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GB virus C: the good boy virus?

Nirjal Bhattarai[1,2] and **Jack T. Stapleton**[1,2,3]

[1]Interdisciplinary Program in Molecular and Cellular Biology, University of Iowa, Iowa City, IA 52242, USA

[2]Iowa City Veterans Affairs Medical Center, University of Iowa, Iowa City, IA 52242, USA

[3]Departments of Internal Medicine and Microbiology, University of Iowa, Iowa City, IA 52242, USA

Abstract

GB virus C (GBV-C) is a lymphotropic human virus discovered in 1995 that is related to hepatitis C virus (HCV). GBV-C infection has not been convincingly associated with any disease; however, several studies found an association between persistent GBV-C infection and improved survival in HIV-positive individuals. GBV-C infection modestly alters T cell homeostasis *in vivo* through various mechanisms, including modulation of chemokine and cytokine release and receptor expression, and by diminution of T cell activation, proliferation and apoptosis, all of which may contribute to improved HIV clinical outcomes. *In vitro* studies confirm these clinical observations and demonstrate an anti-HIV replication effect of GBV-C. This review summarizes existing data on potential mechanisms by which GBV-C interferes with HIV, and the research needed to capitalize on this epidemiological observation.

Keywords

GBV-C; HIV; T cell; activation; IL-2

GBV-C discovery

Abbott Laboratories reported a novel human virus in the serum of a West African patient with non-(A–E) hepatitis in 1995. They named the virus GB virus C (GBV-C) based on nucleotide sequence similarities with two primate viruses called GB virus A and B (GBV-A and GBV-B) [1, 2]. GBV-A and GBV-B were discovered in tamarins that developed hepatitis following inoculation with the serum of a surgeon whose initials were G.B. [3]. Concurrently, investigators at Genelabs Technologies discovered a virus in the plasma of a patient with chronic hepatitis which they named hepatitis G virus (HGV) [1, 4]. Genome sequence analysis of GBV-C and HGV revealed 96% homology, indicating that they were two isolates of the same virus [1, 2, 4]. Subsequently, numerous studies investigated diverse populations at risk for liver disease, and when controlled for transmission exposure risks, no conclusive association between GBV-C/HGV and hepatitis was identified (reviewed in [5]). Because GBV-C/HGV does not cause hepatitis, the name ‘hepatitis G virus’ is misleading and we will refer to it as GBV-C.

Corresponding author: Stapleton, J.T. (jack-stapleton@uiowa.edu).

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Classification and genome organization

GBV-C is classified as a member of the family *Flaviviridae* based on its nucleotide sequence and genome organization, and it is the most closely related human virus to hepatitis C virus (HCV) (reviewed in [6]). Unlike HCV, GBV-C appears to be lymphotropic, and the virus is produced *in vitro* by T and B lymphocytes removed from GBV-C infected individuals [7]. The primary site of GBV-C replication is not completely characterized. Early studies found GBV-C RNA in liver samples, consistent with it being a hepatitis virus (HGV). However, subsequent studies found that the relative amount of GBV-C RNA in blood compared to liver was high, whereas HCV levels were higher in the liver than in blood, suggesting that the liver may not be the site of replication (reviewed in [6]). In addition, negative strand GBV-C RNA, indicative of viral transcription within cells, was found in bone marrow and spleen samples suggesting a hematopoietic site of replication. Negative strand RNA was not found in peripheral blood lymphocytes in some studies, even though peripheral blood mononuclear cells (PBMCs) produce virus *in vitro* (reviewed in [6]). These findings raise the possibility that lymphocyte progenitor cells may represent the primary permissive cell for GBV-C replication.

GBV-C is not currently assigned to any of the three *Flaviviridae* genera (flavi, pesti and hepaci). Recently GBV-C, along with GBV-A and a bat GB virus (GBV-D), were proposed to form a fourth genus within the *Flaviviridae* named ‘Pegivirus’ for ‘persistent G virus’ and GBV-C was proposed to be renamed as ‘human Pegivirus’ or HPgV (reviewed in [8]).

The GBV-C genome is a positive sense single stranded RNA (9.4 kb) that contains a long open reading frame (ORF) [2, 4, 6]. The genome organization is similar to HCV with a nontranslated region (NTR) at the 5′ end containing an internal ribosomal entry site (IRES) directing translation of a polyprotein of approximately 3000 amino acids. The polyprotein is followed by a 3′ NTR that is involved in RNA replication. The polyprotein is post-translationally processed into structural and nonstructural (NS) proteins by cellular signal peptidases and viral proteases (reviewed in [6]). The GBV-C genome organization, protein processing and viral envelope proteins are discussed in detail elsewhere (reviewed in [6, 8]).

Prevalence and transmission

The presence of GBV-C RNA in serum indicates active GBV-C infection whereas detection of antibodies to the GBV-C envelope glycoprotein E2 is associated with prior infection. Unlike HCV, simultaneous detection of viral RNA and antibodies to E2 or other viral proteins is not common [9–11]. In one large multicenter HIV-infected cohort, only 1.8% of patients with GBV-C viremia had detectable E2 antibodies whereas 75% of patients who were negative for GBV-C RNA had E2 antibodies [11]. GBV-C E2 antibodies are also consistently detected more frequently in individuals with GBV-C transmission risk without GBV-C viremia compared to those with GBV-C RNA [10]. Finally, E2 antibodies are found more frequently than viremia among healthy blood donors [9, 10, 12], suggesting prior exposure and viral clearance. On occasion, E2 antibodies are detected in GBV-C viremic subjects; however, in longitudinal studies E2 antibodies are temporally related to subsequent viral clearance [9, 10, 12]. Although E2 antibodies are a marker of prior infection, detection may be lost over time [13], and thus the presence of E2 antibodies presumably underestimates the prevalence of prior infection.

GBV-C infection is common and is distributed worldwide. Like HCV, it may establish persistent infection without clinical symptoms or disease in either immunocompromised or healthy individuals (reviewed in [5, 6]). In developed countries, 1–5% of healthy blood donors are viremic at the time of blood donation. The prevalence is higher in developing countries, with up to 20% of blood donors viremic in some studies (reviewed in [6, 8]). The

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US FDA does not recommend blood screening for GBV-C because it is not associated with any disease state. Based on the prevalence of GBV-C and the number of blood products transfused, approximately 1000 people receive GBV-C viremic blood products daily in the USA (reviewed in [14]). Similar to other lymphotropic viruses, GBV-C is transmitted sexually, vertically and by exposure to contaminated blood. Consequently, it is highly prevalent in populations with other sexually transmitted or bloodborne infections. For example, GBV-C viremia prevalence is approximately 20% among individuals with chronic HCV infection and 20–40% among HIV-positive individuals (reviewed in [6]).

Despite the prevalence of GBV-C infection in the general population and its beneficial effect among HIV-infected individuals, commercial diagnostic assays to detect GBV-C viremia or E2 antibodies are not currently available. Because GBV-C appears to slow HIV disease progression and may play a role in regulating T cell homeostasis *in vivo*, the development of assays to detect active or prior GBV-C infection are warranted.

GBV-C interactions with HIV

Clinical studies

Following the discovery of GBV-C, several studies found an association between GBV-C infection and prolonged survival of HIV-positive individuals, although a few studies failed to demonstrate this beneficial effect [5, 11, 15–21]. The studies that did not show an effect were cross-sectional, conducted during early HIV disease, or were conducted after widespread use of highly active and effective HIV therapy. Two large longitudinal studies found that persistence of GBV-C viremia was significantly associated with prolonged survival compared to those who were persistently negative for GBV-C RNA or who lost viremia [11, 22]. In addition, a meta-analysis found that in studies conducted ‘late’ (>5 years) into HIV infection (n=1294 subjects), GBV-C viremia was associated with about a 2.5-fold reduction in mortality (Relative Hazard for mortality 0.41; 95% confidence intervals 0.23; 0.69) [23]. GBV-C viremia is also associated with improved surrogate markers of HIV disease including higher $CD4^+$ T cell counts, lower HIV viral load, and delayed progression to AIDS in many studies [5, 15, 18, 20], however, the strongest effect has been in the most definitive clinical endpoint of mortality. GBV-C viremia is associated with improved response to antiretroviral therapy (ART) in HIV-infected individuals as measured by a greater reduction of HIV viral load, improved $CD4^+$ T cell count and less frequent changes of ART compared with those without GBV-C viremia [20, 24, 25]. GBV-C viremia is also associated with reduced mother-to-child transmission of HIV in pregnant women, particularly when the infant is infected with GBV-C during parturition [26, 27].

Although a protective effect of GBV-C infection in HIV-positive individuals has been observed in numerous studies, the mechanism by which GBV-C modulates HIV infection and AIDS progression is not fully understood. Several *in vivo* and *in vitro* studies suggest that GBV-C infection may both interfere directly with HIV replication, and affect host cell factors that support the HIV life cycle. The effects of GBV-C infection on T cells in HIV-positive individuals are summarized in Box 1.

GBV-C infection alters HIV entry receptors

The low surface expression of the two major HIV entry coreceptors (CCR5 and CXCR4) and high plasma level of the ligands for these receptors [MIP-1α (CCL3), MIP-1β (CCL4), RANTES (CCL5) and SDF-1 (CXCL12)] have been associated with slower HIV disease progression [28, 29]. In HIV-positive individuals, GBV-C viremia is associated with low surface expression of both CCR5 and CXCR4 [30, 31]. Confirming this clinical observation, *in vitro* GBV-C infection decreases CCR5 surface expression, induces CCR5 and CXCR4

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ligands and inhibits replication of both CXCR4 (X4) and CCR5 (R5) tropic HIV isolates in PBMCs [32].

GBV-C proteins inhibit HIV replication

Expression of the GBV-C E2 glycoprotein and the NS5A phosphoprotein in $CD4^+$ T cells inhibit HIV replication *in vitro* [33–36]. Based on single cycle replication studies, both viral proteins inhibit HIV at least in part at the HIV entry step. The GBV-C E2 protein directly inhibits HIV pseudovirus entry, and peptides derived from the E2 protein interfere with HIV cellular binding and fusion, independent of the viral effect on CD4 cell homeostasis [33, 34]. Synthetic peptides derived from GBV-C E1 protein also inhibit HIV entry, and appear to interact with HIV fusion peptides [37]. By contrast, NS5A protein expression downregulates CXCR4 surface expression and induces the release of the CXCR4 ligand (SDF-1) in $CD4^+$T cells [35, 36]. GBV-C NS5A protein also decreases CD4 surface expression via reduction in steady state CD4 mRNA levels [38]. Thus, downregulation of HIV entry receptors and secretion of ligands for chemokine receptors by GBV-C proteins contributes to HIV inhibition. The effects of GBV-C NS5A and E2 proteins on T cells that could contribute to the limitation of HIV replication are summarized in Figure 1.

As noted, GBV-C antibodies are usually not detected during viremia but antibodies against GBV-C E2 appear following viral clearance (reviewed in [5, 6]). Although GBV-C viremia is associated with the best survival in HIV-positive individuals, GBV-C E2 antibodies are also associated with improved survival in HIV-positive individuals without GBV-C viremia or E2 antibodies [11, 20]. GBV-C E2 antibodies were recently shown to immunoprecipitate HIV-1 particles and neutralize diverse X4- and R5-tropic HIV isolates [39], suggesting that the E2 protein may contain an immunogenic structural motif that cross-reacts with either a cellular or an HIV antigen present on HIV particles. The E2 antibodies bound to HIV-1 particles and interfered with HIV entry. A similar finding with HIV-1 envelope glycoprotein gp41 is well characterized. HIV-1 gp41 is involved in fusion of the viral membrane with the cellular membrane, and a peptide motif within HIV gp41 inhibits HIV replication at the fusion step. Human monoclonal antibodies that react with this peptide motif (e.g. 2F5) neutralize diverse HIV isolates *in vitro* [40].

GBV-C enhances innate immune responses

Innate immune responses including type I interferons (IFNs) play an important role in both controlling HIV infection and in activating other components of the immune system (reviewed in [41]). Loss of IFN-producing cells and low levels of IFN-α are associated with a high HIV viral load, and are thought to play an important role in HIV disease progression [42]. Plasmacytoid dendritic cells (pDCs) are major producers of IFN-α during viral infection and suppress HIV replication [43]. pDCs are frequently depleted during HIV infection and aberrant IFN-α production is thought to contribute to HIV pathogenesis [44–46]. The frequency of activated pDCs and both IFN-γ and RNA-dependent protein kinase R (PKR) mRNA levels were higher in GBV-C viremic individuals compared to non-viremic individuals, suggesting that GBV-C alters innate immunity [47]. GBV-C viral load correlated with the frequency of activated pDCs and IFN-γ expression, and GBV-C induced IFN-γ expression and activated pDC *in vitro* [47]. PBMCs from GBV-C viremic individuals also express higher levels of mRNA from IFN-related genes [2–5-oligoadenylate synthetase (OAS), myxovirus resistance 1 (MxA), IFN AR-1 and PKR] compared to PBMCs from HIV-mono-infected individuals [48]. Although the mechanism by which GBV-C enhances innate immune responses is unexplored, the increased frequency of activated pDCs and IFN expression during GBV-C infection may enhance the antiviral immune response to HIV infection.

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GBV-C polarizes cytokines towards a T helper 1 (Th1) profile

Immune responses mediated by Th1 cells are involved in HIV disease, and serum Th1 cytokine levels are typically decreased in individuals with chronic and progressive HIV infection whereas T helper 2 (Th2) cytokines are increased [49–51]. The cytokine disruption during HIV infection contributes to HIV and opportunistic pathogenesis (reviewed in [52]). Nunnari *et al.* found that GBV-C viremia was associated with stable serum Th1 cytokine levels (IL-2 and IL-12) compared to decreased IL-2 and IL-12 levels in HIV-mono-infected individuals in a longitudinal study of HIV-infected Sicilians [21]. Conversely, serum levels of Th2 cytokines (IL-4 and IL-10) increased in HIV-mono-infected people whereas IL-4 and IL-10 levels were low and did not increase in GBV-C coinfected individuals [21]. The high level of Th1 cytokines and low level of Th2 cytokines found with GBV-C coinfection suggest that GBV-C polarizes T cells toward a Th1 cytokine profile, which may in turn be beneficial to HIV-positive individuals.

Consistent with these clinical findings, Rydze *et al.* recently found that *in vitro* infection of PBMCs, and the expression of the GBV-C NS5A protein in a $CD4^+$ T cell line resulted in increased IL-2, IL-12b and IFN-γ mRNA expression, decreased IL-4 and IL-13 mRNA expression and decreased secretion of IL-10 [53]. These studies further suggest that GBV-C may promote Th1 differentiation and induce a Th1-specific cytokine milieu that is protective against HIV infection and that the NS5A protein contributes to this effect. Because many parasitic and allergic diseases are also influenced by Th1/Th2 cytokines, further studies on a potential role for GBV-C in the natural history of other diseases appears warranted.

GBV-C protects $CD4^+$ T cells from apoptosis

Fas-mediated apoptosis contributes to $CD4^+$ T cell depletion during HIV infection (reviewed in [54]). HIV-infected individuals have an increased frequency of Fas-expressing lymphocytes compared to uninfected individuals [55]. However, the frequency of Fas-expressing lymphocytes is significantly lower in people with GBV-C and HIV-coinfection compared to those with HIV-mono-infection [55]. Fas expression on T cells directly correlated with Fas-mediated apoptosis of T cells, thus suggesting that GBV-C may protect against CD4 T cell depletion during HIV infection.

HIV-induced $CD4^+$ T cell depletion may result from direct lysis or lysis by HIV-specific cytotoxic T cells. However, since most $CD4^+$ T cells do not contain HIV, CD4 depletion requires killing of bystander (uninfected) $CD4^+$ T cells [56, 57]. These bystanders are thought to be depleted through either pro-apoptotic HIV proteins released from the infected cells, or by activation-induced cell death (AICD) induced by persistent immune activation (reviewed in [58]). The Fas/FasL pathway has been suggested to play a major role during AICD of bystander cells [59, 60], and GBV-C may influence CD4 T cell depletion by its affects on Fas expression and Fas-mediated apoptosis.

GBV-C effect on lymphocyte activation

Immune dysfunction and chronic immune activation are the characteristic features of HIV infection and AIDS progression. The aberrant activation of T cells during HIV infection is associated with an increased expression of cellular activation markers, reduced $CD4^+$ T cell rise with antiretroviral therapy and lower $CD4^+$ T cells counts [61, 62]. Immune activation involves bystander T and B cells in addition to the HIV-infected $CD4^+$ cells, and contribute greatly to HIV disease progression by enhancing HIV replication, increasing AICD of bystander cells, and perturbing immune cell function [61, 63].

Recent studies provide insight into the effects of GBV-C on immune activation, which may also contribute to the beneficial association between GBV-C and HIV survival. GBV-C

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viremic HIV-infected subjects have lower surface expression of T cell activation markers (CD38, CD69, CD25 and CCR5) on $CD4^+$ and $CD8^+$ T cells than GBV-C negative subjects, independent of HIV viral load [30, 31, 64]. CD38 expression on $CD8^+$ T cells was inversely related to GBV-C viral load [64], further suggesting that GBV-C coinfection dampens T cell activation.

Because GBV-C replicates in primary T ($CD4^+$ and $CD8^+$) and B cells, GBV-C infection may directly lower the activation state in these cells leading to clinical benefit in HIV-infected individuals. However, based on activation marker expression on bulk $CD4^+$ and $CD8^+$ T cells, the effect of GBV-C on activation is not limited to actively infected cells. Although GBV-C replication is inefficient in primary PBMCs [65, 66], the lower expression of T cell activation markers in bulk $CD4^+$ and $CD8^+$ T cells from GBV-C viremic subjects suggests that the effect of GBV-C on immune activation must result from paracrine effects of GBV-C on bystander cells. Despite the low percentage of cells infected with GBV-C, viral loads may average more than 1×10^7 genome copies/ml plasma [20]. This level of viremia is not surprising when one considers that approximately 4.6×10^{11} lymphocytes are present in a young adult human [67]. If 1% of these cells produces only one copy of GBV-C per day, the daily production would be approximately 5×10^9. It is tempting to speculate that GBV-C infection induces cellular or viral soluble factors, which mediate this paracrine effect on bystander cells. Importantly, the effect of GBV-C on immune activation is incomplete because a more potent reduction in immune activation would result in immune deficiency.

Although understanding the cause of reduced immune activation during GBV-C coinfection requires further characterization, data identifying potential mechanisms by which GBV-C modulates T cell activation are emerging. T cell activation in response to foreign antigens is mediated by T cell receptor (TCR) signaling and IL-2 production (reviewed in [68]). IL-2 is a key cytokine that promotes T cell activation, proliferation and supports HIV replication (reviewed in [69]). GBV-C viremic subjects had significantly reduced response to IL-2 therapy compared to GBV-C non-viremic subjects [70] suggesting GBV-C infection may alter IL-2 signaling pathways and affect T cell activation. Consistent with this, Berzsenyi *et al.* found that intra-hepatic T cell signaling is impaired in GBV-C coinfected (HCV− and HIV−) positive individuals [71]. Liver samples from GBV-C coinfected HIV− and HCV− positive individuals had significantly lower expression of lymphocyte-specific protein tyrosine kinase (Lck) compared to GBV-C negative HIV- and HCV-positive individuals, however Lck expression in PBMCs did not differ in GBV-C status [71]. Lck plays a crucial role in proximal TCR signaling, thus downregulation of Lck expression during GBV-C coinfection could alter TCR signaling pathways. Together, these studies suggest that GBV-C might affect immune activation pathways resulting in reduced activation in coinfected HIV-positive individuals. Future studies on the effects of GBV-C on immune activation pathways are required to understand the mechanism by which GBV-C modulates immune activation.

GBV-C interferes with IL-2-induced $CD4^+$ T cell expansion

As noted, IL-2 (originally called ‘T cell growth factor’) is a key cytokine involved in growth, differentiation and survival of T cells (reviewed in [68]). Administration of recombinant IL-2 as adjunctive immunotherapy is efficacious in a subset of people with renal cell carcinoma and melanoma (reviewed in [72]), and because IL-2 therapy leads to $CD4^+$ T cell proliferation and expansion, IL-2 immunotherapy was extensively studied in HIV disease (reviewed in [69, 73]). Although IL-2 infusions significantly increased $CD4^+$ T cell counts in HIV-infected individuals, a large prospective randomized trial conducted during the era of highly active combination antiretroviral therapy found no clinical benefit [74]. In one study, GBV-C replication was diminished when PBMCs were cultured in IL-2 and PHA [7]. To examine the potential interaction between GBV-C and IL-2, study subjects

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participating in a prospective randomized trial of IL-2 were evaluated for GBV-C [70]. As in other studies, subjects randomized to receive intravenous (IV) IL-2 had significantly increased $CD4^+$ T cell counts compared to those who received either subcutaneous IL-2 or no IL-2 [70]. However, when stratified by GBV-C viremia status, subjects without GBV-C who received IV IL-2 had a significantly greater increase in CD4 counts compared to GBV-C viremic subjects (859 vs. 180 cell increase at week 60). $CD4^+$ T cells were no greater in GBV-C viremic subjects who received IV IL-2 compared to those who did not receive IV IL-2 [75], indicating a significant interaction between GBV-C and the IL-2 cytokine. Thus, these studies suggest that GBV-C may interfere with both proliferation and IL-2 signaling pathways contributing to HIV inhibition. Figure 2 summarizes GBV-C infection effects on T cells that can potentially limit HIV infection.

Concluding remarks

Like all viruses, GBV-C depends upon its human host for replication. To date, GBV-C has not been convincingly associated with any disease. However, it appears to be protective against HIV infection and may influence other diseases as well, suggesting a mutually beneficial symbiotic relationship, hence the intended pun of calling GBV-C the ‘good boy’ virus. Recent studies of GBV-C and its interaction with host cells provide new insights into the observed associations between GBV-C infection and improved survival in HIV-positive individuals. GBV-C infection leads to diminished immune activation and T cell proliferation that limits HIV replication and slows disease progression. Future studies are needed to further understand the mechanisms by which GBV-C alters immune activation and T cell proliferation pathways.

Although GBV-C infection is common and may persist for decades, most healthy individuals clear viremia within 2 years of infection (reviewed in [76, 77]). Although the mechanisms that control GBV-C persistence and clearance are not defined, it is unlikely owing to differences in viral sequences because full-length GBV-C genomes from different genotypes share more than 85% nucleotide and 94% amino acid sequence identity. Because no geographic differences in clearance rates are reported (reviewed in [6]), it is probable that, similar to HCV infection, host genetic factors are responsible for differences in viral persistence [75]. Because persistent GBV-C infection is important for the beneficial effect, understanding the mechanisms by which GBV-C persists in its host should provide insights into the protective effect of GBV-C.

Although data are beginning to provide insight into how GBV-C interacts with host cells and limits HIV infection, several underlying questions remain unanswered (Box 2). Ultimately, characterizing the molecular interactions between GBV-C and host cells may shed light on novel approaches to influence HIV disease progression or to circumvent HIV infection. In addition, given the numerous effects of GBV-C on lymphocyte homeostasis, investigation to determine if GBV-C infection influences the course of immunologically mediated diseases seems warranted.

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Box 1. Summary of the effects of GBV-C infection in HIV-positive individuals

- GBV-C infection downregulates HIV entry co-receptors CCR5 and CXCR4, and increases secretion of their ligands RANTES, MIP-1α, MIP-1β and SDF-1.
- *In vitro* GBV-C NS5A and E2 proteins inhibit X4- and R5-tropic HIV replication, and NS5A protein downregulates CD4 and CXCR4 gene expression.
- HIV-infected individuals positive for GBV-C E2 antibodies have survival benefit over HIV-infected individuals with neither GBV-C viremia nor E2 antibodies; *in vitro* GBV-C E2 antibodies immunoprecipitate HIV particles and inhibit X4- and R5-tropic HIV replication.
- GBV-C induces activation of interferon-related genes and pDCs.
- GBV-C promotes Th1 polarization and the NS5A protein contributes to this effect.
- GBV-C infection reduces surface expression of activation markers on T lymphocytes, suggesting its role in T cell activation signaling pathways.
- GBV-C protects the T cell from Fas-mediated apoptosis and as a result of its effect on immune activation may also play a role in protecting lymphocytes from activation-induced cell death.
- GBV-C viremia reduces IL-2-mediated T cell proliferation suggesting a significant interaction between GBV-C, IL-2 and IL-2 signaling pathways.

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Box 2. Outstanding questions

- What are the mechanisms by which GBV-C alters T cell activation and IL-2 signaling pathways?
- What factors are important for paracrine effects of GBV-C infection on T cell activation and proliferation?
- Does GBV-C block B cell activation and proliferation pathways?
- Does GBV-C affect cellular reservoirs of latent HIV?
- What factors influence GBV-C persistence in the host?

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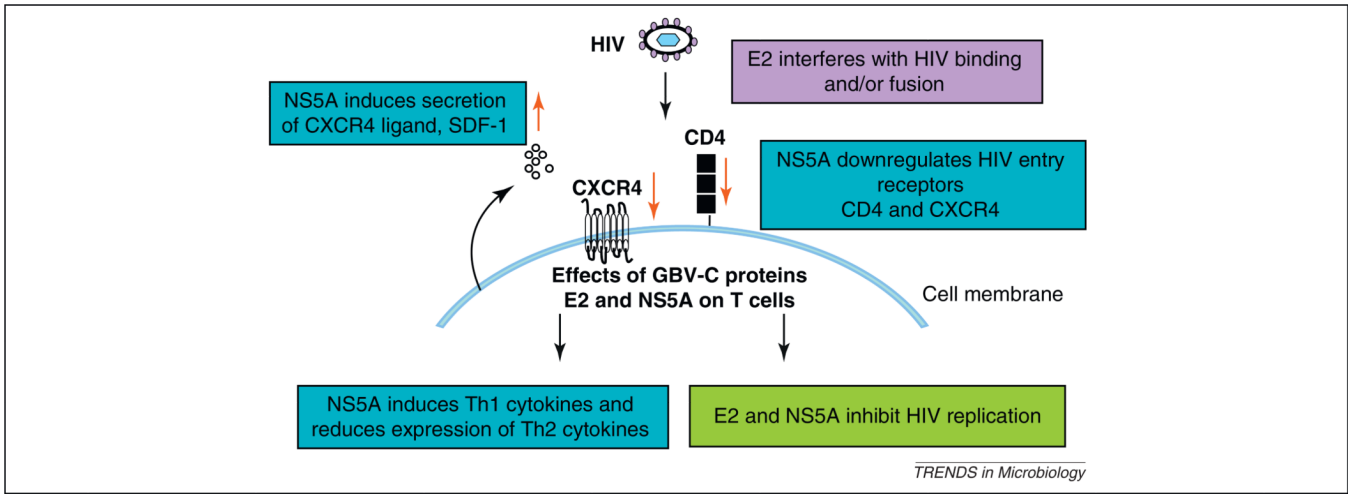

Figure 1.

In vitro effects of GB virus C (GBV-C) proteins E2 and NS5A on $CD4^+$ T cells. The E2 protein interferes with HIV cellular binding and/or fusion (purple box), whereas the NS5A protein downregulates CD4 and CXCR4 expression and induces SDF-1, the soluble ligand for CXCR4. NS5A protein also induces Th1 cytokines and blocks expression of Th2 cytokines (blue boxes). GBV-C E2 and NS5A proteins inhibit HIV replication (green box).

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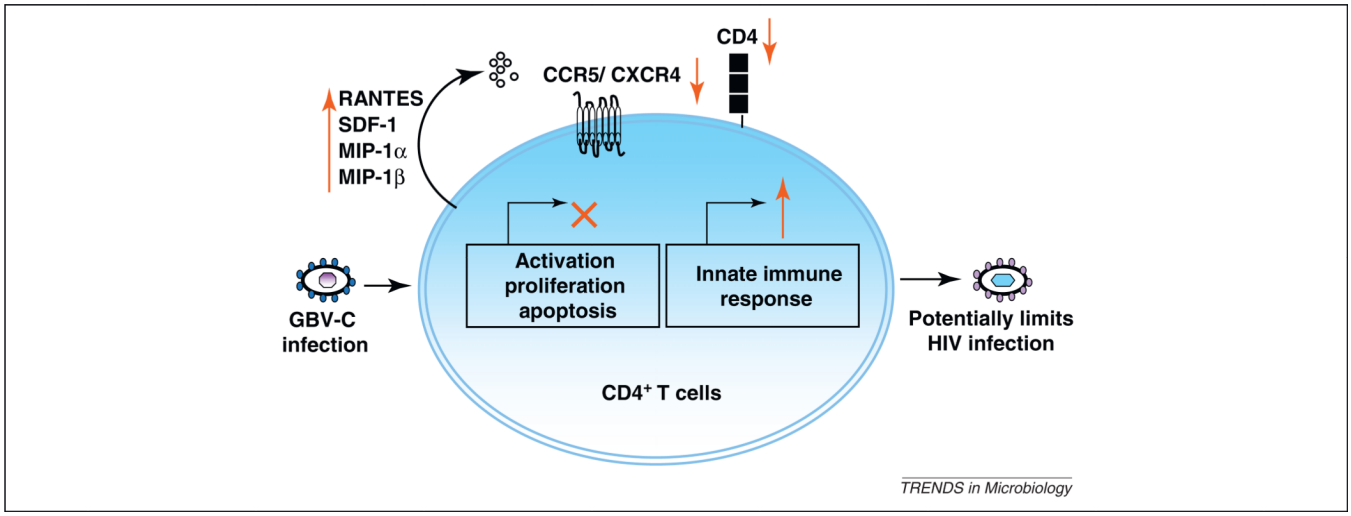

Figure 2.

In vivo effects of GB virus C (GBV-C) infection that can potentially interfere with HIV replication. GBV-C infection reduces CXCR4 and CCR5 surface expression and induces soluble ligands for CCR5 (RANTES, MIP-1α, and MIP-1β) and CXCR4 (SDF-1). GBV-C infection reduces activation, proliferation and apoptosis in T cells. GBV-C also enhances expression of interferons, activates plasmacytoid dendritic cells and promotes Th1 cytokines leading to an enhanced innate immune response. These effects can potentially limit HIV replication and slow disease progression.