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Torque Teno Virus, the Still Elusive Human Pathogens: A Review

Manar Fawzi Al-Taee[1], Enas Yaseen Shehab[2], Anmar A. Altaie[3]*
1,3*Department of Biology, Science College, University of Mosul, Mosul, Iraq
2Department of Dental Basic Sciences, Dentistry College, University of Mosul, Mosul, Iraq
E-mail: 1 manar_fawzi@uomosul.edu.iq , 2 enasbarhawe76@uomosul.edu.iq,
3* anmaraltaee1978@uomosul.edu.iq
Orcid: 0009-0000-8332-0066, 0000-0003-3154-1005, 0000-0003-4893-8164

Abstract :

One of the "orphan" viruses, Torque Teno Virus (TTV), is prevalent and is found worldwide, as well as one of the 45% of commensal viruses. The TTV virus has been the subject of numerous studies by researchers as a result of its prevalence among people of all ages (young children, adults, and the elderly) and in various health conditions, as studies have proven its presence in healthy individuals who do not exhibit any clinical symptoms, as well as in those who suffer from several different diseases. TTV is one of the very small viruses that belong to the Anellovirus genus known to infect humans. Although studies have proven the association between the virus's existence and many diseases, including respiratory diseases, autoimmune diseases, cancer, and others, The virus's lifetime within the human body and its relevance to disease causation remain contentious to this day. It has historically been related to liver diseases, particularly following blood transfusions, where damage to the liver's cells and tissues has been noted, indicating the virus's multiplication in it. It has been regarded as both a sign of graft failure and a biomarker of immunocompetence in organ transplant recipients. Intracranial aneurysm (IA) patients have also been linked to its presence in the artery walls. We summarize in this article the most significant findings from studies on the link of TTV to the liver, organ transplantation, and vascular diseases.

Keywords: Intracranial aneurysms; Liver; Pathogenesis; Organ transplant; Torque Teno Virus.

فيروس تورك تينو، مسببات الأمراض البشرية التي لا تزال بعيدة المنال: مقالة

منار فوزي الطائي[1] ، إيناس ياسين شهاب [2] ، أنمار أحمد الطائي[3*]
1،3* قسم علوم الحياة، كلية العلوم، جامعة الموصل، الموصل، العراق
2 قسم علوم طب الأسنان الأساسية، كلية طب الأسنان، جامعة الموصل، الموصل، العراق

مستخلص:

يعد فيروس تورك تينو (TTV) أحد الفيروسات «اليتيمة» المنتشرة والمتواجدة في جميع أنحاء العالم، كما أنه يعد من بين ٪45 من الفيروسات المتعايشة. وقد كان فيروس تورك تينو موضوعًا للعديد من الدراسات التي أجراها الباحثون نتيجة لانتشاره بين الأشخاص من جميع الأعمار (الأطفال الصغار، البالغين، وكبار السن) وفي ظروف صحية مختلفة، حيث أثبتت الدراسات وجوده لدى الأفراد الأصحاء الذين لا تظهر عليهم أي أعراض سريرية، وكذلك لدى الاشخاص الذين يعانون من العديد من الامراض المختلفة. يعد TTV أحد الفيروسات الصغيرة جدًا التي تنتمي إلى جنس Anellovirus المعروف بإصابته للبشر. وعلى الرغم من أن الدراسات أثبتت الارتباط بين وجود الفيروس والعديد من الأمراض، بما في ذلك أمراض الجهاز التنفسي وأمراض المناعة الذاتية والسرطان وغيرها، إلا أن حياة الفيروس داخل جسم الإنسان وأهميته في التسبب في المرض لا يزال مثيرًا للجدل حتى يومنا هذا. وقد ارتبط تاريخيًا بأمراض الكبد، وخاصة بعد عمليات نقل الدم، حيث لوحظ تلف لخلايا وأنسجة الكبد، مما يشير إلى تكاثر الفيروس فيه. وقد تم اعتباره علامة على فشل الطعم وعلامة حيوية على كفاءة المناعة لدى متلقي زراعة الأعضاء. كما تم ربط المرضى الذين يعانون من تمدد الأوعية الدموية داخل الجمجمة بتواجد الفيروس في جدران الشرايين. نلخص في هذه المقالة أهم النتائج المستخلصة من الدراسات حول ارتباط TTV بأمراض الكبد، زراعة الأعضاء، وكذلك امراض الأوعية الدموية.

الكلمات المفتاحية: فيروس تورك تينو؛ الامراضية؛ الكبد؛ تمدد الأوعية الدموية داخل الجمجمة؛ زراعة الأعضاء.

Introduction

In Japan, more than twenty years ago, after an elderly man had received blood during heart surgery, the TTV was isolated from the serum of this man who had hepatitis by Nishizawa et al. [1]. The original name of the virus (TT) was based on the initials of the name of the patient from whom the sample was collected; the acronym torque teno virus is the result of the Latin terms "torque," meaning necklace, and "tenuis," meaning narrow, referring to the circular structure of the virus's genome[1,2].

TTV is a diminutive, non-enveloped virus that is pathogenic, characterized by its single-stranded, circular, negative-sense DNA molecules. The whole genome is roughly 3.8 kb in length and is divided into coding and non-coding regions (approximately 2.6 kb and 1.2 kb in length) [3,4,5] Figure (1). TTV was initially considered a member of the Parvoviridae family [6,7] Table (1).

Due to its great genetic diversity, generally believed to be the result of replication, the family Anelloviridae is large and diverse, with 155 species and 30 genera. Take advantage of the latest ICTV virus classification updates [2,4,8]. Three of these genera have been documented to infect humans: Alpha, Beta, and Gammatorquevirus, also known as Torque teno virus (TTV), Torque teno mini virus (TTMV), and Torque teno midi virus (TTMDV), respectively [2,5,8].

It is known that viruses from the Anelloviridae family may infect both birds and mammals. Additionally, they have been isolated from a wide variety of animal species, including cats, pigs, dogs, bats, cattle, sheep, camels, horses, pigeons, etc[9,10]. In addition, the global prevalence of TTV varies greatly according to geography, health, social, and economic conditions; for example, the prevalence in Iran is 4% and in Jordan, it is 96% [11,12,13].

According to studies, TTV can be found in natural killer cells, granulocytes, monocytes, T and B lymphocytes, and other polymorphonuclear cells[14,15,16]. Furthermore, it has been isolated from a wide range of medical samples, including blood, tears, saliva, secretions, urine, milk, semen, gums, liver, bile, and brain[17,18]. Thus, the illness can spread by a variety of routes, including the respiratory sys-

tem, the fecal-oral route, intercourse, placenta, blood transfusion, and feeding[19,20].

The study of TTV led to a major change in the view of its role in the development of human diseases. Furthermore, serum TTV DNA levels have recently been suggested to be an endogenous marker of the immune system in organ transplant patients [15].

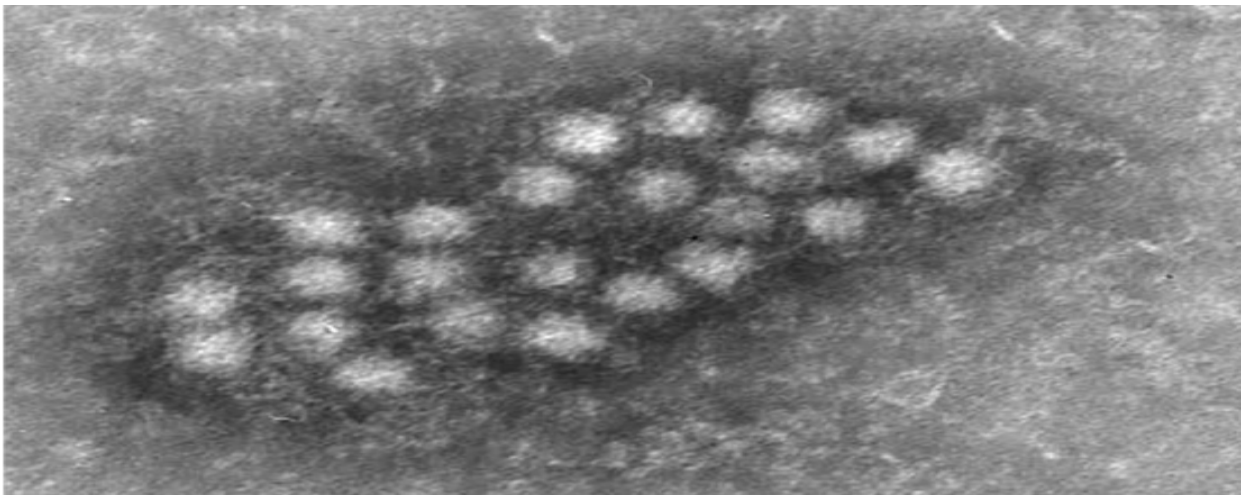

Figure (1): TTV's appearance under an electron microscope [3].

Table (1): Anelloviridae family [7].

Species	Genus	Host
Torque teno virus	*Alphatorquevirus*	Human, chimpanzee
Torque teno mini virus	*Betatorquevirus*	Human, non-human primate
Torque teno tupia virus	*Deltatorquevirus*	Tupaias
Torque teno tamarin virus	*Epsilontorquevirus*	Tamarin
Torque teno felis virus	*Etatorquevirus*	Cat
Torque teno midi virus	*Gammatorquevirus*	Human, chimpanzee
Chicken anemia virus	*Gyrovirus*	Chicken
Torque teno sus virus 1	*Iotatorquevirus*	Swine
Torque teno sus virus k2	*Kappatorquevirus*	Swine
Torque teno zalophus virus 1	*Lambdatorquevirus*	Sea lion
Torque teno canis virus	*Thetatorquevirus*	Dog
Torque teno douroucouli virus	*Zetatorquevirus*	Douroucouli

Torque Teno Virus: Host Relationship and Pathogenesis

Scientists from all around the world have been researching TTV for the last 20 years. This illness can persist in the human body for extended periods without exhibiting any symptoms and is thought to be non-contagious. According to studies, this virus can affect healthy persons as well as those with liver disease [15, 21]. Also, this virus causes lifelong viremia. Consequently, this disease may impact multiple organs, such as the spleen, liver, lungs, bone marrow, and other lymphoid organs. Despite not being regarded as a direct illness, research has indicated that TTV contributes to many illnesses, such as cancer, AIDS, liver, renal, respiratory, and autoimmune disorders. More research is needed on these relationships to investigate the effects of the virus on the host and how it causes disease.

The factors that enable the virus to remain in the human body for the whole of a person's life are yet unclear, but they have to do with genetic variations and the immunological illness that develops when the virus eludes the immune system. The host cell's transcripts, including a cofactor known as N-myc-interactor, have been suggested to be targeted by the DNA contained in the TTV genome. This is thought to suppress interferon signaling and hence degrade the host response. TTV viremia appears to be inversely associated with T lymphocyte percentage, making it a possible indicator of immunocompetence in humans, also can alter the host cell's metabolism via proteases. This virus may interfere with antigen processing and presentation and express novel epitopes that would act as autoimmune triggers after infecting immune system cells, including T cells and macrophages. Additionally, as a cytomegalovirus, it might interfere with the MHC class I molecule expression [22,23].

Identifying the target organ has been the subject of several investigations since the discovery of TTV. Viral nucleic acids have been found in samples of plasma, serum, saliva, secretions, nasopharyngeal, kidneys, spleen, lung tissue, the central nervous system, gastric and intestinal mucosa, umbilical cord blood, semen, and breast milk, notwithstanding early findings that the

virus may be able to multiply in liver cells. It is now essential to determine whether reproduction takes place in each of these organs [24,25].

Torque Teno Virus and Liver Diseases

Viral hepatitis is caused by some viruses, which is a significant cause of morbidity and mortality worldwide, especially in tropical regions. The World Health Organization reported 1.34 million fatalities from viral hepatitis, which is greater than the number of deaths from HIV infection in 2015[26,27].

TTV was first detected in a patient in Japan who had hepatitis, which led to the belief that hepatitis is the most common disease linked with TTV infection [1]. Early studies of this virus related to liver disease have revealed substantially lower prevalence rates than recent studies, which researchers have attributed to the use of inappropriate primers in PCR [15].

It is not yet known whether TTV plays a supporting or direct causal role in liver disease, but it has been proposed as a potential diagnostic marker for liver disease, especially in individuals with chronic hepatitis (HBV and HCV), hepatocellular carcinoma, and more advanced cirrhosis . A Lack of information about the discovery of the viral agent that causes10%-20% of patients with acute hepatitis, 5%-10% of patients with chronic hepatitis, and about 50% of instances of fulminant hepatitis contributed to the necessity of study and detection of this virus [15,28].

Although the virus's high population prevalence may suggest that it belongs to the human virome and that its presence in the body is not harmful, in the event of unfavorable conditions, it contributes to the disease by harming susceptible cells, such as hepatocytes and bile duct epithelium. Others claim that it is the sole viral indicator in liver disease instances where bile duct epithelial destruction and morphological alterations in liver tissue have been observed [15].

Tokita *et al*. [29] found that individuals with nonalcoholic steatohepatitis in the TTV-positive group had focal necrosis and fibrosis surrounding cells and veins in liver tissue, whereas the negative group did not exhibit these symptoms. The complications caused by this virus may be associated with a

weakened immune system in some individuals, indicating that its effect may vary in different population groups. The mechanisms by which TTV may contribute, if any, to the development of liver disease or hepatocellular carcinoma are not completely understood. Some hypotheses include modulation of the immune system, possible indirect impacts on liver function, or interactions with various other viruses [30].

Future studies must aim to evaluate the potential hepatic orientation of the virus and study the exact role it plays in the development of obscure liver diseases, in addition to investigating co-infection with recognized hepatitis viruses. In summary, the significance of TTV concerning cirrhosis, alcohol-related liver disease, fulminant hepatitis, transfusion-associated hepatitis, chronic non-alcoholic liver disease, and hepatocellular cancer requires further investigation and it is essential for those who have concerns about the virus and its potential effects on liver health to speak with healthcare professionals for the most up-to-date information and advice to their condition.

Torque Teno Virus and Intracranial Aneurysms

Abnormal dilatations of the cerebral arteries that have the potential to burst and cause a dangerous subarachnoid hemorrhage are known as intracranial aneurysms, the facts concerning aneurysm expansion and rupture are still unclear and insufficiently understood. Although arterial hypertension, smoking, alcohol, age, and heredity are risk factors for aneurysm formation, studies have found a link between aneurysm formation and inflammation[31, 32]. Recently, Rabello *et al*., [18] who conducted an unprecedented study concerning the detection of TTV in the IA, hypothesized that the disease's mechanism is the virus's deposition in cerebral blood vessels after entering the body and migrating into the bloodstream, resulting in chronic inflammation. This inflammation, in turn, triggers an immunological response that includes the infiltration of white blood cells and T cells, complement activation, and the production of interleukins, as a result of which the blood artery wall is altered, leading to expansion and rupture. Rabello investigated the presence of TTV in intracranial blood vessel walls using

PCR. Their results found the presence of TTV in 15 (42.9%) of 35 specimens, of which 10 (45.4%) were isolated from ruptured vessels and 5 (38.4%) from unruptured vessels, although the virus was more present in the ruptured aneurysm, this difference was not statistically significant. The researcher suggested that this may be due to the small size of the study sample, as he considered it an exploratory study. He considered that the presence of the virus may be another risk factor that would cause the blood vessels to rupture and deteriorate. Therefore, to fully understand the links between viral infection, inflammation, angiogenesis, rupture, and degeneration, more extensive research is needed.

Torque Teno Virus and Solid Organ Transplant

A therapeutic option for end-stage organ failure is solid organ transplantation, which includes the kidney, liver, pancreas, heart, and lungs. A donor's healthy organ is surgically removed and transplanted into a recipient whose organ has failed or been damaged. It frequently provides the recipient with a second, joyous opportunity in life and saves their life. However, organ transplantation is a major surgery with risks and drawbacks, including the possibility that the transplanted organ would be rejected by the body's immune system [33,34].

Organ transplant rejection is associated with a person's high immunity, so the person is subjected to immunosuppressive drugs before the transplant to ensure the survival of the graft. Research has revealed that after transplantation, the number of viral copies rises in immunocompromised individuals and their TTV load is high[35,36,37]. TTV's potential as a biomarker of immunosuppression and graft rejection risk is especially encouraging because antiviral medications and prophylactics currently used for organ transplant patients do not affect this virus prevalence or quantity of copies [4] and studies have been conducted to evaluate the benefit of TTV-guided immunosuppression enhancement in kidney transplant recipients [38]. A population study of healthy individuals has shown that virus load is age-related, being highest in the elderly, and this appears to be related to the immune system's normal aging process [39,40].

Regarding the diversity of TTV in kidney transplant recipients, a recent study by Reyes *et al*., [41]. Detected 15 TTV types in 30 plasma samples using real-time PCR assay, RCA-NGS, and ORF1 evolutionary analysis. Variation was identified in three patients with two consecutive samples (pre- and post-transplant). TTV3 and TTV13 were the most common types in pre-transplant samples (75% each), whereas TTV3 was the most common in post-transplant samples (56%). Another study showed significant variation in TTV types when comparing pre- and post-transplant samples [42]. The above researchers attributed this variation and high virus diversity to several factors such as recipient age, blood transfusions, higher exposure to virus infection throughout dialysis, early commencement of immunosuppressive medication, as well as viral evasion mechanisms.

From a TTV perspective, individuals who receive transplants of kidneys are the most researched group, they comprise the majority of all transplant patients. It was demonstrated that patients who had not yet developed a cellular or antibody-based rejection mechanism had a higher rate of this virus replication [39,43]. Other research has demonstrated that the administration of immunosuppressant drugs to these patients is associated with a higher load of virus [44]. For patients who have a liver or lung transplant, studies have demonstrated that the virus exhibits the same behavior pattern as patients who have a kidney transplant [45]. Current investigations and studies seek to include this virus as a significant component of the puzzle that attempts to explain the interactions between the virus and the host regarding immune responses. It's very hoped that TTV could be employed as a biomarker to assess the status of immunity alongside the administration of immunosuppressive drugs to patients in transplant situations that would reduce the likelihood of rejection and allow life to continue for these patients.

Conclusions

Briefly, TTV is a widely dispersed virus, and understanding its precise role in human health and disease is critical for accurate patient diagnosis. Therefore, we hope that future studies will highlight the relationship between

TTV and the host and confirm its role in disease pathogenesis (cofactor or pathogen).

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Conflict of Interest

No conflicts of interest exist.

References

1. T. Nishizawa, H. Okamoto, K. Konishi, H. Yoshizawa, Y. Miyakawa, and M. Mayumi, "A novel DNA virus (TTV) associated with elevated transaminase levels in posttransfusion hepatitis of unknown etiology," *Biochem. Biophys. Res. Commun.*, vol. 241, no. 1, pp. 92-97, Dec. 1997. https://doi.org/10.1006/bbrc.1997.7765.
2. A. Varsani, T. Opriessnig, V. Celer, F. Maggi, H. Okamoto, A.L. Blomström, D. Cadar, B. Harrach, P. Biagini, and S. Kraberger, "Taxonomic update for mammalian anelloviruses (family Anelloviridae)," *Arch. Virol.*, vol. 166, no. 10, pp. 2943-2953, Oct. 2021. https://doi.org/10.1007/s00705-021-05192-x.
3. Y. Itoh, M. Takahashi, M. Fukuda, T. Shibayama, T. Ishikawa, F. Tsuda, T. Tanaka, T. Nishizawa, and H. Okamoto, "Visualization of TT virus particles recovered from the sera and feces of infected humans," *Biochem. Biophys. Res. Commun.*, vol. 279, no. 2, pp. 718-724, Dec. 2000. https://doi.org/10.1006/bbrc.2000.4013.
4. D. Focosi, G. Antonelli, M. Pistello, and F. Maggi, "Torquetenovirus: the human virome from bench to bedside," *Clin. Microbiol. Infect.*, vol. 22, no. 7, pp. 589-593, Jul. 2016. https://doi.org/10.1016/j.cmi.2016.04.007.
5. E.M. Adriaenssens, M.B. Sullivan, P. Knezevic, L.J. van Zyl, B.L. Sarkar, B.E. Dutilh, P. Alfenas-Zerbini, M. Łobocka, Y. Tong, J.R. Brister, and A.I. Moreno Switt, "Taxonomy of prokaryotic viruses: 2018-2019 update from the ICTV Bacterial and Archaeal Viruses Subcommittee," *Arch. Virol.*, vol. 165, no. 5, pp. 1253-1260, May 2020. https://doi.org/10.1007/s00705-020-04577-8.

6. A. Kuczaj, P. Przybyłowski, and T. Hrapkowicz, "Torque Teno Virus (TTV)—A potential marker of immunocompetence in solid organ recipients," *Viruses*, vol. 16, no. 1, p. 17, Jan. 2023. https://doi.org/10.3390/v16010017.
7. E.J. Lefkowitz, D.M. Dempsey, R.C. Hendrickson, R.J. Orton, S.G. Siddell, and D.B. Smith, "Virus taxonomy: the database of the International Committee on Taxonomy of Viruses (ICTV)," *Nucleic Acids Res.*, vol. 46, no. D1, pp. D708-D717, Jan. 2018. https://doi.org/10.1093/nar/gkx932.
8. A. Varsani, S. Kraberger, T. Opriessnig, F. Maggi, V. Celer, H. Okamoto, and P. Biagini, "Anelloviridae taxonomy update 2023," *Arch. Virol.*, vol. 168, no. 11, p. 277, Nov. 2023. https://doi.org/10.1007/s00705-023-05903-6.
9. W.M. de Souza, M.J. Fumagalli, J. de Araujo, G. Sabino-Santos Jr, F.G. Maia, M.F. Romeiro, S. Modha, M.S. Nardi, L.H. Queiroz, E.L. Durigon, and M.R. Nunes, "Discovery of novel anelloviruses in small mammals expands the host range and diversity of the Anelloviridae," *Virology*, vol. 514, pp. 9-17, Jan. 15, 2018. https://doi.org/10.1016/j.virol.2017.11.001.
10. C. A. Arze, S. Springer, G. Dudas, S. Patel, A. Bhattacharyya, H. Swaminathan, C. Brugnara, S. Delagrave, T. Ong, A. Kahvejian, and Y. Echelard, "Global genome analysis reveals a vast and dynamic anellovirus landscape within the human virome," *Cell Host & Microbe*, vol. 29, no. 8, pp. 1305–1315, Aug. 2021. https://doi.org/10.1016/j.chom.2021.07.001.
11. Görzer, P. Jaksch, M. Kundi, T. Seitz, W. Klepetko, and E. Puchhammer-Stöckl, "Pre-transplant plasma Torque Teno virus load and increase dynamics after lung transplantation," *PloS One*, vol. 10, no. 4, p. e0122975, Apr. 2015. https://doi.org/10.1371/journal.pone.0122975.
12. E. J. Gore, L. Gard, H. G. Niesters, and C. C. Van Leer Buter, "Understanding torquetenovirus (TTV) as an immune marker," *Frontiers in Medicine*, vol. 10, p. 1168400, Jun. 2023. https://doi.org/10.3389/fmed.2023.1168400.
13. R. Rotundo, F. Maggi, M. Nieri, L.

Muzzi, M. Bendinelli, and G. P. Prato, "TT virus infection of periodontal tissues: a controlled clinical and laboratory pilot study," *Journal of Periodontology*, vol. 75, no. 9, pp. 1216–1220, Sep. 2004. https://doi.org/10.1902/jop.2004.75.9.1216.

14. T. Yu, S. Pan, Y. Zhang, J. Pei, J. Liu, Y. Xie, and X. Feng, "Occurrence and quantification of Anelloviruses and Herpesviruses in gingival tissue in Chinese Shanghai sub-population," *BMC Oral Health*, vol. 20, no. 1, pp. 1–9, Dec. 2020. https://doi.org/10.1186/s12903-020-01188-2.
15. V. I. Reshetnyak, I. V. Maev, A. I. Burmistrov, I. A. Chekmazov, and T. I. Karlovich, "Torque teno virus in liver diseases: On the way towards unity of view," World Journal of Gastroenterology, vol. 26, no. 15, p. 1691, Apr. 2020. https://doi.org/10.3748/wjg.v26.i15.1691.
16. E. Albert, E. Giménez, R. Hernani, J. L. Piñana, C. Solano, and D. Navarro, "Torque Teno Virus DNA load in blood as an immune status biomarker in adult hematological patients: The state of the art and future prospects," *Viruses*, vol. 16, no. 3, p. 459, Mar. 2024. https://doi.org/10.3390/v16030459.
17. K. J. Olival, P. R. Hosseini, C. Zambrana-Torrelio, N. Ross, T. L. Bogich, and P. Daszak, "Host and viral traits predict zoonotic spillover from mammals," *Nature*, vol. 546, no. 7660, pp. 646–650, Jun. 2017. https://doi.org/10.1038/nature22975.
18. N. N. Rabelo, M. H. Yoshikawa, J. P. Telles, G. Coelho, C. S. de Souza, N. P. de Oliveira, T. R. Mendoza, P. H. Braz-Silva, A. L. Boechat, M. J. Teixeira, and E. G. Figueiredo, "Torque Teno virus DNA is found in the intracranial aneurysm wall—Is there a causative role?" *Frontiers in Medicine*, vol. 10, p. 1047310, Jan. 2023. https://doi.org/10.3389/fmed.2023.1047310.
19. O. Rezahosseini, C. H. Drabe, S. S. Sørensen, A. Rasmussen, M. Perch, S. R. Ostrowski, and S. D. Nielsen, "Torque-Teno virus viral load as a potential endogenous marker of immune function in solid organ transplantation," Transplantation Reviews, vol. 33, no. 3, pp. 137-144, Jul. 2019. https://doi.org/10.1016/j.trre.2019.03.004.

20. N. Redondo, D. Navarro, J. M. Aguado, and M. Fernández-Ruiz, "Viruses, friends, and foes: The case of Torque Teno Virus and the net state of immunosuppression," *Transplant Infectious Disease*, vol. 24, no. 2, p. e13778, Apr. 2022. https://doi.org/10.1111/tid.13778.
21. S. Hino and H. Miyata, "Torque teno virus (TTV): current status," Reviews in Medical Virology, vol. 17, no. 1, pp. 45-57, Jan. 2007. https://doi.org/10.1002/rmv.524.
22. F. de Luca A.C., G.B. Marinho, J.B. Franco, J.D. Tenório, N.S. Andrade, A.M. Batista, A.C. Mamana, T.R. Tozetto-Mendoza, M. Pérez Sayáns, P.H. Braz-Silva, and K.L. Ortega, "Quantification of Torque Teno Virus (TTV) in plasma and saliva of individuals with liver cirrhosis: a cross-sectional study," *Front. Med.*, vol. 10, pp. 1184353, Jun. 22, 2023. https://doi.org/10.3389/fmed.2023.1184353.
23. W. Mouton, A. Conrad, A. Bal, M. Boccard, C. Malcus, S. Ducastelle-Lepretre, et al., "Torque Teno virus viral load as a marker of immune function in allogeneic Haematopoietic stem cell transplantation recipients," *Viruses*, vol. 12, no. 11, p. 1292, Nov. 2020, doi: 10.3390/v12111292. https://doi.org/10.3390/v12111292.
24. D. Focosi, L. Macera, U. Boggi, L. C. Nelli, and F. Maggi, "Short-term kinetics of torque teno virus viremia after induction immunosuppression confirms T lymphocytes as the main replication-competent cells," Journal of General Virology, vol. 96, no. 1, pp. 115-117, Jan. 2015. https://doi.org/10.1099/vir.0.070094-0.
25. E. A. Lolomadze and D. V. Rebrikov, "Constant companion: clinical and developmental aspects of torque teno virus infections," Archives of Virology, vol. 165, no. 12, pp. 2749-2757, Dec. 2020. https://doi.org/10.1007/s00705-020-04841-x.
26. L. P. van Leeuwen, W. de Jong, L. Doornekamp, E. C. van Gorp, P. J. Wismans, and M. Goeijenbier, "Exotic viral hepatitis: A review on epidemiology, pathogenesis, and treatment," Journal of Hepatology, vol. 77, no. 5, pp. 1431-1443, Nov. 1, 2022. https://doi.org/10.1016/j.jhep.2022.06.031.

27. H. Razavi, "Global epidemiology of viral hepatitis," *Gastroenterology Clinics of North America*, vol. 49, no. 2, pp. 179-189, Jun. 1, 2020. https://doi.org/10.1016/j.gtc.2020.01.001. https://doi.org/10.1016/j.gtc.2020.01.001.
28. M. Asim, R. Singla, R. K. Gupta, and P. Kar, "Clinical & molecular characterization of human TT virus in different liver diseases," Indian Journal of Medical Research, vol. 131, no. 4, pp. 545-554, Apr. 2010. https://doi.org/10.1016/j.hepres.2005.01.014.
29. H. Tokita, S. Murai, H. Kamitsukasa, M. Yagura, H. Harada, A. Hebisawa, M. Takahashi, and H. Okamoto, "Influence of TT virus on the histopathological features of nonalcoholic fatty liver disease," *Hepatol. Res.*, vol. 19, pp. 197-211, 2001. https://doi.org/10.1016/s1386-6346(00)00124-8.
30. H. Tokita, S. Murai, H. Kamitsukasa, M. Yagura, H. Harada, M. Takahashi, and H. Okamoto, "High TT virus load as an independent factor associated with the occurrence of hepatocellular carcinoma among patients with hepatitis C virus-related chronic liver disease," *J. Med. Virol.*, vol. 67, no. 4, pp. 501-509, 2002. https://doi.org/10.1002/jmv.10129.
31. M. J. Pyysalo, L. M. Pyysalo, J. Hiltunen, J. Järnstedt, M. Helminen, P. J. Karhunen, and T. Pessi, "The dental infections in patients undergoing preoperative dental examination before surgical treatment of saccular intracranial aneurysm," BMC Research Notes, vol. 11, p. 1-6, Dec. 2018. https://doi.org/10.1186/s13104-018-3704-z.
32. J. Hallikainen, A. Lindgren, J. Savolainen, T. Selander, A. Jula, M. Närhi, T. Koivisto, J. Kellokoski, P. Ylöstalo, A. L. Suominen, and J. Frösen, "Periodontitis and gingival bleeding associate with intracranial aneurysms and risk of aneurysmal subarachnoid hemorrhage," Neurosurgical Review, vol. 43, pp. 669-679, Apr. 2020. https://doi.org/10.1007/s10143-019-01097-1.
33. M. W. Adelman, A. A. Connor, E. Hsu, A. Saharia, C. M. Mobley, D. W. Victor III, M. J. Hobeika, J. Lin, K. A. Grimes, E. Ramos, and C. Pedroza, "Bloodstream infections after solid organ transplanta-

tion: clinical epidemiology and antimicrobial resistance (2016–21)," JAC-Antimicrobial Resistance, vol. 6, no. 1, p. dlad158, Feb. 2024. https://doi.org/10.1093/jacamr/dlad158.

34. N. Weiss, H. Pflugrad, and P. Kandiah, "Altered mental status in the solid-organ transplant recipient," in Seminars in Neurology, Thieme Medical Publishers, Inc., Aug. 2024.. https://doi.org/10.1055/s-0044-1789004.
35. A. L. van Rijn, H. F. Wunderink, I. A. Sidorov, C. S. de Brouwer, A. C. Kroes, H. Putter, A. P. de Vries, J. I. Rotmans, and M. C. Feltkamp, "Torque teno virus loads after kidney transplantation predict allograft rejection but not viral infection," Journal of Clinical Virology, vol. 140, p. 104871, Jul. 2021. https://doi.org/10.1016/j.jcv.2021.104871.
36. S. Mafi, M. Essig, J. P. Rerolle, G. Lagathu, R. Crochette, V. Brodard, B. Schvartz, S. Gouarin, N. Bouvier, I. Engelmann, and A. Garstka, "Torque teno virus viremia and QuantiFERON®-CMV assay in prediction of cytomegalovirus reactivation in R+ kidney transplant recipients," Frontiers in Medicine, vol. 10, p. 1180769, Jun. 22, 2023. https://doi.org/10.3389/fmed.2023.1180769.
37. J. Zeng, Y. Tang, T. Lin, and T. Song, "Torque-teno virus for the prediction of graft rejection and infection disease after kidney transplantation: A systematic review and meta-analysis," Journal of Medical Virology, vol. 95, no. 3, p. e28677, Mar. 2023. https://doi.org/10.1002/jmv.28677.
38. F. Haupenthal, J. Rahn, F. Maggi, F. Gelas, P. Bourgeois, C. Hugo, B. Jilma, G. A. Böhmig, H. Herkner, M. Wolzt, and K. Doberer, "A multicentre, patient-and assessor-blinded, non-inferiority, randomised and controlled phase II trial to compare standard and torque teno virus-guided immunosuppression in kidney transplant recipients in the first year after transplantation: TTVguideIT," Trials, vol. 24, no. 1, p. 213, 2023. https://doi.org/10.1186/s13063-023-07216-0.
39. M. Schiemann, E. Puchhammer-Stöckl, F. Eskandary, P. Kohlbeck, S. Rasoul-Rocken-

schaub, A. Heilos, N. Kozakowski, I. Görzer, Ž. Kikic, H. Herkner, and G. A. Böhmig, "Torque Teno virus load—inverse association with antibody-mediated rejection after kidney transplantation," Transplantation, vol. 101, no. 2, pp. 360-367, Feb. 1, 2017. https://doi.org/10.1097/tp.0000000000001455.

40. R. Strassl, M. Schiemann, K. Doberer, I. Görzer, E. Puchhammer-Stöckl, F. Eskandary, Ž. Kikić, G. A. Gualdoni, M. G. Vossen, S. Rasoul-Rockenschaub, and H. Herkner, "Quantification of torque teno virus viremia as a prospective biomarker for infectious disease in kidney allograft recipients," The Journal of Infectious Diseases, vol. 218, no. 8, pp. 1191-1199, Sep. 8, 2018. https://doi.org/10.1093/infdis/jiy306.
41. N. S. Reyes, P. G. Spezia, R. Jara, F. Filippini, N. Boccia, G. García, E. Hermida, F. A. Poletta, M. Pistello, G. Laham, and F. Maggi, "Torque Teno Virus (TTV) in Renal Transplant Recipients: Species Diversity and Variability," Viruses, vol. 16, no. 3, p. 432, Mar. 11, 2024. https://doi.org/10.3390/v16030432.
42. D. Kulifaj, V. Tilloy, E. Scaon, E. Guerin, M. Essig, N. Pichon, S. Hantz, A. De Bernardi, M. Joannes, C. Barranger, and S. Alain, "Viral metagenomics analysis of kidney donors and recipients: Torque teno virus genotyping and prevalence," Journal of Medical Virology, vol. 92, no. 12, pp. 3301-3311, Dec. 2020. https://doi.org/10.1002/jmv.26298.
43. M. Solis, A. Velay, P. Gantner, J. Bausson, A. Filipputtu, R. Freitag, B. Moulin, S. Caillard, and S. Fafi-Kremer, "Torquetenovirus viremia for early prediction of graft rejection after kidney transplantation," Journal of Infection, vol. 79, no. 1, pp. 56-60, Jul. 1, 2019. https://doi.org/10.1016/j.jinf.2019.05.010.
44. L. Cañamero, A. Benito-Hernández, E. González, C. Escagedo, M. Rodríguez-Vidriales, M. D. García-Saiz, R. Valero, L. Belmar, M. A. De Cos, M. V. Francia, and J. C. Ruiz, "Torque Teno virus load predicts opportunistic infections after kidney transplantation but is not associated with maintenance immu-

nosuppression exposure," Biomedicines, vol. 11, no. 5, p. 1410, May 9, 2023. https://doi.org/10.3390/biomedicines11051410.

45. R. Roberto, L. Cinti, A. Napoli, D. Paesani, R. J. Riveros Cabral, F. Maggi, M. Garofalo, R. Pretagostini, A. Centofanti, C. Carillo, and F. Venuta, "Torque teno virus (TTV): A gentle spy virus of immune status, predictive marker of seroconversion to COVID-19 vaccine in kidney and lung transplant recipients," Journal of Medical Virology, vol. 95, no. 2, p. e28512, Feb. 2023. https://doi.org/10.1002/jmv.28512.