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REVIEW

Hepatitis C Virus (HCV) and Hepatitis D Virus (HDV): Divergent Pathways to Hepatocellular Carcinoma (HCC)

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Abstract

Hepatitis C virus (HCV) and hepatitis D virus (HDV) are two significant viral agents that can lead to hepatic injury, particularly hepatocellular carcinoma (HCC). HCV is an RNA virus that primarily leads to infection via blood contact and ultimately causes chronic liver inflammation. Studies indicate that HCV infection induces genetic and cellular alterations that subsequently increase the risk of liver cancer. HDV plays a crucial role in exacerbating liver disease through both HCV-dependent and independent pathways. By causing dual damage to hepatocytes and increasing cirrhosis risk, HDV significantly elevates HCC incidence. Coinfection with HCV and HDV is particularly hazardous, as both viruses promote hepatocarcinogenesis through alterations in cellular signaling pathways, chromosomal instability, and inhibition of tumor suppressor genes in hepatocytes. Despite preventive advances such as hepatitis B virus vaccination (which prevents HDV superinfection) and direct-acting antivirals for HCV treatment, the burden of virus-associated cancers remains prevalent, especially in low and middle-income countries. Understanding the complex molecular mechanisms underlying viral hepatitis-related hepatocarcinogenesis, along with improved epidemiology of HCV/HDV, creates new opportunities for diagnosis and treatment. This article emphasizes the importance of early detection, antiviral therapy, innovative treatment approaches, and regular surveillance in high-risk populations to reduce HCC incidence.

Keywords: Liver, Hepatocellular carcinoma, Hepatitis C virus, Hepatitis D virus.

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INTRODUCTION

Liver cancer (LC) ranks among the most prevalent neoplasms and constitutes a leading cause of cancer-related mortality worldwide(1). This is the only one of the five deadly cancers that shows an annual increase in incidence percentage and is the leading cause of cancer-related mortality worldwide(2). Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) account for approximately 85% and 15% of primary LCs, respectively(3, 4). Significant temporal shifts have occurred in the geographical distribution of HCC mortality with traditionally low-incidence regions (North America and parts of Europe) now demonstrating rising rates, while historically endemic areas (notably Japan and China) show declining trends(5). Established risk factors for hepatocarcinogenesis include alcohol abuse, metabolic disorders (particularly non-alcoholic fatty liver disease (NAFLD) spectrum pathologies spanning simple steatosis to non-alcoholic steatohepatitis (NASH)), (obesity, and diabetes mellitus), hereditary conditions hemochromatosis and Wilson's disease(6, 7). Alongside additional determinants such as aflatoxin exposure (predominantly HCC-specific) and biliary tract inflammation (primarily ICC-associated) with underlying etiologies including primary sclerosing cholangitis, chronic cholestasis, hepatolithiasis, and liver fluke infestation(6). Although hepatitis D virus (HDV) infection elevates HCC risk, novel therapeutic agents have recently received approval(8). The impact of successful hepatitis C virus (HCV) eradication via direct-acting antivirals (DAAs) on reversing HCV-associated metabolic dysregulation and preventing atherosclerosis remains controversial, warranting further investigation(9). This comprehensive review examines key aspects of viral hepatitis, detailing viral structures, life cycles, and pathogenic mechanisms. We synthesize extensive epidemiological data on temporal trends and clinical outcomes, with particular emphasis on transmission dynamics, disease manifestations, and contemporary therapeutic approaches.

Comparative Virology of Hepatitis C Virus and Hepatitis Delta Virus: Implications for Liver Cancer Pathogenesis

Global public health faces a serious threat from LC, the sixth most common cancer globally and a leading cause of cancer-related mortality(10, 11). The World Health Organization projects this disease will cause over one million fatalities annually by 2030(12). The incidence of LC varies significantly geographically, with the highest rates in East Asia and North Africa, and China accounting for nearly half of global cases. In contrast, incidence rates in developed regions are generally lower. Globally, the incidence in males is about 2.7 times higher than in females(13). HCC and cholangiocarcinoma represent the primary histological subtypes, with HCC constituting the majority of cases(14). Established risk factors include alcohol consumption, tobacco use, aflatoxin exposure, dietary patterns, oral contraceptive use, obesity, type 2 diabetes, age, and gender. NAFLD among the most prevalent chronic liver conditions exacerbates LC risk, with its progression potentially leading to NASH and HCC(15). Crucially, hepatotropic viruses including hepatitis B virus (HBV), HCV, and HDV significantly contribute to pathogenesis(16, 17). HCV, a single-stranded positive-sense RNA virus of the Hepacivirus genus (Flaviviridae family), is a blood-borne pathogen transmitted through direct blood exposure (e.g., transfusion) or indirect contact with contaminated materials/equipment (18, 19). The viral life cycle is highly dependent on the host, and its key stages, such as entry and morphogenesis, are closely linked to human lipid metabolism. The virus circulates as lipid-containing particles and enters liver cells through interactions with lipoprotein receptors(20). During chronic infection, combined viral actions and host immune responses induce dysregulation, impairing viral clearance. This immune failure establishes persistent hepatic inflammation that progresses to cirrhosis, liver failure, or HCC(21). HCV exhibits exceptional genetic diversity due to error-prone RNA-dependent RNA polymerase activity. Genomic replication occurs within double-membrane vesicles derived from endoplasmic reticulum (ER) membranes, facilitated by the viral replication complex (NS3-NS5B proteins)(19). As one of medicine's most challenging viral infections, HCV demonstrates global genotype predominance: HCV genotype 1 (HCV-1) (44%), HCV-3 (25%), and HCV-4 (15%). Disease progression correlates with this molecular diversity, while inadequate testing leaves many infections undiagnosed(22). Given acute HCV patients' susceptibility to advanced liver disease and potential for viral transmission, establishing effective clinical management strategies is imperative(23). HDV, a defective RNA virus requiring HBV for virion assembly and transmission (though autonomous in replication)

(24). Forms 36 nm particles containing a 1.7 kb RNA genome(25). Classified in the Deltavirus genus, it encodes a single structural protein hepatitis D antigen (HDAg) and features self-cleaving ribozyme activity(26). Despite multiple open reading frames, only HDAg undergoes active transcription(27). Two HDAg isoforms exist: small HDAg (S-HDAg) and a longer form large HDAg (L-HDAg), the latter produced via RNA editing(28). Eight genotypes (HDV-1 to HDV-8) display distinct distributions: HDV genotype 1 (HDV-1) is pandemic, while HDV-2 to HDV-8 demonstrate regional prevalence(29). During replication, HDAg forms ribonucleoprotein complexes that acquire HBV-derived envelopes (hepatitis B surface antigens: S-HBsAg, M-HBsAg, L-HBsAg) from the ER(30, 31). This shared envelope structure critically influences viral interactions. Acute HDV infection manifests either as HBV coinfection or superinfection in HBsAg-positive individuals(32). Chronic HDV infection markedly accelerates liver fibrosis progression and triples HCC risk compared to HBV monoinfection(33).

Mechanisms of Hepatitis C Virus Entry and Replication

As an obligate intracellular pathogen, HCV exhibits absolute dependence on host cells for replication. Its life cycle comprises sequential stages: viral entry, RNA replication, protein translation, and viral assembly(34). The entry process initiates with HCV binding to surface proteoglycans (e.g., heparan sulfate) and the tetraspanin receptor cluster of differentiation 81 (CD81), followed by lateral translocation to tight junctions where occludin (OCLN) and claudin-1 (CLDN1) mediate viral internalization(35). Virions undergo clathrin-mediated endocytosis and subsequently fuse with endosomal membranes under low-pH conditions(36). The RNA-dependent RNA polymerase NS5B drives replication by transcribing positive-strand genomic RNA into complementary negative-strand RNA, which then serves as the template for synthesizing new positive-strand genomes(37). Long non-coding RNAs (lncRNAs) significantly modulate HCV replication, as infection-mediated lncRNA dysregulation promotes viral dissemination by suppressing interferon (IFN) mediated antiviral responses at multiple levels. HCV infection profoundly alters lncRNA transcription profiles, and despite their genomic abundance, many lncRNAs undergo degradation in infected cells(38). HCV cellular entry represents one of the best characterized viral uptake mechanisms, with its complexity reflecting extensive viral adaptation to hepatic environments. While the human liver contains multiple cell types, HCV primarily targets hepatocytes(39). Penetration of HCV into hepatocytes is contingent upon the presence of specific surface molecules, including CD81, scavenger receptor class B type I (SR-BI), CLDN1, and OCLN. Although CD81 is ubiquitously expressed in nucleated cells, the simultaneous availability of this quartet of host factors governs permissiveness to HCV entry into liver cells(40). Beyond coreceptors that directly engage viral glycoproteins (e.g., CD81, SR-B1), indirect cellular factors regulate entry without viral interaction. CD81-binding partners critically orchestrate entry processes, with factors controlling tight junction protein localization/activity significantly influencing HCV internalization. Notably, the CD81 interactor Rho-associated protein kinase 1 operates during post-binding entry stages and is recruited to CD81 during HCV uptake (41, 42).

Mechanism of Hepatitis Delta Virus: From Entry to Exit

Research indicates that HDV virions primarily utilize the pre-S1 domain of large HDAg to bind sodium taurocholate co-transporting polypeptide (NTCP) receptors on hepatocyte basolateral membranes(43). However, HDV entry may also occur through HBsAg-L-dependent mechanisms, with evidence suggesting utilization of non-HBV viruses or other hepadnaviruses as helper viruses for hepatocyte entry. HDV can additionally infect non-hepatic cells via receptors employed by alternative helper viruses(44). HBV/HDV particle infectivity depends on two critical determinants: 1) the presence of L-HBsAg in the viral envelope containing an essential NTCP-binding domain within its N-terminal preS1 region and 2) the antigenic loop of S-HBsAg. NTCP (encoded by SLC10A1) expressed on hepatocyte basolateral membranes facilitates clathrin-mediated endocytosis, with its regulation governed by host factors including E-cadherin and post-translational modifications(45). Following entry, viral uncoating triggers HDAg-mediated nuclear translocation signals. HDV genomic replication proceeds through three phases: RNA synthesis, cleavage, and ligation. Host DNA-dependent RNA polymerases initially catalyze repetitive transcription of circular double-stranded templates to generate oligomeric RNAs. Nuclear replication occurs via a symmetric roll-

ing circle mechanism mediated by dual self-cleaving ribozymes (genomic and antigenomic strands) facilitated by RNA chaperones(46). RNA polymerase I transcribes antigenomic RNA from genomic templates, while RNA polymerase II synthesizes new genomic RNAs from antigenomic templates. ADAR1 mediated editing of antigenomic RNA enables L-HDAg production, whereas unedited transcripts encode S-HDAg(47). Newly synthesized genomic RNA associates with both HDAg isoforms to form viral ribonucleoproteins, which undergo cytoplasmic translocation. Mature virions acquire envelopes through interactions with L-HBsAg/S-HBsAg in the ER, with subsequent Golgi processing enabling secretory release from infected cells(48) (Figure 1).

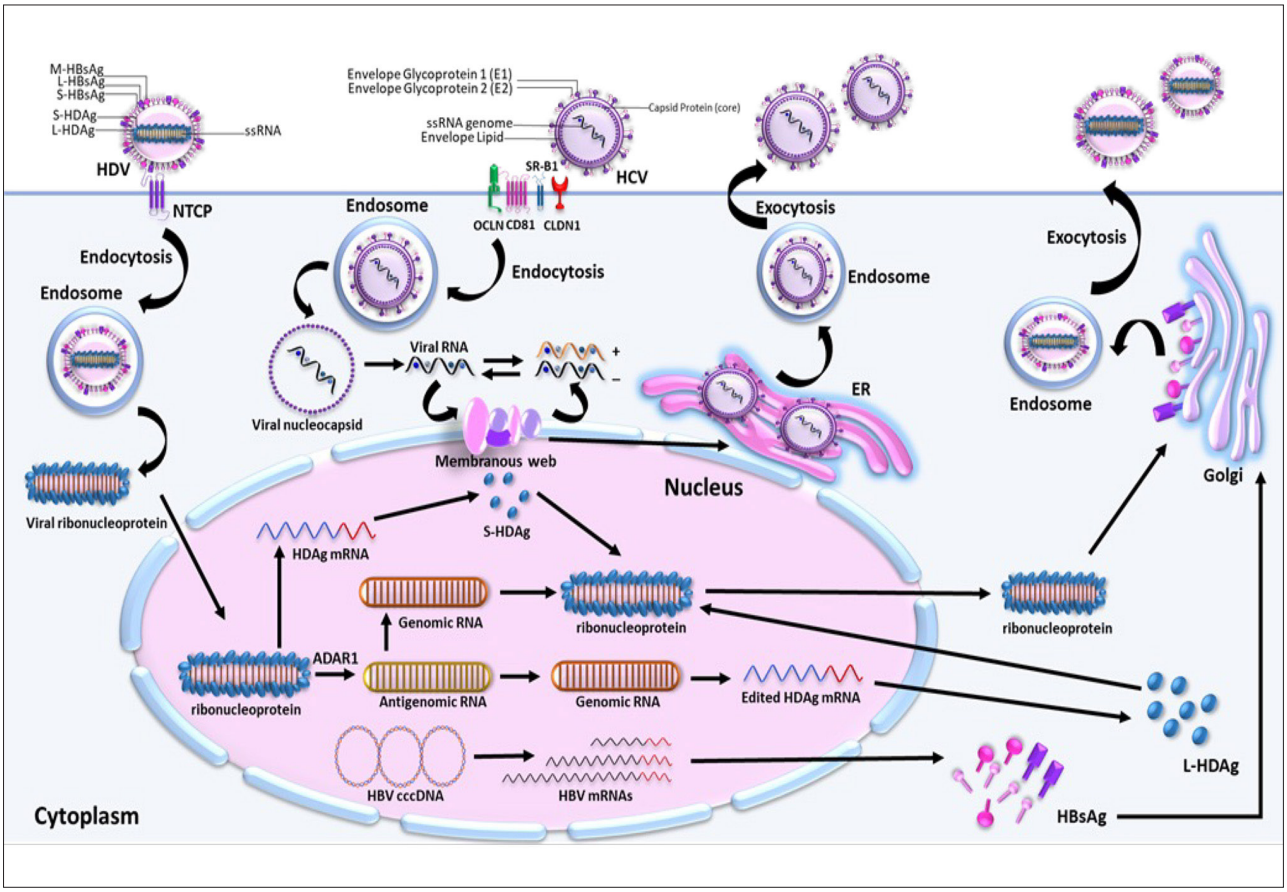

Figure 1: . Illustrates the life cycles of HDV and HCV as follows: 1) Through HBsAg-assisted endocytosis, HDV first attaches itself to the NTCP membrane receptor, after which the internalized ribonucleoprotein complex is discharged into the cytoplasm; 2) viral transport into the nucleus is mediated by a nuclear localization signal produced by L-HDAg and SHDAg; 3) HDAg mRNA is transcribed by cellular RNA polymerase II; 4) HDAg mRNA is exported to the cytoplasm where S-HDAg is translated, and RNA polymerase I uses the HDV genomic RNA as a template to produce antigenomic RNA; 5) The antigenomic RNA is edited by ADAR1 and then replicated back into genomic RNA, which first encodes HDAg and then L-HDAg; 6) Both HDAg isoforms react with freshly generated genomic RNA to create novel viral ribonucleoprotein complexes, which are then exported to the cytoplasm and processed via the ER-Golgi pathway prior to the release of mature HDV virions from the cell; 7) HCV binds to heparan sulfate proteoglycans, CD81, and SR-B1 receptors to enter hepatocytes; 8) CLDN-1 and OCLN interact to acidify the endosome that contains HCV virions, which causes the low pH environment to cause the release of viral RNA into cytosol; 9) The NS5B RNA-dependent RNA polymerase catalyzes RNA through the membranous web at the nuclear membrane; 10) Finally, the nucleocapsid assembles and the enveloped virion is transported through the ER lumen to the Golgi apparatus before being released from the host hepatocyte.

Novel Diagnostic Approaches for Hepatitis C Virus and Hepatitis D Virus

Approximately 90% of LC diagnoses correspond to HCC(49). While blood-based biomarkers like alpha-fetoprotein have advanced early HCC detection, their limited sensitivity, specificity, and accuracy necessitate improved diagnostic approaches. Novel serum protein markers are currently under investigation to address this need(50). Radiomics has emerged as a significant technique for early diagnosis, disease classification, and outcome prediction. Studies demonstrate that logistic regression models can effectively correlate radiomic features with immunological factors to predict recurrence and guide therapeutic planning(51). Initial HCC symptoms are often subtle and typically manifest only after disease progression. Consequently, traditional diagnostic methods with restricted accuracy are increasingly supplemented by surgical interventions combined with chemotherapy. Given surgery's invasiveness, combined diagnostic strategies are essential for treatment optimization and survival improvement. Biopsy remains fundamental for differentiating HCC from ICC, combined HCC-ICC, or metastases particularly gastrointestinal tumors(52). Nanoparticles conjugated to aptamers, through specific binding to viral core proteins, show promise as HCV biosensors and enable easy detection. Laboratory diagnosis of HCV involves serological assays to identify anti-HCV antibodies and molecular tests to detect HCV RNA genomes for viral load quantification and genotyping(53). HDV transmission mirrors HBV pathways, primarily involving percutaneous or mucosal exposure to contaminated blood/body fluids(54). Major routes include unprotected sexual contact, sharing contaminated needles/syringes, transfusion of infected blood products, unsterilized tattooing/piercing equipment, and vertical mother-to-neonate transmission(55, 56). Since seropositivity cannot distinguish active from resolved infection, confirmatory testing requires HDV RNA detection alongside HBsAg positivity, anti-HDV serology, and elevated liver enzymes (alanine aminotransferase (ALT) or aspartate aminotransferase (AST)) (57). Most HDV infections originate from contaminated blood products, leading to hematogenous spread. While HDV can independently enter hepatocytes and replicate its genome for at least six weeks (single infection), productive infection and virion assembly require the subsequent presence of HBV. Notably, chronic infection is more associated with secondary infection in chronic HBV carriers than with coinfection in HBV-naive individuals(58). Acute HDV manifests after a 3-7 week incubation with elevated ALT/AST. Diagnosis parallels HBV using IgM/IgG serology. In chronic hepatitis D (CHD), HDV-mediated suppression of HBV replication typically yields low HBV DNA levels. CHD diagnosis requires anti-HDV IgM/IgG and HDV RNA detection(59). While quantitative nucleic acid analysis aids HDV management, conventional polymerase chain reaction (PCR) is unsuitable due to HDVs RNA genome(60). Instead, reverse transcription PCR (RT-PCR) detects serum HDV RNA, while nucleic acid hybridization techniques enabled by cloned HDV RNA probes quantify HDV in serum and liver tissue(61). HDV accounts for 70% of cirrhosis cases over the past decade. HDV/HBsAg coinfection triples progression risk versus HBV monoinfection. Anti-HDV antibodies are less frequent in asymptomatic carriers than cirrhotic patients, where they indicate both exposure and active replication. Occult HDV infections represent latent states in some carriers. HBV vaccination remains the primary prevention method by reducing HBsAg carrier rates(62).

Prevention and Treatment of Viral Infections

The primary objective of HCV treatment is to eradicate the virus from the body. This viral clearance subsequently stops or reverses hepatic pathological changes, thereby preventing disease progression through successive stages of its natural course(63). HCV infection increases the risk of hepatic and extrahepatic complications, leading to higher morbidity and mortality. Since their introduction in recent years, DAAs have revolutionized clinical practice and patient management, achieving cure rates of up to 99% in HCV treatment(64). The proven efficacy and safety of DAAs in liver transplant recipients allow for antiviral therapy initiation as early as the immediate post-transplant period optimally within one month after transplantation once HCV viremia is confirmed. When transplantation occurs during active antiviral treatment, the decision to continue or discontinue therapy should be individualized(65). A major therapeutic advance occurred with polymerase inhibitors, which are unique among DAAs due to their high resistance barrier, making them ideal for combination regimens. The three core DAA classes have driven rapid innovation, yielding successive generations of com-

bination therapies(66). Since 1990, IFN-α monotherapy has been used to treat HCV infection. IFNs are essential antiviral defense proteins, with recombinant administration amplifying their effects. They induce apoptosis, inhibit cell growth, and interact with immune responses, enhancing T-helper cell differentiation and IFN-γ production. Treatment response is assessed through sustained virological response(67). Although recent clinical trials have demonstrated the effectiveness and safety of this treatment even in special populations, several unresolved issues remain. These include the emergence of resistance-associated variants following DAA treatment failure and the occurrence of HCC after DAA therapy(68). While DAAs remain inaccessible to many chronic hepatitis C patients in developing countries, they are transforming the previously poor prognosis of HCV related liver diseases and significantly improving clinical outcomes. Unfortunately, even after achieving sustained virologic response, the risk of HCC persists in patients with HCV-induced cirrhosis(69). The foundation of HDV prevention remains HBV vaccination, as immunity against HBV inherently protects against HDV infection. Two yeast-derived recombinant vaccines, Recombivax (Merck) and Engerix-B (GSK), are administered in a standard three-dose schedule (months 0, 1, and 6) for adults, with each injection containing 10 or 20 μg(70). Clinical studies confirm that HDV maintains infectivity in the presence of detectable HBsAg, even when HBV or HDV viral loads are low. This finding underscores that HBsAg clearance would effectively eliminate HDV infection(71). Pegylated interferon alfa (PEG-IFN-α) remains the only treatment option with demonstrated efficacy against HDV, achieving virological, biochemical, and histological responses in a subset of patients. PEG-IFN-α therapy, while showing limited long-term virological response rates, is associated with both reduced risk of clinical complications and improved long-term outcomes when sustained virological response is achieved(72). Bulevirtide, a large polypeptide mimicking the pre-S1 domain of HBsAg, was developed through the search for NTCP binding inhibitors. It exerts its antiviral effect by competitively blocking HBV/HDV viral entry(73). Lamivudine, ribavirin, famciclovir, adefovir, and entecavir show minimal or no antiviral efficacy against HDV when administered as monotherapy, regardless of treatment duration(74) (Table 1).

Table 1. Should be moved before the conclusion

Parameter	HCV	HDV	References
Oncogenic mechanisms	Epigenetic dysregulation and STAT3 pathway activation	TGF-β/Smad pathway hyperactivation	(75-77)
Molecular signatures	miR-122 downregulation, p53 mutations, Wnt/β-catenin activation	IL-6STAT3 sustained activation	(78-80)
Incubation period	5 to 12 weeks	15 to 60 days	(81, 82)
Immune response	Chronic immune activation contributes to liver injury	Stronger immune-mediated liver injury than HBV alone	(33)

CONCLUSION

List of Abbreviation

HCV: Hepatitis C Virus, HDV: Hepatitis Delta Virus, HCC: Hepatocellular Carcinoma, LC: Liver Cancer, ICC: Intrahepatic Cholangiocarcinoma, NAFLD: Non-Alcoholic Fatty Liver Disease, NASH: Non-Alcoholic Steatohepatitis, DAAs: Direct-acting antivirals, HBV: Hepatitis B Virus, ER: Endoplasmic Reticulum, HCV-1: HCV genotype 1, HDAg: Hepatitis D Antigen, S-HDAg: Small-Hepatitis D Antigen, L-HDAg: Long-Hepatitis D antigen, HDV-1: HDV genotype 1,CD81: Cluster of differentiation 81, OCLN: occluding, CLDN1: claudin-1, lncRNAs: Long non-coding RNAs, IFN: interferon, SR-B1: Scavenger receptor class B member 1, NTCP: sodium taurocholate co-transporting polypeptides, ALT:

Alanine Aminotransferase, AST: Aspartate Aminotransferase, CHD: Chronic Hepatitis D, PEG-IFN-α: Pegylated interferon alfa.

Statement Contribution of the Authors

Idea: A.J.S, M.P; Data Collection or Processing: A.J.S; Writing-Review & Editing: P.N.D, S.H.N.A, S.K.T, A.G, Z.G, S.N; Figure design: P.N.D; Table design: P.N.D; Supervision: A.J.S, M.P. All authors reviewed the results and approved the final version of the manuscript.

Ethics Declarations

Ethical approval and consent to participate

None.

Consent for publication

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Conflicts of Interests

Authors declare that there is no conflict of interests.

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