

MINI-REVIEW

GB virus C as a potential vaccine against human immunodeficiency virus: A review

Youssef Mahmoud Kayed^{1*}, Sahar Abdel Raouf², and Wafaa Eltayeb³

¹Faculty of Pharmacy, Misr International University, El-Obour, Qalyubiyah, Egypt

²Department of Biochemistry, Faculty of Pharmacy, Misr International University, El-Obour, Qalyubiyah, Egypt

³Department of Microbiology, Faculty of Pharmacy, Misr International University, El-Obour, Qalyubiyah, Egypt

Abstract

Human immunodeficiency virus (HIV) is a pathogenic virus capable of entering the human body and replicating within T cells, ultimately leading to acquired immunodeficiency syndrome. In contrast, GB-virus C (GBV-C), a member of the *Flaviviridae* family, also infects humans but, according to current studies, is not associated with any known pathogenic effects. Unlike most RNA viruses, GBV-C encodes a single polyprotein. It is primarily transmitted through blood and sexual contact. GBV-C comprises three strains: GBV-C, hepatitis G virus (HGV), and other less-studied strains. The HGV strain has been detected in patients with liver cirrhosis; however, there is no evidence that it causes liver disease. Notably, GBV-C reduces immune activation in HIV-infected patients. It has been shown to have a significant effect on the target cell receptors for HIV, indicating its potential as a model for vaccine development against HIV. However, there is a lack of information and studies concerning this virus. GBV-C-based vaccine development faces many challenges, such as concerns about safety and efficacy, limited understanding of its mechanisms of action and immunogenicity, HIV strain variability, ethical and regulatory considerations, production and delivery logistics, long-term outcomes, and public perception and acceptance. Nevertheless, bioinformatic techniques can play a crucial role in overcoming these challenges through approaches such as comparative genomics, epitope mapping, structural bioinformatics, and vaccine design and optimization.

*Corresponding author:

Youssef Mahmoud Kayed
(youssef2308985@miuegypt.edu.eg)

Citation: Kayed YM, Raouf SA, Eltayeb W. GB virus C as a potential vaccine against human immunodeficiency virus: A review. *Microbes & Immunity*. 2026;3(4):025150032. doi: 10.36922/MI025150032

Received: April 10, 2025

1st revised: May 31, 2025

2nd revised: June 10, 2025

Accepted: June 16, 2025

Published online: July 25, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Keywords: GB virus-C; Hepatitis G virus; Human immunodeficiency virus; Acquired immunodeficiency syndrome; Bioinformatics

1. Introduction

Viruses consist of a protein coat that encloses their genetic components, which can either be RNA or DNA. They are incapable of replicating independently and must infect specific living host cells to replicate by exploiting the host's metabolic machinery. Human immunodeficiency virus (HIV) is a well-known virus that replicates in immune cells, especially T cells, causing acquired immunodeficiency syndrome.¹ At present, there is no specific vaccine for many viruses, including HIV, which remains a significant threat

to human health. In addition to replicating within immune cells, HIV progressively impairs their function, ultimately causing severe immunodeficiency.

Public perception often portrays viruses and microbes as harmful and contagious pathogens. However, viruses and microorganisms can also play beneficial roles, especially in bioprospecting applications. For example, bacteriophages are increasingly recognized for their potential to control antimicrobial-resistant bacteria.² Beneficial microorganisms are abundant in the human body, especially in the large intestines. It is estimated that for every human cell, there are ten microbial cells residing in the body. These microorganisms help humans in many ways, such as aiding digestion and producing vitamin K. These microorganisms are also essential in the synthesis of certain foods, such as bread and cheese.³ Similarly, viruses may play helpful roles, including in combating other viral infections. GB virus C (GBV-C) is a recently discovered virus that has no known pathogenic effects. While it might be considered latent, it is not. GBV-C is found in a high percentage of HIV-infected individuals, and some studies suggest that it may be beneficial against HIV.

However, significant challenges arise when considering its usage as a treatment or a vaccine for HIV. Between 1995 and 2005, there was considerable debate and focused research on GBV-C, but interest waned around 2012. Since then, no new studies have been published. Therefore, by outlining the difficulties in employing viruses as vaccines, this article aims to highlight the key findings surrounding GBV-C and its potential role in HIV research. The main goal of the current mini-review is to explicitly encourage the scientific community to renew and intensify research on GBV-C, particularly by examining how bioinformatics can be used to help overcome existing obstacles.

2. GB virus C

GB virus C is a non-pathogenic virus capable of entering the human body without causing any known harmful effects. It is phylogenetically related to the *Flaviviridae* family, particularly to the hepatitis C virus. *In vitro* studies have shown that GBV-C interferes with several biological mechanisms in ways that may facilitate the body's ability to combat HIV.⁴

2.1. History of discovery

In 1995, Abbott Laboratories identified a virus in a West African patient that showed no genomic similarities to known hepatitis viruses (A - E). Due to its genomic resemblance to previously discovered viruses GB virus A and B, it was named GB virus C. Concurrently, researchers at Genelabs Technologies uncovered a similar virus in

the plasma of a patient with chronic hepatitis. This virus, named hepatitis G virus (HGV), shared approximately 96% genetic homology with GBV-C.⁵

2.2. Epidemiology

GB virus C comprises a positive-sense single-stranded RNA that encodes a single polyprotein of approximately 3,000 amino acids. Its epidemiology remains an active topic of research. The current evidence indicates that antibodies against GBV-C typically emerge only after the viral RNA is no longer detected in the body. GBV-C has a high prevalence in the general population, present in about 1.7 – 2% of individuals, and in approximately 39% of HIV-infected persons.⁶ The presence of the virus has been reported in patients with liver cirrhosis and hepatocellular carcinoma, and in almost 20% of patients with hematological malignancies, in which the bone marrow cells were found to be infected with GBV-C. However, in patients with cirrhosis or hepatocellular carcinoma who undergo liver transplantation, no signs of GBV-C were observed.⁷ A study conducted in Denmark investigated the transmission routes of GBV-C and the associated risk factors. The study population included children between the ages of 9 and 15, blood donors, hospital employees, and prisoners who both injected and did not inject drugs. Testing was performed using methods: in-house real-time quantitative polymerase chain reaction for GBV-C RNA and enzyme-linked immunosorbent assay for anti-E2 antibodies. The GBV-C RNA was found in 1.4% of 901 children, 2.2% of 5,203 blood donors, 2.2% of 1,432 hospital employees, 12.5% of 407 non-injecting drug prisoners, and 34.9% of 407 drug-injecting prisoners. Among healthcare professionals, risk factors included blood exposure and sexual behavior, while in prisoners, injection drug use and high-risk sexual activity were strongly associated with GBV-C infection. In children, transmission was most likely due to birth in childhood, causing chronic infection. In adulthood, sexual transmission was identified as the predominant route.⁸

3. Evolution of GB virus C

The viral composition of this virus differs from most known RNA viruses, which typically lack proofreading enzymes to ensure fidelity during RNA genome replication. It is an enveloped positive-strand RNA with a genomic size of about 9.3 kilobases. The genome contains a large open reading frame that encodes a single polyprotein. The structural proteins, E1 and E2, and non-structural proteins, NS2, NS3, NS4, NS5A, and NS5B, are located at the N-terminal and C-terminal, respectively. A study conducted to trace the evolutionary history of this virus through several phylogenetic analyses confirmed its ancient

African evolutionary origin. By analyzing different isolates for the virus, closely related Southeast Asian strains were identified, showing a relationship to the African isolates.⁹

3.1. Different strains of GB virus C

Understanding the different strains of any virus will help identify its effect on the human body, including its impact on HIV. Like many viruses, GBV-C comprises multiple strains. In 1997, a group of scientists designed a study to characterize the different strains of GBV-C by constructing a phylogenetic analysis based on restriction fragment length polymorphism¹⁰. They analyzed the 5'-untranslated region sequences of 33 GBV-C (also known as HGV) that was obtained from different locations. These sequences were determined using reverse transcription polymerase chain reaction and dideoxy termination sequencing. The GBV-C isolates originated from West Africa, while the HGV isolates were obtained from patients in the United States. Phylogenetic trees were constructed based on all three accepted methods: unweighted pair group method with arithmetic mean, neighbor-joining, and the PHYLogeny Inference Package. All three strategies revealed a phylogenetic relationship among the isolates. The isolates were separated into three phylogenetic branches (or genotypes) of three strains: GBV-C, HGV, and an unknown strain that has not been reported before. The GBV-C type was identified in isolates from Africa and Saudi Arabia; HGV in isolates from the United States, Mongolia, and Japan; and the new strain in isolates from Korea and Israel. The three phylogenetic trees illustrated these relationships clearly. Within each strain, high sequence homology was observed: 87.4 – 98.4% for GBV-C, 88.0 – 98.9% for HGV, and 94 – 99.5% for the new type. In contrast, the homology between different types was lower: 70.9 – 84.1% between GBV-C and HGV, 83.1 – 91.3% between HGV and the new strain, and 79.1 – 89.0% between GBV-C and the new strain.¹⁰

3.1.1. HGV and liver disease

HGV can be considered another name for GBV-C but represents one of its strains, sharing 70.9 – 84.1% homology. Studies have demonstrated that HGV is a form of non-A-E hepatitis and does not produce any immune response. In 1999, a study was designed to investigate the effects of HGV, involving 50 non-alcoholic cirrhosis patients and 50 healthy blood donors as the control group.¹¹ Detection was performed using reverse transcription and nested polymerase chain reaction. HGV was detected in six (12%) of cirrhosis patients and in two (4%) of healthy blood donors. Among the six HGV-infected patients, two were co-infected with hepatitis B virus, one with hepatitis C virus, and the remaining three were not classified under

either B or C categories. No differences were observed between HGV-positive and HGV-negative individuals. Most studies have not found any clear association between liver disease and HGV infection. However, this does not rule out the possibility that HGV may be pathogenic or play a role in certain diseases that have not yet been identified.^{11,12}

4. GB virus C effect on immunity and its relationship with HIV

Several studies have proved the beneficial effect of GBV-C on HIV-infected individuals, both directly and indirectly. In 2009, a study compared patients co-infected with HIV and GBV-C to those infected with HIV only.¹³ The study showed that individuals with GBV-C had a lower percentage of T cells positive for CD38, CD4, CD8, and C-C chemokine receptor type 5 markers compared to those with HIV only. Furthermore, lower CD38 expression was observed on CD4⁺ and CD8⁺ T cells, and reduced C-C chemokine receptor type 5 expression was found on CD8⁺ T cells in the co-infected group. In addition, there was a total reduction in activation of CD4⁺ and CD8⁺ T cells.¹³ In 2012, a study showed that the expression of the Ki-67 proliferative marker coding protein was lower in individuals co-infected with GBV-C and HIV compared to patients with HIV only.¹⁴

Another study investigated that the effects of GBV-C envelope glycoprotein E2 on interleukin 2 receptor signaling and T cell receptor-mediated signaling. While GBV-C does not affect non-stimulated cells, it decreases activation in positive CD4⁺ and CD8⁺ T cells, thereby reducing immune activation without completely blocking it.¹⁵ In 2013, a study investigating HIV pathogenesis reported that HIV increases global immune activation by promoting microbial translocation, which exposes immune cells to endotoxin and cytokines.¹⁶ Another study proved that GBV-C reduces activation of natural killer cells and monocytes and observed a trend toward reduced B-cell activation. Hence, by decreasing HIV entry into cells, GBV-C contributes to global immune suppression in natural killer cells, monocytes, and B cells.¹⁷ Supporting these findings, a study in 2005 identified GBV-C replication in CD19⁺ B cells, suggesting that GBV-C is a pan-lymphotropic virus.¹⁸

5. Challenges in using GB virus C as a vaccine for HIV

There are several challenges in using any virus, including GBV-C, as a vaccine. Ethical and regulatory issues are significant hurdles; ensuring vaccine safety requires extensive trials across multiple populations before public

approval. Moreover, public acceptance of injecting a virus into their body is still a significant concern, as most people are afraid of viruses and microorganisms despite their potential therapeutic benefits. These challenges apply generally to any virus-based vaccine. Specific challenges related to GBV-C include the need to guarantee safety and efficiency before administration. Although no studies have demonstrated harmful effects of GBV-C, the limited number and age of available studies – most recent from 2012 – indicate that its safety profile is not fully established. Moreover, the mechanism of action for GBV-C against HIV is not fully understood and needs further investigation. Immunogenicity is another critical consideration; the virus must elicit a strong, HIV-specific immune response without causing generalized immune activation, which could lead to serious complications.

Furthermore, the extensive variability of HIV strains complicates vaccine design. HIV has two types: type 1 and type 2, with type 1 further divided into six strains and multiple clades.¹⁹ Thus, a GBV-C vaccine would need to protect the body against all these strains. Production, delivery, and logistical challenges also arise with vaccines containing viruses. Addressing these challenges requires comprehensive research, practical trials, and consideration of scientific and ethical issues.

6. Role of bioinformatics in addressing key challenges associated with virus-based vaccine development

Bioinformatics can play a critical role in developing a safe and effective HIV vaccine by leveraging genomic and proteomic data from various viruses, including GBV-C (a virulent disease intently associated with HIV), through multiple methods.²⁰

The first technique is comparative genomics. By evaluating the genomic sequences of GBV-C and HIV, conserved areas and variations may be identified. This evaluation facilitates information on how GBV-C would contribute to immune responses and which viral additives are conserved or differ between these viruses. Such insights guide the design of vaccine antigens that are much more likely to elicit the most significant immune reaction.²¹ Moreover, bioinformatic tools can examine the protein sequences of GBV-C and HIV to identify potential vaccine targets, including epitopes shared by both viruses. These targets can be used to design vaccines that induce cross-reactive immunity against HIV, leveraging the immune response elicited by GBV-C components.²²

The second technique is epitope mapping. Advanced bioinformatic techniques, such as peptide-major histocompatibility complex binding prediction algorithms,

can help identify epitopes likely to elicit robust immune reactions. These tools anticipate which components of the GBV-C and HIV proteins are more likely to be recognized by the immune system, aiding in the selection of optimal candidates for vaccine development.²¹ In addition, modeling molecular interactions between the immune system and viral proteins can offer insights into how an HIV vaccine might be designed to elicit protective immunity. This includes understanding how viral proteins interact with immune cells and predicting how vaccine-induced immunity could enhance these interactions.²³

The third technique is structural bioinformatics. Structural bioinformatics can provide information on the three-dimensional structures of GBV-C and HIV proteins, enabling the identification of conformational epitopes relevant for vaccine design. By mimicking these structural features, vaccines can be engineered to provoke more effective immune responses.²² Integrating data from genomic, proteomic, and clinical studies can offer a comprehensive view of how GBV-C and HIV interact with the host, facilitating the identification of patterns and correlations that support the design of safer and more effective vaccines. Moreover, bioinformatic methods may be used to predict how distinct vaccine candidates might perform based on historical data and simulations, including potential side effects, efficacy, and the probability of cross-reactivity with HIV.

The fourth technique is vaccine design and optimization. Using bioinformatics, artificial vaccines primarily based on GBV-C sequences can be designed and their efficacy tested *in silico* before moving to laboratory experiments. This method accelerates vaccine development by optimizing vaccine constructs and reducing time and costs.²⁴ By integrating these bioinformatic approaches, the refinement of HIV vaccines can be advanced, making them safer and more effective by leveraging insights gained from GBV-C research.

7. Conclusion

GB virus C is a pan-lymphotropic virus present in approximately 1.7 – 2% of the global population and in about 39% of HIV-infected individuals. It comprises three different strains: GBV-C, HGV, and other less-studied variants, each showing higher prevalence in specific geographic locations. The name HGV is misleading, as it is not related to hepatitis viruses. Phylogenetic analyses confirm an ancient evolutionary history, tracing a major migration route of the virus alongside ancient humans from Africa to Southeast Asia. GBV-C exerts significant effects on the immune system, notably counteracting HIV by reducing the global immune activation in HIV-infected

patients. While it does not cure HIV and no studies claim it treats the infection, GBV-C may prolong the survival of infected individuals. This potential benefit warrants further research into how this virus might be harnessed therapeutically.

Despite these promising aspects, GBV-C remains poorly studied, and its safety profile is not fully understood. Its envelope glycoprotein, E2, interferes with interleukin 2 signaling and T cell receptor-mediated signaling, reducing immune activation without complete suppression. This viral protein envelope can be explored as a candidate for HIV vaccine development or as a drug that enhances survival against it. However, significant challenges exist in using this virus as a basis for an HIV vaccine. Information on GBV-C is limited, with the most updated study dating back to 2013. Nevertheless, bioinformatic principles could be applied to address these challenges. Techniques such as comparative genomics, epitope mapping, structural bioinformatics, and vaccine design and optimization can provide critical insights. In conclusion, leveraging bioinformatics to address vaccine design obstacles related to GBV-C and HIV is essential. Further research applying these methods will be valuable for advancing safe and effective HIV vaccine strategies.

Acknowledgments

The authors would like to acknowledge Yousef Ahmed Ismail for his constant encouragement and insightful feedback, which significantly contributed to the refinement of the paper.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Yousef Mahmoud Kayed, Wafaa Eltayeb

Writing – original draft: Yousef Mahmoud Kayed

Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. U.S. Department of Health and Human Services. *The HIV Life Cycle*. National Institutes of Health; 2021. Available from: <https://hivinfo.nih.gov/understanding/hiv/fact/sheets/hiv-life-cycle> [Last accessed on 2025 Jan 20].
2. Rogovski P, Cadamuro RD, Da Silva R, *et al.* Uses of bacteriophages as bacterial control tools and environmental safety indicators. *Front Microbiol.* 2021;12:793135. doi: 10.3389/fmicb.2021.793135
3. Stark LA. Beneficial microorganisms: Countering microbephobia. *CBE Life Sci Educ.* 2010;9(4):387-389. doi: 10.1187/cbe.10-09-0119
4. George SL, Varmaz D. What you need to know about GB virus C. *Curr Gastroenterol Rep.* 2005;7(1):54-62. doi: 10.1007/s11894-005-0067-0
5. Bhattarai N, Stapleton JT. GB virus C: The good boy virus? *Trends Microbiol.* 2012;20(3):124-130. doi: 10.1016/j.tim.2012.01.004
6. Zhang W, Chaloner K, Tillmann H, Williams C, Stapleton J. Effect of early and late GB virus C viraemia on survival of HIV-infected individuals: A meta-analysis. *HIV Med.* 2006;7(3):173-180. doi: 10.1111/j.1468-1293.2006.00366.x
7. Mulrooney-Cousins PM, Michalak TI. Molecular testing in hepatitis virus related disease. In: *Diagnostic Molecular Pathology*. Netherlands: Elsevier; 2017. p. 63-73. doi: 10.1016/B978-0-12-800886-7.00006-6
8. Christensen PB, Fisker N, Mygind LH, *et al.* GB virus C epidemiology in Denmark: Different routes of transmission in children and low- and high-risk adults. *J Med Virol.* 2003;70(1):156-162. doi: 10.1002/jmv.10359
9. Pavesi A. Origin and evolution of GBV-C/Hepatitis G virus and relationships with ancient human migrations. *J Mol Evol.* 2001;53(2):104-113. doi: 10.1007/s002390010198
10. Mukaide M, Mizokami M, Orito E, *et al.* Three different GB virus C/hepatitis G virus genotypes. Phylogenetic analysis and a genotyping assay based on restriction fragment length polymorphism. *FEBS Lett.* 1997;407(1):51-58. doi: 10.1016/s0014-5793(97)00136-1
11. Jain A, Kar P, Gopalkrishna V, Gangwal P, Katiyar S, Das BC. Hepatitis G virus (HGV) infection & its pathogenic significance in patients of cirrhosis. *Indian J Med Res.* 1999;110:37-42.
12. Ramia S, Al Faleh FZ. Hepatitis G virus (HGV) and liver diseases. *Saudi J Gastroenterol.* 1999;5(2):50-55.

13. Maidana-Giret MT, Silva TM, Sauer MM, *et al.* GB virus type C infection modulates T-cell activation independently of HIV-1 viral load. *AIDS*. 2009;23(17):2277-2285.
doi: 10.1097/QAD.0b013e32832d7a11
14. Stapleton JT, Fong S, Muerhoff AS, Bukh J, Simmonds P. The GB viruses: A review and proposed classification of GBV-A, GBV-C (HGV), and GBV-D in genus Pegivirus. *J Gen Virol*. 2011;92(Pt 2):233-246.
doi: 10.1099/vir.0.026989-0
15. Bhattarai N, McLinden JH, Xiang J, Kaufman TM, Stapleton JT. GB virus C envelope protein E2 inhibits TCR-induced IL-2 production and alters IL-2-signaling pathways. *J Immunol*. 2012;189(5):2211-2216.
doi: 10.4049/jimmunol.1201324
16. Klatt NR, Funderburg NT, Brenchley JM. Microbial translocation, immune activation, and HIV disease. *Trends Microbiol*. 2013;21(1):6-13.
doi: 10.1016/j.tim.2012.09.001
17. Stapleton JT, Martinson JA, Klinzman D, Xiang J, Desai SN, Landay A. GB virus C infection and B-cell, natural killer cell, and monocyte activation markers in HIV-infected individuals. *AIDS*. 2013;27(11):1829-1832.
doi: 10.1097/QAD.0b013e328363089f
18. George SL, Varmaz D, Stapleton JT. GB virus C replicates in primary T and B lymphocytes. *J Infect Dis*. 2006;193(3):451-454.
doi: 10.1086/499435
19. Verma A, Singh U, Mallick P, Dwivedi P, Singh A. NeuroAIDS and omics of HIVvpr. *J Med Microbiol Immunol Res*. 2012;1:477-512.
20. Mount DW. *Bioinformatics: Sequence and Genome Analysis*. United States: Cold Spring Harbor Laboratory Press; 2006.
21. Setubal JC, Stadler PF, Stoye J. *Comparative Genomics: Methods and Protocols*. Totowa: Humana Press; 2024.
22. Martini S, Nielsen M, Peters B, Sette A. The immune epitope database and analysis resource program 2003-2018: Reflections and outlook. *Immunogenetics*. 2019;72(1-2): 57-76.
doi: 10.1007/s00251-019-01137-6
23. Mohan CG. *Structural Bioinformatics: Applications in Preclinical Drug Discovery Process*. Berlin: Springer; 2019.
24. Thomas S. Vaccine design. In: *Vaccines for Human Diseases: Methods and Protocols*. Vol. 1. Totowa: Humana Press; 2022.