Attenuation of HIV-1 Infection by Other Microbial Agents

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Although potentiation of human immunodeficiency virus (HIV) type 1 (HIV-1) infection has been known to occur in coinfection with a variety of pathogens and types of vaccination, there are emerging data on specific infectious agents that may attenuate HIV-1 infection. New literature suggests that certain pathogens are capable of inhibiting HIV-1 replication. These include GB virus C, measles virus, Orientia tsutsugamushi, and human T lymphotropic virus types 1 and 2. In addition, there are conflicting data on the effects of Mycobacterium tuberculosis on the replication of HIV-1, with some suggesting that this organism may inhibit HIV-1 replication. Also remaining controversial are the possible protective effects of HIV type 2 against HIV-1 infection. In this review, we summarize and critically discuss the body of emerging literature concerning infections that may have the ability to attenuate HIV-1 infection.

In the past, organisms have been described that have the ability to potentiate HIV-1 infection. Herpes simplex virus (HSV), Mycobacterium tuberculosis, and other AIDS-associated opportunistic infections have been shown to increase HIV-1 replication. For example, a median increase in plasma HIV-1 RNA level of 3.4-fold has been demonstrated during acute HSV outbreaks [1]. Zhang et al. demonstrated that M. tuberculosis increases transcription of HIV-1 in monocytic cell lines by stimulating the HIV-1 long terminal repeat [2]. In vivo, local and systemic enhancement of HIV-1 replication has been described in association with M. tuberculosis infection [3, 4]. Furthermore, antigenic challenge with influenza vaccine, tetanus toxoid, or pneumococcal vaccine can transiently stimulate HIV-1 replication [5–7]. Postulated mechanisms of enhanced HIV-1 replication include an increase in counts of activated CD4+ T cells susceptible to infection, an increase in proinflammatory cytokine levels, and an elevation in immune marker levels [8, 9]. In contrast, new studies suggest that certain pathogens may have the ability to attenuate HIV-1 infection (table 1).

GB VIRUS C (GBV-C)

A potential benefit of coinfection with GBV-C has been described in HIV-1–infected individuals. GBV-C is an RNA virus of the Flaviviridae family. GBV-C is a relative of hepatitis C virus but has no clear association with a disease state. The prevalence of GBV-C viremia is ∼20%–24% in intravenous drug users, and higher rates are found in HIV-1–infected persons, regardless of intravenous drug use [10–12]. GBV-C inhibits HIV-1 replication in vitro [13]. Interactions between GBV-C and HIV-1 in vivo demonstrate a survival benefit. Williams et al., in an analysis of the Multicenter AIDS Cohort Study, demonstrated that, 5–6 years after HIV-1 seroconversion, patients are less likely to die of HIV-1 disease if they are coinfected with GBV-C [14]. A survival advantage was not observed during the first 12–18 months after seroconversion. This time-dependent response may account for the contradictory results of prior studies [15, 16] that have evaluated the clinical outcome of patients with HIV-1 and GBV-C coinfection.

Another study, by Sathar et al., demonstrates a potential protective effect of GBV-C coinfection in HIV-1–infected mothers in KwaZulu Natal, South Africa.
This was the first study to report the dynamics of GBV-C dual infection in a cohort of HIV-1–infected African mothers and their infants. In a sample of 75 antiretroviral-naïve African mothers with HIV-1 infection, 27 (36%) tested positive for GBV-C RNA. Significantly higher CD3+ T cell counts (due to increased T cell activity), increased γδ T cell counts, and decreased cell expression of CD30 (reflecting decreased activation status and increased Th1 response) was demonstrated in HIV-1–seropositive mothers with GBV-C viremia. These findings suggest a possible protective effect of GBV-C coinfection for the mothers. In this cohort, there did not appear to be evidence for in utero or intrapartum GBV-C transmission.

Mechanisms for the potential protective benefit of GBV-C were suggested in a prospective cohort study by Nunnari et al. [18]. The 8-year longitudinal follow-up study of HIV-1–infected individuals coinfectd with GBV-C evaluated AIDS-free survival rates, plasma HIV-1 RNA levels, and selected immunologic variables in 80 patients with and without GBV-C coinfection. Serum cytokine levels were measured by enzyme immunoassay. HIV-1–infected individuals coinfected with GBV-C were found to maintain an intact Th1 cytokine profile. GBV-C–negative patients had significantly decreased Th1 cytokine (interleukin [IL]–2, IL-12, and interferon [IFN]–γ) levels and increased Th2 cytokine (IL-4 and IL-10) levels. Progression to AIDS has been correlated with decreased production of IL-2, IL-12, and IFN-γ and with increased production of IL-4 and IL-10 in HIV-1–infected individuals. This 8-year longitudinal follow-up study demonstrated that patients coinfected with GBV-C maintained an intact Th1 cytokine profile and had lower plasma HIV-1 RNA levels, higher CD4 T cell counts, and a higher AIDS-free survival rate than did HIV-1–infected patients who were GBV-C negative. GBV-C viremia was associated with better survival even after highly active antiretroviral therapy (HAART), and this study suggested that coinfection might improve the efficacy of HAART.

Moreover, recent studies demonstrate that GBV-C may block entry of HIV-1 into important cellular targets. In vitro, in T cells, GBV-C envelope protein E2 decreased entry of HIV-1 by down-regulating a major chemokine receptor of HIV-1, CCR5. This appears to result from direct binding of GBV-C E2 to CD81 on CCR5+ cells, which alters the quantity of CCR5 on the cell surface [19]. Certain chemokines, especially RANTES, may be up-regulated in patients with dual infection. E2 induces such up-regulation in vitro, and RANTES binds to CCR5 and may block entry directly or act through down-regulation of CCR5 [19]. There may also be innate immune mechanisms that inhibit HIV-1 replication. Although this has not been studied, GBV-C may increase levels or augment activity of intracellular inhibitors of HIV-1 internalization and could have cell-specific effects on important cellular targets of HIV-1, such as dendritic cells and macrophages.

However, further data reveal that the issue of HIV-1 attenuation in GBV-C dual infection may be controversial [20]. In a prospective cohort study by Bjorkman et al., 230 patients not receiving antiretroviral therapy had baseline and follow-up serum samples analyzed for GBV-C markers over time [21]. The purpose of the study was to evaluate whether GBV-C viremia at the time of diagnosis of HIV-1 infection predicts disease outcome and whether longitudinal changes in GBV-C levels are associated with disease progression. The study revealed that testing for GBV-C markers at diagnosis of HIV-1 infection did not show significant effects of GBV-C viremia on mortality or AIDS incidence during long-term follow-up in this cohort. The findings also suggested that GBV-C viremia might not represent an independent prognostic factor in coinfected patients. This information contrasts with many of the prior studies that suggest a beneficial effect of GBV-C dual infection. Then again,
conflicting data were reported in the Bjorkman et al. study, in which a subgroup analysis showed an association between GBV-C viremia and lower mortality in patients with advanced HIV-1 disease at inclusion who had lower baseline CD4+ T cell counts [21].

Furthermore, the effect of GBV-C co-infection on HIV-1 disease progression also remains controversial because of the Amsterdam Cohort Study by Van der Bij et al. [22]. The effect of GBV-C infection in 326 homosexual men infected with HIV-1 was studied. Their estimated dates of seroconversion, longitudinal follow-up, and serum samples allowed measurement of GBV-C RNA and E2 antibodies early and late during HIV-1 infection. Results of the study revealed no protective effect of GBV-C RNA or E2 antibodies on disease progression. However, GBV-C RNA loss was associated with HIV-1 disease progression. One hypothesis suggests that GBV-C persistence depends on CD4+ T cells that are susceptible to infection and that the CD4+ T cell count decrease associated with HIV-1 disease progression may be a cause, rather than a result, of GBV-C RNA loss [22].

MEASLES VIRUS

Another virus for which data concerning dual infection and HIV-1 attenuation are emerging is measles virus. Measles virus has a high incidence in central and eastern Africa. It is known to be highly immunosuppressive, and mortality from measles is often a result of secondary infections. However, the effects of measles virus on the immune system are complex and often involve both immune suppression and immune activation. Suppression of HIV-1 replication during acute measles has been suggested in a study by Moss et al. [23] and in a study of human lymphoid tissue ex vivo [24].

In the study by Moss et al., conducted in Zambia, children hospitalized with a clinical and serologically confirmed diagnosis of measles had HIV-1 RNA levels measured at study entry, hospital discharge, and at 1-month follow-up. The median plasma HIV-1 RNA level in 33 HIV-1–infected children with measles was 8216 copies/mL at study entry, increased to 107,567 copies/mL at hospital discharge, and was 373,748 copies/mL at 1-month follow-up [23]. The median plasma HIV-1 RNA level in 22 children without acute illness was 228,454 copies/mL [23]. This plasma HIV-1 RNA level was significantly higher than the median level in HIV-1–infected children with measles at study entry but was not significantly different from the levels in children with measles at discharge or follow-up.

Several possible mechanisms have been postulated to explain the transient suppression of HIV-1 replication during the early stage of measles. Infection with measles virus results in lymphopenia, with a reduction in CD4+ T cell count. The early reduction in CD4+ T cell count could reduce the number of target cells susceptible to HIV-1 replication (“predator vs. prey relationship”). Another hypothesis relates to measles virus production of soluble factors capable of suppressing HIV-1 replication, such as β chemokines, the CD8+ T cell antiviral factor, and the cytokines IL-10 and IL-16. Median plasma levels of RANTES were also highest in HIV-1–infected children with measles. Other trends in plasma markers of immune activation were noted after acute measles in HIV-1–infected children, including increasing soluble CD4 and β2-microglobulin levels and decreasing soluble CD8, soluble IL-2R, and soluble TNF-RII levels. However, there were insufficient numbers of patients to determine whether the differences were statistically significant.

Chemokine and cytokine modulation in coinfection with HIV-1 and measles virus was further demonstrated ex vivo in studies by Grivel et al. [25, 24]. Lymphoid tissues and organs are prominent sites of both measles virus and HIV-1 replication. Human lymphoid tissues ex vivo were infected with the CCR5-specific (R5-tropic) HIV-1 isolate SF162 or the CXCR4-specific (X4-tropic) HIV-1 isolate LAV-04, either alone or in combination with measles strains. Viral replication was evaluated and levels of cytokines and chemokines were measured in culture medium of infected tissues. In coinfections with HIV-1, measles virus appeared to dramatically suppress HIV-1 replication, particularly that of the R5 phenotype. In coinfected tissues from 6 donors, replication of R5-tropic SF162 was inhibited by 88% ± 4%, and replication of X4-tropic LAV-04 was inhibited by 44% ± 17% (values are mean ± SE). RANTES secretion increased by 2.5-fold, among 18 cytokines measured in culture medium [25]. Therefore, measles virus likely suppresses HIV-1 replication in lymphoid tissues ex vivo by inducing up-regulation of RANTES. These data also support the postulate that regulation of chemokines suppresses HIV-1 replication in dual infection.

SCRUB TYPHUS

Scrub typhus is an additional infectious disease that has demonstrated a potential suppressive effect on plasma HIV-1 RNA level. Orientia (formerly Rickettsia) tsutsugamushi, a gram-negative intracellular bacillus, is the causal agent of scrub typhus. In vitro and in vivo data suggest that HIV-1 suppression occurs during acute scrub typhus. Philpott et al. tested serum from HIV-1–negative patients with scrub typhus for the ability to inhibit replication of R5-tropic and X4-tropic strains of HIV-1 in vitro; replication of HIV-1 was inhibited by 2–10-fold in vitro by addition of serum from patients with scrub typhus [26]. However, in contrast to measles virus infection, which demonstrated preferential suppression of the R5-tropic viral phenotype, serum from patients with scrub typhus appeared to suppress only X4-tropic strains. Depletion of chemokines had no influence on HIV-1 replication, but depletion of antibody negated the HIV-1 inhibitory effects of the serum. In vivo, transfer of plasma from patients with scrub typhus into
HIV–1–infected individuals caused a significant decrease in plasma HIV–1 RNA level in 7 of 10 recipients [26]. A shift in the viral population from X4-tropic to R5-tropic strains accompanied the reduction in plasma HIV–1 RNA level. Interestingly, individuals with no reduction in HIV–1 RNA level were infected only with R5-tropic strains.

Another study demonstrating HIV–1 suppression during acute scrub typhus was performed in Thailand by Watt et al. [27]. In this study, serial plasma HIV–1 RNA levels were measured in 10 Thai adults with acute scrub typhus who were not receiving antiretroviral therapy, as well as in 5 patients with HIV–1 infection who had other acute infections (4 with malaria and 1 with leptospirosis). Plasma HIV–1 RNA levels 3 days after admission were significantly lower in the group with scrub typhus than in the group without scrub typhus (percentage of day 28 values, 193% vs. 376%) [27]. There was a ≥3-fold reduction in HIV–1 RNA level in 4 of 10 patients with scrub typhus, and HIV–1 RNA levels even fell below the limit of detection in 2 patients with scrub typhus [27]. An alternate hypothesis has been proposed to explain the inhibition of HIV–1 replication during acute scrub typhus: instead of an inhibitory antibody, restriction of syncytia formation has been postulated as an explanation. The presence of the syncytia-inducing phenotype of HIV–1 has been suggested to be an indicator of decline in CD4+ T cell counts and progression of disease [28]. Although the association is not clearly understood, significant numbers of HIV–1 strains from patients with AIDS who have CD4+ T cell counts <200 cells/mL may be expected to have a syncytia-inducing phenotype. Interestingly, all isolates from patients with scrub typhus were actually of the non-syncytia-inducing phenotype. Therefore, maintenance of the non-syncytia-inducing phenotype during acute scrub typhus may play a role in inhibition of HIV–1 replication.

**HUMAN T LYMPHOTROPIC VIRUS TYPES 1 AND 2 (HTLV-1 AND -2)**

HTLV-1 and -2 are additional viruses that appear to attenuate HIV–1 infection. A long-term observational study, performed in Louisiana, that included 209 patients with HIV–1 and HTLV–1 or -2 coinfection demonstrated that coinfected patients had higher CD4+ T cell counts at baseline and exhibited slower rates of CD4+ T cell count decrease over time [29]. After antiretroviral therapy, age, race, sex, and history of intravenous drug use were adjusted for, the study also indicated that coinfection with HIV–1 and HTLV–2 was associated with delayed progression to AIDS. This trend occurred with HTLV–1, but statistical significance was not demonstrated. Patients with HTLV–1 or -2 coinfection were more likely to have thrombocytopenia, respiratory infections, urinary tract infections, and neurologic complications, which suggests both qualitative and quantitative differences in CD4+ T cell function, compared with that in individuals infected with only HIV–1. This observational study did not attempt to address the mechanisms of delayed progression to AIDS in coinfected patients. However, some in vitro data exist that may explain this effect. For instance, CD8+ T cells infected with HTLV–2 may produce C–C chemokines that may interfere with HIV–1 replication. In vitro, preferential expression of the chemokine CCL3L1/LD78β in HTLV–2/HIV–1–coinfected peripheral blood mononuclear cells (PBMCs) has been demonstrated [30]. CCL3L1/LD78β has exhibited potent activity in inducing down-regulation of the CCR5 receptor on monocyte/macrophage subsets in vitro. Up-regulation of the potent HIV–1 inhibitory chemokine CCL3L1/LD78β in dually infected patients may thus explain delayed progression to AIDS.

**HIV–2**

Evidence also exists that suggests a protective benefit of HIV–2 against HIV–1 infection. HIV–2, similar to HIV–1, is a lentivirus. However, HIV–2 is only ∼40% homologous to HIV–1 in nucleotide sequence [31]. Infection with HIV–2 is uncommon in the United States, and prevalence remains highest in western Africa. The 2 viruses show critical similarities and differences. They both can cause AIDS, but HIV–2 is less readily transmitted and less pathogenic [32, 33]. The possibility of a protective effect of HIV–2 against HIV–1 infection has remained controversial. Among cohorts of sex workers, Travers et al. found a higher incidence of HIV–1 infection in HIV–2–negative subjects than in HIV–2–positive subjects, even though the incidence of gonorrhea, a marker for exposure to sexually transmitted diseases, was significantly higher in HIV–2–positive subjects [34]. Further studies have also demonstrated a protective effect of HIV–2 against HIV–1 infection [35, 36], and lower plasma HIV–1 RNA levels have been observed in patients with HIV–1/HIV–2 coinfection [37].

Although epidemiologic evidence supporting the protective effects of HIV–2 against HIV–1 infection has been controversial, potential mechanisms for a beneficial effect have been postulated. Arya et al. demonstrated that HIV–2 suppresses HIV–1 replication at the molecular level, through a complex pathway [38]. A cross-reactive immune response in coinfected individuals, including cytotoxic T lymphocytes and a broad neutralizing antibody response, has been suggested. Studies of Senegalese sex workers infected with HIV–2 have shown resistance to HIV–1 infection in peripheral blood lymphocytes [39, 40]. Depletion of CD8+ T cells or β chemokines decreased the ability to resist HIV–1 infection. Further studies concerning the possible protective effects of HIV–2 against HIV–1 are needed to support these findings.

**M. TUBERCULOSIS**

Varying effects of *M. tuberculosis* on HIV–1 replication have been described in the past, both in vitro and in vivo. In HIV–1–infected...
In summary, although acute infectious processes that potentiate HIV-1 replication have been well described, novel data concerning infectious agents that may actually attenuate HIV-1 infection are now emerging. Although past literature has described a more favorable environment for HIV-1 replication during generalized immune activation after infection or vaccination, through mechanisms such as elevated proinflammatory cytokine levels and increased counts of CD4+ T cells susceptible to infection, recent evidence suggests that certain infections are capable of promoting inhibitory effects on HIV-1 infection. These infectious agents include GBV-C, measles virus, O. tsutsugamushi, HTLV-1 and -2, HIV-2, M. tuberculosis, influenza virus, HHV-6, and other organisms. The molecular and immunological mechanisms by which these organisms attenuate HIV-1 infection appear to be complex and divergent and may include direct inhibition of HIV-1 replication at the molecular and cellular levels, various indirect immune mechanisms, and alteration in clinical disease progression without clear effects on viral replication.

For example, evidence from molecular studies suggests that M. tuberculosis inhibits HIV-1 replication in vitro at an early postentry step of viral infection, and HIV-2 has also been shown to suppress HIV-1 replication at the molecular level. Blocking at a transcriptional and translational stage has been postulated as a mechanism for HIV-1 suppression in dendritic cell cultures coinfected with HHV-6.

Measles and scrub typhus demonstrate inhibition of plasma HIV-1 RNA levels during acute infection, and various immune mechanisms have been postulated as possible causes of this HIV-1 suppression. Chemokine and cytokine modulation and reduction in counts of CD4+ T cells susceptible to infection have been implicated as possible mechanisms for transient suppression of HIV-1 replication during acute measles infection. Furthermore, inhibitory antibodies and restriction of HIV-1-induced syncytia formation have been suggested as causes of decreased HIV-1 replication during acute scrub typhus.

Another manifestation of HIV-1 attenuation in coinfection is alteration of disease progression. This process has been described in coinfection with GBV-C and HTLV-1 and -2. Coinfection with GBV-C has demonstrated a survival benefit, one that is possibly attributable to maintenance of an intact Th1 cytokine profile. Moreover, HIV-1 and HTLV-1 or -2 coinfection have been associated with slower rates of CD4+ T cell count decline and delayed progression to AIDS.

A compendium of these data lead us to conclude that the mechanisms of HIV-1 attenuation in dual infection are complex and multilayered and likely include direct molecular and cellular suppression of HIV-1 replication, innate immune processes, and effects on clinical disease progression. Further research is required to elucidate the underlying mechanisms of
various coinfections and HIV-1 suppression. These future studies may potentially lead to novel therapeutic approaches to combat HIV-1 disease.

Acknowledgments
We thank Rita M. Victor and Brenda O. Gordon for excellent secretarial assistance.

References


