Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Short Communication
Volume 22 Issue 4- July 2026
DOI: 10.19080/ARGH.2026.22.556095

Adv Res Gastroentero Hepatol

The Pivotal Role of the Liver in Ebola Virus Pathogenesis: Its Connection with Glucose and Ascorbate Homeostasis

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Submission: June 29, 2026 **Published:** July 13, 2026

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Keywords: Ebola Virus Pathogenesis; Pivotal Role; Glucose; Ascorbate Homeostasis

Introduction

According to Fields Virology book, volume1 Emerging viruses, authored by Jens H. Kuhn, Gaya K. Amarasinghe and Donna L. Perry, Ebola virus (EBOV) [1] at the exposure site targets dermal or submucosal resident tissue, dendritic cells and macrophages and begins replicating. Infected mononuclear cells migrate to the lymphatics and enter regional lymph nodes, and both mature virions and infected monocytes spread the virus systematically. The liver is a major target organ of infection. Systemic filovirus spread results in the infection of hepatocytes and Kupffer cells (tissue macrophages), causing acute degeneration and increases in ALT and AST transaminases. The increases in AST activity could be associated with ischemic damage and/or haemorrhage in cardiac muscle, skeletal muscle, the kidneys, pancreas, spleen, lungs, and importantly, red blood cells, in addition to the liver. The abrupt increases in AST activity seen typically by 4 days postexposure are thought to be derived from hepatocytes. As the disease progresses, ongoing hepatocellular damage is thought to decrease the production of albumin and hepatocellular-synthesized coagulation factors, potentiating the coagulopathy.

In a previous article [2], it was disclosed that EBOV could interact with the ascorbate and glucose universal transporter GLUT-1 and membrane-trafficking-associated proteins, altering the flux of glucose and ascorbate to maintain intracellular pools, and causing oxidative stress. Some receptors of attachment factors described for EBOV entry, as are TIM-1 and Axl could perturb the function of GLUT -1, as they are functionally associated, which is ultimately linked to metabolic complications and severe inflammatory response. Disruption of glucose and ascorbate homeostasis could be the reason of both enhanced inflammatory cytokine storming and haemorrhagic manifestations at the level of endothelial cells and vasculature injury [3-7]. Endothelial damage during EBOV infection with no evidence of direct endothelial cytolysis has previously been described [8], reinforcing the idea that other indirect mechanisms governing vasculature injury are present. Apoptosis in endothelial cells can be induced by hyperglycemia and ascorbate helps to prevent endothelial dysfunction, stimulates type-IV collagen synthesis and enhances cell proliferation [9]. Haemorrhages and vasculature disfunctions are a clinical feature not only of viral haemorrhagic fevers, but also in scurvy, diabetes and thrombotic microangiopathic hemolytic anaemia. Inflammatory cytokine concentrations were found to be acutely increased by hyperglycaemia in humans [6,7]. Hypoascorbinaemia and diabetes mellitus share several clinical symptoms including microangiopathy, capillary hyper perfusion and hemorrhages.

Interestingly, expression of Glut-1 on the erythrocyte membrane is associated with the inability to synthesize ascorbate [10] and is restricted to that very species that are susceptible to filoviruses or are considered to be the reservoir of the virus in nature (primates, humans and fruit bats). Glucose and ascorbate metabolism represent probably an Achilles' heel in Filoviral haemorrhagic fevers and Glut-1 may play a pivotal role in haemorrhagic fever pathogenesis. In other words, Glut-1 on erythrocytes and inability to synthesize ascorbate may account for the pathophysiology of filovirus haemorrhagic fevers in susceptible species. Ebola and Marburg viruses cause haemorrhagic fever in human and non-human primates. Guinea pigs are frequently used as an animal model after a trivial virus strain adaptation. Fruit bats are considered the reservoir of filoviruses in nature.

The pivotal role of the liver in Ebola virus pathophysiology

Basing on the central role of glucose and ascorbate homeostasis in the pathogenesis of EBOV, and its role in the haemorrhagic manifestations and inflammatory response, we could conclude that the liver plays the same role as an organ, as ascorbate and glucose play as metabolic products. The liver maintains stable blood glucose levels by balancing glucose storage and production via glycogenesis, glycogenolysis and gluconeogenesis. The liver takes up excess glucose from the blood stream and converts it into glycogen for storage. Additionally, when blood sugar begins to drop, the liver responds by breaking down its stored glycogen back into glucose and releasing it into the bloodstream. As for the ascorbate, the liver acts as the central regulator of systemic ascorbate homeostasis, controlling its storage, catabolism and distribution throughout the body. As mentioned, humans, the same case as fruit bats and non-human primates, lack the enzymes to synthesize Vitamin C (ascorbate) and the liver actively absorbs, oxidizes and clears circulating ascorbate, while utilizing it to regulated hepatic lipid metabolism. Hepatic enzymes that metabolize xenobiotics, as is the case of cytochrome P450, rely on ascorbate as cofactor and electron donor. Ascorbate downregulates lipid synthesis genes and activates metabolic pathways like AMPK, that promote fatty acid β-oxidation.

Assuming the implications of the hypotheses presented, supportive care of EBOV haemorrhagic fever could be significantly improved, acting on the metabolic keys that govern the pathophysiological process. A treatment strategy would focus on the administration of glucose or insulin at convenience, in order to maintain constant and normal levels of glucose in plasma, and on the administration of sufficient quantities of ascorbate and glutathione (which participates intracellularly, along with NADH, in the reduction of DHA to ascorbate) in order to combat the oxidative and inflammatory stress, and avoiding its worst consequence: septic shock. Maintaining ascorbate levels could mitigate the "scurvy-like" vascular collapse during infection. The liver is the key organ regulating ascorbate and glucose homeostasis, along with other metabolic implications of the liver in EBOV disease, and so, the control of liver damage and liver function during the EBOV disease would be a monitoring factor in the surveillance of the disease progress. New insights could be developed confronting liver function status and ascorbate and glucose systemic physiology, approaching new treatment strategies oriented to focally prevent hepatocyte infection and maintain liver function. Hepatoprotectives work by reducing oxidative stress, lowering inflammation and supporting cellular repair. As such, ascorbate could be considered in a treatment strategy also as hepatoprotective, but it would be interesting to add other treatment substances in EBOV disease, like N-acetylcysteine (broadly used to treat acetaminophen overdose), corticosteroids and pentoxifylline, often prescribed for severe alcoholic liver disease to reduce inflammation. In fact, as described in Fields Virology, adrenal cortical cells are also often infected by EBOV. EBOV infection could decrease both mineralocorticoid and glucocorticoid production, leading to reductions in blood volume and vascular tone [1].

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How to cite this article: Ivan C W. The Pivotal Role of the Liver in Ebola Virus Pathogenesis: Its Connection with Glucose and Ascorbate Homeostasis. Adv Res Gastroentero Hepatol, 2026; 22(4): 556095. DOI: 10.19080/ARGH.2025.22.556095

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