Hepatitis Delta: Seek and Ye Shall Find

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(See the article by Kucirka et al, on pages 845–852.)

Hepatitis delta virus (HDV) was discovered in 1977 by Rizzetto and colleagues [1], and—as he expressed it 30 years later—HDV “would have possibly died away as another odd antigenic subtype” of hepatitis B virus (HBV) had it not been for an international collaboration among investigators from Turin, Italy, the National Institutes of Health, and Georgetown University [2]. Chimpanzee experiments demonstrated that the delta antigen, rather than being a component of HBV, was its own defective form that required HBV for its infection and replication, a “virus’s virus.” Dual HBV-HDV infection was quickly recognized to have worldwide distribution, to be associated with more severe and rapidly progressive hepatitis, and to be especially resistant to treatment.

In the past few decades, remarkable strides in understanding the complex interplay between HBV and HDV at the molecular level have been achieved [3]. But many mysteries remain when these insights are applied to human disease, in which levels of HBV DNA and HDV RNA may fluctuate in relation to each other or not at all in individual patients [4]. Furthermore, some of the groups with HBV-HDV coinfection, such as injection drug users, also have hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfections. Unrecognized coinfections with these viruses—ie, before the availability of reliable screening tests for HIV (1985) or HCV (1992)—may have confounded early observations of the clinical course of patients with HBV-HDV coinfections. Indeed, one of the helpful observations of the article by Kucirka and colleagues [5] in the current issue of the Journal is the still very high infection rate found among a sample of injection drug users from 2005 to 2006 when tested for HCV (92%) or HIV (38%).

When first examined in the 1980s, it was clear that there were areas of high endemicity, especially in the Amazon Basin, Eastern Europe, and several regions of Africa and the Middle East, of intermediate endemicity in Southern Europe, and low endemicity in Northern Europe and North America. Over the next 10 years, there was a dramatic decline in HDV infection prevalence in Europe, considered to be the result of declining numbers of hepatitis B surface antigen (HBsAg)—positive injection drug users, vaccination for hepatitis B, and the effects of public health interventions related to the HIV epidemic. However, it has been noted that no additional declines in HDV have been observed in the past decade [6], perhaps because of the influx of immigrants dually infected with HBV-HDV to the United States from highly endemic areas.

In the United States, several early studies in the late 1970s through the mid-1980s showed antibodies to delta antigen in HBsAg-positive blood donors (3.8%) in 1979 [7], persons with acute and chronic hepatitis B infection in Los Angeles (homosexual men, 15%; injection drug users, 22%) [8, 9], and developmentally disabled persons in Illinois state facilities (30%) [10]. Relatively high rates of HDV prevalence were seen in injection drug users in New York City (67%) [11]. Furthermore, a retrospective study of serum collected from 1972 to 1975 from drug-using HBsAg-positive patients at several Veterans Administration facilities at US locales showed that 42% had antibodies to delta antigen [12].

Few outbreaks of HDV in the United States (and these among injection drug users) have been detected and examined in the last 25 years. Over a 21-month period between 1983 and 1985, Lettau and colleagues [13] investigated an outbreak of severe hepatitis among injection drug users in western Massachusetts associated with dual delta and hepatitis B viruses. Another 15 years elapsed before there was detection and investigation of a similar outbreak among injection drug users in Pierce County, Washington, by the Centers for Disease Control and Prevention (CDC) [14]. However, aside from these outbreaks, in recent years only about 6–10 cases of “confirmed” infections with
HDV have been reported to the CDC from various states each year. Thus, it is quite difficult to know what is happening with HDV without specific reports such as the one by Kucirka and colleagues [5].

So, where is HDV headed in this country? On the one hand, there has been a gratifying decrease in prevalence of HDV in Asia and Europe, attributed to the expanding rate of hepatitis B vaccination activities over the last 20 years. We should expect a similar decline in HDV in the United States as we progressively remove its “host virus.” Or should we?

Previous outbreaks have shown a high prevalence of HDV coinfection among HBV-infected injection drug users—54% in Massachusetts and 34.5% in Washington state—whereas HBV-infected non-drug users in those outbreaks had much lower HDV coinfection rates (9% in both states) [13, 14]. Indeed, a study of female prostitutes showed that, among those who used intravenous drugs, HBV and HDV coinfection rates were 21%, whereas the HBV-infected women who were not injection drug users had an HDV coinfection rate of 6% [15]. Similarly, early analyses demonstrated high hepatitis D infection rates among hemophilic men (19%) [16] but not in gay men (0%) [17].

One unifying explanation for these numbers is that HDV, like other blood-borne pathogens, may be more efficiently transmitted parenterally than by sexual contact. If this is the case, perhaps we should not expect the same drop-off in HDV coinfection rates as seen between 1980 and 2000 in places as diverse as Italy, Japan, Taiwan, and Turkey [6], where proportionately more HBV infection is acquired perinatally, sexually, or horizontally (in households), and proportionately less as the result of injection drug use. This hypothesis would also fit the current observation, albeit from a small sample, that fully 50% of HBV-infected injection drug users in Baltimore in 2003–2006 had concurrent HDV infection.

Trends in HDV-HBV coinfection and morbidity are contingent on successes in hepatitis B vaccination and screening. Approximately 15% of persons reported with acute hepatitis B infection in the United States are injection drug users [18]. In 1991, the United States adopted a vaccine-based strategy to eliminate HBV transmission, with subsequent gains in immunization coverage particularly among children and adolescents [19]. Despite a long-standing recommendation for hepatitis B vaccination, hepatitis B vaccine coverage among injection drug users remains low. As a result, 20%–70% of injection drug users have evidence of past or current HBV infection, with many lacking serologic evidence of hepatitis B vaccination and thus greater susceptibility to HBV [20]. When barriers to vaccination such as vaccine costs are removed, drug treatment centers successfully integrate hepatitis B vaccination as a routine service and greatly increase the numbers of injection drug users vaccinated [21]. To increase vaccination of injection drug users, the CDC recommends hepatitis B vaccination for all adults in correctional institutions and drug abuse prevention and treatment clinics; the CDC and other federal resources are available to defray the cost of vaccine purchase for these settings [19, 21]. In addition to vaccination, all injection drug users should be screened for HBV [19]. An estimated 3%–11% of injection drug users have chronic HBV infection, and many remain undiagnosed, reflecting inadequate HBV screening services in settings such as drug treatment programs [22]. Management of persons with chronic hepatitis B infection should include interventions to reduce behavioral risks of HBV transmission and referral for medical care. The data from Kucirka et al [5] highlight the importance of HDV testing as a component of clinical management for persons with chronic HBV infection. Unfortunately, few data are available to monitor whether injection drug users are receiving recommended hepatitis B prevention and care services.

Indeed, the study by Kucirka and colleagues [5] is not only useful as a marker of where we are in the US hepatitis D epidemic, but of where we are not. Very few studies such as this can or will be done, simply because there are too few cohorts of injection drug users currently being followed in the United States. The HIV/AIDS epidemic stimulated federal agencies such as the National Institute on Drug Abuse and (then) the CDC to establish studies of HIV and, eventually, of hepatitis virus infections among large populations of injection drug user in several cities. At present, the Baltimore study (ALIVE [AIDS Link to Intravenous Experience]) as reported here is the longest running US cohort study; in fact, its predecessor, “Man ALIVE,” predated the AIDS epidemic but is now one of few such studies left. This stymies our understanding not only of HDV and the “carrier” HBV epidemics in the United States but also of the continuing HCV and, to a lesser extent, HIV epidemics. Thus, we should expect our understanding of the evolution of the HDV epidemic—as well as HBV, HCV, and HIV epidemics—in this country, especially in one of the transmission risk groups most affected, to remain spotty and infrequent. It is a truism to write that “more research is needed,” but there is probably no more fitting comment on the implications of the research of the companion paper in this issue of the Journal.

References
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