encoded agnoprotein has been proposed as a negative

regulator of HIV-1 Tat–mediated transcription, suggesting a complex mechanism of interaction between JCV and HIV-1 in coinfected cells [30].

Measles Virus

Measles virus (MV) belongs to the *Paramyxoviridae* family. Although no longer endemic in countries that have implemented vaccination programs, MV still infects 20 million people yearly worldwide. In coinfected children in Zambia, acute measles infection was shown to be associated with a transient reduction of HIV-1 load [31]. Several mechanisms demonstrated in vivo and ex vivo have been suggested to explain this reduction; MV-induced transient lymphopenia, increased production of RANTES [32], and the blockage of the CD4 T-cell cycle appear to prevent the completion of HIV-1 reverse transcription [33].

Human Herpesviruses

In the early 1980s, severe clinical expressions of herpesvirus infection were among the first recognized manifestations of AIDS. Later, severe mucocutaneous herpes simplex virus (HSV) infection, Kaposi's sarcoma, Burkitt's lymphoma, cytomegalovirus (CMV) disease, and retinitis were included by the Centers for Disease Control and Prevention in the list of AIDS-defining conditions [2]. Accumulating data show that human herpesviruses (HHVs) interact with HIV-1, affecting HIV transmission and pathogenesis.

HSV-2 is the most prevalent cause of genital ulceration worldwide. It is generally accepted that genital ulceration facilitates acquisition and transmission of HIV-1 by disrupting the mucosal barrier and generating local inflammation [34••]. However, it seems that HSV-2 reactivations, which are particularly frequent in individuals with HIV infection, are mainly subclinical or asymptomatic. These reactivation episodes increase genital shedding of HIV-1 independently of the level of immunosuppression, thus increasing the probability of HIV-1 transmission. The molecular mechanisms of HIV-1/HSV-2 interactions include transactivation of HIV-1 LTR by HSV-encoded regulatory proteins and HSV-mediated decrease of an endogenous mucosal anti–HIV-1 protein [34••,35]. It is also possible that during reactivations, the recruitment of cells necessary to clear HSV-2 increases HIV-1 shedding by attracting HIV-1–infected cells to the genital tract, promoting HIV infection of activated cells, and awakening HIV production in latently infected cells [34••].

CMV is an opportunistic pathogen responsible for serious clinical consequences in patients with AIDS. It is still a matter of debate whether the presence of CMV viremia is a determinant or just a marker of HIV-1 disease progression. In support of the former hypothesis, HIV progression is accelerated in children infected with CMV during the first 18 months of life [36]. HIV transmission may also be affected by CMV, as emphasized by the observation of a positive correlation between CMV and HIV-1 load in semen [37,38•]. Also, HIV may affect CMV, as demonstrated in tissues ex vivo in which HIV coinfection upregulates CMV replication [37].

As with other persistent viruses, CMV's strategies to divert the host's immune response could affect HIV-1 replication. CMV alters the expression and the function of major histocompatibility complex classes I and II, increases the production of several chemokines (IL-1, tumor necrosis factor-α, monocyte chemoattractant protein-1, macrophage inflammatory protein (MIP)-1β, RANTES, and IL-8), and encodes viral homologue chemokines (vIL-10, vCXC-1, vCXC-2) and chemokine-like receptors (US33, US78, US27, US28), among which US28 can also serve as coreceptor for HIV-1 entry [39].

HHV-6 and HHV-7 are highly prevalent lymphotropic β-herpesviruses. Primary infection with these viruses can occasionally cause *roseola infantum*, an acute exanthematous illness

of early childhood. Generally, these viruses are considered of low morbidity, and they persist in the human host under control of the immune system. However, in immunocompromised hosts, this control is less stringent and HHV-6 and HHV-7 can act as opportunistic agents [40].

Several pieces of evidence obtained in clinical and experimental studies have indicated that HHV-6 (in particular HHV-6A) is an important cofactor in HIV-1 disease progression [40]. HHV-6 infects, among others, CD4 T cells, the very same targets of HIV-1, and exhibits a preference for activated cells. In addition to a direct cytopathic effect on CD4 T cells, HHV-6 may affect HIV-1 pathogenesis through several other mechanisms: transactivation of the HIV-1 LTR, induction of expression of CD4 on CD8 T cells and natural killer cells, downregulation of CD3 and the complement regulatory protein CD46 with consequent alteration of T-cell function, expression of two virally encoded chemokine receptors and a viral homologue of CCL4, suppression of IL-12, and induction of RANTES [40,41].

In general, HHV-6 reactivation in individuals with HIV-1 infection may disturb an already misbalanced immune system, introducing new immunomodulatory mechanisms. In particular, HHV-6–induced production of RANTES inhibits the replication of R5 HIV-1 and may promote the emergence of X4 HIV-1 variants [41]. Also, the induction of CD4 expression on CD8 T and natural killer cells can allow the infection of these cells by HIV-1, thus extending the pool of HIV-1 targets.

HHV-7, despite its genetic similarities with HHV-6, has different molecular features. It strongly downregulates its receptor, CD4, but does not increase RANTES production. In the context of HHV-7/HIV-1–coinfected human lymphoid tissue, the massive downregulation of CD4 suppresses the replication of HIV-1 R5 variants. In contrast, X4 HIV-1 suppresses HHV-7, preventing CD4 downregulation.

Although the molecular mechanisms of HHV-6 and HHV-7 interactions with HIV-1 are different, in vivo, both HHVs may favor a switch of dominance from R5 to X4 HIV-1, accelerating HIV disease progression [42].

HHV-8 and EBV are lymphotropic γ-herpesviruses responsible for several AIDS-related malignancies (Kaposi's sarcoma, multicentric Castleman's disease, primary effusion lymphoma, Burkitt's lymphoma, and other non-Hodgkin's lymphomas) [43]. A direct interaction between Epstein-Barr virus and HIV-1 and between HHV-8 and HIV-1 in vivo has been hypothesized [44]. Molecular mechanisms of these interactions include production of HHV-8–encoded and Epstein-Barr virus–encoded immunomodulatory proteins, chemokines, and chemokine receptors. In particular, HHV-8–encoded vMIP-1 and vMIP-2 are ligands of CCR5 and block HIV entry in vitro [45].

HIV-1 Coinfection and Superinfection

Various HIV-1 variants can interact with each other as well. They can be sequentially transmitted to the same recipient after the immune response to the initial HIV-1 virus has been established (superinfection). Alternatively, different HIV-1 variants can be transmitted simultaneously or at least before the immune response for the initial virus is mounted (coinfection) [46].

In both cases, the simultaneous presence of HIV-1 variants from two different clades in the same host may give rise to recombination viruses known as *circulating recombinant forms* (CRFs). New CRFs are continuously reported, and it is estimated that 10% of HIV infections worldwide involve CRFs. Moreover, in patients with HIV-1 superinfection, the disease progression is accelerated and the set point of the HIV-1 load is elevated [46].

Ex vivo studies have demonstrated that HIV-1 variants interact with each other in coinfected human lymphoid tissue; X4 HIV-1 suppresses R5 replication by inducing CC chemokine production [47]. In vivo, such a phenomenon may greatly affect the course of HIV disease by giving an advantage to HIV-1 variants that accelerate the progression to AIDS.

Mechanisms of Viral Interactions With HIV-1: Implications for HIV Therapy

The striking amount of bacteria in the gut exceeding the number of human cells by 10-fold indicates the importance of the host–microbe ecosystem. Although the number of viruses in the body is much lower, some of them, like HHV-6 and HHV-7, are ubiquitous and have evolved from a common herpesvirus ancestor already present 200 million years ago, becoming part of the above-mentioned ecosystem [48]. How does the host benefit from this symbiosis? It has been hypothesized that these “low-pathogenic” viruses evolved as elements of the defense system against pathogens. HHV-6 and HHV-7 suppress (at least ex vivo) the R5 variants of HIV-1 that predominantly transmit infection, which indirectly supports this hypothesis [41,42].

On the other hand, “pathogenic” viruses that enter the host–microbe ecosystem after HIV infection misbalance it, typically in their own favor. However, what favors one virus may be detrimental to another (eg, HIV). It is important to understand the mechanisms by which other microbes affect HIV-1 in order to try to manipulate them.

As of now, the following mechanisms for HIV interactions with other viruses have been described: 1) upregulation of chemokines that are ligands for HIV-1 coreceptors, 2) change of cytokine spectra or of the expression of their receptors, 3) downregulation of HIV-1 receptors/coreceptors, 4) systemic or local immune activation, and 5) transactivation of HIV-1 LTR.

Some of these mechanisms, like the upregulation of CC chemokines or downregulation of HIV receptors, clearly constitute a negative signal for HIV, suppressing its cell entry. Others, like immune activation, seem to benefit HIV, as it replicates most efficiently in activated cells [14••]. Changing cytokine spectra may constitute either positive or negative signals, depending on which cytokines are up- or downregulated. The mechanisms listed above are not alternative, and a copathogen may exert several of these effects, with the net result being a complex superimposition of several effects. Apparently, the situation is even more complex. In particular, HIV-1 modulates non-HIV viruses, thus changing how these viruses affect HIV. For example, X4 HIV-1 suppresses HHV-7 in coinfected human tissue but conversely facilitates CMV replication [42]. Moreover, because certain other viruses, like HIV, replicate more efficiently in activated cells, the general activation of the immune system by HIV-1 may influence the spreading and rate of their replication. These viruses may compete with HIV for these activated cell targets, and the result of this competition may vary.

Importantly, different HIV-1 variants have different sensitivities to the factors generated by other viruses. For example, in human tissue, HHV-6 infection upregulates RANTES and suppresses R5 but not X4 HIV-1 [41]. Also, R5 is more sensitive to downregulation of CD4, and therefore, HHV-7 may be more efficient in suppressing R5 rather than X4 HIV-1 in tissue ex vivo [42]. As it is well established that a switch of dominance from R5 to X4 coincides with accelerated progression to AIDS, these and other coinfecting viruses should affect HIV-1 evolution. Moreover, the R5–X4 switch is only the most studied example of HIV evolution associated with the disease progression, but many others exist. Evolution toward higher pathogenicity also occurs when R5 HIV-1 dominates through the entire course of the disease; this evolution also may be driven by copathogens. Moreover, it was shown recently that only one or few HIV-1 variants out of the entire swarm in the donor’s

body are transmitted to a recipient [49••]. It is conceivable that various coinfecting microbes, both in donors and recipients, play a role in the selection of these variants.

Although most of the complex mechanisms of HIV-1 interaction with other microbes in coinfected human tissues are not yet understood, those that we already know may become a basis for new anti-HIV strategies. These strategies may use either the negative signals sent to HIV by the coinfecting viruses or suppress positive signals. Nowadays, no regulating agency would allow the experimental infection of humans with live viruses, even the "harmless" ones, as it may be risky, especially in immunocompromised hosts. Although such an approach was used in the past, starting from Jenner's vaccinations in 1796 and continuing through Sabin's polio vaccines, in the era of molecular biology, by packing isolated genes into vectors or using viral proteins, we can avoid using live or attenuated viruses, providing exclusively the ones that are responsible for HIV-1 suppression.

Moreover, new strategies for HIV-1 suppression that involve coinfecting viruses have recently been reported; the specific metabolic activity of non–HIV-1 viruses can convert exogenous compounds into anti-HIV drugs in situ. This is the case with the ability of acyclovir (ACV) to suppress HIV-1 in HHV-coinfected tissues [50•]. ACV is a guanosine analogue that has commonly been used as an antiherpetic drug for about 30 years. It acts through a well-known mechanism—ACV is phosphorylated by HHV kinases and then converted by cellular enzymes into triphosphorylated ACV. In this form, it is incorporated into the nascent HHV DNA chain, blocking its elongation. Because the ability of HHV kinases to phosphorylate ACV is unique, this drug is not active against other viruses. However, it has been found that ACV triphosphate also suppresses HIV-1 reverse transcriptase, revealing the mechanism of ACV suppression of HIV in HHV-coinfected tissues. This discovery suggests a strategy of exploiting metabolic activity of a coinfecting virus to convert a drug into an HIV suppressor (Table 1).

Conclusions

In the human body, HIV interactions with other viruses affect HIV pathogenesis, largely determining the course of HIV disease. The study of these interactions is evolving into a new field of research that requires systematic approaches and may lead to the design of new and original anti-HIV therapies.

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Table 1

Relations between coinfecting viruses and HIV-1

Virus	Mechanisms	Potential effects on HIV-1*
HBV	Several anti-HBV drugs are also HIV-1 RT inhibitors	HBV treatment also decreases HIV replication; emergence of HIV-1 RT-resistant mutants
HCV	Systemic immune activation	Facilitation of HIV-1 replication
GBV-C	CCR5 and CXCR4 downregulation; induction of RANTES and SDF-1	Suppression of HIV-1 replication
HTLV-1	LTR transactivation; induction of CC chemokines	Facilitation of HIV-1 replication; suppression of HIV-1 R5 replication
HTLV-2	Induction of CC chemokines; decreased systemic immune activation	Suppression of HIV-1 replication
HIV-2	Cross-reactive immune response; induction of CC chemokines	Decreased HIV-1 acquisition; suppression of HIV-1 R5 replication
JCV	Suppression of Tat functions	Suppression of HIV-1 replication in vitro
Measles virus	Induction of RANTES; blockage of CD4 T-cell cycle	Suppression of HIV-1 replication
HSV-2	Genital ulceration; increased LTR transactivation	Increased HIV-1 transmission; facilitation of HIV-1 replication
CMV	Increased HIV-1 load in semen; induction of chemokines, virokines, and viroceptors	Increased HIV-1 transmission; variable results were reported for the net effect
HHV-6	Induction of RANTES, virokines, LTR transactivation, CD3 and CD46 downregulation	Decreased replication of HIV-1 R5 ex vivo; net effect on HIV-1 replication in vivo to be studied
HHV-7	Downregulation of CD4	Decreased replication of HIV-1 R5 ex vivo; net effect on HIV-1 replication in vivo to be studied
HHV-8	Chemokines and virokines	Net effect of HIV-1 replication in vivo to be studied

*In vivo, some of the potential effects of coinfecting microbes on HIV-1, especially those that were identifi ed in in vitro system only, may be masked (eg, due to several opposite signals triggered by the same or different microbes, or by other host factors that determine HIV disease). CMV—cytomegalovirus; GBV-C—GB virus C; HBV—hepatitis B virus; HCV—hepatitis C virus; HHV—human herpesvirus; HSV—herpes simplex virus; HTLV—human T-cell leukemia virus; JCV—JC virus; LTR—long terminal repeat; RANTES—regulated upon activation, normal T-cell expressed and secreted; RT—reverse transcriptase; SDF—stromal cell-derived factor.